DAREON®-9: A Phase Ib Open-Label Dose Escalation/Confirmation Study of Obrixtamig (BI 764532) Plus Topotecan in Patients with Extensive-Stage Small Cell Lung Cancer (ES-SCLC) – Topotecan Use Analysis

#3827P

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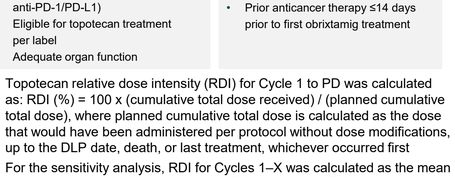
Introduction

- SCLC is a type of NEC with poor survival outcomes[1]
- DLL3 is an inhibitory Notch ligand that is expressed on ~94% of SCLC tumor cells[2]

Obrixtamig is a novel DLL3/CD3 IgG-like T-cell engager[3–5]



- DAREON®-9 (NCT05990738) is an ongoing Phase I dose-escalation/confirmation trial assessing the combination of obrixtamig + topotecan in patients with advanced relapsed/refractory ES-SCLC
- Data from the dose-escalation phase demonstrated encouraging efficacy and an acceptable safety profile in patients with previously treated ES-SCLC[6]
- This analysis assessed whether topotecan treatment patterns affect the safety or efficacy of the combination

Methods

Part A: dose escalation (BLRM with overdose control; N=44)

Obrixtamig with 3 target dose levels (10, 30, 60 mg) + topotecan†

RP2D

Part B: dose confirmation (N=16)

Obrixtamig 60 mg + topotecan†‡

Obrixtamig was given as step-up dosing followed by target dose (3 dose levels; IV Q1W for three weeks, then Q3W); topotecan was given per label (QD on Days 1–5 of each cycle, 2.3 mg/m² orally or 1.5 mg/m² IV). G-CSF use was permitted from the start of topotecan treatment, per label and local clinical practice

Patients were treated until disease progression, undue toxicity, consent withdrawn, or any other reasons requiring discontinuation. Patients could continue obrixtamig ± topotecan† beyond disease progression (according to RECIST v1.1) if, in the opinion of the investigator, they were deriving clinical benefit

Key inclusion criteria

- Histologically/cytologically confirmed SCLC
- ES-SCLC that progressed/recurred following ≥1 line of platinum-based treatment as per SoC (including anti-PD-1/PD-L1)
- Eligible for topotecan treatment per label
- Adequate organ function

Key exclusion criteria

- Previous treatment with T-cell engagers or DLL3-targeting therapies
- Untreated/symptomatic brain metastases
- Prior anticancer therapy ≤14 days prior to first obrixtamig treatment

- Topotecan relative dose intensity (RDI) for Cycle 1 to PD was calculated as: RDI (%) = 100 x (cumulative total dose received) / (planned cumulative total dose), where planned cumulative total dose is calculated as the dose that would have been administered per protocol without dose modifications, up to the DLP date, death, or last treatment, whichever occurred first
- For the sensitivity analysis, RDI for Cycles 1–X was calculated as the mean of per-cycle RDIs through the cycle of PD; cycles after PD were excluded

†Topotecan was planned at the full label dose in Cycle 1; dose reductions were permitted from Cycle 2 per label. Receipt of <80% of the planned dose during Cycles 1–2 excluded patients from MTD determination unless due to a drug-related AE, in which case it was considered a DLT; ‡after completion of topotecan, the investigator could choose to only administer obrixtamig

Patients

- As of November 11, 2025, 60 patients had been enrolled and received ≥1 dose of obrixtamig

	Total (N=60)
Median age, years (range)	64.5 (33–81)
Male, n (%)	37 (62)
Prior lines of treatment 1/2/≥3, n (%)	31 (52) / 18 (30) / 11 (18)
Prior use of PD-1/PD-L1 antibodies, n (%)	57 (95)
ECOG PS 0/1, n (%)	24 (40) / 36 (60)
Median number of cycles of obrixtamig / topotecan, n (range)	8 (1–28) / 8 (1–16)
Median treatment exposure of obrixtamig / topotecan, months (range)	5.4 (0.3–19.6) / 6.7 (0.2–10.8)

- 15 (25%) patients continued receiving topotecan beyond PD and 20 (33%) patients continued receiving obrixtamig beyond PD

