NETwerk
ENETS Center of Excellence

Revolutionaire vooruitgang tegen NEN

Dr. Willem Lybaert

10/11/2024

Ik heb geen relevante disclosures met betrekking tot deze spreekbeurt

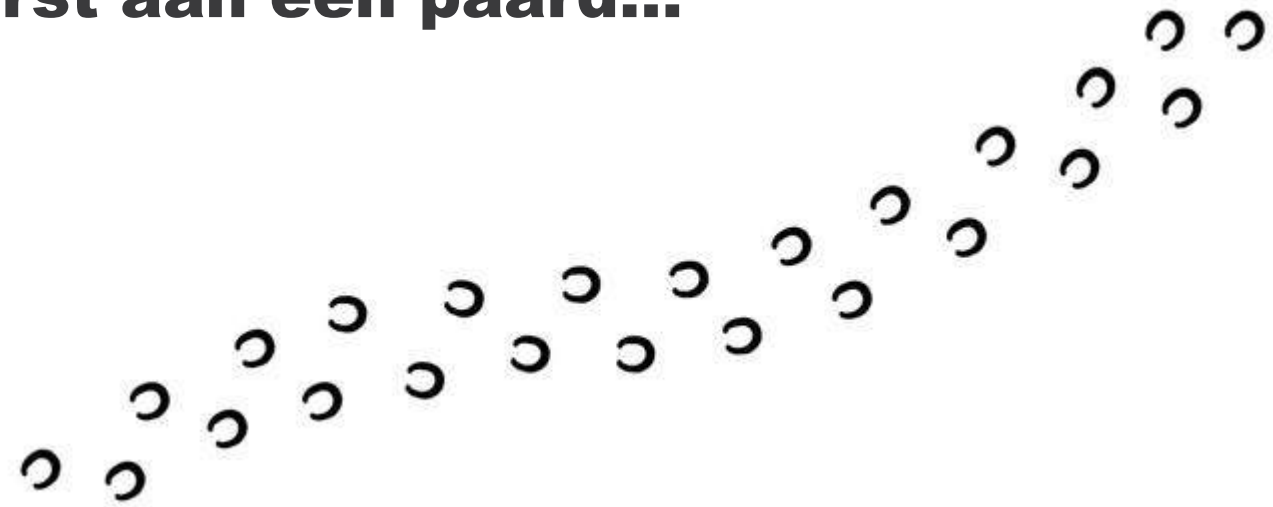
NETwerk
ENETS Center of Excellence

Klinische aspecten van NEN

NETwerk
ENETS Center of Excellence

Van het dierenrijk…

Als je hoefgetrappel hoort,
denk dan eerst aan een paard…

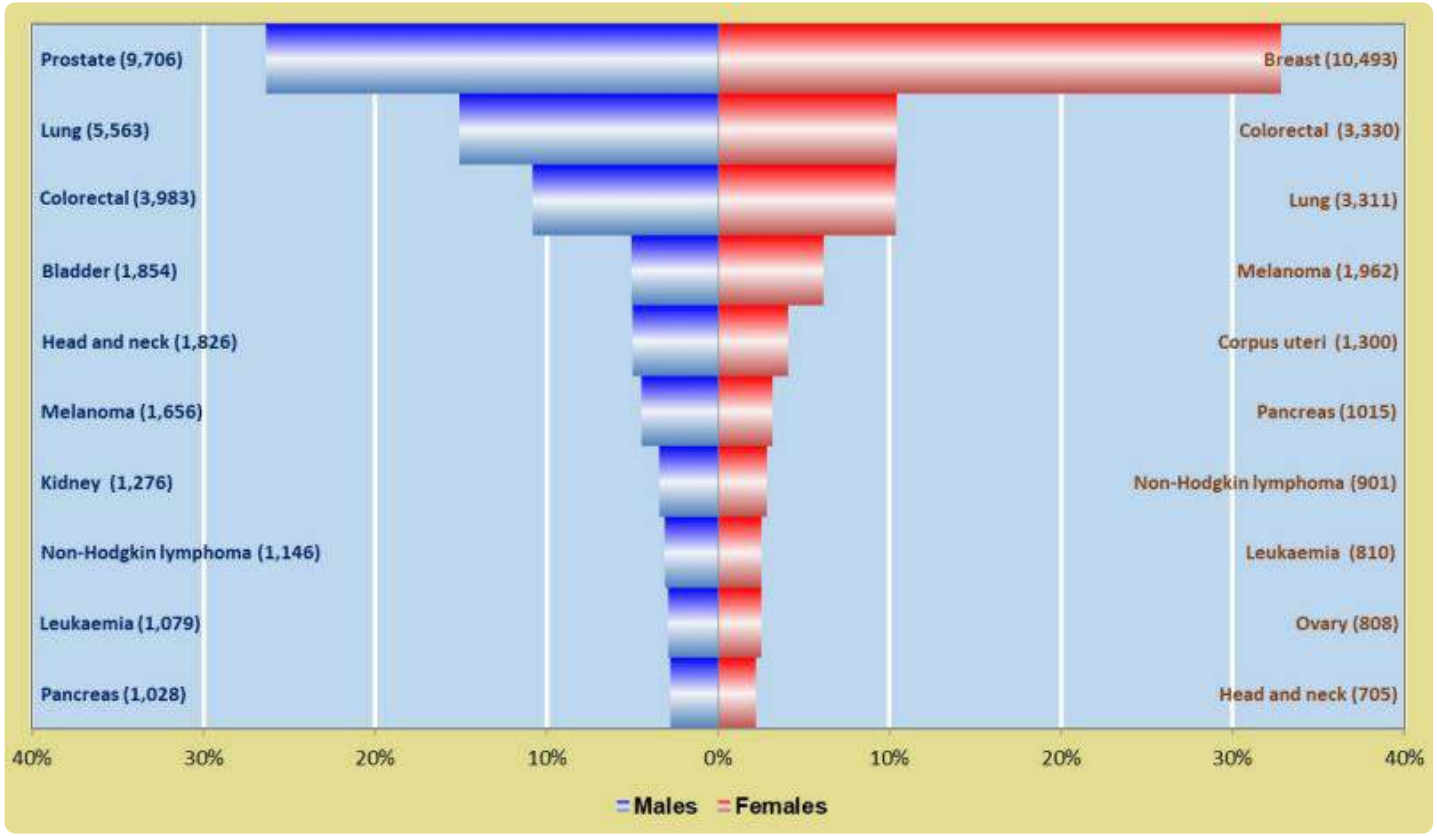


NETwerk
ENETS Center of Excellence

… tot kanker

De tien meest frequente tumoren per geslacht, België 2020

Bron: Belgisch Kankerregister



NETwerk
ENETS Center of Excellence

… tot kanker

22% van alle kankerpatiënten in Europa lijdt aan een zeldzame vorm van kanker

Ref.: *EORTC, 2023*

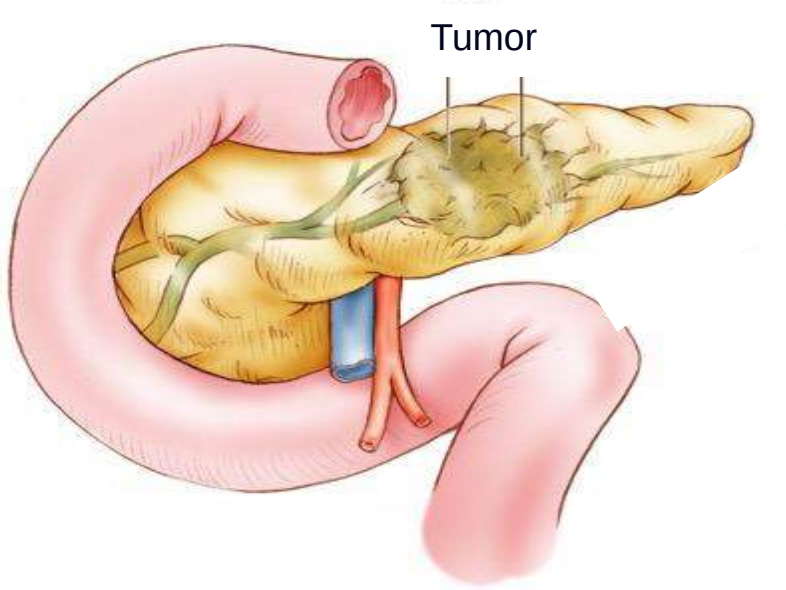
NETwerk
ENETS Center of Excellence

Maar…

Als je hoefgetrappel hoort, denk dan ook eens even aan andere dieren…

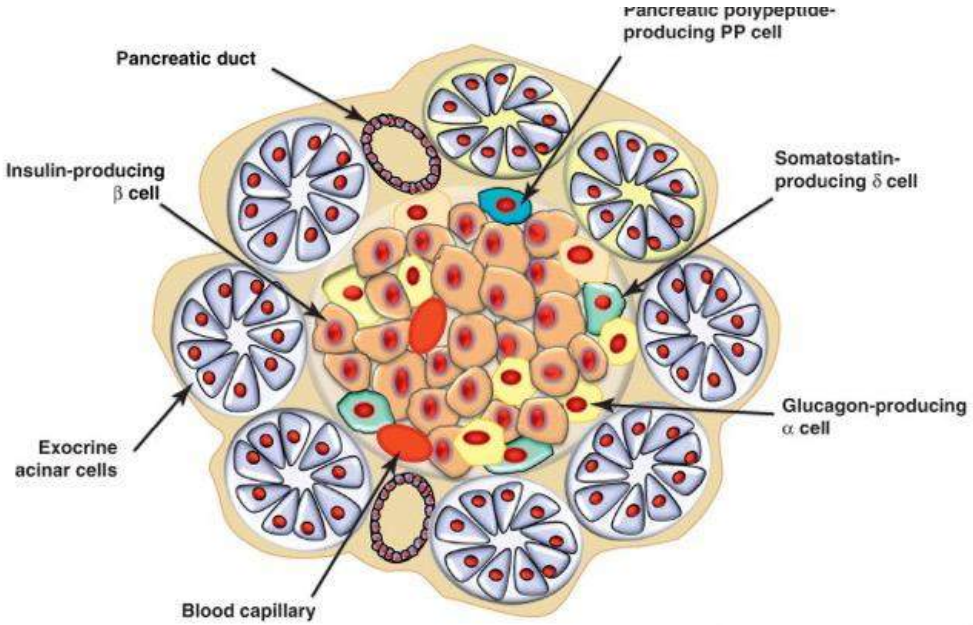
Origine van neuro-endocriene neoplasieën (1)

- **Meeste kankers zijn adenocarcinomen:**
  - Ontstaan uit “**exocrien**” klierweefsel: cellen in het klierweefsel scheiden stoffen af naar de buitenwereld (dus niet in de bloedbaan):
  - Voorbeelden:
    - Borst: melk
    - Colon: verteringssappen
    - Long: mucus
    - Pancreas: verteringssappen



Origine van neuro-endocriene neoplasieën (2)

- **Neuro-endocriene neoplasieën:**
  - Ontstaan uit “**endocrien**” klierweefsel: cellen in het klierweefsel scheiden stoffen af in het bloed (= hormonen)
  - Voorbeelden:
    - Schildklier: schildklierhormoon
    - Dunne darm: serotonine
    - Pancreas: insuline,…



Classificatie van neuro-endocriene neoplasieën (NEN)

- **WHO 2019 classificatie voor (GEP) NEN:**

Terminology	Differentiation	Grade	Mitotic rate*, mitoses/2 mm^2	Ki-67 index*, %
NET, G1	Well differentiated	Low	<2	<3
NET, G2	Well differentiated	Intermediate	2–20	3–20
NET, G3	Well differentiated	High	>20	>20
NEC, small cell type	Poorly differentiated	High	>20	>20
NEC, large cell type	Poorly differentiated	High	>20	>20
Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)	Well or poorly differentiated	Variable	Variable	Variable

NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma. * Final grade is based on whichever of the two proliferation indexes places the neoplasm in the higher category.

- **WHO 2019 classificatie voor long NEN:**

NET type	WHO grading (6)	Histology	Mitosis per 2 mm^2	Presence of necrosis
Low grade (well-differentiated)	G1	Typical carcinoid	<2 (6)	No necrosis
Intermediate grade (well-differentiated)	G2	Atypical Carcinoid	2–10 (6)	Necrosis
High grade (poorly differentiated)	G3	Large cell	>10 (6)	Extensive necrosis
		Small cell		High necrosis

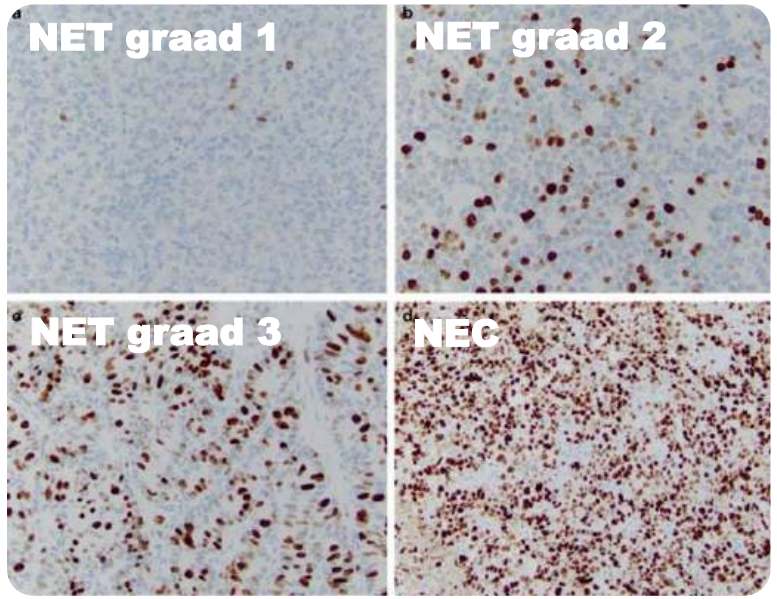
Algemeen: ‘NEN’ is overkoepelende term, en er bestaan enkele subtypes

NETwerk ENETS Center of Excellence

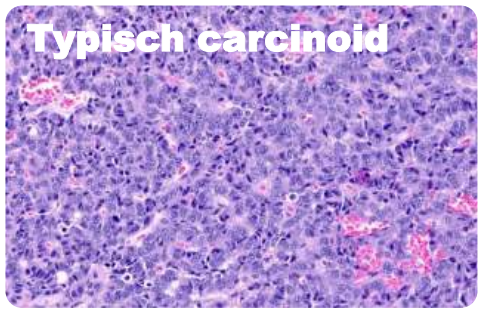
Intermezzo: wat is Ki-67 index?

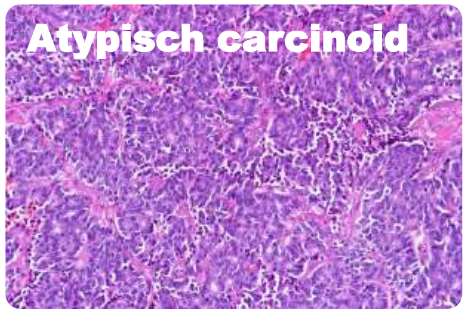
- **Weefseldiagnose ligt aan de basis voor diagnose en classificatie van NEN:**
  - Ki-67 index (en mitotische index) = maat voor aggressiviteit van tumorcellen
  - Wordt bepaald a.d.h.v. kleuringen (zie voorbeelden)

GEP NEN



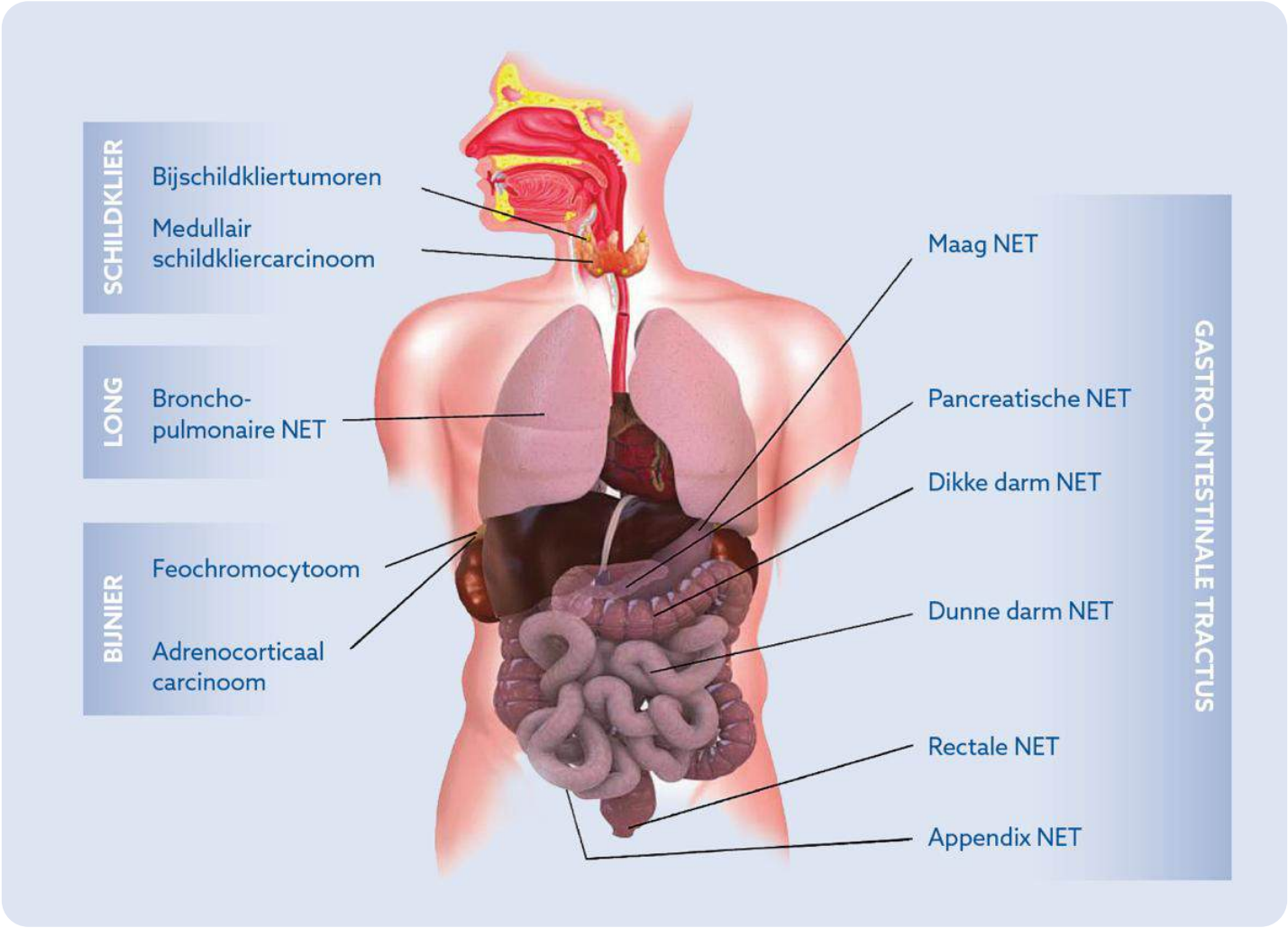
long NEN





NETwerk
ENETS Center of Excellence

Locatie van neuro-endocriene neoplasieën (NEN)



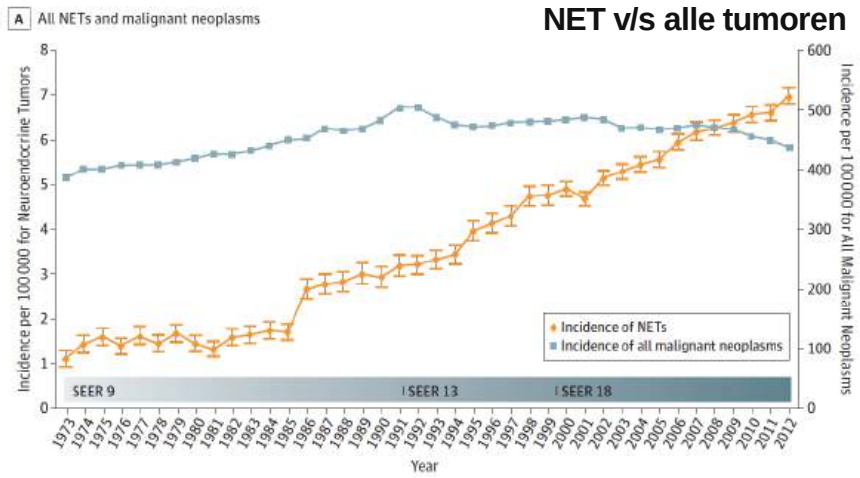
NETwerk
ENETS Center of Excellence

NEN als zeldzame ziekte?

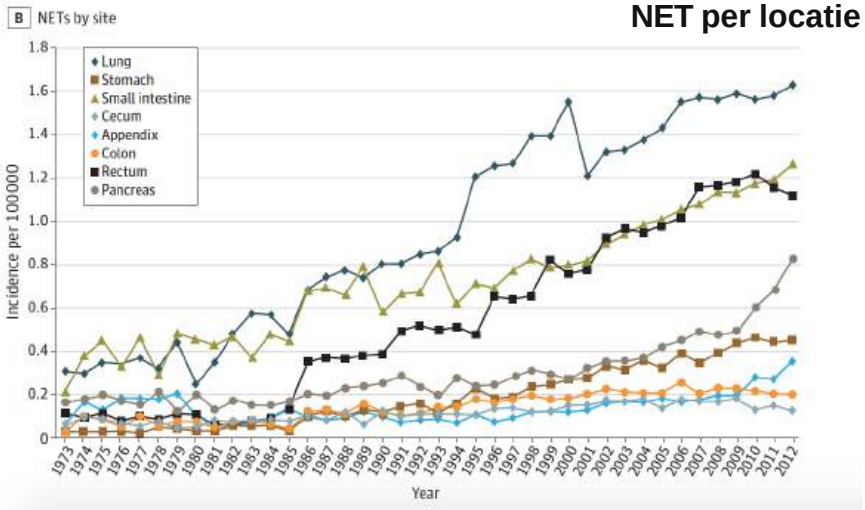
- **‘Lagere’ incidentie:**
  - 6-7/100 000 personen/jaar
  - 2% van alle tumoren
  - Long > dunne darm en rectum > pancreas
  - Gestegen incidentie: betere detectie?

- **Hoge prevalentie:**
  - Tweede meest voorkomende gastro-intestinale tumor na darmkanker

NET v/s alle tumoren



NET per locatie



NETwerk
ENETS Center of Excellence

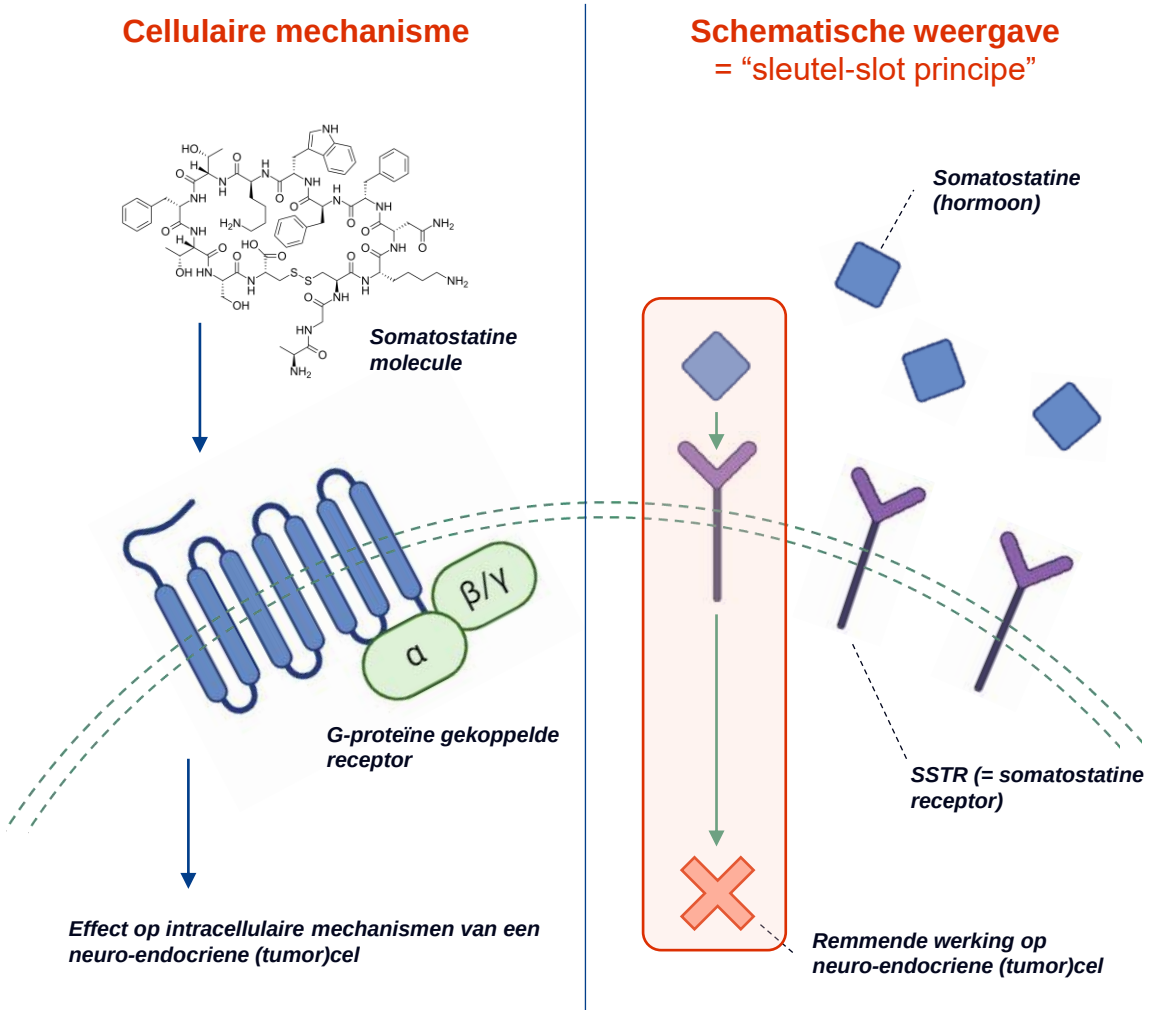
Diagnostische oppuntstelling

- **Patiënt presenteert met bepaalde klachten → aanvullende onderzoeken worden ingezet:**
  - Klinisch onderzoek → vaak aspecifieke bevindingen die richting geven, maar geen definitieve diagnose
  - Biomerkers → geven ook richting, maar veel kans op vals positieven/vals negatieven
  - Conventionele beeldvorming:
    - CT-scan thorax/abdomen
    - MRI pancreas/lever
    - Echo(-endoscopie)

    } handig voor zowel diagnose als opvolging
  - Biopsie/histopathologisch onderzoek:
    - cfr. WHO 2019 gradering,…
- **Na doorlopen van voorgaande onderzoeken is diagnose van een NEN (NET/NEC) gesteld:**
  - Volgende stap is het achterhalen van de kenmerken + uitgebreidheid van ziekte (= staging)
  - Gebeurt vaak met nucleaire beeldvorming of PET-CT-scan

Intermezzo: wat is somatostatine?

