Abstract: S162

Title: 7-YEAR UPDATE ON A PHASE 2 TRIAL OF FIXED-DURATION OBINUTUZUMAB, IBRUTINIB, AND VENETOCLAX FOR CLL

Abstract Type: Oral Presentation

Session Title: Frontline therapy for CLL and Richter

Background:

Fixed-duration combination regimens with a BTK inhibitor and BCL2 inhibitor with or without an anti-CD20 antibody are highly effective for the treatment of chronic lymphocytic leukemia (CLL) and allow for durable remissions after treatment. These regimens have been increasingly investigated and it is imperative to understand the duration of disease control as well as patient and disease features predictive of undetectable measurable residual disease (uMRD) status and progression-free survival (PFS).

Aims:

To describe the PFS after treatment with combination obinutuzumab, ibrutinib, and venetoclax as well as factors associated with uMRD status through additional follow up of a phase 2 trial in CLL.

Methods:

Adults with treatment naïve (TN) or relapsed/refractory (RR) (≥1 prior treatment) CLL requiring treatment were eligible. Treatment was given for 14 cycles (C) of 28 days each. Obinutuzumab was started C1 and given monthly through C8, ibrutinib was started in C2 and given through 14, and venetoclax was started in C3 with standard dose escalation and continued through C14. Response was assessed 2 months after C14 (EOT) by iwCLL 2008 criteria. uMRD was determined by 10-color flow cytometry with a cutoff of <1x10-4. Patients were considered uMRD if CLL was not detected in the blood or bone marrow at EOT. The method of Kaplan-Meier was used to describe PFS and overall survival (OS). Cox regression model was used to correlate clinical factors with PFS, and logistic regression was used for uMRD status at EOT.

Results:

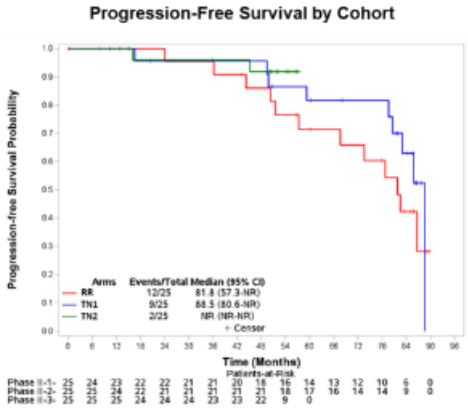
A total of 75 patients were treated in 3 cohorts with one RR (n=25, median follow-up [FU] 83.0 [range: 0.2-89.7] months) and two TN which differed only by enrollment period (TN1; n=25, median FU 85.6 [range: 10.3-91.1] months, TN2 n=25, median FU 51.7 [range: 35.8-57.3] months). The median age was 58 (24-77) years and 36% were women. The CLL was IGHV unmutated in 55 (75%), had complex karyotype (≥3 abnormalities) in 27 (36%), and FISH positive for del(17p) in 6 (8%) patients. For RR patients the median prior treatments was 1 (range 1-3).

uMRD status was achieved in 11 (44%) of RR, 14 (56%) of TN1, and 15 (60%) of TN2 patients. The median PFS for the RR cohort was 81.8 (95% CI: 57.3-NR) months and for the TN1 cohort it was 88.5 (95% CI: 80.6-NR) months. The median PFS was not reached in the TN2 cohort and the estimated 48-month PFS was 91.8% (95% CI: 71.1-97.9). Median overall survival (OS) was not reached in any cohort and the 48-month estimates were 100% for RR, 95.7% for TN1, and 91.8% for TN2. (Figure)

On univariable analysis (UVA) both lactate dehydrogenase (LDH) (OR 0.26 [95% CI: 0.10-0.67] for 2-fold increase, p=0.0055) and beta-2-microglobulin (B2M) (OR 0.69 [95% CI: 0.49-0.98] for 1-unit increase, p=0.04) were associated with uMRD status, and only LDH remained significant in multivariable analysis (MVA). On UVA both prior therapies (HR 1.66 [95% CI:1.06-2.62] for 1 additional, p=0.03) and B2M (HR 1.52 [95% CI: 1.13-2.05] for 1-unit increase, p=0.006) were associated with PFS. Only B2M remained significant in MVA. In a landmark analysis, there was no difference in PFS from the EOT timepoint for those who achieved uMRD and those who did not (p=0.76).

Summary/Conclusion:

In a phase 2 study of fixed-duration obinutuzumab, ibrutinib, and venetoclax the median PFS was 81.8 months for RR and 88.5 months for TN patients. This demonstrates durable efficacy for a limited duration treatment of just over a year. Longer PFS was not observed in patients with uMRD status and only baseline B2M was associated with PFS on MVA. This suggests that additional biomarkers are needed.



Keywords: Chronic lymphocytic leukemia