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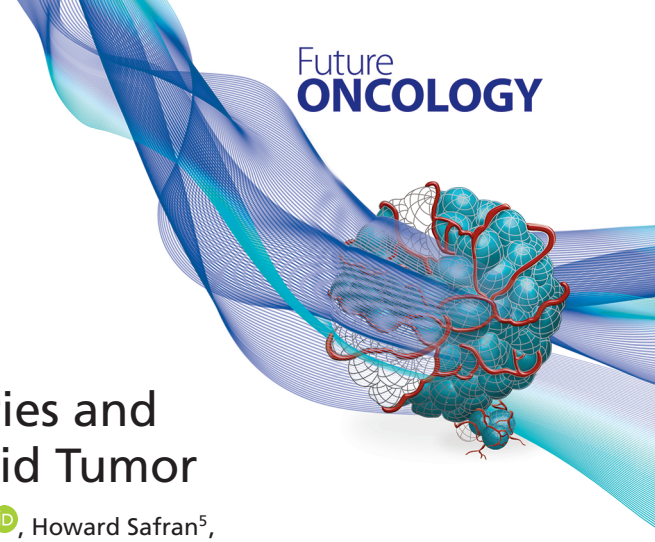

Long-term avelumab in advanced non-small-cell lung cancer: summaries and *post hoc* analyses from JAVELIN Solid Tumor

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Background: This study examined patients with advanced non-small-cell lung cancer who received long-term avelumab (anti-PD-L1) in a large phase Ib trial (JAVELIN Solid Tumor). **Methods:** Patients receiving >2 years of avelumab were reviewed and exploratory descriptive analyses were conducted. **Results:** Individuals with varying baseline characteristics who had received up to 6 years of avelumab were reviewed. Overall, 37/340 (10.9%) had received ≥2 years of treatment; in this subgroup, best response was complete response in 5.4%, partial response in 59.5% and stable disease in 29.7%; 51.4% had continued treatment beyond disease progression. **Conclusions:** In this study, 11% of patients with advanced non-small-cell lung cancer received ≥2 years of avelumab treatment and experienced prolonged response or continued clinical benefit.

Clinical Trial Registration: NCT02395172 (ClinicalTrials.gov)

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Keywords: clinical trials • immunotherapy • lung • metastasis • solid tumors

Background

In recent years, several anti-PD-1/PD-L1 antibodies have become established therapeutic options for the treatment of advanced non-small-cell lung cancer (NSCLC) in both the first-line (1L) and second-line (2L) settings [1–4]. Avelumab is a human IgG1 anti-PD-L1 monoclonal antibody that has been approved in some countries as monotherapy for the treatment of metastatic Merkel cell carcinoma, as monotherapy for advanced urothelial carcinoma that has not progressed with platinum-containing chemotherapy (1L maintenance therapy) or following disease progression, and in combination with axitinib as 1L treatment for advanced renal cell carcinoma [5,6]. Avelumab has a wild-type Fc region and has been shown to induce antitumor activity via adaptive and innate effector cells in preclinical models [7–9].

In the phase I JAVELIN Solid Tumor trial, avelumab monotherapy showed clinical activity as a 1L or 2L or later treatment for advanced NSCLC, including objective response rates of 20 and 14%, respectively [10,11]. In these cohorts, avelumab had acceptable safety, with grade ≥3 treatment-related adverse events occurring in 12 and 13% of

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patients, respectively [10,11]. Avelumab was subsequently assessed in JAVELIN Lung 200, an open-label, randomized, phase III trial in patients with advanced NSCLC with disease progression after platinum-doublet treatment [12]. Avelumab showed clinical activity, but the trial did not meet its primary end point of significantly improving overall survival (OS) compared with docetaxel; however, OS analyses were affected by the high proportion of patients in the docetaxel arm who received subsequent immune checkpoint inhibitor therapy [13]. In the avelumab and docetaxel arms, grade ≥3 treatment-related adverse events occurred in 10 and 49% of patients, respectively [13]. Results from the 1L NSCLC cohort from the JAVELIN Solid Tumor trial led to the initiation of the phase III JAVELIN Lung 100 trial of avelumab versus platinum-doublet chemotherapy as 1L treatment for patients with recurrent or stage IV PD-L1+ NSCLC.

