Preferences for speed of access versus certainty of the survival benefit of new cancer drugs: a discrete choice experiment

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Summary

Background The extent to which patients with cancer are willing to accept uncertainty about the clinical benefit of new cancer drugs in exchange for faster access is not known. This study aims to examine preferences for access versus certainty, and to understand factors that influence these preferences.

Methods A US nationally representative sample of older adults were recruited via Cint, an online platform for survey research, to take part in an online discrete choice experiment. To be eligible, respondents had to self-report some experience with cancer—ie, they themselves, a close friend or a family member, previously or currently diagnosed with cancer. In the experiment, respondents chose between two cancer drugs, considering five attributes: functional status, life expectancy, certainty of the survival benefit of a new drug, effect of the drug on a surrogate endpoint, and delay in US Food and Drug Administration (FDA) approval time. The first primary outcome was the relative importance of certainty of survival benefit and wait time to respondents. The second primary outcome was willingness to wait for greater certainty of survival benefit, including subgroup analysis by cancer experience, age, education status, race or ethnicity and income. Secondary outcomes were changes in sensitivity to certainty and wait time, depending on the drug's effect on a surrogate endpoint, respondents' functional status, and life expectancy. The study plan was registered with ClinicalTrials.gov, NCT05936632.

Findings Between July 7 and July 20, 2023, 998 eligible respondents completed the survey. 870 respondents (461 [53%] male, 406 [47%] female, and three [<1%] other) were included in the final analysis. Respondents showed strong preferences for high certainty of survival benefit (coefficient 2·61, 95% CI 2·23 to 2·99), and strong preferences against a 1-year delay in FDA approval time (coefficient –1·04, 95% CI –1·31 to –0·77). Given very low certainty a drug would provide survival benefit (no evidence linking a surrogate endpoint to overall survival), respondents were willing to wait up to 21·68 months (95% CI 17·61 to 25·74) for high certainty (strong evidence) of survival benefit. A drug's effect on a surrogate endpoint had no significant impact on drug choices (coefficient 0·02, 95% CI –0·21 to 0·25). Older respondents (aged ≥55 years), non-White, lower-income (<$40 000 per year) individuals, and those with the lowest life expectancy, were most sensitive to wait time.

Interpretation Many cancer drugs approved through the FDA's accelerated approval pathway do not offer any survival benefit to patients. In this study, individuals expressed strong preferences for certainty that a cancer drug would offer survival benefit. Some individuals also expressed a higher willingness to wait for greater certainty than would be necessary to assess the survival benefit (over progression-free survival benefit) of most cancer drugs used in the metastatic setting.

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Introduction

The US Food and Drug Administration (FDA) is faced with an inherent trade-off between ensuring certainty of clinical benefit and speed of access when approving new drugs. To be approved, the FDA usually requires novel drugs to be supported by substantial evidence showing safety and efficacy.[1] To speed up access to drugs that address unmet needs in serious conditions, the FDA provides substantial flexibilities in its evidence requirements.[2] According to the FDA, this more flexible approach reflects patients' and caregivers' "willingness to accept less certainty about effectiveness in return for earlier access to much needed medicines".[1]

For cancer drugs, overall survival is broadly considered the most direct measure of clinical benefit that matters most to patients.[3] However, the FDA's accelerated approval pathway only requires demonstration of a drug's effect on a surrogate endpoint that is reasonably likely to predict clinical benefit.[2] Surrogate endpoints used by the FDA to grant accelerated approvals in oncology include progression-free survival, among others.[4,5] After receiving accelerated approval, the FDA

Research in context

Evidence before this study

Since 1992, more than 200 cancer drug indications have been granted accelerated approval by the US Food and Drug Administration (FDA) based on evidence from surrogate endpoints that are only required to be reasonably likely to predict clinical benefit. Although studies show overall survival as the most reliable and patient-centred endpoint for demonstrating clinical benefit of cancer drugs, over half of all cancer drugs receiving accelerated approval do not offer any improvement in overall survival. According to the FDA its accelerated approval pathway reflects "patients and caregivers' willingness to accept less certainty about effectiveness in return for earlier access to much needed medicines". We searched MEDLINE using OVID (from 1990 to April 1, 2024) for any studies, in English, that empirically measured preferences for certainty of clinical benefit or wait time, or both, with respect to new cancer drugs, or studies that empirically estimated willingness to wait for greater certainty of the clinical benefit of new cancer drugs. To perform this search, we used the search terms: "preferences", "wait", "willingness to wait", "delay", "certainty", "clinical benefit", "survival benefit", "overall survival", "benefit", "cancer", "oncology", "drugs", "medicines", "pharmacotherapy", "Food and Drug Administration", "FDA", and "regulatory agencies". We supplemented this search with a targeted review of FDA regulatory documents, FDA online guidance, and the grey literature. We found no empirical evidence to demonstrate the extent to which individuals are willing to accept uncertainty of clinical benefit in exchange for faster access to new cancer drugs.

Added value of this study

To our knowledge, this is the first empirical study to elicit preferences for certainty of the survival benefit of new cancer drugs versus speed of access, and the first to estimate individuals' willingness to wait for greater certainty of the survival benefit of new cancer drugs.

