ORIGINAL RESEARCH

Safety and clinical activity of atezolizumab plus erlotinib in patients with non-small-cell lung cancer

C. M. Rudin[1*], A. Cervantes[2], A. Dowlati[3], B. Besse[4,5], B. Ma[6], D. B. Costa[7], P. Schmid[8], R. Heist[9], V. M. Villaflor[10], J. Spahn[11], S. Li[11], E. Cha[11], G. J. Riely[1] & S. Gettinger[12]

[1]Memorial Sloan Kettering Cancer Center, New York, USA; [2]University of Valencia, Valencia, Spain; [3]University Hospitals Case Medical Center, Cleveland, USA; [4]Gustave Roussy, Villejuif; [5]University of Paris-Sud, Orsay, France; [6]Phase I Clinical Trial Center, Chinese University of Hong Kong, Hong Kong, China; [7]Beth Israel Deaconess Medical Center, Boston, USA; [8]Barts Cancer Institute, London, UK; [9]Massachusetts General Hospital, Boston; [10]City of Hope, Duarte; [11]Genentech, Inc, South San Francisco; [12]Yale Cancer Center, New Haven, USA

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Background: Acquired resistance limits long-term epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) efficacy in patients with *EGFR* mutation-positive non-small-cell lung cancer (NSCLC) in whom anti-programmed death-ligand 1 (PD-L1) efficacy is also limited. We hypothesized that combining atezolizumab with erlotinib could enhance antitumor immunity and extend efficacy in these patients.

Patients and methods: This open-label phase Ib trial was conducted in adults aged ≥18 years who had advanced, unresectable NSCLC. Stage 1 (safety evaluation) enrolled EGFR TKI-naive patients regardless of *EGFR* status. Stage 2 (expansion) enrolled patients with *EGFR*-mutant NSCLC treated with ≤1 prior non-EGFR TKI therapy. Patients received 150 mg erlotinib orally once daily. After a 7-day erlotinib run-in, atezolizumab 1200 mg was administered intravenously every 3 weeks. The primary endpoint was the safety and tolerability of the combination in all patients; secondary endpoints included antitumor activity per RECIST 1.1 in stage 2 patients.

Results: At the data cut-off on 7 May 2020, 28 patients (8 in stage 1, 20 in stage 2) were assessable for safety. No dose-limiting toxicities or grade 4 or 5 treatment-related adverse events occurred. Grade 3 treatment-related adverse events occurred in 46% of patients; the most common were increased alanine aminotransferase, diarrhea, pyrexia, and rash (each in 7% of patients). Serious adverse events occurred in 50% of patients. Pneumonitis (grade 1) was reported in a single patient (4%). The objective response rate was 75% [95% confidence interval (CI) 50.9% to 91.3%]), median response duration was 18.9 months (95% CI 9.5-40.5 months), median progression-free survival was 15.4 months (95% CI 8.4-39.0 months), and median overall survival was not estimable (NE) (95% CI 34.6-NE).

Conclusions: Atezolizumab combined with erlotinib demonstrated a tolerable safety profile and encouraging, durable clinical activity in patients with advanced *EGFR* mutation-positive NSCLC.

Key words: *EGFR*-mutant NSCLC, PD-L1 inhibitor, immune checkpoint inhibitor, tyrosine kinase inhibitor

INTRODUCTION

Lung cancer remains the leading cause of cancer mortality worldwide, with non-small-cell lung cancer (NSCLC) accounting for 80% to 85% of cases.[1] Epidermal growth factor receptor (*EGFR*) mutations are present in ∼15% of patients with NSCLC in the USA and in up to 50% of patients of Asian descent; 90% of all patients with *EGFR*-mutant NSCLC have mutations associated with sensitivity to EGFR tyrosine kinase inhibitors (TKIs).[2]

TKI therapy is recommended as first-line treatment of patients with NSCLC whose tumors harbor an oncogenic *EGFR* mutation.[3,4] Approved EGFR TKIs include the first-generation agents erlotinib and gefitinib, second-generation agents afatinib and dacomitinib, and the third-generation agent osimertinib.[5] Substantial efficacy has been seen with these agents, with objective response rates (ORRs) of 56% to 83%, median progression-free survival (PFS) of 9.2-18.9 months, and median overall survival (OS) of 19.3-38.6 months.[5,6] Nevertheless, despite the high-level activity observed with these TKIs in patients with *EGFR*-mutant NSCLC, the resulting clinical benefits are almost always transient; acquired resistance is typically inevitable regardless of the agent used in the first-line setting,[7-10] highlighting the need for more effective treatment options for these patients.

