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Impact of *TP53* Mutation Status in Elderly AML Patients When Adding All-*Trans* Retinoic Acid or Valproic Acid to Decitabine

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ABSTRACT

In a randomized phase II trial (AMLSG 14-09, NCT00867672) of elderly, newly diagnosed AML patients, ATRA combined with decitabine (DEC) significantly improved the overall response rate (ORR) and survival also in patients with adverse-risk genetics, without adding toxicity. We performed a post hoc analysis to determine the predictive impact of *TP53* status. Despite a nominally higher ORR, the clinically meaningful survival benefit when adding ATRA to DEC was diminished, but not completely negated, in *TP53*-mutated patients. Indeed, 2 out of 14 *TP53*-mutated patients (14%) randomized to a DEC + ATRA-containing regimen

lived for > 36 months. Further studies of ATRA combined with hypomethylating agents appear warranted in non-M3 AML patients ineligible for HMA/venetoclax therapy.
Trial Registration: ClinicalTrials.gov identifier: NCT00867672

1 | Introduction

Older AML patients often display *TP53* mutations (MUT) and complex-monosomal karyotype, with poor response to cytosine arabinoside (AraC) based treatment. In contrast, the DNA-hypomethylating agents (HMAs) azacitidine (AZA), and decitabine (DEC) induce encouraging clinical responses in AML patients with these genotypes [1, 2]; one study reported a 100% complete remission rate in *TP53* MUT patients treated with 10-day DEC [3]. Increased response rates in *TP53* MUT AML patients, as also reported in the VIALE-A trial when AZA was combined with venetoclax (VEN) [4], are not robust and hence do not translate into clinically relevant survival extension.

Preclinical [5, 6] and clinical evidence is emerging that also in non-M3 AML, all-*trans* retinoic acid (ATRA), when combined with DNA-HMAs, may exert antileukemic activity in patients with different genetic risk groups [7–9]. We conducted a randomized phase II trial (AMLSG 14-09, NCT00867672, 2 × 2 factorial design) asking whether the in vitro cooperativity of DEC with the histone deacetylase (HDAC) inhibitor valproic acid (VPA) or ATRA translates into clinical benefit. While VPA added to DEC affected neither the overall response rate (ORR) nor overall survival (OS), ATRA significantly improved ORR and OS, without added toxicity [8]. We now performed a post hoc analysis to determine the predictive impact of *TP53* status.

2 | Methods

Key inclusion criteria for the DECIDER trial were newly diagnosed AML patients aged > 60 years (non-M3) unfit for induction, ECOG performance status (PS) 0–2. Treatment included DEC 20 mg/m^2 intravenously on days 1–5 (arms A/B/C/D), VPA orally from day 6 (arms B/D), ATRA 45 mg/m^2 orally days on 6–28 (arms C/D) of each 28-day course. For *TP53* mutation analyses, the Illumina TruSight Myeloid Sequencing Panel was used for library preparation and an Illumina MiSeq device for sequencing. Key endpoints were ORR (CR/CRi/PR, ELN 2010 criteria [according to the study protocol]) and OS. The original sample size calculation of 200 patients was based on the primary endpoint ORR. ORR was analyzed with logistic regression and OS with Cox regression. Odds ratios (OR) for the effect on ORR and hazard ratios (HR) for the effect on OS with 95% confidence intervals (CI) are presented in the genetic subgroups *TP53* MUT and *TP53* WT, including tests for interactions (TFI) between treatment and *TP53*. These are post hoc exploratory analyses, hence *p* values have to be interpreted in a descriptive sense.

De-identified individual participant data that underlie the reported results are included as a data supplement. The study protocol, a description of ethics approval [8] and more information about the underlying clinical trial are available at ClinicalTrials.gov.