- **1973: ontdekking van somatostatine**
- **Eigenschappen:**
  - Lichaamseigen hormoon dat als ‘rem’ dient op secretie van:
    - endocriene stoffen (hormonen) ←
    - exocriene stoffen
  - Heeft zeer kort halfleven in bloed (< 3 min)
- **Achterliggend mechanism:**
  - Bindt eigen receptor SSTR (= somatostatine receptor)
  - >90% van NET hebben SSTR op hun cel-oppervlak *(⇔ NEC veel minder/geen)*



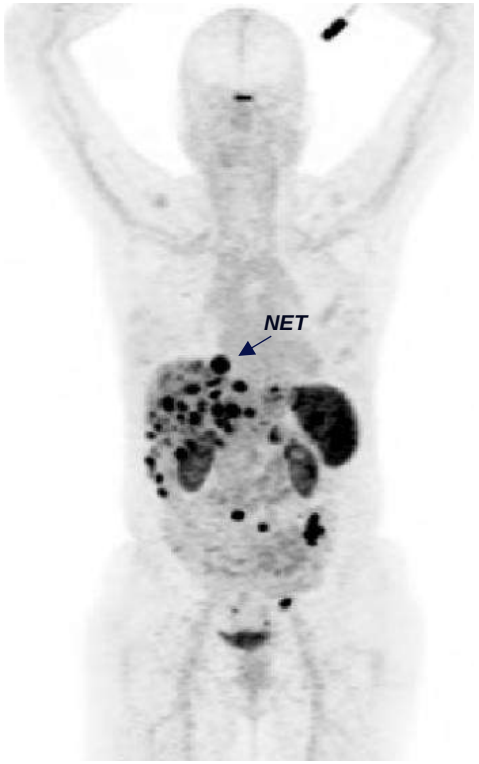
Adapted from: *Veenstra et al, 2013*

NETwerk ENETS Center of Excellence

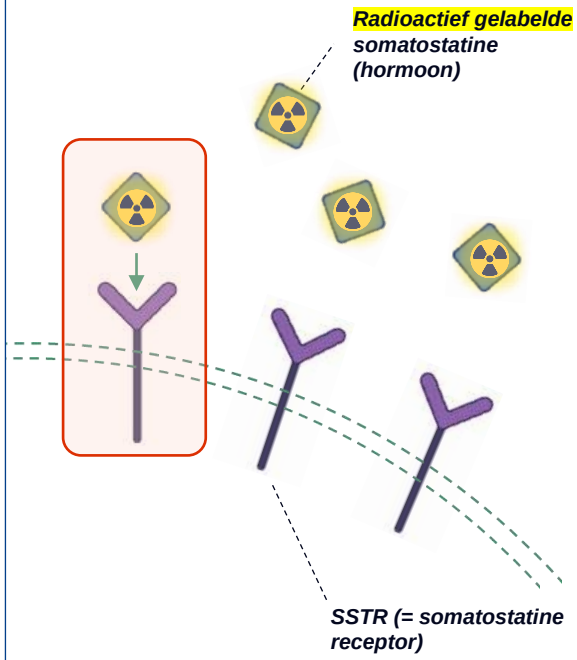
Functionele beeldvorming bij NEN

- **‘Klassieke’ PET-scan = o.b.v. FDG:**
  - Meet suikeropname van cellen
  - Wordt gebruikt bij aggressieve NET of NEC → maar niet gevoelig genoeg voor meeste NEN
- **Voor NEN wordt somatostatine-scan of 68-Ga-DOTANOC-scan gebruikt:**
  - Radioactief gelabelde somatostatine wordt aan patiënt toegediend
  - Deze bindt enkel aan cellen in lichaam die SSTR op hun celoppervlak hebben
  - Zoals aangehaald hebben >90% NET deze type receptor
  - Dus dan kleuren enkel deze cellen (en bijhorende organen) aan op de scan

68-Ga-DOTANOC PET/CT



Schematische weergave
= “sleutel-slot principe”



NETwerk ENETS Center of Excellence

Behandeling van NEN

NEN = NET + NEC

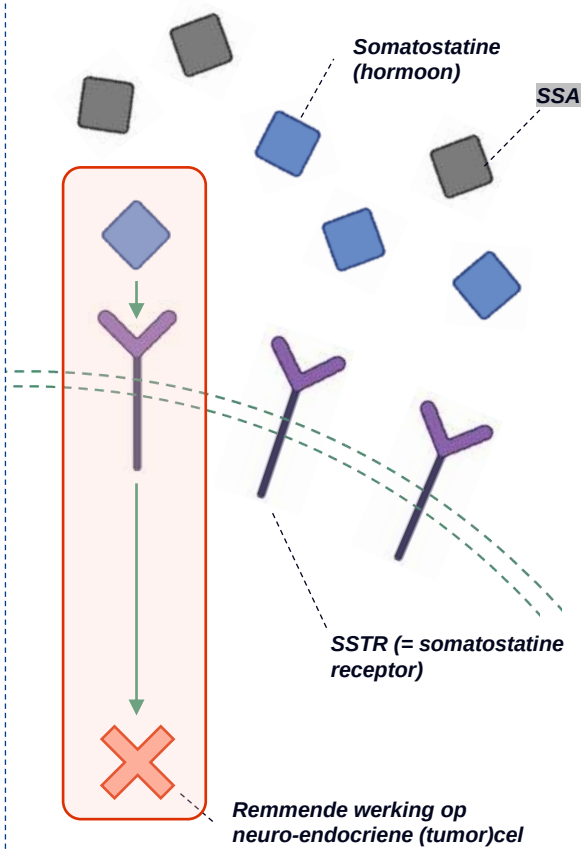
- **Huidige therapieën**:
  - Heelkunde
  - Somatostatine-analogen
  - Everolimus
  - Sunitinib/surufatinib
  - PRRT
  - Chemotherapie: cisplatinum/carboplatinum+etoposide, CAPTEM, FOLFOX, FOLFIRI
  - Levergerichte therapie: bland embolisatie, chemo-embolisatie en SIRT
  - Studies

  - Immunotherapie: atezolizumab en durvalumab in eerste lijn SCLC, bij de andere NENs onduidelijke positie: mogelijks bij longorigine en bij GEP NECs…

Somatostatine analogen (1)

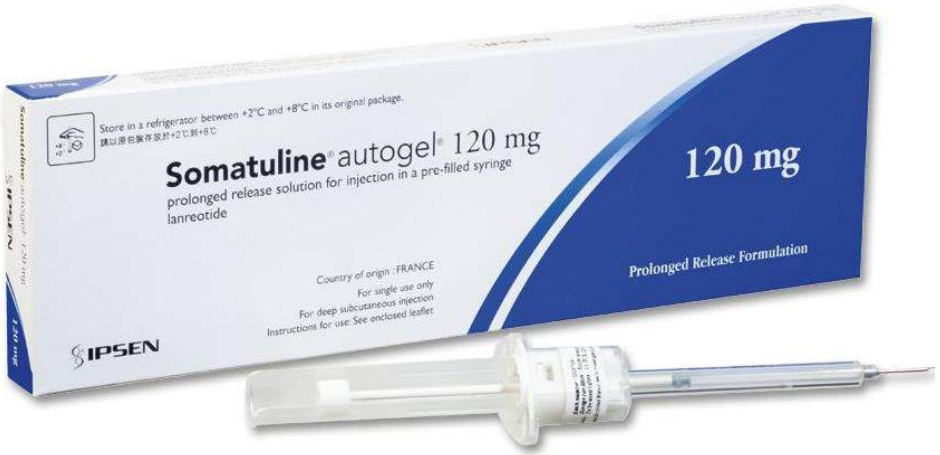
- **Somatostatine:**
  - Somatostatine is een kleine cyclische peptide dat aangemaakt wordt in het centrale en perifere zenuwstelsel → remt afscheiding hormonen en celdeling
  - Gezien lichaamseigen, wordt het 'standaard' al aangemaakt
- **Somatostatine analogen (SSA):**
  - Synthetisch gemaakte moleculen die gelijken op somatostatine
  - Worden toegediend om effect van lichaamseigen somatostatine te versterken
  - Principe:
    - Binden ook aan SSTR dat op celoppervlak van NEN cellen zit
    - Zorgen voor remming van afscheiding van hormonen, celgroei,… → belangrijkste medicatie voor symptoomcontrole (carcinoïd syndroom)
  - Praktisch:
    - Injectie om de 28 dagen – soms om de 14 dagen
    - Worden goed verdragen (soms nausea, vetabsorptie, galstenen,…)

Schematische weergave
= "sleutel-slot principe"



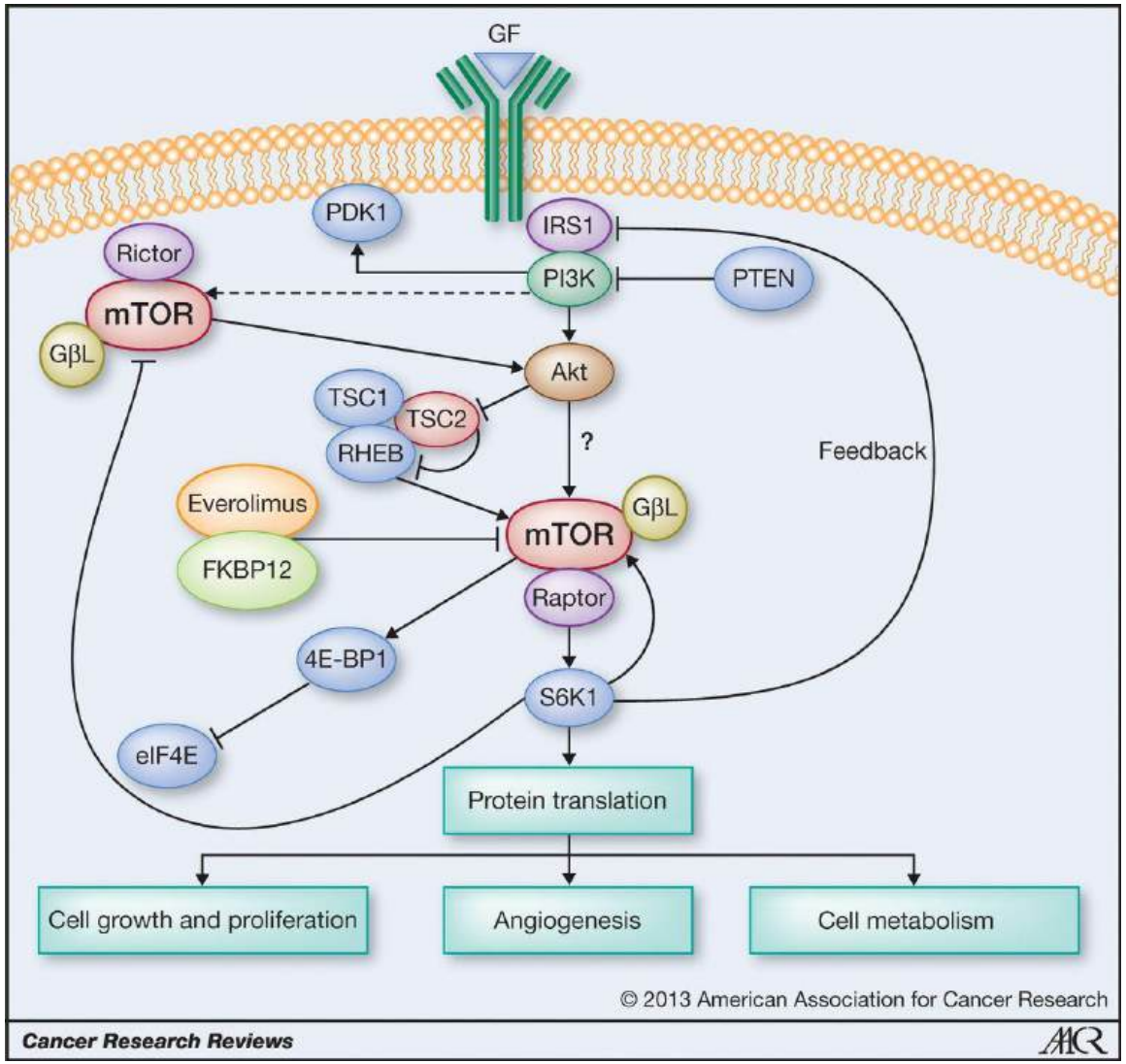
NETwerk
ENETS Center of Excellence

Somatostatine analogen (2)



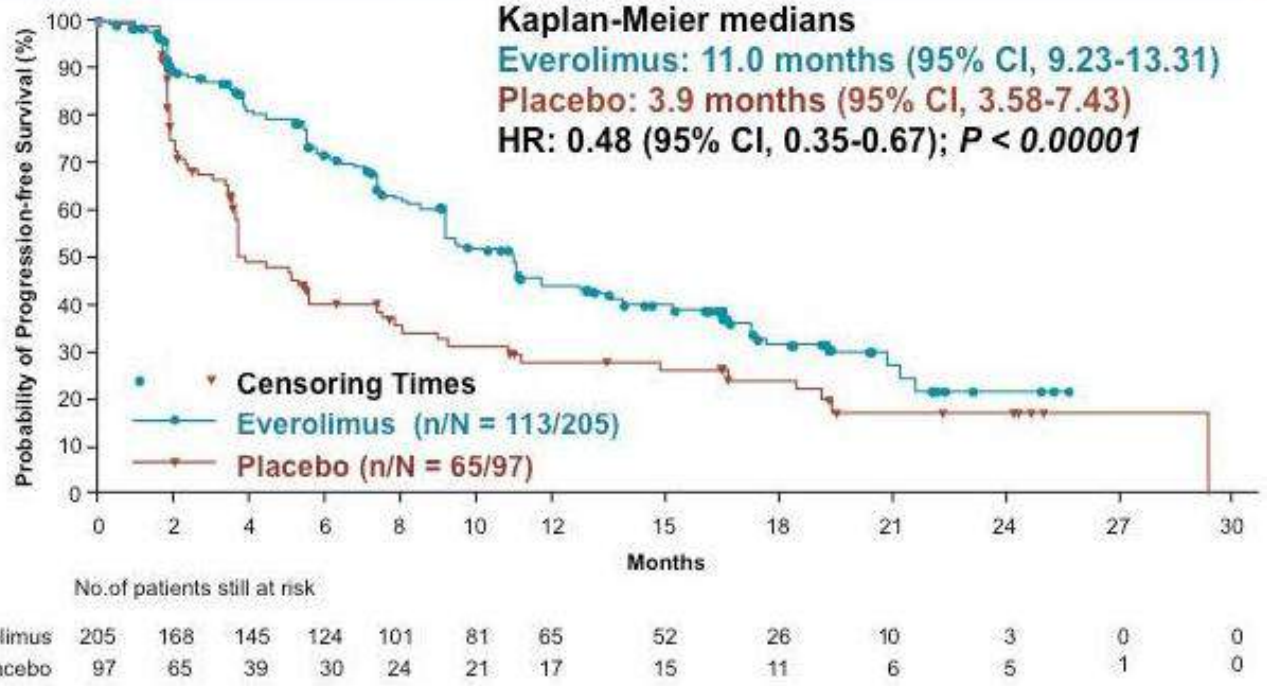
NETwerk
ENETS Center of Excellence

Doelgerichte therapie: everolimus



Everolimus

52% reduction in the relative risk of progression or death with everolimus vs placebo

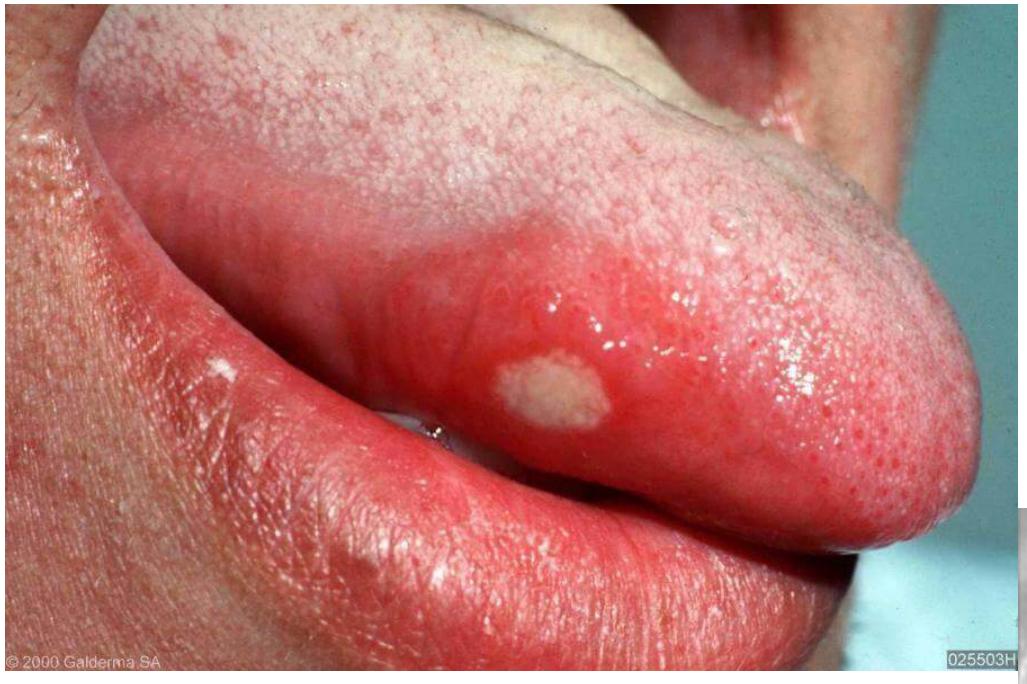


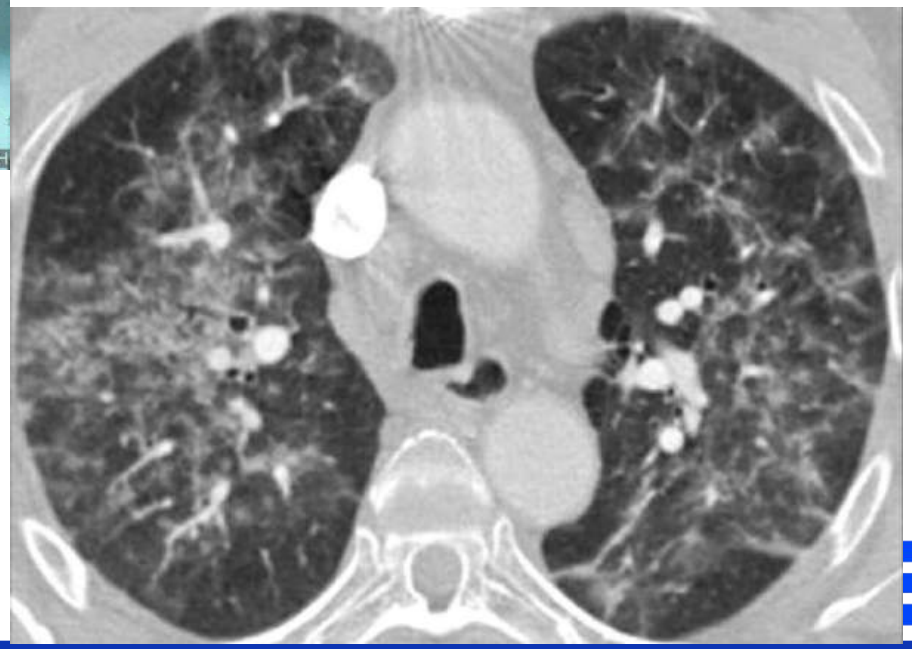
No.of patients still at risk

verolimus	205	168	145	124	101	81	65	52	26	10	3	0	0
Placebo	97	65	39	30	24	21	17	15	11	6	5	1	0

P-value is obtained from the stratified one-sided log-rank test; Hazard ratio is obtained from stratified Cox model.

Everolimus nevenwerkingen





SUNITINIB (SUTENT®)

Uw arts heeft u sunitinib (merknaam: Sutent®) voorgeschreven in het kader van uw behandeling.

Wat is sunitinib?

Sunitinib, de werkzame stof van het geneesmiddel Sutent®, is een zogenaamde tyrosine kinase remmer. Sunitinib belet de groei van kankercellen en doet dit door onder andere de bloedvatvorming af te remmen of zelfs te stoppen. De kankercellen krijgen op deze manier minder zuurstof en voedingsstoffen.

Praktisch

Sunitinib wordt klassiek toegediend in een dosis van 37,5 mg (= 1 tablet van 25 mg en 1 tablet van 12,5 mg) éénmaal daags zonder geprogrammeerde rustperiode. Het onderstaande schema geeft een overzicht van het verloop van één cyclus van de therapie. Eén cyclus duurt 4 weken (28 dagen). Dag 1 is altijd de eerste dag van een nieuwe cyclus. De volgende cyclus start in principe 4 weken na dag 1, als de bloeduitslagen en uw algemene toestand dit toelaten.

Generieke naam	*Merknaam*	*Dag 1-28 week 1 tem. 4*	*Wijze van toediening*
Sunitinib	Sutent®	x	Capsule(s), 1 maal per dag

Op geregelde tijdstippen wordt er bij u een bloedname verricht en wordt u gezien door de behandelende arts. Sunitinib tabletten zijn enkel in de ziekenhuisapotheek te verkrijgen na voorschrift van uw arts.

Sunitinib mag zowel met als zonder voedsel worden ingenomen. Bij het vergeten innemen van een dosis sunitinib mag u deze enkel inhalen als u dit nog dezelfde dag opmerkt. Anders slaat u de dosis over en neemt u de volgende dosis op het vaste tijdstip. U neemt dus nooit 2 dosissen op 1 dag. Bij braken vlak na de inname van sunitinib mag de dosis niet meer ingenomen worden. De capsules mogen niet worden geopend en er mag niet op worden gekauwd. Als de capsule beschadigd geraakt, probeer dan het contact van de huid of mucosa met het poeder te vermijden. Als dit toch gebeurt, spoel dan overvloedig met water.

Sunitinib tabletten kunnen niet met alle medicijnen gelijktijdig worden toegediend. Meld bij elk doktersbezoek welke medicatie u inneemt. Eet geen pompelmoes, drink geen pompelmoessap of gebruik geen preparaten op basis van Sint-Janskruid. Pompelmoes en Sint-Janskruid kunnen de werking van sunitinib immers nadelig beïnvloeden.

De behandeling wordt voortgezet zolang uw kanker goed onder controle blijft zonder al teveel bijwerkingen. De behandeling met sunitinib kan door uw arts tijdelijk worden onderbroken of de dosis kan bijgesteld worden naar een lagere dosis bij optreden van vervelende neveneffecten.

U mag dit middel niet gebruiken als u zwanger bent. Sunitinib brengt mogelijk schade toe aan de ongeboren baby. Het is dan ook aangewezen om tijdens en tot 2 weken na uw behandeling een voorbehoedsmiddel te gebruiken. Ook borstvoeding wordt afgeraden, omdat niet bekend is welk effect dit zou kunnen hebben op uw baby.

Bij deze behandeling worden schadelijke producten via de urine en de stoelgang uitgescheiden. Daarom sluit u na het gebruik van het toilet het deksel en spoelt 2 keer door. Zo zijn alle restproducten verwijderd.

Wat te doen indien u teveel tabletten heeft ingenomen?

Neem zo snel mogelijk contact op met uw arts en neem voorlopig geen nieuwe dosis in.

Mogelijke nevenwerkingen

Het is mogelijk dat er tijdens de behandeling bijwerkingen optreden. De intensiteit van deze bijwerkingen verschilt van persoon tot persoon. Het is steeds belangrijk om uw arts en/of de verpleegkundige op de hoogte te brengen als u bepaalde bijwerkingen ervaart. Ze zullen u adviezen verstrekken om de klachten te verminderen of te behandelen. Wanneer u te lang wacht om een bijwerking te behandelen, kan het soms moeilijker worden om ze te verhelpen. Wees niet ongerust als u weinig bijwerkingen ervaart. Dit betekent niet dat de therapie onvoldoende werkt. De bijwerkingen komen niet steeds in het begin van de therapie voor, maar kunnen ook pas na enkele cycli optreden.

Vermoeidheid

Klachten van vermoeidheid en algemene zwakte komen vaak voor onder sunitinib. Soms wordt er een verminderde werking van de schildklier vastgesteld, wat geregeld wordt gecontroleerd bij u via een bloedname. Deze vermoeidheid kan uw rijvaardigheid of uw vermogen om machines te gebruiken, beïnvloeden. Deze vermoeidheid kan een sterke impact hebben op uw dagelijkse activiteiten. Met onderstaande tips kan u toch de mogelijke ongemakken beperken:

- Las korte pauzes in.
- Vraag hulp aan anderen indien dit nodig is.
- Maak voldoende tijd voor ontspanning.
- Zorg voor een evenwichtige voeding en drink voldoende.
- Zorg voor een goede nachtrust.
- Geef voorrang aan activiteiten die werkelijk nodig zijn, voer die uit op uw eigen tempo.
- Vermijd het gebruik van alcohol en cafeïnerijke dranken (koffie, cola,...).

In ons ziekenhuis worden op regelmatige basis vermoeidheidssessies georganiseerd voor patiënten en hun familie. Bij vragen hieromtrent kan u steeds terecht bij de verpleegkundigen of uw arts.

Misselijkheid-braken, gebrek aan eetlust

Misselijkheid en braken zijn klachten die regelmatig voorkomen. Bij dergelijke klachten kan Primperan® (10 mg) of Litican® (50 mg) worden gebruikt. Deze medicijnen mogen samen met uw andere medicatie ingenomen worden. De standaarddosis voor deze middelen is driemaal daags 1 tablet vóór de maaltijd. Indien nodig, mag de dosis Litican® verhoogd worden tot maximaal 3x2 tabletten per dag. Er bestaan smelttabletten, tabletten, siroop en suppositoria (wat soms handig kan zijn).

