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Advances in the Management of NETs

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What Are NENs?

COMPLEX AND CONFUSING TERMINOLOGY

WHERE DO NENs ORIGINATE FROM?

WHAT CAUSES NENs?

What! NENs!? Are They Not Called NETs anymore…?

- NETs, NECs or NENs, what's the difference…?
  - **NEN**: NeuroEndocrine **Neoplasm**
  - **NET**: NeuroEndocrine **Tumor**
  - **NEC**: NeuroEndocrine **Carcinoma**
- **Neoplasm:** An abnormal mass of tissue that results when cells divide more than they should or do not die when they should
- **Tumor:** Essentially the same definition but…
  - The current WHO NEN classification has a different definition for a tumor…
- **Carcinoma:** Malignant neoplasm with the ability to invade and spread
  - Cancer that begins in the skin or in tissues that line or cover internal organs.

NCI Dictionary of Cancer Terms (https://www.cancer.gov/publications/dictionaries)

What Are NENs?

- NENs are malignancies (cancers) that can arise almost anywhere in the human body
  - NETs most commonly occur in the small intestines, lungs, pancreas and rectum
- NENs are an extremely heterogeneous group of cancers
  - The presentation, symptoms, diagnostic methods, therapy and prognosis vary widely among patients
- NENs arise from neuroendocrine cells which are widespread throughout the body
  - These cells have certain characteristics of both neural cells and endocrine cells

Why Do Humans Get NENs…?

- In most cases, we do not know…
- The risk factors for NENs are poorly understood
- Some can be related to genetic syndromes
  - Up to 10% of pancreatic NENs are related to certain inherited syndromes
    - Multiple Endocrine Neoplasia, Type 1 (MEN1)
    - von Hippel Lindau disease (VHL)
    - Tuberous Sclerosis
    - Neurofibromatosis
- First-degree relatives of patients with small bowel NETs have 5-10-fold risk of developing NETs compared to the general population
- Some studies suggest increased risk of NENs related to certain exposures
  - Chemicals (mining towns)
  - Certain occupations

Kaerlev L et al. J Occup Environ Med. 2002;44:516-22.
VanDerslice J et al. PLoS One. 2020;15:e0231991.
Neklason DW et al. Endocr Relat Cancer. 2016;23:93-100.

How Common Are NENs?

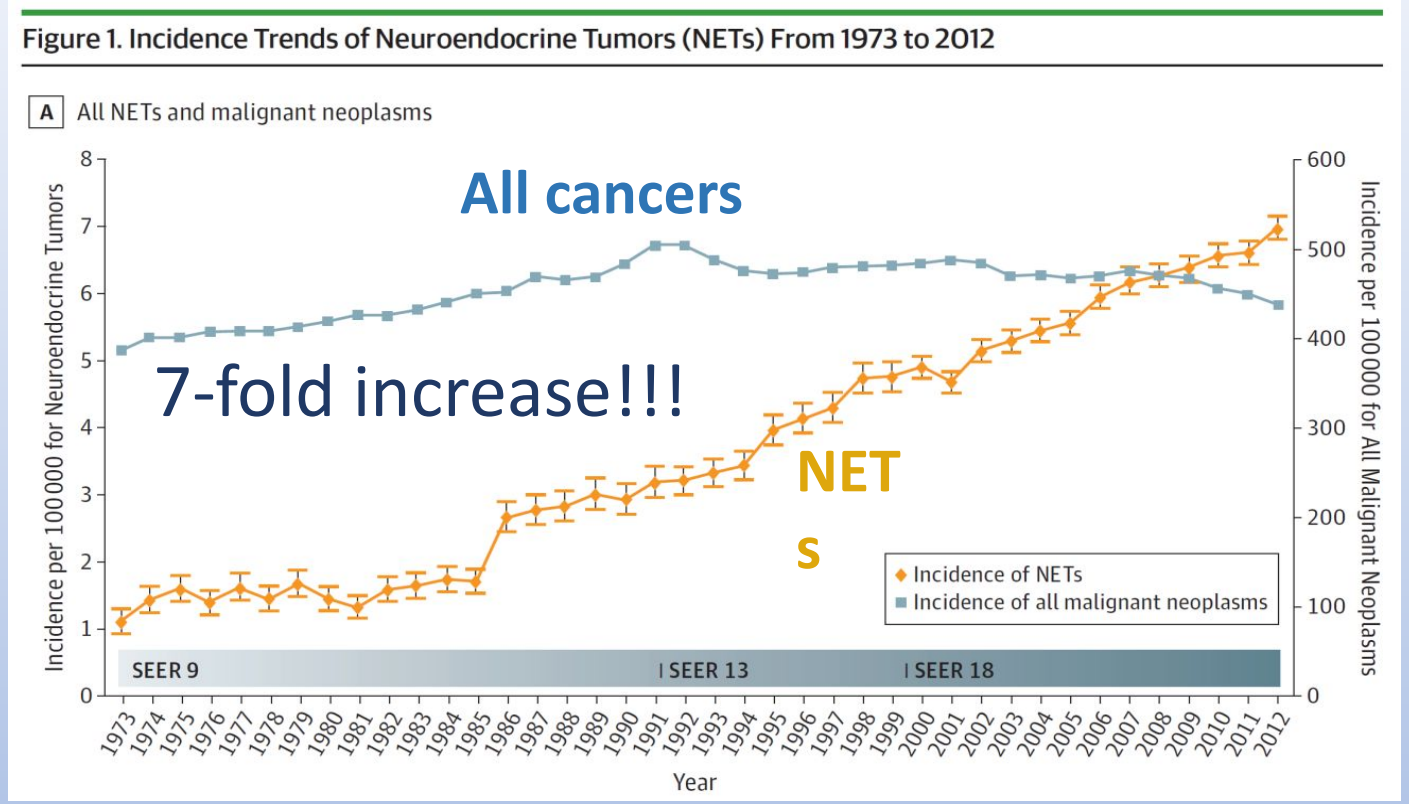
ACTUALLY, NOT SO RARE…

MORE NENs OVER TIME

EARLIER DIAGNOSIS

The Number of New NET Cases is Rising

- The incidence is rising (they are getting more common…)
  - All sites: 7/100,000
  - GI NETs: 3.65/100,000
- Median age at diagnosis: 63 years
- The most common sites of NETs
  - Lung
  - Small bowel
  - Pancreas
  - Rectum
  - Appendix



- **Incidence:** The number of new cases over a certain period of time
  - Compared with many cancers, the incidence of NETs is low (rare cancer)
- **Prevalence**: The number of subjects living with the disease at a particular time point
  - How many have an active NET today…?
  - High prevalence of NETs as patients live long

Dasari A et al. JAMA Oncol 2017;3:1335-1342.

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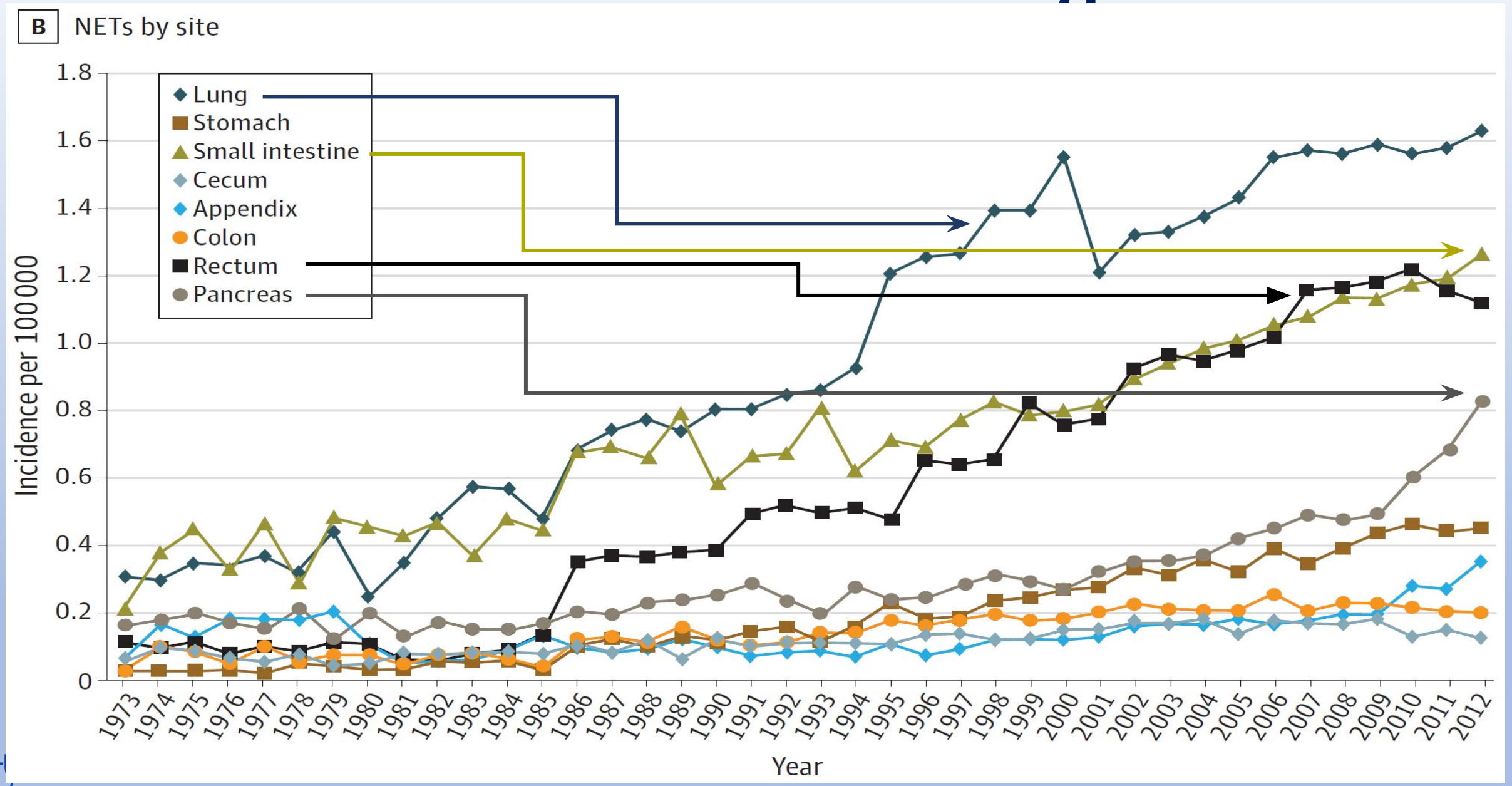
The Increase Is Seen Across All Types of NETs



Dasari A et al. JAMA Oncol 2017;3:1335-1342.

Why Are NETs Becoming More Common?

- Better diagnostic methods
  - Better scans
- Patients getting scanned for other reasons than looking for NETs
  - Incidental diagnosis
- Better awareness among healthcare providers and patients
- A real increase in incidence…?
  - If so, why…?

Tumor Grade and Differentiation

KNOW YOUR TUMOR – GRADE AND DIFFERENTIATION

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The Behavior of NETs Varies Greatly

- NETs can be among the slowest growing as well as the fastest growing cancers in humans
- The tumor grade and differentiation determine growth rate

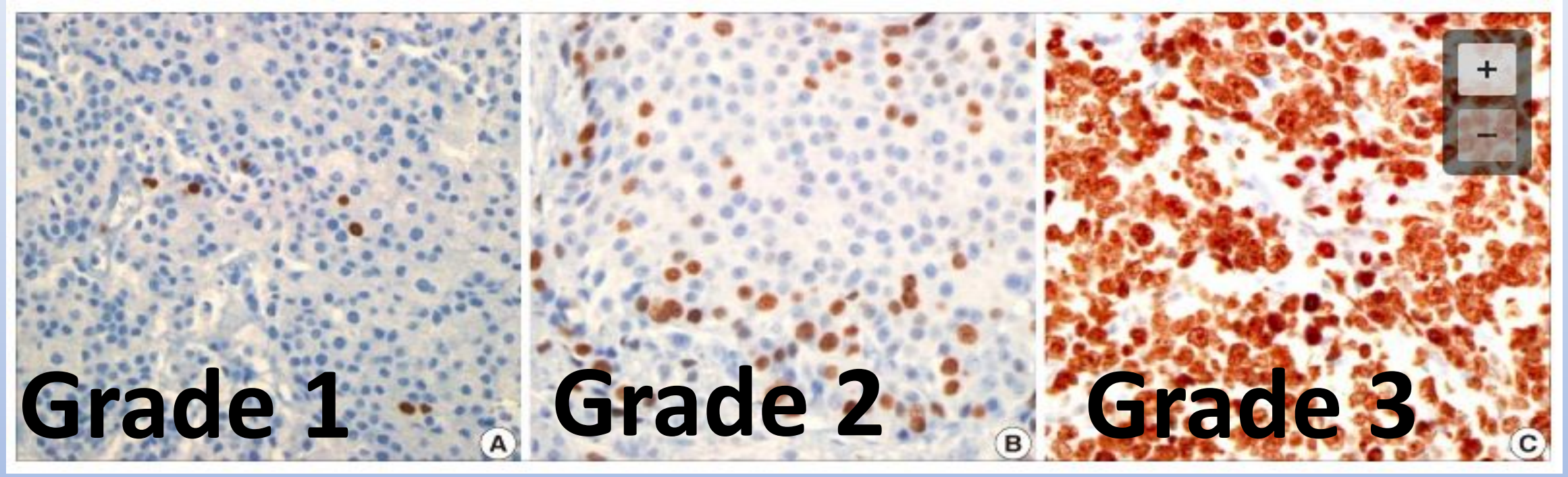
Grade 1 ⟷ **Grade 3**

What is Tumor Grade…?

