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MEETING SUMMARY
UPPER GI CANCER HIGHLIGHTS FROM ESMO 2022

Dr. Samuel J. Klempner, MD
Medical Oncologist, Massachusetts General Hospital, Boston, USA

Dr. Yelena Y. Janjigian, MD
Medical Oncologist, Memorial Sloan Kettering Cancer Center, New York, USA

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FIRST LINE DATA ESMO 2022

REGORAFENIB WITH NIVOLUMAB AND FOLFOX IN HER2 NEGATIVE ESOPHAGOGASTRIC CANCER

Cytryn S, et al. ESMO 2022. Abstract #1227P

FOLFOX, folinic acid/fluorouracil/oxaliplatin; HER2, human epidermal growth factor receptor 2

BACKGROUND AND STUDY DESIGN

- Nivolumab plus chemotherapy demonstrated superior overall survival versus chemotherapy in metastatic esophagogastric (EGC)[1]
- Regorafenib plus nivolumab demonstrated an ORR of 40% in 3L EGC suggesting synergistic activity[2]
- Regorafenib plus FOLFOX did not previously improve PFS over 1L chemotherapy
- This study evaluated the efficacy of regorafenib, nivolumab and FOLFOX in previously untreated, locally advanced unresectable or metastatic EGC

INVESTIGATOR-INITIATED SINGLE ARM, OPEN LABEL, PHASE 2 STUDY

Study population

- Patients with untreated, M1 oesphageal, GEJ or gastric adenocarcinoma
- ECOG PS 0-1
- RECIST v1.1 measurable or evaluable disease
- Patients with adequate organ function, uncontrolled hypertension or active autoimmune disease were excluded

REGORAFENIB 80 mg daily + NIVOLUMAB 240 mg qw2 + FOLFOX

N=35

Primary endpoint

- 6-month PFS

Secondary endpoints:

- ORR
- DCR
- Median PFS
- OS
- Safety

- **Exploratory biomarker analyses:** (PD-L1, ctDNA, mutational status, PBMC, tumour infiltrating lymphocytes, T-cell receptor clonality)

1L, first line; 3L, third line; ctDNA, circulating tumour DNA; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; EGC, esophagogastric cancer; FOLFOX, folinic acid/fluorouracil/oxaliplatin; GEJ, gastroesophageal junction; M1, metastatic; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; PBMC, peripheral blood mononuclear cells; Qw2, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumours

1. Janjigian et al, Lancet 2021. 398: 27-40; 2. Fukuoka S, et al. J Clin Onc 2020, 38: 2053-2061; 3. Moy R, et al. Oncologist 2020, 25: e68-e74; 4. Cytryn S, et al. Ann Oncol. 2022;33 (suppl_7): S555-S580 (ESMO 2022, poster presentation)

RESULTS

EFFICACY

Survival Results	Pts with evaluable disease N=34
6-month PFS	71% (53-85%)
12-month PFS	51% (35-74%)
Median PFS	13.0 months (7.6-NR)
6-month OS	97% (92-100%)
12-month OS	83% (68-100%)
Median OS	NR
Median follow up	11.1 months
Tumour response	**Pts with measurable disease N=29**
ORR (%)	66
DCR (%)	97
CR (%)	7

- Response rate and 6-month PFS were comparable among patients with PD-L1 CPS negative (<1), low (1-4) and high (≥5) tumours

SAFETY

Grade 3 or 4 adverse events occurring in ≥5%	Number (%) N=35
Neutropenia	18 (51%)
Hypertension	5 (14%)
Rash	4 (11%)
Anaemia	4 (11%)
Nausea/vomiting	3 (9%)
LFT elevation	3 (9%)
Acute kidney injury	3 (9%)
Palmar-plantar erythrodysesthesia (PPE)	2 (6%)
Fatigue	2 (6%)

- Most common any-grade AEs were fatigue (89%), PPE (69%), neutropenia (63%), peripheral neuropathy (60%) and rash (49%)
- 18 (51%) of patients had grade 3/4 AE
- Regorafenib was dose reduced in 31% of pts and discontinued in 17%.
- Nivolumab was discontinued in 11% of pts.

AE, adverse event; CR, complete response; DCR, disease control rate; LFT, liver function tests; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; ; PPE, palmar-plantar erythrodysaesthesia; pt, patient

Cytryn S, et al. Ann Oncol. 2022;33 (suppl_7): S555-S580 (ESMO 2022, poster presentation)

SUMMARY

- The study met its primary endpoint of 6-month PFS
- Nearly all patients had disease control and 66% had a partial or complete response
- There was a lower-than-expected CPS ≥5 positive rate in our cohort using PD-L1 IHC E1L3N compared to Checkmate 649 (PDL1 IHC 28.8) and Orient 16 (PD-L1 IHC 22C3) cohorts
- The addition of regorafenib to FOLFOX/nivolumab was tolerated with manageable adverse events

Clinical Perspective

- **The majority of patients had a response, irrespective of PDL1 status, with no new safety signals**
- **Further investigation of the regorafenib, nivolumab, FOLFOX combination is warranted**

CPS, combined positive score; FOLFOX, folinic acid/fluorouracil/oxaliplatin; IHC, immunohistochemistry; PDL1, programmed death ligand-1; PFS, progression-free survival

Cytryn S, et al. Ann Oncol. 2022;33 (suppl_7): S555-S580 (ESMO 2022, poster presentation)

FIRST-LINE LENVATINIB PLUS PEMBROLIZUMAB PLUS CHEMOTHERAPY VERSUS CHEMOTHERAPY IN ADVANCED/METASTATIC GASTROESOPHAGEAL ADENOCARCINOMA: LEAP-015 SAFETY RUN-IN

