

4th Milan NET Conference

A meeting among active Italian Neuroendocrine Tumor Boards

Tuesday June 12th, 2018

Current treatment of G3 NENs



Halfdan Sorbye

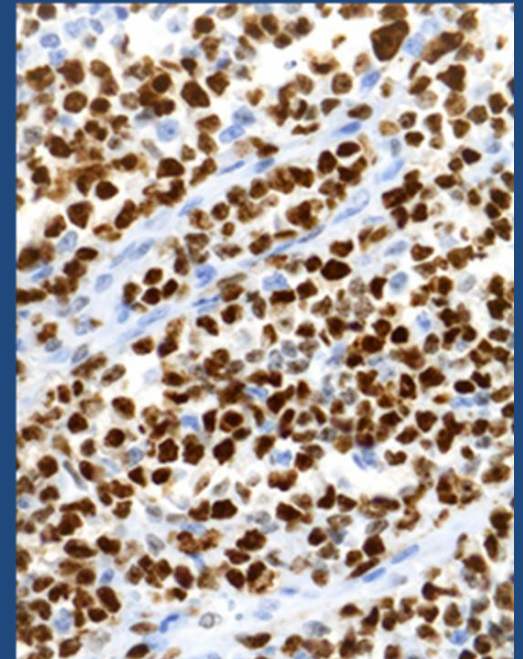
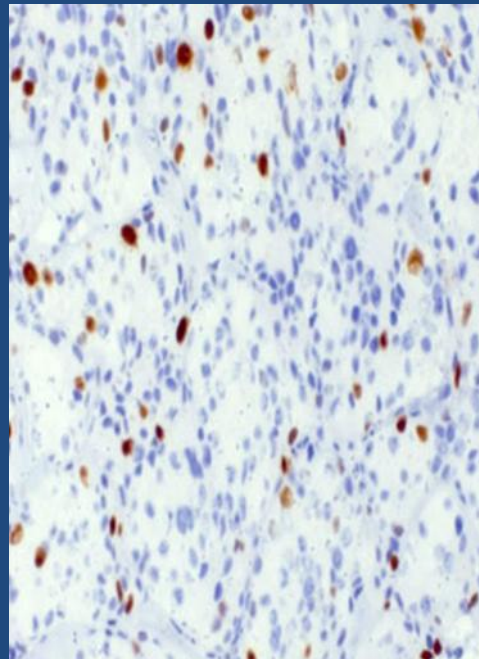
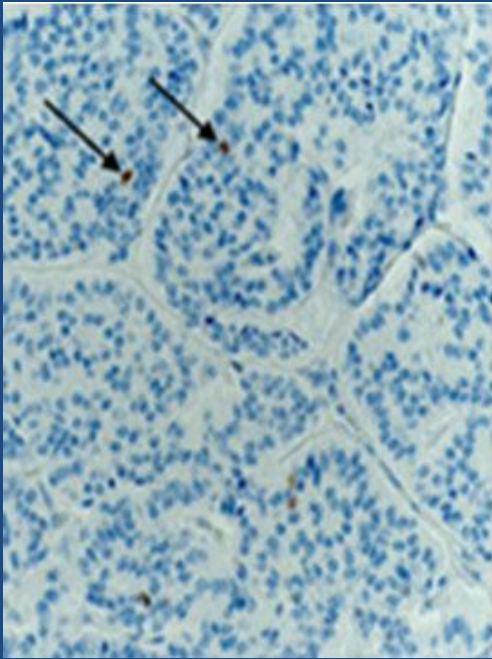
Professor, MD

Haukeland Univ Hospital

Bergen, Norway



G3- a different disease

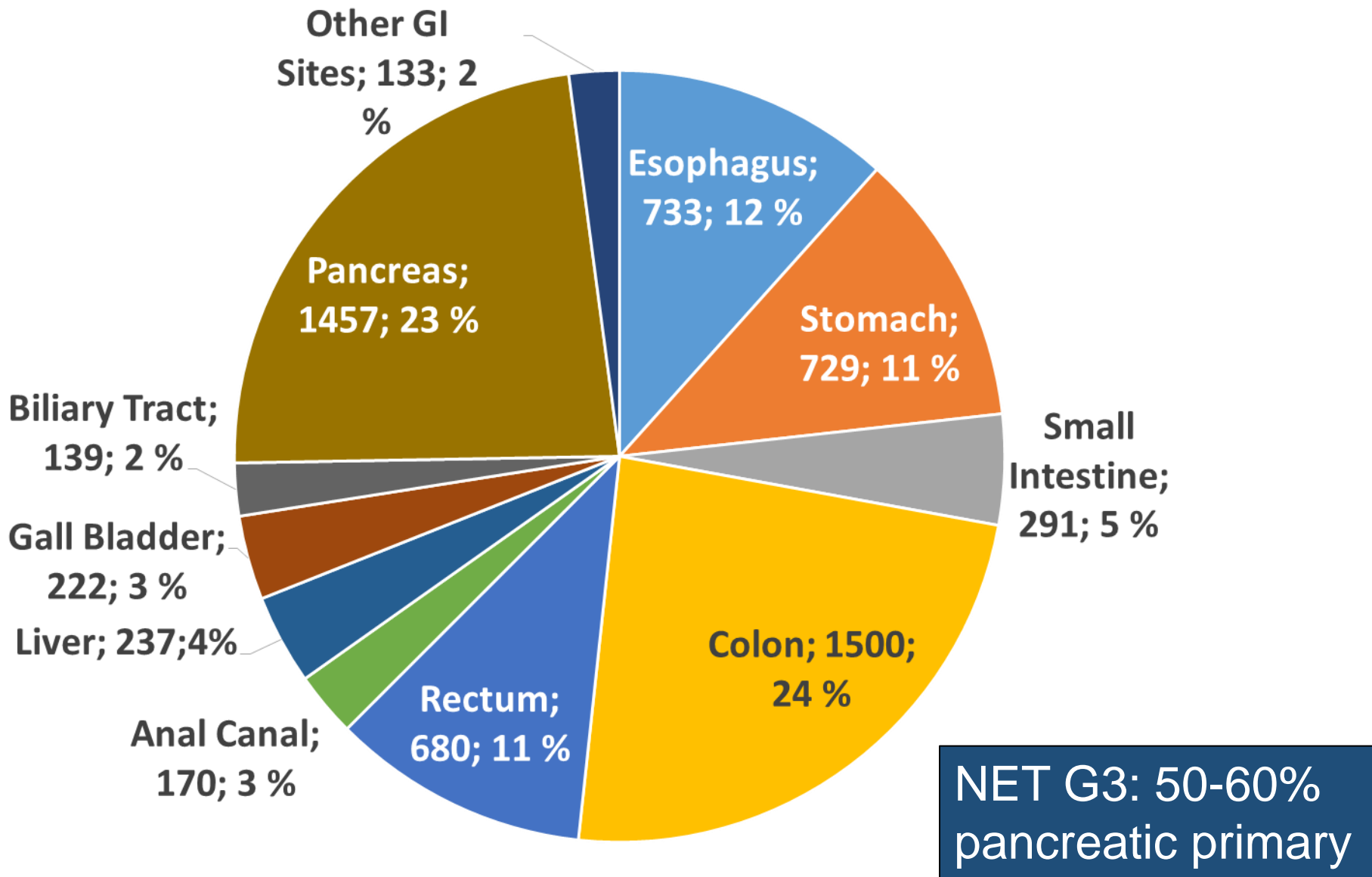


	G1	G2	G3
Primary	Sm-intestine	Pancreas	GEP
Ki-67	1-2%	5-10%	>20 %. Usually 70-90%
Differentiation	Well	Well	85% Poorly, 15% well
mOS stage 4 medically treated	10-12 years	3-4 years	11-13 months

Nomenclature for GEP NEN G3

	Used for	
NET G3	Well-differentiated, Ki-67 > 20%	
NEC	Poorly differentiated, Ki-67 > 20%	
NEN G3	Addressing both NET G3 and NEC	If differentiation is uncertain
MiNEN	Neoplasms with both >30% neuroendocrine and gland-forming component	

Approved by Kloppel, Klimstra, Scoazec and Perren.



