Table of contents

eTable 1 | Landmark regulatory guidance concerning drug clinical trial design, analysis, and implementation in China, by 31 December 2023 1

eMethods 3

Cancer drug categorization 3

Identification of pivotal studies 3

Keywords and search strategies to identify publications of trials supporting cancer drug indication approvals in China 3

Identification of trial protocols 4

Assessment of risk of bias in randomized trials 4

Disagreements and solutions in randomized trials risk of bias assessment 4

Statistical analysis 5

eTable 2 | Modeling fitting for multivariable logistic regression on the association with trial features and risk of bias. 6

eTable 3 | Sources and availability of relevant information 7

eTable 4 | Detailed information of 77 sample cancer drugs, corresponding to 148 indications supported by 205 pivotal studies 8

eFigure 1 | Number of pivotal efficacy trials supporting original and supplemental cancer drug indication approvals by National Medical Products Administration, 2017-2021 23

eTable 5 | Univariate analysis for identifying potential factors with risk of bias 24

eFigure 2 | Time of pivotal single-arm trial and external control group supporting cancer indication approval in China. 25

eTable 6 | Multivariate meta-regression results 26

eTable 7 | Detailed justifications for risk of bias judgments for randomized controlled trials 28

eTable 1 | Landmark regulatory guidance concerning drug clinical trial design, analysis, and implementation in China, by 31 December 2023

Issue Date	Regulatory Guidance	Main Content Relevant to Clinical Trial Design of Cancer Drugs
2012/5/15	Technical Guidance on Clinical Trial of Cancer Drug	Regarding the pivotal evidence supporting drug approval, including the number and type of clinical trials, in most cases, at least two well-controlled and adequate clinical trials are required. Phase III clinical trials must adopt a randomized design. The primary advantage of randomization is that it reduces selection bias when grouping participants by the researchers. For clinical situations where it is impossible to implement a positive control or placebo control, dose control or historical data may be chosen as a control. The selection of historical data as a control should be done cautiously. It is important to note that due to continuous advancements in diagnostic technology, imaging techniques, supportive care, and the understanding of diseases, there may be significant differences between the cases included in historical data and the cases in the current trial group, leading to notable bias in the results. Special attention should be given to controlling for information selection bias.
2012/5/15	Technical Guidance on Clinical Trial Endpoint of Cancer Drug	When selecting tumor measurement-based endpoints in clinical trials, an evaluation should be conducted to address the uncertainty and bias related to the assessment of clinical benefit in cancer drug trials.
2012/5/15	Technical Guidance on Adding Supplement Indication of Authorized Cancer Drug	If the newly added indication already has effective treatment options in clinical practice, meaning that existing treatments provide benefits, a randomized controlled trial (RCT) should typically be conducted with clinical endpoints such as overall survival. Results from single-arm trials or using surrogate endpoints to evaluate efficacy are generally not sufficient for approval. However, if there is no effective treatment available for the newly added indication, meaning that existing treatments do not provide significant benefits, randomized controlled trials with a placebo control group or results from single-arm studies may be considered as supportive evidence. Endpoints can include overall survival, progression-free survival, and/or other surrogate endpoints.
2016/6/3	Technical Guidance on Biostatistics of Drug Clinical Trials	Clinical trials must apply statistical principles in advance to make reasonable and effective arrangements for trial-related factors, in order to maximally control confounding and bias, reduce experimental errors, improve trial quality, and ensure scientific analysis and reasonable interpretation of the trial results. Bias, also known as systematic error, refers to errors that arise during the design, execution, measurement, or analysis of clinical trials that can interfere with the evaluation of efficacy and safety. In clinical trials, bias includes various types of deviations from the study protocol. Since bias can affect the evaluation of

Issue Date	Regulatory Guidance	Main Content Relevant to Clinical Trial Design of Cancer Drugs
		efficacy and safety, and even the accuracy of the trial conclusions, it is essential to control bias throughout the entire clinical trial process.
2017/1/18	Technical Guidance on General Consideration of Drug Clinical Trials	A well-designed clinical trial is the prerequisite for obtaining valuable conclusions. Approaches to control bias: randomization, blinding, and adherence.
2020/12/31	Technical Guidance on Statistical Design of Cancer Drug Clinical Trials *(Trial version)*	Randomized Controlled Trial (RCT) is the gold standard for evaluating the efficacy and safety of a drug. If it is not feasible to conduct an RCT, the **strength of the evidence** supporting conclusions on efficacy and safety will be diminished. Since subjects lost to follow-up often have a higher risk of death, an imbalance in censoring times or censoring rates between groups may lead to biased analysis results. Therefore, it is necessary to assess the balance of censoring patterns between groups. Additionally, it is important to ensure that the most up-to-date survival data collected by the follow-up cutoff date is used for all subjects in the analysis.
2020/12/31	Technical Guidance on Clinical Trial of Cancer Drug Combination Therapy	Typically, pivotal studies for combination therapies do not accept single-arm trial designs.
2023/3/14	Technical Guidance on the Applicability of Single-Arm Clinical Trial Designs for Cancer Drug Approval	Since external control data, such as historical controls, come from different studies conducted at various times, using Single-Arm Trials (SAT) for evaluation without a randomized parallel control can introduce bias. This results in multiple uncertainties when using SAT results as a basis for benefit-risk assessment, including but not limited to: 1. Differences in populations 2. Variations in evaluators/methods of evaluation 3. Uncertainty regarding the correlation between response rates and survival benefits 4. Interference from other factors in clinical trials

Note: *Guidelines were obtained from the official website of the Center for Drug Evaluation, National Medical Products Administration (https://www.cde.org.cn/zdyz/index). The original version is in Chinese.*

eMethods

Cancer drug categorization

Cancer drugs were categorized as those authorized in China only and those also authorized by the FDA or the EMA, based on information from the Drugs@FDA, the FDA Center for Biologics Evaluation and Research, and EMA (ema.europa.eu/en/medicines) databases, up to 31 December 2021.

Identification of pivotal studies

Generally, pivotal clinical studies were described as "main clinical data supporting this import registration or new drug application" in the review documents. If no study was explicitly marked as "pivotal" (n=9), we included all efficacy studies and excluded those that only provided pharmacokinetics or safety data. For indications without publicly available review documents (n=5), we identified all premarketing trials included in the 'Clinical Trials' section in the latest label through 31 December 2021, and defined them as "pivotal".[1]

Keywords and search strategies to identify publications of trials supporting cancer drug indication approvals in China

Information sources

- MEDLINE (via PubMed)
- clinicaltrial.gov (if no result was obtained from MEDLINE)
- China National Know Infrastructure database (if no result was obtained from the former data sources)

Stepwise search strategy

1. **PubMed:** National Clinical Trial number
2. **clinicaltrial.gov:** National Clinical Trial number
3. **PubMed:** (Generic Name [Title]) AND (Study Title [Title/Abstract]), Filters applied: Clinical Trial
4. **China National Know Infrastructure database:** (Chinese Generic Name [Title]) AND (Indication [Title/Abstract]) AND (clinical trial)

Selection process

- **Include:** original research reporting preplanned trial results
- **Exclude:** post hoc analysis, exploratory exposure-response analysis, subgroup analysis for indications not approved in China, etc.

[1] National Medical Products Administration Center for Drug Evaluation. General format and writing guidelines for chemical drug and biologic labels. 2022.

Identification of trial protocols

We used a stepwise approach to search for trial protocols. First, we checked whether the protocol was contained in the supplementary materials of the trial publications. Second, we screened ClinicalTrials.gov using National Clinical Trial identifiers. If the protocol was unavailable in the aforementioned approaches, we searched the pharmaceutical company sponsor's website.

Assessment of risk of bias in randomized trials

For RCTs, we used the Cochrane revised tool for assessing risk of bias (RoB 2, the 22 August 2019 version) to assess their risk of bias, by answering a series of signaling questions in five bias domains: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.[2] Each domain includes several signaling questions, some only answered if the response to a previous question indicates they are applicable. The possible results are: low risk of bias, some concerns, and high risk of bias. In line with the guidance document, an RCT will be considered at "high risk of bias" if any domain was rated as high risk, or have some concerns in multiple domains in a way that substantially lowers confidence in the result; Trials will be considered at "low risk of bias" if all domains are low risk. "Some concern" will be assigned when at least one domain was rated 'some concerns' and none were rated 'high risk'.

For RCTs with available publications, we assessed their risk of bias using the publications reporting the results for the primary endpoints, and if available, their protocols and supplementary appendices, in line with previous literature. For trials that adopted clinical (i.e., overall survival, OS) and surrogate measures as coprimary efficacy endpoints, when their results were both reported, we evaluated the risk of bias on the clinical outcome (i.e., OS).[3] The assessment of risk of bias was conducted between April, 2024 and August, 2024.

Disagreements and solutions in randomized trials risk of bias assessment

Disagreements were principally on the judgment of Domain 3: Risk of bias due to missing outcome data, signaling question 3.1: **"Were data for this outcome available for all, or nearly all, participants randomized?"**

[2] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. Bmj. 2019;366:l4898.

[3] Naci H, Davis C, Savović J, Higgins JPT, Sterne JAC, Gyawali B, et al. Design characteristics, risk of bias, and reporting of randomised controlled trials supporting approvals of cancer drugs by European Medicines Agency, 2014-16: cross sectional analysis. Bmj. 2019;366:l5221.

In the guidance of the revised Cochrane risk-of-bias tool for randomized trials: [4]

"Nearly all" *should be interpreted as that the number of participants with missing outcome data is sufficiently small that their outcomes, whatever they were, could have made no important difference to the estimated effect of intervention.*

For continuous outcomes, availability of data from ***95%*** *of the participants will often be sufficient. For dichotomous outcomes, the proportion required is directly linked to the risk of the event. If the observed number of events is* ***much greater than*** *the number of participants with missing outcome data, the bias would necessarily be small.*

Most of the endpoints in cancer drug trials were time-to-event endpoints (i.e., dichotomous outcomes). The absence of clarification of "much greater than" makes the assessment more subjective. After scrutinizing other research and the regulatory guidance, we adopted the following criteria as "nearly all":

- For continuous outcomes, over 95% of the participants have available outcomes.
- For dichotomous outcomes,
  - over 95% of the participants have available outcomes, or
  - the observed number of events is 10 times or more than the number of participants with missing outcome data, and
  - the proportion of patients with available outcomes was balanced between the experimental and control groups.

Statistical analysis

In the univariable logistic regression, Firth's penalized likelihood method was applied to correct potential bias from the small number of events.[5] For categorical variables, the most common level was selected as the reference group to reduce instability in estimated odds ratios [ORs]. The meta-epidemiological analysis and reporting adhere to the relevant sections of the guidelines.[6] All modeling analyses were performed in R (version 4.3.3), using the logistf package (version 1.26.0) for Firth's corrected logistic regression and metafor package (4.8.0) for meta-regression.[7]

[4] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. Bmj. 2019;366:l4898.
[5] Firth D. Bias reduction of maximum likelihood estimates. Biometrika. 1993;80(1):27-38.
[6] Murad MH, Wang Z. Guidelines for reporting meta-epidemiological methodology research. Evid Based Med. 2017;22(4):139-42.
[7] Viechtbauer W. Conducting meta-analyses in R with the metafor package. Journal of statistical software. 2010;36:1-48.

eTable 2 | Modeling fitting for multivariable logistic regression on the association with trial features and risk of bias.

Covariates	Model								
	(1)	**(2)**	**(3)**	**(4)**	**(5)**	**(6)**	**(7)**	**(8)**	**(9)**
Agent type									√
Approved country/region								√	√
Approval type							√	√	√
Sequence of Approval						√	√	√	√
Cancer type					√	√	√	√	√
Regimen				√	√	√	√	√	√
Line of therapy		√	√	√	√	√	√	√	√
Trial location		√	√	√	√	√	√	√	√
Primary Endpoint			√	√	√	√	√	√	√
Trial comparator	√	√	√	√	√	√	√	√	√
AIC	**141.9**	**142.1**	**144.04**	**145.02**	**146.7**	**148.7**	**150.2**	**152.1**	**156.9**

Note*: In the univariable logistic regression, trial location, primary endpoint, and trial comparator showed statistically significant association with some concern or high risk of bias.*

Abbreviation: *AIC, Akaike Information Criterion.*

eTable 3 | Sources and availability of relevant information

Data sources	Number (%)
Indication, all	148 (100)
Data source for pivotal trials	
Review Document	143 (96.6)
Label	5 (3.4)
Trials, all	205 (100)
Data source for trial characteristics	
Publication reporting pre-planned results	184 (89.8)
Randomized controlled trials with publication (of all 135 randomized trials)	128 (94.8)
Single-arm or dose-optimization trials with publication (of all 70 samples)	56 (80.0)
clinicaltrials.gov OR chinadrugtrials.org.cn	21 (10.2)
Data source for trial protocol	
Supplement of peer-reviewed publications	56 (27.3)
Available in both publication supplement and clinicaltrials.gov	49 (23.9)
clinicaltrials.gov	31 (15.1)
Not publicly available	68 (33.2)

Note: *by 31 December 2023.*

eTable 4 | Detailed information of 77 sample cancer drugs, corresponding to 148 indications supported by 205 pivotal studies

Cancer drug	FDA/EMA authorized by Dec 2021	Indication	Indication Approval Year	Indication Approval Type	Pivotal Trial	Trial NCT	Trial Type	Efficacy Publication Available
abemaciclib	FDA, EMA	initial endocrine-based therapy, locally advanced or metastatic breast cancer with HR positive, HER2 negative, in combination with an aromatase inhibitor	2020	regular	MONARCH 3	NCT02246621	RCT	yes
					MONARCH plus Cohort A	NCT02763566	RCT	yes
		in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with HR-positive, HER2 negative, node-positive, early breast cancer at high risk of recurrence.	2021	regular	monarchE	NCT03155997	RCT	yes
		initial endocrine-based therapy, locally advanced or metastatic breast cancer with HR positive, HER2 negative, in combination with fulvestrant	2020	regular	MONARCH 2	NCT02107703	RCT	yes
					MONARCH plus Cohort B	NCT02763566	RCT	yes
afatinib	FDA, EMA	first-line treatment of patients with metastatic NSCLC whose tumors have non-resistant EGFR mutations	2017	regular	LUX-Lung1	NCT00656136	RCT	yes
					LUX-Lung2	NCT00525148	SAT	yes
					LUX-Lung3	NCT00949650	RCT	yes
					LUX-Lung5	NCT01085136	RCT	yes
					LUX-Lung6	NCT01121393	RCT	yes
		for the treatment of patients with metastatic, squamous NSCLC progressing after platinum-based chemotherapy	2017	regular	LUX-Lung8	NCT01523587	RCT	yes
alectinib	FDA, EMA	ALK mutation positive locally advanced or metastatic NSCLC	2018	regular	ALEX	NCT02075840	RCT	yes
almonertinib	no	2nd-line, locally advanced or metastatic NSCLC with EGFR T790M mutation positive	2020	conditional	HS-10296-12-01	NCT02981108	SAT	yes
		1st-line advanced or metastatic NSCLC with EGFR mutation (exon 19 deletion or L858R allele)	2021	regular	HS-10296-03-01	NCT03849768	RCT	yes
anlotinib	no	3rd-line advanced or metastatic NSCLC	2018	regular	ALTER0303	NCT02388919	RCT	yes
		2nd-line, acinar soft tissue sarcoma, clear cell sarcoma and other advanced soft tissue sarcoma	2019	regular	ALTER0203	NCT02449343	RCT	no
		3rd-line progressed or relapse SCLC	2019	conditional	ALTER1202	NCT03059797	RCT	yes

Cancer drug	FDA/EMA authorized by Dec 2021	Indication	Indication Approval Year	Indication Approval Type	Pivotal Trial	Trial NCT	Trial Type	Efficacy Publication Available
		for the treatment of unresectable locally advanced or metastatic medullary thyroid cancer patients with clinical symptoms or disease progression	2021	conditional	ALTER01031	NCT02586350	RCT	yes
apalutamide	FDA, EMA	non-metastatic CRPC, with a high risk of metastasis	2019	conditional	SPARTAN	NCT01946204	RCT	yes
		metastatic castration-sensitive prostate cancer	2020	regular	TITAN	NCT02489318	RCT	yes
atezolizumab	FDA, EMA	in combination with pemetrexed and platinum for the first line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations	2020	regular	IMpower133	NCT02763579	RCT	yes
					IMpower133 China Expansion Cohort	NCT02763579	RCT	no
		for the first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained ⩾ 50% of tumor cells [TC ⩾ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ⩾ 10% of the tumor area [IC ⩾ 10%]), as determined by an NMPA approved test, with no EGFR or ALK genomic tumor aberration	2021	conditional	IMpower110	NCT02409342	RCT	yes
		in combination with pemetrexed and platinum for the first line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations	2021	regular	IMpower132	NCT02657434	RCT	yes
					IMpower132 China Cohort	NCT02657434	RCT	yes
		in combination with bevacizumab for the treatment of adult patients with unresectable or metastatic HCC who have not received prior systemic therapy	2020	regular	IMbrave150	NCT03434379	RCT	yes
					IMbrave150 China Expansion Study	NCT03434379	RCT	no
avapritinib	FDA, EMA	for the treatment of adults with unresectable or metastatic GIST harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutation	2021	conditional	NAVIGATOR	NCT02508532	SAT	yes
					CS3007-101	NCT04254939	SAT	yes
axicabtagene ciloleucel	FDA, EMA	for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines	2021	regular	FKC876-2018-001	CTR20181687	SAT	no

Cancer drug	FDA/EMA authorized by Dec 2021	Indication	Indication Approval Year	Indication Approval Type	Pivotal Trial	Trial NCT	Trial Type	Efficacy Publication Available
		of systemic therapy, including diffuse large B-cell lymphoma not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma						
					ZUMA-1	NCT02348216	SAT	yes
azacitidine	FDA, EMA	acute myeloid leukemia (AML) according to the World Health Organization classification	2017	regular	AZA-MDS-002	NCT01599325	SAT	no
		chronic myelomonocytic leukemia	2017	regular	AZA-MDS-002	NCT01599325	SAT	no
bendamustine	FDA	2nd-line, adult CLL/SLL	2018	regular	C18083/3076	NCT01596621	SAT	yes
blinatumomab	FDA, EMA	relapsed or refractory precursor B-cell acute lymphoblastic leukemia	2020	conditional	TOWER	NCT02013167	RCT	yes
					20130316	NCT03476239	SAT	yes
brentuximab vedotin	FDA, EMA	relapsed or refractory systemic anaplastic large-cell lymphoma	2020	regular	SG035-0004	NCT00866047	SAT	yes
					C25010	NCT02939014	SAT	yes
		for the treatment of adult patients with CD30-expressing primary cutaneous anaplastic large cell lymphoma (pcALCL) or mycosis fungoides (MF) who have received prior systemic therap	2021	regular	ALCANZA	NCT01578499	RCT	yes
		relapsed or refractory classical Hodgkin lymphoma	2020	regular	C25007	NCT01990534	SAT	yes
					SG035-0003	NCT00848926	SAT	yes
camrelizumab	no	previously treated advanced HCC	2020	conditional	SHR-1210-II/III-HCC	NCT02989922	DO	yes
		1st-line, unresectable locally advanced or metastatic non-squamous NSCLC with EGFR and ALK mutation negative, in combination with pemetrexed and carboplatin	2020	regular	CameL	NCT03134872	RCT	yes
		2nd-line, locally advanced or metastatic esophageal squamous cell carcinoma	2020	regular	ESCORT	NCT03099382	RCT	yes
		in combination with carboplatin and paclitaxel, as first-line treatment of patients with locally advanced or metastatic squamous NSCLC	2021	regular	CameL-Sq	NCT03668496	RCT	yes
		for the treatment of adults with recurrent unresectable or metastatic nasopharyngeal carcinoma with disease progression on or after two or more prior chemotherapies	2021	conditional	CAPTAIN	NCT03558191	SAT	yes

Cancer drug	FDA/EMA authorized by Dec 2021	Indication	Indication Approval Year	Indication Approval Type	Pivotal Trial	Trial NCT	Trial Type	Efficacy Publication Available
		in combination with cisplatin and gemcitabine, for first-line treatment of adults with metastatic or with recurrent locally advanced nasopharyngeal carcinoma	2021	regular	CAPTAIN-1st	NCT03707509	RCT	yes
		for treatment of: adult patients with relapsed or refractory classical Hodgkin lymphoma, who have received at least two prior systemic chemotherapies	2019	conditional	SHR-1210-II-204	NCT03155425	SAT	yes
		in combination with paclitaxel and cisplatin, for the treatment of patients with locally advanced or metastatic esophageal squamous cell carcinoma that is not amenable to surgical resection	2021	regular	ESCORT-1st	NCT03691090	RCT	yes
carfilzomib	FDA, EMA	for the treatment of adult patients with relapsed or refractory multiple myeloma who have received two lines of therapy in combination with dexamethasone	2021	conditional	20140242	NCT03029234	SAT	yes
ceritinib	FDA, EMA	2nd-line, locally advanced or metastatic NSCLC with ALK mutation positive	2018	regular	ASCEND-5	NCT01828112	RCT	yes
					CLDK378A2109	NCT02040870	SAT	no
					CLDK378A2112	NCT02299505	DO	no
		1st-line, locally advanced or metastatic NSCLC with ALK mutation positive	2020	regular	ASCEND-4	NCT01828099	RCT	yes
dabrafenib	FDA, EMA	unresectable or metastatic melanoma with BRAF V600E or V600K mutations, in combination with trametinib	2019	regular	COMBI-d	NCT01584648	RCT	yes
					COMBI-v	NCT01597908	RCT	yes
					113220 PartC	NCT01072175	SAT	yes
					CDRB436B2205	NCT02083354	SAT	yes
		adjuvant therapy, melanoma with BRAF V600 mutations, in combination with trametinib	2020	regular	COMBI-AD	NCT01682083	RCT	yes
dacomitinib	FDA, EMA	1st-line advanced or metastatic NSCLC with EGFR mutation (exon 19 deletion or L858R allele)	2019	regular	ARCHER1050	NCT01774721	RCT	yes
dalpiciclib	no	For the treatment of patients with HR-positive, HER2-negative, relapsed or metastatic breast cancer who have progressed following prior endocrine therapy, in combination with fulvestrant.	2021	regular	DAWNA-1	NCT03927456	RCT	yes
daratumumab	FDA, EMA	relapsed or refractory multiple myeloma	2019	conditional	GEN501	NCT00574288	SAT	yes
					MMY1003	NCT02852837	SAT	yes

Cancer drug	FDA/EMA authorized by Dec 2021	Indication	Indication Approval Year	Indication Approval Type	Pivotal Trial	Trial NCT	Trial Type	Efficacy Publication Available
					SIRIUS	NCT01985126	DO	yes
		in combination with lenalidomide and dexamethasone, or in combination with bortezomib and dexamethasone, in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy	2021	regular	MMY3003	NCT02076009	RCT	yes
					MMY3004	NCT02136134	RCT	yes
					MMY3009	NCT03234972	RCT	yes
		in combination with lenalidomide and dexamethasone, or in combination with bortezomib, melphalan and prednisone, in newly diagnosed patients who are ineligible for autologous stem cell transplant	2021	regular	MMY3007	NCT02195479	RCT	yes
					MMY3008	NCT02252172	RCT	yes
					OCTANS	NCT03217812	RCT	yes
darolutamide	FDA, EMA	non-metastatic CRPC	2021	regular	ARAMIS	NCT02200614	RCT	yes
degarelix	FDA	for treatment of patients with advanced prostate cancer	2018	regular	FE200486 CS21	NCT00295750	RCT	yes
					000006	NCT01744366	RCT	no
disitamab vedotin	no	for the treatment of patients with HER2-overexpressing locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received at least two prior systemic chemotherapy regimens. HER2 overexpression is defined as immunohistochemistry (IHC) 2+ or 3+.	2021	conditional	RC48-C008	NCT03556345	SAT	yes
		for the treatment of patients with HER2-overexpressing locally advanced or metastatic urothelial carcinoma who have previously received platinum-based chemotherapy. HER2 overexpression is defined as immunohistochemistry (IHC) 2+ or 3+	2021	conditional	RC48-C005	NCT03507166	SAT	yes
					RC48-C009	NCT03809013	SAT	yes
donafenib	no	for the first-line treatment of patients with unresectable HCC	2021	regular	ZGDH3	NCT02645981	RCT	yes
durvalumab	FDA, EMA	maintenance treatment, unresectable stage III NSCLC following platinum-based chemotherapy and radiation therapy	2019	regular	PACIFIC	NCT02125461	RCT	yes

Cancer drug	FDA/EMA authorized by Dec 2021	Indication	Indication Approval Year	Indication Approval Type	Pivotal Trial	Trial NCT	Trial Type	Efficacy Publication Available
		in combination with etoposide and either carboplatin or cisplatin, as first-line treatment of adult patients with extensive-stage small cell lung cancer	2021	regular	CASPIAN	NCT03043872	RCT	yes
ensartinib	no	for the treatment of adult patients with ALK-positive locally advanced or metastatic NSCLC who have progressed after previous treatment with crizotinib or are intolerant to crizotinib	2020	conditional	BTP-42322	NCT03215693	SAT	yes
envafolimab	no	for the treatment of patients with unresectable or metastatic MSI-H or dMMR solid tumors, including: • patients with advanced colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan; • patients with other advanced solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	2021	conditional	KN035-CN-006	NCT03667170	SAT	yes
enzalutamide	FDA, EMA	non-metastatic CRPC with a high risk of metastasis	2020	regular	PROSPER	NCT02003924	RCT	yes
		for the treatment of patients with metastatic castration-resistant prostate cancer, who have no symptoms or mild symptoms after failure of androgen deprivation therapy and have not received chemotherapy	2019	regular	PREVAIL	NCT01212991	RCT	yes
					TERRAIN	NCT01288911	RCT	yes
					AsianPREVAIL	NCT02294461	RCT	yes
					STRIVE	NCT01664923	RCT	yes
eribulin	FDA	3rd-line advanced or metastatic breast cancer after anthracycline and taxane-based chemotherapy	2019	regular	E7389-C086-304	NCT02225470	RCT	yes
					EMBRACE	NCT00388726	RCT	yes
fluazolepali	no	maintenance treatment, platinum-sensitive recurrent epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer	2021	regular	FZOCUS-2	NCT03863860	RCT	yes
		3rd-line, advanced epithelial ovarian, fallopian tube or primary peritoneal cancer with BRCA mutation	2020	conditional	HR-FZPL- | b-OC	NCT03509636	SAT	no
flumatinib	no	Philadelphia chromosome-positive chronic phase chronic myeloid leukemia	2019	regular	FESTnd	NCT02204644	RCT	yes
fruquintinib	no	for the treatment of adult patients with mCRC who have been previously treated with fluoropyrimidine-,	2018	regular	FRESCO	NCT02314819	RCT	yes

Cancer drug	FDA/EMA authorized by Dec 2021	Indication	Indication Approval Year	Indication Approval Type	Pivotal Trial	Trial NCT	Trial Type	Efficacy Publication Available
		oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type and medically appropriate, an anti-EGFR therapy.						
furmonertinib	no	for the treatment of adult patients with metastatic EGFR T790M mutation positive NSCLC, whose disease has progressed on or after EGFR TKI therapy	2021	conditional	20180208	NCT03452592	SAT	yes
gilteritinib	FDA, EMA	for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FLT3 mutation	2021	conditional	ADMIRAL	NCT02421939	RCT	yes
ibrutinib	FDA, EMA	2nd-line, MCL	2017	regular	MCL-3001	NCT01646021	RCT	yes
					PCYC-1104-CA	NCT01236391	SAT	yes
		previously treated Waldenström's macroglobulinemia, or 1st-line treatment of Waldenström's macroglobulinemia unsuitable for chemoimmunotherapy	2018	regular	PCYC-1118E-CA	NCT01614821	SAT	yes
					iNNOVATE	NCT02165397	SAT	yes
		for the treatment of adult patients with CLL/SLL	2017	regular	PCYC-1102-CA	NCT01105247	SAT	yes
					RESONATE	NCT01578707	RCT	yes
					PCI-32765 CLL3002	NCT01973387	RCT	yes
		in combination of rituximab, for the treatment of waldenström's macroglobulinemia	2018	regular	PCYC-1127-CA	NCT02165397	RCT	yes
inetetamab	no	for metastatic breast cancer patients who have received one or more chemotherapy regimens, in combination with vinorelbine	2020	regular	A Phase 3 Study	2004L02352	RCT	yes
inotuzumab ozogamicin	FDA, EMA	for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) in adult a	2021	regular	INO-VATE	NCT01564784	RCT	yes
ipilimumab	FDA, EMA	for the treatment of adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with nivoluma	2021	conditional	CheckMate 743	NCT02899299	RCT	yes
ixazomib	FDA, EMA	2nd-line, multiple myeloma, in combination with lenalidomide and dexamethasone	2018	regular	TOURMALINE-MM1	NCT01564537	RCT	yes
					TOURMALINE-MM1 China Continuation study	NCT01564537	RCT	yes

Cancer drug	FDA/EMA authorized by Dec 2021	Indication	Indication Approval Year	Indication Approval Type	Pivotal Trial	Trial NCT	Trial Type	Efficacy Publication Available
lenvatinib	FDA, EMA	locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer	2020	conditional	SELECT	NCT01321554	RCT	yes
		for the first-line treatment of patients with unresectable HCC	2018	regular	REFLECT	NCT01761266	RCT	yes
neratinib	FDA, EMA	for the extended adjuvant treatment of adult patients with early-stage HER2-positive breast cancer, to follow adjuvant trastuzumab based therapy	2020	regular	ExteNET	NCT00878709	RCT	yes
niraparib	FDA, EMA	maintenance treatment, advanced epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer, after platinum-based chemotherapy	2020	regular	PRIMA	NCT02655016	RCT	yes
		maintenance treatment, platinum-sensitive recurrent epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer	2019	regular	NOVA	NCT01847274	RCT	yes
nivolumab	FDA, EMA	2nd-line, EGFR and ALK mutation negative, locally advanced or metastatic NSCLC, after platinum-based chemotherapy	2018	regular	CheckMate 078 (CA209078)	NCT02613507	RCT	yes
		2nd-line, relapsed or refractory SCCHN expressing PD-L1 tumor proportion score ⩾1, with disease progression after or during platinum-containing regimens	2019	regular	CheckMate 141 (CA209141)	NCT02105636	RCT	yes
		3rd line, advanced or relapsed gastricor or gastroesophageal junction cancer	2020	regular	ONO-4538-12	NCT02267343	RCT	yes
		for the treatment of adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with ipilimumab	2021	conditional	CheckMate 743	NCT02899299	RCT	yes
		for the first-line treatment of adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma, in combination with fluoropyrimidine- and platinum-containing chemotherapy	2021	regular	CheckMate-649	NCT02872116	RCT	yes
obinutuzumab	FDA, EMA	in combination with chemotherapy followed by obinutuzumab monotherapy in patients achieving at least a partial remission, for the treatment of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma	2021	regular	GALLIUM	NCT01332968	RCT	yes
olaparib	FDA, EMA	maintenance treatment, recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in	2018	regular	SOLO2	NCT01874353	RCT	yes

Cancer drug	FDA/EMA authorized by Dec 2021	Indication	Indication Approval Year	Indication Approval Type	Pivotal Trial	Trial NCT	Trial Type	Efficacy Publication Available
		complete or partial response to platinum-based chemotherapy						
					D0810C00019	NCT00753545	RCT	yes
		for the maintenance treatment of adult patients with germline or somatic BRCA-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy	2019	regular	SOLO1	NCT01844986	RCT	yes
		for the treatment of adult patients with BRCA-mutated metastatic castration-resistant prostate cancer (mCRPC).	2021	conditional	PROfound	NCT02987543	RCT	yes
olverembatinib	no	for the treatment of adult patients with chronic-phase or accelerated-phase chronic myeloid leukemia (CML) who are resistant to prior tyrosine kinase inhibitors and have a T315I mutation	2021	conditional	HQP1351CC201	NCT03883087	SAT	yes
					HQP1351CC202	NCT03883100	SAT	yes
orelabrutinib	no	2nd-line, adult CLL/SLL	2020	conditional	ICP-CL-00103	NCT03493217	SAT	no
		2nd-line, adult MCL	2020	conditional	ICP-CL-00102	NCT03494179	SAT	yes
osimertinib	FDA, EMA	1st-line advanced or metastatic NSCLC with EGFR mutation (exon 19 deletion or L858R allele)	2019	regular	FLAURA	NCT02296125	RCT	yes
					FLAURA China	NCT02296125	RCT	yes
		adjuvant therapy after tumor resection in adult patients with stage IB-IIIA NSCLC whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations	2021	regular	ADAURA	NCT02511106	RCT	yes
		for the treatment of adult patients with metastatic EGFR T790M mutation positive NSCLC, whose disease has progressed on or after EGFR TKI therapy	2017	regular	AURA17	NCT02442349	SAT	no
palbociclib	FDA, EMA	initial endocrine-based therapy, locally advanced or metastatic breast cancer with HR positive, HER2 negative, in combination with an aromatase inhibitor	2018	conditional	PALOMA-2	NCT01740427	RCT	yes
pamiparib	no	3rd-line, advanced epithelial ovarian, fallopian tube or primary peritoneal cancer with BRCA mutation	2021	conditional	BGB-290-102	NCT03333915	SAT	yes
pazopanib	FDA, EMA	1st-line or 2nd-line advanced RCC	2017	regular	COMPARZ	NCT00720941	RCT	yes
					VEG113078	NCT01147822	RCT	no

Cancer drug	FDA/EMA authorized by Dec 2021	Indication	Indication Approval Year	Indication Approval Type	Pivotal Trial	Trial NCT	Trial Type	Efficacy Publication Available
pembrolizumab	FDA, EMA	2nd-line, unresectable or metastatic melanoma	2018	conditional	KEYNOTE-151	NCT02821000	SAT	yes
		2nd-line, locally advanced or metastatic ESCC expressing PD-L1 CPS ⩾1	2020	regular	KEYNOTE-181	NCT02564263	RCT	yes
		in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations	2019	conditional	KEYNOTE-189	NCT02578680	RCT	yes
		as a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ⩾1%] as determined by an NMPA-approved test, with no EGFR or ALK genomic tumor aberrations	2019	regular	KEYNOTE-042	NCT02220894	RCT	yes
					KEYNOTE-042 China Study	NCT03850444	RCT	yes
		in combination with carboplatin and paclitaxel, as first-line treatment of patients with metastatic squamous NSCLC	2019	regular	KEYNOTE-407	NCT02775435	RCT	yes
					KEYNOTE-407 China extension study	NCT03875092	RCT	yes
		as a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ⩾1]	2020	conditional	KEYNOTE-048	NCT02358031	RCT	yes
		in combination with platinum- and fluoropyrimidine-based chemotherapy, for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction carcinoma that is not amenable to surgical resection	2021	regular	KEYNOTE-590	NCT03189719	RCT	yes
		for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer, with KRAS, NRAS, and BRAF genes are all wild-type	2021	conditional	KEYNOTE-177	NCT02563002	RCT	yes
penpulimab	no	for treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma, who have received at least two or more lines of systemic chemotherapy	2021	conditional	AK105-201	NCT03722147	SAT	no
pertuzumab	FDA, EMA	metastatic or unresectable locally relapsed HER2-positive breast cancer, in combination with trastuzumab and docetaxel	2019	regular	CLEOPATRA	NCT00567190	RCT	yes

Cancer drug	FDA/EMA authorized by Dec 2021	Indication	Indication Approval Year	Indication Approval Type	Pivotal Trial	Trial NCT	Trial Type	Efficacy Publication Available
					PUFFIN	NCT02896855	RCT	yes
		adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence, in combination with trastuzumab and chemotherapy	2018	regular	APHINITY	NCT01358877	RCT	yes
		neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer, in combination with trastuzumab and chemotherapy	2019	regular	PEONY	NCT02586025	RCT	yes
					NEOSPHERE	NCT00545688	RCT	yes
pralatrexate	FDA	relapsed or refractory PTCL	2020	conditional	FOT12-CN-301	NCT03349333	SAT	yes
					PDX-008	NCT00364923	SAT	no
pralsetinib	FDA, EMA	adult patients with metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer	2021	conditional	ARROW	NCT03037385	SAT	yes
pyrotinib	no	2nd line relapsed or metastatic HER2 positive breast cancer after anthracycline and taxane-based chemotherapy, in combination with capecitabine	2018	conditional	HR-BLTN-I/II-MBC	NCT02422199	RCT	no
radium[223ra]	FDA	mCRPC with symptomatic bone metastasis and no visceral metastasis	2020	regular	ALSYMPCA	NCT00699751	RCT	yes
					15397	NCT01810770	SAT	no
regorafenib	FDA, EMA	for the treatment of patients with HCC who have been previously treated with sorafenib	2017	regular	RESORCE	NCT01774344	RCT	yes
		for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti VEGF therapy, and, if RAS wild-type, an anti-EGFR therapy	2017	conditional	CONCUR	NCT01584830	RCT	yes
					CORRECT	NCT01103323	RCT	yes
		for the treatment of locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib	2017	conditional	GRID	NCT01271712	RCT	yes
relmacabtagene autoleucel	no	for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines	2021	conditional	JWCAR029-002	NCT04089215	SAT	yes

