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Benmelstobart With or Without Anlotinib After Chemoradiotherapy for Unresectable Non–Small Cell Lung Cancer
The R-ALPS Randomized Clinical Trial

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IMPORTANCE Consolidation immunotherapy improves outcomes after chemoradiotherapy for unresectable stage III non–small cell lung cancer (NSCLC). Disease progression remains common, and more effective consolidation strategies are needed.

OBJECTIVE To evaluate the efficacy and safety of benmelstobart with or without anlotinib as consolidation therapy after chemoradiotherapy for unresectable stage III NSCLC.

DESIGN, SETTING, AND PARTICIPANTS This multicenter double-blind phase 3 randomized clinical trial took place at 42 centers in China from 2020 to 2023 among patients with unresectable stage III NSCLC without progression after concurrent or sequential chemoradiotherapy. In stage 1, patients were randomized 1:1:1 to 2 active regimens or placebo; in stage 2, additional patients were randomized 1:1 between the active regimens to power their direct comparison. Data cutoffs were November 30, 2023, for stage 1 and July 8, 2024, for the pooled analysis. Data analysis was performed from January 17 to March 23, 2025.

INTERVENTIONS Patients were randomized to receive benmelstobart plus anlotinib, benmelstobart plus anlotinib placebo, or their matching placebos.

MAIN OUTCOMES AND MEASURES Primary end point was independent review committee (IRC)–assessed progression-free survival (PFS).

RESULTS Of 553 participants (median [IQR] age, 62 [56-67] years; 495 male individuals [89.5%]), 390 were randomized in stage 1 and 163 in stage 2. In stage 1, median PFS was 15.1 months (95% CI, 9.4-21.7) with benmelstobart plus anlotinib, 9.7 months (95% CI, 6.0-34.4) with benmelstobart alone, and 4.2 months (95% CI, 3.2-6.8) with placebo. The hazard ratios (HRs) were 0.49 (95% CI, 0.36-0.66; $P < .001$) for benmelstobart plus anlotinib vs placebo and 0.53 (95% CI, 0.39-0.72; $P < .001$) for benmelstobart vs placebo. In the pooled stage 1 and 2 analysis, median PFS was 17.4 (95% CI, 12.5-24.8) months with benmelstobart plus anlotinib and 11.2 (95% CI, 7.0-20.7) months with benmelstobart alone (HR, 0.82; 95% CI, 0.63-1.08; $P = .12$). Grade 3 to 5 treatment-related adverse events occurred in 48.8%, 29.4%, and 19.7% in the benmelstobart plus anlotinib, benmelstobart alone, and placebo groups, respectively; grade 5 events occurred in 7.2%, 1.4%, and 1.5%, respectively.

CONCLUSIONS AND RELEVANCE This randomized clinical trial found that benmelstobart with or without anlotinib significantly improved PFS compared with placebo. Adding anlotinib did not significantly improve PFS compared with benmelstobart alone and increased severe and fatal treatment-related adverse events.

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Supplemental content

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Approximately 30% of patients with non-small cell lung cancer (NSCLC) present with stage III disease at diagnosis, and a substantial proportion have unresectable tumors.[1] After definitive concurrent chemoradiotherapy (cCRT), phase 3 PACIFIC[2] established anti-programmed cell death 1-ligand 1 (PD-L1) durvalumab as standard consolidation. Subsequent evidence from GEMSTONE-301[3] and PACIFIC-5[4] further supported clinical benefit of immunotherapy after either cCRT or sequential chemoradiotherapy (sCRT). However, outcomes with monotherapy consolidation remain suboptimal (2-year progression-free survival [PFS], 45.0% in PACIFIC).[1,2] Progression risk with immunotherapy consolidation was higher in sCRT-treated population, with 2-year PFS of 30.5% in GEMSTONE-301,[5] 33.1% in PACIFIC-5,[4] and 35.5% in PACIFIC-6.[6] These findings underscore the need for intensification strategies to further improve efficacy.

Innovative approaches, such as adding oleclumab or monalizumab to durvalumab in phase 2 COAST,[7,8] have shown more favorable PFS signals than durvalumab alone. Beyond dual immunotherapy, targeting tumor microenvironment offers promising alternative. Aberrant tumor angiogenesis creates physical and biochemical barrier that impairs drug delivery and immune-cell trafficking.[9,10] Consequently, combining antiangiogenic therapy with PD-L1 blockade may synergistically enhance antitumor immunity through vascular normalization and microenvironmental remodeling.[9]

Anlotinib is an oral multitarget antiangiogenic tyrosine kinase inhibitor, and benmelstobart (TQB2450) is a novel IgG1 anti-PD-L1 antibody. In a randomized phase 1B clinical trial, benmelstobart plus anlotinib prolonged PFS over benmelstobart alone (8.7 vs 2.8 months) in pretreated stage IIIB to IV NSCLC.[11] Therefore, we conducted this phase 3 R-ALPS trial to evaluate efficacy and safety of benmelstobart plus anlotinib, benmelstobart monotherapy, or placebo as consolidation in patients with unresectable stage III NSCLC without progression after cCRT or sCRT.

Key Points

Question Does benmelstobart with or without anlotinib as consolidation therapy improve progression-free survival (PFS) after chemoradiotherapy in patients with unresectable stage III non–small cell lung cancer?

