24th Congress of the European Hematology Association

PS1155 A PHASE II STUDY OF THE SYK INHIBITOR ENTOSETINIB IN COMBINATION WITH OBINUTUZUMAB IN PATIENTS WITH RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

A. Kittel,1 T. Hashiguchi,1 B. Thurlow1, B. Gokcay1, A. Stadnik2, R. MacKinnon1, S. Monette1, L. Moore1, D. Persky1, B. Park1, S. Spurgeon1, A. Danilov1.

1Oregon Health and Science University, Portland, 2Arizona Cancer Center, Tucson, United States

Aims: Armed with this mechanistic knowledge, we designed a Phase II/II investigator-sponsored trial of ENTO in combination with Obin in patients with relapsed/refractory (R/R) CLL and non-Hodgkin lymphoma (NHL).

Methods: Eligible pts were aged ≥18 years, had CLL/NHL (Phase I) or CLL (Phase II), relapsed and/or refractory to ≥1 prior therapies (no prior SYK inhibitor), ECOG performance status ≤2, and preserved organ function. The Phase I part of the study followed a standard 3+3 design with two dose levels (DL1: ENTO 200 mg PO BID; DL2 – ENTO 400 mg PO BID). Obin was given IV on days 1, 3, 8, 15 of Cycle 1 and D1, D2, D8 of Cycle 2 in standard doses. ENTO was given until disease progression. Primary study objectives were toxicity (Phase I) and efficacy (objective response rate (ORR); Phase II).

Results: At DL1 of Phase I, six pts were enrolled (4 - CLL; 2 - follicular lymphoma). One pt experienced a dose-limiting toxicity (DLT: grade 3 asymptomatic LFT abnormalities which failed to resolve within 72 hours) attributed to ENTO. Other grade 3 toxicities included 2 grade 3 infections in one patient and one transient grade 4 neutropenia (attributed to Obin). Four pts remain on therapy after a median follow-up of 15 months. Three pts were enrolled at DL2 without DLTs.

In Phase 2, 18 pts with CLL received ENTO 400 mg PO BID (in combination with Obin). One pt was deemed ineligible due to Richter's transformation at study entry. Of the 17 evaluable pts, 71% were men. Median age was 66 years (range 47–76), and 76% were aged ≥65 years. 94% had ECOG performance status ≤1. Four pts (24%) had a complex karyotype. 2 (12%) had del(17p) and 8 (48%) had del(15q). Median number of prior therapies was 2 (range, 1–6); 47% had received prior fludarabine and 29% received prior ibritinib. As of February 1, 2019, with median follow-up of 8 months (range, 6–14 months), 83% of pts (14/17) remain on treatment. Median relative dose intensity of ENTO (ratio of actual to planned cumulative dose during drug exposure period) was 80%. ORR was 76% (95% CI: 50–93%); 12 (70%) pts with partial response, one (6%) pt had confirmed CR. Four (24%) pts had improvement in lymphadenopathy. Median duration of response and median progression-free survival (PFS) were not reached. All pts are alive. Two (12%) pts experienced neutropenia ≥3 lines of ≥3 days (RR = 1.97, 95% CI 0.5–3) and initial neutropenia (1,75 vs 0,47), simultaneous use of steroids (1,96 vs 0,39).

Summary/Conclusion: Patients with ECOG status >2 and initial neutropenia (HR: 1.75 vs 0.47, p = 0.004). In a multivariate analysis male gender (HR 1.89, 95% CI 0.5–3, p = 0.73–2.13), as well as in males (HR: 1.8; 95% CI 1.16–2.8, p = 0.004). In a multivariate analysis male gender (HR 1.89, 95% CI 0.5–3, p = 0.73–2.13), as well as in males (HR: 1.8; 95% CI 1.16–2.8, p = 0.004). In a multivariate analysis male gender (HR 1.89, 95% CI 0.5–3, p = 0.73–2.13), as well as in males (HR: 1.8; 95% CI 1.16–2.8, p = 0.004). In a multivariate analysis male gender (HR 1.89, 95% CI 0.5–3, p = 0.73–2.13), as well as in males (HR: 1.8; 95% CI 1.16–2.8, p = 0.004).

L. Van Der Straten1,2, A. P. Kater1, J. K. Doodijn3, E. C. Van den Broek1, E. F. Posthuma1,2, A. G. Dimmerhame1,4, M.-D. Levin2

1Research, Netherlands Comprehensive Cancer Organisation, Utrecht, 2Internal Medicine, Albert Schweitzer hospital, Dordrecht, 3Hematology, Amsterdam UMC, University of Amsterdam, Amsterdam, 4Hematology, Erasmus MC Cancer Institute, Rotterdam, 5PALGA, Houten, 6Internal Medicine, Reinder de Graaf hospital, Delft, 7Hematology, Leiden University Medical Center, Leiden, 8Public Health, Erasmus Medical Center, Rotterdam, Netherlands

Background: Chemoimmunotherapy with rituximab is a well-established treatment approach for patients with chronic lymphocytic leukaemia (CLL) that still holds therapeutic value in this era of novel agents, especially among specific patient subsets in the upfront setting. At present, the effectiveness of rituximab-based chemoimmunotherapy as first salvage therapy is ill-defined. Furthermore, it is unclear whether first-line therapy with rituximab hampers the effectiveness of second-line chemotherapy with rituximab.

Aims: The aim of this population-study was to assess the effectiveness of first-line rituximab-based chemotherapy, as compared to chemotherapy without rituximab, in first- and second-line treatment. Special emphasis was put on the effectiveness of second-line treatment with rituximab-based chemotherapy with or without previous rituximab exposure.

Methods: We selected all 1,735 CLL patients diagnosed in The Netherlands between 2004–2010 from the Dutch Population-based Haematological Registry for Observational studies (PHAROS) in CLL, with follow-up through December 31, 2014. We divided patients into three treatment cohorts, namely (1) first- and (2) second-line treatment, and (3) rituximab-based chemotherapy only in second-line. The primary end point was treatment-free survival (TFS). The Kaplan-Meier method was used for time-to-event analyses and the log-rank test to compare survival distributions in a univariable fashion. Multivariable evaluation of TFS was performed using Cox regression with adjustment for covariates (listed in Table 1). A P < 0.05 indicates statistical significance.

Results: First- and second-line treatment were initiated in 663 (38%) and 286 (16%) patients, respectively. Second-line treatment with rituximab was applied in 121 (42%) patients, of whom 32 (26%) were previously exposed to rituximab and 89 (74%) were not. In first-line treatment, median TFS was 19.7 and 67.1 months for chemotherapy without (n = 455; 67%) and with (n = 76; 218; 33%) rituximab, respectively (P < 0.001; Fig 1A). Median TFS among recipients of second-line chemotherapy without (n = 165) and with rituximab (n = 121) was 15.0 and 15.3 months, respectively (P = 0.318; Fig 1B). Of the 121 patients who received rituximab-based chemotherapy in second-line, median TFS was 18.3 and 12.1 months for those who received chemotherapy without (n = 89) and with (n = 32) rituximab in first-line, respectively (P = 0.243; Fig 1C). The multivariable analysis confirmed the