Here we present summaries of patients from the two NSCLC cohorts (1L and 2L) of the phase I JAVELIN Solid Tumor trial who had long durations of clinical benefit from avelumab treatment. Individual cases were summarized based on provision of detailed case histories by treating investigators, and exploratory statistical descriptive analyses of all patients with NSCLC from these cohorts who received long-term avelumab treatment (defined as ≥2 years) are reported.

Materials & methods

Study design & treatment

JAVELIN Solid Tumor (NCT01772004) was an international, multicohort, open-label, phase I trial assessing avelumab monotherapy in various tumor-specific cohorts. Two phase Ib dose-expansion cohorts enrolled patients with NSCLC unselected for PD-L1 status. In the 1L cohort, patients had histologically confirmed stage IV or recurrent NSCLC with no prior treatment for metastatic or recurrent disease. In the 2L cohort, patients had histologically or cytologically confirmed stage IIIB/IV NSCLC that had progressed after treatment with platinum-doublet therapy for metastatic disease; the cohort included some patients who received avelumab as third-line or later treatment. In both cohorts, patients received avelumab 10 mg/kg every 2 weeks until confirmed progression, unacceptable toxicity or withdrawal. Full eligibility criteria and methods for dose-expansion cohorts from the JAVELIN Solid Tumor trial have been reported previously [10,14]. The study protocol was approved by institutional review boards and ethics committees at each institution. The study was done in accordance with the trial protocol, Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent.

Selection of case summaries & subsequent analyses in the overall patient group

Following anecdotal reports of long-term benefit with avelumab treatment, profiles of patients with long durations of treatment were requested from treating investigators.

Subsequently, exploratory descriptive analyses were used to identify potential commonalities in patient and disease characteristics among patients who received long-term treatment. Because several previous studies have established 2 years as a standard threshold to define long-term survival in patients with advanced NSCLC [15–17], a 2-year duration was chosen as the cutoff to define long-term treatment. Descriptive summary statistics included minimum, maximum, mean and median values for continuous covariates and frequency tables for categorical covariates describing patient and disease characteristics. Changes in tumor burden over time and occurrence of response and progressive disease (by Response Evaluation Criteria in Solid Tumors v1.1 [RECIST 1.1] and immune-related RECIST [irRECIST]) in individual patients during long-term treatment were explored using spider plots and swimmer plots. The data cutoff for exploratory analyses was 21 March 2019.

Results

Case summaries of patients with long-term benefit during avelumab treatment

From a subgroup of patients with NSCLC who received ≥2 years of avelumab treatment within the JAVELIN Solid Tumor Trial, treating investigators selected five patients and provided their case histories (Table 1).

Patients had varying demographics and disease characteristics, and no specific commonalities were noted. Patients were aged between 57 and 71 years, with two patients enrolled in the 1L NSCLC cohort and three patients enrolled in the 2L NSCLC cohort (who received avelumab as second-, third- or fifth-line therapy). Best response prior to 1L platinum-based chemotherapy among patients in the 2L cohort was partial response or stable disease. Four of five patients had tumors with adenocarcinoma histology, and three of five patients had PD-L1+ tumors (the other two patients were not evaluable for PD-L1 status). Duration of avelumab treatment ranged from approximately 3 years to more than 6 years. Best response to avelumab was partial response in three patients (one patient shown

Table 1. Summary of individual patients with long-term avelumab treatment (>2 years).

