CRC-P4-16-01	Statistical Analysis Plan
Version 1.0	

CRC-P4-16-01

Prospective Registry of Transarterial Chemoembolization of Metastatic Colorectal Cancer to the Liver with HepaSphere™ Microspheres Loaded with Irinotecan

NCT 04866290

Document Version History

Version Date	Version	Author	Change Description	Reason/Comment
08/Jun/2021	1.0	[redacted], Biostatistician	Initial release	Not applicable

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LIST OF ABBREVIATIONS

AE	Adverse event
CRC	Colorectal cancer
CI	Confidence interval
CR	Complete response
CT	Computed tomography
LTFU	Lost to follow-up
MRI	Magnetic resonance imaging
mCRC	Metastatic colorectal cancer
ORR	Objective response rate
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
TACE	Transarterial chemoembolization
TTP	Time to progression
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class

1. STUDY OBJECTIVES

1.1. PRIMARY OBJECTIVE

The primary study objective is the median overall survival of subjects treated with HepaSphere Microspheres loaded with irinotecan. Analysis will be performed when all subjects enrolled have been followed for survival for two years (24 months), are considered lost to follow up, or have died, whichever comes first. Survival time will be calculated in months and utilize the date of the first TACE procedure, the date of death (from any cause), and/or the last successful contact with the subject before they were considered lost to follow-up.

1.2. SECONDARY OBJECTIVES

Objective response rate (ORR), best tumor response, median liver progression-free survival, and time to progression will be analyzed based on mRECIST criteria as secondary objectives. Safety summaries will also be included.

1.3. EXPLORATORY OBJECTIVES

Other study objectives include analyzing pharmacokinetic (PK) blood samples, additional transarterial chemoembolization (TACE) cycles, RECIST 1.1 criteria, and clinical success.

2. BACKGROUND/INTRODUCTION

2.1. STUDY DESIGN

This prospective, single arm, post-market clinical trial is designed to demonstrate safety and efficacy of Merit Medical Systems' HepaSphere Microspheres loaded with irinotecan for subjects with metastatic colorectal cancer to the liver. There will be two hospitals participating in this study, one in Greece (N=100) and one in France (N=5). Hospitals and physicians with experience in routine use of chemoembolization for metastatic colorectal cancer (mCRC) to the liver will participate. Subject recruitment and offer to participate in the study will be at the investigator's discretion (ensuring that subjects are existing patients receiving care at the hospital and that they meet inclusion and exclusion criteria). All enrolled and treated subjects will be followed for survival until data analysis. Data analysis will be performed when all treated subjects actively being followed for survival have individually cumulated a minimum of two years (24 months) since the date of their first study TACE procedure.

2.2. TREATMENT GROUPS

The study is single arm and includes subjects with mCRC to the liver treated with HepaSphere Microspheres loaded with irinotecan.

2.3. STUDY POPULATION

Subjects (meeting inclusion/exclusion criteria and having signed informed consent) will be included in the study analysis if they have had at least one protocol specified TACE procedure.

2.3.1. Inclusion Criteria

The following inclusionary information must be evaluated by the investigator/institution to confirm the patient meets all the following criteria:

- Histologically or radiologically confirmed colorectal cancer metastases to the liver
- Patient is able to have either computed tomography (CT) or magnetic resonance imaging (MRI)
- Hepatic tumor burden ≥50% of total tumor burden
- Hepatic tumor burden ≤50% of total liver volume
- Not suitable for treatment by resection or percutaneous ablation at time of TACE treatment

- Life expectancy ≥ 3 months
- World health organization (WHO) performance status ≤ 2

2.3.2. Exclusion Criteria

The following exclusionary information must be evaluated by the investigator/institution to confirm the patient does NOT meet any of the criteria below:

- Previous treatment with any form of hepatic transarterial embolization
- Total bilirubin ≥ 3.0 mg/dL
- Any contraindication for irinotecan administration
- Partial or complete thrombosis of the main portal vein
- Cardiovascular or respiratory failure
- Any other condition deemed exclusionary by the Investigator

2.4. INTERVENTION

Embolizations may be performed using the 30-60µm or 50-100µm size HepaSphere Microspheres. Embolic size is determined by the Investigator based on their judgment of tumor size and vascularity.

