DAREON®-NEC-1: Phase III Trial of First-Line (1L) Obrixtamig Plus Carboplatin and Etoposide (SoC) vs SoC in Patients with Delta-Like Ligand 3 (DLL3)-Positive Extrapulmonary Neuroendocrine Carcinoma (epNEC)

#T-6

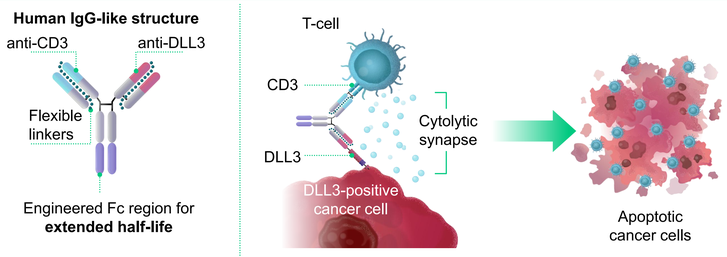
Thorvardur R. Halfdanarson[1]*, Timon Vandamme[2], Marianne E. Pavel[3], Masafumi Ikeda[4], Simron Singh[5], Lin Shen[6], Thomas Boerner[7], Zohreh Schmitz[8], Zilu Liu[9], Valeria Lifke[10], Jaume Capdevila[11]

[1]Department of Oncology, Mayo Clinic Cancer Center, Rochester, Minnesota, USA; [2]Center for Oncological Research (CORE), University of Antwerp; NETwerk & Department of Oncology, Antwerp University Hospital, Antwerp, Belgium; [3]Department of Medicine 1, Uniklinikum Erlangen and Comprehensive Cancer Center CCC-EMN, Friedrich Alexander University Erlangen-Nürnberg, Erlangen, Germany; [4]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [5]Sunnybrook Health Sciences Centre, Odette Cancer Centre; Department of Medicine, University of Toronto, Ontario, Canada; [6]Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing, China; [7]Global Clinical Development, Boehringer Ingelheim International GmbH, Biberach an der Riss, Germany; [8]Global Clinical Development Operations, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany; [9]Global Biostatistics & Data Sciences, Boehringer Ingelheim (China) Investment Co., Ltd., Shanghai, China; [10]Global Experimental Medicine Oncology, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany; [11]Department of Medical Oncology, Vall d'Hebron University Hospital & Vall d'Hebron Institute of Oncology, Barcelona, Spain

Introduction

- There is a high unmet need for effective 1L treatments for advanced epNEC. Patients typically present with aggressive disease and substantial symptom burden; current SoC (platinum + etoposide) provides only modest clinical benefit with typical median overall survival of ≤12 months[1–4]
- DLL3 is an inhibitory Notch ligand that is frequently expressed on the cell surface in epNEC (~83% of patients),[5] but with minimal expression in healthy adult tissue, making it a rational therapeutic target in epNEC
- Obrixtamig is a novel IgG-like DLL3/CD3 T-cell engager designed to selectively target DLL3-positive tumor cells: simultaneous binding to DLL3 and CD3 redirects T cells to kill tumor cells[6–8]

Mechanism of action of obrixtamig[6–8]



- The Phase Ib DAREON®-7 trial assessed the combination of obrixtamig + SoC in patients with 1L epNEC. The combination showed manageable safety and encouraging preliminary efficacy in patients with DLL3-positive epNEC[9]

Key findings of DAREON®-7 Patients with DLL3-positive NEC (N=44; data cut-off: February 3, 2026)[9]

- **No additive or unexpected toxicities**
- **No grade ≥3 CRS**
- **Two cases of ICANS, both grade 1**

ORR	6-month DoR	6-month PFS
77%	68%	64%
95% CI: 63–87	95% CI: 49–87	95% CI: 48–80

The results of DAREON®-7 support further clinical development of obrixtamig plus SoC in patients with 1L DLL3-positive epNEC, an area of considerable unmet medical need

Plain Language Summary

Extrapulmonary neuroendocrine carcinoma (epNEC) is a rare and aggressive cancer. Current treatment options often have limited effectiveness, highlighting the need for new therapies

