Activity of decitabine combined with all-*trans* retinoic acid in oligoblastic acute myeloid leukemia: results from a randomized 2x2 phase II trial (DECIDER)

Treatment options for patients with high-risk myelodysplastic syndrome (MDS) ineligible for allogeneic stem cell transplantation (allo-SCT) are limited. DNA-hypomethylating agents (HMA) form the backbone of the treatment of these patients, but only very rarely provide long-term survival as single agents.[1–5] The addition of venetoclax to HMA proved to be a highly active treatment in acute myeloid leukemia (AML)[6] and this concept was successfully adapted in studies for high-risk MDS.[7] Within the DECIDER trial (*clinicaltrails gov. Identifier: NCT00867672*), the combination of decitabine (DEC) and all-*trans* retinoic acid (ATRA) also resulted in an improved response rate and survival in AML compared to DEC alone, and was likewise active in patients with prior hematologic disorder (mostly MDS).[8] The prospective, randomized, observer-blind, active-control, parallel-group, multicenter, phase II DECIDER trial has a 2x2 factorial design and compared treatment with DEC alone to DEC +/- ATRA and +/- valproic acid (VPA) in newly diagnosed AML patients ineligible for allo-SCT. No benefit was seen when VPA was added to the treatment. We here present an exploratory, not preplanned subgroup analysis of the DECIDER trial, where we evaluated the effect of the combination of DEC and ATRA on patients with 20-30% bone marrow blasts. This subgroup is often referred to as oligoblastic AML, formerly RAEB-T according to the French-American-British classification.[9,10] The new International Consensus Classification and the new classification of myeloid neoplasms of the World Health Organization are focused on biological and genetic drivers of myeloid malignancies for the prognosis of affected patients. Nevertheless, we believe that the result of this analysis could indicate whether the combination of HMA and a retinoid could also be active in high-risk MDS patients with excess blasts, since the presence of blasts is still an independent high-risk feature, which is reflected in the new classifications.

Patients and methods of the DECIDER trial have been reported previously.[8] In short, patients were randomly assigned to four different arms with DEC 20 mg/m^2 day 1-5 (treatment arms A/B/C/D), ATRA orally (p.o.) day 6-28 (arms C/D), VPA p.o. continuously from day 6 (arms B/D) of each 28-day course (repeated until relapse/progression, prohibitive toxicity, withdrawal or death) (Figure 1). Study endpoints were objective response rate (ORR), defined as complete remission with or without count recovery and partial remission (CR/CRi/PR), and overall survival (OS) time. For patient characteristics and methods of the statistical analysis, we refer to the original publication, emphasizing again that all analyses were not preplanned in the study protocol and are, thus of exploratory nature.

Between December 2011 and February 2015, 200 patients were randomly assigned and received study medication at 27 centers.[8] Of these, 56 fulfilled the criteria of an oligoblastic AML with 20-30% (median 24.6%) blasts by central hematopathology. Patient and disease characteristics are shown in the *Online Supplementary Table S1*. Of the 56, 22 (39.3%) were treated with DEC + ATRA +/- VPA, with nine (40.9%) in arm C and 13 (59.1%) in arm D, in the following referred to as the “ATRA” group, and 34 (60.7%) were treated with DEC +/- VPA, with 13 (38.2%) in arm A and 21 (61.8%) in arm B, in the following referred to as the “no ATRA” group.

The majority (76.8%) of patients was male, but sex was evenly balanced between the ATRA *versus* no ATRA groups. The median age (75 years) was similar in both groups, however the proportion of patients >= 75 years of age was higher in the ATRA group (68.2% *vs*. 41.2%). Regarding genetic risk according to the 2010 European LeukemiaNet genetic risk classification, the ATRA group displayed a higher proportion of intermediate-risk (77.3% *vs*. 55.9%) and a lower proportion of adverse-risk (13.6% *vs*. 32.4%) patients, which constitutes a certain limitation to this analysis. All other characteristics like Eastern Cooperative Oncology Group performance status (ECOG PS), comorbidities, prior hematologic disorder or white blood count (WBC) were evenly balanced.

