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Limitations in Clinical Trials Leading to Anticancer Drug Approvals by the US Food and Drug Administration

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IMPORTANCE While there have been multiple assessments of clinical trials leading to anticancer drug approvals by the US Food and Drug Administration (FDA), the cumulative percentage of approvals based on trials with a limitation remains uncertain.

OBJECTIVE To assess the percentage of clinical trials with limitations in 4 domains—lack of randomization, lack of significant overall survival advantage, inappropriate use of crossover, and use of suboptimal control arms—that led to FDA approvals from June 30, 2014, to July 31, 2019.

DESIGN, SETTING, AND PARTICIPANTS This observational analysis included all anticancer drug indications approved by the FDA from June 30, 2014, through July 31, 2019. All indications were investigated, and each clinical trial was evaluated for design, enrollment period, primary end points, and presence of a limitation in the domains of interest. The standard-of-care therapy was determined by evaluating the literature and published guidelines 1 year prior to the start of clinical trial enrollment. Crossover was examined and evaluated for optimal use. The percentage of approvals based on clinical trials with any or all limitations of interest was then calculated.

MAIN OUTCOMES AND MEASURES Estimated percentage of clinical trials with limitations of interest that led to an anticancer drug marketing authorization by the FDA.

RESULTS A total of 187 trials leading to 176 approvals for 75 distinct novel anticancer drugs by the FDA were evaluated. Sixty-four (34%) were single-arm clinical trials, and 123 (63%) were randomized clinical trials. A total of 125 (67%) had at least 1 limitation in the domains of interest; 60 of the 125 trials (48%) were randomized clinical trials. Of all 123 randomized clinical trials, 37 (30%) lacked overall survival benefit, 31 (25%) had a suboptimal control, and 17 (14%) used crossover inappropriately.

CONCLUSIONS AND RELEVANCE Two-thirds of cancer drugs are approved based on clinical trials with limitations in at least 1 of 4 essential domains. Efforts to minimize these limitations at the time of clinical trial design are essential to ensure that new anticancer drugs truly improve patient outcomes over current standards.

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Supplemental content

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Clinical trials leading to marketing authorization of anticancer drugs by the US Food and Drug Administration (FDA) are heterogeneous, with varying strengths and weaknesses. Nonrandomized clinical trials that show tumor shrinkage in response to a novel therapy are limited by uncertainty as to whether these agents are superior to the prevailing standard of care or if they improve survival or quality of life. When randomized clinical trials (RCTs) are conducted, limitations of interest may be related to trial design, for example, using a control arm that is considered suboptimal or inappropriate use of crossover, or in outcome, such as failing to demonstrate an overall survival (OS) benefit when an improvement in a surrogate end point is met.

Prior studies have characterized the frequency of single-arm studies leading to drug approval[1] and the use of surrogate end points.[2] We previously assessed the frequency of substandard control arms.[3] However, these studies did not assess errors of crossover and the cumulative percentage of these limitations coexisting in the same trial. For example, what percentage of FDA approvals are made on the basis of improved survival in a trial without limitations?

Crossover in cancer RCTs occurs when a patient randomized to the control arm is given the investigational therapy after disease progression or toxic effects (unidirectional crossover). There are 2 errors of crossover in trials. The first occurs when crossover from the control arm to the investigational agent is allowed without established efficacy of the investi-

gational agent. In these cases, crossover from control arm to the investigational agent can confound interpretations of end points, such as OS, and may even lead to spurious survival benefits.[4,5] For instance, in a study of a novel, unproven cancer therapeutic vaccine in prostate cancer, crossover resulted in fewer patients receiving docetaxel and only at a delayed time point, which may have harmed the control arm.[6] Survival differences in this setting could be due to either a successful therapy or harm to the control arm.

The second error is to omit crossover when a drug has proven benefit in a subsequent line of therapy, when a trial seeks to advance the agent to the frontline setting. For instance, in a study evaluating pembrolizumab, an immune checkpoint inhibitor, for previously untreated programmed cell death ligand 1 (PD-L1)-expressing metastatic non-small cell lung cancer, omission of crossover resulted in fewer patients being offered pembrolizumab—an agent that had been approved in the second-line setting—after progression on the control arm.[7] Here, crossover is mandatory, and its absence may lead to the false inference that early administration is superior to the current standard of care (ie, sequential treatment). We sought to perform a single analysis that examined all 4 of the aforementioned limitations in a modern cohort of cancer drug approvals using a comprehensive resource and estimate the frequency of these limitations coexisting in the same trials.

