ORIGINAL ARTICLE

Clinical Activity, Tolerability, and Long-Term Follow-Up of Durvalumab in Patients With Advanced NSCLC

Scott J. Antonia, MD,[a,*] Ani Balmanoukian, MD,[b] Julie Brahmer, MD,[c] Sai-Hong I. Ou, MD, PhD,[d] Matthew D. Hellmann, MD,[e] Sang-We Kim, MD, PhD,[f] Myung-Ju Ahn, MD,[g] Dong-Wan Kim, MD, PhD,[h] Martin Gutierrez, MD,[i] Stephen V. Liu, MD,[j] Patrick Schöffski, MD, MPH,[k] Dirk Jäger, MD,[l] Rahima Jamal, MD, BSc, FRCPC,[m] Guy Jerusalem, MD, PhD,[n] Jose Lutzky, MD, FACP,[o] John Nemunaitis, MD,[p] Luana Calabrò, MD,[q] Jared Weiss, MD,[r] Shirish Gadgeel, MD,[s] Jaishree Bhosle, MD,[t] Paolo A. Ascierto, MD,[u] Marlon C. Rebelatto, PhD,[v] Rajesh Narwal, PhD, MS,[v] Meina Liang, BS,[v] Feng Xiao, BS,[v] Joyce Antal, MS,[v] Shaad Abdullah, MD, FACP,[v] Natasha Angra, PharmD,[v] Ashok K. Gupta, MBBS, MD, PhD,[v] Samir N. Khleif, MD,[w] Neil H. Segal, MD, PhD[e]

[a]*Moffitt Cancer Center, Tampa, Florida*
[b]*The Angeles Clinic and Research Institute, Los Angeles, California*
[c]*Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland*
[d]*Department of Medicine, Division of Hematology-Medical Oncology, University of California Irvine School of Medicine, Irvine, California*
[e]*Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York*
[f]*Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*
[g]*Sunkyunkwan University School of Medicine, Samsung Medical Center, Seoul, South Korea*

***Corresponding author.**

Disclosure: Dr. Antonia has participated on advisory boards with Bristol-Myers Squibb, Novartis, Merck, CBMG, Boehringer Ingelheim, FLX Bio, Nektar, AstraZeneca, Memgen, and Venn. Dr. Balmanoukian has received personal fees from AstraZeneca, Genentech, Merck, and Bristol-Myers Squibb. Dr. Brahmer has received grants from Bristol-Myers Squibb and AstraZeneca; and has received personal fees from AstraZeneca, Merck, Bristol-Myers Squibb, and Genentech. Dr. Ou is a member of the scientific advisory board and has stock ownership with TP Therapeutics; and has received personal fees from AstraZeneca, Pfizer, Roche, Foundation Medicine, Inc., and Takeda/ARIAD. Dr. Hellmann has received grants from Bristol-Myers Squibb; has received personal fees from AstraZeneca, Merck, Bristol-Myers Squibb, Genentech/Roche, Janssen, Nektar, Syndax, Mirati, and Shattuck Labs; and holds a licensed patent filed by MSK related to the use of tumor mutation burden to predict response to immunotherapy (PCT/US2015/062208). Dr. D.W. Kim has received personal fees from Novartis. Dr. Gutierrez has received personal fees from Bristol-Myers Squibb, Merck, Eli Lilly, Guardant 360, Esanex, Foundation Medicine, and AstraZeneca. Dr. Liu has received grants from AstraZeneca, Bayer, Blueprint, Clovis, Corvus, Esanex, Genentech/Roche, Lilly, Merck, Molecular Partners, OncoMed, Pfizer, and Threshold; and has received personal fees from AstraZeneca, Genentech/Roche, Lilly, Pfizer, Bristol-Myers Squibb, Celgene, Heron, Regeneron, Taiho, and Takeda/Ariad. Dr. Schöffski has received grants from Blueprint Medicines, Boehringer Ingelheim, Cobiores nv, Eisai, Eli Lilly, Exelixis, G1Therapeutics, Novartis, PharmaMar, and Plexxikon; and has received personal fees from 6th Element Capital, Adaptimmune, Amcure, Blueprint Medicines, Bristol-Myers Squibb, Deciphera, Eisai, Eli Lilly, Ellipses Pharma, Epizyme Pharma, Genzyme, Ipsen, Loxo Oncology, Medpace, Merck, Nektar, Piqur Therapeutics, Plexxikon, PharmaMar, and AstraZeneca. Dr. Jamal has received grants from AstraZeneca. Dr. Jerusalem has received grants from Novartis and Roche; and has received personal fees from Novartis, Roche, Pfizer, Lilly, Celgene, Amgen, Bristol-Myers Squibb, Puma Technology, AstraZeneca, Daiichi Sankyo, and AbbVie. Dr. Lutzky has received personal fees from Bristol-Myers Squibb. Dr. Nemunaitis has received personal fees from AstraZeneca. Dr. Weiss has received grants from AstraZeneca, Celgene, Merck, and Novartis; and has received personal fees from AstraZeneca, Celgene, Pfizer, Regeneron, and EMD Serono. Dr. Gadgeel has received personal fees from AstraZeneca, Genentech/Roche, AbbVie, Takeda, and Bristol-Myers Squibb. Dr. Bhosle has received nonfinancial support from AstraZeneca. Dr. Ascierto has served on advisory boards and/or provided consultancy for Bristol-Myers Squibb, Roche/Genentech, MSD, Array, Novartis, Merck Serono, Pierre Fabre, Incyte, Genmab, Newlink Genetics, AstraZeneca, Syndax, Sun Pharma, Sanofi, Idera, and Ultimovacs, and has received research funding from Bristol-Myers Squibb, Roche/Genentech, and Array. Drs. Rebelatto, Narwal, and Liang are employees of AstraZeneca, and own stock in AstraZeneca. Drs. Xiao, Antal, Abdullah, and Angra are employees of AstraZeneca. Dr. Gupta is an employee of AstraZeneca, owns stock in AstraZeneca and Bristol-Myers Squibb, and holds a patent for the use of immunotherapy in the treatment of cancer issued by Bristol-Myers Squibb. Dr. Khleif is a member of NewLink SAB and has a preclinical research agreement with Genentech. Dr. Segal has received grants from Roche/Genentech, Pfizer, Merck, Bristol-Myers Squibb, MedImmune/AstraZeneca, and Incyte; and has received personal fees from Roche/Genentech, Merck, Bristol-Myers Squibb, MedImmune/AstraZeneca, Boehringer Ingelheim, Pfizer, Pieris, PsiOxus, Synlogic, Aduro, Kyn Therapeutics, Pure Tech Ventures, Horizon Pharma, EMD Serono, Gritstone Oncology, Chugai, TRM Oncology, and IFM Therapeutics. The remaining authors declare no conflict of interest.

Address for correspondence: Scott J. Antonia, MD, Moffitt Cancer Center, Tampa, Florida 33612. E-mail: Scott.Antonia@Moffitt.org

ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2019.06.010

[h]Seoul National University Hospital, Seoul, South Korea
[i]Hackensack University Medical Center, Hackensack, New Jersey
[j]Georgetown University Medical Center, Washington, DC
[k]University Hospitals Leuven, Leuven, Belgium
[l]Nationales Centrum für Tumorerkrankungen Heidelberg, Heidelberg, Baden-Württemberg, Germany
[m]Hôpital Notre-Dame, CHUM, University of Montréal, CHUM Research Center (CRCHUM), Montreal, Quebec, Canada
[n]CHU Sart Tilman Liège and Liège University, Liège, Belgium
[o]Mount Sinai Comprehensive Cancer Center, Miami Beach, Florida
[p]University of Toledo College of Medicine and Life Sciences, Toledo, Ohio
[q]Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy
[r]University of North Carolina Hospitals, Chapel Hill, North Carolina
[s]University of Michigan, Ann Arbor, Michigan
[t]Royal Marsden NHS Foundation Trust, London, United Kingdom
[u]Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Napoli, Italy
[v]AstraZeneca, Gaithersburg, Maryland
[w]Georgetown Lombardi Comprehensive Cancer Center, Georgetown University Medical School, Washington, DC

Received 4 December 2018; revised 28 May 2019; accepted 10 June 2019
Available online - 20 June 2019

ABSTRACT

Introduction: Durvalumab is a selective, high-affinity human immunoglobulin G1 monoclonal antibody that blocks programmed cell death ligand 1 (PD-L1) binding to programmed death 1. Here we report safety and clinical activity in the NSCLC cohort of a phase I/II trial that included multiple tumor types (Study 1108; NCT01693562).

