260 PROGNOSTIC VALUE OF ELEVATED POLYCLONAL SERUM FREE LIGHT CHAINS IN STAGE A CHRONIC LYMPHOCYTIC LEUKAEMIA PATIENTS

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Introduction: Recent reports have suggested that elevated polyclonal serum free light chain (FLC) levels are associated with poor prognosis in patients with non-Hodgkin's lymphoma and lymphoma transformation in HIV patients. Here we present data evaluating the prognostic value of elevated polyclonal FLC in untreated Binet stage A chronic lymphocytic leukaemia (CLL) patients.

Materials and methods: This was a retrospective study of 167 (103 men and 64 women) stage A CLL patients. FLC measurements were made using commercially available immunoassays (The Binding Site Group, Birmingham, UK) and these results compared to previously measured clinical markers (Zap70, CD38, *IGHV* mutational status, age, gender, β2-M and abnormal FLC ratio). Time to first treatment (TTFT) was assessed using Kaplan Meier and Cox regression analysis.

Results: Patient characteristics were as follows: Zap70 positive / negative (Zap70$^+$ve / Zap70$^-$ve) (38/112), CD38 positive / negative (CD38$^+$ve / CD38$^-$ve) (43/117), mutated / unmutated (123/17), β2-M >3.5mg/L / <3.5mg/L (58/109) and FLC ratio abnormal / normal (51/116). The median value for summated FLC measurement was 35mg/L (range 5-374mg/L). Serum levels of FLC were significantly associated with a shorter TTFT (Table 1). An arbitrary cut-off of >70mg/L identified a population of patients with a significantly shorter TTFT compared to patients with FLC <70mg/L (48 months v 126 months; p=0.002). Zap70$^+$ve, CD38$^+$ve, *IGHV* mutational status and FLC >70mg/L were associated with shorter TTFT using univariate analysis. Multivariate analysis indicated that Zap70$^+$ve and FLC >70mg/L were independently associated with shorter TTFT. Using Zap 70$^+$ve and FLC >70mg/L, a risk stratification model was constructed. Patients with 0, 1 (Zap70$^+$ve or FLC >70mg/L) or 2 (Zap70$^+$ve and FLC >70mg/L) risk factors had significantly shorter TTFT (median 218, 115, 46 months respectively; p=1.68x10-6). Additionally 16/17 *IGHV* unmutated patients identified had either 1 or 2 risk factors.

Conclusions: Elevated polyclonal FLC identifies aggressive stage A CLL patients. Table 1 Characteristics for 167 untreated stage A chronic lymphocytic leukaemia patients

Parameter	Hazard Ratio	P value
	Univariate Analysis	
CD38$^+$ve	2.05	0.01
Zap70$^+$ve	2.87	$1.6*10^{-4}$
IGHV mutational status	0.35	0.005
β2-M >3.5 mg/L	1.11	0.680
FLC ratio (abnormal)	1.41	0.176
FLC concentration (mg/L)	1.005	0.046
FLC >70mg/L	3.10	0.002
	Multivariate Analysis	
Zap70$^+$ve	2.71	0.001
FLC >70mg/L 2.80	2.80	0.013

261 PRETREATMENT CHARACTERISTICS CORRELATED WITH OUTCOMES IN PATIENTS WITH FLUDARABINE-REFRACTORY CLL TREATED WITH OFATUMUMAB: FINAL RESPONSE ANALYSIS

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Background: Prognosis for pts with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab (FA-ref) or refractory to fludarabine with bulky (>5 cm) lymphadenopathy (BF-ref) is poor with salvage therapies. Ofatumumab (OFA) is a human CD20 monoclonal antibody approved in the US and Europe for treatment of FA-ref CLL based on the interim analysis of this international, pivotal trial. Final response results for 206 pts with FA-ref (n=95) or BF-ref (n=111) CLL and subgroup analyses are reported.

Methods: Pts received 8 wkly doses of OFA followed by 4 mthly doses (dose 1, 300 mg; doses 2–12, 2000 mg). Primary endpoint (overall response rate, 1996 NCI-WG criteria) was evaluated over the 24-wk tx period by an Independent Endpoint Review Committee. Secondary endpoints included duration of response, progression-free survival, overall survival and safety.

