Abstract #3075

Updates on phase1b/2 trial of the indoleamine 2,3-dioxygenase pathway (IDO) inhibitor indoximod plus checkpoint inhibitors for the treatment of unresectable stage 3 or 4 melanoma.

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INTRODUCTION

In the U.S., melanoma is the fifth most common cancer in men and the seventh in women (1). Locally confined, fully resectable disease may be curable with current therapy; but Stage IV metastatic disease (or relapsed/recurrent disease) is highly refractory to therapy. Thus, experimental clinical trials provide an accepted treatment option for metastatic or relapsed/refractory melanoma.

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 malignant melanoma (3-6). The IDO pathway mediates an acquired immune tolerance towards tumors, allowing tumors to thwart an immune response by the host. Therefore, the IDO pathway is an attractive target for cancer drug development.

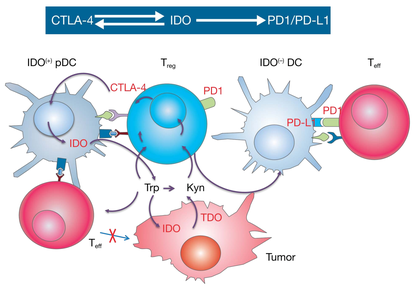
IDO is an enzyme that catalyzes the initial and rate limiting step in the conversion of tryptophan to kynurenine. Tryptophan depletion enhances the number and function of Treg cells (suppressive arm of the immune system) and inhibits effector T cells (stimulatory arm). In addition, it has been shown that kynurenine metabolites may augment the suppressive effects on inflammation (7,8). Pharmacological inhibition of IDO with indoximod has been shown to result in T cell–dependent antitumor responses in murine models (8, 9). Initial Phase 1 and Phase 1b studies have had favorable safety profile with evidence of clinical activity.

Anti- CTLA-4 (ipilimumab) and anti-PD-1 (pembrolizumab and nivolumab) are monoclonal antibodies that block the immunosuppressive receptor CTLA-4/ PD-1 on T cells, thus enhancing immune responses against tumors. They are currently the standard of care (SOC) in metastatic melanoma (10).

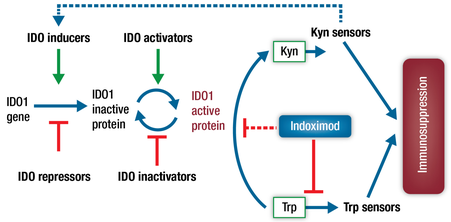
Tumor models have shown synergistic effects with anti-CTLA-4 treatment in combination with indoximod providing a rational combination therapy for the treatment of melanoma (11).

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

KEY IMMUNE CHECKPOINTS



IDO PATHWAY



PHASE I CLINICAL TRIAL RESULTS

The phase 1 part of ipilimumab and indoximod in patients with treatment naïve metastatic melanoma was completed in a standard 3+3 design.

Indoximod (twice daily [BID] orally) was dose escalated in combination with ipilimumab (3 mg/kg every 3 weeks × 4 doses) in four 21-day cycles; treatment with indoximod beyond treatment with ipilimumab (which was halted either due to reaching 4 doses or due to toxicity) then continued in 28-day cycles at the appropriate dose level until toxicity or disease progression.

Two dose levels of indoximod (600 mg BID and 1200 mg BID) were tested according to the following table:

DOSE LEVEL	INDOXIMOD DOSE (ORAL)	IPILIMUMAB (IV)
1	600 MG BID X 28 days	3 mg/kg q 3 weeks x 4 doses
2	1200 mg BID x 28 days	3 mg/kg q 3 weeks x 4 doses

9 patients were enrolled, (3 patients at 600 mg BID and 6 patients at 1200 mg BID) (12).

Median age was 64 years (range: 45-83 years), 3 were female (33%).

Indoximod and ipilimumab were well tolerated when combined in a clinical trial setting, without potentiation of autoimmune adverse events and no dose-limiting toxicities (DLT).

The Phase 2 dose for indoximod has been established as the 1200-mg BID dose.

1 complete response by RECIST criteria at 13 months.

The most common (observed in ≥3 patients) AEs, regardless of attribution, were fatigue (7 patients, 78%), pruritus (6 patients, 67%), diarrhea and rash (4 patients each, 44%), and abdominal pain and headache (3 patients each, 33%).

