Evaluation of immunomodulatory effects of ifinatamab deruxtecan (I-DXd) in the IDeate-PanTumor01 Phase 1/2 study in patients with advanced solid tumors

#629

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OBJECTIVE

- To evaluate whether I-DXd has immunomodulatory activity (ie, whether it interrupts B7-H3 signaling) by performing pharmacodynamic biomarker analysis as part of the IDeate-PanTumor01 study

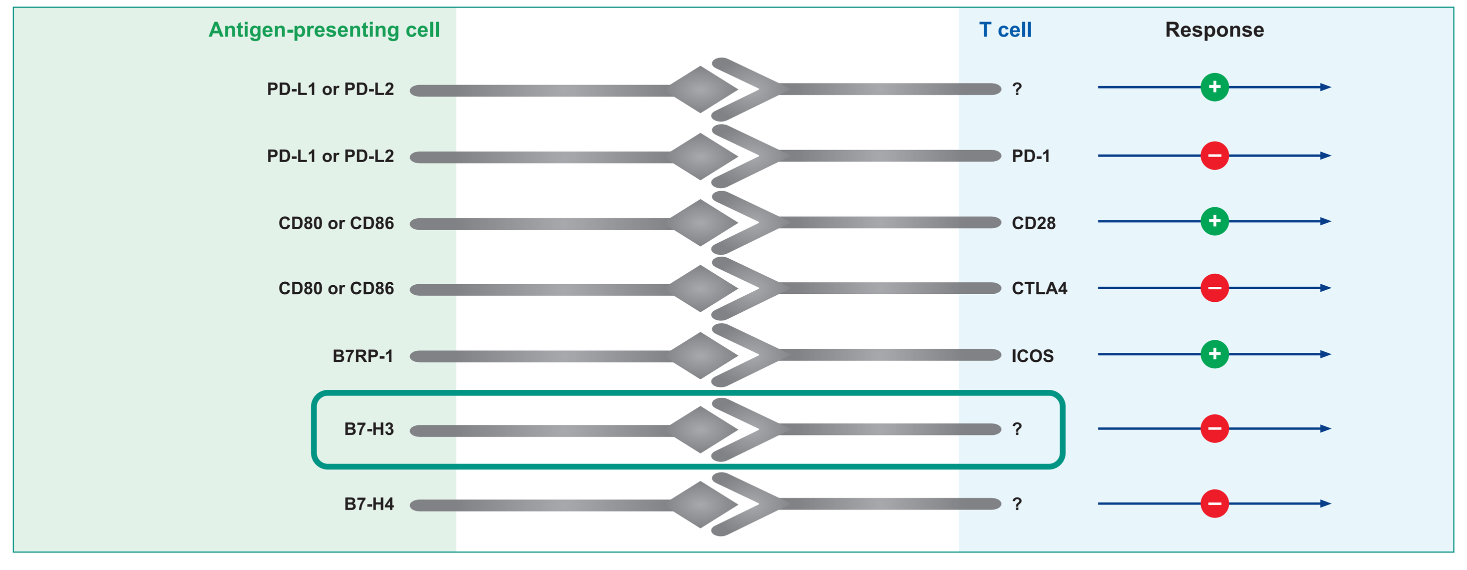
CONCLUSION

- This pharmacodynamic biomarker analysis suggests that I-DXd does not exert direct immunomodulatory effects in patients treated with I-DXd

