ONLINE ONLY: APPENDIX/SUPPLEMENTARY MATERIAL

Detailed statistical methods

Demographics and baseline characteristics are summarized descriptively. Safety was assessed in all patients who received at least one dose of spartalizumab and had at least one post-baseline safety assessment. The incidence of treatment-emergent AEs is summarized by preferred term, grade, and relation to study treatment.

All efficacy endpoints were assessed in the full analysis set, which includes all patients who received at least one dose of spartalizumab. The ORR and disease control rate per RECIST v1.1 and irRC are summarized with accompanying 95% exact binomial confidence intervals (CI). The ORR per RECIST v1.1 is also provided by baseline PD-L1 category, CD8 category, and BRAF V600 mutation status; associations were assessed using exact Fisher's tests. Spearman correlation coefficient with 95% CI was estimated for IFNγ signature level with best percentage change in the sum of diameters of target lesions (RECIST v1.1). For OS and PFS, survival functions were estimated using the Kaplan-Meier product limit method and displayed graphically by baseline PD-L1 category; median estimates with two-sided 95% CI are presented.

Table A1. Adverse Events (Any Grade, Occurring in ⩾5% of Patients) Regardless of Study Treatment Relationship

Preferred Term – no. (%)	Spartalizumab 400 mg Q4W (N = 42)	
	All	Grade 3/4
Total	41 (97.6)	29 (69.0)
Anemia	11 (26.2)	6 (14.3)
Dyspnea	11 (26.2)	4 (9.5)
Asthenia	9 (21.4)	3 (7.1)
Pyrexia	9 (21.4)	0
Diarrhea	7 (16.7)	0
Edema peripheral	7 (16.7)	0
Cough	6 (14.3)	0
Fatigue	6 (14.3)	2 (4.8)
Constipation	5 (11.9)	0
Decreased appetite	5 (11.9)	1 (2.4)
Hypokalemia	5 (11.9)	4 (9.5)
Pruritus	5 (11.9)	0
Arthralgia	4 (9.5)	0
Back pain	4 (9.5)	0
Dysphagia	4 (9.5)	0
Hemoptysis	4 (9.5)	0
Hypercalcemia	4 (9.5)	2 (4.8)
Hypocalcemia	4 (9.5)	0
Neck pain	4 (9.5)	1 (2.4)
Oropharyngeal pain	4 (9.5)	0
Pneumonia	4 (9.5)	3 (7.1)
ALT increased	3 (7.1)	1 (2.4)
Atrial fibrillation	3 (7.1)	1 (2.4)

Dehydration	3 (7.1)	2 (4.8)
Dizziness	3 (7.1)	0
Dry mouth	3 (7.1)	0
Hypomagnesemia	3 (7.1)	0
Hyponatremia	3 (7.1)	1 (2.4)
Musculoskeletal pain	3 (7.1)	0
Myalgia	3 (7.1)	0
Pleural effusion	3 (7.1)	2 (4.8)
Productive cough	3 (7.1)	0
Rash	3 (7.1)	1 (2.4)
Tumor pain	3 (7.1)	0
Vomiting	3 (7.1)	0

Abbreviations: ALT, alanine aminotransferase; Q4W, once every 4 weeks.

Table A2. Adverse Events of Special Interest (Any Grade) Regardless of Study Treatment Relationship

Preferred Term – no. (%)	Spartalizumab 400 mg Q4W (N = 42)	
	All	Grade 3/4
Total	21 (50.0)	5 (11.9)
Diarrhea	7 (16.7)	0
Pruritus	5 (11.9)	0
ALT increased	3 (7.1)	1 (2.4)
Rash	3 (7.1)	1 (2.4)
AST increased	2 (4.8)	1 (2.4)
Hyperglycemia	2 (4.8)	1 (2.4)
Hypothyroidism	2 (4.8)	0
Acute kidney injury	1 (2.4)	1 (2.4)
Blood ALP increased	1 (2.4)	0
Blood bilirubin increased	1 (2.4)	1 (2.4)
Blood TSH increased	1 (2.4)	0
Dry skin	1 (2.4)	0
GGT increased	1 (2.4)	0
Hyperlipasemia	1 (2.4)	1 (2.4)
Intestinal obstruction	1 (2.4)	0
Lipase increased	1 (2.4)	1 (2.4)
Peripheral sensory neuropathy	1 (2.4)	0
Generalized pruritus	1 (2.4)	0
Rash macular	1 (2.4)	0
Rash maculo-papular	1 (2.4)	0
Vitiligo	1 (2.4)	0

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; Q4W, once every 4 weeks; TSH, thyroid stimulating hormone.

