

Welcome to the **ENETS – INCA NET Cancer Day Educational Webinar**

12 November 2024, 18:00 – 20:15 CET



ENETS – INCA NET Cancer Day Educational Webinar | 12 November 2024

Today's moderators



Stephanie ALBAND

INCA President
Carlsbad, CA, United States



Rocio GARCIA-CARBONERO

ENETS Chair
Hospital Universitario Doce de Octubre
Madrid, Spain



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Today's speakers



Simona BARBI

NET Italy



Nehara BEGUM

Johannes-Wesling-Klinikum
Minden, Germany
Surgery



Roy Aleksander FARSTAD

CarciNor
Norway



Hans HOFLAND

Erasmus MC Rotterdam,
The Netherlands
Endocrinology



Anna KOUMARIANOU

National and Kapodistrian University
Hematology Oncology Unit
Athens, Greece
Oncology

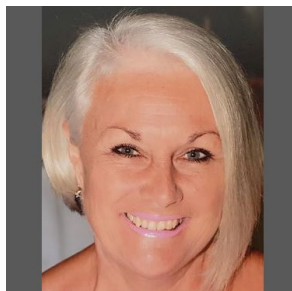


Ilaria MARINONI

University of Bern
Switzerland
Molecular Biology



Today's panellists (in addition to our speakers)



Meredith CUMMINS

NeuroEndocrine Cancer
Australia



Wanda GEILVOET

Erasmus MC
Rotterdam
The Netherlands
Nurse



Gregory KALTSAS

National and Kapodistrian Univ.
Dept. of Pathophysiology
Athens, Greece
Endocrinology



Wendy MARTIN

Kings College Hospital NHS
Foundation Trust London
United Kingdom
Nurse



Mark McDONNELL

NET Patient Network
Ireland



Marj WALKER

CNETS
Canada



Lisa YEN

LACNETS
United States



Webinar agenda

Moderators & Chairs:

Rocio GARCIA-CARBONERO / ENETS Chair (ESP) & Stephanie ALBAND / INCA President (USA)

18:00 – 18:10 | OPENING

18:10 – 18:45 | PART ONE | Most frequent symptom control

18:10 – 18:20 Patient stories

- MEN2A – **Roy Aleksandar FARSTAD (NOR)**
- Metastatic ileum NET – **Simona BARBI (ITA)**

18:20 – 18:30 Clinician's perspective: Setting the scene – **Nehara BEGUM (GER)**

18:30 – 18:45 Panel discussion

Panellists: Simona BARBI (ITA), Nehara BEGUM (GER), Roy Aleksander FARSTAD (NOR), Wanda GEILVOET (NED), Gregory KALTSAS (GRE)

18:45 – 19:15 | PART TWO | Treatment line sequencing: What are the rules?

18:45 – 18:55 Clinician's perspective: Setting the scene – **Anna KOUMARIANOU (GRE)**

18:55 – 19:15 Panel discussion

Panellists: Nehara BEGUM (GER), Wanda GEILVOET (NED), Anna KOUMARIANOU (GRE), Marj WALKER (CAN), Lisa YEN (USA)

19:15 – 19:45 | PART THREE | (New) treatments

19:15 – 19:25 Clinician's perspective: Setting the scene – **Hans HOFLAND (NED)**

19:25 – 19:45 Panel discussion

Panellists: Meredith CUMMINS (AUS), Hans HOFLAND (NED), Anna KOUMARIANOU (GRE), Wendy MARTIN (GBR), Mark McDONNELL (IRL)

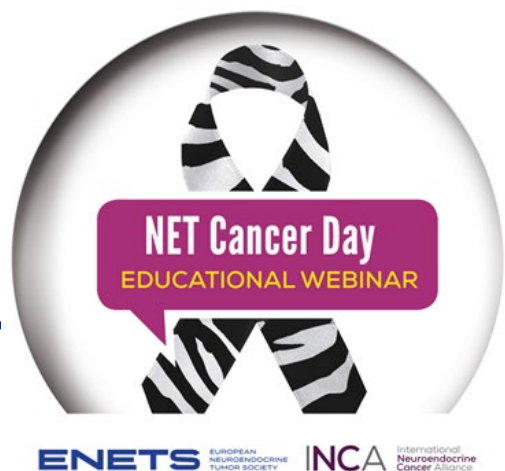
19:45 – 20:10 | PART FOUR | Update on genomics

19:45 – 19:55 Clinician's perspective: Setting the scene – **Hans HOFLAND (NED)**

19:55 – 20:10 Panel discussion

Panellists: Meredith CUMMINS (AUS), Hans HOFLAND (NED), Ilaria MARINONI (SUI), Wendy MARTIN (GBR), Mark McDONNELL (IRL)

20:10 – 20:15 | CLOSING



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1. Live Poll Question:

Which continent are you from?

1. Europe
2. Africa
3. Asia
4. North America
5. South America
6. Australia



Q & A sessions

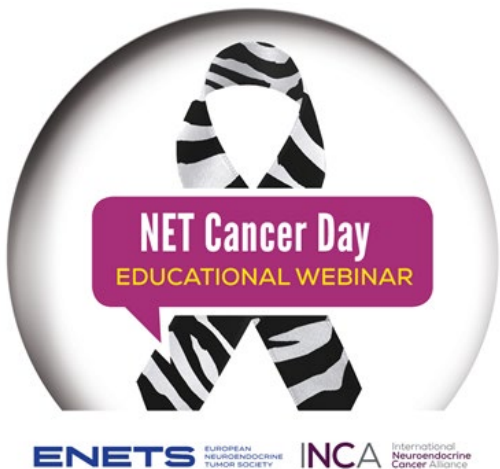
We will have a Q&A session at the end of each segment. Please submit your questions using the Q&A tool in Zoom, located at the bottom of your screen.



Participant survey

Please fill out the ***participant survey*** that will appear automatically on your screen once you have left the Zoom webinar. Your feedback helps us to improve future webinars.

Thank you!



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PART ONE | Most frequent symptom control

Patient story:

MEN2A – *Roy Aleksander FARSTAD (NOR)*



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PART ONE | Most frequent symptom control

Patient story:

Metastatic ileum NET – *Simona BARBI (ITA)*



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Simona Barbi
President, NET Italy

Hi everyone. My name's Simona,

PART ONE | Most frequent symptom control

Setting the scene: Practitioner's view

Nehara Begum, MD

Secretary of the German NET-Registry

Department of General-, Visceral-, Thoracic- and Endocrine Surgery

Johannes Wesling Klinikum Minden

Germany

Associate Professor University Hospital Lübeck



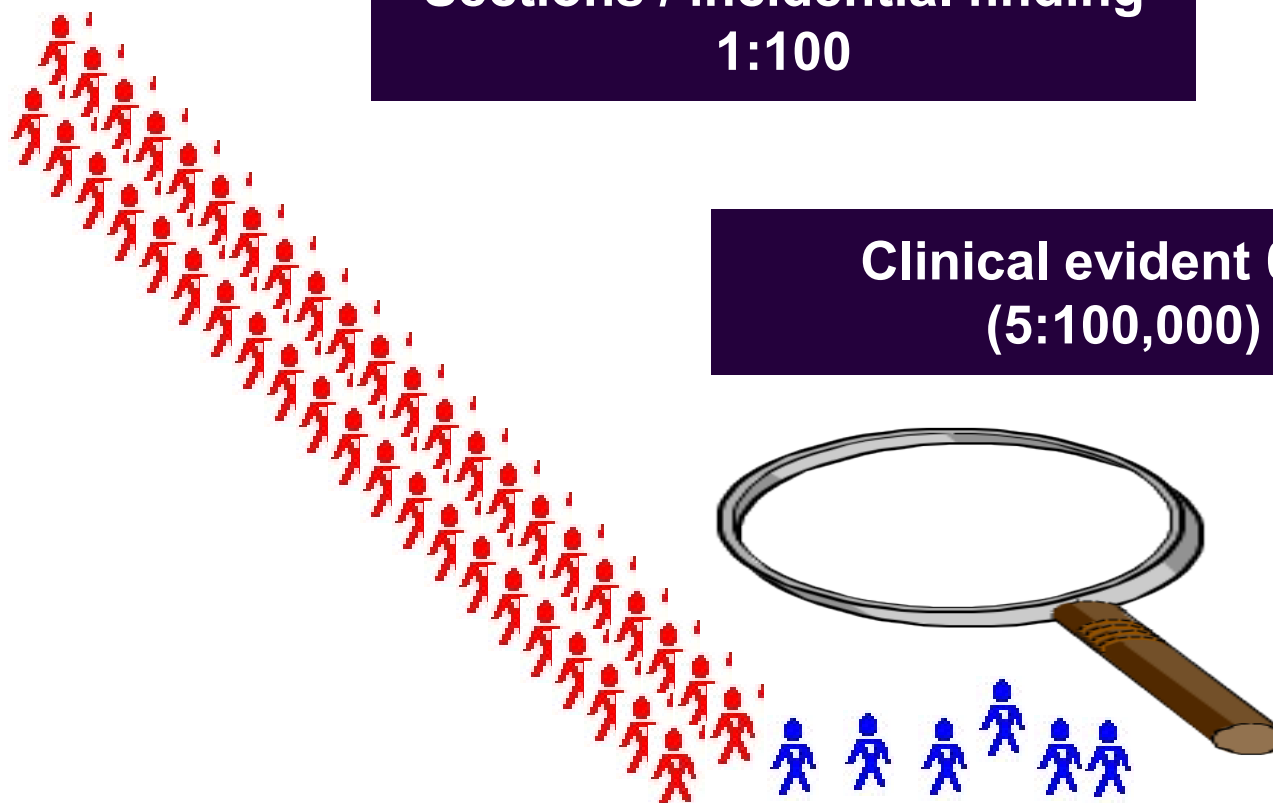
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Clinical presentation of NEN

Sections / incidental finding
1:100

Clinical evident 0,5%
(5:100,000)



Metz D., Jensen R.T. Gastroenterology 2008



Most frequent symptom control – Clinician's view

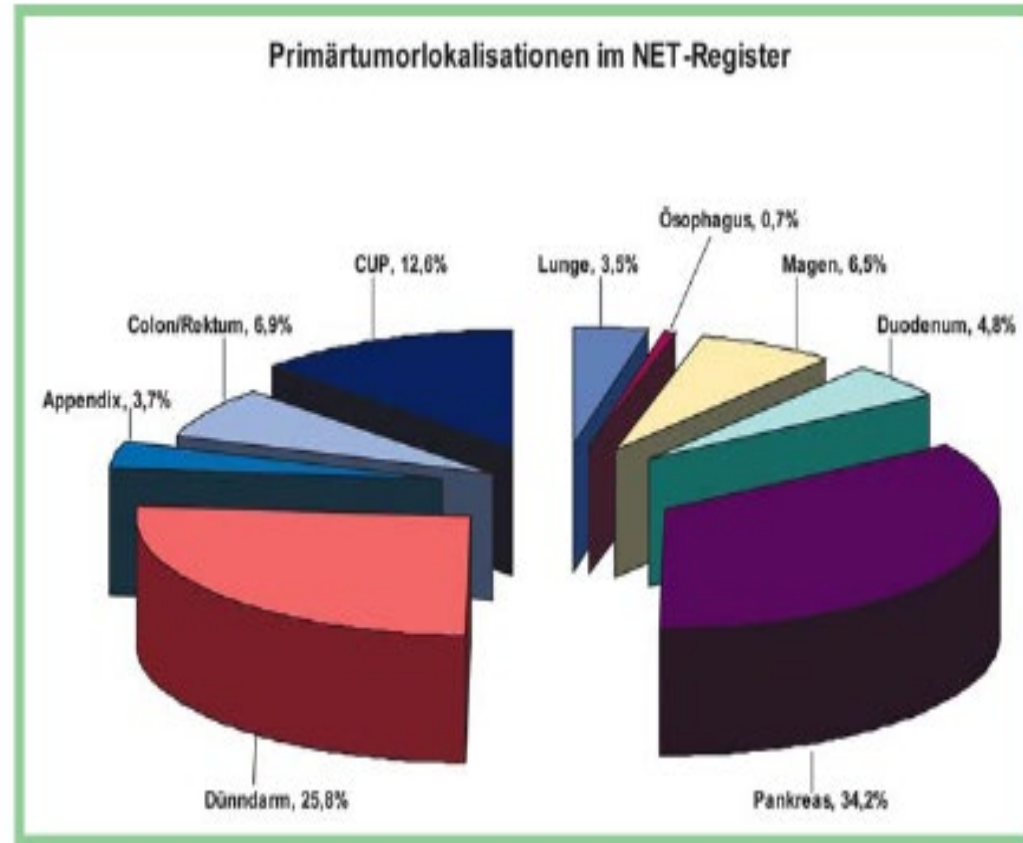
*Most frequent primaries
(NEN)*

Pancreas

Small bowel

Neuroendocrine CUP

*Incidence 4-6/100,000
Prevalence 65/100,000*



NEN are the most frequent neoplasia of the small bowel 0/.6-0.8/100,000)