Implications of all the available evidence

Patients with cancer simultaneously value faster access to new cancer drugs, and high certainty that these drugs will offer survival benefit. The competing nature of these preferences characterises the challenging trade-off faced by the FDA during its drug approval decisions. In its accelerated approval decisions of new cancer drugs, the FDA might be underestimating the willingness of some patients to wait for greater certainty of survival benefit.

requires sponsors to conduct confirmatory trials to verify or refute the drug's clinical benefit. In the meantime, there remains considerable clinical uncertainty for patients about whether a treatment will benefit them.[6]

To date, over 200 cancer drug indications have received accelerated approval.[7] Accelerated approval has had a marked impact on access to, and uncertainty surrounding, many new cancer drugs. As intended, cancer drugs receiving accelerated approval have shorter clinical development times.[8,9] However, surrogate endpoints do not always reliably correlate to overall survival.[10,11] Over half of all cancer drugs granted accelerated approval also do not ultimately offer benefit in overall survival or quality of life, but can result in toxicities for patients.[11,12] In addition, confirmatory studies are often delayed or not conducted at all, and some cancer drug indications have remained on the market for over a decade without verification of their clinical benefit.[13] During this period, substantial expenditure occurs on these drugs with unknown clinical benefit.[14,15]

Currently, it is not known whether patients are willing to accept greater uncertainty in exchange for faster access to new cancer drugs. In this study, we sought to elicit preferences of people with personal experience of cancer for certainty of a drug's effect on overall survival versus time until FDA approval. We also evaluated factors influencing these preferences, and how individuals would trade-off between these attributes, when making hypothetical treatment choices.

For **Cint** see https://www.cint.com/market-research-and-insights/

Methods

Study design and participants

We conducted a discrete choice experiment to simulate the trade-offs and uncertainties intrinsic to the accelerated approval of cancer drugs, from a patient perspective. Discrete choice experiments measure preferences by assuming that products or policies can be characterised by their attributes (and levels of these attributes), and that individuals make choices to maximise their utility, and in doing so revealing their preferences and the relative importance of attributes.[16]

The London School of Economics and Political Science ethics review committee approved the study, and the study plan was registered with ClinicalTrials.gov, NCT05936632. The study was conducted in line with the American Association for Public Opinion Research best practices for survey research.[17] Written informed consent was obtained from all respondents.

Study design with respect to wording of the scenario, design and presentation of choice tasks, and specification of attributes and attribute levels was informed by a literature review and collaboration with a clinical academic oncologist (AA) to ensure clinical and policy relevance. The survey and tasks were also refined through pretesting in 15 respondents to ensure comprehension.

Adults in the USA were contacted, screened, and recruited between July 7 and July 20, 2023 via Cint. Cint is an online platform for survey research that combines hundreds of panel providers, each with a unique set of recruitment and sourcing methodologies to ensure

sampling is not overly reliant on one demographic or segment of the population. Respondents were compensated for their time by individual panel providers. Cint subsequently charged a set fee for sample recruitment.

To be eligible, respondents had to self-report personal experience with cancer—ie, either themselves had been, or had a close friend or family member, previously or currently diagnosed with cancer. Quota-based sampling of sociodemographic characteristics was used to achieve a nationally representative sample with respect to self-reported sex, race or ethnicity, income, and education status. Age quotas were implemented to disproportionately target older respondents (relative to national demographics) to align the sample with US cancer incidence by age.[18] We excluded respondents completing the survey in less than 40% of median response time. This approach is considered standard practice, and a conservative cutoff given the complexity of the choice tasks.

Procedures

Respondents were first shown a short video (and transcript) detailing a scenario in which they had been diagnosed with cancer, that there were treatments available to them, but these treatments could not cure their disease. In this scenario, two new drugs (drug A and drug B) were currently being evaluated in clinical trials, but there remained uncertainty about their effectiveness (appendix p 3).

Based on the scenario, respondents were asked to answer 12 choice tasks in which they chose either drug A or drug B. When making choices, respondents were asked to consider five attributes in total—life expectancy, functional status, certainty of survival benefit, effect of the drug on a surrogate endpoint, and delay in FDA approval time (table 1). Two example choice tasks are shown in the appendix (p 3). Attributes (and levels of these attributes) were based on published literature.

The first two attributes in each choice task (functional status and life expectancy) were health state attributes, used to help respondents imagine the prognoses of individuals treated for cancer in the metastatic setting on a current standard treatment—ie, without drug A or drug B. The functional status attribute described a level of functioning in terms of an individual's ability to care for themselves, daily activity, and physical ability. Attribute levels were based on Eastern Cooperative Oncology Group performance score, ranging from 1 (able to carry out light work) to 4 (completely disabled).[19] The life expectancy attribute consisted of four levels ranging from 6 months to 3 years, approximated from survival statistics of the most common cancer types in the USA.[18]

The three remaining attributes in each choice task (certainty of survival benefit, effect of a drug on a surrogate endpoints, and delay in FDA approval time) described characteristics of the drug alternatives.

	Attribute-level wording
Life expectancy (on current treatment)	
Level 1	6 months
Level 2	1 year
Level 3	2 years
Level 4	3 years
Functional status (on current treatment)	
Level 1	Restricted only during physically strenuous activity; able to walk around and carry out light work
Level 2	Up and about more than 50% of waking hours; can walk around, cannot work
Level 3	Confined to bed or chair more than 50% of waking hours; capable of limited selfcare, cannot work
Level 4	Completely disabled; cannot carry on any selfcare or work; totally confined to bed or chair
Effect on a surrogate endpoint (how well the drug worked at slowing cancer growth in clinical trials)	
Level 1	Small improvement: both drugs prevented cancer growth by 1 additional month compared to your current treatment
Level 2	Moderate improvement: both drugs prevented cancer growth by 3 additional months compared to your current treatment
Level 3	Substantial improvement: both drugs prevented cancer growth for 5 additional months compared to your current treatment
Certainty of clinical benefit (how certain doctors are that slowing cancer growth means you will live longer)	
Level 1	Very low certainty you will live 1 to 5 months longer; there is no evidence linking cancer growth and life expectancy
Level 2	Low certainty you will live 1 to 5 months longer; there is weak evidence linking cancer growth and life expectancy
Level 3	Moderate certainty you will live 1 to 5 months longer; there is some evidence linking cancer growth and life expectancy
Level 4	High certainty you will live 1 to 5 months longer; there is strong evidence linking cancer growth and life expectancy
FDA approval time (effective wait time)	
Level 1	FDA approved the drug now (available to you now)
Level 2	FDA approves the drug in 6 months (available to you in 6 months)
Level 3	FDA approves the drug in 1 year (available to you in 1 year)
Level 4	FDA approves the drug in 2 years (available to you in 2 years)

See appendix (p 3) for layout of attribute level wording.

