

Manuscript Title:

Safety, Efficacy and Survival of patients with Primary malignant brain tumours (PMBT) in Phase I (Ph1) trials: the 12-year Royal Marsden Experience.

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Abstract

Background: PMBT constitute less than 2% of all malignancies and carry a dismal prognosis.

Treatment options at relapse are limited. First-in-human solid tumour studies have historically excluded patients with PMBT due to the poor prognosis, concomitant drug interactions and concerns regarding toxicities.

Methods: Retrospective data were collected on clinical and tumour characteristics of patients referred for consideration of Ph1 trials in the Royal Marsden Hospital (RMH) between June 2004 and August 2016. Survival analyses were performed using the Kaplan-Meier method, Cox proportional hazards model. Chi-squared test was used to measure bivariate associations between categorical variables.

Results: 100pts with advanced PMBT were referred. At initial consultation, patients had a median ECOG PS 1, median age 48 years (range 18-70); 69% were men, 76% had glioblastoma; 68% were on AEDs, 63% required steroid therapy; median number of prior treatments was 2. Median OS for patients treated on a Ph1 trials was 9.3 mo(95% CI: 5.9-12.9) vs. 5.3 mo(95% CI 4.1-6.1) for patients that did not proceed with a Ph1 trial, $p=0.0094$. Steroid use, poor PS, neutrophil-to-lymphocyte ratio and treatment on a Ph1 trial were shown to independently influence OS.

Conclusions: We report a survival benefit for patients with PMBT treated on Ph1 trials. Toxicity and efficacy outcomes were comparable to the general Ph1 population. In the absence of an internationally recognized standard second line treatment for patients with recurrent PMBT, more Ph1 trials should allow enrolment of patients with refractory PMBT and Ph1 trial participation should be considered at an earlier stage.

Five key words for indexing in the manuscript document:

malignant brain tumour; high grade glioma; glioblastoma; drug development; phase I

Background

Primary malignant brain tumours (PMBT) are a rare tumour group, constituting less than 2% of all malignancies, and carry a dismal prognosis[1], [2]. Despite recent incremental gains and therapeutic advances, including the emerging understanding of underlying genetic alterations, these tumors remain incurable and invariably recur. Treatment options at relapse remain limited.

The primary objectives of first-in-human solid tumor studies are to determine the safety, toxicity, maximum-tolerated dose (MTD), preliminary efficacy, and recommended dosing of novel agents for phase II and III studies[3] and efficacy data are now increasingly used to look for a signal in particular tumors. Phase I studies use strict eligibility criteria and have historically excluded patients with PMBT such as glioblastoma[4], [5] due to a number of concerns, including poor prognosis, concomitant drug interactions, concerns about excessive toxicities and limited efficacy as a result of poor penetration across the blood-brain barrier[4], [5]. Such concerns of course, are less relevant in the molecular era, and we suggest that the reasons for excluding these patients are largely archaic.

We conducted a retrospective analysis of our experience of patients with PMBT referred for consideration of Phase I trials in the Royal Marsden Hospital, and analyzed baseline patient characteristics and organ function, toxicities, responses, and survival.

Patients and Methods

This retrospective study considered consecutive patients with PMBT referred for consideration of Phase I trials in the Royal Marsden Hospital between June 2004 and August 2016. We defined patients with PMBT as patients with grade III or above malignant intracranial neoplasms involving the brain. Phase I trials of molecular agents and/or single-agent cytotoxic for which complete data were available were included. Molecular agents are defined as drugs that target an extra- or intracellular mechanism different from those associated with conventional chemotherapy such as DNA, tubulin, or cell division machinery. Eligible patients were ≥ 18 years of age with histologically proven PMBT. All patients had recurrent PMBT and had received at least one line of prior treatment.

