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Original Article

The Effect of Biomarker Use on the Speed and Duration of Clinical Trials for Cancer Drugs

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Abstract

Background: The purpose of this study was to explore the effects biomarkers have on the duration and speed of clinical trials in oncology.

Materials and Methods: Clinical trial data was pooled from www.clinicaltrials.gov within the 4 cancer indications of non-small cell lung cancer, breast cancer, melanoma, and colorectal cancer. Heatmaps of clinical timelines were used to display differences in the frequency and timing of clinical trials across trials that used or did not use biomarkers, for all 4 indications.

Results: Screening of 8630 clinical trials across the 4 indications yielded 671 unique drugs corresponding to 1224 eligible trials used in our analysis. The constructed heatmaps visually represented that biomarkers did not have an effect on the time gap between trial phases for non-small cell lung cancer and melanoma but did for colorectal and breast cancer trials, reducing the speed of trial timelines. It was also observed that biomarker trials were more often concurrent over shorter periods of time and began later in the timeline for non-small cell lung and colorectal cancers.

Conclusion: The novel visualization method revealed longer gaps between trial phases, later clinical trial start times, and shorter periods of concurrently run trials for drugs that used biomarkers. The study highlights that biomarker-driven trials might impact drug approval timelines and need to be considered carefully in clinical development plan.

Key words: biomarker; clinical trial; breast cancer; lung cancer; melanoma; visualization.

Implications for Practice

The use of biomarkers, depending upon the indication in oncology, may delay or lengthen the trial for the patients involved.

Introduction

Drug development is lengthy, high risk, and high cost; out of 10 compounds entering first study in humans (phase I), only one compound reaches the market after an average of 14 years with a cost of $2.7 billion.[1] In today's drug development paradigm, late-stage failure is principally a result of insufficient efficacy.[2] An oncology compound that is entering phase I has about a 5% chance of ultimately achieving FDA approval.[2] A major challenge today is to develop ways to improve oncology clinical trial success rates and reduce risks. In this context, biomarkers are increasingly used in oncology.[3,4]

Predictive biomarkers in clinical trials could potentially derive benefit by refining the clinical trial recruitment process and identifying likely responders. Biomarker usage in oncology trials was associated with higher rate of success in clinical trials,[5] with effects seen in breast, melanoma, and lung cancer.[6-8] An article by Parker et al studied 4 cancer indications and trials utilizing biomarkers to create cancer therapies and observed that the use of biomarkers such as HER2 in breast cancer resulted in a 5-fold reduction in clinical trial risk.[9] However, biomarkers also introduce challenges such as increased trial complexity[10] and unknown patient outcomes for exploratory biomarkers.[11] An important aspect that has not yet been extensively explored is how biomarkers may affect timelines in oncology drug development. The objective of this study was to observe impacts of biomarker inclusion in a preliminary analysis of clinical trial timelines for 4 indications in oncology; these were metastatic breast cancer, metastatic colorectal cancer, metastatic melanoma, and non-small cell lung cancer. Ideally, the outputs of this research would allow parties involved in the clinical trial process to make informed decisions on which clinical trials would be worth pursuing, especially considering the extensive efforts required to conduct these trials.

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Improving our understanding of how biomarkers impact clinical trial development length could help us direct our effort toward trials that result in better patient outcomes sooner. Therefore, in this study, we examine trends in the distribution of clinical trials across time between clinical studies in oncology that use a biomarker and those that do not. We pay particular attention to the differences in duration of gaps between trial phases and when trials run most frequently throughout the clinical development process.

Materials and Methods

Study Eligibility

Methods used for analysis in this study draws upon similar methodology found in previously run studies assessing clinical trial success rates with respect to biomarker use.[6-9] Data pertaining to clinical trials for compounds designed to treat metastatic or locally advanced breast cancer, metastatic stages IIIb-IV non-small cell lung cancer (NSCLC), metastatic stage IV colorectal cancer (mCRC), and unresectable stages III and IV metastatic melanoma were collected from the National Institutes of Health clinical trials database (clinicaltrials.gov). Studies were excluded if their phase I began before 1998, did not treat outcomes related to survival, studied reformulations of already approved drugs, and if the study was not industry sponsored.

