Efficacy, safety and PKPD of 23ME-00610, a first-in-class anti-CD200R1 antibody, in patients with advanced or metastatic clear-cell renal cell carcinoma (ccRCC): Results from a multi-center multi-country Phase 1/2a expansion cohort

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BACKGROUND

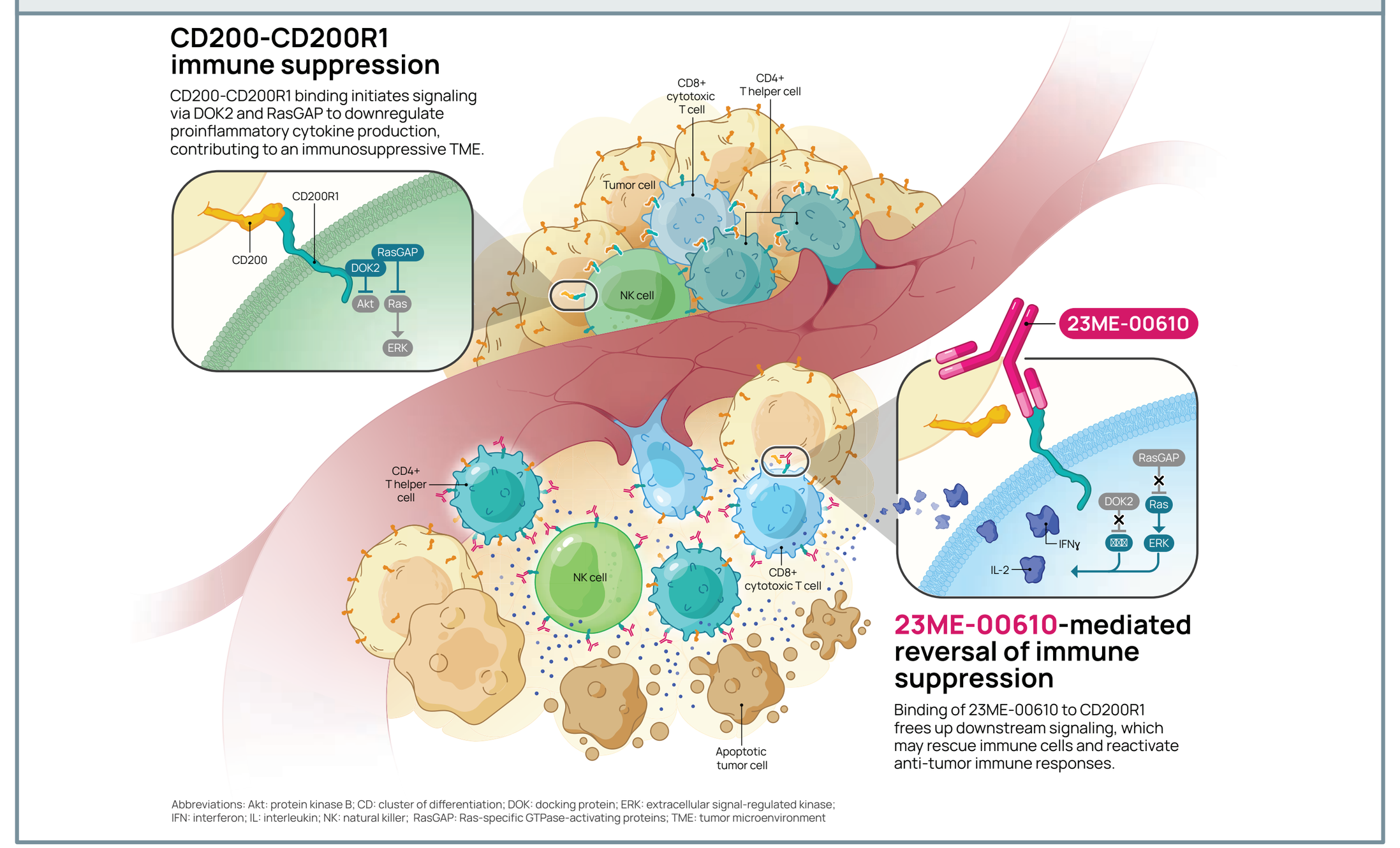
CD200R1

- 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, 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

