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

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Summary

Background New cancer drugs can be approved by the US Food and Drug Administration (FDA) on the basis of surrogate endpoints while data on overall survival are still incomplete or immature, with too few deaths for meaningful analysis. We aimed to evaluate whether clinical trials with immature survival data generated evidence of overall survival benefit during the period after marketing authorisation, and where that evidence was reported.

Methods In this retrospective analysis, we searched Drugs@FDA to identify cancer drug indications approved between Jan 1, 2001, and Dec 31, 2018, on the basis of immature survival data. We systematically collected publicly available data on postapproval overall survival results in labelling (Drugs@FDA), journal publications (MEDLINE via PubMed), and clinical trial registries (ClinicalTrials.gov). The primary outcome was availability of statistically significant overall survival benefits during the period after marketing authorisation (until March 31, 2023). Additionally, we evaluated the availability and timing of overall survival findings in labelling, journal publications, and ClinicalTrials.gov records.

Findings During the study period, the FDA granted marketing authorisation to 223 cancer drug indications, 95 of which had overall survival as an endpoint. 39 (41%) of these 95 indications had immature survival data. After a minimum of 4·3 years of follow-up during the period after marketing authorisation (and median 8·2 years [IQR 5·3–12·0] since FDA approval), additional survival data from the pivotal trials became available in either revised labelling or publications, or both, for 38 (97%) of 39 indications. Additional data on overall survival showed a statistically significant benefit in 12 (32%) of 38 indications, whereas mature data yielded statistically non-significant overall survival findings for 24 (63%) indications. Statistically significant evidence of overall survival benefit was reported in either labelling or publications a median of 1·5 years (IQR 0·8–2·3) after initial approval. The median time to availability of statistically non-significant overall survival results was 3·3 years (2·2–4·5). The availability of overall survival results on ClinicalTrials.gov varied considerably.

Interpretation Fewer than a third of indications approved with immature survival data showed a statistically significant overall survival benefit after approval. Notable inconsistencies in timing and availability of information after approval across different sources emphasise the need for better reporting standards.

Funding None.

Introduction

Overall survival is the most reliable outcome when assessing the effectiveness of new cancer drugs.[1] In the past, clinical trials supporting cancer drug approvals by the US Food and Drug Administration (FDA) primarily focused on overall survival as the main endpoint.[2] However, regulators are increasingly relying on surrogate measures of efficacy, such as disease progression (eg, progression-free survival) or tumour shrinkage (eg, response rate), to shorten the duration of clinical development and expedite the marketing authorisation of new cancer drugs,[3] even though there is no reliable link between improvements in surrogate endpoints and patient-relevant outcomes such as survival and quality of life in most indications.[4,5]

The reliance on surrogate endpoints has led to a substantial number of new cancer drugs gaining approval based on their effects on these measures.[6] Only about a third of new cancer drugs have evidence of improving overall survival.[7] In fact, many clinical trials supporting drug approvals are not designed to evaluate overall survival.[8] When overall survival is included as one of the trial endpoints, the FDA might grant approval for a new cancer drug once it shows a statistically significant effect on the primary surrogate endpoint while the trial is still ongoing. In such cases, data on overall survival might be considered immature at the time of FDA approval, with too few deaths for meaningful analysis. For example, when the FDA approved sunitinib for treating gastrointestinal stromal tumours, the drug label stated that the data were not mature enough to determine the overall survival benefit.[9] The frequency with which new cancer drug indications

Research in context

Evidence before this study

Regulatory agencies such as the US Food and Drug Administration (FDA) face the challenging task of balancing timely access to new cancer drugs for patients with unmet needs against ensuring comprehensive evidence regarding the benefits and risks of these medications. Within oncology, the use of surrogate endpoints, rather than overall survival, expedites the development and approval of new drugs. We searched MEDLINE (from database inception to March 1, 2023) with no language restrictions, using the search terms "cancer", "oncology", "drugs", "medicines", "pharmacotherapy", "Food and Drug Administration", "FDA", "regulatory agencies", and "overall survival" to identify studies evaluating the evidence base supporting new cancer drug approvals. Approximately a third of new cancer drugs approved over the past two decades have evidence supporting improved overall survival. Regulatory approval of a growing proportion of new cancer indications is primarily supported by data on surrogate endpoints.

Added value of this study

Our study focuses on a previously overlooked category of cancer drugs approved on the basis of their effects on surrogate endpoints while data on overall survival remain immature, suggesting an insufficient number of deaths for meaningful analysis. To our knowledge, this is the first systematic evaluation of survival benefits of cancer drug indications initially approved by the FDA on the basis of immature survival data.

