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MEETING SUMMARY
ESMO 2021, VIRTUAL MEETING

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HIGHLIGHTS FROM NET CONNECT

SEPTEMBER 2021

NET, neuroendocrine tumour

DISCLAIMER AND DISCLOSURES

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KEY DATA

FIRST INTERNATIONAL RANDOMISED STUDY IN MALIGNANT PROGRESSIVE PHEOCHROMOCYTOMA AND PARAGANGLIOMAS (FIRSTMAPPP): AN ACADEMIC DOUBLE-BLIND TRIAL INVESTIGATING SUNITINIB

Baudin E, et al.

Abstract #567O_PR. ESMO 2021

FIRSTMAPPP: BACKGROUND AND STUDY DESIGN

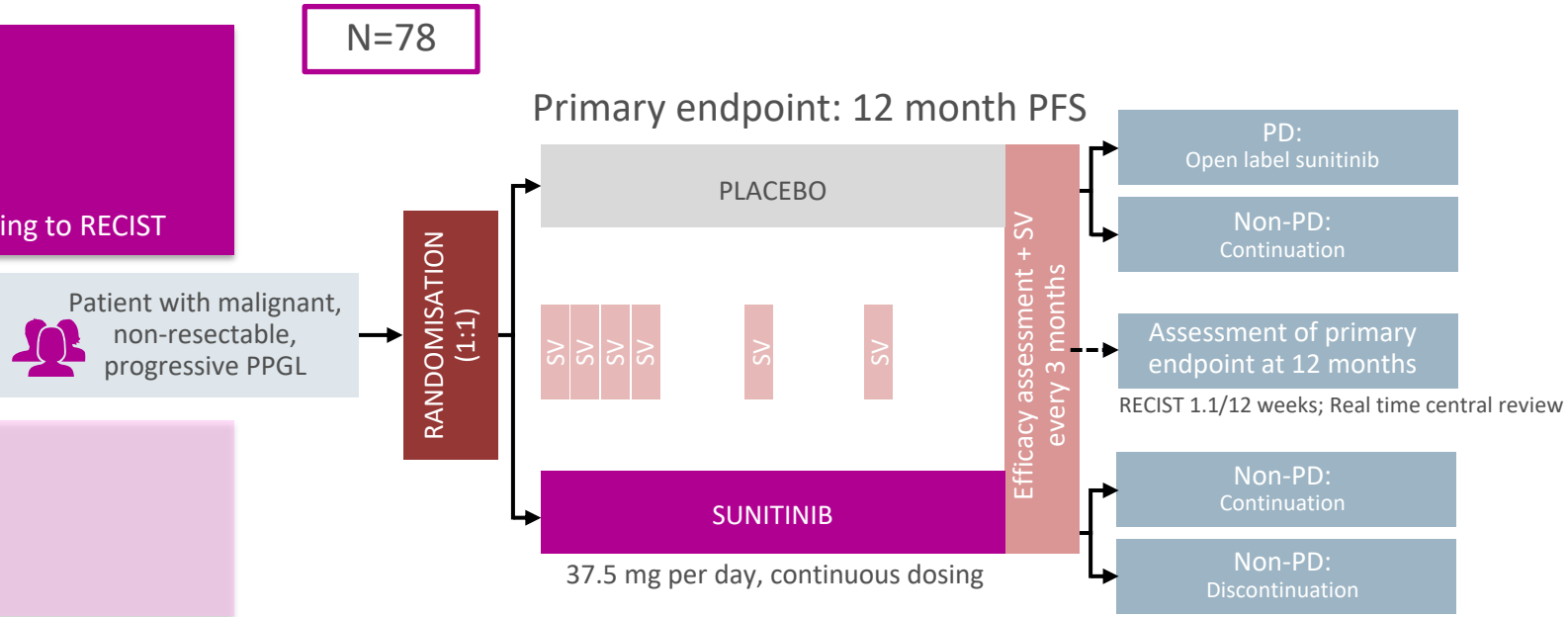
- **Malignant pheochromocytoma and paraganglioma** (MPPGL) are **very rare cancers** (annual incidence <1 per million) and have a very high unmet medical need
- Pheochromocytoma and paraganglioma tumours (PPGL) have been **shown to overexpress VEGF**
- **FIRSTMAPPP** is the first academic randomised double-blind phase 2 study results **assessing sunitinib efficacy compared to placebo** in MPPGL

