Ibrutinib plus venetoclax with measurable residual disease-guided duration of treatment is superior to both ibrutinib monotherapy and fludarabine-cyclophosphamide-rituximab for previously untreated chronic lymphocytic leukaemia: Report of the Phase III UK NCRI FLAIR study

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1. Introduction

- Continuous BTK inhibitor therapy leads to improved outcomes but can induce resistance and toxicity.
- Due to their discrete modes of action, the combination of ibrutinib and venetoclax has been studied in pre-clinical models and clinical trials2. GLOW and CAPTIVATE trials studied ibrutinib-venetoclax 15 months fixed-duration combination, leading to improved progression-free survival.
- FLAIR is a phase III, multicenter, open-label, parallel-group, randomized, controlled, adaptive trial platform involving patients with previously untreated CLL
- The FLAIR trial was adapted to include ibrutinib monotherapy and ibrutinib-venetoclax combination using MRD-guided duration of therapy, comparing it to FCR in previously untreated CLL patients.
- Here, we present the preplanned analysis comparing MRD-guided ibrutinib-venetoclax with ibrutinib and FCR with extended follow-up..

Aim: To ascertain outcomes of MRD-guided ibrutinib-venetoclax to ibrutinib and FCR

2. Methods

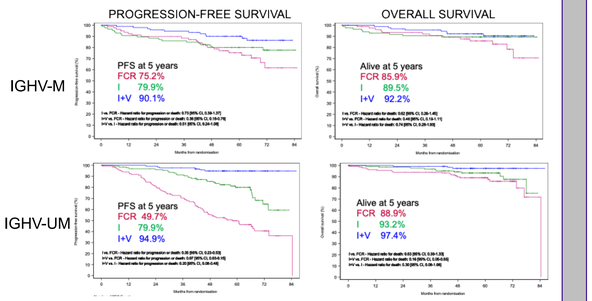
- Key inclusion criteria included previously untreated CLL or small lymphocytic lymphoma requiring treatment; considered fit for FCR, between 18 and 75 years of age. Key exclusion criteria were Richter's transformation, symptomatic cardiac disease and >20% 17p deletion assessed by FISH
- Participants were randomly assigned (1:1:1) to receive FCR, ibrutinib or ibrutinibvenetoclax with the use of a computer-generated minimization algorithm with a random element.
- Primary endpoint comparing MRD-guided ibrutinib-venetoclax with ibrutinib was uMRD in the bone marrow within 2 years after randomization
- A powered secondary endpoint comparing MRD-guided ibrutinib-venetoclax with ibrutinib was progression-free survival.
- Other secondary endpoints were overall survival, the proportion of participants with uMRD at 9 months and safety

3. Results

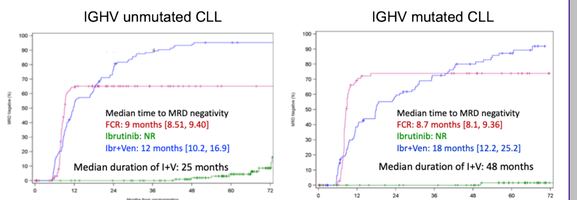
BASELINE CHARACTERISTICS

		FCR (n=263)	Ibrutinib (n=263)	Ibrutinib+venetoclax (n=260)	Total (n=786)
Age	Median (years)	62	62	62	62
	>65 years	82 (31.2%)	84 (31.9%)	81 (31.2%)	247 (31.4%)
Gender	Male	187 (71.1%)	186 (70.7%)	186 (71.5%)	559 (71.1%)
Binet stage	Prog A or B	152 (57.8%)	153 (58.2%)	151 (58.1%)	461 (58.7%)
	C	111 (42.2%)	110 (41.8%)	109 (41.9%)	325 (41.3%)
Duration of CLL prior to randomisation	Median (months)	33.7	36.2	37.9	35.9
B symptoms	Yes	121 (46.5%)	126 (47.9%)	128 (49.2%)	375 (47.7%)
IGHV	Mutated	82 (31.2%)	87 (33.1%)	97 (37.3%)	266 (33.2%)
	Unmutated	139 (52.8%)	129 (49%)	123 (47.3%)	391 (49.9%)
	BCR Subset 2	14 (5.3%)	23 (8.7%)	16 (6.2%)	53 (6.7%)
	Not available	28 (10.6%)	24 (9.1%)	24 (9.2%)	76 (9.7%)
FISH Hierarchy					
	17p deletion*	0(0%)	0 (0%)	1 (0.4%)	1 (0.1%)
	11q deletion	50(19%)	36 (13.7%)	45 (17.3%)	131 (16.7%)
	Trisomy 12	29(11%)	45 (17.1%)	57 (21.9%)	131 (16.7%)
	Normal	69(26.2%)	64 (24.3%)	52 (20%)	185 (23.5%)
	13q deletion	100(38%)	106 (40.3%)	87 (33.5%)	295 (37.5%)
	Failed/	15(5.7%)	12 (4.6%)	16 (6.2%)	43 (5.5%)

