Supplemental Online Content

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

eAppendix 1. History of the statistical analysis plan finalization, IDMC meeting, and interim efficacy analysis

Date	Event
August 5, 2020	Last patient enrolled.
June 11, 2021	Protocol amendment approved: the primary PD-L1 positive population was amended from patients with CPS ≥10 to patients with CPS ≥5.
July 20, 2021	IDMC charter approved
July 30, 2021	The statistical analysis plan (SAP) approved.
August 3, 2021	Database lock for interim efficacy analysis (with data cut-off date June 20, 2021)
August 14, 2021	The independent data monitoring committee (IDMC) meeting for interim efficacy analysis. The IDMC advised the investigative team that the efficacy boundaries of OS for both the total and CPS ≥5 populations were crossed and suggested an additional 6-month follow-up of OS without unblinding to investigators.
August 15, 2021	One independent team of the sponsor was unblinded to perform interim efficacy analysis (with another independent team still blinded to continue to monitor the trial)
December 20, 2021	Fully unblinded
October 21, 2022	Database lock for final analysis

eAppendix 2. Definition of measurable tumor lesion at baseline

At the baseline level, tumor lesions/lymph nodes will be categorized into measurable and non-measurable ones according to the following definitions:

Measurable lesion:

Tumor lesion: At least one diameter line that can be accurately measured (recorded as the maximum diameter), and its minimum length is as follows:

• 10 mm as indicated by CT scan (CT slice thickness ≤ 5 mm)

• 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)

• 20 mm by chest X-ray

• Malignant lymph nodes: measurable with pathological enlargement and a short diameter of a single lymph node by CT scanning of ≥ 15 mm (it is recommended that the slice thickness measured by CT scanning should be no more than 5 mm). At baseline and follow-up, only the minimum diameter will be measured and followed up.

Non-measurable lesion:

All other lesions, including small lesions (with the maximum diameter of < 10 mm or the minimum diameter of a pathological lymph node of ≥ 10 mm to < 15 mm) and non-measurable lesions. Non-measurable lesions include: meningeal disease, ascites, pleural or pericardial effusion, inflammatory breast cancer, cancerous lymphangiitis of the skin/lung, abdominal masses that cannot be diagnosed and followed up by imaging, and cystic lesions.

Special considerations for lesion measurement:

Bone lesions, cystic lesions, and lesions previously treated with local therapy must be specified:

Bone lesions:

• Bone scan, PET scan, or plain films are not suitable for measuring bone lesions, but can be used to confirm the presence or disappearance of bone lesions;

• In case of osteolytic lesions or mixed osteolytic/osteogenic lesions that have a definite soft tissue composition with the soft tissue composition meeting the above measurability definition, these lesions can be considered as measurable lesions provided that they can be evaluated using tomographic imaging techniques such as CT and MRI;

• Osteogenic lesions are non-measurable lesions.

Cystic lesions:

• A lesion that meets the definition criteria for simple cysts in radiography should not be considered as a malignant lesion because it is a simple cyst by definition, which should be neither a measurable lesion nor a non-measurable lesion;

• If such lesion is cystic metastatic and meets the above measurability definition, it can be regarded as a measurable lesion. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

• Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional treatment, are usually not considered measurable unless there has been demonstrated progression in the lesion. The conditions under which these lesions are measurable should be detailed in the study protocol.

eTable 1. Additional baseline disease characteristics

	Sintilimab plus chemotherapy (n=327)	Placebo plus chemotherapy (n=323)
PD-L1 expression (CPS)		
<5	130 (39.8)	123 (38.1)
≥5	197 (60.2)	200 (61.9)
<1	52 (15.9)	52 (16.1)
≥1	275 (84.1)	271 (83.9)
PD-L1 expression (TPS)		
<10%	296 (90.5)	291 (90.1)
≥10%	31 (9.5)	32 (9.9)
<5%	277 (84.7)	276 (85.4)
≥5%	50 (15.3)	47 (14.6)
<1%	239 (73.1)	249 (77.1)
≥1%	88 (26.9)	74 (22.9)

Data are n (%).