Key Points

Question How often are anticancer drugs approved by the US Food and Drug Administration (FDA) based on clinical trials with the following limitations: nonrandomized design, lack of demonstrated survival advantage, inappropriate use of crossover, or the use of suboptimal control arms?

Findings In this observational study, 187 trials leading to anticancer drug approvals between June 30, 2014, and July 31, 2019, were reviewed. A total of 125 (67%) trials leading to anticancer drug indications had limitations in at least 1 of the 4 domains of interest.

Meaning Despite the increase in the number of drug approvals by the FDA, a substantial number of drugs are authorized based on data that do not demonstrate efficacy over established standards of care.

Methods

We sought to assess what percentage of clinical trials leading to new or supplemental marketing approvals of anticancer drugs by the FDA had any of the following limitations: (1) nonrandomized clinical trial design, (2) RCTs that failed to show an OS advantage, (3) RCTs that used a suboptimal control, and (4) RCTs that inappropriately used crossover. This study of published reports did not involve patient-identifying data and was not submitted for institutional review board approval.

Data Set

We examined all approvals by the FDA from June 30, 2014, through July 31, 2019. Inclusion criteria were all indications for every single novel anticancer drug approval in adults (≥18 years). Novel anticancer drugs were identified using the FDA hematology/oncology approvals and safety notifications web page[8] and tabulated. Then, the name of each novel anticancer drug was entered into the FDA approved drug products search engine.[9] Approval date(s), history, and labels (including new indications) were extracted. Notably, our prior study of control arms relied exclusively on the FDA hematology/oncology approvals and safety notifications web page,[8] which does not report on new or expanded marketing approvals for an already approved investigational agent (eg, ibrutinib vs ofatumomab in previously treated chronic lymphocytic leukemia).

Every clinical trial cited on the drug label at the time of marketing authorization as the basis for an FDA approval was identified using the National Clinical Trial identifier on the label and confirmed by reviewing the FDA approvals and safety notifications web page when listed. The trial article was identified using PubMed, and the protocols were reviewed if available with the published article in the supplement. The FDA statistical review reports were not used because many were not accessible and/or not available for supplementary indication approvals. From the article of each trial, we identified the accrual period, setting of the clinical trial (national vs international), indication, control arm, primary end point, OS end point, and the presence or absence of crossover in RCTs.

Assessing the Control Arm

For each RCT, we assessed the quality of the control arm as suboptimal if (a) restrictions were placed on the choice of control that excluded another potentially equivalent agent, or (b) the control arm was specified but not the recommended agent and potentially inferior (eg, the control arm was a single agent when doublet therapy is recommended). We then evaluated whether a suboptimal control arm was chosen because of the international scope of the trial and would not have been considered a US standard-of-care option.

We assessed control arms using 2 methods independently. First, the first and second authors (T.H. and M.G.-V.) performed a search of the National Comprehensive Cancer Network (NCCN) guidelines through the *Journal of the National Comprehensive Cancer Network* (*JNCCN*) dated at least 1 year prior to the start of accrual of an RCT of interest that led to an FDA marketing authorization to determine the standard-of-care therapy for each specific cancer. When guidelines were not available for the year of interest in *JNCCN*, we used the Wayback Machine, a digital archive that stored previous versions of NCCN guidelines. Second, the first and second authors separately and independently read the published clinical trial data presented in articles as well as the appendices and supplements, when relevant, and determined the adequacy of the control arm compared with what would be considered the standard of care 1 year prior to the start of trial accrual. Conflicts were resolved by the third author (V.P.).

Assessing Crossover

We assessed for the presence or absence of protocol-specified unidirectional crossover from published articles and

by searching protocols available with the articles. Two authors (T.H. and M.G.-V.) determined separately and independently whether the presence or absence of crossover was desirable based on established definitions.[5]

Appropriate crossover was defined as allowing crossover in situations where the efficacy of the investigational agent had already been established from a previous RCT in a latter line of therapy (eg, second line or beyond), had an FDA approval in a latter line of therapy, or was considered the standard of care in a subsequent line at the time of or within 1 year of enrollment of participants. In these situations, the absence of crossover in the protocol or the absence of a protocol amendment was deemed inappropriate.

