STATISTICAL ANALYSIS PLAN

A Phase 1b Study of the OxPhos Inhibitor ME-344 Combined with Bevacizumab in Previously Treated Metastatic Colorectal Cancer

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SIGNATURE PAGE

A Phase 1b Study of the OxPhos Inhibitor ME-344 Combined with Bevacizumab in Previously Treated Metastatic Colorectal Cancer

This Statistical Analysis Plan has been reviewed and approved by the representatives listed below:

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABBREVIATION	DEFINITION
AE	Adverse event
CBC	Complete blood count
CI	Confidence interval
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
DOT	Duration of treatment
ECOG	Eastern Cooperative Oncology Group
EOS	End of Study
mCRC	metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
ORR	Overall response rate
OS	Overall Survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PT	Preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
TEAE	Treatment-emergent adverse event
TFLs	Tables, figures, and listings

1. INTRODUCTION

This Statistical Analysis Plan (SAP) is created based on Protocol ME-344-003 (Original version, 10 August 2021, not implemented, Amendments 1 and 2, not implemented, Amendment 3, 06 January 2023, Amendment 4, 09 February 2024) and it describes in detail the statistical methodology and the statistical analyses to be conducted for the aforementioned protocol. The mockup shells of the Tables, Figures, and Listings (TFLs) for the statistical analysis described in this SAP are described as the appendix in this document.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are as follows:

- To estimate PFS at 16 weeks of treatment in subjects with metastatic colorectal cancer (mCRC) administered ME-344 in combination with bevacizumab

2.2 Secondary Objectives

The secondary objectives of the study are as follows:

- To evaluate the preliminary efficacy of ME-344 administered in combination with bevacizumab in subjects with mCRC
- To determine the safety and tolerability of ME-344 administered in combination with bevacizumab
- To evaluate the pharmacokinetics (PK) of ME-344 administered in combination with bevacizumab

2.3 Exploratory Objectives

The exploratory objectives of the study are as follows:

- To evaluate correlatives of mitochondrial metabolism

3. STUDY DESIGN

3.1 General Study Design and Plan

3.1.1 Overall Study Design

This is a Phase 1b open-label, multiple dose/schedule sequential study to determine the safety and efficacy of the OxPhos inhibitor ME-344 in combination with bevacizumab in subjects with recurrent mCRC.

This study will enroll subjects with mCRC, including but not limited to subjects with RAS wild-type or mutant tumors, MSI-H/pMMR, and BRAF V600E, who have progressed or demonstrated intolerability to standard approved therapies which include fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, cetuximab/panitumumab, programmed cell death protein 1 (PD-1) inhibitors, or BRAF inhibitors (if clinically indicated), and/or checkpoint inhibitors.

This study consists of 3 periods: (i) screening, (ii) treatment, and (iii) follow-up. During screening, each potential subject will provide informed consent prior to starting any study-specific procedures. Screening assessments will be completed within 28 days prior to administration of ME-344 combined with bevacizumab.

During the treatment period, subjects enrolled in Cohort 1 will receive ME-344 at a dose of 10 mg/kg IV on Days 1, 8, and 15 in combination with bevacizumab at a dose of 5 mg/kg IV administered on Days 1 and 15 of each 28-day cycle.

The criterion to initiate Cohort 2, at least 4 subjects in Cohort 1 having completed 16 weeks of therapy without evidence of disease progression (i.e., have achieved SD or a response), was met based on an interim analysis of 23 subjects enrolled in Cohort 1. However, there were no objective responses and since there was no increased toxicity, the ME-344 dosing schedule has been revised in Amendment 4 for Cohort 2 to add a Day 8 dose to match the schedule of Cohort 1 (i.e., on Days 1, 8, and 15 of the cycle). The intent of this amendment was to provide a larger sample size of subjects administered the same dosing schedule to increase the precision level of the 16-week PFS point estimate and overall PFS. However, despite meeting the PFS threshold for opening Cohort 2, the Sponsor decided not to open enrollment in Cohort 2.

There is no maximum duration of treatment for this study; subjects will discontinue study drug once there is disease progression, unacceptable AEs, withdrawal of consent, start of new anticancer therapy, or death.

Follow-up includes the End of Treatment (EOT) visit and survival follow-up. After subjects have discontinued treatment for any reason, they will be followed every 3 months, or more

frequently as needed, until withdrawal of consent, the subject is lost to follow-up, death, or defined end of study. If subjects withdraw consent, they will be asked if they are willing to be contacted via telephone for survival status. If the subject refuses to be contacted, attempts to determine survival status should be made via access to public records, where permitted by the local laws.

All radiographic tumor assessments, preferably computed tomography (CT) with contrast, or alternatively magnetic resonance imaging (MRI; if CT is considered not indicated), will be carried out in accordance with RECIST v1.1, and are to be performed every 8 weeks (±7 days) relative to first dose of study drug for the first 6 months, then every 3 months in Months 7–12, and every 4 months thereafter. Tumor assessments will be repeated until progressive disease (PD), or as per standard practice post-progression.

Safety will be assessed via TEAEs, physical examinations, vital signs, 12-lead ECGs, and clinical laboratory evaluations (hematology, serum chemistry, coagulation [at screening for all subjects and Day 1 of every cycle for subjects on anticoagulation therapy], urinalysis). Severity grading of TEAEs will use the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Blood samples for PK analysis will be collected during Cycle 1 on Days 1 and 15 pre-dose, 5 minutes after the end of infusion, and 1, 2, 3, 6, and 24 hours after the completion of the ME-344 infusion.

The metabolomic correlative study will be performed on samples obtained from Cohort 1 subjects enrolled at Rutgers Cancer Institute of New Jersey. For Cohort 2, the metabolomic correlative study will be performed on samples from all subjects enrolled. Plasma samples will be collected at timepoints specified in the Schedule of Assessments (**Error! Reference s ource not found.**). Samples will be stored at -70°C until analyzed. Specific markers of the mitochondrial OxPhos pathway will be analyzed, including changes in isoleucine/leucine, TCA cycle intermediates, short chain acyl carnitine, and nucleotide and TCA cycle intermediates.

