Phase 2 expansions of OR502, an antibody targeting leukocyte immunoglobulin-like receptor B2 (LILRB2) ± cemiplimab in patients with advanced solid tumors

Poster 315b
Abst. TPS2669

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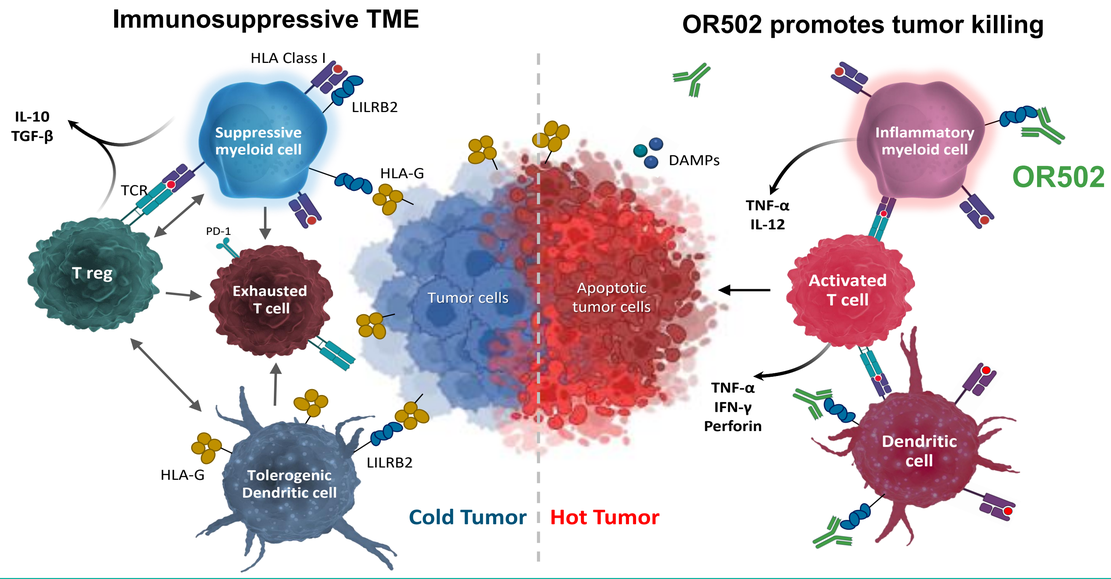
Myeloid cell LILRB2 binding to HLA-class I proteins is associated with poor outcomes in multiple cancers[1-4]

- OR502 is a humanized immunoglobulin G1 antibody that blocks LILRB2 binding to HLA-class I proteins and reprograms myeloid cells[5]
- Targeting immunosuppression and improving T cell-mediated responses in the TME makes OR502 and checkpoint inhibitors a rational combination (Fig. 1)

Fig 1: OR502 co-engages FcγR to reprogram myeloid cells



- This ongoing first-in-human, phase 1-2 study of OR502 ± cemiplimab (NCT06090266) is supported by robust preclinical data:
  - OR502 reduced and prevented new and existing TAMs from developing immunosuppressive phenotypes[5]
  - OR502 + anti-PD-1 increased activity in M2c/T-cell coculture[5]

Methods

- Dose escalation (Parts A1 and A2) enrolled 39 subjects with advanced solid tumors
- OR502 100–1600 mg was administered Q3W ± standard dose cemiplimab (350 mg), using a modified toxicity probability interval-2 design

Parts A1 and A2 objectives

Primary	• Evaluate safety, tolerability and identify OR502 dose for further development ± cemiplimab
Secondary	• Characterize PK, immunogenicity and anti-tumor activity
Exploratory	• Assess association between PD markers and tumor responses • Evaluate impact on TME

- As Part A dose escalation completed, it was clear adaptations were needed to meet the FDA's Project Optimus requirements:
  - demonstration of objective efficacy prior to exploring dose-response in indication(s) exhibiting efficacy
  - identification of minimal effective dose[6]
- In conjunction with Safety Committee oversight, the protocol's adaptive elements facilitated the necessary modifications without protocol amendment