INTRODUCTION

- B7-H3 is a transmembrane protein in the B7 family, which includes the immune checkpoint molecule PD-L1 (**Figure 1**)[1]
  - The physiological function of B7-H3 remains to be fully elucidated but may involve immune modulation[1,2]
- B7-H3 is either absent or expressed at low levels in normal tissues but is highly expressed in a range of solid tumors[2–4]; high B7-H3 expression is associated with poor prognosis[5–10]
- I-DXd is a B7-H3–directed ADC designed with an optimized drug-to-antibody ratio, a plasma-stable linker-payload and a tumor-selective cleavable linker, a topoisomerase I inhibitor payload with high potency and a short systemic half-life, and a bystander antitumor effect[11–12]
- Preclinical studies have demonstrated that I-DXd provides efficient, selective, target-dependent payload delivery to B7-H3–expressing tumor cells[11–12]
- I-DXd has shown promising efficacy and a manageable safety profile in patients with heavily pretreated advanced solid tumors in the Phase 1/2 IDeate-PanTumor01 study (NCT04145622)[13] and in patients with pretreated ES-SCLC in the Phase 2 IDeate-Lung01 study (NCT05280470)[14]
- In addition to its target-mediated payload delivery and cytotoxic effects in tumor cells, I-DXd may possess immunomodulatory activity by modulating B7-H3 signaling and this is investigated in the current analysis

Figure 1. B7-H3 role remains to be fully elucidated[1]



METHODS

- Tumor samples from patients in IDeate-PanTumor01 who received clinically effective doses of I-DXd (4.8–16.0 mg/kg intravenously every 3 weeks) were used for the pharmacodynamic biomarker analysis
  - Tumor types included bladder cancer, breast cancer, endometrial cancer, ESCC, HNSCC, mCRPC, melanoma, sarcoma, SCLC, and sqNSCLC
- The change from baseline to Cycle 2 Day 8–15 of I-DXd treatment was assessed in samples from patients with available paired samples, which included deriving median values for the overall analysis set and absolute values for individual patients
  - Data are presented for all tumor types combined and select tumors with reasonable sample sizes
- The following pharmacodynamic biomarker analyses were performed:
  - Percentage of PD-L1–expressing immune cells, per IHC
  - Cell density (number of cells/mm²) of immune cell subsets, per multiplex IHC analysis
  - Expression of two inflammation-associated gene signatures through RNA sequencing:
    - 4-gene signature (*PD-L1 [CD274], LAG3, CD8A, and STAT1*)[15]
    - Ribas signature (*HLA-DRA, CXCL9, GZMA, PRF1, CCR5, IFNG, CXCL10, IDO1, STAT1, and CXCL11*)[16,17]
  - The PD-L1 IHC assay was performed by Mosaic Laboratories, and the multiplex IHC and RNA sequencing analyses were conducted at the Daiichi Sankyo laboratories (Toyko, Japan)
- The 95% nominal confidence interval of the median was estimated using the bootstrapping method

RESULTS

- The most common tumor types enrolled in the IDeate-PanTumor01 study were mCRPC, ESCC, and SCLC[13]
- A total of 164 patients had received I-DXd at doses ≥4.8 mg/kg at the August 31, 2023 data cutoff, of whom 150 had received ≥2 cycles of treatment (mCRPC, n=71; ESCC, n=25; SCLC, n=18)
- Of these patients, 41, 55, and 57 had paired samples and were evaluable for immune cell PD-L1 expression, immune cell subset, and inflammation-associated gene signature expression analyses, respectively (**Table 1**)
  - Baseline characteristics were similar to the overall study cohort (N=164)

Table 1. Patient baseline characteristics[a]

	Overall IDeate-PanTumor01 study cohort (N=164)	PD-L1 immune cell analysis set (n=41)[b]	Immune cell subsets analysis set (n=55)[b]	Inflammation gene signature scores analysis set (n=57)[b]
Age, median (range), years	66 (39–84)	64 (42–84)	64 (39–80)	64 (39–80)
Sex, n (%)				
Male	139 (84.8)	37 (90.2)	49 (89.1)	51 (89.5)
Female	25 (15.2)	4 (9.8)	6 (10.9)	6 (10.5)
ECOG PS, n (%)				
0	59 (36.0)	20 (48.8)	26 (47.3)	28 (49.1)
1	105 (64.0)	21 (51.2)	29 (52.7)	29 (50.9)
Country of enrollment, n (%)				
United States	112 (68.3)	21 (51.2)	29 (52.7)	29 (50.9)
Japan	52 (31.7)	20 (48.8)	26 (47.3)	28 (49.1)
Number of prior systemic regimens, median (range)	5 (1–12)	5 (1–10)	5 (1–12)	5 (1–12)
Tumor type, n (%)				
mCRPC	73 (44.5)	16 (39.0)	24 (43.6)	23 (40.4)
ESCC	28 (17.1)	10 (24.4)	14 (25.5)	14 (24.6)
sqNSCLC	24 (14.6)	3 (7.3)	3 (5.5)	3 (5.3)
SCLC	21 (12.8)	6 (14.6)	6 (10.9)	5 (8.8)
HNSCC	7 (4.3)	3 (7.3)	5 (9.1)	6 (10.5)
Sarcoma	5 (3.0)	1 (2.4)	0	2 (3.5)
Endometrial cancer	3 (1.8)	2 (4.9)	3 (5.5)	3 (5.3)
Melanoma	1 (0.6)	0	0	1 (1.8)
Bladder cancer	1 (0.6)	0	0	0
Breast cancer	1 (0.6)	0	0	0

