ΝΕΟΤΕΡΑ ΔΕΔΟΜΕΝΑ ΣΤΗΝ ΘΕΡΑΠΕΙΑ ΤΩΝ GEP-NETs

ΔΕΜΙΡΗ ΣΤΑΜΑΤΙΝΑ
ΓΑΟΝΑ ΑΓΙΟΣ ΣΑΒΒΑΣ

TYROSINE-KINASE INHIBITORS (TKI)

NEW TKI

Compound	VEGFR			PDGFR		FGFR				CSF1-R	C-Kit-R	Flt-3-R	RET	MET	Clinical trial phase
Sunitinib	✓	✓	✓	✓	✓					✓	✓	✓	✓		**II-III**
Cabozantinib	✓	✓	✓									✓	✓	✓	**II-III**
Lenvatinib	✓	✓	✓	✓		✓	✓	✓	✓		✓		✓		**II**
Pazopanib	✓	✓	✓	✓	✓	✓		✓			✓	✓			**II**
Surufatinib	✓	✓	✓			✓				✓		✓			**II-III**
Axitinib	✓	✓	✓												**II/III**

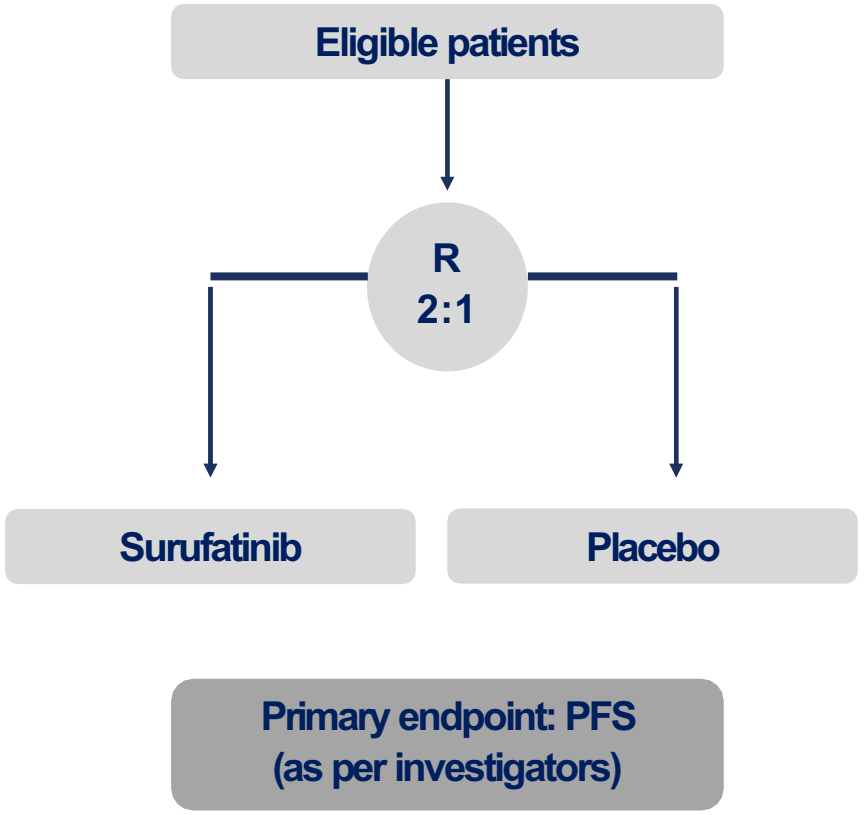
VEGFR: vascular endothelial growth factor receptor; PDGFR: plateled-derived growth factor receptor; FGFR: fibroblast growth factor receptors; CSF: colony stimulating factor; RET: rearranged during transfection; MET: mesenchimal epithelial transition.

ESMO

Fazio N. et al. Exp Opin Drug Metabol & Toxicol 2019

SURUFATINIB

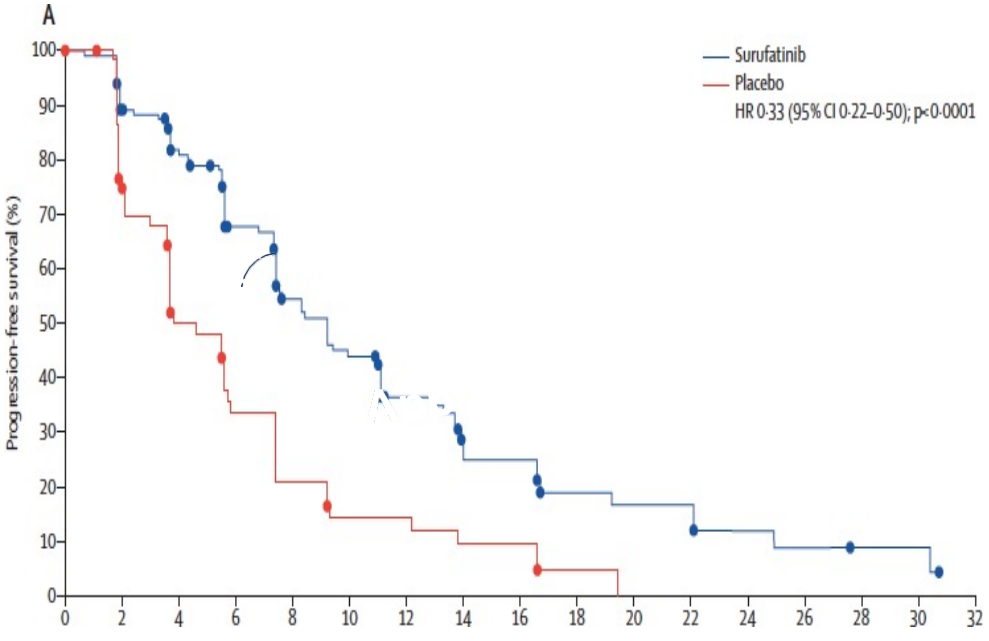
- Encouraging efficacy in NETs
  based on 2 phase III randomized trials
- Separate trials in PanNETs and extra-PanNETs (SANET-p and SANET-ep)
- Grade 1-2 NETs, ECOG PS 0
- Similar design, placebo controlled, randomized



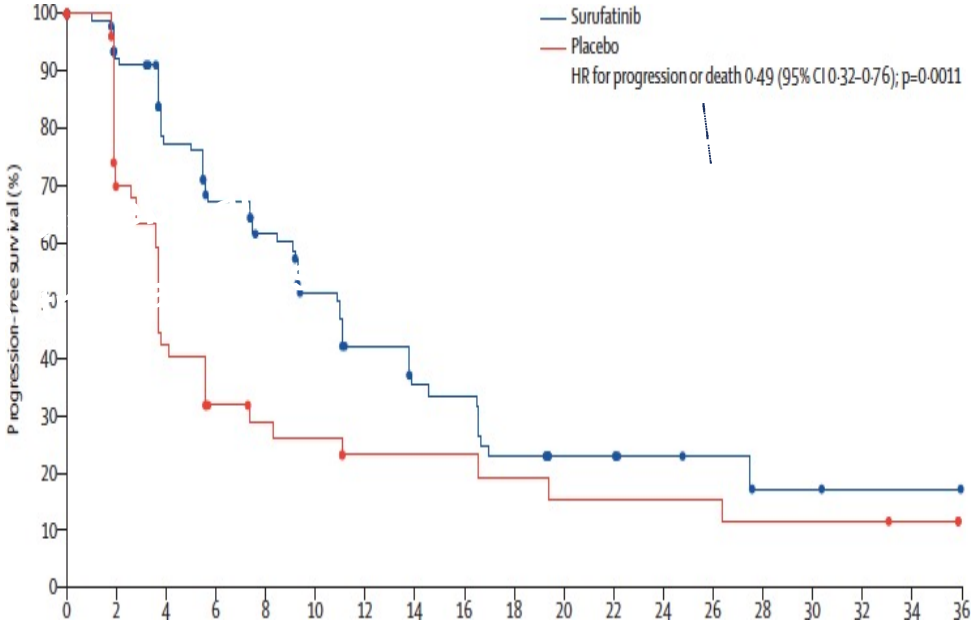
Xu J et al, Lancet Oncol 2020; Xu J at al, Lancet Oncol 2020

