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626.AGGRESSIVE LYMPHOMAS: PROSPECTIVE THERAPEUTIC TRIALS

A Randomized, Open-Label, Phase 3 Study of Acalabrutinib in Combination with Rituximab and Reduced Dose CHOP (R-miniCHOP) in Older Adults with Untreated Diffuse Large B-Cell Lymphoma (ARCHED / GLA 2022-1)

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Background

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma subtype, and its incidence increases with age. Approximately 40% of patients with DLBCL are older than 70 years. Since the addition of the anti-CD20 antibody rituximab to CHOP regime (cyclophosphamide, doxorubicin, vincristine, and prednisone) prognosis in elderly patients has improved but still remains worse compared to their younger counterparts. Adequate dosage of chemotherapy in older adults is limited by comorbidities/frailty, especially in patients >80 years of age. An attenuated chemotherapy regimen, R-miniCHOP, has been evaluated in prospective trials and seems to provide a good balance between safety and efficacy in this vulnerable patient population (Peyrade et al, 2011). However, even with this regime, outcomes remain modest with 2-year overall survival at 50-60%, underlining the need for more effective treatment in this population.
Acalabrutinib is a selective, irreversible, second-generation small molecule inhibitor of Bruton Tyrosine Kinase (BTK) with a more favorable safety profile compared to first generation BTK inhibitors. Although, not yet approved for the treatment of

DLBCL, acalabrutinib showed promising results both as a single agent (Strati et al, Haematologica 2021) and in combination with full dose R-CHOP (Davies et al, ASH 2022), in patients aged up to 80 years. Furthermore, acalabrutinib carries the potential of improved efficacy in specific subgroups. The activated B-cell like (ABC) DLBCL subtype has been shown to depend on chronic active B-cell receptor signaling involving many downstream kinases including BTK. Additionally, the genetically defined subgroups MCD/C5, N1, and BN2/C1 and also may serve as potential predictive biomarkers for acalabrutinib.

Study design and endpoints

ARCHED is an investigator initiated, randomized, multicenter, open-label, phase III trial of R-miniCHOP with or without acalabrutinib in older adults with untreated DLBCL. Patients in the standard arm will receive 6 cycles of R-miniCHOP every 21 days followed by 2 cycles of rituximab alone, while patients in the experimental arm will receive the same regimen and additionally acalabrutinib 100 mg p.o. twice daily from day 1 to day 21 for 8 cycles (Figure 1). The primary endpoint of the study is investigator assessed progression-free survival (PFS). Secondary endpoints include overall survival, PFS per blinded independent review, event-free survival, outcomes according to cell of origin and molecular genotype, response rates, duration of response, progression, relapse and central nervous system (CNS) relapse rates as well as toxicity.

Key eligibility criteria

Patients are eligible for enrolment if they are >80 years old or >60 years old and ineligible for full-dose R-CHOP according to investigator assessment after standardized simplified geriatric evaluation and are diagnosed with untreated CD20+ DLBCL according to the 2017 WHO classification. Primary mediastinal lymphoma, high grade B-cell lymphoma and follicular lymphoma 3B as well as concurrent diagnosis of indolent lymphoma is allowed, but Richter's transformation is an exclusion criterion. Ann Arbor stage I patients can be included only in the presence of concomitant bulky disease ($\geq$ 7.5 cm). Further exclusion criteria are CNS involvement, stroke or intracranial hemorrhage in the past 6 months and relevant organ dysfunction. An ECOG performance status score of 0 - 2 is required for enrolment but an ECOG score of 3 is acceptable if lymphoma associated.

Statistical analysis

With an expected 5% drop out rate, we aim to recruit 330 patients (165 in each arm) to achieve 80 % power at a 5 % significance level (two-sided) to observe a PFS difference of 15 % in favor of the experimental arm. An interim analysis for efficacy comparing PFS between the two treatment arms will be performed with n=200 patients and 1 year follow-up for the last patient, with approximately 50% of events. Additionally, an interim analysis for safety regarding treatment completion rates and all-cause mortality will take place when 92nd patient in each group has completed the sixth R-mini-CHOP cycle or died.

ARCHED is an academic study of the German Lymphoma Alliance and is coordinated by the Saarland University Clinical Trials Unit. This study is funded by AstraZeneca GmbH. The trial is approved in the EU and is open for recruitment in Germany. (EU-CTN: 2022-501187-18-00, NCT05820841).