Implications of all the available evidence

Although approval based on surrogate endpoints enables earlier access to new cancer drugs, relying on these endpoints from an ongoing study for regulatory approval might inadvertently complicate the generation of data on overall survival due to participant crossover and use of subsequent treatments.

have incomplete or immature survival data at the time of FDA approval is not known.

The category of cancer drug indications approved on the basis of ongoing studies with immature survival data has received little attention in existing literature. It is important to examine evidence underlying approval of these indications, as FDA approval based on surrogate endpoints of an ongoing study might complicate the assessment of overall survival. In particular, when statistical significance of the trial's primary surrogate endpoint has been reached, participants often switch from the control to the investigational drug group following disease progression.[10] This crossover is justified on ethical grounds as participants seek access to the investigational treatment with benefits on surrogate endpoints. However, participant crossover is a special case of non-adherence with the assigned treatment, leading to measurement bias in the intention-to-treat estimates and selection bias in the per-protocol estimates. Crossover might therefore dilute the observed drug effects on overall survival.[11,12] Similarly, access to subsequent anticancer therapies after discontinuing assigned treatments might be imbalanced between study groups.[13] Although several analytical methods exist to control for participant crossover and subsequent treatments, some of these methods are complex and can yield substantially different results under different assumptions;[14] there is also no methodological consensus on the use of these analyses.[15,16] Whether clinical trials with immature survival data ultimately generate evidence of overall survival benefit after approval has not been explored.

To make informed treatment decisions in clinical practice, timely availability and accurate communication of new data on overall survival for drugs with immature survival data at the time of FDA approval are essential. Such data could be reported in drug labelling, which provides a comprehensive summary of approved drugs' benefits and risks.[17] Additionally, journal publications or clinical trial registries could report new data on the overall survival benefits of cancer drugs after approval. The extent to which different information sources effectively communicate the availability of mature overall survival data after approval has not been systematically investigated.

We aimed to investigate if and when postapproval survival data became available for cancer drug indications initially approved on the basis of ongoing studies with immature survival data. Specifically, we aimed to compare the timing and availability of overall survival findings in labelling, journal publications, and ClinicalTrials.gov records during the period after marketing authorisation. Additionally, we evaluated the role of factors that might influence the measurement of overall survival after approval.

Methods

Data sources and extraction

In this retrospective analysis, we identified all new cancer drug approvals from Jan 1, 2001, to Dec 31, 2018, using Drugs@FDA, the FDA-approved drugs database. Our sample included both original and supplementary indication approvals. We considered each numbered indication in the indications and usage section of the full prescribing information as a distinct indication. Our approach relied on the FDA's categorisation of indications; we did not distinguish between lines of therapy or different combinations unless the FDA explicitly listed these as distinct numbered indications. For example, abemaciclib was included once in our

For **Drugs@FDA** see https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

dataset, because the label listed different combinations under the same numbered indication.

We noted whether indications in our sample received accelerated approval, which permits approval based on surrogate measures that are reasonably likely to predict clinical benefit. In the accelerated approval pathway, manufacturers are required to verify the clinical benefit of their products after approval. We excluded vaccine products, radiotherapies (eg, ^{223}Ra), and supportive therapies.

To identify the cancer drug indications that had any overall survival data at the time of initial approval, we used the Drugs@FDA database to examine the labelling for each drug. We reviewed the clinical studies sections of the labels to identify the pivotal studies that corresponded to each of the numbered indications in our sample. We noted whether each indication approval was supported by at least one randomised controlled trial and whether available trials reported any information on overall survival. We excluded indications that were initially approved without randomised controlled trials, even if such evidence became available during the period after approval (eg, alectinib for anaplastic lymphoma kinase-positive, metastatic non-small-cell lung cancer).

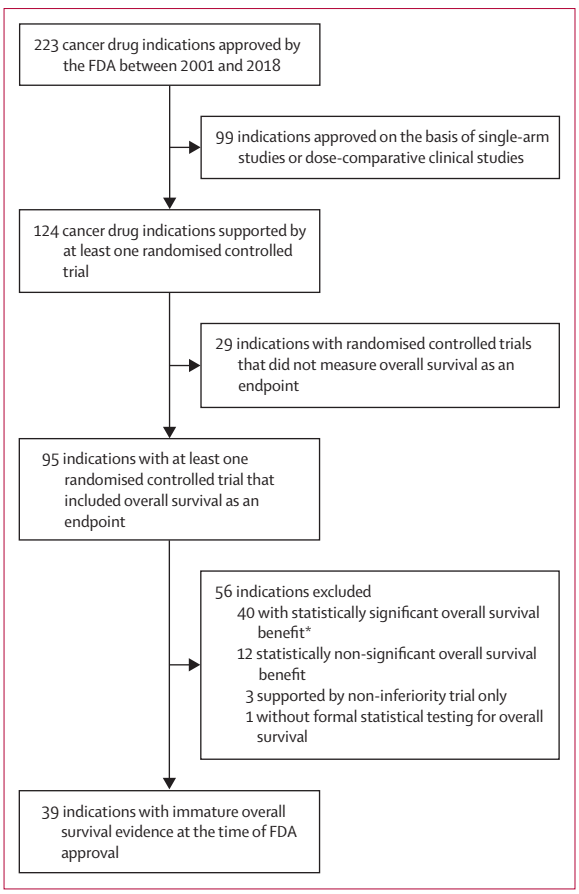

Figure 1: **Identification of cancer drug indications approved with immature overall survival data**

