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PUBLICATION SNAPSHOT #3

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CHARACTERISATION OF ON-TARGET ADVERSE EVENTS CAUSED BY TRK INHIBITOR THERAPY

Liu D, et al. Ann Oncol. 2020;31:1207-15

TRK, tropomyosin receptor kinase

BACKGROUND: POOLED ANALYSIS OF AEs WITH LAROTRECTINIB

Data cutoff:
19 February 2019

Adult in Phase 1
Advanced solid tumours
NCT02122913
N=12

Paediatric in Phase 1/2
Advanced solid tumours
SCOUT: NCT02637687
N=50

Adult/adolescent in Phase 2
Advanced solid tumours
NAVIGATE: NCT02576431
N=97

	Adverse events, regardless of attribution*			Treatment-related adverse events*	
	Grade 1-2	Grade 3	Grade 4	Grade 3	Grade 4
Fatigue	79 (30%)	6 (2%)	0	1 (<1%)	0
Alanine aminotransferase increased	64 (25%)	7 (3%)	2 (<1%)	7 (3%)	1 (<1%)
Cough	71 (27%)	1 (<1%)	0	0	0
Constipation	69 (27%)	1 (<1%)	0	0	0
Anaemia	44 (17%)	25 (10%)	0	6 (2%)	0
Aspartate aminotransferase increased	62 (24%)	6 (2%)	1 (<1%)	2 (<1%)	0
Dizziness	64 (25%)	2 (<1%)	0	1 (<1%)	0
Nausea	62 (24%)	2 (<1%)	0	2 (<1%)	0
Vomiting	62 (24%)	2 (<1%)	0	0	0
Diarrhoea	59 (23%)	3 (1%)	0	0	0
Pyrexia	50 (19%)	2 (<1%)	1 (<1%)	0	0
Dyspnoea	35 (13%)	6 (2%)	0	0	0
Myalgia	38 (15%)	3 (1%)	0	2 (<1%)	0
Peripheral oedema	40 (15%)	1 (<1%)	0	0	0
Headache	38 (15%)	1 (<1%)	0	1 (<1%)	0
Neutrophil count decreased	18 (7%)	12 (5%)	2 (<1%)	4 (2%)	1 (<1%)
Lymphocyte count decreased	22 (8%)	7 (3%)	2 (<1%)	2 (<1%)	0
Hypokalaemia	12 (5%)	8 (3%)	1 (<1%)	0	0
Hypophosphatemia	5 (2%)	9 (3%)	0	0	0

AEs, adverse events

Hong DS, et al. Lancet Oncol 2020;21:531-40. *Data are n (%). n=260. The adverse events listed here are those that occurred at any grade in at least 15% of patients, or at grade 3 or worse in at least 3% of patients, regardless of attribution. Refer to NTRK CONNECT for full publication details: https://ntrkconnect.info/ntrk-connect-key-publication-snapshot-1-larotrectinib-and-entrectinib-efficacy-and-safety-profile-in-solid-tumours/

BACKGROUND: INTEGRATED SAFETY DATA FOR ENTRECTINIB

Data cutoff:
31 May 2018

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

STARTRK-1: Phase 1/2
Solid tumours
NCT02097810
N=2

STARTRK-2: Phase 2
Solid tumours
NCT02568267
N=51

Treatment-related adverse events (n=68)*	Grade 1–2	Grade 3	Grade 4
Dysgeusia	32 (47%)	0	0
Constipation	19 (28%)	0	0
Fatigue	19 (28%)	5 (7%)	0
Diarrhoea	18 (27%)	1 (2%)	0
Oedema peripheral	16 (24%)	1 (2%)	0
Dizziness	16 (24%)	1 (2%)	0
Blood creatinine increased	12 (18%)	1 (2%)	0
Paraesthesia	11 (16%)	0	0
Nausea	10 (15%)	0	0
Vomiting	9 (13%)	0	0
Arthralgia	8 (12%)	0	0
Myalgia	8 (12%)	0	0
Weight increased	8 (12%)	7 (10%)	0
AST increased	7 (10%)	0	1 (2%)
ALT increased	6 (9%)	0	1 (2%)
Muscular weakness	6 (9%)	1 (2%)	0
Anaemia	5 (7%)	8 (12%)	0
Asthenia	5 (7%)	0	0
Peripheral sensory neuropathy	4 (6%)	1 (2%)	0
Neutrophil count decreased	4 (6%)	0	0
Rash	4 (6%)	0	0