Main inclusion criteria

Metastatic disease
Pre-treated or not
Inherited or not
Evaluable, RECIST 1.1 criteria
Progressing disease within 18 months according to RECIST

Main exclusion criteria

- Hypertension that cannot be controlled
- Abnormal cardiac function
- Prior tyrosine kinase inhibitors or anti-VEGF angiogenic inhibitors



PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; SV, site visit; VEGF, vascular endothelial growth factor
Baudin E, et al. Abstract #567O_PR. ESMO 2021. Oral presentation

FIRSTMAPPP: RESULTS

PRIMARY ENDPOINT: PFS AT 12 MONTHS

- FIRSTMAPPP met its primary endpoint of PFS at 12 months

PFS AT 12 MONTHS PER CENTRAL REVIEW (ITT)

Patients in the sunitinib arm	N	%
No progression at 1 year	**14**	**35.9**
Progression or death at 1 year	25	64.1

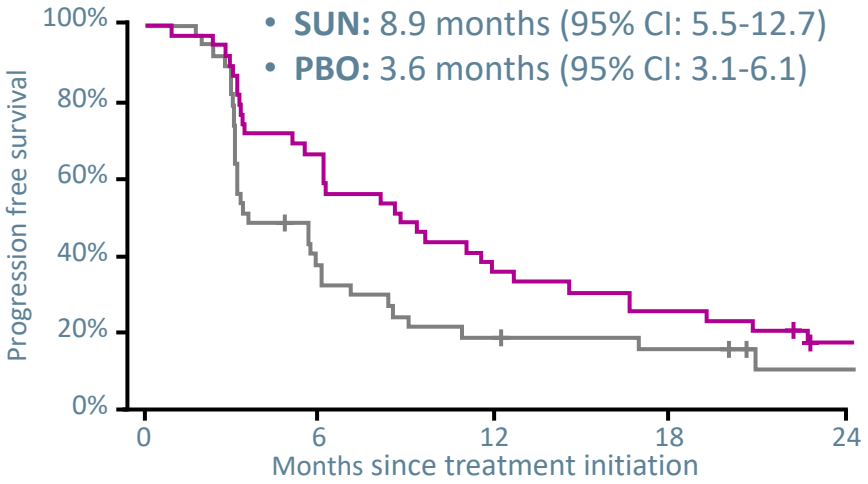
The **placebo group** served as an internal control: 12 month PFS (90% CI) was **18.9% (10.7-31.4)**

SAFETY

- Drug withdrawal due to adverse events (AEs): 14% SUN and 0% PBO
- Serious AEs experienced by 54% SUN vs 49% PBO patients
- Most frequent grade 3 or 4 AEs were asthenia/fatigue (18% SUN vs 3% PBO) and hypertension (10% SUN vs 6% PBO); 3 deaths in SUN arm and 1 death in placebo arm

MEDIAN PFS IN BOTH ARMS

Median PFS is
- **SUN:** 8.9 months (95% CI: 5.5-12.7)
- **PBO:** 3.6 months (95% CI: 3.1-6.1)



AE, adverse events; CI, confidence interval; ITT, intent-to-treat; PBO, placebo; PFS, progression free survival; SUN, sunitinib

Baudin E, et al. Abstract #567O_PR. ESMO 2021. Oral presentation

FIRSTMAPPP: SUMMARY

- **FIRSTMAPPP is a positive trial** and showed that sunitinib is active in MPPGLs
- First randomised study in the field of MPPGLs and **provides the highest level of evidence ever reached in this very rare cancer**
- **Safety profile manageable** and similar to other sunitinib trials
- Sunitinib is the therapeutic option for these patients with the most robust data in MPPGLs
- **Sunitinib becomes the first-line option in patients with progressive MPPGL**

MPPGL, metastatic pheochromocytoma and paraganglioma

Baudin E, et al. Abstract #567O_PR. ESMO 2021. Oral presentation; Garcia-Carbonero R. Discussant of abstract #567O_PR. ESMO 2021. Oral presentation

THE AXINET TRIAL (GETNE1107): AXITINIB PLUS OCTREOTIDE LAR IMPROVES PFS BY BLINDED CENTRAL RADIOLOGICAL ASSESSMENT VS PLACEBO PLUS OCTREOTIDE LAR IN GRADE 1 OR 2 EXTRAPANCREATIC NETs

