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ORAL ABSTRACTS

627.AGGRESSIVE LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

Synthetic Control Arm from Clinical Trials and Real-World Data from Lysa Group for Untreated Diffuse Large B Cell Lymphoma Patients Aged over 80 Years: A *Bona Fide* Strategy for Innovative Clinical Trials

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Introduction
Diffuse large B cell lymphoma (DLBCL) is the most common lymphoid malignancy among older patients (pts), and about 25% of new diagnoses involve population aged > 80y.o. Most clinical trials (CTs) exclude the very older (Kanapuru et al, 2017). Rituximab + miniCHOP is considered gold-standard for untreated DLBCL aged >80 y.o with an overall survival (OS) of ˜60% at 2y and improving outcomes for this frail population is challenging. Synthetic control arms (SCA) may engender more innovative randomized trials, by allowing indirect comparisons with enhanced statistical confidence and by sparing a part of the control population. We present SCA built from CTs and real-world (RW) data, and their applications to a randomized phase 3 protocol in this clinical setting.
Methods
We used 3 CTs, with >80 y.o pts treated by anti-CD20+miniCHOP. Two phase 2 CTs for sourcing of SCA patients, LNH03-7B and LNH09-7B, which assessed efficacy of 6 anti-CD20+miniCHOP, preceded in the latter trial by pre-phase treatment, reducing early non-disease related mortality (Peyrade F. et al, 2011 and 2017). SENIOR trial was a phase III randomized trial comparing 6 R-miniCHOP to R-miniCHOP+Lenalidomide, showing no differences in terms of OS (HR= 0.996, 95% CI= 0.66-1.51) (Oberic L. et al, 2022). We further used prospective REALYSA cohort (Ghesquières et al, 2021) with enrolled pts with at least 18 months follow-up and treated by R-miniCHOP as RW pool. We excluded non-compliant diagnoses, as well as early deaths within 3 first months of follow-up from CTs, to avoid the bias for absence of pre-phase from LNH03-7B trial. First step was to build SCA matched with internal SENIOR control arm to check reproducibility of pts outcomes. Then, SENIOR experimental arm was used as the matching source for SCA constructions.
Propensity scores (PS) were estimated for each pt using relevant baseline covariates as described in Figure 1. If data was missing, CTs pts were excluded. For RW pts, multiple imputations method was used. Pts between groups were matched using stabilized inverse probability of treatment weighting (IPTW) method, the probability of treatment being assessed by PS, after removing pts with extreme PS from analyses. We subsequently performed sensitivity analyses using 1 : 1 PS matching (PSM). Standardized mean differences (SMD) were calculated for each covariate to assess matching efficacy. The endpoint was OS.
Results

Control SCAs matched to SENIOR internal control arm have no significant different OS with an HR of 0.81 (95%CI= 0.51-1.27, p = 0.397) using CTs data and an HR of 1.00 (95% CI= 0.62-1.61, p = 0.998) using RW data, with stabilized IPTW.
PS set is the baseline population after applying exclusion criteria and including only pts for whom PS could be assessed. For SCA-CT, PS set was composed of 91 pts from experimental SENIOR arm and 169 from LNH03-7B and LNH09-7B. Thirty one pts were excluded for early death, mostly not disease-related. IPTW and PSM methods were both efficient with all SMD <0.10. With SCA-CT, OS curves comparison with stabilized IPTW was very close to SENIOR results: HR of 0.98 (95%CI= 0.643-1.492, p=0.93) (Figure 2).
For SCA-RW, PS set included 104 pts from SENIOR experimental arm and 93 from REALYSA database. All SMD were below 0.10 with IPTW and all but one were below 0.15 with PSM. Regarding the outcome analysis, censorship was chosen at 24 months of follow-up as too few patients were still at risk. OS was not significantly different with an HR of 0.84 (95%CI=0.51-1.39, p= 0.551) with stabilized IPTW.
Sensitivity analyses with PSM, for SCA-CT and SCA-RW are consistent with results after IPTW, but exclusion process for matching led to a loss of power (84 pts in each arm for SCA-CT and 71 pts in each arm for SCA-RW)
Discussion
We demonstrated that well matched SCAs built from historical CTs data can achieve a high level of confidence to replicate randomized phase III results in DLBCL pts >80 y.o. We replicated with a SCA the internal control arm with similar OS comparisons (HR= 0.996 (95% CI= 0.66-1.51) for SENIOR, HR= 0.98 (95% CI = 0.643-1.492) for SCA-CT).
Matching procedures with RWD patients were also efficient, and SCA-RW OS behaved the same way as SCA-CT and internal control arm of SENIOR trial. The loss of power due to the pool shrinkage for matching procedures could be limited by mixing 50%/50% pts from internal control arm and historical CTs pts. These complementary data will be presented during the meeting.

Disclosures Ghesquieres: *Gilead, Roche, Bristol Myers Squibb, AbbVie, Novartis:* Honoraria; *Gilead, Roche:* Consultancy. **Jardin:** *Janssen, Gilead, AbbVie, F. Hoffmann-La Roche Ltd, BMS, Takeda:* Honoraria. **Sesques:** *KITE/GILEAD , BMS, JANSSEN, NOVARTIS, CHUGAI:* Consultancy. **Carras:** *Janssen Cilag:* Membership on an entity's Board of Directors or advisory committees, Other: travel fees, Research Funding; *Beigene:* Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Other: Travelfees; *Astrazeneca:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Kitegilead:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Tessoulin:** *Incyte:* Honoraria; *Kite:* Honoraria; *Abbvie:* Honoraria; *Gilead:* Honoraria.

Figure 1. Baseline covariates used for propensity score assessment

Variable	Transformation in logistic regression
Sex	NA
Age at randomization (years)	Spline
Ann Arbor	I-II vs III-IV
Performance Status (ECOG)	NA
Number of extranodal sites involved	≤1 vs >1
IPI in classes	0-2 vs 3-5
B symptoms	NA
LDH	Normal vs > limit
Mass > 10 cm	NA
Diagnosis classification (for SCA-RW)	HGBL vs other DLBCL
Albumin (g/L)	Spline

Figure 2. OS according to treatment arm : SCA-CT (historical) and SENIOR experimental arm (experimental)

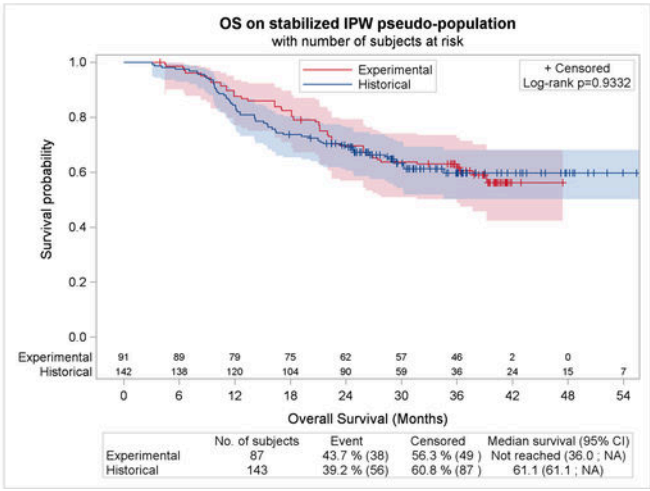

Figure 1

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