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Clinical Trial Results

A phase II trial of larotrectinib in tumors with NTRK fusions or extremes of NTRK mRNA overexpression identified by comprehensive genomic profiling

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Abstract

Background: TRK-inhibitors have demonstrated efficacy across several cancers with *NTRK* fusions. Their activity in cancers with NTRK overexpression remains unclear.

Methods: This trial enrolled patients with advanced cancers harboring *NTRK* fusions or extreme mRNA overexpression, defined as *NTRK1/2/3* expression by RNA profiling >5 SDs for a given cancer type. The primary endpoint was objective response rate (ORR), with secondary endpoints including time-to-progression (TTP) ratio [TTP on study to TTP on previous systemic therapy (TTP1)], progression-free survival (PFS), and overall survival (OS). Initially planned for 2 non-comparator groups: primary central nervous system (CNS) and non-CNS tumours with *NTRK* fusions, the protocol was amended to permit *NTRK* overexpression.

Results: Seventeen patients were treated with larotrectinib: one glioblastoma with a *SPECC1L::NTRK2* fusion (group 1), and a peripheral nerve sheath tumor with a *TPM3::NTRK1* fusion and 15 patients with overexpression (group 2). The ORR was 6%. An additional 3 of 12 (25%) TTP1-evaluable patients achieved a TTP ratio ≥1.3 and 2 of 5 without an evaluable TTP1 had a PFS >6 months. Median PFS and OS were 3.5 (95% CI, 1.4-6.0) and 15.9 months (95% CI, 6.4-NR), respectively.

Conclusion: Unlike its efficacy in *NTRK*-fusion positive cancers, larotrectinib did not demonstrate a signal of efficacy among tumors with *NTRK* overexpression.

Key words: TRK inhibitor; larotrectinib; *NTRK* fusions; *NTRK* overexpression.

Lessons learned

- This study suggests that larotrectinib lacks clinical activity in tumors with *NTRK* overexpression. Conversely, 1 of 2 patients with *NTRK* fusions achieved a durable objective response.
- A TTP2/1 ratio ≥1.3, capturing disease stabilization or a favorable shift in disease trajectory was achieved in a minority of the study cohort, all squamous cell carcinomas.
- Molecular eligibility based on normalized *NTRK* expression by histotype permitted a pan-cancer approach, including rare cancers like desmoplastic small round cell tumors.

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Discussion

Here we report that larotrectinib fails to demonstrate efficacy in a small cohort of patients with tumors harboring *NTRK* mRNA overexpression. Only two patients with *NTRK* fusions were identified during recruitment: one with a primary central nervous system (CNS) tumor and the other with a non-CNS, peripheral nerve sheath tumor. The latter, harboring a *TPM3::NTRK1* fusion achieved a durable partial response for over 39 months, without progression or significant toxicities.

None of the tumors with *NTRK* mRNA overexpression demonstrated an objective tumor response (OTR), despite stringent molecular eligibility for inclusion requiring a *z*-score ≥ 5 and at least 20% of cells demonstrating positivity on immunohistochemistry. A TTP2:1 ratio ≥ 1.3 was seen in 3 of 12 patients with an evaluable TTP1, indicating no improvement in disease trajectory for the majority of patients.[1] Patients achieving a TTP2:1 ratio ≥ 1.3 included a lung large cell neuroendocrine carcinoma with a squamous cell carcinoma (SCC) component, an anal SCC, and a SCC of unknown origin with *z*-scores of 9 *(NTRK2)*, 16.9 *(NTRK3)*, and 5.8 *(NTRK3)*, respectively (Figure 1). Among the 5 patients with an unevaluable TTP1, only the 2 patients with adenoid cystic carcinoma (ACC) remained progression-free at 6 months, possibly reflecting the natural history of ACCs. While pre-clinical data suggests that the *EWSR1-WT1* oncogenic driver in desmoplastic small round cell tumors (DSRCT) can activate *NTRK3* transcription and overexpression, with abrogation of *NTRK3* diminishing tumor cell growth,[2] our data does not support this. We had 4 DSRCTs with a median *z*-score of 7.0 (range 5-10) for *NTRK3* expression, which failed to demonstrate an OTR, or a favorable change in their disease trajectory based on TTP ratios.

