Title

A randomized phase II trial of atezolizumab with or without tiragolumab before and after definitive chemoradiation for unresectable stage III non-small cell lung cancer (NSCLC; AFT-57)

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Atezolizumab Before and After Chemoradiation for Unresectable Stage III Non–Small Cell Lung Cancer
A Phase II Nonrandomized Controlled Trial

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IMPORTANCE Outcomes for patients with unresectable stage III non–small cell lung cancer (NSCLC) treated with chemoradiation therapy (CRT) have improved with adjuvant immune checkpoint inhibitors, with a reported 5-year overall survival benefit of approximately 10% for adjuvant durvalumab vs placebo after completion of CRT without progression and with preserved performance status. Starting atezolizumab prior to CRT may allow more patients to benefit from immunotherapy.

OBJECTIVE To evaluate clinical outcomes of patients treated with atezolizumab before and after CRT for unresectable stage III NSCLC.

DESIGN, SETTING, AND PARTICIPANTS This single-cohort, phase II, nonrandomized controlled trial was conducted at 11 US sites. Patients with pathologically confirmed, unresectable stage III NSCLC who were treatment naive and had good performance status were enrolled between January 3, 2018, and July 24, 2019. Data were locked on March 21, 2023.

INTERVENTIONS Patients received four 21-day cycles of atezolizumab, 1200 mg intravenously, with therapy administered on day 1 of each cycle. Patients not experiencing tumor progression continued to CRT (60 Gy to involved fields) concurrent with weekly carboplatin area under the curve of 2 and paclitaxel, 50 mg/m^2, followed by planned consolidation carboplatin area under the curve of 6 and paclitaxel, 200 mg/m^2, for two 21-day cycles. Patients not experiencing progression continued atezolizumab, 1200 mg, every 21 days to complete 1 year of therapy.

MAIN OUTCOMES AND MEASURES The primary end point was the disease control rate at 12 weeks. Secondary end points were progression-free survival, overall survival, overall response rate, safety, and translational science end points.

RESULTS A total of 62 patients (median [range] age, 63.9 [38.1-86.5] years; 32 female [51.6%]) were enrolled and received at least 1 dose of atezolizumab. The disease control rate at 12 weeks was 74.2% (80% CI, 65.7%-81.4%). Median progression-free survival was 30.0 months (95% CI, 15.8 to not evaluable), and the median overall survival was not reached. The overall survival rate at 24 months was 73.7% (95% CI, 63.4%-85.7%), and the overall response rate was 66.2%. Seventeen patients (27.4%) experienced grade 3 or higher immune-related adverse events, including 1 with grade 5 pneumonitis and 1 with grade 4 Guillain-Barré syndrome. Thirty patients (48.4%) experienced grade 3 or higher treatment-related adverse events.

CONCLUSIONS AND RELEVANCE These findings suggest that neoadjuvant atezolizumab merits further study based on safety and encouraging outcomes.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03102242

Editor's Note

Supplemental content

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Attempts to improve outcomes for unresectable stage III non-small cell lung cancer (NSCLC) with induction chemotherapy, new chemotherapy combinations, or radiation dose escalation have been unsuccessful.[1-3] The phase III PACIFIC (MEDI4736 Following Concurrent Chemoradiation in Patients With Stage III Unresectable NSCLC) trial found that adjuvant durvalumab increased curability.[4,5] The PACIFIC participants had completed chemoradiation therapy (CRT) with preserved performance status and without progressive disease or major lingering toxic effects prior to study entry. Results must be interpreted cautiously since eligibility did not require positron emission tomography–computed tomography (CT) and brain magnetic resonance imaging (MRI), and radiation quality assurance data were not captured. The PACIFIC 5-year update reported survival rates of 42.9% (durvalumab) and 33.4% (placebo).[5]

This study, the Alliance Foundation Trial (AFT)-16, evaluated the feasibility of neoadjuvant atezolizumab to allow more patients to receive immune checkpoint inhibitor (ICI) therapy and to potentially better prime the immune system before CRT. The primary end point, disease control rate (DCR) at 12 weeks, was designed to ensure that delayed CRT would not compromise outcomes.

