



HAL
open science

Avelumab Versus Docetaxel in Patients With Platinum-Treated Advanced NSCLC: 2-Year Follow-Up From the JAVELIN Lung 200 Phase 3 Trial

Florian Roisné-Hamelin, Sabrina Pobiega, Kévin Jézéquel, Simona Miron, Jordane Dépagne, Xavier Veaute, Didier Busso, Marie-Hélène Le Du, Isabelle Callebaut, Jean-Baptiste Charbonnier, et al.

► To cite this version:

Florian Roisné-Hamelin, Sabrina Pobiega, Kévin Jézéquel, Simona Miron, Jordane Dépagne, et al.. Avelumab Versus Docetaxel in Patients With Platinum-Treated Advanced NSCLC: 2-Year Follow-Up From the JAVELIN Lung 200 Phase 3 Trial. *Journal of Thoracic Oncology*, 2021, 16 (8), pp.1369-1378. 10.1016/j.jtho.2021.03.009 . hal-03627353

HAL Id: hal-03627353

<https://amu.hal.science/hal-03627353>

Submitted on 2 Aug 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Title: Avelumab vs docetaxel in patients with platinum-treated advanced non-small-cell lung cancer: 2-year follow-up from the JAVELIN Lung 200 phase 3 trial

Keunchil Park, MD, PhD,^a Mustafa Özgüroğlu, MD,^b Johan Vansteenkiste, MD, PhD,^c David Spigel, MD,^d James C.-H. Yang, MD, PhD,^e Hidenobu Ishii, MD,^f Marina Garassino, MD,^g Filippo de Marinis, MD,^h Aleksandra Szczesna, MD,ⁱ Andreas Polychronis, PhD, MBBCh, MRCP,^j Ruchan Uslu, MD,^k Maciej Krzakowski, MD, PhD,^l Jong-Seok Lee, MD,^m Luana Calabrò, MD,ⁿ Osvaldo Arén Frontera, MD,^o Huiling Xiong, PhD,^p Marcis Bajars, MD,^p Mary Ruisi, MD,^p Fabrice Barlesi, MD, PhD^{q,r,*}

^aDivision of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; ^bDepartment of Internal Medicine, Division of Medical Oncology, Cerrahpaşa Medical Faculty, Istanbul University-Cerrahpaşa, Istanbul, Turkey; ^cDepartment of Respiratory Oncology, University Hospital KU Leuven, Leuven, Belgium; ^dSarah Cannon Research Institute, Nashville, Tennessee; ^eDepartment of Medical Oncology, National Taiwan University Cancer Center, Taipei, Taiwan; ^fDepartment of Internal Medicine, Kurume University School of Medicine, Kurume, Japan; ^gThoracic Oncology Unit, Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; ^hThoracic Oncology Division, European Institute of Oncology, IRCCS, Milan, Italy; ⁱDepartment of Lung Diseases, Regional Lung Disease Hospital, Otwock, Poland; ^jDepartment of Medical Oncology, Mount Vernon Cancer Centre, Northwood, Middlesex, United Kingdom; ^kDepartment of Medical Oncology, Ege University Hospital, Izmir, Turkey; ^lCentrum

Onkologii-Instytut im. Marii Skłodowskiej—Curie w Warszawie, Warsaw, Poland;
^mDepartment of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Republic of Korea; ⁿCenter for Immuno-Oncology, Medical Oncology and Immunotherapy, University Hospital of Siena, Siena, Italy; ^oInstituto Nacional del Cáncer, Santiago, Chile; ^pEMD Serono Research & Development Institute, Inc., Billerica, MA, USA; an affiliate of Merck KGaA, Darmstadt, Germany; ^qAix Marseille University, CNRS, INSERM, CRCM, Marseille, France[†];
^rGustave Roussy Cancer Campus, Villejuif, France.

***Corresponding author**

Address for correspondence: Fabrice Barlesi, MD, PhD, Cancer Campus, Institut Gustave Roussy, Villejuif, France. E-mail: Fabrice.BARLESI@gustaveroussy.fr

[†]Affiliation at the time the study was conducted.

Disclosure: Dr. Park has provided advisory or consultancy and speaker services to and received research funding from AstraZeneca; has provided advisory or consultancy and speaker services to Boehringer Ingelheim; has provided advisory or consultancy services to AbbVie, Amgen, Blueprint Medicines, Bristol Myers Squibb, Daiichi Sankyo, Lilly, Loxo Oncology, Merck KGaA, Darmstadt, Germany, Merck Sharp & Dohme, and Ono Pharmaceutical; and has received research funding from AstraZeneca and MSD Oncology. Dr. Vansteenkiste has received honoraria from AstraZeneca, Bristol Myers Squibb, and MSD Oncology; has provided advisory or consultancy services to

AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Merck KGaA, Darmstadt, Germany, MSD Oncology, Novartis, and Roche; and has received institutional research funding from MSD. Dr. Spigel is a member of the ASCO Adjuvant Lung Cancer Guideline Committee; has provided advisory or consultancy services to Aptitude Health, AstraZeneca, Bayer, Bristol Myers Squibb, Celgene, Dracen, EMD Serono, Evelo Therapeutics, Genentech/Roche, GSK, Iksuda Therapeutics, Illumina, Merck & Co., Molecular Templates, Nektar, Novartis, Pfizer, PharmaMar, Seattle Genetics, Takeda, TRIPTYCH Health Partners, TRM Oncology, and Williams and Connolly LLP; has received institutional research funding from Aeglea Biotherapeutics, Astellas, AstraZeneca, BIND Therapeutics, Bristol Myers Squibb, Celgene, Celldex, Clovis Oncology, Daiichi Sankyo, Eisai, EMD Serono, G1 Therapeutics, Genentech/Roche, GRAIL, ImClone Systems, Immunogen, Ipsen, Janssen Oncology, Lilly, MedImmune, Merck & Co., Molecular Partners, Nektar, Neon Therapeutics, Novartis, Takeda, Transgene, and University of Texas Southwestern Medical Center–Simmons Cancer Center; and has received travel, accommodations, and expenses from Amgen, AstraZeneca, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Genentech, GSK, Janssen Oncology, Merck & Co., Novartis, Pfizer, Seattle Genetics, Spectrum, and Takeda. Dr. Yang has received personal fees from Amgen, AstraZeneca, Bayer, Blueprint Medicines, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Chugai Pharmaceutical, Daiichi Sankyo, Eli Lilly, Hansoh Pharmaceuticals, Merck KGaA, Darmstadt, Germany, Merck Sharp & Dohme, Novartis, Ono Pharmaceuticals, Pfizer, Roche/Genentech, Takeda Oncology, and Yuhan Pharmaceuticals. Dr. Garassino has received grants and personal fees from Astra Zeneca, Bayer, Blueprint Medicine,

Bristol-Myers Squibb, Celgene, Eli Lilly, GlaxoSmithKline S.p.A., Incyte, Janssen, MSD, Novartis, Otsuka Pharma, Pfizer, Roche, Sanofi-Aventis and Spectrum Pharmaceuticals; has received grants from Clovis, Exelisis, Ipsen, MedImmune, Merck KGaA, Merck Serono and Tiziana Sciences; has received personal fees from Boehringer Ingelheim, Daiichi Sankyo, Inivata, Mirati Therapeutics, Regeneron Pharmaceuticals, Seattle Genetics and Takeda; and has received non-financial support from Eli-Lilly and MSD. Dr. de Marinis has provided advisory and consultancy services for AstraZeneca, Bristol Myers Squibb, MSD Oncology, Pfizer, and Roche/Genentech. Dr. Polychronis has received personal fees from Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Lilly, Merck Sharp & Dohme, and Roche. Drs. Xiong, Bajars, and Ruisi are employees of EMD Serono Research & Development Institute, Inc., Billerica, MA, USA; an affiliate of Merck KGaA, Darmstadt, Germany; Dr Ruisi also owns stock in Bristol-Myers Squibb. Dr. Barlesi has received honoraria only from AstraZeneca; has received honoraria and provided advisory or consultancy services to AstraZeneca/MedImmune, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Genentech/Roche, Lilly, Merck KGaA, Darmstadt, Germany, MSD Oncology, Novartis, Pfizer, Pierre Fabre, and Takeda; has received institutional research funding from AbbVie, Amgen, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eisai, Innate Pharma, Ipsen, Lilly, Merck KGaA, Darmstadt, Germany, MSD Oncology, Novartis, Pfizer, Pierre Fabre, Roche/Genentech, Sanofi/Aventis, and Takeda; and has received travel, accommodation or expenses from AstraZeneca/MedImmune, Bristol Myers Squibb, MSD Oncology, and Roche/Genentech. The remaining authors declare no conflict of interest.

