CHEMOTHERPY FOR NETS… SHOULD WE STILL USE IT?

CNETS Annual Meeting
April 22, 2017

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Objectives

- Review evidence for chemotherapy
- Consider chemotherapy predictive factors
- Discuss current practice
- Discuss future practice

Are NETs still rare?

Year	Annual incidence rate per 100,000	US prevalence count estimate
2004	5.25	103,312[1]
2012	6.98	
2014		171,321[2]

[1]29-year limited duration prevalence. [2]20-year limited duration prevalence.

Yao *et al* (2008). J Clin Oncol 26(18) 3063-3072
Shen *et al* NANETS 2016
Daseri *et al* JAMA Oncology, In Press 2017

Courtesy J Yao, ENETS

Systemic Therapy

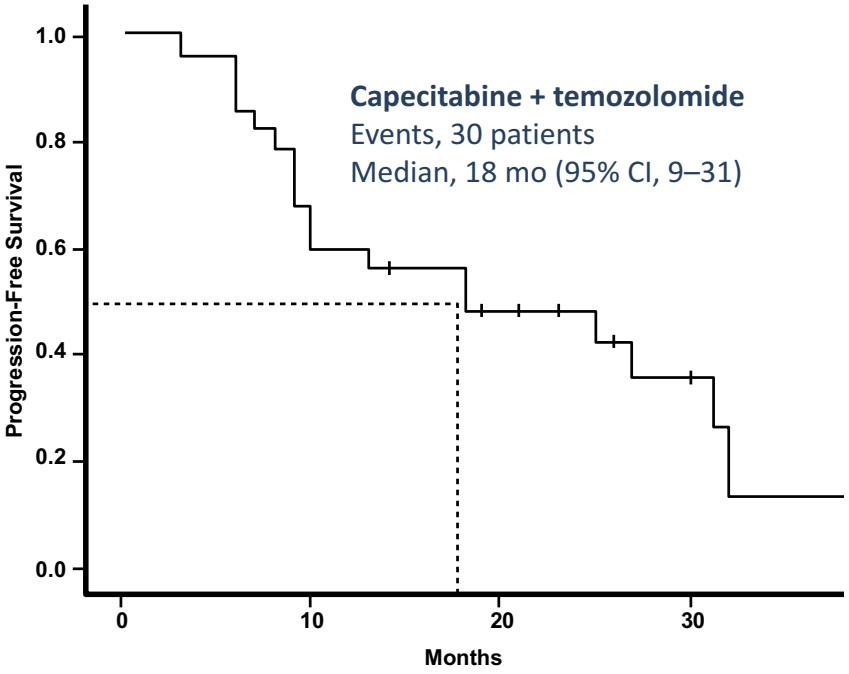
Site	Octeotride	Lanreotide	^{177}Lu-DOTATATE	Streptozocin/ TMZ	Sunitinib	Everolimus
Disease status	Tx Naive	Stable	Progressive over 3 yrs	Historical	Progressive over 12 mo	Progressive
Lung						Phase III
Stomach		Phase III				Phase III
Duodenum		Phase III				Phase III
Pancreas		Phase III		Historic	Phase III	Phase III
Small bowel Appendix	Phase III	Phase III	Phase III	Historic		Phase III
Colon		Phase III				Phase III
Rectum		Phase III				Phase III
Unknown 1°				Historic		Phase III

Rinke A, *et al*. J Clin Oncol 2009; Caplin ME *et al*. NEJM 2014, Strosberg J *et al.* NEJM 2017, Raymond E *et al*. NEJM 2011, Yao JC *et al.* J Clin Oncology 2008, Yao JC *et al.* NEJM 2011, Yao JC *et al.* Lancet 2016.

J Yao, ENETS 2017

PNETs: Capecitabine and Temozolomide

- A single-arm retrospective review investigating the combined use of oral temozolamide and capecitabine in 30 patients with pNETs
- Objective response rate: 70% (95% CI, 54%–86%)
- Median progression-free survival: 18 months
- Estimated rate of overall survival at 2 years: was 92% (95% CI, 72%–98%)



Strosberg et al. *Cancer*. 2011;117:268-275.