Findings In this randomized clinical trial of 553 patients, benmelstobart with or without anlotinib demonstrated significantly improved PFS compared to placebo (15.1 vs 9.7 vs 4.2 months). However, benmelstobart plus anlotinib did not show significant improvement over benmelstobart alone (17.4 vs 11.2 months).

Meaning These findings support the consolidation activity of benmelstobart but do not support routine addition of anlotinib in an unselected population.

Methods

The R-ALPS trial was conducted in accordance with the principles of the Declaration of Helsinki and the international standards of good clinical practice. This study was approved by institutional review board or independent ethics committee at all 42 participating sites. Independent data monitoring committee (IDMC) oversaw the trial and assessed PFS interim analysis data. All participants were encouraged to receive standard immunotherapy, and only those who declined durvalumab for these reasons and provided written informed consent were screened. The study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.[12]

Study Design and Participants

R-ALPS was a randomized, double-blind, placebo-controlled, phase 3 trial conducted at 42 centers across China. A placebo control was used because durvalumab had not received National Medical Products Administration approval in China at study application. Although approved in December 2019, durvalumab remained limitedly accessible because of high out-of-pocket costs and lack of insurance coverage, making CRT alone followed by observation common in practice.

Patients were screened for eligibility from May 26, 2020, to May 12, 2023. Eligible patients were aged 18 to 75 years with histologically or cytologically confirmed unresectable stage III NSCLC and had received at least 2-cycle platinum-based chemotherapy, either concurrently or sequentially, with definitive radiotherapy (54-66 Gray [Gy]). Additional inclusion criteria included Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, no disease progression after CRT, and receipt of first study treatment within 42 days after CRT completion. Key exclusion criteria included having received previous immunotherapy or antiangiogenic agents, known sensitizing *EGFR/ALK/ROS1* gene alterations, and grade 2 or greater pneumonitis. Those excluded were patients with squamous cell carcinoma who had tumor cavitation with grade 2 or greater tumor-related bleeding occurring during radiotherapy; hemoptysis (≥2.5 mL/d) within 1 month before first dose or with other clinically significant bleeding symptoms or known bleeding tendency; or high risk of fatal bleeding due to potentially further tumor invasion into critical blood vessels based on tumor invasion into major blood vessels on imaging. Sex and race and ethnicity were self-reported by patients. Full eligibility is provided in the trial protocol (Supplement 1).