Search Criteria

Data collection involved the usage of search terms "metastatic breast cancer", "Non–small cell Lung Cancer", "metastatic colorectal cancer," and "metastatic melanoma" which were subsequently filtered to include interventional studies in phases I, II, and III. Studies were included if the compound has completed phase I studies between 1998 and 2020. These clinical trials were then classified for use of biomarkers in study criteria. If the study drug used any biomarker in its protocol to include or exclude patients' eligibility at any point in its clinical development (phases I-III), the drug was classified as having used a biomarker. We further classified biomarkers by type as either exploratory or validated biomarkers, based on their FDA approval status. Trials were classified as having used validated biomarkers if the biomarker was used at least 2 years after its FDA approval within each indication. All other biomarkers not approved by the FDA were considered exploratory, including their use in trials where the biomarker was first approved. Finally, for a trial to be included in the analysis, it had to have transitioned to a succeeding trial phase or have been completed, withdrawn, or terminated. Start dates and end dates were collected for the earliest trials using each compound as a monotherapy per indication.

Visualization

Using the aggregated clinical trial data, we constructed a heatmap that overlayed all the trials on a timeline for each of the 4 indications and for all 3 trial phases. This heatmap visualization displayed various levels of gray-scale saturation which directly reflected the number of trials run concurrently at each given point in time. In essence, when a proportionately high number of trials were running concurrently at a given point in time, the visualization would appear with higher saturation, and when fewer trials were running concurrently at a given point in time, the visualization would appear with a lower saturation. For each trial phase, the trial distribution was visualized on a timeline, with normalization applied such that the time scale was all relative to the start date of the first phase I trial in the indication, with the units of measurement being the number of months after this baseline (0). Because the number of trials differ between trial phases within each indication, we normalized them such that the gray-scale saturation was proportional to the highest number of trials run concurrently within each trial phase. This was to allow for comparisons to be made across trial phases pertaining to when most trials were run within each indication. Similarly, each indication had a different number of clinical trials, and so the saturation level was normalized in proportion to the highest number of trials run concurrently within each trial phase of each indication. An additional bar chart figure was created to capture comparisons between exploratory, validated, and non-biomarker trials with respect to average trial duration. As part of a separate analysis, biomarker type was also broken down into protein and genomic biomarker trials and compared with non-biomarker trials for average trial duration.

Given the reduction in risk of clinical trial failure in the 4 indications described in Parker et al,[9] we hypothesized that the use of biomarkers in the inclusion or exclusion criteria of clinical trials would also have an impact on the duration of clinical trials and would affect the length of time spent between consecutive phases of the trials (eg, gap between the end of a phase I trial and start of a phase II trial). To compare between the 2 biomarker groups, the heatmap visualization was supplemented with the average durations of each trial phase and time gap between the trial phases, stratified by biomarker use, indication and biomarker type. Finally, hazard ratios using cox proportional-hazards model were included to evaluate the time to clinical trial failure between biomarker trials and non-biomarker trials. These hazard ratios were calculated using the aggregate of trials that failed (ie, did not advance to the next trial phase or get approved in the case of phase III) against the time it took to reach this conclusion. These ratios were generated to see if there is any difference in the time it takes for a clinical trial to fail based on biomarker status.

Results

Using the search criteria described in the methods section, 8630 trials were screened across all 4 indications, 1224 of which were included in analysis. These trials were spread across 671 unique drugs; 322 (65 with biomarkers) indicated for NSCLC 177 (52 with biomarkers) for colorectal cancer, 89 (44 with biomarkers) for breast cancer and 83 (28 with biomarkers) for melanoma (Table 1). Across all 4 indications, average trial duration did not differ significantly between drugs that used a biomarker ("biomarker trials") and drugs that did not use a biomarker ("non-biomarker trials").

For NSCLC, breast cancer, and colorectal cancer trials (Figs. 1, 2, and 3), there was an overall trend for biomarker trials to be concentrated later (further to the right) in the clinical development timeline when compared to non-biomarker trials, relative to the baseline (ie, time from the start of the first phase I trial). For example, when comparing biomarker with non-biomarker trials in phase I NSCLC trials, saturation rose to a sustained peak 105 months after the baseline in non-biomarker trials whereas biomarker trials rose to their peak saturation later at 130 months after the baseline (Fig. 1). A similar trend was observed for both

Table 1. Clinical trial duration and gaps between trial phases.