Obrixtamig is an investigational treatment. It has been designed to help the body's immune system recognize and attack cancer cells by targeting a protein called delta-like ligand 3 (DLL3), which is found on epNEC tumors in most patients

DAREON®-NEC-1 is the first global Phase III clinical trial that will compare obrixtamig plus standard chemotherapy versus standard chemotherapy alone to determine whether adding obrixtamig can help patients with DLL3-positive epNEC live longer

This study was funded by Boehringer Ingelheim. The authors were fully responsible for all content and editorial decisions, were involved at all stages of poster development and have approved the final version. The authors did not receive payment related to the development of the poster. Medical writing support for the development of this poster, under the direction of the authors, was provided by Tamara Bailey, PhD, of Ashfield MedComms, an Inizio company, and funded by Boehringer Ingelheim

Disclosures: TR. Halfdanarson reports advisory council or committee work for Camurus, Crinetics, Perspective Therapeutics, and ITM; personal advisory board work for Biomea Fusion, Boehringer Ingelheim, Curium, and Exelixis; institutional advisory board work for Ipsen, ITM, Novartis, Perspective Therapeutics, and RayzeBio; institutional local PI work for Crinetics, Novartis, Perspective Therapeutics, RayzeBio, Rezolute, Thermo Fisher Scientific; advisory role for NCCN; and leadership role for NANETS

Reused with permission from the European Society for Medical Oncology (ESMO). This abstract was accepted and previously presented by Timon Vandamme et al. at ESMO, FPN: #2432TiP, *Annals of Oncology*, Volume 37, 2026 Supplement 2. All rights reserved

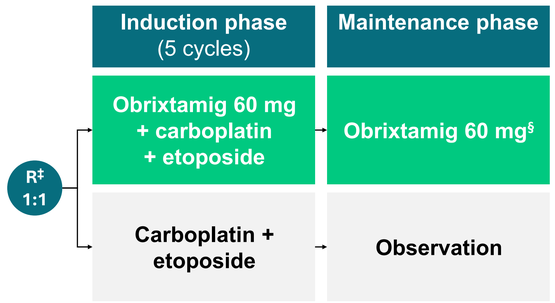
DAREON®-NEC-1 (NCT07544654) is the first global Phase III randomized, open-label trial evaluating obrixtamig plus SoC (carboplatin + etoposide) versus SoC alone as 1L treatment of patients with unresectable, locally advanced or metastatic DLL3-positive epNEC

Trial Design

Trial population:

- Adult patients with DLL3-positive epNEC, including NEC of unknown origin
- Unresectable, locally advanced or metastatic disease
- No prior anticancer therapy, except for one cycle of platinum† + etoposide (Cycle 0) before randomization
- ECOG PS 0 or 1

N≈390



Key stratification factor: DLL3 expression status (high/low)

Endpoints:

- **Primary:** Overall survival
- **Secondary:** PFS (RECIST v1.1; investigator assessed), PROs (EORTC QLQ-C30), ORR, DoR, disease control, safety
- **Other:** PK, biomarkers

- Obrixtamig is administered intravenously using a step-up dosing regimen QW for the first two cycles, followed by target dose Q3W thereafter
- Carboplatin + etoposide SoC is given Q3W per label

†Patients who receive cisplatin in Cycle 0 and switch to carboplatin for Cycle 1 are eligible to participate
‡Crossover to investigational arm not permitted
§Until disease progression, unacceptable toxicity, or other protocol-defined discontinuation criteria, for a maximum of 36 months. A patient with disease progression may continue to receive obrixtamig if they are deriving clinical benefit based on the investigators' medical judgment

DLL3 Testing

DAREON®-NEC-1 requires prospective central testing of DLL3 expression status before randomization; patients must have DLL3-positive tumors

- DLL3 expression status is determined using an investigational antibody for DLL3 (SP347; Roche Diagnostics) performed at central laboratories
- DLL3 expression status will be categorized by the proportion of tumor cells exhibiting moderate-to-strong (2+/3+) membranous and/or cytoplasmic staining intensity
  - DLL3-positive: >0% tumor cells exhibiting moderate-to-strong (2+/3+) membranous and/or cytoplasmic staining intensity

