Journal of Clinical Trials
ISSN: 2167-0870

Boixader et al., J Clin Trials 2018, 8:3
DOI: 10.4172/2167-0870.1000347

Research Article Open Access

Changes in Numbers of Randomized *vs.* Non-Randomized Clinical Trials: Recent Evidence of Shifting Cancer Drug Development Pathways

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Received date: June 19, 2018; **Accepted date:** July 10, 2018; **Published date:** July 12, 2018

Abstract

Objective: Randomized clinical trials are most often used to demonstrate efficacy of novel anti-cancer drugs. Recently, several oncology drugs have shown efficacy in early phase studies and received regulatory approval based on data from non-randomized studies. We sought to determine that changes in numbers of non-randomized (NRCT) *vs.* randomized (RCT) oncology trials in recent years.

Methods: We reviewed a database of oncology clinical trials conducted by Syneos Health and classified them by RCT *vs.* NRCT, grouped by year (≤ 2010 or >2010). We queried Citeline® Trialtrove database for industry sponsored, phase 2 trials (P2T) initiated from 2007-2016 and examined numbers of RCT *vs.* NRCT by year. We analyzed non-small cell lung cancer (NSCLC) trials categorized by immuno-oncology (IO) *vs.* all other mechanisms of action (NIO).

Results: 190 Syneos-conducted trials were reviewed. 58 trials (31%) were performed ≤ 2010 and 132 trials (69%) >2010. Over this period, NRCT (n=107, 56%) outnumbered RCT (n=83, 44%). Whereas NRCT outnumbered RCT prior to 2010, (52% *vs.* 47%), after 2010, the gap widened (58% *vs.* 42%). Citeline® Trialtrove search revealed 4776 P2T initiated from 2007-2016. The proportion of phase 2 RCT increased from 27% (n=166) in 2006 to around 37%-39% from 2011-2014, then decreased to 33% in 2015 and 29% in 2016. Among IO studies, RCT declined in 2015-2016 *vs.* previous years, and a decrease was seen for all trials of oncology drugs in 2016 *vs.* previous years. For studies in NSCLC, declines in RCT were evident from 2015-2016 *vs.* previous years (45% in 2007-2014 *vs.* 25% in 2015-2016).

Conclusion: Fewer oncology RCT and more NRCT are being performed over time. This change reflects shifts in oncology drug development pathways related to a better understanding of cancer biology and a more flexible regulatory drug approval process.

Keywords: Oncology clinical trials; Trial design; Drug development; Phase 2 trials

Introduction

With increased knowledge of cancer biology and the availability of sophisticated molecular testing techniques, development of oncology drugs better tailored to an individual patient's tumor now is occurring, an era called "precision medicine." As new targeted- and immuno-oncology drugs enter clinical development, emphasis is placed on testing them in patients most likely to benefit, usually identified by way of a companion diagnostic test, or biomarker. As a result, the traditional drug development pathway in which studies are conducted in 3 sequential phases (early clinical safety, early clinical efficacy, registration trial) is switching from a series of linear, landmark events to a more flexible and iterative process based on the drug and the intended population [1]. The standard paradigm of a Phase 1 trial to establish the recommended dose, a Phase 2 trial to obtain preliminary evidence of efficacy and finally a Phase 3 trial to compare with a standard therapy represented an idealized scenario that was established more than 30 years ago; this compartmentalization of trials into these three standard phases was a convenient and simple approach, but with non-overlapping aims, and proved to slow the clinical development of antitumor agents [2]. Furthermore, it is recognized that Phase 3 trials have a high failure rate and are a tremendous cost to the health care system [3].

Early randomization was proposed as a strategy to optimize the design of Phase 2 studies and to select the most promising agents for testing in Phase 3 [4]. Randomization in Phase 2 was proposed as a useful strategy for studies in a new patient population where historical data were not available, or when an endpoint such as progression free survival was desired, which is more heavily influenced by factors beyond therapy than the traditional endpoint of tumor response. This strategy led to an increase in the use of randomization in the Phase 2 setting in the 2000s, [2] which were typically followed by multiyear confirmatory trials leading to full approval based on more traditional end points.

