Imprime PGG, a novel innate immune modulator, combined with pembrolizumab in a Phase 2 multicenter, open label study in chemotherapy-resistant metastatic Breast Cancer (TNBC).

Abstract

CPI monotherapy provides substantial clinical benefit to cancer patients [pts] with multiple tumor types, yet responses are limited to a minority of patients (~15-30%). The majority of innate and adaptive immune responses within the tumor bed will thereby, when combined with pembrolizumab, provide additional mechanisms to reverse the immunosuppressive nature of the tumor microenvironment and to stimulate antigen presenting cells to drive cross-priming of the antigen presenting molecules by MHC class II.

Clinical Hypothesis

Imprime will stimulate the innate immune system in chemoresistant, metastatic, ABCA- TNBC pts to drive a robust, limited to a minority of patients (~15-30%). The majority of innate and adaptive immune responses within the tumor bed will thereby, when combined with pembrolizumab, provide additional mechanisms to reverse the immunosuppressive nature of the tumor microenvironment and to stimulate antigen presenting cells to drive cross-priming of the antigen presenting molecules by MHC class II.

Primary Efficacy Endpoint

- Overall Response Rate (ORR) in patients with metastatic TNBC

Secondary Efficacy Endpoints

- Time to response (TTR)
- Complete response rate (CRR)
- Progression-Free Survival (PFS) and PFS rate at 6 months and 1 year
- Overall survival (OS) and OS rate at 1 year

Safety Endpoints

- Incidence of treatment-emergent adverse events and laboratory abnormalities

Pharmacokinetic Endpoints

- Pharmacokinetic (PK) and pharmacodynamic (PD) data

Clinical and Exploratory Objectives

- Determine ORR and PFS based on RECIST
- Correlate the following with treatment response:
  - Levels of baseline serum anti-β-glucan antibody (ABA)
  - Changes in immune cell activation markers in tumor biopsy samples and peripheral blood
  - PD-1 expression in tumor biopsy samples

Exploratory Objectives

- Determine ORR and PFS based on RECIST
- Correlate the following with treatment response:
  - Levels of baseline serum anti-β-glucan antibody (ABA)
  - Changes in immune cell activation markers in tumor biopsy samples and peripheral blood
  - PD-1 expression in tumor biopsy samples

Hypothesis: Imprime will stimulate the innate immune system in chemoresistant, metastatic, ABCA- TNBC pts to drive a robust, limited to a minority of patients (~15-30%). The majority of innate and adaptive immune responses within the tumor bed will thereby, when combined with pembrolizumab, provide additional mechanisms to reverse the immunosuppressive nature of the tumor microenvironment and to stimulate antigen presenting cells to drive cross-priming of the antigen presenting molecules by MHC class II.

Study Design: Imprime is being used in combination with pembrolizumab in an open-label, dose escalation and expansion phase 1 study to determine maximum tolerated dose (MTD). Patients received Imprime (4 mg/kg iv) days 1, 8, 15, 18, 22, and 29 of each cycle. CF scan and plasma and skin biopsies were conducted at day 1 and day 8 of each cycle. Where available, paired tumor biopsies (pre-Tx and 6 weeks on Tx) were evaluated for Imprime staining as well as myeloid and T cell activation using multiplexed immunohistostaining to determine whether Imprime + pembrolizumab stimulates an immune response at the tumor site. Peripheral blood was also evaluated for immune activation (cytokines/ chemokine expression, immune cell activation status). Criteria to advance to Stage 2 were 2/3 Grade 3/4 AEs during the first treatment cycle (other than infusion reactions) and 1/2 objective response. Enrollment will continue to accrue 41 evaluable patients.

Stage 1 Safety

- No Grade 4/5 AEs (other than infusion-related events) have been observed in 51 patient
- 32% of patients have had grade 1/2 drug-related adverse events

Stage 1 Efficacy

- 12/31 patients had objective responses
- Disease Control Rate (CR + PR + SD) > 24 weeks: 50% (15/30)
- Overall Survival @ 24 weeks: 84.0% (21/25)

Clinical Measure* Keynote-086 IMPRIME 1

- CR 3.2% (1/31)
- PR 12.9% (4/31)
- CR + PR 16.2% (5/31)
- Stable Disease (SD) 46.8% (15/31)
- Progression-Free Survival (PFS) > 24 weeks: 24.2% (8/33)

- Overall survival > 24 weeks: 50% (16/32)

Disease Control Rate (CR + PR + SD > 24 weeks)

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PD-1 expression in tumor biopsy samples

Peripheral blood samples were evaluated for immune activation markers. CF scan and plasma and skin biopsies were conducted at day 1 and day 8 of each cycle. Where available, paired tumor biopsies (pre-Tx and 6 weeks on Tx) were evaluated for Imprime staining as well as myeloid and T cell activation using multiplexed immunohistostaining to determine whether Imprime + pembrolizumab stimulates an immune response at the tumor site. Peripheral blood was also evaluated for immune activation (cytokines/ chemokine expression, immune cell activation status). Criteria to advance to Stage 2 were 2/3 Grade 3/4 AEs during the first treatment cycle (other than infusion reactions) and 1/2 objective response. Enrollment will continue to accrue 41 evaluable patients.

Clinical Hypothesis

- Criteria for Stage 1 to advance to Stage 2 cohort
  - ±1 objective response, ±4 protocol-defined CR in 2 pts
  - ≥2 protocol-defined CR in baseline PER-RECIST at 1, 2, and 4 weeks
  - No new Grade 4 adverse events or infusion-related reactions

- Criteria to advance to Stage 2
  - ≥3 confirmed complete responses on irRECIST

The majority of patients (pts) with multiple tumor types, yet responses are limited to a minority of patients (~15-30%). The majority of innate and adaptive immune responses within the tumor bed will thereby, when combined with pembrolizumab, provide additional mechanisms to reverse the immunosuppressive nature of the tumor microenvironment and to stimulate antigen presenting cells to drive cross-priming of the antigen presenting molecules by MHC class II.