ORIGINAL ARTICLE

Avelumab in Combination With Cetuximab and Chemotherapy as First-Line Treatment for Patients With Advanced Squamous NSCLC

Zoran Andric, MD,[a] Gabriella Gálffy, MD,[b] Manuel Cobo Dols, MD,[c] Barna Szima, MD,[d] Goran Stojanovic, MD,[e] Marina Petrovic, MD,[f] Enriqueta Felip, MD,[g] David Vicente Baz, MD,[h] Santiago Ponce Aix, MD,[i] Oscar Juan-Vidal, MD,[j] Zsuzsanna Szalai, MD,[k] Gyorgy Losonczy, MD,[l] Antonio Calles Blanco, MD,[m] Reyes Bernabe, MD,[n] Gema García Ledo, MD,[o] Andrés Aguilar Hernández, MD,[p] Klaus Duecker, PhD,[q] Dongli Zhou, PhD,[r] Andreas Schroeder, MD,[q] Guelseren Guezel, MD,[q] Fortunato Ciardiello, MD, PhD[s,*]

[a]*Department of Medical Oncology, Clinical Hospital Center Bezanijska Kosa, Belgrade, Serbia*
[b]*Pulmonology Hospital Törökbálint, Törökbálint, Hungary*
[c]*Department of Medical Oncology, Hospital Regional Universitario de Málaga, Institute of Biomedical Research of Málaga (IBIMA), Málaga, Spain*
[d]*Department of Pulmonology, Markusovszky Hospital, Szombathely, Hungary*
[e]*Institute of Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia*
[f]*Clinic for Pulmonology, Clinical Center Kragujevac, Kragujevac, Serbia*
[g]*Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain*
[h]*Department of Medical Oncology, Hospital Universitario Virgen Macarena, Seville, Spain*
[i]*Medical Oncology Department, H120-CNIO Lung Cancer Unit, Hospital Universitario 12 de Octubre, Madrid, Spain*
[j]*Department of Medical Oncology, Hospital Universitari I Politècnic La Fe, Valencia, Spain*
[k]*Department of Pulmonology, Aladar Petz University Teaching Hospital, Győr, Hungary*
[l]*Faculty of Medicine, Semmelweis University, Budapest, Hungary*
[m]*Medical Oncology Department, Hospital General Universitario Gregorio Marañon, Madrid, Spain*
[n]*Department of Medical Oncology, Hospital Universitario Virgen del Rocio, Seville, Spain*

*Corresponding author.

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Address for correspondence: Fortunato Ciardiello, MD, PhD, Division of Medical Oncology, Department of Precision Medicine, University of Campania Luigi Vanvitelli, Naples, Italy. E-mail: Fortunato.CIARDIELLO@unicampania.it

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[o]Centro Integral Oncológico Clara Campal HM CIOCC, Hospital Universitario HM Sanchinarro, Madrid, Spain
[p]Instituto Oncológico Dr Rosell, Hospital Universitari Quiron Dexeus, Barcelona, Spain
[q]The Healthcare Business of Merck KGaA, Darmstadt, Germany
[r]Merck Serono (Beijing) Pharmaceutical R&D Co., Ltd., Beijing, China, an affiliate of Merck KGaA, Darmstadt, Germany
[s]Division of Medical Oncology, Department of Precision Medicine, The University of Campania Luigi Vanvitelli, Naples, Italy

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ABSTRACT

Introduction: We present the results of a phase 2a trial of first-line avelumab (anti–programmed death-ligand 1 antibody) plus cetuximab (anti–EGFR antibody) in patients with advanced squamous NSCLC.

Methods: Patients with recurrent or metastatic squamous NSCLC received avelumab 800 mg (d 1 and 8), cetuximab 250 mg/m^2 (d 1) and 500 mg/m^2 (d 8), cisplatin 75 mg/m^2 (d 1), and gemcitabine 1250 mg/m^2 (d 1 and 8) for four 3-week cycles, followed by avelumab 800 mg and cetuximab 500 mg/m^2 every 2 weeks. The primary end point was the best overall response; the secondary end points were progression-free survival, duration of response, overall survival, and safety. Efficacy analyses were reported from an updated data cutoff.

Results: A total of 43 patients were enrolled. The median follow-up was 6.6 months for the primary analyses and 9.2 months for the efficacy analyses. In the efficacy analyses, 15 patients had a confirmed partial response (objective response rate, 34.9% [95% confidence interval: 21.0%–50.9%]), and the median duration of response was 7.1 months (95% confidence interval: 4.2–12.5 mo). The median progression-free survival and overall survival were 6.1 months and 10.0 months, respectively. In the safety analyses (primary analysis), 38 patients (88.4%) had a treatment-related adverse event, of whom 24 (55.8%) had a grade 3 or higher treatment-related adverse event.

