Tarlatamab with first-line chemo-immunotherapy for extensive-stage small cell lung cancer (ES-SCLC): DeLLphi-303 study

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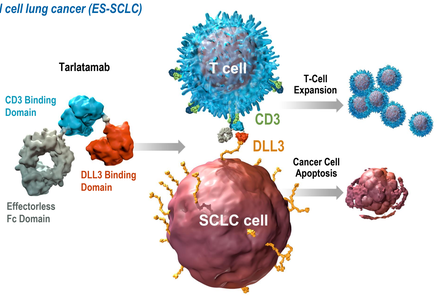
BACKGROUND

Tarlatamab in extensive-stage small cell lung cancer (ES-SCLC)

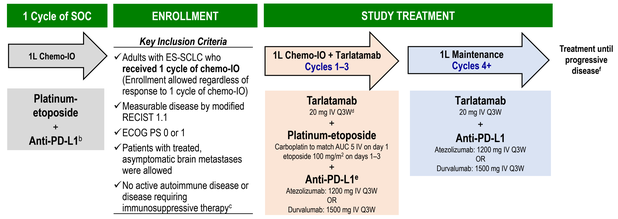
- The current standard of care 1L treatment for ES-SCLC, chemo-immunotherapy followed by anti-PD-(L)1 maintenance, has yielded an ORR of 60-80% with median DOR of 4.2–5.6 months and median OS of 12–15 months and reported grade ≥ 3 AEs in 62–83% of patients.[1-5]
- Tarlatamab, a bispecific T-cell engager (BiTE®) immunotherapy, achieved noteworthy survival outcomes with a favorable safety profile when administered as 2L monotherapy (phase 3 DeLLphi-304 study) or as 1L maintenance therapy with an anti-PD-L1 (phase 1b DeLLphi-303 study; parts 5, 6, and 8) in patients with ES-SCLC.[6,7]



We present safety and efficacy outcomes from the phase 1b DeLLphi-303 study (parts 2, 4, 7), investigating tarlatamab in combination with 1L chemo-immunotherapy followed by tarlatamab with anti-PD-L1 maintenance therapy in patients with ES-SCLC.

METHODS

Phase 1b DeLLphi-303 study[a]



Primary Endpoints[g]: Dose-limiting toxicities[h], treatment-emergent and treatment-related adverse events
Secondary Endpoints[i]: Objective response, duration of response, disease control, PFS, and OS

[a]Only data for cohorts 2.1, -2.1, 4, and 7 investigating tarlatamab in combination with 1L chemo-immunotherapy and anti-PD-L1 maintenance therapy are presented. [b]Patients without access to anti-PD-L1 were allowed. [c]Patients with active autoimmune disease requiring systemic treatment (except replacement therapy) within the past 2 years were excluded. [d]Tarlatamab was administered with step dosing: 1 mg on cycle 1 day 1 followed by tarlatamab 20 mg Q3W. For patients in cohort -2.1 (n=7), step dosing began on cycle 1 day 8. [e]Patients received either atezolizumab or durvalumab in a non-randomized manner; switch to a different PD-L1 inhibitor from that received with SOC before study start was allowed. [f]Treatment beyond progressive disease allowed if clinical benefit per investigator. [g]Also included vital signs, electrocardiograms, and clinical laboratory tests ≥DLTs were assessed in cohorts 2.1 and -2.1 only. [h]Also included serum concentrations of tarlatamab.

RESULTS

Baseline characteristics

	Tarlatamab + EP + atezolizumab n = 56	Tarlatamab + EP + durvalumab n = 40	Overall[a] N = 96
Age, median (range), years	63.0 (41–86)	65.0 (37–77)	**63.0 (37–86)**
Male, %	68	65	**67**
Race, Asian / Black or African American / White / Other, %	23 / 2 / 70 / 5	5 / 0 / 80 / 15	**16 / 1 / 74 / 9**
Disease stage at diagnosis, limited-stage/extensive-stage, %	29 / 71	15 / 85	**23 / 77**
ECOG performance status, 0/1, %	50 / 50	38 / 63	**45 / 55**
Smoking history, current/former/never, %	14/77/9	23/73/5	**18 / 75 / 7**
Prior anti-PD-L1 in first SOC cycle, %	75	55	**67**
Presence of treated, asymptomatic brain metastases, %	21	8	**16**
Presence of liver metastases, %	39	53	**45**
Median sum of diameters of target lesions, mm (range)	66.0 (12.0–358.2)	94.5 (10.0–314.0)	**82.3 (10.0–358.2)**

DeLLphi-303 was not designed as a comparative study between anti-PD-L1 agents and no randomization between treatment arms occurred. Imbalances in baseline characteristics were observed between the atezolizumab and durvalumab groups.

