ENETS – NANETS Webinar

PART 3:
New insights, directions & signals

Wednesday, 10 July 2024, 18:00 – 18:45 CEST

Live poll question:
Getting to know the audience

In which medical discipline are you trained and/or work in?

Please click on this button above the video: Select the medical discipline you are trained and/or work in (before webinar)

1. Oncology
2. Gastroenterology
3. Endocrinology
4. Pathology
5. Radiology
6. Nuclear medicine
7. Surgery
8. Tumor & cell biology
9. Other

Tonight's faculty

Moderator & Panel:

Chandrikha CHANDRASEKHARAN

University of Iowa
Iowa City, Iowa, USA
Medical Oncology

Speakers & Panel:

Jaume CAPDEVILA

Vall d'Hebron University Hospital
Barcelona, Spain
Oncology

Daniel HALPERIN

The Univ. of Texas MD Anderson Cancer Center
Houston, Texas, USA
Oncology

Tonight's faculty

Panel:

Tom HOPE

University of California San Francisco
San Francisco, California, USA
Radiology

Luka Ležaič

Principle Investigator TECANT ERA Trials
University Medical Centre Ljubljana
Slowenia
Nuclear Medicine

Amr MOHAMED

UH Seidman Cancer Center,
Case Western Reserve University
Cleveland, Ohio, USA
Medical Oncology

Tonight's agenda

Moderator: Chandrikha CHANDRASEKHARAN

18:00 - 18:05 CEST: Opening – **Chandrikha CHANDRASEKHARAN**

18:05 - 18:25 CEST: Current trials

- 18:05 - 18:15 CEST: Paltusotine, 2 DLL3 trials and anti CD2000R1 – **Jaume CAPDEVILA**
- 18:15 - 18:25 CEST: Alphamedix, ACTION-1 and TECANT ERA – **Daniel HALPERIN**

18:25 - 18:40 CEST: Discussion –
Panel speakers: **Chandrikha CHANDRASEKHARAN, Tom HOPE, Luka LEŽAIČ, Amr MOHAMED** + presenters

18:40 - 18:45 CEST: Closing – **Chandrikha CHANDRASEKHARAN**

- **This webinar is intended for HCPs qualified by law to prescribe medicine.**
- UEMS accreditation: the webinar is accredited **with 0.5 CME points**.
  - *Participants must attend the **whole live webinar** and complete a feedback form*

Trials ongoing:

- **Paltusotine**
- **Anti CD200R1**
- **DLL3 bi & trispecific mAbs**

Jaume Capdevila

Vall Hebron University Hospital
Barcelona

DISCLOSURE INFORMATION

- Personal conflicts of interest: Scientific consultancy role (speaker and advisory roles) from Novartis, Pfizer, Ipsen, Exelixis, Bayer, Eisai, Advanced Accelerator Applications, Amgen, Sanofi, Roche, Lilly, HUTCHMED, ITM, Merck Serono, Advanz, Esteve.

- Research support : Research grants from Novartis, Pfizer, Astrazeneca, Advanced Accelerator Applications, Eisai, Amgen, Bayer, Gilead, Roche, Ipsen, ITM

- Leadership roles: Chair of the Spanish Task Force for Neuroendocrine and Endocrine Tumors Group (GETNE)

Interim Safety and Exploratory Efficacy Results of a Phase 2, Randomized, Parallel-Group Study of Oral Paltusotine Treatment in Patients With Carcinoid Syndrome

Presenter: Simron Singh, MD, MPH, FRCPC, on Behalf of Study Author Group

Associate Professor, University of Toronto
Sunnybrook Health Sciences Center, Toronto, Canada

ENETS EUROPEAN NEUROENDOCRINE TUMOR SOCIETY

21st Annual ENETS Conference | 13 – 15 March 2024

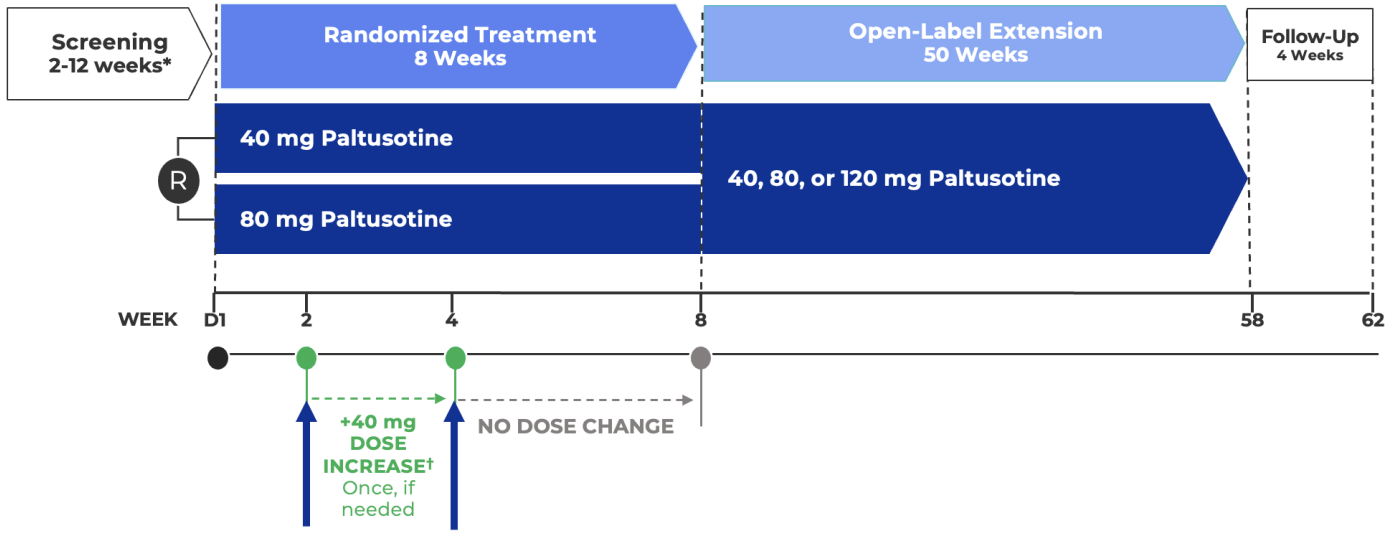
Paltusotine: Oral SST2 agonist

In development for acromegaly and NETs

Entry criteria: patients with locally advanced or metastatic, well-differentiated, grade I or II NETs with carcinoid syndrome *either*

- Naïve to somatostatin receptor ligands (SRLs) and actively symptomatic (average of ≥4 BMs per day or >2 flushing episodes per day in ≥2 days over a 2-week period) *or*
- On SRL with demonstrated symptom worsening after SRL washout