Abbreviations: TPS, tumor proportion score; CPS, combined positive score, defined as the number of PD-L1 staining cells (tumor cells, lymphocytes and macrophages) divided by the total number of viable tumor cells present in the sample multiplied by 100. The maximum score is defined as 100 when the calculation exceeds 100. A combined positive score ≥5 was defined as PD-L1 positive.

eTable 2. Subsequent anticancer therapy at interim efficacy anaysis

	PD-L1 CPS ≥5 patients		All randomized patients	
	Sintilimab plus chemotherapy (n=197)	**Placebo plus chemotherapy (n=200)**	**Sintilimab plus chemotherapy (n=327)**	**Placebo plus chemotherapy (n=323)**
Any subsequent therapy	76 (38.6)	92 (46.0)	119 (36.4)	153 (47.4)
Radiotherapy	9 (4.6)	1 (0.5)	12 (3.7)	3 (0.9)
Surgery	8 (4.1)	9 (4.5)	8 (2.4)	14 (4.3)
Systemic anti-cancer therapy	67 (34.0)	90 (45.0)	109 (33.3)	150 (46.4)
Most frequent systemic anticancer therapies				
Fluoropyrimidine	31 (15.7)	41 (20.5)	52 (15.9)	67 (20.7)
Taxane	55 (27.9)	67 (33.5)	87 (26.6)	119 (36.8)
Platinum	14 (7.1)	18 (9.0)	22 (6.7)	30 (9.3)
Targeted Therapy	19 (9.6)	29 (14.5)	30 (9.2)	45 (13.9)
Immunotherapy	14 (7.1)	26 (13.0)	22 (6.7)	34 (10.5)
Others	26 (13.2)	27 (13.5)	38 (11.6)	43 (13.3)

Data are n (%).

Abbreviations: CPS, combined positive score, defined as the number of PD-L1 staining cells (tumor cells, lymphocytes and macrophages) divided by the total number of viable tumor cells present in the sample multiplied by 100. The maximum score is defined as 100 when the calculation exceeds 100. A combined positive score ≥5 was defined as PD-L1 positive.

eTable 3. Antitumour activity at interim efficacy analysis

	PD-L1 CPS ≥5 patients		All randomized patients	
	Sintilimab plus chemotherapy (n=162)	**Placebo plus chemotherapy (n=166)**	**Sintilimab plus chemotherapy (n=261)**	**Placebo plus chemotherapy (n=254)**
Confirmed objective response[a]	103 (63 .6; 56.2-71.0)	82 (49.4; 41.8-57.0)	152 (58.2; 52.3-64.2)	123 (48.4; 42.3-54.6)
Objective response rate difference	13.91 (3.56, 24.26)		9.60 (1.27, 17.93)	
Two-sided *P* value	.008		.02	
Best overall response				
Complete response	2 (1.2)	2 (1.2)	2 (0.8)	2 (0.8)
Partial response	101 (62.3)	80 (48.2)	150 (57.5)	121 (47.6)
Stable disease	43 (26.5)	58 (34.9)	77 (29.5)	91 (35.8)
Progressive disease	8 (4.9)	9 (5.4)	15 (5.7)	21 (8.3)
Not evaluable	0	0	1 (0.4)	0
Missing[b]	8 (4.9)	17 (10.2)	16 (6.1)	19 (7.5)
Disease control rate	146 (90.1; 85.5-94.7)	140 (84.3; 78.8-89.9)	229 (87.7; 83.8-91.7)	214 (84.3; 79.8-88.7)
Disease control rate difference	5.18 (-2.44, 12.81)		3.73 (-2.52, 9.98)	
Two-sided *P* value	.18		.24	
Duration of response, months	9.8 (7.1-21.1)	7.1 (5.4-9.0)	9.8 (8.3-17.4)	7.0 (5.5-8.3)
Stratified hazard ratio (95% CI)	0.62 (0.42-0.91)		0.57 (0.42-0.78)	
Two-sided *P* value	.01		< .001	

Data are n (%; 95% CI), % (95% CI), n (%), or median (95% CI) unless otherwise stated. Percentages might not sum to 100 because of rounding.

Abbreviations: CPS, combined positive score, defined as the number of PD-L1 staining cells (tumor cells, lymphocytes and macrophages) divided by the total number of viable tumor cells present in the sample multiplied by 100. The maximum score is defined as 100 when the calculation exceeds 100. A combined positive score ≥5 was defined as PD-L1 positive.

[a] Defined as an investigator-assessed response (complete or partial) confirmed by two consecutive tumor assessments among all randomized patients who had at least one measurable lesion at baseline per RECIST version 1.1.