Cancer drug	FDA/EMA authorized by Dec 2021	Indication	Indication Approval Year	Indication Approval Type	Pivotal Trial	Trial NCT	Trial Type	Efficacy Publication Available
		of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma						
ripretinib	FDA, EMA	for the treatment of adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with 3 or more kinase inhibitors, including imatinib	2021	conditional	INVICTUS	NCT03353753	RCT	yes
savolitinib	no	for the treatment of adult patients with metastatic NSCLC whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping, who experience disease progression or intolerance to platinum chemotherapy	2021	conditional	2016-504-00CH1	NCT02897479	SAT	yes
selinexor	FDA, EMA	in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma whose disease is refractory to at least one proteasome inhibitors, at least one immunomodulatory agents, and an anti-CD38 monoclonal antibody	2021	conditional	MARCH	NCT02227251	SAT	yes
					STORM	NCT02336815	SAT	yes
sintilimab	no	3rd-line, relapsed or refractory classical Hodgkin lymphoma	2018	conditional	ORIENT-1	NCT03114683	SAT	yes
		in combination with bevacizumab for the treatment of adult patients with unresectable or metastatic HCC who have not received prior systemic therapy	2021	regular	ORIENT-32	NCT03794440	RCT	yes
		in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with unresectable locally advanced or metastatic nonsquamous NSCLC, with EGFR or ALK mutation-negative	2021	regular	ORIENT-11	NCT03607539	RCT	yes
		in combination with gemcitabine and platinum chemotherapy, as first-line treatment of patients with unresectable locally advanced or metastatic squamous NSCLC	2021	regular	ORIENT-12	NCT03629925	RCT	yes
sonidegib	FDA, EMA	for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy	2021	regular	BOLT	NCT01327053	DO	yes

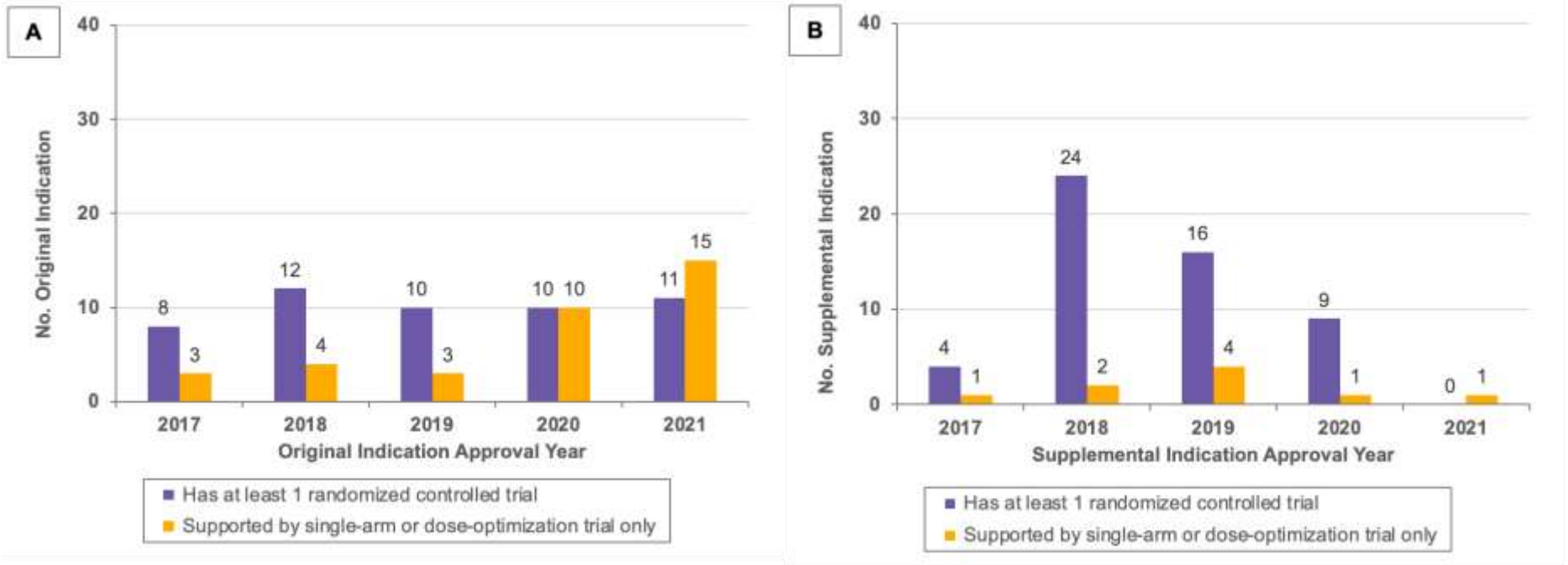
Cancer drug	FDA/EMA authorized by Dec 2021	Indication	Indication Approval Year	Indication Approval Type	Pivotal Trial	Trial NCT	Trial Type	Efficacy Publication Available
					CLDE225X2101	NCT00880308	SAT	no
sugemalimab	no	in combination with pemetrexed and carboplatin, as first-line treatment of patients with metastatic nonsquamous NSCLC with EGFR/ALK mutation negative	2021	regular	GEMSTONE-302	NCT03789604	RCT	yes
		in combination with paclitaxel and carboplatin, as first-line treatment of patients with metastatic squamous NSCLC	2021	regular	GEMSTONE-302	NCT03789604	RCT	yes
surufatinib	no	unresectable, locally advanced or metastatic, well differentiated, non-functioning grade 1 or 2 extrapancreatic neuroendocrine tumours	2020	regular	SANET-ep	NCT02588170	RCT	yes
		unresectable, locally advanced or metastatic, well differentiated, grade 1 or 2 pancreatic neuroendocrine tumours	2021	regular	SANET-p	NCT02589821	RCT	yes
tislelizumab	no	for treatment of: adult patients with relapsed or refractory classical Hodgkin lymphoma, who have received at least two prior systemic chemotherapy	2019	conditional	BGB-A317-203	NCT03209973	SAT	yes
		for the treatment of locally advanced or metastatic PD-L1 positive urothelial carcinoma that has failed platinum-based chemotherapy, including neoadjuvant or adjuvant chemotherapy, and has progressed within 12 months	2020	conditional	BGB-A317-204	NCT04004221	SAT	yes
		in combination with paclitaxel and carboplatin or nab-paclitaxel and carboplatin, as first-line treatment of patients with unresectable locally advanced or metastatic squamous NSCLC	2021	regular	BGB-A317-307	NCT03594747	RCT	yes
		in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with unresectable locally advanced or metastatic nonsquamous NSCLC, with EGFR or ALK mutation-negative	2021	regular	BGB-A317-304	NCT03663205	RCT	yes
		for the treatment of patients with HCC who have been previously treated with at least one prior therapy	2021	conditional	BGB-A317-208	NCT03419897	SAT	no
		for the treatment of adult patients with unresectable locally advanced or metastatic nonsquamous NSCLC who have are EGFR/ALK negative and whose disease has progressed on or who are intolerant to prior platinum-based chemotherapy, as well as adult patients with squamous NSCLC who are EGFR/ALK negative or of unknown	2021	regular	BGB-A317-303	NCT03358875	RCT	yes

Cancer drug	FDA/EMA authorized by Dec 2021	Indication	Indication Approval Year	Indication Approval Type	Pivotal Trial	Trial NCT	Trial Type	Efficacy Publication Available
		status, and have progressed on or are intolerant to prior platinum-based chemotherapy						
toripalimab	no	previously treated advanced melanoma	2018	conditional	POLARIS	NCT03013101	SAT	yes
		in combination with cisplatin and gemcitabine, for first-line treatment of adults with metastatic or with recurrent locally advanced nasopharyngeal carcinoma	2021	regular	JS001-015-III-NPC	NCT03581786	RCT	yes
		for the treatment of adults with recurrent unresectable or metastatic nasopharyngeal carcinoma with disease progression on or after two prior or more therapies	2021	conditional	JS001-Ib-CRP-1.0	NCT02915432	SAT	yes
		for the treatment of locally advanced or metastatic urothelial carcinoma that has failed platinum-based chemotherapy, including neoadjuvant or adjuvant chemotherapy, and has progressed within 12 months	2021	conditional	POLARIS-03	NCT03113266	SAT	yes
trametinib	FDA	adjuvant therapy, melanoma with BRAF V600 mutations, in combination with trametinib	2020	regular	COMBI-AD	NCT01682083	RCT	yes
		unresectable or metastatic melanoma with BRAF V600E or V600K mutations, in combination with dabrafenib	2019	regular	COMBI-d	NCT01584648	RCT	yes
					COMBI-v	NCT01597908	RCT	yes
					DRB436B2205	CTR20150733	SAT	no
					113220 PartC	NCT01072175	SAT	yes
trastuzumab emtansine	FDA, EMA	adjuvant therapy, residual invasive HER2-positive early breast cancer, after taxanes plus trastuzumab based neoadjuvant therapy	2020	regular	KATHERINE	NCT01772472	RCT	yes
		For the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane. Patients should have either: • received prior therapy for metastatic disease, or • developed disease recurrence during or within six months of completing adjuvant therapy	2021	regular	EMILIA	NCT00829166	RCT	yes
					BO29919	NCT03084939	RCT	no
trifluridine and tipiracil	FDA	3rd line, mCRC	2019	regular	RECOURSE	NCT01607957	RCT	yes
					TERRA	NCT01955837	RCT	yes

Cancer drug	FDA/EMA authorized by Dec 2021	Indication	Indication Approval Year	Indication Approval Type	Pivotal Trial	Trial NCT	Trial Type	Efficacy Publication Available
utidelone	no	2nd-line relapsed or metastatic breast cancer after anthracycline and taxane-based chemotherapy, in combination with capecitabine	2021	regular	BG01-1323L	NCT02253459	RCT	yes
vemurafenib	FDA, EMA	unresectable or metastatic melanoma with BRAF V600 mutations	2017	regular	NP22657	NCT00949702	SAT	yes
					YO28390	NCT01910181	SAT	yes
					BRIM-3	NCT01006980	RCT	yes
venetoclax	FDA, EMA	in combination with azacitidine	2020	conditional	M14-358	NCT02203773	SAT	yes
					M15-656	NCT02993523	RCT	yes
zanubrutinib	FDA, EMA	2nd-line, adult CLL/SLL	2020	regular	BGB-3111-205	NCT03206918	SAT	yes
		2nd-line, adult MCL	2020	regular	BGB-3111-206	NCT03206970	SAT	yes
		for the treatment of adult patients with waldenström's macroglobulinemia who have received treatment	2021	conditional	BGB-3111-210	NCT03332173	SAT	yes
zimberelimab	no	for treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma, who have received at least two or more lines of systemic chemotherapy	2021	conditional	YH-S001-04	NCT03655483	SAT	yes

Abbreviations: *ALK, anaplastic lymphoma kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CRPC, castration-resistant prostate cancer; EGFR, epidermal growth factor receptor; EMA, European Medicine Agency; FDA, the US Food and Drug Administration; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; HR, hormone receptor ; MCL, mantle cell lymphoma; mCRC, metastatic colorectal cancer; NMPA, National Medical Products Administration; NSCLC, non-small cell lung cancer; RCT, randomized controlled trial; SAT, single-arm trial; SCLC, small-cell lung cancer.*

eFigure 1 | Number of pivotal efficacy trials supporting original and supplemental cancer drug indication approvals by National Medical Products Administration, 2017-2021



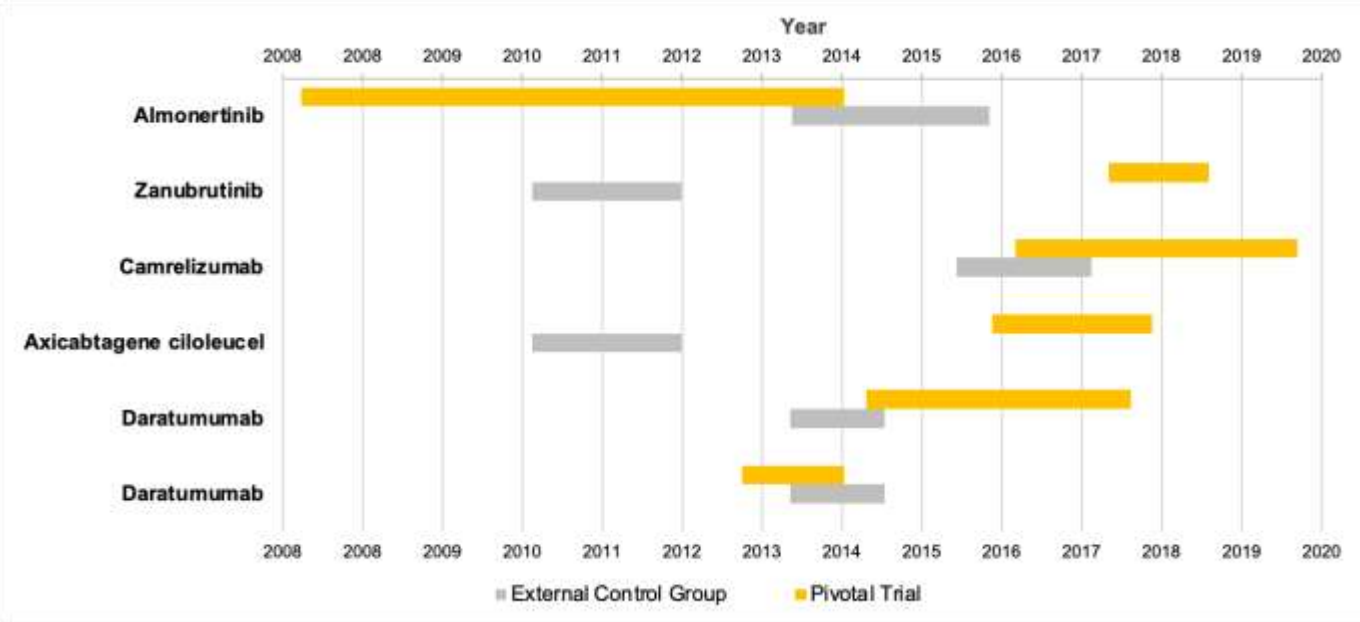
eTable 5 | Univariate analysis for identifying potential factors with risk of bias

Variable	Trial, No (%)		Odds Ratio (95%CI) [a]
	Low risk of bias	Some concern or high risk of bias	
Agent type			
Target therapy	17 (21.3)	63 (78.8)	Reference
Immunotherapy	11 (32.4)	23 (67.6)	0.386 (0.069 to 2.472)
Chemotherapy	2 (40)	3 (60)	0.512 (0.130 to 2.333)
Hormone therapy	3 (33.3)	6 (66.7)	0.563 (0.234 to 1.381)
Approved country/region			
Authorized by the FDA/EMA by Dec 2021	23 (22.8)	78 (77.2)	Reference
China-only	10 (37.0)	17 (63.0)	0.465 (0.190 to 1.165)
Approval type			
Regular	30 (27.5)	79 (72.5)	Reference
Conditional	3 (15.8)	16 (84.2)	1.809 (0.584 to 7.282)
Sequence of Approval			
Original	16 (24.2)	50 (75.8)	Reference
Supplemental	17 (27.4)	45 (72.6)	0.886 (0.402 to 1.942)
Cancer type			
Solid tumor	29 (26.6)	80 (73.4)	Reference
Hematological malignancy	4 (21.1)	15 (78.9)	1.262 (0.434 to 4.378)
Regimen			
Single agent	15 (20.8)	57 (79.2)	Reference
Combination therapy	18 (32.1)	38 (67.9)	0.561 (0.252 to 1.232)
Primary Endpoint			
Surrogate endpoint	23 (28.8)	57 (71.3)	Reference
Overall survival	10 (20.8)	38 (79.2)	1.582 (0.689 to 3.865)
Line of therapy			
First-line	17 (23.9)	54 (76.1)	Reference
Later-line	11 (26.8)	30 (73.2)	0.852 (0.360 to 2.062)
Neoadjuvant or Adjuvant	1 (11.1)	8 (88.9)	1.820 (0.368 to 17.942)
Maintenance	4 (57.1)	3 (42.9)	0.250 (0.051 to 1.124)
Trial location			
International multicenter	18 (20.5)	70 (79.5)	Reference
Regional multicenter	15 (37.5)	25 (62.5)	0.384 (0.169 to 0.864)
Trial comparator			
Placebo/add-on	27 (35.5)	49 (64.5)	Reference
Chemotherapy	4 (14.8)	23 (85.2)	3.866 (1.274 to 15.441)
Target therapy	1 (5.3)	18 (94.7)	7.101 (1.652 to 66.506)
Hormone therapy	1 (25.0)	3 (75.0)	1.343 (0.209 to 14.362)
Other	0	2 (100)	2.879 (0.224 to 402.515)

Note:

[a.] *Univariable logistic regression with firth's correction, using logistf package in in R (version 4.3.3).*

eFigure 2 | Time of pivotal single-arm trial and external control group supporting cancer indication approval in China.



Note: *The two pivotal trials for daratumumab supporting the approval of the same indication used the same external control group.*

eTable 6 | Multivariate meta-regression results

Variable	Trial, No (%)	Pooled HR (95%CI)	Ratio of Hazard Ratio (95%CI)	P-value
Risk of bias arising from the randomization process				
Low	116 (95.1)	0.54 (0.51 to 0.58)	Reference	
Some concern or high	6 (4.9)	0.38 (0.29 to 0.51)	0.678 (0.532 to 0.864)	0.0017
Risk of bias due to deviations from the intended interventions				
Low	65 (53.3)	0.52 (0.48 to 0.57)	Reference	
Some concern or high	57 (46.7)	0.55 (0.50 to 0.60)	1.045 (0.939 to 1.164)	0.4196
Risk of bias due to missing outcome data				
Low	78 (63.9)	0.51 (0.47 to 0.56)	Reference	
Some concern or high	44 (36.1)	0.57 (0.52 to 0.62)	1.114 (1.004 to 1.237)	0.0426
Risk of bias in measurement of the outcome				
Low	115 (94.3)	0.54 (0.50 to 0.57)	Reference	
Some concern or high	7 (5.7)	0.48 (0.35 to 0.66)	1.036 (0.809 to 1.327)	0.7769
Primary Endpoint				
Overall Survival	45 (36.9)	0.70 (0.67 to 0.73)	Reference	
PFS	66 (54.1)	0.46 (0.42 to 0.50)	0.785 (0.688 to 0.894)	0.0003
MFS	3 (2.5)	0.32 (0.25 to 0.41)	0.446 (0.329 to 0.606)	<.0001
DFS/iDFS	5 (4.1)	0.53 (0.35 to 0.79)	0.713 (0.531 to 0.957)	0.0245
RFS	2 (1.6)	0.47 (0.41 to 0.54)	0.648 (0.465 to 0.902)	0.0102
Time to prostate-specific antigen progression	1 (0.8)	0.38 (0.27 to 0.53)	0.586 (0.346 to 0.992)	0.0464
Line of Therapy				
First line	68 (55.7)	0.57 (0.53 to 0.62)	Reference	
Later line	40 (32.8)	0.49 (0.44 to 0.56)	0.901 (0.796 to 1.020)	0.0999
Maintenance	7 (5.7)	0.44 (0.35 to 0.56)	1.381 (1.035 to 1.841)	0.0281
Adjuvant or neoadjuvant therapy	7 (5.7)	0.51 (0.39 to 0.68)	NA	
Trial location				
International multicenter	83 (68)	0.55 (0.51 to 0.59)	Reference	
Regional multicenter	39 (32)	0.49 (0.44 to 0.55)	0.940 (0.842 to 1.049)	0.2706
Trial comparator				
Placebo/add-on	75 (61.5)	0.51 (0.47 to 0.55)	Reference	
Chemotherapy	25 (20.5)	0.62 (0.56 to 0.68)	1.060 (0.919 to 1.223)	0.4254
Target therapy	17 (13.9)	0.58 (0.49 to 0.70)	0.952 (0.809 to 1.121)	0.5552
Hormone therapy	3 (2.5)	0.33 (0.23 to 0.47)	0.663 (0.459 to 0.957)	0.0283
Other	2 (1.6)	0.55 (0.34 to 0.88)	1.235 (0.845 to 1.807)	0.2759
Cancer site				
Lung	37 (30.3)	0.55 (0.50 to 0.62)	Reference	

Variable	Trial, No (%)	Pooled HR (95%CI)	Ratio of Hazard Ratio (95%CI)	P-value
Prostate	10 (8.2)	0.42 (0.32 to 0.54)	1.090 (0.849 to 1.399)	0.5001
Liver	5 (4.1)	0.71 (0.58 to 0.87)	1.209 (0.958 to 1.524)	0.1096
Breast	17 (13.9)	0.58 (0.51 to 0.66)	1.168 (1.009 to 1.352)	0.0371
Thyroid	2 (1.6)	0.33 (0.13 to 0.81)	0.690 (0.450 to 1.058)	0.089
Ovary	6 (4.9)	0.37 (0.27 to 0.49)	0.545 (0.401 to 0.741)	0.0001
Melanoma	8 (6.6)	0.58 (0.49 to 0.69)	1.033 (0.835 to 1.278)	0.7637
Multiple myeloma	7 (5.7)	0.48 (0.38 to 0.61)	1.140 (0.906 to 1.433)	0.2648
Colon and rectum	6 (4.9)	0.69 (0.63 to 0.76)	1.225 (0.999 to 1.502)	0.0513
Esophagus	4 (3.3)	0.69 (0.62 to 0.77)	1.131 (0.902 to 1.418)	0.2869
Nasopharynx	2 (1.6)	0.53 (0.42 to 0.68)	1.078 (0.760 to 1.529)	0.6738
Stomach	1 (0.8)	0.63 (0.51 to 0.78)	1.059 (0.697 to 1.609)	0.7897
Pleural mesothelioma	2 (1.6)	0.74 (0.64 to 0.86)	1.059 (0.781 to 1.437)	0.7119
Stomach/Esophagus	1 (0.8)	0.71 (0.59 to 0.86)	0.954 (0.635 to 1.431)	0.8188
Kidney	1 (0.8)	1.05 (0.90 to 1.22)	2.133 (1.454 to 3.130)	0.0001
GIST	2 (1.6)	0.21 (0.12 to 0.37)	0.469 (0.309 to 0.712)	0.0004
Lymphoma	4 (3.3)	0.34 (0.19 to 0.59)	0.645 (0.471 to 0.885)	0.0065
Waldenström macroglobulinemia	1 (0.8)	0.20 (0.11 to 0.37)	0.363 (0.179 to 0.738)	0.0051
Leukemia	4 (3.3)	0.69 (0.60 to 0.79)	1.012 (0.796 to 1.288)	0.9197
Neuroendocrine tumor	2 (1.6)	0.40 (0.27 to 0.59)	0.859 (0.583 to 1.266)	0.4423

Abbreviation: *CI, confidence interval; GIST, gastrointestinal stromal tumor; HR, hazard ratio; RoB, risks of bias; RHR, ratio of hazard ratio.*

eTable 7 | Detailed justifications for risk of bias judgments for randomized controlled trials

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	**Reference (PMID)**	**Outcome**	**1.0 Assessor's Judgement**	**1.0 General note**	**2.0 Assessor's Judgement**	**2.0 General Notes**	**3.0 Assessor's judgement**	**3.0 Gerenal notes**	**4.0 Assessor's Judgement**	**4.0 General note**	**5.0 Assessor's Judgement**	**5.0 General note**	**Assessor's overall Judgement**
NCT00656136	22452896	OS	Low	Publication: The randomisation sequence was generated by an in-dependent team from the trial sponsor with a validated computer system (clinical trial supply system). This team was not involved in the rest of the trial. The randomisation sequence was then implemented centrally via an inter- active voice response system. Publication: Baseline characteristics were much the same between the two groups (table 1).	Low	Publication: LUX-Lung 1 was a randomised, double-blind, multicentre, phase 2b/3 trial. Although drug-related serious adverse events occurred in 39 (10%) patients in the afatinib group and one (<1%) patient in the placebo group, these were not considered to be substantial enough to break blinding of participants and personnel. Publication: The primary endpoint was overall survival (from date of randomisation to death), analysed on an intention-to-treat basis.	Low	Figure 1: Of the 390 assigned to afatinib plus best supportive care, 8 withdrew consent, 5 lost of follow-up. Of the 195 assigned to placebo plus best supportive care, 7 withdrew consent, 3 lost of follow-up. The proportion of patient with missing outcome data is 3.9%.	Low	Publication: Tumour assessments were done by CT or MRI scans of patients' chest to pelvis at screening, at weeks 4, 8, and 12, and at 8-week intervals thereafter. Although both methods were available, almost all tumour assessments were with CT scans of the chest and abdomen. Brain imaging or bone scans were done as needed. Independent review (BioClinica, Newtown, PA, USA) consisted of two primary radiologist reviewers and a third for adjudication. Final review was by an oncologist and the adjudicator, with integration of radiological assessment with clinical information.	Some concerns	The protocol is not available. Study protocol was not available to answer this question fully.	Some concerns
NCT00949650	23816960	PFS	Low	Protocol: Randomisation will be performed by IVRS/IWRS. Boehringer Ingelheim Pharma GmbH & Co. KG, Clinical Trial Support Group or a CRO appointed by the Sponsor will provide the randomisation lists using a validated randomisation number generating system. Access to the randomisation codes will be controlled and documented	Some concerns	Publication: LUX-Lung 3 was a global, randomized, open-label phase III study There is not enough information to answer this question. Publication: All efficacy analyses were performed in an intent-to-treat manner and included all randomly assigned patients.	Low		Low	Publication: Tumor assessments were performed by computed tomography or magnetic resonance imaging every 6 weeks for the first 48 weeks and then every 12 weeks thereafter until disease progression or start of new anticancer therapy. Scans were reviewed by an independent central imaging group incorporating both radiologist and oncologist reviewers blinded to treatment assignments. same as above	Low	Publication: PFS analysis in patients with common EGFR mutations (L858R and exon 19 deletions) was prespecified. Protocol: The primary analysis of PFS will be conducted when at least 217 patients have progressed or died. The PFS event in the publication was 319. Analyses specified in the statistical	Some concerns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				Publication: Treatment arms were balanced in terms of patient demographics and clinical characteristics						Scans were reviewed by an independent central imaging group incorporating both radiologist and oncologist reviewers blinded to treatment assignments.		analysis plan appear consistent with those reported in the results section in the publication.	
NCT010 85136	266467 59	PFS	High	The only information about randomization methods is a statement that the study is randomized. In the afatinib plus paclitaxel group, the proportions of patient with ECOG 0 and 1 were 35.1% and 57.5%, respectively. While in the chemotherapy group, these proportion were 20.6% and 67.6%. Patient performance status seems inferior in the control group.	Some concer ns	It was not clarified whether this trial was blinded or open-label. As afatinib was oral and the chemotherapy in the control group was injection, it is reasonable to speculate this is an open-label trial. There is no enough information to answer this question. According to the Figure 1 in the article, the primary endpoint might be analysed on an intention-to-treat basis.	High	Supplementary Figure S1: in the afatinib + paclitaxel group, 9.1% and 5.3 of patients with refusal or other reason, respectively. In the control group, these numbers were 11.7% and 5.0%. In total, 23.8% of patients did not have outcome data. No methodology approach or sensitivity analyses was used to correct for bias. There is no enough information for this question.	Low	Publication: In support, recent studies in- dicate that local site evaluation has a high correlation to blinded independent central review and does not bias trial outcomes. Publication: Tumor assessments were carried out by computed tomography or magnetic resonance imaging of less than or equal to five target lesions at baseline and every 8 weeks thereafter. Response was evaluated by the investigator. It is reasonable to assume this is an open-label trial. Publication: Tumor assessments were carried out by computed tomography or magnetic resonance imaging of less than or equal to five target lesions at baseline and every 8 weeks thereafter.	Some concer ns	Publication: the calculated number of 351 eligible patients (279 PFS events) was considered unachievable, and the protocol was amended following discussion with the DMC on 18 January 2013. The planned time points for the primary analysis of PFS and OS were amended to be under- taken once the final randomized patients had the chance to be followed for at least 6 months. The protocol is not available.	High
NCT011 21393	244399 29	PFS	Low	Publication: A block size of three was used and randomisation was done centrally with a validated random number-generating system at Boehringer Ingelheim, verified by a trial-independent statistician, and	Some concer ns	Publication: Clinicians and patients were not masked to treatment assignment. The study investigators who did assessments of patient-reported outcomes and safety, along with supportive assessments of tumour response (used for sensitivity	Low	Figure 1: of the 242 patients assigned to afatinib, 1 lost to follow-up. Of the 122 assigned to gemcitabine and cisplatin, 3 not compliant with protocol. According to the Protocol: "A patient will be	Low		Low	Protocol: The primary analysis of PFS will be conducted when at least 217 patients have progressed or died.Publication: Data cutoff date for the primary analysis was Oct 29, 2012. The primary	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				implemented centrally via an interactive internet and voice-response system. Access to the randomisation code was supervised by the clinical trial support group; those directly involved in the conduct and analysis of the trial had no access to the randomisation schedule.Publication: Baseline demographics and patient characteristics were generally balanced between treatment groups (table 1), with the exception of performance score: a higher proportion of patients had a score of 0 in the gemcitabine and cisplatin group than in the afatinib group (table 1). EGFR mutations were mainly exon 19 deletions and Leu858Arg mutations (table 1); uncommon mutation types were not balanced between treatment groups (appendix).		analyses), were not masked to treatment assignment.No information was available to answer this question.Publication: The primary endpoint was progression-free survival assessed by independent central review (intention-to-treat population).		withdrawn from further study treatment in the following circumstances: Significant deviation from the protocol or eligibility criteria". The overll proportion of missing outcome data is 1.1%.				analysis was done after 221 progression events had occurred as assessed by independent review.Protocol: The primary endpoint of this study is progression-free survival, defined as the time from the date of randomisation to the date of disease progression, or to the date of death if a patient died earlier.Outcome measurements reported in the article appeared consistent with those specified in the protocol and SAP.	
NCT01523587	26156651	PFS	Low	Publication: Randomisation was done with a validated random number generating system at Boehringer Ingelheim, verified by a trial-independent statistician, and	Some concer ns	Publication: Clinicians and patients were not masked to treatmentassignment. In Figure 1, 32 (of 398) and 22 (of 397) patients in the intervention and comparison group refused to continue	Low	Figure 1: Of the 398 assigned to afatinib, 6 did not receive treatment, 28 refused to continue treatment with study drug, 4 non-compliance with protocol, 2 lost to follow-up, 3 for other	Low		Low	Publication: As planned, the primary analysis of progression-free survival was done when the requisite number of events judged by central independent review	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				implemented centrally via an interactive voice or web-based response system.individuals directly involved in the conduct and analysis of the trials did not have access to the randomisation schedule. Publication: Baseline characteristics were generally well balanced (table 1).		treatment, or not comply to the protocol. However, the reason for protocol deviation was not reported. Publication: The primary endpoint was progression-free survival assessed by independent central review (intention-to-treat population).		reasons. Of the 397 assigned to erlotinib , 2 did not receive treatment, 19 refused to continue treatment with study drug, 3 non-compliance with protocol, 2 lost to follow-up, 5 for other reasons. The total proportion of missing outcome data was 9.3%.				was reached (Oct 7, 2013). Publication: The primary endpoint was progression-free survival assessed by independent central review.	
NCT020 75840	285862 79	PFS	Low	Publication: Patients were randomly assigned (in a 1:1 ratio by means of a block-stratified randomization procedure with the use of an interactive or Web- based response system). Protocol: Central randomization will be performed via an interactive voice or web-based response system (IxRS). Publication: Baseline characteristics were well balanced between the two treatment groups, including the presence of CNS metastases (42% in the alectinib group and 38% in the crizotinib group) (Table 1).	Some concer ns	Publication: The BO28984 (ALEX) trial was an interna- tional, randomized, open-label, phase 3 trial. Publication: Efficacy end points were evaluated in the inten- tion-to-treat population, comprising all randomly assigned patients.	High	Publication: of the 152 patients assigned to receive alectinib, 17 were lost to follow-up or declined to participate. Of 151 patients assigned to receive crizotinib, 27 were lost to follow-up or declined to participate and 2 were withdrawn by physician. In total, 15.2% patients did not have available outcomes. Analysis methods that correct for bias and sensitivity analysis were not adopted. Figure 1: The proprotion of patient with missing outcome data is imbalance between the intervention (11.2%) and control groups (19.2%).	Low	Publication: Tumor re- sponse was assessed with the use of RECIST, version 1.1. Two assessments by the independent review committee (according to RECIST, version 1.1) were performed, one for overall systemic disease and one solely for the evaluation of CNS end points. Publication: All the patients underwent tumor imaging at baseline, including scans of the brain. Subsequent tumor evaluation, including systematic brain imaging in all patients, was performed every 8 weeks until disease progression. Tumor response was assessed with the use of RECIST, version 1.1. Publication: The primary end point was investigator-assessed progression-free survival. Publication: Tumor response was assessed with the use of RECIST, version 1.1.	Low	Protocol: A total of 170 PFS events are required to achieve 80% power at a two-sided alpha level of 5%. Publication: At the date of primary data cutoff (February 9, 2017), an event of disease progression or death had occurred in 164 patients in the intention-to-treat. Outcome measurements specified in the protocol appear consistent with those reported in the published article. Analyses specified in the statistical analysis plan appear consistent with those reported in the results section in the paper.	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
NCT038 49768	355802 97	PFS	Low	Protocol: Randomization numbers and study drug numbers will be obtained via the IWRS. The blinded control of the drug uses a double dummy technique. The packaging, mode of administration, labeling, appearance, taste and odor of HS-10296 tablets and HS-10296 placebo tablets (and gefitinib tablets and gefitinib placebo tablets) will be exactly the same to conceal the true information of the treatment drug.Publication: emographic and baseline characteristics were well-balanced between the groups (Table 1).	Some concer ns	Publication: AENEAS was a multicenter, double-blind, randomized phase III trial. Adverse events of grade ≥ 3 severity (any cause) were observed in 36.4% and 35.8% of patients in the aumolertinib and gefitinib groups, respectively. Publication: Primary efficacy analysis was performed on the full analysis set, including all randomly assigned patients who received the study drug at least once.Publication: The medication compliance was 99.3% and 98.5% for patients receiving aumolertinib and gefitinib, respectively.	Low	Publication: A total of 105 patients in the aumolertinib group (data maturity of 49.1%) and 158 patients in the gefitinib group (data maturity of 73.5%) had experienced an event of RECIST-defined progression or death. A total of 93 patients (43.5%) in the aumolertinib group and 34 patients (15.8%) in the gefitinib group had continued to receive study drug treatment as of the data cutoff date. 11.1% of patients did not have available outcome data.	Some concer ns	Publication: Systemic response was assessed by the investigators and by blinded independent central review and was classified according to RECIST 1.1. Computed tomog- raphy imaging was performed at baseline and every 6 weeks (67 days) from the start of aumolertinib until the 15-month time point, after which imaging was performed at 12-week intervals. Prestudy CNS imaging was mandatory.Publication: The primary end point was progression-free survival (PFS), as determined by investigator assessment.Assessment of the outcome was likely to be influenced by knowledge of intervention received due to the potentially subjective nature of progression- free survival which incorporates radiological progression.	Low	Protocol: with a power of 90% to detect the statistical differences between the two groups based on 262 events, approximately 410 patients need to be enrolled.Publication: A total of 105 patients in the aumolertinib group (data maturity of 49.1%) and 158 patients in the gefitinib group (data maturity of 73.5%) had experienced an event of RECIST-defined progression or death.Protocol: Efficacy endpoints will be analyzed using the results assessed by the Investigator per RECIST 1.1. Protocol: The results of the central review will be used for sensitivity analysis.	Some concer ns
NCT019 46204	294201 64	MFS	Low	Protocol: After patients have provided their written informed consent, completed all Screening assessments and received confirmation of eligibility, they will be randomized into the study using an Interactive Voice Randomization System (IVRS). Publication:	Some concer ns	Publication: We conducted a double-blind, placebo-controlled, phase 3 trial. The following adverse events occurred at a higher rate with apalutamide than with placebo: rash (23.8% vs. 5.5%). We assumed that such differences could potentially break the blinding of the trial, and resulting in	High	Publication: The final analysis for metastasis-free survival was performed after distant metastasis or death had been observed in 378 patients (1207 men underwent randomization, 806 to the apalutamide group and 401 to the placebo group). A	Low	Publication: Disease assessments, including technetium-99m bone scans and CT of the pelvis, abdomen, and chest, were performed every 16 weeks and at additional time points if distant metastasis was suspected. Evidence of distant metastasis on imaging was determined on the basis of Response Evaluation Criteria in Solid Tumors, version 1.1.	Low	Protocol: The primary efficacy analysis will be completed when approximately 372 MFS events have occurred. Publication: In the planned primary analysis, which was performed after 378 events had occurred. Publication: The	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				Demographic and disease char- acteristics were well balanced between the two groups (Table 1, and Table S2 in the Supplementary Appendix).		participants, carers and personnel correctly guessing their treatment allocation. There is no enough information to answer this question. Protocol: 13.1 ANALYSISPOPULATIO NS, Full Analysis (Intent-to-Treat) Population [ITT]		total of 7.0% of the patients in the apalutamide group and 10.6% of those in the placebo group withdrew consent from the trial. The observed number of events is only 4 times the number of participants with missing outcome data. According to the Protocol, Investigator assessments may be used for sensitivity analyses, as described in the Statistical Analysis Plan. However, there was no analysis methods that correct for bias, or sensitivity analyses in the main text. No information was available to answer this question.		Publication: Evidence of dis- tant metastasis on imaging was determined on the basis of Response Evaluation Criteria in Solid Tumors, version 1.1x Publication: All imaging studies were assessed prospectively by means of blinded independent central review.		primary end point was metastasis-free sur- vival, which was defined as the time from random- ization to the first detection of distant metastasis on imaging (as assessed by means of blinded independent central review) or death from any cause, whichever occurred first.	
NCT024 89318	311505 74	radiog raphic progre ssion- free surviv al and overall surviv al	Low	Publication: The randomization will be balanced by using randomly permuted blocks. The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his own user identification and personal identification number when	Some concer ns	Publication: The TITAN trial was a phase 3, randomized, double- blind, placebo- controlled, multinational trial. The frequency of grade 3 or 4 adverse events was 42.2% in the apalutamide group and 40.8% in the placebo group; rash was more common in the apalutamide group (27.1% vs. 8.5%). We assumed that such differences in skin adverse reaction could potentially break the	Low	Supplementary Figure S1: of the 1052 ITT population, one patient did not receive study drug, 22 and 23 patient withdrawn in the intervention and comparator groups, respectively. Nine patient discountinued due to physician decision, three patients have protocol violation, one for other reason. In total, 5.6% of patients did not have available outcome data.	Low	Publication: Overall survival was defined as the time from randomization to the date of death from any cause.OS endpoint is objective.	Low	Protocol: For the co- primary OS endpoint, 2 interim analyses are planned for this study after observing 60% (246 events) and 80% (328 events) of the total number of required (410) events.Publication: The first interim analysis for overall survival oc- curred after 200 deaths were observed (83 in the apalutamide	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.Publication: Demographic and clinical characteristics at baseline were well balanced (Table 1, and Table S1 in the Supplementary Appendix).		blinding of the trial, and resulting in participants, carers and personnel correctly guessing their treatment allocation.There is no enough information to answer this question.Protocol: The primary analysis population will use the intent-to-treat (ITT) population, which includes all randomized subjects.						group and 117 in the placebo group).Publication: Overall survival was defined as the time from randomization to the date of death from any cause.	
NCT027 63579	302806 41	PFS and OS	Low	Publication: Randomization was performed with the use of a permuted-block randomization method (IxRS). Publication: Baseline character- istics were well balanced between the groups (Table 1, and Tables S2 and S3 in the Supple- mentary Appendix).	Low	Publication: The IMpower133 trial is a multinational, phase 1 (safety) and phase 3 (efficacy), double-blind, randomized, placebo-controlled trial. According to Table 3, the proportion of grade 3 or 4 adverse events were similar between groups. Publication: The primary end points were assessed in the intention-to-treat population and were analyzed according to the assigned treatment, regardless of the actual treatment received.	High	Figure 1: of 201 patients assigned to receive atezolizumab, 3 were lost to follow-up, 20 were withdrawn by physician or patient. Of 202 patients assigned to receive placebo, 1 were lost to follow-up, 9 withdrawl. Publication: A total of 104 patients (51.7%) in the atezolizumab group and 134 patients (66.3%) in the placebo group had died. In total, 8.2% of patient did not have available outcome. This proportion imbalanced between groups (11.4% and 4.6%). The observed number of events was 7.2 times the number of participants with missing outcome data (4.5 vs 13.4). Analysis methods that	Low	Publication: The primary end points were overall survival (the time from randomization to death from any cause) and investigator-assessed progression-free survival (the time from randomization to disease progression according to RECIST or death from any cause, whichever occurred first) in the inten- tion-to-treat population. This is a double-blind study.	High	Publication: Two OS interim analyses will be performed. One will be at the time of PFS analysis. It is projected that approximately 179 OS events in the ITT population will be observed at the time of PFS analysis. The other OS interim analysis will take place when approximately 258 OS events in the ITT population are observed, which is expected at approximately 30 months after the first patient is randomized. The final analysis of OS will be performed when approximately 298 OS events in the ITT population have beenobserved, which is expected at approximately37 months after the	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								correct for bias or sensitivity analyses was not reported. According to Figure 1, the propriton of patient without available outcome data differed between groups (12.4% vs 5.0%). However, there was not enough information to answer this question.				first patient is randomized.	
NCT034 34379	324021 60	OS and PFS	Low	Protocol: Patients will be grouped according to the treatment assigned at randomization by the interactive voice or web-based response system (IxRS), whether or not the assigned treatment was received.Publication: Base line characteristics were generally well balanced between treatment groups (Table 1, and Table S2).	Low	This is an open-label trial.Figure S2. Trial Profile: only one patient deviated from protocol.Publication: The coprimary end points were overall survival and progressionfree survival in the intentiontotreat population.	High	Figure S2. Trial Profile: of the 501 randomized patietns, seven and nine patients did not receive assigned treatment in the intervention and control group. 12 and 19 patients in the intervention and comparison group withdrew consent, respectively.In total, 5.7% and 17.0% of patients in the two groups did not have availabel outcomes. This is imbalanced between groups.According to the publication, analysis methods that correct for bias and sensitivity analysis were not used.Table 3:the proportion of serious adverse event (38.0% vs 30.8%) and the proportion of patient withdrawal due to adverse event differed between the intervention and	Low	Publication: The coprimary end points were overall survival (the time from randomization to death from any cause) and progressionfree survival (the time from randomization to disease progression ac cording to RECIST 1.1, as assessed at an inde pendent review facility, or death from any cause, whichever occurred first).The coprimary endpoints were assessed by independent review facility.Publication: a blinded independent review of imaging for progression free survival was selected for the coprimary end point.	Low	Protocol: One interim analysis of OS will be performed at the time of the primary ORR analysis, estimated to occur at approximately 22 months after FPI. It is anticipated that at this time, approximately 185 deaths will have been observed.Publicatio n: A total of 96 patients (28.6%) in the atezo lizumab–bevacizumab group and 65 (39.4%) in the sorafenib group died.Analyses reported in the article and supplementary appendix appeared consistent with those specified in the protocol.	Low