Methods: Patients with stage IIIB–IV NSCLC (squamous or nonsquamous) received durvalumab 10 mg/kg every 2 weeks for 12 months or until confirmed progressive disease or unacceptable toxicity. Primary objectives were safety and antitumor activity. Tumoral PD-L1 expression was assessed using the VENTANA SP263 Assay. Responses were assessed by blinded independent central review (Response Evaluation Criteria in Solid Tumors v1.1). Adverse events were graded according to National Cancer Institute's Common Terminology Criteria for Adverse Events (v4.03).

Results: Of 304 patients, 79.0% were previously treated. Confirmed objective response rate was 21.8% in patients with greater than or equal to 25% PD-L1 expression and 6.4% in those with less than 25%; 25.9% in first-line patients and 12.7% in previously treated patients; and 14.0% in squamous and 16.7% in nonsquamous disease. Median overall survival was 12.4 months and median progression-free survival was 1.7 months; both were numerically longer in the PD-L1 greater than or equal to 25% group than in the PD-L1 less than 25% group (overall survival 16.4 versus 7.6 months, respectively; progression-free survival 2.6 versus 1.4 months, respectively). Treatment-related adverse events occurred in 57.2%, were grade 3/4 in 10.2%, and led to discontinuation in 5.6%. One patient (0.3%) died of treatment-related pneumonia with underlying pneumonitis.

Conclusions: Durvalumab was clinically active irrespective of histology in this mostly pretreated population, with a manageable safety profile. Response rates and survival appeared to be enhanced in patients with greater tumoral PD-L1 expression.

Keywords: NSCLC; Safety; Efficacy; Immunotherapy; Durvalumab

Introduction

Checkpoint inhibitors targeting the programmed cell death ligand 1 (PD-L1)/programmed cell death 1 (PD-1) pathway confer improvements in survival over standard-of-care therapies in NSCLC and other tumor types, and are now approved in several countries.[1-7]

PD-L1 binds to two regulatory receptors on T cells: PD-1 and CD80 (B7.1). Binding of PD-L1 to PD-1 inhibits T-cell proliferation and binding of PD-L1 to CD80 blocks T-cell activation, hindering antitumor responses.[8,9] Durvalumab is a selective, high-affinity human immunoglobin G1 monoclonal antibody that inhibits PD-L1 binding to PD-1 (concentration that inhibits 50% [IC_{50}]: 0.1 nM) and CD80 (IC_{50}: 0.04 nM).[10] It was shown to be tolerable and clinically active in urothelial carcinoma (UC), hepatocellular carcinoma, head and neck squamous cell carcinoma, gastroesophageal cancer, and SCLC in a phase I/II, global, multicenter, open-label, first-in-human study (Study 1108; NCT01693562) and in a phase 3 trial of patients with stage III, locally advanced, unresectable NSCLC (PACIFIC; NCT02125461).[6,11-15] It has since been approved in the United States for locally advanced or metastatic UC after platinum-based chemotherapy, and in the United States and European

Union for unresectable stage III NSCLC that has not progressed following concurrent chemoradiotherapy; the European Union approval is restricted to patients with PD-L1 expression greater than or equal to 1%.[16,17]

This report describes the safety and clinical activity of durvalumab in patients with NSCLC from the dose-escalation and dose-expansion phases of Study 1108 (described here as the NSCLC 10 mg/kg-every-2-weeks cohort) (Supplementary Fig. 1). Safety in multiple tumor types is also summarized for the dose-exploration phase (20 mg/kg every 4 weeks) and the full 1108 study population. Pharmacokinetics (PK), pharmacodynamics, and immunogenicity results are presented for the full 1108 study population.

Methods

Study Design

Patients in the dose-escalation phase had NSCLC (squamous or nonsquamous), melanoma, colorectal cancer, or renal cell carcinoma. They received durvalumab every 2 weeks or every 3 weeks via intravenous infusion for 12 months or until confirmed progressive disease, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or discontinuation of treatment for other reasons. Following this phase, tumor-specific expansion cohorts were enrolled using 10 mg/kg every 2 weeks. An additional dose of 20 mg/kg every 4 weeks was evaluated in patients with melanoma, nonsquamous and squamous NSCLC, pancreatic adenocarcinoma, gastroesophageal cancer, hepatocellular cancer, head and neck squamous cell carcinoma, and triple-negative breast cancer in the dose-exploration phase.

In the event of confirmed progressive disease during the 12-month treatment period, patients could continue receiving durvalumab in the absence of clinical deterioration and if investigators deemed that they would continue to benefit. Patients who achieved and maintained disease control or clinical benefit through to the end of the 12-month treatment period entered follow-up. Upon evidence of progressive disease during follow-up, patients were offered retreatment with durvalumab at the dose and schedule previously received for up to another 12 months. Further retreatment was not permitted. Patients who had confirmed disease progression during the 12-month initial treatment or retreatment period and could not continue to receive durvalumab entered follow-up for 90-day tolerability assessments and survival evaluation.

This study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Council on Harmonization guidelines on Good Clinical Practice, any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee that has approved this study to be conducted in its territory. The study protocol was reviewed and approved by the Institutional Review Boards or Ethics Committees of the participating centers, and informed consent was obtained.

Assessment

The primary objective of the dose-escalation phase was to establish the maximum tolerated dose or optimal biological dose, based on dose-limiting toxicities, safety, and related endpoints, including PK, pharmacodynamics, and immunogenicity. The primary objectives of the dose-expansion phase were safety based on adverse events (AEs), serious AEs (SAEs), laboratory evaluations, and physical examinations, and antitumor activity in the NSCLC and UC cohorts. Secondary objectives included clinical activity in tumor types other than UC and NSCLC, as well as PK and immunogenicity in all tumor types. The primary objective for the dose-exploration cohort was safety, evaluated as for the expansion phase.

Assessments of antitumor activity included objective response rate (ORR), disease control rate greater than or equal to 24 weeks, duration of response, and progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors version 1.1 guidelines, as well as overall survival (OS).[18] Modifications to Response Evaluation Criteria in Solid Tumors guidelines (confirmation of progressive disease within 4 weeks of first documentation) were made to discourage early discontinuation and provide a more complete evaluation of antitumor activity. Response was assessed by blinded independent central review (BICR). Disease assessments were performed at baseline, and at 6, 12, and 16 weeks, and every 8 weeks thereafter.

Assessment of AEs and SAEs, physical examinations, vital sign measurements, and laboratory evaluations were performed at baseline and at regular intervals throughout the study. AEs were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events v4.03.

Eligibility Criteria

Patients in all study phases and cohorts were required to be 18 years old or older and have an Eastern Cooperative Oncology Group performance status of 0 or 1, with adequate organ and marrow function. Patients were eligible if they had received any number of prior therapies, or if they were refractory to a standard therapy, or if there was no standard therapy for their solid tumor. Where an approved first-line treatment was available, patients must have been ineligible for, intolerant of, had declined, or progressed on treatment. They were ineligible if they had previously experienced any

prior grade greater than or equal to 3 immune-mediated adverse event (imAE) while receiving immunotherapy, had prior exposure to any anti–PD-1 or anti–PD-L1 antibody or had any active or prior documented autoimmune disease within the past 2 years, or had untreated central nervous system metastases.