Results: For the FA-ref and BF-ref groups, respectively: median age, 64 yrs (both groups); median time from diagnosis, 6.5 and 6.2 yrs; median no. of prior txs, 5 and 4; median beta-2 microglobulin, 6.6 and 7.2 mg/L; and % male, 75 and 73. Overall, 89% and 50% of pts completed 8 and 12 OFA doses, respectively. Outcomes by pretreatment baseline pt characteristics are shown in the Table. 63% of pts had infusion-related reactions that occurred mainly during infusions 1 and 2 and decreased with subsequent infusions; 95% were grade 1–2 and none were fatal. Infection (24%; 8% of these were pneumonia), neutropenia (12%) and anemia (5%) were the most common (≥5% of all pts) grade ≥3 adverse events. Early death (within 8 wks of tx) occurred in 7 pts in the FA-ref group (infections, n=7) and 4 pts in the BF-ref group (infections, n=2; myocardial infarction, n=1; pulmonary edema, n=1).

Conclusions: These data demonstrate that OFA monotherapy is safe and efficacious in heavily pretreated populations with FA-ref and BF-ref CLL. Responses were seen in pts with high-risk features, including advanced stage and age, presence of 11q deletion, high no. of prior txs and prior exposure to rituximab.

This study is registered at clinicaltrials.gov: NCT00349349. Financial support was provided by GlaxoSmithKline and Genmab.

Table. Characteristics and response to therapy

Baseline characteristic	FA-ref				BF-ref			
	n	% ORR	Median PFS, mth	Median OS, mth	n	% ORR	Median PFS, mth	Median OS, mth
All patients	95	51	5.5	14.2	111	44	5.5	17.4
Age								
<64 yrs	44	55	5.5	18.6	53	38	5.6	17.3
≥64 yrs	51	47	4.5	10.7	58	50	5.5	21.7
No. of prior treatments								
<4	18	61	7.1	23.5	38	47	5.5	21.7
≥4	77	48	4.6	12.3	73	42	5.7	16.3
ECOG PS								
0	36	64	8.0	23.2	36	50	5.6	24.5
1–2	58	43	4.1	10.7	75	41	5.5	15.5
Palpable LN								
≤5 cm	66	52	5.5	12.3	56	52	5.7	20.2
>5 cm	22	36	3.7	13.9	49	35	4.6	14.8
Beta-2 microglobulin								
≤7 mg/L	50	62	6.8	23.2	48	60	6.4	23.4
>7 mg/L	43	35	3.7	8.9	62	31	4.9	15.0
Rai stage								
I–II	35	51	5.9	17.3	33	55	5.6	24.8
III–IV	58	48	4.6	10.7	78	40	5.5	15.4
Prior rituximab								
No	39	59	5.5	17.6	50	48	5.6	21.7
Yes	56	45	4.1	14.2	61	41	5.5	15.8
Prior FCR								
No	66	55	5.5	17.1	86	49	5.6	21.7
Yes	29	41	4.1	10.2	25	28	5.3	15.8
FISH								
17p del	27	37	3.3	6.5	18	22	3.7	23.4
No 17p del	64	56	5.5	17.1	89	49	5.6	17.4
11q del	32	50	5.5	15.5	38	55	5.7	17.3
No 11q or 17p del	33	61	5.5	17.6	53	45	5.6	15.0

ORR, overall response rate; PFS, progression-free survival; OS, overall survival; PS, performance status; LN, lymph node; FCR, fludarabine, cyclophosphamide and rituximab; FISH, fluorescence *in situ* hybridization

262 GENOMIC ABNORMALITIES PRECEDING THE CLINICAL ONSET OF CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: The pathogenesis of Chronic Lymphocytic Leukaemia (CLL) is not fully clarified. A neoplastic population identified by a monoclonal IGH gene rearrangement may last longer than 7 years before diagnosis (Frezzato 2005, Landgren 2009) but events leading to progression and the time of onset of cytogenetic abnormalities are undefined. To this aim we searched for genetic abnormalities preceding diagnosis with Multiplex Ligation-dependent Probe Amplification (MLPA) (Al Zaabi, 2010) on preserved DNA of subjects who subsequently developed CLL.