Conclusions: The combination of avelumab + cetuximab and chemotherapy showed antitumor activity and tolerable safety; however, the ORR was not improved compared with those reported for current standards of care (NCT03717155).

Keywords: Avelumab; Cetuximab; PD-L1; EGFR; Non–small cell lung cancer

Introduction

Since 2015, the availability of immune checkpoint inhibitor (ICI)–based treatments has led to a paradigm shift in the treatment of advanced NSCLC. For targeted therapies, the selection is on the basis of histologic subtype (squamous versus nonsquamous) and the presence of actionable mutations (e.g., *EGFR* mutations or *ALK* rearrangements). In the absence of mutations, ICIs (as monotherapy or combination regimens) are preferred treatment options for advanced NSCLC in the first- (1L) and second-line (2L) settings.[1,2] Pembrolizumab, cemiplimab (both anti–programmed cell death protein-1 [anti–PD-1]), and atezolizumab (anti–programmed death-ligand 1 [anti–PD-L1]) monotherapy are recommended 1L options for patients with squamous and nonsquamous tumors with greater than or equal to 50% PD-L1 expression.[3–5] Pembrolizumab plus chemotherapy, atezolizumab plus chemotherapy, and nivolumab (anti–PD-1) plus ipilimumab (anti–CTLA4) plus chemotherapy are also recommended 1L options for advanced squamous and nonsquamous NSCLC irrespective of PD-L1 expression (chemotherapy combinations are tailored to histologic subtype).[6–10] Atezolizumab plus bevacizumab (anti–vascular endothelial growth factor) and chemotherapy is also approved as 1L treatment but only for metastatic nonsquamous NSCLC.[11]

Avelumab is an anti–PD-L1 monoclonal antibody approved for the treatment of metastatic Merkel cell carcinoma (monotherapy, 1L or later) and advanced urothelial carcinoma (monotherapy, 1L maintenance or 2L), and in combination with axitinib for advanced renal cell carcinoma (1L).[12,13] Avelumab has also exhibited clinical activity and tolerable safety in patients with advanced or metastatic NSCLC (1L and 2L), including patients with squamous tumors.[14–16] Preclinical evidence suggests that ICIs in combination with cetuximab (an anti–EGFR) may provide enhanced antitumor activity compared with either therapy alone.[17] Furthermore, several clinical studies, including the phase 3 FLEX study of cetuximab plus chemotherapy versus chemotherapy alone, have exhibited synergy for cetuximab in combination with chemotherapy as 1L treatment in patients with advanced NSCLC, most notably in a subpopulation of patients with EGFR-expressing squamous tumors.[18–21]

These findings provided the rationale for assessing the efficacy and safety of avelumab in combination with

cetuximab and chemotherapy in patients with advanced squamous NSCLC.

Materials and Methods

Study Design and Patients

This was a phase 2a, single-arm, multicenter trial of 1L avelumab plus cetuximab, gemcitabine, and cisplatin in patients with advanced squamous NSCLC. Eligible patients were aged 18 years or older and had histologically confirmed, *EGFR/ALK*–wild-type, stage IV, metastatic or recurrent squamous NSCLC with no previous systemic treatment for metastatic disease. Patients were also required to have a European Cooperative Oncology Group performance status of 0 or 1, available tumor tissue for biomarker assessment, and adequate hematologic, hepatic, and renal function. Patients with brain metastases were not eligible unless their brain metastases had been treated locally and were clinically stable for at least 4 weeks before enrollment, they had no ongoing neurologic symptoms, and they were either not receiving steroids or receiving a decreased dose of prednisone (or equivalent) less than or equal to 10 mg daily.

The study protocol and amendments were approved by institutional review boards and ethics committees at each institution. The trial was conducted in accordance with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the International Conference on Harmonization Guidelines for Good Clinical Practice, and the Declaration of Helsinki. All patients provided written informed consent.

Procedures and Assessments

Patients were treated with four 3-week cycles of avelumab 800 mg intravenously (IV) on days 1 and 8, cetuximab 250 mg/m^2 IV on day 1 and 500 mg/m^2 on day 8, cisplatin 75 mg/m^2 IV on day 1, and gemcitabine 1250 mg/m^2 IV on days 1 and 8. Patients then received maintenance treatment with avelumab 800 mg plus cetuximab 500 mg/m^2 every 2 weeks until progressive disease, unacceptable toxicity, or study withdrawal. Patients receiving avelumab were permitted to have modifications of infusion rate in the event of infusion-related reactions (IRRs), but dose reductions were not permitted. The protocol was amended on May 6, 2019, so patients could switch from cisplatin to carboplatin in the event of unmanageable cisplatin-related toxicity.

