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Clinical trial

A three-arm randomised phase II study of the MEK inhibitor selumetinib alone or in combination with paclitaxel in metastatic uveal melanoma

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ABSTRACT

Aims: The MAPK pathway is constitutively activated in uveal melanoma (UM). Selumetinib (AZD6244, ARRY-142886), a MEK inhibitor, has shown limited activity as monotherapy in metastatic UM. Pre-clinical studies support synergistic cytotoxic activity for MEK inhibitors combined with taxanes, and here we sought to assess the clinical efficacy of combining selumetinib and paclitaxel.

Patients and methods: Seventy-seven patients with metastatic UM who had not received prior chemotherapy were randomised to selumetinib alone, or combined with paclitaxel with or without interruption in selumetinib two days before paclitaxel. The primary endpoint was progression free survival (PFS). After amendment, the combination arms were combined for analysis and the sample size adjusted to detect a hazard ratio (HR): 0.55, 80% power at 1-sided 5% significance level.

Results: The median PFS in the combination arms was 4.8 months (95% CI: 3.8 - 5.6) compared with 3.4 months (2.0 - 3.9) in the selumetinib arm (HR 0.62 [90% CI 0.41 - 0.92], 1-sided p-value = 0.022). ORR was 14% and 4% in the combination and monotherapy arms respectively. Median OS was 9 months for the combination and was not significantly different from selumetinib alone (10 months) with HR of 0.98 [90% CI 0.58 - 1.66], 1-sided p-value = 0.469. Toxicity was in keeping with the known profiles of the agents involved.

Conclusions: SelPac met its primary endpoint, demonstrating an improvement in PFS for combination selumetinib and paclitaxel. No improvement in OS was observed, and the modest improvement in PFS is not practice changing.

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1. Introduction

Metastatic UM is a distinct form of melanoma that is in most cases refractory to therapies that are standard of care for the management of metastatic cutaneous melanoma. *BRAF* is not mutated in UM and only a small minority of patients experience significant clinical benefit from the currently available immune checkpoint inhibitors (ICI) [1–3]. Tebentafusp is the first systemic agent with a proven overall survival benefit in metastatic UM [4] and has become a new standard of care. It is however HLA restricted with less than 50% of the overall population eligible for treatment, and provides palliative benefit only. Whilst patients with liver only (or predominant) metastases may additionally derive benefit from liver directed therapies (most notably percutaneous perfusion with melphalan [5]), and other agents are under investigation [6], survival benefits remain modest and patients invariably progress on treatment. There therefore remains a significant need for new therapies for metastatic UM.

Despite the absence of *BRAF* or *RAS* mutations, the MAP kinase pathway is constitutively activated in UM [7]. Activating mutations in *GNAQ* and *GNA11* are found in approximately 90% of cases [8,9], with many of the remaining patients having mutations in either *CYSLTR2* or *PLCB4* [10,11]; all leading to downstream MAPK activation and thus suggesting inhibition of the pathway may have clinical utility. Single agent selumetinib (AZD6244, ARRY-142886), an orally available MEK1/2 inhibitor, showed improved PFS compared to dacarbazine or temozolomide chemotherapy with a hazard ratio of 0.46 for PFS ($p < 0.001$), as well as increased ORR (14% vs 0%) in a randomised phase II clinical trial [12]. Median overall survival was not significantly different (11.8 vs 9.1 months, $p = 0.09$). A subsequent randomised phase III study examining the combination of dacarbazine and selumetinib compared with dacarbazine alone showed no improvement in PFS (HR 0.78, $p = 0.32$) or OS (HR 0.75, $p = 0.40$) [13], suggesting the need for alternative combinations to improve clinical efficacy.

