

## Inefficiencies in phase II to phase III transition impeding successful drug development in glioblastoma

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### Abstract

**Background.** Improving outcomes of patients with glioblastoma (GBM) represents a significant challenge in neuro-oncology. We undertook a systematic review of key parameters of phase II and III trials in GBM to identify and quantify the impact of trial design on this phenomenon.

**Methods.** Studies between 2005 and 2019 inclusive were identified through MEDLINE search and manual bibliography searches. Phase II studies (P2T) were restricted to those referenced by the corresponding phase III trials (P3T). Clinical and statistical characteristics were extracted. For each P3T, corresponding P2T data was “optimally matched,” where same drug was used in similar schedule and similar population; “suboptimally matched” if dis-similar schedule and/or treatment setting; or “lacking.” Phase II/III transition data were compared by Pearson Correlation, Fisher’s exact or chi-square testing.

**Results.** Of 20 P3Ts identified, 6 (30%) lacked phase II data. Of the remaining 14 P3T, 9 had 1 prior P2T, 4 had 2 P2T, and 1 had 3 P2T, for a total of 20 P3T-P2T pairs (called dyads). The 13 “optimally matched” dyads showed strong concordance for mPFS ( $r^2 = 0.95$ ,  $P < .01$ ) and mOS ( $r^2 = 0.84$ ,  $P < .01$ ), while 7 “suboptimally matched” dyads did not ( $P > .05$ ). Overall, 7 P3Ts underwent an ideal transition from P2T to P3T. “Newly diagnosed” P2Ts with mPFS < 14 months and/or mOS < 22 months had subsequent negative P3Ts. “Recurrent” P2Ts with mPFS < 6 months and mOS < 12 months also had negative P3Ts.

**Conclusion.** Our findings highlight the critical role of optimally designed phase II trials in informing drug development for GBM.

### Key Points

- Optimal use of phase II data may reduce chances of failure in subsequent phase III studies.
- Inappropriate utilization or a lack of phase II data appears to contribute to phase III failure.
- Only 35% of phase III trials in our review transitioned from phase II to III in an optimal manner.

Improving the outcomes of patients with glioblastoma (GBM) represents one of the most significant challenges in neuro-oncology. Since the landmark publication involving

chemoradiotherapy followed by adjuvant chemotherapy using oral Temozolomide in 2005,<sup>1</sup> there has been only one phase III trial that has demonstrated a modest overall survival (OS)

## Importance of the Study

Our systematic review found some recurrent problems that may contribute to the near universal failure of drugs entering GBM phase III trials since 2005. Only 35% transitioned from phase II to phase III testing in an optimal manner. In the remaining 65%, we found an absence of supportive phase II data, or a lack of their utilization in a rigorous manner. We did not find significant biases with phase II data, which correlated well with subsequent results

in phase III studies. We found thresholds for efficacy in the phase II setting that could be reliably be used to make a Go/No-Go decision. Thereafter, should a “Go” decision be made, our data points to some cautions about how to utilize the phase II data in designing the subsequent phase III design. This may increase the chances of finding efficacious drugs and reduce the human and financial cost of unsuccessful phase III trials.

benefit.<sup>2</sup> Indeed, most patients succumb to the disease within 2 years of diagnosis, and the OS of GBM patients has not improved substantially in the last 3 decades.<sup>2,3</sup> This is despite a better understanding of fundamental molecular pathology and improved imaging techniques. These sobering results in GBM are in marked contrast to survival improvements gained in most other solid organ malignancies.<sup>4,5</sup>

Several factors may contribute to this lack of progress in the treatment of GBM. Anecdotally, we have observed inefficiencies in the availability and use of phase II data when planning phase III studies with others also providing descriptive data on this phenomenon.<sup>6</sup> Such inefficiencies may result in patients being exposed to ineffective drugs in large phase III trials designed with missing or suboptimal data. Conversely, efficacious drugs may not be approved due to underpowered phase III studies. Here, we undertook a detailed review of key design parameters of phase II and III trials in GBM to identify and quantify the impact of this phenomenon. This may inform future neuro-oncology trials to reduce unnecessary patient exposure to ineffective drugs while improving patient outcomes.

## Methods

We performed a MEDLINE search for phase III clinical trials in GBM from January 2005 to August 2019. Our search strategy included the Medical Subject Headings (MeSH) “Glioblastoma,” “Clinical Trial, Phase III,” and “Clinical trial, Controlled Clinical Trial,” including all relevant subheadings. We also used keyword searches for “astrocytoma,” “grade IV,” “glioblastoma,” or “glioma.” Key inclusion criteria were studies with a prespecified statistical methodology that examined outcomes of novel drugs or devices in adult patients with GBM and have mature results published. Studies were excluded if they enrolled patients with other glioma subtypes, used radiotherapy as a primary intervention, or did not provide a full description of statistical methods used. Data from eligible studies were extracted using a prespecified template by 2 authors (A.B. and A.G.). Baseline data collected included patient demographics, sponsor information, tumor molecular characteristics, and drug class of investigational product. Trial characteristics

collected included the year of publication, treatment line (first line or recurrent), treatment schedule, funding source, investigator group, primary endpoint(s), gain expected for superiority designs (hazard ratio and absolute), statistical design characteristics (including alpha, beta values, and sample size calculations), the number of patients screened, enrolled, patient attributes, response criteria utilized, and patient outcomes (including OS, progression-free survival (PFS), and response by both local and central review if relevant). Where applicable, study design characteristics were also retrieved from the trial’s relevant registration website. A phase III trial was considered successful if it met all conditions of its prespecified expected endpoints.