There were no new safety concerns identified among our study cohort. There were 14 grade 3/4 adverse events, requiring 8 dose reductions among 7 patients, but no serious adverse events were considered attributable to larotrectinib. Median PFS was 3.5 months and median OS was 15.9 months for the overall cohort. Our prospective trial, which found that larotrectinib lacks clinical activity in tumors with *NTRK* mRNA overexpression, adds substantially to the limited available literature in this unique molecular subset.

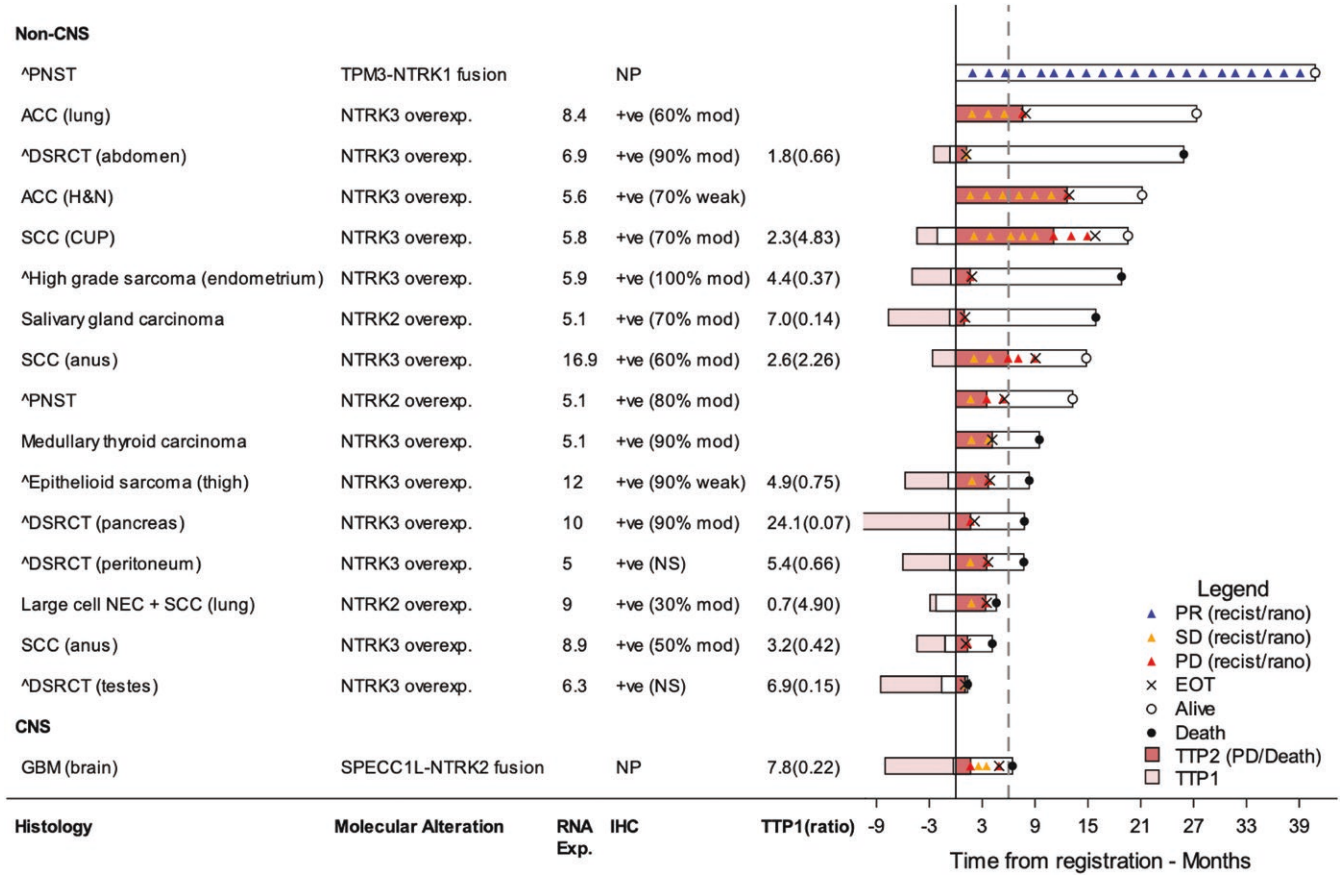

Figure 1. Swimmerplot of individual patient data for the study cohort, highlighting cancer types and molecular eligibility. The plot depicts best response, time to progression (TTP) 1, 2, TTP2:1 ratio. Sarcoma cases are indicated with a caret (^). Abbreviations: ACC, adenoid cystic carcinoma; CNS,central nervous system; CUP, carcinoma of unknown primary; DSRCT, desmoplastic small round cell tumour; EOT, end of treatment; GBM, glioblastoma; H&N, head and neck; IHC. immunohistochemistry; mod, moderate; NEC, neuroendocrine carcinoma; NP, not performed; NS, not scored; PD, progressive disease; PNST, peripheral nerve sheath tumor; PR, partial response; RNA exp, RNA expression (*z*-score); SCC, squamous cell carcinoma; SD, stable disease; TTP1, time to progression 1 (prior treatment); TTP2, time to progression 2 (on study).

Trial Information	
Disease	**Pan-cancer**
Stage of disease/treatment	Metastatic/advanced
Prior therapy	No designated number of regimens
Type of study	Phase II, single arm
Primary endpoint	Objective response rate
Secondary endpoints	Time-to-progression on study (TTP2) to time-to-progression on prior line of systemic therapy (TTP1) ratio, safety, progression-free survival (PFS), overall survival (OS)

Additional details of endpoints or study design

