

CT184

First-in-human trial of TIGIT inhibitor M6223 as monotherapy or in combination with bintrafusp alfa (BA) in patients with advanced solid unresectable tumors

Aung Naing¹, Meredith McKean², Anthony W. Tolcher³, Anja Victor⁴, Ping Hu⁵, Keyvan Tadjalli Mehr⁶, Thomas Kitzing⁴, Daniel Holland⁴, Emilia Richter⁴, Lillian L. Siu^{*6}

*Presenting and corresponding author (Lillian.Siu@uhn.ca)

¹The University of Texas MD Anderson Cancer Center, Houston, TX, USA; ²Sarah Cannon Research Institute, Nashville, TN, USA; ³NEXT Oncology and Texas Oncology, San Antonio, TX, USA; ⁴the healthcare business of Merck KGaA, Darmstadt, Germany; ⁵EMD Serono, Billerica, MA, USA; ⁶Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada



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CONCLUSIONS

- M6223 ± BA had a manageable safety profile.
RDEs were 1600 mg Q2W and 2400 mg Q3W for M6223 monotherapy, and 1600 mg M6223 + 1200 mg BA (both Q2W) for the combination; no MTD was identified.
M6223 ± BA showed a linear PK profile, along with dose-dependent, saturated, and prolonged TIGIT receptor occupancy.

- Paired biopsy samples pointed to a trend of anti-TIGIT MoA-related biological activity in individual patients with robust baseline expression of biomarkers, despite overall predominantly "immune-excluded" tumors.
Further evaluation of M6223 is ongoing in combination with the PD-L1 inhibitor avelumab in patients with advanced urothelial carcinoma (JAVELIN Bladder Medley; NCT05327530).

INTRODUCTION

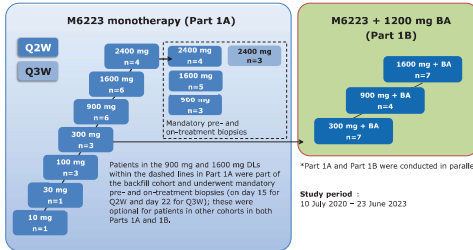
- TIGIT, an inhibitory receptor, is over-expressed and upregulated on T cells, Tregs, and NK cells in the TME, where it can directly inhibit their effector function and proliferation.
As TIGIT and programmed cell death receptor 1 (PD-1) are co-expressed on T cells, dual inhibition of both immune checkpoints may enhance antitumor activity.
M6223 is an IV-administered, human, antagonistic, IgG1 anti-TIGIT antibody with an Fc-mediated effector region.
BA is an IV-administered, first-in-class, bifunctional fusion protein that simultaneously blocks two nonredundant immunosuppressive pathways, namely TGF-β and PD-L1.
This Phase I, first-in-human, open-label, multicenter study (NCT04457778) in patients with advanced solid tumors, assessed the safety, tolerability, maximum tolerated dose (MTD), and recommended dose for expansion (RDE) of M6223 as monotherapy (Part 1A) or in combination with BA (Part 1B).

OBJECTIVES

- Primary objectives: Safety, tolerability, MTD, and RDE of M6223 ± BA
Secondary and exploratory objectives: Pharmacokinetics, pharmacodynamics, clinical activity, and biomarkers of M6223 ± BA

METHODS

Figure 1. Trial design and M6223 dose levels*



- Patients with locally advanced or metastatic solid tumors for whom no effective standard therapy was available, aged ≥18 years with ECOG PS of ≤1, were eligible.
Both M6223 and BA were IV-administered.
Dose levels (Figure 1) were recommended by the safety monitoring committee, supported by a Bayesian 2-parameter logistic regression model.
For determination of the MTD, posterior probabilities of DLTs were estimated by a Bayesian 2-parameter logistic regression model; the target toxicity of the model for MTD was 30%.
Objective response was investigator-assessed and graded according to RECIST version 1.1.

RESULTS

- At final analysis, 58 patients were treated: M6223 monotherapy (Part 1A, n=40) and M6223 + BA (Part 1B, n=18). Patients were, predominantly, White (Part 1A, 85%; Part 1B, 55.6%), <65 years of age, with an ECOG PS of 1 (Suppl. Table S1).
Median duration of therapy in Part 1A was 8.00 weeks (range, 2.0-78.1); in Part 1B, this was 4.95 weeks (range, 2.0-86.1) for M6223 and 4.00 weeks (range, 2.0-42.1) for BA.

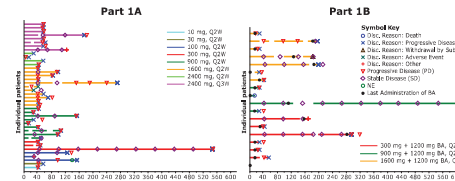
Table 1. Safety overview

Table with 12 columns: Patients, n (%), Part 1A: M6223 monotherapy (Q2W) [10 mg, 30 mg, 100 mg, 300 mg, 900 mg, 1600 mg, 2400 mg], (Q3W), Q2W + Q3W, Part 1B: M6223 + BA (1200 mg) [300 mg, 900 mg, 1600 mg, Total]. Rows include TEAE, Any Grade, Grade ≥3, TRAE, Any Grade, Grade ≥3.

*TRAEs related to M6223; †TRAEs related to both M6223 and BA.