Materials And Methods: Six CLL cases (Cheson, 1996) were identified in a cohort of 14396 healthy subjects enrolled from 1993 to 1996 in an ongoing prospective clinical survey also providing DNA samples preservation. In 5 of them the IGH gene rearrangement found at diagnosis was already present at enrolment, 39 to 89 months earlier (Frezzato, 2010). We studied these patients by FISH at diagnosis and, if a chromosomal abnormality was detected, by MPLA both at diagnosis and at enrolment. Interphase FISH with SEC63 (6q21), C-MYC (8q24), ATM (11q22), GLI (12q13), DLEU1 (13q14 and p53 (17p13) probes was performed according to the ISCN criteria (Brothman, 2009). DNA was analysed with MLPA P040 test kit (MRC Holland), including set probes for 11q23 (ATM), 12p12.3-12p13, 12q14-12q24.3, 13q14.2 (RB1), 13q14.3 (KCNRG-ATP7B), 17p13.1 (p53) chromosomal regions, according to the manufacturer's protocol.

Results: A del:13q14 was found at diagnosis in 3 and 2 patients by FISH and MPLA respectively. MPLA revealed the same deletion to be present 54 months earlier in one subject (see Table for details)

Sex Age	FISH at diagnosis % interphases	MLPA at CLL diagnosis RCN	MLPA at enrolment RCN	Enrolment to CLL diagnosis Months
F 65	del 13q14 90%	del13q14 (KCNRG-DLEU7) RCN: 0,63	del13q14 (KCNRG-DLEU7) RCN: 0,73	54
M 56	del 13q14 10%	Neg	Neg	83
F 62	del 13q14 90%	del13q14 (KCNRG-DLEU2) RCN: 0,55	inadequate material	89

RCN: relative copy number

Conclusions: We detected a CLL-associated genetic deletion a long time before diagnosis. It includes the DLEU1 locus, proposed as a tumor-associated suppressor gene (Ouillette, 2008), and was present at the same time of the IGH gene rearrangement. We have been able to evaluate only few cases but our results could prompt investigations on the role of genetic abnormalities in the pathogenesis of CLL.

263 PROGRESSIVE TELOMERE SHORTENING DURING THE NATURAL HISTORY OF CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: Telomere lenght (TL) at diagnosis has been established as an independent outcome predictor in CLL. However data on TL dynamics over time are scant and anedoctical. This issue has been here addressed on a series of 86 CLL patients (pts) with a median follow-up of 83 months (m) (range: 35-284).

Methods: TL was analyzed as previously described (Rossi, Leukemia 2009; Ladetto, Blood 2004) at diagnosis and during subsequent phases of CLL history with a median time between determinations of 43m (range: 12-231). Between baseline and follow-up determinations 23 pts were treated while 63 were in "watch and wait" (WW). Among WW pts, 15 received treatment after the second TL assessment (median 40m, range: 12-181). Binet stage, ALC, CD38, ZAP-70, VH mutational status, stereotyped receptors, cytogenetics, detailed clinical history were available in all pts. More than 70% had LDH, B2microglobulin, p53 mutations and CD49d available. Telomere loss was calculated in terms of both absolute (AL) and yearly loss (YL). Comparisons were made using the Mann-Whitney or Wilcoxon T-test as required and survival analysis using the Kaplan-Meyer method.

Results: Telomeres were shorter at follow-up compared to baseline with a median loss of 669bp (range +493, -5874; p<0.001). AL and YL were greater in cases with higher baseline TL while those with short telomeres at diagnosis had only modest additional erosion (NS for those in the 25th lowest percentile). AL and YL did not correlate with any clinical parameter with the exception of VH-M status (p<0.05). We then restricted our analysis to WW pts to assess the impact of telomere-related parameters on TFS. As expected the validated cut-off value of 5000bp for baseline TL (Rossi, Leukemia 2009) identified a subset of pts (25.3%) with an inferior TFS (median TFS 40m vs 181m; p<0.001). Surprisingly, also an YL above the median value was predictive of a poor outcome (median TFS 62m vs 181m; p<0.01). Pts having at least one of these two features had a considerably shorter TFS compared to those with long and stable telomeres (median TFS 50m vs not reached; p<0.001). The latter population had indeed only two events for TFS at 107m and 181m.

