Tarlatamab with a PD-L1 Inhibitor as First-Line Maintenance After Chemo-Immunotherapy for ES-SCLC: DeLLphi-303 Phase 1b Study

Sally C. M. Lau[1], Myung-Ju Ahn, Mor Moskovitz, Michael Pogorzelski, Simon Häfliger, Kelly G. Paulson, Amanda Parkes, Yuyang Zhang, Ali Hamidi, Martin Wermke

[1] Department of Medicine, Perlmutter Cancer Center, NYU Grossman School of Medicine, New York, NY, USA

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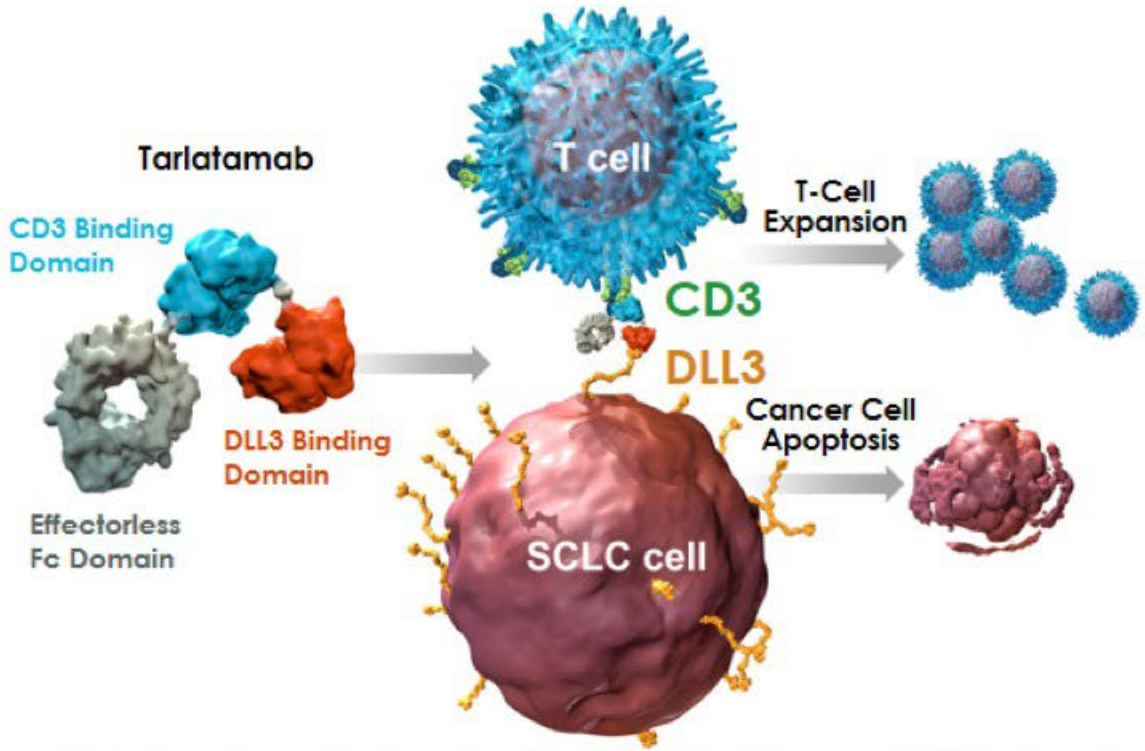
Tarlatamab in Small Cell Lung Cancer (SCLC)

DeLLphi 303

- Tarlatamab, a bispecific T-cell engager (BiTE®) immunotherapy that targets DLL3 on SCLC cells and CD3 on T cells, achieved durable responses and promising survival outcomes in patients with previously treated SCLC[1]
- Standard-of-care treatment for 1L ES-SCLC involves platinum-etoposide chemotherapy + PD-L1 inhibitor followed by PD-L1 inhibitor in maintenance[2,3]
- An exploratory substudy of survival from the start of maintenance therapy with atezolizumab in 1L ES-SCLC showed:
  - Median PFS: 2.6 months
  - Median OS: 12.5 months[4]
- In preclinical studies, tarlatamab upregulated PD-L1 expression and showed increased cytotoxic activity in combination with a PD-L1 inhibitor[5,6]



Tarlatamab activates T cells without relying on MHC class I

WE PRESENT EFFICACY AND SAFETY OUTCOMES OF TARLATAMAB IN COMBINATION WITH A PD-L1 INHIBITOR AS FIRST-LINE MAINTENANCE (1LM) AFTER CHEMO-IMMUNOTHERAPY FOR ES-SCLC.

1L, first-line; **CD3**, cluster of differentiation 3; **DLL3**, delta-like ligand 3; **ES**, extensive-stage; **Fc**, fragment crystallizable; **MHC**, major histocompatibility complex; **OS**, overall survival; **PD-L1**, programmed death-ligand 1; **PFS**, progression-free survival.

1. Ahn M-J et al. *N Engl J Med.* 2023; 389:2063-2075. **2.** NCCN Clinical Practice Guidelines in Oncology. Small Cell Lung Cancer. v3.2024. **3.** Dingemans AC, et al. *Ann Oncol.* 2021;32: 839-863. **4.** Reck M et al. *J Thorac Oncol.* 2022; 17:1122-1129. **5.** Giffin MJ, et al. *Clin Cancer Res* 2021;27:1526–37. **6.** You R, et al. Presentation at SITC 2023; November 1-5, 2023. San Diego, CA. Abstract #1189.

