Supplementary Online Content

Hassan R, Thomas A, Nemunaitis JJ, et al. Efficacy and safety of avelumab treatment in patients with advanced unresectable mesothelioma: phase 1b results from the JAVELIN Solid Tumor trial. *JAMA Oncol.* Published online January 3, 2019. doi:10.1001/jamaoncol.2018.5428

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

eMethods. Additional Methods

Inclusion criteria

1. Signed written informed consent.
2. Male or female patients aged ≥18 years.
3. Histologically or cytologically confirmed mesothelioma (pleural or peritoneal) with unresectable disease. Patients must have received and progressed after either a platinum-pemetrexed containing regimen or a platinum-containing regimen followed by pemetrexed (or vice versa) after disease progression. Patients must have presented with at least 1 measurable lesion that had not been irradiated.
4. Availability of tumor archival material or fresh biopsies (excluding bone biopsies).
5. ECOG performance status of 0 to 1 at trial entry and an estimated life expectancy of at least 3 months.
6. Adequate hematological function defined by white blood cell count ≥3 × 10^9/L with absolute neutrophil count ≥1.5 × 10^9/L, lymphocyte count ≥0.5 × 10^9/L, platelet count ≥100 × 10^9/L, and hemoglobin ≥9 g/dL (may have been transfused).
7. Adequate hepatic function defined by a total bilirubin level ≤1.5 × upper limit of normal and an aspartate aminotransferase level ≤2.5 × upper limit of normal and an alanine aminotransferase level ≤2.5 × upper limit of normal for all patients. Adequate renal function defined by an estimated creatinine clearance >30 mL/min according to the Cockcroft-Gault formula or measured 24-hour creatinine clearance (or local institutional standard method). Highly effective contraception (that is, methods with a failure rate of <1% per year) for both male and female patients if the risk of conception existed, to be used 28 days prior to first study treatment administration, for the duration of study treatment, and at least for 60 days after stopping study treatment. Should a woman have become pregnant or suspected she was pregnant while she or her partner were participating in this study, the treating physician should have been informed immediately.)

Exclusion criteria

1. Concurrent treatment with a non-permitted drug, including any immunotherapy, immunosuppressive drugs, experimental pharmaceutical products, vaccine therapies (with the exception of inactivated vaccines) or growth factors.
2. Prior therapy with any antibody/drug targeting T cell co-regulatory proteins (immune checkpoints) such as anti-PD-1, anti-PD-L1, or CTLA-4 antibody.
3. Concurrent anticancer treatment within 28 days before the start of trial treatment (eg, cytoreductive therapy, radiotherapy [with the exception of palliative bone directed radiotherapy], immune therapy, or cytokine therapy except for erythropoietin); major surgery within 28 days before the start of trial treatment (excluding prior diagnostic biopsy); use of hormonal agents within 7 days before the start of trial treatment; or use of any investigational drug within 28 days before the start of trial treatment. Patients receiving immunosuppressive agents (such as steroids) for any reason should have been tapered off these drugs before initiation of the study treatment (with the exception of patients with adrenal insufficiency, who could continue corticosteroids at physiologic replacement dose, equivalent to ≤10 mg prednisone daily). Steroids with no or minimal systemic effect (topical, inhalation) were allowed.
4. Previous malignant disease other than the target malignancy to be investigated in this trial within the last 5 years with the exception of basal or squamous cell carcinoma of the skin or cervical carcinoma in situ.
5. Rapidly progressive disease (eg, tumor lysis syndrome).
6. Active or history of CNS metastases.
7. Receipt of any organ transplantation including allogeneic stem-cell transplantation.
8. Significant acute or chronic infections including, among others:
    - known history of testing positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
    - positive test for HBV surface antigen and/or confirmatory HCV RNA (if anti-HCV antibody tested positive).

9. Active or history of any autoimmune disease (patients with diabetes Type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment were eligible) or immunodeficiencies.
10. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥3 National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] v4.0), any history of anaphylaxis, or uncontrolled asthma (ie, 3 or more features of partly controlled asthma).
11. Persisting toxicity related to prior therapy > Grade 1 NCI-CTCAE v4.0 however, sensory neuropathy ≤ Grade 2 was acceptable.
12. Pregnancy or lactation period. Note: a negative pregnancy test was required for women of childbearing potential. Women who were postmenopausal (age-related amenorrhea ≥12 consecutive months or follicle-stimulating hormone (FSH) >40 milli international units per mL), or who had undergone hysterectomy or bilateral oophorectomy were exempt from pregnancy testing. If necessary to confirm postmenopausal status, a FSH level was included at screening.
13. Known alcohol or drug abuse.
14. Clinically significant (ie, active) cardiovascular disease: cerebral vascular accident/stroke (<6 months prior to enrollment), myocardial infarction (<6 months prior to enrollment), unstable angina, congestive heart failure (New York Heart Association Classification Class ≥II), or serious uncontrolled cardiac arrhythmia requiring medication.
15. All other significant diseases (eg, inflammatory bowel disease), which, in the opinion of the investigator, might have impaired the patient's tolerance of trial treatment.
16. Any psychiatric condition that would have prohibited the understanding or rendering of informed consent.
17. Legal incapacity or limited legal capacity.
18. Vaccination within 4 weeks of the first dose of avelumab and while on study was prohibited except for administration of inactivated vaccines (eg, inactivated influenza vaccines).