The following patient and laboratory characteristics were reviewed: age at diagnosis, sex, Eastern Cooperative Oncology Group (ECOG) performance status, prior surgery, prior radiation therapy, prior chemotherapies, tumour location, class of investigational agent, and baseline laboratory evaluations including neutrophil to lymphocyte ratio (NLR) at the first clinic appointment and at screening. RMH score at the first clinic appointment and at screening was also assessed; (the RMH score is derived from the albumin value, the lactate dehydrogenase value, and the number of metastatic sites). It has been developed as a predictive factor of patient survival in phase I trials, and has been validated as a predictor of survival in large numbers of patients with lung, pancreatic, and head and neck tumors treated on phase I trials [6]. Where possible, tumor molecular data including MGMT status, 1p19q status, IDH-1 mutation status was collected. In addition, the type of concurrent antiepileptic drug (enzyme inducing versus non enzyme inducing) and steroid use was documented. All drug-related serious adverse events (SAEs) were recorded, and toxicities were graded using Common Terminology Criteria for Adverse Events (CTCAE version 4.0). The study proposal was reviewed and passed by the ethics committee at the Royal Marsden hospital.

Statistics

Patient characteristics were summarized using means and standard deviations (SD), or medians and ranges if the data were continuous and normally or non-normally distributed, respectively. The Chi-squared test was used to measure bi-variate associations between categorical variables, respectively. Median survival was estimated using Kaplan Meier methods, and the log rank test was used to establish group differences. Cox proportional hazards modeling was used to examine the associations between survival and clinically relevant prognostic factors thought to influence outcome. Hazard ratios and their 95% confidence intervals were estimated and presented. Statistical significance levels were set at 5% for all tests carried out.

Results

Patients and Trial Characteristics

A total of 100 patients were referred for consideration of participation in a phase I trial from 2004 to 2016 (Table 1). The median age was 48 years (range, 18 to 70 years) with a median Eastern Cooperative Oncology Group performance status of 1 (range, 0 to 3). All patients had a diagnosis of recurrent refractory PMBT and had received at least one line of prior treatment; 76% (n=76) had glioblastoma. The median number of prior chemotherapies was two (1-5), with temozolomide the first-line treatment in 76% of 100 patients. Ninety-two percent of patients received prior radiation therapy as part of initial management of PMBT; while data on prior treatments were missing for five patients (5%). Sixty-eight percent of all patients seen in clinic for an initial consultation (n=68) were on treatment with at least one antiepileptic drug (AED). Data were unavailable for seven patients (7%); 31% were taking enzyme-inducing AEDs (EIAEDs), and 18% of patients were on two or more AEDs. Sixty-three percent of all patients required steroid therapy on first assessment. Sixteen percent of all patients had a documented co-morbidity.

With regards to patient allocation, fifty-nine percent of patients were allocated to a phase I trial (n=59); forty-two patients (42%) went on to receive investigational agent in a phase I trial (Figure 1); classes of compounds are shown in Table 2. Of the patients allocated to a phase I trial, but were unable to go on to receive drug, six patients failed screening, three patients declined treatment, seven patients underwent rapid deterioration following initial review or there was no suitable trial available (n=1); data were unavailable for one patient. The most common reason for the patients who were not allocated to a trial was lack of suitable trials available at the time (n=20). Fourteen percent of patients (n=14) were not allocated due to poor performance status / deemed unsuitable for phase I trial participation. Five percent (n=5) of patients were not interested in participating in a phase I trial.

Toxicities

Thirty-seven of the total forty-two patients treated on a phase I trial demonstrated drug-related toxicities of various grades; five patients had no drug-related adverse events. The majority of investigational agents, with or without the addition of chemotherapy, were well-tolerated, with minimal

side effects, and patterns similar to many molecularly targeted treatments. Of note, these toxicities were typically in the grade 1 category. All toxicities were assessed according to the CTCAE v 4.0 set. The most common drug related adverse events documented were grade 1 diarrhoea, with thirteen events (33%), nine events (21%) of grade 1 fatigue, eight events (19%) of grade 1 nausea; seven events of grade 1 rash (17%) and six events (14%) of grade 1 transaminitis were noted, while the most common grade 2 toxicities observed were fatigue with five events (12%) and nausea with four events (9%). There were two grade 4 toxicities, hyponatraemia (2%) and creatinine kinase elevation (2%); there were no grade 5 toxicities. There were no study related deaths. Table 3 shows a detailed description of events and grading of drug related toxicities observed in the population studied.