Shitara K, et al. ESMO 2022. Abstract #1223P

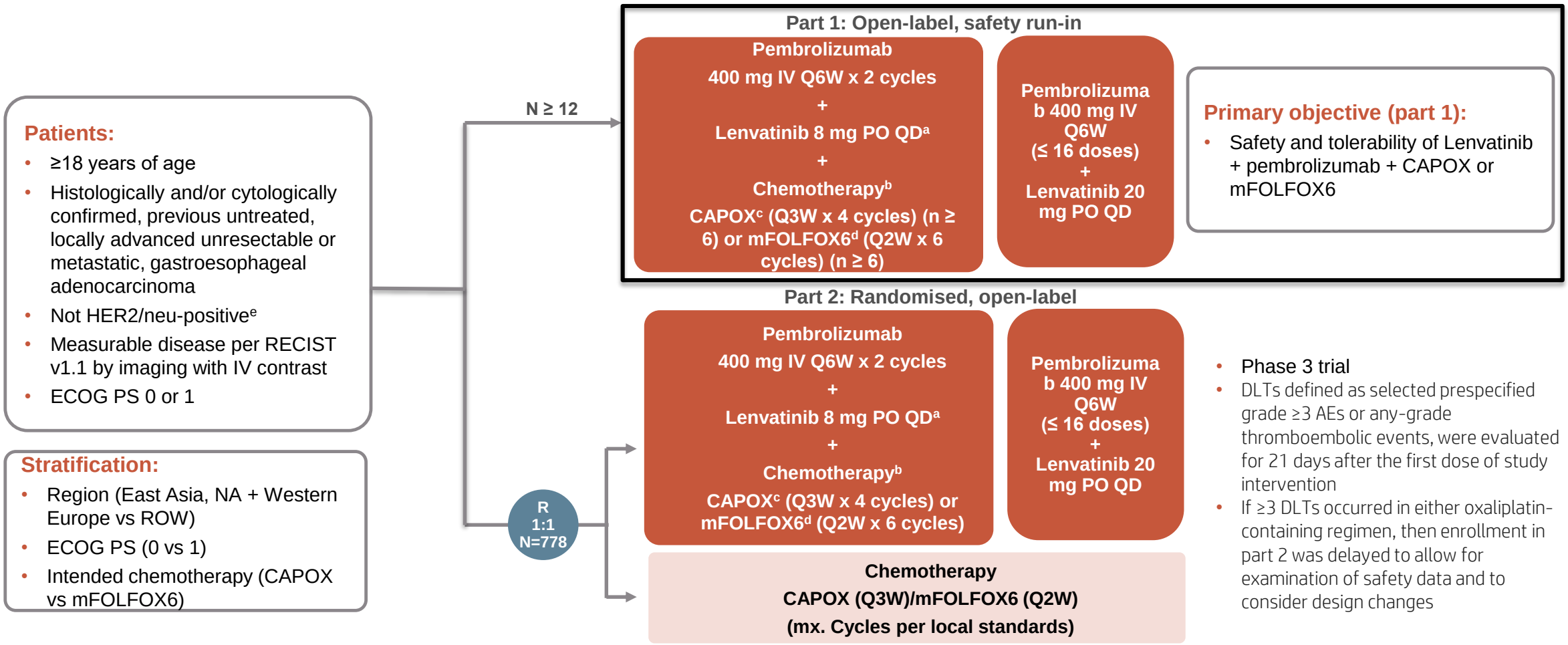
LEAP-015: BACKGROUND

- The combination of chemotherapy with fluoropyrimidine (nivolumab) and platinum therapy is recommended by the NCCN as a first-line treatment in patients with advanced gastric cancer.[1] However, there is a need for more effective therapies.
- Previous findings have shown that the PD-1 inhibitor pembrolizumab in combination with the multiple receptor tyrosine kinases inhibitor lenvatinib demonstrated synergistic antitumor activity and an acceptable safety profile in these patients.[2]

NCCN, National Comprehensive Cancer Network; PD-1, programmed cell death protein-1

1. NCCN. J Natl Compr Canc Netw. 2022;20(2):167-192; 2. Kawazoe A et al. Lancet Oncol. 2020;21:1057-1065

LEAP-015: STUDY DESIGN



[a]After the last cycle of the induction phase, Lenvatinib will be maintained at the current dose until the start of the consolidation phase; [b]Selection of chemotherapy backbone by investigator must be determined before allocation; [c]CAPOX: oral capecitabine 1000mg/m^2 BID for 14 days and IV oxaliplatin 130 mg/m^2; [d]mFOLFOX6: bolus IV 5-FU 400 mg/m^2 and continuous IV 5-FU 2400 mg/m^2, IV leucovorin 400 mg/m^2 or IV levoleucovorin 200 mg/m^2; and IV oxaliplatin 85 mg/m^2; [e]If HER2/neu status is unknown, HER2/neu testing will be conducted according to local standard-of-care requirements, if any.