Discussion: The results of the first systematic analysis on TL dynamics in CLL indicate the following: i) progressive telomere erosion occurs as part of the natural history of CLL; ii) YL is more pronounced when baseline TL is higher; iii) YL associates to an inferior TFS; iii) pts with long and stable telomeres have an excellent long-term outcome.

264 RITUXIMAB MAINTENANCE AFTER COMBINED FCR IN PREVIOUSLY UNTREATED PATIENTS WITH ACTIVE B-CELL CLL: INTERIM ANALYSIS OF AN ONGOING PHASE II MULTICENTER TRIAL ON BEHALF OF THE SPANISH CLL STUDY GROUP (GELLC)

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Introduction: Combined FCR is claimed to be the standard first-line treatment in CLL. However, more than 30% of patients (pts) relapse at 4 yrs after FR or FCR therapy. We report on the efficacy and safety results of an interim analysis after 18 mths of R maintenance (Rm) following FCR as front-line therapy.

Patients and Methods: Between October 07-December 10, a cohort of 84 untreated pts with CD20+ CLL received 6 cycles of FCR (R:375mg/m^2 iv cycle-1 and 500mg/m^2 iv, cycles 2-6; F:25mg/m^2 iv and C:250mg/m^2 iv days 1-3; every 28 days). Pts achieving a response were treated with Rm: 375mg/m^2 iv every 2 mths for 3 yrs. The median age was 59.5, 16.6% were Binet stage A, 63.1% B and 20.3% C. MRD was evaluated by multicolor flow cytometry. The primary end point was to evaluate the response rates and adverse events (AE) profile of FCR and Rm therapy. Secondary endpoints included progression free and overall survival, correlation of MRD response after FCR and Rm.

Results: All 84 pts assigned to FCR were evaluable for response. On an intent to treat analysis, OR, CR, PR, NR and progression rates were 95.2%, 73.8%, 21.4%, 3.6% and 1.2% respectively. Of 79 pts evaluable for bone marrow MRD status, MRD-negative (n) and positive (p) CR, MRD-n and p PR rates were 40.5%, 38%, 3.8% and 17.7% respectively. The most common AE after FCR were R infusion (65.1%), myelotoxicity (33.7%), infections (34%) and non hematological SAEs (14.2%). Rm was given to 75(89.2%)/84 pts, 9 were withdrawn by progression (1), toxicity (5) and investigator decision (3). As of January 2011, 57(76%)/75 pts had completed 1 year of Rm and were evaluable for response, 18 (24%) pts were withdrawn by progression (4), toxicity (10), consent withdrawal (2), others (2). Out of 57 pts, 24 (42.1%) remained in MRD-n CR and 1 pts converted to MRD-p CR; 24 (42.1%) pts were in MRD-p CR and 10 converted to MRD-n CR, while 14 remained in MRD-p CR and 2/9 (15.8%) pts in MRD-p PR converted to MRD-n PR. In addition, 35 pts completed 18 mths of Rm: 5 converted to MRD-n CR and 1 to MRD-p CR. The most common AEs after Rm were grade 3/4 neutropenia in 22.5% pts, infections in 41.7% pts and there were 5.6% SAEs.

Conclusion: The addition of Rm following FCR is feasible and effective in untreated CLL pts and increases the number of MRD-negative CR in responding cases and with an acceptable safety profile.

265 RETHERAPY WITH BENDAMUSTINE/MITOXANTRONE/ RITUXIMAB (BMR) IN PATIENTS WITH RELAPSED/REFRACTORY CLL AND INDOLENT LYMPHOMAS ACHIEVES HIGH RESPONSE RATES AND SOME LONG LASTING REMISSIONS

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Background: BMR was developed in 1999 and has shown high response rates and long lasting remissions in relapsed/refractory indolent B-cell-malignancies. Here we have evaluated the efficacy of BMR-retherapies in this patient population.