FDA=US Food and Drug Administration. *Of the 40 indications with statistically significant overall survival benefit, six showed statistically significant results in an interim analysis, and one in an exploratory subgroup analysis.

Our final sample included original and supplementary cancer drug indications that received initial approval with incomplete or immature survival data, as reported by the FDA. To be included in the study, the labelling had to explicitly designate the survival data as immature or not mature. Additionally, we inferred immaturity when interim analyses found no statistically significant effects on overall survival owing to a small number of deaths. We characterised how immature survival data were described in labelling at the time of initial approval.

We identified whether additional survival data became available in labelling, trial publications, or both during the period after marketing authorisation for indications initially approved with immature data. Immature data added to an already-approved indication in a trial after approval were not included. We also checked ClinicalTrials.gov to assess the availability of mature overall survival data.

We reviewed labelling updates chronologically until mature overall survival data from the pivotal trials were reported, if available. We also searched for published reports of pivotal trials that supported the initial FDA approval. For each cancer drug indication, we used a stepwise approach to systematically search for publications, consistent with the approach adopted in earlier studies.[18] First, we screened ClinicalTrials.gov using National Clinical Trial identifiers and reviewed all corresponding publications. Second, we searched MEDLINE (via PubMed) using a combination of terms for drug name, approved indication, and a sensitivity and precision-maximising search strategy for randomised controlled trials.[19] When database searches did not yield relevant publications, we ran complementary searches using Google Scholar to identify any relevant grey literature, such as conference presentations and abstracts. We noted when additional data on overall survival were first available (if at all) in publications. We also noted the availability of mature data on overall survival from ClinicalTrials.gov. The last date of the searches was March 31, 2023, allowing a minimum of 4·3 years for additional data on overall survival to become available following FDA approval.

We noted if randomised controlled trials with additional data on overall survival reported statistically significant results during the period after marketing authorisation. In the absence of an explicit statement confirming that the drug had evidence of a statistically significant overall survival benefit in the approved indication, we relied on numerical data. Consistent with the approach adopted in earlier studies,[17,20,21] we considered results to be statistically significant if the 95% CIs for the hazard ratio between the experimental and control groups or for the difference in median overall survival did not cross the line of no difference (null), or if the corresponding p value was lower than the prespecified threshold for

statistical significance (accounting for multiple testing, when relevant).

In cases when randomised controlled trials reported statistically significant evidence of overall survival benefit during the period after marketing, we recorded the difference in median overall survival between the treatment and comparator groups. In some cases, we were only able to extract the proportions of participants who were alive at the end of the study period. To establish whether the observed overall survival results were clinically meaningful, we extracted the publicly available European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (MCBS) scores.

We checked whether participant crossover and use of subsequent treatments was mentioned in journal publications that reported the findings of randomised controlled trials with additional overall survival data. We also noted whether any analytical strategies (eg, rank preserving structural failure time models) were used to adjust for participant crossover or subsequent treatments.[22]

We identified whether adjustment methods were responsible for any differences in reporting between labelling and publications. We specifically looked for instances of presenting or reframing non-significant survival findings as significant using adjustment methods.

Sample identification and data extraction were conducted independently by two investigators, with disagreements resolved through discussion. Because we used publicly available data, this study was determined to not constitute research in human participants by the