SURUFATINIB

Sanet-ep



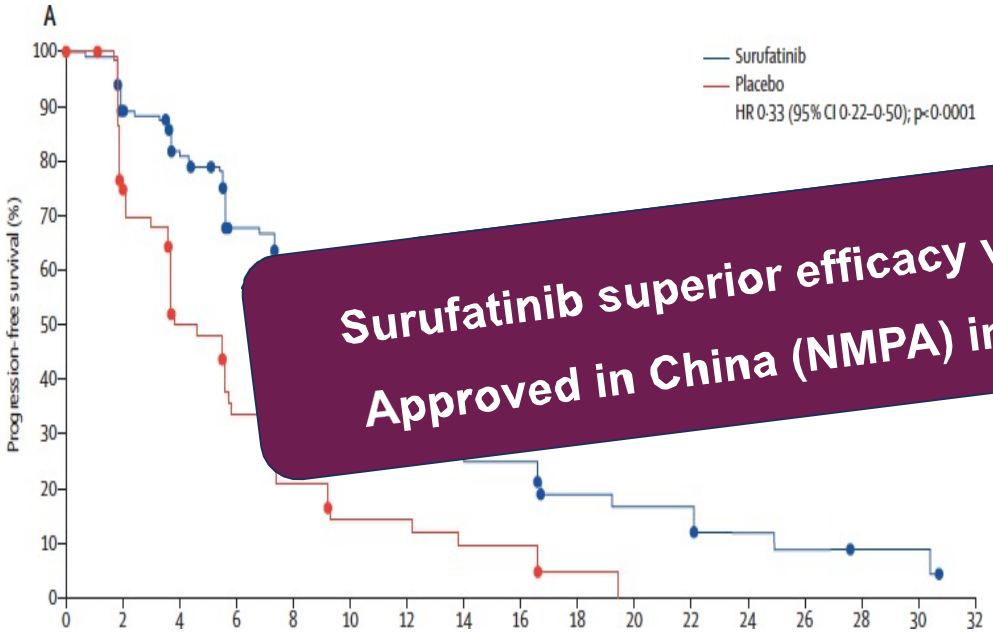
Sanet-p



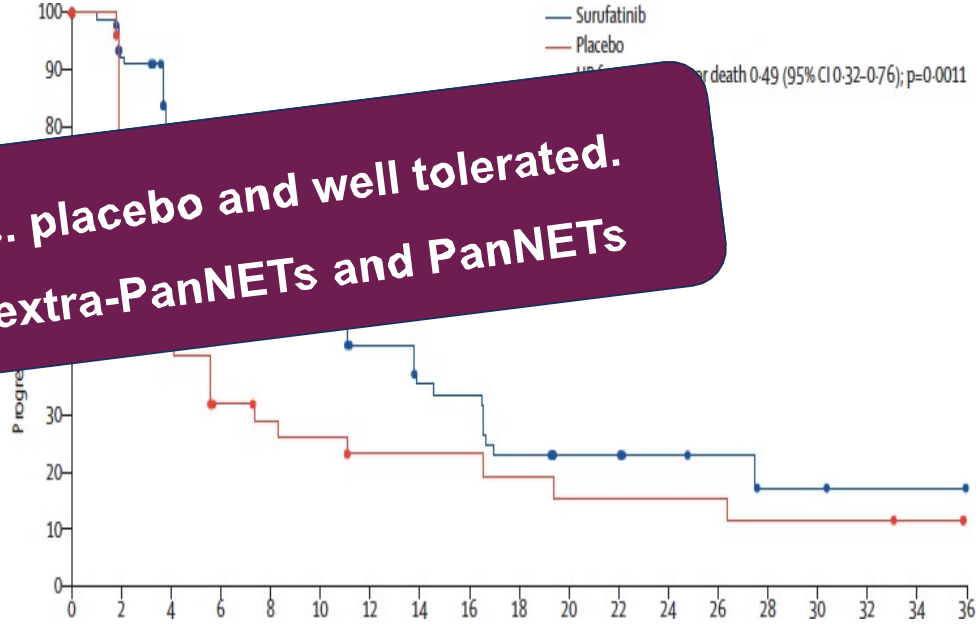
Xu J et al, Lancet Oncol 2020; Xu J at al, Lancet Oncol 2020

SURUFATINIB

Sanet-ep



Sanet-p



Surufatinib superior efficacy vs. placebo and well tolerated.
Approved in China (NMPA) in extra-PanNETs and PanNETs

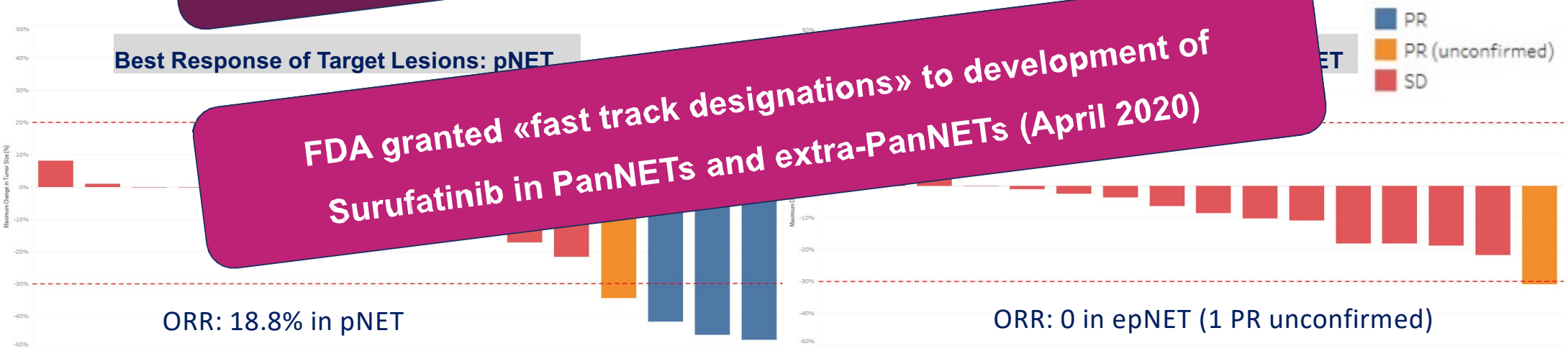
Xu J et al, Lancet Oncol 2020; Xu J at al, Lancet Oncol 2020

SURUFATINIB: ONGOING US PHASE I STUDY (NCT02549937)

- Clinical efficacy irrespective of prior lines of therapy (including everolimus or sunitinib)
- Tumor growth was controlled in all NET patients.
- Manageable safety profile

Promising antitumor activity in US patients with progressive NETs and manageable safety profile.

