

Supplemental Online Content

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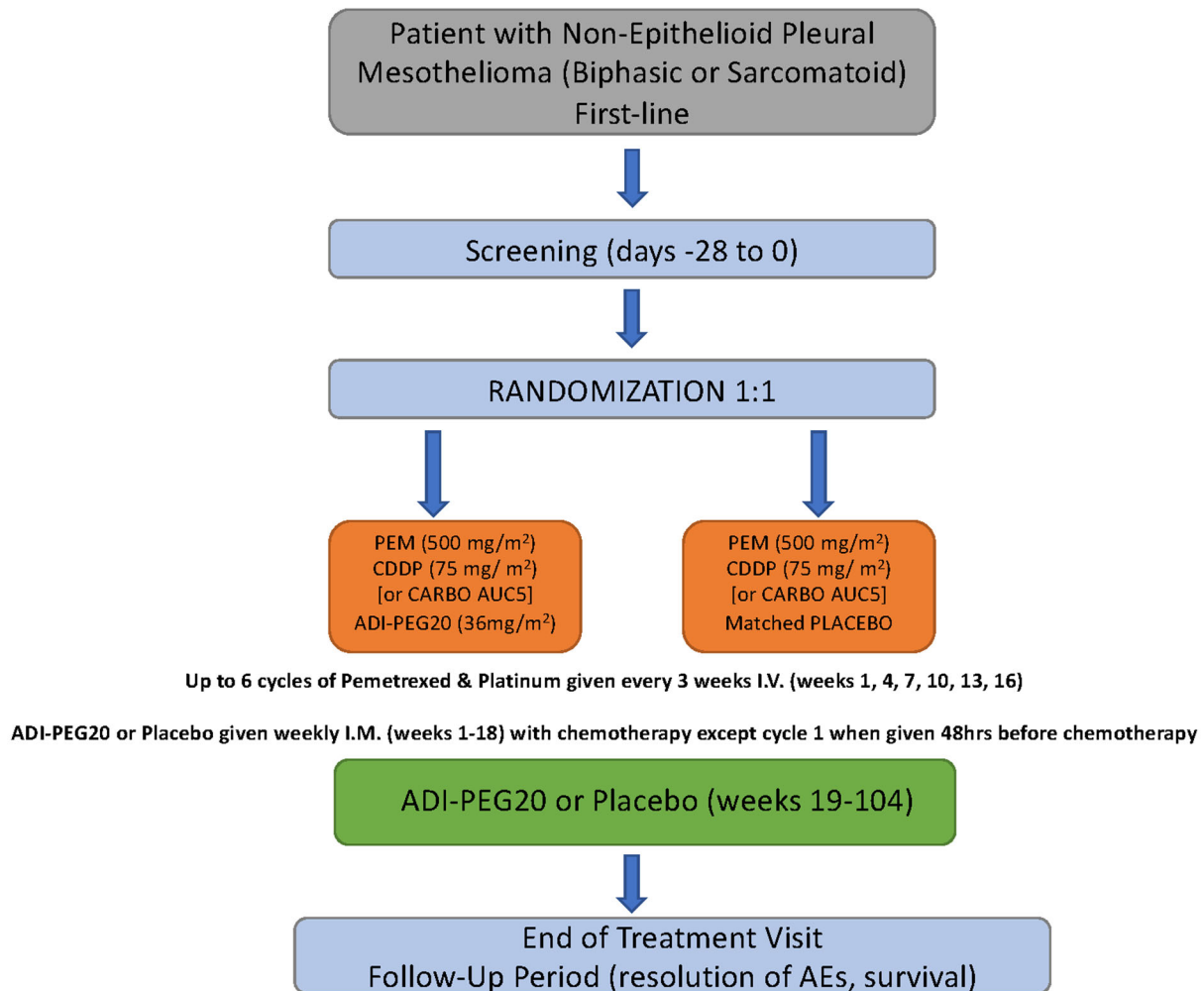
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This supplemental material has been provided by the authors to give readers additional information about their work.