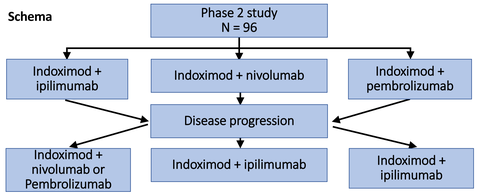
PHASE 2 OVERVIEW AND SCHEMA

This ongoing phase 2 study is an open-label, combination, single arm study, designed to gather preliminary efficacy data of indoximod combined with other immune checkpoint inhibitors.

Standard of care immune checkpoint inhibition, consisting of 4 cycles of concomitant ipilimumab, repeat cycles of nivolumab, or repeat cycles of pembrolizumab, per provider choice are given in combination with indoximod 1200 mg BID.

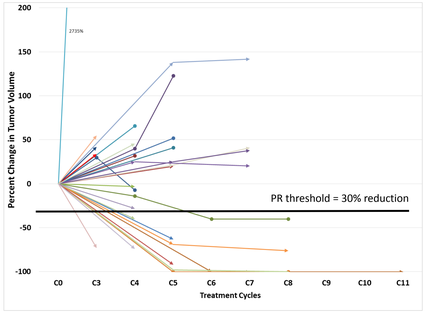
In the event of progression, the provider can change therapy from one checkpoint inhibitor (anti-CTLA-4 or anti-PD-1) to another (ipilimumab to pembrolizumab or nivolumab as well as pembrolizumab or nivolumab to ipilimumab) while continuing indoximod.

Schema



ClinicalTrials.gov Identifier: **NCT02073123**

TUMOR RESPONSES ALL PATIENTS



Response data per site reported imaging results from initial 40 subjects enrolled in phase1b and phase 2 combined. Response data available on 28 subjects as of poster preparation.

Choice of initial checkpoint used in combination with indoximod

- 22 patients were treated with pembrolizumab
- 14 patients were treated with ipilimumab
- 4 patients were treated with nivolumab

Response rate ORR is 36% (10/28) including 3 CRs

PHASE 2 ENROLLMENT ELIGIBILITY AND ENDPOINTS

Enrollment

- The phase 2 portion is designed to enroll up to 96 patients in a non-randomized study.

Eligibility

- Unresectable Stage III or Stage IV melanoma.
- Exclusions: prior molecular targeted therapy or radiotherapy, prior immune checkpoint inhibitors or indoximod.

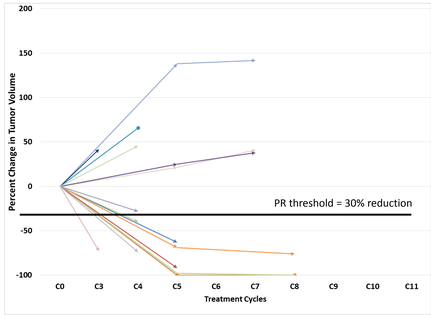
Primary Objectives

- Safety of the study combination.
- Preliminary efficacy of the established dose of indoximod in combination with SOC checkpoint inhibitors as measured by the overall response rate (ORR) in patients with unresectable Stage III or Stage IV melanoma.

Secondary Objectives

- Median progression free survival and overall survival.
- Investigation of mechanisms of activity/resistance to IDO and checkpoint inhibitor therapy through correlative studies.
- Qualitative analysis of IDO expression by immunohisto-chemistry in tumor samples.

RESPONSES WITH INDOXIMOD AND PEMBROLIZUMAB

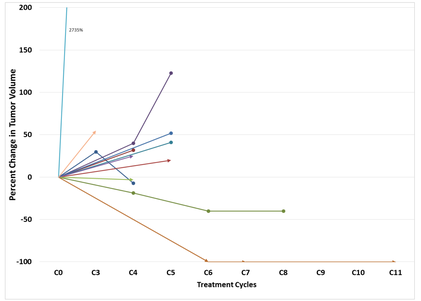


Response data per site reported imaging results from 15 patients in Phase 2 that received pembrolizumab in combination with indoximod as initial therapy

Response rate is 53% (8/15) with two CRs

Data only available at this time on one patient who received nivolumab

RESPONSES WITH INDOXIMOD AND IPILIMUMAB



Response data per site reported imaging results from 12 patients (9 in Phase 1) who received ipilimumab initially

SUMMARY

- Phase 1b has been successfully concluded without significant toxicities.
- No increase in toxicity observed thus far in Phase 2
- Objective response rate in combination with pembrolizumab is promising at 53% with 2CRs seen.
- Indoximod / pembrolizumab combination well tolerated thus far, particularly when compared to well described toxicity seen with PD-1 inhibtior / ipilimumab combinations.
- Phase 2 is ongoing. Currently 64 patients enrolled (55 in Phase 2) at 6 clinical sites

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