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DeLLphi-303: Tarlatamab with PD-L1 Inhibitor as 1LM

DeLLphi 303

- Phase 1b, multicenter, open-label study (NCT05361395)

- Must initiate C1D1 of maintenance phase within 8 weeks of the start of the last cycle of 1L chemo-immunotherapy
- Median follow-up time (N = 88): 10.0 months (range: 1.4+–20.4)

PRIMARY ENDPOINTS†: DOSE-LIMITING TOXICITIES, TREATMENT-EMERGENT / TREATMENT-RELATED ADVERSE EVENTS (TEAEs, TRAEs)

SECONDARY ENDPOINTS‡: DISEASE CONTROL AND PFS PER LOCAL RECIST 1.1 ASSESSMENT, OS

Data cutoff was May 31, 2024. *Tarlatamab was initiated with step dosing: 1 mg on Day 1, followed by 10 mg on Days 8, 15, and Q2W thereafter. †Also includes vital signs, electrocardiograms, and clinical laboratory tests. ‡Also includes objective response, duration of response, and serum concentrations of tarlatamab. **+**, censored; **1L**, first-line; **1LM**, first-line maintenance; **C1D1**, cycle 1 day 1; chemo, chemotherapy; **DLL3**, delta-like ligand 3; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **IO**, immuno-oncology agent; **IV**, intravenous; **LS**, limited-stage; **OS**, overall survival; **PD-L1**, programmed death-ligand 1; **Q2W**, once every two weeks; **Q4W**, once every four weeks; **RECIST**, response evaluation criteria in solid tumors; **SCLC**, small cell lung cancer.

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Baseline Characteristics

	Tarlatamab + Atezolizumab n = 48	Tarlatamab + Durvalumab n = 40	Tarlatamab + IO (Total) N = 88
Age, median (range), years	64 (27-79)	64 (37-85)	64 (27-85)
Male, %	67	58	63
White / Asian / Other,* %	71 / 19 / 10	70 / 20 / 10	71 / 19 /10
ECOG performance status 0 / 1, %	38 / 63	45 / 55	41 / 59
Prior number of 1L platinum-etoposide cycles, 4 / 5 / 6, %	85 / 8 / 6	88 / 3 / 10	86 / 6 / 8
Prior PD-L1 therapy, %	85	88	86
Median sum of diameters of target lesions at baseline (mm)	29.2	37.0	33.0
Presence of brain / liver metastases, %	19 / 35	33 / 43	25 / 39
Median time from start of 1L chemo-IO to 1LM, months (range)	3.6 (2.9–5.9)	3.5 (2.9–5.4)	3.6 (2.9–5.9)

- Of patients with evaluable baseline tumor sample (fresh or archival allowed), 97% had DLL3 expression detected

*Includes 7 patients recruited in France where the collection of information related to race and ethnicity is prohibited. **1L**, first-line; **1LM**, first-line maintenance; **chemo**, chemotherapy; **DLL3**, delta-like ligand 3; **ECOG**, Eastern Cooperative Oncology Group; **IO**, immuno-oncology agent; **PD-L1**, programmed cell death ligand 1.