- **Tumor Grade:** A system to predict how fast cancers will grow and spread
  - A tissue stain called Ki-67 (MIB-1) determines grade
    - Only stains actively dividing cells and not resting cells
    - More dividing cells □□ More aggressive NET
  - The tumor grade strongly predicts outcomes such as how fast the tumor will grow and how long it can be controlled with therapy

Ki67 – How Many Cells Stain Positive…?

< 3% 3 - 20% >20%



Less Aggressive More Aggressive

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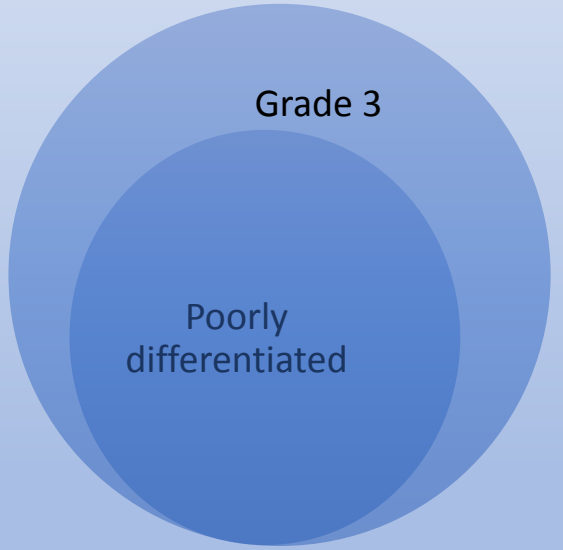
Cho M-Y et al. Korean Journal of Pathology 2013; 47: 227-237.

Not All Grade 3 NENs Are The Same…

- The key for predicting behavior of grade 3 (G3) NENs is the differentiation
  - Well-differentiated grade 3 NETs behave similarly to grade 2 NETs – on average a little faster growing
  - Poorly differentiated grade 3 NECs are aggressive tumors
- The distinction between G3 NECs and G3 NETs requires the eyes of an experienced pathologist
  - Substantial disagreement among expert pathologists
- The G3 NETs have a very variable behavior among patients

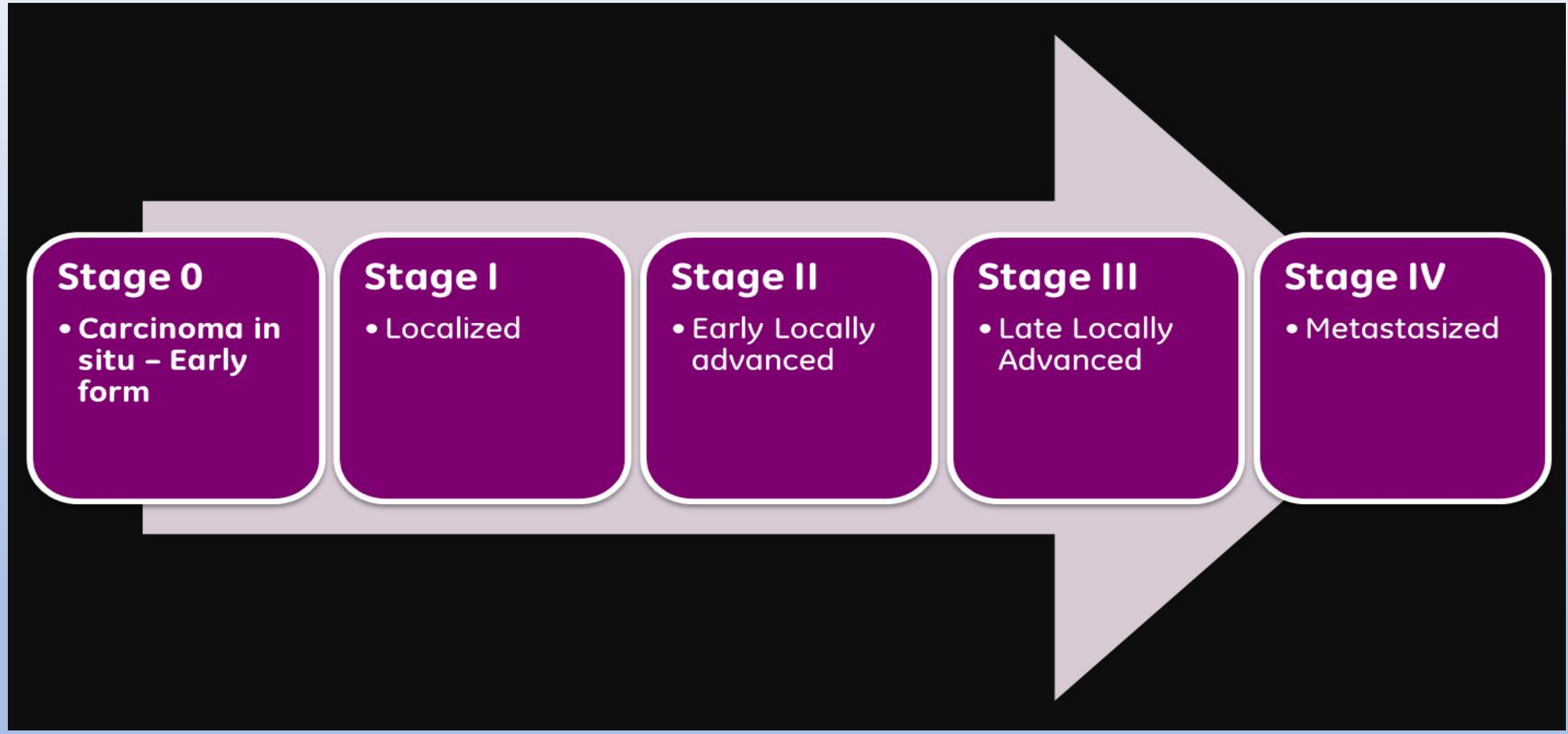
What is Tumor Differentiation…?

- **Tumor Differentiation:** How much the cancer resembles the normal cells it originated from
  - Does it look quiet and well-behaved (well differentiated) or does it look aggressive (poorly differentiated)?
  - Poorly differentiated tumors are more aggressive



- All poorly differentiated tumors are high grade (grade 3)
- Not all high-grade tumors are poorly differentiated

Stage – The Most Important Determinant of Prognosis



Staging systems vary among different NETs

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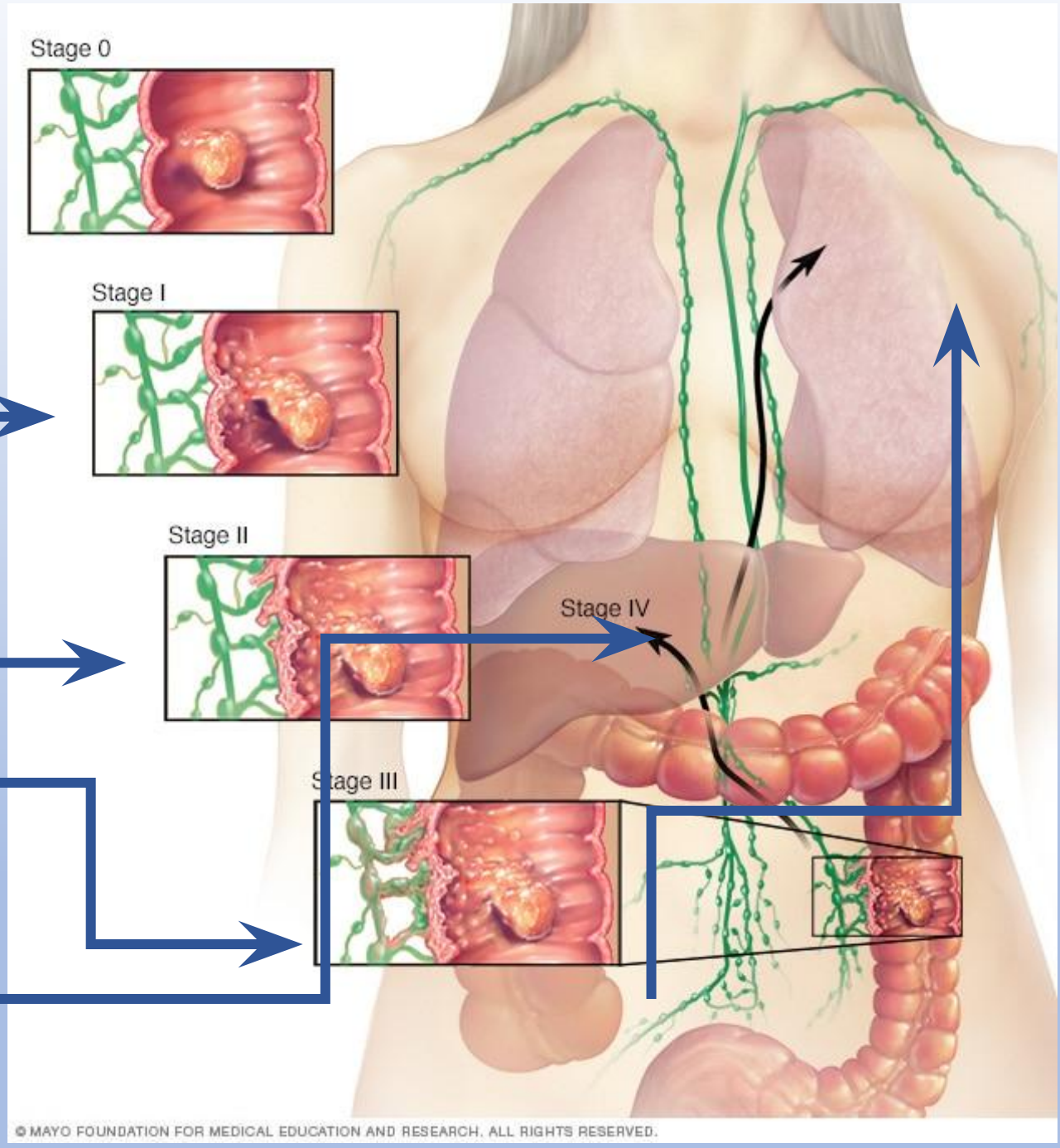
Wikimedia Commons

Stage

Stages 1-2
- Limited to the organ of origin

Stage 3
- Involvement of lymph nodes

Stage 4
- Metastases to other organs



The Mayo Clinic NET Program

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The Mayo NET Program

- Mayo Clinic has a longstanding history of running a very active NET program
- Comprehensive NET care requires complex multidisciplinary care
- Multiple teams make up the NET Team
  - Medical oncology
  - Surgery (abdominal and thoracic)
  - Radiology (including Nuclear Medicine and Interventional Radiology)
  - Gastroenterology (including nutrition)
  - Pathology
  - Pulmonology
  - Radiation Oncology
  - Cardiology and Cardiothoracic Surgery

The Referral Process at Mayo Clinic

- After the initial referral, we decide where the patients should be seen
- Most patients will be screened by medical oncology
  - If primary tumor is either within the abdomen or unknown, patients will be seen by a provider in the NET clinic
  - If the primary tumor is in the lung, the patient will be seen by thoracic oncology (the lung cancer clinic)
  - Rare patients will have a different primary such as bladder or prostate, female organs or the head and neck region and then will be seen by the appropriate tumor group/clinic
- Mayo has a strong tradition of multidisciplinary evaluation, very frequently utilizing what is called a tumor board

What Happens at the First Visit?