Twenty-seven patients were receiving AEDs during their participation on a phase I trial, while twenty-four were on steroids. The incidence of grade 1 diarrhoea was markedly higher in the group of patients on AEDs (26%) compared with those patients not taking AEDs (7%) but there was no difference in more severe grade diarrhoea, or in any other toxicities. There was also no significant difference in toxicity prevalence in the group of patients using steroids compared with those patients not receiving steroids. Table 3 demonstrates a detailed description of the toxicities seen in these two groups. Of those patients treated on study, reasons for study discontinuation included disease progression (88%, n=37), drug toxicity (5%, n=2), patient withdrawal (5%, n=2), and other causes (2%, n=1).

Survival

There was no statistically significant difference in median progression-free survival (PFS) between patients (n=41) treated on a phase I trial (3.4 months, 95% CI: 2.7-4.7), and those patients (n=56) who did not proceed with treatment on a phase I trial (5.3 months, 95% CI: 4.1-6.1; P=0.1356), respectively (Figure 2). However, there was a statistically significant difference in overall survival (OS) between the two groups. Median OS for patients treated on a phase I trials was 9.3 months (95% CI: 5.9-12.9) vs. 5.3 months (95% CI 4.1-6.1) for patients that did not proceed with a phase I trial, P=0.0094, respectively (Figure 2).

Factors influencing survival

Factors with a potential influence upon survival were examined using univariate and multivariate models, respectively. The statistically significant factors that were shown to independently influence overall survival were steroid use, poor performance status, neutrophil-to-lymphocyte ratio (NLR), RMH prognostic score and treatment on a phase I trial. The use of steroids was associated with shorter overall survival in both univariate (HR 2.33, 95% CI 1.44-3.77, $p=0.001$) and multivariate analysis (HR 1.84, 95% CI: 1.05-3.24, $p=0.034$; Figure 3), an association which was repeated when examining progression-free survival (HR 1.93, 95% CI: 1.21-3.06, $p=0.005$) (Table 4,5). Perhaps unsurprisingly, poor performance status (ECOG PS 2/3) was also predictive of poorer outcomes, in both univariate and multivariate models (HR 16.01, 95% CI: 3.12-83.26, $p=0.001$; HR 44.9, 95% CI: 5.95-338.58, $p=0.000$) (Table 4,5).

NLR was also examined; An elevated $NLR \geq 4$ proved significant for survival and was associated independently with poorer outcomes in all models (Table 4,5; OS, multivariate analysis: HR 1.73, 95% CI 1.02-2.94, p -value 0.043). Patients with $NLR \geq 4$ were more likely to require steroids compared to patients with an $NLR < 4$ (81% vs 38%). Use of steroids did not modify the association between NLR and outcomes, as patients with an elevated $NLR \geq 4$ and requiring steroids had the poorest outcome ($p = 0.0364$). Median OS for patients with $NLR \geq 4$ on steroids was 4.1month (SE 0.29, 95% CI 3.29-5.42), vs 19months median OS for patients not taking steroids (SE 8.61 95% CI.36-not reached)[Figure 3].

The RMH score is calculated with albumin value, lactate dehydrogenase value, and the number of metastatic sites to predict patient survival in phase I trials. RMH score 0-1 was an independent variable that predicted survival in multivariate analysis (HR 0.48, 95% CI:0.25-0.90, $p=0.023$; Table 5).