2.5. SAMPLE SIZE

This prospective registry is observational and single arm, so there are no cohorts on which to perform comparisons or sample size calculations. A minimum sample size of 100 patients was chosen as being similar in size to studies conducted by Aliberti (N=82) and Fiorentini (N=74) for a similar product CE marked for the same indication.

2.6. STUDY PROCEDURE

Study subjects (once screened, enrolled, and consented) must undergo a complete baseline evaluation. The evaluation includes haematology and serum chemistry assessments and imaging (CT or contrast-enhanced MRI of the liver).

Subjects must have two TACE cycles. A TACE cycle is defined as one embolization for patients with unilobar disease or two embolizations for subjects with bilobar disease (one for each lobe of the liver). The second TACE cycle should be performed within 2-4 weeks after the first TACE cycle. Subsequent TACE cycles may be performed for residual or new disease as needed (at the investigators discretion), based on tumor response. See ‘Schedule of Procedures’ below for additional information.

Schedule of Procedures

	Screening [1]	TACE Procedure [2]	Follow Up Visits [3]	Survival Follow-up [4]
Informed Consent	X			
Eligibility criteria assessment	X			
Demographics	X			
Medical History	X			
Tumor Evaluation / Imaging	X		X	
Hematology / Serum Chemistry	X			
Embolization procedures (TACE)		X		
Pharmacokinetic Sampling[5]		X		
Additional cancer treatments			X	
Adverse Events		X	X	
Survival status				X

[1] Screening imaging must be within 4 weeks of first TACE cycle.
[2] First TACE cycle must be within 4 weeks of screening imaging. If the patient has bilobar disease, the embolization of the first lobe must be within 4 weeks of screening imaging and the second lobe must undergo embolization within 3 weeks (± 2 weeks) of the first lobe. A second TACE cycle is required for all patients 2-4 weeks after the first TACE cycle. Additional TACE cycles can be performed for residual or new disease as needed.
[3] Follow up Visits will start 4-6 weeks after the second TACE cycle and occur every 12 weeks (± 2 weeks) thereafter during the first year of follow-up. Follow-up may be more frequent if medically indicated.
[4] If patients are no longer indicated for TACE, they will continue to be followed for survival for 2 years after the first TACE procedure, with contacts performed every 3 months (± 2 weeks).
[5] Blood samples will be drawn for PK analysis from a portion of study patients after the first TACE procedure at the following time points; 30 min, 1 hour, 4 hours, 12 hours, and 24 hours or prior to discharge (whichever comes first).

3. ANALYSIS POPULATION

3.1. EFFICACY ANALYSES

All patients who have at least one TACE procedure and who have at least one post-baseline tumor evaluation will be included in the efficacy analyses.

3.2. SAFETY ANALYSES

All patients who have at least one TACE procedure will be included in the safety analyses (safety summary).

4. OUTCOME VARIABLES

4.1. PRIMARY OUTCOME

Patient survival will be calculated in months from the date of the first TACE procedure until a date of death is obtained or the subject is lost to follow up (utilizing the last successful contact with the patient). Median overall survival time will be the primary outcome of the study.

4.2. SECONDARY PARAMETERS OUTCOMES

Objective Response Rate

Objective Response Rate (ORR) will be based on the last post-TACE liver MRI or CT response recorded for each patient, as determined by mRECIST criteria. ORR will be calculated for the efficacy population as the number of patients with a confirmed complete response (CR) or partial response (PR) based on mRECIST criteria divided by the number of patients [ORR=(# CR + # PR)/total # patients].

Best Tumor Response
Best tumor response will be assessed utilizing tumor evaluation response categories (CR, PR, stable disease [SD], and progressive disease [PD]) and will be in the period from treatment initiation through the date of the last post TACE liver MRI or CT based on mRECIST criteria.

