NEN PRECEPTORSHIP
LA PRATICA CLINICA NELLE NEOPLASIE NEUROENDOCRINE

5/6 Aprile 2018 | IEO, Istituto Europeo di Oncologia - Milano

NEN Preceptorship

IEO
Istituto Europeo di Oncologia

Criteri di scelta della terapia non chirurgica

Carlo Carnaghi
Humanitas Cancer Center

Original Article

Effect of Tumor Heterogeneity on the Assessment of Ki67 Labeling Index in Well-differentiated Neuroendocrine Tumors Metastatic to the Liver: Implications for Prognostic Stratification

Zhaohai Yang, MD, PhD, Laura H. Tang, MD, PhD, and David S. Klimstra, MD

Abstract: The Ki67 labeling index is known to correlate with survival in patients with neuroendocrine tumors (NETs). A grading scheme recently endorsed by the World Health Organization for gastroenteropancreatic NETs classifies well-differentiated NETs into 2 categories based on the Ki67 labeling index: low (G1) and intermediate grades (G2). Tumor heterogeneity is a common finding in many tumors including NETs. Metastatic NETs to the liver are often diagnosed by radiographically guided needle core biopsy from which the Ki67 index is determined, which randomly samples the lesion without being targeted to regions that may show a higher proliferative rate. Whether the Ki67 index obtained from this type of limited material represents the whole tumor has been questioned. Forty-five surgically resected liver metastases of well-differentiated NETs were retrieved. A 9 core (3 core-triplets) tissue microarray (TMA) was constructed from the paraffin blocks of each tumor, each triplet considered to represent a virtual biopsy. Immunohistochemical staining for Ki67 was performed on TMA and whole slides, and the Ki67 labeling indices were determined by digital image analysis. Correlation of the Ki67 index with patient survival was analyzed. Forty-seven percent of cases showed intratumoral heterogeneity in Ki67 index that translated into discrepant grades among subsections on the whole slide. A similar trend was recapitulated on the virtual biopsies, although to a lesser degree. When the definitive grade of the tumor was based on the highest Ki67 index identified on the whole slide, the virtual biopsies perfectly predicted G1 cases (100%), but were much less accurate for G2 cases (47.8% with 3 biopsies and 34.8% with single biopsy). Accordingly, the predictive value for G1 on the virtual biopsies was low (64.7% and 59.5% for 3 and 1 biopsy, respectively), but was perfect for G2 (100%). By Kaplan-Meier survival analysis, there was a statistically significant difference between G1 and G2 in terms of overall survival, disease-free survival, and progression-free survival when graded on either whole-slide subsections or virtual biopsies. On the whole slides, the highest Ki67 grade showed a better correlation with overall survival than the mean Ki67 grade. In summary, by image analysis, we found that about half of the NETs metastatic to the liver show intratumoral heterogeneity resulting in discrepant Ki67 grade. In most cases, in particular G1, the virtual biopsy is representative of the whole slide, but for G2 the representation is < 50%. Nevertheless, grades based on virtual biopsy had statistically significant prognostic values on patient survival, and there is no clear difference between the 3 and single virtual biopsy. Ki67 staining of core biopsies usually provides an adequately reliable method of proliferation assessment for prognosis of metastatic NETs to the liver, although the choice of treatment may be affected by intratumoral grade heterogeneity.

Key Words: Ki-67 antigen, neuroendocrine tumors, liver, microarray analysis, Kaplan-Meier estimate

(*Am J Surg Pathol* 2011;35:853–860)

Well-differentiated neuroendocrine tumors (NETs) arising from the lung, gastrointestinal tract, and pancreas share many histologic features. The cells are usually positive for neuroendocrine markers such as chromogranin A and synaptophysin. Well-differentiated NETs include low-grade and intermediate-grade examples, which are distinguished from the much more aggressive category of poorly differentiated (high grade) neuroendocrine carcinomas. Up to 40% of the patients with well-differentiated NETs present with distant metastases, commonly in the liver.[13] In most cases, however, the tumors progress slowly. Even in the presence of liver metastases, the patient may survive for many years; thus NETs are often called "cancers in slow motion."[10] The 5-year survival for NETs with distant metastases is approximately 40% for gastrointestinal and 20% for pancreatic primaries, respectively.[3]

The classification of NET has been evolving. During the past decades, several parameters including the Ki67 labeling index have been shown to correlate with survival.[7,12] In 2006 and 2007, the European Neuroendocrine Tumour

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The preliminary results of this study were presented at the 99th annual meeting of the United States and Canadian Academy of Pathology in Washington DC, March 2010.