Inappropriate crossover was defined as use of crossover in situations where the fundamental efficacy of an experimental agent had not been established in a prior RCT, and/or an FDA approval was not available at the time of or within 1 year of enrollment of participants. In these situations, the presence of crossover was considered inappropriate, as it has potential to obscure signals of true benefit (eg, OS advantage) or harm from the investigational agent (both arms of the trial will receive it). A protocol amendment made during study periods to allow crossover when a drug was approved by the FDA or an RCT confirmed its efficacy in a latter line setting was considered appropriate.

Statistical Analysis

Descriptive statistics are reported throughout. We analyzed the study data from November 1 to November 20, 2019.

Results

Between June 30, 2014, and July 31, 2019, the FDA granted 176 approvals for 75 distinct novel anticancer drugs based on 187 trials. The number of anticancer trials leading to FDA approval doubled over time with 68 in the first half of the study period (June 2014 to December 2016) to 119 in the second half of the study period (January 2017 to July 2019). Of the 187 trials, 123 (66%) were RCTs, and 64 (34%) were nonrandomized clinical trials. Of the 187 trials, 38 (20%) were for lymphoid malignant neoplasms, 37 (20%) for lung and head and neck malignant neoplasms, and 19 (10%) were for genitourinary malignant neoplasms. To better characterize these limitations, we separated them into limitations in design (uncontrolled study, suboptimal control, inappropriate use of crossover) and limitation in outcome (lack of OS benefit).

Limitations in Design

Nonrandomized Trials/No Control Arm

We found that 64 of 187 (34%) pivotal trials lacked a control arm. Two drug indications were based on data from a subset of patients in an open-label phase 1b trial (eg, KEYNOTE-013, pembrolizumab in refractory primary mediastinal B-cell lymphoma, after 2 or more lines of therapy[10]) and a post hoc analysis of a subset of patients from multiple trials (eg, LUX-Lung, afatinib in first-line metastatic non-small cell lung cancer without resistant *EGFR* mutations[11]). The remainder were largely single trials or pooled analyses of 2 single-arm trials. The primary end point was overall response rate in 53 trials (83%) and complete remission in 5 trials (8%). The majority of marketing approvals based on nonrandomized clinical trials (43 trials [67%]) were granted under the accelerated approval program.

Suboptimal Control Arms

There were 123 RCTs leading to 120 approvals. The majority of drug indication approvals (117 [97%]) were based on data from a single RCT, while the remainder (3 [3%]) were based on data from 2 RCTs. The majority of approvals based on RCTs (110 [92%)] were regular approvals. Of the 123 RCTs, 1 was a noninferiority trial and 122 were superiority trials.

Of the 122 RCTs powered for superiority, 31 (25%) had a suboptimal control arm. A list of all RCTs with a suboptimal control arm and the reasons they were deemed suboptimal is provided in eTable 1 in the Supplement. When categorized by type of suboptimal control, 22 (71%) clinical trials omitted active treatment in the control arm by using a control known or likely to be inferior to other available agents or not allowing combinations, and 9 (29%) limited the investigator's choice in selecting an active treatment. When assessed by whether the international scope of the trial led to a suboptimal choice of the control arm in the US, 3 (10%) trials chose a control arm that was deemed more accessible outside the US but that may not have been the treatment of choice in the US. Of the 31 RCTs with a suboptimal control arm leading to FDA approval, 1 was reversed due to a subsequent phase 3 trial showing a lack of superiority over the control.[12]