- The NET team will include other teams as indicated
- We frequently consult with the various surgical specialties
- Having top-notch pathology and radiology is absolutely crucial for getting the diagnosis correct
- Other teams may get involved including:
  - Nuclear Medicine: For diagnosis and planning of systemic radionuclide therapy
  - Gastroenterology: For various abdominal complaints and needs for certain procedures
  - Pulmonology: For diagnostic procedures and management of certain complications

At The First Visit, We Ask Ourselves…

- Did we get the diagnosis right…?
  - Somewhat surprisingly often, the diagnosis is not correct
  - Especially important for tumor grade and differentiation
- What is the stage of the cancer…?
  - This will determine if we are aiming for cure or for control
- Do we have everything we need to recommend on therapy
  - Often, there are tests that need to be done
- What are the patient's wishes for therapy and what are the goals?
  - Arguably, the most important question…

Things to Consider Before Starting Therapy

- Carefully consider patient and tumor characteristics before starting therapy
  - What may be appropriate for one is not appropriate for the other…
  - Patient comorbidities such as diabetes and hypertension may influence choice of therapy
- Consider financial toxicity
  - Many of the newer cancer therapies come at substantial financial cost to patients
- Consider reproductive toxicity
- Consider long-term toxicities and candidly discuss risks such as leukemia from PRRT (uncommon)
  - A younger patient with advanced but indolent NET may want to choose another treatment than PRRRT

Things to Consider Before Starting Therapy

- The Team Approach
  - There is usually no rush in starting therapy
  - It is better to get NET experts in other specialties involved early
  - Tumor Board
    - Multidisciplinary meeting
    - Not every patient needs to be presented at tumor board
    - Typically, the following specialties are present
      - Surgery
      - Oncology
      - Radiology/Nuclear medicine
      - Interventional Radiology
      - Pathology

Why Tumor Board…?

- Because more brains work better…
- Having multiple specialties involved early may change the initial approach
  - Medical oncologists are not good determining who is a surgical candidate
  - Sometimes there are several reasonable approaches
    - Discussion of the pros and cons of each approach
- Use the tumor board wisely
  - Especially useful when surgery or other regional/local therapy (such as liver-directed therapy) is being considered
- Tumor board presentation may translate to fewer visits for the patient

Recent Advances in NET Therapy

WELL-DIFFERENTIATED NETs

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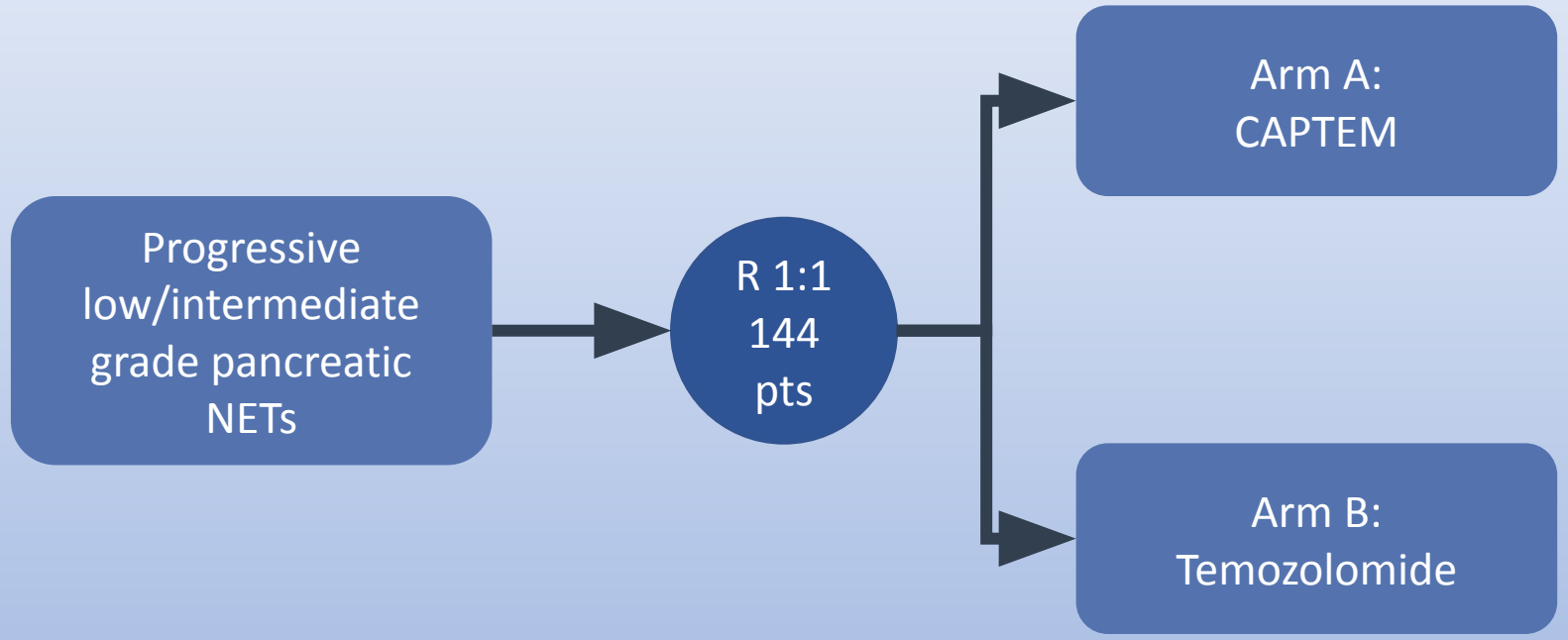
One Size Does NOT Fit All…

- In most NET case scenarios, there are several treatment options
- The options can range from observation only (doing nothing but observe) to various options of interventions
- Often, there are several equally appropriate options
  - Observation is often very appropriate
- If so, take into account:
  - The patient's wishes (always the most important thing)
  - The short and long term side effects
  - Cost of the intervention
  - Convenience of the intervention

Clinical Trials

WELL-DIFFERENTIATED NETs

ECOG E2211 – CAPTEM vs. Temozolomide



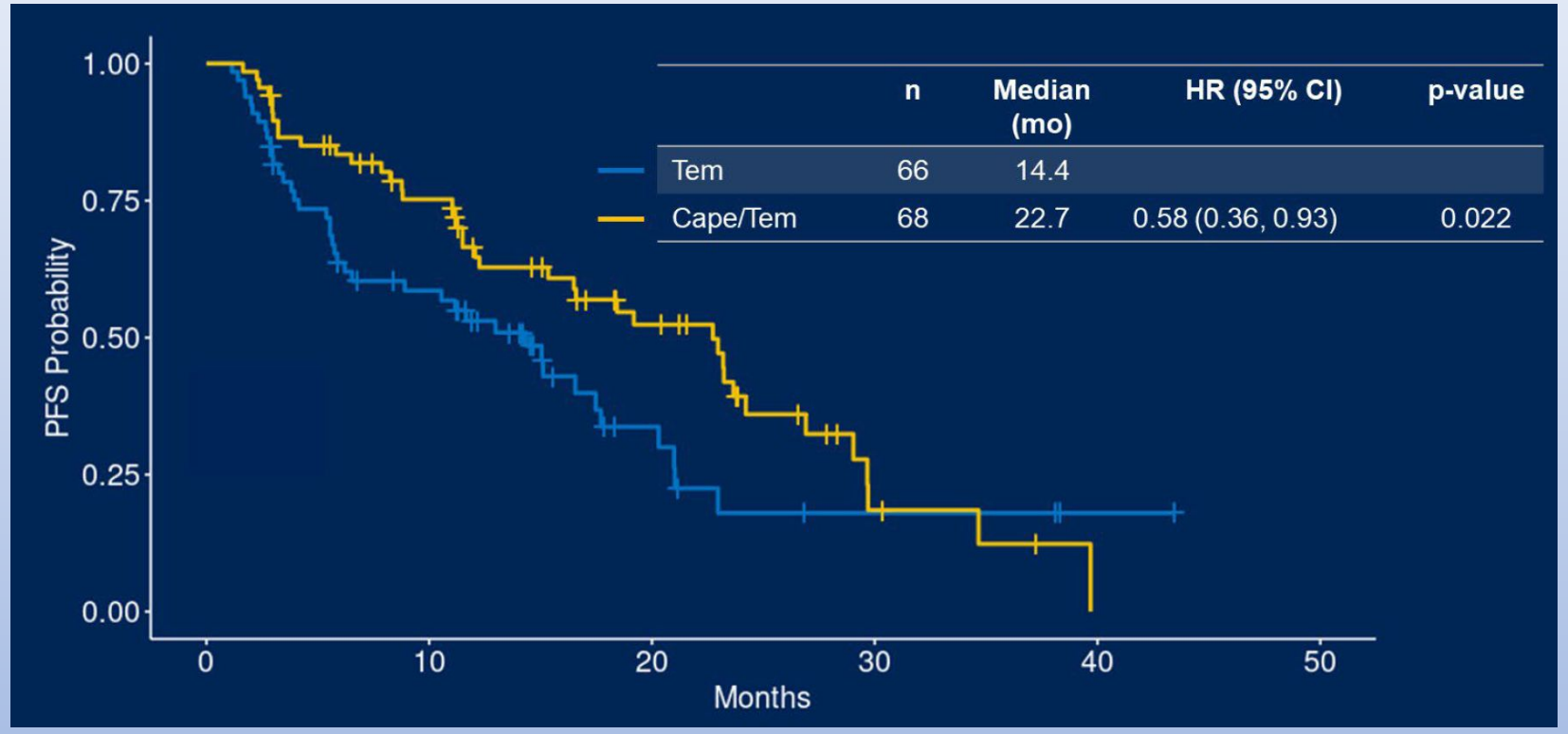
Primary Endpoint
- PFS

Secondary Endpoints
- ORR
- OS
- Safety/toxicity

Exploratory Endpoints
- MGMT analysis

Kunz PL et al. ASCO 2022.
Kunz PL et al. J Clin Oncol 2022

ECOG E2211 – Progression-Free Survival



Chemo	ORR	PFS	G3/G4 AEs
CAPTEM	40%	22.7 months	44%
TMZ	34%	14.4 months	22%

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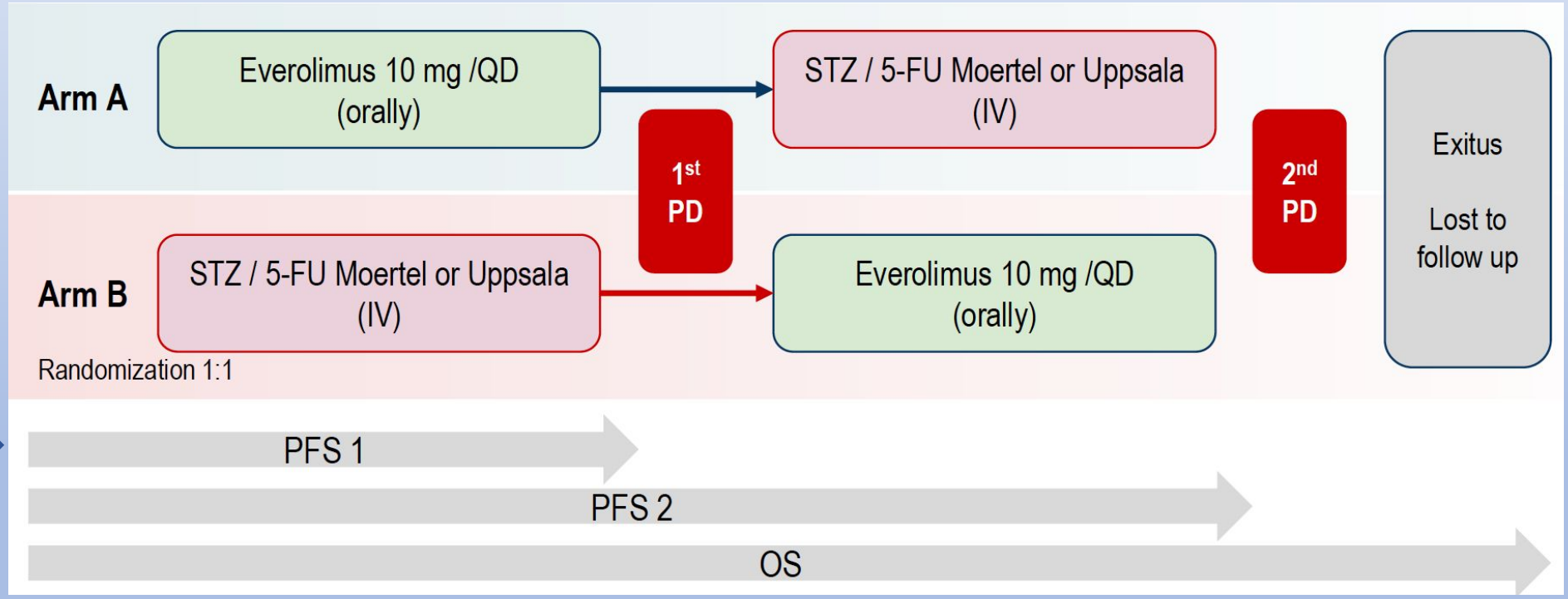
Kunz PL et al. ASCO 2022.
Kunz PL et al. J Clin Oncol 2022

