A Phase I Study of Duvelisib and Venetoclax in Patients with Relapsed or Refractory CLL/PLL

Jennifer L. Crombie, MD,1 Svitlana Tyekucheva, PhD2,3 Alexandre Savell, BS1 Karen Francoeur, RN4,5 Mark Choiniere, BA1, Josie Montegaard, NP1, Jacob D. Soumerai, MD,6 Jon E. Arnanson, MD,6 David C. Fisher, MD,1 Jennifer R. Brown, MD, PhD1 and Matthew S. Davids, MD, MMSc1

1Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; 2Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Harvard T.H. Chan School of Public Health, Boston, MA; 3Verastem Oncology, Needham, MA; 4Center for Lymphoma, Massachusetts General Hospital, Boston, MA; 5Beth Israel Deaconess Medical Center, Boston, MA

Background

Rationale
- Duvelisib (DUV), an oral inhibitor of PI3K-δ, and venetoclax (VEN), an oral inhibitor of BCL-2, are approved for relapsed/refractory (R/R) CLL.
- Duration of response to monotherapy is limited, especially for patients who have failed BTK inhibitors or have TP53 dysfunction.
- PI3K inhibitors kill ex vivo CLL cells even in the presence of stroma and enhance cell dependence on the anti-apoptotic protein, BCL-2, for survival. (Fig. A/B).
- DUV plus VEN are synergistic in Richter’s syndrome PDX model (Iannello et al., ASH Abstract #2862, 2019).
- We hypothesized that DUV plus VEN would lead to deep remissions with high rates of uMRD that allow for an all oral, time-limited therapy.

Aims/Methods

Key Eligibility Criteria

Inclusion Criteria:
- Confirmed diagnosis of CLL or SLL requiring therapy, as per IW-CLL 2008 criteria.
- Disease that has progressed during or relapsed after at least one previous CLL/SLL therapy.
- Hematologic criteria (unless marrow involvement): Absolute neutrophil count ≥500 cells/mm³ and platelet count ≥25,000 cells/mm³.

Exclusion Criteria:
- Previous treatment with VEN or DUV.
- Currently active gastrointestinal disease, including colitis, inflammatory bowel disease and diarrhea requiring therapy.
- Confirmed CNS involvement.
- Use of warfarin, other anticoagulants allowed with warfarin INR ≤2.

Endpoints

Primary Endpoint:
- MTD and RP2D for VEN when given in combination with DUV in R/R CLL/SLL.

Secondary Endpoints:
- Pharmacokinetics (PK) of DUV and VEN.
- Preliminary efficacy: ORR, CR rate, DOR, PFS, OS.

Pharmacokinetics

No grade 4 non-hematologic toxicities observed.

Conclusions

- DUV plus VEN is promising in pts with R/R CLL/SLL, with no DLTs observed.
- RP2D of VEN is 400 mg QD in combination with DUV 25 mg BID.
- No significant drug-drug interaction was observed.
- Although neutropenia was common, febrile neutropenia and other infections were rare.
- Early efficacy data for this 1-year, time-limited, all oral regimen are encouraging, with CRs and uMRD already observed despite short follow-up.
- A phase II portion of the trial is now accruing for R/R CLL/SLL and includes a separate cohort for Richter’s syndrome.

Acknowledgments

- This investigator-sponsored trial (NCT03534323) is supported by Verastem Inc., the ASCO VIA Award (A.L.C.), the FLAMES Award (A.L.C.), and the LSLS Scholar in Clinical Research Award (M.S.D.).
- The authors thank the patients and their families for participating.
- COI: SAB/consulting fees: JM, Jansen, Pharmacyclics, JS; AbbVie, Verastem, JA, Caligene/Luna Resorts, Regeneron, JBR AbbVie, AstraZeneca, Boehringer, Celgene, Dynavax, Genentech/Roche, Oleada, Juno, Caligene, Kite, Loxo, Novartis, Pharmacyclics, Sunesis, TG Therapeutics, Verastem, janssen, Teva, Merck, Wyeth, Incyte, Octapharma, MSD-Medarex, AstraZeneca, Genentech, Jansen, MEI, Pharmacyclics, Synos, Verastem.

Matthew Davids, MD, PhD
(PI and Corresponding Author)