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A REVIEW OF *NTRK* GENE FUSIONS AND TRK INHIBITOR THERAPY IN GASTROINTESTINAL TUMOURS

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EXECUTIVE SUMMARY

- *NTRK* gene fusions are rare in GI tumours
- *NTRK* gene fusions are associated with microsatellite instability high (MSI-H) metastatic colorectal cancer (mCRC) and exclusive with other genomic alterations such as *BRAF* and *KRAS* mutations
- Positive safety and efficacy data with TRK inhibitors; larotrectinib and entrectinib in patients with gastrointestinal (GI) tumours harbouring *NTRK* gene fusions are available
- Results with larotrectinib and entrectinib demonstrated that such targeted therapies are efficacious in patients with GI tumours harbouring *NTRK* gene fusions

GI, gastrointestinal; NTRK, neurotrophic receptor tyrosine kinase; TRK, tropomyosin receptor kinase

NTRK FUSION PREVALENCE AMONG SOLID TUMOURS INCLUDING GI TUMOURS

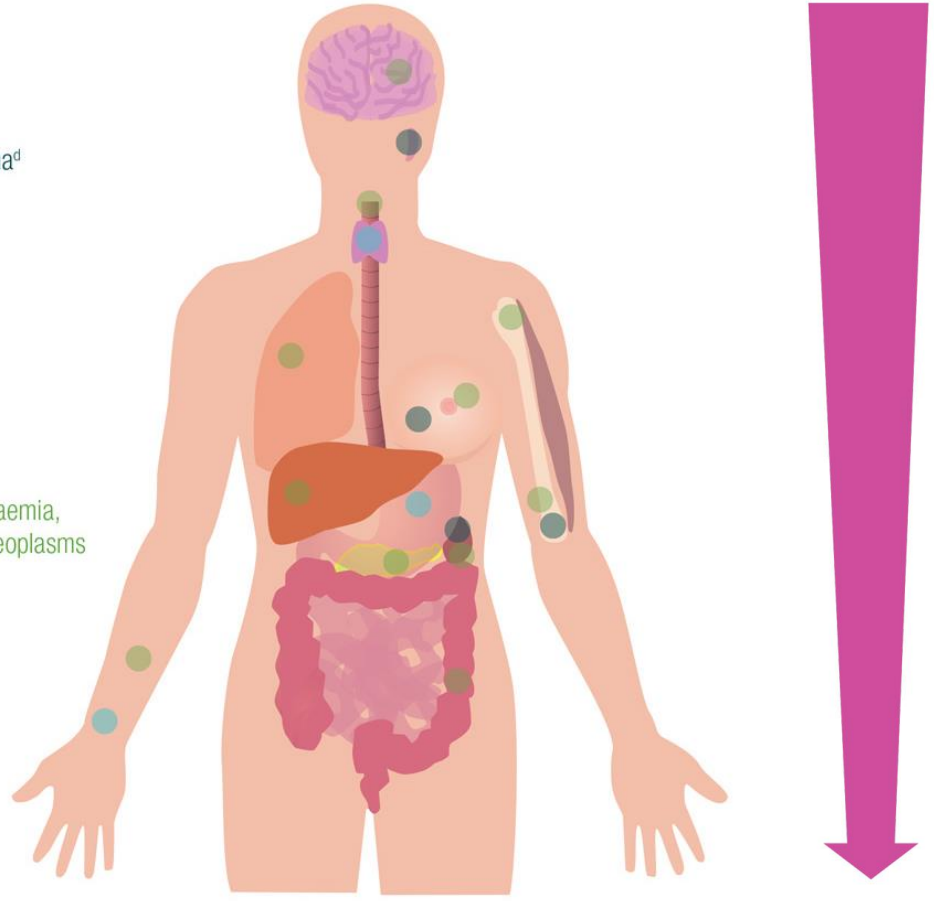
Cancers enriched for TRK fusions

Frequency >90%
- MASC
- Secretory breast carcinoma[b]
- Cellular and mixed congenital mesoblastic nephroma[d]
- Infanfile fibrosarcoma

