blood neoplasia

American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
bloodneoplasia@hematology.org

Comparative Effectiveness of HMA with Venetoclax Versus Intensive Chemotherapy in AML with Very-High-Risk Cytogenetics

Tracking no: NEO-2025-000876R2

Luis Aguirre(,Yale School of Medicine,United States;,Dana-Farber Cancer Institute (primary), Harvard T.H. Chan School of Public Health (tertiary),United States) Jan Bewersdorf(,Yale School of Medicine University,United States) Yiwen Liu(,Dana Farber Cancer Institute,United States) Rory Shallis(,Moffitt Cancer Center,United States) Leora Boussi(,Memorial Sloan Kettering Cancer Center,United States) Andrius Zucenka(,Vilnius University Hospital Santaros Klinikos,Lithuania) Sylvain Garciaz(,Aix-Marseille Univ, Inserm, CNRS, Institut Paoli-Calmettes, CRCM, Marseille, France,France) Rebecca Bystrom(,Duke University Medical Center,United States) Daniel DeAngelo(Medical Oncology,Dana-Farber Cancer Institute,United States) Richard Stone(Medical Oncology,Dana-Farber Cancer Institute,United States) Marlise Luskin(Medical Oncology,Dana-Farber Cancer Institute,United States) Jacqueline Garcia(Medical Oncology,Dana-Farber Cancer Institute,United States) Eric Winer(Medical Oncology,Dana-Farber Cancer Institute,United States) Kelly Ling(,Dana Farber Cancer Institute,United States;,Yale Cancer Center,United States) Evan Chen(,Dana-Farber Cancer Institute,United States) Martha Wadleigh(,Dana Farber Cancer Institute,United States) Guillaume Berton(Hematology,Institut Paoli-Calmettes, INSERM, CNRS, Aix-Marseille University, Marseille, France,France) Eytan Stein(Leukemia Service, Department of Medicine,Memorial Sloan Kettering Cancer Center,United States) Aaron Goldberg(Leukemia Service, Department of Medicine,Memorial Sloan Kettering Cancer Center,United States) Lourdes Mendez(,Yale University School of Medicine,United States) Amer Zeidan(,Yale University,United States) David Sallman(,Moffitt Cancer Center and Research Institute,United States) Shai Shimony(Leukemia,Dana-Farber Cancer Institute,United States) Maximilian Stahl(Department of Internal Medicine,Yale University School of Medicine,United States;,Dana-Farber Cancer Institute (primary),United States)

Abstract:
The optimal frontline therapy for acute myeloid leukemia (AML) with very-high-risk cytogenetics (vHRC)—defined by complex karyotype (CK), monosomal karyotype (MK), or inv(3)/t(3;3)—remains uncertain. We retrospectively analyzed 358 newly diagnosed AML-vHRC cases treated at five academic centers (2014–2024), stratified by intensive chemotherapy (IC) versus hypomethylating agent plus venetoclax (HMA+ven). Cytogenetic features included CK in 90.2%, MK in 64%, and inv(3)/t(3;3) in 9.8%; TP53 mutations occurred in 51%. Frontline therapy was IC in 40% and HMA+ven in 60%, with a median age of 67 years (range, 22–92). Median overall survival (OS) for AML-vHRC was 8 months compared with 31 months for non-vHRC AML (p<0.0001). Composite complete remission (cCR) rates were similar with IC versus HMA+ven (55% vs 54%, p=0.91). Patients with inv(3)/t(3;3) had inferior responses (cCR 36%) compared with CK/MK-AML (67%; p<0.001). No OS differences by frontline regimen were observed among patients aged 60–75 years (7.7 vs 6.6 months, p=0.43), those with TP53-mutated disease (8.1 vs 5.8 months, p=0.17), or following alloHSCT (35 vs 25 months, p=0.56). On multivariable analysis, older age (HR 1.02, p=0.0003), inv(3)/t(3;3) (HR 2.12, p=0.0002), and TP53mt (HR 2.07, p<0.0001) independently predicted inferior OS, whereas alloHSCT improved OS (HR 0.42, p<0.0001); frontline regimen (HMA+ven vs IC) was not associated with OS (HR 0.84, p=0.2814). In AML-vHRC, IC and HMA+ven yield comparable remission and survival outcomes. Given equivalent efficacy and similar early mortality, HMA+ven represents a reasonable frontline option for patients aged 60–75 years, those with TP53mt disease, and patients intended for alloHSCT.

Conflict of interest: COI declared - see note

COI notes: Luis E. Aguirre: Consultancy for Cardinal Health, Research To Practice. Honoraria from Cardinal Health, Research To Practice, MD Education DAVA Oncology. Jan Philipp Bewersdorf: No COI disclosed. JPB is supported by the Edward P. Evans Foundation Yiwen Liu: No COI disclosed. Rory M. Shallis: Consultancy/advisory and honoraria from Servier (also serves on Steering Committee), Rigel, Kura Oncology, and Gilead Sciences Leora Boussi: No COI disclosed. Andrius Zucenka: Consultancy and/or honoraria from Pfizer, Astellas, AbbVie, Novartis, and Johnson & Johnson; travel support from AbbVie, Novartis, Johnson & Johnson, and Takeda. Sylvain Garciaz: Consultancy/advisory and/or honoraria from Janssen, Servier, and AbbVie; consultancy from ImCheck Therapeutics, Sanofi, AbbVie, and Bristol Myers Squibb; travel grants from Sanofi and AbbVie. Rebecca P. Bystrom: No COI disclosed. Daniel J. DeAngelo: Consultancy for Kite, Servier, Incyte, Pfizer, Gilead, Novartis, Jazz, Autolos, Amgen, and Blueprint; Honoraria from Amgen and Bristol-Meyers Squibb; Research funding from Servier, Novartis, Glycomimetics, AbbVie, and Takeda; Other: DSMB for MT Sinai MPN Consortium, Fibrogen, Daiichi-Sankyo. Richard M. Stone: Research funding from Janssen and AbbVie; Consultancy for Glaxosmithkline, Curis Oncology, Daiichi Sankyo, ENSEM, Epizyme, BerGenBio, AMGEN, Syntrix, Hermavant, Glycomimetrics, CTI Biopharma, Bristol Meyers Squibb, Rigel, Syndax, AvenCell, Takeda, Jazz, Kura Oncology, Lava Therapeutics, Cellarity, Ligand Pharma, Novartis, Aptevo, and Redona therapeutics; Other: DSMB for Epizyme, Syntrix, Takeda, and Novartis. Marlise R. Luskin: Honoraria from Pfizer, KITE, Jazz, and AbbVie; Research funding from Novartis and AbbVie. Jacqueline S. Garcia: Research funding from Newave and Taiho; Consultancy for Servier, AbbVie, and Genentech; Membership on the Board of Directors or advisory committees for Genentech; Research funding from AbbVie and Genentech. Eric S. Winer: No COI disclosed. Kelly Ling: No COI disclosed. Evan C. Chen: Consultancy for AbbVie and Rigel. Martha Wadleigh: No COI disclosed. Guillaume Berton: No COI disclosed. Eytan M. Stein: Consultancy/advisory and consulting fees from AstraZeneca, Servier, Agios Pharmaceuticals, Genentech, Gilead, Jazz Pharmaceuticals, AbbVie, Daiichi Sankyo, Celgene (Bristol Myers Squibb), and Astellas. Aaron D. Goldberg: Consultancy/advisory roles and/or board/advisory committee memberships with Astellas, Bristol Myers Squibb, Molecular Partners, Syndax, Genentech, AbbVie, and Daiichi Sankyo; consultancy with Ikena Oncology; honoraria from Kura Oncology and DAVA Oncology; research funding from Aptose, Pfizer, Celularity, Kura Oncology, Aprea, AbbVie, and AROG. Lourdes Mendez: No COI disclosed. Amer M. Zeidan: Consultancy/advisory and/or honoraria from AbbVie, Agios, Akesobio, Amgen, Astellas, BeiGene, BioCryst, Boehringer Ingelheim, Bristol Myers Squibb (including Celgene), Chiesi/Cornerstone Biopharma, Daiichi Sankyo, Dr. Reddy's Laboratories, Epizyme, Faron, FibroGen, Genentech, Geron, Gilead, GlaxoSmithKline (GSK), GlycoMimetics, Janssen, Jasper Therapeutics, Karyopharm Therapeutics, Keros Therapeutics, Kura Oncology, Kyowa Kirin, Lava Therapeutics, Notable, Novartis, Orum, Otsuka, Pfizer, Regeneron, Rigel, Schrödinger, Seagen (formerly Seattle Genetics), Servier, Shattuck Labs, Syndax, Syros, Taiho, Takeda, Treadwell Therapeutics, Vincerx, and Zentalis. David A. Sallman: Research funding from Syntrix Pharmaceuticals; Membership on the Board of Directors or advisory committees for Nemucore, Lixte, Novartis, Intellia, Syndax, Kite, Shattuck Labs, BMS, Aprea, Agios, AbbVie, and Takeda; Patents & Royalties for LB-100 (Lixte); Consultancy for Magenta, Novartis, Intellia, Syndax, Kite, Incyte, Shattuck Labs, BMS, Aprea, Agios, AbbVie, and Takeda; Speakers Bureau for Incyte, BMS. Shai O. Shimony: No COI disclosed. Maximilian Stahl: Advisory board for Novartis, Kymera, Sierra Oncology, GSK, Rigel, BMS, Sobi and Syndax, Kura; consulted for Boston Consulting, GLG and Dedham group and participated in CME activity for Novartis, Curis Oncology, Haymarket Media and Clinical Care Options and is member of the Medical Safety Monitoring Board for Keros Pharmaceuticals. All other authors have no conflicts of interest to declare.

