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# TIGIT inhibitor M6223 as monotherapy or in combination with bintrafusp alfa in patients with advanced solid tumors: a first-in-human, phase 1, dose-escalation trial

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## ABSTRACT

**Background** M6223 is an intravenous (IV), Fc-competent, fully human, antagonistic, anti-T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) antibody. Bintrafusp alfa (BA) is a bifunctional fusion protein that simultaneously blocks nonredundant immunosuppressive TGF-β and PD-(L)1 pathways.

**Methods** This first-in-human, dose-escalation study in patients with advanced solid tumors (N=58; aged ≥18 years, ECOG PS≤1) evaluated M6223 alone (Part 1A, n=40; M6223 10–2400 mg every 2 weeks, n=32; M6223 2400 mg every 3 weeks, n=8) or with BA (Part 1B, n=18; M6223 300–1600 mg with BA 1200 mg; both every 2 weeks, intravenous). Primary objectives were safety, tolerability, maximum tolerated dose (MTD) and recommended dose for expansion (RDE). Additional objectives included pharmacokinetics, pharmacodynamics and clinical activity (NCT04457778).

**Results** Two dose-limiting toxicities were observed: grade 3 adrenal insufficiency (Part 1A: M6223 900 mg every 2 weeks) and grade 3 anemia (Part 1B: M6223 300 mg, only BA related). MTD was not reached. Overall, median overall survival and progression-free survival were 7.6 (95% CI 4.9, 12.0) and 1.4 (95% CI 1.3, 1.8) months, respectively. Stable disease as best response was observed in 13 (32.5%) and 5 (27.8%) patients in parts 1A and 1B, respectively. M6223±BA displayed a linear pharmacokinetic profile. Anti-TIGIT mode-of-action-related pharmacodynamic effects were observed in peripheral blood and in tumor tissue. RDEs were 1600 mg every 2 weeks or 2400 mg every 3 weeks for M6223 monotherapy and 1600+1200 mg every 2 weeks for M6223+BA.

**Conclusions** M6223±BA had a manageable safety profile, with RDEs defined for both monotherapy and combination therapy. Further evaluation of M6223 is ongoing in combination with the PD-L1 inhibitor avelumab in patients with advanced urothelial carcinoma (JAVELIN Bladder Medley; NCT05327530).

**Trial registration number** NCT04457778.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) is an inhibitory receptor that is overexpressed on immune cells present in the tumor microenvironment. Inhibition of TIGIT can enhance antitumor T cell responses through multiple mechanisms, encompassing its role as a ligand, receptor, or competitor for costimulatory receptors. M6223 is an intravenous, Fc-competent, fully human, antagonistic, anti-TIGIT antibody. Bintrafusp alfa (BA) is a bifunctional fusion protein that simultaneously blocks nonredundant immunosuppressive TGF-β and PD-(L)1 pathways.

### WHAT THIS STUDY ADDS

⇒ This first-in-human, dose-escalation study in patients with advanced solid tumors shows that M6223, an anti-TIGIT antibody, has a manageable safety profile, either as monotherapy or in combination with BA (anti–PD-L1 and TGFβ trap).

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ M6223 is currently being evaluated in combination with avelumab (anti-PD-L1) in advanced urothelial carcinoma (JAVELIN Bladder Medley; NCT05327530).

## BACKGROUND

Harnessing the antitumor immune response is fundamental to cancer immunotherapy and both effector and memory T lymphocytes play central roles.[1] T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domains (TIGIT) is an inhibitory receptor within the poliovirus receptor (CD155)/nectin family of proteins and belongs to the immunoglobulin (Ig) superfamily. TIGIT

consists of an extracellular Ig variable domain, a type I transmembrane domain and a short intracellular domain with an immunoglobulin tail tyrosine-like motif and ITIM.[2 3] TIGIT expression is observed in several human cancers, including colorectal cancer (CRC)[2] and on multiple immune cells, with the highest levels observed on regulatory T cells (Tregs), effector $CD8^+$ and $CD4^+$ T cells and natural killer (NK) cells.[1 2] Notably, TIGIT is overexpressed on immune cells present in the tumor microenvironment (TME),[4 5] leading to immune exhaustion of T and NK cells and stronger immune suppression of Tregs.[6]

Inhibition of TIGIT can enhance antitumor T cell responses through multiple mechanisms, encompassing its role as a ligand, receptor, or competitor for costimulatory receptors.[3] Preclinical studies in murine models have shown that $TIGIT^{-/-}$ mice exhibit significantly reduced tumor growth and that treatment with TIGIT-blocking antibodies elicits antitumor immune responses.[6 7] TIGIT is often coexpressed with PD-1 on $CD8^+$ T cells, NK cells, helper T cells and Tregs,[8 9] and can suppress $CD8^+$ T cell effector function within the TME in combination with programmed cell death-ligand (PD-L1).[4] In preclinical models, concurrent blockade of TIGIT and PD-L1 was necessary to restore the potency of $CD8^+$ T cells within the highly suppressive TME and confer protection against tumor rechallenge.[4] Considering their coexpression on T cells, the dual inhibition of TIGIT and PD-1 represents a promising strategy to enhance the antitumor activity.[10] M6223 is a fully human IgG1 antibody that inhibits the interaction of TIGIT with its ligands CD112 and CD155, thereby inhibiting the TIGIT-related immunosuppressive pathway. M6223 can also interrupt the interaction of TIGIT with its costimulatory receptor CD226, which enhances CD226 dimerization and costimulatory signaling.

Transforming growth factor-beta (TGF-β) plays a critical role in modulating immune responses in the TME and is associated with immune evasion and immune checkpoint inhibitor (ICI) resistance.[11 12] Hence, simultaneous blockade of TGF-β and PD-L1 may represent an important therapeutic strategy. Bintrafusp alfa (BA) is an investigational 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 via a flexible linker to the C-terminus of each heavy chain of an IgG1 antibody that blocks programmed cell death ligand 1 (anti-PD-L1).[13] In preclinical studies using humanized mice with huTIGIT knock-in sequences, M6223+BA significantly enhanced the antitumor activity and prolonged survival compared with treatment with the respective monotherapies (median, 74 vs 39 days)[14]; this finding is supported by the fact that TIGIT expression is associated with PD-1 expression on T cells.[15] Thus, this study aimed to evaluate the safety, tolerability and preliminary efficacy of M6223, as monotherapy and in combination with BA, in patients with advanced solid tumors.

