Safety, efficacy, and PKPD of 23ME-00610, a first-in-class anti-CD200R1 antibody, in patients with advanced neuroendocrine cancers: Results from a multi-center multi-country Phase 1/2a expansion cohort.

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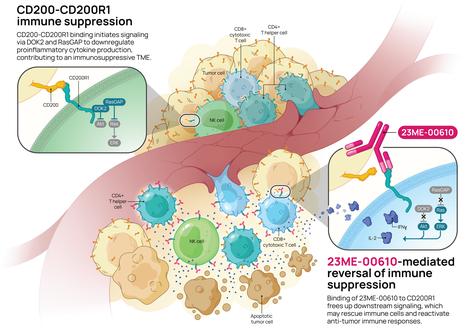
BACKGROUND

- 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 for 3 critical components of the CD200R1 pathway, including CD200R1, its sole ligand CD200, and the downstream signaling protein DOK2.
- CD200R1 is expressed on immune cells and binds to CD200, its only known ligand in humans. Binding CD200 by CD200R1 can downregulate proinflammatory cytokines by activated T and myeloid cells and promote an immunosuppressive microenvironment in human cancers, where CD200 is highly expressed [2-9] (**Figure 1**).
- 23ME-00610 ('610) 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**). From the 28 patient Phase 1 portion, 23ME-00610 has demonstrated acceptable 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, > 50% stable disease rate, and tumor shrinkage [10-12].

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



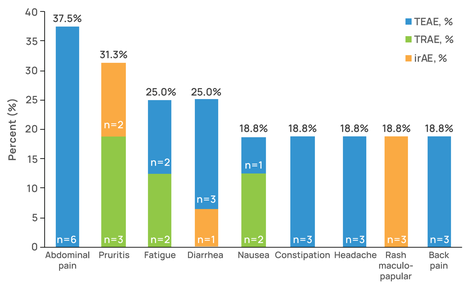
Abbreviations: Akt, protein kinase inhibitor B; CD, cluster of differentiation; DOK, docking protein; ERK, extracellular signal-regulated kinase; IFN, interferon; IL, interleukin; NK, natural killer; RasGAP, Ras-specific GTPase-activating proteins; TME, tumor microenvironment

RESULTS

Table 1. Patient Demographics and Disease Characteristics

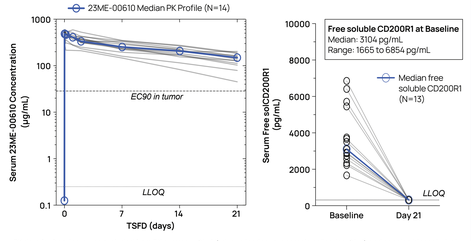
Enrolled, n	16
Age, years, median (range)	57.5 (33 – 74)
Sex, n (%)	
Female	8 (50.0%)
Race, n (%)	
White	11 (68.8%)
Asian	3 (18.8%)
Other	1 (6.3%)
Not Reported	1 (6.3%)
Ethnicity, n (%)	
Not Hispanic or Latino	14 (87.5%)
Hispanic or Latino	1 (6.3%)
Unknown	1 (6.3%)
ECOG [0 to 1], n (%)	
0	8 (50.0%)
Primary Tumor Location, n (%)	
Pancreas	8 (50.0%)
Lung	2 (12.5%)
Small intestine	2 (12.5%)
Cervix	1 (6.3%)
Ethmoid sinus	1 (6.3%)
Liver	1 (6.3%)
Thymus	1 (6.3%)
Differentiation/Grade, n (%)	
Well differentiated	6 (37.5%)
Grade 1	2 (12.5%)
Grade 2	2 (12.5%)
Grade 3	2 (12.5%)
Moderately differentiated	2 (12.5%)
Poorly differentiated	5 (31.3%)
Unknown	3 (18.8%)
Prior Systemic Cancer Therapy, n (%)	
Somatostatin analog	9 (56.3%)
Capecitabine/temozolomide	7 (43.8%)
Platinum/etoposide	7 (43.8%)
Everolimus	6 (37.5%)
Somatostatin receptor radiotherapy	4 (25.0%)
FOLFOX or FOLFIRINOX	4 (25.0%)
Anti-PD-1/L1	2 (12.5%)
Time Since Initial Diagnoses, months, median (range)	50.5 (14 – 117)
Prior Lines of Treatment, n, median (range)	3.5 (1 – 10)

Figure 4. Overall 23ME-00610 AE Profile, including TEAEs, TRAEs, and irAEs



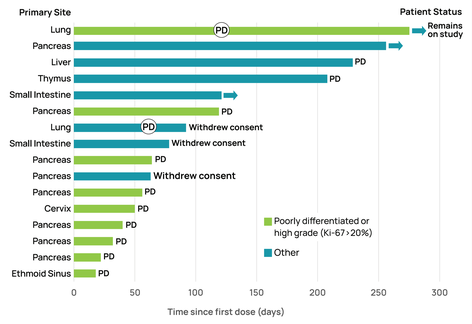
AEs observed in 3 or more patients (≥ 15%). AEs of anemia, dyspnea, abdominal distension, arthralgia, gastro-esophageal reflex disease, and weight decreased were observed in N=2 patients each (12.5%).
TEAE, treatment emergent adverse event; TRAE, treatment related adverse event; irAE, immune related adverse event
Note: irAEs are considered related to study drug, and therefore not double counted in related category