3.2 Number of Subjects

Approximately 40 subjects will be enrolled in 2 cohorts of approximately 20 efficacy evaluable subjects each.

3.3 Study Treatment

Enrollment into Cohort 1 will continue until 20 subjects complete radiological assessments at 16 weeks or discontinue, progress, start new anticancer therapy, or die, whichever happens earlier.

Subjects enrolled in Cohort 1 will receive ME-344 at a dose of 10 mg/kg IV on Days 1, 8, and 15 in combination with bevacizumab at a dose of 5 mg/kg IV administered on Days 1 and 15 of each 28-day cycle.

If Cohort 1 demonstrates adequate safety, tolerability, and efficacy, Cohort 2 will open to enrollment of approximately 20 subjects.

Subjects enrolled in Cohort 2 will receive ME-344 at a dose of 10 mg/kg IV on Days 1, 8, and 15 combined with bevacizumab at a dose of 5 mg/kg IV administered on Days 1 and 15 of each 28-day cycle.

Subjects who discontinue bevacizumab due to tolerability may continue treatment with the single agent ME-344 at the investigator's discretion, if in the investigator's opinion they benefit from single-agent treatment. Subjects with persistent proteinuria ≥2 g/24 hours must discontinue bevacizumab and ME-344. The results of the Phase I study demonstrated that ME-344 alone treatment displayed single agent activity leading to partial responses [PRs] or SD in subjects with solid tumors.

3.4 Randomization and Blinding

Not applicable.

3.5 Study Assessments

For the detailed schedule of expected events and study procedures to be conducted at each visit, please refer to the protocol.

4. SAMPLE SIZE DETERMINATION

The PFS rate ≥20% is considered as a positive efficacy signal to proceed to a later stage trial. With a sample size of approximately 20 efficacy evaluable subjects in each cohort, assuming the true PFS rate at 16 weeks is 30%, there is an 89% chance to observe PFS rate ≥20% (i.e., ≥4 of 20 subjects are progression-free) based on binomial distribution. With a sample size of approximately 40 efficacy evaluable subjects in combined cohorts 1 and 2, assuming the true PFS rate at 16 weeks is 30%, there is an 94% chance to observe PFS rate ≥20% (i.e., ≥8 of 40 subjects are progression-free) based on binomial distribution. If 7 out of 20 subjects

achieve PFS at 16 weeks (observed PFS rate of 35%), there is 90% confidence that the true PFS rate is >20% as the lower bound of 80% confidence interval (CI) is 20.7%. If 12 out of 40 subjects achieve PFS at 16 weeks (observed PFS rate of 30%), there is 90% confidence that the true PFS rate is >20% as the lower bound of 80% CI is 20.5%. Thus, increasing sample size will allow a lower observed PFS rate with the lower bound of 80% CI to pass the 20% bar.

Table 1 summarizes the 95% and 80% exact CIs when observed PFS rate ranges between 20% to 50%.

Table 1: Observed Progression-free Survival Rate with Exact 95% and 80% Confidence Intervals

	N=20			N=40		
Observed PFS Rate	**Number of PFS Subjects**	**95% CI (%)**	**80% CI (%)**	**Number of PFS Subjects**	**95% CI (%)**	**80% CI (%)**
20%	4	5.7, 43.7	9.0, 36.1	8	9.1, 35.6	12.0, 30.4
25%	5	8.7, 49.1	12.7, 41.5	10	12.7, 41.2	16.2, 35.9
30%	6	11.9, 54.3	16.6, 46.7	12	16.6, 46.5	20.5, 41.2
35%	7	15.4, 59.2	20.7, 51.8	14	20.7, 51.7	24.9, 46.3
40%	8	19.1, 63.9	24.9, 56.7	16	24.9, 56.7	29.4, 51.4
45%	9	23.1, 68.5	29.3, 61.5	18	29.3, 61.5	34.1, 56.3
50%	10	27.2, 72.8	33.8, 66.2	20	33.8, 66.2	38.8, 61.2

If 10 (50%) of 20 subjects experience Grade ≥3 treatment-emergent neuropathy, the 95% CI for incidence rate of Grade ≥3 neuropathy will be (27.2%, 72.8%) based on exact method.

5. STUDY ENDPOINTS

5.1 Primary Endpoints

- PFS rate at 16 weeks

5.2 Secondary Endpoints

- PFS
- Overall or Objective response rate (ORR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Duration of Response (DOR)
- Overall survival (OS)

- Incidence and severity of treatment-emergent adverse events (TEAEs) and their relationship to study drug; change from baseline in physical examinations, vital signs, 12-lead electrocardiograms (ECGs), and clinical laboratory evaluations
- Maximum observed concentration (Cmax), last observed quantifiable concentration (Clast), area under the concentration-time curve from time zero to time of last measurable concentration (AUClast)

5.3 Exploratory Endpoint

- Untargeted metabolomics assessments that will include changes in isoleucine/leucine, tricarboxylic acid (TCA) cycle intermediates, short chain acyl carnitine, oxidative phosphorylation (OxPhos) biomarkers, and nucleotide and TCA cycle intermediates

6. ANALYSIS POPULATION

- The Safety Population includes all subjects who receive at least 1 dose of ME-344. Safety analyses will be performed on the Safety Population.

7. GENERAL STATISTICAL CONSIDERATIONS

7.1 Definition of Study Day

Study day will be calculated in reference to the first dose date of study drug as follows:

- Assessment/event date – first dose date of study drug + 1, if assessment/event date is on or after the first dose date;
- Assessment/event date – first dose date of study drug, if assessment/event date is before the first dose date.

Under the convention specified above, there will be no Study Day 0.

7.2 Baseline Definition

Baseline value for any given parameter is defined as the last assessment obtained prior to the first dose of study drug.

7.3 Handling of Missing Data

Missing values will not be assumed/imputed and only observed values will be used in data analyses and presentations unless otherwise stated.

8. STATISTICAL ANALYSIS

All data analyses will be conducted based on the Safety Population.

