First-in-class Anti-CD200R1 Antibody 23ME-00610 in Patients with Advanced Solid Malignancies: Phase 1 Results

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#CT174

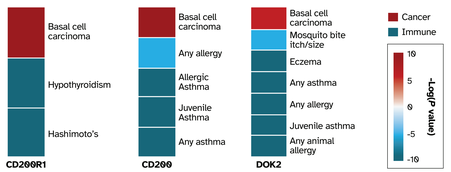
POSTER PRESENTED AT THE AACR ANNUAL MEETING; APRIL 14–19, 2023; ORLANDO, FL

INTRODUCTION

- 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 in 3 components of the CD200R1 pathway (**Figure 1**).
- CD200R1 is expressed on immune cells and binds to CD200, its only known ligand in humans, leading to downregulation of proinflammatory cytokines by activated T cells and/or myeloid cells (**Figure 2**).[2,3,4,5,6]
- The CD200R1 pathway has been shown to promote an immunosuppressive tumor microenvironment in human cancers where CD200 is highly expressed.[7,8,9]
- 23ME-00610 is a first-in-class IgG1 antibody that binds CD200R1 with high affinity (K_D < 0.1 nM) and inhibits immunosuppressive signaling, leading to restoration of T cell activity and killing of CD200-expressing tumor cells in preclinical studies.[10]

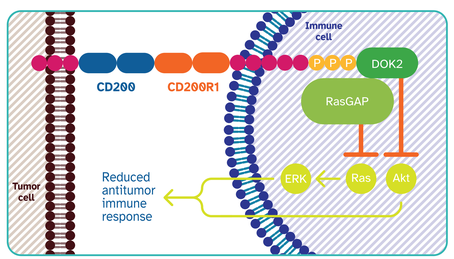
Figure 1. CD200R1, CD200, and DOK2 IO Signature

Genetic associations with an IO signature driven by variants that were respectively linked to three genes in the CD200R1 pathway were identified. Variants were mapped to functional effects on genes of the pathway by identifying expression quantitative trait loci (eQTLs) and coding single nucleotide polymorphisms (SNPs) that were either themselves the most strongly associated variant at these loci or in strong linkage equilibrium (r^2 ≥ 0.8) with the most strongly associated variant.



CD200R1 (inhibitory cell surface receptor), CD200 (CD200R1 ligand), and DOK2 (involved in the CD200/CD200R1 signaling pathway).

Figure 2. CD200-CD200R1 Signaling Cascade



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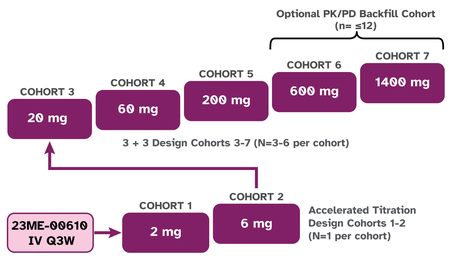
ACKNOWLEDGEMENTS

We would like to thank all participating investigators, patients and their families.

Phase 1 Study Design

- The phase 1 portion of the Phase 1/2a, open-label, multi-center study (NCT05199272) evaluated the safety and tolerability of 23ME-00610 and determined its recommended phase 2 dose (RP2D) for the treatment of patients with locally advanced (unresectable) or metastatic solid malignancies.
- Saliva-based genotyping using the 23andMe platform was performed to determine CD200R1 pathway single nucleotide polymorphisms (SNPs)[1] and polygenic risk score (PRS) for immune- and cancer-related phenotypes for participants with evaluable data.