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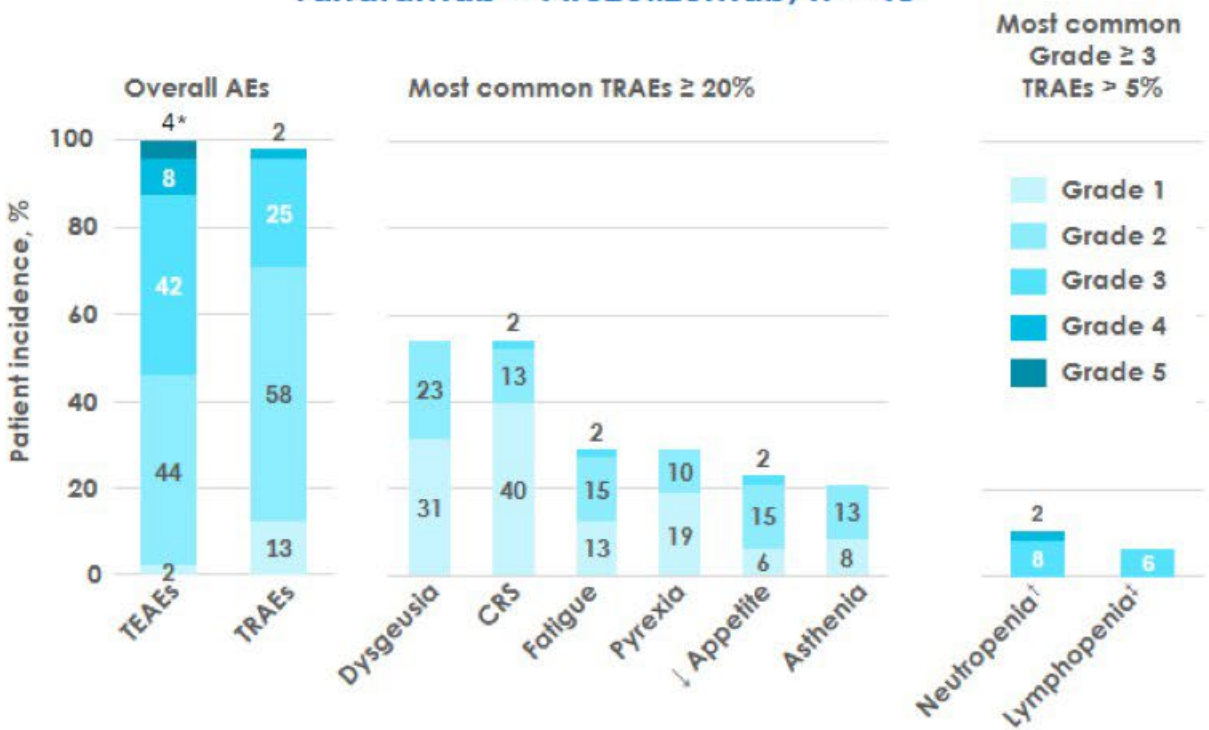
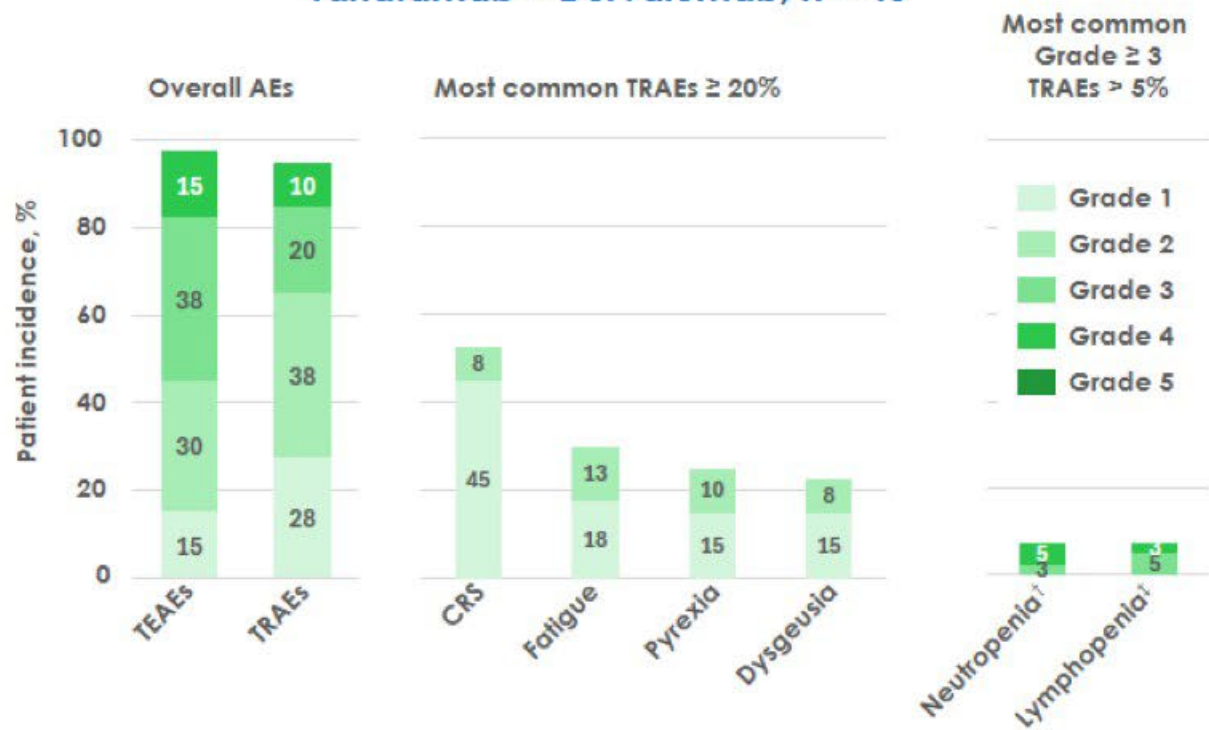
Safety profile

Tarlatamab + Atezolizumab, n = 48



TRAEs led to dose interruption in 17% and tarlatamab discontinuation in 4% of patients[§]

Tarlatamab + Durvalumab, n = 40



TRAEs led to dose interruption in 15% and tarlatamab discontinuation in 8% of patients[‖]

- **TARLATAMAB WITH A PD-L1 INHIBITOR AS 1LM HAD A MANAGEABLE SAFETY PROFILE WITH NO DLTs AND NO FATAL TRAEs**
- **THERE WERE NO NEW OR UNEXPECTED TOXICITIES, AND IMMUNE RELATED ADVERSE EVENTS (IRAEs) WERE RARE (2.3%)[¶]**

*Fatal TEAEs were due to disease progression. †Adverse events for MedDRA-preferred terms "neutropenia" and "neutrophil count decreased." ‡Adverse events for MedDRA-preferred terms "lymphopenia" and "lymphocyte count decreased." §Discontinuations due to dysgeusia (n =1) and COVID-19 (n =1). ‖Discontinuations due to pneumonitis and general physical health deterioration (n =1), cerebrovascular accident and general physical health deterioration (n =1), and maculopapular rash (n =1). ¶irAEs defined using MedDRA SMQ narrow search, excluding CRS and ICANS. Two irAEs identified in tarlatamab + atezolizumab group: 1–Sjogren's syndrome, 1–immune-mediated hypothyroidism. **1LM,** first-line maintenance; **AE,** adverse event; **CRS,** cytokine release syndrome; **DLT,** dose-limiting toxicity; **ICANS,** immune effector cell-associated neurotoxicity syndrome; **MedDRA,** Medical Dictionary for Regulatory Activities; **PD-L1,** programmed cell death ligand-1; **SMQ,** standardized MedDRA queries; **TEAE,** treatment-emergent adverse event; **TRAE,** treatment-related adverse event.