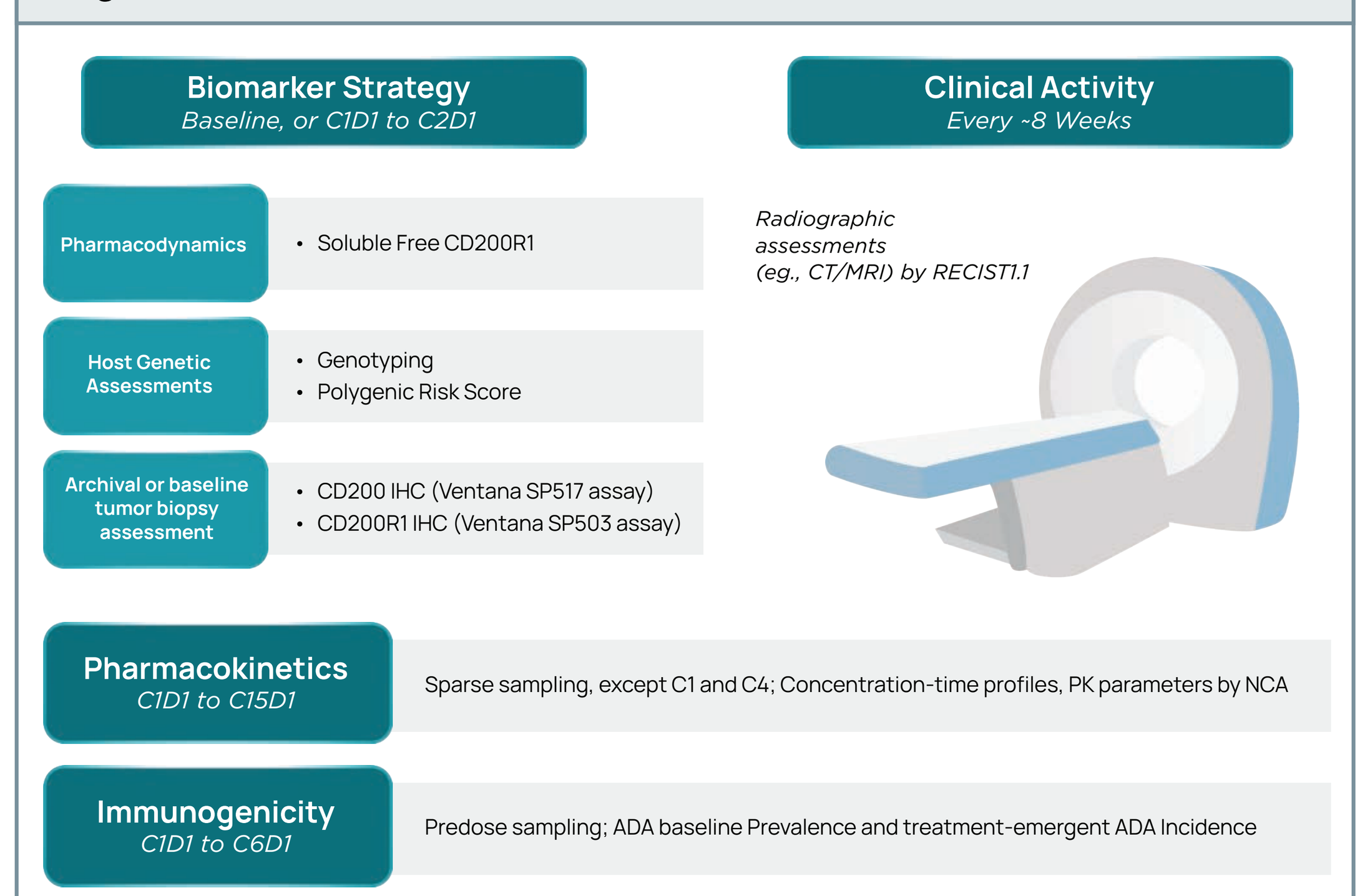
- 23ME-00610 is a first-in-class IgG1 antibody that binds CD200R1 with high affinity (K_D < 0.1 nM) and inhibits immunosuppressive signaling, leading to restoration of T cell activity and killing of CD200-expressing tumor cells in preclinical studies [1] **(Figure 1)**.
- 23ME-00610 is currently in the Phase 2a portion of a Phase 1/2a clinical trial in participants with advanced solid malignancies (NCT05199272). Based on the data from the first N=28 patients in all tumor cohorts, 23ME-00610 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, a > 50% stable disease rate, and preliminary evidence of clinical benefit in multiple indications including neuroendocrine and ovarian cancer[10-12].