5-FU, 5-fluorouracil; AE, adverse event; BID, twice daily; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2/neu, human epidermal growth factor receptor 2; IV, intravenously; NA, North America; PO, by mouth; Q2W, every 2 weeks; Q3W, every weeks; Q6W, every 6 weeks; QD, every day; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; ROW, rest of world

Shitara K, et al. Ann Oncol. 2022;33 (suppl_7): S555-S580 (ESMO 2022, poster presentation)

LEAP-015: RESULTS (PART 1)

Summary of Safety and Tolerability	N=15
All-cause AEs, N (%)	15 (100)
Grade 3-5	10 (67)
Serious AE	5 (33)
Leading to death	0 (0)
Dose interruption of PEM	10 (67)
Dose interruption of LEN	10 (67)
Dose interruption of both LEN and PEM	6 (40)
Dose reduction[a]	4 (27)
Discontinued any study treatments	4 (27)
Discontinued all study treatments	0 (0)
Treatment-related AEs, N (%)	14 (93)
Grade 3-5	8 (53)
Serious AE	2 (13)
Leading to death	0 (0)
Discontinued any study treatments	4 (27)
Discontinued all study treatments	0 (0)
Immune-mediated AEs or infusion reactions, N (%)	4 (27)
Grade 3-5	0 (0)
Serious AE	0 (0)
Discontinued any study treatments	1 (7)
Discontinued all study treatments	0 (0)

Treatment-related AEs with a frequency of ≥ 10%	Frequency %
Nausea	47
Diarrhoea	40
Asthenia	33
Peripheral neuropathy	33
PPE	33
Vomiting	33
Decreased appetite	27
Neutrophil count decreased	27
Lipase increased	20
Neutropenia	20
Stomatitis	20
Blood TSH increased	13
Fatigue	13
Gingivitis	13
Hypertension	13
Hyopthyroidism	13
Mucosal inflammation	13
Platelet count decreased	13
Rash	13
White blood cell count decreased	13

Tumour response per RECIST v1.1	N=15 N (% [95% CI])
ORR	11 (73 [45-92])
CR	1 (7 [0-32])
PR	10 (67 [38-88])
SD[b]	3 (20 [4-48])
DCR[c]	14 (93 [68-100])
PD	1 (7 [0-32])

[a]The dose reduction for only lenvatinib; [b]Includes patients with both SD and non-CR/non-PD; [c]Includes patients with CR, PR, and SD.
AE, adverse event; CI, confidence interval; CR, complete response; DCR, disease control rate; LEN, lenvatinib; ORR, objective response rate; PD, progressive disease; PEM, pembrolizumab; PPE, palmar-plantar erythrodysaesthesia; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD stable disease; TSH, thyroid-stimulating hormone

Shitara K, et al. Ann Oncol. 2022;33 (suppl_7): S555-S580 (ESMO 2022, poster presentation)

LEAP-015: SUMMARY

- In the safety run-in of LEAP-015, **LEN + PEM + CHEMO was associated with a manageable safety profile in the first-line treatment of advanced/metastatic gastroesophageal adenocarcinoma**
- Preliminary antitumor activity was observed for lenvatinib plus pembrolizumab plus chemotherapy (ORR, 73%; DCR, 93%)
- Part 2 is currently enrolling and will evaluate the efficacy and safety of LEN + PEM + CHEMO vs CHEMO in this same patient population

CHEMO, chemotherapy; DCR, disease control rate; LEN, Lenvatinib; ORR, objective response rate; PEM, pembrolizumab

Shitara K, et al. Ann Oncol. 2022;33 (suppl_7): S555-S580 (ESMO 2022, poster presentation)

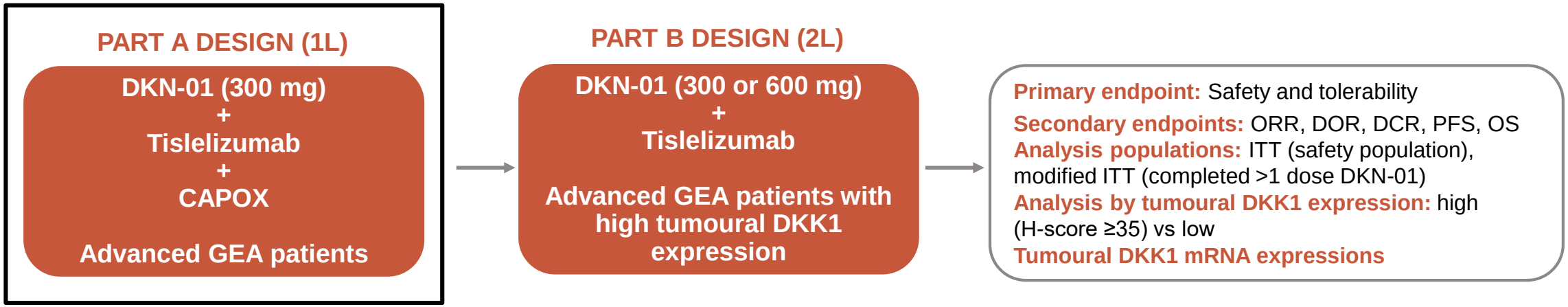
DKN-01 AND TISLELIZUMAB + CHEMOTHERAPY AS 1L INVESTIGATIONAL THERAPY IN GEA: DisTinGuish TRIAL

Klempner S, et al. ESMO 2022. Abstract #1213P

1L, first line; GEA, gastro-oesophageal adenocarcinoma

DisTinGuish TRIAL: BACKGROUND AND DESIGN

- Despite recent approval of anti-PD-1 antibodies as 1L therapy in advanced GEA, benefit is largely limited to PD-L1 combined positive scores (CPS) ≥5 patients (pts); novel therapeutic approaches are needed
- DKN-01 is a targeted anti-DKK1 mAb which has demonstrated activity in GEA pts with elevated tumoral DKK1 expression, a subset of pts with more aggressive disease and shorter overall survival
- **DisTinGuish is a phase 2a, single arm, two-part trial. Part A is reported**



1L, first line; 2L, second line; CAPOX, capecitabine and oxaliplatin; CPS, combined positive score; DCR, disease control rate; DOR, duration of response; GEA, gastroesophageal adenocarcinoma; ITT, intention-to-treat; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; pt, patient

Klempner S, et al. Ann of Oncol. 2022;33 (suppl_7): S555-S580 (ESMO 2022, poster presentation)

