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MEETING SUMMARY
ESMO 2020, VIRTUAL MEETING

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HIGHLIGHTS FROM NET CONNECT
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DISCLAIMER AND DISCLOSURES

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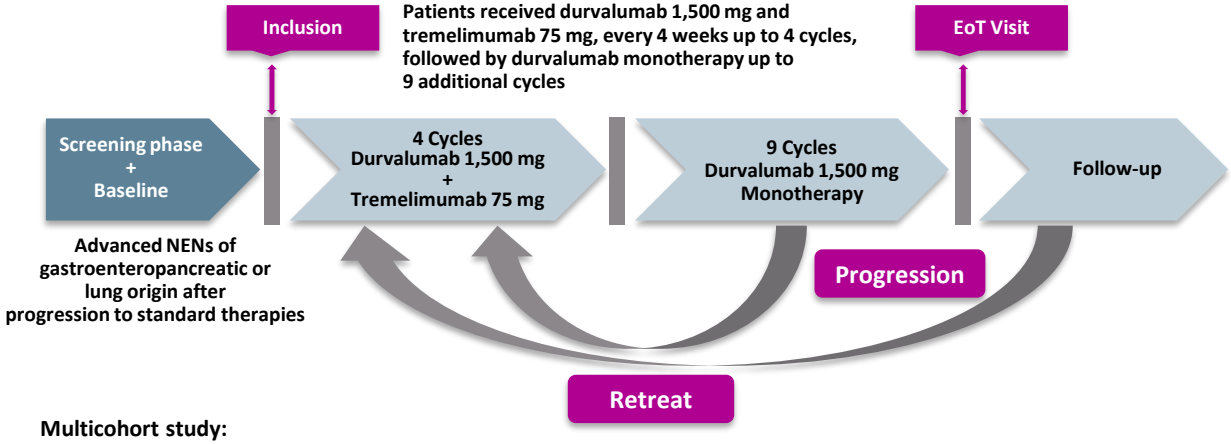
A MULTI-COHORT PHASE 2 STUDY OF DURVALUMAB PLUS TREMELIMUMAB FOR THE TREATMENT OF PATIENTS WITH ADVANCED NENs OF GEP OR LUNG ORIGIN: THE DUNE TRIAL (GETNE 1601)

Capdevila J, et al.
ESMO 2020. Abstract #1157O. Oral presentation

GEP, gastroenteropancreatic; NENs, neuroendocrine neoplasm

BACKGROUND

- **Immune checkpoint blockade (ICB) has shown limited activity in advanced NENs to date**, mainly due to the background biology of these neoplasms, with usually low tumour mutational burden, low expression of PD-L1 and low lymphocyte filtration
- **Targeting both PD-L1 and CTLA-4 may increase the efficacy of ICB in NENs** and revert the intrinsic resistance:
  - The PD-1 inhibitors, pembrolizumab and spartalizumab, have shown limited activity in well differentiated NETs[1,2]
  - The combination of anti-PD-L1 (nivolumab) and anti-CTLA-4 (ipilimumab) has shown promising activity in high-grade NENs[3,4]
- **The DUNE study investigated the activity of durvalumab (anti-PD-L1) plus tremelimumab (anti-CTLA-4)**



Primary endpoint:
- Cohorts 1-3: 9-month CBR
- Cohort 4: 9-month OS rate

Secondary endpoints:
- Safety, PFS, OS, ORR, DOR and biomarker analysis

Multicohort study:
C1: Typical/atypical lung carcinoids. Prior therapy with somatostatin analogues and/or targeted therapies or chemotherapy
C2: Grade 1/2 gastrointestinal. Prior treatment with somatostatin analogues and targeted therapy such as everolimus or radionucleotides
C3: Grade 1/2 pancreatic. Prior treatment with chemotherapy, somatostatin analogues and targeted therapies. 2-4 systemic treatment lines
C4: Grade 3 gastroenteropancreatic origin. After first line of chemotherapy with a platinum-based regimen

