Title

PHASE 1B TRIAL OF AVL-292, A COVALENT INHIBITOR OF BRUTON'S TYROSINE KINASE (BTK), IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) AND B-NON-HODGKIN LYMPHOMA (B-NHL)

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with mitoxantrone (FCM, n=16). Less intense treatment approaches with single-agent chemotherapies, such as F (n=37), Clb (n=21) or bendamustine (B, n=15) were chosen in 87 patients. 10 patients receiving a stem cell transplantation, experimental drugs, irradiation or splenectomy were excluded from further analyses.Treatment regimen were allocated to three different relapse treatment groups: combined chemo(immuno)therapy or single-agent antibody-treatment (e.g. A, FC, FCR, BR), single-agent chemotherapies (e.g. F, B, Clb) and chemo (immuno) therapy with anthracyclines and/or ≥3 cytotoxic agents (e.g. CHOPR, CHOP, FCM). Median treatment free survival (time from 2nd-line to 3rd-line therapy or death) was 24.5, 18.7 and 16.4 months respectively (p=0.009). These inequalities in treatment efficacy translated into a significant difference in overall survival (OS): the median OS was 78.3 and 58.2 months in patients treated with either combined chemo(immuno)therapies/single agent antibody-therapies or single-agent chemotherapies, whereas patients with combined chemo(immuno)therapies containing anthracyclines and/or ≥3 chemotherapies had the worst median OS of 42.0 months (p=0.012). A higher median age in the single-agent chemotherapy group (67 versus 60 and 61 years) might have biased the treatment selection. All other patient characteristics, such as prognostic markers (IgHV status, cytogenetics, thymidine kinase and ß2-microglobuline), response to 1st-line therapy, time between 1st- and 2nd-line therapy and ECOG status did not differ between the three groups. **Summay and Conclusions.** Patients with a relapse <24 months who received therapies that contain ≥3 cytotoxic agents and/or anthracyclines had an impaired OS. Therefore, therapies such as CHOPR, CHOP or FCM appear to be inferior in comparison to standard chemoimmunotherapies or single-agent alemtuzumab. However, the worse outcome of early relapsing patients underscores the need for alternative treatment approaches with either allogeneic stem cell transplantation or use of novel drugs.

