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The evidence base of US Food and Drug Administration approvals of novel cancer therapies from 2000 to 2020

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Abstract

Concerns have been raised that regulatory programs to accelerate approval of cancer drugs in cancer may increase uncertainty about benefits and harms for survival and quality of life (QoL). We analyzed all pivotal clinical trials and all non-pivotal randomized controlled trials (RCTs) for all cancer drugs approved for the first time by the FDA between 2000 and 2020. We report regulatory and trial characteristics. Effects on overall survival (OS), progression-free survival and tumor response were summarized in meta-analyses. Effects on QoL were qualitatively summarized. Between 2000 and 2020, the FDA approved 145 novel cancer drugs for 156 indications based on 190 clinical trials. Half of indications (49%) were approved without RCT evidence;

Abbreviations: EMA, European Medical Agency; FDA, Food and Drug Administration; IQR, interquartile range; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RCT, randomized controlled trail; TR, tumor response.

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82% had a single clinical trial only. OS was primary endpoint in 14% of trials and QoL data were available from 25%. The median OS benefit was 2.55 months (IQR, 1.33-4.28) with a mean hazard ratio for OS of 0.75 (95%CI, 0.72-0.79, $I^2 = 42$). Improvement for QoL was reported for 7 (4%) of 156 indications. Over time, priority review was used increasingly and the mean number of trials per indication decreased from 1.45 to 1.12. More trials reported results on QoL (19% in 2000-2005; 41% in 2016-2020). For 21 years, novel cancer drugs have typically been approved based on one single, often uncontrolled, clinical trial, measuring surrogate endpoints. This leaves cancer patients without solid evidence that novel drugs improve their survival or QoL and there is no indication towards improvement.

KEYWORDS
drug approval, evidence-based medicine, health care policy, quality of life

What's new?

Concerns have been raised that regulatory programs to accelerate the approval of cancer drugs may increase uncertainty about survival and quality-of-life benefits and harms. Here, the authors analyzed all pivotal clinical trials and non-pivotal randomized controlled trials for the 145 novel cancer drugs approved by the FDA between 2000 and 2020. Cancer drugs were typically approved based on one single small trial, often without a control group and measuring only surrogate endpoints. This leaves cancer patients without solid evidence that the novel drugs improve their survival or quality of life, with no trend towards change.

1 | INTRODUCTION

Approval of novel anti-cancer drugs by the US Federal Drug Administration (FDA) demands evidence on efficacy and safety from high quality pivotal trials.[1] In the last three decades, the FDA has been equipped with additional programs to respond more flexibly to medical needs and expedite approval when needed (eg, during the HIV crisis).[2] Those additional approval programs include the orphan drug act (1983), accelerated approval pathway (1992), priority review program (1992) and the breakthrough therapy program (2012).[2] While those programs add flexibility and increased regulatory review speed to the approval process,[3] numerous concerns have been raised regarding their implication for the quality of evidence at the time of approval.[4,5] Concerns are related to the growing use of surrogate endpoints[4] (with mostly uncertain validity)[6] and to approvals increasingly being based on single trials,[7] or on non-controlled trials only.[5] There are examples where approvals based on surrogate endpoints had to be withdrawn at a later stage.[8-10] However, once approved, drugs are often kept on the market despite the lack of evidence for a benefit beyond surrogate endpoints,[11,12] emphasizing the importance of high quality evidence at the date of approval. And even when there is evidence on survival benefits of novel cancer drugs, analyses on approval evidence showed that these are only modest with average survival gains in the range of a few months.[4,5,13,14] Considering the modest improvement of survival, the importance of data on quality of life (QoL) in the assessment of new cancer treatments has been emphasized.[15] However, approval evidence on QoL has only been investigated in a few studies. Most analyses on QoL were not based on available results at the time of approval,[16] but on post-approval publications,[17] and health technology assessments.[13]

We recently assessed the treatment effects of all novel cancer drugs approved by the FDA between 2000 and 2016 on overall survival (OS), progression-free survival (PFS) and tumor response (TR).[18] Here we expand these data and now include approval evidence up to December 2020; provide information on QoL effects; include non-randomized clinical trials; give a closer assessment of study design characteristics; and describe trends of the approval evidence over the last two decades.

2 | METHODS

This study is part of the Comparative Effectiveness of Innovative Treatments in Cancer (CEIT-Cancer) project.[19] The database and identification, selection, extraction and handling of data have been described elsewhere in detail.[5,18,20] Our reporting follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.[21]

2.1 | Identification of novel cancer drugs and corresponding trials

We identified all novel anti-cancer drugs that have been approved by the FDA as treatment for any malignant disease for the first time

between January 2000 and December 2020.[18] We identified the novel cancer drugs by using the FDA official website.[22] We included all clinical trials that we identified as pivotal or that were described as "main" or "primary" clinical trials by the FDA in review strategy section of the approval documents. These were either randomized controlled trials (RCTs) or trials without control arm (ie, single arm or randomized dose-comparison trials). We also extracted information on all other RCTs that were conducted in the target population and compared the novel drug with a control that did not contain the novel drug and were additionally reported in the approval document but were not declared as pivotal. Randomized dose-comparison clinical trials, in which all patients received the novel drug at different doses without a control arm, were considered as clinical trials without control arm. We obtained the FDA approval documents for all novel cancer drugs from drugs@FDA.[22]

2.2 | Data extraction

We extracted data on indication, regulatory and clinical trial characteristics, and the reported treatment outcomes for OS, PFS, TR and QoL.