[b] Included patients who had no post-treatment tumor assessment.

eTable 4. Sensitivity analysis on overall survival at interim efficacy analysis

	PD-L1 CPS ≥5 patients		All randomized patients	
	Sintilimab plus chemotherapy	Placebo plus chemotherapy	Sintilimab plus chemotherapy	Placebo plus chemotherapy
Sensitivity analysis on overall survival in the PPS set				
Overall survival	18.7 (14.8, NC)	12.9 (11.1, 15.4)	15.4 (13.0, 18.4)	12.3 (11.3, 13.8)
Stratified hazard ratio; 2-sided P	0.658 (0.502, 0.861); 0.0021		0.761 (0.622, 0.931); 0.0078	
Unstratified hazard ratio; 2-sided P	0.641 (0.490, 0.839); 0.0011		0.734 (0.601, 0.898); 0.0025	
Sensitivity analysis on overall survival in the ITT set				
Unstratified hazard ratio; 2-sided P	0.644 (0.493, 0.842); 0.0012		0.739 (0.605, 0.903); 0.0029	

Data are n (%; 95% CI), % (95% CI), n (%), or median (95% CI).

Abbreviations: CPS, combined positive score, defined as the number of PD-L1 staining cells (tumor cells, lymphocytes and macrophages) divided by the total number of viable tumor cells present in the sample multiplied by 100. The maximum score is defined as 100 when the calculation exceeds 100. A combined positive score ≥5 was defined as PD-L1 positive. PPS, per-protocol set (defined as subjects who had no major protocol deviations that affected the efficacy evaluation and had completed the minimum exposure to study treatment); NC, not calculated; ITT, intention to treat.

eTable 5. Sensitivity analysis on progression-free survival at interim efficacy analysis

	PD-L1 CPS ≥5 patients		All randomized patients	
	Sintilimab plus chemotherapy	Placebo plus chemotherapy	Sintilimab plus chemotherapy	Placebo plus chemotherapy
Sensitivity analysis on progression-free survival in the PPS set				
Progression-free survival	7.8 (6.9, 9.7)	5.8 (5.5, 6.9)	7.1 (6.9, 8.5)	5.7 (5.5, 6.9)
Stratified hazard ratio; 2-sided P	0.626 (0.487, 0.803); 0.0002		0.630 (0.519, 0.764); <0.0001	
Unstratified hazard ratio; 2-sided P	0.639 (0.499, 0.819); 0.0003		0.637 (0.526, 0.771); <0.0001	
Sensitivity analysis on progression-free survival in the ITT set				
Unstratified hazard ratio; 2-sided P	0.642 (0.502, 0.821); 0.0004		0.642 (0.531, 0.776); <0.001	
Sensitivity analysis on progression-free survival with censoring rule 1* in the ITT set				
Progression-free survival	7.2 (6.9, 9.7)	5.8 (5.5, 7.0)	7.1 (6.9, 8.3)	5.7 (5.5, 6.9)
Stratified hazard ratio; 2-sided P	0.633 (0.498, 0.805); 0.0002		0.660 (0.549, 0.793); <0.0001	
Unstratified hazard ratio; 2-sided P	0.643 (0.507, 0.816); 0.0002		0.663 (0.553, 0.794); <0.0001	
Sensitivity analysis on progression-free survival with censoring rule 2# in the ITT set using				
Progression-free survival	6.9 (5.8, 7.8)	5.6 (5.3, 6.9)	6.9 (5.8, 7.2)	5.6 (5.4, 5.9)
Stratified hazard ratio; 2-sided P	0.733 (0.587, 0.915); 0.0057		0.733 (0.617, 0.871); 0.0004	
Unstratified hazard ratio; 2-sided P	0.738 (0.593, 0.919); 0.0064		0.732 (0.617, 0.867); 0.0003	

Data are n (%; 95% CI), % (95% CI), n (%), or median (95% CI).

*PFS was deemed as an event and progression at recorded date of death or progression if death or disease progression occurred after ≥2 consecutive missing complete imaging assessments.

#For subjects who continued to receive randomized study treatment or complete 24 months of study treatment, or the sponsor terminates the study, the PFS data was censored at the last complete imaging assessment. Otherwise they was progressed at the investigational drug discontinuation. For subjects who accepted gastric cancer resection after dose and before treatment discontinuation, the PFS data was censored at gastric cancer resection, otherwise they were progressed at new anti-tumor treatment other than gastric cancer resection. PFS was deemed as an event and progression at recorded date of death or progression if death or PD occurred after ≥2 consecutive missing complete imaging assessments.