Most frequent symptom control – Clinician's view

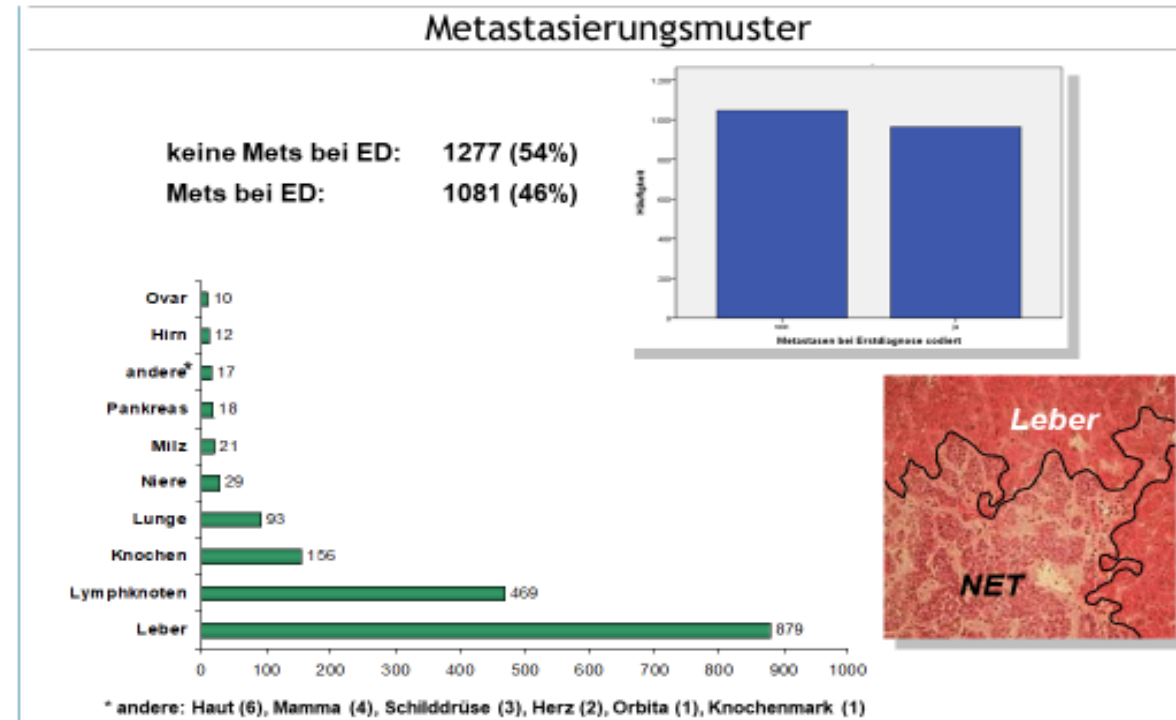


Around 50% distant metastases
At time of diagnosis

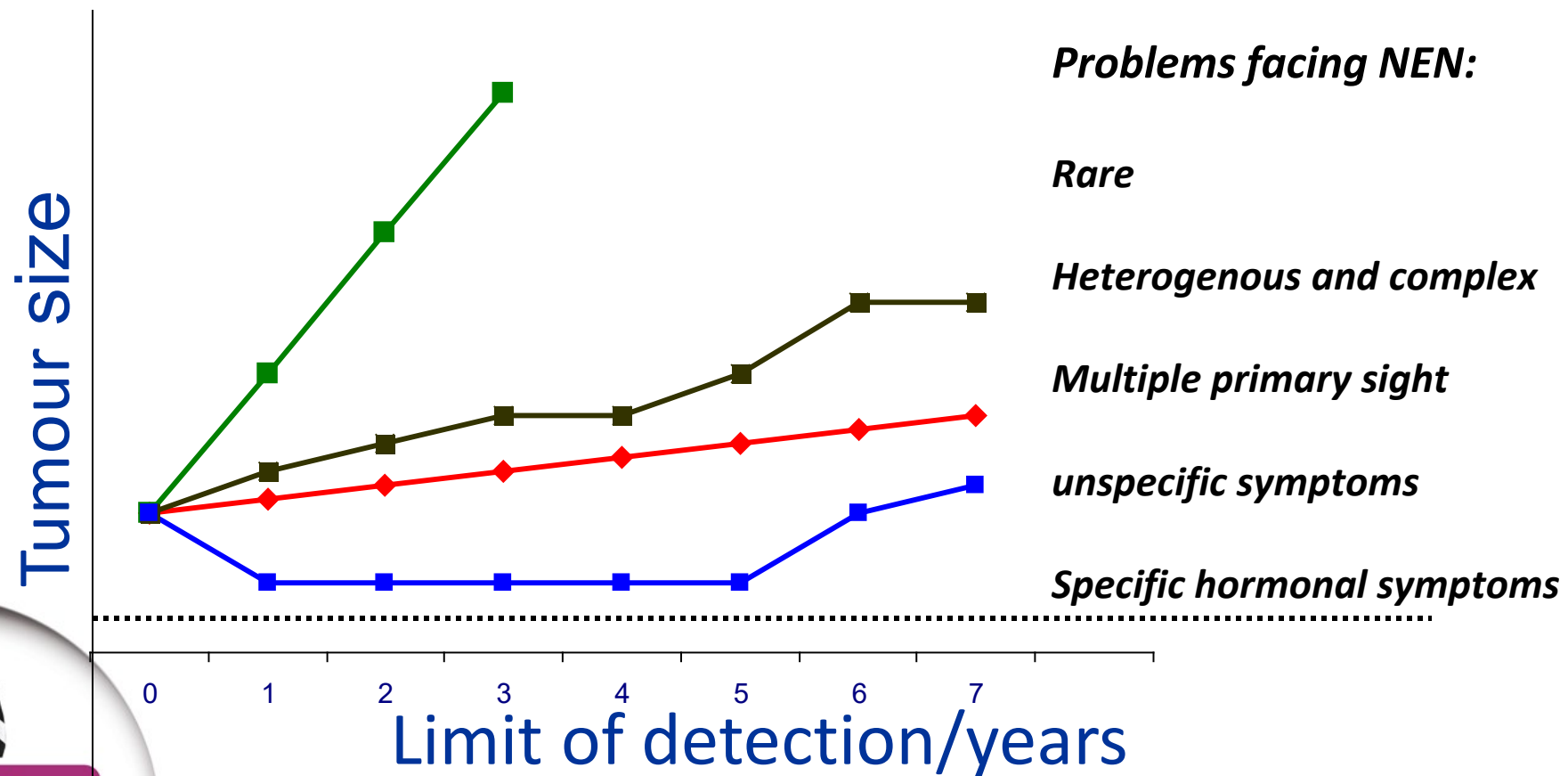
Most frequent metastatic sites:

Liver

Lymph nodes



Prognosis – Natural course of NEN



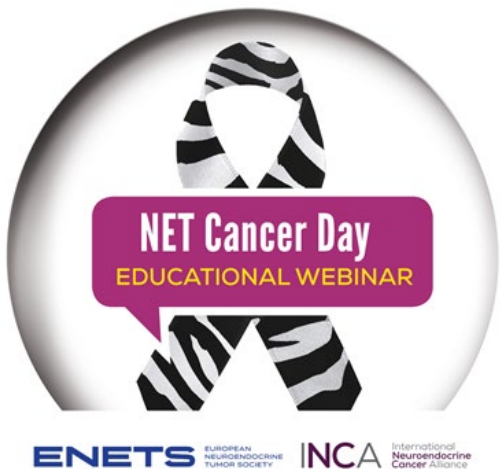
Arnold R, Onkologe, 2004



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Clinical presentation of NEN

- 50% are asymptomatic
- Abdominal pain
- Carcinoid syndrome (flush, diarrhea, wheezing, 20%)
- Hypoglycemia
- Hypercalcemia (urinary tract stones, ulcers, psychiatric disorder)

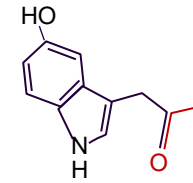


Nehara Begum, 12.11.2012 | Johannes-Wesling-Klinikum Minden, Germany

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Immunohistochemical diagnostics – Pathology and functional activity

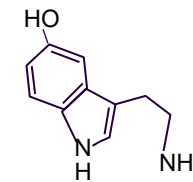
24 h urine collection



5-Hydroxy-Indole acetic acid
(5-HIAA)

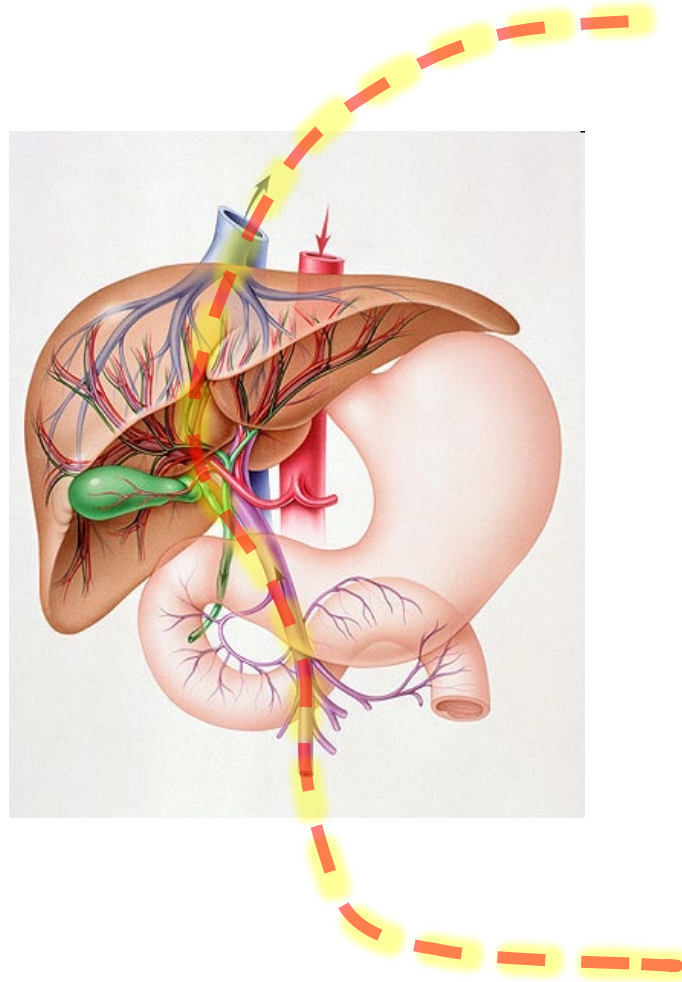


Small intestinal NET



Serotonine

Nehara Begum, Mannheim 19.10.2024
Johannes-Wesling-Klinikum Minden,
Klinik für Allgemein-, Viszeral-Thorax-,
Kinder- und Endokrine Chirurgie