FDA granted «fast track designations» to development of Surufatinib in PanNETs and extra-PanNETs (April 2020)



Dasari A et al. Abstract/Poster 4610/218. Poster discussion, ASCO 2020

SURUFATINIB: IN EUROPE

An open label phase II study of surufatinib in patients with Neuroendocrine Tumours in Europe

Primary endpoint:
DCR at 6-mo

INCOMING in EU: 17 centres (non yet recruiting)

a. Choort A: lung NET
b. Choort B: midgut NET
c. Choort C: non-midgut, non-pancreas, non-lung NET
d. Choort D (DDI sub-study): NET of any origin

ClinicalTrials.gov Identifier: NCT04579679

SURUFATINIB: IN SUMMARY

- Clearly an active drug
- Good safety profile (28% G3 HTN)
- Active in heavily pre-treated NET patients (ORR:9.4%)
- Active in PanNETs and extra-PanNETs and functioning tumours in ASIA and US
- In Europe? Registrative phase II trial is incoming

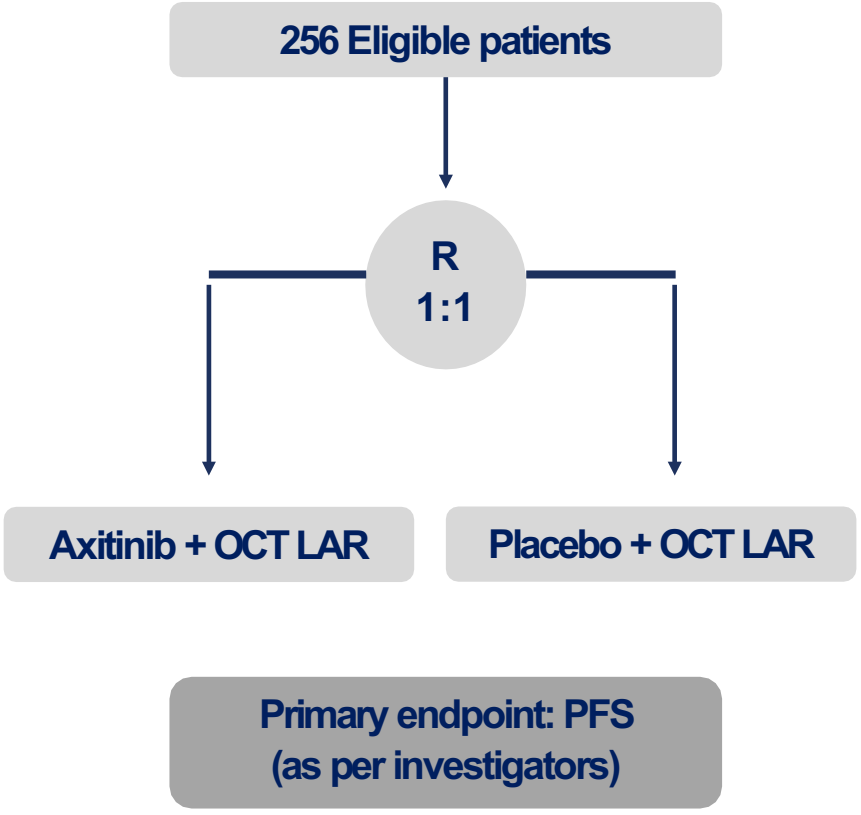
AXITINIB: AXINET / GETNE-1107

Randomized phase II/III double blind study of OCT LAR + axitinib + vs. OCT LAR + placebo in patients with advanced G1-2 NETs of non-pancreatic origin.

- Axitinib is a potent VEGF 1-3 inhibitor

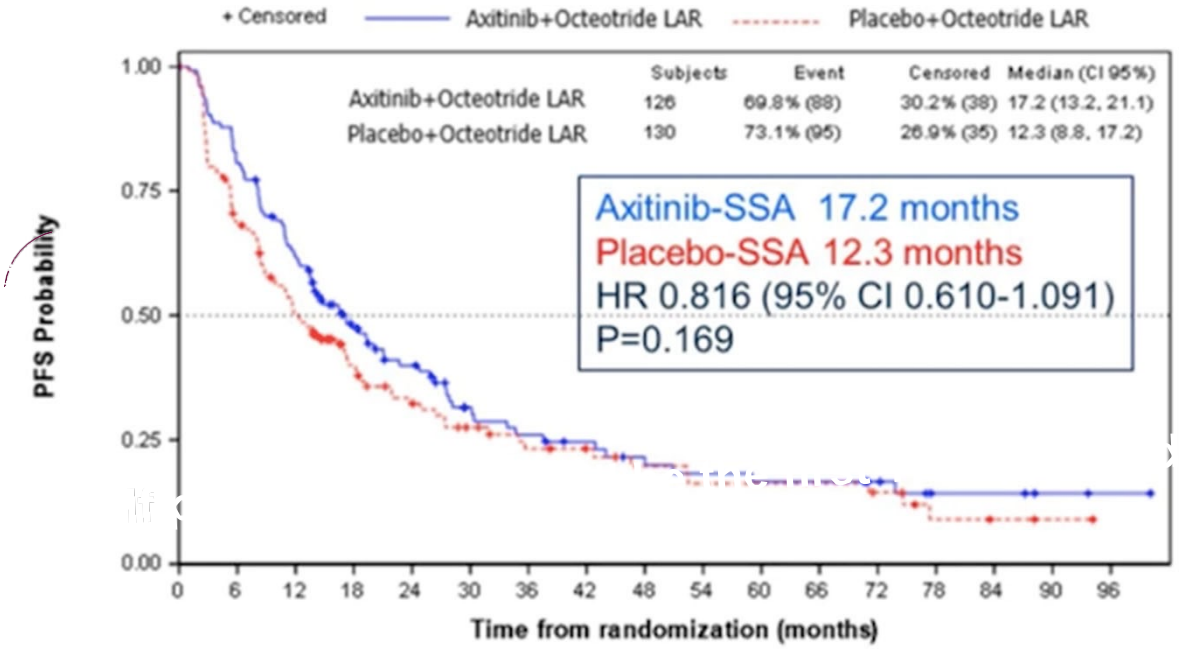
	AXITINIB	PLACEBO
Median age	62 yr.	61 yr.
G2	77.8%	56.9%
GI / Lung	61.1% / 29.4%	56.9% / 26.2%
Previous LDT	56.3%	56.8%
Previous EVE	13.5%	11.5%
Previous SSA	48.4%	46.9%
Previous chemo.	11.3%	10.8%