A substudy module size of 16 was chosen as sufficient for detecting a signal of therapeutic efficacy, analogous to the first of the 2 stages of the Simon phase II trial design with 10-16 participants. This signal-seeking phase is typical when determining whether formal expansion into a larger phase II trial is justifiable with ≥3/16 responding participants considered sufficiently interesting to investigate further.[3] The ratio of time to progression (TTP) on study (TTP2) to TTP on prior line of therapy (TTP2:TTP1) accounts for disease stabilization. This is important given the limited historical data for rare cancer types and the heterogeneity within a pan-cancer study. By applying the TTP2:TTP1 ratio, each patient acts as their own control and, Von Hoff et al established a ratio ≥1.3 (equating to TTP2 exceeding the documented TTP1 by at least 30%) as sufficient to indicate disease stabilization.[1] When TTP1 is not available, the minimum period of time for stable disease was set at 6 months. PFS was defined as the interval from date of registration to the date of first evidence of disease progression or death from any cause, whichever occurred first. OS was defined as the interval from the date of registration to date of death from any cause.

Investigator's Analysis	
	Active and should be pursued further
	Active but results overtaken by other developments
	Active but too toxic as administered in this study
X	Inactive because results did not meet primary endpoint
	Correlative endpoints met but not powered to assess activity
	Correlative endpoints not met but clinical activity observed
	Evidence of target inhibition but no or minimal anti-tumor activity
	Poorly tolerated/not feasible
	Level of activity did not meet planned end point
	Other (Specify)

Drug Information	
Generic/working name	Larotrectinib
Company name	Bayer
Drug type	Selective tyrosine receptor kinase
Drug class	TRK inhibitor
Dose	100 mg twice daily for adult patients
Unit	25 mg, 100 mg, 20 mg/mL
Route	Per oral (PO)
Schedule of administration	Larotrectinib 100 mg twice daily, days 1-28 of a 28-day cycle on a continual basis until disease progression, participant withdrawal, or prohibitive toxicity. Up to 2 dose reductions of larotrectinib and dose interruptions for a maximum of 28 days on each occasion was permitted.