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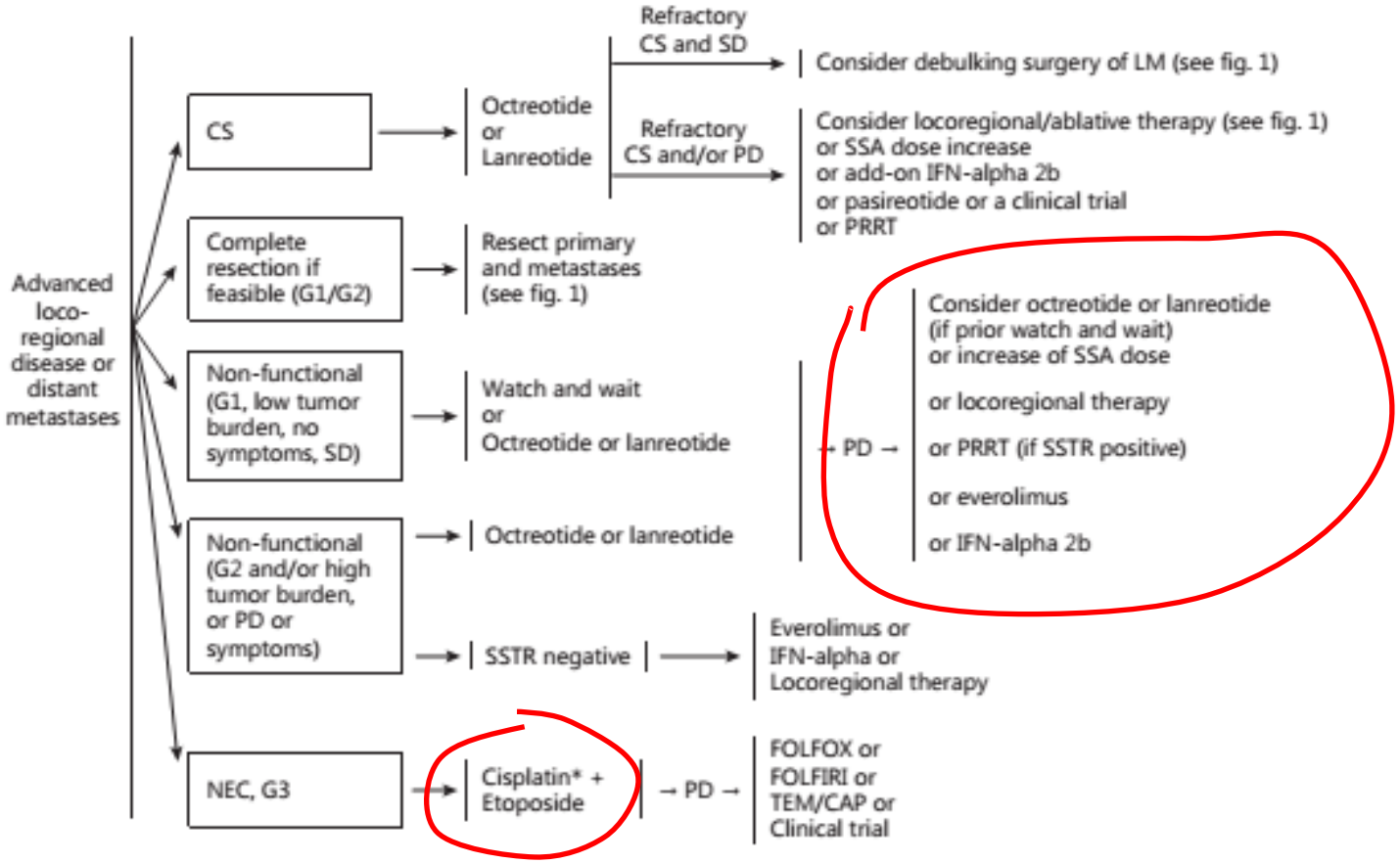
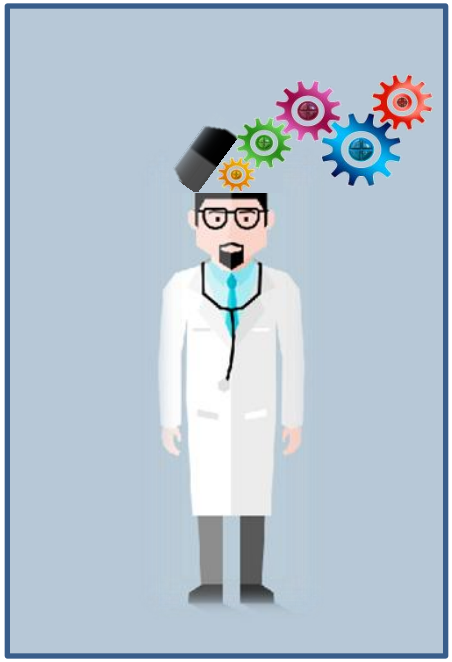
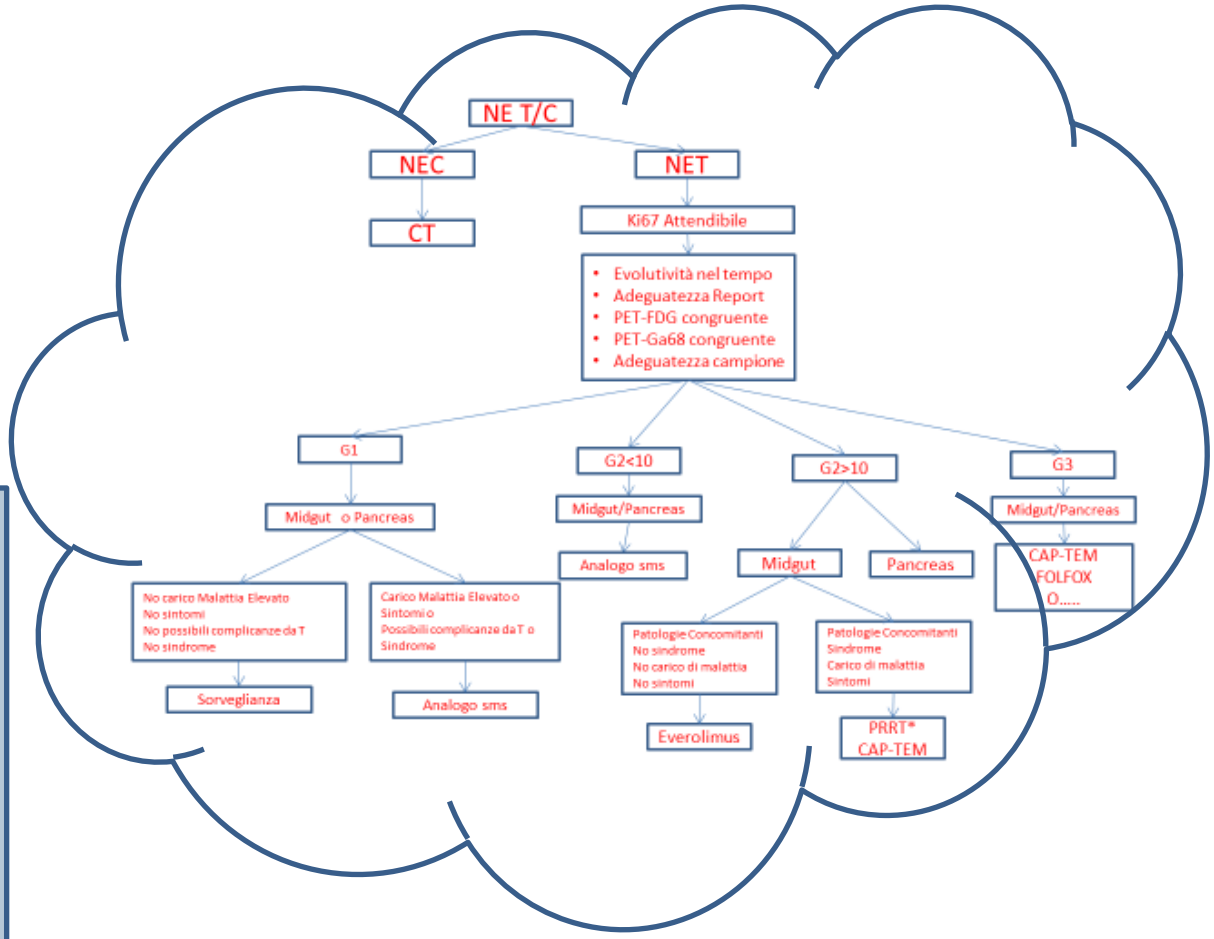
1
326
LEGO
System
2
3
4


NCCN
National
Comprehensive
Cancer
Network
ENETS
ESMO
?
NANETS
Aiom
It.a.net
ROL
Rete Oncologica
Lombarda



Pavel M, et al. Neuroendocrinolgy 2016

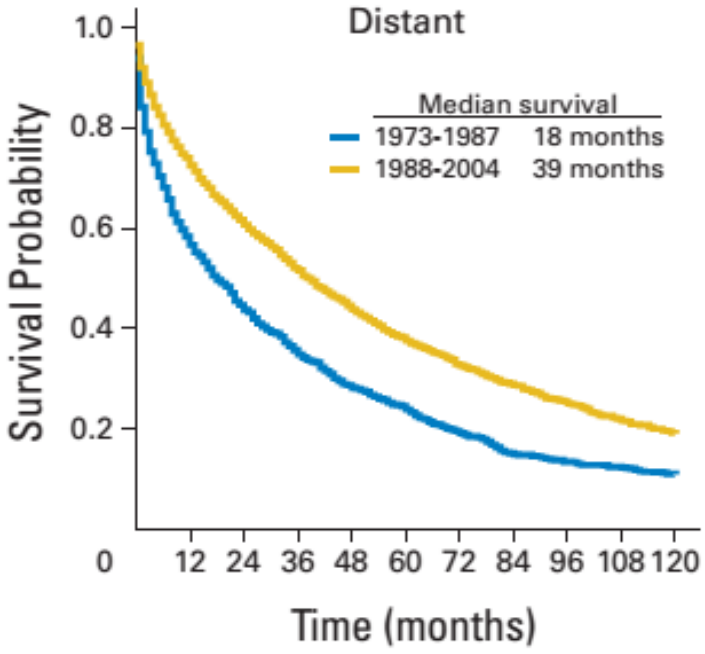



NE T/C
NEC
NET
CT
Ki67 Attendibile
Evolutività nel tempo
Adeguatezza Report
PET-FDG congruente
PET-Ga68 congruente
Adeguatezza campione
G1
G2<10
G2>10
G3
Midgut o Pancreas
Midgut/Pancreas
Midgut/Pancreas
Analogo sms
Midgut
Pancreas
CAP-TEM
FOLFOX
O.....
No carico Malattia Elevato
No sintomi
No possibili complicanze da T
No sindrome
Carico Malattia Elevato o
Sintomi o
Possibili complicanze da T o
Sindrome
Patologie Concomitanti
No sindrome
No carico di malattia
No sintomi
Patologie Concomitanti
Sindrome
Carico di malattia
Sintomi
Sorveglianza
Analogo sms
Everolimus
PRRT*
CAP-TEM

One Hundred Years After "Carcinoid": Epidemiology of and Prognostic Factors for Neuroendocrine Tumors in 35,825 Cases in the United States