The primary end point was confirmed best overall response (BOR) according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, per investigator assessment. The secondary end points included progression-free survival (PFS) and duration of response (DOR) according to RECIST 1.1 per investigator assessment, overall survival (OS), and safety. Exploratory biomarker analyses tested PD-L1 expression or EGFR gene amplification status in archival tumor samples ($<$6 mo old) or fresh baseline tumor samples obtained from a nonirradiated area. Definitions of all end points are given in the Supplementary Methods. The PD-L1 expression level was categorized using less than 1%, 1% to less than 50%, 50% to less than 80%, and greater than or equal to 80% expression cutoffs per the PD-L1 immunohistochemistry (IHC) 73-10 assay (Agilent; Santa Clara, CA). EGFR fluorescence in situ hybridization (FISH) status was assessed using the Vysis EGFR/chromosome 7 centromere (CEP 7) FISH Probe Kit (Abbott Molecular; Libertyville, IL). In brief, five histopathologically representative formalin-fixed, paraffin-embedded tumor sections were selected. Within each region, an average of 10 nuclei were selected for analysis, for a total of 50 nuclei. The number of EGFR and CEP 7 signals was counted for each selected nucleus. Interpretation of the EGFR FISH results was done according to previously published criteria.[22,23] Cases identified as EGFR "high polysome" had at least 40% of counted nuclei with greater than or equal to four EGFR signals. EGFR "amplified" was defined by one of the following criteria: (1) EGFR to CEP7 ratio greater than or equal to two over all scored nuclei; (2) greater than or equal to 15 copies of the EGFR signal in greater than or equal to 10% of counted nuclei; or (3) presence of gene cluster (closely spaced groupings of $\geq$4 spots) in greater than or equal to 10% of counted nuclei. Positive EGFR FISH tumors included those with EGFR amplified or high-polysome status (both defined on the basis of previously published criteria[22,23]); negative EGFR FISH status was defined as no amplification of EGFR or no high-polysome status. All biomarker analyses were prespecified, and testing was performed centrally; PD-L1 IHC was performed at Q2S (Scotland, United Kingdom), whereas EGFR IHC and FISH were tested centrally at Targos (Germany).

Tumors were assessed radiologically by the investigator per RECIST 1.1 every 9 weeks postbaseline for the first 6 months, then every 12 weeks thereafter. Safety was assessed at each treatment visit, and adverse events (AEs) were coded in accordance with Medical Dictionary for Regulatory Activities, version 21.0 or higher, and graded according to the National Cancer Institute Common Terminology Criteria for AEs, version 5.0. IRRs (including drug hypersensitivity reactions) and immune-related AEs were identified as AEs of special interest for avelumab.

Outcomes were reported using three data cutoff dates. The primary analysis was on the basis of a data cutoff date of July 2, 2020. Other analyses, including patient disposition and efficacy analyses (except analyses of tumor shrinkage), were reported using an updated data cutoff date of November 4, 2020. OS and PFS were also further characterized at final analysis, with a data cutoff date of June 25, 2021.

Statistical Analysis

Enrollment of approximately 40 patients was planned; however, no formal statistical hypotheses were tested. The probability to observe greater than or equal to 18 patients with an objective response rate (ORR) of 45.0% (95% confidence interval [CI]: 29.3%–61.5%) was 78.5%, assuming a true response rate of 50% (a clinically relevant effect). If the true response rate was 30% (a nonrelevant effect), the probability of observing at least 18 patients with a response was 3.2%. If 18 patients responded, the posterior probability for a true response rate of at least 40% (a minimum relevant effect) was 75%.

Results

Patient Characteristics and Disposition

In total, 43 patients received at least one dose of avelumab, cetuximab, gemcitabine, and cisplatin; 34 patients (79.1%) received four cycles of chemotherapy, and two patients (4.7%) switched from cisplatin to carboplatin because of cisplatin-related toxicity (Supplementary Fig. 1). Baseline characteristics and demographics (on the basis of the primary analysis) are presented in Table 1. The median patient age was 65 years (range: 41–72 y), and 35 patients (81.4%) were men. At baseline, most patients had recurrent disease (93.0%), and the remainder (7.0%) had de novo metastatic disease. More than half of all patients (55.8%) had intrathoracic metastasis. No patients had brain metastases, nine patients (20.9%) had bone metastases, and seven patients (16.3%) had liver metastases. The PD-L1 expression level was 1% to less than 50% in 16 patients (37.2%), 50% to less than 80% in four patients (9.3%), 80% or higher in 10 patients (23.3%), and less than 1% in 13 patients (30.2%). A total of 15 patients (34.9%) had EGFR FISH–positive tumors. The median follow-up was 6.6 months for the primary analysis (range: 0.3–18.2 mo) and 9.2 months (range: 0.3–21.4 mo) for the updated analysis; the median follow-up was not calculated for the final analysis. Of the 43 patients, 34 (79.1%) received avelumab plus cetuximab in the maintenance phase; among these patients, the median duration of overall treatment was 6.0 months (range: 3.7–12.8 mo), and the duration of maintenance treatment was 3.2 months (range: 0.9–10.1 mo).

