Developing a therapeutic algorithm in small bowel NETs

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DISCLOSURES

- RESEARCH FOUNDING
  - NOVARTIS
  - PFIZER

- SPEAKER/ADVISORY ROLE
  - NOVARTIS
  - PFIZER
  - IPSEN
  - ADACAP/AAA

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SUGGESTED GUIDELINES FOR ADVANCED SI-NET MANAGEMENT

Unresectable SI-NET

G1 <2%	G2 2-10%	G2 11-20%	NET 20-55%	NEC>55%
Somatostatin Analogues PROMID / CLARINET				
Everolimus RADIANT-4	Everolimus + SSAs RADIANT-2			
PRRT NETTER-1				
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		Chemotherapy – no Phase 3		
			Chemotherapy	
			G2 therapy approach?	

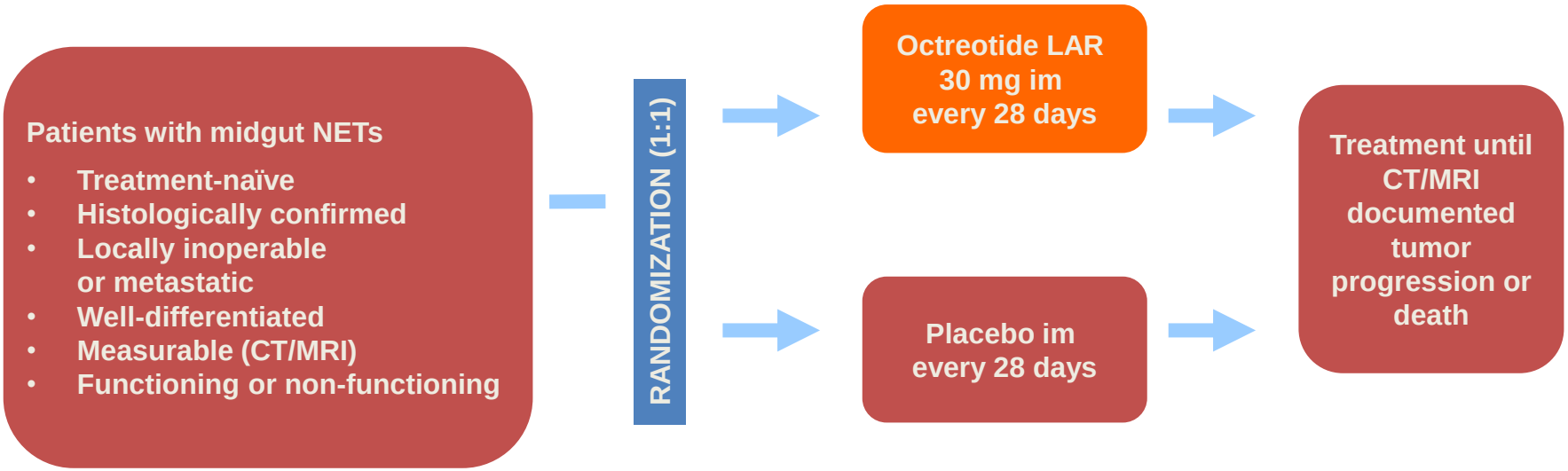
Caplin M et al., NEJM 2014; Rinke A et al., J Clin Oncol 2009; Strosberg J, et al. ECC 2015; Yao JC, et al. Lancet 2015; Yao JC, et al. ASCO 2015

PROSPECTIVE TRIALS OF SSA IN SMALL INTESTINE NETS

Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine MIDgut tumors: A Report From the PROMID Study Group

Phase III, randomized, double-blind, placebo-controlled

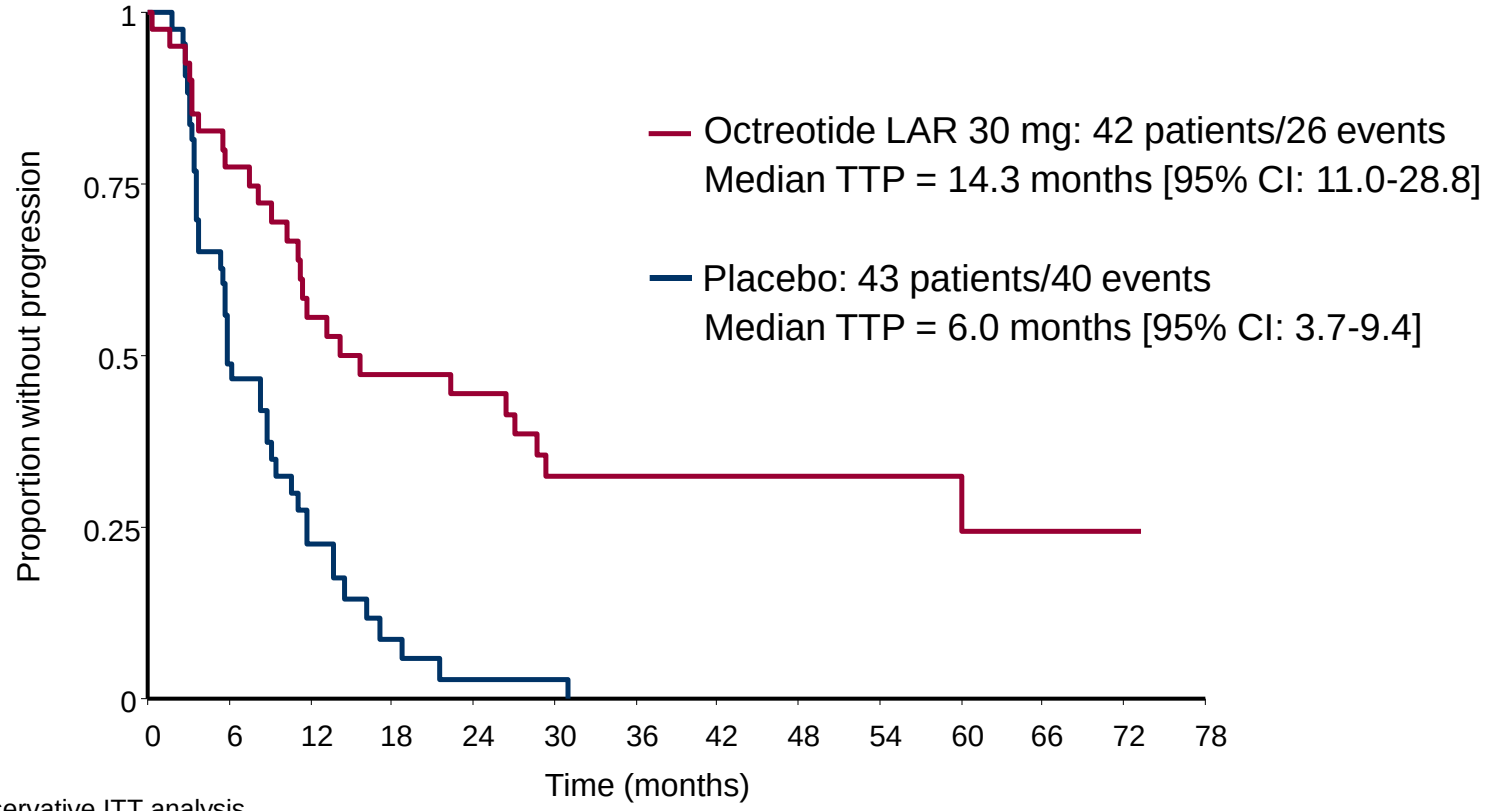
18 centers in Germany (2001–2008)



Rinke A, et al. *J Clin Oncol.* 2009

PRIMARY ENDPOINT
PROGRESSION-FREE SURVIVAL

66% reduction in the risk of tumour progression
HR = 0.34; 95% CI: 0.20-0.59; *P* = .000072



Based on the conservative ITT analysis
TTP = time to progression

Rinke A, et al. *J Clin Oncol.* 2009

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THE PROMID STUDY: OCTREOTIDE LAR IN MIDGUT NETS – WHAT DID WE LEARN?

Lessons

Octreotide LAR shows antitumor effect in:

- **Midgut tumors**
- **Low hepatic tumor burden (<10%)**
- **Grade 1 tumors**
- **Fx & non-Fx**

Limitations

The efficacy of Octreotide LAR is uncertain in:

- **Non-midgut tumors**
- **Higher liver tumor burden (>10%)**
- **Grade 2 tumors**
- **Progressive disease**

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THE CLARINET STUDY

A randomized double-blind placebo-Controlled phase III study of Lanreotide Antiproliferative Response In enteropancreatic NET

Patients with GEP-NET

- Histologically confirmed
- Measurable (CT / MRI)
- Grade 1 / grade 2 well / mod differentiated (Ki67 <10%) [WHO 2010 classification]
- Locally inoperable or metastatic
- Nonfunctioning only

n = 204

RANDOMIZATION (1:1)

Lanreotide Autogel 120 mg sc every 28 days

Placebo every 28 days

Treatment continued until tumor progression or death

12 24 36 48 72 96 weeks

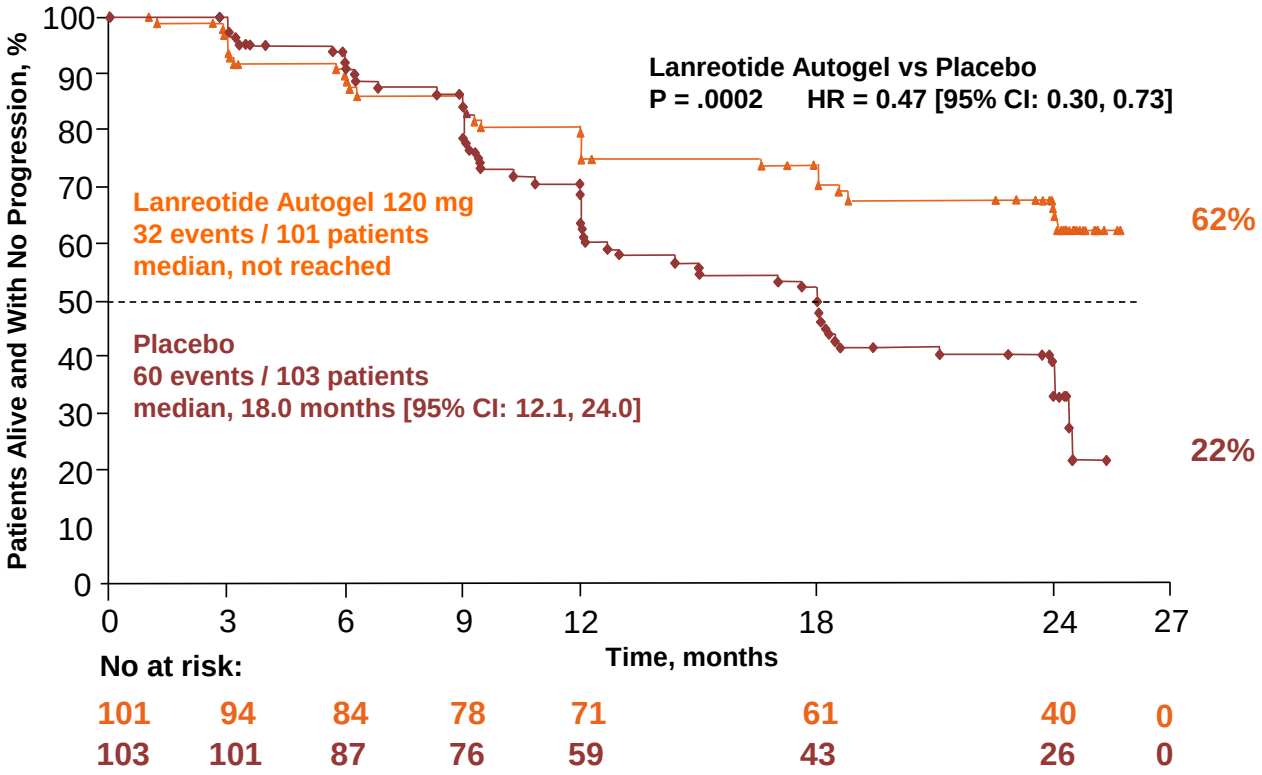
- Primary endpoint: PFS
- Secondary endpoints: Adverse events, pharmacokinetics, quality of life, CgA serum levels

ClinicalTrials.gov NCT00353496
EudraCT 2005-00490435

Caplin ME, et al. *N Engl J Med.* 2014

CLARINET: LANREOTIDE PROLONG PFS IN ENTEROPANCREATIC NET

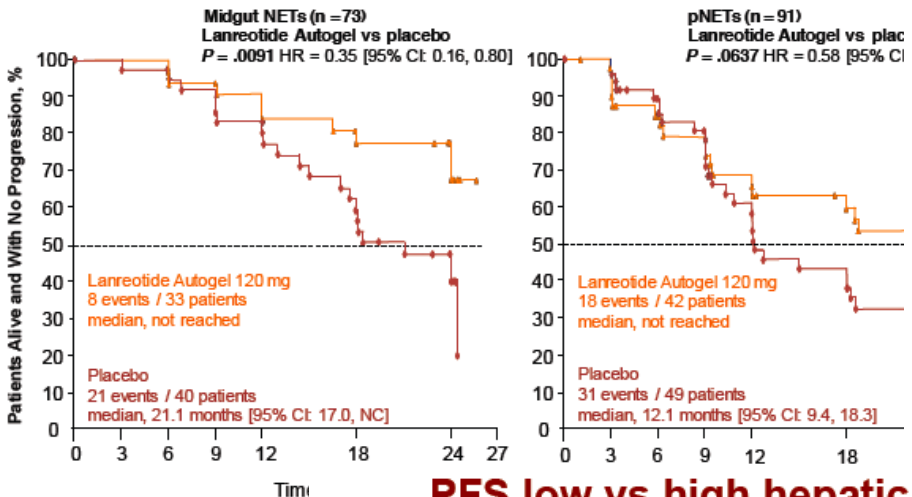
PFS (intention to treat population)