	Patient summary 1	Patient summary 2	Patient summary 3	Patient summary 4	Patient summary 5
Cohort	2L	2L	2L	1L	1L
Sex	Female	Male	Female	Male	Female
Age, years	57	69	59	64	71
Histology	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma	Squamous cell carcinoma
PD-L1 status (≥1% of tumor cells)	Positive	Positive	Positive	Not evaluable	Not evaluable
Date of diagnosis of metastatic disease	May 2012	September 2010	August 2010	January 2015	August 2015
Treatment before avelumab	1L: carboplatin, paclitaxel, bevacizumab and MEGF0444A 2L: vinorelbine	1L: carboplatin, pemetrexed and bevacizumab	1L: cisplatin and etoposide 2L: pemetrexed 3L: docetaxel 4L: gemcitabine 5L: erlotinib	Prior to metastatic disease: surgery, lung radiotherapy	–
Best response to prior chemotherapy	Stable disease	Partial response	Partial response	N/A	N/A
Prior radiotherapy	No	No	Yes	Yes	No
Baseline lesions	Target: lung, pleura, lymph node, liver Non-target: lymph node, bone	Target: lymph node Non-target: none	Target: liver, adrenal gland Non-target: lymph node, pleura	Target: lung Non-target: lung, lymph node	Target: lung, lymph node, adrenal gland Non-target: lung/bone
Date of first avelumab dose	January 2014	April 2014	June 2014	June 2015	September 2015
Duration of avelumab treatment at last follow-up	6 years, 5 months	3 years, 9 months	5 years, 5 months	2 years, 11 months	4 years, 8 months
Best response to avelumab per RECIST	Partial response	Stable disease	Partial response	Stable disease	Partial response
Local radiotherapy after progressive disease	Yes	Yes	No	No	Yes
Subsequent treatment	No	No	No	No	No
Avelumab treatment beyond progression	Yes	Yes	Yes	Yes	Yes
Avelumab treatment ongoing at last follow-up	Yes	No	Yes	No	Yes
Vital status at last follow-up	Alive	Alive	Alive	Died	Alive

1L: First-line; 2L: Second-line; N/A: Not applicable; RECIST: Response Evaluation Criteria in Solid Tumors.

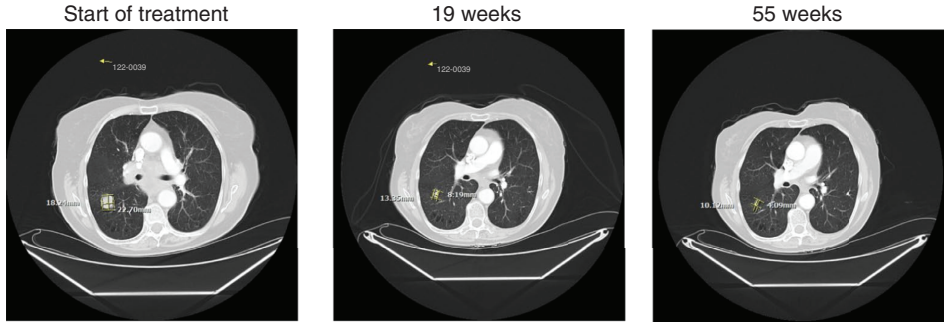

Figure 1. Computerized tomography scan images of patient summary 5.

in Figure 1) and stable disease in two patients. All patients continued avelumab treatment beyond RECIST-defined progression due to ongoing clinical benefit. More detailed descriptions of individual patients are provided in Supplementary Results.

Observations of long-term clinical benefit in individual patients triggered exploratory analyses in the pooled NSCLC trial population, which aimed to identify commonalities and investigate outcomes in patients who had received ≥2 years of treatment.