Treatment-related adverse events (n=68)*	Grade 1–2	Grade 3	Grade 4
Disturbance in attention	3 (4%)	0	0
Pain of skin	3 (4%)	0	0
Neutropenia	3 (4%)	2 (3%)	0
Localised oedema	2 (3%)	1 (2%)	0
Hyperaesthesia	2 (3%)	0	0
Ataxia	2 (3%)	0	0
Platelet count decreased	2 (3%)	0	0
Hyperuricaemia	2 (3%)	0	2 (3%)
Hypophosphatemia	2 (3%)	2 (3%)	0
Dehydration	2 (3%)	0	0
Diplopia	1 (2%)	1 (2%)	0
Hypotension	1 (2%)	1 (2%)	0
Pyrexia	1 (2%)	0	0
Lymphocyte count decreased	1 (2%)	0	0
Pruritus	1 (2%)	0	0
Hypoxia	1 (2%)	0	0
Fall	1 (2%)	0	0
Osteoarthritis	0	1 (2%)	0
Blood uric acid increased	0	0	1 (2%)
Hypermagnesemia	0	1 (2%)	0
Cardiac failure	0	1 (2%)	0
Cardiac failure congestive	0	1 (2%)	0

AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase
Doebele RC, et al. Lancet Oncol 2020;21:271-82 *Data are n (%). n=68. The treatment-related adverse events listed here are those that occurred in the *NTRK* fusion-positive safety-evaluable population. Refer to NTRK CONNECT for full publication details: Refer to NTRK CONNECT for full publication details: https://ntrkconnect.info/ntrk-connect-key-publication-snapshot-1-larotrectinib-and-entrectinib-efficacy-and-safety-profile-in-solid-tumours/

BACKGROUND: LIST OF TRK INHIBITORS AND CURRENT DEVELOPMENT STAGE

TRK inhibitors	Targets	Development status in *NTRK*-positive population[1]
larotrectinib, LOXO-101	***NTRK1/2/3***	Approved*
entrectinib, RXDX-101	***NTRK1/2/3****; ALK; ROS1*	Approved**
selitrectinib, LOXO-195,	***NTRK1/3*** (resistant)	Phase I/II, recruiting
repotrectinib, TPX-0005	***NTRK1/2/3,*** *ALK, ROS1* (resistant) *JAK2, SRC, DDR1, FAK*	Phase I/II, recruiting
belizatinib, TSR-011	***NTRK1/2/3,*** *ALK*	Phase I/IIa, completed
merestinib, LYS2801653	***NTRK1/2/3****, MET, MST1R, FLT3, AXL, MERTK, TEK, ROS1, DDR1/2; MKNK1/2*	Phase II, active, not recruiting
sitravatinib, MGCD516	***NTRK1/2/3,*** *MET, KIT, PDGFRA, KDR, DDR2, RET, CBL*	Phase I/II, active, not recruiting
DS-6051b, AB-106	***NTRK1/2/3,*** *ROS1*	Phase I/II, active, not yet recruiting
altiratinib, DCC2701	***NTRK1/2/3,*** *MET, MET mutant*	Phase I, terminated
PLX7486	***NTRK1/2/3****, CSF1R*	Phase I, terminated
PF-06273340	***NTRK1/2/3***	Phase I, completed
CH7057288	***NTRK1/2/3***	No studies found
GNF-5837	***NTRK1/2/3***	No studies found