C, cohort; CBR, clinical benefit rate; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DOR, duration of response; EoT, end of treatment; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumour; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival

1. Strosberg J, et al. Clin Cancer Res. 2020;26:2124-30; 2. Yao J, et al. Ann Oncol. 2018;29 suppl 8:viii467-78; 3. Patel S, et al. Clin Cancer Res. 2020:26:2290-6;
4. Klein O, et al. Clin Cancer Res. 2020;26:4454-9. Capdevila J, et al. ESMO 2020. Abstract #1157O. Oral presentation

RESULTS

- 123 patients were included (C1=27, C2=31, C3=32,C4=33)
- Median age 62 years, 59% males, 43% ECOG PS 0
- 91% of C4 (grade 3 GEP-NEN) had poorly differentiated tumours

PRIMARY ENDPOINTS

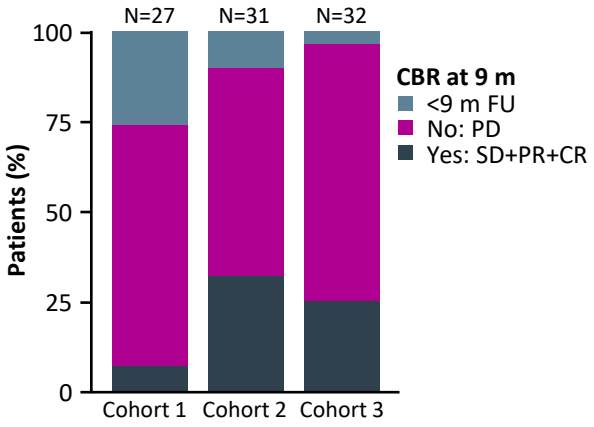
With a median follow-up of 10.8 m:

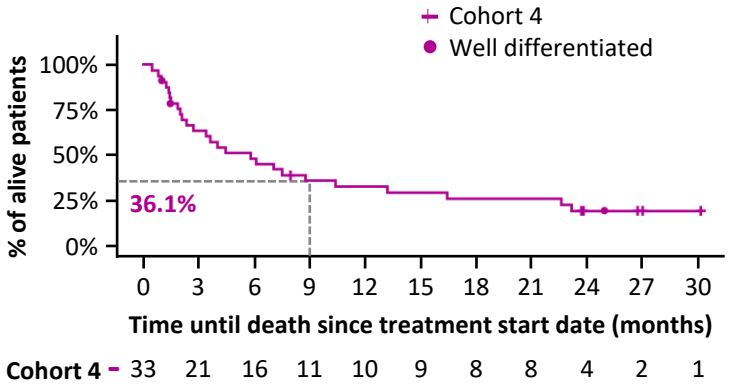
CBR at 9 months (by RECIST v1.1) was:

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

OS rate at 9 months for cohort 4 was:

- Cohort 4, Grade 3 GEP: 36.1% (95% CI: 22.9-57) (N=33)





	irORR, %		
	All	PD-L1 +	PD-L1 -
Cohort 1: Typical/atypical lung carcinoids	7.4	16.6*	0
Cohort 2: Grade 1/2 gastrointestinal	0	0	0
Cohort 3: Grade 1/2 pancreatic	6.3	25	0
Cohort 4: Grade 3 GEP	9.1	0	7.7

* PD-L1 expression only enriched irORR in cohort 1 (p=0.033)

SAFETY

- Most common TRAEs: fatigue (43.0%), diarrhoea (31.7%), pruritus (23.6%), nausea (13.8%), hypothyroidism (9.8%)
- Most frequent grade ≥3 TRAEs: liver toxicity (9.7%), diarrhoea (6.5%), fatigue (2.4%) and vomiting (2.4%)