Patients in the NSCLC cohorts had histologically or cytologically confirmed stage IIIB–IV squamous or nonsquamous disease. They were enrolled according to line of therapy for advanced and metastatic disease; those with no history of chemotherapy or systemic antineoplastic therapy for advanced disease (outside of the neoadjuvant or adjuvant setting) were recruited to the first-line cohort. Patients who experienced disease progression or recurrence following one prior platinum-based doublet chemotherapy, or for patients with sensitizing *EGFR* mutations or ALK receptor tyrosine kinase (*ALK*) rearrangements, following either a tyrosine kinase inhibitor (TKI) therapy or prior platinum-based doublet chemotherapy, were recruited to the second-line cohort. For third-line or greater, patients who had experienced disease progression or recurrence after both a platinum-doublet based chemotherapy regimen and at least one additional systemic therapy for advanced disease were recruited; for patients with sensitizing *EGFR* mutations or *ALK* rearrangements, the additional therapy must have included a TKI therapy. Within each cohort, patients were grouped according to tumor histology (squamous or nonsquamous) and PD-L1 expression level in baseline tumor samples. Initially, patients were enrolled regardless of PD-L1 expression. Tumor samples were used to develop an immunohistochemical assay to determine PD-L1 expression (SP263 assay; Ventana Medical Systems, Inc., Oro Valley, Arizona). After assay validation, protocol amendments in June and November 2013 specified enrichment for patients with PD-L1 greater than or equal to 25% expression, defined as greater than or equal to 25% of tumor cell membranes staining positive for PD-L1 at any intensity. This cutoff was chosen based on a number of considerations, including the prevalence of PD-L1 expression in the population, ease of scoring by pathologists, optimizing for higher negative predictive value, and delineating between responders and nonresponders.[19] In November 2014, another protocol amendment required that all remaining nonsquamous patients have greater than or equal to 25% PD-L1 expression. Both fresh biopsy specimens and archival tumor samples were used for measurement of PD-L1 status; in the case of multiple specimens, baseline PD-L1 expression from the most recent tumor sample (before first dose of study treatment) was used.

PK and Pharmacodynamics

Soluble PD-L1 (sPD-L1) was measured at dose 1, dose 2, and then every 12 weeks starting at dose 3. Serum levels of durvalumab and sPD-L1 not bound to durvalumab were measured using validated immunoassays. The sPD-L1 method used a sandwich format and electrochemiluminescent detection system. sPD-L1 was captured with antibody 2.7A4, which binds to a competing epitope of durvalumab, and detected with a mouse anti–PD-L1 antibody. The immunogenic potential of durvalumab was assessed with a tiered approach including screening, confirmation, titering, anti-triple mutation specificity, and neutralizing activity. Validated immunoassays were used for these assessments. Potential markers of immune activation, including CD4+Ki67+ and CD8+Ki67+ lymphocytes, were evaluated in peripheral blood samples at baseline and following treatment with durvalumab using a validated flow cytometry-based method.

Statistical Analysis

The data analyses were conducted using the SAS System (SAS Institute, Inc., Cary, North Carolina) version 9.3 or above in Unix (Sun OS) environment. All SAS programs used to generate analytical results were developed and validated according to AstraZeneca SAS programming standards and AstraZeneca SAS validation procedures.

Across the total Study 1108 population, the as-treated population was defined as all patients who received any dose of durvalumab. Among NSCLC patients in the escalation and expansion phases who received 10 mg/kg (described as the NSCLC 10-mg/kg-every-2-weeks cohort), the full analysis set (FAS) was defined as patients with measurable disease at baseline per BICR with 24 weeks or more of follow-up by the data cutoff. Within the NSCLC 10-mg/kg-every-2-weeks cohort, planned enrollment specified a minimum of approximately 110 patients with nonsquamous histology, including approximately 10 who were treatment-naive, 20 who had received one prior line of therapy, and 80 who had received at least two prior lines of therapy. Up to 30 additional patients could have been recruited to each of the first-line and second-line groups. For patients with squamous histology, planned enrollment specified a minimum of approximately 170 patients, including approximately 10 who were treatment-naive, 80 who had received one prior line of therapy, and 80 who had received at least two prior lines of therapy. Up to 30 additional patients could have been recruited to the first-line therapy group. The sample size of 80 patients each as third-line or greater therapy and as second-line therapy in nonsquamous NSCLC as well as third-line or greater therapy for squamous NSCLC, respectively, was

chosen to provide formal statistical testing of the following hypothesis: H_0: ORR $\leq$ 10% versus H1: ORR $>$ 10%. If the true ORR for durvalumab was 25%, then the sample size of 80 patients would provide 92% power to reject the null hypothesis H_0 at one-sided 0.025 alpha level (or equivalently, two-sided 0.05 alpha level).

Results

NSCLC 10 mg/kg-Every-2-Weeks Cohort

Baseline Characteristics and Patient Disposition. Between May 23, 2013, and October 16, 2017, 304 NSCLC patients were treated with durvalumab 10 mg/kg every 2 weeks (two in the dose-escalation phase and 302 in the dose-expansion phase). The population was mostly pretreated: 32.6% of patients had received one prior line of therapy; 46.4% had received two prior lines of therapy. The remaining 21.1% were treatment-naive. During treatment with durvalumab, 44 nonsquamous patients and 55 squamous patients were treated beyond investigator-assessed progressive disease. Baseline demographics and disease characteristics of the as-treated population are shown in Table 1. The FAS consisted of 275 patients.

Table 1. Baseline Demographics and Disease Characteristics of the NSCLC 10-mg/kg-Every-2-Weeks Cohort (As-Treated Population)

	Overall		
Characteristic	PD-L1 ≥25%[a] (n = 165)	PD-L1 <25%[a] (n = 120)	Total[b] (N = 304)
Median age, years (range)	65.0 (26-85)	64.0 (35-87)	65.0 (26-87)
Sex			
Male	100 (60.6)	60 (50.0)	171 (56.3)
Female	65 (39.4)	60 (50.0)	133 (43.8)
Histology			
Nonsquamous	65 (39.4)	68 (56.6)	144 (47.4)
Squamous	100 (60.6)	52 (43.3)	160 (52.6)
Tobacco use			
Never smoker	21 (12.7)	22 (18.3)	46 (15.1)
Former smoker	123 (74.5)	84 (70.0)	222 (73.0)
Current smoker	21 (12.7)	14 (11.7)	36 (11.8)
ECOG PS			
0	42 (25.5)	28 (23.5)	74 (24.4)
1	123 (74.5)	91 (76.5)	229 (75.6)
Line of treatment			
First	50 (30.3)	12 (10.0)	64 (21.1)
Second+	115 (69.7)	108 (90.0)	240 (78.9)

Values shown are n (%) unless otherwise stated.
[a]Greater than or equal to 25%/less than 25% of tumor cell membranes stained for PD-L1 at any intensity.
[b]Includes patients for whom PD-L1 expression level was not determined due to missing or non-evaluable tumor samples.
ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death ligand-1.

Treatment Exposure and Follow-up. Patients received a median of six doses (range, 1–27) of durvalumab and were followed for a median of 40.05 months (range, 0.3–52.2 months); 87.2% of patients were followed for 6 months or longer and 82.2% for 12 months or longer. Median treatment exposure was 16.3 weeks for the PD-L1 greater than or equal to 25% group and 12.0 weeks for the PD-L1 less than 25% group. Median exposure was 16.0 weeks for patients with squamous NSCLC and 12.0 weeks for those with nonsquamous NSCLC. Median follow-up was longer for previously treated patients than for first-line patients (Supplementary Table 1). Forty-two patients (15.3% of the FAS) completed 12 months of therapy; 13 of them (31.0%) were treatment-naive.

Safety and Tolerability. All-causality AEs are summarized in Supplementary Table 2. Overall, 57.2% of patients had treatment-related AEs and 10.2% had grade 3/4 treatment-related AEs (Table 2). The most common treatment-related AEs were fatigue (17.4%), decreased appetite (9.2%), diarrhea (8.9%), hypothyroidism (8.2%), and rash (8.2%). The most common treatment-related AEs of special interest were diarrhea (8.9%), hypothyroidism (8.2%), rash (8.2%), and pruritus (5.3%) (Supplementary Table 3).