Exploratory descriptive analysis of patients with long-term avelumab treatment

Patients

Of 340 patients pooled from the 1L (n = 156) and 2L (n = 184) NSCLC dose-expansion cohorts, 37 (10.9%) had received ≥2 years of avelumab treatment (18 [11.5%] in the 1L cohort and 19 [10.3%] in the 2L cohort), and 303 patients (89.1%) had received <2 years of treatment (Table 2). In total, 19 (5.6%) and six patients (1.8%) had received ≥3 years and ≥4 years of avelumab treatment, respectively. Some patient and disease characteristics appeared to be slightly more common in patients with ≥2 years versus <2 years of treatment, including ECOG performance status of 0 (37.8 vs 28.7%), absence of liver metastases at baseline (89.2 vs 80.9%), prior radiotherapy (48.6 vs 37.3%) and disease control (objective response or stable disease) on prior chemotherapy (37.8 vs 27.7%). Baseline tumor burden also appeared to be smaller in those with ≥2 versus <2 years of treatment (Table 2). In patients with ≥2 versus <2 years of treatment, there was a minor increase in the proportion of patients with PD-L1+ tumors (≥1% cutoff, 70.3 vs 60.4%; ≥80% cutoff, 29.7 vs 22.1%, respectively), although a high proportion were not evaluable for PD-L1 expression (25.6%). Other biomarker analyses were not feasible due to the small patient population. However, no patient or disease characteristic showed a large difference between patients with ≥2 or <2 years of avelumab treatment.

Outcomes

In the subgroup of 37 patients who eventually received ≥2 years of avelumab treatment, best overall response per RECIST was complete response in two (5.4%; one patient each from the 1L and 2L cohorts), partial response in 22 (59.5%; 10 and 12 patients in the 1L and 2L cohorts, respectively), stable disease in 11 (29.7%; five and six patients in the 1L and 2L cohorts, respectively) and progressive disease in two (5.4%; both in the 1L cohort). At data cutoff, 14 of the 37 patients (37.8%) had ongoing avelumab treatment (Figure 2; nine and five patients in the 1L and 2L cohorts, respectively). Nine patients (24.3%) did not have progressive disease recorded during follow-up, whereas 21 (56.8%) had both RECIST-defined and irRECIST-defined progressive disease, and seven (18.9%) had RECIST-defined progressive disease only, without irRECIST-defined progressive disease. Of patients with ≥2 years of avelumab treatment, 19 (51.4%) continued treatment for >12 months beyond RECIST-defined progression and subsequently had a decrease in tumor burden or maintained clinical benefit at the next tumor assessment, including patients who received local treatment for a solitary new lesion or progressing target lesion. Consistent sustained reductions in tumor burden from baseline were seen in both the 1L and 2L cohorts (Figure 3).

Discussion

Anecdotal reports of patients with NSCLC who had exceptionally long durations of treatment with avelumab within the JAVELIN Solid Tumor trial prompted collation of five patient summaries. Patients had varying demographics and disease characteristics and had received avelumab as 1L treatment or after varying numbers of prior lines of therapy. Avelumab treatment was extended to >3 years and >5 years in 3 and 2 patients, respectively. These cases, which had varying courses and outcomes, included patients who had a prolonged objective response or stable disease and patients who had continued treatment beyond RECIST-defined progression with local treatment administered for new lesions. No specific commonalities were noted in the cases examined.

To further explore characteristics that might be associated with long-term clinical benefit with avelumab, we conducted descriptive analyses using the pooled 1L and 2L NSCLC population from the JAVELIN Solid Tumor trial. Of 340 patients, 37 (10.9%) had ≥2 years of avelumab treatment. Within this subset, a slight trend was observed for a higher frequency of some disease characteristics potentially associated with less aggressive disease compared with those who received <2 years of avelumab treatment, which included a better performance status, smaller tumor burden, a lower prevalence of liver metastases at baseline and a higher frequency of disease control achieved with prior chemotherapy. In addition, a higher proportion of patients with long-term avelumab treatment had received prior radiotherapy than those without long-term treatment; of the five individual patients summarized,

Table 2. Exploratory descriptive analyses of patient and disease characteristics in patients with non-small-cell lung cancer with ≥2 years or <2 years of avelumab treatment.

