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
Algoritmo di ragionamento nell'impostazione terapeutica.
Francesca Spada

Caso clinico

Tumore neuroendocrino del pancreas

Presentazione clinica

- M, 44 aa
- Ex fumatore (10 sigarette/die)
- **Anamnesi patologica:** nefrolitiasi
- **Familiarità oncologica:**

- Padre deceduto per neoplasia polmonare (ex fumatore)

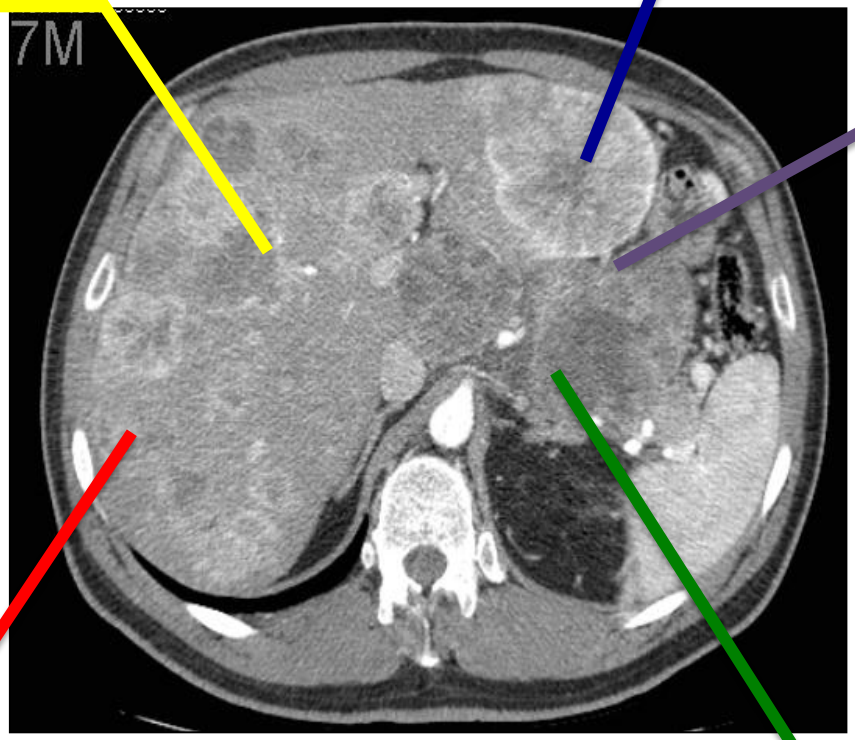
Dicembre 2017:

Calo ponderale del <10% (in 3 mesi) + dispepsia

NET ben differenziato, Ki-67 19% (G2 sec. WHO 2010)

SD RECIST in 3 mesi (lenta PD)