Een gebrek aan eetlust wordt ook vaak waargenomen. Het is belangrijk om de voedingstoestand zo optimaal mogelijk te behouden. Er wordt aangeraden om frequent te eten, steeds in kleine porties. Voor vragen hieromtrent kunt u steeds terecht bij onze voedingsdeskundigen.

Volgende zaken worden best vermeden:

- Gebruik van sterke kruiden en geuren.
- Gebruik van alcohol.
- Roken van tabakswaren.
- Vetrijke maaltijden.

Diarree

Eén van de mogelijke nevenwerkingen van sunitinib is diarree. U mag starten met 2 pilletjes Imodium®, om verlies van vocht en voedingsstoffen als gevolg van de diarree te vermijden. Bij elke volgende losse stoelgang diezelfde dag neemt u nog 1 pilletje Imodium® extra. U mag tot 8 comprimés per dag innemen. Het is belangrijk om voldoende te blijven drinken, liefst dranken met wat extra suiker en zout zoals cola, bouillon, slappe thee met suiker,... Het is best om tijdelijk geen rauwe groenten en fruit of vette spijzen te eten, doch wel gekookte rijst en gekookte groenten (zoals wortelen), vis en kip. Als de diarree echter heftig is en u het thuis onvoldoende kunt afremmen, moet u gehospitaliseerd worden voor bijkomende medicatie en vochttoediening. Neem steeds contact op met uw arts bij overvloedige diarree (meer dan 4 platte stoelgangen per dag).

Hoge bloeddruk of arteriële hypertensie

Hoge bloeddruk is een veel voorkomende neverwerking van sunitinib: het is dan ook aan te raden regelmatig (best dagelijks) uw bloeddruk te controleren thuis. Hoofdpijn of duizeligheid kunnen eventueel wijzen op bloeddrukproblemen. Uw arts dient indien nodig bloeddrukverlagende medicatie voor te schrijven; noteer altijd welke medicatie u neemt wanneer u op doktersbezoek gaat.

Enkele tips hierbij:

- Beperk het gebruik van zout.
- Vermijd vet- en calorierijke maaltijden.
- Vermijd tabak en alcohol.

Smaakveranderingen

Smaak- en reukveranderingen kunnen optreden door uw behandeling. Wat u eet, kan plots heel anders smaken, terwijl het niet anders is klaargemaakt. Het is dan plotseling erg zoet, bitter, zuur, zout of juist flauw. Probeer er achter te komen welke voedingsmiddelen u graag hebt en vermijd de andere. Een goede mondhygiëne onderhouden, kan helpen: tanden poetsen, mondspoelingen gebruiken en eventuele tandprothese verzorgen.

Mucositis of slijmvliesirritatie

Sunitinib kan in wisselende mate de slijmvliezen aantasten (oogvlies, mond-keel-neusholte, slokdarm, maag- en darmwand, vaginaslijmvlies). Zo nodig zal u een spoelmiddel voorgeschreven worden (Iso-Betadine®, Corsodyl®, magistrale bereiding,...). Wanneer er sprake is van een schimmelinfectie, zal u ook hiervoor een behandeling voorgeschreven krijgen (Diflucan®, Sporanox®, Nystatine®,...). Meld eventuele klachten in ieder geval bij uw volgend bezoek aan het dagziekenhuis.

Hand-voetsyndroom

Deze klachten treden gewoonlijk op tijdens de eerste 6 weken van de behandeling, vaak zelfs al binnen 2 weken. Contacteer steeds uw arts. Meestal krijgt u eerst last van tintelingen of een voos gevoel ter hoogte van de handpalmen en voetzolen. De huid kan rood en droog worden. Dit kan gepaard gaan met een branderig gevoel op de voetzolen of handpalmen. Soms treedt er zwelling op van de huid. Soms ontstaan er al dan niet pijnlijke kloven of eeltige blaren. Bij het ontstaan van pijn of kloven dient u steeds uw arts te raadplegen. Eventueel dient de inname tijdelijk onderbroken te worden of dient de dosis te worden aangepast. U kan deze klachten voorkomen door extreme temperaturen te mijden. Draag geen knellende schoenen, en vermijd wrijving op de huid. Gebruik handschoenen bij tuinwerk en andere vuile karweitjes, ook voor de afwas. Breng meermaals per dag een verzachtende hydraterende crème aan. Eventueel kan u een pedicure inschakelen.

Huiduitslag

Deze klachten treden gewoonlijk op tijdens de eerste 6 weken van de behandeling. Contacteer steeds uw arts. Er zijn verschillende vormen mogelijk: van een rode schilfering ter hoogte van de haargrens in het gezicht, tot het ontstaan van rode jeukende papels en vlekken verspreid over het ganse lichaam. Soms ontstaan er ook kleine pustels.

Enkele tips:

- U kan deze klachten voorkomen door extreme temperaturen te vermijden. Zoek bij warm weer frisse of schaduwrijke plaatsen op. Vermijd contact met heet water en directe blootstelling aan zonlicht. Neem lauwe douches.
- Geef uw voeten en handen 's avonds een lauw badje. Dep u nadien droog en vermijd wrijven met een ruwe handdoek.
- Draag geen strakzittende kledij (knellende beha, nauwe jeans, ...). Vermijd het dragen van juwelen.
- Breng meermaals per dag een verzachtende hydraterende crème aan. U kan gebruik maken van een anti-roos shampoo om de klachten ter hoogte van de hoofdhuid te verlichten. U kan er ook ter verlichting van de jeuk uw lichaam mee wassen.

Onderdrukking van het beenmerg

Sunitinib kan soms de werking van het beenmerg onderdrukken, waardoor u een tekort krijgt aan rode bloedcellen met vermoeidheid tot gevolg, tekort aan witte bloedcellen met verhoogde vatbaarheid voor infecties en tekort aan bloedplaatjes met verhoogde bloedingsneiging. Dit wordt mee opgevolgd door uw arts bij de regelmatige bloedafnames.

Bloedarmoede (anemie) of een tekort aan rode bloedcellen

Bloedarmoede leidt tot vermoeidheid. Meestal herstelt dit spontaan; een bloedtransfusie is zelden nodig.

Een tekort aan witte bloedcellen

Een tekort aan witte bloedcellen vermindert uw afweer en maakt u daardoor meer vatbaar voor infecties. U dient bij koorts (>38°C), rillingen of algemeen ziektegevoel direct contact op te nemen met uw huisarts of het ziekenhuis. Indien u niemand kunt bereiken, dient u zich aan te melden op de afdeling spoedgevallen van ons ziekenhuis. Uw bloed zal gecontroleerd worden en indien het aantal witte bloedcellen veel te laag is, kan het zijn dat u moet worden gehospitaliseerd om langs intraveneuze weg (langs de ader) antibiotica toegediend te krijgen.

Een tekort aan bloedplaatjes

Een ernstig tekort aan bloedplaatjes treedt zelden op. Tekenen van abnormale bloedingsneiging (bijv. bloedneus, blauwe plekken, onderhuidse bloedinkjes, tandvleesbloedingen,...) moeten steeds dringend gemeld worden. Het regelmatige gebruik van andere geneesmiddelen die een effect hebben op de bloedstolling, moet worden vermeden tijdens de behandeling.

Bespreek steeds alle geneesmiddelen die u gebruikt of wenst te gebruiken met de arts die u onderzoekt tijdens elk bezoek aan het dagziekenhuis. Het gaat hierbij vooral om middelen zoals Sintrom®, Marcoumar®, Marevan®, Plavix®, Aspirine®, Sedergine®, Perdolan compositum®, Xarelto®, Eliquis®, Pradaxa® en ook bepaalde ontstekingswerende middelen. Bij koorts of pijn kan wel paracetamol gebruikt worden.

Griepachtige symptomen

U kunt onder sunitinib hoofdpijn, koorts, spierpijn en pijnlijke gewrichten krijgen. U mag hiervoor thuis steeds paracetamol innemen.

Haarverlies

Volledig haarverlies komt meestal niet voor onder sunitinib, al kan het haar wel enigszins worden uitgedund. Vaak begint het haar weer te groeien tijdens de verdere behandeling. Haarkleurveranderingen treden wel klassiek op onder sunitinib.

Hartproblemen

In zeldzame gevallen kan sunitinib leiden tot een verminderde hartfunctie. Stop met de medicatie en neem onmiddellijk contact op met uw arts bij pijn op uw borst, duizeligheid, flauwvallen, transpireren en kortademigheid.

Gevoeligheid voor zonlicht

Sunitinib zorgt ervoor dat de huid gevoeliger wordt voor de zon, waardoor ze sneller verbrandt. In de praktijk wil dit zeggen dat zonnebaden tijdens de warme middagzon af te raden is, maar dat beperkte zonneblootstelling mits goede protectie wel kan (hoge zonnefilter).

Doelgerichte therapie

- Vooral bij pancreatische lokalisatie veel gebruikt
- Vooral ziektestabilisatie, geeft minder respons
- Minder, maar ook bij darm- of longlokalisatie: RADIANT-4
- Forse impact op levenskwaliteit, coaching belangrijk
- Sunitinib (**Sutent®**) – everolimus (**Afinitor®**)

Chemotherapie

- Vooral bij pancreatische en hooggradige carcinomen
- Tal van schema's
- Voor de pancreas meestal:

  - Streptozotocine – 5-FU

  - Capecitabine-temozolomide (**CAPTEM**)

  - **mFOLFOX**

- Hoge kans op respons
- Vanwege nevenwerkingen weinig vriendelijk als onderhoudstherapie
- NECs: **cisplatine/carboplatine-etoposide**

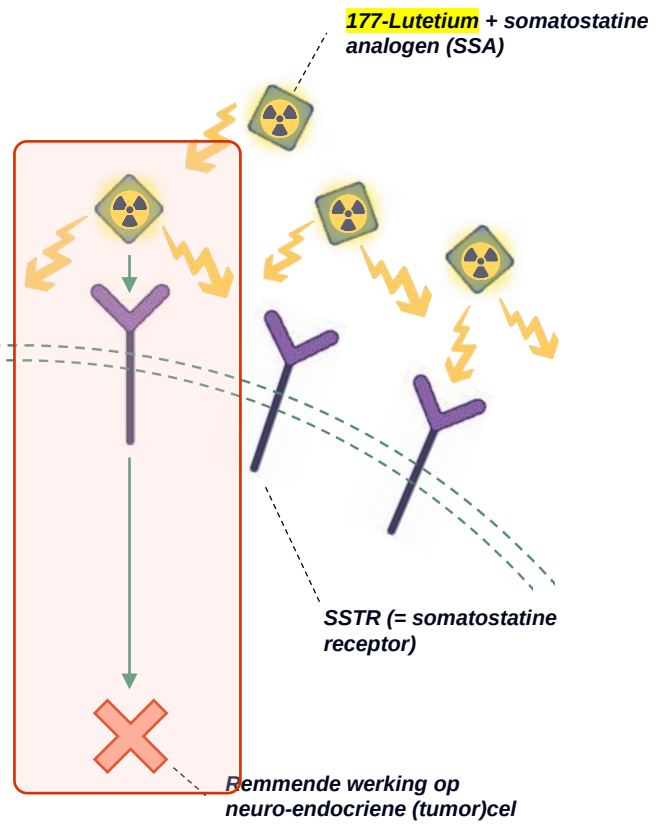
Peptide receptor radionucleotide therapie (PRRT) (1)

- **Achterliggend mechanisme:**
  - Combinatie van werking van somatostatine analogen en van DOTANOC-scan
  - Radioactief gelabelde somatostatine analogen (SSA) worden toegediend:
    - Vooral binding op SSTR-2 receptor (= subtype van SSTR-receptor) → cfr. aangegeven hebben NEN (vnl. NET) veel van zo'n receptoren
    - Radioactief gelabelde SSA bindt op SSTR-2, en heeft 'gewone' werking om hormoonproductie en celgroei te stoppen door receptor zelf

    → MAAR: bijkomend gaat het lokaal ook straling geven (= lokale bestraling van de tumorcellen)

    → Radionuclide = 177-Lutetium

Schematische weergave
= "sleutel-slot principe"



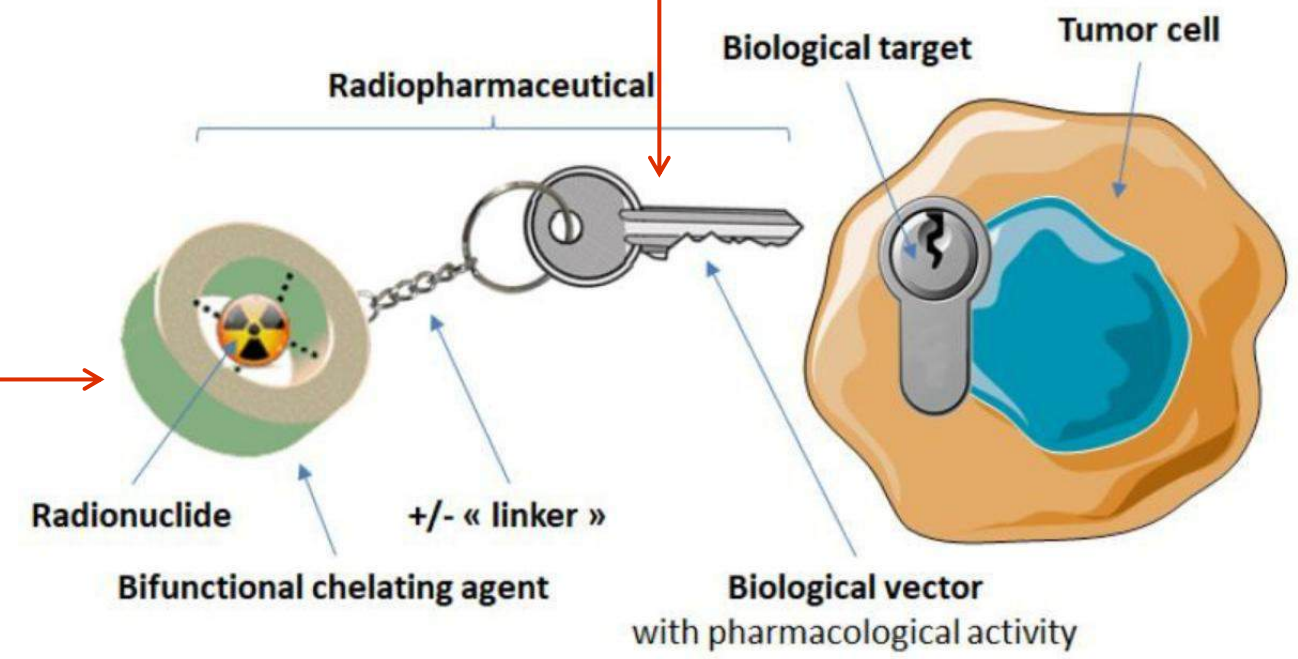
NETwerk ENETS Center of Excellence

Peptide receptor radionucleotide therapie (PRRT) (2)

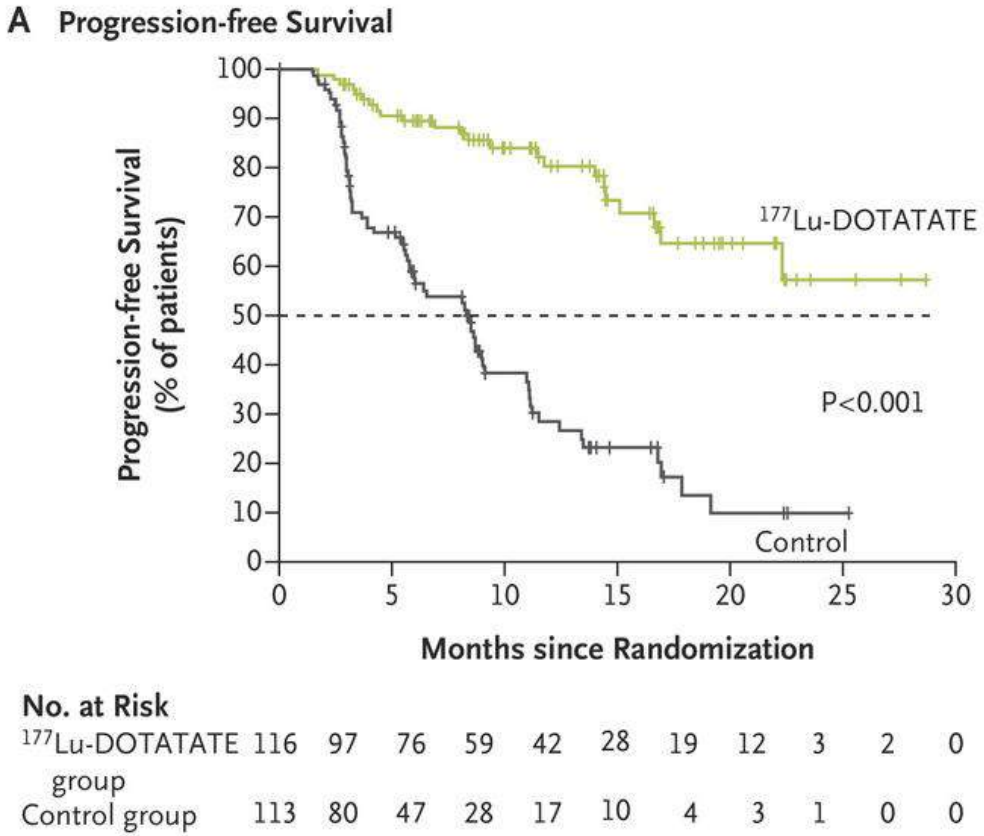
- **Andere weergave:**

SSA
- Binding vnl. op SSTR-2
- Komt vaak voor op NET (op celoppervlak)

Radiolabel
- 117-Lutetium
- Celdodend effect door lokale DNA-schade



NETTER-1 studie TOP!!



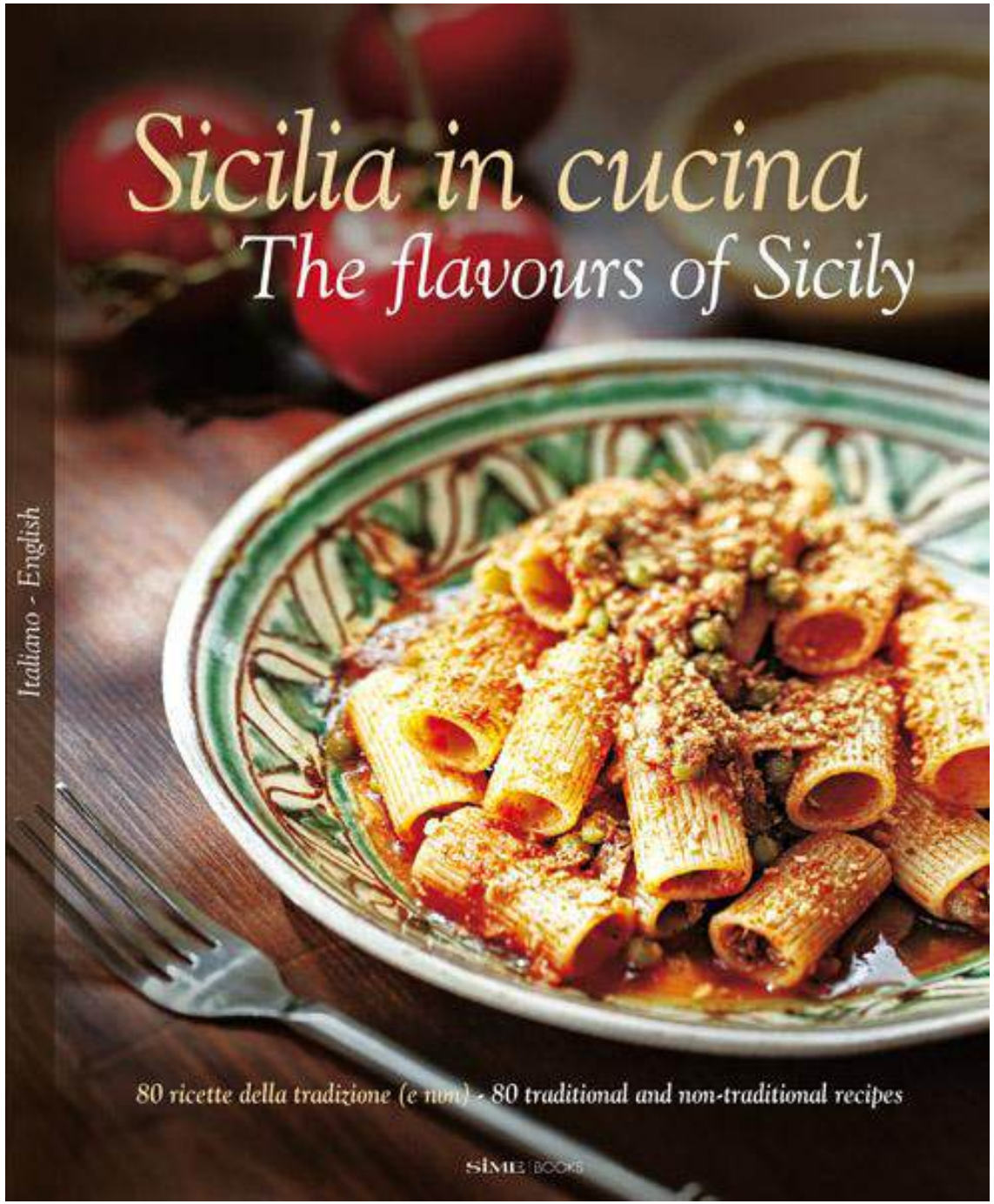
Peptide receptor radionucleotide therapie (PRRT) (3)

- **Resultaten:**
  - Duidelijke respons in ~30-35% van patiënten
  - Effect op verschillende lokalisaties
  - Mediane overleving meer dan 90 maanden voor bepaalde subtypes tumoren
- **Veelbelovende vooruitzichten:**
  - Initieel enkel voor NET graad 1-2 → maar o.b.v. recente data (2023-2024) uitbreiding naar NET graad 3
  - Initieel enkel na x-aantal lijnen therapie reeds gehad te hebben → in praktijk o.b.v. nieuwe data steeds meer shift naar 2e en zelfs 1e lijnstherapie
  - Andere types van PRRT therapie zijn in volle ontwikkeling → hoop op betere effectiveit en bredere toepassing
  - …

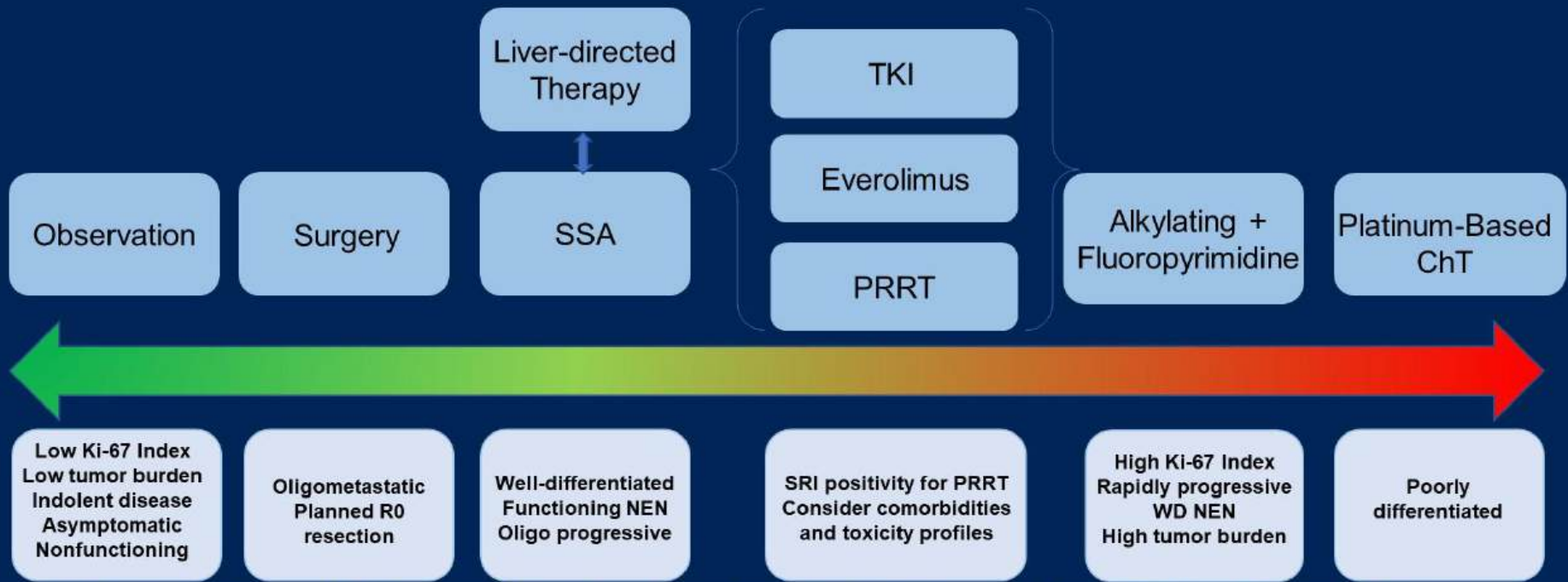
Peptide receptor radionucleotide therapie (PRRT) (4)

- **Beschikbaarheid in België:**
  - PRRT beschikbaar in UZA, UZ Leuven, H.U.B, AZ Groeninge, AZ Delta, UCL Saint-Luc
  - Sinds september 2022 ook officieel terugbetaald voor NET graad 1-2 vanaf 2e lijnstherapie
  - MAAR, zoals aangehaald, in toekomst hoop op terugbetaling in 1e lijn en ook voor NET graad 3