Table 1: **Attributes and levels for scenario and drug A and B**

See Online for appendix

Certainty of clinical benefit was described to respondents as "How certain doctors are that slowing cancer growth means you will live longer". Four certainty levels (very low, low, moderate, and high; see table 1 for full definitions) described the certainty that respondents would live 1–5 months longer based on the median additional overall survival benefit (ie, over existing treatments) observed for cancer drugs approved by the FDA in 2003–21.[20] Each certainty level also included a statement about the strength of the evidence (none, weak, some, and strong) linking cancer growth and life expectancy, based on evidence from studies evaluating the association between surrogate endpoints and overall survival in oncology.[10] The drugs' effect on a surrogate endpoint was presented to individuals as "How well the

	Participants (n=870)
Sex	
Male	461 (53%)
Female	406 (47%)
Other	3 (<1%)
Age, years	
≤18	2 (<1%)
19–24	38 (4%)
25–34	65 (7%)
35–44	157 (18%)
45–54	179 (21%)
55–64	200 (23%)
65–74	170 (20%)
≥75	59 (7%)
Race or ethnicity	
White	697 (80%)
Black or African American	87 (10%)
Hispanic or Latino	36 (4%)
Two or more races or ethnicities	20 (2%)
Asian	16 (2%)
Native American or Alaska Native	7 (1%)
Other	7 (1%)
Income (individual, annual)	
<$20 000	130 (15%)
$20 000–39 999	235 (27%)
$40 000–59 999	188 (22%)
$60 000–79 999	135 (16%)
$80 000–99 999	72 (8%)
≥$100 000	110 (13%)
Education (highest attained)	
Less than high school	24 (3%)
High school or GED	396 (46%)
College degree*	343 (39%)
(Table 2 continues in next column)	

	Participants (n=870)
(Continued from previous column)	
Graduate degree†	107 (12%)
Experience of cancer‡	
Personally diagnosed§	180 (21%)
Family diagnosed§	707 (81%)
Close friend diagnosed§	311 (36%)
Political ideology	
Very liberal	76 (9%)
Liberal	115 (13%)
Somewhat liberal	72 (8%)
Moderate	316 (36%)
Somewhat conservative	104 (12%)
Conservative	110 (13%)
Very conservative	77 (9%)
FDA trust	
Not at all	42 (5%)
Very little	82 (9%)
A little	109 (13%)
Some	296 (34%)
A lot	269 (31%)
Complete	72 (8%)
Physician trust	
Not at all	16 (2%)
Very little	37 (4%)
A little	80 (9%)
Some	233 (27%)
A lot	391 (45%)
Complete	113 (13%)

Data are n (%). FDA=Food and Drug Administration. GED=General Educational Development. *College degree (eg, Bachelor's degree). †Graduate degree (eg, Master's degree or Doctoral degree). ‡Multiple choice. §Currently or previously.

Table 2: **Sample demographics and characteristics**

drug worked at slowing cancer growth in clinical trials" compared with their current standard treatment. Levels varied from 1 additional month to 5 additional months, based on the median additional progression-free survival benefit (ie, over existing treatments) of all cancer drugs approved by the FDA in 2003–21.[20] FDA approval time was used to describe the effective wait time for access to either drug. Four levels ranged from 0 months (available now) to 2 years, based on the time required to generate overall survival data for cancer drugs (11–19 months).[21]

Experimental design software Ngene was used in a two-step process to distribute attributes and levels between choice tasks optimally for parameter estimation and to estimate a minimum required sample size.[22] Final sample size was estimated based on planned subgroup analysis. First, an orthogonal design was created using noninformative priors and piloted on 77 individuals in the respondent population.[23] Using informative priors from analysis of the pilot, a final Bayesian efficient experimental design was generated which consisted of 40 choice tasks (ie, four blocks of ten tasks) in total.[24] To reduce the number of required choice sets, restrictions on the design removed tasks which were nonsensical (eg, where wait time exceeded life expectancy). Ngene also removed tasks with dominant drug alternatives. Each respondent answered a subset of ten choice tasks, plus a dominance check (ie, a task in which one drug alternative was purposely made preferable) and a consistency check (ie, an exact duplicate of one of the ten choice tasks), totalling 12 tasks. Order of the choice tasks, and profiles of drug A and drug B, were randomised to minimise response bias.

Outcomes

The first primary outcome was the relative importance of certainty of survival benefit and wait time to respondents, defined as the marginal utility of each attribute level. The second primary outcome was willingness to wait for greater certainty of survival benefit, defined as the

marginal rate of substitution between certainty and wait time, including subgroup analysis by cancer experience, age, education status, race or ethnicity, and income. Secondary outcomes were changes in sensitivity to certainty and wait time, depending on the drug's effect on a surrogate endpoint, respondents' functional status, and life expectancy.

Statistical analysis

Analysis of choice data was conducted using maximum likelihood estimation in the Apollo choice modelling package (version 0.3.0) in R (version 4.3.1).[25] The primary analysis was conducted using a multivariable model (mixed multinomial logit model), with utility functions prespecified during the experimental design stage.