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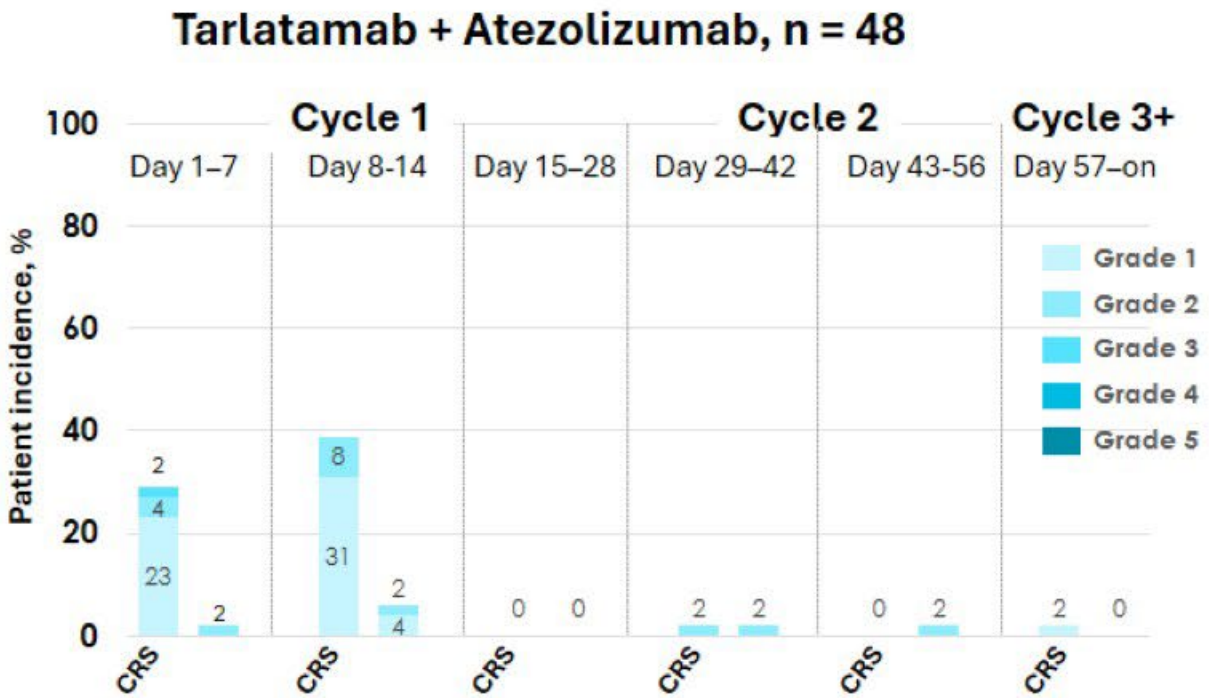
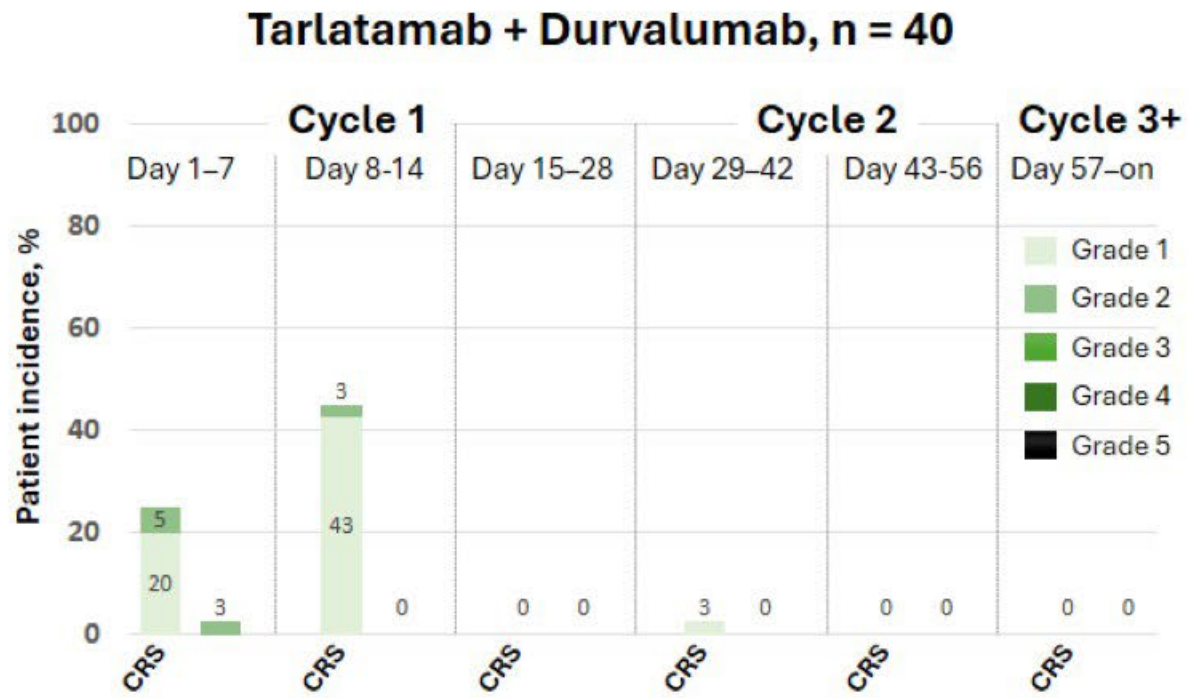
CRS and ICANS* in 1L maintenance