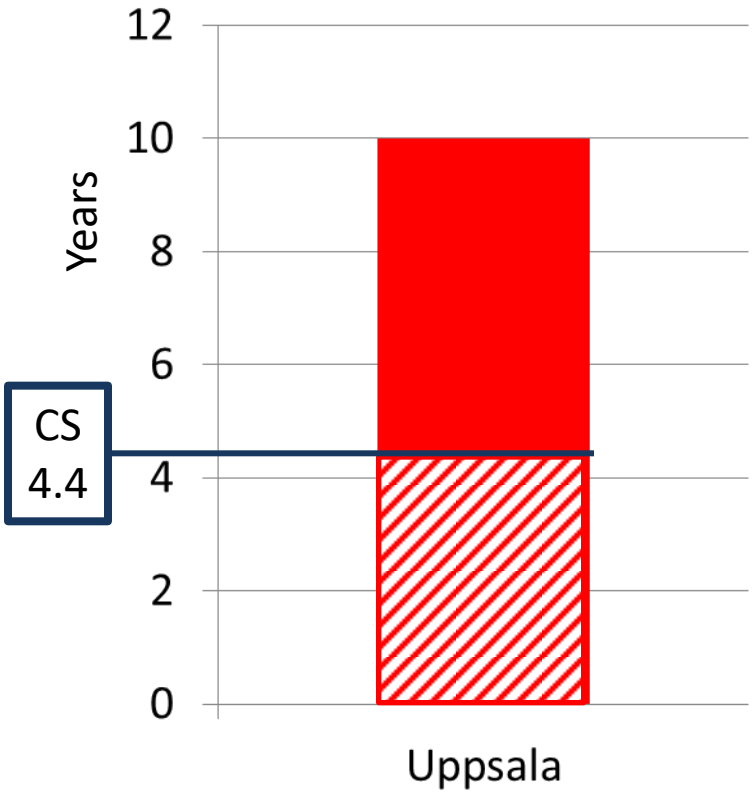
NETs survival has improved since the introduction of SSAs

The median OS of pts diagnosed with advanced NETs was significantly longer in 1998-2004 compared to 1973-1987 timeframe(SEER database)



Yao JC et al. JCO 2008

Median Survival in Metastatic Midgut NETs



Erickson B.,
Presented at ENETS
Barcelona 2016

G1

↓

Midgut o Pancreas

↓

Basso carico di malattia
Assenza di sintomi
Basso rischio complicazioni da T
Assenza sindrome
Anziano
Assenza di evoluzione

↓

Sorveglianza «attiva»

Watch and wait policy in advanced neuroendocrine tumors: What does it mean?

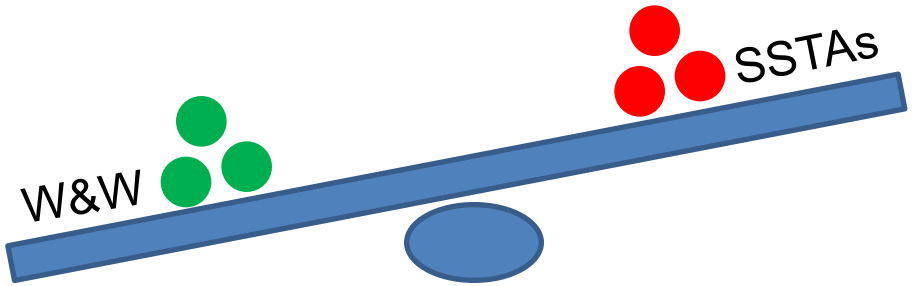
It has never been specifically investigated…!
How to define morphological (radiological), functional (receptorial? metabolic?) or biochemical progression ?
With which threshold?
Could be detrimental to start therapy only when tumor -related symptoms arise?

Fazio N. World J Clin Oncol2017

	W & W	Octreotide and Lanreotide
Cost of administration	🟢	The estimated per-cycle were $5241.73 for 30-mg octreotide LAR and $6000 for 120-mg lanreotide
Risk of delay	🔴	Time since diagnosis < 4 vs > 4 months (p 0.08)
Time of exposure	🟢	62 months
Adverse events	🟢	Occurring more often than with placebo, and in >5% of patients.
Cost per episode	🟢	Cholelithiasis $7839.24 Abdominal pain $1997.73

ClinicalTrials.gov NCT03084770

Asympotmatic Small Pancreatic Endocrine Neoplasms (ASPEN)



Ortendahl JD, et al. Am Health Drug Benefits. 2017.

G1

↓

Midgut o Pancreas

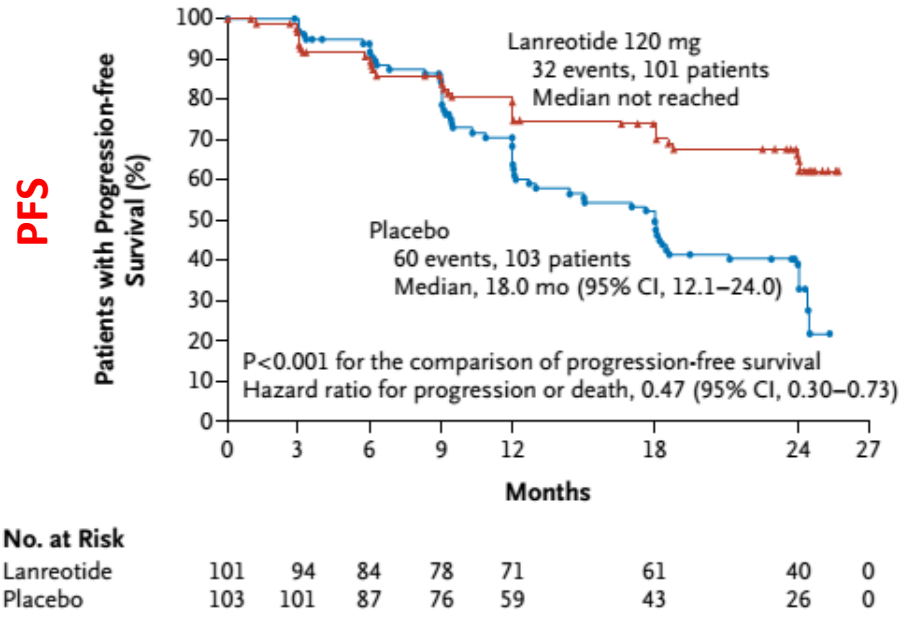
↓

- Carico Malattia Elevato o
- Sintomi o
- Possibili complicanze da T o
- Sindrome o
- Lieve PD