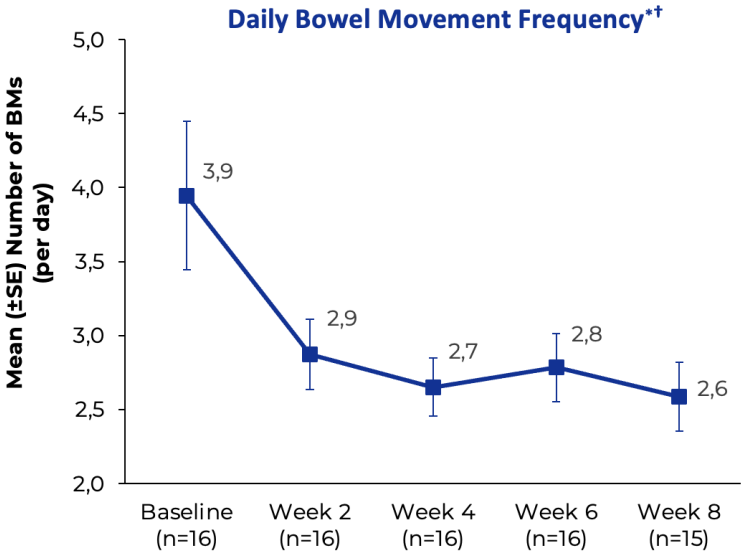
Study Design

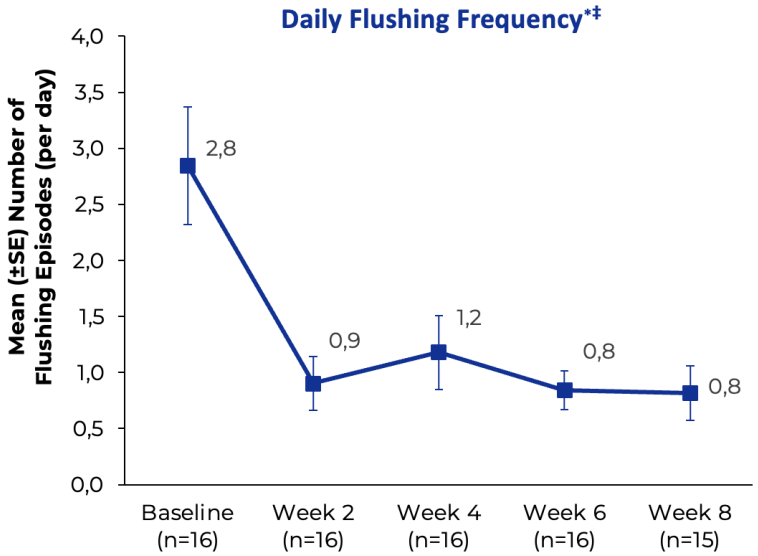


*Depending on rapidity of symptom worsening in washout patients.
†During the first 4 weeks, dose uptitration by 40 mg/d is an option, based on symptomatology.

Singh S, et al. ENETS 2024

Key Carcinoid Syndrome Symptoms





16 pts (6 naïve)

*Findings were similar in SRL-naïve and SRL-washout patients.
†Mean change from baseline in daily BM frequency was -1.3 at Week 8.
‡Mean change from baseline in daily flushing frequency was -2.2 at Week 8.

Paltusotine showed preliminary activity in carcinoid syndrome

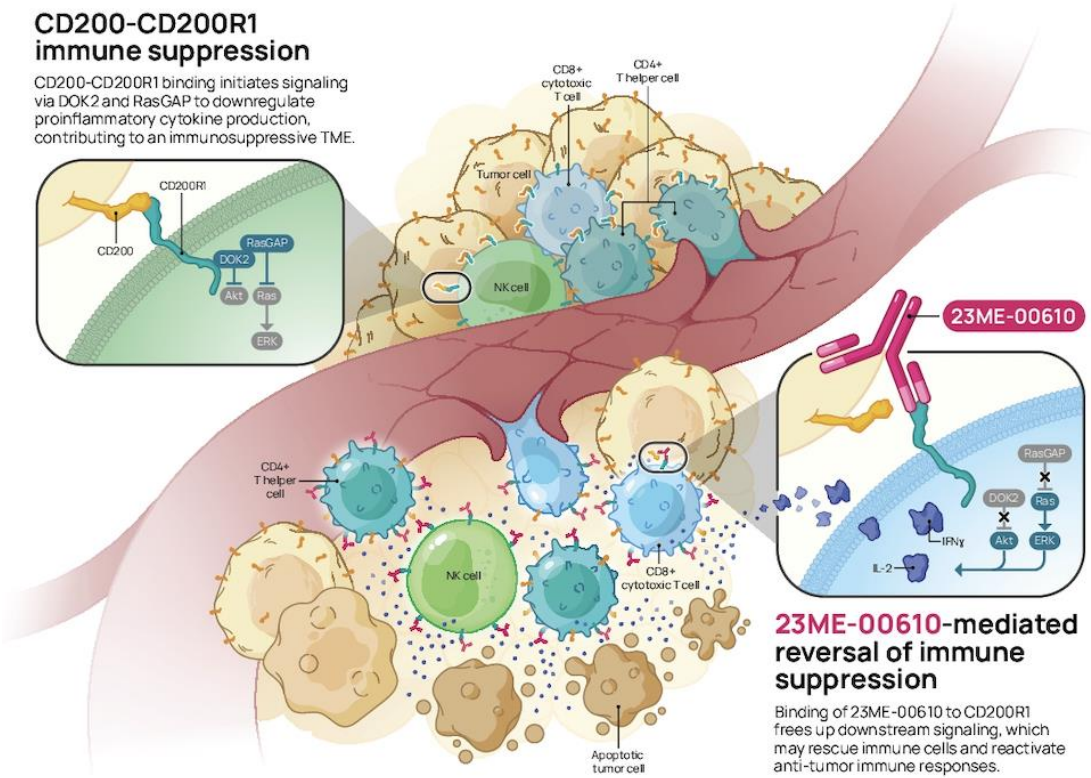
Outcome by Symptom Frequency Subgroup at Baseline

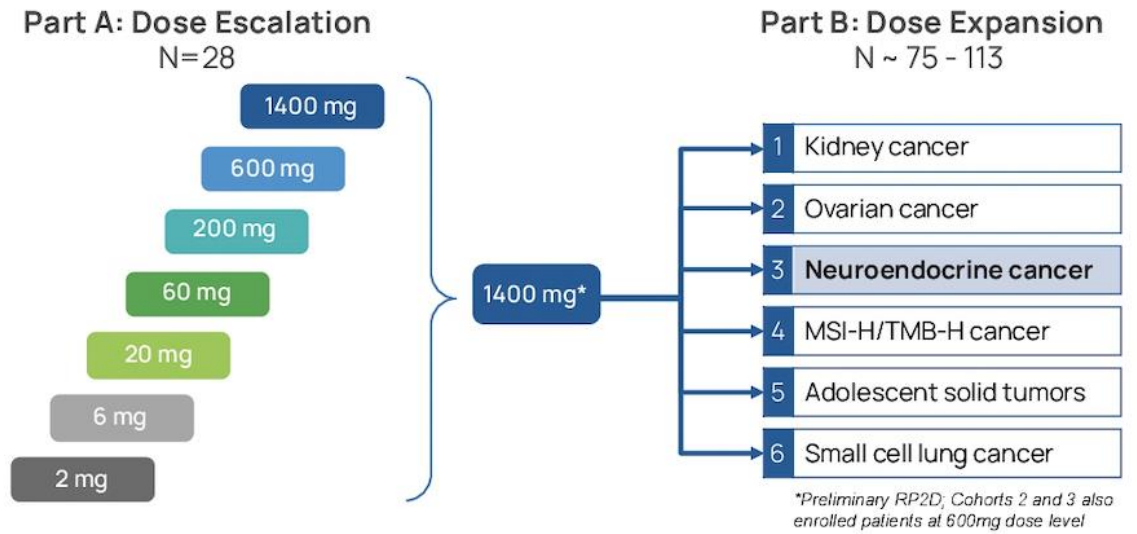
	Excess* Daily BM Frequency in Patients With >3/day at Baseline (n=8)	Daily Flushing Frequency in Patients With ≥1/day at Baseline (n=13)
Baseline, mean	2.53	3.40
Week 8, mean	0.65	0.93
Percent change in mean value	-74.3%	-72.6%

*Defined as daily BMs above the upper limit of normal (3 per day).