Key Points

Question What are the clinical outcomes of using atezolizumab before and after chemoradiation therapy for unresectable stage III non–small cell lung cancer (NSCLC)?

Findings In this nonrandomized controlled trial of 62 adults with unresectable stage III NSCLC, the disease control rate for neoadjuvant atezolizumab at 12 weeks was 74.2%. The median progression-free survival was 30.0 months, and the 24-month survival rate was 73.7%.

Meaning These findings suggest the need for further study of neoadjuvant immunotherapy for unresectable stage III NSCLC in randomized clinical trials.

Methods

Study Design and Patients

This single cohort, phase II, nonrandomized controlled trial enrolled patients between January 3, 2018, and July 24, 2019, at 11 US Alliance sites and followed Good Clinical Practice guidelines and the Declaration of Helsinki.[6] The protocol was approved by the AFT/Advarra Central Institutional Review Board and the institutional review boards at participating sites. Data and safety were monitored by the study team and by the AFT data safety monitoring board. All patients provided written informed consent prior to initiation of study procedures. The trial protocol is provided in Supplement 1. The study followed the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) reporting guideline.

Patients eligible for the study were treatment naive; had unresectable, histologically confirmed stage IIIA/B (by the seventh edition of the *AJCC Cancer Staging Manual*[7]) NSCLC; were aged 18 years or older; and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, adequate laboratory and pulmonary function (forced expiratory volume in 1 second >1.2 L), and measurable disease by Response Evaluation Criteria in Solid Tumors, version 1.1.[8] Patients were excluded if they had a clinically significant autoimmune condition, heart or lung disease, or pneumonitis. Tissue was required for programmed cell death ligand 1 (PD-L1) expression and correlative science.

At the time of study design, patients with epidermal growth factor receptor or anaplastic lymphoma kinase alterations were not excluded from immunotherapy trials, and variant testing was not routine for patients with locally advanced NSCLC. The epidermal growth factor receptor and anaplastic lymphoma kinase alteration status of participants is unknown.

History and physical examination, contrast-enhanced CT of the chest and upper abdomen, MRI of the brain with contrast (or CT with contrast if MRI was medically contraindicated), and fluorodeoxyglucose positron emission tomography–CT were required within 6 weeks prior to entry. Participant demographics included self-identified race and ethnicity to comply with National Institutes of Health guidelines for clinical trials.[9]

Treatment

Participants received 4 cycles of intravenous (IV) atezolizumab, 1200 mg, every 21 days preceding involved-field CRT (60 Gy in 30 fractions) plus weekly carboplatin area under the curve of 2 and paclitaxel, 50 mg/m^2. Conformal 3-dimensional or intensity-modulated radiation therapy treatment planning was used. The Imaging and Radiation Oncology Core Rhode Island Quality Assurance Review Center reviewed the treatment plans in advance.

Two cycles of consolidation carboplatin area under the curve of 6 and paclitaxel, 200 mg/m^2, every 21 days preceded adjuvant atezolizumab, 1200 mg IV, every 21 days to complete 1 year of therapy. Consolidation carboplatin and paclitaxel could be omitted at the discretion of the treating investigator with study team concurrence.

