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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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Running head: Meta-Analysis of metastatic uveal melanoma trials

Abstract

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 performed a meta-analysis using individual patient level trial data.

METHODS: Individual patient variables and survival outcomes were requested from 29 trials published from 2000-2016. Univariable and multivariable analysis were performed 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 to 3.6) and 6-month PFS rate was 27% (95% CI 24 to 30). Univariable analysis showed male sex, elevated (i.e. > vs ≤ upper limit of normal (ULN)) lactate dehydrogenase (LDH), elevated alkaline phosphatase (ALP) and diameter of the largest liver metastasis (≥3cm vs <3cm) to be significantly associated with shorter PFS. Multivariable analysis showed male sex, elevated LDH, and elevated ALP were significantly associated with shorter PFS. The most significant 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 to 11.0) and 1 year OS was 43% (95% CI 40 to 47). The most significant 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.

Abstract: 271 words

Body: 3070 words

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

Key message: A meta-analysis of early phase trials in metastatic uveal melanoma to establish survival benchmarks for future trial design. Prognostic factors are also defined for stratification purposes.

Introduction

Uveal melanoma is the most common intraocular tumor in adults and accounts for 3% of all melanomas[1]. Whereas treatment for the primary melanoma is successful in the majority of cases, metastatic relapse occurs in approximately 30% of patients[2-4]. Assays using a variety of techniques have the ability to analyse the primary tumor 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 to 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-randomized 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 1) To estimate PFS and OS benchmarks to facilitate planning of future clinical trials, 2) To identify prognostic markers which could serve as stratification variables in future trials and 3) 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 2 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 (ESMO) 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 loco-regional 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] are shown in supplementary figure 1.

Individual patient variables at baseline were requested, including age, sex, 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 (> vs ≤ ULN), and presence or absence of extrahepatic metastases were summarized with counts and percentages. Continuous variables such as LDH and ALP were dichotomized and presented as categorical variables. Variable age was summarized as median with range, and was categorized (≥65 vs < 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 vs 2006-2015).

The following variables were considered in the assessment of prognostic value in univariate and multivariable analysis: ECOG, age (≥65 vs <65 years), sex, LDH and ALP level, diameter of the largest liver metastasis (<3cm vs ≥3cm) and site of metastases (hepatic vs non hepatic vs 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 (AJCC) substaging of metastatic uveal melanoma[20] and allowed for appropriate patient numbers in each group (<3cm (n=232) vs ≥3cm (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 significant 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 endpoint (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 modelling, 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. Generalized 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 performed 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 performed 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 performed 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 randomized study of intrahepatic vs intravenous chemotherapy)[39-45] and 7 studies involved intrahepatic treatment (chemotherapy or immunotherapy)[46-52] (supplementary table 1).

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 was 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.

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 (≥3cm vs. <3cm) were associated with shorter PFS (figure 2A-G). Multivariable analysis revealed that the same variables except larger diameter of the largest liver metastasis (≥3cm vs. <3cm) were associated with shorter PFS. Elevated LDH and elevated ALP were significant 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 vs 0), male sex, elevated LDH, elevated ALP and larger diameter of the largest liver metastasis (≥3cm vs <3cm vs). Higher age (≥65 vs <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 significant 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 performed 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 2A-B) 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% vs 26% for overall 6-month PFS) and 88% vs 42.5% for overall 1-year OS.

Patient characteristics per treatment group were determined (supplementary table 2) 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 3). In order to examine the effect of treatment modality when controlling for prognostic factors on PFS and OS, we performed a multivariable analysis including treatment modality (liver directed vs medical treatment) which suggested that liver directed treatment was prognostic for PFS and OS (Supplementary Tables 4 and 5 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 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 tumor bulk.

The difference in outcomes in the different treatment groups is intriguing. It appears that patients selected for liver directed 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 if the site of first metastases was significant as previously reported[57] nor if time from diagnosis of primary tumor 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 if 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 criteria 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 data and tables 6-8). 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% to 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% to 63%) at 90% power; if 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 7-8)

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 performed 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 post 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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Figure legends

Figure 1

Kaplan-Meier curves and 95% confidence intervals, for the whole dataset, regarding A) Progression free survival and B) Overall survival

Figure 2

Kaplan-Meier curves for progression free survival from start of treatment according to: A) ECOG, B) Age, C) Sex, D) LDH, E) ALP, F) Diameter of the largest liver metastasis G) Site(s) of metastases

Figure 3

Kaplan-Meier curves for overall survival according to: A) ECOG, B) Age, C) Sex, D) LDH, E) ALP, F) Diameter of the largest liver metastasis, G) Site(s) of metastases

Figure 4

Kaplan-Meier curves according to treatment modality received, regarding A) Progression free survival and B) Overall survival

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.