Abbreviations: CPS, combined positive score, defined as the number of PD-L1 staining cells (tumor cells, lymphocytes

and macrophages) divided by the total number of viable tumor cells present in the sample multiplied by 100. The maximum score is defined as 100 when the calculation exceeds 100. A combined positive score ≥5 was defined as PD-L1 positive. PPS, per-protocol set (defined as subjects who had no major protocol deviations that affected the efficacy evaluation and had completed the minimum exposure to study treatment); NC, not calculated; ITT, intention to treat; PFS, progression-free survival.

eTable 6. Treatment-related adverse events leading to treatment discontinuation at interim efficacy analysis

	Sintilimab plus chemotherapy (n=328)		Placebo plus chemotherapy (n=320)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any treatment-related adverse events leading to treatment discontinuation	32 (9.8)	20 (6.1)	18 (5.6)	12 (3.8)
Platelet count decreased	5 (1.5)	3 (0.9)	5 (1.6)	3 (0.9)
Hypersensitivity	4 (1.2)	2 (0.6)	0	0
Immune-mediated enterocolitis	3 (0.9)	1 (0.3)	0	0
Acute kidney injury	2 (0.6)	1 (0.3)	0	0
Cardiac failure	2 (0.6)	1 (0.3)	0	0
Cystitis	2 (0.6)	1 (0.3)	0	0
Hepatic function abnormal	2 (0.6)	1 (0.3)	0	0
Hypophysitis	2 (0.6)	1 (0.3)	0	0
Myelosuppression	2 (0.6)	1 (0.3)	0	0
Pneumonitis	2 (0.6)	2 (0.6)	0	0
Anaemia	1 (0.3)	1 (0.3)	2 (0.6)	2 (0.6)
Neutrophil count decreased	1 (0.3)	1 (0.3)	3 (0.9)	1 (0.3)
Palmar-plantar erythrodysaesthesia syndrome	1 (0.3)	0	2 (0.6)	2 (0.6)

Data are n (%).

eTable 7. Treatment-related serious adverse events at interim efficacy analysis

	Sintilimab plus chemotherapy (n=328)		Placebo plus chemotherapy (n=320)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any treatment-related serious adverse events	86 (26.2)	65 (19.8)	70 (21.9)	55 (17.2)
Platelet count decreased	27 (8.2)	26 (7.9)	33 (10.3)	25 (7.8)
Vomiting	10 (3.0)	5 (1.5)	5 (1.6)	4 (1.3)
Hepatic function abnormal	6 (1.8)	5 (1.5)	2 (0.6)	2 (0.6)
Immune-mediated enterocolitis	6 (1.8)	5 (1.5)	0	0
Pneumonia	5 (1.5)	3 (0.9)	1 (0.3)	1 (0.3)
Diarrhea	4 (1.2)	3 (0.9)	2 (0.6)	2 (0.6)
Immune-mediated lung disease	3 (0.9)	2 (0.6)	5 (1.6)	3 (0.9)
Anemia	2 (0.6)	2 (0.6)	6 (1.9)	6 (1.9)

Data are n (%).

eTable 8. Treatment-related adverse events leading to death at interim efficacy analysis

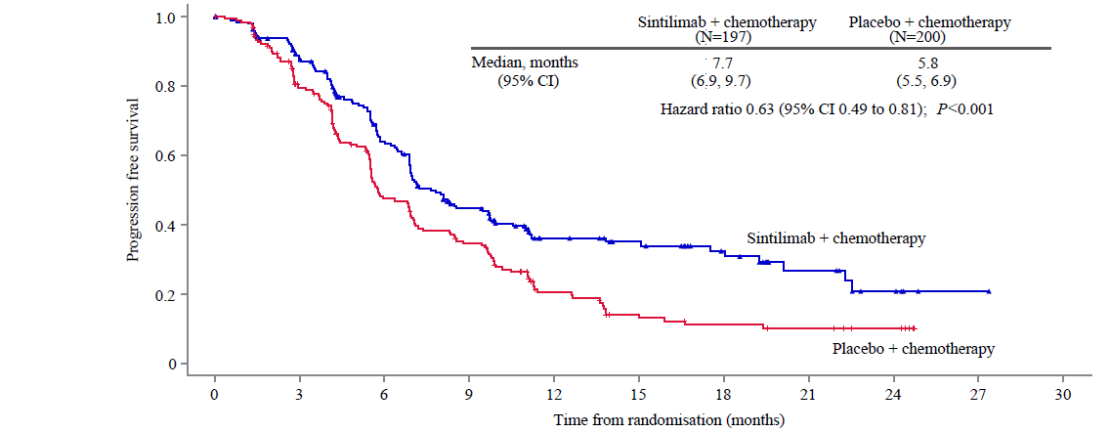
	Sintilimab plus chemotherapy (n=328)	Placebo plus chemotherapy (n=320)
Any treatment-related adverse event leading to death	6 (1.8)	2 (0.6)
Immune-mediated lung disease	1 (0.3)	0
Pneumonitis	1 (0.3)	0
Neutrophil count decreased	1 (0.3)	0
White blood cell count decreased	1 (0.3)	0
Platelet count decreased	1 (0.3)	2 (0.6)
Cystitis	1 (0.3)	0
Immune-mediated hepatitis	1 (0.3)	0
Myelosuppression	1 (0.3)	0