Serious treatment-related AEs occurred in 4.6% of patients, and 5.6% discontinued due to treatment-related AEs (Table 2). The number of patients who experienced any-grade treatment-related AEs was similar across treatment lines. Treatment-related pneumonitis occurred in six patients (2.0%), including

Table 2. Summary of Treatment-Related AEs in the NSCLC 10-mg/kg-Every-2-Weeks Cohort (As-treated Population)[a]

	Overall		
Characteristic	PD-L1 ≥25%[b] (n = 165)	PD-L1 <25%[b] (n = 120)	Total[c] (N = 304)
Any AE	103 (62.4)	67 (55.8)	174 (57.2)
AEs of grade 3/4 severity	23 (13.9)	6 (5.0)	31 (10.2)
Serious AEs	12 (7.3)	2 (1.7)	14 (4.6)
AEs leading to discontinuation	11 (6.7)	4 (3.3)	17 (5.6)[d]
AEs leading to death	1 (0.6)	0	1 (0.3)[e]

Values shown are n (%).
[a]Causality assigned by investigator; grade refers to maximum severity.
[b]Greater than or equal to 25%/less than 25% of tumor cell membranes stained for PD-L1 at any intensity.
[c]Includes 19 patients with unknown PD-L1 expression level.
[d]Colitis (n = 3); pneumonitis (n = 2); diarrhea (n = 2); elevated aspartate aminotransferase, elevated transaminases, tubulointerstitial nephritis, autoimmune hepatitis, thyroiditis, lichenoid keratosis, headache, fatigue, erythema nodosum, and thrombocytopenia (each n = 1).
[e]Pneumonia.
AE, adverse event; PD-L1, programmed cell death ligand-1.

one grade greater than or equal to 3 event. One fatal case of bacterial pneumonia in a patient with underlying grade 4 pneumonitis was judged by the investigator to be related to treatment in a 64-year-old male patient who had received three doses of durvalumab (Table 2).

Treatment-emergent imAEs occurred in 54 patients (17.8%) and were grade 3/4 in nine patients (3.0%). The median time to onset of first imAE was 72.5 days overall (range, 8–280); 63.0 days (range, 8–280) in the PD-L1 greater than or equal to 25% group, and 73.5 days (range, 15–265) in the PD-L1 less than 25% group. The most common imAEs were hypothyroidism (6.9%), diarrhea (3.3%), pneumonitis (2.6%), and colitis, rash, and hyperthyroidism (all 1.6%) (Table 3). Serious imAEs occurred in six patients (2.0%), but there were no deaths due to imAEs. Treatment was discontinued due to imAEs in 11 patients (3.6%).

Patients with squamous disease had numerically higher rates of grade 3/4 treatment-related AEs (13.1% versus 6.9%) and discontinuations due to treatment-related AEs (6.9% versus 4.2%) compared to patients with nonsquamous disease. Neither of these safety measures differed markedly in male versus female patients. There were no notable differences by histology or sex in treatment-related serious AEs.

Clinical Activity in the NSCLC 10-mg/kg Cohort

Antitumor Activity. Confirmed ORR by BICR was 15.3% (95% confidence interval [CI]: 11.2–20.1) in the overall FAS population and was numerically greater in patients

Table 3. Treatment-Emergent Immune-Mediated AEs in the NSCLC 10 mg/kg-Every-2- Weeks Cohort by System Organ Class (As-Treated Population)[a]

	PD-L1 ≥25%[b] (n = 165)		PD-L1 <25%[b] (n = 120)		Total[c] (N = 304)	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4[d]
Overall	34 (20.6)	8 (4.8)	18 (15.0)	0	54 (17.8)	9 (3.0)
Endocrine						
Adrenal insufficiency	0	0	1 (0.8)	0	1 (0.3)	0
Autoimmune hypothyroidism	1 (0.6)	0	0	0	1 (0.3)	0
Autoimmune thyroiditis	1 (0.6)	0	0	0	1 (0.3)	0
Hyperthyroidism	5 (3.0)	0	0	0	5 (1.6)	0
Hypothyroidism	12 (7.3)	0	9 (7.5)	0	21 (6.9)	0
Thyroiditis	2 (1.2)	1 (0.6)	1 (0.8)	0	3 (1.0)	1 (0.3)
Gastrointestinal						
Colitis	5 (3.0)	3 (1.8)	0	0	5 (1.6)	3 (1.0)
Diarrhea	8 (4.8)	1 (0.6)	2 (1.7)	0	10 (3.3)	1 (0.3)
Hepatobiliary disorders						
Autoimmune hepatitis[d]	0	0	0	0	1 (0.3)	1 (0.3)
Investigations						
ALT elevation[d]	1 (0.6)	0	1 (0.8)	0	3 (1.0)	1 (0.3)
AST elevation[d]	1 (0.6)	0	0	0	2 (0.7)	1 (0.3)
Blood bilirubin increased[d]	0	0	0	0	1 (0.3)	0
Blood creatinine increased	2 (1.2)	0	0	0	2 (0.7)	0
Blood TSH increased	1 (0.6)	0	1 (0.8)	0	2 (0.7)	0
Transaminases increased	0	0	1 (0.8)	0	1 (0.3)	0
Renal						
Tubulointerstitial nephritis	1 (0.6)	1 (0.6)	0	0	1 (0.3)	1 (0.3)
Respiratory						
Pneumonitis[d]	5 (3.0)	1 (0.6)[e]	2 (1.7)	0	8 (2.6)	1 (0.3)
Skin						
Erythema	1 (0.6)	0	1 (0.8)	0	2 (0.7)	0
Pruritus	2 (1.2)	0	1 (0.8)	0	3 (1.0)	0
Rash	3 (1.8)	1 (0.6)	2 (1.7)	0	5 (1.6)	1 (0.3)
Rash macular	1 (0.6)	1 (0.6)	0	0	1 (0.3)	1 (0.3)

Values are shown as n (%).
[a]Causality assigned by investigators. AEs of scientific and medical interest specific to understanding of the investigational product.
[b]Greater than or equal to 25%/less than 25% tumor cell membranes stained for PD-L1 at any intensity.
[c]Includes 19 patients with unknown PD-L1 expression level.
[d]Among patients with unknown PD-L1 expression, the following immune-mediated AEs occurred: grade 1/2 blood bilirubin increased, grade 1/2 pneumonitis, grade 3/4 autoimmune hepatitis, grade 3/4 ALT elevation, and grade 3/4 AST elevation (each n = 1).
[e]One patient experienced grade 3/4 pneumonitis and grade 5 pneumonia.
AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; PD-L1, programmed cell death ligand-1; TSH, thyroid stimulating hormone.

Table 4. ORR by PD-L1 Expression Level in the NSCLC 10-mg/kg-Every-2-Weeks Cohort per Blinded Independent Central Review (Full Analysis Set Population)

	PD-L1 ≥25% (n = 147) n/N (%) 95% CI	PD-L1 <25% (n = 109) n/N (%) 95% CI
RECIST response (ORR)	32/147 (21.8) 15.4-29.3	7/109 (6.4) 2.6-12.8
Treatment setting		
First-line	11/41 (26.8) 14.2-42.9	2/11 (18.2) 2.3-51.8
Male	5/24 (20.8) 7.1-42.2	2/9 (22.2) 2.8-60.0
Female	6/17 (35.3) 14.2-61.7	0/2 (0) 0.0-84.2
Second-line+	21/106 (19.8) 12.7-28.7	5/98 (5.1) 1.7-11.5
Male	15/65 (23.1) 13.5-35.2	2/44 (4.5) 0.6-15.5
Female	6/41 (14.6) 5.6-29.2	3/54 (5.6) 1.2-15.4
Histology		
Squamous	17/87 (19.5) 11.8-29.4	3/48 (6.3) 1.3-17.2
First-line	4/18 (22.2) 6.4-47.6	1/7 (14.3) 0.4-57.9
Second-line+	13/69 (18.8) 10.4-30.1	2/41 (4.9) 0.6-16.5
Nonsquamous	15/60 (25.0) 14.7-37.9	4/61 (6.6) 1.8-15.9
First-line	7/23 (30.4) 13.2-52.9	1/4 (25.0) 0.6-80.6
Second-line+	8/37 (21.6) 9.8-38.2	3/57 (5.3) 1.1–14.6
Smoking history		
Never		
First-line	1/5 (20.0) 0.5-71.6	0/1 (0) 0.0-97.5
Second-line+	2/15 (13.3) 1.7-40.5	1/17 (5.9) 0.1-28.7
Former		
First-line	7/29 (24.1) 10.3-43.5	2/8 (25.0) 3.2-65.1
Second-line+	16/80 (20.0) 11.9-30.4	4/70 (5.7) 1.6-14.0
Current		
First-line	3/7 (42.9) 9.9-81.6	0/2 (0) 0.0-84.2
Second-line+	3/11 (27.3) 6.0-61.0	0/11 (0) 0.0-28.5