3 | Results

Between December 2011 and February 2015, 200 patients were randomized and treated. Information on *TP53* status was available for 168 of 200 patients (84%; Table 1); 155 of them (92%) had died at the last follow-up (June 2021). *TP53* mutations were detected in 39 patients (23.2%), with 1 ($n = 24$) or 2 mutations ($n = 12$, median variant allele frequency 44%, range, 17%–99%) in 36 patients, and chromosomal deletions of both *TP53* alleles in 3 additional patients. As expected, *TP53* MUT patients more frequently presented with a monosomal karyotype (78%) than patients with *TP53* WT (9%; Table 1). According to the New International Consensus Classification of Myeloid Neoplasms and Acute Leukemias [10], 79% of the *TP53* mutated population qualified for multi-hit involvement at the *TP53* genetic locus (Table S1). We also analyzed a panel of 53 other genes commonly mutated in AML. 20 out of 39 *TP53* mutated patients (51%) had additional mutations (Table S2), with a distribution similar to a comparable *TP53* MUT patient cohort [11].

The 39 patients with *TP53* MUT had a nominally higher ORR (23.1%) than the 129 patients with *TP53* WT (ORR 15.5%), with an OR of 1.90 (95% CI 0.76–4.77), which was not statistically significant ($p = 0.17$). OS in the *TP53* MUT vs. WT patients was not different (HR, adjusted for treatment, ECOG, HT-CI, sLDH, Hb: 1.15 [95% CI 0.78–1.71], $p = 0.48$; Figure 1A). In both genetic groups, the addition of ATRA had a non-significant effect on ORR (ATRA vs. no ATRA in *TP53* MUT: 28.6% vs. 20.0%, OR 1.60 [95% CI 0.35–7.30]; ATRA vs. no ATRA in *TP53* WT: 19.7% vs. 10.3%, OR 2.14 [95% CI 0.76–5.97], TFI $p = 0.76$) (Figure 1B). Survival by the four treatment arms and TP53 status are depicted in Figure S1.

Median OS in *TP53* WT patients was increased by 3.8 months (see Figure S2A: 8.5 vs. 4.7 months with ATRA vs. no ATRA, HR 0.59 [95% CI 0.40–0.87]). In contrast, the addition of ATRA in *TP53* MUT patients resulted in the extension of median OS by only 1.1 months (Figure S2B: 5.3 vs. 4.2 months with ATRA vs. no ATRA, HR 0.74 [95% CI 0.36–1.51], all results adjusted for VPA, ECOG, HCT-CI, sLDH, Hb, TFI $p = 0.59$). Interestingly, 2 of the 14 *TP53* MUT patients receiving DEC + ATRA (14.2%), both with multi-hit *TP53* MUT and complex-monosomal karyotype, survived for over 3.0 years (Figure 1C). This is highly unusual for older AML patients with this genotype, even after allografting [12, 13]. Patient 20/003 (82 years old) received 30 cycles of DEC + ATRA, attaining a complete hematologic and cytogenetic remission that was maintained, with good tolerability and quality of life, resulting in survival of 3.7 years. Given this remarkably long OS, we decided to conduct an in-depth study, performing whole-genome sequencing and enhancer mapping, and addressing also aspects of patient autonomy, resilience, and determination to undergo an extended nonintensive treatment in the face of adverse-risk genetics AML [14]. Patient 04/005 (74 years old) received only 3 cycles of DEC + ATRA + VPA, and later opted for intermittent AZA treatment, with an OS of 3.4 years.

TABLE 1 | Characteristics of all AML patients and according to their *TP53* status at baseline; data are *n* (%) unless otherwise indicated.