Descriptive statistics for continuous data will include the number of observations (n), mean, standard deviation, median, minimum, first and third quartiles, and maximum. For discrete variables, descriptive analyses will be based on estimates of the number of subjects and related percentages. Unless otherwise stated, confidence intervals, when presented, are 2-sided with 95% confidence level.

All analyses will be performed using SAS® Version 9.4 (SAS Institute Inc., Cary NC).

8.1 Subject Disposition

The following categories of subject disposition will be included:

- Subjects who were treated with ME-344
- Subjects who were treated with Bevacizumab
- Subjects who discontinued from ME-344
- Subjects who discontinued from the study

For subjects who discontinued from the study, the primary reason for ending the study will be summarized. The number and percentage of subjects will be tabulated as appropriate.

All deaths that occur on study will be reported in a subject listing, which will include the primary cause of death and the number of days between the date of the first (and last) dose of study drug and death.

8.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively. Sex, race, ethnicity, baseline ECOG performance status, disease stage at diagnosis and prior lines of therapy (1-2 versus > 2) will be summarized with contingency tables. Age at informed consent (years), baseline weight and number of prior lines of therapy will be presented with descriptive statistics.

8.3 Exposure and Duration of Treatment

Duration of treatment (DOT) will be summarized descriptively. Additionally, the swimmer plot of DOT will be generated. For subjects who either completed or discontinued the treatment by the EOS visit, DOT will be calculated as follows:

DOT (months) = (Last Dose Date – First Dose Date + 1) / 30.4375

Number of ME-344 infusions will be presented with descriptive statistics.

8.4 Duration of Follow-up

Duration of follow-up is calculated as (end of study date – first dose date + 1)/30.4375.

Duration of follow-up will be summarized descriptively.

8.5 Efficacy Analyses

8.5.1 Progression-Free Survival (PFS)

PFS will be calculated from the day of first study drug dose to the first observation of progressive disease (PD) as assessed by the Investigator per RECIST v.1.1 or death from any cause. For the primary PFS analysis, subjects without a PD or death event will be censored at last adequate assessment date or first dose date if no adequate postbaseline assessment is available. For the exploratory analysis for PFS, subjects without a PD or death event will be censored at the end of treatment discontinuation date.

PFS will be summarized descriptively using the Kaplan-Meier method. The Kaplan-Meier estimates of the median PFS and the corresponding 2-sided 95% confidence intervals, calculated using the method of Brookmeyer and Crowley, will be presented. Number of patients with PFS events and number of patients censored will be provided. Also, the Kaplan-Meier estimates of PFS rates along with the corresponding 2-sided 95% confidence intervals will also be provided at 4 months, 6 months and 12 months. Plots of the Kaplan-Meier estimate of PFS rates will be generated with number of subjects at risk noted by 30 days intervals.

8.5.2 Overall Survival (OS)

OS is defined as the time from first study drug dose to death from any cause. Subjects without a death event will be censored at the last date when the subject was known to be alive.

OS will be summarized descriptively using the Kaplan-Meier method. The Kaplan-Meier estimates of the median OS and the corresponding 2-sided 95% confidence intervals, calculated using the method of Brookmeyer and Crowley, will be presented. Number of patients with OS events and number of patients censored will be provided. Plots of the Kaplan-Meier estimate of OS rates will be generated with number of subjects at risk noted by 30 days intervals.

8.5.3 Overall Response Rate (ORR)

ORR will be derived by calculating the proportion of subjects with best response of Complete Response (CR) or Partial Response (PR) per RECIST v.1.1. The 2-sided exact 95% CI based on the Clopper-Pearson method will be provided.

8.5.4 Waterfall Plot

Waterfall plot of best change in sum of target lesion size will be provided to present each subject's best percent change from baseline in sum of target lesion size.

8.6 Safety Analyses

Safety will be assessed and relevant parameters will include AEs, serious adverse events (SAEs), and laboratory safety tests including hematology (complete blood count [CBC]), and serum chemistry.

Safety analyses in general will be presented in tabular format with the appropriate summary statistics.

8.6.1 Adverse Events (AE)

A TEAE is defined as an AE starting or worsening per CTCAE grade after the first dose until 30 days after the last dose of study drug or start of new anticancer therapy, whichever is earlier. Safety will be assessed through the analysis of the reported incidence, severity, and relationship of TEAEs, including SAEs, AEs leading to withdrawal of study drug, and AEs related to study treatment.

AEs will be summarized by MedDRA coded Preferred Term (PT).

The number and percentage of subjects with TEAEs will be summarized by PT and Grade. Treatment-related TEAEs, treatment-emergent SAEs, and TEAEs leading to discontinuation of study drug will be summarized by PT. For these summaries, subjects with multiple adverse events will be counted only once per PT.

8.6.2 Clinical Laboratory Tests

Hematology parameters including Hemoglobin, Lymphocyte count, Neutrophil count, Platelet, and Leukocytes and Chemistry parameters including AST, ALT, Total Bilirubin, and Alkaline Phosphatase will be assigned toxicity grades, using NCI CTCAE v5.0.

The number and percentage of subjects with laboratory abnormalities (any grade) will be presented for the above mentioned hematology and chemistry laboratory parameters by grade.

9. APPENDIX: TLF SHELL

Table 1 Disposition Summary - Safety Population

Characteristic	Total (N=23) n(%)
Total Patients Treated With ME-344 [b]	23
Discontinued From ME-344	21
Completed treatment as defined in protocol	0
Adverse Event	2 (8.7)
Death	0
Lost To Follow-Up	0
Physician's Decision	2 (8.7)
Pregnancy	0
Progressive Disease	15 (65.2)
Non-Compliance	0
Site Terminated by Sponsor	0
Study Terminated By Sponsor	0
Withdrawal by Subject	2 (8.7)
New Anti-Cancer Therapy	0
Other	0
Did Not Discontinue From ME-344 [c]	2
Total Patients Treated With Bevacizumab [d]	23
Discontinued From Study	11
Lost To Follow-up	0

Characteristic	Total (N=23) n(%)
Progressive Disease	1 (4.3)
New Anti-Cancer Therapy	0
Non-Compliance	0
Withdrawal by Subject	1 (4.3)
Site Terminated by Sponsor	0
Study Terminated By Sponsor	0
Death	9 (39.1)
Other	0
Did Not Discontinue From Study [e]	12

Percentage is based on the number of subjects in the safety population.