Main effect estimates from the model were used to interpret the relative importance of certainty of a drug's effect on overall survival versus wait time to individuals when choosing between drugs. Marginal rates of substitution (appendix p 2) between these attributes were used to measure tradeoff behaviour (ie, willingness to wait). Subgroup willingness to wait analysis was carried out based on cancer experience, age, education status, race or ethnicity, and income. Interaction effects in the model were used to interpret the impact of a drugs' effect on a surrogate endpoint on respondents' sensitivity to certainty and wait time. Predicted probability analysis (appendix p 2) was used to model the potential impact of a respondent's health state (ie, functional status and life expectancy) on preferences for certainty of survival benefit and wait time.

We compared the direction and magnitude of model estimates before and after exclusion criteria were applied to evaluate any potential effects on results.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

3427 individuals in the USA were contacted between July 7 and July 20, 2023, and 1382 (40%) met screening criteria by self-reporting personal experience with cancer. 998 (72%) of the eligible respondents completed the survey. 128 (13%) eligible respondents who completed the survey in less than 40% of median response time were excluded (appendix p 4). Analysis showed that exclusion of these individuals had negligible effect on the direction and magnitude of model estimates (data not shown). 870 respondents were included in the final analysis (appendix p 5).

The characteristics of the sample were consistent with those of a US nationally representative sample of older adults (table 2). Of the 870 included respondents, 180 (21%) had personally (previously or currently) been diagnosed with cancer, 707 (81%) had a family member diagnosed, and 311 (36%) had a close friend diagnosed with cancer (table 2). Measures of internal validity were satisfactory (appendix p 6).

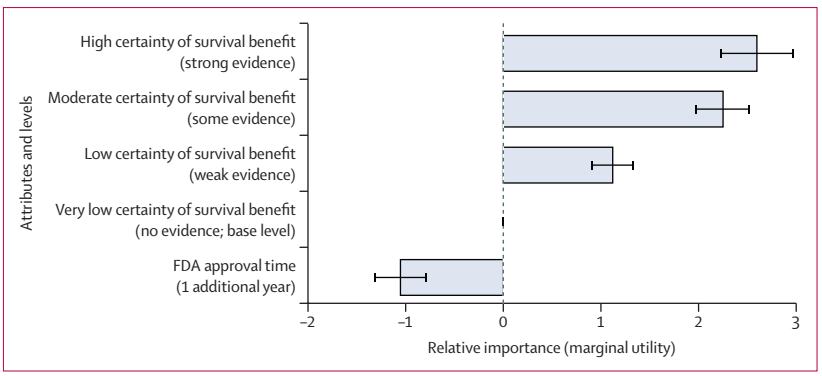

Figure 1: **Relative importance of attributes**
FDA=Food and Drug Administration. For the certainty attribute levels, marginal utility values illustrate the positive utility associated with increasing certainty, relative to the lowest (reference) level of certainty. For the FDA approval time attribute, marginal utility values present the disutility associated with a 1-year increase in FDA approval time. Error bars represent 95% CIs. Complete marginal utility data are provided in the appendix (p 7). Levels of evidence (strong, some, weak, and none) refer to the evidence linking cancer growth (progression-free survival) to overall survival, which was described to respondents in each choice task. Full definitions of attributes and levels shown to respondents are provided in table 1.

Main effect estimates in the primary model (model 1, appendix p 7) demonstrate strong positive preferences for increased certainty of living longer and strong negative preferences against an increase in FDA approval time (figure 1). For example, a relative increase from very low to low certainty of living longer yielded a positive marginal utility of 1·13 (95% CI 0·91 to 1·35). An increase from very low to high certainty of living longer was more than twice as preferred by individuals (positive marginal utility of 2·61, 95% CI 2·23 to 2·99). A 1-year increase in FDA approval time yielded a negative marginal utility of –1·04 (95% CI –1·31 to –0·77).

Willingness to wait estimates were robust across subgroups prespecified as part of our analysis plan with respect to cancer experience, age, education status, income and race or ethnicity (figure 2). Presented with very low certainty (no evidence linking surrogate endpoint to survival), on average, respondents were willing to wait 7·86 months (95% CI 6·19–9·53) for low certainty (weak evidence) a drug would extend survival (figure 2). Similarly, respondents were willing to wait 16·34 months (95% CI 13·43–19·25) for moderate certainty (some evidence) or 21·68 months (17·61–25·74) for high certainty (strong evidence) a drug would extend survival. In comparison, when presented with moderate certainty, respondents were willing to wait 5·3 months (3·6–7·0) for high certainty (strong evidence) a drug would extend survival. All willingness to wait estimates for each level of certainty, by subgroup, are shown in the appendix (pp 8–10) Relatively older individuals (aged ≥55 years), non-White, and lower-income groups were less willing to wait for greater certainty (evidence) on the survival benefits of new drugs. Those with a personal or close friend diagnosis, higher-income groups, and graduates

