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Phase I study of TIGIT inhibitor M6223 ± bintrafusp alfa in patients with metastatic/locally advanced unresectable solid tumours

Lillian L. Siu*[1], Meredith McKean[2], Anthony W. Tolcher[3], Anja Victor[4], Thomas Kitzing[4], Vadryn Pierre[5], Stephan Gleicher[4], Daniel Holland[4], Emilia Richter[4], Aung Naing[6]

*Presenting and corresponding author (lillian.siu@uhn.ca)

[1]Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; [2]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [3]NEXT Oncology and Texas Oncology, San Antonio, TX, USA; [4]Merck Healthcare KGaA, Darmstadt, Germany; [5]EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA; [6]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

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CONCLUSIONS

M6223 ± bintrafusp alfa (BA) had an acceptable safety profile with favourable pharmacokinetics (PK) and target engagement

At this preliminary interim analysis, clinical benefit rate was 38% with M6223 monotherapy and 12% with M6223 + BA (all stable disease at 6 weeks)

M6223 at the recommended every two weeks (Q2W) dose for expansion of 1600 mg will be further studied in combination with avelumab for advanced urothelial carcinoma in the Phase II JAVELIN Bladder Medley trial (NCT05327530)

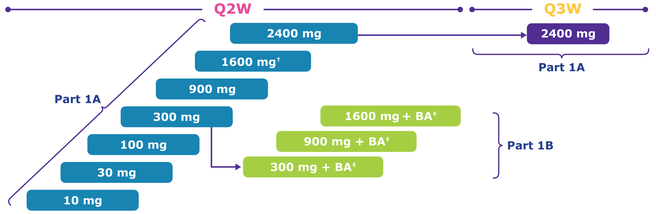
INTRODUCTION

- T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) is an inhibitory receptor expressed on T cells, including regulatory T cells (Tregs) and natural killer (NK) cells[1]
- TIGIT is overexpressed in the tumour microenvironment,[2–4] directly inhibits both T cell and NK cell effector function and proliferation, and is also involved in regulating Treg function[2,5–7]
- M6223 is an intravenously (IV) administered, human, antagonistic, immunoglobulin G1 (IgG1) anti-TIGIT antibody with an Fc-mediated effector region
- Bintrafusp alfa (BA) is an IV-administered first-in-class bifunctional fusion protein composed of the extracellular domain of the human transforming growth factor β receptor II (TGF-βRII or TGF-β 'trap') fused to a human IgG1 antibody blocking programmed death ligand 1 (PD-L1)[2]
- As TIGIT and programmed death receptor 1 (PD-1) are co-expressed on T cells, dual inhibition of both immune checkpoints may enhance antitumour activity
- This Phase I, first-in-human, open-label multicentre study (NCT04457778) is assessing the safety, tolerability, maximum tolerated dose (MTD) and recommended dose for expansion (RDE) of M6223 as monotherapy (part 1A; M6223 given Q2W and every 3 weeks [Q3W]) or in combination with BA (part 1B; M6223 given Q2W) in patients with advanced solid tumours. We report here preliminary interim data

METHODS

- This study includes patients aged ≥18 years with an Eastern Cooperative Oncology Group performance status of ≤1 and locally advanced or metastatic solid tumours for whom no effective standard therapy was available, and who had not previously been treated with a TIGIT-targeting agent or BA

Figure 1. Trial design and M6223 dose levels*



*Part 1A and part 1B are being conducted in parallel and are ongoing; †RDE reached; ‡BA was administered at a dose of 1200 mg
BA, bintrafusp alfa; **Q2W**, every 2 weeks; **Q3W**, every 3 weeks

- In part 1A, patients receive M6223 at one of seven Q2W dose levels or M6223 Q3W; in part 1B, patients receive M6223 at one of three Q2W dose levels in combination with BA (**Figure 1**)
- Additional patients are currently enrolled and receiving monotherapy to collect biomarker data from paired biopsies (dose levels [DLs] 900 and 1600 mg Q2W and DL 2400 mg Q3W)
- Doses were recommended by the safety monitoring committee, supported by a Bayesian 2-parameter logistic regression model

Primary objectives
Safety, tolerability, MTD and RDE of M6223 with and without BA

Secondary and exploratory objectives
These include PK, pharmacodynamics, clinical activity and biomarkers

RESULTS

- By 31 May 2022, 31 patients (14 male, 17 female, age range 24–78 years) had received M6223 and 18 (seven male, 11 female, age range 34–80 years) had received M6223+BA
- To date, 2 dose-limiting toxicities (DLTs) have been observed: one with M6223 900 mg (adrenal insufficiency) and one with M6223 300 mg + BA (anaemia)
- 10/31 (32%) had experienced grade ≥3 treatment-emergent adverse events (TEAEs) with M6223 and 13/18 (72%) with M6223 + BA (**Tables 1 and 2**)
- 11/31 (35%) and 5/18 (28%) patients receiving M6223 and M6223 300 mg + BA, respectively, achieved clinical benefit (stable disease at first on-treatment assessment) and 3/31 (10%) and 4/18 (22%) patients, respectively, were on treatment for ≥20 weeks (**Figure 2**)
- Across all doses, M6223 exhibited approximately dose-proportional PK properties with an estimated serum half-life ranging from 7 to 10 days (**Figure 3**)
- Blood TIGIT receptor occupancy (RO) was >95% at M6223 dose levels ≥900 mg for the Q2W regimen across all patients at cycle 1 (day 2) and at cycle 2 (day 1)
- Detectable M6223 anti-drug antibodies (ADA) post-baseline occurred in 5 of 23 (22%) patients with available ADA results
- Treatment-driven immunophenotype changes in peripheral blood were observed, including depletion of TIGIT+ regulatory T cells
- MTD has not been reached in monotherapy or in combination Q2W therapy; the estimated median DLT probability for all tested doses was below 15%
- RDE for the Q2W M6223 monotherapy regimen was 1600 mg