The corresponding phase II trials used to determine the clinical and statistical rationale for the design of the phase III trial selected in this study were subsequently identified by a bibliography search based on the final publication of the phase III trial. If the phase III trial did not reference a phase II study, we also performed a secondary search of the MEDLINE database, again by 2 authors (A.B. and A.G.). Our search strategy was limited to phase II trials from the same time period. We included the MeSH terms “Glioblastoma,” “Clinical Trial, Phase II” - and combined them with the keywords as described for phase III search strategy. We also searched for trials using drug names as keywords. Data from phase II studies were extracted with a phase II extraction template that comprised the same data elements as the phase III template. Phase II trials from our secondary search were only included in our analysis if they were completed recruitment prior to the stated date of commencement of the phase III study on the basis that it would be unlikely/inadvisable that data from an incompletely study would be used as the basis of a phase III study.

Phase II trials were categorized as “optimally matched” with their phase II counterpart if they satisfied all of the following criteria: (a) exclusively recruited patients with GBM, (b) recruited patients in the same line of treatment (first line or recurrent) as their corresponding phase III trial, and (c) utilized the same drug/device (or combination) in a similar schedule as their corresponding phase III study. Regimens classified as having “similar schedules” included those with the same drug/device (either alone or in the same combination), in the same line of treatment. Dosing variance of up to 50% for the investigational product was allowed between optimally matched phase II and III trials.

Identified phase II trials that did not satisfy all 3 of these criteria were classified as “suboptimally matched.” For analysis of how data was utilized in the progression from phase II data to phase III planning, we restricted phase II trials to those referenced by the corresponding phase III study, given these phase II trials informed the trial design of the subsequent phase III study according to CONSORT guidelines.<sup>7</sup> Where a phase III trial had more than one relevant phase II trial, each pairing (or dyad) was considered unique and analyzed as such.

### Statistical Analysis

Quantitative and descriptive statistical analysis was performed using SPSS version 22.0. Regression analysis was performed using Pearson correlation to determine the concordance of survival outcomes between phase III and corresponding phase II trials. Categorical variables were compared with chi-square analysis or Fisher’s exact tests where appropriate.

For the analysis of progression from phase II to phase III, the percentage difference between the expected value of the primary endpoint in the experimental arm of the phase III study and the value of the same variable in the phase II study was determined. If the absolute value for the experimental arm was unavailable from the phase III manuscript, we calculated this number by dividing the expected HR for the experimental arm into the prespecified expected value for the control group. The percentage difference was calculated as follows:

$$\text{Percentage difference (\%)} = \frac{\text{Value in phase III study minus value in phase II study}}{\text{Value in phase II study}} \times 100$$

If the same values were used in both the phase II and III studies, then the percentage difference would be zero (eg, the median survival in the phase II study was 30 months and the phase III study was designed with the expectation that the survival with that same treatment would be 30 months, the percentage difference would be zero). A positive difference would indicate that the phase III study was designed with the expectation of a larger benefit than had been seen with the same experimental agent in the preceding phase II study (eg, the median survival in the phase II study was 30 months and the phase III study was designed with the expectation that survival with the same treatment would be 45 months, with a difference of 15 months; the percentage difference would be + 50%). A negative difference would indicate that the phase III study was designed with the expectation of a more conservative benefit than had been seen with the same experimental agent in the phase II study (eg, the median benefit in the phase II study was 30 months and the phase III study was designed with the expectation that survival with the same treatment would be 27 months, with a percentage difference of 10%). Where there were PFS and OS co-primary endpoints used for the phase III study, we preferentially examined OS values.

Phase III trials that (a) optimally matched phase II trials, (b) where the phase II results met their predefined target

for efficacy, and (3) utilized a value for expected benefit in the phase III study that was reasonably concordant with that of the preceding phase II study (ie, <5% greater than outcome derived from phase II) were classified as those with “ideal transition.”

## Results

### Characteristics of Phase III Trials

A total of 210 phase III trials were identified using our systematic search strategy. Of these, 182 (87%) phase III trials were excluded as they were secondary analyses and/or early phase trials. A further 8 studies were excluded, as they did not meet this study prespecified criteria. In total, 20 eligible phase III trials were identified and included in the analysis (Table 1, Supplementary Table S1, and Figure 1).<sup>1–3,8–24</sup> Of these 20 eligible studies, 14 (70%) were in the first-line setting and 6 (40%) were in patients with recurrent GBMs. Twelve (60%) were conducted in Europe, 6 (30%) in Northern America, and 2 (10%) in the Asia-Pacific region. Half were industry sponsored, and the remainder was by academic/co-operative groups. There were 6 (30%)