CI, confidence interval; ORR, objective response rate; PD-L1, programmed cell death ligand-1; RECIST, Response Evaluation Criteria in Solid Tumors.

with tumoral PD-L1 expression greater than or equal to 25% (21.8% [95% CI: 15.4–29.3]) than in those with less than 25% expression (6.4% [95% CI: 2.6–12.8]) (Table 4). Antitumor activity was observed across histologies and treatment lines (Fig. 1; Table 4). The ORR was similar in patients with nonsquamous histology (16.7% [95% CI: 10.7–24.1]) and squamous histology (14.0% [95% CI: 8.8–20.8]). Treatment-naive patients with PD-L1 expression greater than or equal to 25% had an ORR of 26.8% (95% CI: 14.2–42.9) and those with less than 25% expression had an ORR of 18.2% (95% CI: 2.3–51.8). Previously treated patients with PD-L1 expression greater than or equal to 25% had a higher ORR (19.8% [95% CI: 12.7–28.7]) than those with less than 25% expression (5.1% [95% CI: 1.7–11.5]). In the overall population, most responses were partial, but two patients had a complete response: one in the first-line group and one in the previously treated group.

In the PD-L1 greater than or equal to 25% group, response rates were numerically greater in current smokers (33.3%) and former smokers (21.1%) than in never-smokers (15.0%). Response rates in the PD-L1 less than 25% group showed no apparent relationship to smoking, although conclusions are limited by the small number of patients (Table 4).

Of the 17 TKI-pretreated patients with sensitizing *EGFR* mutations or *ALK* rearrangements, one (5.9%) had a partial response (PR), three (17.6%) had stable disease, eight (47.1%) had progressive disease, and five (29.4%) were non-evaluable. The one patient with a PR harbored an *EGFR* mutation; duration of response was 729 days and PFS was 762 days, both ongoing at the time of data cutoff.

Generally, responses occurred early (median time to response: 2.56 months [95% CI: 1.4–2.7]), with no numeric difference between treatment-naive patients (2.61 months [95% CI: 1.3–2.8]) and previously treated patients (2.56 months [95% CI: 1.4–2.8]). Responses remain durable (Fig. 1; Supplementary Fig. 2), with 40.6% of responses ongoing in patients with PD-L1 expression greater than or equal to 25%. Disease control rate greater than or equal to 24 weeks was 32.0% in the greater than or equal to 25% group and 12.8% in the less than 25% group. In the overall FAS population, duration of response ranged from 1.4+ to 41.2+ months (median, 17.74 months), and duration of stable disease ranged from 1.2+ to 40.3+ (median, 3.94 months). Median duration of response was 10.64 months in the PD-L1 greater than or equal to 25% group and 12.12 months in the less than 25% group.

Survival. Median OS was 12.4 (95% CI: 9.3–15.2) months in the total NSCLC 10-mg/kg-every-2-week cohort (as-treated population), 16.4 (95% CI, 13.0–20.2) months in the PD-L1 greater than or equal to 25% group, and 7.6 (95% CI: 5.7–10.0) months in the PD-L1 less than 25% group (Fig. 2). The OS rate at 24 months was 29.6% (95% CI: 23.9–35.5) in the overall population, 46.0% (95% CI: 32.0–58.9) in treatment-naive

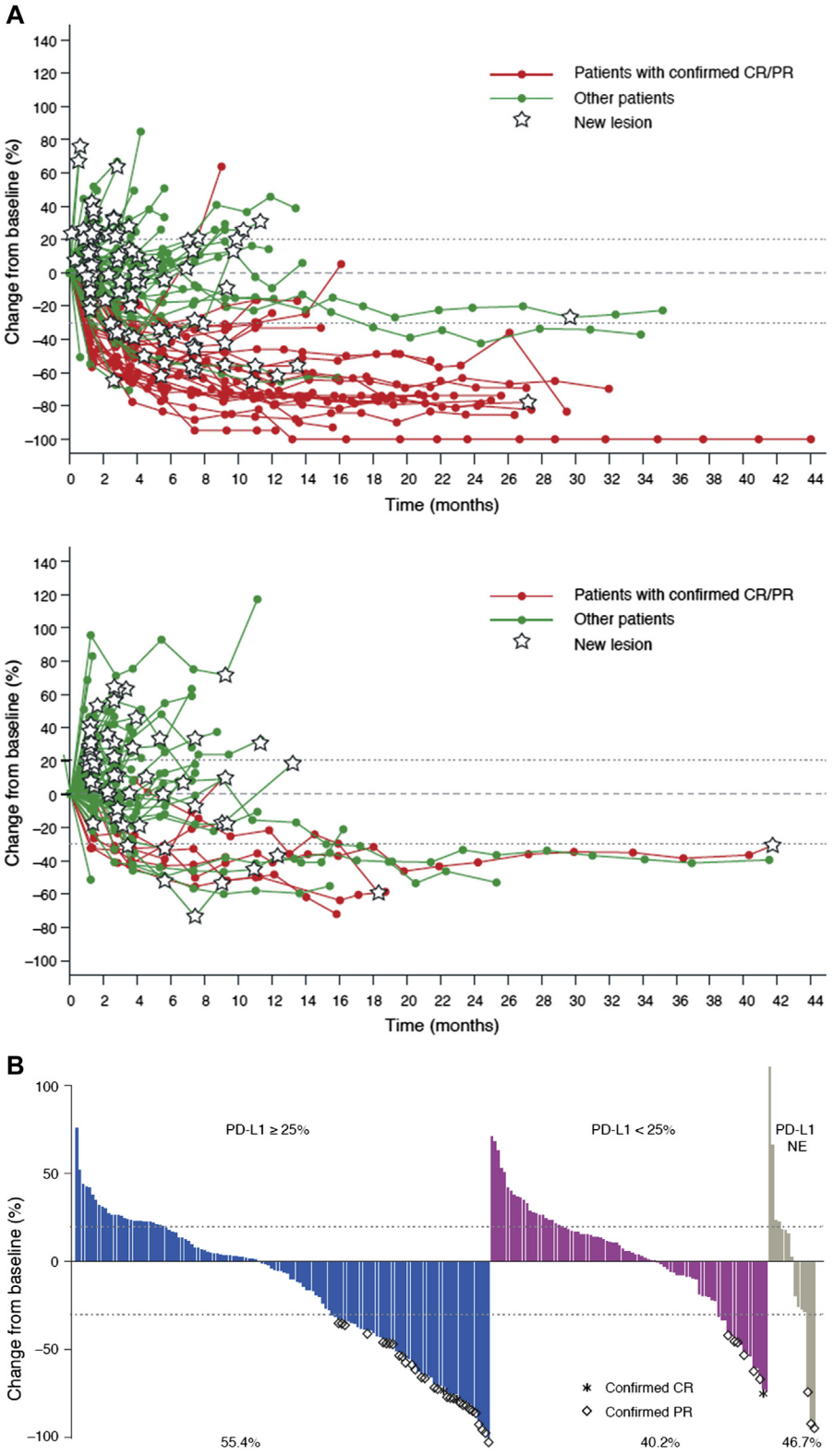

Figure 1. Antitumor activity of durvalumab per blinded independent central review (BICR) in the NSCLC 10-mg/kg-every-2-weeks cohort (full analysis [FAS] set population). (*A*) Change in tumor size by programmed death ligand 1 (PD-L1) expression level. PD-L1 greater than or equal to 25% subgroup (n = 147) (*top*); and PD-L1 less than 25% subgroup (n = 109) (*bottom*). (*B*) Best change in size of selected target lesions from baseline by BICR (FAS population). Denominators for percentage of patients with any tumor shrinkage are based on the number of patients who have baseline and at least one post-baseline data point. Percentages of patients with any tumor shrinkage are shown below the plots. CR, complete response; PR, partial response. NE, not evaluable.

