Optimisation approach with anti-targeted therapies in NETs

Optimización del abordaje con fármacos antidiana

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Disclosures

Travel and educational support from Ipsen, Pfizer, Bayer, AAA, SirtEx, Novartis and Delcath.

Speaker honoraria from Merck, Pfizer, Ipsen and Incyte.

Advisory honoraria from Nutricia and EISAI.

Member of the Knowledge Network and NETConnect Initiatives funded by Ipsen.

Right treatment, right patient

Optimising dose and managing toxicity

Assessing response

Right treatment, right patient

Optimising dose and managing toxicity

Assessing response

Appropriate treatment choice

Treatment optimisation starts with patient assessment and appropriate treatment choice

Multidisciplinary approach

Baseline assessment

Disease status

- Symptom assessment
- Clinical assessment
- Tumour tissue
- Biochemistry
- CT / MR scan
- ^{68}Ga PET / octreotide scan

To establish…

- Primary site
- Grade
- Stage
- Functional assessment
- Liver predominance
- Progression

Treatment options

- Surgery
- Biological therapy
- Targeted therapy
- Peptide receptor radionuclide therapy (PRRT)
- Chemotherapy
- Loco-regional therapy

CT, computerised tomography; MR, magnetic resonance; PET, positron emission tomography.

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WHO classification update 2017: G3-NET

Classification relies on grade (Ki-67 / mitotic index) and tumour morphology

- NEN: neuroendocrine neoplasms (NET + NEC; regardless of morphology / grade)
- NET: neuroendocrine tumours (well-differentiated morphology)
- NEC: neuroendocrine carcinoma (poorly-differentiated morphology)

Classification / grade	Ki-67 proliferation index (%)	Mitotic index
Well-differentiated NENs		
NET G1	<3	<2
NET G2	3–20	2–20
NET G3	>20	>20
Poorly-differentiated NENs		
NEC G3	>20	>20

Lloyd RV, *et al*. WHO Classification of Tumours of Neuroendocrine Organs 4th Ed 2017

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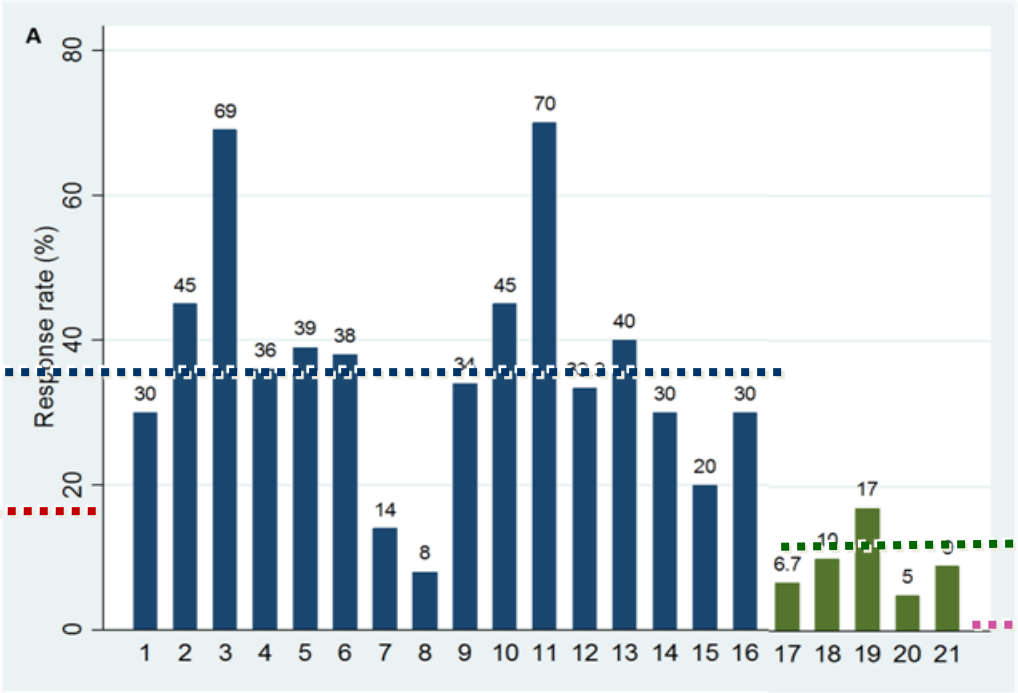
Understanding the effect of different systemic treatments

Radiological response rate



Chemotherapy(20–50%)

PRRT (18%)
May be higher in PanNETs (58%)

Targeted (5-10%)
Higher with Lenvatinib?

SSA (0%)

SSA: somatostatin analogue; PRRT: Peptide Receptor Radionuclide Therapy; Adapted from Lamarca A, *et al.* J Oncopathol 2014;; Caplin ME, *et al.* N Engl Med 2014; Strosberg J, *et al.* N Engl J Med 2017; Ramage J, *et al.* Semin Oncol. 2018.

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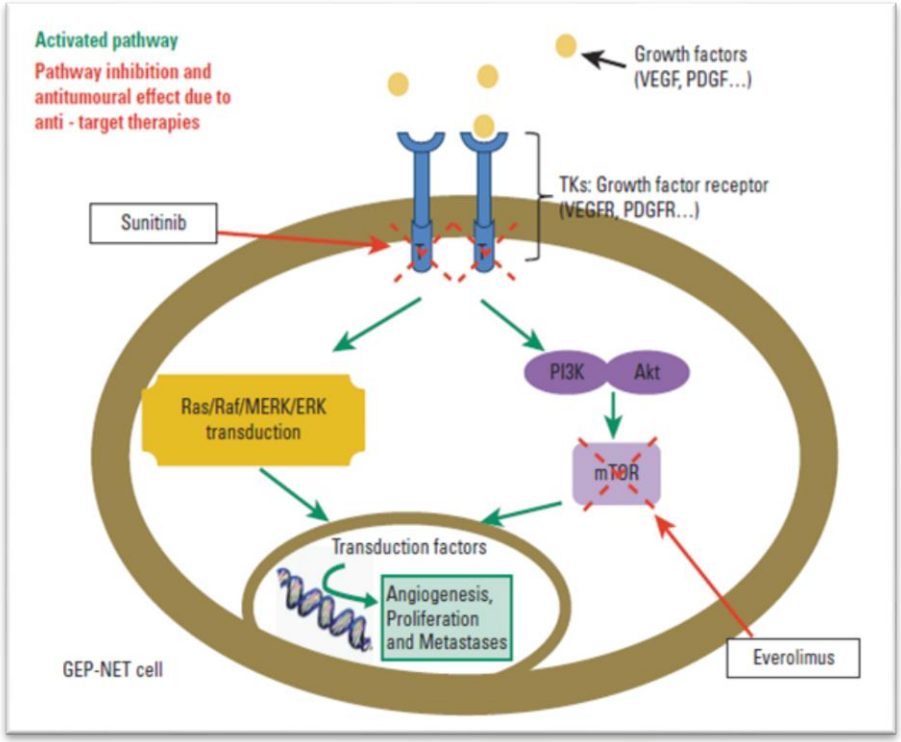
Current ENETS guidelines – Targeted therapies

Potential pathways to target

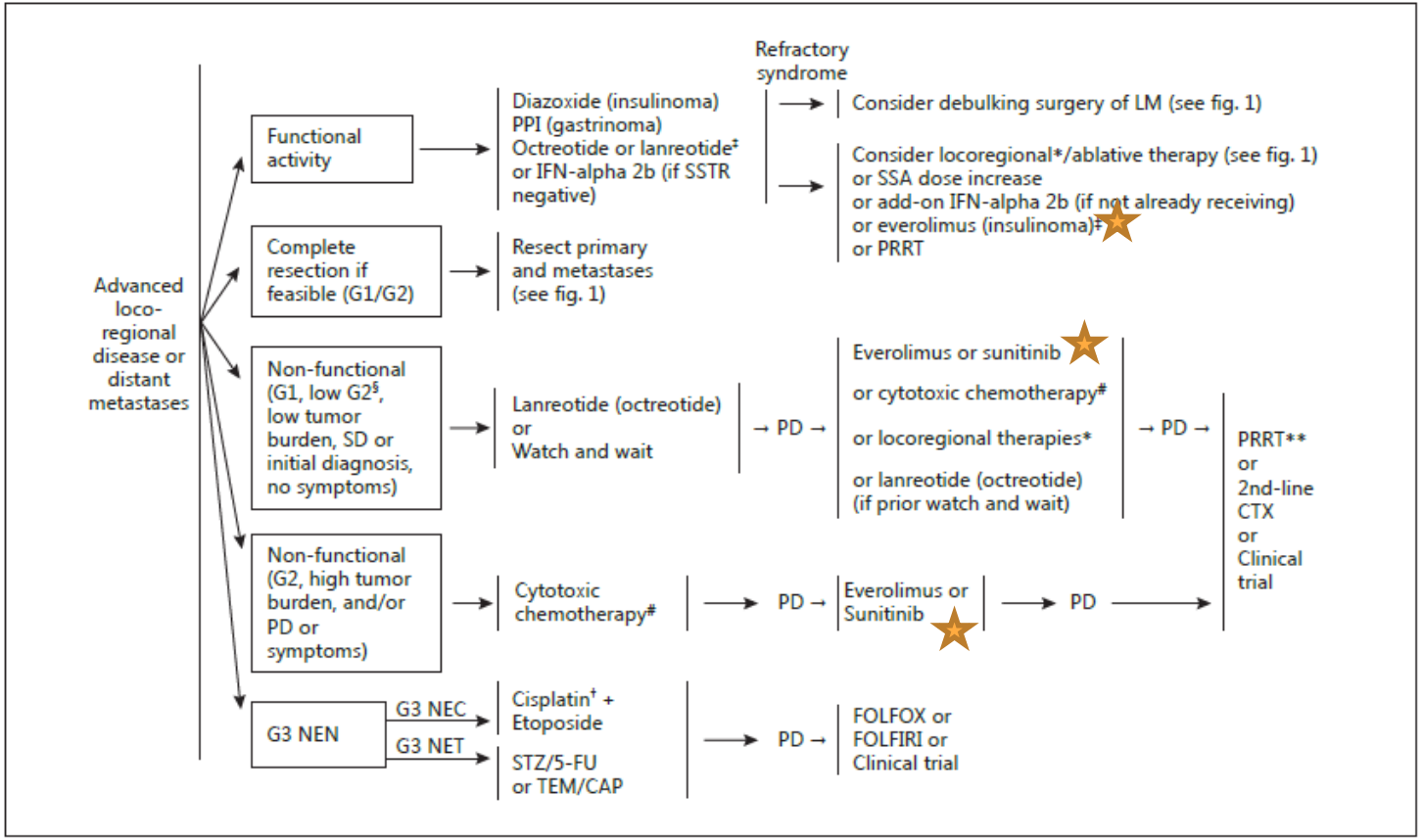
- Two main pathways to target:
  - mTOR (everolimus)
  - Angiogenesis (sunitinib)
- Others under development
  - Surufatinib
  - Lenvatinib
  - Axitinib
  - Cabozantinib