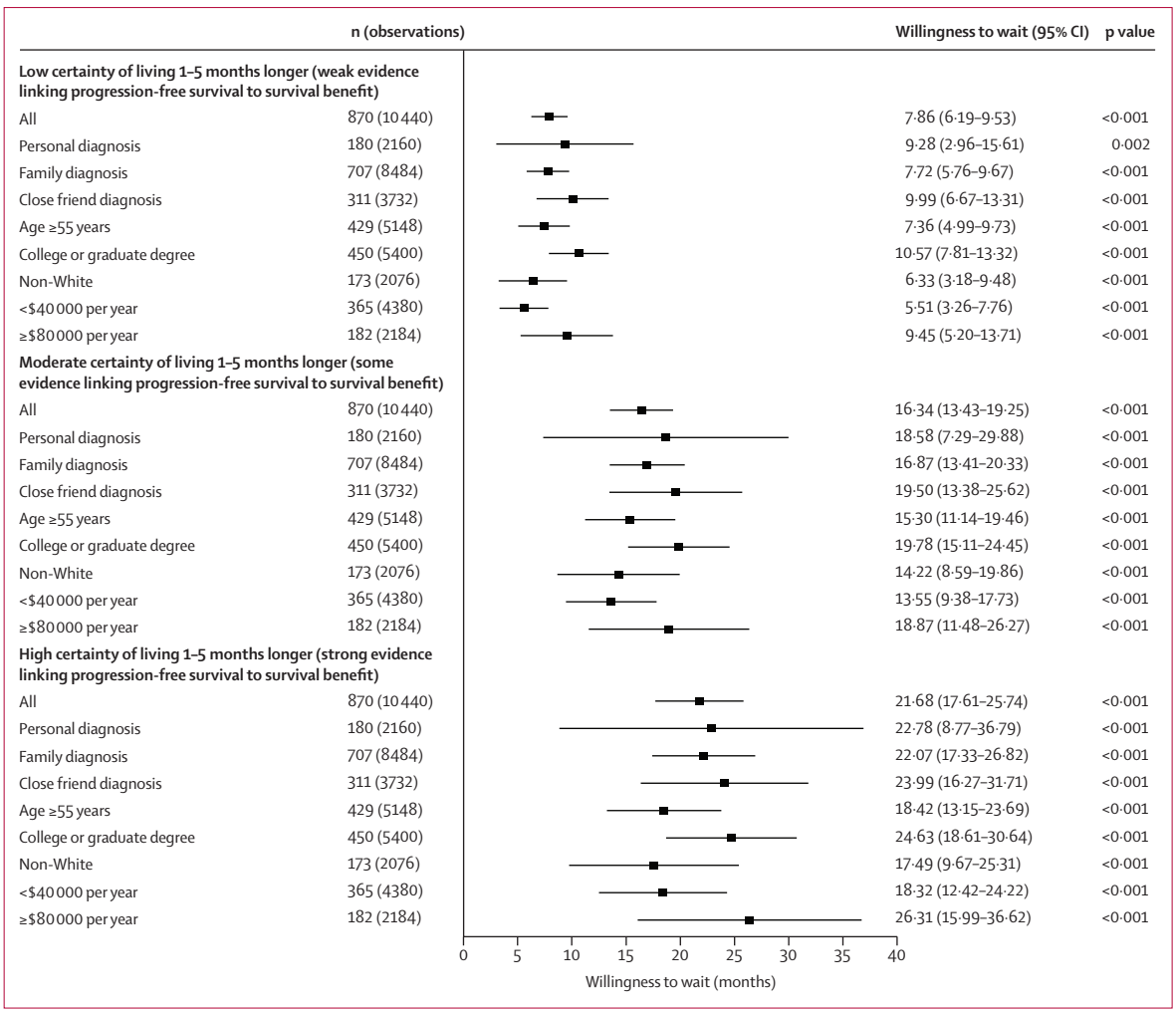

Figure 2: **Willingness to wait for greater certainty of the survival benefit of new cancer drugs**
Willingness to wait (in months) for "low", "moderate", or "high" certainty of the survival benefit of a new cancer drug, given very low certainty (no evidence linking cancer growth to life expectancy) as a reference level. Willingness to wait estimates and 95% CIs were calculated using marginal rates of substitution between certainty of survival benefit and FDA approval time attribute estimates (see appendix p 2 for additional information). Willingness to wait was only estimated for subgroups pre-specified as part of our analysis plan.

were more willing to wait than the general population (figure 2, appendix pp 8–10).

No statistically significant interactions between progression-free survival benefit and certainty of survival benefit were estimated (model 1, appendix p 7). This finding suggests a drug's effect on a surrogate endpoint (progression-free survival) had no impact on respondents' preferences for certainty, regardless of the degree of certainty that the same drug would allow them to live longer. For example, even when there was very low certainty and no evidence that a drug would extend survival, respondents placed no significant value on whether the drug substantially slowed cancer growth (coefficient 0·02, 95% CI –0·21 to 0·25; appendix p 7). In other words, substantial progression-free survival benefit of a drug did not compensate for lack of certainty about a drug's benefit on survival in respondents' drug choices.

Significant interaction effects for functional status and life expectancy suggest they both significantly influenced sensitivity to certainty and wait time (model 1, appendix p 7). For example, respondents with the highest (best) functional status were less sensitive to increasing FDA wait time than the general population (coefficient 0·31, 95% CI 0·18 to 0·44). As life expectancy increased, respondents also became less sensitive to increasing wait time (coefficient 0·10, 95% CI 0·02 to 0·19). Scenario analysis (figure 3) is used to illustrate the impact of these interaction effects on respondents' choices.

As the certainty of a drug's effect on living longer increased, the probability of choosing that drug also increased relative to the reference level of very low (overall positive trend observed in figure 3A). For example, the overall population were more than twice as likely to choose a drug that had moderate certainty (or

some evidence) of a drug's effect on living longer than one with very low certainty or no evidence the drug would allow them to live longer (relative change in choice probability 1·02, 95% CI 0·97–1·05). The overall negative trend observed in figure 3B shows the opposite effect—ie, an increase in wait time for FDA approval reduced the probability of an individual choosing a given drug.