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



METHODS

Figure 2: Schedule of Assessments



RESULTS

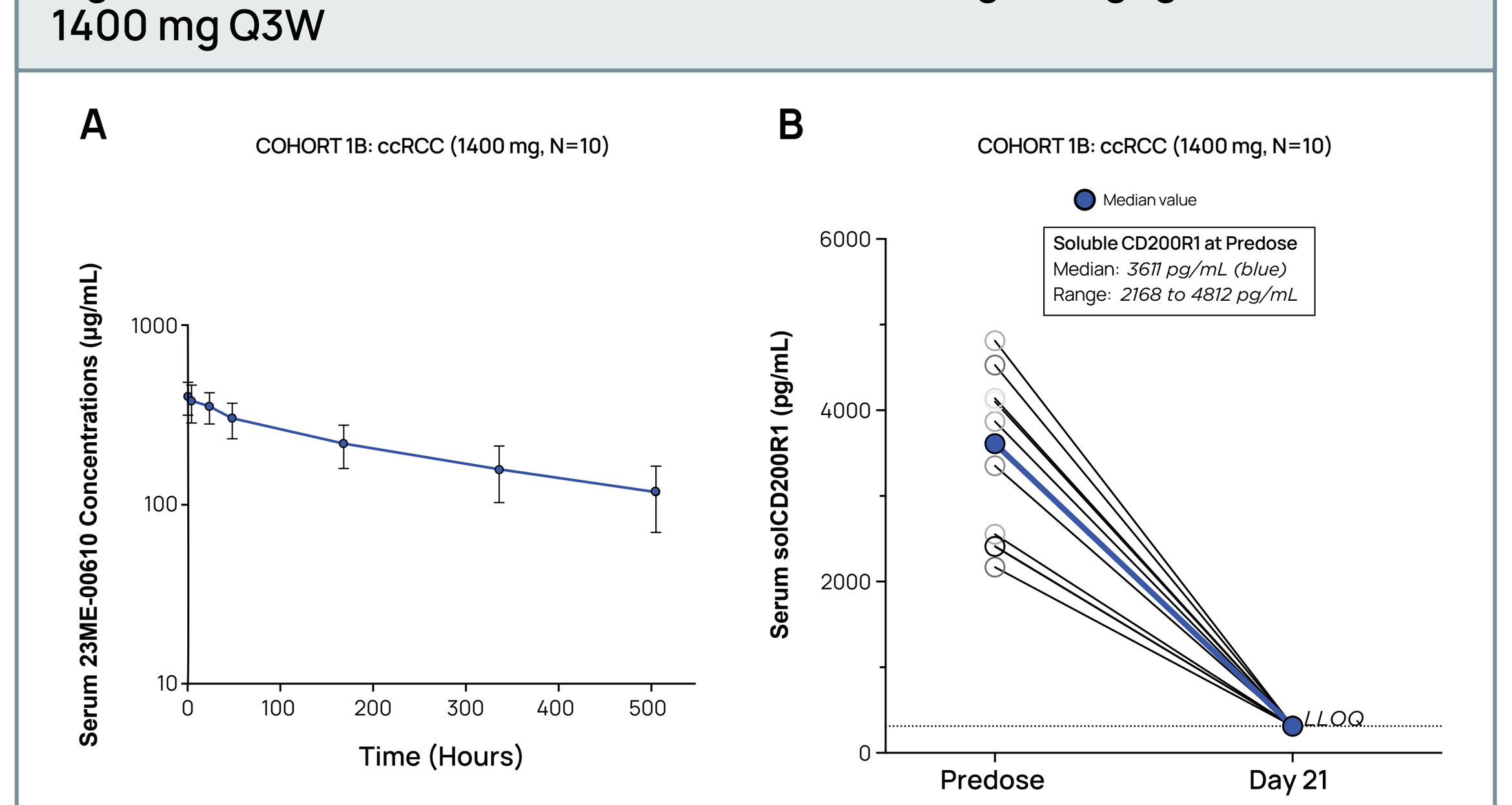
Table 1: ccRCC Patient Demographics and Disease Characteristics

