ESMO FPN: 750P

# 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



## 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)**

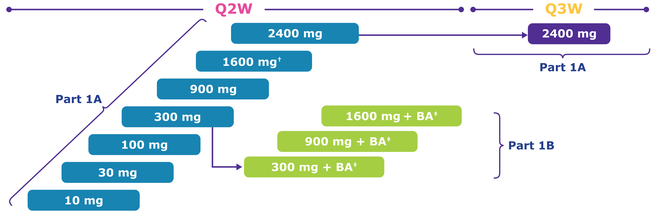
## INTRODUCTION

- 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) |

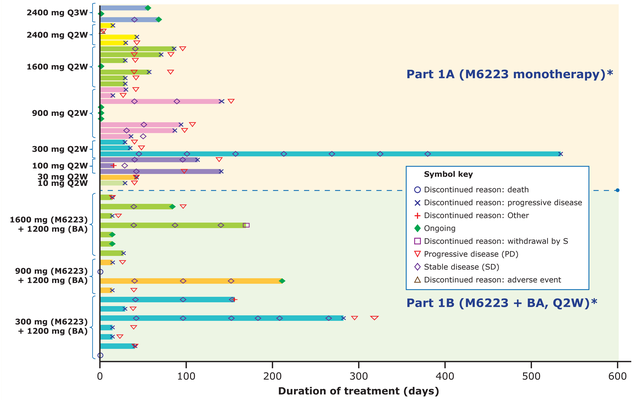
*Some patients only started treatment shortly before data cut off
**AST**, aspartate aminotransferase; **BA**, bintrafusp alfa; **PT**, preferred term; **TEAE**, treatment-emergent adverse event

**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) |

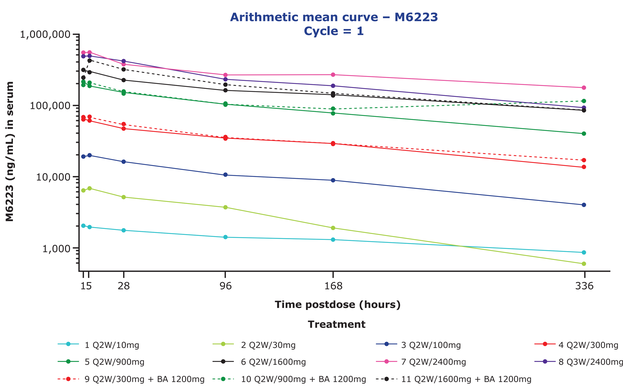
*Some patients only started treatment shortly before data cut off; †There was one death considered to be related to M6223 + BA in the M6623 300mg + BA Q2W group; ‡SAEs included anaemia (related to BA), death and rash (related to both M6223 and BA) in the M6223 + BA group, occurring in one patient each
**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

**References:** **1.** Harjunpää H & Guillerey C. Clin Exp Immunol 2019;200:108–119; **2.** Johnston RJ, et al. Cancer Cell 2014;26:923–937; **3.** Wang F, et al. Eur J Immunol 2015;45:2886–2897; **4.** Chauvin J-M, et al. J Clin Invest 2015;125:2046–2058; **5.** Wang M, et al. Clin Immunol 2018;190:64–73; **6.** Stanietsky M, et al. Eur J Immunol 2013;43:2138–2150; **7.** Kurtulus S, et al. J Clin Invest 2015;125:4053–4062

**Acknowledgements:** The authors would like to thank patients, investigators, co-investigators, and the study teams at each of the participating centres and Merck. The trial was sponsored by Merck (CrossRef Funder ID: 10.13039/100009945). Medical writing assistance was provided by Melody Watson of Bioscript Group, Macclesfield, UK, and funded by Merck

