association of several mutations is common. VAF is very variable, whether patients appear in clinical response or progressive. These results raise the question of the clinical significance of these mutations and a follow-up is required to determine if all these mutations are actually predictive of disease progression. **Keywords:** chronic lymphocytic leukemia, ibrutinib, mutations, resistance

CLL-229

TP53, XPO1 and ATM Mutations Exclusive Distribution in the Adverse Prognosis Chronic Lymphocytic Leukemia (CLL) Group

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Therapeutic options for patients with CLL have dramatically improved in the last years, and various molecular markers have been proposed for the stratification of patients before treatment.

On a cohort of 126 CLL we performed IGHV mutational status, karyotype, FISH analysis of trisomy 12, 11q, 13q and 17p deletions, NGS determination of TP53, NOTCH1, SF3B1, POT1, MYD88, BIRC3, EGR2, ATM, XPO1 mutations. Our aim was to assess the distribution of these markers and their relevance.

A TP53 alteration was present in 41 patients: 19 with both TP53 mutation and 17p deletion, 19 with TP53 mutation and 3 with 17p deletion only. Among the 85 patients with no TP53 alterations, 31 presented mutated IGHV and 54 unmutated IGHV. As expected the incidence of the other mutations was higher in the unmutated IGHV group (59 mutations) than in the mutated IGHV group (9 mutations).

There was a strong imbalance of the other mutations between the TP53 altered and the other group. SF3B1 mutations were more frequent in the TP53 mutated group (14/41 vs 11/85, $p<0,005$), whereas NOTCH1 mutations incidence appeared similar in both groups (9/41 vs 15/85). XPO1 and ATM mutations were mutually exclusive, and TP53 mutations and XPO1 or ATM mutations were almost mutually exclusive as well (2/41 vs 19/85, $p<0,01$). This is in line with the impact of these 2 mutations on the TP53 pathway.

We next considered the added value of complex karyotype (CK). As expected, whether considering 3 (CK3) or 5 (CK5) alterations, it was significantly more frequent in the presence of TP53 alterations than in germline TP53 cases. As most of patients were tested before first line treatment, CK5 was quite rare (11/126). Among these 11 cases, 7 harbored a TP53 alteration, and the other 3 either an ATM, XPO1 mutation. Only one patient presented a CK5 without any observed mutation.

In conclusion, study of the impact of other mutations affecting the TP53 pathway is warranted notably for patients on targeted therapies. CK remains of interest within clinical trials but does not help further stratifying patients when a targeted NGS panel is used in clinical practice. **Keywords:** chronic lymphoid leukemia, TP53, molecular stratification

CLL-278

Impact of Ibrutinib in Quality of Life (QoL) in Patients with Chronic Lymphocytic Leukemia (CLL): Preliminary Results of Real-World Experience

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Context: Clinical data from controlled trials report an improvement in QoL in patients with CLL in ibrutinib monotherapy. Real-life evidence is necessary to confirm this data. **Objective:** The disease control when treatment is initiated could lead to decreased fatigue. It is likely that treatment with ibrutinib could result in an improvement in QoL in our real-world population. Primary objective: evaluate impact of ibrutinib treatment in QoL. We defined a clinically meaningful improvement $\geq$3 points in FACIT-fatigue score. Secondary Endpoints: Detect a 10% improvement by EQ5D VAS. Correlate baseline and follow-up hemoglobin levels (meaningful improvement $\geq$ 1g/dL). **Design:** This is a prospective, longitudinal, single arm study enrolling consecutive CLL patients under ibrutinib monotherapy either as first or further line of treatment. Median follow-up was 7 months (range 1-28). **Setting:** Patients are recruited in an academic referral center in Buenos Aires. **Interventions:** QoL was explored with FACIT-fatigue and EQ5D visual-analogue-scale (VAS) questionnaires (with copyright permission). Assessment by results reported by patient questionnaires are completed on months 0-1-3-6 and 12 since the beginning of treatment. **Main Outcomes Measures:** We are reporting preliminary results after 3 months of treatment compared to baseline. **Statistical Analysis:** data was analyzed with the Sign Test (Binomial Test). **Results:** A total of 21 CLL patients who started ibrutinib between 2016 and 2018 were included. Median age was 75 years (range 57-84); 12 patients (57%) were males. Ibrutinib was first-line therapy in 7 patients (33%), second-line in 7 patients (33%) and 7 patients (33%) received $\geq$ 3 previous lines. After 3 months of treatment, the median change in FACIT-fatigue score $\geq$ 3 points was reached in 13 patients (62%) as compared to baseline ($p=0.024$). After 3 months of treatment there was no evidence of a median change >10% on the EQ5D VAS ($p=0.593$) nor a

significant improvement on hemoglobin level (p=0.105). **Conclusions:** These results suggest an early improvement of fatigue within the first 3 months of treatment with ibrutinib. Longer follow-up and larger number of patient are necessary to confirm this data and determine the further improvements of QoL with continuous treatment and correlation with hemoglobin changes. **Keywords:** leukemia, novel therapy, ibrutinib, quality of life