Characteristic	N = 10
Age, median years (range)	64 (43-75)
Sex, n (%)	
Male	7 (70%)
Female	3 (30%)
Race, n (%)	
White	10 (100%)
Ethnicity, n (%)	
Hispanic or Latino	3 (30%)
Not Hispanic or Latino	5 (50%)
Unknown	2 (20%)
Geographic Region, n (%)	
USA	7 (70%)
Canada	3 (30%)
ECOG	
0	3 (30%)
1	6 (60%)
2	1 (10%)
Years since Initial Diagnosis, median (range)	4.9 (1.4-17.3)
IMDC Risk Group	
Favorable	2 (20%)
Intermediate	7 (70%)
Poor	1 (10%)
Prior Lines of Treatment, median (range)	4 (2-7)
Prior Systemic Cancer Therapy, n (%)	
anti-PD/PD-L1	10 (100%)
VEGF TKI	10 (100%)
anti-CTLA4	3 (30%)
mTOR inhibitor	3 (30%)

Safety Summary

- 9 of 10 patients reported adverse events (AEs) in the ccRCC cohort.
- 3 of 10 patients had treatment related AEs all of which were either grade 1 or 2.
- Related AEs reported in this cohort included (one each): fatigue, nausea, vomiting, ALT increased, AST increased, dry mouth, headache, gastroesophageal reflux disease, and constipation and generally similar to the adverse events reported across the entire study.
- No high grade AEs or AEs leading to discontinuation were reported.
- Across the entire study, two SAEs were reported as related by the investigators, including deep vein thrombosis (DVT) (G3) and diarrhea (G2).