Median Liver progression-free survival
Median liver progression-free survival (PFS) will be calculated (in months) from the date of the first TACE procedure to the date of diagnosis of colorectal cancer liver metastasis to the date of death, or date last known to be alive for patients who are lost to follow up, during which follow up imaging by MRI or CT demonstrates a lack of tumor progression in the liver as determined by mRECIST criteria.

Time to Progression
Time to progression (TTP), including progression of extrahepatic disease, will be calculated in months from the date of the first study TACE procedure until the date of disease progression, determined by MRI, CT, positron emission tomography (PET) scan, or equivalent imaging.

Safety Summary
Safety summaries will include the incidence of treatment-related adverse events (AEs) in patients who had at least one TACE procedure. Treatment-related adverse events are defined as any event that began on or after the date of the first embolization or worsened in severity or frequency after embolization was initiated, and are evaluated as possibly, probably, or definitely related to study treatment by the investigator. Events worsening in severity will be considered new AEs.

4.3. OTHER PARAMETERS

Pharmacokinetic (PK) Analyses
PK blood samples drawn from a portion of the subjects after the first TACE cycle (at four pre-determined time periods) will undergo bioanalytical analysis using validated assays. The assays will measure the subject's plasma concentrations of irinotecan and its active metabolite, SN38.

Additional TACE Cycles
Overall survival time will be compared between standard TACE cycles and additional TACE cycles (any TACE procedure(s) beyond the protocol specified number of TACE cycles).

RECIST 1.1
Clinical outcomes will be re-analyzed based on RECIST 1.1 criteria. The best tumor response will be compared between mRECIST and RECIST 1.1.

Clinical Success
Similar to ORR, clinical success will be based on the last post-TACE liver response evaluated through mRECIST and RECIST 1.1 criteria. Clinical success is defined as the total number of confirmed subjects who exhibit a CR or PR [clinical success = (# CR + #PR)].

Demography and Baseline
Subject demographic information and other baseline data will be included and summarized. Sex, age, race, and ethnicity will be included as demographic characteristics. Medical history will be described through system organ class (SOC) and baseline risk factors. Subject hepatic health status such as prior hepatic treatment and tumor location will also be provided.

5. STATISTICAL METHODOLOGY

5.1. GENERAL METHODOLOGY

Analysis will be performed when all subjects enrolled have been followed for survival for two years (24 months) from the date of their first TACE, are considered lost to follow up, or have died, whichever comes first.

For continuous variables, outputs will be presented with mean, standard deviation (SD), median, minimum, and maximum values. Mean and median will be rounded to a single decimal while SD will be rounded to two decimals. When appropriate, a corresponding 95% confidence interval (CI) will be calculated. Categorical variables (e.g., sex and race) will be reported using frequencies and percentages. All percentages will be rounded to single decimal. If percentages do not add up to 100% due to rounding, a footnote mention will be provided accordingly.

Correlation analyses will be used to analyze relationships for continuous variables. Fisher's exact test will be used to analyze relationships between categorical variables. P-values less than or equal to 0.05 will be considered significant. All p-values will be rounded to 3 decimal places and will be presented as "<0.001" if less than 0.0005.

Survival analyses will be performed using Kaplan-Meier with corresponding median survival times and 95% CIs.

Descriptive statistics will be used to examine demographic and baseline characteristics and to perform other efficacy analyses.

Each table generated will have headers that include the total sample size (N). Frequencies and percentages for categorical variables will be calculated using the number of subjects (n) with non-missing values.

DATA SOURCE

All data will be extracted from Medidata. Datasets will be merged and cleaned prior to data analysis. Data processing procedures will be documented to ensure replicability and error checking.

REPORTING OUTPUTS

SAS 9.4® and SPSS 27.0® will be used to produce all statistical analysis and figure outputs. Tables will be formatted through Microsoft® Word.

HANDLING OF MISSING DATA

There will be no imputation of missing data as the study is observational and all analyses performed should not require such methods.