Pre-clinical studies of the combination of MEK inhibitors (MEKi) and chemotherapy support synergistic activity for the combination of MEKi with taxanes in particular [14–16]. We therefore initiated a multicentre randomised three arm clinical trial in patients with metastatic UM to examine whether the combination of weekly paclitaxel with selumetinib led to improved clinical outcomes compared to single agent selumetinib. As withdrawal of MEK inhibition prior to exposure to taxane has been shown to significantly increase anti-tumour cytotoxicity [17], we included two combination arms, in one of which selumetinib was interrupted pior to paclitaxel doses. However, due to slow recruitment, the protocol was amended to combine the selumetinib with paclitaxel arms for the primary analysis.

2. Methods and patients

2.1. Trial design

SelPac was designed as a multicentre, open-label, phase II, three-arm randomised parallel group trial in patients with metastatic uveal melanoma. Patients were randomised on a 1:1:1 basis to receive either A) continuous selumetinib, B) continuous selumetinib plus weekly paclitaxel or C) intermittent selumetinib plus weekly paclitaxel. The null hypothesis for the study was that the addition of paclitaxel had no impact on patients outcome with the primary analysis performed by comparing continuous selumetinib (A) vs selumetinib (delivered either continuously or intermittently) plus paclitaxel (B +C).

2.2. Patients

Patients were eligible if they had histologically or cytologically confirmed metastatic uveal melanoma with measurable disease defined by RECIST 1.1, an ECOG performance status of 0–2 and life expectancy greater than 3 months. Patients were excluded if they had received prior chemotherapy, MEK, RAS, or RAF inhibitors for uveal melanoma or had known or suspected brain metastasis; prior immunotherapy or non-chemotherapy based liver directed therapies were permitted. Full details of inclusion/exclusion criteria are included in the study protocol (Supplementary Material 1).

2.3. Interventions

Selumetinib was administered twice daily at 75 mg for patients who received the drug continuously (arms A & B). Those patients randomised to receive selumetinib intermittently (arm C) had 75 mg on days 1 − 5, 8–12 and 15–26 of each 28 day cycle, with the morning dose also omitted for days 1, 8 and 15. Paclitaxel (Arms B & C) was administered at 80 mg/m2 on days 1, 8, 15 of a 4 week cycle, for a maximum of 6 cycles. Radiologicical disease assement was performed using CT scanning of chest and abdomen at baseline and 8 weekly until progression. Where lesions were not well visualised by CT, and MRI of liver was additionally performed at assessment time points.

2.4. Outcome

The primary outcome for the study was investigator assessed progression-free survival (PFS) measured from the date of randomisation to the date of progressive disease or death by any cause. Secondary outcomes included overall survival (OS), measured from the date of randomisation until death by any cause; objective response rate, defined as observing a complete (CR) or partial (PR) response as per RECIST (version 1.1) and toxicity measured as the occurrence of Adverse Events (AE) and Serious Adverse Events (SAE) using the Common Terminology Criteria for Adverse Events (CTCAE) (version 4).

2.5. Sample size

Sample size calculations were based on a clinically relevant difference in PFS given by a hazard ratio of 0.55. Using a one-sided alpha level of 0.05 and a 2:1 allocation ratio, a total of 68 events were required to obtain a power of 80%. The study had initially been powered to produce two estimates of efficacy; continuous selumetinib vs continuous selumetinib plus weekly paclitaxel and continuous selumetinib vs intermittent selumetinib plus weekly paclitaxel. This design would have required 116 events and 123 patients. Due to slow recruitment, and with the support of the study oversight committees, the trial was simplified to combine arms B and C and produce only a single estimate of efficacy which reduced the size of the study. A PFS function for patients receiving selumetinib alone was assumed to be characterised by a Weibull distribution with shape and scale parameters of 1.56 and 4.68 respectively. With a minimum patient follow-up of 6 months, recruitment of 72 patients was required.

2.6. Randomisation

Randomisation was performed using randomly permuted blocks using lists which were pre-generated by a statistician at the Liverpool Clinical Trials Centre otherwise unconnected to the study. No stratification was employed. Allocation was implemented by the LCTC using an interactive web response system. As an open-label study, there was no blinding in the study.

