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POSTER ABSTRACTS

615.ACUTE MYELOID LEUKEMIAS: COMMERCIALLY AVAILABLE THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Venetoclax in Combination with Intermediate Doses of Cytarabine in Consolidation Phase for Acute Myeloid Leukemia Patients in First Complete Remission; Results of the Part 1 of the Phase 1/2 Multicentric Covenidac Study

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Background: The French ALFA-FILO AML intergroup launched the BIG-1 trial (EudraCT No.: 2014-000699-24) in 2015 to evaluate different intensive chemotherapy (ICT) strategies aiming at improving the survival of younger adults with acute myeloid leukemia (AML). All patients (pts) with previously untreated non-APL and non-CBF AML aged 18-60 years were eligible for this trial. The trial design included several randomization types. Results of the R1 and R2 randomizations, namely idarubicin *vs* daunorubicin for induction and IDAC *vs* HDAC for consolidation, will be reported at this meeting. In patients who achieved first complete remission (CR), randomizations R4 consisted of nested randomized Phase 2 or 1/2 studies evaluating the addition of new drugs to the IDAC/HDAC consolidation cycles. The protocol was designed to allow several sequential multicenter R4 evaluations of various new agents over the trial period. Venetoclax (VEN) has proved its efficacy when combined to azaci-

tidine or low dose cytarabine in unfit AML pts (DiNardo et al. 2020; Wei et al. Blood 2020). Its role in fit patients treated with ICT is still under investigation. The COVENIDAC Phase 1/2 R4 sub-study is evaluating the safety and efficacy of VEN added to IDAC during the consolidation cycles of CR pts. We report herein the result of the Phase 1 part.

Methods: The primary objective of this Phase 1 study was to determine the maximum tolerated dose (MTD) of VEN in combination with IDAC during the consolidation cycles, which will be the recommended dose for the Phase 2 (RP2D). Dose limiting toxicities (DLTs) were assessed during the first cycle of consolidation (C1) according to a 3+3 design. A maximum of 3 consolidation cycles was planned depending on the AML risk group. Hematological DLT was defined as no peripheral blood count recovery within 56 days from day 1 of the cycle. Non-hematological DLTs were defined as Grade $\geq$4 toxicities or Grade $\leq$3 toxicities which have not recovery by day 56 and deemed related to VEN per investigator opinion. VEN was started at dose level (DL) 1: 100 mg/d from day 1 to 8. In the absence of DLTs at DL1, 3 others DL were planned: 200 mg/d from day 1 to 8 (DL2); 400 mg/d from day 1 to 8 (DL3), and 400 mg/d from day 1 to 14 (DL4). IDAC was administrated at 1.5 gr/m² twice daily on day 1/3/5 for DL1, DL2 and DL3 pts, then on day 1/2/3 for DL4 pts after a protocol amendment. Main inclusion criteria were: pts in first CR following 1 or 2 courses of induction chemotherapy fit for further ICT; favorable and intermediate risk AML as defined by the protocol; ECOG PS $\leq$2; written informed consent. Measurable residual disease (MRD) was assessed by multiparametric flow cytometry (MFC) in all pts as well as NPM1-qPCR in *NPM1*-mutated pts.

Results: Between 06/2021 and 04/2022, 15 pts from 9 centers were screened and enrolled. Pt characteristics were as follows: median age, 42 years (IQR, 30-49); 2 males/7 females; ECOG-PS, 0 in 10 pts and 1 in 5 pts; favorable/intermediate/adverse ELN-2017 risk, 9/2/4. Neutropenia and thrombocytopenia durations are shown in **Table 1**. Only 1 hematological DLT was observed at DL3 (platelet count of 96 giga/L at day 56 in a patient who was infected by Covid-19). Overall, there were very few non hematological AEs (**Table 2**, no grade 4) and only 4 SAEs (1 related to IDAC/VEN during C1, 3 non-related). No non-hematological DLT was observed. No patient died during the DLT observation period, 1 experienced a septic shock (C2, DL2). One pt received only C1 (due to DLT), 7 received 2 cycles, and 7 received 3 cycles. Median time between initiation of subsequent consolidation cycles was 37.5 days (IQR, 35-41) for C1/C2 and 40 days (IQR, 35-43) for C2/C3. One pt had to stop VEN during C3. Six pts received an allogeneic HSCT (5 in CR1, 1 after salvage). With a median follow-up of 13.5 months, 3 pts relapsed and 2 died. MRD results will be presented.

Conclusion: VEN/IDAC combination appears to be feasible and safe as consolidation therapy, with expected thrombocytopenia and neutropenia durations. These durations appeared even shorter at DL4, when IDAC was given on 3 consecutive days. VEN at 400 mg/d from day 1 to 14 combined with IDAC on day 1/2/3 was thus retained as RP2D for the randomized Phase 2 with RFS as primary endpoint. This phase 2 has already recruited 29 of the 200 pts planned.

Disclosures Raffoux: *Pfizer, Inc.:* Honoraria; *Celgene:* Honoraria; *AbbVie:* Honoraria; *Astellas:* Honoraria; *Daiichi-Sankyo:* Honoraria. **Bertoli:** *Abbvie:* Honoraria, Other: Travel; *Jazz Pharmaceuticals:* Honoraria, Other: Travel; *BMS-Celgene:* Honoraria; *Astellas:* Honoraria; *Novartis:* Honoraria; *Servier:* Honoraria. **Lambert:** *AbbVie:* Honoraria; *Bristol Meyers Squibb:* Honoraria; *Gilead:* Honoraria; *Jazz Pharmaceuticals:* Honoraria; *Pfizer, Inc.:* Honoraria. **Pigneux:** *Roche:* Research Funding; *Servier:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Support for attending meetings, Research Funding; *Abbvie:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Support for attending meetings; *Gilead:* Honoraria; *Jazz Pharmaceuticals:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *BMS:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Astellas:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Novartis:* Honoraria; *Pfizer:* Membership on an entity's Board of Directors or advisory committees. **Dombret:** *Jazz Pharmaceuticals:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Pfizer:* Research Funding; *Servier:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *BMS:* Research Funding; *Astellas:* Research Funding; *Incyte:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Support for attending meetings. **Recher:** *Abbvie:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Astellas:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Amgen:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *BMS:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Jazz Pharamceuticals:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Iqvia:* Research Funding; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Servier:* Honoraria, Membership on an entity's Board of Directors or advisory committees.

Table 1. Thrombocytopenia and neutropenia durations by consolidation cycle

	All (n=15)	DL1 (n=3)	DL2 (n=3)	DL3 (n= 6)	DL4 (n= 3)
Time for platelets >100 G/L, median days (IQR)					
C1	22 (19-28)	27 (17-29)	22 (19-22)	24 (20-28)	19 (19-36)
C2	28 (26-35)	29 (19-29)	35 (27-43)	25 (20-31)	27 (26-38)
C3	33 (27-42)	33 (33-33)	56 (56-56)	40 (29-42)	17 (7-27)
Time for PMNs >1G/L, median days (IQR)					
C1	18 (16-20)	18 (18-20)	18 (16-22)	18 (17-28)	15 (15-16)
C2	18 (17-19)	19 (17-22)	35 (18-43)	17 (16-18)	19 (17-19)
C3	19 (18-27)	19 (19-19)	27 (27-27)	19 (18-33)	10 (0-20)

Table 2. Non-hematological AE by consolidation cycle

Number of pts	With at least 1 AE	With <Grade 2 AE(s)	With Grade 2 AE(s)	With Grade 3 AEs
C1	9	1	7	1
C2	6	0	6	0
C3	5	0	4	1

Figure 1

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