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Patient-reported outcomes (PROs) from IMforte: A Phase 3 study of first-line maintenance treatment with lurbinectedin + atezolizumab versus atezolizumab in patients with extensive-stage small cell lung cancer (ES-SCLC)

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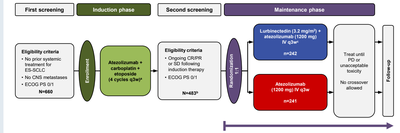
BACKGROUND

- IMforte (NCT05091567) is the first Phase 3 study to demonstrate statistically significant and clinically meaningful improvements in independently-assessed progression-free survival (PFS; stratified hazard ratio [HR], 0.54; 95% CI: 0.43, 0.67; P<0.0001) and overall survival (OS; stratified HR, 0.73, 95% CI: 0.57, 0.95; P=0.0174) with lurbinectedin + atezolizumab vs atezolizumab as first-line maintenance treatment in patients with ES-SCLC[1]
- The U.S. Food and Drug Administration has approved the use of lurbinectedin + atezolizumab as a maintenance treatment for adult patients with ES-SCLC whose disease had not progressed after first-line induction therapy with atezolizumab, carboplatin, and etoposide,[2,3] subsequent to the results obtained from IMforte
- Using well-established patient-reported outcome (PRO) questionnaires, we report the impact that the addition of lurbinectedin to atezolizumab maintenance therapy has on patient-reported tolerability, health-related quality of life (HRQoL), functioning, and lung cancer symptoms in patients with ES-SCLC

METHODS

- Eligible patients were those with ES-SCLC, Eastern Cooperative Oncology Group performance status (ECOG PS) 0/1, and no disease progression after four cycles of first-line induction treatment with atezolizumab, carboplatin, and etoposide every 3 weeks (q3w)
- Patients were randomized 1:1 to receive maintenance treatment q3w with lurbinectedin 3.2 mg/m^2 intravenously (IV, with granulocyte colony-stimulating factor prophylaxis) + atezolizumab 1200 mg IV or atezolizumab alone until disease progression or unacceptable toxicity (**Figure 1**)
- Secondary and exploratory PRO were analyzed and reported at the clinical cutoff date of July 29, 2024 (**Table 1**)
- Patients completed PRO questionnaires at maintenance baseline, on Day (D)1 of Cycle (C)2–C6, D10 of C1 and C2 (PRO-Common Terminology Criteria for Adverse Events [PRO-CTCAE] only), then on D1 of every second cycle from C8 until treatment discontinuation, and at 3- and 6-month follow-up (except PRO-CTCAE; **Table 2**)

Figure 1. IMforte study design



Primary endpoints
IRF-PFS and OS

Secondary endpoints included
INV-PFS, ORR, DOR, safety, PROs of TTCD analysis of Physical Functioning and GHS/QoL scales from EORTC QLQ-C30

Exploratory endpoints included
PROs of side effects bother, symptomatic AEs, lung cancer symptoms, and functional status, and biomarker analyses

Stratification factors for randomization
- ECOG PS (0/1)
- LDH (ULN/>ULN)
- Presence of liver metastases (Y/N) at induction baseline
- Prior receipt of PCI (Y/N)

ClinicalTrials.gov ID: NCT05091567. a Administered per standard doses. b 73% (n=483) of 660 patients continued from induction to maintenance treatment. c With prophylactic granulocyte colony-stimulating factor and anti-emetics.
AE, adverse event; C1D1, Cycle 1 Day 1; CNS, central nervous system; CR, complete response; DOR, duration of response; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer QoL Questionnaire-Core 30; GHS, global health status; INV-PFS, investigator-assessed progression-free survival; IRF-PFS, independent review facility-assessed progression-free survival; LDH, lactate dehydrogenase; PCI, prophylactic cranial irradiation; PD, progressive disease; PR, partial response; QoL, quality of life; SD, stable disease; TTCD, time-to-confirmed deterioration; ULN, upper limit of normal; Y/N, yes/no.
Paz-Ares L, et al. Lancet 2025;405:2129-2143.