## METHODS

### Study design

This open-label, first-in-human, sequential dose-escalation study evaluated M6223 as monotherapy (M6223, Part 1A) or in combination with BA (M6223+BA, Part 1B). Adults with histologically or cytologically proven locally advanced/advanced solid malignancies (Eastern Cooperative Oncology Group Performance status, ECOG PS ≤1) that were refractory to or had progressed under standard treatment were included; all patients had adequate hematological, hepatic, renal and coagulation functions at study entry. Patients with persistent, clinically relevant toxicity related to a previous therapy/ICI treatment, previous organ transplantation, or known brain metastases were excluded. Detailed inclusion/exclusion criteria are provided in online supplemental material.

Patients in Part 1A received escalating doses of M6223 monotherapy, either once every 2 weeks or once every 3 weeks, at a starting dose of 10 mg every 2 weeks. Except for the first two cohorts (at 10 mg and 30 mg with a single participant each), each cohort typically enrolled three participants. However, the safety monitoring committee (SMC) could recommend changing the size of these dose escalation cohorts to 3–6 participants. The total sample depends on the number of cohorts to be evaluated and data obtained (eg, DLTs) during trial conduct. In this trial, the sample size for the recommended dose for expansion (RDE) DL was required to be at least 6. Patients in Part 1B received escalating doses of M6223+1200 mg BA (both every 2 weeks, intravenous) starting at 300 mg M6223; enrolment in Part 1B commenced after safety data for DLs of 10 mg, 30 mg, 100 mg and 300 mg M6223 every 2 weeks in Part 1A were available. Detailed study design is presented in figure 1. Dose escalations in parts 1A and 1B proceeded according to recommendations of the SMC, supported by results from a Bayesian two-parameter logistic regression model.[16] RDEs were declared by the SMC based on the totality of available pharmacokinetic (PK), pharmacodynamic (Pd), and safety data, and to enable a high TIGIT TO (≥90%) in the TME at the trough for the majority of the participant population, while also taking into consideration the observed variability in M6223 PK. An integrated PK/Pd model framework was developed to predict high TIGIT TO in the TME to help support RDE selection.[17] Briefly, emerging clinical PK/Pd data were used to inform posology by optimizing TIGIT TO in the tumor. A model was created that combined a site-of-action component and a TME compartment. The model was used to first simulate peripheral and intratumoral TIGIT TO associated with clinically evaluated doses of other anti-TIGIT molecules (eg, tiragolumab), including recommended phase 2 doses. Patients were treated until disease progression, withdrawal, or attainment of defined discontinuation criteria. This study included a safety follow-up period, that is, a patient visit scheduled at 30±5 days after the last M6223 or BA dose and a telephone call at 90 days±2 weeks after the last dose. Survival follow-up was performed every 3 months.

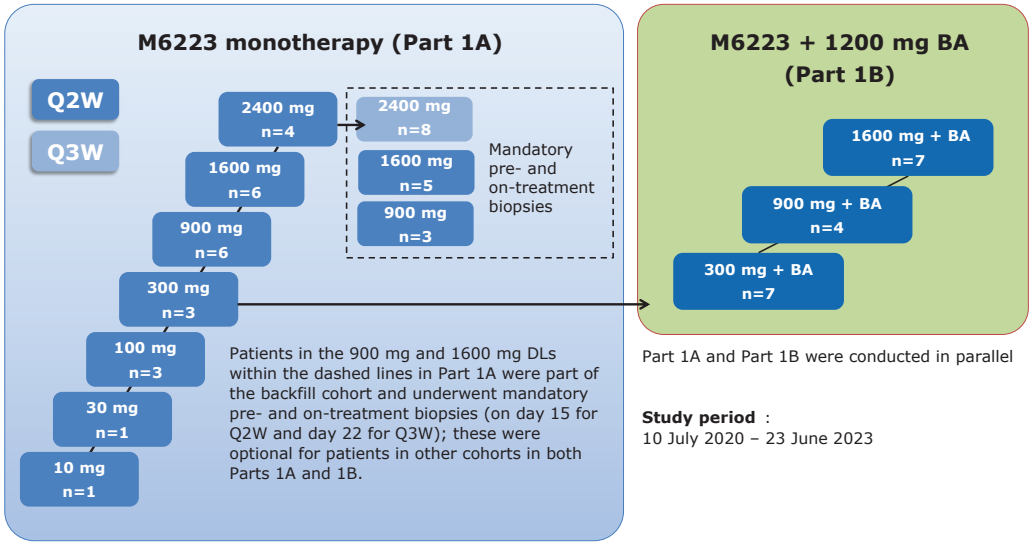


**Figure 1** Study design. Study design depicting dose-expansion and number of patients in each dose level in parts 1A and 1B. Patients in the 900 mg and 1600 mg every 2 weeks and 2400 mg every 3 weeks DL cohorts within the dashed lines in Part 1A were part of the backfill cohort and underwent mandatory pretreatment and on-treatment biopsies; these were optional for patients in other cohorts in both Parts 1A and 1B.

## Objectives and assessments

The primary objectives of this study were assessment of safety, tolerability, maximum tolerated dose (MTD) (if observed) and RDE of M6223, both as monotherapy (every 2 weeks and every 3 weeks regimens; Part 1A) and in combination with BA (Part 1B). Secondary objectives included characterization of the PK profiles of M6223 alone and in combination with BA, PK profile of BA and clinical efficacy of M6223 in parts 1A and 1B. Exploratory objectives were Pd parameters of M6223 alone and in combination with BA, including TIGIT TO and tumor immune cell profiling. Eight patients from DLs of 900 mg (n=3) and 1600 mg (n=5), were enrolled as a backfill cohort. Patients in the 2400 mg every 3 weeks dose-escalation cohort and in the backfill cohort underwent mandatory paired biopsies during screening (−1 to −28 days before study entry) and on-treatment (on study day 15 for every 2 weeks and study day 22 for every 3 weeks). Paired biopsy samples were used for Pd testing and confirmation of selected RDE(s) based on the PK/Pd relationship. Detailed methodology for primary and secondary objectives is provided in online supplemental material.