Reasons for withdrawal from study

Patients were withdrawn in the event of any of the following.
1. Occurrence of an exclusion criterion, which was clinically relevant and affected the patient's safety, if discontinuation was considered necessary by the investigator and/or sponsor.
2. Therapeutic failure that required urgent additional drug (if applicable).
3. Occurrence any grade ≥3 AE except for those specified below.
4. Occurrence of AEs resulting in the discontinuation of trial drug being desired or considered necessary by the investigator and/or the patient.
5. Occurrence of pregnancy.
6. Use of a nonpermitted concomitant drug, for which the predefined consequence was withdrawal from the investigational medicinal product.
7. Noncompliance.

Adverse events (AEs) requiring treatment discontinuation or modification

Any Grade 4 AE except for single laboratory values out of normal range that were unlikely to be related to trial treatment as assessed by the investigator, did not have any clinical correlate, and resolved within 7 days with adequate medical management.

Any Grade 3 AE except for any of the following.
- Transient (≤6 hours) Grade 3 flu-like symptoms or fever, which was controlled with medical management.
- Transient (≤24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolved to ≤ Grade 1.

- Single laboratory values out of normal range (excluding ≥ Grade 3 liver function test increase) that were unlikely to be related to trial treatment according to the investigator, did not have any clinical correlate, and resolved to ≤ Grade 1 within 7 days with adequate medical management.
- Tumor flare phenomenon, defined as local pain, irritation, or rash localized at sites of known or suspected tumor.
- Any Grade ≥3 drug-related amylase or lipase abnormality that was not associated with symptoms or clinical manifestations of pancreatitis did not require dose delay. The Study Medical Monitor should have been consulted for such Grade ≥3 amylase or lipase abnormalities.
- Increases in ECOG performance status ≥3, which did not resolve to ≤2 by cycle Day 14 of the following cycle (infusions should not have been given on the following cycle, if the ECOG performance status was ≥3 on the day of study drug administration).

Grade 2 AEs were managed as follows.

- Infusions should not have been given in case of ongoing Grade 2 AE on the day of trial treatment administration.
- Treatment was permitted to be resumed according to original schedule once the AE resolved to Grade ≤1. Up to 2 subsequent study drug doses were permitted to be omitted. If >2 doses were skipped, treatment could have been resumed after consultation with study Medical Monitor.
- Infusion-related reactions, hypersensitivity reactions (Grades 1 to 4), tumor lysis syndrome, and immune-related AEs were managed using specific guidance provided in the study protocol.

Sites of enrolment

PI name	Site name	Patients
Gulley, James	National Cancer Institute, Bethesda, MD, USA	9
Nemunaitis, John	Mary Crowley Cancer Research Centers, Dallas, TX, USA	6
Patel, Manish	Florida Cancer Specialists, Sarasota, FL, USA	4
Bennouna, Jaafar	ICO - Site René Gauducheau, Saint Herblain, France	3
Dowlati, Afshin	University Hospitals Case Medical Center, Cleveland, OH, USA	3
Taylor, Matthew	Oregon Health & Science University, Portland, OR, USA	3
Chen, Franklin	Novant Health Oncology Specialists, Winston-Salem, NC, USA	2
Delord, Jean-Pierre	Institut Claudius Regaud-Oncopole, Toulouse, France	2
Kochuparambil, Samith	Virginia Piper Cancer Institute, Minneapolis, MN, USA	2
Powderly, John	Carolina BioOncology Institute, Huntersville, NC, USA	2
Vaishampayan, Ulka	Karmanos Cancer Institute, Detroit, MI, USA	2
Verschraegen, Claire	University of Vermont Medical Center, Burlington, VT, USA	2
Agrawal, Manish	Maryland Oncology Hematology, Rockville, MD, USA	1
Assikis, Vasileios	Peachtree Hematology-Oncology Consultants, Atlanta, GA, USA	1
Bourgeois, Hugues	Clinique Victor Hugo - Centre Jean Bernard, Sarthe, France	1
Ellerton, John	Southern Nevada Cancer Research Foundation, Las Vegas, NV, USA	1
Freilich, Bradley	Kansas City Research Institute, Kansas City, MO, USA	1
Gordon, Michael	Pinnacle Oncology Hematology, Scottsdale, AZ, USA	1
Infante, Jeffrey	SCRI - Tennessee Oncology, Nashville, TN, USA	1
Isambert, Nicolas	Centre Georges François Leclerc, Dijon, France	1
Kotecki, Nuria	Centre Oscar Lambret, Lille, France	1
Lee, Wes	St Joseph Heritage Healthcare, Santa Rosa, CA, USA	1
Lockhart, Albert	Washington University, St Louis, MO, USA	1
Morris, John	University of Cincinnati Health Clinical Trials Office, Cincinnati, OH, USA	1
Rueckert, Anja	Schwarzwald-Baar Klinikum Villingen-Schwenningen, Baden Wuerttemberg, Germany	1

eTable 1. Confirmed Objective Responses Based on RECIST v1.1.