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								control groups (15.5% vs 10.3%).					
NCT024 09342	329979 07	OS	Low	Protocol: For patients eligible for enrollment, the study site will obtain the patient's randomization number and treatment assignment from the IxRS. Publication: The baseline characteristics of the patients were generally balanced between the treatment groups (Table 1 and Table S1).	Low	Publication: IMpower110 is a global, randomized, open-label, phase 3 trial According to Figure S2, there was no protocol deviation. Publication: Overall survival (primary end point) was tested hierarchically according to PD-L1 expression status among patients in the intention-to-treat population.	High	Figure S2: of the randomized patients, 4/107 (3.7%) and 8/98 (8.2%) patient who had high PD-L1 expression withdraw. Publication: In the specified population, 101 of 205 patients (49.3%) who had high PD-L1 expression had died. The overall proporiton of withdrawn is 5.9%. The observed number of events was 8.4 times the number of participants with missing outcome data. Publication: The results of an exploratory sensitivity analysis of overall survival with adjustment for patients whose data were censored owing to early withdrawal are shown in Table S2. However, this was based on multiple imputation.	Low	Publication: Overall survival was the primary end point. The primary endpoint is overall survival. Publication: IMpower110 is a global, randomized, open-label, phase 3 trial. The primary endpoint is overall survival.	Low	Protocol: an interim analysis of OS in the TC3 or IC3-WT population will be conducted when both of the following criteria have been met: An approximately 45% event-patient ratio has been observed in the TC3 or IC3-WT subpopulation; Approximately 96 deaths have occurred in the TC3 or IC3-WTsubpopulation. Protocol: The interim and final analyses are expected to occur approximately 40 and 55 months, respectively.	High
NCT026 57434	333333 28	OS and PFS	Low	Publication: Permuted-block randomization with a block size of four was used to allocate patients in a one-to-one ratio to each treatment group.Publication:	Some concer ns	Publication: IMpower132 is a randomized, phase 3, multicenter, open-label study.No information was available to answer this question.Publication: The co-primary end	High	Figure 1: the proportion of patient without outcome is 10.9% (63/578).No analysis methods that correct for bias or sensitivity analyses was used.Figure 2: the proportion of	Low	The primary endpoint we assessed is overall survival.Publication: IMpower132 is a randomized, phase 3, multicenter, open-label study.Overall survival endpoint is objective.	Low	Protocol: The interim OS analysis will be conducted when approximately 312 OS events in the ITT population have been observed. The final OS analysis will be	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overall Bias
Study ID	Reference (PMID)	Outcome	1.0 Assessor's Judgement	1.0 General note	2.0 Assessor's Judgement	2.0 General Notes	3.0 Assessor's judgement	3.0 Gerenal notes	4.0 Assessor's Judgement	4.0 General note	5.0 Assessor's Judgement	5.0 General note	Assessor's overall Judgement
				Baseline demographic and clinical characteristics were similar between treatment arms (Table 1).		points were investigator- assessed PFS (measured per RECIST 1.1) and OS in the intention-to-treat (ITT) population.		patient without outcome is imbalanced between the two groups (6.5% vs 15.4%).				conducted when approximately 398 OS events in the ITT population have been observed.Publication: As of the interim OS analysis (data cutoff, May 22, 2018), 137 patients (46.9%) in the APP arm and 154 patients (53.8%) in the PP arm had died.As of the final OS analysis (data cutoff, July 18, 2019), 192 patients (65.8%) in the APP arm and 197 patients (68.9%) in the PP arm had died.	
NCT02657434 (IMpower132 China Cohort)	36052772	OS and PFS	Low	Publication of IMpower132: Permuted-block randomization with a block size of four was used to allocate patients in a one-to-one ratio to each treatment group. Publication: Baseline characteristics were generally balanced between treatment arms, although a slightly higher proportion of patients in the APP arm (n = 12, 14.6%) had baseline liver metastases than in the PP arm (n = 5, 6.2%; Table 1).	Some concerns	Publication: IMpower132 is a global randomized, open-label, Phase III study (NCT02657434). No information was available to answer this question. Publication: The co-primary endpoints for the study were investigator- assessed PFS measured per RECIST 1.1 and OS in the ITT population.	High	Figure 1: 27/82 and 32/81 patients lost to follow-up or withdrew. The total proportion of patient without outcome is 36.2%. No analysis methods that correct for bias or sensitivity analysis was performed. The proportions of missing outcome data is similar between the two groups. However, there is no enough information to answer these questions.	Low	The primary endpoint is overall survival. Publication: IMpower132 is a global randomized, open-label, Phase III study. Overall survival is objective outcome.	Low	IMpower132 Protocol Date: 09-Oct-17. Publication cutoff date: July 18, 2019. Publication: The final PFS and OS analyses in Chinese patients were planned to be conducted after approximately 115 recorded PFS events and approximately 120 recorded OS events had occurred in the ITT population. At the primary PFS analysis, a total of 52 PFS events (63.4%) had occurred in the APP arm and 54 events	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
												(66.7%) had occurred in the PP arm. Interim OS data for these patients were not mature at this data cut. Final OS analysis was not reported. Although the death events for interim OS analysis was not reported, it was reported together with final PFS analysis, which is consisted with the protocol.	
NCT022 25470	309288 06	PFS	Low	Publication: Patients were randomly assigned 1:1 to treatment with either eribulin or vinorelbine using an interactive web-response system.Publication: Baseline characteristics were balanced between groups (Table 1).	Some concer ns	This is an open-label trial.No information was available to answer this question.Publication: Primary efficacy analyses were performed on the intent-to-treat population.	Low	Figure 1: of 264 patients randomized to eribulin, 2 lost to follow-up, 18 patients withdrew consent, 27 discontinued for other reasons. of 266 patients randomized to vinorelbine, 22 patients withdrew consent, 47 discontinued for other reasons. We assumed patient discontinued due to "other reason" meant that outcome data could not be collected. Overall, 116/530 (21.9%) patients did not have available outcome.Publication: The favourable impact of eribulin on PFS was sup- ported by a post hoc sensitivity analysis, where the PFS time	Low	Publication: Tumour assessments per RECIST v1.1 (by independent radiologic review and by investigator) were performed at baseline, then every 6 weeks until disease progression or initiation of other anticancer therapy.Publication: The primary efficacy end-point was PFS by independent review.	Some concer ns	No study protocol was available to fully answer this question.Publication : The proportion of censoring during the course of the study, according to independent review, was higher than ex-pected; therefore, the sample size was increased to 530 patients (n Z 265 in each treatment arm) to ensure the target number of 380 events would be reached in a reasonable time frame. However, no study protocol was available to fully answer this question.	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								ratio of eribulin to vinorelbine was 1.19 (95% CI: 1.03-1.37, P=0.020).					
NCT003 88726	213763 85	OS	Low	Publication: Patients were randomised centrally by an interactive voice recognition system to receive eribulin or TPC. Publication: Baseline demographic characteristics were well balanced across treatment groups (table 1).	Some concer ns	Publication: Patients and investigators were not masked to treatment allocation. No information was available to answer this question. Publication: Primary analysis of overall survival included the intention-to-treat (ITT) population.	High	Figure 1: Of the 508 patients assigned eribulin, 19 discontinued study due to physician's decision, 10 withdrew consent, 5 lost to follow-up, 6 for other reasons. Of the 254 patients assigned treatment of physician's choice, 12 discontinued study due to physician's decision, 7 withdrew consent, 2 lost to follow-up, 10 for other reasons. Publication: 274 (54%) deaths in the eribulin group and 148 (58%) deaths in the treatment of physician's choice group. The overall proportion of patient without available outcome was 9.3% (7.9% vs 12.2%). The observed number of events was 5.9 time the number of participants with missing outcome data (6.85 vs 4.77). No analysis methods that correct for bias or sensitivity analyses was reported. Not enough information was available to answer this question.	Low	Publication: The primary endpoint was overall survival in the intention-to-treat population. Publication: We defined overall survival from date of randomisation to death or to last date known alive (censored). The EMBRACE trial (study E7389-G000-305) was a phase 3, global, multicentre, randomised, open-label study. PFS was assessed by independent review. Overall survival is an objective endpoint.	Some concer ns	Publication: We originally planned to enrol 630 patients to achieve the 411 events (deaths) that were needed for the primary analysis. This number was later increased to a maximum of 1000 patients when the masked evaluation of the overall event rate suggested that deaths were occurring slower than expected. However, study protocol was not available to fully answer this question.	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
NCT023 88919	300981 52	OS	Low	Publication: Patients were randomly assigned in a 2-to-1 ratio to receive an-lotinib or placebo with a block randomization scheme (block size of 4) using a double-blind, computerized, randomized list generator.Publication: baseline characteristics were well balanced across the 2 groups.	Some concer ns	This is a double-blind trial. Adverse events of grade 3 or higher were reported in 182 patients (61.9%) in the anlotinib group and 53 patients (37.1%) in the placebo group. We assumed that such differences could potentially break the blinding of the trial, and resulting in participants, carers and personnel correctly guessing their treatment allocation.There is no enough information to answer this question.Publication: All cases were treated with study drugs at least once in accordance with the intention-to-treat principle.	High	Figure 1: 41/296 and 29/143 of patients withdrew consent, violated study procedures, or lost to follow-up. Overall, the proportion of patients without available outcome is 15.9%.No analysis methods that correct for bias or sensitivity analyses was performed.No information was available to answer this question.	Low	Protocol: OS is defined as the time from randomization to death for any reason.This is an open-label trial.Overall survival endpoint is objective.	Low	Protocol: 291 cases of OS events occurred in the two groups, thereby revealing statistically significant difference in the two groups.Publication: At the time of data cutoff, 189 of 294 patients (64.3%) in the anlotinib group died compared with the 103 of 143 patients (72.0%) in the placebo group who died.Analyses reported in the article appeared consistent with those specified in the protocol.	High
NCT030 59797	340069 26	PFS	Low	Publication: Permuted block randomisation with predefined block size at six was used within each stratification. Randomisation was done centrally via the interactive web response system provided by the Department of Biostatistics, School of Public Health Nanjing Medical University. Publication: The two treatment groups were balanced with regard to demographics and disease characteristics (Table 1).	Low	Publication: This was a double-blinded, randomised, placebo-controlled, multi- centre Phase 2 trial. Publication: Comparisons on PFS, OS, ORR and DCR were performed in a full analysis set (FAS). FAS is defined as the analysis set including all the randomised subjects without serious violation of the protocol according to the principle of intention to treat (ITT).	Low	Figure 1: Of the 120 randomized patients, five withdrew consent, one terminated as advised by investigation. The overall proportion of patient without available outcome is 5%	Low	Publication: Tumour assessments were evaluated according to the RECIST 1.1 version by investigators. Publication: This was a double-blinded, randomised, placebo-controlled, multi-centre Phase 2 trial.	Some concer ns	Study protocol was not available to fully answer this question.	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
NCT025 86350	338329 49	PFS	Some concer ns	The only information about randomization methods is a statement that the study is randomized. Publication: As shown in Table 1, no significant difference was detected between the two groups with respect to baseline characteristics.	Low	Publication: This was a multicenter, randomized, double-blind, placebo-controlled phase IIB study. The incidence of grade 3 or higher TRAEs was 58.1% in the anlotinib group, and less than 25% in the placebo group. We assumed that such differences could potentially break the blinding of the trial, and resulting in participants, carers and personnel correctly guessing their treatment allocation. There is no enough information to answer this question. Publication: The primary outcome was assessed in all patients who received randomization (intention to treat analysis).	Low	Figure 1: no patient was censored due to lost follow-up.	Low	Publication: Tumor response was evaluated and confirmed on the basis of radiographic imaging according to RECIST 1.1 every two cycles of treatment for the first 12 cycles, then every four cycles. Publication: The radiographic image was assessed and the final result was determined by IRC independently.	Some concer ns	Study protocol was not available to fully answer this question.	Some concer ns
NCT018 74353	287544 83	PFS	Low	Publication: The randomisation scheme was produced by a computer software program that generates random numbers (Global Randomisation System) and was loaded into an interactive voice and web response system database. Investigators (or nominated assistants) contacted the interactive voice and	Low	This is a double-blind trial. Although serious adverse events were experienced by 35 (18%) patients in the olaparib group and eight (8%) patients in the placebo group., these were not considered to be substantial enough to break blinding of participants and personnel.Publication: The efficacy analyses were done on the intention-to-treat population.	Low	Supplement: In the full analysis set, 27/196 (13·8%) patients in the olaparib group and 14/99 (14·1%) patients in theplacebo group were classified as having been informatively censored.Supplement : For patients with informative censoring, the distribution of censoring times was spread evenly from randomisation. When	Low	Publication: The primary endpoint was investigator assessment of progression-free survival, defined as the time from randomisation until objective radiological disease progression or death using modified RECIST version 1.1.Although the primary endpoint was investigator assessment of progression-free survival, this is a double-blind trial.	Low	The trial protocol was not attached. We obtained the protocol from the final analysis (10.1016/S1470-2045(21)00073-5).Protocol: The data cut off date for the statistical analysis for the primary objective of the study will be established when ~192 confirmed progression events (~65% maturity for	Low

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				web response system centralised randomisation centre for allocation of randomised therapy.fPublication: Demographic and baseline characteristics seemed to be well balanced between the two groups (table 1).				potential informatively censored patients are assumed to have had an event at the next scan (+12 weeks), PFS by blinded independent central review was still significantly longer with olaparib than placebo (hazard ratio 0·26 [95% confidence interval 0·19–0·35], p<0·0001; median 19·6 [IQR 8·0–not calculable] months vs 5·5 [IQR 2·8–8·4] months). The results of this sensitivity analysis demonstrate the robustness of the primary PFS data.				PFS analysis) are expected to have occurred.Publication : We did the efficacy analysis after 187 investigator-assessed events of disease progression or death (63% maturity: 107 [55%] of 196 in the olaparib group vs 80 [81%] of 99 in the placebo group). The actual number of progression-free survival events was five (2·6%) fewer than the number detailed in the statistical plan (~192 events).	
NCT007 53545	224523 56	PFS	Low	Protocol: The actual treatment given to individual patients will be determined by a randomisation scheme that has been loaded into the Interactive Voice Response System (IVRS) database. The randomisation scheme will be produced by a computer software program called GRand (AZ Global Randomisation system) that incorporates a standard procedure for generating random numbers. Publication: Demographic and baseline characteristics of the	Some concer ns	This is a double-blind trial. Adverse events more commonly reported in the olaparib group than in the placebo group (by more than 10% of patients) were nausea (68% vs. 35%), fatigue (49% vs. 38%), vomiting (32% vs. 14%), and anemia (17% vs. 5%); the majority of adverse events were grade 1 or 2. We assumed that such differences could potentially break the blinding of the trial, and resulting in participants, carers and personnel correctly guessing their treatment allocation. There is no enough information to answer this question.	High	Figure 1: Of the 265 patient that underwent randomization, 17/136 withdrew consent or lost to follow-up in the intervention group, 19/129 withdrew consent or lost to follow-up in the control group. The overall proportion of patients without available outcome is 13.6%. Protocol: Sensitivity analyses will be performed to assess potential censoring bias and possible time- assessment bias. In order to assess symptomatic progression a further	Low	Publication: The primary end point was progression-free sur- vival, as assessed by the site investigator and de- fined as the time from randomization (on comple-tion of chemotherapy) until objective assessment of disease progression according to RECIST guide- lines27 or death (from any cause in the absence of progression of disease). Although the primary endpoint is the investiagator assessed PFS, this is a double-blind trial.	Low	Protocol: The primary analysis will be performed when a total of 137 PFS events have been observed in the overall population. Publication: An analysis performed after 153 progression events had occurred (in 57.7% of patients) showed that progression-free survival was significantly longer in the olaparib group than in the placebo group. Outcome measurements reported in the published article and supplementary	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				patients (Table 1) and any protocol devia- tions with the potential to affect the primary anal- ysis (Table 1 in the Supplementary Appendix) were well balanced between the two study groups.		Protocol: Efficacy data will be summarised and analysed on an intention-to-treat (ITT) basis using randomised treatment.		sensitivity analysis that censors RECIST progressions (not deaths) will be performed. However, this was not reported in the main text. No information was available to answer this question.				appendix appeared consistent with those specified in the protocol.	
NCT018 44986	303458 84	PFS	Low	Protocol: Obtain the randomisation code (patient number) through IVRS/IWRS.Publicatio n: Randomization was performed centrally with a block design.Publication: The baseline characteristics were well balanced between the trial groups (Table 1).	Low	This is a double-blind trial. According to Table 2, although grade 3 or 4 adverse events were higher in the olaparib group (39% vs 18%), these were not considered to be substantial enough to break blinding of participants and personnel.Protocol: all efficacy and health-related quality of life (HRQoL) data will be summarised and analysed using the FAS on an intention-to-treat (ITT) basis.	Low	Figure 1: Of the 391 patients, underwent randomization, 43/260 patients in the intervention group had severe violation of protocol or discontinued therapy without having PFS events, and 14/131 patients in the control group withdrew, lost to follow-up, or discontinued therapy. The overall proportion of patient without available therapy was 14.3%Supplement: In the sensitivity analysis to assess possible attrition bias, thehazard ratio (HR) for olaparib versus placebo was 0.31 (95% confidence interval [CI],0.230.41; P<0.0001) with a median progression-free survival of 49.9 months witholaparib versus 13.8 months with placebo, yielding a progression-free survival benefit of36.1 months. In the sensitivity analysis to assess possible	Low	Publication: Progression-free survival was defined as the time from ran- domization to objective disease progression on imaging (according to modif ied RECIST, version 1.1) or death from any cause.Although the primary end point was progression-free survival as assessed by investigators, this is a double-blind trial.	Low	Protocol: Approximately 344 patients will be recruited (2:1 ratio) so that data maturity for the PFS analysis is approximately 60%. Assuming 18 months non-linear recruitment, 206 PFS events are expected to occur approximately 36 months after first subject in is enrolled in the study (FSI). This will be the primary analysis of PFS.Publication: The analysis of the primary end point was per- formed after 198 of the 391 patients had had investigator-assessed disease progression or had died (data maturity, 51%).	Low

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								informative censoring (usingblinded independent central review), the HR for olaparib versus placebo was 0.31 (95%CI, 0.240.42; P<0.0001) with a median progression-free survival of 46.9 months with olaparib versus 11.8 months with placebo, yielding a progression-free survival benefit of 35.1 months.Publication: The results of sensitivity analyses and subgroup analyses of progression-free survival were consistent with the results of the primary analysis.					
NCT029 87543	323438 90	PFS	Low	Protocol: The randomization codes will be computer generated using a randomization system (AZRand) and loaded into the interactive voice response system/interactive web response system (IVRS/IWRS) database. Publication: Although baseline characteristics appeared balanced overall between the olaparib group and the control group, the control group had a higher percentage of	Some concer ns	Publication: This was a prospective, randomized, open-label, phase 3 trial. Protocol: The primary statistical analysis of the efficacy of olaparib in comparison to investigator choice of either enzalutamide or abiraterone acetate in Cohort A will include all randomized subjects regardless of the treatment actually received.	Low	Figure 1 legend: Overall, at the time of the analysis of imaging-based progression- free survival by blinded independent central review, 10 patients (4%) in the olaparib group and 8 (6%) in the control group had withdrawn consent, and their data were censored. (For interim overall survival in the overall population, see Fig. S3.) Publication: Analysis of the primary end point was performed after 174 of 245	Low	Publication: Imaging-based progression-free survival was defined as the time from randomization until soft-tissue disease progression (by RECIST, ver- sion 1.1), bone lesion progression (by Prostate Cancer Clinical Trials Working Group 3 criteria), or death (see the Supplementary Appendix). Publication: The primary end point was imaging-based pro- gression-free survival, assessed by an indepen- dent review committee.	Low	Protocol (date 2017/3/2): The primary analysis of rPFS primary endpoint will be performed after approximately 143 progression or death events have been accrued in 240 subjects in Cohort A (60% maturity). Publication: Analysis of the primary end point was performed after 174 of 245 patients in cohort A had had imaging-based progression by independent review	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				patients with visceral metastases and a higher median baseline PSA concentration, and the olaparib group had a higher percentage of patients with an ATM alteration (Table 1).				patients in cohort A had had imaging-based progression by independent review or had died (data maturity, 71%; data cutoff date, June 4, 2019). The overall proportion of patient without available therapy was 7.3%. The observed number of events was 9.7 times the number of participants with missing outcome data. Publication: A sensitivity analysis including death as an event in the absence of pain progression yielded similar results (Table S7)				or had died (data maturity, 71%; data cutoff date, June 4, 2019).	
NCT022 96125	291513 59	PFS	Low	Protocol: At Visit 2, once the patient is confirmed to be eligible, the Principal Investigator or suitably trained delegate will obtain a unique randomisation number via IVRS/IWRS.Eligible patients will be centrally randomised to receive either AZD9291 80 mg orally once daily or the site pre-selected EGFR-TKI (gefitinib 250 mg orally once daily or erlotinib 150 mg orally once daily) in a 1:1 ratio using the	Some concer ns	This is a double-blind trial. Adverse events of grade 3 or higher were less frequent with osimertinib than with standard EGFR-TKIs (34% vs. 45%). The most commonly reported adverse events due to any cause (treatment-related or not) were rash or acne (58% in the osimertinib group and 78% in the standard EGFR-TKI group). We assumed that such differences in skin adverse reaction could potentially break the blinding of the trial, and resulting in	Low	Figure S1. Patient disposition: of the 279 patients allocated to osimertinib, 12 (4.3%) discontinued treatment for other reason. Of the 277 patients allocated to standard EGFR-TKI, 5 (1.8%) discontinued for other reason.Publication: At the time of data cutoff, an event of RECIST- defined progression or death had occurred in 136 patients (49%) in the osimertinib group and 206 (74%) in the standard EGFR-TKI	Low	Publication: The primary end point was the duration of pro- gression-free survival as determined by investigator assessments, according to RECIST, version 1.1. RECIST, version 1.1 was used to assess PFS.This is a double-blind trial.	Low	Protocol: The primary analysis will be performed when approximately 359 PFS events have occurred.Publication : At the time of data cutoff, an event of RECIST- defined progression or death had occurred in 136 patients (49%) in the osimertinib group and 206 (74%) in the standard EGFR-TKI group.Outcome measurements reported in the published article appeared consistent	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				IVRS/IWRS system.Publication: Baseline characteris-tics were well balanced between the trial groups and in line with the intended population per the protocol (Table 1).		participants, carers and personnel correctly guessing their treatment allocation.There is no enough information to answer this question.Publication: The full analysis set included all randomly assigned patients and was used for efficacy assessments.		group. We assumed that patients discontinued due to "other reason" did not have available outcome. The overall patient without outcome data was 3.1%. The observed number of events was 20.1 times the number of participants with missing outcome data.				with those specified in the protocol.	
NCT022 96125 (FLAUR A China)	335443 37	PFS	Low	Protocol of FLAURA: At Visit 2, once the patient is confirmed to be eligible, the Principal Investigator or suitably trained delegate will obtain a unique randomisation number via IVRS/IWRS. Eligible patients will be centrally randomised to receive either AZD9291 80 mg orally once daily or the site pre-selected EGFR-TKI (gefitinib 250 mg orally once daily or erlotinib 150 mg orally once daily) in a 1:1 ratio using the IVRS/IWRS system. Publication: Patient demographics and clinical characteristics at baseline were generally well balanced between treatment groups (Table 1) with the exception of a higher proportion of female	Some concer ns	Publication: FLAURA China was a double-blind, randomized, phase III study. Grade 3 or higher adverse events (AEs) were reported in 54 and 28% of patients in the osimertinib and comparator groups, respectively. We assumed that such differences in skin adverse reaction could potentially break the blinding of the trial, and resulting in participants, carers and personnel correctly guessing their treatment allocation. There is no enough information to answer this question. Publication: The full analysis set consisted of all randomized patients in the FLAURA China study. The safety analysis set consisted of all patients in the full	Low	Supplementary Figure 1. Patient disposition: Of the 71 patients assigned to osimertinib, 2 discontinued due to other reason. Of the 65 patients assigned to other EGFR-TKI, 2 discontinued due to other reason. Publication: RECIST-defined disease progression or death had occurred in 40 (56%) and 51 (78%) patients in the osimertinib and comparator EGFR TKI groups, respectively, resulting in an overall 67% PFS maturity. We assumed that patients discontinued due to "other reason" did not have available outcome. The overall patient without outcome data was 2.9%. The observed number of events was	Low	Publication: The primary endpoint was investigator-assessed PFS according to RECIST v1.1. This is a double-blind trial.	Low	Protocol: These analyses will be performed when the PFS data from the China patients is of similar maturity to when the analysis of PFS for the globally recruited patients will be conducted; i.e. approximately 68% maturity or 82 PFS events out of the approximately 120 China patients. Publication: At the DCO for the primary endpoint PFS (10 January 2018), RECIST-defined disease progression or death had occurred in 40 (56%) and 51 (78%) patients in the osimertinib and comparator EGFR TKI groups, respectively, resulting in an overall 67% PFS maturity.	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				patients in the comparator EGFR TKI group (71%) than in the osimertinib group (61%), more patients with CNS metastases (32 vs. 24%), and more patients with extrathoracic visceral metastases (46 vs. 35%).		analysis set who received at least one dose of study treatment.		22.75 times the number of participants with missing outcome data.				Analyses specified in the protocol appeared consistent with those reported in the published paper and supplementary appendix.	
NCT025 11106	329551 77	DFS	Low	Protocol: At randomization Visit, once the patient is confirmed to be eligible, the Principal Investigator or suitably trained delegate will obtain a unique randomization number via IVRS/IWRS.Publicatio n: Baseline characteristics were balanced between the two groups (Table 1 and Table S1).	Low	This is a double-blind trial.Publication: The full analysis set, which included all the pa- tients who underwent randomization, was used for demographic summaries and efficacy analyses.	Low	Figure S2. Patient disposition: Of the 682 randomized patient, 2/339 patients in the osimertinib group did not receive allocated treatment.Publication: The number of patients who discontinued osimertinib or placebo was 92 (27%) and 174 (51%), respectively.Protocol: Patients who discontinue treatment prior to disease recurrence will continue to be followed for DFS according to study plan.	Low	Publication: Disease-free survival was defined as the time from randomization to disease recurrence (determined by computed tomography or magnetic resonance imaging, pathological disease on biopsy, or both) or death from any cause.Protocol: Disease recurrence is defined as evidence of disease recurrence on CT or MRI scan and/or pathological disease on biopsy by investigational site assessment.Although the primary endpoint was investigator assessed DFS, this is a double-blind study.	High	Protocol: The primary analysis of DFS will be conducted when approximately 247 disease recurrence events have been observed in approximately 490 patients who are in Stage IIA-IIIA (i.e. non- IB).Publication: Among the 470 patients with stage II to IIIA disease, disease recurrence or death occurred in 156 patients (33% maturity); there were 26 events in the osimertinib group (11% maturity) and 130 events in the placebo group (55% maturity). Publication: The planned data cutoff date for the primary event-based analysis was February 2022. The data cutoff date for this unplanned interim analysis was January 17, 2020.	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
NCT017 74721	289585 02	PFS	Low	Publication: A randomisation list was generated using a computergenerated random code that was assigned by a central interactive web response system (IWRS). The allocation sequence, based on a randomisation-requirement specification form (prepared by the IWRS vendor in accordance with the requirements of the study sponsor), was generated by the IWRS. The investigators at the clinical sites enrolled the patients by using the IWRS, entered each patient's race and EGFR mutation type (the stratification variables), and assigned each patient to a treatment group on the basis of the IWRS output. Publication: Demographic characteristics and baseline clinical characteristics were generally well balanced between the treatment groups (table 1).	Some concer ns	Publication: ARCHER 1050 was an international, multicentre, randomised, openlabel, phase 3 trial. No information was available to answer this question. Publication: The primary endpoint was progression-free survival assessed by masked independent review in the intention-to-treat population.	Low	Figure 1: of the 452 patients randomly assigned to treatment, 1 patient withdrew consent, 12 no longer willing to participate, 1 lost to follow-up, 13 discontinued due to other reasons. We assume they did not have available outcome. Overall, the proportion of patients without available outcome was 6.0%.	Low	Publication: Objective tumour responses were measured using RECIST version 1.1. Publication: Objective tumour responses were measured using RECIST version 1.1 and assessed by a masked independent radiological central (IRC) review and by the investigator. Publication: The primary endpoint was progression-free survival as determined by masked IRC review.	Low	The protocol version 7 was revised in 4 November 2015, before the cutoff date 29 July 2016. Protocol: The analysis of PFS will take place when a minimum of 256 PFS events per IRC review are observed. Figure 2: 315 patients had PFS events. Analyses specified in the protocol appeared consistent with those reported in the published paper and supplementary appendix.	Some concer ns
NCT015 84648	252654 92	PFS	Low	Protocol: Randomization will be done centrally using a randomization schedule generated by the GSK	Low	Protocol: Study treatment will be double-blinded.Publication: Grade 3 or 4 adverse events occurred in 73	High	Figure S1. Trial Consort Diagram: Of the 211 patients randomized to dabrafenib plus trametinib, 102	Low	Publication: Tumor assessments were conducted according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,18 at	Some concer ns	Publication: this This report is based on data as of August 2013, when the prespecified number of disease	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				Biostatistical DepartmentPublicatio n: Baseline characteristics were similar in the two study groups (Table 1)		patients (35%) in the dabrafenib–trametinib group and 79 patients (37%) in the dabrafenib-only group.Publication: Efficacy was determined in all patients in the intention-to-treat population.		progressed or died, 17 (8.1%) withdraw. Of the 212 patients randomized to dabrafenib plus placebo, 109 progressed or died, 10 withdraw (4.7%).Overall, the proportion of patients without available outcome was 6.4%. This proportion imbalanced between groups (8.1% and 4.7%). The observed number of events was 7.8 time the number of participants with missing outcome data (6 vs 10.9).Publication: Of the 18 patients in the dabrafenib-only group for whom data were censored, 13 had disease progression on the basis of clinical indications (without radiologic confirmation), as determined by the investigator, or had started a new anticancer therapy. In preplanned sensitivity analyses, when clinical progression or initiation of a new anticancer therapy was considered as an event, the hazard ratio for progression and the median progression-free survival for the dabrafenib–trametinib		baseline, at week 8, every 8 weeks until week 56, and then every 12 weeks until disease progression, death, or withdrawal from the study.Publication: Tumor assessments were conducted according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1Publication: The primary end point was investigator-assessed progression-free survival. This is a double-blind trial.		progressions or deaths(whichever came first)had occurred.Protocol version 07 effective date: 14 Oct 2013. The primary analysis for this study was originally planned to be conducted when 155 events have occurred; 155 would have equated to 45.6% of the targeted enrollment of 340. This study enrolled 423 subjects instead of 340 subjects (24% over enrollment). To increase the precision of the median PFS estimate in combination therapy arm, the final analysis will be performed when 193 (0.456x423) events have occurred; 193 events represents the same percentage (45.6%) of total enrolment as originally planned.	