2.7. Statistical methods

Continuous data were described as median (inter-quartile ranges [IQR]) and categorical data described as frequencies of counts with associated percentages. Analyses were performed on the full patient group following the intention-to-treat principle retaining all patients in their randomised groups irrespective of any protocol violations.

The primary outcome compared PFS between continuous

selumetinib and continuous or intermittent selumetinib combined with paclitaxel using a log-rank test. PFS was estimated using the Kaplan Meier approach with estimates of hazard ratios obtained using Cox proportional hazards modelling. The assumption of proportional hazards was assessed via inspection of Schoenfeld residuals. The analysis approach to overall survival replicated that of the primary outcome. Objective response rate was analysed as a binary covariate with results presented in terms of an odds ratio and statistical significance determined using a Fishers exact test. For toxicity, the number and percentage of patients reporting a Serious Adverse Event (SAE) and Grade 3 or higher toxicity that led to study discontinuation were summarised by treatment arm and preferred term. Comparisons of toxicity data between treatment groups are performed using Fishers' exact test with results presented as odds ratios.

The primary outcome was assessed using a one-sided alpha level of 0.05 with hazard ratios presented using a two-sided 90% confidence interval. All other analyses were evaluated using a two-sided 0.05 alpha level and presented with two-sided 95% confidence intervals. Analyses were performed using Stata (V14).

2.8. Study Administration

The study was administered by the LCTC and sponsored by the University of Liverpool. Ethical approval for the study was obtained from London City & East Multi-centre Research Ethics Committee (MREC) on 8th April 2015. The study was registered with International Standard Randomised Controlled Trial Number (ISTCTN) number 29621851. The study is reported in line with CONSORT (2010) guidelines.

3. Results

Seventy-seven patients were recruited between 24th November 2015 and 25th October 2018. Of these, 26/77 (34%) were randomised to receive selumetinib alone with 51/77 (66%) randomised to receive selumetinib plus paclitaxel (Figure 1). The median age of patients (IQR)