Inappropriate Inclusion or Omission of Crossover

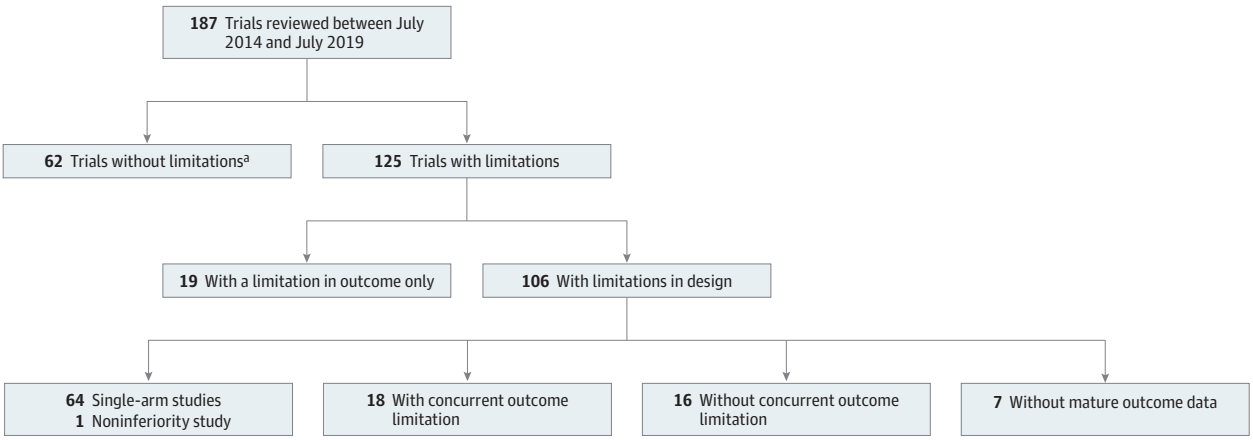
Of the 122 clinical trials powered for superiority, 17 (14%) had errors in crossover (eTable 2 in the Supplement). Of those, 8 (47%) prespecified crossover in the protocol when crossover was not desirable (ie, crossover to the investigational agent was allowed on disease progression in the control without previous studies or FDA approvals establishing efficacy of the investigational treatment in a latter line of therapy), and 9 (53%) did not prespecify crossover in the protocol when crossover was desirable (ie, crossover to the investigational agent was not allowed despite the established efficacy and/or FDA approval of the investigational agent in a latter line of therapy).

Limitations in Outcome: Resulting OS

The primary end point was progression-free survival in 63 of 122 clinical trials (51%), OS (primary or coprimary) in 38 (30%), and an alternative surrogate end point in 23 (19%). Overall survival was either a primary or a secondary end point in 121 RCTs (98%). One was a noninferiority trial with OS as a primary end point.

Of the 122 RCTs powered for superiority, OS was superior in the investigational arm in 65 trials (52%), failed to show advantage in the investigational arm in 36 trials (30%), was not reported at the time of analysis in 19 trials (16%), and was not a prespecified end point in 2 trials (2%), one of which would have been desirable.

Figure. Flowchart of All Cancer Drug Trials From July 2014 Through July 2019



[a] Includes 12 trials without design limitations but with immature outcome data.

Cumulative Limitations

Among 187 trials, we found that 125 (67%) were trials with limitations in design and outcome. Specifically, 106 (57%) had limitations in design, 37 (20%) had limitations in outcome, and 18 (10%) had concurrent design and outcome limitations (**Figure**). The **Table** summarizes the limitations among RCTs and those without mature OS data as of November 2019.

Discussion

Our results show that of 187 anticancer drug trials leading to 176 marketing authorizations by the FDA over a 5-year period, 125 (67%) had at least 1 of 4 limitations in design (control arm, crossover, single arm) and/or lack of OS benefit (including 1 noninferiority trial). Our findings raise important concerns.

Nonrandomized clinical trials constitute the basis for one-third of all marketing authorizations. Although results of nonrandomized clinical trials are markers of drug activity, many drugs approved on the basis of these trials exaggerate treatment efficacy when tested in RCTs.[13,14] Furthermore, when evaluated by value scales (eg, the European Society for Medical Oncology Magnitude of Clinical Benefit Scale, only one-third of single-arm trials were shown to meet the criteria for substantial clinical benefit.[15,16] To balance the risk and benefit of early market authorization of investigational agents without proven superiority over standards of care, the accelerated approval pathway was developed by the FDA. Accelerated approval expedites the availability of potentially effective therapies with the requirement to conduct postapproval confirmatory trials. However, we found that approximately one-third of these approvals (21 of 64 [32%]) are regular approvals and not subject to confirmatory efficacy trials. This leaves substantial uncertainty as to their overall benefit over prevailing standards of care. Previous work estimated that only 20% of anticancer drugs receiving accelerated approval are shown to improve survival, although some studies remain ongoing.[17]

Surrogate end points were common, with 86 of 122 RCTs (70%) having a surrogate end point as the primary end point. Approvals for new drugs based on surrogate end points should be limited to specific circumstances where limited treatment options exist, the possible benefit is high, and the likelihood of harm is low. Overall survival, considered the criterion standard clinical end point, particularly for lethal conditions, was almost always assessed in RCTs (98%). However, approximately one-third (30%) of anticancer drug approvals based on RCTs failed to show a statistically significant improvement in OS. Approximately half of all trials (46%) had either unknown effects on OS or failed to show gains in OS. Our results show similar findings to previous reports, wherein two-thirds of cancer drugs were approved on the basis of a surrogate end point and half were reported to have unknown effects or failed to show gains in OS.[2,18,19]