Response	**N=53**
Best overall response, n (%)	
Complete response	1 (2)
Partial response	4 (8)
Stable disease	26 (49)
Progressive disease	18 (34)
Not evaluable	4 (8)
Objective response rate, % (95% confidence interval)	9.4 (3.1–20.7)
Disease control rate, %	58

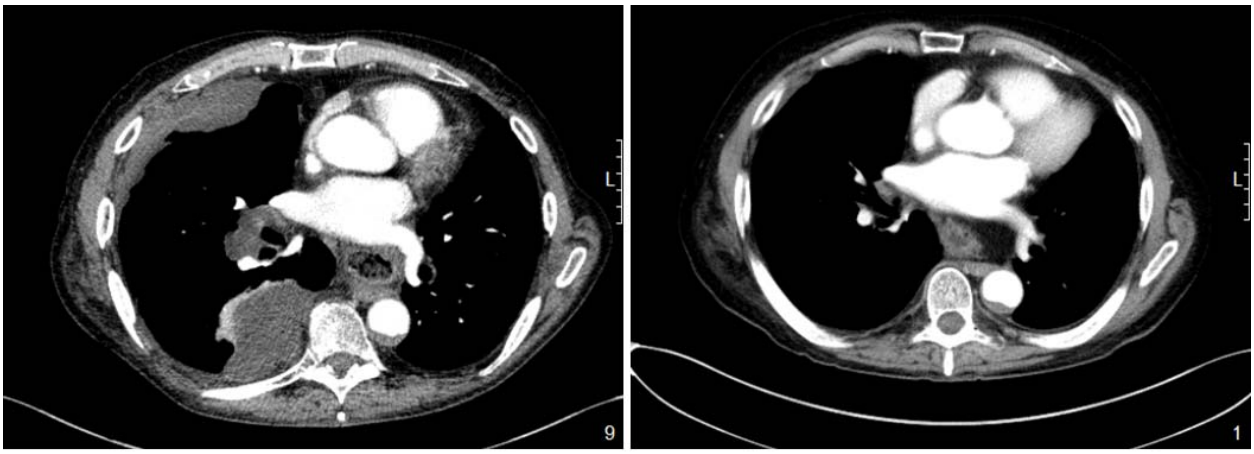
eTable 2. Antitumor Activity According to PD-L1 Expression on Tumor Cells (≥1% and ≥5% Cutoffs) in Evaluable Patients (n=43).

	PD-L1+ tumors	PD-L1− tumors	P-value	Hazard ratio (95% CI)
≥1% tumor cells				
Patients	22	21	–	–
ORR, n (%) [95% CI]	3 (14) [2.9–34.9]	2 (10) [1.2–30.4]	1.000	–
Median PFS, months (95% CI)	5.3 (1.4–12.0)	1.6 (1.4–6.8)	–	0.68 (0.34–1.36)
6-month PFS, % (95% CI)	39.6 (18.2–60.4)	39.4 (18.6–59.7)	–	–
12-month PFS, % (95% CI)	26.4 (8.8–48.1)	16.9 (4.3–36.6)	–	–
Median OS, months (95% CI)	20.2 (6.1–NE)	7.5 (3.8–21.0)	–	0.56 (0.26–1.23)
12-month OS, % (95% CI)	71.0 (46.4–85.8)	33.3 (14.9–53.1)	–	–
≥5% tumor cells				
Patients	16	27	–	–
ORR, n (%) [95% CI]	3 (19) [4.0–45.6]	2 (7) [0.9–24.3]	0.344	–
Median PFS, months (95% CI)	5.3 (1.4–17.8)	1.7 (1.4–8.3)	–	0.64 (0.30–1.34)
6-month PFS, % (95% CI)	37.5 (14.1–61.2)	42.0 (23.1–59.8)	–	–
12-month PFS, % (95% CI)	30.0 (9.5–54.0)	15.7 (4.1–34.1)	–	–
Median OS, months (95% CI)	20.2 (4.9–NE)	10.2 (3.8–21.0)	–	0.62 (0.27–1.42)
12-month OS, % (95% CI)	72.5 (42.1–88.8)	40.7 (22.5–58.2)	–	–

CI, confidence interval; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

eFigure 1. CT Scans of a Patient Who Achieved a Complete Response During Avelumab Treatment.