Correspondence to: Dr Charles M. Rudin, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065, USA. Tel: +1-646-497-9163

E-mail: rudinc@mskcc.org (C. M. Rudin).

Recent advances in the development of immune check-point inhibitors (ICIs), including monoclonal antibodies targeting programmed death-ligand 1 (PD-L1) and pro-grammed cell death protein 1 (PD-1), have significantly improved treatment outcomes in NSCLC. Patients whose tumors harbor *EGFR* mutations, however, experience limited efficacy with PD-L1/PD-1 inhibition relative to those with wild-type tumors. Single-agent PD-L1 and PD-1 in-hibitors have not shown a significant survival benefit compared with cytotoxic agents such as docetaxel in patients with previously treated *EGFR*-mutant disease.[11-14]

The transient nature of TKI benefit has prompted attempts to improve the durability of response to EGFR TKIs. One such strategy, combining EGFR TKIs with PD-L1/PD-1 inhibition, is predicated on preclinical and correlative analyses demon-strating that PD-L1 is frequently up-regulated in NSCLC tu-mors with activating *EGFR* mutations, and that activation of the PD-1 pathway contributes to immune escape in *EGFR*-driven lung cancer models.[15-18] Initial studies evaluating combinations of EGFR TKIs and PD-L1/PD-1 inhibitors in NSCLC suggested rare durable responses,[19] but have been limited by unanticipated combinatorial toxicities, including grade 3/4 liver toxicity in >40% of patients treated with gefitinib and either durvalumab or pembrolizumab, and interstitial lung disease (ILD) in patients treated with osi-mertinib and durvalumab.[20-22] The high incidence of ILD in particular resulted in early termination of the CAURAL trial, which had been designed to test osimertinib and durvalu-mab versus osimertinib monotherapy.[23]

Atezolizumab is an anti-PD-L1 monoclonal antibody that inhibits binding of PD-L1 to its receptors, PD-1 and B7-1.[24] Atezolizumab is currently approved as first-, second-, and later-line treatment of advanced or metastatic NSCLC, and as adjuvant treatment in patients with PD-L1-positive early-stage NSCLC, after demonstrating efficacy and safety alone and in combination with chemotherapy, with or without bevacizumab.[14,25-30] Atezolizumab monotherapy is approved in both the USA and Europe for treatment of patients with *EGFR*-mutant NSCLC who have had disease progression on an approved TKI therapy.[25,31-33]

In the global, randomized phase III IMpower150 trial, first-line treatment with atezolizumab, bevacizumab, carboplatin, and paclitaxel prolonged PFS and OS versus bevacizumab, carboplatin, and paclitaxel in non-squamous advanced or metastatic NSCLC, including for patients with *EGFR*-mutant tumors.[26,34] Subgroup analyses of IMpower150 patients suggested an OS benefit for atezoli-zumab, bevacizumab, carboplatin, and paclitaxel versus bevacizumab, carboplatin, and paclitaxel in patients with sensitizing *EGFR* mutations, including those with prior TKI failures.[34,35] These results support the hypothesis that combining atezolizumab with other targeting agents such as EGFR TKIs could offer durable treatment benefits for pa-tients with *EGFR*-mutant NSCLC.