## Statistical analyses

This was an exploratory study. No formal significance level was defined for this study and all analyses were descriptive. All analyses were done by study part, regimen and dose level, and descriptive statistics were used to summarize study data. Unless otherwise specified, all analyses were based on the safety analysis set that included all participants who had received at least one dose of study intervention, with exceptions listed below. A Bayesian 2 parameter logistic regression model was used to estimate posterior DLT probabilities for potential next doses. Among these potential next DLs, the model suggested the next best dose based on a loss function.[16] The final recommendation on the next dose was with the SMC and this analysis was based on the DLT analysis set. For Part 1A, the DLT analysis set included 36 (90.0%) patients while for Part 1B it included 15 (83.3%) patients. Four participants in Part 1A and 3 in Part 1B were excluded from DLT analysis set because they did not receive at least two doses of study intervention or had a delay >7 days of the second dose for reasons other than DLT. The DLT analysis set included all participants experiencing a DLT and those without DLT that received the treatment at sufficient dosing as judged by SMC (at least two subsequent cycles). The decision to exclude a patient from the DLT analysis set was taken by the SMC.

OS and progression-free survival (PFS) (per RECIST V.1.1) were estimated using the Kaplan-Meier method. The CIs for median were calculated according to Brookmeyer and Crowley,[18] and the CIs for the survival function estimates at defined time points were derived using the log-log transformation according to Kalbfleisch and Prentice[19] with back transformation to a CI on the untransformed scale. The estimate of the SE was computed using Greenwood's formula. All analyses were performed using statistical software SAS (V. 9.1 or above), R and the R-package bcrm.[20 21]

PK parameters were calculated using standard non-compartmental methods and Phoenix WinNonlin (V.8.3.4; Certara USA, 2021). For PK and Pd data, concentration values that were below the level of quantification were set to zero. Unless otherwise specified, data were not recoded, rescaled, truncated, or removed or normalized; biomarker data that met the assay requirements (based on assay validation) and were deemed evaluable, were

included in the analysis. Any data not meeting the assay requirements were excluded. Further, all data were evaluated as observed and no imputation method for missing values was used. All participants in the safety analysis set contributed some PK data and were considered in the PK analysis set.

## RESULTS

### Patients and exposure

Between July 10, 2020, and June 23, 2023, a total of 58 patients were included in the study (Part 1A: M6223 monotherapy, n=40; Part 1B: M6223+BA, n=18). In Part 1A, patients received M6223 at dose levels (DLs) of 10 mg (n=1), 30 mg (n=1), 100 mg (n=3), 300 mg (n=3), 900 mg (n=9), 1600 mg (n=11), 2400 mg (n=4) (all every 2 weeks) or 2400 mg every 3 weeks (n=8); among these, eight patients were part of the backfill cohort (900 mg every 2 weeks: n=3; 1600 mg every 2 weeks: n=5) and underwent mandatory paired biopsies. Paired biopsy samples were also analyzed from patients in the 2400 mg every 3 weeks cohort (figure 1). In Part 1B, patients received M6223 at DLs of 300 mg (n=7), 900 mg (n=4), or 1600 mg (n=7), all in combination with BA at 1200 mg (both drugs were administered every 2 weeks, intravenous).

Table 1 provides an overview of the baseline and demographic characteristics of all patients. In Part 1A, patients were predominantly white (n=34; 85%), with "other" (non-whites) encompassing African American (n=2; 5%), Asian (n=2; 5%), Native Hawaian or other Pacific islander (n=1; 2.5%) and other (n=1; 2.5%), In contrast, in Part 1B, among 18 patients, 10 patients (55.6%) identified as White, while non-Whites were African American (n=4; 22.2%), Asian (n=3; 16.7%), and other (n=1; 5.6%). Primary tumor site was heterogeneous across parts 1A and 1B; specifically, in Part 1A, the most common site of primary tumor was either colon not otherwise specified (NOS) or rectum NOS (n=4 each, 10.0%), followed by ovary (n=3; 7.5%), and pancreas, lung, or unknown (n=2 each; 5%), while in Part 1B, these were sigmoid colon (n=3; 16.67%), followed by endometrium and extrahepatic bile duct (n=2 each; 11.11%).

The median duration of M6223 therapy was 8.00 (range, 2.0–78.1) and 4.95 (range, 2.0–86.1) weeks in parts 1A and 1B, respectively, whereas that of BA was 4.00 (range, 2.0–42.1) weeks.

### Tolerability and safety

An overview of the safety data for parts 1A and 1B is provided in table 2.

Overall, two dose-limiting toxicities were reported—grade 3 adrenal insufficiency at 900 mg every 2 weeks (Part 1A) and grade 3 anemia at 300 mg M6223+1200 mg BA (Part 1B; the event was deemed related only to BA).

In Part 1A, 38 (95.0%) patients experienced at least one treatment-emergent adverse event (TEAE) while M6223-related TEAEs (treatment-related adverse event; TRAE) were seen in 19 (47.5%) patients. Fatigue (n=5, 12.5%) and nausea (n=4, 10.0%) were the most common TEAEs (≥20% overall); grade ≥3 TEAEs were observed in 14 (35.0%) patients. Diarrhea (n=1; 100 mg every 2 weeks) and adrenal insufficiency (n=1; 900 mg every 2 weeks) were the only reported grade 3 TRAEs. Grade ≥4 TEAEs were arthralgia (grade 4) and metastases to central nervous system (grade 5), reported in one patient each in the 900 mg every 2 weeks and 2400 mg every 2 weeks cohorts, respectively; no grade ≥4 TRAEs were observed. One serious TRAE was reported (grade 3 adrenal insufficiency; 900 mg every 2 weeks). An overview of the most frequently reported TEAEs (>10% of patients) and serious TEAEs in Part 1A are provided in online supplemental tables S1 and S2, respectively. Detailed information on TRAEs is provided in online supplemental table S3. Adverse events of special interest (AESIs) observed in Part 1A included pneumonitis, adrenal insufficiency (also a DLT), embolism and infusion-related reaction. Details of AESIs are provided in online supplemental table S4. In Part 1A, no M6223-related TRAE led to death during the study.

