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Article

Proportion of patients in phase 2 oncology trials receiving treatments that are ultimately approved

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Abstract

Background: Many patients enroll in phase 1 dose expansion cohorts or phase 2 clinical trials (together referred to below as "phase 2") seeking access to novel treatments. Little is known about the extent to which they benefit by enrolling. Herein, we use a novel metric of benefit—therapeutic proportion—to assess the probability that patients in phase 2 trials receive treatment that eventually advances to FDA (Food and Drug Administration) approval for their condition.

Methods: We randomly sampled 400 trials identified in a search of Clinicaltrials.gov for cancer phase 2 trials initiated between November 1, 2012 and November 1, 2015. We determined whether the drug/dose/indication tested in each trial advanced to FDA approval within 7.5 years. We determined whether the drug/dose/indication presented substantial clinical benefit using the ESMO-MCBS (European Society for Medical Oncology - Magnitude of Clinical Benefit Scale), or whether it received off-label recommendation in NCCN (National Comprehensive Cancer Network) guidelines.

Results: Collectively, trials in our sample enrolled 25 002 patient-participants in 608 specific treatment cohorts. A total of 4045 patients received a treatment that advanced to FDA approval (16.2%; 95% CI = 10.3 to 22.7). The therapeutic proportion increased to 19.4% (95% CI = 14.1 to 25.8) when considering NCCN off-label recommendations and decreased to 9.3% (95% CI = 4.7 to 14.6) for FDA-approved regimens considered being of substantial clinical benefit by ESMO-MCBS. Bootstrap test of mean difference showed no statistical difference in proportions based on drug class, trial phase, or sponsorship.

Conclusion: One in 6 patients in phase 2 clinical trials receives treatments that are eventually approved. This represents a higher therapeutic value than phase 1 trials.

Introduction

Clinical development of new drugs typically follows 3 stages. In phase 1 trials, drugs are tested for safety and dosing. Phase 2 clinical trials or dose expansion cohorts in phase 1 are then used to evaluate whether a new drug shows signs of efficacy—typically using a surrogate endpoint.[1] Drugs showing promise in phase 2 are then tested in phase 3 trials, which often inform regulatory approvals.

Numerous studies have sought to address the risk/benefit balance for phase 1 cancer trials.[2-8] These studies show an approximate objective response rate ranging from 3.8% to 13.2%, with a rate of life-threatening toxicity ranging from 10% to 19%.[6,9,10] Several commentators have used these findings, as well as principled arguments, to suggest that the ethical justification for risk associated with giving new drugs to patients in phase 1 trials rests on their scientific value, not their prospect of therapeutic benefit.[10-13] This position has implications for trial design, ethical review, consent, and reporting.

In contrast, little is known about risk/benefit for trials of new drugs after initial phase 1 testing (ie, phase 1 dose expansion cohorts or classic phase 2 trials—hereafter called "phase 2" for short). Such phase 2 trials typically enroll patients who, like those in phase 1 trials, have advanced cancer and have exhausted standard care. However, unlike initial phase 1 trials, all patients receive drugs at doses that are expected to have biological activity and are more likely to have side effects. The high failure rate of drugs entering phase 2 trials (7%–11% advance to FDA (Food and Drug Administration) approval in cancer, 16%–21% in all therapeutic areas) provides grounds for thinking that patients in phase 2 trials are unlikely to receive a drug that will prove to have a risk/benefit balance that could be considered therapeutic.[11-13] Previous work has assessed the risk/benefit balance of phase 2 clinical trials by meta-analyzing the response rate and rate of adverse events in pediatric phase 2 clinical trials.[14] However, such methods depend on surrogate measures of benefit that are weakly correlated with survival.[15-19]

An alternative approach to estimating the risk/benefit is to assess the probability that patients entering a trial receive a drug, at an appropriate dose, that FDA or other administrative entities later classify as therapeutic. This approach exploits the premise that such administrative classifications represent a community-accepted standard of therapeutic activity that

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incorporates a consideration of risk.[20] It also reflects that a treatment's status as a therapy is defined prospectively: giving a patient a drug that is expected to have clinical activity is a therapeutic act, even if the patient happens not to respond to that drug. Previous work suggests that 83 patients are enrolled in phase 1 cancer trials for one to receive a treatment that advances to FDA approval.[21] The present study extends similar methods to phase 2 cancer trials.