This open-label, multicenter phase Ib study was con-ducted to evaluate the safety and clinical activity of ate-zolizumab in combination with erlotinib in EGFR TKI treatment-naive patients with advanced NSCLC. Erlotinib

inhibits epidermal growth factor-dependent proliferation of cells at submicromolar concentrations, blocks cell cycle progression in the G1 phase, and can promote cell death in EGFR-dependent tumors.[36] Additionally, like other EGFR TKIs, erlotinib can influence immune/inflammatory re-sponses by directly modulating major histocompatibility complex expression, which may enhance priming and activation of effector T-cell responses.[37] Therefore, we hy-pothesized that combining erlotinib with atezolizumab might provide durable antitumor effects in patients with *EGFR*-mutant NSCLC.

METHODS

Study design, patients, and treatment

This open-label, multicenter, global phase Ib trial (NCT02013219) was conducted to investigate the safety, tolerability, and clinical activity of atezolizumab combined with erlotinib in patients with advanced, unresectable NSCLC. During the safety evaluation stage (stage 1), patients with advanced NSCLC who were EGFR TKI treatment-naive were enrolled regardless of *EGFR* mutation status. This stage was designed to establish the safety and tolerability of the combination and to identify a recommended phase II dose (RP2D) and schedule for atezolizumab in combination with erlotinib. The expansion stage (stage 2) was conducted to evaluate the dose combination established as RP2D in stage 1 in an expansion cohort of patients with *EGFR* mutation-positive advanced NSCLC who had not been pre-viously treated or who had received one prior treatment that was not an EGFR TKI.

Eligible patients were ≥18 years of age and had histologically or cytologically documented advanced or metastatic NSCLC, measurable disease per Response Eval-uation Criteria in Solid Tumors (RECIST) 1.1 and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. Patients in stage 1 were not required to have tumors with *EGFR* mutations and could have received prior systemic treatment (except for EGFR TKIs) for advanced or metastatic disease. Patients in stage 2 were required to have *EGFR*-mutant tumors and could have received at most one prior systemic treatment (except for *EGFR* TKIs) for advanced or metastatic disease. Key exclusion criteria included prior treatment with any EGFR TKI, known primary central nervous system metastases, and prior treatment with approved anticancer agents within 3 weeks of study initiation or with any other investigational agent(s) within 4 weeks of randomization.

The study conformed to Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Indepen-dent ethics committees or institutional review boards approved the study protocol at each site, and all patients provided written informed consent to participate in the study. The trial was registered with ClinicalTrials.gov (NCT02013219).

The study design called for the first patient in stage 1 to be given a starting dose of 150 mg erlotinib (i.e. the rec-ommended single-agent dose) orally once daily. Following a

1-week run-in period of erlotinib, a starting dose of 1200 mg atezolizumab was to be administered intravenously every 3 weeks. If the first patient did not experience unacceptable toxicity during the first 3 weeks of receiving the combination therapy, the remaining patients would be enrolled into stage 1 and receive the same combination regimen. If the starting combination regimen was not tolerated, alternative dosing and/or schedules of atezolizumab and erlotinib would be tested to define the RP2D.

The dose-limiting toxicity (DLT) window in stage 1 was 21 days, starting from the first administration of atezolizumab plus erlotinib. A DLT was defined as treatment-related grade ≥ 4 neutropenia lasting ≥ 7 days; grade ≥ 4 thrombocytopenia lasting ≥ 7 days or associated with bleeding; grade ≥ 3 non-hematologic, non-hepatic organ toxicity; grade ≥ 3 symptomatic hepatic toxicities lasting ≥ 48 h; or grade ≥ 3 asymptomatic hepatic toxicities lasting > 7 days, with exceptions. The highest dose level(s) at which less than one-third of the first dose cohort planned to be enrolled in stage 1 experienced a DLT was declared the combination maximally tolerated dose and defined the RP2D. All patients enrolled in stage 2 began treatment at the RP2D for this combination.

Treatment could continue in both stages for as long as a patient experienced clinical benefit, as determined by the investigator after assessment of radiographic data, biopsy results, and the patient's clinical status. Patients who discontinued atezolizumab for reasons other than disease progression could continue erlotinib treatment on study until disease progression per RECIST 1.1.

