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Consolidative Thoracic Radiotherapy With Atezolizumab Maintenance in Extensive-Stage Small Cell Lung Cancer
The Phase 2 TREASURE Randomized Clinical Trial (AIO-TRK-0320)

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IMPORTANCE Chemoimmunotherapy followed by immunotherapy maintenance is the standard first-line treatment for extensive-stage small cell lung cancer (ES-SCLC), yet data regarding efficacy and safety of consolidative thoracic radiotherapy (TRT) are lacking.

OBJECTIVE To determine whether combining consolidative TRT with immunotherapy maintenance in ES-SCLC is safe and improves patients' overall survival (OS) and progression-free survival (PFS).

DESIGN, SETTINGS, AND PARTICIPANTS This was a multicenter open-label phase 2 randomized clinical trial recruiting patients from September 2020 to August 2022 in Germany and Austria, with the last follow-up visit in September 2024. Eligible patients had ES-SCLC with at least stable disease after induction chemoimmunotherapy (carboplatin–etoposide–atezolizumab). Although the database was locked in April 2025, a post hoc survival update was performed in April 2026. Data were analyzed from April 2025 to April 2026.

INTERVENTIONS Randomized (1:1) to either atezolizumab maintenance combined with consolidative TRT (30 Gy in 10 fractions) (arm A) or atezolizumab maintenance alone (arm B).

MAIN OUTCOME AND MEASURE OS (time from randomization to death due to any cause).

RESULTS Of 96 patients assessed for eligibility, 68 patients were randomized; recruitment was prematurely terminated due to safety concerns. Median OS in the combination arm was numerically shorter compared to atezolizumab only (6.7 months [95% CI, 5.1-9.0] vs 13.4 months [95% CI, 10.7-17.5]; HR, 1.55 [95% CI, 0.90-2.69]; $P = .34$), while median PFS was similar (2.4 months [95% CI, 1.3-3.9] vs 2.6 months [95% CI, 1.2-3.9]; HR, 0.92 [95% CI, 0.54-1.55]; $P = .85$). TRT plus atezolizumab was accompanied by higher frequency of severe adverse events (SAEs) (19 patients [61.3%] vs 6 patients [18.2%]; $P < .001$) and fatal outcomes (6 patients [19.4%] vs 1 patient [3.0%]; $P = .04$). Safety analysis revealed predominance of infection and respiratory disorder–related SAEs, possibly facilitated by a depletion of lymphocytes observed specifically in patients after TRT, and by a lower single breath diffuse capacity of the lungs for carbon monoxide in patients with fatal AEs in arm A. No further risk factors were identified, given that baseline characteristics were well balanced between both arms and between patients with and without SAEs, including fatal SAEs.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, TRT combined with immunotherapy increased toxic effects in unselected patients with ES-SCLC without survival benefit, presumably due to radiation-induced lymphocyte depletion facilitating infections. Cautious patient selection and further investigation to identify those who may benefit without undue risk are required.

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Atezolizumab combined with carboplatin–etoposide was established as the new standard of care for extensive-stage small cell lung cancer (ES-SCLC) based on the IMpower133 randomized clinical trial,[1] which reported a significant overall survival (OS) benefit in the atezolizumab arm compared to placebo. Combining photon radiotherapy (RT) with immunotherapy is being explored as a synergistic approach, based on the hypothesis that RT itself promotes an in situ vaccination through tumor-associated antigen exposure and immune cells recruitment.[2] In non–small cell lung cancer, this combination has shown encouraging improvements in outcomes, with good tolerability.[3-5] For ES-SCLC, the role of consolidative thoracic radiotherapy (TRT) added to immunotherapy remains poorly defined.[6-8] The CREST[9] trial previously demonstrated a modest OS benefit with TRT after chemotherapy in the preimmunotherapy era. The TREASURE trial aimed to further improve outcomes demonstrated by the CREST and IMpower133 results by adding TRT to atezolizumab maintenance for treatment of patients with ES-SCLC.

Key Points

Question Is consolidative thoracic radiotherapy (TRT) added to standard immunotherapy maintenance in first-line extensive-stage small cell lung cancer (ES-SCLC) safe and more effective than immunotherapy alone?

