Phase 1/2a Dose Selection of 23ME-00610, a First-in-Class Anti-CD200R1 Antibody, in Participants with Advanced Solid Malignancies

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BACKGROUND

- CD200R1 was identified as a promising immune-oncology (IO) target by the 23andMe genetic database[1]
- Pleotropic casual variants with opposing effect on risks for cancer and immune diseases, referred to as an IO signature, were observed in three 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 tumor cells in preclinical studies[1]
- This work highlights the approaches used to select doses for the Phase 1/2a study in participants with advanced solid malignancies (NCT05199272)

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.

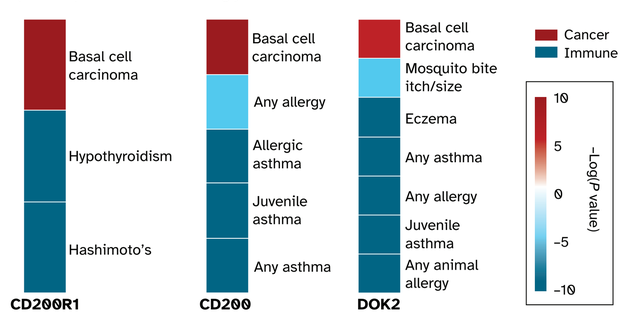
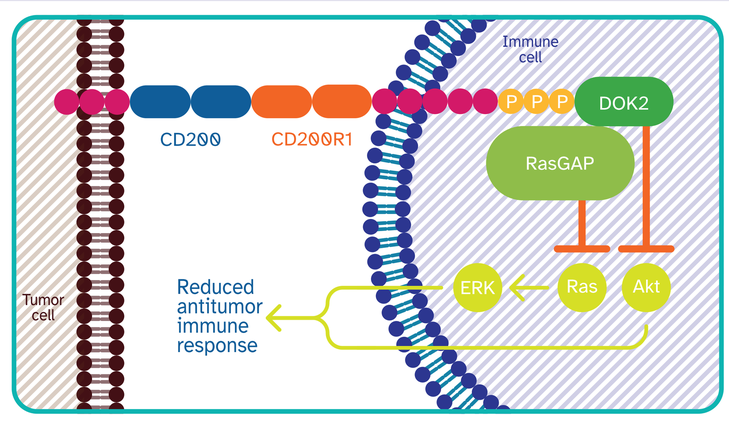


Figure 2. CD200-CD200R1 Signaling Cascade



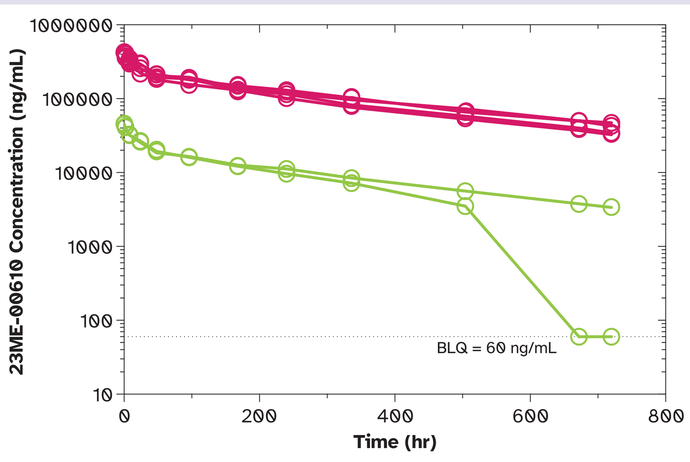
RESULTS

Phase 1 Dose Selection

23ME-00610 Serum PK in Monkeys

- 23ME-00610 PK was biphasic with linear elimination, except for one animal with an ADA-confounding profile (**Figure 3**)
  - 23ME-00610 exposure (C_{max} and AUC) was approximately dose proportional, similar in males and females, and mean $T_{1/2}$ was 10-13 days
  - Mean values for clearance and volume of distribution were similar for the 2 dose levels and consistent with values for therapeutic humanized IgG with linear PK in monkeys[10], supporting the use of allometric scaling from monkeys to predict human PK[11,12,13]

