Phase 1 results of OR502, an antibody against leukocyte immunoglobulin-like receptor B2, in subjects with advanced solid cancers

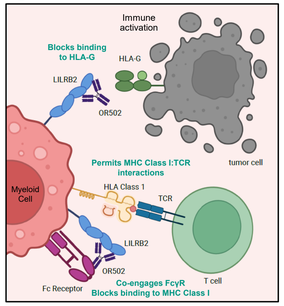
Poster 1464
SITC 2024

Sen S[1], Vandross A[2], Sommerhalder D[3], Salkeni M[4], Puri K[5], Bouchlaka MN[5], Cronier D[6], Sarapa N[6], Skingley L[6], Yefimenko M[6], Bexon A[6]

OR502 is the best-in-class LILRB2 antagonist

- OR502 is a humanized IgG1 antibody that binds to LILRB2 and blocks its binding to HLA-A, HLA-B and HLA-G ligands[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]

Figure 1: OR502 mode of action



Monotherapy dose escalation design

- Phase 1-2 first-in-human study in subjects with advanced solid cancers
- OR502 IV monotherapy dose escalation (100–1600 mg) every 3 weeks

Table 1: Study objectives

Primary	Evaluate safety, tolerability and identify dose for further development
Secondary	Characterize pharmacokinetics, immunogenicity and anti-tumor activity
Exploratory	Evaluate effect on tumor microenvironment Assess association between pharmacodynamic markers and tumor responses

For full study design, see poster #680

- Progressive, histologically confirmed, metastatic or unresectable solid tumors
- One or more prior systemic standard of care (SOC) anti-cancer therapy, or could not tolerate or refused SOC, or no suitable SOC option available
- 19 patients: 100 mg (n=4), 200 mg (n=2), 400 mg (n=3), 800 mg (n=3), 1600 mg (n=7)

A typical phase 1 population with solid tumors

Table 2: Demographics and clinical characteristics (n=19)

Characteristic	n (%)
Median age, years (range)	62 (47–82)
Male	7 (37)
Female	12 (63)
ECOG PS = 0	4 (21)
ECOG PS = 1	15 (79)

Characteristic	n (%)
Median prior systemic anticancer regimens (range)	3 (0–11)
Most common (n > 2) cancer types	
Soft tissue sarcoma	7 (37)
NSCLC	4 (21)
Other	8 (42)

OR502 was well tolerated

- No DLTs, treatment-related deaths, SAEs, or grade ≥ 3 treatment-related AEs
- No significant findings in vital signs, electrocardiogram or laboratory safety test results
- One subject (400 mg cohort) discontinued OR502 due to CTCAE grade 2 pneumonitis associated with grade 2 hypothyroidism
- Infusion-related reactions (IRRs) in 3/19 subjects (15.8%): 1 at 800 mg and 2 at 1600 mg; all grade 1 or 2
- OR502 infusion extended to 60 minutes
- Secondary prophylaxis recommended following a grade 1 or 2 IRR, mandatory for 1600 mg cohort
- No other dose-related safety findings

Table 3: Related AEs in ≥ 10% subjects (n=19)

MedDRA preferred term	CTCAE Grade		Total n (%)
	1–2 n (%)	≥ 3 n (%)	
Any related TEAE	10 (52.6)	0	10 (52.6)
Fatigue	3 (15.8)	0	3 (15.8)
IRR	3 (15.8)	0	3 (15.8)
Nausea	2 (10.5)	0	2 (10.5)

OR502 has single agent anti-tumor activity

- Seventeen subjects (89.5%) were evaluable for efficacy assessment per RECIST 1.1
- One subject with melanoma (200 mg cohort) had a confirmed partial response (cPR) and is still on treatment after 15 doses (Figure 2)
- One subject with NSCLC (800 mg cohort) had a PR but discontinued treatment after 6 doses due to a new intrabronchial lesion (Figure 3)

Table 4: Best objective response per RECIST 1.1 (n=17)

Response	n
Complete response (CR)	0
PR	2
cPR	1
Unconfirmed PR	1

Response	n
Stable disease (SD)	9
Durable SD (≥ Week 12)	7
Best overall response rate	12%
Disease control rate (CR+PR+SD)	65%

Figure 2: cPR in male, 62 yrs, with melanoma liver mets, prior pembro and ipi/nivo

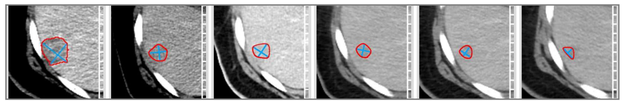
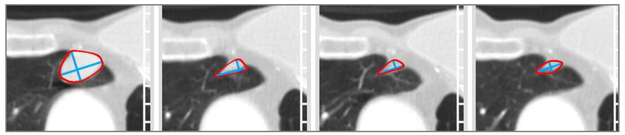