Design adaptations were supported by PK/PD and early efficacy signals

- PK/PD and safety support an OR502 800 mg dose
- 3 PRs in dose escalation: melanoma, NSCLC and liposarcoma[7]
  - 2 confirmed, 1 unconfirmed per RECIST v 1.1

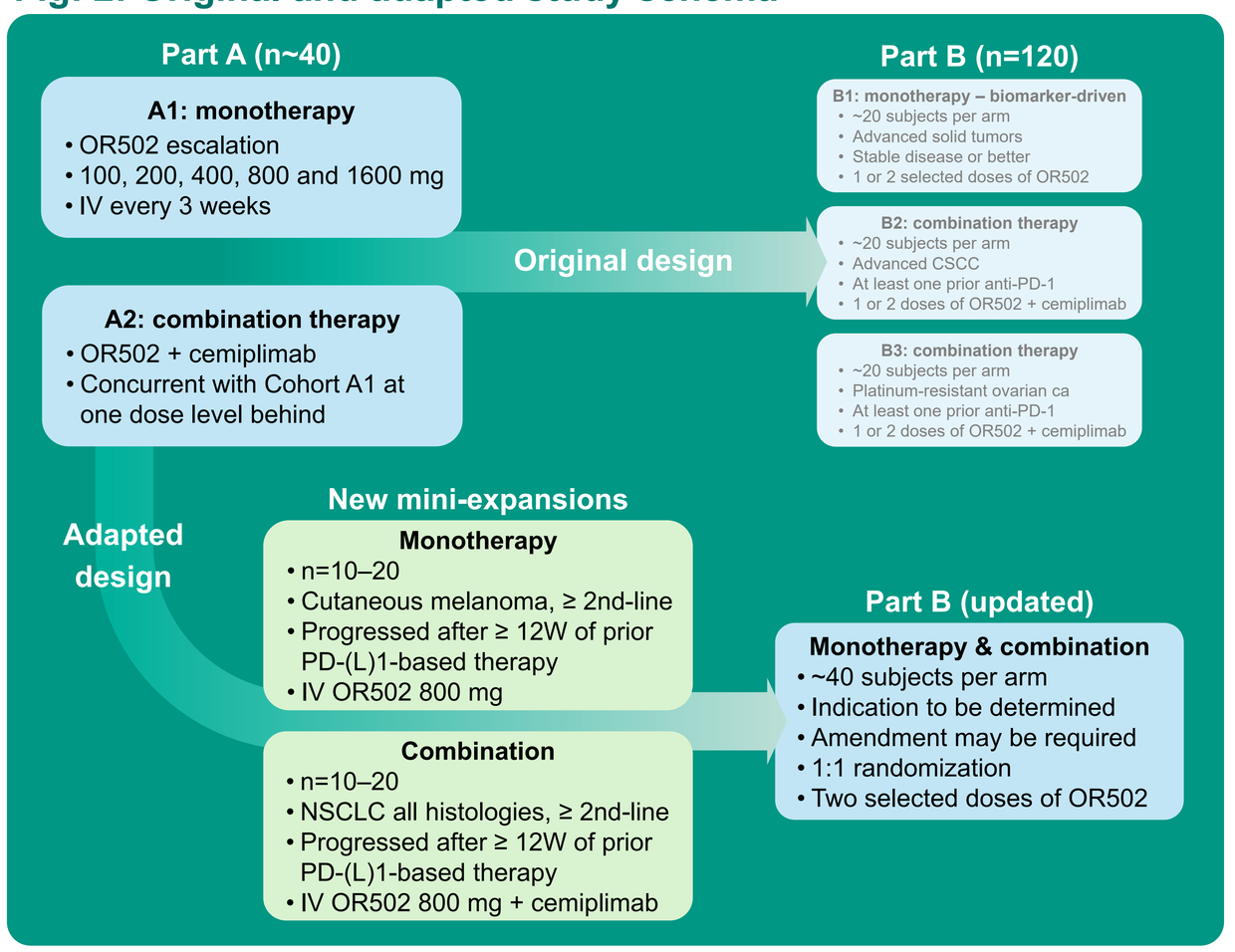
For further details, see **Poster 171**

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.clinicaltrials.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, Fairfax, VA, USA. **2.** NEXT Oncology, San Antonio, TX, USA. **3.** NEXT Oncology, Austin, TX, USA. **4.** OncoResponse, Inc., Seattle, WA, USA. **5.** Bexon Clinical Consulting, Montclair, NJ, USA. **6.** NEXT Oncology, Dallas, TX, USA. **References: 1.** Chen HM, et al. J Clin Invest. 2018;128(12):5647-62. **2.** Cai Z, et al. Int J Oncol. 2019;54(6):1943-54. **3.** Li Q, et al. Biomark Res. 2020;8:11. **4.** Lin A, Yan WH. Front Immunol. 2021;12:698677. **5.** Bouchlaka M, et al. J Immunother Cancer. 2023;11(Suppl 1):A556. **6.** Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases. Draft FDA Guidance for Industry, 2023. **7.** ASCO 2025 Poster 171. **Abbreviations:** DAMPs: damage-associated molecular patterns. HLA: human leukocyte antigen. IFN: interferon. IL: interleukin. IV: intravenous. LILRB2: leukocyte immunoglobulin-like receptor B2. mTPI-2: modified toxicity probability interval. NSCLC: non-small cell lung cancer. PD-(L)1: programmed cell death-ligand 1 / protein 1. PD: pharmacodynamics. PK: pharmacokinetics. PR: partial response. Q3W: every 3 weeks. RECIST: Response Evaluation Criteria in Solid Tumors. RO: receptor occupancy. T reg: regulatory T cell. TAM: tumor-associated macrophage TCR: T cell receptor. TGF: transforming growth factor. TME: tumor microenvironment. TNF: tumor necrosis factor. W: weeks.