Patients and Methods: All patients with CLL or indolent B-cell-malignancies (NHL) who previously had been treated with BMR and were retreated with BMR between 2000-2010 were analysed retrospectively. Data were collected from patient files into a database and analysed statistically using SPSS.

Results: 32 patients received BMR-retherapies consisting of: B:90mg/m2 day 1+2, M:6mg/m2 day 1 and R:375mg/m2 day 8,15,22,29. BM was repeated on day 36 x 1-3 every 4 weeks. The median age of the patients at first retherapy was 74 (56-86), 10 patients were female 22 male, 16 patients suffered from CLL and 16 from NHL. The median number of pretherapies was 3 (1-8), the median number of BMR/BR-pretherapies was 1 (1-2). The median number of BMR-retherapies was 1 (1-4). The overall response rate (ORR) of all BMR-retherapies was 86% achieving a CR (8%) or PR (78%). ORR after the first, second and third BMR-retherapy was 88%, 83% and 100% (n=5) respectively. ORR was 92% in CLL and 79% in NHL. The mean / median time between the first BMR-therapy and subsequent chemoimmunotherapy was 22 / 16

months in CLL (5-70) and 22 / 13 months in NHL (1-97). The mean / median time to next chemoimmunotherapy after the first BMR-retherapy (second BMR-therapy) was 14 / 7 months in CLL (0-49) and 8 / 6 months in NHL (0-29). 4 of the 16 patients suffering from CLL (25%) and 2 of the 16 patients suffering from NHL (13%) did not receive further chemoimmunotherapy after the first BMR-retherapy (second BMR-therapy) until the end of the analysis. Main toxicity in all BMR-retherapies was a reversible grade 3+4 hematotoxicity in 38% of patients with CLL and 50% of patients with NHL. Therapy associated hospitalisation was seen in 3/32 patients. No therapy-associated death occurred.

Conclusion: BMR-retherapy achieves high response rates in patients with relapsed/refractory CLL and NHL. Hematotoxicity is moderate and therapy associated hospitalisation is low.

266 BENDAMUSTINE AND ALEMTUZUMAB (BEN CAM) COMBINATION IN RELAPSED AND REFRACTORY CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL): PRELIMINARY REPORT OF THE ITALIAN TRIAL

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Introduction: Bendamustine (Ben) and alemtuzumab (Cam) are effective in CLL exhibiting an unique mechanism of action. A synergistic or additive effect might be expected when used in combination. We designed a multicentric, single arm, dose escalation study to determine maximum tolerated dose (MTD) and efficacy of Ben Cam combination in refractory relapsed CLL.

Materials and Methods: Previously treated CLL pts requiring therapy were enrolled. A stepwise dose escalation exploring MTD has been evaluated. Starting dosages were: Ben 50 mg/m^2 d 1,2 and Cam 20 mg sc d 1-3. If MTD was not reached within the 1st cohort, 2nd cohort received an increased dose of Cam 30 mg with a subsequent further increase of Ben 70 mg/m^2 if MTD was not reached. Treatment was repeated every 28 d up to 4 cycles. In Phase I (12 pts) resulted Ben 70 mg/m^{2}d 1,2 and Cam 30 mg sc d 1-3 as the MTD.

Results: Overall 26 pts, median age 67 y (54-82), 42% Binet C, refractory 23%, have been enrolled. Median prior regimens were 2 (1–6), 73% received previously fludarabine based regimens and 46% monoclonal antibodies. Biological characteristics are shown below

	IgVH		ZAP70		CD38		FISH			
	mut	unmu	pos	neg	pos	neg	13 q	12 +	11 q	17 p
% pts*	23	62	62	31	50	43	15	15	15	31

*data not available in all pts

The 26 pts received overall 94 courses, median 4 (2-4). Response is available in 20 pts, pending in 6. Response rate was 60%, 30% CRs and 30% PRs. Disease progression during treatment was observed in 20% of cases. Grade III-IV haematological toxicity consisted of: neutropenia 33% of courses, anemia 7%, thrombocytopenia 10%. FUO developed in the 20% of cycles; 4 major infections (2 sepsis, 1 pneumonia, 1 enteritis) were observed. CMV reactivation occurred in 7 pts: no CMV recorded. Extra-hematological toxicity was mild.