Disclosures Christofyllakis: *Celgene:* Other: Educational/travel grant; *Hexal:* Other: Educational/travel grant; *Takeda:* Consultancy; *Novartis:* Consultancy, Other: Educational/travel grant; *Roche:* Honoraria; *AstaZeneca:* Other: Educational/travel grant, Research Funding; *Jazz Pharmaceuticals:* Other: Educational/travel grant; *Abbvie:* Other: Educational/travel grant. **Poeschel:** *Swedish Orphan Biovitrum GmbH:* Membership on an entity's Board of Directors or advisory committees; *PentixaPharm GmbH:* Membership on an entity's Board of Directors or advisory committees; *Amgen:* Other: travel expenses, congress support; *Abbvie:* Other: travel expenses, congress support; *Genmab:* Consultancy; *Roche:* Other: travel expenses, congress support; *Janssen-Cilag:* Consultancy; *AstraZeneca:* Honoraria; *Bristol-Myers Squibb:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: travel expenses, congress support; *EUSA Pharma:* Consultancy; *BeiGene:* Membership on an entity's Board of Directors or advisory committees; *Gilead:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: travel expenses, congress support; *Lilly:* Membership on an entity's Board of Directors or advisory committees. **Lesan:** *Pierre Fabre:* Other: Travel and Congress Grant. **Age Kos:** *Pfizer:* Other: Travel funds. **Neuendorff:** *Pfizer:* Consultancy; *Hexal:* Consultancy. **Nickelsen:** *AstraZeneca:* Consultancy, Honoraria; *Roche:* Consultancy, Honoraria; *AbbVie:* Honoraria; *BMS:* Honoraria; *Incyte:* Consultancy, Honoraria; *Lilly:* Consultancy, Honoraria; *Sobi:* Consultancy, Honoraria; *AMGEN:* Honoraria; *Janssen:* Consultancy, Honoraria; *Takeda:* Consultancy. **Held:** *Abbvie:* Consultancy, Honoraria; *MSD:* Consultancy, Honoraria; *Amgen:* Consultancy, Honoraria; *Bristol-Myers Squibb:* Consultancy, Honoraria, Research Funding; *Janssen:* Consultancy, Honoraria. **Dreyling:** *Astra Zeneca, Beigene, Gilead/Kite, Janssen, Lilly, Novartis, Roche:* Honoraria; *Abbvie, Astra Zeneca, Beigene, BMS/Celgene, Gilead/Kite, Janssen, Lilly/Loxo, Novartis, Roche:* Other: Scientific advisory boards; *Abbvie, Bayer, BMS/Celgene, Gilead/Kite, Janssen, Roche:* Research Funding. **Zettl:** *AMGEN:* Patents & Royalties: transfer agreement. **Buske:** *BeiGene:* Consultancy, Honoraria, Speakers Bureau; *Novartis:* Consultancy, Honoraria; *Pfizer:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *Incyte:* Consultancy, Honoraria; *Abbvie:* Consultancy, Honoraria, Speakers Bureau; *Gilead Sciences:* Consultancy, Honoraria, Speakers Bureau; *Celltrion:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *MorphoSys:* Consultancy, Honoraria, Speakers Bureau; *Regeneron:* Consultancy, Honoraria; *Sobi:* Consultancy, Honoraria, Speakers Bureau; *Lilly:* Consultancy, Honoraria, Speakers Bureau; *MSD:* Research Funding; *Amgen:* Research Funding; *Bayer:* Research Funding; *Janssen:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *Roche/Genentech:* Consultancy, Honoraria, Research Funding, Speakers Bureau. **Lenz:** *University Hospital Munster:* Current Employment; *Celgene:* Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *NanoString:* Membership on an entity's Board of Directors or advisory committees; *BeiGene:* Membership on an entity's Board of Directors or advisory committees; *Hexal/Sandoz:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Lilly:* Consultancy; *Genase:* Consultancy; *Immagene:* Consul-

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OffLabel Disclosure: Acalabrutinib is a BTK inhibitor, currently not approved for patients with DLBCL.

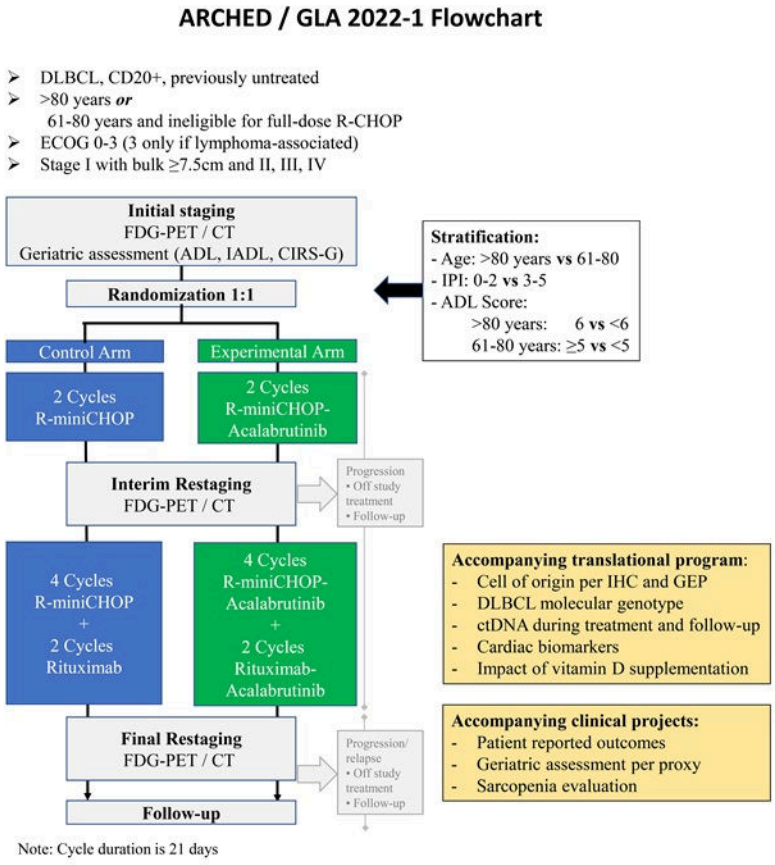

Figure 1

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