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ORIGINAL ARTICLE

Meta-analysis in metastatic uveal melanoma to determine progression free and overall survival benchmarks: an international rare cancers initiative (IRCI) ocular melanoma study

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Background: Despite the completion of numerous phase II studies, a standard of care treatment has yet to be defined for metastatic uveal melanoma (mUM). To determine benchmarks of progression free survival (PFS) and overall survival (OS), we carried out a meta-analysis using individual patient level trial data.

Methods: Individual patient variables and survival outcomes were requested from 29 trials published from 2000 to 2016. Univariable and multivariable analysis were carried out for prognostic factors. The variability between trial arms and between therapeutic agents on PFS and OS was investigated.

Results: OS data were available for 912 patients. The median PFS was 3.3 months (95% CI 2.9–3.6) and 6-month PFS rate was 27% (95% CI 24–30). Univariable analysis showed male sex, elevated (i.e. > versus ≤ upper limit of normal) lactate dehydrogenase (LDH), elevated alkaline phosphatase (ALP) and diameter of the largest liver metastasis (≥3 cm versus <3 cm) to be substantially associated with shorter PFS. Multivariable analysis showed male sex, elevated LDH and elevated ALP were substantially associated with shorter PFS. The most substantial factors associated with 6-month PFS rate, on both univariable and multivariable analysis were elevated LDH and ALP. The median OS was 10.2 months (95% CI 9.5–11.0) and 1 year OS was 43% (95% CI 40–47). The most substantial prognostic factors for shorter OS by univariable and multivariable analysis were elevated LDH and elevated ALP. Patients treated with liver directed treatments had statistically significant longer PFS and OS.

Conclusion: Benchmarks of 6-month PFS and 1-year OS rates were determined accounting for prognostic factors. These may be used to facilitate future trial design and stratification in mUM.

Key words: meta-analysis, uveal melanoma, trial design, survival benchmarks

Introduction

Uveal melanoma is the most common intraocular tumour in adults and accounts for 3% of all melanomas [1]. Whereas treatment of the primary melanoma is successful in the majority of cases, metastatic relapse occurs in ∼30% of patients [2–4]. Assays using a variety of techniques have the ability to analyse the primary tumour to predict ultimate progression free (PFS) and overall survival (OS) [5–10]; however to date, there are no prognostic models in newly diagnosed metastatic disease in clinical use and reported OS estimates remain in the range of 3–12 months in unselected populations [11].

Further, there is no standard of care treatment in the metastatic setting where dacarbazine remains a standard control arm in contemporary studies despite limited activity [12–14]. Systemic treatment with a variety of agents has been tested in a multitude of phase I–II studies examining anti-angiogenics, kinase inhibitors, chemotherapies and immunotherapy [11, 15]. These studies have been relatively small and, although some have reported encouraging response rates with heterogeneous survival outcomes, none have resulted in a successful practice changing phase III trial. Indeed, it has been challenging to discern the relative significance of results from early phase non-randomised trials, due to lack of standard of care therapies and established benchmarks for comparison. Understanding prognostic factors and benchmarks for metastatic uveal melanoma will ultimately facilitate rational trial design to target appropriate subgroups given the heterogeneity of disease outcomes. For example, unlike other cancers, a common therapeutic modality is liver directed therapy as >80% of patients initially relapse with liver metastases [1, 16]; however data to support improved survival outcomes with this modality are sparse [11, 15]. Surgical resection may result in long-term survival outcomes for a few but is not feasible in the majority due to extent of disease [17]. Given these considerations [18], we set out to perform a meta-analysis of phase Ib/III trials in metastatic uveal melanoma using patient level data to address critical clinical questions.

Methods

Aims of the study

The primary aims were to: (i) To estimate PFS and OS benchmarks to facilitate planning of future clinical trials, (ii) To identify prognostic markers which could serve as stratification variables in future trials and (iii) To explore whether different classes of treatment are associated with differential outcomes.

Study selection and individual patient level data

Trials were identified from a literature search and reviewed independently by two investigators (LK, AJ). The literature search was conducted using PubMed, www.clinicaltrials.gov, the American Society of Clinical Oncology website (for congress abstracts), Cochrane register of controlled trials and European Society of Medical Oncology meeting abstracts. Studies were restricted to those published between January 1988 and January 2015 and with a minimum of 10 patients prospectively enrolled using a therapy for metastatic disease (either systemic or locoregional which could be given as any line of treatment). Individual investigators were then approached by a steering committee (AJ, LK, SS, SP, RC) to contribute data of all patients treated on protocol. The flow of information through the phases of the review process (of the literature search results) according to the PRISMA statement [19] is shown in supplementary Figure S1 (available at *Annals of Oncology* online).

Individual patient variables at baseline were requested, including age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), time from diagnosis of metastatic disease to start of treatment, treatment received, number of cycles of treatment, line of treatment, number of liver metastases (≥10 or <10), percentage involvement of the liver (>50% or ≤50%), diameter (cm) of the largest liver metastasis, presence of extra-hepatic liver involvement, the response criteria used in the trial, as well as the best response achieved and date of best response, date of progression or last disease evaluation, date of death or last known to be alive. PFS was measured from the date of first treatment to the date of progression or death (or censoring). OS was measured from the date of first treatment to death (or censoring). This meta-analysis was registered in http://www.crd.york.ac.uk/PROSPERO (registration number CRD42014006965) and approved by the University Health Network research ethics board (13-7182-CE).

Statistical analysis

Categorical variables of sex, ECOG status, LDH and ALP [> versus ≤upper limit of normal (ULN)], and presence or absence of extra-hepatic metastases were summarised with counts and percentages. Continuous variables such as LDH and ALP were dichotomised and presented as categorical variables. Variable age was summarised as median with range, and was categorised (≥65 versus <65 years). Within the limits of the data available, the possible prognostic value of all patient characteristics was assessed, including the year the study was published [analysed as a binary covariate (2003–2005 versus 2006–2015)].

The following variables were considered in the assessment of prognostic value in univariate and multivariable analysis: ECOG, age (≥65 versus <65 years), sex, LDH and ALP level, diameter of the largest liver metastasis (<3 versus ≥3 cm) and site of metastases (hepatic versus non hepatic versus both). Binary partitioning techniques were used to obtain the optimum cut-off for the continuous variable of age (65 years). A cut-off for the diameter of the largest liver metastasis of 3 cm was used, aligned with the American Joint Committee on cancer substaging of metastatic uveal melanoma [20] and allowed for appropriate patient numbers in each group [<3 cm ($n = 232$) versus ≥3 cm ($n = 365$), $n = 315$ were missing) for statistical analysis. Other factors relating to liver involvement such as percentage liver involvement were not included in the model as such variables were highly correlated with the diameter of the largest liver metastasis. Factors identified as substantial or of interest in univariate analysis were then assessed in the multivariable setting. In order to account for missing values in the categorical covariates of interest we included an additional 'unknown' category to prevent loss of power in testing the remaining non-missing covariates of interest.