- Median time from last prior tarlatamab dose to onset of 1st CRS event: 19.5 hours (IQR: 11.1–31.6)
- Median time to resolution of CRS: 2 days (95% CI: 2–3)
- ICANS* occurred in 12.5% any grade, 4.2% grade 1, 8.3% grade 2

- Median time from last prior tarlatamab dose to onset of 1st CRS event: 24.3 hours (IQR: 12.0–31.1)
- Median time to resolution of CRS: 3 days (95% CI: 2–4)
- ICANS* occurred in 1 patient (2.5%) in Cycle 1, Day 1–7 and was grade 2

- **CRS WAS MOSTLY GRADE 1–2, PRIMARILY OCCURRED IN CYCLE 1, AND WAS MANAGEABLE WITH SUPPORTIVE CARE**
- **ICANS* OCCURRED INFREQUENTLY OVERALL, WITH A LOWER INCIDENCE AND A LOWER GRADE OBSERVED WITH TARLATAMAB + DURVALUMAB COMPARED TO TARLATAMAB + ATEZOLIZUMAB**

*ICANS includes associated neurologic events based on a broad search using 61 selected preferred terms from MedDRA version 27.0. **1L**, first line; **AE**, adverse event; **CI**, confidence interval; **CRS**, cytokine release syndrome; **ICANS**, immune effector cell-associated neurotoxicity syndrome; **IQR**, interquartile range; **MedDRA**, Medical Dictionary for Regulatory Activities.

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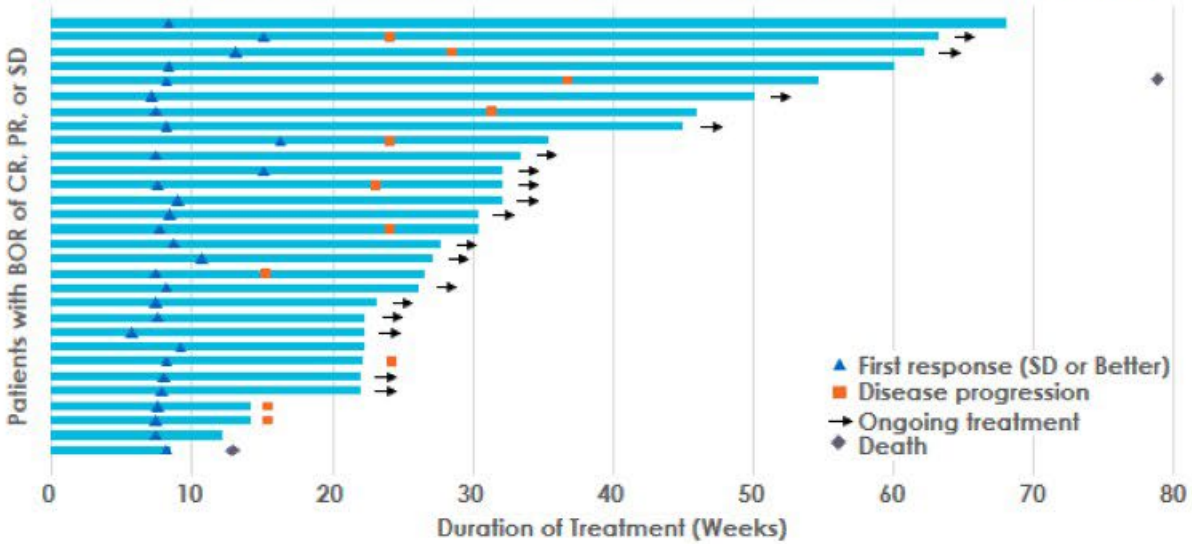
DCR and duration of disease control, beginning from 1L maintenance

Given study eligibility required non-PD to 1L **chemo +/- IO**, DCR and mDoDC were favored over ORR and mDOR in assessing clinical benefit.

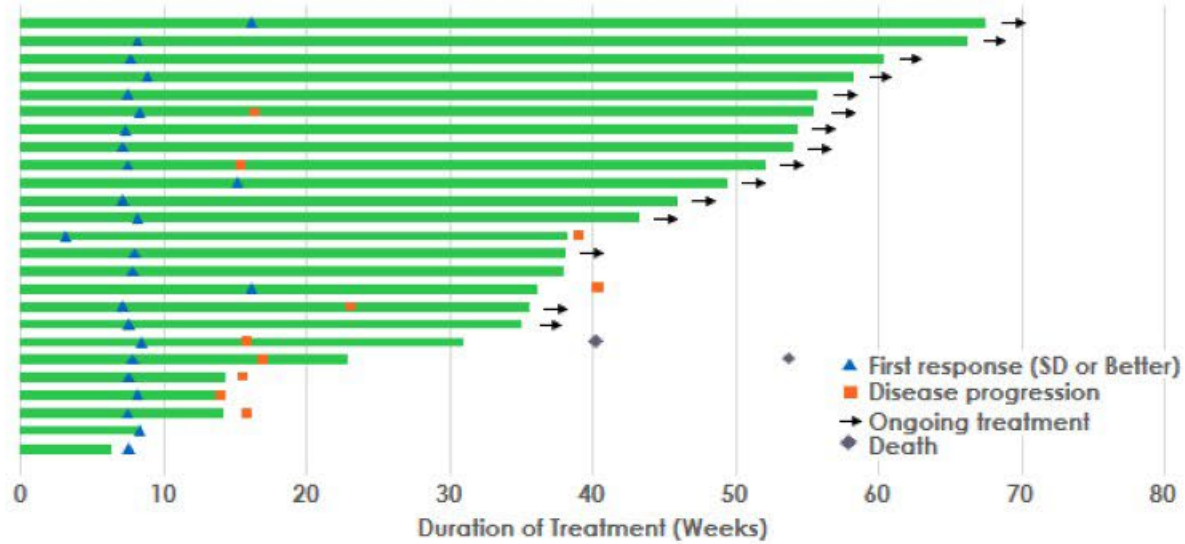
Tarlatamab + Atezolizumab, n = 30

- DCR: 30/48 = 62.5% (95% CI: 47.4-76.0)
- Median duration of DC = 7.2 months (95% CI: 5.6–NE)