Abstract

Introduction

In the JAVELIN Lung 200 trial, avelumab (anti-PD-L1 antibody) did not significantly prolong overall survival (OS) vs docetaxel in patients with platinum-treated PD-L1+ NSCLC. We report >2-year follow-up data.

Methods

Patients with stage IIIB/IV or recurrent NSCLC with disease progression following platinum-doublet chemotherapy were randomized 1:1 to avelumab 10 mg/kg every 2 weeks or docetaxel 75 mg/m² every 3 weeks. The primary endpoint was OS in patients with PD-L1+ tumors ($\geq 1\%$ tumor cell expression; IHC 73-10 pharmDx assay).

Results

Of 792 patients, 529 had PD-L1+ tumors (264 vs 265 in the avelumab vs docetaxel arms, respectively). As of March 4, 2019, median duration of follow-up for OS in the PD-L1+ population was 35.4 months in the avelumab arm and 34.7 months in the docetaxel arm; study treatment was ongoing in 25 (9.5%) vs 0 patients, respectively. In the PD-L1+ population, 2-year OS rates (95% CI) with avelumab vs docetaxel were 29.9% (24.5%-35.5%) vs 20.5% (15.6%-25.8%); in $\geq 50\%$ PD-L1+ subgroups, 2-year OS rates were 36.4% (29.1%-43.7%) vs 17.7% (11.8%-24.7%), and in the $\geq 80\%$ subgroup were 40.2% (31.3%-49.0%) vs 20.3% (12.9%-28.8%), respectively. Median duration of response (investigator assessed) was 19.1 months (95% CI: 10.8-34.8) vs 5.7 months (95% CI: 4.1-8.3). Safety profiles for both arms were consistent with the primary analysis.

Conclusions

Although the JAVELIN Lung 200 primary analysis (reported previously) showed that avelumab did not significantly prolong OS vs docetaxel in patients with platinum-treated PD-L1+ NSCLC, post hoc analyses at 2 years of follow-up showed that 2-year OS rates were doubled with avelumab in subgroups with higher PD-L1 expression ($\geq 50\%$ and $\geq 80\%$).

Keywords: Avelumab; PD-L1; Non-small cell lung cancer; Second-line; Phase 3

Introduction

Since 2015, immune checkpoint inhibitors that inhibit the programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) interaction have become established therapeutic options for the treatment of advanced non-small cell lung cancer (NSCLC) based on data from randomized trials of nivolumab, pembrolizumab, and atezolizumab.¹⁻⁴

Avelumab (anti-PD-L1) has been approved in metastatic Merkel cell carcinoma as first-line and above monotherapy, in advanced urothelial carcinoma as first-line maintenance and as second-line therapy following disease progression on platinum-based chemotherapy, and in combination with axitinib as first-line treatment for advanced renal cell carcinoma.^{5, 6}

Avelumab has also shown clinical activity in patients with advanced NSCLC as first-line or second-line treatment in two phase 1 cohorts.^{7, 8} In a subsequent phase 3 open-label trial, JAVELIN Lung 200, avelumab did not significantly improve overall survival (OS; primary endpoint) compared with docetaxel in patients with stage IIIB or IV PD-L1+ (defined as expression on $\geq 1\%$ of tumor cells using the 73-10 PD-L1 assay [Agilent Technologies/Dako, Carpinteria, CA]) NSCLC that had progressed after treatment with platinum-containing doublet chemotherapy.⁹ In the primary analysis, reported after a median follow-up of 18.3 months, median OS in the PD-L1+ population was 11.4 months (95% CI, 9.4-13.9 months) with avelumab vs 10.3 months (95% CI, 8.5-13.0 months) with docetaxel (hazard ratio [HR], 0.90 [96% CI, 0.72-1.12]). However, post hoc analyses suggested that OS was affected by the high frequency of post-study immune checkpoint inhibitor use in the docetaxel arm.¹⁰ Prespecified exploratory analyses from JAVELIN Lung 200 showed longer OS with avelumab vs docetaxel in

patients with tumors with higher PD-L1 expression⁹; median OS in patients with ≥50% PD-L1 expression was 13.6 vs 9.2 months (HR, 0.67 [95% CI, 0.51-0.89]) and in patients with ≥80% PD-L1 expression was 17.1 vs 9.3 months (HR, 0.59 [95% CI, 0.42-0.83]). The ≥80% PD-L1 cut-off for the 73-10 assay is comparable to a tumor proportion score of ≥50% with the 22C3 (pembrolizumab) assay, each identifying approximately 30% of patients with advanced NSCLC^{1, 9, 11}

We report updated data from the JAVELIN Lung 200 study with an additional 16 months of median follow-up (≥24 months in all patients).

Materials and Methods

Study Design and Treatment

JAVELIN Lung 200 is an open-label, multicenter, randomized phase 3 trial assessing avelumab vs docetaxel as second-line treatment in patients with advanced NSCLC. Full eligibility criteria for this trial were reported previously.⁹ Briefly, eligibility criteria included patients with histologically confirmed stage IIIB/IV or recurrent NSCLC with disease progression following platinum doublet treatment with tumor material available for biomarker assessment, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and adequate hematologic, renal, and hepatic function. Patients were not eligible if they had received prior immune checkpoint inhibitor therapy or systemic anticancer treatment after disease progression with platinum-based therapy.

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, and all patients provided written informed consent.

Procedures and Assessments

All procedures, assessments, and statistical methodologies were reported previously.⁹ Patients were randomized 1:1 to receive either avelumab 10 mg/kg every 2 weeks or docetaxel 75 mg/m² every 3 weeks. Allocation was stratified by PD-L1 status (PD-L1+ vs PD-L1-) and NSCLC histology (squamous vs nonsquamous). PD-L1+ status was defined as PD-L1 expression on ≥1% of tumor cells, assessed centrally using the 73-10 assay. No crossover to the avelumab arm was permitted. The primary endpoint was OS, and the primary analysis population was patients with PD-L1+ tumors. Analyses of PD-L1+ subgroups defined by ≥50% and ≥80% expression were prespecified exploratory endpoints. Tumors were assessed via radiographic imaging at baseline, every 6 weeks for the first 12 months, and then every 12 weeks thereafter. In this update, tumor responses were determined by investigator assessment according to Response Evaluation Criteria in Solid Tumors v1.1. Safety was assessed at each treatment visit, and adverse events (AEs) were coded in accordance with Medical Dictionary for Regulatory Activities (MedDRA) v21.1 and graded according to National Cancer Institute Common Terminology Criteria for AEs v4.03. Infusion-related reactions with avelumab were assessed as AEs of special interest and identified according to a prespecified list of MedDRA preferred terms, including infusion-related reaction, drug hypersensitivity, hypersensitivity, type 1 hypersensitivity, and anaphylactic reaction occurring on the day of or the day after the study drug infusion or various signs and

symptoms of infusion-related reaction (including abdominal pain, back pain, chills, dyspnea, flushing, hypotension, pyrexia, urticaria, and wheezing) occurring on the day of the study drug infusion and resolving within 2 days. Immune-related AEs (irAEs) were identified using a prespecified list of MedDRA preferred terms followed by a comprehensive medical review.