**Proportion of high grade neuroendocrine carcinomas according to primary sites.
Dasari A; Cancer 2018**

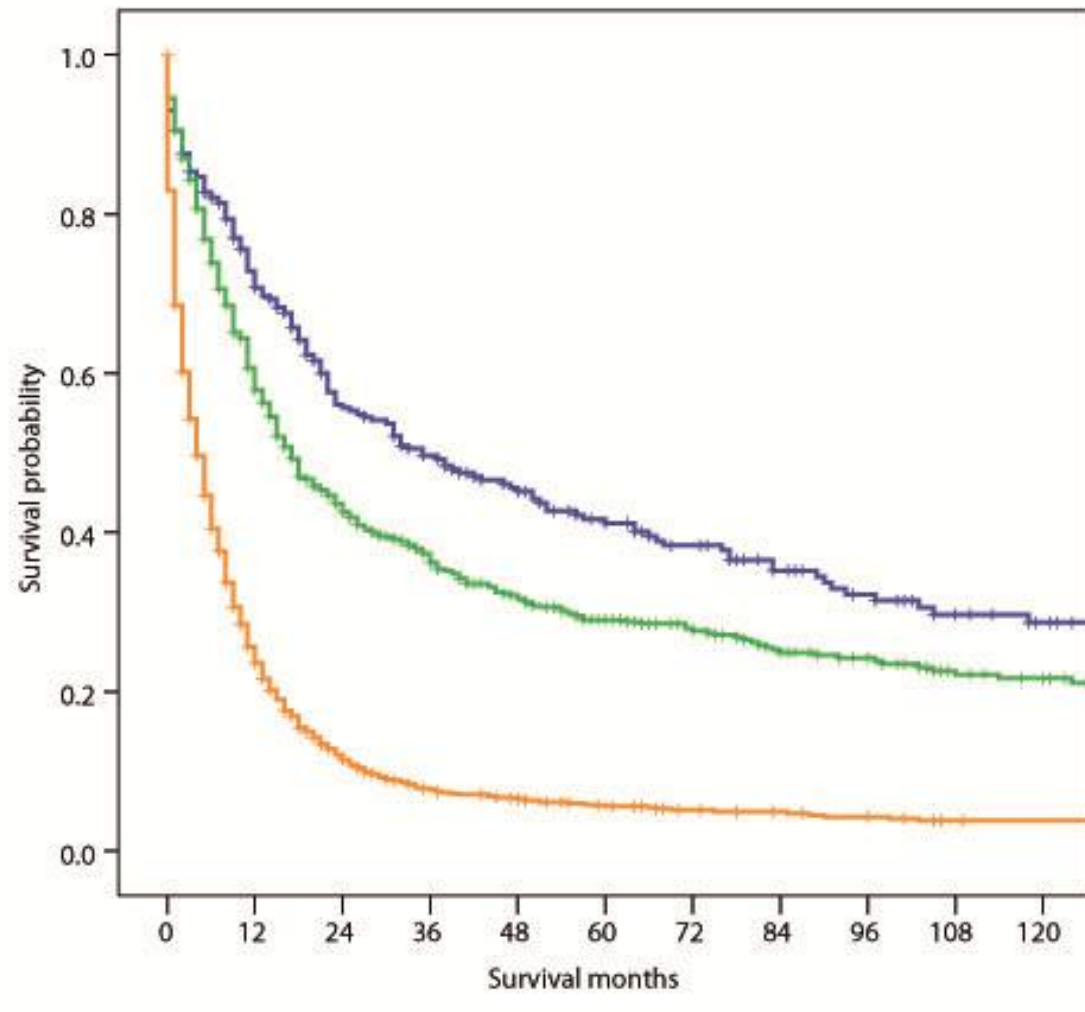
Difficult to separate NET G3 and NEC

- No strict established criteria
- Even NET expert pathologist disagree (MSCCC 66% disagreement)
- Molecular alterations in Rb1 and TP53 may aid diagnosis

ENETS guidelines for surgery in G3.

ENETS 2016 (Neuroendocrinology)

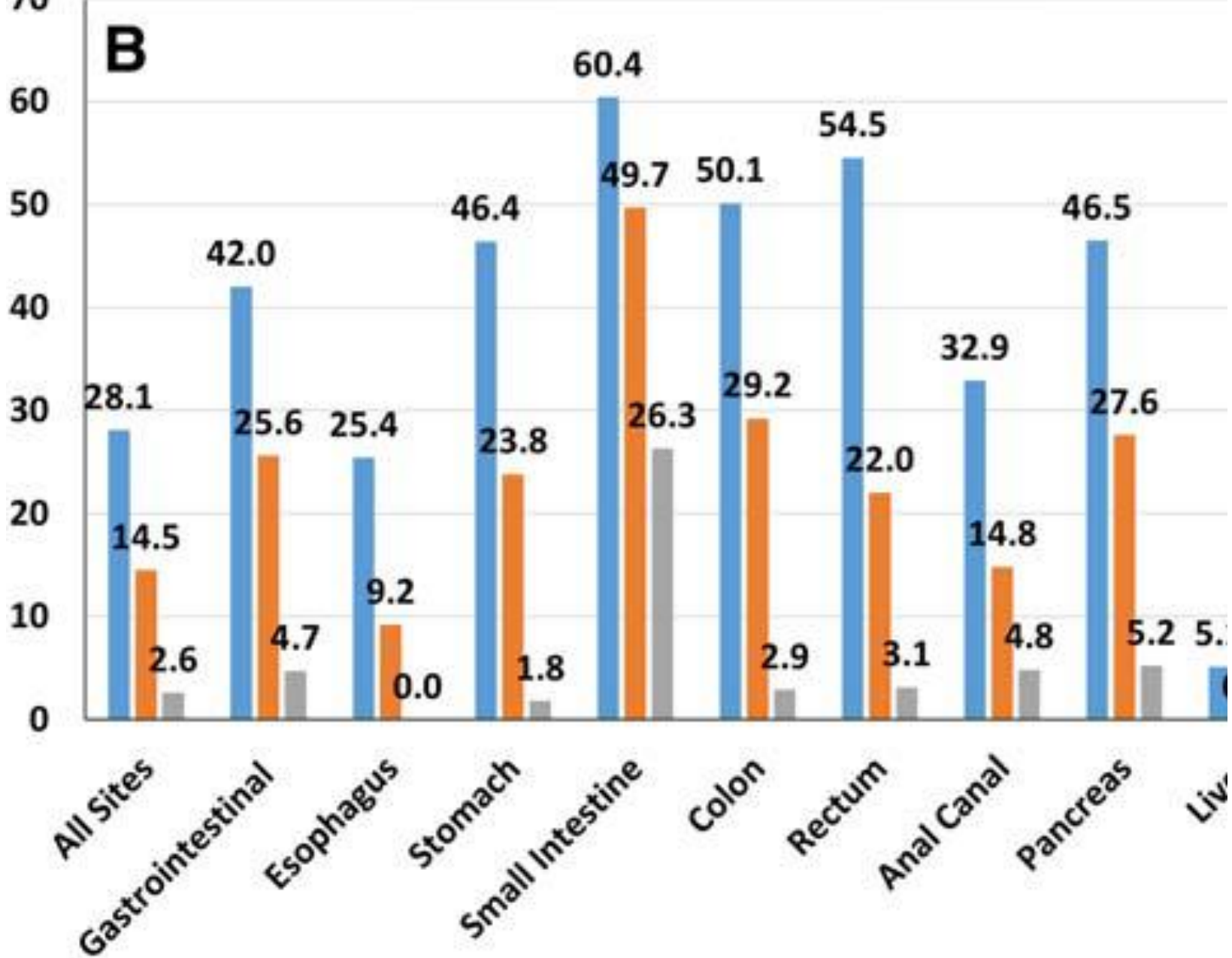
- Curative surgery is usually attempted in localized disease, although retrospective series indicate that it is rarely curative as a sole therapeutic modality.



Many can be cured.
Often later metastasis
in initial localized/
regional disease

Localized
Regional
Distant

Survival by stage in G3/4 GEP-NEC patients from SEER 1973-2012 .
Sorbye: Cancer 2014.



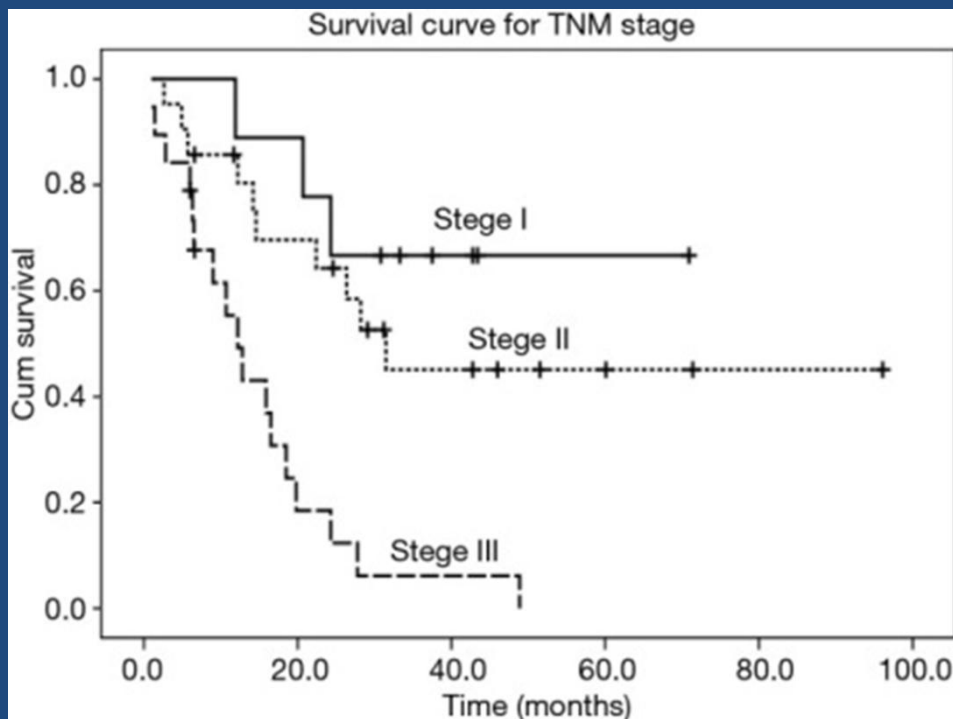
GEP NEN G3 5-y survival (Dasani Cancer 2018)

Local Regional Distant

Esophageal NEC

- Chemoradiation probably better than surgery
- Surgery vs CRT: N1 disease (mOS 12 vs 45 m)

[Meng MB, et al. Radiother Oncol 2013; 106:317]