[b] Patients who received at least one dose of ME-344.

[c] Patients without a reason for ME-344 discontinuation.

[d] Patients who received at least one dose of bevacizumab

[e] Patients without a reason for study discontinuation

Table 2 Summary of Demographics and Baseline Characteristics - Safety Population

	Total (N=23)
Sex	
Female	12 (52.2)
Male	11 (47.8)
Race	
American Indian or Alaska Native	0
Asian	3 (13.0)
Black or African American	2 (8.7)
Native Hawaiian or Other Pacific Islander	0
White	18 (78.3)
Other	0
Ethnicity	
Hispanic or Latino	1 (4.3)
Not Hispanic or Latino	22 (95.7)
Age at Informed Consent (Years)	
n	23
Mean (Standard Deviation)	59.1 (11.10)
Median	58.0
Min, Max	43, 83
First,Third Quartile (Inter-Quartile Range)	50.0, 65.0 (15.0)
Baseline ECOG Performace Status	
0	13 (56.5)

	Total (N=23)
1	9 (39.1)
2	1 (4.3)
Baseline Weight (kg)	
n	23
Mean (Standard Deviation)	81.57 (16.178)
Median	82.20
Min, Max	44.4, 109.7
First,Third Quartile (Inter-Quartile Range)	73.0, 96.2 (23.2)
Disease Stage at Diagnosis	
Stage 2	2 (8.7)
Stage 3	9 (39.1)
Stage 4	12 (52.2)

Table 3 Summary of Prior Therapies - Safety Population

	Total (N=23)
Number of Prior Lines of Therapy Regimens	
n	23
Mean (Standard Deviation)	4.39 (1.828)
Median	4.00
Min, Max	1.0, 8.0
Number (%) of Patients Receiving	
1 - 2 Prior lines of therapy	4 (17.4)
> 2 Prior lines of therapy	19 (82.6)

Table 4 ME-344 Exposure - Safety Population

	Total (N=23)
Duration of Treatment (Days)	
n	23
Mean (Standard Deviation)	59.52 (44.442)
Median	44.00
Min, Max	8.0, 156.0
First,Third Quartile (Inter-Quartile Range)	29.0, 106.0 (77.0)
Number of ME-344 Infusions	
n	23
Mean (Standard Deviation)	7.09 (4.242)
Median	6.00
Min, Max	2.0, 18.0
First,Third Quartile (Inter-Quartile Range)	4.0, 9.0 (5.0)

Table 5 Summary of Duration of Follow-up - Safety Population

	Total (N=23)
Follow-up Time (Months)	
n	23
Mean (Standard Deviation)	4.04 (1.686)
Median	4.01
Min, Max	0.5, 7.0
First,Third Quartile (Inter-Quartile Range)	3.1, 5.2 (2.1)

Table 6.1Summary of Progression Free Survival (Primary Analysis) - Safety Population

Characteristic	Number (%) of patients [a] (N=23)
Number of patients with events	17 (73.9)
Number of patients censored[1]	6 (26.1)
Median Time to Event (95% CI)[2]	1.89 (1.61, 5.19)
Event Rates	
4 months (95% CI)	31.17 (13.51, 50.71)
6 months (95% CI)	0.00 (., .)
12 months (95% CI)	0.00 (., .)

[a]N=Number of subjects; the denominator for % calculations should be N for each column (number in study part or total).

Note: PFS is defined as the time from first dose of study drug (Day 1) until first disease progression or death from any cause.

Note: Percentages are based on the number of overall subjects (N).

[1] Censored at the last disease assessment or first dose date if no progression, or death.

[2] Kaplan-Meier estimate with 95% CI based on Brookmeyer-Crowley log(-log) transformation.

Table 6.2Summary of Progression Free Survival (Exploratory Analysis) - Safety Population

Characteristic	Number (%) of patients [a] (N=23)
Number of patients with events	17 (73.9)
Number of patients censored[1]	6 (26.1)
Median Time to Event (95% CI)[2]	1.89 (1.61, 5.19)
Event Rates	
4 months (95% CI)	31.17 (13.51, 50.71)
6 months (95% CI)	0.00 (., .)
12 months (95% CI)	0.00 (., .)

[a]N=Number of subjects; the denominator for % calculations should be N for each column (number in study part or total).

Note: PFS is defined as the time from first dose of study drug (Day 1) until first disease progression or death from any cause.

Note: Percentages are based on the number of overall subjects (N).

[1] Censored at the end of treatment discontinuation date if no progression, or death.

[2] Kaplan-Meier estimate with 95% CI based on Brookmeyer-Crowley log(-log) transformation.

Table 7 Summary of Overall Survival - Safety Population

Characteristic	Number (%) of patients [a] (N=23)
Number of patients with events	8 (34.8)
Number of patients censored	15 (65.2)
Median Time to Event (95% CI)[1]	6.67 (3.42, NA)

[a]N=Number of subjects; the denominator for % calculations should be N for each column (number in study part or total).

Note: OS is defined as the time from first dose of study drug (Day 1) until death from any cause.

Note: Percentages are based on the number of overall subjects (N).

[1] Kaplan-Meier estimate with 95% CI based on Brookmeyer-Crowley log(-log) transformation.

Table 8 Summary of Disease Response - Safety Population

Characteristic	Number (%) of patients [a] (N=23)
Best Overall Response	0
Complete Response	0
Partial Response	0
Stable Disease	10 (43.5)
Progressive Disease	9 (39.1)
Not Evaluable	0
Not Available	4 (17.4)
Overall Response Rate (Complete Response + Partial Response)	0
95% CI (LCL, UCL)	(0.0, 14.8)

[a]N=Number of subjects; the denominator for % calculations should be N for each column (number in study part or total).

[b] 2-sided exact 95% confidence interval (CI) based on the Clopper-Pearson method; LCL – Lower confidence limit; UCL – Upper confidence limit.