SEQTOR (GETNE-1206)

Sequencing study: Everolimus followed by streptozocin (STZ) plus 5-FU or the reverse sequence in patients with grade 1 or 2 pancreatic NETs

Key eligibility:

- Advanced G1/2 pNET
- Prior SSA allowed
- No prior chemo, mTOR, inhibitor, TKI



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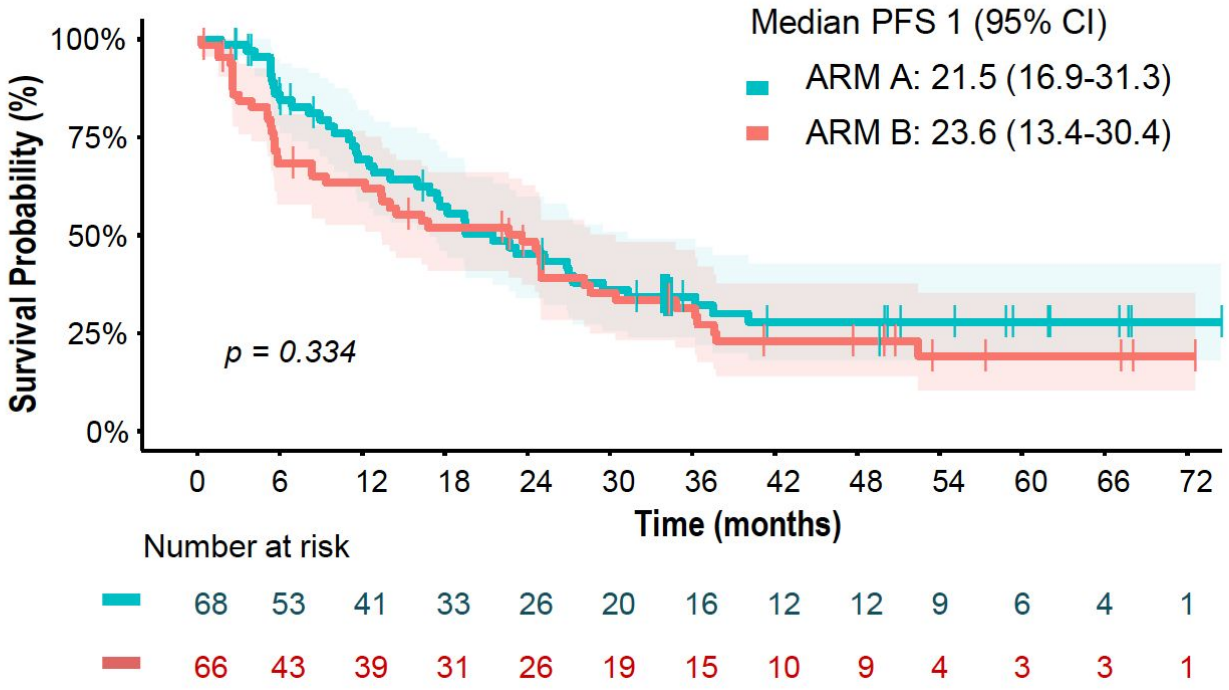
Salazar R et al. ESMO 2022

SEQTOR - PFS



PFS 1 rate; m (95% CI)	Arm A N = 68	ARM B N = 66
12 m	69.3 (58.7-81-9)	63.5 (52.7-76.6)
24 m	45.2 (34.1-59.8)	48.5 (37.5-62.8)
36 m	34.3 (24-49.1)	31.5 (21.4-53.9)

The primary endpoint (12-m PFS1): was similar for both arms (p= 0.425)

Comparison by fisher exact test

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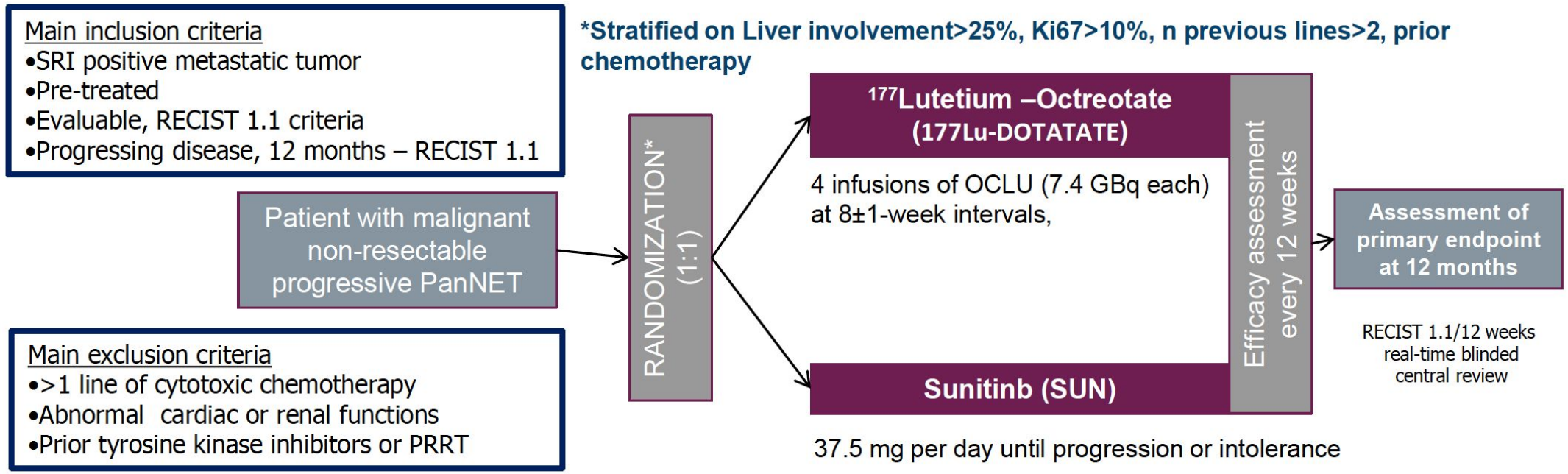
Salazar R et al. ESMO 2022

OCLURANDOM

^{177}Lu DOTATATE PRRT vs. sunitinib in patients with progressive pancreatic NETs

Inclusion between Feb 2015 – July 2020 in 10 French expert centers (GTE-RENATEN)



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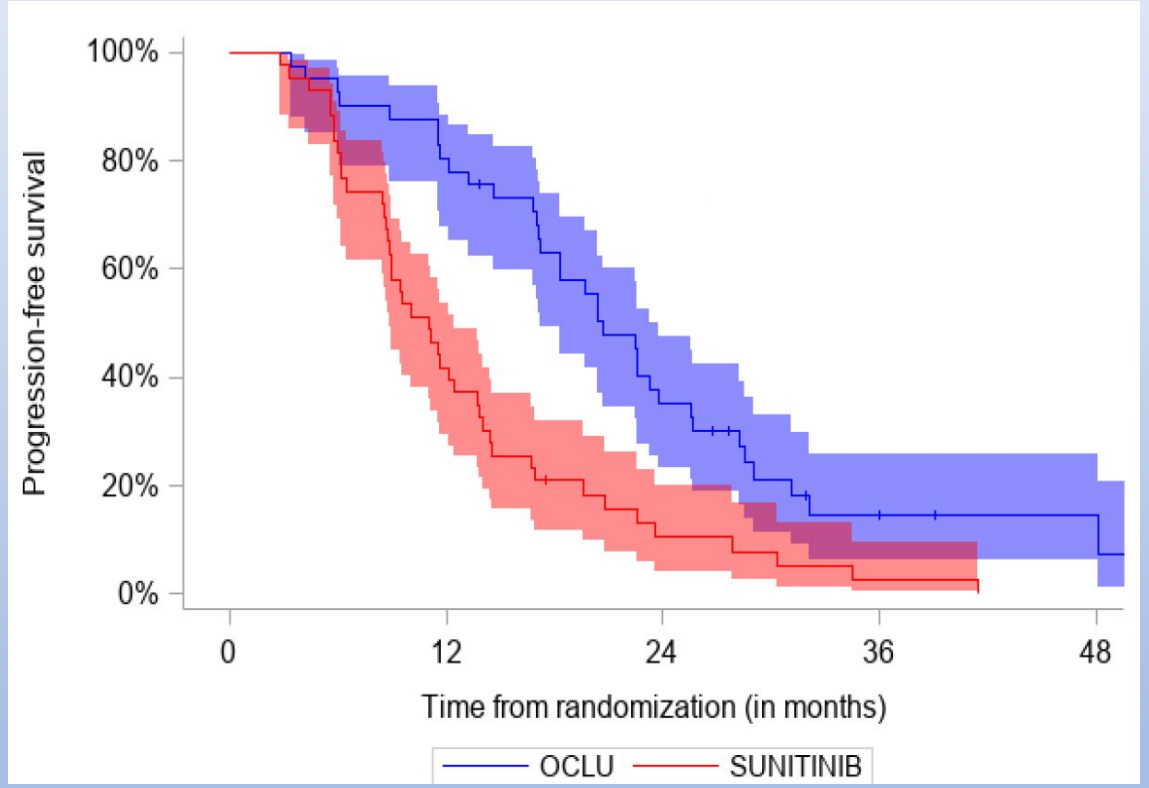
Baudin E et al. ESMO 2022

OCLURANDOM – Results

^{177}Lu-Dotatate Arm (n = 41)	n	%
12 month PFS	33	80%
PD or death at 12 months	8	20%

Sunitinib Arm (n = 43)	n	%
12 month PFS	18	42%
PD or death at 12 months	25	58%



Baudin E et al. ESMO 2022

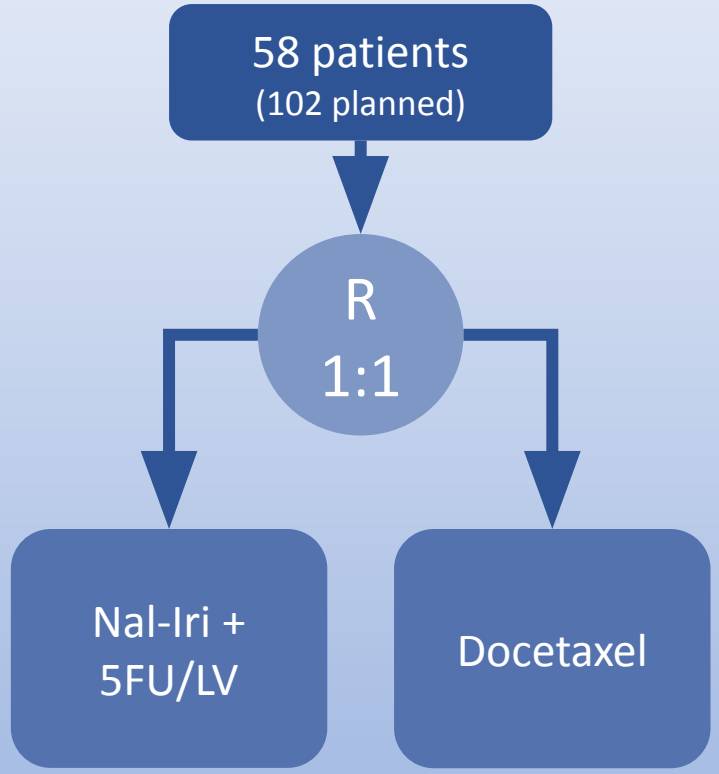
Take-Home Points…

E2211 CAPTEM vs. TMZ	• Longer PFS and higher ORR with CAPTEM • MGMT status associated with response to TEM
SEQTOR Everolimus vs. STZ/5-FU	• Similar PFS with both sequential strategies • STZ/5-FU with higher ORR
OCLURANDOM PRRT vs. Sunitinib	• PRRT resulted in longer PFS than sunitinib