Cancers harbouring TRK fusions at lower frequencies

Frequency 5% to 25%
- Gastrointestinal stromal tumour (pan-negative)
- Thyroid cancer[c]
- Spitzoid tumours

Frequency <5%
- Acute lymphoblastic leukaemia, acute myeloid leukaemia, histiocytosis, multiple myeloma and dendritic cell neoplasms
- Infantile sarcoma[d]
- Breast cancer
- Colorectal cancer
- Cholangiocarcinoma
- High-grade glioma[b]
- Head and neck cancer
- Lung cancer
- Pancreatic cancer
- Melanoma
- Renal cell carcinoma[a]
- Sarcoma



Tumour Type	*NTRK* gene fusions involved	Frequency
Breast secretory carcinoma	*NTRK3*	96%
Infantile fibrosarcoma	*NTRK3*	95.5%
MASC ~90%	*NTRK3*	89.1%
Congenital mesoblastic nephroma	*NTRK3*	72.0%
Spitz tumours and spitzoid melanoma	*NTRK1*	16.4%
Papillary thyroid carcinoma	*NTRK1,3*	8.8%
Intrahepatic cholangiocarcinoma	*NTRK1*	3.6%
Astrocytoma	*NTRK2*	3.1%
High-grade glioma	*NTRK1,2,3*	2.1%
Uterine sarcoma	*NTRK1,3*	2.1%
GIST	*NTRK3*	1.9%
Lung cancer	*NTRK1,2*	1.7%
Thyroid carcinoma	*NTRK1,3*	1.2%
Glioblastoma	*NTRK1,2*	1.2%
Sarcoma	*NTRK1*	1.0%
Ph-like ALL	*NTRK3*	0.7%
Colorectal cancer	*NTRK1,3*	0.61%
Melanoma	*NTRK3*	0.3%
Head and neck cancer	*NTRK2,3*	0.24%
Invasive breast cancer	*NTRK3*	<0.1%

As reported by Chen and Chi (2018)[1]

[a] Found in adult cancers only, unless indicated; [b] found in adult and paediatric cases;
[c] found in adult cases as thyroid cancer and papillary thyroid cancer in paediatric cases;
[d] found in paediatric cases only

Source: ESMO oncologyPRO module provided by NTRK Connect

GI, gastrointestinal; GIST, gastrointestinal stromal tumours; MASC, mammary analogue secretory carcinoma; NTRK, neurotrophic receptor tyrosine kinase; Ph-like ALL, Philadelphia chromosome-like acute lymphoblastic leukaemia; TRK, tropomyosin receptor kinase

1. Chen Y and Chi P. J Hematol Oncol. 2018;11:78

NTRK FUSION OCCURRENCE WITH OTHER GENOMIC ALTERATIONS

- Retrospective study of Flatiron Health-Foundation Medicine Clinico-Genomic Database (CGDB) who had next-generation sequencing (NGS) between Jan 2011 and July 2018
- Evaluable sample: 15,971 of 33,398 patients in the CGDB had one of 18 histologies where at least one *NTRK* fusion patient was identified
- *NTRK* gene fusions identified in 29 patients

Co-occurring biomarkers*, (%)	Cohort 1 (*NTRK* fusion) (N=29)	Cohort 2 (*NTRK* wild-type) (N=12,456)
TMB high (≥20 mut/mB)	6 (20.7)	657 (5.3)
TMB medium (<20, >5 mut/mB)	3 (10.3)	3239 (26.0)
MSI-H	3/17** (17.6)	94/7961 (1.2)
ALK rearrangement	0	162 (1.3)
BRAF rearrangement	1 (3.4)	820 (6.6)
ERBB2 rearrangement	0	470 (3.8)
EGFR rearrangement	1 (3.4)	962 (7.7)
ROS1 rearrangement	0	90 (.07)
KRAS rearrangement	3 (10.3)	4836 (38.8)

* Variants of "known" or "likely" functional status were included
** MSI status missing for 12 patients

Co-occurrence of the biomarkers *ALK*, *BRAF*, *ERBB2*, *EGFR*, *ROS1*, or *KRAS* = uncommon
What about MSI-H and tumour mutation burden high (TMB-H) tumours?