AEs, adverse events; ALK, anaplastic lymphoma kinase; CBL, casitas B-lineage lymphoma; CSF1R, colony stimulating factor 1 receptor; DDR1/2, discoidin domain receptor tyrosine kinase 1/2; FAK, focal adhesion kinase; FLT3, FMS-like tyrosine kinase 3; JAK2, Janus kinase 2; KDR, kinase insert domain receptor; MKNK1/2, MAP kinase-interacting serine/threonine-protein kinase 1/2; MST1R, macrophage stimulating 1 receptor; NTRK, neurotrophic tyrosine receptor kinase; PDGFRA, platelet-derived growth factor receptor alpha; RET, rearranged during transfection; *ROS1*, c-ros oncogene 1; TRK, tropomyosin receptor kinase
*Larotrectinib is approved in the US, Canada, Brazil, European Union, Hong-Kong, Saudi Arabia, South Korea and Israel **Entrectinib is approved in the US, European Union and Japan
1. Source : ClinicalTrial.gov website visited on 27 August 2020

OBJECTIVES OF THE PAPER

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Based on the identified TRK inhibitors related AEs in prospective trials, the objectives of the paper are:

1. **To characterise these AEs**
2. **To define a management strategy for these AEs**

AEs, adverse events; TRK, tropomyosin receptor kinase

DEFINITION & RETROSPECTIVE STUDY DESIGN

- **On-target** refers to exaggerated and adverse pharmacologic effects at the target of interest in the test system[1].
- **Off-target** refers to adverse effects as a result of modulation of other targets; these may be related biologically or totally unrelated to the target of interest[1].

Eligibility criteria

- Treated in the Early Drug Development Service of Memorial Sloan Kettering Cancer Center between January 1st 2013→ April 1st 2019
- Pathologic evidence of a solid tumour
- Advanced or unresectable disease
- treated with at least one dose of a tyrosine kinase inhibitor with potent anti-TRK activity

n= 96

Data collection

- Demographics
- Toxicity assessment
- AEs management

Treatment-emergent AEs Analysis

AEs likely to be mediated by TRK inhibition were analysed:

- Paraesthesias
- Weight gain
- Dizziness with or without ataxia
- Pain with temporary or permanent TRK inhibitor withdrawal

AEs, adverse events; TRK, tropomyosin receptor kinase

1. DG Rudmann, Toxicol Pathol. 2013;41(2):310-4

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Clinicopathologic features of the study population (n=96)	n (%) and continuous as median (range)
Age* (years)	52 (5-81)
Female sex	49 (51%)
Histology	
Lung	43 (45%)
Gastrointestinal	10 (10%)
Salivary	8 (8%)
Sarcoma	8 (8%)
Thyroid	6 (6%)
Melanoma	6 (6%)
Primary brain tumor	5 (5%)
Neuroblastoma	5 (5%)
Other	7 (7%)