Kaplan–Meier product-limit method was used to estimate time-to-event end point (PFS and OS) distributions, from which, medians and rates at pre-specified time points (6-month PFS and 1-year OS rates)

were obtained. Cox proportional hazards model, using sandwich estimator of variance to account for the collinearity of patients within studies, was used to assess the prognostic importance of different variables (except treatment modalities) both at univariate and multivariable level, based on analyses stratified by treatment modalities. Proportional hazards assumption on each of the prognostic factors was also assessed graphically by using plots of log of minus log survival probability by log of time-to-event. Generalised linear mixed models (PROC GLIMMIX with logit link), that account for the collinearity among patients in the same study, were used to assess the impact of each of the potential prognostic factors to the binary events (6-month PFS rate and 1-year OS rate). Exploration of between trial-arm variability in event rates was carried out comparing event rate of each of the treatment arms with the overall event rate, and whether the trial-arm event rate lies within 95% confidence interval (CI) of the overall mean based on sample size from each trial-arm and by examining for outliers.

We carried out sample size calculations for future phase II trials, aiming to improve the 6-month PFS and/or 1-year OS rates observed in our pooled data [21–26]. Power and sample size were computed using binomial enumeration of all possible outcomes.

All tests were two-tailed, with a probability of <0.05 considered statistically significance. Statistical analyses were carried out using version 9.4 of the SAS System for Windows (SAS Institute, Cary, NC) and the open source statistical software R version 3.3.1 R Core Team, (R Foundation for Statistical Computing, Vienna, Austria) (available at http://www.r-project.org/).

Results

A total of 38 prospective studies were identified and data were obtained from 29 (76%). Reasons for data not being available included a lack of investigator response to requests for data and archived data that were no longer available. Of the 29 studies for which data were available, 5 involved immunotherapy [27–31], 7 involved a kinase inhibitor (of which 2 were randomised studies against temozolomide or dacarbazine, respectively) [12, 32–36], 2 used an anti-angiogenic agent [37, 38], 8 involved chemotherapy (1 of which was a randomised study of intrahepatic versus intravenous chemotherapy) [39–45] and 7 studies involved intrahepatic treatment (chemotherapy or immunotherapy) [46–52] (supplementary Table S1, available at *Annals of Oncology* online).

Data were available for a total of 965 patients. Response data were available for 793 (82%), whilst PFS data were available for 881 (91%) patients, of whom 840 (95%) had progressed or died and 41 (5%) patients were censored. OS data were available for 912 (95%), of whom 817 (90%) had died and 95 (10%) patients were alive. There was both PFS and OS data for 873 (90% of $n = 965$) patients. Therefore, the maximum data available for analysis were for 912 patients, of which 873 were used for PFS analysis. Patient characteristics were reflective of contemporary practice (Table 1). A small number of observations that were censored before the relevant time point (6 months for PFS and 1 year for OS) were omitted from analysis of 6-month PFS rate and 1-year OS rate: 21 (2.4%) and 28 (3%) of patients, respectively.

Table 1. Characteristics of patients (data from n = 912)

Characteristic	Categories	Number (%) ($N = 912$)
Sex	Male	475 (52)
	Female	437 (48)
Age, years (median 61, range 18–90)	<65	550 (60)
	≥65	335 (37)
	Missing	27 (3)
ECOG/performance status	0	475 (52)
	1	229 (25)
	2–3	21 (2)
	Missing	187 (21)
LDH	Normal	330 (36)
	Elevated (greater than ULN)	386 (42)
	Missing	196 (22)
ALP	Normal	428 (47)
	Elevated (greater than ULN)	162 (18)
	Missing	322 (35)
Site of metastases	Hepatic alone	473 (52)
	Hepatic and extra-hepatic	234 (26)
	Extra-hepatic alone	92 (10)
	Missing	113 (12)
Diameter of largest liver metastasis (cm)	<3	232 (25)
	≥3	365 (40)
	Missing	315 (35)
Therapy received	Immunotherapy	133 (15)
	Anti-angiogenic agents	44 (5)
	Kinases	198 (22)
	Chemotherapy	306 (34)
	Liver directed treatment	231 (25)
Line of therapy (as defined on individual trials)	First line	567 (62)
	Second line	126 (14)
	Third line or higher	46 (5)
	Missing	173 (19)

ALP, alkaline phosphatase; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Determining benchmarks of survival for PFS and OS

We analysed the complete dataset ($n = 912$ for OS and $n = 873$ for PFS with matching OS data available) to define historical benchmarks of OS and PFS. The median PFS was 3.3 months (95% CI 2.9–3.6). The 6-month PFS rate was 27% (95% CI 24 –30); Figure 1A. The median OS was 10.2 months (95% CI 9.5–11.0). The 1-year OS rate was 43% (95% CI 40–47); Figure 1B.

Prognostic variables for PFS

Univariate analysis showed that male sex, elevated LDH, elevated ALP and larger diameter of the largest liver metastasis (≥3 versus <3 cm) were associated with shorter PFS (Figure 2A–G). Multivariable analysis revealed that the same variables except larger diameter of the largest liver metastasis (≥3 versus <3 cm) were associated with shorter PFS. Elevated LDH and elevated ALP were important factors by multivariable analysis for inferior 6-month PFS rates (Table 2).

Prognostic variables for OS

Prognostic features for shorter OS by both univariate and multivariable analysis included higher ECOG (≥1 versus 0), male sex,

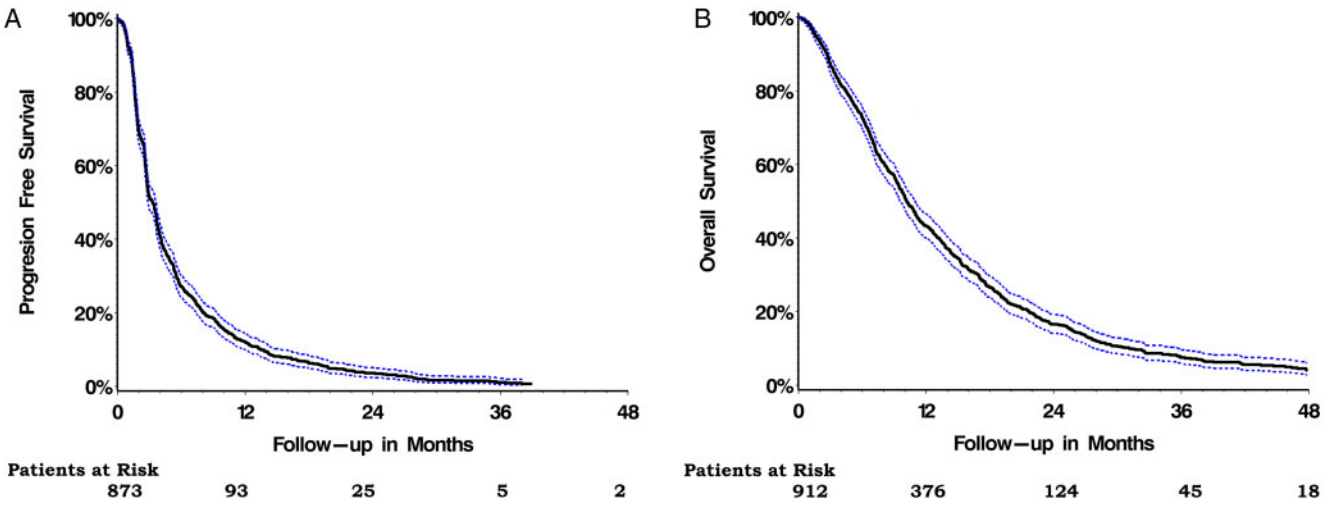

Figure 1. Kaplan–Meier curves and 95% confidence intervals, for the whole dataset, regarding (A) progression free survival and (B) overall survival.