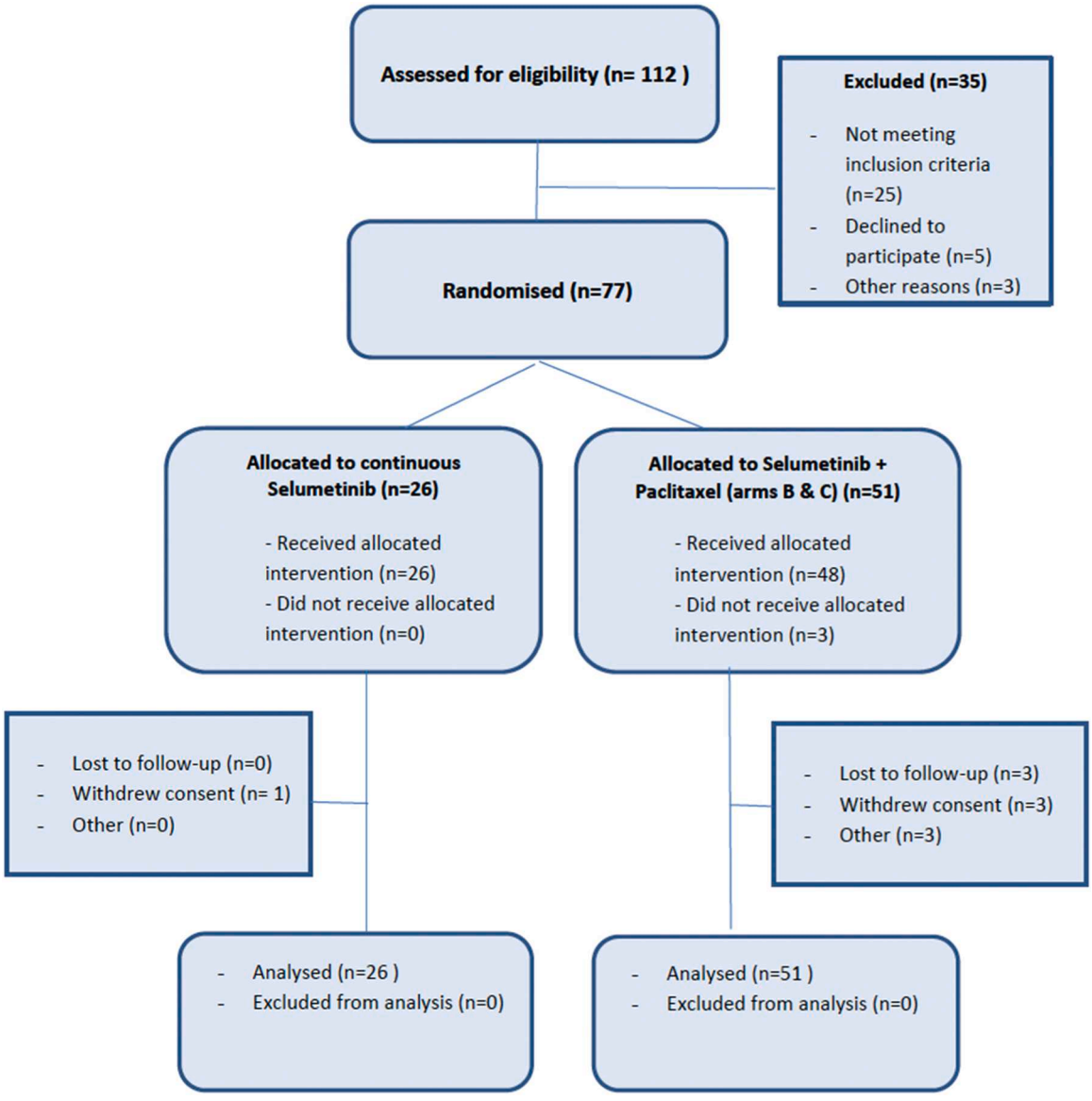

Fig. 1. Consort diagram. All patients randomised to the study were included in the primary ITT analysis of PFS as well as comparison of overall survival between arms, while all patients who received at least one dose of treatment were included in AE analyses. Other reasons for ending study included 1) contrast reaction preventing RECIST assessment of response, 2) clinical deterioration at visit, and further follow up not discussed', and 3) blood tests taken at C1 D1 out of range and therefore unable to proceed with trial treatment.

was 64 (55, 70) with 37/77 (48%) female. A summary of patient demographics in arms A versus B&C is provided in Table 1.

During the study, 4 patients withdrew consent (1 on selumetinib and 3 on combination), whilst 3 patients (all on combination) were lost to follow up and a further 3 patients on combination withdrew for other reasons (Figure 1). Under the ITT principle none of these patients were excluded from the study and analyses were performed on the full population of 77 patients. Median (95% CI) follow-up time for patients was 11.2 (5.8 – undefined).

Median (95% CI) progression free survival was 3.4 (2.0 – 3.9) months for selumetinib alone and 4.8 (3.8 – 5.6) months for selumetinib plus paclitaxel. A statistically significant difference showing improved PFS in the group who received selumetinib plus paclitaxel was observed [HR (90% CI) = 0.62 (0.41 – 0.92); p = 0.022; Figure 2a]. An inspection of Schoenfeld residuals did not show any evidence of non-proportionality. Comparisons between intermittent selumetinib plus paclitaxel vs continuous selumetinib alone [HR (90% CI) = 0.60 (0.37 – 0.98)] and continuous selumetinib plus paclitaxel vs continuous selumetinib alone [HR (90% CI) = 0.66 (0.41 – 1.06)], were consistent with the primary analysis (supplementary figure 1).

The median (95%) OS was 10 (3.8 – 14.6) months for selumetinib alone and 9.0 (6.6 – 12.3) months for selumetinib plus paclitaxel. There was no evidence of difference between treatment arms with respect to overall survival [HR (95% CI) = 0.98 (0.280 – 3.44); p = 0.469; Figure 2b]. There were no complete response observed on the study. Partial responses were observed in 8 patients, with an objective response rate of 4% (1/26) in the selumetinib arm and 14% (7/51) in the selumetinib plus paclitaxel arm [OR (95%CI) = 4.16 (0.48, 25.52); p-val = 0.196].