Patients receiving an investigational agent, with or without combination of other agents or chemotherapy, in the context of a phase I trial performed better than those patients who were not treated (HR 0.59, 95% CI 0.35- 0.99, $p=0.048$), with the patients participating in a phase I trial displaying an almost double likelihood of improved overall survival (Table 5). Other factors that were

analysed such as age, sex, use of AEDs, and tumour location and laterality, however these did not provide any statistical significance relating to outcomes.

Discussion

In the United States, the annual incidence rate of primary CNS tumours in adults is 27.86 per 100,000, with gliomas accounting for 65% of malignant tumors[2]. With the advent of targeted therapies in this era of precision medicine, treatment of other solid tumors has dramatically changed in the past decade, while progress in the management of malignant brain tumours has disappointingly trailed behind. For patients with recurrent PMBT, there are few active treatments approved, and as such these patients have limited treatment options. The Cancer Genome Atlas (TCGA) data have demonstrated a wide range of mutations involved in glioblastoma that could potentially be targeted by novel drugs[7]. However, patients with PMBT are frequently unable to gain access to most phase I clinical trials under current eligibility criteria[4], [5], [8].

We report a significant survival benefit for patients with PMBT treated on Phase I trials. This survival benefit may perhaps be due to the novel investigational agents these patients received while on phase I trials. Traditionally, the majority of phase I trials of novel agents in oncology have excluded patients with PMBT due to a number of concerns. These include poor prognosis, poor performance status, fear of excessive CNS toxicities, concomitant drug interactions, and limited efficacy as a result of poor penetration across the blood-brain barrier[4], [5]. Our data further confirm that patients with PMBT who meet standard strict phase I eligibility criteria and are enrolled onto trials of appropriately chosen compounds, successfully meet phase I end points, such as safety and toxicity. Based on our results, these patients tolerate investigational agents similarly to other groups. We have demonstrated that the use of steroids does not affect the incidence of toxicities. The use of AEDs, however did increase the prevalence of a single toxicity. Inherent selection bias of course, could contribute to the survival benefit noted. Patients treated on trial could be selected as they appear healthier and they may live longer, which may or may not be due to treatment effect on outcome. Indeed, from our dataset, patients with ECOG performance status 1 had better reported survival regardless of their participation on a phase I trial. Nonetheless, this selection bias does not detract from our conclusion, that patients with PMBT can be enrolled and treated safely the Phase I setting. To the best of our knowledge, this is the first single-centre published experience of patients with PMBT treated in the Phase I setting.

In our opinion, historical reasons for excluding patients with brain tumors from phase I trials are no longer valid. As demonstrated in our cohort, patients with PMBT included on clinical trials tend to have few co-morbidities, are typically relatively young (the median age of glioblastoma trial patients 55 is years), have usually received fewer lines of prior systemic treatments and tend to have no systemic metastases, without the compromise in organ function seen in patients with systemic metastatic disease. Furthermore, patients with recurrent glioblastoma with reasonable performance status typically have a life expectancy of 4 to 7 months[9], [10], which is comparable to the expected survival of patients with other solid tumors included on phase I trials. Our results further demonstrate that select patients with PMBT who meet standard phase I eligibility criteria have comparable fitness and organ function as their solid tumor counterparts, disproving the old belief that the performance status of patients with PMBT is too poor for participation in phase I studies.

With regards to antiepileptic drugs (AEDs), historically patients with PMBT would have been treated with cytochrome P450 enzyme-inducing antiepileptic drugs (EIAEDs), such as carbamazepine[11]. Increasingly however, there has been a trend in neuro-oncology towards the use of safer second and third generation non-EIADs such as levetiracetam and lamotrigine, drugs cleared through the kidney, with no CYP450 enzyme interaction. Indeed, prophylactic AEDs are no longer recommended[12], and the majority of patients who require AEDs, including patients in our cohort, are treated with non-EIAEDs, thus removing the potential for concomitant drug interactions.