Temozolomide in NETs

	Regimen	Pancreas	Ileum	Bronchial	Others
Ekeblad et al Clin Cancer Res 2007	100-2000 mg/m^2 5d Retrospect RECIST	8% PR (12)	-	**N=13 31% PR (4)** 31% SD (4)	0 PR (11)
Kulke M et al JCO 2009	Various Retrospect	34% PR (53)	0 (19)	**N=8 13% PR**	0 (17)
Crona et al Neuroendocrinol 2013	TMZ 100-200 mg/m^2 5d Retrospect/RECIST	-	-	**N=21 14% PR (3)** 52% SD (11)	
Chan JA et al JCO 2012	150 mg/m^2 2/4w +Bevacizumab 5mg/Kg D1=D15	33% PR (15)	0 (7)	**N=4 0% PR**	0 (8)
Muller et al BMC Cancer 2016	Dacarbazin (650 mg/m^2 q 4 wks)	32% PR (50 33% SD	1 (13)	**N=6 33% PR (2) 50% SD (3)**	1 (6)

Oxaliplatin-based in well-differentiated NETs

Study	Population	RR	TTP/PFS mo
Spada et al 2016 (CAPOX/FOLFOX/GEMOX)	78 pts Pancreas (46) GI (24) Lung (15)	26% 33% 26% 13% PR 67% SD	8
Walter et al 2016 (GEMOX/FOLFOX)	45 pts* TC (8) AC (24) Other (10)	20% PR 64% SD	15 (13/16)

*79% PD

Bajetta et al Cancer Chemother Pharmacol 2007, Cassier et al cancer 2009, Spada et al Neuroendocrinology 2016, Walter et al, Lung Cancer 2016

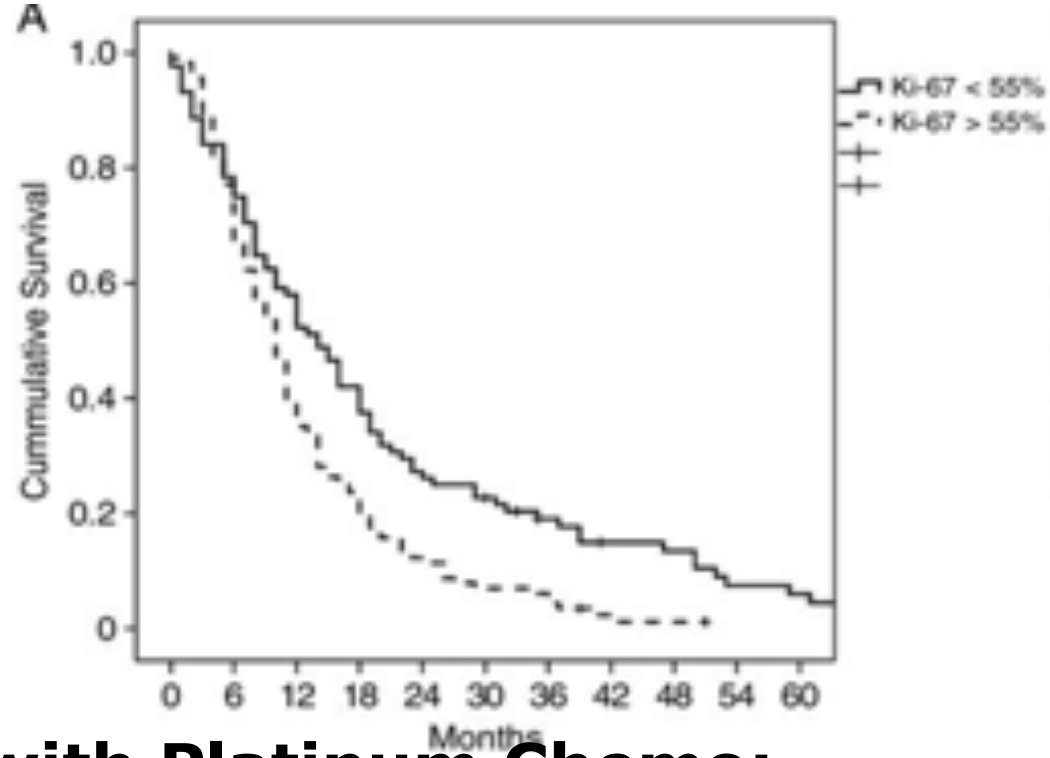
How can we predict who needs chemo?