Methods

Aims

Our aim was to estimate the proportion of cancer patients in phase 2 trials who receive interventions that are later deemed safe and effective according to several administrative benchmarks. For our primary aim, we estimated the proportion of patients enrolled in phase 2 trials or phase 1 dose expansion cohorts who receive a treatment regimen that was later approved by the FDA—a metric we define as "therapeutic proportion."

Secondary aims included estimating the therapeutic proportion for a more permissive benchmark of therapy (FDA approval or recommendation for the trial indication [regardless of line of treatment] in the National Comprehensive Cancer Network (NCCN) guidelines, including off-label applications) and a more stringent criterion (an FDA approval that is deemed to present substantial clinical benefit using the European Society for Medical Oncology Magnitude of Clinical Benefit Scale [ESMO-MCBS]). We also performed a bootstrap test of mean difference examining the impact of various trial characteristics on therapeutic proportion.

Sampling

To create a sample of phase 2 cancer trials, we searched Clinicaltrials.gov for all phase 1, phase 1/2, and phase 2 oncology trials beginning November 2012 to November 2015. We selected this timeframe to allow for 7.5 years after trial launch for a drug to advance to a regulatory approval. This interval was based on a pilot study suggesting that 80% of FDA cancer drug approvals occur within this time span (Supplementary Methods 1).

We included all interventional phase 2 cancer trials testing drug-indication pairings that were not FDA approved at the time of trial start. We excluded trials with ambiguous product names (eg, stem cell therapy), adjuvant or neoadjuvant trials, trials without an efficacy endpoint, trials without a registered primary completion date, and trials addressing symptoms of treatment. We restricted our sample to trials with at least one US location, since our endpoints included 2 US-based administrative actions (ie, FDA and NCCN decisions).

After establishing a high inter-rater agreement on 12.5% of the sample ($\kappa = 0.816$), all remaining screening was pursued by a single individual. We used simple randomization to select 400 trials for inclusion.

Trial extraction

Data were extracted from trial registration records or, when necessary, from publications (Supplementary Methods 2). The following data were extracted: drug name, trial type, enrollment, biomarker eligibility requirement, indication, dosage, monotherapy vs combination therapy, and sponsorship (Supplementary Methods 3). For trials involving multiple arms, data were extracted on a per cohort basis.

We classified each captured drug as either immunotherapy, targeted therapy, cytotoxic, or other using NCI (National Cancer Institute) thesaurus and DrugBank (Supplementary Methods 4). For trials that tested drug combinations, we classified the study intervention based on the investigational agent in the combination that had not yet been approved by the FDA for the trial indication. When multiple novel drugs were tested, the combination was classified based on the drug that was most recently put into development for the trial indication. Only one drug had to be unapproved in the trial indication for the cohort to be included. To direct our focus on strategies where patients and physicians are likely to be more hopeful about therapeutic benefit, we excluded trials only testing cytotoxic drugs. We classified all trials based on whether they involved the first instance of the drug being tested for efficacy. All data were independently double extracted (C.O., B.F.), with disagreements resolved through discussion or consultation with a third party (J.K.).

Identifying therapeutic benchmarks for therapy

For all trials in our sample, we determined whether interventions eventually attained one of 3 administrative benchmarks that varied in their stringency in defining therapeutic value. Our stringent benchmark of therapeutic value was FDA approval with a scoring of substantial clinical benefit by ESMO-MCBS. We used this benchmark because patients entering trials are mostly likely to be motivated by the prospects of accessing a drug that delivers substantial benefit. We also applied a more general benchmark, as defined by attainment of FDA approval, recognizing that some FDA approvals deliver incremental, uncertain, or nil benefits in terms of increased survival.[22,23] Third, we used a permissive standard, namely FDA approval and/or recommendations for off-label use in NCCN guidelines. This permissive benchmark reflects the fact that some treatments are widely used without regulatory approval, particularly in rare diseases.