Clinical Trials

POORLY-DIFFERENTIATED NECs

NET-02: Nal-Iri/5FU/LV vs. Docetaxel



Nal-Iri: Liposomal irinotecan; 5FU: 5-fluorouracil; LV: Leucovorin

Key Eligibility

- Extrapulmonary NEC (Ki67 >20%)
- Prior therapy with platinum-based regimen
- Progressive cancer
- ECOG PS ≤ 2

Primary Endpoint

- 6 month PFS

Secondary Endpoints

- ORR
- PFS
- OS
- Safety/toxicity
- QOL

Exploratory Endpoints

- NSE

Second-Line Chemotherapy

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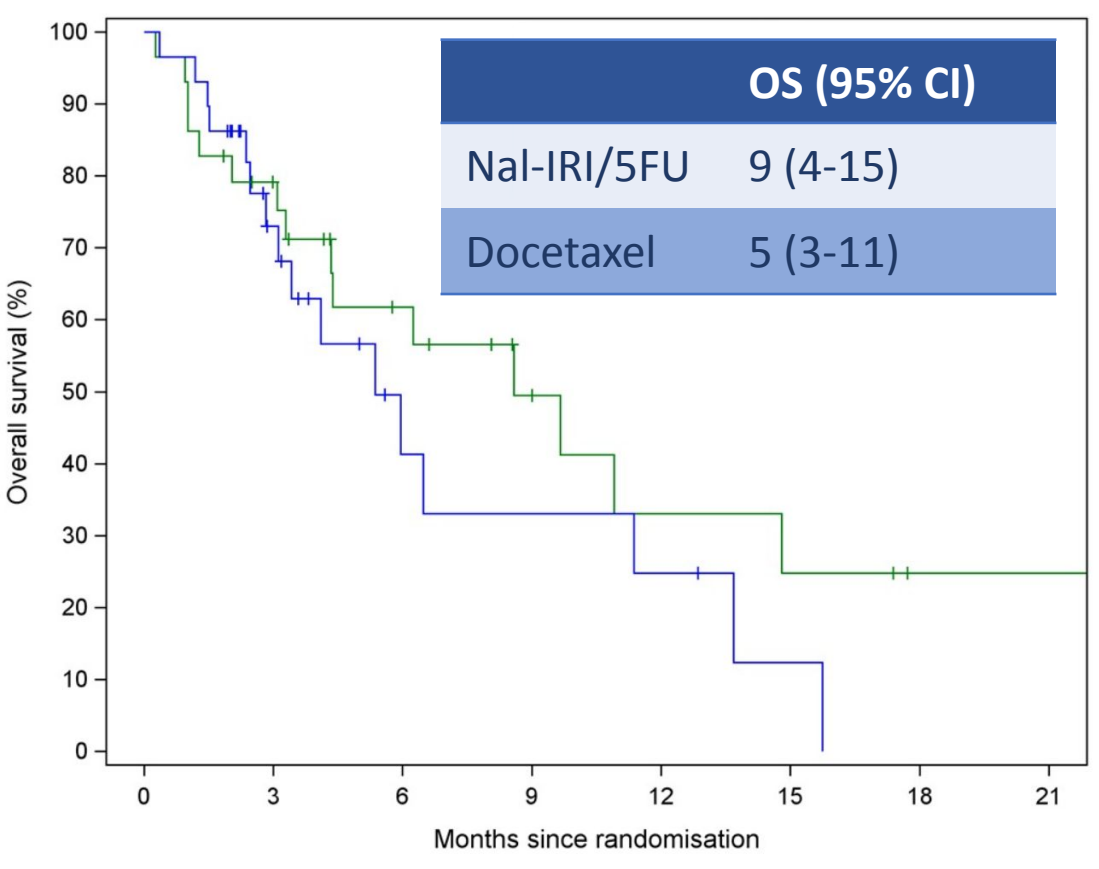
McNamara MG et al. ASCO 2022

NET-02: Nal-Iri/5FU/LV vs. Docetaxel

The overall survival was longer in the Nal-Iri group



	OS (95% CI)
Nal-IRI/5FU	9 (4-15)
Docetaxel	5 (3-11)

The primary endpoint was met

	PFS at 6 months
Nal-IRI/5FU (n=3)	31%
Docetaxel (n=3)	13.8%

Objective response rate similar across groups

	ORR % (95% CI)
Nal-IRI/5FU (n=3)	10.3 (2.2-27.4)
Docetaxel (n=3)	10.3 (2.2-27.4)

Unimpressive median PFS in both groups

	Median PFS (95% CI)
Nal-IRI/5FU	3 (2 – 6)
Docetaxel	2 (2 – 2)

McNamara MG et al. ASCO 2022

PRODIGE 41-BEVANEC

Second-line/salvage therapy: All patients previously progressed on platinum/etoposide

Randomized, **non-comparative** phase II trial, with no factor of stratification

- Advanced, refractory GEP and unknown primary NEC (**TENpath review**)
- PS 0-2
- Progression after first-line PE chemotherapy
- Unresectable locally advanced or metastatic
- Measurable disease (RECIST 1.1)

R 1:1

N = 126

Folfiri IV every 2 weeks + bevacizumab 5mg/kg IV every 2 weeks

Folfiri IV every 2 weeks

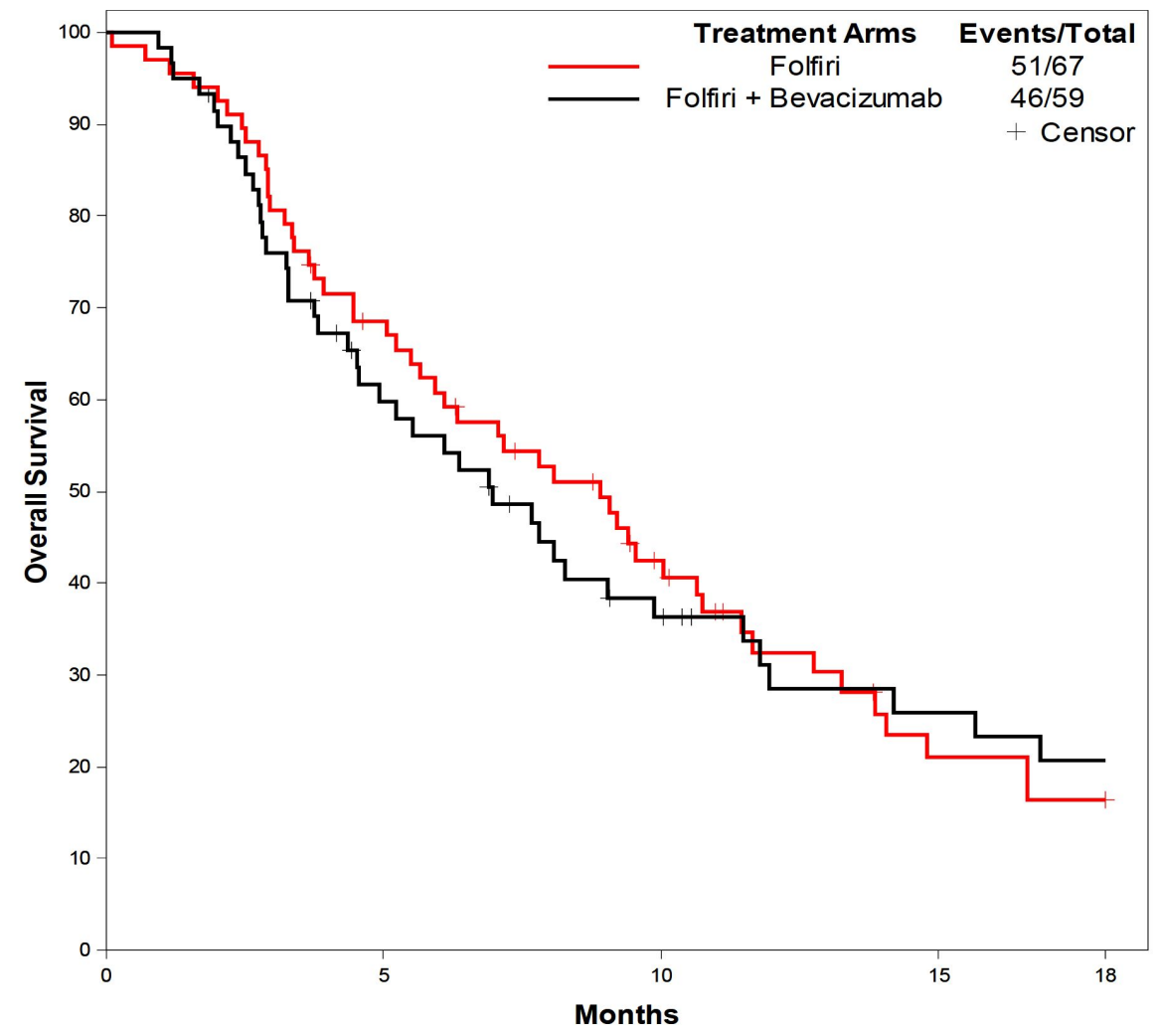
Until progression or unacceptable toxicity (2 years max)

Primary endpoint: >50% of patients alive at 6 months in experimental arm (type I error 10%, power 85% => 59 pts starting CT)

(Folfiri as control arm)

Walter T et al. ESMO 2022.

PRODIGE 41-BEVANEC - Results



Overall survival similar across groups

Regimen	OS at 6 months	Median OS
FOLFIRI/Bev (n=59)	52.5%	7 months
FOLFIRI (n=67)	58.2%	8.9 months

Objective response

Regimen	Overall Response Rate
FOLFIRI/Bev (n=59)	25.5%
FOLFIRI (n=67)	18.3%

Bottom Line

- No added benefit of bevacizumab
- This trial provided evidence for FOLFIRI in patients with NECs

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Walter T et al. ESMO 2022.

ECOG-ACRIN EA2142

RANDOMIZE

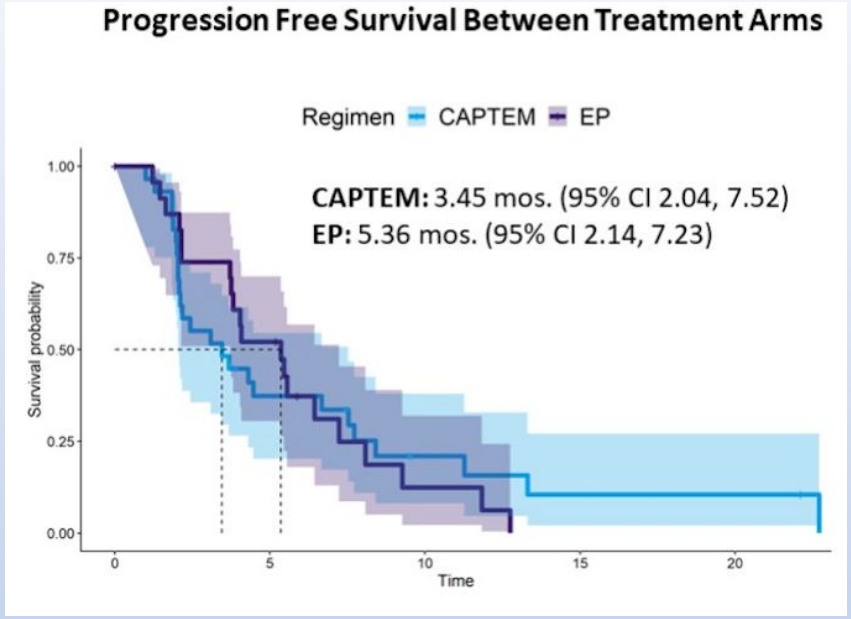
n=80

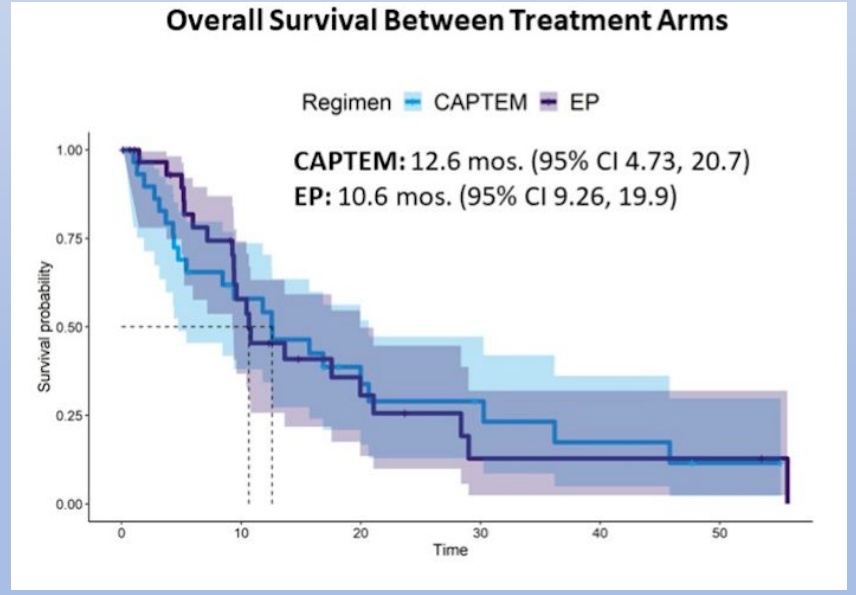
Arm A
- Capecitabine 750 mg/m² orally every 12 hours on days 1-14
- Temozolomide 200 mg/m² orally daily on days 10-14
- Cycle is 28 days

