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TEMPLE - Thiopurine Enhanced Mutations for PD-1/Ligand-1 Efficacy
A Phase 1b/2 Clinical Trial

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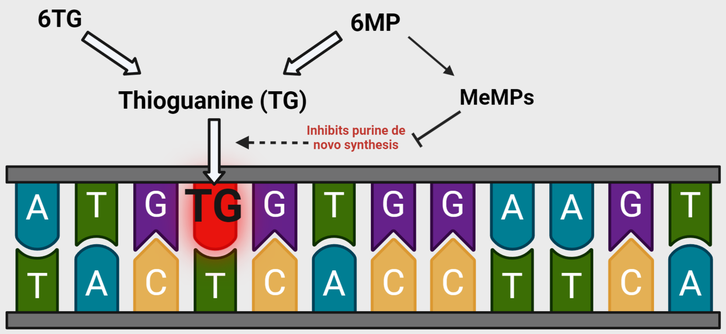
BACKGROUND: A prerequisite for response to immune checkpoint inhibitors (ICI) is the presence of neoepitopes on cancer cells that trigger the immune system. The likelihood hereof increases with the number of mutations in the cancer, and patients with a high tumor mutational burden (TMB) often have higher response rates to ICI therapy. The TEMPLE treatment strategy is a novel approach aiming at improving response to ICI by applying an innovative thiopurine combination.

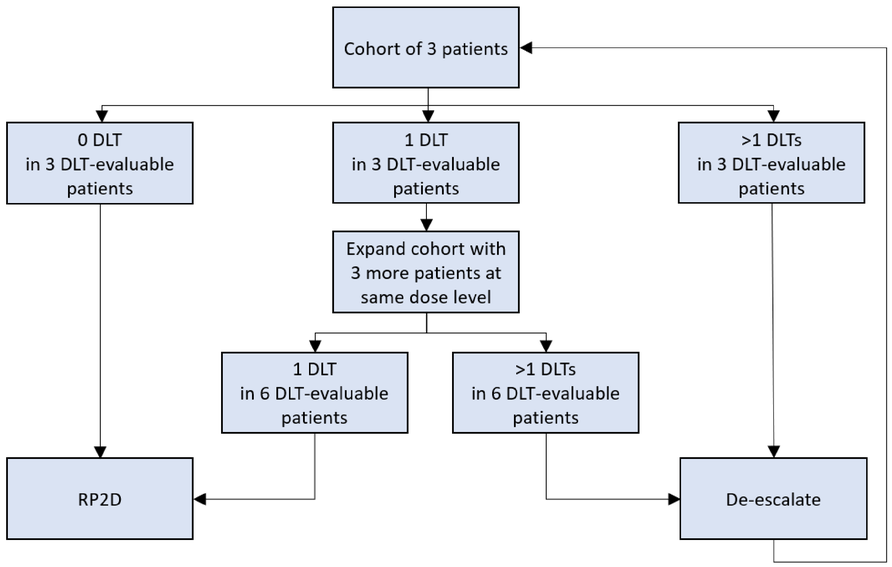
The thiopurines 6-mercaptopurine (6MP) and 6-thioguanine (6TG) are converted into cytotoxic metabolites and incorporated into DNA causing DNA-damage and mutations through futile DNA mismatch repair attempts. The TEMPLE project has been tested in a preclinical setting in an immune competent mouse model of inducible melanoma, where 6TG exposure increased the TMB, reshaped the tumor microenvironment by increasing T and NK immune cells making the tumors more responsive to therapy with immune checkpoint inhibitors (PMID: 365452).

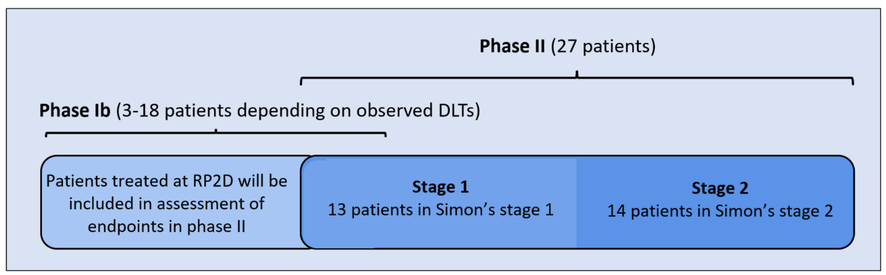


AIM: To increase the proportion of patients with advanced solid tumors responding to treatment with immune checkpoint inhibitors

HOW: By using thiopurines to increase the likelihood of immune checkpoint inhibitors response by inducing DNA damage and increasing the tumor mutational burden.

STUDY DESIGN





STUDY DESIGN: The TEMPLE study (NCT05276284) is an investigator-initiated single-center prospective phase 1b/2 trial to determine the safety, tolerability and efficacy of atezolizumab (1200 mg Q3W) given in combination with thiopurines 6MP and 6TG in patients with metastatic solid tumors with an intermediate TMB (5-10 mutations/megabase).

Recommended phase 2 dose (RP2D) will be determined in a single arm, open label phase 1b trial with a dose-limiting toxicity (DLT) period of 4 weeks. Phase 2 will be an open label, single arm phase 2 trial enrolling additional patients up to a total of 27 patients treated at RP2D in a Simon's 2 stage design. Extensive exploratory analyses will include characterization of the tumor mutational and neoantigen landscape on serial biopsies using whole genome sequencing and RNA sequencing.

CURRENT STATUS: The study was initiated in September 2022 and currently 12 patients have been included in the study. RP2D has been determined and recruitment for phase 2 has begun.

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