Results

Patient Characteristics and Disposition

In total, 792 patients were enrolled (intention-to-treat population) and randomized 1:1 to avelumab or docetaxel (396 per arm). Of these, 529 (66.8%) had PD-L1+ tumors (primary population, defined as expression on $\geq 1\%$ of tumor cells; 264 patients in the avelumab arm and 265 patients in the docetaxel arm).

Patient demographics and disease characteristics were similar between avelumab and docetaxel arms and were reported previously.⁹ Briefly, in the avelumab and docetaxel arms of the PD-L1+ population, 182 (68.9%) vs 185 (69.8%) were male, ECOG PS was 0 in 96 (36.4%) vs 91 (34.3%) and 1 in 168 (63.6%) vs 174 (65.7%), tumor histology was squamous in 88 (33.3%) vs 92 (34.7%) and nonsquamous in 176 (66.7%) vs 173 (65.3%), and smoking status was ever smoker in 220 (83.3%) vs 224 (84.5%), respectively. Of 792 total patients, 315 (39.8%) patients had $\geq 50\%$ PD-L1+ tumors (168 [21.2%] in the avelumab arm and 147 patients [18.6%] in the docetaxel arm) and 226 (28.5%) had $\geq 80\%$ PD-L1+ tumors (120 [15.2%] in the avelumab arm and 106 patients [13.4%] in the docetaxel arm).

At data cutoff (March 4, 2019), median duration of follow-up for OS in the PD-L1+ population was 35.4 months (range, 0.2-45.3 months) for avelumab and 34.7 months (range, 0.03-44.4 months) for docetaxel. In the PD-L1+ population, study treatment was ongoing in the avelumab arm only (25 patients [9.5%]). Reasons for permanent treatment discontinuation (avelumab vs docetaxel arm) were progressive disease (172 [65.2%] vs 153 [57.7%] patients), AE (40 [15.2%] vs 41 [15.5%]), loss to follow-up (0 vs 2 [0.8%]), withdrawal of consent (7 [2.7%] vs 17 [6.4%]), death (15 [5.7%] vs 11 [4.2%]), and other reasons (physician's decision in 2 [0.8%] vs 10 [3.8%], patient's decision in 1 [0.4%] vs 1 [0.4%], and maximum number of docetaxel cycles completed per local practice in 10 [3.8%]). Median duration of treatment was 3.4 months (range, 0.5-42.3 months) with avelumab and 2.8 months (range, 0.7-21.8 months) with docetaxel. In avelumab and docetaxel arms, subsequent immune checkpoint inhibitor was received by 17 patients (6.4%) vs 74 patients (27.9%), respectively. In the docetaxel arm, a higher proportion of patients received subsequent immune checkpoint inhibitor treatment among those with nonsquamous tumors (61/173 [35.3%] vs squamous tumors (13/92 [14.1%]).

Efficacy

In the PD-L1+ population ($\geq 1\%$ expression), median OS with avelumab vs docetaxel was 11.4 months (95% CI, 9.4-13.8 months) vs 10.6 months (95% CI, 8.5-12.9 months), respectively (HR, 0.87 [95% CI, 0.71-1.05]; 1-sided $p=0.0721$) (**Fig. 1A**). Two-year OS rates were 29.9% (95% CI, 24.5%-35.5%) vs 20.5% (95% CI, 15.6%-25.8%), respectively. Of patients who had ≥ 2 -year OS in the PD-L1+ population, 10 of 77

patients (13.0%) in the avelumab arm and 30 of 45 patients (66.7%) in the docetaxel arm received subsequent immune checkpoint inhibitor therapy. The difference in OS increased with increasing PD-L1 expression (**Fig. 1B and 1C**). With avelumab vs docetaxel, 2-year OS rates in the $\geq 50\%$ PD-L1+ subgroup were 36.4% (95% CI, 29.1%-43.7%) vs 17.7% (95% CI, 11.8%-24.7%) and in the $\geq 80\%$ PD-L1+ subgroup were 40.2% (95% CI, 31.3%-49.0%) vs 20.3% (95% CI, 12.9%-28.8%), respectively. Median OS values were consistent with the primary analysis of these subgroups. In the full analysis set (all patients irrespective of PD-L1 status), 2-year OS rates were 26.6% (95% CI, 22.3%-31.1%) in the avelumab arm vs 19.8% (95% CI, 15.9%-24.1%) in the docetaxel arm (**Supplementary Fig. 1**).

OS findings for avelumab vs docetaxel were different between patients with squamous vs nonsquamous NSCLC in the PD-L1+ population (**Supplementary Fig. 2**). In patients with squamous NSCLC, the HR for OS was 0.72 (95% CI, 0.52-1.01), and 2-year OS rates were 31.9% (95% CI, 22.4%-41.9%) with avelumab vs 16.6% (95% CI, 9.6%-25.3%) with docetaxel. In patients with squamous NSCLC with $\geq 50\%$ (n=120) and $\geq 80\%$ (n=80) PD-L1+ tumors, HRs were 0.64 (95% CI, 0.43-0.97) and 0.55 (95% CI, 0.34-0.90), respectively. In patients with nonsquamous NSCLC, the HR for OS was 0.95 (95% CI, 0.75-1.21), and 2-year OS rates were 28.9% (95% CI, 22.3%-35.7%) with avelumab vs 22.5% (95% CI, 16.3%-29.2%) with docetaxel. However, in patients with nonsquamous NSCLC with $\geq 50\%$ (n=195) and $\geq 80\%$ (n=139) PD-L1+ tumors, HRs were 0.67 (95% CI, 0.49-0.93) and 0.67 (95% CI, 0.45-0.99), respectively. Analyses of OS in other subgroups of the PD-L1+ population were consistent with those reported previously (**Figure 2**).⁹ Subgroup analyses in the full analysis set were similar.

In the PD-L1+ population, objective response rates (ORRs) by investigator assessment with avelumab and docetaxel were 18.9% (95% CI, 14.4%-24.2%) vs 10.6% (95% CI, 7.1%-14.9%), respectively. ORRs with avelumab increased with increasing PD-L1 expression (**Fig. 3**). ORRs in the full analysis set were 15.2% (95% CI, 11.8%-19.1%) with avelumab vs 10.6% (95% CI, 7.8-14.1) with docetaxel. Median duration of response by investigator assessment in the avelumab and docetaxel arms in the PD-L1+ population was 19.1 months (95% CI, 10.8-34.8 months) vs 5.7 months (95% CI, 4.1-8.3 months), respectively, and differences were consistent across PD-L1 expression subgroups (**Figs. 3 and 4**). Of responding patients in the PD-L1+ population in the avelumab (n=50) and docetaxel (n=28) arms, proportions with an objective response lasting ≥ 2 years (calculated by Kaplan-Meier analysis) were 44.9% (95% CI, 30.3%-58.5%) in the avelumab arm compared with 4.9% (95% CI, 0.4%-19.5%) in the docetaxel arm. In the full analysis set, median duration of response by investigator assessment in the avelumab and docetaxel arms was 15.4 months (95% CI, 10.6-30.4) vs 5.6 months (95% CI, 4.1-8.3), respectively, and responses lasted ≥ 2 years in 40.6% (95% CI, 27.7%-53.1%) vs 6.1% (95% CI, 1.2%-17.2%) of responders, respectively.