Singh S, et al. ENETS 2024

23ME-00610: First-in-class mAb against CD200 receptor 1





- 23ME-00610 administered IV every 21 days (Q3W)
- Expansions had target enrollment of 15 patients per cohort
- Neuroendocrine cohort eligibility included well-differentiated Grade 3 neuroendocrine tumors, poorly differentiated neuroendocrine carcinomas, and tumors with neuroendocrine features with Sponsor approval

CD200R1 expression described in GI & GU tracts, neural system, lung and neuroendocrine tissues

Rasco RW, et al. ASCO 2024

23ME-00610: First-in-class mAb against CD200 receptor 1

Figure 7. Tumor CD200 and CD200R1 Expression Shows ~50% Neuroendocrine Patients with Moderate or High Tumor CD200

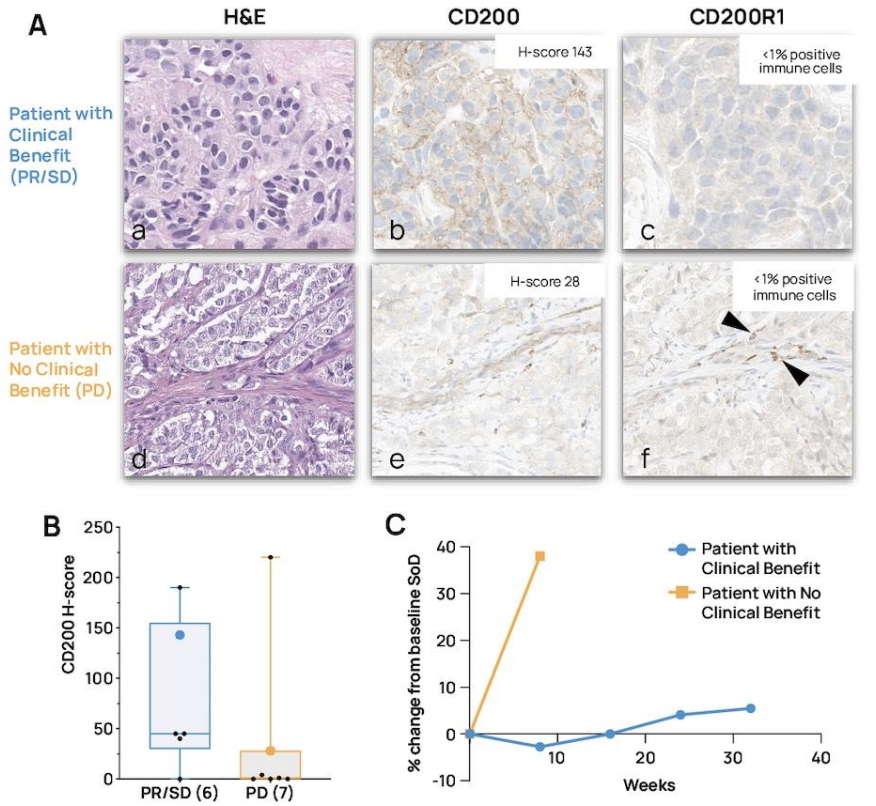
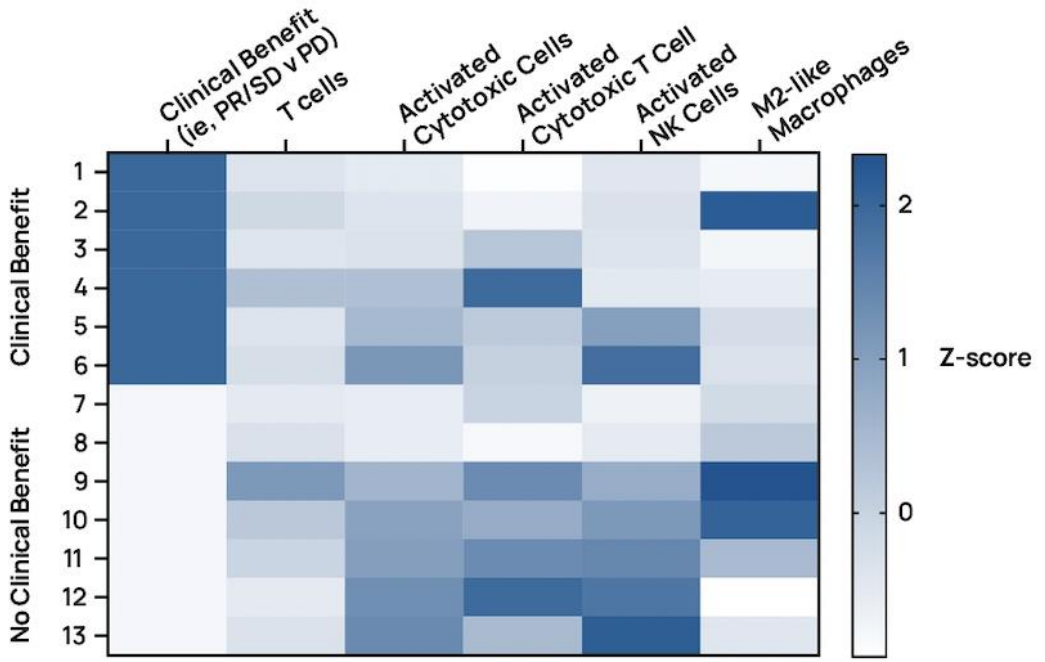


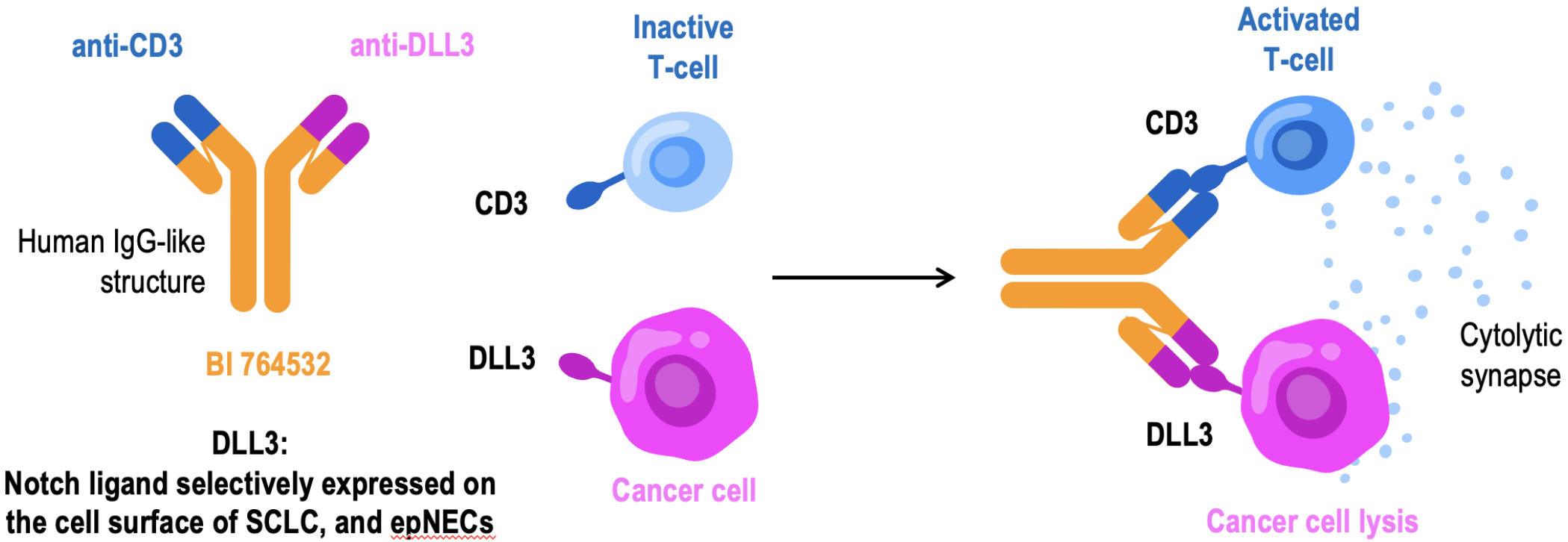
Figure 8. Tumors of patients deriving benefit may have a more immune suppressed phenotype at baseline



Tumors that responded to 23ME-00610 tended to have been less inflamed at baseline than tumors that progressed. Specifically, tumors that progressed on treatment tended to have more immunosuppressive M2-like macrophages at baseline. Multiplex IHC was performed on tumors collected at screening (n = 13 evaluable tumors). CD3, CD8, granzyme B, CD163 and CD68 positive cells were quantified as positive cell numbers / tumor area using image analysis and immune cell densities were standardized as a z-score for the heatmap. CD3+ = T cells, GRZB+ = all cytotoxic cells, GRZB+CD3+CD8+ = activated cytotoxic T cells, GRZB+CD3-CD8- = activated NK cells, CD163+CD68+ = M2-like macrophages.