Assessments and endpoints

The primary safety endpoint was the incidence and nature of DLTs, with secondary endpoints being the incidence, nature, and severity of adverse events (AEs) according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0, as well as changes in vital signs and laboratory abnormalities. AEs of any cause were recorded until 30 days after the last dose of the study treatment or until study discontinuation/termination, initiation of subsequent anticancer therapy, consent withdrawal, or death, whichever occurred first. Patients continuing to experience treatment-related adverse events (TRAEs) beyond 30 days following the last dose of study treatment were followed until the event had resolved to baseline grade, the event was stable per investigator assessment, or the patient had begun a subsequent anticancer treatment, whichever occurred first.

Clinical activity endpoints evaluated were investigator-assessed ORR and PFS per RECIST 1.1, as well as duration of confirmed objective response [duration of response (DOR)] and OS.

Tumors were assessed by computed tomography scan at baseline; 7 weeks after treatment start (cycle 1, day 1); every 6 weeks thereafter through week 37; and every 12 weeks thereafter until radiologic disease progression per RECIST 1.1, patient death, consent withdrawal, or termination of study by sponsor, whichever occurred first. Responses were documented as complete response (CR), partial response (PR), stable disease, or progressive disease per RECIST 1.1.

Statistical analysis

It was planned that approximately 26 to 32 patients would be enrolled into the study, with 6-12 patients in the safety evaluation stage and ~20 in the expansion stage. Determination of sample sizes was based on goals of obtaining preliminary safety, efficacy, pharmacokinetic, and pharmacodynamic data; explicit power and type I error considerations were not made for this study.

Analyses were carried out in either the safety-evaluable population, defined as all patients who received any amount of any study treatment, or the efficacy-evaluable population, defined as all patients who received at least one dose of atezolizumab plus erlotinib, and had measurable disease per RECIST 1.1. Means, standard deviations, medians, and ranges were used to summarize continuous variables, and categorical variables were summarized using counts and percentages. All summaries were tabulated or listed by dose cohort. Safety was assessed through summaries of AEs by mapped term and National Cancer Institute Common Terminology Criteria for Adverse Events toxicity grade, changes in laboratory test results, and changes in vital signs.

Data on ORR, DOR, PFS, and OS were listed for all patients by study stage and summarized overall. ORR was defined as the proportion of patients with a PR or CR, as determined by investigator assessment per RECIST 1.1 and confirmed by repeat assessments ≥ 4 weeks after initial documentation. Patients who did not meet these criteria, including those without any post-baseline tumor assessment, were considered to be non-responders. DOR for patients who achieved an objective response was defined as the time from the initial CR or PR to the time of disease progression or death, whichever occurred first. DOR for patients who did not experience disease progression or death before the end of the study was censored at the day of the last tumor assessment. PFS was defined as the time from the first day of study treatment to disease progression or death, whichever occurred first; PFS was censored at the day of the last tumor assessment for patients who did not experience disease progression or death at the end of the study. OS was defined as the time from the first dose of study treatment to the time of death from any cause during the study. Time to event analyses for DOR, PFS, and OS were done using the Kaplan—Meier method, with accompanying 95% confidence intervals (CIs) constructed using the Brookmeyer and Crowley method.

RESULTS

Patient characteristics

Between 3 April 2014 and 12 August 2015, 28 patients were enrolled into this study at 10 sites in Spain, France, Great Britain, Hong Kong, and the USA; 8 patients were enrolled

Table 1. Baseline characteristics

Characteristic	Stage 1 (n = 8)	Stage 2 (n = 20)	All patients (n = 28)
Median age (range), years	72 (47-84)	57.5 (47-74)	61 (47-84)
Sex, n (%)			
Male	4 (50)	4 (20)	8 (29)
Female	4 (50)	16 (80)	20 (71)
Race, n (%)			
Asian	0	6 (30)	6 (21)
Black/African American	1 (13)	2 (10)	3 (11)
White	6 (75)	8 (40)	14 (50)
Other	0	1 (5)	1 (4)
Unknown	1 (13)	3 (15)	4 (14)
ECOG performance status, n (%)			
0	0	7 (35)	7 (25)
1	8 (100)	13 (65)	21 (75)
Smoking status, n (%)			
Current	0	1 (5)	1 (4)
Prior	8 (100)	7 (35)	15 (54)
Never	0	12 (60)	12 (43)
Histology type			
Squamous	1 (13)	0	1 (4)
Non-squamous	7 (88)	20 (100)	27 (96)
Prior cancer therapy	7 (88)	3 (15)	10 (36)
Prior radiotherapy	5 (63)	7 (35)	12 (43)
EGFR mutation, n	5	20	25
Exon 19 deletion	1 (14)	11 (55)	12 (48)
Exon 20 insertion	0	1 (5)	1 (4)
L858R	0	5 (25)	5 (20)
L861Q	0	1 (5)	1 (4)
Other	1 (14)	2 (10)	3 (12)
Not done	3 (60)	0	3 (12)