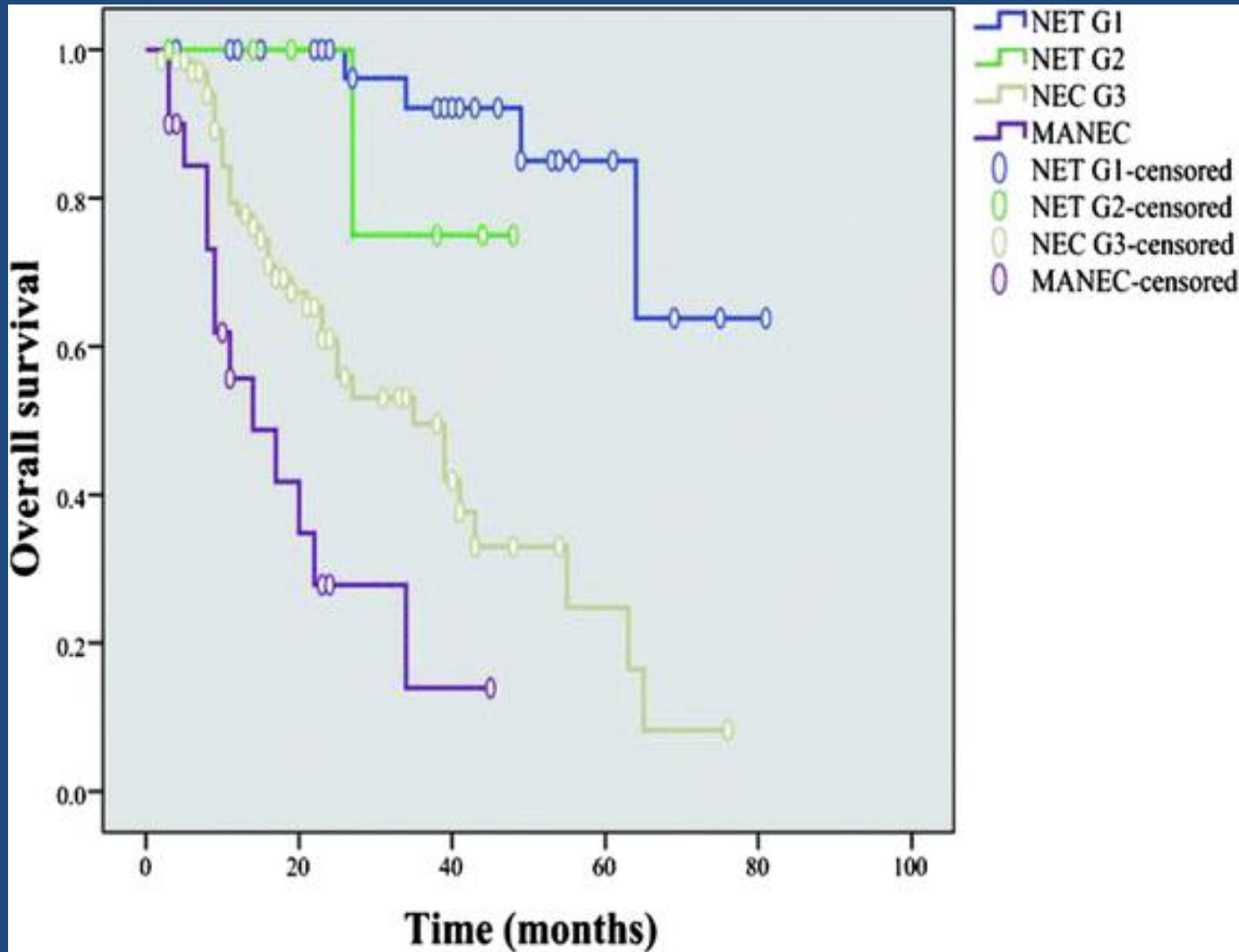
Surgery for esophageal NEC

Deng HY et al. J Thorac Dis. 2016 8:1250-6.

Gastric NEC

Surgical treatment of Gastric neuroendocrine neoplasms:
a single-center experience.(135 cases)

Shen C et al. BMC Gastroenterol. 2016 Sep 9;16:111.



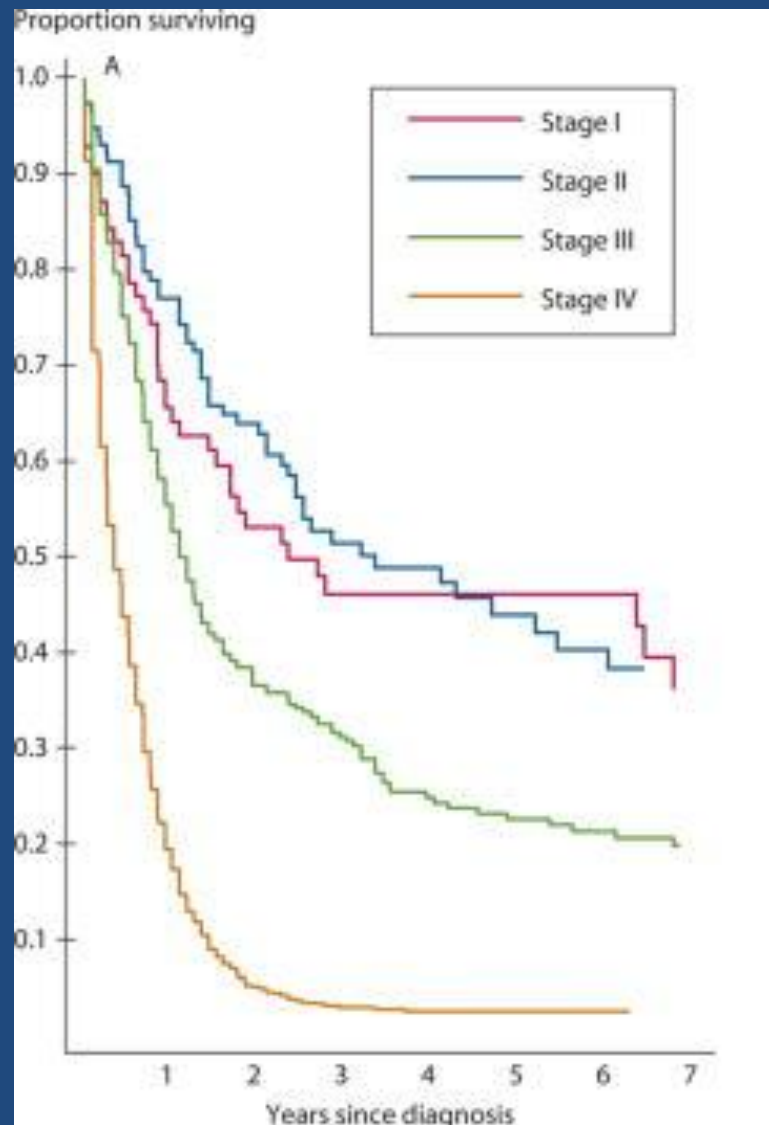
69 NEC
(60 M₀)
20 MANEC
(14 M₀)

Survival of patients with neuroendocrine carcinoma of the colon and rectum: a population-based analysis.

Shafqat H: Dis Colon Rectum. 2015 58:294-303.

Surgery in 440/502 (88%) Stage I-III.

Subgroup	Neuroendocrine carcinoma		
	N	Median survival, months (95% CI)	Relative survival at 5 y, (95% CI)
All cases	1367	7.1 (7.0–8.0)	16.3% (13.8–19.1)
Stage			
I	70	28.0 (17.1–81.1)	57.4% (41.0–70.7)
II	115	40.0 (27.0–72.0)	56.4% (37.7–71.4)
III	317	13.1 (11.0–16.0)	26.3% (20.0–33.0)
IV	791	4.0 (3.1–5.1)	3.0% (1.9–4.7)



Liver surgery for metastatic disease?

- Generally not recommended
- Survival much better for NET G3 than for NEC
- Liver surgery for NET G3 as for NET G2?

- Nordic Cohort: some PD NEC patients benefit
Galleberg et al 2017 EJSO

Adjuvant treatment

- 4–6 cycles of cis/carboplatin and etoposide are recommended.

Another option is neoadjuvant (preoperative) chemotherapy before surgical resection.

Adjuvant treatment for NET G3 or NEC with lower range Ki-67 21-55%?

