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POSTER ABSTRACTS

616.ACUTE MYELOID LEUKEMIAS: INVESTIGATIONAL THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Bisantrene in Combination with Fludarabine and Clofarabine As Salvage Therapy for Adult Patients with Relapsed or Refractory Acute Myeloid Leukemia (AML)- an Open-Label, Phase II, Study

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Background:
Bisantrene (Bis), is a topoisomerase-II inhibitor with anthracycline-like activity, lower cardiotoxicity, and activity in patients (pts) with relapsed (rel)/primary refractory (PR) acute myeloid leukemia (AML) (Am J Hematol, 2021). Bis was also found to synergize with the cytotoxic purine nucleoside analogs clofarabine (Clo) and fludarabine (Flu) in vitro (J Clin Exp Oncol, 2021). We now conducted a phase II study combining Bis with Clo and Flu in pts with Rel/PR AML (NCT04989335).

Methods:
This was a phase II open-label single-center study with 2 stages: a stage with 3+3 dose escalation to assess the safety and provide phase 2 dose (RP2D, 4 vs 5 days) of infusion (i.v.) with up to 12 pts and an expansion phase with up to 17 pts (Simon 2-stage design 9+8) to assess the primary efficacy and confirm the safety of f Bis/Clo/Flu combination pts with Rel/PR AML. Flu (10 mg/m ^{2}) was administered i.v. over 1 hour (h), followed by a 1-h infusion of Clo (30 mg/m ^{2}), and then a 2-h infusion of Bis at 250 mg/m ^{2}, with a 1-hour break for 4 days. The primary endpoint was achieving a partial response (PR). Efficacy was assessed by bone marrow (BM) examination 21 - 30 days post-therapy. Safety included treatment-emergent adverse events (TEAEs), all-cause mortality, and cardiac monitoring with ECG and troponins Toxicity was assessed as per Common Terminology Criteria for Adverse Events (CTCAE *v5.0*). Interim analysis was planned after the first 12 pts.

Results:
20 pts were included from August 2021. The median age was 48 (19-69) years and 55% were male.14 pts had de novo AML and 5 had secondary AML, 11 pts were in rel, while 9 had PR disease. Median lines of therapy were 4(3-9), 12 with ≤ 4 and 8 >4 lines of therapy. All pts were refractory to the last line of therapy.15 pts (75%) were in relapse post allogeneic transplantation (HSCT). 5 (25%) pts had active extramedullary disease (EMD, 1 with CNS involvement). Median bone marrow blasts pre-Bis/Clo/Flu treatment was 50%. Cytogenetic was normal in 10 (50%) of the pts, 5 had a complex karyotype, 2 MLL rearrangements, 1 t8; 21 and 2 pts had other chromosomal abnormalities. The maximum tolerated dose of the Bis/Clo/Flu combination was 4 days of infusion due to grade 3 liver toxicity in 2 pts and 1 pt that died from sepsis in the first stage of the study. Overall 10 pts developed liver toxicity with elevated liver enzymes and bilirubin in 9 of them (grade 1-4 pts; grade 2-3 pts and grade 3-3 pts). Liver toxicity was transient and resolved in all pts. Two pts had treatment interruption due to liver toxicity. 4 pts had grade I renal toxicity, 7 had mild fluid retention, and 18 developed neutropenic fever of which 10 pts had verified bacteremia. Five pts had pneumonia, 4 invasive fungal infections, and 2 sepsis (1/2 died).1 additional pt died from *cerebral venous sinus thrombosis. Overall 5 pts died early and could not be evaluated for response. Clinical-relevant cardiac toxicity was not observed in any*

of the pts and no one developed ECG changes Transient grade 1 elevation of troponin levels was observed in 4 pts. Six pts responded (CR-5, PR-1) 3 with EMD, however, responses were short-lived and lasted up to 3 months. Five pts (responding-4, active disease-1, being the second transplant in 4) underwent HSCT 1-3 months post-Bis/Clo/Flu with reduced /intermediate intensity conditioning. Stem cell donors were haploidentical-2, matched unrelated -1, and matched sibling-2, respectively. Three pts died: one from graft versus host disease and the other from relapse within 4 months post-transplant and the third from sepsis 2 years post-HSCT. Two of the transplanted pts are in complete remission with a 2-month follow-up.

Conclusions *:*

In this Phase II study in a very advanced group of relapsed refractory AML ptsresistant to multiple previous lines of chemotherapy including transplantation and with a median of 50% blasts at study initiation, Bis/Clo/Flu combination therapy was found to be safe and well tolerated without cardiac toxicity or tumor lysis syndrome. The maximum length of Bis/Clo/Flu administration was 4 days due to rapidly reversible liver toxicity, and transaminitis. As expected in this highly pretreated population, the infection rates were high. Six /15 evaluable pts (40%) respond, enabling an HSCT in 5 of them. These rather impressive results in such a heavily pretreated population support further studies of Bisantrene-based combinations, including those with venetoclax or hypomethylating agents.

Disclosures Avigdor: *BMS:* Membership on an entity's Board of Directors or advisory committees; *Roche:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees; *Gilead:* Membership on an entity's Board of Directors or advisory committees; *AbbVie:* Membership on an entity's Board of Directors or advisory committees, Other: Travel/Accommodations/Expenses; *Takeda:* Membership on an entity's Board of Directors or advisory committees; *MSD:* Research Funding.

OffLabel Disclosure: Bisantrene is a topoisomerase-II inhibitor with anthracycline-like activity and lower cardiotoxicity

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