SITE POOLING

To assess the consistency of observed treatment effect across investigational sites, a data poolability analysis will be performed on the primary efficacy outcomes of overall survival. Median overall survival data will be summarized by site, including Kaplan-Meier plots.

CLASSIFICATION OF PROTOCOL VIOLATION

Protocol deviations will be summarized in the final clinical study report. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected.

5.2. PRIMARY DATA ANALYSES

Median overall survival times will be calculated using the Kaplan-Meier (product-limit) method and corresponding 95% confidence intervals will be generated. One- and two-year survival rates and corresponding 95% confidence intervals will also be calculated.

5.3. SECONDARY DATA ANALYSES

Objective Response Rate
Descriptive statistics will be used to analyze and summarize ORR. Ninety-five percent confidence intervals will be calculated.

Best Tumor Response
Best tumor response will be summarized as the number and percentage of patients in each response category (CR, PR, SD, PD) for the effectiveness population using descriptive statistics.

Median Liver progression-free survival
Median liver PFS will be calculated using Kaplan-Meier (product-limit) and corresponding 95% confidence intervals will be generated.

Time to Progression
TTP will be summarized using descriptive statistics and corresponding 95% confidence intervals will be generated.

Safety Summary
Safety summaries will be summarized using descriptive statistics and will include information regarding AEs, serious adverse events (SAEs), and TACE-related AEs.

5.4. EXPLORATORY DATA ANALYSES

Pharmacokinetic (PK) Analyses
Data will be summarized by descriptive statistics, including mean, standard deviation, coefficient of variation, minimum, maximum, and median. The correlation between circulating levels of irinotecan and SN38 and overall survival, tumor response, and treatment-related adverse events will be evaluated to the extent possible with the available PK data. A Pearson's correlation or a Spearman's rank correlation will be performed depending on whether the variable being compared to levels of irinotecan and SN38 is continuous or categorical.

Additional TACE Cycles
Kaplan-Meier estimator with log-rank testing will be used to compare overall survival of standard TACE cycles to additional TACE cycles. Comparison of additional TACE cycles between tumor response will be performed using Fisher's exact test.

RECIST 1.1
The best tumor response will be compared between mRECIST and RECIST 1.1 using Fisher's exact test.

Clinical Success
Clinical success will be summarized using descriptive statistics.

6. TABLES AND FIGURES

6.1. PLANNED TABLES AND FIGURES

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1. Demographics and Baseline Characteristics
2. Prior Chemotherapy History
3. Safety Summary
4. Median Survival (Overall and Liver PFS) and TTP
5. ORR and Clinical Success
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3. Kaplan-Meier survival curve for overall survival between sites
4. Kaplan-Meier survival curve for overall survival (standard vs. additional TACE cycles)

6.2. EXAMPLES

Table 1. Demographics and Baseline Characteristics

Characteristic	N = 105 n (%)	Mean	SD	Median	Min	Max
Age (Years)		xx.x	xx.xx	xx.x	xx	xx
Sex						
Male	xx (xx.x)					
Female	xx (xx.x)					
Prior Chemotherapy Treatment						
Yes	xx (xx.x)					
No	xx (xx.x)					
Baseline Disease Status						
Tumor Location						
Bilobar	xx (xx.x)					
Unilobar	xx (xx.x)					
Who Performance Status						
0 - Fully active, able to carry on all pre-disease performance without restriction	xx (xx.x)					
1 - Restricted in physically strenuous activity but ambulatory and able to carry out work	xx (xx.x)					
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities	xx (xx.x)					

Table 2. Prior Chemotherapy History

Characteristic	N=101 n (%)	Total	Mean	Median	Minimum	Maximum
Previous Chemotherapy Cycles		xx	xx.x	xx.x	xx	xx
Previous Chemotherapy Treatment						
5FU	xx (xx.x)	xx				
Oxaliplatin	xx (xx.x)	xx				
Capecitabine (Xeloda)	xx (xx.x)	xx				
Cetuximab	xx (xx.x)	xx				
Regorafenib	xx (xx.x)	xx				
Leucovorin	xx (xx.x)	xx				
Irinotecan	xx (xx.x)	xx				
Bevacixumab (Avastin)	xx (xx.x)	xx				
Other	xx (xx.x)	xx				