In Part 1B, all 18 (100%) patients reported TEAEs, with 11 (61.1%) patients experiencing both M6223-related and BA-related TRAEs. The most common TEAEs (≥20% overall) were anemia (n=7, 38.9%), fatigue and maculopapular rash (n=6 (each), 33.3%), apart from constipation, nausea, pruritus and fever (n=4 (each), 22.2%). Anemia was the most common grade ≥3 TEAE (n=6; 33.3%). An overview of the most frequently reported TEAEs (>10% of patients) and serious TEAEs in Part 1B is provided in online supplemental table S5 and S6, respectively. No grade ≥3 TRAEs attributed to only M6223 were reported in Part 1B (online supplemental table S7). Four (22.2%) patients had grade ≥3 TRAEs that were related to both M6223 and BA: one event each of death, increased lipase level, maculopapular rash and increased aspartate aminotransferase level. BA-only TRAEs were reported in 13 (72.2%) patients. Two serious TRAEs were reported: anemia (grade 3, related to BA alone) and death (related to both M6223 and BA at the DL 300 mg every 2 weeks M6223+1200 mg every 2 weeks BA). One participant (aged >75 years) suffering from an extrahepatic cholangiocarcinoma with liver involvement (stage IV) died on study day 178, which was 21 days after the last administration of study interventions. This event (PT "Death") was reported as an serious adverse event and was considered related to both M6223 and BA therapies. Study treatments were already permanently discontinued due to SCC and keratoacanthoma of the skin, cellulitis, and discovery of a meningioma. The participant's clinical status had declined over the last weeks with lethargy and anorexia. As scans did not reveal clear evidence of disease progression, the investigator felt that the participant's death might be, in part, due to the investigational drugs. Two other patients died within 30 days after the last M6223 and BA doses; however, these two events (one each at 900 mg M6223+1200 mg

**Table 1** Baseline and demographic characteristics

| Baseline/demographic characteristics | Part 1A: M6223 monotherapy (Q2W) | | | | | | | (Q3W) | Q2W+Q3W | Part 1B: M6223+BA (1200 mg) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 10 mg | 30 mg | 100 mg | 300 mg | 900 mg | 1600 mg | 2400 mg | 2400 mg | Total | 300 mg | 900 mg | 1600 mg | Total |
| | n=1 | n=1 | n=3 | n=3 | n=9 | n=11 | n=4 | n=8 | n=40 | n=7 | n=4 | n=7 | n=18 |
| Age in years, mean (±SD) | 69.0 (NC) | 46.0 (NC) | 50.7 (NC) | 62.0 (NC) | 59.0 (14.65) | 60.3 (13.75) | 61.3 (NC) | 62.5 (11.20) | 59.8 (13.14) | 62.6 (12.88) | 57.5 (NC) | 58.3 (13.19) | 59.8 (12.45) |
| Female, n (%) | 1 (100.0) | 0 | 3 (100.0) | 1 (33.3) | 4 (44.4) | 5 (45.5) | 3 (75.0) | 2 (25.0) | 19 (47.5) | 5 (71.4) | 2 (50.0) | 4 (57.1) | 11 (61.1) |
| Male, n (%) | 0 | 1 (100.0) | 0 | 2 (66.7) | 5 (55.6) | 6 (54.5) | 1 (25.0) | 6 (75.0) | 21 (52.5) | 2 (28.6) | 2 (50.0) | 3 (42.9) | 7 (38.9) |
| Race, n (%) | | | | | | | | | | | | | |
| White | 1 (100.0) | 1 (100.0) | 3 (100.0) | 2 (66.7) | 7 (77.8) | 8 (72.7) | 4 (100.0) | 8 (100.0) | 34 (85.0) | 5 (71.4) | 2 (50.0) | 3 (42.9) | 10 (55.6) |
| Other | 0 | 0 | 0 | 0 | 0 | 1 (9.1) | 0 | 0 | 1 (2.5) | 1 (14.3) | 0 | 0 | 1 (5.6) |
| Prior anti-cancer therapy regimens, n (%) | | | | | | | | | | | | | |
| 1 | 0 | 0 | 1 (33.3) | 0 | 1 (11.1) | 0 | 0 | 0 | 2 (5.0) | 1 (14.3) | 0 | 0 | 1 (5.6) |
| 2 | 0 | 0 | 0 | 0 | 2 (22.2) | 1 (9.1) | 0 | 1 (12.5) | 4 (10.0) | 1 (14.3) | 1 (25.0) | 1 (14.3) | 3 (16.7) |
| 3 | 0 | 0 | 1 (33.3) | 0 | 0 | 3 (27.3) | 0 | 2 (25.0) | 6 (15.0) | 1 (14.3) | 0 | 1 (14.3) | 2 (11.1) |
| ≥4 | 0 | 1 | 1 (33.3) | 3 (100) | 6 (66.7) | 6 (54.5) | 4 (100.0) | 5 (62.5) | 26 (65.0) | 4 (57.1) | 2 (50) | 5 (71.4) | 11 (61.1) |

In Part 1A, the most common site of primary tumor was either colon NOS or rectum NOS (n=4 each, 10.0%), and TNM classification at initial diagnosis was predominantly T3 (n=13, 32.5%), Nx (n=11, 27.5%) and M1 (n=17, 42.5%). In Part 1B, the most common site of primary tumor was the sigmoid colon (n=3; 16.7%) and TNM classification at initial diagnosis was predominantly T1 and T2 (n=4 each, 22.2%), N1 (n=7, 38.9%) and M0 and M1 (n=6 each, 33.3%).
NOS, not otherwise specified; Q2W, every 2 weeks; Q3W, every 3 weeks.