DisTinGuish TRIAL: RESULTS

EFFICACY	ORR N (%)	CR N (%)	PR N (%)	SD N (%)	PD N (%)	NE N (%)	Median DOR, (mos) N=15 [a]	Median PFS, (mos) N=25
mITT pop[n,] n=22	15 (68)	1 (5)	14 (64)	6 (27)	0	1 (5)	10.0	11.3
DKK1 high, n=10	9 (90)	0	9 (90)	0	0	1 (10)	10.6	11.3
DKK1 low, n=9	5 (56)	1 (11)	4 (44)	4 (44)	0	0	10.6	12.0
DKK1 Unk, n=3	1 (33)	0	1 (33)	2 (67)	0	0	7.0	8.4

[a]4 responders ongoing (2 low, 2 high)

EFFICACY

- Median duration of treatment 11.3 mos
- Median OS not mature with 14/25 pts (56%) still alive at data cut

SAFETY

- Combination of DKN-01 + tislelizumab + CAPOX was well tolerated with manageable toxicity
- Most common DKN-01 AEs were G1 or 2: fatigue, nausea, diarrhoea, decreased neutrophil count or platelet count, decreased appetite, headache

SAFETY – AE preferred term	Patients N=25; N, (%)
TEAEs leading to death[a]	3 (12%)
Any adverse event	25 (100%)
DKN-01 related	14 (56%)
Grade ≥3 events	16 (64%)
DKN-01 related	5 (20%)
Serious adverse events	10 (40%)
DKN-01 related	2 (8%)
Events leading to DKN-01 discontinuation	3 (12%)
DKN-01 related	1 (4%)
Events leading to DKN-01 dose reduction	2 (8%)

[a] within 30 days of last dose – pulmonary embolism, aspiration pneumonia and hepatic failure

AE, adverse event; CAPOX, capecitabine and oxaliplatin; CR, complete response; DoR, duration of response; mITT, modified intention-to-treat; mos, months; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; pop, population; PR, partial response; SD, stable disease; pt, patient; Unk, unknown

Klempner S, et al. Ann of Oncol. 2022;33 (suppl_7): S555-S580 (ESMO 2022, poster presentation)

DisTinGuish TRIAL: SUMMARY

- DKN-01 plus tislelizumab and CAPOX was well-tolerated and an active 1L combination, including in DKK1-high and CPS low patients, aggressive subpopulations of GEA
- With only 44% of pts deceased as of the data cut, OS is not mature
- Further study with DKN-01 plus standard of care therapy in IL GEA is warranted

Clinical Perspective

- **Initial results demonstrated encouraging clinical activity with the first line combination of DKN-01 plus tislelizumab and CAPOX in patients with advanced GEA**

1L, first line; CAPOX, capecitabine and oxaliplatin; CPS, combined positive score; GEA, gastro-oesophageal adenocarcinoma; OS, overall survival; pt, patient

Klempner S, et al. Ann of Oncol. 2022;33 (suppl_7): S555-S580 (ESMO 2022, poster presentation)

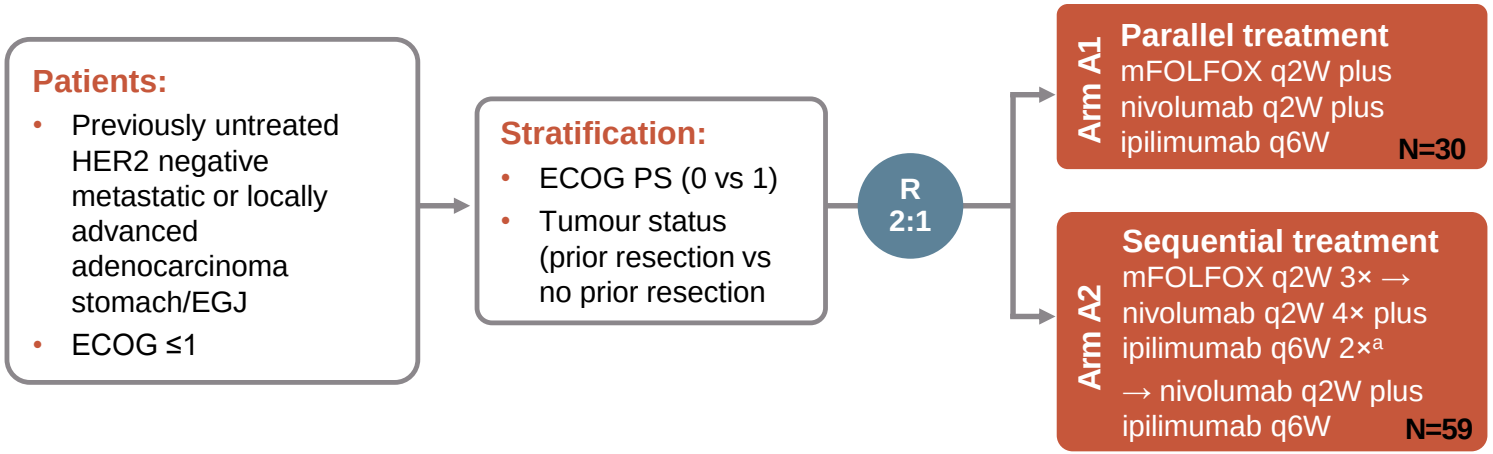
FOLFOX PLUS NIVO AND IPI VERSUS FOLFOX INDUCTION FOLLOWED BY NIVO AND IPI IN PTS WITH PREVIOUSLY UNTREATED ADVANCED OR METASTATIC ADENOCARCINOMA OF THE STOMACH OR GEJ: RESULTS FROM THE RANDOMISED PHASE 2 MOONLIGHT TRIAL OF THE AIO