C, cohort; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; FU, follow up; GEP-NEN, gastroenteropancreatic neuroendocrine tumours; irORR, immune-related objective response rate; PD, progressive disease; PD-L1, programmed death-ligand 1;
RECIST, Response Evaluation Criteria In Solid Tumours; SD, stable disease; TRAE, treatment-related adverse event
Capdevila J, et al. ESMO 2020. Abstract #1157O. Oral presentation

SUMMARY

- Durvalumab and tremelimumab combination showed modest activity in this heavily pre-treated population
- In WHO grade 3 NENs (cohort 4), the combination therapy met the predefined threshold for OS at 9 months and deserves further evaluation
- Objective radiological responses were infrequent
- No new safety concerns were identified in this large population of advanced NENs

NEN, neuroendocrine neoplasm; OS, overall survival; WHO, world health organisation

Capdevila J, et al. ESMO 2020. Abstract #1157O. Oral presentation

EFFICACY AND SAFETY OF LANREOTIDE AUTOGEL 120 MG EVERY 14 DAYS IN PROGRESSIVE PANCREATIC OR MIDGUT NETs: CLARINET FORTE STUDY RESULTS

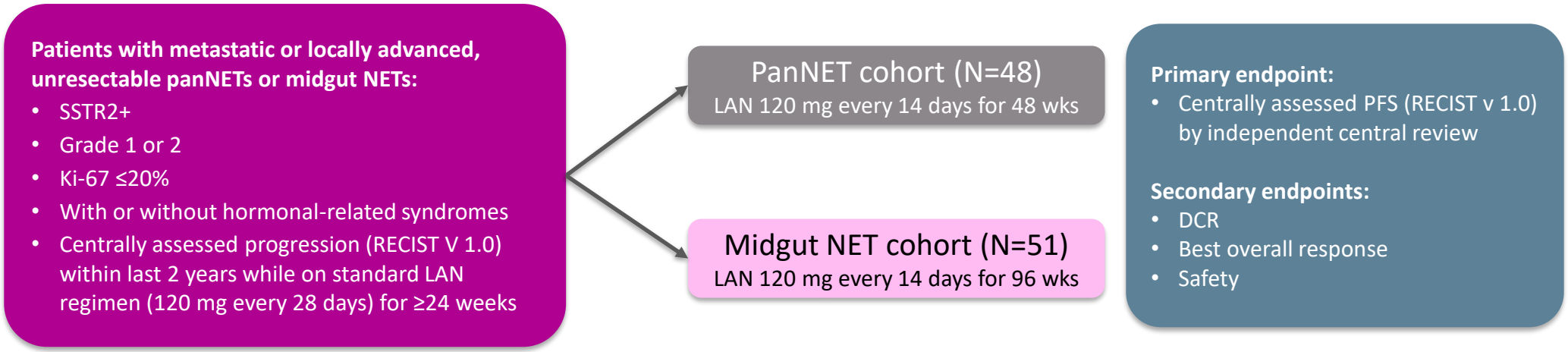
Pavel M, et al.

ESMO 2020. Abstract #1162MO. Mini oral presentation

NETs, neuroendocrine tumours

BACKGROUND

- Currently, **patients with progressive disease after treatment with lanreotide** (120 mg every 28 days) **have limited treatment options** and receive less well-tolerated systemic chemotherapy or molecular targeted therapies
- **CLARINET FORTE** is a prospective, open label, exploratory, European phase 2 study that **investigated the efficacy and safety of an increased dosing frequency of lanreotide** in patients with progressive pancreatic neuroendocrine tumours (panNETs) and midgut NETs