Figure 3. 23ME-00610 Serum PK in Monkeys for Single-dose IV Injection

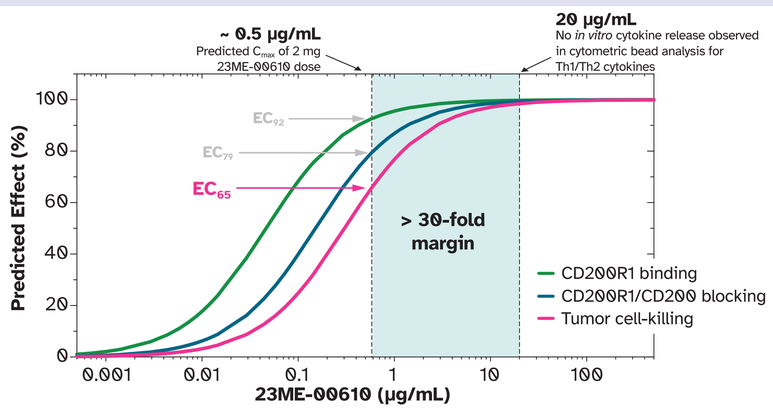


2 mg/kg (green, N=2; 1M/1F) or 20 mg/kg (magenta, N=4; 2M/2F)
Pre-dose BLQ values set to missing; Post-dose BLQ values set to the LLOQ (60 ng/mL)

23ME-00610 MABEL FIH Starting Dose

- As a novel immune checkpoint inhibitor, the minimal anticipated biologic effect level (MABEL) approach was used to select the 23ME-00610 first-in-human (FIH) starting dose in participants with cancer
  - 23ME-00610 MABEL of EC_{65}, corresponding to a starting dose of 2 mg, was selected based on the tumor-cell killing assay (%EC) (**Figure 4**) and supported by the totality of available data, including analysis of FIH doses of immune-activating antibodies[14]

Figure 4. MABEL Determination and Selection of 2 mg Starting Dose for the FIH Study

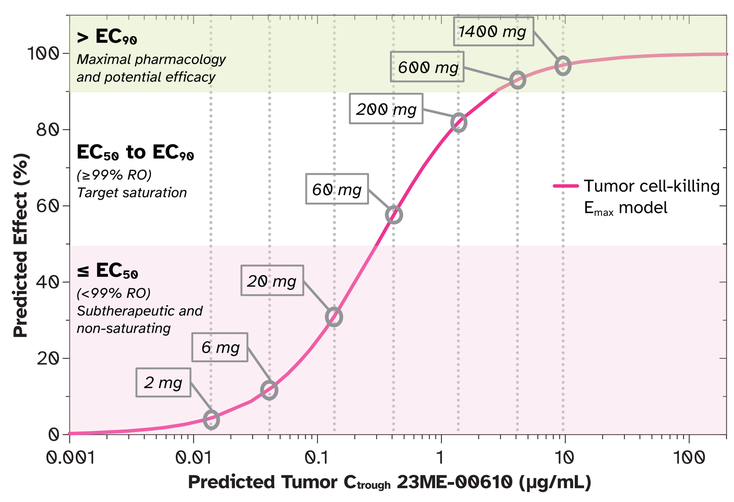


The *in vitro* tumor-cell killing assay that assesses 23ME-00610-mediated tumor-cell killing in primary human immune cultures was used to predict 23ME-00610 activity in participants. Key considerations for the MABEL determination included its antagonist MOA[1], no observed cytokine release in soluble or plate-bound Th1/Th2 cytokine release assays at concentrations 30-fold higher than EC_{65}, and no hazards of CD200R1 inhibition identified in a monkey GLP toxicology study with surrogate antibody.[15]

23ME-00610 Human Dose Projections

- Doses of 2 to 1400 mg selected for the FIH study based on concentration-effect modeling

Figure 5. 23ME-00610 FIH Dose Projections



Doses of 2 and 6 mg were anticipated to be subtherapeutic based on $C_{trough} \leq EC_{90}$ and < 99% RO, and supported accelerated titration for these dose levels. Doses ≥ 60 mg were anticipated to achieve peripheral target saturation ($C_{trough} \geq$ ~99% RO). Doses ≥ 600 mg were projected to be efficacious based on predicted tumor $C_{trough} > EC_{90}$. A maximum dose of 1400 mg was selected based on sensitivity analyses, accounting for variability in PK, tumor uptake, and potential differences between *in vitro* and clinical activity.