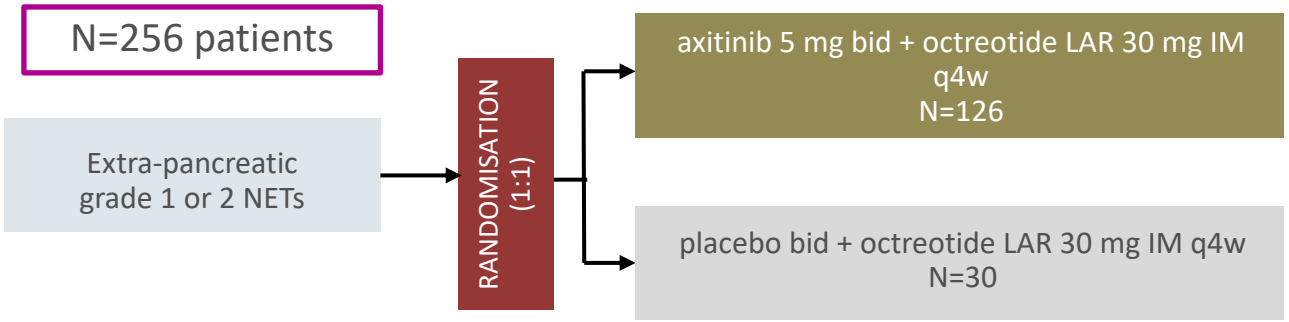
Garcia-Carbonero R, et al.

Abstract #1097O. ESMO 2021

NET, neuroendocrine tumour; PFS, progression free survival

AXINET: BACKGROUND AND STUDY DESIGN

- Neuroendocrine tumours (**NETs**) are highly vascular neoplasms **overexpressing VEGF** as well as VEGF receptors (**VEGFRs**)
- **Axitinib is a potent and selective VEGFR-1,-2,-3 inhibitor** with proven activity against other vascular-dependent solid tumours
- **AXINET** is a double-blind phase 2/3 randomised study **investigating the efficacy of axitinib in patients with advanced grade 1 or 2 extra-pancreatic NETs**
  - Study did not meet primary endpoint of PFS per investigator assessment (ASCO 2021)



Study endpoints

Primary: PFS per investigator assessment

Secondary: PFS per central blinded reading, ORR, DoR, OS, safety, biochemical response, biomarkers

ECOG PS 0-2

Up to 2 prior systemic treatment lines

No prior antiangiogenics

PD within prior 12 months

Stratification factors:

- Time from diagnosis to study entry (> or ≤12 months)
- Primary tumour site (GI tract vs non-GI)
- Ki-67 index (≤5% vs >5%)

bid, twice daily; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal; IM, intramuscular; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; q4w, every 4 weeks

Garcia-Carbonero R, et al. Abstract #1097O. ESMO 2021. Oral presentation; Garcia-Carbonero R, et al . J Clin Oncol 39, 2021 (suppl 3; abstr 360)

AXINET: RESULTS

EFFICACY

Central vs investigator assessment

Assessment	Tx arm	ORR	OR	p value	PFS	HR	p value
Central	axitinib placebo	13.2% 3.2%	4.58	0.0045	16.6 m 9.9 m	0.71	0.017
Investigator*	axitinib placebo	17.5% 3.8%	5.29	0.0004	17.2 m 12.3 m	0.82	0.169

*presented at ASCO GI 2021

- Safety profile consistent with known profile of axitinib and octreotide

BEST OVERALL RESPONSE

Central blinded assessment

Best overall response	axitinib-SSA N=114, n (%)	placebo-SSA N=125, n (%)	OR p value
ORR	**15 (13.2)**	**4 (3.2)**	**OR 4.58** **χ^2: 0.0045** **Fisher: 0.007**
CR	2 (1.8)	0 (0.0)	
PR	13 (11.4)	4 (3.2)	
SD	98 (86.0)	109 (87.2)	
PD	1 (0.9)	12 (9.6)	
NE	3 (2.6)	1 (0.8)	
NA*	9	4	

*Images not available

CR, complete response; HR, hazard ratio; m, months; NA, not available; NE, not evaluable; OR, odds ratio; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SSA, somatostatin analogue; Tx, treatment