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								group remained stable (i.e., the median remained the same when clinical progression was considered or decreased by 0.1 month when the initiation of a new anticancer therapy was considered). In contrast, the median progression-free survival in the dabrafenib-only group decreased by 1.2 months when clinical progression was considered and by 1.6 months when the initiation of a new anticancer therapy was considered.Publicatio n: In addition, the preplanned sensitivity analysis showed that the median progression-free survival for dabrafenib was unstable. Data for patients who had clinical progression or received a new anticancer therapy without radiographic evidence of progression were censored (which oc-curred more frequently in the dabrafenib-only group than in the combination-therapy group in the first 2 months of the study). Thus, the median					

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								progression-free survival for the dabrafenib group decreased from 8.8 months to 7.6 months when clinical progression was included as an event and decreased from 8.8 months to 7.2 months when receipt of a new anticancer therapy was included.					
NCT015 97908	253995 51	OS	Low	Protocol: Randomization will be done centrally using a randomization schedule generated by the GSK Biostatistical Department. Publication: Baseline characteristics of the patients are provided in Table 1. Known prognostic measures were well balanced in the two groups except for sex (59% men in the combination-thera-py group vs. 51% in the vemurafenib group).	Some concer ns	Protocol: This is an open-labeled study. According to Figure S1, 3/352 patients assigned to vemurafenib group withdrew consent before receiving intervention. However, the underlying reason was not reported. Publication: The interim analysis for overall survival was per-formed in the intention-to-treat population of 352 patients in each group.	High	Figure S1. Trial CONSORT Diagram: of the 704 randomized patients, 16/352 (5%) of patients in the dabrafenib plus trametinib withdraw, and 28/352 (8%) of patients in the vemurafenib withdraw. Publication: For the overall survival analysis, 100 patients (28%) in the combination-therapy group and 122 (35%) in the vemurafenib group had died Overall, the proportion of patient without available outcome was 6.25%. The observed number of events was 5.1 time the number of participants with missing outcome data (6 vs 10.9). No analysis methods that correct for bias or sensitivity analyses was reported.	Low	Publication: The primary end point was overall survival. This is an open-label trial. Overall survival is an objective endpoint.	Some concer ns	Publication: At the data-cutoff date of April 17, 2014, the interim analysis was performed after 222 events had occurred. Protocol Amendment No. 5 date: 7 Aug 2014. The interim OS analysis will be performed when the minimal enrolment target is met and approximately 70% of the total number of events (deaths) required for the final analysis have been observed across the arms (i.e., 202 total deaths). It is estimated that this will occur at approximately 17 months after the start of the study.	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								Not enough information was available to answer this question.					
NCT016 82083	288914 08	RFS	Low	Protocol: Randomization will be done centrally using a randomization schedule generated by the GSK Biostatistical Department.Publicatio n: The baseline characteristics of the patients were similar in the two groups (Table 1).	Low	This is a double-blind trial. In the combination-therapy group, 114 patients (26%) had adverse events leading to permanent discontinuation of a trial drug, 167 (38%) had ad- verse events leading to a dose reduction, and 289 (66%) had adverse events leading to a dose inter- ruption, as compared with 12 (3%), 11 (3%), and 65 (15%), respectively, in the placebo group.We assumed that such differences could potentially break the blinding of the trial, and resulting in participants, carers and personnel correctly guessing their treatment allocation.According to Figure S1, only 3/438 patients assigned to the combination group withdrew consent before receiving treatment. No protocol violantion was reported.Publication: Efficacy analyses included all the patients who had undergone randomization (intention-to-treat population).	High	Figure S1. Trial Consort Diagram: of the 870 randomized patient, 47/438 and 62/432 patients in the dabrafenib plus trametinib and placebo group withdraw, respectively. The overall proportion of patient without available outcome data was 12.5%.No analysis methods that correct for bias or sensitivity analyses was performed.Not enough information was available to answer this question.	Low	Publication: Disease assessments included clinical examination and imaging by means of computed tomography, magnetic resonance imaging, or both.Publication: All disease-recurrence analyses were based on investigator assessment.	Low	Publication: the data cutoff date for the primary analysis (June 30, 2017). As of the data cutoff, disease recurrence had been reported in 163 of 438 patients (37%) in the combination-therapy group and in 247 of 432 patients (57%) in the placebo group.Release date of Protocol Amendment No. 7: 31-May-2017Protocol: As per Protocol Amendment 7, the final primary RFS analysis will be performed at the pre-defined cut-off date, by which time it is expected that approximately 410 RFS events will have been accrued.	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	**Refere nce (PMID)**	**Outco me**	**1.0 Asses sor's Judge ment**	**1.0 General note**	**2.0 Asses sor's Judge ment**	**2.0 General Notes**	**3.0 Asses sor's judge ment**	**3.0 Gerenal notes**	**4.0 Asses sor's Judge ment**	**4.0 General note**	**5.0 Asses sor's Judge ment**	**5.0 General note**	**Asses sor's overall Judge ment**
NCT032 34972	341081 27	PFS	Some concer ns	The only information about randomization methods is a statement that the study is randomized. Publication: Randomization was stratified by International Staging System disease stage (I, II, or III) at screening (based on central laboratory results), number of prior lines of therapy (1, 2 or 3, > 3), and prior treatment with bortezomib (no, yes). Publication: Patient demographic, baseline disease, and clinical characteristics were generally balanced between treatment groups, although lower percentages of patients had high- risk cytogenetic abnormalities (D-Vd, 33.3%; Vd, 39.7%) and were refractory to lenalidomide (D-Vd, 24.8%; Vd, 30.0%), and a higher percentage of patients were refractory to their last prior line of therapy in the D-Vd group versus the Vd group (D-Vd, 68.1%; Vd, 55.7%; Table 1).	Low	Publication: LEPUS (MMY3009; ClinicalTrials.gov Identifier: NCT03234972) is a randomized, open-label trial. The primary endpoint was estimated in the intention-to-treat population.	Low	Publication: The reasons for treatment discontinuation were progressive disease (21.4% and 29.4%, respectively), death (3.6% and 8.8%), AEs (4.3% and 2.9%), noncompliance with study drug (2.1% and 2.9%), and patient withdrawal (1.4% and 2.9%).	Low	Publication: Response and disease progression were assessed by a validated computer algorithm in accordance with IMWG criteria. Although this is an open-label trial, response and disease progression were assessed by a validated computer algorithm in accordance with IMWG criteria.	Some concer ns	Study protocol was not available to fully answer this question.	Some concer ns
NCT021 36134	275573 02	PFS	Some concer ns	The only information about randomization methods is a statement that the study is randomized. Publication: The	Some concer ns	This is an open-label trial. No information was available to answer this question.	Low	Figure S2. CONSORT patient flow diagram: of the 498 randomized patients, 1/251 and 9/247 patients in the	Low	Publication: We assessed response to treatment and disease progression using a computerized algorithm (details are provided in the Supplementary Appendix)	Low	Publication: data-cutoff date January 11, 2016. After a median follow-up period of 7.4 months, a total of	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				demographic, disease, and clinical characteristics of the two groups were well balanced at baseline (Table 1).		Publication: Efficacy analyses were based on the intention-to-treat population.		experimental and control group discontinued due to non-complicance or withdrawl by patient, respectively. The overall patient without availabel outcome was 2%.		that combined all pertinent laboratory results and the results of imaging, as assessed by the investigator, for each patient and derived the outcome in accordance with IMWG criteria. This is an open label trial. The patient response was asssesseed by investigator.		189 events of disease progression or death had occurred (64% of the 295 planned events for the final analysis). Protocol DATE FINAL: 23 December 2014. Two interim analyses are planned for this study; the first interim analysis will be performed after 80 subjects have been treated for at least 8 weeks to evaluate safety and the second when 177 PFS events have been accumulated to evaluate cumulative interim safety and efficacy data.	
NCT020 76009	277052 67	PFS	Low	Protocol: Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. Publication: The demographic and clinical characteristics of the patients were well balanced at	Some concer ns	This is an open-label trial.No information was available to answer this question.Protocol: Definition of Analysis Populations, Intent-to-treat (ITT) population: All randomized subjects.	Low	Figure S2. CONSORT patient flow diagram: of the 569 randomized patient, 2 (0.3%) lost to follow0-up, 6 (1%) withdraw. The overall patient without available outcome was 1.4%.	Low	Publication: The primary end point was progression-free survival, with progression determined with the use of a validated computer algorithm that combined laboratory results (e.g., M-protein level) and applicable imaging and generated the outcome according to IMWG criteria.Publication: Disease assessments (blood and 24-hour urinary values) were performed every 28 days (within a 3-day window before and after) by a central laboratory for 18	Low	Protocol DATE FINAL: 20 Novermber 2014. Two interim analyses are planned. The first interim analysis will be performed after 80 subjects have been treated for at least 8 weeks or discontinued the study treatment to evaluate safety. The second interim analysis will be performed when 177 PFS events,	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				baseline (Table 1, and Table S1 in the Supplementary Appendix).						months and every other cycle thereafter until progression.		which is 60% of the total planned events, have been accumulated to evaluate cumulative interim safety and efficacy data.Publication: clinical cutoff date March 7, 2016. At a median follow-up of 13.5 months in a protocol-specified interim analysis, 169 events of disease progression or death were observed (in 53 of 286 patients [18.5%] in the daratumumab group vs. 116 of 283 [41.0%] in the control group.	
NCT032 17812	370244 20	very good partial respon se or better rates	Some concer ns	Publication: Patients were randomized by means of a computer-generated randomization schedule. Publication: Demographic and baseline characteristics were generally well balanced between treat- ment groups (Table 1)	Some concer ns	Publication: OCTANS (ClinicalTrials.gov Identifier: NCT03217812) is a multicenter, randomized, open-label trial. Publication: The primary analysis popula- tion was the intent-to-treat (ITT) population.	Low	Figure 1 CONSORT patient flow diagram: of 146 patients allocated to the experimental group, 1 discontinued due to patient withdrawl, 1 physician decision, and 1 for other reason. Of the 74 patients allocated to the control group, 3 patient withdraw, 1 discontinued due to physician decision. Overall, the proportion of patients without available outcome was 3.2%<5%.	Low	Publication: Response and disease progression were assessed by a validated computer algorithm in accordance with International Myeloma Working Group criteria. Response and disease progression were assessed by a validated computer algorithm, although this is an open-label trial.	Some concer ns	Study protocol was not available to fully answer this question.	Some concer ns
NCT022 52172	311416 32	PFS	Low	Publication: The method of randomization is	Low	This is an open-label trial. According to Figure S2.	Low	Figure S2. CONSORT Patient Flow Diagram: of the	Low	Supplement: Progression-free survival was defined as the duration from the date	Low	Protocol AMENDMENT INT-4 date: 22 May	Low

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				randomly permuted blocks. An interactive web response system (IWRS) will be used. Publication: Demographic and clinical characteristics of the two groups were well balanced at baseline (Table 1).		CONSORT Patient Flow Diagram, no protocol deviation was reported. Efficacy was analysis in the intention-to-treat population.		368 patients allocated to daratumumab, 2 patients discontinued treatment due to other reasons. Of the 369 patients allocated to the control group, 1 lost to follow-up. The overall proportion of patient without available outcome was 0.4%		of randomization to either progressive disease, in accordance with the International Myeloma Working Group criteria, or death, whichever occurred first. Protocol: Disease progression must be consistently documented across clinical study sites. This is an open-label trial. Protocol: Disease evaluations will be performed by a central laboratory (unless otherwise specified). This study will use the IMWG consensus recommendations for multiple myeloma treatment response criteria (Durie 2006, Rajkumar 2011) presented in Table 8. For quantitative immunoglobulin, M-protein, and immunofixation measurements in serum and 24 hour urine, the investigator will use results provided by the central laboratory.		2017. The second interim analysis will be performed when 234 PFS events, which is 60% of the total planned events, have been accumulated. The purpose of this interim analysis is to evaluate cumulative interim safety and efficacy data. Publication: cutoff for the primary analysis (September 24, 2018). At a median follow-up of 28.0 months (range, 0 to 41.4), disease progression or death had occurred in 240 patients Reported outcome data appeared consistent with those specified in the study protocol.	
NCT021 95479	292311 33	PFS	Low	Protocol: The method of randomization is randomly permuted blocks. An interactive web based randomization system (IWRS) will be used.Publication: Demographic and clinical characteristics were generally well balanced between the two groups (Table 1,	Low	This is an open-label trial.According to Figure S2. CONSORT Patient Flow Diagram, no protocol deviation was reported.Efficacy was assessed in the intention-to-treat population	High	Figure S2. CONSORT Patient Flow Diagram: of the 350 patients allocated to daratumumab group, 17 discontinued due to other reasons. Of the 356 patients allocated to control group, 29 discontinued due to other reasons.Figure 1 legend: The interim	Low	Publication: Progressive disease was defined according to International Myeloma Working Group criteria.Protocol: Disease progression must be consistently documented across clinical study sites.Protocol: Disease evaluations will be performed by a central laboratory (unless otherwise specified). This	Low	Protocol Amendment 4: date 11 November 2016. The second interim analysis will be performed when approximately 216 PFS events, which is 60% of the total planned PFS events, have been accumulated.Public ation: clinical cutoff	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				and Table S2 in the Supplementary Appendix).				analysis of median progression-free sur-vival was performed after 231 events of disease progression or death had occurred.We assume they did not have available outcome. Overall, the proportion of patients without available outcome was 6.5%. This proportion imbalanced between groups (4.9% and 8.1%). The observed number of events was 5.02 time the number of participants with missing outcome data.No analysis methods that correct for bias or sensitivity analyses was performed.The principal reason for discontinued treatment was "other reason". Not enough information was available to answer this question.		study will use the IMWG consensus recommendations for multiple myeloma treatment response criteria (Durie 2006, Rajkumar 2011). For quantitative immunoglobulin, M-protein, and immunofixation measurements in serum and 24 hour urine, the investigator will use results provided by the central laboratory.		date (June 12, 2017). The interim analysis of median progression-free survival was performed after 231 events of disease progression or death had occurred.Analyses specified in the protocol appeared consistent with those reported in the published paper and supplementary appendix.	
NCT002 95750	190358 58	suppre ssion of testost erone to ≤0.5 ng/mL	Low	Publication: Randomization lists were prepared centrally by the Department of Biometrics, Ferring Pharmaceuticals A/S, using a validated computer program. Publication: The baseline characteristics and demographics were comparable across	Some concer ns	This is an open-label trial. Publication: 26 patients (4%) violated at least one predefined criteria, constituting a major protocol deviation, and thus were excluded from the PP analysis set. No enough information to answer this question.	High	FIG. 2. Patient flow: Of the 620 patients randomized, 6 lost to follw-up, 62 discontinued for other reasons. The overall proportion of patient without available outcome was 11.0%>5%. Not enough information was	Low	Publication: Serum testosterone levels were determined using a validated liquid chromatography system with tandem mass spectrometry assay. PSA was analysed using a validated immunoassay. LH and FSH were analysed using a validated immunochemiluminometric method. Publication: Central	Some concer ns	Study protocol was not available to fully answer this question.	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				the treatment groups (Table 2).		Publication: Both the intent-to-treat (ITT) and per protocol populations were analysed.		available to answer this question.		laboratories were used to measure all serum hormone (testosterone, LH and FSH) and PSA samples. Publication: Central laboratories were used to measure all serum hormone (testosterone, LH and FSH) and PSA samples.			
NCT021 25461	288858 81	PFS and OS	Low	Protocol: The actual study drug given to patients will be determined by the randomisation scheme in the IVRS/IWRS. The randomisation scheme will be produced by a computer software program called GRand (AstraZeneca Global Randomisation system) that incorporates a standard procedure for generating randomisation numbers. Publication: Baseline charac- teristics were well balanced in the two groups (Table 1, and Table S1 in the Supplementary Appendix)	Low	Publication: We report results from an interim analysis of the randomized, double-blind, international, phase 3 PACIFIC study. Publication: Efficacy was assessed in the intention-to-treat popula- tion.	Low	Figure S1. CONSORT Diagram: Of the 476 patients allocated to durvalumab, 4 discontinued due to other reason. Of the 237 patients allocated to placebo, 0 discontinued due to other reason. We assume they did not have available outcome. Overall, the proportion of patients without available outcome was 0.6%.	Low	Publication: The coprimary end points were progression-free survival (according to the Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1, as assessed by means of blinded independent central review) and overall survival. PFS was assessed by blinded independent central review	Low	Protocol Amendment 4 date 11 February 2016. The data cut-off for the interim PFS analysis (first analysis) will be done when 367 PFS events have occurred (52% maturity), approximately 30 months after the first patient is randomised. Publication: As of February 13, 2017 (the data cutoff point for this interim analysis), 371 patients had disease progression (214 in the durvalumab group and 157 in the placebo group). Analyses specified in the protocol appeared consistent with those reported in the published paper and supplementary appendix.	Low

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
NCT030 43872	315909 88	OS	Low	Publication: Treatment was allocated in blocks of six in each stratum via a schedule generated by Parexel (Waltham, MA, USA) who used a computerised randomised list generator.Publication: Baseline demographics and disease characteristics were well balanced between the durvalumab plus platinum–etoposide and platinum–etoposide groups (table 1).	Low	Publication: This randomised, open-label, sponsor-blind, phase 3 trial was performed at 209 sites in 23 countries. Any-cause adverse events of grade 3 or 4 occurred in 163 (62%) of 265 treated patients in the durvalumab plus platinum-etoposide group and 166 (62%) of 266 in the platinum-etoposide group.Publication: Important protocol deviations, defined as those that could substantially affect the completeness, accuracy, or reliability of the study data, or a patient's rights, safety, or wellbeing, were reported in 19 (4%) of 537 ran- domised patients: 11 in the durvalumab plus platinum– etoposide group and eight in the platinum–etoposide group (appendix p 12). Table S3: Important protocol deviations in the intention-to-treat population: 6/11 deviation in the durvalumab group due to patients who deviated from key entry criteria as per theprotocol.Publication: Efficacydatawereanalys edonanintention-to-treat basis including all randomised patients	Low	Publication: There were 336 deaths across the durvalumab plus platinum–etoposide and platinum–etoposide groups (62·6% maturity); 155 (58%) patients had died in the durvalumab plus platinum–etoposide group and 181 (67%) had died in the platinum–etoposide group.Figure 1: Trial profile: of the 268 patients randomly assigned to durvalumab plus platinum–etoposide, 11 discontinued due to withdraw consent, 2 lost to follow-up, 27 other reasons. Of the 269 patients assigned to control group, 19 discontinued due to withdraw consent, 9 other reasons. We assume they did not have available outcome. Overall, the proportion of patients without available outcome was 8.3%. This proportion imbalanced between groups (14.9% and 10.0%). The observed number of events was 5.0 time the number of participants with missing outcome data.Publication: The overall survival benefit with	Low	The primary endpoint was overall survival (time from randomisation to death from any cause).This is a sponsor-blind trial.	Some concer ns	Publication: Data cutoff was March 11, 2019. There were 336 deaths across the durvalumab plus platinum–etoposide and platinum–etoposide groups (62·6% maturity).Protocol 6.0 obtained from clinicaltrials.gov was 16 January 2020. The interim analysis of OS will occur when approximately 318 OS events have occurred (60% maturity) in the durvalumab + tremelimumab + EP and EP treatment arms and approximately 318 OS events have occurred (60% maturity) in the durvalumab + EP and EP treatment arms (approximately 28 months after the first patient is randomized).Analys es specified in the protocol appeared consistent with those reported in the published paper and supplementary appendix.	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								durvalumab plus platinum–etoposide was consistently observed across prespecified patient subgroups defined by baseline clinical and demographic characteristics (figure 2B) and across the prespecified sensitivity analysis of the effect of additional covariates on the HR estimate (data not shown).					
NCT017 72472	305161 02	iDFS	Low	Publication: After written informed consent has been obtained and eligibility has been established and approved, the study site will obtain the patient randomization number and treatment assignment from the interactive voice response system/interactive web response system (IVRS/IWRS). Publication: Baseline charac- teristics were well balanced in the two groups (Table 1, and Table S1 in the Supplementary Appendix).	Some concer ns	This is an open-label trial. Publication: Efficacy was assessed in the intention-to-treat population.	Low	Publication: Invasive disease occurred in 91 patients who received T-DM1 (12.2%) and 165 patients who received trastuzumab (22.2%). Figure S2. Patient Flow Diagram: Of the 743 patienst randomized to trastuzumab emtansine group, 8 lost to follow-up, 5 discontinued treatment due to other reasons. Of 743 patients randomized to trastuzumab, 12 lost to follow-up, 5 discontinued treatment due to other reasons. We assume they did not have available outcome. Overall, the proportion of patients without available outcome was 2.7%. The observed number of events was 8.5	High	Publication: Clinical assessments for disease recurrence occurred every 3 months from the date of randomization to year 2, then every 6 months to year 5, and annually thereafter to year 10. Protocol: Mammograms of any remaining breast tissue should be performed at least annually during follow-up. Bone scan, computed tomography (CT), MRI, and/or PET-FDG scans may be performed as clinically indicated according to the investigator. Samples for the following laboratory tests will be sent to one or several central laboratories or to Roche for analysis. Assessment of the outcome was likely to be influenced by knowledge of intervention received due to the potentially subjective nature of DFS which	Low	Protocol Version 6: See date stamp below (not disclosed). The interim efficacy analysis of IDFS is planned after 67% (n=257) of the targeted IDFS events have occurred, which is estimated to be approximately 48 months after the first patient is enrolled in the study. Publication: The early reporting efficacy boundary was crossed at the prespecified interim analysis, which triggered full trial analysis. Invasive disease occurred in 91 patients who received T-DM1 (12.2%) and 165 patients who received	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								time the number of participants with missing outcome data.		incorporates radiological progression.		trastuzumab (22.2%). Analyses reported in the published article and supplementary appendix appeared consistent with those specified in the protocol.	
NCT008 29166	230201 62	PFS, OS, Safety	Low	Protocol: After receiving approval to enroll, the study site will obtain the patient's study randomization number and randomization assignment from the IVRS.Publication: Baseline demographic and disease characteristics were similar in the two groups (Table 1; see Ta- ble 2 in the Supplementary Appendix for addition- al baseline information)	Some concer ns	Publication: The EMILIA study is a randomized, open-label, international trial.Figure S1 showed the number of patients withdraw from the trial. However, there was no enough information to answer this question.Publication: The primary end points were assessed in the intention-to-treat population.	Low	Figure S1: Of the 495 patients allocated to the T-DM1 group, 129 withdraw due to death (n=129), lost to follow-up (n=1), physician decision (n=2), patient decision (n=46) or other reason (n=2). Of the 496 patients allocated to lapatinib plus capecitabine, 180 withdraw due to death (n=94), lost to follow-up (n=2), physician decision (n=4), patient decision (n=25) or other reason (n=4).We assumed that patients lost to follow-up or withdraw due to "other reason" did not have available outcome. Overall, the proportion of patients without available outcome was 0.7%.	Low	Publication: Overall sur\vival was defined as the time from randomization to death from any cause.This is an open-label trial.Overall survival is an objective endpoint.	Low	Publication: The first data-cutoff date of January 14, 2012. The first interim analysis of overall survival (223 deaths).Protocol Version A4: 30 May 2012. An interim analysis of OS will be performed at the time of the primary efficacy analysis of PFS. Table 2 presents a summary of the planned OS analyses, Interim #1 No. of Deaths=290.Analys es reported in the published article and supplementary appendix appeared consistent with those specified in the protocol.	Some concer ns
NCT012 12991	248817 30	PFS and OS	Low	Protocol: The IVRS/IWRS will assign the patient a study drug bottle number available at the site according to the randomization code. The IVRS/IWRS will also assign the Patient	Low	Publication: The PREVAIL study was a multinational, double-blind trial. Although grade 3 or higher adverse events were more common in enzalutamide-treated patients than in	Low	Figure S1. CONSORT Diagram: Of the 872 patients allocated to enzalutamide, 2 lost to follow-up, 21 patient withdraw consent. Of the 845 patients allocated to	Low	Protocol: The duration of overall survival will be calculated for all randomized patients from the date of randomization to the date of death due to any cause.	Low	Protocol Version 5.0: date 14 March 2013. A formal interim analysis for overall survival will be performed at approximately 516 deaths or 67% of the required total	Low

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				ID Number. Publication: Baseline demographic and disease characteristics were well balanced between the two groups.		placebo-treated patients (43% vs. 37%), these were not considered to be substantial enough to break blinding of participants and personnel. Publication: The coprimary end points were analyzed in the intention-to-treat population.		placebo, 40 withdraw consent. The overall proportion of patient without available outcome was 3.7%.		This is a double-blind trial.		number of death events for the primary overall survival analysis. Publication: The results presented here are based on a cutoff date of September 16, 2013. Fewer deaths occurred in the enzalutamide group than in the placebo group (241 of 872 patients [28%] vs. 299 of 845 patients [35%]). Analyses reported in the published article and supplementary appendix appeared consistent with those specified in the protocol.	
NCT012 88911	267745 08	PFS	Low	Publication: The designated contract research organisation (ICON Clinical Research, Dublin, Ireland) generated the randomisation schedule and then the study site (investigator or designee) contacted the interactive web response system to randomly assign a patient to a study treatment. The permuted block method (block size of four) was used to generate the random allocation sequence.Publication:	Low	Publication: TERRAIN was a double-blind, randomised phase 2 study. Adverse events were similar between groups.Publication: Analysis of the primary endpoint was a between-group comparison of progression-free survival in the full analysis set (all randomly assigned patients).	High	Figure 2: Of 184 patients allocated to enzalutamide, 10 withdrawal by patient. Of the 191 patients allocated to bicalutamide, 2 lost to follow-up, 20 withdrawal by patient.Publication: 99 (54%) of 184 patients in the enzalutamide group had a progression-free survival event based on central radiographic assessments during the study compared with 141 (74%) of 191 patients in the bicalutamide	Low	Publication: The primary endpoint was progression-free survival, defined as the time from randomisation to the first progression event (ie, the earliest incidence of centrally determined radiographic disease progression, a skeletal-related event, or initiation of a new antineoplastic therapy) or death from any cause, whichever occurred first.Protocol: Radiographic evaluation of metastatic disease is determined separately for soft -tissue and bone disease. Radiographic disease assessment for soft tissue disease is based on CT or MRI scan and is defined by	Low	Publication: The data analysis cutoff date was Oct 19, 2014. 99 (54%) of 184 patients in the enzalutamide group had a progression-free survival event based on central radiographic assessments during the study compared with 141 (74%) of 191 patients in the bicalutamide group.Protocol Version 5.0 date 28 July 2014. The final analysis will be conducted with a minimum of 220 progression events	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				Baseline demo- graphic and disease characteristics were well balanced between the two treatment groups, although a larger proportion of patients in the enzalutamide group had a history of cardiac disorders than did those in the bicalutamide group (table 1).				group.The overall proportion of patient without available outcome was 8.5%. This number imbalance between the two groups (5.4% vs 11.2%). The observed number of events was 7.5 time the number of participants with missing outcome data.No analysis methods that correct for bias or sensitivity analyses was reported.Not enough information was available to answer this question.		RECIST 1.1. Radiographic disease assessment for bone lesions is based on bone scan and is considered when a minimum of two new lesions are observed.Publication: Radiographic assessments (CT or MRI and bone scans) were done at screening, weeks 13 and 25, and then every 12 weeks subsequently. Radiographic results were submitted for independent central review.Clinical laboratory assessments (haematology and chemistry) were obtained at every scheduled visit before the administration of the study drug and analysed at a central laboratory.		which provides at least 85% power to detect a target hazard ration of 0.67.Analyses reported in the published article and supplementary appendix appeared consistent with those specified in the protocol.	
NCT022 94461	353977 72	time to prostat e- specifi c antige n progre ssion	Low	Publication: Following screening, eligible patients were centrally randomized 1:1 according to a com- puter-generated, permuted-block randomiza- tion schedule, stratified by the investigative site, to receive enzalutamide (160 mg/day) or placebo. Publication: Baseline character- istics were balanced between treatment groups.	Low	Publication: This was a randomized, double- blind, placebo- controlled, phase III study. Adverse-event incidence was similar between enzalutamide and placebo. Publication: Efficacy and QoL analyses were conducted on the intent- to-treat population.	High	Fig. S1 Patient disposition: Of the 62 patients assigned to enzalutamide, 22 withdraw consent, 1 discontinued follow- up due to other reasons. Of the 190 patients assigned to placebo group, 53 withdrawn consent, 6 discontinued follow- up due to other reasons. We assumed that patients discontinued long-term follow-up due to withdraw consent or "other reason" did not have available outcome. Overall, the proportion of patients	Low	Table S1 Definition of disease progression at study entry and study endpoints: PSA progression was defined as minimum of two rising PSA levels with an interval ofat least 1 week between measurements and a minimumPSA of 2 µg/L or greater at screening. This is a double-blind trial.	Some concer ns	Study protocol was not available to fully answer this question. Study protocol was not available to fully answer this question.	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								without available outcome was 21.1%. The proportion of patients without available outcome imbalanced between the two groups (11.6% vs 31.1%). However, analysis methods that correct for bias or sensitivity analyses was not reported. Publication: One limitation of this study was the high proportion of patients discontinuing treatment and long-term follow-up because of withdrawal of consent, particularly in the placebo group, which may have impacted the availability of longitudinal data in these patients. However, there was no enought information to answer this question.					
NCT016 64923	268115 35	PFS	Low	Protocol: The sponsor or designee will generate the randomization schedule. The investigator or designee will contact the Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) to randomize the patient. The	Low	Publication: STRIVE (Safety and Efficacy Study of Enzalutamide Versus Bicalutamide in Men With Prostate Cancer) was a multicenter, randomized, double-blind phase II trial. Serious adverse events, grade ≥ 3 adverse events, and adverse events resulting in death were reported at	Low	Fig1. CONSORTdiagram: of the 198 patients allocated to enzalutamide, 11 discontinuded intervention due to patient withdrew consent, 5 due to other reaons. Of the 198 patients allocated to bicalutamide, 1 lost to follow-up, 5 withdraw consent, 1	Low	Protocol: Progression-free survival is defined as the time from randomization to the earliest objective evidence of radiographic progression, PSA progression by PCWG2 criteria, or death due to any cause. Patients will be followed for radiographic and PSA progression at regularly scheduled intervals. Radiographic progression is defined by	Low	Publication data cutoff date: February 9, 2015. Although the number of events was not reported, there seemed no interim analysis.Protocol Version 2.0 (date 31 Oct 2012): With an expected drop out of 10%, 360 patients will be	Low

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				investigator or designee will provide the necessary patient identifying information. The study drug kit numbers of the study drug to be dispensed will be provided by the IVRS/IWRS.Publicatio n: Baseline demographic and disease characteristics were well balanced between groups (Table 1 and Appendix Table A3 [online only]).		similar rates in both treatment groups. Publication: The intent-to-treat population included all randomly assigned patients.		discontinued intervention due to other reasons.We assumed that patients lost to follow-up, withdraw consent or discontinued due to "other reason" did not have available outcome. Overall, the proportion of patients without available outcome was 5.8% (8.1% vs 3.5%).		RECIST v1.1 for soft tissue disease or the appearance of 2 or more new lesions on bone scan. Radiographic progression of bone disease at the first scheduled reassessment at Week 13 requires a confirmatory bone scan 6 or more weeks later (at least 4 additional lesions compared to the Screening bone scan).This is a double-blind trial.		required to achieve231 progression events within approximately 30 months (24 months for accrual and6 months for follow-up) from the date the first patient is randomized assuming a uniform accrual of 17 patients per month.Outcome measurements reported in the published article and supplementary appendix appeared consistent with those specified in the protocol.	
NCT020 03924	299494 94	MFS	Low	Protocol: Study site personnel will access the IXRS to randomly assign patients to blinded study treatment after receiving approval by the medical monitor (signed randomization authorization form or email correspondence). Publication: The demographic and clinical characteristics of the patients at baseline were well balanced (Table 1).	Low	This is a double-blind trial. Although adverse events of grade 3 or higher occurred in 31% of the patients receiving enzalutamide, as compared with 23% of those receiving placebo, these were not considered to be substantial enough to break blinding of participants and personnel. Publication: The primary end point was analyzed in the intention-to-treat population.	Low	Figure S1. CONSORT Diagram: of the 933 patients allocated to enzalutamide, 49 withdraw consent, 2 lost to follow-up, 18 discontinued intervention for other reasons. Of the 468 patients allocated to enzalutamide, 34 withdraw consent, 1 lost to follow-up, 19 discontinued intervention for other reasons. Publication: At the time of data cutoff, 219 patients (23%) in the enzalutamide group and 228 (49%) in the placebo group had had a primary end-point event.	Low	Publication: Radiographic imaging was performed every 16 weeks until radiographic progression was con- firmed. Independent radiologists who were un- aware of the trial-group assignments determined the status of progressive disease according to the Response Evaluation Criteria in Solid Tumors, version 1.1, for soft tissue and the appearance of one or more lesions for bone (bone lesions that were found in a single region necessitated con- firmation with a second imaging method). Publication: Independent radiologists who were un-aware of the trial-group assignments determined	Low	Protocol (Amendment 3, 11 August 2017): The primary analysis of MFS will be performed when approximately 440 MFS events based on independent central radiology review are observed. Publication: At the time of data cutoff, 219 patients (23%) in the enzalutamide group and 228 (49%) in the placebo group had had a primary end-point event. Outcome measurements reported in the published article	Low