	All	*TP53* WT	*TP53* MUT
Total, *n*	168	129	39
Age ≥ 75 years	103 (61)	87 (67)	16 (41)
Sex male	107 (64)	86 (67)	21 (54)
ECOG performance status			
0	32 (19)	24 (19)	8 (21)
1	104 (62)	83 (64)	21 (54)
2	32 (19)	22 (17)	10 (26)
HCT-comorbidity index ≥ 3	89 (53)	69 (53)	20 (51)
Prior hematologic disorder	85 (51)	65 (50)	20 (51)
Treatment-related AML	22 (13)	15 (12)	7 (18)
2022 European LeukemiaNet genetic risk classification			
Favorable	11 (7)	11 (9)	0 (0)
Intermediate	29 (17)	29 (22)	0 (0)
Adverse	126 (75)	87 (67)	39 (100)
NA	2 (1)	2 (2)	0 (0)
Bone marrow blasts < 50%	73 (44)	49 (39)	24 (63)
White-blood-cell count ≥ 30.000/μL	32 (19)	31 (24)	1 (3)
Platelet count < 50.000/μL	83 (49)	60 (47)	23 (59)
Serum lactate dehydrogenase ≥ 300 U/L	88 (52)	66 (51)	22 (56)
Hemoglobin < 8 g/dL	36 (21)	25 (19)	11 (28)
Monosomal karyotype			
Present	38 (25)	10 (9)	28 (78)
Unknown	15	12	3

VPA did not affect ORR in either of the two genetic groups (VPA vs. no VPA in *TP53* WT: 16.4% vs. 14.5%, OR 1.18 [95% CI 0.45–3.09], VPA vs. no VPA in *TP53* MUT: 22.7% vs. 23.5%, OR 0.95 [95% CI 0.21–4.31]; TFI $p = 0.81$). The impact of VPA on OS differed between *TP53* WT patients (VPA vs. no VPA: median OS of 8.3 vs. 4.8 months, HR 0.68 [95% CI 0.47–1.00]) and *TP53* MUT patients (VPA vs. no VPA: median OS of 4.0 vs. 4.8 months, HR 1.34 [95% CI 0.69–2.61], all results adjusted for ATRA, ECOG, HCT-CI, sLDH, Hb; TFI $p = 0.084$; Figures 1D and S2C,D).

4 | Discussion

The addition of VEN to HMAs has significantly improved the treatment of older patients with AML [4] and is now also being investigated as a first-line treatment for younger patients [15]. However, the development of secondary resistance remains a challenge. ATRA has regained interest in non-M3 AML, with studies suggesting that ATRA's role is not limited to the induction of differentiation [5, 6, 16–19]. Because of its good tolerability, ATRA therefore is a promising candidate for combination therapies. In the DECIDER trial, adding ATRA to DEC led to prolonged OS, to a degree that cannot be fully explained by the enhanced ORR. We therefore hypothesize that adding ATRA to an HMA-based treatment may delay the development of resistance [8]. The randomized phase III DECIDER-2 trial (EUDRACT 2020-005495-36) investigates this triple combination: elderly AML patients are treated with DEC + VEN and either placebo or ATRA, with the hypothesis that ATRA exerts a beneficial effect on AML outcome also when combined with DEC + VEN.

AML patients with *TP53* WT derive clinically significant benefits from the addition of ATRA to DEC, with continued treatment feasible in this elderly, medically non-fit population. The addition of ATRA was beneficial in improving OS in *TP53* WT patients by 3.8 months. However, the effect on OS in *TP53* MUT patients was clearly diminished, though not completely negated, with a 1.1-month improvement. VPA did not show a relevant impact on ORR or OS. Interestingly, the survival of 2/14 *TP53* MUT patients receiving DEC + ATRA was extended for over 3 years, proof of the feasibility of long-term treatment (also recently reported for an elderly *TP53* WT patient with adverse cytogenetics and sAML [20] receiving 52 cycles of DEC + ATRA within the

DECIDER trial). Detailed molecular characterization of these patients with prolonged survival is underway and may help identify patients who could benefit from the addition of ATRA to HMAs.