Pre-section question

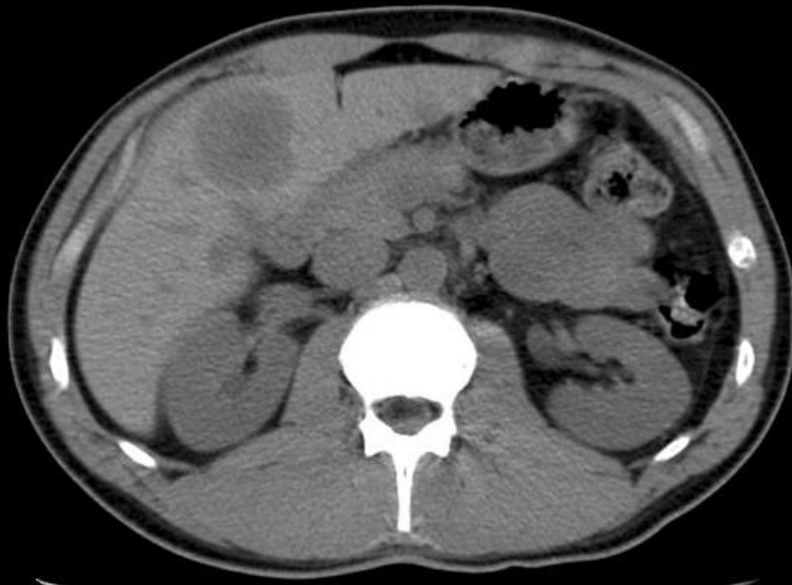
- 57 year old man, multiple un-resectable liver metastases and a pancreatic tumor. Liver biopsy shows a neuroendocrine carcinoma (G3), positive for Syn and CgA. Large cell morphology, Ki-67 30%. SRI positive.
- Your choice of 1-line palliative treatment is:
 - 1. Platinum-based chemotherapy
 - 2. Temozolomide-based chemotherapy
 - 3. FOLFOX or FOLFIRI
 - 4. Everolimus or sunitinib
 - 5. Somatostatin analog or PRRT

Palliative chemotherapy

- Rapid referral
- «See an oncologist within a week or not at all», before PS is too poor for treatment.
- Platinum/etoposide has been a standard
- Median OS without chemotherapy 1 month
(Sorbye; NORDIC NEC Ann Oncol 2012)

Recent large retrospective 1-line chemotherapy studies in metastatic GEP NEN G3

	Chemo	No	Diff	RR%	PD %	PFS	mOS
Sorbye et al Cancer 2013	Cisplatin or carboplatin + etoposide	252	?	31	36	4 m	11 m
Yamaguchi et al Cancer Sci 2014	Cisplatin + irinotecan or etoposide	258	Poor?	50/27		5.2 m	11.5 m
Heetfeld et al Endo Rel Cancer 2015	Platinum/ etoposide	113	Poor	35	27	5 m	16.4 m Stage mix
Walter et al Eur J Can 2017	Platinum/ etoposide	152	Poor	50	27	6.2 m	11.6 m



NEC, Ki-67 90%.
PR to platinum.
PR after 2 cycles.
Progression after 6 m.

Colorectal NEC

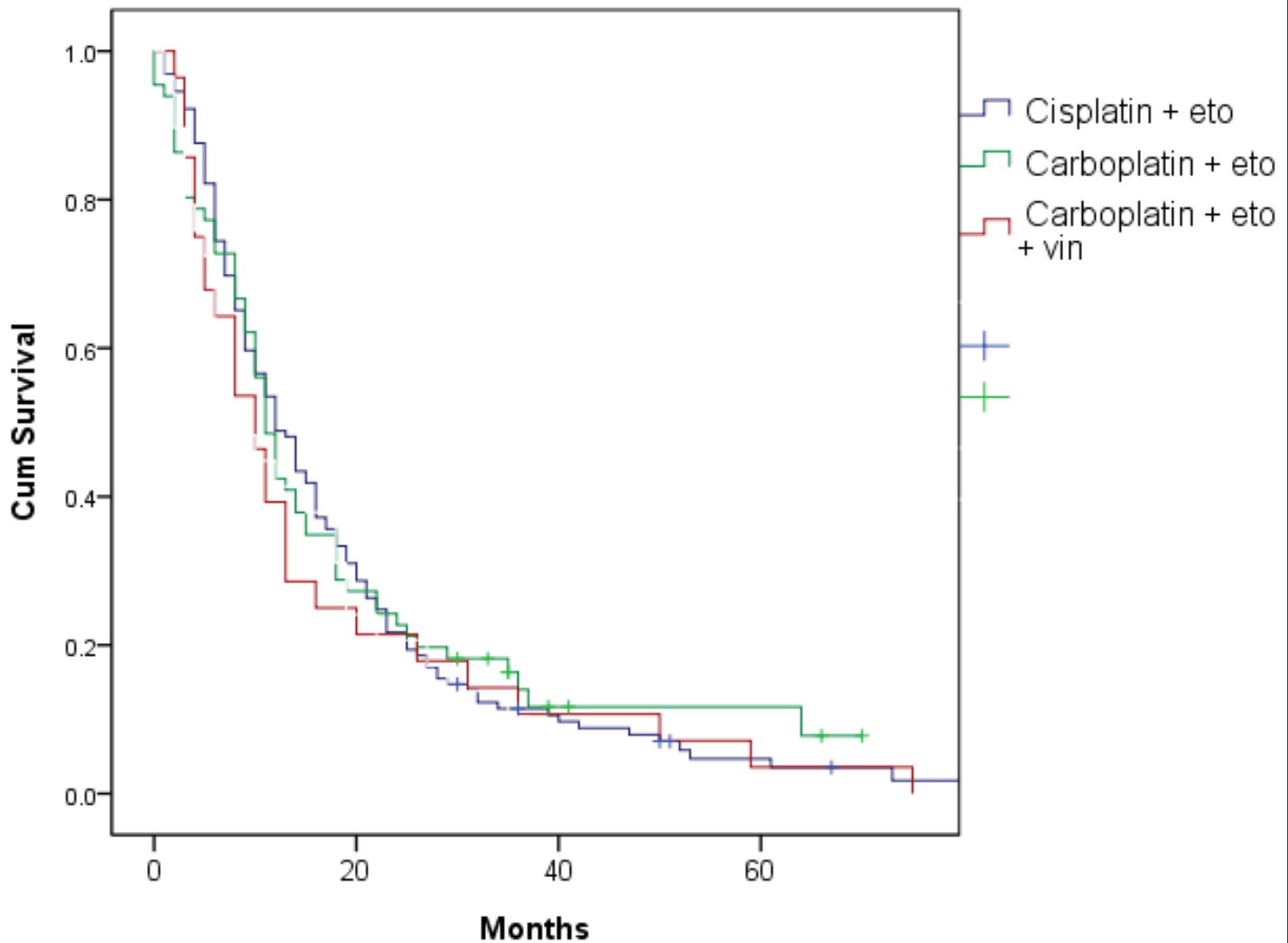
Colon NEC poor response to platin/eto (Nordic NEC).

	PR/CR	SD	PD	PFS (95% CI)	OS (95% CI)
All patients	31%	33%	36%	4 (3.4-4.6)	11 m (9.4-12.6)
Colon	16%	28%	56%	3 m (2.1-3.9)	8 m (6.0-9.9)

mCRC chemo as FOLFOX used (especially US)

- FOLFIRINOX case reports....

Nordic NEC (Sorbye Ann Oncol 2013).
Carboplatin- and cisplatin-based chemotherapy
do not differ in response nor survival.



2-line chemotherapy for NEC

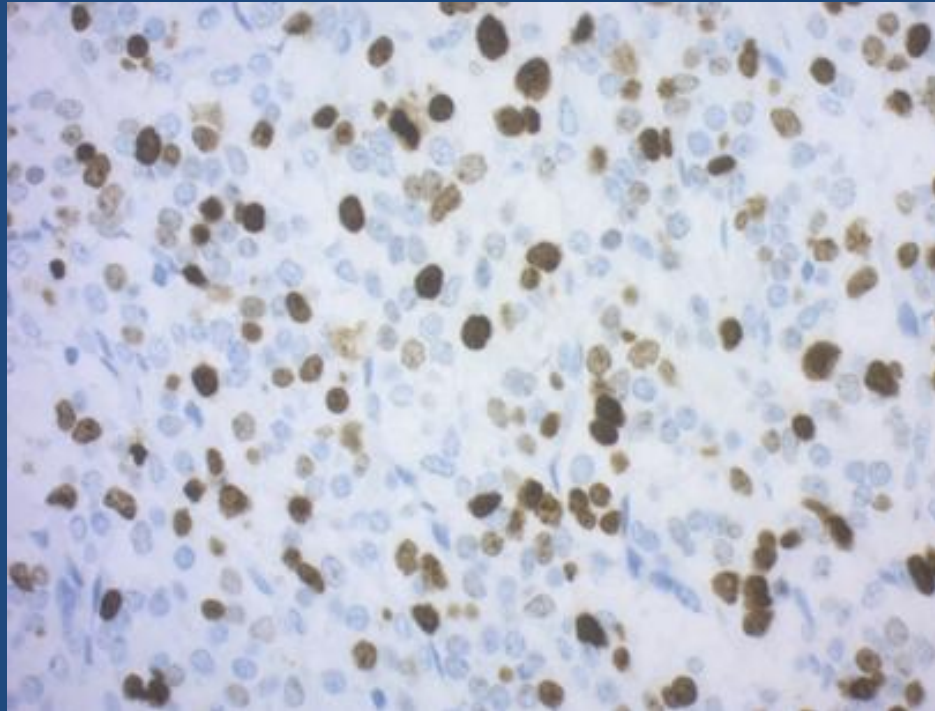
Temozolomide + capecitabine 2-line after cisplatin/etoposide progression (Welin: Cancer 2011)

- PR 27%, SD 27%. PFS 6 months
- Better response in patients with Ki-67 < 60%

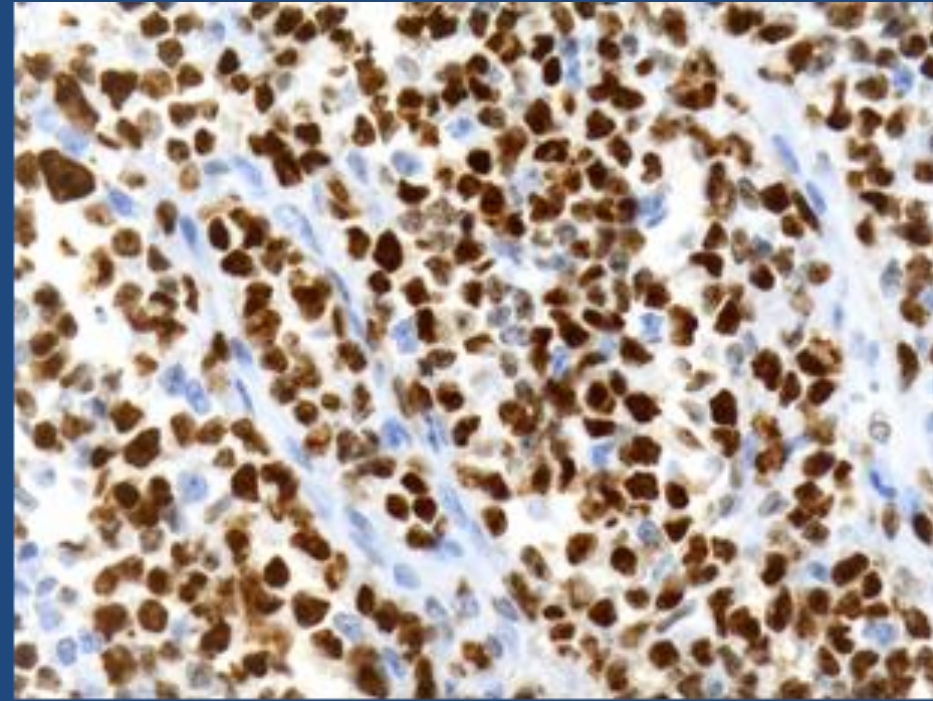
Other options: FOLFIRI or FOLFOX .