**Table 1.** Trial Characteristics

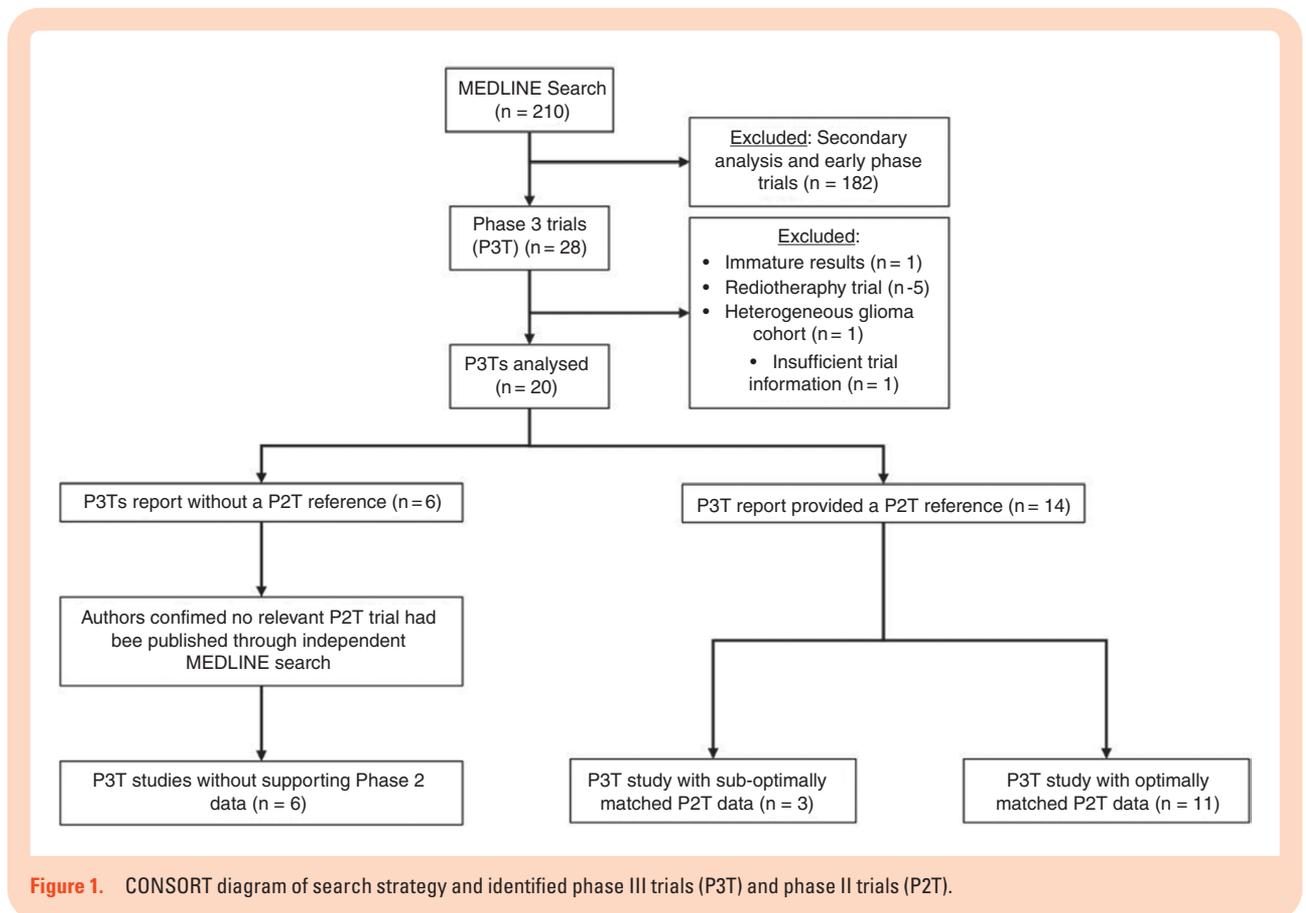
	Phase III Trials (total of 8928 patients) N of Studies (% of studies)	Phase II Trials (total of 996 patients) N of Studies (% of studies)
First line	14 (70%)	13 (68.4%)
Recurrent	6 (30%)	6 (31.6%)
Biomarker enriched		
MGMT methylated	2 (10%)	3 (15.8%)
EGFRvIII	1 (5%)	3 (15.8%)
Age	1 (5%)	1 (5.3%)
Sponsor description		
Industry led	10 (50%)	3 (15.8%)
Co-operative group led	9 (45%)	12 (63.2%)
Not stated	1 (5%)	4 (21.1%)
Region		
European	11 (60%)	6 (31.6%)
North American	6 (30%)	12 (63.2%)
Asia Pacific	2 (10%)	1 (5.3%)
Primary Endpoint		
OS	11 (55%)	4 (21.1%)
PFS	6 (30%)	7 (36.8%)
Co-primary	2 (10%)	1 (5.3%)
RR	0 (0%)	2 (10.5%)
Other	1 (5%)	3 (15.8%)
Not stated	0 (0%)	2 (10.5%)

OS, overall survival; PFS, progression-free survival; RR, response rate.

**Table 2.** Median Outcomes for Survival in the Intervention Arms, Across Phase III Trials (P3Ts) and Phase II Trials (P2Ts) in Biomarker Unselected (age/MGMT status) and MGMT Methylated Populations

Outcome	Biomarker Unselected		MGMT Methylated	
	P3Ts	P2Ts	P3Ts	P2Ts
First-line mOS	16.8 months ( <i>n</i> = 11, range 11.0–28.4 months)	17.4 months ( <i>n</i> = 13, range 8.4–23.1 months)	37.2 months ( <i>n</i> = 2, range 26.3–48.1 months)	30.0 months ( <i>n</i> = 3, range 23.2–34.3 months)
First-line mPFS	7.3 months ( <i>n</i> = 10, range 4–10.7 months)	9.5 months ( <i>n</i> = 9, range 5.9–13.6 months)	15.1 months ( <i>n</i> = 2, range 13.5–16.7 months)	16.2 months ( <i>n</i> = 2, range 13.4–19 months)
Recurrent setting mOS	7.3 months ( <i>n</i> = 6, range 4.8–9.1 months)	8.3 months ( <i>n</i> = 6, range 4.4–12.0 months)	N/A	N/A
Recurrent setting mPFS	2.2 months ( <i>n</i> = 5, range 1.4–4.2 months)	3.6 months ( <i>n</i> = 6, range 1.3–5.6 months)	N/A	N/A

OS, overall survival; PFS, progression-free survival.