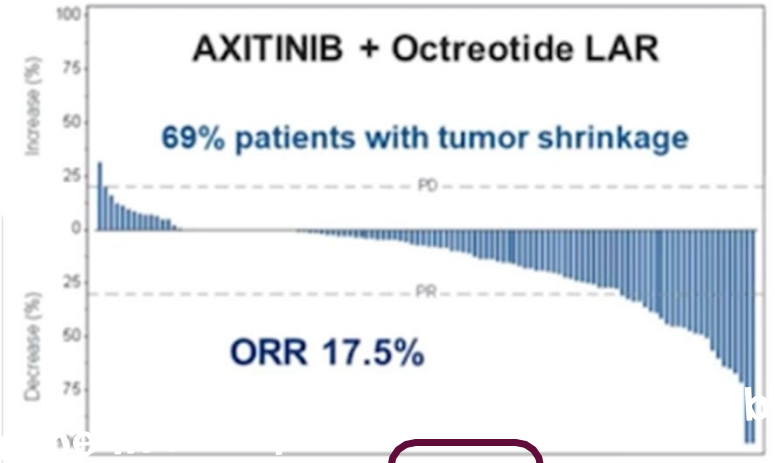
LDT = liver directed therapy



Garcia-Carbonero R. et al. ASCOGI 2021

AXITINIB: AXINET / GETNE-1107

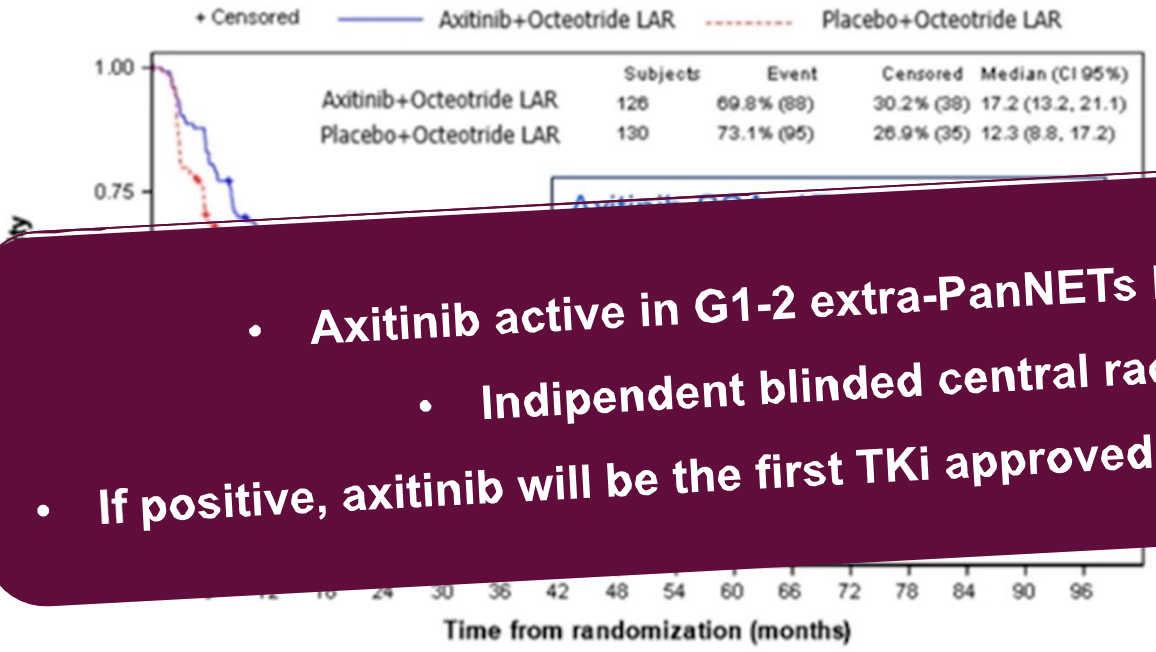


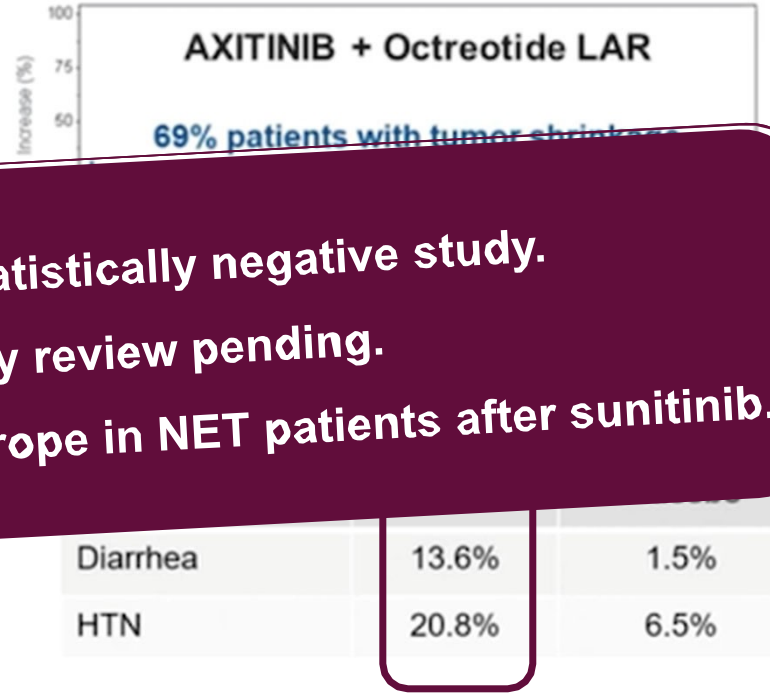


Grade 3/4 AEs	Axitinib	Placebo
Diarrhea	13.6%	1.5%
HTN	20.8%	6.5%

Garcia-Carbonero R. et al. ASCOGI 2021

AXITINIB: AXINET / GETNE-1107





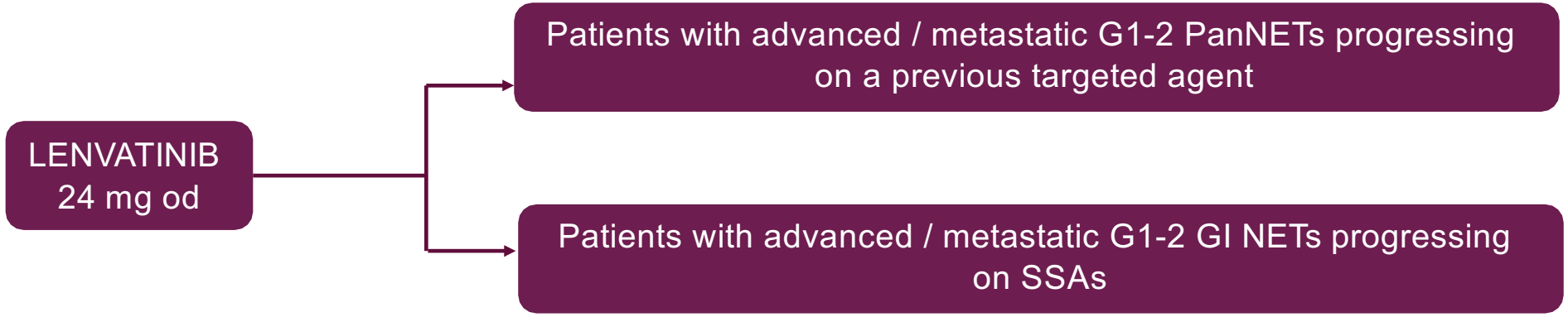
- Axitinib active in G1-2 extra-PanNETs but statistically negative study.
- Indipendent blinded central radiology review pending.
- If positive, axitinib will be the first TKi approved in Europe in NET patients after sunitinib.

Garcia-Carbonero R. et al. ASCOGI 2021

LENVATINIB: TALENT / GETNE-1509

Lenvatinib in patients with advanced grade 1/2 pancreatic and GI NET: results of the phase II TALENT trial.

- **Primary endpoint:** ORR (RECIST) by central radiology assessment
- **Secondary endpoints**: PFS, OS and safety



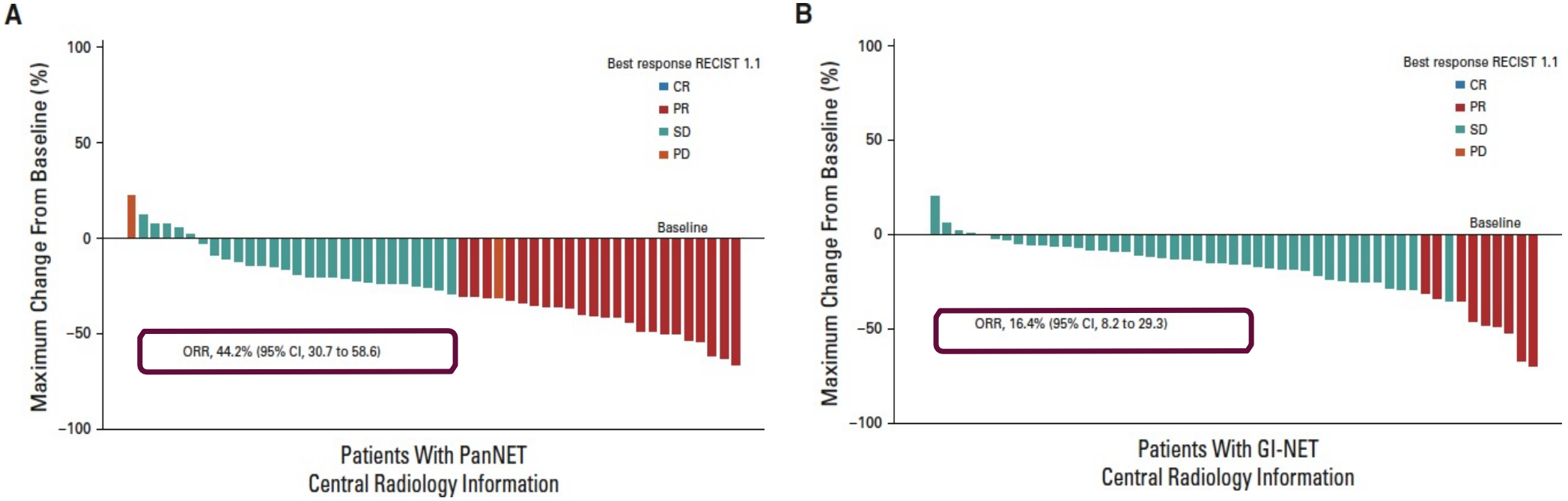
21 European centers

Capdevila J. et al. JCO 2021

LENVATINIB: TALENT / GETNE-1509

Lenvatinib in patients with advanced grade 1/2 pancreatic and GI NET: results of the phase II TALENT trial.

