INFLECTION-003: A Phase 2 study investigating the activity of neoadjuvant PRTX007, a novel orally administered TLR7 agonist prodrug, combined with pembrolizumab in participants with stage III melanoma

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Background

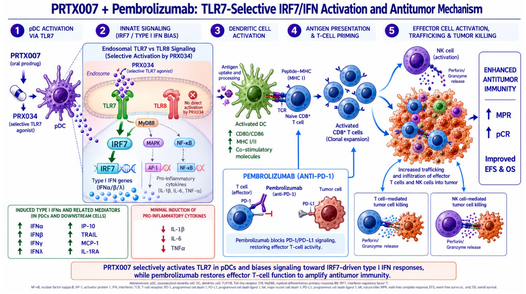
- Neoadjuvant PD-1 blockade improves event-free survival compared with adjuvant therapy alone in resectable stage III melanoma[1]
- Interferon-associated signatures correlate with response to neoadjuvant immunotherapy in stage III melanoma[2]
- However, many patients do not achieve a pathologic complete response (pCR), which is associated with improved long-term survival
- Intensifying neoadjuvant immunotherapy (e.g., adding ipilimumab or high-dose IFN-α2b) can increase pathologic response rates, but is accompanied by substantial grade 3/4 toxicity[3,4]
- **Goal: enhance pathologic responses to neoadjuvant PD-1 blockade without increasing grade 3/4 toxicity**

PRTX007: Oral TLR7/IRF7 Agonist Prodrug

- **PRTX007** is an orally administered selective TLR7/IRF7 agonist (prodrug of PRX034)
- **PRTX007** has demonstrated a favorable safety and tolerability profile in two Phase 1 studies in 116 healthy volunteers.
- **PRX007** activates plasmacytoid dendritic cells (pDCs), central regulators of antitumor immunity through type I interferon production and promotion of innate and adaptive immune responses[5]
- **PRX007** was designed to preferentially activate IRF7 and downstream IFN response genes with limited NFkappaB mediated proinflammatory cytokines (IL-6, TNF)

PRXT007 Mechanism of Action

Figure 1. PRTX007 + pembrolizumab: Mechanism of Action with activation of Innate and Adaptive Immunity



Phase I Clinical Trials with PRTX007

- Two Phase 1 studies in 116 healthy volunteers: PRTX007-001 (SAD 50–800 mg; MAD 300–750 mg QOD) and PRTX007-002 (750 mg, intermittent 3-days-on/4-days-off) have been completed[6,7]
- No serious adverse events were reported. Robust, dose-dependent activation of interferon-regulated cytokine and gene-expression pathways was observed with minimal induction of IL-1β, IL-6, and TNF-α.
- Dose-proportional PRX034 exposure without accumulation on repeated dosing [6.] Three healthy volunteers at 750mg dose level elected to discontinue due to IFN related AE including fevers, chills, malaise.
- **Systemic CD8+ T-cell and NK-cell activation, 750-mg MAD cohort (n=8), baseline → end of dosing** [6]
  - CD38+ (activated) CD8+ T cells: **11.8% → 21.9%;** Ki67+ (proliferating) CD8+ T cells: **1.1% → 9.8%**
  - CD38+ (activated) NK cells: **59.4% → 80.0%;** Ki67+ (proliferating) NK cells: **3.6% → 10.3%**
- **Robust induction of plasma IFNα and interferon-response genes (IP-10, MCP-1, IL-1RA). Coordinated induction of IRF7, TLR7, IRF5, CCL2, and CXCL10 transcripts in circulating immune cells.** Limited induction of pro-inflammatory cytokines (IL-6, TNFα)

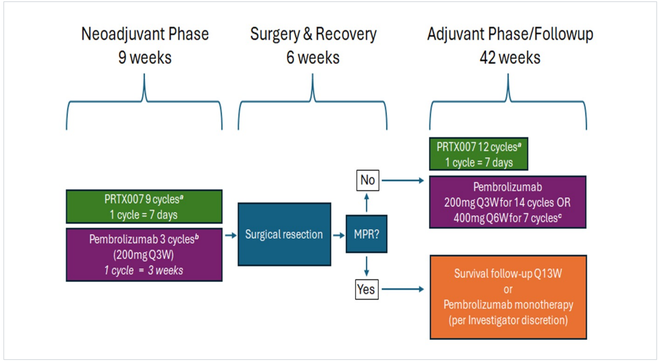
Phase 2 Study Rationale and Hypothesis

Rationale: Preclinical studies combining our TLR7 agonist with anti-PD-1 immunotherapy have demonstrated increased immune cell infiltration and enhanced tumor control. Phase 1 trials with PRTX007 have demonstrated a favorable safety and tolerability profile with robust activation of type I interferon–associated responses.