Table 9 Subject Incidence of TEAEs by Grade - Safety Population

	All Subjects (N=23)					
N(%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**All Grade**
Subjects with at least one TEAE	17 (73.9)	14 (60.9)	15 (65.2)	1 (4.3)	1 (4.3)	21 (91.3)
Fatigue	4 (17.4)	2 (8.7)	3 (13.0)	0	0	9 (39.1)
Abdominal pain	3 (13.0)	3 (13.0)	2 (8.7)	0	0	8 (34.8)
Diarrhoea	2 (8.7)	4 (17.4)	1 (4.3)	0	0	7 (30.4)
Constipation	4 (17.4)	1 (4.3)	0	0	0	5 (21.7)
Blood sodium decreased	2 (8.7)	2 (8.7)	0	0	0	4 (17.4)
Nausea	2 (8.7)	1 (4.3)	1 (4.3)	0	0	4 (17.4)
Vomiting	2 (8.7)	1 (4.3)	1 (4.3)	0	0	4 (17.4)
Blood bilirubin increased	1 (4.3)	0	2 (8.7)	0	0	3 (13.0)
Dehydration	0	0	3 (13.0)	0	0	3 (13.0)
Hypertension	0	1 (4.3)	2 (8.7)	0	0	3 (13.0)
Leukocytosis	0	0	3 (13.0)	0	0	3 (13.0)
Non-cardiac chest pain	3 (13.0)	0	0	0	0	3 (13.0)
Abdominal pain upper	1 (4.3)	1 (4.3)	0	0	0	2 (8.7)
Aspartate aminotransferase increased	2 (8.7)	0	0	0	0	2 (8.7)

If a patient had multiple events with same preferred term and different grades, the event will be shown in the highest grade of the table.

If a patient had multiple events with different preferred terms, these events will be shown in the corresponding highest grades of the table.

Table 10 Subject Incidence of Serious Adverse Events (SAE) by Preferred Term - Safety Population

	Total (N=23)
Subjects with at least one SAE	11 (47.8)
Dehydration	3 (13.0)
Abdominal Pain	2 (8.7)
Pulmonary Embolism	2 (8.7)
Sepsis	2 (8.7)
Atrial Fibrillation	1 (4.3)
Blood Bilirubin Increased	1 (4.3)
Cholecystitis	1 (4.3)
Decreased Appetite	1 (4.3)
Diarrhoea	1 (4.3)
Fall	1 (4.3)
Gastritis	1 (4.3)
Haematochezia	1 (4.3)
Hepatic Failure	1 (4.3)
Hyponatraemia	1 (4.3)
Large Intestinal Obstruction	1 (4.3)
Rectal Haemorrhage	1 (4.3)
Urinary Retention	1 (4.3)
Vomiting	1 (4.3)

Table 11 Subject Incidence of Related TEAEs by Preferred Term - Safety Population

	Total (N=23)
Subjects with at least one Related TEAE	14 (60.9)
Fatigue	8 (34.8)
Abdominal Pain	3 (13.0)
Diarrhoea	2 (8.7)
Headache	2 (8.7)
Hypertension	2 (8.7)
Leukocytosis	2 (8.7)
Peripheral Sensory Neuropathy	2 (8.7)
Vomiting	2 (8.7)
Abdominal Pain Upper	1 (4.3)
Arthralgia	1 (4.3)
Asthenia	1 (4.3)
Atrial Fibrillation	1 (4.3)
Blood Sodium Decreased	1 (4.3)
Chills	1 (4.3)
Constipation	1 (4.3)
Decreased Appetite	1 (4.3)
Hyponatraemia	1 (4.3)
Nausea	1 (4.3)

Table 12 Subject Incidence of TEAEs Leading to Study Discontinuation by Preferred Term - Safety Population

	Total (N=23)
Subjects with AE leading to study discontinuation	2 (8.7)
Fatigue	1 (4.3)
Sepsis	1 (4.3)

Table 13 Summary of Decreased Haematology Parameters - Safety Population

	Total (N=23)
Hemoglobin	22
Grade 1	11 (47.8)
Grade 2	7 (30.4)
Grade 3	0
Lymphocyte Count	22
Grade 1	4 (17.4)
Grade 2	6 (26.1)
Grade 3	3 (13.0)
Grade 4	1 (4.3)
Neutrophils count	22
Grade 1	0
Grade 2	1 (4.3)
Grade 3	0
Grade 4	0
Platelet	22
Grade 1	3 (13.0)
Grade 2	0

	Total (N=23)
Grade 3	0
Grade 4	1 (4.3)
Leukocytes	22
Grade 1	2 (8.7)
Grade 2	1 (4.3)
Grade 3	0
Grade 4	0

Table 14 Summary of Elevated Chemistry Parameters - Safety Population

	Total (N=23)
AST	22
Grade 1	7 (30.4)
Grade 2	3 (13.0)
Grade 3	1 (4.3)
Grade 4	0
ALT	22
Grade 1	6 (26.1)
Grade 2	0
Grade 3	1 (4.3)
Grade 4	0
Total Bilirubin	22
Grade 1	4 (17.4)
Grade 2	0
Grade 3	2 (8.7)
Grade 4	1 (4.3)
Alkaline Phosphatase	22
Grade 1	2 (8.7)