Table 1
Baseline characteristics. Time from primary or metastatic diagnosis is reported to time of randomisation. *Current site of disease was missing for one patient and no patients had extrahepatic metastases only. Please note, normative p-values are included for illustrative purposes only as a tool to measure baseline imbalance.

	Arm A (26)	Arms B & C (51)	p-value
Demographics			
Age in years, median (IQR)	64.5 (54.0, 71.0)	64 (57.5, 70.0)	0.527
Sex, n(%)			
Female, n(%)	14 (53%)	23 (45%)	
Male, n(%)	12 (46%)	28 (54%)	0.482
Medical History			
Months from primary diagnosis, median (IQR)	39.4 (32.2, 61.9)	55 (30.0, 90.8)	0.219
Months from diagnosis of metastasis, median (IQR)	2.3 (0.9, 12.7)	5.1 (1.8, 9.2)	0.275
Sites of current metastatic disease* , n (%);			
Liver only	10 (38%)	20 (39%)	
Liver + other	16 (61%)	30 (58%)	1
Previous treatment for metastatic disease			
Prior Immunotherapy	13 (50%)	17 (33%)	
Prior Surgery or locoregional therapy	7 (26%)	21 (41%)	
Other	9 (34%)	18 (35%)	
None recorded	7 (26%)	16 (31%)	0.511
Clinical			
ECOG performance at baseline n(%)			
0	12 (46%)	27 (52%)	
1	13 (50%)	21 (41%)	
2	1 (3%)	3 (5%)	0.849
Helsinki stage n(%)			
A	8 (30%)	14 (27%)	
B	13 (50%)	27 (52%)	
C	5 (19%)	10 (19%)	0.949
Biochemistry			
LDH >Upper Limit of Normal n(%)	11 (42%)	34 (66%)	0.052
LDH > 2 *Upper Limit of Normal n(%)	8 (30%)	14 (27%)	0.794
ALP U/l, median (IQR)	103.0 (68.0-142.0)	95.0 (75.0-126.0)	0.613

Table 2
Objective Response Rates.

	Selumetinib alone (n = 26)	Selumetinib + Paclitaxel (B+C) (n = 51)
Complete Response (CR)	0 (0%)	0 (0%)
Partial Response (PR)	1 (4%)	7 (14%)
Stable Disease (SD)	13 (50%)	30 (59%)
Progressive Disease/ Death (PD)	12 (46%)	12 (24%)
Missing		2 (4%)
Objective Response Rate	1 (4%)	7 (14%)
ORR Odds ratio (90% CI), p-value	4.16 (0.68, 25.52); 0.196	

Adverse event incidence and severity in the selumetinib alone (arm A) and selumetinib combined with paclitaxel (Arms B&C) are summarised in Table 3 (including only events where one or more grade 3 event observed). 20/26 (77%) patients on selumetinib alone reported at least one grade 3 or higher adverse event compared to 27/51 (53%) in the selumetinib plus paclitaxel group [OR = 2.92 (0.93, 19.42); p = 0.073]. 11/26 (42%) patients on selumetinib alone and 24/51 (47%) patients on the selumetinib plus paclitaxel group reported at least one SAE [OR = 0.81 (0.28, 2.36); p = 0.827].

Treatment compliance was measured as the percentage of reduced/omitted doses. Selumetinib had a mean percentage reduction/omission of 32% in the selumetinib alone arm and 26% in the selumetinib and paclitaxel arms, while paclitaxel had a mean reaction/omission of 24%. Discontinuations of treatment due to reasons other than death were observed in 23 patients, 17 due to adverse events (6 Selumetinib; 11 Selumetinib + Paclitaxel), one due to intercurrent disease (Selumetinib) and 5 due to 'other' reasons (all Selumetinib + Paclitaxel).