Figure 3: 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 4: Swimmer Plot

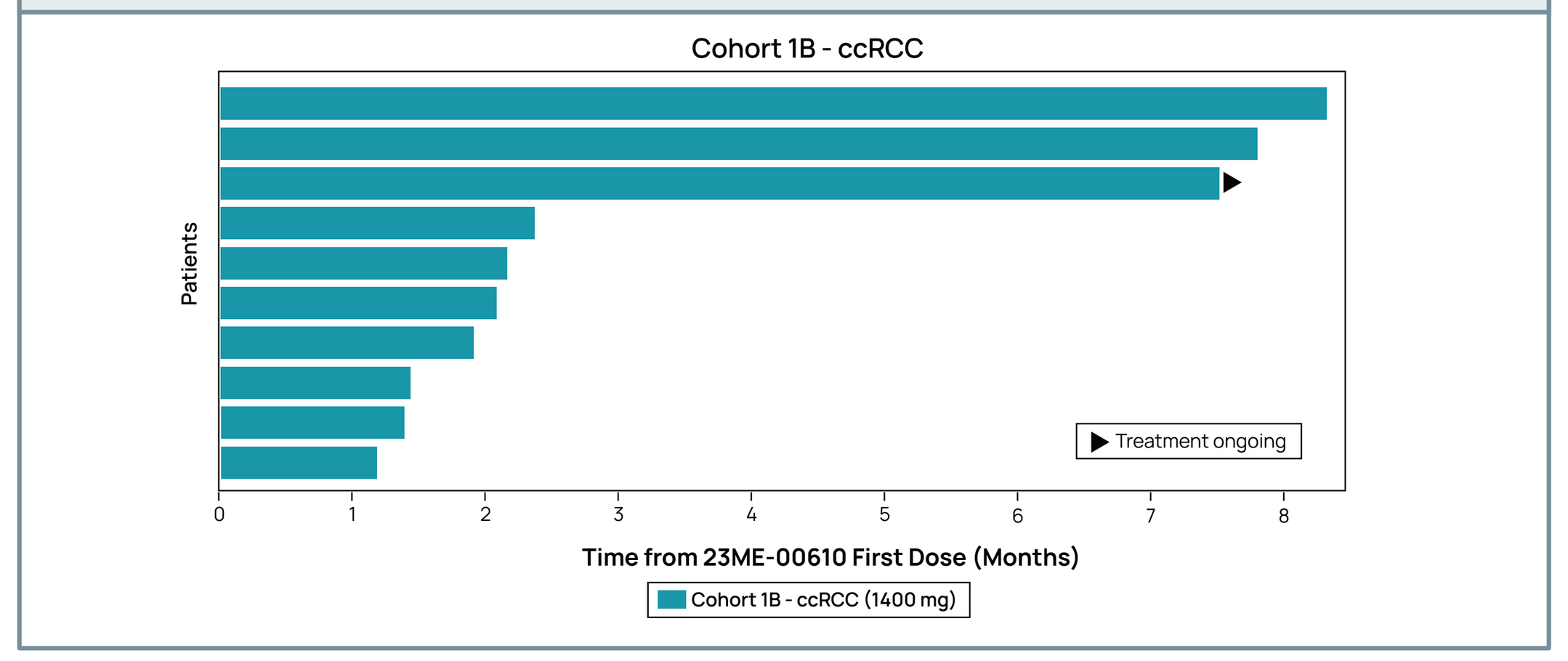