Lorenzen S, et al. ESMO 2022. Abstract #1203O

AIO, Arbeitsgemeinschaft Internistische Onkologie (Working Group for Internal Oncology); FOLFOX, folinic acid/fluorouracil/oxaliplatin; GEJ, gastroesophageal junction; IPI, ipilimumab; NIVO, nivolumab; PTS, patients

MOONLIGHT: BACKGROUND AND STUDY DESIGN

- Chemotherapy plus nivolumab is a new standard of care for 1L therapy of patients with oesophagogastric adenocarcinomas[1]
- Nivolumab plus ipiliumumab has demonstrated clinically meaningful anti-tumour benefit in patients with chemo-refractory oesophagogastric cancer[2]
- **Moonlight trial is a four-arm investigator-initiated trial. Two arms (A1/A2 are presented here):**
  - The aim of this part of the Moonlight trial was to evaluate if mFOLFOX induction therapy followed by nivolumab plus ipiliumumab is less toxic but equally effective compared to both regimens combined together
  - The study also explored whether outcomes varied for the subgroup of patients with high PD-L1 expression



- Phase II trial
- 240 mg nivolumab, 1 mg/kg ipilimumab
- **Primary endpoint:** Progression-free survival at 6 months
- **Main secondary endpoints:** OS, PFS, response rate and safety
- 90 patients were randomised (30 Arm A1 60 Arm A2) at 27 German sites from June 2020 through March 2021
- PD-L1 expression assessed centrally

At data cutoff (July 22, 2022), the median follow-up was 9.3 months. [a]In arm A2, upon investigators decision the sequence may be repeated if medically reasonable. After discontinuation of chemotherapy, immunotherapy will be continued with nivolumab Q2W and ipilimumab Q6W

1L, first line; ECOG PS, Eastern Cooperative Oncology Group performance status; EGC, esophagogastric cancer; FOLFOX, folinic acid/fluorouracil/oxaliplatin; HER2, human epidermal growth factor receptor 2; mFOLFOX, modified FOLFOX; PD-L1, programmed death ligand-1; q2W, every 2 weeks; q6W, every 6 weeks

1. Janjigian Y, et al. Lancet 2021; 398: 27-40; 2. Janjigian Y, et al. J Clin Oncol 2018; 36: 2836-2844; 3. Lorenzen S, et al. Ann Oncol. 2022;33 (suppl_7): S555-S580 (ESMO 2022, oral presentation)

MOONLIGHT: RESULTS

- **Baseline characteristics:** median age 62y, GEJ, 51%, intestinal type, 33%. 41% PD-L1 CPS ≥1 (available in 74% of patients), median of 11 cycles in A1 vs 7 cycles in A2

Efficacy	A1	A2
PFS at 6 months (All patients)	N= 30	N=60
Median (95% CI), months	7.29 (4.99-10.68)	3.98 (3.55-5.39)
P-value (censored log-rank)	P=0.0261	
OS (All patients)	N= 30	N=60
Median (95% CI) , months	10.12 (6.60-/)	7.85 (6.44-12.25)
p-value (censored log-rank)	P=0.3604	
OS (PD-L1 CPS ≥ 1)	N= 13	N=24
Median (95% CI) , months	16.46 (2.07-/)	6.87 (5.13-7.59)
Stratified p-value (censored log-rank)	P=0.4512	
PFS (PD-L1 CPS < 1)	N = 14	N = 17
Median (95% CI) , months	6.87 (2.07-9.53)	3.98 (2.23-6.21)
Stratified p-value (censored log-rank)	0.6009	
PFS (PD-L1 CPS ≥ 1)	N=13	N=24
Median (95% CI) , months	5.22 (2.07-/)	3.75 (3.06-5.55)
Stratified p-value (censored log-rank)	P=0.2876	

Efficacy	A & A1	A2
PFS (All patients)	N= 90	N=60
Median (95% CI), months	5.78 (5.36-7.56)	3.98 (3.55-5.39)
p-value (log-rank)	P=0.0356	
PFS (PD-L1 CPS ≥ 1)	N= 40	N=24
Median (95% CI), months	5.36 (3.45-6.08)	3.75 (3.06-5.55)
Stratified p-value (log-rank)	P=0.5196	
Response and duration of response	**A1 N=30**	**A2 N=60**
ORR (%), (95% CI)	46.7 (28-66)	30.0 (19-43)
Best overall response, (%) CR PR SD PD	 10.0 36.7 33.3 10.0	 6.7 23.3 43.3 15.0
Median DOR (range), months	8.4 (3.0-18.8)	4.3 (1.9-8.7)

SAFETY: Grade ≥3 AEs: 93% pts in arm A1 and 73% in arm A2. SAEs: 70% in arm A1 and 62% in A2. Median follow-up 7.3 months

AE, adverse event; CI, confidence interval; CR, complete response; CPS, combined positive score; DoR, duration of response; GEJ, gastro-oesophageal junction; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed death ligand-1; PFS, progression-free survival; PR, partial response; SAE, serious adverse event; SD, stable disease

Lorenzen S, et al. Ann Oncol. 2022;33 (suppl_7): S555-S580 (ESMO 2022, oral presentation)

MOONLIGHT: SUMMARY

- FOLFOX chemotherapy plus nivolumab and ipilimumab administered in parallel was clearly more effective than FOLFOX induction followed by nivolumab and ipilimumab.
- Although associated with lower toxicity, the Moonlight study does not support the use of sequential treatment in the first-line setting