NETwerk
ENETS Center of Excellence



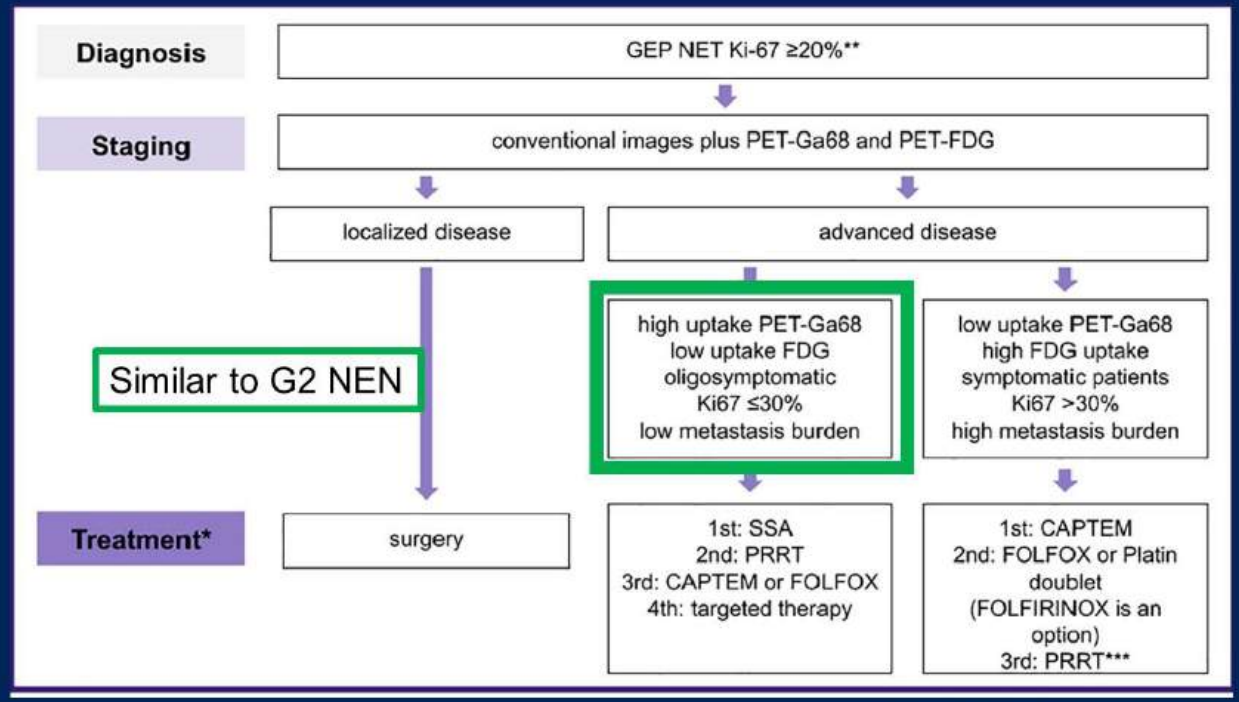
Therapeutic sequencing strategies for patients with advanced G1-2 GEP NEN



SSA: somatostatin analogues; TKI: Tyrosine kinase inhibitor; PPRT: peptide receptor radionuclide therapy; SRI: somatostatin receptor imaging; Ch: chemotherapy

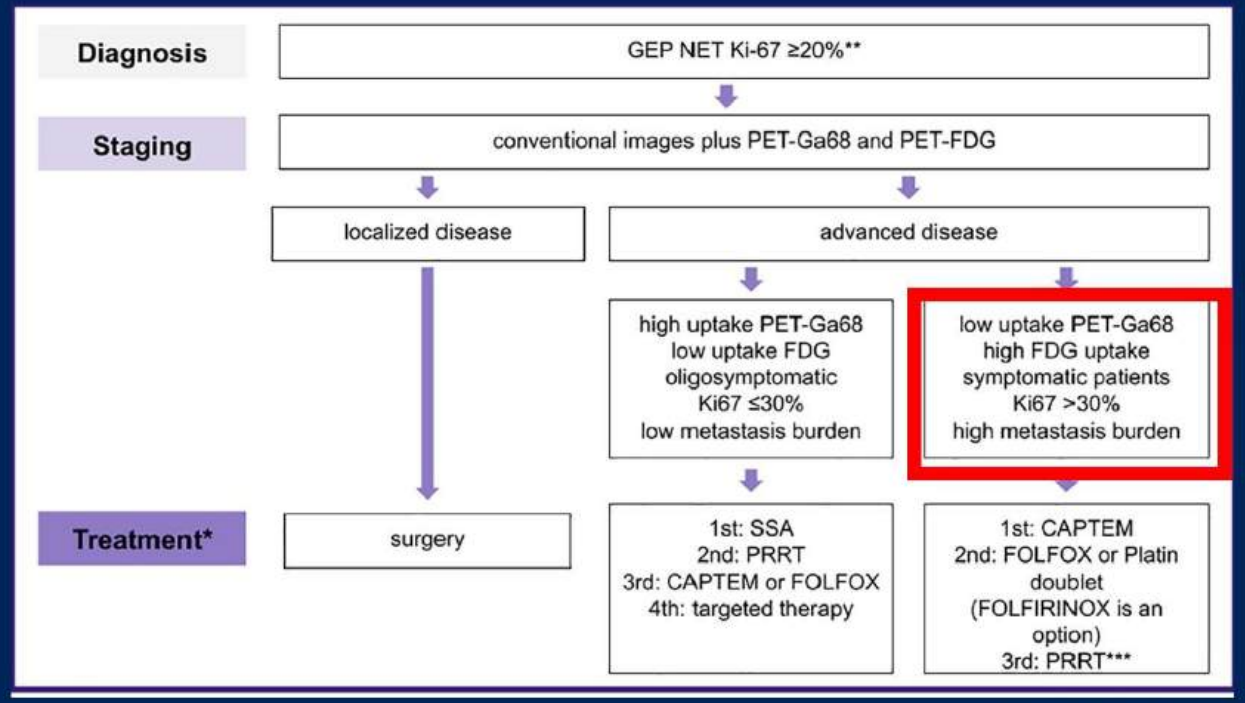
Figure from the American Society of Clinical Oncology Educational Book 43. 10.1200/EDBK_389278). e389278

Therapeutic sequencing strategies for patients with well-differentiated G3 NEN



Donadio, Brito, Riechelmann. Ther Adv Med Oncol 2023, Vol. 15: 1

Therapeutic sequencing strategies for patients with well-differentiated G3 NEN



Not NEC

Prefer chemotherapy

Donadio, Brito, Riechelmann. Ther Adv Med Oncol 2023, Vol. 15: 1

NETwerk

Tsunami van ‘treatment sequencing’ trials

SEQTOR

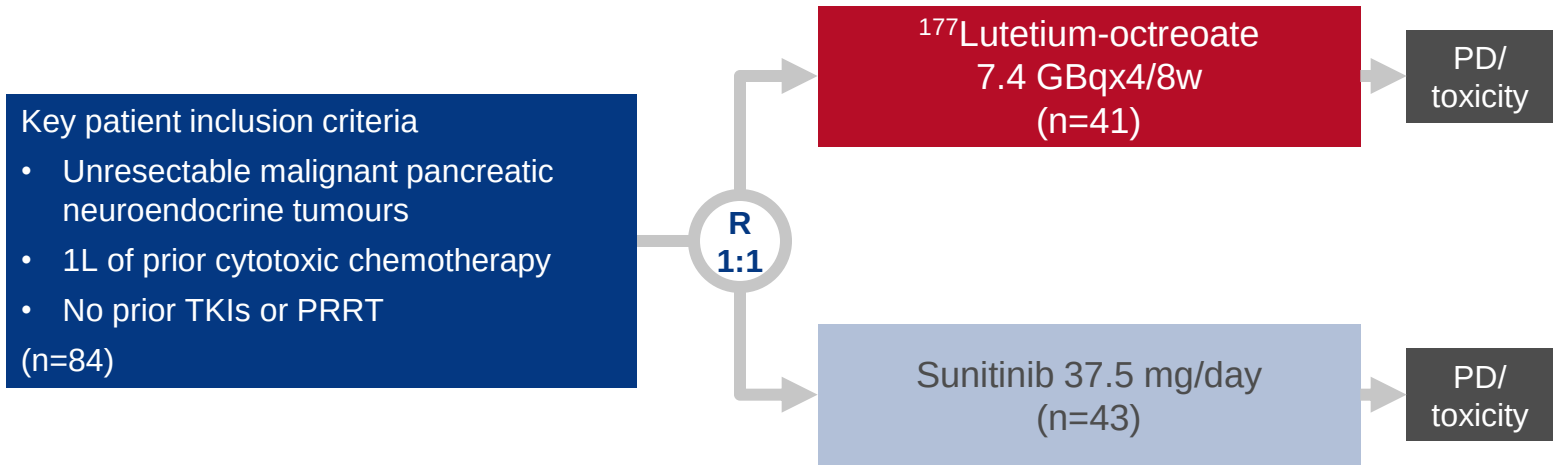
OCCLURANDOM (sunitinib vs. PRRT)

CABINET

887O: First multicentric randomized phase II trial investigating the antitumor efficacy of peptide receptor radionucleide therapy with 177Lutetium-Octreotate (OCLU) in unresectable progressive neuroendocrine pancreatic tumor: results of the OCLURANDOM trial – Baudin E, et al

Study objective

- To evaluate the efficacy and safety of peptide receptor radionucleide therapy (PRRT) with ^{177}lutetium-octreotate in patients with unresectable neuroendocrine pancreatic tumours in French centres in the phase 2 OCLURANDOM study



PRIMARY ENDPOINT

- 12-mo PFS rate

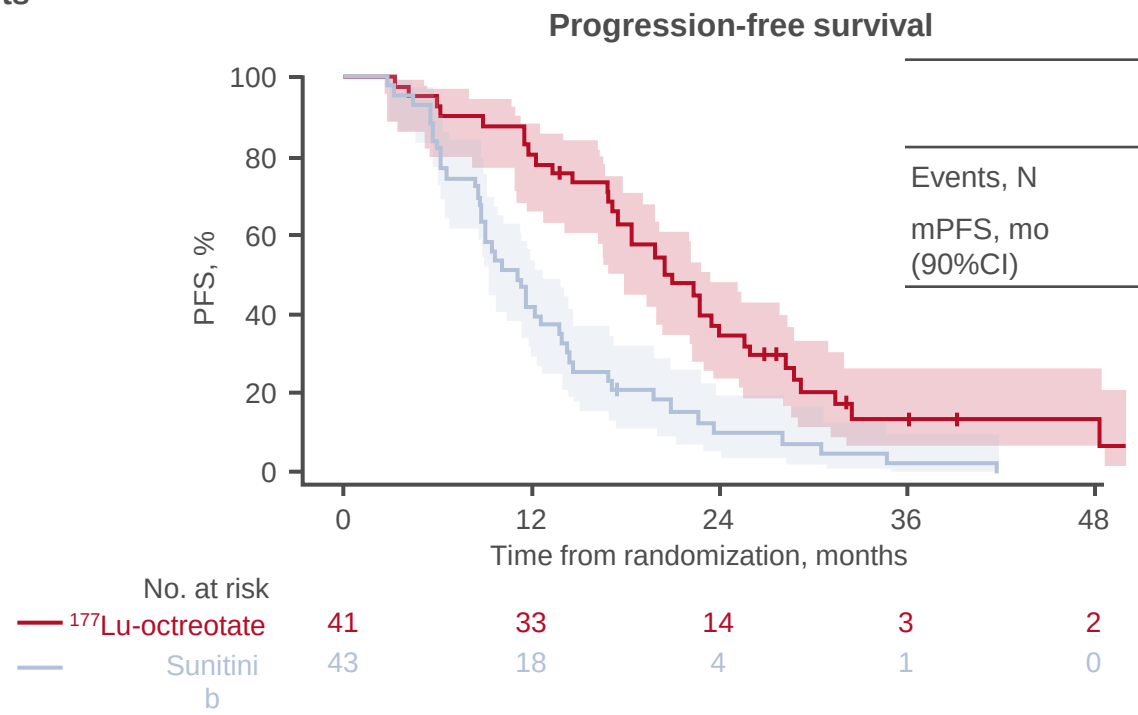
SECONDARY ENDPOINTS

- TTP, BOR, OS, QoL, safety

Presented at ESMO Congress 2022
Baudin E, et al. Ann Oncol 2022;33(suppl):abstr 887O

887O: First multicentric randomized phase II trial investigating the antitumor efficacy of peptide receptor radionucleide therapy with 177Lutetium-Octreotate (OCLU) in unresectable progressive neuroendocrine pancreatic tumor: results of the OCLURANDOM trial – Baudin E, et al

Key results



	^{177}Lu-ocreotate (n=41)	Sunitinib (n=43)
Events, N	34	42
mPFS, mo (90%CI)	20.7 (17.2, 23.7)	11.0 (8.8, 12.4)

Baudin E, et al. Ann Oncol 2022;33(suppl):abstr 887O

887O: First multicentric randomized phase II trial investigating the antitumor efficacy of peptide receptor radionucleide therapy with 177Lutetium-Octreotate (OCLU) in unresectable progressive neuroendocrine pancreatic tumor: results of the OCLURANDOM trial – Baudin E, et al

Key results

	^{177}Lu-octreotate (n=41)	Sunitinib (n=43)
12-mo PFS rate, n (%)	33 (80)	18 (42)

Grade 3–4 AEs, n (%)	^{177}Lu-octreotate (n=41)	Sunitinib (n=43)
Any	18 (44)	27 (63)
Blood	5 (12)	10 (23)
Digestive	5 (12)	9 (21)
Fatigue	3 (7)	5 (12)
Hypertension	5 (12)	8 (19)
Led to discontinuation	2 (5)	9 (21)

Conclusions

- **In patients with unresectable progressive pancreatic neuroendocrine tumours, ^{177}Lu-octreotate demonstrated promising antitumor activity and was generally well-tolerated with no new safety signals observed**

Baudin E, et al. Ann Oncol 2022;33(suppl):abstr 887O

Van San Francisco over Wenen naar Munchen

2024 ESMO GASTROINTESTINAL CANCERS
Annual Congress

FIRST-LINE EFFICACY OF [^{177}Lu]Lu-DOTA-TATE IN PATIENTS WITH ADVANCED GRADE 2 AND GRADE 3, WELL-DIFFERENTIATED GASTROENTEROPANCREATIC NEUROENDOCRINE TUMORS BY TUMOR GRADE AND PRIMARY ORIGIN: SUBGROUP ANALYSIS OF THE PHASE 3 NETTER-2 STUDY

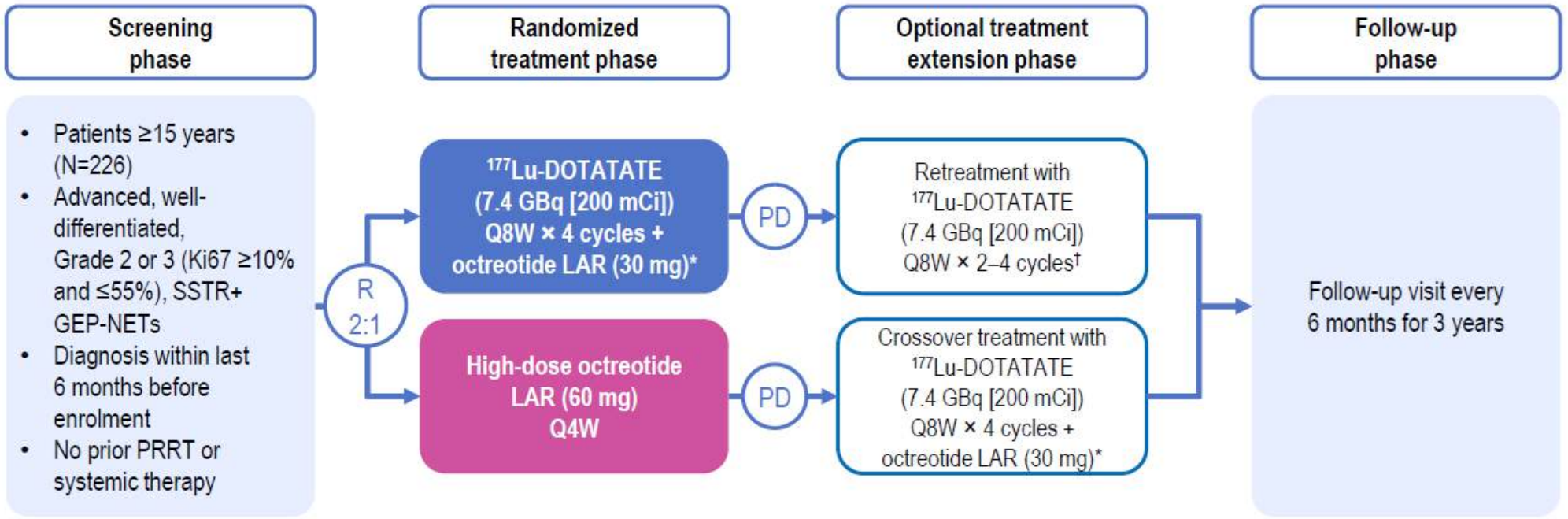
S. Singh,[1] D. Halperin,[2] S. Myrehaug,[1] K. Herrmann,[3] M. Pavel,[4] P. L. Kunz,[5] B. Chasen,[2] J. Capdevila,[6] S. Tafuto,[7] D-Y. Oh,[8] C. Yoo,[9] S. Falk,[10] T. Halfdanarson,[11] I. Folitar,[12] Y. Zhang,[13] W. W. de Herder,[14] D. Ferone[15]

[1]University of Toronto, Sunnybrook Odette Cancer Centre, Toronto, ON, Canada; [2]MD Anderson Cancer Center, Houston, TX, USA; [3]University of Duisburg-Essen, and German Cancer Consortium (DKTK)-University Hospital Essen, Essen, Germany; [4]Uniklinikum Erlangen, Friedrich Alexander University Erlangen-Nürnberg, Erlangen, Germany; [5]Yale School of Medicine, Yale University, New Haven, CT, USA; [6]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [7]Oncologia Clinica e Sperimentale Sarcomi e Tumori Rari, Istituto Nazionale Tumori IRCCS, Fondazione G. Pascale, Naples, Italy; [8]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; [9]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [10]Bristol Haematology and Oncology Centre, University Hospitals Bristol NHS Foundation Trust, Bristol, UK; [11]Mayo Clinic, Rochester, MN, USA; [12]Novartis Pharma AG, Basel, Switzerland; [13]Novartis Pharmaceuticals Corp, East Hanover, NJ, USA; [14]Erasmus MC, Rotterdam, The Netherlands; [15]Endocrinology, IRCCS Policlinico San Martino and DiMI, University of Genova, Genova, Italy

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

NETTER-2

First-line efficacy of ^{177}Lu-DOTATATE in patients with advanced, well-differentiated, Grade 2 or 3 GEP-NETs



2024 ESMO GASTROINTESTINAL CANCERS

Simron Singh

*Q8W during ^{177}Lu-DOTATATE treatment and then Q4W; †Octreotide LAR in retreatment phase is at the investigator's discretion.
GEP-NET, gastroenteropancreatic neuroendocrine tumor; LAR, long-acting repeatable; PD, progressive disease; PRRT, peptide receptor radionuclide therapy; Q#W, every # weeks; R, randomization; SSTR, somatostatin receptor.
Singh S, et al. J Clin Oncol 2024;42(Number 3_suppl):LBA588.

NETTER-2

^{177}Lu-DOTATATE significantly improved median PFS and increased ORR versus high-dose octreotide

Primary endpoint: PFS

- ^{177}Lu-DOTATATE significantly improved median PFS by 14 months versus high-dose octreotide

	^{177}Lu-DOTATATE (n=151)	High-dose octreotide (n=75)
Median PFS, months	22.8	8.5
Stratified hazard ratio	0.276	
95% CI	0.182, 0.418	
p-value	<0.0001	

Key secondary endpoint: ORR

- ^{177}Lu-DOTATATE significantly improved ORR by 34% versus high-dose octreotide

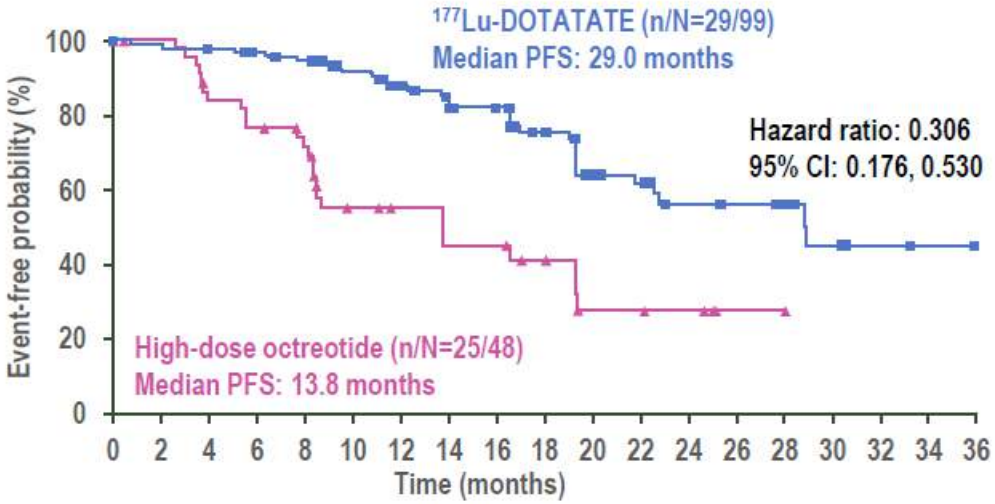
	^{177}Lu-DOTATATE (n=151)	High-dose octreotide (n=75)
ORR, n (%)	65 (43.0)	7 (9.3)
Stratified odds ratio	7.81	
95% CI	3.32, 18.40	
p-value	<0.0001	

2024 ESMO GASTROINTESTINAL CANCERS Simron Singh

CI, confidence interval; ORR, objective response rate; PFS, progression-free survival.
Singh S, et al. J Clin Oncol 2024;42(Number 3_suppl):LBA588.

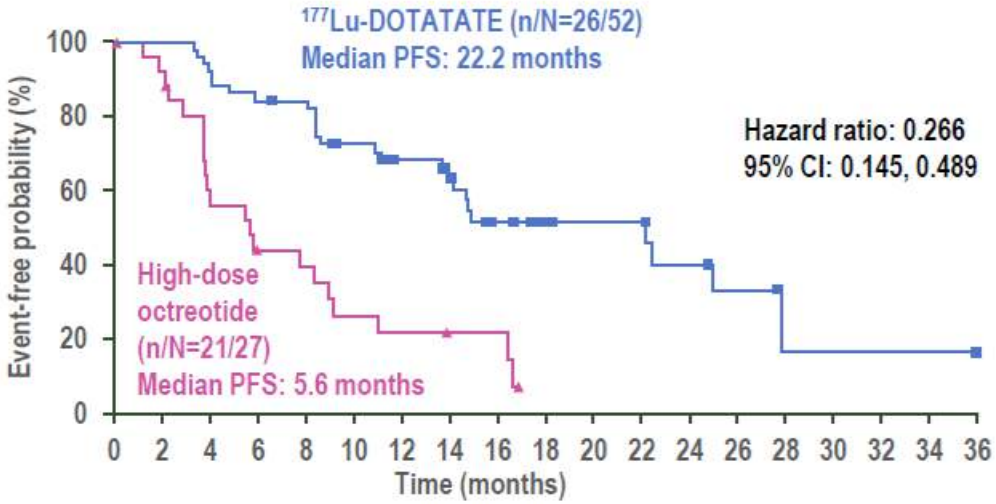
PFS BENEFIT WITH ^{177}Lu-DOTATATE WAS EVIDENT FOR PATIENTS WITH GRADE 2 AND GRADE 3 NETS

Grade 2 NET



No. at risk																			
^{177}Lu-DOTATATE	99	91	90	85	82	70	63	56	52	42	31	27	16	14	12	8	3	1	0
High-dose octreotide	48	43	35	32	28	18	16	13	13	10	5	5	4	1	1	0	0	0	0

Grade 3 NET

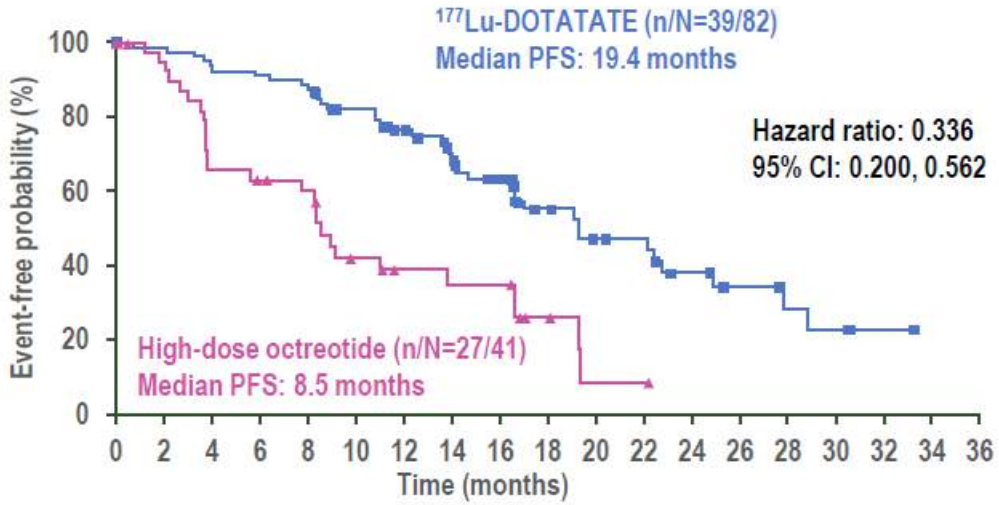


No. at risk																			
^{177}Lu-DOTATATE	52	52	48	44	43	34	29	24	16	11	10	10	7	5	1	1	1	1	0
High-dose octreotide	27	24	14	10	9	6	5	3	3	0	0	0	0	0	0	0	0	0	0

Subgroups are defined based on data from electronic case report forms.
CI, confidence interval; NET, neuroendocrine tumor; PFS, progression-free survival.