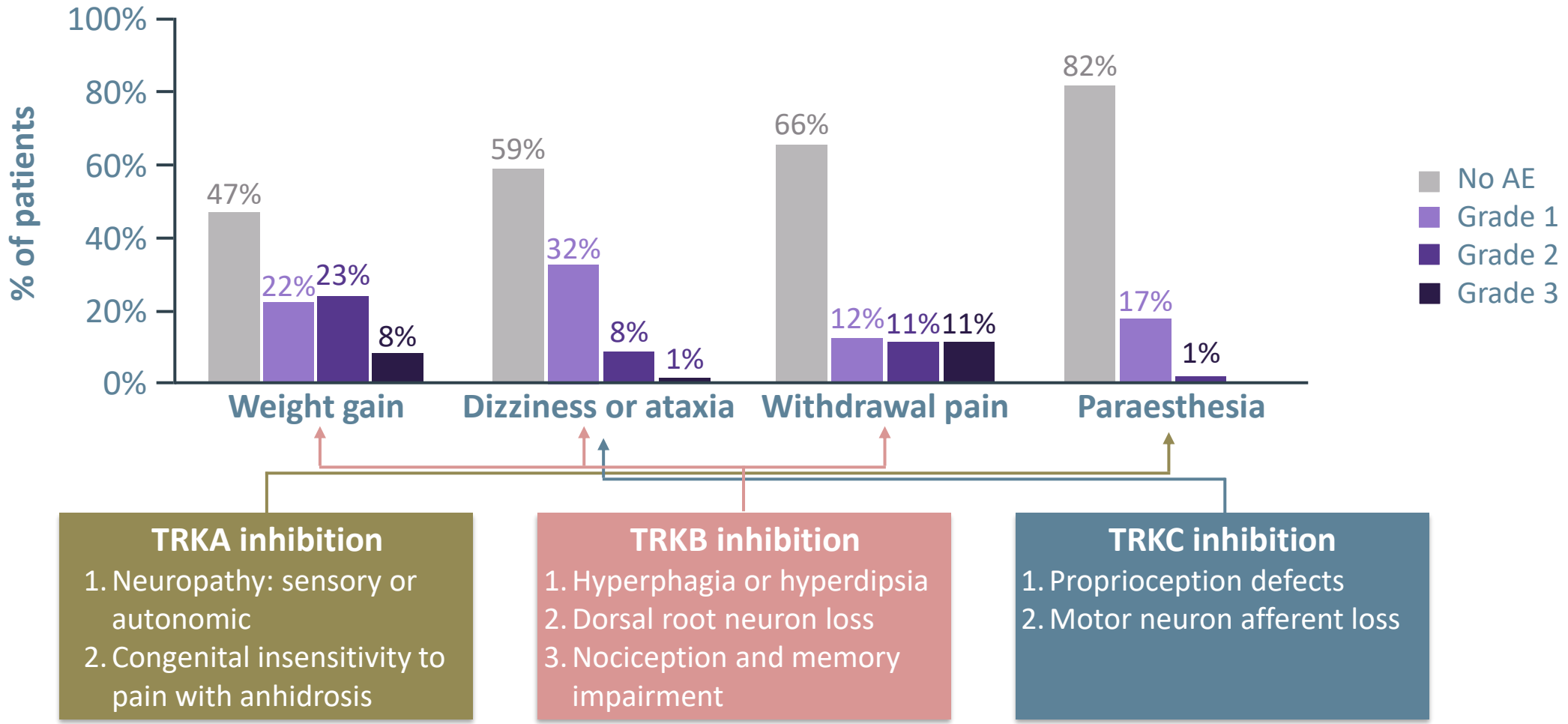
Clinicopathologic features of the study population (n=96)	n (%) and continuous as median (range)
Genomic alteration	
***NTRK* fusion**	**39 (41%)**
ROS1 fusion	24 (25%)
Other**	29 (30%)
Unknown	4 (4%)
TRK inhibitor	
First-generation TKI	81 (84%)
Other TKI	30 (31%)
TRK inhibitor duration (months)	6 (1-42)

ALK, anaplastic lymphoma kinase; NTRK, neurotrophic tyrosine receptor kinase; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor; TRK, tropomyosin receptor kinase

*Seven patients were < 18years old

**Other alterations included *NTRK* mutation (N = 1), *NTRK* amplification (N = 2), *ROS1* mutation (N = 1), and *ALK* fusion/mutation (N = 25)