However, in recent years we have observed that emerging data from Phase 1 testing (such as a drug's pharmacodynamics and initial evidence of clinical effect) have been used to justify adding expansion cohorts to a Phase 1 trial to further test hypotheses and explore clinical effect in larger populations of several tumor types [5]. At the same time, regulatory approval of oncology drugs has been granted based on uncontrolled data from large Phase 1 studies [6,7]. Relying on efficacy results from uncontrolled clinical trials has resulted in expedited drug approval, but some are calling attention to the disadvantages of this practice and the requirement for randomization; for example, the apparent improvements in outcomes observed in an early single-arm trial of a new therapy might reflect the prognostic nature of the target, rather than a true treatment effect. Additionally, it may be impossible to definitively ascertain the predictive role of biomarkers unless patients are randomized to a control arm [8].

While such trends in oncology drug development are apparent, no studies have been published to quantify the rate at which this is occurring. We therefore hypothesized that randomized clinical trial designs in oncology have become less common in recent years, owing to the ability to observe clinical activity of a drug early in development. To test this hypothesis, we examined trends in numbers of industry-sponsored randomized Phase 2 trials initiated each year since 2007, to see if a decrease in the number of such studies was apparent, to corroborate the dynamic and evolving clinical development pathways in oncology.

Methods

To better understand changes in trial designs of novel anti-cancer drugs, we searched both an internal database of clinical trials conducted by Syneos Health (a global contract research organization headquartered in Raleigh, North Carolina, USA) and a publicly available database (Citeline® Trialtrove) for Phase 2 studies. For the Citeline® Trialtrove search, we restricted the search to industry-sponsored Phase 2 studies only, excluding Phase 1 and 1/2 trials. Search terms included "oncology" for therapeutic area, phase 2, industry sponsored and specified date ranges (for Citeline® Trialtrove search, a 10-year period, or 1/1/2007 to 12/31/2016, and for Syneos Health search, 1/1/2004 to 12/31/2016, to increase the number of studies available for analysis). Disease, patient segment, MeSH (Medical Subject Header) trial status, mechanism of action, therapeutic class, location, study design, accrual status and sites were search items we did not restrict.

Each Phase 2 trial we identified was categorized as having randomized (RCT) or non-randomized (NRCT) design, and year of trial initiation was recorded. We analyzed trends in industry sponsored Phase 2 trial design according to sub-groups: number and percentage of RCT *vs.* NRCT by the year of study initiation (2007-2010 *vs.* 2011-2016); and number and percentage of RCT *vs.* NRCT by type of drug-immuno-oncology (IO) *vs.* all other mechanisms of action (non-immuno-oncology, NIO; the NIO group included targeted therapies and chemotherapy). We also performed a sub-group analysis of number and percentage of industry sponsored Phase 2 trials by design (RCT *vs.* NRCT) and drug type (NIO *vs.* IO) in a specific indication (non-small cell lung cancer, NSCLC).

Next, we analyzed trends in industry sponsored Phase 2 trial designs for the checkpoint inhibitors atezolizumab, nivolumab and pembrolizumab. We again searched the Citeline® Trialtrove database, restricting the search to "oncology" therapeutic area, Phase 2, industry sponsored, date ranges 1/1/2007 to 12/31/2016 and drug tested "atezolizumab, nivolumab or pembrolizumab." We then categorized the number and percentage of RCT *vs.* NRCT for each of these drugs by year of trial initiation.

We then narrowed the scope of our review to look only at industry sponsored Phase 2 trial designs of drugs receiving FDA approval from 2004-2016. We again searched the Citeline® Trialtrove database, and we also searched clinicaltrials.gov to identify the phase of trial (1-3) that led to approval of the drug as well as any stand-alone Phase 2 studies conducted with these agents either before or as the registration trial. For all agents with Phase 2 studies conducted prior to approval, we analyzed the Phase 2 trial design, again grouping the studies according to NRCT or RCT, as well as according to primary endpoint, year of approval and drug type (NIO *vs.* IO). We then calculated percentages of RCT or NRCT by year and drug type to detect changes in frequency of trial design over time.

