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The role of biomarkers in clinical endpoint success

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Summary

Nearly half of all clinical trials now employ some type of biomarker, but little has been reported on the correlation of the number of biomarkers used or the role of the biomarker on achieving the clinical trial endpoints. We aimed to understand the association between trial endpoint success, trial phase and the influence of different biomarker roles. Using a global dataset of 4,450 phase I to phase IV trials that includes specific indexing for biomarker strategy and trial outcomes, we found a correlation between the average number of biomarkers employed and reported trial outcomes. We also observed that those that employed a toxicity marker were more likely to be successful while those that used a disease marker were less likely. While this cohort is small it is still significant enough to show that correlation of the types and number of biomarkers used can be correlated to endpoint success. These points should be considered when developing clinical trial protocols.

Key words: Biomarker – Clinical trial – Endpoints

Introduction

The increased use of biomarkers in clinical trials is well documented (1), with nearly half of all clinical trials now employing some type of biomarker. However, little has been reported on the correlation of the number of biomarkers employed or the role of the biomarker on achieving clinical trial endpoint. Specifically, we wanted to understand the association between trial endpoint success, trial phase and the influence of different biomarker roles. While previous studies have looked at phase transition as a measure of biomarker utility (2, 3), we chose endpoint success since it takes into account situations where a trial may reach the desired outcomes of efficacy and safety yet not move to the next phase of trials due to strategy decisions, lack of robust differentiation to standard of care, or inability to compete to be first or best in market.

In this analysis we compared the reported success of trials as measured by a definitive statement from the sponsors that the endpoints measured were met and the use of a biomarker. Using the data in Clarivate Analytics *Cortellis Clinical Trials Intelligence* (CTI) over the previous 10 years, we identified a cohort of 4,450 phase I through phase IV trials for which an explicit statement, identified in a variety of company and scientific publications from the sponsor, indicated either a positive or negative result in respect to the desired clinical endpoints.

Within the cohort of trial records we observed 3,459 (76%) of trials in the cohort were reported with a positive endpoint outcome, while 1,091 (24%) were explicitly reported with a negative endpoint outcome. Numerous studies have shown success rates as measured by phase transition are significantly lower than represented in this cohort (2, 3). This may indicate a bias by sponsors to reporting only positive results, and therefore the results of any study measuring trial outcomes to biomarkers must be looked at with that in mind, similar to reports by others (3).

Number of Biomarkers and Endpoint Success

Our analysis suggested there is a correlation between the average number of biomarkers employed for a given trial and reported trial outcomes for phases II-IV. As shown in Table I for phase II trials that did not meet the intended endpoint, only 2.5 biomarkers on average were employed. For those phase II trials reaching their endpoint, an average of 3.0 biomarkers were used. This pattern is even more pronounced for phase III trials where those with endpoints not met reported an average of 2.6 biomarkers and those which

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Table I. *The average number of biomarkers used in each phase of clinical trials as a function of endpoint.*

Phase	I	II	III	IV
Average endpoints met	1.4	3.0	4.3	2.5
Average endpoints not met	2.3	2.5	2.6	1.9

achieved endpoints employed an average of 4.3 biomarkers. Similar results are seen in phase IV trials although the difference is much smaller.

Phase I trials exhibited a reverse correlation in that the more biomarkers employed the less the chance of achieving endpoints (Fig. 1). The small number of data points compared to phases II and III may help explain the trend as phase I studies employ biomarkers at a much lower rate than phase II and III trials (4).

Biomarker Role and Endpoint Success

When applying biomarkers it is typical to categorize them into three main biomarker roles: disease, efficacy and toxicity. Disease markers are used if a disease already exists (diagnostic biomarker), or predict how a disease may develop in an individual case regardless of the type of treatment (prognostic biomarker). Efficacy biomarkers provide an indication of the probable effect of treatment on the patient, and toxicity biomarkers indicate a treatment-related adverse reaction. Our cohort of trials included 11% with disease markers, 51% with efficacy markers and 18% with toxicity markers. Some studies may have been counted multiple times if more than one biomarker role was employed in those studies.

We set out to understand the role of the biomarker in predicting endpoint success (Fig. 2). We plotted the type of biomarkers used in the trial in decreasing order of percent of trials successfully meeting endpoint using a particular combination of biomarkers (Fig. 2). All of the three categories most associated with trial endpoint success (left side of graph) employed a toxicity marker, while all of the lowest associated categories employed a disease marker. Efficacy biomarkers correlated with higher percentages of endpoints met but to a lesser degree than toxicity biomarkers.

Conclusions

As with all retrospective analyses, the more data that can be incorporated, the greater the confidence in the conclusions. While the number of trials in this cohort is small it is still significant enough to show that correlation of the types and number of biomarkers used can be correlated to endpoint success. These points should be considered when developing clinical trial protocols.

Disclosures

The author is an employee of Clarivate Analytics.