Scenario analysis suggests that functional status and life expectancy had a significant impact on respondents' sensitivity to certainty and wait time (presented within clusters of figure 3A, B). For example, respondents who were confined to bed or chair more than 50% of the time and cannot work were 40% less likely (95% CI 38–43), and respondents who were able to carry out light work were 29% less likely (95% CI 26–32), to choose a drug with a 2-year wait time than if a drug were available now (figure 3B). As life expectancy decreased, respondents expressed less sensitivity to lower certainty of survival benefit (shown within clusters of figure 3A) and more sensitivity to wait time (within clusters of figure 3B).

Discussion

In this nationally representative discrete choice experiment, 870 individuals with personal experience of cancer, living in the USA, showed simultaneously strong—but counteracting—preferences for increased certainty of survival benefit and faster FDA approval, when choosing between new cancer drugs. Given that achieving greater certainty about the survival benefit of new cancer drugs would take time, this finding highlights the trade-off faced by the FDA when approving new cancer drugs. Heterogeneity of preferences among respondents identified in this study also shows the fine balance between access and certainty, and to some extent validates the intent behind the FDA's accelerated approval for certain populations such as those with serious conditions.

To our knowledge, this study is the first to empirically estimate willingness to wait for greater certainty of a cancer drug's survival benefit. We find that, given very low certainty a drug would provide survival benefit (no evidence linking a surrogate endpoint to overall survival), respondents were willing to wait up to 16·34 months for moderate certainty (some evidence), or 21·68 months for high certainty (strong evidence) of survival benefit. Given that the estimated additional time to assess the survival benefit (over progression-free survival benefit) of a cancer drug in the metastatic setting is approximately 11 months,[21] our results indicate that some patients (except those with the poorest prognoses) would find the additional time required to generate evidence on the survival benefit of new cancer drugs an acceptable trade-off. Paradoxically, these findings suggest that the FDA might at times be underestimating the willingness of individuals to wait for greater certainty that a new cancer drug will provide survival benefit, when granting accelerated approvals. Considering the global influence of the FDA, and that its decisions are closely followed by other regulatory agencies internationally (including many low-income and middle-income countries that rely on FDA approval),[26] the implications of our findings have relevance to patients with cancer globally. Our results also suggest preferences varied between groups, notably in lower-income and non-White groups, and among non-graduates, highlighting the need for further work to elicit preferences in these populations that already tend to endure the poorest cancer outcomes.[27]

In this study, respondents placed no significant value on the effect of a drug on a surrogate endpoint (progression-free survival), without commensurate certainty of living longer. This was despite defining the progression-free survival benefit of a drug to respondents in a simpler way than in other studies involving patients.[28] This finding adds empirical evidence to the body of literature suggesting patients place little value on

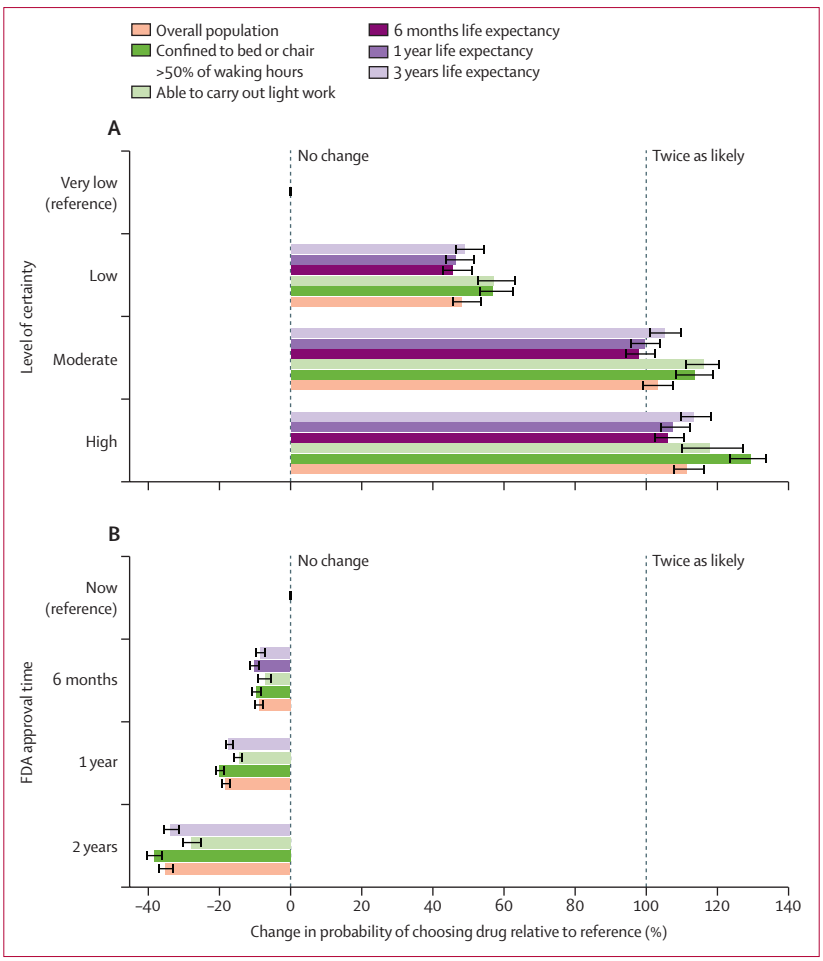

Figure 3: **Marginal effect of functional status and life expectancy on drug choice probability—a predicted probability analysis**

FDA=Food and Drug Administration. (A) Positive change in probability that a respondent will choose a given drug as certainty of survival benefit increases. (B) Negative change in probability that a respondent will choose a given drug as FDA approval time increases. Scenario analysis within A and B illustrates differences in sensitivities of respondents to certainty and FDA approval time, depending on functional status and life expectancy (see appendix p 2 for additional information). Experimental design was used to restrict scenarios so that wait time (until FDA approval) could not exceed life expectancy.