Trial details and biomarker use	No. of drugs	Average duration of phase I trials, months	Average time gap between phase I and phase II trials, months	Average duration of phase II trials, months	Average time gap between phase II and phase III trials, months	Average duration of phase III trials, months
Breast (n = 89)						
No	45	38.42 (18.46)	−15.65 (37.27)	32.62 (19.7)	−25.19 (49.87)	44.83 (47.54)
Yes	44	35.16 (17.25)	−6.43 (29.2)	29.31 (16.67)	4.25 (35.12)	41.47 (17.18)
Colorectal (n = 177)						
No	125	51.17 (35.59)	−20.85 (64.96)	37 (27.13)	−21.64 (55.75)	49.33 (28.67)
Yes	52	49.81 (32.52)	−3.92 (46.07)	35.82 (22.44)	−22.04 (47.6)	66.74 (32.77)
Melanoma (n = 83)						
No	55	43.31 (32.25)	−23.97 (54.98)	35.44 (25.29)	−11.1 (76.09)	24.61 (10.39)
Yes	28	50.01 (28.4)	−14.99 (36.85)	29.54 (19.35)	−14.09 (22.85)	43.76 (35.07)
Non-small cell lung cancer (n = 322)						
No	257	40.48 (21.5)	−20.56 (37.82)	36.75 (21.77)	−9.41 (35.52)	40.64 (17.97)
Yes	65	41.35 (18.49)	−20.27 (50.03)	39.8 (21.53)	−12.26 (29.03)	37.05 (22.18)
All indications (n = 671)						
No	482	37.53 (27)	−17.85 (45.4)	30.22 (23.31)	−5.53 (43.64)	37.05 (22.79)
Yes	189	37.53 (24.34)	−12.58 (42.11)	29.47 (20.59)	−8.97 (33.2)	35.07 (26.21)

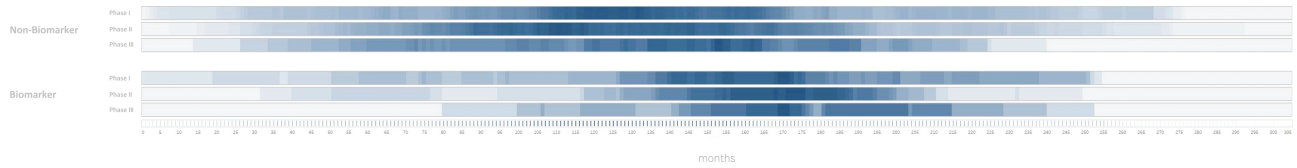

Figure 1. Clinical trial distribution over time for non-small cell lung cancer. Spots of high saturation indicates more concentrated trial activity (ie, higher number of trials run concurrently). The scale is measured in months after the first phase I trial in non-small cell lung cancer captured in the dataset, for each drug in question. Biomarker trials in this indication (bottom half) appear later than non-biomarker trials. There does not appear to be a gap between trial phases for either biomarker or non-biomarker trials.

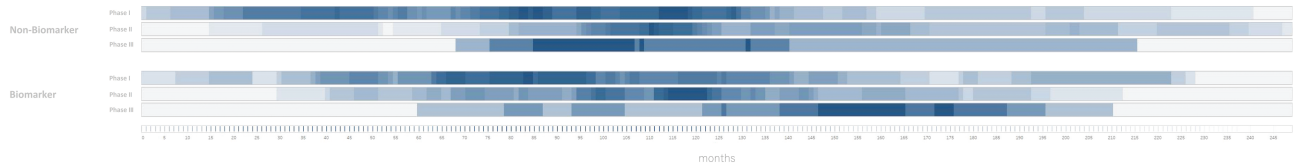

Figure 2. Clinical trial distribution over time for breast cancer. Similar to Fig. 1, higher saturation of color implies a greater sum of trials run concurrently and the scale is measured in months after the first phase I breast cancer trial. Biomarker trials appear around the same time as non-biomarker trials with respect to the first phase I breast cancer trial, with the exception of phase III. There appears to be a large gap between trial phases in the biomarker trials, but no gap between phases in the non-biomarker trials.

phase II and phase III trials, where biomarker trials appeared in greater frequencies later when compared to non-biomarker trials. Similarly, in phase III breast cancer trials, non-biomarker trials peaked 70 months after the first phase I trial (baseline) whereas biomarker trials peaked much later at 135 months after baseline. Colorectal cancer trials shared this same pattern in phase II, where non-biomarker trials peaked 110 months after baseline, compared to biomarker trials which peaked later after 130 months (Fig. 3). In contrast to the last 3 indications, melanoma presented a different pattern when comparing biomarker trials with non-biomarker trials peaks (Fig. 4). The overall trend in melanoma displayed biomarker trials concentrated earlier in the clinical development timeline (further to the left) in comparison to non-biomarker trials which presented in higher saturations later on in the last third of the timeline. Therefore, with melanoma as the exception, it appeared that biomarker use was associated with later clinical trials relative to baseline, with the effect most pronounced with NSCLC, followed by colorectal cancer, then breast cancer.