Rasco RW, et al. ASCO 2024

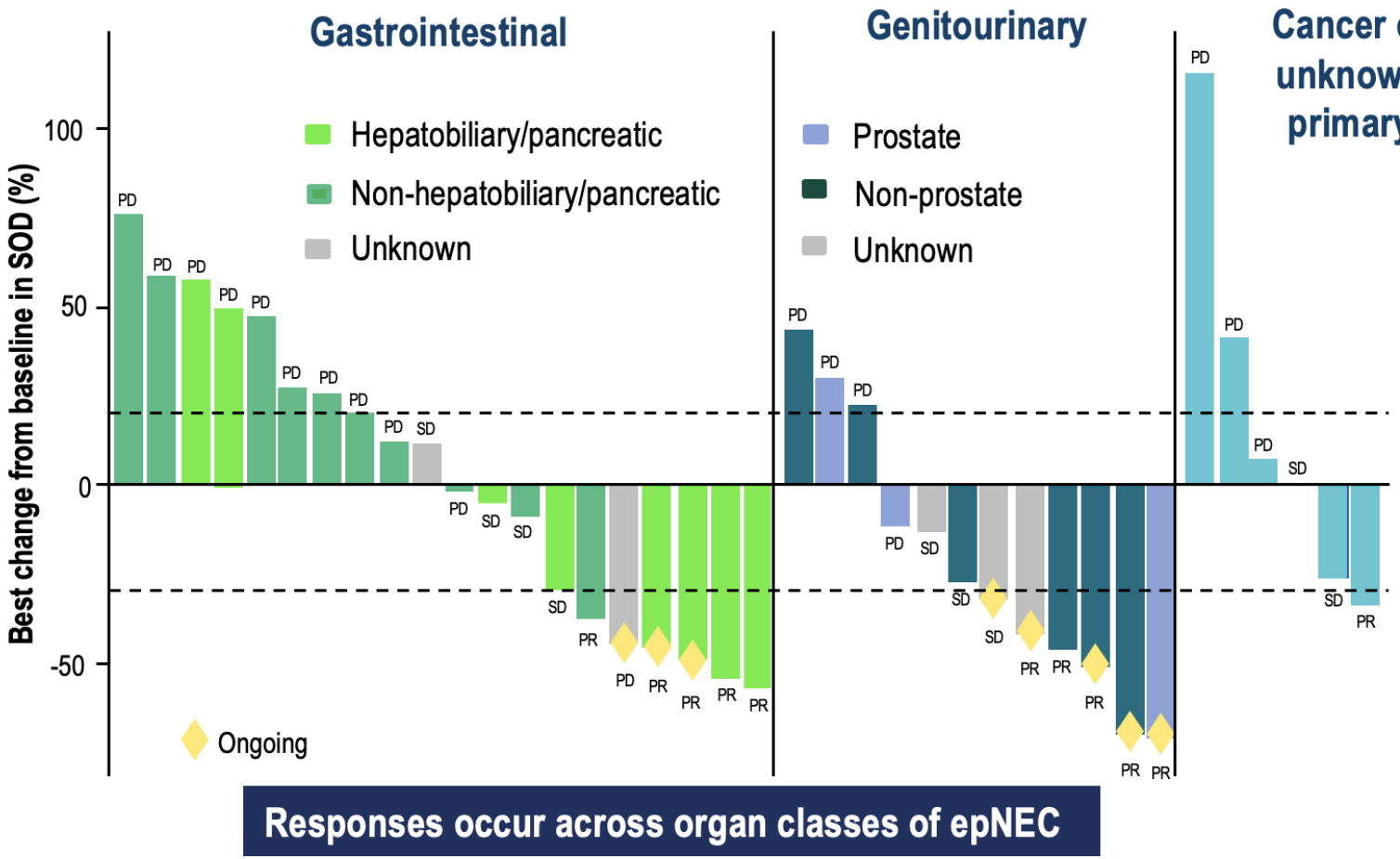
BI 764532: a novel DLL3-targeting T-cell engager



- BI 764532 redirects the patient's own T-cells to lyse DLL3-expressing cancer cells
- Potent preclinical activity against DLL3-positive cells and xenograft models[1]

Capdevila J, et al. ENETS 2024

Efficacy in patients with epNEC by organ system (≥90 µg/kg)



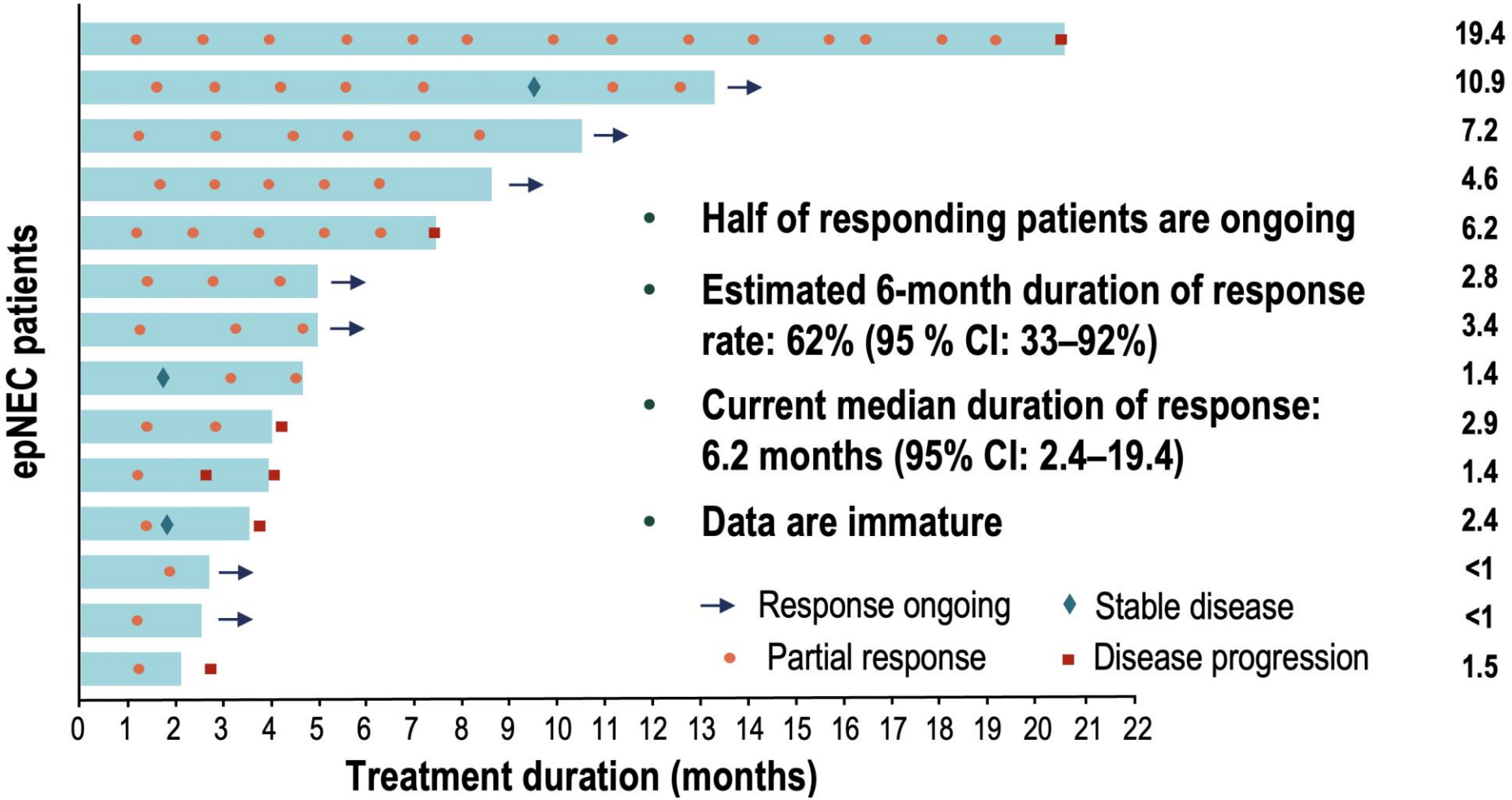
N (%)	epNEC (n=53)	GI (n=23)	GU (n=15)	CUP (n=6)
PR	14 (26)	5 (22)	6 (40)	1 (17)
SD	10 (19)	4 (17)	2 (13)	2 (33)
PD	20 (38)	11 (48)	4 (27)	3 (50)
DCR	24 (45)	9 (39)	8 (53)	3 (50)
Missing*	9 (17)	3 (13)	3 (20)	0