Safety

The overall safety profile of avelumab with long-term follow-up was consistent with the primary analysis. Among all treated patients, AEs (related or unrelated) occurred in 375 of 393 patients (95.4%) in the avelumab arm and 346 of 365 patients (94.8%) in the docetaxel arm (**Table 1 and Supplementary Table 1**). Treatment-related AEs (TRAEs) of any grade occurred in 252 patients (64.1%) in the avelumab arm (1 additional patient

compared with the primary analysis) and 313 patients (85.8%) in the docetaxel arm (identical to the primary analysis). In the avelumab and docetaxel arms, a grade ≥ 3 TRAE occurred in 41 (10.4%) vs 180 (49.3%), respectively, representing 2 additional patients in the avelumab arm compared with the primary analysis. In the avelumab arm, the most common TRAEs of any grade were decreased appetite (34 [8.7%]), asthenia (31 [7.9%]), and fatigue (31 [7.9%]) and of grade ≥ 3 were increased lipase (5 [1.3%]), alanine aminotransferase increased (3 [0.8%]; 1 additional patient vs the primary analysis), γ -glutamyltransferase increased (3 [0.8%]), and pneumonitis (3 [0.8%]). In the docetaxel arm, the most common TRAEs of any grade were alopecia (97 [26.6%]), anemia (69 [18.9%]), and decreased appetite (66 [18.1%]) and of grade ≥ 3 were neutropenia (51 [14.0%]), febrile neutropenia (37 [10.1%]), and decreased neutrophil count (36 [9.9%]), with incidences of these TRAEs unchanged since the primary analysis.

Infusion-related reaction in the avelumab arm using an expanded definition (see Methods for signs and symptoms included) occurred at any grade in 107 patients (27.2%) and at grade ≥ 3 in 6 patients (1.5%), unchanged from the primary analysis. In avelumab-treated patients, irAEs of any grade occurred in 68 patients (17.3%) (**Supplementary Table 2**). The most common irAEs were hypothyroidism (20 [5.1%]), rash (14 [3.6%]), and pneumonitis (9 [2.3%]). Three additional patients had an irAE in this analysis compared with the primary analysis. Newly reported irAEs were blood thyroid stimulating hormone increased, dermatitis acneiform, drug eruption, and skin toxicity, which each occurred in 1 patient each (0.3%). Compared with the primary analysis, rates of the following irAEs were reported in 1 additional patient each:

hypothyroidism, rash, alanine aminotransferase increased, aspartate aminotransferase increased, and blood creatine phosphokinase. Grade ≥ 3 irAEs occurred in 12 patients (3.1%) with avelumab treatment in this analysis, an increase of 1 patient compared with the primary analysis (**Supplementary Table 2**). The only newly reported grade ≥ 3 irAE was aspartate aminotransferase increased (1 [0.3%]). Compared with the primary analysis, rates of the following grade ≥ 3 irAEs were reported in 1 additional patient each: increased alanine aminotransferase and increased blood creatine phosphokinase.

Discussion

Consistent with the primary analysis, 2-year follow-up from the JAVELIN Lung 200 trial showed no improvement in OS with avelumab vs docetaxel in the primary population of patients with PD-L1+ tumors ($\geq 1\%$ cutoff); however, 2-year follow-up data from this trial substantiate the previous finding of markedly increased efficacy for avelumab vs docetaxel in subgroups with higher levels of tumor PD-L1 expression ($\geq 50\%$ and $\geq 80\%$ expression cutoffs). Two-year OS rates for avelumab vs docetaxel in the $\geq 1\%$ population were 29.9% vs 20.5%, whereas 2-year OS rates were doubled in higher PD-L1+ subgroups: 36% vs 18% in the $\geq 50\%$ subgroup and 40% vs 20% in the $\geq 80\%$ subgroup (equivalent to a tumor proportion score of $\geq 50\%$ in pembrolizumab trials¹¹), respectively. Furthermore, in the $\geq 80\%$ subgroup, the ORR was increased by >4-fold for avelumab vs docetaxel (31.7% vs 7.5%, respectively). Of note, more than two-thirds of patients in the $\geq 50\%$ subgroup had $\geq 80\%$ PD-L1 expression, suggesting that the $\geq 80\%$ subgroup may be the main driver of improved efficacy. Randomization of patients in the trial was

stratified by PD-L1 status ($\geq 1\%$ expression) but not by higher PD-L1 expression, which is a limitation of the comparisons between arms in the higher PD-L1+ subgroups.

Several trials of other immune checkpoint inhibitor monotherapies in the first-line and post-platinum NSCLC settings have also reported the greatest efficacy benefits in subgroups with the highest PD-L1 expression.^{1, 2, 12-15} Duration of response was longer with avelumab vs docetaxel irrespective of PD-L1 status (median 19.1 vs 5.7 months in the PD-L1+ population and 15.4 vs 5.6 months in the full analysis set, respectively). The safety profile of avelumab after extended treatment remained consistent with the earlier analysis,¹⁰ including a lower rate of grade ≥ 3 TRAEs vs docetaxel (10.4% vs 49.3%, respectively) and only small increases in AE rates; no new safety signals were identified with prolonged treatment.

Long-term survival in a subset of patients has been reported for other anti-PD-1/PD-L1 agents in the second-line NSCLC treatment setting after 2 to 3 years of follow-up. In the phase 3 KEYNOTE-010 trial, 36-month OS rates for pembrolizumab vs docetaxel in patients with $\geq 50\%$ PD-L1 expression were 35% vs 13%, respectively.¹⁶ In a 2-year updated analysis from the CheckMate 017 and CheckMate 057 phase 3 trials, 2-year OS rates for nivolumab vs docetaxel were 23% vs 8% for squamous NSCLC and 29% vs 16% for nonsquamous NSCLC (both trials included patients with NSCLC unselected for PD-L1 expression).¹³ In an updated analysis from the phase 3 OAK trial, 2-year OS rates for atezolizumab vs docetaxel in patients with $\geq 50\%$ PD-L1 expression (assessed using the Ventana SP142 IHC assay) were 43% vs 17%.¹⁷ OS rates in docetaxel arms across different studies appear to have increased over time, consistent with the increasing availability of immune checkpoint inhibitors as subsequent

treatment.¹⁷ However, direct cross-trial comparison of OS rates should be interpreted with caution due to differences in study designs and patient populations.

In this trial, patients with squamous NSCLC had a nonsignificant trend for longer OS with avelumab vs docetaxel, whereas OS was similar between arms in patients with nonsquamous NSCLC, as noted in the primary analysis. In the docetaxel arm, the proportion of patients who received subsequent immune checkpoint inhibitor treatment was lower in those with squamous vs nonsquamous histology (14% vs 35%).

Since the JAVELIN Lung 200 trial was initiated, use of ICIs as 1L treatment for NSCLC without *EGFR* or *ALK* genomic tumor aberrations, either as monotherapy or within combination regimens, has become standard.¹⁸ A phase 3 trial, JAVELIN Lung 100 (NCT02576574), is assessing avelumab monotherapy as first-line treatment vs platinum-based doublet therapy in patients with PD-L1+ NSCLC. The primary analysis population is patients with high PD-L1–expressing tumors ($\geq 80\%$ expression on tumor cells using the 73-10 assay).¹⁹

In conclusion, 2-year follow-up data from the JAVELIN Lung 200 trial suggested that a subset of patients experienced long-term efficacy benefits with avelumab, which were increased with increasing tumor PD-L1 expression. No new safety signals were observed, and avelumab continued to show a lower rate of TRAEs compared with docetaxel.