Another trend was observed in NSCLC and melanoma, where biomarker trials sustained peaks of high saturation for shorter periods of time than non-biomarker trials (with

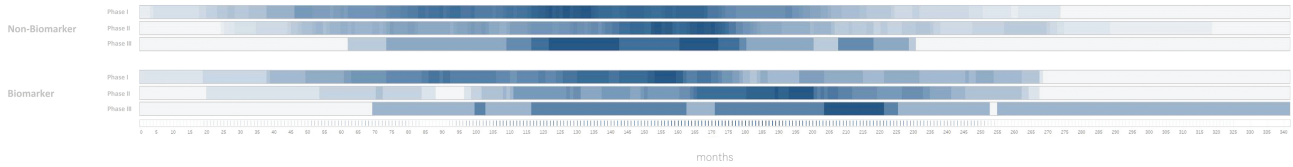

Figure 3. Clinical trial distribution over time for colorectal cancer heatmap timeline. Biomarker trials appear around the same time as non-biomarker trials with respect to the first phase I colorectal cancer trial. There appears to be a gap between trial phases in biomarker trials, but none for non-biomarker trials.

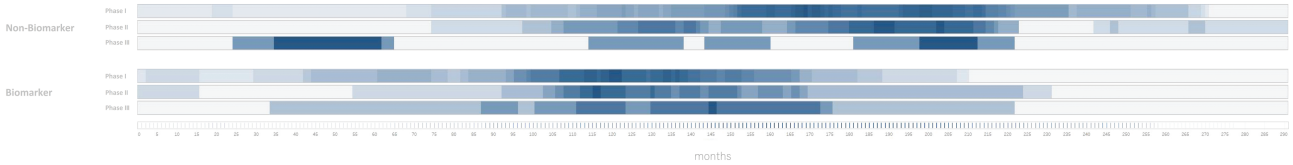

Figure 4. Clinical trial distribution over time for Melanoma. Biomarker trials appear earlier on in the clinical development timeline than non-biomarker trials. There does not appear to be a gap between trial phases in this indication for both biomarker and non-biomarker trials.