Molecular biology in NETs



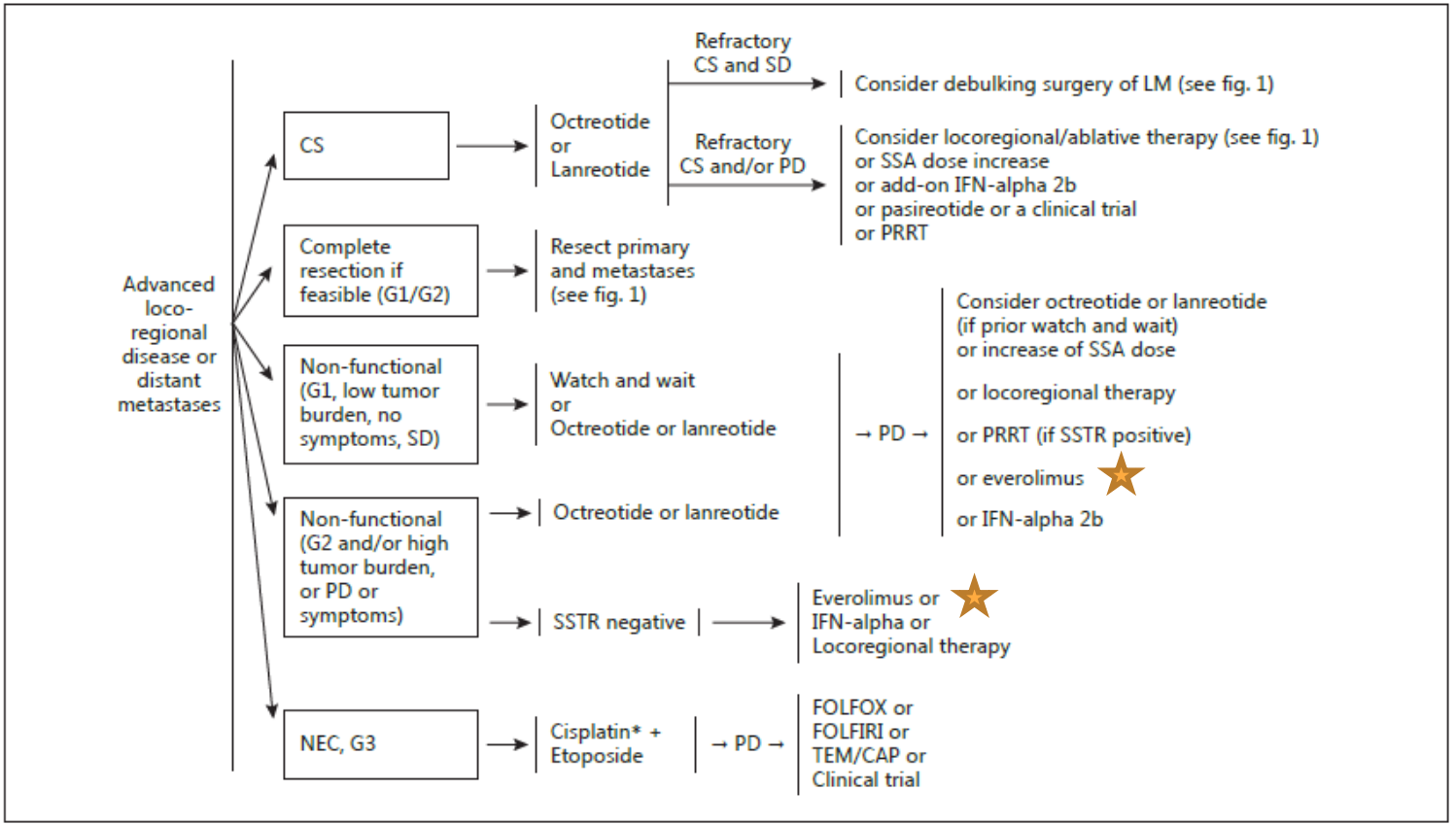
Adapted from Lamarca A, *et al.* J Oncopathol 2014

Current ENETS guidelines - PanNETs



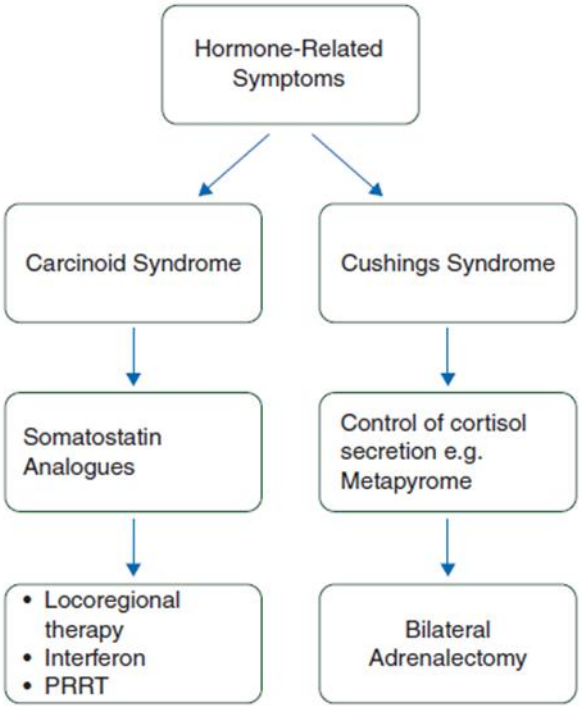
Pavel, Neuroendocrinology 2016

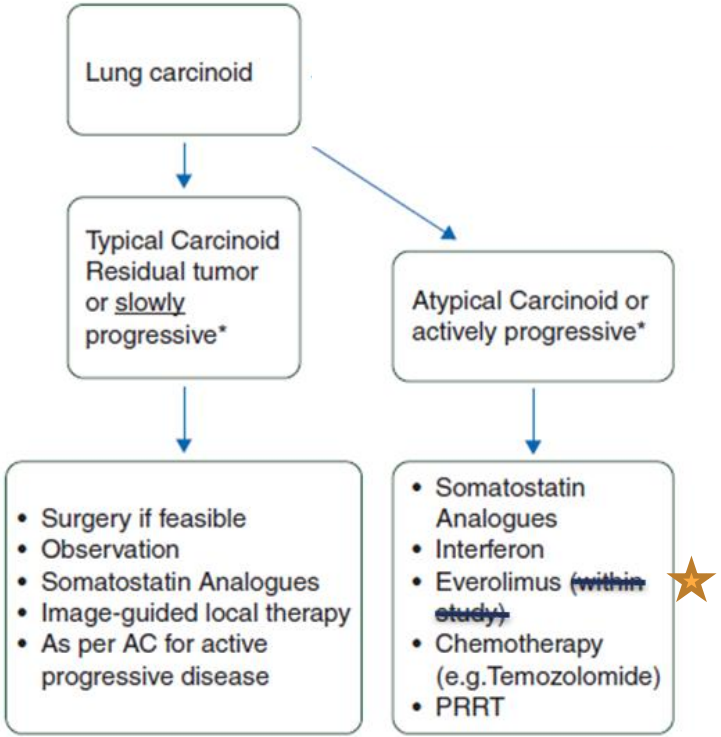
Current ENETS guidelines - siNETs



Pavel, Neuroendocrinology 2016

Current ENETS guidelines - LungNETs



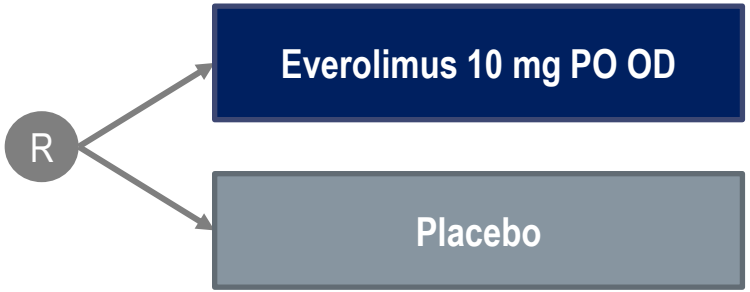


Caplin, Annals of Oncol 2014

Current ENETS guidelines – Targeted therapies

Everolimus	+/–	G1/G2	lung	atypical carcinoid and/or SSTR negative
			pancreas	insulinoma or contraindication for CTX
			midgut	if SSTR negative
Sunitinib	+/–	G1/G2	pancreas	contraindication for CTX