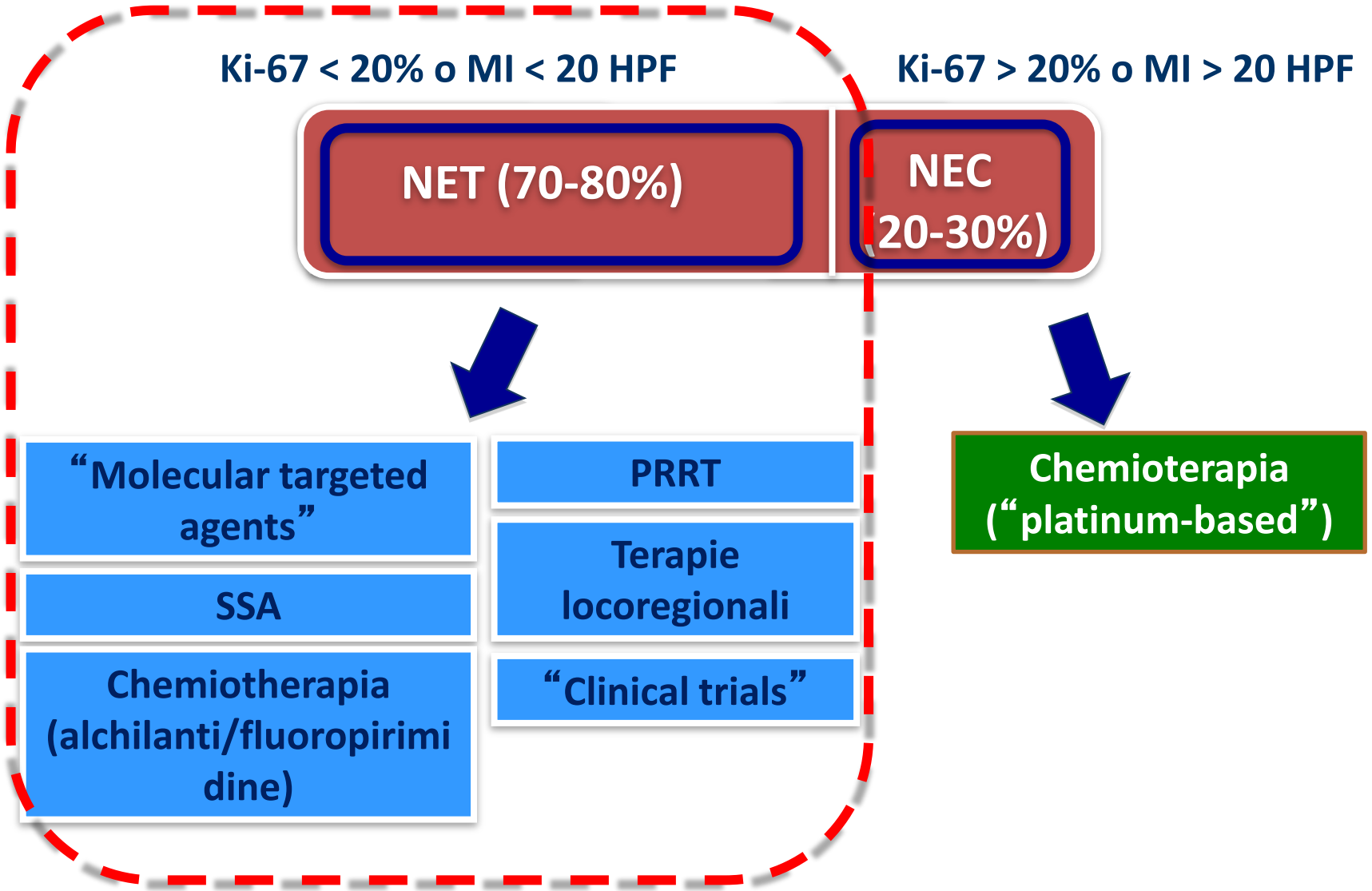
SINTOMATICO



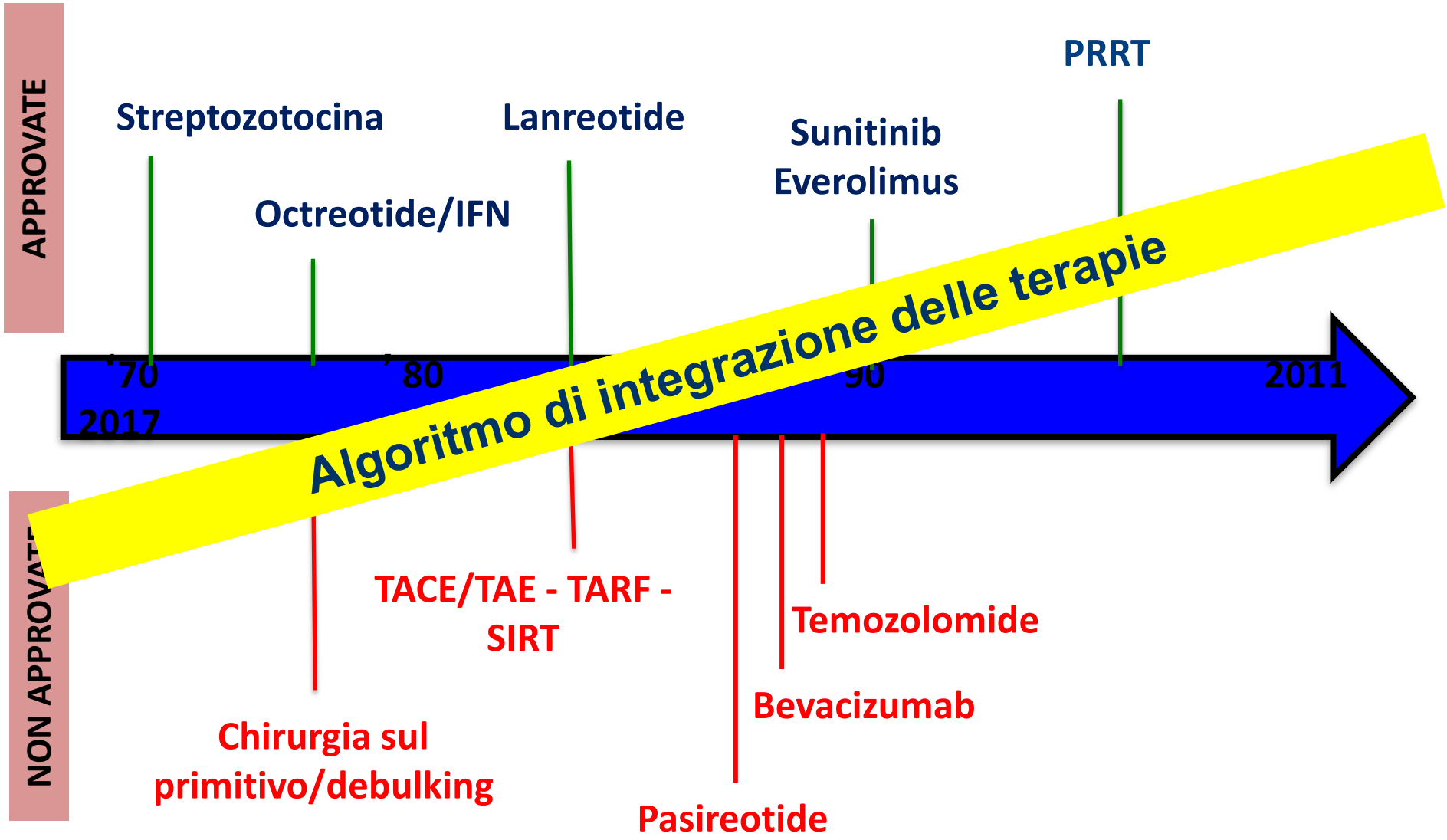
PET/TC Ga68 ++-

PET/TC FDG +++

GEP NEN: eterogeneità dei trattamenti



Evoluzione delle terapie



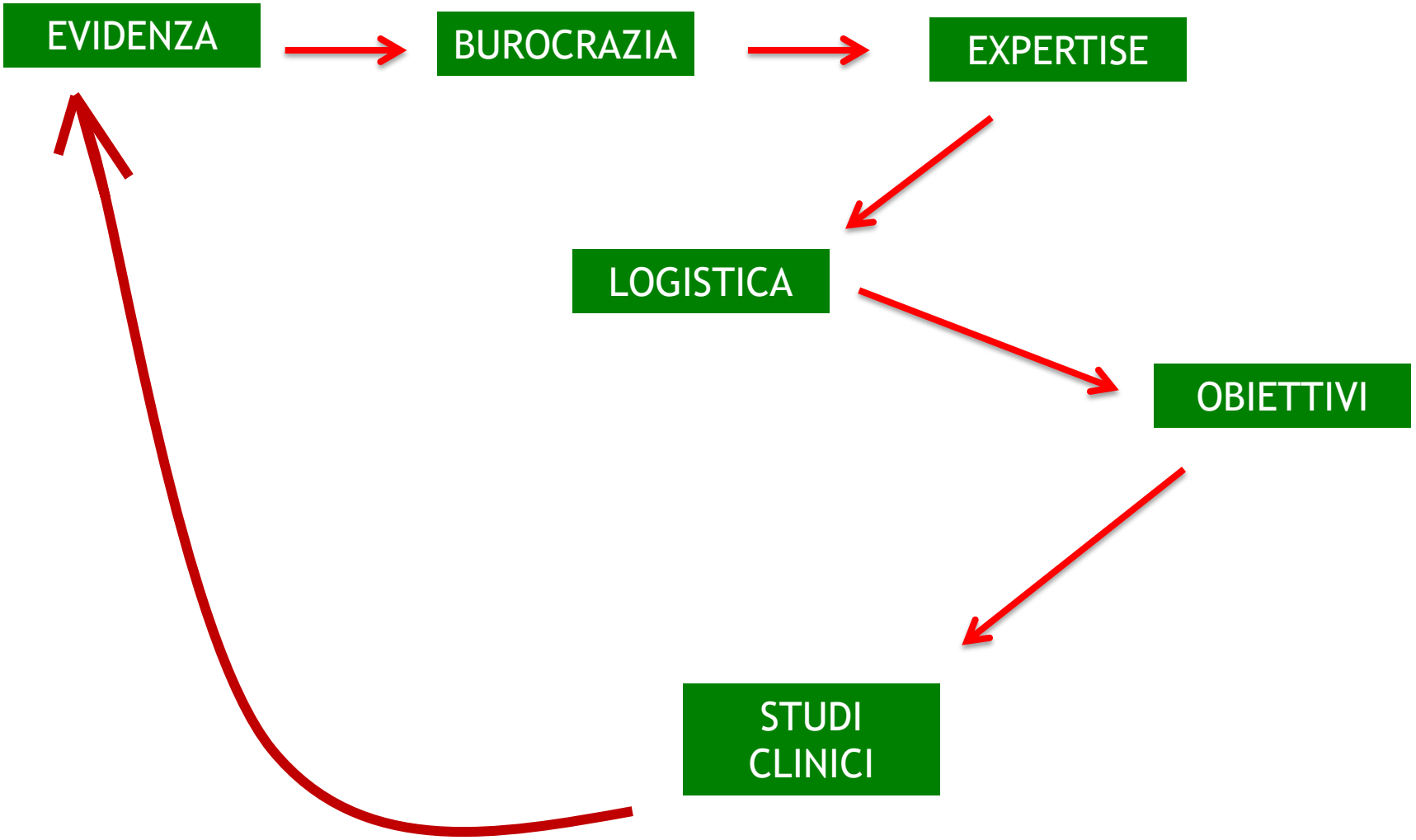
Evoluzione degli studi clinici

Primitivo	Octreotide	Lanreotide	177-Lu-DOTATATE	STZ/TMZ	SUN	EVE
Stato di malattia	NAIVE	SD	PD > 3 anni	Non specificato	PD > 12 mesi	PS > 6
Polmone						
Stomaco		CLARINET				RADIANT-4
Pancreas					FASE III	RADIANT-3
Pie			NETTER-1			RADIANT-4
		CLARINET				RADIANT-4
Retto		CLARINET				RADIANT-4
Ignoto						RADIANT-4

Livello di evidenza e approvazioni in setting differenti per sede del tumore primitivo

Yao J. ENETS 2018

Criteri per l'integrazione delle terapie



Evidenza

	Braccio di trattamento	Braccio di controllo	Popolaz.	N. Paz.	1° linea	SSA Prec.	SSA concomit.	CT Prec.
CLARINET Caplin NEJM 2014	Lanreotide autogel	Placebo	Entero-Pancreatici NF	204	84 %	no	/	/
RADIANT-3 Yao NEJM 2011	Everolimus +/- octreotide LAR	Placebo +/- octreotide LAR	PanNET	410	?	49 %	40 %	50%
A6181111 Raymond NEJM 2014	Sunitinib	Placebo	PanNET	171	?	35%	28 %	66%

Evidenza

	Braccio di trattamento	Braccio di controllo	Popolaz.	N. Paz.	1° linea	SSA Prec.	SSA concomit.	Ki67
CLARINET Caplin NEJM 2014	Lanreotide autogel	Placebo	Entero-Pancreatici NF	204	84 %	no	/	≤10%
RADIANT-3 Yao NEJM 2011	Everolimus +/- octreotide LAR	Placebo +/- octreotide LAR	PanNET	410	?	49 %	40 %	?
A6181111 Raymond NEJM 2014	Sunitinib	Placebo	PanNET	171	?	35%	28 %	?