4. Discussion

In the SelPac study we show that selumetinib in combination with paclitaxel was tolerable and resulted in a modest improvement in PFS but with no improvement in overall survival. While these data show that gains can be obtained through judicious combination of MEK inhibitors with other agents in uveal melanoma, this combination lacks sufficient clinical benefit to justify further evaluation in larger scale trials. We saw little difference in outcome (both in treatment response and toxicity) between the use of continuous selumetinib plus paclitaxel and interrupted selumetinib for 48 h prior to treatment with paclitaxel. While the study was not powered after protocol amendment to compare these combinations, the data nonetheless suggest that clinically they were not associated with significantly different outcomes.

Metastatic uveal melanoma remains an area of significant clinical need, with limited treatment options Tebentafusp is now a first line standard of care for patients who are HLA A2.01 positive and who are fit enough to receive the drug [4]. The median OS in this SelPac study of 9–10 months is significantly less than that seen in either control (16 months) or experimental arm (21 months) of the 1st line tebentafusp phase III study [4]. This likely reflects the poorer prognosis of the SelPac population (mixed first and second line population and 40–60% with elevated LDH). Patients who progress post tebentafusp or those who are ineligible because of HLA restriction require improved treatment options.

Activating, driver mutations in either *GNAQ* or *GNA11* are present in the majority of uveal melanoma cases [8,9], providing a potential target for therapy. However, while dual inhibitors of GNAQ and GNA11 have been discovered and show potential activity in preclinical experiments [18], significant concerns remain regarding toxicity as the molecules inhibit both wildtype and mutant *GNAQ/GNA11* and most studies to date (including ours) have instead investigated inhibition of