**Table 2** Safety overview

| | Part 1A: M6223 monotherapy (Q2W) | | | | | | | (Q3W) | | Part 1B: M6223+BA (1200 mg) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 10 mg | 30 mg | 100 mg | 300 mg | 900 mg | 1600 mg | 2400 mg | 2400 mg | Total | 300 mg | 900 mg | 1600 mg | Total |
| Patients, n (%) | n=1 | n=1 | n=3 | n=3 | n=9 | n=11 | n=4 | n=8 | n=40 | n=7 | n=4 | n=7 | n=18 |
| TEAE | | | | | | | | | | | | | |
| Any grade | 1 (100.0) | 1 (100.0) | 3 (100.0) | 3 (100.0) | 9 (100.0) | 11 (100.0) | 3 (75.0) | 7 (87.5) | 38 (95.0) | 7 (100.0) | 4 (100.0) | 7 (100.0) | 18 (100.0) |
| Any grade ≥3 | 0 | 0 | 1 (33.3) | 1 (33.3) | 4 (44.4) | 4 (36.4) | 2 (50.0) | 2 (25.0) | 14 (35.0) | 5 (71.4) | 4 (100.0) | 5 (71.4) | 14 (77.8) |
| Any serious | 0 | 0 | 0 | 0 | 2 (22.2) | 4 (36.4) | 2 (50.0) | 2 (25.0) | 10 (25.0) | 6 (85.7) | 4 (100.0) | 2 (28.6) | 12 (66.7) |
| Leading to permanent treatment discontinuation | 0 | 0 | 0 | 0 | 0 | 2 (18.2) | 1 (25.0) | 0 | 3 (7.5) | 1 (14.3)* | 1 (25.0)* | 2 (28.6)* | 4 (22.2)* |
| TRAE | | | | | | | | | | | | | |
| Any grade | 1 (100.0) | 0 | 2 (66.7) | 2 (66.7) | 7 (77.8) | 6 (54.5) | 0 | 1 (12.5) | 19 (47.5) | 6 (85.7)† | 1 (25.0)† | 4 (57.1)† | 11 (61.1)† |
| Any grade ≥3 | 0 | 0 | 1 (33.3) | 0 | 1 (11.1) | 0 | 0 | 0 | 2 (5.0) | 1 (14.3)† | 1 (25.0)† | 2 (28.6)† | 4 (22.2)† |
| Any serious | 0 | 0 | 0 | 0 | 1 (11.1) | 0 | 0 | 0 | 1 (2.5) | 1 (14.3)† | 0 | 0 | 1 (5.6)† |
| Leading to permanent treatment discontinuation | 0 | 0 | 0 | 0 | 0 | 1 (9.1) | 0 | 0 | 1 (2.5) | 1 (14.3)‡ | 1 (25.0)‡ | 1 (14.3)‡ | 3 (16.7)‡ |
| AESI | 0 | 0 | 0 | 0 | 1 (11.1) | 2 (18.2) | 0 | 0 | 3 (7.5) | 3 (42.9) | 1 (25.0) | 5 (71.4) | 9 (50.0) |

*Discontinuation of BA alone.
†In Part 1B, all adverse events listed here are related to both M6223 and BA.
‡In Part 1B, permanent discontinuation of BA alone.
AESI, adverse event of special interest; BA, bintrafusp alfa; Q2W, every 2 weeks; Q3W, every 3 weeks; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

BA and 1600 mg M6223+1200 mg BA) were attributed to disease progression and were deemed unrelated to either M6223 or BA therapy.

The observed AESIs in Part 1B included anemia (considered a DLT), stomatitis, hypothyroidism, keratoacanthoma, adrenal insufficiency, increased levels of amylase/lipase/Alanine aminotransferase (ALT)/Aspartate aminotransferase (AST), rash, squamous cell carcinoma of skin, pruritus, maculopapular rash, pulmonary embolism and dermatitis bullous. Details of AESIs in Part 1B are provided in online supplemental table S8.

Overall, TEAEs led to treatment interruptions in six patients. The occurrence of pemphigoid (rash) and hyperbilirubinemia (n=1 each, 1600 mg every 2 weeks, both grade 2) and central nervous system metastases (n=1, 2400 mg every 2 weeks, grade 5) were TEAEs that led to permanent discontinuation of M6223 in Part 1A. Of these, only pemphigoid (rash) was considered to be related to M6223 therapy. No TEAEs led to dose reduction or permanent discontinuation of M6223 in Part 1B; however, anemia (grade 3; 300 mg M6223+1200 mg BA), celiac artery aneurysm (grade 3; 900 mg M6223+1200 mg BA) and squamous cell carcinoma of the skin (grade 2; 1600 mg M6223+1200 mg BA) required permanent discontinuation of BA. The BA dose was reduced to 600 mg in one patient due to grade 2 anemia (1600 mg M6223+1200 mg BA).

## Clinical activity

No patient in parts 1A or 1B exhibited complete response (CR) or partial response (PR) (figure 2). Stable disease (SD) as the best overall response was observed in 13 (32.5%) patients in Part 1A and in 5 (27.8%) patients in Part 1B. Disease control rate (DCR) was defined as CR, PR, or SD after at least 14 or 28 weeks and no documentation of progressive disease (PD) before this. DCR at 14 and 28 weeks was 7.5% (n=3) and 2.5% (n=1) in Part 1A and 27.8% (n=5) and 16.7% (n=3) in Part 1B, respectively. PD or death during the study occurred in 33 (82.5%) and 13 (72.2%) patients in parts 1A and 1B, respectively. Overall, median overall survival (OS) and PFS were 7.6 (95% CI 4.9, 12.0) and 1.4 (95% CI 1.3, 1.8) months, respectively. Median OS and PFS were 7.6 (95% CI 4.9, 12.3) and 1.7 (95% CI 1.3, 1.9) months in Part 1A and 5.8 (95% CI 3.0, 14.2) and 1.3 (95% CI 0.8, 1.3) months in Part 1B, respectively (online supplemental figure 1A, B).