- Ki 67
- MGMT methylation
- 18F-FDG PET
- G3 NET or G3 NEC

Ki 67: G3 NECs

Patients with advanced NEC treated with chemotherapy (n=232)

Sorbye Ann Onc 2013

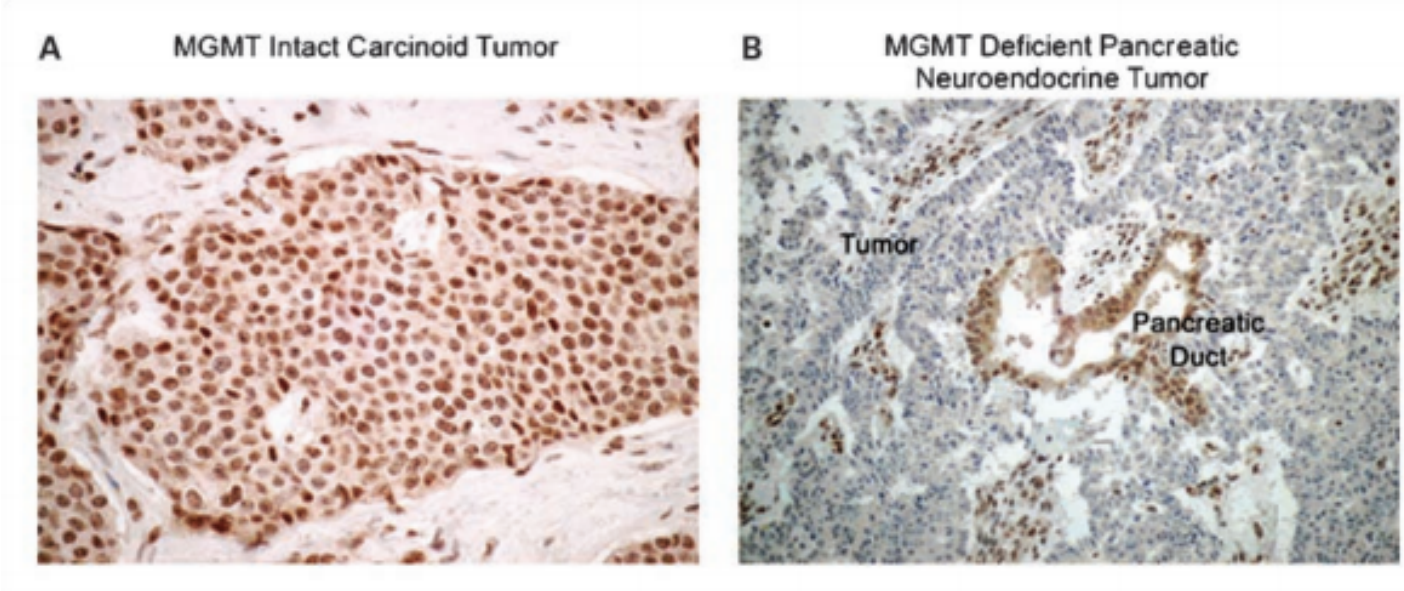


Outcomes with Platinum Chemo:

Ki-67 < 55% had lower Response (15 vs. 42%) but better survival vs. Ki-67>55% (14 vs. 10 mo).

Alternative: Alkylating chemo?