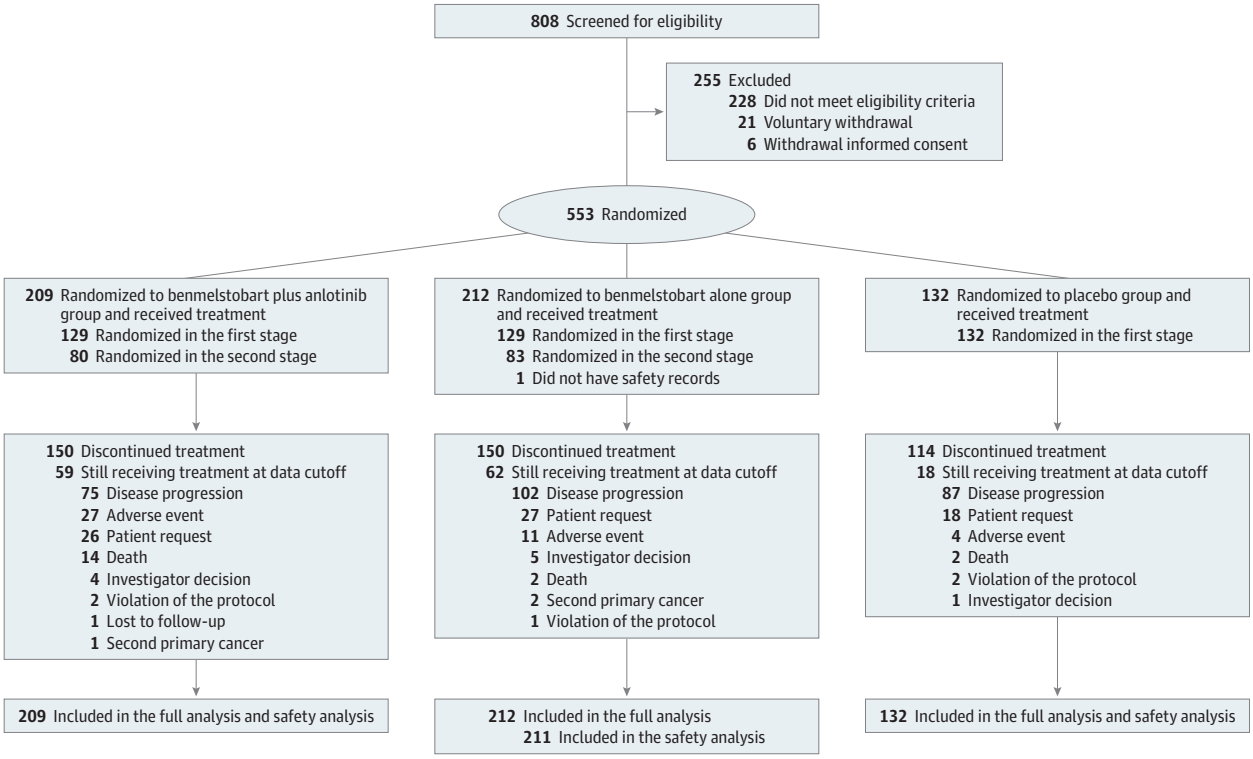
Randomization and Masking

Eligible patients underwent centralized stratified randomization. Block sizes were 3 (first stage) and 4 (second stage), with stratification by smoking status (yes vs no) and previous CRT (sequential vs concurrent). Randomization list was generated using SAS, version 9.4 or higher (SAS Institute) and implemented via eRand system, version 2.0 (Nanjing Oude Data Technology). Patients underwent first-stage randomization at 1:1:1 ratio to receive benmelstobart plus anlotinib, benmelstobart plus anlotinib placebo, and benmelstobart placebo plus anlotinib placebo. To meet regulatory requirement of Center for Drug Evaluation for additional comparison between benmelstobart plus anlotinib and benmelstobart alone, the protocol was amended on September 16, 2022, to enroll patients

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Figure 1. Flow Diagram of Included Participants



Stage 1 participants were randomized 1:1:1 to benmelstobart plus anlotinib, benmelstobart plus placebo (benmelstobart alone), or placebo. Stage 2 participants were randomized 1:1 to the 2 intervention groups without a placebo group. The safety population included all patients randomized to receive at least 1 dose of study treatment and had at least 1 postbaseline safety assessment. One patient in the benmelstobart-alone group had no postbaseline safety assessment and was excluded from the safety population but remained in the full analysis set.

for adequate power. Second-stage randomization was conducted in 1:1 ratio between the benmelstobart plus anlotinib and benmelstobart groups.

With double-blinded design, investigators, assessors involved in the efficacy evaluation, personnel responsible for data management, statisticians, and patients and their families or guardians were masked to treatment allocation. Full procedure details are provided in the trial protocol (Supplement 1) and the statistical analysis plan (Supplement 2).

Interventions

Benmelstobart, 1200 mg, or matching placebo was given intravenously once on day 1 and anlotinib, 8 mg, or its placebo was administered orally daily for the first 14 days of each 21-day cycle. Treatment was given for up to 36 cycles until disease progression, unacceptable toxic effects, or withdrawal of consent.

Tumor assessment was performed by investigators and independent review committees (IRCs) by imaging at baseline and every 2 cycles until radiologically confirmed disease progression. After 36-cycle assigned treatment, patients were followed up for survival every 3 months. Adverse events (AEs) were graded using the Common Terminology Criteria for Adverse Events, version 5.0 (National Cancer Institute).

Primary and Secondary Outcomes

Primary end point was IRC-assessed PFS per Response Evaluation Criteria in Solid Tumors, version 1.1, (the US National Cancer Institute) which was defined as time from randomization to disease progression or all-cause death. Secondary end points included investigator-assessed PFS, OS, objective response rate (ORR), disease control rate, duration of response (DoR), 6- and 12-month PFS rates, and safety.

Statistical Analysis

PFS was primary end point, tested using prespecified fixed-sequence procedure to control family-wise type I error rate for multiple comparisons across treatment groups (eFigure 1 in Supplement 3). Hypothesis testing proceeded sequentially in the following order: benmelstobart plus anlotinib vs placebo, benmelstobart monotherapy vs placebo, and benmelstobart plus anlotinib vs benmelstobart monotherapy. Testing continued only if statistical significance was achieved at the preceding step. Each test was conducted at 2-sided α of .05 without additional multiplicity adjustment. With 16-month accrual and 18-month follow-up, 372 patients in the first-stage randomization (1:1:1) provided 80% power with 2-sided α of .05 to detect median PFS improvement from 6 (placebo) to 9 months (benmelstobart). Second-stage randomization added

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Table 1. Baseline Characteristics of Patients in the Full Analysis Set of Benmelstobart With or Without Anlotinib After Chemoradiotherapy for Unresectable Non–Small Cell Lung Cancer

Characteristic	No. (%)		
	Benmelstobart + anlotinib (n = 209)	Benmelstobart alone (n = 212)	Placebo (n = 132)
Age, y			
Median (IQR)	61 (56-67)	62 (57-67)	62.5 (56-68)
<65	132 (63.2)	133 (62.7)	72 (54.5)
≥65	77 (36.8)	79 (37.3)	60 (45.5)
Sex			
Female	21 (10.0)	24 (11.3)	13 (9.8)
Male	188 (90.0)	188 (88.7)	119 (90.2)
Ethnicity[a]			
Han ethnic group	198 (94.7)	197 (92.9)	127 (96.2)
Other	11 (5.3)	15 (7.1)	5 (3.8)
Disease stage			
IIIA	59 (28.2)	59 (27.8)	30 (22.7)
IIIB	98 (46.9)	108 (50.9)	77 (58.3)
IIIC	51 (24.4)	45 (21.2)	24 (18.2)
Other	1 (0.5)	0	1 (0.8)
Histologic type			
Squamous cell carcinoma	153 (73.2)	149 (70.3)	89 (67.4)
Adenocarcinoma	52 (24.9)	54 (25.5)	41 (31.1)
Other	4 (1.9)	9 (4.2)	2 (1.5)
CRT type			
Sequential	37 (17.7)	37 (17.5)	27 (20.5)
Concurrent	172 (82.3)	175 (82.5)	105 (79.5)
Radiotherapy dose			
<60 Gy	29 (13.9)	31 (14.6)	17 (12.9)
≥60 Gy	180 (86.1)	181 (85.4)	115 (87.1)
Best response to CRT			
Complete response	1 (0.5)	5 (2.4)	0
Partial response	151 (72.2)	154 (72.6)	80 (60.6)
Stable disease	56 (26.8)	53 (25.0)	52 (39.4)
Not estimable	1 (0.5)	0	0
Smoking status			
Never	29 (13.9)	31 (14.6)	17 (12.9)
Former	154 (73.7)	153 (72.2)	98 (74.2)
Current	26 (12.4)	28 (13.2)	17 (12.9)
ECOG performance status			
0	83 (39.7)	74 (34.9)	48 (36.4)
1	125 (59.8)	137 (64.6)	83 (62.9)
Unknown	1 (0.5)	1 (0.5)	1 (0.8)
PD-L1 tumor proportion score, %			
<1	26 (12.4)	30 (14.2)	16 (12.1)
1-50	24 (11.5)	32 (15.1)	8 (6.1)
>50	21 (10.0)	9 (4.2)	5 (3.8)
Unknown	138 (66.0)	141 (66.5)	103 (78.0)

