Long Term Integrated Safety Analysis Of Umbralisib (TGR-1202), A PI3Kδ/Ck1ε Inhibitor With A Differentiated Safety Profile, In Patients With Relapsed/Refractory Lymphoid Malignancies

Abstract # PF444

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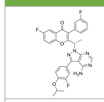
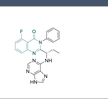
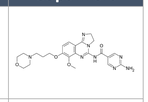
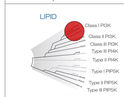
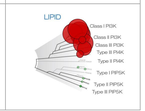
Background

- First generation PI3Kδ inhibitors such as idelalisib and duvelisib are active in patients (pts) with lymphoid malignancies but are often associated with significant immune-mediated adverse events, including transaminitis, diarrhea/colitis, and pneumonitis, as well as an increased risk of serious infections. These toxicities can be severe, and frequently lead to treatment discontinuation.
- The intravenous PI3Kα,δ inhibitor, copanlisib, recently received FDA approval exhibiting a lower rate of immune-mediated adverse events; however, Gr. 3/4 hyperglycemia occurred in >40% of patients, and Gr. 3/4 hypertension occurred in 26% of patients.
- Previously, an integrated analysis of 347 patients treated with umbralisib monotherapy or umbralisib + the glycoengineered anti-CD20 mAb ublituximab ("U2") demonstrated a favorable safety profile, with infrequent immune mediated adverse events (Davids et al., ASH 2017).
- 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 month) tolerability.

Umbralisib

- Umbralisib (TGR-1202) is a next generation PI3Kδ inhibitor, with a unique structure and activity profile distinct from other PI3Kδ inhibitors in development, including:
  - A differentiated safety profile from other PI3Kδ inhibitors, notably with respect to hepatic toxicity and colitis;
  - A prolonged half-life that enables once-daily dosing;
  - High selectivity to the δ isoform of PI3K; and
  - Also targets casein kinase-1 epsilon (CK-1ε), a protein which may inhibit regulatory T-cell function (Burris et al., 2018)

Comparison of Structure and Lipid Kinase Inhibition Profile for Umbralisib and Approved PI3K Inhibitors

Umbralisib	Idelalisib	Copanlisib
		
		

DiscoverRx KinomeScan

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 ≤ 2 without limit to number of prior therapies. Adverse events were graded by CTCAE v4.03 criteria.

TGR-1202-101: Single Agent Umbralisib

Phase 1, first-in-human, dose-escalation study evaluating umbralisib monotherapy in patients with relapsed or refractory hematologic malignancies. Umbralisib administered daily until progression or off study (50 mg – 1800 mg). (*Burris et al., Lancet Oncology 2018*)

UTX-TGR-103: Umbralisib + Ublituximab +/- Ibrutinib or +/- Bendamustine

Phase 1, dose-escalation study evaluating the combination of umbralisib + ublituximab (U2), U2 + ibrutinib, and U2 + bendamustine, in patients with hematologic malignancies. Umbralisib administered daily; UTX administered D1, 8 and 15 of Cycles 1 & 2, and D1 of Cycles 2-6; Ibrutinib 420 mg CLL/560 mg NHL; Benda 90 mg/m^2. (*Nastoupil et al., ICML 2017; Lunning et al., ICML 2017*)

TGR-1202-201: TKI Intolerant CLL

Phase 2, multi-center, single arm study evaluating umbralisib monotherapy (800 mg QD) in CLL patients who are intolerant to prior PI3Kδ or BTK therapy. Umbralisib administered daily until progression or off study. (*Mato et al., EHA 2018*)

TGR-IB-105: Umbralisib + Ibrutinib in CLL & MCL

Phase 1, dose-escalation study evaluating umbralisib + ibrutinib in patients with relapsed or refractory CLL or MCL. Umbralisib (400, 600, or 800 mg) + Ibrutinib (420 mg CLL/560 mg MCL) administered daily. (*Davids et al., ICML 2017*)

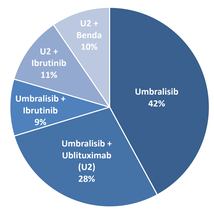
Prior Integrated Analysis of Safety (Davids et al., ASH 2017)

Demographics

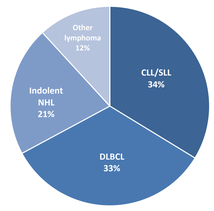
Evaluable for Safety, n	347
Age, median (range)	66 (22 – 96)
Prior Therapies, median (range)	3 (0-14)*
Patients with ≥ 3 Prior Therapies, n (%)	175 (50%)

*3 treatment naïve patients

Umbralisib Regimen



Histology



All Grades, All Causality, AEs Occurring in >15% of Patients

Diarrhea	44%
Nausea	39%
Fatigue	35%
Neutropenia	22%
Anemia	20%
Vomiting	19%
Dizziness	18%
Thrombocytopenia	18%
Cough	17%
Decreased appetite	16%
Headache	16%

Grade 3/4, All Causality, AEs Occurring in >2% of Patients

Neutropenia	16%
Anemia	5%
Thrombocytopenia	5%
Diarrhea	4%
Pneumonia	4%
Dyspnea	3%
Hypokalemia	3%