Linee Guida ed evidenza

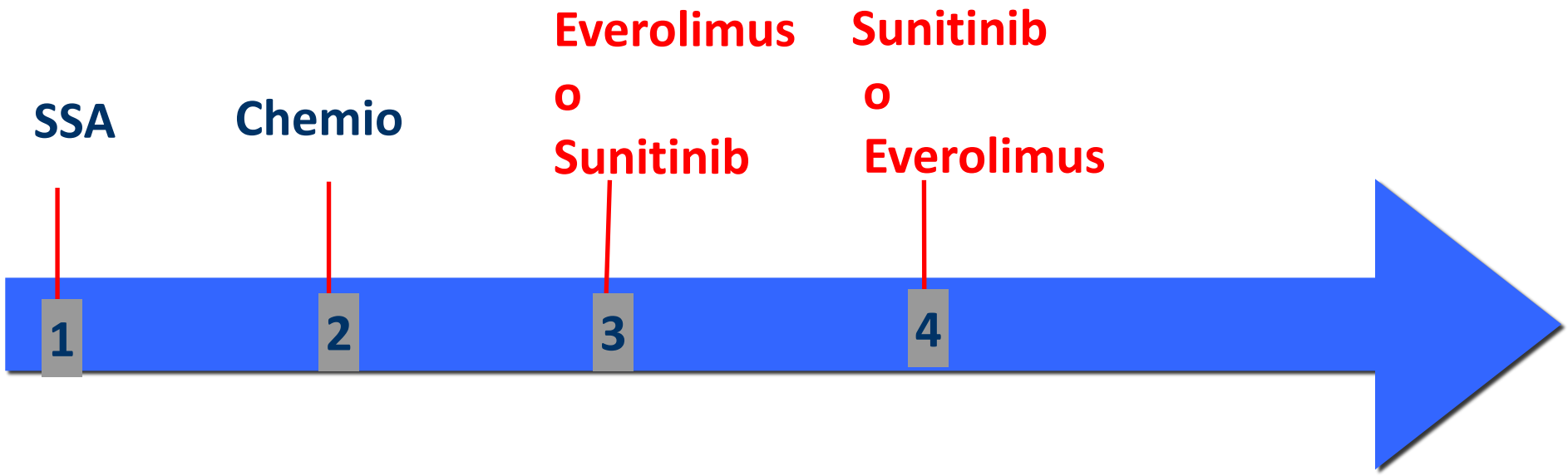
Minimal consensus statement:

Everolimus or sunitinib are generally recommended **after failure of SSA or chemotherapy in pancreatic NET.**

Everolimus and sunitinib …….. can be considered a **first line therapy**, especially if SSA is not an option, and if systemic chemotherapy is not clinically required, not feasible or not tolerated.

