# A biomarker guided Bayesian response-adaptive phase II trial for metastatic melanoma: The Personalized Immunotherapy Platform (PIP)-Trial design

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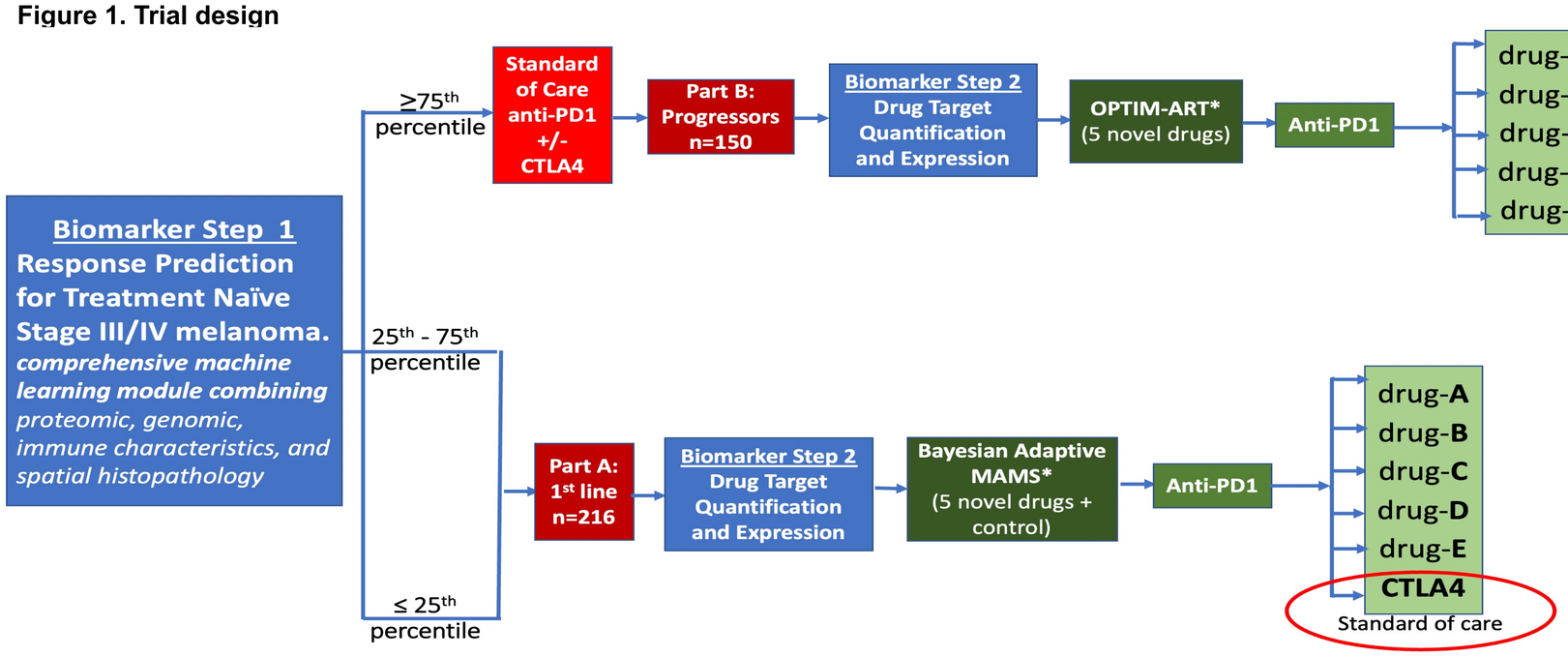
## Background

- **Anti-PD1 based immunotherapy** has **revolutionized** cancer treatment in recent years. These drugs have been approved for many cancer types, and are now a standard front-line treatment for metastatic melanoma, which has the highest response rate of any cancer type. Despite this, approximately half of metastatic melanoma patients (pts) fail to respond to therapy.
- It is therefore critical to **predict resistance** to current treatment and to **identify alternative** effective drug therapy options in order to improve survival, decrease the use of futile toxic therapies, and decrease health costs.