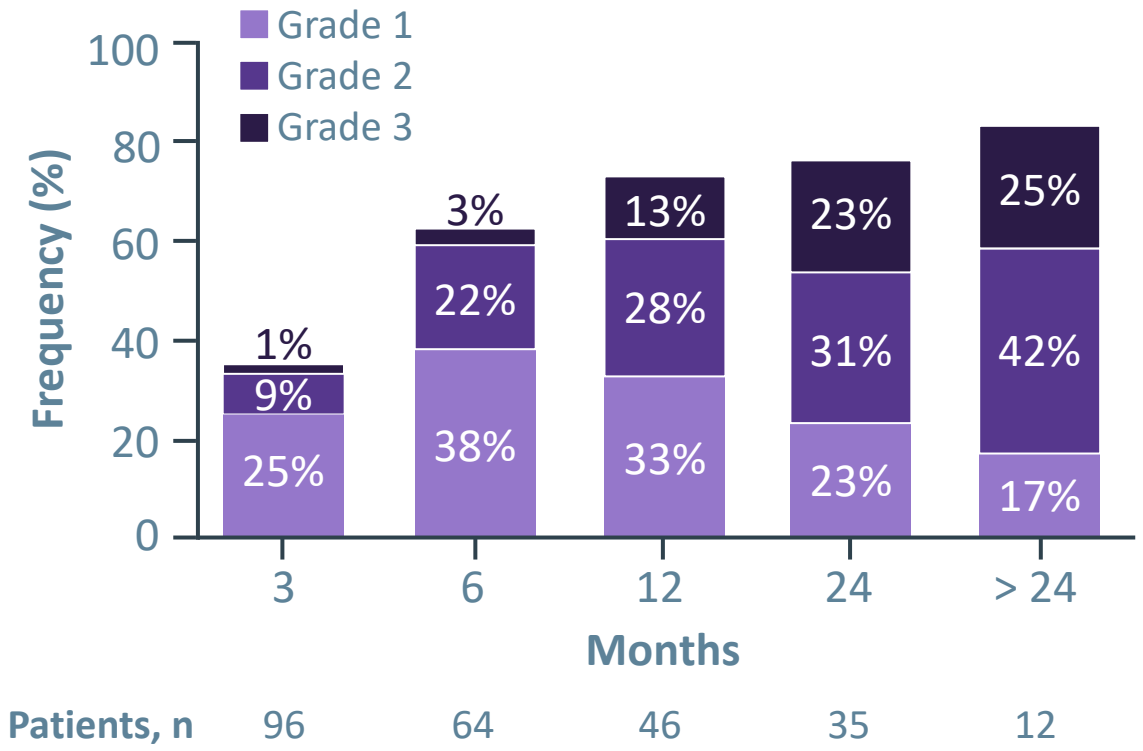
SAFETY PROFILE OF ON-TARGET AEs WITH TRK INHIBITION