Preprint server: No;

Author contributions and disclosures: 1. Conception and design: LA, MS 2. Administrative support: YL, RB, MS 3. Provision of study materials or patients: LA, RB, MS, and all other authors 4. Collection and assembly of data: LA, YL, RB, LB, AZ, SG, MS 5. Data analysis and interpretation: LA, YL, MS 6. Manuscript writing: LA, MS 7. Final approval of manuscript: All authors

Non-author contributions and disclosures: No;

Agreement to Share Publication-Related Data and Data Sharing Statement: Access to de-identified individual patient-level data presented in this study may be made available to qualified researchers upon reasonable request following the publication of the article in its final form. Data will be provided in a de-identified format in compliance with institutional and ethical guidelines. Requests must include a detailed research proposal and should be directed to the corresponding authors for consideration.

Clinical trial registration information (if any):

Comparative Effectiveness of HMA with Venetoclax Versus Intensive Chemotherapy in AML with Very-High-Risk Cytogenetics

Luis E. Aguirre[1,2,3], Jan Philipp Bewersdorf[2], Yiwen Liu[4], Rory M. Shallis[5], Leora Boussi[6], Andrius Zucenka[7], Sylvain Garciaz[8], Rebecca P. Bystrom[9], Daniel J. DeAngelo[1], Richard M. Stone[1], Marlise R. Luskin[1], Jacqueline S. Garcia[1], Eric S. Winer[1], Kelly Ling[2], Evan C. Chen[1], Martha Wadleigh[1], Guillaume Berton[8], Eytan M. Stein[6], Aaron D. Goldberg[6], Lourdes Mendez[2], Amer M. Zeidan[2], David A. Sallman[5], Shai Shimony[1], Maximilian Stahl[1,2]

[1] Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, US
[2] Department of Internal Medicine, Section of Hematology and Medical Oncology, Yale School of Medicine, New Haven, CT, US
[3] Harvard T.H. Chan School of Public Health, Boston, MA, US
[4] Department of Data Science, Dana-Farber Cancer Institute, Boston, MA, US
[5] Department of Malignant Hematology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, US
[6] Memorial Sloan Kettering Cancer Center, New York, NY, US
[7] Vilnius University, Faculty of Medicine, Institute of Clinical Medicine, Department of Hematology and Oncology, Vilnius, Lithuania
[8] Aix-Marseille Univ, Inserm, CNRS, Institut Paoli-Calmettes, CRCM, Marseille, France
[9] Division of Hematologic Malignancies and Cellular Therapy, Duke Blood Cancer Center, Durham, NC, US

Running Head: Frontline HMA+ven versus IC in AML-vHRC

Corresponding authors:
Luis E. Aguirre, MD, MPH(c)
Department of Internal Medicine, Section of Hematology and Medical Oncology, Yale School of Medicine
37 College Street
New Haven CT 06510
Email: luis.aguirre@yale.edu

Maximilian Stahl, MD
Department of Internal Medicine, Section of Hematology and Medical Oncology, Yale School of Medicine
37 College Street
New Haven CT 06510
Email: maximilian.stahl@yale.edu

Data-sharing statement
Access to de-identified individual patient-level data presented in this study may be made available to qualified researchers upon reasonable request following the publication of the article in its final form. Data will be provided in a de-identified format in compliance with institutional and ethical guidelines. Requests must include a detailed research proposal and should be directed to the corresponding authors for consideration

Ethical Statement
The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review boards at Dana-Farber Cancer Institute and the H. Lee Moffitt Cancer Center. Individual consent for this retrospective analysis was waived.

Word Count
Abstract: 250 words
Main text: 4470 words
Tables: 3
Figures: 6
Supplementary Tables: 6
Supplementary Figures: 2
References: 26

Key Points

- In AML with vHRC, *TP53* mutations and inv(3)/t(3;3) were associated with inferior OS, whereas alloHSCT significantly improved outcomes
- No significant OS difference was observed between IC and HMA+ven in patients 60-75 and those undergoing HSCT, with comparable cCR rates

Abstract

The optimal frontline therapy for acute myeloid leukemia (AML) with very-high-risk cytogenetics (vHRC)—defined by complex karyotype (CK), monosomal karyotype (MK), or inv(3)/t(3;3)—remains uncertain. We retrospectively analyzed 358 newly diagnosed AML-vHRC cases treated at five academic centers (2014–2024), stratified by intensive chemotherapy (IC) versus hypomethylating agent plus venetoclax (HMA+ven). Cytogenetic features included CK in 90.2%, MK in 64%, and inv(3)/t(3;3) in 9.8%; *TP53* mutations occurred in 51%. Frontline therapy was IC in 40% and HMA+ven in 60%, with a median age of 67 years (range, 22–92). Median overall survival (OS) for AML-vHRC was 8 months compared with 31 months for non-vHRC AML ($p<0.0001$). Composite complete remission (cCR) rates were similar with IC versus HMA+ven (55% vs 54%, $p=0.91$). Patients with inv(3)/t(3;3) had inferior responses (cCR 36%) compared with CK/MK-AML (67%; $p<0.001$). No OS differences by frontline regimen were observed among patients aged 60–75 years (7.7 vs 6.6 months, $p=0.43$), those with *TP53*-mutated disease (8.1 vs 5.8 months, $p=0.17$), or following alloHSCT (35 vs 25 months, $p=0.56$). On multivariable analysis, older age (HR 1.02, $p=0.0003$), inv(3)/t(3;3) (HR 2.12, $p=0.0002$), and *TP53mt* (HR 2.07, $p<0.0001$) independently predicted inferior OS, whereas alloHSCT improved OS (HR 0.42, $p<0.0001$); frontline regimen (HMA+ven vs IC) was not associated with OS (HR 0.84, $p=0.2814$). In AML-vHRC, IC and HMA+ven yield comparable remission and survival outcomes. Given equivalent efficacy and similar early mortality, HMA+ven represents a reasonable frontline option for patients aged 60–75 years, those with *TP53*mt disease, and patients intended for alloHSCT.