Pavel et al., Neuroendocrinology 2016

PanNET avanzato in accordo alle LG



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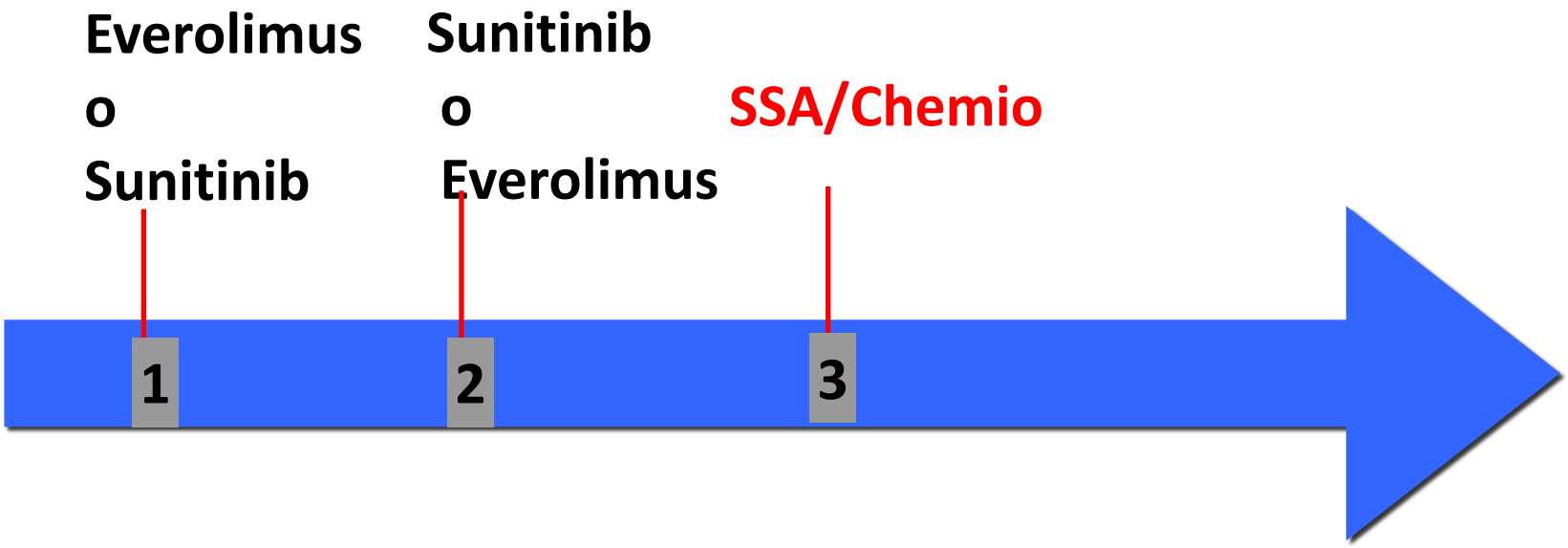
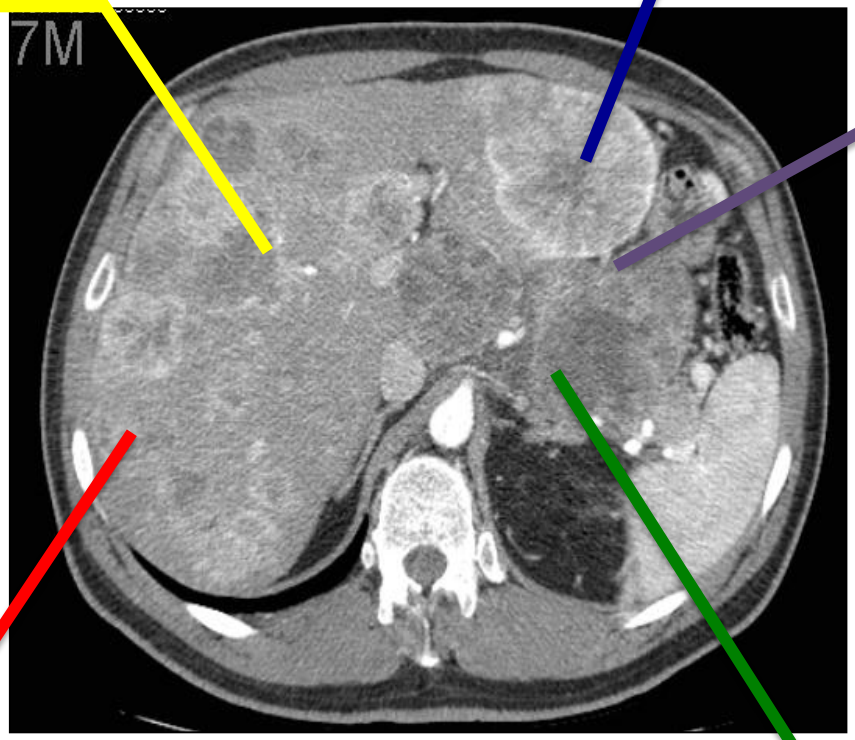


NET ben differenziato, Ki-67 19% (G2 sec. WHO 2010)

SD RECIST in 3 mesi (lenta PD)

PD CLINICA



PET/TC Ga68 ++-

PET/TC FDG +++

Table 2. Objective Tumor Response.*

Response Category	^{177}Lu-Dotatate Group (N=101)	Control Group (N=100)	P Value†
Complete response — no. (%)	1 (1)	0	
Partial response — no. (%)	17 (17)	3 (3)	
Objective response			
No. with response	18	3	
Rate — % (95% CI)	18 (10–25)	3 (0–6)	<0.001

Strosberg J, NEJM 2017

Obiettivi della terapia

Immediati

Controllo dei sintomi

Tardivi

Controllo della progressione nel tempo

Terapie citoriduttive?

Terapie citoriduttive

Farmaci	N paz.	Ki67	SSTR+	PR	TTP/PFS	Tipo studio	Autore
STZ/ADM/FU	84	?	?	34 %	9 m	Retrosp.	Kouvaraki 2004
TMZ	36	?	?	14 %	7 m	Retrosp	Ekeblad 2007
XELOX	11	?	?	27 %	20 m	Phase II	Bajetta 2007
STZ/DDP/FU	49	25	39	38 %	9 m	Retrosp.	Turner 2010
CAP/TEM	30	?	?	70 %	18 m	Retrosp.	Strosberg 2011
PRRT 177Lu	91	?	91	42 %	33 m(tot)	Retrosp.	Kweekk. 2008
Sunitinib/Pl.	86 85	36 36	?	7 % 0 %	11.4 m 5.5 m	Phase III	Reymond,2011
Everolimus/Pl.	207 203	?	?	5 % 2%	11 m 4.6 m	Phase III	Yao 2011