progression-free survival, when it is presented alongside information on survival or quality of life.[29] Our findings also add to ongoing debate about the validity of using surrogate endpoints that do not reliably correlate with overall survival as a means to speed up access to new cancer drugs.[30]

One potential justification for the FDA's reliance on surrogate endpoints could be that there is no alternative option for patients with few or no treatment options. However, this better than nothing approach does not guarantee that cancer drugs receiving accelerated approval provide any meaningful benefit to patients.[31] Moreover, this approach could unduly prioritise patients with particularly poor performance status who (due to substantial disease progression or severe medical morbidity and deconditioning) might be unable to tolerate or derive meaningful benefit from these drugs. This approach also overlooks the fact that best supportive care might offer patients with limited life expectancy, a better quality of life, or longer survival, than further treatment with anticancer drugs offering no meaningful clinical benefit.[32] High levels of unmet need should not absolve the FDA from its responsibility to do what is best for patients by ensuring new drugs provide meaningful clinical benefit before approval,[3] or withdrawing products shown to have no clinical benefit after approval.[13]

Future work to elicit patient preferences surrounding certainty of clinical benefit and access is needed. The trade-offs presented to respondents in this experiment were designed only to elicit preferences, and simulate uncertainty, surrounding the common scenario in which progression-free survival is used as a surrogate for overall survival to obtain accelerated approval. However, preferences across different tumour types, treatment intents (eg, early [neo-adjuvant] or adjuvant setting), in orphan settings, in rare cancers, in settings where there are no available treatments, and in populations with different demographics or prognoses are likely to vary. We also recognise that obtaining high certainty of clinical benefit before approval is not always attainable (eg, due to trial design or crossover), and in some cases the potential benefits of treatments are larger than we investigated and presented to respondents in this experiment. Greater understanding of preferences relating to avoidable uncertainty stemming from additional aspects of trial design (ie, where there is uncertainty about clinical benefit in the real-world setting,[33] or comparative effectiveness) might also be of high value to regulators.

To ensure future accelerated approvals are well justified, the FDA should place greater emphasis on understanding, and empirical evidence in support of, patients' willingness to accept uncertainty in exchange for faster access. Efforts to understand broader perspectives of physicians, payers, drug companies, and other stakeholders on the access–certainty trade-off could also provide relevant considerations for future use of accelerated approval. In addition, greater recognition of the substantial benefits of accelerated approval for companies developing cancer drugs (in the form of lower barriers to entry and faster returns on investment), and the considerable barriers faced by payers and physicians caused by uncertainty, could help refine future use of the accelerated approval pathway. Issuing greater transparency on the benefits and risks of each accelerated approval drug to patients and to each of these stakeholders would be a useful initial step towards greater clarity on the FDA's accelerated approval decisions.

Our study has several limitations. First, discrete choice experiments are limited by hypothetical bias. Although evidence suggests that discrete choice experiments have acceptable external validity of health behaviours,[34] individual behaviours in the real world might deviate from expressed preferences. Second, it can be difficult to distinguish decision heuristics from respondents' preferences. Respondents in our experiment might have ignored some attributes either to simplify tasks or those they valued less. In addition, only 75% of included respondents correctly answered the consistency check (appendix p 6). This could have been due to fatigue, complexity of the task, or several other reasons. Third, there is a trade-off between information gained from the experiment and the cognitive burden for respondents. We therefore made this experiment as simple as possible, while also providing the information most pertinent to the access–certainty trade-off. To avoid over-complicating the discrete choice experiment, we restricted anticipated drug benefits to progression-free survival, and certainty of clinical benefit related to overall survival. Use of additional attributes or indeed levels (eg, larger drug benefits, different life expectancies, etc) would have probably led to different results and thus warrant further research. Finally, the population of this sample is not exclusively patients with cancer, facing in real-life and time, the scenarios presented to them in this experiment.

FDA accelerated approvals, granted based on surrogate endpoints, are guided by the perceived willingness of patients to accept uncertainty in exchange for faster access. Although people with experience of cancer place high value on faster access to new drugs, they also place utmost value on high certainty that new cancer drugs will ultimately offer survival benefit. In this nationally representative experiment, many participants showed a higher willingness to wait than would be required to assess the survival benefit of cancer drugs in the metastatic setting. In some cases, the FDA might not be striking the optimal balance in terms of the trade-off between ensuring certainty that new drugs offer clinical benefit and speed of access in its accelerated approval decisions.

Contributors

RF obtained study funding. RF and HN conceptualised the study with the help of ML and AA. RF, ML, and HN developed the methodology. RF curated the data. RF conducted formal analysis of the data with the

help of ML. HN and AA provided supervision of the analysis. AA and HN validated the study methodology and scope. RF produced the data visualisation. RF developed the original draft manuscript. All authors contributed to review and editing of the final manuscript. RF and HN directly accessed and verified the underlying data reported in the manuscript. All authors had access to all the data reported in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Choice data (including data dictionaries) that underlie the results reported in this article will be made available at reasonable request for academic use beginning 9 months following Article publication. Researchers should direct requests to the corresponding author.

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References

1 United States Food and Drug Administration. Demonstrating substantial evidence of effectiveness for human drug and biological products. Draft guidance for industry. 2019. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products (accessed July 9, 2024).

2 United States Food and Drug Administration. Guidance for industry: expedited programs for serious conditions–drugs and biologics. 2014. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics (accessed July 9, 2024).

3 Booth CM, Sengar M, Goodman A, et al. Common sense oncology: outcomes that matter. *Lancet Oncol* 2023; **24:** 833–35.

