REVERT study: a phase Ib/IIa study to assess the efficacy of the first-in-class RIPK2 inhibitor OPM-101 in patients with advanced melanoma resistant to anti-PD-1-based regimens

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Study sponsored by OPM

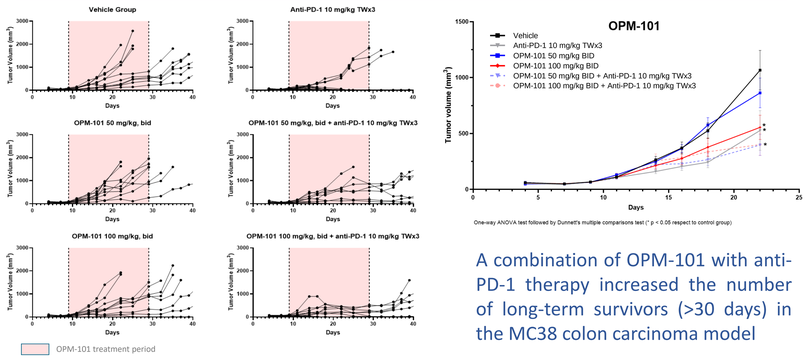
Introduction

Melanoma is the most aggressive form of skin cancer, with a high risk of metastasis. Immune checkpoint inhibitors (ICIs) are standard of care in advanced melanoma regardless of mutational status, promoting durable remissions. However, over 50% of patients develop resistance to ICIs. RIPK2, a key regulator of innate immunity and inflammation via NF-κB activation, is overexpressed in several cancers and correlates in melanoma with T-cell dysfunction, reduced ICI benefit, and shorter Progression-Free Survival (Song J, Mol Med, 2022).

OPM-101 is a first-in-class, selective, and potent small-molecule RIPK2 inhibitor. Previously, a First-in-Human (FIH), double-blind, placebo-controlled Phase I study in healthy volunteers demonstrated a favourable safety profile, predictable pharmacokinetics (PK), and robust target engagement (TE).

Background information

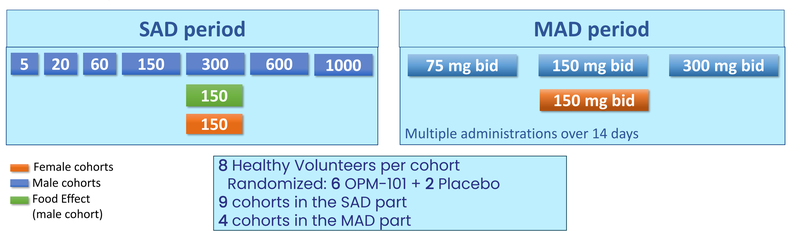
RIPK2 inhibition counteracts acquired resistance to anti-PD-1 therapy



A combination of OPM-101 with anti-PD-1 therapy increased the number of long-term survivors (>30 days) in the MC38 colon carcinoma model

Phase I Study in Healthy Volunteers

A double-blind randomized FIH phase I clinical trial, OPM-101 (or placebo) was administered in male and female healthy volunteers. DRC convened at the end of each cohort to decide on the study continuation and on dose to be used for the next cohort.



8 Healthy Volunteers per cohort
Randomized: 6 OPM-101 + 2 Placebo
9 cohorts in the SAD part
4 cohorts in the MAD part

3 Objectives

1. Safety

15 OPM-101-related TEAEs in 12 subjects (15%)
- 12 (80%) were **mild**
- 3 (20%) were **moderate**
- No severe TEAE

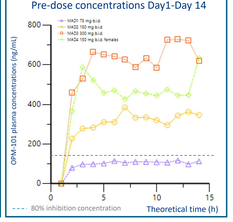
1 TEAE leading to treatment interruption

No SAE

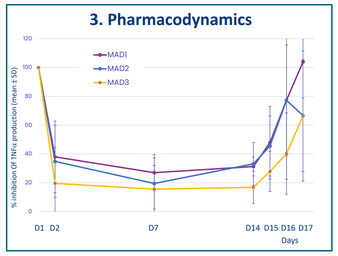
No early study withdrawal

2. Pharmacokinetics

Pre-dose concentrations Day1-Day 14



3. Pharmacodynamics



OPM-101 is well tolerated, with good PK properties and significant TE

FIH: First-in-Human. **DRC**: Data Review Committee. **SAD**: Single Ascending Dose. **MAD**: Multiple Ascending Dose. **PK**: Pharmacokinetics. **TE**: Target Engagement. **PD**: Pharmacodynamics. **TEAE**: Treatment-Emergent Adverse Event. **SAE**: Serious Adverse Event.