Implementing adaptive elements

- We adapted the design to explore the efficacy signals in subjects with melanoma and NSCLC
- Based on efficacy signals and excellent safety, PK and PD results, we selected OR502 800 mg Q3W
- Two new mini-expansion cohorts are recruiting 10–20 subjects each (Fig 2.)
  - primary objective: confirm efficacy in chosen indications
  - secondary objectives: safety, PK and RO
- Mini-expansion cohort sizes were chosen to exclude a response rate of ~10%, with a target of ~35%
- If < 2 responses occur in the first 10 subjects, the cohort will be discontinued

Fig: 2: Original and adapted study schema



Protocol adaptive elements

Element	When applicable
mTPI-2 design permits escalation cohorts from 2–9 subjects	**Part A**
Ability to add expansion cohorts of specific tumor histology and/or biomarkers based on efficacy	**Part B**
Choice of 2 expansion doses: based on all available data with non-overlapping PK between doses	**Part B**
Evaluation of dosing regimens other than Q3W	Part A
Backfill of cleared dose cohorts to support dose selection	Part A
Expansion cohorts may run in parallel or sequentially	Part B
Requirement for biopsies may be waived by Sponsor	Expansion B1
Adjustment of PK sampling, including extra samples (not to exceed specified total blood volume/cycle)	Parts A and B

Shaded cells indicate adaptive elements implemented. Part A = dose escalation. Part B = dose expansion.

Summary

- Adaptive elements are key for modern phase 1 trials
- Flexibility (with oversight) can reduce delay and increase phase 1–2 efficiency
- Our adaptive approach is designed to satisfy Project Optimus and confirm:
  - objective efficacy
  - effective doses prior to two-dose expansion
  - the minimum effective dose

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