Communication of Survival Data in FDA-Approved Labeling of Cancer Drugs

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Introduction

Overall survival (OS) – how long patients live after treatment – is arguably the most definitive patient-relevant outcome when evaluating cancer drugs in clinical trials.[1] Consistently communicating the effects of cancer drugs on OS in FDA-approved labeling can help inform treatment decisions. How information on OS benefits of novel cancer drug indications is communicated in labeling, however, has not been evaluated.

Methods

We used the publicly available Drugs@FDA database to identify approved indications for cancer drugs from 1 January 2014 to 31 December 2018. For each indication, we reviewed the Clinical Studies sections of labeling and extracted data on availability of OS information in pivotal studies that supported approvals.

Next, we conducted a content analysis to systematically identify mutually exclusive and exhaustive categories of how OS data were reported in labeling.[2] We adopted an iterative emergent coding strategy whereby three investigators (H.N., X.G., A.K.W.) independently reviewed a subset of labeling and developed an initial set of categories. We refined these categories after multiple rounds of discussion among four investigators (H.N., X.G., S.W., A.K.W.). Our final list distinguished between labeling that reported data from interim and final analyses. We further noted if labeling reported statistically significant results and whether these were explicitly stated in text.

Results

FDA approved 125 cancer drug indications from 1 January 2014 through 31 December 2018. Sixty-five approvals were supported by at least one RCT. Our sample focused on labeling for the 50 of these indications that reported any OS data. Of these, 23 reported OS information obtained from interim analyses and 27 reported data from final analyses (**Figure 1**).

Labeling for the 23 indications reporting interim OS data included 3 with a statement that statistically significant effects were observed in pre-specified analyses. The remaining 20 either (1) included a statement suggesting that the drug did not have a statistically significant survival benefit in interim analyses or (2) mentioned that survival data were not yet mature (too few deaths had occurred at the time of analysis) (**Figure 2**).

Of 27 labels that reported data from final analyses, 12 explicitly stated statistically significant OS gains and 2 explicitly stated that results were not statistically significant (**Figure 2**). Labeling for 1 indication reported survival data obtained from a non-inferiority trial. For the remaining 12 of these 27 labels (44%), there was no explicit statement about the statistical significance of OS findings. For 7 indications it was possible to infer from numerical data presented in either tables or graphs that the reported drug effects on OS compared to a placebo or standard of care at final analysis were statistically significant (**Figure 2**). For 5 indications, it was possible to infer that the OS findings were not statistically significant. Patient cross-over from control to treatment group (which could underestimate drug effect on survival) was mentioned as a potential reason for the absence of OS benefit in 2 of the indication approvals.

Discussion

We found substantial variation in how information on OS was reported in cancer drug labeling. Such variation complicates ascertaining whether a cancer drug improves OS in its labelled indication. For example, for almost half the indications approved based on final analyses, there were no explicit statements on statistically significant OS benefit. Instead, readers had to infer the statistical significance of findings from numerical data reported in Kaplan Meier curves or in tables. Such interpretation often requires familiarity with advanced epidemiological and statistical concepts.[3,4] It is not clear why labels

only variably contain explicit statements on OS results from pivotal trials supporting their approved indications.

Labeling forms the basis of diverse information sources across the health care system: web-based point of care information compendia such as UpToDate reproduce labeling fully or in part, Prescribers' Digital Reference routinely integrates labeling into electronic health record systems,[5] and labelling is the basis for permissible advertising or other promotional claims by the manufacturer.

Labeling should be consistent in communicating what is or is not known at the time it is issued, so prescribers understand how well new drugs work and what important open questions remain.[6] Currently, relevant information on cancer drugs' OS benefits is variably reported in labeling text, tables, figures, or footnotes. FDA should harmonize survival data reporting in cancer drug labeling. For example, labeling should routinely contain clear non-technical statements of whether or not trials show statistically significant OS benefit, and, if applicable, statements on the magnitude of OS benefit. The potential role of cross-over in diluting the effects on survival should be consistently mentioned when labeling reports statistically non-significant trial findings.

Limitations of this study include not evaluating the reporting of endpoints other than OS, not using an instrument to measure clarity of reporting, and not examining the magnitude of OS benefits for indications with such evidence. Notwithstanding these limitations, our findings reveal that labeling frequently fails to consistently communicate the survival benefits of cancer drugs, or lack thereof.

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References

1. Wilson MK, Karakasis K, Oza AM. Outcomes and endpoints in trials of cancer treatment: the past, present, and future. *Lancet Oncol*. 2015;16(1):e32-e42. doi:10.1016/S1470-2045(14)70375-4

2. Krippendorff K. *Content Analysis: An Introduction to Its Methodology*. Sage publications; 2018.

3. Kahwati L, Carmody D, Berkman N, Sullivan HW, Aikin KJ, DeFrank J. Prescribers' Knowledge and Skills for Interpreting Research Results: A Systematic Review. *J Contin Educ Health Prof*. 2017;37(2):129-136. doi:10.1097/CEH.0000000000000150

4. Weir IR, Marshall GD, Schneider JI, et al. Interpretation of time-to-event outcomes in randomized trials: an online randomized experiment. *Ann Oncol Off J Eur Soc Med Oncol*. 2019;30(1):96-102. doi:10.1093/annonc/mdy462

5. Fotsch EJ. Electronic health records: the new vehicle for drug labeling, safety, and efficacy. *Clin Pharmacol Ther*. 2012;91(5):917-919.