## Study Design

**Figure 1. Trial design**




***MAMS:** Multi-Arm Multi-Stage

**OPTIM-ART:** **O**pen **P**latform **T**rial **I**nvestigating **M**ultiple compounds—**A**daptive **R**andomized design with **T**reatment **S**election design

### Sample size justification

- With **216** pts, **Part A** has **>85% power** to detect a 30% absolute improvement in ORR with respect to control – Table above.
- With a maximum of **150** pts, **Part B** was able to select two promising treatments in the expansion phase and formally test their efficacy against a minimum ORR of 25% at **80% power**.

| Scenarios | Probability of declaring a treatment effective | | | | | Average sample size per arm | | | | | | Expected trial sample size |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Arm A | Arm B | Arm C | Arm D | Arm E | Control | Arm A | Arm B | Arm C | Arm D | Arm E | |
| 1 | 0.05 | 0.04 | 0.05 | 0.04 | 0.04 | 46 | 29 | 28 | 29 | 29 | 29 | 190 |
| 2 | 0.05 | 0.05 | 0.24 | 0.58 | 0.91 | 48 | 25 | 25 | 33 | 40 | 45 | 216 |
| 3 | 0.04 | 0.04 | 0.04 | 0.90 | 0.92 | 49 | 26 | 25 | 25 | 45 | 46 | 216 |
| 4 | 0.21 | 0.21 | 0.87 | 0.85 | 0.86 | 42 | 29 | 29 | 38 | 39 | 39 | 216 |

## Study Objectives

**Primary Objectives:** To assess **RECIST objective response rate (ORR)** to 5 novel anti-PD-1 drug combinations as first and subsequent line therapy.

**Primary Outcomes:** 6-month RECIST objective response rate.

**Secondary outcomes include:** PFS, OS, ORR, Safety and QOL.

## Outcomes & Significance

- ✓ This response-adaptive study design will likely become the standard for clinical trials of novel drugs, aiming to rapidly assess drug activity in the most 'at-need' cancer populations.
- ✓ Establishing infrastructure for biomarker driven selection of drug therapy (standard or novel trials) is a critical step for the future of cancer management

The **PIP-Trial** is an investigator initiated, multi-centre clinical trial that consists of 3 phases:

1) **Biomarker-driven** treatment selection phase (*using a nomogram to predict pt's likelihood of response to standard immunotherapy based on a **comprehensive machine learning module** that incorporates detailed proteomic, genomic, immune characteristics, and spatial histopathology*). Patients will be classified in **responder** or **resistant** to either anti-PD-1 alone or combined with ipilimumab. **i) Predicted responders** will (>75th percentile) will receive standard checkpoint inhibitor therapy (**Pragmatic phase + Part B**); and **ii) Predicted resistants** will be randomized in an Adaptive Design with 5 arm (4 novel agents + standard therapy) (**Part A**).
2) **Part A** is a **Bayesian Adaptive MAMS** design using response adaptive randomisation after a burn-in period where pts are randomised to the existing arms with equal probability. From then on, interim analyses will be carried out with the objective to either drop poorly performing arms or continue.
3) **Part-B** is an **OPTIM-ART** that combine a selection and an expansion phase to identify best novel agent(s) as second-line therapy.

The operational characteristics of the design were investigated through simulations considering 4 plausible scenarios with 40% ORR in the control arm, a maximum absolute ORR improvement for a poor novel drug is +10% and the minimum absolute ORR for an effective novel drug is 20%. **All simulations were conducted using the upcoming R package BATS**

## Key Eligibility Criteria

- ✓ Adult pts (>18 years) with unresectable, histologically confirmed unresectable Stage III or Stage IV cutaneous melanoma.
- ✓ Eligible to receive PBS (Australian Government program that subsidizes some medicines) standard of care checkpoint inhibitor immunotherapy (anti-PD-1 monotherapy either pembrolizumab or nivolumab, or anti-PD-1 combined with anti-CTLA4 i.e., nivolumab + ipilimumab).
- ✓ Have a formalin-fixed paraffin-embedded (FFPE) tumour sample within 2 years of the current clinical assessment.
- ✓ ECOG performance status 0 - 2.
- ✓ No active brain metastases
- ✓ A life expectancy of over 6 months.
- ✓ **Part B** only - refractory to anti-PD-1+/- ipilimumab therapy as defined by the Society for Immunotherapy Resistance Task Force

## Acknowledgements

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## References

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