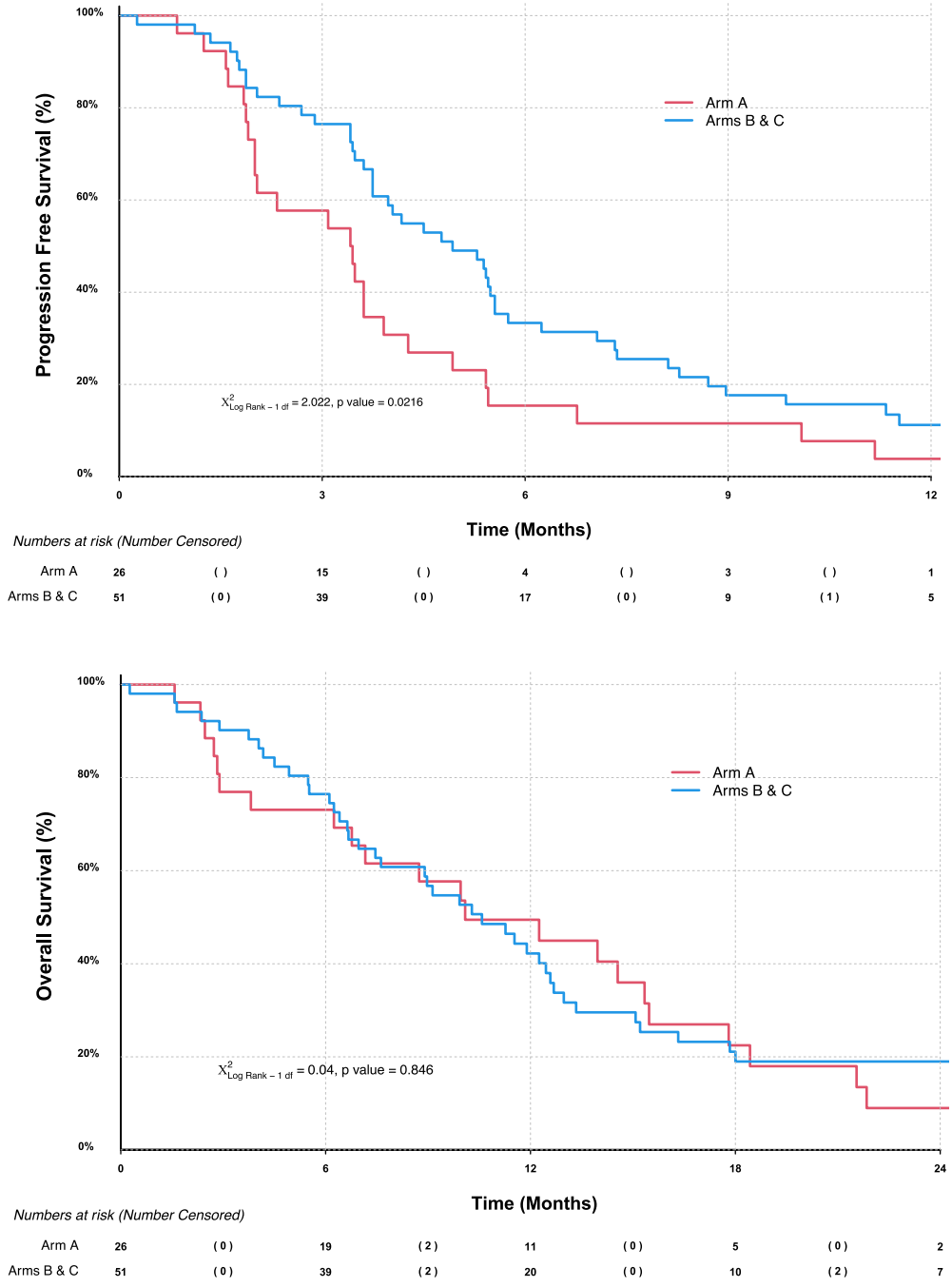

Fig. 2. Kaplan- Meier analyses of (A) progression free survival (PFS) and (B) overall survival (OS).

downstream signalling molecules. The majority of these studies have targeted MEK, for which selective, and well tolerated, inhibitors have been developed and which are licenced in other settings. Whilst some activity has been suggested in MEKi monotherapy studies in UM, this is very modest [12]. This likely reflects the activation of multiple downstream pathways of *GNAQ/GNA11* and cross talk between pathways, providing ongoing survival and proliferative signals. Combinations of MEK inhibitors with other agents targeting the PI3K pathway and/or PKC (a key downstream signalling node), aimed at overcoming this, have to date been hampered by significant additive toxicity. An alternative strategy, utilising a combination of the PKC inhibitor, darovasertib, and the ALK/MET inhibitor, crizotinib, has however shown a promising efficacy signal in an early clinical study (https://www.ideayabio.com/wp-content/uploads/2023/01/20230110_IDEAYA-Investor-Corporate-Presentation-JP-Morgan-Conf-Jan-2023_vFF.pdf) and, subject to confirmation in larger studies, may provide a new therapeutic option in future.

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Cancer Research UK and AstraZeneca. Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures and appendices), will be available 9 - 36 months following article publication to investigators whose proposed use of the data has been approved by an independent review committee (“learned intermediary”) identified for this purpose, for individual participant data meta-analysis. Proposals may be submitted up to 36 months

Table 3
Summary of Toxicity; AEs reported as the number of patients (number of events). Only Adverse events with at least one grade 3 + event were included.