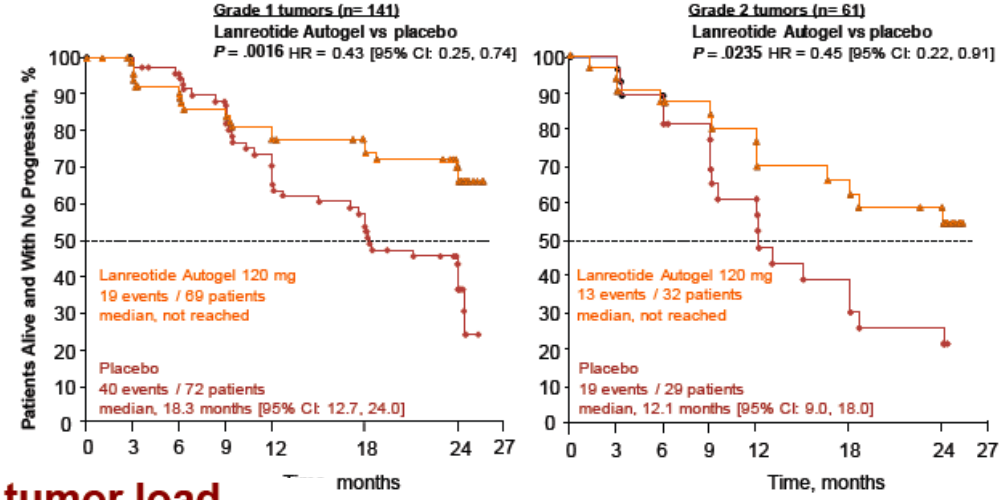
Caplin ME, et al. *N Engl J Med.* 2014

CLARINET: LANREOTIDE PROLONG PFS IN ENTEROPANCREATIC NET

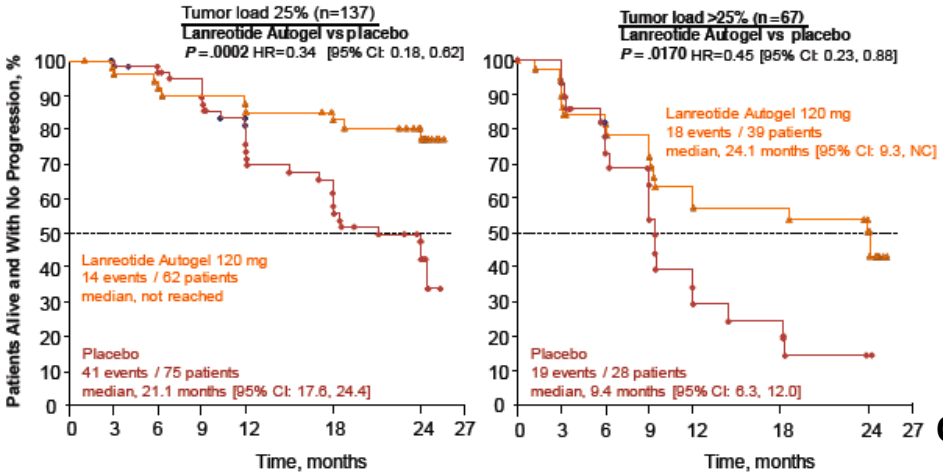
PFS in midgut vs pancreatic NET



PFS in grade 1 vs grade 2 (Ki-67<10%) NET



PFS low vs high hepatic tumor load



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			G2 therapy approach?	

Caplin M et al., NEJM 2014; Rinke A et al., J Clin Oncol 2009; Strosberg J, et al. ECC 2015; Yao JC, et al. Lancet 2015; Yao JC, et al. ASCO 2015

RADIANT-4 STUDY DESIGN

Patients with well-differentiated (G1/G2), advanced, progressive, nonfunctional NET of lung or GI origin (N=302)

- Absence of active or any history of carcinoid syndrome
- Pathologically confirmed advanced disease
- Radiologic disease progression in ≤ 6 months

RANDOMIZE

2:1

Everolimus 10 mg/day N=205

Placebo N=97

Treated until PD, intolerable AE, or consent withdrawal

Endpoints:

- **Primary:** PFS (central)
- **Key Secondary:** OS
- **Secondary:** ORR, DCR, safety, HRQoL (FACT-G), WHO PS, NSE/CgA, PK

Stratified by:

- Prior SSA treatment (yes vs. no)
- Tumor origin (stratum A vs. B)*
- WHO PS (0 vs. 1)

*Based on prognostic level, grouped as: **Stratum A (better prognosis)** – appendix, caecum, jejunum, ileum, duodenum, and NET of unknown primary. **Stratum B (worst prognosis)** – lung, stomach, rectum, and colon except caecum.

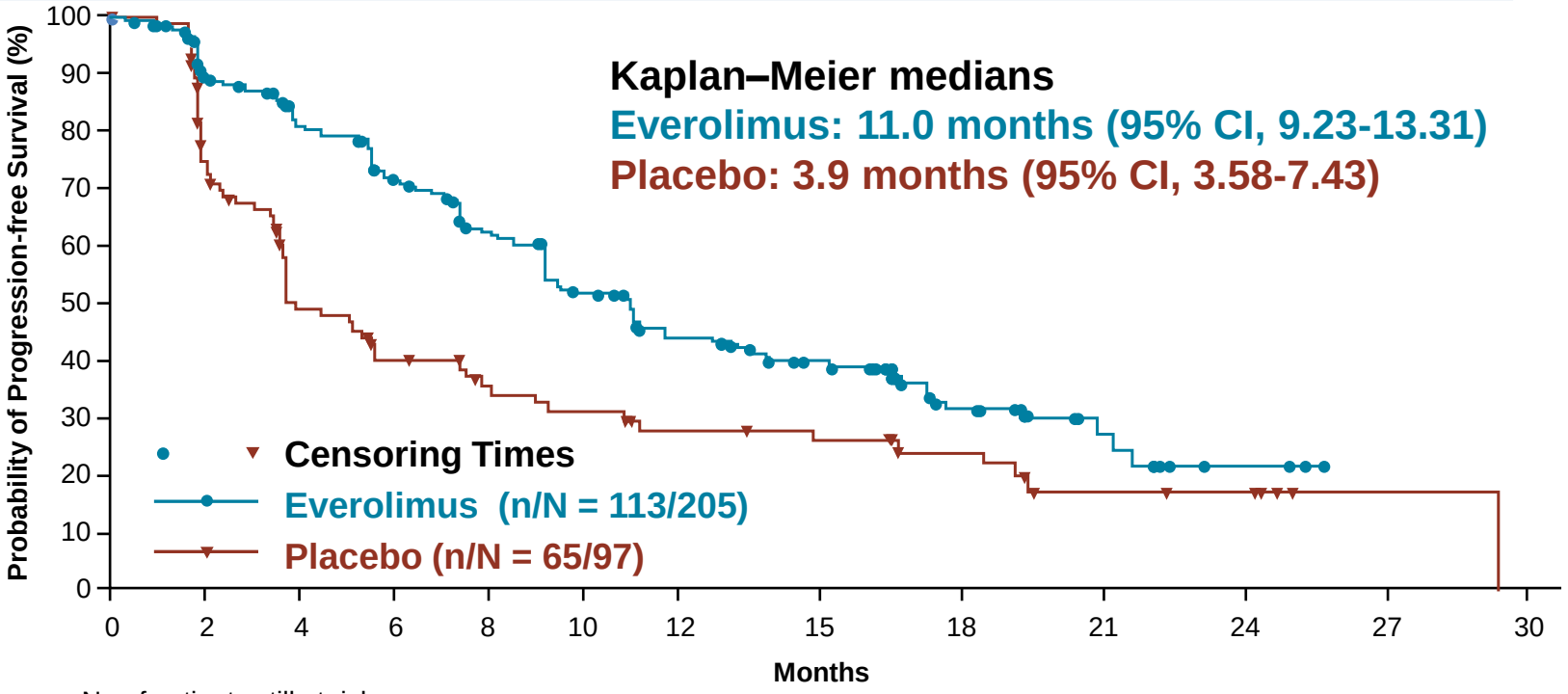
Crossover to open-label everolimus after progression in the placebo arm was not allowed prior to the primary analysis.

Yao JC, et al. *Lancet* 2016

PRIMARY ENDPOINT: PFS BY CENTRAL REVIEW

52% reduction in the relative risk of progression or death with everolimus vs placebo

HR = 0.48 (95% CI, 0.35-0.67); *P* < 0.00001

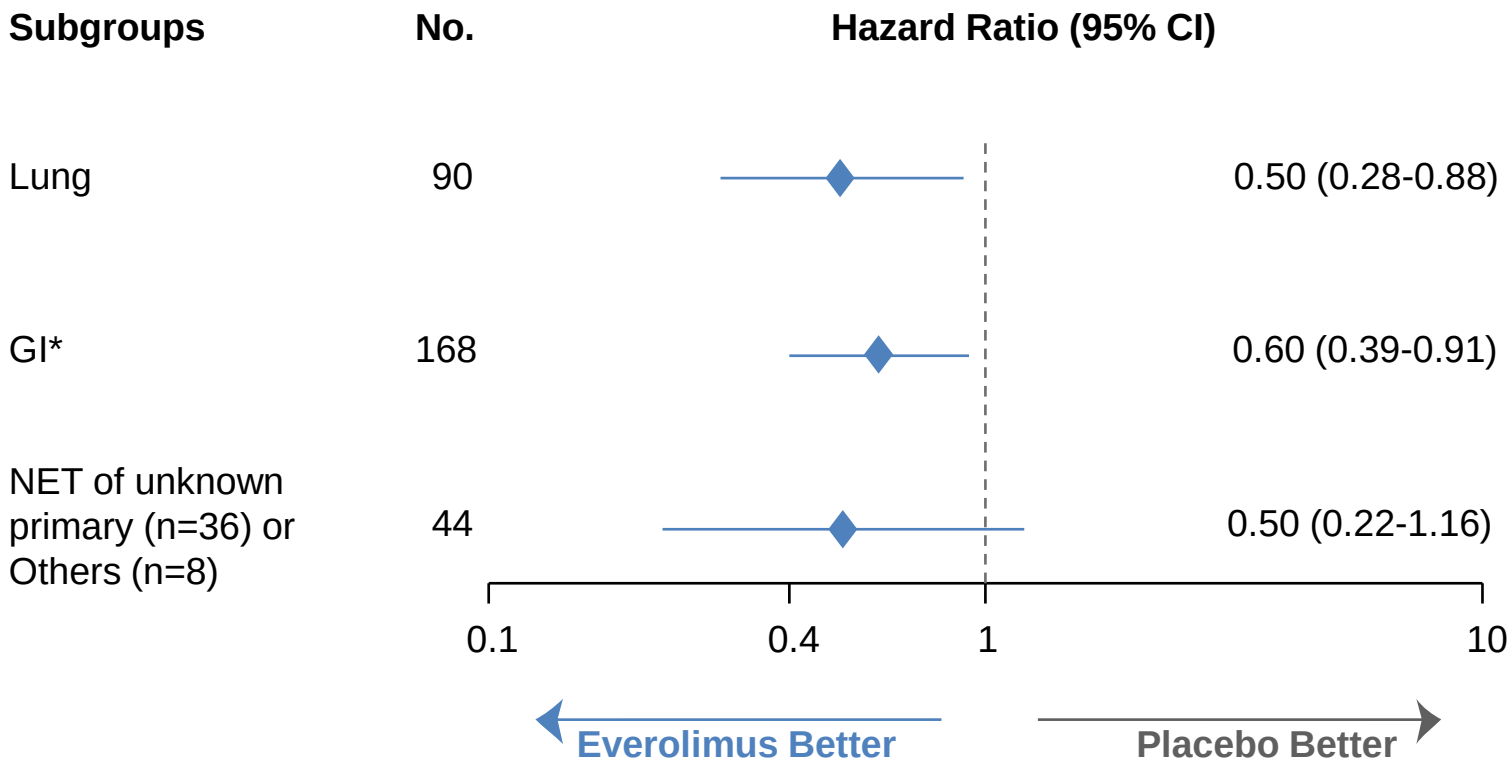


No.of patients still at risk

Everolimus	205	168	145	124	101	81	65	52	26	10	3	0	0
Placebo	97	65	39	30	24	21	17	15	11	6	5	1	0