- G1 or G2 metastatic or locally advanced well diff, functioning or non-functioning Lung/siNETs
- Progressed within previous therapy
- Randomisation 2:1 (n=302 patients)



Primary endpoint: Progression-free survival (central radiology review)

Pavel, Neuroendocrinology 2016; Yao, Lancet 2015

Current ENETS guidelines – Targeted therapies

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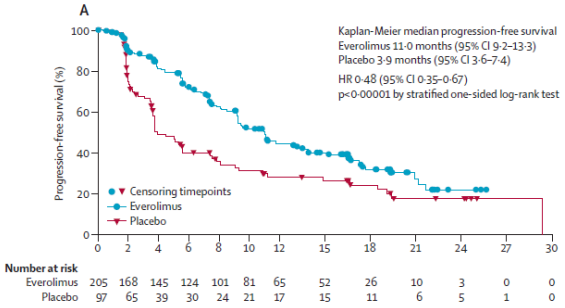

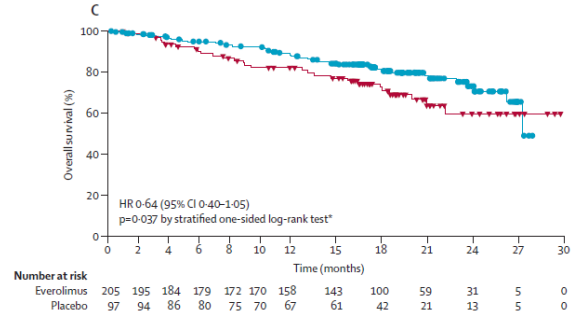

	Everolimus (n=205)	Placebo (n=97)	Difference	Hazard ratio* for disease progression or death with everolimus (95% CI)	p value†
Central radiology review					
Progression-free survival events‡	113 (55%)	65 (67%)	..	..	..
Number censored	92 (45%)	32 (33%)	..	..	..
Median progression-free survival, months	11·0 (9·2–13·3)	3·9 (3·6–7·4)	7·1	0·48 (0·35–0·67)	<0·00001
Local radiology review					
Progression-free survival events‡	98 (48%)	70 (72%)	..	..	..
Number censored	107 (52%)	27 (28%)	..	..	..
Median progression-free survival, months	14·0 (11·2–17·7)	5·5 (3·7–7·4)	8·5	0·39 (0·28–0·54)	<0·00001

Data are n (%) or median (95% CI) unless otherwise indicated. *Hazard ratio was obtained from the stratified Cox model. †p value was obtained from the one-sided stratified log-rank test. ‡Progression-free survival events include disease progression and death.

Table 2: **Progression-free survival (full analysis set)**

Pavel, Neuroendocrinology 2016; Yao, Lancet 2015

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Current ENETS guidelines – Targeted therapies

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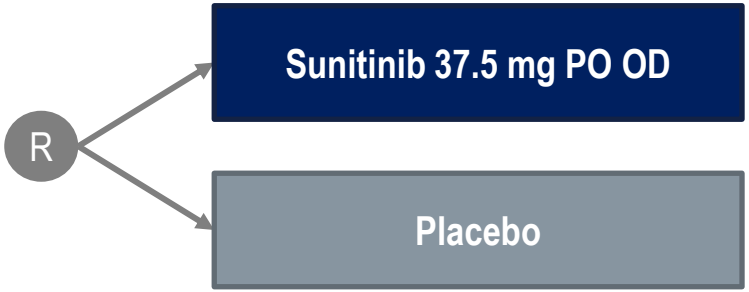
Sunitinib	+/–	G1/G2	pancreas	contraindication for CTX

- G1 or G2 metastatic or locally advanced well diff, functioning or non-functioning PanNETs
- Progressed within previous 12 m
- Randomisation 1:1 (n=171 patients randomised*)



Primary endpoint: Progression-free survival

*Enrolment completed in the first interim analysis (therefor recruitment not fully completed)

Pavel, Neuroendocrinology 2016; Raymond E, et al. N Engl J Med 2011

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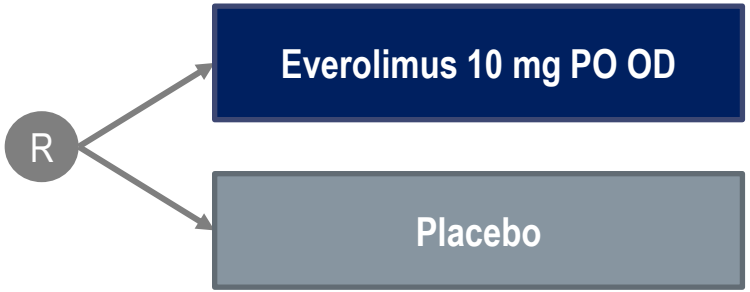
- G1 or G2 metastatic or locally advanced well diff, functioning or non-functioning PanNETs
- Progressed within previous 12 m
- Randomisation 1:1 (n=410 patients)



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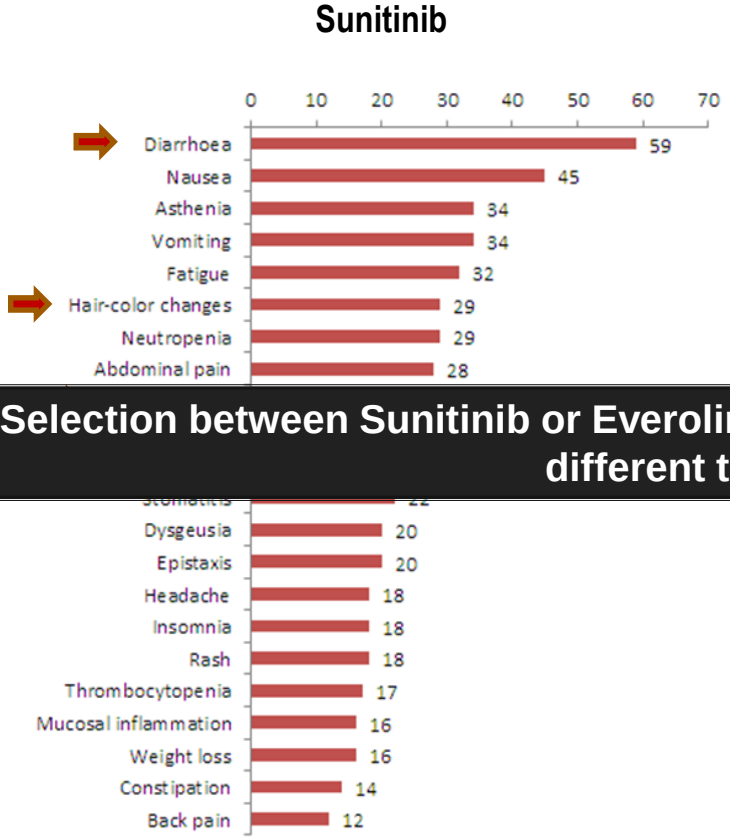
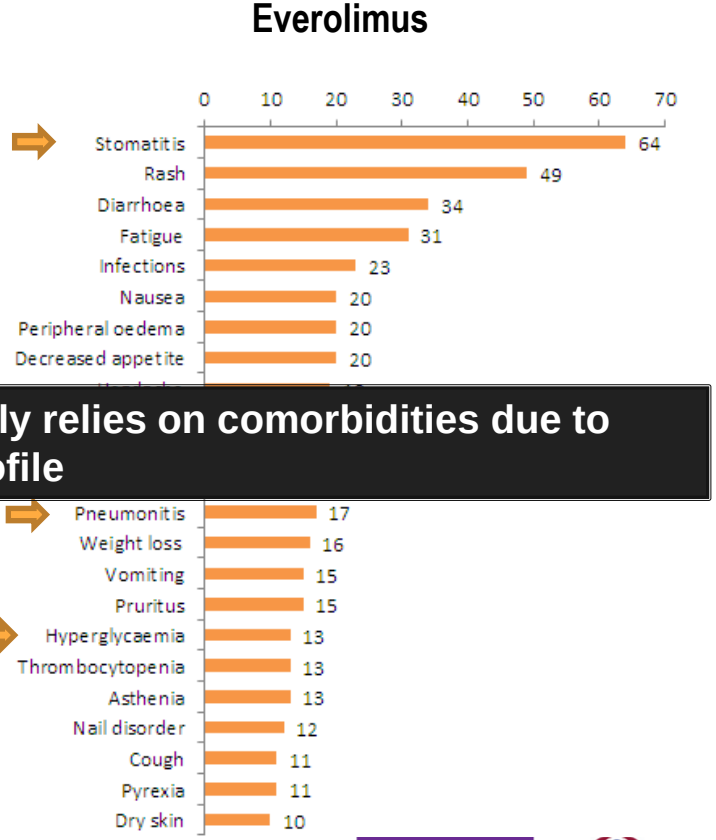
	Sunitinib 37.5 mg once daily (Phase 3 *vs.* placebo)	Everolimus 10 mg once daily (Phase 3 *vs.* placebo)
Population of patients	Unresectable or metastatic, well- or moderately-differentiated **PanNETs**	Unresectable or metastatic, well- or moderately-differentiated **PanNETs**
Documented disease progression at study entry	Yes	Yes
Objective response rate	9.3% vs. 0%	5% vs. 2%
Median PFS (experiment *vs.* placebo) (months)	11.4 vs. 5.5 HR 0.42 (95% CI 0.26, 0.66); p<0.001.	11.0 vs. 4.6 HR 0.35 (95% CI 0.27, 0.45); p<0.001.
Comments	AEs: increased blood pressure Patients benefit regardless of prior chemotherapy use Benefit regardless of tumour burden	AEs: hyperglycaemia Patients benefit regardless of prior chemotherapy use Benefit regardless of tumour burden