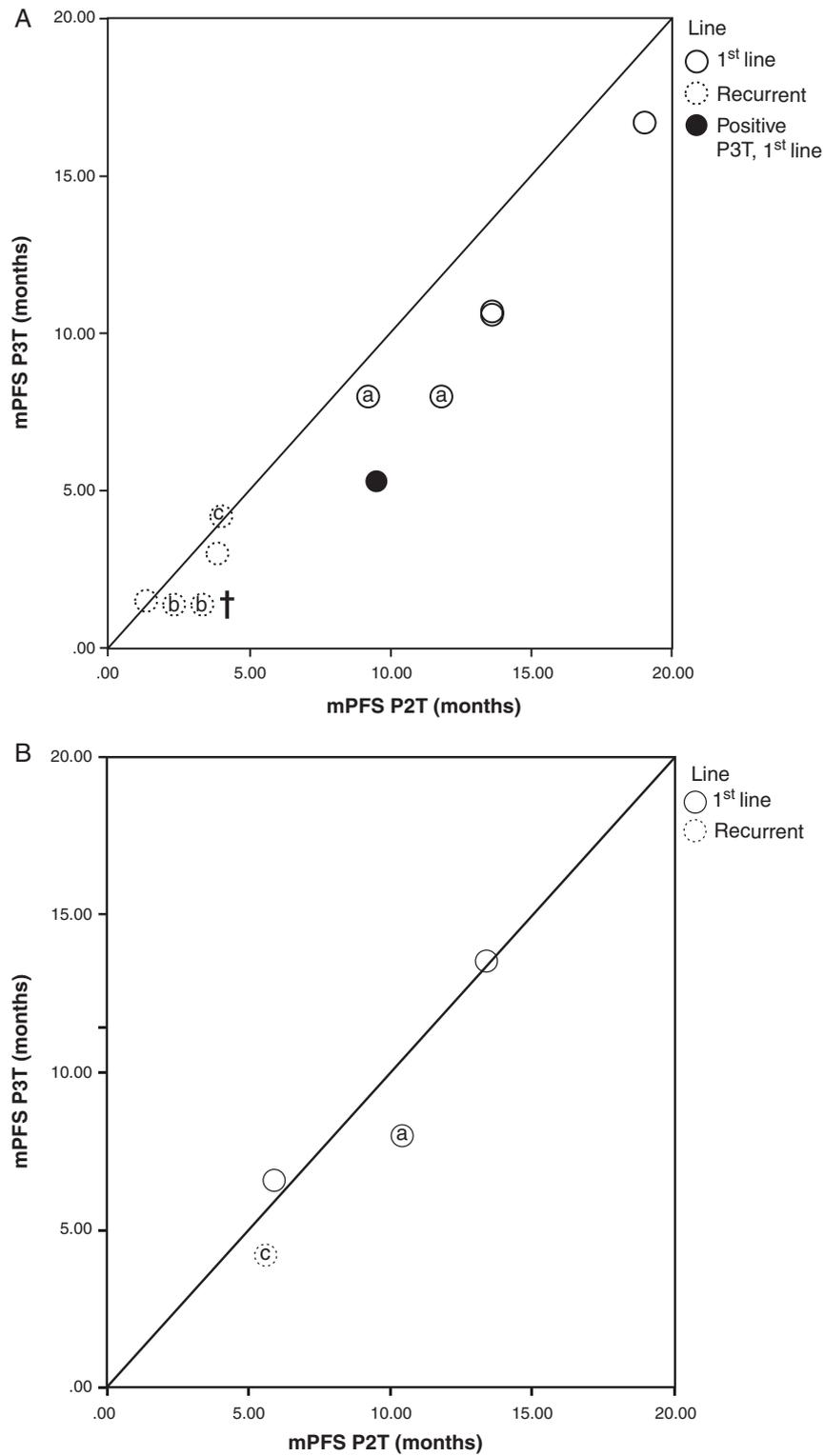
**Figure 1.** CONSORT diagram of search strategy and identified phase III trials (P3T) and phase II trials (P2T).

studies with investigational anti-angiogenic agents. The median values for PFS (mPFS) and OS (mOS) in analyzed phase III trials in the first-line setting were 7.7 and 18.5 months, respectively and 2.2 and 7.3 months, respectively for recurrent studies (Table 2). As expected, most studies used OS as a primary endpoint (65%). In total, 4 (20%) phase III trials were reported as positive trials. However, only 3 (15%) met the prespecified endpoints for the intervention arm to demonstrate superiority over control treatments. Separately, one phase III trial was designed to demonstrate improved PFS at 12 months (PFS12) yet was reported as a positive study based on