Table 3. Safety Summary

Summary Variables	N=105 n (%)
Number of Adverse Events (AEs)	xx
Number of Subjects with at Least One AE	xx (xx.x)
Number of Serious Adverse Events (SAE)	xx
Number of Subjects with at Least One SAE	xx (xx.x)
Number of Adverse Events by Severity Level (N= xx*)	
Grade 1 (Mild)	xx (xx.x)
Grade 2 (Moderate)	xx (xx.x)
Grade 3 (Severe)	xx (xx.x)
Grade 4 (Life Threatening)	xx (xx.x)
Grade 5 (Fatal)	xx (xx.x)
Number of TACE-Related AEs	xx
Number of Subjects with at Least One TACE-related AE	xx (xx.x)
Number of TACE-Related AEs Leading to Death	xx
Number of Subjects with at Least One TACE-related AE Leading to Death	xx (xx)

*Denominator used for percentage calculations

Table 4. Median Survival (Overall and Liver PFS) and TTP

Outcomes	Median (in months)	Survival Rate	95 % CI
Overall Survival	xx.x		xx.xx – xx.xx
1-Year Survival		xx.x%	xx.xx – xx.xx
2-Year Survival		xx.x%	xx.xx – xx.xx
Liver PFS	xx.x		xx.xx – xx.xx
TTP			
Hepatic	xx.x		xx.xx – xx.xx
Extrahepatic	xx.x		xx.xx – xx.xx

Table 5. ORR and Clinical Success

Outcomes	mRECIST (N = 83)	RECIST 1.1 (N= 78)
CR: n	xx	xx
PR: n	xx	xx
Clinical Success*	xx	xx
ORR** (95% CI)	xx.x% (xx.x – xx.x)	xx.x% (xx.x – xx.x)

*Calculated as CR + PR
**Calculated as CR + PR / N

Table 6. Best Tumor Response

Outcomes	mRECIST (N =83) n (%)	RECIST 1.1 (N = 78) n (%)	*p*-value
Best Tumor Response			0.xxx
CR	xx (xx.x)	xx (xx.x)	
PR	xx (xx.x)	xx (xx.x)	
SD	xx (xx.x)	xx (xx.x)	
PD	xx (xx.x)	xx (xx.x)	

Note: Percentages may not add up exactly due to rounding

Table 7. Additional TACE Cycles

Outcomes	Standard TACE Cycles (N=76)	Additional TACE Cycles (N=29)	Log rank test	Fisher's exact test
Median Overall Survival (in months)	xx.x	xx.x	*p* = 0.xxx	
Best Tumor Response: n (%)				*p* = 0.xxx
CR	xx (xx.x)	xx (xx.x)		
PR	xx (xx.x)	xx (xx.x)		
SD	xx (xx.x)	xx (xx.x)		
PD	xx (xx.x)	xx (xx.x)		
Not Assessed	xx (xx.x)	xx (xx.x)		

