**SUMMARY**

**TIGIT** (T-cell immunoreceptor with Ig and ITIM domains) is an immune checkpoint receptor shown to inhibit T cell and NK cell activation and suppress anti-cancer immune response.

Etiglimab (OMP-313M32) is a humanized IgG1 monoclonal anti-TIGIT antibody. It was designed to inhibit TIGIT signaling and is hypothesized to deplete T regulatory cells (Tregs) expressing high levels of TIGIT through antibody directed cellular cytotoxicity (ADCC).

In a Phase I clinical trial (NCT03194283) in advanced solid tumors, etiglimab was dosed from 0.3 to 20 mg/kg every other week. Initial pharmacodynamic biomarker analysis results are presented here.

Flow cytometry of patients’ peripheral blood mononuclear cells (PBMCs) showed significant reduction of peripheral Tregs and an increase in the CD8/Treg ratio after etiglimab treatment, but no significant decreases in total CD4, CD8 T cells and NK cells were observed.

The reduction of Tregs and the increase of CD8/Treg ratio in blood were confirmed by epigenetic quantification of immune cells. Etiglimab decreased TIGIT+ Tregs among CD4+, CD8+ and Treg populations.

Etiglimab increased intracellular IL-2 levels in patients’ T effector memory cells.

Etiglimab increased proliferation of T cell subsets in peripheral blood.

**MATERIALS AND METHODS**

**ETICAL REVIEW:** This study was performed in accordance with the ethical principles of the Declaration of Helsinki. All patients enrolled on this study provided written informed consent.

**313M32-001 Phase 1a trial of Etiglimab in Advanced Solid Tumors**

**ETICAL REVIEW:** This study was performed in accordance with the ethical principles of the Declaration of Helsinki. All patients enrolled on this study provided written informed consent.

**Patients** were included in the trial if they were at least 18 years old with advanced, relapsed or refractory solid tumors with no approved therapeutic options or for which treatment with the agents was felt to be inappropriate.

**SUGGESTED REGIMEN:** The recommended dose for phase 2 trials was 3 mg/kg every 2 weeks (Q2W).

**ETICAL REVIEW:** This study was performed in accordance with the ethical principles of the Declaration of Helsinki. All patients enrolled on this study provided written informed consent.

**RESULTS**

Etiglimab reduces Tregs in blood of Phase 1a pts, consistent with ADCC mode of action

Gene expression of peripheral blood suggests reduction of Tregs of Phase 1a pts

Etiglimab enhances proliferation and intracellular IL-2 in immune subpopulations

Etiglimab reduced the frequency of peripheral Treg+ cells as well as TIGIT gene expression levels, demonstrating target engagement

**CONCLUSIONS**

- Etiglimab treatment reduced Tregs in peripheral blood, more pronounced at >10mpk, with a corresponding increase in the Treg/CD8 ratio. This was observed both by flow cytometry and epigenetic immune quantification.
- Etiglimab decreased Treg-related gene expression in blood, including RTKN2 and CTLA4.
- Etiglimab also reduced TIGIT staining on cell surface by flow cytometry, and increased TIGIT gene expression in blood RNA.
- Etiglimab activated immune cells as measured by increases in Ki67+ TIGIT+ CD4+ cells and intracellular cytokines.
- Activation of immune cells correlated with immune-related adverse events, including patient rash.

**ACRONYMS:** ADCC = Antibody-dependent cellular cytotoxicity

**REFERENCES:**


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