Arm B
- Cisplatin 25 mg/m2 IV daily days 1-3
- Etoposide 100 mg/m2 daily days 1-3

OR

- Carboplatin AUC 5 on day 1
- Etoposide 100 mg/m2 daily days 1-3
- Cycle is 21 days





- The study was closed early due to futility
- No difference in PFS and OS between arms

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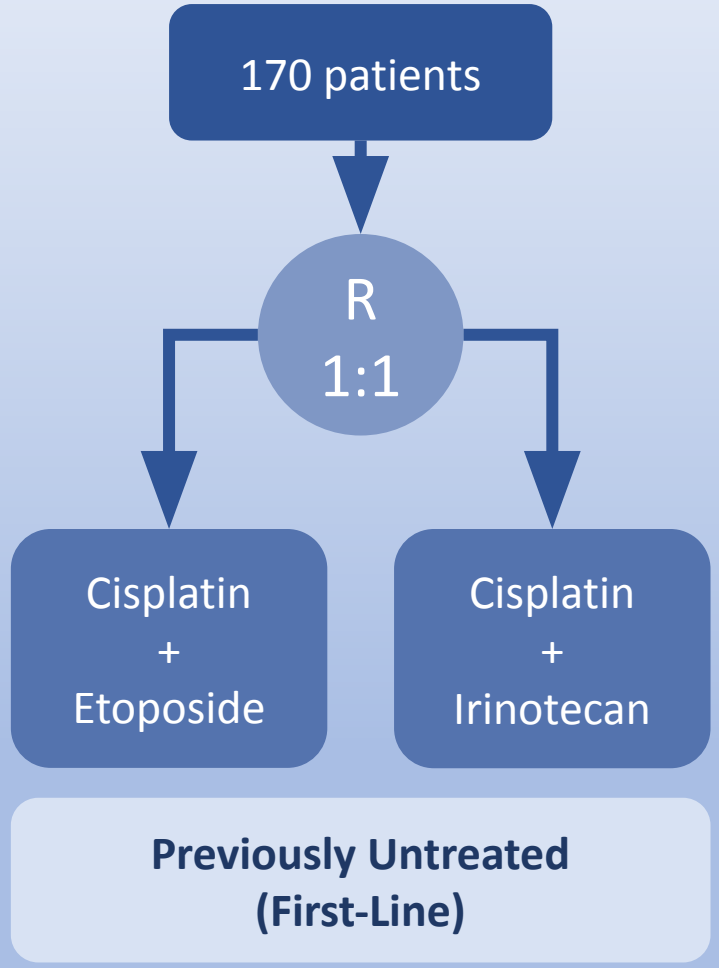
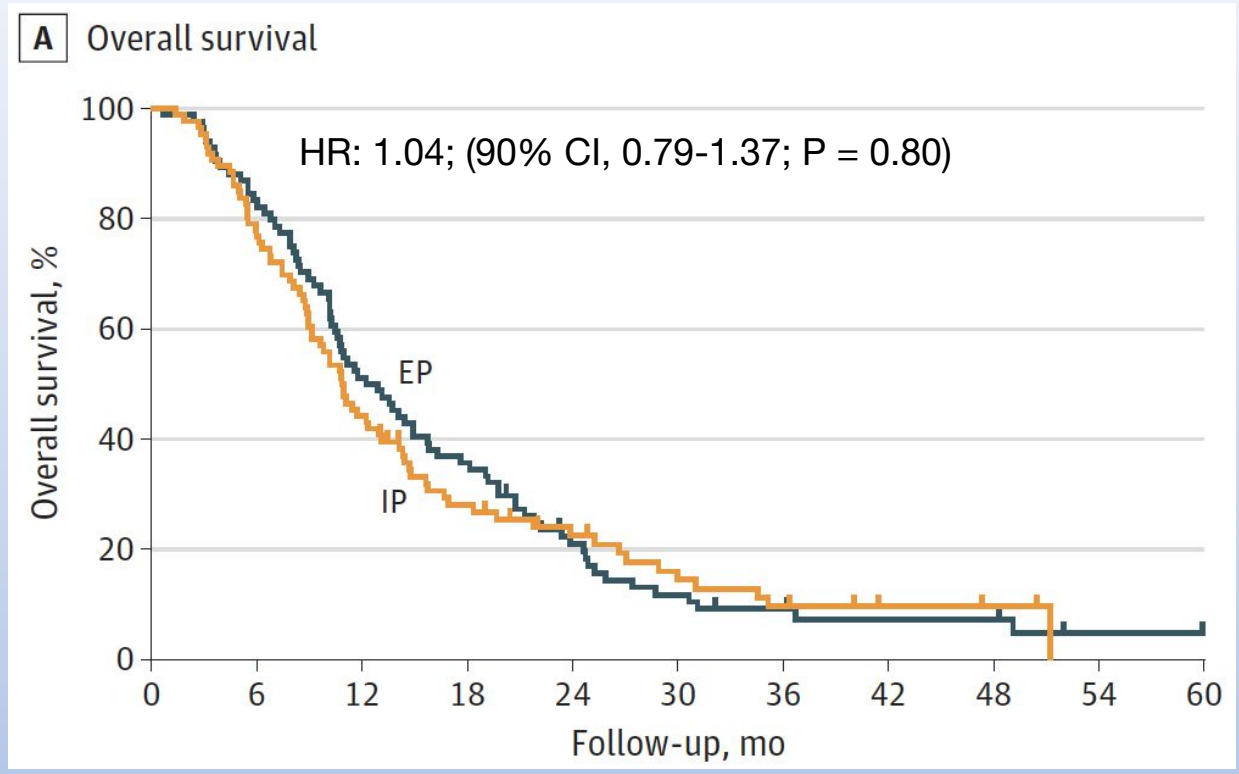
Eads J et al. ASCO 2022

TOPIC – NEC





Regimen	ORR	PFS	OS
EP (Eto+Cis)	55%	5.6 months	12.5 months
IP (Iri+Cis)	53%	5.1 months	10.9 months

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Morizane C et al. JAMA Oncol. 2022;8:1447-1455.

Take-Home Points…

NET-02 Nal-Iri/5FU vs. Docetaxel	• Nal-Iri/5FU with modestly longer PFS and OS • Outcomes in both groups were poor
BEVANEC FOLFIRI vs. FOLFIRI/Bev	• No added benefit from bevacizumab • FOLFIRI is an effective second-line regimen
ECOG ACRIN EA2142 Platinum/etoposide vs. CAPTEM	• No significant difference (trial closed early) • G3 NETs and NECs need separate trials
TOPIC NEC EP vs. IP	• Both regimens effective • Do these results apply in the Western world?

Other Studies

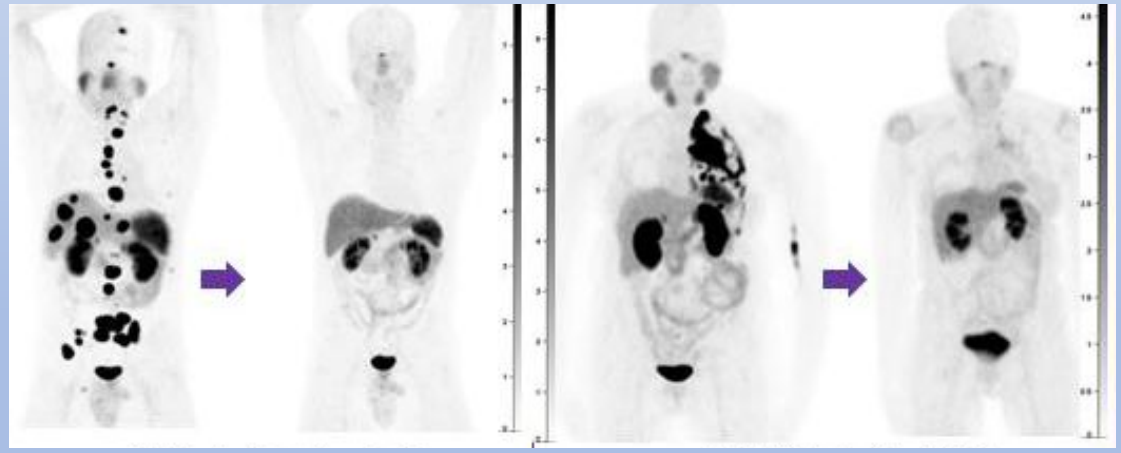
ADVANCES IN RADIONUCLIDE THERAPY

OTHER PRACTICE CHANGING STUDIES

Alpha Particle PRRT

- ^{225}Ac PRRT + capecitabine
  - 91 patients
    - 63% prior ^{177}Lu PRRT
    - 22% prior chemo
    - 33% pancreatic NETs
    - 31% ECOG PS 2-3
  - 24-month OS: 71%
    - Prior PRRT refractory: mOS 26 months
  - 24-month PFS: 68%
    - Prior PRRT refractory: mPFS 30 months
  - ORR: 52%
  - Prior PRRT predicted worse outcome

- ^{212}Pb-DOTAMTATE
  - 20 patients
  - Dose-escalation trial
    - 10 patients received the highest dose
  - ORR 80%



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Ballal S et al. J Nucl Med 2022
Delpassand E et al. J Nucl Med 2022

When Less is More…

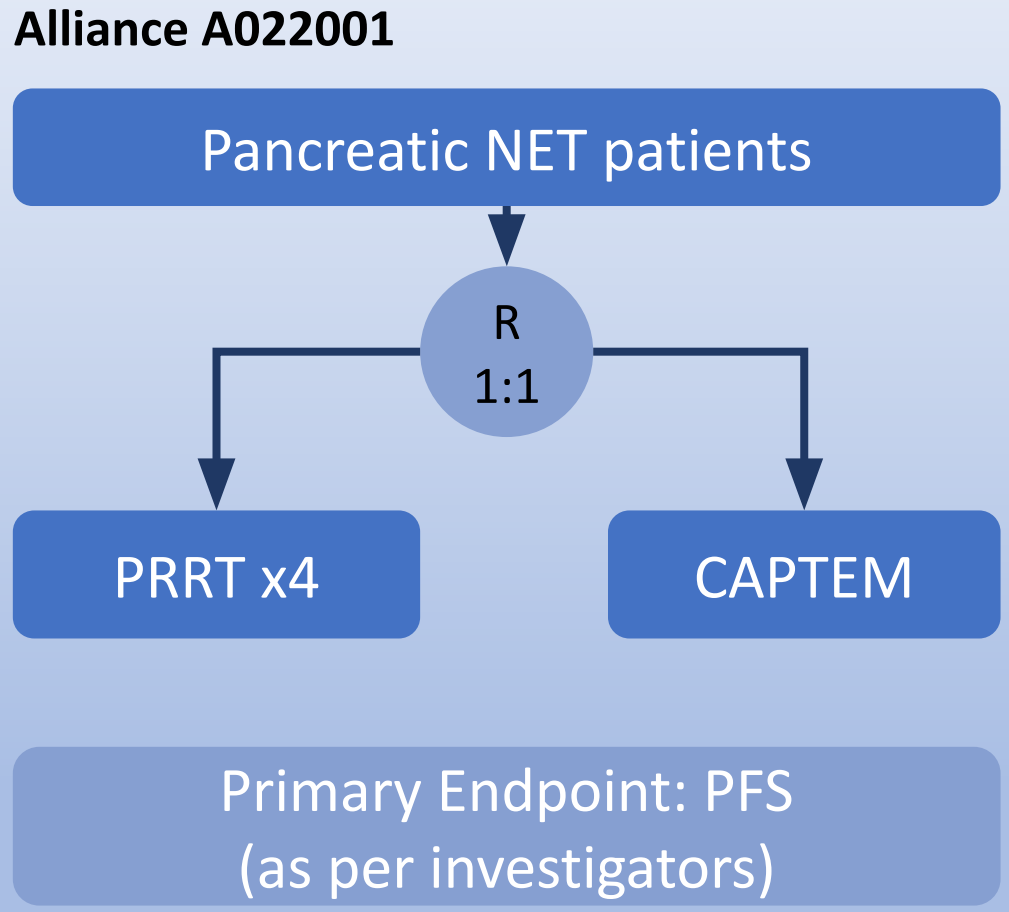
- Localized pancreatic NETs (pNETs)
  - Small pNETs (<2 cm) can be safely observed in most cases
  - Observation is not appropriate if there are symptoms of hormone production
  - A large study of 500 patients with small pNETs showed that observation is very safe and most tumors do not grow
  - Eventually, there maybe growth requiring intervention
- Small appendix NETs (aNETs)
  - A recent large study showed that a simple appendectomy is sufficient for less than 2 cm in size
  - Before, many patients underwent a 2nd surgery called right hemicolectomy
    - That is probably not needed for most patients
  - Small aNETs are very unlikely to come back after appendectomy