Abbreviations: 1L, first-line; CD3, cluster of differentiation 3; CI, confidence interval; CRS, cytokine release syndrome; DLL3, delta-like ligand 3; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; epNEC, extrapulmonary neuroendocrine carcinoma; Fc, fragment crystallizable; FFPE, formalin-fixed, paraffin-embedded; ICANS, immune effector cell-associated neurotoxicity syndrome; IgG, immunoglobulin G; NEC, neuroendocrine carcinoma; ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetic; PROs, patient-reported outcomes; Q3W, once every 3 weeks; QW, once a week; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SoC, standard of care

Presented at the North American Neuroendocrine Tumor Society (NANETS) Symposium, Las Vegas, NV, USA, November 5–7, 2026

*Corresponding author email address: halfdanarson.thor@mayo.edu

Key Points

- The substantial symptom burden and poor outcomes associated with current SoC (platinum + etoposide) highlight the urgent need for more effective 1L treatments for patients with epNEC
- DLL3 is expressed in ~83% of patients with epNEC, making it a therapeutic target in epNEC
- Obrixtamig is a novel IgG-like DLL3/CD3 T-cell engager that has demonstrated manageable safety and encouraging preliminary efficacy in combination with 1L SoC in a Phase Ib trial
- DAREON®-NEC-1 is the first global Phase III multicenter, open-label, randomized trial evaluating obrixtamig in combination with SoC (carboplatin plus etoposide) versus SoC alone in patients with previously untreated, DLL3-positive, unresectable, locally advanced or metastatic epNEC
- The primary endpoint of the trial is overall survival

Key Eligibility Criteria

Inclusion criteria

- Poorly differentiated, unresectable, locally advanced or metastatic epNEC, including NEC of unknown primary site
- Adequate archival FFPE tumor tissue with confirmed DLL3-positive expression status before randomization
- Treatment-naïve, except for the completion of one cycle of mandatory platinum + etoposide before randomization (Cycle 0)
- ECOG PS 0 or 1

Exclusion criteria

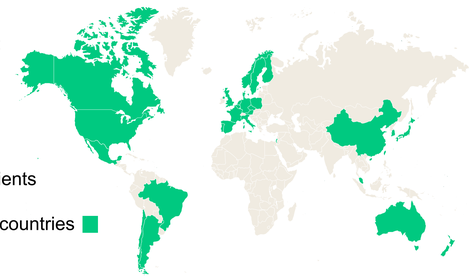
- Merkel cell carcinoma
- Medullary thyroid carcinoma
- Neuroendocrine prostate cancer
- Well-differentiated neuroendocrine tumors of any grade
- Symptomatic central nervous system metastases

Not all criteria are listed. Further details available at: https://clinicaltrials.gov/study/NCT07544654; https://pro.boehringer-ingelheim.com/therapeutic-areas/oncology/dareon-nec-1/

Recruitment

DAREON®-NEC-1 is the first global Phase III trial in patients with 1L DLL3-positive epNEC; patient recruitment is ongoing

- The trial will enroll patients at 167 sites across 29 countries in:
  - Europe
  - North and South America
  - Asia
  - Oceania
- The target enrollment is 390 patients



References

1. Stumpo S, et al. J Clin Med 2023;12:7715; **2.** Sorbye H, et al. Br J Cancer 2025;133:316–24; **3.** Eads J, et al. Endocr Relat Cancer 2023;30:e220206; **4.** Sorbye H, et al. Ann Oncol 2013;24:152–60; **5.** Gambardella V, et al. J Clin Oncol 2026;44(suppl 16):abstr2642; **6.** Hipp S, et al. Clin Cancer Res 2020;26:5258–68; **7.** Wermke M, et al. Future Oncol 2022;18:2639–49; **8.** Albayrak G, et al. Br J Cancer 2025;133:1241–9; **9.** Capdevila J, et al. ESMO 2026:abstr3648

Scan this QR code or visit the URL to access the poster presentation
https://go.Boehringer.com/SAv_

Scan this QR code or visit the URL to access the infographic summary
https://go.Boehringer.com/eMjnR

Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from NANETS or the authors of this presentation