[a]As of August 31, 2023 data cutoff; patients who received I-DXd doses of 4.8–16.0 mg/kg intravenously every 3 weeks.
[b]Evaluable patients with paired samples (baseline and Cycle 2).

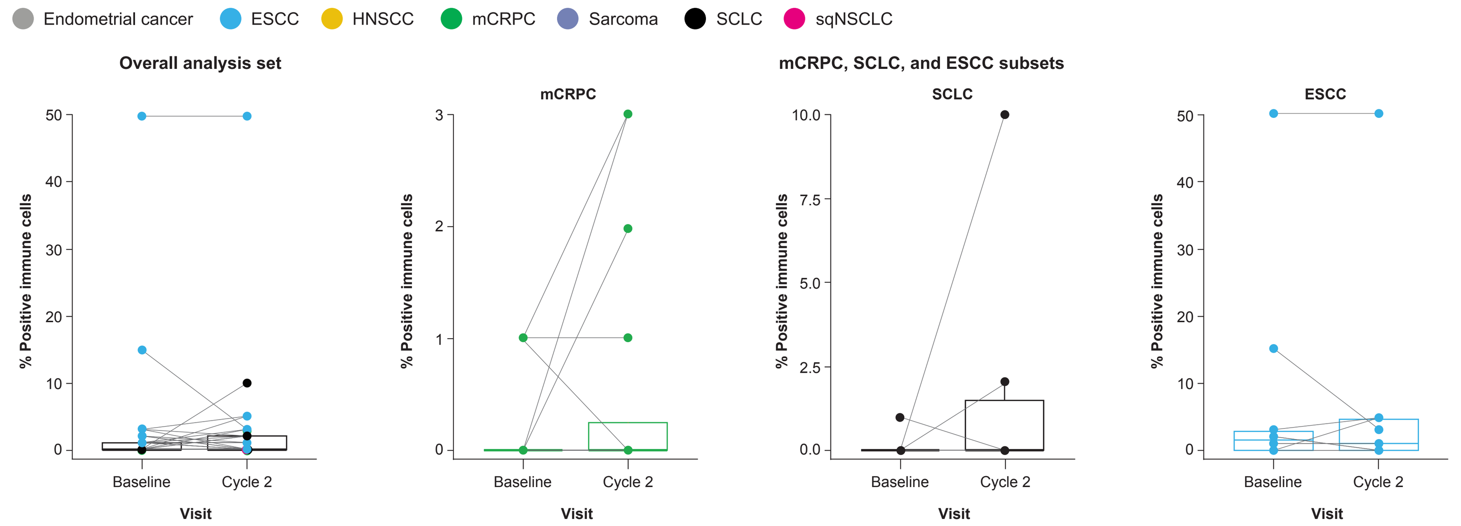
- For the percentage of PD-L1–expressing immune cells, there was no consistent change following I-DXd treatment (**Table 2** and **Figure 2**)
  - Among 41 patients with paired samples, the median percentage of PD-L1–expressing cells was 0% (range, 0–50%) at both baseline and Cycle 2; 17 (41.5%) and 16 (39.0%) patients, respectively, had PD-L1–positive samples (immune cell score ≥1%) at these timepoints
  - There was no consistent change in the percentage of PD-L1–expressing immune cells within the mCRPC, SCLC, and ESCC subsets
- In terms of immune cell subsets in tumor tissue, there was no consistent change from baseline to Cycle 2 of I-DXd treatment (**Table 2** and **Figure 3**)
- No change was observed in inflammation-associated gene signature expression levels following I-DXd treatment (**Table 2** and **Figures 4** and **5**), with median (range) signature levels at baseline and Cycle 2 of 0.019 (−0.153 to 0.372) and 0.011 (−0.111 to 0.424), respectively, for the 4-gene inflammation signature, and 0.014 (−0.237 to 0.32) and −0.025 (−0.221 to 0.356), respectively, for the Ribas inflammation signature
  - There was no consistent trend of change in inflammation-associated gene signature expression levels among the mCRPC, SCLC, and ESCC subsets (**Figures 4** and **5**)