The frequent use of corticosteroids in patients with PMBT is another argument used to exclude these patients from phase I trials. Corticosteroids, such as dexamethasone, are relatively weak inducers of CYP450 enzymes, however there are data confirming effect of corticosteroids on drug exposure is minimal, and they have little effect on the exposure or safety profile of drugs like irinotecan in high-grade glioma and bortezomib in patients with myeloma or lymphoma[12], [13]. Our data revealed patients on corticosteroids suffered with poorer survival regardless of whether or not they proceeded with a phase I trial. High-dose steroids are frequently used to control peri-tumoural oedema in glioblastoma patients, and can result in metabolic complications, such as hyperglycemia, obesity and type 2 diabetes. These metabolic complications are associated with increased cancer risk and poor outcomes in cancer patients[14], and indeed a number of studies suggest that glioblastoma patients affected by these metabolic complications have worse prognosis compared with those with normal

metabolic conditions[15]–[17]. Consequently, we would advocate for reducing corticosteroid-use in brain tumour patients when possible.

We have demonstrated in our cohort of the patients treated with investigational agents, alone or in combination with other agents or chemotherapies, that the toxicities encountered do not hinder quality of life. Most events described were grade 1 and grade 2 events (Table 3), while the grade 3 and grade 4 events in our cohort were significantly less than the general population treated on phase 1 trials. Historically, grade 3 and 4 toxicity rates for single-agent and combination phase I studies are estimated to range from 10.3% to 36%[18], [19]. More recently, there are data reporting grade 3 and 4 toxicity rates during cycle 1 of 14.1% and 1.9%, respectively, with single-agent molecular drugs[20]. Our cohort of patients demonstrated a maximum of 10% in grade 3 toxicities and a maximum of 2% of grade 4 drug related toxicities. There were no drug-related deaths, nor deaths on trial, irrespective of cause. Furthermore, it is noteworthy that there were no toxicity-related trial withdrawals. Our toxicity outcomes are comparable to the general phase I patient population.

Neutrophil-lymphocyte ratio (NLR) is a marker of systemic inflammatory response, and elevated levels have been associated with aggressive disease and poorer outcome in multiple tumour streams, including prostate, lung and colon cancer[21]–[25]. In patients with GBM, there are published data that elevated NLR prior to any initial therapy, including surgery or corticosteroids, is predictive for worse outcomes[26]. In our population of patients with recurrent PMBT, elevated $NLR \geq 4$ remained an independent prognostic indicator for poor outcome, independent of corticosteroid use. In our cohort, patients with elevated $NLR > 4$ requiring steroids also demonstrated the worst outcomes – a reminder of the potential relevance of host immunity in malignant brain tumours. Given the ease and reduced cost of NLR testing, we hypothesize that NLR testing could prove to be a useful addition in predicting prognosis in PMBT patients.

The RMH score uses albumin (≥ 3.5 g/dL vs < 3.5 g/dL), lactate dehydrogenase (less than or equal to the upper limit of normal [\leq ULN] vs $>$ ULN), and the number of metastatic sites (≤ 2 sites vs ≥ 3 sites) to predict patient survival in phase I trials, and has been validated as a predictor of survival in large number of patients with lung, pancreatic, and head and neck tumours treated on phase I trials [6].

Somewhat surprisingly, given the lack of systemic metastases of PMBT, in our population, RMH score 0-1 was an independent variable that predicted survival in multivariate analysis, suggesting a possible prognostic role for the RMH score in this patient population. While the RMH score has been validated in patients with solid tumours treated on Phase I trials, it has not yet been validated in patients with PMBT. Serum albumin level however, is thought to be a reliable and convenient marker of the nutritional status in patients, and has previously been identified as a prognostic marker in high grade glioma[27]. Thus, it is conceivable that, lactate dehydrogenase levels are also of some significance in this patient population. Given that systemic metastases are rare in this patient population, perhaps an adjusted-RMH score could have a prognostic role in this patient population.