Garcia-Carbonero R, et al. Abstract #1097O. ESMO 2021. Oral presentation

AXINET: SUMMARY

- **Axitinib in combination with octreotide LAR** vs placebo and octreotide LAR in patients with advanced progressive grade 1 or 2 extra-pancreatic NETs:
  - **Significantly improved PFS** as per central blinded radiological review
  - **Significantly improved ORR**
- Combination treatment had a **tolerable safety profile** in line with the known safety profiles for axitinib and octreotide

NET, neuroendocrine tumour; ORR, objective response rate; PFS, progression-free survival

Garcia-Carbonero R, et al. Abstract #1097O. ESMO 2021. Oral presentation

LANREOTIDE AUTOGEL/DEPOT IN PATIENTS WITH ADVANCED BRONCHOPULMONARY NETs: RESULTS FROM THE PHASE 3 SPINET STUDY

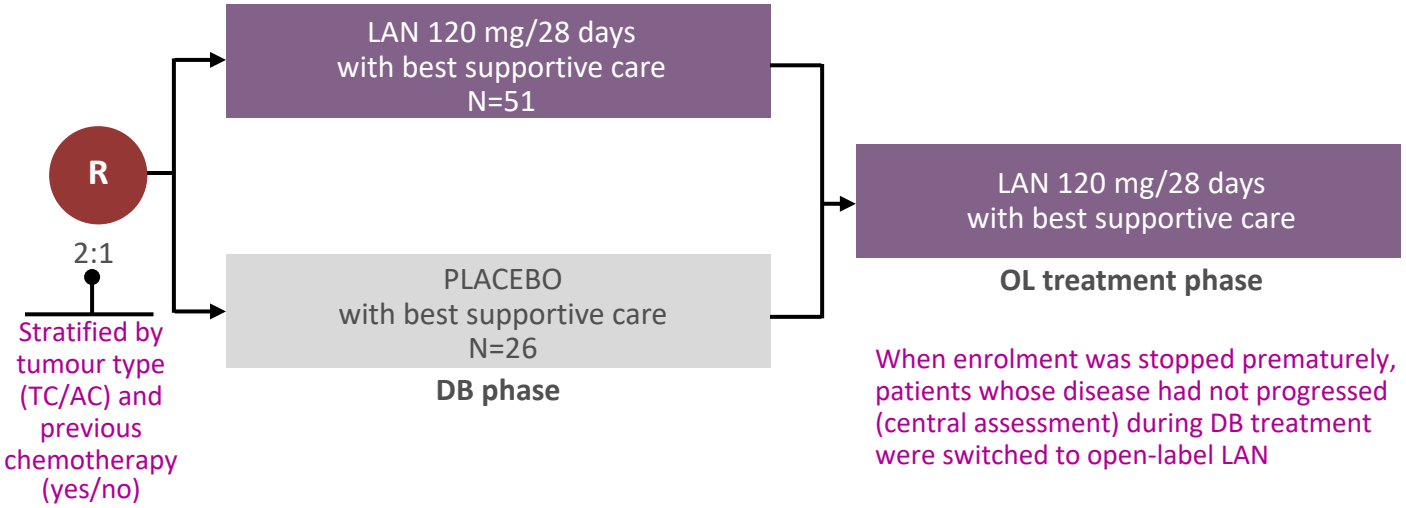
Horsch D, et al.

Abstract #1096O. ESMO 2021

NET, neuroendocrine tumour

SPINET: BACKGROUND AND STUDY DESIGN

- Well-differentiated bronchopulmonary neuroendocrine tumours **(BP-NETs) (typical and atypical carcinoids; TC and AC) account for ~25% of all NETs[1]**
- **Somatostatin analogues** (SSAs) are among targeted treatments that have **demonstrated increased PFS among patients with NETs**, particularly those with gastroenteropancreatic NETs[2]
- **High levels of expression of the somatostatin receptors** (SSTR)2A and 3 **in BP-NET** malignancies **provide a rationale for treatment with SSAs[2]**; however, there is a lack of prospective data with SSAs in BP-NETs[1]
- SPINET evaluated lanreotide (LAN) in advanced SSTR-positive BP-NETs[1]