Table A3. Best Overall Response (Investigator Assessed)

	RECIST v1.1	irRC
Best overall response – no. (%)		
Complete response	3 (7.1)	3 (7.1)
Partial response	5 (11.9)	7 (16.7)
Stable disease	5 (11.9)	5 (11.9)
Progressive disease	21 (50.0)	19 (45.2)
Unknown	8 (19.0)	8 (19.0)
Overall response rate – % (95% CI)	19.0 (8.6–34.1)	23.8 (12.1–39.5)
Disease control rate – % (95% CI)	31.0 (17.6–47.1)	35.7 (21.6–52.0)

Abbreviations: CI, confidence interval; irRC, immune-related response criteria; Q4W, once every 4 weeks; RECIST, Response Evaluation Criteria In Solid Tumors.

Table A4. Biomarker Analyses and Sequence Data Per Patient

Pt	PD-L1+ Cells by IHC,* %	CD8+ Staining by IHC,† %	*BRAF* Mutation Status		TMB, Mutations/ Mb	Mutations by NGS,‡ Gene (Alteration, Where Available)	Efficacy		
			NGS‡	PCR§			BOR, RECIST v1.1	BOR, irRC	Best Percentage Change
1	80	3.2	Non-mutant	Non-mutant	13.87	CIC (S146fs*1); DNMT3A (R736H); EP300 (splice site 1282+1G>A); JAK1 (K860fs*16); KDM5A (R266Q); MSH6 (F1088fs*2); NF1 (D618fs*12); PTEN (R233*); RB1 (R552*); SMARCA4 (R801H); TP53 (R156P)	CR	irCR	–100
2	0	–	Unknown	Unknown	–	–	PD	irPD	63.64
3	20	1.32	Non-mutant	Non-mutant	3.78	CDKN2A (x0); CDKN2B (x0); DAXX (I253fs*15); HGF (x7); MTAP (x0); NPM1; PDGFRA (x15); QKI	PD	irPD	38.81
4	0	0.23	Non-mutant	Non-mutant	1.26	CDKN2A (x0); CDKN2B (x0); DAXX (S53fs*91); EGFR (x17); KDR (x18); KIT (x33); MTAP (x0); PDGFRA (x29); TP53 (E285K)	SD	irSD	17.91
5	90	9.45	Non-mutant	Non-mutant	2.52	MCL1 (x8); MYC (x10); RB1 (F482fs*9); TERT (promoter -146C>T); TP53 (M237I)	CR	irCR	–100
6	20	0.04	Non-mutant	Non-mutant	1.26	MLL2 (E225fs*36); PTEN (M134fs*47); RB1 (x0); TP53 (P85fs*38)	PD	irPD	65.85
7	70	1.45	Non-mutant	Non-mutant	0	BRCA2 (W2626C); NRAS (Q61R); TP53 (G244D)	SD	irSD	–19.44
8	60	1.38	Non-mutant	Non-mutant	6.3	NF1 (V1157fs*1); RB1 (R556*); TERT (promoter -124C>T); TP53 (x0)	PD	irPD	–
9	3	10.25	Unknown	Non-mutant	–	–	PR	irPR	–69.09
10	0	0.04	Non-mutant	Non-mutant	0	CASP8 (x0); PIK3R1 (splice site 1986-3_1995delTAG GGTGGACGGC); PTEN (H61R); TP53 (M44fs*74)	PD	irPD	–
11	0	0.11	K601E	Non-mutant	2.52	ARID1A (Q566*, Q576*); BRAF (K601E); PIK3CA (N345K); TERT (promoter -124C>T); TP53 (L111P); TSC2 (S1431L)	PD	irPD	–
12	–	–	Unknown	Unknown	–	–	PD	irPD	39.17
13	0	0.4	V600E	V600E	2.52	BRAF (V600E); CDKN2A (x0); CDKN2B (x0); MTAP (x0); PIK3CA (E545K);	PD	irPD	34.92