AEs, adverse events; TRK A/B/C, tropomyosin receptor kinase A/B/C

WEIGHT GAIN MANAGEMENT

Weight Gain

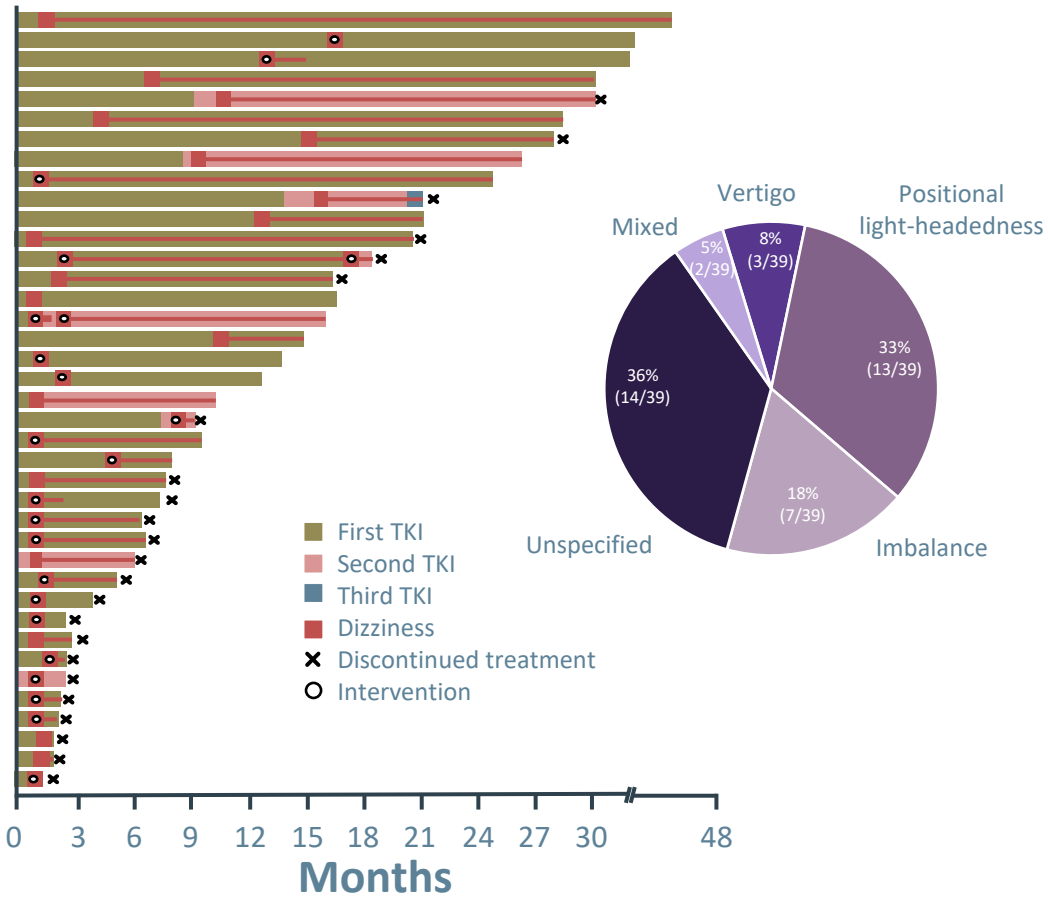


Supportive medication in weight gain	
Agent(s)	**Mechanism of action**
Liraglutide	GLP-1 analogue
Orlistat	Inhibits fat absorption
Phentermine/ topiramate combination	Increases norepinephrine release; GABA receptor agonist
Lorcaserin	5-HT_{2C} receptor agonist
Naltrexone/ bupropion combination	μ-opioid receptor antagonist; dopamine and norepinephrine reuptake inhibitor
Metformin	Modulates hypothalamic appetite regulatory centers

➔Authors recommend to monitor serially weight gain during treatment with TRK Inhibitor

5-HT_{2C}, 5-hydroxytryptamine; GABA, γ-aminobutyric acid; GLP-1, glucagon-like peptide-1; TRK, tropomyosin receptor kinase