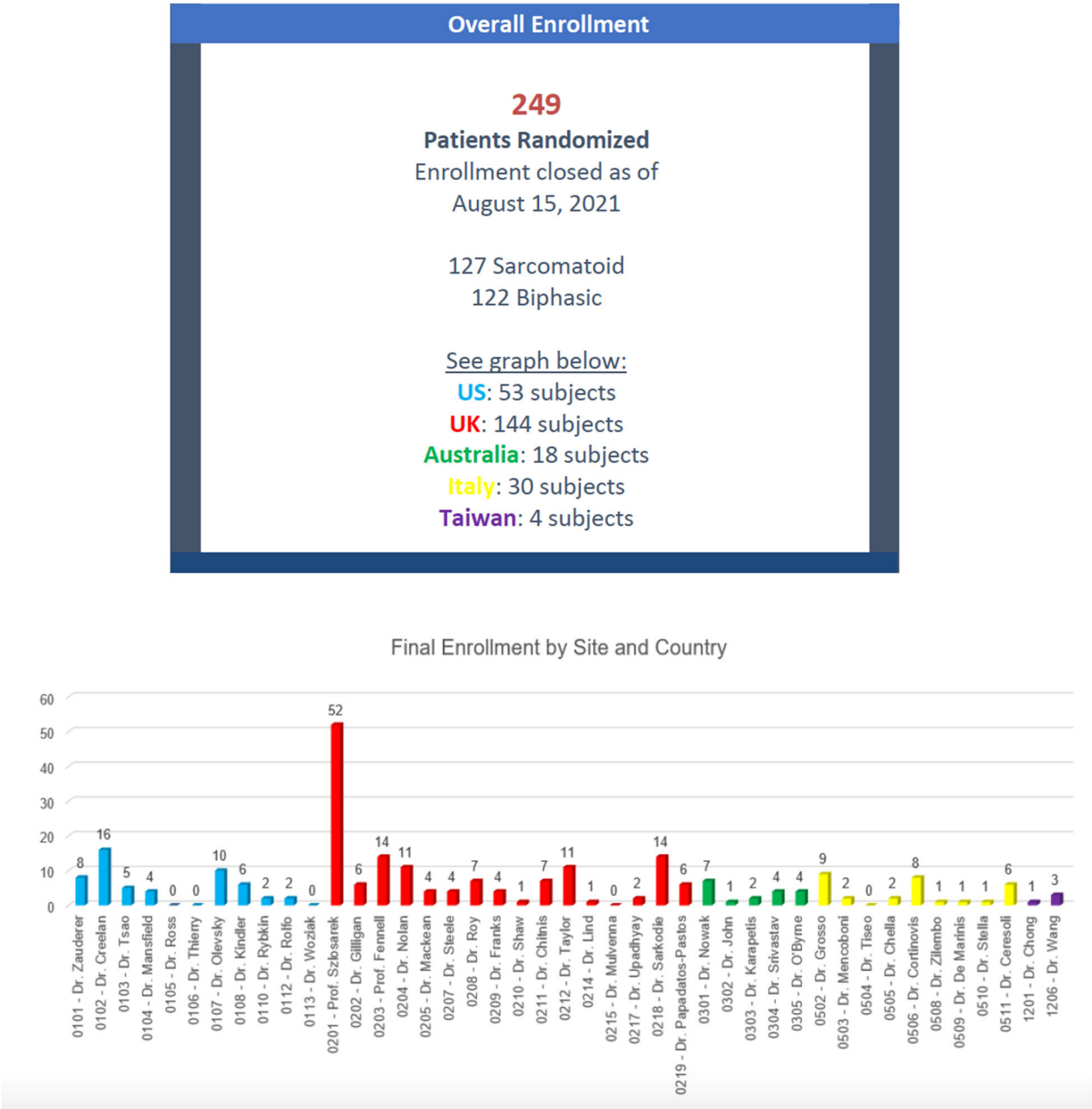
eFigure 1. ATOMIC-Meso Treatment schema



Notes:

PEM = pemetrexed; CDDP = cisplatin; CARBO = carboplatin; I.M. = intramuscular; I.V. = intravenous

eFigure 2. ATOMIC-Meso Enrollment by Site and Country



eTable 1. Subject Disposition (All Randomized Subjects)

	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)	Total (N = 249)
Safety Population ^a	125 (100%)	124 (100%)	249 (100%)
ITT Population ^b	125 (100%)	124 (100%)	249 (100%)
PP Population ^c	125 (100%)	124 (100%)	249 (100%)
Primary Reason for Discontinuing ADI-PEG 20 or Placebo			
Adverse Event	19 (15.2%)	14 (11.3%)	33 (13.3%)
Death ^d	5 (4.0%)	10 (8.1%)	15 (6.0%)
Lack of Efficacy	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to Follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non-Compliance	0 (0.0%)	0 (0.0%)	0 (0.0%)
Physician Decision	2 (1.6%)	3 (2.4%)	5 (2.0%)
Pregnancy	0 (0.0%)	0 (0.0%)	0 (0.0%)
Progressive Disease	85 (68.0%)	84 (67.7%)	169 (67.9%)
Protocol Violation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sponsor Request	0 (0.0%)	0 (0.0%)	0 (0.0%)
Start Other Anti-Cancer Treatment	0 (0.0%)	0 (0.0%)	0 (0.0%)
Study Terminated	0 (0.0%)	0 (0.0%)	0 (0.0%)
Withdrawal by Subject	8 (6.4%)	12 (9.7%)	20 (8.0%)
Other ^e	6 (4.8%)	0 (0.0%)	6 (2.4%)
Missing	0 (0.0%)	1 (0.8%)	1 (0.4%)
Primary Reason for Study Termination			
Withdrawal by Subject	2 (1.6%)	0 (0.0%)	2 (0.8%)
Lost to Follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)
Study Terminated	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death ^f	105 (84.0%)	116 (93.5%)	221 (88.8%)
Other ^g	18 (14.4%)	8 (6.5%)	26 (10.4%)

^a Safety Population includes all randomized subjects who received at least one dose of the study medication.

Treatment group assignment is based on the treatment actually received.

^b ITT Population includes all randomized subjects. Treatment group assignment is based on the randomized treatment assignment.

^c PP Population includes all ITT subjects who had no major protocol violations that may potentially affect the primary and secondary efficacy measures. Treatment group assignment is based on the randomized treatment assignment.

^d 2 (Grade 5 neutropenic sepsis and grade 5 sudden death) are possibly related to ADI -PEG 20, as well as being definitely or possibly related to pemetrexed and the platinum.

^e Included subjects who completed treatment.

^f Three additional subjects stopped the study and a date of death was obtained and entered into EDC (reasons for study termination of subject decision to withdraw consent for 2 subjects and "other: relocated to Oregon).

^g Includes subjects who were still alive and in follow-up at the end of the study.

eTable 2. Post-study therapy

Therapy	ADIPemPlatinum (N=125)	PlaceboPemPlatinum (N=124)	Total (N=249)
Any therapeutic procedure	60 (48.0%)	63 (50.8%)	123 (49.4%)
Radiotherapy	14 (11.2%)	14 (11.3%)	28 (11.2%)
Surgery	1 (0.8%)	1 (0.8%)	2 (0.8%)
Chemotherapy/Immunotherapy ^a	57 (45.6%)	58 (46.8%)	115 (46.2%)
Bevacizumab	2 (1.6%)	0 (0.0%)	2 (0.8%)
Bevacizumab + Pemetrexed	0 (0.0%)	1 (0.8%)	1 (0.4%)
Carboplatin + Pemetrexed	3 (2.4%)	8 (6.5%)	11 (4.4%)
Carboplatin + Pemetrexed + Bevacizumab	1 (0.8%)	0 (0.0%)	1 (0.4%)
Cisplatin + Pemetrexed	1 (0.8%)	1 (0.8%)	2 (0.8%)
Durvalumab	0 (0.0%)	1 (0.8%)	1 (0.4%)
Gemcitabine	7 (5.6%)	4 (3.2%)	11 (4.4%)
Gemcitabine + Carboplatin	3 (2.4%)	3 (2.4%)	6 (2.4%)
Gemcitabine + Ramucirumab	1 (0.8%)	0 (0.0%)	1 (0.4%)
Gemcitabine + Cisplatin + Methotrexate	2 (1.6%)	0 (0.0%)	2 (0.8%)
Investigational Agent, Clinical Trial	4 (3.2%)	3 (2.4%)	7 (2.8%)
Ipilimumab	1 (0.8%)	0 (0.0%)	1 (0.4%)
Ipilimumab + Nivolumab ^b	21 (16.8%)	11 (8.9%)	32 (12.9%)
Nivolumab	9 (7.2%)	5 (4.0%)	14 (5.6%)
Nivolumab + Galinpepimut-S, Clinical Trial	0 (0.0%)	1 (0.8%)	1 (0.4%)
Nivolumab + Ramucirumab	4 (3.2%)	3 (2.4%)	7 (2.8%)
Nivolumab vs Placebo, Clinical Trial	5 (4.0%)	4 (3.2%)	9 (3.6%)
Pembrolizumab	13 (10.4%)	11 (8.9%)	24 (9.6%)
Placebo, Clinical Trial	0 (0.0%)	1 (0.8%)	1 (0.4%)
Unknown Chemotherapy	1 (0.8%)	1 (0.8%)	2 (0.8%)
Unknown Immunotherapy	0 (0.0%)	1 (0.8%)	1 (0.4%)
Vinorelbine ^c	8 (6.4%)	14 (11.3%)	22 (8.8%)