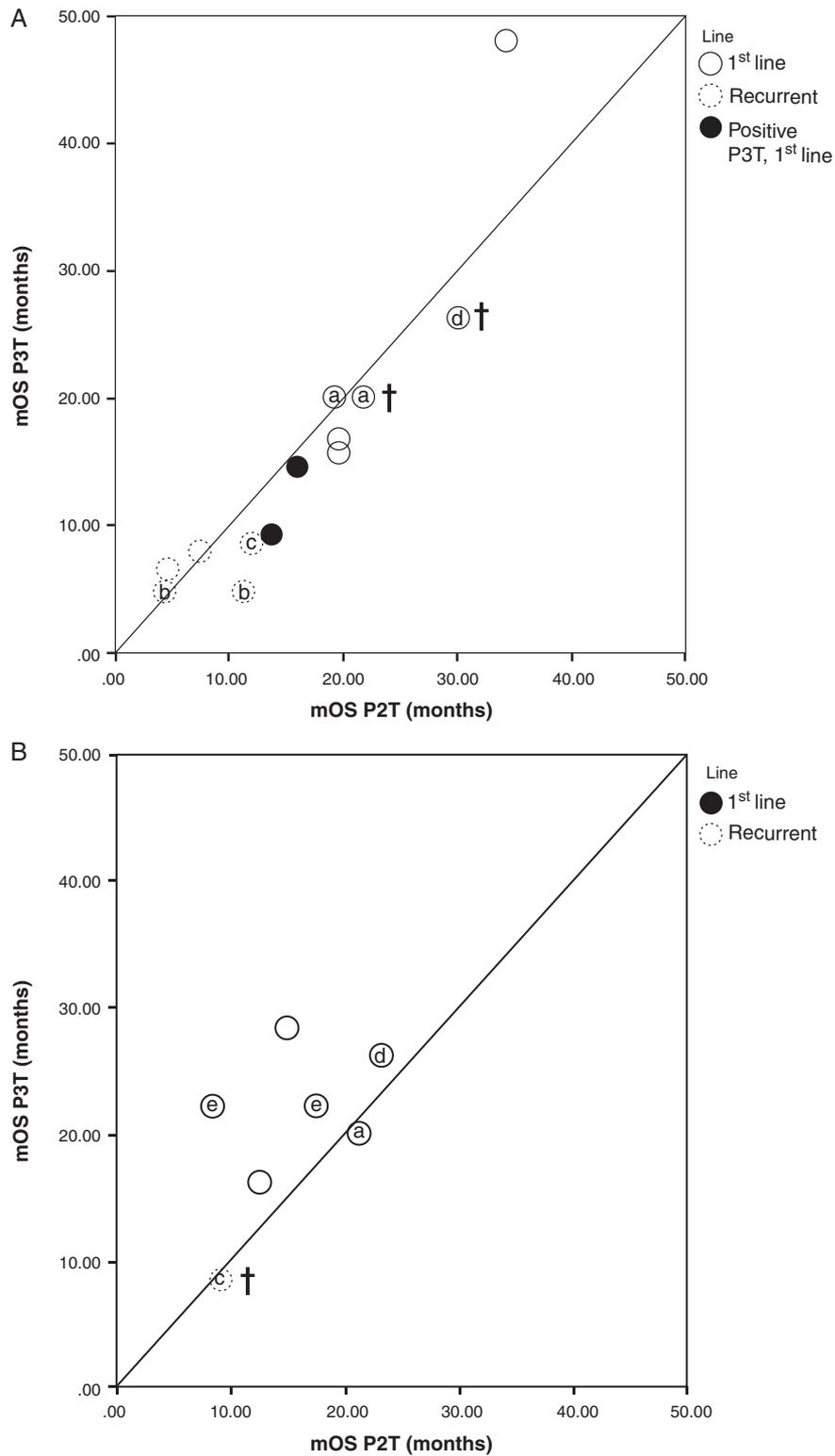
improved mPFS. For the purpose of this review, it was considered a negative study. Of all phase III trials, 2 first-line trials enrolled patients based on their O6-methylguanine-methyltransferase (MGMT) promoter methylation status, and 1 first-line study enrolled patients with tumors that expressed the EGFRvIII variant.

### Characteristics of Phase II Trials

We then identified and reviewed phase II studies that were matched to the phase III studies above. For 6 (30%)



**Figure 2.** Pearson's correlation of mPFS for P3Ts with (a) optimally matched P2Ts, and (b) suboptimally matched P2Ts. Continuous circles represent first-line studies and dashed circles represent recurrent studies. Solid circles represent studies which had a positive outcome and hollow circles represent negative studies. Note some P3Ts had more than one referenced P2T. These dyads are indicated by matched letters (ie, "a") inside each circle. †: Phase III expected outcome based on this phase II/III dyad.



**Figure 3.** Pearson's correlation of mOS for P3Ts with (a) optimally matched P2Ts and (b) suboptimally matched P2Ts. Continuous circles represent first-line studies and dashed circles represent recurrent studies. Solid circles represent studies which had a positive outcome and hollow circles represent negative studies. Note some P3Ts had more than one referenced P2T. These dyads are indicated by matched letters (ie, "a") inside each circle; for consistency, the same letter is used in this figure as in Figure 2, that is, each letter references the same phase III study in each figure. †Phase III expected outcome based on this phase II/III dyad.