While the combination of HMA and VEN has revolutionized the treatment of elderly AML patients since the start of the DECIDER-1 trial, it is limited by variable sensitivity and frequent emergence of resistance to VEN-based therapies. ATRA could be a valuable addition to the evolving landscape of less intensive treatment options for elderly patients with AML, for example, for *TP53* WT patients ineligible for VEN. A long-term follow-up study of the VIALE-A trial showed that *TP53*-mutated AML had a very limited long-term survival with VEN + HMA, with only 8% of *TP53* MUT patients treated with VEN + AZA surviving ≥ 2 years [21]. Within the DECIDER trial, 14% of *TP53* MUT patients treated with DEC + ATRA survived ≥ 3 years; however, the overall limited response in both studies demonstrates the continued need for better treatment options for this high-risk subgroup. In addition, the search for more effective triplet drug combinations is ongoing, for example, in the DECIDER-2 trial where the interaction of the *TP53* genotype with ATRA-containing treatment is studied prospectively.

Limitations of this post hoc study are the overall limited number of patients with *TP53* mutations, as NGS profiling was only available for 168 (84%) of the 200 patients. Sample size limitations did not allow interesting subgroup analyses, for example,

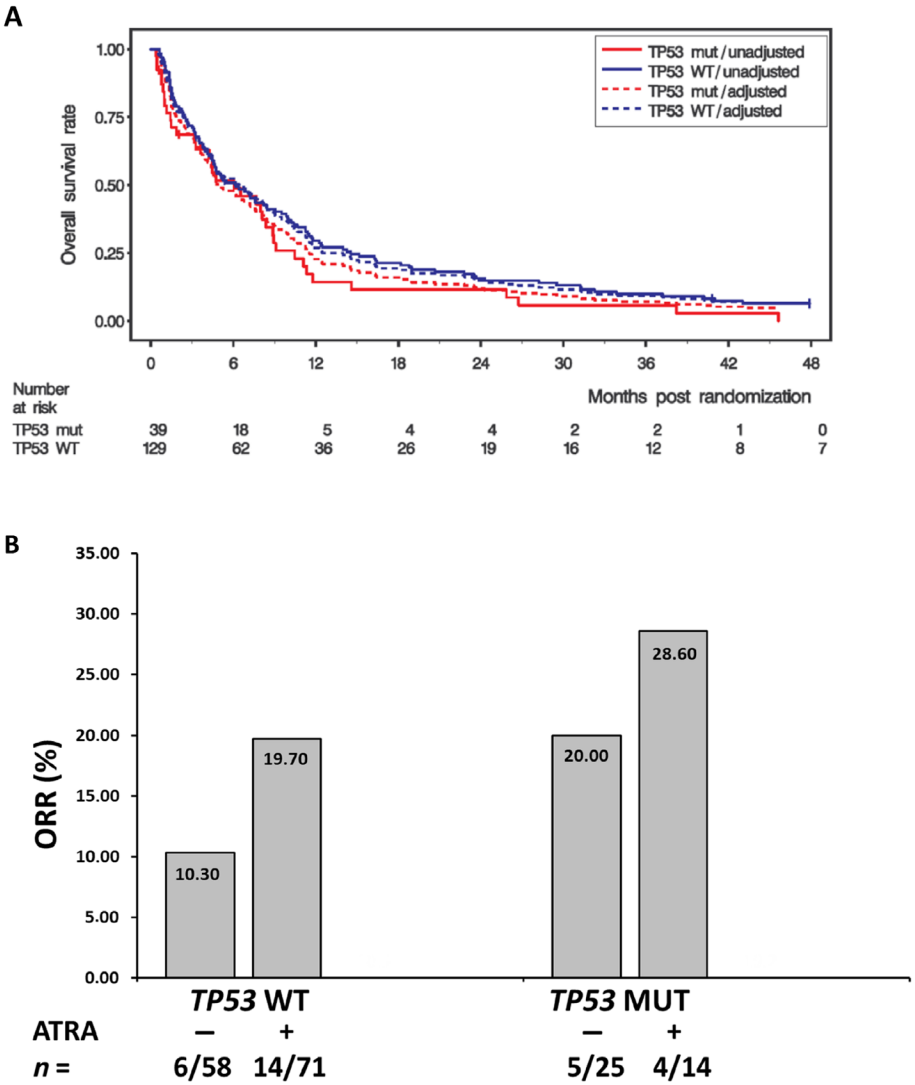

FIGURE 1 | Impact of *TP53* mutational status in the DECIDER trial. (A) Overall survival rates of 168 pts. treated on the DECIDER trial, *TP53* WT (blue curve: $n = 129$), *TP53* MUT (red curve: $n = 39$), unadjusted (Kaplan–Meier method), and adjusted for ATRA, VPA, ECOG, HCT-CI, LDH, Hb (Cox model). (B) Objective response rates (ORR: complete remission with or without complete hematologic recovery, partial remission) of pts. with *TP53* WT or *TP53* MUT receiving DEC with or without ATRA. (C) Prolonged survival of pts. treated in the DECIDER trial, with (red) or without (green) the addition of ATRA. Shown are pts. with wildtype (WT; $n = 19$) or mutated (MUT; $n = 4$) *TP53*, who lived > 2 years, 14.7% and 10.2%, respectively. This criterion was met by 5/58 WT pts. treated without ATRA (8.6%) and 14/71 WT pts. treated with ATRA (19.7%) as well as 2/25 MUT pts. treated without ATRA (8.0%) and 2/14 MUT pts. treated with ATRA (14.2%). (D) Effect of add-on treatment (ATRA or VPA added to DEC) on overall survival in pts. with *TP53* WT or *TP53* MUT, estimated as hazard ratios with 95% confidence intervals. ATRA: all-*trans* retinoic acid; DEC: decitabine; VPA: valproic acid.