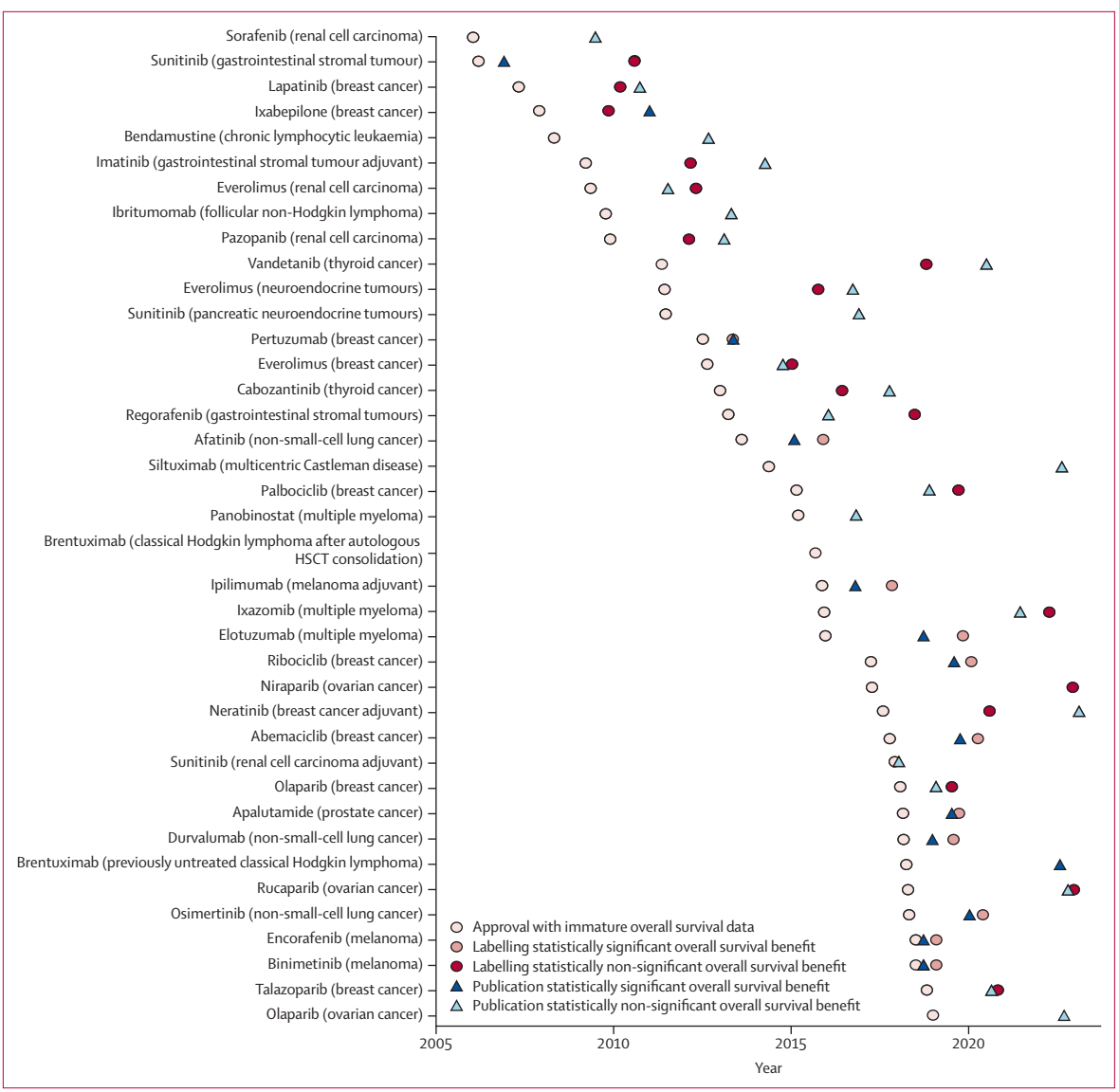

Figure 2: **Availability of overall survival data after approval for 39 drug indications approved with immature survival data**
Each row represents a different cancer drug indication. The same pivotal trial supported the approval of both encorafenib and binimetinib. HSCT=haematopoetic stem-cell transplantation.

Harvard Pilgrim Health Care Institute institutional review board, and informed consent was therefore not required.

Statistical analysis

The primary outcome was availability of data showing statistically significant overall survival benefits during the period after marketing. The secondary outcome was the timing of overall survival data availability. We used descriptive statistics to summarise the availability (frequency) and timing (median and IQR) of postapproval evidence of overall survival benefit in the sample of cancer drug indications. We tested whether median time

