Efficacy, safety and PKPD of 23ME-00610, a first-in-class anti-CD200R1 antibody, in patients with tumor mutational burden-high (TMB-H) or microsatellite instability-high (MSI-H) cancers: Results from an expansion cohort

23andMe Therapeutics

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BACKGROUND

Genetic Signature

- CD200R1 was identified as a promising immuno-oncology (IO) target from the 23andMe database [1]. Pleiotropic causal variants with opposing effect on risks for cancer and immune diseases, referred to as an IO signature, were observed for 3 critical components of the CD200R1 pathway, including CD200R1, its sole ligand CD200, and the downstream signaling protein DOK2.

CD200R1

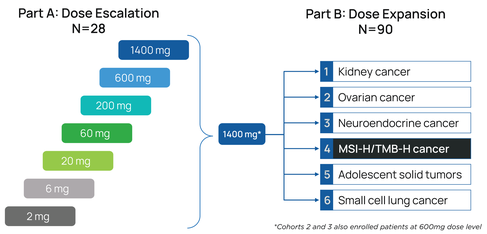
- CD200R1 is expressed on immune cells and binds to CD200, its only known ligand in humans, downregulating proinflammatory cytokines by activated T and myeloid cells and/or hindering immune cell infiltration into tumors, and promoting an immunosuppressive microenvironment in human cancers, where CD200 is highly expressed[2-9] **(Figure 1)**.

23ME-00610

- 23ME-00610 is a first-in-class IgG1 antibody that binds CD200R1 with high affinity (KD < 0.1 nM) and inhibits immunosuppressive signaling, leading to restoration of T cell activity and killing of CD200-expressing tumor cells in preclinical studies [1] **(Figure 1).**
- 23ME-00610 is currently in the Phase 2a portion of a Phase 1/2a clinical trial in participants with advanced solid malignancies (NCT05199272) **(Figure 2)**. Based on data from the first N=28 patients, 23ME-00610 demonstrated excellent safety and tolerability, a favorable PK profile supporting Q3W dosing, full target engagement with peripheral saturation at doses ≥ 60 mg, and pharmacodynamic evidence of activity, including on-target immune-related AEs, a > 50% stable disease rate, and emerging evidence of clinical activity in neuroendocrine, renal and ovarian cancer[10,11].

METHODS

Figure 2: Phase 1/2 Study Design in Patients with Locally Advanced or Metastatic Solid Malignancies



- 23ME-0610 administered IV every 21 days
- Expansions had target enrollment of 15 patients per cohort

Figure 3: Schedule of Assessments

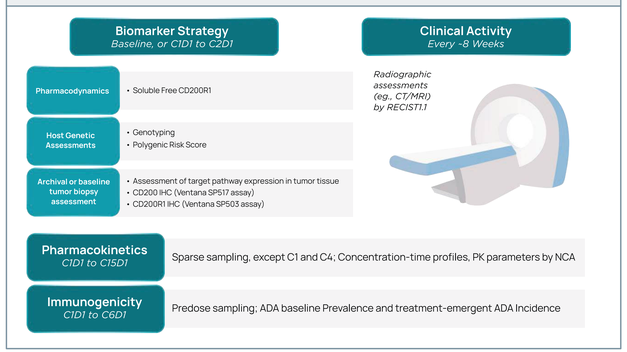
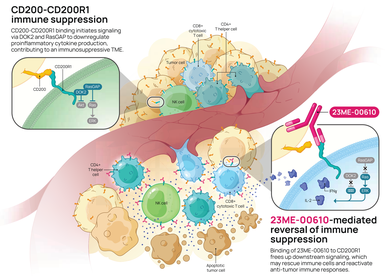


Figure 1: 23ME-00610 ('610), a Fully Humanized, Effectorless IgG1, Inhibits Immunosuppressive CD200/R1 Signaling via High Affinity Binding to CD200R1



Abbreviations: Akt: protein kinase B; CD: cluster of differentiation; DOK: docking protein; ERK: extracellular signal-regulated kinase; IFN: interferon; IL: interleukin; NK: natural killer; RasGAP: Ras-specific GTPase-activating proteins; TME: tumor microenvironment

RESULTS

Table 1: Patient Demographics and Disease Characteristics

Characteristic	N = 13
Age, median years (range)	60 (36-79)
Sex, n (%)	
Male	6 (46%)
Female	7 (54%)
Race, n (%)	
White	9 (69%)
Black	2 (15%)
Other/unknown	2 (15%)
Ethnicity, n (%)	
Hispanic or Latino	1 (8%)
Not Hispanic or Latino	11 (85%)
Unknown	1 (8%)
Geographic Region, n (%)	
USA	11 (85%)
Canada	2 (15%)
ECOG, n (%)	
0	1 (8%)
1	12 (92%)
Years since Initial Diagnosis, median (range)	3.0 (1.4-13.2)
Prior Lines of Treatment, median (range)	5 (3-11)