4 United States Food and Drug Administration. Table of Surrogate endpoints that were the basis of drug approval or licensure. 2022. https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure (accessed July 9, 2024).

5 Chen EY, Haslam A, Prasad V. FDA acceptance of surrogate end points for cancer drug approval: 1992–2019. *JAMA Intern Med* 2020; **180:** 912–14.

6 Fashoyin-Aje LA, Mehta GU, Beaver JA, Pazdur R. The on- and off-ramps of oncology accelerated approval. *N Engl J Med* 2022; **387:** 1439–42.

7 United States Food and Drug Administration. Accelerated approval program. 2024. https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program (accessed June 20, 2024).

8 Hwang TJ, Darrow JJ, Kesselheim AS. The FDA's expedited programs and clinical development times for novel therapeutics, 2012–2016. *JAMA* 2017; **318:** 2137–38.

9 Wong AK, Mooghali M, Ramachandran R, Ross JS, Wallach JD. Use of expedited regulatory programs and clinical development times for FDA-approved novel therapeutics. *JAMA Netw Open* 2023; **6:** e2331753.

10 Prasad V, Kim C, Burotto M, Vandross A. The strength of association between surrogate end points and survival in oncology: a systematic review of trial-level meta-analyses. *JAMA Intern Med* 2015; **175:** 1389–98.

11 Gyawali B, Hey SP, Kesselheim AS. Assessment of the clinical benefit of cancer drugs receiving accelerated approval. *JAMA Intern Med* 2019; **179:** 906–13.

12 Naci H, Zhang Y, Woloshin S, Guan X, Xu Z, Wagner AK. Overall survival benefits of cancer drugs initially approved by the US Food and Drug Administration on the basis of immature survival data: a retrospective analysis. *Lancet Oncol* 2024; **25:** 760–69.

13 Gyawali B, Rome BN, Kesselheim AS. Regulatory and clinical consequences of negative confirmatory trials of accelerated approval cancer drugs: retrospective observational study. *BMJ* 2021; **374:** n1959.

14 Rome BN, Feldman WB, Kesselheim AS. Medicare spending on drugs with accelerated approval, 2015–2019. *JAMA Health Forum* 2021; **2:** e213937.

15 Skydel JJ, Egilman AC, Wallach JD, Ramachandran R, Gupta R, Ross JS. Spending by the centers for Medicare & Medicaid services before and after confirmation of benefit for drugs granted US Food and Drug Administration accelerated approval, 2012 to 2017. *JAMA Health Forum* 2022; **3:** e221158.

16 O'Hara NN. Eliciting health care preferences with discrete choice experiments. *JAMA Netw Open* 2022; **5:** e228794.

17 American Association for Public Opinion Research. Best practices for survey research. 2024. https://aapor.org/wp-content/uploads/2023/06/Survey-Best-Practices.pdf (accessed July 9, 2024).

18 Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin* 2023; **73:** 17–48.

19 Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5:** 649–55.

20 Michaeli DT, Michaeli T. Overall survival, progression-free survival, and tumor response benefit supporting initial US Food and Drug Administration approval and indication extension of new cancer drugs, 2003–2021. *J Clin Oncol* 2022; **40:** 4095–106.

21 Chen EY, Joshi SK, Tran A, Prasad V. Estimation of study time reduction using surrogate end points rather than overall survival in oncology clinical trials. *JAMA Intern Med* 2019; **179:** 642–47.

22 ChoiceMetrics. Ngene 1·3 user manual and reference guide. 2021. https://www.choice-metrics.com/NgeneManual130.pdf (accessed July 9, 2024).

23 Street DJ, Burgess L, Louviere JJ. Quick and easy choice sets: constructing optimal and nearly optimal stated choice experiments. *Int J Res Mark* 2005; **22:** 459–70.

24 Bliemer MCJ, Rose JM, Hess S. Approximation of Bayesian efficiency in experimental choice designs. *J Choice Model* 2008; **1:** 98–126.

25 Hess S, Palma D. Apollo: a flexible, powerful and customisable freeware package for choice model estimation and application. *J Choice Model* 2019; **32:** 100170.

26 Akhade A, Sirohi B, Gyawali B. Global consequences of the US FDA's accelerated approval of cancer drugs. *Lancet Oncol* 2022; **23:** 201–03.

27 Islami F, Guerra CE, Minihan A, et al. American Cancer Society's report on the status of cancer disparities in the United States, 2021. *CA Cancer J Clin* 2022; **72:** 112–43.

28 Raphael MJ, Robinson A, Booth CM, et al. The value of progression-free survival as a treatment end point among patients with advanced cancer: a systematic review and qualitative assessment of the literature. *JAMA Oncol* 2019; **5:** 1779–89.

29 Fallowfield LJ, Fleissig A. The value of progression-free survival to patients with advanced-stage cancer. *Nat Rev Clin Oncol* 2011; **9:** 41–47.

30 Gyawali B, Kesselheim AS, Ross JS. The accelerated approval program for cancer drugs—finding the right balance. *N Engl J Med* 2023; **389:** 968–71.

31 Lynch HF, Largent EA. Considering tomorrow's patients in today's drug approvals. *BMJ* 2023; **381:** e075000.

32 Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010; **363:** 733–42.

33 Wilson BE, Hanna TP, Booth CM. Efficacy-effectiveness gaps in oncology: looking beyond survival. *Cancer* 2024; **130:** 335–38.

34 Quaife M, Terris-Prestholt F, Di Tanna GL, Vickerman P. How well do discrete choice experiments predict health choices? A systematic review and meta-analysis of external validity. *Eur J Health Econ* 2018; **19:** 1053–66.