Supplementary Figure 1-online

Flow of information through the phases of review process (of the literature search results) according to the PRISMA statement. 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 (ESMO) meeting abstracts. Studies were restricted to those published between 1988 and Jan 2016 and with a minimum of 10 patients prospectively enrolled using a therapy in metastatic disease (either systemic or loco-regional which could be given as any line of treatment).

Supplementary Figure 2-online

The outcomes for each trial arm compared to the sample size for each of the trial arms for A) Progression free survival (PFS) at 6 months and B) Overall survival (OS) at 1 year. Each trial is colour coded according to treatment modality evaluated; immunotherapy (blue), kinases (black), anti-angiogenic agents (green), chemotherapy (brown) or liver directed therapy (red)

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

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

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

Variable	No 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 ≥1 Unknown	463 250 160	Ref 1.15 (0.96-1.38) 1.32 (0.98-1.79)	0.08	Ref 1.04 (0.92-1.18) 1.41 (1.01-1.98)	0.13	Ref 0.85 (0.58-1.27) 0.47 (0.25-0.91)	0.07	Ref 1.07 (0.71-1.62) 0.42 (0.21-0.84)	0.04
Age < 65 Years ≥ 65 Years	540 333	Ref 1.10 (0.93-1.30)	0.28			Ref 0.80 (0.57-1.11)	0.19		
Sex Female Male	419 454	Ref 1.22 (1.10-1.35)	<0.001	Ref 1.26 (1.10-1.45)	<0.001	Ref 0.81 (0.59-1.11)	0.20	Ref 0.76 (0.55-1.06)	0.10
LDH Normal Elevated>ULN Unknown	330 386 157	Ref 1.66 (1.35-2.04) 0.98 (0.73-1.33)	<0.001	Ref 1.53 (1.29-1.82) 0.97 (0.75-1.26)	<0.001	Ref 0.33 (0.22-0.49) 0.92 (0.55-1.54)	<0.001	Ref 0.37 (0.24-0.56) 0.84 (0.47-1.51)	<0.001
ALP Normal Elevated>ULN Unknown	428 162 283	Ref 1.91 (1.49-2.43) 1.06 (0.85-1.32)	<0.001	Ref 1.56 (1.25-1.93)	<0.001	Ref 0.33 (0.19-0.57)	<0.001	Ref 0.46 (0.26-0.82) 0.89 (0.50-1.60)	0.03

				0.98 (0.79-1.21)		0.82 (0.48-1.38)			
Diameter of the largest liver metastasis < 3 cm ≥ 3 cm Unknown	215 355 303	Ref 1.37 (1.13-1.66) 1.24 (0.90-1.69)	0.005	Ref 1.20 (1.03-1.39) 1.10 (0.85-1.44)	0.06	Ref 0.66 (0.43-1.01) 0.87 (0.50-1.51)	0.14	Ref 0.93 (0.59-1.46) 1.28 (0.72-2.28)	0.53

HR: hazard ratio, OR: odds ratio, ref: reference subgroup

Table 3: Prognostic factors by univariable and multivariable analysis for overall survival (OS; data were not available for all variables, the maximum number of patients analysed for any variable was 912).

Variable		OS Distribution				1 Year OS Rates			
	No. of Patients	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 ≥1 Unknown	 475 250 187	 Ref 1.49 (1.25-1.78) 1.13 (0.85-1.49)	 <0.001 	 Ref 1.26 (1.11-1.44) 1.04 (0.86-1.26)	 0.002 	 Ref 0.48 (0.34-0.68) 0.76 (0.47-1.23)	 <0.001 	 Ref 0.69 (0.47-1.01) 0.91 (0.56-1.49)	 0.16
Age < 65 Years ≥ 65 Years Unknown	 550 335 27	 Ref 1.21 (1.02-1.43) 1.59 (1.16-2.17)	 0.01 	 Ref 1.12 (0.97-1.31) 1.76 (1.30-2.38)	 <0.001 	 Ref 0.66 (0.50-0.89) 0.30 (0.09-1.08)	 0.01 	 Ref 0.68 (0.49-0.93) 0.28 (0.09-0.87)	 0.01
Sex Female Male	 437 475	 Ref 1.38 (1.18-1.60)	 <0.001 	 Ref 1.41 (1.16-1.72)	 <0.001 	 Ref 0.60 (0.45-0.79)	 <0.001 	 Ref 0.56 (0.41-0.75)	 <0.001
LDH Normal Elevated>ULN Unknown	 330 386 196	 Ref 2.64 (2.11-3.30) 1.89 (1.38-2.59)	 <0.001 	 Ref 2.31 (1.87-2.87) 1.64 (1.13-2.36)	 <0.001 	 Ref 0.16 (0.11-0.22) 0.34 (0.22-0.52)	 <0.001 	 Ref 0.19 (0.13-0.28) 0.41 (0.27-0.64)	 <0.001
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)	