elevated LDH, elevated ALP and larger diameter of the largest liver metastasis (≥3 versus <3 cm). Higher age (≥65 versus <65), male sex, elevated LDH, elevated ALP were significant by multivariable analysis for 1-year OS (Table 3 and Figure 3A–G).

Of note, the year the study was published was not substantial for PFS or OS. For all prognostic factors, the proportional hazards assumption appeared not violated (data not shown).

Survival outcomes between treatment groups and trial-arm variability in 6-month PFS and 1-year OS

Recognising that the time of radiological assessment of disease varied between studies limiting the accuracy and utility of analysis, we carried out an exploratory summary of PFS and OS according to treatment groups. The median PFS for each treatment group was: immunotherapy 2.8 months (95% CI 2.7–3.1), kinase 2.8 months (95% CI 2.7–3.5), anti-angiogenic 2.8 months (95% CI 2.6–5.4), chemotherapy 2.6 months (95% CI 2.3–3.0) and liver directed therapy 5.2 months (95% CI 4.3–5.9), respectively. The median OS for each treatment group was: immunotherapy 8.9 months (95% CI 7.0–11.6), kinase 9.1 months (95% CI 7.0–10.4), anti-angiogenic 11.0 months (95% CI 8.2–15.2), chemotherapy 9.2 months (95% CI 8.4–10.4) and liver directed therapy 14.6 months (95% CI 12.6–17.5), respectively, Figure 4A–B. As an exploratory analysis each treatment group was analysed individually (supplementary Figure S2A–B, available at *Annals of Oncology* online) and the 6-month PFS rates and the 1-year OS rates for treatment group plotted against group sample size. This suggested that only the liver directed treatment arms had a numerically different rate to other treatment modality arms (77% versus 26% for overall 6-month PFS) and 88% versus 42.5% for overall 1-year OS.

Patient characteristics per treatment group were determined (supplementary Table S2, available at *Annals of Oncology* online) and the difference in prognostic factors explored firstly between medical treatment modalities and secondly between medical (all grouped together) and liver directed therapies. ALP and the diameter of the largest liver metastasis differed between trials grouped according to medical treatment modality. When comparing medical to liver directed treatment, gender, age and diameter of the largest liver lesion differed between these two groupings (supplementary Table S3, available at *Annals of Oncology* online). In order to examine the effect of treatment modality when controlling for prognostic factors on PFS and OS, we carried out a multivariable analysis including treatment modality (liver directed versus medical treatment) which suggested that liver directed treatment was prognostic for PFS and OS (supplementary Tables S4 and S5, available at *Annals of Oncology* online, respectively).

Determining separate benchmarks of survival for PFS and OS for medical and liver directed therapy

Given the differences in survival and the prognostic benefit of liver directed treatment described above we additionally explored separate benchmarks for medical directed therapy and liver directed therapy. For medical treatment the median PFS was 2.8 months (95% CI 2.7—2.9), 6-month PFS rate was 21.5% (95% CI 18.4—24.8), Figure 5A. The median OS was 9.3 months (95% CI 8.4–10.1). The 1-year OS rate was 38.4% (95% CI 34.7–42.1), Figure 5B. For liver directed therapy the median PFS was 5.2 months (95% CI 4.3–5.9), the 6-month PFS rate was 43.3% (95% CI 36.7–49.9); Figure 5C. The median OS was 14.6 months (95% CI 12.6–17.5). The 1-year OS rate was 57.2% (95% CI 50.5–63.3); Figure 5D.

Discussion

We aimed to establish benchmarks of survival and prognostic factors to guide patient care and future trial design. The survival outcomes we used (6-month PFS and 1-year OS rates) are in line with a previous analysis of cutaneous melanoma [18], and have added relevance in the era of immunotherapeutics where traditional RECIST response rates may imprecisely correlate with OS [53].

Several prognostic factors for overall survival in metastatic uveal melanoma patients have been proposed from previous studies [54–56]. Here we sought to validate and build upon these

