Phase 1/2 Trial of the Indoleamine 2,3-dioxygenase Pathway (IDO) Inhibitor Indoximod plus Ipilimumab for the Treatment of Unresectable Stage III or IV Melanoma

Eugene Kennedy, Gabriela R. Rossi, Nicholas N. Vahanian, Charles J. Link

NewLink Genetics, Ames, IA

TPS9117

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.

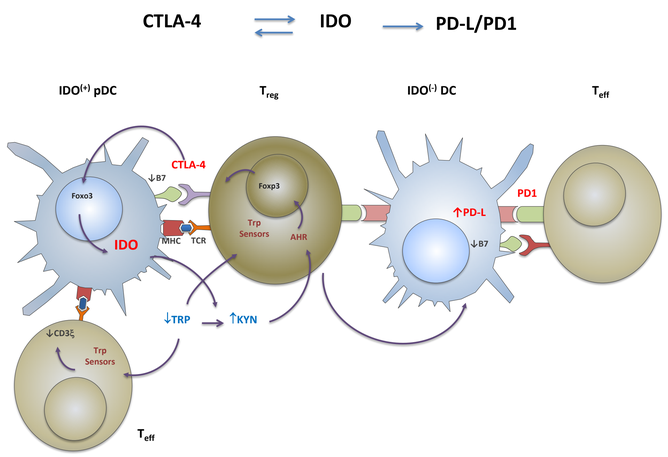
The main function of the IDO pathway is the regulation of acquired local and peripheral immune tolerance in normal and pathological conditions, particularly in the tumor microenvironment. IDO is up-regulated in many human tumors and tumor-draining lymph nodes (2), including malignant melanoma (3-6). 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 and immune responses (7,8).

Ipilimumab is a monoclonal antibody that blocks the immunosuppressive receptor CTLA-4 on T cells, thus enhancing immune responses against tumors. Ipilimumab has been approved for treatment of unresectable and metastatic melanoma. Treatment with ipilimumab increases median overall survival in both previously untreated and previously treated patients with metastatic stage III or IV melanoma (9). The increase in median survival was approximately 2 to 4 months, but >90% of patients eventually progressed. Although the effect of ipilimumab has been encouraging, the impact on survival of ipilimumab as a single agent remains limited.

Tumor models have shown synergistic effects with anti-CTLA-4 treatment in combination with indoximod providing a rationale for combination therapy for the treatment of melanoma. This phase 2b study is designed to evaluate the combination of indoximod and ipilimumab in late stage melanoma.

KEY IMMUNE CHECKPOINTS



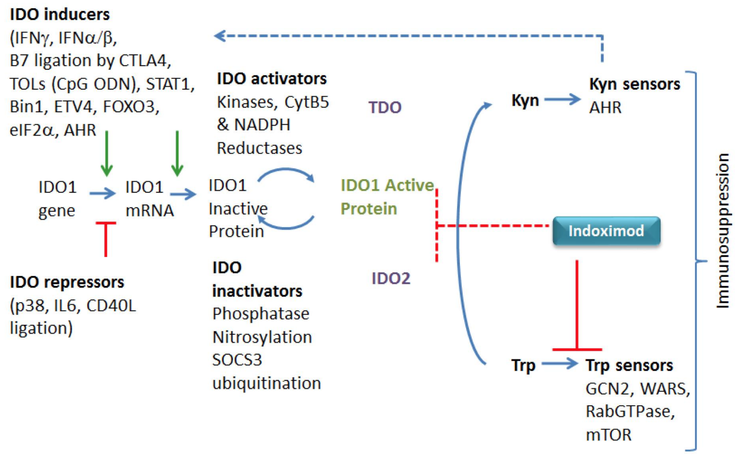
PHASE I SINGLE AGENT STUDIES

The Phase 1 trials of indoximod enrolled 65 patients with solid tumors (breast, colon, melanoma, sarcoma, pancreatic, lung) (10, 11)

Results showed:

- Indoximod was well tolerated and good oral bioavailability was demonstrated.
- Some patients demonstrated prolonged stabilization of disease (>6 months) and some mixed responses were observed including regression of visceral metastases
- Three patients treated at the lowest dose level who had previously been treated with other experimental immunotherapy (2 with ipilimumab, 1 with CD40-agonist antibody) developed autoimmune hypophysitis. These patients were managed by interrupting indoximod, treating with corticosteroids and hormone replacement therapy until stable, and then re-starting indoximod at the same dose. All three patients tolerated this well, and all had stable disease >6 months after re-starting therapy.
- In the remainder of the phase 1 trial, patients were excluded if they had received prior immunotherapy

IDO PATHWAY



OVERVIEW

This phase 1/2 study is an open-label, 2-segment, combination, single arm study. Phase 1 is designed to determine the recommended phase 2 dose (RP2D) and associated toxicities of the dose-escalation for indoximod plus standard fixed-dose ipilimumab. Phase 2 is designed to gather preliminary efficacy data in a single-arm expansion phase testing the new regimen.

