Targeted Therapy of Pancreatic Neuroendocrine Tumors

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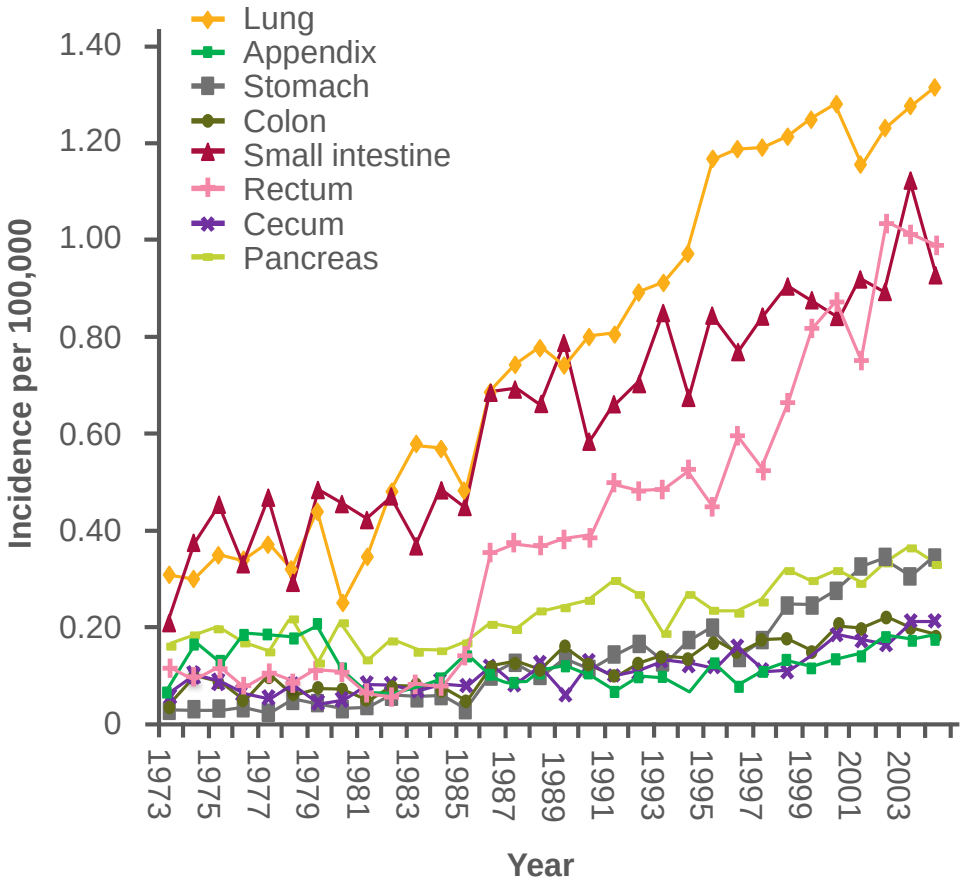
Incidence of pancreatic NET has increased steadily over time

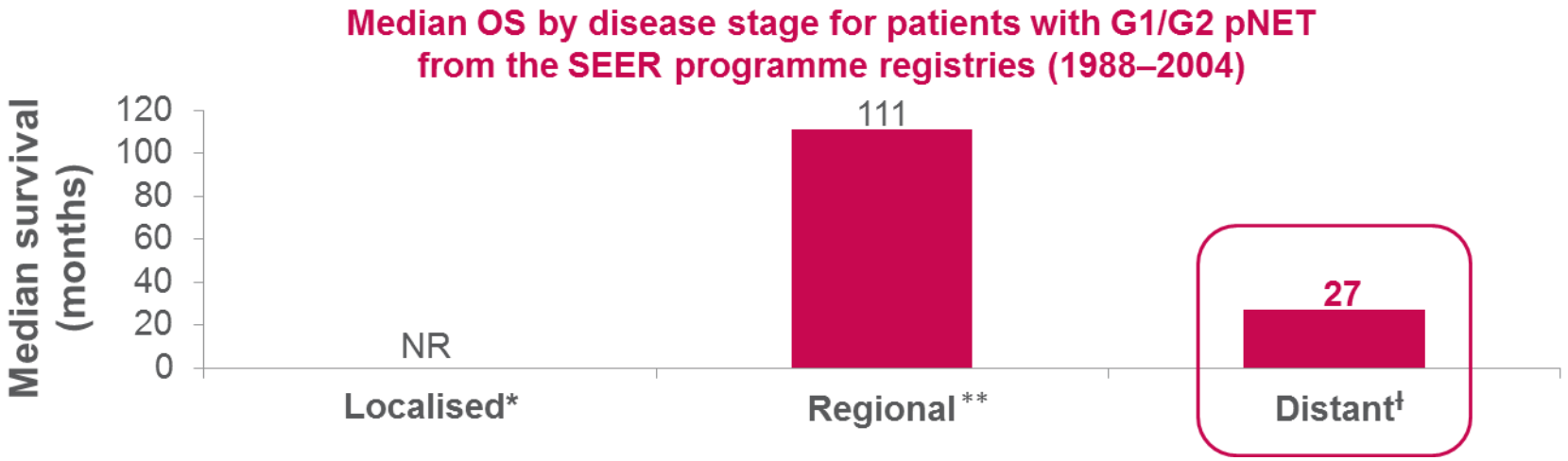


Incidence of pNET over the past four decades has shown a statistically significant increase ($p<0.001$)

Research data from SEER: surveillance, epidemiology, and end results program
Yao JC *et al*. *J Clin Oncol* 2008;26:3063–3072

Over 60% of pancreatic NET is advanced at diagnosis

- Data from the SEER programme registries (1973−2004) demonstrated that, of pNET cases at diagnosis:
  - 14% were localised
  - 22% were regional
  - 64% were distant



- Corresponding 5-year survival rates for localised, regional and distant disease were 79%, 62% and 27%, respectively

SEER, Surveillance, Epidemiology and End Results. *Defined as an invasive neoplasm confined entirely to the pancreas; **Defined as a neoplasm that (1) extended beyond the limits of the pancreas directly into surrounding organs or tissue, and/or (2) involved regional lymph nodes; †Defined as a neoplasm that spread to parts of the body remote from the primary tumour.

Yao JC *et al*. *J Clin Oncol* 2008;26:3063–3072

Several criteria are available to classify NET

Differentiation and grade[1]	Mitotic count*[1]	Ki-67 index† (%)[1]	Traditional classification[2]	ENETS/WHO classification[3]	Moran, *et al*.[4]
Well differentiated					
Low grade (grade 1)	<2	≤3	Carcinoid, islet cell, pancreatic (neuro)endocrine tumour	NET, grade 1	NEC, grade 1
Intermediate grade (grade 2)	2–20	3–20	Carcinoid, atypical carcinoid,‡ islet cell, pancreatic (neuro)endocrine tumour	NET, grade 2	NEC, grade 2
Poorly differentiated					
High grade (grade 3)	>20	>20	Small-cell carcinoma Large-cell NEC	NEC, grade 3, small cell NEC, grade 3, large cell	NEC, grade 3, small cell NEC, grade 3, large cell

*Per 10 high-power fields; †Cellular proliferation marker; ‡Applies only to intermediate-grade NET of the lung

ENETS, European Neuroendocrine Tumor Society; NEC, neuroendocrine carcinoma; WHO, World Health Organization

1. Klimstra DS *et al*. The spectrum of neuroendocrine tumors. ASCO educational book 2015:92–103;
2. Kulke MH *et al. J Clin Oncol* 2011;29:934–943; 3. WHO Classification of Tumours of the Digestive System, 4th ed. 2010;
4. Moran CA *et al. Am J Clin Pathol* 2009;131:206–221

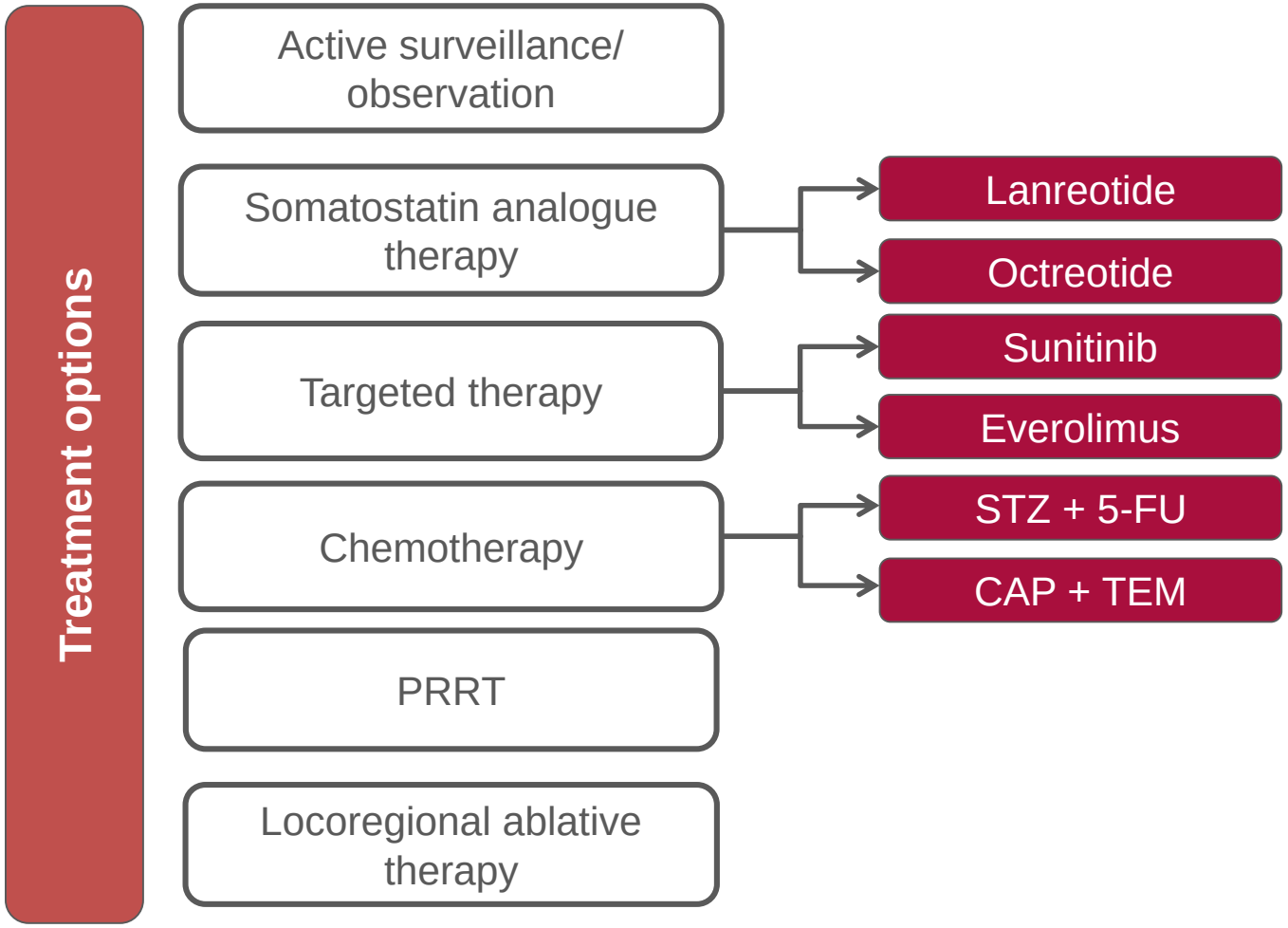
Key factors influencing treatment decisions for patients with unresectable, advanced pNET

Tumour grade (Ki-67)	• High grade/low grade • Progressive or stable disease – Pace of progression

Tumour stage	• Extent/burden of disease
	  – Localised or metastatic disease
	  – Low tumour burden/high tumour burden

Tumour functionality	• Functional tumour • Non-functional tumour

Treatment options available for the management of patients with unresectable, advanced pNET



CAP, capecitabine; FU, fluorouracil; PRRT, peptide receptor radionucleotide therapy; STZ, streptozocin; TEM, temozolomide

Phase 3 Clinical Evidence (guidelines sourcing)

GI/lung NET	Pancreatic NET
PROMID[1]: Oct LAR • Improves TTP vs PBO in UP F/NF G1/2[a] midgut	Sunitinib[9] • Improvement PFS vs PBO in P G1/2 pNET
CLARINET[2]: LAN Depot • Improves PFS vs PBO in NP NF G1/2[b] GEP NET	CLARINET[2]: LAN Depot • Improves PFS vs PBO in NP NF G1/2[b] GEP NET
RADIANT-2[3]: EVE + Oct LAR • NS improvement in PFS vs Oct LAR alone in P F G1/2 lung/GI	RADIANT-3[10]: EVE + BSC[c] • Improves PFS vs PBO in P G1/2 pNET
NETTER-1[4]: PRRT + Oct LAR • Improves PFS vs Oct LAR alone in P F/NF G1/2 midgut	
RADIANT-4[5]: EVE • Improves PFS vs PBO in P NF G1/2 lung/GI	
TELESTAR[6]: Telotristat etiprate • Improves daily bowel movement frequency in G1/2 RF CS	
SWOG S0518[7,8]: BEV or IFN, both with concomitant Oct LAR • No difference in PFS in PP[d] (incl P) G1/2	

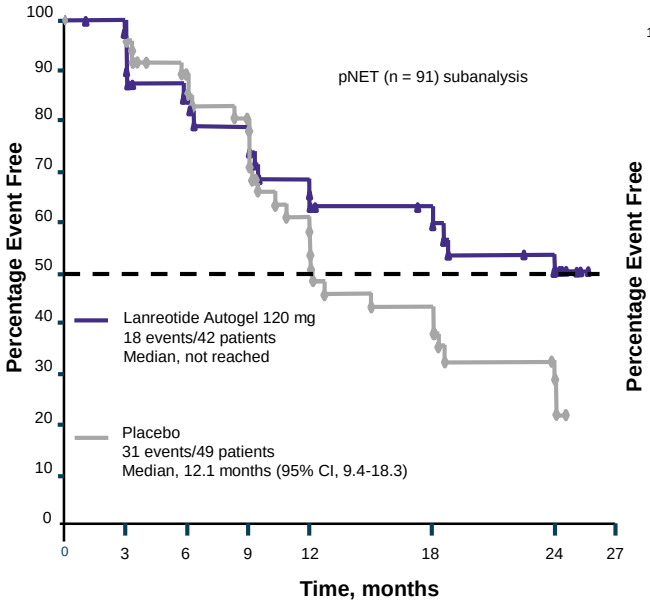
See notes for references.

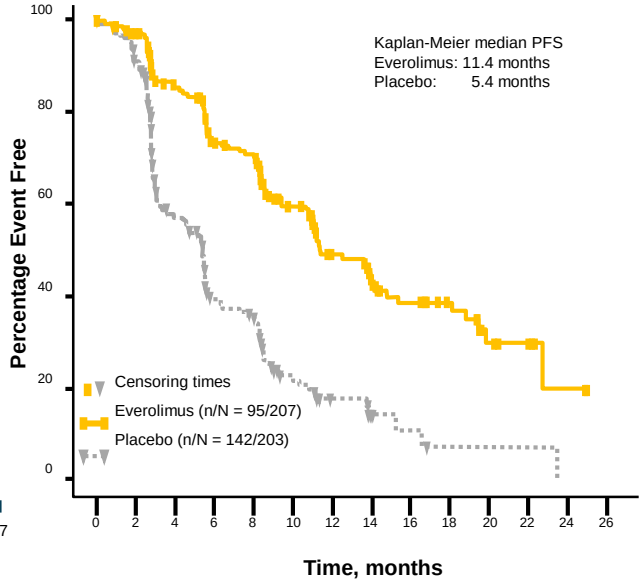
BEV, bevacizumab; EVE, everolimus; F, functional; IFN, interferon; LAN Depot, lanreotide Depot; NF, nonfunctional; NP, nonprogressive; NS, nonsignificant; Oct LAR, octreotide LAR; P, progressive; PBO, placebo; PFS, progression-free survival; pNET, pancreatic NET; PP, poor prognosis; PRRT, peptide receptor radionuclide therapy; RF, refractory; TTP, time to progression; UP, unknown progression status at baseline.