ALK, anaplastic lymphoma kinase; BRAF, serine/threonine-kinase B-Raf/proto-oncogene B-Raf; EGFR, epidermal growth factor receptor; NTRK, neurotrophic receptor tyrosine kinase; MSI-H, microsatellite instability high; mut/mB, mutations per megabase; TMB, tumour mutation burden

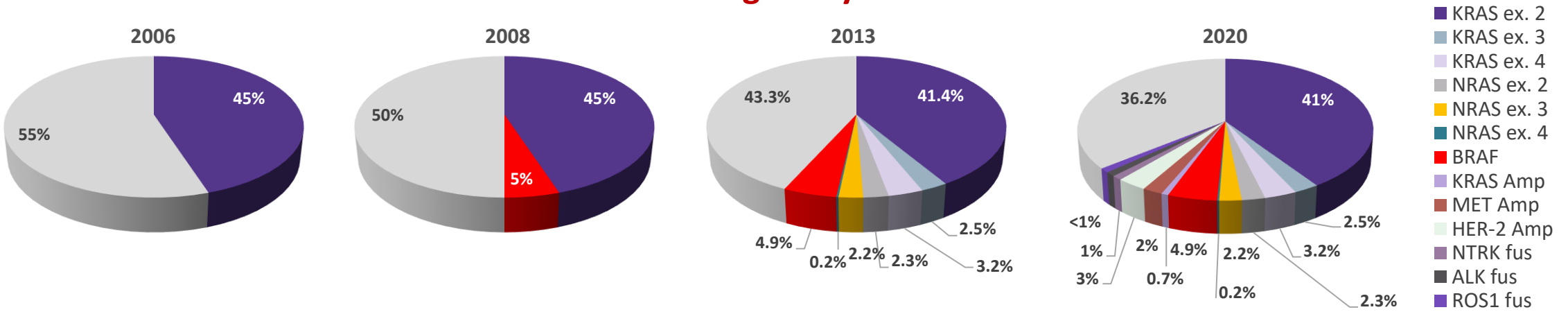
Jiao X. et al. Ann Oncol. 2019;30 (Suppl_5):v-25-v54

NTRK FUSIONS IN THE MOLECULAR SEGMENTATION OF CRC[1]

CRC has significant molecular heterogeneity

NTRK gene rearrangements are known to be enriched in certain CRC subpopulations, in particular microsatellite instability status

Molecular heterogeneity in metastatic CRC



Laurent-Puig, et al. Cancer Res. 2006
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Douillard, et al. N Eng J Med. 2013

Misale, et al. Cancer Discov. 2014
Aisner, et al. Mol Cancer Res. 2014
Valtorta, et al. Mod Pathol. 2015
Amatu, et al. Br J Cancer. 2015
Sartore Bianchi, et al. J Natl Cancer Inst. 2015
Sartore Bianchi, et al. Lancet Oncol. 2016

Adapted from Sartore-Bianchi A and Siena S[1]

ALK, anaplastic lymphoma kinase; Amp, amplification; BRAF, serine/threonine-kinase B-Raf/proto-oncogene B-Raf; CRC, colorectal cancer; ex, exon; fus, fusion; NTRK, neurotrophic receptor tyrosine kinase

1. Sartore-Bianchi A and Siena S. Handb Exp Pharmacol 2018;249:145-69

PREVALENCE OF TARGETABLE FUSIONS IN COLON CANCER

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Around 21,000 CRC tissue specimens characterized by Foundation Gene panels