For all the drugs captured in our sample, we searched for approvals on Drugs@FDA. We recorded the approved indication, drug combination, and dose. For all approvals, we recorded the pivotal trial cited in Section 14 of the FDA label. We obtained ESMO-MCBS scores for all pivotal trials by searching the scorecard database or, if unavailable, by having our oncologist coauthor (J.D.P.) score them.[24] We searched NCCN guidelines for instances in which the unapproved drug-indication pairings were recommended off-label following the trial start date.

Matching trial and benchmark for therapy

For patients in a trial to be scored as receiving a therapy, a trial needed to align with the same drug, indication, and dosage as established by the benchmark. For example, the clinical trial NCT01846416 was considered therapeutic because it was a monotherapy trial of Atezolizumab for PD-L1 positive non-small cell lung cancer (NSCLC). In this trial, Atezolizumab was administered at 1200 mg every 3 weeks. The subsequent approval of Atezolizumab by the FDA mirrors this trial, reflecting the same indication (PD-L1 positive NSCLC), the same drug (Atezolizumab), and the same dosing regimen (1200 mg every 3 weeks). This same drug, at the same dose, was given a score of 5 (maximum score) by ESMO-MCBS for this indication. For dose, we allowed the trial dose to fall within the recommended dose and dose reduction reflected on the FDA label. For trials assessing drug combinations, both therapies had to be included in the label to meet the criteria.

We applied the same matching criteria for recommendations in NCCN guidelines. However, because NCCN guidelines do not specify dose, we consulted the FDA label to determine the recommended dosage.

Statistical analysis

Our primary endpoint was the proportion of patients enrolled in phase 2 trials involving interventions attaining a therapeutic benchmark (as a post hoc analysis suggested in review, we also estimate the proportion of patients receiving a regimen that advanced to phase 3 testing). We calculated therapeutic proportion by dividing the number of patients receiving a therapeutic regimen by the total number of patients enrolled in phase 2 trials. Patients assigned to control groups were included in the denominator of the therapeutic proportion, but not in the numerator, since they had joined a trial but received a treatment that, in principle, would have been available off-trial. We tested whether proportions varied according to the following categories: solid vs hematological malignancy, single indication vs mixed malignancy, combination vs monotherapy, prior drug approval for a different indication, drug class, sponsorship, biomarker enrichment, first indication tested for efficacy, and phase 2 vs phase 1 dose expansion cohort. In post-hoc analyses, we also tested large vs small trial cohorts, and randomized vs non-randomized trials. We defined the former as cohorts with an enrolment greater than the median enrolment of all trials included in our analysis. We performed a bootstrap test of mean difference in therapeutic proportion by creating a null distribution by pooling over the different aforementioned characteristics as though there was no difference between them using R (Version 2023.03.1 + 446). All statistical tests were 2-sided. We reported the 95% confidence interval and defined a P-value less than .05 as statistically significant.

Anticipating that some drug-indication pairings might take more than 7.5 years to attain approval, we performed a sensitivity analysis using only the trials that had at least 9.5 years follow-up time following trial initiation.

We prospectively registered our protocol on Open Science Framework (https://osf.io/3f5c6/). We described all protocol deviations in the supplementary materials (Supplementary Methods 5).

Results

Sample characteristics

Our search identified 2730 phase 2 clinical trials, 1154 of which met eligibility (Figure 1) and 400 of which were randomly sampled for inclusion (Table 1). These phase 2 trials had a total patient enrollment of 25 002 patient-participants in 608 specific cohorts testing 332 drugs, 279 (84%) of which were present only in experimental arms (Table 2). Twenty-five drugs were tested in more than 10 trials, 155 in 2-10 trials, and 152 in 1 trial only. A small number of patients (3669, or 15%) were enrolled in the control arms of trials. The median enrollment per trial was 62 patients. Most patients (18 174, or 73%) had advanced or metastatic disease. Of those that did not, 37% involved hematological malignancies, and another 46% had enrolled in combination therapy trials, where it seems likely the backbone was standard of care. In total, 149 (24.5%) phase 2 trial cohorts advanced to phase 3 testing for the same drug-indication pairing.