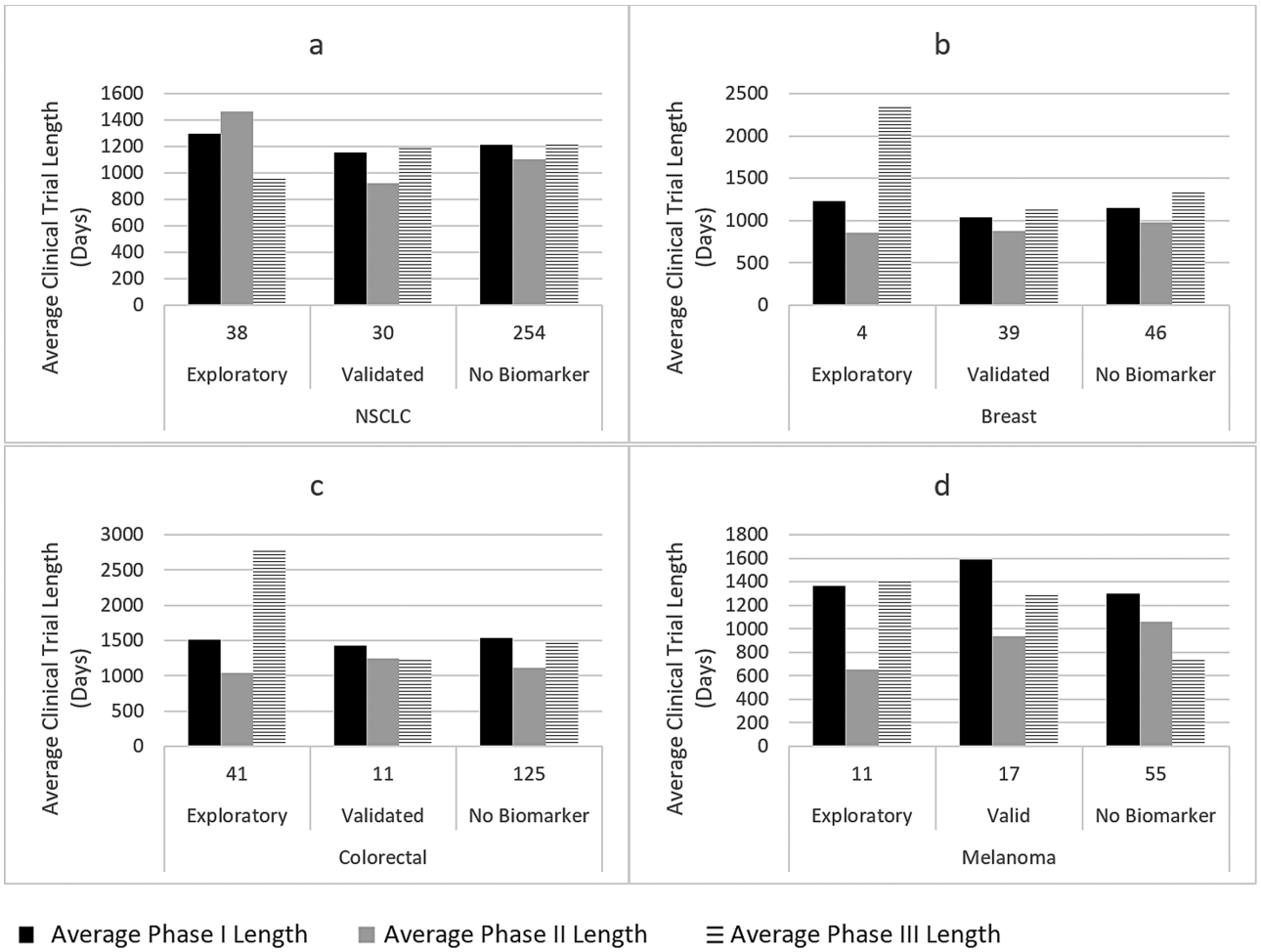

Figure 5. Average clinical trial duration stratified by biomarker type.

the exception of phase III for melanoma) (Figs. 1 and 4). Colorectal cancer and breast cancer did not share in this trend, and each trial phase appeared to peak for a comparable duration between biomarker and non-biomarker trials (Figs. 2 and 3). Despite this trend, biomarker trials finished earlier than non-biomarker trials in each respective phase for breast cancer. Lastly, another shared trend between colorectal cancer and breast cancer could be seen in the duration of gaps between trial phases. In both indications, biomarker trials displayed a distinct gap between trial phases in a staircase

pattern while non-biomarker trials seemed to have no clear gap (ie, trial phases were all overlapping). In breast cancer biomarker trials (Fig. 2), phase I trials reached peak saturation after 60 months, phase II peaked after 110 months, and phase III peaked after 145 months, illustrating distinct gaps. In melanoma and NSCLC, no such pattern was distinguishable in either biomarker or non-biomarker trials, with both groups having peak saturation overlap across each trial phase. In NSCLC for example (Fig. 1), phase III non-biomarker trials saturation peaked over a long time span from 60 to 195 months after baseline, which overlapped with phase II non-biomarker trials which peaked at 60 to 180 months after baseline (average gap –20.56 months, sd = 37.82). In comparison, phase III biomarker trials peaked at around 140 to 220 months after baseline, which also had significant overlap with phase II biomarker trials which peaked at 120 to 200 months after baseline (average gap –20.27 months, sd = 50.03).

When considering biomarker type (exploratory and validated), key differences in average trial duration were observed in phase II and phase III, but not in phase I. Across all 4 indications in phase I, exploratory and validated biomarkers were observed to have similar average trial duration to non-biomarker trials (Fig. 5a). However, in phase II, the presence of an exploratory biomarker corresponded with longer average trial duration in NSCLC (Fig. 5a) and shorter average trial duration in melanoma (Fig. 5d) compared to non-biomarker trials. In contrast, phase II trials using validated biomarkers did not display significant differences in average trial duration compared to non-biomarker trials. In phase III, trials with exploratory biomarkers had significantly longer average trial duration when compared to non-biomarker trials in breast cancer, colorectal cancer, and melanoma (Fig. 5b-d). This pattern is not visible for validated biomarkers, which typically had average trial duration comparable to non-biomarker trials (melanoma as the exception).

When stratifying biomarkers into protein and genomic categories, earlier trial phases did not differ much in trial length, with the most significant differences in trial length observed in phase III for each of the 4 indications (Fig. 6). Protein based, genomic, and non-biomarker trials did not differ in average trial length in phase I, with the exception of colorectal protein-based only and genomic only biomarker cancer trials which were slightly longer on average than genomic biomarker only trials (Fig. 6c). Similarly, in phase II, there is no significant difference in average trial length between the biomarker categories except for colorectal where protein-based only biomarker trials were the shortest compared to genomic and non-biomarker trials. Biomarker type in phase III was observed to be much more varied; protein-based only biomarker trials were much shorter on average than genomic only and non-biomarker trials in both NSCLC (Fig. 6a) and breast cancer (Fig. 6b). In contrast, phase III protein-based biomarker trials in colorectal cancer and melanoma were longer than genomic only and non-biomarker trials (Fig. 6c,d).