18,107 patients tested for microsatellite instability (MSI) (4.5% of MSI CRC tumours)

KINASE	N (%) 18,107	% MSI
ALK	17 (0.09%)	14.3%
BRAF	23 (0.12%)	16.7%
FGFR2	4 (0.02%)	75%
NTRK1	**26 (0.14%)**	**84.6%**
NTRK3	**3 (0.0016%)**	**100%**
RET	28 (0.15%)	50%
TOTAL	101 (0.5%	46%

MSI-H enriched with *NTRK* gene fusions

ALK, anaplastic lymphoma kinase; BRAF, serine/threonine-kinase B-Raf/proto-oncogene B-Raf; CRC, colorectal cancer; FGFR2, fibroblast growth factor receptor 2; MSI-H, microsatellite instability high; NTRK, neurotrophic receptor tyrosine kinase

Source: Madison R. Ann Oncol. 2018;29 (Suppl_8):viii150-viii204

IN dMMR CRC, GENE FUSIONS ARE ENRICHED WITH *MHL1* HYPERMETHYLATION

***NTRK* gene fusions associated with *MHL1* hypermethylation and mutually exclusive with *BRAF* and *KRAS* mutations**

BRAF, serine/threonine-kinase B-Raf/proto-oncogene B-Raf; CRC, colorectal cancer; dMMR, deficient mismatch repair; LOH, loss of heterozygosity; LS, Lynch syndrome; MLH1, MutL homolog 1; pMMR, mismatch repair proficient