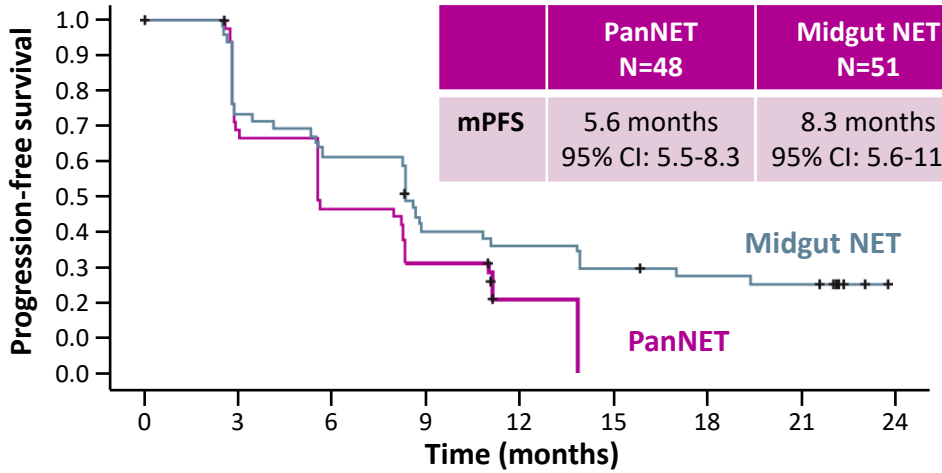


DCR, disease control rate; LAN, lanreotide; NET, neuroendocrine tumour; PFS, progression free survival; RECIST, Response Evaluation Criteria In Solid Tumours; SSTR2, somatostatin receptor type 2; wks, weeks

https://clinicaltrials.gov/ct2/show/NCT02651987; Pavel M, et al. ESMO 2020. Abstract #1162MO. Mini oral presentation.

RESULTS

PFS (PRIMARY ENDPOINT)



	PanNET N=48	Midgut NET N=51
mPFS	5.6 months 95% CI: 5.5-8.3	8.3 months 95% CI: 5.6-11.1

POST-HOC SUBGROUP ANALYSIS

mPFS by Ki-67	PanNET
Ki-67 ≤10% (n=43)	8.0 months 95% CI: 5.6-8.3
Ki-67 >10% (n=5)	2.8 months 95% CI: 2.8-2.9

SECONDARY ENDPOINTS

	PanNET N=48	Midgut NET N=51
DCR at week 24, % (95% CI)	43.8 (29.5-58.8)	58.8 (44.2-72.4)
DCR at week 48, % (95% CI)	22.9 (12.0-37.3)	33.3 (20.8-47.9)

SAFETY

Adverse event	PanNET N=48	Midgut NET N=51
TRAEs, %	37.5	51.0
TRAEs grade ≥3, n (%)	1 (2.1)*	-
Most common (≥10%) TRAEs, % Gastrointestinal disorders General disorders/administration site conditions	 25.0 13.7	 37.3 -

* Grade 3 TRAE of fatigue

- TRAEs of note:
  - hyperglycaemia (n=2), bile stones (n=1), steatorrhea (n=1)

CI, confidence interval; DCR, disease control rate; mPFS, median progression free survival; NET, neuroendocrine tumour; panNET, pancreatic NET; TRAE, treatment-related adverse event

Pavel M, et al. ESMO 2020. Abstract #1162MO. Mini oral presentation

SUMMARY

- **Lanreotide (LAN) 120 mg every 14 days** in patients with progressive panNETs or midgut NETs (progressive on standard LAN dose) **provided encouraging PFS and disease control rate data**
  - In the panNET cohort, the outcome was more favourable in patients with Ki-67 ≤10%
- No new safety concerns were identified with the increased dose frequency of LAN
  - The **safety was consistent with the known safety profile of LAN**
- Escalating LAN dosing frequency in patients with progressive NETs **may be an alternative treatment option before switching to more toxic agents** such as PRRT/targeted therapies/chemotherapy

NET, neuroendocrine tumour; panNET, pancreatic NET; PFS, progression free survival; PRRT, peptide receptor radionuclide therapy