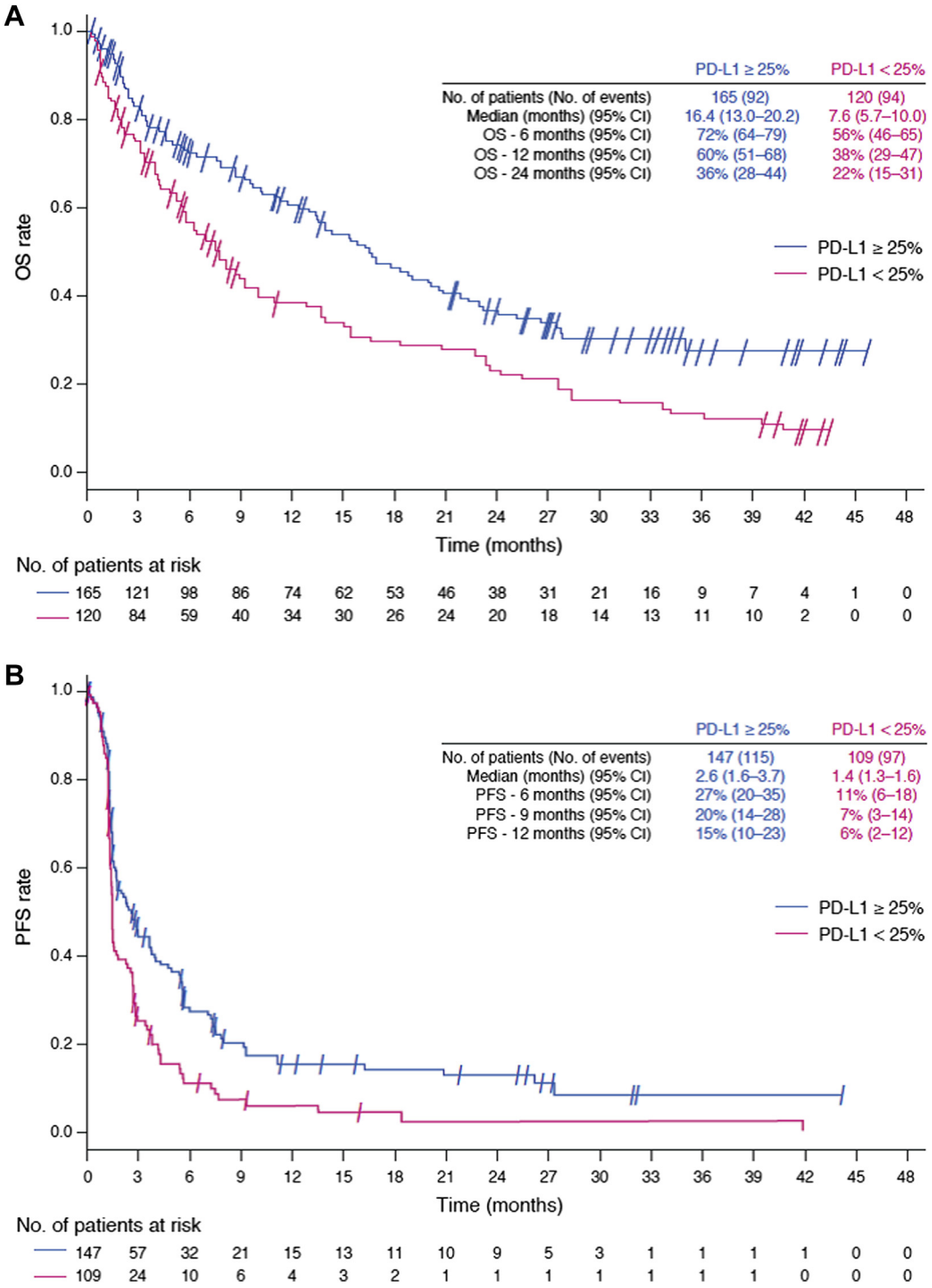

Figure 2. Kaplan-Meier curves in the NSCLC 10-mg/kg-every-2-weeks cohort for (*A*) overall survival (OS) (as-treated population) and (*B*) progression-free survival (PFS) (full analysis set population) per blinded independent review by programmed death ligand 1 (PD-L1) expression level. CI, confidence interval.

patients, and 25.2% (95% CI: 19.2–31.7) in previously treated patients. In treatment-naive patients, median OS was 21.9 (95% CI: 14.5–not evaluable) months in the PD-L1 greater than or equal to 25% group and 7.4 (95% CI: 1.7–36.2) months in the PD-L1 less than 25% group. In previously treated patients, median OS was 13.7 (95% CI: 9.8–18.4) months in the greater than or equal to 25% group and 7.6 (95% CI: 5.6–9.4) months in the less than 25% group (Supplementary Fig. 3). Median OS in the patients with *EGFR* mutations or *ALK* rearrangements was 9.8 (95% CI: 2.1–23.6) months and the 12-month OS rate was 36.0% (95% CI: 13.8%–59.0%).

Median PFS by BICR was 1.7 (95% CI: 1.4–2.6) months in the overall FAS population, 2.6 (95% CI: 1.6–3.7) months in the PD-L1 greater than or equal to 25% group, and 1.4 (95% CI: 1.3–1.6) months in the PD-L1 less than 25% group (Fig. 2). PFS was greater than or equal to 18 months in 16.6% (95% CI: 7.3–29.2) of first-line patients and 9.9% (96% CI: 6.0–14.8) of previously treated patients. In treatment-naive patients, median PFS was 5.4 (95% CI: 1.7–7.2) months in the PD-L1 greater than or equal to 25% group and 1.7 (95% CI: 1.2–3.4) months in the PD-L1 less than 25% group. In previously treated patients, median PFS was 2.1 (95% CI: 1.4–2.9) months in the PD-L1 greater than or equal to 25% group and 1.4 (95% CI: 1.3–1.5) months in the PD-L1 less than 25% group (Supplementary Fig. 3). Median PFS in the patients with *EGFR* mutations or *ALK* rearrangements was 1.4 (95% CI: 0.8–2.2) months and the PFS rate at all milestones up to 18 months was 5.9% (n = 1).

In the 42 patients who completed 12 months of therapy, median PFS was 13.4 (95% CI: 5.8–26.1) months and median OS was 40.8 (95% CI: 33.7–NE) months.

In a recent analysis of the study population, 21 patients (6.9%) were re-treated upon disease progression after the initial 12-month treatment period. Three patients had a best overall response of PR. The 12-month PFS rate was 31%. These patients remain in follow-up for survival, and analyses are ongoing.

Safety in the Total 1108 Population and Dose-Exploration Phase

Safety results from the total Study 1108 population across all investigated tumor types and doses of durvalumab (as-treated population) are shown in Supplementary Table 4 and include data collected up to October 16, 2017. Results for the dose-exploration phase based on the same data cutoff, including treatment exposure and safety, are also in the Supplementary Data (Supplementary Table 5). This cohort includes patients who received at least two doses of durvalumab and completed the safety follow-up through the dose-limiting toxicity evaluation period.