Keywords: AML, very-high-risk cytogenetics, HMA+venetoclax, intensive chemotherapy, complete remission, allogeneic stem cell transplant, monosomal karyotype, complex karyotype, inv(3)/t(3;3)

Introduction

Treatment strategies for acute myeloid leukemia (AML) vary widely, ranging from intensive chemotherapy (IC) regimens to lower-intensity therapeutic approaches. Selection is primarily guided by disease features, patient age, and performance status. The 2022 European LeukemiaNet (ELN) risk classification for IC-treated patients stratifies prognosis into favorable, intermediate, and adverse categories based on integrated mutational and cytogenetic data (1). In contrast, the 2024 ELN genetic risk classification—developed for patients receiving less intensive therapies—relies solely on mutational profiles, without incorporating cytogenetic abnormalities into its risk stratification framework (2).

AML with very-high-risk cytogenetic features (vHRC) represents a distinct and biologically aggressive subgroup, defined by three principal cytogenetic abnormalities, each associated with particularly poor outcomes: monosomal karyotype (MK) (3,4), complex karyotype (CK) (5), and inv(3)(q21q26.2) or t(3;3)(q21;q26.2) involving *MECOM (EVI1)* rearrangement (6–8). The dismal outcomes observed in these subgroups are attributed to inherently aggressive disease biology, which manifests as high rates of treatment refractoriness, brief remissions, and a limited proportion of patients ultimately proceeding to allogeneic stem cell transplantation (alloHSCT) (4,6).

Given the poor prognosis of AML-vHRC, the optimization of therapeutic strategies remains critical to improving outcomes and survival. However, it remains unclear whether IC can be safely omitted in these patients, and whether lower-intensity regimens can achieve comparable efficacy. To address this question, we sought to compare response rates and survival outcomes between IC and lower-intensity treatment approaches—specifically, the combination of hypomethylating agents (azacitidine or decitabine) with venetoclax (HMA+ven)—in patients with AML harboring vHRC abnormalities. In addition, we sought to assess outcomes in prespecified subgroups of interest, including patients with *TP53* co-mutated disease, those undergoing alloHSCT, individuals aged 60 to 75, and by cytogenetic subtype—specifically comparing CK/MK versus inv(3)/t(3;3). We hypothesized that response rates and survival would vary according to frontline treatment strategy, and that distinct disease subgroups would demonstrate differential prognostic trajectories.

Methods

Study Design and Population

This was a retrospective, multicenter cohort study evaluating outcomes in patients with AML-vHRC. Demographic, clinical, cytogenetic, molecular, treatment, and outcomes data were extracted in de-identified form from institutional databases and electronic medical records from April 2014 to May 2024 across five academic cancer centers: Dana-Farber Cancer Institute, Memorial Sloan Kettering Cancer Center, Yale Cancer Center, Institut Paoli-Calmettes (Marseille, France), and the National Cancer Institute in Vilnius, Lithuania. Of 1,198 patients with newly diagnosed AML reviewed, only those meeting vHRC criteria were

included. vHRC was defined by the presence of at least one of the following: inv(3)/t(3;3)(q21.3;q26.2), CK, or MK. All patients received frontline therapy with either IC ("7+3" cytarabine plus anthracycline or CPX-351) or a lower-intensity regimen of HMA+ven. Patients lacking vHRC features or with incomplete clinical or cytogenetic data were excluded. IRB approval was obtained at all sites. Informed consent was waived per institutional and federal guidelines due to use of de-identified data.

Cytogenetic and Molecular Profiling

Cytogenetic profiling to characterize CK and MK, as well as to identify inv(3)/t(3;3), was performed using conventional cytogenetic analysis of G-banded metaphase cells and fluorescent in-situ hybridization (FISH). CK was defined as ≥3 unrelated chromosomal abnormalities; MK as ≥2 autosomal monosomies (excluding −X/−Y) or one monosomy with ≥1 structural abnormality (excluding core-binding factor rearrangements) (1). inv(3)/t(3;3) was a class-defining feature.

Molecular profiling was performed using targeted next-generation sequencing (NGS) on DNA extracted from peripheral blood or bone marrow mononuclear cells at the time of presentation. *TP53*-mutated AML was defined by the presence of a pathogenic somatic *TP53* mutation with a VAF ≥10% (4), or any known mutation if VAF was unavailable.

Clinical Outcomes

The primary outcome was the composite complete remission (cCR) rate, defined as the sum of complete remission (CR) and CR with incomplete count recovery (CRi). Response was assessed according to the 2022 ELN criteria—following induction in the IC-treated group and at best response in the HMA+ven-treated group. The secondary outcome was overall survival (OS), defined as the time from initiation of therapy to death from any cause or censored at the date of last follow-up.

Statistical Analysis

Descriptive statistics were used to summarize both categorical and continuous variables. Categorical variables were presented as frequencies and percentages, with comparisons between groups performed using chi square test. Continuous variables were reported as medians with ranges and compared using the Wilcoxon rank-sum test. OS was estimated using the Kaplan–Meier method with 95% confidence intervals (CIs). Time-to-event outcomes were compared using log-rank tests. Cox proportional hazards models were used to assess the association between covariates and OS. Univariable models identified variables with p-values <0.10, which were then evaluated in multivariable models using backward elimination. Treatment type (HMA+ven vs. IC) was included as a predefined covariate. Transplant was modeled as a time-dependent covariate. Final model selection was based on the Akaike Information Criterion (AIC), with the optimal model yielding the lowest AIC value (AIC = 2755.17).

Pre-specified subgroups for comparative analysis included patients aged 60–75 years, those who underwent alloHSCT, individuals stratified by cytogenetic profile (CK/MK vs. inv(3)/t(3;3)), and by *TP53* mutation status.

Results

Patient Demographics and Baseline Characteristics by Treatment

Baseline characteristics are summarized in ***Table 1***. Of 1,198 patients with newly diagnosed AML, 358 (30%) had vHRC features. Median age was 67 years (range, 22–92), with balanced sex distribution across treatment groups.

Patients received IC (n=142, 40%) or HMA+ven (n= 216, 60%). Those receiving HMA+ven were older (median 72 vs. 60 years, p<0.001) and more likely to harbor MK (71% vs. 53%, p<0.001). Inv(3)/t(3;3) was more frequent in the IC group (14% vs. 7.4%, p=0.047). CK was comparably distributed (87% IC vs. 93% HMA+ven, p=0.10).

Prior myeloid malignancy was observed in 26% of IC-treated and 32% of HMA+ven-treated patients (p=0.24). Therapy-related AML occurred in 24% (IC) and 28% (HMA+ven) (p=0.39). Prior HMA exposure was 15% in IC vs. 9.3% in HMA+ven (p=0.093). Cytogenetic overlap was frequent, with most patients harboring multiple high-risk features. CK was found in 90.2% (n=323), MK in 64% (n=229), and inv(3)/t(3;3) in 10.1% (n=36).

Clonal Landscape and Mutational Spectrum

Targeted NGS panels identified ≥1 mutation in 91.6% of patients (n=328), with ≥2 mutations in 61.2% (n=219). Median number of mutations per patient was 2 (range, 0–7).