Patient Characteristics	
Multi-arm trials: find tables for additional cohorts here	
Number of patients, male	9
Number of patients, female	8
Stage	Metastatic or advanced, unresectable
Molecular eligibility+	
NTRK fusions	2 (1 CNS, 1 non-CNS)
NTRK overexpression	15 (12 *NTRK3*, 3 *NTRK2*)

Age: median (range)	61 (29-83) years	
Number of prior systemic therapies: median (range)	1 (0-6)	
Performance status: ECOG	0	10
	1	5
	2	2
	3	0
	4	0

[+]Molecular eligibility was determined by somatic *NTRK1-3* rearrangements/fusions OR extreme overexpression of *NTRK1, 2 or 3 (defined as NTRK1, 2 or 3* expression by RNA profiling above the 5th SD [*z*-score ≥ 5] for the distribution of expression within that histotype normalized against the entire MoST screening cohort. NTRK protein expression by immunohistochemistry (IHC) of at least 20% of tumor cells demonstrating moderate expression of NTRK 1-3 using the Roche Ventana EPR17341 antibody. Tumors eligible based on extreme overexpression of NTRK1-3 were not permitted to harbor co-occurring gain-of-function mutations in *KRAS*, *NRAS*, *BRAF*, *MAP2K1*, *EGFR*, *ALK*, *RET*, *ROS1*, *KIT*, or *PDGFRA*.

Cancer types by group	Number
Group 1—CNS tumors	
Glioblastoma*	1
Group 2—non-CNS tumors	
Adenoid cystic carcinoma (lung, palate)	2
Anal, squamous cell carcinoma	2
CUP, squamous cell carcinoma	1
Desmoplastic small round cell tumor^	4
Epithelioid sarcoma^	1
Large cell neuroendocrine carcinoma, lung	1
Malignant peripheral nerve sheath tumor^*	2
Medullary thyroid carcinoma	1
Salivary gland carcinoma	1
Stromal sarcoma^	1

^sarcomas, **NTRK* fusions.
Abbreviation: CUP, carcinoma of unknown primary.

Primary Assessment Method

[Multi-arm trials: Find tables for additional arms and assessments here]

Title	Objective response rate
Number of patients screened	18 (One participant did not enrol as they did not demonstrate disease progression following prior therapy)
Number of patients enrolled	17
Number of patients evaluable for toxicity	17
Number of patients evaluated for efficacy	17

Evaluation Method

Evaluation method		RECIST 1.0
	X	RECIST 1.1 (n = 16)
		WHO
		Tumor marker
	X	Other (specify)—RANO for primary CNS tumor (n = 1)
Response assessment	*N*	%
CR	0	0.0 %
PR	1	5.9%
SD	12	70.6%
PD	4	23.5%

Outcome Notes

The primary outcome of objective response was achieved in only one of 17 patients (6%, 95% CI, 1%-27%). This response occurred in the only non-CNS tumor with an *NTRK* fusion and was maintained over at least 39 months. Of the remaining 15 non-CNS tumors included based on *NTRK* overexpression, 11 achieved stable disease and 4 had progressive disease. The only CNS tumor enrolled in the study harbored an *NTRK* fusion and achieved stable disease.

Secondary Objectives			
(Median) Duration assessments	#	Day/week/month	95% CI
PFS (TTP2)	3.5	Months	1.35-5.95
OS	15.9	Months	6.4-NR
Duration of Treatment	3.9	(range 1.2 to 5.5) months	

Secondary Outcome Notes

Median PFS was 3.5 months. The TTP2/1 ratio was evaluable in 12 of 17 patients, of whom 3 had a TTP2/1 ratio ≥1.3. This included 2 squamous cell carcinomas, one of unknown origin and the other of the anal canal, as well as a mixed large cell neuroendocrine/squamous cell carcinoma of the lung. Additionally, 2 of 5 patients without an evaluable TTP1 did not progress for >6 months on trial. The median OS was 15.9 months.

