Long term Results of a Phase I/II Study of Ibrutinib in Combination with Umbralisib in Patients with Relapsed/Refractory CLL or MCL
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Leukemia & Lymphoma Society | Blood Cancer Research Partnership (LLS/BCRP)

Background

Ibrutinib is highly active in R/R CLL and MCL

Study Endpoints

Primary

- Maximum tolerated dose (MTD) of umbralisib when used in combination with ibritunib in patients with relapsed or refractory CLL or MCL
- Safety and dose limiting toxicities (DLTs) of umbralisib in combination with ibritunib in patients with relapsed or refractory CLL or MCL

Secondary

- Clinical efficacy: ORR, CR, PR, PR-L, PFS, and remission duration
- Association of CLL prognostic factors (e.g. FISH, IGVM, etc.) with response

Key Eligibility Criteria

- CLL/GCL or MCL progressed after at least 1 prior standard therapy, an indication for therapy, and at least 1 measurable site of disease
- ECOG PS ≤2
- Adequate hematologic and organ function
- In Ph I portion, patients with prior BTK or PI3K inhibitor therapy were eligible
- Exclusion
- AutoHCT within 3 mo. or alloHCT within 12 mo. of study entry
- Post-allo patients must not have active GVHD and be off immune suppression
- Active hepatitis, HIV infection, or central nervous system involvement
- Patients who require warfarin for anticoagulation

Study Design

- Patients received continuous simultaneous daily oral dosing of ibritunib (420 mg daily) and umbralisib starting in an initial cohort at 400 mg daily and escalating in a standard 3 + 3 design to 600 and 800 mg cohorts
- Radioactivity scans for CLL patients and PET/CT for MCL patients

Umbralisib is a potent, well-tolerated next-generation PI3K inhibitor

Efficacy

Safety

Table: Patient Characteristics (N = 42)

Patient Characteristics

<table>
<thead>
<tr>
<th>Grade ≥ 3 (N = 42)</th>
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<tbody>
<tr>
<td>Neutropenia, N (%)</td>
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<tr>
<td>Infection, N (%)</td>
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<tr>
<td>Fatigue, N (%)</td>
</tr>
<tr>
<td>Nausea, N (%)</td>
</tr>
<tr>
<td>Hemorrhage, N (%)</td>
</tr>
<tr>
<td>Anemia, N (%)</td>
</tr>
<tr>
<td>Thrombocytopenia, N (%)</td>
</tr>
<tr>
<td>Nausea, N (%)</td>
</tr>
<tr>
<td>Transient MDS, N (%)</td>
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<tr>
<td>Hypertension, N (%)</td>
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</tbody>
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Safety Analysis

- All of the updated data cut on 8 Feb 2020
- Median follow-up among survivors is now 43.5 months (range 8.4-61)
- As previously reported, the recommended phase 2 dose of umbralisib was 800 mg daily when given with standard dose ibritunib
- All-grade adverse events occurring in ≥25% of patients, and Grade 3-4 AEs in all patients are presented in the table below
- No cumulative or recurrent late onset toxicities observed, including no new episodes of atrial fibrillation (rate still 10%) and no Gr 3/4 bleeding events
- Only 1 additional patient developed hypertension (updated rate 14%)
- The rate of transaminitis rose from 24% to 38%, but all of these were Gr1
- No other new immune-mediated toxicities arose, with a cumulative rate of Gr3 diarrhea of 10% and no colitis or G4 diarrhea
- Two additional SAEs occurred: a patient with a G2a gastric ulcer admitted and medically managed, and a patient with prior FCR, in radiographic CR on this study and diagnosed with G4 MDS about 3 years into this study
- 129 episodes of atrial fibrillation (rate still 10%), and no Gr 3/4 bleeding events
- 10 patients discontinued due to PD, 7 due to AEs, 5 due to treatment decision, 4 due to death (2 PD, 1 AE, 1 CR put on hospice due to progressive dementia), and 2 due to intercurrent illness

Efficacy Analysis

- Best ORR in CLL and MCL rose to 95% and 71%, respectively
- The best CR rate for CLL remained 29%, and rose in MCL to 24% and 71% for ibrutinib and umbralisib, respectively
- Radiographic CR rate in CLL was 43% (2 of these pts did not have a concomitant marrow, I had low-level residual marrow disease)

Conclusions

- With long term follow-up, ibrutinib plus umbralisib continues to demonstrate good tolerability, with the convenience of an all oral regimen
- In R/R MCL, efficacy is similar as would be expected for ibrutinib alone
- In R/R CLL, the 4-year PFS and OS are 79% and 90%, respectively, are promising in light of historical results with ibrutinib alone
- This approach warrants further study, particularly in BTK-naive CLL patients, including those with either intolerance or progression on a venetoclax-based regimen