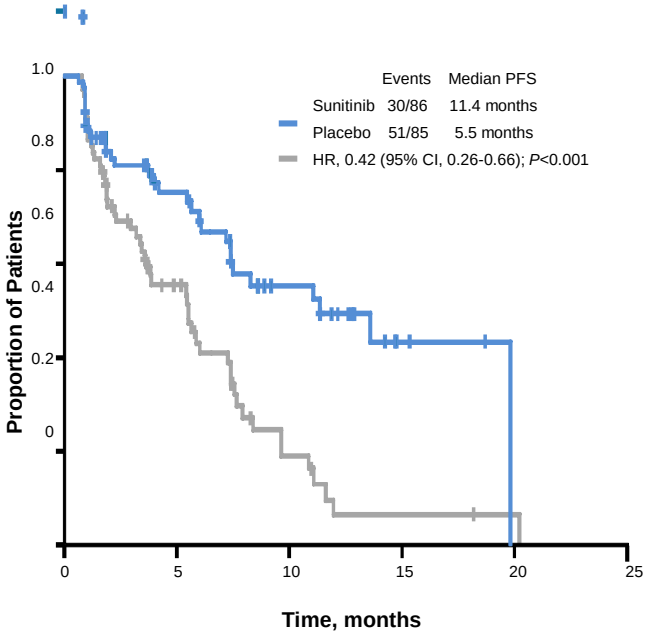
[a]Ki-67<2% for 95.3% of patients; [b]Ki-67<10%; [c]Concurrent use of somatostatin analogues was permitted; [d]Poor prognosis patients had at least one of the following: (1) PD, (2) refractory carcinoid syndrome, (3) atypical histology and more than 6 lesions, (4) metastatic colorectal carcinoid tumor, (5) metastatic gastric carcinoid tumor.

Recent Phase 3 Clinical Evidence: pNET

CLARINET[1,2]	RADIANT-3[3]	Sunitinib[4]

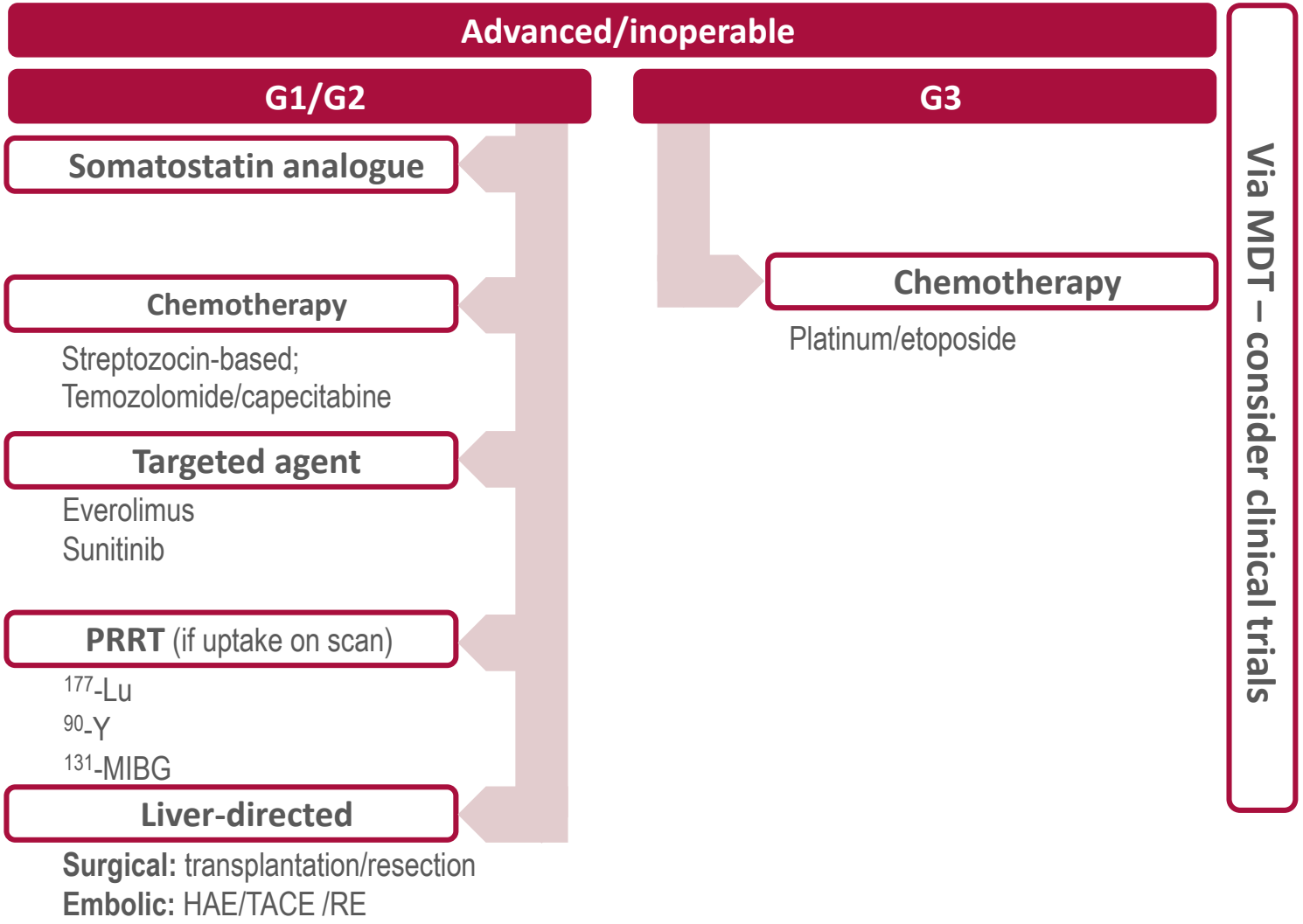






1. Caplin ME et al. *N Engl J Med.* 2014;371:224-233. 2. Caplin M et al. *Eur J Cancer*. 2013;49(suppl 2). Abstract LB3. 3. Yao JC et al. *N Engl J Med*. 2011;364:514-523. 4. Raymond E et al. *N Engl J Med*. 2011;364:501-513.

Treatment options for advanced pNET



Chemotherapy for the management of advanced pNET

Treatment	Phase	No. of patients	Tumour response rate (%)	mOS (mos)	PFS (mos)	Year
Prospective studies						
STZ + 5-FU	3	42	63	26	-	1980[1,2]
STZ	3	42	36	16.5	-	
STZ + DOX	3	36	69	26.4	-	1992[3]
STZ + 5-FU	3	33	45	16.8	-	
Chlorozotocin	3	33	30	18	-	
Dacarbazine	2	50	34	19.3	-	2001[4]
TEM + thalidomide	2	11	45	NR	NR	2006[5]
TEM + Bev	2	15	33	41.7	14.3	2012[6]
TEM + everolimus	1/2	24	35	-	-	2010[7]

- **Efficacy of chemotherapy in pNET is variable and evidence is limited**
- **Response in early studies were not assessed using RECIST criteria**

Bev, bevacizumab; DOX, doxorubicin; FU, fluorouracil; mos, months; NR, not reached; RECIST, Response Evaluation Criteria in Solid Tumors; STZ, steptozotocin; TEM, temozolomide

1.Moertel CG *et al. N Engl J Med* 1980;303:1189–1194; 2. Valle JW *et al. Cancer Treatment Reviews* 2014;40:376-389;3 Moertel CG *et al. N Engl J Med* 1992;326:519–523;4. Ramanathan RK *et al. Ann Oncol* 2001;12:1139–1143; 5. Kulke MH *et al. J Clin Oncol* 2006;24:401–406; 6. Chan JA *et al. J Clin Oncol* 2012;30:2963–2968; 7. Kulke MH *et al. ASCO Gastrointestinal Cancers Symposium* 2010 (abstract 223)

Variable response seen with chemotherapy in advanced pNET

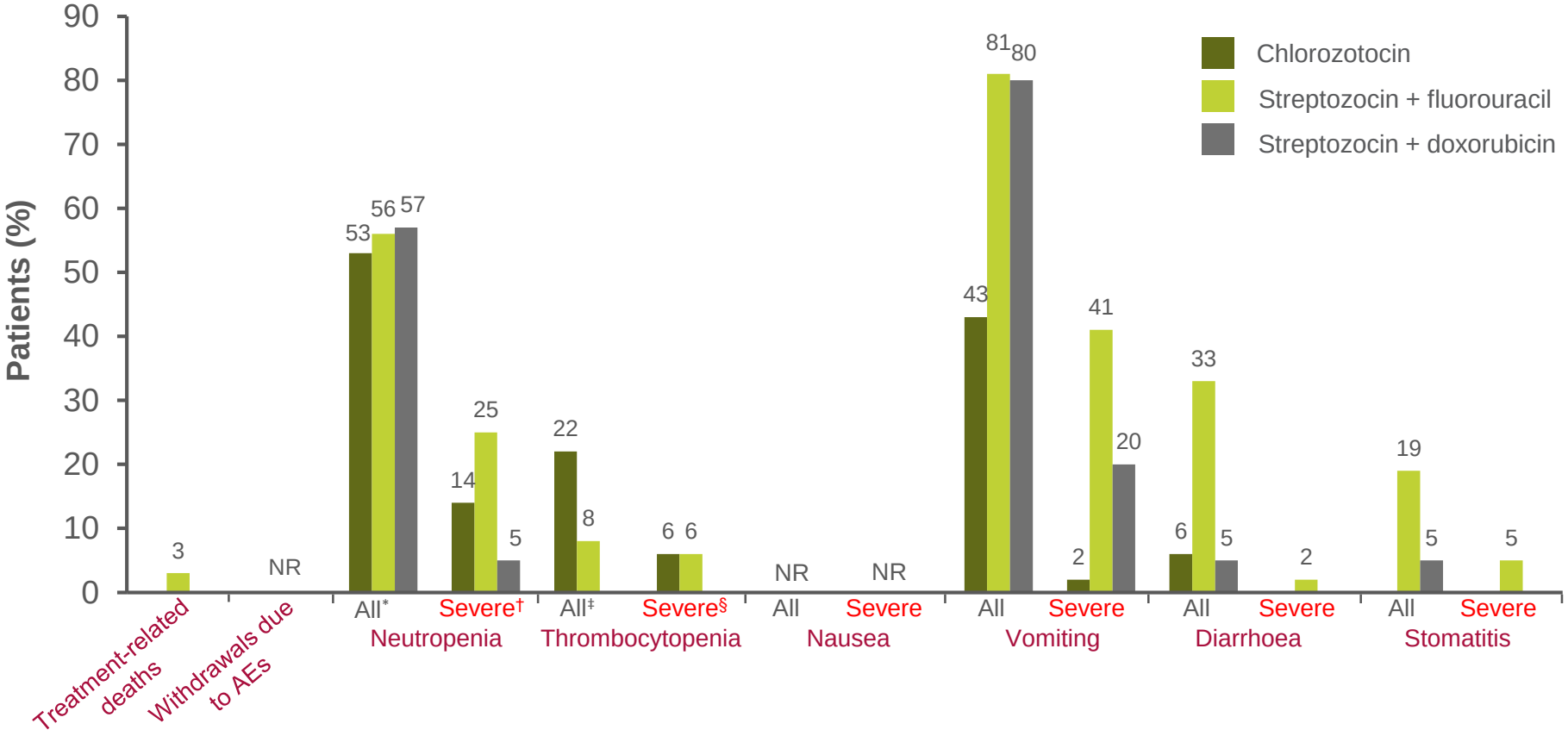
Treatment	Phase	No. of patients	Tumour response rate (%)	mOS (mos)	PFS (mos)	Year
Retrospective studies						
STZ + DOX + 5-FU	-	84	39	37	18	2004[1]
STZ + 5-FU + cisplatin	-	47	38	31.5	9.1	2010[2]
TEM (diverse regimens)	-	53	34	35.3	13.6	2009[3]
TEM (single agent)	-	12	14	-	-	2007[4]
TEM + CAP	-	30	70	-	18	2010[5]

- **Recent studies employing standard RECIST criteria failed to confirm the high response rates observed in earlier studies**
- **Small (N=30) retrospective analysis of TEM + CAP is suggestive of efficacy with accepted tolerability in advanced pNET – larger prospective analysis expected**

CAP, capcitabine; DOX, doxorubicin; FU, fluorouracil; mos, months; STZ, steptozotocin; TEM, temozolomide

1. Kouvaraki MA *et al. J Clin Oncol* 2004;22:4762–4771; 2. Turner NC *et al. Br J Cancer* 2010;102:1106–1112; 3. Kulke MH *et al. Clin Cancer Res* 2009;15:338–345; 4. Ekeblad S *et al. Clin Cancer Res* 2007;13:2986–2991; 5. Strosberg J *et al. Cancer* 2011;117:268–275

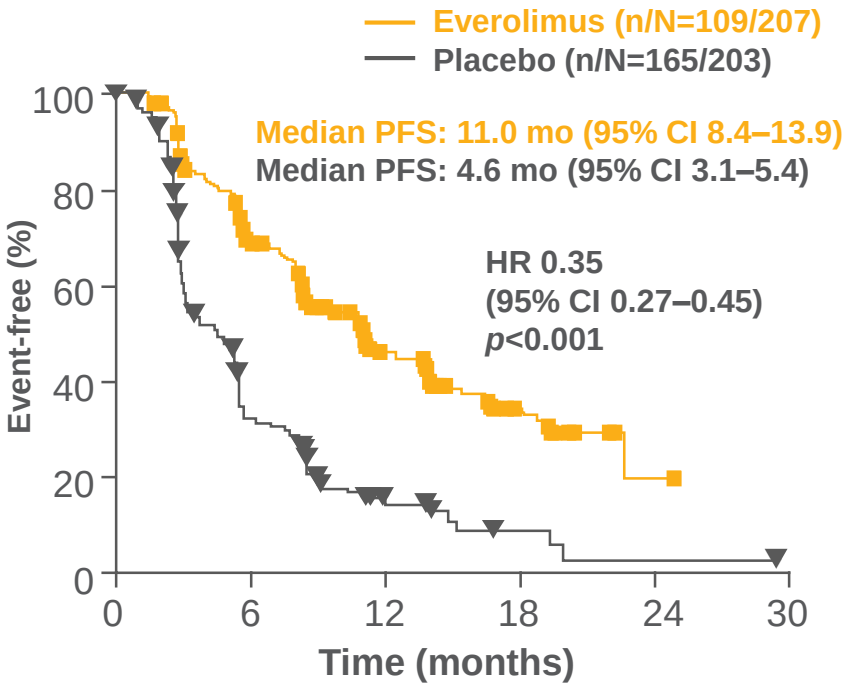
Chemotherapy toxicity profile in advanced pNET