For the years 2000 to 2016, we used the previously published information.[5] For this period, data for trial without control arm were extracted by one single reviewer (VG). Data for 2017 to 2020 from trials without control arm and RCTs were extracted by two independent reviewers (VG with either CA, CL, HK, JH, MPL, MWC or TVP). Any disagreement was resolved by consensus or by a third reviewer (AMS, LGH).

2.3 | Statistical Analysis

We used descriptive statistics to analyze drugs, indications, clinical and regulatory details, clinical trial characteristics, treatment outcomes and changes over time.

For the analysis of treatment effects, we used RCTs only because trials without control arm do not provide comparative treatment effects. In RCTs that compared different doses of a novel cancer drug to a control, we selected the comparison with the later-approved dose. Three studies were included twice in the analysis because they were relevant to two different indications but for the same drug. For the meta-analyses, we used random-effects models[23] and the I^2 statistic to describe statistical heterogeneity among the pooled effect estimates.[24] Hazard ratios for OS and PFS were directly taken from the FDA documents. For TR, we first calculated the relative risks for the individual trials based on reported events, before pooling them as unadjusted relative risks. We used a continuity correction of 0.5 to account for cases of 0 events.[25] We calculated the improvement in OS and PFS per study as the difference between the median OS or PFS of the experimental vs control arm before calculating an overall median improvement across all studies. Results on QoL were qualitatively summarized. Changes over time for indication and trial characteristics, and treatment effects were reported descriptively by using five-year time intervals. Additionally, we analyzed trends with regression models using year of approval as the exposure variable. We used logistic or linear regression models as applicable. All analyses were exploratory.

We stratified results by cancer type (solid cancers vs hematological cancers), indications that demanded a biomarker vs those that did not, line of treatment and by indications for which results were reported for QoL.

Data were analyzed using R software, version 3.5.1 (R Foundation for Statistical Computing); RStudio software, version 4.0.3 (Rstudio, PBC).[26]

3 | RESULTS

3.1 | Indication and regulatory characteristics

Between 2000 and 2020, the FDA approved 145 novel cancer drugs for 156 indications. Of those 156 indications, 60 (38%) were for hematological cancers, and 96 (62%) were for solid cancers. Most indications contained first (38%), or second line (42%) treatments. For 36% of the indications, a specific biomarker was demanded. The FDA designated priority review to 82% of the indications and to 28% breakthrough therapy. Accelerated approval was assigned to 46% of the indications. The FDA designated orphan drug status to 68% of the drugs (Table 1). Four of five indications (81%) were supported by only one clinical trial. Almost half of the indications (49%) received FDA approval without supporting evidence from at least one RCT. Eleven indications (7%) were approved with evidence from two RCTs (Table 1).

3.2 | Trial characteristics

Overall, we identified 190 clinical trials, with a median of 233 participants (interquartile range [IQR] 124-455). Half of these trials (48%) were randomized controlled with a median of 420 participants (IQR, 236-675). The trials without control arm included a median of 133 participants (IQR, 86-236). The control groups in RCTs were frequently an active comparator agent or placebo (40% and 39%, respectively) (Table 2).

At approval, results on OS were available for 61% of all trials (83% of RCTs, 41% of trials without control), on PFS for 59% trials (83% of RCTs, 37% of trials without control), and on TR for 86% trials (76% of RCTs, 96% of trials without control). OS was the primary endpoint for 14% of all trials (28% of RCTs, none of trials without control), PFS for 26% trials (51% of RCTs, 2% of trials without control), and TR for 54% of trials (13% of RCTs, 93% of trials without control). Although approval documents contained information that the trials have assessed QoL in 55% (51/92) of RCTs and in 30% (29/98) of pivotal trials without control, results on QoL were reported for 25% of trials (34% of RCTs, 16% of trials without control) (Table 2). QoL was the primary outcome for no trial.

TABLE 1 Indication and regulatory characteristics

	Overall	2000-2005	2006-2010	2011-2015	2016-2020
No. (%)	156	22	21	53	60
Solid malignancy	96 (62)	11 (50)	12 (57)	32 (60)	41 (68)
Breast cancer	17 (11)	1 (5)	4 (19)	3 (6)	9 (15)
Endocrine or neuroendocrine	4 (3)	0 (0)	0 (0)	3 (6)	1 (2)
Gastrointestinal	10 (6)	4 (18)	1 (5)	4 (8)	1 (2)
Genitourinary	20 (13)	3 (14)	6 (29)	4 (8)	7 (12)
Gynecological	3 (2)	0 (0)	0 (0)	1 (2)	2 (3)
Neurological	2 (1)	0 (0)	0 (0)	1 (2)	1 (2)
Other solid	5 (3)	0 (0)	0 (0)	0 (0)	5 (8)
Respiratory and Thoracic	15 (10)	3 (14)	0 (0)	6 (11)	6 (10)
Sarcoma or GIST	6 (4)	0 (0)	1 (5)	1 (2)	4 (7)
Skin	12 (8)	0 (0)	0 (0)	9 (17)	3 (5)
Hematological	60 (38)	11 (50)	9 (43)	21 (40)	19 (32)
Chronic myelogenous leukemia	6 (4)	1 (5)	2 (10)	3 (6)	0 (0)
Leukemia	13 (8)	4 (18)	1 (5)	2 (4)	6 (10)
Lymphoma	26 (17)	4 (18)	5 (24)	8 (15)	9 (15)
Multiple myeloma	10 (6)	1 (5)	0 (0)	6 (11)	3 (5)
Other	7 (4)	1 (5)	1 (5)	2 (4)	3 (5)
Line of treatment					
1st	59 (38)	6 (27)	6 (29)	18 (34)	29 (48)
2nd	65 (42)	10 (45)	12 (57)	25 (47)	18 (30)
3rd or later	32 (21)	6 (27)	3 (14)	10 (19)	13 (22)
Biomarker driven indication	56 (36)	6 (27)	5 (24)	17 (32)	28 (47)
Regulatory approval designation					
Priority review	128 (82)	16 (73)	16 (76)	41 (77)	55 (92)
Orphan designation	106 (68)	13 (59)	10 (48)	40 (75)	43 (72)
Accelerated approval	71 (46)	12 (55)	7 (33)	21 (40)	31 (52)
Breakthrough therapy[a]	43 (28)	–	0	12 (23)	31 (52)
Indication tested in at least one RCT	80 (51)	10 (45)	13 (62)	32 (60)	25 (42)
Trials per Indication, mean (SD)	1.22 (0.52)	1.41 (0.59)	1.29 (0.90)	1.21 (0.41)	1.13 (0.39)
Randomized trial	0.59 (0.62)	0.64 (0.79)	0.62 (0.50)	0.70 (0.64)	0.47 (0.57)
Trial without control arm	0.63 (0.74)	0.77 (0.87)	0.67 (1.02)	0.51 (0.67)	0.67 (0.63)