Carcinoid Syndrome

Telangiectasia
(25%)

Bronchoconstriction
(3% – 19%)

Abdominal pain
(10% – 55%)

Arthritis
(7%)

Flush
(63% – 94%)

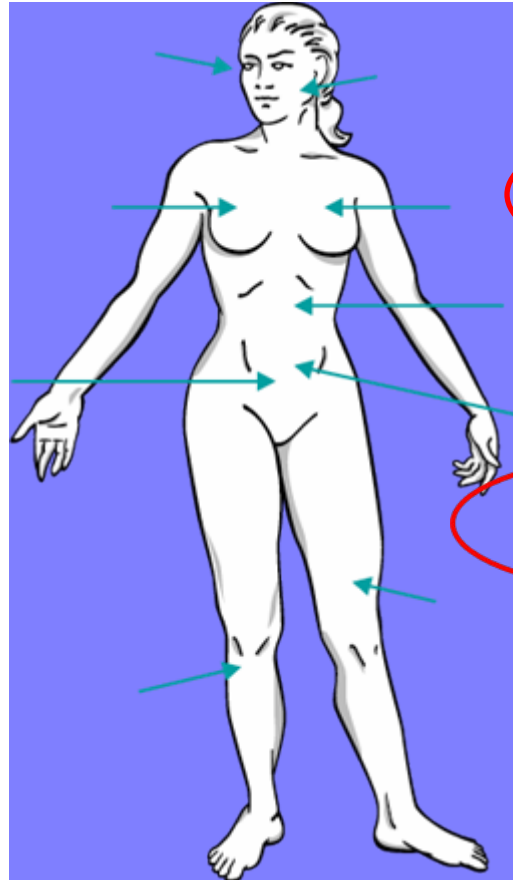
Carcinoid heart disease
(14% – 41%)

Cyanose
(18%)

Diarrhoe
(68% – 84%)

Dermatitis
(5%)

Hedinger-Syndrom!

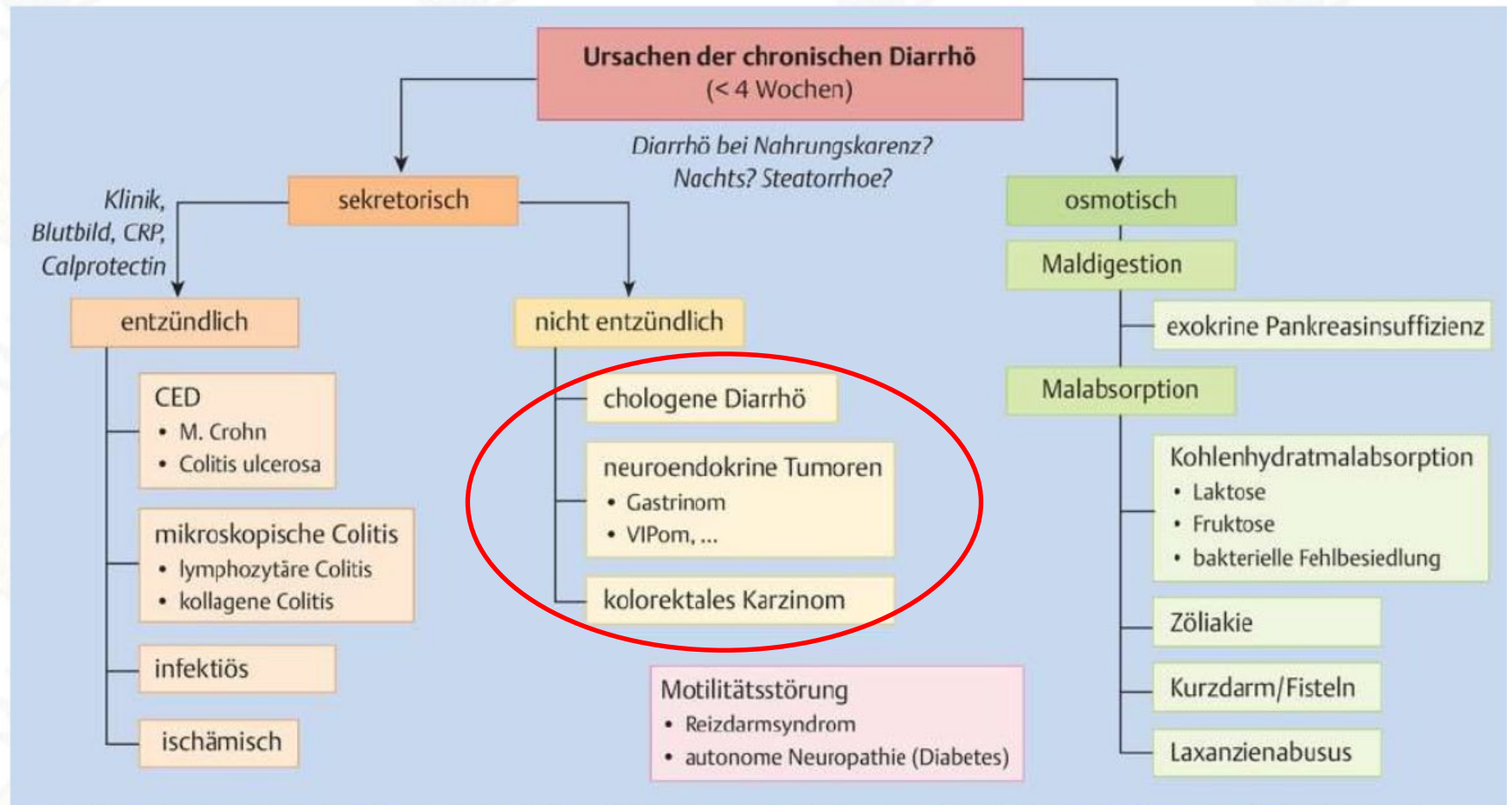


Problems in NEN outpatient clinic

- Diarrhea (normal?)
- Malnutrition
- Weight loss
- Vitamin deficiency
- Inherited disease?



Reason for diarrhea



• Hasselblatt P. Physiologische Grundlagen. In: Blum H, Müller-Wieland D, Hrsg. *Klinische Pathophysiologie*. 11., unveränderte Auflage. Stuttgart: Thieme; 2020. doi:10.1055/b000000121



Reason for diarrhea

- Bowel surgery
- Lost of biliary acids (chologen)
- Bacterial overgrowth
- Colitis by Clostridia (after antibiotica therapy)
- Subileus/Ileus
- Stenosis

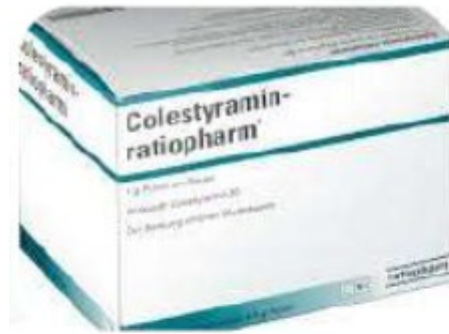


Nehara Begum, 12.11.2012 | Johannes-Wesling-Klinikum Minden, Germany

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Treatment option after SI surgery

Diarrhea as a
result of loss
of bile acid



Colestyramin®



Lipocol®-



Colesavelam



Other symptomatic treatment options

Drug therapy
of chronic
diarrhea



Codein drops



Opium
Tinktura® BTM



Dropizol®
Country specific packaging and bottles
DK version shown



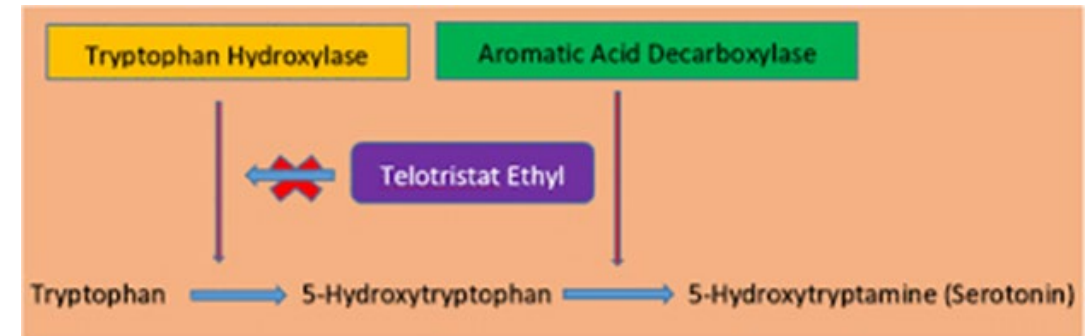
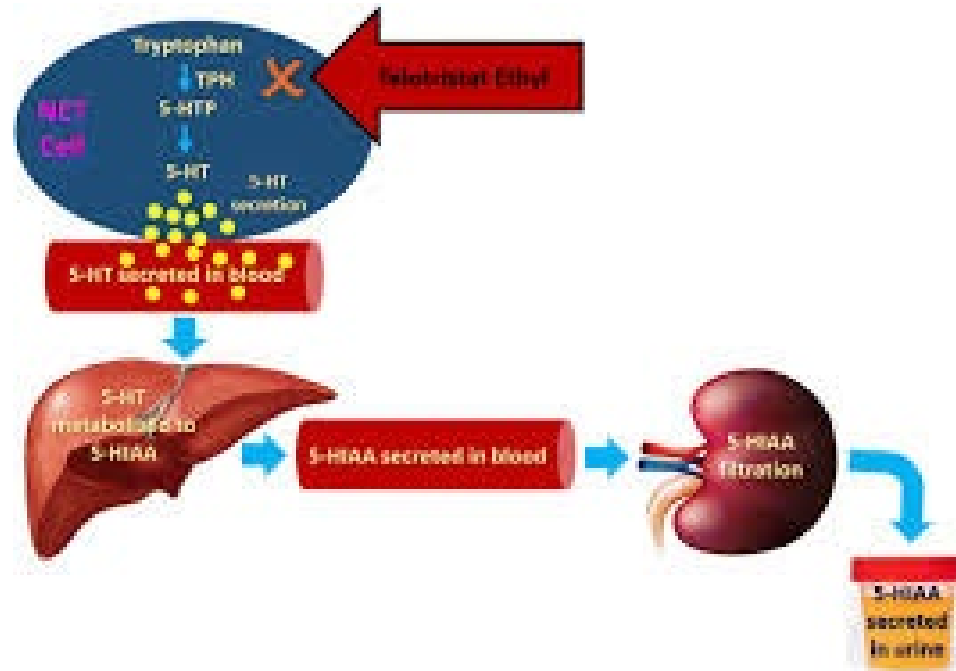
Protonenpumpenhemmer

Wirkstoffe	Pantoprazol, Omeprazol, Esomeprazol, Rabeprazol
Wirkung	Hemmung der Protonenpumpe in den Belegzellen des Magens → Verminderung von Magensäuresekretion
Dosierung (Erw.)	Omeprazol / Pantoprazol: 1x tgl. 20 – 40mg oral oder i.v.
Besonderheiten	- Einsatz in Hypersekretionsphase - Immer magensaftresistent überzogene Tabletten: Resorption im Duodenum - Nüchterne Einnahme

Last but not least

Telotristat Ethyl – Peripheral serotonin synthesis inhibitor

Inhibits the biosynthesis of peripheral serotonin in the gut by inhibiting tryptophan hydroxylase!