Figure 1 illustrates the clonal architecture by cytogenetic subgroup. In the overall vHRC cohort, the most common mutations were: *TP53* (50.6%), *TET2* (15%), *DNMT3A* (12.6%), *RUNX1* (11%), and *ASXL1* (10.6%). In CK/MK cases, the same mutations predominated: *TP53* (54%), *TET2* (15.8%), *DNMT3A* (12.4%), *RUNX1* (10.9%), and *ASXL1* (10.2%). Among inv(3)/t(3;3) cases, the most common mutations were *SF3B1* (30.6%), *NF1* (26.3%), *TP53* (19.4%), *WT1* (16.7%), and *PTPN11* (15.6%).

Table 2 summarizes mutational differences between cytogenetic subgroups. *TP53* mutations were significantly more common in CK/MK (54% vs. 19%, p<0.001). Conversely, mutations in *RAS* pathway genes (60% vs. 33%, p=0.014), *SF3B1* (31% vs. 4%, p<0.001), splicing factors (40% vs. 16%, p=0.002), *NF1* (26% vs. 8.8%, p=0.032), and *WT1* (17% vs. 0.6%, p<0.001) were more prevalent in inv(3)/t(3;3) AML.

De novo AML was more frequent among patients treated with IC than with HMA+ven (42% vs. 14%, p<0.001), and secondary ontogeny was likewise more common in the IC cohort (29% vs. 18%, p<0.001). Mutational landscapes also differed by treatment: *TP53* mutations were more frequent in patients receiving HMA+ven

(65% vs. 28%, p<0.001), whereas *FLT3* (9.2% vs. 3.7%, p=0.039), *GATA2* (4.3% vs. 0.5%, p=0.035), and *RAS* pathway mutations (57% vs. 28%, p<0.001) occurred more frequently in those receiving IC (***Table 1***).

Response Patterns and Treatment Outcomes

Table 3 summarizes response and outcome data. cCR rates were similar between IC and HMA+ven (54% vs. 55%, p=0.908). Among HMA+ven recipients, CR was 32.9%, CRh/CRi 21.8%, morphologic leukemia-free state (MLFS) 14%, and progressive disease (PD) 31.2%. In the IC group, CR was 50%, CRh/CRi 3.8%, MLFS 3.8%, and PD 42%.

Median OS for the vHRC cohort was 8.1 months (95% CI, 7.2–9.8), significantly shorter than non-vHRC AML (31 months; p<0.0001) (***Figure 2A***). In unadjusted analyses, vHRC patients treated with IC demonstrated longer OS than those receiving HMA+ven (11.0 vs. 6.5 months, p<0.0001) (***Figure 2B***).

Early mortality was comparable between IC and HMA+ven, with 30-day rates of 4.9% versus 4.6% (p>0.99) and 60-day rates of 9.9% versus 15% (p=0.15).

Response Patterns and Survival did not Differ Between IC and HMA+ven in Patients Aged 60–75 Years

As patients treated with HMA+ven were on average, older, a subgroup analysis was performed among individuals aged 60–75 years. Baseline demographic and disease characteristics for this age group are summarized in ***Supplemental Table 1***.

Among molecular subsets, treatment distribution did not differ significantly, with the exception of *TP53*-mutated disease, which was present in 52% of the cohort (n=95/184). Within this subgroup, 63% received HMA+ven and 33% received IC (p<0.001).

Response and transplantation outcomes for this subset are detailed in ***Supplemental Table 2***. Composite CR rates were comparable between IC- and HMA+ven-treated patients (50% vs. 53%, p=0.74). Overall, 54 patients (29%) proceeded to alloHSCT, with a significantly higher proportion among those initially treated with IC (42% vs. 22%, p=0.004). Median OS was not statistically different between treatment groups: 7.7 months (95% CI, 5.7–11) with IC versus 6.6 months (95% CI, 5.6–9.0) with HMA+ven (p=0.43; ***Figure 3A***). 30- and 60-day mortality rates were likewise similar between IC and HMA+ven (5.8% vs. 4.3%, p=0.73; 10% vs. 15%, p=0.50).

Survival After alloHSCT was Independent of Induction Strategy

Overall, 110 patients (31%) underwent alloHSCT in first complete remission (CR1), with a significantly higher proportion among those initially treated with IC (54% vs. 16% with HMA+ven, p<0.001). Median OS among transplanted patients did not differ by frontline therapy: 35 months (95% CI, 21–64) for IC versus 25 months

(95% CI, 19–NR) for HMA+ven (p=0.56; ***Figure 3B***). Twelve- and 24-month OS were 76% and 59% in the IC cohort, compared with 73% and 56% in the HMA+ven cohort, respectively.

In patients aged 60–75 years who underwent alloHSCT, median OS was likewise not significantly different by frontline regimen, with 16 months (95% CI, 12–51) for IC versus 27 months (95% CI, 18–NR) for HMA+ven (p=0.57; ***Figure 3C***). Twelve- and 24-month OS were 62% and 45% in the IC group and 75% and 57% in the HMA+ven group, respectively.

TP53-Mutated AML-vHRC was Associated with Poor Outcomes Irrespective of Treatment Regimen

Given that more than half of patients with vHRC harbored a *TP53* mutation (*TP53mt*), survival outcomes were analyzed according to *TP53mt* status and treatment strategy. When stratified by *TP53mt* status, patients with *TP53* wild-type (*TP53wt*) AML-vHRC had significantly superior outcomes compared with those carrying *TP53mt*, with median OS of 12.0 months (95% CI, 9.3–17) versus 6.2 months (95% CI, 5.2–7.8), respectively (p<0.0001; ***Figure 4A***).

Among *TP53*mt patients with concomitant vHRC, median OS was 6.2 months (95% CI, 5.2–7.8) and did not differ by treatment: 8.1 months (95% CI, 5.6–12) with IC versus 5.8 months (95% CI, 4.8–7.6) with HMA+ven (p=0.17; ***Figure 4B***). In the 60–75-year AML-vHRC subgroup with *TP53*mt, survival was likewise similar, with median OS of 5.7 months (95% CI, 3.4–11) for IC and 5.6 months (95% CI, 3.7–7.6) for HMA+ven (p=0.82; ***Supplemental Figure 1***). Twelve- and 24-month OS were 16% and 10% in the IC group versus 25% and 17% in the HMA+ven group, respectively.

By contrast, among *TP53wt* patients, in unadjusted analysis, IC conferred a significant survival advantage over HMA+ven, with median OS of 16.0 months (95% CI, 10–30) compared with 8.6 months (95% CI, 6.4–15) (p=0.0036; ***Figure 4C***).

AML with inv(3)/t(3;3) conferred a Significantly Worse Prognosis Compared with Cases Harboring CK/MK

To investigate differences in survival outcomes and treatment responses based on cytogenetic subtypes within the vHRC cohort, patients were stratified into two groups: those harboring CK/MK-AML and those harboring inv(3)/t(3;3) ***(Table 2).*** Treatment characteristics and clinical outcomes, stratified by vHRC subgroup, are summarized in ***Supplemental Table 3.***

Patients with inv(3)/t(3;3) were significantly less likely to achieve a cCR compared to those with CK/MK-AML (36% vs. 67%, p<0.001). Stratified by frontline treatment, patients with CK/MK-AML had a markedly higher likelihood of achieving cCR to IC than those with inv(3)/t(3;3) (58.7% vs. 22.2%, p=0.0047). Similarly, CK/MK-AML patients showed significantly higher cCR rates to HMA+ven than those with inv(3)/t(3;3) (58.1% vs. 26.7%, p=0.0279).