Table 1. Evaluation of PROs

Endpoint/Questionnaire	Analysis	Population analyzed	Statistical analysis methodology
Secondary endpoint			
EORTC QLQ-C30	TTCD in Physical Functioning and GHS/QoL scales	FAS[a]	Time-to-event[b]
Exploratory endpoints			
EORTC IL46	Extent to which patients were troubled by the side effects of treatment	SAS[c]	Descriptive
PRO-CTCAE	Frequency and/or severity of patient-reported treatment toxicities	SAS[c]	Descriptive
EORTC QLQ-LC13	Mean change from baseline in lung cancer symptoms	FAS[a]	Descriptive
EORTC QLQ-C30	Mean change from baseline in cancer-specific HRQoL, functioning, and symptoms	FAS[a]	Descriptive
Post hoc exploratory analysis			
EORTC QLQ-C30	First TTD in Physical Functioning and GHS/QoL scales	FAS[b]	Time-to-event[b]

a Full analysis set, defined as all patients randomized into the maintenance phase regardless of whether or not the assigned study treatment was received. b Descriptive; not α-controlled.
c Safety analysis set, defined as patients who were randomly assigned to the maintenance treatment phase and had received ≥1 dose of lurbinectedin or atezolizumab.
EORTC IL46, EORTC Item Library 46; EORTC QLQ-LC13; EORTC QLQ Lung Cancer Module 13; FAS, full analysis set; QLQ, QoL Questionnaire; SAS, safety analysis set; TTD, time to deterioration.

Table 2. PRO administration schedule

	Maintenance treatment Lurbinectedin + atezolizumab vs atezolizumab										
PRO questionnaire	C1D1 (baseline)	C1D10	C2D1	C2D10	C3D1	C4D1	C5D1	C6D1, then every second cycle onwards	Treatment discontinuation	3-month follow-up	6-month follow-up
EORTC IL46	✓	✗	✓	✗	✓	✓	✓	✓	✓	✓	✓
PRO-CTCAE	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✗
EORTC QLQ-LC13	✓	✗	✓	✗	✓	✓	✓	✓	✓	✓	✓
EORTC QLQ-C30	✓	✗	✓	✗	✓	✓	✓	✓	✓	✓	✓

QLQ-Core 30; FAS, full analysis set; HRQoL, health-related QoL; PRO-CTCAE, PRO-Common Terminology Criteria for Adverse Events; PRO, patient-reported outcome; QLQ, QoL Questionnaire; SAS, safety analysis set; TTCD, time to confirmed deterioration; TTD, time to deterioration.

RESULTS

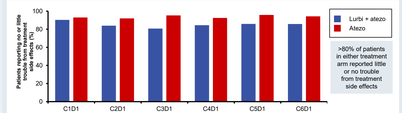
PRO questionnaire completion rates

- At clinical cutoff, July 29, 2024, PRO completion rates were high at baseline (>85%) and remained high throughout the maintenance treatment phase for both arms, relative to the number of patients still on treatment at each time point
  - PRO data were only interpreted from cycles where ≥25% of the randomized patients were still eligible to complete the PRO questionnaire, i.e. until C10 (≈Week 30) for the lurbinectedin + atezolizumab arm and until C6 (≈Week 18) for the atezolizumab arm. Therefore, any comparison between treatment arms was evaluated up to C6
  - PRO completion rates were low (<35%) at the treatment discontinuation visit and at 3- and 6-month follow-up, limiting the interpretation of the data

Patient-reported tolerability—Overall side-effect bother for EORTC IL46

- The EORTC IL46 questionnaire showed that 90.3% (n=205) of patients in the lurbinectedin + atezolizumab arm reported being "not at all" or "a little" troubled by treatment side effects at C1D1, with rates ranging from 80.7% to 85.9% between C2 and C6 (**Figure 2**)
- In the atezolizumab arm, 93.0% (n=199) of patients reported being "not at all" or "a little" troubled by treatment side effects at baseline; and remained above 90% for each visit between C2 and C6

Figure 2. Extent to which patients on treatment are troubled by the side effects of treatment determined by EORTC IL46[a]



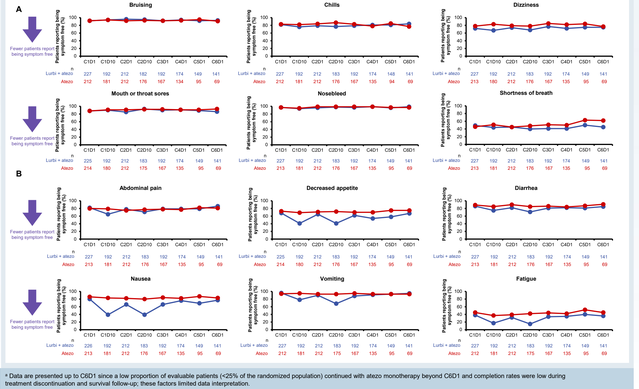
>80% of patients in either treatment arm reported little or no trouble from treatment side effects

a Data are presented up to C6D1 since a low proportion of evaluable patients (<25% of the randomized population) continued with atezo monotherapy beyond C6D1 and completion rates were low during treatment discontinuation and survival follow-up; these factors limited data interpretation. n is the number of patients who completed the EORTC IL46 questionnaire at these timepoints.
atezo, atezolizumab; lurbi, lurbinectedin.

