Clinical pharmacokinetics and peripheral receptor occupancy of OR502, a best-in-class antibody against leukocyte immunoglobulin-like receptor B2 (LILRB2), alone and in combination with cemiplimab

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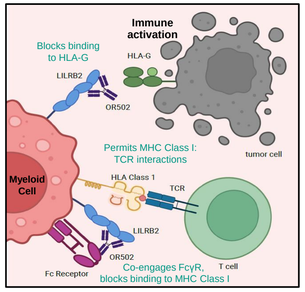
LB299

Background

- OR502 is a humanized IgG1 antibody that binds to LILRB2 and blocks more broadly LILRB2 binding to its ligands, including HLA-A, HLA-B and HLA-G[1]
- Preclinical studies demonstrate that OR502:
  - Reverses and prevents immunosuppressive phenotype of tumor associated macrophages leading to rescue of T cell effector functions[1]
  - Amplifies anti-PD-1 activity[1]
  - Co-engages FcγR to reprogram myeloid cells[1]
  - Induces in vivo anti-tumor activity in a human xenograft melanoma murine model[1]

Mode of action



- This phase 1 study [NCT06090266] was designed to evaluate safety and tolerability of OR502 and select a dose ± cemiplimab for future study
- Safety and early efficacy data have been previously reported[2]
- Here we report pharmacokinetic (PK) and receptor occupancy (RO) data

Demographics and clinical characteristics

Parameter	Mono (n=19)	Combo (n=20)
Median age (range)	62 (47–82)	64 (23–85)
Female (%)	63	50
ECOG PS = 1 (%)	79	80
Median prior systemic regimens (range)	3 (0–11)	3 (0–7)
Most common tumor types (%)		
Sarcoma	37	25
NSCLC	21	15
Colon or CRC	0	20

Methods

- IV OR502 100–1600 mg ± cemiplimab (standard dosing) administered in 21-day (D) cycles (C)
- Monotherapy: 100 mg (n=4), 200 mg (n=2), 400 mg (n=3), 800 mg (n=3), 1600 mg (n=7). Combination with cemiplimab: 100 mg (n=3), 200 mg (n=3), 400 mg (n=4), 800 mg (n=4), 1600 mg (n=6)
- Serial PK sampling during C1 and C3, then pre-dose D1 every other C: PK data analyzed using PKanalix®
- Peripheral RO assessed using flow cytometry, weekly during C1 and C3 and on D1 of C2 and C4
- LILRB2 RO measured before and after OR502 dosing

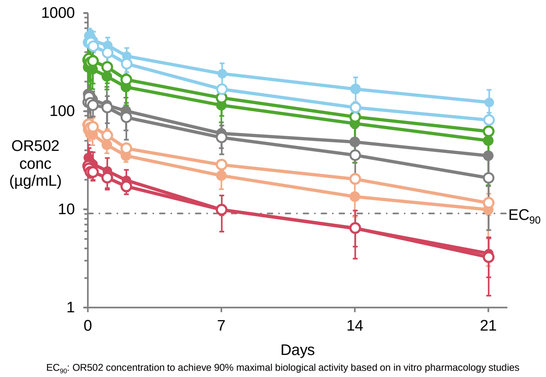
For further details, see poster **CT248**

Clinical results

- OR502 was well tolerated up to highest dose (1600 mg) every 3 weeks[2]
- The only reproducible toxicity was manageable grade 1–2 IRRs[2]
- AE incidence and severity did not increase with dose[2]
- Early efficacy signals with OR502 monotherapy and combination[2]
- 3 PR in PD-(L)1 pretreated mucosal melanoma, NSCLC and dedifferentiated liposarcoma[2]

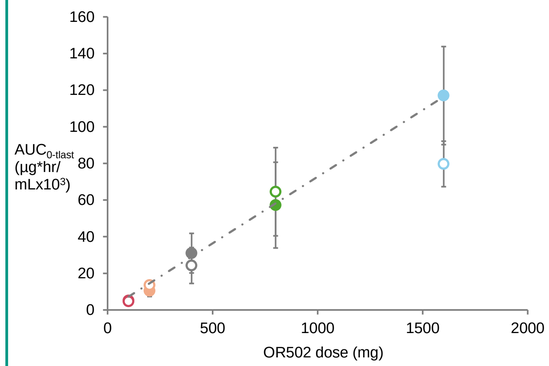
OR502 achieves pharmacologically active serum exposures within dose range tested

Time course of OR502 serum concentration during C1



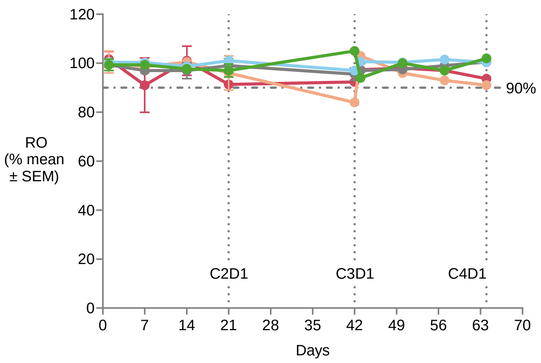
EC_{90}: OR502 concentration to achieve 90% maximal biological activity based on in vitro pharmacology studies