Abbreviations: CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; Gy, gray; PD-L1, programmed death ligand 1.

Data are based on analyses of all patients enrolled in the first and second randomization.

[a] Ethnicity was self-reported; other was any other ethnicity or unknown.

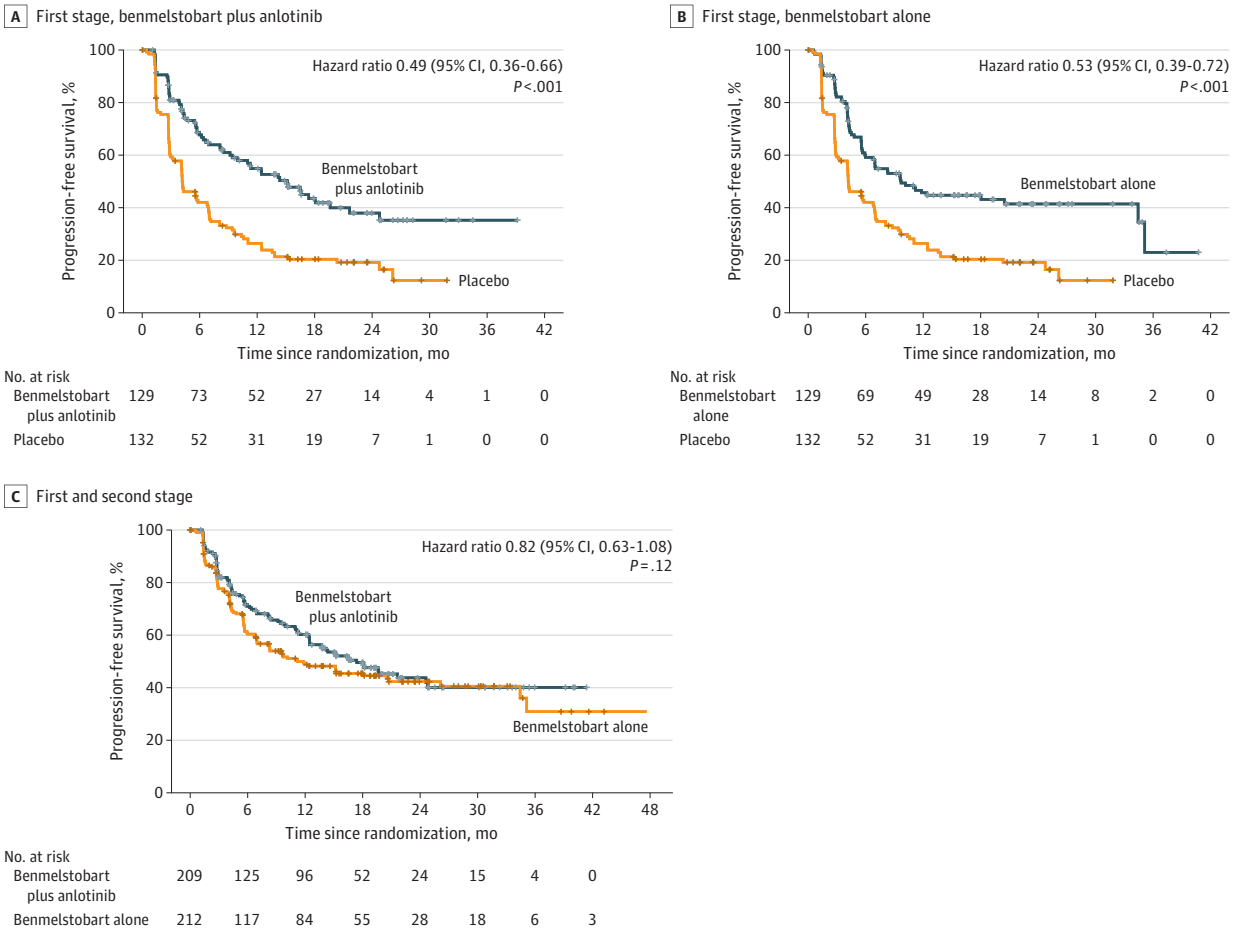
162 patients (1:1) into 2 intervention groups to detect median PFS improvement from 9 months (benmelstobart) to 12.5 months (benmelstobart plus anlotinib) under the same parameters as the first randomization. Final analysis required 402 PFS events, with a planned total of 534 patients assuming 10% dropout rate. Full sample size determination and interim analyses using SAS, version 9.4, are provided in Supplement 1 and Supplement 2.