*Assessable patients who did not have any tumour assessment due to early toxicity, start of subsequent anti−cancer therapy, death or any other reason

Responses occur across organ classes of epNEC

Capdevila J, et al. ENETS 2024

Responses to date appear durable



Capdevila J, et al. ENETS 2024

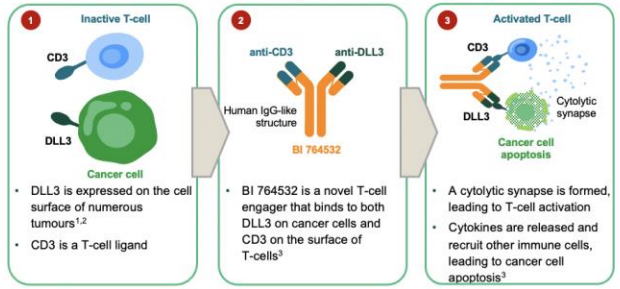
DAREON™-7: A Phase I, open-label, dose escalation and expansion cohort trial of the delta-like ligand (DLL3)-targeting T-cell engager BI 764532, plus first-line platinum-based chemotherapy in patients with DLL3-positive neuroendocrine carcinomas

Jaume Capdevila[1], Timon Vandamme[2], Patricia Niccoli[3], Saori Mishima[4], Ken Kato[5], Yiyuan Ma[6], Ping Sun[7], Lijiang Geng[8], Ulrich M. Lauer[9]

[1]Department of Medical Oncology, Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [2]Center for Oncological Research (CORE), Integrated Personalized and Precision Oncology Network (IPPON), University of Antwerp and Department of Oncology, Antwerp University Hospital, Antwerp, Belgium; [3]Institut Paoli-Calmettes, Department of Oncology, Marseille, France; [4]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [5]Department of Head and Neck, Esophageal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; [6]Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; [7]Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA; [8]Boehringer Ingelheim (China) Investment Co., Ltd., Shanghai, China; [9]Department of Medical Oncology & Pneumology, University Hospital Tübingen, Tübingen, Germany

Introduction

Mechanism of action of BI 764532, a novel DLL3-targeting T-cell engager



- DLL3 is expressed on the cell surface of numerous tumours[1,2]
- CD3 is a T-cell ligand
- BI 764532 is a novel T-cell engager that binds to both DLL3 on cancer cells and CD3 on the surface of T-cells[3]
- A cytolytic synapse is formed, leading to T-cell activation
- Cytokines are released and recruit other immune cells, leading to cancer cell apoptosis[3]

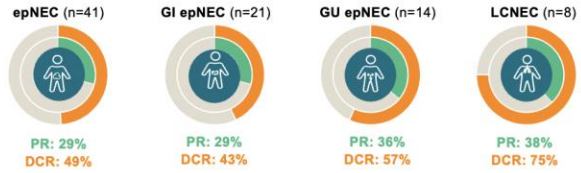
DLL3 is highly expressed in NECs

- A large proportion of LCNEC and epNEC tumours express DLL3

~75% of LCNEC[4] | **19–77%** of GI epNECs[5] | **68–81%** of GU epNECs[5]

A prior Phase I study indicates that BI 764532 is effective as monotherapy in patients with pretreated NEC (NCT04429087)

- A Phase I, dose escalation and expansion study with BI 764532 is ongoing in patients with SCLC, epNEC, or LCNEC (N=107)[6]
- Promising efficacy has been seen in patients with epNEC and LCNEC. Dose optimisation is ongoing[7,8]



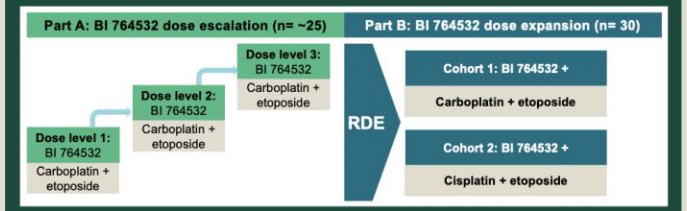
Rationale for DAREON™-7: to assess BI 764532 in a front-line setting combined with SoC chemotherapy

- Currently, there are limited treatment options for people with LCNEC or epNEC, and better first-line treatment options are an unmet need
- DLL3 an attractive target, particularly in light of the BI 764532 efficacy data in NECs reported to date

CD3, cluster of differentiation 3; DLL3, delta-like canonical Notch ligand-3; DCR, disease control rate; epNEC, extrapulmonary NEC; GI, gastrointestinal; GU, genitourinary; IgG, immunoglobulin G; LCNEC, large cell NEC; NEC, neuroendocrine carcinoma; PR, partial response; SCLC, small cell lung cancer; SoC, standard of care

Trial design

- DAREON™-7 is a Phase I, non-randomised, open-label, multicentre dose escalation (Part A) and expansion (Part B) trial of first-line BI 764532 + SoC chemotherapy (carboplatin or cisplatin + etoposide) in patients with DLL3-positive LCNEC of the lung, epNEC, or NEC with unknown primary site (**NCT06132113**)
- In Part A, successive cohorts of will receive increasing doses of BI 764532 + SoC chemotherapy until the MTD is reached, or upon decision of the Dose Escalation Committee. In Part B, two expansion cohorts will receive BI 764532 at the RDE/RP2D + SoC chemotherapy



MTD, maximum tolerated dose; RDE, recommended dose for expansion; RP2D, recommended Phase II dose

- BI 764532 will be administered IV with step-in doses followed by the target doses
- Dose escalations will be a maximum 200% increase from the previous dose level (in the absence of DLTs)
- In Part A, SoC chemotherapy will be carboplatin + etoposide administered as per label. In Part B, SoC chemotherapy will be carboplatin or cisplatin + etoposide
- Dose escalation for BI 764532 will be guided by a Bayesian Logistic Regression Model with overdose control
- The trial will be conducted in approximately 20 sites across multiple countries