	Total (N=23)
Grade 2	2 (8.7)
Grade 3	1 (4.3)
Grade 4	0

Figure 1 Swimmer Plot – Safety Population

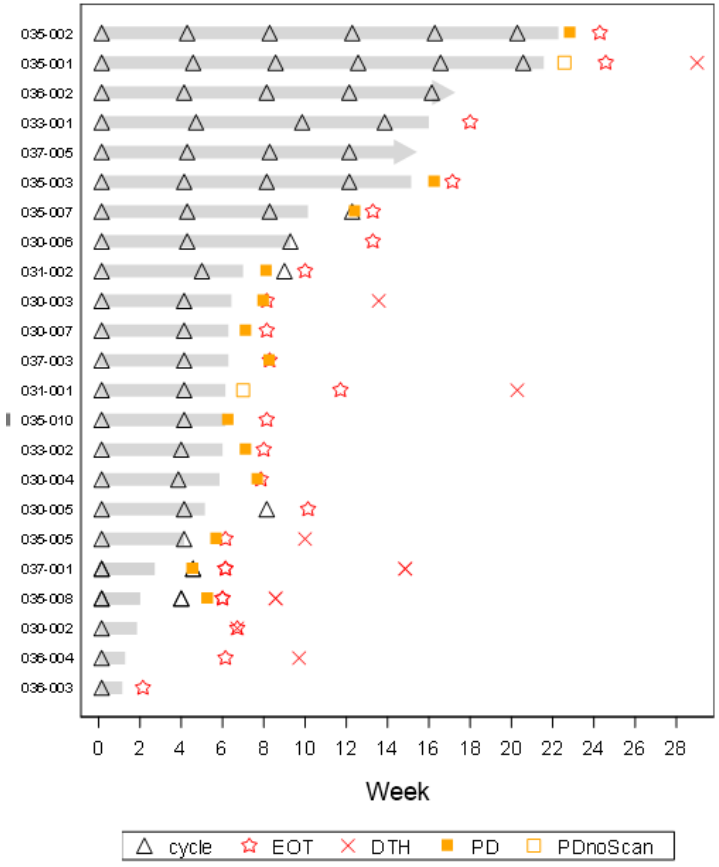
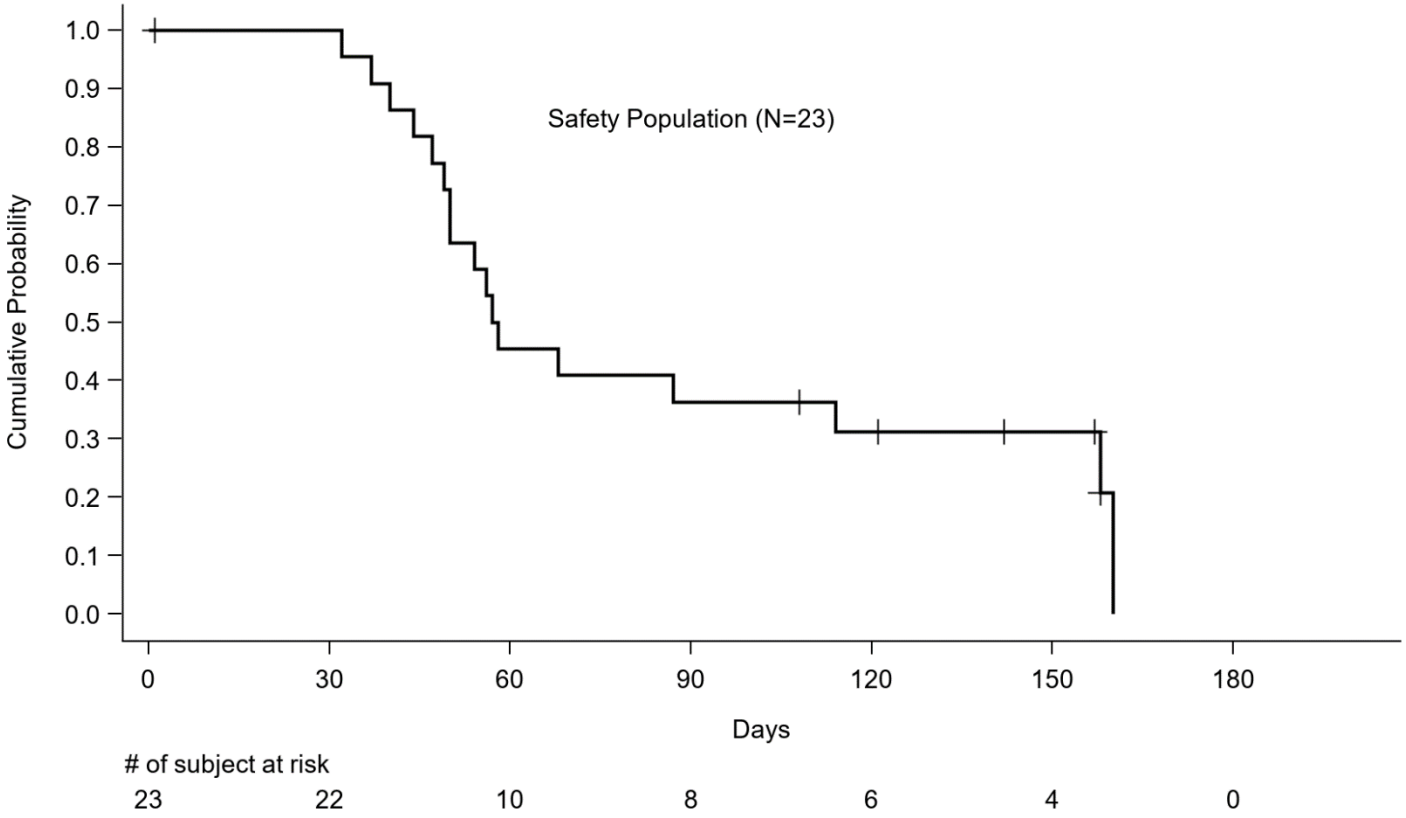
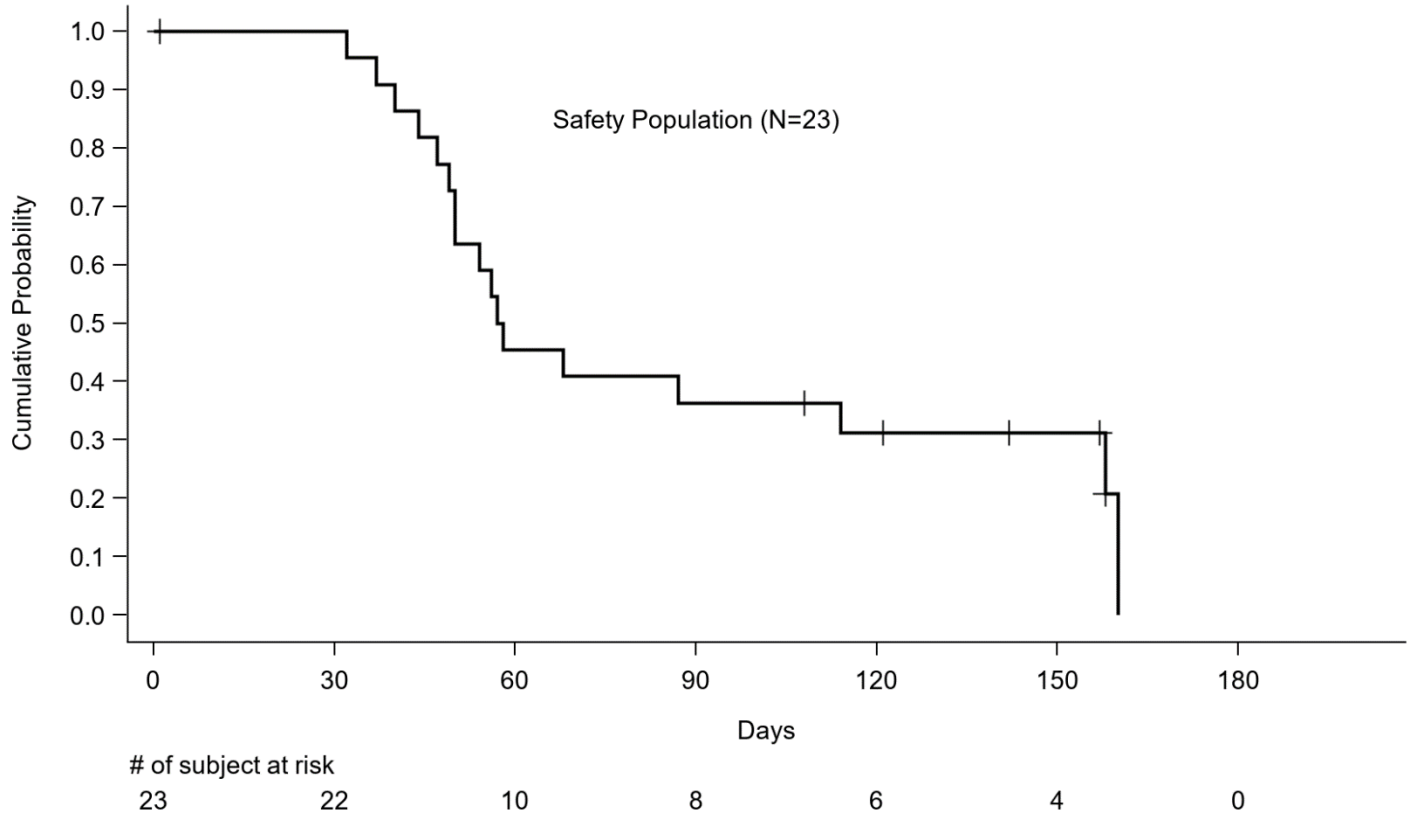