Three hazard ratio values were calculated using the Cox proportional-hazards model for each corresponding trial phase across all 4 indications. Of the 3 trial phases, there appears to be the most marked difference in the time to clinical trial failure in phase III trials; about half as many biomarker trials failed at a given point in time compared to non-biomarker trials (HR = 0.50, 95% [CI]; 0.29 to 0.87; $P < .05$). For phase I trials, there seems to be no impact of biomarkers on the time to failure (HR = 1.06, 95% [CI]; 0.52 to 2.15; $P = .88$). Similarly, the hazard ratio for clinical trial failure for phase II was not statistically significant (HR = 0.77, 95% [CI]; 0.42 to 1.40; $P = .41$).

Discussion

While the use of biomarkers has generated higher rates of success in cancer drug approval,[6-9] visualizing clinical trial distribution over time revealed the patterns and impact of biomarker use in clinical trial development duration and timing. This study explored how the presence of biomarkers in clinical trials affected clinical trial development timelines. Though the indications explored showed different distributions of trials across time, we were able to identify patterns between the biomarker and non-biomarker trials that persisted across them. Firstly, differences between the 2 groups could be identified in the duration of gaps between trial phases, where we found that biomarkers increased the length of time between trials for colorectal and breast cancer. Secondly, by looking at the duration of peaks in saturation when clinical trials take place in the timeline, we found that clinical trials that used biomarkers were concentrated over shorter periods of time in NSCLC and melanoma. Additionally, we found drugs that used biomarkers had trials concentrated later in the timeline than those that did not. Furthermore, biomarker type may have an impact on trial duration; exploratory biomarker trials had longer trial length than valid and non-biomarker trials in phase III for breast cancer, colorectal cancer, and melanoma. Through further stratification of biomarker type, we also found that protein-based biomarker trials may benefit from increased speed over genomic or non-biomarker trials for breast cancer and NSCLC. Finally, in the hazard ratio analysis, we determined that there may be reduced risk of clinical trial failure at any given point in time for biomarker trials compared to non-biomarker trials.

Our analysis revealed that there are discernable patterns and trends that imply biomarkers have an impact on increasing the duration of time spent between trial phases. In the breast cancer (Fig. 2) and colorectal cancer (Fig. 3) biomarker trials, we observed a descending staircase pattern with the gaps between phases, with each succeeding trial phase peaking some time after the preceding one, whereas non-biomarker trials seemed to have little or no gap. This implies that in the aggregate, relative to the first phase I trial for each of the 2 indications, that biomarkers appeared to lengthen the gaps between trial phases for these breast and colorectal indications. This trend is surprising because biomarker use in these 2 indications had differing effects on clinical trials in previous studies; colorectal cancer saw no effect of biomarkers in clinical trial failure rates whereas breast cancer improved.[6] Despite those findings, the trend here displayed (Figs. 2 and 3) an effect of biomarkers for both indications in the form of longer gaps between trial phases, implying slower speed. Furthermore, despite breast cancer's reduced clinical trial failure risk from the use of biomarkers,[6,9] this observed trend implies that this came at the cost of reduced clinical development speed driven by longer gaps between trial phases. It is plausible that this cost of using biomarkers is present in breast cancer because there is a lack of variety of biomarkers used in this indication; the use of biomarkers is dominated by HER2 as a predictor of aggressive disease.[12-14] In contrast to breast cancer and colorectal cancer, there does not appear to be a discernable difference in the gaps between