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

Table 2. Safety summary and highest grade of TRAEs

n (%)	Stage 1 (n = 8)	Stage 2 (n = 20)	All patients (n = 28)
Any AE	8 (100)	20 (100)	28 (100)
Grade 3 AE	5 (63)	15 (75)	20 (71)
Grade 4 or 5 AE	0	0	0
Serious AE	5 (63)	9 (45)	14 (50)
Any TRAE	8 (100)	20 (100)	28 (100)
Grade 3 TRAE[a]	3 (38)	10 (50)	13 (46)
Grade 4 or 5 TRAE	0	0	0
Treatment-related SAE[b]	2 (25)	6 (30)	8 (27)
AE leading to atezolizumab withdrawal	1 (13)	5 (25)	6 (21)
AE leading to erlotinib withdrawal	2 (25)	1 (5)	3 (11)
AE leading to dose modification/interruption	6 (75)	15 (75)	21 (75)
Grade 3 AEs related to atezolizumab[c]			
Rash	0	2 (10)	2 (7)
ALT increase	0	2 (10)	2 (7)
Pyrexia	0	2 (10)	2 (7)
Any AESI	7 (88)	20 (100)	27 (96)
Grade 3 AESI	2 (25)	7 (35)	9 (32)
Liver-related AESI			
Immune-mediated hepatitis (diagnosis and laboratory abnormalities)	1 (13)	9 (45)	10 (36)
Grade 3 immune-mediated hepatitis (diagnosis and laboratory abnormalities)[d]	0	4 (20)	4 (14)[d]
Lung-related AESI			
Pneumonitis[e]	0	1 (5)	1 (4)

AE, adverse event; AESI, adverse events of special interest; ALT, alanine aminotransferase; SAE, serious adverse events; TRAE, treatment-related adverse event.
[a]No grade 4 or 5 TRAEs occurred.
[b]Atezolizumab-related serious AEs were colitis, diarrhea, hemorrhoidal hemorrhage, pyrexia, increased liver function test, myopathy, occipital neuralgia, and deep vein thrombosis (each in 1 patient).
[c]Occurring in ≥2 patients.
[d]ALT increased (n = 2), blood bilirubin increased (n = 1), and liver function test increased (n = 1).
[e]Grade 1 or 2.

into stage 1 and 20 patients into stage 2. The median age of the study population was 61 years (range 47-84 years); 20 patients (71%) were women, 21 (75%) had ECOG PS of 1, and 12 (43%) had never smoked (Table 1). Ten patients (36%) had prior cancer therapy and 12 (48%) had prior radiotherapy. Two patients (28%) in stage 1 had EGFR mutations. In stage 2, which enrolled only patients with EGFR mutations, the most common were exon 19 deletions in 11 of 20 tested patients (55%) and L858R mutations in 5 patients (25%) (Table 1).

Safety

The median treatment duration in the safety population of 28 patients was 314 days (range 1-1592 days). The median number of atezolizumab doses was 13 (range 1-75).

The safety profile of the combination of atezolizumab and erlotinib was acceptable, with no DLTs, no grade 4 or 5 AEs, and no grade 4 or 5 TRAEs reported. Although TRAEs were reported by all patients (Table 2), they were mostly grade 1 and 2. Thirteen patients experienced grade 3 TRAEs; each occurred only in one patient, except for increased alanine aminotransferase (ALT), pyrexia, and rash, which each occurred in two patients (Table 2).