Figure 5. 23ME-00610 Optimized PKPD Profile at 1400 mg Q3W



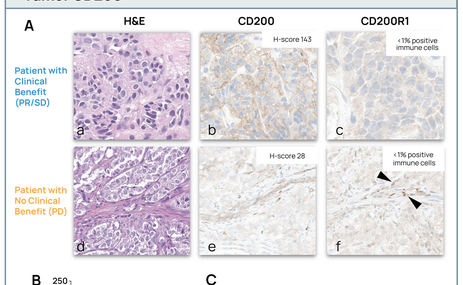
PK data for 2 patients was excluded from PK summary (N=14) due to inadequate sample collection (N=1) and ongoing bioanalytical re-analysis (N=1). Free soluble CD200R1 data were available for 13 patients due to Baseline and/or Day 21 data unavailable for 3 individuals. 23ME-00610 is administred IV every 3 week (Q3W). TSFD, time since first dose; Day 21 = C2D1 predose; Baseline was collected at C1D1 predose; LLOQ = lower limit of quantitation. BLQ values for PK concentration were set to 1/2 LLOQ. BLQ values for free soluble CD200R1 were set to LLOQ.

Figure 6. 23ME-00610 Treatment Duration and Tumor Response per RECIST v1.1



Patients were sorted by time on treatment and shaded based on tumor histology: poorly differentiated and Grade 3 (green) or Other (blue). Patients had an mean study drug exposure of 97 days (median 54 days; maximum 275 days).

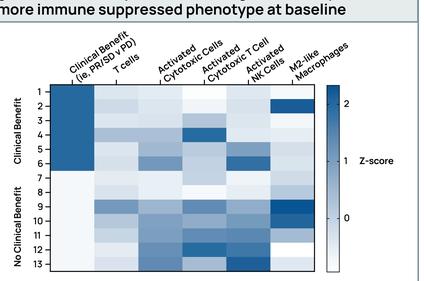
Figure 7. Tumor CD200 and CD200R1 Expression Shows ~50% Neuroendocrine Patients with Moderate or High Tumor CD200



Higher CD200 tumor expression (H-score, membranous CD200 staining on tumor cells) may drive tumor response with 23ME-00610 treatment as demonstrated by these two grade 3 pancreatic NETs that have different clinical outcomes in this study. Distribution of CD200 H-scores of patient tumors with clinical benefit (partial response or durable SD, PR/SD) vs tumors that progressed (PD). Enlarged dots represent the H-scores of the tumors in the IHC panel.

Clinical benefit is defined as PR or durable SD (> 6 months) per RECIST v1.1. No Clinical Benefit is defined as Progressive Disease (PD) or withdrawal consent due to clinical progression.

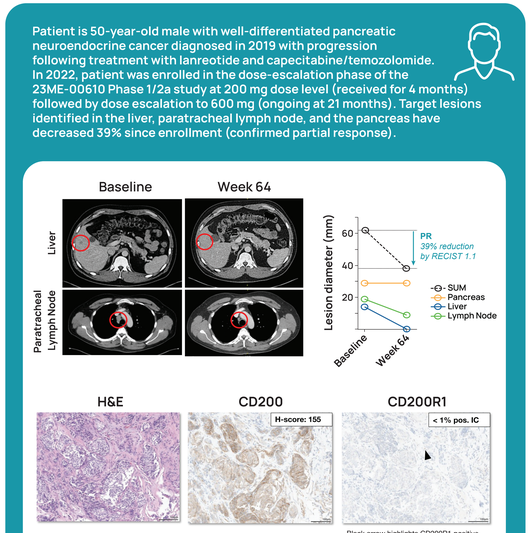
Figure 8. Tumors of patients deriving benefit may have a more immune suppressed phenotype at baseline



Tumors that responded to 23ME-00610 tended to have been less inflamed at baseline than tumors that progressed. Specifically, tumors that progressed on treatment tended to have more immunosuppressive M2-like macrophages at baseline. Multiplex IHC was performed on tumors collected at screening (n = 13 evaluable tumors). CD3, CD8, granzyme B, CD163 and CD68 positive cells were quantified as positive cell numbers / tumor area using image analysis and immune cell densities were standardized as a z-score for the heatmap. CD3+ = T cells, GRZB+ = all cytotoxic cells, GRZB+CD3+CD8+ = activated cytotoxic T cells, GRZB+CD3-CD8- = activated NK cells, CD163+CD68+ = M2-like macrophages.