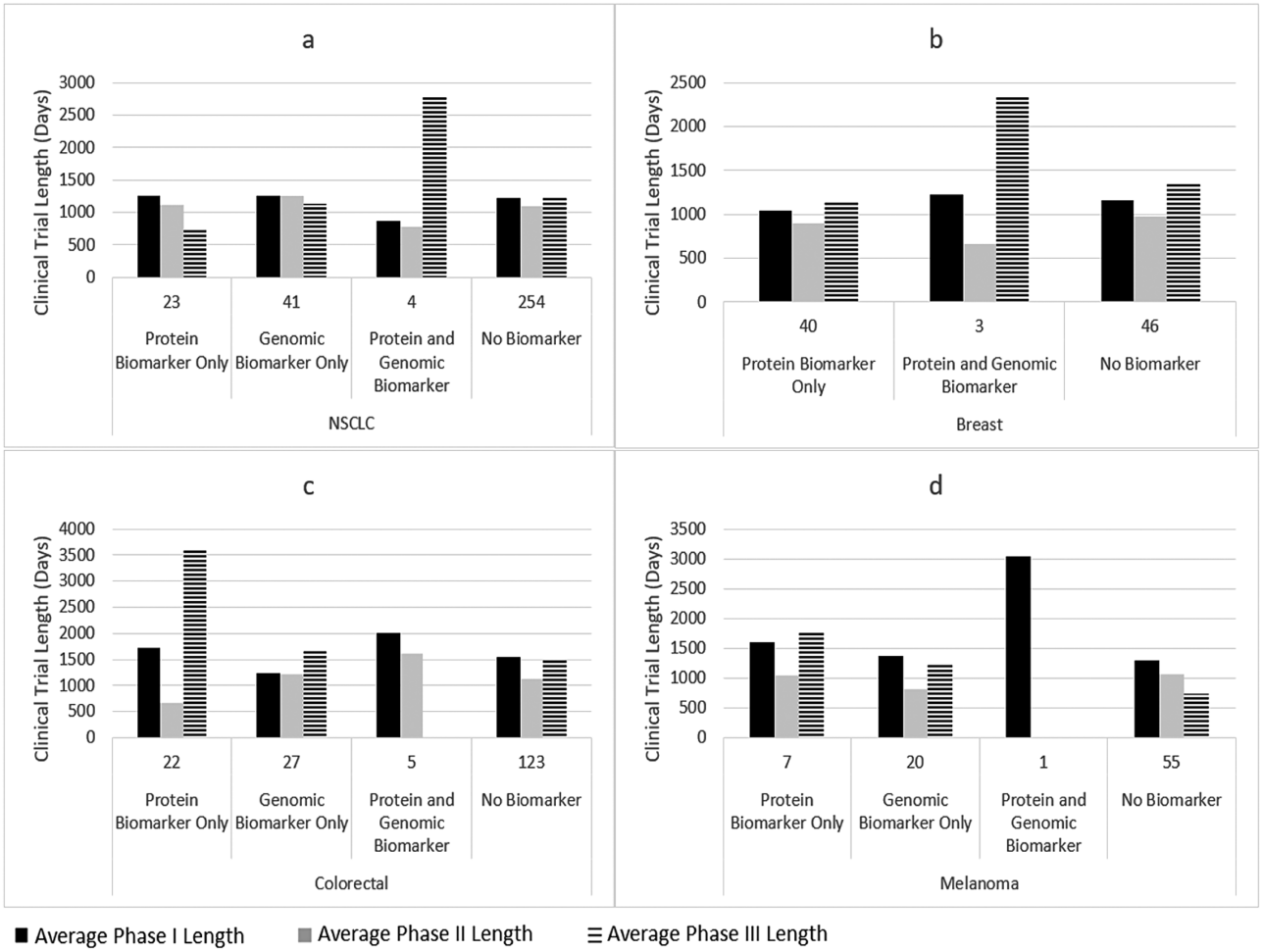

Figure 6. Average clinical trial duration stratified by biomarker classification.

trial phases between biomarker and non-biomarker trials in melanoma and NSCLC. In both indications, the gaps between trial phases appear to be short irrespective of biomarker use.

Another important observation is that the duration of peaks in saturation varied between biomarker and non-biomarker trials. The biomarker trials remained at a peak for a shorter time than the non-biomarker trials for NSCLC and melanoma, but not for colorectal cancer and breast cancer. The reason for this is unclear; however, it could imply biomarker trials were more likely to run concurrently and end around the same time across similar families of drugs compared to non-biomarker trials which may have been more staggered in the latter 2 indications. This is perhaps not surprising, as the introduction of new biomarkers to clinical trials may drive certain classes of drugs to be explored and studied in waves, such as with the advent of biomarker trials involving CTLA4 in melanoma.[15]

Biomarker trials appeared to be positioned and concentrated later in the timeline than non-biomarker trials. For NSCLC (Fig. 1), breast cancer (Fig. 2) and colorectal cancer (Fig. 3), there appeared to be a delay in the presence of peaks for biomarker (concentrated in middle to right) trials compared to non-biomarker trials (concentrated in middle to left) in all 3 trial phases. A possible explanation for this is that as new biomarkers were validated or discovered, more trials were designed to stratify patient populations for better outcomes. Interestingly, melanoma did not share this trend, which may have been due to its identification as an atypically immunogenic cancer prior to the other 3 indications.[16] This may have led to biomarkers being used earlier and in higher frequency in melanoma since it was well characterized for immunotherapy.

Further insights on the effects of biomarkers on clinical trial duration were illuminated in the stratification of biomarker type. While it was difficult to detect any significant differences in trial duration between all biomarker trials and non-biomarker trials, distinguishing between exploratory and validated biomarkers revealed that average trial duration was longer for exploratory biomarker trials in phase II for NSCLC and in phase III for breast cancer, colorectal cancer, and melanoma (relative to non-biomarker trials) (Fig. 5). Since this trend was not visible for validated biomarkers (except for melanoma), it is likely that there could be some risk of reduced speed in using biomarkers that are not yet validated. This may be because many exploratory biomarkers may not be regularly tested at clinical trial research sites, which may affect the ability of clinicians to screen and enroll patients, increasing the time it takes for completion. This is as opposed to validated biomarkers, which may be part of regular screening, which may explain why there is little difference in average trial duration between validated biomarker trials and non-biomarker trials. This analysis suggests clinicians would benefit from faster screening and subsequent treatment for patients in biomarker trials that use

validated rather than exploratory biomarkers for NSCLC, colorectal, and breast cancers.