Abbreviation: RCT, randomized controlled trial.
[a]Was only created in 2012.

3.3 | Treatment outcomes in clinical trials

On average, novel drugs improved OS relatively by 25% (HR 0.75; 95%CI, 0.72-0.79; $I^2 = 42\%$; Figure 1 and Table 3) and increased the absolute median OS by 2.55 months (IQR, 1.33-4.28). The mean hazard ratio for PFS was 0.51 (95%CI, 0.47-0.55; $I^2 = 88\%$, Figure S1), with a median increase of PFS of 3.3 months (IQR, 2.02-5.06). The relative tumor response was increased with a risk ratio of 2.14 (95%CI, 1.88-2.43; $I^2 = 90\%$, Figure S2). An improvement in QoL was reported for 8% (7/92) of RCTs (Table 3).

3.4 | Subgroup analyses

The FDA designated orphan drug status to all drugs (100%) that were approved for hematological cancers, and to 48% of drugs for solid cancers. Whereas in solid cancers 62% of the indications were approved based on evidence from at least one RCT, it was 35% in hematological cancers (Table S1). Typically, trials on drugs for solid cancers were larger than trials on hematological cancers (median participants 492; IQR, 328-753 vs 206; 154-310). Whereas OS and PFS are more frequently used as primary outcome in solid cancers (19% vs 5% and 33% vs 14%), TR is more frequently used in hematological

TABLE 2 Trial characteristics

	Overall	2000-2005	2006-2010	2011-2015	2016-2020
All trials					
Number of trials	190	31	27	64	68
Participants, median (IQR)	232 (124, 455)	216 (62, 390)	170 (85, 422)	240 (136, 531)	254 (130, 461)
Endpoints					
Overall survival	116 (61)	14 (45)	13 (48)	48 (75)	41 (60)
Progression-free survival	112 (59)	12 (39)	13 (48)	46 (72)	41 (60)
Tumor response	164 (86)	27 (87)	25 (93)	56 (88)	56 (82)
Quality of life	47 (25)	6 (19)	1 (4)	12 (19)	28 (41)
Other[a]	10 (5)	3 (10)	2 (7)	1 (2)	4 (6)
Primary endpoints					
Overall survival	26 (14)	3 (10)	3 (11)	15 (23)	5 (7)
Progression-free survival	49 (26)	3 (10)	5 (19)	23 (36)	18 (26)
Tumor response	103 (54)	21 (68)	16 (59)	27 (42)	39 (57)
Other[b]	22 (12)	5 (16)	4 (15)	4 (6)	9 (13)
Randomized controlled trials					
Number trials	92	14	13	37	28
Participants, median (IQR)	420 (236, 675)	364 (206, 470)	435 (312, 626)	356 (193, 723)	442 (251, 626)
Blinding					
Double-blind	40 (43)	6 (43)	3 (23)	21 (57)	10 (36)
Open label	52 (57)	8 (57)	10 (77)	16 (43)	18 (64)
Control					
Active	37 (40)	6 (43)	5 (38)	12 (32)	14 (50)
No comparator	19 (21)	4 (29)	5 (38)	6 (16)	4 (14)
Placebo	36 (39)	4 (29)	3 (23)	19 (51)	10 (36)
Endpoint					
Overall survival	76 (83)	8 (57)	10 (77)	35 (95)	23 (82)
Progression-free survival	76 (83)	9 (64)	10 (77)	34 (92)	23 (82)
Tumor response	70 (76)	10 (71)	12 (92)	30 (81)	18 (64)
Quality of life	31 (34)	5 (36)	1 (8)	9 (24)	16 (57)
Other[a]	6 (7)	3 (21)	1 (8)	0 (0)	2 (7)
Primary endpoints					
Overall survival	26 (28)	3 (21)	3 (23)	15 (41)	5 (18)
Progression-free survival	47 (51)	3 (21)	5 (38)	22 (59)	17 (61)
Tumor response	12 (13)	6 (43)	3 (23)	2 (5)	1 (4)
Other[b]	16 (17)	3 (21)	3 (23)	3 (8)	7 (25)
Trials without control arm					
Number trials	98	17	14	27	40
Participants, median (IQR)	133 (86, 236)	94 (49, 235)	101 (72, 123)	134 (104, 220)	145 (107, 337)
Endpoints					
Overall survival	40 (41)	6 (35)	3 (21)	13 (48)	18 (45)
Progression-free survival	36 (37)	3 (18)	3 (21)	12 (44)	18 (45)
Tumor response	94 (96)	17 (100)	13 (93)	26 (96)	38 (95)
Quality of life	16 (16)	1 (6)	0 (0)	3 (11)	12 (30)
Other[a]	4 (4)	0 (0)	1 (7)	1 (4)	2 (5)
Primary endpoints					
Overall survival	0	0	0	0	0