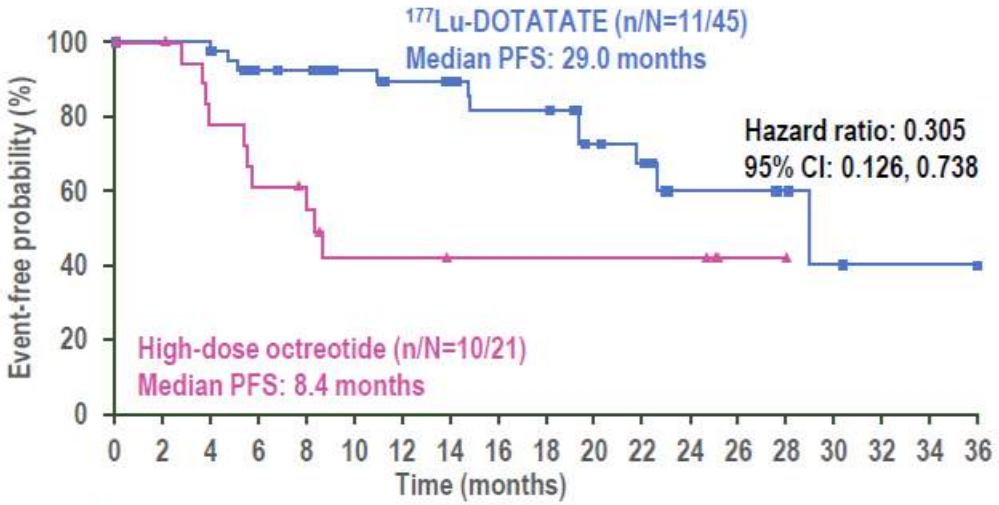
PFS BENEFIT WITH ^{177}Lu-DOTATATE WAS EVIDENT FOR PATIENTS WITH PANCREATIC AND SMALL INTESTINE NETS

Pancreatic NETs



No. at risk																		
^{177}Lu-DOTATATE	82	78	74	72	70	59	51	43	35	22	17	16	11	7	5	4	2	0
High-dose octreotide	41	36	25	23	21	13	10	9	9	4	1	1	0	0	0	0	0	0

Small intestine NETs



No. at risk																		
^{177}Lu-DOTATATE	45	41	41	35	34	28	25	24	21	21	15	13	5	5	4	2	1	1	0
High-dose octreotide	21	19	14	11	9	6	6	4	4	4	4	4	4	1	1	0	0	0	0

Subgroups are defined based on data from electronic case report forms.
CI, confidence interval; NET, neuroendocrine tumor; PFS, progression-free survival.

SUMMARY

- For PFS and ORR, a clinical benefit in favor of ^{177}Lu-DOTATATE versus high-dose octreotide was evident across all subgroups (Grade 2, Grade 3, pancreatic, and small intestine NETs)
- First-line ^{177}Lu-DOTATATE efficacy was maintained across Grade 2 and 3 NETs
  - Median PFS was 29.0 and 22.2 months, and ORR was 40.4% and 48.1%, respectively
- First-line ^{177}Lu-DOTATATE efficacy was maintained across pancreatic and small intestine NETs
  - Median PFS was 19.4 and 29.0 months, and ORR was 51.2% and 26.7%, respectively
- Time to response was similar across all subgroups
- A durable response was evident across all subgroups
- First-line ^{177}Lu-DOTATATE should be considered a standard of care for this patient population with advanced, well-differentiated, Grade 2 or 3 (Ki67 ≥10% and ≤55%), SSTR+ GEP-NETs

GEP, gastroenteropancreatic; NET, neuroendocrine tumor; ORR, objective response rate; PFS, progression-free survival; SSTR, somatostatin receptor.

Eerste reactie: nucleaire geneeskunde rukt op als DE eerstelijnstherapie voor NET

Maar tijd brengt inzicht 😇

Who are these people for PRRT first-line?

- **Meeste GEP-NET in onze praktijk zijn graad 1 of graad 2 met Ki-67 ≤10%, dus Ki-67 >10% populatie = ongeveer 20%.**
- **Niet iedereen van die 20% heeft de noodzakelijke SSTR-expressie voor PRRT.**
- **Binnen die 20% populatie zijn de pNET dominant boven de dunne darm NET.**
- **SSA in eerste lijn functioneren ook niet zo slecht in de NETTER-2 studie en geen bewijs vandaag dat 'later' gebruik van PRRT de overall survival negatief gaat beïnvloeden.**
- **Comorbiditeiten van patiënt in rekening nemen: nierfunctie en hematologische reserve…**
- **Wat wil onze patiënt eigenlijk?**
  - SSA in eerste lijn: gekende en veilige optie bij een ziekte met een globaal langer verloop.
  - PRRT toch wat complexere behandeling om het traject mee te beginnen met wat meer toxiciteiten: focus op hematologische consequenties voor therapieën in latere lijn…
  - Buiten klinische kenmerken die keuze kunnen sturen, zijn er geen goede biomerkers voorhanden…
  - Nog geen quality of life data voorhanden van NETTER-2…
  - Wat met het financieel plaatje: kosten-baten PRRT vs. SSA?
  - Als wachttijd voor PRRT ergens in de wereld een issue is…

Faire conclusie op dit moment

DNETS
2e DBNETS congres • 2024

- **<u>EEN TE INDIVIDUALISEREN</u> standard-of-care optie bij de advanced, well-differentiated SSTR+ GEP-NET graad 2-3 (Ki-67 ≥10% en ≤ 55%):**
  - Hogere tumor burden, wanneer response ratio belangrijk is
  - Symptomatische ziekte
  - Agressievere NET ziekte

- **Graad 3 gastro-intestinale NET (extra-pancreatisch).**
- **Hogere graad 2 gastro-intestinale NET met symptomatische ziekte tengevolge van tumor burden.**

- **Symptomatische/bulky graad 3 pNET: concurrentie van 'snel' capecitabine + temozolomide.**
- **Symptomatische/bulky hogere graad 2 pNET: concurrentie van 'snel' capecitabine + temozolomide.**
- **Rustige hogere graad 2 GEP-NET (Ki-67 10-20%): concurrentie van everolimus.**

- **Rustige GEP-NET met Ki-67 aan het lagere segment van de 10-55% range: 'kat uit de boom kijken' met SSA.**

SPINET: niet helemaal gelukt, maar duidelijke conclusie

Society for Endocrinology

Endocrine-Related Cancer (2024) **31** e230337
https://doi.org/10.1530/ERC-23-0337

Received 11 December 2023
Accepted 24 June 2024
Available online 24 June 2024
Version of Record published 22 July 2024

RESEARCH

Treatment of advanced BP-NETS with lanreotide autogel/depot vs placebo: the phase III SPINET study

E Baudin[1], J Capdevila[2], D Hörsch[3], S Singh[4], M E Caplin[5], E M Wolin[6], W Buikhuisen[7], M Raderer[8], E Dansin[9], C Grohe[10], D Ferone[11], A Houchard[12], X-M Truong-Thanh[13] and D Reidy-Lagunes[14] on behalf of the SPINET Study Group

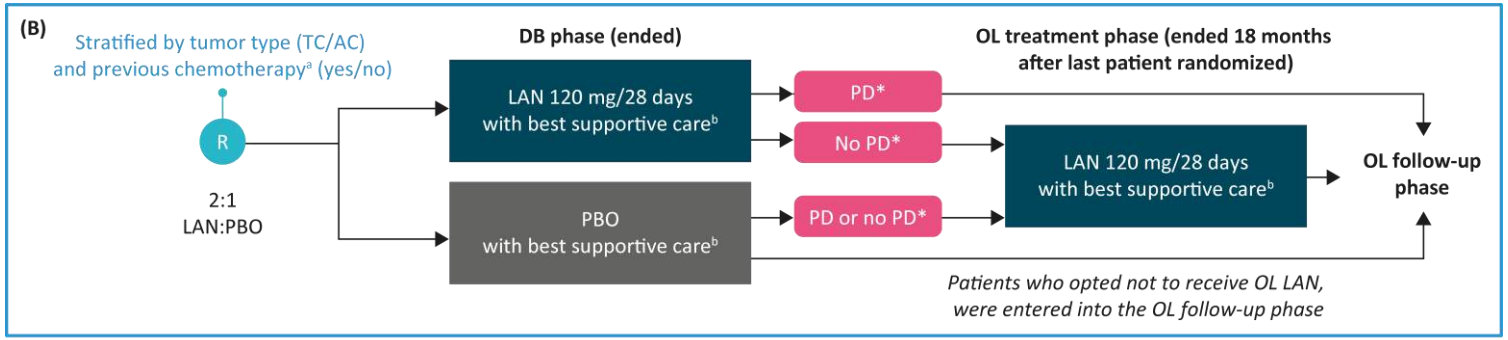
Phase 3 SPINET study design

ENETS EUROPEAN NEUROENDOCRINE TUMOR SOCIETY

NETS 2e DBNETS congres • 2024

- **Protocol terminated early owing to slow accrual of patients and amended**
  - DB LAN patients without PD and all DB PBO patients could transition to OL-LAN
- **Primary endpoint (adapted):**
  - Centrally assessed median PFS in patients randomized to LAN (DB and OL-LAN phases)

- **Secondary endpoint:**
  - Changes from baseline in serum CgA levels (x ULN)
- **Exploratory endpoint:**
  - Centrally assessed TGR (% increase in target-tumor volume per month)

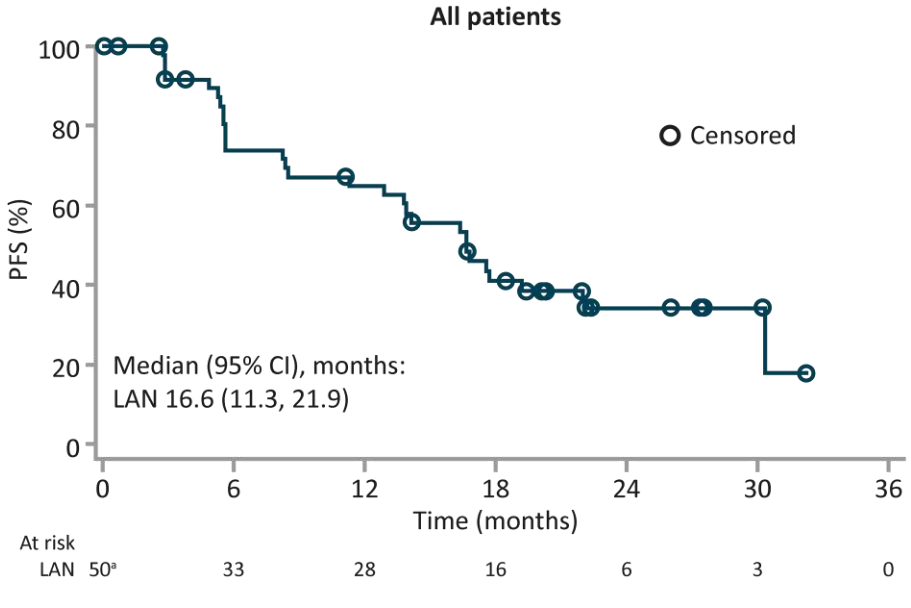


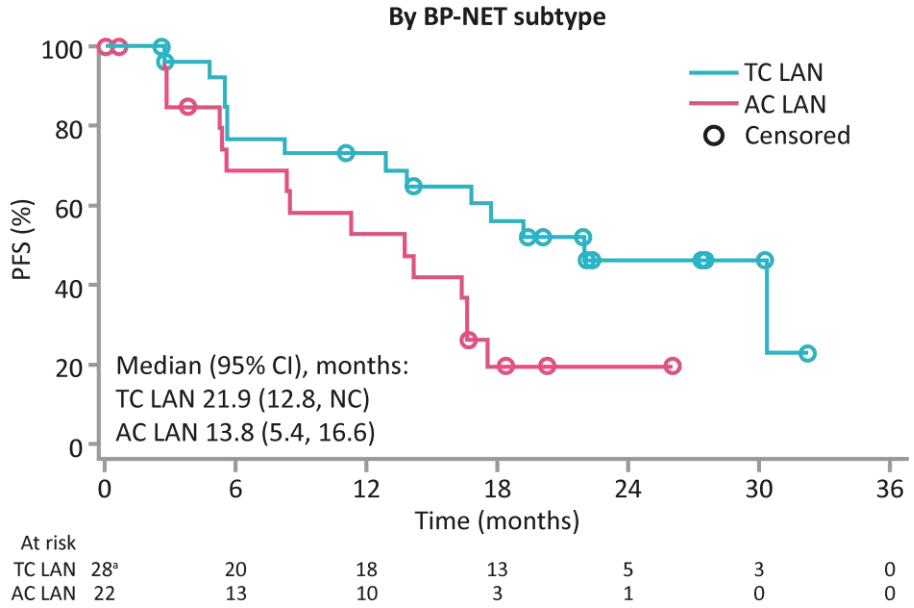
- **Patients were randomized 2:1 to LAN or PBO (planned sample size, N = 216), and stratified by tumor type and previous chemotherapy**
- **Overall, 77 patients were randomized and treated during the DB phase**
  - LAN, n = 51; Placebo, n = 26
- **In total, 40 patients from the DB phase entered the OL-LAN phase**
  - LAN/LAN, n = 21; Placebo/LAN, n = 19

*Centrally confirmed. [a]Includes cytotoxic chemotherapy, molecular targeted therapy, or interferon-alpha. [b]Symptomatic treatment for acid reflux, pain, etc
AC, atypical carcinoid; CgA, chromogranin A; DB, double blind; LAN, lanreotide autogel/depot; OL, open label; OL-LAN, open-label lanreotide autogel/depot; PBO, placebo; PFS, progression-free survival; PD, progressive disease; R, randomization; TC, typical carcinoid; TGR, tumor growth rate; ULN, upper limit of normal

Results: PFS during DB and OL-LAN phases (ITT population)

- **Median (95% CI) PFS was:**
  - 16.6 months (11.3, 21.9) in the LAN-randomized group
  - 21.9 months (12.8, NC) in TC type BP-NETs
  - 13.8 months (5.4, 16.6) in AC type BP-NETs





PFS was assessed by central review. **Analysis updated in 2022.** [a]One patient should have been censored in the PFS analysis for treatment discontinuation for toxicity or other reasons; however, the baseline central radiological assessment was performed prior to the randomization date and the patient was therefore excluded from the analysis. AC, atypical carcinoid; BP-NET, bronchopulmonary neuroendocrine tumor; CI, confidence interval; DB, double blind; ITT, intention-to-treat; LAN, lanreotide autogel/depot; NC, not calculable; OL, open label; OL-LAN, open-label lanreotide autogel/depot; PFS, progression-free survival; TC, typical carcinoid

Faire conclusie SPINET

- **Despite lower-than-target enrolment, SPINET is the largest prospective study to date of SSA therapy in SSTR-positive TC and AC. The study provides clinically important data about the activity and tolerability profile of LAN 120 mg every 28 days in unresectable and/or metastatic BP-NET.**

- **The results of SPINET provide much-needed data to support the clinical use of SSA in BP-NET, mainly TC.**

➢ **Eerst dus SSA en dan everolimus bij rustige SSTR+ ziekte.**

➢ **Everolimus bij minder rustige SSTR+ ziekte en bij SSTR- ziekte… chemotherapie later…**

➢ **Uitkijken naar phase 3 LEVEL trial:**

^{177}Lu-edotreotide vs. everolimus in patients with advanced NET of lung or thymic origin (treatment naïve or progressed on SSA or ≤2 additional systemic treatments)

Update SEQTOR op ESMO 2024

BARCELONA 2024 ESMO congress

Multivariable Analysis of Streptozotocin plus 5-Fluorouracil and Everolimus Sequences in Advanced Pancreatic Neuroendocrine Tumor patients: The SEQTOR Trial (GETNE-1206)

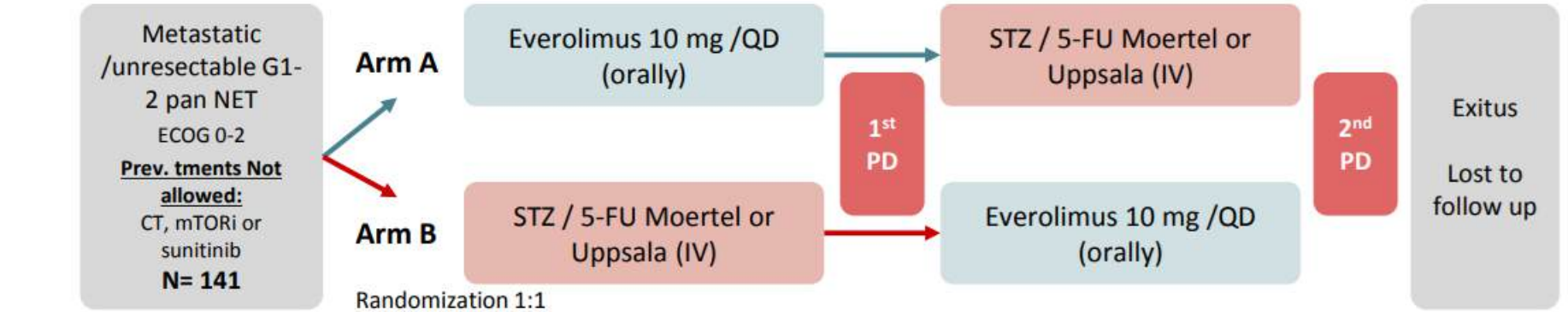
Jaume Capdevila, Salvatore Tafuto, Merete Krogh, Alex Teulé, Rocio Garcia-Carbonero, Heinz Josef Klümpen, Birgit Cremer, Isabel Sevilla, Barbro Eriksson, Elizaveta Mitkina Tabaksblat, Jean-Philippe Metges, Nicholas Simon Reed, Joerg Schrader, Silvia Bozzarelli, Ulrich Knigge, Paula Jiménez-Fonseca, Marta Benavent Vinuales, Marino Venerito, Valentí Navarro, Ramón Salazar.

Grupo Español de Tumores Neuroendocrinos y Endocrinos (GETNE)

Update SEQTOR op ESMO 2024

STUDY DESIGN & METHODS

GETNE
Grupo Español de Tumores Neuroendocrinos y Endocrinos



Today we present the multivariable analysis of PFS_1 and OS (Cox Regression) and RR (Logistic Regression) adjusted by treatment arm.

BARCELONA 2024 ESMO congress

Presented by Dr. SALAZAR in ESMO 2024

Update SEQTOR op ESMO 2024

SUMMARY & CONCLUSIONS

GETNE
Grupo Español de Tumores Neuroendocrinos y Endocrinos

Summary	❖ High tumor burden, ECOG 1/2 and sex (female) are independent poor prognostic factor. ❖ The sequence of everolimus followed by STZ/5-FU performed better in patients with grade 1 in PFS_1 and in treatment-naïve patients in OS. ❖ Upfront STZ/5-FU is more effective to obtain treatment responses in patients with grade 2 tumors.
Conclusion	❖ In the SEQTOR trial, everolimus upfront showed better outcomes in patients with treatment-naïve or grade 1 panNETs, whereas STZ/5-FU can be recommended in patients with grade 2 when tumor shrinkage is clinically relevant.

BARCELONA 2024 ESMO congress

Presented by Dr. SALAZAR in ESMO 2024

Update CABINET op ESMO 2024

NETS
2e DBNETS congres • 2024

BARCELONA 2024 ESMO congress

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

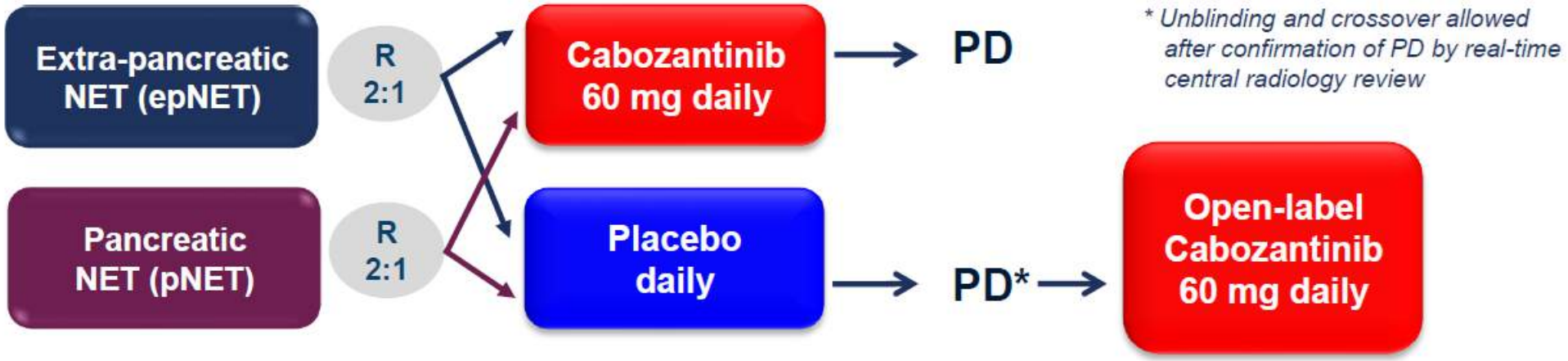
NCI National Clinical Trials Network
a National Cancer Institute program

Cabozantinib Versus Placebo for Advanced Neuroendocrine Tumors after Progression on Prior Therapy (CABINET Trial/Alliance A021602)

Updated Results Including Progression Free-Survival by Blinded Independent Central Review and Subgroup Analyses

Jennifer A Chan, Susan Geyer, Tyler Zemla, Michael V Knopp, Spencer Behr, Sydney Pulsipher, Jared Acoba, Ardaman Shergill, Edward M Wolin, Thorvardur R Halfdanarson, Bhavana Konda, Nikolaos A Trikalinos, Shagufta Shaheen, Namrata Vijayvergia, Arvind Dasari, Jonathan R Strosberg, Elise C Kohn, Matthew H Kulke, Eileen M O'Reilly, Jeffrey A Meyerhardt

CABINET Trial Design



Stratification factors:

- epNET: Concurrent SSA & Primary site (midgut GI/unknown vs. non-midgut GI/lung/other)
- pNET: Concurrent SSA & Prior sunitinib

Study Endpoints:

- **Primary Endpoint per cohort:**
  - **Progression-free survival (PFS) by blinded independent central review (BICR)**
- **Secondary Endpoint per cohort:**
  - **Overall survival (OS)**
  - **Objective response rate (ORR)**
  - **Safety and tolerability**

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Key Inclusion Criteria

- Well- to moderately differentiated NET, grades 1-3
- Disease progression by RECIST within 12 months prior to randomization
- Progression or intolerance of at least 1 prior FDA-approved systemic therapy, not including somatostatin analogs (SSA)
  - Includes everolimus, sunitinib, or Lu-177 dotatate for pNET
  - Includes everolimus for lung NET
  - Includes everolimus or Lu-177 dotatate for GI-NET
- Concurrent SSA allowed provided stable dose for ≥ 2 months

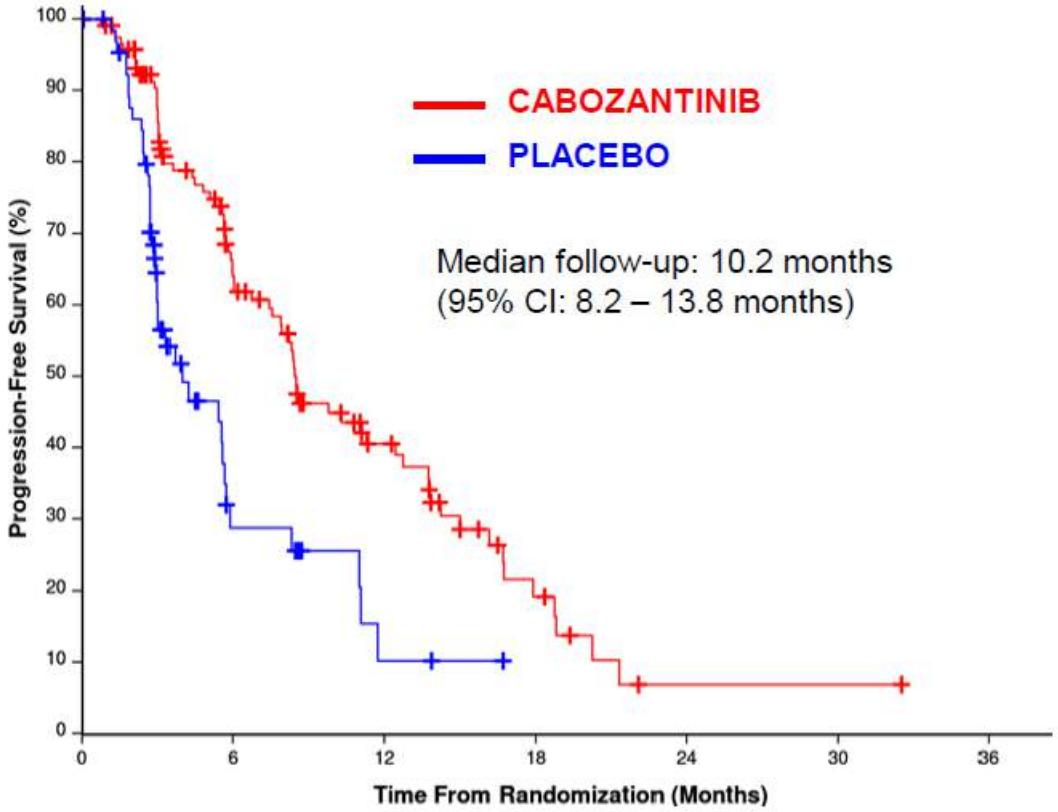
Extra-pancreatic NET: Baseline Characteristics

	CABOZANTINIB (N=134)	PLACEBO (N=69)
Time from diagnosis to randomization, months, median (range)	65 (10-489)	76 (13-340)
Age, years, median (range)	66 (28-86)	66 (30-82)
Female sex, n (%)	74 (55)	31 (45)
White race, n (%)	115 (86)	55 (80)
ECOG PS, n (%)		
0	49 (37)	32 (46)
1	84 (63)	36 (52)
2	1 (1)	1 (1)
Differentiation, n (%)		
Well	118 (88)	61 (88)
Moderate	6 (5)	5 (7)
Not specified	10 (8)	3 (4)
Grade, n (%)		
G1	37 (28)	15 (22)
G2	86 (64)	48 (70)
G3	8 (6)	5 (7)
Unknown	3 (2)	1 (1)

	CABOZANTINIB (N=134)	PLACEBO (N=69)
Primary tumor site, n (%)		
Gastrointestinal	70 (52)	46 (67)
Lung	27 (20)	12 (17)
Thymus	6 (5)	4 (6)
Unknown	22 (16)	2 (3)
Other	5 (4)	2 (3)
Pancreas*	4 (3)	3 (4)
Hormone syndrome present, n (%)	41 (31)	25 (36)
Concurrent SSA, n (%)	92 (69)	48 (70)
Prior SSA, n (%)	125 (93)	64 (93)
Number of prior systemic therapies, median (range)	2 (1-6)	2 (1-6)
Prior systemic therapy, n (%)		
Lu-177 dotatate	80 (60)	41 (59)
Everolimus	96 (72)	44 (64)
Temozolomide +/- capecitabine	43 (32)	20 (29)
Platinum + etoposide	11 (8)	8 (12)