Safety

The median treatment duration was 3.9 months. There were no treatment delays; however, 8 dose reductions were required among 7 patients (41%). There were no treatment cessations due to toxicity, although one patient chose to withdraw from study treatment. Fifteen patients ceased larotrectinib due to disease progression and one patient remains on study at time of analysis. There were 137 adverse events (AEs) of any grade, 14 of which were at least grade 3 in severity (Table 1). There were two serious adverse events—grade 4 anaphylaxis and a grade 3 vasovagal event, both not considered to be related to larotrectinib.

Assessment, Analysis, And Discussion		
Completion:		**Study completed**
	X	**Study terminated prior to completion**
Investigator's assessment		Active and should be pursued further
		Active but results overtaken by other developments
		Active but too toxic as administered in this study
	X	Inactive because results did not meet primary endpoint
		Correlative endpoints met but not powered to assess activity
		Correlative endpoints not met but clinical activity observed
		Evidence of target inhibition but no or minimal anti-tumor activity
		Poorly tolerated/not feasible
		Level of activity did not meet planned end point
		Other (Specify)

Extended discussion

In this signal-seeking trial, none of 15 patients with tumors displaying *NTRK* overexpression achieved an objective tumor response (OTR). Of the two tumors with an *NTRK* fusion, only the non-CNS, peripheral nerve sheath tumor achieved an OTR. A TTP ratio >1.3 was achieved in an additional 3 of 12 patients with an evaluable TTP1. Median PFS and OS were 3.5 and 15.9 months respectively. There were no new safety concerns seen.

The neurotrophic receptor tyrosine kinase (*NTRK*) genes encode tropomyosin receptor kinase (TRK) proteins whose expression is mainly confined to the nervous system after embryogenesis. However, *NTRK* fusion events result in an overexpression of the chimeric protein and ligand-independent downstream signaling that leads to an oncogene addiction regardless of tissue origin.[4,5] Clinically, this has translated to overall response rates of 75% across 17 unique *NTRK*-fusion positive tumor types[6] with a median duration of response over 43 months.[7] The impressive response data in *NTRK* fusions, and low rates of toxicity[6,8] provided strong rationale for assessing their activity in tumors with other *NTRK* alterations. While The Cancer Genome Atlas reports a higher prevalence of these other *NTRK* alterations compared with fusions,[9] the evidence for effectively targeting them therapeutically, has been substantially weaker.[10,11] A phase I trial of larotrectinib in tumors with *NTRK* point mutations did not yield any objective responses and a single patient with an *NTRK1* amplified tumor achieved an objective response in a solitary target lesion for 3.7 months.[12] Additionally, patients with desmoplastic small round cell tumors (DSRCT) are known to harbor an *EWSR1-WT1* oncogenic driver which can bind to *NTRK3* upstream, activate its transcription, and produce high levels of *NTRK3* mRNA expression. In vivo data suggests that an abrogation of *NTRK3* expression can diminish DSRCT cell growth.[2] Our study was initially designed to evaluate the efficacy of larotrectinib in tumors with fusions, with a full arm ($n = 16$) dedicated to primary CNS tumors. However based on these emerging case reports of effectively targeting *NTRK* expression, we modified the trial to include *NTRK* overexpression.