	Treatment ≥2 years (n = 37)	Treatment <2 years (n = 303)	All patients (n = 340)
Trial cohort, n (%)			
1L NSCLC	18 (48.6)	138 (45.5)	146 (45.9)
2L NSCLC	19 (51.4)	165 (54.5)	184 (54.1)
Median age (range), years	68.0 (39.0–80.0)	66.0 (31.0–90.0)	66.5 (31.0–90.0)
Sex, n (%)			
Male	18 (48.6)	165 (54.5)	183 (53.8)
Female	19 (51.4)	138 (45.5)	157 (46.2)
Region, n (%)			
America	35 (94.6)	276 (91.1)	311 (91.5)
Asia	0	4 (1.3)	4 (1.2)
Europe	2 (5.4)	23 (7.6)	25 (7.4)
Smoking status, n (%)			
Smoker	34 (91.9)	264 (87.1)	298 (87.6)
Never smoker	3 (8.1)	38 (12.5)	41 (12.1)
Not reported	0	1 (0.3)	1 (0.3)
ECOG PS, n (%)			
0	14 (37.8)	87 (28.7)	101 (29.7)
≥1	23 (62.2)	216 (71.3)	239 (70.3)
Histology			
Squamous	10 (27.0)	89 (29.4)	99 (29.1)
Nonsquamous	27 (73.0)	214 (70.6)	241 (70.9)
Median time since diagnosis (range), years	1.05 (0.04–12.0)	0.66 (0.02–14.4)	0.67 (0.02–14.4)
Median sum of lesion diameters at baseline (range), mm	53.7 (10.0–129)	70.0 (10.0–267)	67.0 (10.0–267)
Presence of metastases at baseline, n (%)			
Liver	4 (10.8)	58 (19.1)	62 (18.2)
Bone	7 (18.9)	67 (22.1)	74 (21.8)
Lymph node	5 (13.5)	49 (16.2)	54 (15.9)
Prior lines of treatment, n (%)†			
≤1	28 (75.7)	246 (81.2)	274 (80.6)
2	7 (18.9)	39 (12.9)	46 (13.5)
≥3	2 (5.4)	18 (5.9)	20 (5.9)
Prior radiotherapy, n (%)			
Yes	18 (48.6)	113 (37.3)	131 (38.5)
No	19 (51.4)	190 (62.7)	209 (61.5)
Response to prior chemotherapy, n (%)			
Complete response	1 (2.7)	4 (1.3)	5 (1.5)
Partial response	2 (5.4)	33 (10.9)	35 (10.3)
Stable disease	11 (29.7)	47 (15.5)	58 (17.1)
Progressive disease	4 (10.8)	78 (25.7)	82 (24.1)
Not evaluable	6 (16.2)	22 (7.3)	28 (8.2)
PD-L1 expression, n (%)			
≥1%	26 (70.3)	183 (60.4)	209 (60.8)
≥5%	20 (54.1)	140 (46.2)	160 (46.5)
≥50%	13 (35.1)	93 (30.7)	106 (30.8)
≥80%	11 (29.7)	67 (22.1)	78 (22.7)
Not evaluable	8 (21.6)	80 (26.4)	88 (25.6)

†Includes prior adjuvant chemotherapy.
ECOG PS: European Cooperative Oncology Group performance status; NSCLC: Non-small-cell lung cancer.

two had received prior radiotherapy. It is well established that radiotherapy enhances the immunogenicity of tumors and affects immunomodulation within the tumor microenvironment [18–20]. A single-center analysis reported that patients with advanced NSCLC with prior radiotherapy had longer PFS and OS with pembrolizumab than those without prior radiotherapy [21]. Analyses in other NSCLC populations are needed to confirm whether prior radiotherapy increases the likelihood of long-term clinical benefit with avelumab treatment. The proportion of patients with PD-L1+ tumors (≥1% of tumor cells) was slightly elevated in the long-term treatment subgroup versus other patients (70.3 vs 60.4%, respectively), with smaller differences in proportions with higher level PD-L1 expression, suggesting that PD-L1+ status may not be associated with long-term benefit. However, all analyses reported in this manuscript were *post hoc* and purely explorative and should be interpreted in the context of their acknowledged limitations. In particular, subgroups were defined based on treatment duration (≥2 or <2 years of