Challenges in NEN

- Correct and timely diagnosis!
- Correct treatment
- Adequate company along the disease
(chronic disease, common side effects,
ensure QoL, ensure normal life)

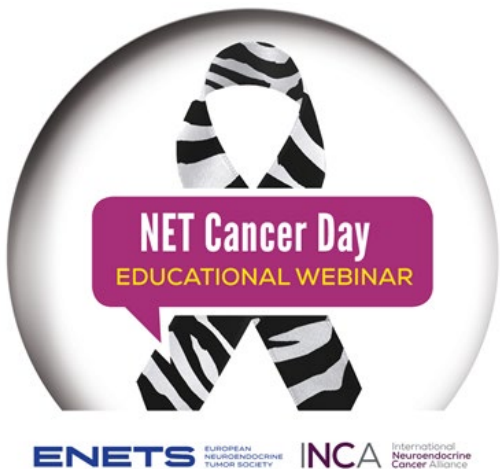


Nehara Begum, 12.11.2012 | Johannes-Wesling-Klinikum Minden, Germany

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NEN outpatient 11.12.2024, Female, *1963

- Diarrhea, flushing, flatulence since 2 years Delayed, but correct diagnosis
- Colonoscopy, Ileal NET, G1
- 16.09.2024: Ileocoecal resection (instead of hemicolectomy right) Inadequate therapy
- Presentation in our center by patient for Dotatoc-PET Incomplete diagnostic work-up

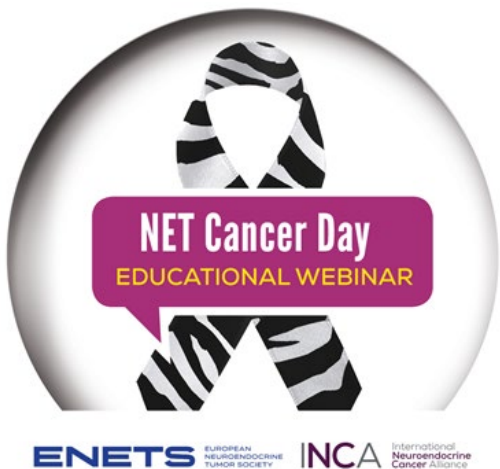


Nehara Begum, 12.11.2012 | Johannes-Wesling-Klinikum Minden, Germany

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What we need

- Specialized centers
- Awareness in the field (practioner)
- Cooporation with the patients
- Patient organization



Nehara Begum, 12.11.2012 | Johannes-Wesling-Klinikum Minden, Germany

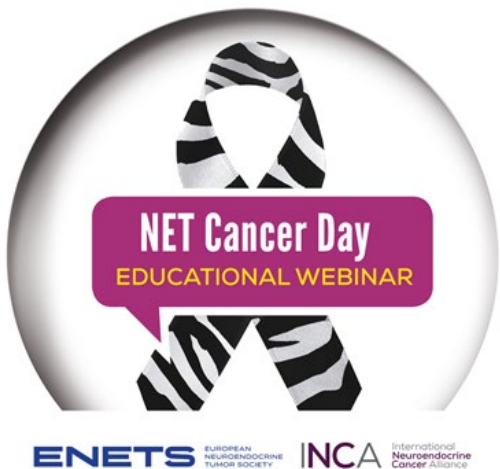
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What we can do

Learn from the patient!

Go and meet the patient!

(Cycling together)



Nehara Begum, 12.11.2012 | Johannes-Wesling-Klinikum Minden, Germany

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Thank you!!!



Prof. Wiedenmann

Prof. Plöckinger



Patientenorganisation:
[www. www.netzwerk-net.de](http://www.netzwerk-net.de)

www.net-register.org

World NET day, 10.11.2023
JWK Minden



PANEL DISCUSSION



PART TWO | Treatment Line Sequencing in Neuroendocrine Tumours: What are the Rules?

Anna Koumarianou M.D Ph.D

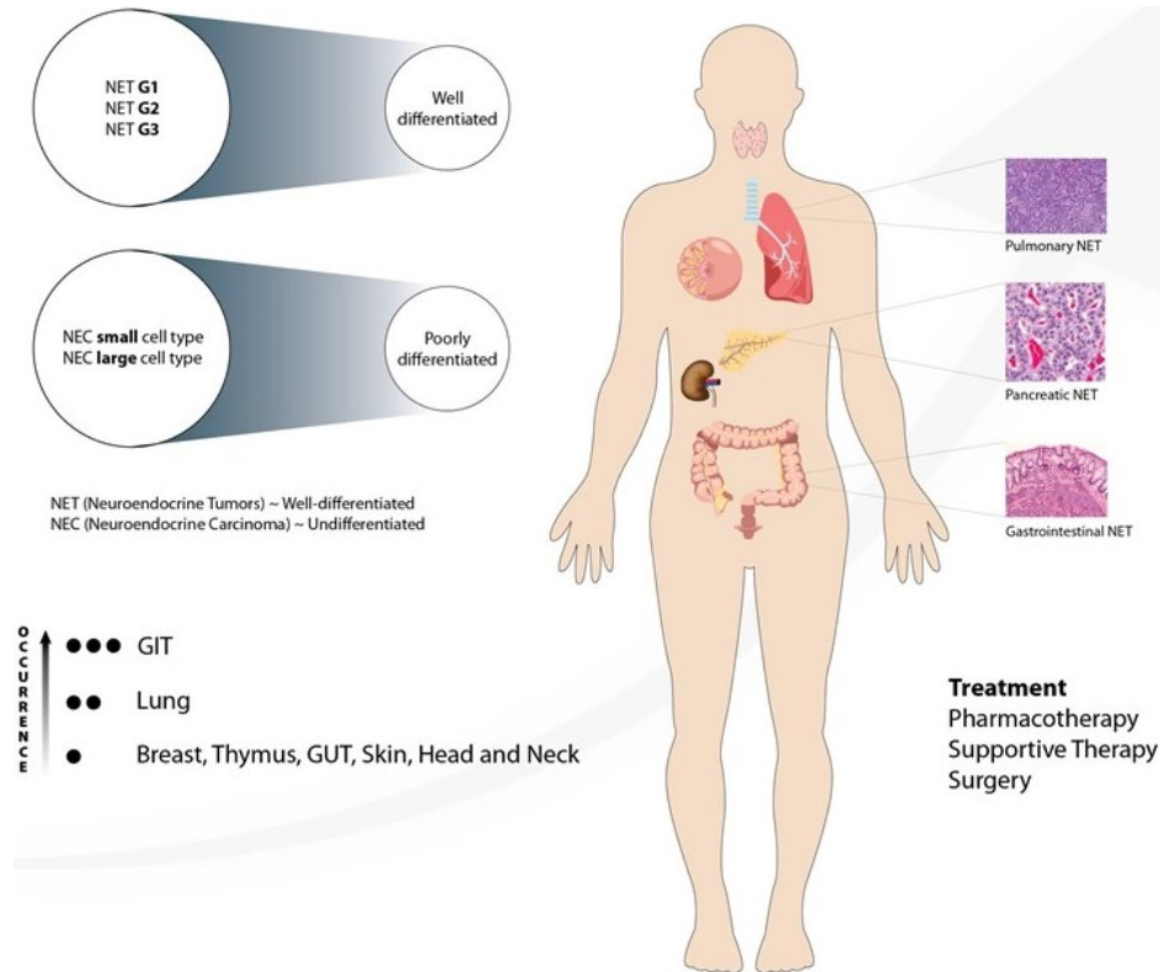
Medical Oncologist
Attikon University Hospital
Athens
Greece



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Introduction

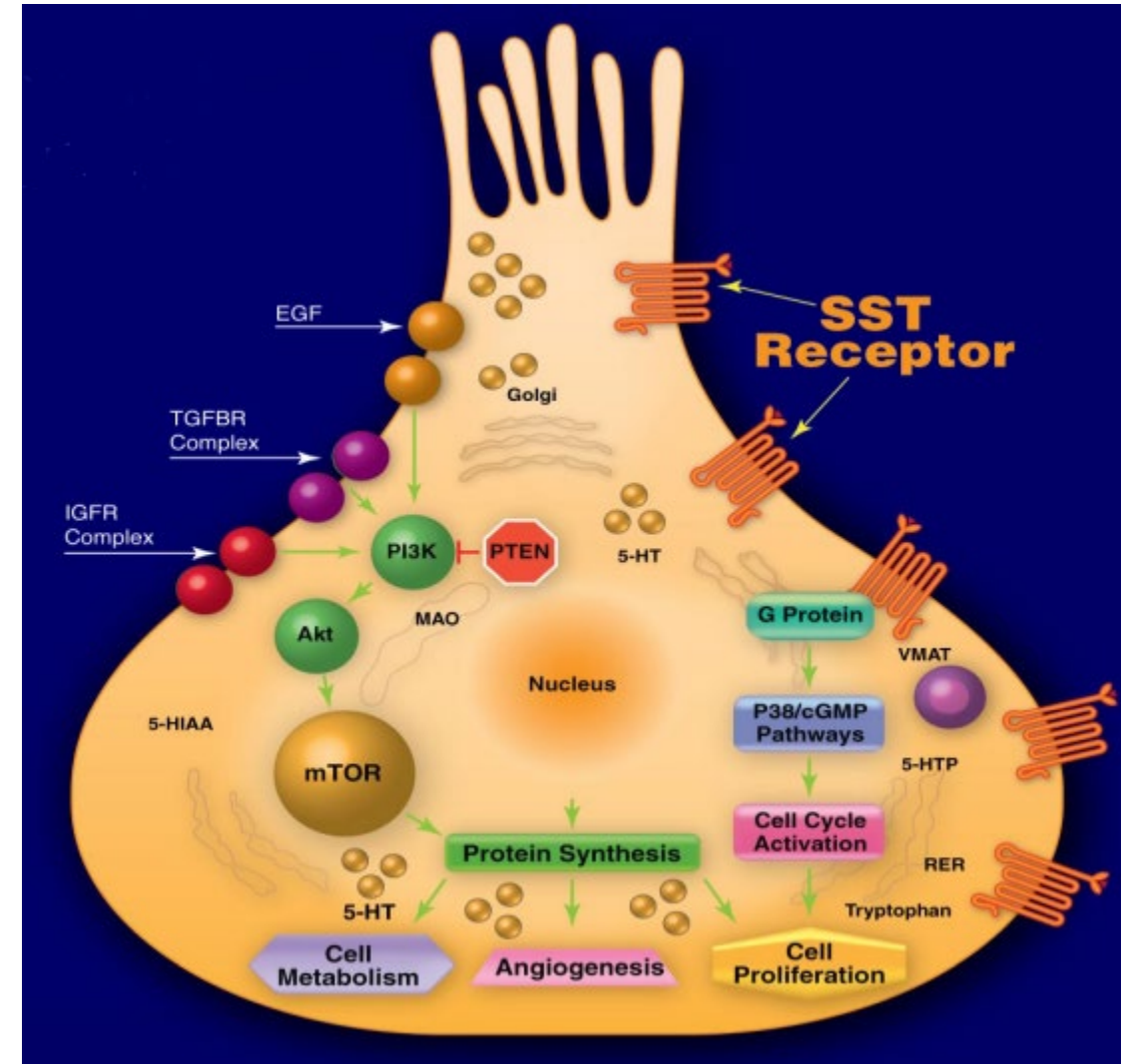
- Neuroendocrine tumours (NETs) can develop in various sites within the body
- The most commonly affected organs are the gastrointestinal, and the lungs