At the updated data cutoff, eight patients (18.6%) remained on treatment. The most common reason for discontinuing avelumab or cetuximab was progressive disease (n = 21 [48.8%] and n = 19 [44.2%], respectively).

Table 1. Patient Baseline Characteristics (Data Cutoff: July 2, 2020)

Characteristics	N = 43
Median age (range), y	65 (41-72)
Sex, n (%)	
Male	35 (81.4)
Female	8 (18.6)
Country, n (%)	
Hungary	11 (25.6)
Serbia	17 (39.5)
Spain	15 (34.9)
ECOG PS, n (%)	
0	16 (37.2)
1	27 (62.8)
Smoking status, n (%)	
Regular smoker	23 (53.5)
Former smoker	20 (46.5)
Metastases at baseline, n (%)	
Liver	7 (16.3)
Brain	0
EGFR FISH status, n (%)[a]	
Negative	28 (65.1)
Positive	15 (34.9)
PD-L1 expression cutoff, n (%)	
<1%	13 (30.2)
≥1% to <50%	16 (37.2)
≥50% to <80%	4 (9.3)
≥80%	10 (23.3)

[a]Negative EGFR FISH status is defined as no amplification of EGFR or no "high-polysome" status; positive EGFR FISH status is defined as amplification of EGFR or "high-polysome" status.
ECOG PS, European Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; PD-L1, programmed death-ligand 1.

Efficacy

The efficacy outcomes from the primary analysis are presented in Supplementary Table 1. In the updated analysis, 15 patients had a confirmed BOR of partial response (PR), resulting in a confirmed ORR of 34.9% (95% CI: 21.0%–50.9%) (Table 2). A total of 23 patients had an unconfirmed BOR of PR, resulting in an unconfirmed ORR of 53.5% (95% CI: 37.7%–68.8%). For confirmed responses, the median DOR was 7.1 months (95% CI: 4.2–12.5 mo), and the median time to response was 9.0 weeks (range: 5.9–18.1 weeks), consistent with the timing of the first on-study tumor assessment. The proportion of patients with a response lasting at least 6 months was 69.2% (95% CI: 37.3%–87.2%), and the proportion of those with a response lasting at least 12 months was 23.7% (95% CI: 3.9%–52.9%). Of the 39 patients assessable for change in tumor size, 35 (89.7%) had tumor shrinkage (Fig. 1) and 23 (59.0%) had tumor shrinkage of at least 30% (Fig. 1). At data cutoff, 21 patients were progression free for more than 24 weeks; of these, four were censored without progression reported (Fig. 2*A*). The median PFS was 6.1 months (95% CI: 4.3–9.0 mo), and the 6- and 12-month PFS was 57.6% (95% CI: 40.3%–71.6%) and 8.5% (95% CI: 1.6%–23.2%), respectively (Fig. 2*B*). The median OS was 10.0 months (95% CI: 8.6–17.1 months), and the 6-, 12-, and

Table 2. Confirmed and Unconfirmed BOR (Data Cutoff: November 4, 2020)

	Confirmed BOR (n = 43)	Unconfirmed BOR (n = 43)
Complete response	0	0
Partial response	15 (34.9)	23 (53.5)
Stable disease	19 (44.2)	12 (27.9)
Progressive disease	4 (9.3)	4 (9.3)
Not evaluable	5 (11.6)	4 (9.3)
ORR (95% CI), %	34.9 (21.0-50.9)	53.5 (37.7-68.8)
DCR (95% CI), %	79.1 (64.0-90.0)	81.4 (66.6-91.6)

Note: All values are n (%) unless otherwise specified.
BOR, best overall response; CI, confidence interval; DCR, disease control rate; ORR, objective response rate.

18-month OS was 85.7% (95% CI: 70.9%–93.3%), 40.9% (95% CI: 24.6%–56.6%), and 23.4% (95% CI: 6.2%–46.9%), respectively (Fig. 3). At the final PFS analysis, the median PFS was consistent with the previous analysis (median, 6.1 mo; 95% CI: 4.3–9.0 mo); the 6- and 12-month PFS rates were 57.6% and 17.6%, respectively, and no patients were progression free by 18 months (Supplementary Table 2). The median OS at the final analysis was 10.1 months (95% CI: 8.6–14.5 mo); the 6-month OS rate was consistent with the previous analysis (85.7%; 95% CI: 70.9%–93.3%), whereas the 12-, 18-, and 24-month OS rates were 41.6% (95% CI: 26.6%–56.0%), 27.4% (95% CI: 14.4%–42.2%), and 21.9% (95% CI: 9.3%–38.0%), respectively (Supplementary Table 2).