Dose Escalation Study Design[a] (N= ~20-28)



KEY ELIGIBILITY CRITERIA
- Locally advanced (unresectable), or metastatic carcinoma or sarcoma that has progressed after all standard therapies
- ≥ 18 years of age
- ECOG PS 0-1

ENDPOINTS

Primary:
- Safety, tolerability (DLTs, AEs, SAEs, withdrawal due to treatment-related AEs)
- RP2D determination

Secondary:
- Efficacy (ORR, DoR, DCR, PFS using RECIST 1.1, and OS)
- Pharmacokinetics
- Immunogenicity

Exploratory:
- Pharmacodynamic biomarkers

TREATMENT AND EVALUATION
- Participants received 23ME-00610 intravenously every 3 weeks (Q3W) infused over 30 minutes.
- 23ME-00610 was administered until disease progression (by iRECIST), unacceptable toxicity, withdrawal of consent or death.
- The DLT observation period was 21 days following the first dose of 23ME-00610.

[a]Sentinel period of 24 hours between the first 2 patients at each dose level in the 3+3 portion.

AE, adverse event; DCR, disease control rate; DLT, dose limiting toxicity; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; RP2D, recommended phase 2 dose; SAE, serious adverse event

RESULTS

- Between January 5th 2022 and January 20th 2023, 27 participants were enrolled and received at least 1 dose of 23ME-00610.
  - 20 participants were enrolled in dose escalation and 7 participants in the PKPD backfill cohorts at the 600 mg (N=4) and 1400 mg (N=3) dose levels.

Baseline Characteristics

Table 1. Baseline Characteristics

Characteristic	Total Population, N=27
Median age, years (range)	60 (21-80)
Female sex, n (%)	13 (48)
Race, n (%)	
American Indian or Alaska Native	1 (3.7)
Asian	2 (7.4)
Black or African American	1 (3.7)
Unknown	1 (3.7)
White	22 (82)
Hispanic or Latino ethnicity, n (%)	6 (22)
ECOG Performance Status, n (%)	
0	10 (37)
1	17 (63)
Median number of prior anti-cancer therapies, n (range)	3.5 (1-9)
Prior immunotherapy, n (%)	14 (52)

Treatment Exposure and Adverse Event Summary

- No dose limiting toxicities or serious AEs related to 23ME-00610 were observed.
- One patient experienced a treatment-related, treatment-emergent adverse event (TEAE) leading to discontinuation of 23ME-00610.
  - Non-serious grade 3 AE of maculopapular rash (23ME-00610 600 mg) during Cycle 1 which resolved to baseline after treatment with oral and topical steroids and led to treatment discontinuation.
- The majority of treatment-related TEAEs were Grade 1 or 2, and 11% were Grade 3 AEs.
  - Treatment-related Grade 3 TEAEs included maculopapular rash, elevated blood creatinine phosphokinase and elevated blood alkaline phosphatase.
- There were no Grade 4 treatment-related TEAEs.

Table 2: Treatment Exposure and Adverse Events Summary (Safety Population)

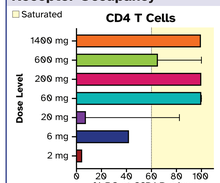
	2 mg (N=1)	6 mg (N=1)	20 mg (N=3)	60 mg (N=4)	200 mg (N=3)	600 mg (N=8)	1400 mg (N=7)	Total (N=27)
Number of doses received								
Median (range)	11	11	3 (2-13)	3 (2-6)	6 (6-9)	2 (1-7)	3 (1-5)	3 (1-13)
Overview of adverse events, n (%)								
All TEAEs	1 (100.0)	1 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	6 (75.0)	5 (71.4)	23 (85.2)
23ME-00610-related AEs	1 (100.0)	0	2 (66.7)	2 (50.0)	3 (100.0)	5 (62.5)	3 (42.9)	16 (59.3)
23ME-00610-related AEs leading to discontinuation	0	0	0	0	0	1 (12.5)	0	1 (3.7)
Grade ≥3 AEs	0	0	1 (33.3)	2 (50.0)	1 (33.3)	4 (50.0)	2 (28.6)	10 (37.0)
23ME-00610-related Grade ≥3 AEs	0	0	0	0	0	2 (25.0)	1 (14.3)	3 (11.1)

AE, adverse event; TEAE, treatment emergent adverse event

23ME-00610 Target Engagement During Cycle 1

- Saturation of peripheral receptor occupancy (RO) on CD4+ T cells was observed at doses ≥ 60 mg (**Figure 4**). Similar results were observed for RO on neutrophils (data not shown).
- Saturation of peripheral free soluble CD200R1 was also observed at doses ≥ 60 mg (**Figure 5**).