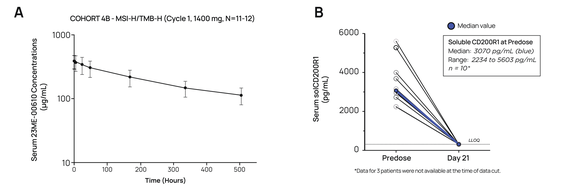
Characteristic	N = 13
Prior Systemic Cancer Therapy, n (%)	
Anti-PD/PD-L1	11 (85%)
Anti-VEGF	5 (38%)
Anti-CTLA4	1 (8%)
Anti-TIGIT	1 (8%)
Microsatellite or TMB status, n (%)	
MSI-High	5 (38.5%)
Not MSI-High (Stable or Low)	5 (38.5%)
TMB-High	11 (84.6%)
TMB Status Unknown	1 (7.7%)
TMB-Median (range), n=11	18.3 (10-66)
Primary tumor location, n (%)	
Colorectal	6 (46%)
Endometrial	2 (15%)
Cervical	1 (8%)
Breast (HR+/HER2+)	1 (8%)
Head and neck	1 (8%)
Skin	1 (8%)
Unknown primary	1 (8%)

Safety Assessment

- All patients reported adverse events in the TMB-H / MSI-H cancer cohort, of which, 9 patients (69%) reported adverse events related to study treatment.
- Related AEs reported in more than two patients in this cohort included: fatigue (n=4), headache (n=2), and nausea (n=2), with other adverse events generally similar across the entire study.
- 1 of 13 patients had 2 related irAEs (grade 1 nausea and grade 2 hypothyroidism).
- Across the entire study, two SAEs were reported as related by the investigators, including a grade 3 deep vein thrombosis (DVT) and grade 3 diarrhea.

RESULTS (continued)

Figure 4: 23ME-00610 Excellent PK and Full Target Engagement at 1400 mg Q3W



- PK of 23ME-00610 is generally similar in dose escalation and dose expansion cohorts
- A dose of 1400 mg achieves prespecified PK target at trough > EC90 in tumor
- Apparent median Cycle 1 half life of ~13-15 days supports Q3W or better dosing
- Minimal treatment-emergent ADA; ADA does not appear to meaningfully affect PK
- Complete saturation of free sCD200R1 by C2D1 observed in all evaluable patients

Figure 5. Response and Duration of Treatment (Swimmer's Plot)

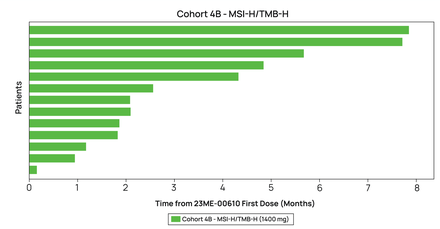


Table 2. Response and Duration of Treatment

Best Overall Response	n (%)
Complete Response (CR)[1]	0 (0.0)
Partial Response (PR)	0 (0.0)
Stable Disease (SD)	4 (30.8)
Progressive Disease (PD)	7 (53.8)
Not Evaluable (NE)	2 (15.4)
Disease Control Rate (DCR)	4 (30.8)

1. Complete response, partial response, table disease and progressive disease as defined by RECIST 1.1 criteria

Figure 6. Maximum RECIST Change vs. CD200 Expression vs. Prior Therapy

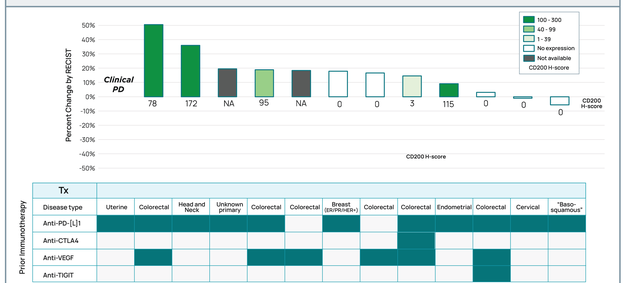
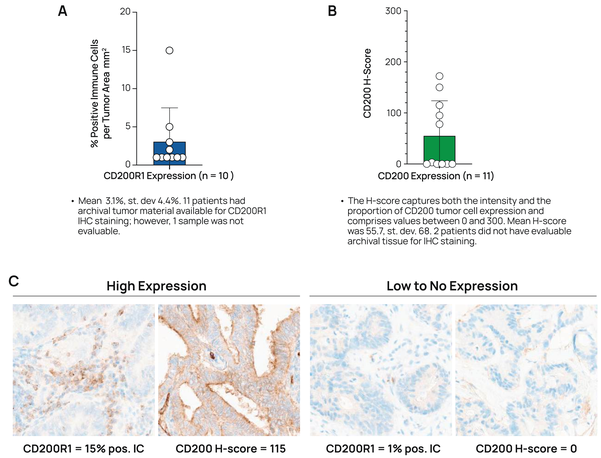


Figure 7: Tumor Expression of CD200R1 Pathway Components



- Mean 3.1%, st. dev 4.4%. 11 patients had archival tumor material available for CD200R1 IHC staining; however, 1 sample was not evaluable.
- The H-score captures both the intensity and the proportion of CD200 tumor cell expression and comprises values between 0 and 300. Mean H-score was 55.7, st. dev. 68. 2 patients did not have evaluable archival tissue for IHC staining.

Representative images depicting range of CD200R1 and CD200 expression.

CONCLUSIONS

- 23ME-00610 continues to show an acceptable safety and tolerability profile, full peripheral target engagement, and PK that supports Q3W dosing, though limited anti-tumor activity as monotherapy in a small cohort of participants with TMB-H/MSI-H tumors.
- Related AEs were generally grade 1 or 2 in severity.
- Related irAEs occurred in 1 patient, were grade 1 and 2 in severity, and manageable in nature.
- No grade 4 AEs or AEs that led to death or discontinuation occurred.
- 1400 mg results in full peripheral saturation with limited ADA with no apparent impact on exposure or safety.

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DISCLOSURES

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