PFS < 3 m and OS <6 m (Walter 2017).

NEC: Variation of Ki-67

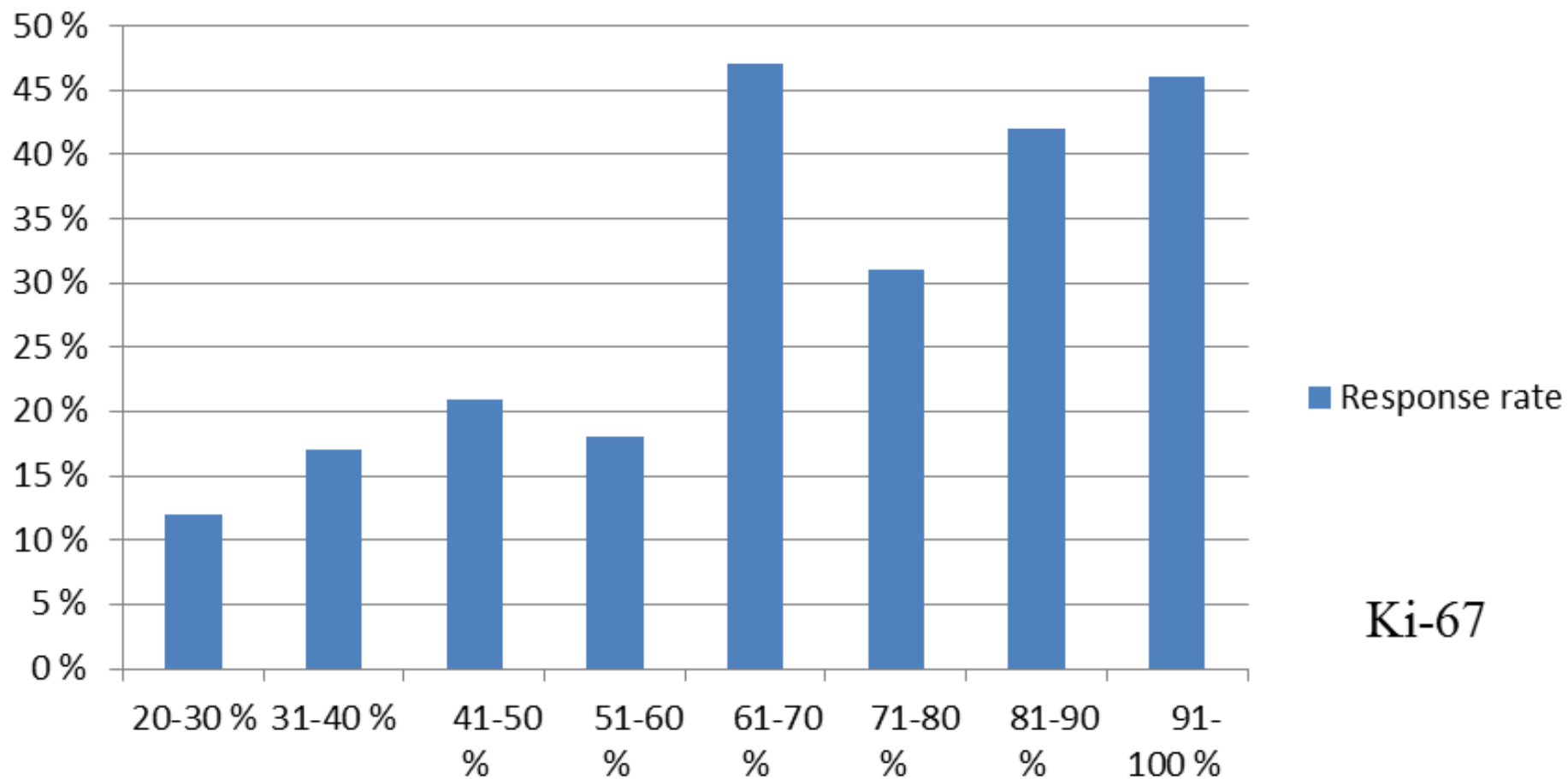


Ki-67 40%.



Ki-67 90%

Response rate

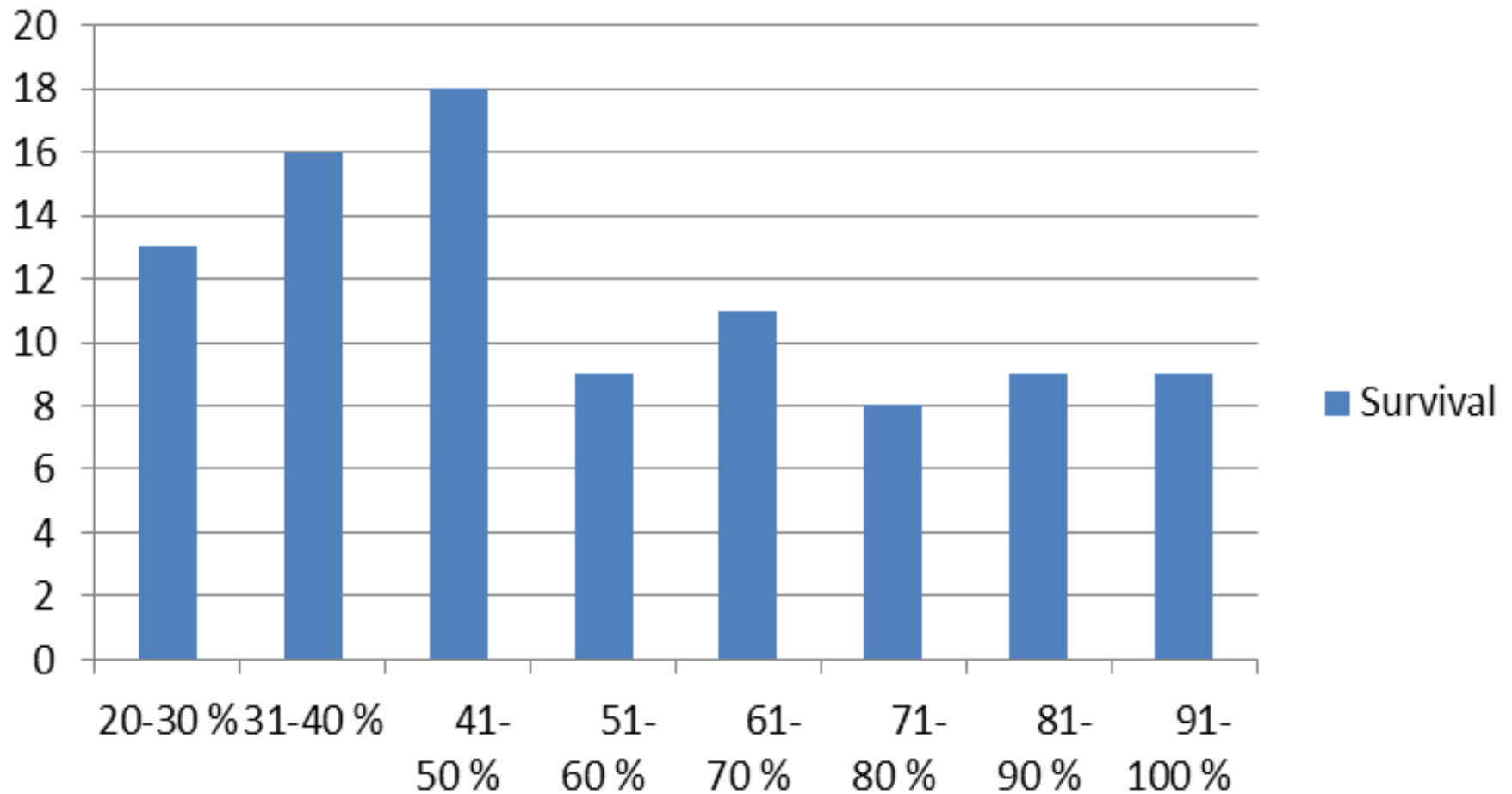


Ki-67

Nordic NEC

Months

Survival

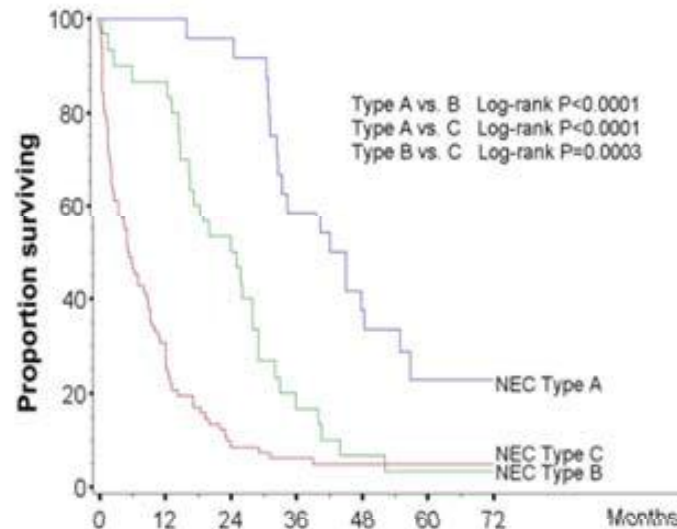


Nordic NEC

Should NEC Ki-67 21-55% be
treated differently?