						RAD51C (L219S); TERT (promoter -124C>T); TET2 (Q744*)			
14	100	0.14	Non-mutant	Non-mutant	0	NUTM1; TP53 (M237K)	PD	irPD	39.55
15	5	0.6	Non-mutant	Non-mutant	2.52	CCNE1 (x8); CDKN2A (x0); CDKN2B (x0); CRKL (x6); DAXX (E214*); JUN (x6); MTAP (x0); PARK2 (N52fs*29); PRKCI (x6); PTEN (Y178*); RAD21 (x6); TERC (x6); TP53 (R273C); TSC2	PD	irPD	77.78
16	0	0	Non-mutant	Non-mutant	6.3	NFKBIA (x6); NKX2-1 (x6); RB1 (splice site 607+1G>T); TP53 (splice site 994-1G>C)	PD	irPD	31.88
17	60	0.27	Non-mutant	Non-mutant	3.78	DAXX (V582fs*10); IGF1R; RB1 (splice site 2489+1G>C); TP53 (E285*, E287K)	SD	irSD	–14.08
18	100	0.76	Non-mutant	Non-mutant	2.52	CD274 (x10); JAK2 (x10); KEAP1 (F111fs*45); KRAS (G12C); MCL1 (x8); NFKBIA (x12); NKX2-1 (x12); PDCD1LG2 (x9); TET2 (S1686fs*8); TP53 (G244D)	PR	irPR	–67.19
19	0	1.88	Non-mutant	Non-mutant	6.3	ERBB4 (A773V); NF1 (Q2288*); PTEN (G165E); TERT (promoter -124C>T); TP53 (C176Y)	SD	irSD	0
20	5	7.91	V600E	V600E	0	BRAF (V600E); HRAS (G13R); NF1 (E517fs*9); NF2 (D277fs*19); PIK3CA (E545K); RICTOR (x6); TERT (promoter -124C>T)	SD	irPR	–40.82
21	100	0.12	V600E	V600E	3.78	BRAF (V600E); CDKN2A (x0); HRAS (A59T); MTAP (x0)	PR	irPR	–80.95
22	10	0.97	Unknown	Non-mutant	–	–	PD	irPD	65.52
23	85	0.88	Non-mutant	Non-mutant	3.78	CDKN2A (x0); CDKN2B (x0); MTAP (x0); NRAS (Q61R); TERT (promoter -146C>T); TP53 (Y205H)	PD	irPD	32.91
24	90	–	Unknown	Unknown	–	–	PR	irPR	–72.73
25	5	1.73	Unknown	V600E	–	–	PD	irPD	36.36
26	0.5	–	Unknown	V600E	–	–	UNK	irUNK	–
27	0.5	2.39	Unknown	Non-mutant	–	–	UNK	irUNK	–
28	0.5	0.64	V600E	V600E	6.3	BRAF (V600E); NFKBIA (x6); PAX5 (x0); TERT (promoter -124C>T); TP53 (D281G)	UNK	irUNK	–

29	50	0.06	V600E	V600E	–	BRAF (V600E); RAD21 (x9); TERT (promoter -146C>T); TP53 (Q136del)	PD	irPD	14.29
30	0	0.46	Non-mutant	Non-mutant	3.78	MCL1 (x7); PDGFRB (N666K); PTEN (M270fs*28); TP53 (R280*)	UNK	irUNK	–
31	–	–	Unknown	Unknown	–	–	PD	irPD	37.3
32	90	1.25	Unknown	V600E	–	–	PD	irPD	73.91
33	80	2.69	Non-mutant	Non-mutant	–	–	PR	irPR	–73.24
34	80	3.83	V600E	V600E	0	ARID1A (Q1894*); BRAF (V600E); MUTYH (G382D); TERT (promoter -124C>T); TP53 (Q192*)	UNK	irUNK	–
35	0	0	Unknown	Non-mutant	–	–	PD	irPR	–30.34
36	100	2.55	V600E	V600E	3.78	AKT1 (E17K); ATM (splice site 3285-5_3287del TTAAGATT); BRAF (V600E); CDKN2A (x0); CDKN2B (x0); FGFR1 (x8); TERT (promoter -124C>T); WHSC1L1 (x8)	PD	irSD	22.67
37	100	0.02	Non-mutant	Non-mutant	2.52	BCL2L1 (x8); CHEK2 (I157T); KEAP1 (R507*); NF1 (R487fs*11); PTEN; TERT (promoter -124C>T); TP53 (E224fs*1)	PD	irPD	32.79
38	25	0.74	V600E	V600E	–	BRAF (V600E); CBL (L380P); CHEK2 (I157T); PIK3CA (Q546E); TERT (promoter -124C>T); TP53 (R248G, S215N)	PD	irPD	–44.12
39	5	0.39	Non-mutant	Non-mutant	6.3	BRD4 (K1181fs*57); CDKN2A (x0); CDKN2B (x0); NF2 (splice site 600-1G>A); PIK3CA (E545G); TERT (promoter -124C>T)	CR	irCR	–100
40	80	2.76	Unknown	Non-mutant	–	–	UNK	irUNK	–
41	2	1.31	Non-mutant	Non-mutant	5.04	DAXX (Q307*); MEN1 (D82fs*32); NF2 (R198*); PTEN (Y68H); RB1 (R579*); RICTOR (N1065S); TP53 (T256P)	UNK	irUNK	–
42	10	0.16	V600E	V600E	3.78	BRAF (V600E); CDKN2A (S56fs*64); PDGFRB (D850Y); TERT (promoter -124C>T)	UNK	irUNK	–