Current ENETS guidelines – Targeted therapies





Selection between Sunitinib or Everolimus usually relies on comorbidities due to different toxicity profile

Pavel, Neuroendocrinology 2016; Raymond E, et al. N Engl J Med 2011; Yao JC, et al. N Engl J Med 2011

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Baseline Assessment

Patient status – Holistic assessment

General

Performance status
Haematological baseline
Liver and kidney function
Concomitant medications
Baseline symptoms
–Fatigue
–Weight (loss)
–Diarrhoea
–Oral hygiene

Treatment-specific requirement

Sunitinib
- Blood pressure
- Thyroid function tests
- Urinalysis

Everolimus
- Glucose / HbA1C
- Viral hepatitis status
- Respiratory parameters

Right treatment, right patient

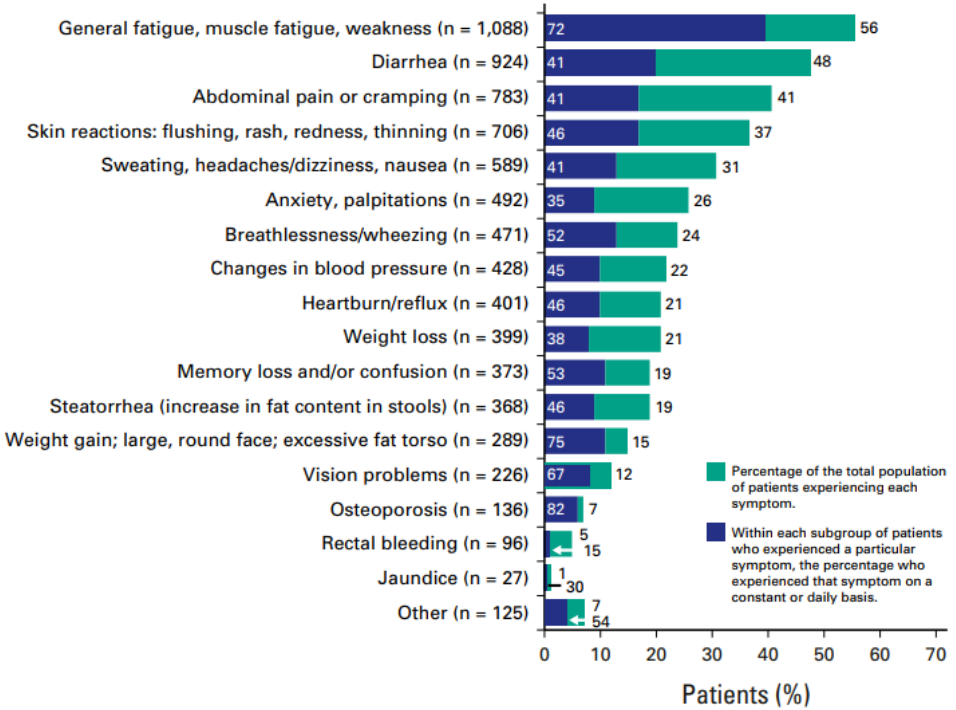
Optimising dose and managing toxicity

Assessing response

Burden of disease in NETs is high: patients already experience many symptoms on an almost daily basis

Important to differentiate drug toxicity from underlying symptoms

Adequate symptom relief before initiation of targeted therapy is likely to improve tolerance to treatment

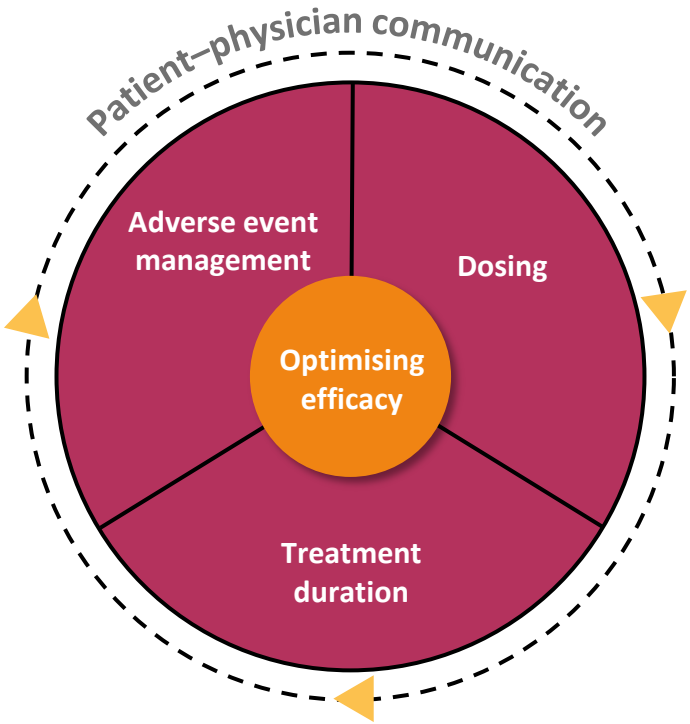


Singh S et al. J Global Oncol 2017;3:43–53.

Importance of effective AE management

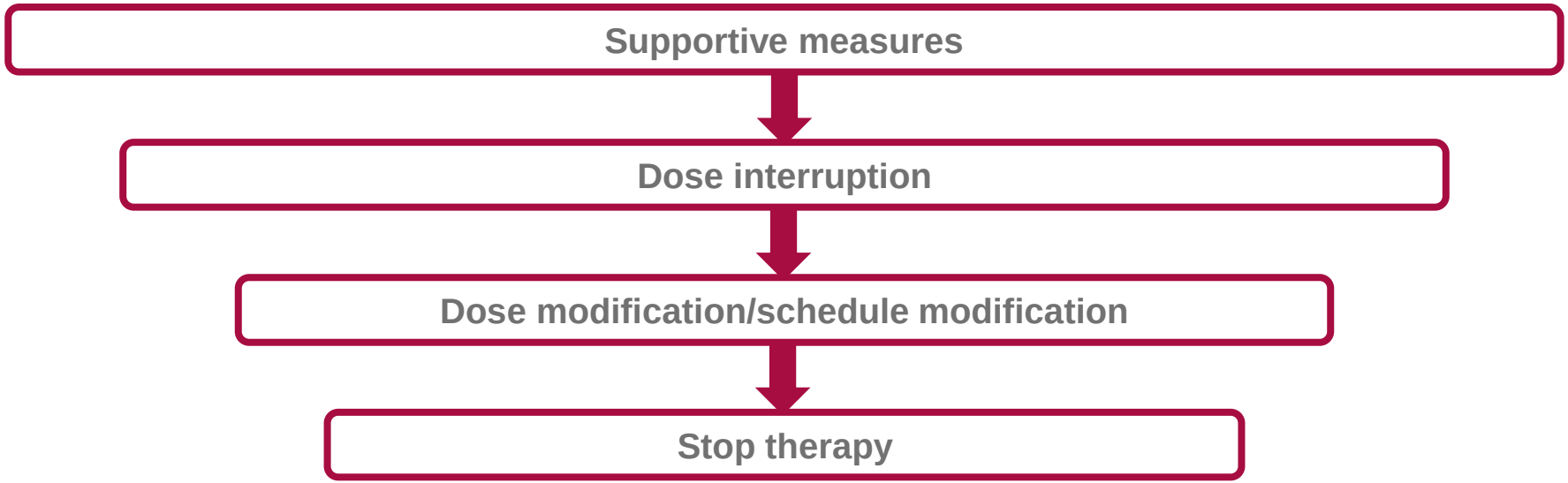
Effective AE management strategies are essential to ensure that patients remain on therapy for as long as they continue to benefit clinically