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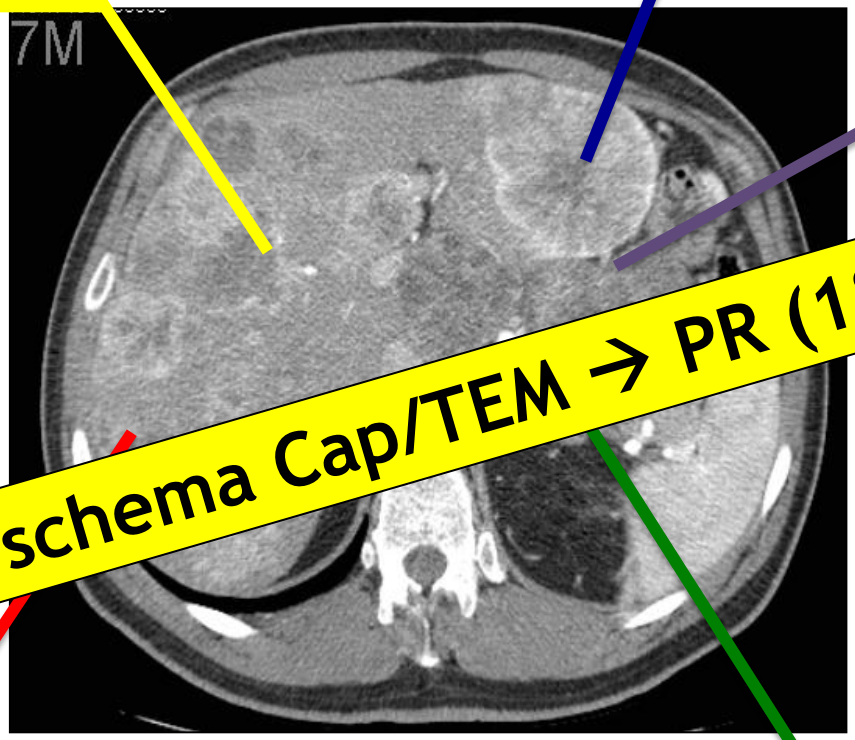
SD RECIST in 3 mesi (lenta PD)

PD CLINICA

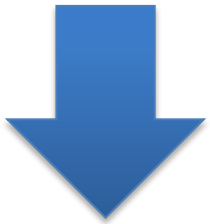


Chemio schema Cap/TEM → PR (18 mesi)

PET/TC Ga68 ++-

PET/TC FDG +++

Controllo della progressione nel tempo



Controllo della tossicità nel tempo

Clinica: tossicità

The Oncologist®

Gastrointestinal Cancer

Real-World Study of Everolimus in Advanced Progressive Neuroendocrine Tumors

Table 3. Predictors for severe toxicity during everolimus treatment

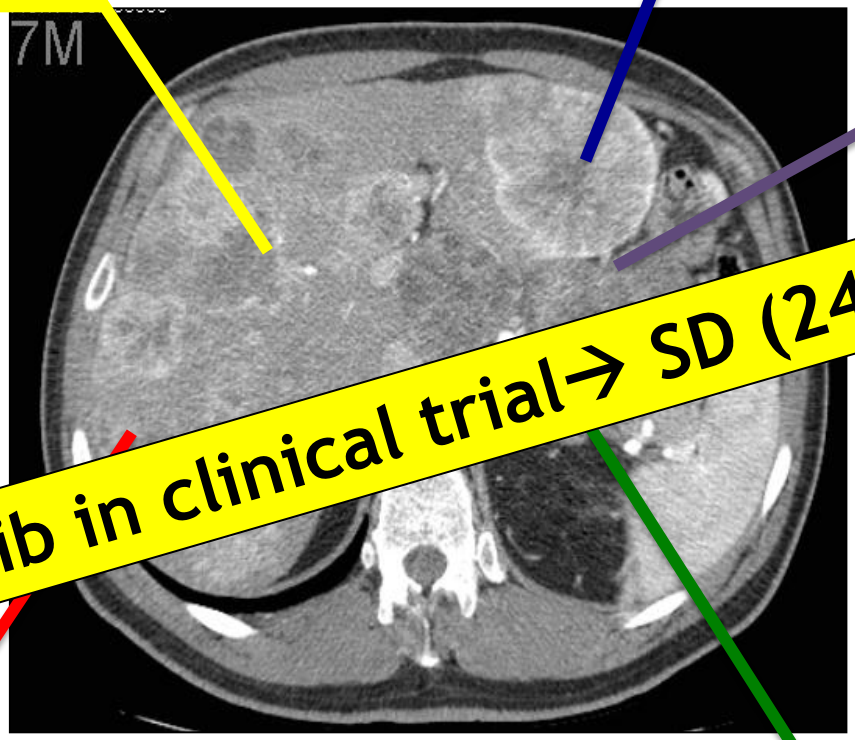
Variable	HR	95% CI	*p* value
Univariate analysis			
Age[a]	0.99	0.97–1.02	.748
Performance status (1/2 vs. 0)	1.33	0.72–2.44	.353
pNETs vs non-pNETs	0.97	0.53–1.79	.943
Previous treatment			
Somatostatin analogs	0.84	0.26–2.74	.781
Chemotherapy	3.68	1.94–6.97	<.0001
PRRT	2.58	1.38–4.81	.002
Chemotherapy and PRRT	12.61	4.60–34.53	<.0001
Time from initial diagnosis (months)[a]	1.00	1.00–1.01	.026

Panzuto et al., The Oncologist 2015

NET ben differenziato, Ki-67 19% (G2 sec. WHO 2010)

SD RECIST in 18 mesi (lenta PD)