Subgroup Analyses

Subgroup analyses were on the basis of the primary analysis. ORRs were generally consistent across all subgroups. However, a numerically higher ORR was observed in patients with EGFR FISH–positive–versus negative tumors (40.0%; 95% CI: 16.3%–67.7% versus 25.0%; 95% CI: 10.7%–44.9%, respectively) (Supplementary Fig. 2). The median PFS was 4.4 months (95% CI: 2.3–6.2 mo) in patients with 1% to less than 50% tumor PD-L1 expression, 8.1 months (95% CI: 4.3–11.9 mo) in patients with 50% to less than 80% PD-L1 expression, and not estimable (95% CI: 2.0 mo–not estimable) in patients with greater than or equal to 80% PD-L1 expression. In patients with EGFR FISH–positive or –negative tumors, the median PFS was 6.2 months (95% CI: 4.2–11.8 mo) and 4.4 months (95% CI: 4.1–11.9 mo), respectively. Tumor shrinkage occurred irrespective of EGFR FISH status or PD-L1 status (Supplementary Fig. 3A and B).

Safety

Safety was evaluated using the primary analysis (Table 3). Of the 43 patients, 40 (93.0%) had an AE of any grade, of whom 38 (88.4%) had a treatment-related AE (TRAE) attributed to any study treatment. The most common TRAEs of any grade were rash (n = 20 [46.5%]), anemia (n = 18 [41.9%]), and neutropenia (n = 15 [34.9%]). TRAEs attributed to avelumab, cetuximab, gemcitabine, or cisplatin occurred in 20 (46.5%), 33 (76.7%), 30 (69.8%), and 34 patients (79.1%), respectively. A total of 24 patients (55.8%) had a grade 3 or higher TRAE; the most common grade 3 or higher TRAEs are presented in Table 3. Grade 3 or higher TRAEs related to avelumab, cetuximab, gemcitabine, or cisplatin occurred in five (11.6%), 12 (27.9%), 18 (41.9%), and 17 patients (39.5%), respectively. Both patients who switched from cisplatin to carboplatin had grade 3 or higher TRAEs related to carboplatin. TRAEs leading to permanent discontinuation of any treatment

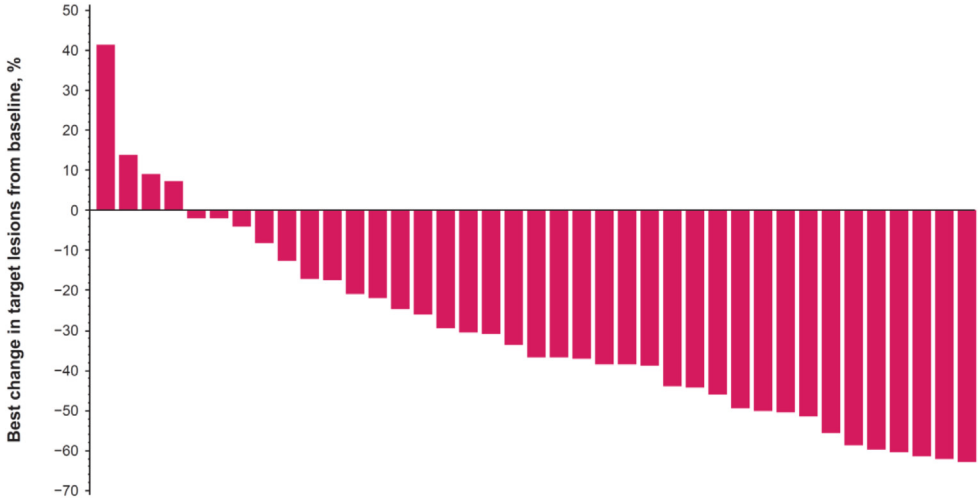

Figure 1. Best change in the sum of target lesions from baseline in assessable patients (data cutoff, November 4, 2020; N = 39).