Full statistical analysis plan (Supplement 2) prespecified 1 PFS interim analysis (70% of targeted events) and 1 final analysis (402 PFS events). Lan-DeMets method with O'Brien-Fleming spending function were used to control the type I error, at the nominal 2-sided α of 0.0148 for interim analysis and 0.0456 for final analysis. Prespecified interim analysis was reviewed by the IDMC after 288 PFS events (approximately 70% of the planned events). As prespecified information fraction for the 2 intervention groups had not been reached, IDMC recommended study continuation as planned. Interim analysis was conducted by an independent statistical team, and treatment assignments remained blinded after IDMC review. All data

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Figure 2. Kaplan-Meier Curves of Independent Review Committee–Assessed Progression-Free Survival in the Full Analysis Set of Benmelstobart With or Without Anlotinib for Unresectable Non–Small Cell Lung Cancer



Patients enrolled in the first stage and treated with benmelstobart plus anlotinib and placebo or benmelstobart alone and placebo and those enrolled in the first and second stage and treated with benmelstobart plus anlotinib and benmelstobart alone. Hazard ratio and 95% CI were estimated with a Cox proportional-hazards model.

reported were based on IDMC-reviewed interim analysis on September 19, 2024.

All principal efficacy analyses were performed in the full analysis set , which included all randomized patients who received at least 1 dose of study treatment, in accordance with the intention-to-treat principle. Comparisons of each active group vs placebo used first-stage patients only; the comparison between the 2 active groups used the combined first- and second-stage population. Time to event end points were estimated with the Kaplan-Meier method and compared with the stratified log-rank test. For PFS, patients who were alive without disease progression were censored at the date of the last tumor imaging. Hazard ratios (HRs) with a 95% CIs were assessed with a Cox proportional hazards model with randomization strata as covariates. Hazard proportionality was checked using Schoenfeld residuals test. Patients without baseline or postbaseline data were classified as nonresponders and counted in the denominator. Response rates and their 95% CIs were estimated using the Clopper-Pearson method, and between-group differences were analyzed using stratified Mantel-Haenszel tests. Prespecified subgroup analyses were done for PFS using unstratified Cox proportional hazards models with treatment as a covariate, to assess the consistency of treatment effects in key subgroups. Safety was analyzed in all randomized patients who received at least 1 dose of study treatment and had safety records. Baseline characteristics and safety outcomes were analyzed descriptively using median (range or IQR) for continuous variables and frequencies (percentage) for categorical variables. Statistical analyses were performed using SAS, version 9.4, from January 17 to March 23, 2025.

Results

Of 808 patients screened, 553 eligible participants (median [IQR] age, 62 [56-67] years; 495 male individuals [89.5%]) were randomized in 2 stages. In the first stage, 390 patients were randomized to either the benmelstobart plus anlotinib group (129 patients), benmelstobart alone group (129 patients), or the placebo group (132 patients). In the second

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Table 2. Grade of Treatment-Related Adverse Events (TRAEs) for Benmelstobart With or Without Anlotinib Among the Safety Population, by Group[a]

