Long Term Integrated Safety Analysis of Umbralisib With A Differentiated Safety Profile, In Patients With Relapsed/Refractory Lymphoma

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Background

Umbralisib (TGR-1202) is a next generation PI3K δ inhibitor, with a unique structure and activity profile distinct from other PI3K inhibitors in development, including:

- A differentiated safety profile from other PI3K inhibitors, with notable respect to lymphoid tissues and nodes.
- A prolonged half-life that enables once-daily dosing.
- High selectivity to the 5 soluble PI3Ks, and
- Also targets cancer-1-selectin protein (Cxcr4), a protein which may inhibit regulatory T-cell function (Burris et al., 2018).

In a Phase 2, multi-institutional, open-label, dose-escalation study evaluating umbralisib monotherapy in patients with relapsed or refractory hematologic malignancies with an ECOG PS of 2 or less without limit to number of prior therapies, adverse events were graded by CTCAE v4.03 criteria.

Prior Integrated Analysis of Safety (Davids et al., ASH 2017)

1. First generation PI3Kδ inhibitors such as idelalisib and duvelisib are active in patients (pts) with lymphoma malignancies but are often associated with significant immunemediated adverse events, including transaminitis, diarrhea/colitis, and pneumonitis, as well as an increased risk of other toxicities that can be severe, and frequently lead to treatment discontinuation.

2. The intracellular PI3Kδ inhibitor, copanlisib, recently received FDA approval exhibiting a lower rate of immune-mediated adverse events, however, Grade 3/4 hyperglycemia occurred in 14% of patients, and Grade 3-4 hyperglycemia occurring in 20% of patients.

3. Previously, an integrated analysis of 547 patients treated with umbralisib monotherapy or umbralisib + the glycoengineered anti-CD20 mAb, ofatumumab (“U2”) demonstrated a favorable safety profile, with infrequent immune mediated adverse events (Davids et al., ASH 2017).

4. Here we present an updated integrated analysis of patients treated with umbralisib either as monotherapy or in combination with other agents with a focus on long-term (≥6 months) tolerability.

Study Design/Methods

Safety data were pooled from 4 completed or ongoing Phase 1 or 2 studies containing umbralisib. All studies shared similar key eligibility criteria: enrolling patients with hematologic malignancies with an ECOG PS of 2 or less without limit to number of prior therapies. Adverse events were graded by CTCAE v4.03 criteria.

Results

Long Term Safety Analysis: Patients on Umbralisib For ≥6 Months

Evaluate for safety, n = 177

- Grade 3/4 Adverse Events Occurring After ≥6 Months on Umbralisib
- Serious adverse events occurring in >1% of patients were limited to pneumonitis (3%), diarrhea/colitis (2%), and cellulitis (2%)