Phase 1 Results and Phase 2a Dose Selection

Baseline Characteristics

- Between January 5, 2022 and the May 15, 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 eight 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)

Safety

- As of the May 15, 2023 data cut-off date, 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 TEAE leading to discontinuation of 23ME-00610:
  - Non-serious Grade 3 AE of maculopapular rash (23ME-00610 600 mg) occurred 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; three participants (11%) experienced a Grade 3 treatment-related AE
- See **Poster 619** for further details about the safety and efficacy of 23ME-00610

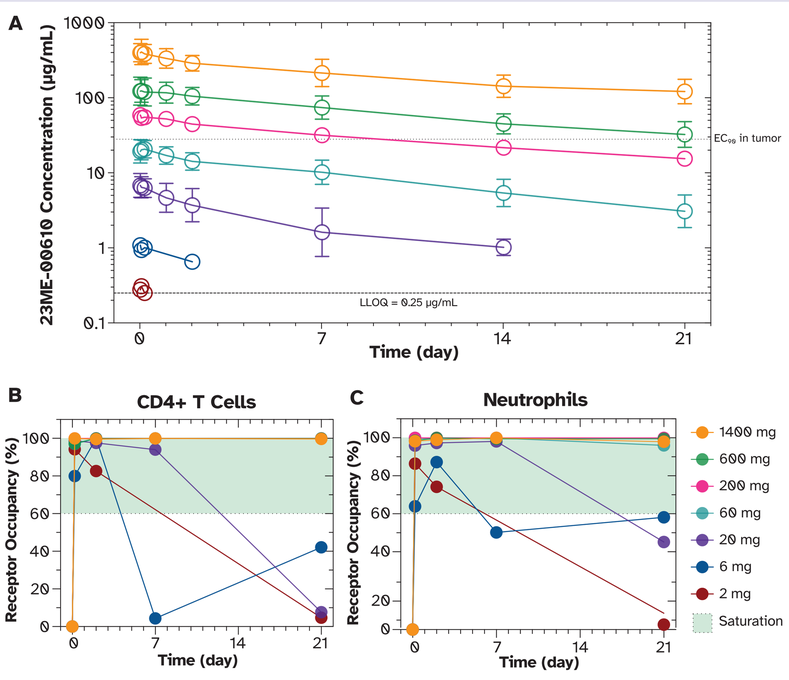
Table 2. Summary of Treatment Exposure and Adverse Events by Dose Level

	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=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 (AEs), n (%)								
All TEAEs	1 (100)	1 (100)	3 (100)	4 (100)	3 (100)	8 (100)	7 (87.5)	27 (96.4)
Any immune-related AEs	0	0	0	1 (25)	1 (33.3)	3 (37.5)	4 (50)	9 (32.1)
23ME-00610-related AEs	1 (100)	0	2 (66.7)	2 (50)	3 (100)	6 (75)	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 AEs	0	0	1 (33.3)	2 (50)	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)	1 (12.5)	3 (10.7)

Cycle 1 PK and Receptor Occupancy (RO)

- 23ME-00610 serum PK is linear and dose proportional for doses ≥ 60 mg, and half-life was 11-13 days for doses ≥ 200 mg (**Figure 6A, Table 3**)
- Peripheral receptor occupancy (%) for CD4+ T cells and neutrophils was saturated at doses ≥ 60 mg, consistent with the dose range of linear PK (**Figure 6B and C**)
- Q3W dosing regimen is supported by the 23ME-00610 PK and Cycle 1 tumor $C_{trough} > EC_{90}$ for 1400 mg (**Figure 6A, Table 3**)

Figure 6. 23ME-00610 Serum PK and Peripheral RO by Dose Level for Cycle 1



A) Geometric mean concentration-time profiles by dose. Error bars represent the geometric standard deviation. BLQ values set to missing. **B)** and **C)** Median receptor occupancy (%) for Cycle 1 by dose.