Tarlatamab + Durvalumab, n = 25

- DCR: 25/40 = 62.5% (95% CI: 45.8, 77.3)
- Median duration of DC = NE (95% CI: 3.9–NE)



- **TARLATAMAB WITH A PD-L1 INHIBITOR AS 1LM DEMONSTRATED SUSTAINED DISEASE CONTROL**
- **FOR TARLATAMAB + PD-L1 INHIBITOR, DCR WAS 62.5% (95% CI: 51.5–72.6) AND mDoDC WAS 9.3 MONTHS (95% CI: 5.6–NE)**

1L, first-line; **1LM**, first-line maintenance; **BOR**, best overall response; **chemo**, chemotherapy; **CI**, confidence interval; **CR**, complete response; **DC**, disease control; **DCR**, disease control rate; **IO**, immuno-oncology agent; **mDoDC**, median duration of disease control; **mDOR**, median duration of response; **NE**, not estimable; **ORR**, objective response rate; **PD**, progressive disease; **PD-L1**, programmed cell death ligand-1; **PR**, partial response; **SD**, stable disease.

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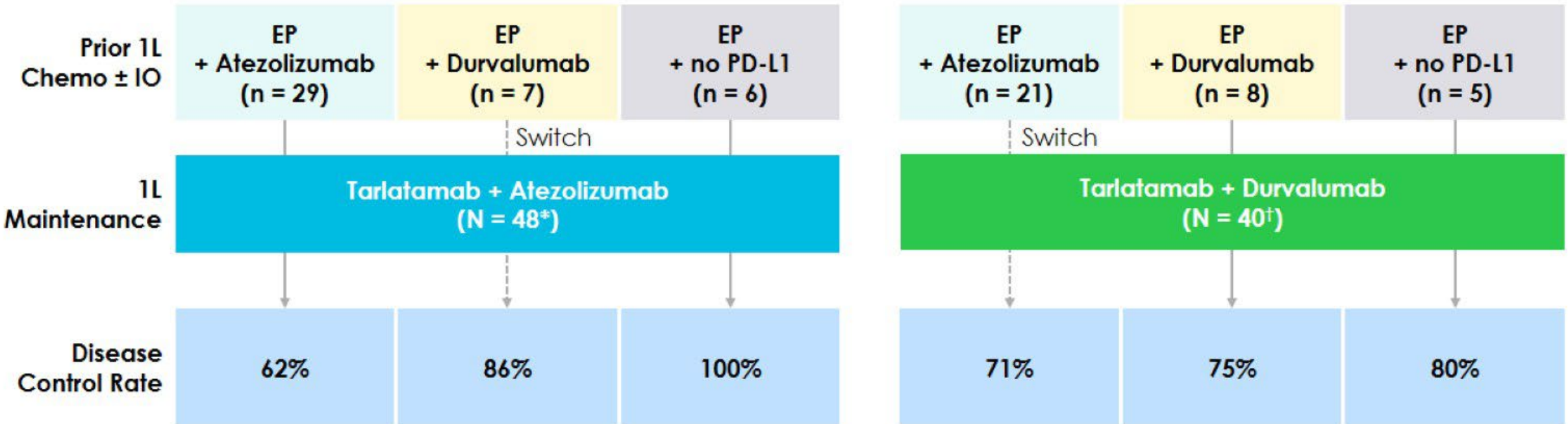
Impact of PD-L1 inhibitor switch on disease control rate



THERE WAS NO CLEAR ASSOCIATION BETWEEN PD-L1 INHIBITOR SWITCH AND DISEASE CONTROL RATE.

The interim efficacy analysis set includes patients who have had the opportunity to be followed for at least 9 weeks after the first dose date of any treatment regimen. Patients who stopped disease assessments prior to 9 weeks are included in this analysis set if the data cutoff is at least 9 weeks after their first dose date of any treatment regimen. *Includes 2 –not evaluable and 4–no postbaseline scan. †Includes 4 –not evaluable and 2–no postbaseline scan. **1L**, first-line; **chemo**, chemotherapy; **EP**, platinum-etoposide; **IO**, immuno-oncology agent; **PD-L1**, programmed cell death-ligand-1.