For the 2007-2016 time periods, we calculated standard deviations (SD) for the percentage change in industry sponsored Phase 2 RCT *vs.* NRCT initiated from the prior year. For NSCLC studies, we calculated the overall mean number (SD) of industry sponsored Phase 2 studies initiated from 2007-2010 *vs.* 2011-2016, as well as the mean percentage (SD) of industry sponsored Phase 2 RCT initiated from 2007-2014 *vs.* 2015-2016, and mean percentage (SD) of industry sponsored Phase 2 RCT initiated from 2007-2014 *vs.* 2015-2016 by NIO and IO category. All other comparisons of numbers of studies initiated by year, percentage of RCT *vs.* NRCT, type of drug and disease setting were descriptive in nature.

Results

We identified over 4000 industry sponsored Phase 2 trials from the database searches. Of these, 77 were Phase 2 trials conducted for drugs that received eventual FDA approval from 2004-2016. Among them, 582 were Phase 2 trials in NSCLC initiated from 2007-2016. 189 Phase 2 trials were identified for the checkpoint inhibitor drugs.

Year	Randomized	Non-randomized	Total	Percent randomized	Standard deviation from previous year
2007	166	455	621	27%	
2008	177	387	564	31%	0.52
2009	155	349	504	31%	-1.04
2010	157	333	490	32%	0.09
2011	179	305	484	37%	1.04
2012	171	280	451	38%	-0.38
2013	168	288	456	37%	-0.14
2014	158	245	403	39%	-0.47
2015	141	287	428	33%	-0.80
2016	107	268	375	29%	-1.61

Table 1: Numbers of randomized and non-randomized industry sponsored phase 2 trials initiated from 2007 to 2016.

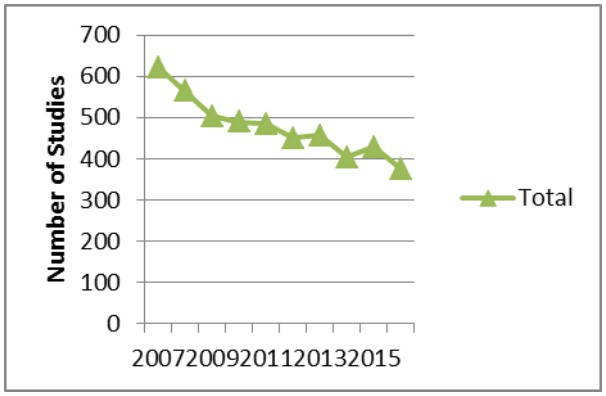

Figure 1: Number of industry sponsored phase 2 trials initiated from 2007-2016.

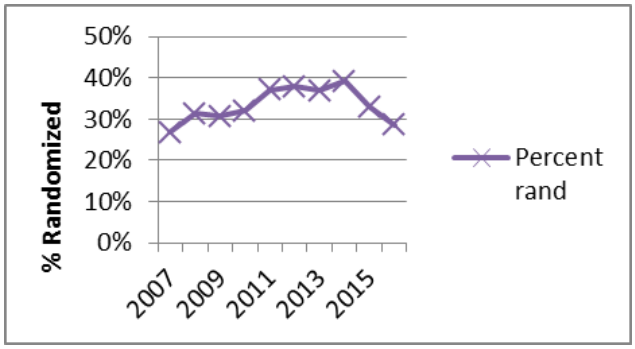

Figure 2: Percentage of industry sponsored phase 2 randomized trials initiated from 2007-2016.

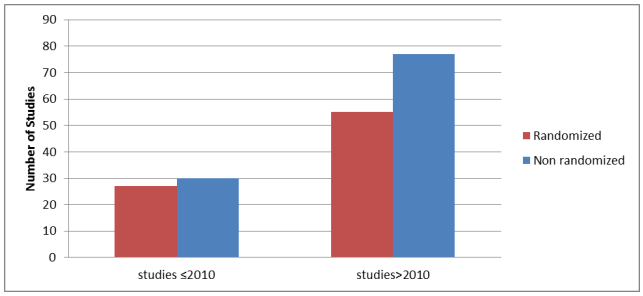

Figure 3: Number of industry sponsored randomized *vs.* non-randomized Syneos Health-conducted trials (≥ phase 2) before *vs.* after 2010.