The proportion of patients receiving therapeutic regimens

Regulatory approval was granted to 71 drug regimens in the tested indication, 17 (24%) of which involved accelerated approvals. In total, 4045 patients received treatment in phase 2. This corresponded to a therapeutic proportion of 16.2% (95% CI = 10.3 to 22.7) of patients participating in phase 2. Using the more permissive benchmark of NCCN off-label recommendations in addition to FDA approval, the therapeutic proportion increased to 19.4% (95% CI = 14.1 to 25.8) and decreased to 9.3% (95% CI = 4.7 to 14.6) when considering FDA approvals deemed to be of substantial clinical benefit by ESMO-MCBS (Table 3). The proportion of patients who participated in a trial where the drug-indication pairing continued to phase 3 testing was 32.5%. (95% CI = 26.0 to 38.8).

We did not detect significant differences in therapeutic proportions based on trial characteristics, such as drug class, trial phase, or sponsorship. Our analysis trended towards patients receiving monotherapy being more likely to receive a therapeutic regimen than patients receiving combination therapy (19.4% vs 13.2%, P-value = .301). Receiving an immunotherapy drug, being enrolled in a trial that utilized biomarker enrichment, receiving a hitherto unapproved drug, participating in a phase 2 trial, a large trial cohort, a non-randomized trial, and in an industry-sponsored trial also trended towards a higher therapeutic proportion (Figure 2).

Sensitivity analysis

A re-analysis using the 159 trial cohorts with 9.5 years of follow-up in our sample resulted in a therapeutic proportion of 17.5% (95% CI = 11.0 to 24.9) (Table S1). The therapeutic proportion increased to 21.0% (95% CI = 14.0 to 25.9) when also considering NCCN off-label recommendations and decreased to 12.1% (95% CI = 4.6 to 14.6) when considering FDA approvals deemed to be of substantial clinical benefit by ESMO-MCBS. We performed a post-hoc analysis classifying trials registered as Phase 1/2 (where, in our primary analysis, the phase 2 portion was considered as a dose expansion cohort) as Phase 2 trials. This reclassification did not result in meaningful a change in therapeutic proportions (Supplementary Methods 6).

Discussion

One in 6 patients who enrolled in phase 2 trials of cancer drugs received a treatment that was later approved by the FDA at an appropriate dose for their cancer. This proportion improved to 1 in 5 when considering NCCN off-label recommendations and decreased to 1 in 11 when considering FDA approvals deemed to present substantial clinical benefit by ESMO-MCBS. Our analysis did not suggest that therapeutic proportions were sensitive to follow-up time.

Our analysis hints at the possibility that certain types of trials present better prospects of receiving a therapy that advances to approval. Phase 2 trials involving biomarker enrichment or immunotherapy increased the probability of receiving a later-approved therapy to 1 in 4. Trials testing unapproved drugs showed a therapeutic proportion of 1 in 5, compared to 1 in 11 for trials testing approved drugs in a new indication. In terms of funding, the ratio was 1 in 6 for industry-funded and 1 in 9 for non-industry-funded. We also observed that immunotherapy trials presented a therapeutic proportion of 1 in 4 compared to 1 in 7 for trials testing targeted therapy. That none of these showed statistical significance may reflect the limited statistical power for these secondary outcomes. Nevertheless, these trends are consistent with what has been observed by others.[11,13,25]

The proportion of patients receiving therapeutic regimens in phase 2 trials exceeds that previously estimated for phase 1 trials by a large margin (16.2% vs 1.2%).[21] This suggests that phase 1 cancer trials are very effective in screening out clinical hypothesis that are unlikely to advance to approval.