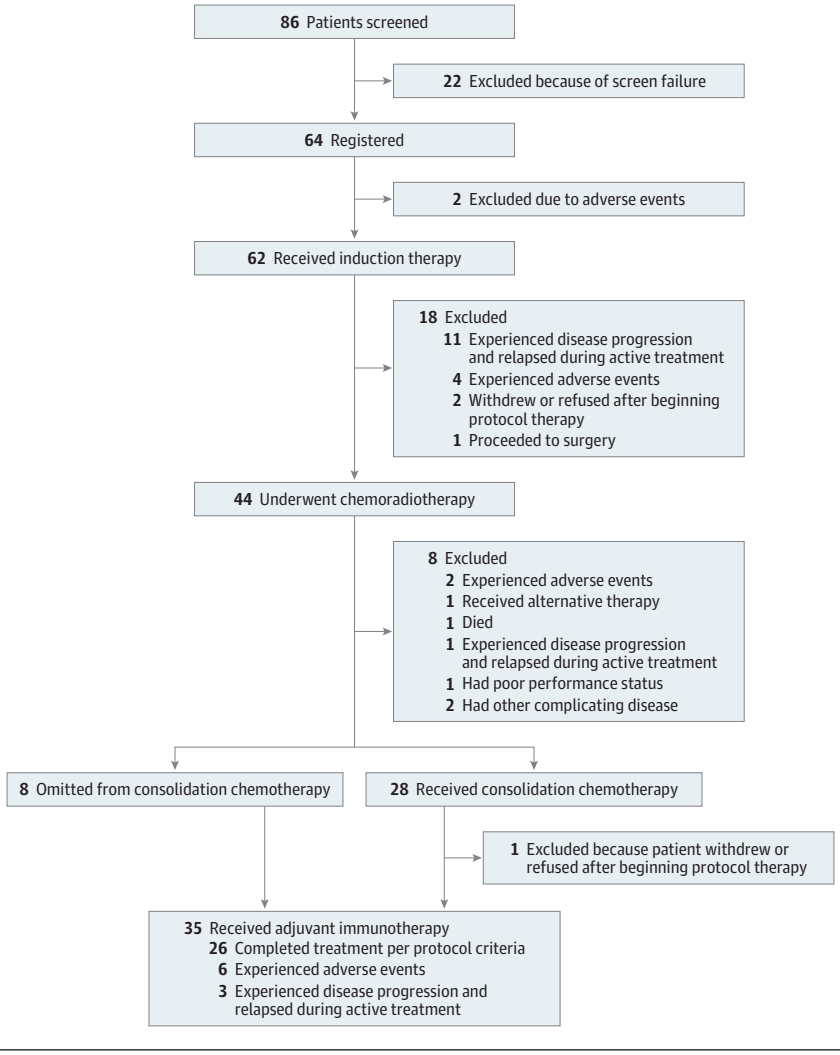
Assessments

Toxicity assessments ensured patient suitability for ongoing study participation at each visit. Computed tomography was performed at baseline, during and after neoadjuvant atezolizumab, after CRT, every 3 months during adjuvant atezolizumab, and after completion of adjuvant atezolizumab, with assessed response per Response Evaluation Criteria in Solid Tumors, version 1.1.[8] Pulmonary function was assessed at baseline, between atezolizumab treatment and CRT, and at 12 months. Adverse events were assessed using Common Terminology Criteria for Adverse Events, version 4.0.[10]

End Points

The primary end point was DCR at 12 weeks. Secondary end points were progression-free survival (PFS), overall survival (OS), overall response rate (ORR), and safety. Exploratory analysis of PFS and OS in participants completing concurrent CRT provided a rough comparison with historical PACIFIC data.

Figure 1. Patient Flow Diagram



Translational science end points included correlation of PD-L1 expression with the DCR and assessment of the T-cell receptor (TCR) repertoire with outcome.[11] The eMethods in Supplement 2 provide more details.

Statistical Analysis

The DCR is the proportion of participants with a complete response, a partial response, or stable disease after neoadjuvant atezolizumab. The DCR from historical control recipients of neoadjuvant therapy was estimated at 50%. We projected a DCR for neoadjuvant immunotherapy at 67%, with a 17% increase considered clinically meaningful. Sixty treated patients meeting the eligibility criteria were estimated to provide approximately 90% power to detect a null hypothesis of $P \leq .50$ vs an alternative hypothesis of $P \geq .67$, where P is the DCR after 12 weeks of neoadjuvant atezolizumab with a 1-sided binomial test at a significance level of .10. The modified intention-to-treat population included all patients receiving at least 1 cycle of atezolizumab. The binomial exact test for the primary end point calculated an 80% 2-sided exact CI so that its coverage level is consistent with the level of the 1-sided test. The DCR at 6 weeks and its CI were also estimated. Data were kept in Medidata Rave (Medidata). Data quality assurance by the principal investigator (H.J.R.) followed Alliance policies.