TABLE 2 (Continued)

	Overall	2000-2005	2006-2010	2011-2015	2016-2020
Progression-free survival	2 (2)	0 (0)	0 (0)	1 (4)	1 (2)
Tumor response	91 (93)	15 (88)	13 (93)	25 (93)	38 (95)
Other[b]	6 (6)	2 (12)	1 (7)	1 (4)	2 (5)

Abbreviation: IQR, interquartile range.
[a]Other endpoints included asparaginase activity, testosterone suppression, time to tumor progression, metastatic free survival, reduction in spleen size.
[b]All trials for whom neither Overall survival, progression-free survival nor tumor response was the primary endpoint.

cancers (68% vs 45%). Additionally, QoL is more often reported in trials investigating solid cancers (32%), compared with hematological cancers (14%) (Table S2).

Indications with first line treatment were more often approved based on evidence from at least one RCT (68%) compared with indications of second- or third-line treatments (48% and 31%, Table S1). Treatment outcomes for OS, PFS and TR were similar in analyses stratified by cancer type and line of treatment. There were no stronger effects of drugs in cancers with specific biomarkers (Table S3).

3.5 | Changes in the years 2000 to 2020

The number of approvals continuously increased from 2000 to 2020 (22 approvals in 2000-2005 compared with 60 in 2016-2020) (Tables 1, S4 and Figure 2). The proportion of indications approved under priority review increased from 73% to 92%, and breakthrough therapy designation increased after its introduction in 2012 to 52%. In parallel, the mean number of trials per indication decreased from 1.45 to 1.12 (Figure 2 and Table S4). The proportion of drugs with orphan drug designation, accelerated approval, and supporting evidence from at least one RCT remained stable. The proportions of drugs for solid cancers increased from 50% to 68% and for drugs approved as first line treatments (from 27% to 48%). Furthermore, the proportion of indications which included a specific biomarker increased from 27% to 47%.

There was no relevant increase in the median number of participants from 2000 to 2020 (Tables 1 and S4). The proportion of trials that reported results for OS and PFS increased from 45% to 60% for OS and from 39% to 60% for PFS. Over time, more trials reported results on QoL (19%, 4%, 19% and 41% in the consecutive five-year intervals). There was a trend to use PFS as a primary endpoint more often (10% in 2000-2005; 26% in 2016-2020). For OS, there was no trend towards increasing use as primary endpoint.

The hazard ratios for OS or PFS and the relative risk for TR were stable over time. The median improvement in OS in the years 2016 to 2020 (median OS in months 5.65; IQR 2.05-8.38) was higher compared with the years 2000 to 2005 (2.80; 1.99-4.40), 2006 to 2010 (1.75; 0.29-2.48), 2011 to 2015 (2.40; 1.40-3.94), without a clear trend in the linear regression (Table S4).

4 | DISCUSSION

In the last two decades, the FDA approved 145 novel drugs for 156 cancer treatment indications. Most received priority review and about half underwent accelerated approval. Four of five approvals were based on evidence from a single trial only, in every second case without evidence from an RCT and on the base of surrogate endpoints other than OS, that is, PFS or TR. Trials are typically small (<250 patients). For almost all trials without control arm, TR was the primary endpoint; in RCTs, OS was the primary endpoint in only 28%, while the most frequent primary outcome was PFS (51%). Although this practice has been criticized for years,[4,5,14] we could not observe a trend during the last 20 years to employ RCTs to test novel cancer drugs or provide results on OS more often. Considering that several countries with small national regulators adopt FDA approvals or approve drugs in collaboration with the FDA,[27,28] the evidence base for approval of novel cancer drugs by the FDA has an impact beyond the borders of the US healthcare system.

Despite the large volume of approvals of different drugs, the benefits for patients they convey seem modest. While novel cancer drugs showed strong effect sizes for surrogate endpoints like PFS (mean HR 0.51) and TR (RR 2.14), the effect on OS were more modest with a mean HR of 0.75 and the absolute benefit is in the range of 2 to 4 months longer progression-free and overall survival. This emphasizes the importance of considering surrogacy issues in case when drugs are approved based on limited evidence on OS.[5,29] Our findings may suggest a trend to measure QoL more often but only a small minority of cancer drugs were shown to improve QoL in a RCT (7 of 145, 5%). We saw a trend towards new cancer drugs being more often approved for first line treatment and a higher proportion of biomarker driven therapies. Since its introduction, priority review has now become the standard process for assessment of approval applications; after its creation in 2012, the breakthrough therapy designation is now used for every second approved indication. The circumstance that indications are mostly approved based on a single pivotal trial and without RCT evidence in half of the indications seems to be unchanged over time; in fact, the number of trials per approval decreased during the last two decades. FDA authors are discussing these uncertainties and have recently described potential remedies,[30] for example starting single-arm trials and RCTs in parallel with the aim that solid evidence follows soon after accelerated approval based only on a single arm trial.[30] On December 29, 2022, Consolidated