Overall, there has been a gradual decline in the number of industry sponsored Phase 2 trials over time. As shown in Figure 1, from a high of over 600 Phase 2 trials initiated by industry in 2007, each year has seen a decrease in the number of new Phase 2 trials initiated, to 375 in 2016. These numbers are shown additionally in Table 1. Table 1 also shows the number, percentage and standard deviation from prior year of RCT *vs.* NRCT industry sponsored Phase 2 trials initiated by year from 2007-2016, noting in particular a decrease in percentage of RCT initiated in the period of 2011-2014 (37%-39% per year) to 29% in 2016. These numbers are illustrated graphically in Figure 2.

There were similar trends for studies identified in the Syneos Health database. Prior to 2011, 27/57 (47%) of Phase 2 or higher oncology studies were randomized, whereas since 2011, 55/132 (42%) were randomized. This trend is shown in Figure 3.

A trend toward fewer RCT for the 3 checkpoint inhibitors we analyzed (atezolizumab, nivolumab and pembrolizumab) also was seen. As shown in Figure 4, there are increasingly more non-randomized designs in recent years, with RCT peaking at 64% in 2013 and declining to 23% in 2016.

Looking at NSCLC, of the 582 industry sponsored Phase 2 trials found in the Citeline® Trialtrove search, 516 were for NIO drugs and 66 were for IO drugs. As with industry trends as a whole, a decrease in newly initiated Phase 2 trials in NSCLC over time is evident. From 2007-2010, a mean of 64 (SD, 16.5) Phase 2 NSCLC trials were initiated per year, whereas from 2011-2016, 44 (SD, 5.5) new Phase 2 NSCLC trials per year were initiated on average. Declines in RCT designs were again apparent, from mean of 45% (SD, 0.04) RCT in 2007-2014 to 25% (SD, 0.12) in 2015-2016 (Figure 5). These shifts were present for both IO and NIO drugs. For NIO drugs, the mean percentage of RCT from 2007-2014 was 46% (SD 0.04), but decreased to 25% (SD, 0.1) in 2015-2016. For IO drugs, the mean percentage of RCT from 2007-2014 was 42% (SD, 0.32) compared to 34% in 2015-2016 (SD, 0.42). These trends are illustrated in Figure 6.

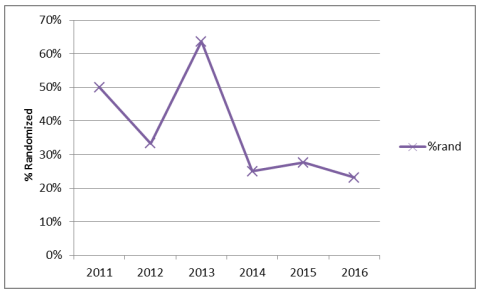

Figure 4: Percentage of industry sponsored randomized immuno-oncology trials by year.

For drugs receiving FDA approval, we identified a total 102 FDA-approved agents across 29 oncology indications. Phases of trials leading to approval of a drug for a specific indication were: Phase 1 (n=2); Phase 1/2 (n=5); Phase 2 (n=35); Phase 3 (n=60). We observed an increase in Phase 1, 1/2 and 2 trials leading to approval starting in 2012, with 47% of trials leading to approval occurring in one of these phases (n=30 of 64 trials) compared to 32% (n=12 of 38 trials) from 2004-2011 (Figure 7).

As shown in Figure 8, NRCT design in studies leading to FDA-approval has increased over time. The rate of NRCT design leading to FDA-approval increased from 25% (n=7/28) from 2004 to 2010 to 36% (n=27/75) of studies from 2011 to 2016.

77 FDA-approved agents had a stand-alone Phase 2 study conducted prior to approval. Of these, 42 agents had a Phase 2 study followed by a Phase 3 registration trial, whereas 35 agents had Phase 2 studies only from which the data were used to support registration, without a

subsequent Phase 3 trial. Most studies used NRCT design in Phase 2, and this did not differ by drug type (NIO: n=54/65, 83%; IO: n=9/12, 75%).

Year period and drug type	NR	R	Total	%RCT
2004-2010	18	6	24	25%
IO	1		1	0%
Non-IO/Biologic	17	6	23	26%
2011-2016	45	8	53	15%
IO	8	3	11	27%
Non-IO/Biologic	37	5	42	12%
Grand Total	63	14	77	18%
IO: Immuno-oncology; NR: Non-randomized; R: randomized; RCT: Randomized clinical trial				

Table 2: Number and percentage of non-randomized and randomized phase 2 trials for FDA-approved drugs by drug type and time period, 2004-2010 and 2011-2016.