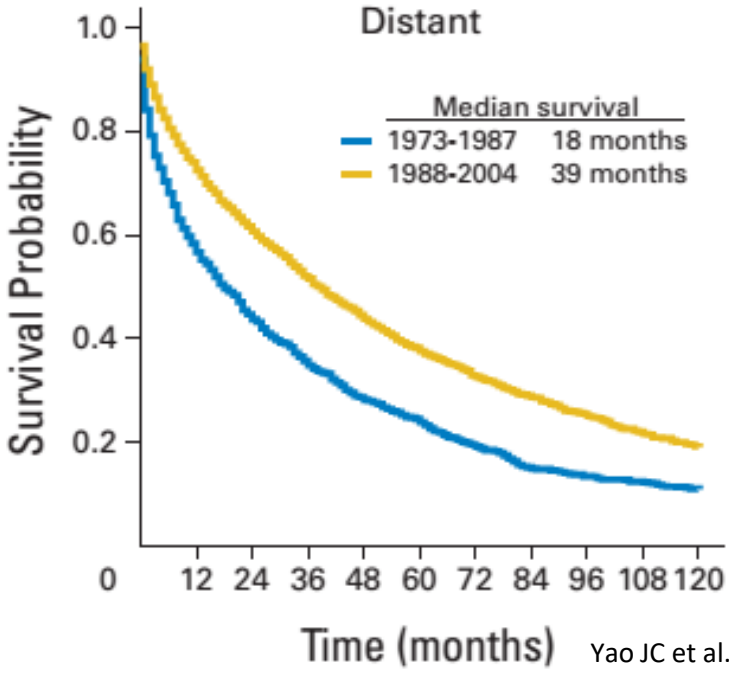
↓

Analogo SST

PFS



Caplin ME et al. NEJM 2014



Yao JC et al. JCO 2008

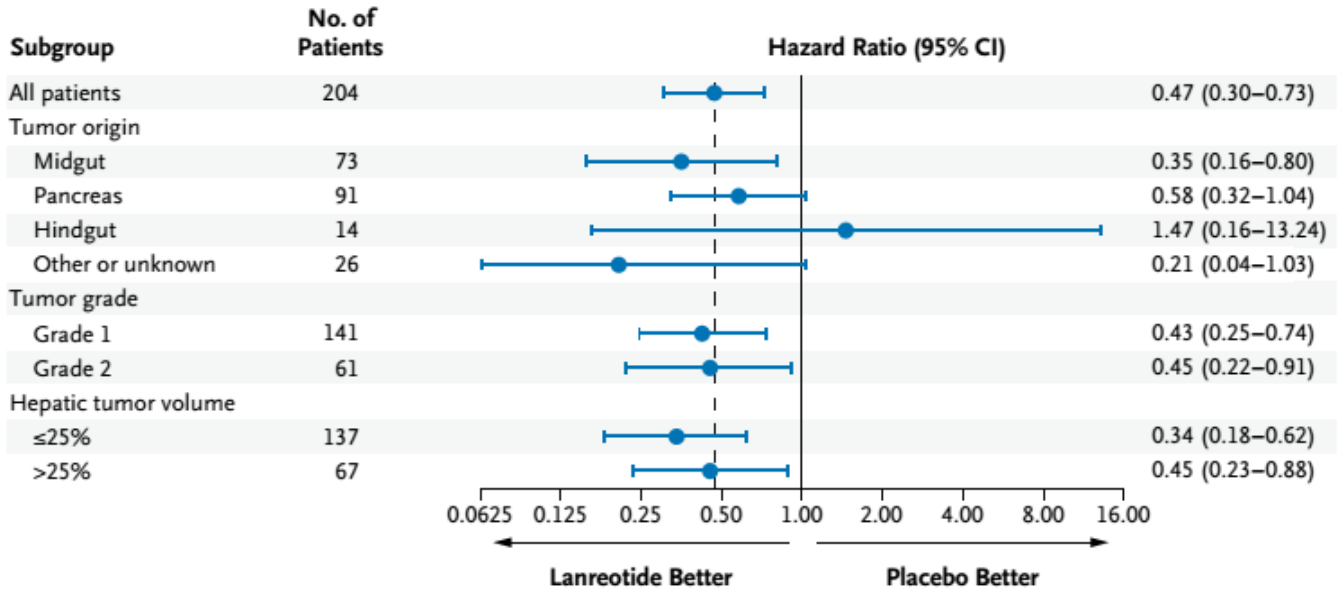
G2 (SSTRs+) Ki67 <10%

↓

Midgut o Pancreas

↓

Analogo SST



Caplin ME et al. NEJM 2014

Table 3. Prognostic Factors for Time to Progression or Tumor-Related Death Adjusted for Treatment Based on the Per-Protocol Analysis

	Bivariate Analysis			Multivariate Analysis		
Factor	*P*	HR	95% CI	*P*	HR	95% CI
Octreotide LAR *v* placebo*				< .0001	0.27	0.14 to 0.49
Functional active tumor *v* inactive tumor	.2420	1.38	0.81 to 2.37			
Liver involvement > *v* ≤ 10%	.0009	2.81	1.53 to 5.18	.0023	2.63	1.41 to 4.90
Chromogranin A elevated *v* not elevated	.3098	1.36	0.75 to 2.48			
Karnofsky performance status ≤ *v* > 80%	.6518	1.21	0.54 to 2.71			
Age ≥ *v* < 63 years	.1709	1.47	0.85 to 2.56			
Primary tumor not resected *v* resected	.1040	1.60	0.91 to 2.80	.6784	1.45	0.60 to 2.20
Time since diagnosis ≥ *v* < 4.3 months	.0806	0.62	0.36 to 1.06	.2883	0.71	0.38 to 1.34

Abbreviation: HR, hazard ratio.
**P* value and effect size are only presented for multivariate analysis.

Rinke A, et al. JCO 2009

G2 Ki67 >10%

↓

Midgut

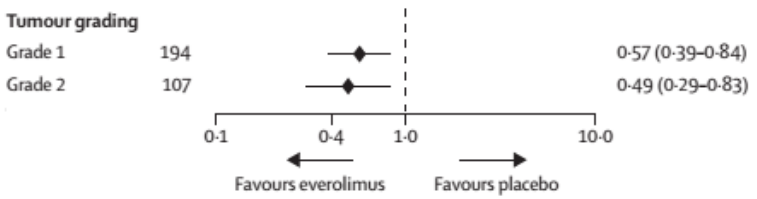
↓

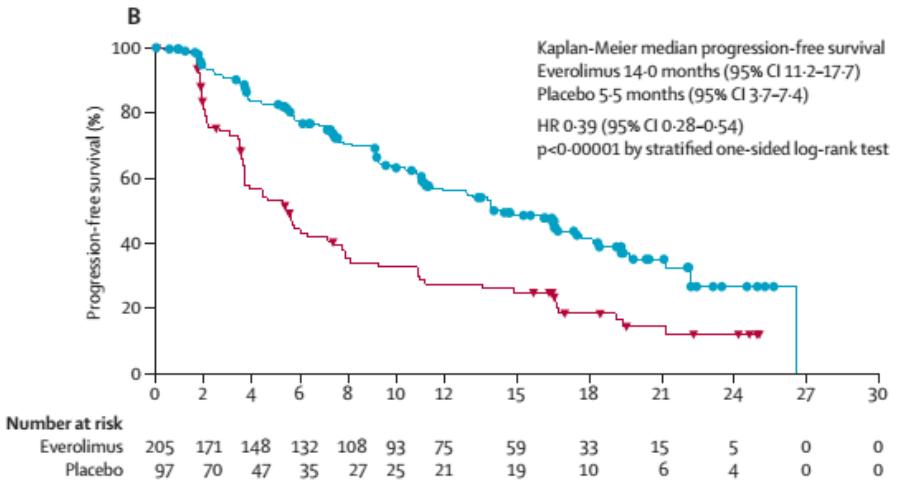
- Basso carico di malattia
- Assenza sintomi
- No controindicazioni

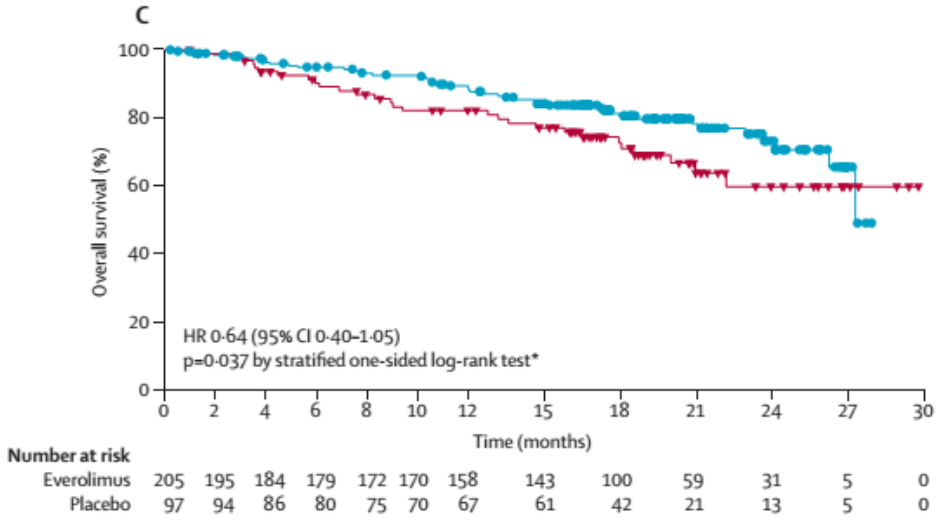
↓

Everolimus
(Analogo SST)

