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POSTER ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Ibrutinib and Rituximab Versus Fludarabine, Cyclophosphamide, and Rituximab for Patients in NCRI FLAIR Study with Previously Untreated CLL: Assessment of Mutational Landscape of Patients at Baseline and Prognostic Impact

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Introduction: Recent studies using next generation sequencing have revealed recurrent mutated genes in CLL are associated with clinical outcome. We assessed the baseline mutational profile of 771 patients from FLAIR treated with either fludarabine, cyclophosphamide and rituximab (FCR) or ibrutinib and rituximab (IR). The prognostic impact of individual gene mutations on disease progression was investigated.

Method: FLAIR is a phase III, multicentre, randomised, controlled, open, parallel group trial for previously untreated CLL requiring therapy according to IWCLL criteria. Patients with >20% chromosome 17p deletion were excluded. Patients were randomised to FCR or IR. Somatic hypermutation (SHM) status was determined by PCR amplification of *IGHV-IGHD-IGHJ* gene rearrangements using IGHV leader/FR1 primers. Bidirectional Sanger sequencing was analysed using IMGT V-Quest and the ARResT/AssignSubsets tool. Extracted DNA was sequenced using an Illumina MiSeq and analysed using an in-house pipeline. Amplicon based targeted sequencing of 33 recurrently mutated genes in lymphoid malignancies were performed in parallel. Detected variants were reported down to minimum variant allele fractions of 3-5% and coverage of 100X. Low level variants were confirmed by repeat sequencing.

Results: 771 patients were randomly assigned to receive FCR (385) or IR (386). *IGHV* gene SHM status was available for 728/771 (94.4%): 388 (53.3%) *IGHV* unmutated (>98% of nucleotide identity to germline), 294 (40.4%) *IGHV* mutated and 46 (6.3%) stereotyped subset #2 (n=28 *IGHV* mutated, n=18 *IGHV* unmutated). Gene mutations were assessed in 767/771 (99.5%) patients at baseline and mutations (>1) were detected in 480/767 (62.6%). Mutation frequencies ranged from 0.1-18.8% with mutations in *SF3B1* (18.8%), *ATM* (14.5%), *NOTCH1* (10.0%), *MYD88* (6.1%), *POT1* (5.7%), *TP53* (5.0%), *BRAF* (4.4%) and *RPS15* (4.0%) being the most frequent. No detectable mutations at baseline were found in 287/767 (37.4%) and there was no significant difference in PFS or OS compared to patients with >1 mutation.

A significantly shorter PFS and OS was observed for *TP53* mutated patients compared to wildtype (HR 2.23 [95% CI 1.31-3.79]; p=0.003 and HR 2.43 [95% CI 1.04-5.66]; p=0.039 respectively). When further subdivided by treatment, a trend for shorter PFS was observed in *TP53* mutated patients in both arms compared to wildtype, but significance was only achieved for FCR (HR 2.48 [95% CI 1.25-4.91]; p=0.009) and not IR (HR 2.27 [95% CI 0.97-5.30]; p=0.059). A significantly shorter PFS was observed for FCR compared to IR in patients with *ATM* mutations at baseline (HR 0.35 [95% CI 0.16-0.80]; p=0.012) and *RSP15* (HR 0.19 [95% CI 0.04-0.96]; p=0.044). A trend for shorter PFS was also observed in *NOTCH1* mutated patients treated with FCR however, this was not found to be significant when compared to wildtype or *NOTCH1* mutated IR patients.

CREBBP mutation at baseline (n=19; 2.5%) was associated with shorter PFS (HR 2.63 [95% CI 1.29-5.35]; p=0.008) and OS (HR 4.37 [95% CI 1.75-10.94]; p=0.002) compared to wild type (Fig). When further subdivided by treatment arm, shorter PFS and OS was also observed for *CREBBP* mutated patients treated with FCR compared to wildtype (n=11; HR 4.37 [95% CI 1.75-10.94]; p=0.002 and HR 10.14 [95% CI 3.83-26.83]; p<0.001 respectively). A similar trend was not observed with IR (n=8; PFS HR 0.79 [CI 0.11-5.74]; p=0.819 and OS HR NE [95% CI NE-NE]; p=0.988). *CREBBP* mutated patients treated with FCR had a shorter PFS compared to IR (HR 0.1 [95% CI 0.01-0.86]; p=0.036).
The PFS and OS for *IGHV* subset #2 was similar to *IGHV* mutated patients (Fig). In FCR treated patients there was no difference between mutated (n=13) and unmutated subset #2 (n=7) but with IR there was a trend that *IGHV* mutated subset #2 patients (n=15) had better PFS and OS than their *IGHV* unmutated counterparts.
Conclusions: Our study confirms that *TP53* mutations result in shorter PFS and OS in CLL. We demonstrate improved PFS when patients with *ATM* or *RPS15* mutations are treated with IR compared to FCR. Mutations in the *CREBBP* gene have recently been described as a novel candidate driver in CLL. We report a significant improvement in disease progression in *CREBBP* mutated patients treated with IR when compared to FCR. In contrast to previous studies in frontline CLL *IGHV* subset #2 patients had a similar outcome to good risk *IGHV* mutated patients.