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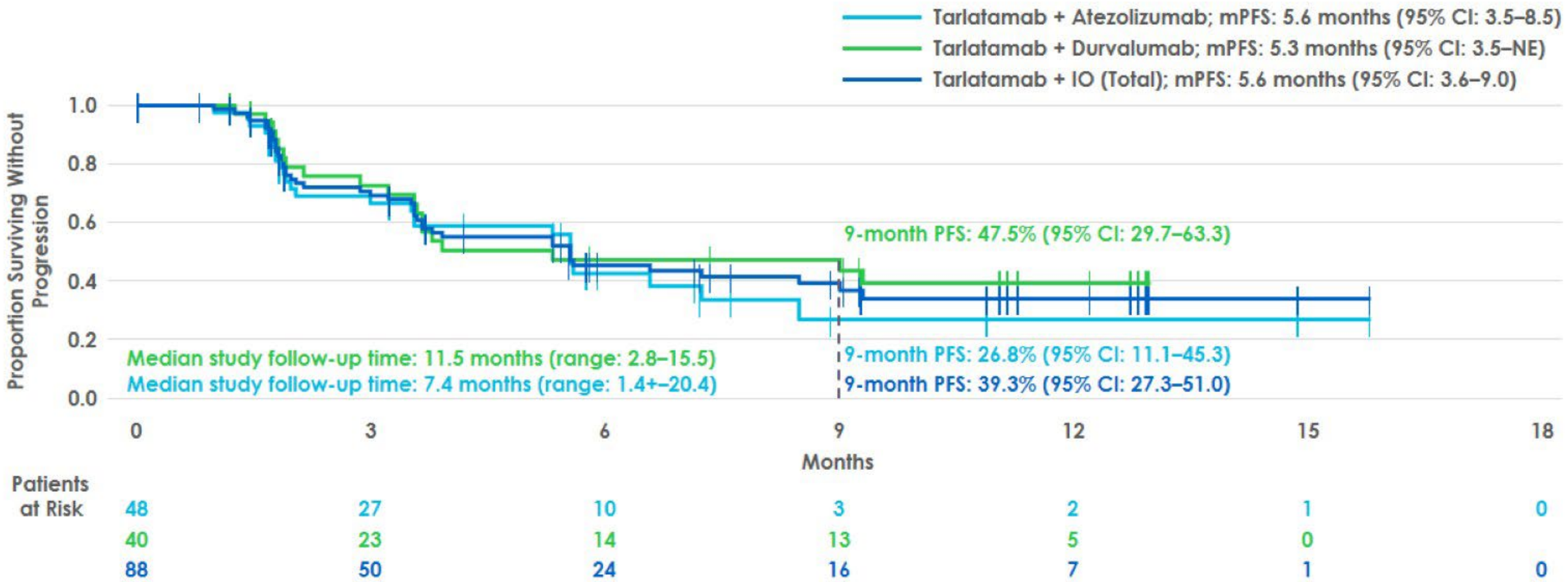
PFS, beginning from 1L maintenance



AFTER A MEDIAN TIME FROM 1L CHEMOIMMUNOTHERAPY TO 1LM OF 3.6 MONTHS, TARLATAMAB WITH A PD-L1 INHIBITOR AS 1LM SHOWED PROMISING PFS, WITH mPFS OF 5.6 MONTHS.

+, censored; **1L**, first-line; **1LM**, first-line maintenance; **CI**, confidence interval; **IO**, immuno-oncology agent; **mPFS**, median progression-free survival; **NE**, not estimable; **PD-L1**, programmed death-ligand; **PFS**, progression-free survival.

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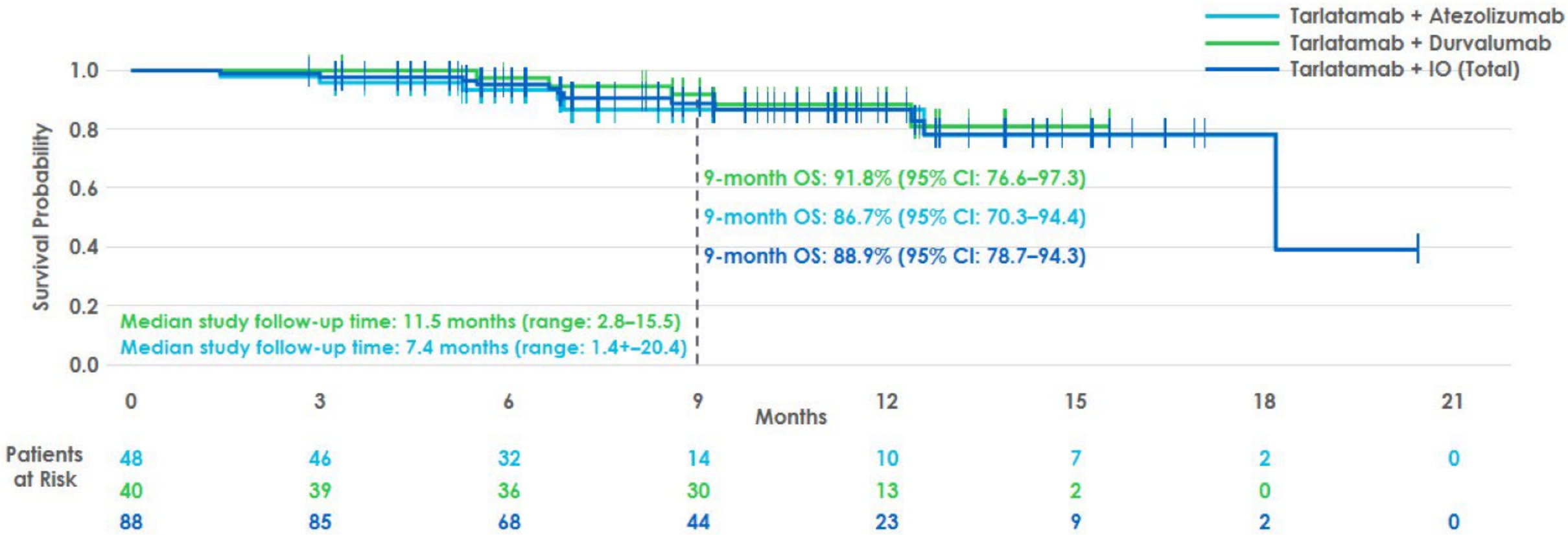
OS, beginning from 1L maintenance



AFTER A MEDIAN TIME FROM 1L CHEMOIMMUNOTHERAPY TO 1LM OF 3.6 MONTHS, TARLATAMAB WITH A PD-L1 INHIBITOR AS 1LM SHOWED A 9-MONTH OS OF 89%.

