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

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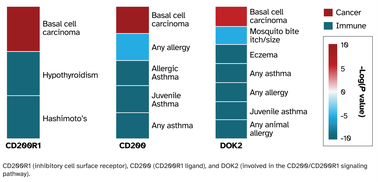
BACKGROUND

- 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**).[2–6]
- The CD200R1 pathway has been shown to promote an immunosuppressive tumor microenvironment in human cancers where CD200 is highly expressed.[7–9]
- 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.[1]
- 23ME-00610 demonstrated acceptable safety and tolerability, and a favorable pharmacokinetic (PK) profile with saturation of peripheral CD200R1 in participants with advanced solid malignancies in a first-in-human Phase 1 study.[10] Longer term safety and efficacy data from Phase 1 are reported here.

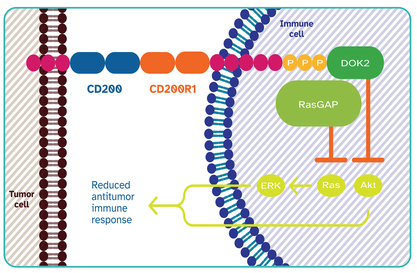
Figure 1. CD200R1, CD200, and DOK2 IO Signature

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 ($r^2 \geq 0.8$) 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



RESULTS

Baseline Characteristics

- Between January 5th 2022 and the May 15th 2023 data cut-off date, 28 participants were enrolled and received at least 1 dose of 23ME-00610.
  - 20 participants were enrolled in dose escalation and 8 participants in the PKPD backfill cohorts at the 600 mg (N=4) and 1400 mg (N=4) dose levels

Table 1. Baseline Characteristics

Characteristic	Total Population (N=28)
Median age, years (range)	62 (21-80)
Female sex, n (%)	14 (50)
Race, n (%)	
American Indian or Alaska Native	1 (3.6)
Asian	2 (7.1)
Black or African American	1 (3.6)
Other	1 (3.6)
White	22 (79)
Unknown	1 (3.6)
Hispanic or Latino ethnicity, n (%)	6 (21)
ECOG Performance Status, n (%)	
0	11 (39)
1	17 (61)
Median weight, kg (range)	79 (53-152)
Median number of prior anti-cancer therapies, n (range)	3 (1-9)
Prior immunotherapy, n (%)	15 (54)
Primary Cancer Type, n (%)	
Colorectal	5 (17.9)
Pancreatic	4 (14.3)
Esophageal	2 (7.1)
Melanoma	2 (7.1)
Sarcoma	2 (7.1)
Breast	1 (3.6)
Osteosarcoma	1 (3.6)
Prostate	1 (3.6)
Endometrial	1 (3.6)
Other	9 (32.1)

Disposition

Table 2. Participant Disposition

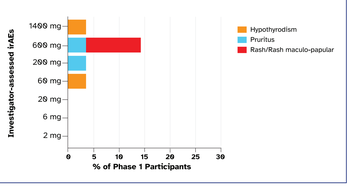
Participant Status	Total Population (N=28)
On Treatment, n (%)	5 (17.9)
Discontinued Treatment, n (%)	23 (82.1)
Disease Progression	22 (78.6)
Adverse Event	1 (3.6)
Discontinued Study, n (%)	13 (46.4)
Withdrew Consent	3 (10.7)
Lost to follow-up	1 (3.6)
Death*	9 (32.1)

*All deaths were cancer-related

Immune-Related Adverse Events

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

Figure 3. Investigator-assessed Immune-Related AEs (irAEs) in ≥ 5% of Participants by Dose Level



Treatment Exposure and Adverse Event Summary

- No dose limiting toxicities or serious AEs related to 23ME-00610 were observed. The maximum tolerated dose (MTD) was not reached.
- One patient experienced a treatment-related treatment-emergent adverse events (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; 3 participants (11%) experienced a Grade 3 AE.
  - Treatment-related Grade 3 TEAEs included maculopapular rash, elevated blood creatinine phosphokinase and elevated blood alkaline phosphatase.
- There were no Grade ≥ 4 TEAEs.
- Preliminary immunogenicity data suggests no evidence of treatment-induced anti-drug antibodies (ADA) following repeated administration of 23ME-00610 across the 2 mg to 1400 mg doses.