Pavel M, et al. ESMO 2020. Abstract #1162MO. Mini oral presentation

SURVIVAL AND PROGNOSTIC ANALYSIS OF 535 GRADE 3 GEP-NEN: DATA FROM THE SPANISH TASKFORCE OF NEUROENDOCRINE TUMOURS REGISTRY (R-GETNE)

Jimenez Fonseca P, et al.
ESMO 2020. Abstract #1159MO. Mini oral presentation

GEP-NEN, gastroenteropancreatic neuroendocrine neoplasm

BACKGROUND

- Grade 3 neuroendocrine carcinomas (NECs) represent the most aggressive spectrum of neuroendocrine neoplasms (NENS) and have limited treatment options
- A previous analysis from the GETNE (Spanish) registry confirmed the worse prognosis associated with grade and Ki-67 index in patients with gastroenteropancreatic neuroendocrine tumours (GEP-NETs)[1]
- The R-GETNE database includes 4807 GEP-NENs patients diagnosed between 2004-2019
- The study cohort for this analysis included 535 patients with grade 3 NECs with a Ki-67 index >20%[2]

Results	Grade 3 NEC KI-67 >20% N=535
≥70 years	29% (median age 64)
Women	40%
ECOG PS 0-1	85%
Most common primary sites	
Colorectum	30%
Pancreas	24%
Unknown	16%
Stomach	13%
Small Intestine	4%
Stage at diagnosis	
I	3%
II	9%
III	20%
IV	68%

Results

- 87% stage I-III NECs were resected
  - 54% of these received adjuvant chemotherapy
- 73% of patients with advanced NECs received platin and etoposide
  - Response rate: 64%
  - median progression-free survival (mPFS): 6.1 months

ECOG PS, Eastern Cooperative Oncology Group performance status; R-GETNE, Registry of Grupo Español de Tumores Neuroendocrinos

1. Nuñez-Valdovinos B, et al. Oncologist. 2018;22:1-11; 2. Jimenez Fonseca P, et al. ESMO 2020. Abstract #1159MO. Mini oral presentation

RESULTS

- Median overall survival (OS) was 14 months; 353 patients died (67%)
- Median follow up of 4 years
- Prognostic factors: stage, primary site, ECOG PS and gender were identified as independent prognostic factors for OS ($p<0.05$)

Overall Survival	Results
Median OS, months	14
Median OS by stage (95% CI), years	
I	6.1 (1.8-NA)
II	5.8 (1.9-NA)
III	2.1 (1.5-6.7)
IV (months)	9.7 (6.7-12.9)
Median OS by site in stage IV (95% CI), months	
Small Intestine	14.0 (12.6-15.8)
Pancreas	10.1 (9.5-11.8)
Rectum	9.9 (8.2-11.2)
Stomach	7.3 (5.2-9.3)
Colon	4.7 (2.8-7.0)
Unknown primary	2.7 (1.9-3.8)

Prognostic Factor	HR	95% CI HR	
		Min	Max
Stage			
IV	Reference		
I-III	0.43	0.27	0.81
Primary tumour			
Others	Reference		
Small intestine, pancreas, rectum	0.63	0.44	0.92
ECOG PS			
2	Reference		
0-1	0.64	0.37	0.77
Gender			
Male	Reference		
Female	0.89	0.74	0.95

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio

Jimenez Fonseca P, et al. ESMO 2020. Abstract #1159MO. Mini oral presentation

SUMMARY

- One of the largest reported series of grade 3 GEP-NECs to date, providing important information to help stratify patients for clinical decisions
- Performance status, stage and primary tumour location are known prognostic factors for NETs but this is the first cohort study to identify gender as a potential new variable
  - Requires validation in clinical trials

GEP-NECs, gastroenteropancreatic neuroendocrine carcinomas; NET, neuroendocrine tumour