Table 2. Summary of pharmacodynamic biomarker analysis results: Overall analysis sets (all tumor types combined)

Pharmacodynamic biomarker analysis	Baseline	Cycle 2
PD-L1+ immune cells, % positive cells, median (range) (n=41)	0 (0–50)	0 (0–50)
Patients with PD-L1–positive tumor samples,[a] n (%) (n=41)	17 (41.5)	16 (39.0)
Immune cell subsets, cells/mm², median (range) (n=55)		
Total T cells	87.0 (0–8610.7)	81.6 (1.6–4437.3)
Total CD4+ T cells	39.3 (0–5532.6)	20.7 (0–4430.7)
Total CD8+ T cells	31.5 (0–7240.8)	37.7 (0–3159.5)
Total PD-1+ immune cells	3.4 (0–1839.3)	2.4 (0–1870.9)
CD4+ PD-1+	0 (0–246.9)	0 (0–955.2)
CD8+ PD-1+	0 (0–1600.0)	0 (0–1442.4)
Total PD-L1+ T cells	0 (0–1369.9)	0 (0–388.9)
Total macrophages	487.2 (45.3–7324.4)	532.1 (53.7–5461.4)
PD-L1+ macrophages	20.1 (0–6626.4)	42.0 (0–5405.0)
Inflammation-associated gene signature expression level, ssGEAE score, median (range) (n=57)		
4-gene signature[15,b]	0.019 (−0.153 to 0.372)	0.011 (−0.111 to 0.424)
Ribas signature[16,17,c]	0.014 (−0.237 to 0.32)	−0.025 (−0.221 to 0.356)

[a]Immune cell score ≥1%. [b]*PD-L1 (CD274), LAG3, CD8A, STAT1.* [c]*HLA-DRA, CXCL9, GZMA, PRF1, CCR5, IFNG, CXCL10, IDO1, STAT1, CXCL11.*

Figure 2. PD-L1 expression on immune cells: Overall analysis set (all tumor types) and mCRPC, SCLC, and ESCC subsets



Overall analysis set

Visit	Baseline	Cycle 2
n	41	41
Min	0	0
Max	50	50
Median	0	0
95% CI	0, 0	0, 0
Mean	2.171	2.244

mCRPC

Visit	Baseline	Cycle 2
n	16	16
Min	0	0
Max	1	3
Median	0	0
95% CI	0, 0	0, 0
Mean	0.188	0.562