PRIMARY ENDPOINT



Capdevila J. et al. JCO 2021

LENVATINIB: TALENT / GETNE-1509

Lenvatinib in patients with advanced grade 1/2 pancreatic and GI NET: results of the phase II TALENT trial.

- **Lenvatinib active in a pre-treated population PanNETs and GI NETs.**
- **Unclear further research program**

PFS (mo.)	15.6	15.7
OS (mo.)	32	NR
DoR (mo.)	19.9	33.9

	5.5	16.1
Hypertension	21.8	23.2
Diarrhea	7.3	14.3
At least 1-dose reduct. required (median 20 mg od)	81.1	
Definitive tr. discontinuation	10.9	17.8

Capdevila J. et al. JCO 2021

CABOZANTINIB

- Potent inhibitor of VEGFR2 but it is the only TKI inhibitor of MET
- The concurrent inhibition of VEGF and MET signalling can reduce the invasive and metastatic capability of PanNET.
- Preclinical study on activity and resistance mechanism (MCL-1 / AKT) in NET treated with cabozantinib (ongoing at IEO, Milan)

Sennino B. et al Cancer Discovery 2012; Elgendy M. et al. J. Clin. Invest. 2017

CABOZANTINIB

- **Phase II (ASCOGI 2017):** ORR: 15% in PanNETs; PFS: 22 mo in PanNETs
- **Phase III (CABINET) ongoing in US:** to assess the efficacy of cabozantinib in patients with NET previously treated with everolimus
- **Phase II (LOLA) ongoing in ITALY:** to assess the safety and activity of the combination of cabozantinib plus lanreotide in GEP and thoracic NETs.

Chan JA et al., J. Clin. Oncol. 2017, *35(4_suppl):* 228; clinical trial: NCT03375320; clinical trial: NCT04427787

CABOZANTINIB

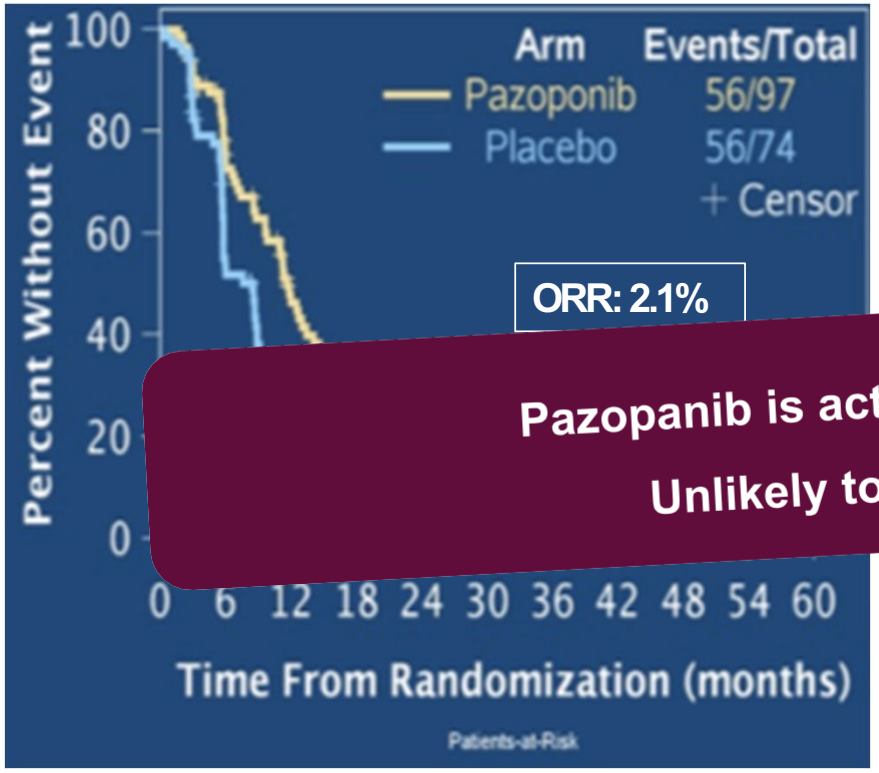
- **Phase II (ASCOGI 2017):** ORR: 15% in PanNETs; PFS: 22 mo in PanNETs
- **P**
- safety and activity of the combination of plus lanreotide in GEP and thoracic NETs.

- Cabozantinib has future opportunity to be registered in NETs.
- What is driving the research with TKI in NET (clinical, biological, strategic reasons)?

Chan JA et al., J. Clin. Oncol. 2017, *35(4_suppl):* 228; clinical trial: NCT03375320; clinical trial: NCT04427787

PAZOPANIB: (ALLIANCE A021202)

Randomized phase II trial of pazopanib vs. placebo in patients with progressive carcinoid tumors



	PAZOPANIB	PLACEBO
12-mo PFS	46.4%	22.9%
Median PFS	11.6 mo.	8.5 mo.
HR	0.53	Ref.
P value		

Pazopanib is active but more toxicity than expected.

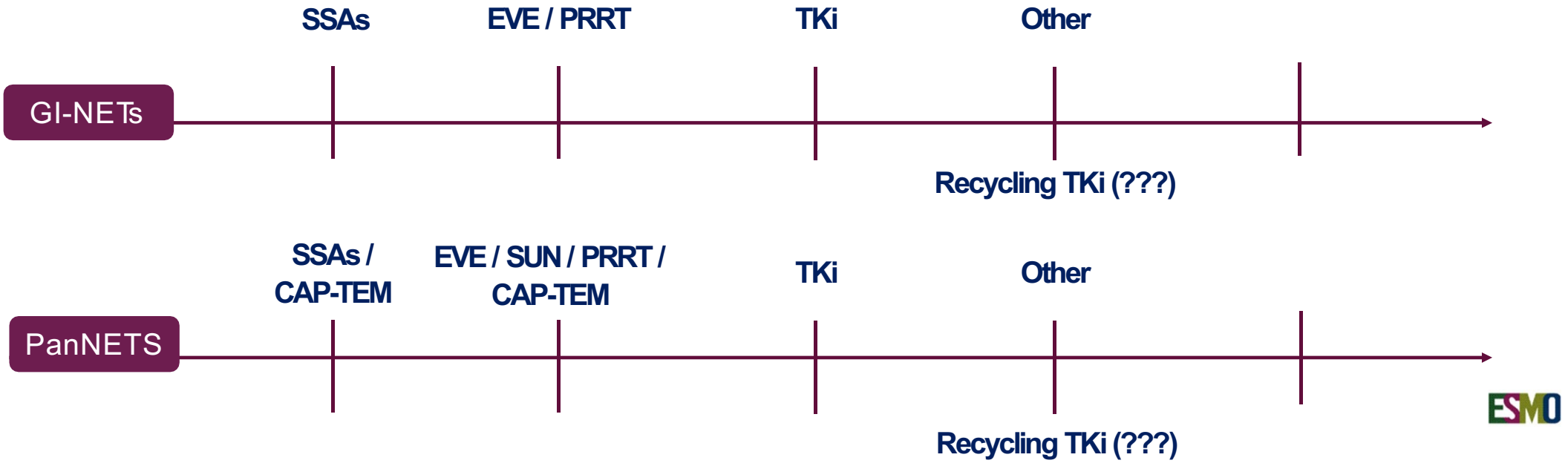
Unlikely to be further developed in NETs.