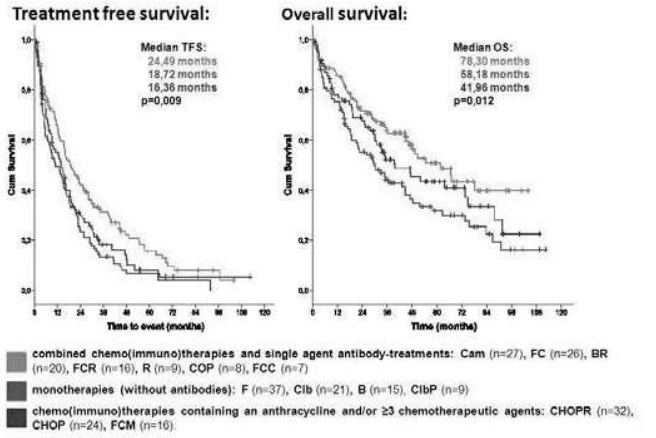

Figure 1

0148

GENETIC PROFILE OF CHRONIC LYMPHOCYTIC LEUKEMIA

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Background. With the increasing complexity of recurrent mutations in chronic lymphocytic leukemia (CLL), the clinical application and translation of genetic information is challenging. As CLL patients with *TP53* abnormalities require alternative treatment approaches, there is an urgent need for rapid and reliable assessment of genetic lesions that can easily be transferred to clinical practice. **Aims.** Our aim was to apply state-of-the-art technology to genotyping of leukemia. **Methods.** We designed a sensitive and reliable multiplex PCR system to analyze recurrent mutations in CLL. Based on a test set (n=59) with parallel Sanger sequencing, we developed a 454-based next-generation sequencing (NGS) approach to rapidly profile a panel of mutations in CLL-relevant and cancer consensus genes (*BRAF, EZH2, KRAS, MYD88, NOTCH1, NRAS, PIK3CA, SF3B1, TP53*). We validated the performance of the assay in a separate validation set (n=181) and thus contribute to mapping of the genetic profile of CLL. Exons with hotspot mutations in candidate genes and *TP53* (exons 4-10) were amplified for sequencing in 2 multiplex PCRs. We aimed at a minimum coverage of 30 reads per amplicon and achieved a medium coverage of 175 reads per amplicon. **Results.** We found a total of 40 non-synonymous sequence variants in the initial patient set. The most common mutations were found in *TP53* (17/40), *SF3B1* (11/40), and *NOTCH1* (9/40) (Figure 1). To confirm the assay performance and CLL mutation profile, we used a validation set of 181 CLL patients. The incidence of mutations and the most commonly mutated genes were similar in both data sets. All variants were verified by Sanger sequencing. In addition to known recurrent mutations in CLL, we also identified rare (but in part targetable) mutations in *BRAF* (1/40), *MYD88* (1/40), and *KRAS* (1/40) (Figure 1). Importantly, mutations in small subclones were only detectable using our newly established multiplex PCR and 454 sequencing approach. **Summary and Conclusions.** Our results provide evidence that recurrent gene mutations can be analyzed robustly with higher sensitivity than Sanger sequencing by using a NGS approach based on multiplex PCR. The in-depth analysis of the genetic profile of patients with CLL is a prerequisite for the design of genotype-specific treatment approaches. In accordance with previous studies, we show that *TP53*, *SF3B1,* and *NOTCH1* are commonly mutated in CLL.

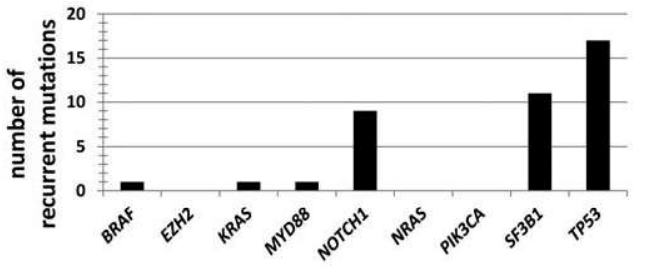

Figure 1. Distribution of recurrent mutations in CLL patients.

0149

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Background. Btk supports activation, survival, and proliferation of malignant B cells in CLL and B-NHL. AVL-292 is an oral, potent (IC_{50} < 0.5nM), selective small molecule covalent inhibitor of Btk. **Aims.** To characterize the safety, dose limiting toxicity (DLT), maximum tolerated dose (MTD), pharmacokinetics (PK), pharmacodynamics (Btk occupancy), recommended phase 2 dose, and preliminary efficacy of AVL-292 in CLL and B-NHL. **Methods.** Following informed consent, patients (pts) with previously treated CLL or B-NHL received AVL-292 in escalating doses of 125, 250, 400 or 625 mg po QD per cohort using a 3+3 design in continuous 28 day cycles until progressive disease (PD) or toxicity. Plasma AVL-292 levels were assessed by LC-MS-MS. Btk occupancy by AVL-292 was assessed by covalent probe assay in blood mononuclear cells. **Results.** 16 pts have enrolled (3 each @ 125 and 250 mg, 6 @ 400 mg, and 4 @ 625 mg: 8M/8F; median age 66 years (range 45-79); median 2 prior therapies (range 1-10)) including 9 CLL (2 with del17p, 2 with del11q22, 2 with both del17p/del11q22; 2 mutated *IGHV*, 5 unmutated *IGHV*, 2 missing) and 7 B-NHL (1 diffuse large B cell lymphoma (DLBCL); 3 follicular (FL); 2 marginal zone (MZL); 1 mantle cell). Median time on treatment is 94 days, range 15-204. Thir-