Although crossover is often cited as a reason for failure to see an OS gain after an improvement in a surrogate end point, we found that only in the minority of clinical trials (17 of 122 [14%]) could the absence of an OS advantage be due to inappropriate crossover. This finding suggests that either the investigational agents are not effective in improving OS or that the trial was not powered to detect an OS benefit.[20] Many of the trials that failed to show an OS benefit were of anticancer drugs used for treating relatively indolent malignant neoplasms for which postprogression therapy or crossover was prevalent (eg, ibrutinib plus rituximab vs placebo plus rituximab for Waldenstrom macroglobulinemia). Another group of approvals that failed to show an OS benefit were of maintenance therapies in which OS can be difficult to measure owing to the use of subsequent lines of therapy (eg, rucaparib maintenance therapy in recurrent ovarian cancer) (eTables 1 and 2 in the Supplement).

Suboptimal control arms in our study were similar to prior reports in this comprehensive data set that included multiple indications for the same agent (25% vs 17%, respectively).[3] The use of a substandard control arm may result in a trial that is more likely to be positive (ie, meet its primary end point) but

Table. Patterns of Limitations in Randomized Clinical Trials

Trial	ClinicalTrials.gov identifier	Drug, indication	Category of limitation
AETHERA	NCT01100502	Brentuximab vedotin, classical HL after ASCT consolidation	OS advantage not proven Crossover error
ALCANZA	NCT01578499	Brentuximab vedotin, pcALCL, or CD30-expressing mycosis fungoides in patients who received prior therapy	OS advantage not proven Suboptimal control arm
ALCYONE	NCT02195479	Daratumumab, newly diagnosed multiple myeloma in patients who are transplant ineligible	Suboptimal control arm
ALEX	NCT02075840	Alectinib, ALK-positive metastatic NSCLC, first line	OS advantage not proven Crossover error
ALFA-0701	NCT00927498	Gemtuzumab ozogamicin, previously untreated AML	OS advantage not proven
APHINITY	NCT01358877	Pertuzumab, adjuvant treatment of ERBB2-positive early breast cancer with chemotherapy and trastuzumab	OS advantage not proven
ARAMIS	NCT02200614	Darolutamide, nonmetastatic castration-resistant prostate cancer	Suboptimal control arm
ARCHER1050	NCT01774721	Dacomitinib, first-line metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations	OS data not mature
ARIEL3	NCT01968213	Rucaparib, maintenance for recurrent ovarian, fallopian tube, or primary peritoneal cancer, at least 2 prior lines of therapy	OS advantage not proven—planned interim analysis[a]
ASCEND-4	NCT01828099	Ceritinib, metastatic ALK-positive NSCLC	OS advantage not proven Suboptimal control arm
AUGMENT	NCT01938001	Lenalidomide, follicular lymphoma and marginal zone, previously treated (with rituximab)	Suboptimal control arm Crossover error
AURA3	NCT02151981	Osimertinib, metastatic EGFR T790M-mutated NSCLC after progression	OS data not mature
AURELIA	NCT00976911	Bevacizumab, platinum-resistant, recurrent ovarian cancer with paclitaxel and liposomal doxorubicin	OS advantage not proven Crossover error