+, censored; **1L**, first-line; **1LM**, first-line maintenance; **CI**, confidence interval; **IO**, immuno-oncology agent; **OS**, overall survival; **PD-L1**, programmed death-ligand 1.

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Conclusions

Tarlatamab with a PD-L1 inhibitor as 1L maintenance in ES-SCLC demonstrated:

- **A manageable safety profile**
  - There were no DLTs, no fatal TRAEs, no new or unexpected toxicities; tarlatamab discontinuation due to TRAEs was low (6%)
  - The most common TRAE was CRS, which primarily occurred after the first or second dose of cycle 1, and was mostly grade 1 (fever)
  - CRS incidence, severity, and median time to onset from last prior tarlatamab dose were similar to that seen in previously treated patients[1]
- **Sustained disease control**
  - Median duration of DC was 9.3 months, with no discernable association between a PD-L1 inhibitor switch and DCR
- **Unprecedented survival outcomes**
  - Beginning from 1LM, the mPFS for tarlatamab + PD-L1 inhibitor was 5.6 months, promising relative to a PD-L1 inhibitor alone in 1LM (mPFS: 2.6 months for 1LM atezolizumab)[2]
  - Beginning from 1LM, the mOS for tarlatamab + PD-L1 inhibitor was not yet mature and 9-month OS was 89%, unparalleled relative to a PD-L1 inhibitor alone in 1LM (mOS, 12.5 months; 9-month OS: ~ 60% for 1LM atezolizumab)[2]

THESE RESULTS DEMONSTRATE A FAVORABLE BENEFIT-TO-RISK PROFILE AND SUPPORT A RANDOMIZED CONTROLLED STUDY OF TARLATAMAB WITH DURVALUMAB AS 1L MAINTENANCE, WHICH IS UNDERWAY (PHASE 3 DELLPHI-305; NCT06211036)

1L, first-line; **1LM**, first-line maintenance; **CRS**, cytokine release syndrome; **DC**, disease control; **DCR**, disease control rate ; **DLT**, dose-limiting toxicity; **ES**, extensive-stage; **mos.**, median overall survival; **miffs**, median progression-free survival; **OS**, overall survival; **PD-L1**, programmed cell death ligand-1; **SCLC**, small cell lung cancer; **TRAE**, treatment-related adverse event.

1. Ahn M-J, et al. *N Engl J Med.* 2023; 389:2063-2075. **2.** Reck M, et al. *J Thoric Oncol.* 2022; 17:1122-1129.

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DeLLphi-303 Principal Investigators

Australia: Michael Boyer

Belgium: Kristof Cuppens, Ingel Demedts, Paul Germonpre, Hans Prenen

Canada: Nicolas Marcoux, Adrian Sacher

France: Stéphane Champiat, Kassia Ouali, Elvire Pons-Tostivint, Aurelie Swalduz

Germany: Michael Pogorzelski, Cornelius Waller, Martin Wermke

Israel: Jair Bar, Talia Shentzer Kutiel, Hovav Nechushtan, Salomon Stemmer

Italy: Diego Cortinovis, Lorenza Landi, Pierfrancesco Tassone

Japan: Satoru Kitazono, Makoto Nishio, Tetsuya Sakai

Netherlands: Jeroen Hiltermann

South Korea: Myung-Ju Ahn, Tae Min Kim, Sang-We Kim

Spain: Enric Carcereny Costa, Pedro Filipe Simões Da Rocha, Luis Paz-Ares Rodriguez

Switzerland: Simon Häfliger, David Koenig

Taiwan: Chi-Lu Chiang, Chun-Hui Lee, Chih-Hsin Yang

United States: Mohammed Almubarak, Shirish Gadgeel, Missak Haigentz, Sally Lau, Jamal Misleh, Jorge Nieva, Shetal Patel, Kelly Paulson, Benjamin Solomon

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- **Authors:**
  - **Sally C.M. Lau:** Department of Medicine, Perlmutter Cancer Center; NYU Grossman School of Medicine; New York, NY, USA
  - **Myung-Ju Ahn:** Samsung Medical Center, Sungkyunkwan University School of Medicine; Seoul, South Korea
  - **Mor Moskovitz:** Davidoff Cancer Center, Rabin MC Haifa, Haifa District, Israel
  - **Michael Pogorzelski:** West German Cancer Center, Universitätsmedizin Essen – Ruhrlandklinik; Essen, Germany
  - **Simon Häfliger:** Inselspital, University Hospital Bern, University Clinic for Medical Oncology, Bern, Switzerland
  - **Kelly G. Paulson:** Swedish Cancer Institute, Medical Oncology; Edmonds, WA, USA
  - **Amanda Parkes, Yuyang Zhang, Ali Hamidi:** Amgen Inc., Thousand Oaks, CA, USA
  - **Martin Wermke:** University Hospital Dresden; Dresden, Germany
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