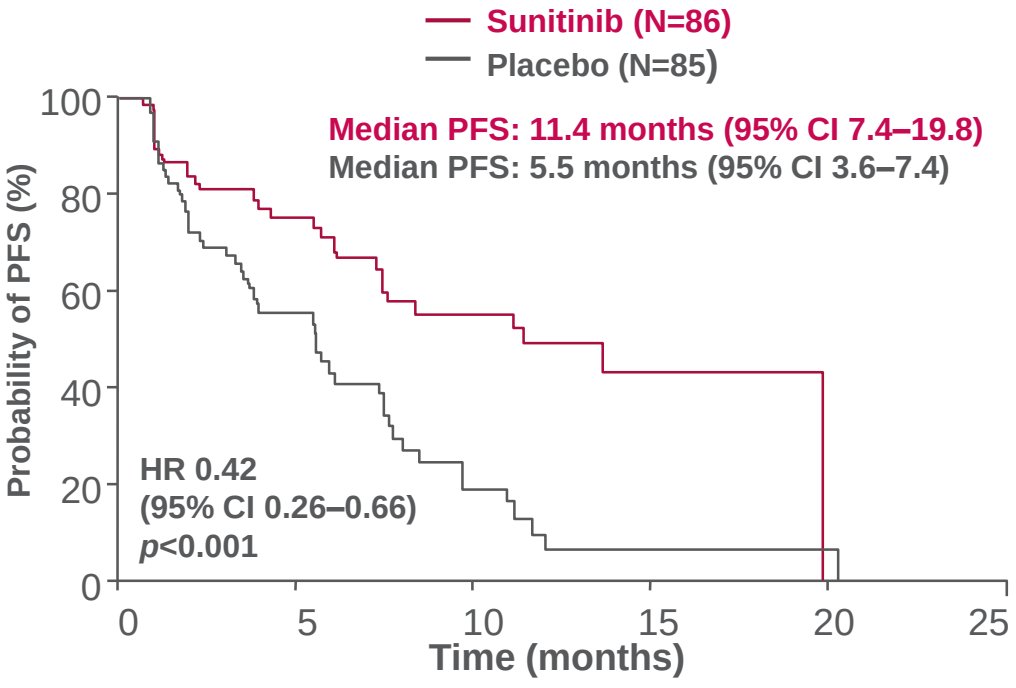
*Leukopenia: all <4 × 10^9 cells/litre †leukopenia: severe, <2 × 10^9 cells/litre; ‡Thrombocytopenia: all, <100 × 10^9 cells/litre
§thrombocytopenia: severe, <50 × 10^9 cells/litre
Moertel CG *et al. N Engl J Med* 1992;326:519–523; Valle JW *et al. Cancer Treatment Reviews* 2014;40:376-389

Improvement in PFS with targeted agents in advanced, progressive pNET

RADIANT-3: Study population
- Grade 1 or 2



SUN1111: Study population
- Grade 1 or 2

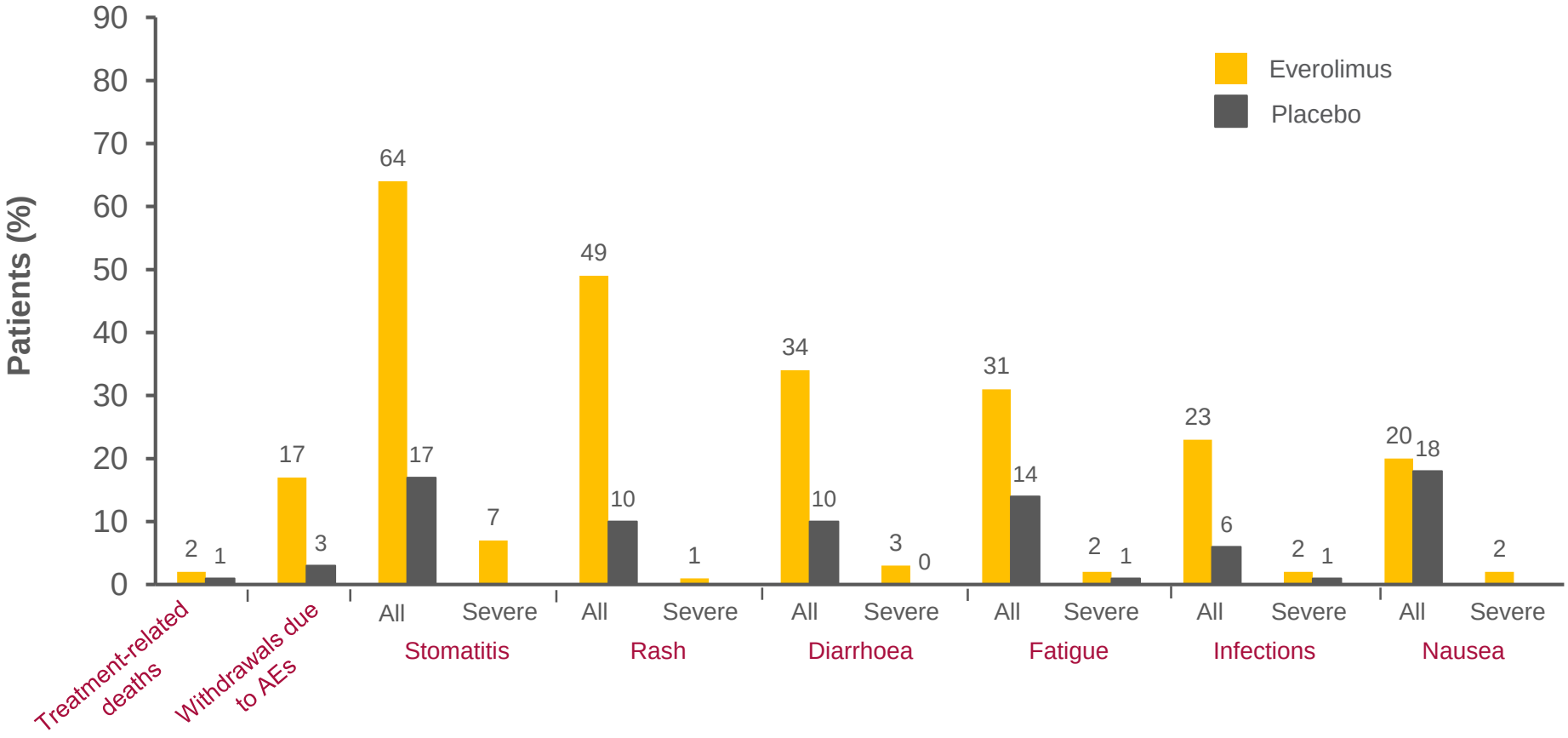


Targeted agents have been shown to prolong median PFS compared with placebo in patients with advanced pNET

PFS, progression-free survival.

Yao JC *et al*. *N Engl J Med* 2011;364:514–523; Raymond E *et al*. *N Engl J Med* 2011;364:501–513

Toxicity profile of everolimus

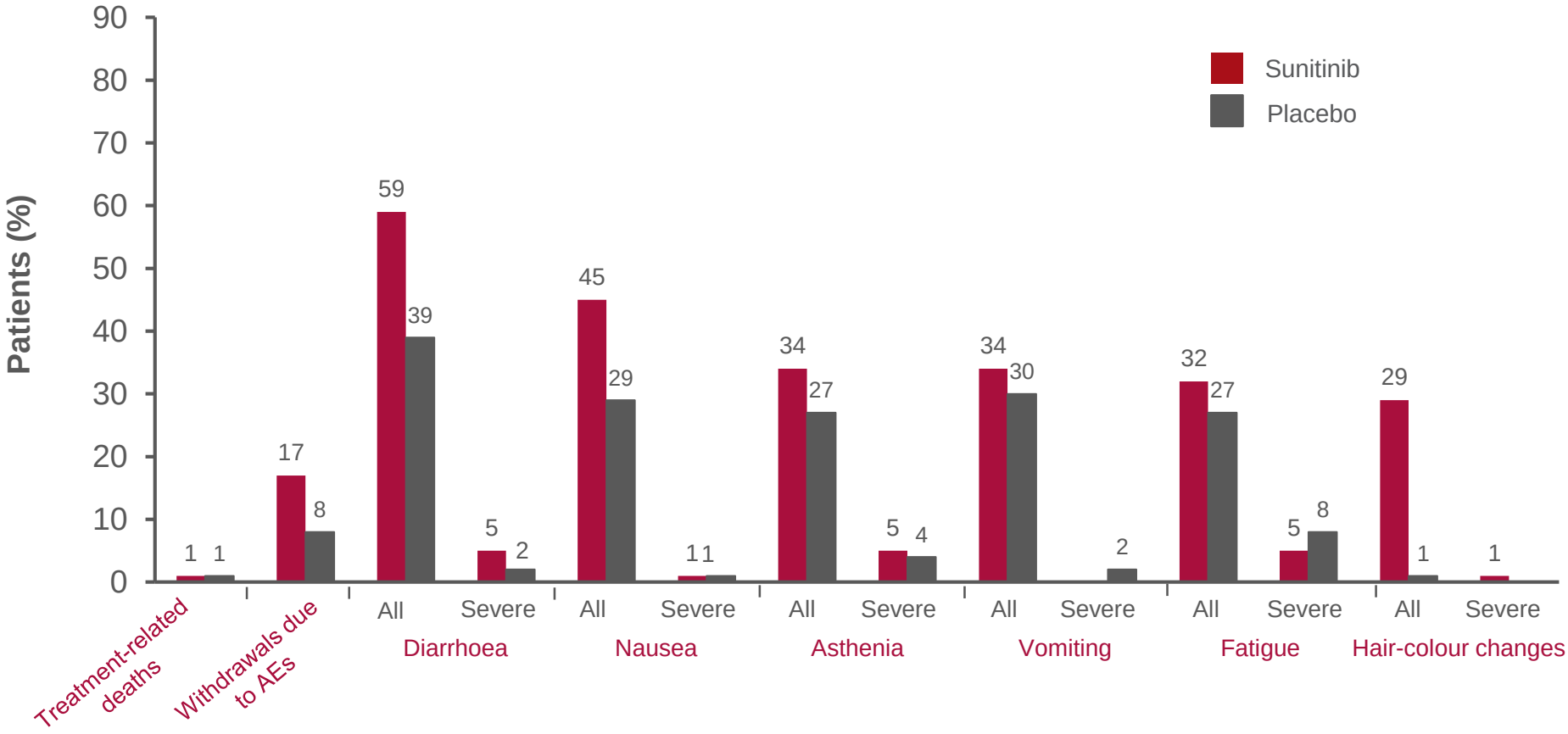


Everolimus is associated with a low incidence of severe events

Most common drug-related AEs
Yao JC *et al*. *N Engl J Med* 2011;364:514–523

Please refer to the Summary of Product Characteristics for full safety information

Toxicity profile of sunitinib

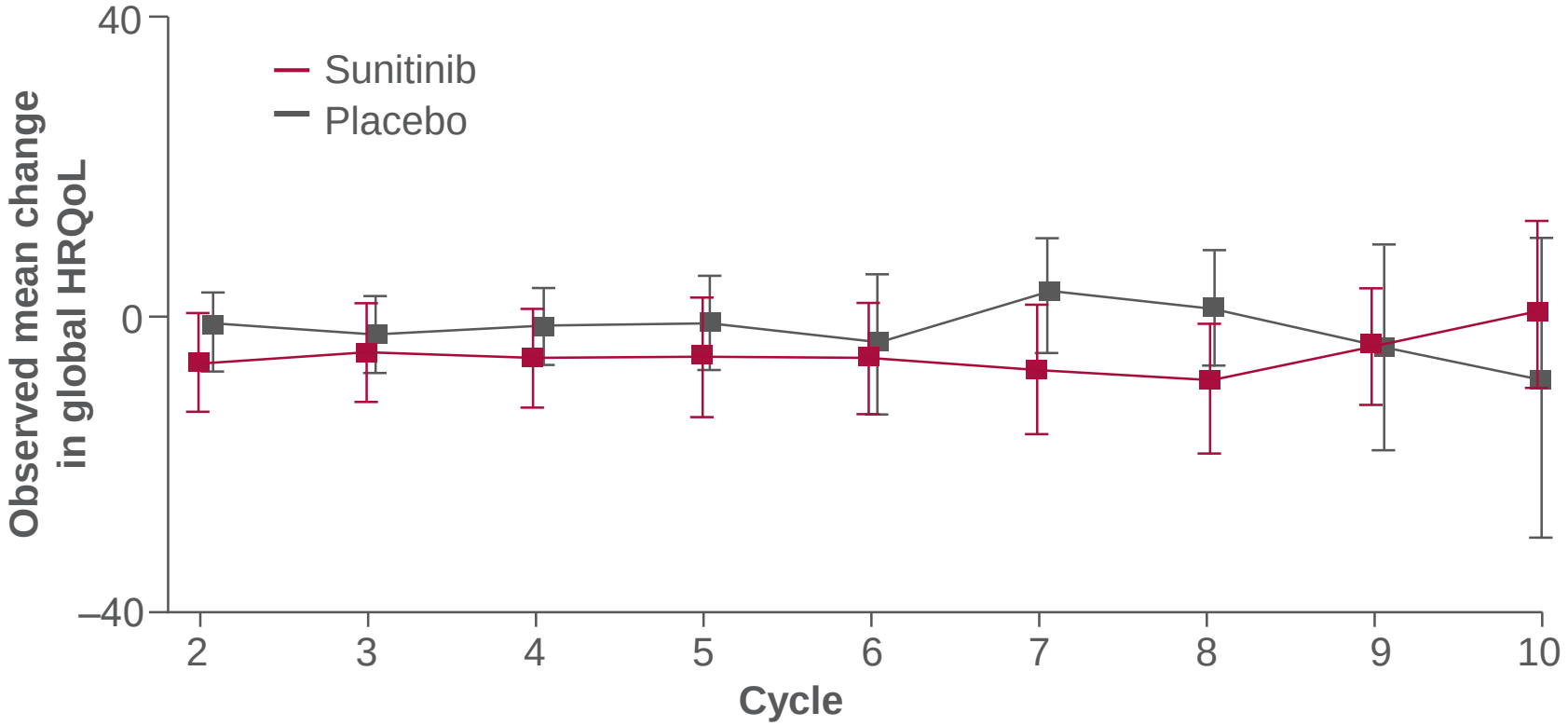


Sunitinib is associated with a low incidence of severe events

Most common AEs reported in the safety population
Raymond E *et al*. *N Engl J Med* 2011;364:501–513

Please refer to the Summary of Product Characteristics for full safety information

Global HRQoL was comparable between treatments



Sunitinib provides clinical benefits without impacting on patient QoL

Vinik A *et al. J Clin Oncol* 2010;28 (suppl; abstract 4003)

Updated survival analyses of targeted therapy in PNET

ENETS 2016

Sunitinib in Patients With Advanced, Progressive Pancreatic Neuroendocrine Tumors: Final Overall Survival Results From a Phase III Randomised Study, Including Adjustment for Crossover

E Raymond[1], P Niccoli[2], DE Castellano[3], JW Valle[4], P Hammel[1], J-L Raoul[5], AI Vinik[6], Y-J Bang[7], S-H Lee[7], I Borbath[8], C Lombard-Bohas[9], P Metrakos[10], DM Smith[11], J-S Chen[12], J-F Seitz[2], S Patyna[13], DR Lu[13], J Ishak[14], S Faivre[1], P Ruszniewski[1]

[1]Beaujon Hospital, Clichy, France; [2]University Hospital Timone, Marseille, France; [3]University Hospital 12 de Octubre, Madrid, Spain; [4]University of Manchester, The Christie NHS Foundation Trust, Manchester, UK; [5]Institut Paoli Calmettes, Marseille, France; [6]Eastern Virginia Medical School, Norfolk, VA, USA; [7]Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Republic of Korea; [8]Cliniques Universitaires Saint-Luc, Brussels, Belgium; [9]Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon, France; [10]McGill University Hospital Centre, Montreal, QC, Canada; [11]University Hospital, Bordeaux, France; [12]Linkou Chang Gung Memorial Hospital and Chang Gung University, Tao-Yuan, Taiwan; [13]Pfizer Oncology, La Jolla, CA, USA; [14]Evidera, St-Laurent, Canada