Endpoints

- **Adapted primary endpoints:** PFS (centrally assessed, RECIST 1.1) during DB and OL phases in patients randomised to LAN

Adapted after enrolment stopped

- **Secondary endpoints** included:
  - PFS, ORR, and TTF in LAN and placebo groups during DB phase
  - Safety

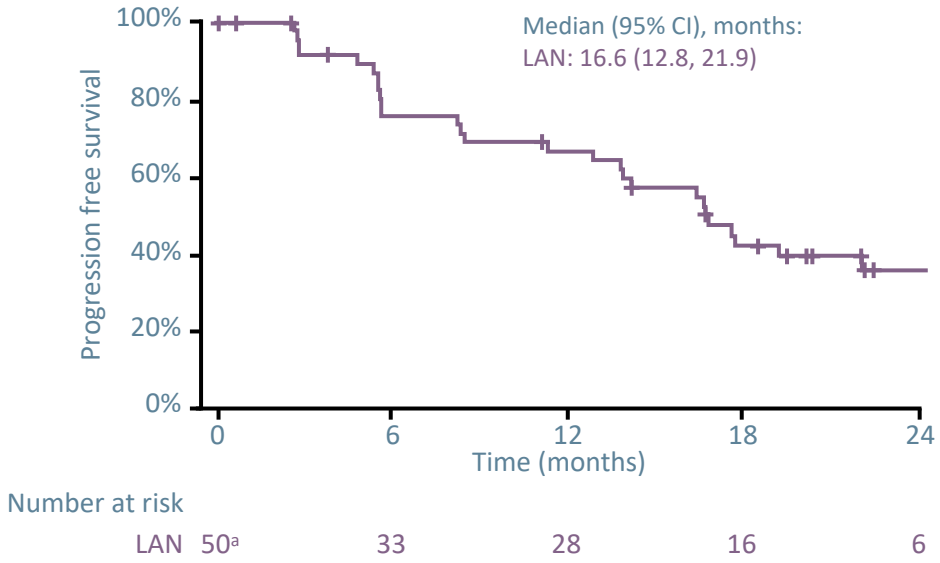
BSC, best supportive care; DB, double blind; NET, neuroendocrine tumour; OL, open label; ORR, objective response rate; PFS, progression free survival; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; TTF, time to treatment failure

1. Horsch D, et al. Abstract #1096O. ESMO 2021. Oral presentation; 2. Reidy-Lagunes D, et al. NANETS 2016. Poster presentation

SPINET: RESULTS

PRIMARY ENDPOINT - PFS in all patients

During DB and OL treatment phase in patients randomised to LAN (ITT)
Centrally assessed (RECIST 1.1)



SECONDARY ENDPOINTS

	Double-blind period		
	LAN (N=51)	PBO (N=26)	HR [95% CI][b]
PFS (all patients), median (95% CI), mo	16.6 (11.3–21.9)	13.6 (8.3–NC)	0.90 [0.46–1.88]
PFS (AC), median (95% CI), mo	13.8 (5.6-16.6)	11.0 (2.8-16.9)	–
PFS (TC), median (95% CI), mo	21.9 (13.8-NC)	13.9 (13.4-NC)	–
ORR, % (95% CI)	14.0 (5.8–26.7)	0 (0.0–13.7)	–
TTF, median (95% CI), mths	13.3 (5.6–14.1)	9.8 (5.4–13.6)	0.86 [0.50–1.50]

	Double-blind period		OL-LAN
TEAEs, n (%)[c]	LAN (N=51)	PBO (N=26)	All patients (n=40)
Any	49 (96.1)	25 (96.2)	26 (65.0)
Related	38 (74.5)	14 (53.8)	13 (32.5)
Grade 1, 2, 3, 4, 5	44 (86.3), 37 (72.5), 13 (25.5), 1 (2.0), 1 (2.0)	23 (88.5), 19 (73.1), 825 (62.5), 14 (35.0), 3 (30.8), 00	(7.5), 00
Leading to study treatment withdrawal	2 (3.9)	3 (11.5)	0
Serious AEs	10 (19.6)	7 (26.9)	1 (2.5)
Related	2 (3.9)	1 (3.8)	0

[a]one patient excluded from analysis because he/she was censored at baseline; [b]LAN vs PBO; [c]excludes death/progression (part of PFS assessment)

