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Trial Synopsis

Regarding Protocol Version V01.4-F of 08th March 2023

Title of clinical trial	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)
Short title	ARCHED / GLA 2022-1
EU CT number	2022-501187-18-00
UTN	U1111-1284-7084
Investigational product	Acalabrutinib / Calquence® 100mg hard capsules
Sponsor	Saarland University, Saarbrücken, Germany

Trial number:	GLA 2022-1
Short title of study:	ARCHED
Title of study:	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)
Number of centers	40
Number of patients	330 (= 314 + 5% dropouts)
Indication:	Older adults with newly diagnosed previously untreated CD20 positive Diffuse large B-cell lymphoma (DLBCL).
Primary objective of study:	To evaluate if the addition of acalabrutinib to R-miniCHOP prolongs progression-free survival (PFS), compared to R-miniCHOP alone in patients >80 years or >60 years and ineligible for full-dose R-CHOP with previously untreated DLBCL, based on investigator-assessed response

Secondary efficacy objectives:	• To evaluate overall survival (OS) with acalabrutinib plus R-miniCHOP compared with R-miniCHOP alone in patients >80 years or >60 years and ineligible for full-dose R-CHOP with previously untreated DLBCL. • To evaluate PFS with acalabrutinib plus R-miniCHOP compared with R-miniCHOP alone in patients >80 years or >60 years and ineligible forfull-dose R-CHOP with previously untreated DLBCL, based on blinded independent central review (BICR) • To evaluate event-free survival (EFS) with acalabrutinib plus R-miniCHOP compared with R-miniCHOP alone in patients >80 years or >60 years and ineligible for full-dose R-CHOP with previously untreated DLBCL, based on investigator assessment and BICR. • To analyze outcomes according to cell of origin (COO) as per immunohistochemistry and gene expression analysis with acalabrutinib plus R-miniCHOP compared with R-miniCHOP alone in patients >80 years or >60 years and ineligible for full-dose R-CHOP with previously untreated DLBCL. • To analyze outcomes according to DLBCL molecular genotype with acalabrutinib plus R-miniCHOP compared to R-miniCHOP alone in patients >80 years or >60 years and ineligible for full-dose R-CHOP with previously untreated DLBCL. • To analyze outcomes with acalabrutinib plus R-miniCHOP versus R-miniCHOP alone between age groups (>60 - 80 years vs >80 years) and according to gender and serum albumin. • To compare complete (CR), partial (PR) and overall (ORR) remission rates as well as duration of response (DoR) between both treatment (acalabrutinib plus R-miniCHOP versus R-miniCHOP alone) and molecular groups (COO, molecular genotype). • To compare progression rate, relapse rate and central nervous system (CNS) relapse rate between both treatment (acalabrutinib plus R-miniCHOP versus R-miniCHOP alone) and molecular groups (COO, molecular genotype).
Secondary safety objectives:	• To evaluate the safety and tolerability of acalabrutinib plus R-miniCHOP relative to R-miniCHOP alone in patients >80 years or >60 years and ineligible for full-dose R-CHOP. • To evaluate protocol adherence of acalabrutinib plus R-miniCHOP relative to R-miniCHOP alone in patients >80 years or >60 years and ineligible for full-dose R-CHOP

