Use of adaptive elements in a Phase 1-2 study of OR502, a novel antibody against leukocyte immunoglobulin-like receptor B2 in response to evolving Phase 1 data and a changing regulatory environment

Poster 680
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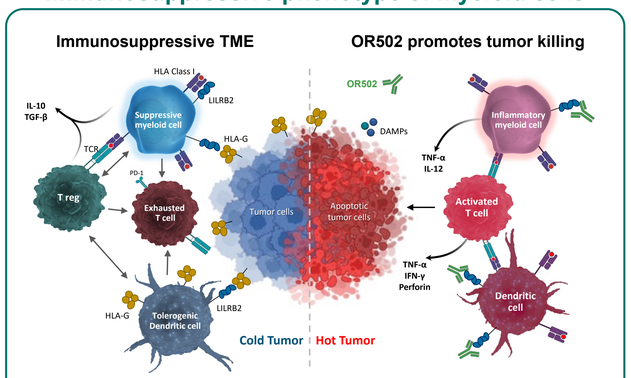
Background: a novel immune MoA

- LILRB2 is an inhibitory receptor that binds to HLA class I proteins[1]
- 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
  - co-engages FcγR to reprogram myeloid cells[5]
- Strong preclinical data supported first-in-human trial[5]

OR502 prevents and reverses immunosuppressive phenotype of myeloid cells



Early efficacy supports design adaptations

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

For further details, see poster **#1464**

Methods: innovative trial design to address FDA's Project Optimus

Rationale for design adaptations

- Allows flexibility to address changes in oncology development and evolving standards of care
- FDA's guidance on dose optimization for cancer drugs requires
  - dose-response demonstration
  - identification of minimal effective dose prior to later-phase trials[6]
- This presents a new challenge for the design of Phase 1-2 studies
- OR502-101 was designed to meet requirements of Project Optimus

Implementing adaptive elements

- As Part A concluded, despite efficacy signals, it was clear Part B needed expanding
- FDA requires that objective efficacy be demonstrated before exploring dose-response in the indication(s) exhibiting efficacy
- Protocol's adaptive elements allow
  - Design modification without amendment with Safety Committee oversight
  - Expansions at different doses, providing valuable additional PK data

Original study design (NCT06090266)

Part A (n~40)

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

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

Dose selection

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 mini-expansion study design

Part A

New mini-expansions

Monotherapy
- n=10–20
- Cutaneous melanoma, ≥ 2nd-line
- Progressed after ≥ 12W of prior PD-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 OR502 doses

Protocol adaptive elements

Element	When applicable
Evaluation of dosing regimens other than Q3W	Part A
mTPI-2 design permits escalation cohorts from 2–9 subjects	Part A
Backfill of cleared dose cohorts to support dose selection	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
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.

Part A objectives

Primary
- Evaluate safety, tolerability and identify dose for further development in monotherapy and in combination with cemiplimab

Secondary
- Characterize PK, immunogenicity and anti-tumor activity

Exploratory
- Evaluate the effect on the TME
- Assess association between PD markers and tumor responses

- Adaptive elements are an important design feature of the modern Phase 1 trial
- Permits flexibility (with oversight) to execute efficient Phase 1-2 development without undue delays
- Our approach will confirm objective efficacy and highest effective dose prior to two-dose expansion to identify minimum effective dose and meet the FDA's requirements
- By embracing adaptive elements, the development of OR502 has been particularly rapid

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