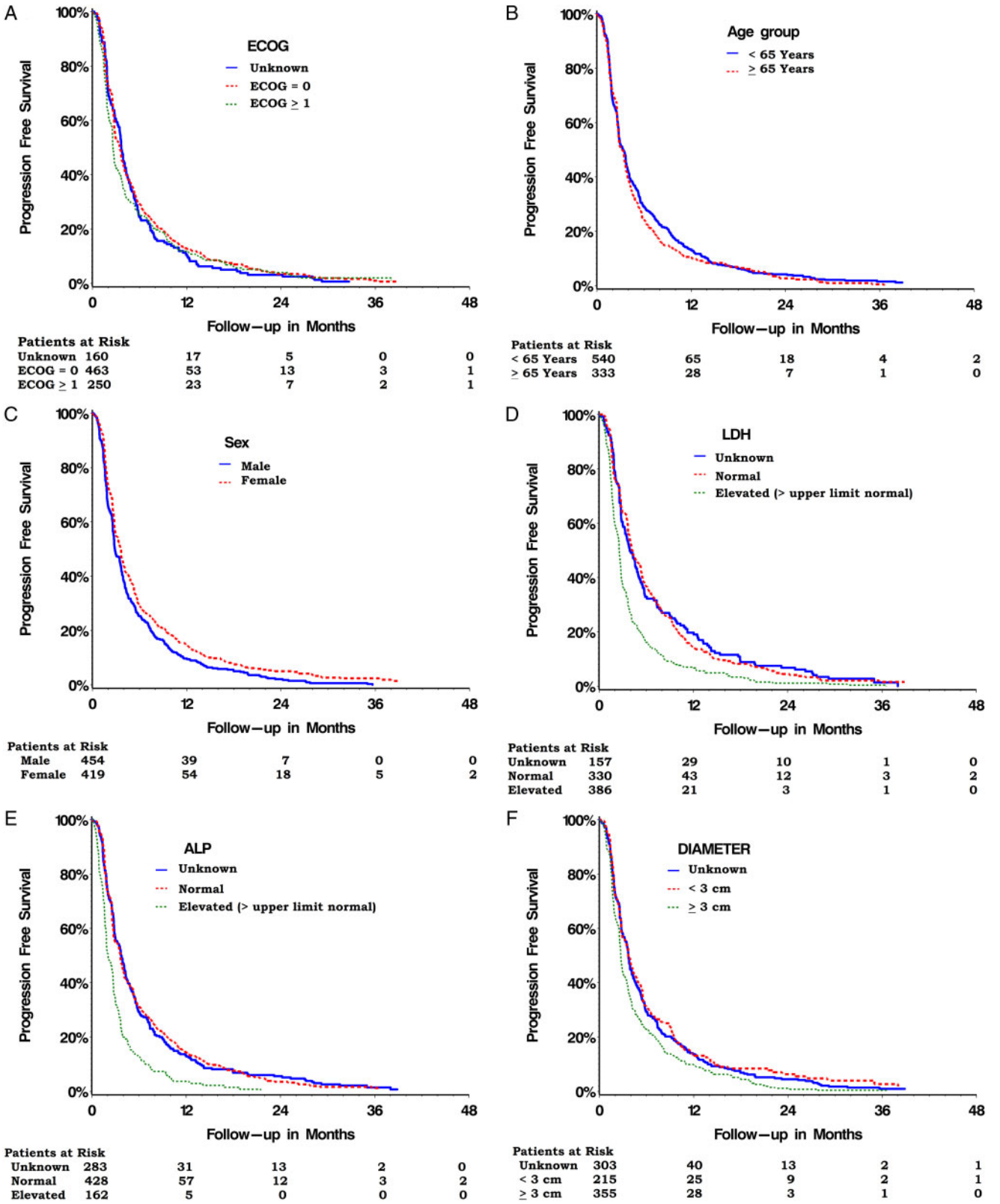

Figure 2. Kaplan–Meier curves for progression free survival from start of treatment according to: (A) Eastern Cooperative Oncology Group (ECOG), (B) Age, (C) Sex, (D) lactate dehydrogenase (LDH), (E) alkaline phosphatase (ALP), (F) diameter of the largest liver metastasis and (G) site(s) of metastases.

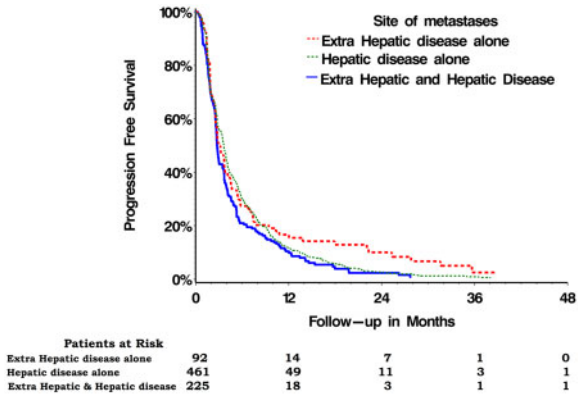

Figure 2. Continued.

Table 2. Prognostic factors by univariable and multivariable analysis for progression free survival (PFS)

Variable	No. of patients ($n = 873$)	PFS distribution				6-month PFS rates			
		Univariable		Multivariable		Univariable		Multivariable	
		HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value	OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
ECOG Performance									
0	463	Ref	0.08	Ref	0.13	Ref	0.07	Ref	0.04
≥1	250	1.15 (0.96–1.38)		1.04 (0.92–1.18)		0.85 (0.58–1.27)		1.07 (0.71–1.62)	
Unknown	160	1.32 (0.98–1.79)		1.41 (1.01–1.98)		0.47 (0.25–0.91)		0.42 (0.21–0.84)	
Age									
< 65 years	540	Ref	0.28			Ref	0.19		
> 65 years	333	1.10 (0.93–1.30)				0.80 (0.57–1.11)			
Sex									
Female	419	Ref	<0.001	Ref	<0.001	Ref	0.20	Ref	0.10
Male	454	1.22 (1.10–1.35)		1.26 (1.10–1.45)		0.81 (0.59–1.11)		0.76 (0.55–1.06)	
LDH									
Normal	330	Ref		Ref		Ref		Ref	
Elevated > ULN	386	1.66 (1.35–2.04)	<0.001	1.53 (1.29–1.82)	<0.001	0.33 (0.22–0.49)	<0.001	0.37 (0.24–0.56)	<0.001
Unknown	157	0.98 (0.73–1.33)		0.97 (0.75–1.26)		0.92 (0.55–1.54)		0.84 (0.47–1.51)	
ALP									
Normal	428	Ref		Ref		Ref		Ref	
Elevated > ULN	162	1.91 (1.49–2.43)	<0.001	1.56 (1.25–1.93)	<0.001	0.33 (0.19–0.57)	<0.001	0.46 (0.26–0.82)	0.03
Unknown	283	1.06 (0.85–1.32)		0.98 (0.79–1.21)		0.82 (0.48–1.38)		0.89 (0.50–1.60)	
Diameter of the largest liver metastasis									
<3 cm	215	Ref		Ref		Ref		Ref	
>3 cm	355	1.37 (1.13–1.66)	0.005	1.20 (1.03–1.39)	0.06	0.66 (0.43–1.01)	0.14	0.93 (0.59–1.46)	0.53
Unknown	303	1.24 (0.90–1.69)		1.10 (0.85–1.44)		0.87 (0.50–1.51)		1.28 (0.72–2.28)	

Data were not available for all variables, the maximum number of patients analysed for any variable was 873 for whom both PFS and OS data were available.

ALP, alkaline phosphatase; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; OR, odds ratio; Ref, reference subgroup; ULN, upper limit of normal.

in patients participating in clinical trials. Heterogeneity or interactions of factors may imply that many overlap in their prognostic significance and further study will better define the significance of factors and optimal cut-off values. For example, the diameter of the largest liver lesion and the percentage liver involvement are both utilised, but both measure tumour bulk.

The difference in outcomes in the different treatment groups is intriguing. It appears that patients selected for liver directed

Table 3. Prognostic factors by univariable and multivariable analysis for overall survival (OS)