Introduction

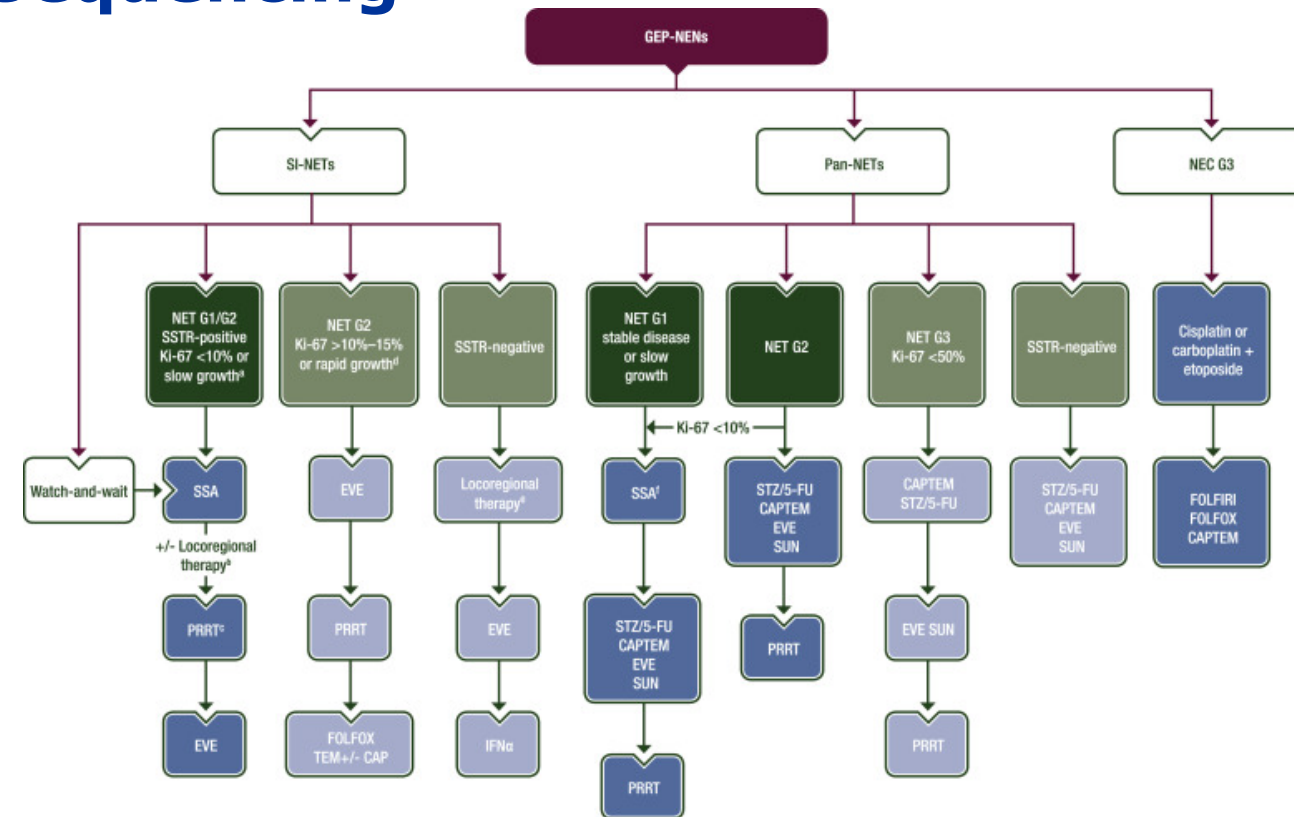
Cancerous cells in neuroendocrine tumours:

- are characterised by the presence of somatostatin receptors on their outer membrane
- can function as protein factories, often producing hormones that can lead to symptoms, such as serotonin production that may cause diarrhea.



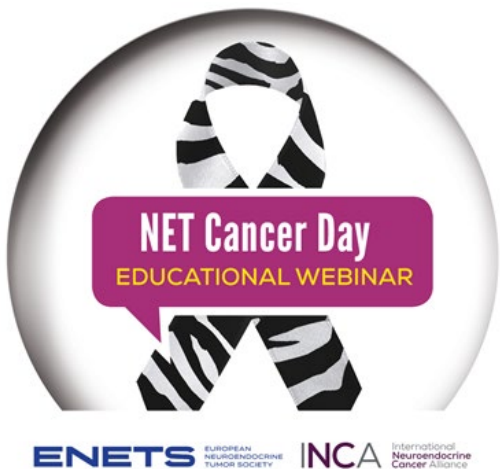
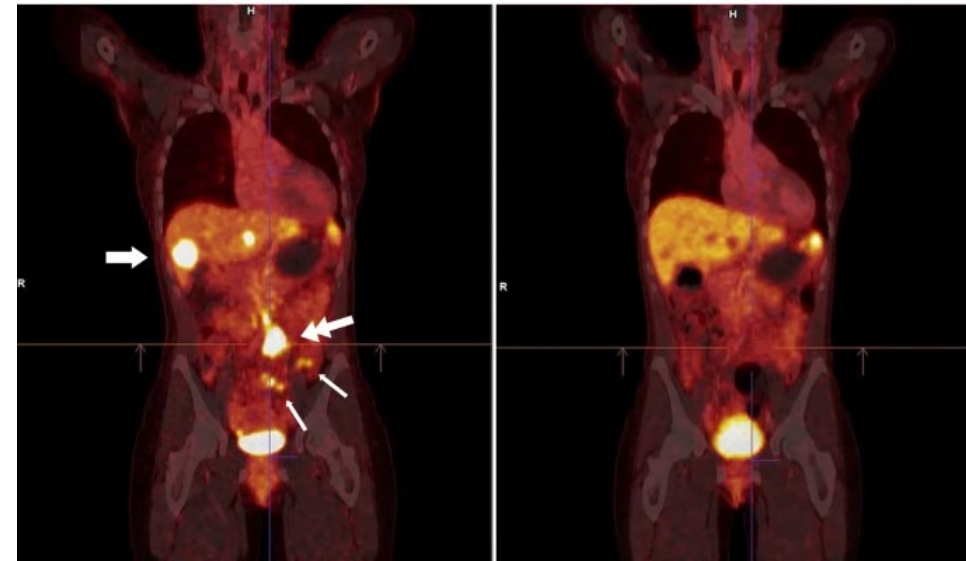
Understanding Treatment Line Sequencing

- Treatment sequencing, or the strategic allocation of therapies, depends on the specific organ involved, histologic characteristics, presence of metastatic disease (disease stage), and presenting symptoms
- Decisions are made in multidisciplinary tumour board meetings, guided by international treatment algorithms and tailored to individual patient characteristics (personalized medicine)



First-line Treatments

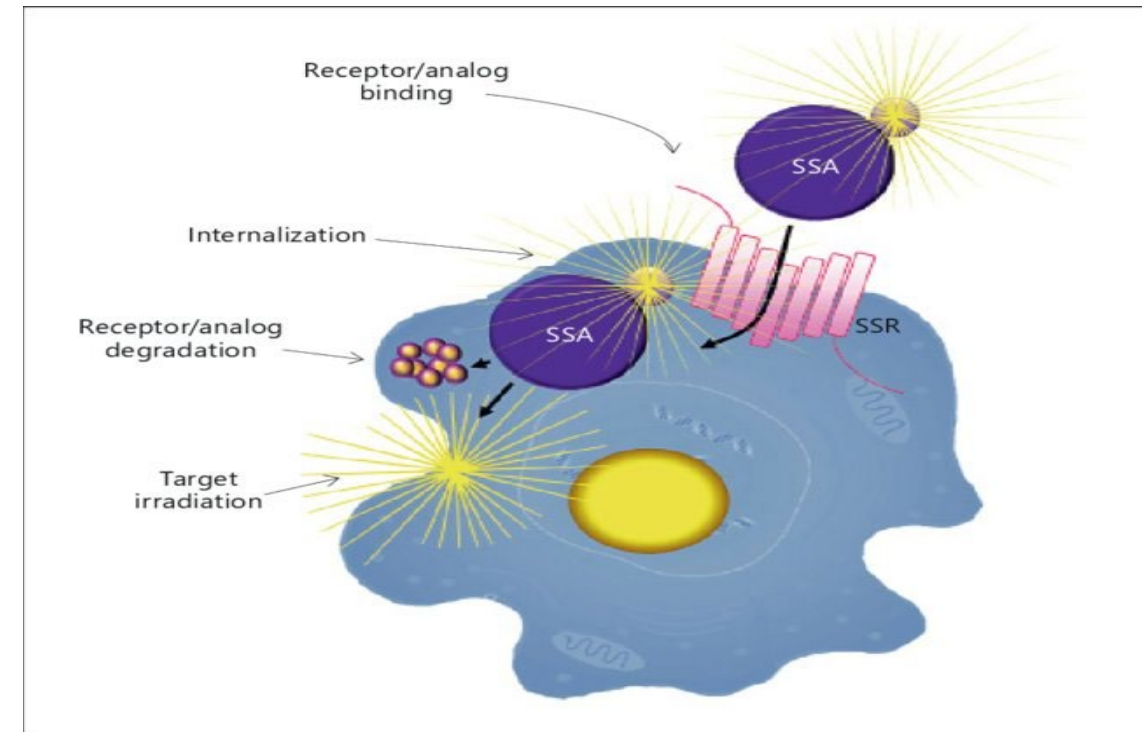
- If the tumour is resectable:
Surgery is often the first line option
- If the tumour is not resectable:
Monthly injections of Somatostatin Analogues (SSAs) help slow tumour growth by targeting the somatostatin receptors on tumour cells



Second-line Treatments

When first-line therapies become less effective, other drugs may be used:

- Peptide Receptor Radionuclide Therapy (PRRT) delivers radiation directly to tumor cells (intravenous agents).
- Targeted therapies, like everolimus or sunitinib, act by blocking specific signals that promote tumor growth (tablets).



Third-line Treatments and Beyond

If second-line treatments are not successful, additional options include :

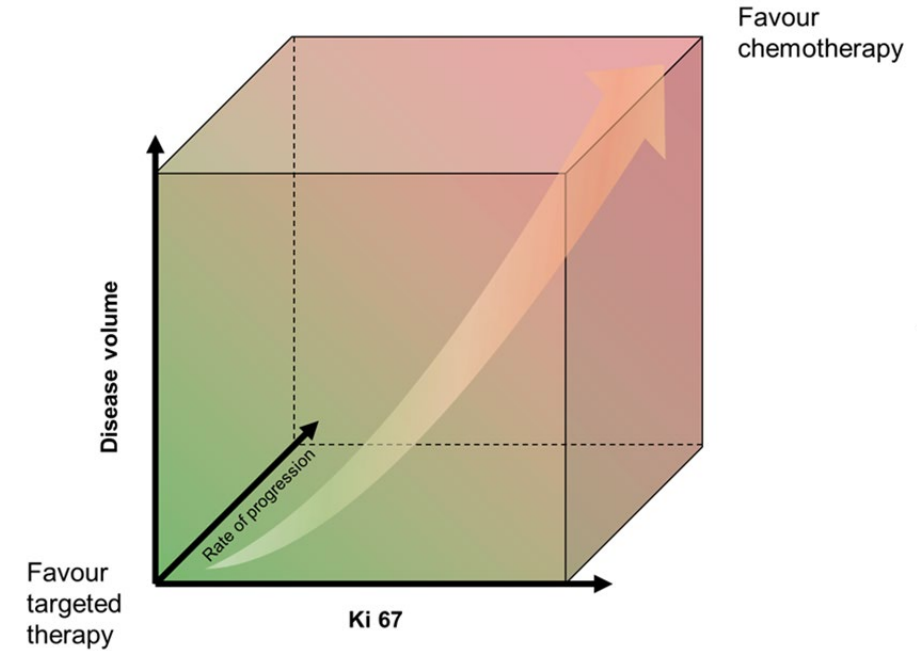
- Chemotherapy
 - such as the CAPTEM combination of oral drugs capecitabine and temozolomide
 - or intravenous drug combinations with platinum for more aggressive tumours
- Clinical trials



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What influences treatment outcomes

- Treatment outcomes depend on **patient factors**, such as age, overall health, and genetic profile, as well as **tumour factors**, including grade/Ki67 index, disease burden, and rate of progression.
- These considerations and **patient preferences** help guide the selection of the most effective and personalised treatment approach.
- Given the typically long survival associated with this disease, treatment decisions consistently prioritise maintaining **quality of life**.



