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ORAL ABSTRACTS

613.ACUTE MYELOID LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

The Addition of Venetoclax to Induction Chemotherapy in No Low-Risk AML Patients: A Propensity Score-Matched Analysis of the Gimema AML1718 and AML1310 Trials

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Abstract Background. Venetoclax combined with intensive chemotherapy proved to be safe with promising activity in fit patients with no-low-risk newly diagnosed acute myeloid leukemia (AML), as demonstrated also by an intermediate analysis of the GIMEMA AML1718 trial (NCT03455504). The latter trial, still ongoing, is based on the administration of venetoclax-FLAI to intermediate/high-risk ELN2017 AML and produced a complete remission (CR) rate of 84%, a minimal residual disease (MRD)-negativity rate of 74% and a 12-month Overall Survival (OS) and disease-free survival (DFS) of 75.7% (95%CI: 64.1%, 89.5%) and 80.7% (95%CI: 67.9%, 95.9%), respectively.
In order to evaluate the actual advantage of the addition of venetoclax to chemotherapy, the GIMEMA AML1718 was matched to AML1310, which entailed a "3+7"-like induction and a risk-adapted, MRD-directed post-remission transplant allocation (NCT01452646, Venditti et al - Blood 2019). To generate a reliable comparison, AML1718 and AML1310 were matched by using a propensity score and then compared in terms of CR achievement, MRD-negativity and survival outcomes.
Methods. Patient-level data from GIMEMA AML1718 (n=57) and AML1310 (N=445) with ELN2017 risk classification available were used to conduct a propensity score matching analysis, widely used for reducing the effects of confounding when estimating the effects of treatment on outcomes. Conditional on the propensity score, the distribution of measured variables is expected to be the same in treated (i.e. AML1718) and control (i.e. AML1310) subjects.
In the present propensity score model, we included the following variables: age at diagnosis, gender, ELN2017 risk classification and transplant. Different methods for matching were attempted, including 1:1 nearest neighbor, full-matching, optimal matching (1:2, 1:3 and 1:4) and 1:2 genetic matching. The methods employed for assessing balancing were: i) Standardized Mean Difference - Love plot, ii) Empirical cumulative density function, iii) Variance ratio, iv) Empirical QQ-plot. Weights were calculated with probit or logit regression models according to the propensity score method used. Weights obtained from full-matching were used to adjust outcomes (CR, MRD negativity and survival outcomes). No patients were dropped in the full-matching process. A standardized bias score less than 0.25 was used as a criterion for adequate balancing. We used balance tables and Love plots to assess for covariate balance before and after matching. Survival curves were compared by Log-rank test and Restricted Mean Survival Time (RMST) at 12 months.
Results. AML1718 and AML1310 cohorts differed in terms of age (median: 54 *vs* 49 years, p=0.003) and risk category (p< .0001) - since the low risk was not represented in AML1718 trial - and female sex (35% vs 48%, p=0.069), though to a lesser extent. Contrariwise, the percentage of transplanted patients was comparable before matching (49% vs 49%, p=0.96). Being more recent, AML1718 median follow-up was shorter than AML1310 (10.5 *vs* 75.8 months).
Full-matching, 1:2 optimal matching and 1:2 genetic matching produced the best balancing. Table 1 shows the results of the analysis for the unmatched and matched data. After balancing, according to all matching methods, the CR rate observed in

the AML1718 was significantly higher than AML1310, as well as MRD-negativity rate. Comparing survival outcomes at 12 months, emerged that, upon matching, OS and DFS estimates of the AML1718 were higher than those of AML1310, though a slight statistical significance was reached only with the optimal matching on DFS (p=0.042). This result was confirmed by a statistically significant difference between the two RMST at 12 months (p=0.036). Despite this, a longer AML1718 follow-up is needed to provide a robust comparison between the two protocols.

Conclusions. Our propensity-score analysis showed that combining venetoclax with chemotherapy in newly diagnosed AML patients resulted in improved outcomes in terms of CR rate and MRD-negativity: these achievements are crucial to allow transition to allogenic transplantation in first remission. With regards to survival outcomes, a solid conclusion will be drawn when a longer AML1718 follow-up is available. These preliminary results highlight the incremental benefit of venetoclax added to intensive induction chemotherapy and paves the way to novel combination regimens based on venetoclax.

Table 1. Comparison of outcomes of AML1718 vs AML1310 before and after matching using different propensity score methods.

		Unmatched	Matched		
			Full matching	1:2 Optimal matching	1:2 Genetic matching
AML1718	N	57	57	57	57
AML1310	N	445	445	114	114
CR	AML1718	48 (84%)	48 (84.2%)	48 (84%)	48 (84%)
	AML1310	322 (73%)	302 (68.6%)	76 (67%)	76 (68%)
	p-value	0.076	0.015	0.019	0.028
MRD-Neg	AML1718	28 (74%)	28 (73.7%)	28 (74%)	28 (74%)
	AML1310	121 (51%)	121 (48.4%)	27 (47%)	28 (47%)
	p-value	0.011	0.004	0.009	0.008
12 months-OS	AML1718	75.7% (64.1%,89.5%)	75.7% (64.1%,89.5%)	75.7% (64.1%,89.5%)	75.7% (64.1%,89.5%)
	AML1310	71.8% (67.7%,76.2%)	66.9% (58.1%,77.0%)	68.0% (59.8%,77.4%)	63.3% (54.8%,73.1%)
	p-value	0.79	0.79	0.42	0.21
12 months-DFS	AML1718	80.7% (67.9%,95.9%)	80.7% (67.9%,95.9%)	80.7% (67.9%, 95.9%)	80.7% (67.9%,95.9%)
	AML1310	68.8% (63.8%, 74.1%)	53.0% (42.0%,66.7%)	50.0% (39.7%, 63.0%)	54.4% (44.0%,67.2%)
	p-value	0.42	0.42	0.042	0.065

Figure 1.

Disclosures Marconi: *menarini/stemline:* Honoraria, Speakers Bureau; *astellas:* Honoraria; *servier:* Honoraria; *pfizer:* Honoraria, Research Funding, Speakers Bureau; *abbvie:* Research Funding. **Martinelli:** *Abbvie:* Consultancy; *Daiichi Sankyo:* Consultancy; *Incyte:* Consultancy; *Jazz Pharmaceuticals:* Consultancy; *Roche:* Consultancy; *Stemline:* Consultancy; *Celgene/BMS:* Consultancy, Speakers Bureau; *Astellas:* Consultancy, Speakers Bureau; *Pfizer:* Consultancy, Speakers Bureau. **Venditti:** *Servier:* Membership on an entity's Board of Directors or advisory committees; *Janssen & Cylag:* Honoraria; *Astellas:* Membership on an entity's Board of Directors or advisory committees; *Amgen:* Membership on an entity's Board of Directors or advisory committees; *astrazeneca:* Honoraria; *abbvie:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Jazz Pharmaceuticals:* Honoraria, Research Funding; *Medac:* Consultancy; *Novartis:* Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Honoraria, Speakers Bureau.

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