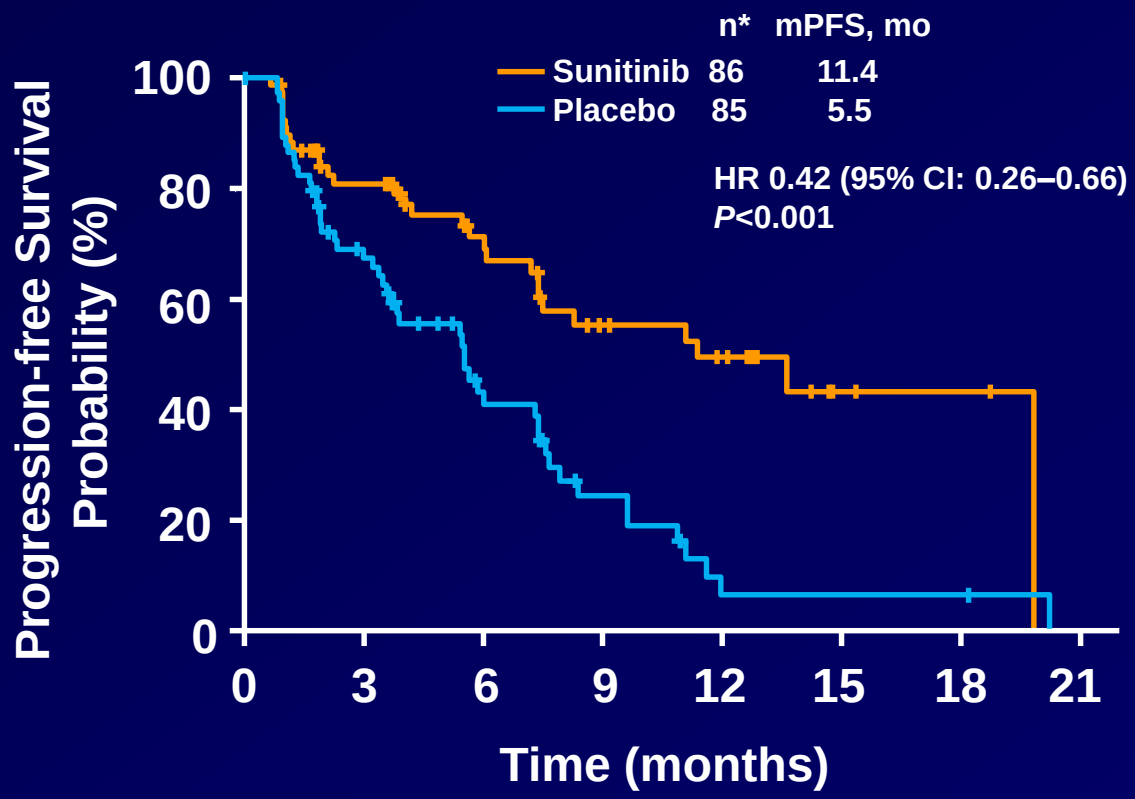
The 13th Annual ENETS Conference, 9–11 March 2016, Barcelona, Spain

Disclosures

- **E Raymond has worked as consultant and received research grants from :**
  - **Pfizer**
  - **Novartis**
  - **Ipsen**
  - **Eli Lilly**

Background

- Sunitinib malate (SUTENT®) is approved in the EU since 2010 and US since 2011 for the treatment of patients with pancreatic neuroendocrine tumors (NETs)[1]
- The pivotal, phase III, double-blind study in patients with advanced, well-differentiated pancreatic NETs reported a significantly longer median mPFS* (primary endpoint) with sunitinib vs placebo[2]



* ITT population

1. SUTENT® (sunitinib malate) prescribing information. Pfizer Inc; April 2015.
2. Raymond E, et al. N Engl J Med 2011;364:501-13.

ITT=intent to treat; mPFS=median progression-free survival

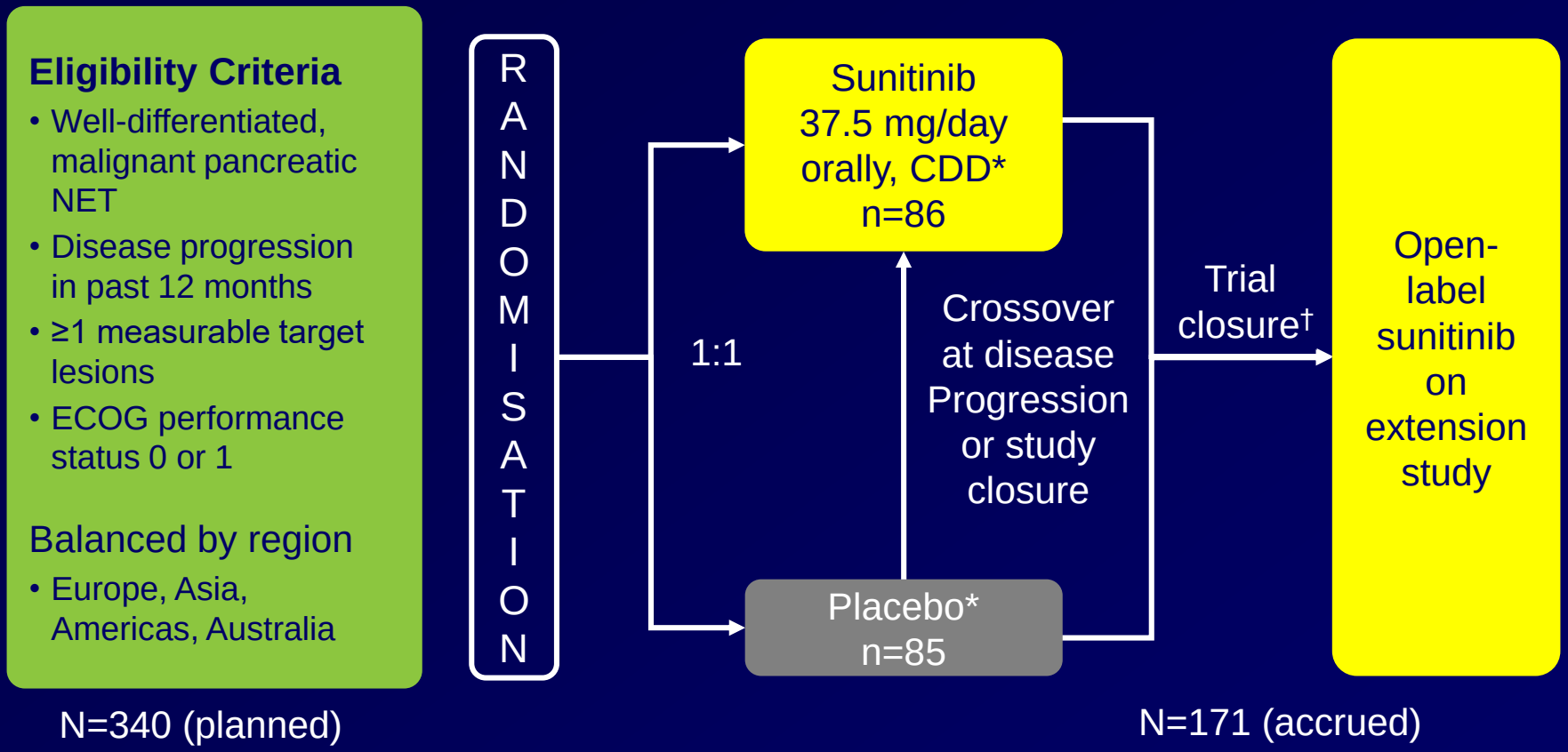
Background (II)

- **Overall survival (OS) results in the ITT population at the time of study closure (2009) favoured sunitinib over placebo (HR 0.41, 95% CI: 0.19–0.89; *P*=0.02); however, median OS was not reached**
- **At 2 years after study closure, median OS in the ITT population was 33.0 vs 26.7 months with sunitinib vs placebo (HR 0.71, 95% CI: 0.47–1.09; *P*=0.115)[1]**
- **Here we report the final OS data for 5-year follow-up after study closure**
- **Using exploratory analyses, we evaluated the treatment effect of sunitinib on OS with and without adjustment for treatment crossover in the placebo arm**

1. **Vinik A, et al. J Clin Oncol 2012;30(suppl): abstr 4118.**

CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat

Study Design and Endpoint



* With best supportive care; somatostatin analogs permitted
† Early trial closure occurred due to differences in deaths, serious AEs, and PFS

- Primary endpoint: investigator-assessed PFS
- Secondary endpoints: OS, ORR, time to tumor response, duration of response, safety, PROs

1. Raymond E, et al. N Engl J Med 2011;364:501-13.

CDD, continuous daily dosing; ECOG=Eastern Cooperative Oncology Group; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PROs, patient-reported outcomes

Statistical Analysis

- OS at 5 years after study closure was analyzed using the Kaplan–Meier method and Cox proportional hazards model in the ITT population
- Rank-preserving structural failure time (RPSFT) analysis was used to adjust for the impact of crossover
  - This analysis assumes a constant effect for sunitinib on OS across patients and over time[1]
- OS data were also analyzed using 2 other approaches:
  - Censoring placebo-arm data at crossover
  - Cox model analysis with treatment as a time-dependent covariate
  - Both approaches attempt to adjust for crossover but are ultimately prone to selection bias and thus, not fully robust

1. Ishak KJ, et al. Pharmacoeconomics. 2014 Jun;32(6):533-46
ITT=intent-to-treat

Demographic and Baseline Characteristics

- 171 patients were enrolled between June 2007 and April 2009[1]

	Sunitinib n=86	Placebo n=85
Age, yr		
Median (range)	56 (25–84)	57 (26–78)
≥65	22 (26)	23 (27)
Male / Female	42 / 44 (49 / 51)	40 / 45 (47 / 53)
Tumour functionality at baseline		
Nonfunctioning	42 (49)	44 (52)
Functioning	25 (29)	21 (25)
Unknown/missing	19 (22)	20 (24)
No. involved disease sites		
≤2	61 (71)	49 (58)
≥3	24 (28)	35 (41)
Not reported	1 (1)	1 (1)
Prior systemic therapy*	45 (52)	50 (59)
Anthracyclines	27 (31)	35 (41)
Streptozocin	24 (28)	28 (33)
Fluoropyrimidines	20 (23)	25 (29)

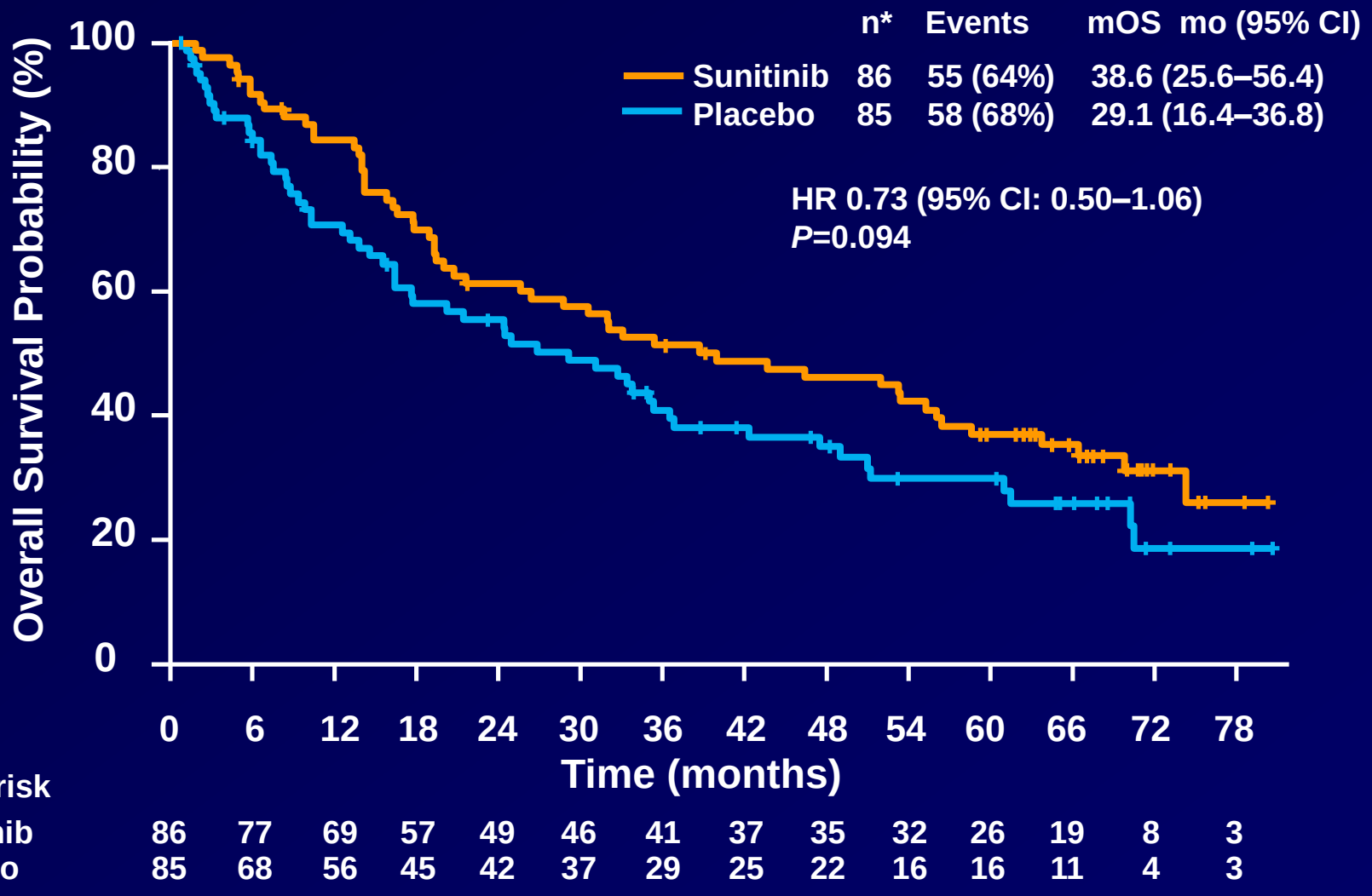
Values are n (%) unless otherwise stated.

* Excluding chemoembolization and regimens with somatostatin analog only

1. Raymond E, et al. N Engl J Med 2011;364:501-13.

ECOG=Eastern Cooperative Oncology Group

Kaplan-Meier OS at 5 Years After Study Closure



*** ITT population**

CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; mOS=median overall survival

Crossover in Placebo Arm

- As of April 2014 (5 years after study closure): 55 (64%) and 58 (68%) patients in the sunitinib and placebo arms, respectively, died
- Median duration of follow-up: 67.4 months
- 59 (69%) patients randomised to placebo crossed over to sunitinib
  - 38 patients crossed-over upon disease progression prior to study closure
  - 21 patients who had not progressed crossed-over after study closure
- Crossover occurred early*
  - 31% of patients crossed over by 3 months
  - 52% of patients crossed over by 6 months

* The proportion of patients who crossed over among those still alive and in the study

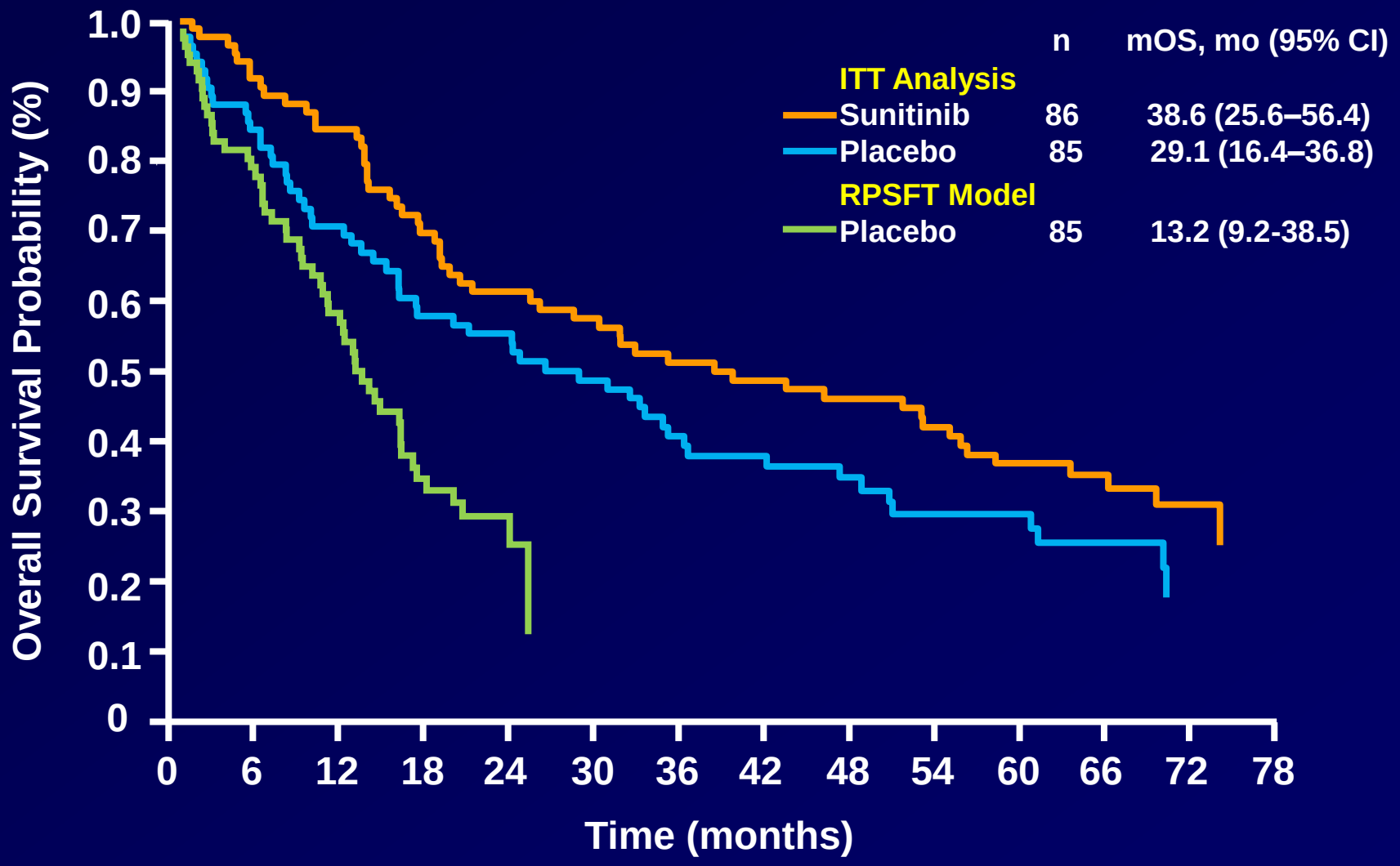
Analysis of OS with Adjustment for Crossover