The ORR is the rate of complete or partial response as the best overall response. Progression-free survival is the time from registration to disease progression or death. Overall survival is the time to death from any cause. Post hoc exploratory analysis estimated PFS and OS from the end of radiation therapy for participants who completed CRT. The Kaplan-Meier estimator was used for median PFS, OS, and event-free survival rates at 12 and 24 months.[12] Confidence intervals for median PFS and OS were estimated using the Brookmeyer-Crowley method.[13] The CIs for event-free rates at 12 and 24 months were estimated using the Greenwood method.

Other than the CI of the DCR at 12 weeks, all reported 2-sided CIs were computed at the 95% level without adjusting for multiplicity and may not be used in place of hypothesis testing. Correlative science statistical methods included Fisher exact test and log-rank test (PD-L1 comparisons) and

Wilcoxon rank sum test (TCR richness and Shannon diversity index comparisons), with a 2-sided $P < .05$ considered significant.

All participants receiving any atezolizumab were included in adverse event assessments. Treatment-related and immune-related adverse events were summarized by type and grade. Data were locked on March 21, 2023, and analyses were conducted by the study statisticians (X.F.W., G.D.N., J.G.). Data management, statistical analysis, and Kaplan-Meier plots were performed using SAS, version 9.4 software (SAS Institute Inc). Graphs were generated using R, version 3.6.3 (R Foundation).

Results

Patients

Sixty-four patients at 11 sites were enrolled (**Figure 1**). Two patients did not initiate study therapy; thus, 62 were included in the baseline characteristic, treatment, safety, and efficacy analyses. In accordance with the modified intention-to-treat analysis, 1 patient who was deemed ineligible (forced expiratory volume in 1 second <1.2 L) but received study therapy was included in the safety and efficacy analyses.

Participant characteristics are presented in **Table 1**. The median age of the participants was 63.9 years (range, 38.1-86.5 years), 32 were female (51.6%) and 30 male (48.4%), and 4 self-reported their race as Asian (6.5%), 9 as Black (14.5%), 48 as White (77.4%), and 1 as other race (1.6%). Seventeen participants (27.4%) were current smokers, and 38 (61.3%) were former smokers. Thirty-five participants (56.5%) had an ECOG performance status of 0. Expression of PD-L1 was positive (tumor proportion score ≥1%) in 13 of 49 participants (26.5%) with results available.

Table 1. Patient Characteristics

Characteristic	No. (%)
No. of patients	62
Age, y	
Median (IQR)	63.9 (57.7-71.1)
Range	38.1-86.5
Race	
Asian	4 (6.5)
Black, African American, or African heritage	9 (14.5)
White	48 (77.4)
Other (not further specified)	1 (1.6)
Sex	
Female	32 (51.6)
Male	30 (48.4)
Smoking history	
Current	17 (27.4)
Never	7 (11.3)
Former	38 (61.3)
Stage	
IIIA	33 (53.2)
IIIB	29 (46.8)
ECOG performance status	
0	35 (56.5)
1	27 (43.5)
Recurrent disease after resection	
No	60 (96.8)
Yes	2 (3.2)
Tumor PD-L1 status	
Positive (≥1%)	13 (26.5)
Negative (<1%)	36 (73.5)
Missing	13

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death ligand 1.

Treatment Outcomes

Forty-seven participants (75.8%) completed neoadjuvant therapy, and 44 (71.0%) completed CRT (Figure 1). The median number of treatment cycles was 8 (range, 1-17 cycles). Twenty-six participants (41.9%) completed all study therapy per protocol. Fifteen participants (24.2%) experienced disease progression during therapy (11 during neoadjuvant therapy, 1 during CRT, and 3 during adjuvant treatment).

The DCR after 12 weeks of neoadjuvant atezolizumab was 74.2% (80% CI, 65.7%-81.4%; 95% CI, 61.5%-84.5%); 17 participants (27.4%) had a partial response, and 29 (46.8%) had stable disease. The DCR after 6 weeks was similar at 77.4% (80% CI, 69.2%-84.3%; 95% CI, 65.0%-87.1%), including 1 participant classified as having stable disease with an immune flare during cycle 2.

