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ORAL ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Using Peripheral Blood (PB) Measurable Residual Disease (MRD) Levels to Predict <0.01% Bone Marrow Disease (BM uMRD4): Identification of Effective PB Targets for CLL Treatment Cessation in the Ibrutinib+Venetoclax Arm of the FLAIR Trial

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INTRODUCTION Time-limited treatments for CLL are under investigation but the optimal target for treatment cessation is not fully clear. Bone marrow (BM) measurable residual disease (MRD) is usually the most sensitive measure but would be too invasive to guide treatment in a routine setting. The iwCLL threshold of BM uMRD4 (<0.01%) has been demonstrated to be a powerful indicator of improved outcomes across multiple different trials and the aim of this analysis is to determine the feasibility of using PB MRD analysis to identify patients who have attained BM uMRD4.

METHODS FLAIR (ISRCTN01844152) is an open-label, randomised, controlled, phase 3 trial comparing ibrutinib plus rituximab (IR) with fludarabine, cyclophosphamide and rituximab (FCR), subsequently amended to compare ibrutinib plus venetoclax (I+V) and ibrutinib alone (I) with FCR. Paired PB & BM samples were scheduled at: (1) response assessment 9 months after randomization in all arms (n=1086); (2) end of treatment after 72 months in the ibrutinib-containing arms (n=137, most I/I+V participants have not reached this timepoint yet); and (3) confirmation of BM uMRD4 for initiation of planned stopping rules in participants with sustained PB uMRD4 defined as <0.01% PB MRD at 3 timepoints over 6 months (n=188 in the I+V arm). MRD analysis was performed using an ERIC-compliant 8-colour flow cytometry assay targeting acquisition of 2.2 million events (detection limit MRD5/0.001%). As the target could not always be met due to sample/laboratory limitations, stringent uMRD4 assessing 500 thousand leucocytes (detection limit 0.005%) was also evaluated.

RESULTS Table 1 shows the BM vs. PB MRD levels for different treatment arms and timepoints. The greatest discrepancy was observed in participants receiving FCR with a median 0.8log higher disease in the BM vs. PB. Participants receiving ibrutinib monotherapy had similar PB and BM MRD levels while the addition of either rituximab or venetoclax was associated with slightly higher (median <0.1 log) BM vs. PB MRD levels for both IR and I+V arms. The difference did not persist in the IR arm but remained during I+V treatment in some cases, with median >0.59 log higher BM vs. PB MRD levels in 29/182 participants achieving PB uMRD4 but with detectable BM MRD.
Table 1 also shows the proportion of cases that attain BM uMRD4 according to different PB MRD thresholds. For participants with rituximab exposure in the past 3 months, BM uMRD4 was attained in 75-88% of participants with PB uMRD5, and only 43-76% of participants with stringent uMRD4. For participants with PB dMRD5 (0.001-0.01% MRD), only 14-52% achieved BM uMRD4. However, participants on I+V with either PB uMRD5 or stringent uMRD4 attained BM uMRD4 in 94-96% of cases.

Planned cessation of treatment in the FLAIR trial was guided by sustained PB uMRD4, defined as 3 successive results with <0.01% PB disease over six months with confirmation of BM uMRD4 at the final time point. This strategy in the I+V arm is highly effective in achieving improved progression-free and overall survival compared to FCR [see related abstract]. Sustained PB uMRD4 led to BM assessments in 188 participants of which 173/188 (92%) attained BM uMRD4. High sensitivity PB MRD gave concordant results to BM MRD4 analysis in 91% of participants (172/188), while 9/188 (5%) had PB dMRD5 / BM uMRD4 (7/9 had detectable BM MRD in the range 0.002-0.007% and 2/9 had BM uMRD5/<0.001%) and 7/188 (4%) had PB uMRD5/stringent uMRD4 but with persistent BM dMRD4 (median 0.02% BM MRD, range 0.01-0.055%).

CONCLUSIONS PB MRD level correlates closely with BM MRD level but there is lower concordance at the 0.01%/MRD4 threshold after recent cessation of therapeutic antibody. PB uMRD4 is not a suitable target for treatment cessation as the majority of patients with 0.001%-0.01% PB MRD have >0.01% BM disease. For the identification of people attaining BM uMRD4 (<0.01%) on I+V treatment, sustained PB uMRD4 was >90% effective. For translation into MRD-guided treatment in future routine clinical practice, BM assessment may be replaced with PB MRD monitoring if the 0.001%/MRD5 threshold is applied.

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Treatment arm / timepoint:	# cases with paired PB & BM samples / #ITT	Log difference in BM vs. PB MRD level for cases with detectable BM MRD (# BM dMRD cases)	Proportion of BM samples showing uMRD4 (<0.01%) according to PB MRD level			
9 months after randomisation			**PB uMRD5 (<0.001%)**	**Stringent uMRD4 (<0.005%)**	**dMRD5 (0.001 - 0.01%)**	**dMRD4 (>0.01%)**
FCR: 3 months after last treatment	415/590	0.82, range -1.25 to 2.66 (n = 184)	59/67 (88.1)	180/237 (75.9)	4/29 (13.8)	1/82 (1.2)
I only: on continuous ibrutinib	167/274	0, range -0.65 to 2.52 (n = 167)	0/0 (-)	0/0 (-)	0/0 (-)	0/167 (0)
IR: 3 months after last rituximab, on continuous ibrutinib	293/377	0.07, range -0.86 to 2.54 (n = 286)	3/4 (75)	6/14 (42.9)	0/1 (0)	0/274 (0)
I+V: on continuous ibrutinib (9 months) and venetoclax (7 months)	211/274	0.07, range -1.05 to 1.82 (n = 138)	50/53 (94.3)	26/27 (96.3)	6/20 (30)	3/111 (2.7)
Later timepoints						
IR month 72: end of continuous ibrutinib treatment (68 months since last rituximab)	137/377	0.00, range -1.59 to 2.03 (n = 131)	5/5 (100)	3/4 (75)	4/10 (40)	1/118 (0.8)
I+V BM to assess stopping rule after sustained PB uMRD4 (3 PB samples with <0.01% PB MRD over six months)	188/274	0.59, range -0.51 to 1.9 (n = 29)	111/115 (96.5)	53/56 (94.6)	9/17 (52.9)	N/A

Figure 1