OS Analysis/ Treatment Group	n	Deaths	Median, mo (Range)	HR* (95% CI)	*P*
ITT − no adjustment for crossover					
Sunitinib	86	55	38.6 (25.6-56.4)	0.73 (0.50–1.06)	0.094
Placebo	85	58	29.1 (16.4-36.8)		
Adjustment for crossover (placebo)					
RPSFT model	85	54†	13.2 (9.2-38.5)	0.34 (0.14–1.28‡)	0.094§
Additional OS analyses					
Censoring at crossover	85	21	16.3 (12.5-24.3)	0.40 (0.23–0.71)	0.001
Time-dependent Cox model	85	–	–	0.46 (0.27–0.78)	0.004

*** Sunitinib vs placebo.**
† Deaths occurring after crossover may become censored at an earlier time after adjustment for the impact of crossover in RPSFT.
‡ From 20,000 bootstrap samples.
§ The RPSFT method does not alter the P value obtained using the ITT method.

CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; OS=overall survival; RPSFT=rank-preserving structural failure time

OS at 5 Years After Study Closure With and Without Adjustment for Crossover



CI=confidence interval; ITT=intent-to-treat; mOS=median overall survival; RPSFT=rank-preserving structural failure time

Conclusions

- 5 years after closure of this pivotal phase III study, final OS based on the ITT population continued to favour sunitinib, with an improvement of 9.5 months in median OS vs placebo
- This OS result did not reach statistical significance due to the relatively small size of the study population and the effect of crossover on OS in the placebo arm
- Adjusting for the effect of crossover on OS revealed a much larger benefit than observed in ITT analyses

Acknowledgments

- This study was sponsored by Pfizer Inc
- We would like to thank all of the participating patients and their families, as well as the global network of investigators, research nurses, study coordinators, and operations staff
- The authors thank Rickard Sandin (Pfizer AB, Sollentuna, Sweden) and Irina Proskorovksy (Evidera St-Laurent, Canada) for their support with the crossover analyses
- Medical writing support was provided by Vardit Dror, PhD, of Engage Scientific Solutions, and was funded by Pfizer

How to select first line treatment for patients with PNET ?

SSA *versus* chemo *versus* targeted therapy

Treatment decisions: criteria for choosing treatment for advanced pNET

Criteria for choosing somatostatin analogues	• Functional tumours • Low-volume disease • G1 and subset of G2 (Ki-67 <10%) • Non-progressive disease • **Aim is to delay time to disease progression**
Criteria for choosing targeted therapies	• Moderate–low volume disease • G1/G2 tumours (Ki-67 <20%) • Moderate-low rate of disease progression • **Aim is to delay time to disease progression**
Criteria for choosing chemotherapy	• Bulky disease/high volume disease • More rapid disease progression • G2/G3 tumours (occasionally G1 tumours) • **Response required**

Systemic therapy of advanced pNET: the patient continuum

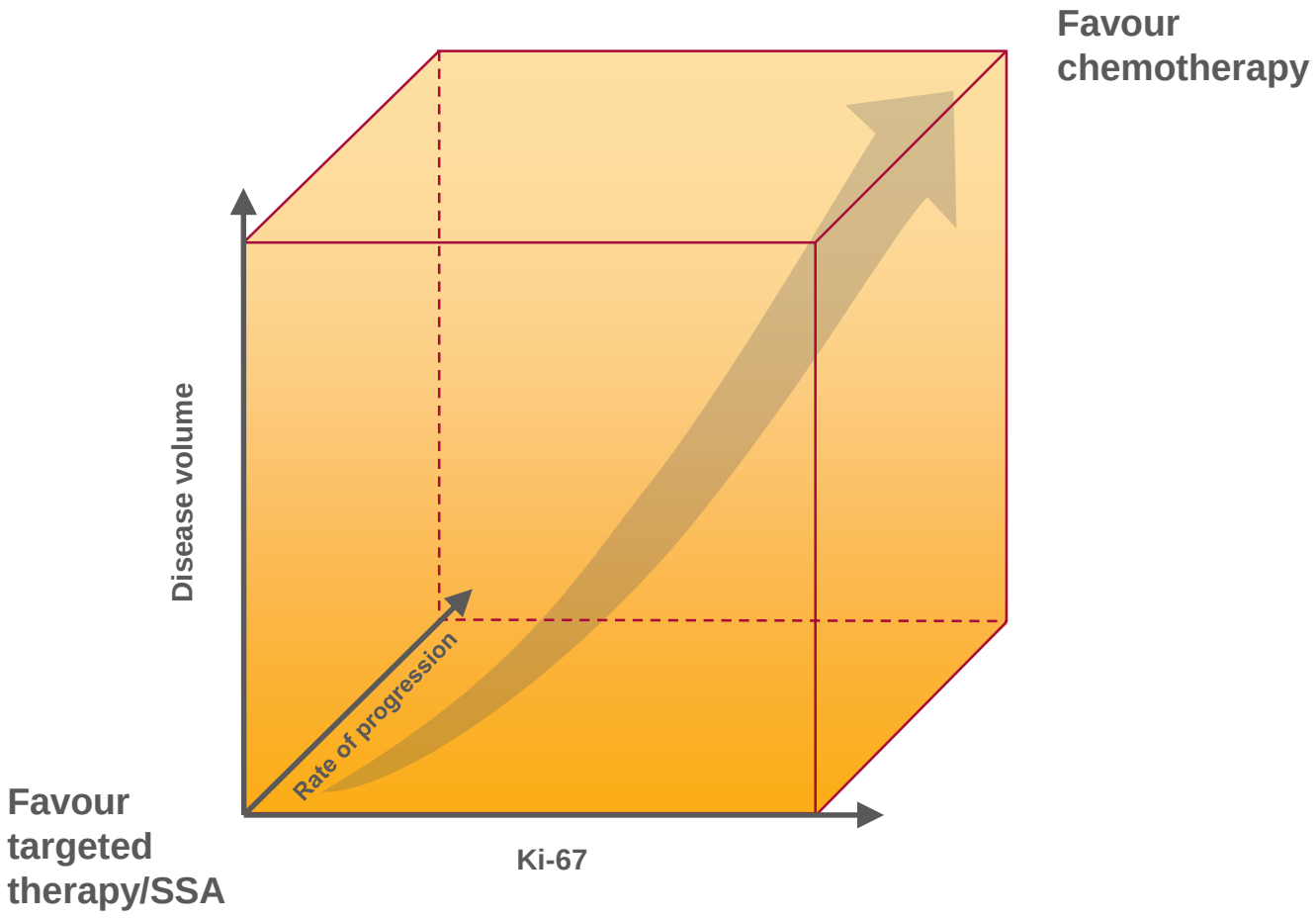


Figure adapted from Lamarca A *et al. TJOP* 2014;2:15–25
Diez M *et al. Ann Gastroenterol* 2013;26(1):29-36

Systemic therapy of advanced pNET: the patient continuum

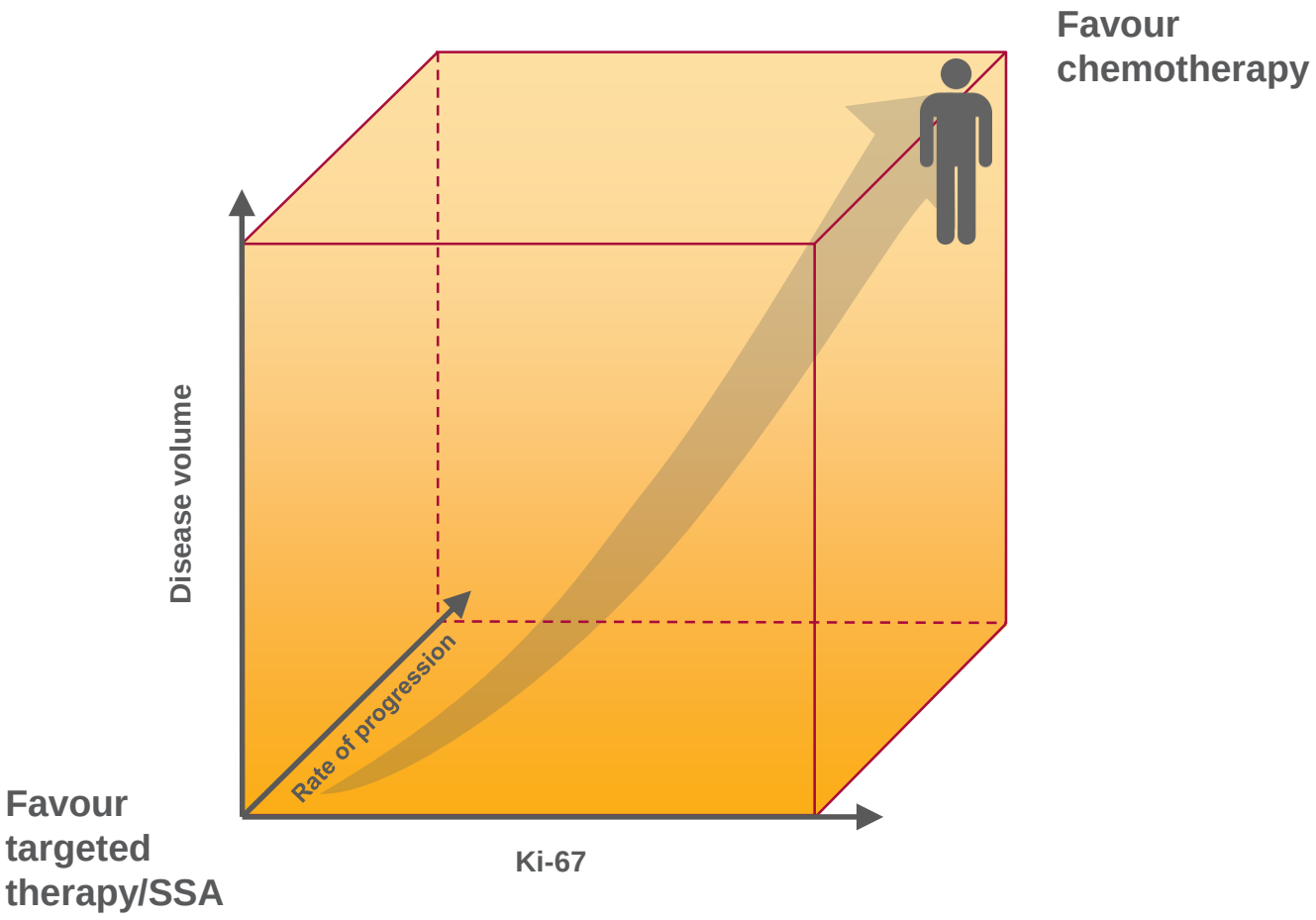


Figure adapted from Lamarca A *et al. TJOP* 2014;2:15–25
Diez M *et al. Ann Gastroenterol* 2013;26(1):29-36

Systemic therapy of advanced pNET: the patient continuum

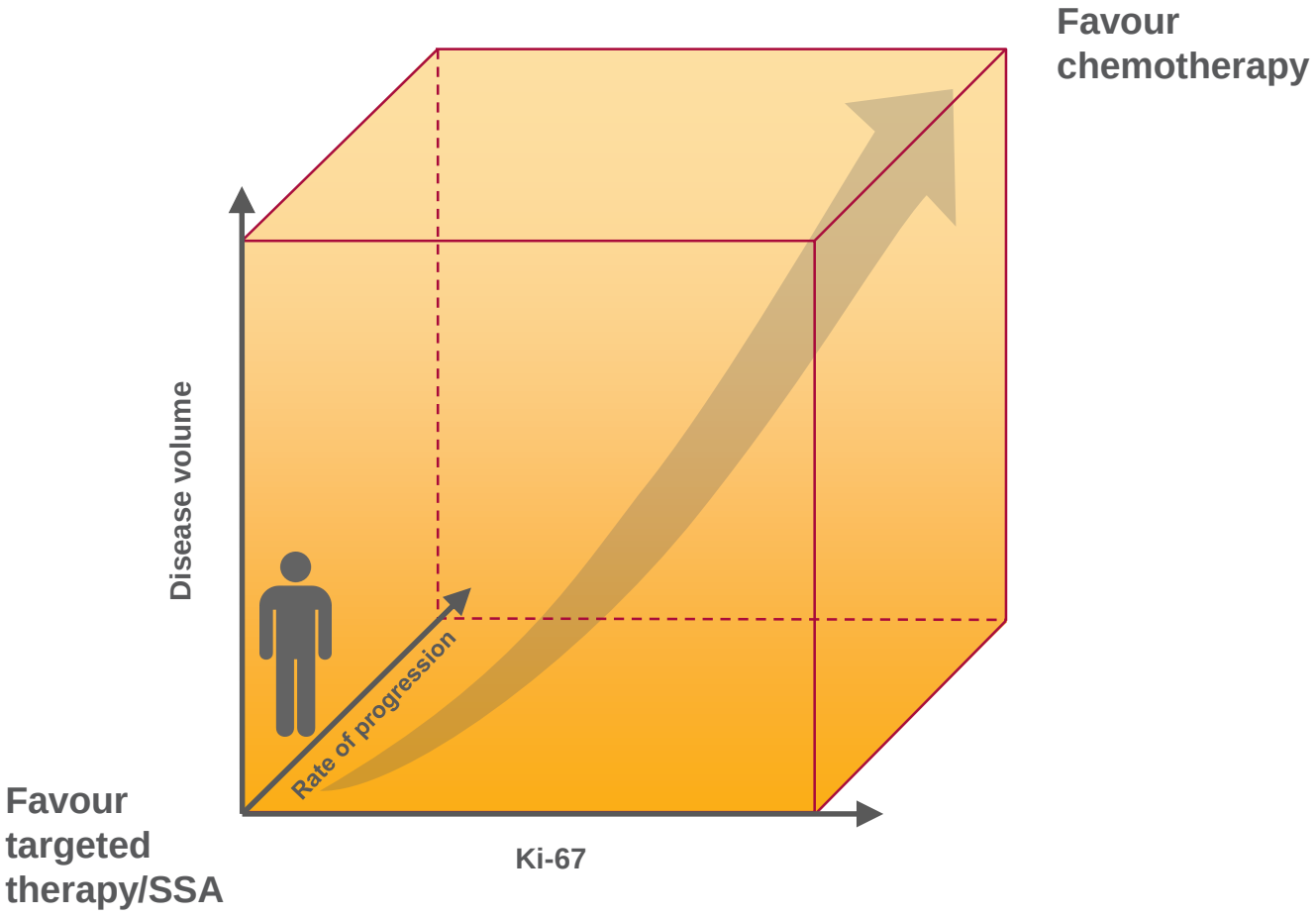


Figure adapted from Lamarca A *et al. TJOP* 2014;2:15–25
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Systemic therapy of advanced pNET: the patient continuum