Patient-reported tolerability—Overall frequency or severity of symptomatic AEs for PRO-CTCAE

- In the lurbinectedin + atezolizumab arm, 6 of 12 symptomatic adverse events (AEs) did not change (<10% difference in the number of patients reporting any frequency or severity of symptoms) from baseline: bruising, chills, dizziness, mouth or throat sores, nosebleed, and shortness of breath (**Figure 3A**)
- In the lurbinectedin + atezolizumab arm, the remaining 6 of 12 symptomatic AEs transiently worsened in frequency or severity, with a difference of ≥10% in the number of patients reporting any frequency or severity of symptoms from baseline, but returned to baseline levels between C3 and C6: abdominal pain, decreased appetite, diarrhea, fatigue, nausea, and vomiting (**Figure 3B**). The biggest changes were in nausea, decreased appetite, and vomiting
- In the atezolizumab arm, 11 symptomatic AEs did not change from baseline to C6 (<10% difference), with the exception of shortness of breath, for which a higher proportion of patients reported being symptom free at C6 than at baseline (C1D1: 45.5%; C6D1: 62.3%)
- High rates (>50%) of fatigue and shortness of breath were reported at baseline and through C6 by patients in both treatment arms

Figure 3. Frequency or severity of symptomatic AEs determined for PRO-CTCAE with (A) no change (<10% difference) and (B) transient change (≥10% difference) from baseline[a]



a Data are presented up to C6D1 since a low proportion of evaluable patients (<25% of the randomized population) continued with atezo monotherapy beyond C6D1 and completion rates were low during treatment discontinuation and survival follow-up; these factors limited data interpretation.

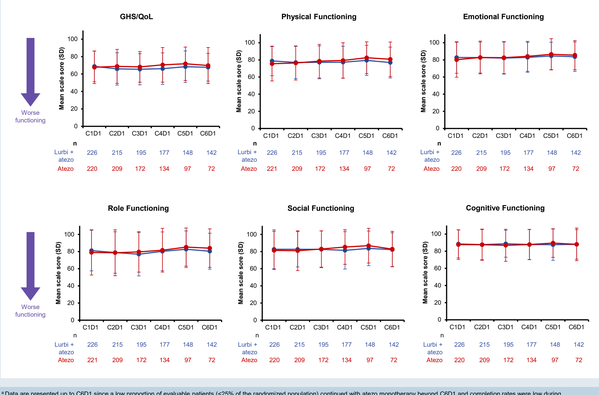
Assessment of lung cancer symptoms—EORTC QLQ-LC13

- Overall, mean scores were maintained and stable (<10-point change from baseline in mean scale scores)[a] for lung cancer symptoms from baseline to C6 for either treatment arm and between treatment arms for arm or shoulder pain, chest pain, coughing, dysphagia, dyspnea, hemoptysis, mouth sores, pain other parts, and peripheral neuropathy (data not shown)
- A clinically meaningful improvement (≥10 points) in mean alopecia scores from baseline to C6 was seen in patients from both treatment arms (lurbinectedin + atezolizumab arm: C1D1, 41.4; C6D1, 6.1; atezolizumab arm: C1D1, 41.2; C6D1, 7.7)

Assessment of all functional scales and GHS/QoL scale—EORTC QLQ-C30

- No clinically meaningful difference in mean scores was seen in any of the functional scales (Physical, Emotional, Role, Social, and Cognitive Functioning) and GHS/QoL scale from baseline to C6, indicating that functional health remained stable for patients remaining on treatment, with no differences between treatment arms (**Figure 4**)
- For symptom items and scales, no clinically meaningful difference in mean scores was observed from baseline to C6, with no differences seen between treatment arms: appetite loss, constipation, diarrhea, dyspnea, fatigue, financial difficulties, insomnia, nausea and vomiting, and pain (data not shown)

Figure 4. Mean scale scores for all functional scales and GHS/QoL scale as assessed by EORTC QLQ-C30[a,b]



a Data are presented up to C6D1 since a low proportion of evaluable patients (<25% of the randomized population) continued with atezo monotherapy beyond C6D1 and completion rates were low during treatment discontinuation and survival follow-up; these factors limited data interpretation. b Higher scores mean better functioning and QoL. SD, standard deviation.