Disclosures Rawstron: *Abbvie:* Honoraria, Research Funding; *Janssen:* Honoraria, Research Funding; *Pharmacyclics:* Consultancy, Research Funding; *Beigene:* Consultancy, Honoraria, Research Funding; *Gilead:* Research Funding. **Cairns:** *Takeda:* Research Funding; *Celgene BMS:* Honoraria, Research Funding; *Sanofi:* Research Funding; *Amgen:* Research Funding; *Janssen:* Honoraria. **Hockaday:** *Abbvie:* Speakers Bureau. **Bloor:** *Abbvie:* Consultancy, Honoraria, Speakers Bureau; *Gilead, Janssen:* Honoraria. **Munir:** *Janssen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Abbvie:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *AstraZeneca:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Roche:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Sobi:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Alexion:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *BeiGene:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau. **Hillmen:** *Apellis Pharmaceuticals:* Current Employment, Current equity holder in publicly-traded company.

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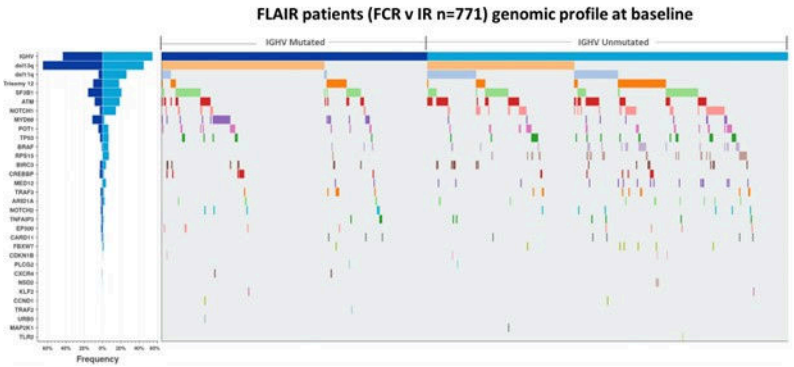
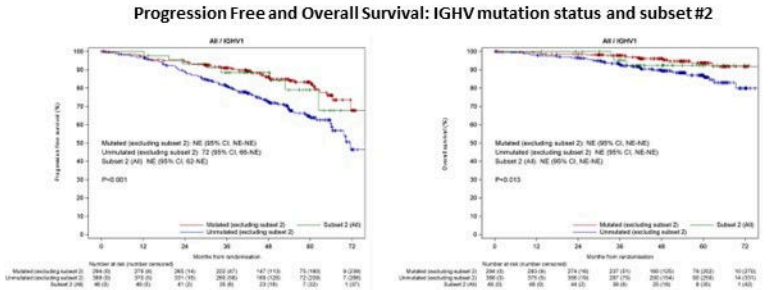
Figure





Progression Free and Overall Survival analysis of gene mutations

Gene		PFS			OS		
		HR	95%CI	P	HR	95%CI	P
CREBBP	Mutated vs wildtype	2.63	1.29-5.35	0.008	4.37	1.75-10.94	0.002
	FCR mut vs wild type	4.37	1.75-10.94	0.002	10.14	3.83-26.83	<0.001
	FCR mut vs IR mut	0.1	0.01-0.86	0.036			
TP53	Mutated vs wildtype	2.23	1.31-3.79	0.003	2.43	1.04-5.66	0.039
	FCR mut vs wild type	2.48	1.25-4.91	0.009			
ATM	FCR mut vs wild type	0.35	0.16-0.80	0.012			
RPS15	FCR mut vs wild type	0.19	0.04-0.96	0.044			

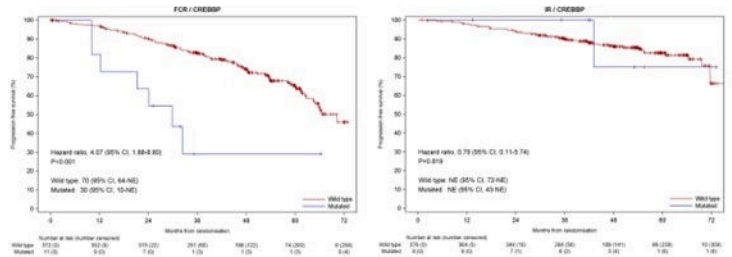


Figure 1