	Indication	Combined agents	Control group	Trial details	Overall survival findings	ESMO–MCBS
Abemaciclib	In combination with fulvestrant for the treatment of women with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy	Fulvestrant	Fulvestrant plus placebo	MONARCH 2 (NCT02107703)[23]	Overall survival control: 37·3 months; overall survival benefit: 9·4 months; overall survival HR: 0·76 (95% CI 0·61–0·95)	4
Afatinib	First-line treatment of patients with metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (Leu858Arg) substitution mutations as detected by an FDA-approved test	None	Cisplatin plus pemetrexed	LUX – Lung 3 (NCT00949650)[24]	Overall survival control: 21·1 months; overall survival benefit: 12·2 months; overall survival HR: 0·54 (95% CI 0·36–0·79)	5
Apalutamide	Treatment of patients with non-metastatic castration-resistant prostate cancer	Androgen deprivation therapy	Androgen deprivation therapy plus placebo	TITAN (NCT02489318)[25]	Overall survival control: 73·5%; overall survival benefit: 8·9%; overall survival HR: 0·67 (95% CI 0·51–0·89)	4
Binimetinib	In combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a *BRAF*^{V600E} (ie, Val600Glu) or *BRAF*^{V600K} (ie, Val600Lys) mutation, as detected by an FDA-approved test	Encorafenib	Vemurafenib	COLUMBUS (NCT01909453)[26]	Overall survival control: 16·9 months; overall survival benefit: 16·7 months; overall survival HR: 0·64 (95% CI 0·50–0·81)	A 5
Brentuximab	Treatment of patients with primary cutaneous anaplastic large cell lymphoma or CD30-expressing mycosis fungoides who have received previous systemic therapy	Doxorubicin plus vinblastine plus dacarbazine	Doxorubicin plus bleomycin plus vinblastine plus dacarbazine	ECHELON-1 (NCT01712490)[27]	Overall survival control: 89·4%; overall survival benefit: 4·5%; overall survival HR: 0·59 (95% CI 0·40–0·88)	Not available
Durvalumab	Treatment of patients with unresectable, stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiotherapy	None	Placebo	PACIFIC (NCT02125461)[28]	Overall survival control: 29·1 months; overall survival benefit: 18·4 months; overall survival HR: 0·72 (95% CI 0·59–0·89)	4
Ipilimumab	Adjuvant treatment of patients with cutaneous melanoma with pathological involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy	None	Placebo	EORTC 18071 (NCT00636168)[29]	Overall survival control: 54·4%; overall survival benefit: 11%; overall survival HR: 0·72 (95% CI 0·58–0·88)	A
Pertuzumab	In combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received previous anti-HER2 therapy or chemotherapy for metastatic disease	Trastuzumab plus docetaxel	Trastuzumab plus docetaxel plus placebo	CLEOPATRA (NCT00567190)[30]	Overall survival control: 40·8 months; overall survival benefit: 16·3 months; overall survival HR: 0·69 (95% CI 0·58–0·82)	4
Ribociclib*	In combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer	Letrozole	Letrozole plus placebo	MONALEESA-2 (NCT01958021)[31]	Overall survival control: 51·4 months; overall survival benefit: 12·5 months; overall survival HR: 0·76 (95% CI 0·63–0·93)	4
Osimertinib	First-line treatment of patients with metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 Leu858Arg mutations, as detected by an FDA-approved test	None	Gefitinib or erlotinib	FLAURA (NCT02296125)[32]	Overall survival control: 31·8 months; overall survival benefit: 6·8 months; overall survival HR: 0·80 (95% CI 0·64–1·00)	4
Encorafenib†	In combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a *BRAF*^{V600E} or *BRAF*^{V600K} mutation, as detected by an FDA-approved test	Binimetinib	Vemurafenib	COLUMBUS (NCT01909453)[26]	Overall survival control: 16·9 months; overall survival benefit: 16·7 months; overall survival HR: 0·64 (95% CI 0·50–0·81)	A 5
Elotuzumab	In combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three previous therapies	Lenalidomide plus dexamethasone	Lenalidomide plus dexamethasone	ELOQUENT-2 (NCT01239797)[33]	Overall survival control: 39·6 months; overall survival benefit: 8·7 months; overall survival HR: 0·82 (95% CI 0·69–1·00)	Not available

ESMO–MCBS=European Society for Medical Oncology–Magnitude of Clinical Benefit Scale. FDA=US Food and Drug Administration. HR=hazard ratio. NSCLC=non-small-cell lung cancer. *Overall survival results for ribociclib were available earlier in the MONALEESA-7 trial compared with MONALEESA-2. Because both trials are listed under the same numbered indication, we considered the date of MONALEESA-7's overall survival results the date of availability. †The COLUMBUS trial is counted twice, as it supported the separate approval of both binimetinib and encorafenib. Therefore, we considered these as distinct cancer drug indications.

Table: **Postapproval overall survival results for the 12 cancer drug indications with mature data showing a statistically significant overall survival benefit**

to availability of statistically significant and statistically non-significant findings was different using a non-parametric *k*-sample test. Stata version 17 was used for statistical analysis. A p value of less than 0·05 was considered statistically significant.

Role of the funding source

There was no funding source for this study.

Results

Between Jan 1, 2001, and Dec 31, 2018, the FDA granted marketing authorisation to 223 cancer drug indications. 99 (44%) indications were approved on the basis of single-arm studies or dose-comparative clinical studies alone. Of the 124 cancer drug indications supported by at least one randomised controlled trial, 29 (23%) did not measure overall survival (appendix p 2). Among the 95 indications with overall survival as an endpoint, 40 (42%) were approved with statistically significant overall survival benefits (figure 1, appendix p 5).