Close collaboration between patient and physician is very important



Larkin J Am J Clin Oncol; Schwandt Onco Targets Ther 2009

Strategy for toxicity management



Dose modifications: Sunitinib

Meta-analysis (solid tumours) indicated that increased exposure to sunitinib was associated with improved clinical outcomes (longer time to progression and longer OS)

Recent data from the Phase IV trials in NETs aligns with this:

- ORR and mPFS appeared to be greater
- **no consistent trends reported with mOS**

No clear detriment derived from dose reduction

Population stratified into above and below the median sunitinib† blood drug levels ↓ †Incl. its active metabolite	**Ph IV total population Median PFS (95% CI), months**		
	Cycle 1, D15 (n=51)	Cycle 2, D1 (n=50)	Cycle 3, D1 (n=47)
< median trough	13.2 (8.9–18.2)	13.0 (7.4–16.7)	13.2 (8.9–16.7)
≥ median trough	**16.7** (10.9–25.4)	16.7 (11.0–25.4)	**16.7** (11.0–37.9)

Houk BE Cancer Chemother Pharmacol. 2010; Raymond E, Neuroendocrinology 2018

Dose modifications: Everolimus

- Most everolimus-related AEs are manageable through dose modification

- Impact of cumulative dose and dose intensity on PFS and OS
  - Retrospective analysis: 116 PanNETs treated with everolimus
  - Response rate similar
  - Median OS and PFS longer with increased dose intensity

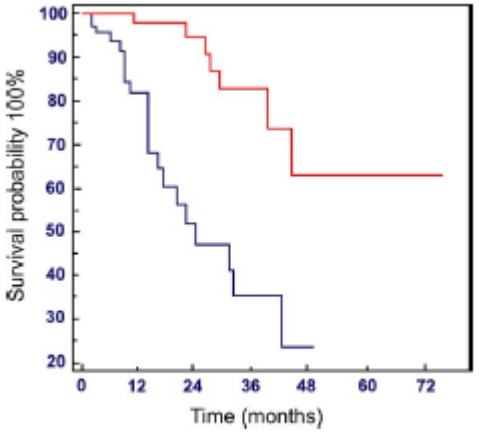


Figure 2. Overall survival stratified by the everolimus cumulative dose (CD): ___ ≤3000 mg (Group A) and ___ >3000 mg (Group B).

HR 0.16; Adjusted p-value <0.0001

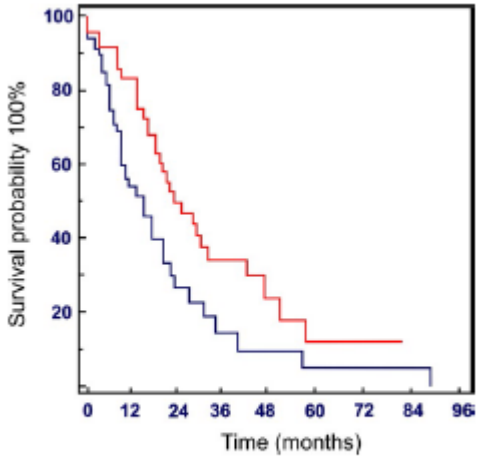


Figure 3. Progression-free survival stratified by the everolimus cumulative dose (CD): ___ ≤3000 mg (Group A) and ___ >3000 mg (Group B).

HR 0.56; Adjusted p-value 0.047

"This should prompt efforts to continue everolimus administration in responsive patients up to at least 3000 mg despite delays or temporary interruptions."

Berardi Cancer Med 2017

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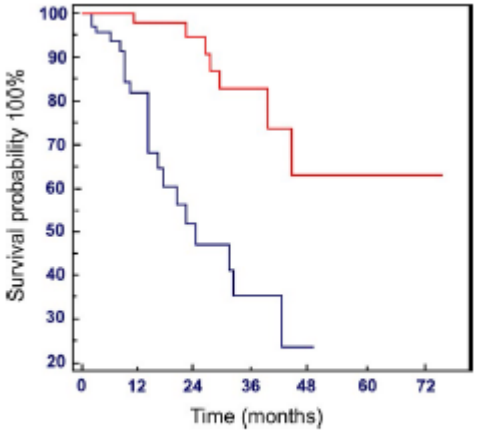
  - Limitations!



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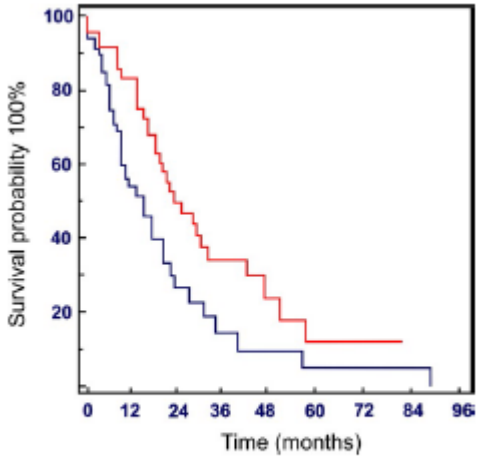

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HR 0.56; Adjusted p-value 0.047

"This should prompt efforts to continue everolimus administration in responsive patients up to at least 3000 mg despite delays or temporary interruptions **if well tolerated**."

Berardi Cancer Med 2017

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Right treatment, right patient

Optimising dose and managing toxicity

Assessing response

Cross-sectional response – RECIST

- With targeted therapies: main effect is cytostatic (rather than cytotoxic)
  Findings consistent across different targeted therapies

	Pancreas		Intestinal + lung
	Phase III trial Sunitinib (n=86)	Phase III trial Everolimus (n=191)	Phase III trial Everolimus (n=205)
Complete response, %	2	0	0
Partial response, %	7	5	2
Stable disease, %	63	73	80.5
Progressive disease, %	14	14	9.3
Not estimable, %	14	8	8.3

Pavel, Neuroendocrinology 2016; Raymond E, et al. N Engl J Med 2011; Yao JC, et al. N Engl J Med 2011; Yao Lancet 2014; Capdevila ESMO 2018

Cross-sectional response – RECIST

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  Exception: lenvatinib?

	Pancreas			Intestinal + lung	
	Phase III trial Sunitinib (n=86)	Phase III trial Everolimus (n=191)	Phase II Lenvatinib (n=55)	Phase III trial Everolimus (n=205)	Phase II Lenvatinib (n=56; intestinal)
Complete response, %	2	0	0	0	0
Partial response, %	7	5	34.6	2	20.3
Stable disease, %	63	73	57.7	80.5	79.6
Progressive disease, %	14	14	7.7	9.3	0
Not estimable, %	14	8	0	8.3	0

Pavel, Neuroendocrinology 2016; Raymond E, et al. N Engl J Med 2011; Yao JC, et al. N Engl J Med 2011; Yao Lancet 2014; Capdevila ESMO 2018

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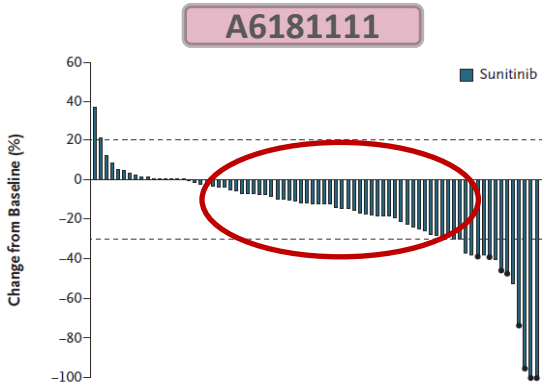
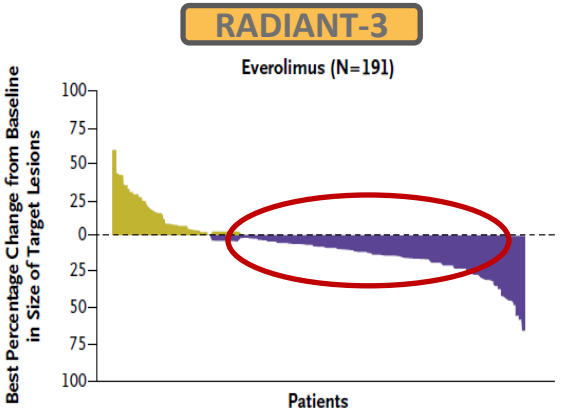
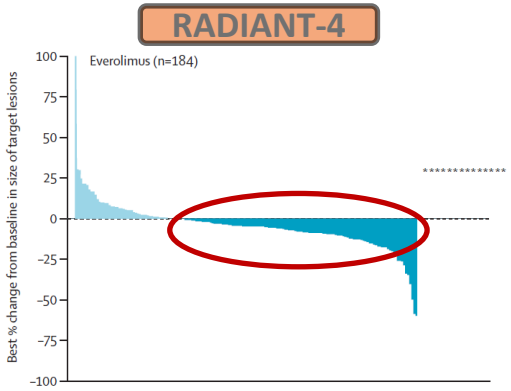
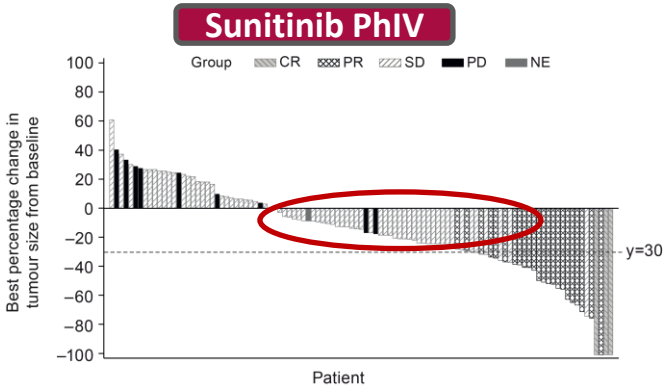
Cross-sectional response – RECIST