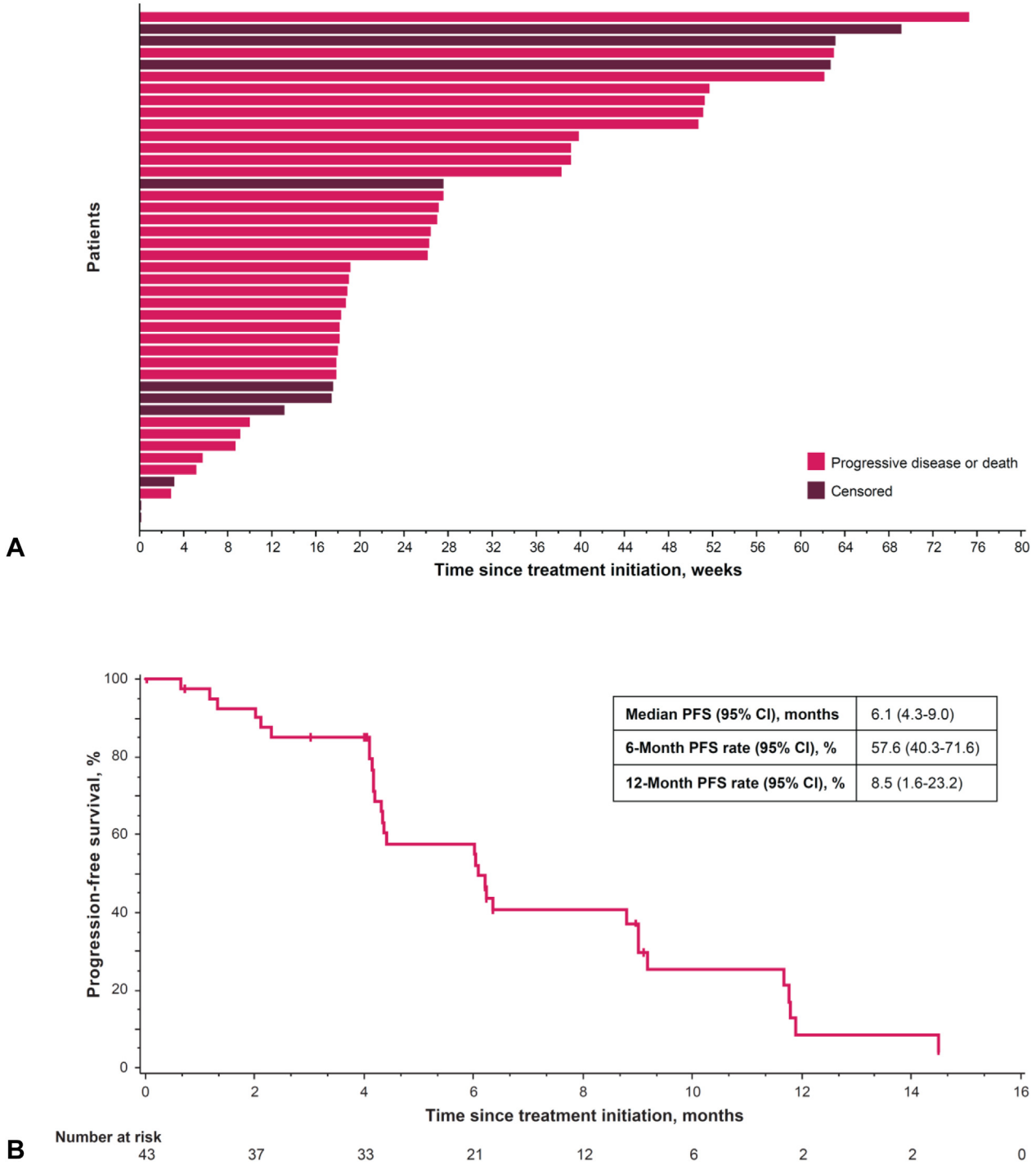

Figure 2. (*A*) Time to PFS per patient and (*B*) Kaplan-Meier analysis of PFS (data cutoff, November 4, 2020; N = 43). CI, confidence interval; PFS, progression-free survival.

occurred in seven patients (16.3%); increased blood creatinine was the most common (n = 2 [4.7%]). TRAEs leading to permanent discontinuation of avelumab, cetuximab, gemcitabine, or cisplatin occurred in two (4.7%), four (9.3%), two (4.7%), and four patients (9.3%), respectively. Nine patients (20.9%) had serious TRAEs that were related to avelumab, cetuximab, gemcitabine, or cisplatin in one (2.3%), three (7.0%), five (11.6%), and six patients (14.0%), respectively; one of two patients had a serious AE related to carboplatin. For AEs of special interest, 10 patients (23.3%) had an immune-related AE, and four patients (9.3%) had an IRR. One patient (2.3%) died owing to a TRAE, which was reported as being of unknown cause and attributed to all