Figure 4: Percent CD200R1 Receptor Occupancy[a]

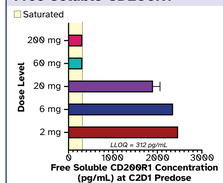


Plot depicts median % RO and interquartile range.

[a]Receptor occupancy assay measures 23ME-00610 saturation of CD200R1 on CD4 T cells in blood. Target engagement in the qualitative RO assay is defined as RO>60% on each cell population.

Sample size for participants with evaluable data by dose cohorts: 1400 mg (N=1), 600 mg (N=3), 200 mg (N=3), 60 mg (N=4), 20 mg (N=3), 6 mg (N=1), 2 mg (N=1).

Figure 5: Amount of Free Soluble CD200R1[a]



Plot depicts median soluble free soluble CD200R1 concentration and interquartile range.

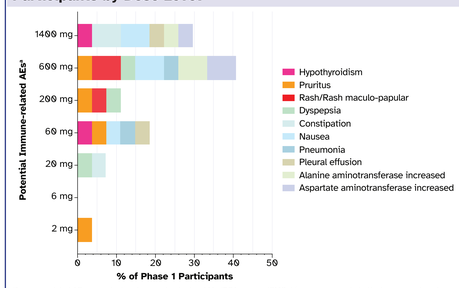
[a]Free soluble CD200R1 assay measures unbound soluble CD200R1 in plasma. Target engagement is defined as a reduction of detectable levels at baseline to below the lower limit of quantitation (LLOQ).

Sample size for participants with evaluable data by dose cohorts: 200 mg (N=2), 60 mg (N=4), 20 mg (N=3), 6 mg (N=1), 2 mg (N=1).

Immune-Related Adverse Events

- Increased irAEs were observed at higher, pharmacologically relevant dose levels.

Figure 3: Potential Immune-Related AEs[a] in ≥ 5% of Participants by Dose Level

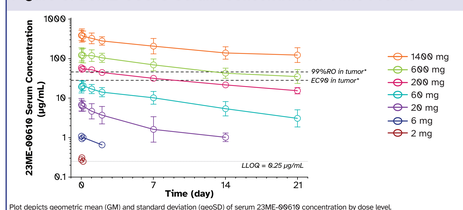


[a]Immune-related AEs were identified using standardized MedDRA queries (SMQs) for immune-mediated/autoimmune disorders, drug reaction with eosinophilia and systemic symptoms syndrome, CNS vascular disorders, not specified as haemorrhagic or ischaemic, interstitial lung disease, thyroid dysfunction, GI nonspecific inflammation and dysfunctional conditions and hepatitis, non-infectious.

23ME-00610 Pharmacokinetics During Cycle 1

- The pharmacokinetics of 23ME-00610 were dose-proportional for doses > 60 mg (**Figure 6**), consistent with saturation of peripheral receptor occupancy (RO) and free soluble CD200R1 at doses ≥ 60 mg (**Figures 4 and 5**).
- At 1400 mg, the 23ME-00610 half-life was ~12 days supporting Q3W dosing. The clearance was faster at doses < 60 mg likely due to incomplete saturation of peripheral CD200R1.

Figure 6: 23ME-00610 Serum Concentration-Time Profile



Plot depicts geometric mean (GM) and standard deviation (geoSD) of serum 23ME-00610 concentration by dose level.

*Reference lines for 99%RO in tumor and EC99 in tumor are based on in vitro data and assume 10% partition from blood to tumor.[11,12]

Sample size for participants with evaluable data by dose cohorts: 1400mg (N=7), 600 mg (N=8), 200 mg (N=3),60 mg (N=4), 20 mg (N=3), 6 mg (N=1), 2 mg (N=1).