Clinical Perspective

- **The Moonlight study does not support the concept of chemotherapy induction followed by immunotherapy as 1L in patients with oesophagogastric cancer**
- **Results must be interpreted with caution due to small patient numbers and low PD-L1 expression**

FOLFOX, folinic acid/fluorouracil/oxaliplatin; PD-L1, programmed death ligand-1

Lorenzen S, et al. Ann Oncol. 2022;33 (suppl_7): S555-S580 (ESMO 2022, oral presentation)

SECOND LINE DATA ESMO 2022

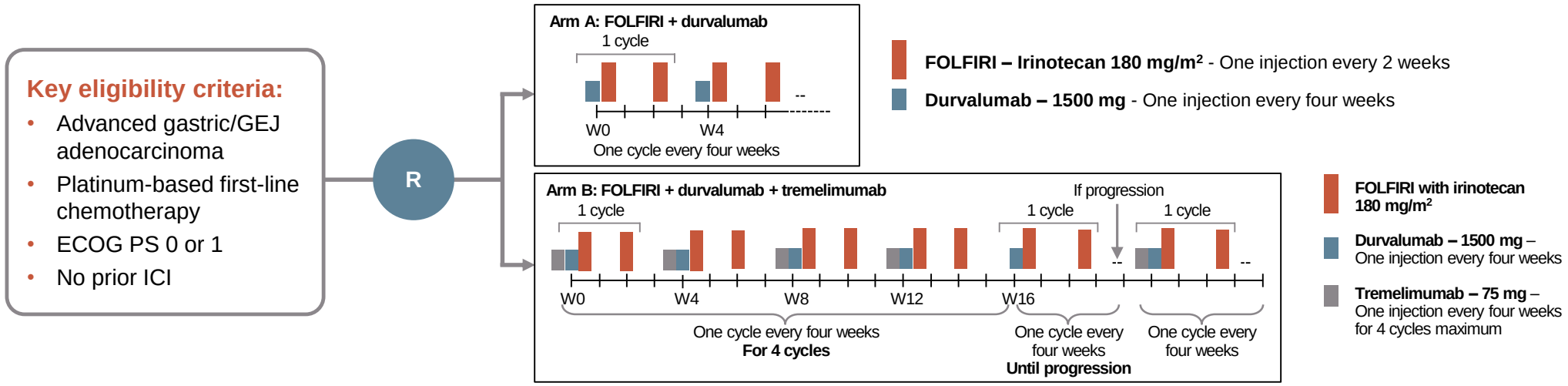
PRODIGE 59 - DURIGAST TRIAL: A RANDOMISED PHASE 2 STUDY EVALUATING FOLFIRI PLUS DURVALUMAB AND FOLFIRI PLUS DURVALUMAB PLUS TREMELIMUMAB IN 2L TREATMENT OF PATIENTS WITH ADVANCED GASTRIC OR GASTRO-OESOPHAGEAL JUNCTION ADENOCARCINOMA

Tougeron D, et al. ESMO 2022. Abstract #1204MO

2L, second-line

PRODIGE 59 – DURIGAST: BACKGROUND AND STUDY DESIGN

- There is limited efficacy of both immune checkpoint inhibitors (ICIs) combined with chemotherapy as second line treatments for advanced gastric/GEJ adenocarcinoma
- This is the first study to evaluate the efficacy of two ICIs plus chemotherapy for the treatment of advanced gastric/GEJ adenocarcinoma



- **The primary endpoint is PFS at 4 months (H1: 70% and H0: 50%)**
- 92 patients were randomised, 47 in FD arm and 45 in FDT arm

ECOG PS, Eastern Cooperative Oncology Group performance status; FD, FOLFIRI + durvalumab; FDT, FOLFIRI + durvalumab + tremelimumab; FOLFIRI, folinic acid/fluorouracil/irinotecan; GEJ, gastro-oesphageal junction; H, hypothesis; PFS, progression-free survival; R, randomisation; W, week

Tougeron D, et al. Ann Oncol. 2022;33 (suppl_7):S555-S580ESMO 2022 (ESMO 2022, oral presentation)

PRODIGE 59 – DURIGAST: RESULTS

EFFICACY

- **Primary endpoint of PFS at 4 months was not met** (PFS at 4 months inferior to 70%)
- An impressive disease control was seen over 12 months in FDT arm (N=7, 15.2%) compared to FD arm (n=2, 4.3%)
- An overall survival (OS) of 13.3 months was observed for the FD arm and 9.5 months for the FDT arm

	Folfiri + Durvalumab	FOLFIRI + durvalumab + tremelimumab
PFS at 4 months, % (90% CI)	**44.7 (32.2-57.7)**	**55.6% (42.3-68.3)**
Disease control rate, %	67.4%	68.9%
Median duration of response, months	5.1 months	4.3 months

SAFETY

- Adverse events (AEs) were well balanced between treatment groups
  - 47.8% of grade 3-5 AEs related to treatment were observed in each arm
- The main adverse events were: GI disorders, neutropenia and lymphocytopenia

CI, confidence interval; FD, FOLFIRI + durvalumab; FDT, FOLFIRI + durvalumab + tremelimumab; FOLFIRI, folinic acid/fluorouracil/irinotecan; GI, gastrointestinal disorders; PFS, progression-free survival

Tougeron D, et al. Ann Oncol. 2022;33 (suppl_7):S555-S580ESMO 2022 (ESMO 2022, oral presentation)

PRODIGE 59 – DURIGAST: SUMMARY

- **Primary endpoint of PFS at 4 months was not met** but a clinically relevant PFS and OS was observed
- An acceptable safety profile was seen with two ICIs plus FOLFIRI as 2L treatment for advanced gastric/GEJ adenocarcinoma