AC, atypical carcinoid; AE, adverse event; DB, double blind; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; LAN, lanreotide; mo, months; OL, open label; ORR, objective response rate; PBO, placebo; PFS, progression free survival; TC, typical carcinoid; TEAE, treatment emergent adverse event; TFF, time to treatment failure

Horsch D, et al. Abstract #1096O. ESMO 2021. Oral presentation

SPINET: SUMMARY

- **SPINET**, the largest prospective study to date with an SSA in SSTR-positive BP-NETs
- **LAN 120 mg was associated with a median PFS of 16.6 months**
  - The effect on median PFS was greater in patients with TC than AC
- Safety profile of LAN was consistent with known profile of LAN
- Results suggest that **LAN 120 mg could be an appropriate treatment option for BP-NETs,** especially for TCs

AC, atypical carcinoid; BP-NET, bronchopulmonary neuroendocrine tumour; LAN, lanreotide; PFS, progression-free survival; SSA, somatostatin analogue; SSTR, somatostatin receptor; TC, typical carcinoid

Horsch D, et al. Abstract #1096O. ESMO 2021. Oral presentation

OTHER DATA OF INTEREST

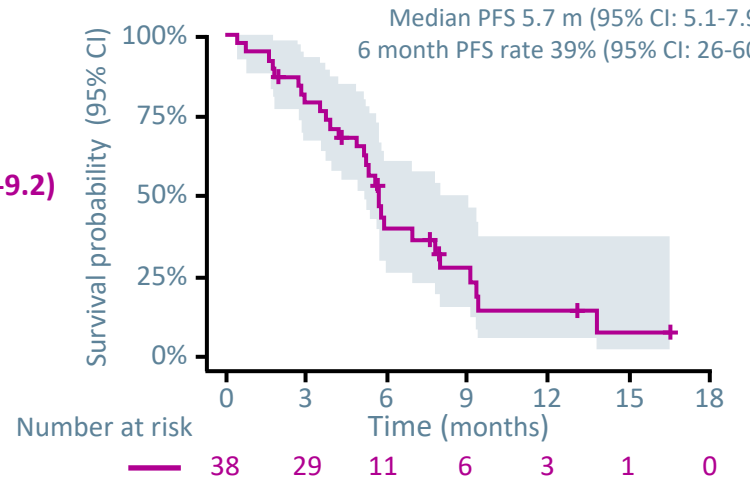
NIVOLUMAB PLUS PLATINUM-DOUBLET CT AS 1L THERAPY IN UNRESECTABLE, LOCALLY ADVANCED OR M1 GRADE 3 NENs OF THE GEP TRACT OR UNKNOWN ORIGIN: NICE-NEC TRIAL

- The phase 2, **NICE-NEC trial** assessed the safety and synergy of the **combination of CT plus immunotherapy (IT) in advanced CT-naïve grade 3 NENs**
  - Standard front-line platinum-based CT has limited efficacy
  - Grade 3 NENs are associated with a high mutational burden and PD-L1 expression that might lead to a favourable response to IT

EFFICACY RESULTS	
DCR	84%
ORR	50%
Best ORR*, n (%)	**N=38**
CR	0 (0)
PR	20 (52.6)
SD	12 (31.6)
PD	3 (7.9)
NE	3 (7.9)

Median follow up to 8.2 months (95% CI: 6-9.2)

*According to RECIST 1.1



- Preliminary results show **promising activity of adding nivolumab to CT as 1L therapy for grade 3 NENs**
  - Nivolumab did not significantly increase the toxicity profile of standard CT
  - Final survival results require further follow-up and translational studies are ongoing

1L, first-line; CI, confidence interval; CR, complete response; CT, chemotherapy; DCR, disease control rate; GEP, gastroenteropancreatic; m, months; M1, metastatic; NEN, neuroendocrine neoplasm; ORR, objective response rate; PD-L1, programmed death ligand-1; PFS, progression-free survival; PR, partial response

Riesco-Martinez MC, et al. Abstract #1098O. ESMO 2021. Oral presentation

DEVELOPMENT OF CAR T-CELLS FOR FUTURE TREATMENT OF NETs

- NETs overexpress SSTRs. The antitumor activity of chimeric antigen receptor (CAR) T-cells directed against SSTRs was investigated