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								We assumed that patients lost to follow-up, withdraw consent or discontinued due to "other reason" did not have available outcome. Overall, the proportion of patients without available outcome was 8.8%). This number imbalance between the two groups (7.4% vs 11.5%. The observed number of events was 3.6 time the number of participants with missing outcome data. Publication: The results of a prespecified sensitivity analysis in which deaths without radiographic progression were included regardless of timing were consis-tent with the results of the primary analysis of metastasis-free survival (hazard ratio for radio- graphic progression or death, 0.30; 95% CI, 0.25 to 0.36) (Table S1 in the Supplementary Appendix).		the status of progressive disease.		and supplementary appendix appeared consistent with those specified in the protocol.	
NCT023 14819	299467 28	OS	Low	Protocol: The randomized number of each subject will be assigned to the investigator through the interactive web	Some concer ns	Publication: FRESCO (Fruquintinib Efficacy and Safety in 3+ Line Colorectal Cancer Patients) was a randomized, double-	Low	Figure 1: By the end of study period, of the 278 patients randomized to fruquintinib group, 4 withdraw informed	Low	Publication: The primary efficacy outcome was overall survival, defined as the time from randomization until death.Publication: The investigators, sponsor, and	Low	Publication cutoff date (January 17, 2017): 297 deathsProtocol Version 3.0, dated 5 Dec 2014: The final	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				response system (IWRS).Publication: Most baseline demographics, disease characteristics, and prior treatments were similar between the treatment groups, except the proportion of men was higher in the placebo group than in the fruquintinib group.		blind trial. Grades 3 and 4 treatment-emergent adverse events occurred in 61.2% (170) of patients who received fruquintinib and 19.7% (27) who received placebo. We assumed that such differences could potentially break the blinding of the trial, and resulting in participants, carers and personnel correctly guessing their treatment allocation.There is no enough information to answer this question.Publication: The efficacy analyses were based on the intention-to- treat population.		consent and did not provide follow-up information, 3 lost to follow-up. Of the 138 patients randomized to the placebo group, 4 withdraw informed consent and did not provide follow-up infromation, 1 lost to follow-up.The overall proportion of patients without available outcome was 2.9%		patients were blinded to treatment allocation until database lock (sponsor) or study completion (investigators).		analysis of OS will be performed when about 280 OS (or death) events have been observed in 7 months after the end of enrollment.Outcome measurements reported in the published article and supplementary appendix appeared consistent with those specified in the protocol.	
NCT022 04644	329287 96	major molec ular respon se at 6 month s	Some concer ns	the only information about randomization methods is a statement that the study is randomized. Publication: Baseline characteristics and distributions of the Sokal risk score were well-balanced in the two study groups (Table 1).	Low	This is an open-label trial. According to Table 2, there was no protocol deviation. Publication: The efficacy analysis populations included the intention-to-treat population.	Low	Table 2: Of the 196 patients randomized to flumatinib, 3 withdraw consent, 1 lost to follo-up. Of the 197 patients randomized to imatinib, 5 withdraw consent. The overall proportion of patient without available outcome was 2.3% < 5%.	Low	Publication: RT- PCR assays were performed in a central laboratory (KingMed, with kit provided by MolecularMD), with the ABL gene as reference gene. The assay was standardized through an exchange of samples from patients with the molecular laboratory in Adelaide, Australia. Publication: RT- PCR assays were performed in a central laboratory.	Some concer ns	Study protocol was not available to fully answer this question. Study protocol was not available to fully answer this question.	Some concer ns
NCT031 34872	333478 29	PFS	Low	Protocol: This study will use the block randomization method. Randomization is performed using the	Low	This is an open-label trial. According to Figure 1, only 2/209 patients deviated protocol.	High	Figure 1: Of 209 patients assigned to receive camrelizumab, 12 withdraw consent, 4 were withdrawn by	Low	The two primary endpoints were progression-free survival per blinded independent central review, in all patients and in patients who were PD-L1	Low	Publication: As of March 31, 2019, 205 events of progression or death had occurred. The number of	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				HRTAU RTSM system. Publication: Baseline characteristics were generally well balanced between the groups, except the proportion of patients with a PD-L1 tumour proportion score of 1% or higher (138 [67%] of 205 patients in the camrelizumab plus chemotherapy group vs 117 [57%] of 207 patients in the chemotherapy alone group; table 1).		Protocol: Full analysis set (FAS): Based on the intention-to-treat (ITT) principle, all randomized subjects who have received at least one dose of study medication. Publication: Efficacy was assessed in the full analysis set, including all randomised patients with at least one dose of the study treatment.		investigators. Of the 210 patients assigned to receive chemotherapy, 25 withdraw consent, 6 were withdrawn by investigators. The overall proportion of patients without available outcome was 11.4%. This number imbalanced between the two groups (7.6% vs 14.8%). According to the Protocol, when subjects are not censored on the date of study discontinuation or the date of starting new anti-tumor treatment, the scheduled sensitivity analysis will confirm PFS based only on the time of radiologically confirmed progression events. However, no analysis methods that correct for bias or sensitivity analyses was reported. No information was available to answer this question.		positive, defined as the time from randomisation to Response Evaluation Criteria in Solid Tumours-defined progression or death from any cause. Tumour imaging assessments were done every 6 weeks for the first 54 weeks and every 12 weeks thereafter. The outcome was assessed by blinded independent central review.		progression-free survival events at the interim analysis was more than planned, mainly due to the delays in process of blinded independent central review (periodic review; batch by batch). Protocol Final Version 3.0, 25 Sep., 2017: Interim analysis: the interim analysis is performed when at least 172 PFS events are observed in the all subjects population. Outcomes reported in the published article and supplementary appendix appeared consistent with those specified in the protocol.	
NCT030 99382	324160 73	OS	Low	Protocol: The generation, review, quality assurance, testing and validation of the randomized procedure will be in strict accordance with applicable Hengrui SOP (HRSOP STAT	Low	This is an open-label trial.According to Figure 1, there was only two protocol deviation.Publication: All patients who were randomly assigned and received at least one dose of treatment were	Low	Figure 1: Of the 228 patients received camrelizumb, 6 withdraw consent. Of the 220 patients received chemotherapy, 21 withdraw consent.Protocol:	Low	The primary endpoint was overall survival, which was defined as the time from randomisation to death from any cause.This is an open-label trial.Overall survival is an objective endpoint.	Low	Publication: data cutoff date on May 6, 2019. 172 (75%) deaths occurred in the camrelizumab group and 191 (87%) in the chemotherapy group.Protocol	Low

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				01 randomization and blinding). Randomization will be performed in the HRTAU RTSM system. However, the sequence generation process was not reported.According to Table 1, the baseline seems balanced between the two groups.		included in the full analysis set.		Withdrawal of informed consent refers to the subject withdrawing the consent to be further contacted, or no longer agreeing to provide information from a previously authorized person.Publication: 172 (75%) deaths occurred in the camrelizumab group and 191 (87%) in the chemotherapy group. The overall proportion of patient without available outcome was 6.0%. This number imbalanced between the two groups (2.6% vs 9.5%). The observed number of events was 9.7 time the number of participants with missing outcome data (28.7 vs 9.1). Figure S1. Kaplan-Meier plot of overall survival after sensitivity analysis to adjust the postdiscontinuation anti-PD-1 or anti-PD-L1 treatments: HR=0.71 (0.56-0.88). This is similar to the primary analysis (HR=0.71 [0.57-0.87]).				Version Number: 5.0 Version Date (12 Apr., 2018): at least 365 OS events need to be collected to obtain a power of 80% according to the calculation by East v6.3.Outcomes reported in the published article and supplementary appendix appeared consistent with those specified in the protocol.	
NCT037 07509	341741 89	PFS	Low	Publication: Allocation was done via an interactive web-response system with a block size of four. An investigator at	Low	This is a double-blind trial. Adverse-event incidence was similar between enzalutamide and placebo.	High	Figure 1: Of the 134 patients assigned and received camrelizumab plus chemotherapy, 13 withdraw. Of the 129	Low	Publication: Tumour response was assessed by an independent review committee and investigators, according to RECIST version 1.1, with	Low	Publication: As of data cutoff on June 15, 2020, there were 149 disease progression events per independent	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				each hospital site registered patients via the web response system and assigned them to a treatment group on the basis of the randomisation sequences generated by an independent randomisation group. Publication: Baseline demographic and disease characteristics were well balanced between treatment groups (table 1).		Publication: Efficacy and safety analyses were done in all patients who underwent randomisation and received at least one dose of study treatment (full analysis set).		patients assigned and received placebo plus chemotherapy, 13 withdraw. Publication: As of data cutoff on June 15, 2020, there were 149 disease progression events per independent review committee or death. The overall proportion of patient without available therapy was 9.9 % (9.7% vs 10.1%). The observed number of events was 5.7 time the number of participants with missing outcome data. No analysis methods that correct for bias or sensitivity analyses was reported. No information was available to answer this question.		CT and MRI scans every 6 weeks for the first 16 months, and every 12 weeks thereafter. Publication: During the radiological review process, the independent radiologists were masked to treatment group assignment to avoid potential bias.		review committee or death. Protocol Version 4.0, September 16, 2020: The interim analysis of PFS will be performed when 121 (60%) events are collected. Analyses specified in the protocol appeared consistent with those reported in the published paper and supplementary appendix.	
NCT036 91090	345198 01	OS and PFS	Low	Publication: Randomization was done using a centralized interactive web-response system with the block size randomly generated as 4 or 6. According to Table 1, the baseline seems similar between the two groups.	Low	This is a double-blind trial. Treatment-related adverse events of grade 3 or higher occurred in 189 patients (63.4%) in the camrelizumab-chemotherapy group and 201 (67.7%) in the placebo-chemotherapy group. Protocol: The ITT set is the primary analysis set for the efficacy analysis of this study.	Low	Figure 1: Of the 596 patients randomized, only 1 lost to follow-up. Protocol: Survival status should still be followed even if the subject refuses to visit the study site, unless the subject withdraws consent to provide further information or consent to be further contacted.	Low	The coprimary end points were progression-free survival assessed by the independent review committee (the time from randomization to disease progression or death from any cause, whichever occurred first) and overall survival (the time from randomization to death from any cause). This is a double-blind trial.	Low	Protocol Version 6.0, 28 Sep., 2020: The interim analysis will be performed when 269 (66%) OS events (approximately 22.1 months) are collected. Publication: data as of October 30, 2020 (planned cutoff date). A total of 309 deaths (51.8%) deaths occurred. Analyses specified	Low

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
												in the protocol appeared consistent with those reported in the published paper and supplementary appendix.	
NCT036 68496	349231 63	PFS	Low	Publication: Investigator at each site regis- tered patients through the web response system and assigned them on the basis of a randomization sequence generated by the sponsor's randomization specialist with Statistical Analysis System version 9.4 (SAS Institute, Cary, NC). The patients, investigators, evaluators, and the sponsor were blinded to treatment allocation.Publication: Baseline characteristics were well balanced between treatment groups (Table 1).	Low	Publication: CameL-sq, a double-blind, randomized phase 3 trial. Grade 3 or more treatment-related adverse events occurred in 142 (74%) patients in the camrelizumab group and 141 (72%) patients in the placebo group.Publication: All efficacy analyses were performed in the full analysis set, including all eligible patients who were randomized and received at least one dose of study treatment.	Low	Figure S1: Of the 193 patients received camrelizumab, 14 withdraw consent, 2 discontinued due to other reasons. Of the 196 patients received placebo, 11 withdraw consent, 1 lost to follow-up, 1 discontinued due to other reasons. Publication: At data cutoff, 123 (64%) patients in the camrelizumab plus chemotherapy group and 167 (85%) patients in the placebo group had disease progression or died.We assumed that patients lost to follow-up, withdraw consent or discontinued due to "other reason" did not have available outcome. Overall, the proportion of patients without available outcome was 7.5% (8.3% vs 6.6%). The observed number of events was 10 times the number of participants with missing outcome data.	Low	Publication: The primary end point was BICR-assessed PFS, defined as the time from randomization to the first RECIST version 1.1–defined disease progression or death from any cause, whichever occurred first. Tumor imaging with high-resolution computed tomography or contrast-enhanced magnetic resonance imaging was performed every 6 weeks for the first 48 weeks and every 9 weeks thereafter until radiographic disease progression. Complete or partial response or stable disease was required to be confirmed with a subsequent scan at least 4 weeks after the initial documentation.Publication: progressive disease is confirmed by blinded independent central review.	Some concer ns	Study protocol was not available to fully answer this question.Study protocol was not available to fully answer this question.	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
NCT017 61266	294338 50	OS	Low	Publication: A randomisation block size of 2 was used. The randomisation sequence was generated by an independent statistician by the system vendor, and the investigators obtained the randomisation assignments from the system directly. Publication: Patient baseline characteristics were similar be- tween treatment groups, except for baseline hepatitis C aetiology and α-fetoprotein concentrations (table 1).	Low	Publication: This was an open-label, phase 3, multicentre, non-inferiority trial. Publication: Major protocol deviations were few and balanced. Publication: The efficacy analysis followed the intention-to-treat principle.	Low	Figure 1: Of the 476 patients received lenvatinib, 3 lost to follow-up, 9 withdraw consent, 3 discontinued treatment for other reasons. Of the 475 patients received sorafinib, 1 lost to follow-up, 5 withdraw consent, 7 discontinued for other reasons. We assumed that patients lost to follow-up, withdraw consent or discontinued due to "other reason" did not have available outcome. Overall, the proportion of patients without available outcome was 2.9% (3.2% vs 2.7%).	Low	Publication: The primary endpoint was overall survival, measured from the date of randomisation until the date of death from any cause. This is an open-label trial. Overall survival is an objective endpoint.	Some concer ns	Figure 1 legend: At the time of data cutoff (Nov 13, 2016; for the required 700 death events), 701 deaths had occurred (351 in the lenvatinib arm, 350 in the sorafenib arm). However, study protocol was not available to fully answer this question. However, study protocol was not available to fully answer this question.	Some concer ns
NCT013 21554	256712 54	PFS	Low	Protocol: Randomization will be performed centrally by an interactive voice/web response system (IVRS/IWRS) vendor.Publication: Block randomization was performed centrally by means of an interactive voice-response and Web-response system.Publication: The baseline character- istics of the patients were similar in the two groups (Table 1).	Some concer ns	This is a double-blind trial. The incidence of treatment-related adverse effects (of all grades) as assessed by the investigator was 97.3% in the lenvatinib group and 59.5% in the placebo group, and the incidence of treatment-related adverse effects of grade 3 or higher was 75.9% in the lenvatinib group and 9.9% in the placebo group. We assumed that such differences could potentially break the blinding of the trial, and resulting in participants, carers and personnel correctly guessing their	Low	Figure 1: Of the 261 patients assigned to receive and received lenvatinib, withdrew consent. Of the 131 patients assigned to receive and received placebo, 1 discontinued study drug due to other reason.The overall proportion of patient without available outcome was 1.3%.	Low	Publication: Tumor assessments, consisting of computed tomographic or magnetic resonance imaging of the neck, chest, abdomen, pelvis, and all other known sites of disease, were evaluated in a blinded fashion by a central imaging laboratory, according to RECIST, version 1.1, criteria, every 8 weeks in the randomization phase.The disease progression was assessed by independent radiologic review.	Low	Protocol v1.0 (19 Jan 2011).Amendment 05 (date19 Feb 2014): A total of approximately 214 progression events or deaths prior to disease progression will be required for the final analysis of PFS.Publication: data cutoff (November 15, 2013). At the time of the primary analysis of progression- free survival, there were 220 primary events.Outcome measurements reported in the	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
						treatment allocation.There is no enough information to answer this question.Publication: The primary end point was progression-free survival in the intention-to-treat population (all patients who underwent randomization).						published article and supplementary appendix appeared consistent with those specified in the protocol.	
NCT006 99751	238630 50	OS	Low	Protocol: Randomisation will occur through an IVRS system. Site users will call into the IVRS and enter their user specific caller identification number and PIN code. Publication: Baseline clinical and demographic characteris- tics were well balanced between the study groups (Table 1)	Low	This is a double-blind trial. Grade 3 or 4 adverse events (339 patients [56%] vs. 188 patients [62%]), serious adverse events (281 patients [47%] vs. 181 patients [60%]), and study-drug discontinuation because of adverse events (99 patients [16%] vs. 62 patients [21%]). Publication: The intention-to-treat popula- tion included all randomly assigned patients.	High	Figure S1B: Number (%) of patients withdrawn early from the study 582 (63%). Patients who withdrew prior to their 3-year follow-up visit were considered to have withdrawn early from the study. Protocol: It is planned that patients who withdrew early from the study will be followed for survival. For withdrawals with no survival status data or who are lost to follow up, time to death will be censored at the time of withdrawal (i.e. the last date on which these patients were known to be alive). As this is the interim analysis with a follow-up duration less than 3 years, there is no information about the number of missing outcome data. No analysis methods that correct for bias or sensitivity analyses was reported.	Low	Publication: The primary end point was overall survival, defined as the time from randomization to the date of death, regardless of cause. This is a double-blind trial.	Low	Protocol 6 Amendment date: 24 June 2011: Under these assumptions, a total of 900 patients are required, with the final analysis to be conducted after 640 events have been observed. The formal interim efficacy analysis, as described in the protocol, is planned to be performed after approximately 50% of the events have been observed. With the increase in power, this corresponds to approximately 320 events. Publication: A prespecified interim analysis, conducted when 314 deaths had occurred, assessed the effect of radium-223 versus placebo on survival. An updated analysis, when 528 deaths had occurred, was	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								Not enough information was available to answer this question.				performed before crossover from placebo to radium-223.	
NCT026 13507	306599 87	OS	Low	Publication: Patients were randomly assigned 2:1 to receive nivolumab or docetaxel using an interactive voice response system. Randomization was performed via permuted blocks separately within each stratum, with a block size of sixPublication: Baseline characteristics of all randomized patients were generally well balanced between treatment groups (Table 1).	Some concer ns	Publication: CheckMate 078 was a randomized, open-label, phase III clinical trialNot enough information was available to answer this question.Protocol: Approximately 500 subjects will be randomized (Intent-To-Treat (ITT) population) to the nivolumab and docetaxel arms in a 2:1 ratio.	Low	Figure S2. CONSORT Diagram: of the 338 patients assigned to nivolumab, 1 lost to follow-up. Of the 166 patients randomly assigned to docetaxel, 2 withdrew consent.The overall proportion of patient without available outcome was 0.6%.	Low	Publication: The primary endpoint of the study was OS, defined as the time from randomization to the date of death.This is an open-label trial.Overall survival is an objective endpoint.	Low	Publication: The database lock for the current analyses was October 27, 2017. Based on 301 deaths at the interim analysis (78.8% of the number of deaths required for final analysis), the boundary for statistical significance required the p value to be less than 0.0231.Protocol (revised date 13-Dec-2017): Overall survival (OS) is the primary endpoint of this study. The final analysis will be performed when a total of 382 OS events have occurred. There will be one interim analysis of OS (DMC monitored) when at least 291 OS events have been observed (76% of total events).Outcome measurements reported in the published article and supplementary appendix appeared consistent with	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
												those specified in the protocol.	
NCT021 05636	277187 84	OS	Low	Protocol: The randomization procedures will be carried out via permuted blocks within each stratum. Publication: The treatment groups were balanced with respect to most demographic and clinical characteristics (Table 1), although the standard-therapy group included higher percentages of patients 65 years of age or older and of patients who had never smoked.	Some concer ns	This is an open-label trial. Not enough information was available to answer this question. Publication: Analyses of baseline characteristics and effi- cacy followed the intention-to-treat principle.	High	Figure S1: of the 240 patients allocated to nivolumab, 195 patient discontinued treatment. Of the 121 patients allocated to standard therapy, 108 discontinued treatment. However, the reason for discontinue treatment was not reported. No analysis methods that correct for bias or sensitivity analyses was reported. There was not enough information to answer this question.	Low	Publication: The primary end point was overall survival, which was defined as the time from randomization to the date of death from any cause. This is an open-label trial. Overall survival is an objective endpoint.	Low	Publication: The data cutoff point for the analyses of over- all survival, progression-free survival, and safety was December 18, 2015, which was the date of the planned interim analysis. Among 361 patients who underwent randomiza- tion, 133 deaths (55.4% of patients) occurred in the nivolumab group and 85 deaths (70.2% of patients) occurred in the standard-therapy group. Protocol revised date 11-Feb-2016: One formal interim analysis of OS is planned for this study. The interim analysis of OS is planned after 70% (195) of the total required number of OS events have been reached.	High
NCT022 67343	289930 52	OS	Low	Publication: Following enrolment by the principal investigators at each study site, patients were randomly assigned (2:1) via an interactive web response system to receive nivolumab	Low	This is a double-blind trial. Grade 3 or 4 treatment-related adverse events occurred in 34 (10%) of 330 patients who received nivolumab and seven (4%) of 161 patients who received	High	Figure 1: of the 330 patietns received nivolumab, 25 discontinued treatment due to other reasons. Of the 163 patients received placebo, 19 discontinued	Low	The primary endpoint was overall survival.This is an open-label trial.Overall survival is an objective endpoint.	Some concer ns	Study protocol was not available to answer this question.Study protocol was not available to answer this question.	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				or placebo.Publication: Baseline patient and disease characteristics were balanced across treatment groups (table 1).		placebo; treatment-related adverse events led to death in five (2%) of 330 patients in the nivolumab group and two (1%) of 161 patients in the placebo group. These were not considered to be substantial enough to break blinding of participants and personnel.Publication: The primary endpoint was overall survival in the intention-to-treat population.		treatment due to other reasons.Publication: The final analysis was done when 367 overall survival events had occurred. 226 (68.5%) of 330 patients in the nivolumab group died versus 141 (86.5%) of 163 patients in the placebo group.We assumed these patients did not have available outcome. The overall proportion of patient without outcome was 8.9%. This number imbalanced between the two groups (7.6% vs 11.7%). The observed number of events was 8.3 time the number of participants with missing outcome data (9.04 vs 7.4). No analysis methods that correct for bias or sensitivity analyses was reported.Not enough information was available to answer this question.				
NCT028 99299	334854 64	OS	Low	Publication: Patients were enrolled and randomly assigned (1:1) using an interactive web response system. Publication: Baseline characteristics were well balanced between treatment groups (table 1).	Some concer ns	This is an open-label trial. Figure 1: 1/303 vs 11/302 patients withdraw consent after randomization. However, the underlying reason was not reported. Publication: The primary	Low	Figure 1: Of the 303 patients assigned to nivolumab plus ipilimumab, 6 patient withdrew consent, 13 discontinued due to other reason, 4 reason not reported. Of the 284 patients received allocated intervention, 3 patient withdrew consent, 1	Low	Publication: Overall survival was defined as the time from randomisation to the date of death due to any cause. This is an open-label trial. Overall survival is an objective endpoint.	Low	Publication (database lock April 3, 2020): At the time of database lock for the interim analysis, 419 patients had died (89% of total anticipated events). Protocol revised date 25-Apr-2019: A formal interim analysis for	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
						endpoint was overall survival in all patients randomly assigned to treatment after the US Food and Drug Administration provided guidance to change progression-free survival from a coprimary endpoint to a secondary endpoint .		lost to follow-up, 2 for other reasons, 189 reason not reported (176 completed six cycles). Publication: At the time of database lock for the interim analysis, 419 patients had died (89% of total anticipated events); We assumed that patients withdrew consent, discontinued due to "other reason", and lost to follow-up did not have available outcome. The overall proportion of patient without outcome was 3.9% (6.3% vs 1.4%). The observed number of events was 18.2 times the number of participants with missing outcome data.				superiority of OS in subjects who were randomized to Arm A vs. subjects who were randomized to Arm B will be performed on all randomized subjects when ap-proximately 403 deaths have been observed (approximately 85% (403/473) of the total number of deaths required for the final analysis). Outcome measurements reported in the published article and supplementary appendix appeared to be consistent with those specified in the protocol.	
NCT028 72116	341021 37	OS and PFS (in patient s whose tumou rs had a PD-L1 combi ned positiv e score (CPS) of five or more)	Low	Publication: Randomisation was done using interactive web response technology (block sizes of six)Publication: Baseline characteristics were balanced across the treatment groups in the primary population (patients with a PD-L1 CPS of ≥5) and all randomly assigned patients (table 1, appendix p 4).	Low	This is an open-label trial.Figure 1 legend: Relevant protocol deviations were noted in 21 (1%) patients—ie, use of prohibited on-treatment anticancer therapy (n=12), baseline Eastern Cooperative Oncology Group performance status more than 1 (n=5), incorrect cancer diagnosis (n=2), and one case each of prohibited previous anticancer therapy (at study entry) and no baseline (measurable or evaluable)	High	Figure 1: Of the 789 patients assigned to nivolumab plus chemotherapy, 35 discontinued treatment due to patient request or consent withdrawal, 2 loss to follow-up. Of the 792 patients assigned to chemotherapy alone, 54 discontinued treatment due to patient request or consent withdrawal, 2 loss to follow-up.We assumed that patients discontinued due to "patient request or	Low	Publication: Dual primary endpoints for the nivolumab plus chemotherapy versus chemotherapy alone groups were OS (time from randomisation to death) or progression- free survival (PFS; time from randomisation to the date of first documented tumour progression or death) by blinded independent central review per RECIST version 1.1, evaluated in patients with a PD-L1 CPS of five or more.This is an open-label trial and we assessed overall survival endpoint here.Overall survival is an objective endpoint.	Low	Protocol reivised date 16-Sep-2019: The interim analysis will be conducted after at least 12 months minimum follow-up, and the final analysis will be conducted after at least 24 months minimum follow-up.Publication: Both primary endpoints were met. At a minimum follow-up (time from concurrent randomisation of the last patient to data cutoff of May 27,	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
						disease.Publication: The primary population comprised all randomly assigned patients whose tumours had a PD-L1 CPS of five or more.		consent withdrawal", and lost to follow-up did not have available outcome. The overall proportion of patient without outcome was 5.9% (4.7% vs 7.1%). According to Fig 2A, at the 12-month after randomization, the proporiton of censor was imbalanced between the groups (14/261 [5.4%]vs 21/211 [10.0%]).No analysis methods that correct for bias or sensitivity analyses was performed.No information was available to answer this question.				2020) of 12.1 months, nivolumab plus chemotherapy showed superior OS.Outcome measurements reported in the published article and supplementary appendix appeared to be consistent with those specified in the protocol.	
NCT008 78709	268749 01	iDFS	Low	Publication: The randomisation sequence was generated with permuted blocks, then implemented centrally via an interactive voice and web-response system. Publication: Baseline characteristics were similar between groups (table 1).	Some concer ns	This is an double-blind trial. The most common grade 3-4 adverse events in patients in the neratinib group were diarrhoea (grade 3, n=561 [40%] and grade 4, n=1 [<1%] vs grade 3, n=23 [2%] in the placebo group), vomiting (grade 3, n=47 [3%] vs n=5 [<1%]), and nausea (grade 3, n=26 [2%] vs n=2 [<1%]). We assumed that such differences could potentially break the blinding of the trial, and resulting in participants, carers and personnel correctly guessing their treatment allocation. There is no enough information to answer this question.	Low	Figure 1: of the 1420 patients allocated to neratinib, 4 lost to follow-up, 23 discontinued treatment due to other reasons, 1 missing. Of the 1420 patients allocated to placebo, 4 lost to follow-up, 17 discontinued due to other reasons. Publication: At 2 year follow-up, 70 invasive disease-free survival events had occurred in patients in the neratinib group versus 109 events in those in the placebo group. We assumed that patients lost to follow-up, discontinued due to "other reason", and	Low	Publication: Theprimaryendpointwasinv asivedisease-freesurvival at 2 years after randomisation where invasive disease was defined as invasive ipsilateral tumour recurrence, invasive contralateral breast cancer, local or regional invasive recurrence, distant recurrence, or death from any cause (appendix p 13). This is a double-blind trial.	Some concer ns	Study protocol was not available to answer this question fully. Study protocol was not available to answer this question fully.	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
						Publication: Analysis was by intention to treat.		missing did not have available outcome. The overall proportion of patient without outcome was 1.7%, although the observed number of events was only 3.9 time the number of participants with missing outcome data.					
NCT026 55016	315627 99	PFS (in patient s who had tumors with homol ogous-recom binatio n deficie ncy and in those in the overall popula tion)	Low	Publication: Randomization was performed in a double-blind manner with the use of an interactive Web- response system.Publication: The demographic and clinical characteristics of the patients at baseline were balanced in the two trial groups (Table 1).	Some concer ns	This is an double-blind trial. According to Table 2, the proportions of grade 3 or 4 adverse event were 70.5% vs 18.9%. We assumed that such differences could potentially break the blinding of the trial, and resulting in participants, carers and personnel correctly guessing their treatment allocation.There is no enough information to answer this question.Protocol: The ITT population is the primary analysis population for the efficacy analysis.	High	Figure 1: of the 487 patients assigned to receive niraparib, 12 withdrew, 19 discontinued treatment due to other reasons. Of the 246 patients assigned to receive placebo, 1 withdrew, 7 discontinued treatment due to other reasons.Figure 3: The primary efficacy analysis was performed after disease progression or death had occurred in 154 patients with homologous-recombination deficiency and in 386 patients in the overall population.We assumed that patients withdraw or discontinued due to "other reason" did not have available outcome. The overall proportion of patient without outcome was 5.3%. This proportion was imbalanced between groups	Low	Publication: We performed computed tomography or mag- netic resonance imaging to assess progressive disease every 12 weeks until treatment discon- tinuation. The objective assessment of progres- sive disease was determined by central radio- logic and clinical review in a blinded manner, according to RECIST (Response Evaluation Criteria in Solid Tumors), version 1.1Publication: The objective assessment of progres- sive disease was determined by central radio- logic and clinical review in a blinded manner.	Low	Protocol Date of Amendment 3 12 February 2018: The study is sized for a minimum of 258 PFS events.Publication: data cutoff on May 17, 2019: The primary efficacy analysis was performed after disease progression or death had occurred in 154 patients with homologous-recombination deficiency and in 386 patients in the overall population.Outcome measurements reported in the published article and supplementary appendix appeared to be consistent with those specified in the protocol.	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								(6.4% vs 3.3%). The observed number of events was 9.9 times the number of participants with missing outcome data. No analysis methods that correct for bias or sensitivity analyses was performed.No information was available to answer this question.					
NCT018 47274	277172 99	PFS	Low	Protocol: Each patient who completes the study screening assessments, meets all eligibility criteria, and is accepted for the study will be assigned a unique identification number and will receive the corresponding treatment/sequence according to a randomization scheme generated by the IWRS vendor. The randomization schedule will be prepared by the IWRS vendor using a validated program. IWRS personnel not involved with any of the protocol operations will prepare the randomization schedule. Publication: Demographic and clinical characteristics were well balanced in the two cohorts at baseline (Table 1).	Low	This is an double-blind trial. Although 14.7% of patients who received niraparib discontinued treatment because of an adverse event of any grade, as compared with 2.2% in the placebo group, these were not considered to be substantial enough to break blinding of participants and personnel. Publication: Efficacy data were analyzed in the intention- to-treat population, which was defined as all the patients who underwent randomization in each of the two cohorts.	Low	Publication: The efficacy analysis was performed after the occurrence of disease progression or death in 103 patients in the gBRCA cohort and in 101 in the HRD-positive subgroup of the non-gBRCA cohort. At that time, 213 such events had occurred in the overall non-gBRCA cohort. We assumed these patientd did not have available outcome. The overall proportion of patients without outcome was 2.0%.	Low	Publication: The primary end point of the duration of pro- gression-free survival was defined as the time from treatment randomization to the earliest date of disease progression or death from any cause. Publication: Independent radiologic review and central review by a clinician who was unaware of study-group assignments were used to define disease progression, with an identical schedule of assess- ments used in the two cohorts.	Low	Protocol Date of Amendment 09 March 2016: The gBRCAmut cohort sample size is determined based on the assumption that niraparib will result in an improvement in median PFS of 4.8 to 9.6 months (corresponding to a hazard ratio [HR] = 0.50) (niraparib relative to placebo). For a true HR = 0.50, 100 PFS events will provide > 90% power assuming a 2:1 randomization (1-sided alpha = 0.025). Publication: The efficacy analysis was performed after the occurrence of disease progression or death in 103 patients in the gBRCA cohort and in 101 in the HRD-	Low

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
												positive subgroup of the non-gBRCA co- hort. At that time, 213 such events had occurred in the overall non-gBRCA cohort.	
NCT025 78680	296588 56	OS and PFS	Low	Publication: Randomization was performed by means of an integrated interactive voice-response and Web-response system (i.e., treatment assignments could be provided by following a series of prompts on a touch-tone phone or by following the same prompts in a Web-based portal).Publication: The baseline demographic and disease characteristics were gen- erally well balanced between the groups, although the percentage of men was higher in the pembrolizumab-combination group than in the placebo-combination group (62.0% vs. 52.9%, P = 0.04) (Table 1).	Low	This is an double-blind trial.Publication: Efficacy was assessed in the intention-to-treat population, which included all the patients who had undergone randomization.	Low	Figure S2: Of the 410 patients allocated to pembrolizumab group, 16 withdrew consent. Of the 206 patients allocated to placebo group, 8 withdrew consent. Protocol: Subjects will have post- treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, becoming lost to follow-up or entering the Second Course Phase.The proportion of patient without outcome data was 3.9%.	Low	Publication: The two primary end points were overall survival (time from randomization to death from any cause) and progression-free survival (time from random- ization to disease progression, as assessed by blinded, independent central radiologic review, or death from any cause, whichever occurred first).This is a double-blind trial.	Low	Publication: Results were reviewed by the external monitoring com- mittee on January 10, 2018. 235 deaths in the intention-to-treat population.MK-3475-189-07 Final Protocol (6-Nov-2017): With 242 deaths at IA1, the study has ~37% power for detecting an OS HR of 0.7.Analyses reported in the published article appeared consistent with those specified in the protocol.	Low
NCT022 20894	309559 77	OS	Low	Publication: Randomisation was computer generated, accessed via an interactive voice-response and integrated web-	Some concer ns	This is an open-label trial. Figure 1: Of the 637 patients randomly assigned to chemotherapy group, 46 (7.2%) patients	High	Figure 1: of the 637 patients allocated to pembrolizumab, 3 withdrew because eligibility criteria not met, 26 withdrew consent. Of the 637	Low	Primary endpoints were overall survival This is an open-label trial. Overall survival is an objective endpoint.	Low	MK-3475-042-06 Final Protocol (09-Jan-2018): Amendment introducing third primary endpoint of OS in the PD-L1	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				response system. Publication: The patient demographics and disease characteristics were similar between groups and across the TPS populations at baseline (table 1).		withdrew consent; 3 patient had protocol violation after receiving treatment. However, the underlying reason was not reported. Publication: Response and progression- free survival were assessed in the intention-to-treat population, defined as all patients randomly allocated to treatment.		patients allocated to chemotherapy, 89 withdrew consent. Protocol: Subjects who discontinue for reasons other than disease progression will be monitored for disease status in the Observation Phase until disease progression is confirmed by the site, a non-study cancer treatment is initiated, consent is withdrawn, or the subject is lost to follow-up. Publication: In the TPS 1% or greater population, 809 patients died The proportion of patient without outcome data was 9.0%. This number was imbalanced between the two groups (4.5% vs 14.0%). The observed number of events was 6.9 time the number of participants with missing outcome data. No analysis methods that correct for bias or sensitivity analyses was reported. No information was available to answer this question.				TPS ≥20% population (April 2017), first interim OS analysis: ≥250 death in the PD-L1 TPS ≥50% stratum AND ≥6 months after last patient enrolled Publication: The first interim analysis was planned for around 6 months after the final patient was enrolled and was done using a data cutoff of Aug 30, 2017. After reviewing results, the external data monitoring committee recom-mended that the study continue as planned. The second interim analysis was based on a cutoff date of Feb 26, 2018, and was done 38·3 months after enrolment of the first patient.	
NCT038 50444	332312 85	OS	Low	We present results from patients in KEYNOTE-042 enrolled from China in	Some concer ns	This is an open-label trial.Supplemental Figure S1 legend: Eight patients withdrew	High	Supplemental Figure S1. Of the 128 patients allocated to pembrolizumab	Low	Primary endpoints were overall survivalThis is an open-label trial.Overall	Some concer ns	Although the study protocol identical to global study, no statistical analyaisis	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				the global or extension study (NCT03850444; protocol identical to global study).KEYNOTE-042 global study: Randomisation was computer generated, accessed via an interactive voice-response and integrated web-response system.Publication: Baseline characteristics were similar between treat-ment arms (Table 1).		consent to receive chemotherapy after being randomized, and 1 patient had rapid disease progression 7 days post-randomization, precluding initiation of chemotherapy. However, the underlying reason was not reported.Publication: Data for randomized patients from mainland China were analyzed by assigned treatment for efficacy (intention-to-treat population [ITT]) and by treatment received for safety.		group, 2 withdrew consent. Of the 134 patients allocated to chemotherapy, 8 withdrew consent before receiving treatment, 13 withdrew consent after treatment.The overall proportion of people without available outcome was 9.5%. This number imbalanced between the two groups (1.6% vs 15.7%)No analysis methods that correct for bias or sensitivity analyses was reported.No information was available to answer this question.		survival is an objective endpoint.		plan specific for China cohort was reported in the global protocol. There is not enough information to answer this question.	
NCT027 75435	302806 35	OS and PFS	Low	Publication: In this double-blind trial, randomization was performed with the use of an interactive voice- response and integrated Web-response system. Publication: Baseline demographic and disease characteristics were as expected for a trial involving patients with metastatic, squamous NSCLC and were well bal- anced between groups (Table 1).	Low	This is an double-blind trial. Although there were some differences in the adverse event leading to discontinuation of all treatment componentsprofiles across the groups (13.3% vs 6.4%), these were not considered to be substantial enough to break blinding of participants and personnel. Publication: Efficacy was assessed in the intention-to-treat population, which included all patients	Low	Figure S2: Of the 278 patients allocated to pembrolizumab group, 5 withdrew consent, 0 lost to follow-up. Of the 281 patients allocated to placebo, 9 withdrew consent, 2 lost to follow-up. The overall proportion of patients without available outcome was 2.9% (1.8% 3.9%)	Low	Publication: The trial had dual primary end points of overall survival and progression-free survival, which was assessed by means of blinded, independent central review of radiologic images. This is a double-blind trial.	Low	Publication: As of April 3, 2018, there were 349 events of disease progression or death and 205 deaths. MK-3475-407-03 Final Protocol (13-Nov-2017): Interim analysis (IA) 1 Timing: To be performed after ~200 subjects have ~28 weeks of follow-up. Outcome measurements reported in the published article appear consistent with those specified in the protocol.	Low

