In the U.S., melanomas is the fifth most common cancer in men and the seventh in women (1). Locally confined, fully excised cancers may provide an option for cure. A stage IV metastatic disease (or refractory melanocytic disease) is highly refractory to therapy. Thus, experimental clinical trials provide an acceptable treatment option for metastatic or relapsing/refractory melanomas.

The main function of the IDO pathway is the regulation of acquired local and peripheral immune tolerance in normal and pathological conditions, particularly in the tumor microenvironment. IDO is up-regulated in many human tumors and tumor draining lymph nodes (2), including melanoma (3). The IDO pathway mediates an acquired immune suppression and functions together with Treg cells (suppressive arm of the immune system) and inhibits effector T cells (stimulatory arm). In addition, it has been shown that kynurenine metabolites may augment the suppressive effects on inflammation (7,8). Pharmacological inhibition of IDO with indoximod (BI 167770) enhances the number and function of anti-tumor CD8+ T-cells in a adoptive T cell-transplantation model of lymphoma (9). Initial Phase 1 and Phase 1b studies have failed dose safety profiles with evidence of clinical activity.

IDO is an enzyme that catalyzes the initial and rate-limiting conversion of tryptophan to kynurenine. Tryptophan depletion enhances the number and function of naïve CD8+ T-cells in lymphocytes (10). Anti-CTLA-4 (ipilimumab) and anti-PD-1 (pembrolizumab and nivolumab) are monoclonal antibodies that target the inhibitory immune checkpoint receptors (CTLA-4 and PD-1, respectively), enhancing immune responses against tumors. They are currently the standard of care (SOC) in metastatic melanoma.

This phase 2 study is designed to evaluate the combination of indoximod and another immune checkpoint inhibitor in treatment-naïve metastatic melanoma.

**IDO PATHWAY**

The IDO pathway (IDO PATHWAY) is shown in the figure. IDO (indoleamine 2,3-dioxygenase) is an enzyme that converts tryptophan to kynurenine, and this process is inhibited by indoximod. IDO expression can be assessed by immunohistochemistry in tumor specimens. The IDO pathway can be activated in response to interferon-γ (IFN-γ) or IL-4, which are produced by activated T cells and natural killer (NK) cells, respectively. Indoximod, a metabolic inhibitor of IDO, has been shown to enhance immune responses against tumors.

**KEY IMMUNE CHECKPOINTS**

- **PD-1/L1**
- **CTLA-4**
- **IDO**
- **Tregs**
- **Tumor**

**INDOXIMOD AND IPILIMUMAB**

Indoximod (formerly BI 167770) is a metabolite of the IDO inhibitor BI 1207699, which has been shown to enhance immune responses against tumors. The IDO pathway can be activated in response to interferon-γ (IFN-γ) or IL-4, which are produced by activated T cells and natural killer (NK) cells, respectively. Indoximod, a metabolic inhibitor of IDO, has been shown to enhance immune responses against tumors.

**THERAPEUTIC AGENTS**

- **Indoximod (BI 167770):**
  - Metabolite of the IDO inhibitor BI 1207699
  - Enhances immune responses against tumors

- **Ipilimumab:**
  - Monoclonal antibody targeting CTLA-4
  - Enhances immune responses against tumors

**DOSAGE LEVELS**

- **1200 mg BID x 28 days**
- **3 mg/kg q 3 weeks x 4 doses**

**FUTURE STUDIES**

- **Phase 2b:**
  - Evaluate the combination of indoximod and another immune checkpoint inhibitor in treatment-naïve metastatic melanoma.
  - Assess the safety and tolerability of the combination.
  - Collect preliminary efficacy data.

**REFERENCE**


**SUMMARY**

- **Phase 1a:**
  - Indoximod / pembrolizumab combination was well tolerated.
  - Preliminary efficacy of the established dose of indoximod in combination with pembrolizumab was observed.

- **Phase 1b:**
  - Indoximod / nivolumab combination was well tolerated.
  - Preliminary efficacy of the established dose of indoximod in combination with nivolumab was observed.

- **Phase 2:**
  - Currently 40 patients enrolled (n=10 Phase 1b, n=30 Phase 2).
  - Safety and tolerability of the combination will be evaluated.
  - Preliminary efficacy data will be collected.

**RESOURCES**

- **ClinicalTrials.gov Identifier:** NCT00978120

**CLINICAL TRIAL RESULTS**

The phase 2 plan of indoximod-containing regimens with treatment-naïve metastatic melanoma was completed in a standard 3+3 design. Indoximod was initially tested at the established dose of 1200 mg BID in combination with ipilimumab (3 mg/kg every 3 weeks x 4 doses). The primary endpoint was overall response rate (ORR) from an intention-to-treat analysis. Secondary endpoints included response duration, median progression-free survival, median overall survival, and safety profile.

**GENERAL PATIENT CHARACTERISTICS**

- **Median age:** 64 years (range: 45-83 years)
- **Sex:** 3 female (33%)
- **Stage:**
  - Unresectable Stage III (n=6)
  - Unresectable Stage IV (n=3)

**RESOURCES**