Yao JC, et al. *Lancet* 2016

PFS HR BY PRIMARY TUMOR ORIGIN – RETROSPECTIVE ANALYSIS, CENTRAL REVIEW

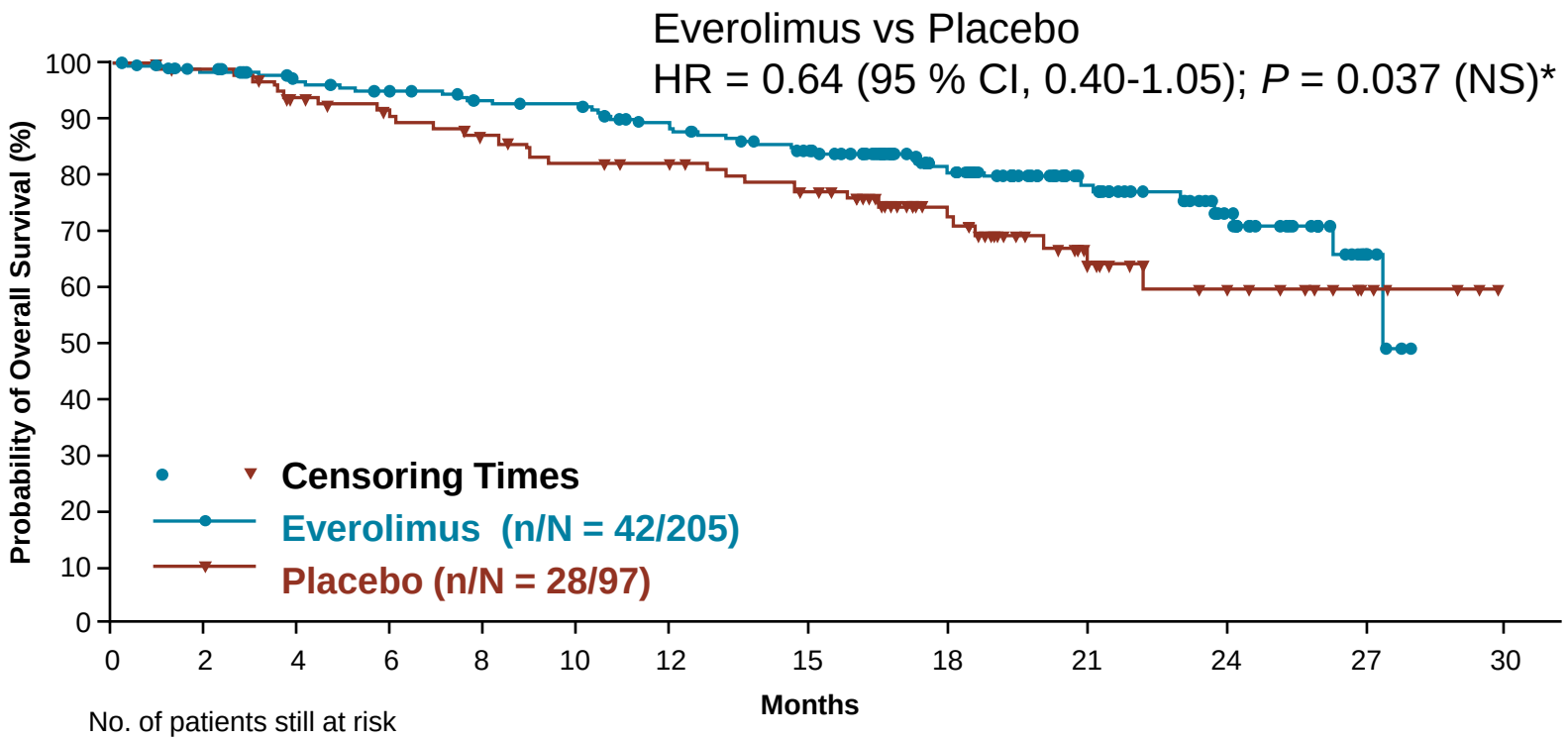


*Stomach, colon, rectum, appendix, cecum, ileum, duodenum, and jejunum are grouped under GI tract.

Yao JC, et al. *Lancet* 2016

INTERIM OVERALL SURVIVAL ANALYSIS

First interim OS analysis performed with 37% of information fraction favored the everolimus arm



No. of patients still at risk

Everolimus	205	195	184	179	172	170	158	143	100	59	31	5	0
Placebo	97	94	86	80	75	70	67	61	42	21	13	5	0

*P-value boundary for significance = 0.0002.
P-value is obtained from the stratified one-sided log-rank test; Hazard ratio is obtained from stratified Cox model.
CI, confidence interval; HR, hazard ratio; NS, not significant; OS, overall survival.

Yao JC, et al. *Lancet* 2016

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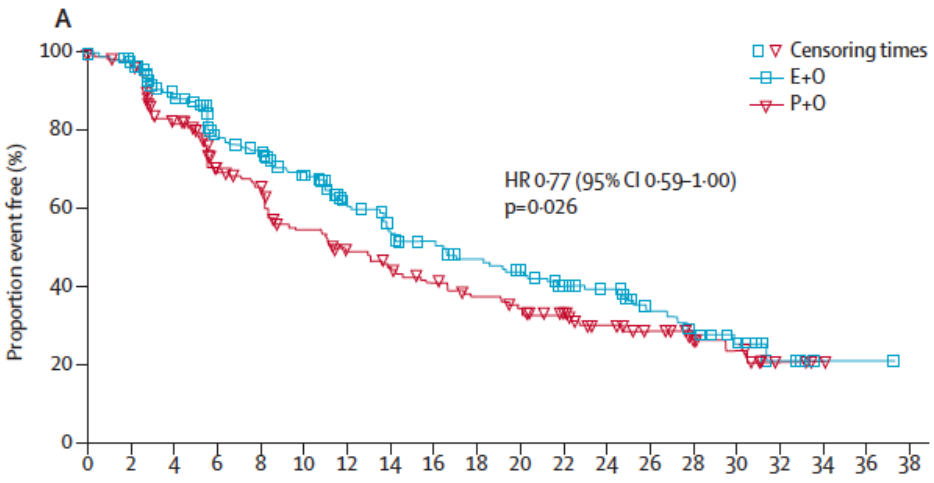
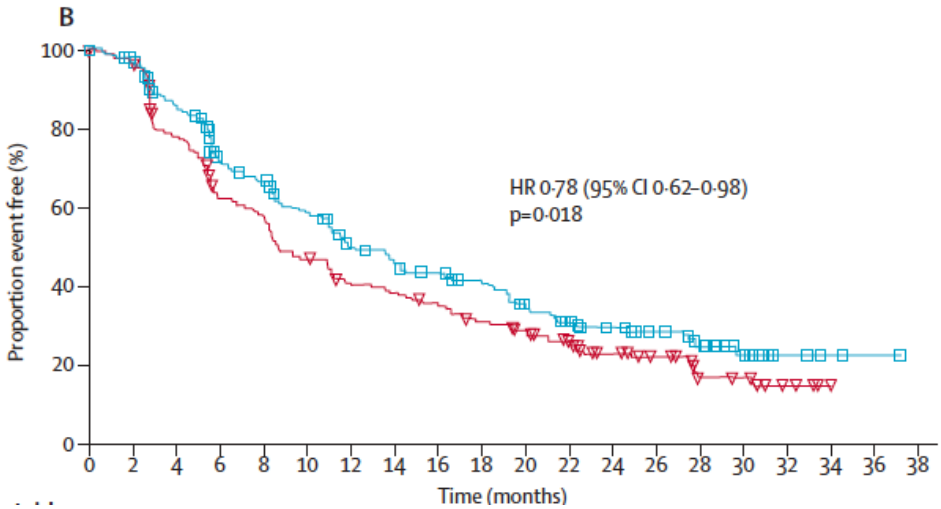
Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study





Pavel M, et al. Lancet, 2011

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Caplin M et al., NEJM 2014; Rinke A et al., J Clin Oncol 2009; Strosberg J, et al. ECC 2015; Yao JC, et al. Lancet 2015; Yao JC, et al. ASCO 2015

NETTER -1 STUDY OBJECTIVES AND DESIGN

Aim	Evaluate the efficacy and safety of ^{177}Lu-Dotatate plus Octreotide30 mg compared to Octreotide LAR 60mg (off-label use)[1] in patients with inoperable, somatostatin receptor positive, midgut NET, progressive under Octreotide LAR 30mg (label use)
Design	International, multicenter, randomized, comparator-controlled, parallel-group

Treatment and Assessments

Progression free survival (Recist criteria) every 12 weeks

Dose 1 Dose 2 Dose 3 Dose 4

Baseline and Randomization

n = 115 — 4 administrations of 7.4 GBq of lutetium Lu-177 dotatate every 8 weeks + Octreotide30 mg

n = 115 — Octreotide LAR 60mg every 4 weeks

5 Years follow up

Strosberg J, et al. *ECC* 2015

PRIMARY ENDPOINT: PROGRESSION-FREE SURVIVAL

N = 229 (ITT)

Number of events: 91

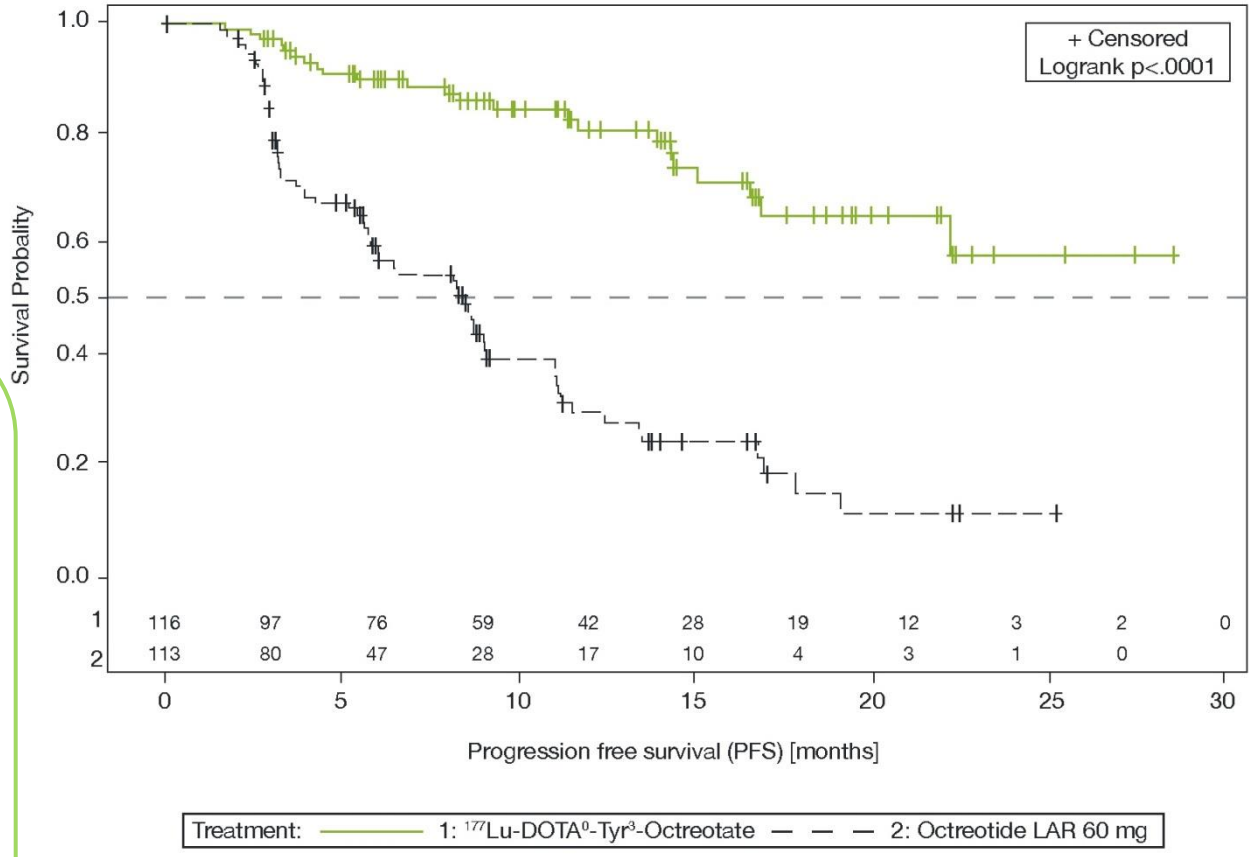
^{177}Lu-Dotatate: 23

Oct 60 mg LAR: 68

Hazard ratio: **0.21**
[0.13 – 0.33]
p < 0.0001

79% reduction in the risk of disease progression/death

Estimated Median PFS in the Lu-DOTATATE arm ≈ 40 months



All progressions centrally confirmed and independently reviewed for eligibility (SAP)