Table 3. 23ME-00610 PK Parameters by Dose Level for Cycle 1

Dose	N	$T_{1/2}$[a] (day)	$AUC_{0\text{-}21D}$ (day*µg/mL)	C_{max} (µg/mL)	C_{trough}[b] (µg/mL)
1400 mg	8	13.2 (9.7, 15.3)	4160 (29.9%)	447 (30.0%)	126* (66.5 to 167)
600 mg	8	11.2 (8.8, 13.8)	1380 (30.9%)	149 (37.5%)	26.4* (23.5 to 62.0)
200 mg	3	13.2 (12.7, 18.7)	611 (9.2%)	59.5 (17.4%)	16.6 (12.5 to 17.7)
60 mg	4	8.2 (7.5, 9.3)	182 (29.1%)	21.0 (30.0%)	3.38 (1.55 to 5.08)
20 mg	3	4.9 (3.1, 5.7)	36.2 (51.2%)	7.08 (33.3%)	BLQ
6 mg	1	3.4	4.80	1.09	BLQ
2 mg	1	NR	NR	0.31	BLQ

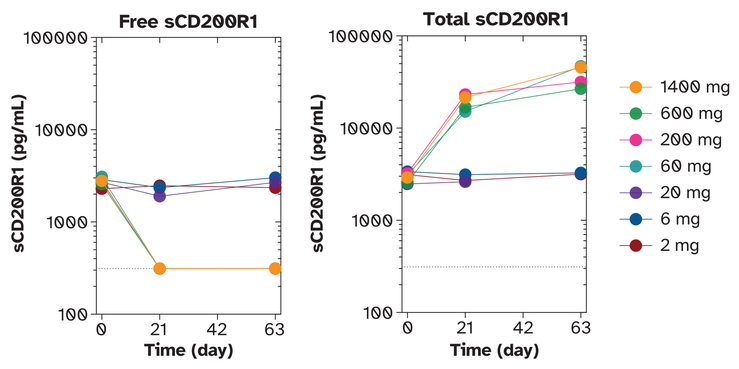
[a]Median (Q1, Q3); [b]Median (min-max); All other parameters are mean (CV%); *N=5.
NR, not reportable (ie., insufficient data to estimate PK parameter); BLQ, below limit of quantitation (i.e., < 0.25 µg/mL)

For doses in the linear PK range (≥ 60 mg), 1.36 to 1.84-fold accumulation was observed for C_{max}, and 1.13 to 2.20-fold accumulation was observed for AUC following repeat Q3W IV administration of 23ME-00610

Cycle 1 Free and Total soluble CD200R1 (sCD200R1)

- For doses ≥ 60 mg, 23ME-00610 depleted free soluble CD200R1 to levels below the limit of quantitation (< 312 pg/mL) and increased levels of total soluble CD200R1, likely driven by 23ME-00610 binding and saturating sCD200R1

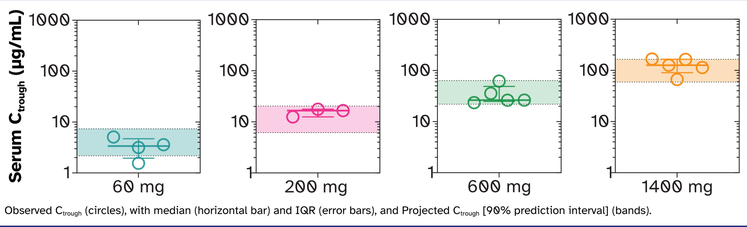
Figure 7. Free and Total sCD200R1 by Dose Level



Relative to baseline (Day 0), predose Cycle 2 (Day 21) and Cycle 4 (Day 63) total sCD200R1 levels increased ~5- to 8-fold and ~9- to 16-fold respectively, with similar increases for all doses in the linear PK range (ie, doses ≥ 60 mg)

Human PK Model Accurately Predicted the Observed 23ME-00610 PK for Doses in the Linear Range

Figure 8. Observed and Projected Cycle 1 Serum C_{trough} for Doses ≥ 60 mg



Observed C_{trough} (circles), with median (horizontal bar) and IQR (error bars), and Projected C_{trough} [90% prediction interval] (bands).