Regarding barriers to phase I enrolment, a lack of suitable trials remains a significant barrier, however this is similar to other rare malignancies. We acknowledge there are a number of limitations in our study; most notably, our small sample size, and inclusion of both single agent and combination studies. Nonetheless, our study adds to the growing body of evidence encouraging investigators to enrol patients with PMBT in Phase I trials.

Finally, in the absence of an internationally recognized standard second line treatment for patients with recurrent primary malignant CNS tumours, more phase I trials should allow enrolment of this patient population, and more brain tumour-specific trials with relevant eligibility criteria should be designed, encouraging phase I trial participation at an earlier stage.

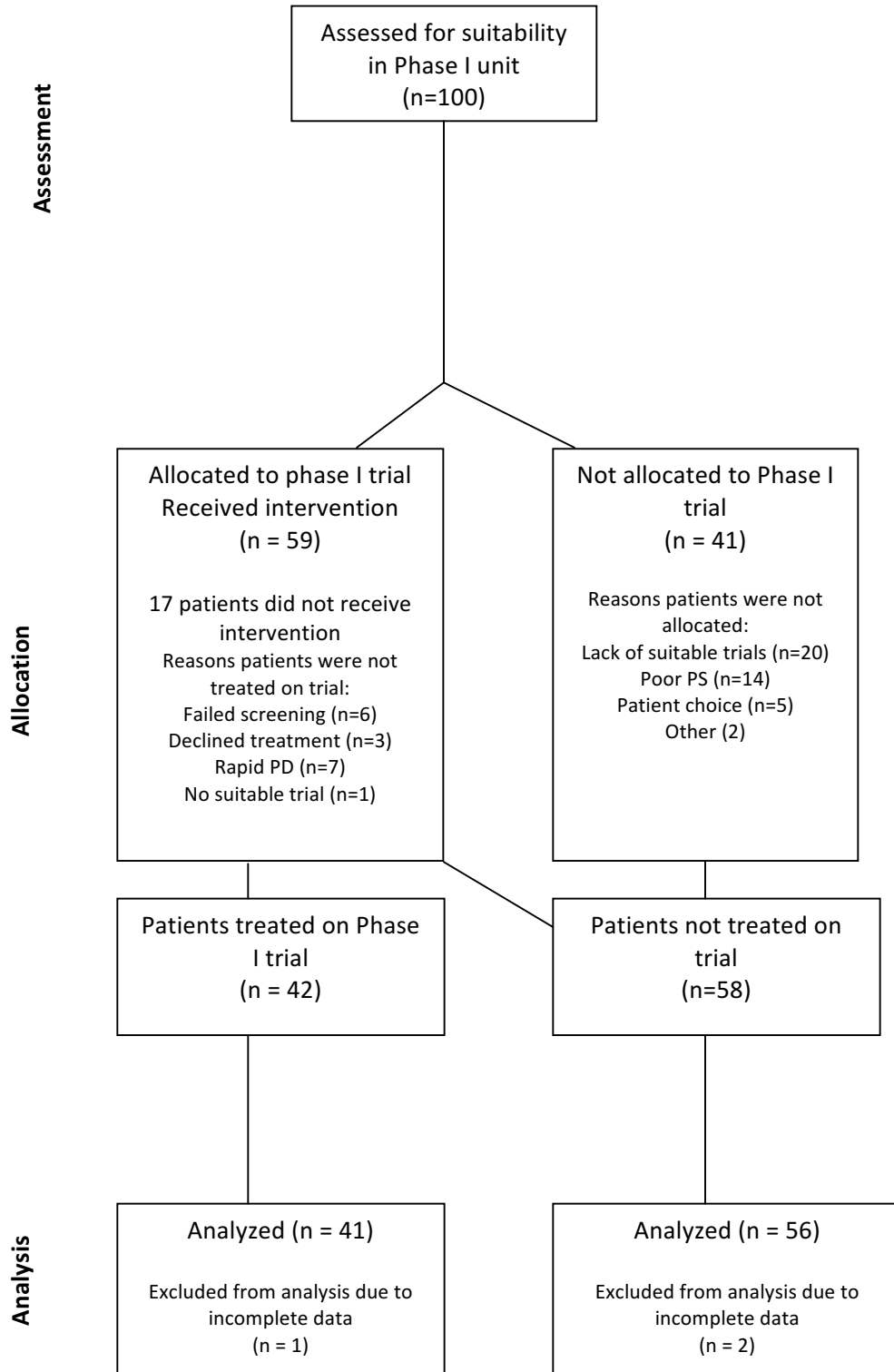
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CONSORT diagram showing all patients with PMBT retrospectively included in study.