Jimenez Fonseca P, et al. ESMO 2020. Abstract #1159MO. Mini oral presentation

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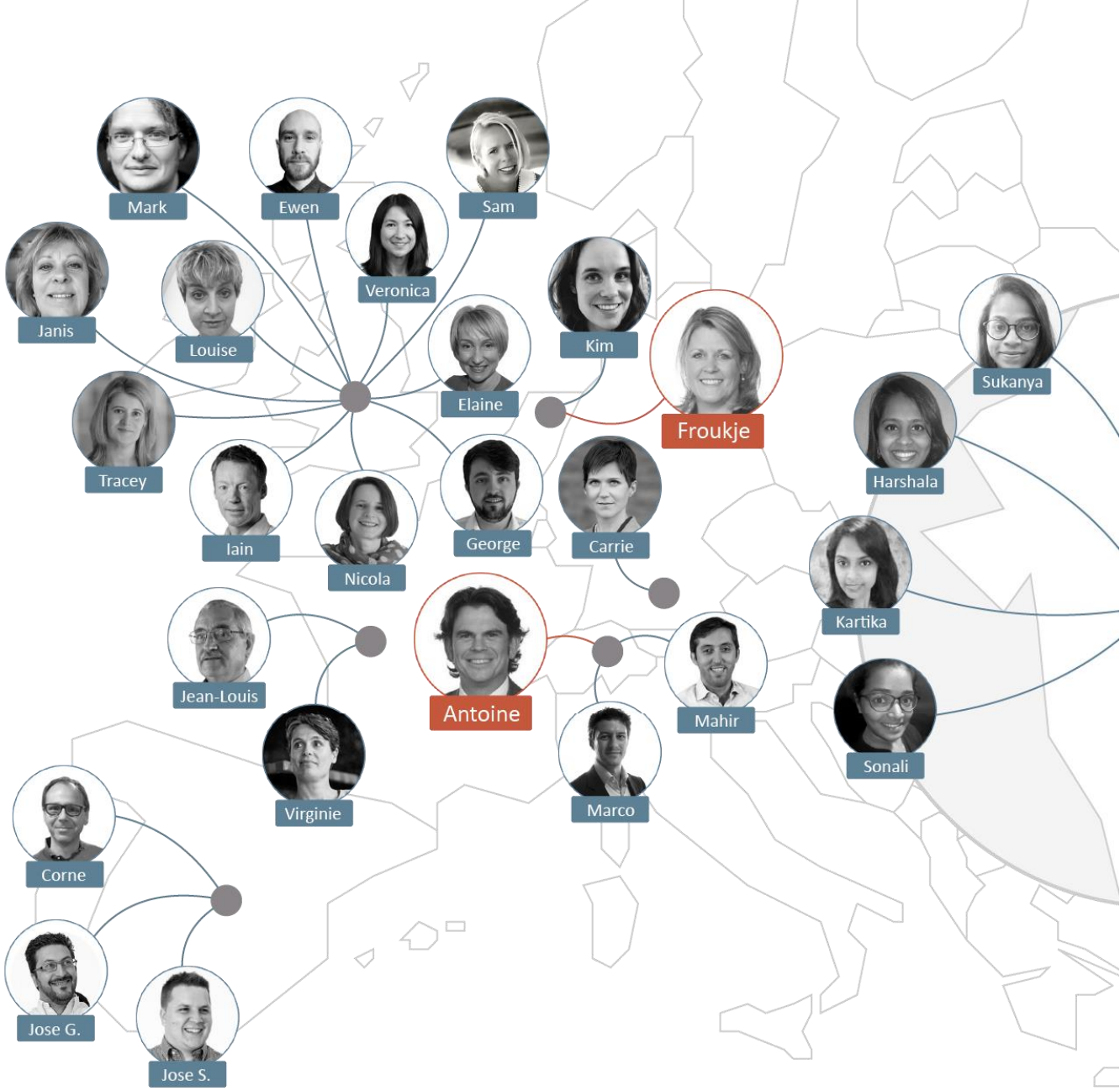

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