AEs that led to atezolizumab withdrawal in six patients (21%) were myopathy, pyrexia, low-grade chest pain, arthralgia, hemorrhoidal hemorrhage, and acneiform dermatitis. AEs that led to erlotinib withdrawal in three

patients (11%) were dyspnea, deep vein thrombosis, and increased ALT. AEs resulted in dose modification or interruption in 12 patients (75%).

Adverse events of special interest (AESIs) for atezolizumab occurred in 27 patients (46%) and in 9 patients (32%) at grade 3 (Table 2). The only grade 3 AESIs associated with liver function were ALT increased in two patients (7%), blood bilirubin increased in one patient (4%), and liver function tests increased in one patient (4%); all other AESIs associated with liver function occurred at grade ≤2, and none led to treatment withdrawal.

No grade ≥3 lung-associated AESIs were reported in this study, although grade 1 pneumonitis, discovered in routine computed tomography imaging, occurred in one patient (4%; Table 2). This was an asymptomatic radiology finding described as 'increased right basilar clustered opacities, probably infectious/inflammatory,' with an indeterminate right middle lobe opacity 'possibly also infectious/inflammatory with/without component of mucoid impaction.' The patient was treated with a 15-day course of prednisone 20 mg daily and the radiological findings improved on subsequent computed tomography scans. Treatment with

Table 3. Summary of efficacy in patients with *EGFR*-mutated NSCLC

	Stage 2 (*n* = 20)
Confirmed ORR, *n* (%)	15 (75)
[95% CI]	[50.9-91.34]
CR, *n* (%)	0
[95% CI]	[0.00-16.84]
PR, *n* (%)	15 (75)
[95% CI]	[50.9-91.34]
SD, *n* (%)	3 (15.0)
[95% CI]	[3.21-37.89]
PD, *n* (%)	2 (10)
[95% CI]	[1.23-31.7]
DCR[a], *n* (%)	18 (90)
[95% CI]	[68.3-98.77]
Median DOR, months	18.9
[95% CI for median]	[9.7-40.5]
Range (censored)	4.2-50.4
Median PFS, months	15.4
[95% CI for median]	[8.4-39.0]
Range (censored)	1.6-53.3
Median OS, months	NE
[95% CI for median]	[34.6-NE]
Range (censored)	11.4-53.3

CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; *EGFR*, epidermal growth factor receptor; NE, not evaluable; NSCLC, non-small-cell lung cancer; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
[a]CR + PR + SD ≥24 weeks.

erlotinib continued throughout; one cycle of atezolizumab was skipped, after which atezolizumab treatment resumed, and the patient remained on erlotinib with atezolizumab for another 9 months.

Efficacy

Efficacy analysis focused on the 20 patients with *EGFR*-mutated NSCLC enrolled in stage 2, and data are presented here based on a data cut-off of 7 May 2020. After a median 44.8 months of survival follow-up, 15 patients had a confirmed PR; hence, the ORR of atezolizumab plus erlotinib was 75% (Table 3). The disease control rate was 90%. In addition to the 15 patients (75%) who had a PR, 3 patients (15%) had durable stable disease (≥24 weeks). Four patients had an ongoing response at the time of study discontinuation.

Median OS was not evaluable (95% CI 34.6-not evaluable), and duration of survival ranged from 11.4 to 53.3 (censored) months (Figure 1A). Median PFS was 15.4 months (95% CI 8.4-39.0 months), ranging from 1.6 to ≥53.3 (censored) months (Figure 1B). Clinical responses to this treatment combination were durable: the median DOR was 18.9 months (95% CI 9.7-40.5 months), ranging from 4.2 to ≥50.4 (censored) months (Figure 1C and D). In three patients, clinical responses continued after discontinuation of atezolizumab treatment throughout the duration of follow-up (Figure 1D).