Conclusion: Preliminary data on the anti-tumor activity of the combination Ben Cam are promising. Major treatment toxicities were myelosuppression and manageable infections. No toxic deaths were recorded while on treatment.

267 T-CELL PROLYMPHOCYTIC LEUKEMIA (T-PLL): A RE-EXAMINATION OF IMMUNOPHENOTYPE AND MORPHOLOGY

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Introduction/Background: T-cell prolymphocytic leukemia (T-PLL) is a rare T-cell lymphoproliferative disorder with an aggressive clinical course. The morphology and immunophenotype of T-PLL have been described, including the classic prolymphocytic morphology and the predominance of CD4-positive cases; however, few case series exist. In the current study, it was hypothesized that CD8 expression and morphologic variation are more common than previously recognized.

Materials and Methods: Cases in which T-PLL was a diagnostic consideration between 1990 and 2010 were collected from the slide archive at the University of Michigan. Twenty-four cases were considered for inclusion. Laboratory values, immunophenotype, and morphology were examined.

Results: The diagnosis of T-PLL was supported in 20 cases. The excluded cases had clinical features or laboratory values more suggestive of another mature T-cell lymphoma. The patients with T-PLL ranged in age from 42-90 years (mean 61.9) with a male predominance (70%). The white blood cell counts at presentation ranged from 9.7 K/μL to 476 K/μL (median 61 K/μL, mean 128 K/μL). CD4 was expressed in 10 cases (50%) and CD8 was expressed in 9 cases (45%). CD4 and CD8 were coexpressed in 1 case (5%). CD4 and CD8 showed no statistical difference in expression (p=0.82, Chi-Square). In 7 of 9 CD8-positive cases, characteristic cytogenetic findings including inversion 14, a translocation involving chromosome 14, and/or abnormalities of chromosome 8, were documented. Material was available for histopathologic review in 17 cases. Morphologic features were variable and the cases were divided into three types: prolymphocytic (41%), small cell (35%), and pleomorphic (24%). The pleomorphic cases had a subset of medium to large cells with markedly irregular nuclear contours and morphological resemblance to cases of adult T-cell leukemia/lymphoma (ATLL). All of the pleomorphic cases expressed CD8, and 3 of 4 cases had serologic studies for HTLV-1 performed to exclude ATLL. The prolymphocytic and small cell cases showed no differences in CD4 and CD8 expression. All three morphologic subtypes showed some degree of nuclear contour irregularity. Other morphologic features included cytoplasmic vacuoles, granules, and blebs.

Conclusion: The findings from this series indicate that CD4 and CD8 expression are seen with approximately equal frequency in T-PLL. While many cases have prolymphocytic morphology, small cell variant is not unusual and pleomorphic cases can occur. CD8 expression and/or morphologic variability should not be used to exclude T-PLL. Diagnosis requires integration of clinical, laboratory, and cytogenetic data.

268 REARRANGEMENTS OF 14Q32.13 TARGETING *TCL1A* ARE RECURRENT IN HAIRY-CELL LYMPHOPROLIFERATIVE DISORDERS

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Introduction: Hairy-cell lymphoproliferative disorders (HCLD) are rare and include 3 indolent B-cell malignancies sharing several pathological features: hairy cell leukemia (HCL), HCL-variant and splenic marginal zone lymphoma. HCLD are poorly characterized at the genetic level, and so far no characteristic chromosomal aberration has been reported in these tumors.

Material and Methods: Discrete or cryptic 14q32 aberrations detected by cytogenetics/FISH in 5 cases of HCLD were further characterized using FISH and CGH-array. Expression analysis of candidate targeted genes was performed by qRT-PCR.