[a]One patient from cohort -2.1 received atezolizumab on cycle 1 day 1 but withdrew before receiving tarlatamab on cycle 1 day 8; this patient is included in all data outputs.

RESULTS

Safety summary

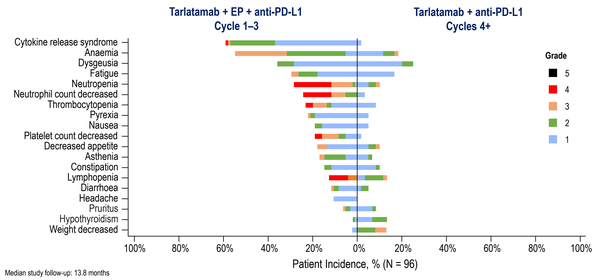
	Tarlatamab + EP + atezolizumab n = 56	Tarlatamab + EP + durvalumab n = 40	Overall N = 96[a]
Median duration of treatment, weeks (IQR)	46 (16–60)	30 (12–62)	**46 (14–60)**
Median study follow-up, months (95% CI)	12.5 (11.3, 14.7)	14.8 (13.2, 15.0)	**13.8 (12.5, 15.0)**
Dose-limiting toxicities[b], n (%)	3 (5)	0	**3 (3)**
Treatment-emergent AEs[c], n (%)	56 (100)	40 (100)	**96 (100)**
Treatment-related AEs, n (%)	56 (100)	40 (100)	**96 (100)**
Grade 3	26 (46)	15 (38)	**41 (43)**
Grade 4	21 (38)	13 (33)	**34 (35)**
Fatal TRAEs	0	1 (3)[d]	**1 (1)**

- Tarlatamab-related AEs led to tarlatamab discontinuation in 6% of patients[e], with no deaths
- Immune-related adverse events[f], excluding CRS and ICANS and associated neurological events, were rare (2%)

Overall, the addition of tarlatamab to chemo-immunotherapy demonstrated a manageable safety profile, consistent with the safety profiles of each individual agent.

[a]One patient from cohort -2.1 received atezolizumab on cycle 1 day 1 but withdrew before receiving tarlatamab on cycle 1 day 8. [b]Dose limiting toxicities included ICANS (n = 1) , platelet count decrease (n = 1), and thrombocytopenia (n = 1). [c]Fatal TEAEs included pneumonia (n = 1), pneumonia aspiration (n = 1), and septic shock (n = 1). [d]Septic shock attributed by the investigator as related to etoposide-carboplatin chemotherapy. [e]Discontinuations include: immune effector cell-associated neurotoxicity syndrome (n = 1), cytokine release syndrome (n = 1), myocardial infarction (n = 1), arthritis allergic, dermatitis allergic, and osteoarthritis (n = 1), hepatitis (n = 1), decreased appetite (n = 1). [f]Immune-related adverse events, defined using MedDRA SMQ narrow search excluding CRS and ICANS and associated neurological events, included autoimmune hypothyroidism (n = 1) and polymyalgia rheumatica (n = 1).

Timing of treatment-related adverse events (≥ 10% incidence)[a]

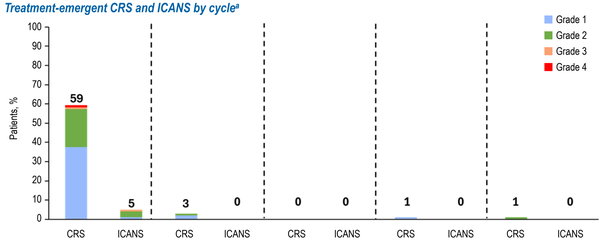


Median study follow-up: 13.8 months

- The most common TRAEs primarily occurred during the first 3 cycles when carboplatin-etoposide chemotherapy was administered
- The observed safety profile was consistent with that reported for the individual treatment components (EP/anti-PD-L1/tarlatamab)

[a]TRAEs related to EP, anti-PD-1, and/or tarlatamab with patient incidence ≥ 10% are shown.