OR502 demonstrated dose-proportional PK

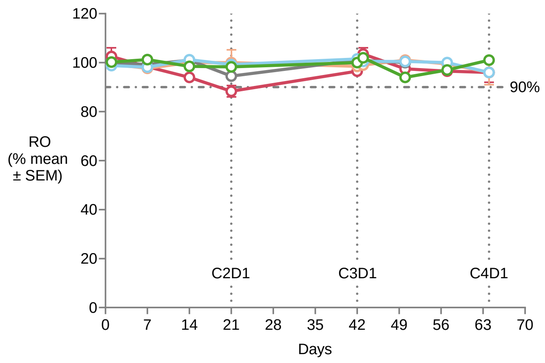


OR502 receptor occupancy consistently high beyond C1

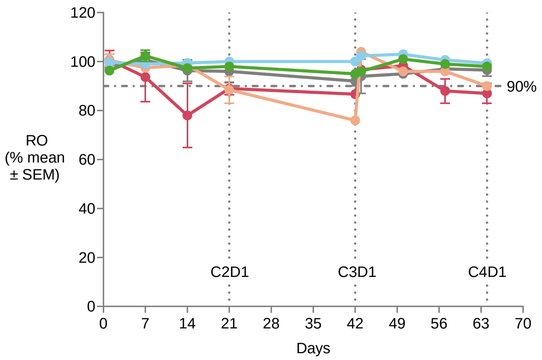
Monotherapy: classical monocytes RO



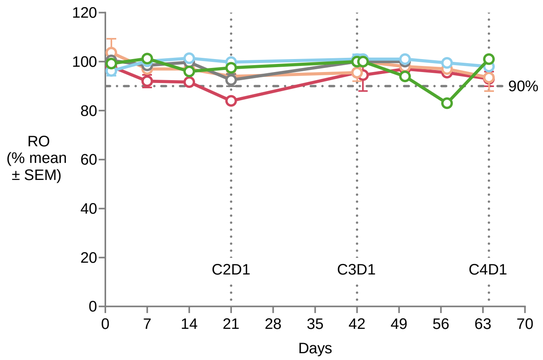
Combination: classical monocytes RO



Monotherapy: neutrophils RO



Combination: neutrophils RO



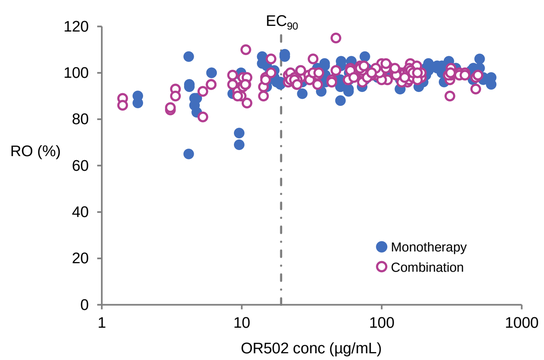
OR502 RO on peripheral classical monocytes (HLA-DR+CD14+CD16-) and neutrophils (HLA-DR- CD11b+CD66b+) from Cycle 1 to Cycle 4 pre-dose. RO measured by flow cytometry using an anti-OR502 (anti-idiotype) fluorochrome- labeled antibody.

OR502 100 mg | OR502 200 mg | OR502 400 mg | OR502 800 mg | OR502 1600 mg | OR502 100 mg + cemiplimab | OR502 200 mg + cemiplimab | OR502 400 mg + cemiplimab | OR502 800 mg + cemiplimab | OR502 1600 mg + cemiplimab

PK and RO results

- Median terminal elimination half-life of OR502 ranges from 7.6 to 15.9 days and appears similar across the dose range for monotherapy and combination
- OR502 trough levels at end of C1 are consistently maintained above in vitro EC_{90} at doses ≥ 400 mg
- OR502 AUC increases in a dose-proportional manner for monotherapy and combination
- Peripheral RO was ≥ 95% on myeloid cells at all times for OR502 doses ≥ 400 mg
- Consistently high RO in classical monocytes, neutrophils and intermediate monocytes (data not shown)

RO saturated for OR502 concentrations above EC_{90} as early as C1



EC_{90}: OR502 concentration to achieve 90% maximal biological activity based on in vitro pharmacology studies

Conclusions

- OR502 showed long half-life and dose-proportional PK
- Cemiplimab does not affect OR502 PK or RO
- Peripheral RO was ≥ 95% on myeloid cells at all times for OR502 doses ≥ 400 mg
- PK and RO data support use of 800 mg as monotherapy or in combination with cemiplimab
- OR502 800 mg confirmed for further study in PD-(L)1-pretreated cutaneous melanoma and NSCLC

Study OR502-101 has been approved by the Salus non-profit Institutional Review Board in Austin, TX. Study OR502-101 is registered as NCT06090266 in www.clinicaltrial.gov **Acknowledgements:** Study OR502-101 is conducted with support from the Cancer Prevention Research Institute of Texas (CPRIT) DP230076. OncoResponse is grateful to the subjects who participated in this study, whose time and dedication is invaluable for the development of OR502 as potential new treatment for advanced cancer. **Author affiliations: 1.** NEXT Oncology Austin, TX, USA. **2.** NEXT Oncology San Antonio, TX, USA. **3.** NEXT Oncology Fairfax, VA, USA. **4.** Bexon Clinical Consulting, Montclair, NJ, USA. **5.** OncoResponse, Inc., Seattle, WA, USA. **6.** NEXT Oncology Dallas, TX, USA. **References: 1.** Bouchlaka M, et al. J Immunother Cancer. 2023;11(Suppl 1):A556. **2.** Sen S, et al. J Immunother Cancer. 2024;12: A1464; plus data on file.