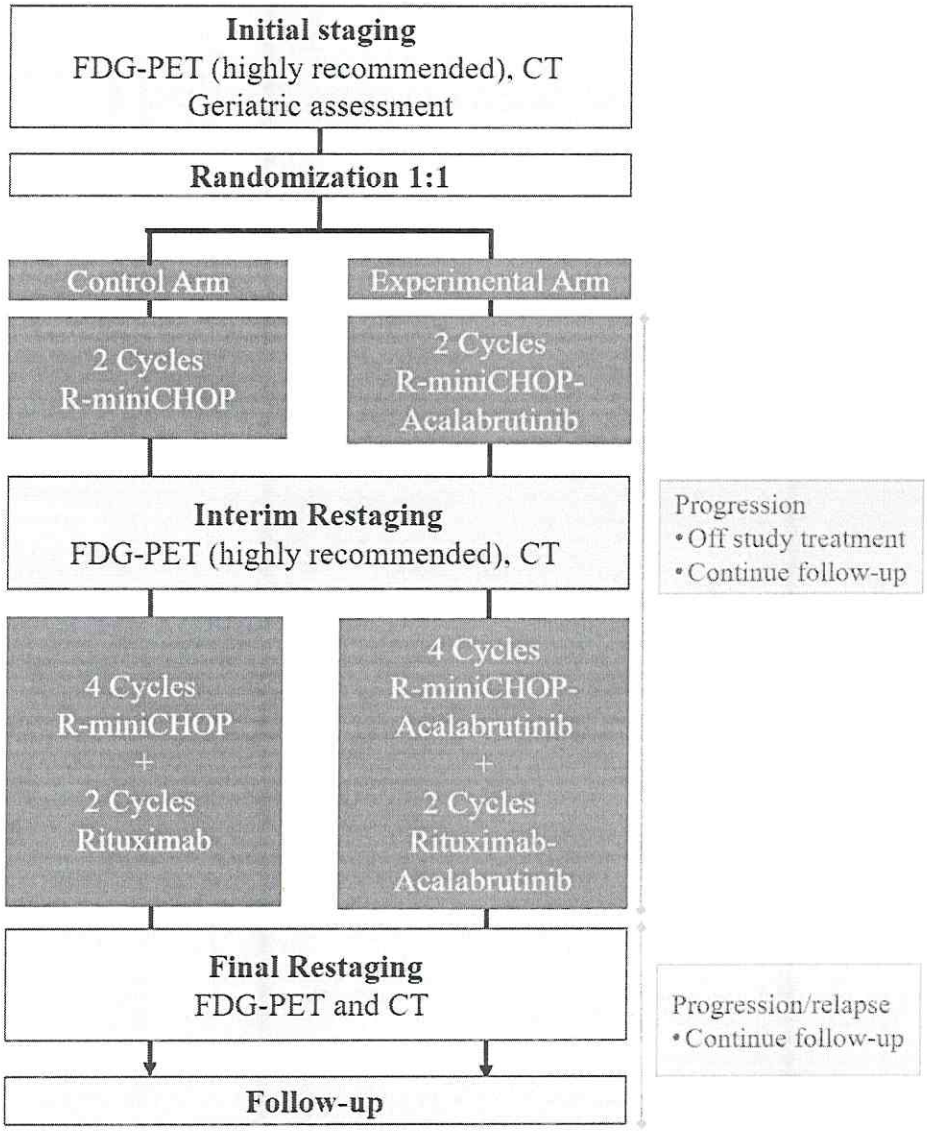
Study design, statistics and patient numbers:	National, multicenter, randomized, open-label, phase 3 study It is hypothesized that PFS at 1-year is 59% in treatment arm without acalabrutinib and 74% in treatment arm with acalabrutinib. A two-sided log rank test with an overall sample size of 314 patients (100 events) achieves 80% power at a 5% significance level (two-sided) to detect these 1-year PFS difference of 15%. This corresponds to a hazard ratio of 0.571. We anticipate that about 5% of patients will be lost to follow-up. Therefore, a total of 330 patients (165 in each arm) will be included.
Study population:	Patients with newly diagnosed, histologically proven, previously untreated CD20+ DLBCL (WHO classification 2017) who are above 80 years of age or above the age of 60 and ineligible for full dose R-CHOP according to investigator assessment*, with Ann Arbor disease stage I with bulk ≥7.5cm, II, III or IV. **We recommend classifying patients aged 61-80 as full-dose R-CHOP ineligible if they fulfill one of the following criteria: ADL <5, IADL <6, CIRS-G ≥1 score = 3, or > 8 score = 2.*
Investigational product	Acalabrutinib 100mg, 1 capsule administered p.o. twice daily starting from D1 of first R-miniCHOP cycle continuously until D21 of cycle 8
Treatment:	**Immunochemotherapy**: 6x R-miniCHOP + 2x R [rituximab i.v.: 375 mg/m² (D0), cyclophosphamide i.v.: 400 mg/m² (D1), doxorubicin i.v.: 25 mg/m² (D1), vincristine i.v.: 1 mg (D1) prednisolone p.o.: 40 mg/m² D1 to D5, repeated every 3 weeks] **Standard arm:** 6x R-miniCHOP + 2x R **Experimental arm:** 6x R-miniCHOP + 2x R together with acalabrutinib 100 mg p.o. twice daily starting from D1 of first R-miniCHOP cycle continuously to D21 of cycle 8
Primary endpoint:	Progression-free survival, investigator assessed