Unanswered question: How best to do surveillance such as how often to scan and role of blood tests

Active Clinical Trials at Mayo

Alliance A022001 – Sequencing in pNETs

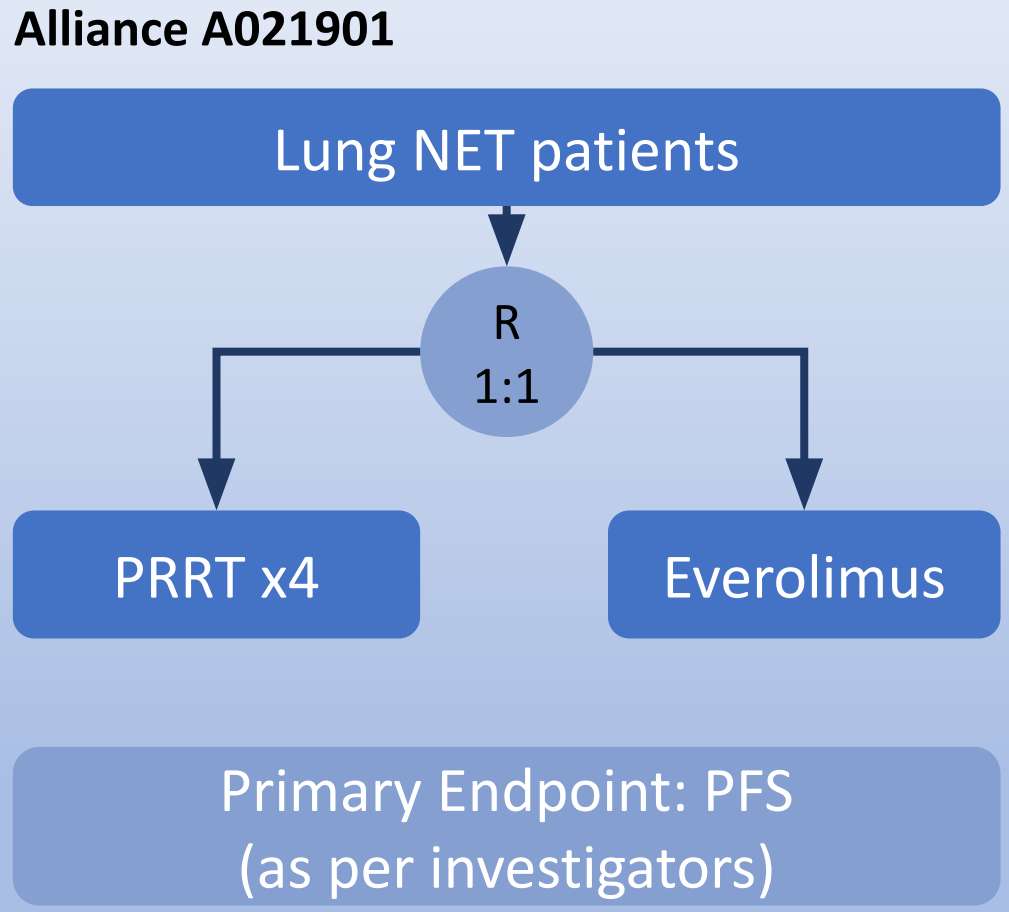
- Alliance A022001
- What is the optimal sequence following progression on SSA therapy
- Randomized phase II trial
- Patients with pancreatic NETs progressing on first-line SSA
- Well-differentiated pancreatic NETs
  - Grades 1-3



PI: T. Hobday, Mayo

Alliance A021901: – PRRT in Lung NETs

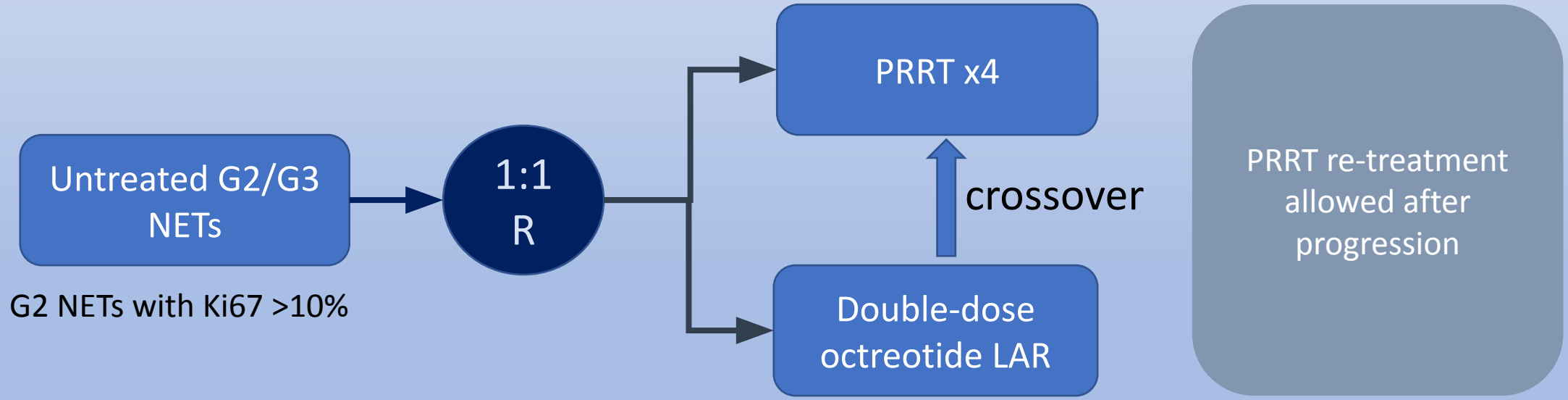
- What is role of PRRT in patients with lung NETs?
- Randomized phase II trial
- Patients with well differentiated lung NETs
- Eligible patients can either be untreated (first-line) or previously treated
  - No prior PRRT or everolimus allowed



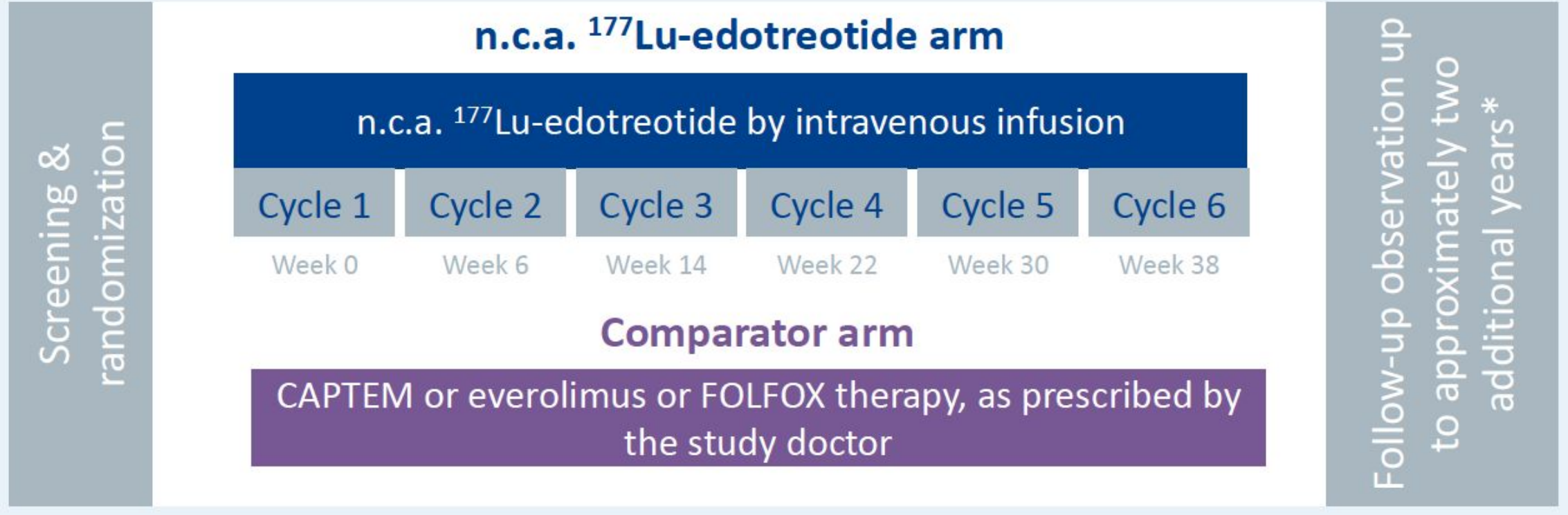
PI: T. Hope, UCSF

NETTER-2 – PRRT in G3 and High-Risk G2 NETs

- Phase III RCT – just completed accrual in October 2022
- Well diff G3 NETs and G2 NETs w/ Ki67 >10%
- Previously untreated
  - SSAs allowed for up to 6 months (but no progression allowed)



COMPOSE – A Phase III Trial



Enrollment Criteria:

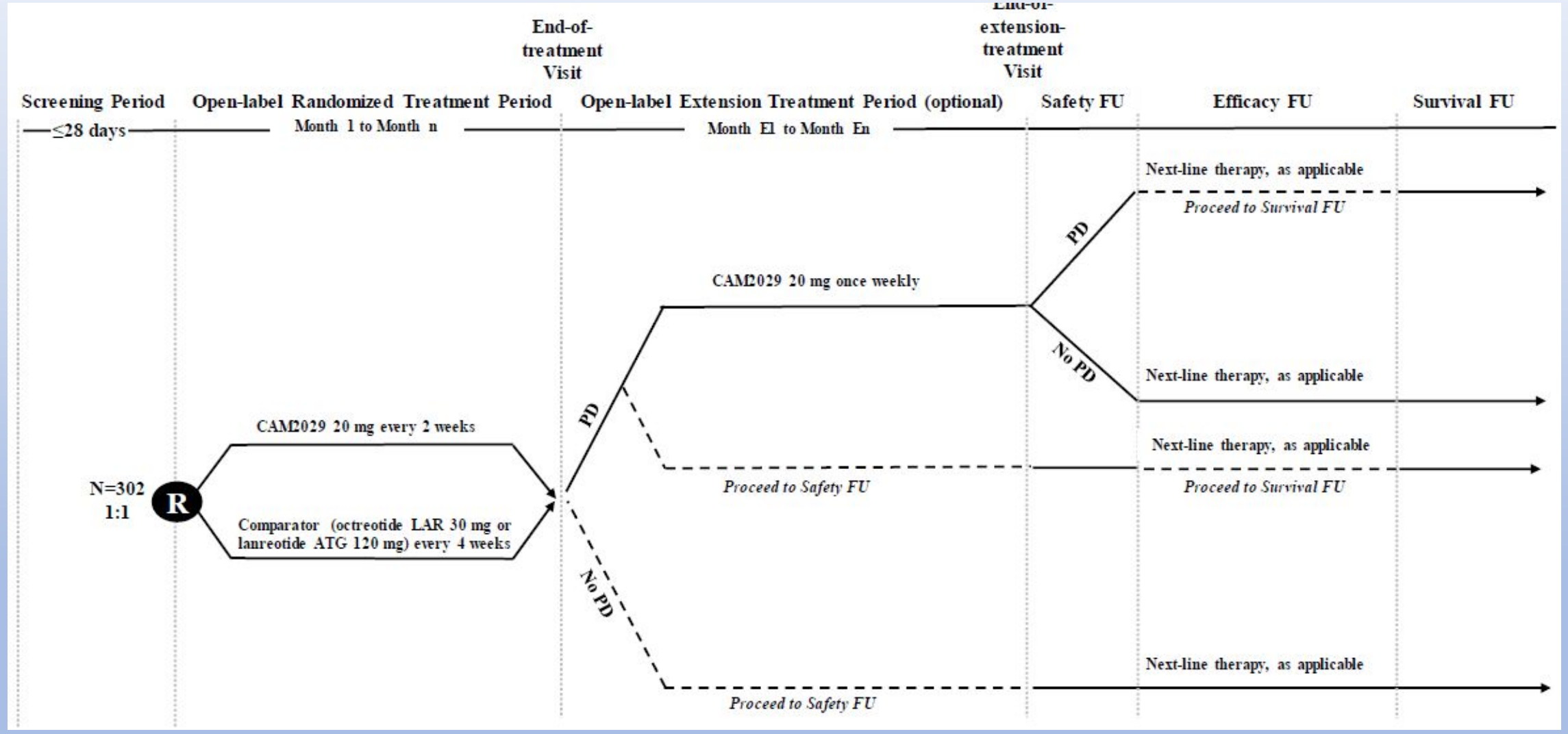
- Well-differentiated grade 2 (Ki67≥15%) and grade 3 (Ki67≤55%)
- Positive somatostatin receptor imaging (SRI)
- First or second line therapy