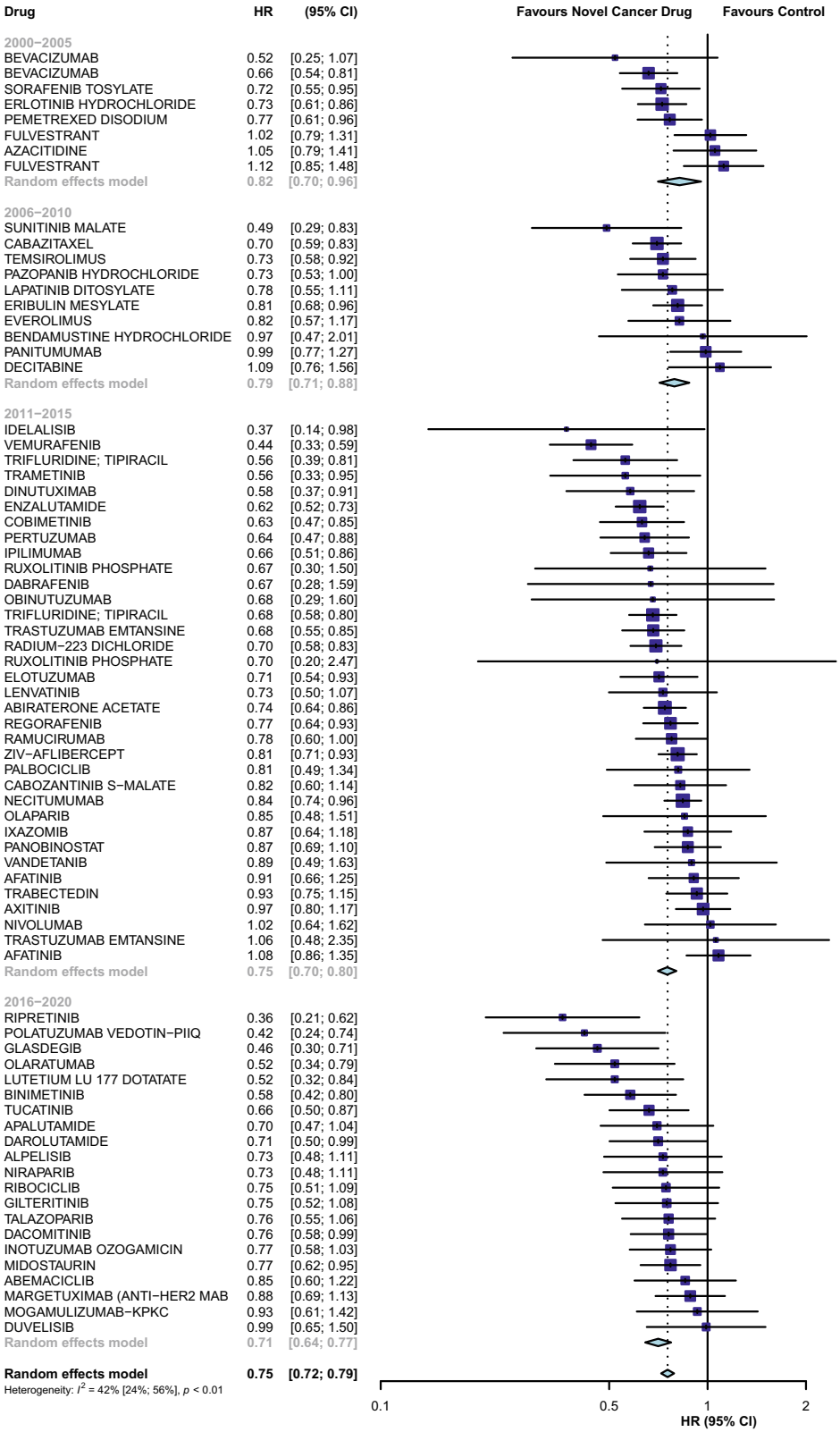

FIGURE 1 Forest plot of all Randomized Clinical Trials with Data on Overall Survival used for approval of novel cancer drugs between 2000 and 2020. Squares represent mean values, with the size of the squares indicating weight and horizontal lines representing 95% CIs. Diamonds represent the pooled mean with the points of the diamonds representing 95% CIs. HR indicates hazard ratio. [Color figure can be viewed at wileyonlinelibrary.com]

Appropriations Act, 2023 (H.R. 2617) was signed by US President Biden, this provides the FDA with the ability to require that post-approval studies be underway prior to grant accelerated approval for novel cancer drugs.[31,32] It remains to be seen to what extent the FDA will use this option.

Median treatment effects for OS seemed to have increased in the last 5 years with a median OS gain of 5.65 months in 2016 to 2020, but this should be interpreted cautiously because it was not supported by linear regressions across all years and it was substantially driven by the approval of olaratumab in 2016 which showed a median

TABLE 3 Overall survival, progression-free survival, overall tumor response and quality of life outcomes of randomized controlled trials