**7 patients with pNET were misallocated to the epNET cohort*

epNET Cohort: Progression-Free Survival
Blinded Independent Central Review



Stratified HR = 0.38
(95% CI: 0.25 – 0.59)
log-rank p<0.0001

Median PFS
Cabozantinib = 8.4 months
(95% CI: 7.6 – 12.7 months)
Placebo = 3.9 months
(95% CI: 3.0 – 5.7 months)

BARCELONA 2024 ESMO congress

Jennifer Chan, MD, MPH

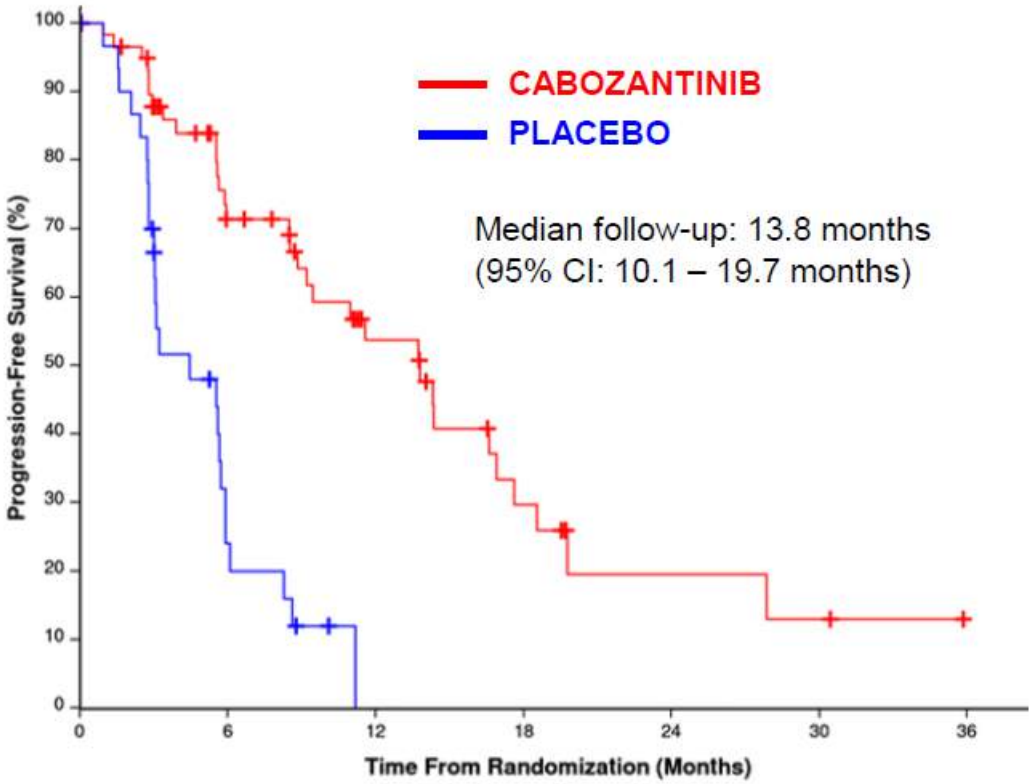
Pancreatic NET: Baseline Characteristics

	CABOZANTINIB (N= 64)	PLACEBO (N=31)
Time from Diagnosis to Randomization, median, months (range)	71 (18-213)	73 (18-230)
Age, years, median (range)	60 (29-79)	64 (39-79)
Female sex, n (%)	27 (42)	13 (42)
White race, n (%)	54 (84)	25 (81)
ECOG PS, n (%)		
0	35 (55)	15 (48)
1	28 (44)	16 (52)
2	1 (2)	0
Differentiation, n (%)		
Well	59 (92)	30 (97)
Moderate	4 (6)	0
Not specified	1 (2)	1 (3)
Grade, n (%)		
G1	14 (22)	7 (23)
G2	39 (61)	19 (61)
G3	8 (13)	3 (10)
Unknown	3 (5)	2 (7)

	CABOZANTINIB (N= 64)	PLACEBO (N=31)
Primary tumor site		
Pancreas	62 (97)	30 (97)
Ileum*	1 (2)	0
Cecum*	0	1 (3)
Stomach*	1 (2)	0
Hormone syndrome present, n (%)	11 (17)	5 (16)
Concurrent SSA, n (%)	35 (55)	17 (55)
Prior SSA, n (%)	63 (98)	30 (97)
Number of prior systemic therapies, median (range)	3 (1-9)	2 (1-7)
Prior systemic therapy, n (%)		
Lu-177 dotatate	38 (59)	18 (58)
Everolimus	51 (80)	25 (81)
Sunitinib	18 (28)	7 (23)
Temozolomide +/- capecitabine	43 (67)	16 (52)

**3 patients with epNET were misallocated to the pNET cohort*

pNET Cohort: Progression-Free Survival
Blinded Independent Central Review



Stratified HR = 0.23
(95% CI: 0.12 – 0.42)
log-rank p<0.0001

Median PFS
Cabozantinib = 13.8 months
(95% CI: 9.2 – 18.5 months)
Placebo = 4.4 months
(95% CI: 3.0 – 5.9 months)

BARCELONA 2024 ESMO congress

Jennifer Chan, MD, MPH

Treatment Exposure and Patient Disposition

epNET Cohort

	CABOZANTINIB (N=132)	PLACEBO (N=67)
Duration of therapy, median (range)	5.5 months (0.2-32.4)	2.8 months (0.6-21.4)
Dose reduction required, %	66%	10%
Average daily dose, median	38.4 mg	59.0 mg
Treatment ongoing, n (%)	21 (16)	7 (10)
Off treatment, n (%)	111 (84)	60 (90)
Progressive disease	52 (47)	38 (63)
Adverse events	34 (31)	9 (15)
Withdrawn consent	7 (6)	4 (7)
Death on Study	6 (5)	3 (5)
Other reason	6 (5)	4 (7)
Alternative therapy	5 (5)	1 (2)
Other disease	1 (1)	1 (2)

pNET Cohort

	CABOZANTINIB (N=63)	PLACEBO (N=31)
Duration of therapy, median (range)	8.3 months (0.5-39.6)	2.9 months (0.5-11.2)
Dose reduction required, %	68%	19%
Average daily dose, median	37.9 mg	56.9 mg
Treatment Ongoing, n (%)	14 (22)	2 (6)
Off treatment, n (%)	49 (78)	29 (94)
Progressive Disease	28 (57)	23 (79)
Adverse Events	10 (20)	0
Withdrawn consent	5 (10)	4 (14)
Other disease	2 (4)	0
Alternative treatment	1 (2)	0
Other reason	3 (6)	2 (7)

epNET: Treatment-Related Adverse Events

	CABOZANTINIB (N=132)		PLACEBO (N=67)	
	Any grade	Grades 3-4	Any grade	Grades 3-4
Any adverse event	130 (98)	82 (62)	55 (82)	18 (27)
AST increase	86 (65)	4 (3)	12 (18)	0
Fatigue	82 (62)	17 (13)	28 (42)	5 (8)
ALT increase	77 (58)	1 (1)	9 (13)	0
Diarrhea	74 (56)	14 (11)	20 (30)	3 (5)
Hypertension	70 (53)	28 (21)	13 (19)	2 (3)
Thrombocytopenia	62 (47)	1 (1)	5 (8)	1 (2)
Mucositis oral	48 (36)	5 (4)	6 (9)	0
Palmar-plantar erythrodysesthesia	48 (36)	4 (3)	5 (8)	0
Nausea	46 (35)	2 (2)	10 (15)	0
Leukopenia	46 (35)	4 (3)	2 (3)	0
Dysgeusia	45 (34)	0	1 (2)	0
Anorexia	40 (30)	2 (2)	6 (9)	0
Neutropenia	40 (30)	4 (3)	2 (3)	0
Hypothyroidism	36 (27)	0	1 (2)	0

BARCELONA 2024 ESMO congress

Grade 5 events in cabozantinib arm possibly related to study therapy:
n=1 gastrointestinal hemorrhage; n=1 cardiac arrest; n=2 death not otherwise specified

pNET: Treatment-Related Adverse Events

	CABOZANTINIB (N=63)		PLACEBO (N=31)	
Adverse Event, n (%)	Any grade	Grades 3-4	Any grade	Grades 3-4
Any Adverse Event	62 (98)	41 (65)	26 (84)	7 (23)
Fatigue	47 (75)	7 (11)	10 (32)	1 (3)
AST increase	40 (63)	1 (2)	9 (29)	0
ALT increase	39 (62)	1 (2)	9 (29)	0
Diarrhea	37 (59)	4 (6)	4 (13)	0
Hypertension	36 (57)	14 (22)	7 (23)	3 (10)
Mucositis oral	30 (48)	5 (8)	1 (3)	0
Palmar-plantar erythrodysesthesia	28 (44)	6 (10)	4 (13)	0
Nausea	24 (38)	5 (8)	7 (23)	1 (3)
Thrombocytopenia	21 (33)	0	3 (10)	0
Dysgeusia	19 (30)	0	3 (10)	0
Neutropenia	17 (27)	1 (2)	2 (7)	0
Thromboembolic event	11 (18)	7 (11)	0	0

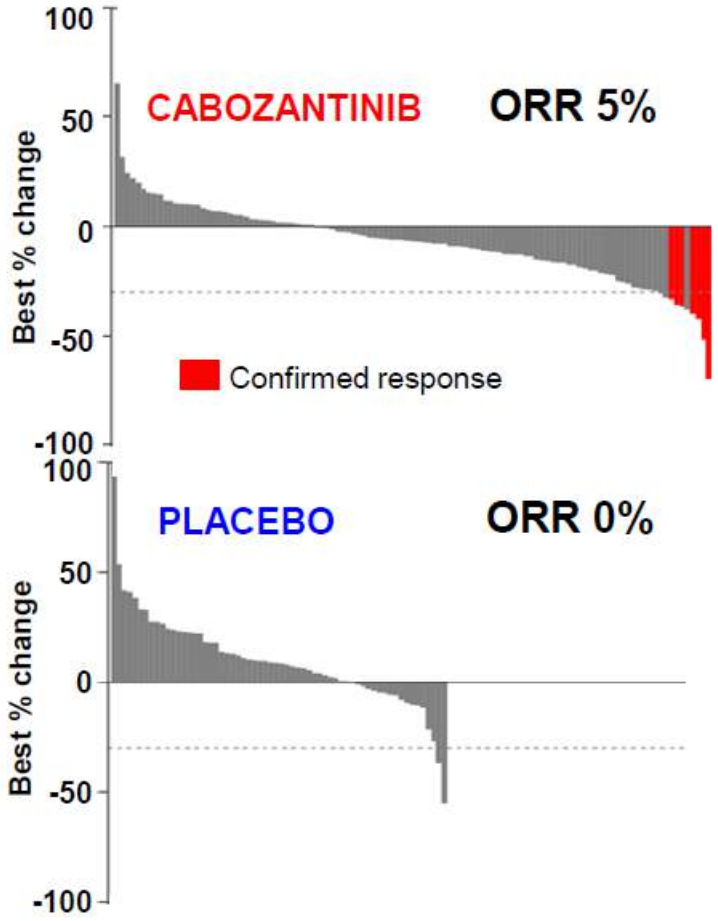
BARCELONA 2024 ESMO congress

*No treatment-related Grade 5 adverse events in the pNET cohort

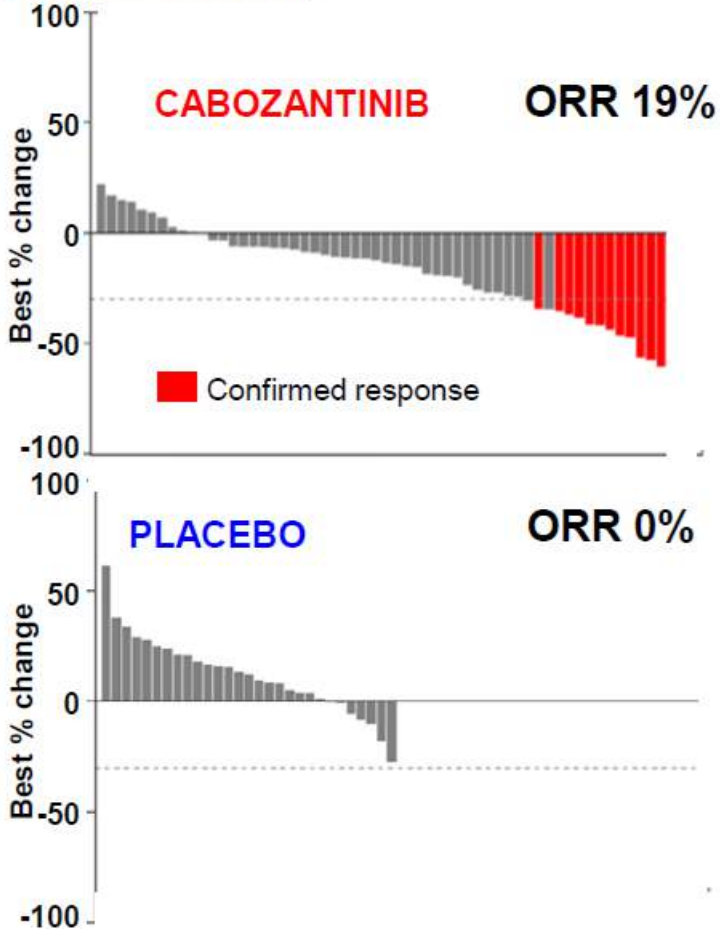
Update CABINET op ESMO 2024

Confirmed Objective Response (BICR)

epNET Cohort

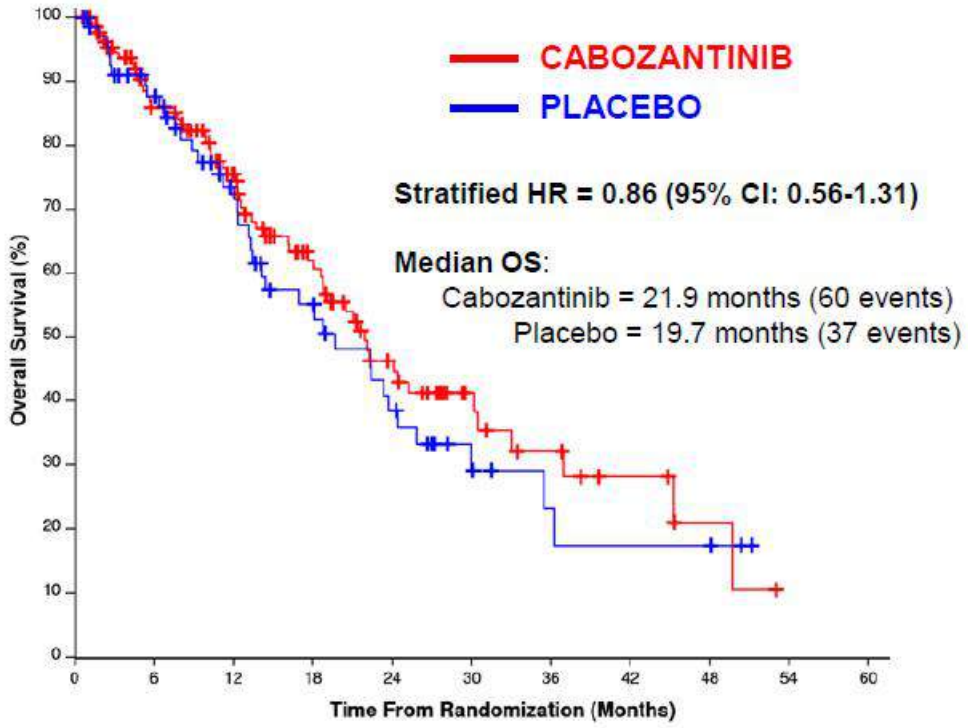


pNET Cohort

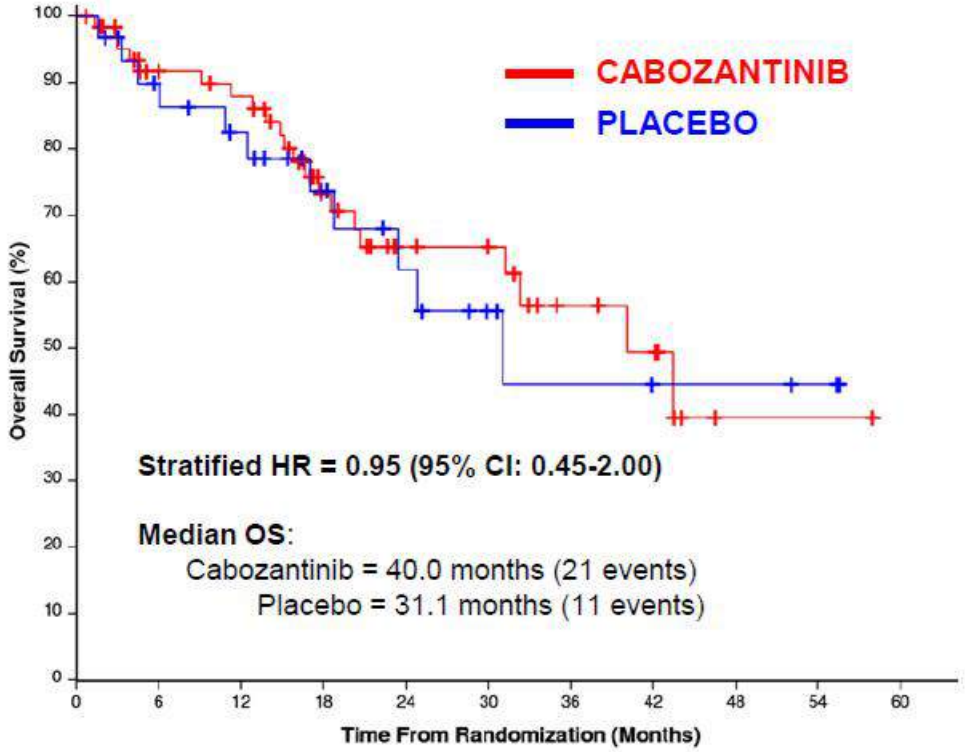


Overall Survival – Interim Analysis

epNET Cohort



pNET Cohort



Conclusions

- Cabozantinib significantly improves PFS in patients with previously treated, progressive extra-pancreatic or pancreatic NET
  - Subgroup analyses suggest benefits for cabozantinib across all clinical subgroups, including primary tumor site, grade, and prior anticancer therapy
- Adverse events are consistent with the known safety profile of cabozantinib
  - A majority of patients treated with cabozantinib required dose modifications or reductions to manage adverse events
- CABINET represents one of the first randomized studies specifically designed to evaluate efficacy of therapy following treatment with Lu-177 dotatate and/or targeted therapy
- Cabozantinib should be a new treatment option for patients with previously treated extra-pancreatic or pancreatic NET

Update CABINET op ESMO 2024

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of Cabozantinib to Treat Advanced Neuroendocrine Tumors

Jennifer A. Chan, M.D., M.P.H., Susan Geyer, Ph.D., Tyler Zemla, M.S., Michael V. Knopp, M.D., Ph.D., Spencer Behr, M.D., Sydney Pulsipher, M.P.H., Fang-Shu Ou, Ph.D., Amylou C. Dueck, Ph.D., Jared Acoba, M.D., Ardaman Shergill, M.D., Edward M. Wolin, M.D., Thorvardur R. Halfdanarson, M.D., Bhavana Konda, M.D., M.P.H., Nikolaos A. Trikalinos, M.D., Bernard Tawfik, M.D., Nitya Raj, M.D., Shagufta Shaheen, M.D., Namrata Vijayvergia, M.D., Arvind Dasari, M.D., Jonathan R. Strosberg, M.D., Elise C. Kohn, M.D., Matthew H. Kulke, M.D., Eileen M. O'Reilly, M.D., and Jeffrey A. Meyerhardt, M.D., M.P.H.

Vragen die open blijven na CABINET…

DNETS
2e DBNETS congres • 2024

- **Waar plaatsen we cabozantinib in het behandelingsalgoritme van NET?** Na SSA en PRRT onmiddellijk cabozantinib of gaan we eerst het rijtje af van de andere therapieën die er zijn?
- **Gezien de toxiciteit van cabozantinib:** beginnen we systematisch met 60 mg/dag en verminderen we de dosis bij toxiciteit, of beginnen we met 40 mg/dag en titreren we de dosis op in functie van neveneffecten?
- **Wat vinden patiënten van cabozantinib?** Quality of life data? Patient-reported outcome measures?

➢ **The Food and Drug Administration (FDA) has accepted for review the supplemental New Drug Application for cabozantinib for adults with previously treated, locally advanced/unresectable or metastatic, well- or moderately-differentiated pNET, and for adults with previously treated, locally advanced/unresectable or metastatic, well- or moderately-differentiated epNET.**

EverSun trial

- **Sequential everolimus and sunitinib treatment in progressive, advanced, pancreatic NEN: real-world data from the Belgian Group of Digestive Oncology DNET & NETwerk**

- **Rationale**
  - Vaak sequentiële behandeling → **optimale behandelingssequentie?**
  - Angelousi et al. 2017
    - Retrospectieve studie
    - 31 patiënten met sequentiële behandeling
    - Ever-Sun groep vs. Sun-Ever groep
    - Geen statistisch significante verschillen in OS of mPFS in beide groepen

Sequential Everolimus and Sunitinib Treatment in Pancreatic Metastatic Well-Differentiated Neuroendocrine Tumours Resistant to Prior Treatments

Anna Angelousi[a] Kimberly Kamp[b] Maria Kaltsatou[a] Dermot O'Toole[c] Gregory Kaltsas[a] Wouter de Herder[b]

[a]Sector of Endocrinology, Department of Pathophysiology, National & Kapodistrian University of Athens, Athens, Greece; [b]Sector of Endocrinology, Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands; [c]St. Vincent's University and Department of Clinical Medicine, St. James Hospital and Trinity College, Dublin, Ireland

EverSun trial

- **Besluit**
  - Meer inzichten in de sequentiële behandeling van goed gedifferentieerde gemetastaseerde pNET met everolimus en sunitinib:
    - Geen statistisch significant verschil in mOS tussen beide behandelgroepen.
    - Geen statistisch significant verschil in mPFS, mPFS1 en mPFS2 tussen beide behandelgroepen.
    - Geen statistisch significant verschil in AE's tussen beide groepen.

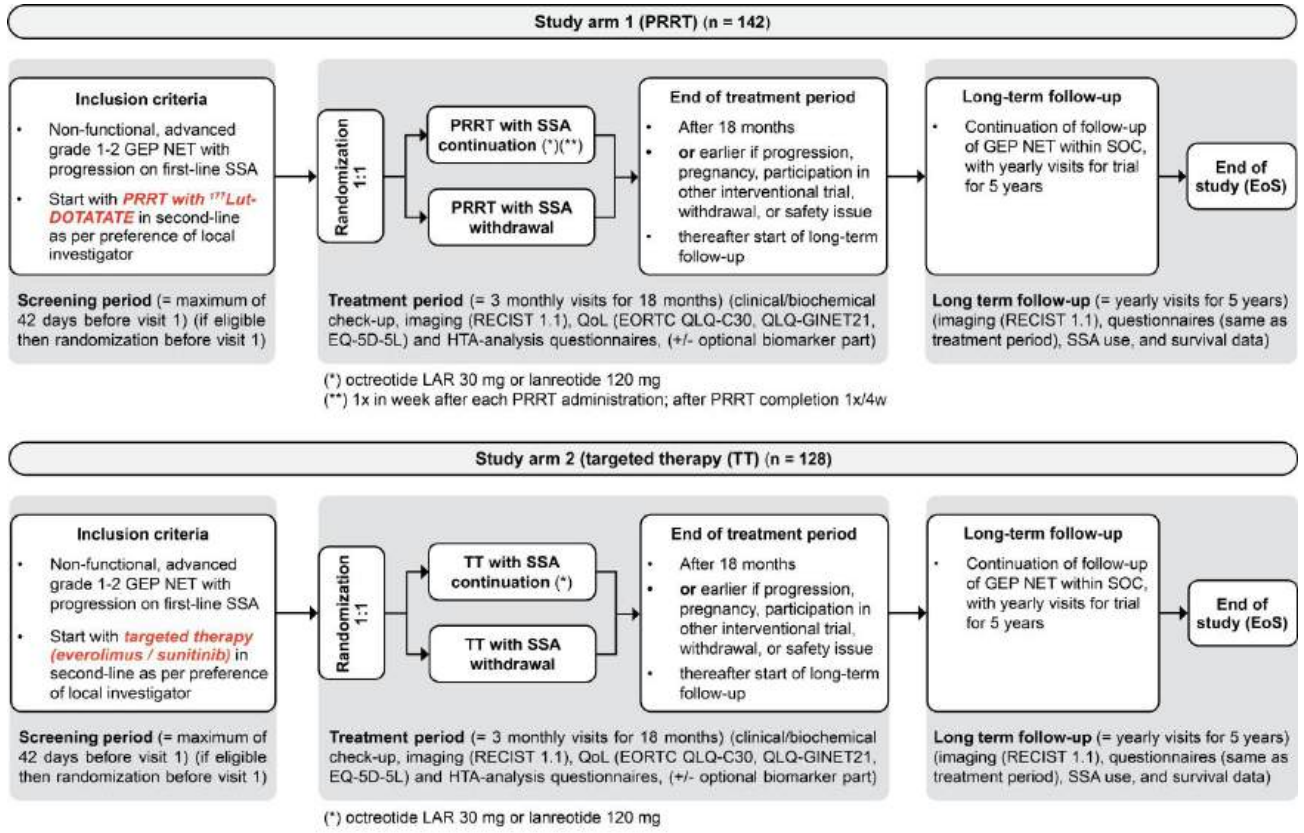
➢ **Behandelingsmodaliteiten lijken gelijkwaardig in beide sequenties.**

➢ Nood aan prospectieve studies voor betere inzichten *die er wellicht niet komen*!