Halfdanarson TR et al. ASCO GI 2022

SORENTO – Self-Administered Octreotide

- CAM2029 is a novel formulation of a long-acting octreotide
- Suitable for injection under the skin by the patient or caregiver
- Comes in a prefilled syringe or a pen and is very easy to administer
- CAM2029 is mixed with a novel vehicle (FluidCrystal) that allows for higher drug concentration and potentially more efficacy
- Eligible patients should have:
  - Well-differentiated GEP-NETs showing up on DOTATATE PET
  - No more than 6 months of prior long-acting somatostatin analog therapy

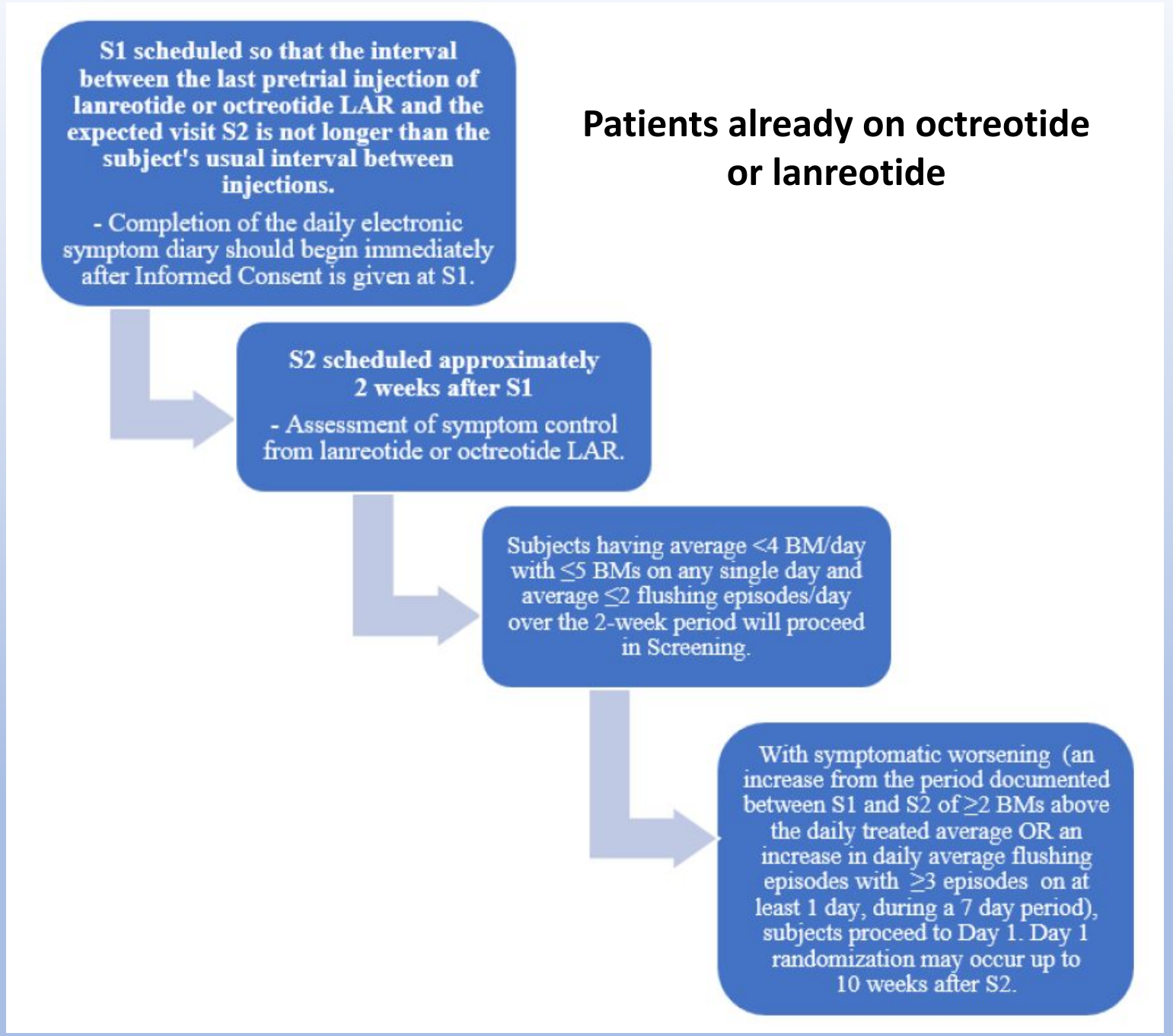
SORENTO – Self-Administered Octreotide



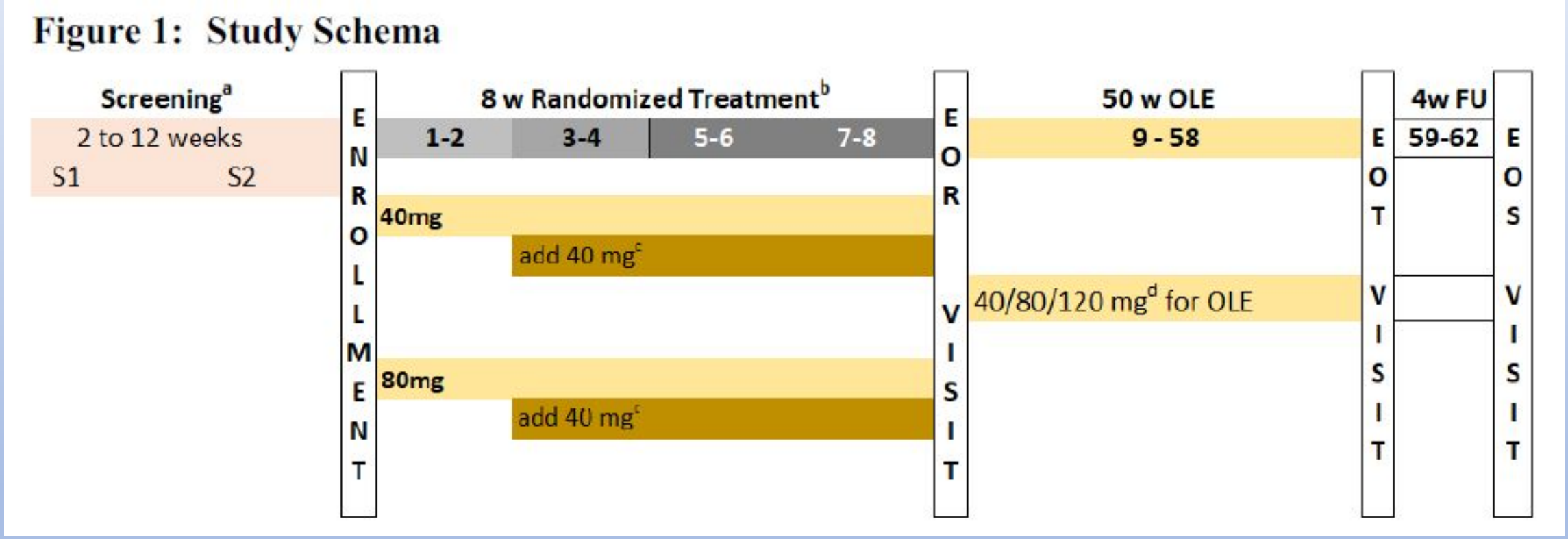
Paltusotine – An Oral Option Instead of SSAs

- Paltusotine is an oral drug that targets the somatostatin receptor
- It may end up being a very valuable option for patients with advanced neuroendocrine tumors
- In this study, patients with carcinoid syndrome and diarrhea or flushing are eligible
- 5 HIAA has to be elevated on at least 1 occasion
- Patients can either be previously untreated or on therapy with injections and willing to stop the injections allowing the symptoms to come back and then start the study drug

Patients already on octreotide or lanreotide



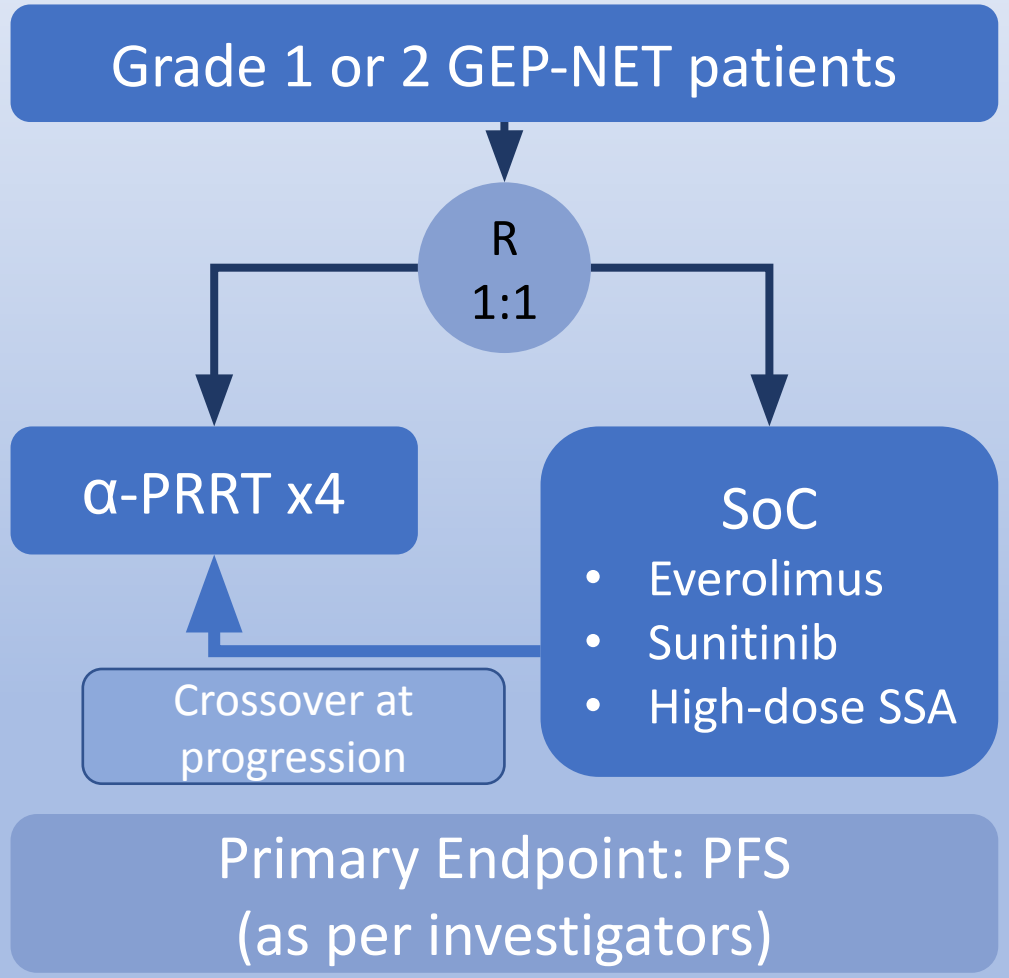
Paltusotine – An Oral Option Instead of SSAs



Soon To Open Clinical Trials at Mayo

ACTION-1 (alpha particle PRRT)

- Patients with grade 1 or 2 NETs who previously received PRRT (Lutathera)
  - There must have been a response to prior PRRT for at least 3 months
- Now with growing tumors following PRRT
- Have to be willing to receive one of 3 standard-of-care (SoC) options



Questions…?