“ITHAKA”

A poem by the Greek Poet Constantine P. Cavafy
(1863-1933)



*You are on your way to Ithaka,
may the road be long,
full of adventures and full of knowledge!*



PANEL DISCUSSION



PART THREE | (New) treatments: Clinician's perspective

Hans Hofland

Endocrinologist
ENETS Center of Excellence
Erasmus MC Cancer Institute
Rotterdam, The Netherlands



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Available treatments for NEN

Interventions

Surgery

**Endoscopic
resection**

Ablation

**Liver
embolization**

Medical therapies

**Somatostatin
analogues**

PRRT

**Targeted
therapy**

Chemotherapy

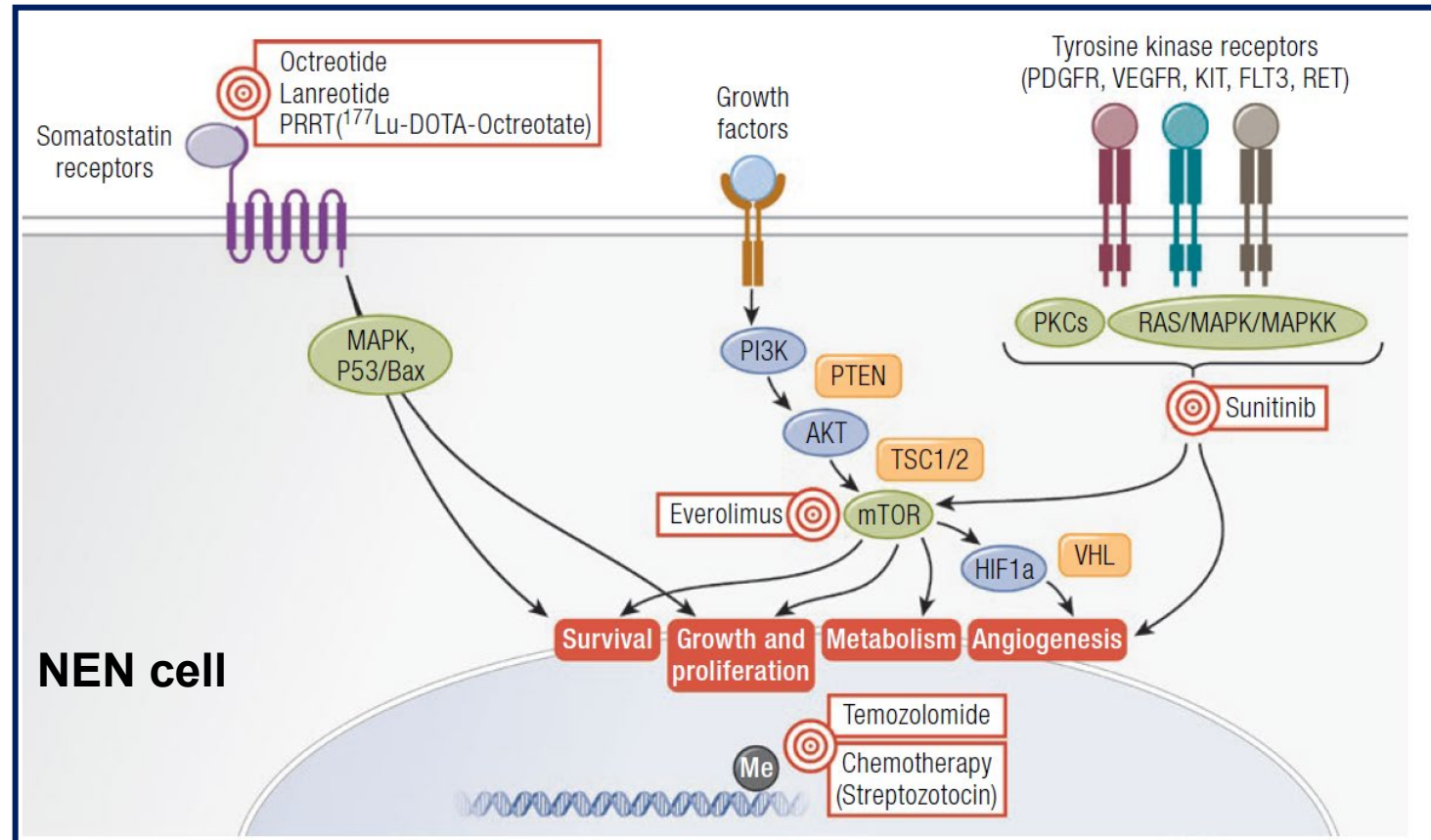
**Hormonal
therapy**

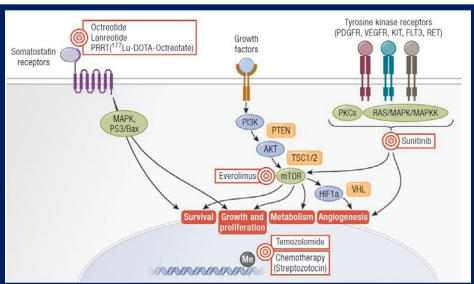
**Immuno
therapy**

**Tumor-
agnostic
therapy**



Several systemic treatments have been introduced over the last four decades

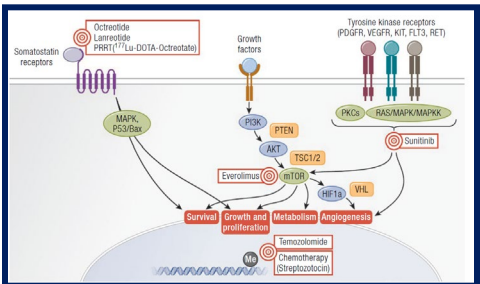




Somatostatin analogues

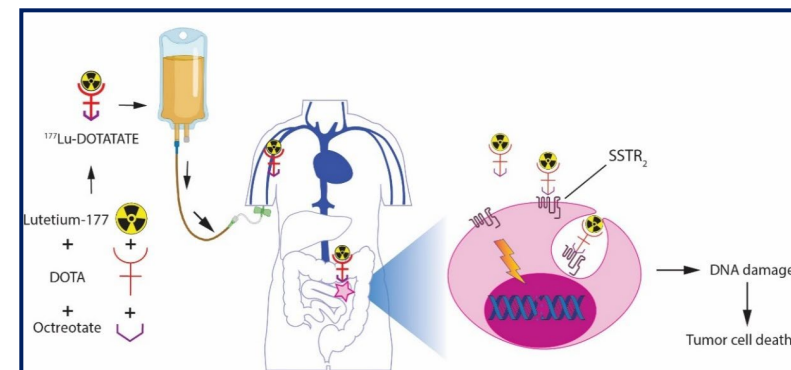
- Somatostatin is a naturally occurring anti-hormone
- Injections with somatostatin analogues octreotide and lanreotide are used in NET patients since the 1980s.
- Decrease hormonal production and improve symptoms
- Reduce tumour growth / stabilise disease
- New oral and subcutaneous (self-administration) octreotide formulations in clinical development

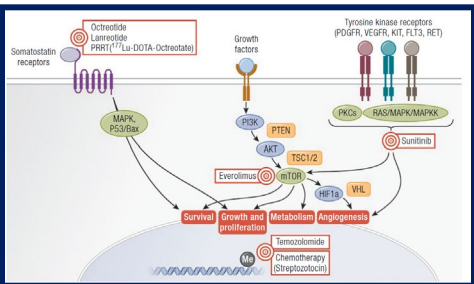




Peptide receptor radionuclide therapy

- Internal radiation therapy through administration of radioactive somatostatin analogues
- ^{177}Lu -DOTATATE is approved for grade 1-2 GEP NET and has recently shown positive effects in high grade 2-3 GEP NET in 1st line
- ^{177}Lu -DOTATOC currently in clinical trials, also for lung NET
- Several combination therapies and alpha emitters in clinical trials

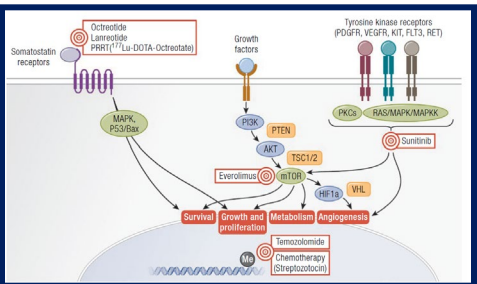




Targeted therapy

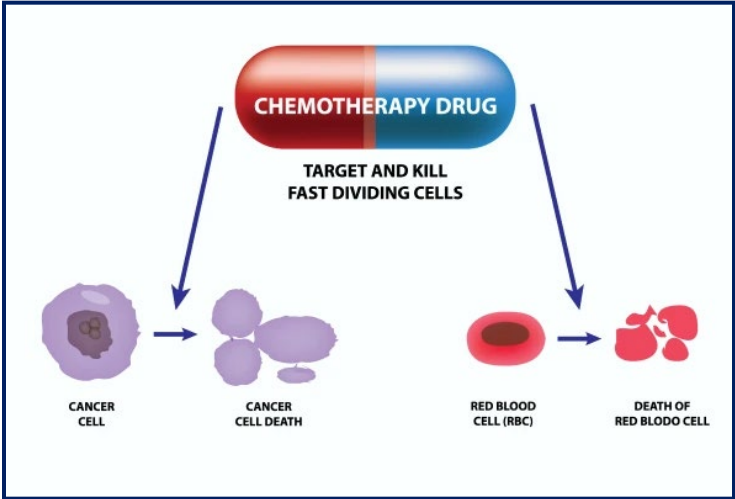
- Inhibits different signals inside tumour cells that lead to growth
- Everolimus:
 - Pancreas NET and non-functioning lung or bowel NET
- Several tyrosine kinase inhibitors:
 - Sunitinib for pancreas NET
 - Surufatinib for GEP NET (in China)
 - Cabozantinib for GEP NET (not yet approved)
 - *more in clinical trials...*