HR: hazard ratio, OR: odds ratio, ref: reference subgroup

Figure 1A

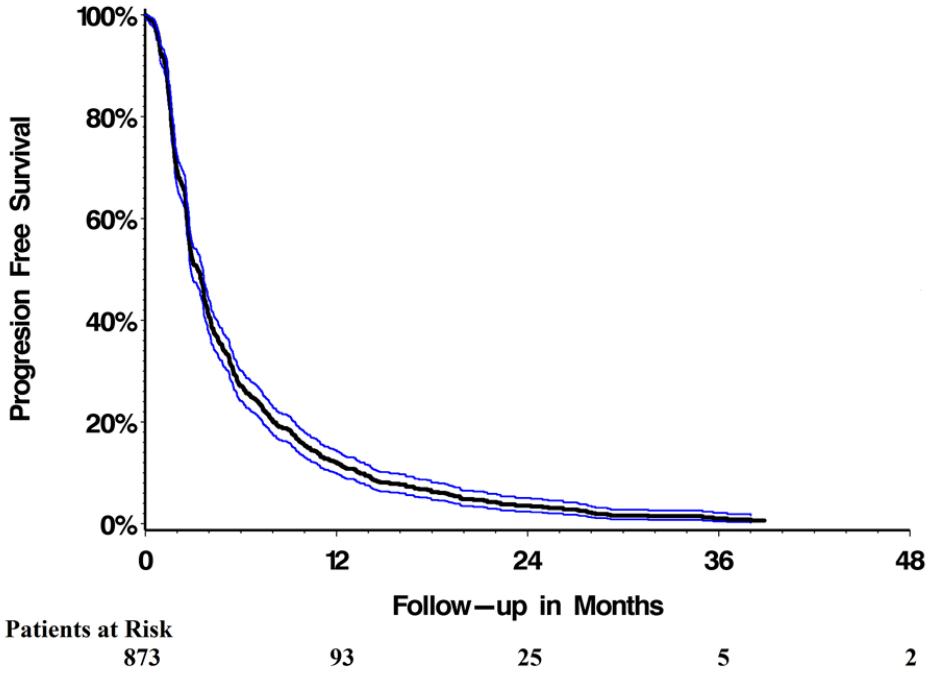

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Figure 1B

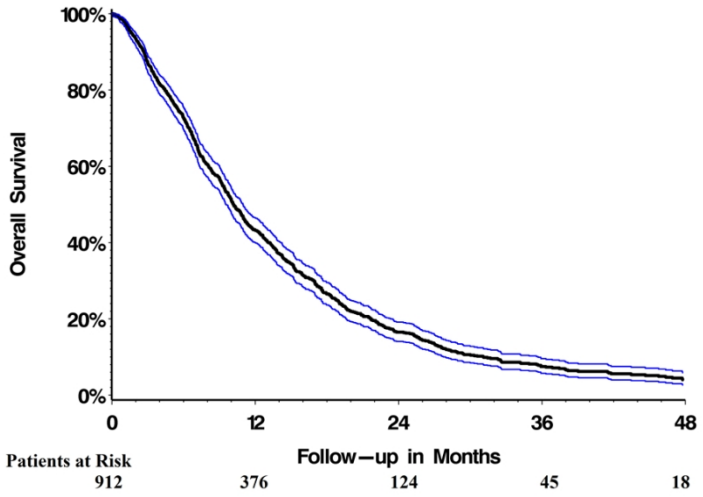

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Figure 2A

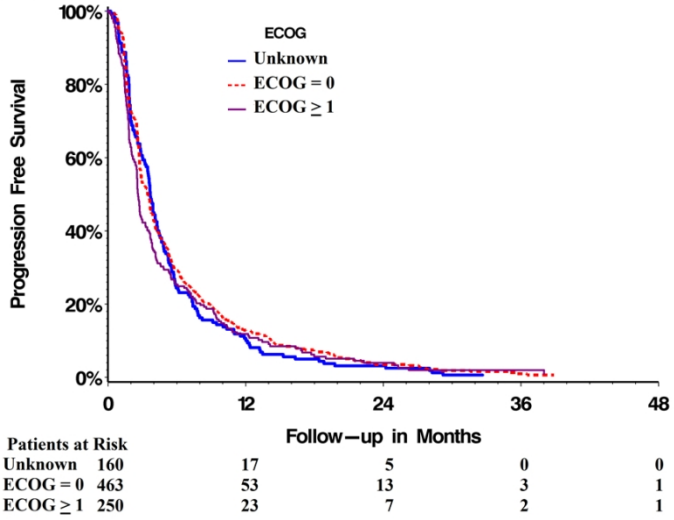

