An Integrated Safety Analysis of the Next Generation PI3Kδ Inhibitor Umbralisib (TGR-1202) in Patients with Relapsed/Refractory Lymphoid Malignancies

Abstract # 4037

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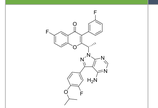
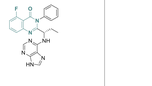
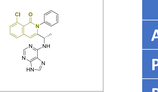
Background

- 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.
- Previously, an integrated analysis of 165 patients with a variety of hematologic malignancies treated with umbralisib monotherapy or umbralisib + the glycoengineered anti-CD20 mAb ublituximab demonstrated a favorable safety profile, with infrequent immune mediated adverse events (Burris et al, ASCO 2016).
- Here we present an updated and expanded integrated analysis of patients treated with umbralisib either as monotherapy or in combination with other agents.

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 (Deng et al, 2016)

Comparison of Structure and Lipid Kinase Inhibition Profile

Umbralisib	Idelalisib	Duvelisib
		
		

DiscoverRx KinomeScan

Study Design/Methods

Safety data were pooled from 5 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).

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

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.

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.

UTX-TGR-205: UNITY-NHL (DLBCL Cohort)

Phase 2b, multi-center study evaluating umbralisib monotherapy compared to U2 in patients with relapsed or refractory DLBCL. Umbralisib (800 mg QD) administered daily; UTX administered D1, 8 and 15 of Cycles 1 & 2, and D1 of Cycles 2-6.

Results

Demographics

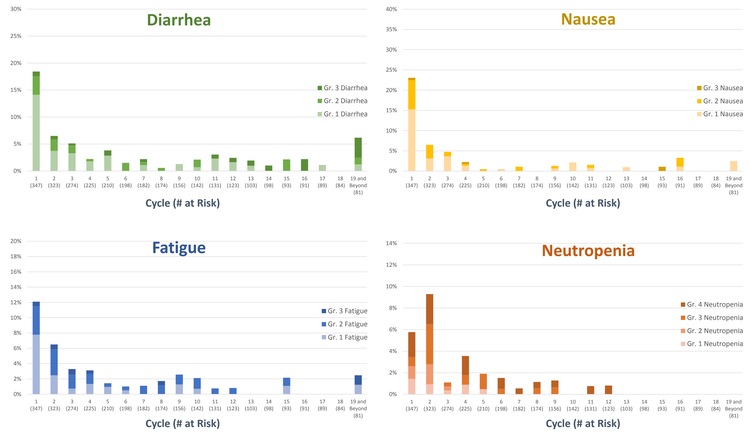
Evaluable for Safety, n	347
Umbralisib Monotherapy	146 (42%)
Umbralisib + Ublituximab	98 (28%)
Umbralisib + Ibrutinib	32 (9%)
Umbralisib + Ublituximab + Ibrutinib	38 (11%)
Umbralisib + Ublituximab + Bendamustine	33 (10%)
CLL/SLL	117 (34%)
DLBCL	116 (33%)
Indolent NHL	73 (21%)
Other lymphoma	41 (12%)
Age, median (range)	66 (22 – 96)
Prior Therapies, median (range)	3 (0-14)
Patients with ≥ 3 Prior Therapies, n (%)	175 (50%)

Safety

- Cumulative duration of drug exposure across all 347 patients was over 270 years
- 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%)

Incidence of Most Prevalent Adverse Events



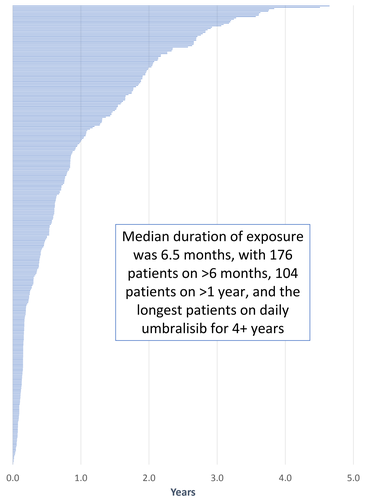
All Grades, All Causality, Adverse Events Occurring in >15% of Patients

	Study 101 Umbra Alone N=90	Study 201 Umbra Alone N=33	Study 105 Umbra + Ibrutinib N=32	Study 103 Umbra + Ubli (U2) N=75	Study 103 U2 + Ibrutinib N=38	Study 103 U2 + Benda N=33	Study 205 U2 or Umbra N=46	TOTAL N=347
Diarrhea	43%	42%	53%	57%	47%	36%	22%	**44%**
Nausea	40%	48%	34%	53%	34%	24%	28%	**39%**
Fatigue	30%	21%	72%	43%	47%	9%	22%	**35%**
Neutropenia	12%	21%	31%	32%	32%	24%	7%	**22%**
Anemia	12%	12%	63%	17%	26%	12%	13%	**20%**
Vomiting	26%	9%	9%	29%	18%	12%	7%	**19%**
Dizziness	12%	18%	31%	21%	37%	6%	11%	**18%**
Thrombocytopenia	11%	24%	59%	12%	29%	15%	4%	**18%**
Cough	21%	18%	13%	21%	32%	3%	2%	**17%**
Decreased appetite	16%	9%	19%	21%	5%	27%	13%	**16%**
Headache	21%	12%	31%	16%	16%	6%	4%	**16%**

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

	Study 101 Umbra Alone N=90	Study 201 Umbra Alone N=33	Study 105 Umbra + Ibrutinib N=32	Study 103 Umbra + Ubli (U2) N=75	Study 103 U2 + Ibrutinib N=38	Study 103 U2 + Benda N=33	Study 205 U2 or Umbra N=46	TOTAL N=347
Neutropenia	11%	18%	13%	28%	18%	24%	2%	**16%**
Anemia	8%	3%	9%	4%	3%	6%	4%	**5%**
Thrombocytopenia	6%	6%	9%	5%	8%	6%	0%	**5%**
Diarrhea	2%	9%	3%	8%	3%	9%	0%	**4%**
Pneumonia	4%	0%	0%	8%	11%	0%	2%	**4%**
Dyspnea	4%	0%	0%	3%	3%	3%	4%	**3%**
Hypokalemia	4%	3%	3%	3%	0%	9%	0%	**3%**
Febrile Neutropenia	3%	9%	0%	4%	3%	0%	2%	**3%**

Duration on Therapy



Median duration of exposure was 6.5 months, with 176 patients on >6 months, 104 patients on >1 year, and the longest patients on daily umbralisib for 4+ years

Conclusions

- In longer follow-up and in an expanded patient population, umbralisib exhibits a differentiated safety profile compared to prior generation PI3Kδ inhibitors.
- No significant differences in safety profile were observed across different lymphoid malignancies
- Improved tolerability with few discontinuations due to AEs has allowed patients to remain on continuous dosing to achieve and sustain promisingly high rates of response:
  - 85% ORR for single agent umbralisib in relapsed/refractory CLL
  - 53% ORR for single agent umbralisib in relapsed/refractory FL
- The mechanism for decreased immune-mediated toxicity of umbralisib is still being elucidated through ongoing pre-clinical and correlative studies selectivity for PI3Kδ over PI3Kγ, complimentary CK1ε inhibition, and enhancement of regulatory T-cell function.

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