DISCUSSION

This is the first study to investigate the safety and clinical activity of combining atezolizumab immunotherapy with the TKI erlotinib in patients with advanced NSCLC. The safety

and efficacy findings from this final analysis after an additional median 18 months of follow-up were consistent with those reported after 26 months of follow-up.[38] The median DOR in patients whose NSCLC had *EGFR* mutations was 18.9 months and the median OS remains not evaluable, with 40% of events having occurred. Whereas the median OS was not reached, the lower bound of the 95% CI was 34.6 months, however, with many of the censored events occurring at 40 months or later. Recent studies of erlotinib monotherapy in patients with *EGFR*-mutant NSCLC have reported median OS >45 months.[39,40] The median PFS and ORR with this combination compared favorably with those observed with erlotinib monotherapy,[41,42] and also with ORRs reported in other phase I/II trials of EGFR TKIs combined with ICIs in patients with *EGFR*-mutant NSCLC, which ranged from 42% to 70% in the first-line setting and from 15% to 67% in the second-line setting.[19-22]

Atezolizumab plus erlotinib demonstrated a tolerable safety profile, with the majority of TRAEs being non-severe and manageable. Although treatment-limiting liver[22] and lung[21] toxicities have been reported with other combinations of immunotherapy and EGFR TKIs, these were notably not observed in this study. In the phase I/II KEYNOTE-021 study that evaluated the feasibility of combining erlotinib or gefitinib with pembrolizumab, pembrolizumab combined with gefitinib was found not to be feasible because grade 3/4 liver toxicity occurred in five of seven patients (71.4%), leading to permanent treatment discontinuation in four of them.[22] Liver toxicity was not observed in the patients treated with pembrolizumab plus erlotinib, consistent with our data using atezolizumab.

ILD was another potential concern, given that more ILD events were reported with osimertinib plus durvalumab compared with either drug alone in the phase Ib TATTON study in patients with *EGFR*-mutant NSCLC.[21] In that study, ILD occurred in 13 of 34 patients (38%) receiving combination treatment and in 2.9% and 2%, respectively, of patients receiving osimertinib and durvalumab alone. Due to the increased incidence of ILD in TATTON, recruitment into CAURAL (NCT02454933), a phase III study of osimertinib plus durvalumab versus osimertinib monotherapy, was terminated early.[23] A total of 1 of 14 patients (7.1%) randomized to the combination arm reported grade 2 ILD while receiving osimertinib monotherapy after discontinuing durvalumab therapy, having received only one dose. Pneumonitis was not a concern when erlotinib was combined with nivolumab or pembrolizumab in the phase I CheckMate 012 (NCT01454102)[19] or phase I/II KEYNOTE-021 (NCT02039674)[22] studies. Together these data suggest that erlotinib may represent a more attractive TKI backbone for immunotherapy combinations for treatment of *EGFR*-mutant NSCLC. Further research will be needed to determine whether the low rate of pneumonitis reported here and in other small studies of erlotinib with ICIs can be confirmed in larger trials. Overall, the data from this study suggest that atezolizumab can be safely combined with erlotinib and may be associated with durable benefit in some patients.
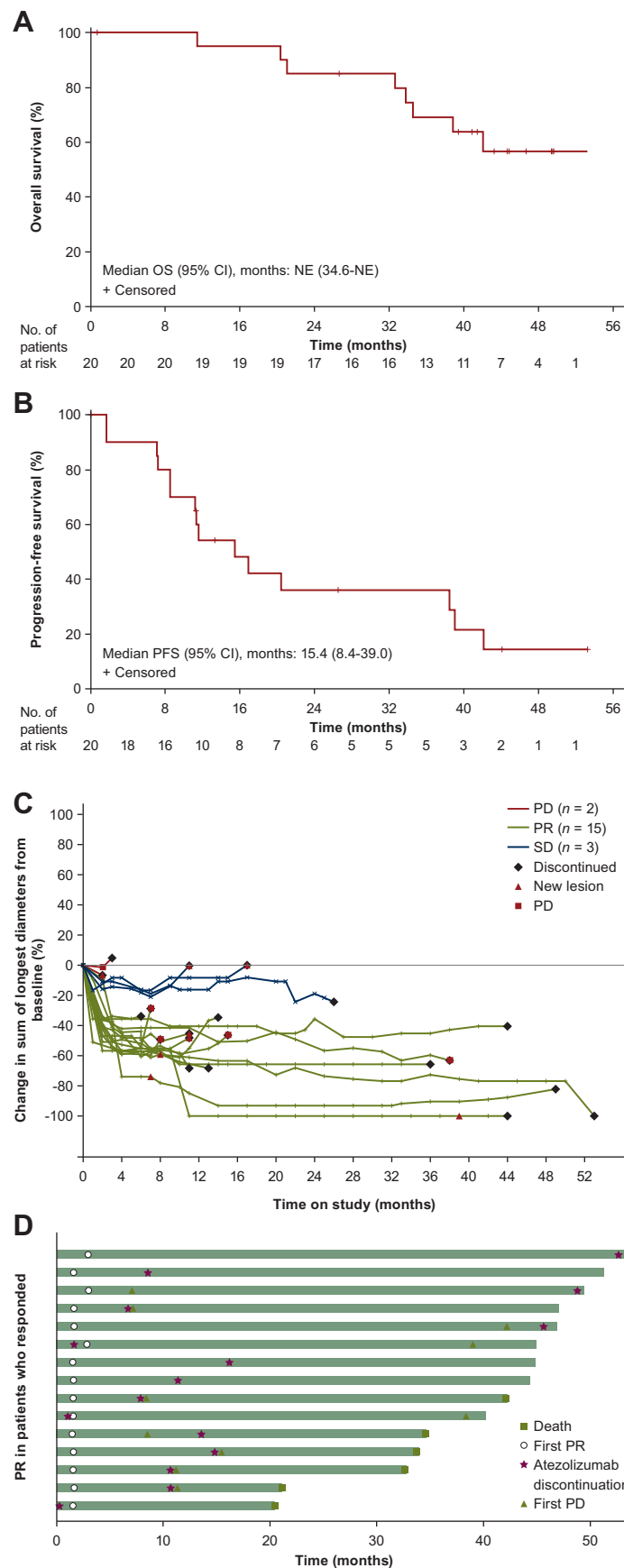
Figure 1. Clinical activity in stage 2 (*n* = 20). Kaplan−Meier curves of (A) overall survival and (B) progression-free survival. (C) Spaghetti plot of tumor burden over time by investigator-confirmed response per RECIST 1.1. (D) Swimlane plot showing duration of investigator-assessed confirmed partial responses per Response Evaluation Criteria in Solid Tumors 1.1.