Notes:

^a = 0.853 ; ^b = 0.062; ^c 0.174. (P-value: comparing ADIPemPlatinum to PlaceboPemPlatinum (Chi-squared test).

eTable 3. Overall Survival – Phase 3 Subjects (ITT Population)

Survival Estimates (Months)	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)
Number (%) of Subjects with Event	108 (86.4%)	116 (93.5%)
Number (%) of Subjects Censored	17 (13.6%)	8 (6.5%)
Quartiles (95% CI) ^a		
25 th Percentile	5.13 (3.75, 5.85)	3.79 (2.79, 4.90)
Median ^b	9.30 (7.85, 11.79)	7.66 (6.14, 9.53)
75 th Percentile	18.30 (13.93, 21.98)	13.27 (10.94, 17.02)
Range (Subjects with Event)	0.23, 36.99	0.69, 40.44
Range (All Subjects)	0.23, 55.69	0.69, 49.22
Hazard Ratio (95% CI) ^c	0.71 (0.55, 0.93)	
P-value ^d	0.0234	

Note: Overall survival was defined as the time from randomization until death. In the event that no death was documented prior to study termination or analysis cutoff, OS was censored at the last known date the subject was known to be alive, either through completion of on-study visits or through survival follow-up contact.

^a Kaplan-Meier product-limit estimates.

^b Median was defined to be the smallest observed survival time for which the value of the estimated survival function was less than or equal to 0.5.

^c Hazard ratio (ADIPemPlatinum/PlaceboPemPlatinum) and corresponding 95% CI were obtained from a Cox proportional hazards model adjusting for tumor histology (biphasic vs sarcomatoid). A hazard ratio less than 1 was favorable to ADIPemPlatinum.

^d P-value comparing the treatment groups was based on the log-rank test stratified by tumor histology (biphasic vs sarcomatoid).

Estimates (and 95% CIs) for overall survival rate (years 1-4):

Timepoint	ADIPemPlatinum	PlaceboPemPlatinum
1 year	0.4137 (0.3267, 0.4985)	0.3141 (0.2346, 0.3966)
2 year	0.1571 (0.0979, 0.2289)	0.0994 (0.0521, 0.1646)
3 year	0.1194 (., .)*	0.0331 (0.0092, 0.0839)
4 year	(., .)*	0.0166 (0.0018, 0.0693)

*Some estimations were not computed due to the large number of censored patients.

eTable 4. Progression-Free Survival – Phase 3 Subjects (ITT Population)

Survival Estimates (Months)	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)
Number (%) of Subjects with Event	71 (56.8%)	74 (59.7%)
Number (%) of Subjects Censored	54 (43.2%)	50 (40.3%)
Quartiles (95% CI) ^a		
25 th Percentile	3.98 (2.89, 4.24)	2.60 (2.14, 3.19)
Median ^b	6.24 (5.78, 7.43)	5.65 (4.14, 5.91)
75 th Percentile	9.53 (7.62, 12.91)	7.62 (6.05, 9.53)
Range (Subjects with Event)	0.23, 19.61	0.69, 15.93
Range (All Subjects)	0.03, 24.15	0.03, 15.93
Hazard Ratio (95% CI) ^c	0.65 (0.46, 0.90)	
P-value ^d	0.0193	

Note: Progression-free survival was defined as the time from randomization until date of tumor progression or death. In the event that no tumor progression or death was documented prior to EOT, analysis cutoff, or the start of confounding anticancer therapy, PFS was censored at the date of the last tumor assessment demonstrating no tumor progression.

^a Kaplan-Meier product-limit estimates.

^b Median was defined to be the smallest observed survival time for which the value of the estimated survival function was less than or equal to 0.5.

^c Hazard ratio (ADIPemPlatinum/PlaceboPemPlatinum) and corresponding 95% CI were obtained from a Cox proportional hazards model adjusting for tumor histology (biphasic vs sarcomatoid). A hazard ratio less than 1 was favorable to ADIPemPlatinum.

^d P-value comparing the treatment groups was based on the log-rank test stratified by tumor histology (biphasic vs sarcomatoid).

eTable 5. Objective response rate – Phase 2 Subjects (ITT population)

Best Tumor Response ^a	ADIPemPlatinum (N = 87)	PlaceboPemPlatinum (N = 89)	P-value ^c	Relative Risk Ratio (95% CI) ^d
CR	0 (0.0%)	1 (1.1%)	-	-
PR	12 (13.8%)	11 (12.4%)	-	-
SD	62 (71.3%)	56 (62.9%)	-	-
PD	6 (6.9%)	10 (11.2%)	-	-
Missing or Not Evaluable	7 (8.0%)	11 (12.4%)	-	-
Objective Response Rate (CR or PR) ^b	12 (13.8%)	12 (13.5%)	0.9489	1.02 (0.50, 2.11)

^a The best tumor response was the best response recorded from the start of the treatment until EOT taking into account any requirement for confirmation.

^b Objective RR was calculated as the proportion of subjects whose best tumor response from all post-baseline tumor assessments was CR or PR.

^c P-value comparing ADIPemPlatinum to PlaceboPemPlatinum was based on the CMH test stratified by tumor histology (biphasic vs sarcomatoid).