BFORE	NCT02130557	Bosutinib, first-line chronic-phase CML	OS advantage not proven Suboptimal control arm Crossover error
BRIGHT AML 1003	NCT01546038	Glasdegib, newly diagnosed AML in 75 or older or who have comorbidities	Suboptimal control arm
CABOSUN	NCT01835158	Cabozantinib, first-line RCC, intermediate and poor risk	OS advantage not proven
CASTOR	NCT02136134	Daratumumab, myeloma after at least 1 prior therapy	OS data not mature
CheckMate 037	NCT01721746	Nivolumab, unresectable or metastatic melanoma and disease progression following ipilimumab	OS advantage not proven
CheckMate 069	NCT01927419	Nivolumab and ipilimumab, *BRAF* V600 wild-type unresectable or metastatic melanoma	Exploratory analysis OS advantage not proven
CheckMate 214	NCT02231749	Nivolumab and ipilimumab, first-line intermediate or poor-risk RCC	Crossover error
CheckMate 238	NCT02388906	Nivolumab, adjuvant melanoma with lymph nodes	Crossover error
CLARINET	NCT00353496	Lanreotide, unresectable or metastatic GEP-NETs, nonfunctional	OS advantage not proven Suboptimal control arm Crossover error
CLL14	NCT02242942	Venetoclax and obinutuzumab, previously untreated CLL with comorbidities	OS data not mature Suboptimal control arm
COLUMBUS	NCT01909453	Encorafenib and binimetinib, metastatic melanoma with *BRAF* V600E or V600K mutation	OS data not mature
COMPLEMENT 2	NCT00824265	Ofatumumab, relapsed CLL	OS advantage not proven Suboptimal control arm
DUO	NCT02004522	Duvelisib, relapsed/refractory CLL or SLL after 2 prior therapies	OS data not mature Suboptimal control arm Crossover error
ECHELON-1	NCT01712490	Brentuximab vedotin, stage III or IV HL	OS advantage not proven—planned interim analysis[a]
EMBRACA	NCT01945775	Talazoparib, germline *BRCA*-mutated ERBB2-negative metastatic breast cancer in patients who have been treated with chemotherapy	OS advantage not proven—planned interim analysis[a] Suboptimal control arm
ENGOT-OV16/ NOVA	NCT01847274	Niraparib, maintenance for recurrent ovarian cancer in CR or PR after platinum-based chemotherapy	OS data not mature
ET743-SAR-3007	NCT01343277	Trabectedin, unresectable or metastatic liposarcoma or leiomyosarcoma	OS advantage not proven
ExteNET	NCT00878709	Neratinib, adjuvant ERBB2-positive breast cancer	OS advantage not proven
GADOLIN	NCT01059630	Obinutuzumab, follicular lymphoma in patients who relapsed after or are refractory to rituximab	Suboptimal control arm
GALLIUM	NCT01332968	Obinutuzumab, previously untreated stage II bulky, III, or IV follicular lymphoma	OS advantage not proven
GOG-0213	NCT00565851	Bevacizumab, platinum-sensitive (>6 mo), recurrent ovarian cancer	OS advantage not proven
GOG-0218	NCT00262847	Bevacizumab, epithelial ovarian, fallopian tube, or primary peritoneal cancer	OS advantage not proven
IFM2005-02	NCT00430365	Lenalidomide, maintenance for myeloma following ASCT	OS advantage not proven
iLLUMINATE	NCT02264574	Ibrutinib, treatment-naive CLL, in patients aged ≥65 y or <65 y with coexisting conditions	OS data not mature Suboptimal control arm
IMpassion130	NCT02425891	Atezolizumab, first-line metastatic TNBC	Suboptimal control arm