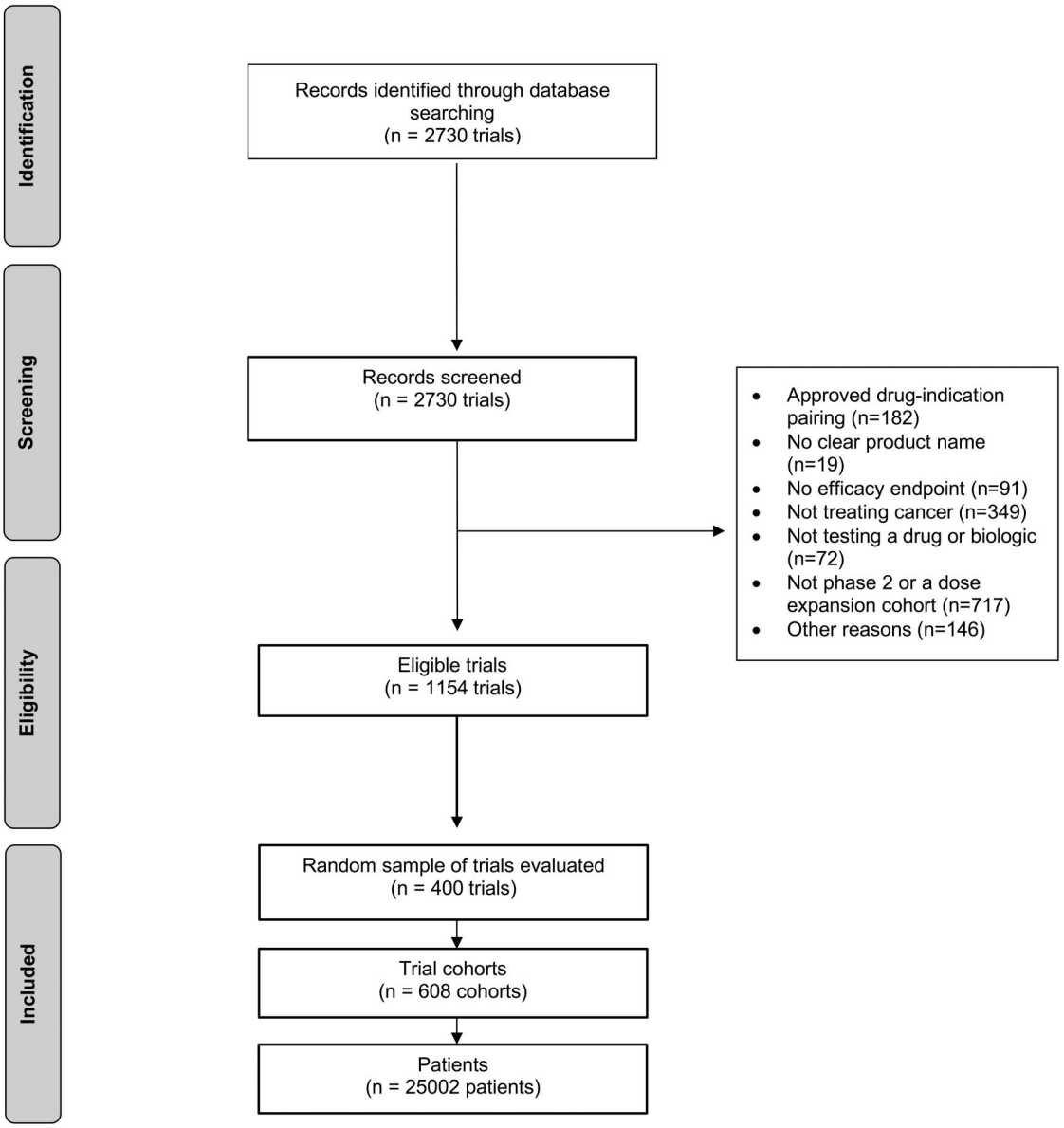

Figure 1. PRISMA flow diagram for creation of cohort sample.

Table 1. Trial characteristics.