^d Relative Risk Ratio (ADIPemPlatinum/PlaceboPemPlatinum) was the common relative risk of having a response (CR or PR) based on the Mantel-Haenszel estimator controlling for tumor histology. A relative risk ratio greater than 1 was favorable to ADIPemPlatinum.

eTable 6. Duration of Response – Phase 2 Subjects (ITT Population)

Survival Estimates (Months)	ADIPemPlatinum (N = 87)	PlaceboPemPlatinum (N = 89)
Number of Subjects with Best Overall Response of CR or PR	12	12
Number (%) of Subjects with Event	4 (33.3%)	9 (75.0%)
Number (%) of Subjects Censored	8 (66.7%)	3 (25.0%)
Quartiles (95% CI) ^a		
25 th Percentile	4.63 (3.71, NA)	3.65 (2.79, 4.63)
Median ^b	NA (NA, NA)	4.63 (3.65, 11.76)
75 th Percentile	NA (NA, NA)	11.76 (4.63, NA)
Range (Subjects with Event)	3.71, 6.11	2.79, 11.99
Range (All Subjects)	2.56, 22.34	2.79, 11.99
Hazard Ratio (95% CI) ^c	0.34 (0.10, 1.14)	
P-value ^d	0.0918	

Note: DOR was defined as the time from date of initial response of CR or PR until date of tumor progression or death. Subjects without tumor progression or death at the EOT were censored using the date of the last tumor assessment demonstrating no tumor progression.

^a Kaplan-Meier product-limit estimates.

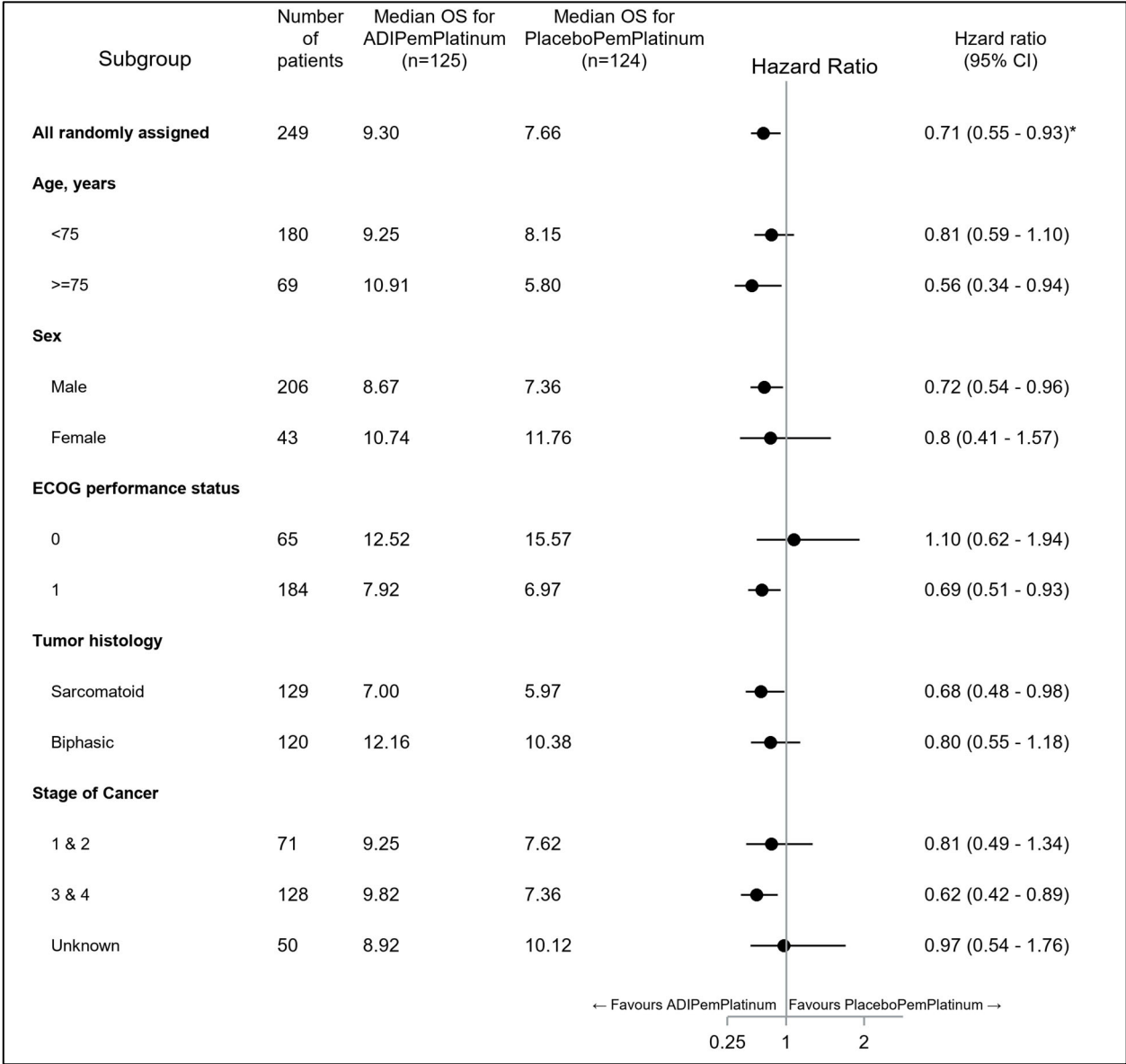
^b Median was defined to be the smallest observed survival time for which the value of the estimated survival function was less than or equal to 0.5.

^c Hazard ratio (ADIPemPlatinum/PlaceboPemPlatinum) and corresponding 95% CI were obtained from a Cox proportional hazards model adjusting for tumor histology (biphasic vs sarcomatoid). A hazard ratio less than 1 was favorable to ADIPemPlatinum.

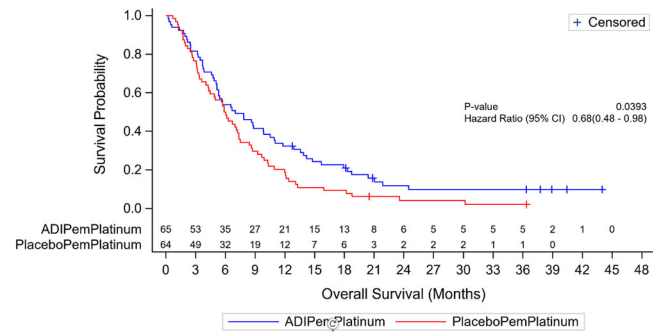
^d P-value comparing the treatment groups was based on the log-rank test stratified by tumor histology (biphasic vs sarcomatoid).