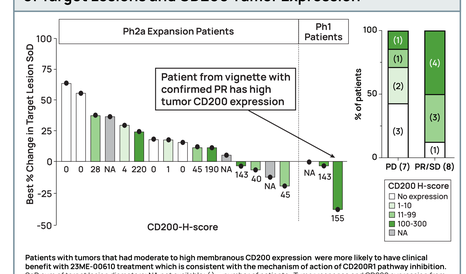
PATIENT VIGNETTE

Patient is 50-year-old male with well-differentiated pancreatic neuroendocrine cancer diagnosed in 2019 with progression following treatment with lanreotide and capecitabine/temozolomide. In 2022, patient was enrolled in the dose-escalation phase of the 23ME-00610 Phase 1/2a study at 200 mg dose level (received for 4 months) followed by dose escalation to 600 mg (ongoing at 21 months). Target lesions identified in the liver, paratracheal lymph node, and the pancreas have decreased 39% since enrollment (confirmed partial response).



Black arrow highlights CD200R1 positive immune cells in the tumor.

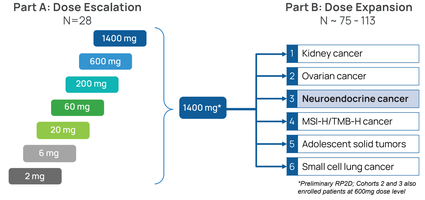
Figure 9. Best % Change of Summary of Diameters (SoD) of Target Lesions and CD200 Tumor Expression



Patients with tumors that had moderate to high membranous CD200 expression were more likely to have clinical benefit with 23ME-00610 treatment which is consistent with the mechanism of action of CD200R1 pathway inhibition. SoD,sum of target lesion diameters; NA,not available; ( ) = number of patients. Tumor response and CD200 expression from 3 neuroendocrine patients from the Phase 1/FIH trial are also shown in the waterfall plot. 4 patients without archival tissue for IHC were not included in the summary statistics (ie, right figure).

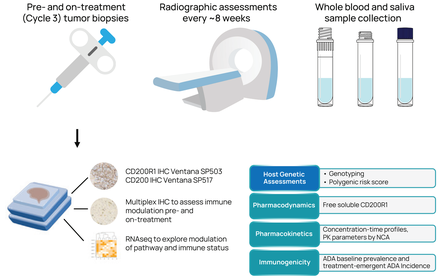
METHODS

Figure 2. Phase 1/2a Study Design in Patients with Locally Advanced or Metastatic Solid Malignancies (NCT05199272)



- 23ME-00610 administered IV every 21 days (Q3W)
- Expansions had target enrollment of 15 patients per cohort
- Neuroendocrine cohort eligibility included well-differentiated Grade 3 neuroendocrine tumors, poorly differentiated neuroendocrine carcinomas, and tumors with neuroendocrine features with Sponsor approval

Figure 3. Schedule of Assessments



CONCLUSIONS

- 23ME-00610 shows acceptable safety and tolerability and optimized PKPD at 1400 mg Q3W in neuroendocrine patients
  - Related AEs were G1/2 in severity
  - irAEs were G1, generally dermatologic in nature, and typically occurred within 30 days
  - No AEs ≥ G4 or AEs that led to death or discontinuation
  - Presumptive RP2D of 1400 mg achieves prespecified PK target and saturates solCD200R1, the PK profile generally supports Q3W dosing, and there was negligible ADA with no adverse impact on clinical activity
- Partial response and ongoing treatment duration > 72 weeks for a well-differentiated pNET with high CD200 tumor expression (155 CD200 H-score)
- Preliminary pharmacodynamic data in a histologically-diverse neuroendocrine cancer cohort suggests that immunosuppressed tumors with high CD200 may be more likely to respond to 23ME-00610 treatment

REFERENCES
1. Fenaux J, et al. *Oncoimmunology*. 2023;12(1):2217737 **2.** Mihrshahi R, et al. *J Immunol*. 2009;183(8):4879-4886; **3.** Timmerman LM, et al. *PLoS One*. 2021;16(3):e0244770; **4.** Misstear K, et al. *J Virol*. 2012;86(11):6246-6257; **5.** Salek-Ardakani S, et al. *Eur J Immunol*. 2019;49(9):1380-1390; **6.** Chouairy F, et al. *J Immunother Cancer*. 2020;8:e000187; **7.** Moreaux J, et al. *Biochem Biophys Res Commun*. 2008;366:117-122; **8.** Vathiotis IA, et al. *Cancers* (Basel). 2021;13:1024; **9.** Love JE, et al. Am J Clin Pathol. 2017;148:236–242; **10.** Kummar S, et al. *Cancer Res*. 2023;83(8_Supplement):CT174; **11.** Rasco D, et al. *J Immunother Cancer*. 2023;11:doi: 10.1136/jitc-2023-SITC2023.0619; **12.** Glatt DM, et al. *J Immunother Cancer*. 2023;11:doi: 10.1136/jitc-2023-SITC2023.0609.