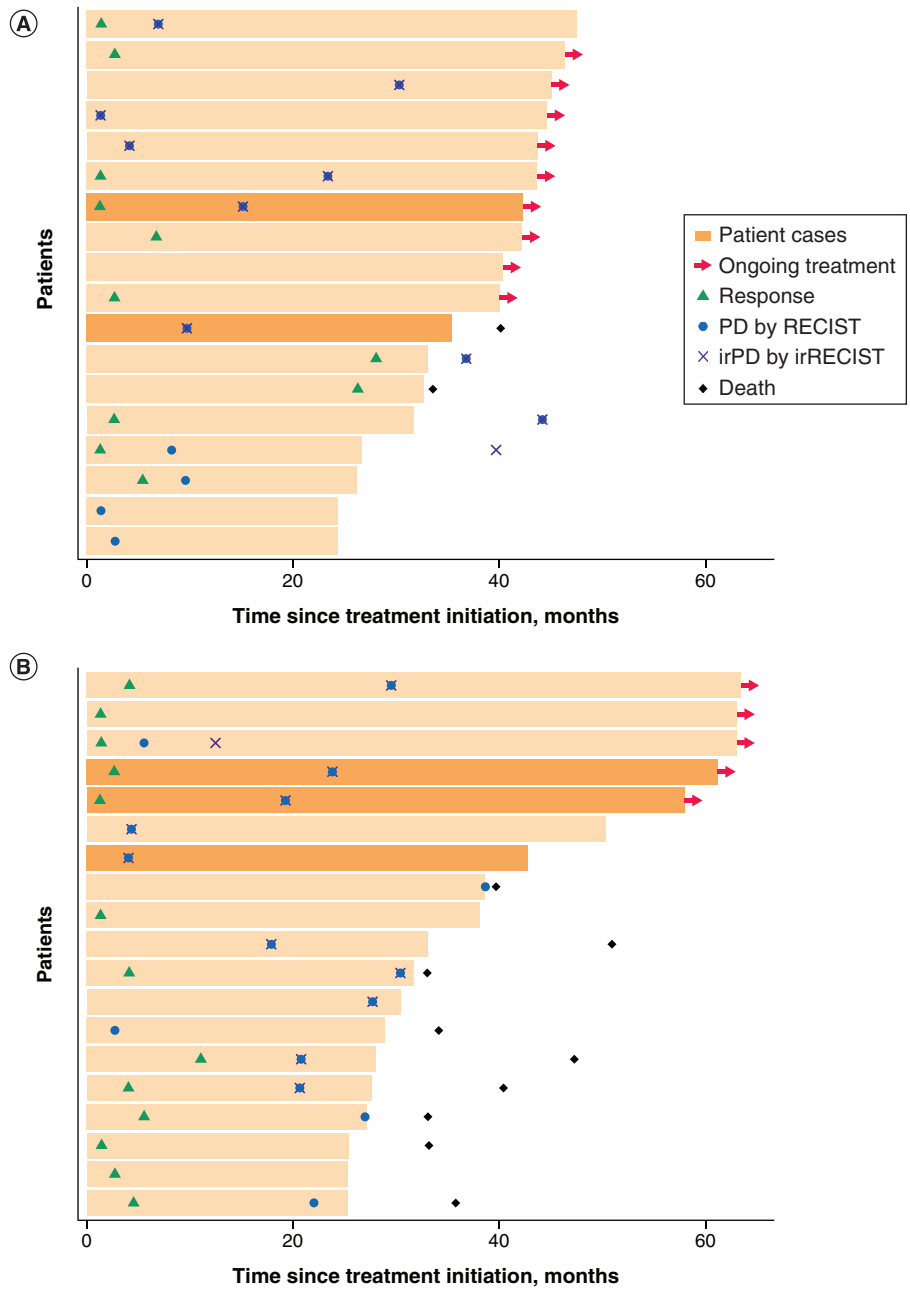

Figure 2. Swimlane plot from the start of treatment in patients with ≥2 years of avelumab treatment (n = 37).
(A) First-line cohort. **(B)** Second-line cohort.
irPD: Immune-related progressive disease; irRECIST: Immune-related Response Evaluation Criteria in Solid Tumor; NSCLC: Non-small-cell lung cancer; PD: Progressive disease.

avelumab treatment), which was driven by efficacy outcomes and may have introduced immortal time bias, and the sample size of patients with long-term treatment was small (n = 37).