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	**Refere nce (PMID)**	**Outco me**	**1.0 Asses sor's Judge ment**	**1.0 General note**	**2.0 Asses sor's Judge ment**	**2.0 General Notes**	**3.0 Asses sor's judge ment**	**3.0 Gerenal notes**	**4.0 Asses sor's Judge ment**	**4.0 General note**	**5.0 Asses sor's Judge ment**	**5.0 General note**	**Asses sor's overall Judge ment**
						who underwent ran- domization.							
NCT038 75092	346611 77	OS and PFS	Low	Protocol: Treat ment allocation/rando mization will occur centrally using an interactive voice response syste m / integrated web response syste m (I V RS/IW RS). Publication: The baseline characteristics and demographics were well balanced between the treatment groups, with the exception of Eastern Cooperative Oncology Group per- formance status of 1 (pembrolizumab– chemotherapy, 69.2%; placebo– chemotherapy, 81.7%).	Low	This is an double-blind trial. Although there were some differences in the adverse event leading to discontinuation across the groups (12.3% vs 1.7%), these were not considered to be substantial enough to break blinding of participants and personnel, as the absolute number is samll (8 vs 1) Publication: Efficacy was assessed in the intention-to- treat population, which included all randomized patients.	Low	Figure 1: Of 65 patients allocated to pembrolizumab– chemotherapy, 3 withdrew. Of 60 patients allocated to placebo– chemotherapy, 2 patient withdrew. The overall proportion of patients without available outcome was 4% (4.6% 3.3%).	Low	Publication: Dual primary end points were overall survival (OS) and progression-free survival (PFS) (based on the Response Evaluation Criteria in Solid Tumors version 1.1 by blinded independent central review). This is a double-blind trial.	Low	Protocol (documented date 30-Oct-2019): Approxi mately 120 Chinese subjects overall will be enrolledinthe global study andtheextension study. (for the global study). With 361 deaths, the study has 92% power for detecting a hazardratio (HR) of 0.7 at 0.025 (one-sided). Publication: At the time of data cutoff (September 30, 2020), 30 deaths had occurred in the pembrolizumab– chemotherapy group and 46 in the placebo– chemotherapy group. Protocol: Because of positive results in the China extension for both PFS and OSobserved at the interim analysis, subsequent analyses will be conducted and reviewed by the Sponsor and may be performed at the planned time of final analysis, or as needed.	Low

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
NCT025 64263	330269 38	OS	Low	Publication: Treatment allocation/randomizati on will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS).Publicati on: Expression of PD-L1 CPS $ 10 was well balanced between the groups, with 222 patients (35.4%) having PD-L1 CPS $ 10 (107 [34%] in the pembrolizumab group and 115 [37%] in the chemo- therapy group).	Some concer ns	This is an open-label trial.Figure 1: 296/314 patients in the chemotherapy group received at least one dose of study treatment. However, the reason for those 18 patients that did not receive treatment was not reportedProtocol: The Intention-to-Treat (ITT) population will serve as the population for primary efficacy analysis.	Low	Figure 1: Of the 314 patients assigned to pembrolizumab, 11 discontinued treatment due to patient/physician decesion. Of the 314 patients assigned to chemotherapy, 18 did not recieve treatment, 26 discontinued treatment due to patient/physician decision.Protocol: Subjects who discountinue/withdraw from treatment prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits, and encouraged to participate in the Survival Follow-Up Phase.	Low		Low	MK-3475-181-05 Final Protocol (8-Mar-2018): Final Analysiso Timing: after approximately 310 OS events and 473 OS eventshave been observed among subjects with squamous cell carcinoma of the esophagus and all subjects, respectively , and 16 months after last subject randomized.Publicat ion: The data cutoff date of the original final analysis of overall survival was October 15, 2018. At final analysis, a total of 190 patients with PD-L1 CPS ≥ 10 had died (87 [81.3%] in the pembrolizumab group and 103 [89.6%] in the chemotherapy group).Outcome measurements reported in the published article appear consistent with those specified in the protocol, although the number of death in the interim analysis was not reported in the main text.	Some concer ns
NCT023 58031	316799 45	OS	Low	Publication: The randomisation schedule was produced by a com	Some concer ns	This is an open-label trial. According to Figure 1, 1/301, 5/281, and	High	Figure 1: of the 301 patients assigned to pembrolizumab alone group, 10 withdrew	Low	Publication: The primary endpoints were overall survival (time from randomisation to death	Some concer ns	MK-3475-048-10 Final Protocol (11-Jan-2019): There will be 2 interim	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				puterised random list generator and housed centrally. Treatment assignments were obtained using an interactive voice-response and integrated web-response system (Almac Clinical Technologies, Souderton, PA, USA). Publication: Baseline demographics and disease characteristics were similar between groups and across the PDL1 CPS and total populations (table 1, appendix pp 22–23).		13/300 patient in the pembrolizumab group, pembolizumab plus chemotherapy group, and cetuximab plus chemotherapy group did not receive assigned therapy. However, the underlying reason was not reported. Publication: Overall survival, progression-free survival, and objective response were assessed in the intentiontotreat popu lation, defined as all participants randomly allocated to a treatment group.		consent, 1 lost to follow-up. Of the 281 patients assigned to pembrolizumab with chemotherapy group, 13 withdrew consent. Of the 300 patients assigned to cetuximab with chemotherapy group, 18 withdrew consent, 1 lost to follow-up. Publication: The interim analysis of overall survival was performed after 165 events (43% of the prespecified total number for the final analysis) had occurred. The overall proportion of patients without outcome was 5.0% (3.7% vs 6.6%). The observed number of events was 5.5 times the number of participants with missing outcome data. No analysis methods that correct for bias or sensitivity analyses was performed. No information was available to answer this question.		from any cause) and progression-free survival (time from randomisation to radiographically confirmed disease progression or death from any cause, whichever came first) in the intention-to-treat population (all participants randomly allocated to a treatment group). This is an open-label trial. Overall survival, the outcome we assessed, is an objective endpoint.		PFS/OS analyses, 1 final OS analysis, 1 planned interim safety analysis, and quarterly safety monitoring. At the time of final PFS analysis, H1, H4: for subjects with PD-L1 CPS 20, it is expected that approximately 237 PFS events will have been observed between one experimental treatment and standard treatment. At the time of the final analysis: H7, H11: for subjects with PD-L1 CPS 20, it is expected that approximately [not disclosed] deaths. Publication: The data and safety monitoring committee reco mmended that the study continue as planned after reviewing the first interim analysis (data cutoff Oct 17, 2017); second interim analysis (data cutoff June 13, 2018); final analysis (data cutoff Feb 25, 2019). Although study protocol was available, the number of events needed of the primary analysis of	

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
												overall survival was not disclosed. There is not enought information to answer this question.	
NCT025 63002	332645 44	PFS and OS	Low	Publication: Randomization was performed centrally with the use of an interactive voice-response system and integrated Web-response system.Publication: Demographic and baseline characteristics, including previous receipt of adjuvant or neoadjuvant therapy, were generally well balanced between groups.	Some concer ns	This is an open-label trial.According to Figure S1, 0/153 and 11/154 (7.1%) patients assigned to the pembrolizumab and chemotherapy did not received the treatment. However, the underlying reason was not reported.Publication: Efficacy was assessed in the intention-to-treat population, which consisted of all patients who underwent randomization.	Low	Figure S1: Of the 153 patients assigned to pembrolizumab, 1 withdrew. Of the 154 patients assigned to chemotherapy group, 11 withdrew, 1 discontinued treatment due to protocol violation or other reason (which we assumed did not have available outcome).Publication: As of the data cutoff date, 56 patients in the pembrolizumab group and 69 in the chemotherapy group had died.The overall proportion of patient without outcome was 4.2% (0.7% vs 7.8%)	Low	Publication: The two primary end points were progression-free survival (the time from randomization to first disease progression, as assessed by central review according to RECIST, version 1.1, or death from any cause) and overall survival (the time from randomization to death from any cause). This is an open-label trial.Overall survival, the outcome we assessed, is an objective enpoint.	Low	MK-3475-177-05 Final Protocol (17-Dec-2019): Two interim analyses will be performed. IA2: to be performed after approximately 209 PFS events have occurred or 24 months after last subject randomized, whichever occurs first.Publication (second interim analysis data cutoff date 19 February 2020): PFS event 195. At the time of data cutoff, data on overall survival were still evolving, with 125 of the required 190 events for the final analysis of overall survival having occurred. As of the data cutoff date, 56 patients in the pembrolizumab group and 69 in the chemotherapy group had died. Outcome measurements reported in the published article appear consistent with those specified in the protocol.	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
NCT031 89719	344546 74	OS and PFS	Low	Publication: Patients were enrolled by the study investigators and randomly assigned (1:1) using an interactive voice response system (IVRS) or integrated web response system (Almac Clinical Technologies, Souderton, PA, USA) with a block size of four to receive pembrolizumab plus chemotherapy or placebo plus chemotherapy. Publication: Baseline patient characteristics and demographics were generally well balanced between the two groups (table 1).	Low	This is an double-blind trial. Although there were some differences in the adverse event leading to discontinuation across the groups (12.3% vs 1.7%), these were not considered to be substantial enough to break blinding of participants and personnel, as the absolute number is samll (8 vs 1) Publication: Primary efficacy analyses were done in the intention-to-treat population of all randomised patients. Safety was assessed in all randomised patients who received at least one dose of study treatment (the as-treated population).	Low	Figure 1: Of the 373 patients assigned to pembrolizumab plus chemotherapy, 39 discontinued treatment due to patient or physician decision. Of the 376 patients assigned to placebo group, 33 discontinued due to patient of physician decision. Protocol: A subject discontinued from treatment will continue to be monitored in the trial.	Low	Publication: The dual primary endpoints were overall survival (time fromrandomisationtodeathfr omanycause)inpatients with oesophageal squamous cell carcinoma and PD-L1 CPS of 10 or more, oesophageal squamous cell carcinoma, PD-L1 CPS of 10 or more, and in all randomised patients; and progression-free survival (time from randomisation to first disease progression or death from any cause) per RECIST version 1.1 by investigator assessment in patients with oesophageal squamous cell carcinoma, PD-L1 CPS of 10 or more, and in all randomised patients. This is a double-blind trial.	High	MK-3475-590-09 Final Protocol (17-Jun-2020): Interim Analysis (IA):• Timing: (1) Enrollment is complete with a minimum follow-up of 13 months and (2) ~460 investigator-assessed PFS events have beenobserved in ESCC and (3) ~391 deaths have occurred in ESCC Publication: At the data cutoff date of July 2, 2020, the median follow-up duration was 22·6 months. Figure 3: death events 571/749. PFS event 630/749. These numbesr of event were greater than those pre-sepcified in the study protocol. Publication: At the data cutoff date of July 2, 2020, the median follow-up duration was 22·6 months. This is differed from that in the protocol (Enrollment is complete with a minimum follow-up of 13months)	High
NCT013 58877	285813 56	iDFS	Low	Publication: A Web-based system was used to collect patient screening information	Some concer ns	This is an open-label trial.Figure S2: Of the 2400 patients randomized to	High	The Figure S2 CONSORT Diagram for the APHINITY Trial and main text did	High	Protocol: this definition of IDFS (which excludes second primary non-breast cancers as events) is not	Low	Protocol: The final analysis will take place when approximately 379	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				and to randomly assign eligible patients in a 1:1 ratio to one of the two treatment groups. A permuted-blocks randomization procedure was used.Publication: The baseline characteristics of the patients were balanced between the two groups.		pertuzumab, trastuzumab and chemotherapy group, 60 did not receive pertuzumab or chemothreapy. Of the 2405 patients assigned to the control group, 37 did not received chemotherapy or pertuzumab. However, the underlying reason was not reported.Publication: The primary analysis was based on the intention-to-treat population.		not reported the number of patient withdraw consent or lost to follow-up.No analysis methods that correct for bias or sensitivity analyses was reported.No information was available to answer this question.		the same as IDFS defined by Hudis et al. [2007] (which includes second primary non-breast cancers as events).However, the rationale of using this definition was not reported. We deemed it no enought information to answer this question.This is an open-label trial. There was no evidence that the primary endpoint was assessed by other independent institution.The approach to assess tumor recurrence was not reported. There was no enough information to answer this question.		IDFS events have occurred. A data cut-off date will be determined when this number of events occurs, and the clinical data on or prior to the data cut-off date will be thoroughly cleaned.Publication: In total, invasive-disease events were reported in 171 patients (7.1%) in the pertuzumab group and 210 patients (8.7%) in the placebo group.Outcome measurements reported in the published article and supplementary appendix appeared consistent with those specified in the protocol.	
NCT025 86025	316475 03	pCR	Low	Protocol: After written informed consent has been obtained and eligibility has been established and approved, the study site will obtain the patient randomization number and treatment assignment from the interactive voice/webbased response system (IxRS). Publication: Baseline demographics and disease char-acteristics were generally well	Low	Publication: The PEONY trial (NCT02586025) is a randomized, multicenter, double-blind, placebo-controlled, phase 3 trial. Publication: Analysis of the primary end point was performed on an intention-to-treat basis.	Low	Figure 1: Of the 219 patients assgined to receive pertuzumab, trastuzumab, and docetaxel, 3 withrew. Of the 110 patients assigned to receive placebo, trastuzumab, and docetaxe, 2 withdrew. The overall proportion of patient without available outcome was 1.5% < 5%.	Low	Protocol: The primary efficacy outcome measure is tpCR, defined as the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of neoadjuvant therapy and surgery (i.e., ypT0/is, ypN0 according to the current AJCC staging system), as assessed by the IRC. Publication: The primary end point was indepen-dent review committee–	Low	Publication: The data cutoff date was October 23, 2017. Independent review committee–assessed tpCR rates were 39.3% (86 of 219) in the pertuzumab group and 21.8% (24 of 110) in the placebo group (intention-to-treat populations). Protocol: A total of 328 patients will be randomized into the study in a ratio of 2:1 to pertuzumab (Arm A) or placebo	Low

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Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				balanced (eTable 1 in Supplement 2).						assessed tpCR rate when patients completed surgery.		(Arm B), respectively. There is no interim analysis planned for the primary efficacy outcome measure, tpCR. Outcome measurements reported in the published article and supplementary appendix appeared consistent with those specified in the protocol.	
NCT005 45688	221538 90	pCR	Low	Publication: We used an interactive voice response system to obtain screening information for every patient. Patients were randomly assigned treatment by a central randomisation procedure with the adaptive randomisation method and stratified by operable, locally advanced, and inflammatory breast cancer, and by positivity for oestrogen or progesterone receptors. Publication: Baseline characteristics were balanced across treatment groups (table 1).	Low	This is an open-label trial. According to Figure 1, only 1 patient withdrew after assigned to intervention. Publication: The primary endpoint, examined in the intention-to-treat population, was pathological complete response in the breast.	High	Figure 1: Of the 107 patients assigned to group A, 5 withdrew. Of the 107 patients assigned to group B, 5 withdrew. Of the 107 patients assgined to group C, 14 withdrew. Of the 96 patients assigned to group D, 6 withdrew. The overall proportion of patient without available outcome was 7.2% > 5%. No analysis methods that correct for bias or sensitivity analyses was reported. No information was available to answer this question.	Low	Publication: The primary endpoint was pathological complete response in the breast, which is defined as the absence of invasive neoplastic cells at microscopic examination of the primary tumour at surgery. Remaining in-situ lesions were allowed. Pathologists at participating centres followed guidelines for the assessment of pathological complete response on serial sections of the surgical specimen (appendix). Alhough this is an open-label trial, the outcome was assessed by pathologists. Publication: Pathologists at participating centres followed guidelines for the assessment of pathological complete response on serial sections of the surgical specimen (appendix). Blinded pathology data were reviewed by a consultant	Some concer ns	Study protocol was not available to answer this question fully. Study protocol was not available to answer this question fully.	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
										pathologist at regular intervals to ensure consistency.			
NCT005 67190	221498 75	PFS	Low	Protocol: An Interactive Voice Response System (IVRS) will be utilized to collect patient screening information and to randomize eligible patients in a 1:1 ratio to one of two treatment arms.A complete block randomization scheme will be applied to achieve balance in treatment assignment within each of the eight strata.Publication: The baseline characteristics of the patients were similar in the two groups (Table 1).	Low	This is an double-blind trial. Although there were some differences in the grade 3 or higher febrile neutropenia across the groups (13.8 % vs 7.6%), these were not considered to be substantial enough to break blinding of participants and personnel.Publication: Analyses of progression-free survival, overall survival, and objective response rate were performed in the intention-to-treat population (all patients who un- derwent randomization).	High	Supplementary Figure 1: Of the 402 patients randomized to receive pertuzumab + trastuzumab + docetaxel, 18 withdrew consent/lost to follow-up. Of the 406 patients randomized to receive placebo + trastuzumab + decetaxel, 23 withdrew consent/lost to follow-up.The number of PFS events were not reported. According to the statistical analysis plan: the primary analysis of progression-free survival would be performed after the occurrence of approximately 381 events of independently assessed disease progression or death from any cause within 18 weeks after the last independent assessment of tumors.The overall proportion of patient without outcome data was 5.1% (4.5% vs 5.7%). The preplanned number of events was 9.3 times the number of	Low	Publication: The primary end point was progression-free survival, as determined on the basis of the assessment of tumors at an independent review facility (independently assessed progression-free survival). Progression-free survival was defined as the time from randomization to the first documented radiographic evidence of progressive disease accord- ing to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0,20 or death from any cause within 18 weeks after the last independent assessment of tumors.The outcome was assessed by independent review facility.	Low	Protocol date: 14-Sep-2007. No interim analysis of efficacy is planned for this study. Final primary analysis of PFS will be performed after 381 IRF-assessed PFS events have occurred.Publication : The cutoff date for collection of data was May 13, 2011. Among the 88 patients who had received adjuvant or neoad- juvant chemotherapy with trastuzumab, the me- dian independently assessed progression-free survival was 10.4 months in the control group, as compared with 16.9 months in the pertuzumab group (hazard ratio, 0.62; 95% CI, 0.35 to 1.07). Among the 288 patients who had received adju- vant or neoadjuvant chemotherapy without trastuz- umab, the median independently assessed pro- gression-free	High

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Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								participants with missing outcome data. No analysis methods that correct for bias or sensitivity analyses was performed.No information was available to answer this question.				survival was 12.6 months in the control group, as compared with 21.6 months in the pertuzumab group (hazard ratio, 0.60; 95% CI, 0.43 to 0.83).Outcome measurements reported in the published article and supplementary appendix appeared consistent with those specified in the protocol.	
NCT028 96855	325642 60	PFS	Low	Publication: Eligible patients were randomized (permuted block scheme via an interactive voice- or web-based response system; block size four; sequence generated by PAREXEL [Waltham, MA]) Publication: The baseline demographics and disease char- acteristics were generally balanced between arms (Table 1).	Low	This is a double-blind trial. Efficacy data was analyzed in intention-to-treat population.	Low	Figure S1: of the 122 patients randomized to pertuzumab group, 1 withdrew consent or lost to follow-up. Of the 121 patients randomized to placebo group, 6 withdrew group or los to follow-up. Publication: PFS events occurred in 57 patients in the pertuzumab arm (46.7%) and 71 patients in the placebo arm (58.7%). The overall proportion of patients without available outcome was 2.9%. The preplanned number of events was 11.1 times the number of participants with missing outcome data.	Low	Publication: The primary endpoint was investigator-assessed PFS, defined as the time from randomization to the first occur- rence of disease progression (assessed per Response Evalu- ation Criteria In Solid Tumors version 1.1 [RECIST v1.1]); or death from any cause within 18 weeks after the last tumor assessment. Although the primary endpoint was investigator-assessed PFS, this is a double-blind trial.	Low	Protocol Version 3: 10 May 2017. No interim analysis of efficacy is planned. The primary analysis of PFS will be performed after 123 PFS events have occurred, and the required PFS events will be reached at approximately 23 months after the first patient is enrolled into the study. Publication: the clinical cut-off date was 27 June 2018. PFS events occurred in 57 patients in the pertuzumab arm (46.7%) and 71 patients in the pla- cebo arm (58.7%). Outcome measurements reported in the	Low

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
												published article and supplementary appendix appeared consistent with those specified in the protocol.	
NCT017 40427	279596 13	PFS	Low	Protocol: The IRT will assign a unique patient identification number. The interactive randomization technology system will also be used to assign study medication.Publication : The baseline characteristics of the intention-to- treat population were well balanced between study groups (Table 1).	Low	Although this is an double-blind trial, grade 3 or 4 hematologic adverse events included neutropenia (occurring in 66.4% of patients in the palbociclib–letrozole group vs. 1.4% in the placebo–letrozole group), leukope- nia (24.8% vs. 0%). We assumed that such differences could potentially break the blinding of the trial, and resulting in participants, carers and personnel correctly guessing their treatment allocation.Figure S1: All of patients allocated to intervention received treatment. The proportion of patient (5/444 in palbociclib group and 2/222 in placebo group) violated protocol or lost to follow-up was similar between groups.Efficacy data was analyzed in the intention-to-treat population.	Low	Figure S1: Of 444 patient randomized to palbociclib group, 9 withdrew consent, 1 lost to follow-up. Of 222 patients randomized to placebo group, 9 withdrew consent. The overall proportion of patient without availabel outcome was 2.9%	Low	Publication: The primary end point was investigator-assessed progression-free survival, which was defined as the time from randomization to radiologically confirmed disease progression, according to RECIST, version 1.1, or death during the study.Although PFS was assessed by investigator, this is a double-blind trial. Publication: Double blinding has been maintained to allow ongoing follow-up to assess overall survival.	Low	Final Protocol Amendment 7, 15 October 2015: A total of 347 events are required in the 2 arms of the study based on a 2:1 randomization to have90% power to detect a difference assuming a true hazard ratio of 0.69 in favor of the PD-0332991 plus letrozole arm using a one-sided, log-rank test at a significance level of 0.025.Publication: By the data cutoff date for the final analysis (February 26, 2016), a total of 331 events of disease progression or death had occurred (194 [43.7%] events in the palbociclib–letrozole group and 137 [61.7%] in the placebo–letrozole groupOutcome measurements reported in the published article appear consistent with those specified in the protocol.	Low

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
NCT007 20941	239649 34	PFS	Low	Protocol: Upon completion of all the required baseline assessments, eligible subjects will be registered into the GSK interactive voice response system called RAMOS (Registration And Medication Ordering System), by the investigator or authorized site staff for stratification and central randomization. Publication: Patients were randomly assigned to one of the two study drugs in a 1:1 ratio in permuted blocks of four. Publication: Demographic and clinical characteristics at baseline were balanced between the treatment groups (Table S3 in the Supplementary Appendix).	Some concer ns	Publication: The study was a randomized, open-label, phase 3 trial. According to Supplementary Figure S2, 7/557 patients allocated to pazopanib and 11/553 patients allocated to sunitinib did not received allocated intervention or deviated protocol respectively. However, the underlying reason was not reported. Publication: Efficacy data were analyzed in the intention- to-treat population (all patients who underwent randomization).	Low	Supplementary Figure S2: Of the 557 patients allocated to pazopanib, 37 withdrew consent, 1 lost to follow-up. Of the 553 patients allocated to sunitinib, 37 withdrew consent. Publication: Disease-progression events occurred in 336 of 557 patients (60%) in the pazopanib group and in 323 of 553 (58%) in the sunitinib group. The overall proportion of paitent without available outcome was 6.8% (6.8% vs 6.7%). The observed number of events was 8.8 time the number of participants with missing outcome data.	Low	Publication: We performed disease assessments with the use of computed tomography or magnetic resonance imaging at baseline, every 6 weeks until week 24, and every 12 weeks thereafter until progression of disease. Imaging data were reevaluated by an independent review committee whose members were unaware of the treatment assignments to assess the primary end point and tumor response according to RECIST, version 1.0. Publication: Imaging data were reevaluated by an independent review committee whose members were unaware of the treatment assignments to assess the primary end point.	Low	Publication: data-cutoff point in May 2012. Disease-progression events occurred in 336 of 557 patients (60%) in the pazopanib group and in 323 of 553 (58%) in the sunitinib group. Protocol UM2008/00127/05 (2011-MAR-25): Note that all of the main statistical design parameters for the study including margin, alpha level and power remain the same, so the total event count required is still 631. Outcome measurements reported in the published article appear consistent with those specified in the protocol.	Some concer ns
NCT016 07957	259700 50	OS	Low	Protocol: Once patient confirmation of eligibility and the criteria for randomization have been met, patients will be centrally randomized in a 2:1 ratio to TAS-102 or placebo via an Interactive Voice/Web Response System (IXRS) based on a dynamic allocation method (biased coin). Publication: Baseline	Low	This is a double-blind trial. Although adverse events of grade 3 or higher occurred more frequently in the TAS-102 group than in the placebo group (in 69% vs. 52% of the patients), , these were not considered to be substantial enough to break blinding of participants and personnel.	Low	Figure S1: of the 534 patients randomized to TAS-102, 12 withdrew consent, 3 lost to follow-up, 9 discontinued treatment due to other reason. Of the 266 patients assigned to placebo group, 1 withdrew, 3 lost to follow-up, 1 discontinued treatment due to other reason. The overall proportion	Low	Publication: The primary end point was overall survival, which was defined as the time from randomization to death from any cause. This is a double blind trial.	Low	Protocol: The OS cut-off date used for the primary analysis will be based on the observations of the 571st death in the study. Publication: At the time that the target was reached (574 deaths), the median overall survival was 7.1 months (95% confidence interval [CI], 6.5 to 7.8) in the TAS-102 group	Low

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Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				demographic and disease character-istics were well balanced between the two study groups (Table 1).		Publication: Overall survival (the primary end point) and radiologically confirmed progression-free survival were analyzed in the intention-to-treat population		of patient without available outcome was 3.5%.				and 5.3 months (95% CI, 4.6 to 6.0) in the placebo group. Outcome measurements reported in the published article appear consistent with those specified in the protocol.	
NCT019 55837	292159 55	OS	Low	Protocol: patients will be centrally randomized in a 2:1 ratio to TAS-102 or placebo via an Interactive Web Response System (IWRS) based on a dynamic allocation method (biased coin).Publication: Patient demographics and baseline characteristics were similar between the two arms (Table 1).	Low	Although this is a double-blind trial, the incidence of grade 3 or 4 adverse event differed between groups (45.8% vs 10.4%). We assumed that such differences could potentially break the blinding of the trial, and resulting in participants, carers and personnel correctly guessing their treatment allocation.According to Fig 1 Patient Flowchart, there is no protocol deviation.Publication: For the primary analysis, OS data in the intent-to-treat (ITT) population were compared between treatment arms.	Low	Fig1: Of the 271 patients assigned to trifluridine/tipiracil, 2 lost to follow-up, 8 withdrew consent, 6 discontinued due to other reason. Of the 135 patients assigned to placebo group, 5 withdrew consent, 2 discontinued treatment due to other reason.Publication: 316 deaths had occurred in the ITT population.We assumed that patients discontinued treatment due to "other reason" did not have available outcome. The overall proportion of patient without outcome was 5.7%. The observed number of events was 13.7 time the number of participants with missing outcome data.	Low	Publication: The primary end point was OS, which was defined as the time from random assignment to the date of death. This is a double-blind trial.	Low	Protocol Ver. P03 (Date: 21st, February, 2014): a target of 288 events (deaths) will be required for the primary analysis.Publication: The cutoff date for OS was February 16, 2016, at which time 316 deaths had occurred in the ITT population. Outcome measurements reported in the published article appear consistent with those specified in the protocol.	Low
NCT015 84648	252654 92	PFS	Low	Protocol: Randomization will be done centrally using a randomization schedule generated by the GSK	Low	Protocol: Study treatment will be double-blinded. Publication: Grade 3 or 4 adverse events occurred in 73 patients	High	Figure S1. Trial Consort Diagram: Of the 211 patients randomized to dabrafenib plus trametinib, 102	Low	Publication: Tumor assessments were conducted according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,18 at	Some concer ns	Publication: This report is based on data as of August 2013, when the prespecified number of disease	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				Biostatistical Department Publication: Baseline characteristics were similar in the two study groups (Table 1)		(35%) in the dabrafenib–trametinib group and 79 patients (37%) in the dabrafenib-only group. Publication: Efficacy was determined in all patients in the intention-to-treat population.		progressed or died, 17 (8.1%) withdraw. Of the 212 patients randomized to dabrafenib plus placebo, 109 progressed or died, 10 withdraw (4.7%). Overall, the proportion of patients without available outcome was 6.4%. This proportion imbalanced between groups (8.1% and 4.7%). The observed number of events was 7.8 time the number of participants with missing outcome data (6 vs 10.9). Publication: Of the 18 patients in the dabrafenib-only group for whom data were censored, 13 had disease progression on the basis of clinical indications (without radiologic confirmation), as determined by the investigator, or had started a new anticancer therapy. In preplanned sensitivity analyses, when clinical progression or initiation of a new anticancer therapy was considered as an event, the hazard ratio for progression and the median progression-free survival for the dabrafenib–trametinib		baseline, at week 8, every 8 weeks until week 56, and then every 12 weeks until disease progression, death, or withdrawal from the study. Publication: Tumor assessments were conducted according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 Publication: The primary end point was investigator-assessed progression-free survival. This is a double-blind trial. Low		progressions or deaths(whichever came first)had occurred.	

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Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								group remained stable (i.e., the median remained the same when clinical progression was considered or decreased by 0.1 month when the initiation of a new anticancer therapy was considered). In contrast, the median progression-free survival in the dabrafenib-only group decreased by 1.2 months when clinical progression was considered and by 1.6 months when the initiation of a new anticancer therapy was considered. Publication: In addition, the preplanned sensitivity analysis showed that the median progression-free survival for dabrafenib was unstable. Data for patients who had clinical progression or received a new anticancer therapy without radiographic evidence of progression were censored (which oc-curred more frequently in the dabrafenib-only group than in the combination-therapy group in the first 2 months of the study). Thus, the median					

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								progression-free survival for the dabrafenib group decreased from 8.8 months to 7.6 months when clinical progression was included as an event and decreased from 8.8 months to 7.2 months when receipt of a new anticancer therapy was included. High					
NCT015 97908	253995 51	OS	Low	Protocol: Randomization will be done centrally using a randomization schedule generated by the GSK Biostatistical Department.Publicatio n: Baseline characteristics of the patients are provided in Table 1. Known prognostic measures were well balanced in the two groups except for sex (59% men in the combination-thera- py group vs. 51% in the vemurafenib group).	Some concer ns	Protocol: This is an open-labeled study.According to Figure S1, 3/352 patients assigned to vemurafenib group withdrew consent before receiving intervention. However, the underlying reason was not reported.Publication: The interim analysis for overall survival was per- formed in the intention- to-treat population of 352 patients in each group.	High	Figure S1. Trial CONSORT Diagram: of the 704 randomized patients, 16/352 (5%) of patients in the dabrafenib plus trametinib withdraw, and 28/352 (8%) of patients in the vemurafenib withdraw. Publication: For the overall survival analysis, 100 patients (28%) in the combination-therapy group and 122 (35%) in the vemurafenib group had diedOverall, the proportion of patient without available outcome was 6.25%. The observed number of events was 5.1 time the number of participants with missing outcome data (6 vs 10.9).No analysis methods that correct for bias or sensitivity analyses was reported.Not	Low	Publication: The primary end point was overall survival.This is an open-label trial.Overall survival is an objective endpoint.	Some concer ns	Publication: At the data-cutoff date of April 17, 2014, the interim analysis was performed after 222 events had occurred.Protocol Amendment No. 5 date: 7 Aug 2014. The interim OS analysis will be performed when the minimal enrolment target is met and approximately 70% of the total number of events (deaths) required for the final analysis have been observed across the arms (i.e., 202 total deaths). It is estimated that this will occur at approximately 17 months after the start of the study.	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								enough information was available to answer this question.					
NCT016 82083	288914 08	RFS	Low	Protocol: Randomization will be done centrally using a randomization schedule generated by the GSK Biostatistical Department. Publication: The baseline characteristics of the patients were similar in the two groups (Table 1).	Low	This is a double-blind trial. In the combination-therapy group, 114 patients (26%) had adverse events leading to permanent discontinuation of a trial drug, 167 (38%) had ad- verse events leading to a dose reduction, and 289 (66%) had adverse events leading to a dose inter- ruption, as compared with 12 (3%), 11 (3%), and 65 (15%), respectively, in the placebo group. We assumed that such differences could potentially break the blinding of the trial, and resulting in participants, carers and personnel correctly guessing their treatment allocation. According to Figure S1, only 3/438 patients assigned to the combination group withdrew consent before receiving treatment. Publication: Efficacy analyses included all the patients who had undergone randomization (intention-to-treat population).	High	Figure S1. Trial Consort Diagram: of the 870 randomized patient, 47/438 and 62/432 patients in the dabrafenib plus trametinib and placebo group withdraw, respectively. The overall proportion of patient without available outcome data was 12.5%. No analysis methods that correct for bias or sensitivity analyses was performed. Not enough information was available to answer this question.	Low	Publication: Disease assessments included clinical examination and imaging by means of computed tomography, magnetic resonance imaging, or both. Publication: All disease-recurrence analyses were based on investigator assessment.	Low	Publication: the data cutoff date for the primary analysis (June 30, 2017). As of the data cutoff, disease recurrence had been reported in 163 of 438 patients (37%) in the combination-therapy group and in 247 of 432 patients (57%) in the placebo group. Release date of Protocol Amendment No. 7: 31-May-2017 Protocol: As per Protocol Amendment 7, the final primary RFS analysis will be performed at the pre-defined cut-off date, by which time it is expected that approximately 410 RFS events will have been accrued.	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
NCT011 03323	231775 14	OS	Low	Pubilcation: Randomisation was on the basis of preallocated block sizes (block size six). Randomisation was concealed so that neither the patient, nor the investigator, nor the sponsor knew which agent was being administered. To maintain mask-ing, study medication was labelled with a unique drug pack number preprinted on each bottle, which was assigned to the patient through the interactive voice response system. Unmasking for individual patients could occur via the voice response system for emergencies only.Publication: Most baseline characteristics were similar in regorafenib and placebo groups (table 1). However, a lower proportion of patients in the regorafenib group (273 of 505, 54%) had a KRAS mutation compared with the placebo group (157 of 255, 62%).	Low	Publication: The study sponsor, participants, and investigators were masked to treatment assignment. Grade 3 or 4 treatment-related adverse events occurred in 270 (54%) patients assigned regorafenib and 35 patients assigned placebo (14%; table 2). We assumed that such differences could potentially break the blinding of the trial, and resulting in participants, carers and personnel correctly guessing their treatment allocation.According to Fig 1, there was only 2 protocol violations in the regorafenib group.Publication: Efficacy analyses were by intention to treat.	Low	Of the 505 patients allocated to regorafenib, 16 withdrew consent. O fhte 255 patients allocated to placebo, 5 withdrew consent.The overall proportion of patient without outcome was 2.8%.	Low	Publication: The primary endpoint was overall survival, defined as the time from randomisation to death from any cause.This is a double-blind trial.	Some concer ns	Study protocol was not available to answer this question fully.Study protocol was not available to answer this question fully.	Some concer ns
NCT015 84830	259818 18	OS	Low	Publication: We randomly assigned patients (2:1) to receive either regorafenib or placebo using a computer-	Low	This is a double-blind trial. Serious adverse events occurred in 43 (32%) of the 136 patients receiving regorafenib and 18	Low	Figure 1: Of the 136 patients assigned regorafenib, 4 withdrew consent, 1 had no follow-up. Of the 68 patients	Low	Publication: The primary endpoint was overall survival.	Some concer ns	Study protocol was not available to answer this question fully. Study protocol was not available to	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				generated randomisation list prepared by the trial funder, with a unicentric randomisation scheme. Investigators received the randomisation number for each participant through an interactive voice response system (IVRS). We used a preallocated block design (block size of six). Publication: In general, baseline characteristics of treatment groups were balanced (table 1).		(26%) of the 68 patients receiving placebo. Adverse events resulted in discontinuation of the study drug in 19 (14%) of the 136 patients receiving regorafenib and four (6%) of 68 patients receiving placebo. these were not considered to be substantial enough to break blinding of participants and personnel. Publication: we analysed data on an intention-to-treat basis.		assigned placebo, 2 withdrew consent. The proportion of patient without available outcome was 3.4%.		This is a double-blind trial.		answer this question fully.	
NCT012 71712	231775 15	PFS	Low	Publication: Patients were randomised in a 2:1 ratio (by computer-generated randomisation list and interactive voice response system; preallocated block design (block size 12) Publication: Baseline characteristics and previous treatments were much the same between the two groups, although by chance a higher proportion of patients in the placebo group had received imatinib therapy for more than 18 months than in the regorafenib group (table 1).	Some concer ns	Although this is a double-blind trial, drug-related adverse events of grade 3 or higher were reported in 81 (61%) patients assigned regorafenib and nine (14%) patients assigned placebo. We assumed that such differences could potentially break the blinding of the trial, and resulting in participants, carers and personnel correctly guessing their treatment allocation. According to Figure 1, 4/133 patients assigned to regorafenib group withdrew consent, 1 violated protocol; 5/66 patients allocated to placebo withdrew consent. However, the underlying reason was	Low	Figure 1: 4/133 patients assigned to regorafenib group withdrew consent. 5/66 patients allocated to placebo withdrew consent. Publication: Analysis was done when the predetermined criteria of 144 PFS events was reached: 81 events among the 133 patients (61%) in the regorafenib group and 63 events among the 66 patients (95%) in the placebo group. The overall proportion of patient without available outcome was 4.5%. The observed number of events was 16 times the number of participants with	Low	Publication: The primary endpoint was PFS per modified Response Evaluation Criteria In Solid Tumors (RECIST) 1.1, assessed by central radiology reviewers who were masked to assignment and data from patients. Tumor progression was centrally assessed.	Some concer ns	Study protocol was not available to answer this question fully. Study protocol was not available to answer this question fully.	Some concer ns

