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POSTER ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Lenalidomide Consolidation Improves Measurable Residual Disease (MRD) Rates and Progression Free Survival in Patients with Chronic Lymphocytic Leukemia Following Initial FCR Chemotherapy - Final Analysis of CLL6 Residuum Study of the Australian Leukaemia and Lymphoma Group (ALLG) and the French Innovative Leukemia Organization (FILO)

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Introduction

Eradication of MRD after first line chemoimmunotherapy (CIT) correlates with longer progression-free survival (PFS) in chronic lymphocytic leukemia (CLL) patients. Lenalidomide (LEN) has antiproliferative and immunomodulatory effects in CLL and may improve response following CIT (Buhler et al 2016; Fink et al 2017). Here we report the final analysis of the phase III, randomized, CLL6 RESIDUUM trial, that aimed to determine whether LEN improves immunophenotypic (IP) complete response (CR) rates and extends remission duration in patients with CLL who have MRD following induction CIT.

Methods

The CLL6 trial was a joint trial of the ALLG and the FILO. CLL patients with CIRS score <6 requiring treatment according to iwCLL received 4 to 6 cycles of fludarabine, cyclophosphamide and rituximab (FCR). After completion of treatment, patients

with clinical, radiological and/or flow cytometry evidence of MRD in blood (PB) or bone marrow (BM) were randomized 1:1 to receive 2 years of 10 mg daily LEN consolidation or observation (OBS). High sensitivity (HS) MRD were scheduled at month 3, 6 and every 6 months until month 24 then every 12 months until month 72 in PB and at screening and on months 12 and 24 in BM. The primary endpoint was time to clinical disease progression, or death, from randomization. The study planned to randomize 192 patients to detect a hazard ratio of 1.94, i.e., an increase in the % of patients remaining progression free at 4 years to 70% in the LEN arm compared with 50% in the OBS arm (two-sided log rank test at alpha = 0.05, no competing risks or loss to follow up, power = 0.86).

Results

The study closed prematurely because of an acute lymphoblastic leukemia (ALL) warning (3 of 56 patients [5.4%]) in the CLLM1 trial (Fink et al., 2017; Fürstenau et al., 2021). Between May 2011 and January 2018, 143 patients were randomized (70 in Australia and 73 in France) to the LEN (n=71) or OBS (n=72) arms. Median age was 63 [range 41-78], and 60 [26-79] years in the LEN and OBS arms respectively, 113 patients were males. At randomization, 27 (38 %) and 23 (32%) patients were in CR, 9 (13%) and 10 (14%) in nPR, 35 (49%) and 39 (54%) in PR in LEN and OBS arms respectively. Forty-nine (69%) and 47 (65%) had PB and 56 (79%) and 58 (81%) had BM detectable MRD in LEN and OBS arm respectively. Median follow-up (FU) is 52.6 months (range 44.9-59.0; LEN 49.8 [41.9-57.1], OBS 55.59 [44.0-61.7]). Twenty-eight (39%) patients progressed in the LEN arm versus 40 (56%) in the OBS arm (χ^2 p=0.01), 8 died in each arm. Median PFS was 64.6 (95%CI 47.7-not reached [NR]) months in the LEN arm versus 42.4 (32.3-61.6) months in the OBS arm (p=0.039). Multivariate analysis did not identify any predictive factor of relapse. Median overall survival was not reached (NR) (77.58-NR) in the LEN arm and 107.7 (107.6-NR) months in the OBS arm. There were 118 adverse events (AE), 87 in the LEN and 31 in the OBS arms respectively, with more neutropenia (n=21 vs n=1), gastrointestinal (n=10 vs n=4), respiratory (n=9 vs n=0) nervous system (n=6 vs n=1) and musculoskeletal (n=4 vs n=1) in the LEN arm. Most of the excess of AEs in LEN arm occurred after the end of the treatment. Severe AEs were reported in 35 patients (24.5%), 24 in the LEN arm and 11 in OBS. Fifteen secondary malignancies occurred: 8 in the LEN arm; 7 in the OBS arm. Six were of hematological origin (2 Richter transformation in each arm, 1 marginal zone lymphoma in the OBS arm and 1 myelodysplastic syndrome in the LEN arm). No case of ALL occurred.