Data are n (%).Treatment-related adverse event was related with any treatment drug.

eFigure 1. Kaplan-Meier plot of progression-free survival at interim efficacy analysis

Abbreviations: PD-L1, programmed cell death ligand 1; CPS, combined positive score, was defined as the number of PD-L1 staining cells (tumor cells, lymphocytes and macrophages) divided by the total number of viable tumor cells present in the sample multiplied by 100. The maximum score is defined as 100 when the calculation exceeds 100. A combined positive score ≥5 was defined as PD-L1 positive.

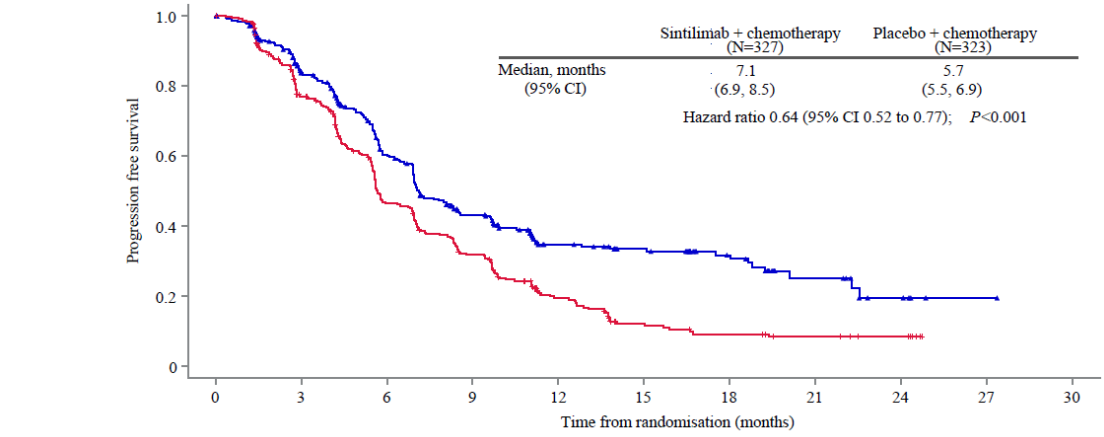
A. Progression-free survival for PD-L1 CPS ≥5 patients at the interim efficacy analysis.



Number at risk (censored)

Sintilimab+chemotherapy	197(0)	157(17)	105(29)	66(37)	37(55)	30(61)	21(68)	11(75)	5(79)	1(83)	0(84)
Placebo +chemotherapy	200(0)	140(22)	79(29)	56(31)	26(40)	15(43)	11(44)	9(45)	6(48)	0(54)	

B. Progression-free survival for all randomized patients at the interim efficacy analysis.



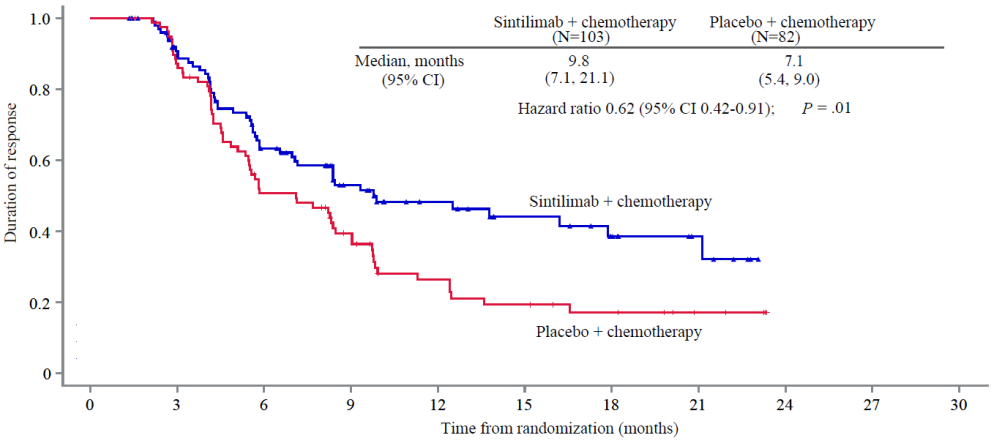
Number at risk (censored)