Overall, patients with inv(3)/t(3;3) exhibited poor survival, with a mOS of 6.8 months (95% CI, 5.7–18 months), showing an inferior trend compared to CK/MK (mOS: 8.3 months; 95% CI, 7.2–10 months), though not statistically significant (p=0.18) (***Figure 5A***). Stratified by treatment, CK/MK patients receiving IC showed a non-significant trend toward improved survival versus inv(3)/t(3;3) receiving IC (mOS: 12 months [95% CI, 9.0–22] vs. 10 months [95% CI, 5.6–35]; p=0.071) (***Figure 5B***). Among HMA+ven-treated patients, survival was comparable between groups: mOS 6.6 months (95% CI, 5.6–8.5) for CK/MK and 6.2 months (95% CI, 2.9–20) for inv(3)/t(3;3) (p=0.49) (***Figure 5C***).

Of note, the total number of patients with inv(3)/t(3;3) in our cohort was limited (n = 36), which constrained the reliability of subgroup analyses and precluded robust statistical inference. Of these 36 patients, 20 received intensive chemotherapy and 16 HMA+ven. Given that only 16 patients met criteria for ELN 2024 classification (7 favorable, 3 intermediate, and 6 adverse), the subgroup sizes were insufficient to support meaningful intergroup comparisons or formal statistical testing. Consequently, these data are presented in the *Supplementary Appendix* descriptively only, and no p-values are reported, consistent with the exploratory nature and inherent limitations of the available cohort. While these observations should be interpreted cautiously given the very small number of evaluable cases, they illustrate how evolving classification schemas may provide additional perspectives on the prognostic heterogeneity of inv(3)/t(3;3) AML. Nevertheless, when viewed through the lens of survival, the ELN 2024 categories showed some numerical separation. Patients classified as favorable had a median OS of 19 months, substantially longer than the 2.9 and 3.6 months observed in the intermediate- and adverse-risk groups, respectively. While these differences cannot be considered definitive given the small sample sizes, they suggest that the updated ELN 2024 framework may be capturing subtle gradations of prognosis within inv(3)/t(3;3) AML that have been previously underappreciated (corresponding descriptive data are shown in ***Supplemental Table 4*** and ***Supplemental Figure 2***).

No OS Difference Between Frontline HMA+ven and IC; *TP53* mutations and inv(3)/t(3;3) were Independent Adverse Predictors on Multivariable Analysis

Lastly, we conducted univariable and multivariable analyses to identify patient-, disease-, and treatment-related factors impacting survival in AML-vHRC (***Supplemental Table 5***). In univariable analysis, several variables were significantly associated with inferior survival, including age at diagnosis (HR: 1.03, 95% CI: 1.02–1.04, p<0.001), disease ontogeny—both secondary (HR: 1.50, 95% CI: 1.04–2.17, p=0.029) and *TP53*-mutated disease (HR: 2.27, 95% CI: 1.67–3.09, p<0.001)—therapy-relatedness (HR: 1.37, 95% CI: 1.06–1.78, p=0.017), prior cancer history (HR: 1.46, 95% CI: 1.13–1.89, p=0.04), prior chemotherapy (HR: 1.34, 95% CI: 1.02–1.76, p=0.039), prior HMA exposure (HR: 1.89, 95% CI: 1.36–2.65, p<0.001), history of alloHSCT (HR: 1.85, 95% CI: 1.16–2.95, p=0.010), monosomal karyotype (HR: 1.79, 95% CI: 1.38–2.32, p<0.001), *TP53* mutation (HR: 1.83, 95% CI: 1.44–2.33, p<0.001), and induction with HMA+ven compared to IC (HR: 1.81, 95% CI: 1.41–2.32, p<0.001). Mutations in *PTPN11* (HR: 1.47, 95% CI: 0.96–2.24, p=0.074) and *KRAS* (HR: 1.54, 95% CI: 0.96–2.45, p=0.071) were associated with a trend toward inferior survival. Notably, alloHSCT

modeled as a time-varying covariate was significantly associated with improved survival (HR: 0.22, 95% CI: 0.16–0.30, p<0.001). In contrast, *NRAS* mutations were linked to improved survival (HR: 0.60, 95% CI: 0.39–0.94, p=0.027), while *IDH1* (HR: 0.58, 95% CI: 0.31–1.09, p=0.092) and *IDH2* (HR: 0.56, 95% CI: 0.30–1.02, p=0.057) mutations showed a favorable trend nearing significance.

Multivariable analysis identified independent predictors of survival. The final model included age at diagnosis, secondary ontogeny, vHRC subtype (inv(3)/t(3;3) vs. CK/MK), induction treatment (HMA+ven vs. IC), *TP53*mt status, and transplant as a time-varying covariate. Age (HR: 1.02, 95% CI: 1.01–1.03; p=0.0003), prior myeloid disease (HR: 1.91, 95% CI: 1.48–2.47; p<0.0001), inv(3)/t(3;3) (HR: 2.12, 95% CI: 1.44–3.14; p=0.0002), and *TP53*mt status (HR: 2.07, 95% CI: 1.58–2.72; p<0.0001) were associated with inferior survival (***Figure 6***). Transplant remained significantly protective (HR: 0.42, 95% CI: 0.29–0.60; p<0.0001). Notably, induction strategy (HMA+ven vs. IC) did not significantly impact OS in the multivariable model (HR: 0.84, 95% CI: 0.62–1.15; p=0.2814).

Discussion

Although AML-vHRC is well recognized to confer poor survival within the ELN adverse-risk category, the optimal frontline approach—whether IC or lower-intensity therapy with HMA+ven—remains a matter of active debate. In our large multicenter cohort, we observed no significant difference in remission rates or OS between IC and HMA+ven among patients with AML-vHRC, after adjusting for age and other clinical covariates. Transplant emerged as the principal determinant of survival across treatment groups. Notably, two subsets of vHRC patients—those with inv(3)/t(3;3) and those with *TP53*mt disease—exhibited particularly low composite CR rates and markedly inferior survival.

Across the aggregate vHRC-AML cohort, survival was dismal with a median OS of only 8.0 months (95% CI, 7.2–9.8), significantly shorter than the 31 months observed in patients without vHRC (p<0.0001). These findings are consistent with prior reports: MK-AML carries a 4-year OS of less than 4%, improved to approximately 25% with alloHSCT (4); CK-AML in the pre–VIALE-A era demonstrated a median OS of 5–11 months (5); and AML with inv(3)/t(3;3) has been associated with median OS ranging from 5.9 to 7.9 months (6).

Our data reaffirm that these patients remain highly refractory to therapy. The cCR rate with HMA+ven was 55% (93/170), which compares favorably with earlier reports. This discrepancy may reflect the historically smaller cohorts treated with HMA+ven, a therapeutic strategy that only entered widespread use following the paradigm-shifting VIALE-A trial in 2020 (9). For example, in one of the largest retrospective series of inv(3)/t(3;3) AML published by the MD Anderson group, patients were notably enriched for *RAS* pathway mutations—a feature associated with an aggressive, proliferative phenotype and more recently implicated in resistance to venetoclax-based regimens (6,10–12). In that cohort, only 25% (2/8) achieved cCR with HMA+ven, compared with 54.5% (30/55) with intensive chemotherapy (6). This disparity in response may

reflect not only the limited number of patients exposed to venetoclax but also the intrinsic resistance conferred by *RAS* pathway mutations, which may attenuate the efficacy of BCL2 inhibition. Our improved cCR rates may reflect a larger, more heterogeneous population, but also underscore the potential limitations of HMA+ven in *RAS*-mutated AML.

The novelty of this study lies in its large, multicenter cohort, which permitted a direct comparison of IC and HMA+ven within a unified vHRC disease category. Our analysis focused on two prespecified subgroups: patients aged 60–75 years and those who subsequently underwent alloHSCT. While patients younger than 60 years are typically treated with IC and those older than 75 years with HMA+ven, therapeutic decision-making is most challenging for the intermediate 60–75-year age group and for transplant-eligible patients. In both contexts, we observed no difference in OS between IC and HMA+ven. Similarly, in the overall cohort, frontline regimen did not confer a survival advantage when adjusting for age, disease-specific covariates, and receipt of alloHSCT. However, given that only 13% of patients receiving HMA+ven were younger than 60 years compared with 49% of those receiving IC, our data cannot definitively establish non-inferiority of HMA+ven in this younger subset.