Table 1. Most frequently occurring TEAEs by PT*

TEAEs occurring in ≥20% of patients, n (%)			
M6223 alone (N=31)		**M6223+BA (N=18)**	
Total (any grade)	**26 (84)**	**Total (any grade)**	**17 (94)**
Fatigue	8 (26)	Fatigue	7 (39)
Arthralgia	6 (20)	Anaemia	6 (33)
Grade ≥3 TEAEs in ≥10% of patients, n (%)		Maculo-papular rash	6 (33)
M6223 alone (N=31)	**M6223+BA (N=18)**	Constipation	4 (22)
None observed	Anaemia 4 (22)	Nausea	4 (22)
	Elevated AST 2 (11)	Pyrexia	4 (22)

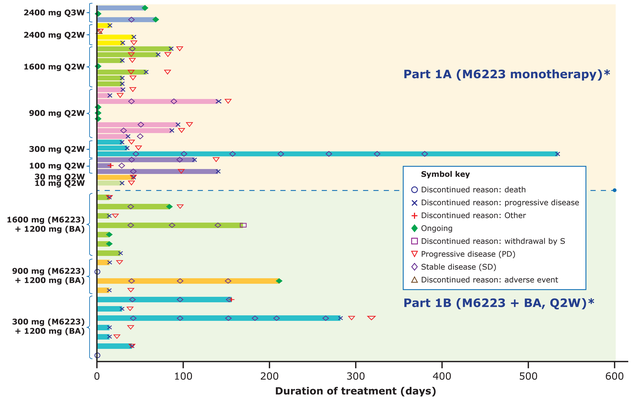
*Some patients only started treatment shortly before data cut off
AST, aspartate aminotransferase; **BA**, bintrafusp alfa; **PT**, preferred term; **TEAE**, treatment-emergent adverse event

Table 2. Safety outcomes by dose level

TEAEs, n (% patients)	M6223 monotherapy								M6223+BA (1200 mg) Q2W		
	10 mg Q2W (n=1)	30 mg Q2W (n=1)	100 mg Q2W (n=3)	300 mg Q2W (n=3)	900 mg Q2W (n=9)*	1600 mg Q2W (n=7)*	2400 mg Q2W (n=4)*	2400 mg Q3W (n=3)*	300 mg† (n=7)	900 mg (n=4)	1600 mg (n=7)*
Any grade ≥3	0	0	1 (33)	1 (33)	3 (33)	2 (29)	2 (50)	1 (33)	5 (71)	4 (100)	4 (57)
Any M6223-related TEAE leading to permanent discontinuation of M6223	0	0	0	0	0	0	0	0	0	0	0
Any BA-related TEAE leading to permanent discontinuation of BA	–	–	–	–	–	–	–	–	1 (14)	0	1 (14)
Any SAE related to M6223‡	0	0	0	0	1 (11)	0	0	0	1 (14)	0	1 (14)
Any SAE related to M6223 + BA‡	–	–	–	–	–	–	–	–	1 (14)	0	1 (14)

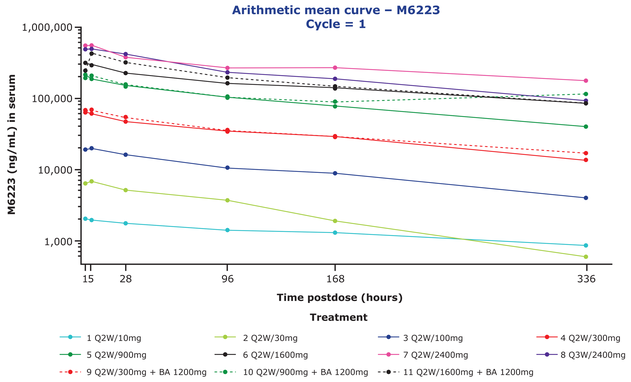
*Some patients only started treatment shortly before data cut off; †There was one death considered to be related to M6223 + BA in the M6623 300mg + BA Q2W group; ‡SAEs included anaemia (related to BA), death and rash (related to both M6223 and BA) in the M6223 + BA group, occurring in one patient each
AE, adverse event; **BA**, bintrafusp alfa; **Q2W**, every 2 weeks; **Q3W**, every 3 weeks; **SAE**, serious adverse event; **TEAE**, treatment-emergent adverse event

Figure 2. Duration of M6223 treatment in Part 1A and Part 1B



*Each bar represents one patient
BA, bintrafusp alfa; **Disc.**, discontinuation; **Q2W**, every 2 weeks; **Q3W**, every 3 weeks

Figure 3. Mean M6223 concentration by dose over time (Part 1A and Part 1B)*



*The difference in the curves of the 2400 mg Q2W and 2400 mg Q3W cohorts was due to individual variations in pharmacokinetic assessments within 168 hours post-dose
Q2W, every 2 weeks; **Q3W**, every 3 weeks

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