Within “stable disease” the majority of patients derive some degree of tumour shrinkage

RECIST evaluation may underestimate the patients who benefit from treatment

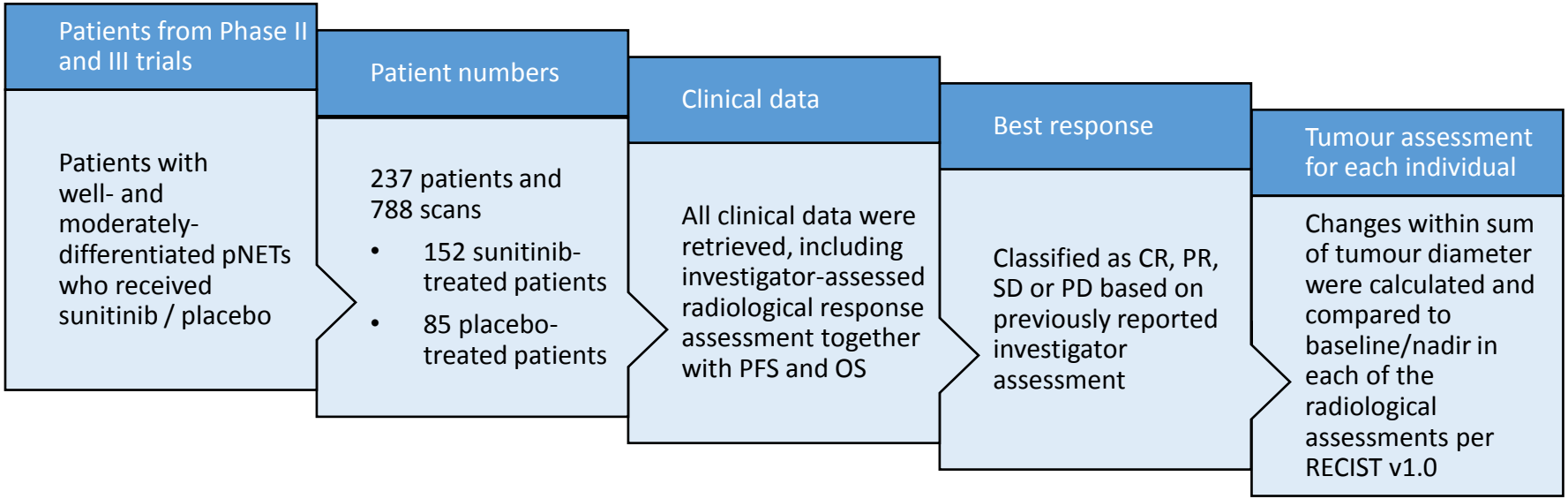
Changes in lesions may be morphological

The (30%) cut-off size for “response” may not be applicable for targeted therapies

Pavel, Neuroendocrinology 2016; Raymond E, et al. N Engl J Med 2011; Yao JC, et al. N Engl J Med 2011; Yao Lancet 2014; Raymond E, et al. Neuroendocrinology 2018;107:237–45; 5. Therasse, et al. J Natl Cancer Inst 2000;92:205–16.

Cross-sectional response – Can we improve RECIST?

Predicting PFS in PanNETS treated with sunitinib



The primary objective: to determine an alternative to the current RECIST criterion for PR by identifying the most informative RECIST response % cut-off value at 11 months (Based on mPFS from the pivotal Phase III study)

Lamarca BJC 2017

Cross-sectional response – Can we improve RECIST?

Predicting PFS in PanNETS treated with sunitinib

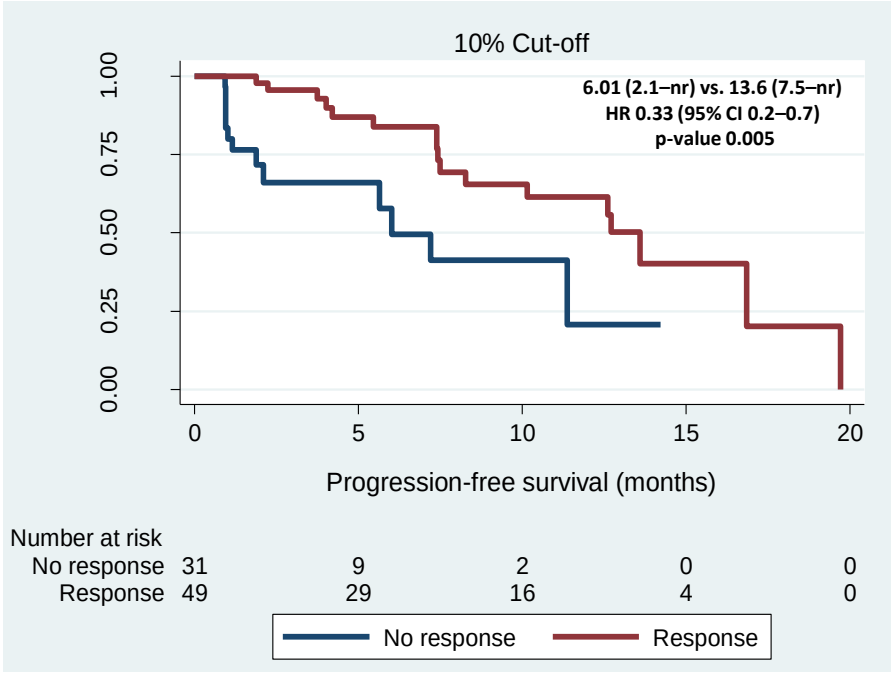
Reduction of **10%** (vs baseline) achieved the highest sensitivity (50%) and specificity (82%)

A 10% reduction in marker lesions was associated with improved PFS in the whole sunitinib population

A 10% reduction in marker lesions and sunitinib treatment independently impacted on PFS

A 10% reduction within marker lesions identifies patients benefiting from sunitinib treatment

PFS in patients treated with 37.5mg sunitinib continuously:



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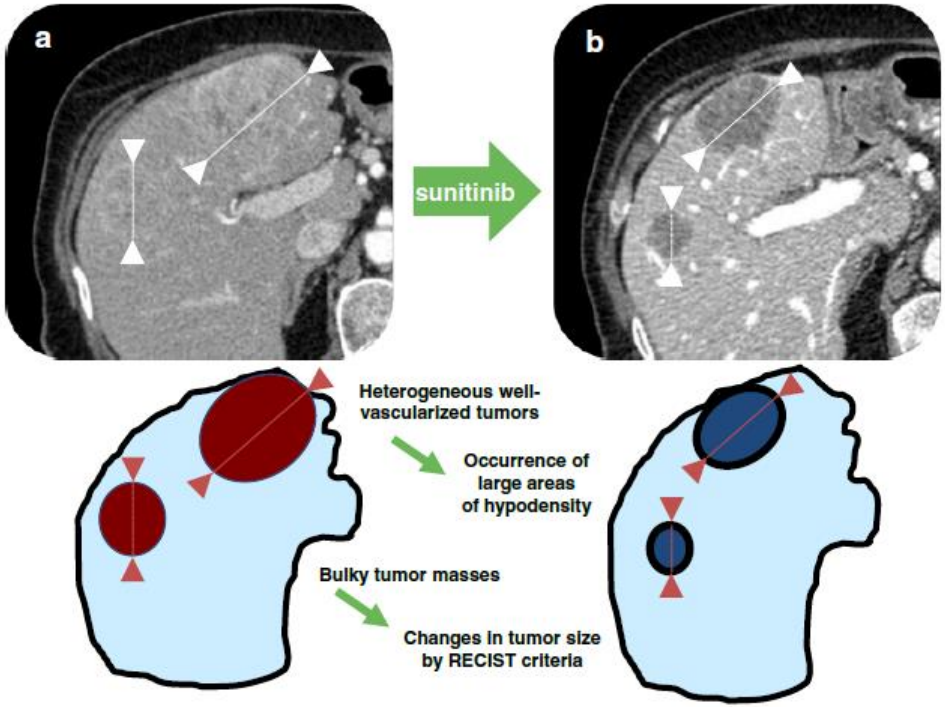
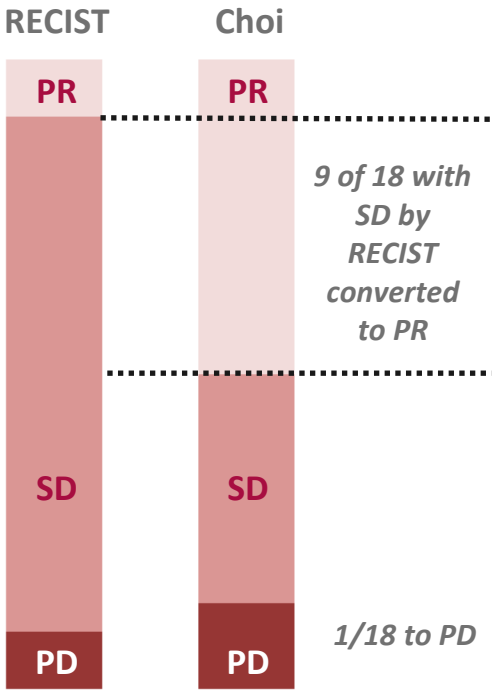
Cross-sectional response – Alternative to RECIST: Choi





Median TTP: PR: 26.1 mo | **SD:** 8.7 mo | **PD:** 3.6 mo; p=0.038

Cystic changes are reflection of response.
Do not confound with progression.