MGMT may predict TMZ response

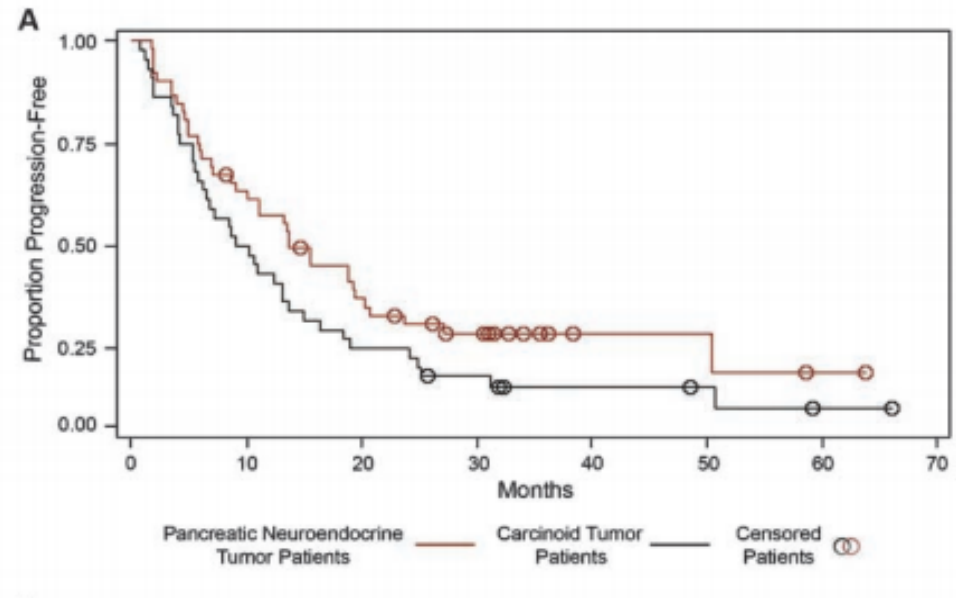


Kulke CCR 2009

MGMT deficient:

0% Carcinoid

51% PNETs



Response with TMZ:

34% PNETS

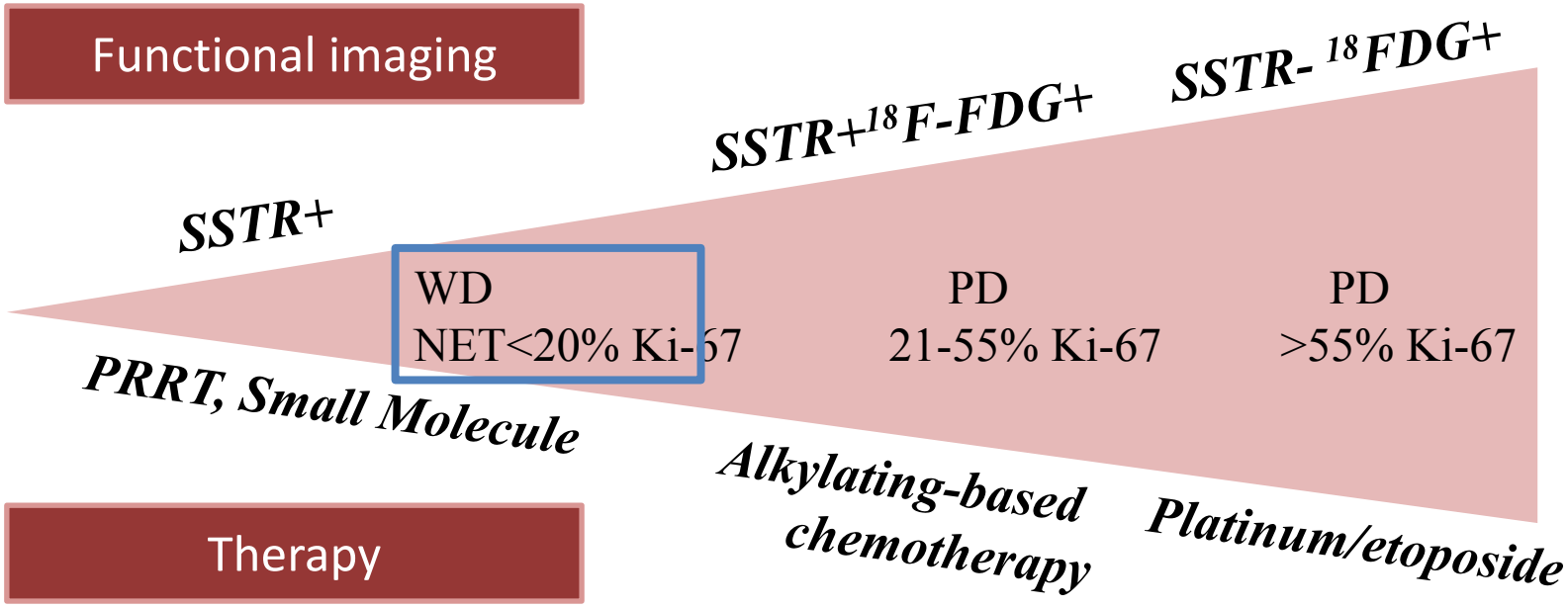
2% Carcinoid

PFS with TMZ therapy:

13.6 mo PNETs

9.6 mo Carcinoid

18F-FDG PET may guide choice of chemotherapy



Adapted from Fazio N and Milione M. Cancer Treat Review 2016: 50: 61-67.

GEP NEC – Gastroenteropancreatic neuroendocrine neoplasms; **SSTR** – somatostatin receptor; **FDG** – fluorodeoxyglucose; **G-** grade; **WD** – well differentiated; **PD** – progressive disease; **NET** –neuroendocrine tumour.

PET-NET Study: What is the effect of DUAL 18F-FDG and 68Ga-DOTATOC PET on NET treatment decisions?

NET
-G1
-G2
-G3

PET-CT

18F-FDG-PET
68Ga- DOTA-TOC PET

Investigator choice

→ Surgery
Liver Directed Tx

→ Cytotoxic:
Cap-TMZ *or*
Streptozotocin
doublet *or*
Cis-Etoposide

→ Somatostatin
Analogue

→ Small molecule:
Sunitinib *or*
Everolimus

→ PRRT: Peptide Receptor
Radiotherapy

→ Observation

Pre-PET survey and stage

Post-PET survey and stage

New 2017 WHO classification will reduce NET confusion!

2010 WHO Classification[1]

	Mitoses (per 10 HPF)	Ki67 index	Morphology
G1 Neuroendocrine tumour (NET)	<2	≤2%	Well differentiated
G2 Neuroendocrine tumour (NET)	2–20	3–20%	Well differentiated
G3 Neuroendocrine carcinoma (NEC)	>20	>20%	Poorly differentiated
Mixed adeno-neuroendocrine carcinoma (MANEC)			

HPF, high-power field

1. Bosman FT et al. *WHO Press.* 2010.

New 2017 WHO NET classification

	Mitoses (per 10 HPF)	Ki67 index	Morphology
G1 NET	<2	<3%	Well differentiated
G2 NET	2–20	3–20%	Well differentiated
G3 NET	>20	>20%	Well differentiated
G3 NEC • Small cell type • Large cell type	>20	>20%	Poorly differentiated

PNET

PNETPathologic features[1]
(mutant genotype / loss of nuclear labelling)

