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626.AGGRESSIVE LYMPHOMAS: PROSPECTIVE THERAPEUTIC TRIALS

Acrue: A Phase 2, Open-Label Study of Acalabrutinib in Combination with Rituximab in Elderly and/or Frail Patients with Treatment-Naive Diffuse Large B-Cell Lymphoma

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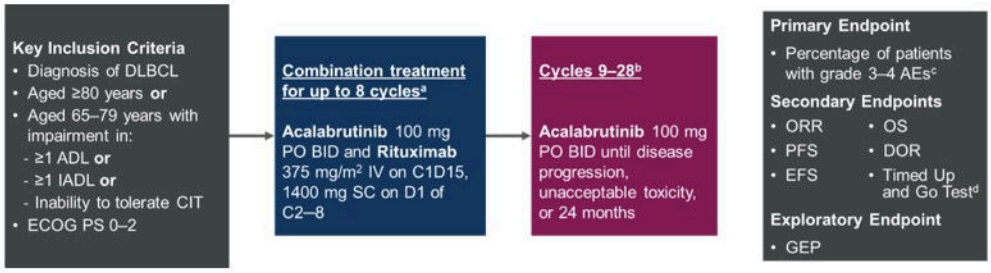
Background and Significance: Patients aged ≥80 years with diffuse large B-cell lymphoma (DLBCL) account for approximately 18% of DLBCL cases in the United States (Morrison et al. *Future Oncol.* 2018). Standard-of-care chemoimmunotherapy (CIT) regimens such as rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP), including reduced doses of CHOP (R-miniCHOP), are not well tolerated in elderly and/or frail patients, leading to high treatment-related mortality rates (Boslooper et al. *Leuk Lymphoma.* 2014; Freudenberger et al. *Ann Hematol.* 2021; Peyrade et al. *Lancet Oncol.* 2011). Therefore, safe, effective, and convenient treatment alternatives to CIT are needed. Acalabrutinib is a highly selective, second-generation Bruton tyrosine kinase inhibitor approved for the treatment of patients with relapsed/refractory mantle cell lymphoma and in patients with chronic lymphocytic leukemia. Acalabrutinib monotherapy has demonstrated encouraging activity in patients with DLBCL in phase 1b (NCT02112526) and phase 2 (NCT04002947) studies (Strati et al. *Haematologica.* 2021; Roschewski et al. *Blood.* 2021). However, neither of these studies were conducted specifically in a population of elderly and/or frail patients.

Study Design and Methods: ACRUE (NCT05952024) is a phase 2, open-label, single-arm, global, multicenter study of acalabrutinib plus rituximab in elderly and/or frail patients with treatment-naive (TN) DLBCL who are unable to tolerate standard CIT (**Figure**). Eligible patients are aged ≥80 years or aged 65-79 years with impairment in ≥1 activity of daily living (ADL) or instrumental ADL (IADL), or with cardiac/renal/liver function impairment or other comorbidities that render them unable to tolerate CIT. Furthermore, patients must have histologically confirmed CD20-positiveDLBCL (not otherwise specified), according to WHO 2016 classification, an Ann Arbor classification of stage II, III, or IV disease, an Eastern Cooperative Oncology Group performance status of 0-2, and ≥1 measurable lesion. Patients with active central nervous system involvement by lymphoma, leptomeningeal disease, or spinal cord compression, or significant cardiovascular disease within 6 months of screening are excluded. Target enrollment is 80 patients. Patients will receive acalabrutinib plus rituximab combination for 8 cycles (acalabrutinib 100 mg orally twice daily beginning on day 1 of cycles 1-8; rituximab 375 mg/m ^{2} intravenously on C1D15, then 1400 mg subcutaneously, on day 1 of cycles 2-8; cycles 1-8 are 21 days/cycle), followed by acalabrutinib monotherapy until disease progression, unacceptable toxicity, or 24 months (cycles 9-28 are 28 days/cycle). The primary endpoint is the percentage of patients with grade 3-4 treatment-emergent adverse events. The key secondary endpoint is investigator-assessed objective response rate per Lugano 2014 criteria. Other secondary endpoints include progression-free survival, event-free survival, overall survival, duration of response, and Timed Up and Go test. Exploratory biomarker analyses may include genomic characterization of baseline samples to evaluate predictors of survival, and of progression samples to evaluate genomic resistance mechanisms. Descriptive safety and efficacy data will be summarized. If patients discontinue treatment prior to completing 28 cycles of therapy, they will be followed every 12 weeks after their last treatment dose for up to 2 years. Patients who are still on treatment at the end of the study and are deriving clinical benefit may receive continued treatment, with assessments reverting to standard of care. Enrollment is planned to begin Q4 of 2023 in approximately 40 sites from North and South America and Asia.

Summary: This study will help determine if acalabrutinib plus rituximab combination therapy is tolerable and effective in elderly and/or frail patients with TN DLBCL who are unable to tolerate CIT.

Disclosures Perini: *AstraZeneca, Janssen, MSD, Merck, Abbvie, Takeda:* Speakers Bureau; *AstraZeneca, Janssen, MSD, Merck, Abbvie, Takeda:* Consultancy. **Graff:** *Mission Cancer and Blood:* Current Employment; *AbbVie, Adaptive Biotechnologies, ADC Therapeutics, Astra-Zeneca, BMS, Beigene, Genentech, Genmab, Gilead, Kite, Lilly, TG Therapeutics:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau. **Roos:** *AstraZeneca:* Current Employment, Current equity holder in publicly-traded company. **Hermann:** *AstraZeneca:* Current Employment, Current equity holder in private company, Current equity holder in publicly-traded company, Current holder of *stock options* in a privately-held company. **Lovenklev:** *AstraZeneca:* Current Employment. **Shaw:** *AstraZeneca:* Current Employment. **Budde:** *AstraZeneca:* Consultancy, Research Funding; *Amgen:* Research Funding; *ADC Therapeutics:* Consultancy; *Roche:* Consultancy; *Merck:* Research Funding; *MustangBio:* Research Funding; *Novartis, Gilead, F. Hoffmann-La Roche Ltd, BeiGene, Genentech, Inc.:* Consultancy.

Figure. ACRUE study design and assessments



[a]Cycles 1–8, 21 days/cycle to align with rituximab dosing schedule.
[b]Cycles 9–28, 28 days/cycle.
[c]Includes adverse events that occur from dose start to 30 days after last dose in all dosed patients.
[d]A functional mobility test: a measurement of time, in seconds, taken by an individual to stand up from a standard armchair, walk a distance of 3 meters, turn, walk back to the chair, and sit down again.

ADL, activity of daily living; AEs, adverse events; BID, twice daily; C, cycle; C1D15, cycle 1, day 15; CIT, chemoimmunotherapy; D, day; D1, day 1; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; GEP, gene expression profiling; IADL, instrumental activity of daily living; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, by mouth; SC, subcutaneous.

Figure 1

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