Stratifying biomarkers into protein-based and genomic categories revealed potentially interesting implications of biomarker type on clinical trial length, specifically in later trial phases. Protein-based only biomarker trials appear to have shorter average phase III clinical trial length than trials with genomic biomarkers included and non-biomarker trials; however, this effect is only pronounced for NSCLC and breast cancer (Fig. 6a,b). In stark contrast, colorectal and melanoma trials with protein-based biomarkers appear to suffer the opposite effect, with longer phase III trials compared to genomic and non-biomarker trials. This suggests that there may be a difference in the characterization of biomarkers across indication. For instance, the prevalence of a narrower range of biomarkers such HER2 in breast cancer[12] may potentially confer an advantage in clinical trial speed when compared to an indication like colorectal cancer which has many more exploratory biomarkers. This distinction is unclear, however, as NSCLC also has a significantly varied array of exploratory and validated biomarkers while also sharing shorter phase III protein-based biomarker trial length. As such, further research is required to identify whether there is a significant difference is trial length based on biomarker type.

With regards to the hazard ratio analysis, the most notable difference in the time to clinical trial failure risk was for phase III trials. Across all 3 indications, biomarker trials were half as likely to have failed at any given point in time compared to non-biomarker trials (HR = 0.50, 95% [CI]; 0.29 to 0.87; $P < .05$). This is interesting because despite there being no significant difference in phase III trial length (Table 1), biomarker trials that fail take longer to do so. This effect was not observed in phase I or II trials; this may be the case for a couple reasons. Firstly, phase I trials primarily focus on safety endpoints, which biomarkers may be less of a factor in influencing. Additionally, biomarkers are often introduced in trials during later trial phases,[11] and so they may not play a part in advancing the trial to the next trial phase. Phase III trials, however, require more scrutiny to determine safety and efficacy of the treatment to their corresponding patient population. As personalized medicine using predictive biomarkers is the new paradigm in modern oncology treatment methods,[10] perhaps the unmet clinical need for personalized cancer treatments is significant enough to warrant deeper analyses for biomarker trials before the drug is determined to be a failure.

This study has limitations which are shared with previous research using the same methodology.[6-9,11] Firstly, our biomarker classification was done by each drug as a whole rather than by the exact trial phase a biomarker was introduced. In other words, we used a binary classification where all trials would be classified as having used a biomarker if the drug had used a biomarker in any phase. This was done to include all possible effects of the intention to use biomarkers, especially since most phase I trials have multiple cancer indications and rarely use biomarkers. Limitations for this study can also be found in the data source, clinicaltrials.gov. An article by Stergiopoulos et al,[17] evaluated the completeness of clinicaltrials.gov and the results of this study showed that as of January 2017, Trialtrove captured 31% more clinical trials (10 786 trials) in selected disease indications, than ClinicalTrials.gov (7419 trials). Thus, we acknowledge the limitations of using this database to create our dataset.

Overall, we were able to determine through our novel visualization method that biomarker use in clinical trials affects the distribution of trials over time differentially by indication, namely in gaps between trial phases and in the duration of peaks in clinical trial activity (concurrent trials). This discovery suggests that the impact of the use of biomarkers on clinical trial duration and speed is indication specific. That is, using a biomarker in colorectal cancer trials may potentially be unfavorable, as there is a chance of a longer gap between trial phases, reducing its speed, and no clear reduction of risk of clinical trial failure. On the contrary, biomarker use in trials for melanoma and non-small cell lung cancer could be favorable, as the risk of clinical trial failure would be lowered[9] and there is potentially no negative impact on duration of gaps between trial phases. Therefore, clinicians deciding on clinical trial participation need to consider whether the indication under consideration risks facing potential delays when biomarkers are included.

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Conflict of Interest

Luqmaan Mohamed: Roche (E); **Gilberto Lopes**: Pfizer, Merck and Serono (C/A, RF); **Jayson Parker** (C/A). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board.

Author Contributions

Conception/design: J.P., D.N., G.L. Provision of study material/patients: S.M., L.M. Collection and/or assembly of data: S.M., L.M. Data analysis and interpretation: J.P., S.M., L.M., D.N. Manuscript writing: L.M., J.P., D.N. Final approval of manuscript: All authors.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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