The ORR was 66.2%, with 5 participants (8.1%) achieving a complete response and 36 (58.1%) a partial response. Seven participants (11.3%) had stable disease.

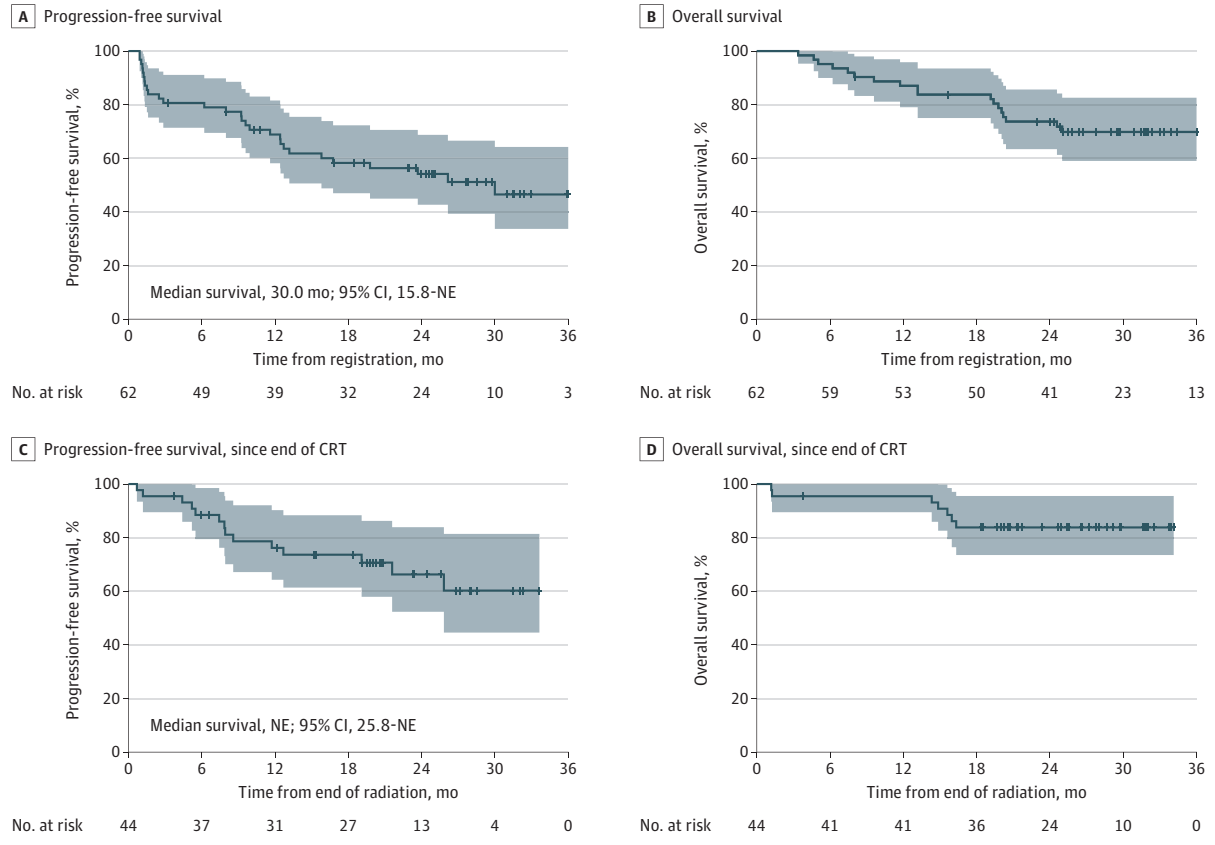
Eighteen participants (29.0%) died. The median follow-up for the 44 living participants was 31.2 months (range, 8.0-40.0 months). Median PFS was 30.0 months (95% CI, 15.8 to not evaluable), and the PFS rates at 12 and 24 months were 68.9% (95% CI, 58.1%-81.6%) and 54.2% (95% CI, 42.7%-68.7%), respectively (**Figure 2**A). The median OS was not reached, and the OS rates at 12 and 24 months were 87.0% (95% CI, 79.0%-95.8%) and 73.7% (95% CI, 63.4%-85.7%), respectively (Figure 2B). Twenty-four participants experienced progression, with lung (16 participants [66.7%]) and lymph nodes (4 participants [16.7%]) the most common sites of first progression (eTable 1 in Supplement 2).