To the best of our knowledge, this is the first study to evaluate the use of larotrectinib in an advanced, pan-cancer population based on *NTRK* mRNA overexpression using comprehensive genomic profiling. Among *NTRK* gene fusions, the 3′ region of the *NTRK* gene joins to the 5′ end of a fusion partner gene.[8] The resulting protein contains the C-terminus of the TRK protein which is recognized by the antibodies used for TRK testing by IHC.[5,13] The sensitivity of pan-TRK IHC can vary by the *NTRK* gene involved, with *NTRK3* staining often weak and more focal.[14] The pattern of TRK expression by IHC can further be influenced by the

fusion partner and cancer histology. Lower specificity by IHC is seen for breast and salivary gland cancers due to cytoplasmic staining, and for sarcomas due to TRK protein expression in non-neoplastic neural and smooth-muscle tissue.[14] Based on this experience in *NTRK* fusion positive tumors, we remained broad in the cancer histologies included but made the molecular eligibility restrictive. Patients needed to demonstrate extremes of overexpression even following normalization for a given cancer histotype, along with at least 20% moderate staining by immunohistochemistry (IHC). Additionally, these tumors with mRNA overexpression were not permitted to harbor competing driver mutations of key pathways, particularly those activating MAP kinase.[14] Our cohort was heterogeneous, comprised of 12 tumors with *NTRK3*, and 3 with *NTRK2* overexpression; 8 carcinomas and 7 sarcomas. This is likely to have introduced variability to the association between the *z*-score and the proportion of cells staining positive by IHC.[5,14]

Comprised of several cancer types, but applying stringent molecular eligibility for *NTRK* overexpression, this study adds substantially to the limited clinical data available to date. Beyond objective tumor response, the study's secondary endpoint of TTP2/1 ratio aimed to capture disease stabilization, using a patient's own disease trajectory as a control. Among 15 patients with *NTRK* overexpression, TTP1 was evaluable in 12, with 3 patients achieving a TTP2/1 ratio of 1.3: all squamous cell carcinomas—one of the anal canal, one of unknown primary, and one of the lung. While preclinical data suggested value in inhibiting *NTRK* overexpression in DSRCT,[2] this did not translate clinically to objective tumor shrinkage amongst 4 patients with this rare cancer type in our study. All four DSRCTs had received prior therapy, with a median TTP1 of 9.6 months, while their median TTP2 (progression-free survival) on study treatment was 1.45 months; none achieving a favorable TTP2/1 ratio >1.3. Of the 5 patients without an evaluable TTP1, only the 2 patients with adenoid cystic carcinomas remained progression-free at 6 months, potentially reflecting the natural history of this cancer type, rather than the beneficial effects of TRK inhibition.

The pan-cancer nature of this study was inclusive of several cancer types, including rare cancers with limited access to trials. The determination of *NTRK* overexpression incorporated cancer type and enriched the study cohort for tumors with extremes of mRNA expression within a given histotype. Another positive aspect of this trial was the incorporation of TTP2/1 ratios to identify possible disease stabilization, or an improvement in the trajectory of disease for an individual patient. The limitations of this study were its small patient numbers and a restructure of the groups to incorporate *NTRK* mRNA overexpression. The use of archival tumor samples may have failed to capture the current *NTRK* expression status, and the sensitivity and specificity of the immunohistochemistry is likely to vary by tissue type.

Overall, this signal-seeking study failed to yield any objective responses among an advanced cancer cohort with tumors demonstrating extremes of *NTRK* expression. While the CNS tumour with an *SPECC1L::NTRK2* fusion also did not achieve an objective response, the peripheral nerve sheath tumor with a *TPM3::NTRK1* fusion achieved a partial response that was maintained for at least 39 months. We did not observe the preclinical data translate to favorable outcomes for our 4 patients with DSRCTs. However, 3 squamous cell carcinomas of varying sites of origin demonstrated an improvement in their disease trajectory when compared to a prior line of therapy.

Trial Information

ClinicalTrials.gov Identifier
ACTRN12619001147178

Sponsor

NHMRC Clinical Trials Centre, University of Sydney

Principal Investigator

David Thomas
IRB approved
St Vincent's Hospital Sydney Human Research Ethics Committee (2019/ETH12026).