Time-to-event analysis of Physical Functioning and GHS/QoL scale scores using TTCD and TTD—EORTC QLQ-C30

- Patients treated with lurbinectedin + atezolizumab had numerically shorter median TTCD for the Physical Functioning and the GHS/QoL scale scores when compared with those treated with atezolizumab (**Figure 5**)
- However, few patients met the conservative TTCD event definition (**Table 3**) for Physical Functioning and GHS/QoL
- Although the approach used to evaluate TTCD was consistent with established methods, the results included a variety of anomalies indicative of a potential bias in favor of the atezolizumab arm:
  - High rates of censoring in both treatment arms relative to the number of observed events
  - An imbalance in the number of censored observations between treatment arms, with fewer events in the atezolizumab arm
  - The median TTCD for Physical Functioning in the lurbinectedin + atezolizumab arm and for both Physical Functioning and GHS/QoL in the atezolizumab arm were numerically longer than median OS (**Figure 5**)
- Taken together, these factors suggested that earlier treatment discontinuation could have restricted the number of observable events in the atezolizumab arm
- Further review of the data confirmed that many patients in the atezolizumab arm did not have sufficient available data to provide confirmation of deterioration as defined in the protocol
- To address this limitation and better account for the poor prognosis of this population,[5] a post hoc analysis was performed based on the first-reported time to deterioration (TTD) for Physical Functioning and GHS/QoL (**Table 3**)

Table 3. Event definitions for the time-to-event analysis

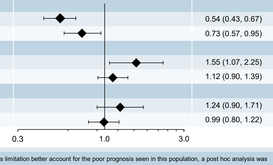
Endpoint	TTCD	TTD
Endpoint type	• Pre-specified secondary endpoint	• Post hoc sensitivity analysis
Event definition	• Two consecutive clinically meaningful[a] deteriorations on scale score, or • One clinically meaningful[a] deterioration on scale score followed by death from PD within 6 weeks of last deterioration	• One clinically meaningful[a] deterioration on scale score, or • Death from any cause

a Clinically meaningful is defined as a deterioration of ≥10 points from baseline.[4]

- The majority of patients met the TTD event definition, resulting in lower rates of censoring (i.e. higher event rates) than in the TTCD analysis, with the number of events balanced between treatment arms for Physical Functioning and GHS/QoL (**Figure 5**). Hence, this analysis provides greater certainty in the interpretation of the results
- Patients treated with lurbinectedin + atezolizumab showed no evidence of difference in the median TTD for the Physical Functioning and GHS/QoL scales when compared with those treated with atezolizumab

Figure 5. Summary of efficacy results and EORTC QLQ-C30 Physical Functioning and GHS/QoL analyses

Measure	Events, n (%)		Median, months		Stratified HR (95% CI)
	Lurbi + atezo (n=242)	Atezo (n=241)	Lurbi + atezo	Atezo	
Primary endpoints[1]					
IRF-PFS	174 (71.9%)	202 (83.8%)	5.4	2.1	0.54 (0.43, 0.67)
OS	113 (46.7%)	136 (56.4%)	13.2	10.6	0.73 (0.57, 0.95)
Physical Functioning[a]					
TTCD	75 (31.0%)	47 (19.5%)	15.9	NE	1.55 (1.07, 2.25)
TTD	187 (77.3%)	175 (72.6%)	3.5	5.0	1.12 (0.90, 1.39)
GHS/QoL[a]					
TTCD	92 (38.0%)	71 (29.5%)	10.8	12.9	1.24 (0.90, 1.71)
TTD	188 (77.7%)	184 (76.3%)	2.3	2.8	0.99 (0.80, 1.22)



a Secondary endpoint TTCD analysis for Physical Functioning and GHS/QoL was limited and biased. To address this limitation better account for the poor prognosis seen in this population, a post hoc analysis was done on the first-reported TTD for Physical Functioning and GHS/QoL. NE, not estimable.

CONCLUSIONS

- Overall, data suggest adding lurbinectedin to atezolizumab in maintenance treatment did not significantly increase treatment burden and lung cancer symptoms, or impact patient-reported functioning and HRQoL in patients with ES-SCLC
- The combination was well tolerated by the vast majority of patients per EORTC IL46 despite a transient increase in the proportion of patients reporting any frequency or severity in a subset of symptomatic AEs per PRO-CTCAE, which returned to baseline generally after C3
- Median TTCD for Physical Functioning and GHS/QoL were numerically shorter in the lurbinectedin + atezolizumab arm than in the atezolizumab arm. Since few patients met the conservative TTCD event definition, the low event rates limited data interpretation of this analysis
  - The post hoc TTD analysis of Physical Functioning and GHS/QoL accounts for the relatively shorter duration of treatment in the atezolizumab arm and the poor prognosis of this population.[5] This TTD analysis, which was more tailored to the study population than the TTCD analysis, did not show a difference between treatment arms in the time to clinically meaningful deterioration in either scale
- These PRO results provide additional evidence supporting the favorable benefit–risk profile of maintenance lurbinectedin + atezolizumab as a new therapeutic option for ES-SCLC management

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DISCLOSURES

Carla Mamolo, PhD, is an employee of Genentech Inc. and owns stocks in F. Hoffmann-La Roche Ltd.