Adverse Event	Arm A (n = 26)			Arms B&C (n = 55)		
	Grade 1/2	**Grade 3**	**Grade 4**	**Grade 1/2**	**Grade 3**	**Grade 4**
Diarrhoea	9 (13)	0	0	32 (64)	2 (2)	0
Rash maculo-papular	14 (38)	4 (6)	0	26 (57)	4 (5)	0
Fatigue	12 (13)	0	0	26 (45)	5 (5)	0
Nausea	4 (5)	0	0	30 (40)	0	0
Pain	9 (13)	1 (1)	0	19 (31)	1 (1)	0
Mucositis oral	3 (4)	0	0	22 (37)	2 (2)	0
Rash acneiform	6 (11)	2 (2)	0	16 (33)	5 (7)	0
Vomiting	3 (4)	0	0	17 (27)	2 (2)	0
Oedema	6 (12)	0	0	14 (17)	1 (1)	0
Hypertension	6 (11)	4 (4)	0	14 (21)	3 (3)	0
Constipation	2 (3)	0	0	18 (24)	0	0
Dysgeusia	1 (1)	0	0	18 (20)	0	0
Alopecia	1 (1)	0	0	18 (23)	1 (1)	0
Anorexia	2 (4)	0	0	16 (22)	0	0
Peripheral sensory neuropathy	1 (1)	0	0	16 (24)	1 (1)	0
Alanine aminotransferase increased	6 (14)	5 (7)	1 (1)	10 (10)	0	0
Dyspnea	2 (3)	0	0	13 (17)	1 (1)	0
Cough	3 (3)	0	0	9 (10)	0	0
Epistaxis	2 (2)	0	0	9 (13)	0	0
Aspartate aminotransferase increased	5 (11)	3 (4)	1 (1)	6 (8)	0	0
Lethargy	2 (2)	0	0	8 (9)	1 (1)	0
Headache	4 (4)	0	0	5 (10)	0	0
Dyspepsia	1 (2)	0	0	8 (11)	0	0
Abdominal pain	2 (3)	1 (1)	0	7 (7)	1 (1)	0
Gastroesophageal reflux disease	2 (2)	0	0	6 (7)	0	0
Fever	1 (1)	0	0	7 (11)	0	0
Dry mouth	3 (3)	0	0	5 (5)	0	0
Blurred vision	2 (4)	0	0	6 (6)	0	0
GGT increased	2 (2)	1 (1)	0	3 (5)	0	0
Rash pustular	2 (2)	1 (1)	0	2 (2)	0	0
Blood bilirubin increased	2 (3)	0	0	2 (5)	1 (1)	0
Alkaline phosphatase increased	2 (2)	0	0	2 (2)	1 (1)	0
Abdominal distension	1 (1)	1 (1)	0	1 (1)	1 (1)	0
Dehydration	1 (1)	0	0	0	1 (1)	0
Biliary tract infection	1 (1)	1 (1)	0	0	0	0

following article publication. After 36 months the data will be available in our University's data warehouse but without investigator support other than deposited metadata. The study protocol will also be made available.

CRediT authorship contribution statement

Ioannis Karydis: Writing – review & editing, Project administration. **Paul Nathan:** Writing – original draft, Project administration, Methodology, Funding acquisition, Conceptualization. **Neil Steven:** Writing – review & editing, Project administration. **Paul Lorigan:** Writing – review & editing, Project administration. **Heather Shaw:** Writing – review & editing, Project administration. **Sebastian Ochsenreither:** Writing – review & editing, Project administration, Funding acquisition. **Serge Leyvraz:** Writing – review & editing, Project administration. **Satish Kumar:** Writing – review & editing, Project administration. **Andrew Goodman:** Writing – review & editing, Project administration. **Louise Handley:** Writing – review & editing, Project administration, Data curation. **James Larkin:** Writing – review & editing, Project administration. **Charlotte Rawcliffe:** Writing – original draft, Project administration, Funding acquisition. **Richard Jackson:** Methodology, Funding acquisition, Formal analysis. **Poulam Patel:** Writing – review & editing, Project administration. **Pippa Corrie:** Writing – review & editing, Project administration. **Eftychia Psarelli:** Writing – review & editing, Formal analysis, Data curation. **Sarah Danson:** Writing – review & editing, Project administration. **Anna Olsson-Brown:** Writing – review & editing, Project administration. **Jeff Evans:** Writing – review & editing, Project administration. **Joseph Sacco:** Writing – original draft, Project administration, Methodology, Funding acquisition, Conceptualisation.

Declaration of Competing Interest

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Data Availability

Data are available upon reasonable request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114009.

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