Conflict of interest

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board. Hao-Wen Sim: AbbVie (RF), Bristol-Myers Squibb (RF), Eli Lilly (H), Servier (H). Jayesh Desai: Consulting/Advisory: Amgen, Bayer, Beigene, Boehringer Ingelheim, GlaxoSmithKline, Merck KGaA, Novartis, Pfizer, Pierre Fabre, Roche/Genentech Research Funding: Amgen, Astra Zeneca, Beigene, BMS, Novartis, Pierre Fabre, Roche/Genentech Scientific Advisory Board: Axelia, Ellipses. John Simes: Scientific Advisory Board (Company, Funds paid to; Role) Detsamma FivepHusion, Institutional, Advisory Board Member Research Funding (Company; Funds Paid to; Interest; Purpose) Astra Zeneca, Research Grant, Institutional, Financial interest, Research Funding for Clinical Trials Bayer, Research Grant, Institutional, Financial interest, Research funding for clinical trials BMS, Research Grant, Institutional, Financial interest, Research Funding for Clinical Trials MSD, Research Grant, Institutional, Financial interest, Research Funding for Clinical Trials Pfizer, Research Grant, Institutional, Financial interest, Research Funding for Clinical Trials Roche, Research Grant, Institutional, Financial interest, Research funding for clinical trial. David Thomas: As CEO of Omico, a non-profit organization has received grants, consultancies or research support from Roche, Astra Zeneca, Pfizer, Eisai, Illumina, Beigene, Elevation Oncology, RedX Pharmaceuticals, Sun-Pharma, Bayer, Abbvie, George Clinical, Janssen, Merck, Kinnate, Microba, BioTessellate, Australian Unity, Foundation Medicine, Guardant, Intervenn, Amgen, Seattle Genetics and Eli Lilly. DT also serves on the advisory boards or committees for Canteen, UNSW SPHERE and NSW government in respect to genomics and translational medicine.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Figures and Tables

Table 1. Adverse events.

Haematological/immune		G1-2	G3-4
	Anaemia	1	
	Anaphylaxis		1*
	Epistaxis	1	
Infections			
	COVID-19	2	
	Flu-like symptoms	1	
	Shingles	1	
	UTI	2	
Cardiac disorders			
	Hypotension	1	
	Sinus tachycardia	1	
Gastrointestinal			
	Abdominal pain	5	1
	Bloating	1	
	Constipation	7	
	Diarrhoea	3	
	Flatulence	1	
	Elevated transaminases	8	2
	elevated GGT/ALP	2	
	Elevated bilirubin	2	1
	Tenesmus	1	
	Nausea	4	
	Vomiting	4	1
	GORD	2	
	Dry mouth	1	
	Oral mucositis/ulcers	2	
	Oral pain	1	
General			
	Anorexia	2	
	Dysgeusia	1	
	Fall	1	
	Fatigue	5	
	Impaired vision	1	
	Insomnia	1	
	Irritability	1	
	Vertigo	1	
	Weight loss	2	
Investigations			
	Hypoalbuminaemia	1	
	Hypomagnesaemia	1	
Musculoskeletal			
	Arthralgia	3	
	Chest wall pain	1	
	Chills	1	
	Flank pain	1	
	Limb edema	2	
	Muscle cramp	1	
	Myalgia	3	
	Neck/facial pain	2	
	Pain	1	
	Torn biceps		1
Skin			
	Maculopapular rash	2	
	Pain	1	
Neurological			
	Dizziness	6	
	Dysaesthesia	2	
	Gait disturbance		1
	Headache	3	
	Impaired memory	1	
	Peripheral sensory neuropathy	3	
	Syncope		2
	Vasovagal		1*
Renal/urinary disorders			
	Dehydration	2	
	Urinary frequency	1	
Respiratory			
	Cough	3	
	Dyspnoea	5	1
	Pleural effusion	2	1
	Pneumonitis	1	
Vascular			
	Flushing	2	
	Thromboembolic event		1
TOTAL		123	14

*Serious adverse event.
Abbreviations: GORD, gastroesophageal reflux disease; UTI, urinary tract infection.