Secondary endpoints:	• Overall survival • Event-free survival, investigator assessed and per blinded independent central review (BICR) • Progression-free survival, per BICR • Complete response rate • Partial response rate • Overall response rate • Duration of response • Progression rate • Relapse rate and CNS relapse rate • Toxicity • Rate of treatment-related deaths • Rate of secondary malignancies • Protocol adherence
Major Analysis:	PFS will be compared according to the two treatment arms (R-miniCHOP + acalabrutinib versus R-miniCHOP) using the log-rank test and Kaplan-Meier curves will be presented. In addition, an estimation of the 1-years PFS-rate with 95% confidence interval will be prepared according to the treatment arms. In a supportive analysis, a Cox multivariable regression model will be applied to test whether the therapy effect that emerged from the univariate Kaplan Meier analysis remains stable after adjustment for known prognostic factors (IPI components) / strata [IPI (0-2 vs 3-5), age groups (age 61-80 years and ineligible for full dose CHOP vs. age > 80 years); ADL score (a. Age 61-80: ADL≥5 vs ADL<5, b. Age >80: ADL=6 vs ADL <6)]. The estimates are given in the form of a hazard ratio with 95% confidence interval and a corresponding p value. In dependence from the median observation time further PFS-rates (e.g. 2-years, 3-years) will be presented.
Interim analysis for safety	The addition of a BTK inhibitor to R-CHOP led to higher treatment discontinuation rates in a previous trial. Thus, an interim analysis for safety will be performed to compare treatment discontinuation rates of any cause with regard to the six planned R-miniCHOP cycles between the two arms. Acalabrutinib discontinuation will not be considered The analysis will take place when the 92nd patient in each group has completed six R-miniCHOP cycles, discontinued miniCHOP, or died. The difference in discontinuation rates for both treatment arms should not be >15% [95% CI (Clopper-Pearson) = 2-28%]. Additionally, an absolute

	treatment completion rate below 70% in the standard arm will not be accepted, corresponding to 64 patients when the sample size in the standard arm is 92 (64/92=70%, 95% CI = 59-79%). Furthermore, treatment related deaths will be evaluated in the interim analysis for safety. With a tenth therapy-related death under experimental therapy within the first 92 patients, recruitment will be halted and the study will be re-evaluated following consultation with the DSMC. If one of the criteria above are fulfilled, the study will be considered for potential termination or modification of the inclusion criteria to exclude patients at risk.
Interim analysis for efficacy	For PFS, the primary endpoint of the study, a formal criterion for early discontinuation will be defined using the alpha spending function (O' Brien-Fleming) to obtain the possibility to stop the trial earlier in case the experimental treatment arm with acalabrutinib is as superior as expected. The interim analysis of efficacy will be performed including the first 200 patients (last patient with approximately 1 year follow-up, median follow-up approximately 2 years, with approximately 50% of events). In case the PFS difference is remarkably smaller than planned conditional power calculations may be performed to check whether it seems to be furthermore realistic to achieve the planned aim of the study.
Timelines:	We expect 3 fully eligible patients per center per year. With 40 centers, this results in approximately 120 patients per year. For recruitment of 330 patients, approximately 3 years are required. We expect a slower recruitment during the beginning of the study, approximately 60 patients in the first, 120 patients in the second, and 150 patients in the third year. The last patient will be followed-up for 2 years after randomization. With the expected start of recruitment in Q1/2023, the recruitment period will finish in Q1/2026 and the follow-up in Q1/2028.
Sponsor:	Saarland University, Saarbrücken, Germany.
Financial Support:	AstraZeneca GmbH, Firesenweg 26, 22763 Hamburg, Germany

Study Flowchart

- DLBCL, CD20+, previously untreated
- >80 years ***or***
  61-80 years and ineligible for full-dose R-CHOP
- ECOG 0-3 (3 only if lymphoma-associated)
- Stage I with bulk ≥7.5cm and II, III, IV



Note: Cycle duration is 21 days