Figure 5: Putative CD200/R1 Activity & Indication Selection for Expansion

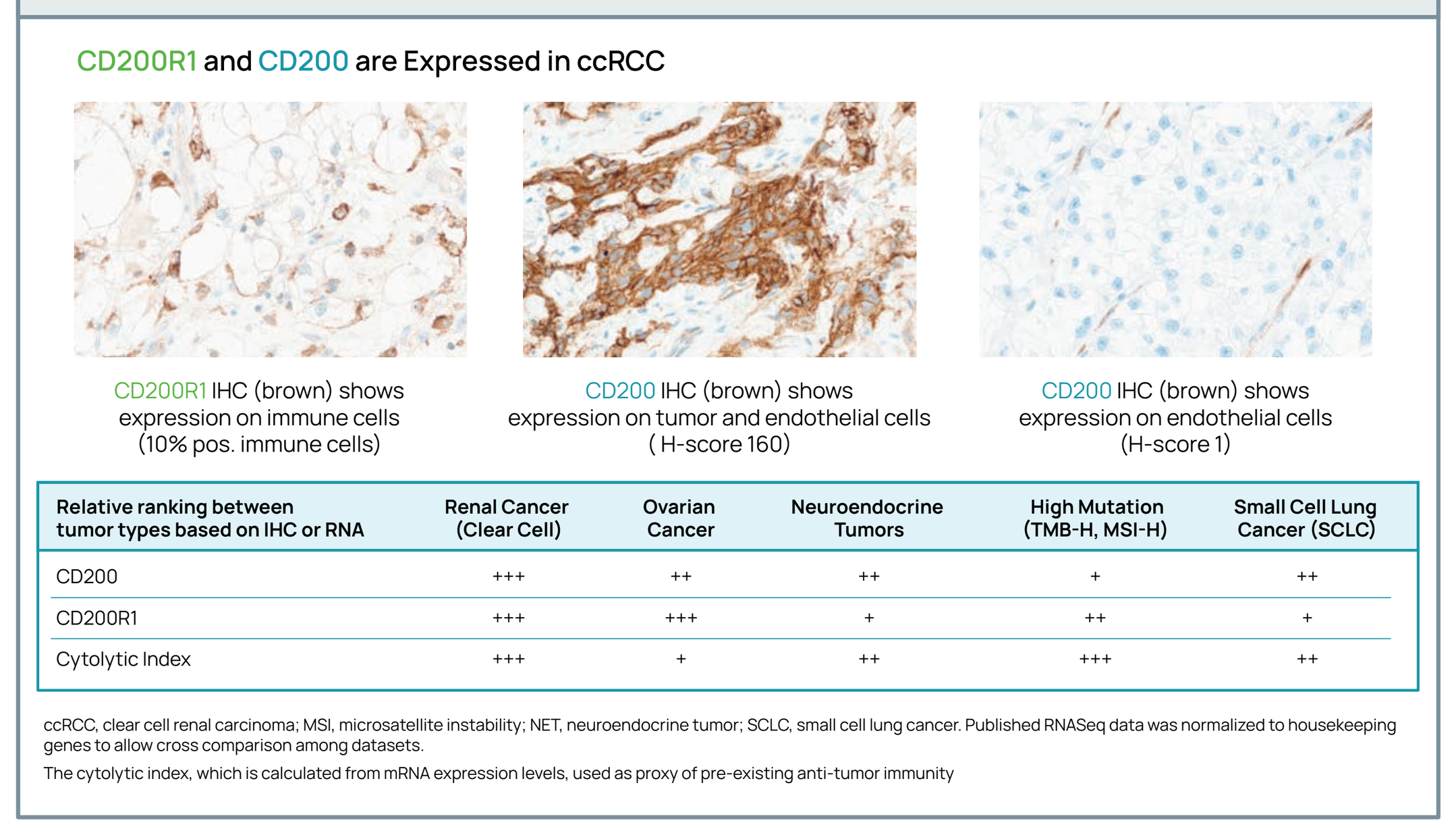


Figure 6: Best % Change of SoD by RECIST v1.1