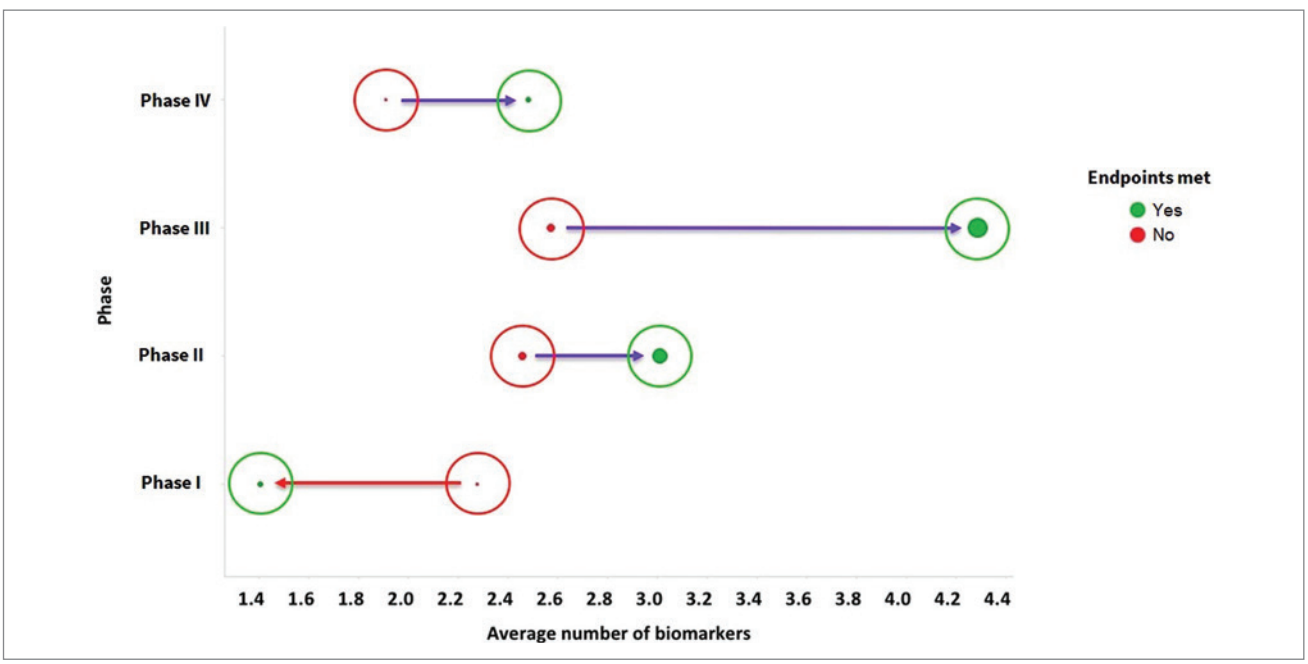

Figure 1. The average number of biomarkers used as a function of phase. The points represent the average number of biomarkers used when endpoints were achieved (green) or not achieved (red). The size of the circle represents the number of trials in the cohort.

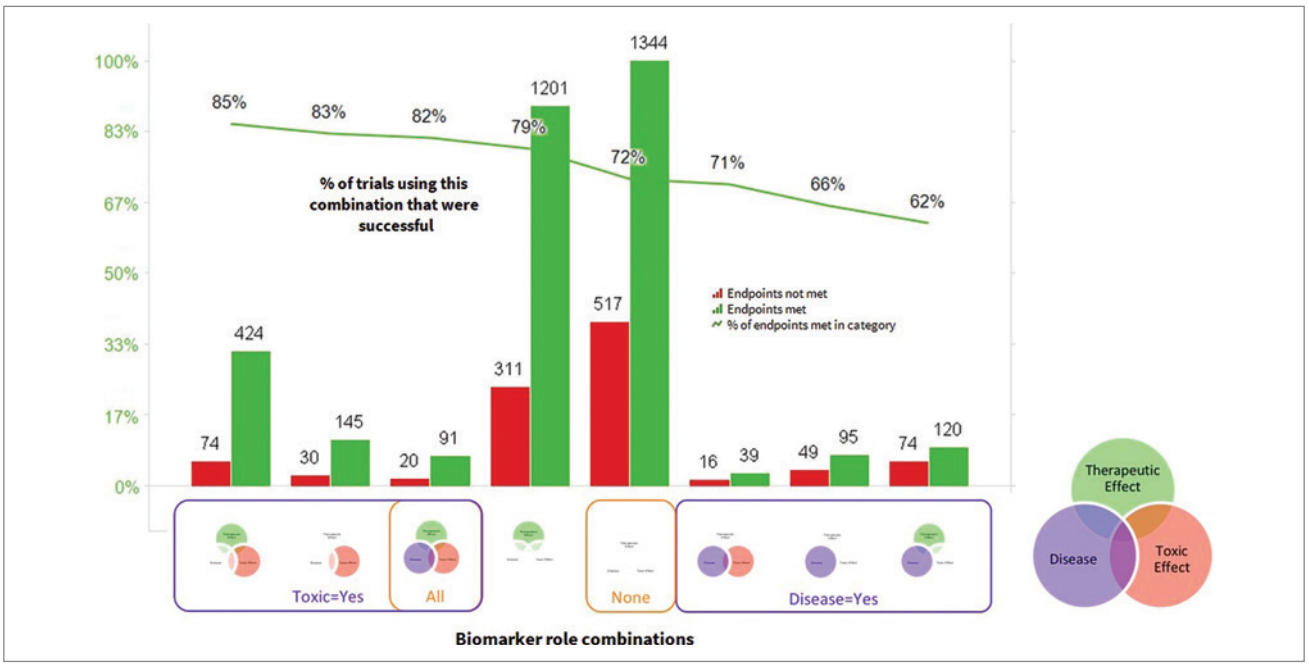

Figure 2. The role of the biomarker as a function of trial success. In the figure the number of trials reaching (green) or not reaching (red) endpoint are plotted as a function of the type of biomarker, either toxicity (orange circle), efficacy (green circle) or disease (purple circle).

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