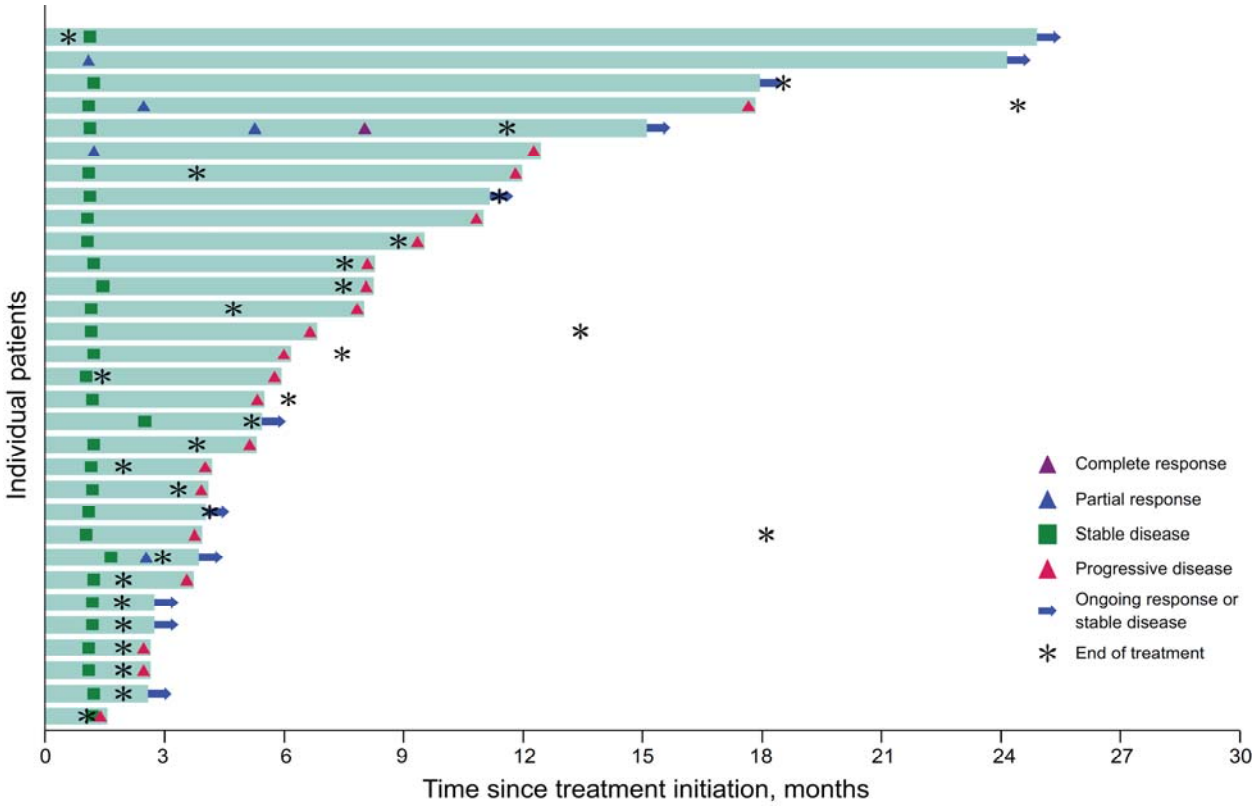
At screening (left panel), target lesions comprised a right pleural base mass, a paramediastinal mass, and a lesion located on the right major fissure. The patient achieved a partial response after 5 months of treatment followed by a complete response after 8 months, based on disappearance of all target lesions. The patient chose to discontinue avelumab after 12 months to take a break from treatment, and the complete response was maintained at last follow-up, 5 months later (right panel).



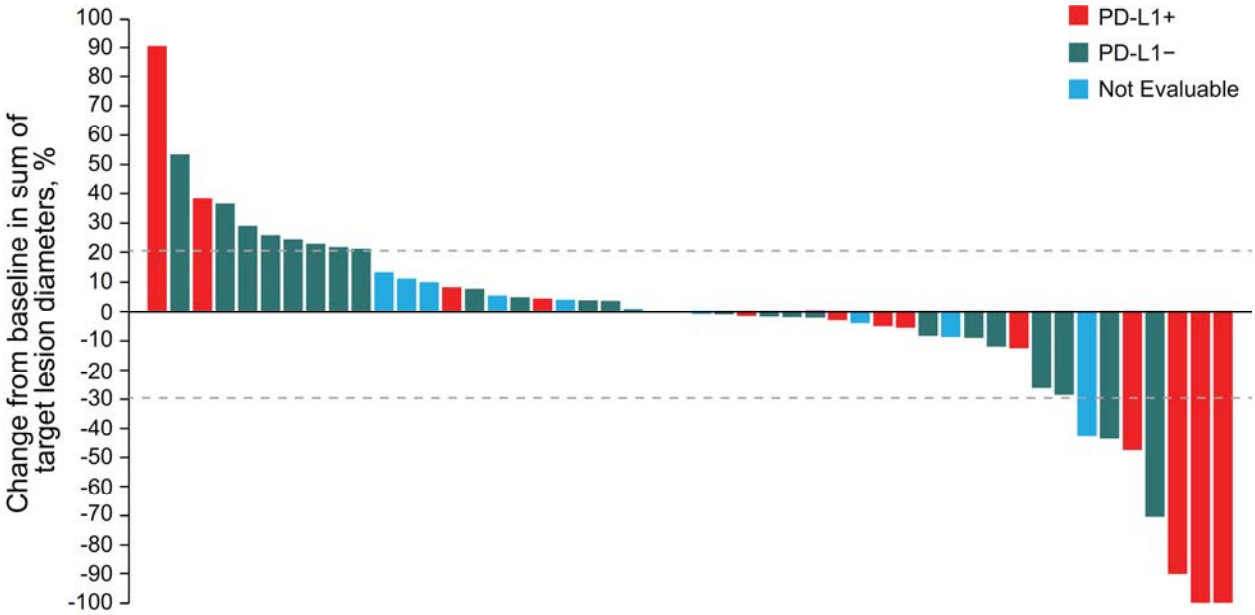
Screening: July 23, 2015 January 10, 2017

eFigure 2. Antitumor Activity of Avelumab.