Faivre, Target Oncol 2012

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Cross-sectional response – Alternative to RECIST: Choi

A meaningful number of patients classified as stable disease by RECIST were reclassified as responders

(26/44=59%)

All patients classified as partial response by RECIST were classified as responders

(10/100=100%)

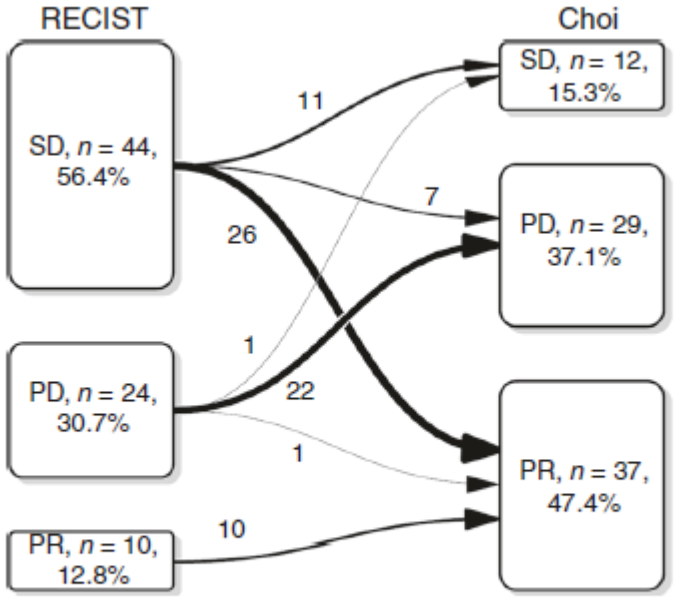


Fig. 2 Transition plot with the reclassification between RECISTv1.1 and Choi criteria. n number, PD progressive disease, PR partial response, SD stable disease

Solis Hernandez, BJC 2019

Cross-sectional response – Alternative to RECIST: Choi

Choi (Figure A) predicted PFS more accurately than RECIST (Figure B)

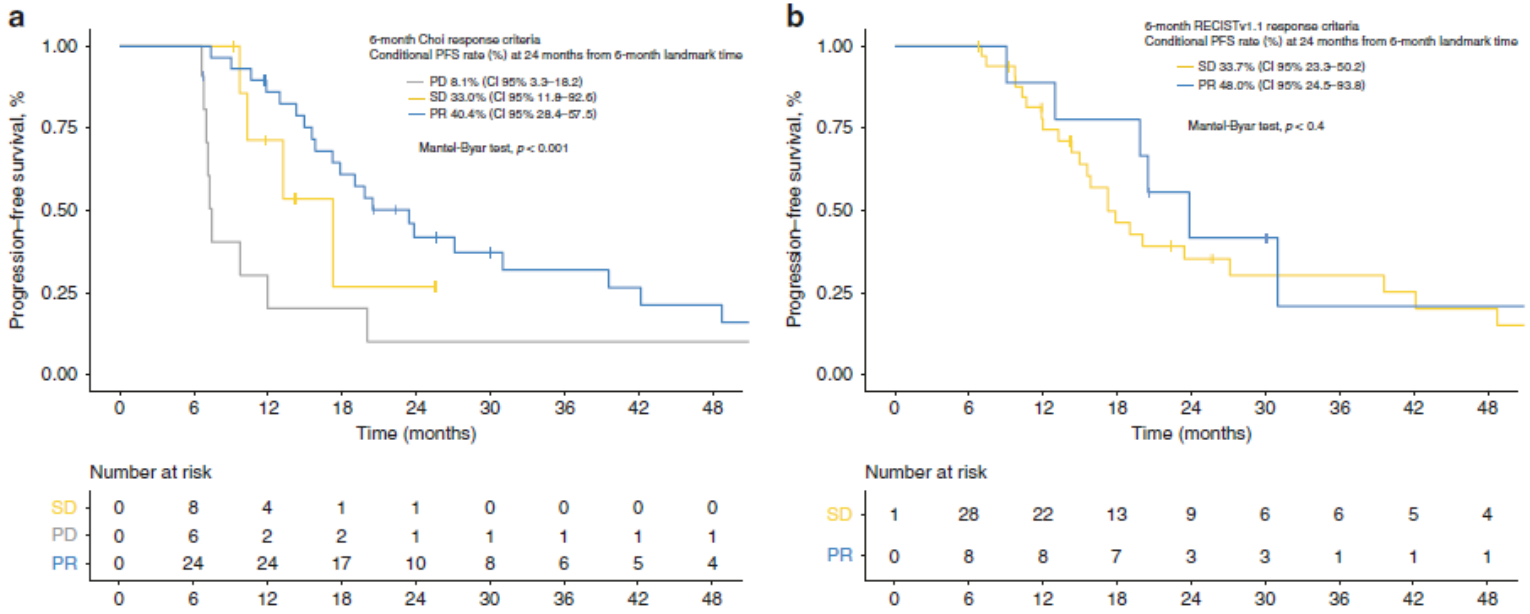


Fig. 3 **a** Kaplan–Meier curves for conditional progression-free survival from 6-month landmark time stratified by Choi. **b** Kaplan–Meier curves for conditional progression-free survival from 6-month landmark time by RECIST. It does not include the PD category by RECIST as it coincides with the endpoint. CI confidence interval, PD progressive disease, PFS progression-free survival, PR partial response, SD stable disease

Solis Hernandez, BJC 2019

Cross-sectional response – Tumour Growth Rate (TGR)

Response evaluation with RECIST has limitations when applied to slow growing malignancies with low ORR, such as NETs

TGR represents the % change in tumour size per month (%/m) and has been proposed to overcome these limitations

TGR		RECIST
Speed of growth dynamic	VS.	Comparison of size static

Lamarca, The Oncologist 2019

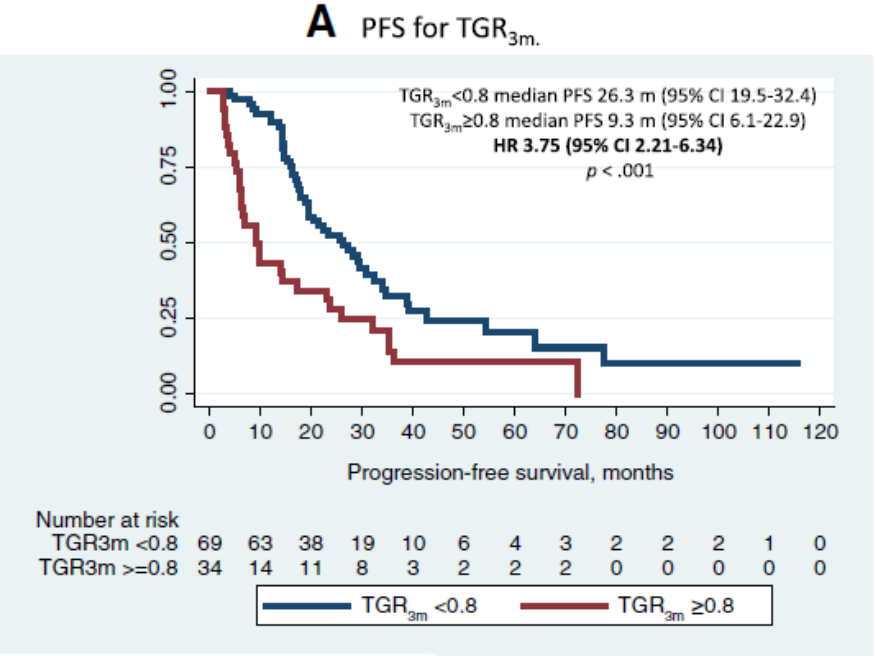
Cross-sectional response – Tumour Growth Rate (TGR)

Retrospective study to assess the impact of TGR_{3m} of starting systemic treatment or watch and wait on patient outcomes (G1/G2 GEP-NETs; various treatments)

0.8%/month proved to be the most informative TGR cut-off for 12 month-progression rate prediction

TGR_{3m} ≥0.8 in 33.1% of patients

Patients with **TGR ≥0.8 had shorter PFS** and were less likely to be progression free at 12 months