Table 3. Summary of Treatment Exposure and Adverse Events by Dose Level

	2 mg (N=1)	6mg (N=1)	20mg (N=3)	60mg (N=4)	200 mg (N=3)	600mg (N=8)	1400mg (N=8)	Total (N=28)
Number of doses received								
Median (Range)	11	11	3 (2-15)	3 (2-6)	6 (6-13)	2.5 (1-13)	3.5 (1-8)	4 (1-15)
Overview of adverse events, n (%)								
All TEAE	1 (100.0)	1 (100.0)	3 (100.0)	4 (100.0)	3 (100.0)	8 (100.0)	7 (87.5)	27 (96.4)
Any immune-related AEs	0	0	0	1 (25.0)	1 (33.3)	3 (37.5)	4 (50.0)	9 (32.1)
23ME-00610-related AEs	1 (100.0)	0	2 (66.7)	2 (50.0)	3 (100.0)	6 (75.0)	5 (62.5)	19 (67.9)
23ME-00610-related AEs leading to discontinuation	0	0	0	0	0	1 (12.5)	0	1 (3.6)
Grade ≥3 TEAEs	0	0	1 (33.3)	2 (50.0)	1 (33.3)	5 (62.5)	3 (37.5)	12 (42.9)
23ME-00610-related Grade ≥3 AEs	0	0	0	0	0	2 (25.0)	1 (12.5)	3 (10.7)
Treatment related AEs of any grade observed ≥5% of participants, n (%)								
Nausea	0	0	0	0	0	2 (25.0)	2 (25.0)	4 (14.3)
Pruritus	1 (100.0)	0	0	0	1 (33.3)	1 (12.5)	0	3 (10.7)
Fatigue	0	0	0	1 (25.0)	2 (66.7)	0	0	3 (10.7)
Arthralgia	0	0	1 (33.3)	0	0	1 (12.5)	1 (12.5)	3 (10.7)
Headache	0	0	0	1 (25.0)	1 (33.3)	1 (12.5)	0	3 (1.7)
Rash	0	0	0	0	0	2 (25.0)	0	2 (7.1)
Hypothyroidism	0	0	0	1 (25.0)	0	0	1 (12.5)	2 (7.1)
Cough	0	0	0	0	0	0	2 (25.0)	2 (7.1)

Interim Monotherapy Efficacy

- Of 27 response evaluable participants, 52% (n=14) had stable disease, with a median duration of 18.6 weeks (range: 0.1-39 weeks) (**Figure 4**).
- A disease control rate* (DCR) of 44% (n=12) was observed (90% CI [30.5%, 65.9%]).

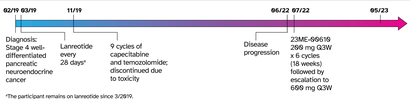
*DCR per RECIST v1.1 is defined as the percentage of participants whose best overall response is confirmed Complete Response (CR) or Partial Response (PR) or Stable Disease (SD) that met the minimum duration of 8 weeks

Figure 4. Treatment Duration and Tumor Response per RECIST v1.1

Note: Treatment Duration = (end of treatment date – first dose date + 1) /30.437. If a participant remained on treatment at the time of data cut-off, the data cutoff date was used. Colored portions of the horizontal bars represent the dose level the participants received. Intra-patient dose escalation to the next cleared dose level was permitted for participants who did not experience a Grade 3 or above study-drug related AE.

Preliminary Clinical Activity of 23ME-00610 in Neuroendocrine Cancer

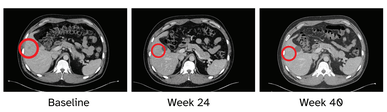
Figure 5. 50 YO Male Participant – Treatment Timeline



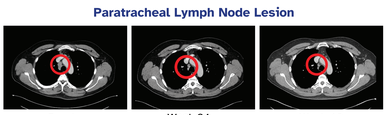
*The participant remains on lanreotide since 3/2019.

23ME-00610 treatment was well tolerated, with **a maximum reduction of 19% in target lesions, which remains ongoing at the Week 40 assessment**. The participant continues on study drug at Cycle 13 with stable disease at the time of data cut-off.

Liver Lesion



Paratracheal Lymph Node Lesion



CONCLUSIONS

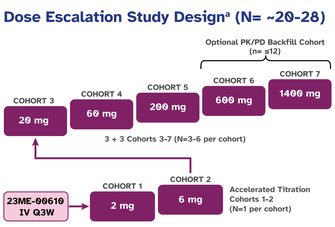
- 23ME-00610 monotherapy is well-tolerated and has a manageable safety profile.
- The observed irAEs at pharmacologically relevant doses are consistent with 23ME-00610-mediated immune modulation.
- 23ME-00610 had a favorable PK profile, with median half-life of ~13 days at the 1400 mg dose (see Poster 609 for further details on the PK and PD profile of 23ME-00610), which supports Q3W IV administration. Preliminary immunogenicity data showed no evidence of treatment-induced ADA.
- Based on the safety profile, PK and PD data, a recommended Phase 2 dose of 1400 mg administered IV Q3W was selected for evaluation in the Phase 2a monotherapy tumor-specific expansion cohorts, which include neuroendocrine cancers, small cell lung cancer, ovarian carcinoma, clear cell renal cell carcinoma and TMB-H/MSI-H cancers. 23ME-00610 is also being evaluated in a cohort of adolescents with advanced solid malignancies.
- The updated data continue to support evaluation of 23ME-00610 in the ongoing Phase 2a.

METHODS

Phase 1 Study Design

- The phase 1 portion of the Phase 1/2a, open-label, multi-center study 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.
- All participants provided informed consent, as approved by an IRB, prior to participating in this study. This study is registered on clinicaltrials.gov as **NCT05199272**.

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 36 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 participants 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

ACKNOWLEDGEMENTS

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