Acknowledgements

We thank the patients and their families; the investigators, co-investigators, and study teams at each participating center and at Merck KGaA, Darmstadt, Germany, EMD Serono Research & Development Institute, Inc., Billerica, MA, USA; an affiliate of Merck KGaA, Darmstadt, Germany, and Quintiles (Durham, NC, USA). Medical writing support was provided by Abhijith Thippeswamy of ClinicalThinking and funded by Merck KGaA and Pfizer.

Funding

This study was sponsored by EMD Serono Research & Development Institute, Inc., an affiliate of Merck KGaA, Darmstadt, Germany, as part of an alliance between Merck KGaA and Pfizer. Employees of the sponsor are coauthors of this manuscript, who contributed to the design, execution, and interpretation of the analyses being reported, writing the report, and the decision to submit the article for publication, along with other coauthors.

References

1. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016;387:1540-1550.
2. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017;389:255-265.
3. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015;373:1627-1639.
4. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015;373:123-135.
5. Bavencio (avelumab) Prescribing information. EMD Serono; 2020.
6. Bavencio (avelumab) Summary of product characteristics. Merck KGaA, Darmstadt, Germany; 2020.
7. Gulley JL, Rajan A, Spigel DR, et al. Avelumab for patients with previously treated metastatic or recurrent non-small-cell lung cancer (JAVELIN Solid Tumor): dose-expansion cohort of a multicentre, open-label, phase 1b trial. *Lancet Oncol* 2017;18:599-610.
8. Jerusalem G, Chen F, Spigel D, et al. JAVELIN Solid Tumor: safety and clinical activity of avelumab (anti-PD-L1) as first-line treatment in patients with advanced NSCLC. *J Thorac Oncol* 2017;12:S252.

9. Barlesi F, Vansteenkiste J, Spigel D, et al. Avelumab versus docetaxel in patients with platinum-treated advanced non-small-cell lung cancer (JAVELIN Lung 200): an open-label, randomised, phase 3 study. *Lancet Oncol* 2018;19:1468-1479.
10. Barlesi F, Özgüroğlu M, Vansteenkiste J, et al. Assessing the impact of subsequent checkpoint inhibitor (CPI) treatment on overall survival: Post hoc analyses from the phase III JAVELIN Lung 200 study of avelumab vs docetaxel in platinum-treated locally advanced/metastatic non-small cell lung cancer (NSCLC). *Ann Oncol* 2019;30:v611-v612.
11. Grote HJ, Feng Z, Schlichting M, et al. PD-L1 immunohistochemistry assay comparison studies in non-small cell lung cancer: characterization of the 73-10 assay. *J Thorac Oncol* 2020.
12. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* 2016;375:1823-1833.
13. Horn L, Spigel DR, Vokes EE, et al. Nivolumab versus docetaxel in previously treated patients with advanced non-small-cell lung cancer: two-year outcomes from two randomized, open-label, phase III trials (CheckMate 017 and CheckMate 057). *J Clin Oncol* 2017;35:3924-3933.
14. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet* 2019;393:1819-1830.

15. Spigel D, De Marinis F, Giaccone G, et al. IMpower110: interim overall survival (OS) analysis of a phase III study of atezolizumab (atezo) vs platinum-based chemotherapy (chemo) as first-line (1L) treatment (tx) in PD-L1–selected NSCLC. *Ann Oncol* 2019;30:Abstract LBA78.
16. Herbst RS, Garon EB, Kim DW, et al. Long-term outcomes and retreatment among patients with previously treated, programmed death-ligand 1–positive, advanced non–small-cell lung cancer in the KEYNOTE-010 study. *J Clin Oncol* 2020;38:1580-1590.
17. Fehrenbacher L, von Pawel J, Park K, et al. Updated efficacy analysis including secondary population results for OAK: a randomized phase III study of atezolizumab versus docetaxel in patients with previously treated advanced non-small cell lung cancer. *J Thorac Oncol* 2018;13:1156-1170.
18. NCCN Clinical Practice Guidelines in Oncology. Non-small cell lung cancer. v2.2020.
19. Reck M, Yang C, Postmus PE, et al. JAVELIN Lung 100: updated design of a phase 3 trial of avelumab vs platinum doublet chemotherapy as first-line (1L) treatment for metastatic or recurrent PD-L1 non-small-cell lung cancer (NSCLC). *Ann Oncol* 2017;28:1377TiP.

TABLES

Table 1. Overview of safety in all treated patients: comparison between the updated analysis and the primary analysis

| | Primary analysis (data cutoff: November 22, 2017) | | ≥24-month follow up (data cutoff: March 4, 2019) | |
|--|--|----------------------|---|----------------------|
| | Avelumab (n=393) | Docetaxel (n=365) | Avelumab (n=393) | Docetaxel (n=365) |
| AE (related or unrelated), n (%) | | | | |
| Any grade | 375 (95.4) | 346 (94.8) | 375 (95.4) | 346 (94.8) |
| Grade ≥3 | 201 (51.1) | 247 (67.7) | 209 (53.2) | 247 (67.7) |
| TRAE, n (%) | | | | |
| Any grade | 251 (63.9) | 313 (85.8) | 252 (64.1) | 313 (85.8) |
| Grade ≥3 | 39 (9.9) | 180 (49.3) | 41 (10.4) | 180 (49.3) |
| Serious AE, n (%) | 163 (41.5) | 143 (39.2) | 167 (42.5) | 145 (39.7) |
| Serious TRAE, n (%) | 34 (8.7) | 75 (20.5) | 35 (8.9) | 75 (20.5) |
| AE leading to permanent treatment discontinuation, n (%) | 84 (21.4) | 89 (24.4) | 91 (23.2) | 90 (24.7) |
| TRAE leading to permanent treatment discontinuation, n (%) | 28 (7.1) | 51 (14.0) | 31 (7.9) | 52 (14.2) |
| irAE, n (%) | | | | |
| Any grade | 65 (16.5) | NA | 68 (17.3) | – |
| Grade ≥3 | 11 (2.8) | NA | 12 (3.1) | – |
| Death due to AE, n (%) | 64 (16.3) | 49 (13.4) | 64 (17.3) | 51 (14.0) |
| Death due to TRAE, n (%) | 3 (0.8) | 14 (3.8) | 3 (0.8) | 14 (3.8) |

irAE, immune-related adverse event; TRAE, treatment-related adverse event.

FIGURES LEGENDS

Figure 1. Overall survival (OS) with avelumab vs docetaxel in patients with (A) $\geq 1\%$ PD-L1+ tumors (primary population), (B) $\geq 50\%$ PD-L1+ tumors, and (C) $\geq 80\%$ PD-L1+ tumors

Figure 2. Subgroup analysis of overall survival (OS) in the PD-L1+ population.

ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand 1.