Treatment-emergent CRS and ICANS by cycle[a]



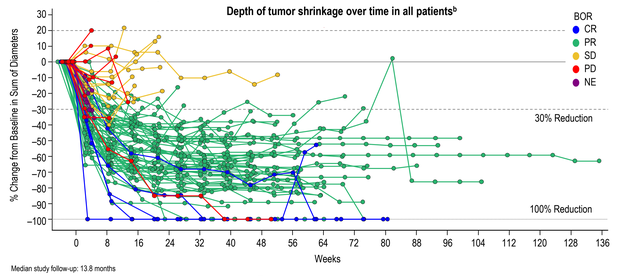
Median study follow-up: 13.8 months

- CRS and ICANS were associated with a low rate of
  - tarlatamab dose interruptions (CRS and ICANS: 1% each)
  - tarlatamab discontinuations (CRS and ICANS: 1% each)
- There were no fatalities related to CRS or ICANS
- The median time to onset of CRS from last prior dose of tarlatamab was 13.3 hours (IQR: 8.0–19.3)
- The median time to onset of ICANS from last prior dose of tarlatamab was 5 days (IQR: 3.0–5.0)

- CRS and ICANS events occurred primarily during cycle 1 of tarlatamab administration and were mostly low grade (grades 1–2) events
- All CRS and ICANS events resolved

[a]Treatment-emergent events by worst grade reported. [b]Grade 4 CRS event was due to use of bilevel positive airway pressure in a patient with concurrent grade 3 pneumonia with positive sputum cultures.

Best overall response and depth of tumor shrinkage over time



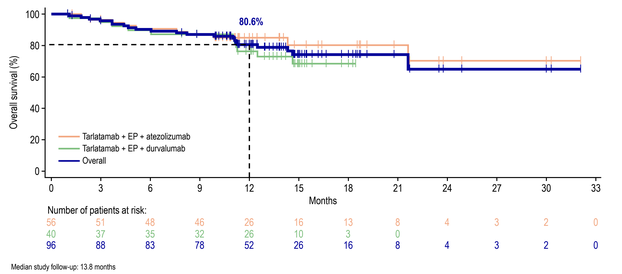
Median study follow-up: 13.8 months

	Overall N = 96
ORR[a], n (%)	**68 (71)**
95% CI	61–80
CR	5 (5)
PR	63 (66)
SD	11 (11)
PD	8 (8)
NE/no post-baseline scan	9 (9)
mDOR, mos (95% CI)	**11.0 (8.5, NE)**
DCR, % (95% CI)	**82 (73–89)**
mDoDC, mos (95% CI)	**10.7 (7.7–18.8)**

- From a baseline scan after 1 cycle of SOC 1L chemo-IO, addition of tarlatamab to 1L ES-SCLC therapy resulted in
  - ORR of 71%, with median duration of response of 11.0 months
  - Disease control sustained for ≥ 52 weeks in 39% of patients
  - Ongoing responses in 49% of patients at data cutoff with data continuing to mature

[a]For objective response endpoints, patients with missing response data (eg, no baseline assessment, missing post-baseline assessment) were treated as non-responders and included in the denominator [b]One patient did not have a post-baseline scan and is not included in the spider plot. Nine patients had 100% reduction in target lesions, including one patient with 100% reduction in target lesions and BOR of PD due to new lesions.

Overall survival with tarlatamab in combination with 1L SOC chemo-IO[a]

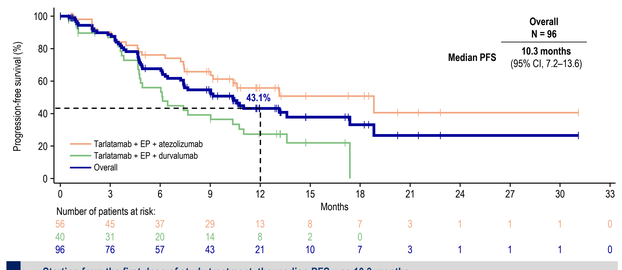


Median study follow-up: 13.8 months

- Starting from the first dose of study treatment, the Kaplan-Meier estimate of OS at 12 months was 80.6%.
- The median OS was not yet estimable.