Update SAUNA trial

2e DBNETS congres • 2024

- **Studie opzet**

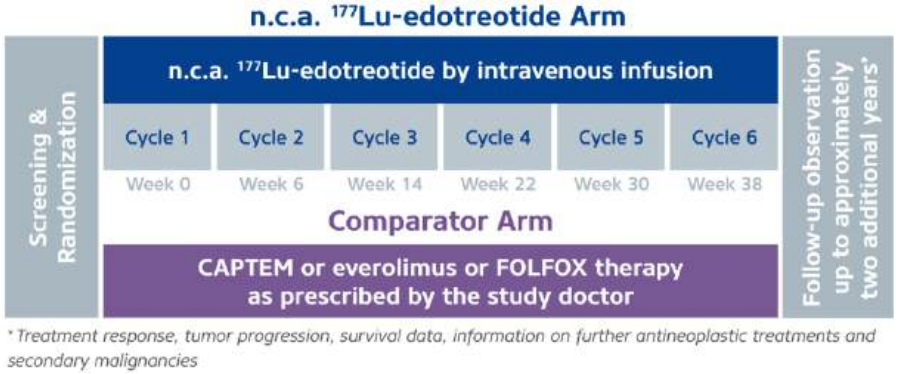


- **Studie status**
  - Studie loopt in 19 ziekenhuizen in BE/NL
  - 29 gerandomiseerde patiënten
    - PRRT: 23
    - Targeted Therapy: 6
  - 5 End of Study patiënten

- **retroSAUNA**
  - Retrospectieve zusje van SAUNA
  - Primair eindpunt: OS per substudie
  - Momenteel in opstart → resultaten in 2026
  - 10 ziekenhuizen in BE/NL/FR

COMPOSE: phase 3 trial of ^{177}Lu-edotreotide versus standard-of-care in well-differentiated (WD) aggressive grade 2 and grade 3 GEP-NET trial

- **BJ Hernando (Spain)**
  - Ongoing phase 3 trial in G2 and G3 GEP-NET exploring efficacy and safety of ^{177}Lu-edotreotide vs. eve/CAPTEM/FOLFOX. COMPOSE (NCT04919226), to extend therapeutic options for ^{177}Lu-edotreotide to high-grade NET
  - Inclusion criteria: patients aged ≥18 years; histologically confirmed diagnosis of unresectable, WD (high G2 or G3) GEP-NET; SSTR+ disease
  - Exclusion criteria: prior PRRT; major surgery within 4 weeks prior to randomization; other known malignancies; renal, hepatic, cardiovascular or hematological organ dysfunction, potentially interfering with the safety of the trial treatments
  - **Primary endpoint: PFS (RECIST v1.1), assessed every 12 weeks**
  - Secondary endpoints: OS, assessed up to 2 years after disease progression



N=202 patients (1:1 randomization)

Recruitment started: September 2021

First patient screened in France

- **Take home messages**
  - Trial in progress
  - To provide first prospective, controlled data for ^{177}Lu-edotreotide, CAPTEM, FOLFOX and eve in treatment of patients with high G2 and G3 GEP-NET, clarifying the positioning of ^{177}Lu-edotreotide in the therapeutic algorithm

CAPTEM: capecitabine + temozolomide; eve: everolimus; FOLFOX: folinic acid, fluorouracil + oxaliplatin; G: grade; GEP-NET: gastroenteropancreatic NET; NET: neuroendocrine tumor; PFS: progression-free survival; PRRT: peptide receptor radionuclide therapy; OS: overall survival; RECIST: response evaluation criteria in solid tumors; SSTR: somatostatin receptor; WD: well-differentiated.

COMPETE phase 3 trial

NETS
2e DBNETS congres • 2024

COMPETE Phase III Trial – Peptide Receptor Radionuclide Therapy (PRRT) with Lutetium (^{177}Lu) Edotreotide vs. Everolimus in Patients with Progressive GEP-NETs

J.R. Strosberg,[1] A.M. Avram,[2] C.M. Aparici,[3] M.M. Wahba[4]

[1]Department of Gastrointestinal Oncology, Moffitt Cancer Center, Tampa, FL, USA; [2]University of Michigan Medical Center, Ann Arbor, MI, USA; [3]Department of Radiology, Stanford University, CA, USA; [4]Corresponding Author: ITM Isotopen Technologien Muenchen AG, Munich, Germany, Email: Mona.Wahba@itm.ag; Study sponsored by: ITM Solucin GmbH, Lichtenbergstrasse 1, 85748 Garching near Munich, Germany

compete

Background

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are relatively rare and complex neoplasms. Their incidence and prevalence are continuously rising[1]. Current standard treatment options for metastasized GEP-NETs include somatostatin (SST) analogs (due to NETs strongly expressing SST receptors) and targeted drugs such as the mTOR inhibitor everolimus and the tyrosine kinase inhibitor sunitinib. While these treatments rarely induce objective tumor remission, disease stabilization may be achieved for a limited time, for instance, median progression free survival (mPFS) with everolimus in prospective phase III trials is 11 months[2]. Some patients may also benefit from systemic chemotherapy.

Peptide Receptor Radionuclide Therapy (PRRT) uses IV-infused radiolabeled ligands to deliver cytotoxic dose of radiation to tumor cells while sparing the surrounding tissue. This therapy is emerging as a promising option, providing more durable response and potentially higher objective response rates than currently approved therapies. PRRT with ^{177}Lu-DOTATATE has increased PFS and achieved higher response rates than high dose octreotide in patients with advanced SSTR+ midgut NETs[3]. These results call for additional prospective, randomized and controlled study of other PRRTs in SSTR+ NETs of the midgut and other locations.

Lutetium (^{177}Lu) edotreotide (^{177}Lu-DOTATOC), tested in the COMPETE trial, is an innovative octreotide-derived somatostatin analog containing the chelator DOTA radiolabeled with the medical radioisotope lutetium (^{177}Lu). Its favorable safety profile and promising efficacy have been demonstrated in a phase II study in 56 patients[4]. Lutetium (^{177}Lu) edotreotide PRRT in metastasized GEP-NETs achieved a median PFS of 34.5 months in patients who received ≥2 treatment cycles (Figures 1 and 2). The COMPETE trial is the first to undertake a direct comparison of PRRT vs. an approved therapeutic.

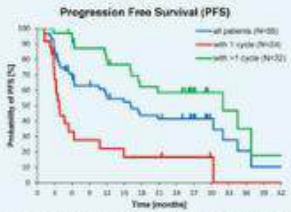


Figure 1: Kaplan-Meier estimates of PFS in the study population depending on number of lutetium (^{177}Lu) edotreotide PRRT cycles (Baum et al, 2016)

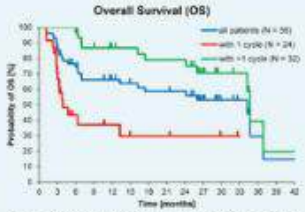


Figure 2: Kaplan-Meier estimates of OS in the study population depending on number of lutetium (^{177}Lu) edotreotide PRRT cycles (Baum et al, 2016)

Method

Trial design

COMPETE is a prospective, randomized, controlled, open-label, multi-center, phase III clinical trial to evaluate the efficacy and safety of lutetium (^{177}Lu) edotreotide PRRT compared to targeted molecular therapy with everolimus in patients with inoperable, progressive, somatostatin receptor-positive (SSTR+) GEP-NETs. The study is ongoing and currently recruiting patients in at least 14 countries[5].

300 patients with progressive Grade 1 and Grade 2 GEP-NETs are being randomized: 200 patients receive up to 4 cycles of lutetium (^{177}Lu) edotreotide PRRT (7.5 GBq/cycle) every 3 months or until diagnosis of progression; 100 patients receive 10 mg everolimus until EOS or diagnosis of progression.
Study duration per patient is 30 months (Figure 3).

Treatment Schedule

* unless diagnosis of progression or EOS
** until diagnosis of progression or EOS
*** or until diagnosis of progression, whichever is earlier

Figure 3: Summary schedule of treatments and follow-up consultation

Study Objectives

Primary Objective

Progression-free survival (PFS). Diagnosis of progression will be established based on morphological imaging (MRI and/or CT) according to RECIST 1.1.

Key Secondary Objectives

Objective response rates (ORR) as best outcome; overall survival (OS); duration of disease control (DDC); safety and tolerability; health-related quality of life (HRQL); dosimetry; pharmacokinetics.

Main Inclusion Criteria

- Written informed consent
- Male or female ≥18 years of age
- Histologically and clinically confirmed diagnosis of well-differentiated NET of non-functional gastrointestinal origin (GI-NET) or both functional or non-functional pancreatic origin (P-NET), tumor grade G1 or G2 (Ki-67 ≤20%), unresectable or metastatic
- Measurable disease per RECIST 1.1, on CT/MRI scans, defined as at least 1 lesion with ≥1 cm in longest diameter and ≥2 radiological tumor lesions in total
- SSTR+ disease, as evidenced by SSTR imaging within 4 months prior to randomization
- Radiological disease progression, defined as progressive disease per RECIST 1.1 criteria, evidenced by CT/MRI with ≥90 days interval during 12 months prior to randomization

Mode of Action

Lock and Key Principle

Targeted radiopharmaceuticals contain a targeting molecule and a medical radioisotope. The targeting molecule binds to the tumor specific receptor according to the lock and key principle (Figure 4). In most cases, the targeting molecule can be used for both diagnostics and therapy, only the radioisotope needs to be changed. This enables the application of theranostics in precision oncology.

Figure 4: Lock and key principle of PRRT with targeting molecule and medical radioisotope

Conclusion

COMPETE is the first pivotal study to compare PRRT with an approved therapeutic in patients with Grade 1 and Grade 2 GEP-NETs. It is expected that COMPETE will increase treatment options, including first-line therapy. Further studies with lutetium (^{177}Lu) edotreotide in patients with NETs and high unmet medical needs are under review.

References

[1]Dasari A et al., JAMA 2017
[2]Yao JC et al., Lancet 2016
[3]Strosberg et al., NEJM 2017
[4]Baum et al., Theranostics 2016
[5]Phase III Trial COMPETE

Access via QR code or find more trial information on www.compete-clinical-trial.com

Access via QR code or find more trial information on ClinicalTrials.gov NCT03049189: https://bit.ly/3uccXds

Poster #CT254 Presented at the AACR Annual Meeting 2021 (virtual meeting), April 10–15, May 17–21

NEC:
Kunnen we echt niet beter?

NET grade 3 and NEC

ENETS
2e DBNETS congres • 2024

Digestive high-grade NEN are rare with limited data on epidemiology, treatment benefit and overall survival (OS). Sorbye et al. presented the Nordic NEC 2 study with new data through a prospectively collected cohort. 861 cases were prospectively included between 2013 and 2017. MINEN were excluded. Centralized pathological re-evaluation was performed in 495/698 cases. All cases with Ki-67 <60% were re-evaluated. 698 high-grade digestive NEN cases were classified as 134 NET grade 3 (19%) and 564 NEC. 511 NEC and 128 NET had advanced disease. NET grade 3 with pancreatic primary in 46%. Median Ki-67 was 31% for NET grade 3 and 90% for NEC. 84% of NET grade 3 and 12% of NEC had Ki-67<55%. Palliative chemotherapy was given to 427 NEC (83% platinum+etoposide) and 115 NET grade 3 patients (39% platinum+etoposide, 57% temozolomide-based). Response rate was 34% for NEC and 28% for NET grade 3, progression at first evaluation seen in 38% of NEC and 21% of NET grade 3. Toxicity led to treatment discontinuation in 13% of NET grade 3 and 9% of NEC. PFS was 9.8 months for NET grade 3 and 6.1 months for NEC (p<0.001). Second-line chemotherapy was given to 68% of NET grade 3 and 51% of NEC. 27% developed bone metastases, 10% of NEC brain metastases. OS after first-line chemotherapy was 21.8 months for NET grade 3 and 7.4 months for NEC (p<0.001). OS for NET grade 3 was 23.7 months if Ki-67 <55% and 8.0 months if >55% (p=0.001). OS for NEC was significantly longer if Ki-67 <55% (p=0.006). Three and 5-year OS was 32% and 10% for NET grade 3 vs. 5% and 2% for NEC.

In conclusion, **in this large prospective cohort of advanced high-grade NEN patients, 1 in 3 patients had no benefit of first-line chemotherapy. Survival was <2 years for NET grade 3 and only 7.4 months for NEC.** These data are in line with the Belgian retrospective analysis from the DNET and NETwerk registry shown last year at the ENETS Conference by Islam et al. Better treatment options for this patient group are thus urgently awaited.

Sorbye H. et al. Nordic NEC 2: Characteristics and treatment outcome in a prospective cohort of 698 patients with high-grade digestive neuroendocrine neoplasms (NET G3 and NEC). Abstract presented at ENETS 2024 in Vienna.

Islam O. et al. Characteristics and management of high-grade gastroenteropancreatic neuroendocrine neoplasms – A Belgian retrospective analysis from the DNET & NETwerk registry. Abstract presented at ENETS 2023 in Vienna.

Mooie retrospectieve reeks over mFOLFIRINOX

ONETS
2e DBNETS congres • 2024

ORIGINAL RESEARCH

Efficacy and Toxicity Analysis of mFOLFIRINOX in High-Grade Gastroenteropancreatic Neuroendocrine Neoplasms

Michele Borghesani, MD[1,*]; Anna Reni, MD[1,*]; Eleonora Lauricella, MD[2]; Alice Rossi, MD[1]; Viola Moscarda, MD[1]; Elena Trevisani, MD[1]; Irene Torresan, MD[1]; Taymeyah Al-Toubah, MPH[3]; Elisabetta Filoni, MD[2]; Claudio Luchini, MD[4]; Riccardo De Robertis, MD[5]; Luca Landoni, MD[6]; Aldo Scarpa, MD[4]; Camillo Porta, MD[2,7]; Michele Milella, MD[1]; Jonathan Strosberg, MD[3]; Mauro Cives, MD[2,7,†]; and Sara Cingarlini, MD[1,†]

Abstract

Background: High-grade neuroendocrine neoplasms (NENs) comprise both well-differentiated grade 3 neuroendocrine tumors (G3 NETs) and poorly differentiated neuroendocrine carcinomas (NECs). Mixed neuroendocrine–non-neuroendocrine neoplasms (MiNENs) nearly always include poorly differentiated NEC as the neuroendocrine component. The efficacy and safety of frontline mFOLFIRINOX chemotherapy has never been investigated in patients with high-grade NENs. **Patients and Methods:** We conducted a multi-institutional retrospective analysis of patients with advanced high-grade NEN of the gastroenteropancreatic tract or of unknown origin seen between February 2016 and April 2023 who received treatment with frontline mFOLFIRINOX. **Results:** A total of 35 patients were included (G3 NETs: n=2; NECs: n=25; MiNENs: n=8; stage III: n=5; stage IV: n=30). The objective response rate was 77% (complete response: 3%; partial response: 74%). Median progression-free survival was 12 months (95% CI, 9.2–16.2 months) and median overall survival was 20.6 months (95% CI, 17.2–30.6 months). No significant differences in efficacy were seen according to primary site, histopathology, and Ki-67 proliferative index. All 5 patients with stage III disease who received mFOLFIRINOX obtained an objective response and underwent radical surgery or definitive radiotherapy with curative intent, with a recurrence rate of 40%. Grade 3 or 4 adverse events were observed in 43% of patients (mainly neutropenia and diarrhea). Females were at significantly increased risk of developing severe toxicities. **Conclusions:** mFOLFIRINOX shows antitumor activity against high-grade NENs. Well-designed, prospective clinical trials are needed to assess the efficacy of mFOLFIRINOX in both the neoadjuvant and metastatic settings.

J Natl Compr Canc Netw, doi:10.6004/jnccn.2024.7005
Published online May 14, 2024

Characteristic	n (%)
Patients, N	35
Sex	
Male	20 (57)
Female	15 (43)
Age at diagnosis, median (range), y	57.5 (38–75)
ECOG performance status	
0	28 (80)
1	7 (20)
Primary site	
Pancreas	23 (66)
Stomach	4 (11)
Esophagus	2 (6)
Papilla of Vater	2 (6)
Gallbladder	1 (3)
Unknown	3 (8)
Histopathology (WHO 2019)	
G3 NET	2 (6)
NEC	25 (71)
MiNEN	8 (23)
Ki-67 index	
Median (range)	70% (25%–100%)
<55%	14 (40)
≥55%	21 (60)
Stage (ENETS)	
III	5 (14)
IV	30 (86)
Location of metastases[a]	
Liver	13 (37)
Bone	6 (17)
Lung	4 (11)
Lymph nodes	12 (34)
None	5 (14)
Synchronous/Metachronous metastases	
Synchronous	27 (77)
Metachronous	3 (9)
None	5 (14)
FDG-PET at diagnosis	
Positive	20 (57)
Not performed	15 (43)
^{68}Ga-DOTA-peptide PET at diagnosis	
Positive	10 (29)
Negative	9 (25)
Not performed	16 (46)
Molecular profiling	
Not performed	21 (60)
Performed	14 (40)
Mutations of *TP53*	6 (43)
Mutations of *RB1*	5 (36)
Mutations of *ATM*	2 (14)
TMB >10 mut/Mb	3 (21)

Abbreviations: ENETS, European Neuroendocrine Tumour Society; G3 NET, grade 3 neuroendocrine tumor; NEC, neuroendocrine carcinoma; MiNEN, mixed neuroendocrine–non-neuroendocrine neoplasm; mut/Mb, mutations per megabase; TMB, tumor mutational burden.
[a]Metastatic sites could be >1 in each patient.

Characteristic	n (%)
Patients, N	35
Cycles, median (range), n	11 (5–19)
Chemotherapy starting dose	
Full dose	28 (80)
20% reduction	3 (8)
25% reduction	3 (8)
50% reduction	1 (4)
Chemotherapy dose reductions throughout treatment course	
Yes	14 (40)
No	21 (60)
Chemotherapy cycle delays throughout treatment course	
Yes	18 (51)
No	17 (49)
G-CSF primary prophylaxis	
Yes	29 (83)
No	6 (17)
Reason for treatment discontinuation	
Progressive disease	14 (40)
Toxicity	5 (14)
Switch to maintenance therapy	11 (31)
Surgery or definitive radiotherapy	5 (14)
Maintenance treatment	
No	24 (69)
Yes	11 (31)
Olaparib	2 (18)
Capecitabine	2 (18)
FOLFIRI	2 (18)
SSA	5 (46)
Locoregional treatments following mFOLFIRINOX	
No	22 (63)
Yes	13 (37)
Surgery	6 (46)
Radiotherapy	7 (54)
Subsequent lines of therapy	
No	14 (40)
Yes	21 (60)
FOLFIRI	8 (38)
Temozolomide or CAPTEM	5 (24)
Etoposide/Platinum	2 (10)
PRRT	2 (10)
Others	4 (19)
Follow-up, median (range), mo	18.2 (2.8–80)

Abbreviations: CAPTEM, capecitabine/temozolomide; FOLFIR, leucovorin/5-FU/irinotecan; G-CSF, granulocyte colony-stimulating factor; mFOLFIRINOX, modified leucovorin/5-FU/irinotecan/oxaliplatin; PRRT, peptide receptor radiotherapy; SSA, somatostatin analog.

nature communications

Article

https://doi.org/10.1038/s41467-024-50969-8

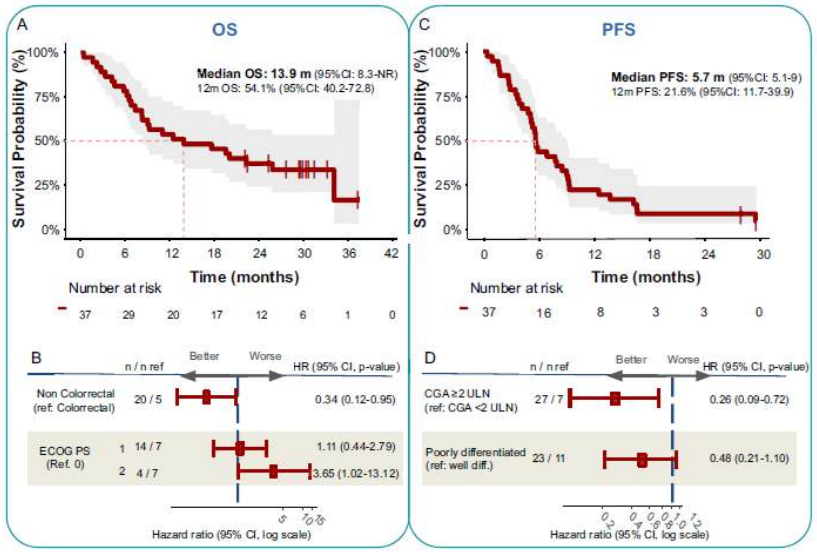
Nivolumab plus platinum-doublet chemotherapy in treatment-naive patients with advanced grade 3 Neuroendocrine Neoplasms of gastroenteropancreatic or unknown origin: The multicenter phase 2 NICE-NEC trial (GETNE-T1913)

Received: 8 February 2024

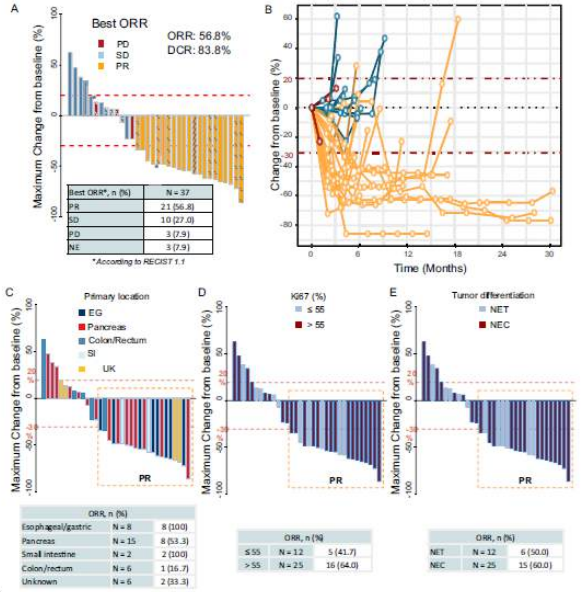
Accepted: 26 July 2024

Published online: 08 August 2024

The prognosis of patients with advanced high-grade (G3) digestive neuroendocrine neoplasms (NENs) is rather poor. The addition of immune checkpoint inhibition to platinum-based chemotherapy may improve survival. NICE-NEC (NCT03980925) is a single-arm, phase II trial that recruited chemotherapy-naive, unresectable advanced or metastatic G3 NENs of gastroenteropancreatic (GEP) or unknown origin. Patients received nivolumab 360 mg intravenously (iv) on day 1, carboplatin AUC 5 iv on day 1, and etoposide 100 mg/m^2/d iv on days 1–3, every 3 weeks for up to six cycles, followed by nivolumab 480 mg every 4 weeks for up to 24 months, disease progression, death or unacceptable toxicity. The primary endpoint was the 12-month overall survival (OS) rate (H_0 50%, H_1 72%, β 80%, α 5%). Secondary endpoints were objective response rate (ORR), duration of response (DoR), progression-free survival (PFS), and safety. From 2019 to 2021, 37 patients were enrolled. The most common primary sites were the pancreas (37.8%), stomach (16.2%) and colon (10.8%). Twenty-five patients (67.6%) were poorly differentiated carcinomas (NECs) and/or had a Ki67 index >55%. The ORR was 56.8%. Median PFS was 5.7 months (95%CI: 5.1-9) and median OS 13.9 months (95%CI: 8.3-Not reached), with a 12-month OS rate of 54.1% (95%CI: 40.2-72.8) that did not meet the primary endpoint. However, 37.6% of patients were long-term survivors (>2 years). The safety profile was consistent with previous reports. There was one treatment-related death. Nivolumab plus platinum-based chemotherapy was associated with prolonged survival in over one-third of chemonaïve patients with G3 GEP-NENs, with a manageable safety profile.



PFS and OS of patients with high-grade NENs of GEP or UK origin treated with nivolumab, carboplatin, and etoposide. A Kaplan Meier showing the OS for the full dataset ($n = 37$). The red line shows the estimated survival proportion and the shadow area the 95% CI. The red dashed lines indicate the 50% survival probability point estimate. **B** Multivariable analysis to find potential baseline prognostic factors for OS. The forest plot shows the hazard ratio of each subgroup and its 95% CI. **C** Kaplan-Meier showing the PFS for the full dataset. **D** Multivariable analysis to find potential baseline prognostic factors for PFS. The forest plot shows the hazard ratio of each subgroup and its 95% CI. Multivariable analyses were performed using the Cox model and are exploratory. Significance tests are two-sided. Source data are provided as a Source Data file. CGA chromogranin A, CI confidence interval, Diff differentiated, ECOG-PS Eastern Cooperative Oncology Group Performance Status, HR hazard ratio, OS overall survival, PFS progression-free survival.



Efficacy of Nivolumab, Carboplatin and Etoposide as first-line treatment of high-grade NENs of GEP or UK origin. A Waterfall plot showing objective response rate (ORR) and the percentage of maximum change from baseline tumor size for each patient ($n = 37$). **B** Spider plot showing the evolution of relative tumor size from the first dose of study treatment until the last tumor evaluation ($n = 37$). Asterisk sign indicates PD-L1 positivity, lined plotted columns indicate MSI, dotted plotted columns MSS. Maximum change in tumor size, shown as percentage from baseline, and ORR rates analyzed by subgroups clustered according to baseline characteristics such as primary tumor site (**C**), Ki-67 proliferation index (**D**), or tumor differentiation (**E**). Three patients, one MSS and two unknown died due to disease progression before the first tumor assessment were not evaluated for response. Exploratory subgroup analyses were performed using Fisher's Exact Test (**C**) and Pearson's Chi-squared test (**D** and **E**). Significance tests are two-sided. Source data are provided as a Source Data file. DCR disease control rate, EG esophageal and gastric, NE not evaluable, NEC neuroendocrine carcinoma, NET neuroendocrine tumor, ORR objective response rate, PD progressive disease, PR partial response, RECIST Response Evaluation Criteria In Solid Tumors, SD stable disease, SI small intestine, UK unknown.