## PK profile

Linear and dose-proportional PK profiles were observed at DLs of 100–2400 mg every 2 weeks and 2400 mg every 2 weeks in Part 1A and at 300–1600 mg every 2 weeks in Part 1B (figure 3A,B). Overall, $t_{max}$, $t_{1/2}$, CL, $V_{ss}$ and $V_z$ values were similar across all DLs, suggesting dose-independent PK (online supplemental table S9).

In Part 1A, the geometric mean $t_{1/2}$ was 93.8–351 hours (approximately 4–15 days) and moderate accumulation was observed at selected RDEs (1600 mg every 2 weeks and 2400 mg every 2 weeks 3 weeks). Accumulation ratios were consistent with the estimated $t_{1/2}$ for M6223. A slightly longer half-life at 2400 mg every 3 weeks (Part 1A) may be attributed to the longer sampling duration in the terminal phase. Importantly, coadministration with BA did not alter the PK profile of M6223 or BA, indicating a lack of PK interactions between M6223 and BA. The observed PK for BA are in agreement with the known values (online supplemental table S10).[20]

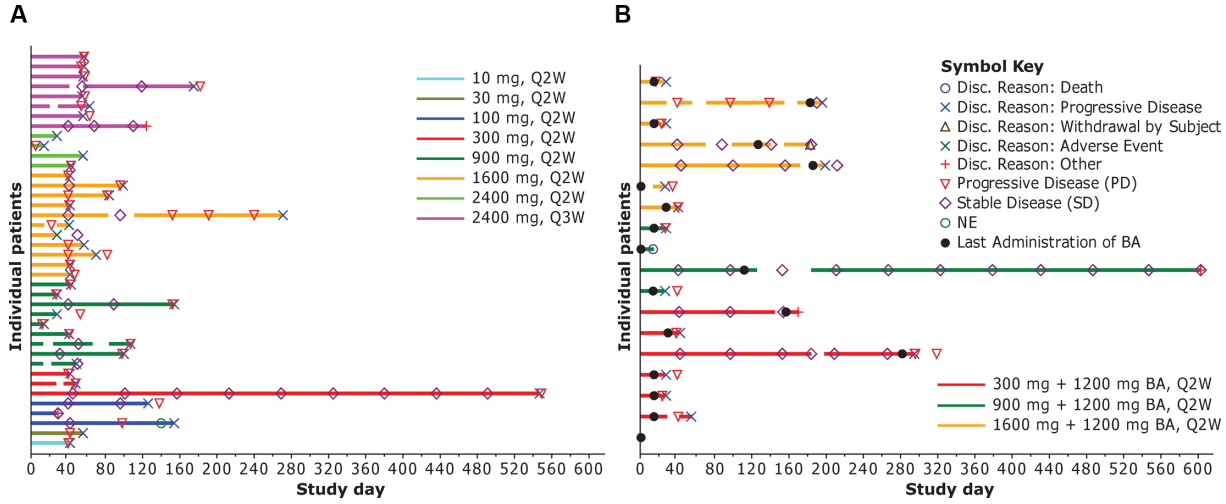


**Figure 2** Clinical efficacy after M6223 monotherapy and in combination with BA. Swimmer plot detailing time on-treatment and response assessments for patients in Part 1A (Panel A) and in Part 1B (Panel B). In Part 1A, M6223 therapy duration for >180 days was noted in 1 patient each in every 2 weeks 300 mg DL and every 2 weeks 1600 mg DLs. In Part 1B, treatment duration for >180 days was noted in four patients: one each in the 300 mg+1200 mg and 900 mg+1200 mg DLs and two participants in the 1600 mg+1200 mg DL. One patient in the 900 mg+1200 mg DL had a very long exposure—this patient was on combination therapy until cycle 9, continued receiving M6223 monotherapy until last dose within the study on relative day 590 and then continued treatment outside of the study (single patient use). BA, bintrafusp alfa.