Abbreviations: BOR, best overall response; CR, complete response; IHC, immunohistochemistry; ir, immune related; irRC, immune-related response criteria;

NGS, next-generation sequencing; PCR, polymerase chain reaction; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; Pt, patient; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TMB, tumor mutational burden.

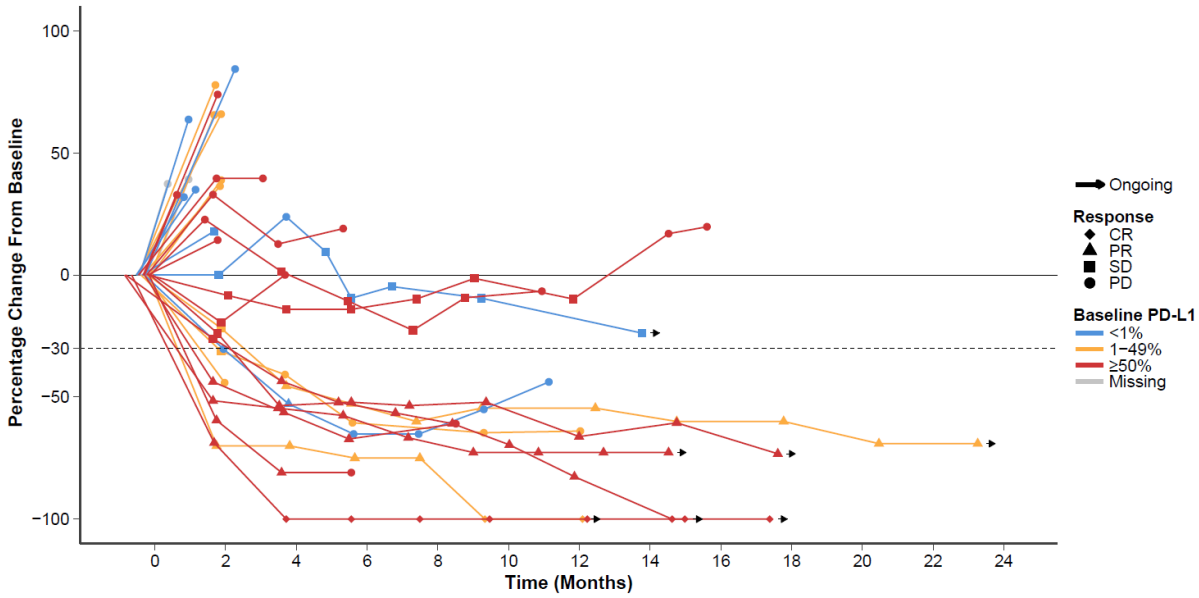
*Baseline PD-L1 cells assessed by IHC, using Dako PD-L1 IHC 22C3 pharmaDx; †Baseline CD8+ staining assessed by IHC, expressed as CD8+ staining as a percentage of the total sample area; ‡NGS performed by Foundation Medicine with median depth of coverage of 864 reads for 331 short variants; §*BRAF* mutational status determined by PCR using Cobas 4800 *BRAF* V600 mutation test.