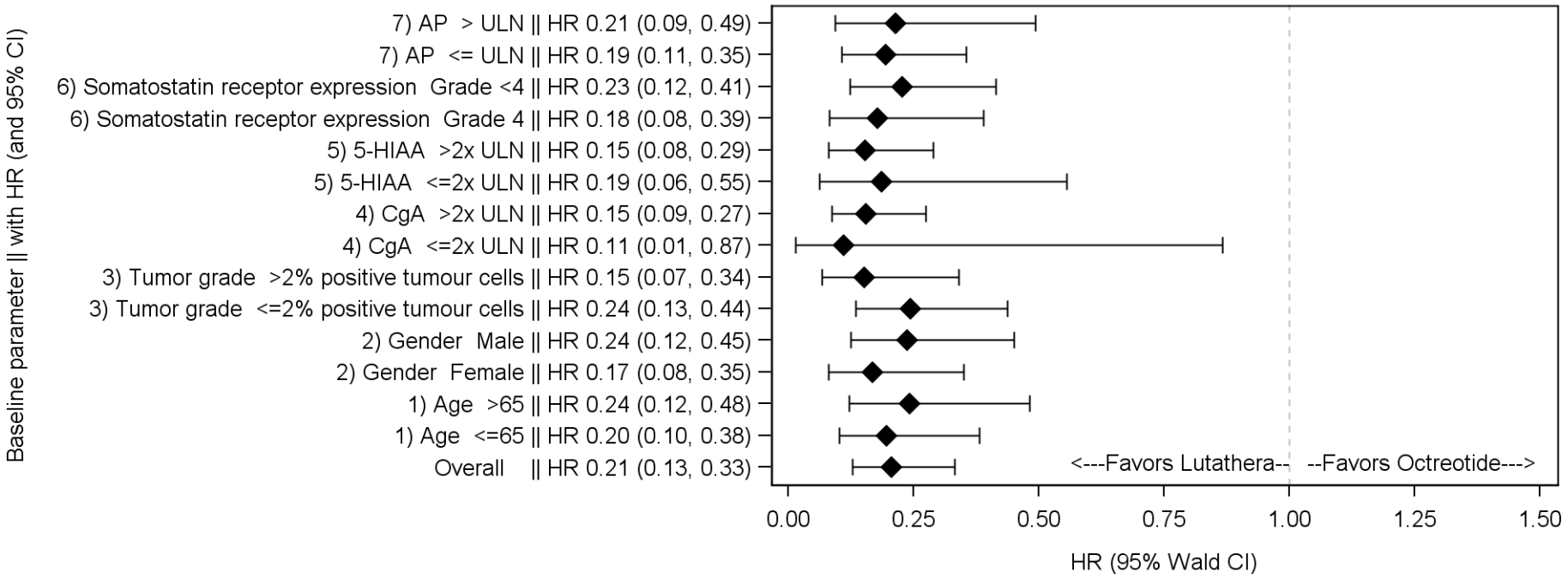
Courtesy of Strosberg J, et al. *ASCO* 2016

SUBGROUP ANALYSES

Sponsor/Project: Advanced Accelerator Applications AAA-III-01 (Netter-1)

Figure 14.2.1.41 Primary efficacy analysis variable: Progression Free Survival (PFS) - Forest plot of Hazard ratios by baseline parameter

Full Analysis Set



Note: Tumor grade is according to Ki67 value. Somatostatin receptor expression is according to Octreoscan tumor uptake score

Note: 5-HIAA and AP assessments are taken at eligibility or baseline visit, whichever is the first valid measurement

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Courtesy of Strosberg J, et al. *ASCO* 2016

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SWOG S0518
STUDY DESIGN

Study population

Advanced G1/2 NET with poor prognosis

- Progressive disease
- Refractory syndrome
- G2 with 6+ lesion
- Colorectal or gastric primary

RANDOMIZE

1:1

Bevacizumab 15 mg/kg q21 d
octreotide LAR 20 mg q21 d

Treatment until disease progression

Interferon α-2b 5 mu 3 d/wk
octreotide LAR 20 mg q21 d

Multiphasic CT or MRI performed every 9 wk

Primary endpoint:

- PFS (Central radiology review)

Stratification factors:

- Primary site: Midgut vs others
- PD since diagnosis
- Histologic grade: G1 vs G2
- Octreotide 2 months prior to registration

Yao JC, et al. ASCO 2015

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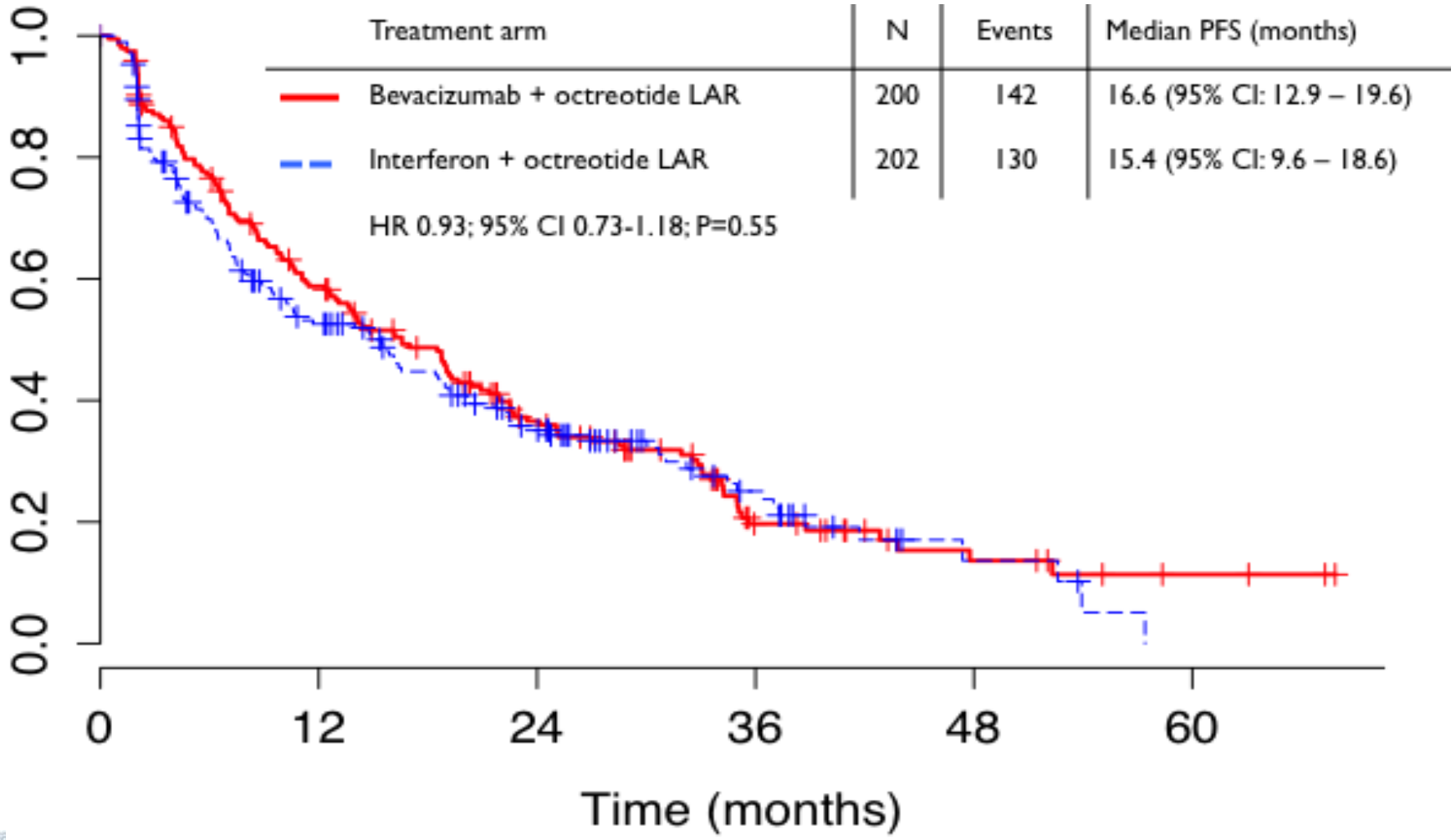
PFS BY CENTRAL RADIOLOGY REVIEW



Yao JC, et al. ASCO 2015

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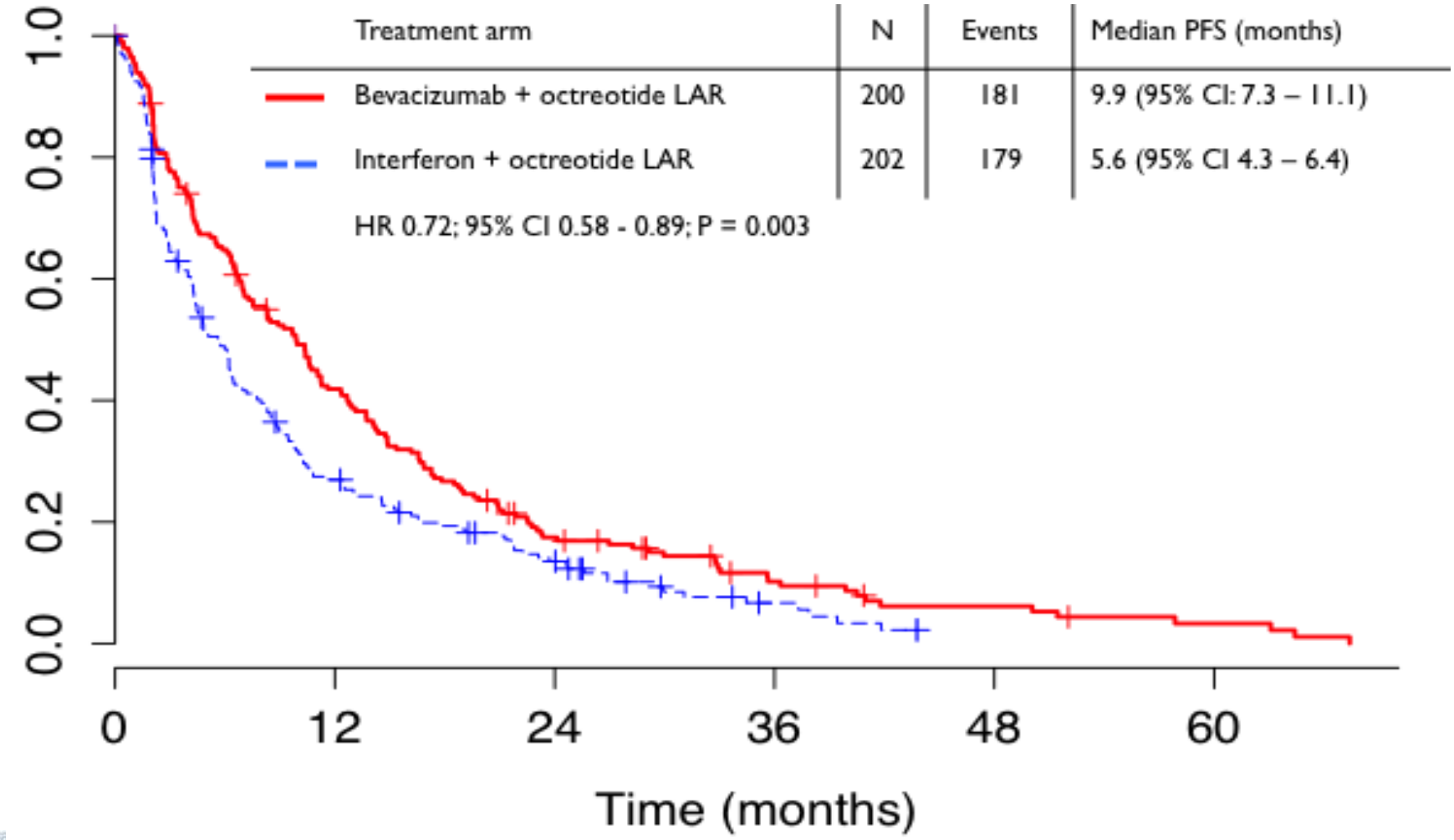
TIME TO TREATMENT FAILURE