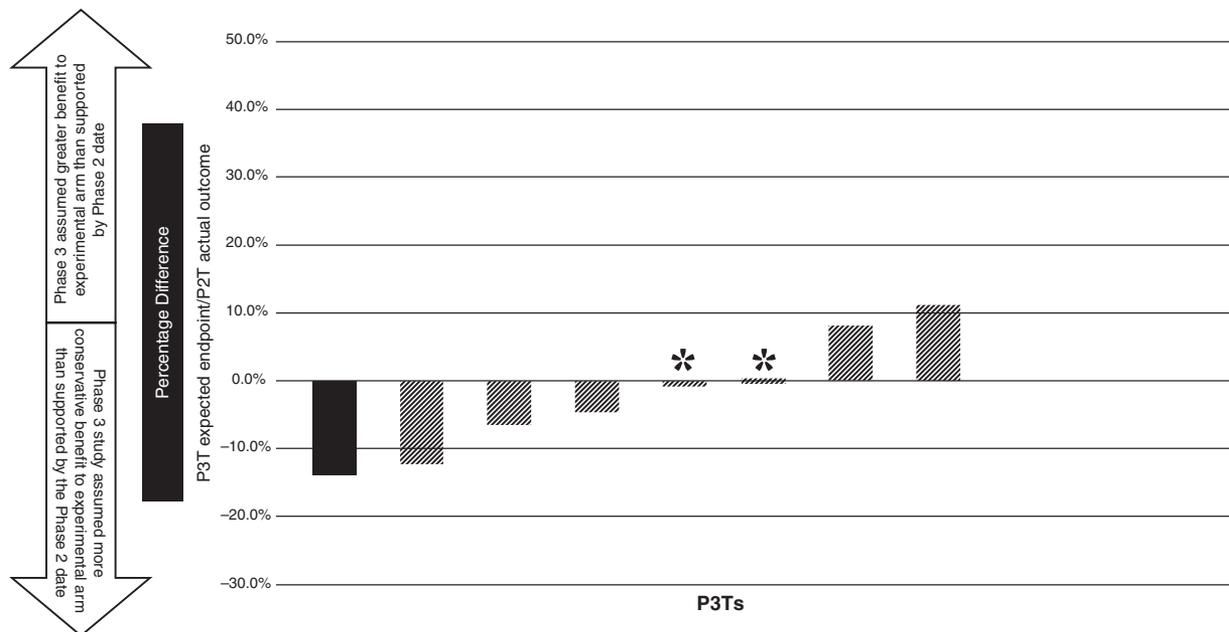
phase III trials, no relevant phase II trial could be identified from the manuscript or a secondary MEDLINE search. Of the remaining 14 phase III studies, there were 19 corresponding phase II trials that were identified (Table 1, Supplementary Table S2, and Figure 1). Seven phase III studies reference 1 individual phase II study (7 dyads), 2 referenced the same phase II study (2 dyads), 4 studies each referenced 2 phase II studies each (8 dyads), and 1 phase III trial had 3 preceding phase II studies (3 dyads), to give a total of 20 dyads.<sup>25-42</sup> Thirteen (68%) phase II trials were in the first-line setting and 6 (32%) were in patients with recurrent GBMs. The majority of these phase II trials were single arm (68%). There were 4 randomized studies (21%), of which 3 had control groups as comparators. One randomized phase II compared the efficacy of 2 different doses of an investigational product. Of the 19 selected phase II studies, 12 (63%) were led in Northern America, 6 in Europe (32%), and 1 (5%) in the Asia-Pacific region. More than half (12 phase II trials, 63%) were run by academic/co-operative groups. Characteristics of eligible phase II trials are summarized in Table 1. Of these studies, 4 out of 7 (57.1%) were studies examining anti-angiogenic agents and utilized a primary endpoint involving response rate or PFS.

In biomarker unselected populations, the median values for mPFS and mOS in phase II trials in the first-line setting were 9.5 and 17.4 months, respectively, and 3.6 and 8.3 months, respectively for recurrent studies. There were 9 phase II trials (47%) that tested for MGMT promoter methylation status. IDH mutation data were provided in only

1 phase II trial (6%). Another 3 studies (17%) enriched for patients with the EGFRvIII variant. There were 17 (89.5%) phase II trials with a description of primary endpoint in their statistical section. Of these studies, the main primary or co-primary endpoint used was PFS6.

### Concordance of Results Between Phase II and Phase III

We compared the concordance for PFS (Figure 2) and OS (Figure 3) between phase II and phase III studies for groups which were “optimally matched” versus those which were “sub-optimally matched.” Only 11 (55%) phase III studies were considered to have at least one “optimally matched” phase II trial, with 6 (30%) having no identifiable phase II trial at all, and the remaining 3 (15%) having only a “sub-optimally matched” phase III trial, respectively. There was no significant difference in the incidence of “optimally matched” phase II trials and “sub-optimally matched or no preceding” phase II trials between industry versus co-operative phase III trials ( $P = 1.00$ ), North American versus “rest of the world” phase III trials ( $P = .64$ ), European vs “rest of the world” phase III trials ( $P = 1.00$ ), and first line versus recurrent phase III trials ( $P = .64$ ). All anti-angiogenic phase III studies had at least one optimally matched phase II study ( $P = .01$  vs other class drugs). These dyads are indicated in Figures 3 and 4 by lower-case characters, with each lower-case character identifying dyads with a common phase III trial.



**Figure 4.** Bar graph showing whether the phase III study assumed a greater benefit for the experimental treatment than suggested by the preceding phase II study (bars with values above 0%) or where the phase III assumed a more conservative benefit for the experimental treatment than suggested by the preceding phase II study (bars with values below 0%). A bar which was exactly on the 0% line would be a study where the phase III study assumed exactly the same benefit for the experimental arm as the had been demonstrated by the preceding phase II study. Solid filled bar indicates a positive P3T while shaded bars indicate negative studies. The asterix (\*) indicate suboptimally matched P3T/P2T dyads.

There was a strong concordance for mPFS ( $r^2 = 0.95$ ,  $P < .01$ ) and mOS ( $r^2 = 0.84$ ,  $P < .01$ ) for phase III trials with “optimally matched” phase II trials (Figures 3 and 4). This remains true in the subset of studies examining anti-angiogenic drugs (mPFS  $r^2 = 0.99$  and mOS  $r^2 = 0.96$ ,  $P < .01$  for optimally matched studies). However, there was no statistically significant correlation for either for mPFS ( $r^2 = 0.87$ ,  $P = .07$ ) or mOS ( $r^2 = 0.27$ ,  $P = .23$ ) for phase III trials with “suboptimally matched” phase II trials. These results remained unchanged when restricted to a subset analysis based only on industry led (mPFS  $r^2 = 0.97$  and mOS  $r^2 = 0.98$ ,  $P < .01$  for optimally matched studies) or anti-angiogenic phase III trials (mPFS  $r^2 = 0.99$  and mOS  $r^2 = 0.96$ ,  $P < .01$  for optimally matched studies).