Figure 2.1 Kaplan-Meier Curve for Progression-Free Survival (Primary Analysis) - Safety Population



Programming note: For the primary PFS analysis, subjects without a PD or death event will be censored at last adequate assessment date or first dose date if no adequate postbaseline assessment is available.

Figure 2.2 Kaplan-Meier Curve for Progression-Free Survival (Exploratory Analysis) - Safety Population



Programming note: For the exploratory PFS analysis, subjects without a PD or death event will be censored at last adequate assessment date or first dose date if no adequate postbaseline assessment is available.

Figure 3 Kaplan-Meier Curve for Overall Survival – Safety Population

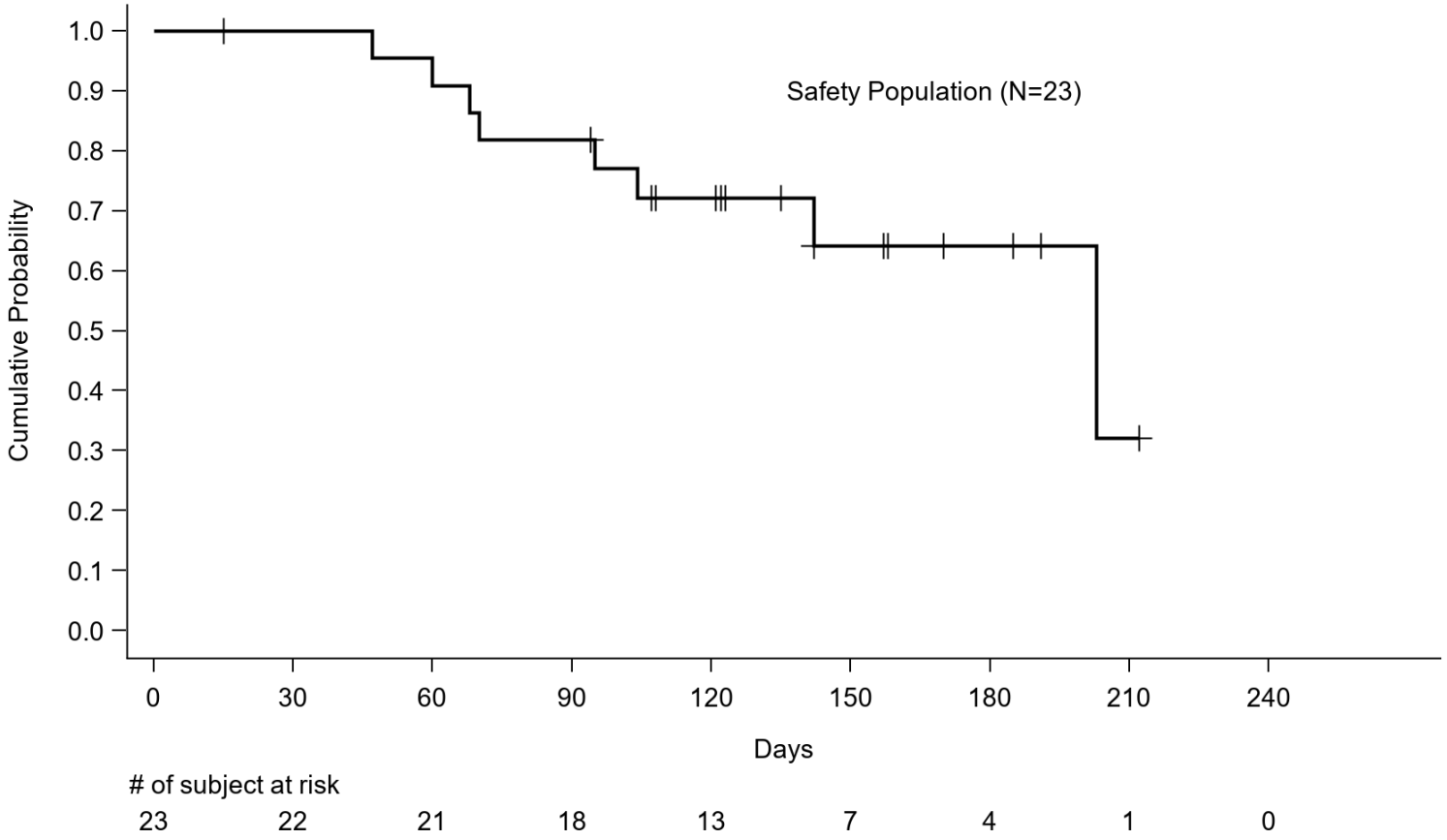
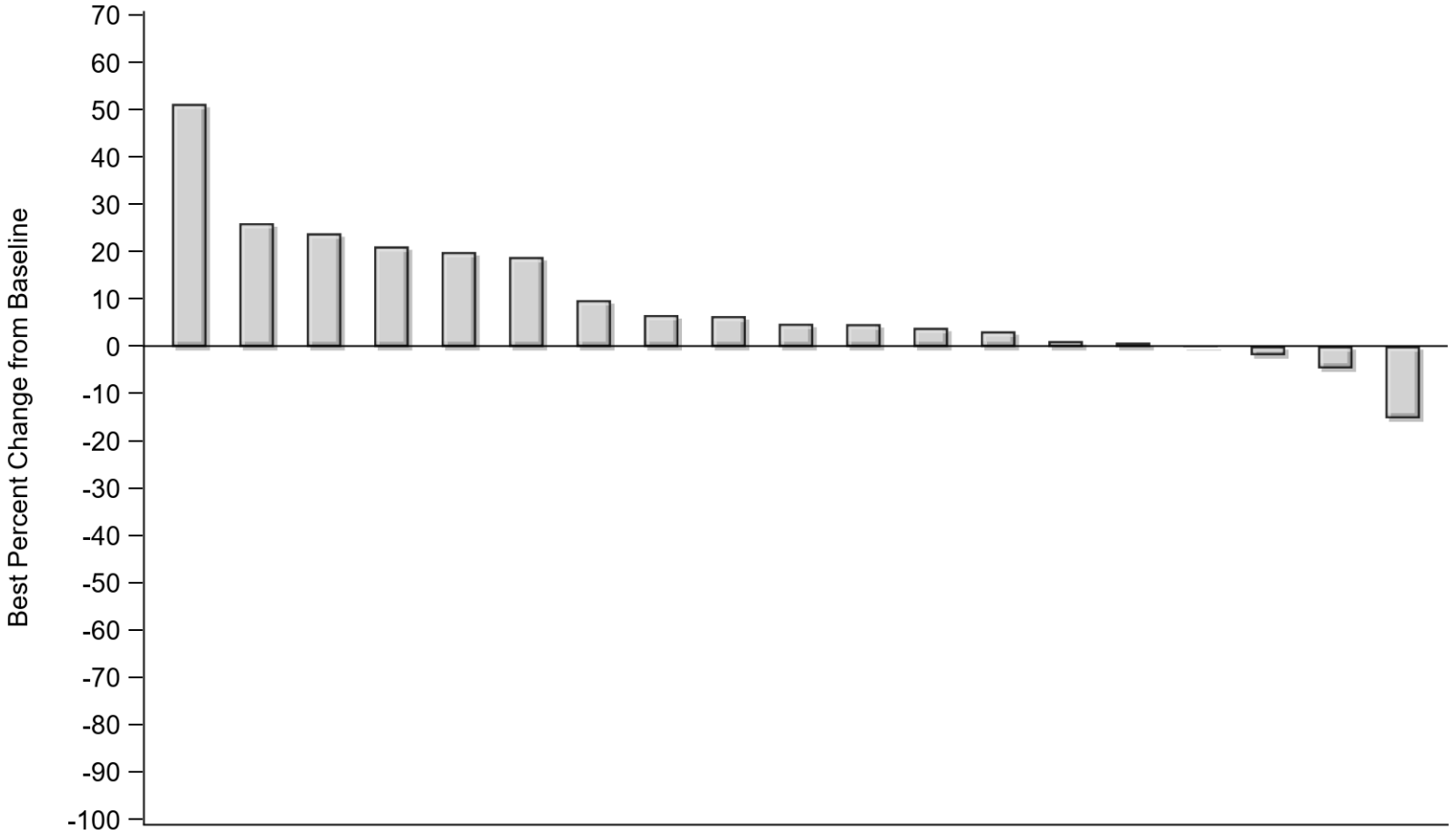


Figure 4 Waterfall Plot of Best Change in Sum of Target Lesion Size - Safety Population



Listing 1. Subjects who died in Study ME-344-003

Subject ID	Sex	Age	Primary Cause of Death	Last ME-344-003 Dose Date (Day)	Death Date (Day)	AE Preferred Term (if Died due to AE)	Relationship to Drug
0037_009	Male	74	Adverse Event	9 Mar 2020 (456)	31 Mar 2020 (478)	Corona virus infection	Not-Related
0102_004	Female	44	Disease Progression	2 Aug 2019 (19)	11 Aug 2019 (28)		
4005_002	Male	79	Unknown	22 Mar 2019 (639)	20 Jun 2019 (729)		
41007-001	Female	50	Adverse Event	27 Mar 2020 (15)	10 Apr 2020 (29)	Tumour lysis syndrome	Related
41008-001	Male	78	Disease Progression	22 Dec 2019 (110)	14 Jan 2020 (133)		