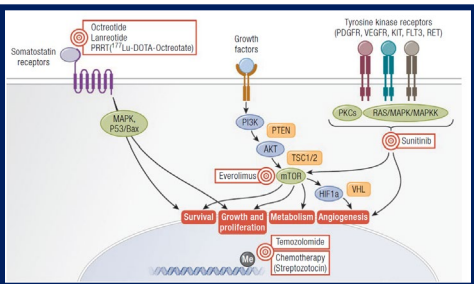




Chemotherapy

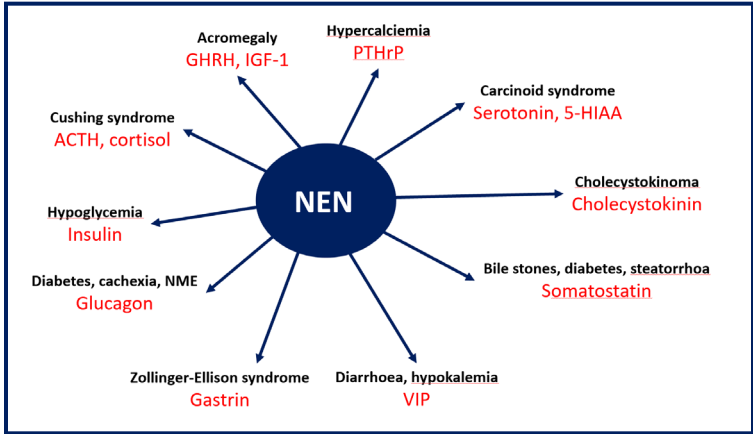
- Inhibition of DNA synthesis
- Streptozotocin & 5-fluorouracil for pancreas NET
- Oral capecitabine & temozolomide
 - Pancreas NET
 - NET grade 3
- Platinum & etoposide for NEC





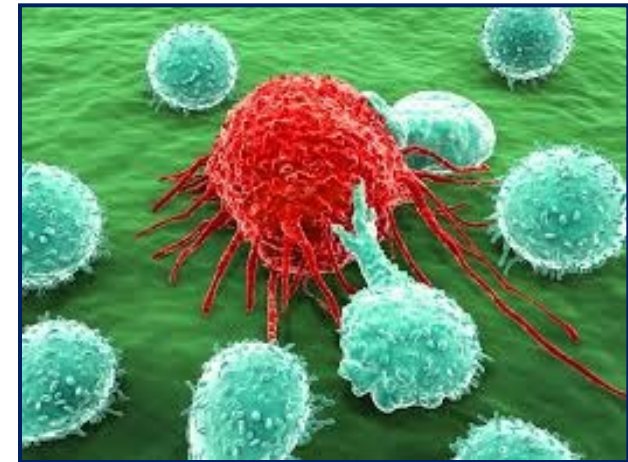
Hormonal therapy

- Somatostatin analogues are backbone of hormonal therapy
- Specific functioning syndromes require dedicated supportive therapy
- Telotristat for diarrhoea in carcinoid syndrome
- New insulin receptor antibody in development for insulinoma



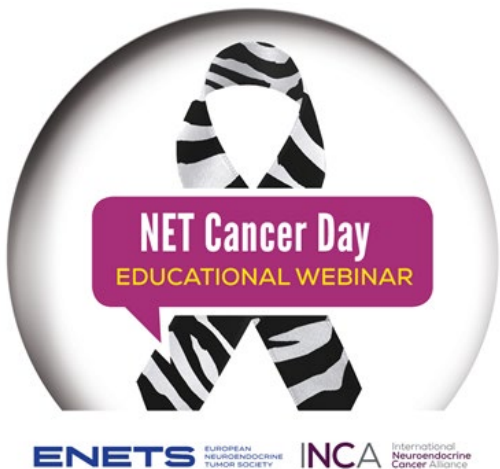
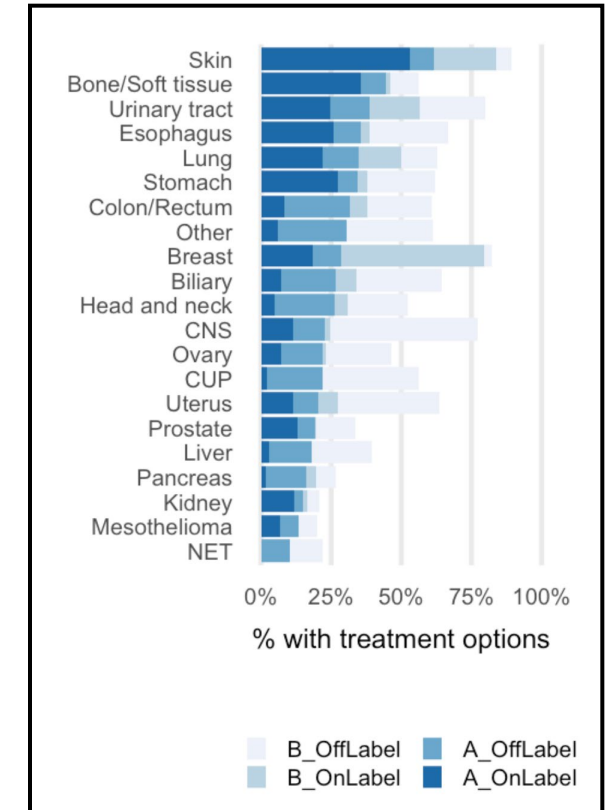
Immunotherapy

- Interferon alpha has been used in NET patients since the 1980s
 - Side effects
 - Limited availability
- Immune checkpoint inhibitors have thus far not shown to be of benefit in NET and might have a limited role in NEC
- CAR-T cells and bispecific T-cell engagers for NEN are still in early stages of development

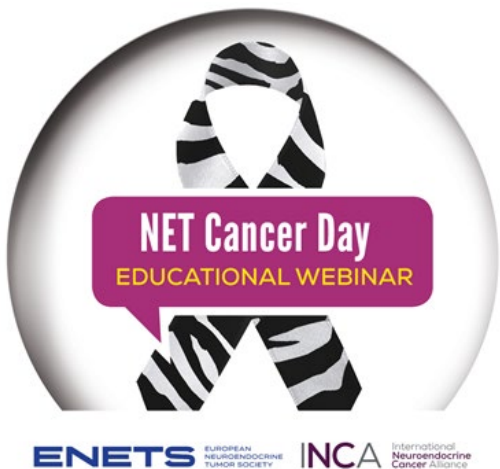


Tumour-agnostic therapy

- Specific DNA mutations can be targeted by precision drugs
- Due to their limited number of DNA mutations, this therapy is rarely available in NET



Thank you for your attention



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PANEL DISCUSSION



PART FOUR | Updates on Genomics

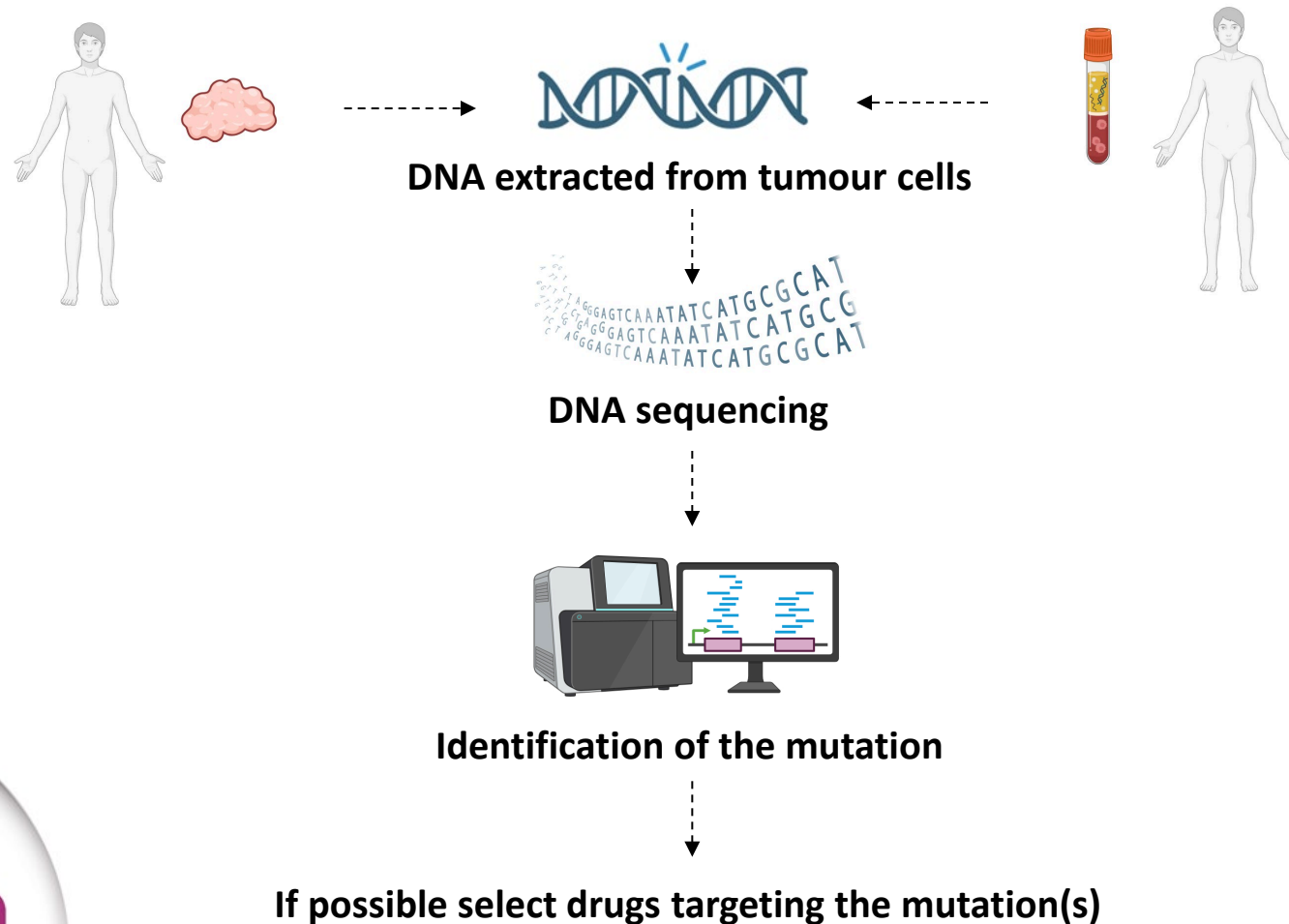
Ilaria Marinoni

Institute for Tissue Medicine and Pathology
University of Bern
Switzerland

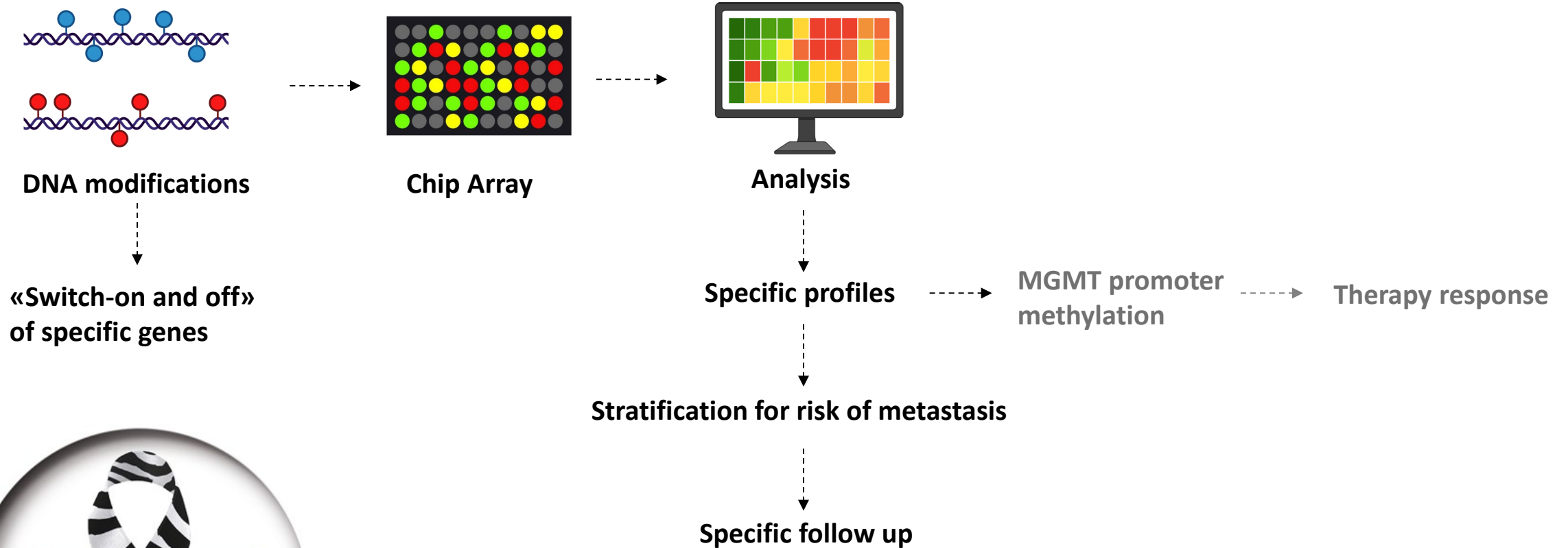


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Gene mutations for target therapy