(continued)

Table. Patterns of Limitations in Randomized Clinical Trials (continued)

Trial	ClinicalTrials.gov identifier	Drug, indication	Category of limitation
iNNOVATE	NCT02165397	Ibrutinib, Waldenstrom macroglobulinemia	OS advantage not proven Suboptimal control arm
JAVELIN Renal 101	NCT02684006	Avelumab, first-line advanced RCC, with axitinib	OS data not mature
JGDG	NCT01185964	Olaratumab, soft tissue sarcoma for which anthracycline is appropriate	Suboptimal control arm
KATHERINE	NCT01772472	TDM-1, adjuvant therapy for ERBB2-positive early breast cancer in patients who previously received trastuzumab and taxane neoadjuvantly with residual disease	OS data not mature
KEYNOTE-006	NCT01866319	Pembrolizumab, unresectable or metastatic melanoma	Crossover error
KEYNOTE-042	NCT02220894	Pembrolizumab, first-line NSCLC (PD-L1 ≥1%)	Crossover error
KEYNOTE-045	NCT02256436	Pembrolizumab, metastatic urothelial carcinoma who progress on platinum therapy	Suboptimal control arm
KEYNOTE-054	NCT02362594	Pembrolizumab, adjuvant melanoma after complete resection	OS data not mature Suboptimal control arm
MAIA	NCT02252172	Daratumumab, newly diagnosed multiple myeloma that are transplant ineligible	OS data not mature Suboptimal control arm Crossover error
METEOR	NCT01865747	Cabozantinib, advanced RCC in following 1 line of therapy	Suboptimal control arm
MONALEESA-2	NCT01958021	Ribociclib, postmenopausal HR-positive, ERBB2-negative breast cancer, first line	OS data not mature
MONARCH 3	NCT02246621	Abemaciclib, postmenopausal HR-positive, ERBB2-negative breast cancer	OS data not mature
Motzer et al, 2015	NCT01136733	Lenvatinib plus everolimus, advanced RCC following 1 line of therapy	OS advantage not proven
MURANO	NCT02005471	Venetoclax, CLL with or without 17p deletion, in patients who received at least 1 line of therapy	Suboptimal control arm
OCEANS	NCT00434642	Bevacizumab, platinum-sensitive (>6 mo), recurrent ovarian cancer	OS advantage not proven
OlympiAD	NCT02000622	Olaparib, germline *BRCA*-mutated ERBB2-negative metastatic breast cancer in patients who have been treated with chemotherapy	OS advantage not proven Suboptimal control arm
PALOMA-1	NCT00721409	Palbociclib, postmenopausal HR-positive, ERBB2-negative breast cancer	OS advantage not proven
PALOMA-2	NCT01740427	Palbociclib, postmenopausal HR-positive, ERBB2-negative breast cancer	OS data not mature
PANORAMA-1	NCT01023308	Panobinostat, myeloma after at least 2 lines of therapy	OS advantage not proven
POLLUX	NCT02076009	Daratumumab, myeloma after at least 1 prior therapy	OS data not mature Suboptimal control arm
PROLONG	NCT01039376	Ofatumumab, extended therapy (maintenance) in recurrent/progressive CLL in PR/CR	OS advantage not proven
PROSPER	NCT02003924	Enzalutamide, nonmetastatic castration-resistant prostate cancer	OS advantage not proven —planned interim analysis[a] Suboptimal control arm
RADIANT-4	NCT01524783	Everolimus, progressive, nonfunctional gastrointestinal and lung NET	OS data not mature Suboptimal control arm
RESONATE	NCT01578707	Ibrutinib, previously treated CLL	Suboptimal control arm
RESONATE-2	NCT01722487	Ibrutinib, first-line CLL	Suboptimal control arm
RESPONSE	NCT01243944	Ruxolitinib, polycythemia vera in patients who had inadequate response to hydroxyurea	OS not studied, but desirable Crossover error
SELECT	NCT01321554	Lenvatinib, metastatic differentiated thyroid cancer	OS advantage not proven Crossover error
SOLAR-1	NCT02437318	Alpelisib, HR-positive, ERBB2-negative, *PIK3CA*-mutated metastatic breast cancer, postmenopausal women and men	OS data not mature
SOLO1	NCT01844986	Olaparib, first-line maintenance for *BRCA*-mutated ovarian cancer in CR or PR after platinum-based chemotherapy	OS advantage not proven—planned interim analysis[a] Crossover error
SOLO2/ ENGOT-Ov21	NCT01874353	Olaparib, maintenance for relapsed ovarian cancer in CR or PR after platinum-based chemotherapy	OS data not mature
SPARTAN	NCT01946204	Apalutamide, nonmetastatic castration-resistant prostate cancer	OS advantage c—second interim Suboptimal control arm Crossover error
S-TRAC	NCT00375674	Sunitinib, adjuvant RCC	OS advantage not proven
Study 0761-010	NCT01728805	Mogamulizumab, relapsed or refractory mycosis fungoides or Sezary syndrome after at least 1 prior systemic therapy	OS advantage not proven Suboptimal control arm Crossover error
TOURMALINE-MM1	NCT01564537	Ixazomib, myeloma after at least 1 prior therapy	OS advantage not proven Suboptimal control arm

Abbreviations: ALK, anaplastic lymphoma kinase; AML, acute myeloid leukemia; ASCT, autologous stem cell transplant; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CR, complete response; EGFR, epidermal growth factor receptor; GEP-NET, gastroenteropancreatic neuroendocrine tumor; HL, Hodgkin lymphoma; HR, hormone receptor; NSCLC, non–small cell lung cancer; OS, overall survival; pcALCL, primary cutaneous anaplastic large cell lymphoma; PD-L1, programmed cell death ligand 1; PR, partial response; RCC, renal cell carcinoma; SLL, small lymphocytic lymphoma; TDM-1, trastuzumab emtansine; TNBC, triple-negative breast cancer.

[a] Refers to specified analysis of OS. These may show an OS advantage in the future.

prevents the trial from addressing the clinically relevant question: Is this new drug better than the current standard of care?