Grade ¾ AEs	PAZOPANIB	PLACEBO
Treatment related	60.7%	20.8%
HTN	26.9%	4.2%

Bercsland EK et al, ASCO 20219

TYROSINE-KINASE INHIBITORS (TKI) - SUMMARY

- Active and manageable drugs.
- Surufatinib, Cabozantinib and maybe Axitinib have a real possibility to be registered in NET
- Is there a preferred TKi in NETs? Where could they fit in, in the near future?



IMMUNE CHECKPOINT INHIBITORS (ICIS)

IMMUNE CHECKPOINT INHIBITORS (ICIS) - SUMMARY

Studies	Drugs	Phase	Population	No. Patients
DUNE	**Durvalumab + Tremelimumab**	**II**	**Mixed** (27 lung NETs*, **31 GI-NETs, 32 PanNETs, 33 G3 GEP NENs**)	**80**
DART S1609	**Nivolumab + Ipilimumab**	**II (basket)**	**Mixed** (6 lung NETs, **6 GI-NETs, 18 high grade NENs)**	**32**
CA209-538	**Nivolumab + Ipilimumab**	**II (basket)**	**Mixed (11 lung NENs, 10 GEP-NENs,** 8 other, **13 high grade)**	**29**

*4 patients with unknown histological grade

Capdevila J. et al. ESMO 2020; Patel SP et al Clin Cancer Res. 2020; Klein O. et al. Clin Cancer Res. 2020

IMMUNE CHECKPOINT INHIBITORS (ICIS) - SUMMARY

Studies	Population	ORR (%)	No. Patients
DUNE	**Mixed (27 lung NETs*,** 31 GI-NETs, 32 PanNETs, **33 G3 GEP NENs with 4 NET G3**)	• **-** • **0% Lung & GI** • **6.9% PanNETs** • **7.2% High grade**	**80**
DART S1609	**Mixed** (6 lung NETs, 6 GI-NETs, **18 High grade NENs)**	• **25%** • **44% high grade (mixed)**	**32**
CA209-538	**Mixed (11 lung NENs, 10 GEP-NENs,** 8 other, **13 high grade)**	• **25%** • **33% lung (carcinoids)** • **43% GEP NENs** • **31% High grade (including 2 PanNET G3, 1 PanNEC)**	**29**

*4 patients with unknown histological grade

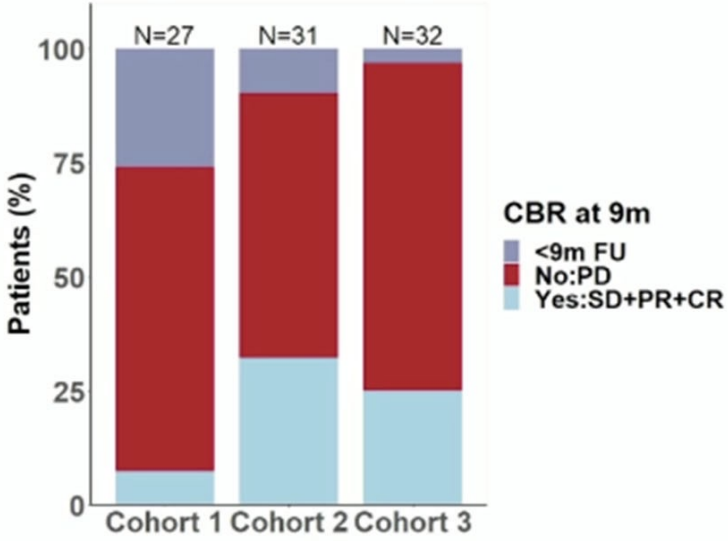
Capdevila J. et al. ESMO 2020; Patel SP et al Clin Cancer Res. 2020; Klein O. et al. Clin Cancer Res. 2020

DUNE - RESULTS

With a median follow-up of 10.8 m:

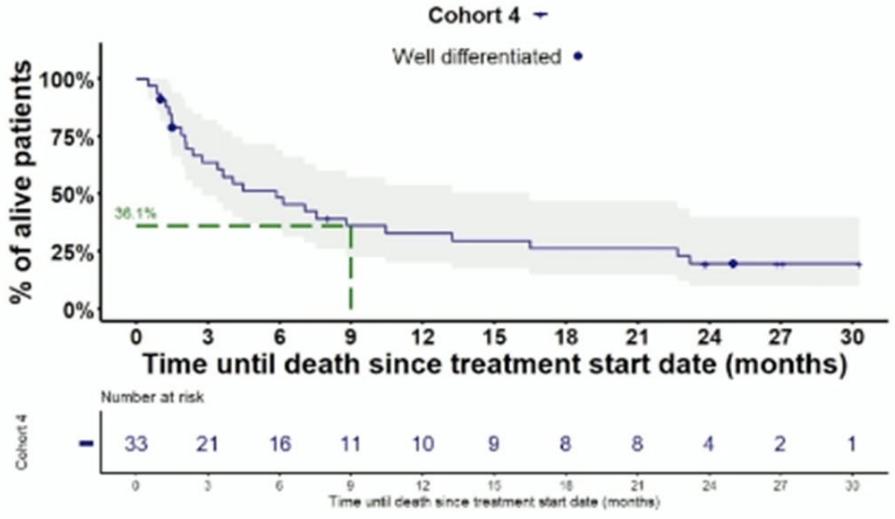
CBR at 9m (by RECIST v1.1) was:

- Cohort 1, Typical/atypical lung carcinoids: 7.4%
- Cohort 2, G1/2 gastrointestinal: 32.3%
- Cohort 3, G1/2 pancreatic: 25%



OS rate at 9-m for cohort 4 was:

- Cohort 4, G3 gastroenteropancreatic: 36.1%. (95% CI: 22.9-57)(n: 33)



Capdevila J. et al. ESMO 2020

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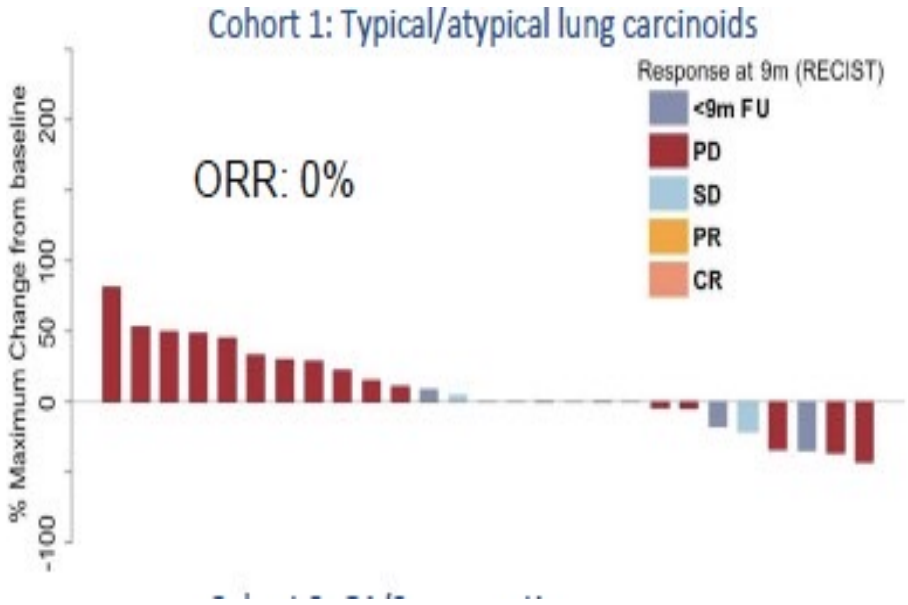
OS rate at 9-m for cohort 4 was:

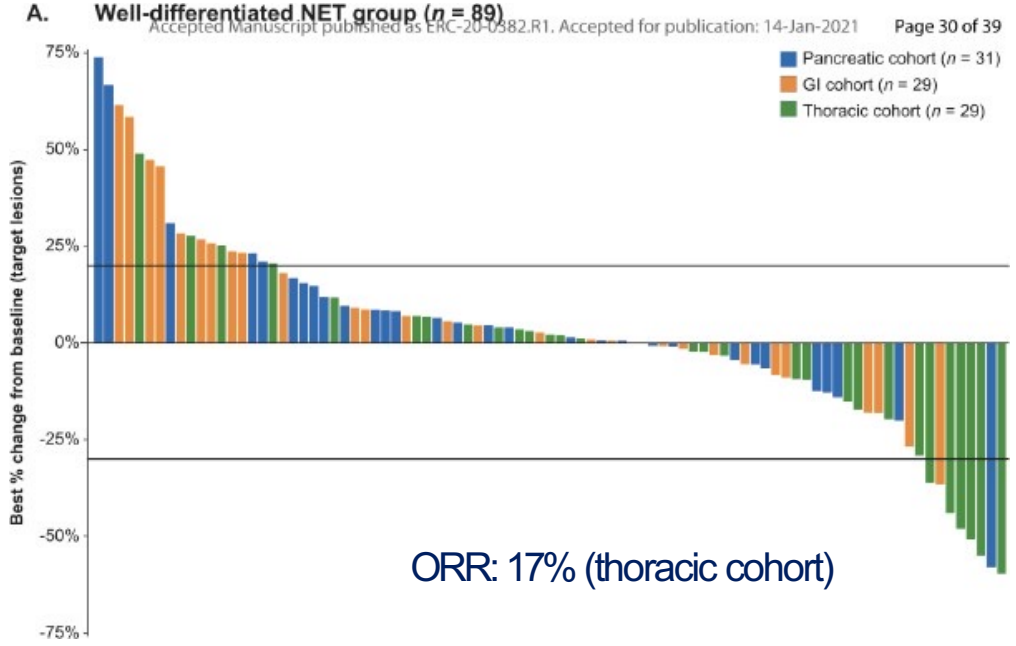
- Cohort 4, G3 gastroenteropancreatic: 36.1%. (95% CI: 22.9-57)(n: 33)

- **Modest activity in GEP NETs / NO new safety concerns.**
- **Further studies in a more selected populations.**