CI, confidence interval; CR, complete response; NE, not evaluable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

In preclinical studies, activation of the EGFR pathway induced PD-L1 expression and other immunosuppressive factors that limit host antitumor immune response, suggesting an active role for *EGFR* in remodeling the tumor microenvironment.[16] *EGFR* mutation has been correlated with increased PD-L1 expression, lack of CD8+ T-cell infiltration, and lower tumor mutation burden in pooled clinical trial and sequence database analyses.[43] Elevated PD-L1 expression has also been correlated with poor response and *de novo* resistance to EGFR TKIs among patients with *EGFR*-mutated NSCLC.[44] These data suggest that the immune microenvironment is an important factor in responses to targeted therapy and imply that patients with poor responses to EGFR TKIs, especially those with *de novo* resistance, might in particular benefit from the addition of ICI.

In conclusion, atezolizumab combined with erlotinib demonstrated a tolerable safety profile and encouraging, durable clinical activity in patients with NSCLC harboring *EGFR* mutations.

DISCLOSURE

CMR has received personal fees from AbbVie, Amgen, AstraZeneca, D2G, Daiichi Sankyo, Epizyme, Genentech/Roche, Ipsen, Jazz, Kowa, Lilly, Merck, Syros, Bridge Medicines, Earli, and Harpoon Therapeutics outside the submitted work.

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DATA SHARING

For eligible studies qualified researchers may request access to individual patient-level clinical data through a data request platform. At the time of writing this request platform is Vivli (https://vivli.org/ourmember/roche/). For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see https://go.roche.com/data_sharing. Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient re-identification.

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