[a]Given allocation between the atezolizumab and durvalumab subgroups was not randomized thus resulting in imbalances in baseline characteristics, comparisons cannot be made between the anti-PD-L1 agents.

Progression-free survival with tarlatamab in combination with 1L SOC chemo-IO[a]



- Starting from the first dose of study treatment, the median PFS was 10.3 months
- The Kaplan-Meier estimate of PFS at 12 months was 43.1% (95% CI, 32.0–53.7)

[a]Given allocation between the atezolizumab and durvalumab subgroups was not randomized thus resulting in imbalances in baseline characteristics, comparisons cannot be made between the anti-PD-L1 agents.

CONCLUSIONS

Tarlatamab in combination with 1L chemo-immunotherapy and anti-PD-L1 maintenance therapy:

- Demonstrated a manageable safety profile, consistent with the individual treatments
  - CRS and ICANS predominantly occurred during cycle 1 and were mostly low grade (grade 1 or 2)
  - No tarlatamab-related fatal events
  - Incidence of neutropenia and thrombocytopenia with tarlatamab added to 1L SOC were comparable to that seen with SOC [3,4]
- Encouraging response rate, durability of response, and survival outcomes from a baseline scan obtained at study start following 1 cycle of standard of care chemo-immunotherapy
  - Objective response rate of 71% with median duration of response of 11.0 months
  - Disease control rate of 82% with disease control sustained for ≥ 52 weeks in 39% of patients
  - Median OS was not yet reached; the Kaplan-Meier estimate of OS at 12 months was 81%, and median PFS was 10.3 months

The combination of tarlatamab with 1L chemo-IO and anti-PD-L1 maintenance therapy for ES-SCLC demonstrated a manageable safety profile with encouraging initial survival outcomes, supporting further investigation of this combination in the phase 3 DeLLphi-312 study (NCT07005128).

DECLARATION OF INTERESTS

M. Wermke declares:
- **Receipt of honoraria** from Amgen, BMS GmbH & Co. KG, Boehringer Ingelheim, GWT, Janssen, Lilly, Merck Serono, MJH/PER, Novartis, Pfizer, Regeneron, SYNLAB, and Takeda
- **Consulting or Advisory Role** for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo Europe GmbH, Genentech, ImCheck Therapeutics, Immatics, Iovance Biotherapeutics, ISA Pharmaceuticals, Lilly, Novartis, PharmaMar, Regeneron, Tacalyx, T-knife, and Zymeworks
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ABBREVIATIONS:

1L: first-line; **AEs:** adverse events; **BiTE:** bispecific T-cell engager; **AUC:** area under curve; **chemo-IO:** chemo-immunotherapy; **CI:** confidence interval; **CR:** complete response; **CRS:** cytokine release syndrome; **DCR:** disease control rate; **ECOG:** Eastern Cooperative Oncology Group; **ECOG PS:** Eastern Cooperative Oncology Group performance status; **EP:** etoposide-platinum chemotherapy; **ES-SCLC:** extensive-stage small cell lung cancer; **ICANS:** immune effector cell-associated neurotoxicity syndrome; **IQR:** interquartile range; **IV:** intravenous; **LS-SCLC:** limited stage small cell lung cancer; **mDoDC:** median duration of disease control; **mDOR:** median duration of response; mos: months; **mos:** months; **NE:** not evaluable; **ORR:** objective response rate; **OS:** overall survival; **PD:** progressive disease; **PD-L1:** programmed cell death-ligand 1; **PFS:** progression-free survival; **PR:** partial response; **RECIST:** Response Evaluation Criteria in Solid Tumors; **SD:** stable disease; **SOC:** standard-of-care; **TEAE:** treatment-emergent adverse event; **TRAE:** treatment-related adverse event.

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