Background

Rationale
- Kinase inhibitor (KI) therapies are generally well tolerated, although intolerance is the most common reason for discontinuation in practice (~20% discontinuation rate due to AE)\(^1\)
- AEs leading to BTK and PI3K\(\delta\) discontinuation are non-overlapping
- Ibrutinib interruptions ≥ 8 days can negatively affect PFS\(^2\)
- Retrospective data show that KI-intolerant patients can be successfully treated with an alternate KI

Umbralisib (TGR-1202) is a next generation PI3K\(\delta\) inhibitor, with a unique structure and activity profile distinct from other PI3K\(\delta\) inhibitors, including:
- A differentiated safety profile from other PI3K\(\delta\) inhibitors, notably with respect to hepatic toxicity and coasts observed to date;
- Oral, once-daily (QD) dosing);
- High selectivity to the \(\delta\) isofrm of PI3K, and
- Also targets casein kinase-1 epsilon (CK-1\(\epsilon\)), a protein which may inhibit regulatory T-cell function

Comparison of Structure and Kinase Inhibition Profile\(^a\)

<table>
<thead>
<tr>
<th>Kinase Inhibition Profile</th>
<th>Umbralisib</th>
<th>Ibrutinib</th>
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<tbody>
<tr>
<td><strong>PI3K(\delta)</strong></td>
<td>99% Selectivity</td>
<td>99% Selectivity</td>
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<tr>
<td><strong>PI3K(\zeta)</strong></td>
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<td><strong>PI3K(\gamma)</strong></td>
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<td><strong>PI3K(\alpha)</strong></td>
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<td><strong>BTK</strong></td>
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<tr>
<td><strong>ITK</strong></td>
<td>99% Selectivity</td>
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Study Design

Study TGR-1202-201

| Phase II, multicenter, single-arm trial of umbralisib monotherapy in CLL pts who are intolerant to prior KI therapy (NCT02742090) |
| Enrolment: Up to 50 patients who have discontinued prior therapy with a BTK or PI3K\(\delta\) inhibitor due to intolerance |
| All patients received umbralisib 800 mg oral, once-daily (QD) |
| Peripheral blood samples were collected at screening for central analysis of high-risk cytogenetics and BTK/PI3K mutations/deletions |
| Study fully accrued as of June 2018 |

Key Eligibility Criteria

- CLL patients whose prior therapy with a BTK inhibitor (ibrutinib, acalabrutinib) or a PI3K\(\delta\) inhibitor (idelalisib, duvelisib) was discontinued due to intolerance within 12 months of CI/D1.
- Meets study KI Intolerance definition
- Off prior KI for at least 14 days following discontinuation w/o disease progression.
- ANC > 1,000/\(\mu\)L, platelet count > 30,000/\(\mu\)L

Results

Demographics

- Evaluatable for Safety, n = 51
- Evaluable for PFS, n = 50
- Measurable Disease at Study Entry, n = 36
- Median Age, years (range) = 70 (48 – 96)
- Male/Female = 28/22
- ECOG, 0/1/2 = 3/24/3
- 17 pts and/or TP53 mutated, n (%) = 12 (24%)
- 11 pts, n (%) = 9 (18%)
- UGH Unmutated, % = 21 (41%)
- Bulky Disease, n (%) = 21 (41%)
- Prior Therapies, median (range) = 2 (1 – 7)
- Prior BTK inhibitor, n (%) = 44 (86%)
- Prior PI3K\(\delta\) inhibitor, n (%) = 7 (14%)
- Median Time on Prior KI, mos (range) = 9 (0.7 – 38 mos)
- Median Time from D/C of Prior KI to Enrollment, mos (range) = 3 (1 – 12)
- Required Tx within 6 mos of Prior KI, n (%) = 39 (76%)

Safety: All Causality Adverse Events in >10% of Patients (N=51)

- Median follow up of 15.7 months
- 4 patients had recurrence of an AE that led to prior KI intolerance, however 3 were of lesser severity and did not lead to dose modification of umbralisib, and 1 patient d/c for recurrent rash (prior ibrutinib)
- 1 case of colitis reported after 6 weeks on treatment – 17p del CLL patient. Recovered after 2 week hold, and did not recur on re-challenge at 600 mg daily - patient achieved a CR and on study for 25 months
- No fatal AEs occurred
- 8 pts (16%) had dose reductions allowing them to continue umbralisib therapy
- 6 pts (12%) discontinued treatment due to an umbralisib AE (pneumonitis (2), pancreatitis, pneumonia, dermatitis, rash)

Efficacy

- Best % Change in Nodal Lesions

  - Progression-Free Survival
  - Estimated median PFS: 23.5 mos (95% CI 13.1 – NE)
  - Median OS not reached

Conclusions

- Favorable safety profile: Umbralisib demonstrates a favorable safety profile in pts intolerant to prior BTK or PI3K\(\delta\) therapy
- Well tolerated: Only 1 pt (2%) discontinued due to a recurrent AE also experienced with prior KI therapy, only 6 pts (12%) discontinued due to an umbralisib AE
- Significant clinical activity: Primary endpoint was met with a median PFS of 23.5 months in a high-risk population, and 94% of patients with measurable disease at baseline had a reduction in lymphadenopathy