In an exploratory analysis of the 44 participants who completed CRT, the median PFS was not reached; PFS rates at 12 and 24 months from the end of CRT were 76.2% (95% CI, 64.3%-90.3%) and 66.3% (95% CI, 52.4%-83.9%), respectively (Figure 2C). Exploratory analysis of OS calculated from the end of CRT showed that OS rates at 12 and 24 months were 95.5% (95% CI, 89.5%-100%) and 83.8% (95% CI, 73.5%-95.5%), respectively (Figure 2D).

Safety

Treatment-related and immune-related grade 3 or higher adverse events occurring in at least 5% of patients or any grade 4 or 5 adverse events are summarized in **Table 2**. Seventeen participants (27.4%) experienced grade 3 or higher immune-related adverse events, including 1 with grade 5 pneumonitis

Figure 2. Progression-Free and Overall Survival and Exploratory Analysis of the Patients Who Completed Concurrent Chemoradiation Therapy (CRT)



Shading indicates the 95% CI; tick marks, survival time censored. NE indicates not evaluable.

and 1 with grade 4 Guillain-Barré syndrome. Thirty participants (48.4%) experienced grade 3 or higher treatment-related adverse events. Twelve participants (19.4%) discontinued study therapy due to adverse events. For those 12 participants, the OS rates at 12 and 24 months were 90.9% (95% CI, 75.4%-100%) and 70.1% (95% CI, 46.5%-100%), respectively. One patient experienced grade 5 sepsis (not attributed to treatment) within 60 days of treatment discontinuation. Grade 3 or higher adverse events, regardless of attribution, are presented in eTable 2 in Supplement 2.

Correlative Science

Tumor PD-L1 Expression

Determination of PD-L1 expression was available for 49 participants and did not correlate significantly with the primary outcome. The DCR at 12 weeks was 72.2% and 76.9%, respectively, for 36 patients with negative (<1%) and 13 patients with positive (≥1%) PD-L1 expression. Tumor PD-L1 did not correlate significantly with PFS or OS in an exploratory analysis.

TCR Clonality as an Estimator of Response

A major attribute of the immune system, diversity of clonotypes comprising a TCR repertoire, includes both naive and antigen-experienced T cells.[14] To evaluate T-cell diversity associated with response to protocol therapy, TCR sequencing of pretherapy samples was compared for participants with PFS of greater than 18 months (23 participants) and with PFS less than 6 months (rapid progression) (14 participants). Richness (the number of unique T-cell sequences or clonotypes) is a measure of the diversity of the TCR repertoire independent of abundance. Richness values were higher in patients with rapid progression, although the differences were not statistically significant (**Figure 3**A).

The Shannon diversity index was used to measure T-cell clonal diversity, where values closer to 0 define oligoclonal repertoires (ie, presence of a few dominant clones) and larger values indicate higher polyclonality. Shannon diversity index values were significantly higher in patients with rapid progression (median [IQR] value, 438 [220-707] for PFS <6 months vs 96 [47-370] for PFS >18 months; $P = .03$) (Figure 3B), suggesting that patients whose baseline clonal TCR populations are more diverse may have a higher risk of progression on protocol therapy.