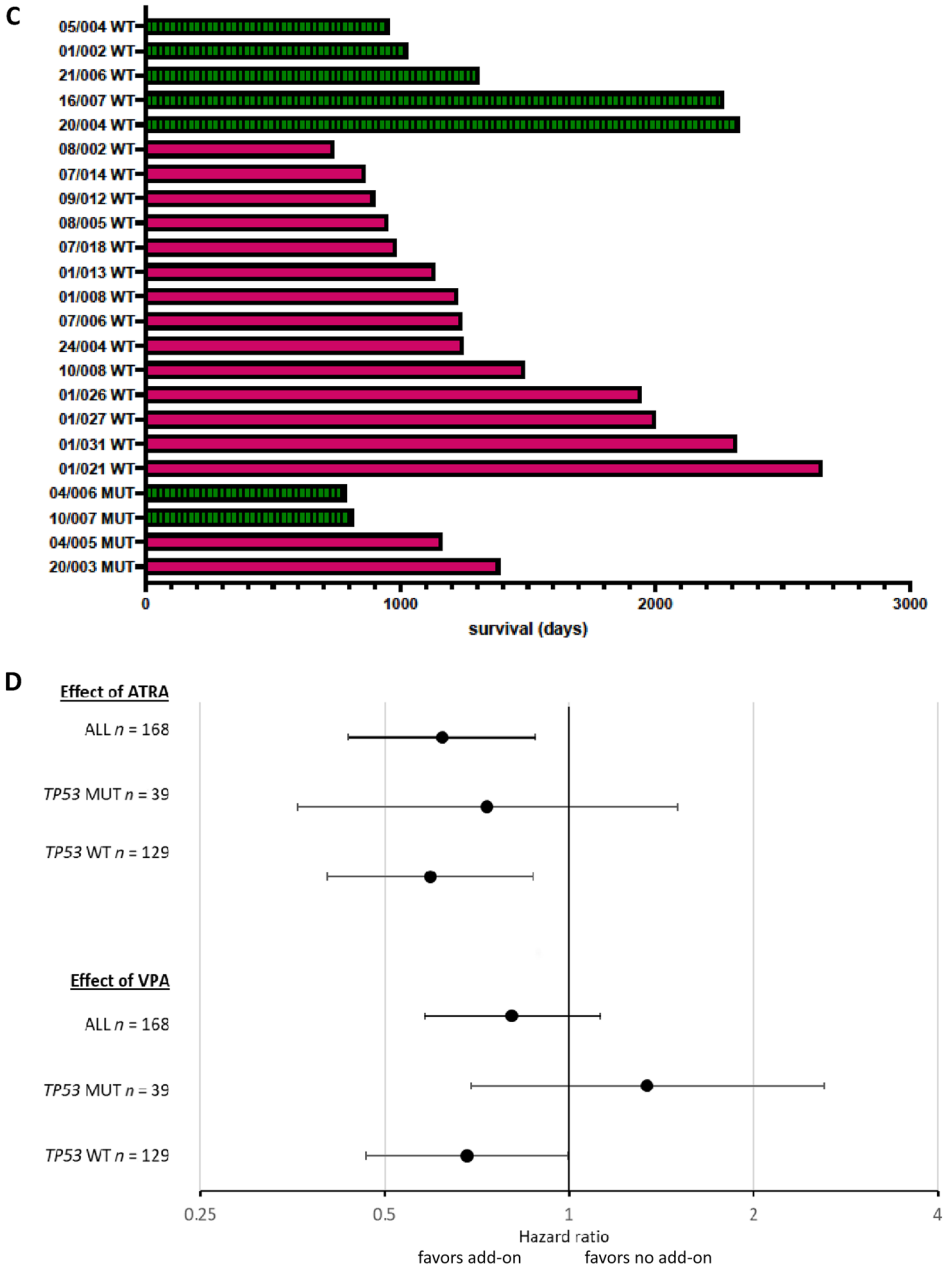

FIGURE 1 | (Continued)

the interaction between ATRA, TP53 status (single- vs. double-hit), karyotype, additional mutations, blast percentage, ELN risk, and so forth. In addition, the DECIDER trial had been conceived and conducted before the first reports of the striking in vivo synergism between HMAs and VEN.

In conclusion, further studies aiming to gain a better mechanistic understanding of the cooperation between HMAs and retinoids in AML, and other cancers where retinoids have a therapeutic role, appear warranted.

Author Contributions

Helena Bresser, Johanna Thomas, and Michael Lübbert drafted the manuscript. Claudia Schmoor performed the statistical analyses. And all the authors contributed to the underlying clinical trial.

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Conflict of Interest

Crysandt

Incyte: Honoraria; Pfizer: Membership on an entity's Board of Directors or advisory committees.

Thol

Abbvie: Honoraria; Pfizer: Honoraria; Astellas: Honoraria; Novartis: Honoraria; BMS/Celgene: Honoraria, Research Funding; Jazz: Honoraria.

Heuser

Roche: Membership on an entity's Board of Directors or advisory committees, Research Funding; Tolremo: Membership on an entity's Board of Directors or advisory committees; Pfizer: Membership on an

entity's Board of Directors or advisory committees, Research Funding; Daiichi Sankyo: Membership on an entity's Board of Directors or advisory committees, Research Funding; Karyopharm: Research Funding; Jazz: Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; Janssen: Honoraria; Novartis: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; AbbVie: Membership on an entity's Board of Directors or advisory committees, Research Funding; BergenBio: Research Funding; BMS/Celgene: Membership on an entity's Board of Directors or advisory committees, Research Funding; Bayer Pharma AG: Research Funding; Astellas: Research Funding.

Götze

Abbvie: Advisory Board; BMS/Celgene: Advisory Board, Research Funding.