At the time of initial FDA approval, 39 (41%) of the 95 indications that measured overall survival as an endpoint had immature survival data (appendix p 13). There was no explicit definition of immature survival data in labelling (appendix p 16). Among 39 indications with immature survival data, 31 (79%) approvals were indicated for the treatment of solid tumours and eight (21%) were for haematological malignancies. Three (8%) of 39 indications received FDA accelerated approvals and four (10%) were indicated for adjuvant settings.

After a minimum of 4·3 years of follow-up during the period after marketing (median follow-up from FDA approval 8·2 years [IQR 5·3–12·0]), additional overall survival data from the pivotal trials became available in either revised FDA drug labelling or journal publications, or both, for 38 (97%) of 39 indications (figure 2).

For 28 (72%) of 39 indications, mature survival data from the same pivotal trial that supported the initial FDA approval were available in both revised labelling and trial publications. Mature survival data were more likely to be reported in publications (37 [95%] of 39 indications) than in labelling (29 [74%]). The availability of survival results on ClinicalTrials.gov varied substantially. ClinicalTrials.gov entries for only ten (26%) of 39 indications reported up-to-date overall survival results that were consistent with the latest drug labelling and publication.

Mature data on overall survival showed a statistically significant benefit in 12 (32%) of 38 indications with additional data, excluding two discrepancies between labelling and publications (figure 2, appendix p 18). The magnitude of the overall survival benefit reported for these 12 indications is shown in the table. Of the 12 indications with statistically significant findings, four reported crossover and differences in the use of subsequent treatments (appendix p 21). Among the nine indications that reported the median duration of overall survival in both treatment and control groups, the median overall survival benefit was 12·5 months (IQR 9·4–16·7). ESMO–MCBS scores were available for ten indications, all showing a substantial magnitude of benefit (table).

Mature data showed statistically non-significant overall survival findings for 24 (63%) indications (excluding the two discrepancies; figure 2). Publications for all trials for these 24 indications included statements about the role of crossover or subsequent treatments in confounding the overall survival results (appendix p 21).

Discrepancies were observed in mature overall survival data reported in updated drug labelling and journal publications for two (5%) indications (sunitinib for gastrointestinal stromal tumour and ixabepilone for breast cancer; appendix p 18). Although trial publications reported statistically significant evidence of overall survival benefit for these two indications, updates to FDA labelling reported statistically non-significant findings.

None of the three indications that received accelerated approvals showed statistically significant overall survival benefits after approval, and panobinostat, in combination with bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least two previous regimens, was subsequently withdrawn from the market. Among the four drug indications for adjuvant treatment, ipilimumab for the adjuvant treatment of patients with cutaneous melanoma showed a statistically significant benefit.

See Online for appendix

Statistically significant evidence of overall survival benefit was available earlier than statistically non-significant evidence (p=0·0060). Statistically significant findings were reported in either labelling or publications after a median of 1·5 years (IQR 0·8–2·3) following initial approval (figure 3). The median time to availability of statistically non-significant overall survival results was 3·3 years (2·2–4·5) from either source. The median time to the availability of statistically significant findings (2·0 years [IQR 1·1–2·4] *vs* 1·4 years [0·8–2·3]) and statistically

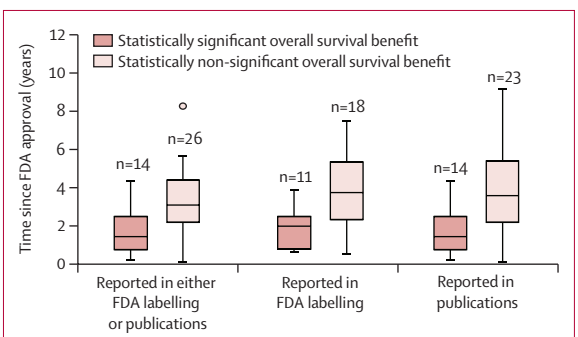

Figure 3: **Timing of availability of postapproval overall survival results in FDA-approved labelling and publications**

Figure is inclusive of the two discrepancies in reporting postapproval overall survival benefits between labelling and publications. Boxes show median and IQR, and whiskers show minimum and maximum. A datapoint is presented as an outlier if it deviates by more than 1·5 times from the IQR. FDA=US Food and Drug Administration.

non-significant findings (3·7 years [2·5–5·2] *vs* 3·6 years [2·5–5·3]) was similar in labelling and publications (figure 3).

Analytical strategies were used to control for participant crossover for seven indications. Of these, six adjusted analyses reported statistically significant overall survival results (figure 4). These adjusted results were only reported in journal publications. These findings were never presented in labelling.

Discussion

We found that between 2001 and 2018, 41% of cancer drug indications that included an assessment of overall survival in pivotal trials did not have complete data at the time of initial FDA approval. Additional survival data became available for nearly all cancer drug indications initially approved with immature data. However, more than 60% of these indications showed no statistically significant survival benefit in their approved indications.