Findings This phase 2 randomized clinical trial found that TRT plus immunotherapy unexpectedly resulted in significantly more frequent and severe toxic effects, particularly infections, without improving survival; therefore, recruitment was halted prematurely. Persistent lymphocyte depletion after TRT suggested a potential contributor to the observed toxic effects.

Meaning These findings indicate that in unselected patients with ES-SCLC, consolidative TRT combined with immunotherapy maintenance increased toxic effects without efficacy benefit, arguing against routine use other than in carefully selected patients; further investigation of radiation-induced lymphocyte depletion as a potential risk factor is warranted.

Methods

This study was approved by the ethics committees at University of Heidelberg (AFmu-199/2020; 06/2020) and Johannes Kepler University of Linz (ECS 1097/2021; 05/2021). Written informed consent was obtained from all participants. The TREASURE randomized clinical trial (AIO-TRK-0320)[10] protocol is available in Supplement 1, and the statistical analysis plan, in Supplement 2. The Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines were followed.

Study Design and Sample Size

This multicenter phase 2 randomized clinical trial included patients with ES-SCLC and at least stable disease after induction with carboplatin–etoposide–atezolizumab at 20 sites in Germany and Austria. Sample size calculation was based on the primary end point OS (2-sided log-rank; $\alpha = .05$), assuming 20% absolute improvement in 12-month survival rate (72% vs 52%; hazard ratio [HR], 0.57), requiring 66 events and 92 patients (46 per arm) for 80% power. Including dropouts, 104 randomized patients were planned, and recruitment began in September 2020. Due to increased incidence of fatal SAEs in arm A vs arm B, the SMC recommended halting recruitment after enrollment of 68 participants (34 patients in each arm). Hence, statistical power was drastically reduced, and interpretation of results remains descriptive.

Treatment Arms

Patients were randomized 1:1 to atezolizumab maintenance combined with consolidative TRT (30 Gy in 10 fractions) (arm A) or atezolizumab maintenance alone (arm B), stratified by presence of brain metastases, response after induction therapy, and prophylactic cranial irradiation following allocation by variance minimization procedure. Target volume delineation was based on postinduction volume of thoracic primary tumor and lymph node metastasis (dosimetric details are available in eTable 1 in Supplement 3).

Outcomes

Primary end point was OS, defined as time from randomization to death due to any cause. Secondary end points included progression-free survival (PFS) and frequency and severity of adverse events (AEs) and serious adverse events (SAEs).

Safety Monitoring

A predefined safety interim analysis assessed grade 3 or greater pneumonitis events after enrollment of 23 patients in arm A, obliging a recruitment halt if more than 1 event occurred, while a Safety Monitoring Committee (SMC) oversaw study progress.[10] After a fatal pneumonitis incident in a patient with preexisting interstitial lung disease (exclusion criterion), mandatory central review for preexisting interstitial lung disease was implemented in April 2021. The last patient was included in August 2022.[11] Treatment and follow-up continued until September 2024. Database lock occurred in April 2025. A post hoc OS analysis was based on an update in April 2026.