Note: Percentages may not add up exactly due to rounding

Table 8. PK Analyses

Variables	N	Mean	SD	Median	Min	Max	R (*p*-value)
Irinotecan (ng/ML): 30 minutes	xx	xxx.x	xxx.xx	xxx	xxx	xxx	
with Overall Survival							x.x (0.xxx)
with Tumor Response							x.x (0.xxx)
with Treatment-Related AEs							x.x (0.xxx)
Irinotecan (ng/ML): 1 hour	xx	xxx.x	xxx.xx	xxx	xxx	xxx	
with Overall Survival							x.x (0.xxx)
with Tumor Response							x.x (0.xxx)
with Treatment-Related AEs							x.x (0.xxx)
Irinotecan (ng/ML): 4 hours	xx	xxx.x	xxx.xx	xxx	xxx	xxx	
with Overall Survival							x.x (0.xxx)
with Tumor Response							x.x (0.xxx)
with Treatment-Related AEs							x.x (0.xxx)
Irinotecan (ng/ML): 24 hours	xx	xxx.x	xxx.xx	xxx	xxx	xxx	
with Overall Survival							x.x (0.xxx)
with Tumor Response							x.x (0.xxx)
with Treatment-Related AEs							x.x (0.xxx)
SN38 (ng/ML): 30 minutes	xx	xxx.x	xxx.xx	xxx	xxx	xxx	
with Overall Survival							x.x (0.xxx)
with Tumor Response							x.x (0.xxx)
with Treatment-Related AEs							x.x (0.xxx)
SN38 (ng/ML): 1 hour	xx	xxx.x	xxx.xx	xxx	xxx	xxx	
with Overall Survival							x.x (0.xxx)
with Tumor Response							x.x (0.xxx)
with Treatment-Related AEs							x.x (0.xxx)
SN38 (ng/ML): 4 hours	xx	xxx.x	xxx.xx	xxx	xxx	xxx	
with Overall Survival							x.x (0.xxx)
with Tumor Response							x.x (0.xxx)
with Treatment-Related AEs							x.x (0.xxx)
SN38 (ng/ML): 24 hours	xx	xxx.x	xxx.xx	xxx	xxx	xxx	
with Overall Survival							x.x (0.xxx)
with Tumor Response							x.x (0.xxx)
with Treatment-Related AEs							x.x (0.xxx)