RP2D Selection

- Safety (**Table 2**) and PD profile were similar for 600 mg and 1400 mg doses
- 60% of participants with evaluable data did not achieve target concentration (tumor $C_{trough} > EC_{90}$) in Cycle 1 for the 600 mg dose; in contrast, all participants (5 out of 5) achieved the target concentration in Cycle 1 for the 1400 mg dose (**Figure 6A, Table 3**)
- The PK, PD, and safety data support 1400 mg Q3W as the recommended Phase 2a expansion dose

Table 4. 23ME-00610 PK and PD for RP2D Selection

Dose	N	Cycle 1 PK (target > 28 µg/mL)	PD at Cycle 1 C_{trough}		
		Median C_{trough} [Min, Max]	RO*	Free sCD200R1^	Total sCD200R1#
600 mg	5	26.4 [23.5, 62.0]	4/5	5/5 BLQ	~6x
1400 mg	5	126 [66.5, 167]	5/5	5/5 BLQ	~ 7x

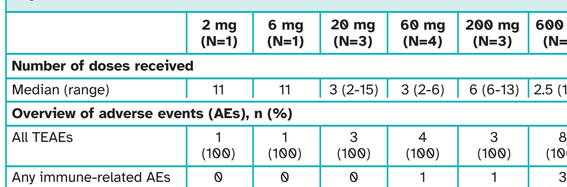
*Number of patients with target saturation on CD4+ T cells and neutrophils. ^Number of patients with free sCD200R1 at BLQ.
#Median fold-increase relative to baseline levels.

CONCLUSIONS

- Predicted human PK based on allometric scaling from monkey and E_{max} PD modeling were used to determine the 23ME-00610 MABEL-based starting dose of 2 mg and the projected efficacious dose of ≥ 600 mg, and supported the accelerated titration, followed by 3+3 FIH Phase 1/2a study design
- In the Phase 1/2a study, 23ME-00610 Cycle 1 half-life ($T_{1/2}$) increased with dose for doses from 2 mg to 60 mg, then plateaued at 11-13 days for doses ≥ 200 mg. 23ME-00610 PK was dose proportional for doses ≥ 60 mg, and doses ≥ 60 mg achieved sustained target saturation
- Clinical PK, PD, safety, and projected efficacy target (Cycle 1 Tumor $C_{trough} \geq EC_{90}$) support a recommended Phase 2a dose of 1400 mg Q3W, which is currently under evaluation in the ongoing Phase 2a
- Based on the Phase 1 results, the approaches used for 23ME-00610 dose projections accurately predicted the PK of 23ME-00610 for the linear dose range (≥ 60 mg) and the dose required for sustained peripheral saturation (≥ 60 mg) in participants with cancer

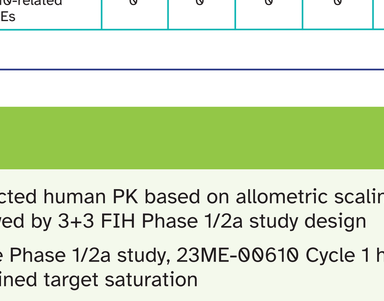
METHODS

Figure 9. Single-dose IV PK Study in Cynomolgus Monkeys



Blood samples were collected pre- and post-dose and processed to serum. Serum 23ME-00610 was quantified using a qualified bioanalytical method (LLOQ = 60 ng/mL) and the serum concentration-time data was used for pharmacokinetic analyses

Figure 10. Two-Compartment PK Model



*23ME-00610 concentration in tumor assumed to be ~10% concentration in the central compartment.[16,17]