Variable	No. of patients ($n = 912$)	OS distribution				1 year OS rates			
		Univariable		Multivariable		Univariate		Multivariable	
		HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value	OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
ECOG performance status									
0	475	Ref		Ref		Ref		Ref	
≥1	250	1.49 (1.25–1.78)	<0.001	1.26 (1.11–1.44)	0.002	0.48 (0.34–0.68)	<0.001	0.69 (0.47-	0.16
Unknown	187	1.13 (0.85–1.49)		1.04 (0.86–1.26)		0.76 (0.47–1.23)		0.91 (0.56–1.49)	
Age									
< 65 years	550	Ref		Ref		Ref		Ref	
> 65 years	335	1.21 (1.02–1.43)	0.01	1.12 (0.97–1.31)	<0.001	0.66 (0.50–0.89)	0.01	0.68 (0.49–0.93)	0.01
Unknown	27	1.59 (1.16–2.17)		1.76 (1.30–2.38)		0.30 (0.09–1.08)		0.28 (0.09–0.87)	
Sex									
Female	437	Ref	<0.001	Ref	<0.001	Ref	<0.001	Ref	<0.001
Male	475	1.38 (1.18–1.60)		1.41 (1.16–1.72)		0.60 (0.45–0.79)		0.56 (0.41–0.75)	
LDH									
Normal	330	Ref		Ref		Ref		Ref	
Elevated > ULN	386	2.64 (2.11–3.30)	<0.001	2.31 (1.87–2.87)	<0.001	0.16 (0.11–0.22)	<0.001	0.19 (0.13–0.28)	<0.001
Unknown	196	1.89 (1.38–2.59)		1.64 (1.13–2.36)		0.34 (0.22–0.52)		0.41 (0.27–0.64)	
ALP									
Normal	428	Ref		Ref		Ref		Ref	
Elevated > ULN	162	2.76 (2.27–3.36)	<0.001	1.98 (1.61–2.42)	<0.001	0.20 (0.12–0.32)	<0.001	0.36 (0.22–0.59)	<0.001
Unknown	322	1.37 (1.13–1.67)		1.12 (0.90–1.38)		0.68 (0.44–1.04)		0.92 (0.62–1.37)	
Diameter of the largest liver metastasis									
<3 cm	232	Ref		Ref		Ref		Ref	
>3 cm	365	1.65 (1.41–1.93)	<0.001	1.26 (1.10–1.45)	0.002	0.42 (0.29–0.60)	<0.001	0.69 (0.46–1.03)	0.17
Unknown	315	1.34 (1.01–1.78)		1.25 (0.97–1.63)		0.70 (0.44–1.10)		0.91 (0.56–1.46)	

Data were not available for all variables, the maximum number of patients analysed for any variable was 912.
ALP, alkaline phosphatase; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; OR, odds ratio; Ref, reference subgroup; ULN, upper limit of normal.

treatment have better survival. They may be earlier in the disease trajectory, but we could not evaluate line of therapy as a factor due to these data being variably defined in each trial, or their improved survival may reflect a more indolent disease due to biological factors or surveillance imaging. Moreover, a recent analysis suggested that performance status, LDH and diameter of the largest liver metastasis at baseline may not efficiently predict prognosis if liver surgery is part of the treatment [56]. Increasing disease burden in the liver appeared to be associated with increased disease elsewhere but we were unable to determine whether the site of first metastases was substantial as previously reported [57] nor if time from diagnosis of primary tumour or metastatic disease to start of treatment correlated with increased disease burden (the data were not obtainable or largely missing in our dataset).

Importantly, the survival curves that we have generated could serve to determine whether a new treatment is worthy of further study and may facilitate the conduction of standard or adaptively designed trials with appropriately informed benchmarks to lead to quicker registration of therapeutic agents. Our study emulates the Korn meta-analysis of phase II trials in cutaneous melanoma published in 2008 [18]. Benchmarks of PFS and OS were established in that study using patient level data from 42 phase II trials and established criteria to support registrational indications. We anticipate these data may have similar utility in the future. The survival curves calculated using our data could be used as the comparator to new trial data and further study warranted if a specific significance criterion is met [18]. Alternatively, the observed PFS or OS rate from our analysis may be used to calculate adequate power and sample size for a prospective trial (supplementary Tables S6–S8, available at *Annals of Oncology* online). Using our data as a whole, 49 patients would be required to test in order to detect whether a new treatment increases the 6-month PFS rate by 20% (from the current 27%–47%), at an alpha error of 5% and a power of 80%; if 19 patients have a PFS >6 months then the new treatment should be investigated further. Similarly 56 patients would be needed to test if the 1-year OS rate is increased by 20% (from the current 43%–63%) at 90% power; if

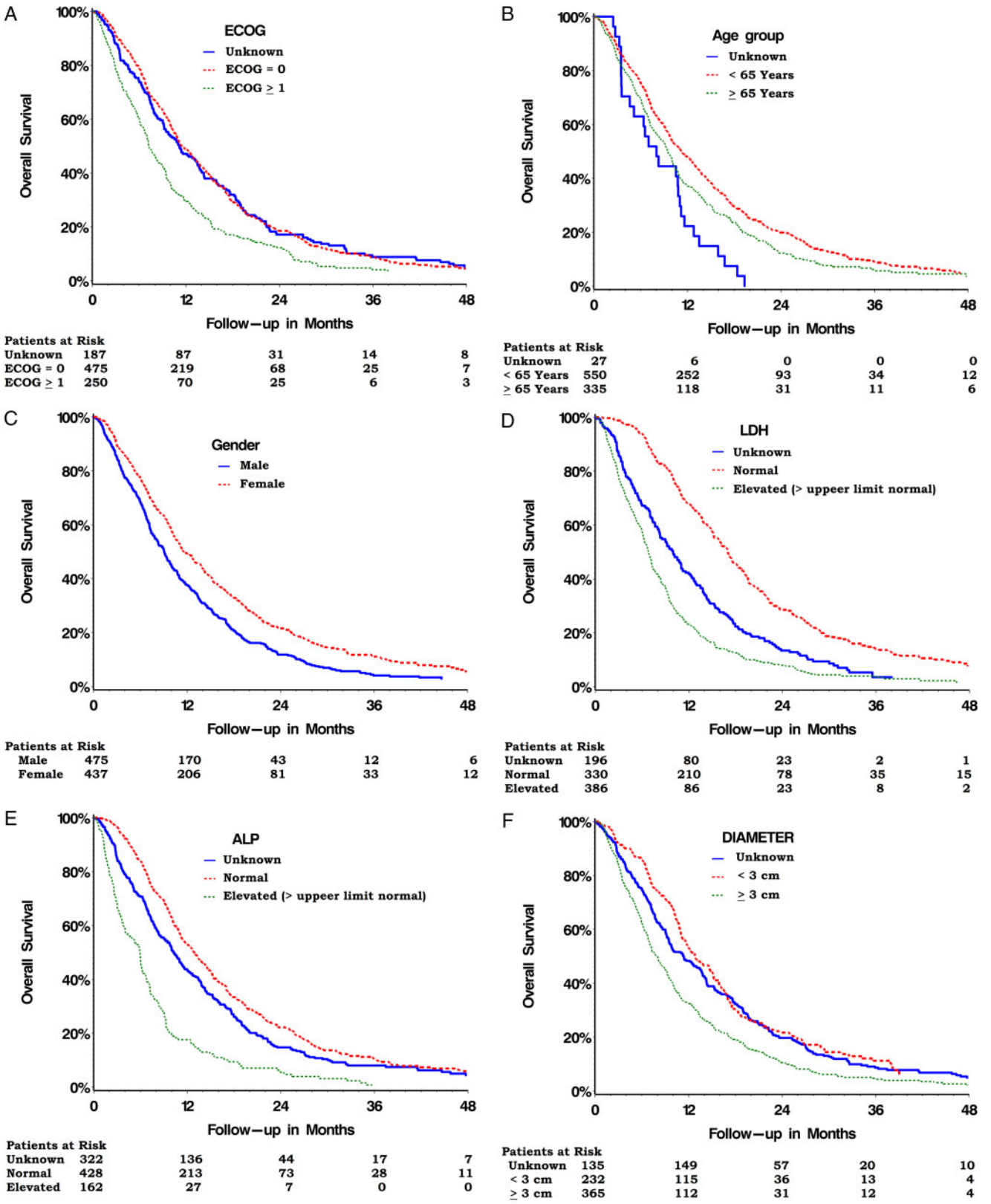

Figure 3. Kaplan–Meier curves for overall survival according to: (A) Eastern Cooperative Oncology Group (ECOG), (B) Age, (C) Sex, (D) lactate dehydrogenase (LDH), (E) alkaline phosphatase (ALP), (F) diameter of the largest liver metastasis, (G) site(s) of metastases.