DNA methylation for risk of relapse stratification and therapy response



Biomarkers

- Expression of specific markers in the cells of the tumour
- Activation of specific mechanisms for growth/progression in the tumour cells

Targeted therapy

Understanding progression of the tumour

Finding better treatment



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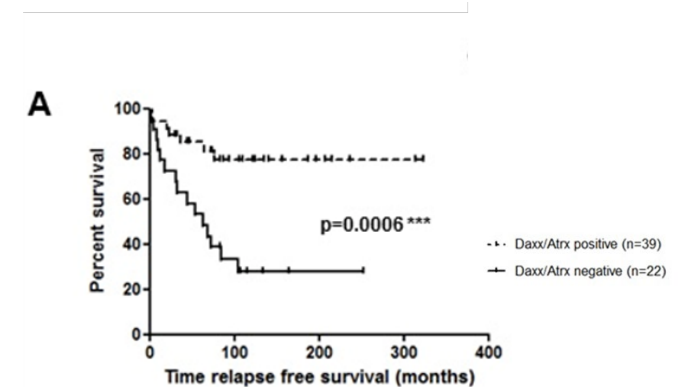
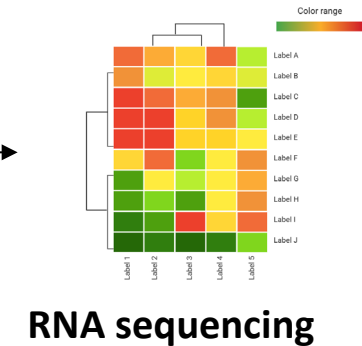
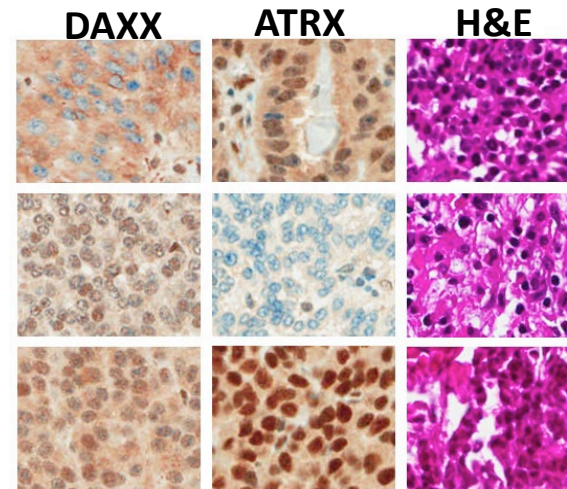
Biomarkers

- Expression of specific markers in the cells of the tumour
- Activation of specific mechanisms for growth/progression in the tumour cells →

Targeted therapy
Understanding progression of the tumour

Finding better treatment

Expression of specific protein

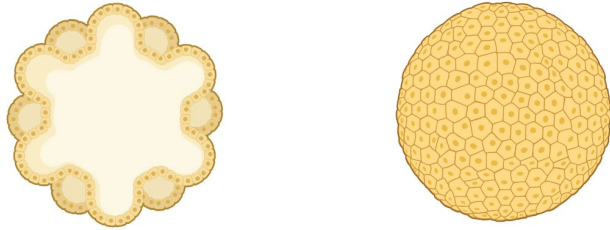


I. Marinoni et al. 2014



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Pre-clinical model



Patient derived organoids/
Patient derived tumoroids

- Understanding better the biology and behaviour of the tumour
- Identify new treatments



PANEL DISCUSSION



Closing Comments

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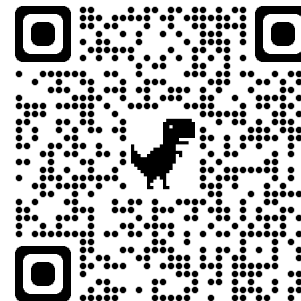
A BIG Thank You...

- To the speakers, moderators and discussants
- INCA Office
(Teodora KOLAROVA & Isabella ORONOVA)
- ENETS Office
(Martina FLESCHEN, Ulrike KNELL & Leah MATTHEWS)
- The ENETS Education Group
- YOU, the participants

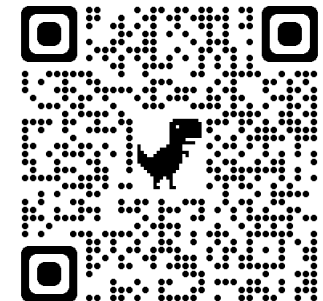
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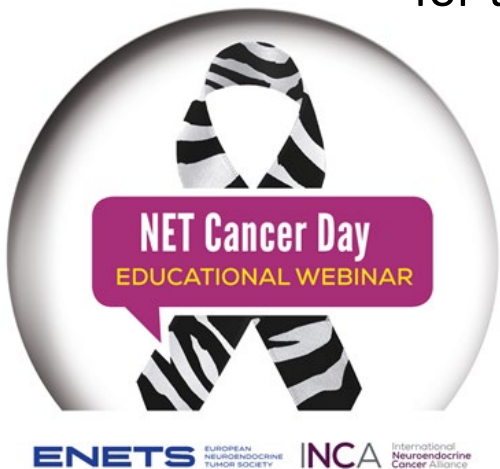
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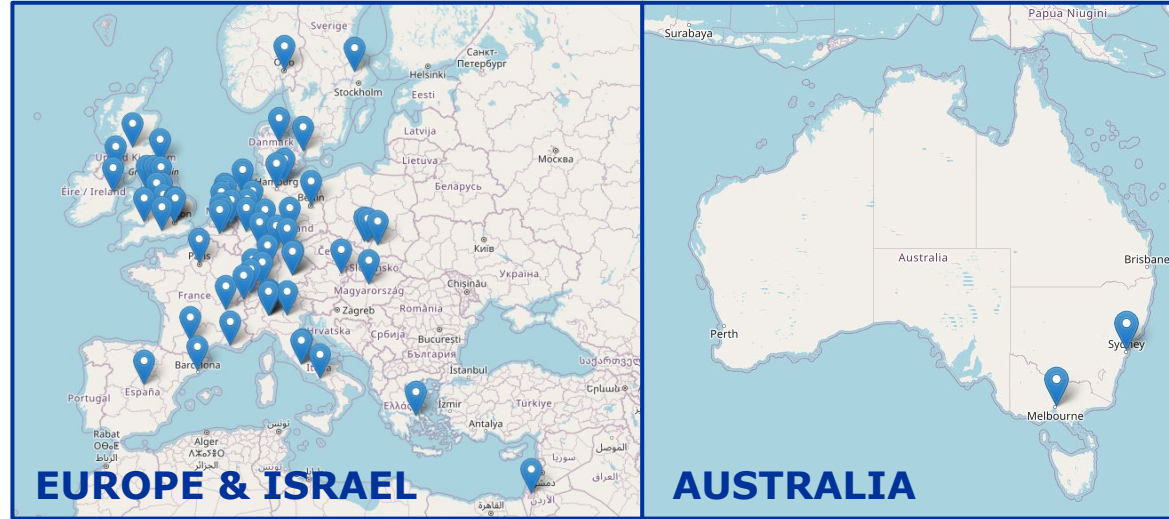


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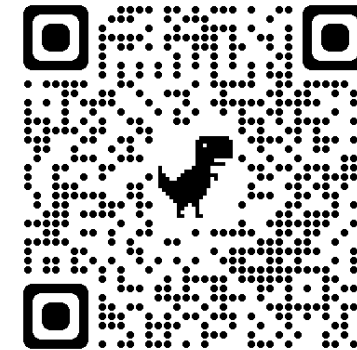


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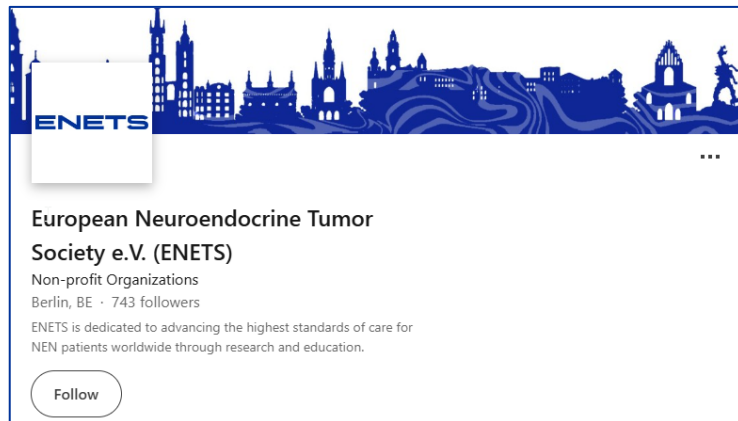
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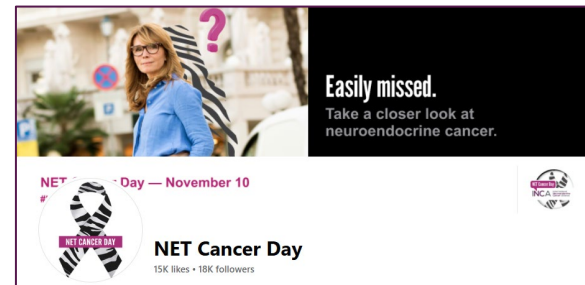
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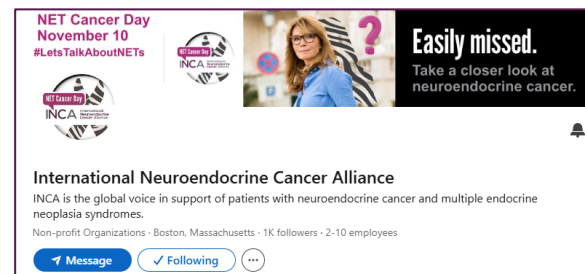
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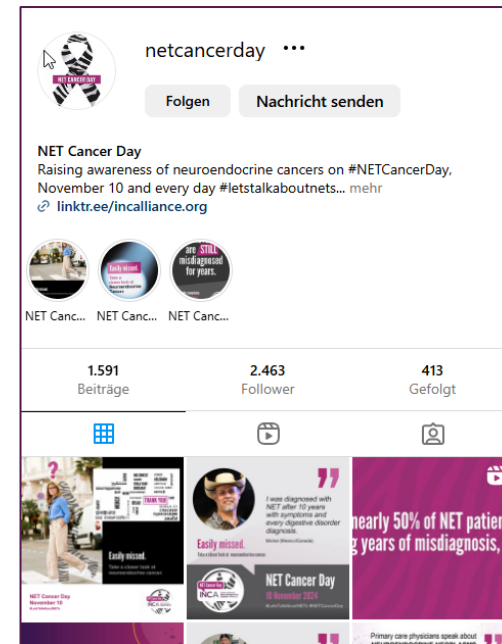
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