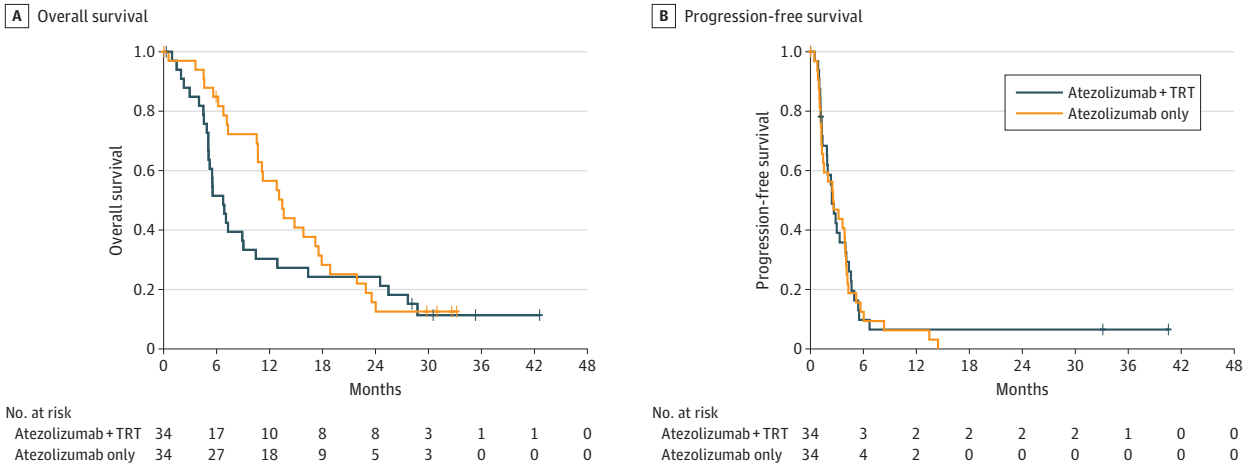
Statistical Analysis

Primary and secondary efficacy analysis used stratified log-rank tests and multivariable Cox regression in the intention-to-treat (ITT) population ($\alpha = .05$) with point estimates of the HR and 95% profile likelihood confidence intervals. Sensitivity analyses were performed in the per-protocol and adjusted ITT set (ITT without fatal adverse events [AEs]).

Safety analysis was conducted in the safety population according to actual treatment in all patients who received at least 1 dose of atezolizumab (both arms) and started TRT (arm A) (eFigure 1 and the eMethods in Supplement 3).

Descriptive statistics, χ^2 tests, *t* tests, and 2-proportion *Z*-tests were used to compare baseline characteristics and safety data between arms. Statistical tests were 2-tailed and *P* values < .05 were considered statistically significant. Data were analyzed from April 2025 to April 2026 using SAS, version 9.4, TS Level 1M6 (SAS Institute Inc).

Figure 1. Kaplan-Meier Estimates of Overall Survival (OS) and Progression-Free Survival (PFS) in the Intention-to-Treat Population



Median OS in arm A was shorter than arm B, without statistical significance (6.7 [95% CI, 5.1-9.0] months vs 13.4 [95% CI, 10.7-17.5] months; HR, 1.55 [95% CI, 0.90-2.69]; *P* = .34). Median PFS was similar (2.4 months [95% CI, 1.3-3.9] vs 2.6 months [95% CI, 1.2-3.9]; HR, 0.92 [95% CI, 0.54-1.55]; *P* = .85).

Stratification factors included in the stratified *P* value and Cox model were the same as those used for randomization. HR indicates hazard ratio; TRT, consolidative thoracic radiotherapy.

Results

Of 96 patients screened, 68 patients (71%) were randomized (eFigure 1 in Supplement 3). The last patient was followed up until September 2024 per protocol.

Median OS in arm A was shorter compared to arm B, without statistical significance (6.7 [95% CI, 5.1-9.0] months vs 13.4 [95% CI, 10.7-17.5] months; HR, 1.55 [95% CI, 0.90-2.69]; *P* = .34) (**Figure 1**A). Estimated 1-year and 2-year OS rates in arm A were 30.3% (95% CI, 15.9%-46.1%) and 24.2% (95% CI, 11.4%-39.6%), and in arm B, 56.6% (95% CI, 37.9%-71.6%) and 15.7% (95% CI, 5.7%-30.2%), respectively. Post hoc OS analysis after additional 19 months of follow-up revealed similar results (eFigure 2 in Supplement 3). PFS was similar between arms (median, 2.4 [95% CI, 1.3-3.9] months vs 2.6 [95% CI, 1.2-3.9] months; HR, 0.92 [95% CI, 0.54-1.55]; *P* = .85) (Figure 1B). Efficacy outcomes and baseline parameters were consistent across adjusted ITT, per-protocol, and safety population (eFigure 2 and eTables 2 and 3 in Supplement 3).