Yao JC, et al. ASCO 2015

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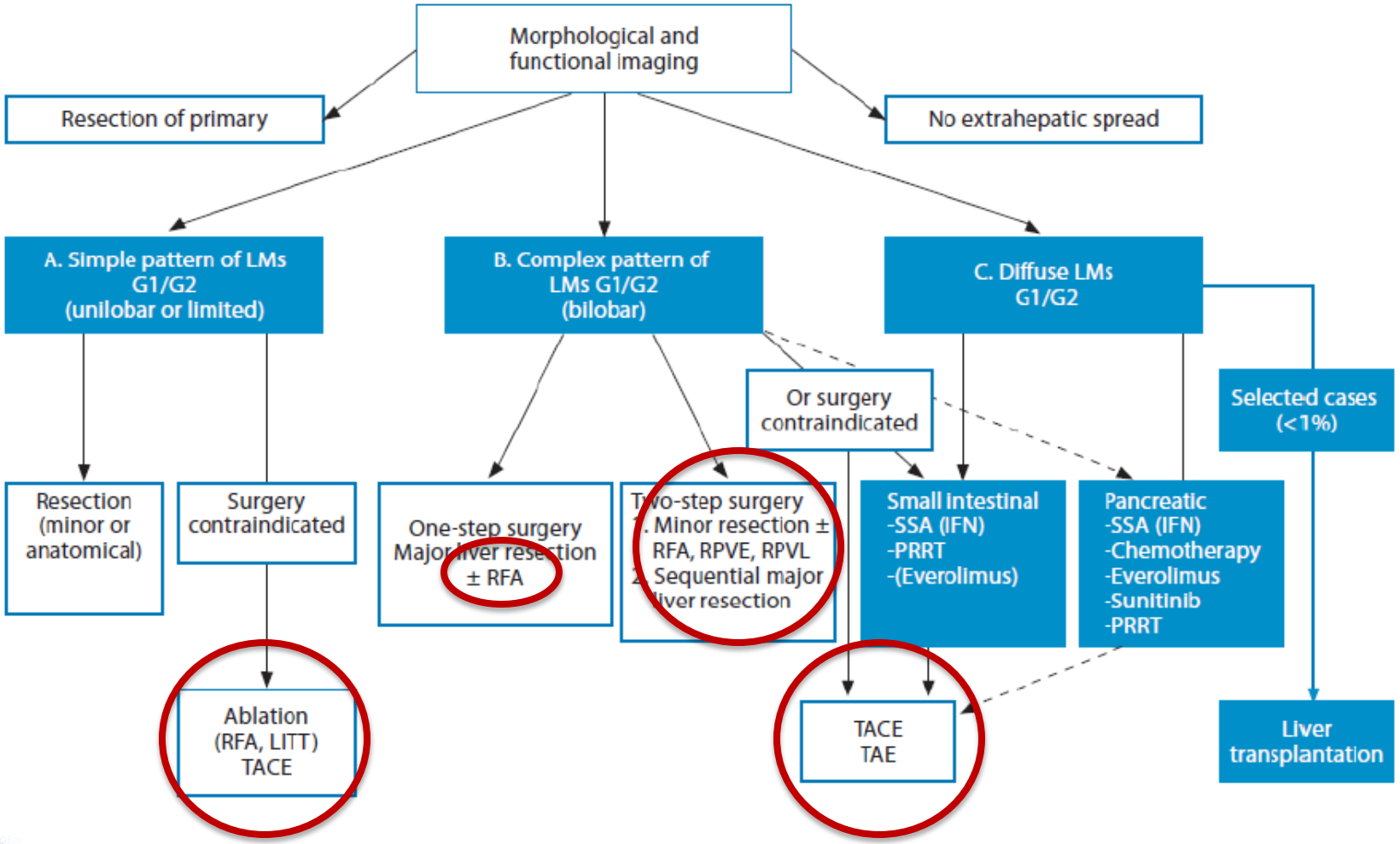
EMBOLIZATION / RADIOFREQUENCY



Pavel M, et al. *Neuroendocrinology* 2016

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RETROSPECTIVE / NON-RCT

Study	Patients, *n*	Device used	Toxicity	Radiological response (RECIST 1.0)	Survival times and rates
Rhee *et al.*[22]	42	Yttrium-90 (glass)	Grade III/IV (14%)	54%	Median: 22 months
		Yttrium-90 (resin)		50%	Median: 28 months
Kennedy *et al.*[18]	148	Yttrium-90 (resin)	33% (grade III), fatigue (6.5%)	63%	Median: 70 months
King *et al.*[19]	58	Yttrium-90 (resin) plus 5-FU	Radiation gastritis (2 patients), duodenal ulcer (1 patient)	39%	Median: 36 months 1-, 2- and 3-year survival: 86%, 58% and 47%, respectively
Saxena *et al.*[23]	48	Yttrium-90 (resin)	0.5% (grade III) 1 patient (biliary obstruction)	54%	Median: 35 months 1-, 2- and 3-year survival: 87%, 62% and 42%, respectively
Cao *et al.*[17]	58	Yttrium-90 (resin) plus 5-FU	Not reported	39.2%	Median: 36 months
Paprottka *et al.*[21]	42	Yttrium-90 (resin)	0% grade III	22.5%	Median: 95% at 16.2 months
Memon *et al.*[20]	40	Yttrium-90 (glass)	Fatigue (63%, all grades), nausea/vomiting (40%, all grades), grade III, IV (bilirubin, 8%; albumin, 2%; lymphocyte, 38%)	WHO: 64.0%; EASL: 71.4%	Median: 34.4 months 1-, 2- and 3-year survival: 72.5%, 62.5%, 45.0%, respectively

Table. Demographics and Outcomes following RF Ablation for NETs (14,15,29–34)

Study, Country of Origin	No. of Pts.	Mean Age (y)	Sex (M/F)	NET Only	Symptoms (%)	Concomitant Resection	Technique	Follow-up (mo)	Morbidity (%)	Procedural Mortality	5-y Survival (%)	Survival after RF (mo)	Local Recurrence (per Lesion)
Akyildiz et al (29), U.S.	89	56	54/35	Yes	44 (n = 39)	No	119 Laparoscopic	30	6.0	1	5-y OS 57	DFS 15, OS 72	7.90%
Gillams et al (30), U.K.	25	56	13/12	Yes	56 (n = 14)	Yes (1/25)	65 Percutaneous, 1 open	21	12	1	NR	OS 29	NR
Amersi et al (31), U.S.	25	NR	NR	No	NR	No	NR	NR	NR	NR	NR	OS 48.3	20% of > 3 cm
Henn et al (34), U.S.	7	56	1/6	Yes	100 (n = 7)	No	7 Percutaneous	22.9*	57	0	NR	NR	NR
Wessels and Schell (32), U.S.	3	39.6	1/2	Yes	100 (n = 3)	No	2 Open, 1 laparoscopic	6	NR	0	NR	NR	NR
Elias et al (14), France	16	48	7/9	Yes	31 (n = 5)	Yes (13/16)	197 Open	27	62.5	0	3-y OS 84	NR	NR
Elvin et al (15), Sweden	42	61.2	19/23	Yes	NR	Yes (23/42)	84 Percutaneous, 25 open	NR	NR	NR	NR	NR	NR
Taner et al (33), U.S.	94	53.7	41/53	Yes	62 (n = 59)	Yes (all 94)	94 Open	58*	1.06	0	5-y OS 80, SFS 16	SFS 24	4.25%

Study	Patients, *n*	Device used	Toxicity	Radiological response (RECIST 1.0)	Survival times and rates
Dong & Carr[7]	123	TACE	Abdominal pain (44%), diarrhoea (30%), weight loss (22%)	62%	Mean: 3.3 years 3-, 5- and 10-year survival: 59%, 36% and 20%, respectively
de Baere *et al.*[6]	20	TACE with doxorubicin eluting beads	Nausea (61%), fever (36%)	80%	Not reported
Vogl *et al.*[16]	48	TACE with mitomycin C	Nausea and vomiting (27.8%), abdominal pain (11.1%)	11.1%	Median: 38.7 months 5 years: 11.11%
		TACE with mitomycin C + gemcitabine	Nausea and vomiting (16.7%), abdominal pain (10%)	23.3%	Median: 57.1 months 5 years: 46.67%
Loewe *et al.*[11]	23	Bland embolization	Not reported	73%	Median: 69 months 1- and 5-year survival: 95.7% and 65.4%, respectively
Eriksson *et al.*[8]	41	Bland embolization	Post-embolization syndrome (all), nausea (33%), fever (*n* = 7), median hospitalization: 12 days	50%	Median: 80 months 5 years: 60%
Pitt *et al.*[13]	100	Bland (*n* = 51) versus TACE (*n* = 49)	Bland: 7/51, (3 liver abscesses, 1 groin hematoma, 2 ileus, 1 hypotension) TACE: none	N/A	Median from diagnosis: TACE, 50.1 months; bland, 39.1 months 1-, 2- and 5-year survival: TACE, 69%, 52%, 19%, respectively; bland, 19%, 70%, 13%, respectively
Ruutiainen *et al.*[15]	67	Bland (*n* = 23) versus TACE (*n* = 44)	Grade 3 or worse toxicity in 25% of TACE and 22% of bland patients TACE (≥Grade 3): pain (3); nausea (1); GET/ALP (4); AST (1), and infection (1) Bland (≥Grade 3): GET/ALP (3); AST (1), and cardiac (1)	TACE: 22% Bland: 38%	1-, 3- and 5-year survival: TACE, 86%, 67%, 50%, respectively; bland, 68%, 46%, 33%, respectively
Gupta *et al.*[10]	49	TACE (*n* = 27) versus bland (*n* = 42)	Serious adverse events in 19 patients (8.5%), hepatorenal syndrome (7), sepsis (6), transient myelosuppression (1), anasarca (1), cortical blindness (1), necrotizing cholecystitis (1), hepatic abscess (2) Overall complications: TACE, 20%; bland, 12%	TACE: 50% Bland: 25%	Median survival for carcinoid tumours: TACE, 33.8 months; bland, 33.2 months; islet tumours: TACE, 31.5 months; bland, 18.2 months
Maire *et al.*[12]	26	TACE (*n* = 12) versus bland (*n* = 14)	TACE: post-embolization syndrome (10), carcinoid crisis (2), acute liver failure (1), neutropoenia (2) Bland: post-embolization syndrome (10), carcinoid crisis (0), acute liver failure (2), neutropoenia (0)	TACE: 100% Bland: 92%	2-year survival: TACE, 80%; bland, 100% Median PFS: TACE, 19.2 months; bland, 23.6 months

Mohan H, et al. *J Vasc Interv Radiol* 2015
Yang TX, et al. *Surgical Oncology* 2012

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NO CLEAR BENEFIT OF CHEMOTHERAPY IN G1/G2 SI-NETS

Treatment	Author	Histology	No.	ORR (%)	Median survival
Doxorubicin	Engstrom [53]	Carcinoid	81	21	12
DTIC	Bukowski [54]	Carcinoid	63	16	20
Paclitaxel	Ansell [55]	Carcinoid	24	8	18
Docetaxel	Kulke [56]	Carcinoid	21	0	24
Gemcitabine	Kulke [57]	Carcinoid	18	0	11.5
Topotecan	Ansell [58]	Carcinoid	22	0	22

Combination regimen	Author	Histology	No.	ORR (%)	Median surviv
Cisplatin + etoposide	Moertel [49]	Poorly differentiated	18	67	16
Carboplatin + paclitaxel + etoposide	Hainsworth [50]	Poorly differentiated	78	53	14.5
Streptozocin + 5-FU	Moertel [62]	Pancreatic NETs	42	63	26
Streptozocin + doxorubicin	Moertel [63]	Pancreatic NETs	36	69	26
Streptozocin + 5-FU	Moertel [63]	Pancreatic NETs	33	45	18
Doxorubicin + 5-FU + cisplatin	Rougier [64]	Pancreatic NETs	15	14	27
5-FU + dacarbazine + epirubicin	Bajetta [65]	Pancreatic NETs	15	27	NR
Temozolomide + capecitabine	Strosberg [66]	Pancreatic NETs	17	71	NR
Streptozocin + 5-FU	Engstrom [53]	Carcinoids/well-differentiated GI-NETs	80	22	16
Streptozocin + 5-FU	Sun [67]	Carcinoids/well-differentiated GI-NETs	88	16	24.3
Doxorubicin + 5-FU	Sun [67]	Carcinoids/well-differentiated GI-NETs	88	16	15.7

Grande E, et al. *Clin Transl Oncol*. 2010

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STANDARD TREATMENT FOR G3 NECS → CISPLATIN + ETOPOSIDE

	pts	*OR*	*Response duration (months)*	*Median Survival (months)*
Moertel 1991	18	67%	8	19
Mitry 1999	41	42%	9	15
Fjallskog 2001	36	47%	9	-
Welin 2011 (TMZ+CPC+BV)	25	33%	19	22

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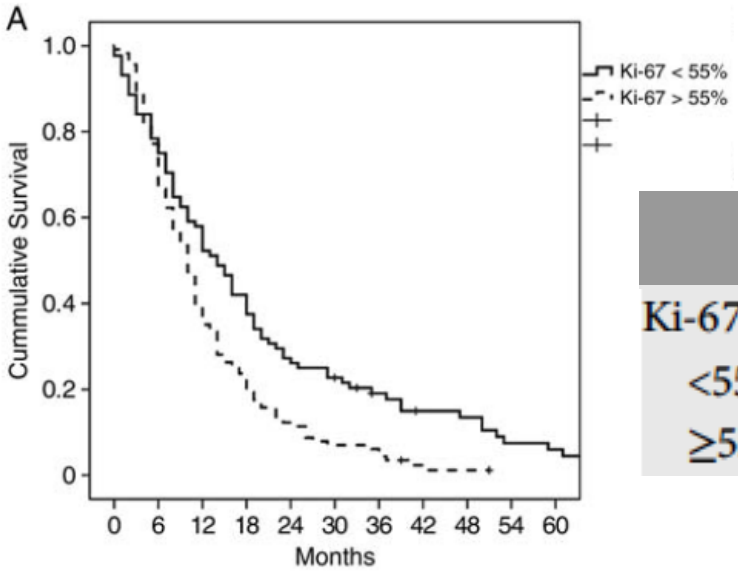
Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): The NORDIC NEC study

H. Sorbye[1*], S. Welin[2,†], S. W. Langer[3,†], L. W. Vestermark[4], N. Holt[5], P. Osterlund[6], S. Dueland[7], E. Hofsli[8], M. G. Guren[9], K. Ohrling[10], E. Birkemeyer[11], E. Thiis-Evensen[12], M. Biagini[13], H. Gronbaek[5], L. M. Soveri[6], I. H. Olsen[14], B. Federspiel[15], J. Assmus[16], E. T. Janson[2,‡] & U. Knigge[14,‡]



	PR/CR (%)	SD (%)	PD (%)
Ki-67[c]			
<55%	15	47	38
≥55%	42	24	34

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SUGGESTED GUIDELINES FOR ADVANCED SI-NET MANAGEMENT

Unresectable SI-NET

G1 <2%	G2 2-10%	G2 11-20%	NET 20-55%	NEC>55%
Somatostatin Analogues PROMID / CLARINET				
Everolimus RADIANT-4	Everolimus + SSAs RADIANT-2			
PRRT NETTER-1				
IFN + SSAs (SWOG S0518)				
Liver-Directed Therapies –no Phase 3				
		Chemotherapy – no Phase 3		
			Chemotherapy	
			G2 therapy approach?	