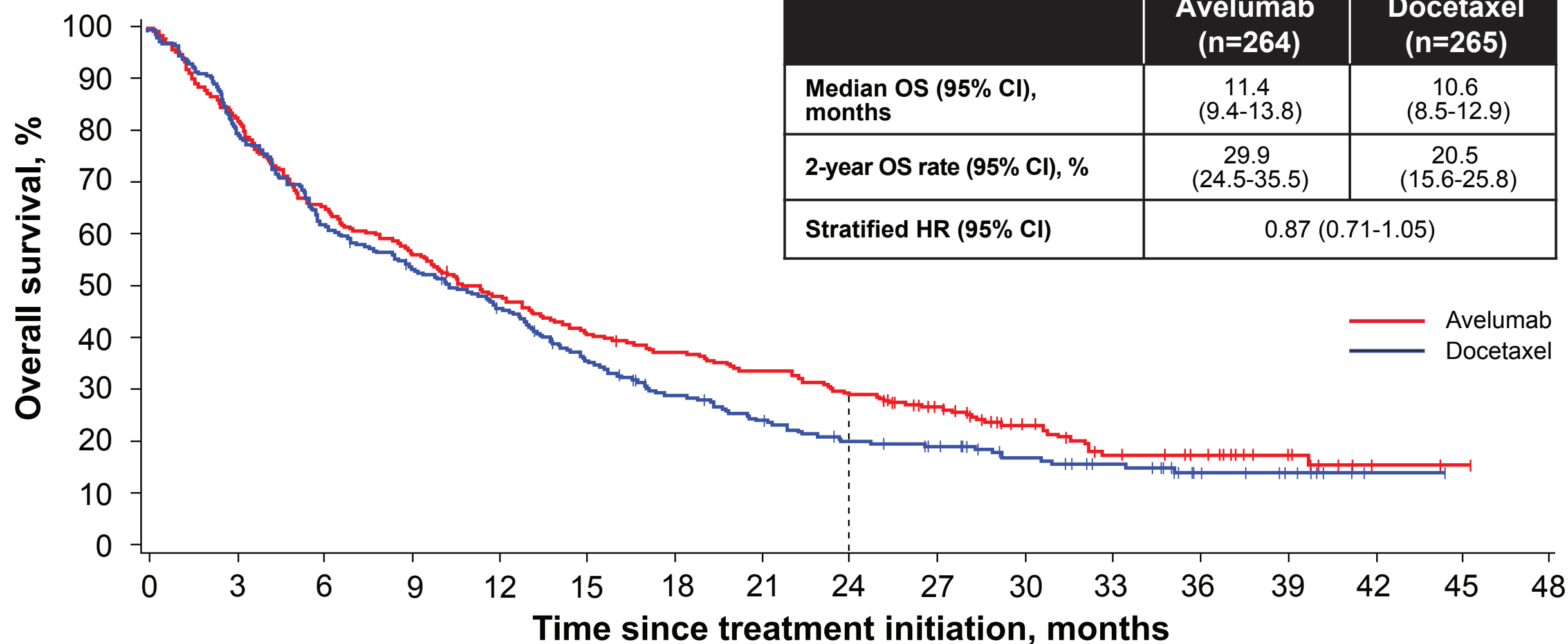
Figure 3. Objective response rate and duration of response by investigator assessment with avelumab vs docetaxel by PD-L1 expression.

PD-L1, programmed death ligand 1.

^a Error bars show 95% CIs; ^b Based on Kaplan-Meier estimates.

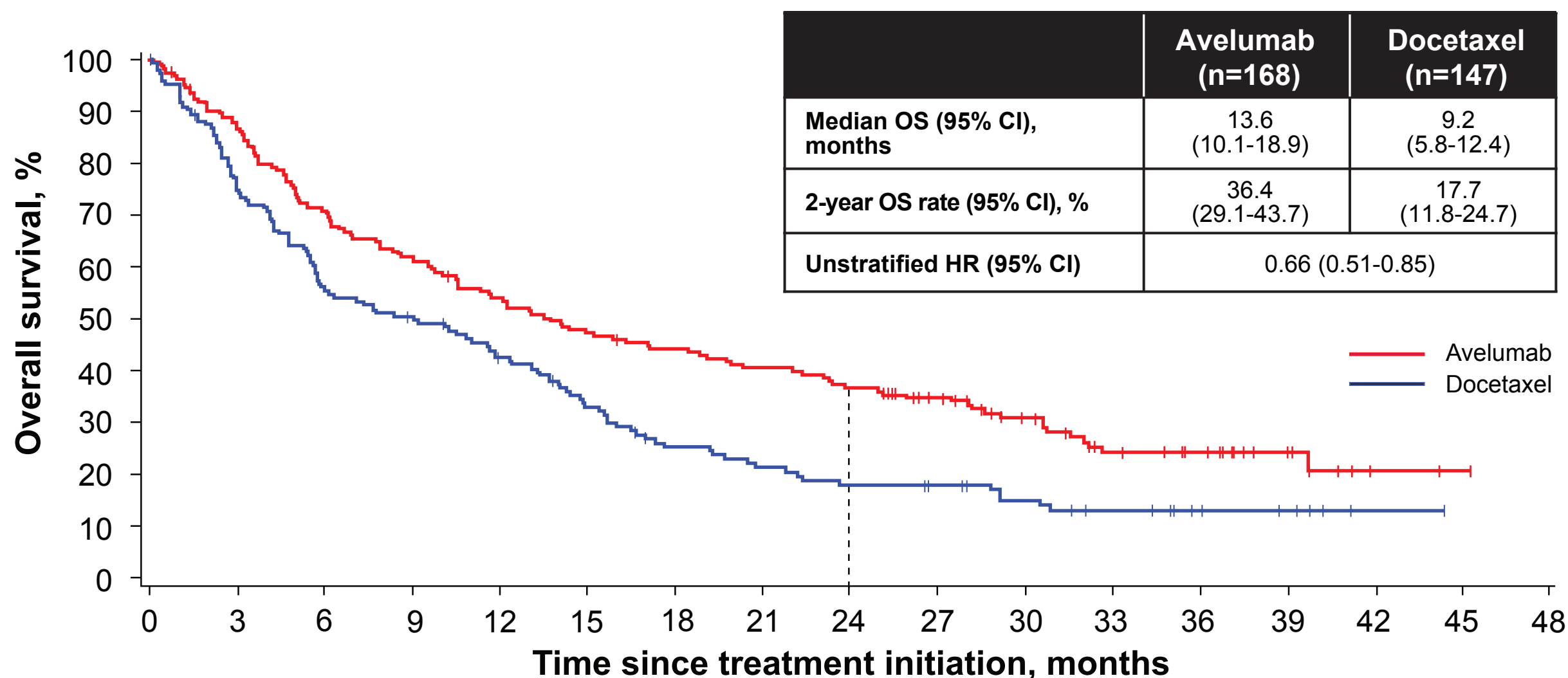
Figure 4. Time to and duration of response with (A) avelumab (n=50) and (B) docetaxel (n=28) by investigator assessment in the PD-L1+ population.

