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POSTER ABSTRACTS

613.ACUTE MYELOID LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

Decider-2: Prospective Randomized Multicenter Phase III Trial of Decitabine and Venetoclax Administered in Combination with All- *Trans* Retinoic Acid (ATRA) or Placebo in Patients with Acute Myeloid Leukemia Who Are Ineligible for Induction Chemotherapy

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Background and Significance

DNA-hypomethylating agent (HMA) based therapy is the treatment backbone for older, medically non-fit AML/MDS pts, and studies have been performed with multiple combination partners over the last years (reviewed by *Stomper et al.*, Leukemia 2021). Recently, the combination of azacitidine or decitabine (DEC) with venetoclax (VEN) has become the novel standard for many of these pts. Based on preclinical evidence of priming of AML cells to all- *trans* retinoic acid (ATRA) by DEC, we have conducted a randomized phase II trial in 200 elderly and medically non-fit AML pts on the effect of ATRA as add-on to DEC (DECIDER-1, Lübbert et al., *J. Clin. Oncol* 2020). Median overall survival (OS) was 8.2 months with ATRA v 5.1 months without ATRA (hazard ratio, 0.65; 95% CI, 0.48 to 0.89; P = .006). Notably, ATRA did not add toxicity, the combination was active also in AML with adverse genetics, and it appeared to prolong time to secondary treatment resistance. A randomized open-label phase II trial (DEC -/+ ATRA) is also being conducted in higher-risk MDS pts (Zhou et al., ASH 2021, 539).

Investigating a triple combination of HMA+VEN+ATRA is a logical next step. We could demonstrate cooperativity between these 3 drugs in AML cell lines irrespective of *TP53* mutation status on cell growth inhibition and apoptosis (Bresser et al., ASH 2022, 11537).

Study Design and Methods

This academic study is a randomized, prospective, double-blind, placebo-controlled, parallel group, multicenter trial. It is planned to randomize 256 pts in a ratio of 1:1 to the treatment arms at ~35 sites in Germany.

The primary objective is to compare the efficacy of ATRA v placebo as add-on to the standard treatment DEC+VEN with respect to OS. Secondary objectives are to compare ATRA v placebo as add-on to DAC+VEN with respect to objective best response (i.e. CR/CRi/MLFS/PR), CR with negative measurable residual disease (MRD), probability of survival with objective best response, health-related quality of life and safety.

Sample size calculation is based on the primary endpoint OS. The study should have a power of 80% to demonstrate superiority of ATRA vs. placebo with respect to OS at one-sided level alpha of 2.5% under the assumption of a hazard ratio of 0.67. This requires the observation of 191 deaths. With a recruitment period of 3 years and an additional one year follow-up period, it is necessary to include 230 pts. To account for the possibility of up to 10% of the pts with incomplete follow-up, 230/0.9 = 256 pts will be randomized in total (ratio 1:1).

Interim safety analyses will be performed after the 2nd cycle of the 10th randomized pt, and after the 3rd cycle of the 50th, the 100th and the 150 th randomized pt, and monitored by an Independent Data Monitoring Committee.

Key inclusion criteria are: age ≥18 years; previously untreated AML (WHO 2016); ineligibility for standard induction chemotherapy; ECOG ≤ 2; WBC <25×109/L (prior cytoreduction allowed). Key exclusion criterion is: acute promyelocytic leukemia.

Treatment

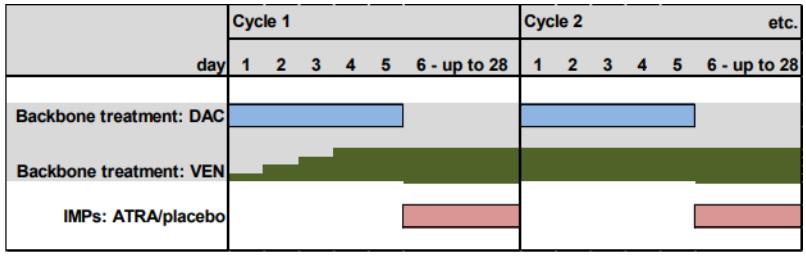
All pts will be treated with DAC+VEN as standard treatment and will additionally either receive ATRA or placebo (Fig. 1). Study treatment is continued until relapse/progression, hematopoietic cell transplantation, death or unacceptable toxicity (whichever occurs first). Correlative investigations include serial MRD measurement, NGS profiling and apoptosis studies.