NA = not applicable

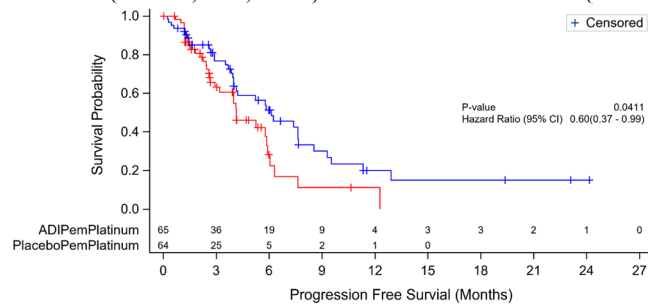
eFigure 3. Additional exploratory subgroup analyses



Kaplan-Meier Plot of OS and PFS – Phase 3 Subjects (sarcomatoid)

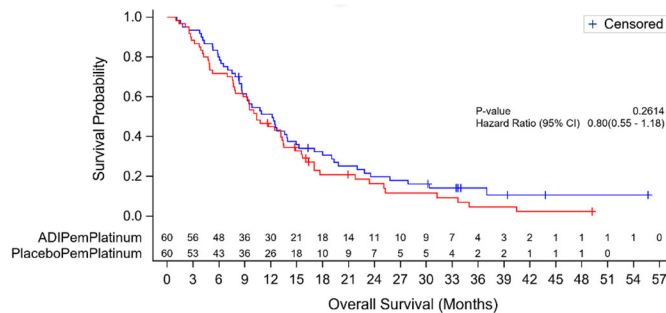


mOS 7.00 (95% CI, 5.13, 10.51) ADIPemPlatinum vs 5.96 (95% CI, 4.27, 7.36) PlaceboPemPlatinum

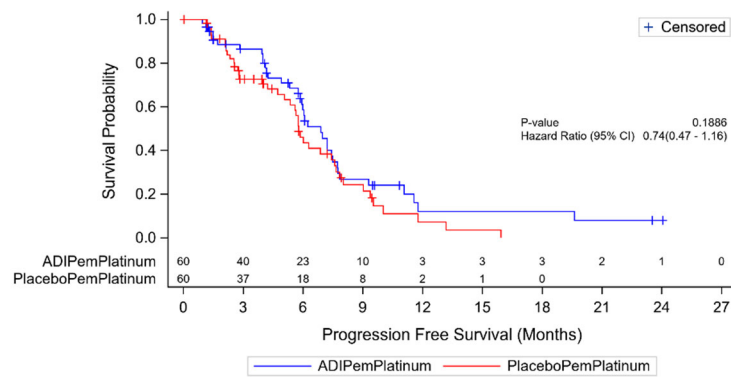


mPFS 6.11 (95% CI, 3.98, 7.66) ADIPemPlatinum vs 4.14 (95% CI, 2.92, 5.85) PlaceboPemPlatinum

Kaplan-Meier Plot of OS and PFS – Phase 3 Subjects (biphasic)



mOS 12.16 (95% CI, 8.64, 13.93) ADIPemPlatinum vs 10.38 (95% CI, 7.82, 13.44) PlaceboPemPlatinum



mPFS 6.90 (95% CI, 5.85, 7.49) ADIPemPlatinum vs 5.78 (95% CI, 5.06, 7.43) PlaceboPemPlatinum

eTable 7. Extent of Drug Exposure

	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)
Number of Doses of ADI-PEG 20/Placebo		
n	125	124
Mean (SD)	22.0 (20.52)	17.0 (13.39)
Median	18.0	14.0
Min, Max	1, 104	1, 69
Total Dose of ADI-PEG 20 Received (mg)		
n	125	NA
Mean (SD)	1475.0 (1393.72)	NA
Median	1151.0	NA
Min, Max	54.7, 7416.0	NA
Subjects With at Least One Dose Withheld of ADI-PEG 20/ Placebo	73 (58.4%)	59 (47.6%)
Dose Withheld Due to ^a :		
Adverse Event	50 (40.0%)	39 (31.5%)
Other Reason	36 (28.8%)	32 (25.8%)
Number of Doses of Pemetrexed		
n	122	124
Mean (SD)	4.3 (1.77)	4.1 (1.73)
Median	4.5	4.0
Min, Max	1, 6	1, 6
Total Dose of Pemetrexed (mg)		
n	122	124
Mean (SD)	3702.5 (1566.31)	3597.8 (1605.93)
Median	3825.0	3600.0
Min, Max	700, 6600	690, 6600
Subjects With at Least One Dose Withheld of Pemetrexed	122 (97.6%)	116 (93.5%)
Dose Withheld Due to ^a :		
Adverse Event	47 (37.6%)	33 (26.6%)
Non-compliance	0 (0.0%)	2 (1.6%)
Not Applicable/ Not Scheduled	120 (96.0%)	116 (93.5%)
Other Reason	23 (18.4%)	10 (8.1%)
Subjects With at Least One Dose Reduced of Pemetrexed	41 (32.8%)	35 (28.2%)
Dose Reduced Due to ^a :		
Adverse Event	31 (24.8%)	30 (24.2%)
Other Reason	12 (9.6%)	9 (7.3%)
Number of Doses of Cisplatin		
n	92	100
Mean (SD)	3.8 (1.93)	3.4 (1.79)
Median	4.0	3.5
Min, Max	1, 6	1, 6
Total Dose of Cisplatin (mg)		
n	92	99
Mean (SD)	489.5 (258.52)	445.6 (239.08)
Median	452.9	435.0
Min, Max	85, 1145	104, 984
Subjects With at Least One Dose Withheld of Cisplatin	123 (98.4%)	116 (93.5%)
Dose Withheld Due to ^a :		
Adverse Event	37 (29.6%)	34 (27.4%)
Non-compliance	0 (0.0%)	3 (2.4%)
Not Applicable/ Not Scheduled	119 (95.2%)	114 (91.9%)
Other Reason	26 (20.8%)	22 (17.7%)

	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)
Subjects With at Least One Dose Reduced of Cisplatin	42 (33.6%)	36 (29.0%)
Dose Reduced Due to ^a :		
Adverse Event	30 (24.0%)	28 (22.6%)
Other Reason	17 (13.6%)	11 (8.9%)
Number of Subjects who Received Any Dose of Carboplatin	46 (36.8%)	42 (33.9%)
Number of Doses of Carboplatin		
n	46	42
Mean (SD)	3.7 (1.86)	3.6 (1.75)
Median	4.0	4.0
Min, Max	1, 6	1, 6
Total Dose of Carboplatin (mg)		
n	46	42
Mean (SD)	1675.9 (835.32)	1604.9 (835.08)
Median	1540.8	1575.0
Min, Max	500, 3618	324, 3500

