Using adaptive design elements to respond to regulatory changes and emerging data in a phase 1–2 study of OR502 - a best-in-class antibody targeting leukocyte immunoglobulin-like receptor B2 (LILRB2)

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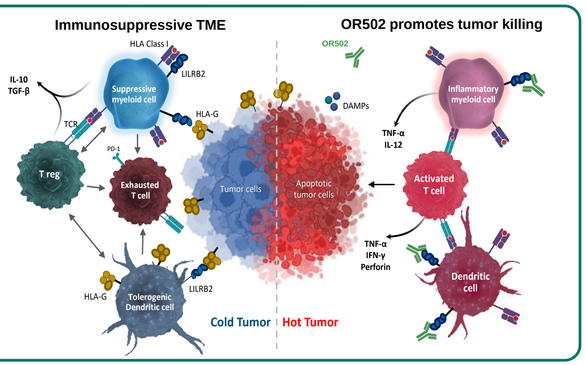
Background: OR502 novel MoA

- LILRB2 expression on myeloid cells in the TME, or expression of its ligand (HLA-G) by tumors, correlates with poor survival in multiple cancers[1-4]
- OR502 is the best-in-class LILRB2 antagonist antibody that co-engages FcγR to reprogram myeloid cells[5]
- Strong preclinical data supported first-in-human trial:
  - OR502 reduces and prevents immunosuppressive phenotype of existing and new TAMs[5]
  - OR502 + anti-PD-1 amplifies activity in M2c/T-cell coculture[5]

OR502 prevents and reverses immunosuppressive phenotype of myeloid cells



Design adaptations supported by early efficacy

- PK/PD and safety support 800 mg dose
- Efficacy signals observed in dose escalation (NSCLC and melanoma)
- 3 partial responses per RECIST v 1.1 (2 confirmed, 1 unconfirmed)

For further details, see poster **LB299**

Part A objectives

Primary
- Evaluate safety, tolerability and identify 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

Methods: innovative design to meet Project Optimus requirements

Rationale for design adaptations

- Provide flexibility to adapt to changing standards of care and developments in oncology
- Project Optimus
  - FDA guidance for dose optimization of cancer drugs
  - a new challenge for phase 1-2 study design
  - requires demonstration of dose-response
  - identification of minimal effective dose[6]
- Our protocol's adaptive elements with Safety Committee oversight allowed for design modification without amendments

Implementing adaptive elements

- Demonstration of objective efficacy is needed prior to exploring dose-response in indication(s) exhibiting efficacy
- Despite efficacy signals in Part A, we needed confirmation of objective efficacy
- We added new mini expansions to confirm efficacy signals
- Two new mini-expansion cohorts are recruiting (see figure):
  - primary objective: confirm efficacy in chosen indications
  - secondary objectives: safety, PK and RO

Original study design (NCT06090266)

Part A (n~40)

A1: monotherapy
- OR502 escalation
- 100, 200, 400, 800 and 1600 mg
- IV every 3 weeks

A2: combination therapy
- OR502 + cemiplimab
- Concurrent with Cohort A1 at one dose level behind

Part B (n=120)

B1: monotherapy – biomarker-driven cohort
- ~20 subjects per arm
- Advanced solid tumors
- Stable disease or better
- 1 or 2 selected doses of OR502

B2: combination therapy
- ~20 subjects per arm
- Advanced CSCC
- At least one prior anti-PD-1
- 1 or 2 doses of OR502 + cemiplimab

B3: combination therapy
- ~20 subjects per arm
- Platinum-resistant ovarian ca
- At least one prior anti-PD-1
- 1 or 2 doses of OR502 + cemiplimab

Adapted design

New mini-expansions

Monotherapy
- n=10–20
- Cutaneous melanoma, ≥ 2nd-line
- Progressed after ≥ 12W of prior PD-(L)1-based therapy
- IV OR502 800 mg

Combination
- n=10–20
- NSCLC all histologies, ≥ 2nd-line
- Progressed after ≥ 12W of prior PD-(L)1-based therapy
- IV OR502 800 mg + cemiplimab

Part B (updated)

Monotherapy & combination
- ~40 subjects per arm
- Indication to be determined
- Amendment may be required
- 1:1 randomization
- Two selected doses of OR502

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.

- Adaptive elements are a key part of modern phase 1 trials
- Permit flexibility (with oversight) to avoid delay and execute rapid phase 1–2 development
- Our approach will confirm:
  - objective efficacy
  - effective doses prior to two-dose expansion
  - minimum effective dose

  …to meet requirements of Project Optimus

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.
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