Figure 5: Percentage of industry sponsored randomized phase 2 non-small cell lung cancer trials by year.

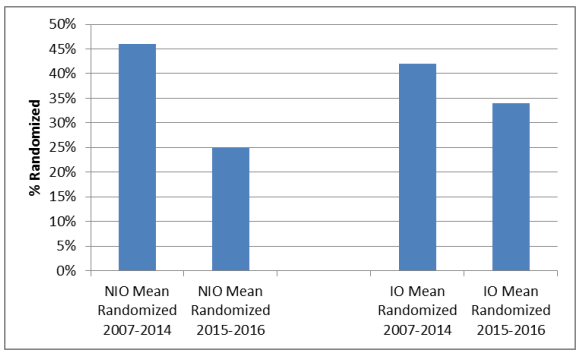

Figure 6: Mean percentage of industry sponsored randomized phase 2 non-small cell lung cancer trials by time period and drug type.

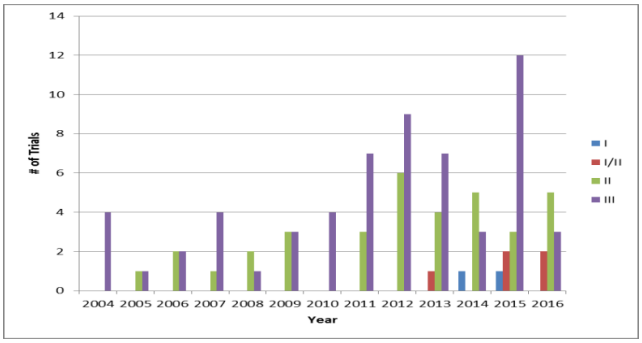

Figure 7: Phases (1-3) of registration trials by year.

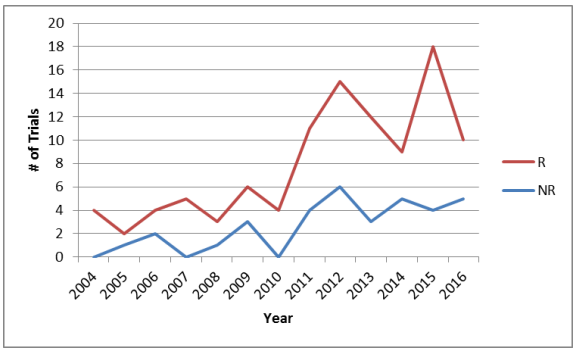

Figure 8: Randomized and non-randomized registration trials by time.

However, over time, RCT design in Phase 2 among FDA-approved drugs has decreased in frequency and NRCT design has increased, as shown in Table 2 and Figure 9. 25% of Phase 2 Trials were RCT from 2004-2010 compared to 15% from 2011-2016 (Table 2). This shift is driven mostly by an increase over time in NRCT design in Phase 2 among studies of NIO drugs: 26% of NIO Phase 2 trials were RCT from 2004-2010, compared to 12% from 2011-2016 (Table 2, Figure 9).

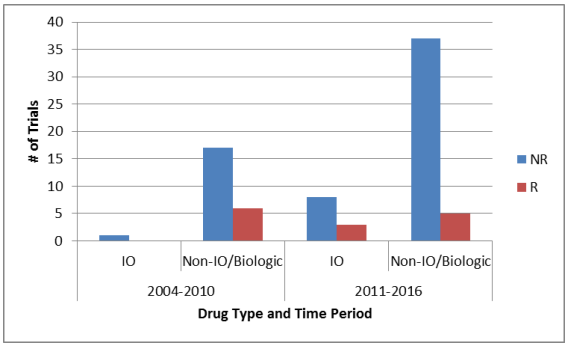

Figure 9: Phase 2 trial designs by drug type and time period, 2004-2010 and 2011-2016.

Discussion and Conclusion

Designs of clinical trials in oncology have undergone profound shifts in recent years. The traditional drug development model of early phase studies establishing drug safety while possibly showing initial evidence of efficacy, followed by later phase studies to determine a new drug's efficacy compared to standard-of-care agent(s), followed by approval by regulatory bodies, has given way to drug approvals based on data from early phase studies, many of which do not use randomized designs. The results of our study show that not only are there fewer Phase 2 studies being conducted in oncology and specifically NSCLC, but also, fewer of those Phase 2 studies that take place use randomized designs. These changes in Phase 2 clinical trials over time are due mainly to the approval of many new drugs based on a "precision medicine" approach, in which efficacy is demonstrated in a carefully selected patient population, obviating the need to show statistical improvements in outcomes in a more general, "unselected," randomized patient population enrolled in a larger Phase 2 or 3 study.