RESULTS

- Tumour cell death was induced in ~40% (±8%) of CM and BON1 cells at E:T ratio of 1:1
- Tumoricidal effect of CAR T-cells was time-dependent and peaked at 72 hours
- Compared with untransduced T-cells, CAR T-cells secreted significantly higher levels of IFN-γ and IL-2 after co-incubation with NET cells ($p<0.01$)
- Anti-SSTR CAR T-cells effectively infiltrated tumours and significantly reduced the growth of subcutaneous CM ($p=0.01$) and BON1 xenografts ($p=0.02$) in mice by in vivo bioluminescence imaging
- No pathological alterations were seen in the brain and pancreas of mice treated with CAR T-cells

- Anti-SSTR CAR T-cells exert antitumor activity against $SSTR^+$ NET cell lines, both *in vitro* and *in vivo*
- Early phase clinical testing is warranted

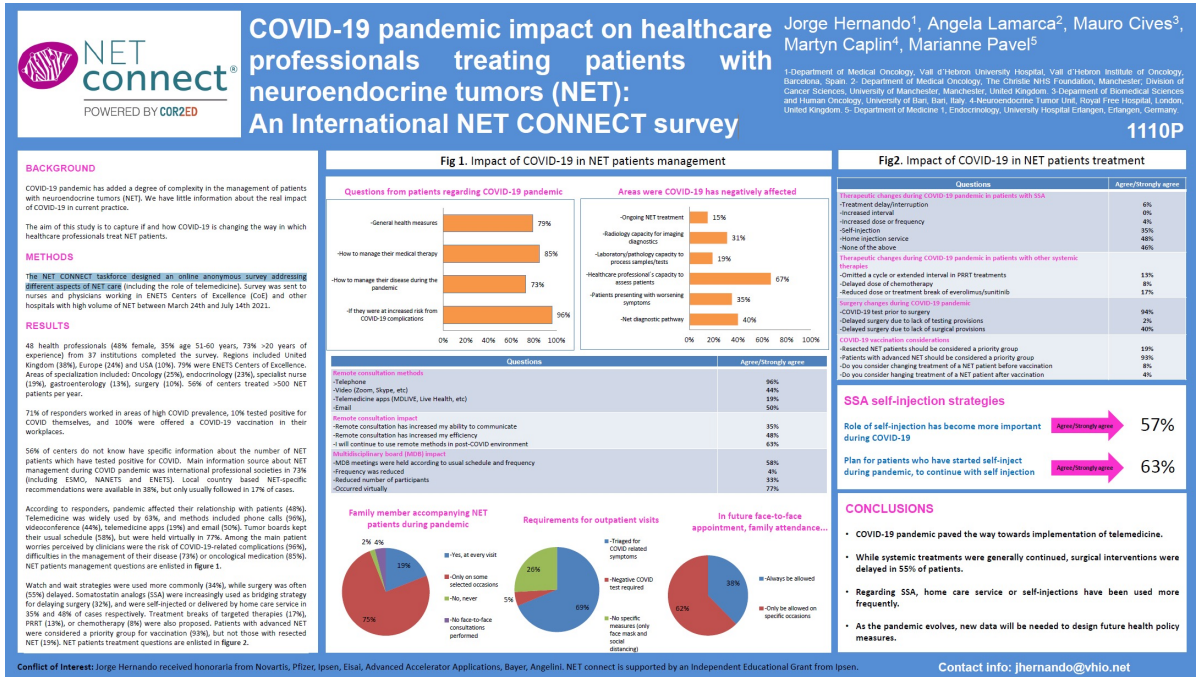
E:T, effector:target; IFN-γ, interferon gamma; IL-2, interleukin-2; NET, neuroendocrine tumour; SSTR, somatostatin receptor

Mandriani B, et al. Abstract #1101MO. ESMO 2021

COVID-19 PANDEMIC IMPACT ON HEALTHCARE PROFESSIONALS TREATING PATIENTS WITH NET

AN INTERNATIONAL NET CONNECT SURVEY

- **NET CONNECT** initiated an anonymous **survey for healthcare professionals** addressing different **aspects of NET care during the COVID pandemic**
  - COVID-19 pandemic paved the way towards implementation of telemedicine
  - While systemic treatments were generally continued, surgical interventions were delayed in 55% of patients
  - Regarding SSA, home care service or self-injections have been used more frequently
  - As the pandemic evolves, new data will be needed to design future health policy measures