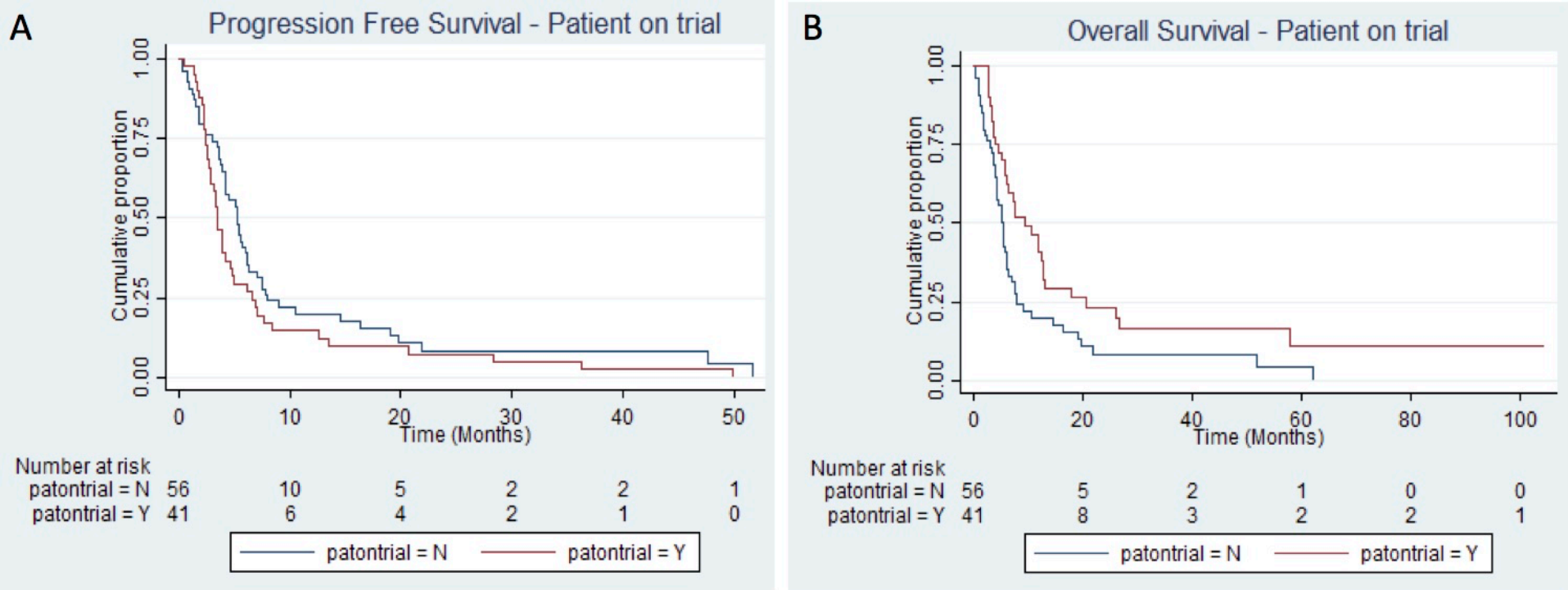


Figure 2. Kaplan –Meier curve of PFS (A) and OS (B) of patients with PBMT considered for phase I trials in Royal Marsden Hospital between 2004 and 2016. A: No statistically significant difference was seen in the median PFS between patients (n=41) treated (3.4 months, 95% CI: 2.7-4.7) and those not treated (n=56) on a phase I trial (5.3 months, 95% CI: 4.1-6.1; $p=0.1356$). B: Statistically significant difference in the median OS was seen between the two groups with 9.3 months (95% CI: 5.9-12.9) for the patients treated on a phase I trial vs. 5.3 months (95% CI: 4.1-6.1) for those who were not.

