Abstract #514

Results of a Phase 1b Trial of the Indoleamine 2,3-Dioxygenase (IDO) Pathway Inhibitor Indoximod Plus Ipilimumab for the Treatment of Unresectable Stage 3 or 4 Melanoma

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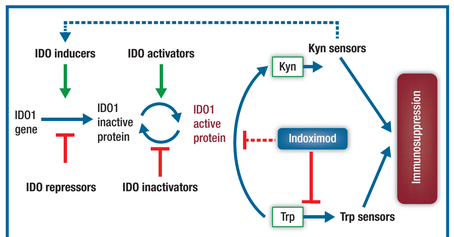
INTRODUCTION

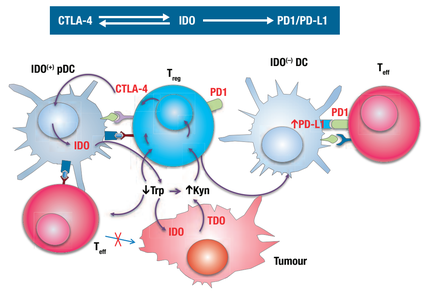
- Locally confined, fully resectable melanoma may be curable with current therapy, but stage 4 metastatic disease (or relapsed/recurrent disease) is highly refractory to therapy[1,2]
- Indoleamine 2,3-dioxygenase (IDO) is a key immunomodulatory enzyme that regulates acquired local and peripheral immune tolerance in normal and pathologic conditions[3] (**Figure 1**)
  - IDO catalyses the initial and rate-limiting step in the conversion of tryptophan to kynurenine
  - IDO inhibits CD8+ T cell infiltration in various cancers,[4,5] and production of kynurenine induces generation of regulatory T cells[6]
- Indoximod is an orally available, small molecule, broad IDO pathway inhibitor that has been shown to potentially interfere with multiple targets within the IDO pathway



IDO, indoleamine 2,3-dioxygenase; Kyn, kynurenine; Trp, tryptophan.

Figure 1. IDO pathway.

- In cancer, IDO can be expressed by tumour cells or by host antigen-presenting cells upon recruitment by tumour cells[3]
  - In the tumour microenvironment, IDO mediates acquired immune tolerance towards tumours, allowing tumours to thwart the host immune response
  - IDO is upregulated in plasmacytoid dendritic cells in melanoma sentinel nodes[7,8]
- Ipilimumab is a monoclonal antibody that blocks the immunosuppressive receptor cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) on T cells, thus enhancing immune responses against tumours[9]
  - Ipilimumab is approved for the treatment of unresectable and metastatic melanoma[9]
  - Although treatment with ipilimumab increased median overall survival by approximately 2 to 4 months in both previously untreated and treated patients with metastatic stage 3/4 melanoma,[10] >90% of patients eventually progress
- Preclinical tumour models have shown synergistic effects of anti–CTLA-4 treatment in combination with indoximod, providing rationale for combining these 2 therapies for melanoma treatment (**Figure 2**)



IDO, indoleamine 2,3-dioxygenase; TDO, tryptophan 2,3-dioxygenase; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; PD1, programmed death receptor 1; PD-L1, programmed death receptor ligand 1; pDC, plasmacytoid dendritic cell; T_{reg}, regulatory T cell; DC, dendritic cell; T_{eff}, effector T cell; Trp, tryptophan; Kyn, kynurenine.

Figure 2. IDO/TDO pathway and immune checkpoints.

METHODS

Study Design

- This Phase 1b, 2-cohort, dose-escalation study utilised 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 (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 (**Figure 3**)
  - The 1200-mg dose of indoximod is the maximum biologically achievable dose of oral indoximod

Dose level	Indoximod dose (oral)	Ipilimumab (IV)
1	600 mg BID × 28 days	3 mg/kg q3 weeks × 4 doses
2	1200 mg BID × 28 days	3 mg/kg q3 weeks × 4 doses

IV, intravenously; BID, twice daily; q, every.

Figure 3. Phase 1b study design.