Liver tumour burden		
None	34 (17%)	14 (14%)
≤10%	119 (58%)	61 (63%)
>10% to 25%	29 (14%)	8 (8%)
>25%	21 (10%)	14 (14%)
Unknown	2 (1%)	0







Yao JC, et al. The Lancet 2015

G2 Ki67 >10%

Midgut

- Elevato carico di malattia
- Sintomi
- (Sindrome)
- No Controindicazioni

RS- | RS+

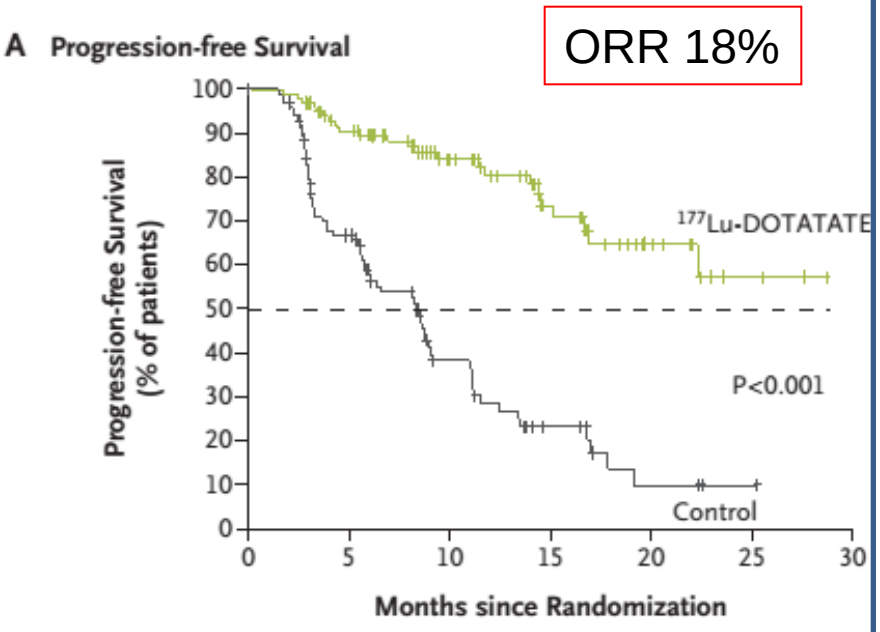
CAP-TEM | PRRT

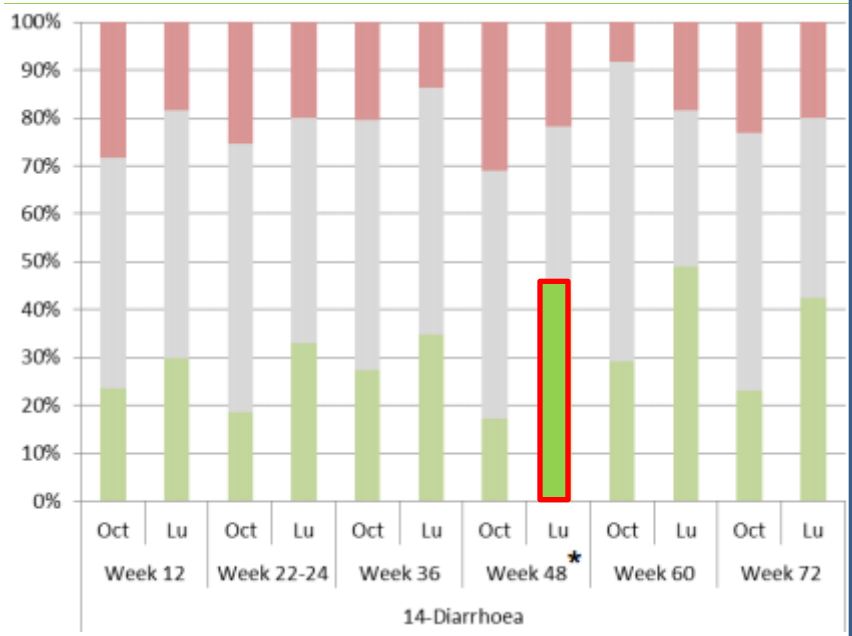
Table 2 Treatment response by RECIST ($n = 18$)

RECIST responses	No. (%)
Complete response (pathologically proven)	1 (5.5)
Partial responses	10 (55.5)
Stable disease	4 (22.2)
Progressive disease	3 (16.8)

Fine RL. et al Cancer Chemother Pharmacol. 2013

ORR 18%





Strosberg J et al.NEJM 2017

G2>10%

Pancreas

Everolimus

Rischio sanguinamento
Sindrome
Interazione farmaci (trova)
Abuso di Pompelmo (;-)
Patologie concomitanti
- Ipertensione Arteriosa
- Cardiopatia
- Tireopatia
- Insufficienza renale
- Concomitanti

Sunitinib

Diabete
Uso steroidi
Dislipidemia
Patologie respiratorie croniche
Sintomi
Carico di malattia
Interazione farmaci (trova)

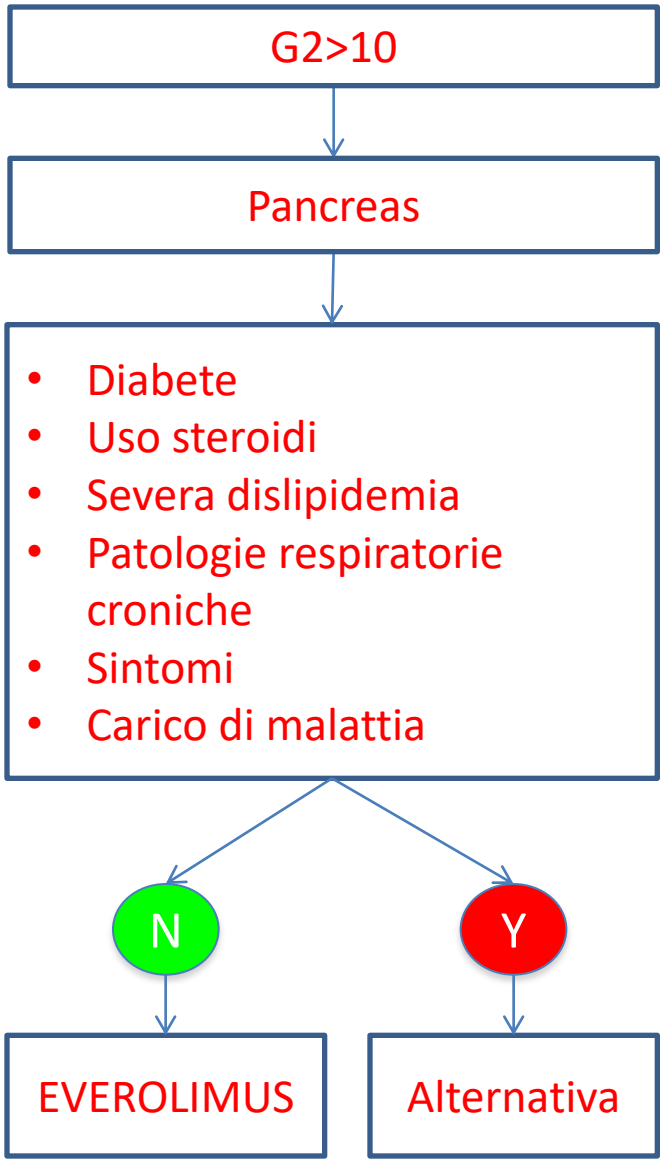
Cap-Tem

Leuco-piastrinopenia
Omozigosi mutazione DPYD
Insufficienza renale
Sindrome

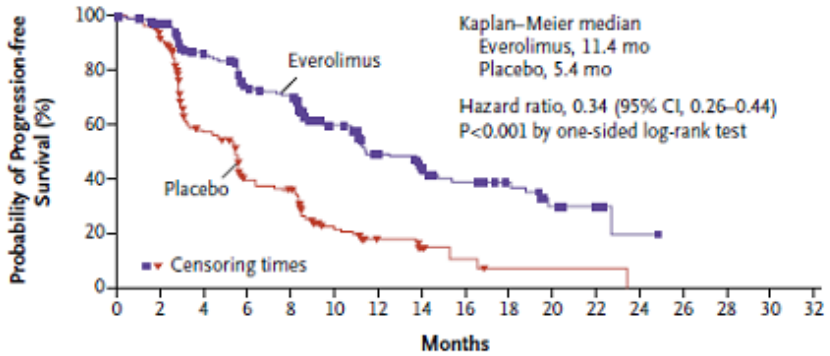
PRRT*

Insufficienza Renale
Leuco-piastrinopenia
Accessibilità geografica
PET gallio negativa/disomogenea