	Participants, No. (%)											
	Benmelstobart + anlotinib (n = 209)				Benmelstobart (n = 211)				Placebo (n = 132)			
TRAE	1/2	3	4	5	1/2	3	4	5	1/2	3	4	5
Any event[b]	101 (48.3)	70 (33.5)	17 (8.1)	15 (7.2)	147 (69.7)	53 (25.1)	6 (2.8)	3 (1.4)	95 (72.0)	19 (14.4)	5 (3.8)	2 (1.5)
Hypothyroidism	58 (27.8)	0	0	0	41 (19.4)	1 (0.5)	0	0	10 (7.6)	0	0	0
HTG	54 (25.8)	14 (6.7)	6 (2.9)	0	42 (19.9)	5 (2.4)	1 (0.5)	0	20 (15.2)	0	2 (1.5)	0
Anemia	52 (24.9)	3 (1.4)	0	0	69 (32.7)	6 (2.8)	0	0	36 (27.3)	1 (0.8)	0	0
Cholesterol high	51 (24.4)	5 (2.4)	2 (1.0)	0	45 (21.3)	2 (0.9)	1 (0.5)	0	17 (12.9)	0	0	0
Cough	48 (23.0)	0	0	0	48 (22.7)	1 (0.5)	0	0	30 (22.7)	0	0	0
WBC decreased	48 (23.0)	0	0	0	27 (12.8)	1 (0.5)	0	0	27 (20.5)	0	0	0
AST increased	47 (22.5)	2 (1.0)	0	0	29 (13.7)	3 (1.4)	0	0	15 (11.4)	0	0	0
Pneumonitis[c]	42 (20.1)	2 (1.0)	1 (0.5)	1 (0.5)	57 (27.0)	7 (3.3)	1 (0.5)	0	31 (23.5)	1 (0.8)	0	0
Hypertension	40 (19.1)	18 (8.6)	0	0	16 (7.6)	2 (0.9)	0	0	11 (8.3)	2 (1.5)	0	0
Occult blood positive	39 (18.7)	0	0	0	42 (19.9)	0	0	0	16 (12.1)	0	0	0
Hyperthyroidism	37 (17.7)	0	0	0	27 (12.8)	0	0	0	3 (2.3)	0	0	0
Proteinuria	35 (16.7)	1 (0.5)	0	0	18 (8.5)	1 (0.5)	0	0	10 (7.6)	0	0	0
Radiation pneumonitis	35 (16.7)	0	0	0	34 (16.1)	4 (1.9)	0	0	24 (18.2)	3 (2.3)	0	0
ALT increased	34 (16.3)	1 (0.5)	0	0	39 (18.5)	3 (1.4)	0	0	16 (12.1)	0	0	0
Blood CPK increased	33 (15.8)	3 (1.4)	1 (0.5)	0	21 (10.0)	1 (0.5)	1 (0.5)	0	3 (2.3)	0	0	0
Hypoalbuminemia	33 (15.8)	1 (0.5)	0	0	26 (12.3)	0	0	0	11 (8.3)	0	0	0
PLT decreased	32 (15.3)	0	0	0	11 (5.2)	0	1 (0.5)	0	15 (11.4)	2 (1.5)	1 (0.8)	0
TSH increased	28 (13.4)	0	0	0	10 (4.7)	0	0	0	4 (3.0)	0	0	0
Hyperglycemia	24 (11.5)	3 (1.4)	0	0	18 (8.5)	2 (0.9)	0	0	11 (8.3)	0	0	0
ANC decreased	24 (11.5)	1 (0.5)	0	0	11 (5.2)	1 (0.5)	0	0	13 (9.8)	0	0	0
Hyperuricemia	23 (11.0)	0	0	0	29 (13.7)	0	0	0	13 (9.8)	0	0	0
Weight gain	22 (10.5)	0	0	0	28 (13.3)	2 (0.9)	0	0	15 (11.4)	0	0	0
Hemoptysis	17 (8.1)	1 (0.5)	0	4 (1.9)	16 (7.6)	1 (0.5)	0	0	10 (7.6)	1 (0.8)	0	0
Pneumonia[d]	7 (3.3)	11 (5.3)	3 (1.4)	4 (1.9)	16 (7.6)	8 (3.8)	2 (0.9)	0	4 (3.0)	7 (5.3)	0	1 (0.8)
Pleural effusion	5 (2.4)	0	0	0	6 (2.8)	0	0	1 (0.5)	1 (0.8)	0	0	0
Pulmonary hemorrhage	4 (1.9)	0	0	1 (0.5)	0	0	0	0	0	0	0	0
Pneumothorax	1 (0.5)	1 (0.5)	0	1 (0.5)	1 (0.5)	2 (0.9)	0	0	0	0	0	0
Respiratory failure	0	0	1 (0.5)	1 (0.5)	2 (0.9)	1 (0.5)	0	0	1 (0.8)	0	0	0
Death	0	0	0	1 (0.5)	0	0	0	0	0	0	0	1 (0.8)
Sudden death	0	0	0	1 (0.5)	0	0	0	0	0	0	0	0
Disease progression	0	0	0	1 (0.5)	0	0	0	0	0	0	0	0
Tumor	0	0	0	1 (0.5)	0	0	0	0	0	0	0	0
Sudden cardiac death	0	0	0	0	0	0	0	1 (0.5)	0	0	0	0
Acute respiratory failure	0	0	0	0	0	0	0	1 (0.5)	0	0	0	0

Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CPK, creatine phosphokinase; HTG, hypertriglyceridemia; PLT, platelet count; TSH, thyroid stimulating hormone; WBC, white blood cell count.

[a] All randomized patients with ≥1 dose and safety data. Included treatment-emergent events—definitely, probably, possibly, or unlikely related to study drugs (excluded unrelated).

[b] Grade 1 and 2 with incidence ≥10.0% and all grade 3-5, by descending frequency in benmelstobart+anlotinib group.

[c] Including interstitial lung diseases, pulmonary inflammation, and immune-mediated pulmonary diseases.

[d] Including infectious, bacterial, *Haemophilus influenzae*, viral, and COVID-19 pneumonia, and lower respiratory tract infection.

stage, an additional 163 patients were randomized, 80 patients to the benmelstobart plus anlotinib group and 83 to the benmelstobart alone group. All patients were treated and included in the full analytical sample (**Figure 1**). One patient without safety records in the benmelstobart alone group was excluded from the safety analysis. At data cutoff (July 8, 2024), 59 patients in the benmelstobart plus anlotinib group, 62 in the benmelstobart-alone group, and 18 in the placebo group continued to received treatment. The most common reason for discontinuation was disease progression (75 of 209 patients [35.9%], 102 of 212 [48.1%], and 87 of 132 [65.9%], respectively).

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Baseline characteristics were generally balanced (**Table 1**; eTable 1 in Supplement 3). Median (IQR) age was 62 (56-67) years, and most patients had stage IIIB disease (283 patients [51.2%]) and squamous cell carcinoma (391 [70.7%]).