SCLC

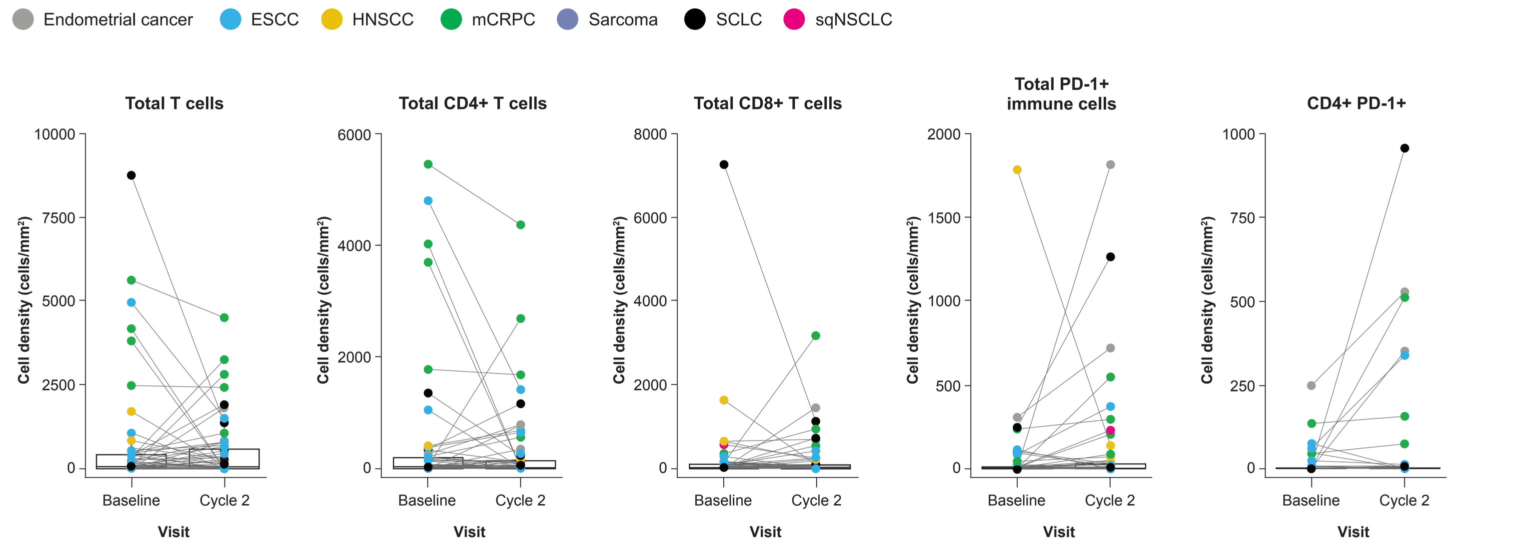
Visit	Baseline	Cycle 2
n	6	6
Min	0	0
Max	1	10
Median	0	0
95% CI	0, 0	0, 0
Mean	0.167	2

ESCC

Visit	Baseline	Cycle 2
n	10	10
Min	0	0
Max	50	50
Median	1.5	1
95% CI	0, 3	0, 2
Mean	7.4	6.5

Boxes on each graph represent the 25% to 75% IQR, and the horizontal line is the median value. Vertical whisker lines represent values 1.5× the upper and lower limits of the IQR.

Figure 3. Density of immune cell subsets in tumors: Overall analysis set (all tumor types)



Total T cells

Visit	Baseline	Cycle 2
n	55	55
Min	0	1.63
Max	8610.74	4437.28
Median	86.99	81.64
95% CI	0, 119.38	0, 118.12
Mean	721.16	515.64

Total CD4+ T cells

Visit	Baseline	Cycle 2
n	55	55
Min	0	0
Max	5532.61	4430.71
Median	39.31	20.75
95% CI	6.73, 57.12	0, 27.66
Mean	478.53	309.02