Discussion

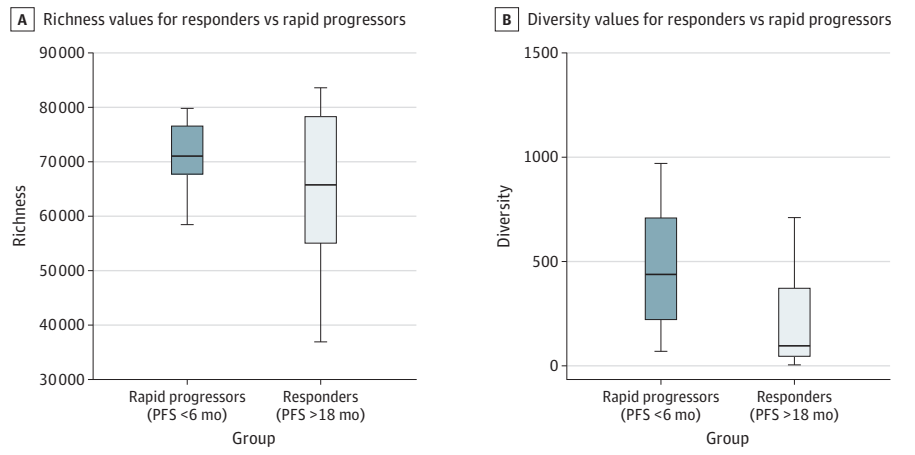
The AFT-16 trial is the first to our knowledge to report outcomes from neoadjuvant atezolizumab preceding definitive CRT for patients with unresectable stage III NSCLC. Neoadju-

Table 2. Adverse Events[a]

Adverse event	No. (%)		
	Grade 3	Grade 4	Grade 5
Aspartate aminotransferase increased	0	1 (1.6)	0
Colitis	3 (4.8)	0	0
Dyspnea	5 (8.1)	2 (3.2)	0
Esophagitis	3 (4.8)	0	0
Fever	4 (6.5)	0	0
Guillain-Barré syndrome	0	1 (1.6)	0
Hyperglycemia	3 (4.8)	0	0
Hypertension	5 (8.1)	0	0
Hyponatremia	4 (6.5)	0	0
Hypotension	0	1 (1.6)	0
Hypoxia	3 (4.8)	0	0
Infusion-related reaction	3 (4.8)	0	0
Lung infection	9 (14.5)	0	0
Lymphocyte count decreased	9 (14.5)	8 (12.9)	0
Neutrophil count decreased	7 (11.3)	1 (1.6)	0
Pericardial effusion	0	1 (1.6)	0
Platelet count decreased	2 (3.2)	2 (3.2)	0
Pneumonitis	3 (4.8)	0	1 (1.6)
Respiratory failure	0	1 (1.6)	0
Sepsis	0	3 (4.8)	1 (1.6)
Thromboembolic event	4 (6.5)	0	0
Treatment-related secondary malignant neoplasm	0	1 (1.6)	0
Upper respiratory infection	1 (1.6)	1 (1.6)	0
Ventricular tachycardia	0	1 (1.6)	0
Vomiting	3 (4.8)	0	0
White blood cell count decreased	7 (11.3)	2 (3.2)	0

[a] Shown are adverse events that occurred in at least 5% (rounded) of patients or any adverse events that were grade 4 or 5 (reported as maximum grade per adverse event per patient).

Figure 3. Richness and Shannon Diversity Index Values for Patients With Rapid Progression vs Responders



The horizontal bar inside the boxes indicates the median, the lower and upper ends of the box are the first and third quartiles, and the whiskers indicate the minimum and maximum for responders (n = 23) and rapid progressors (n = 14). A. Differences were not statistically significant (P = .14). B. Differences were statistically significant (P = .03). PFS indicates progression-free survival.

vant atezolizumab appeared to be safe (DCR, 74.2%), with encouraging PFS (30 months) and OS rates (87% and 73.7% at 12 and 24 months, respectively).

The PACIFIC trial established adjuvant durvalumab as a new standard of care in patients post CRT who were eligible for immunotherapy and reported PFS rates at 12 and 18 months of 55.9% and 44.2%, respectively.[4,5] Because PACIFIC measured outcomes after CRT, we analyzed the 44 AFT-16 participants who completed CRT, estimating outcomes from that point. The PFS rates at 12 and 24 months were 76.2% and 64.3%, respectively, which suggests that neoadjuvant atezolizumab did not compromise outcomes compared with the historical standard and could improve PFS by earlier initiation of ICI therapy. This hypothesis-generating analysis may support ongoing development of the neoadjuvant ICI strategy in unresectable stage III NSCLC.