Among the first 23 patients in arm A, only 1 case of grade 3 or greater pneumonitis occurred, fulfilling interim safety criteria. However, when the SMC noted increased fatal nonpneumonitis SAEs in arm A, recruitment was paused (August 2022), and then permanently stopped in December 2022 when an unplanned preliminary OS analysis (shared exclusively with the SMC to ensure study integrity) revealed a disadvantage of the combination therapy in arm A.[11]

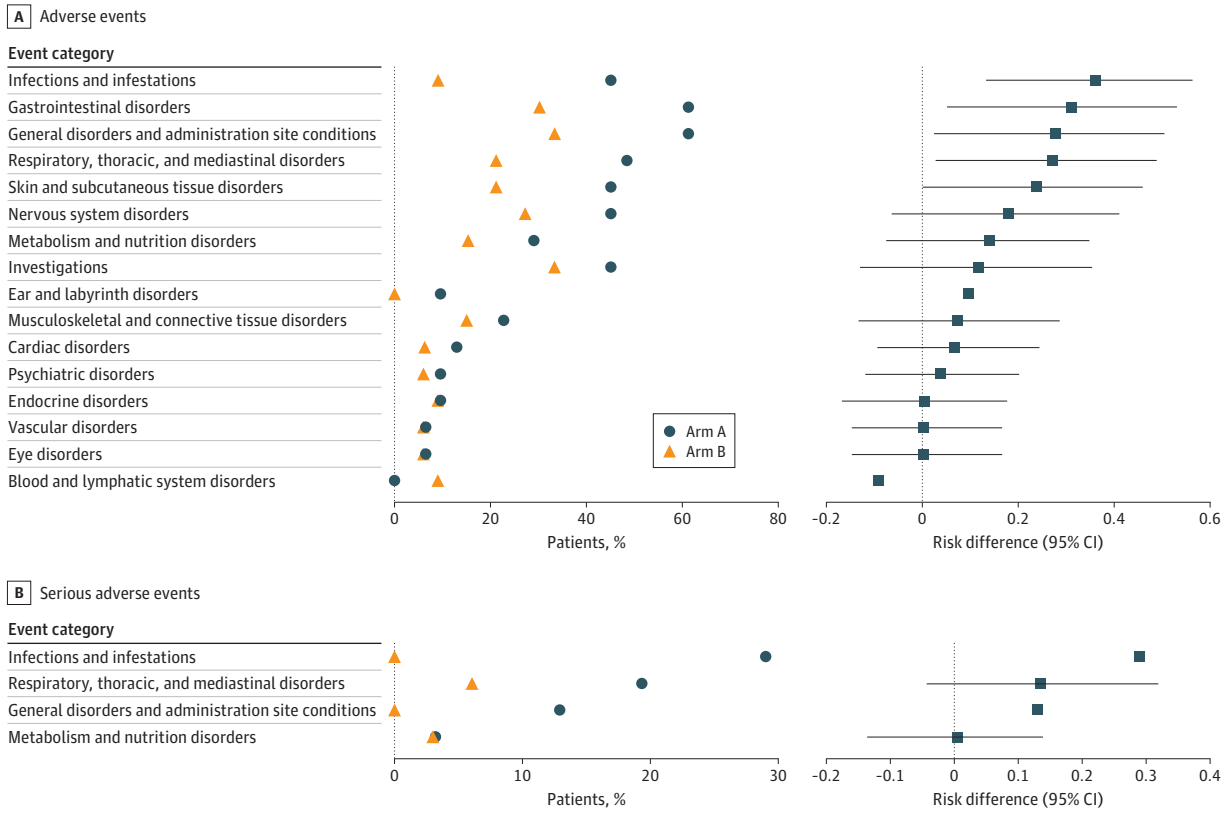
In the final safety analysis, 30 patients (96.8%) in arm A and 25 (75.8%) in arm B experienced toxic effects (95% CI, 3.6%-39.5%; *P* = .02) (eTable 4 in Supplement 3). SAEs occurred in 19 patients in arm A (61.3%) vs 6 in arm B (18.2%; 95% CI, 16.5%-63.6%; *P* < .001). Treatment-related AEs (trAEs) and SAEs (trSAEs) were more frequent in arm A (trAEs, 71.0% vs 30.3%; *P* = .001; trSAEs, 29.0% vs 6.1%; *P* = .01), with greater differences for grade 3 or higher (eFigure 3 and eTable 4 in Supplement 3). Fatal AEs were significantly more frequent in arm A compared with arm B (6 patients [19.4%] vs 1 patient [3.0%]; *P* = .04). Causal attribution diverged between assessors (eTable 5 in Supplement 3); while the treating investigators considered 4 fatalities in arm A as unrelated to either atezolizumab or TRT, the SMC subsequently classified 3 of these as possibly or probably related to study treatment. Thus, causal relationship was not clearcut on a case-by-case basis.