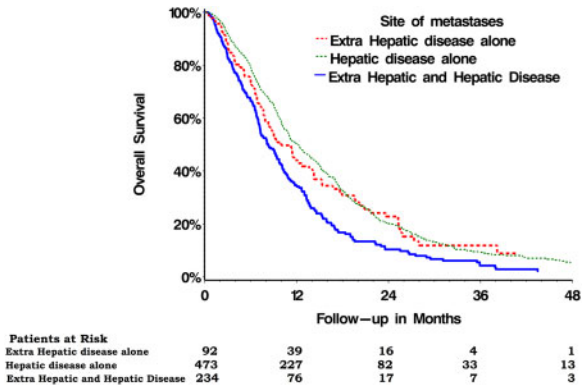

Figure 3. Continued.

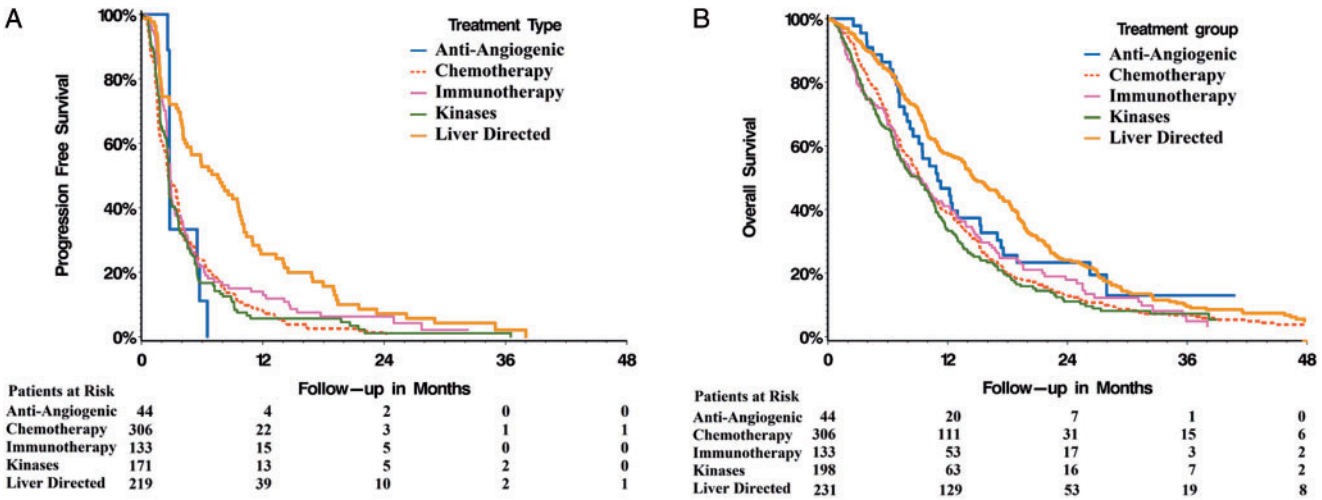

Figure 4. Kaplan–Meier curves according to treatment modality received, regarding (A) progression free survival and (B) overall survival.

31 patients have an OS > 1 year then further trial of this treatment is warranted. The benchmarks for systemic therapy or liver directed therapy could be similarly utilised (supplementary Tables S7 and S8, available at *Annals of Oncology* online).

Whilst informative, our study has limitations: (i) patients included in this analysis were fit for clinical trials, generally ECOG 0–1 with preserved organ function (ii) whilst all trials were carried out prospectively the data used in our analysis was obtained from prospectively collected records or collected retrospectively and in some cases the completeness of the data (not all data fields were collected by all investigators) limited the analysis and (iii) we produced population wide benchmarks and subgroups benchmarks according to therapy. The inclusion of liver directed therapies in an overall benchmark analysis could increase heterogeneity of the study population given that these treatments are given in cases of isolated liver disease and are not consistent with the systemic nature of the other treatments; however, many patients with liver only disease still receive systemic therapies.

Our analysis needs refinement, as our datasets enlarge, to simplify and improve the accuracy and utility of the prognostic factors. We were limited in our ability to explore the effect of liver tumour bulk on prognosis and the effect of subsequent treatments after trial participation on survival was also unknown as we did not have access to this data. Lastly the ability to define a population suitable for liver only directed treatment will lead to distinct treatment paradigms and require different survival benchmarks for trial design, a possibility we explore here but one that requires further work.

In conclusion, our meta-analysis indicates that PFS and OS from metastatic uveal melanoma remain poor in clinical trials published over the last 13 years. The benchmarks and analyses provided here may guide future trial design in metastatic uveal melanoma patients where a standard of care is yet to be defined. In light of our analysis, we encourage investigators globally to continue to collaborate to improve the staging, prognostication and care of patients with metastatic uveal melanoma.

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Disclosure

All authors have declared no conflict of interest.