Table A5. Overall Response Rate According to RECIST v1.1, by Biomarker Status at Baseline

Biomarker status	ORR – % (n/N) [95% CI]
PD-L1–positive cells by IHC	
<1%	0 (0/12) [0, 26.5]
1–49%	18.2 (2/11) [2.3, 51.8]
≥50%	35.3 (6/17) [14.2, 61.7]
Missing	0 (0/2) [0, 84.2]
CD8-positive staining by IHC	
<1%	14.3 (3/21) [3.0, 36.3]
≥1%	25.0 (4/16) [7.3, 52.4]
Missing	20.0 (1/5) [0.5, 71.6]
BRAF V600 mutation by Cobas 4800	
Mutant	8.3 (1/12) [0.2, 38.5]
Non-mutant	23.1 (6/26) [9.0, 43.6]
Missing	25.0 (1/4) [0.6, 80.6]

Abbreviations: IHC, immunohistochemistry; ORR, overall response rate; PD-L1, programmed death-ligand 1; RECIST, Response Evaluation Criteria In Solid Tumors.

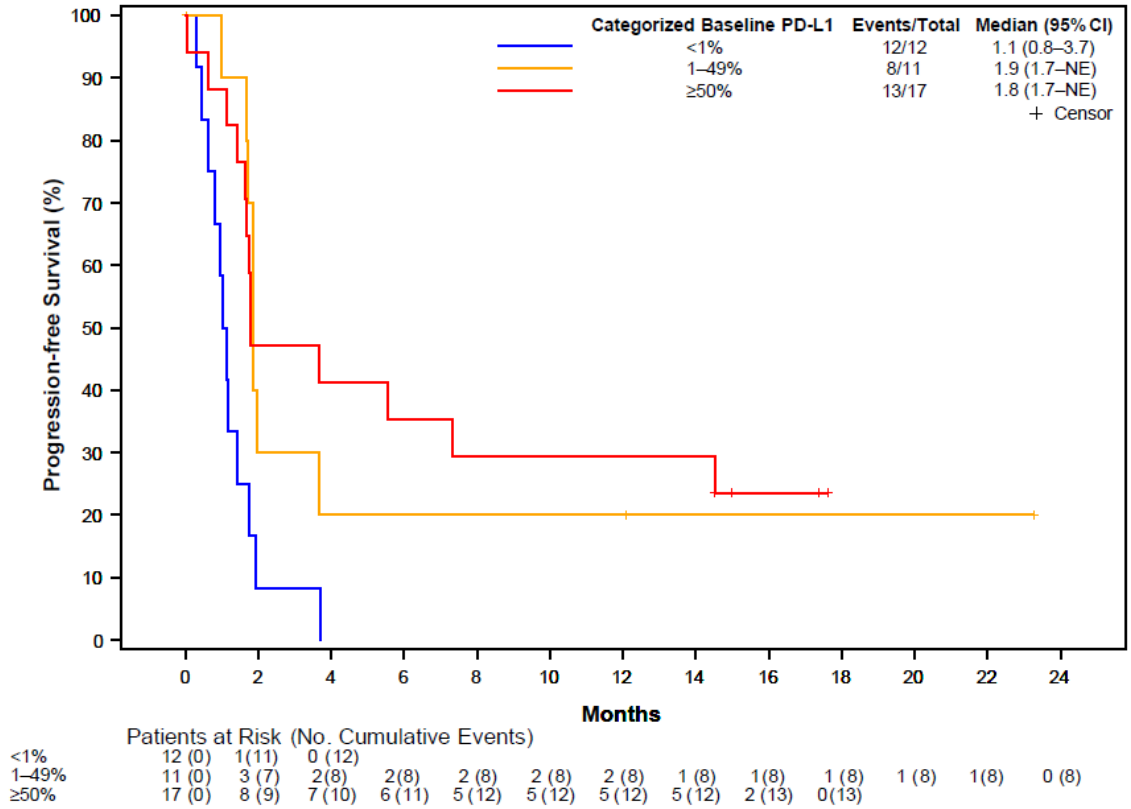
Fig A1. Percentage Change From Baseline in Sum of Diameters of Target Lesions Over Time, by PD-L1 Expression at Baseline



Percentage change from baseline in sum of diameters of target lesions over time. Best overall response by RECIST v1.1 is indicated.

CR, complete response; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.

Fig A2. Progression-Free Survival, by PD-L1 Expression at Baseline



CI, confidence interval; NE, not estimable; PD-L1, programmed death-ligand 1.