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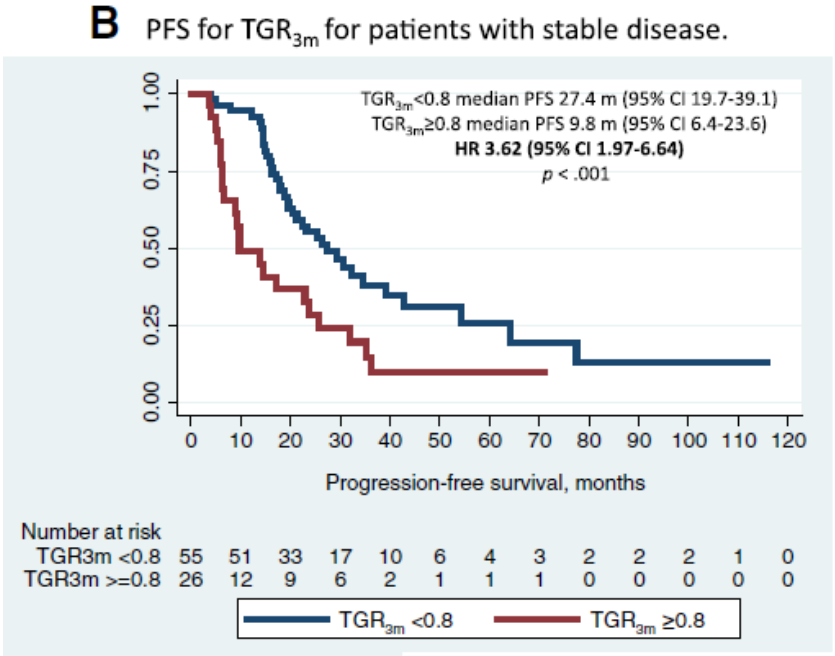
Cross-sectional response – Tumour Growth Rate (TGR)

81% of patients achieved stable disease (defined by RECIST)

TGR was informative also when analysis was focused on patients with Stable Disease by RECIST



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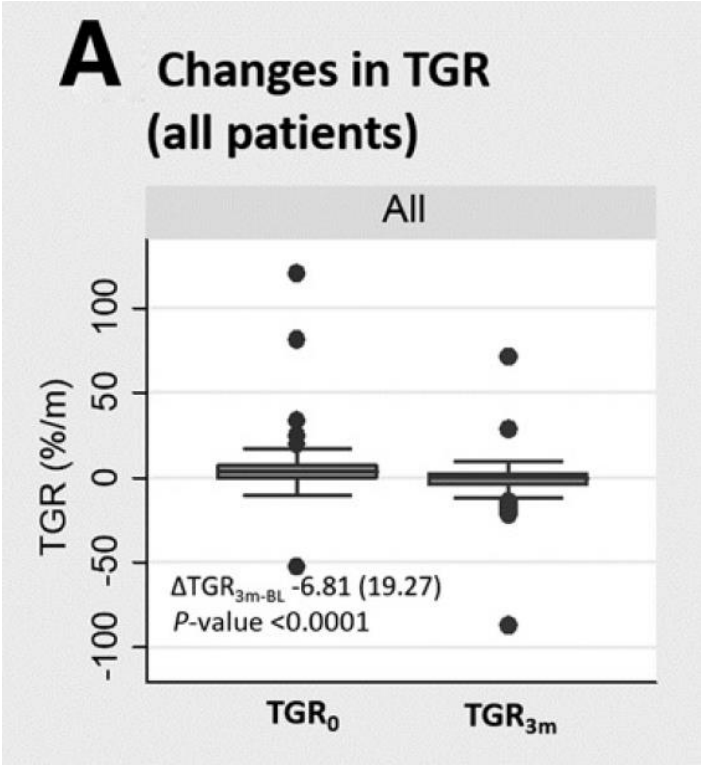
Cross-sectional response – Tumour Growth Rate (TGR)

TGR is also able to capture treatment-induced changes

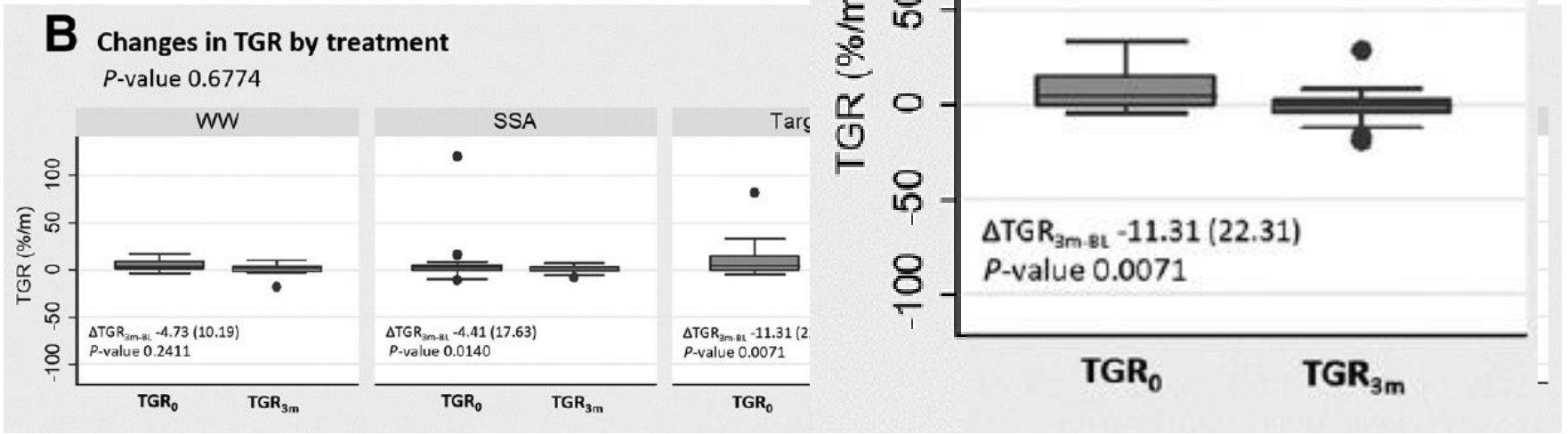
- Changes in baseline TGR (TGR_0) vs TGR_{3m}



Lamarca, Clin Cancer Res 2019

Cross-sectional response – Tumour Growth Rate (TGR)

TGR is also able to capture treatment-induced changes



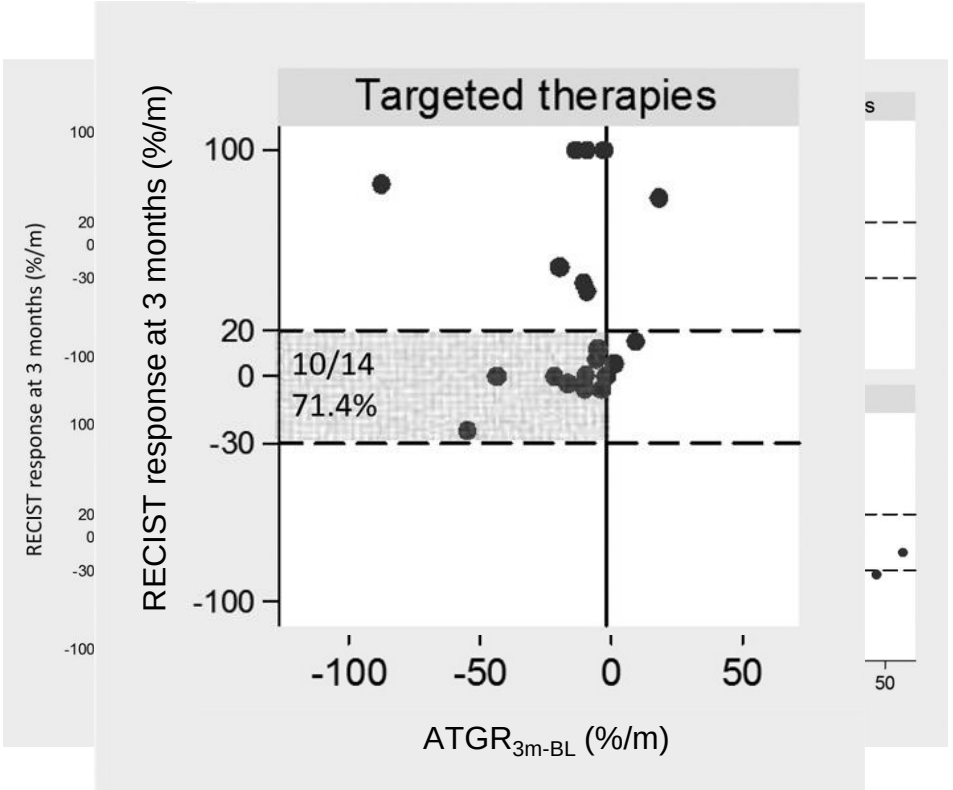
Lamarca, Clin Cancer Res 2019

Cross-sectional response – Tumour Growth Rate (TGR)

TGR is also able to capture treatment-induced changes

More reliably than RECIST

When focusing on patients treated with targeted agents, 71.4% of patients were classified as “stable” by RECIST but did actually have reduction in TGR.



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Summary

- Selection of which targeted therapy based on comorbidities and toxicity profile
- Toxicity vs Symptoms - Adequate control of baseline symptoms

- Important to keep patients on therapy for as long as they continue to derive benefit (if treatment well tolerated)
- Guidelines are available for management of toxicities with supportive medication, dose delays or dose reductions

- Efficacy assessments with RECIST may underestimate benefit (CHOI, TGR)

- Patients are most likely to remain on treatment if they are involved in their therapy management

Acknowledgements

Thank you for your attention

The Christie
CHARITABLE FUND
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Interested on joining our team as a research fellow? Email us!

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