Figure 1. Kaplan-Meier survival curve for overall survival

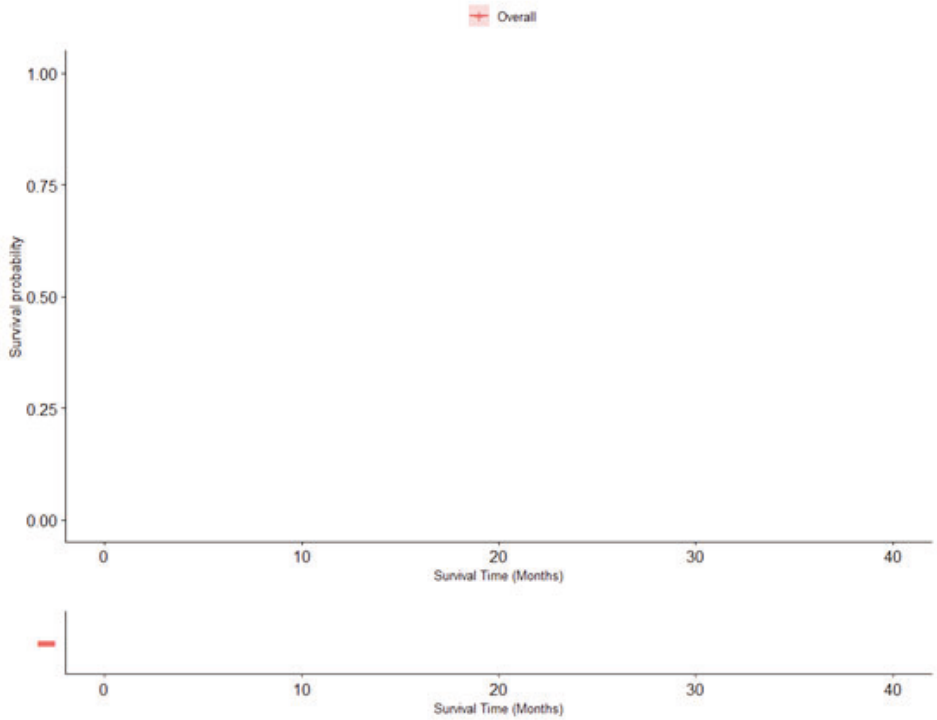


Figure 2. Kaplan-Meier survival curve for progression free survival

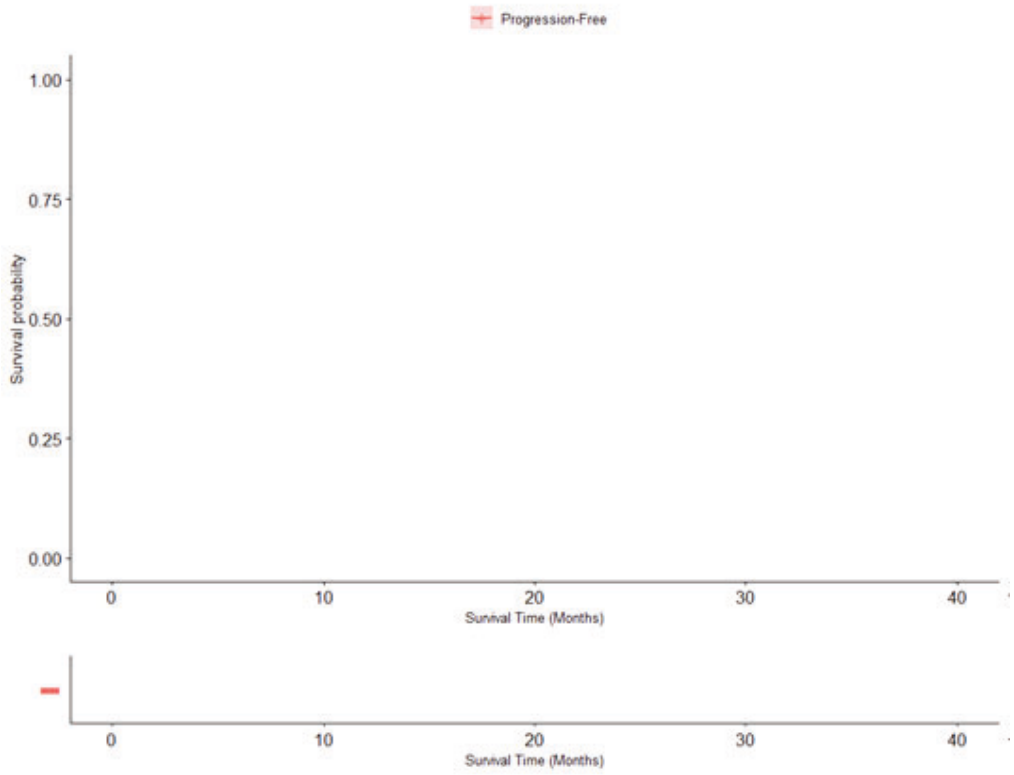


Figure 3. Kaplan-Meier survival curve for overall survival between sites

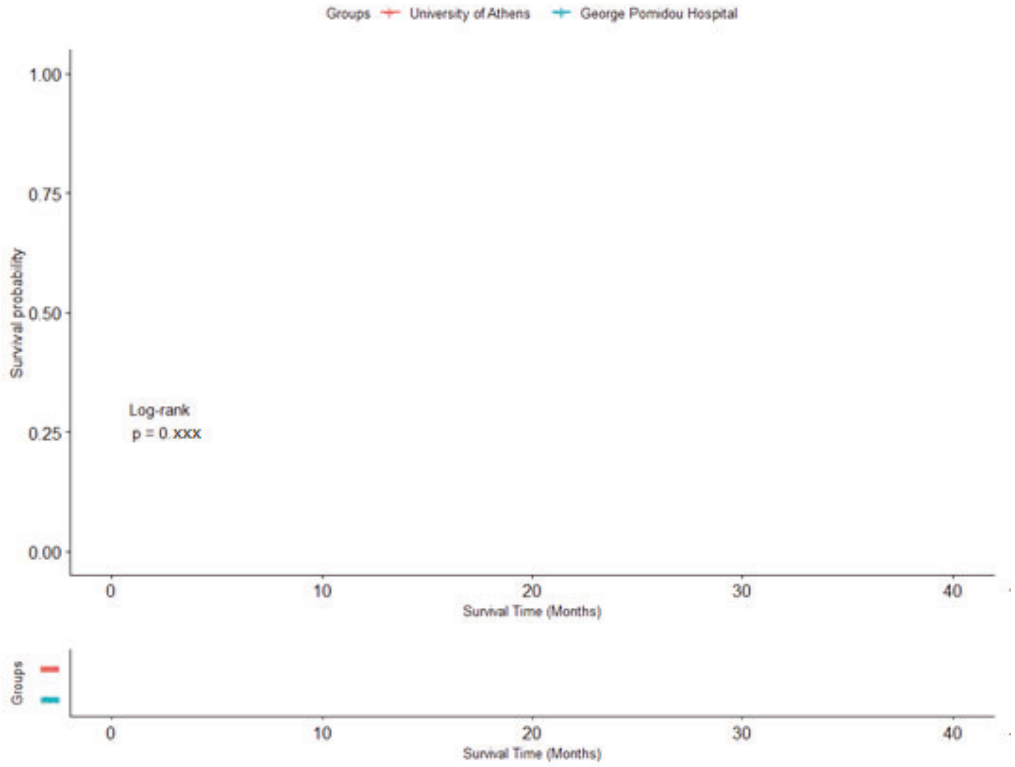
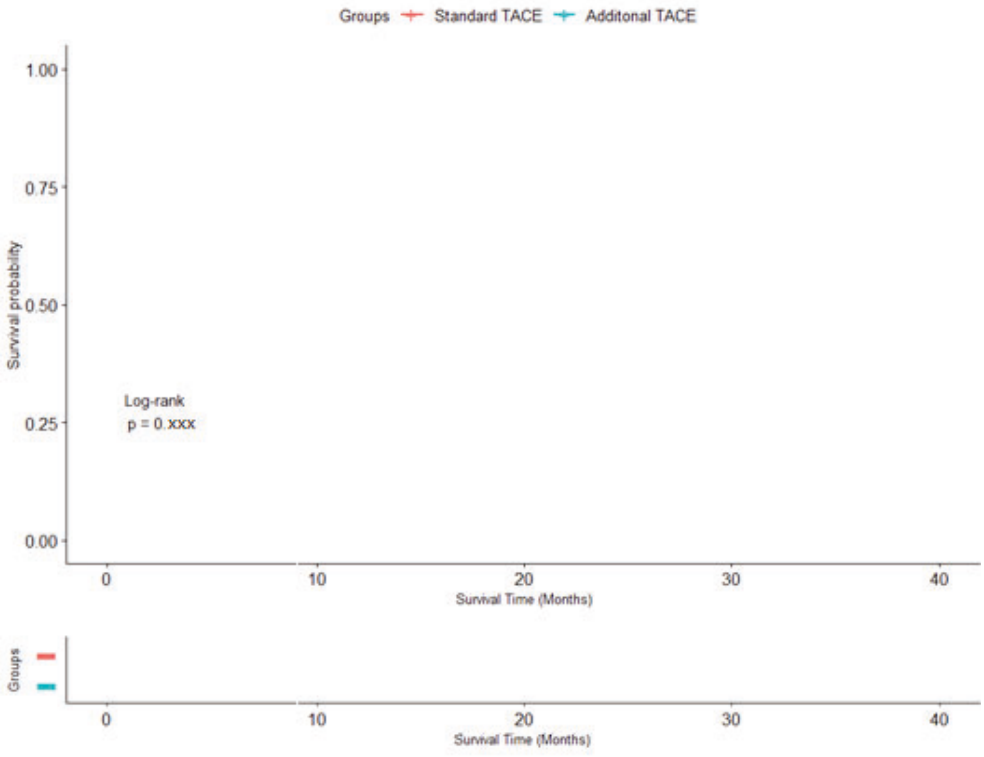


Figure 4. Kaplan-Meier survival curve for overall survival (standard vs. additional TACE cycles)



Statistical Analysis Plan Approval

Name	**Signature**
[redacted] Biostatistician	[redacted] 08 June 2021 | 10:00 AM MDT
[redacted] Senior Director Clinical Operations	[redacted] 08 June 2021 | 9:59 AM MDT
[redacted] Data Management – Clinical Partners Group	[redacted] 09 June 2021 | 5:23 AM MDT