PK, Pharmacodynamics, and Immunogenicity in the Total 1108 Population

A total of 1009 patients across the total Study 1108 population provided evaluable PK data for durvalumab across doses ranging from 0.1 to 10 mg/kg every 2 weeks, 15 mg/kg every 3 weeks, and 20 mg/kg every 4 weeks. Durvalumab exhibited nonlinear PK at doses less than 3 mg/kg every 2 weeks (likely due to saturable target-mediated antibody elimination) and approached linearity at doses greater than or equal to 3 mg/kg every 2 weeks, suggesting complete target saturation (Supplementary Figs. 4*A* and 4*B*).[20] Accumulation of durvalumab was observed following repeated dosing. The steady state was achieved around week 16 (8 every 2 weeks doses of durvalumab). PK modeling indicated that 10 mg/kg every 2 weeks would maintain trough exposure above 50 μg/mL (target exposure level) throughout the dosing interval, with greater than 90% of patients expected to reach almost complete saturation of both soluble and membrane-bound PD-L1 in serum.[21]

Target engagement was assessed by measuring free sPD-L1 in serum. The extent and duration of sPD-L1 suppression was dose-dependent, with complete suppression around the dose of greater than or equal to 0.3 mg/kg. Following the 10 mg/kg every 2 weeks (approved dose), approximately 97% of patients showed complete sPD-L1 suppression throughout the dosing interval. Suppression of free sPD-L1 was similar among 10-mg/kg-every-2-weeks, 15-mg/kg-every-3-weeks, and 20-mg/kg-every-4-weeks cohorts. Peripheral baseline and dynamic changes in sPD-L1 levels did not correlate with clinical activity.

Of 849 patients who were treated with durvalumab and evaluable for the presence of antidrug antibodies (ADAs), 26 (3.1%) patients tested positive for treatment-emergent ADAs. Of 810 patients who received 10 mg/kg every 2 weeks, 22 (2.7%) patients tested positive for treatment-emergent ADAs. Neutralizing antibodies were detected in 0.4% (3 of 849 patients across all dose levels) and 0.1% (1 of 810 patients who received 10 mg/kg every 2 weeks). The development of treatment-emergent ADAs against durvalumab did not have any clinically relevant effect on its PK profile. There was no clear evidence of any potential impact of ADA on safety. The impact of treatment-emergent ADAs on the clinical efficacy of durvalumab was not evaluable due to very few subject samples testing positive for treatment-emergent ADAs.

Discussion

Durvalumab monotherapy represents a novel therapeutic strategy to boost antitumor immune responses by targeting PD-L1 in tissue and on immune cells, and it is currently being investigated as part of novel combinations with other immuno-oncology agents, chemotherapy, and chemoradiation. Results from the NSCLC 10 mg/kg-every-2-week cohort of this study suggest that clinical activity and survival are consistent with those of other PD-1/PD-L1 inhibitors.[2-5]

The median time to response and duration of response were consistent with other checkpoint inhibitors in first and subsequent lines of therapy.[2,3] Antitumor activity was observed in both first-line and

previously treated patients, and in both squamous and nonsquamous disease. The response rate among previously treated patients in the PD-L1 greater than or equal to 25% group of this study was 19.8%, compared to 12.2% in ATLANTIC in heavily pretreated patients with *EGFR* mutations and *ALK* rearrangements (cohort 1), and 16.4% in those who were *EGFR* and *ALK* wild-type (cohort 2).[22] Median OS in previously treated patients in the PD-L1 greater than or equal to 25% group in this study was 13.7 months, compared to 13.3 months in ATLANTIC cohort 1 and 10.9 months in ATLANTIC cohort 2.[22] The current study expands the evidence on the clinical utility of durvalumab beyond ATLANTIC to the first-line setting. More than half of the study population had squamous histology, in contrast with other studies that have enrolled a higher percentage of patients with nonsquamous histology.[4,23] In this study, responses generally occurred early and were durable for both histologic types, both PD-L1 groups, and across lines of treatment. The clinical benefits of durvalumab, including ORR, PFS, and OS, were greater in patients with tumoral PD-L1 expression greater than or equal to 25% irrespective of histologic type and the number of prior lines of treatment.

In the overall Study 1108 population, as well as the escalation and exploration phases across multiple tumor types, and the NSCLC 10-mg/kg-every-2-weeks cohort, durvalumab had a mild toxicity profile. In the NSCLC 10-mg/kg-every-2-weeks cohort, 10.2% of patients had grade 3/4 treatment-related AEs and 5.6% discontinued due to any-grade treatment-related AEs. Although the interactions between PD-1 and its ligands, PD-L1 and PD-L2, have similar IC_{50} values (2.52 and 2.59 nmol/L, respectively), durvalumab does not bind to PD-L2[10,24]; this ligand may play a role in protecting normal tissue physiology.[25] The mild toxicity profile of durvalumab may also be due to the engineered triple mutation in the fragment crystallizable domain, which removes antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity.[26] In addition, durvalumab was associated with a low incidence of ADAs. Neutralizing antibodies were detected in only 0.4% of patients across all dose levels and 0.1% of patients who received 10 mg/kg every 2 weeks.

Because of their mechanisms of action, PD-1/PD-L1 checkpoint inhibitors are associated with a unique spectrum of imAEs.[27] In this study, treatment-emergent grade 3/4 imAEs occurred in 3.0% of patients in the NSCLC 10-mg/kg-every-2-weeks cohort, and imAEs of any grade led to treatment discontinuation in 3.6%. Treatment-related AEs occurred slightly more frequently in the PD-L1 greater than or equal to 25% subgroup (62.4%) than in the PD-L1 less than 25% subgroup (55.8%) in the NSCLC 10-mg/kg-every-2-weeks cohort, and the relationship was similar for treatment-related SAEs, AEs leading to discontinuation, and AEs leading to death, as well as treatment-emergent imAEs (Table 2). This pattern has also been observed with nivolumab.[2] In the current study, the differences might have been partly due to imbalances in baseline patient and disease characteristics. For example, the PD-L1 greater than or equal to 25% group had numerically higher proportions of patients with squamous NSCLC, male patients, and treatment-naive patients compared to the PD-L1 less than 25% group (Table 1). Patients with squamous disease had numerically higher rates of grade 3/4 treatment-related AEs and treatment-related discontinuations compared to patients with nonsquamous disease. Durvalumab exposure was longer in the PD-L1 greater than or equal to 25% group than in the PD-L1 less than 25% group, and longer in the squamous group than in the nonsquamous group, which could have contributed to their higher AE rates.

With durvalumab 10 mg/kg every 2 weeks, the rates of treatment-related AEs of any grade (57.2%) and grade 3/4 (10.2%) were lower than or similar to those of other anti–PD-1/PD-L1 monotherapies in NSCLC (any grade, 58% to 85.1%; grade 3/4, 7% to 19%).[1,2,4,23,28,29] The rate of discontinuations due to treatment-related AEs in the NSCLC 10-mg/kg-every-2-weeks cohort (5.6%) was also consistent with those of other anti–PD-1/PD-L1 monotherapies (1% to 12%).[1-4,23,28,29] One patient in the current study had grade 3/4 treatment-related pneumonitis ongoing at the time of grade 5 treatment-related pneumonia.

The safety profile, linear PK, dose-dependent decreases in peripheral serum PD-L1, clinical activity data, and dose-exploration data supported the selection of 10 mg/kg every 2 weeks for 12 months for further development. Analyses from this study have also shown associations between clinical outcomes and interferon-gamma gene expression, somatic *STK11* mutations, liver metastasis, circulating tumor cell DNA level, tumor mutational burden, and a signature based on PD-L1+ tumor cell and CD8+ tumor infiltrating lymphocyte densities, broadening the understanding of immunotherapy across tumor types.[30-35] Additionally, pivotal monotherapy and combination studies are ongoing: MYSTIC (NCT02453282), ARCTIC (NCT02352948), NEPTUNE (NCT02542293), PEARL (NCT03003962), and POSEIDON (NCT03164616). The phase III MYSTIC trial of first-line durvalumab monotherapy or durvalumab + tremelimumab versus standard of care chemotherapy did not show a statistically significant PFS or OS advantage for either arm in patients with greater than or equal to 25% PD-L1 expression; however, durvalumab showed a clinically meaningful improvement in OS compared to chemotherapy (hazard ratio = 0.76,

97.54% CI: 0.564–1.019; $p = 0.036$).[36] The phase III PACIFIC trial of durvalumab following concurrent chemoradiotherapy in stage III, unresectable NSCLC showed statistically significant improvements in PFS and OS over placebo leading to registration for this indication.[15,37]

Conclusions

Durvalumab was clinically active and exhibited a manageable safety profile in patients with stage IIIB–IV squamous and nonsquamous NSCLC in the first-line setting as well as second-line and beyond. Tumoral PD-L1 expression greater than or equal to 25% was associated with greater antitumor response and longer survival.