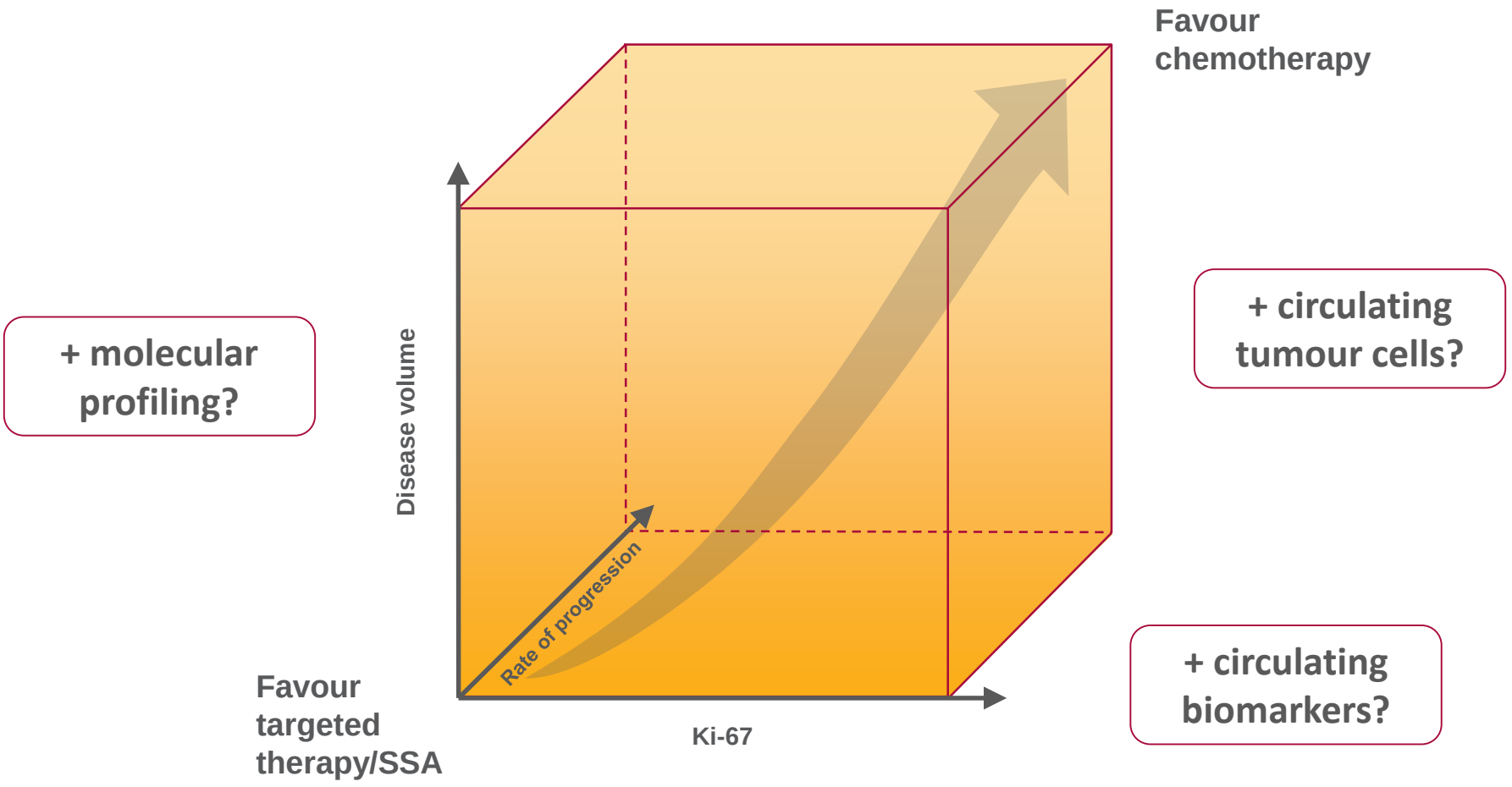
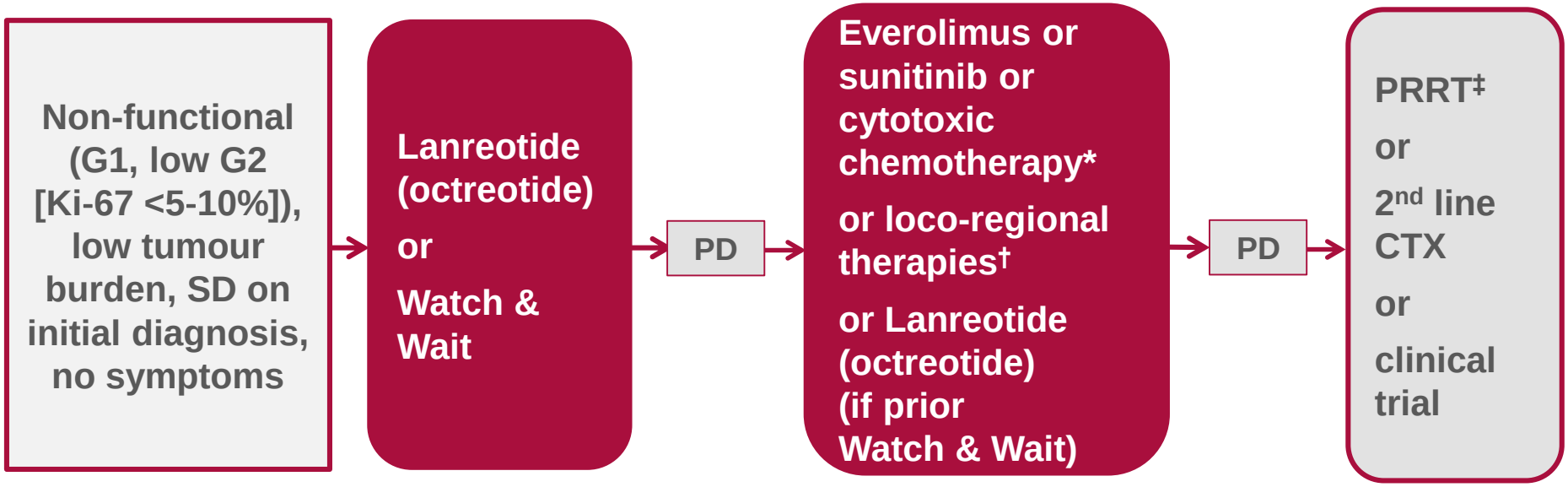


Figure adapted from Lamarca A *et al. TJOP* 2014;2:15–25
Diez M *et al. Ann Gastroenterol* 2013;26(1):29-36

How to select subsequent treatments for patients with PNET ?

Sequencing treatment to delay progression and improve survival

ENETS guidelines (2016): non-functional – advanced unresectable pNET



*Recommended chemotherapy includes STZ/5-FU or STZ/ doxorubicin; TEM/CAP is an alternative regimen if STZ- based chemotherapy is not available; †Loco-regional therapies are contraindicated after Whipple procedure; ‡If somatostatin receptor imaging is positive

CTX, chemotherapy; PD, progressive disease; PRRT, peptide receptor radionuclide therapy
Figure adapted from Figure 3 in Pavel M et *al. ENETS guidelines. Neuroendocrinology* 2016 [Epub ahead of print]

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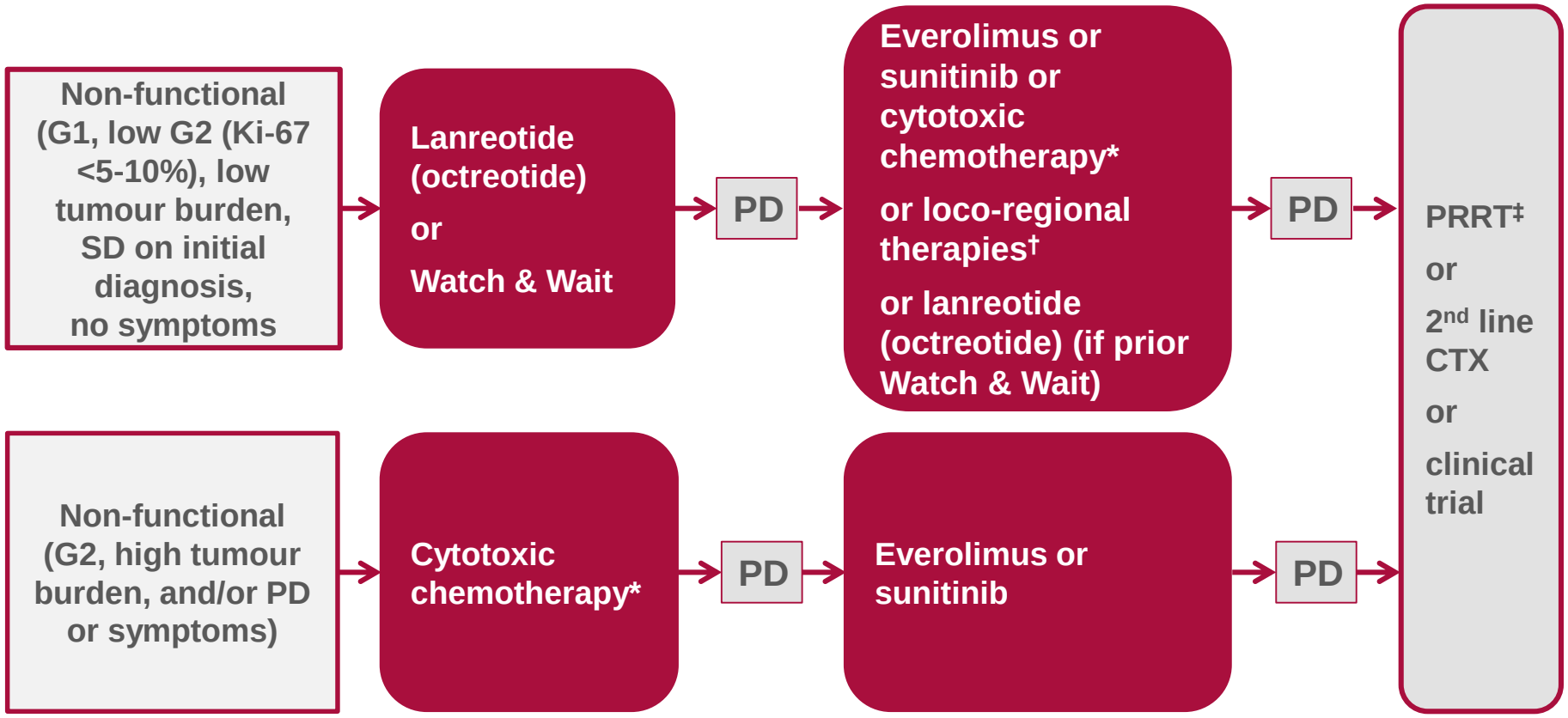

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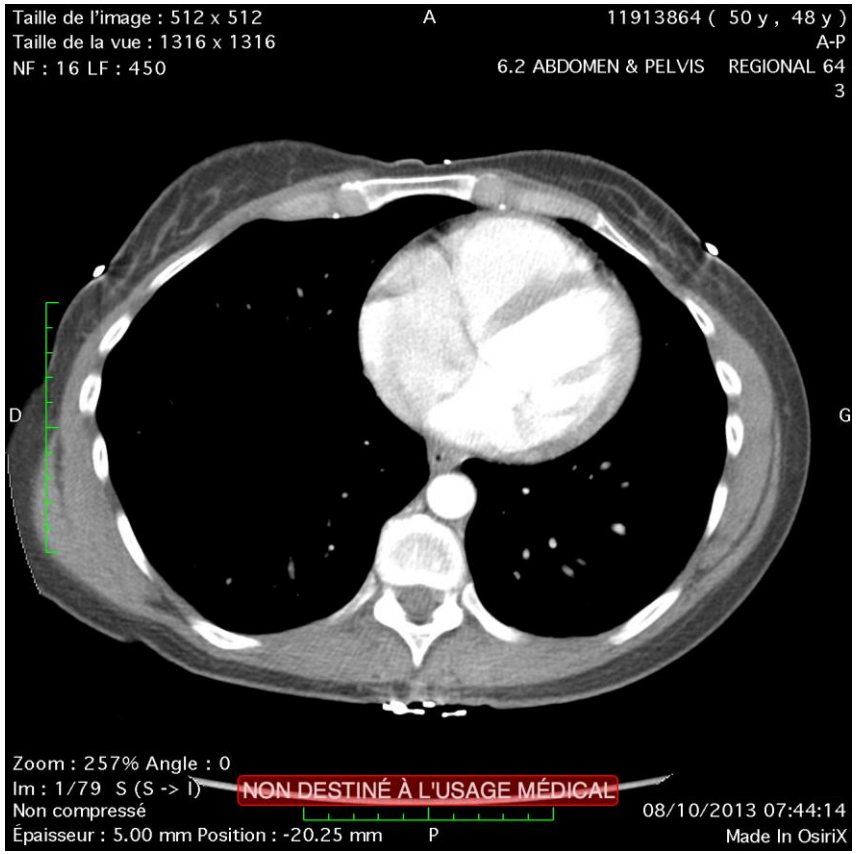
Case report analyses

How to improve survival by delaying progression and adjusting dosing in a patient with advanced PNET

Patient presentation at first admission

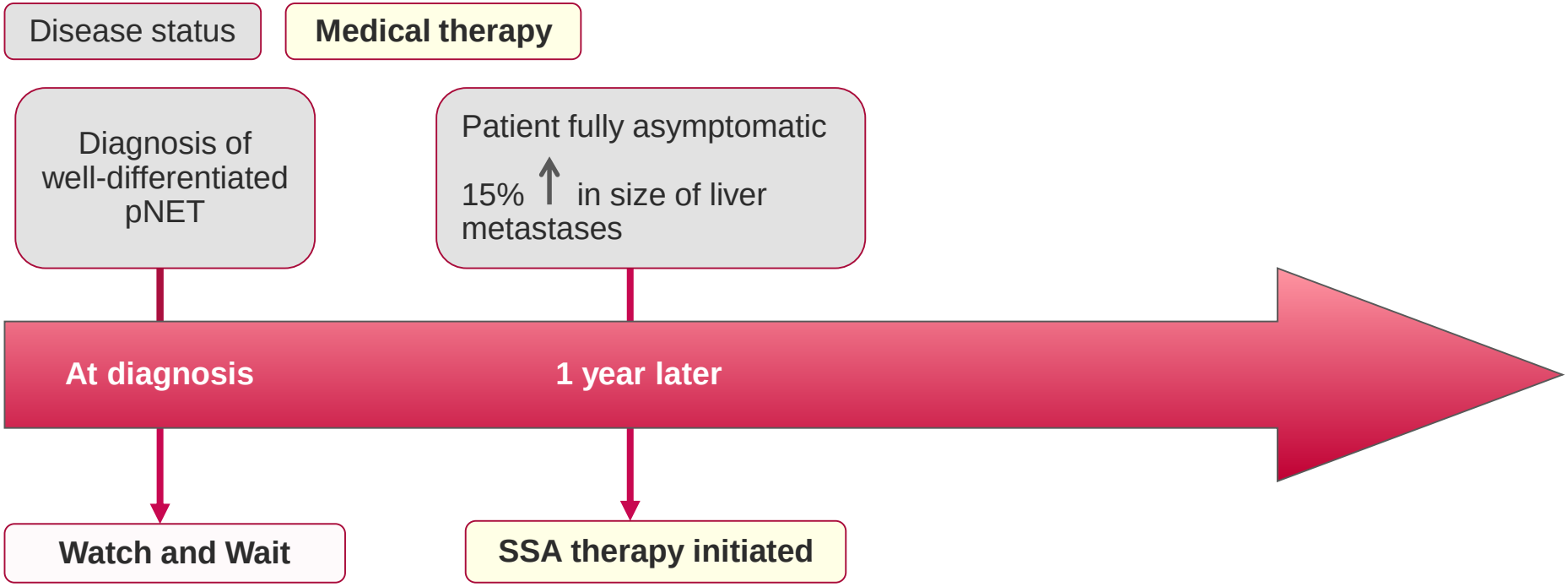
44-year-old female with well-differentiated advanced pNET (Ki-67 4%)