	Overall	2000-2005	2006-2010	2011-2015	2016-2020
Total number of RCTs	92	14	13	37	28
Overall survival					
No. RCTs reporting median OS	44	7	8	19	10
Improvement, median (IQR), months	2.55 (1.33, 4.28)	2.80 (1.99, 4.40)	1.75 (0.29, 2.48)	2.40 (1.40, 3.94)	5.65 (2.05, 8.38)
No. RCTs HR OS	74	8	10	35	21
HR (95% CI), I^2	0.75 (0.72, 0.79), 42	0.82 (0.7, 0.96), 64	0.79 (0.71, 0.88), 27	0.75 (0.7, 0.8), 46	0.71 (0.64, 0.77), 29
Progression-free survival					
No. RCTs reporting median PFS	67	9	10	30	18
Improvement, median (IQR), months	3.30 (2.02, 5.06)	2.10 (1.80, 3.80)	2.30 (1.51, 3.91)	3.25 (2.00, 5.04)	4.88 (3.25, 5.49)
No. RCTs HR PFS	74	9	10	33	22
HR (95% CI), I^2	0.51 (0.47, 0.55), 88	0.61 (0.5, 0.74), 84	0.53 (0.43, 0.65), 87	0.49 (0.43, 0.55), 90	0.5 (0.43, 0.58), 85
Tumor response					
No. RCTs reporting TR	68	10	12	29	17
RR (95% CI), I^2	2.14 (1.88, 2.43), 90	1.91 (1.34, 2.72), 79	2.79 (2.04, 3.8), 54	2.23 (1.83, 2.72), 93	1.84 (1.51, 2.26), 85
Quality of life					
No. RCTs reporting QoL	31	5	1	9	16
Improvement	7 (23)	2 (40)	0 (0)	2 (22)	3 (19)
No improvement	24 (77)	3 (60)	1 (100)	7 (78)	13 (81)

Abbreviations: HR, hazard ratio; IQR, interquartile range; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; RR, risk ratio.

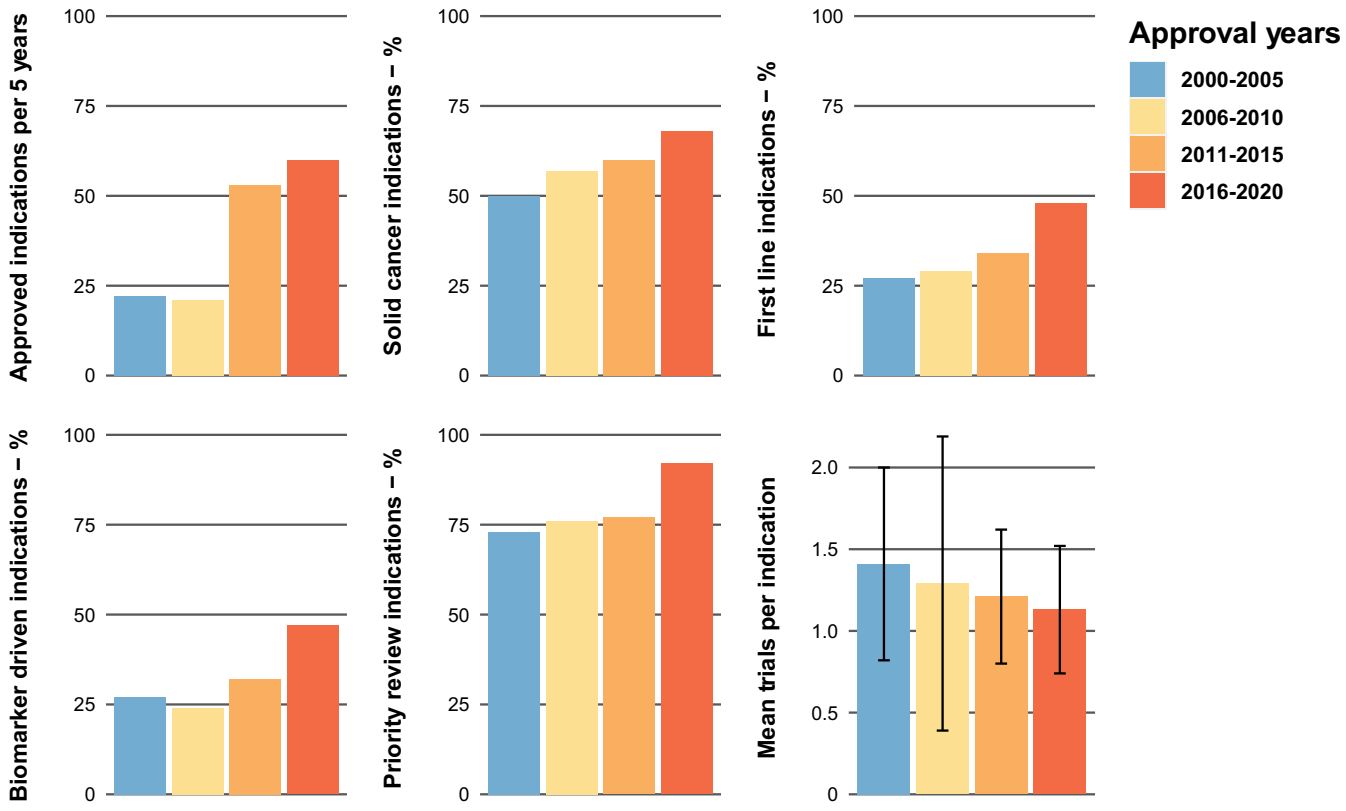

FIGURE 2 Trends of Indications characteristics from 2000 to 2020 stratified by 5-year intervals. (A) Absolute numbers of approved indications per 5 year interval. (B) Proportion of approved indications for solid cancers in percentages per 5 year interval. (C) Portion of approved indications for first line treatment. (D) Proportion of approved indications which are biomarker driven. (E) Proportion of approved indications which underwent priority review. (F) Mean number of pivotal trials per approved indications. Bars indicate SD. [Color figure can be viewed at wileyonlinelibrary.com]

OS gain of 11.8 months in a phase 2 trial.[32,33] A subsequent phase 3 trial did not confirm the survival benefit[8] and approval was subsequently withdrawn.