Schlenk

Agios: Honoraria; Astellas: Honoraria, Research Funding, Speakers Bureau; Celgene: Honoraria; Daiichi Sankyo: Honoraria, Research Funding; Abbvie: Honoraria; Hexal: Honoraria; Neovio Biotech: Honoraria; Novartis: Honoraria; Pfizer: Honoraria, Research Funding, Speakers Bureau; Roche: Honoraria, Research Funding; AstraZeneca: Research Funding; Boehringer Ingelheim: Research Funding.

Salih

Synimmune GmbH: Honoraria; Pfizer: Honoraria; Novartis: Honoraria; Celgene: Honoraria; BMS: Honoraria.

Schittenhelm

Takeda: advisory board; Astellas: advisory board; BMS: advisory board; University of Tuebingen: Patents & Royalties: patent for ASPP2k.

Müller-Tidow

Pfizer: Research Funding; Janssen: Consultancy, Research Funding; Bioline: Research Funding; Astellas: lecture fees. Germing: speakers honorarium: BMS, Novartis, Janssen: speakers honorarium; BMS, Novartis, Abbvie, Jazz: institutional research report; BMS: Advice.

Giagounidis

Novartis: Membership on an entity's Board of Directors or advisory committees; Amgen: Membership on an entity's Board of Directors or advisory committees. Bug: Novartis: Support of Investigator-Initiated Trial to my Institution; Jazz, Gilead, Novartis, BMS, Pfizer: Honoraria; Jazz, Neovii: Travel Grants.

Wäsch

Amgen: Consultancy, Honoraria; Pfizer: Consultancy; Sanofi: Consultancy, Honoraria; Takeda: Consultancy, Honoraria; Janssen: Consultancy, Honoraria; Novartis: Consultancy; BMS/Celgene: Consultancy; Gilead: Consultancy.

Döhner

Jazz Roche: Consultancy, Honoraria; Celgene/BMS: Consultancy, Honoraria, Research Funding; Daiichi Sankyo: Honoraria, Advisory Board; Agios and Astex: Research Funding; Abbvie: Consultancy, Honoraria; Janssen: Honoraria, Advisory Board; Astellas: Research Funding; Novartis: Consultancy, Honoraria, Research Funding.

Ganser

Novartis: Honoraria; Jazz Pharmaceuticals: Honoraria; Celgene: Honoraria.

Döhner

Astellas: Consultancy, Honoraria, Research Funding; Bristol Myers Squibb: Consultancy, Honoraria, Research Funding; Oxford Biomedicals: Consultancy, Honoraria; Gilead: Consultancy, Honoraria; Abbvie: Consultancy, Honoraria, Research Funding; Helsinn: Consultancy, Honoraria; Celgene: Consultancy, Honoraria, Research Funding; AstraZeneca: Consultancy, Honoraria; Novartis: Consultancy, Honoraria, Research Funding; Berlin-Chemie: Consultancy, Honoraria; Astex: Consultancy, Honoraria; Agios: Consultancy, Honoraria, Research Funding; Ulm University Hospital: Current Employment; Jazz: Consultancy, Honoraria, Research Funding; Janssen: Consultancy, Honoraria; Roche: Consultancy, Honoraria; GEMoaB: Consultancy, Honoraria; Amgen: Consultancy, Honoraria, Research Funding; Pfizer: Research Funding.

Hackanson

Roche: Consultancy, Honoraria; Astra Zeneca: Consultancy, Honoraria; Pfizer: Consultancy, Honoraria; BMS: Consultancy, Honoraria; Boehringer-Ingelheim: Consultancy, Honoraria; MSD: Consultancy, Honoraria. Becker: BMS: Honoraria; Pierre Fabre Pharma: Honoraria; Servier: Honoraria; MSD: Honoraria; Novartis: Honoraria; Lilly: Honoraria; GSK: Honoraria.

Lübbert

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Data Availability Statement

See the Supporting Information and NCT00867672 for detailed data and clinical trial information supporting the results of this study.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.