Against this backdrop, multiple randomized studies have directly compared intensive chemotherapy with lower-intensity regimens, collectively informing contemporary treatment selection and reinforcing the growing inclination toward less-intensive strategies in appropriate patient populations. A randomized trial conducted by the European Leukemia Cooperative Group (EORTC) demonstrated that 10-day decitabine monotherapy was equivalent to standard 7+3 in patients aged 60 years and older, with similar rates of transition to alloHSCT and comparable post-transplant outcomes, including among those with monosomal karyotypes and *TP53*-mutated disease (13). In the venetoclax era, a randomized study from China showed that decitabine/venetoclax was noninferior to 7+3 (idarubicin/cytarabine) in adults aged 18 to 59 years, again with similar proportions ultimately proceeding to alloHSCT (14). More recently, the randomized phase II PARADIGM trial (NCT04801797), comparing azacitidine/venetoclax with intensive chemotherapy in adults aged 18 years and older, has completed accrual; preliminary results to be presented at the 67th ASH Annual Meeting indicate that azacitidine/venetoclax achieved superior event-free survival, higher overall and composite complete response rates, a greater proportion of patients proceeding to alloHSCT, numerically fewer serious infectious complications, better early quality-of-life and symptom-burden scores, and substantially reduced ICU utilization and inpatient days, while overall survival data continue to mature (15). Taken together, these randomized data contextualize our findings and provide further rationale for considering HMA+ven as a frontline option in appropriate patients.

When viewed alongside these randomized data, our study similarly demonstrated that, 30- and 60-day mortality rates were comparable between frontline IC and HMA+ven, suggesting that HMA+ven may represent a compelling alternative for patients aged 60–75 years, for those intended to proceed to alloHSCT, and for those with *TP53mt* AML-vHRC, settings in which survival did not differ by regimen and toxicity considerations predominate. This regimen has consistently been associated with lower rates of treatment-related

complications, reduced financial burden, and decreased resource utilization, thereby mitigating strain on healthcare systems (16,17). Prior reports further demonstrate that HMA+ven is linked to shorter hospitalizations, largely attributable to less severe myelosuppression, a lower incidence of febrile neutropenia, and fewer infectious complications, in contrast to IC regimens, which typically necessitate prolonged inpatient care for neutropenia management and infection treatment (18,19). By contrast, among *TP53-wild-type* AML-vHRC, unadjusted OS favored IC, and in inv(3)/t(3;3) AML—particularly when *RAS* pathway–mutated—responses to venetoclax-based therapy may be attenuated; in these contexts, enthusiasm for HMA+ven should be tempered and clinical-trial enrollment or IC considered when feasible.

These observations carry particular relevance in light of the persistent lack of expert consensus regarding the optimal frontline regimen for older adults with *TP53*-mutated AML. A recent Delphi survey demonstrated no agreement on whether intensive chemotherapy or HMA+ven should be preferentially recommended, underscoring the continued uncertainty that surrounds therapeutic decision-making in this genomically defined subgroup (20). Within this setting of unresolved clinical guidance, our findings align with the growing inclination toward less-intensive strategies, particularly when the overarching objective is expeditious progression to alloHSCT (13,14). Furthermore, prior studies have consistently shown that HMA+ven is associated with shorter hospitalizations and reduced requirements for broad-spectrum antibiotics and other supportive-care interventions, reinforcing its practicality in clinical environments where intensive chemotherapy is frequently complicated by prolonged neutropenia, mucositis, and infectious morbidity (14,18,19,21). These considerations are further supported by emerging randomized evidence, including the PARADIGM trial (15).

Biologic drivers of poor prognosis were evident within specific vHRC subsets. In CK/MK-AML, adverse outcomes and therapeutic resistance were predominantly driven by *TP53* mutations, as patients with *TP53*wt AML-vHRC experienced significantly superior survival compared with those harboring *TP53mt*, with median OS of 12.0 versus 6.2 months ($p<0.0001$). Similarly, patients with inv(3)/t(3;3) exhibited distinctly treatment-refractory disease biology, achieving cCR in only 36% of cases compared with 67% in CK/MK AML ($p<0.001$). Patients with CK/MK were more likely to respond to both IC (cCR 59%) and HMA+ven (cCR 58%) than those with inv(3)/t(3;3), in whom cCR rates were 22% and 27%, respectively. These findings suggest that AML with inv(3)/t(3;3) constitutes a distinct, highly treatment-resistant subgroup within the spectrum of AML-vHRC. Accordingly, this cytogenetic subset may warrant hierarchical prioritization over CK/MK in disease taxonomy and prognostic classification systems, particularly when co-occurring with other vHRC features.

Multivariable analysis demonstrated that alloHSCT was significantly associated with improved survival, representing the only potentially curative option among currently available treatment modalities. Notably, survival among transplanted patients was not significantly influenced by induction regimen (IC vs. HMA+ven). Accordingly, donor identification should be initiated without delay in eligible patients, and transplantation pursued as expediently as possible. Given the high risk of relapse, these patients should also be prioritized for clinical trials investigating post-transplant maintenance strategies to reduce relapse incidence.

This study is subject to limitations inherent in its retrospective design, particularly with respect to data collection and treatment selection across diverse institutions. While the cross-institutional setting is a strength in terms of cohort size and diversity, it also introduces potential sources of variability. First, heterogeneity in patient populations across centers may have contributed to differences in treatment response due to variation in demographic and disease characteristics. Second, treatment selection bias based on underlying disease biology must be acknowledged. In our cohort, patients with *TP53*-mutated disease were less likely to receive IC, reflecting established evidence that this mutation portends poor outcomes (22,23); consequently, HMA+ven was preferentially employed in an effort to optimize response and enable eventual transplant (24,25). Despite these limitations, the study provides important insights into real-world outcomes across diverse care environments and underscores the need for prospective evaluation to validate these findings.

In addition to these methodological constraints, the retrospective nature of the study precluded the collection of longitudinal patient-reported outcomes or formal measures of quality of life during or after treatment with IC versus HMA+ven. This represents an important limitation, as regimen selection in older or transplant-eligible patients with AML-vHRC is often influenced not only by efficacy considerations but also by perceived treatment burden and functional impact. Consistent with the clinical relevance of this consideration, in a large international randomized trial of fit older adults with AML, decitabine induction was associated with a significantly lower risk of early deterioration in health-related quality of life at 2 months—driven predominantly by reductions in patient-reported burden of illness—while longer-term quality-of-life trajectories were broadly comparable between decitabine and 7+3, with exploratory analyses suggesting less clinically meaningful post-transplant quality-of-life decline among patients bridged with decitabine (26). Emerging randomized data, including preliminary results from the PARADIGM trial, suggest that azacitidine/venetoclax may be associated with better early quality-of-life and symptom-burden scores and fewer ICU admissions and inpatient days compared with intensive chemotherapy in fit adults with newly diagnosed AML (15); however, these findings have not been specifically validated in genomically defined very high-risk subsets. Furthermore, granular molecular features such as measurable residual disease status and *TP53* allelic state (monoallelic vs. biallelic), which increasingly inform prognostic and therapeutic interpretation, were not uniformly available in our cohort. Future prospective trials comparing intensive and de-escalated approaches in AML-vHRC should therefore incorporate serial, longitudinal quality-of-life assessments alongside systematic MRD evaluation and comprehensive *TP53* characterization to more rigorously define differential tolerability, disease kinetics, and clinical benefit across treatment strategies.