In several patients who received long-term treatment, avelumab was continued beyond RECIST-defined progression, and patients had sustained clinical benefit. It is well documented that some patients treated with immune checkpoint inhibitors develop pseudoprogression, in other words, temporary increases in tumor lesion size classified as disease progression according to RECIST 1.1 [22]. Other criteria for evaluating responses, such as immune-related response criteria, may help to differentiate these patients. These findings support the continuation of anti-PD-L1 treatment beyond RECIST-defined progression based on the clinician's assessment of ongoing clinical benefit.

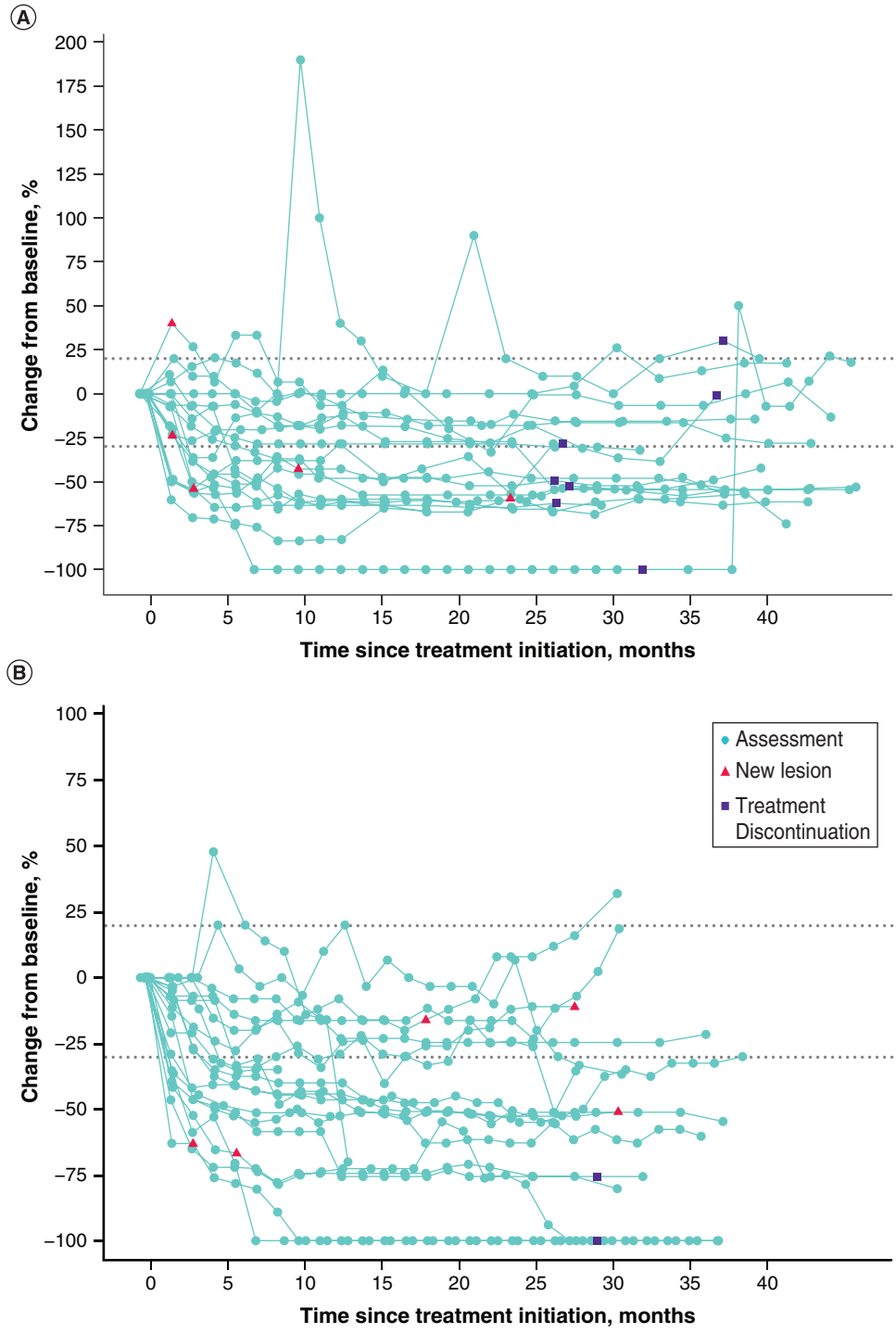

Figure 3. Change in the sum of target lesions over time in patients with ≥2 years of avelumab treatment (n = 37).
(A) First-line cohort. **(B)** Second-line cohort.

Conclusion

Approximately 11% of patients with NSCLC enrolled in the phase I JAVELIN Solid Tumor trial experienced long-term clinical benefit from avelumab treatment, and among this subgroup, a majority had continued avelumab beyond RECIST-defined disease progression. *Post hoc* exploratory analyses did not generate clear hypotheses for

potential associations between baseline characteristics and long-term benefit. Further exploratory analyses of long-term immune checkpoint inhibitor therapy in patients with advanced NSCLC are needed to verify these findings.

Summary points

- Summaries of patients with non-small-cell lung cancer (NSCLC) and long-term treatment benefit with avelumab in the phase Ib JAVELIN Solid Tumor trial were collated.
- Patients had received up to 6 years of avelumab, including individuals with continued clinical benefit with ongoing treatment despite RECIST-defined disease progression.
- Exploratory descriptive analyses of baseline characteristics were performed in the subgroup with ≥2 years of avelumab treatment in comparison to pooled NSCLC cohorts (n = 340).
- Of 340 patients, 37 (10.9%) had ≥2 years of avelumab treatment.
- Of the 37 patients with ≥2 years of treatment, best response was complete response in 5.4%, partial response in 59.5%, stable disease in 29.7% and progressive disease in 5.4%.