Our findings make a novel contribution to the large body of literature evaluating the quantity and quality of data supporting FDA cancer drug approvals. Previous studies have examined the availability and magnitude of overall survival benefits associated with new cancer drugs.[3,34–38] However, these studies have not consistently distinguished between various reasons for the absence of overall survival benefits. Our analysis expands on this body of literature by focusing on a previously overlooked category of cancer drug approvals—those with incomplete survival data at the time of initial regulatory approval. We found that fewer than a third of cancer drug indications with survival data collected in pivotal trials showed a statistically significant overall survival benefit after approval. These findings have global implications because the FDA is typically the first regulator to approve new cancer drugs, and its evidence standards often influence other regulatory settings.[39,40]

Most indications with immature survival data at the time of initial FDA approval showed no statistically significant survival benefit during the period after marketing. Participant crossover from the control group to the treatment group at the time of disease progression, or the use of subsequent anticancer therapies after trial participants discontinued assigned treatments, might have contributed to the lack of overall survival benefit in trials that showed statistically non-significant results. Consistent with earlier literature, reporting on subsequent therapies was highly variable in journal publications.[41] There were also some indications for which showing a statistically significant overall survival benefit might have been infeasible irrespective of participant crossover or subsequent therapies. For example, siltuximab is indicated for a rare condition (Castleman disease), and few deaths were observed during the pivotal study. Additional follow-up or a larger sample size might have been necessary to discern a survival difference between treatment groups.

That only three cancer drug indications in our sample received FDA accelerated approvals merits further discussion. In theory, the accelerated approval pathway is designed to grant marketing authorisation on the basis of ongoing trials measuring surrogate endpoints, while additional data are collected to verify clinical benefit. However, regulatory reliance on surrogate endpoints extends beyond the accelerated approval pathway.[42] In practice, a growing proportion of accelerated approvals

● Primary (unadjusted, intention-to-treat) analysis
● Adjustment for participant crossover

	Median overall survival (drug)	Median overall survival (control)	HR (95% CI)	p value	Crossover adjustment method
Sorafenib	17·8 months	15·2 months	0·88 (0·74–1·04)	0·15	Analysis censoring placebo patients who crossed over to sorafenib
		14·3 months	0·78 (0·62–0·97)	0·029	
Lapatinib	75·0 weeks	64·7 weeks	0·87 (0·71–1·08)	0·21	Regression analysis considering crossover as a time-dependent covariate
		Not reported	0·80 (0·64–0·99)	0·043	
Everolimus	14·8 months	14·4 months	0·87 (0·65–1·15)	0·16	Rank-preserving structural failure time analysis
		10·0 months	Not reported	Not reported	
Pazopanib	22·9 months	20·5 months	0·91 (0·71–1·16)	0·22	Inverse probability of censoring weighted analysis
		Not reported	0·50 (0·32–0·76)	0·002	
Sunitnib	38·6 months	29·1 months	0·73 (0·50–1·06)	0·094	Analysis censoring patients in the placebo group who crossed over to sunitinib
		16·3 months	0·40 (0·23–0·71)	0·001	
Regorafenib	17·4 months	17·4 months	0·91 (0·65–1·27)	Not reported	Rank-preserving structural failure time analysis
		11·9 months	0·62 (0·44–0·87)	Not reported	
Palbociclib	34·9 months	28·0 months	0·81 (0·64–1·03)	0·09	Rank-preserving structural failure time analysis
		27·4 months	0·78 (0·61–1·04)	Not reported	

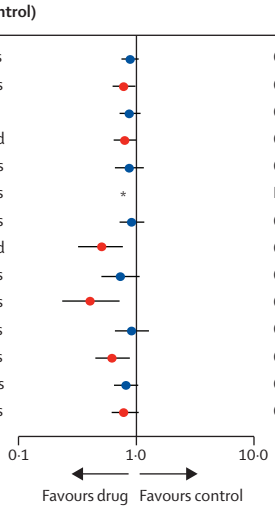

Figure 4: **Postapproval overall survival results with and without crossover adjustment**
HR=hazard ratio. *Although HR and 95% CI were not reported for crossover adjusted analysis for everolimus, the abstract stated that the results were statistically significant (including for everolimus).

are granted based on single-arm trials that cannot measure time-to-event endpoints. Subsequent post-approval trials are then necessary to verify clinical benefit. Even when such trials are conducted, the FDA increasingly considers other surrogate endpoints, such as progression-free survival, as sufficient to confirm benefit.[18,43]