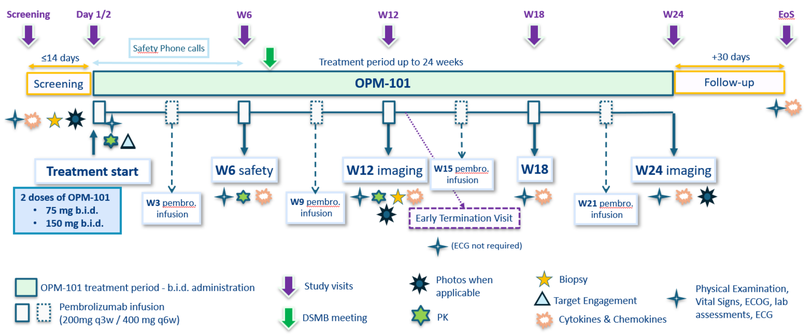
General methodology

REVERT is a Phase Ib/IIa study including a dose escalation part (Phase Ib on 6-18 patients) and an extension part (Phase IIa with 35 additional patients).

Both parts will be open-label, multicentre studies of OPM-101 combined with the anti-PD-1 antibody pembrolizumab per standard of care in patients with metastatic melanoma resistant to an anti-PD-1-based treatment, as defined by the Society for Immunotherapy of Cancer (SITC) criteria. The objective of the study is to assess whether the addition of OPM-101 will resensitise the tumour to anti-PD-1 treatment.

REVERT Phase Ib Study Design

Phase Ib (3+3 design)



Phase Ib objectives and endpoints

Primary objective:

Recommended Phase 2 Dose (RP2D) of OPM-101 to be used in combination with the standard dose of pembrolizumab based on safety evaluation.

Secondary objectives:

Objective Response Rate (CR + PR) per RECIST v1.1 criteria at Week 12 and Week 24.
Disease Control Rate (CR + PR + Stable Disease [SD]) per RECIST v1.1 criteria at Week 12 and Week 24.
Best change of **tumor size**.

Exploratory objectives

PK & **PD** parameters.
Tumor (n=48 markers) and **circulating** (n=30 markers) **biomarkers**, including immune checkpoint and exhaustion markers, pro-inflammatory and regulatory cytokines, chemokines, cytotoxic effector molecules, and vascular and angiogenic factors.

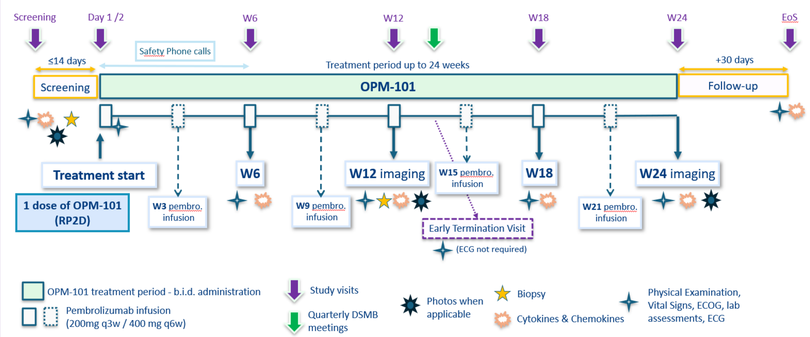
Study population

Adult patients with

- Histologically confirmed **unresectable or metastatic stage III or IV melanoma**.
- ≥1 measurable lesion on a CT or MRI scan per RECIST v1.1 criteria
- Documented **Progressive Disease with an anti-PD-1-based treatment,** either as monotherapy or in combination (excluding combination with an anti-LAG-3 drug).
- ECOG PS 0 or 1
- A fresh biopsy at baseline and after 12 weeks of treatment (Phase Ib only)

REVERT Phase IIa Study Design

Phase IIa Cohort expansion



Phase IIa objectives and endpoints

Primary objective:

DCR at Week 12 evaluated using RECIST v1.1 criteria.

Secondary objectives:

ORR at Week 12 and week 24 evaluated using RECIST v1.1 criteria.
DCR at Week 24 evaluated using RECIST v1.1 criteria.
Best change of **tumor size.**
Determine the incidence and severity of **adverse events** and serious adverse events.

Exploratory objectives

Tumor (n=48 markers) and **circulating** (n=30 markers) **biomarkers**, including immune checkpoint and exhaustion markers, pro-inflammatory and regulatory cytokines, chemokines, cytotoxic effector molecules, and vascular and angiogenic factors.

Conclusion

The FIH Phase I study unveiled OPM-101 as a safe "first-in-class" RIPK2 inhibitor with predictable PK and robust PD properties.

The Phase Ib/IIa REVERT study explores whether OPM-101, by targeting RIPK2-mediated resistance, can restore anti-PD-1 sensitivity and offer a new therapeutic avenue for patients with advanced melanoma.