1 2 3 4



No significant influence of creatinine clearance (25-178 mL/min) was detected on oral clearance (CL/F) of everolimus



Yao JC, et al. NEJM 2011

Adverse Event	Everolimus (n = 204), No. (%) All Grades	Grade 3 or 4
Stomatitis*	137 (67.2)	15 (7.4)
Rash	98 (48.0)	1 (< 1)
Diarrhea	69 (33.8)	7 (3.4)
Fatigue	66 (32.4)	3 (1.5)
Infections†	57 (27.9)	5 (2.5)
Peripheral edema	44 (21.6)	1 (< 1)
Nausea	42 (20.6)	2 (1.0)
Decreased appetite	41 (20.1)	0
Headache	39 (19.1)	0
Epistaxis	37 (18.1)	0
Anemia	34 (16.7)	10 (4.9)
Noninfectious pneumonitis‡	34 (16.7)	5 (2.5)
Weight loss	34 (16.7)	0
Dysgeusia	34 (16.7)	0
Pruritus	31 (15.2)	0
Vomiting	30 (14.7)	0
Hyperglycemia	29 (14.2)	12 (5.9)
Thrombocytopenia	26 (12.7)	8 (3.9)
Asthenia	26 (12.7)	2 (1.0)
Cough	26 (12.7)	0
Nail disorder	25 (12.3)	1 (< 1)
Pyrexia	24 (11.8)	0
Dry skin	21 (10.3)	0

Yao JC, et al. JCO 2016

G2 Ki67 >10

Pancreas

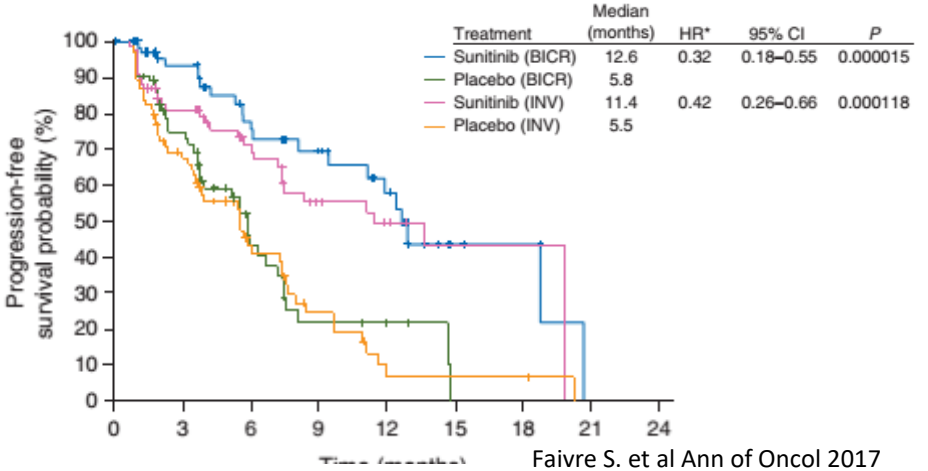
- Rischio sanguinamento
- Trombosi A-V
- Sindrome
- Ipertensione arteriosa
- Cardiopatia
- Tireopatia
- Insufficienza renale

N

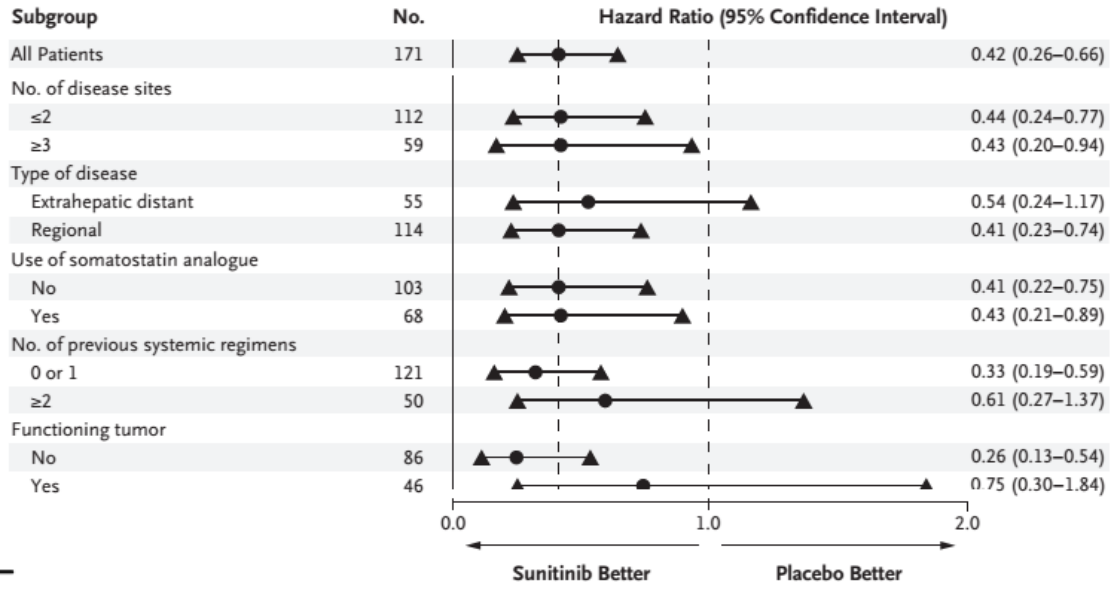
Y

SUNITINIB

Alternativa



Faivre S. et al Ann of Oncol 2017



Raymond E. et al. NEJM 2011

Most frequent adverse events during sunitinib treatment.

Adverse event	Overall	Grade 1-2	Grade 3-4
Hypertension	18 (22.5%)	15 (18.8%)	3 (3.8%)
Asthenia	18 (22.5%)	12 (15%)	6 (7.5%)
Diarrhea	16 (20%)	16 (20%)	–
Neutropenia	15 (18.8%)	8 (10%)	7 (8.8%)
Mucositis	14 (17.5%)	12 (15%)	2 (2.5%)
Palmar-plantar erythrodysesthesia	8 (10%)	7 (8.8%)	1 (1.3%)
Thrombocytopenia	7 (8.8%)	6 (7.5%)	1 (1.3%)
Stomatitis	5 (6.3%)	5 (6.3%)	–
Fever	5 (6.3%)	4 (5%)	1 (1.3%)