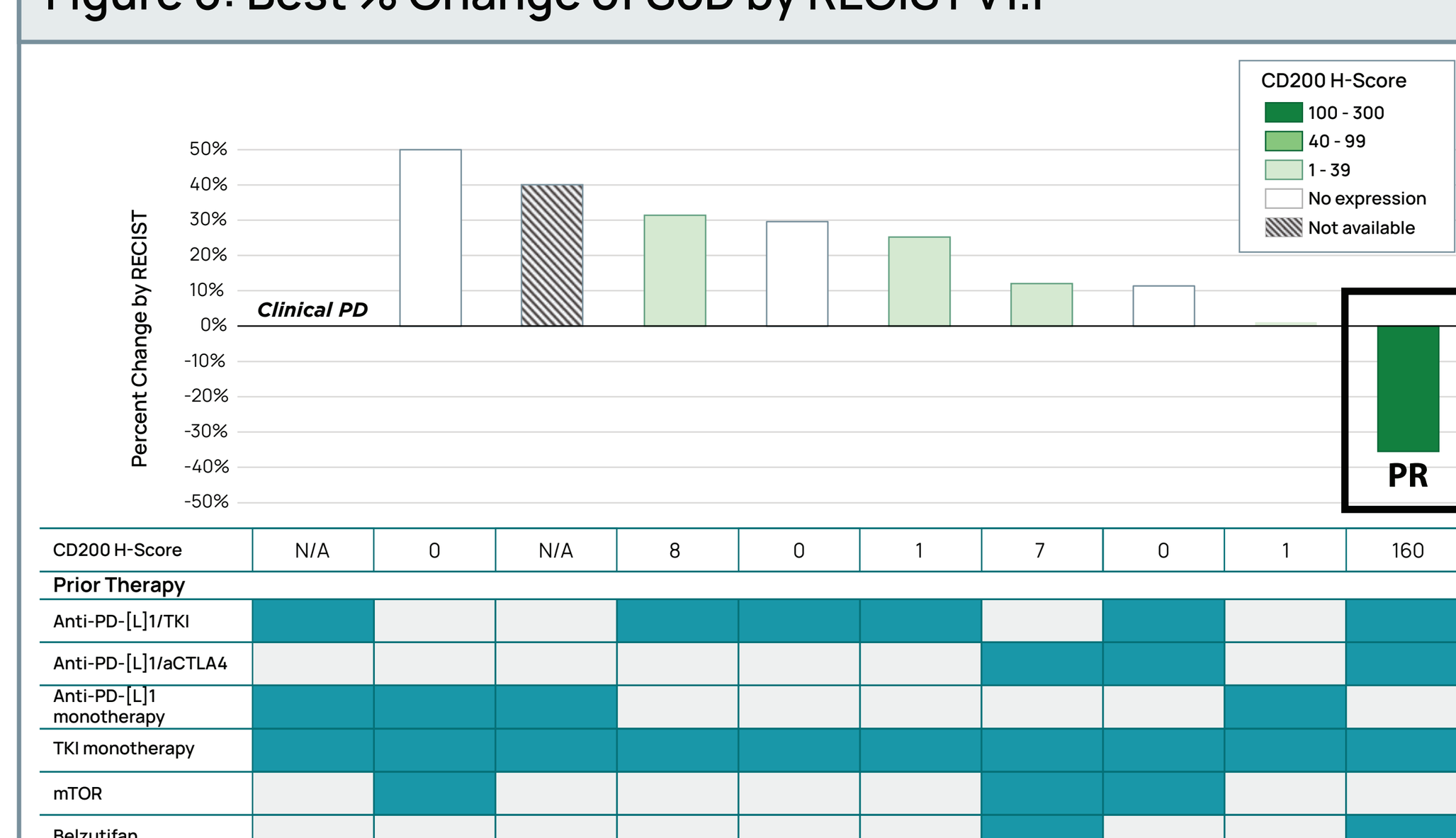
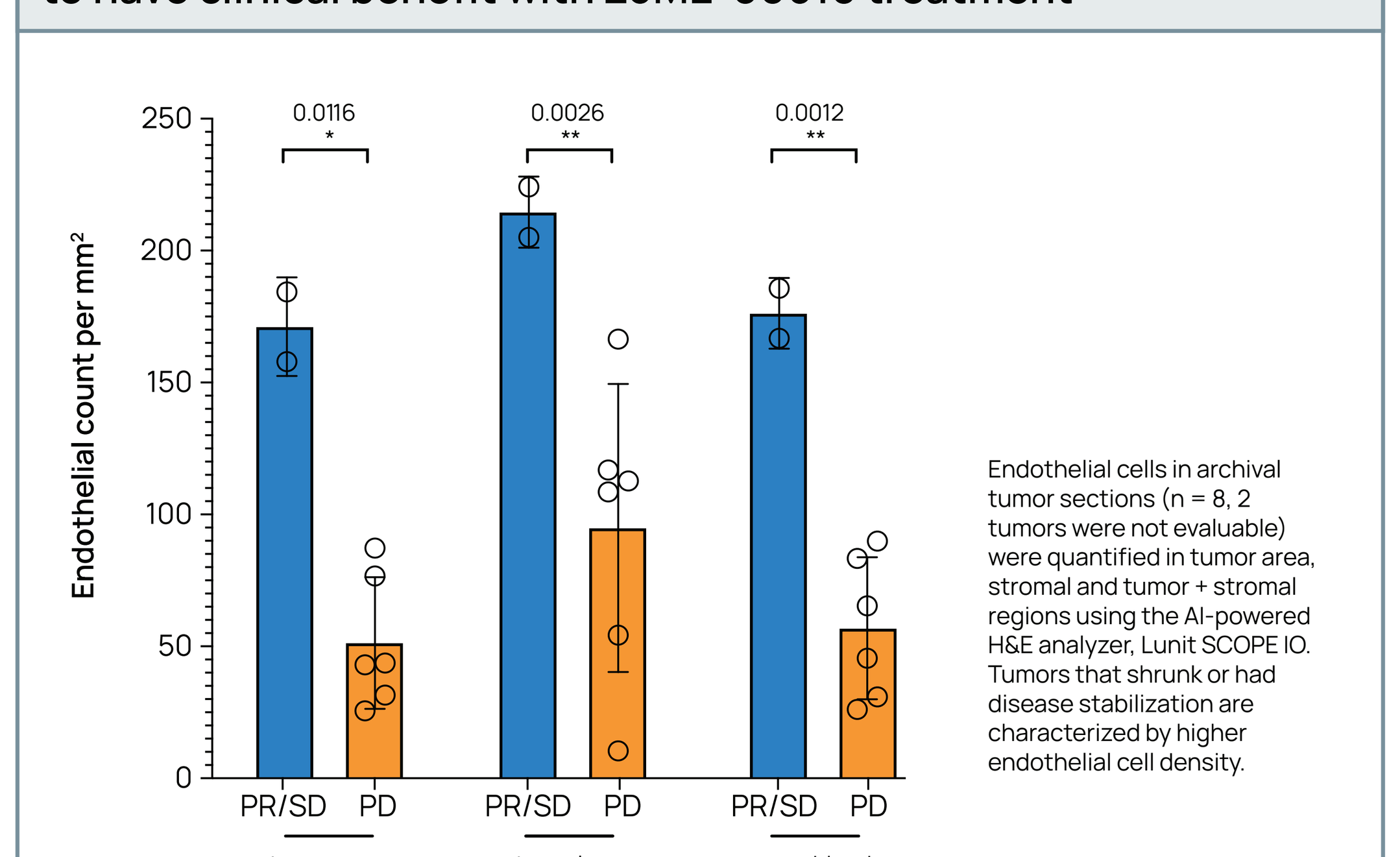
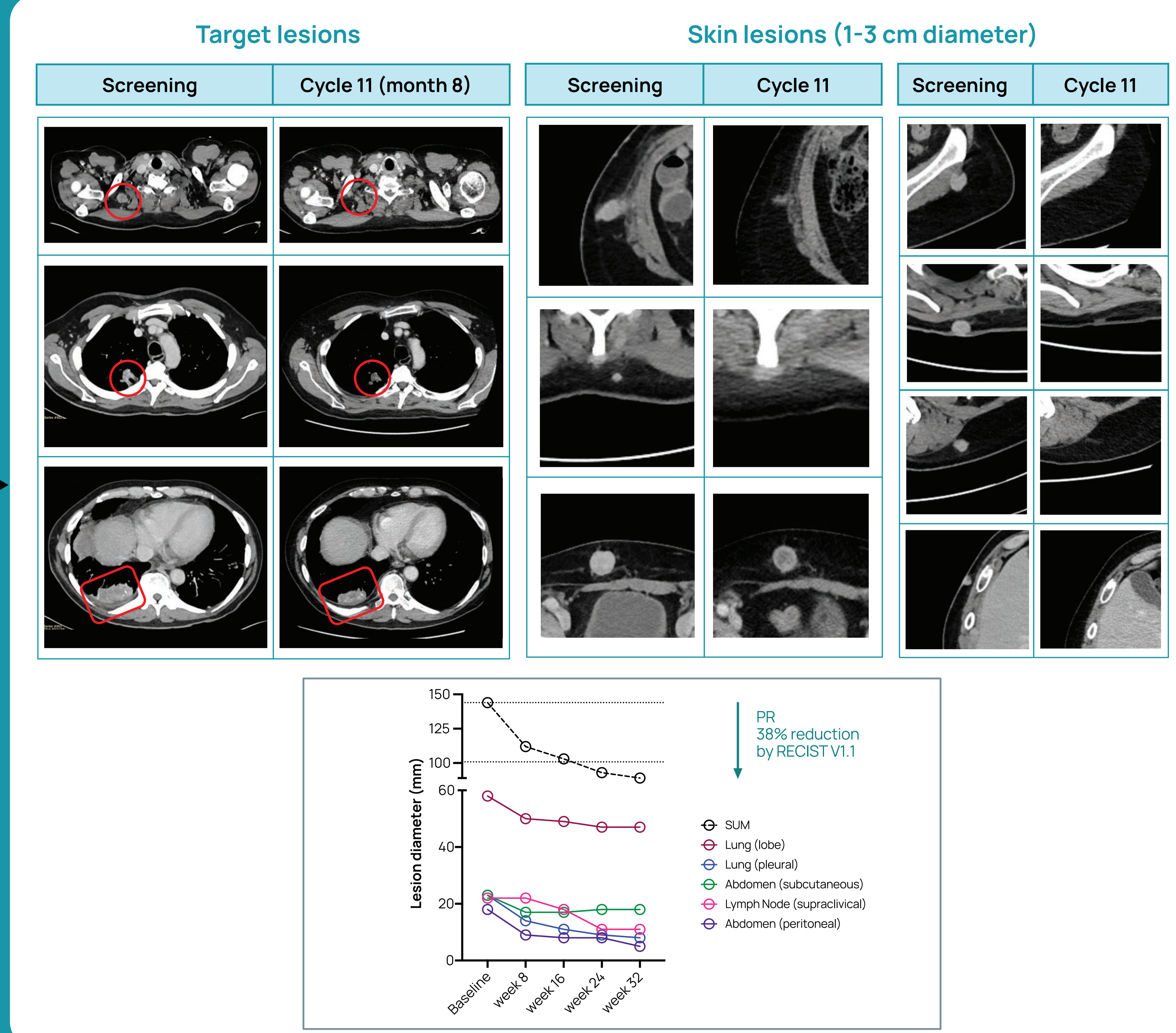