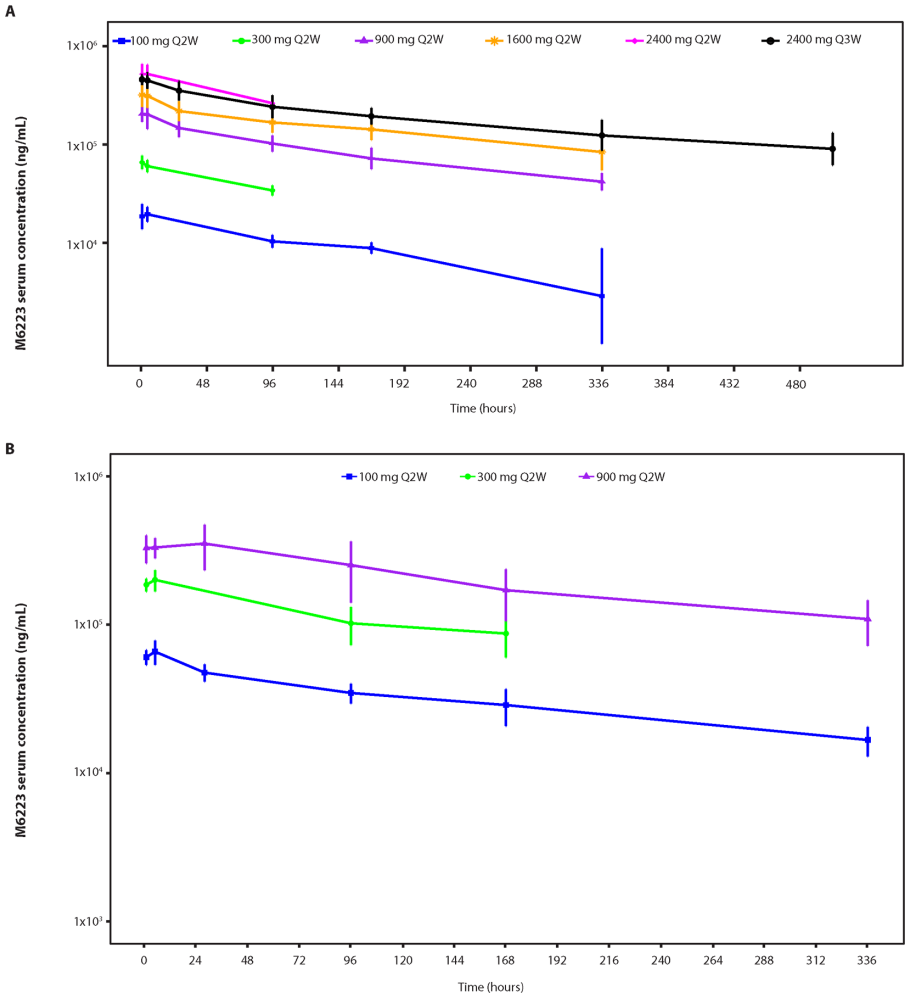


**Figure 3** Pharmacokinetic (PK) profile of M6223 as monotherapy and in combination with BA. PK profile of M6223 on monotherapy (A) or in combination with BA (B) for cycle 1 shows a linear profile that is typical of monoclonal antibodies. PK profile of M6223 is not affected when administered in combination with BA, indicating no PK interactions. BA, bintrafusp alfa.

## Pd profile

A dose-dependent increase in TIGIT target occupancy (TO) on $CD3^{+}$T cells (in blood) was observed at lower doses of M6223 monotherapy (100–300 mg); prolonged and saturated (≥95%) TIGIT TO was detected at M6223 monotherapy DLs of ≥900 mg (figure 4A). TIGIT TO values were comparable between every 2 weeks and every 3 weeks regimens and between M6223 Q2W DLs of 900 and 1600 mg in the backfill cohort and the main study (Part 1A). Notably, TIGIT TO levels were comparable between M6223 and M6223+BA (figure 4B). Image-based multiplex immune profiling of paired pretreatment and on-treatment tumor tissue biopsy samples (n=12/15; 80% success rate) revealed a reduction in TIGIT (n=4 of 6 samples) and Tregs (n=3 of 6 samples) and an increase in CD226 (n=4 of 6 samples) on treatment at 2400 mg M6223 every 3 weeks (figure 4C). Of note, in the majority of samples, baseline levels of TIGIT and FoxP3 (Tregs) were relatively low and thus, interpretation of data with respect to decreased levels on-treatment will need to be done with caution. H&E-based histopathological assessment of baseline tumor samples revealed very low levels of tumor infiltrating lymphocytes (TILs) in most samples, thereby categorizing them as "immune-cold" types (data not shown). Overall, Pd biomarker data showed preliminary signs of anti-TIGIT mechanism of action (MoA)-related biological activity in patients, despite the presence of predominantly immune-desert tumors.

## RDE and MTD

All tested doses had manageable safety and good tolerability. Saturated TIGIT TO in blood was detected at M6223 monotherapy DLs of ≥900 mg every 2 weeks and at 2400 mg every 3 weeks . An integrated PK/Pd model framework was developed to predict the corresponding TIGIT TO in the TME to help support RDE selection.[17] This preliminary PK/Pd model suggested that 1600 mg every 2 weeks and 2400 mg every 3 weeks were associated with a high TIGIT TO (≥90%) in the TME. Thus, RDEs for M6223 monotherapy were determined to be 1600 mg every 2 weeks and 2400 mg every 3 weeks, whereas the RDE for the combination was 1600 mg M6223+1200 mg BA (both every 2 weeks). MTD was not reached for M6223 monotherapy or M6223 in combination with BA.

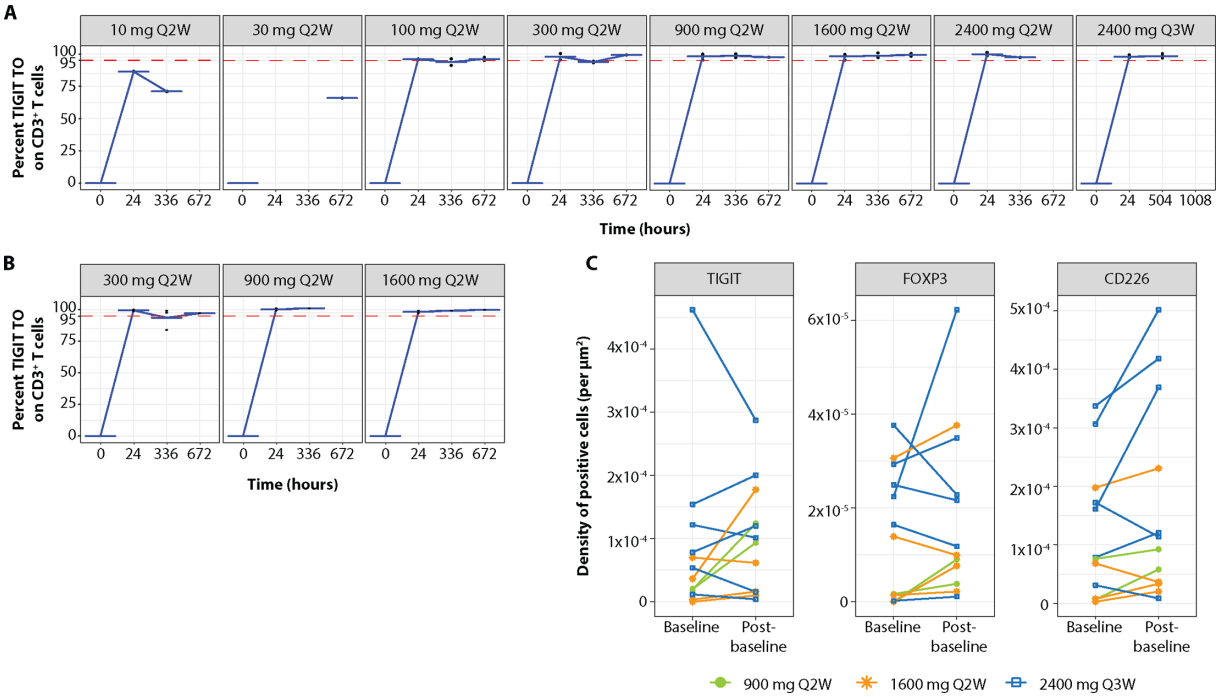


**Figure 4** Pharmacodynamic assessment of M6223 highlights target engagement in blood and in the tumor. TIGIT target occupancy (TO) on T cells (CD3+) in blood after treatment with M6223 in monotherapy (A) or in combination with bintrafusp alfa (B). (C) Changes in TIGIT, Tregs (FoxP3) and CD226 in pretreatment and on-treatment biopsies from patients treated with M6223 at 900 mg every 2 weeks, 1600 mg every 2 weeks, or 2400 mg every 3 weeks. TIGIT, T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domains.

