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STop and Restart Acalabrutinib In fRail Patients With Previously Untreated Chronic Lymphocytic Leukemia (STAIR): a randomized phase 2 study from the FILO-CLL group

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BACKGROUND and RATIONALE: The irreversible Bruton's Tyrosine Kinase inhibitor (BTKi) acalabrutinib (ACA) displays potent clinical activity as a single agent in patients with treatment-naive or refractory/relapsed Chronic Lymphocytic Leukemia (CLL). However, there is growing concern regarding the unlimited administration of such targeted therapies as BTKi. First, long-term treatment expose the patients to an increased risk of adverse events (infections, bleeding or cardiovascular problems). Second, continuous administration could also increase the risk of clonal evolution and therapeutic resistance resulting from genetic alterations, such as *BTK* or *PLCG2* mutations. Discontinuation of therapy after a fixed period is expected to prevent these events. The STAIR study aims to investigate 1-year PFS after ACA discontinuation and the efficacy of restarting ACA upon symptomatic relapse (NCT04963946).

Patients and Methods

This multicenter, non-comparative, randomized phase 2 trial led in French FILO centers aimsedat evaluating the impact of a "stop and restart ACA" strategy on the PFS of CLL patients ≥70-year-old (yo) and/or with coexisting comorbidities (CIRS-G ≥6)

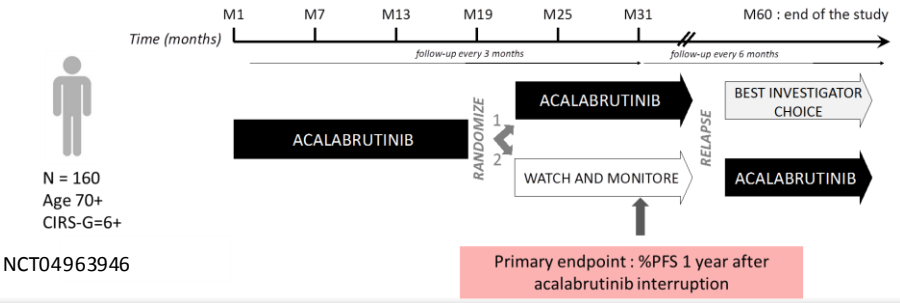
Patients received continuous ACA at 100 mg bid for 18 months (dose adaptations according to labels). At month 19 day 1, 160 patients (to include assuming a drop-out rate before 18 months of 20%) were planned to be randomized 1:2 in two arms (*importantly*: regardless of the response assessed by CT scan/minimal residual disease):

Arm 1 = Control arm continuing ACA

Arm 2 = Experimental arm (watch and monitore) without ACA.

Patients were stratified based on the presence or absence of complex karyotype and del(17p)/*TP53* mutations.

Study Design



Last news of the study

Recruitment began in October 2021 and was completed in June 2023 (10 months ahead of schedule). The first patient was randomized in May 2023. These patients have a median age of 76 yo (range 70-96 yo) and 62% had a CIRS>6 at inclusion.

Upon progression in the experimental arm, all patients will be re-treated with ACA at the last received dose after central reviewing. Upon progression in the control arm, patients will receive next-line therapy at the discretion of their physicians,

Patients will be monitored every three months until M31, then every 6 months until M60 or progression, for both response and toxicity according to CTCAE v.5.

Conclusion: our trial is in progress but has finished recruiting 160 patients (10 months ahead of schedule), demonstrating that trials dedicated to a hard-to-treat population such as elderly, comorbid, frontline patients is feasible. The trial was designed with the aim to demonstrate the absence of PFS disadvantage and even improvement, with less adverse events, of a fixed duration strategy *versus* continued administration of a BTKi. Rapid and deep responses yielded by ACA in elderly pave the way for investigating a limited 18-months period schedule. This study was supported by AstraZeneca, promoted by the French innovative leukemia network for CLL,