Figure 3: PR in female, 76 yrs, with NSCLC lung mets, prior chemo and durva



Promising tumor growth control at 12 weeks

Figure 4: Change in tumor size in all evaluable subjects (n=17)

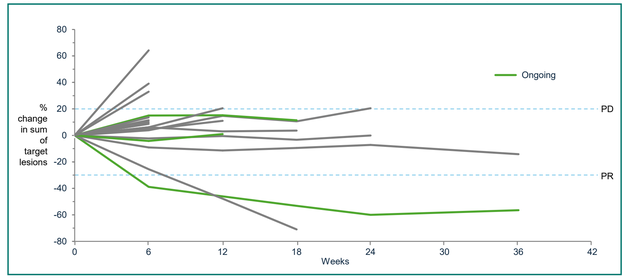
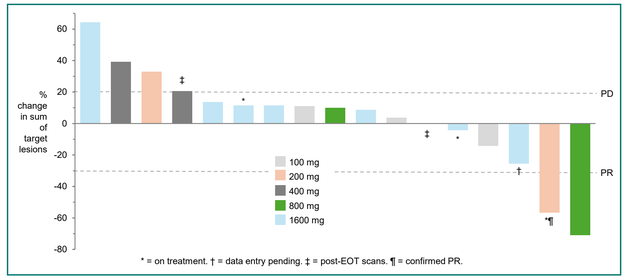
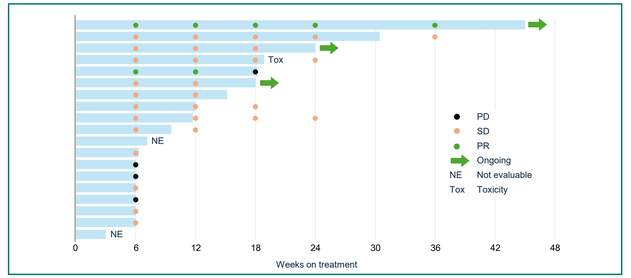


Figure 5: Best response in all evaluable subjects (n=17)



* = on treatment. † = data entry pending. ‡ = post-EOT scans. ¶ = confirmed PR.

Figure 6: Duration of treatment response in all subjects (n=19)

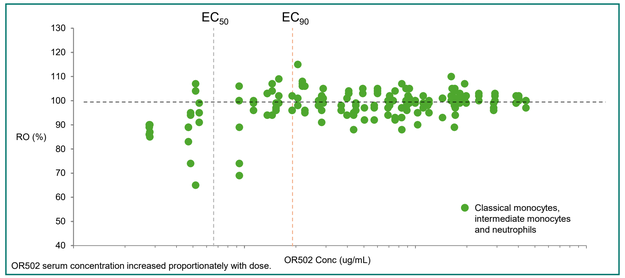


- As of 24 October 2024, 3 patients remain on study treatment
- Reasons for discontinuation were PD (n=15) or toxicity (n=1)

Exposure-RO analysis supports 800 mg dose

- Receptor occupancy (RO) in peripheral myeloid cells achieves sustained and near complete saturation at doses of≥ 400 mg
- Preliminary data suggest PK is dose proportional with $t_{1/2}$ 10–14 days
- Dose of 800 mg predicted to exceed EC_{90} at C_{min} to ensure anti-tumor efficacy

Figure 7: Relationship of LILRB2 RO to OR502 exposure for peripheral myeloid cells



OR502 serum concentration increased proportionately with dose.

Conclusions: OR502 efficacy demonstrated with no safety concerns

- OR502 was well tolerated up to highest dose (1600 mg) every 3 weeks
- The only reproducible toxicity was manageable grade 1-2 IRRs
- AE incidence and severity did not increase with dose
- Early efficacy signals with OR502 monotherapy
  - 2 PR and 9 SD for a disease control rate of 65%
  - responses in PD(L)-1 pretreated mucosal melanoma and NSCLC
- Near complete, sustained receptor occupancy at doses ≥ 400 mg
- OR502 800 mg is being evaluated in mini-expansion cohorts of patients previously exposed to PD(L)-1 for ≥ 12 weeks
  - cutaneous melanoma (monotherapy)
  - NSCLC (combination with cemiplimab)

Study OR502-101 has been approved by the Salus non-profit Institutional Review Board in Austin, TX. Study OR502-101 is registered as NCT06090266 on 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 Dallas, TX, USA. 2. NEXT Oncology Austin, TX, USA. 3. NEXT Oncology San Antonio, TX, USA. 4. NEXT Oncology Fairfax, VA, USA. 5. OncoResponse, Inc., Seattle, WA, USA. 6. Bexon Clinical Consulting, Montclair, NJ, USA. **References:** 1. Bouchlaka M, et al. J Immunother Cancer 2023; 11(Suppl 1): A556.