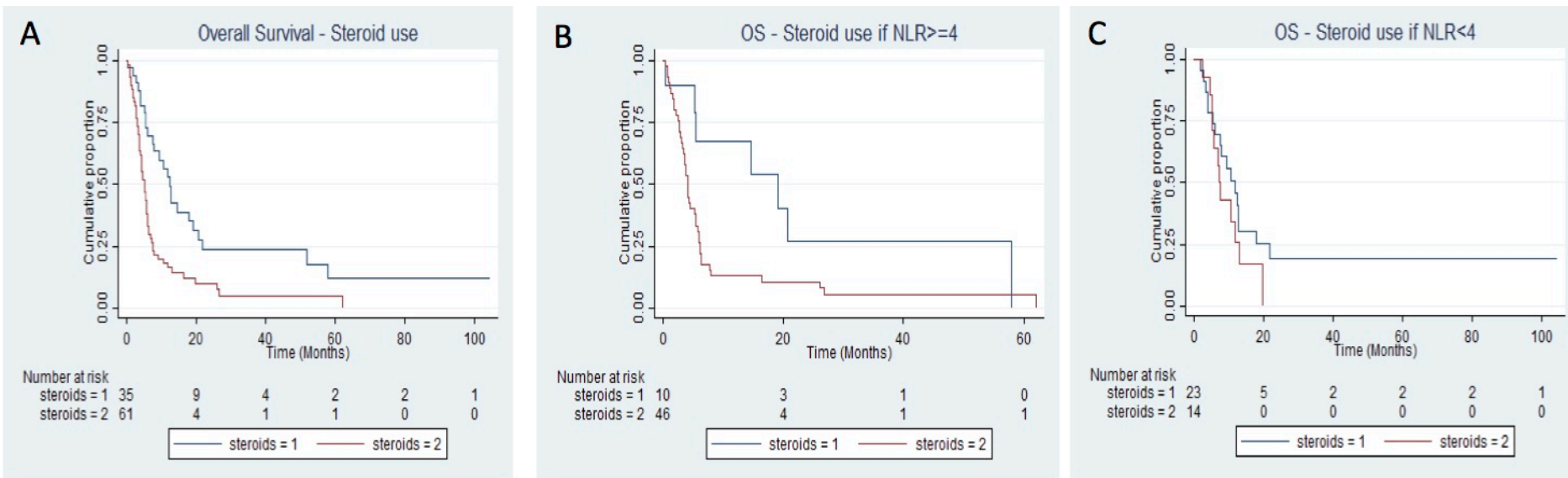


Figure 3. Kaplan – Meier curves of OS in patients with steroid use (A), steroid use and NLR ≥ 4 (B) and steroid use and NLR < 4 (C). A: The use of steroids was associated with shorter overall survival in multivariate analysis (HR 1.84, 95% CI: 1.05-3.24, $p=0.034$). B, C: Median OS for patients with NLR ≥ 4 on steroids was 4.1 months (SE 0.29, 95% CI 3.29-5.42), vs 19 months median OS for patients taking steroids with NLR < 4 (SE 8.61 95% CI.36-not reached).