In summary, this large multicenter cohort confirms that survival in AML-vHRC remains poor overall. Among patients aged 60–75 years, those with *TP53* mutations, and those undergoing alloHSCT after initial therapy, OS did not differ significantly between IC and HMA+ven. In these settings, HMA+ven can be reasonably considered as frontline therapy, particularly when followed by timely alloHSCT in appropriate candidates given its comparatively favorable tolerability profile. Nonetheless, the persistently poor outcomes observed across

AML-vHRC underscore the urgent need for prospective studies and the development of novel therapeutic strategies aimed at improving survival in this high-risk population.

Acknowledgements
Portions of this work were presented in preliminary form at the 2024 American Society of Hematology (ASH) Annual Meeting in San Diego, California, where it received a 2024 ASH Abstract Achievement Award. We are grateful to ASH for the opportunity to disseminate these findings and for their recognition of this contribution. Elements of this manuscript also formed part of the capstone project for Dr. Luis E. Aguirre's Master of Public Health degree at the Harvard T.H. Chan School of Public Health (Class of 2026).

We further acknowledge the Dana-Farber Cancer Institute Hematologic Malignancies Data Repository (DFCI HMDR) for its essential support and integral contributions to the development of this study.

Sources of Funding: The authors declare no sources of funding

Authorship Contributions

1. Conception and design: LA, MS
2. Administrative support: YL, RB, MS
3. Provision of study materials or patients: LA, RB, MS, and all other authors
4. Collection and assembly of data: LA, YL, RB, LB, AZ, SG, MS
5. Data analysis and interpretation: LA, YL, MS
6. Manuscript writing: LA, MS
7. Final approval of manuscript: All authors

Reporting Checklist: The authors have completed the STROBE reporting checklist

Disclosure of Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form.

Luis E. Aguirre: Consultancy for Cardinal Health, Research To Practice. Honoraria from Cardinal Health, DAVA Oncology.

Jan Philipp Bewersdorf: No COI disclosed.

Yiwen Liu: No COI disclosed.

Rory M. Shallis: Consultancy/advisory and honoraria from Servier (also serves on Steering Committee), Rigel, Kura Oncology, and Gilead Sciences

Leora Boussi: No COI disclosed.

Andrius Zucenka: Consultancy and/or honoraria from Pfizer, Astellas, AbbVie, Novartis, and Johnson & Johnson; travel support from AbbVie, Novartis, Johnson & Johnson, and Takeda.

Sylvain Garciaz: Consultancy/advisory and/or honoraria from Janssen, Servier, and AbbVie; consultancy from ImCheck Therapeutics, Sanofi, AbbVie, and Bristol Myers Squibb; travel grants from Sanofi and AbbVie.

Rebecca P. Bystrom: No COI disclosed.

Daniel J. DeAngelo: Consultancy for Kite, Servier, Incyte, Pfizer, Gilead, Novartis, Jazz, Autolos, Amgen, and Blueprint; Honoraria from Amgen and Bristol-Meyers Squibb; Research funding from Servier, Novartis, Glycomimetics, AbbVie, and Takeda; Other: DSMB for MT Sinai MPN Consortium, Fibrogen, Daiichi-Sankyo.

Richard M. Stone: Research funding from Janssen and AbbVie; Consultancy for Glaxosmithkline, Curis Oncology, Daiichi Sankyo, ENSEM, Epizyme, BerGenBio, AMGEN, Syntrix, Hermavant, Glycomimetrics, CTI Biopharma, Bristol Meyers Squibb, Rigel, Syndax, AvenCell, Takeda, Jazz, Kura Oncology, Lava Therapeutics, Cellarity, Ligand Pharma, Novartis, Aptevo, and Redona therapeutics; Other: DSMB for Epizyme, Syntrix, Takeda, and Novartis.

Marlise R. Luskin: Honoraria from Pfizer, KITE, Jazz, and AbbVie; Research funding from Novartis and AbbVie.

Jacqueline S. Garcia: Research funding from Newave and Taiho; Consultancy for Servier, AbbVie, and Genentech; Membership on the Board of Directors or advisory committees for Genentech; Research funding from AbbVie and Genentech.

Eric S. Winer: No COI disclosed.

Kelly Ling: No COI disclosed.

Evan C. Chen: : Advisory boards for AbbVie, Rigel, and Syndax. Consultancy for Merck, Guidepoint, GLG, Dedham Group, Capvision, Third Bridge, Atheneum. Research funding from Takeda, Arcellx, BEAM Therapeutics, Abbvie .

Martha Wadleigh: No COI disclosed.

Guillaume Berton: No COI disclosed.

Eytan M. Stein: Consultancy/advisory and consulting fees from AstraZeneca, Servier, Agios Pharmaceuticals, Genentech, Gilead, Jazz Pharmaceuticals, AbbVie, Daiichi Sankyo, Celgene (Bristol Myers Squibb), and Astellas.

Aaron D. Goldberg: Consultancy/advisory roles and/or board/advisory committee memberships with Astellas, Bristol Myers Squibb, Molecular Partners, Syndax, Genentech, AbbVie, and Daiichi Sankyo; consultancy with Ikena Oncology; honoraria from Kura Oncology and DAVA Oncology; research funding from Aptose, Pfizer, Celularity, Kura Oncology, Aprea, AbbVie, and AROG.

Lourdes Mendez: No COI disclosed.

Amer M. Zeidan: Consultancy/advisory and/or honoraria from AbbVie, Agios, Akesobio, Amgen, Astellas, BeiGene, BioCryst, Boehringer Ingelheim, Bristol Myers Squibb (including Celgene), Chiesi/Cornerstone Biopharma, Daiichi Sankyo, Dr. Reddy's Laboratories, Epizyme, Faron, FibroGen, Genentech, Geron, Gilead, GlaxoSmithKline (GSK), GlycoMimetics, Janssen, Jasper Therapeutics, Karyopharm Therapeutics, Keros Therapeutics, Kura Oncology, Kyowa Kirin, Lava Therapeutics, Notable, Novartis, Orum, Otsuka, Pfizer, Regeneron, Rigel, Schrödinger, Seagen (formerly Seattle Genetics), Servier, Shattuck Labs, Syndax, Syros, Taiho, Takeda, Treadwell Therapeutics, Vincerx, and Zentalis.

David A. Sallman: Research funding from Syntrix Pharmaceuticals; Membership on the Board of Directors or advisory committees for Nemucore, Lixte, Novartis, Intellia, Syndax, Kite, Shattuck Labs, BMS, Aprea, Agios, AbbVie, and Takeda; Patents & Royalties for LB-100 (Lixte); Consultancy for Magenta, Novartis, Intellia, Syndax, Kite, Incyte, Shattuck Labs, BMS, Aprea, Agios, AbbVie, and Takeda; Speakers Bureau for Incyte, BMS.

Shai O. Shimony: No COI disclosed.

Maximilian Stahl: Advisory board for Novartis, Kymera, Sierra Oncology, GSK, Rigel, BMS, Sobi and Syndax, Kura; consulted for Boston Consulting, GLG and Dedham group and participated in CME activity for Novartis, Curis Oncology, Haymarket Media and Clinical Care Options and is member of the Medical Safety Monitoring Board for Keros Pharmaceuticals.

All other authors have no conflicts of interest to declare.