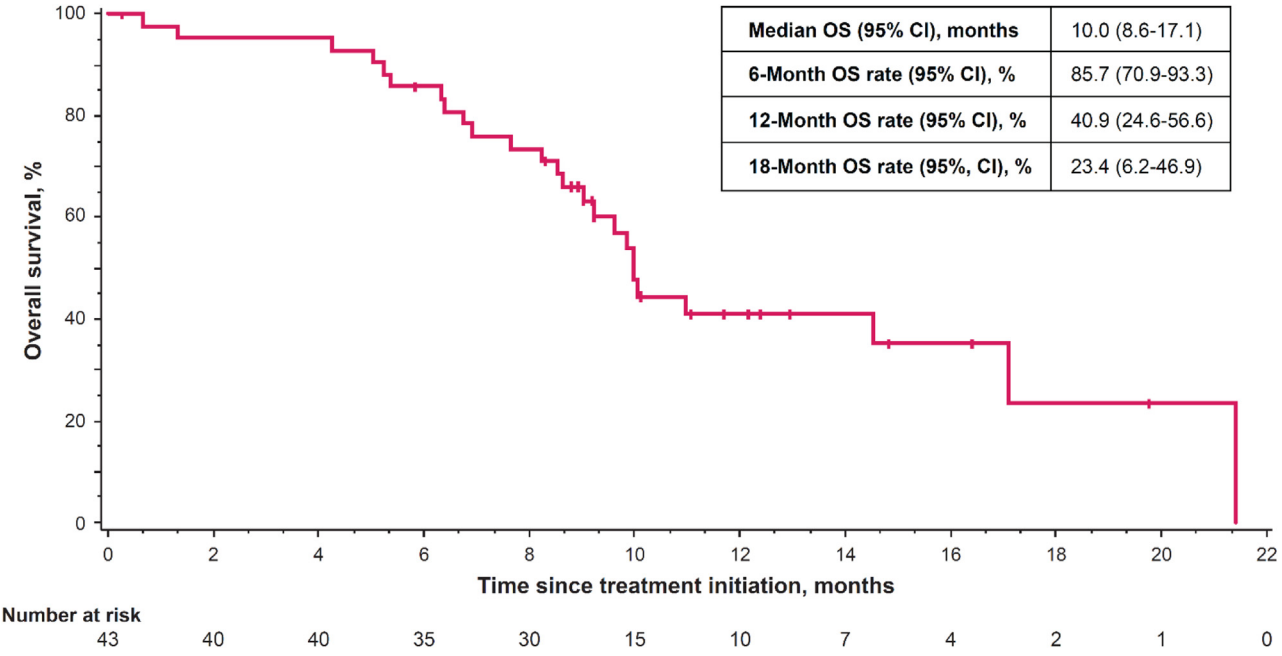

Figure 3. Kaplan-Meier analysis of OS (data cutoff, November 4, 2020; N = 43). CI, confidence interval; OS, overall survival.

Table 3. TRAEs Occurring in At Least Two Patients (Data Cutoff: July 2, 2020; N = 43)

	Any Grade, n (%)	Grade ≥3, n (%)
Rash	20 (46.5)	3 (7.0)
Anemia	18 (41.9)	3 (7.0)
Neutropenia	15 (34.9)	12 (27.9)
Hypomagnesemia	13 (30.2)	4 (9.3)
Nausea	9 (20.9)	0
Thrombocytopenia	9 (20.9)	4 (9.3)
Asthenia	8 (18.6)	1 (2.3)
Vomiting	6 (14.0)	1 (2.3)
ALT increased	4 (9.3)	0
Blood creatinine increased	4 (9.3)	0
Decreased appetite	4 (9.3)	0
Leucopenia	4 (9.3)	1 (2.3)
Dermatitis	3 (7.0)	1 (2.3)
Diarrhea	3 (7.0)	0
Hypocalcemia	3 (7.0)	1 (2.3)
Pyrexia	3 (7.0)	0
Transaminases increased	3 (7.0)	0
Acne	2 (4.7)	0
Amylase increased	2 (4.7)	0
Dermatitis acneiform	2 (4.7)	0
Dry skin	2 (4.7)	0
Dysgeusia	2 (4.7)	0
Fatigue	2 (4.7)	0
Neutrophil count decreased	2 (4.7)	2 (4.7)
Oral candidiasis	2 (4.7)	0
Pneumonitis	2 (4.7)	0
Pruritus	2 (4.7)	0
Stomatitis	2 (4.7)	0

ALT, alanine aminotransferase; TRAE, treatment-related adverse event.

four treatments; the investigator reported that the death was treatment related owing to the inability to exclude causality; however, the underlying cancer was believed to be the most likely cause.

Discussion

This phase 2a study assessed 1L avelumab plus cetuximab, gemcitabine, and cisplatin followed by avelumab plus cetuximab maintenance in 43 patients with advanced squamous NSCLC. A total of 15 patients had a BOR of PR, resulting in a confirmed ORR of 34.9%. The study did not achieve a confirmed ORR of greater than or equal to 45.0%; therefore, the effect of the combination was not considered clinically meaningful. The median PFS was 6.1 months, and the median OS was 10.0 months.