DAXX/ATRX/MEN1

p53/Rb1

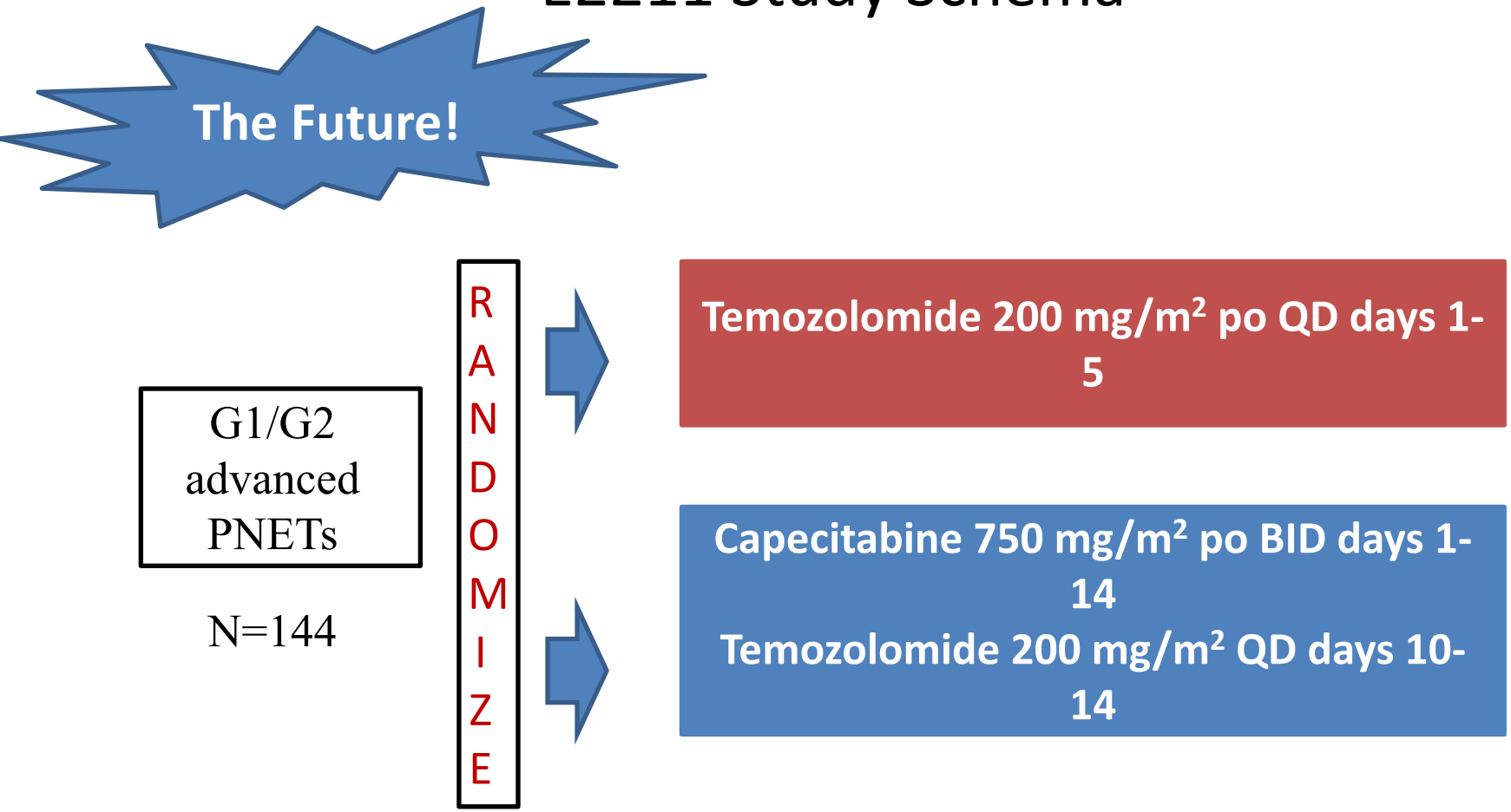
NET, neuroendocrine tumour; NEC, neuroendocrine carcinoma

1. Yachida et al. *Am J Surg Pathol*. 2012;36(2):173–84.
2. Tang et al. *Clin Cancer Res*. 2016;22(4):1011–7.

Conclusions

- PNETs are generally chemosensitive, other GEP NETs are not…bronchial?
- Alkylating agents are active in PNETs.
- Platinum based chemo for NECs – but only for ↑ Ki 67?
- 18F-FDG PET may serve as a guide to chemotherapy.
- WHO 2017 classification will decrease NET confusion.

E2211 Study Schema



Stratified by: Prior everolimus, sunitinib, concurrent octeotride

First randomized NEC trial: what is the best therapy for G3 NECs?