Source: Wang J, et al. Mod Pathol. 2019;32:1053-64

PROGNOSTIC SIGNIFICANCE OF *NTRK* GENE FUSIONS IN dMMR mCRC

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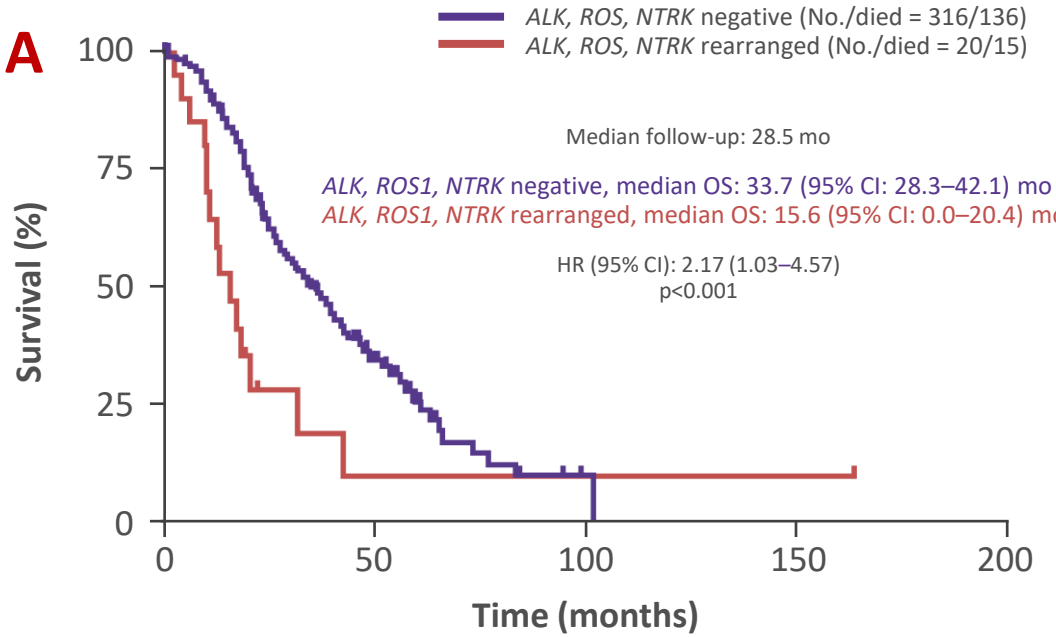
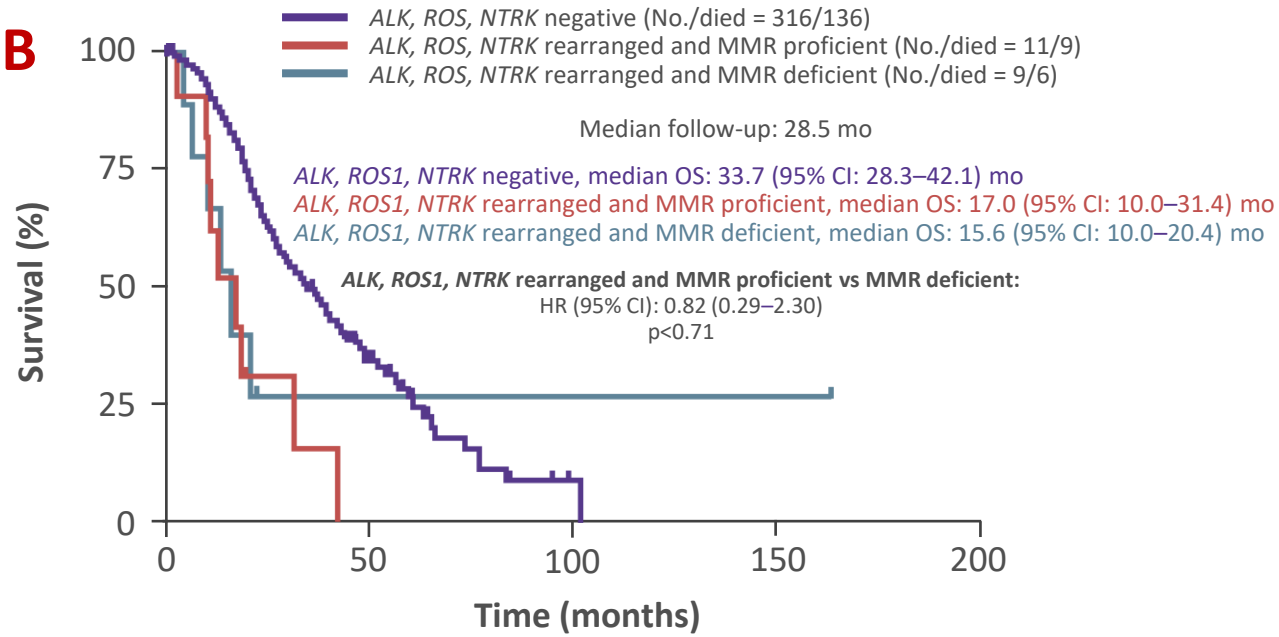
Overall survival in CRC patients with *ALK*, *ROS1*, *NTRK* rearrangements (A) and according to deficient/proficient MMR status (B)

A



Negative	316	24	2	1	0
Rearranged	20	2	1	1	0

B



Negative	316	24	2	1	0
Rearr. MMR proficient	11	0	0	0	0
Rearr. MMR deficient	9	2	1	1	0

could *NTRK* gene fusions be a prognostic biomarker in dMMR mCRC?

ALK, anaplastic lymphoma kinase; CI, confidence interval; dMMR, deficient mismatch repair; HR, hazard ratio; mCRC, metastatic colorectal cancer; MMR, mismatch repair; mo, months; NTRK, neurotrophic receptor tyrosine kinase; OS, overall survival

Source: Pietrantonio F, et al. J Natl Cancer Inst. 2017; 109(12). doi: 10.1093/jnci/djx089

TRK INHIBITORS: ENTRECTINIB EFFICACY AND SAFETY IN *NTRK* FUSION POSITIVE GI TUMOURS

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Entrectinib = potent inhibitor of TRK, ROS1 and ALK tyrosine kinase