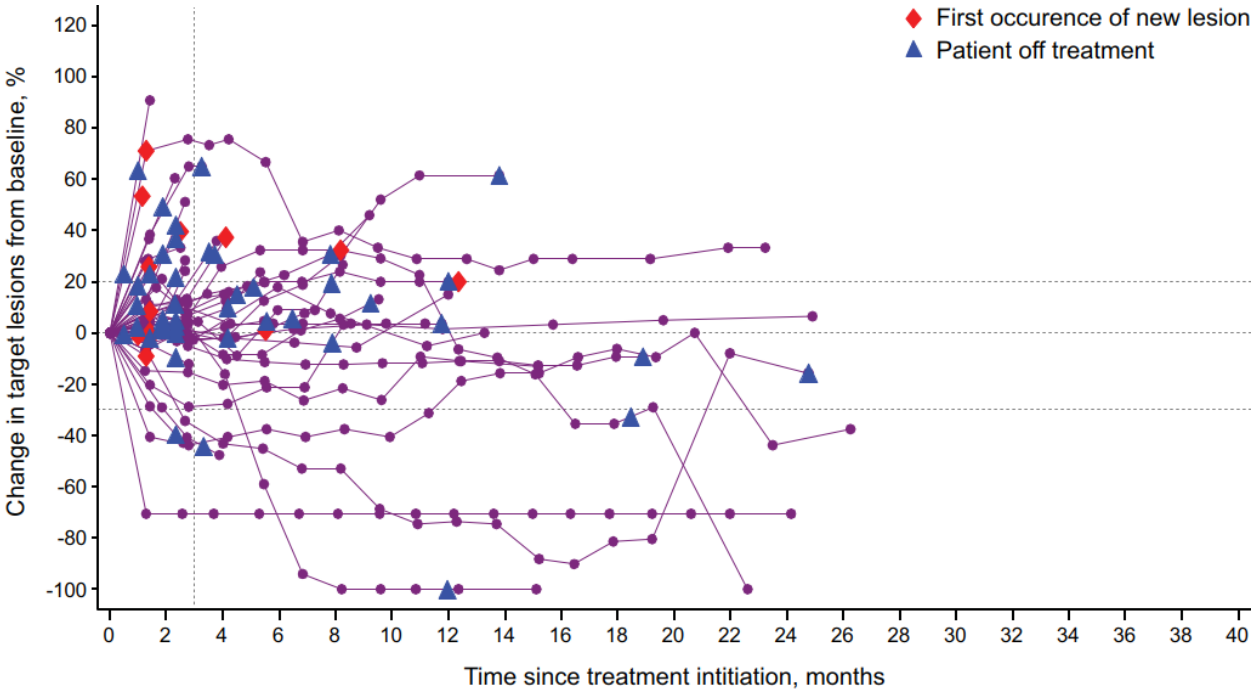
A. Time to and duration of response or stable disease (n=31)



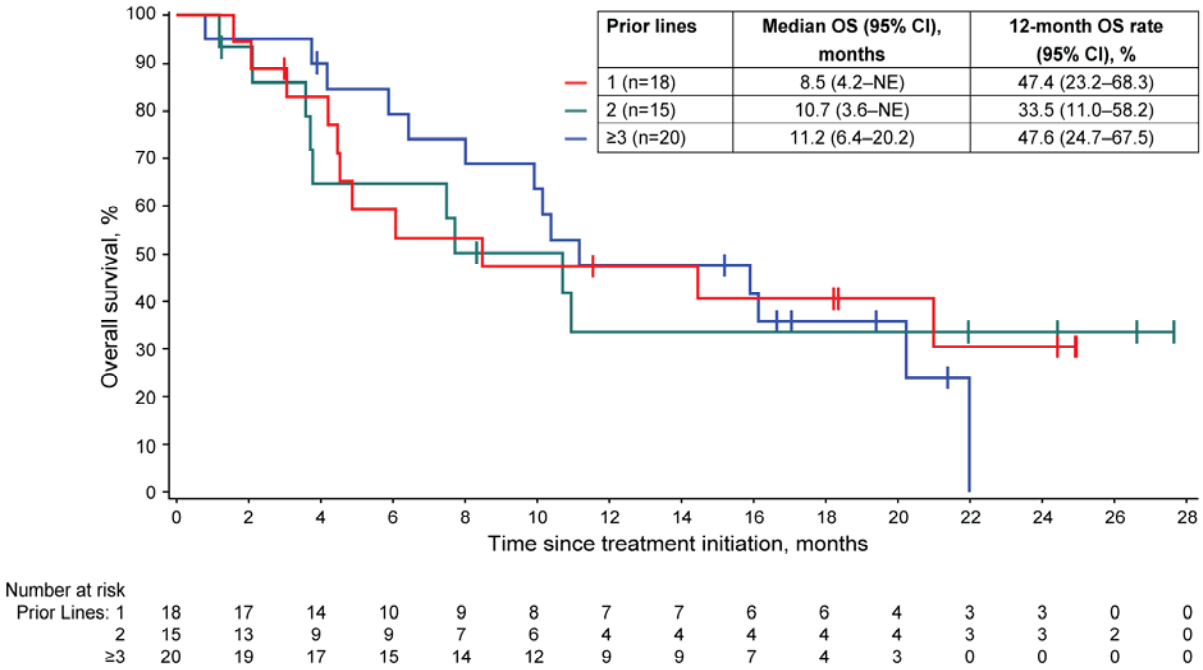
B. Best change in target lesions from baseline in evaluable patients (n=48) classified based on PD-L1 status (≥5% tumor cell cutoff).



