**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 (Figure 1) – IDO catalyzes the initial and rate-limiting step in the conversion of tryptophan to kynurenine
- IDO inhibits CD8+ T-cell infiltration in various cancers,3,4 and production of kynurenine induces generation of regulatory T cells2
- 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

– 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 or 4 melanoma,1,10 30% 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)

**METHODS**

**Study Design**

- This Phase 1b, 2-cohort, dose-escalation study utilized 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

**RESULTS**

- Among the 9 patients:2
  - 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
- The combination therapy showed clinical benefit in response (Table 1)

**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 regimen
  - 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 indoximod, 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