Sintilimab+chemotherapy	327(0)	246(31)	163(49)	105(62)	58(91)	46(101)	29(116)	12(128)	5(133)	1(137)	0(138)
Placebo +chemotherapy	323(0)	224(29)	129(39)	86(42)	42(55)	21(61)	14(63)	10(66)	7(69)	0(76)	

eFigure 2. Kaplan-Meier curve of duration of confirmed response at the interim efficacy analysis

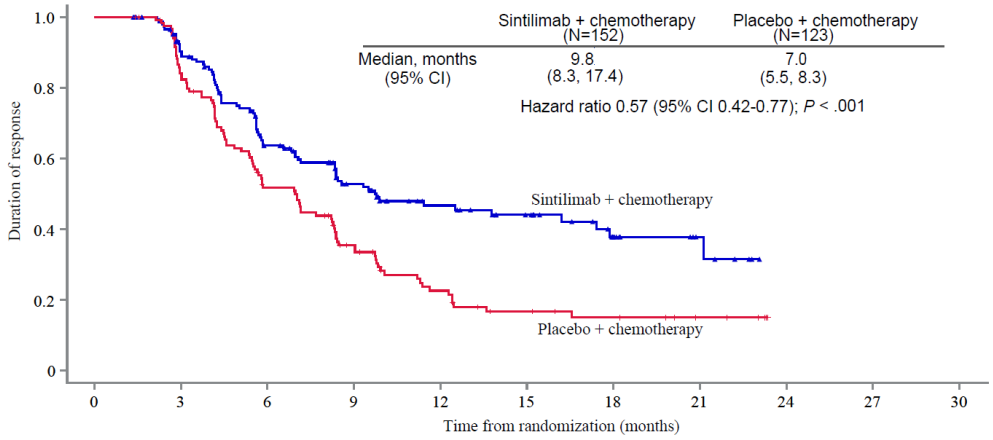
Abbreviation: CPS, combined positive score; mITT, modified intention to treat (defined as all randomized subjects who had measurable lesions at baseline. Analysis was conducted according to treatment group assigned at randomization).

A. Kaplan-Meier curve of duration of confirmed response in PD-L1 CPS ≥5 patients in the mITT population.



Number at risk (censored)									
Sintilimab + chemotherapy	103(0)	84(10)	55(14)	36(25)	24(34)	17(39)	11(43)	6(48)	0(53)
Placebo + chemotherapy	82(0)	68(4)	38(6)	26(10)	15(13)	11(13)	8(15)	4(19)	0(23)

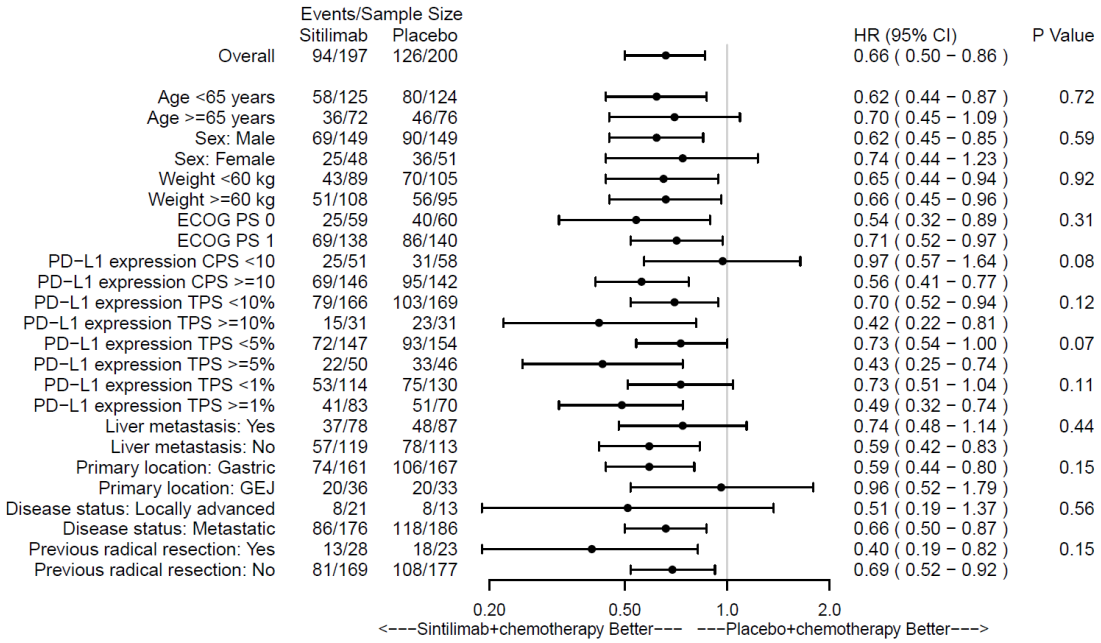
B. Kaplan-Meier curve of duration of confirmed response in mITT population.