DLTs, dose limiting toxicity; IV, intravenously

Objectives

Part A: Dose escalation	Part B: Dose expansion
• **Primary:** Determine the MTD and/or RDE/RP2D of BI 764532 • **Secondary:** Evaluate the BI 764532 dose-tolerability relationship	• **Primary:** Confirm safety and tolerability of BI 764532 at the RDE/RP2D + SoC chemotherapy regimens • **Secondary:** Assess the efficacy of BI 764532 + SoC chemotherapy regimens

Inclusion and exclusion criteria

Inclusion	Exclusion
Locally advanced or metastatic NEC of the following subtypes: • epNEC • LCNEC of the lung • NEC with unknown primary site	Previous treatment with T-cell engagers or cell therapies targeting DLL3
Patients who are eligible for platinum + etoposide as first-line SoC treatment	Diagnosis of Merkel cell carcinoma, medullary thyroid carcinoma or grade 3 neuroendocrine tumour, or presence of leptomeningeal carcinomatosis
At least one evaluable lesion as defined per RECIST 1.1	Diagnosis of immunodeficiency or systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of BI 764532
Tumour positive for DLL3 expression by IHC (central pathology review)	History of/active non-infectious pneumonitis or interstitial lung disease of any grade
Adequate liver, bone marrow and renal organ function	Significant cardiovascular or cerebrovascular diseases

IHC, immunohistochemistry; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1

Endpoints

Part A: Dose escalation	Part B: Dose expansion
• **Primary:** Occurrence of DLTs within the MTD evaluation period • **Secondary:** Occurrence of DLTs and AEs during the on-treatment period	• **Primary:** Occurrence of DLTs during the on-treatment period • **Secondary:** Objective response, defined as best overall response of CR or PR, according to RECIST v1.1; duration of response

AEs, adverse events; CR, complete response

References

1. Saunders LR, et al. Sci Transl Med 2015;7:302ra136; 2. Spino M, et al. Clin Cancer Res 2019;25:1261–71; 3. Wermke M, et al. Future Oncol 2022;18:2639–49; 4. Hermans BCM, et al. Lung Cancer 2019;138:102–8; 5. Yao J, et al. Oncologist 2022;27(11):940–51; 6. Wermke M, et al. J Clin Oncol 2023;41(suppl 16):abstr 8502; 7. Gambardella V, et al. Ann Oncol 2023;34(suppl_2): S498–502; 8. Wermke M, et al. Oral presentation at WCLC, Singapore 2023: abstract OA01.05

This study was industry-sponsored. 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 Lynn Pritchard PhD, of Ashfield MedComms, an Inizio Company, and was industry-sponsored

Presented at the European Neuroendocrine Tumor Society (ENETS) Congress, Vienna, Austria, 13–15 March 2024

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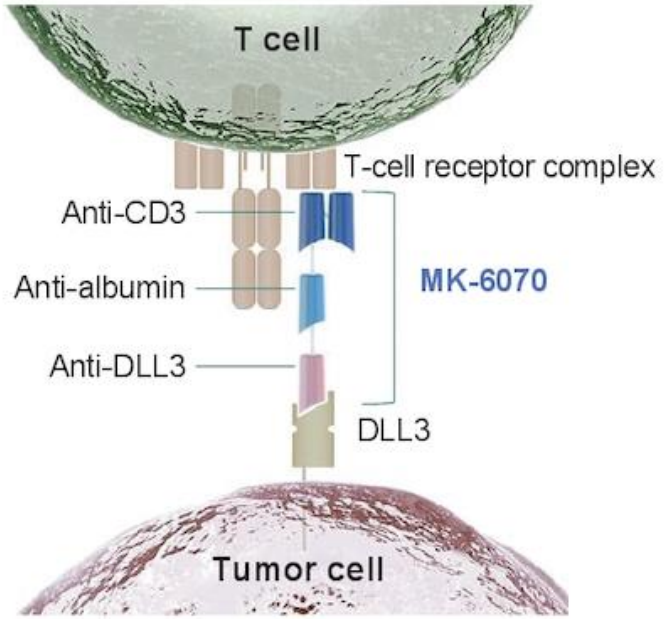
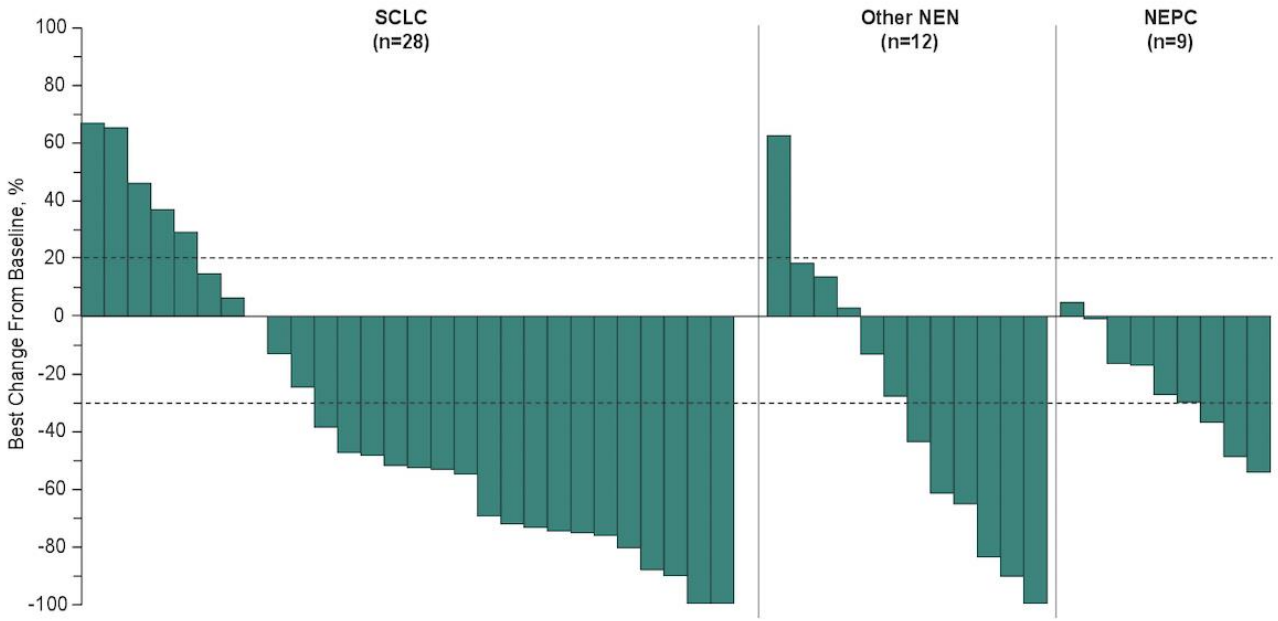
Updated Results From a Phase 1/2 Study of MK-6070 (HPN328), a Tri-Specific, Half-Life Extended DLL3-Targeting T-Cell Engager in Patients With Small Cell Lung Cancer and Other Neuroendocrine Cancers