Figure 7: Tumors that are more vascularized may be more likely to have clinical benefit with 23ME-00610 treatment



PATIENT VIGNETTE

61-year-old male with ccRCC diagnosed in 2012. Previously treated with sunitinib, axitinib, ipilimumab plus nivolumab, cabozantinib, pembrolizumab plus lenvatinib, tivozanib, and belzutifan. Following progression on belzutifan, the patient initiated 23ME-00610 on December 2023, currently cycle >11 cycles with confirmed PR (38% decrease)



CONCLUSIONS

- 23ME-00610 shows acceptable safety and tolerability and at 1400 mg Q3W in patients with ccRCC.
  - Related AEs were G1/2 in severity.
  - No irAEs were reported in ccRCC cohort, although prior immune therapy or counter-selection for patients with past irAE events may have introduced bias.
  - No AEs that led to death or discontinuation.
- Presumptive RP2D of 1400 mg achieves prespecified PK target and fully saturates soluble CD200R1, the PK profile generally supports Q3W dosing, and there was negligible ADA with no adverse impact on exposure nor clinical actiivity.
- Partial response and ongoing treatment duration > 32 weeks for a treatment refractory ccRCC with high CD200 tumor expression (160 CD200 H-score).
- Preliminary baseline tumor analysis suggests that besides CD200 expression, higher vascularization may be associated with benefit from 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. Choueiry F, et al. J Immunother Cancer. 2020;8:e000189; 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., Journal for ImmunoTherapy of Cancer 2023;11:doi: 10.1136/jitc-2023-SITC2023.0619 12. Glatt DM, et al., Journal for ImmunoTherapy of Cancer 2023;11:doi: 10.1136/jitc-2023-SITC2023.0609

DISCLOSURES

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