- The maximum tolerated dose was the largest dose level at which ≤1 of 6 patients experienced a regimen-limiting toxicity
- In the Phase 1b portion, 9 patients were required (3 patients at 600 mg BID and 6 patients at 1200 mg BID) to determine the Phase 2 dose
- Primary endpoints for the Phase 1b portion included safety, toxicity, and determination of a Phase 2 dose

Patient Eligibility

- Inclusion criteria
  - Age ≥18 years
  - Unresectable stage 3 or 4 melanoma
  - Eastern Cooperative Oncology Group performance status score of ≤2
- Exclusion criteria
  - Prior molecular-targeted therapy or radiotherapy, ipilimumab, or indoximod
  - Patients with known active, uncontrolled brain metastases
  - Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit study compliance
  - Patients with autoimmune diseases, a chronic inflammatory condition, or any condition requiring concurrent use of any systemic immunosuppressants or steroids for any reason
  - Laboratory evidence of pancreatitis
  - Patients with any other cancer
  - Patients with an allotransplant

RESULTS

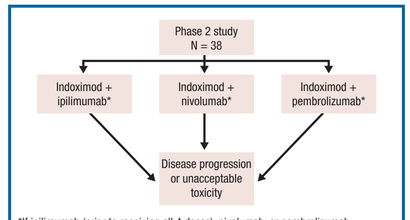
- Among the 9 patients:
  - 3 (33%) were female
  - Median age was 64 years (range: 45-83 years)
- No dose-limiting toxicities were observed
- Most AEs were grade 1 or 2 in severity
- 2 SAEs were reported on study:
  - 1 grade 3 diarrhoea possibly related to the study regimen
  - 1 grade 3 atrial flutter unrelated to the study regimen
- The most common (observed in ≥3 patients) AEs, regardless of attribution, were fatigue (7 patients, 78%), pruritus (6 patients, 67%), diarrhoea and rash (4 patients each, 44%), and abdominal pain and headache (3 patients each, 33%; **Table 1**)
- Currently, 7 of 9 patients are evaluable for response:
  - 1 complete response by RECIST criteria
  - 1 partial response by RECIST criteria
  - 5 patients had progressive disease
  - 2 patients are still awaiting follow up
- All patients are still alive, and we are continuing to follow up on their responses

Table 1. Most Common (Observed in ≥3 Patients) AEs Regardless of Attribution

AE, n (%)	Total N = 9
Fatigue	7 (78)
Pruritus	6 (67)
Diarrhoea	4 (44)
Rash	4 (44)
Abdominal pain	3 (33)
Headache	3 (33)

CONCLUSIONS

- **Indoximod and ipilimumab were well tolerated when combined in a clinical trial setting**
  - **There was no potentiation of autoimmune AEs**
- **The combination therapy showed clinical activity in some patients**
- **The Phase 2 dose for indoximod has been established as the 1200-mg BID dose**
  - **Up to 38 patients are currently being enrolled in the Phase 2 study**
  - **Using a revised study design, standard of care immune checkpoint inhibition, consisting of 4 cycles of concomitant ipilimumab, repeat cycles of nivolumab, or repeat cycles of pembrolizumab, will be given in combination with indoximod (Figure 4)**
- **The primary endpoint of the Phase 2 portion will be preliminary efficacy as measured by median progression-free survival**



*If ipilimumab (prior to receiving all 4 doses), nivolumab, or pembrolizumab treatment is stopped due to toxicity, indoximod can be administered alone after toxicity has been resolved until disease progression or toxicity.

Figure 4. Phase 2 study design.

References

1. Tentori L, et al. *Trends Pharmacol Sci.* 2013;34(12):656-666.
2. National Comprehensive Cancer Network. http://www.nccn.org/professionals/physician_gls/PDF/melanoma.pdf. Accessed 18 September 2015.
3. Johnson TS, Munn DH. *Immunol Invest.* 2012;41(6-7):765-797.
4. Ino K, et al. *Clin Cancer Res.* 2008;14(8):2310-2317.
5. Zhang G, et al. *Clin Dev Immunol.* 2011;2011:384726.
6. Mezrich JD, et al. *J Immunol.* 2010;185(6):3190-3198.
7. Gerlini G, et al. *J Invest Dermatol.* 2010;130(3):898-901.
8. Lee JH, et al. *Clin Cancer Res.* 2005;11(1):107-112.
9. YERVOY® (ipilimumab) injection, for intravenous infusion [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2013.
10. Hodi FS, et al. *N Engl J Med.* 2010;363(8):711-723.

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