Human PK Prediction

- Using Phoenix WNL (v8, Certara USA, Princeton, NJ), individual concentration-time data in monkeys was fit to a 2-compartment model to estimate compartmental PK parameters (**Figure 10**)
- Scaling exponents of 0.85 and 1.0 were used for the clearance terms (CL and Q) and volume terms (V1 and V2), respectively, to estimate human PK parameters[13]
- Simulations were performed in Berkeley Madonna (v10, Berkeley, CA), assuming ~30% variability in fixed effects, a human body weight of 70 kg, and linear PK

E_{max} Model and Human Dose Projections

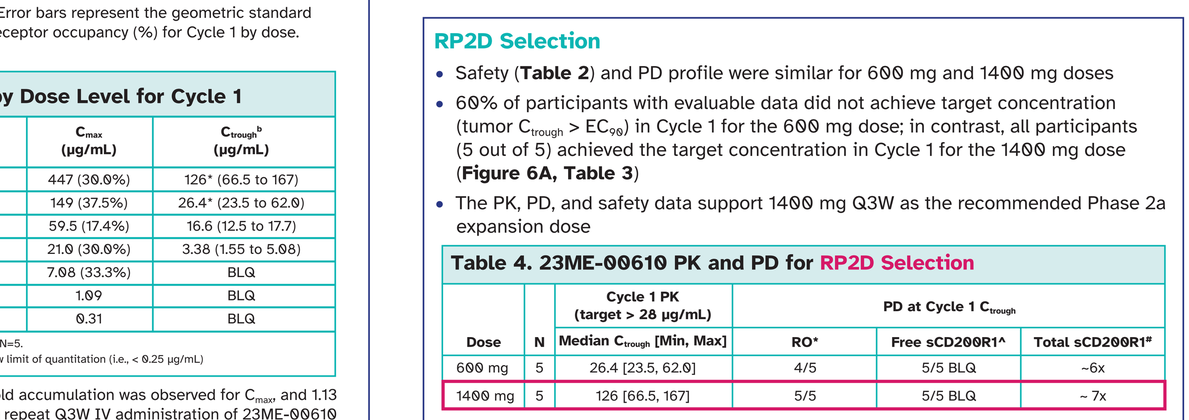
- *In vitro* pharmacology data, including binding, blocking, and tumor-cell killing, was fit to the E_{max} model (**Equation 1**) and integrated with the simulated human concentration-time profiles, including the estimated 23ME-00610 tumor concentration (assuming 10% partition coefficient), to model the predicted 23ME-00610 concentration-effect relationship by dose level
- The predicted effect (%) for each dose level was determined by replacing C (**Equation 1**) with the simulated median concentration of 23ME-00610 in serum or in tumor and E_{max} model parameters normalized to the baseline effect (E_0) and maximum effect (E_{max})

Equation 1. E_{max} Pharmacodynamic Model

$$\text{Effect or RO} = E_0 + E_{max} * C^{\gamma} / (C^{\gamma} + EC_{50}{}^{\gamma})$$

The Hill Slope (γ) was set to 1.0 based on visual inspection and exploratory fits of the raw data.
Receptor Occupancy (RO) was predicted from the EC_{50} from FACS-based saturating bindings experiments, E_0= 0, and E_{max} = 1.0

Figure 11. 23ME-00610 Phase 1/2a Clinical Trial in Participants with Advanced Solid Malignancies (NCT05199272)



Serial blood samples for PK/PD were collected pre-dose and up to Day 21 post-dose in Cycle 1 and Cycle 4, and sparse throughout.
PK parameters (eg., AUC, C_{max}, C_{tau}, T_{max}, $T_{1/2}$) were estimated by non-compartmental methods.
For each dose range tested, the mean estimate for b and its 90% confidence interval were assessed for dose proportionality using the Hummel criteria.
Accumulation ratios (AR) were determined for C_{max}, C_{tau}, and $AUC_{0\text{-}21D}$ using data from Cycle 4 and Cycle 1.

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