ALKA-372-001: Phase 1
Solid tumours
EudraCT 2012-000148-88

STARTRK-1: Phase 1/2
Solid tumours
NCT02097810

STARTRK-2: Phase 2
Solid tumours
NCT02568267

Efficacy

	Total (n=74)	GI tumours (n=12)
BICR ORR, %	63.5	50.0
mPFS, month	11.2	7.1
mOS, month	23.9	16.0
mDoR, month	12.9	12.9

Safety profile

58.7% TRAE: grade 1-2
Dysgeusia (39.7%), fatigue (31.5%), dizziness (27.2%) and constipation (24.0%)
TRAEs led to dose discontinuation in 24.6% of patients, interruptions in 27.0% and discontinuations in 4.6%

ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; GI, gastrointestinal; mDoR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; NTRK, neurotrophic receptor tyrosine kinase; ORR, overall response rate; TRAE, treatment-related adverse event; TRK, tropomyosin receptor kinase

Source: Patel M, et al. Ann Oncol. 2020;31 (suppl_3):232-3

TRK INHIBITORS: LAROTRECTINIB EFFICACY AND SAFETY IN *NTRK* FUSION POSITIVE GI TUMOURS

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larotrectinib = potent TRK specific inhibitor

Adults patients with advanced solid tumours harbouring *NTRK* fusions Phase 1 (NCT02122913)

Paediatric patients with advanced solid tumours harbouring *NTRK* fusions Phase 1/2 SCOUT (NCT02637687)

Adult/adolescent patients with advanced solid tumours harbouring *NTRK* fusions Phase 2 NAVIGATE (NCT02576431)

Larotrectinib 100 mg BID in continuing 28-days cycles

From March 2015 - February 2019

159 patients with TRK fusion cancer were enrolled across those three clinical trials

14/159 (8.8%) had TRK fusion GI cancer:

colon (8), cholangiocarcinoma (2), pancreas (2), appendix (1), and hepatic (1)

Efficacy

mTTR: 1.8 months (range 1.7-2.1)
mPFS: 5.3 months (95% CI 2.2–9.0)
mOS: 33.4 months (95% CI 2.8–36.5)
7/8 patients with colon cancers were MSI-H

Safety profile

Larotrectinib was well tolerated
One patient with TRAE grade 3-4 (grade 3: nausea)
No TRAEs leading to dose reduction or discontinuation or death

BID, twice a day; GI, gastrointestinal; mOS, median overall survival; mPFS, median progression-free survival; MSI-H, microsatellite instability high; mTTR, median time to response; NTRK, neurotrophic receptor tyrosine kinase; TRAE, treatment-related adverse event; TRK, tropomyosin receptor kinase

Source: Berlin J, et al. J Clin Oncol 38 (no. 4_suppl):824-824

CONCLUSIONS

- *NTRK* gene fusions are rare in GI tumours but can represent an impactful therapeutic option
- High likelihood of occurrence of *NTRK* gene fusions in tumours with MSI-H, TMB-H and MHL1 hypermethylation has been demonstrated in colorectal cancer, it is therefore important to look for this therapeutic target at least in this subset of patients
- We now have focused subgroup analyses of pivotal trials with TRK inhibitors demonstrating efficacy and safety of larotrectinib and entrectinib, the two approved and available TRK inhibitors, in patients with GI tumours including colorectal, pancreatic and biliary tract histology
- It should be further investigated how to improve selection of patients with GI tumours to test for *NTRK* fusions in the lab and what are the best strategies to prevent/overcome acquired resistance to TRK inhibitors in the clinic

GI, gastrointestinal; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability high; NTRK, neurotrophic receptor tyrosine kinase; TMB-H, tumour mutation burden high; TRK, tropomyosin receptor kinase