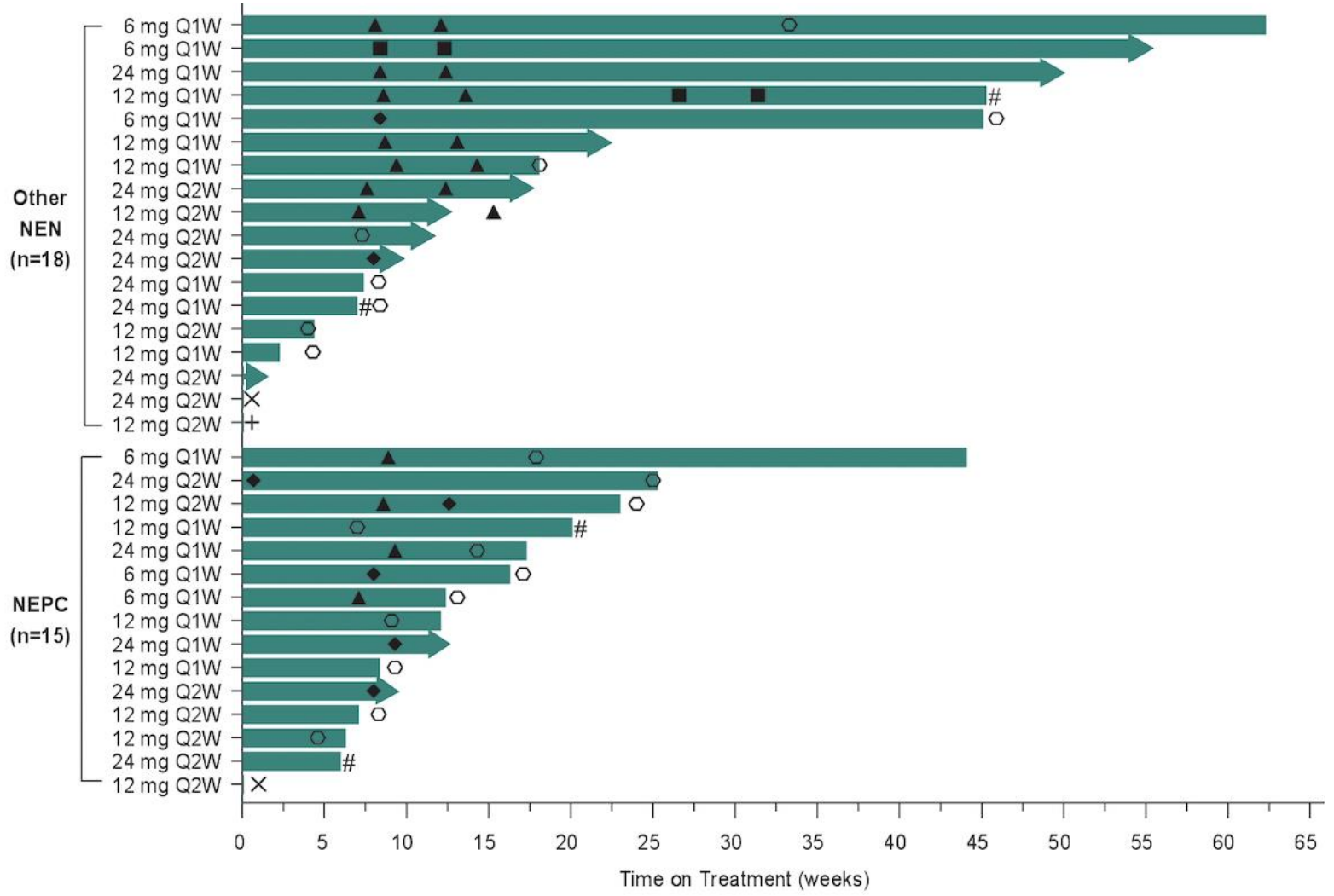
Albumin: half-life extension



	SCLC n=28	Other NEN[a] n=13
RECIST v1.1		
ORR	11 (39%)	6 (46%)
DCR	20 (71%)	6 (46%)
Extracranial response per RECIST v1.1[b]		
ORR	14 (50%)	6 (46%)
DCR	21 (75%)	6 (46%)

Beltran H, et al. ASCO 2024

Also durable responses



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CRS: cytokine release syndrome
ICANs: immune cell-associated neurotoxicity syndrome

Regimen	Pts, n	Dose-limiting toxicities	Tumour Type
RA	1	Grade 3 confusion	SCLC
RB1	0	—	—
RB2	6	**Grade 3 CRS** Grade 4 CRS Grade 3 nervous system disorder Grade 2 infusion-related reaction Grade 3 ICANs **Grade 5 ICANs**	**epNEC** SCLC SCLC SCLC SCLC **epNEC**
RB3	0	—	—

	All Cohorts (N=97)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CRS[a]	33 (34%)	25 (26%)	2 (2%)	1 (1%)	0
ICANS[b]	4 (4%)	3 (3%)	0	0	0

Beltran H, et al. ASCO 2024
Capdevila J, et al. ENETS 2024

Thank you !!

GETNE
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Current Studies of SSTR Radioligands

(a simple medical oncologist's perspective)

Daniel M. Halperin, MD

The Univ. of Texas MD Anderson Cancer Center

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DISCLOSURE INFORMATION
(24months)

- Consultant for Exelixis, Harpoon Therapeutics, ITM, Novartis, Crinetics, Amryt, Camurus, Alphamedix, Chimeric Therapeutics.

- Research funded by Genentech, ThermoFisher Scientific, ITM, AAA/Novartis, Camurus, RayzeBio.

- I **will** discuss off-label and/or investigational use.

Overview

- ALPHAMEDIX-02 (NCT05153772)
- ACTION-1 (NCT05477576)
- TECANT (EudraCT no: 2019-003379-20)

ALPHAMEDIX-02

^{212}Pb-DOTAMTATE

ALPHAMEDIX-02 Design

- Phase II open-label multicenter study
- 36 PRRT-naïve patients with WD GEP-NET
- Up to 4 cycles q8w at 67.6 µCi/kg per cycle (max 5.5 mCi)
- Primary endpoint ORR by RECIST 1.1

Strosberg et al., ASCO 2024

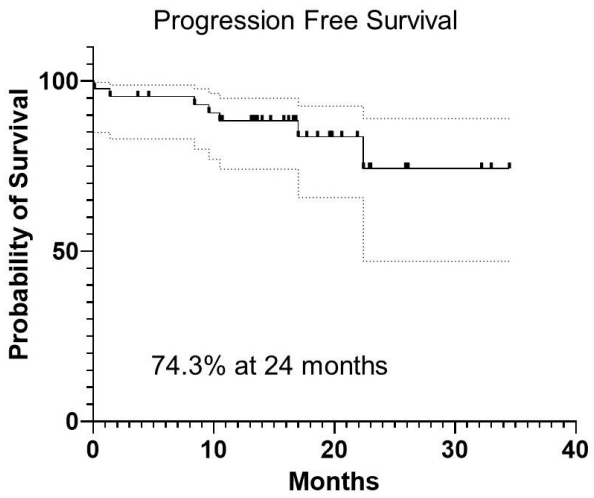
ALPHAMEDIX-02 Results

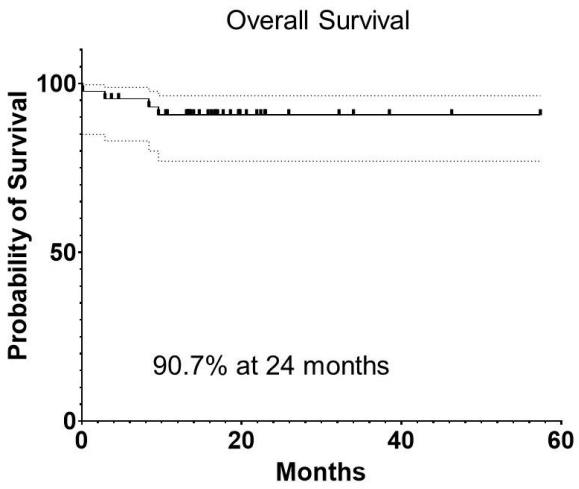
Demographics

- 50/50 Male/Female
- Primary Site
  - 14 (39%) Pancreas
  - 14 (39%) Small bowel
- Grade
  - 8 (22%) G1
  - 24 (67%) G2
  - 2 (6%) G3
- Functional Tumor: 14 (39%)

Efficacy

- 20/36 investigator-assessed response
  - ORR 55.6% (95% CI 39.6-70.5)
  - mDoR 17m (95% CI 17-NE)





Strosberg et al., ASCO 2024

ALPHAMEDIX-02 Discussion

- Encouraging early signals of activity, with ORR of 42-70% (95% CI).
  - Note must be made of the ~40% of patients with pancreatic primary tumors, which tend to have higher ORRs.