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Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
						not reported. Publication: Analyses were by intention to treat.		missing outcome data (20.3 vs 12.6).					
NCT017 74344	279322 29	OS	Low	Publication: Patients were randomly assigned (2:1) to regorafenib or placebo using a computer-generated randomisation list prepared by the funder. The randomisation number for each patient was assigned based on information obtained from the interactive voice-response system.Publication: Treatment groups were similar with respect to baseline demographics, tumour burden, ECOG performance status, aetiology, and severity of liver disease (table 1). We also assessed the pattern of progression during sorafenib treatment because this parameter has been shown to influence outcomes and could distort the results of second-line studies.	Low	This is a double-blind trial. Serious adverse events occurred in 166 (44%) patients assigned to regorafenib and 90 (47%) patients assigned to placebo.Publication: The primary endpoint was analysed by intention to treat.	Low	Figure 1: Of the 379 patients assigned to regorafenib, 26 withdrawal by patient. Of the 194 assigned to placebo, 5 withdrawal by patient.Publication: At the cutoff date for the final analysis (Feb 29, 2016) and a median follow-up of 7·0 months (IQR 3·7–12·6), 373 (65%) of the 573 randomised patients had died (233 [61%] of 379 in the regorafenib group and 140 [72%] of 194 in the placebo group).The overall proportion of patient without available outcome was 5.4% (6.9% vs 2.8%). The observed number of events was 12 times the number of participants with missing outcome data (8.9 vs 28).	Low	Publication: The primary endpoint was overall survival (time from randomisation to death due to any cause), analysed by intention to treat (ITT).This is a double-blind trial.	Some concer ns	Study protocol was not available to answer this question fully.Study protocol was not available to answer this question fully.	Some concer ns
NCT018 28112	286027 79	PFS	Low	Publication: We randomly allocated eligible patients using interactive response technology (IRT) in a 1:1 ratio (block randomisation with a	Low	This is an open-label trial. According to Table 1 legend, there was only one patient did not receive previous chemotherapy (a	Low	According to Figure 1, all patients had available outcome.	Low	Publication: The primary endpoint was progression-free survival (the time from randomisation to the first radiologically documented disease progression [according to RECIST 1.1	Some concer ns	Study protocol was not available to answer this question fully. Study protocol was not available to	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				block size of four used). A patient randomisation list was produced by the IRT provider using a validated, automated system. Publication: Baseline patient characteristics were well balanced between groups, with the exception of the number of patients who were white and ex-smokers (table 1, appendix p 10).		protocol deviation). Publication: We analysed the primary endpoint, secondary efficacy endpoints, and PROs in the intention-to-treat population and analysed secondary safety outcomes in all patients who received at least one dose of study treatment.					and assessed by the masked IRC] or death from any cause). Although this is an open-label trial, PFS was assessed by masked IRC.		answer this question fully.	
NCT018 28099	281263 33	PFS	Low	Publication: The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and Investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. Publication: Baseline and disease characteristics were well balanced between the groups (table 1).	Low	This is an open-label trial. Publication: None of the patients in the ceritinib group and two patients in the chemotherapy group had protocol deviations that led to exclusion from the per-protocol set. Publication: Efficacy endpoints were analysed based on the full analysis set, which consisted ofallrandomlyassignedp atients.	Low	Figure 1: Of the 189 patients assigned to receive ceritinib, 12 discontinued due to other reason. Of the 187 patients assigned to chemotherapy group, 9 discontinued due to other reason. Protocol: All patients who discontinued treatment during the treatment phase for reasons other than death, lost to follow-up, pregnancy or disease progression as per BIRC (Section 7.1.3) will continue tumor and PRO assessments as per Table 7-1 (every 6 weeks until Month 33 and after Month 33 every 9 weeks) thereafter until PD as per BIRC, withdrawal of consent or death. Therefore, all the randomized patients were assumed to	Low	Publication: The primary endpoint was progression-free survival, defined as the time from randomisation to the date of the first radiologically documented disease progression (assessed by the blinded independent review committee according to RECIST 1.1) or death due to any cause. Although this is an open-label trial, the primary endpoint was assessed by the blinded independent review committee.	Low	Amended Protocol Version 03 (11-Dec-2015): the final analysis for PFS when approximately 205 PFS events have been documented by BIRC (expected around 32 months from the date of first patient randomized in the study). Publication (data cutoff June 24, 2016): 202 progression- free survival events had been documented by the blinded independent review committee and 218 by investigator assessment. Outcome measurements reported in the published article and supplementary appendix appear consistent with	Low

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								have available outcome.				those specified in the protocol.	
NCT035 81786	343415 78	PFS	Low	Pubilcation: A permuted block of flexible size (2, 4, 6 or 8) was used to generate the randomization allocation sequence. A new block was assigned to a stratum either when the first patient in that stratum was being randomized or when the randomization allocation sequence in the block assigned to that stratum had been used. Within one block, the randomization allocation sequence was assigned to patient numbers in order from the lowest to the highest.Publication: The baseline demographic and disease characteristics were generally balanced between the two arms, including PD-L1 expression sta- tus, liver/lung/bone metastasis, total number of target and nontar- get lesions and EBV DNA copy number (Table 1).	Low	This is a double-blind trial. The overall incidence of TEAE grade3 or higher was similar in the two arms (89.0% in the toripalimab arm versus 89.5% in the placebo arm), including leukopenia (61.6 versus 58.0%), neutropenia (57.5 versus 63.6%), anemia (47.3 versus 39.9%), thrombocytopenia (32.9 versus 28.7%), pneumonia (10.3 versus 3.5%), lymphopenia (8.9 versus 7.0%), hyponatremia (8.9 versus 4.2%) and hypokalemia (6.8 versus 7.0%)Publication: Efficacy was assessed in the ITT population, which included all patients who had undergone randomization regardless of whether they received the assigned intervention.	Low	Protocol: For patients who discontinue study treatment for any reason other than progressive disease, tumor assessments should continue at the same frequency as would have been followed if the patient had remained on study treatment until disease progression, loss of clinical benefit, initiation of new anti-cancer therapy, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.Extended Data Fig. 1: Of 146 patients assigned to toripalimab group, 3 withdrew consent, 2 started other anti-cancer therapy, 2 discontinued due to physician decision. Of the 143 patients assigned to placebo group, 2 withdrew, 3 starged other anti-cancer therapy, 1 lost to follow-up, 3 discontinued due to physician desicion.Fig 1a: No. PFS event=182The overall proportion of patient without available outcome was 5.5% (4.8% vs 6.2%). The observed number of	Low	Publication: The primary endpoint was PFS in the ITT population as assessed by a BIRC according to RECIST v.1.1. PFS was defined as the time from randomization to that of first documented disease progression or death. The primary outcome was assessed by blinded independent review committee.	Low	Publication: cutoff date 30 May 2020. PFS events 128.The SAP version date was 28 Jun 17; Protocol JS001-015-III-NPC, Version 6.0 (2020-Oct-14): The final analysis of PFS will be conducted when approximately 200 PFS events in the ITT population have been observed.	Low

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Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								events was 8 time the number of participants with missing outcome data (7.0 vs 8.8).					
NCT035 94747	337926 23	PFS	Low	Publication: Patients were randomized (1:1:1) to treatment by using an in- teractive response technology system. Publication: Demographic and disease baseline characteristics were rep- resentative of the target patient population and generally well balanced between treatment arms, including disease stage and PD-L1 expression, which was consistent with ran- domization based on these stratification factors (Table 1).	Some concer ns	This is an open-label trial. Not enough information was available to answer this question. Publication: Efficacy analyses were assessed in the intent- to-treat (ITT) analysis set, which was defined as all randomized patients.	High	Figure 1: Of the 120 patients assigned to tislelizumab + paclitaxel + carboplatin, 9 withdrew consent, 1 lost to follow-up, 1 discontinued due to other reason. Of the 119 patients assigned to tislelizumab + nab- paclitaxel + carboplatin, 8 withdrew consent, 1 discontinued treatment due to other reason. Of the 121 patients assigned to paclitaxel + carboplatin, 9 withdrew consent. Figure 2: PFS event: 60 vs 56 vs 76. The overall proportion of patients without available outcome was 7.8% (8.3% vs 7.6% vs 7.4%). The observed number of events was 7.1 time the number of participants with missing outcome data. No analysis methods that correct for bias or sensitivity analyses was reported. Not enough information was available to answer this question.	Low	Publication: The primary end point was the comparison of PFS assessed by IRC between tislelizumab combined with paclitaxel plus car- boplatin (arm A) or nab-paclitaxel plus carboplatin (arm B) and paclitaxel plus carboplatin alone (arm C). The primary end point was assessed by IRC.	Low	Protocol (09 Feb 2018) Publication: The data cutoff for these analyses was December 6, 2019 Outcome measurements reported in the published article and supplementary appendix appear consistent with those specified in the protocol.	High

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Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
NCT036 63205	340339 75	PFS	Low	Pubilcation: Patients were randomized 2:1 to receive either tisleli- zumab in combination with chemotherapy (arm A) or chemotherapy alone (arm B) using an interactive response technology system.Publication: Demographics and disease baseline characteristics were representative of the target patient population and were generally well balanced between treatment arms, although the percentage of patients aged less than or equal to 65 years was numerically higher in arm A than arm B (Table 1).	Some concer ns	This is an open-label trial.Not enough information was available to answer this question.Efficacy analysis was in the intention-to-treat population.	High	Figure 1: Of 223 patients allocated to tislelizumab group, 17 withdrew consent, 4 discontinued treatment due to other reason. Of the 111 patients allocated to chemotherapy group, 14 withdrew consent, 1 discontinued treatment due to other reason.We assumed that patients withdrew consent and discontinued due to "other reason" did not have available outcome. The overall proportion of patient without outcome was 10.8%. No analysis methods that correct for bias or sensitivity analyses was reported.Not enough information was available to answer this question.	Low	Publication: The primary end point of this study was the com- parison of PFS as assessed by the IRC (PFSIRC) between tislelizumab plus carboplatin or cisplatin in combination with pemetrexed (arm A) versus carboplatin or cisplatin in combination with pemetrexed alone (arm B) in all randomized patients (intent-to-treat [ITT]).Supplement: Progression-free survival was defined as the time from randomization to the first objectively documented disease progression per RECIST v1.1 or death from any cause, whichever occurred first. Although this is an open-label trial, the primary end point of this study was PFS as assessed by the IRC.	Some concer ns	Study protocol was not available to answer this question fully.Study protocol was not available to answer this question fully.	High
NCT033 58875	361840 68	OS	Low	Publication: Patients were randomized (2:1) using an interactive web response technology system The baseline demographic and disease characteristics of the patients were representative of the target popu- lation and were well balanced between those receiving tislelizumab and docetaxel, including PD-L1 expression and	Some concer ns	This is an open-label trial. According to Figure 1, there were 1 and 12 patients randomized to the tislelizumab and docetaxel group but not treated respectively. However, the underlying reason was not reported. Publication: The co-primary end points were OS both in the intent-to-treat (ITT) population, which included all	Low	Protocol: Reasons a patient may be discontinued from the study may include, but are not limited to the following: Patient withdrawal of consent Pregnancy; Any medical condition that the investigator determines may jeopardize the patient's safety, if he or she were to continue in the study; Use of any concurrent antineoplastic therapy (ie, chemotherapy,	Low	The primary endpoint was overall survival. This is an open-label trial. Overall survival is an objective endpoint.	Low	Protocol Amendment 3.0 (09-Mar-2020): As of amendment 3.0, the number of death events that triggers interim analysis has been changed to 426 (approximately 76% of total number of 560 deaths) in the ITT Analysis Set. Publication: The prespecified interim analysis was performedwhen 441 OS events were	Some concer ns

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Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				pathologic type (Table 1).		randomized patients, and in a subset of patients with PD-L1 expression on greater than or equal to 25% of the tumor cells.		hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese (or other Country) herbal medicine and Chinese (or other Country) patent medicines] for the treatment of cancer); Patient noncompliance. Figure 1: Of the 535 patients assigned to tislelizumab, 1 lost of follow-up.				observed in the ITT popula- tion (data cutoff: August 10, 2020). At the final analysis data cutoff of July 15, 2021, there were 571 and 228 OS events in the ITT population and PD-L1 greater than or equal to 25% population, respectively. Outcome measurements reported in the published article and supplementary appendix appeared to be consistent with those specified in the protocol.	
NCT015 78499	286001 32	objecti ve global respon se lasting at least 4 month s	Low	Publication: Patients were randomly assigned (1:1) by an interactive voice and web response system to brentuximab vedotin or conventional therapy. The randomisation list was generated by the Takeda statistician who was not involved in the remainder of the trial.Publication: Baseline characteristics were generally balanced between groups (table 1), with the exception of more patients with stage IVB mycosis fungoides and extracutaneous pcALCL in the	Low	This is an open-label trial.According to Figure 1, there was no protocol violation except two withdrawal by patient.Publication: Efficacy analyses were done in the intention-to-treat population and safety analyses were done in all patients who received at least one dose of study drug.	Low	Figure 1: Only 3/65 (4.6% <5%) patients in the control group withdrew.	Low	Publication: The primary endpoint was the proportion of patients achieving an objective global response lasting (from first to last response) at least 4 months (ORR4). The intent of this endpoint was to capture durable response to the study drug that is minimally affected by other therapies. This endpoint was chosen because in patients with cutaneous T-cell lymphoma, short clinical responses might not equate to meaningful benefit. To determine ORR4 and disease progression, an independent review facility reviewed global response scores using consensus guidelines by the International Society for Cutaneous Lymphomas	Low	Protocol Approve Date: 02 December 2014: Approximately 124 patients (approximately 62 patients per treatment arm) will be randomized to the study, including a minimum of 30 patients (15 per treatment arm) with pcALCL. The sample size was calculated based on providing 90% power to detect a 30% improvement in ORR, lasting at least 4 months.Outcome measurements reported in the published article	Low

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Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				brentuximab vedotin group.						and the European Organisation for Research and Treatment of Cancer.Publication: To determine ORR4 and disease progression, an independent review facility reviewed global response scores using consensus guidelines by the International Society for Cutaneous Lymphomas and the European Organisation for Research and Treatment of Cancer.		and supplementary appendix appeared to be consistent with those specified in the protocol.	
NCT010 06980	216398 08	OS and PFS	Some concer ns	The only information about randomization methods is a statement that the study is randomized. Protocol: The patient randomization numbers will be generated by Roche or its designee. Publication: Baseline characteris- tics of the patients were well balanced (Table 1).	Some concer ns	This is an open-label trial. According to Supplementary Figure, 20/338 patients randomized to the dacarbazine group withdrew consent before receiving treatment. However, the underlying reason was not reported. Publication: Efficacy analyses were performed in the intention-to-treat population.	High	Supplement Fig: Of the 338 patients randomized to dacarbazine group, 20 withdrew consent. Protocol: Patients who withdraw from study treatment for any reason, will have periodic check-ups and be followed for cutaneous squamous cell carcinoma (SCC), head and neck evaluations, chest CT scans, and survival, until death, withdrawal of consent, or lost to follow-up. Publication: A total of 118 patients had died at the time of the interim analysis. The overall proportion of patients without available outcome was 3.0% (0 vs 5.9%). The observed number of events was 5.9 time the number of participants with	Low	Publication: Coprimary end points were rates of overall and progression-free survival. This is an open-label trial. Overall survival, the outcome we assessed, was an objective endpoint.	Some concer ns	Protocol (16-Feb-2011): Regarding OS, approximately 196 deaths are needed to detect a HR of 0.65 with an overall Type I error of 0.045 (2-sided) with 80% power, including one interim analyses with 50% information. Publication: This report is based on data as of December 30, 2010. A total of 118 patients had died at the time of the interim analysis. The data cutoff date was after the protocol amendment date, while the previous protocol was unavailable. Previous study protocol or statistical analysis plan issued before	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								missing outcome data. No analysis methods that correct for bias or sensitivity analyses was reported. Not enough information was available to answer this question.				were not available to answer this question fully.	
NCT036 07539	327812 63	PFS	Low	Publication: An interactive web response system was used to assign patients as per predefined randomization.Publica tion: The demographic and disease characteristics at baseline were well balanced between the two groups (Table 1).	Low	This is a double-blind trial. The incidence of grade 3 or higher adverse events was similar between groups (61.7% in sintilimab-combination group and 58.8% in placebo-combination group).Publication: Efficacy analyses included all patients randomly assigned to a group according to the intention-to-treat principle, whether they had received treatment or not.	Low	Supplementary Fig 1: Of the patients allocated, no one lost to follow-up. Protocol: Since some clinical event data may be important to the study after treatment discontinuation/study withdrawal, this information must be collected until the subject's last scheduled visit, even if the subject has discontinued/withdraw n from study.	Low	Publication: The response was assessed on the basis of the Response Evaluation Criteria in Solid Tumors version 1.1. Complete and partial responses were confirmed by repeat tumor imaging assessment no less than 4 weeks from the date the response was first documented.The primary end point was progression-free survival (PFS) as judged by an independent radiographic review committee.	Low	Protocol Aug 09, 2019/Version 3.0: An interim analysis will be conducted after 70% of the target PFS events (184 events) are observed, and the interim analysis will be based on PFS.Publication: As of the data cutoff on November 15, 2019, there were 198 events of disease progression or deathOutcome measurements reported in the published article and supplementary appendix appeared to be consistent with those specified in the protocol.	Low
NCT036 29925	340489 47	PFS	Low	Publication: The randomization was implemented by an interactive web-response system using permuted block method with block size of 4. The demographic and disease characteristics at baseline were well	Low	This is a double-blind trial. Although treatment-emergent adverse event leading to discontinuation of any treatment component were 10.6% and 14.6%, these were not considered to be substantial enough to break blinding of participants and	Low	Figure 1: Of the patients allocated to intervention, no one lost to follow-up. Protocol: Treatment discontinuation is not the same as withdrawal from the study. Since data on some clinical events after treatment discontinuation may	Low	Publication: The primary end point was PFS (defined as the time from randomization to the first PD or death from any cause), as assessed by the independent radiographic re- view committee (IRRC). The primary endpoint was assessed by the	Low	Protocol Nov. 27, 2019/Version 2.3: An interim analysis will be performed when 70% of PFS events (i.e., 185 PFS events) occur. Publication: At the data cutoff on October 15, 2019 (interim analysis), the median follow-	Low

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				balanced between the two treatment groups (Table 1).		personnel. Publication: Efficacy analyses were performed for all patients who were randomly assigned to either treatment group ac- cording to the intention-to-treat principle, regardless of whether they had received treatment or not.		be important to the study, these information must be collected until the subject's last scheduled visit, even if the treatment has already been discontinued.		independent radiographic re- view committee.		up was 8.0 months (range: 0.5–12.6). An IRRC-assessed PFS event occurred in 99 patients (55.3%) in the sintilimab- GP group and 128 patients (71.9%) in the placebo-GP group. Outcome measurements reported in the published article and supplementary appendix appeared to be consistent with those specified in the protocol.	
NCT037 94440	341439 71	OS and PFS	Low	Publication: Randomisation was done using permuted block randomisation, with a block size of six, via an interactive web response system. Publication: Demographic and disease characteristics at baseline were similar between the two study groups (table 1).	Some concer ns	This is an open-label trial. According to Figure 1, 6/191 patients assigned to sorafenib group withdrew consent. However, the underlying reason was not reported. Publication: Efficacy analyses in the phase 3 part of the trial for overall survival and progression-free survival included all patients randomly assigned to a group according to the intention-to-treat principle, regardless of whether or not they received treatment.	Low	Figure 1: Of the 380 patients assigned sintilimab–bevacizumab biosimilar, 1 withdrew consent. Of the 191 patients assigned to sorafenib, 1 withdrew consent. Protocol: Since some data on clinical events after treatment termination may be very important to the study, the information must be collected until the patient's last scheduled visit, even if the treatment has already been terminated. A patient who withdraws from the study will no longer receive the treatment and protocol-specified follow-up visits.	Low	Publication: For the phase 3 part of the study, the co-primary endpoints were overall survival and progression-free survival as assessed by the IRRC per RECIST version 1.1. This is an open-label trial. Overall survival, the outcome we assessed, is an objective endpoint.	Low	Protocol Apr. 20, 2020 Version 3.0: In this study, an interim analysis of OS endpoint will be carried out when 265 (65%) cases of OS events are observed. Publication: In the first interim analysis of overall survival, 122 (32%) of 380 patients in the sintilimab–bevacizumab biosimilar group and 87 (46%) of 191 patients in the sorafenib group had died. data cutoff Aug 15, 2020 Outcome measurements reported in the published article and supplementary appendix appeared	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
												to be consistent with those specified in the protocol.	
NCT016 46021	266738 11	PFS	Low	Publication: Patients were stratified by previous therapy and simplified mantle-cell lymphoma international prognostic index score, and were randomly assigned with a computer-generated randomisation schedule to receive daily oral ibrutinib 560 mg or intravenous temsirolimus (175 mg on days 1, 8, and 15 of cycle 1; 75 mg on days 1, 8, and 15 of subsequent 21-day cycles). Randomisation was balanced by using randomly permuted blocks.Publication: Baseline demographics and disease characteristics (table 1) were generally well balanced and were consistent with known characteristics of mantle-cell lymphoma.	Some concer ns	This is an open-label trial.Not enough information was available to answer this question.Publication: The analysis followed the intention-to-treat principle.	Low	Figure 1: Of 141 patients allocated to temsirolimus group, only 1 withdrew consent.	Low	Publication: The primary endpoint was progression-free survival, which was defined as the interval from date of randomisation to the date of disease progression (as assessed by the independent review committee) or date of death, whichever occurred first, irrespective of the use of subsequent antineoplastic therapy.Although this is an open-label trial, the primary endpoint was assessed by the independent review committee	Some concer ns	Study protocol was not available to answer this question fully.Study protocol was not available to answer this question fully.	Some concer ns
NCT019 73387	295330 00	PFS	Low	Publication: Patients were assigned to a treatment group between 26 December 2013 and 15 September 2015 using an inter- active web response system. According to Table 1, the baseline seems	Some concer ns	This is an open-label trial. Not enough information was available to answer this question. Publication: The intent-to-treat (ITT) population included all patients	High	Supplementary Figure 3: Of the 106 patients assigned to ibrutinib, 7 withdrew consent. Of the 54 patients assigned to rituximab, 6 withdrew consent. Publication: In the updated analysis, 64 PFS events were	Some concer ns	Publication: The primary endpoint was investigator-assessed PFS, defined as the time from randomization until PD per IWCLL 2008 criteria or death, whichever occurred first. The criteria for PD are described in the Appendix S1. Appendix: A CT scan was	Some concer ns	Study protocol was not available to answer this question fully. Study protocol was not available to answer this question fully.	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				similar between the two groups.		randomized into the study and analyzed according to assigned treatment group, regardless of the actual treatment received.		reported (26 [24.5%] in the ibrutinib arm and 38 [70.4%] in the rituximab arm). We assumed that patients withdrew consent did not have available outcome. The overall proportion of patient without outcome was 10.8%. The observed number of events was 4.9 time the number of participants with missing outcome data. No analysis methods that correct for bias or sensitivity analyses was reported. Not enough information was available to answer this question.		required to evaluate all cases of suspected progressive disease regardless of the modality of disease progression (e.g. lymph node, lymphocytosis, or transformation). This is an open-label trial, the primary endpoint was investigator-assessed PFS. Assessment of the outcome was likely to be influenced by knowledge of intervention received due to the potentially subjective nature of PFS which incorporates radiological progression. Yet, there is no reason to believe that it did.			
NCT015 78707	248816 31	PFS	Low	Publication: This randomization scheme was implemented within the Interactive Web Response System (IWRS). Publication: The baseline characteristics of the patients were generally well balanced between the two study groups (Table 1)	Some concer ns	This is an open-label trial. According to Figure S1, 4/196 patients assigned to ofatumumab withdrewn consent before receiving treatment. However, the underlying reason was not reported. Protocol: The ITT population is defined as all patients who were randomized. All efficacy analysis will be performed using the ITT population and patients in the ITT population will be analyzed as randomized.	Low	Figure S1: Of the 195 patients assigned to ibrutinib group, 1 withdrew consent. Of the 196 patients assigned to ofatumumab, 10 withdrew. Protocol: Patients who withdraw from the study or are considered lost to follow-up without prior documentation of disease progression will be censored on the date of the last adequate disease assessment. The overall proportion of patient without available outcome	Low	Publication: The primary end point was the duration of pro- gression-free survival, as assessed by the inde- pendent review committee, according to the criteria of the International Workshop on Chronic Lymphocytic Leukemia. Although this is an open-label trial, the primary endpoint was assessed by the independent review committee.	Some concer ns	Protocol (AMENDMENT 4: 24 September 2013): A pre-specified interim analysis for both superiority and futility (non-binding) will be performed after approximately 117 IRC confirmed PFS events are reported. However, the data cutoff date and actual number of events in the interim analysis was not reported There was not enough information to answer this	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								was 2.8% (0.5% vs 5.1%).				question. The primary analysis was IRC assessed PFS in the ITT population, which is consistant with the protoco.	
NCT021 65397	298566 85	PFS	Low	Protocol: For Treatment Arms A and B, central randomization was implemented in this study. The randomization scheme was implemented within the Interactive Web Response System (IWRS).Publication: The characteristics of the patients at baseline were generally well balanced (Table 1).	Low	Protocol: This is a randomized, placebo-controlled, double-blind, Phase 3 study.Protocol: The intent-to-treat (ITT) population includes all randomized subjects (Arms A and B), regardless of the actual treatment received. This population will be the primary population for the summary/analyses of efficacy endpoints.	High	Figure S1: Of the 75 patients randomized to ibrutinib group, 3 withdrew of consent. OF the 75 patients randomized to placebo group, 1 lost to follow-up, 4 withdrew consent.The overall proportion Protocol: After the End-of-Treatment Visit (30 days ± 3 days from last dose of study drug) has been performed, subjects will continue to be monitored through either response follow-up or survival follow-up and will continue until death, lost to follow-up, consent withdrawal, or study end, whichever occurs first.Publication: The 30-month progression-free survival rate was 82% in the ibrutinib–rituximab group and 28% in the placebo–rituximab group.The overall proportion of patient without outcome was 5.3%. The observed number of events was 8.5 time the number of	Low	Protocol: The primary endpoint is PFS, as assessed by IRC, which is defined as duration from the date of randomization to the date of disease progression or death, whichever is first reported, assessed per the modified VIth IWWM (NCCN 2014) criteria.Publication: The primary end point was progression-free survival, as assessed by the independent review committee.	Low	Protocol Amendment 3: 9 October 2015: An interim analysis for the randomized treatment arms (Arm A and Arm B) will be conducted at approximately 70% information, ~50 PFS events based on IRC assessment.Publica tion: From July 2014 through January 2016, we en- rolled patients at 45 sites in nine countries. The 30-month progression-free survival rate was 82% in the ibrutinib–rituximab group and 28% in the placebo–rituximab group (median, not reached vs. 20.3 months).Outcome measurements reported in the published article and supplementary appendix appeared to be consistent with those specified in the protocol.	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								participants with missing outcome data.No analysis methods that correct for bias or sensitivity analyses was performed.No information was available to answer this question.					
NCT015 64537	271192 37	PFS	Low	Protocol: Randomization scheme will be generated by an independent statistician at Millennium who is not on the study team. Prior to dosing, a randomization number will be assigned to each patient. The randomization assignment will be implemented by an IVRS. Publication: Baseline characteristics of the patients in the intention-to-treat population were well balanced between the study groups (Table 1).	Low	This is a double-blind trial. The rates of serious adverse events were similar in the two study groups (47% in the ixazomib group and 49% in the placebo group), as were the rates of death during the study period (4% and 6%, respectively) Publication: The intention-to-treat population, which included all patients who underwent randomization, was evaluated for all primary and secondary efficacy analyses.	Low	Figure S1: Of the 360 patients allocated to ixazomib group, 1 withdrew consent before receiving treatment, 7 withdrew, 1 lost to follow-up. Of the 362 patients randomized to placebo group, 11 withdrew. Protocol: Time-to-event parameters will be censored if patients withdraw, drop out, or are lost to follow-up before documentation of the events (PD/death). The overall proportion of patient wihtout available outcome was 2.8%.	Low	Publication: The primary end point was progression-free survival, which was defined as the time from the date of randomization to the date of first docu- mentation of disease progression or death from any cause, as assessed by an independent review committee, whose members were unaware of the study-group assignments. Publication: The primary end point was progression-free survival, as assessed by the independent review committee.	Low	Clinical Study Protocol C16010 Amendment 3, 08 July 2014: The first IA will be performed when approximately 262 of the disease progression/death events have occurred. Publication: At the time of data cutoff for the first analy- sis (October 30, 2014), the median follow-up was 14.8 months in the ixazomib group and 14.6 months in the placebo group. As assessed by an independent review committee, 129 events of disease progression or death occurred in the ixazomib group and 157 in the placebo group. Outcome measurements reported in the published article and supplementary appendix appeared to be consistent with	Low

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
												those specified in the protocol.	
NCT015 64537 (China Continua tion study)	286837 66	PFS	Low	TOURMALINE-MM1 Global Protocol: Randomization scheme will be generated by an independent statistician at Millennium who is not on the study team. Prior to dosing, a randomization number will be assigned to each patient. The randomization assignment will be implemented by an IVRS.Publication: Patient demographics and baseline disease characteristics were generally well balanced between treatment arms (Table 1).	Low	This is a double-blind study. On the ixazomib-Rd and placebo-Rd arms, respectively, 38 (67%) and 43 (74%) patients reported grade ≥3 adverse events (AEs), 19 (33%) and 18 (31%) reported serious AEs, and 4 (7%) and 5 (9%) died on-study. Efficacy data was analyzed in intention-to-treat population.	Low	Fig. 1: Of the 57 patients allocated to ixazomib group, 3 withdrew. Of the 58 patients allocated to placebo group, 2 withdrew, 1 discontinued treatment for other reason. Publication: Per IRC assessment, 67 PFS events (confirmed progression or death) had occurred in 30 (53%) and 37 (64%) patients in the ixazomib-Rd and placebo-Rd arms, respectively.The overall proportion of patient without available outcome was 5.2%. The observed number of events was 11.2 time the number of participants with missing outcome data.	Low		Low	Protocol Amendment 2 (For use in China only): Following completion of enrollment in the global study (703 patients), up to approximately 120 additional patients from China will be enrolled in the China continuation. The primary objective of PFS will be assessed when 50% of PFS events have occurred or a minimum of 18 months after the first patient is enrolled in the China continuation, whichever occurs first.Publication: At data cut-off for the primary and final analysis of PFS, the median follow-up for PFS was 7.4 months in the ixazomib-Rd arm and 6.9 months in the placebo-Rd arm. Per IRC assessment, 67 PFS events (confirmed pro-gression or death) had occurred in 30 (53%) and 37 (64%) patients in the ixazomib-Rd and placebo-Rd arms, respectively.Outcom	Low