^a Subjects were included in all categories that applied.

eTable 8. Overall Summary of TEAEs (Safety Population)

	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)	Total (N = 249)
Total Number of TEAEs	1570	1403	2973
Total Number of TESAEs	106	111	217
Number (%) of Subjects Reporting at Least One:			
TEAE	123 (98.4%)	123 (99.2%)	246 (98.8%)
TEAE by Severity ^a			
Grade 1: Mild	6 (4.8%)	10 (8.1%)	16 (6.4%)
Grade 2: Moderate	25 (20.0%)	35 (28.2%)	60 (24.1%)
Grade 3: Severe	62 (49.6%)	55 (44.4%)	117 (47.0%)
Grade 4: Life-threatening	23 (18.4%)	11 (8.9%)	34 (13.7%)
Grade 5: Death	7 (5.6%)	12 (9.7%)	19 (7.6%)
TESAE	62 (49.6%)	61 (49.2%)	123 (49.4%)
TESAE by Severity ^a			
Grade 1: Mild	4 (3.2%)	3 (2.4%)	7 (2.8%)
Grade 2: Moderate	7 (5.6%)	7 (5.6%)	14 (5.6%)
Grade 3: Severe	35 (28.0%)	34 (27.4%)	69 (27.7%)
Grade 4: Life-threatening	9 (7.2%)	6 (4.8%)	15 (6.0%)
Grade 5: Death	7 (5.6%)	11 (8.9%)	18 (7.2%)
TEAE Leading to Premature Withdrawal from the Study	5 (4.0%)	7 (5.6%)	12 (4.8%)
TEAE Related to ADI-PEG 20/Placebo ^b	86 (68.8%)	79 (63.7%)	165 (66.3%)
TESAE Related to ADI-PEG 20/Placebo ^b	11 (8.8%)	12 (9.7%)	23 (9.2%)
TEAE Leading to Discontinuation of ADI-PEG 20/Placebo	25 (20.0%)	17 (13.7%)	42 (16.9%)
TEAE Requiring Dose Interruption of ADI-PEG 20/Placebo	59 (47.2%)	54 (43.5%)	113 (45.4%)
Number of subjects who received any dose of Pemetrexed	122	124	246
TEAE Related to Pemetrexed ^b	114 (93.4%)	110 (88.7%)	224 (91.1%)
TESAE Related to Pemetrexed ^b	23 (18.9%)	30 (24.2%)	53 (21.5%)
TEAE Leading to Discontinuation of Pemetrexed	17 (13.9%)	17 (13.7%)	34 (13.8%)
TEAE Requiring Dose Interruption of Pemetrexed	50 (41.0%)	38 (30.6%)	88 (35.8%)
TEAE Requiring Dose Reduction of Pemetrexed	28 (23.0%)	23 (18.5%)	51 (20.7%)
Number of subjects who received any dose of Cisplatin	92	100	192
TEAE Related to Cisplatin ^b	87 (94.6%)	94 (94.0%)	181 (94.3%)
TESAE Related to Cisplatin ^b	22 (23.9%)	27 (27.0%)	49 (25.5%)
TEAE Leading to Discontinuation of Cisplatin	18 (19.6%)	27 (27.0%)	45 (23.4%)
TEAE Requiring Dose Interruption of Cisplatin	34 (37.0%)	29 (29.0%)	63 (32.8%)
TEAE Requiring Dose Reduction of Cisplatin	29 (31.5%)	25 (25.0%)	54 (28.1%)
Number of subjects who received any dose of Carboplatin	46	42	88
TEAE Related to Carboplatin ^b	42 (91.3%)	37 (88.1%)	79 (89.8%)
TESAE Related to Carboplatin ^b	6 (13.0%)	5 (11.9%)	11 (12.5%)
TEAE Leading to Discontinuation of Carboplatin	9 (19.6%)	0 (0.0%)	9 (10.2%)
TEAE Requiring Dose Interruption of Carboplatin	17 (37.0%)	14 (33.3%)	31 (35.2%)
TEAE Requiring Dose Reduction of Carboplatin	12 (26.1%)	10 (23.8%)	22 (25.0%)

TESAE: Treatment-emergent serious adverse events

Grade 5 TEAEs (by preferred term): For the ADIPemPlatinum group (n=7), these fatal TEAEs were sudden death (n=2), cardiac arrest (n=2), pneumonia (n=1), neutropenic sepsis (n=1), and myocardial infarction (n=1, > 30 days past the last dose of ADI-PEG 20). For the PlaceboPemPlatinum group (n=12), these fatal TEAEs were pneumonia

(n=4), cerebrovascular accident (n=2), sepsis (n=2), coronavirus infection (n=2), septic shock (n=2), non-cardiac chest pain (n=1), dyspnea (n=1), and acute respiratory failure (n=1).

eTable 9. Most Frequently Occurring (≥ 10% in Either Group) TEAEs

Preferred Term ^a	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)
Nausea	65 (52.0%)	67 (54.0%)
Fatigue	66 (52.8%)	62 (50.0%)
Constipation	54 (43.2%)	41 (33.1%)
Anaemia	34 (27.2%)	38 (30.6%)
Decreased appetite	26 (20.8%)	44 (35.5%)
Dyspnoea	35 (28.0%)	30 (24.2%)
Vomiting	23 (18.4%)	32 (25.8%)
Diarrhoea	20 (16.0%)	24 (19.4%)
Non-cardiac chest pain	26 (20.8%)	17 (13.7%)
Rash	24 (19.2%)	18 (14.5%)
Cough	19 (15.2%)	20 (16.1%)
Neutropenia	28 (22.4%)	10 (8.1%)
Neutrophil count decreased	24 (19.2%)	10 (8.1%)
Dysgeusia	14 (11.2%)	18 (14.5%)
Pyrexia	17 (13.6%)	13 (10.5%)
Oral candidiasis	11 (8.8%)	14 (11.3%)

Note: Subjects reporting more than one AE were counted only once. Summary included all events reported by ≥ 10% of subjects in the Safety Population.

^a AEs were coded to preferred term using MedDRA, version 19.1.