PD-L1, programmed death ligand

A

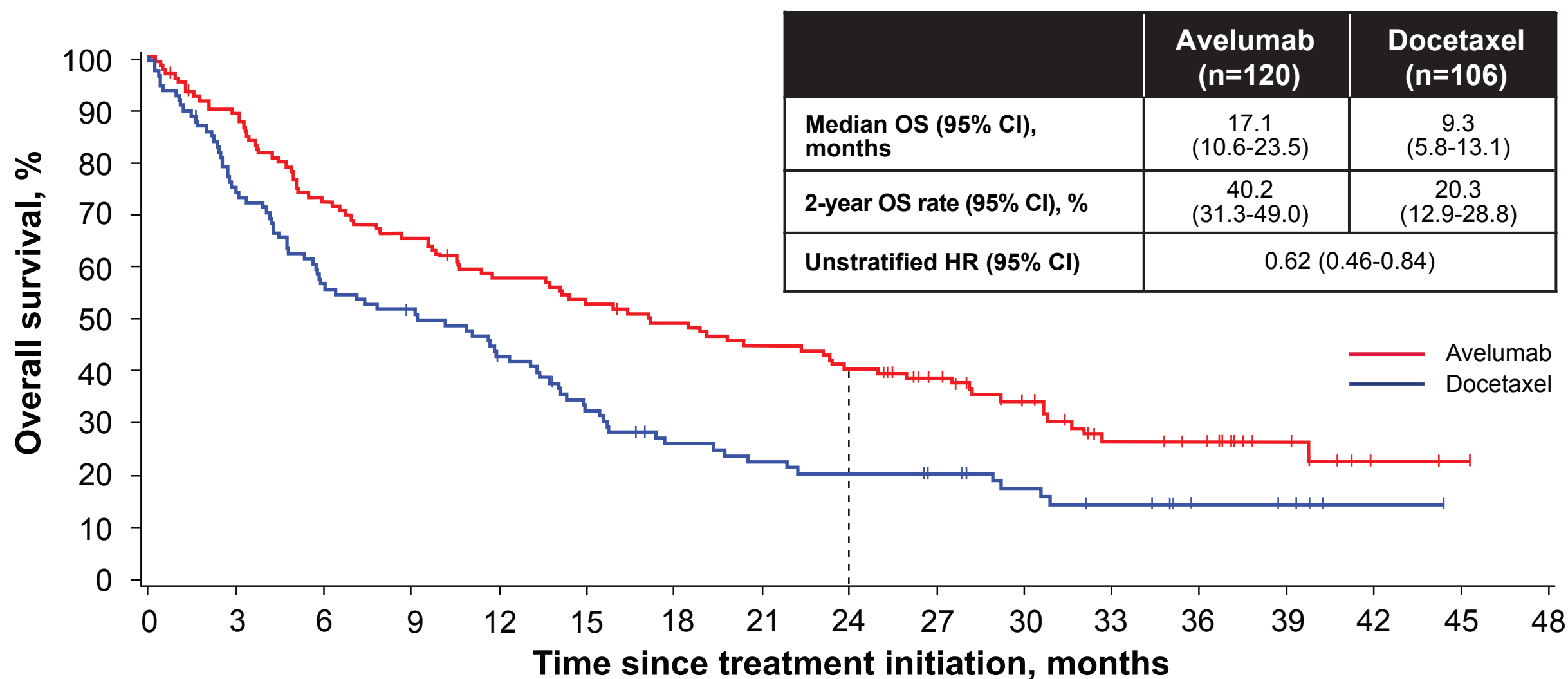
Number at risk

| | | | | | | | | | | | | | | | | | |
|-----------|-----|-----|-----|-----|-----|-----|----|----|----|----|----|----|----|----|---|---|---|
| Avelumab | 264 | 218 | 172 | 150 | 126 | 108 | 97 | 87 | 77 | 59 | 39 | 26 | 21 | 11 | 3 | 2 | 0 |
| Docetaxel | 265 | 210 | 160 | 137 | 115 | 89 | 68 | 56 | 45 | 40 | 29 | 23 | 11 | 7 | 1 | 0 | 0 |