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Figure 2B

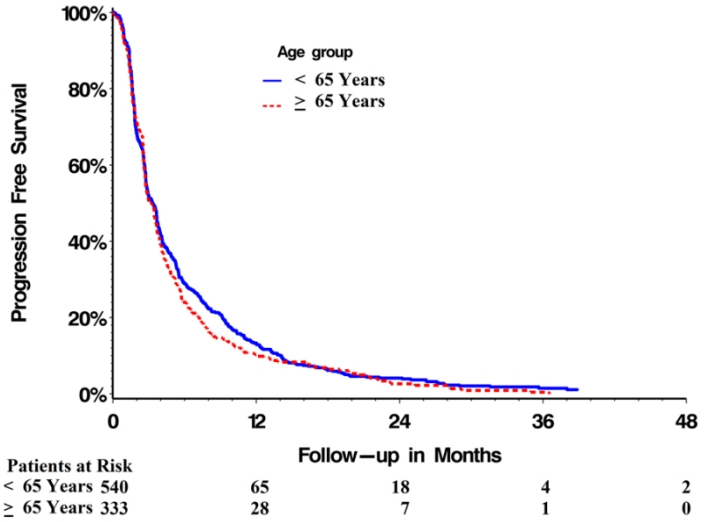

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Figure 2C

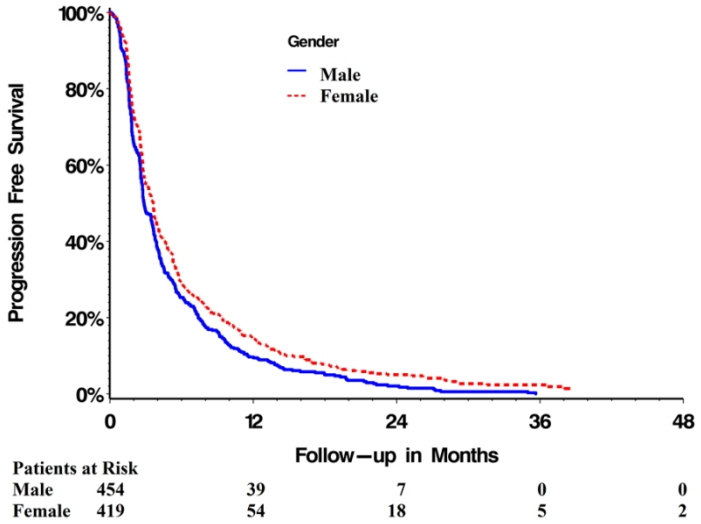

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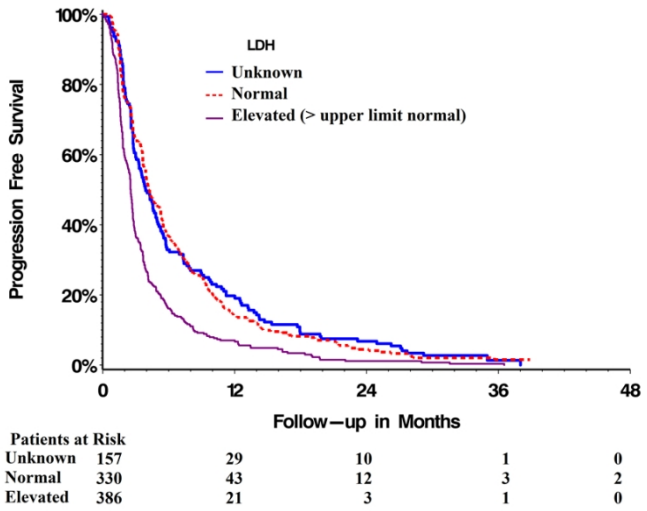
Figure 2D