## DISCUSSION AND CONCLUSIONS

This phase 1 trial showed a manageable safety profile for M6223, both as monotherapy and in combination with BA. The PK profile of M6223 was linear and dose-proportional; notably, combination of M6223 with BA did not alter the PK profile of either M6223 or BA, indicating absence of PK interactions. M6223±BA showed dose-dependent, saturated and prolonged TIGIT TO in blood. Importantly, paired biopsy samples demonstrated a trend of anti-TIGIT MoA-related biological activity in patients with robust baseline expression of biomarkers, despite the presence of predominantly immune-desert tumors. RDEs were determined to be 1600 mg every 2 weeks and 2400 mg every 3 weeks for M6223 monotherapy and 1600 mg M6223+1200 mg BA (both every 2 weeks) for the combination. Model-informed dose selection is acknowledged to be an important step in clinical development, particularly in the context of initiatives such as Project Optimus. Model-informed support for selection of RDEs, as used in this trial,[17] is a crucial aspect of the selection of RDEs.[22]

The study population was heavily pretreated as >60% of patients in both parts 1A and 1B had undergone ≥4 prior anticancer therapies. The most common adverse events reported in this study were consistent with those expected in this population and with the known safety profile of BA. No new safety signals were identified for M6223 even at the highest DLs of 2400 mg every 2 weeks or every 3 weeks, either as monotherapy or in combination with BA. Most TEAEs and TRAEs were lower than grade 3; thus, while dose reductions due to adverse events were not required for M6223, treatment interruptions were seen in six patients. Collectively, these data highlight the manageable safety profile of M6223. SD as the best overall response was observed in 32.5% of patients who received M6223 monotherapy and in 27.8% of patients treated with M6223+BA. Recent trials using various anti-TIGIT agents, such as etigilimab,[23] tiragolumab,[24] domvanalimab,[25] and vibostolimab,[26] have demonstrated limited activity of these agents in solid tumors when used as monotherapy. For example, etigilimab monotherapy reported no CR or PR and only one PR in combination with nivolumab.[23] In contrast, outcomes improved when anti-TIGIT agents were administered in combination with anti–PD-L1 in selected cancers such as non-small cell lung carcinoma (eg, vibostolimab+pembrolizumab).[26] A phase 1 dose-escalation study of ociperlimab plus tislelizumab (anti-PD-1) in patients with advanced solid tumors reported a modest objective response rate of 10%.[27]

This study reports high collection rates for mandatory paired biopsies (n=15/16, 93.75%) and the availability of evaluable results (n=12/15, success rate of 80%). This contrasts with data in literature that indicates a need for significant improvements in reporting biopsy results from clinical trials. For example, a systematic evaluation of oncologic studies registered at ClinicalTrials.gov over a period of 15 years (from January 2000 to January 2015) showed that only 50.8% of all trials that included a research biopsy-related end-point provided relevant results, despite ethical obligations.[28] Another report

that tracked tumor biopsy specimens demonstrated that only 74% of biopsy specimens (83 of 112) collected for research purposes at the NCI Developmental Therapeutics Clinic were sufficient for slide-based Pd assessments.[29]

Primary tumor site was heterogeneous in this study population, and CRC and ovarian tumors were the predominant types with available paired tumor biopsy results. Furthermore, individual samples with robust baseline expression of TIGIT and Tregs showed anti-TIGIT MoA-related biological activity, even though histopathological assessment of these samples revealed that most of them were categorized as "immune-cold." These findings are in line with available literature as immune status data across phase 1 trials showed an overrepresentation of the "immune-desert" type in liver metastases and mCRC.[30] A similar result was reported in a large-scale systematic analysis of lymphoid and myeloid phenotypes of human solid tumors that revealed specific distributions of immune topography phenotypes and pronounced differences among different tumor types in a pan-cancer cohort.[31] Thus, tumor types and tissue biopsy sites, along with the number and quality of tumor samples, are deemed important for accurately analyzing the Pd effects of immunotherapies.

In summary, this first-in-human phase 1 study showed that M6223 has a manageable safety profile with RDEs established for both M6223 monotherapy and in combination with BA. Anti-TIGIT MoA-related biological activity in patients with robust baseline expression of TIGIT is encouraging, and further evaluation of M6223 (1600 mg every 2 weeks) in combination with the PD-L1 inhibitor avelumab (800 mg every 2 weeks) is ongoing in patients with advanced urothelial carcinoma (JAVELIN Bladder Medley; NCT05327530).[32]

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**Patient consent for publication** Not applicable.

**Ethics approval** This study was conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. The study protocol was approved by the institutional review boards/independent ethics committees of all participating institutions (IRB/IEC for four sites are as follows: (1) IntegReview IRB: RM684; (2) Office of Human subject protection, MD Anderson Cancer Center: 2019_0916; (3) IntegReview IRB: NXSAT19.20; and (4) Health Canada: HC6-024-C233202). Written informed consent was obtained from all patients.

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**Data availability statement** Data are available on reasonable request. Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to Merck's Data Sharing Policy. All requests should be submitted in writing to Merck's data sharing portal https://www.merckgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html. When Merck has a coresearch, codevelopment, or comarketing or copromotion agreement, or when the product has been out-licensed, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, Merck will endeavour to gain agreement to share data in response to requests.



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