Asintomatico

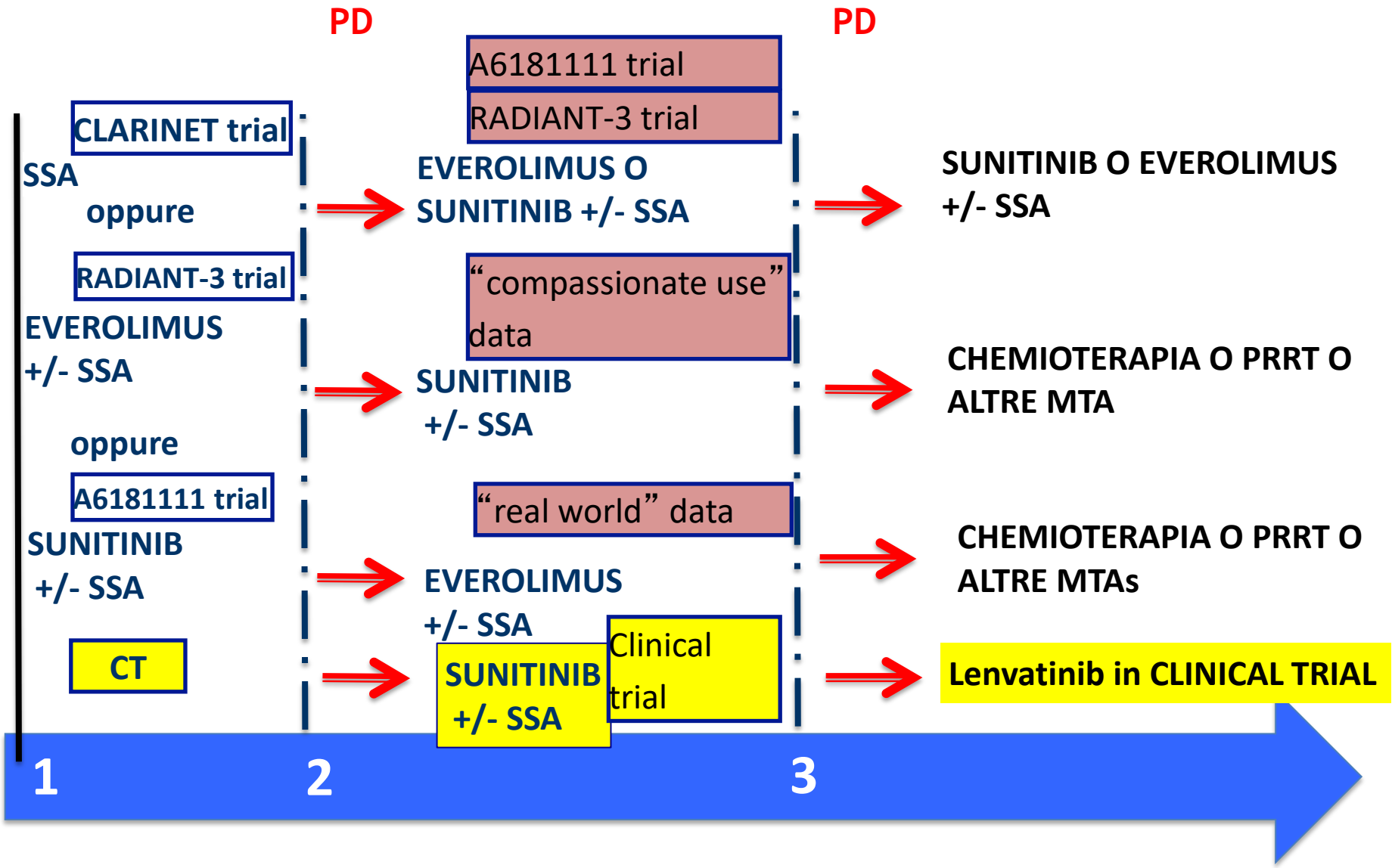


Sunitinib in clinical trial→ SD (24 mesi)