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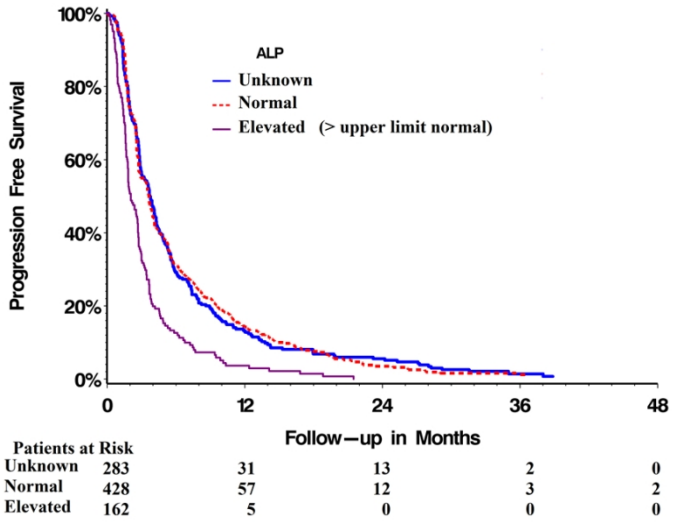

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Figure 2F

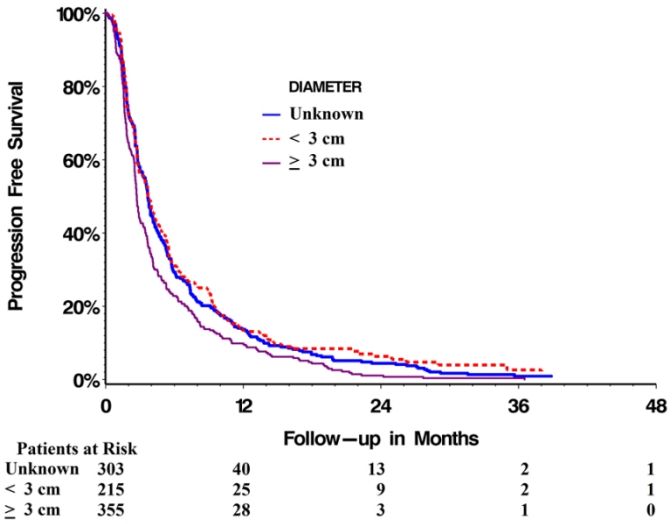

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Figure 2G

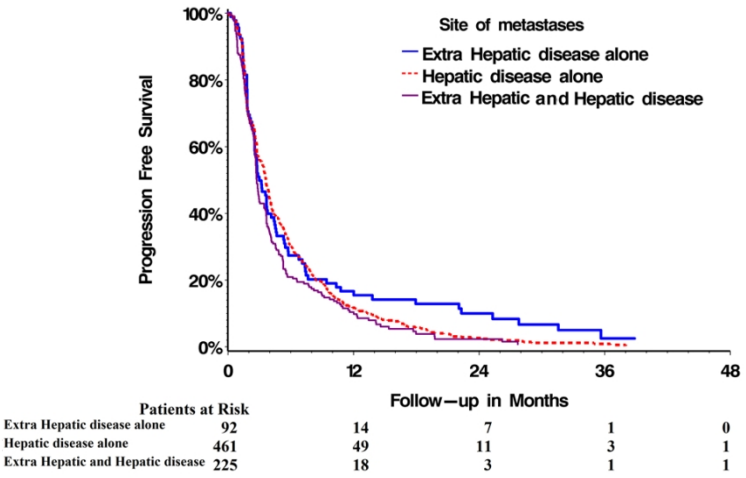

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Figure 3A

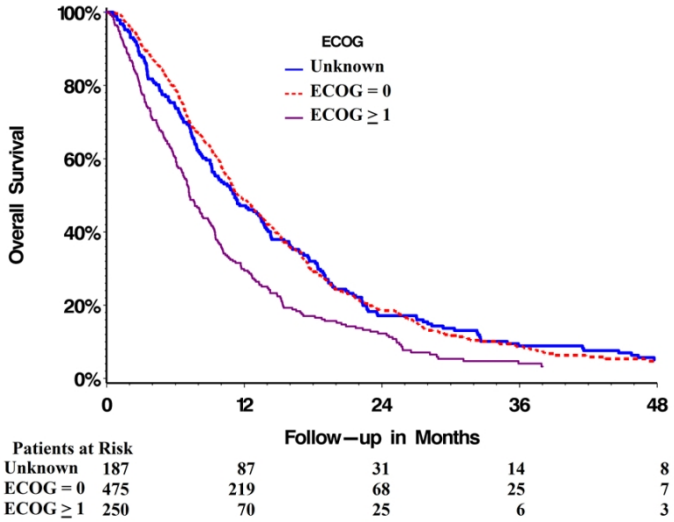

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Figure 3B