6. Schwartz LM, Woloshin S. The Drug Facts Box: Improving the communication of prescription drug information. *Proc Natl Acad Sci U S A*. 2013;110 Suppl 3(Suppl 3):14069-14074.

Figure 1 title: Availability of OS data in FDA-approved labeling for new cancer drug indications.

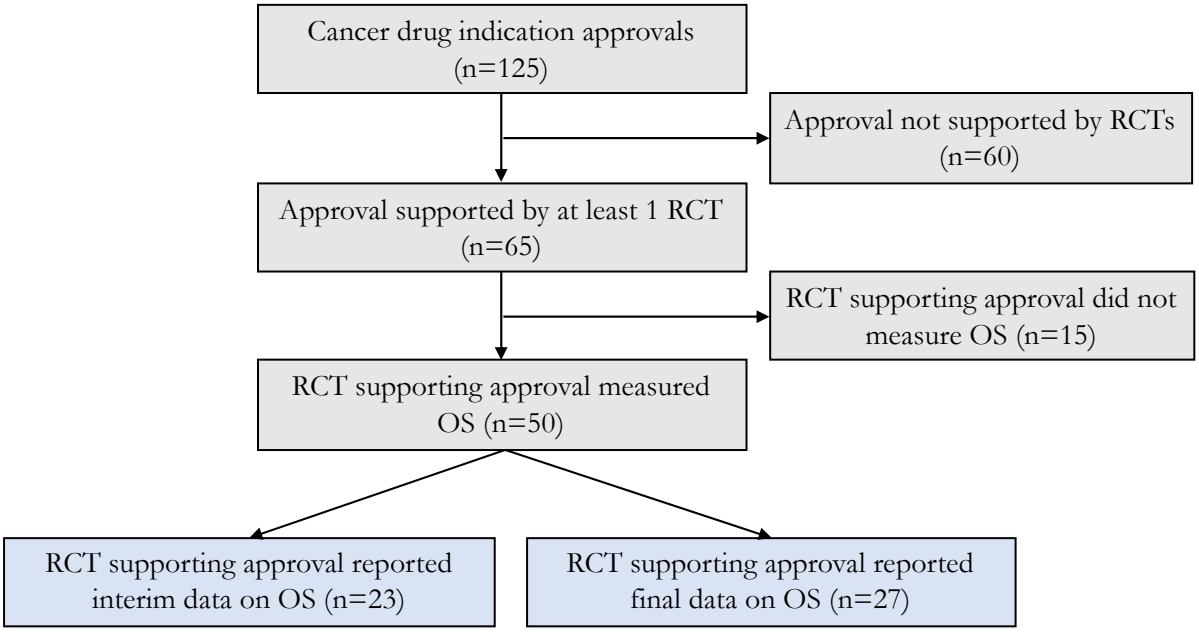

Figure 1 legend: OS: Overall survival; **RCT**: randomized controlled trial

Figure 2 title: Reporting of OS data in FDA-approved labeling for new cancer drug indications.

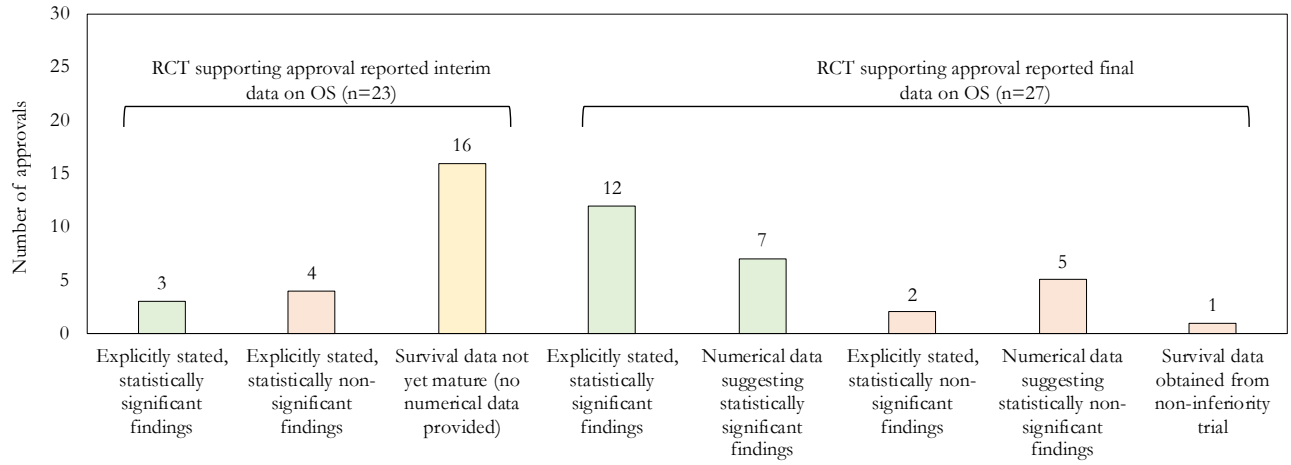

Figure 2 legend: OS: Overall survival; **RCT**: randomized controlled trial.
Bars in green correspond to evidence of OS benefit; bars in orange correspond to no evidence of OS benefit; and the bar in yellow corresponds to immature OS data.