Clinical Perspective

- **2L metastatic gastric cancer is a difficult patient population**
- **Combination of two ICIs and FOLFIRI seems to be active in a sub-group of patients**
  - **Biomarker correlative results need to be reviewed**
- **FOLFIRI + double ICI compares favourably to other established 2L treatments for these patients**

2L, second line; FOLFIRI, folinic acid/fluorouracil/irinotecan; GEJ, gastro-oesphageal junction; ICIs, immune checkpoint inhibitors; OS, overall survival; PFS, progression-free survival

Tougeron D, et al. Ann Oncol. 2022;33 (suppl_7):S555-S580ESMO 2022 (ESMO 2022, oral presentation)

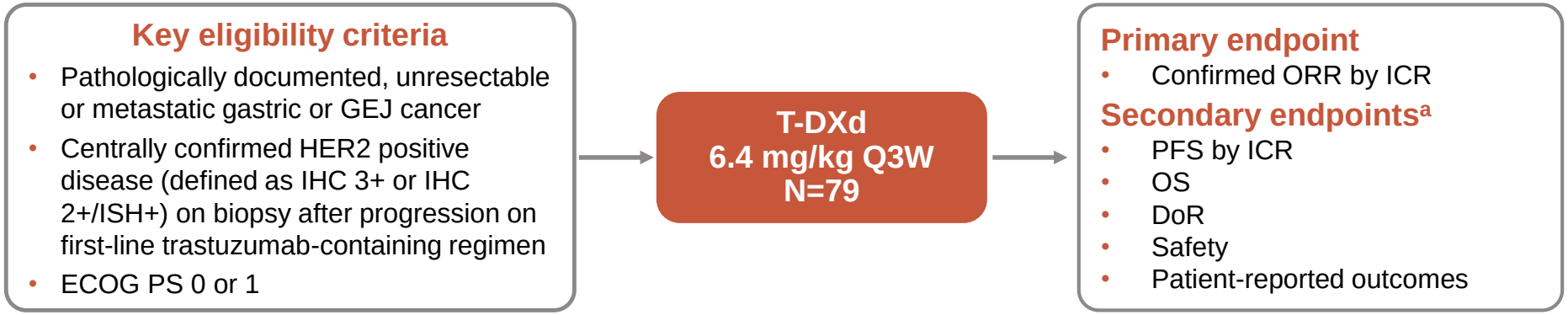
UPDATED ANALYSIS OF DESTINY-GASTRIC02: A PHASE 2 SINGLE-ARM TRIAL OF T-DXd IN WESTERN PTS WITH HER2+ UNRESECTABLE/METASTATIC GASTRIC/GEJ CANCER WHO PROGRESSED ON OR AFTER TRASTUZUMAB-CONTAINING REGIMEN

Ku G.Y, et al. ESMO 2022. Abstract #1205MO

GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; PTS, patients; T-DXd, trastuzumab deruxtecan

DESTINY-GASTRIC02: BACKGROUND AND STUDY DESIGN

- T-DXd is an FDA approved treatment which received approval based on the DESTINY-Gastric01 trial in Asian patients (Japan/South Korea)[1]
  - demonstrated improved responses and OS vs chemotherapy in patients with HER2+ advanced gastric or GEJ cancer previously treated with at least 2 prior therapies including trastuzumab[1]
- DESTINY-Gastric02 was undertaken to evaluate T-DXd in a Western patient population and specifically in the second-line setting[2]
  - Updated data is presented with an additional 7 months of follow up



[a]Other secondary endpoints were ORR, PFS, DOR by investigator assessment, pharmacokinetics and anti-drug antibodies

DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FDA, Food and Drug Administration; GEJ, gastro-oesphageal junction; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ISH, in-situ hybridisation; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; Q3W, every 3 weeks

1. Shitara K, et al. New Engl J Med. 2020;382:2419-2430; 2. Ku G. Y, et al. Ann Oncol. 2022;33 (suppl_7): S555-S580 (ESMO 2022, oral presentation)

DESTINY-GASTRIC02: RESULTS

EFFICACY

Response assessment by ICR	April 9, 2021 data cutoff[a] patients (N=79)	November 8, 2021 data cutoff[b] patients (N=79)
Confirmed ORR[c], % (n) (95% CI)	38.0 (30) (27.3-49.6)	41.8 (33) (30.8-53.4)
Confirmed best overall response, % (n) CR PR SD PD Not evaluable	 3.8 (3) 34.2 (27) 43.0 (34) 16.5 (13) 2.5 (2)	 5.1 (4) 36.7 (29) 39.2 (31) 16.5 (13) 2.5 (2)
Confirmed DCR,[d] % (n) (95% CI)	81.0 (64) (70.6-89.0)	81.0 (64) (70.6-89.0)
Median DoR, months, (95% CI)	8.1 (4.1-NE)	8.1 (5.9-NE)[e]
Median TTR, months, (95% CI)	1.4 (1.4-2.6)	1.4 (1.4-2.7)
Median OS, months	–	12.1 (9.4-15.4)
Median PFS, months	–	5.6 (4.2-8.3)

[a]Median follow up was 5.9 months (range 0.7-15.4 months); [b]Median follow up was 10.2 months (range, 0.7-22.1); [c]Primary endpoint; [d]Exploratory endpoint; [e]Secondary endpoint analysis based on responders (n=33); 18 patients were censored

SAFETY

% (n)	Patients (N=79)
Any TEAE Drug-related	100 (79) 94.9 (75)
TEAE grade ≥3 Drug-related	55.7 (44) 30.4 (24)
Serious TEAE Drug-related	41.8 (33) 12.7 (10)
TEAE associated with study drug discontinuation Drug-related	19.0 (15) 12.7 (10)
TEAE associated with dose reduction Drug-related	21.5 (17) 17.7 (14)
TEAE associated with an outcome of death Drug-related	13.9 (11) 2.5 (2)
Adjudicated drug-related ILD/pneumonitis Adjudicated drug-related ILD/pneumonitis grade 5	10.1 (8) 2.5 (2)