4.1 | Comparison to other studies

Our results are overall consistent with previous less comprehensive reports on approval data for cancer drugs and their impact.[5,14,16,29] That OS plays only a minor role for approval and that most approvals are based on a surrogate endpoint has been shown by Davis et al. for cancer drugs approved by the European Medicines Agency (2009-13).[16] Kim and Prasad also showed a large proportion of cancer drug approvals by the FDA (2008-2015) being based on surrogate endpoints,[34] and that even after approval for 86% of cancer drugs have uncertain effects on OS or fail to show survival benefits.[34] Similarly, Gyawali et al. showed for drugs under accelerated approval that 80% of confirmatory trials found no survival benefit.[35] Our study goes further to differentiate between reported and primary endpoints; OS was reported for 83% of RCTs, but was the primary endpoint only for 28%, that is, many trials are not adequately designed to assess survival benefits.

Previous knowledge on the role of QoL evidence at approval of new cancer drugs is limited. Salas-Vega et al. reported that 42% of cancer drugs approved by the FDA or the European Medical Agency (EMA) between 2003 and 2013 improved QoL, based on an analysis of Health Technology Assessments.[13] Davis et al. reported that for cancer drugs approved by the EMA between 2009 and 2013, evidence for an improvement of QoL was present at the approval in seven of 68 indications (10%).[16] Our study is the first to investigate QoL in approval documents of the FDA and we found an improvement of QoL in just seven of 156 indications (4%). Interestingly, for 51 RCTs, QoL assessment was mentioned in the methods of trials, but results were only available for 31 of them (59%). Incomplete reporting of QoL has been criticized before,[36] considering that the importance of QoL has been emphasized repeatedly[15] and that QoL cannot be extrapolated from surrogate endpoints.[37] There seems to be a trend towards QoL being measured more often, but considering the incomplete reporting of results and the rare improvement of QoL by novel cancer drugs, its importance within the approval process remains unclear and modest.

4.2 | Strengths and limitations

This study has several limitations. First, we examined indications for cancer drugs approved for the first time and did not look at expanded indications. Cancer drugs could have greater effects in expanded indications, for example, when drugs move to an earlier treatment line. Though, in our analysis, 38% of indications were approved for first line treatment and we did not see stronger effects in first line indications. Second, while this report is the first to present information on QoL data in FDA approval documents, we did not quantify potential benefits or harms. This might be of importance, considering that the tools to assess QoL have been criticized for focusing only on limited aspects of life and limited follow-up times.[38] Third, half of trials were non-controlled trials for which we did not quantify and compare effects. For those trials, results on response and survival would have to be interpreted in the context of external controls, for example, historical data. Such comparisons are prone to very high risk of bias, requiring a very careful in-depth analysis and assessment of these factors for a period of over 20 years which would go beyond the scope of this project. Fourth, we only included data which were reported in approval documents. While there may be other studies that have investigated the novel cancer drugs in the same indication, we assume that the manufacturer would present the most supportive evidence to the FDA. For this reason, we think there is a low risk that the included trials would underestimate the efficacy of the approved drugs.

4.3 | Conclusions

Since 2000, novel cancer drugs are approved typically based on one single small trial, often without a control group and measuring only surrogate endpoints. Across all indications, novel cancer drugs have modest beneficial effects on OS, and QoL plays only a minor role in their regulatory assessment. For more than 21 years, patients with cancer have had very little information about the benefits of novel cancer therapies. Although this has been criticized over years, no trend towards improvement could be observed.

AUTHOR CONTRIBUTIONS

The work reported in the paper has been performed by the authors, unless clearly specified in the text. Schmitt, Gloy and Hemkens had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Hemkens. Acquisition of data: Gloy, Schmitt, Düblin, Hirt, Axfors, Kuk, Pereira, Locher, Caquelin, Walter, Lythgoe, Herbrand. Analysis and interpretation of data: Gloy, Schmitt, Kasenda, Hemkens. Drafting of the manuscript: Gloy, Schmitt, Kasenda, Hemkens. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Schmitt. Obtained funding: Hemkens. Administrative, technical, or material support: Düblin, Schmitt. Supervision: Hemkens.

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CONFLICT OF INTEREST

AMS has received an educational grant from Janssen-Cilag AG, and he has received support for conference attendance from Novartis. All other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data are publicly available and can be found online (https://ceit-cancer.org/wp-content/widgets/table). Further information is available from the corresponding author upon request.

ETHICS STATEMENT

Institutional review board approval is not required for this type of research at the University of Basel and University Hospital Basel, Switzerland, as only aggregated, anonymized data available in the public domain was used.