Errors in use of crossover were estimated at approximately 14% of RCTs—that is, trials allowed crossover to the investigational agent without proven efficacy or FDA approval in subsequent lines of therapy or omitted crossover to drugs with established efficacy or FDA approval in subsequent lines of therapy. Allowing patients in the control arm to receive the investigational agent may result in diminution of any effect on OS[21] and is often cited as a reason for cancer trials not demonstrating and OS benefit. In our analysis, only half of the errors in crossover were due to crossover to an unapproved intervention (ie, investigational agent without established efficacy in a latter line of therapy). The opposite error, prohibiting crossover to an approved intervention (ie, investigational agent with established efficacy in a latter line of therapy), may lead to an overestimation of the benefit seen with the investigational agent because patients in the control arm are deprived of an accepted salvage therapy. This type of error was seen in half of the cases in our analysis (ie, no protocol-specified crossover design despite it being more appropriate given that the intervention was an FDA-approved drug in the later-line setting).

The FDA has commented on the ethical considerations with regard to crossover and has been supportive of early crossover in RCTs when a surrogate primary end point (eg, progression-free survival, overall response rate) is met.[22,23] In such trials, patients in the control arm would be allowed to cross over to the investigational agent after a prespecified analysis demonstrates efficacy in a surrogate (eg, response rate or tumor shrinkage). In our analysis, when a protocol amendment allowed crossover due to interim analysis meeting an efficacy end point, we conservatively considered such crossover appropriate. Yet we note that this strategy may limit the ability of a drug to demonstrate an improvement in OS (if one exists) or alternatively may limit the ability to demonstrate a decrease in survival (harm) that may be a late effect of the investigational agent that both arms of the trial will be exposed to. Finally, crossover is not associated with faster trial enrollment, as some hypothesize.[24] Although multiple statistical methods have been developed to model OS in these situations, assuming crossover had not occurred, all such models rely on assumptions regarding the balance of a drug's on-target and off-target effects, and none of these methods are without their own limitations.[25]

Limitations

Our analysis sought to evaluate the presence of clinically relevant limitations of interest in clinical trials leading to marketing authorizations over a 5-year period. Critically addressing limitations during the design of clinical trials can improve the quality of evidence on which we base anticancer drug approvals, decrease erroneous conclusions, and focus more on hard end points (eg, OS). Our findings are complementary to a 2019 analysis[26] that evaluated risk of bias in RCTs supporting approvals in Europe between 2014 and 2016 using the Cochrane risk of bias tool, which assesses different domains than our study. The trial limitations we included in our analysis address questions faced by practicing oncologists.

The main limitation of our analysis is subjectivity in the assessment of acceptable standard of care and the appropriateness of the use of crossover. We attempted to limit subjectivity by individually and separately reviewing the guidelines and establishing consensus standard of care for each malignant neoplasm. Furthermore, whether crossover was specified in the protocol was not always reported in the article, especially when crossover was not allowed. In these cases, the protocol was reviewed, when available, and when no mention was found, lack of protocol-specified crossover was assumed. Postprogression therapy was not always reported in the article, nor the supplement, so non-protocol-specified crossover from the control arm to an agent similar to the investigational agent in the trial (eg, a programmed cell death 1 [PD-1] inhibitor) was not always captured. This made it difficult to interpret the data in light of real-world use of anticancer drugs. For example, in the OCEANS trial,[27] crossover to bevacizumab on progression was not allowed, but 38% of patients who progressed in the control arm received bevacizumab off protocol. Finally, other important design flaws that may limit the validity of trial results were not captured in our limitations. For example, in the PACIFIC trial,[28] standard imaging techniques such as positron emission tomography/computed tomography and brain magnetic resonance imaging for staging were not done prior to enrolling participants. This may have enriched the trial for patients with undiagnosed stage IV non-small cell lung cancer, some of whom received active therapy in the form of durvalumab while others received placebo. Finally, it is inevitable that others may disagree with our categorization, and we encourage further study.

Conclusions

In this study, we found that 67% of trials that led to FDA approval of anticancer agents had 1 or more limitations that include lack of randomization, lack of significant OS benefit, use of suboptimal control arm, and errors in the use of crossover. These limitations identify trials that do not address the clinically relevant question of whether patients will live longer or better lives if a novel agent is used over the current standard of care. As such, trial design and end point should be carefully addressed prior to enrollment to ensure that new anticancer drugs are superior to what most patients would receive in daily practice.

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Study concept and design: Hilal, Prasad.
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Administrative, technical, or material support: Gonzalez-Velez.
Study supervision: Prasad.

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