Although cross-trial comparisons should be interpreted with caution, the confirmed ORR in this trial was numerically lower than those reported in phase 3 trials of ICIs in combination with chemotherapy as 1L treatment in advanced squamous NSCLC. In phase 3 trials of chemotherapy plus pembrolizumab (KEYNOTE-407), atezolizumab (IMpower131), sintilimab (anti–PD-1; ORIENT-12), or tislelizumab (anti–PD-1; RATIONALE 307) followed by ICI maintenance, ORRs were 58%, 49%, 45%, and approximately 70%, respectively.[8,9,24,25] However, the ORR reported in a trial of nivolumab in combination with chemotherapy and ipilimumab (anti–CTLA-4; CheckMate 9LA) of 38% was comparable to this study.[10] In addition, similar response rates were reported in phase 3 trials of targeted therapies in

combination with chemotherapy as 1L treatment for advanced NSCLC. In a trial of chemotherapy with or without cetuximab or bevacizumab (anti–vascular endothelial growth factor; Southwest Oncology Group S0819), the ORR in patients with squamous histology was 39%; in a trial of necitumumab (anti–EGFR) plus gemcitabine and cisplatin in patients with squamous NSCLC (SQUIRE), the ORR was 31%.[20,26]

In this trial, the unconfirmed ORR was 53.5%, whereas approximately 19% of patients had an initial response that was unconfirmed, indicating that the DOR was limited. In addition, relatively few patients had tumors with greater than or equal to 50% PD-L1 expression (33%) or EGFR FISH positivity (35%), which are factors associated with response to avelumab and cetuximab in NSCLC, respectively.[21,27] A previous study also found that EGFR FISH status was a predictive factor for response in patients with NSCLC receiving treatment with cetuximab plus chemotherapy.[28] In addition, in the phase 3 trial of chemotherapy with or without cetuximab and/or bevacizumab, ORRs in patients with squamous tumors treated with cetuximab were slightly higher in those with EGFR FISH–positive versus nonpositive tumors (46% versus 36%, respectively).[20] In this study, a numerically higher confirmed ORR was observed in patients with EGFR FISH–positive versus –negative tumors (40% versus 25%, respectively), although the CIs overlapped. In addition, increased PFS was observed in patients with PD-L1–high tumors, consistent with previous trials of ICIs in NSCLC.[3,7,8,14,16,29,30] Slightly improved PFS was also observed in patients with EGFR FISH–positive tumors, consistent with previous trials of cetuximab.[20] However, patient numbers in subgroup analyses were small, hindering interpretation.

The combination regimen assessed in this study had a tolerable safety profile, and no additional safety signals were observed compared with previous trials of avelumab and cetuximab in NSCLC.[14–16,20] Of the 43 patients, 24 (56%) had a grade 3 or higher TRAE.

In conclusion, the treatment regimen of avelumab in combination with cetuximab and chemotherapy as 1L treatment for squamous NSCLC revealed antitumor activity, with no new safety signals. On the basis of a predefined statistical threshold, the combination did not achieve a clinically meaningful treatment effect; however, clinical outcomes were comparable to trials of other targeted therapies with chemotherapy in squamous NSCLC.

CRediT Authorship Contribution Statement

Zoran Andric, Klaus Duecker, Andreas Schroeder, Guelseren Guezel, Fortunato Ciardiello: Conceptualization.

Dongli Zhou: Formal analysis, Data curation.

Zoran Andric, Gabriella Gálffy, Manuel Cobo Dols, Barna Szima, Goran Stojanovic, Marina Petrovic, Enriqueta Felip, David Vicente Baz, Santiago Ponce Aix, Oscar Juan-Vidal, Zsuzsanna Szalai, Gyorgy Losonczy, Antonio Calles Blanco, Reyes Bernabe, Gema García Ledo, Andrés Aguilar Hernández, Klaus Duecker, Dongli Zhou, Andreas Schroeder, Guelseren Guezel, Fortunato Ciardiello: Writing - original draft, Writing - review & editing, Approval of the final draft.

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Data Availability Statement

Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to the healthcare business of Merck KGaA, Darmstadt, Germany's (CrossRef Funder ID: 10.13039/100009945) Data Sharing Policy. All requests should be submitted in writing to the healthcare business of Merck KGaA, Darmstadt, Germany's data sharing portal (https://www.emdgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html). When the healthcare business of Merck KGaA, Darmstadt, Germany has a co-research, co-development, or co-marketing or co-promotion agreement, or when the product has been out-licensed, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, the healthcare business of Merck KGaA, Darmstadt, Germany will endeavor to gain agreement to share data in response to requests.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO*

Clinical and Research Reports at www.jtocrr.org and at 10.1016/j.jtocrr.2022.100461.

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