Caplin M et al., NEJM 2014; Rinke A et al., J Clin Oncol 2009; Strosberg J, et al. ECC 2015; Yao JC, et al. Lancet 2015; Yao JC, et al. ASCO 2015

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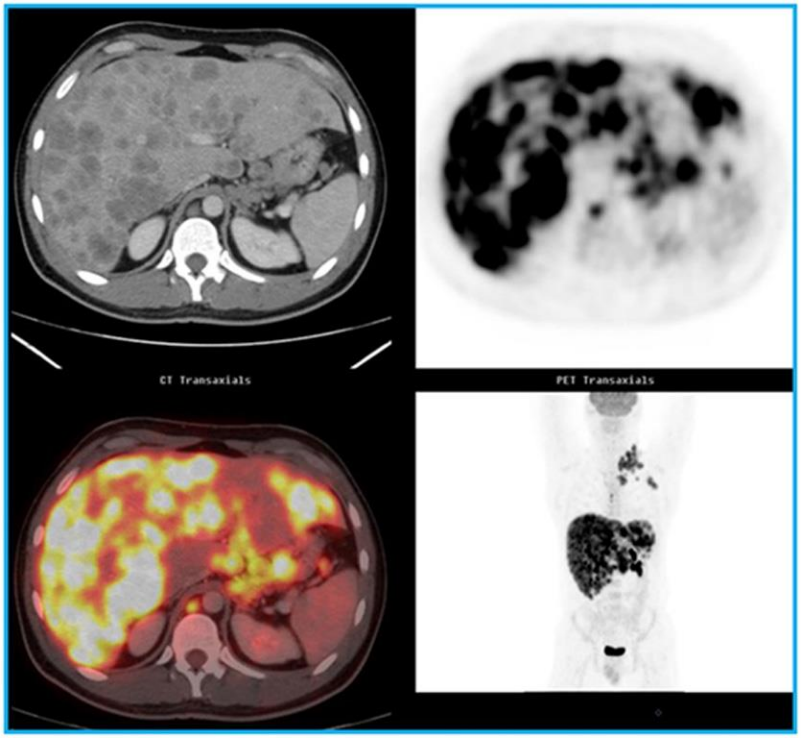
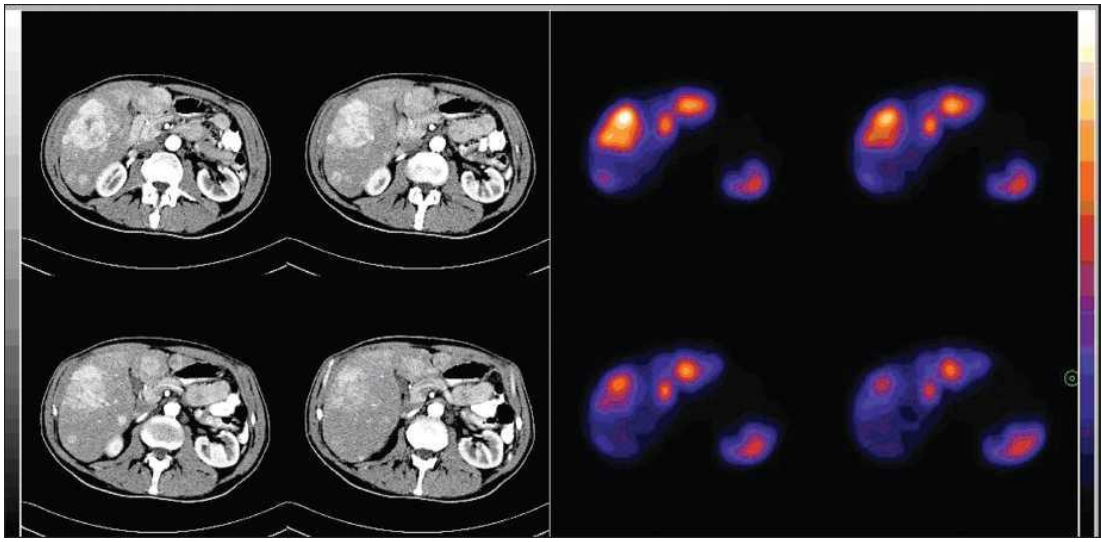
PROLIFERATION & DIFFERENTIATION





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SUNITINIB IN NET G3

Clinical and Biomarker Evaluations of Sunitinib in Patients (pts) With Advanced Grade 3 (G3) & Poorly-Differentiated Neuroendocrine Neoplasms (PD-NEN)

C Dreyer (1), A Couvelard (2), T Walter (3), C Lombard Bohas (3), P Niccoli (4), JF Seitz (5), O Hentic (6), A Pellat (1), T André (1), C Couffignal (7), N Lobbé (7), F Mentré (7), P Bedossa (2), S Faivre (9), M Zappa (8), P Ruszniewski (5), E Raymond (9)

Service d'oncologie médicale, hôpital St Antoine, Paris (2) Département de pathologie Beaujon-Bichat, Clichy-Paris (3) service d'oncologie médicale, GH Edouard Herriot, Lyon ; (4) service d'oncologie médicale, hôpital La Timone, Marseille ; (5) service d'oncologie digestive, hôpital La Timone, Marseille ; (6) service de gastro entéro pancréatologie hôpital Beaujon Clichy ; (7) service de biostatistiques, hôpital Bichat, Paris ; (8) service de radiologie, hôpital Beaujon, Clichy ; (9) service d'oncologie médicale, hôpital Beaujon, Clichy

Figure 2. Sensitivity According to Youden Index

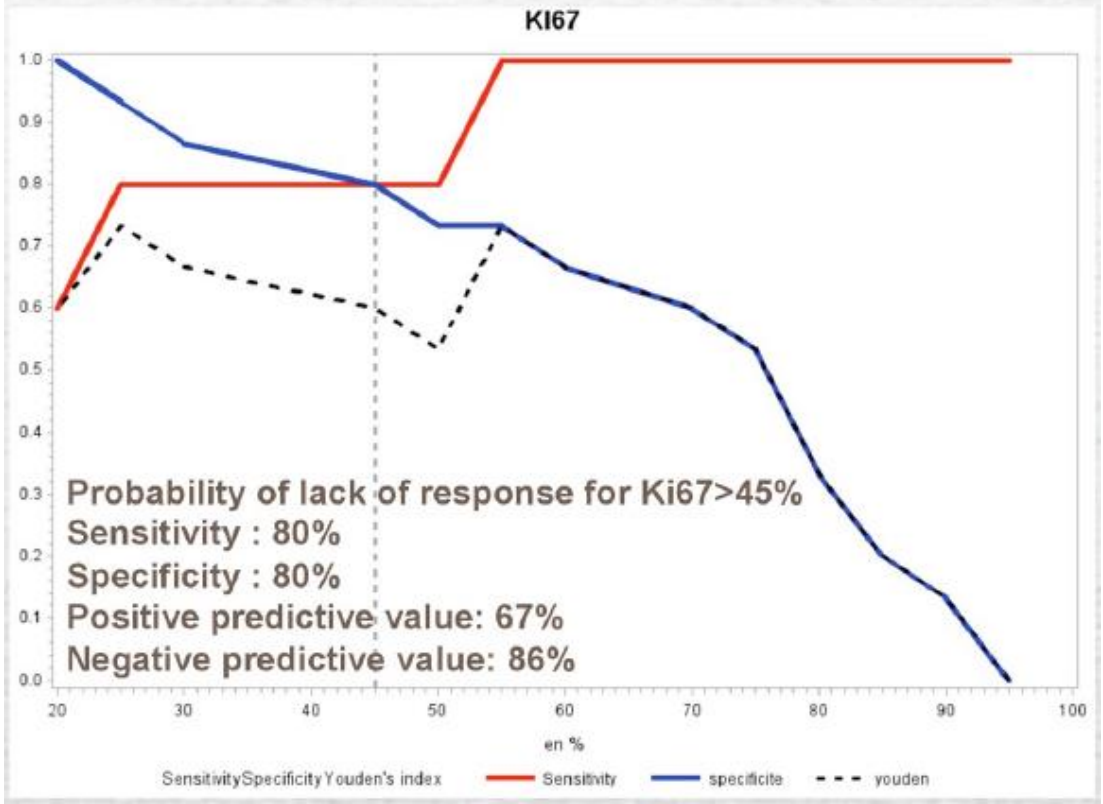


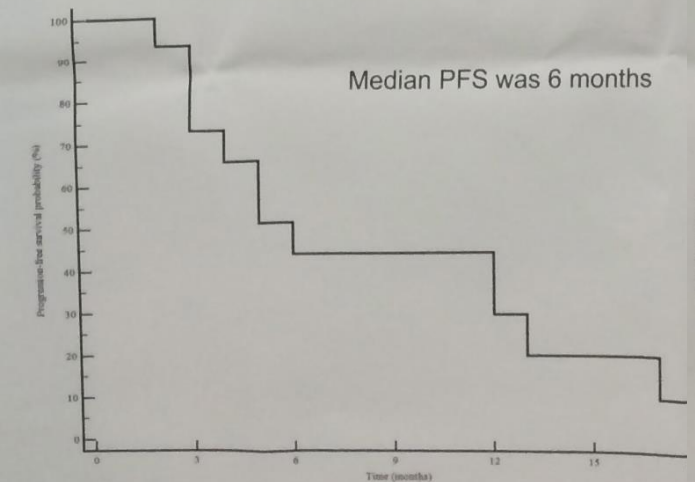
Table 2. Response Evaluation by RECIST	
Number of evaluable patients	26
Non evaluable*	5
Partial response Φ	3 (11.5%)
Tumor stabilization	3 (11.5%)
Tumor control	6 (23%, 95%CI: 6.9%-39.3%)
Tumor progression	20 (77%)

EVEROLIMUS IN NET G3

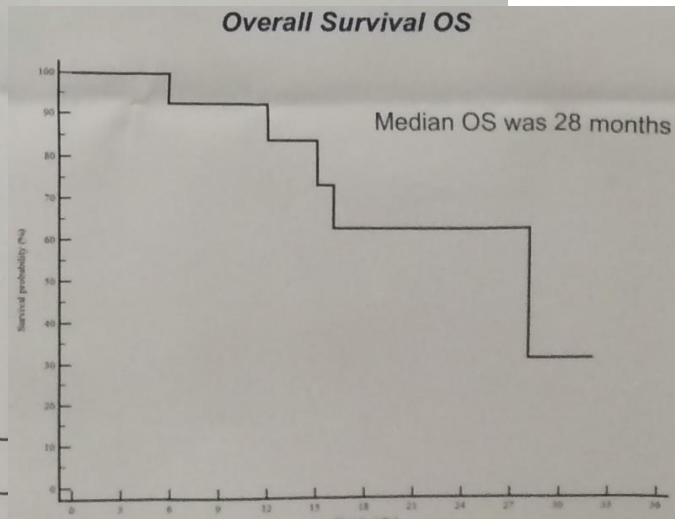
Patients General Features

Pt no.	Age (yr)	Previous treatment	Ki67 (%)	Duration of response to everolimus (months)
1	74	PRRT, som analogs	25	2
2	36	PRRT, som analogs	30	3
3	21	Etoposide+cisplatin, som analogs	30	3
4	62	Etoposide+cisplatin, capecitabin+temozolomide	50	3
5	48	Capecitabin+temozolomide, etoposide+cisplatin	26	3
6	61	Etoposide+cisplatin	30	4
7	32	None	25	5
8	61	PRRT	22	5
9	50	Etoposide+cisplatin, PRRT	40	6
10	58	Etoposide+cisplatin	30	12
11	59	None	35	12
12	25	Etoposide+cisplatin	55	12
13	55	PRRT	30	13
14	63	None	25	17
15	23	None	30	22

Progression free Survival PFS



Overall Survival OS



Panzuto F, et al. ENETS 2016

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TAKE-HOME MESSAGES

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SI-NEN G1/G2

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SI-NEN G1/G2

Targeting functionality

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SI-NEN G1/G2

↓

Targeting functionality

↓

SSA
IFN-α + SSA
Telotristate*

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SI-NEN G1/G2

Targeting functionality

SSA
IFN-α + SSA
Telotristate*

Loco-regional Liver Tx;

Debulking; RFA

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SI-NEN G1/G2

- **Targeting functionality**
  - **SSA**
    IFN-α + SSA
    Telotristate*
    - **Loco-regional Liver Tx;**
    - **Debulking; RFA**
- **Targeting tumor growth**