NET, neuroendocrine tumours; SSA, somatostatin analogues

Hernando J, et al. Abstract #1110P. ESMO 2021; NET CONNECT: COVID-19 Survey presented at ESMO 2021 - NET CONNECT (net-connect.info)

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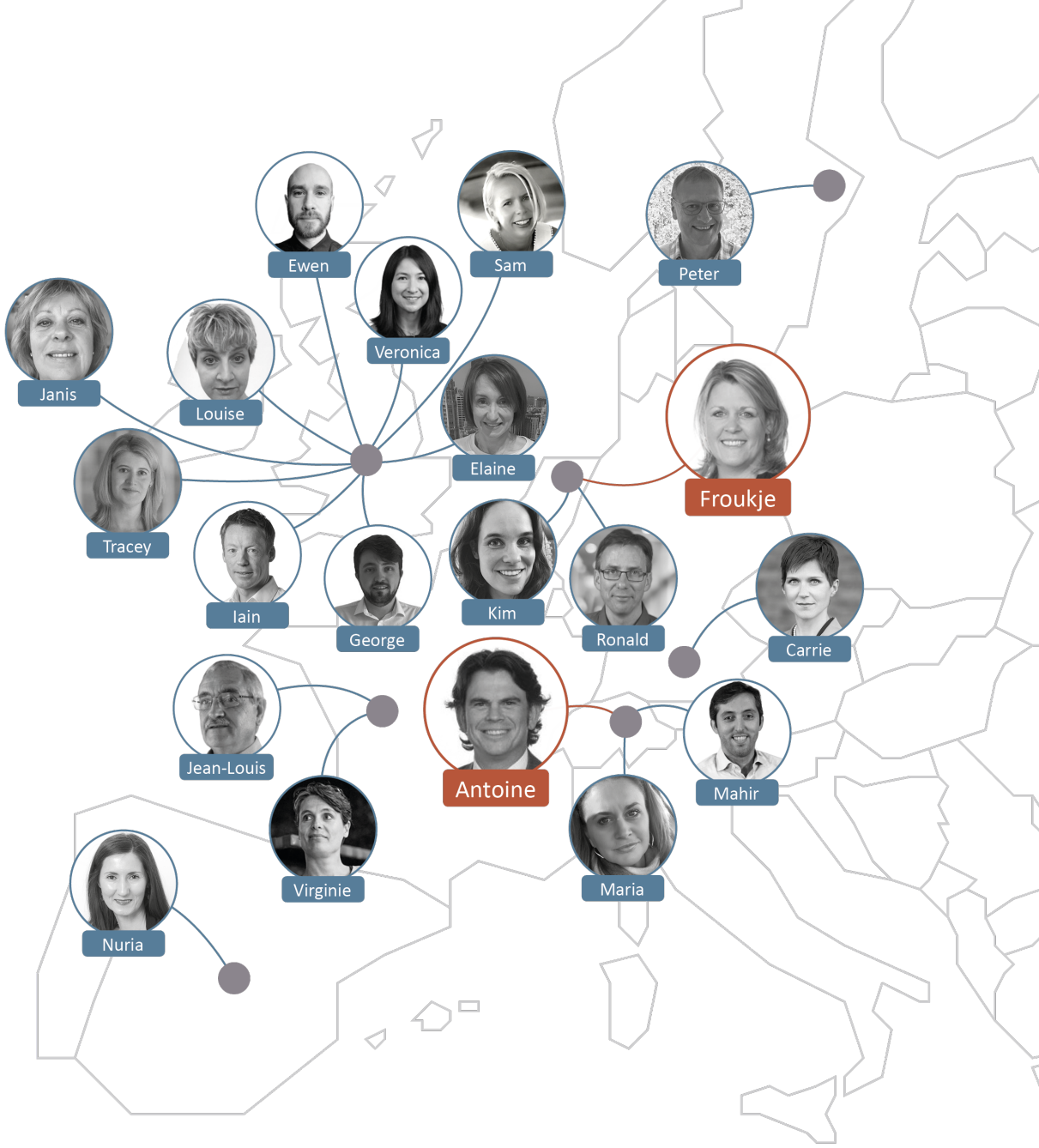

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