Total CD8+ T cells

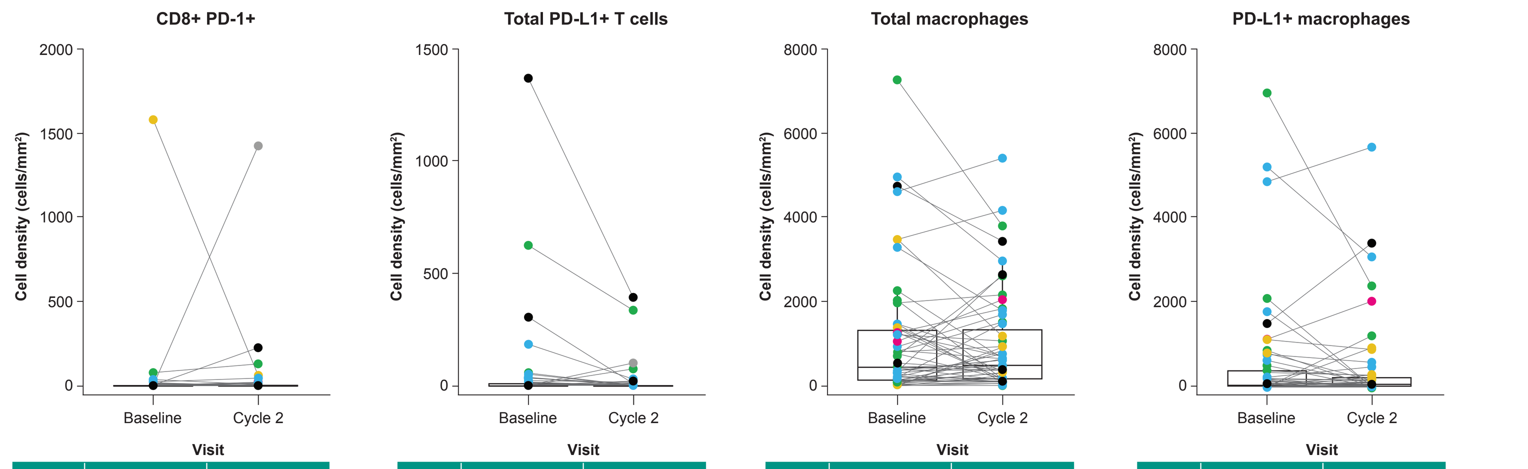
Visit	Baseline	Cycle 2
n	55	55
Min	0	0
Max	7240.85	3159.53
Median	31.49	37.74
95% CI	13.58, 49.95	8.90, 54.02
Mean	242.63	206.62

Total PD-1+ immune cells

Visit	Baseline	Cycle 2
n	55	55
Min	0	0
Max	1839.32	1870.85
Median	3.44	2.37
95% CI	0, 5.99	0, 4.20
Mean	59.94	112.98

CD4+ PD-1+

Visit	Baseline	Cycle 2
n	55	55
Min	0	0
Max	246.91	955.15
Median	0	0
95% CI	0, 0	0, 0
Mean	12.04	53.64



CD8+ PD-1+

Visit	Baseline	Cycle 2
n	55	55
Min	0	0
Max	1599.96	1442.41
Median	0	0
95% CI	0, 0	0, 0
Mean	33.09	36.43

Total PD-L1+ T cells

Visit	Baseline	Cycle 2
n	55	55
Min	0	0
Max	1369.89	388.85
Median	0	0
95% CI	0, 0	0, 0
Mean	50.60	18.25