Immunotherapy for NEN

Not a successful story at this moment in NEN:

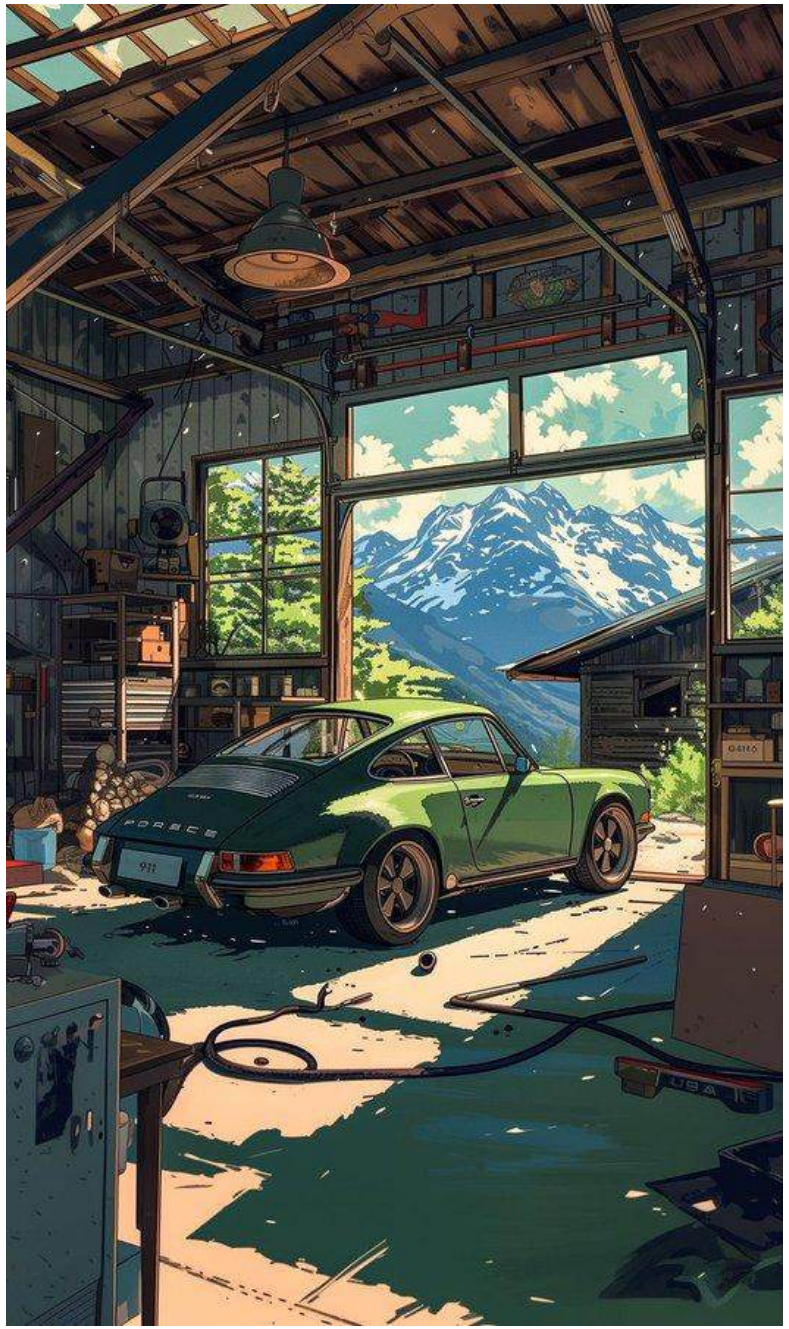
- Spartalizumab maybe signal in lung NEN.
- Nivolumab + ipilimumab high response rates in NEC in 2 Clinical Cancer Research papers, but not encountered in real life.
- Monotherapy immunotherapy does not work well.

- MSI-High not frequent in NEC.
- CPS PD-L1 not good biomarker in NEN for immunotherapy efficacy.
- TMB-high not frequent in NEN.

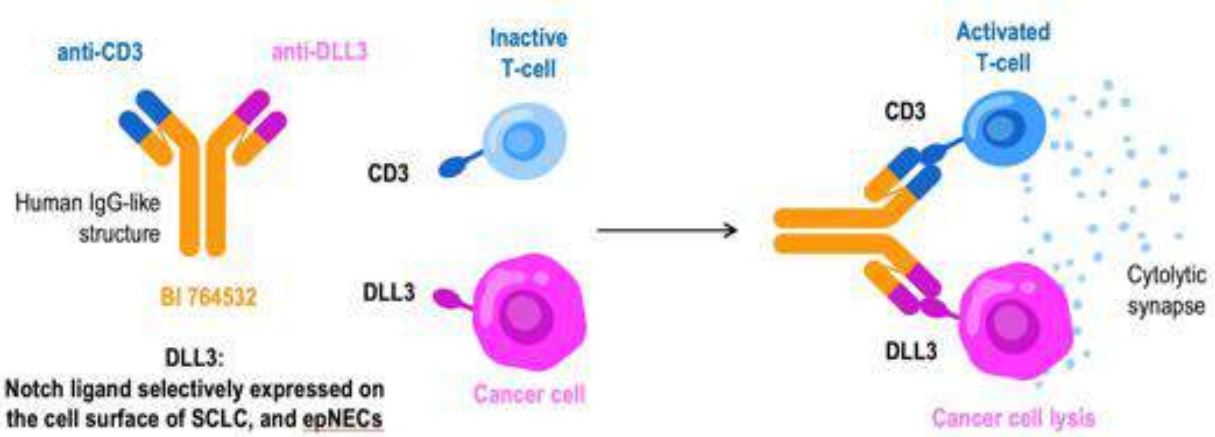
- Spanish durvalumab + tremelimumab study rather disappointing.
- Combination immunotherapy + angiogenesis inhibition is also not the holy grail.
- Combination chemotherapy + nivolumab:
  - Unclear what the extra benefit of immunotherapy is compared with chemotherapy alone in this study.
  - No biomarkers in this study.
  - All tumor types in 1 study?

➢ **Immunotherapy for NEN remains a case by case "trial and error" story: shoot blind and see what happens** 🔫 🔫

Een oldtimer die opgesmukt werd: van rovalpituzumab tesirine naar de bispecific antibodies tegen DLL3

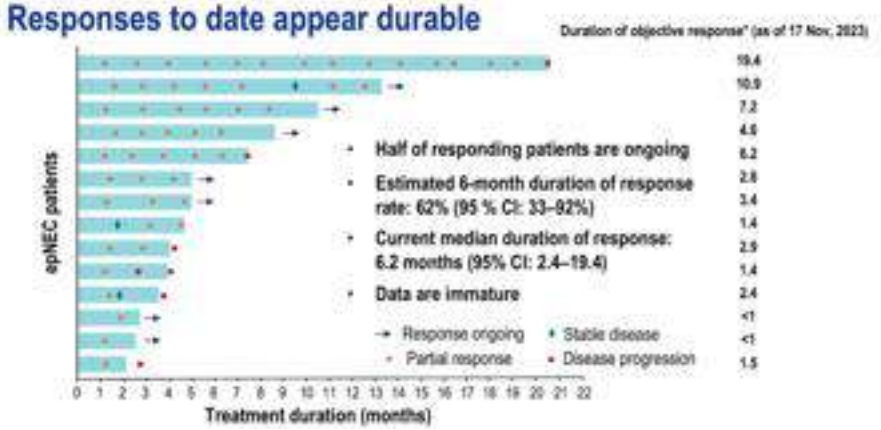


Precision immunotherapy in NEN: delta-like canonical Notch ligand 3 (DLL3) therapy for NEN

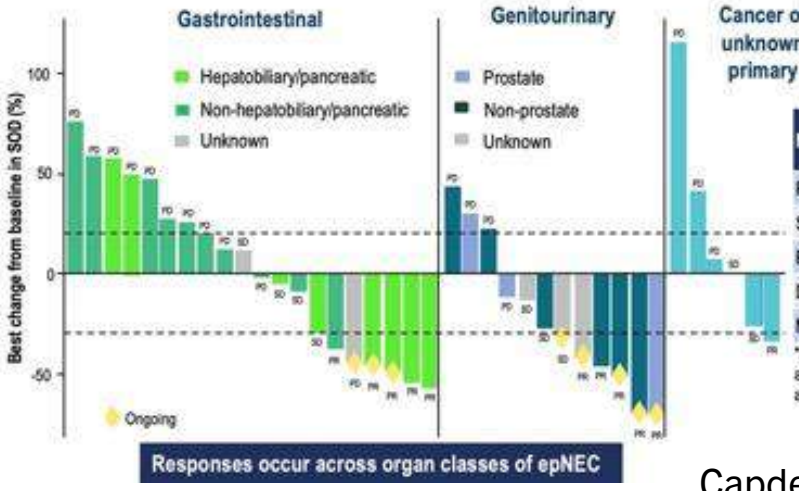


- BI 764532 redirects the patient's own T-cells to lyse DLL3-expressing cancer cells
- Potent preclinical activity against DLL3-positive cells and xenograft models[1]

Responses to date appear durable



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

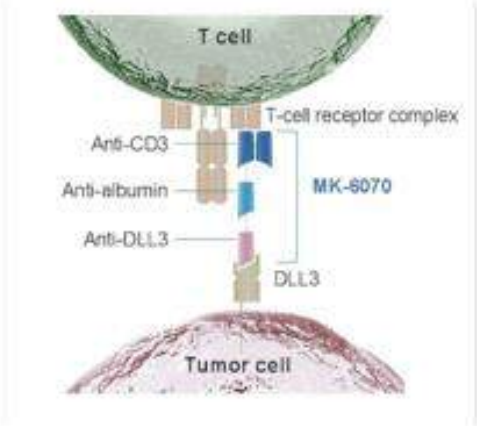
*Assessable patients who did not have any tumour assessment due to early toxicity, start of subsequent anti-cancer therapy, death or any other reason

Responses occur across organ classes of epNEC

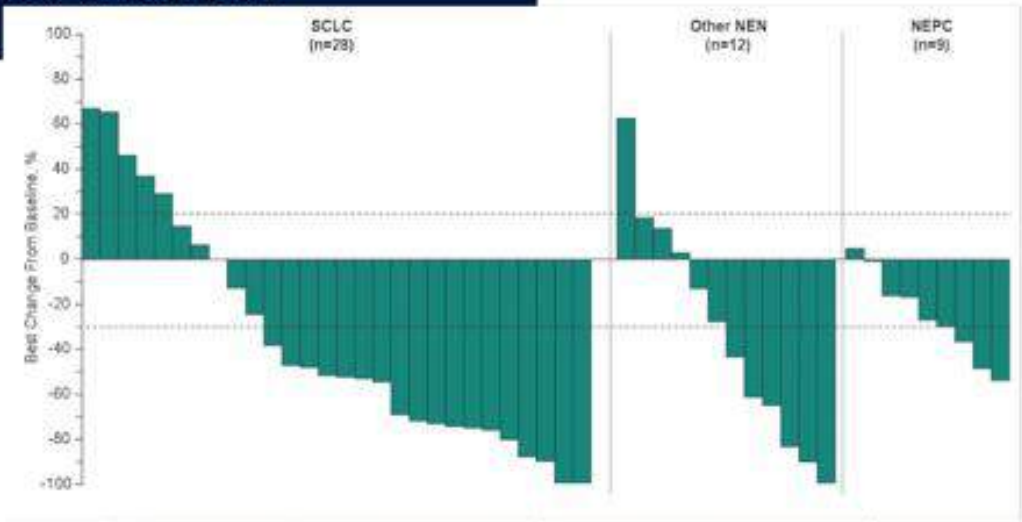
Capdevila J, et al. ENETS 2024

Precision immunotherapy in NEN: delta-like canonical Notch ligand 3 (DLL3) therapy for NEN

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%)

Jaume Capdevila, MD, PhD

Beltran H, et al. ASCO 2024

Tarlatamab scoort in latere lijn SCLC: update 08/2024

Clinical Trial Updates

Sustained Clinical Benefit and Intracranial Activity of Tarlatamab in Previously Treated Small Cell Lung Cancer: DeLLphi-300 Trial Update

Afshin Dowlati, MD[1]; Horst-Dieter Hummel, MD[2]; Stephane Champiat, MD, PhD[3]; Maria Eugenia Olmedo, MD, PhD[4]; Michael Boyer, MB, BS, PhD[5,6]; Kai He, MD, PhD[7]; Neeltje Steeghs, MD, PhD[8]; Hiroki Izumi, MD, PhD[9]; Melissa L. Johnson, MD[10]; Tatsuya Yoshida, MD, PhD[11]; Hasna Bouchaab, MD[12]; Hossein Borghaei, DO[13]; Enriqueta Felip, MD, PhD[14]; Philipp J. Jost, MD[15]; Shirish Gadgeel, MD[16]; Xi Chen, MD, PhD[17]; Youfei Yu, PhD[17]; Pablo Martinez, MD, PhD[17]; Amanda Parkes, MD[17]; and Luis Paz-Ares, MD, PhD[18]

DOI https://doi.org/10.1200/JCO.24.00553

ABSTRACT

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

Tarlatamab, a bispecific T-cell engager immunotherapy targeting delta-like ligand 3, has shown durable anticancer activity and manageable safety in previously treated small cell lung cancer (SCLC) in DeLLphi-300 phase I and DeLLphi-301 phase II trials. Here, we report extended follow-up of DeLLphi-300 (median follow-up, 12.1 months [range, 0.2-34.3]) in fully enrolled cohorts treated with tarlatamab ≥10 mg dose administered once every two weeks, once every three weeks, or once on day 1 and once on day 8 of a 21-day cycle (N = 152). Overall, the objective response rate (ORR) was 25.0%; the median duration of response (mDOR) was 11.2 months (95% CI, 6.6 to 22.3), and the median overall survival (mOS) was 17.5 months (95% CI, 11.4 to not estimable [NE]). Among 17 patients receiving 10 mg tarlatamab once every two weeks, the ORR was 35.3%, the mDOR was 14.9 months (95% CI, 3.0 to NE), the mOS was 20.3 months (95% CI, 5.1 to NE), and 29.4% had sustained disease control with time on treatment ≥52 weeks. No new safety signals were identified. In modified Response Assessment in Neuro-Oncology Brain Metastases analyses, CNS tumor shrinkage of ≥30% was observed in 62.5% of patients (10 of 16) who had a baseline CNS lesion of ≥10 mm, including in a subset of patients with tumor shrinkage long after previous brain radiotherapy. In DeLLphi-300 extended follow-up, tarlatamab demonstrated unprecedented survival and potential findings of intracranial activity in previously treated SCLC.

ACCOMPANYING CONTENT

Data Supplement
Protocol

Accepted July 22, 2024
Published August 29, 2024

J Clin Oncol 00:1-8


DE WARMING-UP

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

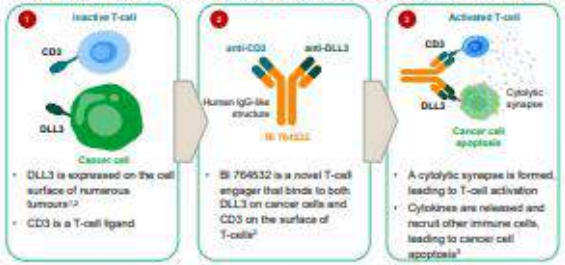
#M02

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[2]
- 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 of the lung[4]

19–77% of GI epNECs depending on site of primary tumour[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)[6,7,8]
- Promising efficacy has been seen in patients with epNEC and LCNEC of the lung. 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 patients with LCNEC of the lung or epNEC, and better first-line treatment options are an unmet need
- DLL3 constitutes 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 ligand 3; DOR, 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

This study is 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 Lyon Pritchard DPhil, of Ashfield MedComms, an Inizio Company, and was industry-sponsored.

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 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
- In Part A, SoC chemotherapy will be carboplatin + etoposide
- 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

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 has been 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; DLTs, dose limiting toxicity

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;138:103–8;
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

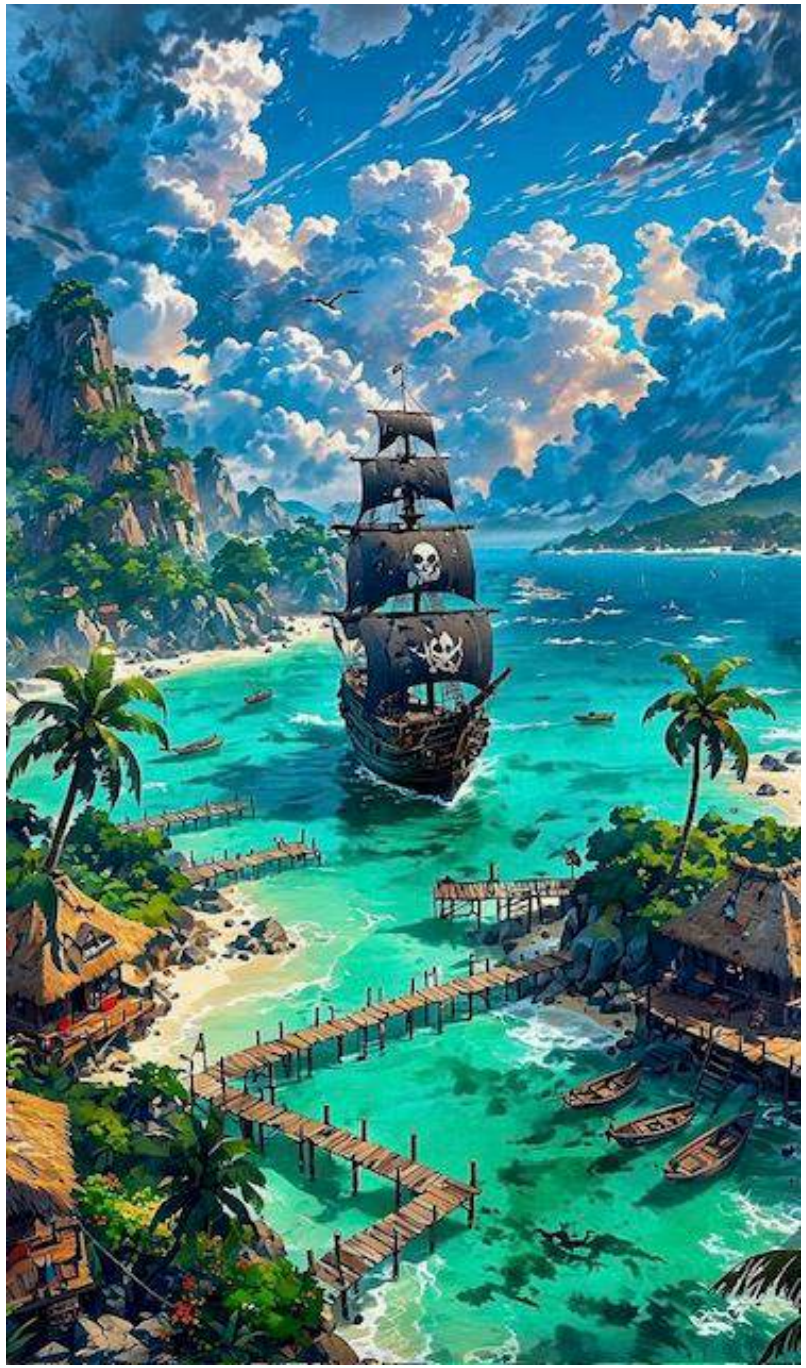
Presented at the European Neuroendocrine Tumor Society (ENETS) Congress, Vienna, Austria, 13–15 March 2024

*Corresponding author email address: jcapdevila@vhio.net

Scan this QR code or visit the URL to access the SMART presentation

Scan this QR code or visit the URL to access the infographic summary

ENETS 2e DBNETS congres • 2024



FDA Grants Orphan Drug Designation for ABD-147 for Neuroendocrine Carcinoma

September 5, 2024
By Ashley Gallagher, Associate Editor

News *Article*

Previously, the FDA granted fast track designation to ABD-147 (Abdera Therapeutics Inc) for extensive stage small cell lung cancer.

The FDA granted orphan drug designation to ABD-147 (Abdera Therapeutics, Inc) for the treatment of neuroendocrine carcinoma. The investigational drug is a next-generation precision radiopharmaceutical biologic that delivers Actinium-225 to solid tumors that express DLL3.

Molecular profiling of metastatic NEC before starting second-line treatment: which biomarkers are relevant nowadays?

When we start up with a first-line treatment in NEC in our patient like platinum + etoposide or CAPTEM/FOLFOX, the question is always which second-line treatment options are possible when retaining an acceptable performance status. In most of our patients a first-line strategy is not long-lasting and in other tumour types we are used to do molecular profiling at diagnosis or at first progression of the tumour. 40 to 60% of GEP-NECs have potentially targetable alterations. However, **in NECs there is only case-based or little series-based experience with so-called theranostic markers and targeted therapy used in case of a molecular aberration**.
The following molecular diagnostics can aid treatment selection for GEP-NEC patients anno 2022, however most outside of reimbursement in Belgium at this moment:

- BRAF V600E mutation (mostly in right colon NEC): consider dabrafenib + trametinib, encorafenib +/- cetuximab…
- MSI (5% of NECs are MSI-High, more frequent in colon NECs): consider pembrolizumab, nivolumab + ipilimumab…
- TMB (tumour mutational burden)(rarely >10 in NECs): consider pembrolizumab…
- BRCA1/2 mutation (0.5-2%): potential for PARP inhibition…
- KRAS G12C mutation: consider sotorasib, adagrasib…
- NTRK-fusion: consider larotrectinib or entrectinib (= reimbursed in Belgium)…
- **CPS-score PD-L1 is not recommended because it is not a good marker in NECs for benefit of immunotherapy.**

Nieuwe target = HER2/neu IHC 3+

Clinical Trial > J Clin Oncol. 2024 Jan 1;42(1):47-58. doi: 10.1200/JCO.23.02005. Epub 2023 Oct 23.

Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2–Expressing Solid Tumors: Primary Results From the DESTINY–PanTumor02 Phase II Trial

Funda Meric-Bernstam [1], Vicky Makker [2,3], Ana Oaknin [4], Do-Youn Oh [5], Susana Banerjee [6], Antonio González-Martín [7], Kyung Hae Jung [8], Iwona Ługowska [9], Luis Manso [10], Aránzazu Manzano [11], Bohuslav Melichar [12], Salvatore Siena [13], Daniil Stroyakovskiy [14], Anitra Fielding [15], Yan Ma [16], Soham Puvvada [15], Norah Shire [15], Jung-Yun Lee [17]

Affiliations + expand

PMID: 37870536 PMCID: PMC10730032 DOI: 10.1200/JCO.23.02005

Abstract

Purpose: Trastuzumab deruxtecan (T-DXd) is a human epidermal growth factor 2 (HER2)-directed antibody-drug conjugate approved in HER2-expressing breast and gastric cancers and HER2-mutant non-small-cell lung cancer. Treatments are limited for other HER2-expressing solid tumors.

Methods: This open-label phase II study evaluated T-DXd (5.4 mg/kg once every 3 weeks) for HER2-expressing (immunohistochemistry [IHC] 3+/2+ by local or central testing) locally advanced or metastatic disease after ≥1 systemic treatment or without alternative treatments. The primary end point was investigator-assessed confirmed objective response rate (ORR). Secondary end points included safety, duration of response, progression-free survival (PFS), and overall survival (OS).

Results: At primary analysis, 267 patients received treatment across seven tumor cohorts: endometrial, cervical, ovarian, bladder, biliary tract, pancreatic, and other. The median follow-up was 12.75 months. In all patients, the ORR was 37.1% (n = 99; [95% CI, 31.3 to 43.2]), with responses in all cohorts; the median DOR was 11.3 months (95% CI, 9.6 to 17.8); the median PFS was 6.9 months (95% CI, 5.6 to 8.0); and the median OS was 13.4 months (95% CI, 11.9 to 15.5). In patients with central HER2 IHC 3+ expression (n = 75), the ORR was 61.3% (95% CI, 49.4 to 72.4), the median DOR was 22.1 months (95% CI, 9.6 to not reached), the median PFS was 11.9 months (95% CI, 8.2 to 13.0), and the median OS was 21.1 months (95% CI, 15.3 to 29.6). Grade ≥3 drug-related adverse events were observed in 40.8% of patients; 10.5% experienced adjudicated drug-related interstitial lung disease (ILD), with three deaths.

Conclusion: Our study demonstrates durable clinical benefit, meaningful survival outcomes, and safety consistent with the known profile (including ILD) in pretreated patients with HER2-expressing tumors receiving T-DXd. Greatest benefit was observed for the IHC 3+ population. These data support the potential role of T-DXd as a tumor-agnostic therapy for patients with HER2-expressing solid tumors.

Conclusies NEN praatje vandaag 🧙‍♂️

DNETS
2e DBNETS congres • 2024

- PRRT rukt meer en meer vroeger op in het behandelingsalgoritme van NET, ook komen er nieuwe nucleaire targets bij en ook targeted alpha-particle therapy toont beloftevolle resultaten… Wordt snel vervolgd! 😍
- PRRT is overal, maar klinische factoren op de Multidisciplinaire Tumor Board spelen ook een belangrijke rol in een juiste behandelingskeuze voor de patiënt op het juiste moment: artsen moeten nadenken samen met patiënt in hun bijzijn!
- Na SSA en PRRT is er nu een heel nieuw landschap van mogelijkheden met niet altijd veel data: cabozantinib klopt wel evidence-based aan de deur met de mooie CABINET studie 👏👏
- Alle ogen zijn nu gericht op DLL3-targeted therapieën bij NEC; immunotherapie is geen gouden kip bij NEN gebleken, toekomst voor CAR T-cel therapie? 👊
- Klinisch bruikbare biomerkers zijn nog een grote afwezige in het NEN-veld: uitkijken naar doorgedreven research projecten zoals FORCE, BE-FORCE, ctDNA, gut microbioom, …
- Klinische studies zijn erg belangrijk voor onze patiënten, dus INCLUDEREN MAAR!

Organisatie van de zorg voor NEN:
“centraal wat moet, decentraal wat kan”

NETwerk
ENETS Center of Excellence

Samenwerken rond NEN

- **Multicentrisch én multidisciplinair samenwerken tussen arts-specialisten van verschillende disciplines en ziekenhuizen**
- **Experten in hun vak + expertise in NEN**
- **Expertise in NEN winnen (grote groep patiënten)**
- **Aanbieden van verschillende diagnose- en behandelingsmodaliteiten**
- **Aanbieden van studies**
- **Vanuit dit idee: oprichting NETwerk (2016) en andere ENETS CoE zoals hier**

NETwerk
ENETS Center of Excellence

Bedankt voor jullie aandacht!

Vragen?

NETwerk
ENETS Center of Excellence

UZA · VITAZ STERK IN ZORG · AZ MONICA · az Rivierenland
ZAS · University of Antwerp · AZ Voorkempen algemeen ziekenhuis emmaüs · AZ Klina voluit voor zorg