Trial characteristic	No. (%)
Sponsorship	
Industry	216 (54)
Non-industry	184 (46)
Number of indications tested	
Mixed	126 (32)
Single	274 (68)
Phase	
Phase 1 (dose expansion)	92 (23)
Phase 1/2	79 (20)
Phase 2	221 (55)
Phase 2/3	8 (2)

Phase 2 trials occupy an ambiguous status regarding how risks of drug administration should be analyzed. The most influential approaches for ethically evaluating risks in trials direct reviewers to divide procedures into various components—those who have a therapeutic justification (or, "net benefit,") and those deriving their justifications solely from scientific value—and assess the risk-benefit of each component separately.[26,27] Thus, in a phase 3 trial, drug administration would count as therapeutic, but blood draws or research biopsies would count as research procedures. Results from earlier phase trials support clinical hypotheses in such studies, making the drugs in phase 3 "therapeutic." Whether procedures are classified as "therapeutic" or "research" has implications for ethical evaluation and consent. We and other commentators have argued that drug administration in phase 1 trials should generally be classified as a research procedure.[28-30] This places greater onus on researchers to maximize the scientific value of the study, minimize patient exposure to drugs, and explain to patients that direct benefits are unlikely.

Our findings reinforce ambiguity in the classification of drug administration in phase 2 trials. Most patients who enroll in phase 2 trials have advanced cancers that lack validated treatment options, as observed in this study. Many such patients are likely to regard a 16% probability of receiving a drug that later secures FDA approval for their condition as favorable odds. We

Table 2. Cohort-specific characteristics.

Cohort characteristics	Experimental arm No. 533 (%)	Comparator arm No. 75 (%)	Total No. 608 (%)
Indication			
Cancer type			
Hematological	121 (23)	7 (9)	128 (21)
Solid tumor	400 (75)	68 (91)	468 (77)
Mixed	12 (2)	0 (0)	12 (2)
Number of indications in cohort			
Single	338 (63)	70 (93)	408 (67)
Mixed	195 (37)	5 (7)	200 (33)
Biomarker enrichment			
Yes	144 (27)	7 (9)	151 (25)
No	389 (73)	68 (91)	457 (75)
Patients with advanced/metastatic disease			
Yes	382 (72)	52 (69)	434 (71)
No	151 (28)	23 (31)	174 (29)
Drug			
Type of therapy			
Monotherapy	225 (42)	38 (51)	263 (43)
Combination therapy	308 (58)	37 (49)	345 (57)
Drug type			
Immunotherapy	120 (23)	0 (0)	120 (20)
Targeted	395 (74)	30 (40)	425 (70)
Cytotoxic	0 (0)	37 (49)	37 (6)
Other	18 (3)	8 (11)	26 (4)
Approval status			
Previously approved	138 (26)	75 (100)	213 (35)
Novel therapy	395 (74)	0 (0)	395 (65)
Trial			
Trial type			
Dose expansion cohort	254 (48)	9 (12)	263 (43)
Phase 2	279 (52)	66 (88)	345 (57)
Sponsorship			
Industry	310 (58)	49 (65)	359 (59)
Not industry	223 (42)	26 (35)	249 (41)
Stage of development			
First early efficacy trial	84 (16)	0 (0)	84 (14)
Not first early efficacy trial	449 (84)	75 (100)	524 (86)

Table 3. Therapeutic proportion when the benchmark for therapy is FDA approval, off-label recommendation in NCCN guidelines or FDA approval with high ESMO-MCBS.

Benchmark for therapy	Therapeutic proportion (%) FDA (95% CI)	Therapeutic proportion (%) FDA and NCCN (95% CI)	Therapeutic proportion (ESMO-MCBS) (95% CI)
Approval (regardless of indication, dose, or biomarker)	37.7 (30.8 to 44.2)	50.9 (42.4 to 58.9)	N/A
Approval in indication (regardless of dose and biomarker)	20.1 (14.2 to 26.6)	23.4 (17.6 to 29.6)	10.5 (5.8 to 16.1)
Approval in indication at the right dose (regardless of biomarker)	17.2 (11.1 to 23.6)	20.5 (14.8 to 27.0)	9.3 (4.5 to 14.5)
Approval in indication at the right dose and with the same biomarker	16.2 (10.3 to 22.7)	19.4 (14.1 to 25.8)	9.3 (4.7 to 14.6)

Abbreviations: ESMO-MCBS = European Society for Medical Oncology Magnitude of Clinical Benefit Scale; FDA = Food and Drug Administration; NCCN = National Comprehensive Cancer Network.

think it can be appropriate to present phase 2 trial participation as offering a small prospect of benefit.