Number at risk (censored)									
Sintilimab + chemotherapy	152(0)	126(12)	83(19)	58(31)	37(46)	28(53)	14(64)	6(72)	0(77)
Placebo + chemotherapy	123(0)	100(4)	59(7)	36(12)	20(16)	12(19)	9(21)	5(25)	0(30)

eFigure 3. Subgroup plot for subgroup analyses of overall survival in patients with CPS ≥5 at the interim efficay analysis.

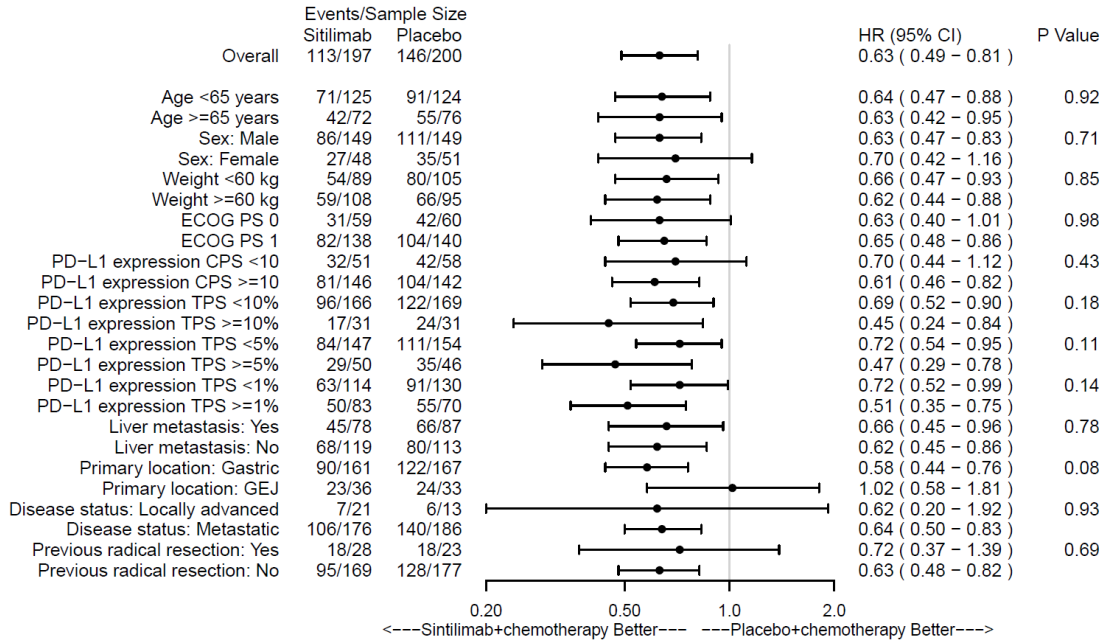
Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status; CPS, combined positive score; TPS, tumor proportion score; GEJ, gastro-esophageal junction.