**eTable 10. TESAEs (Preferred Terms Reported for > 1 Subject in Either Group)
(Safety Population)**

System Organ Class / Preferred Term ^a	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)
Subjects Reporting at Least One TESA	62 (49.6%)	61 (49.2%)
Infections and infestations	19 (15.2%)	20 (16.1%)
Pneumonia	5 (4.0%)	6 (4.8%)
Sepsis	1 (0.8%)	6 (4.8%)
Lower respiratory tract infection	2 (1.6%)	3 (2.4%)
Neutropenic sepsis	3 (2.4%)	2 (1.6%)
Corona virus infection	1 (0.8%)	2 (1.6%)
Septic shock	1 (0.8%)	2 (1.6%)
Urinary tract infection	3 (2.4%)	0 (0.0%)
Lung infection	2 (1.6%)	0 (0.0%)
General disorders and administration site conditions	15 (12.0%)	11 (8.9%)
Pyrexia	5 (4.0%)	8 (6.5%)
Non-cardiac chest pain	6 (4.8%)	3 (2.4%)
Fatigue	1 (0.8%)	2 (1.6%)
Sudden death	2 (1.6%)	0 (0.0%)
Gastrointestinal disorders	9 (7.2%)	16 (12.9%)
Nausea	1 (0.8%)	7 (5.6%)
Vomiting	2 (1.6%)	5 (4.0%)
Constipation	2 (1.6%)	3 (2.4%)
Diarrhoea	2 (1.6%)	2 (1.6%)
Abdominal pain	1 (0.8%)	2 (1.6%)
Respiratory, thoracic and mediastinal disorders	10 (8.0%)	7 (5.6%)
Dyspnoea	6 (4.8%)	2 (1.6%)
Pulmonary embolism	2 (1.6%)	2 (1.6%)
Pleural effusion	2 (1.6%)	1 (0.8%)
Cardiac disorders	9 (7.2%)	2 (1.6%)
Atrial fibrillation	4 (3.2%)	0 (0.0%)
Cardiac arrest	2 (1.6%)	0 (0.0%)
Renal and urinary disorders	6 (4.8%)	4 (3.2%)
Acute kidney injury	6 (4.8%)	4 (3.2%)
Blood and lymphatic system disorders	3 (2.4%)	6 (4.8%)
Anaemia	0 (0.0%)	5 (4.0%)
Febrile neutropenia	2 (1.6%)	0 (0.0%)
Metabolism and nutrition disorders	4 (3.2%)	5 (4.0%)
Dehydration	0 (0.0%)	3 (2.4%)
Hyponatraemia	3 (2.4%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	2 (1.6%)	7 (5.6%)
Musculoskeletal chest pain	1 (0.8%)	3 (2.4%)
Nervous system disorders	3 (2.4%)	6 (4.8%)
Cerebrovascular accident	1 (0.8%)	3 (2.4%)
Lethargy	2 (1.6%)	0 (0.0%)
Injury, poisoning and procedural complications	5 (4.0%)	2 (1.6%)
Fall	2 (1.6%)	1 (0.8%)
Investigations	2 (1.6%)	4 (3.2%)
Alanine aminotransferase increased	0 (0.0%)	2 (1.6%)
Immune system disorders	4 (3.2%)	0 (0.0%)

System Organ Class / Preferred Term ^a	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)
Anaphylactic reaction	2 (1.6%)	0 (0.0%)
Psychiatric disorders	1 (0.8%)	2 (1.6%)
Confusional state	1 (0.8%)	2 (1.6%)

Note: At each level of summarization (any event, system organ class, and preferred term), subjects reporting more than one TESAE were counted only once.

^a AEs were coded to system organ class and preferred term using MedDRA, version 19.1.

eTable 11. TEAEs Leading to ADI-PEG 20/Placebo Discontinuation (Preferred Terms Reported for > 1 Subject in Either Group) (Safety Population)

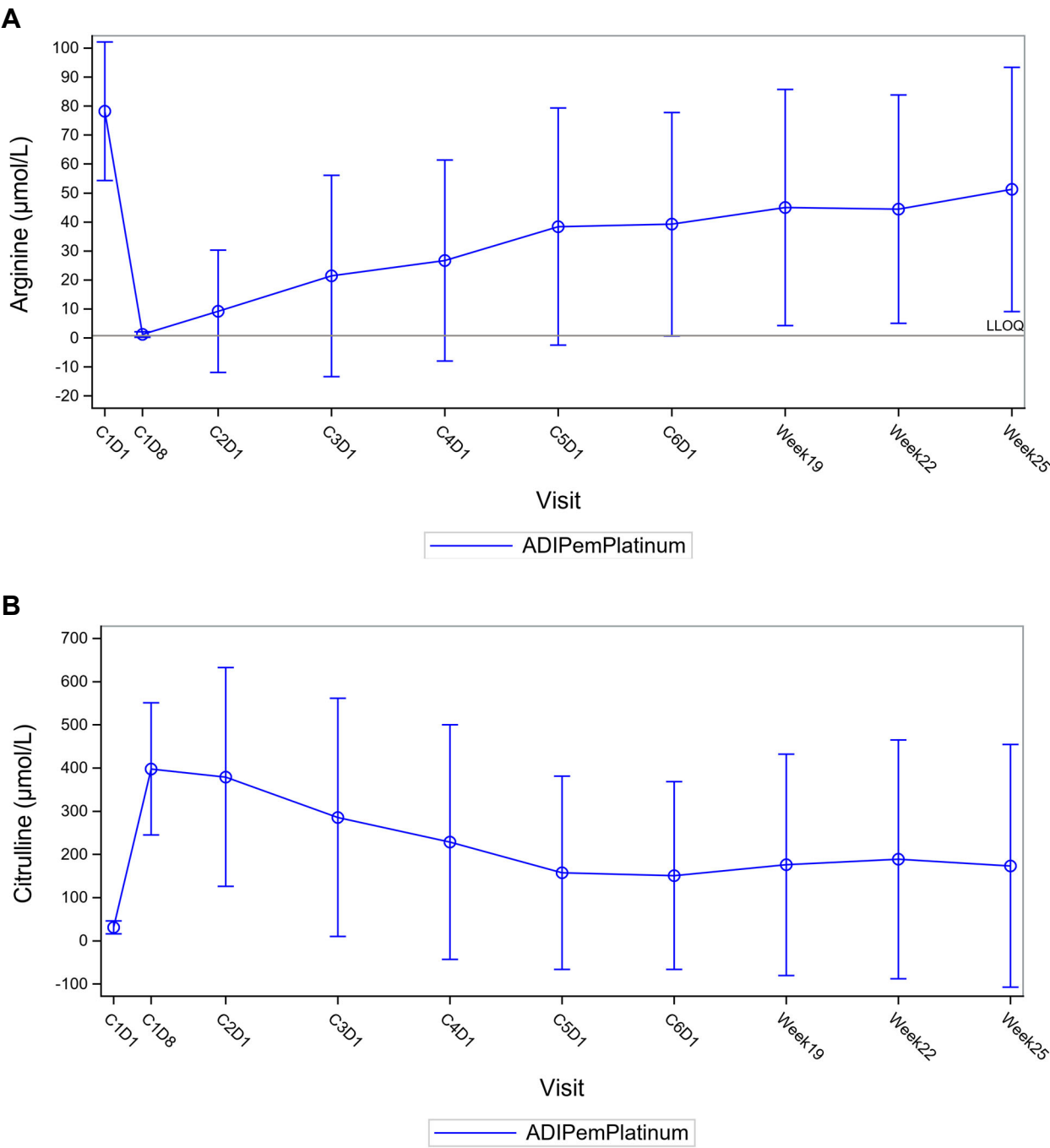
System Organ Class / Preferred Term ^a	ADIPemPlatinum (N = 125)	PlaceboPemPlatinum (N = 124)
Subject Reporting at Least One TEAE Leading to Discontinuation of ADI-PEG 20/Placebo	25 (20.0%)	17 (13.7%)
General disorders and administration site conditions	5 (4.0%)	2 (1.6%)
Fatigue	2 (1.6%)	1 (0.8%)
Pyrexia	2 (1.6%)	0 (0.0%)
Cardiac disorders	3 (2.4%)	1 (0.8%)
Cardiac arrest	2 (1.6%)	0 (0.0%)
Immune system disorders	4 (3.2%)	0 (0.0%)
Anaphylactic reaction ^b	3 (2.4%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	1 (0.8%)	3 (2.4%)
Dyspnoea	1 (0.8%)	2 (1.6%)