C. Change in target lesions from baseline over time in evaluable patients (n=48).

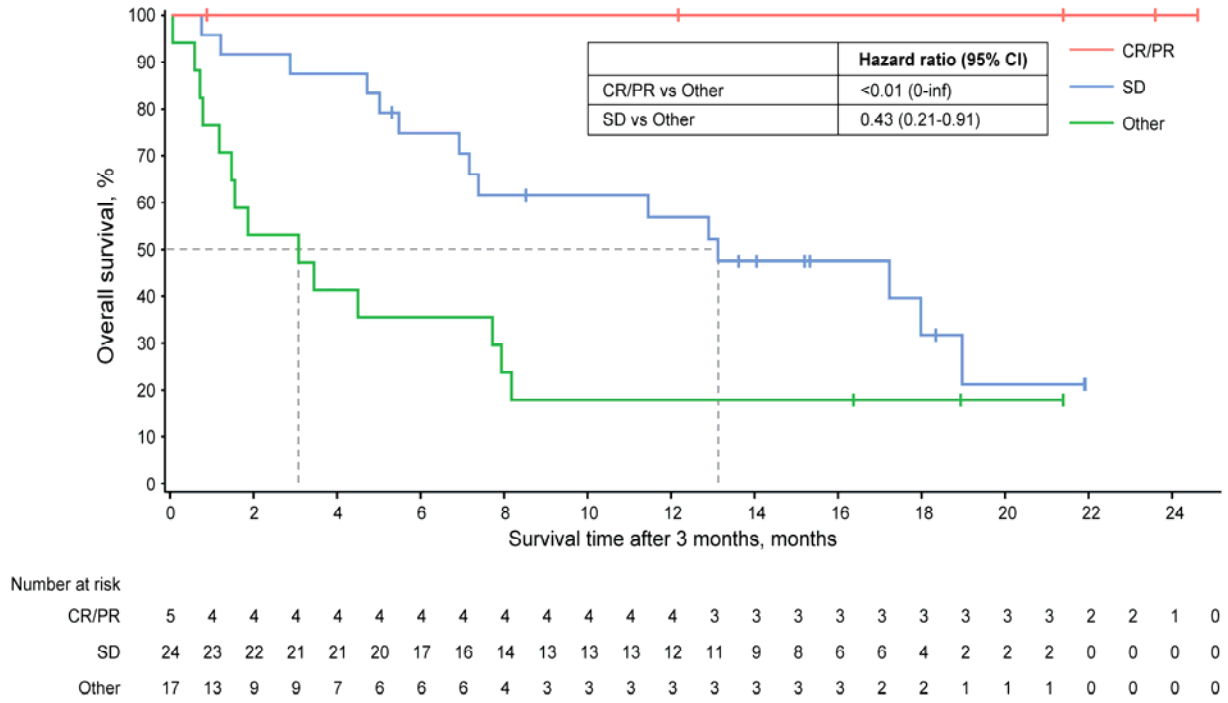


eFigure 3. Kaplan-Meier Analysis of Overall Survival (OS) According to Number of Prior Lines of Therapy Received (n=53).



Number at risk															
Prior Lines: 1	18	17	14	10	9	8	7	7	6	6	4	3	3	0	0
2	15	13	9	9	7	6	4	4	4	4	4	3	3	2	0
≥3	20	19	17	15	14	12	9	9	7	4	3	0	0	0	0

eFigure 4. Landmark Analysis of Overall Survival According to Best Response Achieved at 3 Months (n=46). Best response of 'other' includes patients with progressive disease or not evaluable.