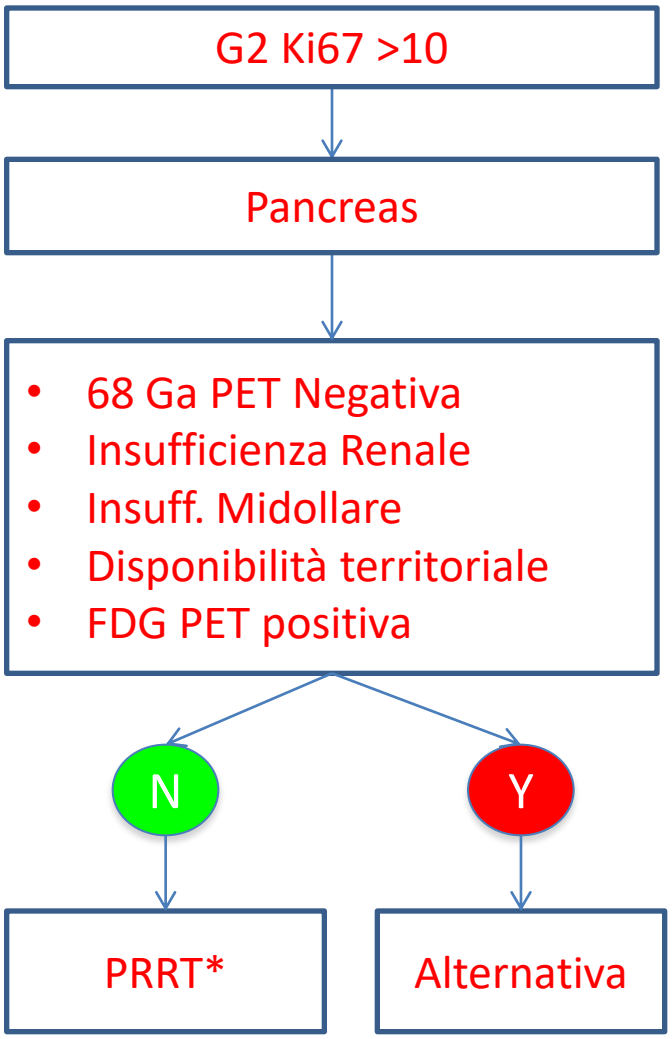
Rinzivillo M. et al Pancreatology 2018

Sunitinib Drug Interactions

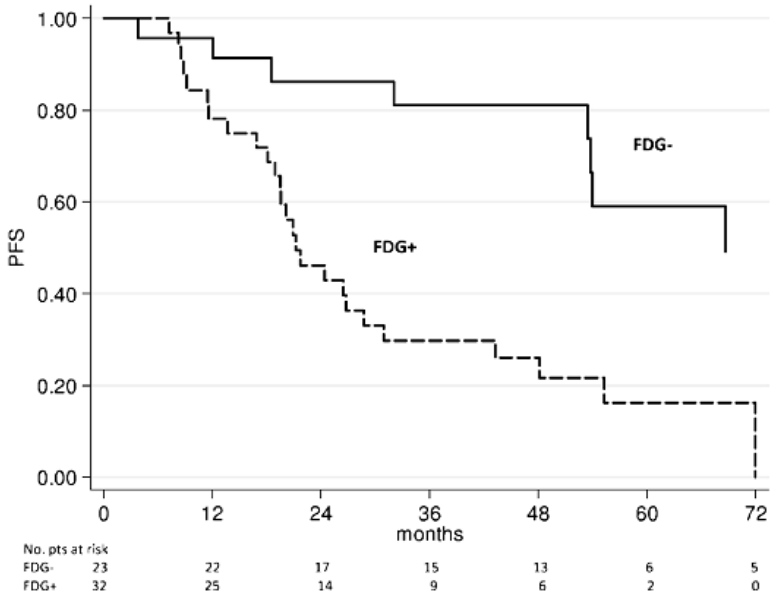
A total of **464 drugs** (1783 brand and generic names) are known to interact with sunitinib.

- 60 major drug interactions (160 brand and generic names)
- 398 moderate drug interactions (1587 brand and generic names)
- 6 minor drug interactions (36 brand and generic names)

www.drugs.com

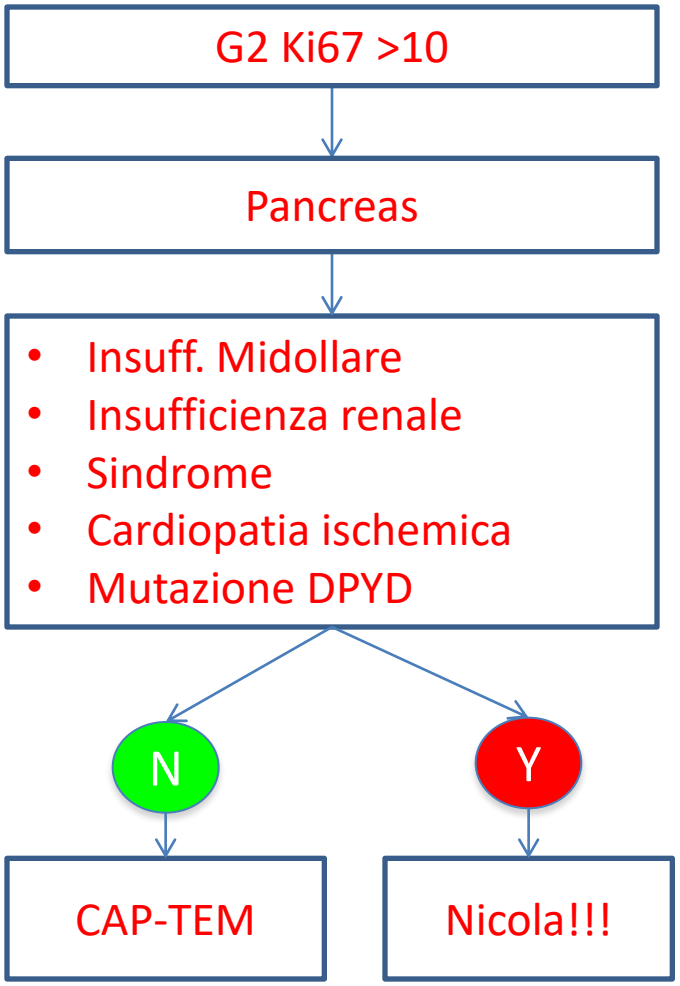


Prospective phase II trial, 60 pts with P-NETs were enrolled. mPFS was 21.1 months in FDG PET positive patients and 68.7 months in the FDG PET-negative group (P< 0.0002)

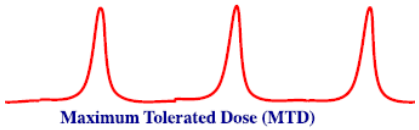


	PFS		mOS	
	HR (95 % CI)	*P*	HR (95 % CI)	*P*
FDG (positive vs. negative)	5.15 (1.42–18.75)	0.013	5.08 (0.85–30.42)	0.075

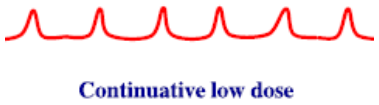
Sansovini Me, et al. Eur J Nucl Med Mol Imaging 2016



Conventional



Metronomic



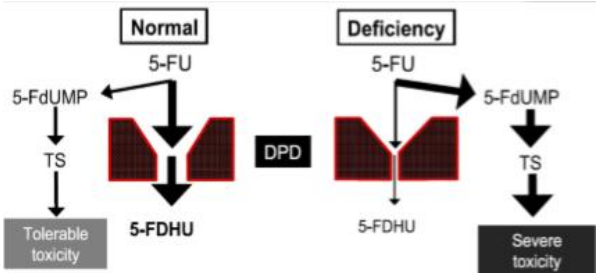
	CAPTEM treatment toxicities			
Toxicity	**Grade I**	**Grade II**	**Grade III**	**Grade IV**
Lymphocytopenia	3	9	3	0
Thrombocytopenia	6	3	1	2
Nausea	11	1	1	0
Hand/foot	6	3	0	0
Fatigue	5	5	0	0
Diarrhea	4	3	2	0
Neutropenia	0	0	0	3
Hypoglycemia	0	0	0	0
Weight loss	1	0	0	0
Anemia	3	0	0	0

