Combination of the Bruton's tyrosine kinase (BTK) inhibitor PCI-32765 with bendamustine (B)/rituximab (R) (BR) in patients (pts) with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL): Interim results of a phase Ib/II study.

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Abstract:

Background: BTK is an essential mediator of B cell receptor signaling and a critical kinase for lymphoma cell survival. PCI-32765 (P), an oral, selective, irreversible inhibitor of BTK, inhibits proliferation, migration and adhesion in CLL cells, and is highly active as a single agent for the treatment of R/R CLL pts. (O'Brien ASH 2011). BR produces an overall response rate (ORR) of 59% in R/R CLL (Fischer JCO 2011). We report interim data on P combined with BR. **Methods:** R/R CLL pts received P 420 mg orally daily for 28-day (D) cycles (C) until disease progression (PD). B was administered 70 mg/m^2 on D1 and D2 combined with R 375 mg/m^2 on D0 for C1 and 500 mg/m^2 on D1 for subsequent courses for a maximum of 6 cycles. Response was evaluated according to IWCLL criteria. **Results:** 30 pts were enrolled. Median age of pts was 62 yrs (range 41-82). 46% of pts were Rai stage III/IV and the median # of prior therapies was 2

(range 1-4). 37% and 13% were considered refractory (treatment free interval <12 mo) to a purine analog containing regimen or BR, respectively. Bulky disease was present in 52%. Adverse events (AE) have been consistent with that expected with BR. Gr 3/4 neutropenia and thrombocytopenia have been noted in 47% and 10% of pts, respectively. Grade >3 non-hematologic AEs potentially related to P included rash (3 pts) and fatigue and tumor lysis reported in 2 pts each. There were no Gr 3/4 infusion reactions. There have been no discontinuations (D/C) due to AE and no deaths on study. At a median follow-up of 4.9 mos (range 2.7-8.3 mo) 16 pts have completed BR and 14 pts are still receiving BR. The ORR is 90% (27/30 pts) (CR 10%, PR 80%). 2 additional pts achieved a nodal response with residual lymphocytosis. Responses appear independent of high-risk clinical or genomic features. 90% of pts remain on study; reasons for D/C include PD (n=2) and 1 pt pursuing SCT. **Conclusions:** PCI-32765, in combination with BR, is highly active. The high ORR, low rate of PD, and good tolerability compares very favorably with historical controls, warranting additional investigation of this combination.