We observed clear shifts away from initiation of new industry sponsored Phase 2 studies in recent years, and of those Phase 2 studies that were initiated, fewer of them used a randomized design. This trend was further apparent in a common oncology indication, NSCLC, where we saw declines in the mean number of industry sponsored Phase 2 RCT in 2015-2016 compared to earlier years, for both NIO and IO drugs. When looking at trends in study designs of drugs that received FDA approval, several drugs have been approved in recent years based on data from Phase 1 or Phase 1/2 studies, and the number of NRCT from which data were used to receive FDA approval has increased. Additionally, we see less use of RCT in the Phase 2 setting for drugs receiving FDA approval, especially for NIO drugs.

To our knowledge, we are the first to quantify this decrease in frequency of Phase 2 trial initiation by year and decrease in percentage of Phase 2 trials that are randomized in the oncology drug development space. Others have shown a recent trend toward to earlier phase oncology studies using a "seamless" design, in which first-in human studies examine both safety and efficacy in a single study by adding expansion cohorts and enrolling over 100 patients. For example, Barata et al. analyzed 1786 early-phase oncology studies presented in abstract form between 2010 and 2017 at the American Society of Clinical Oncology Annual Meeting, finding that 51 trials used a "seamless" Phase 1/2 design (3% of total studies presented), with the majority of such studies (65%) having been presented in recent years (2014-2017). Although representing only a small percentage of the overall number of studies, they accounted for 15% of total patients enrolled [9]. Taken together, our findings and those of Barata et al. and others show clear shifts away from traditional approaches to oncology drug development. The implications of these shifts may include more rapid time to drug approval, but also the potential for initial conclusions about a drug's efficacy to be later refuted when results of randomized studies become available.

For the oncology drugs we studied that received FDA approval based on NRCT data, we did not analyze how many of these drugs received expedited approvals, such as accelerated approval or fast track designation, that require subsequent confirmatory studies, and of those drugs, how many of them have subsequently had their efficacy confirmed or refuted in a RCT. For many of these new drugs, confirmatory studies are on-going. Therefore, we cannot conclude that expedited FDA approval based on NRCT data is in all cases acceptable or whether it is cause for concern. Such analysis will need to be the subject of future work, to look at the numbers of drugs that receive an expedited approval but subsequently do not receive full approval, or do not have a confirmatory study conducted at all. Clearly, given the impressive and in many cases durable responses observed in some patients treated with novel NIO and IO compounds in non-randomized studies, pharmaceutical companies, regulatory bodies and patients alike are eager to bring these drugs to market, but care must be taken still to establish a firm evidence base for these drugs, in most cases *via* conducting a confirmatory RCT.

Drawing conclusions about efficacy of anti-cancer drugs from NRCT data is far from a recent development. As far back as the 1970s, researchers posited that the use of NRCT for testing new cancer drugs and drug combinations was an ethical responsibility of investigators in cases where preliminary studies indicated a new treatment was substantially better than existing treatments. The argument was that if an investigator knew from preliminary studies that a novel treatment showed marked improvement in outcomes compared to existing treatments (i.e., historical controls), it would not be ethical to randomize a patient to existing treatment in a RCT [10]. To account for differences in patient characteristics between studies, it was posited that the outcomes of patients with similar disease characteristics, such as tumor histology and disease stage, treated with existing treatment in previous studies could be compared to outcomes of patients treated with the new drug. However, the concept of selection bias, those known or unknown factors that affect patient treatment decisions, now is widely recognized to occur in non-randomized studies [11]. Thus, comparing outcomes from one NRCT to an historical control may lead investigators to draw inappropriate conclusions about a new treatment's efficacy, especially when considering factors such as stage migration and improvements in supportive care which may impact survival of current patients compared to historical data.