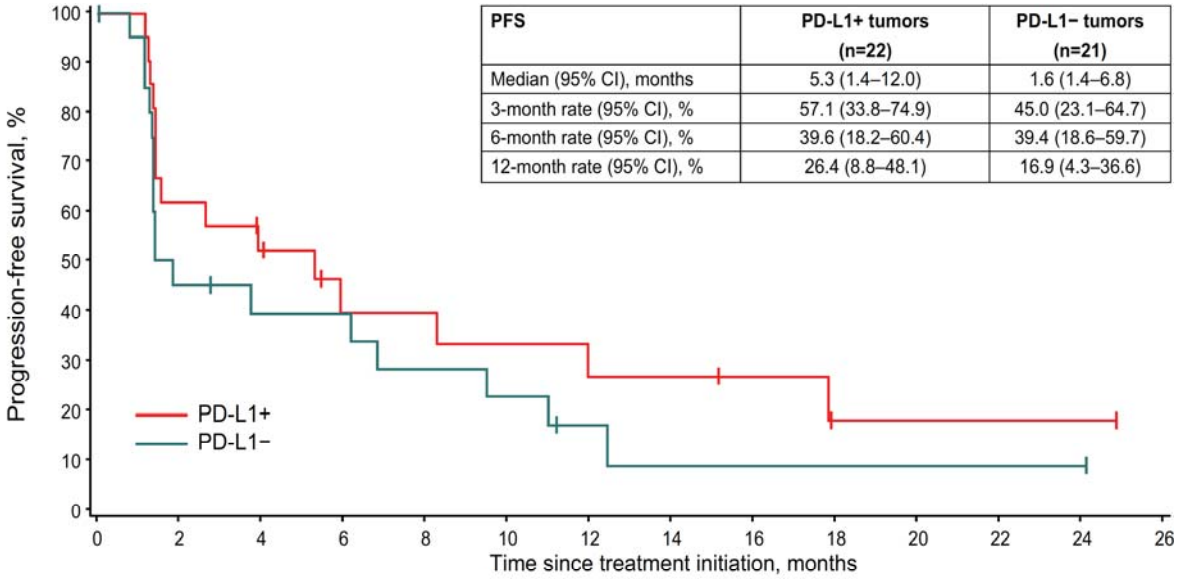


Number at risk

CR/PR	5	4	4	4	4	4	4	4	4	4	4	4	4	3	3	3	3	3	3	3	3	3	2	2	1	0
SD	24	23	22	21	21	20	17	16	14	13	13	13	12	11	9	8	6	6	4	2	2	2	0	0	0	0
Other	17	13	9	9	7	6	6	6	4	3	3	3	3	3	3	3	3	2	2	1	1	1	0	0	0	0

eFigure 5. Kaplan-Meier Analysis of Progression-Free Survival (PFS) and Overall Survival (OS) According To PD-L1 Expression on Tumor Cells in Evaluable Patients (n=43).