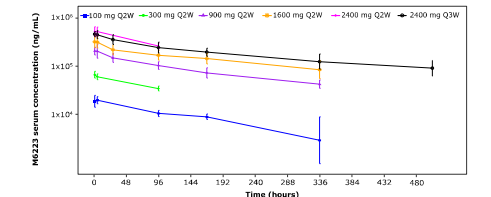
- DLT: Two DLTs were reported: adrenal insufficiency (Part 1A, 900 mg) and anemia (Part 1B, 300 mg; unrelated to M6223); both were Grade 3.
Most frequently (≥20%) reported TEAEs were fatigue (n=9, 22.5%) and nausea (n=8, 20.0%) in Part 1A, and anemia (n=7, 38.9%), fatigue, and maculo-papular rash (n=6 each, 33.3%) in Part 1B. Anemia was the most common Grade ≥3 TEAE in both Part 1A (n=3, 7.5%) and Part 1B (n=6, 33.3%).
No TEAEs led to permanent discontinuation of M6223 in Part 1B. AEs leading to treatment interruptions were seen in 6 patients in Part 1A and in 10 patients in Part 1B.
TEAEs, TRAEs, and SAEs are described in Suppl. Text and in Suppl. Tables S2-S4.
Deaths: In Part 1A, no M6223-related TEAE led to death. In Part 1B, 3 patients (16.7%) died within 30 days after the last dose; of these, only 1 was considered related to both M6223 and BA, others were due to progressive disease (n=2).
RDE and MTD: RDEs were 1600 mg Q2W or 2400 mg Q3W for Part 1A, and 1600 mg + 1200 mg Q2W for Part 1B. No MTD was identified.

Figure 2. Swimmer plot detailing time on-treatment and response to treatment



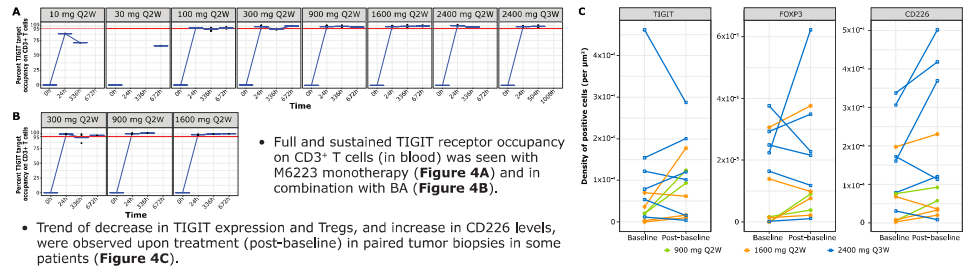
- No patient achieved an objective response; stable disease (≥28 weeks) was observed in 1 (2.5%) patient in Part 1A and in 3 (16.7%) patients in Part 1B (Figure 2).
Overall, median OS and PFS were 7.6 months (95% CI: 4.9, 12.0), and 1.4 months (95% CI: 1.3, 1.8) respectively, (Suppl. Figure 1A, 1B).

Figure 3. Dose-proportional serum PK profile of M6223 in Part 1A (Coz 1)



- Linear PK was observed for M6223 at 100-2400 mg Q2W and 2400 mg Q3W (Figure 3); co-administration with BA did not change the PK profile (Suppl. Figure 2).
Half-life for the two monotherapy RDEs of 1600 mg Q2W and 2400 mg Q3W were 9.0 and 14.6 days, respectively, with moderate accumulation at selected RDEs. Difference in half-life is attributed to longer sampling time in Q3W.

Figure 4. Pharmacodynamic assessment of M6223 ± BA highlights target engagement in blood and tumor biopsies



- Full and sustained TIGIT receptor occupancy on CD3+ T cells (in blood) was seen with M6223 monotherapy (Figure 4A) and in combination with BA (Figure 4B).
Trend of decrease in TIGIT expression and Tregs, and increase in CD226 levels, were observed upon treatment (post-baseline) in paired tumor biopsies in some patients (Figure 4C).

Abstracts: 1000, 1001, 1002, 1003, 1004, 1005, 1006, 1007, 1008, 1009, 1010, 1011, 1012, 1013, 1014, 1015, 1016, 1017, 1018, 1019, 1020, 1021, 1022, 1023, 1024, 1025, 1026, 1027, 1028, 1029, 1030, 1031, 1032, 1033, 1034, 1035, 1036, 1037, 1038, 1039, 1040, 1041, 1042, 1043, 1044, 1045, 1046, 1047, 1048, 1049, 1050, 1051, 1052, 1053, 1054, 1055, 1056, 1057, 1058, 1059, 1060, 1061, 1062, 1063, 1064, 1065, 1066, 1067, 1068, 1069, 1070, 1071, 1072, 1073, 1074, 1075, 1076, 1077, 1078, 1079, 1080, 1081, 1082, 1083, 1084, 1085, 1086, 1087, 1088, 1089, 1090, 1091, 1092, 1093, 1094, 1095, 1096, 1097, 1098, 1099, 1100, 1101, 1102, 1103, 1104, 1105, 1106, 1107, 1108, 1109, 1110, 1111, 1112, 1113, 1114, 1115, 1116, 1117, 1118, 1119, 1120, 1121, 1122, 1123, 1124, 1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1157, 1158, 1159, 1160, 1161, 1162, 1163, 1164, 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