The nonrandomized phase II KEYNOTE-799 trial investigated a single cycle of chemoimmunotherapy before adding thoracic radiation followed by adjuvant pembrolizumab with coprimary end points of ORR and incidence of grade 3 to 5 pneumonitis.[15] The findings showed an ORR of 70.5% for the combined cohort, with grade 3 to 5 pneumonitis in 9 of 112 patients (8.0%). The estimated PFS rates for the combined and nonsquamous cohorts were 67.1% and 71.6% at 12 months, and OS rates at 12 months were estimated at 81.3% and 87.0%, respectively. The AFT-16 PFS and OS rates with neoadjuvant atezolizumab alone compare favorably with those reported in KEYNOTE-799 with chemoimmunotherapy.

The DCR for neoadjuvant atezolizumab did not appear to differ by positive or negative PD-L1 expression based on a cutoff of 1%. While the small sample size precludes assessment of outcomes based on PD-L1 expression, based on analyses of other trials including PACIFIC, PD-L1 expression may not be the best predictor of outcome in this setting.

Findings from the TCR clonality assessment suggest that patients with the most diverse TCR repertoire at baseline may be less likely to have durable responses than those with less baseline clonal diversity. High TCR diversity may indicate a host immune system that has allowed the tumor to grow in an immune-tolerant environment without a specific (ie, clonal or oligoclonal) TCR-mediated antitumor response. Patients who have already begun to mount an antitumor response (indicated by a more clonal T-cell population) may simply benefit more from the boost of an ICI than those with less clonality. Further analysis of TCR and immune-related biomarkers is ongoing for AFT-16 participants and should be considered in future studies in this population.

Safety of neoadjuvant atezolizumab was an important concern in the study design and analysis. While patients had expected adverse events during the study period, there did not seem to be a higher-than-expected incidence of serious immune-related adverse events that could have precluded proceeding with CRT.

Limitations

While AFT-16 outcomes are encouraging, this study has all the limitations of a single-arm phase II trial. There is no simultaneous control group. The comparison with historical control patients (PACIFIC trial) reflects differences in study design and patient profiles that may bias the comparison, especially since AFT-16 enrolled treatment-naive patients while PACIFIC enrolled only patients who had completed CRT with a good ECOG performance status and recovery from toxic effects. While these differences should favor the historical control population rather than the AFT-16 population, direct comparisons are not possible and can only be hypothesis generating. Confirmation in randomized clinical trials should be considered.

Conclusions

The findings of the AFT-16 phase II trial show that atezolizumab administration before and after standard CRT for patients with unresectable stage III NSCLC was safe and appeared to be effective. Based on the favorable outcomes, neoadjuvant atezolizumab therapy merits further study in this patient population.

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Author Contributions: Dr Ross had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Ross, Kozono, Wang, Urbanic, Williams, Carbone, Bara, Schulze, Brockman, Vokes, Stinchcombe.

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Supervision: Ross, Kozono, Wang, Urbanic, Williams, Carbone, DuFrane, Stinchcombe.

Conflict of Interest Disclosures: Dr Ross reported receiving advisory board fees from Gilead Sciences and OncoHost outside the submitted work. Dr Kozono reported receiving personal fees from Genentech outside the submitted work. Dr Carbone reported receiving personal fees from Genentech, AstraZeneca, Merck, Bristol Myers Squibb, Regeneron, Pfizer, Eli Lilly, and Sanofi outside the submitted work. Dr Schulze reported stock ownership from Roche. Ms Brockman reported employment with Gilead outside the submitted work. Dr Stinchcombe reported receiving personal fees from Genentech/Roche during the conduct of the study and personal fees from Janssen Oncology, Daiichi Sankyo, AstraZeneca, Takeda, Eisai/H3 Biomedicine, G1 Therapeutics, Spectrum Pharmaceuticals, Gilead Sciences, Coherus Biosciences, and AbbVie; membership on a data monitoring safety board for GlaxoSmithKline; and grants to his institution from AstraZeneca, Seagen, and Mirati Therapeutics outside the submitted work. No other disclosures were reported.

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