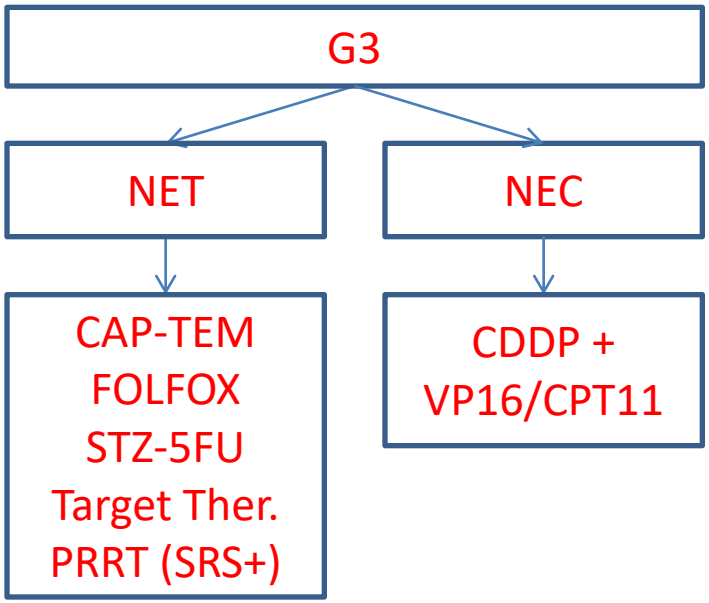
Table 3. Differences in primary tumor site response rates

Response by tumor site	*n* (%)	PR, *n* (%)	SD, *n* (%)	PD, *n* (%)
Pancreatic NET	15 (52)	3 (20)	5 (33)	7 (47)
Nonpancreatic NET	14 (48)	2 (14)	9 (64)	3 (22)
Overall	29 (100)	5 (17)	14 (48)	10 (34)

Abbreviations: NET, neuroendocrine tumor; PD, progressive disease; PR, partial response; SD, stable disease.

Guillermo Crespo et al, Future Oncology 2017





International survey of clinical practice exploring use of platinum-etoposide chemotherapy for extra-pulmonary high grade neuroendocrine carcinoma (EP-G3-NEC).

Angela Lamarca[1], Melissa Frizziero[1], Jorge Barriuso[1,2,&], Mairéad G McNamara[1,3], Richard A Hubner[1], Juan W Valle[1,3]

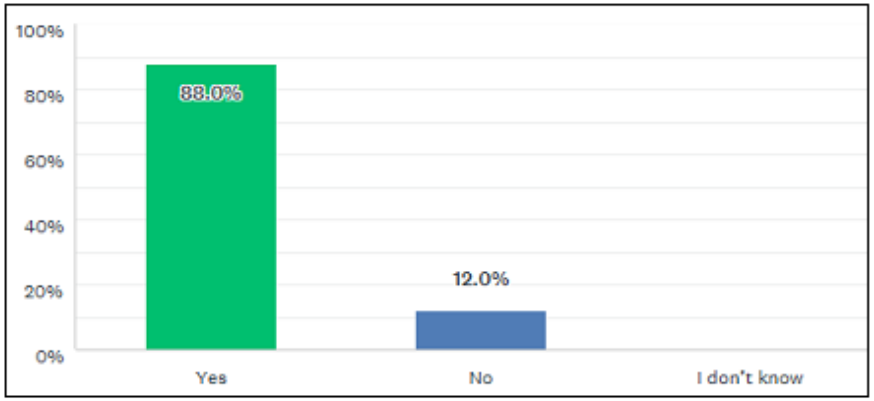


Figure 2: Use of morphology (well-differentiated versus poorly differentiated) to guide the choice of chemotherapy regimen for the management of patients diagnosed with EP-G3-NECs.

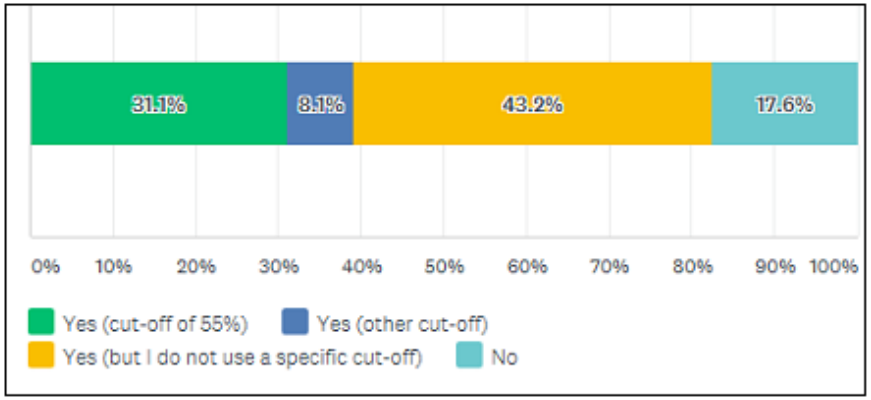
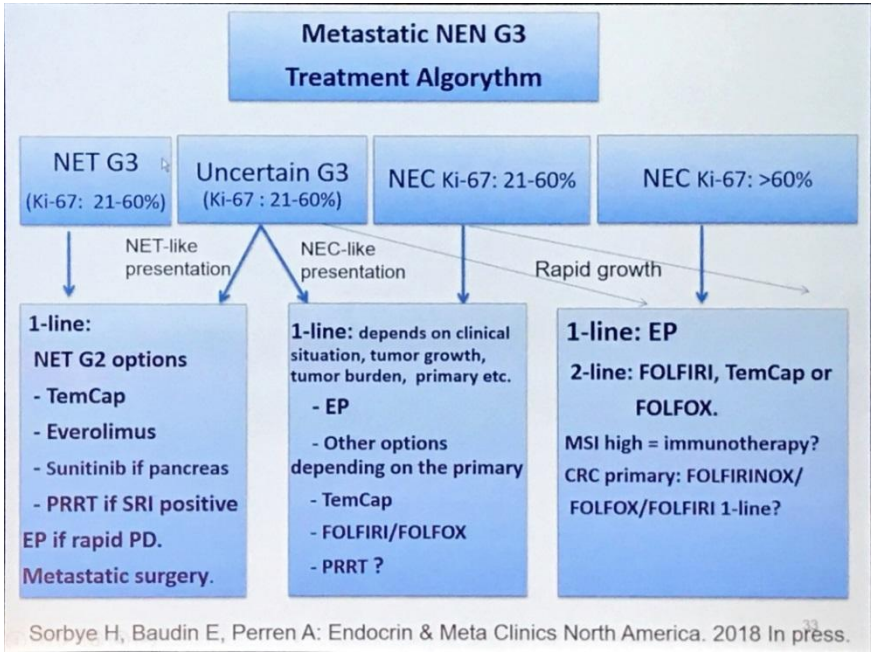
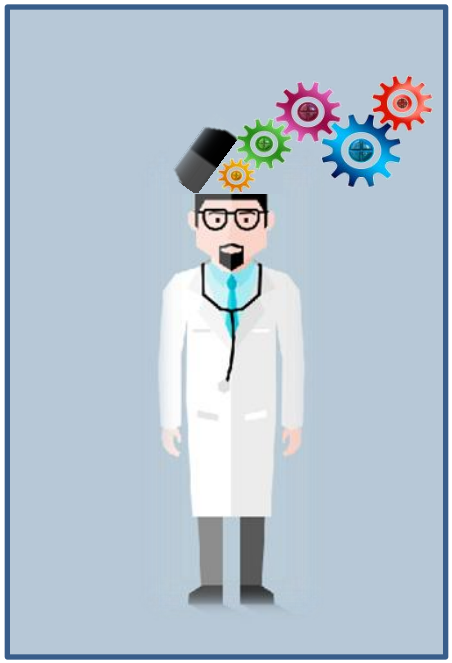


Figure 3: Patients are assumed to have a Ki67 of ≥20%. In addition, is Ki67 used to guide choice of chemotherapy regimen?



Sorbye Presented at ENETS 2018



Errore più comune

 # 1 Non considerare la possibilità di arruolare il paziente in un trial clinico

Grazie!!!

NEN PRECEPTORSHIP
LA PRATICA CLINICA NELLE NEOPLASIE NEUROENDOCRINE

5/6 Aprile 2018 | IEO, Istituto Europeo di Oncologia - Milano

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