Safety

Dose modifications due to AEs

	Due to topotecan-related AEs (N=60)	Due to obrixtamig-related AEs (N=60)
Dose modification of topotecan, n (%)		
Dose delay§	8 (13)	4 (7)
Dose reduction	20 (33)	2 (3)
Discontinuation	12 (20)	2 (3)
Dose modification of obrixtamig, n (%)		
Dose delay§	9 (15)	7 (12)
Discontinuation	0	1 (2)

- There were no dose reductions of obrixtamig

Dose modifications of both treatments due to AEs were primarily attributed to topotecan-related AEs

§During the MTD evaluation period, obrixtamig and topotecan dosing were protocol-mandated to be delayed together until continuation criteria were met for both drugs; thereafter, either treatment could be administered independently if clinically appropriate

Most common hematologic TRAEs (≥5% of patients)

	Total (N=60)	
	Any grade	Grade ≥3
Any TRAE, n (%)	60 (100)	51 (85)
Topotecan-related hematologic AEs		
Thrombocytopenia/decreased platelets	52 (87)	35 (58)
Anemia	47 (78)	19 (32)
Neutropenia/decreased neutrophils	37 (62)	27 (45)
Decreased lymphocytes	7 (12)	7 (12)
Febrile neutropenia	5 (8)	5 (8)
Leukopenia	3 (5)	2 (3)
Obrixtamig-related hematologic AEs		
Decreased lymphocytes	20 (33)	15 (25)
Anemia	5 (8)	0

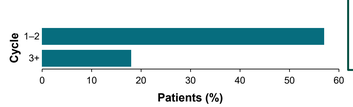
Most hematologic AEs observed in this study were attributed to topotecan

The most common obrixtamig-related hematologic AE was decreased lymphocytes, consistent with the expected effects of obrixtamig's mechanism of action

Safety (cont.)

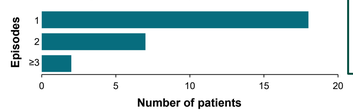
- Median duration of grade ≥3 neutropenia:¶ 8 days (range: 1–16)
- Median time to onset of grade ≥3 neutropenia: 8 days (range: 5–29)

Frequency of grade ≥3 neutropenia onset by cycle**



Grade ≥3 neutropenia mostly occurred in Cycles 1–2

Episodes of grade ≥3 neutropenia



Most patients with grade ≥3 neutropenia had 1–2 episodes

Infection events ≤14 days since neutropenia onset



Hospitalizations due to:

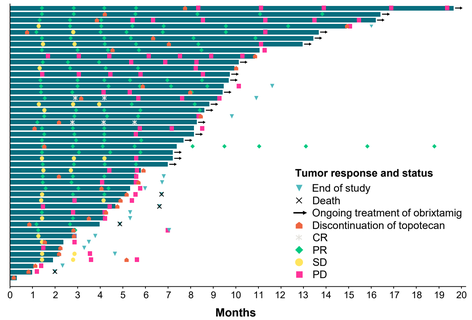
Neutropenia	2 (3%)
Febrile neutropenia	5 (8%)

- No grade 5 neutropenia or treatment-related infection occurred
- Of patients with grade ≥3 treatment-emergent thrombocytopenia and anemia, 33% and 85% received platelet and RBC transfusions, respectively
- G-CSF was commonly used (primary/secondary prophylaxis: 93%/18%)
- Obrixtamig-related CRS: grade 1: 45%; grade 2: 12%; grade 3: 3%
- Median time to CRS onset: 2 days (range: 1–29)
- Obrixtamig-related ICANS/ICANS-like neurotoxicity: n=3 (all grade 1)
- DLTs during MTD evaluation period: n=3 (grade 3 tumor pain; grade 2 increased blood creatinine; grade 3 fatigue)

¶Neutropenia and decreased neutrophils; **patients treated with ≥3 cycles of topotecan, n=44

Efficacy

- Efficacy was evaluable in 46 patients (≥1 assessment performed)

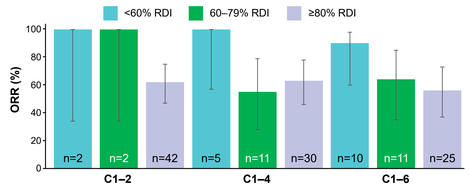


Efficacy (cont.)