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
												e measurements reported in the published article and supplementary appendix appeared to be consistent with those specified in the protocol.	
NCT020 13167	282491 41	OS	Low	Publication: Eligible patients were randomly assigned, in a 2:1 ratio, with the use of an interactive voice- response system to receive open-label treatment with either blinatumomab or standard chemo- therapy (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Publication: The two treatment groups had similar demographic and disease characteristics at baseline when all patients who underwent randomization were assessed (Table 1) as well when patients who did not receive the trial treatment were excluded (Table S3 in the Supplementary Appendix).	Some concer ns	This is an open-label trial. According to Figure S2, 9/271 patients did not receive allocated blinatumomab, 1 due to patient request. 25/134 patients allocated to chemotherapy group did not receive treatment, including 22 (16.4%) due to patient request. However, the underlying reason was not analyzed. Publication: Efficacy analyses included all patients who underwent randomization (intention-to-treat population).	High	Publication: less than 1% of the 271 patients in the blinatumomab group and 16% of the 134 pa- tients in the chemotherapy group withdrew consent before receiving treatment (Fig. S2 in the Supplementary Appendix). Figure S2: Of the 271 patient allocated to blinatumomab, 14 withdrew consent, 1 lost to follow-up. Of the 134 patients allocated to chemotherapy, 15 withdrew consent. Publication: For this prespecified interim analysis, 251 deaths were recorded. The overall proportion of patient without available outcome was 7.4%. This proportion imbalanced between groups (5.5% vs 11.2%). The observed number of events was 8.4 time the number of participants with missing outcome data. No analysis methods	Low	The primary end point was overall survival, which was defined as the time from randomization to death from any cause. This is an open-label trial. Overall surivival is an objective endpoint.	Low	Protocol: Two formal interim analyses are planned to assess OS when approximately 50% and 75% of the total number of OS events have been observed. Stopping for benefit will be based on an O'Brien-Fleming type alpha spending function; the critical p-values corresponding to this spending function are 0.0031 for the first interim analysis, 0.0183 for the second interim analysis, and 0.044 for the primary (ie, final) analysis if the interim analyses occur precisely at 165 (50%) and 248 (75%) deaths. Publication: The data cutoff date was January 4, 2016. For this prespecified interim analysis, 251 deaths were recorded. Outcome measurements reported in the	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								that correct for bias or sensitivity analyses was reported. Not enough information was available to answer this question.				published article and supplementary appendix appeared to be consistent with those specified in the protocol.	
NCT038 63860	354046 84	PFS	Low	Protocol: Randomization will be carried out with a stratified block randomization manner.Publication: Patient characteristics were generally well balanced between the fuzuloparib and placebo groups at baseline (Table 1).	Some concer ns	Although this is a double-blind trial, grade 3 or 4 TEAEs, most of which were anemia (25.1% in the fuzu-loparib group v 0% in the placebo group), decreased platelet count (16.8% v 0%), decreased neutrophil count (12.6% v 0%), and decreased white blood cell count (10.8% v 0%), were reported in 80 (47.9%) patients receiving fuzuloparib and 9 (10.7%) patients receiving placebo. We assumed that such differences could potentially break the blinding of the trial, and resulting in participants, carers and personnel correctly guessing their treatment allocation.According to Figure 1, 6/167 patients assigned to fuzuloparib group withdrew consent; 2/85 patients allocated to placebo withdrew consent. However, the underlying reason was not reported.Publication: Efficacy analyses were conducted in the intention-to-treat population, which	Low	Fig. 1: Of the 167 patients allocated to fuzuloparib group, 6 withdrew. Of the 85 patients allocated to placebo group, 2 withdrew, 1 withdrew consent.Publication: A total of 115 (45.6%) PFS events, according to BIRC assessment, occurred in 55 patients (32.9%) in the fuzuloparib group and 60 patients (70.6%) in the placebo group.The overall proportion of patient without available outcome was 3.6%. The observed number of events was 12.8 times the number of participants with missing outcome data.	Low	Publication: The two primary end points were PFS per BIRC in the overall population and PFS per BIRC in the subpopulation with germline BRCA 1/2 mutation. PFS was defined as the time from random assignment to the time of progression according to RECIST 1.1 or death from any cause, whichever occurred first.The primary endpoint was assessed by blinded independent review committee	Low	Protocol version2.0 (27 May, 2019): Interim Analysis: Account for about 60%, Number of Events: 103Publication: A total of 115 (45.6%) PFS events, according to BIRC as- sessment, occurred in 55 patients (32.9%) in the fuzuloparib group and 60 patients (70.6%) in the placebo group. date of data cutoff (July 1, 2020).Outcome measurements reported in the published article and supplementary appendix appeared to be consistent with those specified in the protocol.	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
						included all randomly assigned patients.							
NCT029 93523	327861 87	OS	Low	Protocol: The site will contact the IRT to complete the randomization process and obtain study drug assignment. Subjects will be enrolled as described in Section 5.5.4 and will receive a separate unique 6-digit randomization number that will be automatically recorded in the eCRF through the IRT system. This randomization number will be used only by AbbVie for loading the treatment schedule into the database. According to Table 1, the baseline seems similar between the two groups.	Low	This is a double-blind study. Although proportion of notable serious adverse events (grade ≥3) were febrile neutropenia (in 30% of the patients in the azacitidine– venetoclax group and 10% of those in the con- trol group), these were not considered to be substantial enough to break blinding of participants and personnel. Publication: Efficacy analyses were performed in the intention-to-treat population.	High	Figure 1: Of the 286 patients assigned to receive azacitidine plus venetoclax, 26 withdrew consent, 5 lost to follow-up. Of the 145 patients assigned to receive azacitidine plus placebo, 22 withdrew consent, 2 lost to follow-up. Protocol: All subjects will have a Final Visit performed when treatment is discontinued unless the subject has withdrawn consent to participate in the study. The overall proportion of patient without available outcome was 12.7%. This proportion imbalanced between groups (10.8% vs 16.5%). No analysis methods that correct for bias or sensitivity analyses was reported. Not enough information was available to answer this question.	Low	Publication: Overall survival was defined as the number of days from randomization to the date of death. This is a double-blind trial.	Low	M15-656 Protocol Amendment 7 (21 August 2019): Interim analysis of OS at 75% of death events with O'Brien-Fleming boundary. Publication: The clinical data cutoff date was January 4, 2020. The prespecified interim efficacy analysis of overall survival after 75% of the target number of deaths had occurred. Outcome measurements reported in the published article and supplementary appendix appeared to be consistent with those specified in the protocol.	High
2004L02 352	10.376 0/cma.j .cn112 137-202001 16-00105	PFS	Some concer ns	本研究是一项随机对照、多中心、前瞻性Ⅲ期临床试验，筛选合格的受试者按 2∶1 比例随机分配至试验组和对照组。 According to Table 1, the baseline seems	Some concer ns	No information was available to answer this question. No information was available to answer this question.	High	No information was available to answer this question. No information was available to answer this question.	High	在试验期间，受试者定期接受生命体征、体格检查和相关实验室检查，每 4 周进行 1 次安全性评估，每 8 周进行 1 次疗效评估。试验组或对照组受试者进入赛普汀单药治疗后，则每 6 周进行 1 次安全性评估和疗效评估。	Some concer ns	The protocol was not available. The protocol was not available.	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				similar between the two groups.		全分析数据集定义：是按照意向性分析（ITT）原则确定的数据集，包括所有随机化入组、至少使用过 1 次试验药的病例。安全性数据集定义：使用过试验药并至少有一次安全性评价记录的病例。				采用 RECIST 1.0 进行疗效评价。主要研究终点为无进展生存期（PFS），定义为从受试者第 1 次用药到第 1 次记录的肿瘤进展或者任何原因导致死亡的时间。 No information was available to answer this question. No information was available to answer this question.			
NCT025 88170	329668 11	PFS	Low	Publication: Patients were centrally randomly assigned (2:1) using stratified block randomisation (block size 3) via an interactive web response system to receive oral surufatinib at 300 mg per day or matching placebo.According to Table 1, the baseline seems similar between the two groups.	Low	This is a double-blind trial. Although treatment-related serious adverse events were reported in 32 (25%) of 129 patients and nine (13%) of 68 patients in the surufatinib and placebo groups respectively, these were not considered to be substantial enough to break blinding of participants and personnel.Publication: The intention-to-treat set, which included all randomly assigned patients, was used for progression-free survival and overall survival outcomes.	Low	Figure 1: Of 129 patients randomly assigned to surufatinib group, 0 lost to follow-up. Of 69 patients randomly assigned to placebo group, 3 (4.3%) withdrew consent.Protocol: Investigators will follow up with the patient by telephone to document survival status and subsequent anti-tumor treatments every 12 (±2) weeks until death, loss to follow-up, withdrawal of informed consent, or until the sponsor ceases to collect related data.	Low	Publication: The primary outcome was investigator-assessed progression-free survival, defined as the time from randomisation to the first documented disease pro- gression, as defined by RECIST 1.1, or death because of any cause. BIIRC-assessed progression-free survival was a supportive outcome.Although the primary outcome was investigator-assessed progression-free survival, this is a double-blind trial.	Low	Protocol (19 October 2017 version 3.0): An interim analysis will be conducted when 70% of the predicted PFS events (i.e., 127 events) have been observed, with a significance level of 0.015 (two-sided).Publication: At the time of data cutoff (March 31, 2019), 77 (60%) patients in the surufatinib group and 51 (74%) in the placebo group had progression-free survival events, as assessed by investi-gators.Outcome measurements reported in the published article and supplementary appendix appeared to be consistent with those specified in the protocol.	Low
NCT025 89821	329668 10	PFS	Low	Publication: The randomisation	Low	This is a double-blind trial. Although The most	Low	Figure 1: Of the 113 patients randomly	Low	Publication: The primary outcome was investigator-	Low	Protocol (19 October 2017	Low

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				sequence was generated independently from the trial by a statistician from a contract clinical research organisation, ICON, using stratified block randomisation with a block size of three. Randomisation was done centrally with an interactive web response system provided by ICON, and the allocation sequence was concealed from patients, investigators, research staff, and the sponsor study team. According to Table 1, the baseline seems similar between the two groups.		common grade 3 or worse treatment-related adverse events were hypertension (43 [38%] of 113 with surufatinib vs four [7%] of 59 with placebo), proteinuria (11 [10%] vs one [2%]), and hypertriglyceridaemia (eight [7%] vs none), these were not considered to be substantial enough to break blinding of participants and personnel. Publication: The intention-to-treat set, which included all patients who were randomly assigned, was used for progression-free survival and overall survival analysis.		assigned to receive surufatinib, 4 withdrew consent. Of the 59 patients randomly assigned to receive placebo, 3 withdrew consent. Publication: A pre-planned interim analysis was to be done when 70% of the predicted progression-free survival events (ie, 92 events) occurred. The overall proportion of patient without available outcome was 4.1%. The observed number of events was 13.1 time the number of participants with missing outcome data.		assessed progression-free survival, defined as the time from randomisation to the first documented disease progression, as per RECIST version 1.1, or death due to any cause. BIIRC-assessed progression-free survival was a supportive outcome. Although the primary outcome was investigator-assessed progression-free survival, this is a double-blind trial.		version 3.0): An interim analysis will be performed when 70% of the expected PFS events (i.e., 92 PFS events) have occurred. Publication: At the time of data cutoff for the interim analysis (Nov 11, 2019), 92 progression-free survival events occurred. Outcome measurements reported in the published article and supplementary appendix appeared to be consistent with those specified in the protocol.	
NCT022 46621	289681 63	PFS	Low	Protocol: Assignment to treatment groups will be determined by a computer-generated random sequence using the IWRS. Publication: Patient baseline characteristics were well balanced between arms (Table 1).	Low	This is a double-blind trial. Although serious adverse events were reported in 27.5% of patients in the abemaciclib arm and 14.9% in the placebo arm, these were not considered to be substantial enough to break blinding of participants and personnel. Publication: The primary statistical analysis included all patients in	Low	Fig 1: Of the 328 patients allocated to abemaciclib + nonsteroidal AI, 3 lost to follow-up. Of the 165 patients allocated to placebo + nonsteroidal AI, 1 lost to follow-up.	Low	Publication: The primary end point, investigator-assessed progression-free survival, was evaluated from random assignment until the time of objective disease progression or death. Although the primary outcome was investigator-assessed progression-free survival, this is a double-blind trial.	Low	Protocol: The interim analysis is planned to take place after approximately 180 (approximately 80% of the planned) investigator - assessed PFS event have occurred. Publication: The interim analysis occurred after 194 progression-free sur- vival events (108 [32.9%] in the abemaciclib arm and 86 [52.1%] in	Low

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
						the intent- to-treat population.						the placebo arm). Outcome measurements reported in the published article and supplementary appendix appeared to be consistent with those specified in the protocol.	
NCT027 63566 (MONA RCH plus Cohort A)	331497 68	PFS in cohort A	Low	Publication: Treatment was determined by a computer-gen- erated random sequence and assigned by study center personnel using an interactive web response system.Publication: Baseline patient characteristics were well balanced between treatment arms in both cohorts (Tables 1 and 2).	Low	Although this is a double-blind trial, the grade 3-4 adverse event was 59% vs 23.2%. We assumed that such differences could potentially break the blinding of the trial, and resulting in participants, carers and personnel correctly guessing their treatment allocation.No information was available to answer this question.Publication: Efficacy analyses were per- formed on the intent-to-treat (ITT) population, which included all randomly assigned patients.	High	Supplementary Figure 1: Among 306 patients enrolled in Cohort A, 7/207 assigned to abemaciclib withdrew, 8/99 assigned to placebo group withdrew, 2/99 lost to follow-up.Publication: The interim analysis occurred after 119 PFS events were observed in the ITT population in cohort A [66 (31.9%) of 207 patients in the abe- maciclib arm and 53 (53.5%) of 99 patients in the placebo arm]The overall proportion of patient without available outcome was 5.6%. The observed number of events was 7 time the number of participants with missing outcome data.No analysis methods that correct for bias or sensitivity analyses was reported.No information was available to answer this question.	Low	Publication: The primary and key secondary endpoints, investigator-assessed PFS in cohort A and cohort B, respectively, were analyzed from the time of random assignment until objective progressive disease (PD) or death for any reason.Although the primary outcome was investigator-assessed progression-free survival, this is a double-blind trial.	Some concer ns	Protoco Approval Date: 14-May-2019: An interim analysis will be conducted after approximately 119 PFS events are observed to provide early efficacy information and allow for potential early communication with regulatory agencies. (see Section 12.2.6 for details).Publication: The interim analysis occurred after 119 PFS events were observed in the ITT population in cohort A [66 (31.9%) of 207 patients in the abe- maciclib arm and 53 (53.5%) of 99 patients in the placebo arm]). Data cut-off of 29 March 2019 was earlier than the protocol approval. In the Revised Protocol Sections: the interim analysis was amended from "70% of the required PFS events have been	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
												observed" to "119 events". However, previous protocol was not available to be used.Outcome measurements reported in the published article and supplementary appendix appeared to be consistent with those specified in the current protocol.	
NCT021 07703	285808 82	PFS	Low	Publication: Using an interactive, web-based randomization scheme, patients were assigned to receive abemaciclib plus fulvestrant or placebo plus fulvestrant in a 2:1 ratio. Protocol: Assignment to treatment groups will be determined by a computer-generated random sequence using the IWRS. Publication: Patients had well-balanced baseline character-istics (Table 1).	Some concer ns	Although this is a double-blind trial, the most common adverse events in the abemaciclib versus placebo arms were diarrhea (86.4% v 24.7%). We assumed that such differences could potentially break the blinding of the trial, and resulting in participants, carers and personnel correctly guessing their treatment allocation. There was not enough information to answer this question. Publication: The primary statistical analyses for investigator-assessed PFS were performed on the ITT population, which included all patients regardless of starting dose.	Low	Fig 1: Of the 446 patients allocated to abemaciclib + fulvestrant, 6 lost-to follow-up. Of the 223 patients allocated to placebo + fulvestrant, 4 lost to follow-up. The overall proportion of patients without available outcome was 1.5%.	Low	Publication: The primary end point, investigator-assessed PFS, was analyzed from the time of random assignment until objective PD or death for any reason. Tumors were measured by computed tomography or magnetic resonance imaging according to RECIST version 1.1 within 28 days before random assignment (baseline) and then every 8 weeks the first year, every 12 weeks thereafter, and within 2 weeks of clinical progression. Although the primary outcome was investigator-assessed progression-free survival, this is a double-blind trial.	Some concer ns	Protocol: Database lock for the final analysis of the PFS endpoint will occur when approximately 378 investigator-assessed PFS events have been observed. However, the protocol approval date was not disclosed. Publication: The data cut off occurred February 14, 2017. In the ITT population, 379 PFS events (documented progression or death without documented progression) occurred (n = 222 [49.8%] in the abemaciclib plus fulvestrant arm and n = 157 [70.4%] in the control arm). Outcome measurements reported in the published article and supplementary appendix appeared	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
												to be consistent with those specified in the protocol.	
NCT027 63566 (MONA RCH plus Cohort B)	331497 68	PFS in cohort A	Low	Publication: Treatment was determined by a computer-gen- erated random sequence and assigned by study center personnel using an interactive web response system.Publication: Baseline patient characteristics were well balanced between treatment arms in both cohorts (Tables 1 and 2).	Low	Although this is a double-blind trial, the grade 3-4 adverse event was 59% vs 23.2%. We assumed that such differences could potentially break the blinding of the trial, and resulting in participants, carers and personnel correctly guessing their treatment allocation.No information was available to answer this question.Publication: Efficacy analyses were per- formed on the intent-to-treat (ITT) population, which included all randomly assigned patients.	Low	Supplementary Figure 1: Among 157 patients enrolled in Cohort A, 4/104 assigned to abemaciclib withdrew, 2/53 assigned to placebo group withdrew, 2/99 lost to follow-up.Publication: In cohort B, at the time of the interim analysis cut-off, 82 PFS events [46 (44.2%) of 104 patients in the abemaciclib arm and 36 (67.9%) of 53 patients in the placebo arm] were observed.The overall proportion of patient without available outcome was 3.8%. The observed number of events was 13.6 times the number of participants with missing outcome data.	Low	Publication: The primary end point, investigator-assessed PFS, was analyzed from the time of random assignment until objective PD or death for any reason. Tumors were measured by computed tomography or magnetic resonance imaging according to RECIST version 1.1 within 28 days before random assignment (baseline) and then every 8 weeks the first year, every 12 weeks thereafter, and within 2 weeks of clinical progression.Although the primary outcome was investigator-assessed progression-free survival, this is a double-blind trial.	Some concer ns	Protocol: Database lock for the final analysis of the PFS endpoint will occur when approximately 378 investigator-assessed PFS events have been observed. However, the protocol approval date was not disclosed.Publicatio n: The data cut off occurred February 14, 2017. In the ITT population, 379 PFS events (documented progression or death without documented progression) occurred (n = 222 [49.8%] in the abemaciclib plus fulvestrant arm and n = 157 [70.4%] in the control arm). Outcome measurements reported in the published article and supplementary appendix appeared to be consistent with those specified in the protocol.	Some concer ns
NCT031 55997	329549 27	iDFS	Low	Protocol: The interactive web-response system (IWRS) will use randomization factors to assign treatment arm to each patient.	Some concer ns	This is an open-label trial. According to Figure 1, 14/2808 patients did not receive allocated abemaciclib. 32/2829 patients allocated to	High	Fig1: Of the 2808 patients allocated abemaciclib, 124 discontinued treatment due to patient decision, includes lost to follow-	High	Publication:The primary end point was invasive disease-free survival (IDFS) per the Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials (STEEP)	Low	Protocol (Approval Date: 18-Sep-2019): The primary analysis of the primary endpoint, invasive disease-free survival (IDFS),	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				Publication: Baseline characteristics were balanced between study arms (Table 1).		control group did not receive treatment. However, the underlying reason was not analyzed. Publication: Efficacy analyses were performed on the ITT population.		up. 158/2829 patients allocated to control group discontinued treatment due to patient decision, includes lost to follow-up. Protocol: If a patient decides at any point during the trial that they do not wish to continue with the full study schedule of assessments but are still willing to provide important study information (for example, disease recurrence information and/or survival status information) then the patient should continue in the study and information should continue to be collected in the clinical database. However, if a patient does not wish to have any further data collected, only then should they be considered as withdrawing consent from the study. Publication: At the time of data cutoff, there were 136 (4.8%) IDFS events in the abemaciclib arm and 187 (6.6%) in the control arm. The overall proportion of patient without available outcome was 5.0%. The		criteria17 and was measured from the date of randomization to the date of first occurrence of ipsilateral invasive breast tumor recurrence, local/regional invasive breast cancer recurrence, distant recurrence, death attributable to any cause, contralateral invasive breast cancer, or second primary nonbreast invasive cancer. This is an open-label trial. Assessment of the outcome was likely to be influenced by knowledge of intervention received due to the potentially subjective nature of DFS which incorporates distant recurrence assessed through radiological image. Yet, there is no reason to believe that it did.		will be performed after approximately 390 IDFS events have been observed in the Intent-to-Treat (ITT) population. Publication: At the time of data cutoff, there were 136 (4.8%) IDFS events in the abemaciclib arm and 187 (6.6%) in the control arm. (data cutoff March 16, 2020) Outcome measurements reported in the published article and supplementary appendix appeared to be consistent with those specified in the protocol.	

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								observed number of events was 1.1 time the number of participants with missing outcome data. No analysis methods that correct for bias or sensitivity analyses was reported. No information was available to answer this question.					
NCT013 32968	289768 63	PFS	Low	Publication: Randomization was performed by means of an interactive voice-response or online response system with the use of a hierarchical dynamic randomization schemePublication: The demographic and disease characteristics, including prognostic fac- tors, of the patients at baseline were well balanced between the two treatment groups (Table 1).	Some concer ns	Protocol: Because of the two different study arms with different administration schedules, it is very difficult to keep blinding for the investigators. Therefore, this study will be conducted in an open-label manner.According to Figure S1, 7/601 patients allocated to G-chemo groupand 3/601 patients allocated to the R-chemo group did not receive treatment. However, the underlying reaon was not reported.Publication: The efficacy analysis included all the patients who underwent randomization, and the safety analysis included all the patients who received any study treatment.	Low	Figure S1: Of the 601 patients randomized to G-chemo group, 10 withdrew consent, 1 lost to follow-up. Of the 601 patients randomized to R-chemo, 13 withdrew consent, 1 lost to follow-up.Protocol: Patients who complete the maintenance treatment or observation period or discontinue early will be asked to return to the clinic within 21–35 days after the last immunotherapy dose for a follow-up visit. Publication: The cutoff date for this analysis was January 31, 2016 (after 245 events had occurred).The overall proportion of patient without available outcome was 2.1%. The observed number of events was 9.8 time the number of participants with	Some concer ns	Publication: The primary end point was progression-free sur- vival, as assessed by the investigator, among pa- tients with follicular lymphoma. Progression-free survival was defined as the time from randomization to the earliest event of progression, relapse, or death from any cause. This is an open-label trial, and the primary end point was progression-free survival, as assessed by the investigator.Assessment of the outcome was likely to be influenced by knowledge of intervention received due to the potentially subjective nature of PFS which incorporates radiological progression. Yet, there is no reason to believe that it did.	Low	Protocol (version A5, 22-Mar-2014): At the time of the third interim analysis (efficacy on PFS) that will be conducted when 67% of the events have occurred (i.e., approximately 248 events), all patients will have been enrolled and followed for an estimated minimum of 11 months.Publication: The cutoff date for this analysis was January 31, 2016 (after 245 events had occurred).Outcome measurements reported in the published article and supplementary appendix appeared to be consistent with those specified in the protocol.	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								missing outcome data.					
NCT022 00614	307631 42	MFS	Low	Protocol: Randomization will be performed centrally blocking by center according to the design of the study using a 2-step procedure. Firstly, a separate master randomization schedule and study treatment package list will be created using randomly permuted blocks. Secondly, randomly permuted blocks from the master randomization schedule are assigned to the study centers. An interactive response technology (IRT) (also called interactive voice response system [IVRS]) system assigns patients to receive either darolutamide or matching placebo using allocation ratio 2:1, respectively.Randomiz ation will be performed centrally blocking by center according to the design of the study using a 2-step procedure. Firstly, a separate master randomization schedule and study treatment package list will be created using randomly permuted	Low	This is a double-blind trial. The incidence of adverse events that occurred or worsened during the treatment period and had a frequency of 5% or more or were of grade 3 or higher was similar in the two groups. Publication: The full intention-to-treat population, which was made up of all patients who underwent randomization, was included in the analysis of the primary end point.	High	Figure S1: Of the 955 patients allocated to darolutamide, 174 lost to follow-up. Of the 554 patients allocated to placebo, 163 lost to follow-up. The overall proportion of patient without available outcome was 22.3%. Protocol: Incomplete event occurrence dates will be imputed as the earliest possible date. Missing event dates e.g., due to withdrawal of consent, lost to follow up or not known to have died at the analysis cut-off date, will be right censored. Summary of sensitivity analyses: All the sensitivity analyses described in the statistical analysis plan were carried outand all except the nonstratified analysis had a HR lower than the primary analysis.MFS by investigator assessment (HR=0.40; P<0.001), as well as others includingcensoring of metastases at baseline, were all supportive of the primary MFS result. However, However, imputing the outcome	Low	Publication: The primary end point was metastasis-free sur- vival, defined as the time from randomization to confirmed evidence of distant metastasis on im- aging or death from any cause, whichever occurred first. The blinded central imaging review for ef- ficacy was performed by a pool of radiologists separate from those who performed the blinded central imaging review for eligibility. Publication: The primary end point was metas- tasis-free survival, with the presence of metastasis determined by independent cen- tral review of radiographic imaging.	Low	Protocol (version 4, 26 FEB 2018): Approximately 385 events will be collected for the MFS analysis. Publication: The data- collection cutoff date for the primary analysis was September 3, 2018. The primary analysis was performed after 437 primary end-point events had occurred. Outcome measurements reported in the published article and supplementary appendix appeared consistent with those specified in the protocol.	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				blocks. Secondly, randomly permuted blocks from the master randomization schedule are assigned to the study centers. An interactive response technology (IRT) (also called interactive voice response system [IVRS]) system assigns patients to receive either darolutamide or matching placebo using allocation ratio 2:1, respectively. Publication: Patient demographic and clinical characteristics were similar in the two trial groups (Table 1).				variable was not assumed to correct for bias due to missing outcome data.				
NCT026 45981	341855 51	OS	Low	Protocol: All eligible subjects are randomly assigned to the experimental or control group using the interactive web response system (IWRS) and dynamic minimization randomisation.Publica tion: Baseline characteristics were well-balanced between the treatment arms.	Low	This is an open-label trial.According to Figure 1, only 1 patient withdrew consent before receiving assigned treatment.Publication: The primary efficacy analysis was based on the full analysis set (FAS, all randomly assigned patients without major eligibility violation who received $ 1 dose of study drug) and the per-protocol set (patients who completed $ 1 treatment course, with no major protocol deviation that might have affected efficacy evaluation). The intention-to-treat (ITT, all randomly	Low	Figure 1: Of the 334 patients assigned to donafenib group, 1 withdrew consent. The overall proportion of patient without available outcome was 0.1%.	Low	The primary end point was OS.This is an open-label trial.Overall survival is an objective endpoint.	Some concer ns	Protocol (Aug. 10, 2016/Version 2.0): When the 553rd death occurs, a final review of data in the eCRF must be carried out. Publication cutoff date September 30, 2019. However, the number of events was not reported.Outcome measurements reported in the published article and supplementary appendix appeared consistent with those specified in the protocol.	Some concer ns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
						assigned cases) population was used for sup- portive analysis.							
NCT024 21939	316655 78	OS and CR with full or partial hemat ologic recove ry	Low	Protocol: Randomization and study drug assignment will be performed via Interactive Response Technology (IRT). According to Table 1, the baseline seems similar between the two groups.	Some concer ns	This is an open-label trial. According to Figure 1, 1/247 patients assigned to gilteritinib group and 15/124 patients assigned to chemotherapy group did not receive assigned treatment. However, the underlying reason was not reported. Publication: Final efficacy and safety analyses were performed in the intention-to-treat population (all patients who underwent randomization) and the safety population (all patients who had re-ceivedatleastonedoseoft rialtreatment),respec-tively.	Low	Protocol: After treatment discontinuation, subjects will have a pre-HSCT/end of treatment visit within 7 days after treatment discontinuation, followed by a 30-day follow-up, in which a telephone contact with the subject is sufficient unless any assessment must be repeated for resolution of treatment-related AEs. After which the subjects will enter the long-term follow-up period for collection of patient reported outcome (PRO) using EQ-5D-5L, subsequent AML treatment, remission status and survival (cause of death and date of death). According to Fig 1, there is no patient that lost to follow-up.	Low	Publication: The two primary end points were overall survival and the percentage of patients who had complete remission with full or partial hematologic recovery. This is an open-label trial. Overall survival, the outcome we assessed, is an objective endpoint.	Low	Protocol (16 May 2018): the final analysis is planned when approximately 258 death events have occurred. Publication: The event cutoff of 258 deaths, which triggered the final analysis, occurred on September 17, 2018. Outcome measurements reported in the published article and supplementary appendix appeared consistent with those specified in the protocol.	Some concer ns
NCT033 53753	325119 81	PFS	Low	Publication: Randomisation was done via an interactive response technology system by use of randomly permuted block sizes of six According to Table 1, the baseline seems similar between the two groups.	Low	This is a double-blind trial. The incidence of adverse events was similar in the two groups. According to Fig 1, only 1/44 patient assigned to placebo Publication: The primary analysis was done in	Low	Figure 1: Of 85 patients assigned to ripretinib, 2 withdrew consent. Of the 44 patients assigned to placebo, 1 withdrew consent. Publication: 51 patients in the ripretinib group and 37 in the placebo group had had	Low	Publication: The primary efficacy endpoint was progression-free survival (the interval between the date of randomisation to the date of documented progressive disease or death due to any cause) according to mRECIST 1.1, as assessed by BICR. The primary endpoint was	Low	Protocol Amendment 5 (30 October 2018): The data cut-off for the primary analysis will occur when 90 PFS events have occurred. Publication: At data cutoff (May 31, 2019), at a median follow-up of 6·3	Low

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
						the intention-to-treat population and safety was assessed in patients who received at least one dose of study drug.		progression-free survival events. The overall proportion of patient without available outcome was 2.3%. The observed number of events was 29.3 time the number of participants with missing outcome data.		assessed by the blinded independent central review.		months (IQR 3·2–8·2) in the ripretinib group and 1·6 months (1·1–2·7) in the placebo group, 51 patients in the ripretinib group and 37 in the placebo group had had progression-free survival events.	
NCT02899299	33485464	OS	Low	Publication: Patients were enrolled and randomly assigned (1:1) using an interactive web response system.Publication: Baseline characteristics were well balanced between treatment groups (table 1).	Some concerns	This is an open-label trial.Figure 1: 1/303 vs 11/302 patients withdraw consent after randomization. However, the underlying reason was not reported.Publication: The primary endpoint was overall survival in all patients randomly assigned to treatment after the US Food and Drug Administration provided guidance to change progression-free survival from a coprimary endpoint to a secondary endpoint .	Low	Figure 1: Of the 303 patients assigned to nivolumab plus ipilimumab, 6 patient withdrew consent, 13 discontinued due to other reason, 4 reason not reported. Of the 284 patients received allocated intervention, 3 patient withdrew consent, 1 lost to follow-up, 2 for other reasons, 189 reason not reported (176 completed six cycles).Publication: At the time of database lock for the interim analysis, 419 patients had died (89% of total anticipated events);We assumed that patients withdrew consent, discontinued due to "other reason", and lost to follow-up did not have available outcome. The overall proportion of patient without outcome was 3.9% (6.3% vs 1.4%). The observed number of events was 18.2	Low	Publication: Overall survival was defined as the time from randomisation to the date of death due to any cause.This is an open-label trial.Overall survival is an objective endpoint.	Low	Publication (database lock April 3, 2020): At the time of database lock for the interim analysis, 419 patients had died (89% of total anticipated events).Protocol revised date 25-Apr-2019: A formal interim analysis for superiority of OS in subjects who were randomized to Arm A vs. subjects who were randomized to Arm B will be performed on all randomized subjects when ap-proximately 403 deaths have been observed (approximately 85% (403/473) of the total number of deaths required for the final analysis).Outcome measurements reported in the published article and supplementary	Some concerns

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								times the number of participants with missing outcome data.				appendix appeared to be consistent with those specified in the protocol.	
NCT022 53459	282092 98	PFS	Low	Publication: The randomisation list was computer-generated by an independent randomisation statistician and loaded into the Interactive Website Response System. Under concealment, eligible patients were randomly assigned centrally in a strict sequential manner; randomisation was restricted with block sizes of six. Publication: Patient baseline demographic and clinical characteristics were generally balanced between treatment groups (table 1).	Some concer ns	This is an open-label trial. According to Figure 1, 6/270 patients allocated to utidelone group and 3/135 patients allocated to the capecitabine group switched to other treatment. No more information was reported to answer this question. Efficacy data was analyzed in the intention-to-treat population.	Low	Publication: After randomisation, seven patients withdrew informed consent, 24 patients did not complete two cycles, 12 did not undergo efficacy assessment, 13 had serious protocol violations, and 12 had missing data from more than two assessments. Publication: By the cutoff date for this report of Sept 1, 2016, 295 progression-free survival events (ie, disease progression or death) had occurred in the ITT population. The overall proportion of patient without outcome was 4.7%. The observed number of events was 15.5 time the number of participants with missing outcome data.	Low	Publication: The primary endpoint was progression-free survival, defined as the time from randomisation to progressive disease, or death due to any cause, whichever occurred first, according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Publication: The primary endpoint was centrally reviewed.	Some concer ns	The protocol was not available. The protocol was not available.	Some concer ns
NCT037 89604 (non-squamo us NSCLC)	350384 32	PFS	Low	Publication: Permuted-block random- isation (block size was a mixture of three and six with random order within each stratum) was done using an interactive voice-response system or	Low	This is a double-blind trial. The incidence of adverse events was similar in the two groups.Publication: Progression-free survival and overall survival were analysed in the intention-to-treat population, which	Low	Protocol: All subjects, except those who discontinue study treatment due to radiologically documented disease progression, must continue to receive the scheduled radiological	Low	Publication: The primary endpoint was investigator-assessed progression-free survival (ie, time from randomisation to disease progression according to RECIST version 1.1 or death from any cause, whichever occurred first) in the intention-to-treat	Low	Protocol (Version 2.0/7th April 2020): The final PFS analysis was planned when 360 PFS events were observed. An interim analysis was planned when about 252 events (70%	Low

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				integrated web-response system.Publication: Demographic and baseline disease characteristics were well balanced in the two groups (table 1).		included all randomly assigned patients.		assessments until radiological disease progression, withdrawal of informed consent, death or end of this study, whichever occurs first.		population.Although the primary endpoint was assessed by the investigator, this is a double-blind trial.		information) were observed or at the last subject randomized, whichever occurred later.Publication: At the prespecified interim analysis (data cutoff June 8, 2020) for progression-free survival, progression or death events occurred in 155 (48%) of 320 patients with sugemalimab and 113 (71%) of 159 with placebo. Outcome measurements specified in the protocol appear consistent with those reported in the published article and data supplement.	
NCT037 89604 (squamo us NSCLC)	350384 32	PFS	Low	Publication: Permuted-block random- isation (block size was a mixture of three and six with random order within each stratum) was done using an interactive voice-response system or integrated web-response system. Publication: Demographic and baseline disease characteristics were well balanced in the two groups (table 1).	Low	This is a double-blind trial. The incidence of adverse events was similar in the two groups. Publication: Progression-free survival and overall survival were analysed in the intention-to-treat population, which included all randomly assigned patients.	Low	Protocol: All subjects, except those who discontinue study treatment due to radiologically documented disease progression, must continue to receive the scheduled radiological assessments until radiological disease progression, withdrawal of informed consent, death or end of this study, whichever occurs first.	Low	Publication: The primary endpoint was investigator-assessed progression-free survival (ie, time from randomisation to disease progression according to RECIST version 1.1 or death from any cause, whichever occurred first) in the intention-to-treat population. Although the primary endpoint was assessed by the investigator, this is a double-blind trial.	Low	Protocol (Version 2.0/7th April 2020): The final PFS analysis was planned when 360 PFS events were observed. An interim analysis was planned when about 252 events (70% information) were observed or at the last subject randomized, whichever occurred later. Publication: At the prespecified interim	Low

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
								According to Fig 1, there is no patient that withdraw Informed consent or lost to follow-up.				analysis (data cutoff June 8, 2020) for progression-free survival, progression or death events occurred in 155 (48%) of 320 patients with sugemalimab and 113 (71%) of 159 with placebo. Outcome measurements specified in the protocol appear consistent with those reported in the published article and data supplement.	
NCT015 64784	272921 04	CR and OS	Low	Publication: Once the patient has signed the informed consent, the Investigator or designee will contact the randomization system (See study manual) to obtain a patient identification number (patient ID). Following full assessment and determination that a patient meets all eligibility criteria, the Investigator or designee will enroll the patient into the study using the randomization system. Publication: The baseline patient characteristics in the remission-analysis population were well-balanced between	Some concer ns	This is an open-label trial. No information was available to answer this question. Publication: survival data as of March 8, 2016, are presented for the 326 patients included in the intention-to- treat population.	High	Publication: An ad-ditional 47 patients underwent randomization after the cutoff date, for a total of 326 patients, so that additional survival data could be obtained. However, no CONSORT diagram of these 326 patients was reported. No analysis methods that correct for bias or sensitivity analyses was reported. No information was available to answer this question.	Low	Publication: The two primary end points were complete remis- sion (including complete remission with incom- plete hematologic recovery) and overall survival. This is an open-label trial. Overall survival, the outcome we assessed, is an objective endpoint.	Low	Final Protocol: 26 January 2012 The final analysis for OS will be performed after 248 complete OS events. Publication: The prespecified requirement of at least 248 events to conduct the final analysis of over- all survival was achieved on March 8, 2016, when 252 events had been observed. Outcome measurements reported in the published article and supplementary appendix appeared consistent with those specified in the protocol.	High

			Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Mising outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overa ll Bias
Study ID	Refere nce (PMID)	Outco me	1.0 Asses sor's Judge ment	1.0 General note	2.0 Asses sor's Judge ment	2.0 General Notes	3.0 Asses sor's judge ment	3.0 Gerenal notes	4.0 Asses sor's Judge ment	4.0 General note	5.0 Asses sor's Judge ment	5.0 General note	Asses sor's overall Judge ment
				treatment groups (Table 1).									
NCT039 27456	347374 52	PFS	Low	Publication: the subjects who passed the screening are assigned at a 2:1 ratio to the SHR6390 combined with fulvestrant group (investigational treatment group) or the placebo combined with fulvestrant group (control group) using stratified block randomization. An Interactive Web Response System (IWRS) will be used in this study for randomization and drug dispensing management. Publication: Baseline characteristics were generally balanced between the two groups (Table 1).	Low	This is a double-blind trial. Although the most common grade 3 or 4 adverse events with dalpiciclib plus fulvestrant were neutropenia (84.2%) and leukopenia (62.1%), these were not considered to be substantial enough to break blinding of participants and personnel.Publication: Efficacy was analyzed in the full analysis set, comprising all randomized patients who met the eligibility criteria, on an intention-to-treat basis.	Low	Protocol: Efficacy follow-up: Subjects who discontinue treatment for reasons other than PD and death will continue tumor assessments at time points specified in the protocol, starting from the last tumor assessment during the treatment period, until PD, start of a new anti- tumor treatment, or death (whichever occurs first).Fig. 1: There was no withdrawl of consent or lost to follow-up.	Low	Publication: The primary end point was investigator-assessed progression-free survival, defined as the time of randomization to the first progression per RECIST v.1.1 or death from any cause, whichever occurred first.Although the primary end point was investigator-assessed progression-free survival, this is a double-blind trial.	Low	Protocol (version3.06 May, 2020): The primary endpoint of this study is the PFS assessed by investigator, and an interim analysis will be conducted when 70% (approximately 159 events) of the PFS events are collected.Publicatio n: The data cutoff date was 15 November 2020. At the time of the interim analysis, 86 (35.7%) of 241 patients in the dalpiciclib plus fulvestrant group and 76 (63.3%) of 120 patients in the placebo plus fulvestrant group had disease progression or died.Outcome measurements reported in the published article and supplementary appendix appeared consistent with those specified in the protocol.	Low