**Disclosures: LS** has been a consultant for Merck, AstraZeneca/MedImmune, Roche, Voronoi Inc., Oncorus, GSK, Seattle Genetics, Arvinas, Navire, Janpix, Relay Therapeutics, Daiichi Sankyo/UCB Japan, Janssen, Hookipa Pharma, InterRNA, Tesa Therapeutics, Sanofi, and Amgen and has received research grants from BMS, Genentech/Roche, GSK, Merck, Novartis, Pfizer, AstraZeneca, Boehringer Ingelheim, Bayer, Amgen, Astellas Pharma, Shattuck Labs, Symphogen, Avid, Mirati Therapeutics, Intensity Therapeutics, and Karyopharm Therapeutics. **MH** has been a consultant for Astellas Pharma, AstraZeneca, BicycleTX Limited, Castle Biosciences, Eisai, Ideaya Biosciences, iTeos, Moderna, Pfizer, and Regeneron Pharmaceuticals and has received research grants from Alpine Immune Sciences, Arcus Biosciences, Arvinas, Ascentage Pharma Group, Bayer, Bicycle Therapeutics, BioMed Valley Discoveries, BioNTech, Dragonfly Therapeutics, EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, Epizyme, Eisai, Exelixis, Foghorn Therapeutics, Genentech, Gilead Sciences, GSK, IDEAYA Biosciences, Ikena Oncology, ImmVira Pharma, Infinity Pharmaceuticals, Jacobio Pharmaceuticals, Kechow Pharma, Kezar Life Sciences, Kinnate BioPharma, MedImmune, Mereo BioPharma, Metabomed, Moderna, NBE Therapeutics, Nektar, Novartis, Oncorus, PACT Pharma, Pfizer, Plexxikon, Prelude Therapeutics, Pyramid Biosciences, Regeneron, Sapience Therapeutics, Scholar Rock, Seattle Genetics, Synthrox, Takeda Pharmaceuticals, Tenebio, Tempest Therapeutics, Tizona Therapeutics, TRUNITY Therapeutics, TopAlliance Biosciences, Xilio. **AT** has been a consultant for Nanobiotix, Pierre Fabre, Ascentage Pharma, AbbVie, EMD Serono, Biocrant, Adagene, Agenus, Aeminium, Bayer, HBM Partners, Mekanistic, NBE Therapeutics, Pelican, Pfizer, Immunome, Glide Healthcare Partners, Immunomet, Mirati Therapeutics, Pieris, Ars Bioterapeutics, Asana, Elucida, Partner Therapeutics, Ryvu Therapeutics, Sotio, Eleven Bio, Zymeworks, Mersana, Trillium Therapeutics, Boehringer Ingelheim International GmbH, Janssen Global Services, LLC, Aclaris Therapeutics, Blu Print Oncology, Daiichi Sankyo, Inc., IDEA Pharma, Immunoenvio, Impact Therapeutics US, Inc., Karma Oncology, Lengo Therapeutics, Menarini Ricerche, Seattle Genetics, SK Life Sciences, Spirea Limited Inc, Sunshine Guojian, Transcenta Therapeutics, Zentalis, Transgene, Deka Biosciences, Hiber Cell, Inc., Ikena Oncology, Jazz Pharmaceuticals, PYXIS Oncology, Vincerx Pharma, ZielBio, Senti Biosciences, Ocellaris Pharma, Lilly, has received research grants from AbbVie, Pfizer, Syndax, Asana Biosciences, ADC Therapeutics, Adagene, Aminex, Ascentage Pharma, Arrys, CStone Pharmaceuticals, Deciphera, GSK, Inhibrx, Innate Pharma, Kromnic, Mersana, Naturewise, NextCure, Nitto BioPharma, Pieris Pharmaceuticals, Symphogen, Tizona Therapeutics, Inc., Zymeworks, Agenus, Amphivena, Astex, Boehringer Ingelheim, Basilea, effECTOR Therapeutics, EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, Gilead Sciences, KeChow, K Group Beta, Janssen Research & Development, MSD, ORIC Pharmaceuticals, Samumed, Spring Bank, Seattle Genetics, Sunshine Guojian, Synthorx, Bicinnet International AB, Birde Biopharmaceuticals, BJ Bioscience Inc., Boston Biomedical, Inc., Daiichi Sankyo, Inc., ImmuneOncia Therapeutics Inc., Mirati Therapeutics Inc., NBE Therapeutics AG, Odonate Therapeutics Inc., Qiu Puget Sound Biotherapeutics Corp, Shanghai Haihe Pharmaceutical Co., Ltd., Takeda, ABL Bio, Apros Therapeutics, Arcelix, ASMO BioSciences, and Artios Pharma Limited, and has received testimony compensation from Immunogen and travel expenses from Sotio. **AV** is an employee of Merck Healthcare KGaA, Darmstadt, Germany, and has stocks and shares in Merck. **TK** is an employee of Merck Healthcare KGaA, Darmstadt, Germany. **VP** is an employee of EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA. **SG** is an employee of Merck Healthcare KGaA, Darmstadt, Germany. **ER** is an employee of Merck Healthcare KGaA, Darmstadt, Germany. **AN** has been a consultant for Novartis, CytomX Therapeutics, OncoSec, STCube Pharmaceuticals Inc, Kymab, Takeda (1), CSL Behring (1), Horizon Pharma (1), Genome & Company, Immune-Onc, Deka Bioscience, and Nouscom, has received research grants from EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, MedImmune, Attercocr, Amplimmune, ARMO BioSciences, Karyopharm Therapeutics, Incyte, Novartis, Regeneron, Merck, Bristol Myers Squibb, Pfizer, CytomX Therapeutics, Neon Therapeutics, Calithera Biosciences, TopAlliance BioSciences Inc, Healios, Lilly, Kymab, PsiOxus Therapeutics, Immune Deficiency Foundation (1), Arcus Biosciences, NeoImmuneTech, ImmuneOncia, Surface Oncology, and Bavaitia (1), and has received travel expenses from ARMO BioSciences

**Presented at the European Society for Medical Oncology (ESMO) Congress 2022 | 9–13 September 2022 | Paris, France**