Milione: Neuroendocrinology 2016

Figure 3. Overall survival of 136 patients with NEC according to subtype.



A: NET G3
 B: NEC Ki-67 21-55%
 C: NEC Ki-67 >55%

Patients at risk (n)							
	0	12	24	36	48	60	72
Type A	24	24	23	14	9	4	3
Type B	30	26	16	5	2	1	1
Type C	82	25	7	5	4	4	4
Overall survival (%)							
Type A	100	100	96	58	38	23	23
Type B	100	87	53	17	7	3	3
Type C	100	31	9	6	5	5	5

Treatment NET G3 vs NEC

	NET G3*	NEC
RR platinum chemotherapy	0-5 %	30-40%
PFS platinum chemotherapy	2.4 - ? m	4-6 m
OS stage 4	41-99 months	8-13 months

* Based on very few cases

First line chemotherapy – NET G3 vs. NEC

Heetfeld M: Endocr Rel Cancer 22, 657-64, 2015

Table 5. Type of first line Chemotherapy

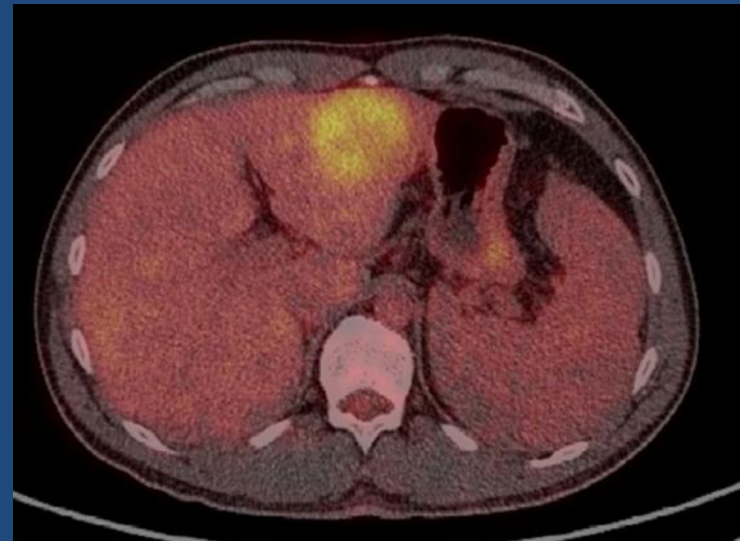
NEC G3		NET G3	
Type of Chemotherapy	Number (%)	Type of Chemotherapy	Number (%)
Platinum based + Etoposide	124 (84%)	Platinum based + Etoposide	7 (24%)
FOLFOX/XELOX/CAPOX	10 (7%)	Temozolomide based	5 (17%)
FOLFIRI	2 (1%)	Dacarbazine based	4 (14%)
Docetaxel/Cisplatin/5-FU	2 (1%)	FOLFOX/XELOX/CAPOX	3 (10%)
Other	6 (4%)	Other	10 (35%)



76% non-platinum based ctx

Exploratory treatment in for NET G3/ low Ki-67 NEC

- ASCO 2018: Promising data for tem/cap for NET G3 + ASCO Kunz panNET G2 results.
- Everolimus to 15 NET G3 pancreatic patients with Ki-67 < 55%. PFS 6 m and OS 28 (Panzuto 2017)
- NET G3 treated with everolimus/tem (ET-NEC study)



Peptide receptor radionucleotide therapy (PRRT) in NEN G3 ?

- In some centers policy up to Ki-67 30%.
- ENETS 2016 guidelines: Consider if NET G3
- Australian experience 29 pat:
Ki-67 < 55% (mOS 41m vs 7m if > 55%) (Thang et al 2017)

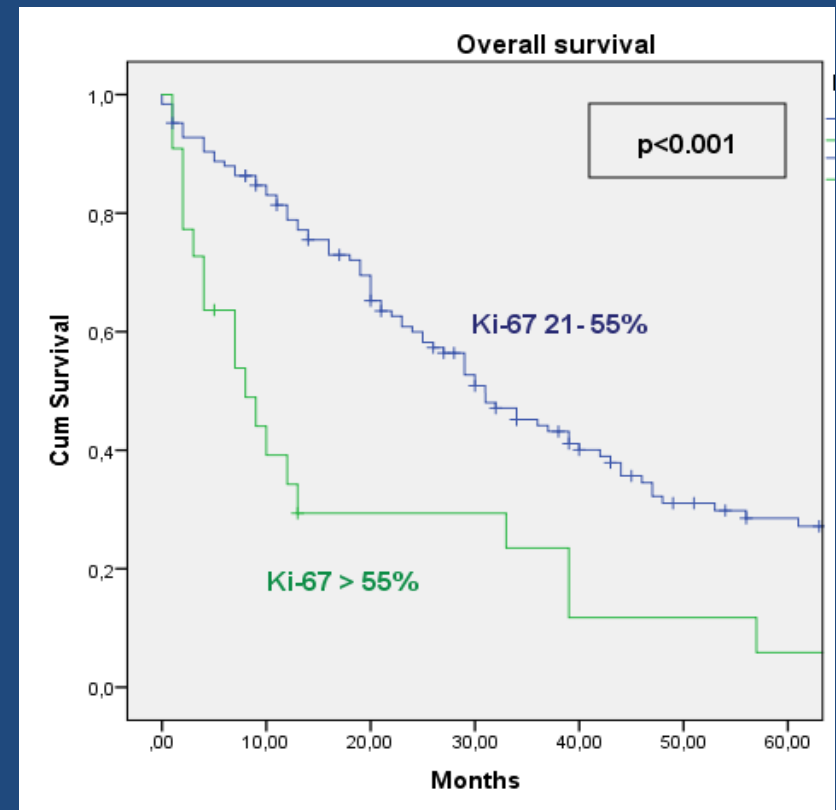
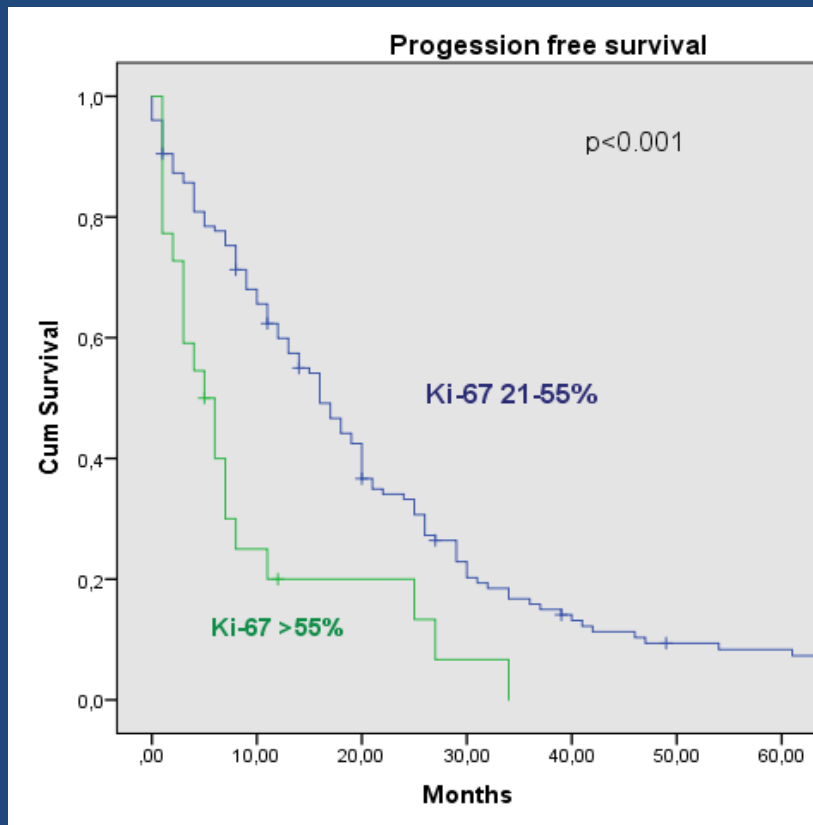
Peptide Receptor Radionuclide Therapy (PRRT) in Gastroenteropancreatic Grade 3 Neuroendocrine Neoplasms: a retrospective international multicenter study in 149 patients.

Sorbye H, Granberg D, Grozinsky-Glasberg S, Ahmadzadehfar H, [Grana CM](#), Zandee WT, Cwikla JB, Walter M, Rinke A, Grossman A, Frilling A, [Gritti S](#), Arveschoug AK, Knigge U, [Fazio N](#).