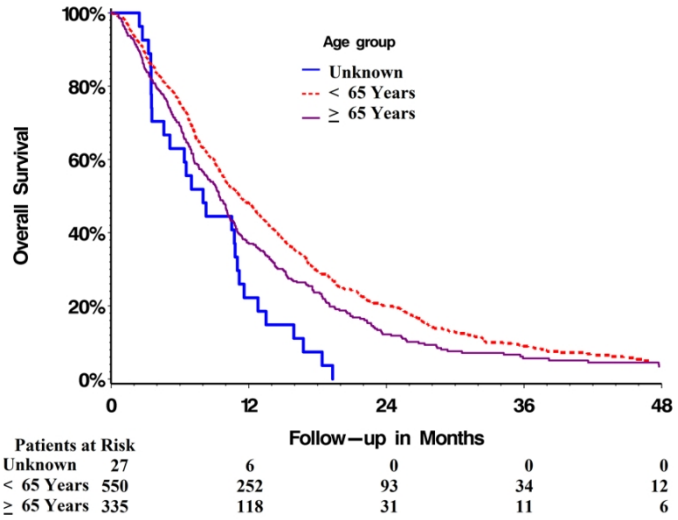

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Figure 3C

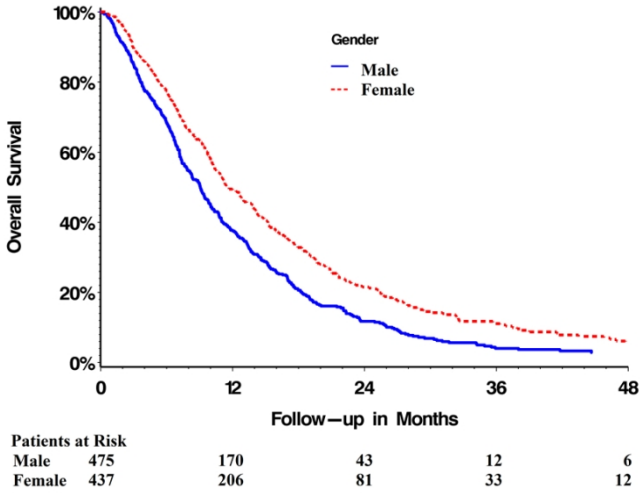

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Figure 3D

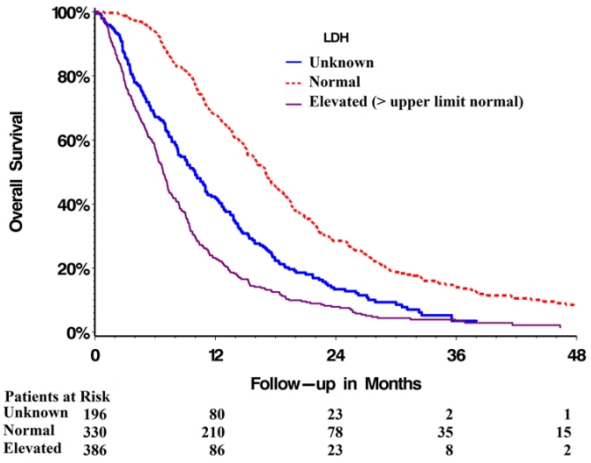

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Figure 3E

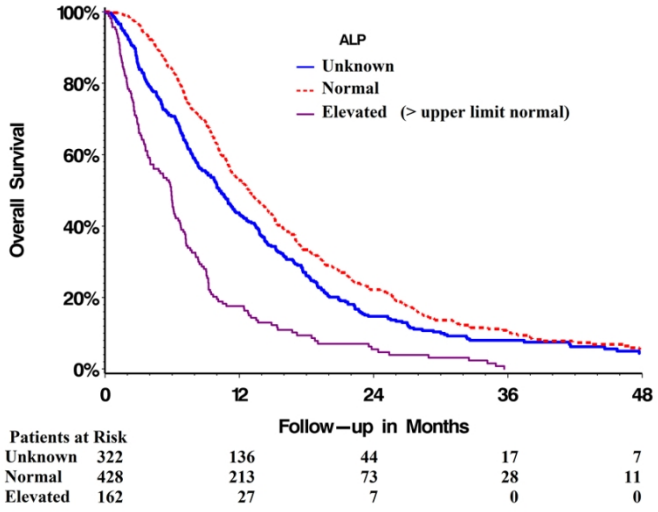

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Figure 3F

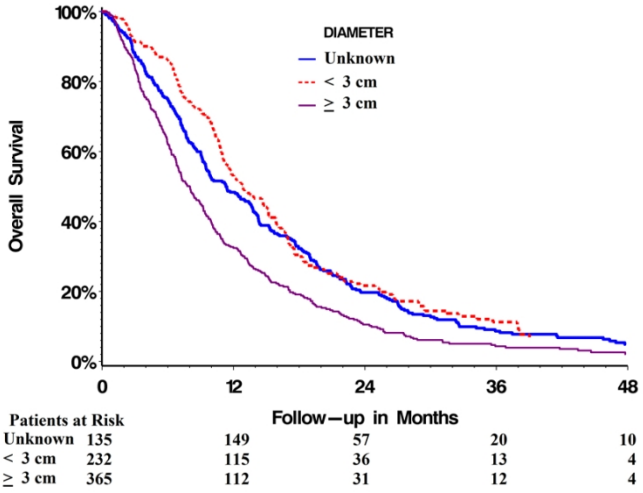