DIZZINESS MANAGEMENT

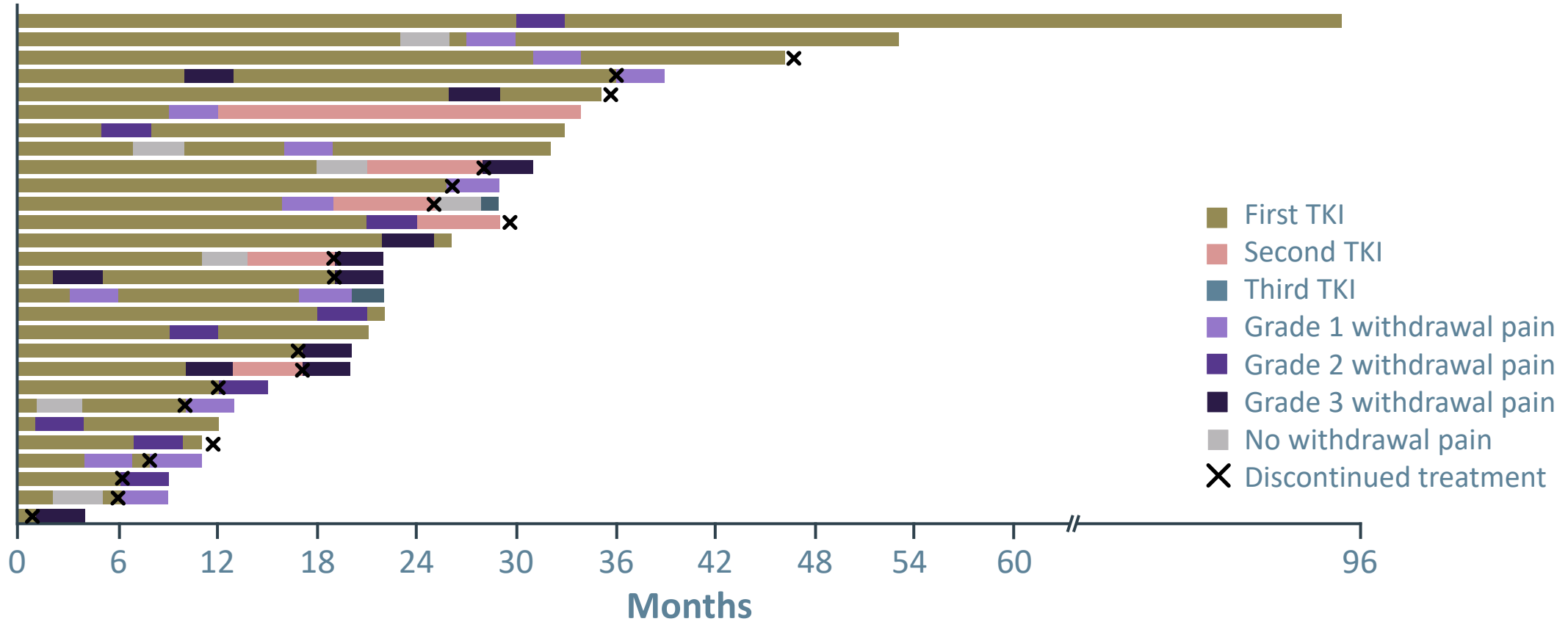


Supportive medication in dizziness management		
	Agent(s)	**Mechanism of action**
Dizziness (ataxia or vertigo)	**Meclizine**	H_1 histamine receptor antagonist, suppresses vestibular stimulation, anticholinergic
	Scopolamine	Antagonizes histamine and serotonin
Dizziness (orthostasis)	**Midodrine**	α_1 adrenergic receptor agonist, increases vascular tone
	Fludrocortisone	Mineralocorticoid
	Droxidopa	Metabolized to norepinephrine, induces vasoconstriction

➔ Authors recommend to characterize the dizziness and to manage it accordingly

TKI, tyrosine kinase inhibitor

WITHDRAWAL PAIN MANAGEMENT



➔ Authors highlight that withdrawal pain can occur with temporary or permanent TKI with anti-TRK activity discontinuation

TKI, tyrosine kinase inhibitor; TRK, tropomyosin receptor kinase

CONCLUSION AND DISCUSSIONS

Conclusion

- **On-target AEs with TRK inhibition can occur** as shown in the retrospective study analysing patients with advanced or unresectable solid tumors treated with at least one dose of a TKI with potent anti-TRK activity
- **Dizziness, weight gain and withdrawal pain are the 3 identified on-target AEs**
- **On-target AEs profile is in line with the known physiological mechanism of the TRK signalling pathway**

Discussion

- **Some cautions should be taken:**
  - The inhibitory actions of TKIs **are not only specific to TRKs**
  - In the retrospective study **only 41% harboured an *NTRK*-positive solid tumour**
- **Due to the small size of the study, further analysis to refine the on-target AEs identification should be undertaken especially with the TRK-specific inhibitors such as larotrectinib**

AEs, adverse events; NTRK, neurotrophic tyrosine receptor kinase; TKI, tyrosine kinase inhibitor; TRK, tropomyosin receptor kinase