Indeed, measuring overall survival is no longer the primary goal in cancer drug trials. During our study period, overall survival was frequently included as a secondary endpoint in clinical trials supporting regulatory approvals. Companies might not be incentivised to measure the impact of their drugs on overall survival. Previous studies found no significant association between survival benefits and higher prices of cancer drugs in the USA, suggesting no financial rewards for showing such survival benefits.[44] Outside the USA, mature overall survival data paradoxically might be a disadvantage in settings with established health technology assessment processes. In England, cancer drug indications with overall survival benefit were less likely to be recommended for funding than those without, as extrapolation beyond trial follow-up made it difficult to rule out potential survival benefits that could justify the incremental costs associated with the drugs.[45,46] These findings suggest the calculus for evidence generation in cancer drug trials has changed in recent years; the prospect of generating evidence on survival now appears to bring more gains than actually demonstrating it.

We identified major shortcomings in the information landscape surrounding cancer drug trials. First, mature data showing statistically significant overall survival benefits were reported sooner than data showing statistically non-significant results. This time lag represents a form of outcome reporting bias, which occurs when the publication timing depends on the statistical significance of the results. Despite the requirement to post clinical trial results on ClinicalTrials.gov within 1 year of completion, our findings suggest that ClinicalTrials.gov did not serve as a useful source of updated overall survival data from pivotal trials of cancer drugs. Results were often inconsistently available, incomplete, and not up to date. Second, journal publications were more likely than FDA-approved labelling to claim survival benefit despite the absence of statistically significant results. Advanced statistical methods to adjust for crossover, which often yielded statistically significant survival benefits (six of seven indications), were only reported in journal publications, and not presented in labelling. Whether this represents spin in reporting should be explored in future research.

There are important opportunities for the FDA to improve its guidance for industry and labelling for health-care professionals. First, we were not able to identify a definition of immature survival data. Statements on data maturity often appear to be primarily based on the proportion of deaths in the trials. Previous analyses have shown that most indications with immature survival data had proportions of deaths below 50%, that is, median survival could not be calculated.[46] It is important for the FDA to provide a clear definition of immature survival data and consistently adopt it in labelling. Second, when the FDA approves new cancer drugs on the basis of immature survival data, the labelling should inform prescribers whether further data analyses are anticipated and provide a timeline for their availability. Third, reporting the appropriateness of participant crossover to investigational groups when their disease progresses is essential. The FDA Oncology Center of Excellence's Guidance for Industry recognises the challenges posed by crossover to the analysis of overall survival data, as it might confound the analysis of cancer therapies. However, the FDA guidance does not specify a preferred strategy for addressing such confounding. If the FDA prefers unadjusted analyses, this should be mentioned in guidance. Fourth, FDA labelling reports mature survival data for a smaller subset of indications than those reported in publications. Legislative change might be necessary to grant the FDA additional authority and resources to mandate timely updates to labelling.

Our study had limitations. First, we did not consider the availability and timing of results reporting on endpoints other than overall survival. Quality of life, another key patient-relevant endpoint, is inconsistently measured and reported in clinical trials supporting new cancer drug approvals.[34] Second, our identification of indications with immature survival data relied solely on FDA-approved labelling. We might have missed other eligible indications if FDA labelling did not provide adequate information. For example, the labelling for dacomitinib (indicated for metastatic non-small-cell lung cancer) did not include overall survival results. However, the pivotal trial's journal publication reported immature survival data. Third, our minimum follow-up period of over 4 years might have been too short for the indications approved in later years in our sample. However, the median time to availability of additional overall survival data was less than 4 years for both statistically significant and non-significant results.

Regulatory approval of new cancer drug indications based on immature survival data is often justified to ensure patients with unmet needs have timely access to new therapeutic alternatives. However, our finding that fewer than a third of indications showed overall survival benefit after approval suggest that regulatory approval based on immature survival data might inadvertently complicate the assessment of a drug's impact on overall survival in its approved indication, highlighting the complex trade-offs involved in regulatory decisions.

Contributors

HN conceptualised the study. HN curated the data with help from YZ and ZX. HN validated the accuracy of all data. HN conducted the

analysis with help from YZ. HN, SW, XG, and AKW supervised the methodology. HN developed the original draft. All authors contributed to revising the final version. HN and YZ 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

HN reported receiving grants from Commonwealth Fund, Health Foundation, National Institute for Health and Care Research, and UK Research and Innovation, and personal fees from Pharmaceutical Group of the European Union, WHO, and *The BMJ* (serving as an adviser). AKW reported receiving grants from the American Cancer Society. SW reported receiving grants from Arnold Ventures. XG reported receiving an award from the National Natural Science Foundation of China. All other authors declare no competing interests.

Data sharing

Dates of FDA approvals, publications, and labelling updates collected for this study are available on request to the corresponding author with publication. All other data are available within the manuscript and appendix.

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