Hypothesis: Activation of type I interferon–associated immune pathways by oral PRTX007 will augment anti-PD-1 mediated antitumor immunity and improve pathologic response rates in resectable stage III melanoma while maintaining a favorable safety profile.

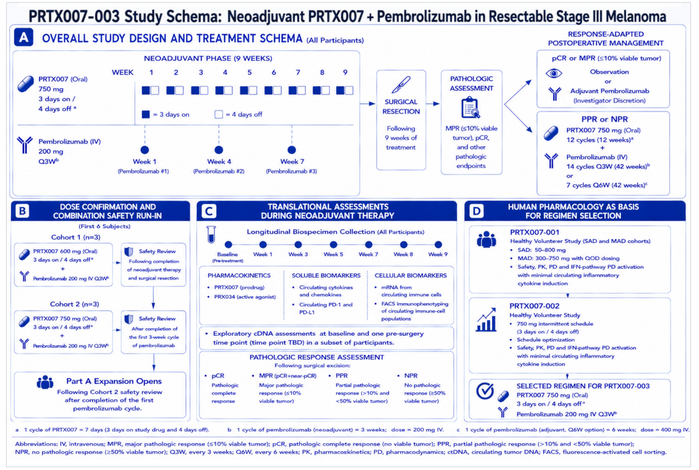
Phase 2 Clinical Trial - INFLECTION-003

Figure 2. PRTX007 + pembrolizumab: Study Schema



Detailed Phase 2 Study Design

Figure 3. Detailed Study Design and Assessments



Participants receive oral PRTX007 on a 3-days-on/4-days-off schedule for 9 weeks with pembrolizumab 200 mg IV every 3 weeks for 3 doses before surgery. Postoperative management is determined by pathologic response.

- Phase 2, multicenter, open-label, single-arm study (NCT07565285) in Australia; approximately **48 participants** with resectable stage III melanoma
- **Neoadjuvant (9 weeks):** PRTX007 750 mg orally, 3 days on/4 days off, plus pembrolizumab 200 mg IV Q3W × 3 (weeks 1, 4, 7), then surgical resection
- **Part A:** 3+3 dose-confirmation and combination safety run-in (Cohort 1: PRTX007 600 mg; Cohort 2: 750 mg; each with pembrolizumab), followed by expansion to n=24
- **Part B:** an additional 24 participants if sufficient activity is observed in Part A

Immune Corelates, Assessments, and Adjuvant Management

Longitudinal blood sampling during neoadjuvant therapy: **baseline and weeks 1, 3, 5, 7, 8, and 9**

Pharmacokinetics	Soluble biomarkers	Cellular biomarkers
PRTX007 (prodrug) PRX034 (active agonist)	Circulating cytokines and chemokines Circulating PD-1 and PD-L1	mRNA from circulating immune cells Flow immunophenotyping of immune-cell populations

Exploratory ctDNA assessment at baseline and one pre-surgery time point in a subset of participants

Response-adapted postoperative management

Response	Viable tumor	Postoperative plan
pCR	None	Observation, or adjuvant pembrolizumab at investigator discretion
MPR (pCR + near-pCR)	≤10%	
PPR	>10% and <50%	PRTX007 750 mg × 12 weeks + pembrolizumab 200 mg Q3W × 14 or 400 mg Q6W × 7 (42 weeks)
NPR	≥50%	

Endpoints

Primary	Major pathologic response (MPR) rate
Secondary	Safety and tolerability · pCR rate · event-free survival · overall survival · pharmacokinetics · pharmacodynamic biomarkers
Exploratory	Longitudinal systemic immune activation · circulating immune-cell populations · tumor-associated biomarkers

Study Status

- Open and Enrolling
- Approved by Bellberry HREC (2026-03-430) and Hunter New England Local Health District (2026/ETH00598)

Conclusions

- INFLECTION-003 will determine whether adding neoadjuvant PRTX007 to Pembrolizumab increases the major pathologic response rate in patients with resectable stage III melanoma.
- Dose, schedule, and combination strategy were informed by prior Phase 1 human pharmacodynamic studies demonstrating activation of type I interferon–associated responses and systemic immune activation
- The response-adapted design reserves adjuvant PRTX007 + pembrolizumab for participants without a major pathologic response
- If positive this combination could be expanded to multiple other cancer types

References

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Acknowledgements & Disclosures

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