For the entire subgroup, a median of five DEC courses were administered (a median of 2 in arm A, 5 in arm B, 11 in arm C and 4 in arm D), resulting in a median of 7.5 courses in the ATRA group and 3.5 courses in the no ATRA group.

In total, six patients attained a CR (9.1% *vs*. 11.8% in the ATRA *vs*. no ATRA group), seven patients a CRi (18.2% *vs*. 8.8% respectively), one patient a PR (4.6% *vs*. 0.0% respectively), ten patients had an antileukemic effect (ALE) (18.2% *vs*. 17.7% respectively), ten patients had stable disease (27.3% *vs*. 11.8% respectively) and 22 patients progressive disease (22.7% *vs*. 50.0% respectively) (*Online Supplementary Table S2*). The ORR was 25%, with a difference between the ATRA and the no ATRA groups of 31.8% *versus* 20.6% with an OR of 1.85 (95% confidence interval [CI]: 0.54- 6.37) and a two-sided *P* value of 0.33 (Table 1). The ORR of patients additionally treated with VPA *versus*

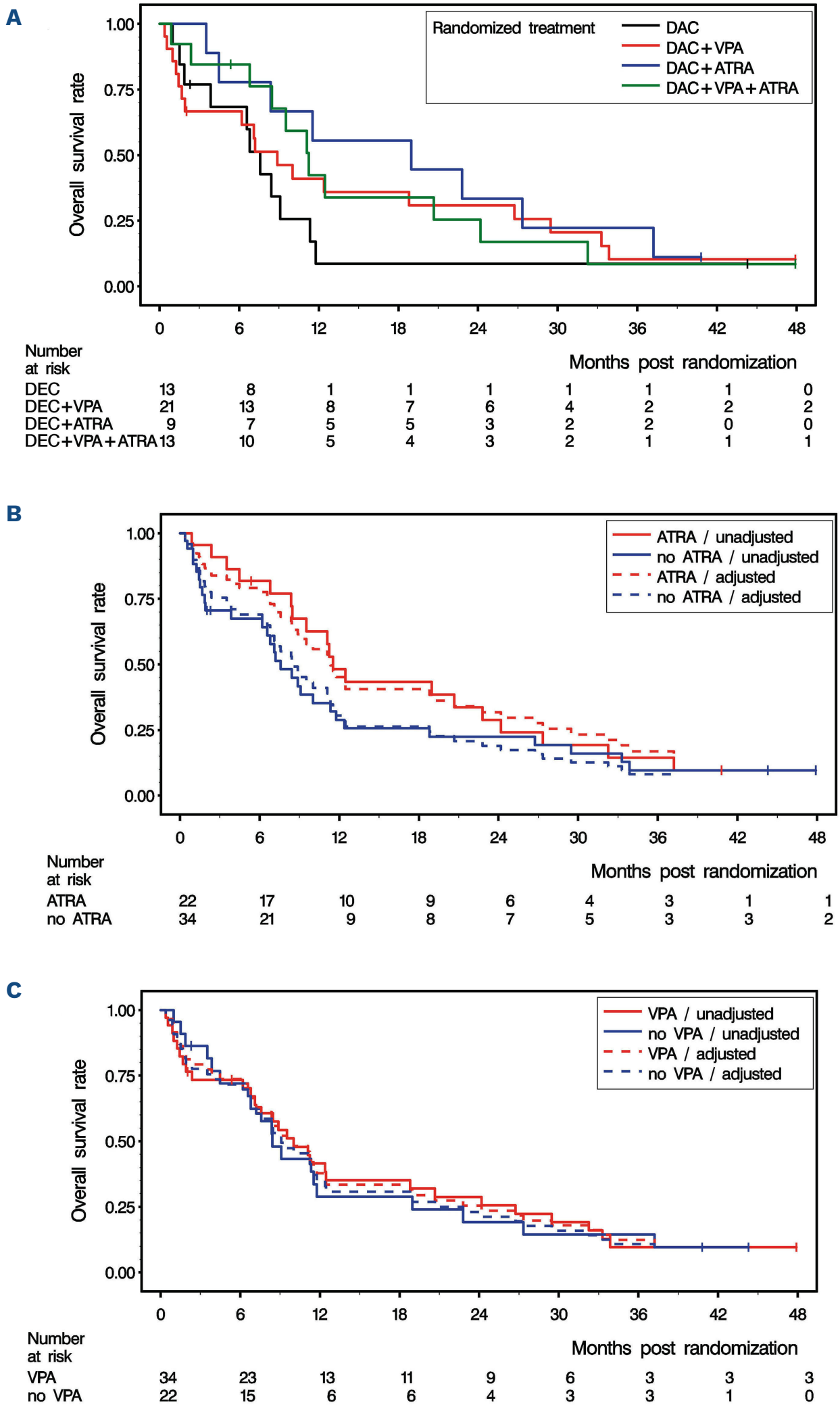

Figure 1. Effects of the addition of all-*trans* retinoic acid and valproic acid to decitabine on overall survival. (A) Overall survival (OS) according to treatment arms: A: black, B: red, C: blue, D: green. (B) OS according to treatment with decitabine plus all-*trans* retinoic acid (DEC + ATRA) (+/- valproic acid [VPA]) (red curves) compared to DEC (+/- VPA) (blue curves, Kaplan-Meier method). Solid curves: unadjusted; broken curves: adjustment for Eastern Cooperative Oncology Group performance status, comorbidities (hematopoietic cell transplantation index), serum lactate dehydrogenase, hemoglobin, genetic risk (ELN 2010). (C) OS according to treatment with DEC + VPA (+/- ATRA) (red curves) compared to DEC (+/- ATRA) (blue curves, Kaplan-Meier method). Solid curves: unadjusted; broken curves: Eastern Cooperative Oncology Group performance status, comorbidities (hematopoietic cell transplantation index), serum lactate dehydrogenase, hemoglobin, genetic risk (ELN 2010).

Table 1. Effects of decitabine + all-*trans* retinoic acid (+/- valproate) *versus* decitabine - all-*trans* retinoic acid (+/- valproate) on objective response and overall survival.

	Objective response				Overall survival			
Treatment	**ORR %**	**Odds ratio**	**95% CI**	***P***	**Median overall survival time in months**	**Hazard ratio**	**95% CI**	***P***
ATRA *vs.* no ATRA		1.85	0.54-6.37	0.33		0.71 0.61*	0.40-1.29 0.32-1.16*	0.26 0.13*
ATRA	31.8				11.5			
no ATRA	20.6				7.6			
VPA *vs.* no VPA		1.93	0.51-7.24	0.33		0.89 0.91*	0.49-1.61 0.43-1.93*	0.71 0.80*
VPA	29.4				10.0			
no VPA	18.2				8.4			

*Adjustment for Eastern Cooperative Oncology Group performance status, hematopoietic cell transplantation index, serum lactate dehydrogenase, hemoglobin, genetic risk. ORR: objective response rate; CI: confidence interval; DEC: decitabine; ATRA: all-*trans* retinoic acid; VPA: valproic acid.

no VPA was 29.4% *versus* 18.2% with an OR of 1.93 (95% CI: 0.51-7.24) and a two-sided *P* value of 0.33 (Table 1).