Efficacy

For patients enrolled in the first stage, at cutoff date (November 30, 2023), disease progression or death occurred in 50.4% of patients (65 of 129) in the benmelstobart plus anlotinib group, 53.5% (69 of 129) in the benmelstobart alone group, and 78.8% (104 of 132) in the placebo group. With median (IQR) follow-up across the respective groups (17.9 [10.2-24.8], 17.9 [13.9-24.8], and 22.1 [16.2-25.2] months), IRC-assessed median PFS was significantly longer in either benmelstobart plus anlotinib group (15.1 [95% CI, 9.4-21.7] vs 4.2 [95% CI, 3.2-6.8] months; HR, 0.49 [95% CI, 0.36-0.66]; $P < .001$) or benmelstobart alone group (9.7 [95% CI, 6.0-34.4] vs 4.2 [95% CI, 3.2-6.8] months; HR, 0.53 [95% CI, 0.39-0.72]; $P < .001$) than in the placebo group (**Figure 2A**-B). PFS rates at 6 months were 67.7% (95% CI, 58.5-75.3) with benmelstobart plus anlotinib, 59.2% (95% CI, 49.8-67.4) with benmelstobart alone, and 42.1% (95% CI, 33.5-50.4) with placebo; at 12 months were 54.9% (95% CI, 45.1-63.6), 45.7% (95% CI, 36.4-54.5), and 26.4% (95% CI, 19.1-34.4), respectively. IRC-assessed PFS benefits with benmelstobart plus anlotinib or benmelstobart alone vs placebo were observed across most prespecified subgroups (eFigure 2 in Supplement 3). Investigator-assessed PFS benefits were consistent with IRC findings in the full analytic sample and most prespecified subgroups (eFigures 3 and 4 in Supplement 3).

IRC-assessed confirmed ORR was 25.6% (33 of 129 patients; 95% CI, 18.3-34.0; $P = .01$) with benmelstobart plus anlotinib or 23.3% (30 of 129; 95% CI, 16.3-31.5; $P = .03$) with benmelstobart alone than 12.9% (17 of 132; 95% CI, 7.7-19.8) with placebo (eTable 2 in Supplement 3). Median DoR had not been reached in 3 groups (eTable 2 in Supplement 3).

For patients enrolled in the first and second stages, at the cutoff date (July 8, 2024), disease progression or death occurred in 45.9% of patients (96 of 209) in the benmelstobart plus anlotinib group, and 52.8% (112 of 212) in the benmelstobart alone group. With median (IQR) follow-up of 18.0 (12.1-24.9) months and 19.3 (13.8-27.5) months in the respective groups, median IRC-assessed PFS was 17.4 (95% CI, 12.5-24.8) months in the benmelstobart plus anlotinib group and 11.2 (95% CI, 7.0-20.7) months in the benmelstobart alone group, with HR of 0.82 (95% CI, 0.63-1.08; $P = .12$) (Figure 2C). Six-month PFS rates were 71.0% (95% CI, 64.0-76.9) with benmelstobart plus anlotinib and 60.4% (95% CI, 53.3-66.8) with benmelstobart alone; 12-month PFS rates were 60.2% (95% CI, 52.7-66.9) and 48.8% (95% CI, 41.6-55.6), respectively. IRC-assessed PFS benefits with benmelstobart plus anlotinib compared to benmelstobart were not observed across most prespecified subgroups (eFigure 2 in Supplement 3). Investigator-assessed PFS was consistent with IRC results (eFigure 5 in Supplement 3).

IRC-assessed confirmed ORR was 25.4% (53 of 209 patients; 95% CI, 20-32) with benmelstobart plus anlotinib vs 21.7% (46 of 212 patients; 95% CI, 16-28) with benmelstobart alone ($P = .40$); median DoR was not reached in either group (eTable 3 in Supplement 3).

Safety

In the benmelstobart plus anlotinib group, median (IQR) treatment duration was 13 (6-19) cycles for benmelstobart or anlotinib. In the benmelstobart alone group, median (IQR) treatment duration for benmelstobart was 11 (6-18) cycles (eTable 4 in Supplement 3).

Safety is summarized in **Table 2** and eTables 5 to 9 in Supplement 3. Grade 3 to 5 treatment-related adverse events (TRAEs) occurred in 48.8% (102 of 209 patients), 29.4% (62 of 211), and 19.7% (26 of 132) of patients in the respective groups (eTable 5 in Supplement 3), with the most common event being hypertriglyceridemia (20 [9.6%] vs 6 [2.8%] vs 2 [1.5%]) (Table 2). Serious TRAEs occurred in 38.3% of patients (80 of 209) receiving benmelstobart plus anlotinib, 33.2% (70 of 211) receiving benmelstobart alone, and 26.5% (35 of 132) receiving placebo; the most frequent event across 3 groups was pneumonia (21 [10.0%] vs 17 [8.1%] vs 7 [5.3%]) (eTable 7 in Supplement 3). Grade 3 to 5 immune-related AEs were more common with benmelstobart plus anlotinib (7.2% [15 of 209 patients]) than benmelstobart alone (4.7% [10 of 211 patients]) or placebo (3.8% [5 of 132 patients]) (eTable 8 in Supplement 3). Treatment discontinuation due to TRAEs occurred in 21.5% (45 of 209 patients), 13.7% (29 of 211), and 9.1% (12 of 132) of patients in the respective groups (eTable 9 in Supplement 3).