PET/TC Ga68 ++-

PET/TC FDG +++

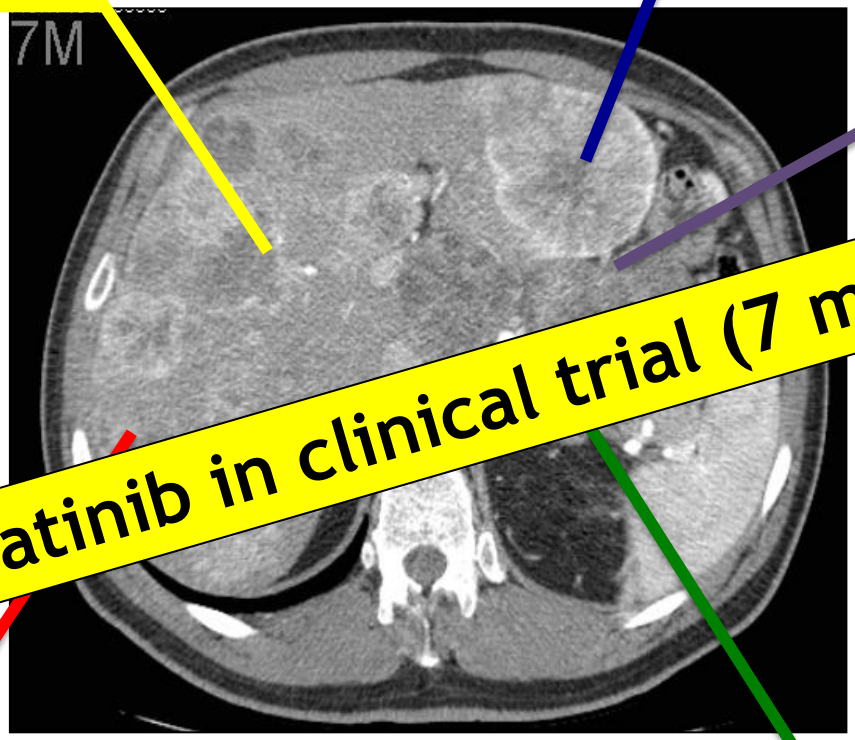
PanNETs: pratica clinica



NET ben differenziato, Ki-67 19% (G2 sec. WHO 2010)

SD RECIST in 3 mesi (lenta PD)

asintomatico

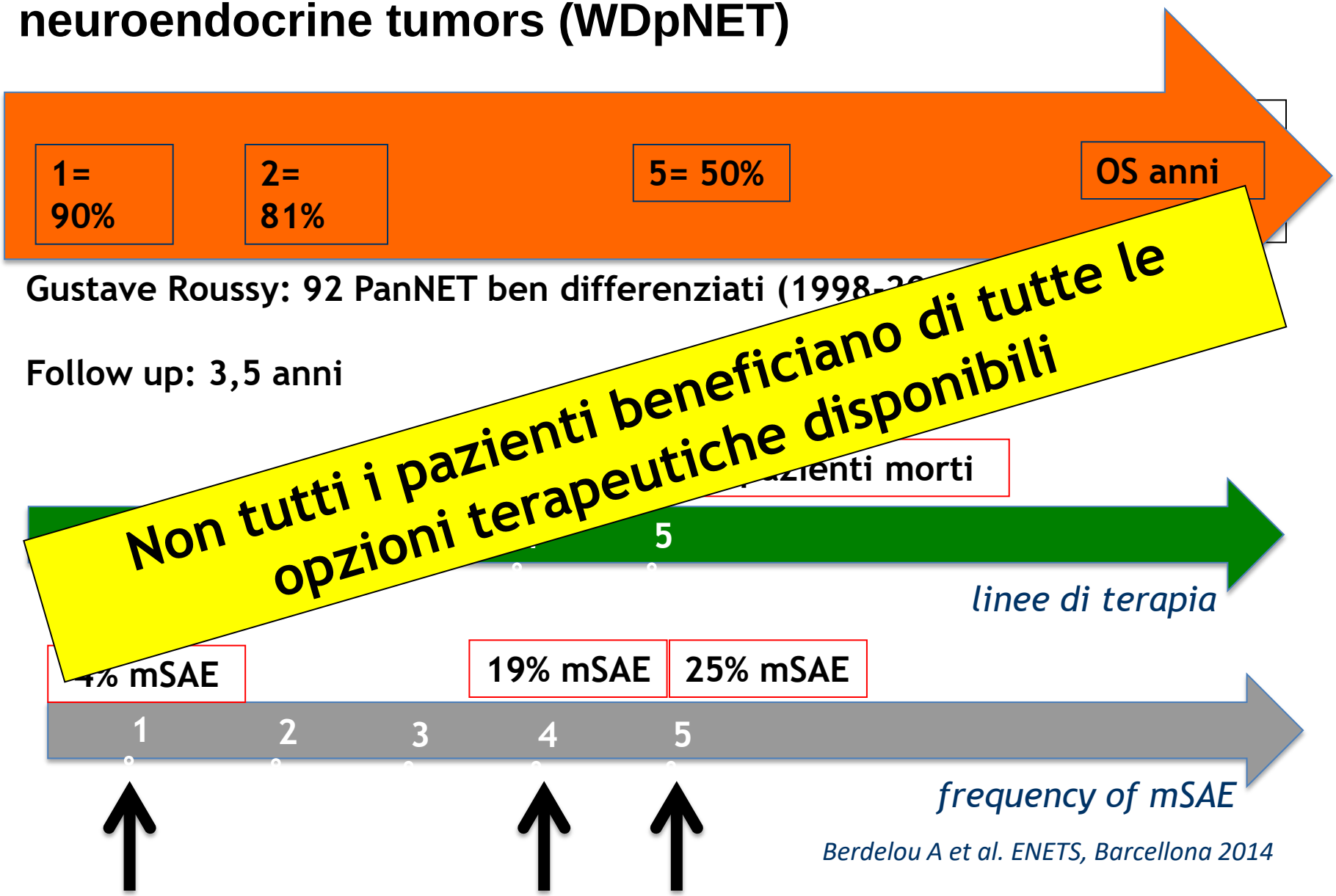


Lenvatinib in clinical trial (7 mesi)

PET/TC Ga68 ++-

PET/TC FDG +++

(M1) Overall survival (OS) as a function of the number of therapeutic lines in patients with well-differentiated neuroendocrine tumors (WDpNET)



Berdelou A et al. ENETS, Barcellona 2014

Take home message

Gruppo Multidisciplinare NET IEO - Centro di Eccellenza ENETS

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