- In total, 19 out of 37 patients (51.4%) continued treatment for >12 months beyond RECIST-defined progression.
- Baseline characteristics associated with less-aggressive disease were slightly more prevalent in patients with ≥2 years versus <2 years of treatment.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2021-0930

Author contributions

B Hrinczenko, M Bajars, J Manitz and M Ruisi conceptualized the manuscript and wrote the original manuscript draft. J Manitz developed the methodology and performed the formal analysis. All authors contributed towards acquisition and interpretation of the data, and were involved in reviewing and editing the manuscript.

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Ethical conduct of research

The study protocol was approved by institutional review boards and ethics committees at each institution. The study was done in accordance with the trial protocol, Good Clinical Practice guidelines, and the Declaration of Helsinki. All patients provided written informed consent.

Availability of data & materials

Data are available upon reasonable request. For all new products or new indications approved in both the European Union and the USA after 1 January 2014, Merck will share patient-level and study-level data after deidentification, as well as redacted study protocols and clinical study reports from clinical trials in patients. These data will be shared with qualified scientific and medical researchers, upon researchers' request, as necessary for conducting legitimate research. Such requests must be submitted in writing to the company's data sharing portal. More information can be found at https://www.merckgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html. Where Merck has a coresearch, codevelopment or comarketing/copromotion agreement or where the product has been out-licensed, it is recognized that the responsibility for disclosure may be dependent on the agreement between parties. Under these circumstances, Merck will endeavor to gain agreement to share data in response to requests.

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Papers of special note have been highlighted as: • of interest; •• of considerable interest

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