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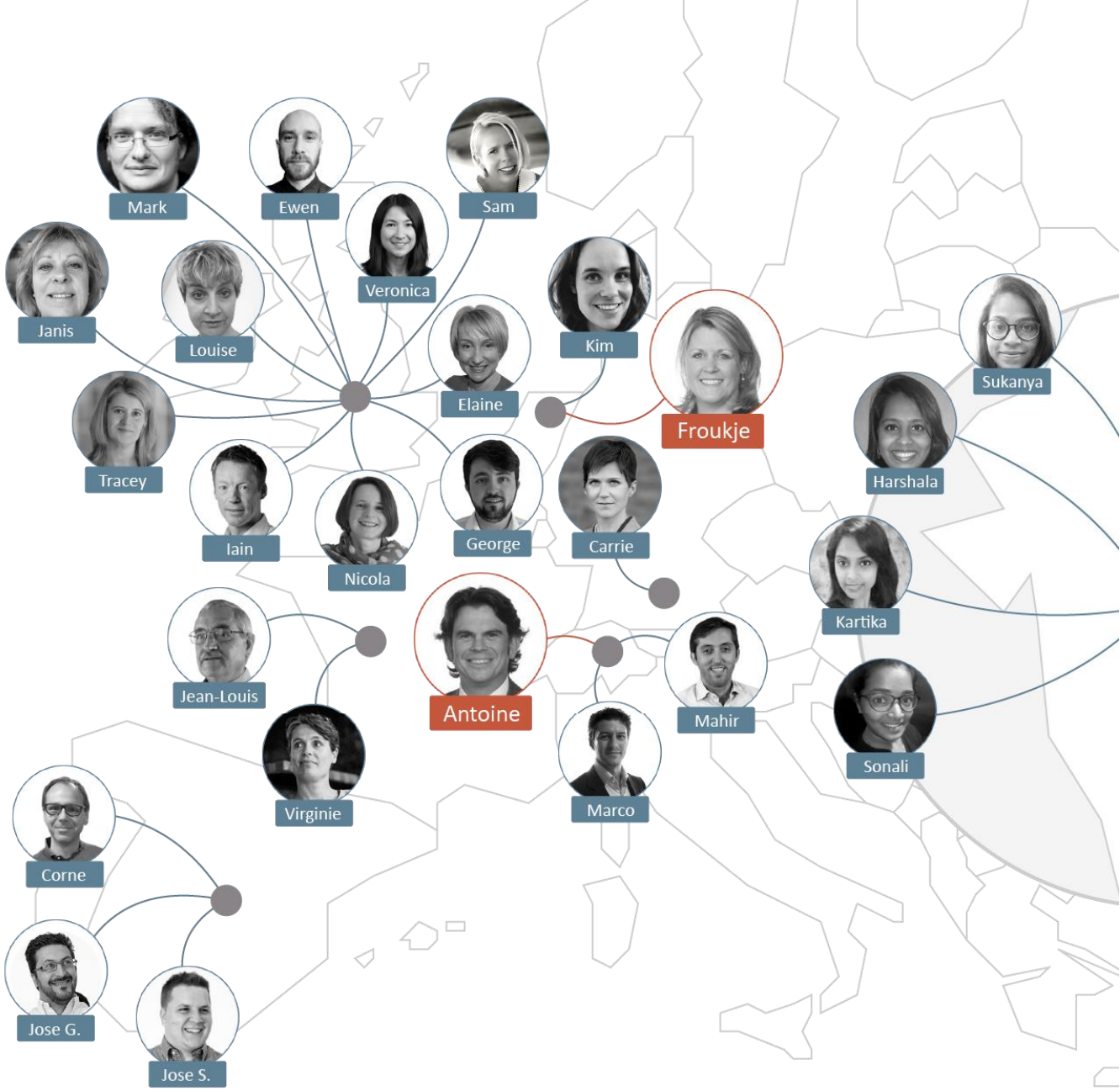

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