Genetics Analysis

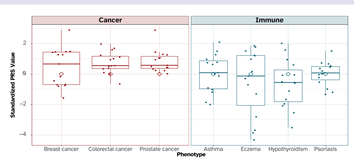
- There was no statistically significant difference in allele frequencies observed in genotyped study participants (N= 15) compared to those in the gnomAD (Genome Aggregation) database for variants relevant to CD200R1 target discovery (**Table 3**). There was no difference in the PRS values of study participants compared to the 23andMe research participants of European ancestry (**Figure 7**).

Table 3: Allele Frequencies for Genetic Variants Relevant to CD200R1 Target Discovery

Gene	Variant ID	Frequency in Trial Participants (95% CI)	Frequency in gnomAD Database
CD200	rs1131199	0.5 [0.33,0.67]	0.619
	rs13972567	0.3 [0.17,0.43]	0.285
	rs2272622	0.27 [0.13,0.4]	0.289
	rs9998216	0.41 [0.27,0.55]	0.456
CD200R1	rs146763487	0 [0,0]	0.009
	rs2171599	0.5 [0.3,0.67]	0.588
	rs4596117	0.5 [0.3,0.67]	0.587
	rs9826398	0.5 [0.3,0.67]	0.588
	rs9865242	0.5 [0.33,0.7]	0.588
DOK2	rs34215892	0 [0,0]	0.020
	rs556994095	0 [0,0]	0.026

The frequency of alternate alleles with associated 95% confidence intervals for variants in genes relevant to CD200R1 target discovery are shown. The frequency of the variants in the gnomAD database are shown for comparison.

Figure 7: PRS Distributions for Cancer and Immune Phenotypes

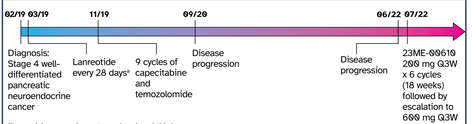


Standardized PRS values for the genotyped individuals are shown in the boxplots. Diamonds represent the mean standardized PRS values for 23andMe research participants of European ancestry.

PRS values for all phenotypes were trained on 23andMe research participants of European ancestry, and then computed for the study participants. For each phenotype, PRS were standardized by subtracting the population mean from the PRS values and dividing by the population standard deviation.

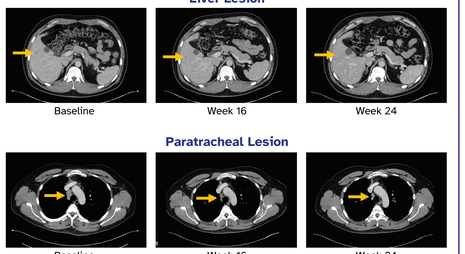
Preliminary Clinical Activity of 23ME-00610 in Neuroendocrine Cancer

Figure 8: 50 YO Male Participant – Treatment Timeline



[a]The participant remains on lanreotide since 3/2019.

23ME-00610 treatment was well tolerated, with a **19% reduction in target lesions at the Week 24 assessment**. Patient continues on study drug at Cycle 9 with stable disease at the time of data cut-off.



- Another participant with poorly differentiated neuroendocrine carcinoma had ongoing stable disease at the Week 40 assessment at the time of the data cut-off.

CONCLUSIONS

- 23ME-00610 demonstrated an acceptable safety and tolerability profile with favorable PK and peripheral CD200R1 saturation on T cells.
  - Peripheral saturation of CD200R1 was observed at doses ≥60 mg; at least 10-fold higher doses are needed to saturate CD200R1 in the tumor microenvironment as ~10% of 23ME-00610 is expected to partition into the tumor.[11,12]
  - Increased immune-related AEs were observed at higher, pharmacologically relevant dose levels.
- Based on the safety, PK and peripheral PD data, 23ME-00610 1400 mg Q3W was identified as the preliminary recommended phase 2 dose to test monotherapy activity in tumor-specific expansion cohorts, including neuroendocrine cancers, small cell lung cancer, ovarian carcinoma, clear cell renal cell carcinoma and MSI-H/TMB-H cancers, in the ongoing Phase 2a.