Registration
EUDRACT 2020-005495-36; DRKS 00023646 (P001516).
Funding
Funded by the German Research Foundation (DFG, project no. 367848349/LU 429/13-1); ATRA is provided free of charge by Cheplapharm (Germany).

Figure 1 Overview of the study treatment

Disclosures Lübbert: *Cheplapharm:* Other: Study drug; *AbbVie:* Membership on an entity's Board of Directors or advisory committees; *Astex Pharmaceuticals, Inc.:* Membership on an entity's Board of Directors or advisory committees; *Janssen-Cilag:* Research Funding; *Otsuka:* Membership on an entity's Board of Directors or advisory committees; *Syros:* Membership on an entity's Board of Directors or advisory committees; *Imago Biosciences:* Other: study drug. **Schmoor:** *Novartis:* Consultancy; *Roche Pharma AG:* Consultancy. **Heuser:** *Amgen:* Consultancy; *Glycostem:* Consultancy, Research Funding; *Janssen:* Honoraria; *Jazz Pharmaceuticals:* Consultancy, Honoraria, Research Funding; *Karyopharm:* Research Funding; *Servier:* Consultancy; *Sobi:* Honoraria; *Certara:* Honoraria; *Pfizer:* Consultancy, Honoraria; *Novartis:* Honoraria; *PinotBio:* Consultancy, Research Funding; *Loxo Oncology:* Research Funding; *Agios:* Research Funding; *Abbvie:* Consultancy, Research Funding; *Bristol-Myers Squibb:* Consultancy, Research Funding; *BergenBio:* Research Funding; *Astellas:* Research Funding; *LabDelbert:* Consultancy. **Döhner:** *Agios:* Research Funding; *Astellas:* Research Funding; *Roche:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria, Research Funding; *Jazz:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria; *Daiichi Sankyo:* Consultancy, Honoraria; *BMS/Celgene:* Consultancy, Honoraria, Research Funding; *AbbVie:* Consultancy, Honoraria; *Ulm University Hospital:* Current Employment. **Döhner:** *Amgen:* Consultancy, Honoraria, Research Funding; *Abbvie:* Consultancy, Honoraria, Research Funding; *Astellas:* Consultancy, Honoraria, Research Funding; *Agios:* Consultancy, Honoraria, Research Funding; *Gilead:* Consultancy, Honoraria; *Celgene:* Consultancy, Honoraria, Research Funding; *AstraZeneca:* Consultancy, Honoraria; *Berlin-Chemie:* Consultancy, Honoraria; *Bristol Myers Squibb:* Consultancy, Honoraria, Research Funding; *Daiichi Sankyo:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria; *Jazz Pharmaceuticals:* Consultancy, Honoraria, Research Funding; *Novartis:* Consultancy, Honoraria, Research Funding; *Syndax:* Honoraria; *Kronos-Bio:* Research Funding; *Pfizer:* Research Funding; *Servier:* Consultancy, Honoraria; *Stemline:* Consultancy, Honoraria. **Becker:** *Servier:* Consultancy, Honoraria; *Pierre Fabre Pharma:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria; *MSD:* Consultancy, Honoraria; *Lilly:* Consultancy, Honoraria; *GSK:* Consultancy, Honoraria; *BMS/Celgene:* Consultancy, Honoraria; *AbbVie:* Consultancy, Honoraria. **Wäsch:** *Sanofi:* Honoraria; *BMS:* Other: Travel support; *Pfizer:* Other: Travel support; *Kite/Gilead:* Other: Travel support; *Janssen:* Other: Travel support; *Takeda:* Honoraria; *Pfizer:* Honoraria; *Kite/Gilead:* Honoraria; *Janssen:* Honoraria; *BMS/Celgene:* Honoraria; *Amgen:* Honoraria; *Abbvie:* Honoraria; *Sanofi:* Research Funding; *Janssen:* Research Funding; *Takeda:* Consultancy; *Sanofi:* Consultancy; *Pfizer:* Consultancy; *Kite/Gilead:* Consultancy; *Novartis:* Consultancy; *Janssen:* Consultancy; *BMS/Celgene:* Consultancy; *Amgen:* Consultancy.

OffLabel Disclosure: ATRA, approved for APL, with activity in a randomized trial of non-APL AML patients



ATRA= all-*trans* retinoid acid; DAC= decitabine; VEN= venetoclax

Figure 1

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