NEC with Ki 67 20-100%

N= 126

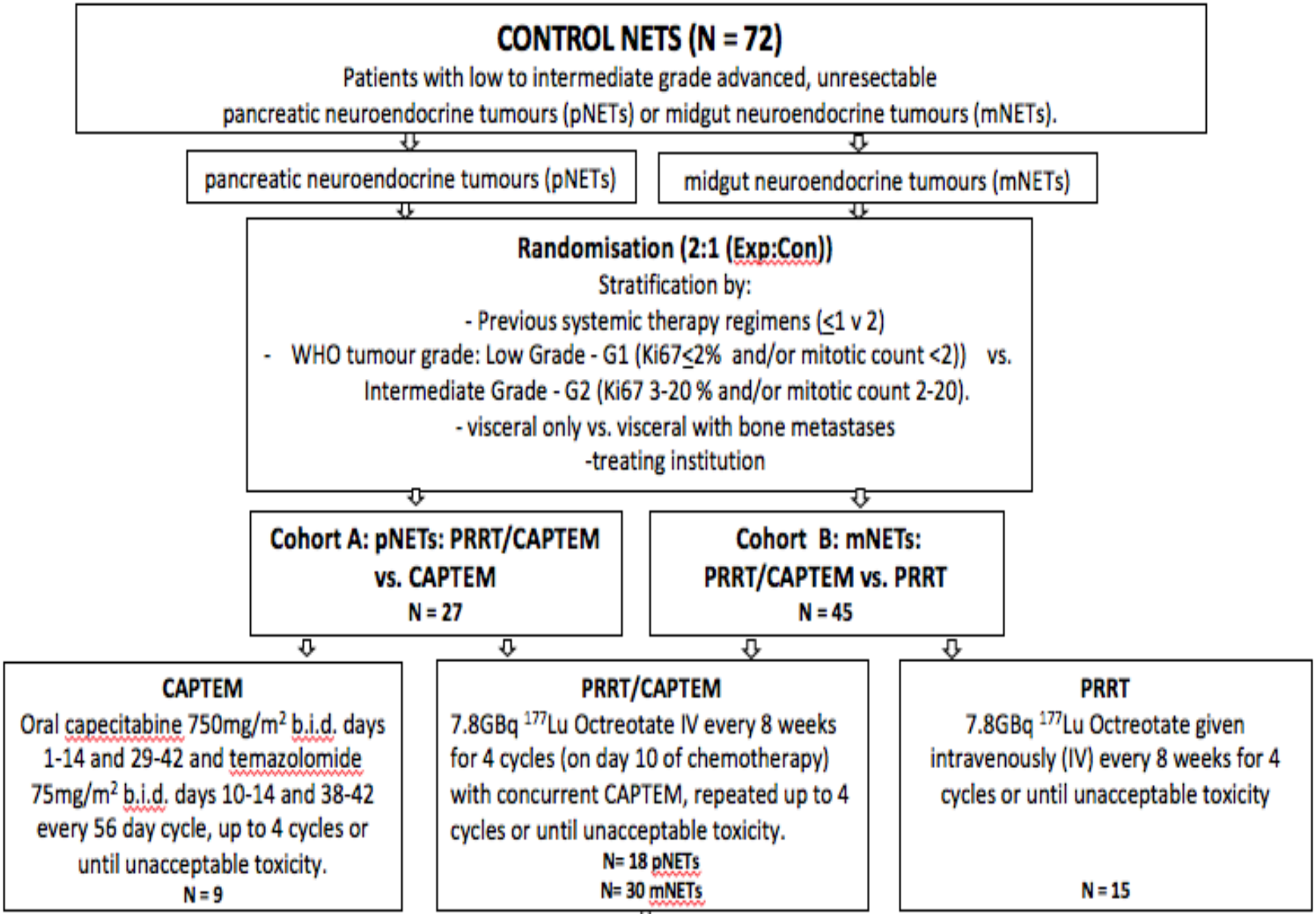
→ Capecitabine d1-14
TMZ d10-14

→ Cisplatin d1
Etoposide d1-3

Primary Endpoint: PFS

Optimal cutoff value in Ki-67

ECOG-ACRIN



Enrolment started Nov 2015; 46 enrolled as of March 13, 2017 of target 72 by 2018.

SYSTEMIC THERAPY- SUMMARY

mTOR

VEGFR TKI

Alkylating Agents

Platinum Agents

NET

PNET

NEC

Small Cell C

Raja Ampat, Indonesia