- Presence of multiple liver nodules and a small pancreatic tail nodule
- Positive octreoscan in the liver and the pancreas
- Molecular evaluation of the tumour revealed potential sensitivity to VEGF/VEGFR inhibitors, tubuline inhibitors, platinum and topoisomerase I



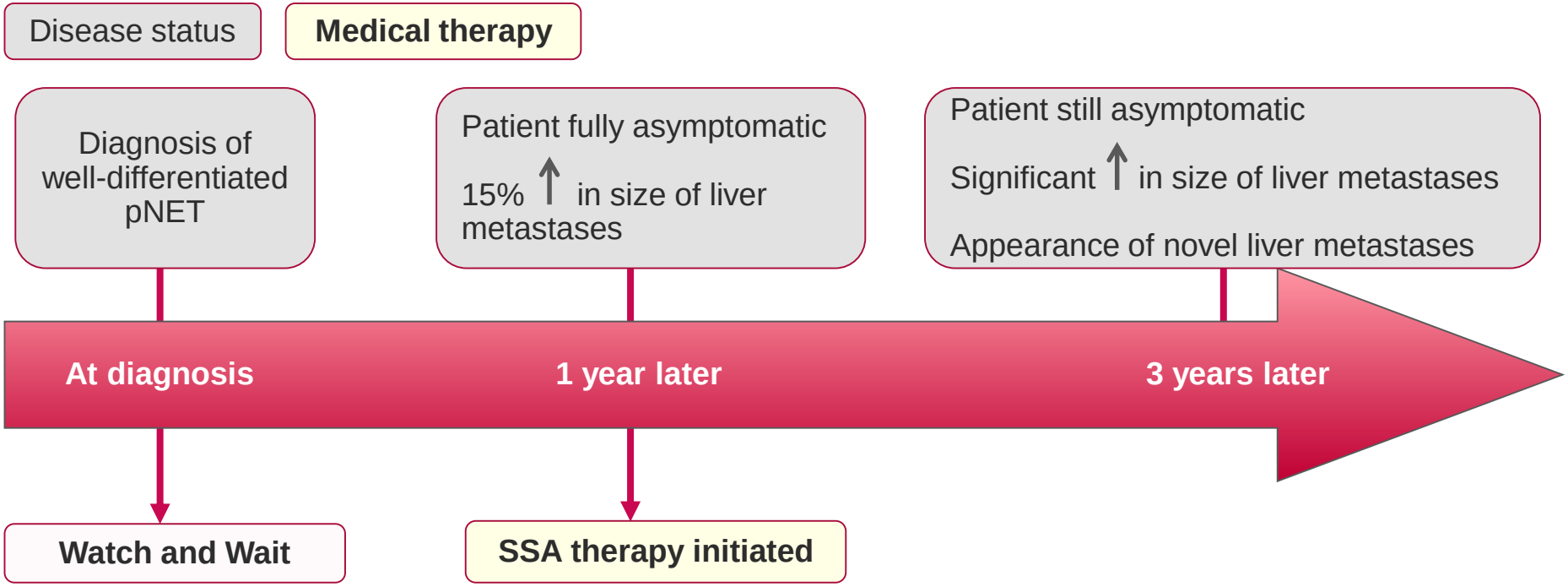
Treatment with SSA

44-year-old female with well-differentiated advanced pNET (Ki-67 4%)

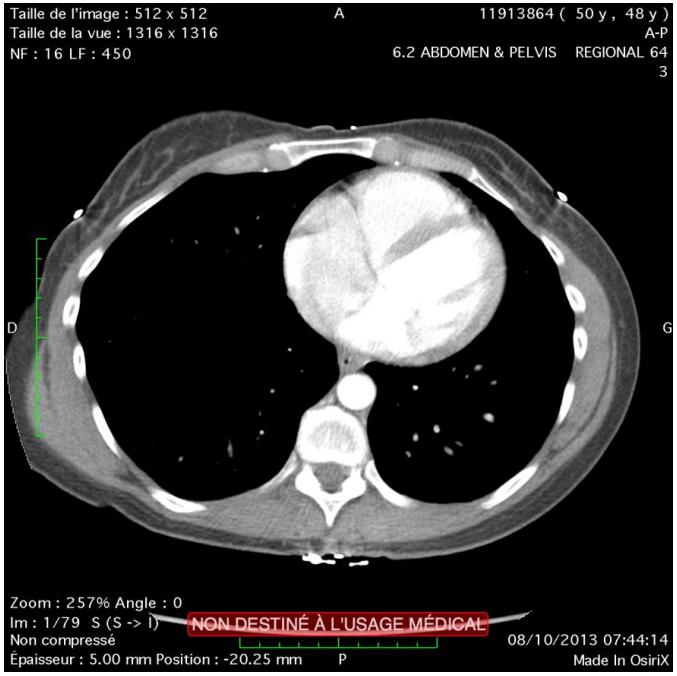


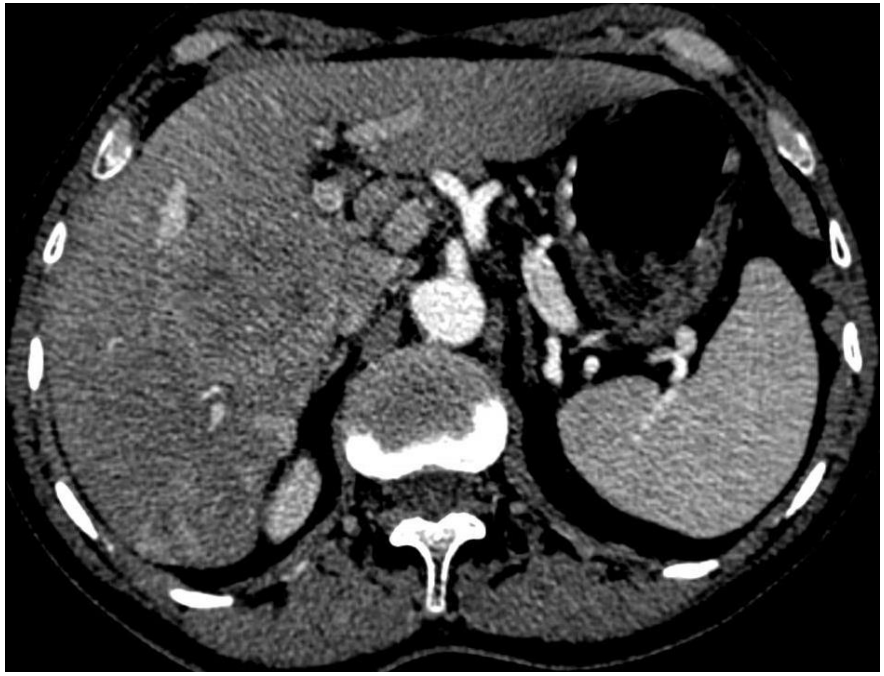
Treatment with SSA

44-year-old female with well-differentiated advanced pNET (Ki-67 4%)



Disease progression



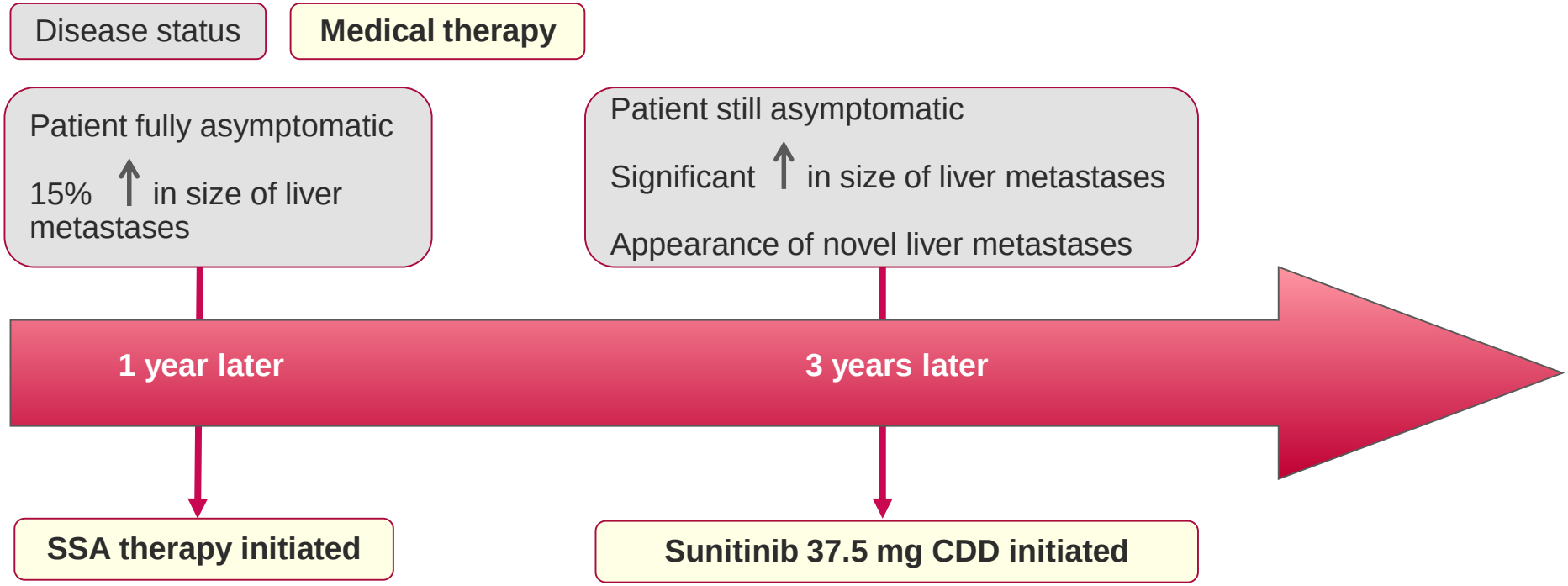


At diagnosis

3 years later

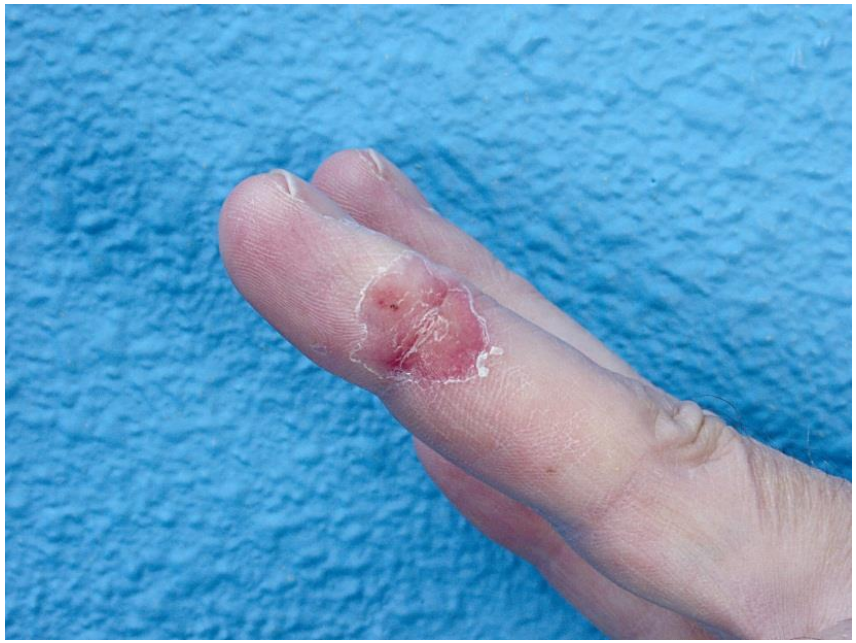
Treatment with sunitinib

44-year-old female with well-differentiated advanced pNET (Ki-67 4%)



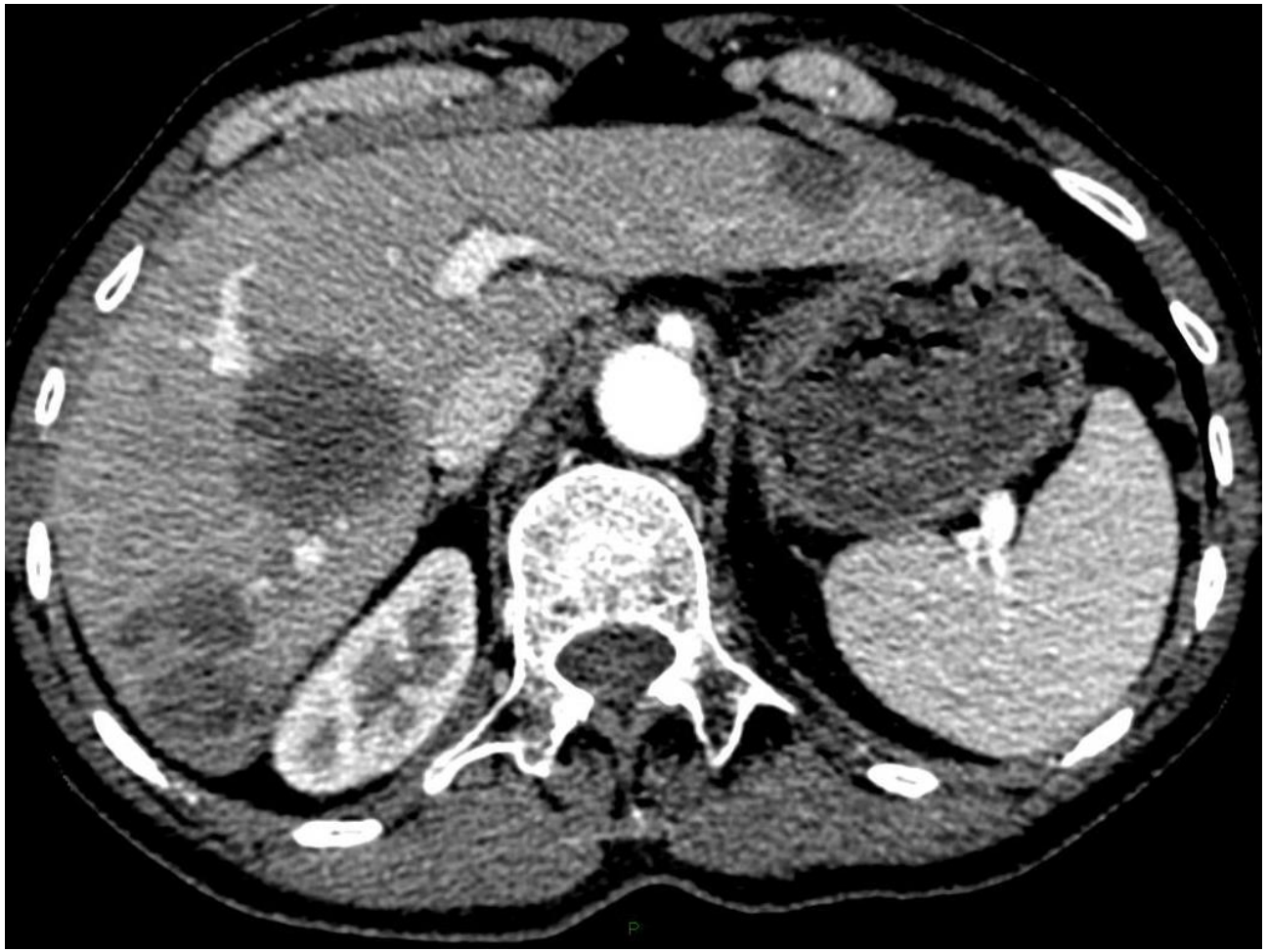
Treatment with sunitinib

- Sunitinib initiated at 37.5 mg CDD
  - No changes in blood pressure
  - No diarrhoea
  - Appearance of liver pain
  - Dryness of the skin and appearance of hand–foot syndrome