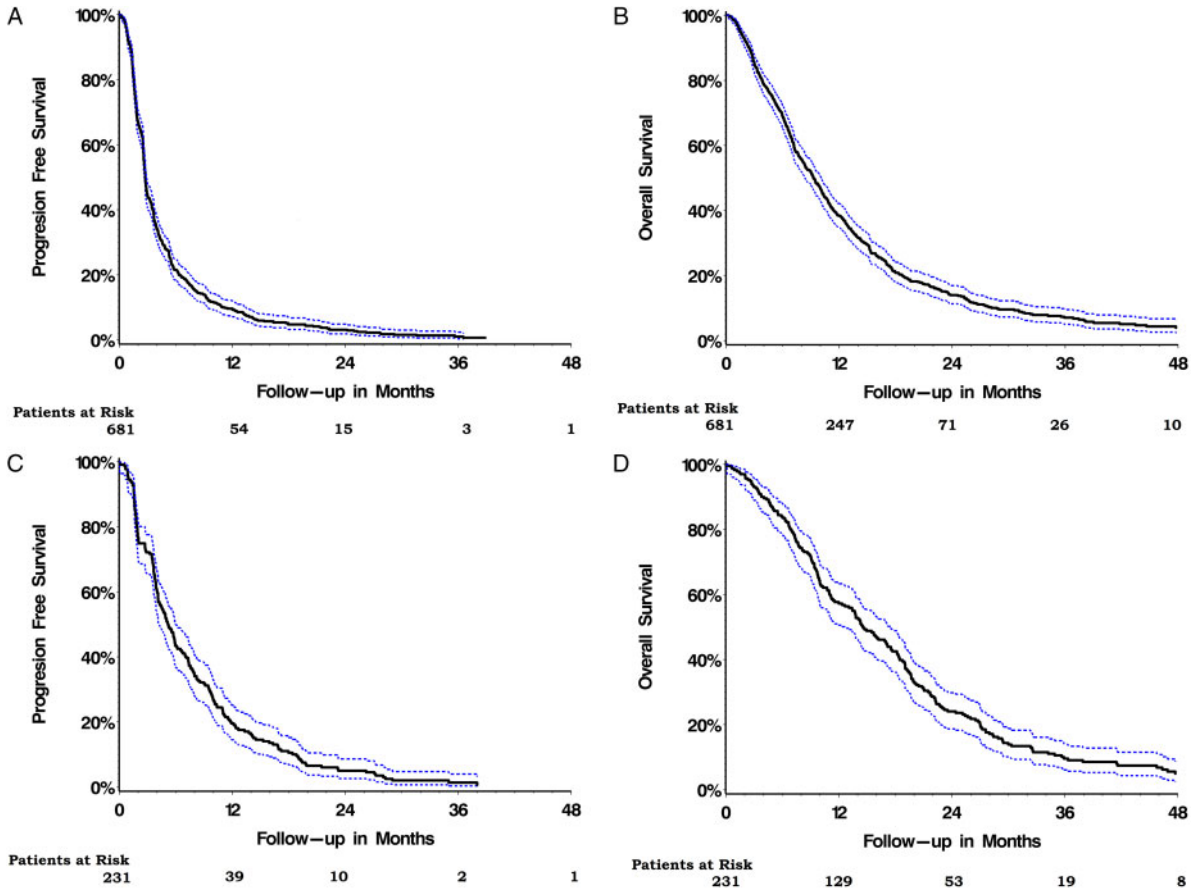

Figure 5. Kaplan–Meier curves and 95% confidence intervals for medical treatment alone, regarding (A) progression free survival and (B) overall survival; and for liver directed therapy alone, regarding (C) progression free survival and (D) overall survival.

References

1. Singh AD, Turell ME, Topham AK. Uveal melanoma: trends in incidence, treatment, and survival. Ophthalmology 2011; 118(9): 1881–1885.
2. Kujala E, Makitie T, Kivela T. Very long-term prognosis of patients with malignant uveal melanoma. Invest Ophthalmol Vis Sci 2003; 44(11): 4651–4659.
3. Diener-West M, Reynolds SM, Agugliaro DJ et al. Screening for metastasis from choroidal melanoma: the collaborative ocular melanoma study group report 23. J Clin Oncol 2004; 22(12): 2438–2444.
4. Collaborative Ocular Melanoma Study Group. Assessment of metastatic disease status at death in 435 patients with large choroidal melanoma in the collaborative ocular melanoma study (COMS): COMS report no. 15. Arch Ophthalmol 2001; 119: 670–676.
5. Coupland SE, Lake SL, Zeschnigk M, Damato BE. Molecular pathology of uveal melanoma. Eye (Lond) 2013; 27(2): 230–242.
6. Onken MD, Worley LA, Char DH et al. Collaborative ocular oncology group report number 1: prospective validation of a multi-gene prognostic assay in uveal melanoma. Ophthalmology 2012; 119(8): 1596–1603.
7. Field MG, Decatur CL, Kurtenbach S et al. PRAME as an independent biomarker for metastasis in uveal melanoma. Clin Cancer Res 2016; 22(5): 1234–1242.
8. Martin M, Maßhöfer L, Temming P et al. Exome sequencing identifies recurrent somatic mutations in EIF1AX and SF3B1 in uveal melanoma with disomy 3. Nat Genet 2013; 45(8): 933–936.
9. Harbour JW, Onken MD, Roberson ED et al. Frequent mutation of BAP1 in metastasizing uveal melanomas. Science 2010; 330(6009): 1410–1413.
10. Moore AR, Ceraudo E, Sher JJ et al. Recurrent activating mutations of G-protein-coupled receptor CYSLTR2 in uveal melanoma. Nat Genet 2016; 48(6): 675–680.
11. Augsburger JJ, Correa ZM, Shaikh AH. Effectiveness of treatments for metastatic uveal melanoma. Am J Ophthalmol 2009; 148(1): 119–127.
12. Carvajal RD, Sosman JA, Quevedo JF et al. Effect of selumetinib vs chemotherapy on progression-free survival in uveal melanoma: a randomized clinical trial. JAMA 2014; 311(23): 2397–2405.
13. Dummer R, Hauschild A, Lindenblatt N et al. Cutaneous melanoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; 26(Suppl 5): v126–v132.
14. Carvajal RD, Piperno-Neumann S, Kapiteijn E et al. Selumetinib in combination with dacarbazine in patients with metastatic uveal melanoma: a phase III, multicenter, randomized trial (SUMIT). J Clin Oncol 2018; 36(12): 1232–1239.
15. Buder K, Gesierich A, Gelbrich G, Goebeler M. Systemic treatment of metastatic uveal melanoma: review of literature and future perspectives. Cancer Med 2013; 2(5): 674–686.
16. Diener-West M, Reynolds SM, Agugliaro DJ et al. Development of metastatic disease after enrollment in the COMS trials for treatment of choroidal melanoma: collaborative ocular melanoma study group report no. 26. Arch Ophthalmol 2005; 123: 1639–1643.
17. Gomez D, Wetherill C, Cheong J et al. The Liverpool uveal melanoma liver metastases pathway: outcome following liver resection. J Surg Oncol 2014; 109(6): 542–547.
18. Korn EL, Liu PY, Lee SJ et al. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. J Clin Oncol 2008; 26(4): 527–534.

19. Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009; 339: b2535.
20. Edge SB, Carducci MA, Compton CC. AJCC Cancer Staging Manual, 7th edition. New York: Springer 2009.
21. A'Hern RP. Sample size tables for exact single-stage phase II designs. Stat Med 2001; 20(6): 859–866.
22. Chow SCS, Wang H. Sample Size Calculations in Clinical Research. Florida: Chapman and Hall 2008.
23. Fleiss JL, Levin B, Paik MC. Statistical Methods for Rates and Proportions. New York: John Wiley & Sons 2003.
24. Lachin JM. Biostatistical Methods. New York: John Wiley & Sons 2000.
25. Machin D, Campbell M, Fayers P, Pinol A. Sample Size Tables for Clinical Studies. Malden, MA: Blackwell Science 1997.
26. Ryan TP. Sample Size Determination and Power. Hoboken, NJ: John Wiley & Sons 2013.
27. Bol KF, Mensink HW, Aarntzen EH et al. Long overall survival after dendritic cell vaccination in metastatic uveal melanoma patients. Am J Ophthalmol 2014; 158(5): 939–947.
28. Joshua AM, Monzon JG, Mihalcioiu C et al. A phase 2 study of tremelimumab in patients with advanced uveal melanoma. Melanoma Res 2015; 25(4): 342–347.
29. Piulats Rodriguez JM, Ochoa de Olza M, Codes M et al. Phase II study evaluating ipilimumab as a single agent in the first-line treatment of adult patients (Pts) with metastatic uveal melanoma (MUM): the GEM-1 trial. J Clin Oncol 2014; 32: 9033.
30. Zimmer L, Vaubel J, Mohr P et al. Phase II DeCOG-study of ipilimumab in pretreated and treatment-naive patients with metastatic uveal melanoma. PLoS One 2015; 10(3): e0118564.
31. Kivela T, Suciu S, Hansson J et al. Bleomycin, vincristine, lomustine and dacarbazine (BOLD) in combination with recombinant interferon alpha-2b for metastatic uveal melanoma. Eur J Cancer 2003; 39: 1115–1120.
32. Nathan PD, Marshall E, Smith CT et al. A cancer research UK two-stage multicenter phase II study of imatinib in the treatment of patients with c-kit positive metastatic uveal melanoma (ITEM). ASCO Meeting Abstr 2012; 30: 8523.
33. Mahipal A, Tijani L, Chan K et al. A pilot study of sunitinib malate in patients with metastatic uveal melanoma. Melanoma Res 2012; 22(6): 440–446.
34. Penel N, Delcambre C, Durando X et al. O-Mel-Inib: a Cancero-pole Nord-Ouest multicenter phase II trial of high-dose imatinib mesylate in metastatic uveal melanoma. Invest New Drugs 2008; 26(6): 561–565.
35. Bhatia S, Moon J, Margolin KA et al. Phase II trial of sorafenib in combination with carboplatin and paclitaxel in patients with metastatic uveal melanoma: SWOG S0512. PLoS One 2012; 7(11): e48787.
36. Mouriaux F, Servois V, Parienti JJ et al. Sorafenib in metastatic uveal melanoma: efficacy, toxicity and health-related quality of life in a multicentre phase II study. Br J Cancer 2016; 115(1): 20–24.
37. Tarhini AA, Frankel P, Margolin KA et al. Aflibercept (VEGF trap) in inoperable stage III or stage iv melanoma of cutaneous or uveal origin. Clin Cancer Res 2011; 17(20): 6574–6581.
38. Piperno-Neumann S, Diallo A, Etienne-Grimaldi MC et al. Phase II trial of bevacizumab in combination with temozolomide as first-line treatment in patients with metastatic uveal melanoma. Oncologist 2016; 21(3): 281–282.
39. Pfohler C, Cree IA, Ugurel S et al. Treosulfan and gemcitabine in metastatic uveal melanoma patients: results of a multicenter feasibility study. Anticancer Drugs 2003; 14: 337–340.
40. Leyvraz S, Piperno-Neumann S, Suciu S et al. Hepatic intra-arterial versus intravenous fotemustine in patients with liver metastases from uveal melanoma (EORTC 18021): a multicentric randomized trial. Ann Oncol 2014; 25(3): 742–746.
41. Bedikian AY, Papadopoulos N, Plager C et al. Phase II evaluation of temozolomide in metastatic choroidal melanoma. Melanoma Res 2003; 13(3): 303–306.
42. Homsi J, Bedikian AY, Papadopoulos NE et al. Phase 2 open-label study of weekly docosahexaenoic acid-paclitaxel in patients with metastatic uveal melanoma. Melanoma Res 2010; 20(6): 507–510.
43. Keilholz U, Schuster R, Schmittel A et al. A clinical phase I trial of gemcitabine and treosulfan in uveal melanoma and other solid tumours. Eur J Cancer 2004; 40(14): 2047–2052.
44. Schmittel A, Schmidt-Hieber M, Martus P et al. A randomized phase II trial of gemcitabine plus treosulfan versus treosulfan alone in patients with metastatic uveal melanoma. Ann Oncol 2006; 17(12): 1826–1829.
45. Schmittel A, Schuster R, Bechrakis NE et al. A two-cohort phase II clinical trial of gemcitabine plus treosulfan in patients with metastatic uveal melanoma. Melanoma Res 2005; 15(5): 447–451.
46. Sato T, Eschelman DJ, Gonsalves CF et al. Immunoembolization of malignant liver tumors, including uveal melanoma, using granulocyte-macrophage colony-stimulating factor. J Clin Oncol 2008; 26(33): 5436–5442.
47. van Iersel LB, Hoekman EJ, Gelderblom H et al. Isolated hepatic perfusion with 200 mg melphalan for advanced noncolorectal liver metastases. Ann Surg Oncol 2008; 15: 1891–1898.
48. Huppert PE, Fierlbeck G, Pereira P et al. Transarterial chemoembolization of liver metastases in patients with uveal melanoma. Eur J Radiol 2010; 74(3): e38–e44.
49. Patel K, Sullivan K, Berd D et al. Chemoembolization of the hepatic artery with BCNU for metastatic uveal melanoma: results of a phase II study. Melanoma Res 2005; 15(4): 297–304.
50. Valsecchi ME, Terai M, Eschelman DJ et al. Double-blinded, randomized phase II study using embolization with or without granulocyte-macrophage colony-stimulating factor in uveal melanoma with hepatic metastases. J Vasc Interv Radiol 2015; 26(4): 523–532.
51. Vogl T, Eichler K, Zangos S et al. Preliminary experience with transarterial chemoembolization (TACE) in liver metastases of uveal malignant melanoma: local tumor control and survival. J Cancer Res Clin Oncol 2007; 133(3): 177–184.
52. Fiorentini G, Aliberti C, Del Conte A et al. Intra-arterial hepatic chemoembolization (TACE) of liver metastases from ocular melanoma with slow-release irinotecan-eluting beads. Early results of a phase II clinical study. In Vivo 2009; 23: 131–137.
53. Gimotty PA, Guerry D, Flaherty K. Using benchmarks based on historical survival rates for screening new therapies for stage IV melanoma patients. J Clin Oncol 2008; 26(4): 517–518.
54. Valpione S, Moser JC, Parrozzani R et al. Development and external validation of a prognostic nomogram for metastatic uveal melanoma. PLoS One 2015; 10(3): e0120181.
55. Eskelin S, Pyrhonen S, Hahka-Kemppinen M et al. A prognostic model and staging for metastatic uveal melanoma. Cancer 2003; 97(2): 465–475.
56. Kivela TT, Piperno-Neumann S, Desjardins L et al. Validation of a prognostic staging for metastatic uveal melanoma: a collaborative study of the European Ophthalmic Oncology Group. Am J Ophthalmol 2016; 168: 217–226.
57. Rietschel P, Panageas KS, Hanlon C et al. Variates of survival in metastatic uveal melanoma. J Clin Oncol 2005; 23(31): 8076–8080.