HS MRD analyses were performed in 71/73 patients in the French cohort. A follow-up was available in 65/71 with a median number of 7 time-points per patients (range 3-10). Different MRD kinetics were observed. While MRD rates in OBS arm increased in 33/34 patients, LEN consolidation led to long-lasting and transient deep IP CR in 4/31 and 9/31 patients respectively, MRD rate stabilization in 10/31 patients, and MRD increase in the remaining 6/31 patients.

Conclusion

The CLL6 RESIDUUM study demonstrated a significant benefit of consolidation therapy with lenalidomide in CLL patients with residual disease after FCR treatment. LEN resulted in a significantly longer PFS, with no unacceptable toxicity including ALL. Although FCR is no longer considered gold standard initial CLL therapy, eradicating residual disease can remain challenging with newer targeted agents. Patients with CLL MRD following initial therapy may experience prolongation in progression free survival from LEN consolidation.

Disclosures Aurran-Schleinitz: *Astrazeneca, Janssen:* Other: congres inscription and travel. **Mulligan:** *Astra Zeneca:* Membership on an entity's Board of Directors or advisory committees; *Janssen:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau. **Cull:** *Beigene, AstraZeneca, Glycomimetics:* Research Funding. **Tam:** *Roche:* Honoraria; *Novartis:* Honoraria; *LOXO:* Honoraria; *BeiGene:* Honoraria, Research Funding; *AbbVie:* Honoraria, Research Funding; *Janssen:* Honoraria, Research Funding. **De Guibert:** *JANSSEN:* Honoraria; *Astra Zeneca:* Honoraria; *Beigene:* Honoraria; *ABBVIE:* Honoraria. **Harrup:** *F. Hoffmann-La Roche Ltd, Takeda:* Current equity holder in publicly-traded company; *F. Hoffmann-La Roche Ltd, Beigene:* Research Funding; *FibroGen:* Research Funding. **Drenou:** *Alexion Pharma France:* Honoraria; *Abbvie, Gilead, Janssen:* Membership on an entity's Board of Directors or advisory committees. **Dartigeas:** *Janssen, AbbVie, BeiGene, astrazeneca:* Membership on an entity's Board of Directors or advisory committees, Other: travel grant. **Forsyth:** *Roche:* Honoraria. **Cymbalista:** *Abbvie:* Honoraria; *AstraZeneca:* Honoraria; *Lilly:* Honoraria.

OffLabel Disclosure: lenalidomide within approved randomized clinical trial

Table 1: PFS at 24, 36, 48, and 60 months in LEN versus OBS arms

Result	Lenalidomide (N=69)	Observation (N=72)	p-value
Number of Progressions	28	40	
Median (Months)	64.56	42.37	
(95% CI)	(47.67,NR)	(32.28,61.64)	
Log rank test			0.0386
PFS 24 Months	92.1% (82.1%,96.6%)	74.4% (62.4%,83.0%)	
PFS 36 Months	74.5% (61.2%,83.8%)	62.0% (49.3%,72.4%)	
PFS 48 Months	64.2% (50.0%,75.4%)	46.1% (33.3%,57.9%)	
PFS 60 Months	54.4% (39.5%,67.1%)	42.1% (29.5%,54.1%)	

Figure 1: Progression-free survival CLL6 RESIDUUM Study

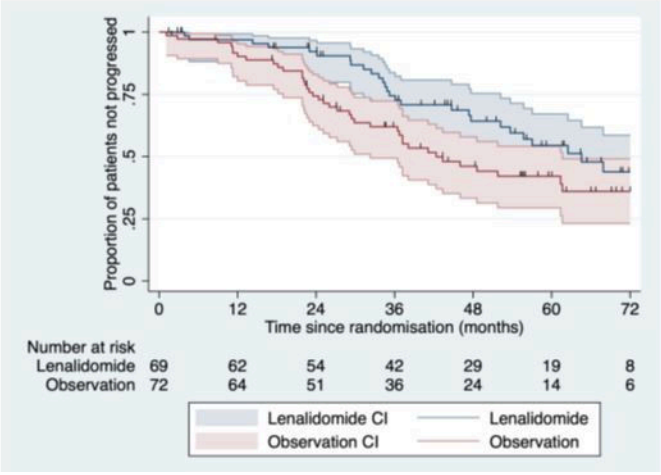

Figure 1

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