B

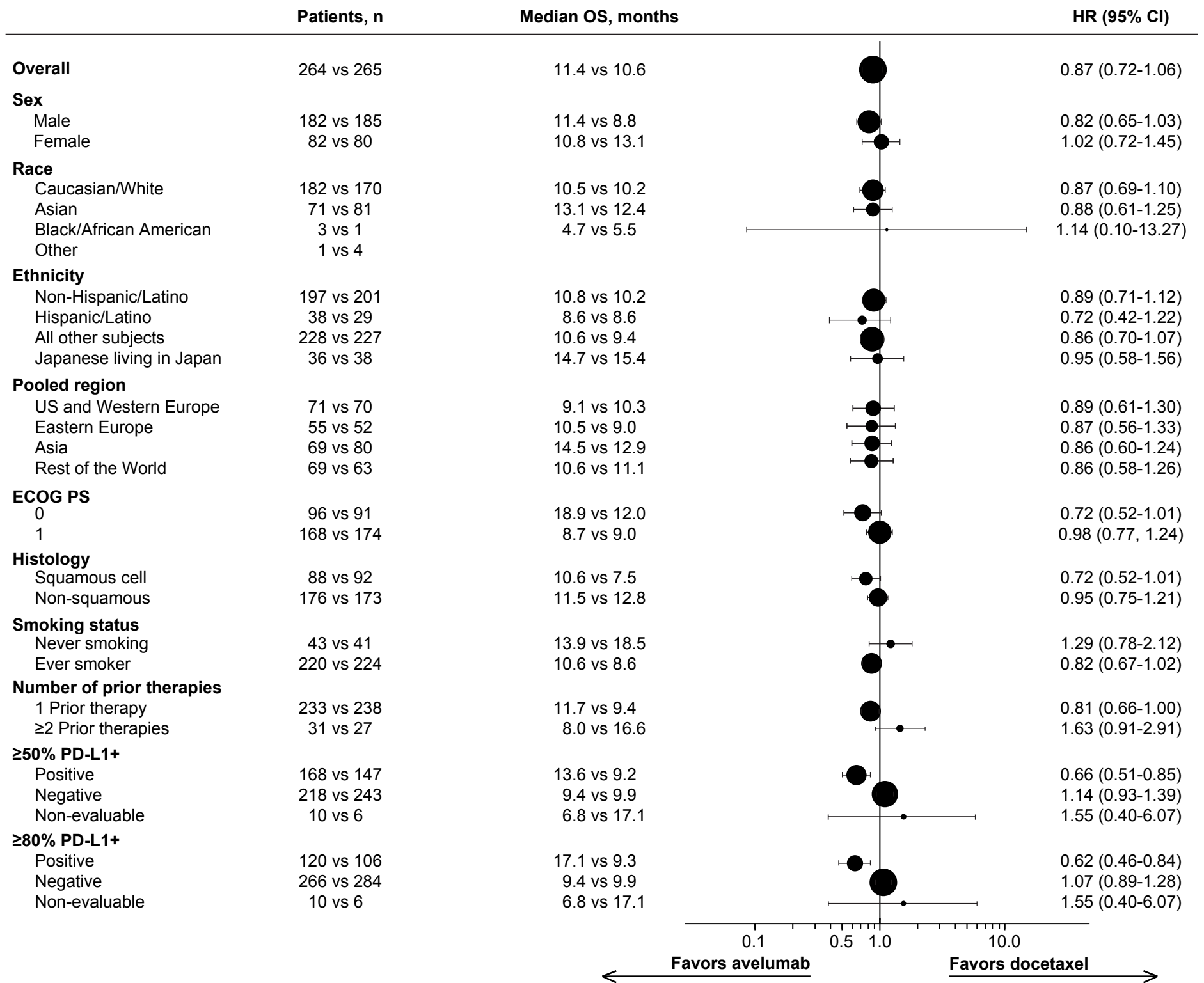
Number at risk

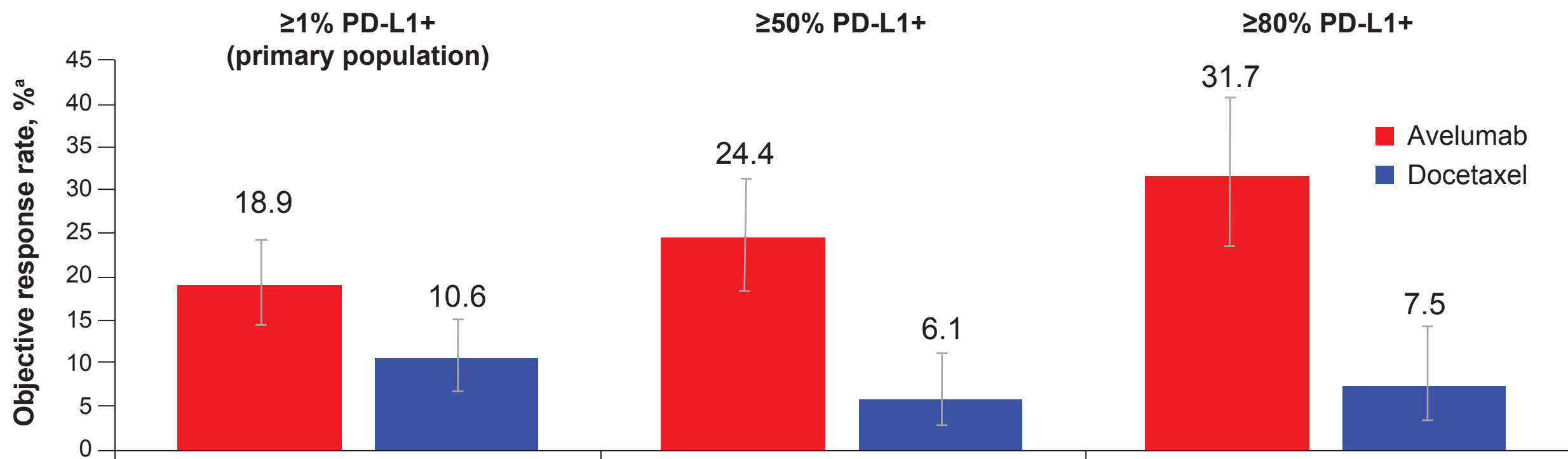
| | | | | | | | | | | | | | | | | | |
|-----------|-----|-----|-----|-----|----|----|----|----|----|----|----|----|----|---|---|---|---|
| Avelumab | 168 | 145 | 117 | 102 | 88 | 78 | 71 | 65 | 59 | 48 | 34 | 23 | 19 | 9 | 2 | 1 | 0 |
| Docetaxel | 147 | 110 | 80 | 71 | 58 | 45 | 31 | 26 | 22 | 20 | 15 | 11 | 7 | 5 | 1 | 0 | 0 |

C

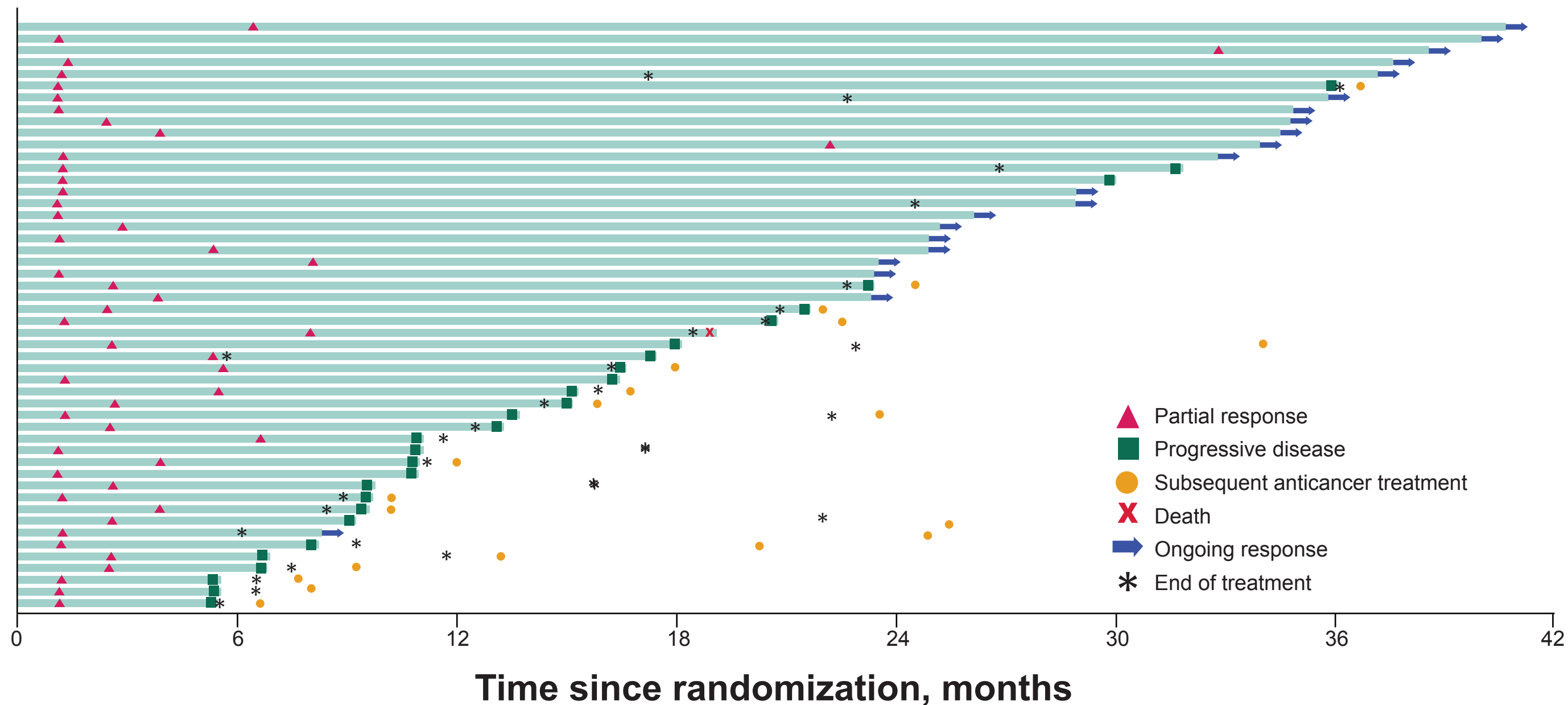
Number at risk

| | | | | | | | | | | | | | | | | | |
|-----------|-----|-----|----|----|----|----|----|----|----|----|----|----|----|---|---|---|---|
| Avelumab | 120 | 105 | 85 | 77 | 67 | 62 | 56 | 51 | 46 | 38 | 28 | 18 | 16 | 8 | 2 | 1 | 0 |
| Docetaxel | 106 | 77 | 58 | 52 | 42 | 32 | 23 | 20 | 18 | 16 | 12 | 9 | 5 | 4 | 1 | 0 | 0 |





| | Avelumab (n=264) | Docetaxel (n=265) | Avelumab (n=168) | Docetaxel (n=147) | Avelumab (n=120) | Docetaxel (n=106) |
|--|------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Odds ratio for objective response rate (95% CI) | 1.98 (1.20-3.26) | | 4.95 (2.31-10.59) | | 5.68 (2.51-12.85) | |
| Responding patients, n | 50 | 28 | 41 | 9 | 38 | 8 |
| Median duration of response (95% CI), months | 19.1 (10.8-34.8) | 5.7 (4.1-8.3) | 19.4 (10.8-34.8) | 6.9 (2.8-22.3) | 19.4 (10.8-34.8) | 7.2 (2.8-22.3) |
| Duration of response ≥1 year (95% CI), %^b | 60.8 (45.6-73.0) | 14.8 (4.7-30.4) | 62.8 (46.0-75.7) | 22.2 (3.4-51.3) | 62.5 (45.1-75.9) | 25.0 (3.7-55.8) |
| Duration of response ≥2 years (95% CI), %^b | 44.9 (30.3-58.5) | 4.9 (0.4-19.5) | 46.4 (30.2-61.1) | 0 | 45.5 (29.0-60.6) | 0 |

A**Patients****B****Patients**