PFS AND OS by IGHV STATUS

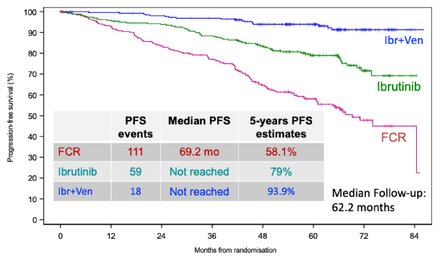


TIME TO ATTAIN MRD NEGATIVITY



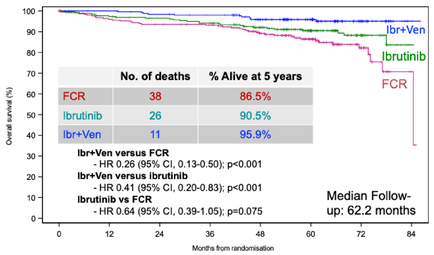
Patients stopping I+V due to MRD stopping rules:
112 (48.3%) at 24 months, 139 (60.4%) at 36 months,153 (68.1%) at 48 months, 158 (73.1%) at 60 months

MRD-guided Ibr-Ven superior to Ibr and FCR- PFS and OS



	PFS events	Median PFS	5-years PFS estimates
FCR	111	69.2 mo	58.1%
Ibrutinib	59	Not reached	79%
Ibr+Ven	18	Not reached	93.9%

Median Follow-up: 62.2 months



	No. of deaths	% Alive at 5 years
FCR	38	86.5%
Ibrutinib	26	90.5%
Ibr+Ven	11	95.9%

Ibr+Ven versus FCR
- HR 0.26 (95% CI, 0.13-0.50); p<0.001

Ibr+Ven versus Ibrutinib
- HR 0.41 (95% CI, 0.20-0.83); p<0.001

Ibrutinib vs FCR
- HR 0.64 (95% CI, 0.39-1.05); p=0.075

Median Follow-up: 62.2 months

SAFETY- DEATHS

	FCR	Ibrutinib	I+V
Allogeneic transplant related complication: infection/GvHD	2	0	0
Aortic dissection	0	1	0
Cardiac	2	5	3
Sudden death	2	3	0
Thromboembolic disease	0	1	0
Cerebrovascular disease	0	2	0
Haemorrhage	1	1	0
Infection	8	4	1
Covid-19 infection	3	2	2
Progressive disease	3	0	1
Richter's transformation/Lymphoma	3	0	1
Right sided heart failure	0	1	0
Solid organ malignancy	2	3	2
Treatment related bone marrow failure/MDS	4	0	1
Unknown	7	2	0
Total	37	25	11

SAFETY- SAE's

	Number of SAEs		
	FCR (n=239)	I (n=260)	I+V (n=257)
Infections and infestations	65 (29.1%)	87 (39.0%)	79 (37.4%)
Blood and lymphatic system disorders	96 (43.0%)	12 (5.4%)	17 (8.1%)
Cardiac disorders	1 (0.4%)	32 (14.3%)	29 (13.7%)
Gastrointestinal disorders	19 (8.5%)	7 (3.1%)	10 (4.7%)
Nervous system disorders	2 (0.9%)	14 (6.3%)	5 (2.4%)
Respiratory, thoracic and mediastinal disorders	8 (3.6%)	7 (3.1%)	4 (1.9%)
Eye disorders	0 (0.0%)	5 (2.2%)	7 (3.3%)

SAFETY- Secondary malignancies

	FCR	Ibrutinib	I+V
Incidence rate of cancers per 100 person-years (95% CI)	5.5 (5.3, 5.8)	3.2 (3.0, 3.4)	2.8 (2.6, 3.0)

4. Conclusions

-Ibrutinib plus venetoclax significantly improved responses, progression-free and overall survival compared to Ibrutinib and FCR in previously untreated CLL

- Significant PFS and OS advantage for MRD-guided I+V over ibrutinib and FCR in IGHV unmutated CLL
- PFS advantage for MRD-guided I+V over FCR in IGHV mutated CLL
- PFS advantage for ibrutinib over FCR

- I+V was well tolerated with no unexpected toxicities
- These updated results with longer follow-up with MRD-guided I+V confirm that directing the duration of therapy according to individual MRD response maximizes outcomes

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