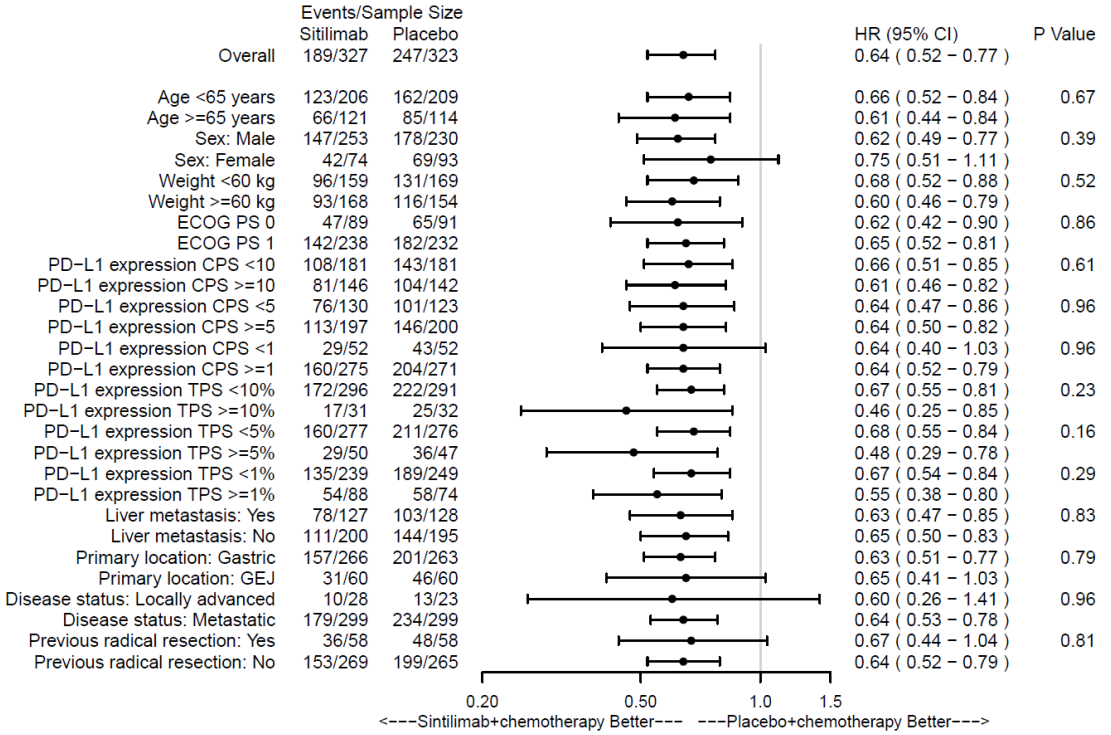
eFigure 4. Subgroup plot for subgroup analyses of progression free survival at the interim efficay analysis.

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status; CPS, combined positive score; TPS, tumor proportion score; GEJ, gastro-esophageal junction.

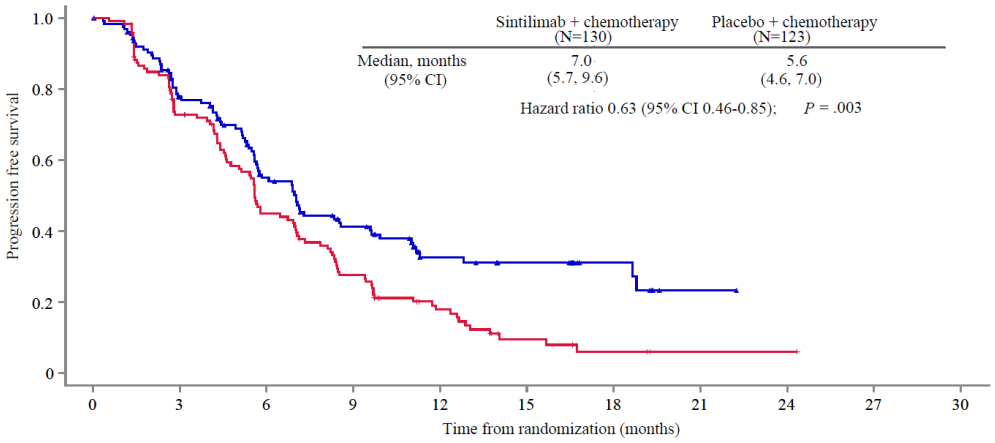
A. Subgroup plot for subgroup analyses of progression free survival in patients with CPS ≥5 at the interim efficay analysis.



B. Subgroup plot for subgroup analyses of progression free survival in all patients at the interim efficay analysis.



eFigure 5. Post hoc Kaplan-Meier plot of progression-free survival per investigator's assessment in patients with PD-L1 combined positive score (CPS) <5 at the interim efficacy analysis



Number at risk (censored)										
Sintilimab + chemotherapy	130(0)	89(14)	58(20)	39(25)	21(36)	16(40)	8(48)	1(53)	0(54)	
Placebo + chemotherapy	123(0)	84(7)	50(10)	30(11)	16(15)	6(18)	3(19)	1(21)	1(21)	0(22)