Efficacy by topotecan RDI

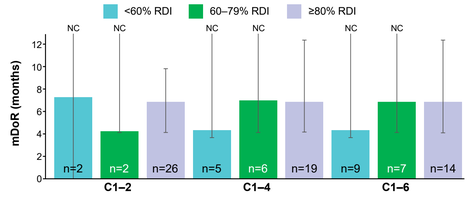
- Overall, confirmed ORR was 65%: 72% in patients with RDI <80% and 61% in patients with RDI ≥80%

Confirmed ORR by topotecan RDI, sensitivity analysis (n=46)



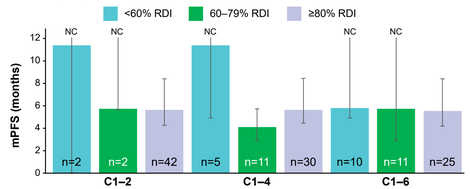
- Overall, confirmed mDoR was 6.9 months: 5.6 months in patients with RDI <80% and 7.3 months in patients with RDI ≥80%

Confirmed mDoR by topotecan RDI, sensitivity analysis (n=30)



- Overall, confirmed mPFS was 5.6 months and was identical in patients with RDI <80% and ≥80% (5.6 months in each group)

mPFS by topotecan RDI, sensitivity analysis (n=46)



- Overall, 33 patients (55%) discontinued topotecan before obrixtamig
- Of these patients, median time from topotecan discontinuation to PD was 2.6 months (95% CI: 1.4–4.3)

Topotecan RDI did not impact ORR or , although mDoR tended to be longer with full-dose topotecan

A sensitivity analysis†† showed no evidence of poorer outcomes with lower topotecan exposure during early cycles

These findings are limited by the small patient numbers

††The sensitivity analysis used an alternative RDI definition, reflecting the proportion of the potential full topotecan dose received during Cycles 1–6

Key Findings and Conclusions

- Obrixtamig + topotecan showed a manageable safety profile in relapsed/refractory ES-SCLC
- Neutropenia occurred early, was manageable, and was consistent with the known topotecan safety profile
- Many patients continued obrixtamig after discontinuing topotecan, including beyond PD, suggesting ongoing clinical benefit
- Minor differences between topotecan RDIs indicate topotecan dose modifications did not have a significant negative impact on overall promising efficacy

Plain Language Summary

ES-SCLC is an aggressive form of cancer with poor survival outcomes

Treatment options for ES-SCLC are limited, and new treatments that can be safely combined are needed

DAREON®-9 is an early-phase trial testing the combination of obrixtamig, a type of immunotherapy, with topotecan, a chemotherapy drug, in people with ES-SCLC

Obrixtamig + topotecan had manageable side effects. Many patients continued obrixtamig after stopping topotecan, and reducing topotecan did not appear to reduce how well treatment worked

References

1. Owen D, et al. J Hematol Oncol 2019;12:61; **2.** Wermke M, et al. J Clin Oncol 2025;43:3021–31; **3.** Hipp S, et al. Clin Cancer Res 2020;26:5258–68; **4.** Wermke M, et al. Future Oncol 2022;18:2639–49; **5.** Albayrak G, et al. Br J Cancer 2025;133:1241–9; **6.** Wermke M, et al. Ann Oncol 2025;36:S1376–7

Abbreviations: AE, adverse event; BLRM, Bayesian Logistic Regression Model; C, cycle; CD3, cluster of differentiation; CI, confidence interval; CR, complete response; CRS, cytokine release syndrome; DLL3, delta-like ligand 3; DLP, data lock point; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; ES-SCLC, extensive-stage small cell lung cancer; Fc, fragment crystallizable; G-CSF, granulocyte colony-stimulating factor; Gr, grade; ICANS, immune effector cell-associated neurotoxicity syndrome; IgG, immunoglobulin G; IV, intravenous; mDoR, median duration of response; (m)PFS, (median) progression-free survival; MTD, maximum tolerated dose; NC, not calculated; NEC, neuroendocrine carcinoma; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PR, partial response; Q1W, once weekly; Q3W, once every three weeks; QD, once daily; RP2D, recommended Phase II dose; RBC, red blood cell; RDI, relative dose intensity; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SCLC, small cell lung cancer; SD, stable disease; SoC, standard of care; TRAE, treatment-related AE

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