In all, 20 grade 5 fatal TRAEs occurred, 15 (7.2%) among those receiving benmelstobart plus anlotinib, with hemoptysis (1.9% [4 patients]) and pneumonia (1.9% [4 patients]) being the most common. One additional patient died of pulmonary hemorrhage, and all 5 fatal pulmonary bleeding events occurred in patients with squamous cell carcinoma.

Discussion

To our knowledge, R-ALPS is the first phase 3 randomized trial to evaluate the addition of an antiangiogenic agent to immunotherapy consolidation after CRT in patients with unresectable stage III NSCLC. In this prespecified interim analysis, benmelstobart alone significantly prolonged PFS compared with placebo. Adding anlotinib produced a further numerical improvement in PFS but did not cross the prespecified interim efficacy boundary and increased severe and fatal TRAEs.

The benefit of benmelstobart alone is consistent with the established role of PD-L1 blockade after definitive CRT.[1-4,13] IRC-assessed median PFS was 9.7 months with benmelstobart and 4.2 months with placebo (HR, 0.53; 95% CI, 0.39 to 0.72). This relative treatment effect was similar to that reported with durvalumab in PACIFIC[1] (HR, 0.52) and within the range reported in GEMSTONE-301[3] and PACIFIC-5[4] (HRs, 0.64 and 0.75, respectively). Median PFS with benmelstobart was shorter than the 16.8 months reported in PACIFIC,[1] possibly because R-ALPS included higher proportions of patients with stage IIIB or IIIC disease and squamous histologic results and also enrolled patients treated with sCRT.

Several phase 3 trials in advanced NSCLC have provided clinical evidence for joint inhibition of immune and angiogenic pathways.[14-17] In CAMPASS,[15] benmelstobart plus anlotinib prolonged median PFS compared with pembrolizumab in patients

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who were previously untreated with driver-negative, PD-L1-positive advanced NSCLC (HR, 0.70; 95% CI, 0.54-0.90). In HARMONi-6,[16] ivonescimab, a PD-1 vascular endothelial growth factor bispecific antibody, plus chemotherapy improved PFS (HR, 0.60; 95% CI, 0.46-0.78) and OS (HR, 0.66; 95% CI, 0.50-0.87) over tislelizumab plus chemotherapy in previously untreated advanced squamous NSCLC. However, whether this strategy confers additional benefit as consolidation after definitive CRT remains uncertain. In R-ALPS, median PFS was 17.4 months with the combination and 11.2 months with benmelstobart alone (HR, 0.82; 95% CI, 0.63-1.08). Although the 6.2-month numerical difference may be clinically meaningful, the comparison did not cross the prespecified interim efficacy boundary. Limited subgroup sample sizes precluded reliable assessment of treatment effect heterogeneity. Thus, the current findings neither establish incremental benefit in the overall population nor exclude benefit in selected patients. Future studies should incorporate biomarkers to identify patients most likely to benefit from this intensification strategy.

Safety was a key consideration in assessing anlotinib intensification. Grade 3 to 5 TRAEs occurred in 48.8%, 29.4%, and 19.7% of patients receiving benmelstobart plus anlotinib, benmelstobart alone, and placebo, respectively; and grade 5 TRAEs, in 7.2%, 1.4%, and 1.5%, respectively. The safety profile of benmelstobart alone was generally consistent with that reported in previous studies of PD-L1 consolidation.[1-4,13] The higher rate of toxic effects observed with the combination was attributable in part to established anlotinib-related adverse events, including hypertriglyceridemia and hypertension.[11,15,18] Of particular concern was fatal pulmonary bleeding, a recognized complication when antiangiogenic agents are administered concurrently with or after thoracic radiotherapy.[19-21] Previous studies[15,18] have reported a relatively low incidence of severe anlotinib-associated pulmonary bleeding in selected patients with advanced squamous NSCLC.[15,18] R-ALPS adopted similar bleeding-related exclusion criteria and used a reduced anlotinib dose of 8 mg rather than 12 mg. Although grade 1 to 4 hemoptysis occurred at similar rates in the combination, benmelstobart-alone, and placebo groups (8.6%, 8.1%, and 8.3%, respectively), 4 patients in the combination group died from hemoptysis and 1 from pulmonary hemorrhage; all 5 had squamous histologic results. Given the uncertain incremental efficacy of anlotinib and the excess fatal toxicity, these findings do not support its routine addition without reliable bleeding-risk stratification.

Limitations

Several limitations should be acknowledged. First, the trial did not include a durvalumab comparator; all patients were enrolled in China; and the proportion with squamous histologic findings was high, all of which limited generalizability. Second, the analysis was interim with immature OS data. Follow-up is ongoing for the prespecified final PFS analysis and to assess OS. Third, PD-L1 testing was not required at enrollment, and PD-L1 status was unknown in 69.1% of patients, precluding reliable assessment of whether treatment effects varied by PD-L1 expression.[22]

Conclusions

In this randomized clinical trial, benmelstobart significantly improved PFS over placebo in patients with unresectable stage III NSCLC, without disease progression after cCRT or sCRT. Adding anlotinib resulted in a numerically longer median PFS but did not cross the prespecified interim efficacy boundary and increased severe and fatal toxic effects. These findings do not support routine addition of anlotinib in an unselected population at present; longer follow-up and biomarker-based studies are needed.

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