Enrollment

- **Up to 12 patients enrolled in the phase 1 portion.**
- **Indoximod is administered concurrently with ipilimumab as a twice daily oral dose, continuously for each 21 day cycle.**
- **Treatment with indoximod will continue beyond treatment with ipilimumab (halted either due to reaching 4 doses or toxicity) until disease progression or toxicity.**
- **The phase 2 portion is designed to enroll up to 38 patients in a non-randomized study. Patients receive ipilimumab at the standard dose with concurrent indoximod at the dose determined in phase 1.**

Eligibility

- **Unresectable Stage III or Stage IV melanoma.**
- **Exclusions: prior molecular targeted therapy or radiotherapy, prior ipilimumab or indoximod**

Endpoints for the phase 1

- **Safety of the combination of indoximod and ipilimumab when given concomitantly.**
- **Establish the recommended phase 2 dose of indoximod in combination with ipilimumab in patients with unresectable melanoma and assess the safety and tolerability of the combined treatments.**

Primary endpoints for the phase 2

- **Safety**
- **Preliminary efficacy of the established dose of indoximod in combination with ipilimumab as measured by the median progression-free survival (PFS) in patients with unresectable Stage III or Stage IV melanoma.**

Secondary Objectives Phase 2

- **Adverse event profile and tolerability of ipilimumab and indoximod in patients with unresectable stage III or Stage IV melanoma**
- **Overall survival of patients with unresectable Stage III or Stage IV melanoma receiving indoximod and ipilimumab**
- **Investigation of mechanisms of activity/resistance to IDO/CTLA-4 inhibitor therapy through correlative studies.**

STUDY SCHEMA

Dose-escalation, indoximod in combination with ipilimumab in four 21-day cycles (segment 1). Treatment with indoximod then continues in 28 day cycles (segment 2) at the appropriate dose level until toxicity or disease progression.

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

- The MTD is the largest dose level at which ≤ 1 of 6 patients experiences a regimen limiting toxicity (RLT). If the MTD is not reached at level 2, no further dose-escalation is allowed.
- No patients are allowed to enroll in the expansion phase until all patients in the dose-escalation component have completed segment 1 of the trial. At that point the recommended phase 2 dose can be determined.
- After the established dose for indoximod in combination with ipilimumab is determined in phase 1, the phase 2 study is designed to enroll 38 patients in a single arm, fixed-dose design. 4 cycles of concomitant ipilimumab and indoximod are administered (segment 1), followed by indoximod given alone until disease progression or unacceptable toxicity (segment 2).

SUMMARY

- IDO is up-regulated in many human tumors and tumor-draining lymph nodes (2), including malignant melanoma (3-6).
- Ipilimumab is currently approved for metastatic or unresectable melanoma at a dose of 3 mg/kg every 3 weeks.
- At the molecular level, the IDO and CTLA-4 pathways are closely linked. CTLA-4 causes induction of IDO gene expression and functional activity (12,13), and IDO contributes to the biologic effect of CTLA-4 as a downstream immunosuppressive pathway (14,15).
- The close molecular links between the IDO pathway and the CTLA-4 pathway, provide the rationale for combination of ipilimumab with the IDO-inhibitor indoximod.

REFERENCES

1. SEER Cancer Statistics Review, 1975-2011, April 2014
2. Munn. Curr Med Chem 2011, 18: 2240-2246
3. Uyttenhove et al., Nat Med 2003, 9: 1269-1274
4. Gerlini et al. J Invest Dermatol 2010, 130: 898-901
5. Lee et al. Clin Cancer Res 2005, 11: 107-112
6. Lee et al. Lab Invest 2003, 83: 1457-1466
7. Mezrich, J.D. et al. (2010) J. Immunol.185, 3190–3198
8. Nguyen, N.T. et al. (2010) . Proc. Natl. Acad. Sci. U.S.A. 107, 19961–19966
9. Hodi et al. N Engl J Med 2010, 363: 711-723
10. Soliman et al. J Clin Oncol May 2009 vol. 27 no. 15S 3004
11. Soliman et al. J Clin Oncol 30, 2012 (suppl; abstr 2501)
12. Fallarino et al. Nat Immunol 2003, 4: 1206-1212
13. Grohmann et al. Nat Immunol 2002, 3: 1097-1101
14. Mellor et al. J Immunol 2003, 171: 1652-1655
15. Sucher et al. J Immunol 2012, 188: 37-46

CLINICAL TRIALS IDENTIFIER

ClinicalTrials.gov Identifier: **NCT02073123**

NewLink GENETICS
UNLEASHING HUMAN POTENTIAL

50th American Society of Clinical Oncology Annual Meeting; May 30-June 3, 2014; Chicago, IL