114 pts evaluable by RECIST
48 (42%) complete or partial response
43 (38%) stable disease
23 (20%) progressive disease.

Survival according to Ki-67

	PFS	OS
Ki-67 21-55%	18 m	31 m
Ki-67 >55%	5 m	8 m



Survival according to differentiation

PFS

OS

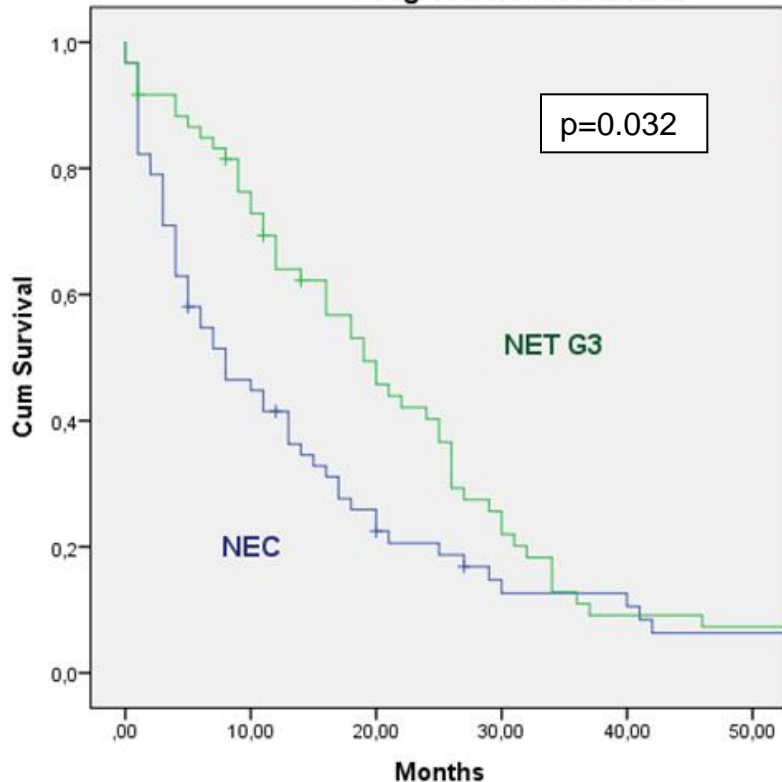
NEC 8 m

19 m

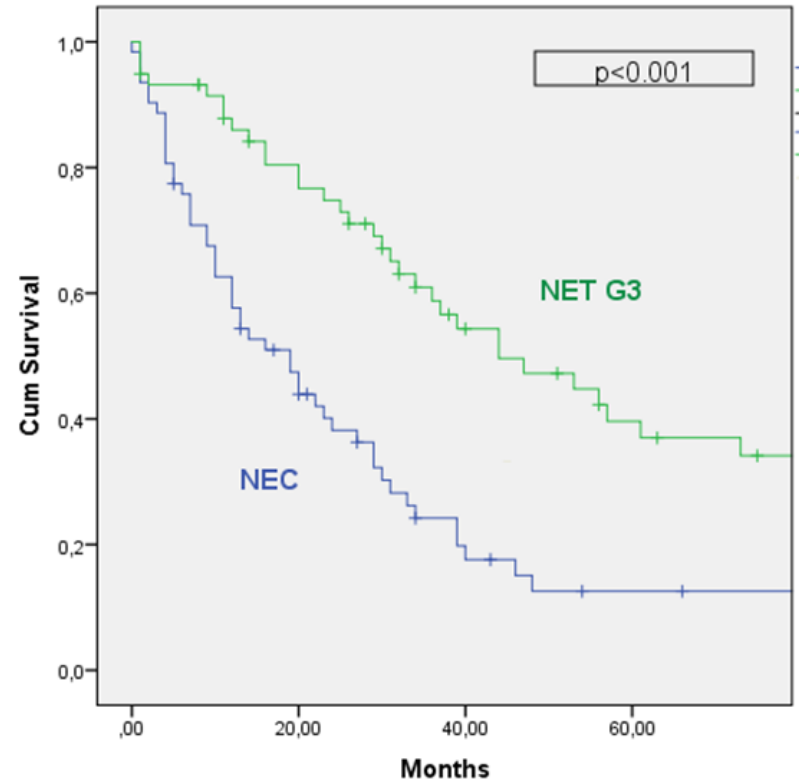
NET G3 19 m

44 m

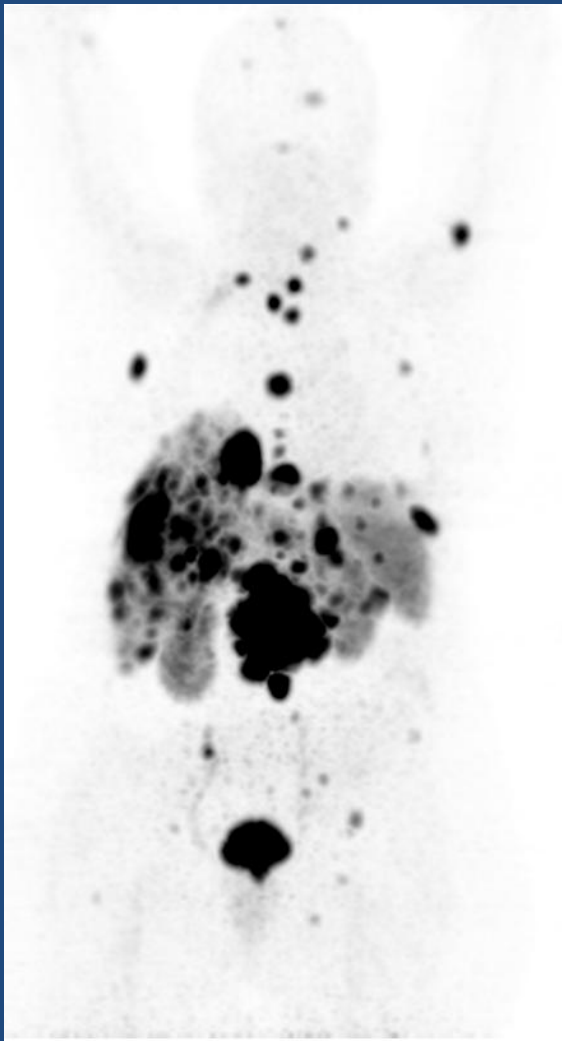
Progression free survival



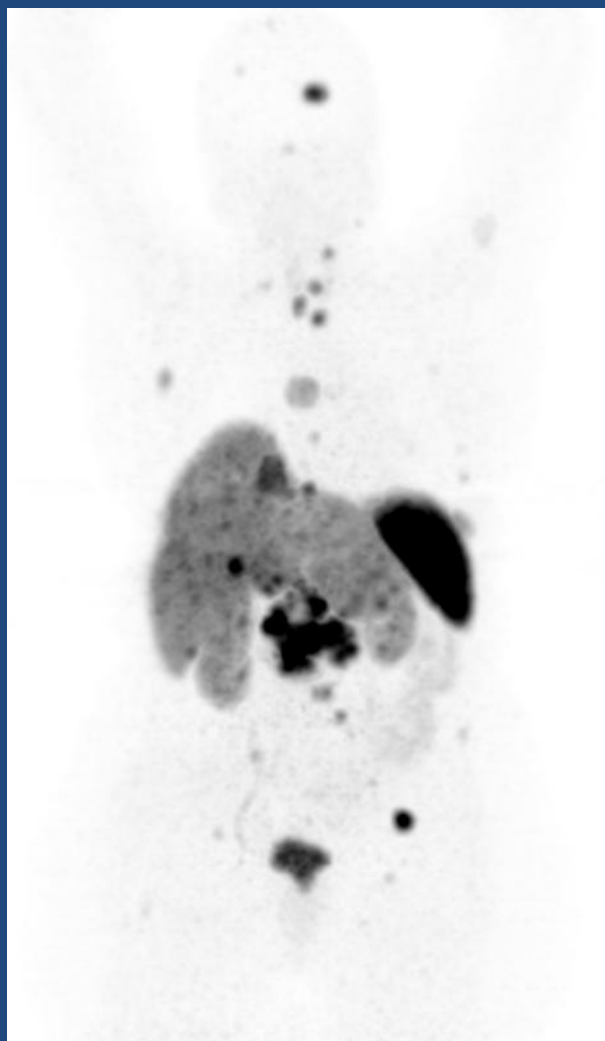
Overall survival



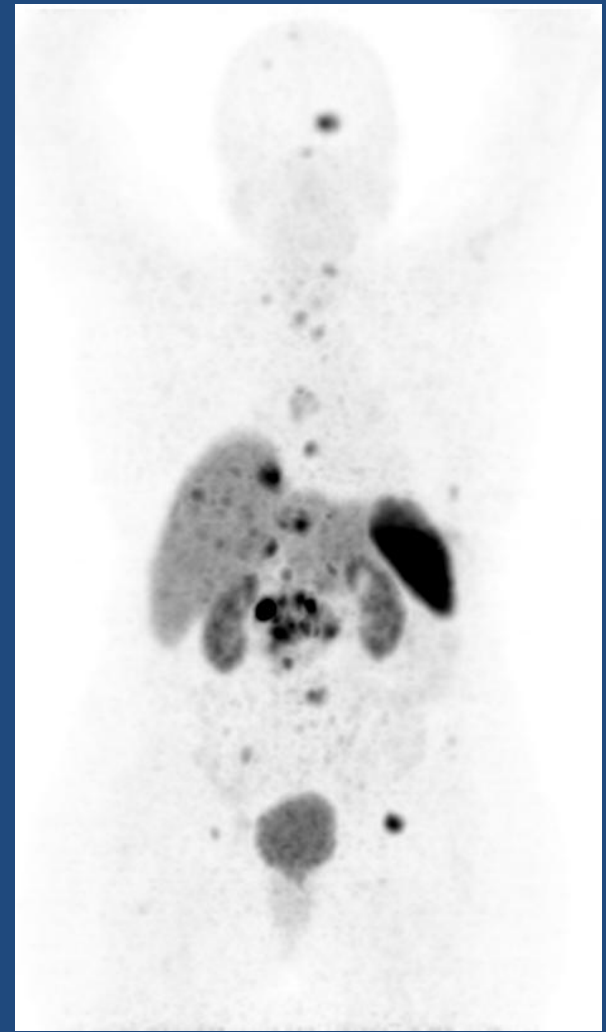
Pancreatic NEC Ki-67 30%



Baseline before PRRT
03/2015



3 months after 4th PRRT
05/2016

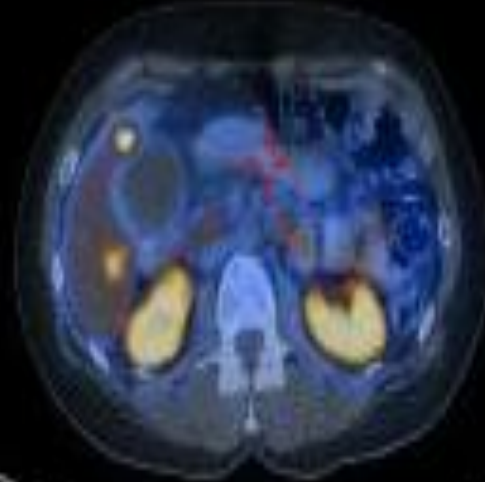
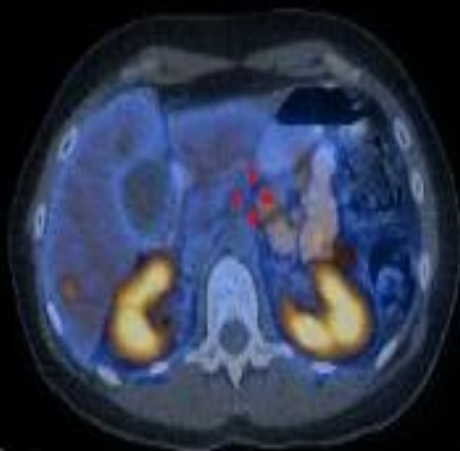
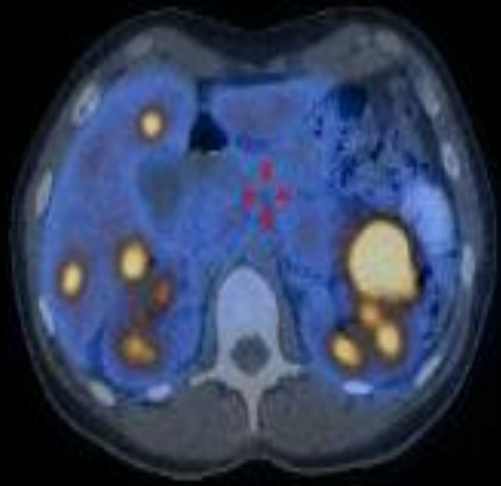


05/2017

Before PRRT, 01/2013

3 m after last PRRT,
02/2014

9 m after last PRRT,
08/2014



Pancreatic NEC Ki-67 70%, metastatic to the liver. Received PRRT x3 with durable PR

ASCO 2018

Immunotherapy for GEP NEN G3

Indication for Merkel cell carcinoma. High hopes.

AB: 4104: Pembrolizumab monotherapy in patients with previously treated metastatic high grade NEN.

Study plan for further development: RR > 5%

21 patients. Most GI: 40% NET G3, 60% NEC.

RR 4%- further development stopped

ASCO 2018

Immunotherapy for GEP NEN G3

Strosberg/Moffat: pembrolizumab after 1-line; no responses among the first 8 pat –to be closed.