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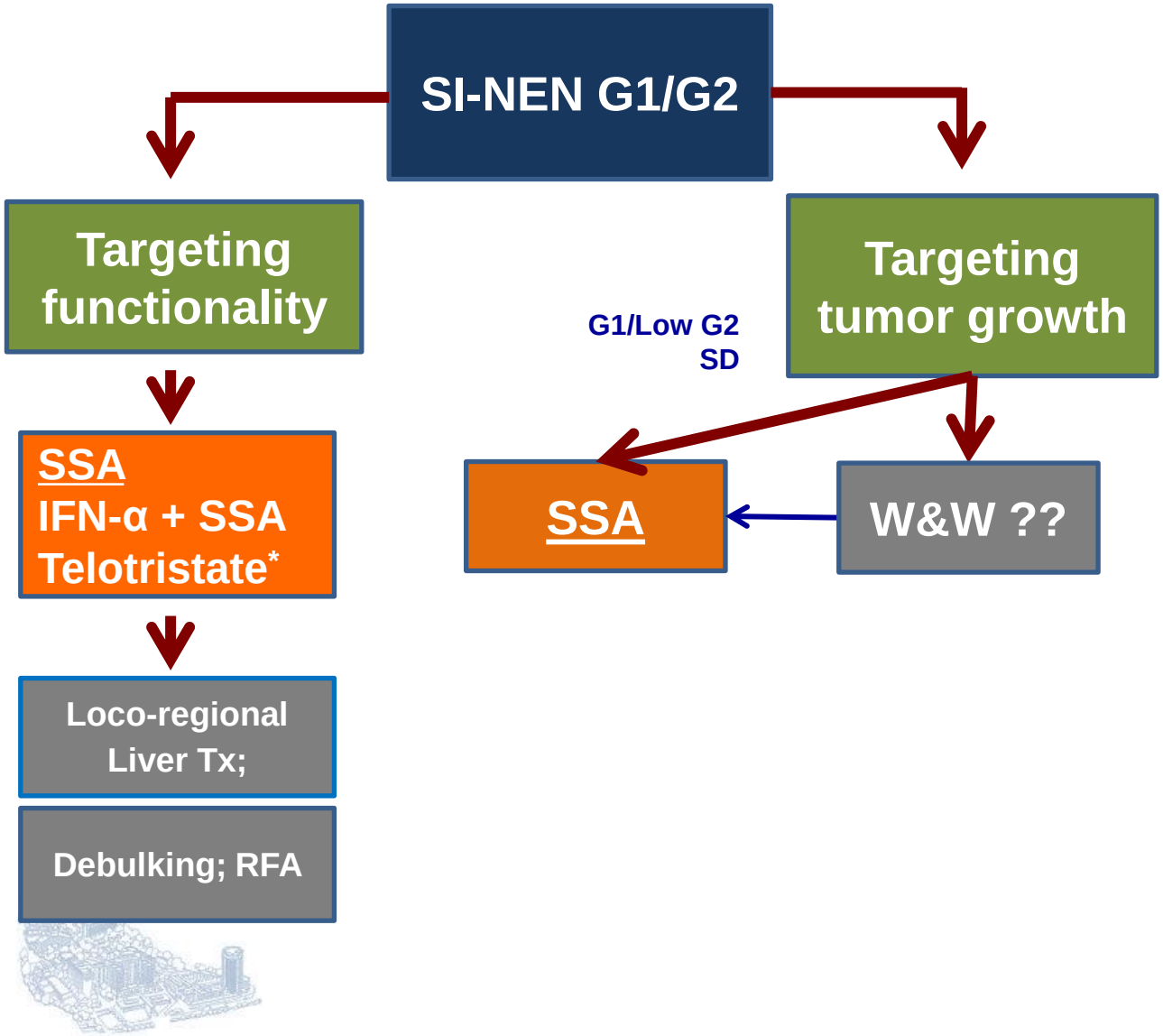

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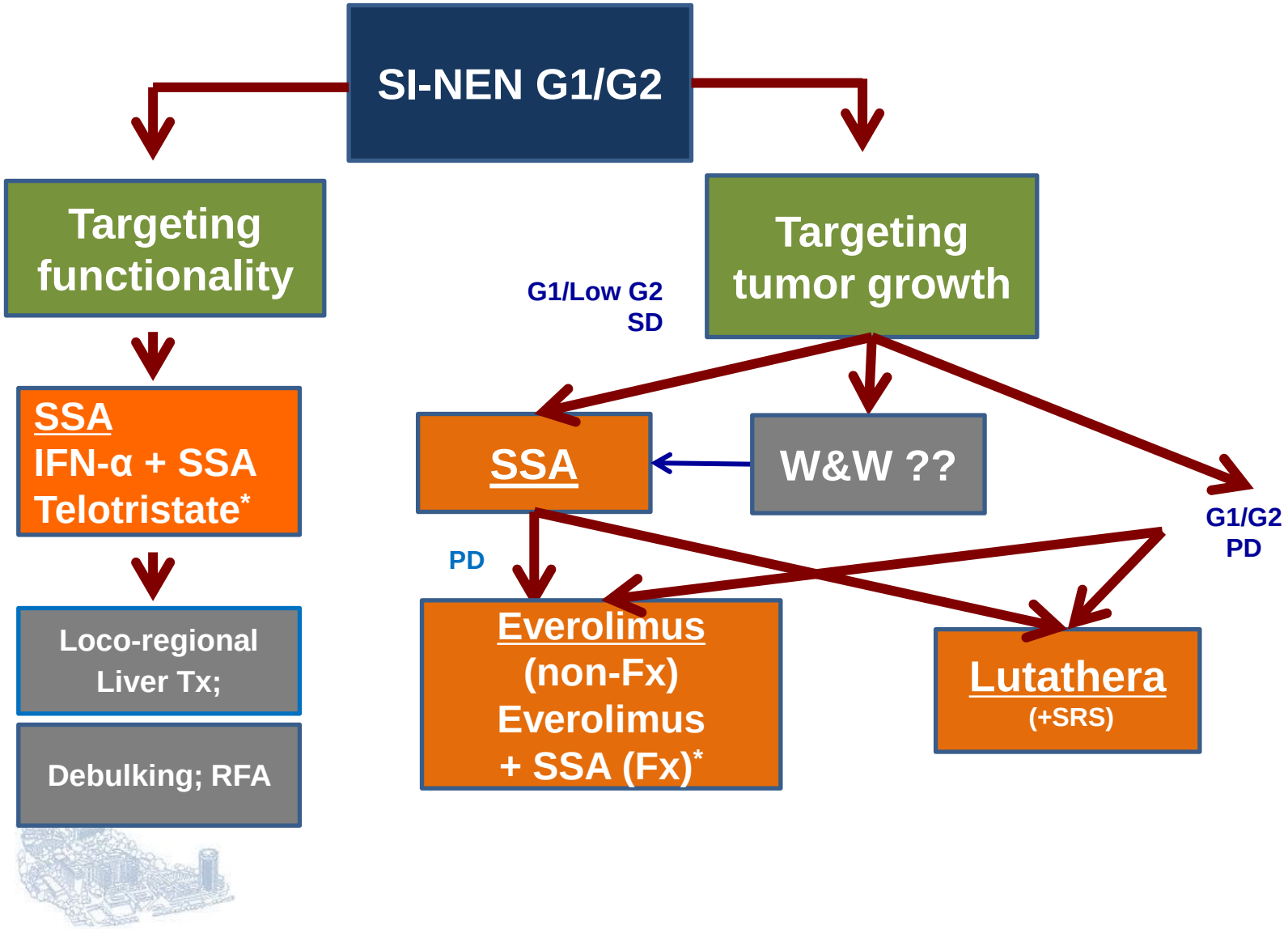

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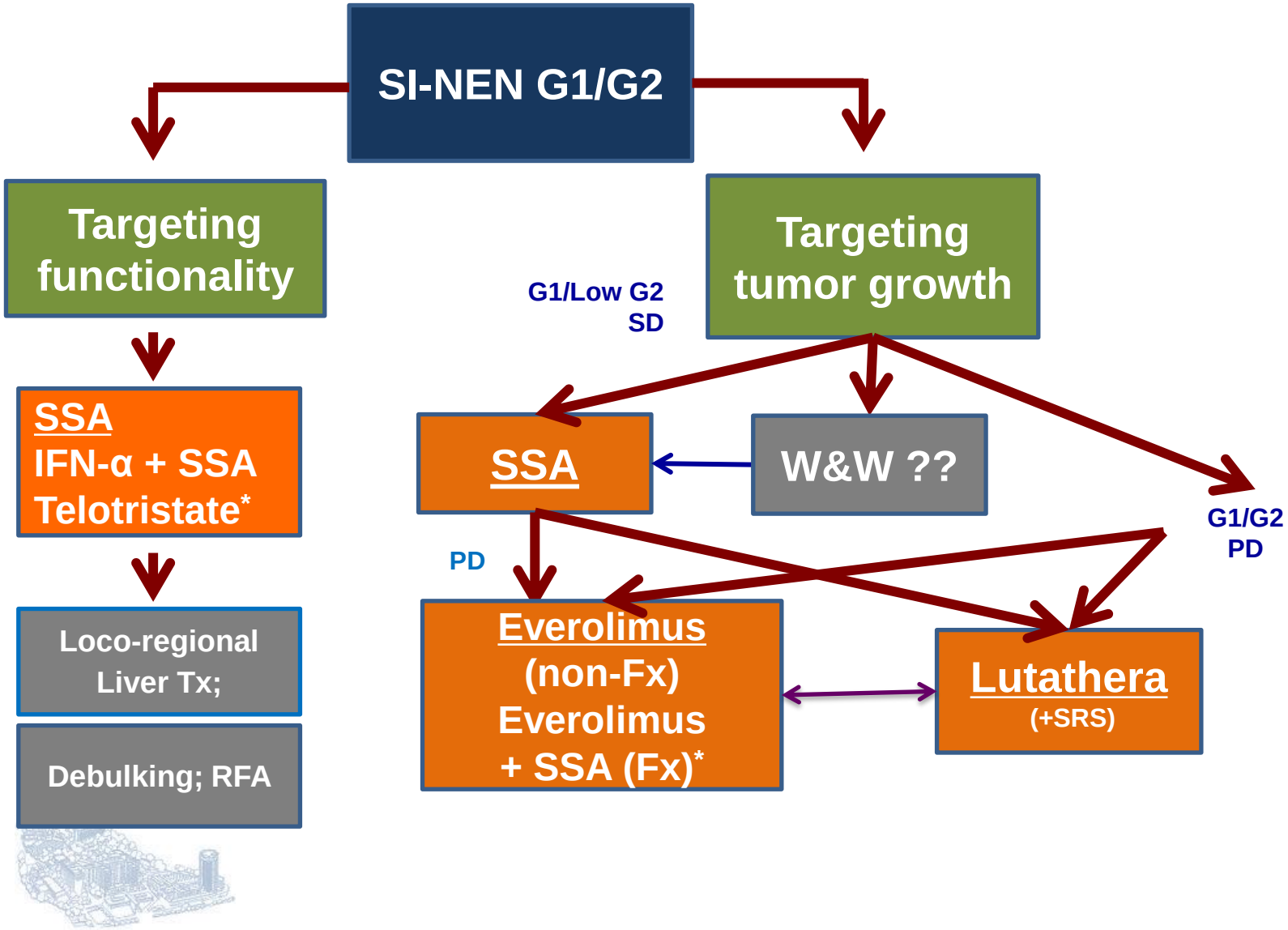

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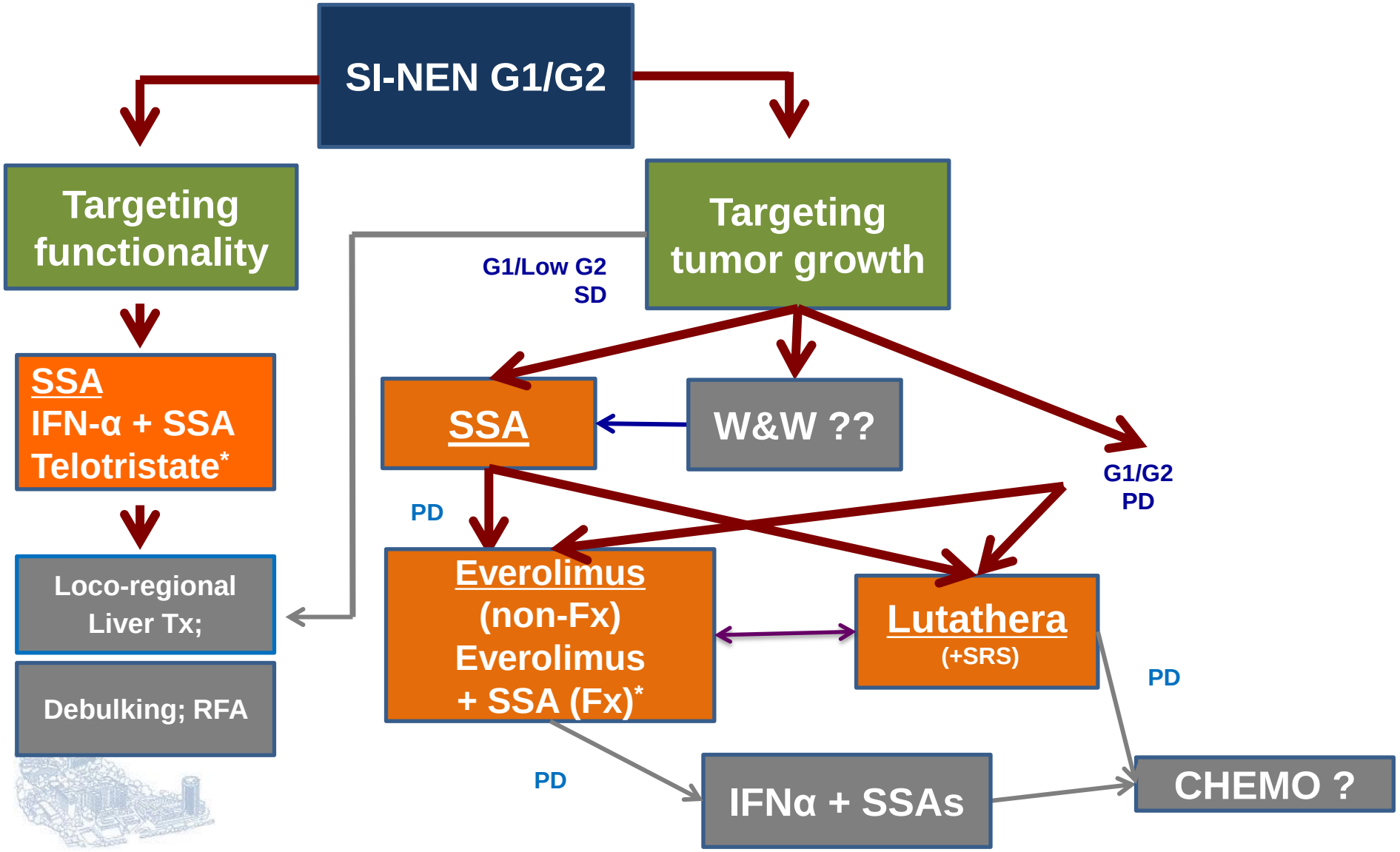