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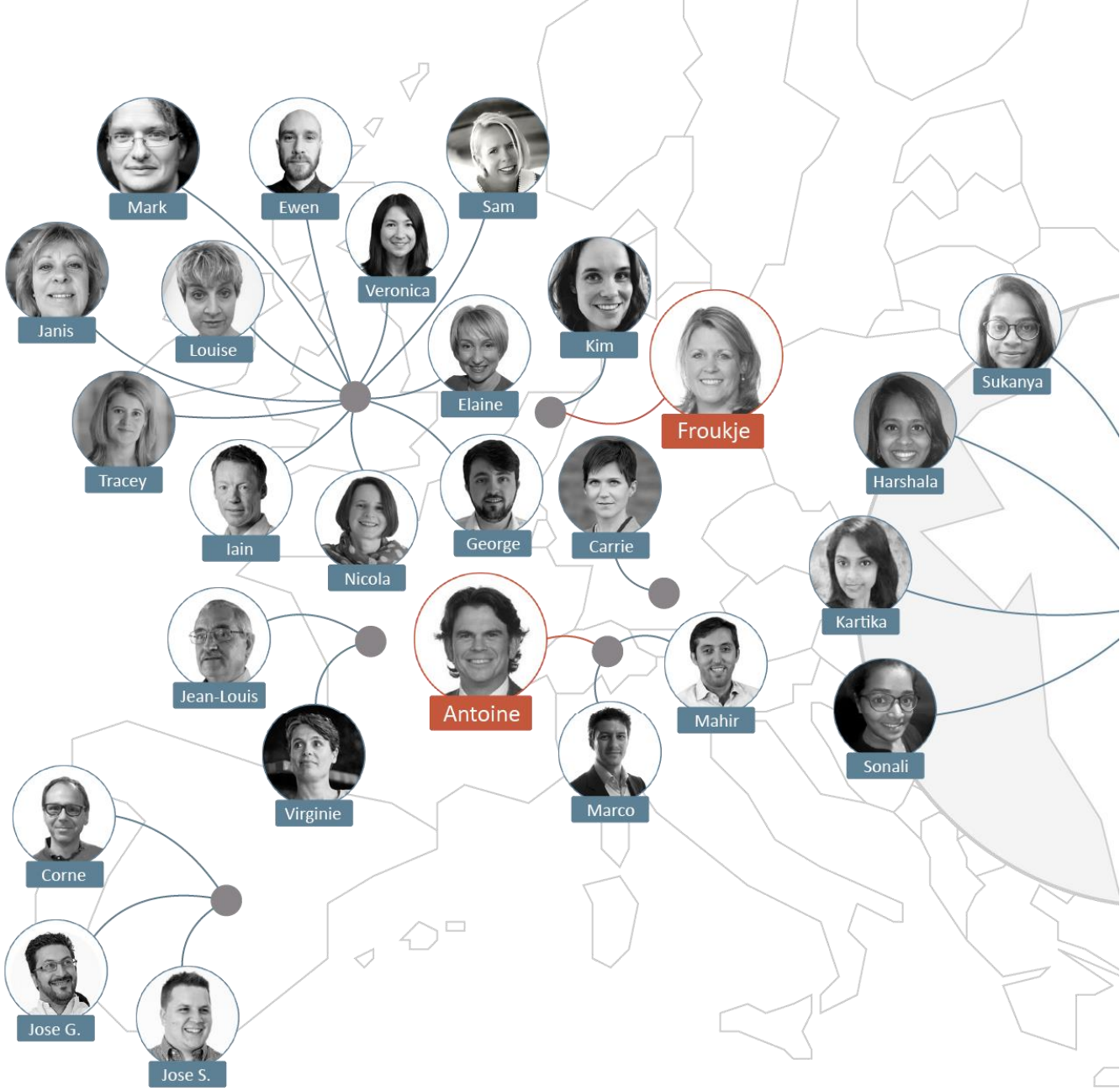

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