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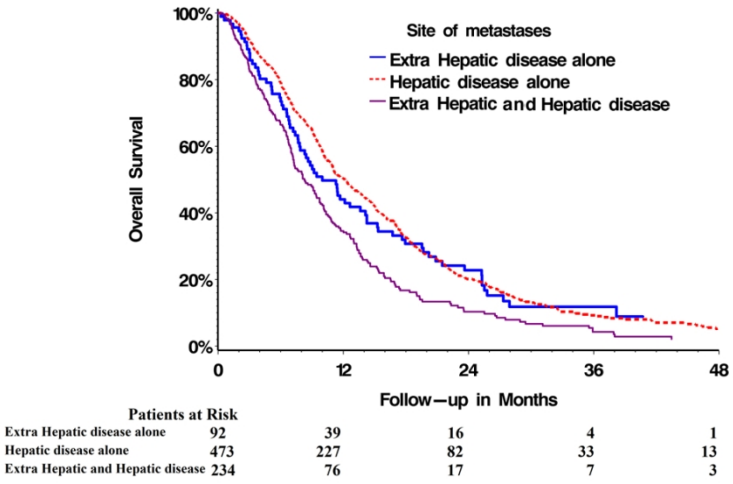
Figure 3G



Patients at Risk					
Extra Hepatic disease alone	92	39	16	4	1
Hepatic disease alone	473	227	82	33	13
Extra Hepatic and Hepatic disease	234	76	17	7	3

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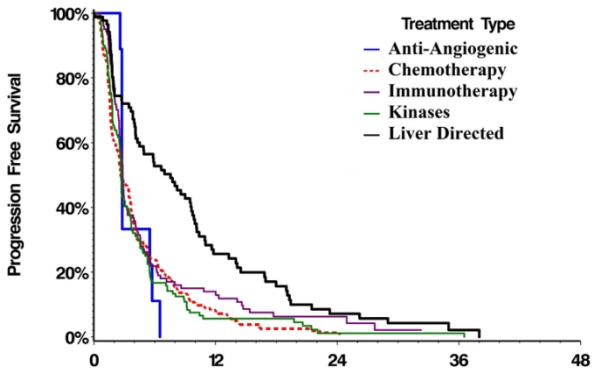
Figure 4A



Patients at Risk					
Anti-Angiogenic	44	4	2	0	0
Chemotherapy	306	22	3	1	1
Immunotherapy	133	15	5	0	0
Kinases	171	13	5	2	0
Liver Directed	219	39	10	2	1