Results: Using FISH approach, we identified a novel breakpoint region at 14q32.13 co-rearranged with *IGH* at 14q32.33 in 5 cases of HCLD. This region, located 10 Mb proximal to *IGH,* was recurrently affected by 3 variant aberrations:

t(14;14)(q32.13;q32.33) (n=3), inv(14)(q32.13q32.33) (n=1) and del(14)(q32.13q32.33) (n=1). The 14q32.13 breakpoints clustered in the region containing the *TCL1A/TCL1B/TCL6* genes, either telomeric of *TCL1A* or centromeric of *TCL1B*, analogous to the *TCRA/D*-mediated t(14;14)(q11;q32)/inv(14)(q11q32) rearrangements occurring in T-cell leukemia/lymphoma. Transcriptional upregulation of *TCL1A* was documented in 3 out of 5 HCLD cases analyzed by qRT-PCR. Further expression analysis of additional 21 candidate genes located centromerically and telomerically to *TCL1A*, including 3 noncoding transcribed ultraconserved regions (T-UCRs), failed to identify a commonly overexpressed 14q32.13 gene in these tumors.

Conclusions: We provide evidence that HCLD, like several other B-cell malignancies, are characterized by *IGH*-mediated chromosomal abnormalities and describe a new recurrent breakpoint at 14q32.13 involved in three variant rearrangements. The target of these discrete or cryptic aberrations is *TCL1A,* a known oncogene involved in pathogenesis of T-neoplasms. This is the first report of*TCL1A* rearrangements in B-NHL.

269 PROGNOSTIC MARKERS OF TREATMENT EFFICACY AND OUTCOME IN PATIENTS WITH HAIRY CELL LEUKEMIA RECEIVING SUBCUTANEOUS CLADRIBINE IN THE ICGHCL2004 PROTOCOL

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Introduction: Single-agent cladribine (2CdA) is highly effective in the majority of Hairy cell leukemia (HCL) patients. However, refractory and relapsing patients still exist and parameters predicting efficacy of 2CdA in HCL are scarcely known. Material and methods: In the ICGHCL2004 Italian multicentre clinical trial, parameters able to predict efficacy of subcutaneous 2CdA were prospectively investigated in classic HCL requiring first treatment. Clinical data and samples were collected centrally for diagnostic revision and for molecular analyses prior to treatment. Tumor IGH and TP53 analyses or Genome-wide DNA profiling was performed in the cases with >10% or >50% hairy cells (HC) in the test sample, respectively *(Forconi, Blood 2009)*. Patients entering the study received 0.5-0.7 mg/kg sc2CdA as a single course. Efficacy endpoints were response to sc2CdA, treatment free interval (TFI), relapse free survival (RFS), and overall survival (OS). Complete (CR) and Partial Remissions (PR) were rated as beneficial responses (CR/PR), while minor (mR) and No Responses (NR) were rated as failures (mR/NR).

Results: 140/148 patients (94,6%) had a CR/PR and 8/148 (5,4%) a mR/NR. Risk factors of sc2CdA failure were splenomegaly (p=.001), HC counts>5x10e9/L (p<.001), and B2M>2X (p=.013). UM-IGH and TP53 were confirmed as risk factors for mR/NR (p<.001 and p=.011). After a median follow-up of 42 months, 5 year TFI, RFS and OS were 69%, 73% and 95%, respectively. Diagnostic risk factors of short TFI were splenomegaly (p=.007), HC>5x10e9/L (p<.001), UM-IGH (p<.001), and TP53 disfunction (p=.002). UM-IGH (HR=8.1, CI 1.7-38.1), high HC (HR=6.9, CI 1.5-31.6) and splenomegaly (HR=3.7, CI 1.1-12.8) scored as independent risk factors. Quality of response also predicted risk of short TFI (NR=mR>PR>CR, p<.001). Univariate analysis of clinical parameters identified HC>5x10e9 (p=.016) and PR (p=.001) as risk factors of short RFS. PR was the sole independent risk factor of relapse after a median of 46 months follow-up (HR=4.5, 95%CI 1,7-12,3).

Conclusions: Tumor UM-IGH status, splenomegaly, high HC count are independent risk factors of treatment failure and progression. RFS analysis identify PR as the sole independent factor of relapse risk in responsive patients. This analysis may have important implications for the selection of HCL patients that will require treatments alternative to single-agent 2CdA.