Viewed through a policy lens, however, we believe our analysis supports the notion that the therapeutic value of phase 2 is more like that of phase 1. We and others have suggested that drug administration in phase 3 trials should be assessed through the lens of clinical equipoise.[26,31-33] This logically entails that, in the long run, new interventions will prove better than their comparator roughly half the time, which is equivalent to a therapeutic proportion of roughly 50%. Indeed, systematic studies of such trials show positivity rates in this range.[34,35] Surveys have shown that physician-investigators regard clinical equipoise as holding for a new treatment until it crosses under the boundary of support from 30% of experts.[36] Confidence intervals for therapeutic proportions estimated in the present study exclude this 30% boundary. This policy-type classification is further supported by the results of a recent meta-analysis of randomized cancer trials in patients with solid tumors. In it, authors estimated the pooled hazard ratio for survival randomized phase 2 trials as 1.02 (95% CI = 0.96 to 1.09), whereas for phase 3 trials the pooled hazard ratio was 0.88 (95% CI = 0.84 to 0.92) with the difference being statistically significant.[37]

Another lens through which to view the therapeutic value of phase 2 trial participation is number needed to treat (NNT). NNT is useful for patients and physicians in understanding potential benefits.[38-41] When discussing phase 2 trials, this metric may be helpful considering the consistent overestimation of the therapeutic value of this phase of research by both parties.[42-48]