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REFERENCES

1. FederalRegister.gov. eCFR:: 21 CFR 314.126: Adequate and well-controlled studies. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-314/subpart-D/section-314.126.
2. Darrow JJ, Avorn J, Kesselheim AS. FDA approval and regulation of pharmaceuticals, 1983-2018. *Jama*. 2020;323(2):164-176.
3. Lythgoe MP, Desai A, Gyawali B, et al. Cancer therapy approval timings, review speed, and publication of pivotal registration trials in the US and Europe, 2010-2019. *JAMA Netw Open*. 2022;5(6):e2216183.
4. Downing NS, Aminawung JA, Shah ND, Krumholz HM, Ross JS. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005-2012. *Jama*. 2014;311(4):368-377.
5. Ladanie A, Schmitt AM, Speich B, et al. Clinical trial evidence supporting US Food and Drug Administration approval of novel cancer therapies between 2000 and 2016. *JAMA Netw Open*. 2020;3(11):e2024406.
6. 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(8):1389-1398.
7. Ladanie A, Speich B, Briel M, et al. Single pivotal trials with few corroborating characteristics were used for FDA approval of cancer therapies. *J Clin Epidemiol*. 2019;114:49-59.
8. Results reported from the phase III ANNOUNCE trial of olaratumab in soft-tissue sarcoma: The ASCO Post.
9. Olivier T, Prasad V. The approval and withdrawal of melphalan flufenamide (melflufen): implications for the state of the FDA. *Transl Oncol*. 2022;18:101374.
10. Center for Drug Evaluation and Research. Withdrawn | Cancer Accelerated Approvals: FDA https://www.fda.gov/drugs/resources-information-approved-drugs/withdrawn-cancer-accelerated-approvals.
11. Pease AM, Krumholz HM, Downing NS, Aminawung JA, Shah ND, Ross JS. Postapproval studies of drugs initially approved by the FDA on the basis of limited evidence: systematic review. *BMJ*. 2017;357:j1680.
12. Sachs RE, Donohue JM, Dusetzina SB. Accelerated approval: taking the FDA's concerns seriously. *N Engl J Med*. 2022;387:199-201.
13. Salas-Vega S, Iliopoulos O, Mossialos E. Assessment of overall survival, quality of life, and safety benefits associated with new cancer medicines. *JAMA Oncol*. 2017;3(3):382-390.
14. 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(35):JCO2200535.
15. Hasanov E, Caceres JOH, Maskens DA, Giles RH, Schmitt AM. Patient-reported outcomes: what really matters to patients? *Lancet Oncol*. 2022;23(5):e198.
16. Davis C, Naci H, Gurpinar E, Poplavska E, Pinto A, Aggarwal A. Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European medicines agency: retrospective cohort study of drug approvals 2009-2013. *BMJ*. 2017;359:j4530.
17. Arciero V, Delos Santos S, Koshy L, et al. Assessment of Food and Drug Administration- and European medicines agency-approved systemic oncology therapies and clinically meaningful improvements in quality of life: a systematic review. *JAMA Netw Open*. 2021;4(2):e2033004.
18. Ladanie A, Speich B, Naudet F, et al. The comparative effectiveness of innovative treatments for cancer (CEIT-cancer) project: rationale and design of the database and the collection of evidence available at approval of novel drugs. *Trials*. 2018;19(1):505.
19. CEIT-Cancer 2018. The comparative effectiveness of innovative treatments for cancer project. https://ceit-cancer.org/.
20. Ladanie A, Ewald H, Kasenda B, Hemkens LG. How to use FDA drug approval documents for evidence syntheses. *BMJ*. 2018;362:k2815.
21. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453-1457.
22. Drugs@FDA: FDA-approved drugs. https://www.accessdata.fda.gov/scripts/cder/daf/.
23. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.
24. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.
25. Deeks JJHJ, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, et al., eds. *The Cochrane Handbook for Systematic Reviews of Interventions*. 2nd ed. Hoboken, NJ: Wiley-Blackwell; 2019.
26. (2020) RCT. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/.
27. Duran CE, Canas M, Urtasun MA, et al. Regulatory reliance to approve new medicinal products in Latin American and Caribbean countries. *Rev Panam Salud Publica*. 2021;45:e10.
28. Lythgoe MP, Sullivan R. Project Orbis: the UK experience after 1 year. *Lancet Oncol*. 2022;23(8):978-981.
29. Chen EY, Raghunathan V, Prasad V. An overview of cancer drugs approved by the US Food and Drug Administration based on the surrogate end point of response rate. *JAMA Intern Med*. 2019;179(7):915-921.
30. Fashoyin-Aje LA, Mehta GU, Beaver JA, Pazdur R. The on- and off-ramps of oncology accelerated approval. *N Engl J Med*. 2022;387(16):1439-1442.
31. Gray R. New FDA Reform Legislation: Congress Gifts a "FDORA" for the Holidays | Ropes and Gray LLP. https://www.ropesgray.com/en/newsroom/alerts/2023/01/new-fda-reform-legislation-congress-gifts-a-fdora-for-the-holidays.
32. H.R.2617 Consolidated Appropriations Act, 2023, (2022).
33. Tap WD, Jones RL, Van Tine BA, et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. *Lancet*. 2016;388(10043):488-497.
34. Kim C, Prasad V. Cancer drugs approved on the basis of a surrogate end point and subsequent overall survival: an analysis of 5 years of US Food and Drug Administration approvals. *JAMA Intern Med*. 2015;175(12):1992-1994.

35. Gyawali B, Hey SP, Kesselheim AS. Assessment of the clinical benefit of cancer drugs receiving accelerated approval. *JAMA Intern Med*. 2019;179(7):906-913.
36. Schandelmaier S, Conen K, von Elm E, et al. Planning and reporting of quality-of-life outcomes in cancer trials. *Ann Oncol*. 2016;27(1):209.
37. Kovic B, Jin X, Kennedy SA, et al. Evaluating progression-free survival as a surrogate outcome for health-related quality of life in oncology: a systematic review and quantitative analysis. *JAMA Intern Med*. 2018;178(12):1586-1596.
38. Haslam A, Herrera-Perez D, Gill J, Prasad V. Patient experience captured by quality-of-life measurement in oncology clinical trials. *JAMA Netw Open*. 2020;3(3):e200363.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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