For this reason, randomization is proposed as a still-essential tool in oncology drug development [8]. However, the failure of up to 60% of oncology drugs to demonstrate significant improvements in outcomes in randomized Phase 3 studies [12] suggests that data from early phase studies, whether using randomized or non-randomized designs, provide an insufficient basis on which to plan a registration trial. In fact, estimations are that under 5% of positive Phase 2 oncology studies are confirmed subsequently in larger Phase 3 trials [13]. The real world impact of these failures includes not only lost hope for patients, but a tremendous cost to the clinical trial system [14]. Therefore, many have called for improvements to be made to the drug development process to lower the cost of drug development and improve the chance of success [15].

Several ideas have been proposed, including use of modelling and simulation at end of Phase 2 and prior to starting a Phase 3 study, [16] use of adaptive Phase 2 trial designs (wherein a randomized design is used, with data analyzed over the course of the study to adjust the randomization scheme using Bayesian methods and correcting for incorrect assumptions made at study start), [17] and perhaps most importantly, selecting the most appropriate patients for studies using biomarkers. The importance of this last strategy was highlighted by a study from Jardim et al., who found that 57% (21 of 37) of anti-cancer drugs that obtained FDA approval between 2009 and 2014 used a biomarker-based selection approach, whereas only 16% (7/43) of drugs that failed in registration studies used such an approach [18]. We did not analyze how many of the Phase 2 trials in our data set used biomarker-based selection; a future study could examine differences in use of biomarkers to select patients in the Phase 2 setting by RCT and

NRCT design, and the correlation between use of biomarkers in Phase 2 (or earlier phases) and eventual regulatory approval.

The increase in early phase studies leading to regulatory approval over the last few years, a trend confirmed by our data, suggests the "seamless" approach to oncology drug development is becoming more widespread. In this approach, the traditional multi-phase development model is replaced with a continuum of development consisting of one or two distinct studies. For example, once a safely tolerated dose of a new anti-cancer drug is established by treating a dozen or more patients, dose expansion phases begin, with progressively more patients added to various expansion cohorts, often selected based on biomarkers. If early evidence of efficacy is observed (for example, a response rate of more than 20%, or prolonged periods of stable disease in a number of patients), the drug is submitted for preliminary regulatory approval. Then, a larger, randomized confirmatory study is launched. However, the potential pitfall of making a type I error still exists with this non-randomized approach, as a new drug's efficacy is concluded by comparison to historical controls. An alternative model in which randomization through the continuum of development is used may help avoid this problem. Saad et al. has suggested such an approach [8]. Their model proposes using seamless transitions from the upfront dose-finding and safety determination, followed by further safety and efficacy testing in cohorts that randomize biomarker-selected patients to a control arm *vs.* a recommended-dose arm (and/or other dose arms if a recommended dose was not firmly established). As the study progresses, randomization can be modified using an adaptive design. Accrual continues, interim analyses occur, sample size is adjusted, randomization to control *vs.* recommended dose or alternate dose arms adjusts, and ultimately the study concludes without need to launch separate Phase 2 and Phase 3 studies (thus not only reducing study start-up costs and time, but also allowing all data obtained on patients accrued to the study to contribute to the overall endpoint, in contrast to a typical Phase 2 followed by Phase 3 approach where none of the data from Phase 2 can be used to support conclusions in the Phase 3 study). An analysis of the number of ongoing oncology studies that are using adaptive designs would shed light on the real world uptake of such proposed study designs and could be the subject of a future analysis.

As evidenced by our data, fewer randomized Phase 2 trials and fewer Phase 2 trials overall are being conducted in oncology. To lower the cost of drug development and shorten the time from "bench-to-bedside," the traditional multi-phase model of drug development is being replaced gradually. While "seamless" Phase 1 trials, in which expansion cohorts are added as pharmacodynamics and clinical data emerge are becoming more common place [19] concern remains that regulatory approval based on data from non-randomized studies may not be appropriate in all cases. Therefore, pharmaceutical companies who use novel trial designs must ensure their studies are selecting appropriate patients and that they consider using randomized, adaptive designs, so as to demonstrate most clearly a new drug's efficacy. As studies using "seamless" designs unfold, close communication among all stakeholders is of paramount importance to maximize data integrity. The era of "precision medicine" holds great hope, but to justify its expense, we must insist upon pathways for drug development that produce high quality evidence.

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