Health-related quality of life in patients with previously untreated chronic lymphocytic leukaemia treated with ibrutinib and rituximab or fludarabine, cyclophosphamide and rituximab: patient-reported outcomes from the multicentre, open-label, randomised, phase 3 FLAIR trial

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1. Introduction

The FLAIR trial (ISRCTN01844152) showed significantly improved progression-free survival (PFS) for ibrutinib and rituximab (IR) when compared with fludarabine, cyclophosphamide and rituximab (FCR) in people with previously untreated chronic lymphocytic leukaemia (CLL).

This analysis is of the patient-reported outcomes (PRO), a predefined secondary end point in FLAIR.

2. Methods

This study is an interim analysis of FLAIR, a phase III, open label, randomised, controlled trial in patients with previously untreated CLL.

Eligible patients were <75y, WHO PS≤2 requiring treatment. Patients with <20% CLL cells with del(17p) were excluded. Participants had to be fit to receive FCR. Allocation was to either IR or FCR.

Participants completed EORTC QLQ-C30 and CLL16, EQ 5D-3L at baseline and pre-determined follow-up timepoints. PROs were analysed on an intent-to-treat (ITT) basis using repeated measures multi-level regression models.

3. Participants

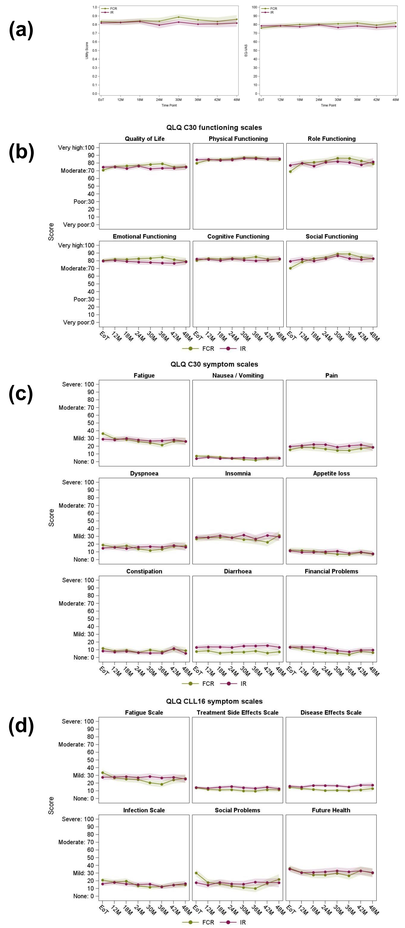
651 participants were in the FLAIR PRO ITT population. Participants were predominantly male (73%), median age 63y (range, 27-75) and PS0 (66%).

Functioning Scales	FCR (N=322)	IR (N=322)	Reference population
Baseline EQ5D-3L			
EQ5D-3L Utility Score	0.81 (0.23)	0.83 (0.22)	0.81
EQ-VAS	75.1 (19.0)	74.6 (18.6)	80.1
Baseline EORTC QLQ-C30			
Physical Functioning	83.0 (19.9)	82.6 (19.2)	80.6
Role Functioning	76.2 (30.0)	73.7 (29.0)	79.8
Emotional Functioning	75.8 (22.7)	78.0 (20.3)	77.1
Cognitive Functioning	82.0 (22.0)	84.0 (19.6)	83.5
Social Functioning	77.7 (28.5)	78.9 (26.3)	83.1
Global health status / QoL	70.6 (20.9)	70.2 (20.7)	61.6
Fatigue	34.4 (25.8)	35.9 (26.0)	30.0
Nausea/vomiting	4.97 (12.7)	4.66 (11.9)	3.8
Pain	18.9 (27.4)	16.9 (23.2)	27.9
Dyspnoea	23.0 (27.8)	21.7 (25.7)	18.8
Insomnia	33.5 (32.2)	32.7 (30.3)	32.9
Appetite Loss	15.1 (24.8)	15.2 (25.2)	10.4
Constipation	7.25 (17.5)	7.09 (16.8)	10.5
Diarrhoea	11.4 (20.2)	8.00 (17.7)	7.4

Table 1: Baseline mean (sd) PRO scores for EQ-5D-3L and EORTC QLQ-C30 with healthy reference populations

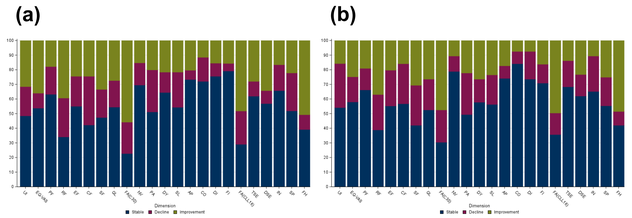
4. Results

Figure 1: Mean scores adjusted for baseline for (a) EQ-5D Utility Score and VAS, (b) C30 Functioning Scales, (c) C30 Symptom Scales and (d) CLL16 Symptom Scales from EoT to 48M