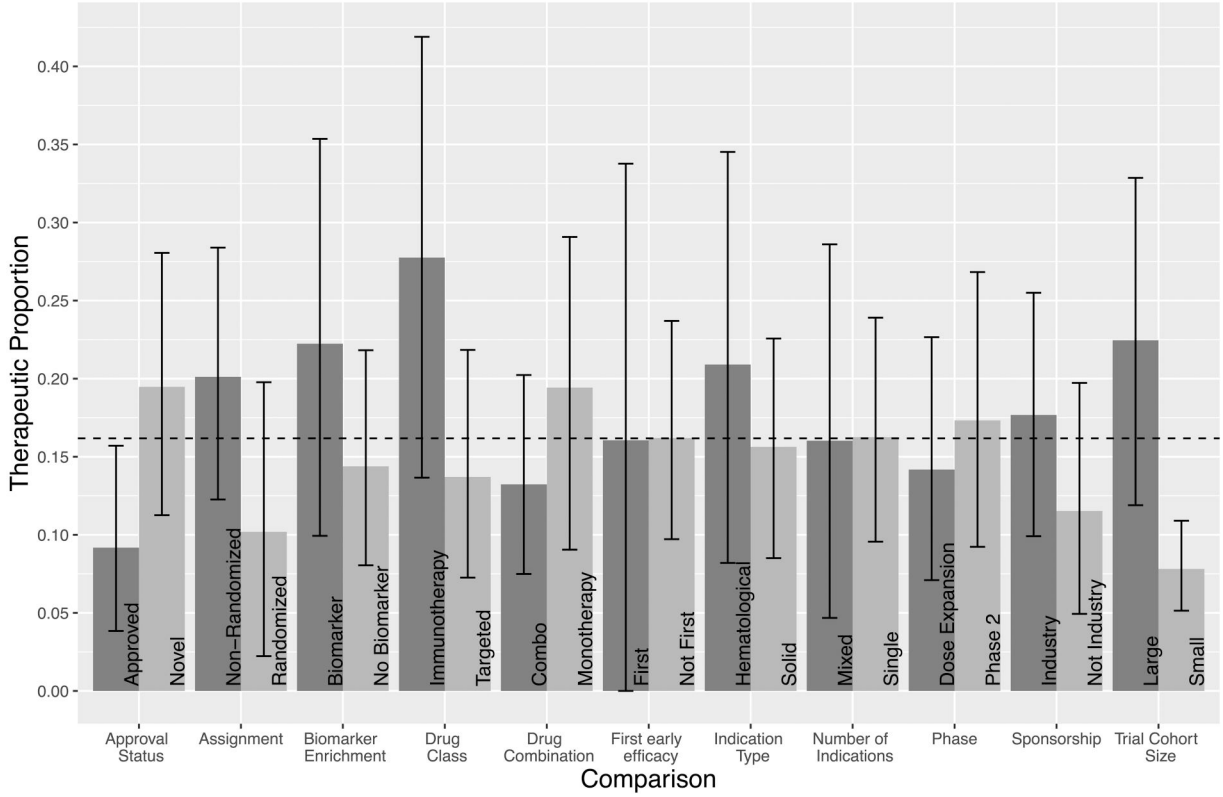

Figure 2. Therapeutic proportion by cohort characteristics. The horizontal dotted line corresponds to the therapeutic proportion 16.2% and error bars the 95% confidence intervals. Assignment and trial cohort size are post-hoc analyses.

Pembrolizumab, for PD-L1 positive non-small cell lung cancer, has been estimated to have a very favorable NNT of 2.63.[49] The NNT for targeted agents like ribociclib and niraparib are estimated as 9.7 and 6 for breast cancer and ovarian cancer, respectively.[50,51] With the provisos that the definition of a good outcome with NNT varies and that multiplying the above NNTs by the therapeutic proportions in our manuscript provides merely a back of the envelope estimate, the NNT for phase 2 participants is likely in the range of 20-60. These values are not especially favorable considered against the side effects and treatment burden associated with receiving these drugs.

Our findings have limitations. First, the longitudinal design of our study necessitated reliance on a historical cohort of phase 2 clinical trials. As cancer research is rapidly evolving, we cannot establish that therapeutic proportions based on this cohort of drugs would hold for present-day drug cohorts. Second, our random sample of 400 trials provided insufficient power to explore which trial characteristics were predictors of higher therapeutic proportion. Third, our analysis did not capture cytotoxic drugs and thus provide a somewhat limited view of drug development. Finally, some drug development timelines for drug-indication pairings in our cohort may exceed the 7.5-year timeframe we used in our primary analysis. Nevertheless, our sensitivity analysis indicates that extending the follow-up period does not alter our results substantially, reducing concerns about the impact of longer approval durations.

Conclusion

Our estimates of therapeutic proportions have implications for many aspects of phase 2 trial conduct and drug development. Regarding design and ethical review, our findings suggest that, when evaluating risk, reviewers should direct their focus on the expected scientific value of the study. Specifically, they should consider the strength of the scientific justification and the soundness of design. With respect to consent, many educational materials emphasize that trials present an opportunity to receive tomorrow's treatments. Our findings move beyond such nondescript statements to meaningful statements—namely, that by entering a phase 2 trial, a patient has a 1 in 6 chance of receiving a treatment that will later be approved for their condition. Finally, the proportions described here, when juxtaposed with those estimated previously for phase 1 trials, suggest a striking improvement for a patient's therapeutic prospects. This suggests that phase 1 trials do a good job at protecting patients downstream from unsafe and ineffective cancer treatments.

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Author contributions

Charlotte Ouimet, MSc (Data curation; Formal analysis; Methodology; Writing—original draft; Writing—review & editing), Bianca Fodor, BSc (Data curation; Formal analysis; Methodology; Writing—review & editing), Joseph C. Del Paggio, MD (Conceptualization; Data curation; Methodology; Writing—review & editing), and Jonathan Kimmelman, PhD (Conceptualization; Funding acquisition; Supervision; Writing—original draft; Writing—review & editing)

Supplementary material

Supplementary material is available at *JNCI: Journal of the National Cancer Institute* online.

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Conflict of interest

The authors have no conflict of interest to report.

Data availability

The data underlying this article are available in Open Science Framework, https://osf.io/3f5c6/.

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