Patients receiving TRT were more prone to microbial infections (urinary and pulmonary) and gastrointestinal (dysphagia and esophagitis), respiratory (particularly pneumonitis), fever, and skin AEs (**Figure 2**; eTable 6 in Supplement 3).

No baseline differences between arms accounted for the higher (S)AE incidence in arm A, including Eastern Cooperative Oncology Group Performance Status, Charlson Comorbidity Index, pulmonary function test results, thoracic tumor burden (**Table 1**) or tumor location (eTable 7 in Supplement 3), and neither clinical nor dosimetric characteristics were associated with SAE occurrences in arm A (eTables 8 and 9 in Supplement 3). However, the mean (SD) of baseline diffuse capacity of the lungs for carbon monoxide single breath (DLCO SB) was significantly worse in patients with fatal AEs vs other patients in arm A (45.3 [13.7] vs 56.7 [11.4]; *P* = .04; eTable 8 in Supplement 3), and organ-at-risk (OAR) analysis revealed a statistically significant, but clinically most likely not relevant, modest increase of total body dose exposure for them (median [range], 4.7 [3.0-6.6] Gy vs 3.4 [1.7-7.0] Gy; *P* = .04; eTable 9 in Supplement 3). Gross target volume was numerically larger in patients with fatal AEs (median [range], 88.6 [12.4-706.3] mL vs 45 [0-301.0] mL; *P* = .08). Radiation doses and volumes were within typical clinical ranges and below established OAR thresholds (eTable 1 in Supplement 3).

In a time-to-event analysis, TRT correlated positively (HR, 2.47; 95% CI, 1.15-5.32; *P* = .01), while atezolizumab expo-

Figure 2. Categories of (Serious) Adverse Events in Arm A (Atezolizumab Maintenance With TRT) vs Arm B (Atezolizumab Maintenance Only)



Adverse event categories, as defined by the Medical Dictionary for Regulatory Activities, which occurred at least 3 times are reported with the number of occurrences and exact 95% CIs. Infection and infestations include lung and urinary tract infections, COVID-19, and sepsis; gastrointestinal disorders include dysphagia, nausea, esophagitis; general disorders include fatigue, pain, and fever; respiratory, thoracic, and mediastinal disorders include dyspnea, cough, and pneumonitis; skin and subcutaneous tissue disorders include rash, dry skin, alopecia, and others. For further details refer to eTable 6 in Supplement 3. TRT indicates consolidative thoracic radiotherapy.

sure was not associated (HR, 0.57; 95% CI, 0.30-1.08; $P = .06$) with AE risk (eTable 10 in Supplement 3). Whether TRT was administered concurrently (ie, atezolizumab during the course of TRT) vs sequentially (ie, atezolizumab before or after TRT) was not associated with AE occurrence (eFigure 4 and eTable 11 in Supplement 3). While initial lymphocyte counts were similar in treatment arms, patients in arm A experienced persisting lymphocyte depletion after TRT, accompanied by an accumulation of AEs (**Table 2**; eFigure 4 in Supplement 3). This was specific for lymphocytes, while leukocyte and neutrophil counts were unaffected (eTable 12 in Supplement 3).

Discussion

To our knowledge, these are the first results reported from a randomized phase 2 trial investigating TRT for ES-SCLC in the immunotherapy era. Addition of consolidative TRT to atezolizumab maintenance unexpectedly yielded a significantly higher incidence of partly fatal infection- and respiratory-related SAEs.

The primary end point was not met: median OS was numerically shorter in arm A vs B (6.7 vs 13.4 months; HR, 1.55; $P = .34$). Median OS and 1-year OS rate in arm B (13.4 months and 56.6%) exceeded the atezolizumab arm in IMpower133 (12.3 months and 51.7%), whereas arm A (6.7 months and 30.3%) fell below this benchmark.[1] The OS curves crossed at approximately 24 months, with 2-year rates numerically favoring arm A (24.2% vs 15.7%), confirmed in an updated OS analysis with extended follow-up, although this observation requires cautious interpretation given the small number of patients remaining at risk. A sensitivity analysis on an adjusted ITT excluding fatal AEs yielded consistent OS results, indicating that the unfavorable outcome in arm A is not solely associated with these fatal events.