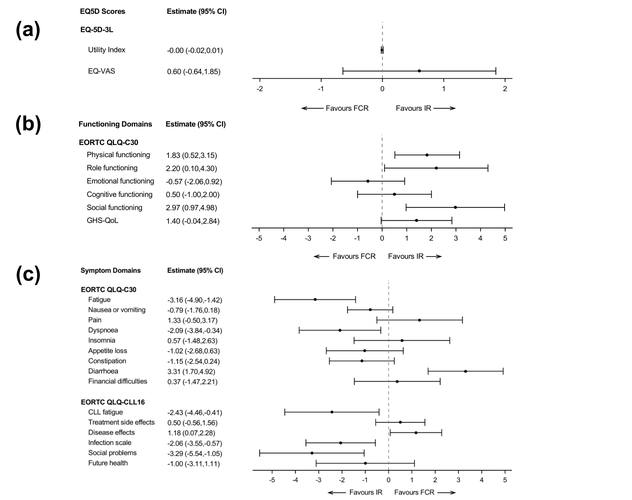
EORTC, European Organisation for Research and Treatment of Cancer; QLQ-C30, Quality of Life C30 Questionnaire; QLQ-CLL16, QLQ CLL Module; GHS-QoL=global health status-quality of life; IR, ibrutinib and rituximab; FCR, fludarabine, cyclophosphamide and rituximab; EoT, End of treatment.

Figure 2: Distribution of changes (declined, improved and remained) in HR-QoL scales between baseline and 48m post-randomisation in (a) FCR and (b) IR.



UI, EQ5D-3L Utility Score; EQ-VAS, EQ5D Visual Analogue, PF, Physical Functioning; RF, Role Functioning; EF, Emotional Functioning; CF, Cognitive Functioning; SF, Social Functioning; QL, Global health status / QoL; FA(C30), Fatigue; NV, Nausea / Vomiting; PA, Pain; DY, Dyspnoea; SL, Insomnia; AP, Appetite loss; CO, Constipation; DI, Diarhoea; FI, Financial Problems; FA(CLL16), Fatigue; TSE, Treatment Side Effects; DSE, Disease Effects; IN, Infection; SP, Social Problems; FH, Future Health.

Figure 3: Differences as estimated from repeated measures multi-level regression models in functioning scales for IR compared with FCR up to month 48 for (a) EQ-5D Utility Score and VAS, (b) C30 Functioning Scales, (c) C30 and CLL16 Symptom Scales



A positive change denotes improvement for the functioning scales of the EORTC QLQ-C30 (including GHS–QoL) and the EQ-5D-3L (utility index and VAS). The difference in least-squares means is in favour of the IR group versus the FCR group when showing positive differences for functioning scales and GHS–QoL. Conversely, a negative change denotes an improvement for the symptom scales of the EORTC QLQ-C30 and EORTC QLQ-CLL16. The difference in least-squares means is in favour of the IR group versus the FCR group when showing negative differences for symptom scales. EORTC, European Organisation for Research and Treatment of Cancer; QLQ-C30, Quality of Life C30 Questionnaire; GHS–QoL=global health status–quality of life; IR, ibrutinib and rituximab; FCR, fludarabine, cyclophosphamide and rituximab.

5. Interpretation

Although moderate differences between the two treatment arms were seen in health-related quality of life (HR-QoL) up to four years post-randomization, generally PRO are similar between the two treatment groups. These findings suggest that up to 48 months the delivery of continuous therapy with IR is associated with similar HR-QoL as compared to FCR.

However, the impact of the late effects of both therapies may become only apparent with prolonged follow-up. A planned future QOL analysis of FCR, IR, ibrutinib and ibrutinib combined with venetoclax will shed further light on the impacts of these therapies.

In future, the updated CLL module EORTC QLQ-CLL17 may enable detection of differences in HR-QoL, specifically in relation to the benefits in contemporary targeted treatments for CLL patients.

6. Conclusions

The FLAIR trial demonstrates that IR is associated with minimal differences in HR-QoL at four years when compared to FCR.

This result may reflect the significant efficacy of both treatments, the nature of the trial population and limitations in the sensitivity of the available tools to assess patient-reported HR-QoL.

As we have shown previously, IR is associated with a significant extension of PFS when compared to FCR. These findings suggests that this extension in PFS is not at the detriment of HR-QoL.

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