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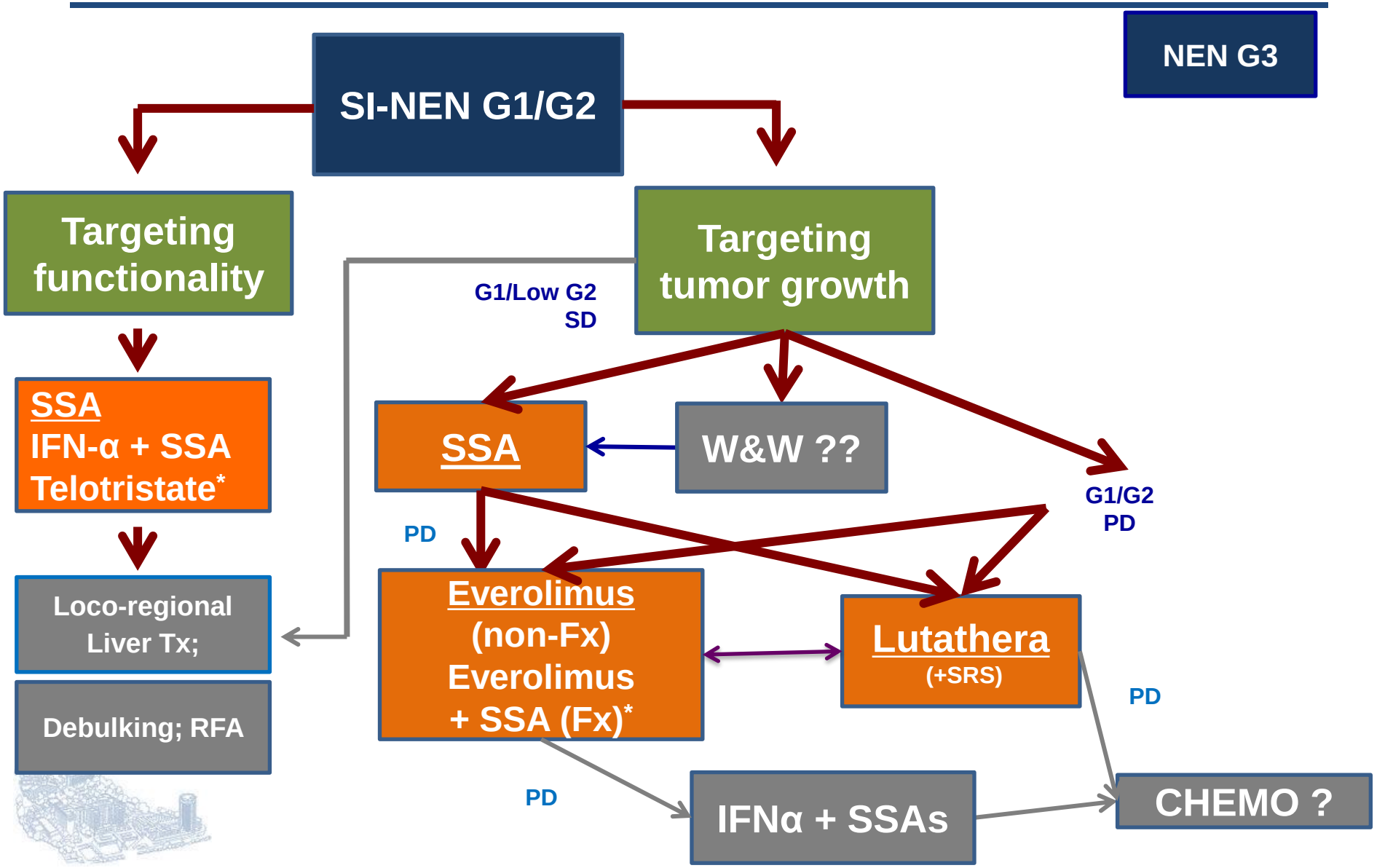

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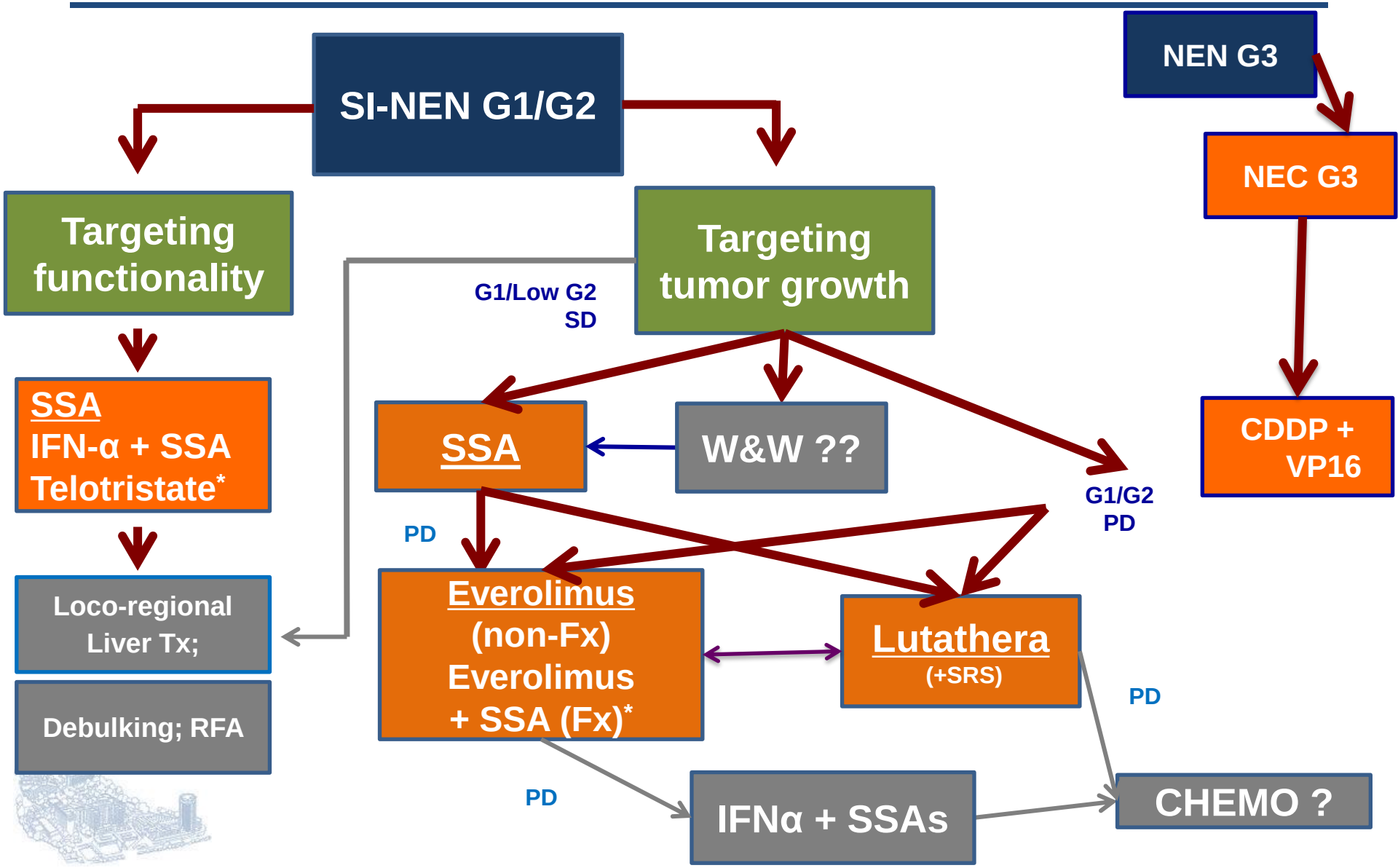

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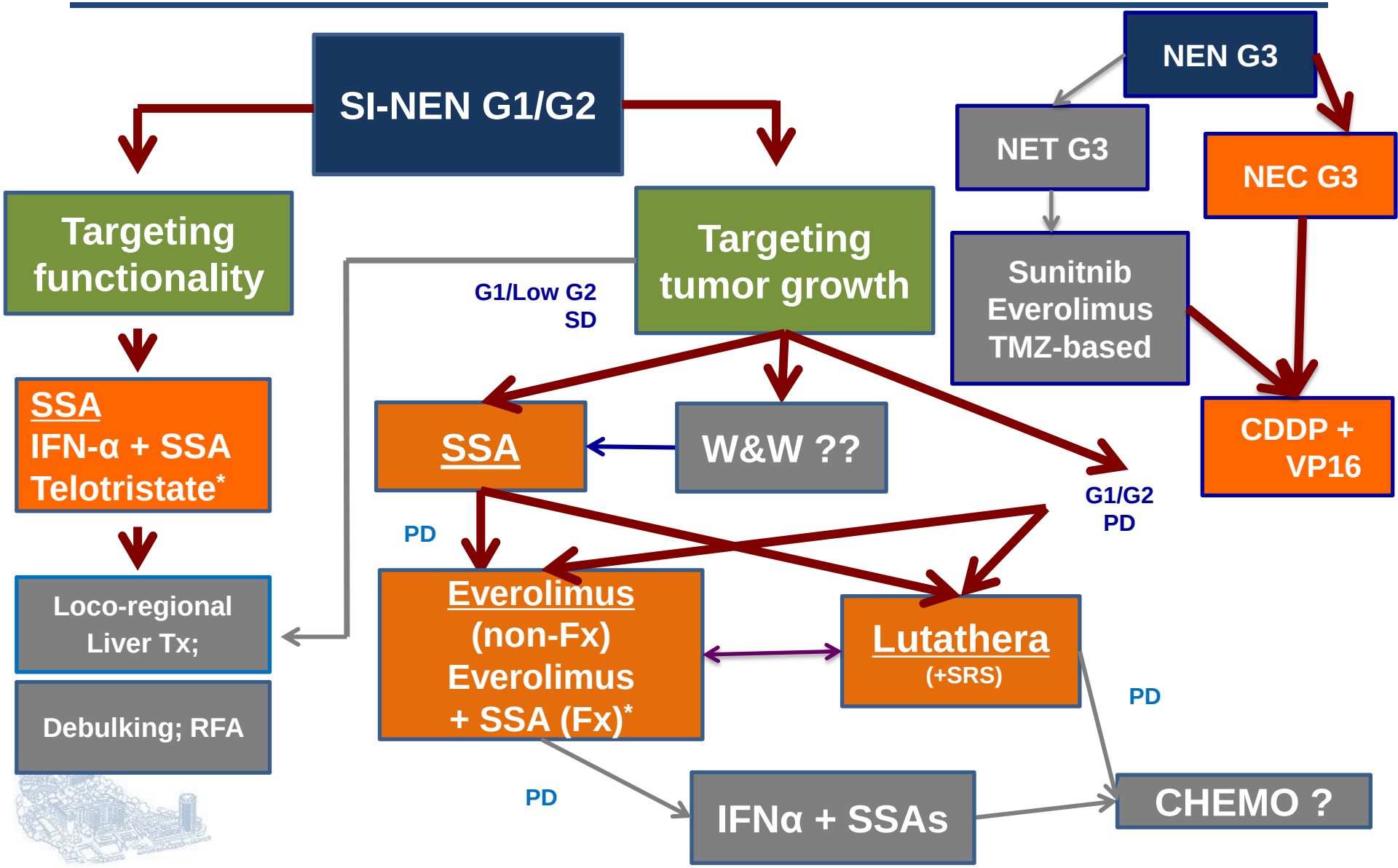

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THANK YOU FOR YOUR ATTENTION

VHIO

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