- > 90% of patients experienced alopecia (there is no grade 3+), nausea, and fatigue, 34% of patients developed dysphagia, and the primary grade 3 toxicity was reversible lymphopenia.

- Randomized data to establish its specific role in the management of GEP-NET patients are eagerly awaited.

ACTION-1

^{225}Ac-DOTATATE

ACTION-1 Ib Design

- Phase Ib/III (Ib complete and data reported)
- PRRT-relapsed G1-2 GEP-NET patients
  - 2-4 cycles with SD for 3 months
- BOIN de-escalation design (+expansion)
  - Dose level 0 (all patients): 4 cycles q8w at 3.2 µCi/kg
- Primary endpoint RP3D

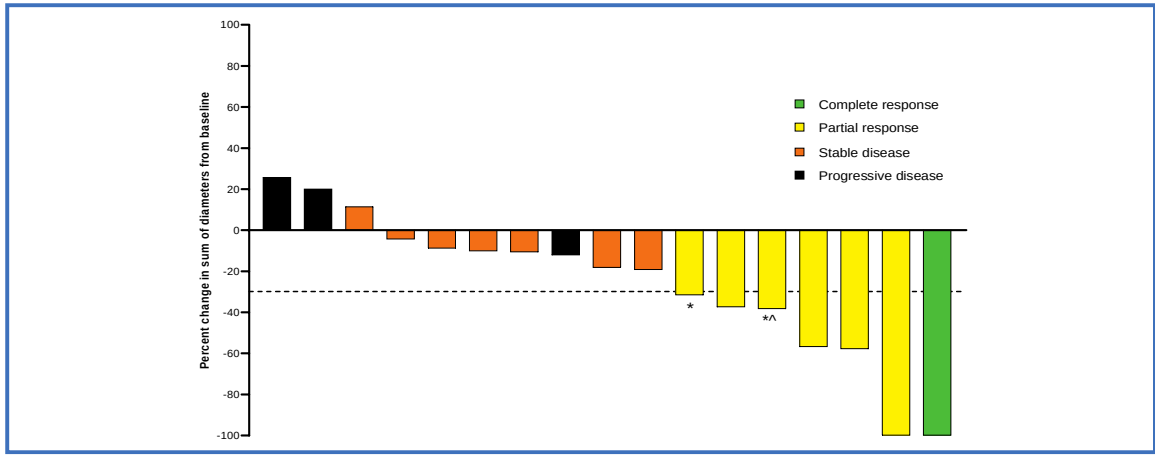
ACTION-1 Ib Results

Demographics

- 65/35 Male/Female
- Primary Site
  - 5 (29%) Pancreas
  - 12 (71%) Small bowel
- Grade
  - 8 (47%) G1
  - 9 (53%) G2
- Functional Tumor: 12 (70%)

Efficacy

- 7/17 investigator-assessed response
  - ORR 41.2% [95% CI NR]
  - DoR/PFS NE



Halperin et al., ASCO 2024

ACTION-1 Ib Discussion

- RP3D of 275 µCi q8w x 4

- Encouraging early signals of activity, with ORR of 18-67% (95% CI* by my/Google's calculation).
  - Note must be made of the ~30% of patients with pancreatic primary tumors, which tend to have higher ORRs.

- 100% of patients experienced some TEAE, with > 50% experiencing nausea, fatigue, anemia (most common grade 3+ AE, along with lymphopenia; 17.6%).

- Randomized data are eagerly awaited from the second portion of ACTION-1.

TECANT

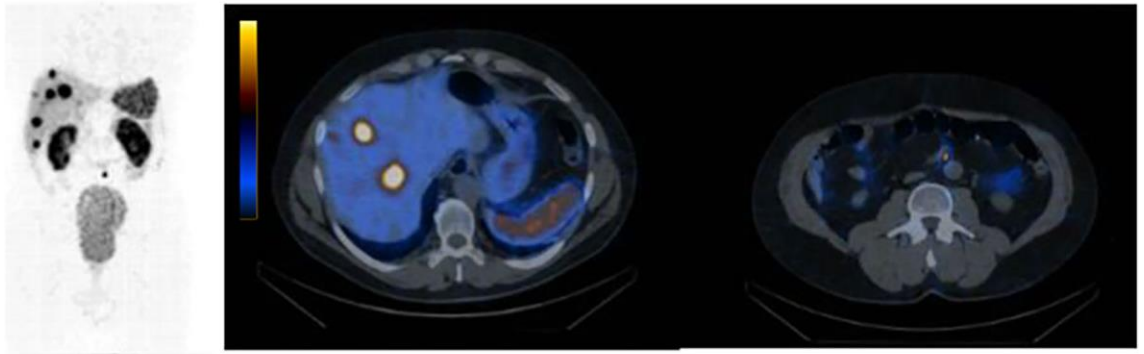
^{99}Tc-TECANT1

TECANT Background/Design

- Multicenter Phase 0/1 study supported by ERA
- Preclinical work of compared ^{99}Tc labelled N4-LM- 3(TECANT1) vs. N4-p-Cl-BASS(TECANT2).
- TECANT1 deemed superior.
- ^{99}Tc-TECANT1 SPECT/CT compared with 68Ga-DOTATATE/TOC in 10 patients

^{99}Tc-TECANT Representative Images

^{99}Tc-TECANT1



TBR (4,07 (range 1,36–7,58)

^{68}Ga-DOTATATE

TBR 2,26 (range 1,15–3,39)

(optimized at 4h p.i.)

Opalinska et al., Eur J of Nucl Med Mol Imaging 2023

TECANT Discussion

- Publicly funded, cooperative work
- Widely available imaging technology (SPECT)

- Conceptually, antagonists have been investigated previously (e.g., JR11) without reaching clinical fruition.
- Clinical value of this higher TBR bears investigation.
- Theragnostic value and change in therapeutic index using LM3 could be of significant interest in subsequent investigation

Overall conclusions

- The future is bright for radioligand therapy.
- International prospective studies are making significant progress.
- Rigorous randomized studies will help us understand the time and place for these novel agents.

THANK YOU!

Discussion

Closing comments

A BIG "thank you"…

- ✓ To the speakers and moderators
- ✓ NANETS Office: Cassandra CLEARE
- ✓ ENETS Office: Leah MATTHEWS, Ulrike KNELL & Martina FLESCHEN
- ✓ Technical partners:
  - Marcus LELLE and colleagues at Antwort:Internet
  - Simon HIRSCHMANN and colleagues at hirschtech
- ✓ The ENETS Education Group
- ✓ YOU, the participants

THANK YOU for attending this webinar!

Your feedback is important to us – please take the time to

fill out the feedback form at the bottom of your screen.

Save the date

The next ENETS webinar will take place on

Wednesday, 25 September 2024 from 18:00 – 19:10 CEST:

What has changed in the new guidance ENETS manuscript in 2023?

– Characterisation and treatment –

For updates, please check our website:

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