- Median treatment duration was 4.3 months (range, 0.7-22.1 months)
- The most common TEAEs were nausea (67.1%), vomiting (44.3%) and fatigue (41.8%)

CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; ICR, independent central review; ILD, interstitial lung disease; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TEAE, treatment emergent adverse event; TTR, time to response

Ku G. Y, et al. Ann Oncol. 2022;33 (suppl_7): S555-S580 (ESMO 2022, oral presentation)

DESTINY-GASTRIC02: SUMMARY

- With longer follow up, T-Dxd continues to provide clinical benefit and a tolerable safety profile whilst maintaining QoL in 2L Western patients with HER2+ unresectable/metastatic gastric/GEJ cancer

Clinical Perspective

- **DESTINY-GASTRIC02 supports the use of T-Dxd in Western patients**
- **Further data are needed for 1L metastatic gastric/GEJ cancer and perioperative treatment of HER2+ localised gastric/GEJ cancer**

1L, first line; 2L, second line; GEJ, gastro-oesphageal junction; HER2, human epidermal growth factor receptor 2; QoL, quality of life; T-DXd, trastuzumab deruxtecan

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GI connect
POWERED BY COR2ED

GI CONNECT
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND

Dr. Froukje Sosef MD

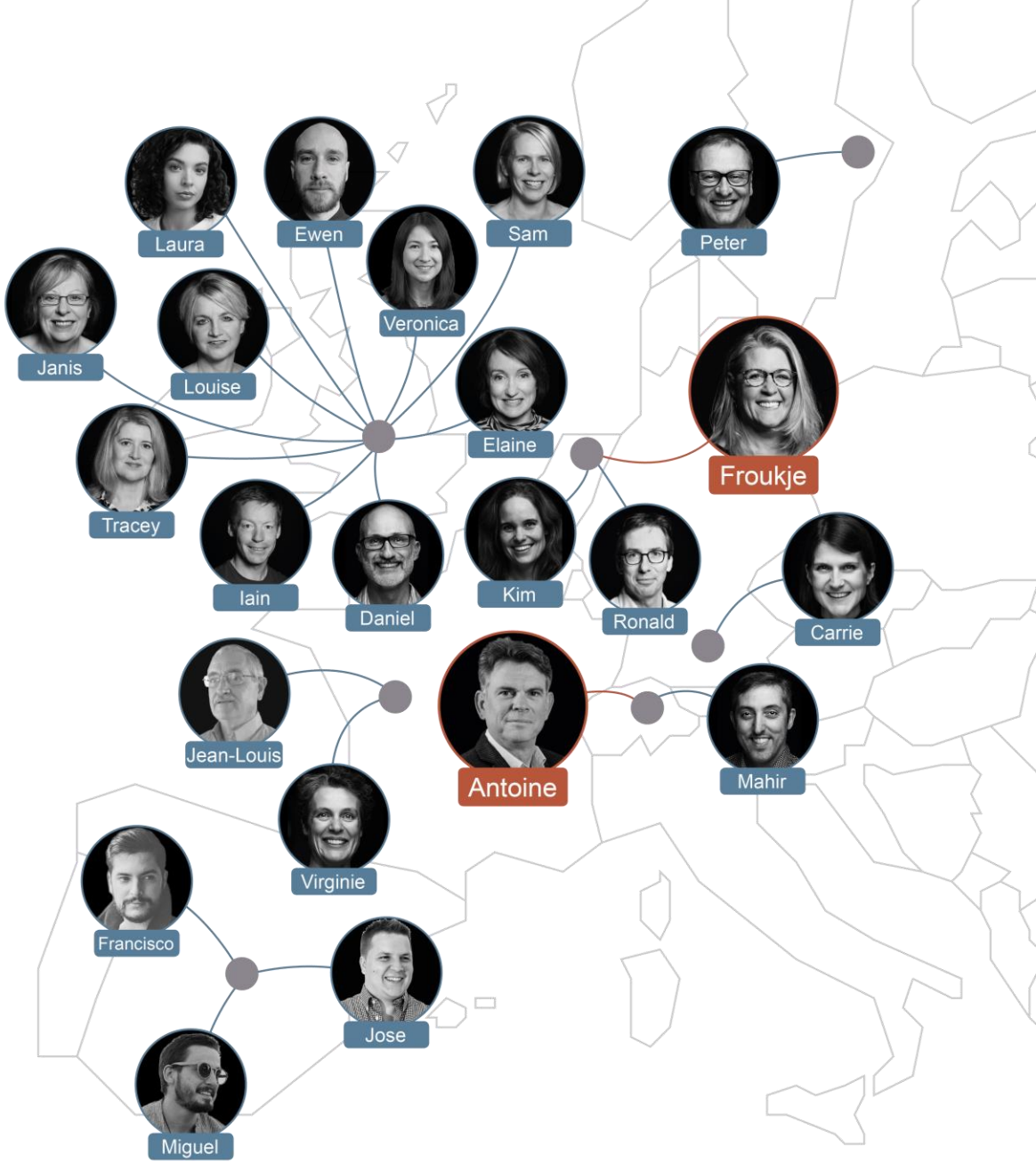
+31 6 2324 3636

froukje.sosef@cor2ed.com

Dr. Antoine Lacombe Pharm D, MBA

+41 79 529 42 79

antoine.lacombe@cor2ed.com



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