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 treatment for CLL is under investigation in multiple trials but the optimal target for treatment cessation is not fully clear. BM MRD is usually the most sensitive measure because therapeutic antibodies preferentially deplete circulating disease to varying degrees. However, using BM MRD to guide treatment in a routine setting would be sub-optimal because the approach is invasive and it can be difficult to obtain representative aspirate samples. BTK inhibition has previously been shown to redistribute disease between compartments, potentially facilitating the use of PB MRD to guide treatment. Although disease eradication is desirable aim, measuring uMRD6 (< 1 CLL cell per million normal leucocytes / <0.0001%) can be difficult to achieve because of the numbers of total cells required and the cost of analysis. The iwCLL threshold of <0.01% disease (uMRD4) in the bone marrow 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:

Participants: FLAIR is an open-label, randomised, controlled, phase 3 trial comparing ibrutinib plus rituximab (IR) with fludarabine, cyclophosphamide and rituximab (FCR), subsequently amended to

compare and ibrutinib plus venetoclax (I+V) and ibrutinib alone (I) with FCR, in 1576 participants with previously untreated CLL. All participants had BM and PB assessments at 9 months and 72 months after randomization, and PB MRD assessments every 6 months. In the I, IR and I+V arms, additional BM assessments were performed if two subsequent PB assessment showed <0.01% MRD in order to initiate planned treatment cessation pathways.

MRD analysis: ERIC-compliant 8-colour flow cytometry was performed with a target acquisition of 2.2 million events (minimum for inclusion 500 thousand events) to achieve a limit of detection (LoD) of MRD5/0.001% (minimum LoD for inclusion 0.004%).

RESULTS: The greatest discrepancy between PB and BM MRD was observed in participants receiving FCR with a median 0.7log higher disease in the BM. Participants receiving ibrutinb monotherapy had similar PB and BM MRD levels after 9 months of exposure, while combination of ibrutinib with either rituximab or venetoclax resulted in a slightly higher (<0.1log) level of disease in BM vs. PB.

The proportion of cases that attain BM uMRD4 according to different PB MRD thresholds is shown in [Table]. The 0.001 – 0.01% (uMRD5 – uMRD4) range was split into two groups around the 0.004% threshold because we have found this to be a practical target for assessing uMRD4

Although the discrepancy between PB and BM is modest in IBR-containing regimens, a 0.01% threshold (uMRD4) in PB is sub-optimal because the majority of cases with 0.004-0.01% PB disease have not attained BM uMRD4. Participants receiving I+V with <0.004% PB MRD had usually (>80%) attained BM uMRD4 but for those receiving rituximab-containing regimens the proportion was lower (<75%). A PB MRD threshold of 0.001% / uMRD5 identified participants with BM uMRD4 in >90% of cases even after recent cessation of rituximab.

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 is highly effective in achieving improved progression-free and overall survival compared to fixed duration chemoimmunotherapy [see clinical abstract]. Sustained PB uMRD4 predicted for BM uMRD4 in 36/39 (92%). Of the remaining 3/39 (8%) of cases, all 3/3 were dMRD5 (i.e. disease detectable between 0.001% and 0.01% in the peripheral blood) with the BM MRD (dMRD4) a median 0.036% of leucocytes (range 0.011 - 0.25%).

CONCLUSIONS: PB MRD correlates closely with BM MRD levels but there is lower concordance at the 0.01%/uMRD4 threshold after recent cessation of therapeutic antibody exposure and higher concordance after prolonged BTKi monotherapy. For the identification of participants attaining BM uMRD4 (<0.01%), sustained PB uMRD4 was >90% effective while confirmation of PB uMRD5 (<0.001%) with >95% effective. For translation into MRD-guided treatment in routine clinical practice, BM assessment may be effectively replaced with PB MRD monitoring if an 0.001%/MRD5 threshold is applied.

Treatment arm	Median log difference in MRD level between BM and PB (range)	Number of participants with BM uMRD4 according to PB MRD level			
		PB MRD <0.001%	PB MRD 0.001 - 0.004%	PB MRD 0.004 - 0.01%	PB MRD >0.01%
IR arm month 9 (3 months after last rituximab on continuous IBR)	0.062 (-0.86 to 2.33)	3/4 (75%)	7/15 (47%)	0/1 (0%)	0/275 (0%)
FCR arm month 9 (3 months after last treatment)	0.73 (-0.48 to 2.66)	61/69 (88%)	182/245 (74%)	1/15 (7%)	1/82 (1%)
IR arm month 72 (end of IBR)	-0.017 (-1.03 to 2.03)	5/6 (83%)	3/5 (60%)	4/8 (50%)	1/118 (1%)
FLAIR I+V arm month 9 (9 months IBR + 6 months VEN)	0.032 (-.1.05 to 1.82)	53/57 (93%)	26/32 (81%)	3/10 (30%)	1/82 (1%)
I only arm month 9 (9 months IBR)	0 (-0.64 to 2.52)	0/0 (%)	0/0 (%)	0/0 (%)	0/167 (0%)
Overall		122/136 (90%)	250/297 (84%)	8/34 (24%)	3/724 (0%)