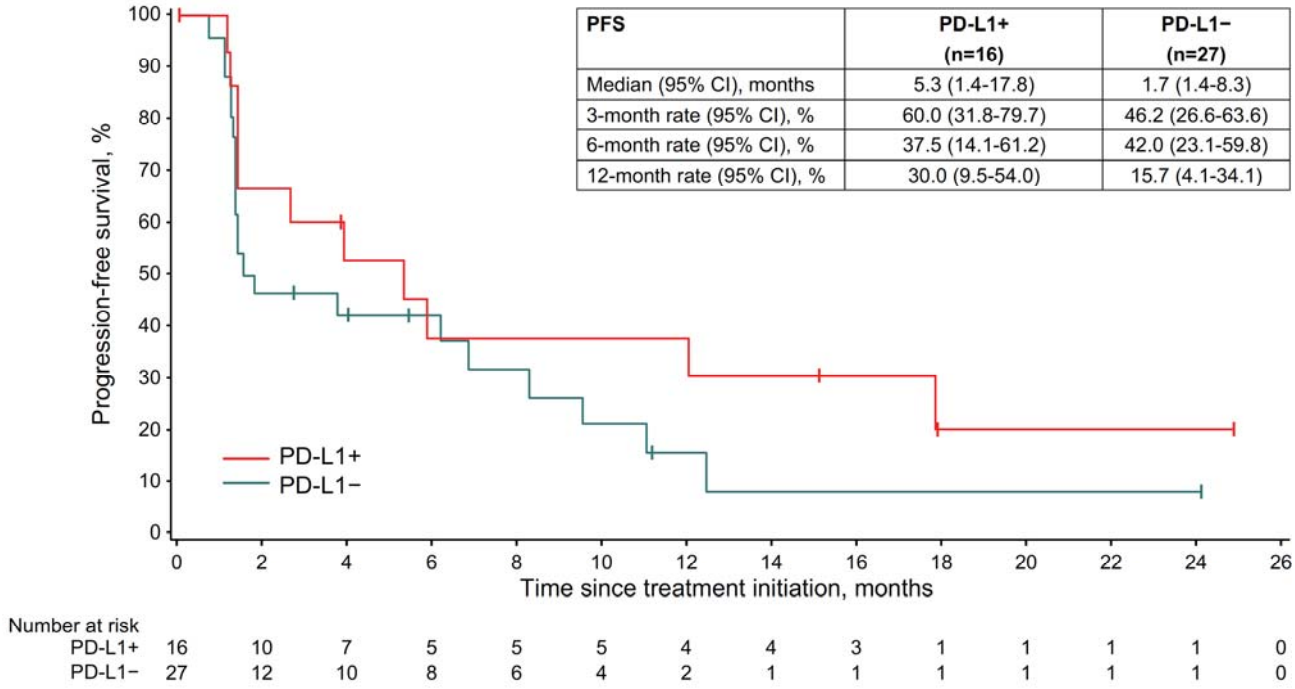
A. PFS based on a ≥1% PD-L1 cutoff



PFS	PD-L1+ tumors (n=22)	PD-L1− tumors (n=21)
Median (95% CI), months	5.3 (1.4–12.0)	1.6 (1.4–6.8)
3-month rate (95% CI), %	57.1 (33.8–74.9)	45.0 (23.1–64.7)
6-month rate (95% CI), %	39.6 (18.2–60.4)	39.4 (18.6–59.7)
12-month rate (95% CI), %	26.4 (8.8–48.1)	16.9 (4.3–36.6)

Number at risk														
PD-L1+	22	13	10	6	6	5	4	4	3	1	1	1	1	0
PD-L1−	21	9	7	7	5	4	2	1	1	1	1	1	1	0

B. PFS based on a ≥5% PD-L1 cutoff.

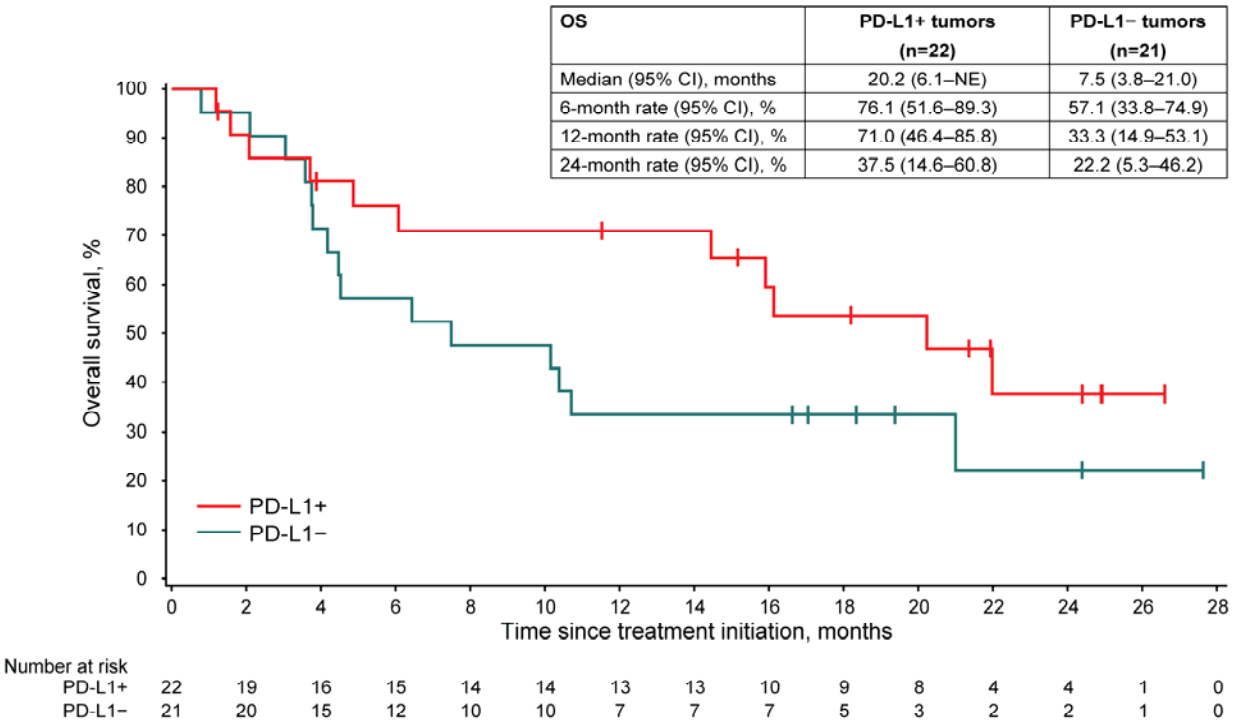


PFS	PD-L1+ (n=16)	PD-L1− (n=27)
Median (95% CI), months	5.3 (1.4-17.8)	1.7 (1.4-8.3)
3-month rate (95% CI), %	60.0 (31.8-79.7)	46.2 (26.6-63.6)
6-month rate (95% CI), %	37.5 (14.1-61.2)	42.0 (23.1-59.8)
12-month rate (95% CI), %	30.0 (9.5-54.0)	15.7 (4.1-34.1)

Number at risk

PD-L1+	16	10	7	5	5	5	4	4	3	1	1	1	1	0
PD-L1−	27	12	10	8	6	4	2	1	1	1	1	1	1	0

C. OS based on a ≥1% PD-L1 cutoff



D. OS based on a ≥5% PD-L1 cutoff