Furthermore, it was interesting to compare the interstudy variability between phase II studies with regards to PFS and OS. There were 3 drugs for which data from 2 or more phase II studies were available. Concordance was good, with the median difference in PFS estimates being 1 month (range 1–3 months). In contrast, the concordance for estimates of OS was much poorer. There were 5 drugs for which data from 2 or more phase II studies were available and the median difference was 5 months (with a range

of 1–9 months). Of note, all the phase III studies which enrolled biomarker defined patients had matched phase III studies which also enrolled similar biomarker defined patient populations.

### Progression From Phase II to Phase III

Next, we examined how well the preceding phase II data appeared to have informed the subsequent phase III study. This was possible in 8 phase III studies, where the statistical section of the phase III publication provided quantitative data about the premises used to inform the phase III study sample size and statistical design. We found that 2 phase III studies (25.0%) had a dyad that used a higher value for the expected benefit of the experimental arm in the phase III study than was reported in the corresponding phase II. Notably, 2 further phase III trials (involving the same investigational anti-angiogenic agent) proceeded despite their shared phase II study not meeting its predefined endpoint for OS. Rather, these phase III studies were undertaken on the basis of a promising PFS data from the same phase II. Overall, only 7

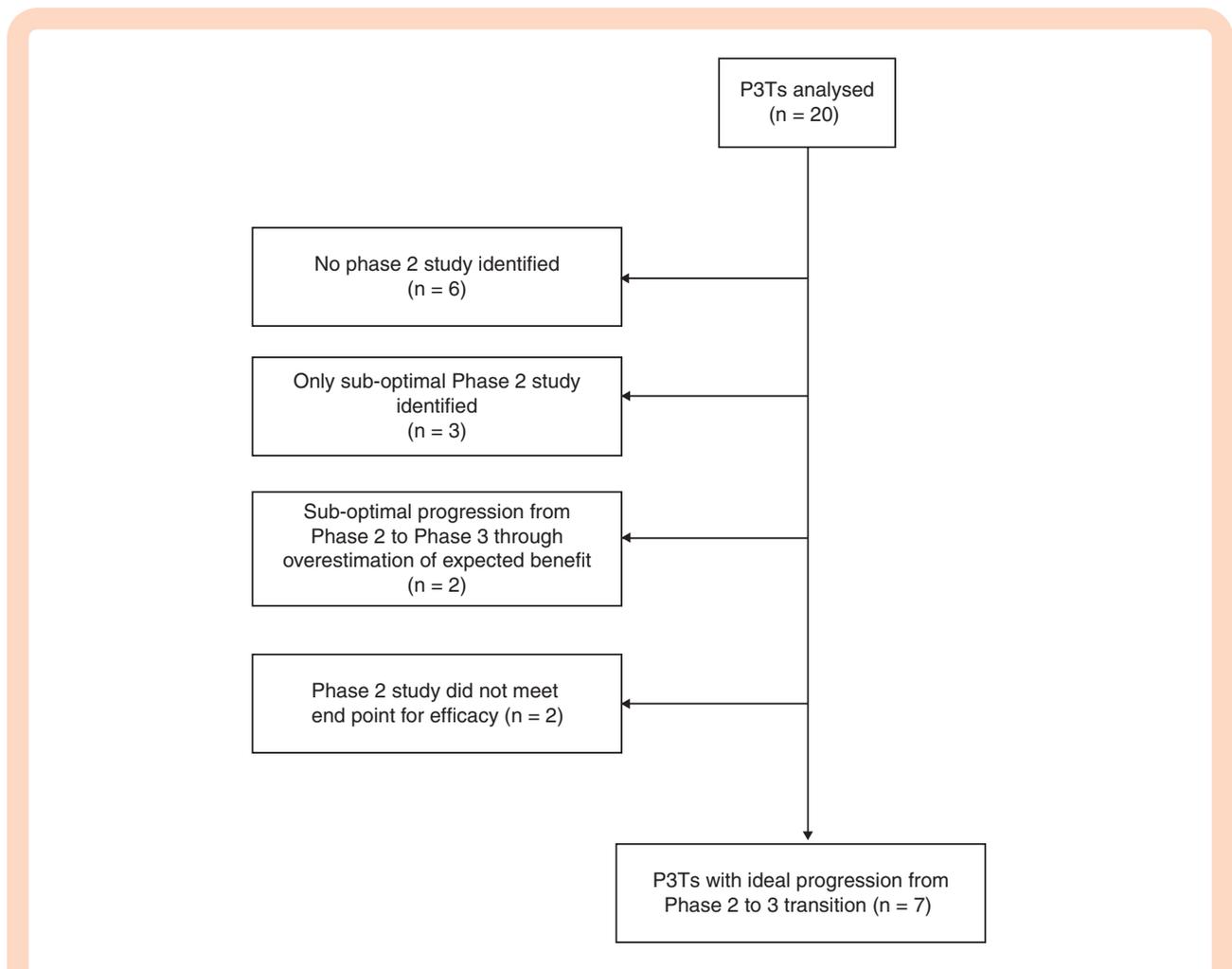


Figure 5. Schema demonstrating phase II to III transition. Only 7 P3Ts had ideal progression from the phase II to III setting.

studies underwent an ideal transition from phase II to phase III (Figure 5).