Acknowledgments

This study was funded by AstraZeneca. Medical writing support, which was in accordance with Good Publication Practice (GPP3) guidelines, was provided by Craig Turner, MSc, of Cirrus Communications (Macclesfield, United Kingdom) and was funded by AstraZeneca (Gaithersburg, Maryland). The authors thank the patients, their families and caregivers, trial nurses, data managers, and all study investigators, including Drs. Joseph Leach and Wen Jen Hwu, for their contributions to study conduct.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2019.06.010.

References

1. 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;373:125–135.
2. 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.
3. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016, 10;375:1823-1833.
4. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet*. 2016;387:1837–1846.
5. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. 2015;372:2018–2028.
6. Powles T, O'Donnell PH, Massard C, et al. Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: updated results from a phase 1/2 open-label study. *JAMA Oncol*. 2017;3:e172411.
7. Chow LQM, Haddad R, Gupta S, et al. Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: results from the phase Ib KEYNOTE-012 expansion cohort. *J Clin Oncol*. 2016;34:3838–3845.
8. Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy — inhibiting programmed death-ligand 1 and programmed death-1. *Clin Cancer Res*. 2012;18:6580–6587.
9. Butte MJ, Keir ME, Phamduy TB, et al. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. *Immunity*. 2007;27:111–122.
10. Stewart R, Morrow M, Hammond SA, et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. *Cancer Immunol Res*. 2015;3:1052–1062.
11. Wainberg ZA, Segal NH, Jaeger D, et al. Safety and clinical activity of durvalumab monotherapy in patients with hepatocellular carcinoma (HCC). *J Clin Oncol*. 2017;35(suppl 15):4071 (abstr).
12. Segal NH, Ou S-HI, Balmanoukian A, et al. Safety and efficacy of durvalumab in patients with head and neck squamous cell carcinoma: results from a Phase I/II expansion cohort. *Eur J Cancer*. 2019;109:154–161.
13. Hollebecque A, Wainberg ZA, Ajani JA, et al. Safety and clinical activity of durvalumab monotherapy in patients with gastroesophageal cancers. *J Clin Oncol*. 2018;36(suppl 15):4032 (abstr).
14. Goldman JW, Dowlati A, Antonia S, et al. Safety and antitumor activity of durvalumab monotherapy in patients with pretreated extensive disease small-cell lung cancer (ED-SCLC). *J Clin Oncol*. 2018;36(suppl 15):8518 (abstr).
15. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in Stage III NSCLC. *N Engl J Med*. 2018;379:2342–2350.
16. AstraZeneca. Durvalumab (Imfinzi). Prescribing information. Updated February 2018. https://www.azpicentral.com/imfinzi/imfinzi.pdf#page=1. Accessed July 12, 2018.
17. Durvalumab (Imfinzi). Summary of product characteristics. https://www.medicines.org.uk/emc/product/9495/smpc. Accessed November 28, 2018.
18. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228–247.
19. Rebelatto MC, Midha A, Mistry A, et al. Development of a programmed cell death ligand-1 immunohistochemical assay validated for analysis of non-small cell lung cancer and head and neck squamous cell carcinoma. *Diagn Pathol*. 2016;11:95.
20. Lutzky J, Antonia SJ, Blake-Haskins A, et al. A phase 1 study of MEDI4736, an anti-PD-L1 antibody, in patients with advanced solid tumors. Oral presentation at the American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, Illinois, May 30—June 3, 2014 (abstr 3001).

21. Baverel PG, Dubois VFS, Jin CY, et al. Population pharmacokinetics of durvalumab in cancer patients and association with longitudinal biomarkers of disease status. *Clin Pharmacol Ther*. 2018;103:631–642.
22. Garassino MC, Cho B-C, Kim J-H, et al. Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): an open-label single-arm, phase 2 study. *Lancet Oncol*. 2018;19:521–536.
23. Gettinger S, Rizvi NA, Chow LQ, et al. Nivolumab monotherapy for first-line treatment of advanced non-small-cell lung cancer. *J Clin Oncol*. 2016;34:2980–2987.
24. Wang C, Thudium KB, Han M, et al. In vitro characterization of the anti-PD-1 antibody nivolumab, BMS-936558, and in vivo toxicology in non-human primates. *Cancer Immunol Res*. 2014;2:846–856.
25. Akbari O, Stock P, Singh AK, et al. PD-L1 and PD-L2 modulate airway inflammation and iNKT-cell-dependent airway hyperreactivity in opposing directions. *Mucosal Immunol*. 2010;3:81–91.
26. Oganesyan V, Gao C, Shirinian L, et al. Structural characterization of a human Fc fragment engineered for lack of effector functions. *Crystallogr D Biol Crystallogr*. 2008;1;64:700-704.
27. Davies M, Duffield EA. Safety of checkpoint inhibitors for cancer treatment: strategies for patient monitoring and management of immune-mediated adverse events. *ImmunoTargets Ther*. 2017;6:51.
28. Hui R, Garon EB, Goldman JW, et al. Pembrolizumab as first-line therapy for patients with PD-L1–positive advanced non-small cell lung cancer: a phase 1 trial. *Ann Oncol*. 2017;28:874–881.
29. Carbone DP, Reck M, Paz-Ares L, et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. *N Engl J Med*. 2017;376:2415–2426.
30. Higgs BW, Morehouse C, Streicher KL, et al. Interferon gamma messenger RNA signature in tumor biopsies predicts outcomes in patients with non-small-cell lung carcinoma or urothelial cancer treated with durvalumab. *Clin Cancer Res*. 2018;24:3857–3866.
31. Higgs BW, Morehouse C, Kuziora M, et al. IFNγ mRNA signature (IFNγ sig), circulating tumor DNA (ctDNA), and survival in NSCLC or urothelial cancer (UC) treated with durvalumab. Poster presentation at the American Society of Clinical Oncology (ASCO)—Society for Immunotherapy of Cancer (SITC) Clinical Immuno-Oncology Symposium, San Francisco, California, January 25–27, 2018 (abstr 51).
32. Jure-Kunkel M, Wu S, Xiao F, et al. Somatic *STK11/LKB1* mutations confer resistance to immune checkpoint inhibitors as monotherapy or in combination in advanced NSCLC. *J Clin Oncol*. 2018;36(suppl 15):3028 (abstr).
33. Paz-Ares L, Sridhar S, Liu H, et al. Association of liver metastases with survival in NSCLC patients treated with durvalumab in two independent clinical trials. Poster presentation at the ASCO Annual Meeting, Chicago, Illinois, June 2–6, 2017 (abstr 3038).
34. Raja R, Kuziora M, Brohawn P, et al. Early reduction in ctDNA predicts survival in lung and bladder cancer patients treated with durvalumab. *Clin Cancer Res*. 2018;24:6212–6222.
35. Althammer S, Tan TH, Spitzmüller A, et al. Automated image analysis of NSCLC biopsies to predict response to anti-PD-L1 therapy. *J Immunother Cancer*. 2019;7:121.
36. Rizvi NA, Cho BC, Reinmuth N, et al. Durvalumab with or without tremelimumab vs platinum-based chemotherapy as first-line treatment for metastatic non-small cell lung cancer: MYSTIC. Proffered paper presentation at the European Society for Medical Oncology – Immuno-Oncology Annual Meeting, Geneva, Switzerland, December 13–16, 2018 (abstr LBA6).
37. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377:1919–1929.