The median follow-up time for OS was 6.2 years. With 48 deaths of 56 patients, the median OS time of the whole subgroup analysis population was 9.1 months (arm A: 7.6 months, arm B: 8.9 months, arm C: 19.0 months, arm D: 11.2 months) (Table 1; Figure 1A). A comparison of the ATRA and the no ATRA group resulted in median OS time of 11.5 *versus* 7.6 months, respectively, with an unadjusted hazard ratio [HR] of 0.71 (95% CI: 0.40-1.29) and a two-sided *P* value of 0.26 (Table 1; Figure 1B). Adjustment for ECOG PS, hematopoietic cell transplantation comorbidity index (HCT-CI), serum lactate dehydrogenase (sLDH), hemoglobin, and genetic risk led to similar results (adjusted HR=0.61; 95% CI: 0.32-1.16; *P*=0.13) (Table 1; Figure 1B). Although no statistically significant difference could be detected, the survival curves of the ATRA and the no ATRA group were separating in the first 2 years after therapy initiation (Figure 1B). By the addition of VPA to the treatment, no difference in OS was observed (median OS: VPA: 10.0 months *vs*. no VPA: 8.4 months, unadjusted HR=0.89; 95% CI: 0.49-1.61; *P*=0.71, adjusted HR=0.91; 95% CI: 0.43-1.93; *P*=0.80) (Table 1; Figure 1C) and the survival curves did not separate at any given time point.

In this subgroup analysis of the DECIDER trial, the addition of ATRA to DEC (+/-VPA) resulted in higher ORR and OS rates in elderly patients with oligoblastic AML ineligible for induction chemotherapy, with no added toxicity, as shown in the original publication.[8] Although the results were not statistically significant, the Kaplan-Meier plots are suggestive of a clinically relevant difference.

In our analysis of the whole study population of the DECIDER trial it was shown that the addition of ATRA did not only improve the ORR but also led to a prolonged response duration.[8] We thus reasoned that ATRA stabilizes the response to HMA therapy and leads to delayed emergence of resistance. The number of patients with oligoblastic leukemia was not sufficient to perform this type of analysis, but we also did not observe any hint that this population should respond differently.

A high proportion of the patients (67.9%) with oligoblastic leukemia had a preceding hematologic disorder, mainly MDS. Due to of the diagnostic continuum from MDS to secondary AML separated by the arbitrary number of 20% bone marrow or peripheral blood blasts at the time of this study, the higher proportion of patients in this subgroup, compared to 51% in the whole study population, does not come as a surprise. The fact that the addition of ATRA to DEC is also leading to clinical benefit of the subgroup of oligoblastic leukemia patients could therefore be sufficient to claim that this combination treatment could be efficacious in MDS patients with excess blasts.

The effort to establish retinoic acid as a therapeutic agent in MDS dates back to the 1980s, however without proof of single-agent activity.[11,12] Over 10 years ago, two phase II trials from Paris and the MD Anderson Cancer Center demonstrated clinical activity of HMA + ATRA + VPA in AML and MDS.[13,14] Our recent study was the first randomized trial to prove the feasibility of the combination of HMA + ATRA in AML.[8] Recently, we also found *in vitro* and *in vivo* evidence for co-operation of decitabine and ATRA.[15] It is only logical to also launch a randomized trial with this combination in high-risk MDS as conducted by the group of Dr. Tong.[16] Since the combination of HMA + venetoclax is likely to also play an important role in the treatment of MDS,[7] a combination of HMA + venetoclax + ATRA is a rational study concept, advanced by us for AML (DECIDER-2 trial). Since the main limitation of HMA + venetoclax in AML is the emergence of resistance[6] and ATRA delayed emergence of resistance in the entire DECIDER study population without adding any toxicity, it appears as a rational partner for a reduced-toxicity triple therapy.

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Disclosures

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Contributions

ML, OG, CS, BH, HD and AG developed the concept and designed the study; CR, OG, MC, MH, KG, RS, KD, HS, CM-T, WB, AK, MW, AG, SS, AN, JK, GB, HA-A, RW, HB, BH, AG, HD and ML collected and assembled data; ML, OG, CS, CR, RS, HS, CM-T, WB, AG, AN, JK, MW, RW, HB, JD, BH and HD analyzed and interpreted data; ML, RS, EJ, MH, HS, AK, KG, GH, SS, GB, AG, AN, JK, WB, MW, RW, KD, BH and HD provided study materials or recruited patients; OG and BH provided administrative support. All authors wrote the manuscript, are accountable for all aspects of the work and approved the final version of the manuscript.

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Data-sharing statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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