### Potential Thresholds of Phase II Trial Outcomes Which Do Not Justify a Phase III Trial

Lastly, we investigated whether there were absolute thresholds for efficacy in the phase II setting that could inform the go/no-go decision. For phase II trials in the newly diagnosed setting, where patients were unselected for age or MGMT methylated populations, all those with mPFS < 14 months and/or OS < 22 months had a subsequently negative phase III study. Similarly, all phase II trials for recurrent disease with mPFS < 6 months and mOS < 12 months had negative phase III studies. We retrospectively applied these thresholds to the studies identified in our review. Had those thresholds been applied, 10 of the 12 negative phase III studies (83%) with matched phase II trials in this review would not have proceeded, sparing 4739 patients from futile trial participation and additional toxicity.

## Discussion

The paucity of successful phase III drugs trial in this field has been described previously.<sup>6</sup> Temozolomide is the only approved drug to provide an OS benefit in the past 15 years, with the only other positive phase III study involving a medical device.<sup>2</sup> Failure to date has been generally considered to be the result of lack of drug efficacy, drug access due to the blood-brain barrier or tumor biology. We have undertaken the first detailed analysis to determine if there are systematic issues at the phase II–III transition which may contribute to the high failure rates of phase III trials. Our data suggest there are inefficiencies at the phase II to III interface which may impact on the success of drug development in neuro-oncology and can be readily modifiable.

Our data strongly support that inefficiencies in the phase II to III transition contribute to the lack of success in finding better drugs for GBM patients. Phase II trials generate vital safety and efficacy data about an investigational treatment which are essential when deciding whether to proceed with a larger phase III study. While promising results from phase II studies are infrequently reproduced in phase III studies in other cancers,<sup>6,43</sup> our study found phase II and phase III GBM studies that were optimally matched had an excellent and highly significant concordance for both OS and PFS. As such, one major contributor to negative phase III studies likely stems for the complete lack of phase II data, or the use of suboptimally matched phase II studies, when designing phase III studies.

However, the interpretation of phase II data, even when of high quality, needs to be done appropriately and we identify that this is a separate problem. Overall, only 35% of studies appeared to follow an ideal pathway where the phase III study was based on a relevant phase II study (using our criteria for optimal matching) data which was used appropriately in the phase III study

design. This figure is likely a conservative estimate given the absence of published expected outcomes in numerous phase III trial manuscripts, which precluded us from comparing them to their respective phase II results. Our data strongly support a future approach to trials development of GBM where there is increased scrutiny of how drugs progress from phase II to phase III. The decision to proceed to phase III is obviously based on many factors but we would argue that drugs should not proceed to phase III testing, where there is no relevant phase II study data available and where this data is below the threshold identified above. Conservative use of early phase data in the design of the phase III study should be encouraged in order to maximize chances of clinically meaningful success. Preventing a futile phase III program is critical given the financial and human resource undertakings that accompany them. The average cost of an oncological phase III trial has been estimated to be up to \$200 million.<sup>44,45</sup> Phase II data should be critically assessed about whether the phase III studies likely to be positive, potentially with some absolute thresholds based on data such as provide in our study. Ideally, drugs with clinically meaningful and statistically significant benefits are developed.

GBM trials appear to have additional issues with a relative lack of supporting phase II data, as well as their inappropriate utilization to inform phase III studies. Where there was phase II data available, most were single arm studies. These trials have been plagued by unreliability of historical controls, intermediary endpoints (such as response rate) and confounding effects.<sup>46</sup> Despite the mitigation of confounders, randomized phase II studies in GBM are challenging. They require significantly increased numbers to provide adequate statistical power, and mandate patient randomization to inadequate standard of care treatments. Randomized phase II trials in oncology have also not demonstrated superior correlation to phase III outcomes compared to single arm studies.<sup>47</sup>

The need to balance methodological rigor with urgency to find better drugs for GBM patients suggest that more innovative trials designs should also be explored. The potential of using randomized phase II data is of particular interest. Phase II trials used heterogeneous historical controls and endpoints to determine whether to proceed an investigational product to phase III (Supplementary Table S2). Interpretation of our own data regarding randomized phase II studies was limited by their paucity. Only 3 phase II studies compared an investigational regimen with a control arm. However, randomized phase II studies are not without their own issues. They require significantly increased numbers to provide adequate statistical power, and have also not demonstrated superior correlation to phase III outcomes compared to single arm studies.<sup>47</sup> Adaptive trial platforms represent another means of accelerating drug discovery by rigorously but speedily transitioning drugs from early phase setting into phase III expansion.<sup>48</sup> This novel trial design may account for the heterogeneity in patient populations between phase II and III trials, while allowing for protocol changes based on interim data.

This is the only study of its kind that we are aware of but it has a number of limitations. The number of studies

identified was small overall and some of the conclusions, particularly about thresholds, could be impacted by the lack of positive phase III studies as a comparator group. Furthermore, it is possible that some of the phase III studies may have been informed by phase II data which were not published or referenced. We have mitigated this as much as possible by undertaking independent online searches as well as manual bibliographic searches. Finally, we acknowledge the mitigating impact of confounding factors such as MGMT methylation status and age in providing cut-offs based on phase II trials of patients unstratified for important biomarkers. Nonetheless, our conclusions are immediately applicable to the planning of future clinical trials and their importance in ensuring that we only enroll patients on trials with a reasonable chance of success strongly suggest that they should be implemented wherever possible.

## Conclusions

Despite several phase III trials examining the utility of various interventions in GBM since 2005, the only positive studies have been those with temozolomide or tumor treating fields in the first-line setting. Our findings highlight the critical role of phase II trials in informing drug development for GBM specifically and strongly argue that high-quality, optimally matched, and conservatively interpreted phase II studies are vital prior to phase III studies.

## Supplementary Material

Supplementary material is available at *Neuro-Oncology Advances* online.

## Keywords

clinical trials | drug development | phase III | phase II | trial design | glioblastoma | glioma

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