Note: At each level of summarization (any event, system organ class, and preferred term), subjects reporting more than one AE leading to discontinuation of ADI-PEG 20/placebo were counted only once.

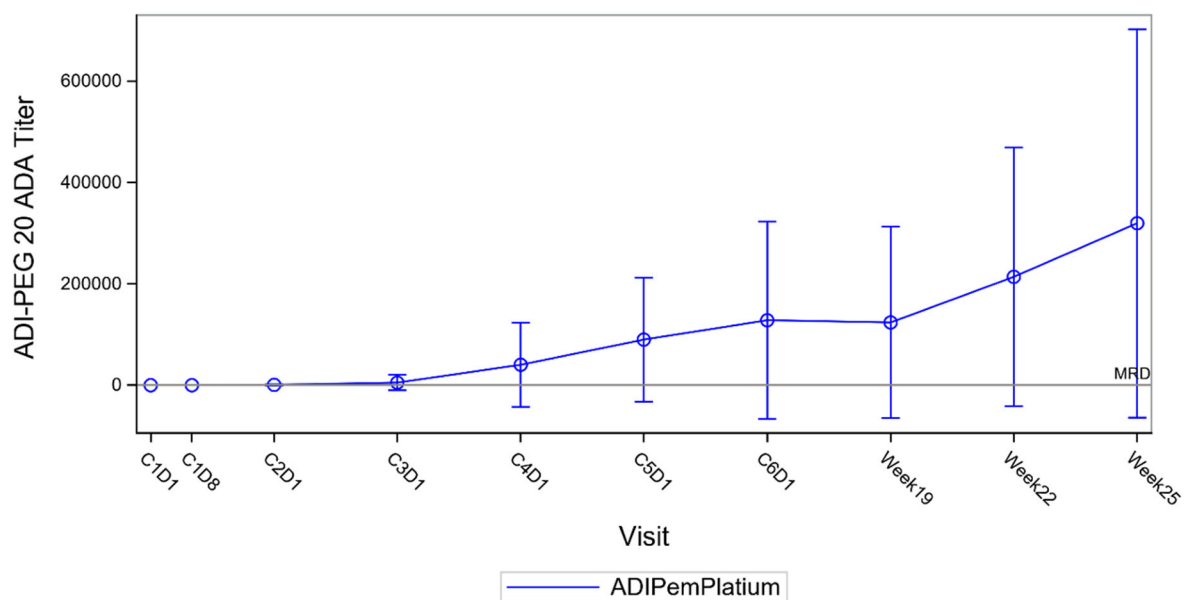
^a AEs were coded to system organ class and preferred term using MedDRA, version 19.1.

^b For one of the subjects (Subject 0209-0004) in the ADIPemPlatinum group who had a Grade 3 anaphylactic reaction TEAE the led to discontinuation of ADI-PEG 20, additional information was obtained that led Polaris to disagree with the diagnosis

eFigure 4. Pharmacodynamic and immunogenicity responses



C



eTable 12. Sensitivity analysis of ipilimumab and nivolumab-treated patients

Survival Estimates (Months)	ADIPemPlatinum (N=21)	PlaceboPemPlatinum (N=11)
Number (%) of Subjects with death	15 (71.4%)	7 (63.6%)
Number (%) of Subjects alive	6 (28.6%)	4 (36.4%)
Quartiles (95% CI) ^[1]		
25 th Percentile	13.88 (8.78, 17.96)	13.52 (13.09, 25.30)
Median ^[2]	19.34 (13.88, 24.51)	25.30 (13.09, 33.72)
75 th Percentile	25.82 (19.34, .)	33.72 (16.35, .)
Hazard Ratio (95% CI) ^[3]	1.146 (0.465, 2.825)	
P-value ^[4]	0.7676	

^[1] Kaplan-Meier product-limit estimates.
^[2] Median is defined to be the smallest observed survival time for which the value of the estimated survival function is less than or equal to 0.5.
^[3] Hazard ratio (ADIPemPlatinum/PlaceboPemPlatinum) and corresponding 95% CI are obtained from a Cox proportional hazards model. An HR less than one is favorable to ADIPemPlatinum.

eFigure 5. Overall survival plot of sensitivity analysis (ipilimumab and nivolumab)