Capdevila J. et al. ESMO 2020

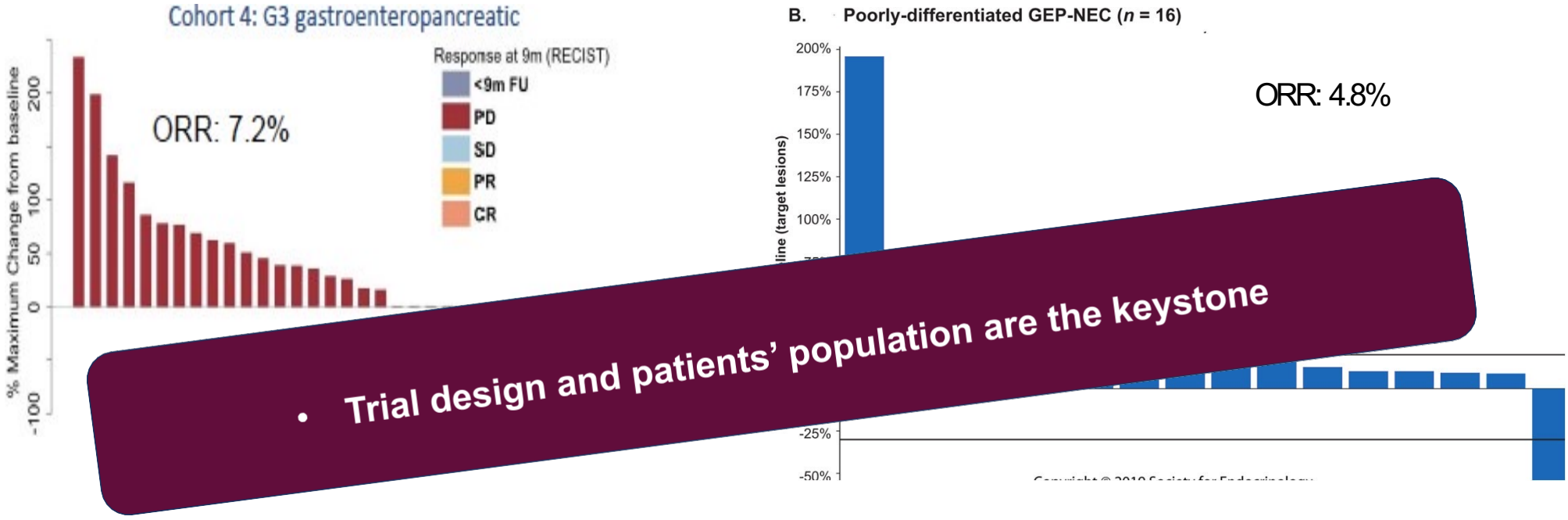
DUNE AND SPARTALIZUMAB: COMPARISON





Capdevila J. et al. ESMO 2020; Yao JC. End. Related Cancer 2021

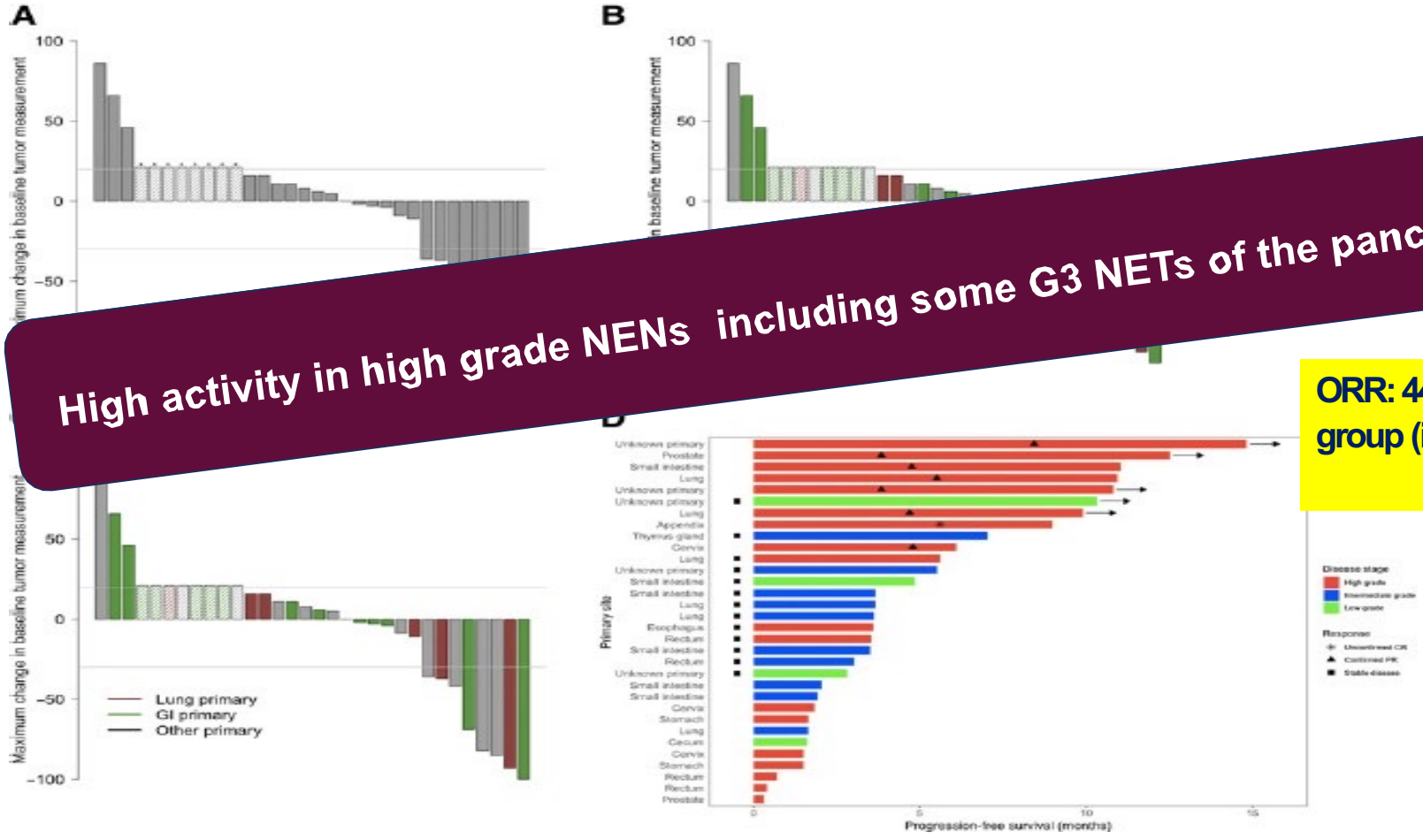
DUNE AND SPARTALIZUMAB: COMPARISON



- **Trial design and patients' population are the keystone**

Capdevila J. et al. ESMO 2020; Yao JC. End. Related Cancer 2021

DART - RESULTS



High activity in high grade NENs including some G3 NETs of the pancreas)

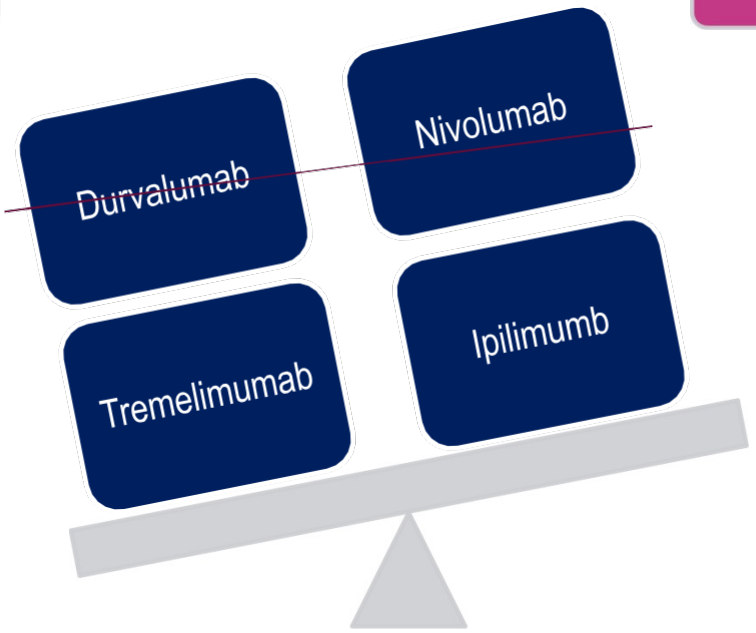
ORR: 44% in the HIGH GRADE group (including 2 G3 PanNETs)

Patel SP et al Clin Cancer Res. 2020

DUNE OR DART?

A

B



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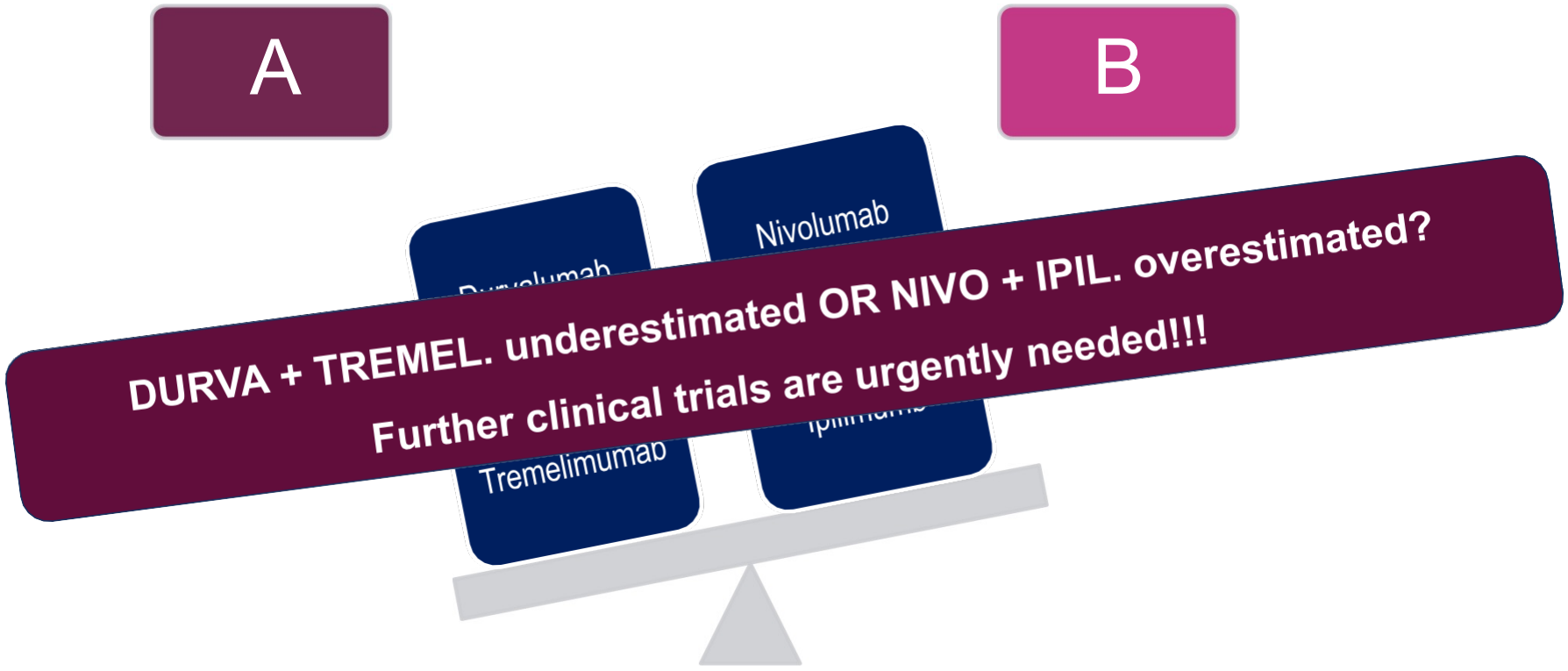
DUNE OR DART?



Capdevila J. et al. ESMO 2020; Patel SP et al Clin Cancer Res. 2020; Klein O. et al. Clin Cancer Res. 2020

IMMUNE CHECKPOINT INHIBITORS (ICIS) - SUMMARY

- Multiple controversial small studies with single agents
- Controversial studies with combinations
- Heterogeneous study populations (grade, primary sites), lack of centralized tissue review
- Further studies are needed with better selection criteria

TAKE HOME MESSAGES

- **Tyrosine kinase inhibitors** are promising, even for heavily pre-treated patients.
- **Immunotherapy** has an unconvincing role in NENs and it could be inappropriate to use these results immediately in clinical practice.

THANK YOU FOR YOUR KIND ATTENTION!