Total macrophages

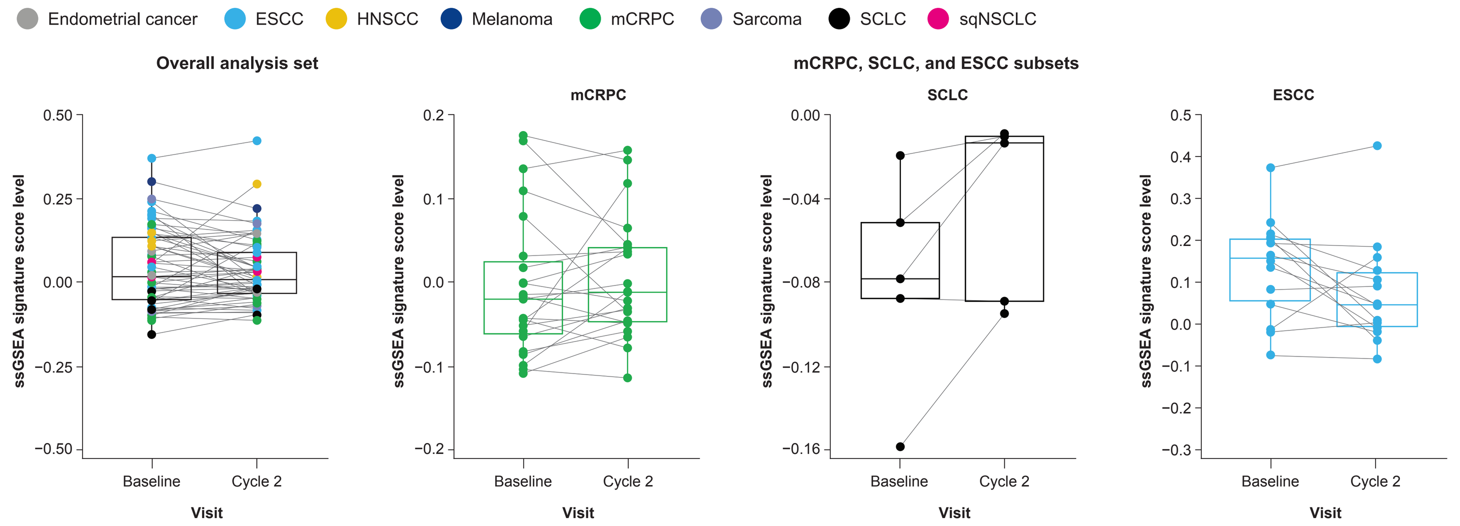
Visit	Baseline	Cycle 2
n	55	55
Min	45.32	53.67
Max	7324.38	5461.36
Median	487.23	532.06
95% CI	87.89, 708.00	308.09, 671.37
Mean	1147.58	1027.91

PD-L1+ macrophages

Visit	Baseline	Cycle 2
n	55	55
Min	0	0
Max	6626.37	5405.04
Median	20.15	41.95
95% CI	0, 27.55	0, 77.14
Mean	531.82	404.36

Boxes on each graph represent the 25% to 75% IQR, and the horizontal line is the median value. Vertical whisker lines represent values 1.5× the upper and lower limits of the IQR.

Figure 4. 4-gene inflammation signature: Overall analysis set (all tumor types) and mCRPC, SCLC, and ESCC subsets



Overall analysis set

Visit	Baseline	Cycle 2
n	57	57
Min	−0.153	−0.111
Max	0.372	0.424
Median	0.019	0.011
95% CI	−0.044, 0.053	−0.022, 0.035
Mean	0.049	0.037

mCRPC

Visit	Baseline	Cycle 2
n	23	23
Min	−0.105	−0.111
Max	0.175	0.158
Median	−0.018	−0.01
95% CI	−0.055, 0.013	−0.058, 0.024
Mean	−0.003	0.005

SCLC

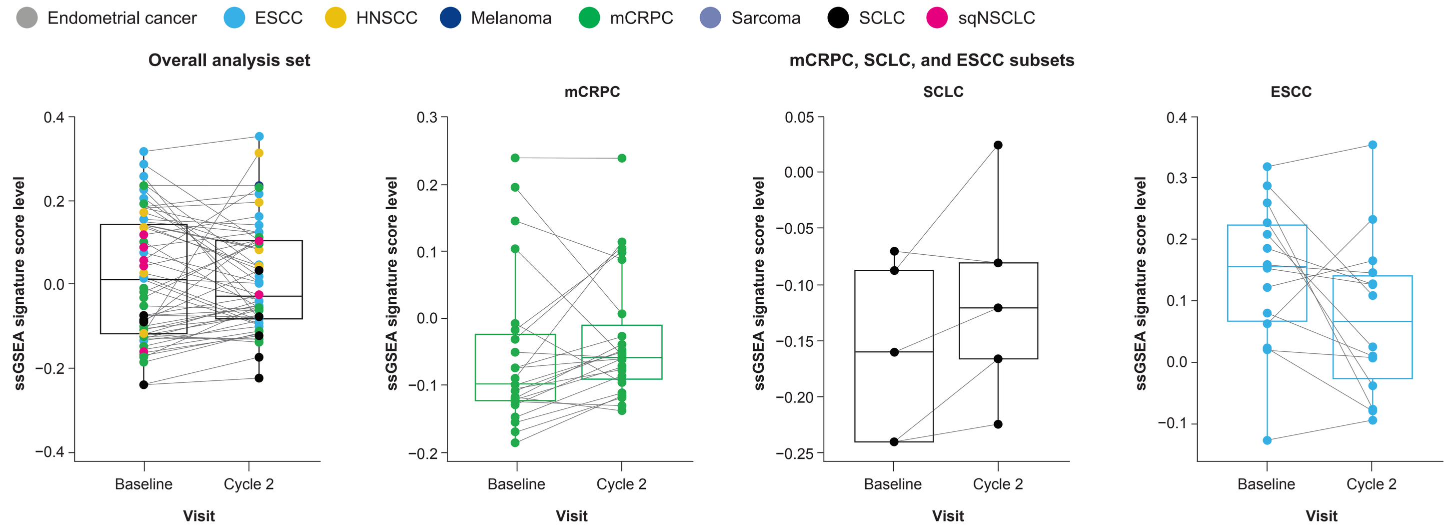
Visit	Baseline	Cycle 2
n	5	5
Min	−0.153	−0.094
Max	−0.023	−0.013
Median	−0.078	−0.018
95% CI	−0.133, −0.003	−0.022, 0.059
Mean	−0.079	−0.045