PFS was similar between arms (2.4 vs 2.6 months; HR, 0.92; $P = .85$). This dissociation between PFS and OS is clinically informative: the absence of a PFS benefit argues against meaningful TRT-driven systemic tumor control, while the OS detriment in arm A (despite similar PFS) points to treatment-related toxic effects as primary driver for survival differences, rather than accelerated progression.

Prospective single-arm studies of TRT added to chemoimmunotherapy in ES-SCLC reported no increase in toxic effects.[6-8] However, in the randomized PACIFIC-2[12] and Checkmate-73L[13] trials, both investigating simultaneous tho-

Table 1. Baseline Patients Characteristics of the Intention-to-Treat Population, by Treatment Arm

Characteristic	No. (%)		
	Arm A (atezolizumab + TRT)	Arm B (atezolizumab only)	Total
Patients, total No.	34	34	68
Sex			
Female	11 (32.4)	14 (41.2)	25 (36.8)
Male	23 (67.6)	20 (58.8)	43 (63.2)
Age, mean (SD), y	63.3 (9.1)	65.6 (5.5)	64.5 (7.5)
Smoking history			
Former	22 (64.7)	21 (61.8)	43 (63.2)
Current	11 (32.4)	13 (38.2)	24 (35.3)
Unknown	1 (2.9)	0	1 (1.5)
Thoracic response after induction therapy			
PR	30 (88.2)	26 (76.5)	56 (82.4)
CR	0	2 (5.9)	2 (2.9)
Thoracic stable disease with extrathoracic PR	3 (8.8)	6 (17.6)	9 (13.2)
Thoracic stable disease with extrathoracic CR	1 (2.9)	0	1 (1.5)
Prophylactic cranial irradiation			
No	33 (97.1)	33 (97.1)	66 (97.1)
Yes	1 (2.9)	1 (2.9)	2 (2.9)
Presence of brain metastases			
No	27 (79.4)	25 (73.5)	52 (76.5)
Yes	7 (20.6)	9 (26.5)	16 (23.5)
ECOG Performance Status			
0	17 (50.0)	10 (29.4)	27 (39.7)
1	17 (50.0)	24 (70.6)	41 (60.3)
Charlson Comorbidity Index			
<2	23 (67.6)	22 (66.7)	45 (67.2)
≥2	11 (32.4)	11 (33.3)	22 (32.8)
Missing data, No.	0	1	1
Pulmonary function, mean (SD), %			
Vital capacity maximum	81.9 (18.9)	82.3 (18.0)	82.1 (18.3)
FEV1	74.6 (12.5)	69.5 (18.5)	72.1 (15.8)
DLCO SB	54.7 (12.7)	53.1 (21.7)	53.9 (17.7)
Missing data, No.	1	1	2
DLCO VA	69.2 (16.0)	67.5 (23.6)	68.3 (20.0)
Missing data, No.	1	1	2
Tumor size, mean (SD), mm			
Lung	33.1 (17.0)	38.8 (30.1)	36.0 (24.3)
Missing data, No.[a]	12	12	24
Mediastinal lymph nodes	28.8 (14.0)	28.8 (12.7)	28.8 (13.1)
Missing data, No.	19	16	35
Overall tumor size in thorax	48.0 (24.4)	50.6 (34.2)	49.4 (29.5)
Missing data, No.	7	6	13

Abbreviations: CR, complete response; DLCO SB, diffusing capacity of the lung for carbon monoxide single breath; DLCO VA, diffusing capacity of the lung for carbon monoxide divided by the alveolar volume; ECOG, Eastern Cooperative Oncology Group; FEV1, forced expiratory volume in 1 second; PR, partial response; TRT, consolidative thoracic radiotherapy.