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Figure 4B

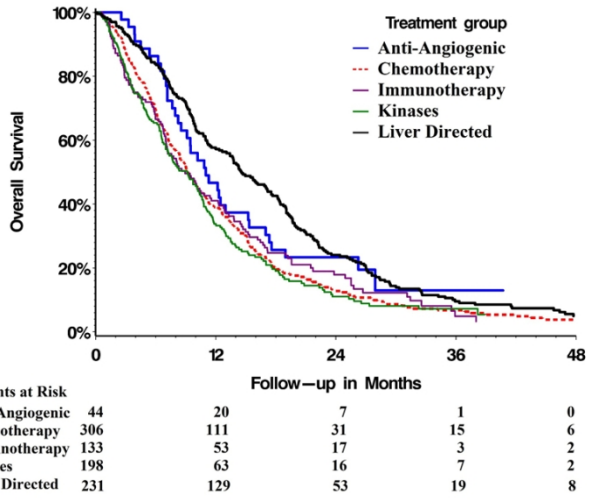

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Figure 5A

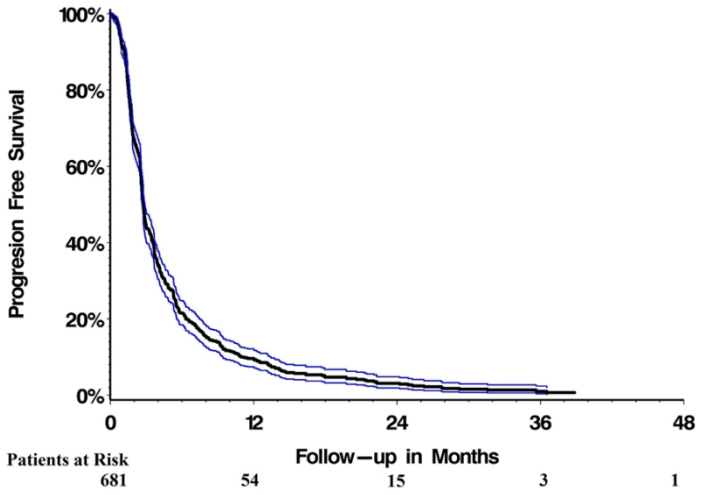

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Figure 5B

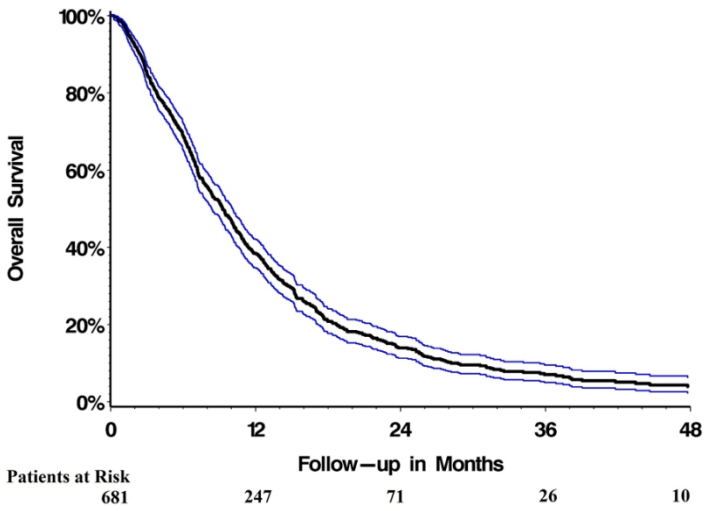

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Figure 5C

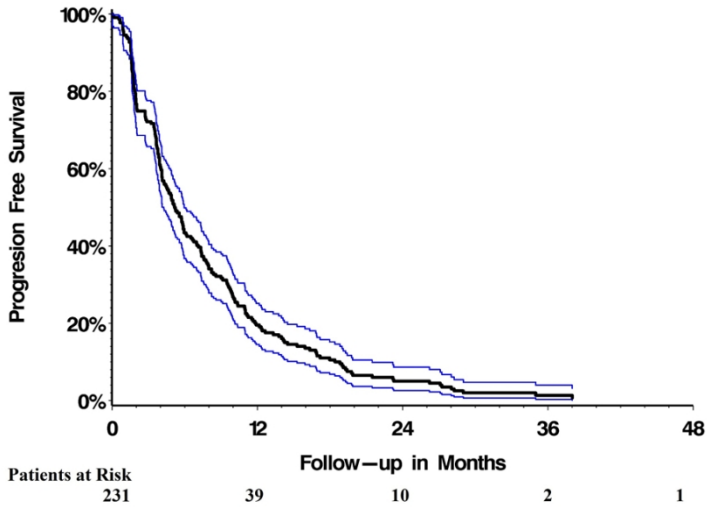

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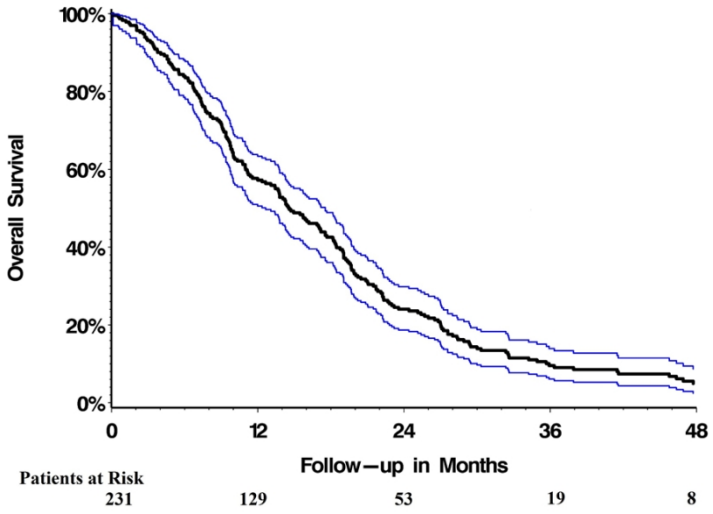
Figure 5D



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