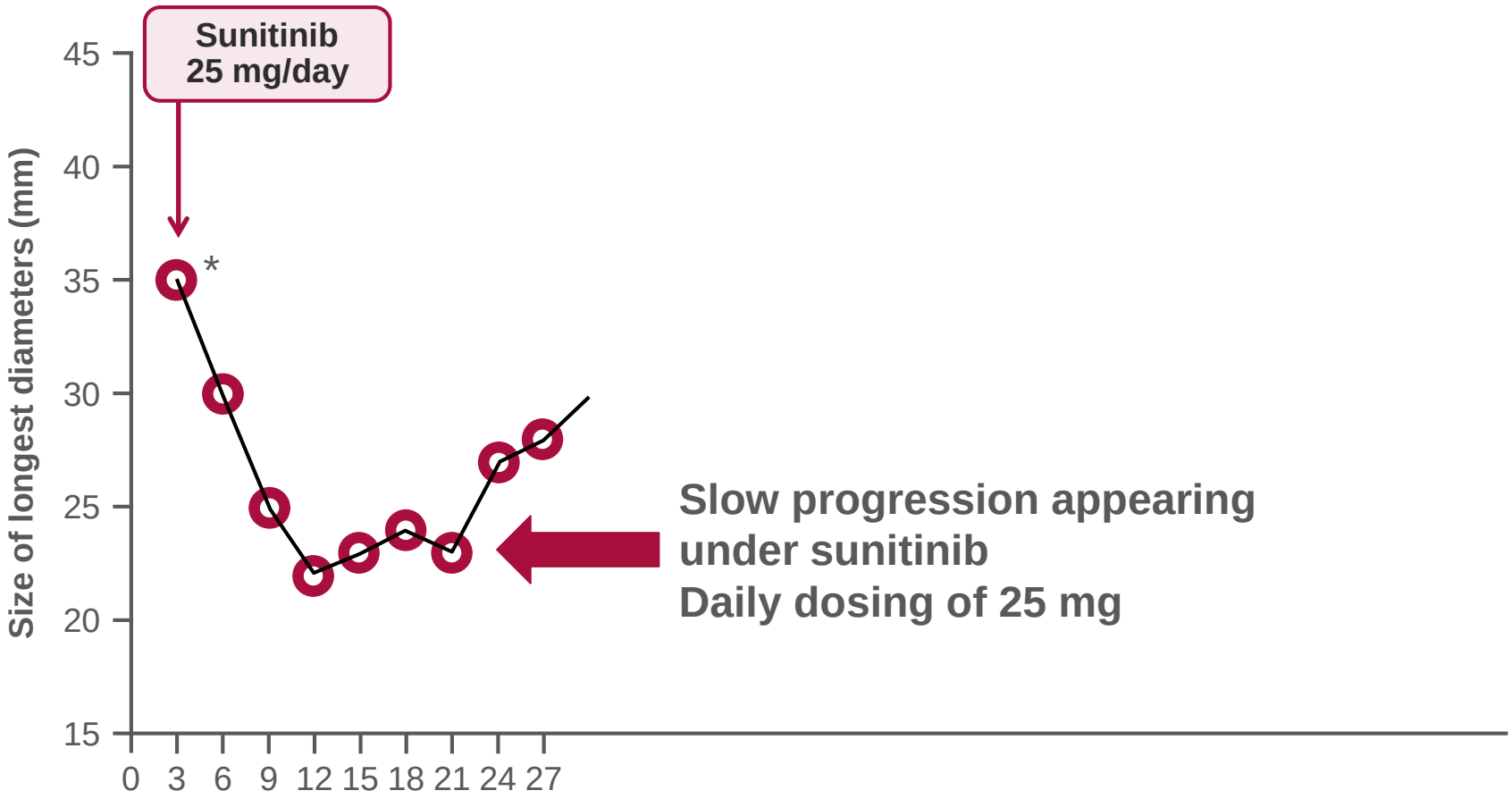


CDD, continuous daily dosing

CT scan (2 months) after sunitinib initiation

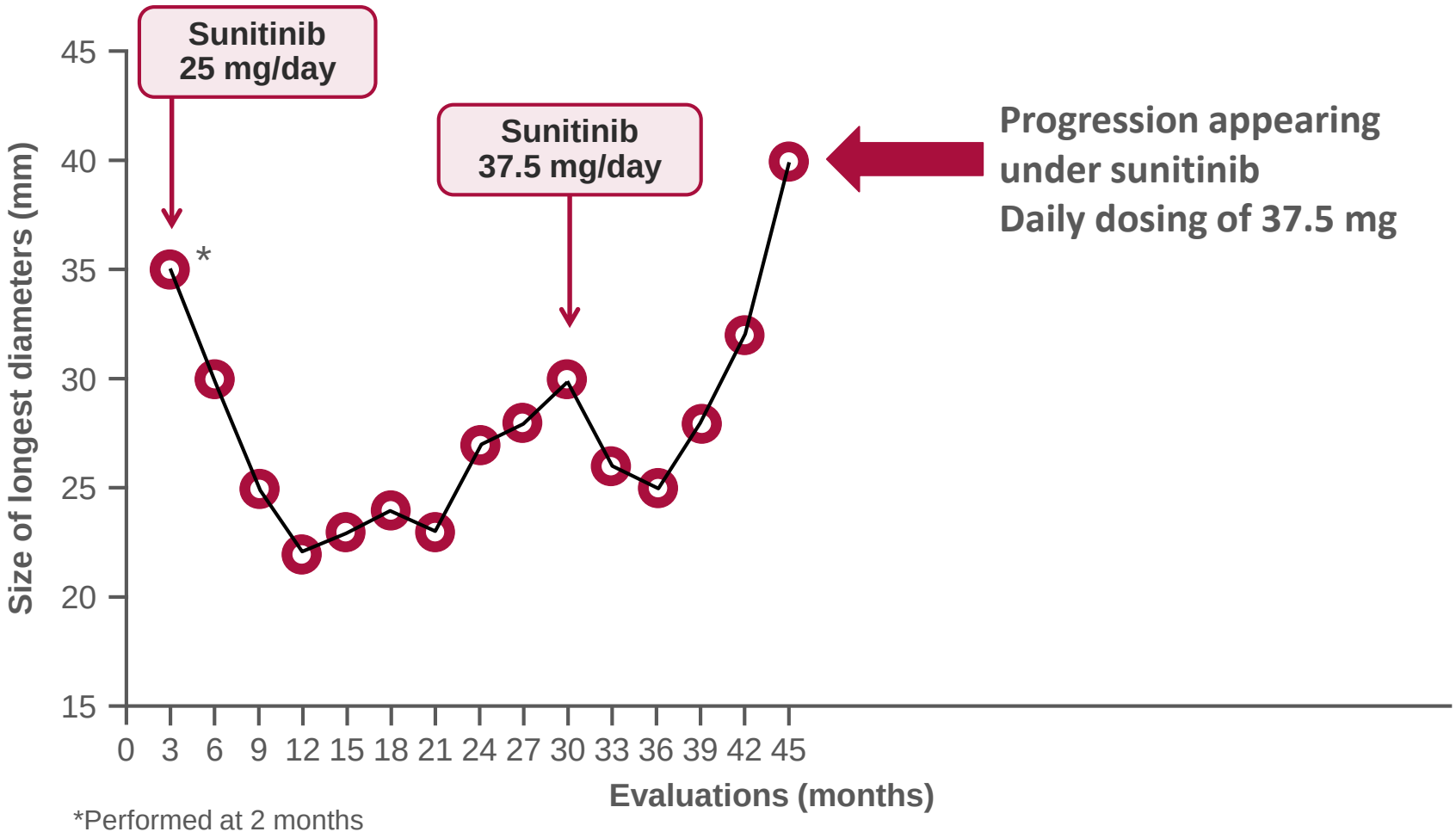


Sunitinib dose was reduced to 25 mg CDD



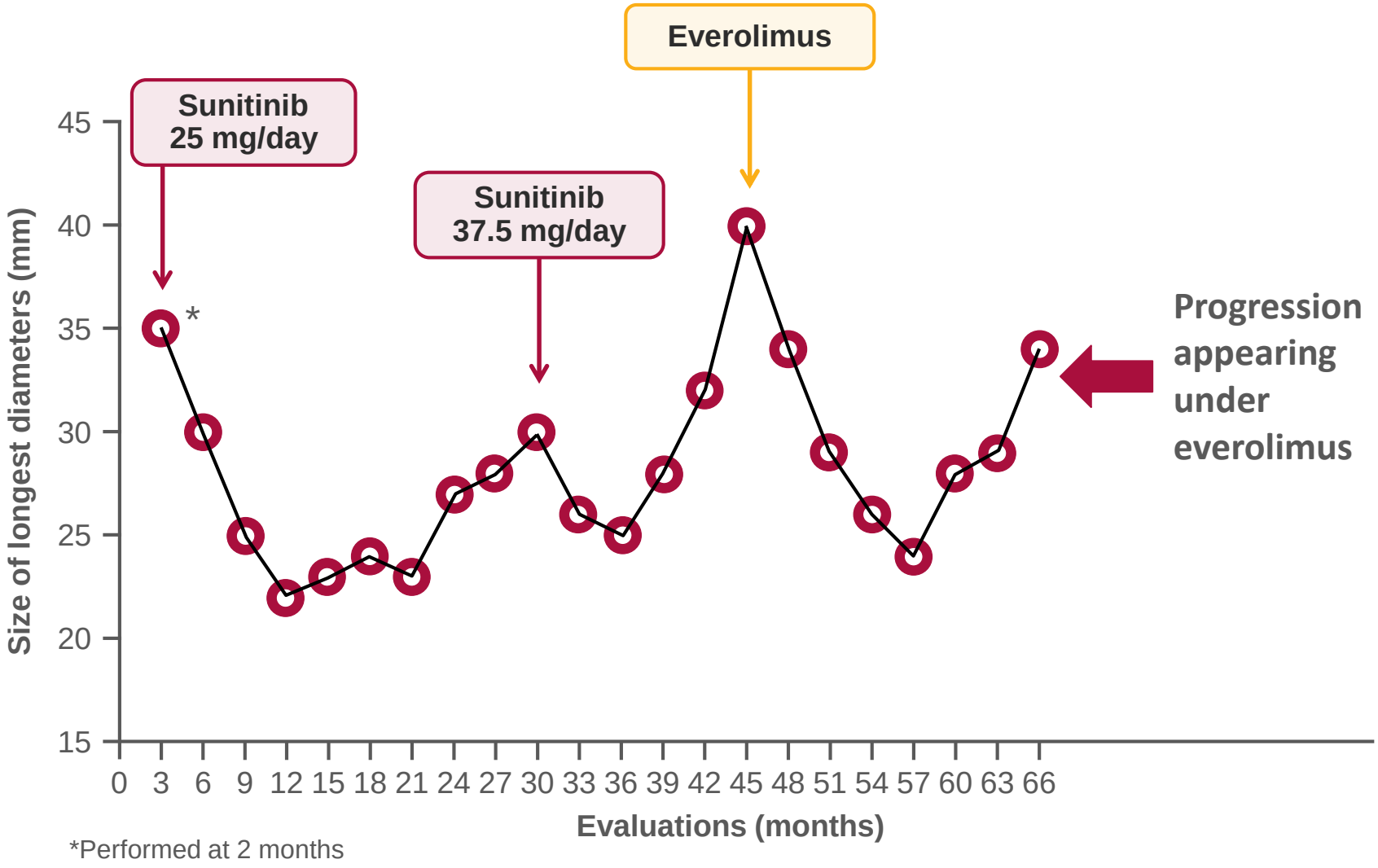
*Performed at 2 months

Dose of sunitinib was increased to 37.5 mg/day



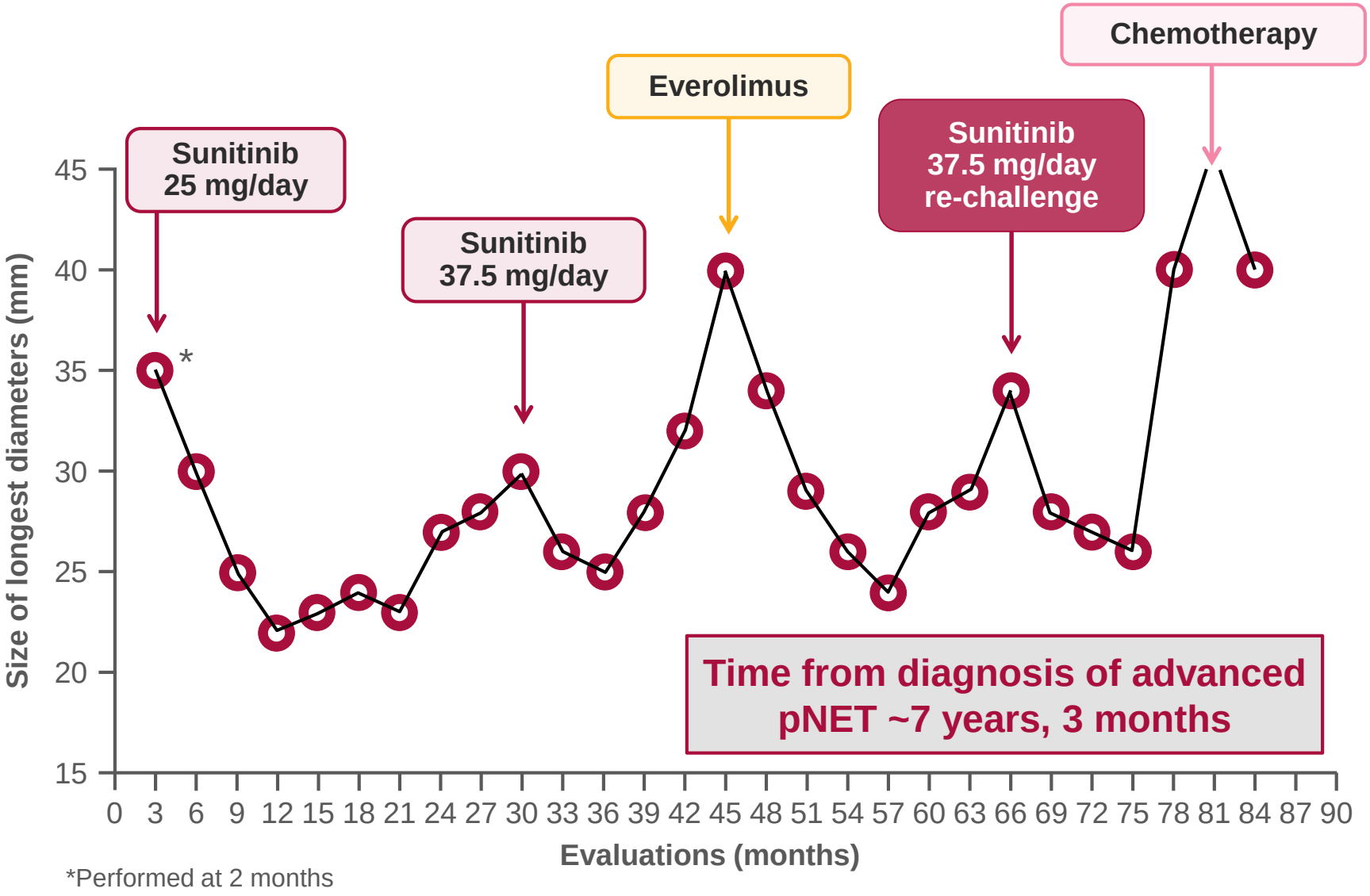
*Performed at 2 months

Everolimus was initiated



*Performed at 2 months

Sunitinib was reintroduced



*Performed at 2 months

Conclusions

- Targeted therapies stand as treatment options with strong evidence-based data compared to chemotherapy and SSA
- Doses of targeted therapies can be adjusted in responding patients to ensure the maintenance of response
- Switch from one targeted therapy to another may allow to sustain control disease progression
- Re-challenge with sunitinib is feasible although the duration of response is likely to be lower