CLL-279

Treatment CLL: Impact in the Dynamic of Clonal Evolution

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Context: Investigating CLL genetic heterogeneity and evolution is mandatory for patient care, particularly in the area of targeted therapies and personalized medicine. **Design:** We have longitudinally analyzed 215 CLL selected on the availability of follow up samples.164 were analyzed before treatment at 1st sample. Samples were analyzed by FISH with the 4 classical probes (detecting del17p, tri12, del11q and del13q), karyotype (K), NGS for major CLL oncogenes (Illumina CLL MASTER PLUS kit), and for *IGHV* status. **Results:** Patients with successful karyotype at 1st and last samples (n=162), showed karyotypic evolution, with more abnormal K (78 vs 64%, p=.005), more complex K ($\geq$ 3 abnormalities) (35 vs 20%, p=.003) and more highly complex K ($\geq$ 5 abnormalities) (20 vs 9%, p=.007) in the last sample.

FISH analyses with the 4 probes performed at 1st and last sample (n=212) showed a similar evolution, with more samples with 3 abnormalities (0.5 vs 6%, p=.002) in the last sample, including more del17p (10 vs 20%, p=.004). Biological data will be detailed with clinical course and treatments of the patients.

We show that CLL acquire complex karyotypes and a high number of FISH abnormalities during progression, in particular del17p. Whereas tri12 is never acquired at relapse, del13q, del11q and del17p can appear in the evolution of the CLL more frequently after treatment than during natural evolution. Whereas del17p always remains at relapse, del13q, tri12, and del11q can disappear after treatment, even if each patient has his own trajectory. Gene mutations (*TP53*, *ATM*, *BIRC3*, *NOTCH1*, *XPO1*, *SF3B1*, *MYD88*, *FBXW7* and *POT1)* could also be maintained, acquired or lost. **Conclusions:** The future challenge may be to characterize each individual tumor, at both cytogenetic and molecular level, to predict dynamic evolution in order to propose a matching therapy. **Keywords:** CLL, clonal evolution

CLL-303

Is CLL the Second Cancer? A Single Center Retrospective Analysis of Secondary Malignancies (SM) in Patients with Chronic Lymphocytic Leukemia (CLL)

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Context: Patients with CLL have increased incidence of SM including genitourinary (GU) cancers. This has been attributed to immune dysregulation caused both by the disease and as a consequence of treatment, especially chemotherapy containing alkylating agents. There exists paucity in literature about the risk factors, timing and outcomes of SM in CLL. We describe the Roswell Park Comprehensive Cancer Center (RPCCC) experience of SM in CLL over a span of 27 years. **Design:** The RPCCC translational lymphoma database was queried for all CLL patients treated between 1/1990 and 6/2017. A total of 977 patients were identified, median follow up was 7.5 yrs. Descriptive analyses were performed with a focus on patients with GU cancers. Latency from CLL was defined as time from diagnosis of CLL to diagnosis of SM. **Results:** The overall incidence of SM was 16.9%. 5.7% patients had GU cancers [prostate- 3.3% (33), renal cell (RCC)-1.2% (12), bladder- 1.1% (11)]. Most GU cancers preceded the diagnosis of CLL with a median latency of -8 months (mo) for prostate cancer, -13.3 mo for RCC and -54.5 mo for bladder cancer. Patients with SM were older at the time of CLL diagnosis (66 vs 60 yrs). There was no association between presence of del(13q), del(17p), trisomy 12 or del(11q) and incidence of SM. Presence of a SM did not influence the progression free survival (PFS) of CLL. However, patients diagnosed with CLL first had a longer PFS and OS as compared to those in whom the SM preceded CLL. Among GU cancers, presence of bladder cancer was associated with a shorter OS in CLL patients (p = 0.049). The 5-year survival rates for prostate cancer (92%), bladder cancer (88%) and RCC (83%) in our cohort were comparable to previously reported population data. **Conclusions:** GU cancers are more frequent in patients with CLL; majority of GU cancers were diagnosed prior to the diagnosis of CLL in our cohort. This suggests that immune dysregulation might be present even at very early stages of CLL and these patients may benefit from early intervention, rather than the traditional 'wait and watch strategy'. **Keywords:** CLL, secondary cancers, prostate cancer, bladder cancer, renal cell carcinoma