Bergsland/UCSF: pembrolizumab after 1-line , if no responses add on irinotecan

ESMO 2018: Novartis PDR001: Negative studie, most received one cycle.

ASCO 2018

Immunotherapy for GEP NEN G3

Re-plan for a new design?

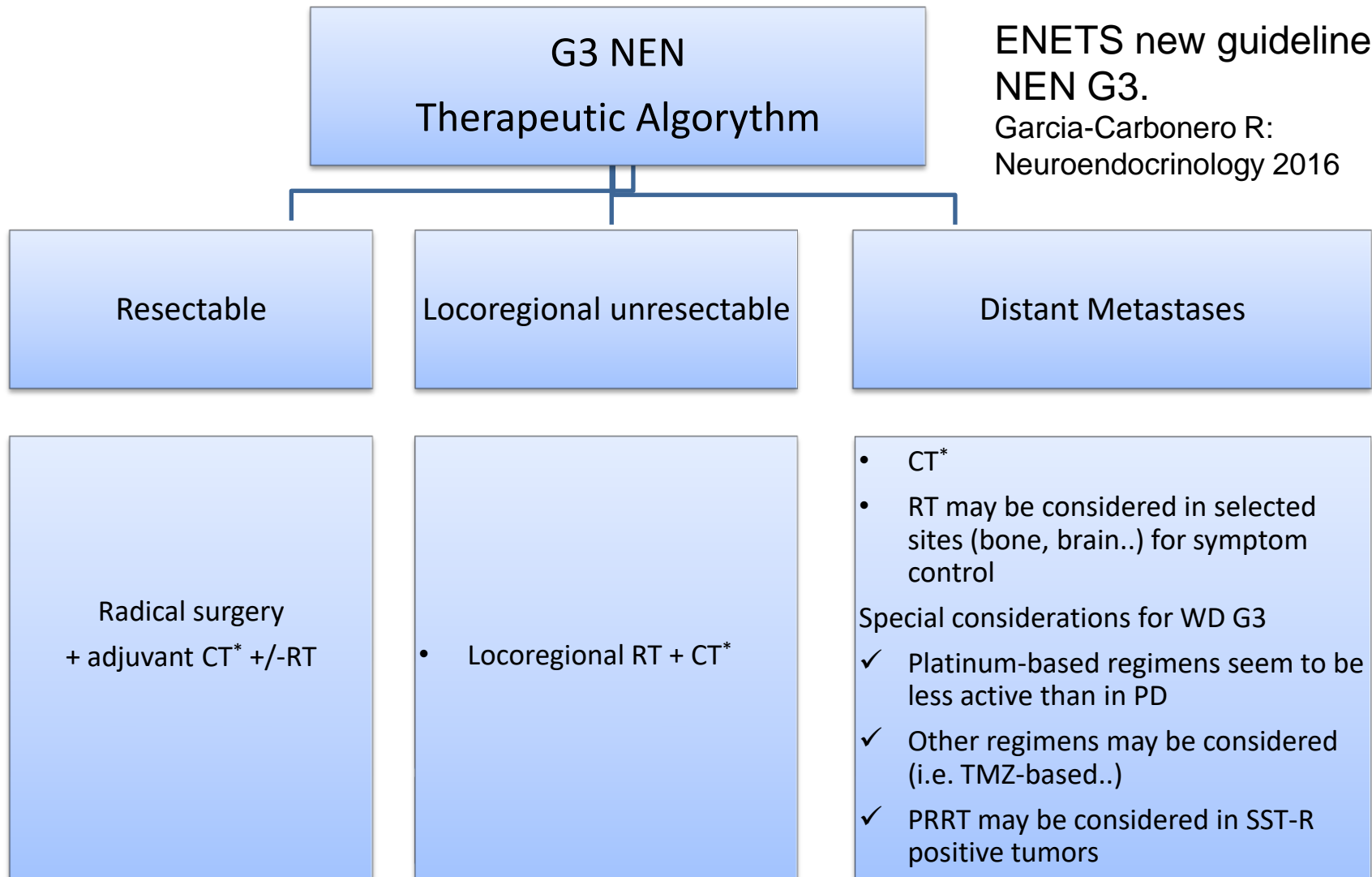
Patient cases with very promising effect of dual inhibition. Dual inhibition: PD-L + ipi ongoing in Spain.

Abstract 4098: Genomic profiling of 724 GEP NENs:
HG NENs mean TMB vs low-grade (9.5mut/MB v 5.1).
Cut-off for IO studies 16/17 (10).

HG NEN: MSI-H 4% vs 0% in low-grade.

ENETS new guidelines NEN G3.

Garcia-Carbonero R:
Neuroendocrinology 2016



- CT: chemotherapy
 - ✓ Cisplatin or carboplatin and etoposide are generally recommended in the adjuvant setting or first line therapy in advanced disease. *Alternative regimens substituting irinotecan for etoposide may also be employed as first-line therapy in advanced disease.*
 - ✓ Irinotecan or oxaliplatin-based regimens may be considered as second line therapy.
- Clinical judgement should be used.

Conclusions

Until better classification and more treatment data are available for NEN G3 patients several factors should be considered prior to selection of treatment for metastatic disease.

Differentiation (poorly vs. well-differentiated)

Ki-67 (middle vs high)

Clinical situation (tumour burden/growth)

Advanced/metastatic NEN G3 Treatment Algorithm