- Median duration of exposure was 6.5 months
- Serious adverse events occurring in >1% of patients were pneumonia (5%), febrile neutropenia (3%), sepsis (2%), and pyrexia (2%).
- Diarrhea events mostly occurred early, and resolved in a median of 7 days
- Discontinuations due to AEs were rare at under 10% for all studies

Immune-mediated adverse events were infrequent:
- transaminitis (9%; Gr.3/4 2%);
- colitis (<1.5%; Gr.3/4 <1%);
- pneumonitis (<1.5%; Gr.3/4 <0.5%)

Results

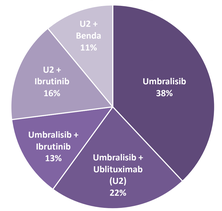
Long Term Safety Analysis: Patients on Umbralisib For 6+ Months

Demographics

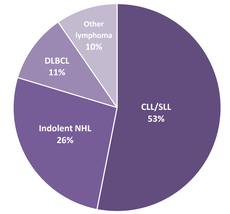
Evaluable for Safety, n	177
Age, median (range)	66 (29 – 96)
Prior Therapies, median (range)	2 (0-8)*
Patients with ≥ 3 Prior Therapies, n (%)	80 (45%)

*3 treatment naïve patients

Umbralisib Regimen

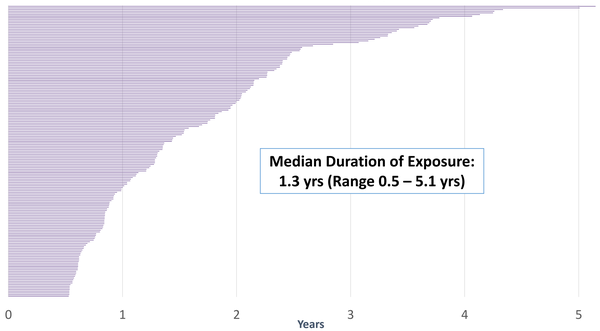


Histology



- Median Duration of Exposure: 1.3 years (Range 0.5 – 5.1 years); with 33% having 2+ years of daily exposure
- No events of Grade 4 diarrhea were reported
- Of the 14 patients with Grade 3 diarrhea:
  - Median time to onset was 14.6 months (range 7.0 – 43.3 months)
  - Median duration of the event was 8 days
  - Dose interruption without supportive care was the most common action taken
  - 1 patient had biopsy confirmed colitis and discontinued umbralisib
- No events of Grade ≥3 rash were reported
- 3 events of pneumonitis were reported (2 Gr. 2, 1 Gr. 3)
- Grade ≥3 transaminitis was reported in 5 patients (3%)
- 12% of patients discontinued umbralisib after 6 months due to an AE, with only 2% of discontinuations for diarrhea/colitis of any grade

Duration on Therapy



All Grades, All Causality, Adverse Events Occurring After 6 Months on Umbralisib

	Grade 1		Grade 2		Grade 3		Grade 4	
	N	%	N	%	N	%	N	%
Diarrhea	18	10%	10	6%	14	8%	-	-
Nausea	17	10%	7	4%	3	2%	-	-
Cough	16	9%	9	5%	-	-	-	-
Neutropenia	6	3%	3	2%	8	5%	7	4%
Fatigue	6	3%	13	7%	2	1%	-	-
Sinusitis	4	2%	15	8%	-	-	-	-
Vomiting	12	7%	4	2%	2	1%	-	-
Anemia	8	5%	5	3%	4	2%	-	-
Insomnia	13	7%	3	2%	-	-	-	-
URT infection	4	2%	12	7%	-	-	-	-
Hypokalemia	10	6%	3	2%	2	1%	-	-
Thrombocytopenia	8	5%	3	2%	3	2%	1	1%
Abdominal pain	7	4%	4	2%	3	2%	-	-
Arthralgia	9	5%	4	2%	-	-	-	-
Dizziness	8	5%	4	2%	1	1%	-	-
Hypophosphatemia	2	1%	5	3%	5	3%	1	1%
Pyrexia	10	6%	2	1%	1	1%	-	-
Headache	8	5%	2	1%	2	1%	-	-
Pneumonia	-	-	3	2%	9	5%	-	-
Creatinine increase	7	4%	4	2%	-	-	-	-
Dyspnea	7	4%	2	1%	1	1%	1	1%
Constipation	7	4%	2	1%	1	1%	-	-

- Serious adverse events occurring in >1% of patients were limited to pneumonia (3%), diarrhea (2%), and cellulitis (2%)

Conclusions

- Umbralisib is associated with low rates of immune-mediated toxicity and exhibits a favorable long-term tolerability profile at a median follow-up of 1.3 years, with up to 5 years of exposure in this integrated cohort of patients. In particular:
  - Only 2% of patients discontinued as a result diarrhea/colitis after being on umbralisib for more than 6 months; and
  - Discontinuations due to other AEs of interest for prior generation PI3K inhibitors were also rare.
- The mechanism for decreased immune-mediated toxicity is still being elucidated through ongoing pre-clinical and correlative studies examining umbralisib's selectivity for PI3Kδ over PI3Kγ, complimentary CK1ε inhibition, and enhancement of regulatory T-cell function.
- Registration directed trials in CLL and NHL for umbralisib have completed enrollment with data pending

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