ESCC

Visit	Baseline	Cycle 2
n	14	14
Min	−0.073	−0.081
Max	0.372	0.424
Median	0.158	0.047
95% CI	0.111, 0.267	−0.023, 0.102
Mean	0.136	0.076

Boxes on each graph represent the 25% to 75% IQR, and the horizontal line is the median value. Vertical whisker lines represent values 1.5× the upper and lower limits of the IQR.

Figure 5. Ribas inflammation signature: Overall analysis set (all tumor types) and mCRPC, SCLC, and ESCC subsets



Overall analysis set

Visit	Baseline	Cycle 2
n	57	57
Min	−0.237	−0.221
Max	0.32	0.356
Median	0.014	−0.025
95% CI	−0.05, 0.1	−0.095, 0.002
Mean	0.018	0.013

mCRPC

Visit	Baseline	Cycle 2
n	23	23
Min	−0.183	−0.135
Max	0.239	0.239
Median	−0.097	−0.056
95% CI	−0.146, −0.078	−0.076, −0.039
Mean	−0.052	−0.028

SCLC

Visit	Baseline	Cycle 2
n	5	5
Min	−0.237	−0.221
Max	−0.071	0.036
Median	−0.16	−0.119
95% CI	−0.249, −0.083	−0.275, −0.018
Mean	−0.157	−0.11

ESCC

Visit	Baseline	Cycle 2
n	14	14
Min	−0.131	−0.098
Max	0.32	0.356
Median	0.155	0.065
95% CI	0.087, 0.25	−0.005, 0.167
Mean	0.141	0.071

Boxes on each graph represent the 25% to 75% IQR, and the horizontal line is the median value. Vertical whisker lines represent values 1.5× the upper and lower limits of the IQR.

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ABBREVIATIONS

ADC, antibody–drug conjugate; **B7-H3**, B7 homolog 3; **B7-H4**, B7 homolog 4; **B7RP-1**, B7-related protein-1; **CD**, cluster of differentiation; **CI**, confidence interval; **CTLA4**, cytotoxic T-lymphocyte-associated protein 4; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ES-SCLC**, extensive-stage small cell lung cancer; **ESCC**, esophageal squamous cell carcinoma; **HNSCC**, head and neck squamous cell carcinoma; **ICOS**, inducible costimulator; **I-DXd**, ifinatamab deruxtecan; **IHC**, immunohistochemistry; **IQR**, inter-quartile range; **Max**, maximum; **mCRPC**, metastatic castration-resistant prostate cancer; **Min**, minimum; **PD-1**, programmed death protein 1; **PD-L1**, programmed death ligand 1; **PD-L2**, programmed death ligand 2; **RNA**, ribonucleic acid; **SCLC**, small cell lung cancer; **sqNSCLC**, squamous non-small cell lung cancer; **ssGSEA**, single sample gene set enrichment analysis.

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