[a] Patients with no measurable thoracic tumor at baseline.

racic chemoradiotherapy with immunotherapy in non–small cell lung cancer (NSCLC), more fatal infections and toxic effects in the interventional arms were observed, consistent with our findings. Along these lines, TRT, but not a longer atezolizumab exposure in the absence of radiotherapy, was associated with increased AE risk in the TREASURE trial. The safety profile observed in arm B is largely consistent with published data on atezolizumab maintenance, whereas the rate of trAE grade 3 or greater (26%) in arm A clearly exceeds benchmarks for both atezolizumab monotherapy and consolidative TRT without immunotherapy (eTable 13 in Supplement 3), despite radiation doses and volumes within or below typical clini-

Table 2. Absolute Lymphocyte Count During the First 4 Cycles of Atezolizumab Maintenance in the Safety Population, by Treatment Arm

Absolute lymphocyte count measure[a]	No. (%)			
	Arm A (atezolizumab + TRT)	Arm B (atezolizumab only)	Total	*P* value[b]
Patients, total No.	31	33	64	NA
Baseline				
<0.001/μL	8 (25.8)	5 (15.2)	13 (20.3)	.31
Normal range	22 (71.0)	28 (84.8)	50 (78.1)	
>0.048/μL	1 (3.2)	0	1 (1.6)	
Atezolizumab maintenance cycle				
Cycle 1				
<0.001/μL	7 (25.9)	5 (20.0)	12 (23.1)	.61
Normal range	20 (74.1)	20 (80.0)	40 (76.9)	
Cycle 2				
<0.001/μL	22 (91.7)	3 (13.6)	25 (54.3)	<.001
Normal range	2 (8.3)	18 (81.8)	20 (43.5)	
>0.048/μL	0	1 (4.5)	1 (2.2)	
Cycle 3				
<0.001/μL	14 (77.8)	4 (26.7)	18 (54.5)	.004
Normal range	3 (16.7)	11 (73.3)	14 (42.4)	
>0.048/μL	1 (5.6)	0	1 (3.0)	
Cycle 4				
<0.001/μL	9 (69.2)	1 (8.3)	10 (40.0)	.002
Normal range	4 (30.8)	11 (91.7)	15 (60.0)	

Abbreviations: NA, not applicable; TRT, thoracic radiotherapy (started after first administration of atezolizumab maintenance therapy).

[a] Normal ALC range, 0.001-0.048/μL (to convert to $\times 10^9$/L, multiply by 0.001).

[b] Per χ^2 test.

cal ranges,[9,14-17] further supporting an interaction between the 2 modalities.

No significant differences in baseline characteristics distinguished patients with and without SAEs in arm A, nor did the concurrent vs sequential TRT timing. Among patients with fatal AEs, low baseline DLCO SB appeared as a potential risk factor, while other clinical and dosimetric parameters were not informative. However, these results should be interpreted cautiously given the small sample size. Furthermore, radiation-induced lymphopenia emerged as a potential risk factor for clinically impactful AEs. Pronounced and persistent lymphocyte depletion after TRT was accompanied by a higher incidence of AEs, predominantly infections and respiratory disorders. Taken together with the previous PACIFIC-2[12] and CheckMate-73L[13] results, these findings suggest that concurrent thoracic immunoradiotherapy may increase clinically relevant toxic effects without clear efficacy benefit, arguing against general use in both NSCLC and SCLC.

Limitations

The main limitation of the study is the exploratory nature of analyses due to the premature termination. That being said, the unfavorable risk-benefit balance in the TREASURE trial affected both toxicity and efficacy outcomes, thereby retrospectively fully justifying the SMC's recommendation to halt the trial.

Conclusions

In this randomized clinical trial, combining consolidative TRT with atezolizumab maintenance resulted in an unexpected increase of toxic effects, including partially fatal infections and pulmonary disorders, associated with a reduced baseline DLCO SB and protracted radiation-induced lymphopenia. Thus, in the maintenance setting after chemoimmunotherapy, addition of consolidative TRT cannot currently be recommended outside of clinical trials for unselected patients, and future studies exploring this strategy should consider mitigation strategies, such as dose exposure to highly perfused organs at risk (ie, lungs, heart, and large vessels), radiotherapy timing relative to immunotherapy cycles, and prospectively defined safety stopping rules. Ongoing biomarker analyses may assist in identifying subpopulations with particular risk or therapeutic benefit from this approach.

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