References

1. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345-1377. doi:10.1182/blood.2022016867
2. Döhner H, DiNardo CD, Appelbaum FR, et al. Genetic risk classification for adults with AML receiving less-intensive therapies: the 2024 ELN recommendations. Blood. 2024;144(21):2169-2173. doi:10.1182/blood.2024025409
3. Medeiros BC, Othus M, Fang M, Roulston D, Appelbaum FR. Prognostic impact of monosomal karyotype in young adult and elderly acute myeloid leukemia: the Southwest Oncology Group (SWOG) experience. *Blood*. 2010;116(13):2224-2228. doi:10.1182/blood-2010-02-270330
4. Fang M, Storer B, Estey E, et al. Outcome of patients with acute myeloid leukemia with monosomal karyotype who undergo hematopoietic cell transplantation. Blood. 2011;118(6):1490-1494. doi:10.1182/blood-2011-02-339721
5. Mrózek K. Cytogenetic, molecular genetic, and clinical characteristics of acute myeloid leukemia with a complex karyotype. Semin Oncol. 2008;35(4):365-377. doi:10.1053/j.seminoncol.2008.04.007
6. Richard-Carpentier G, Rausch CR, Sasaki K, et al. Characteristics and clinical outcomes of patients with acute myeloid leukemia with inv(3)(q21q26.2) or t(3;3)(q21;q26.2). Haematologica. 2023;108(9):2331-2342.
7. Moscvin M, Schwede M, Mannis G, Zhang TY. Acute myeloid leukemia with inv(3) or t(3;3): A clinical and cytogenetic characterization of 40 patients. Blood. 2023;142(Suppl 1):4231.
8. Lugthart S, Gröschel S, Beverloo HB, et al. Clinical, molecular, and prognostic significance of WHO type inv(3)(q21q26.2)/t(3;3)(q21;q26.2) and various other 3q abnormalities in acute myeloid leukemia. J Clin Oncol. 2010;28(24):3890-3898. doi:10.1200/JCO.2010.29.2771
9. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med. 2020;383(7):617-629. doi:10.1056/NEJMoa2012971
10. Sango J, Carcamo S, Sirenko M, et al. RAS-mutant leukaemia stem cells drive clinical resistance to venetoclax. Nature. 2024;636(8041):241-250. doi:10.1038/s41586-024-08137-x
11. Gröschel S, Sanders MA, Hoogenboezem R, et al. Mutational spectrum of myeloid malignancies with inv(3)/t(3;3) reveals a predominant involvement of RAS/RTK signaling pathways. Blood. 2015;125(1):133-139. doi:10.1182/blood-2014-07-591461
12. Halaburda K, Labopin M, Houhou M, et al. AlloHSCT for inv(3)(q21;q26)/t(3;3)(q21;q26) AML: a report from the acute leukemia working party of the European society for blood and marrow transplantation. Bone Marrow Transplant. 2018;53(6):683-691. doi:10.1038/s41409-018-0165-x
13. Lübbert M, Wijermans PW, Kicinski M, et al. 10-day decitabine versus 3 + 7 chemotherapy followed by allografting in older patients with acute myeloid leukaemia: an open-label, randomised, controlled, phase 3 trial. Lancet Haematol. 2023;10(11):e879-e889. doi:10.1016/S2352-3026(23)00273-9
14. Lu J, Xue SL, Wang Y, et al. Venetoclax and decitabine vs intensive chemotherapy as induction for young patients with newly diagnosed AML. Blood. 2025;145(22):2645-2655. doi:10.1182/blood.2024027217
15. Fathi A, Perl A, Fell G, et al. Results from paradigm – a phase 2 randomized multi-center study comparing azacitidine and venetoclax to conventional induction chemotherapy for newly diagnosed fit adults with acute myeloid leukemia. Presented at: 67th ASH Annual Meeting and Exposition; 2025. Accessed November 22, 2025. https://meetings-api.hematology.org/api/abstract/vmpreview/29688
16. Pratz KW, Chai X, Xie J, et al. Cost-Effectiveness Analysis of Venetoclax in Combination with Azacitidine Versus Azacitidine Monotherapy in Patients with Acute Myeloid Leukemia Who are Ineligible for Intensive Chemotherapy: From a US Third Party Payer Perspective. Pharmacoeconomics. 2022;40(8):777-790. doi:10.1007/s40273-022-01145-7
17. Choi M, Song J, Bui CN, et al. Costs per patient achieving remission with venetoclax-based combinations in newly diagnosed patients with acute myeloid leukemia ineligible for intensive induction chemotherapy. *J Manag Care Spec Pharm*. 2022;28(9):980-988. doi:10.18553/jmcp.2022.22021
18. Matthews AH, Perl AE, Luger SM, et al. Real-world effectiveness of CPX-351 vs venetoclax and azacitidine in acute myeloid leukemia. Blood Adv. 2022;6(13):3997-4005. doi:10.1182/bloodadvances.2022007265
19. Desai P, Garcia JS, Zeidner JF, et al. Comparative analysis of clinical outcomes and healthcare resource utilization (HRU) in patients (pts) with newly diagnosed (ND) acute myeloid leukemia (AML) unfit for high-intensity chemotherapy treated with venetoclax (VEN) vs other therapies: results from the AML real world evidence (ARC) initiative. Blood. 2023;142(Suppl 1):5173.
20. Venditti A, Palmieri R, Maurillo L, et al. Fitness assessment in acute myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood Adv. 2025;9(9):2207-2220. doi:10.1182/bloodadvances.2024013744
21. Matthews AH, Perl AE, Luger SM, et al. Real-world effectiveness of intensive chemotherapy with 7&3 versus venetoclax and hypomethylating agent in acute myeloid leukemia. Am J Hematol. 2023;98(8):1254-1264. doi:10.1002/ajh.26991
22. Stengel A, Kern W, Haferlach T, Meggendorfer M, Fasan A, Haferlach C. The impact of *TP53* mutations and *TP53* deletions on survival varies between AML, ALL, MDS and CLL: an analysis of 3307 cases. Leukemia. 2017;31:705–11.

23. Weinberg OK, Siddon A, Madanat YF, et al. *TP53* mutation defines a unique subgroup within complex karyotype de novo and therapy-related MDS/AML. Blood Adv. 2022;6(9):2847-2853. doi:10.1182/bloodadvances.2021006239
24. DiNardo CD, Pratz K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood. 2019;133(1):7-17. doi:10.1182/blood-2018-08-868752
25. Pollyea DA, Pratz KW, Wei AH, Pullarkat V, Jonas BA, Recher C, et al. Outcomes in Patients with Poor-Risk Cytogenetics with or without TP53 Mutations Treated with Venetoclax and Azacitidine. Clin Cancer Res. 2022;28:5272–9
26. Efficace F, Kicinski M, Coens C, et al. Decitabine in older patients with AML: quality of life results of the EORTC-GIMEMA-GMDS-SG randomized phase 3 trial. Blood. 2024;144(5):541-551. doi:10.1182/blood.2023023625

Table 1. Baseline Demographic and Disease Characteristics of Patients with AML with Very High-Risk Cytogenetics, Stratified by Induction Treatment (Intensive Chemotherapy vs. HMA plus venetoclax)

Characteristic	N	Overall, N = 358	IC, N = 142 (40%)	HMA+VEN, N = 216 (60%)	p-value
Age at diagnosis, Median (Range)	358	67 (22, 92)	60 (23, 79)	72 (22, 92)	**<0.001**
Age at diagnosis, n / N (%)	358				**<0.001**
< 60		98 / 358 (27%)	69 / 142 (49%)	29 / 216 (13%)	
> 75		76 / 358 (21%)	4 / 142 (2.8%)	72 / 216 (33%)	
60<= age <=75		184 / 318 (51%)	69 / 142 (49%)	115 / 216 (53%)	
Sex, n / N (%)	358				0.52
Male		199 / 358 (56%)	82 / 142 (58%)	117 / 216 (54%)	
Female		159 / 358 (44%)	60 / 142 (42%)	99 / 216 (46%)	
Antecedent MN, n / N (%)	358	106 / 358 (30%)	37 / 142 (26%)	69 / 216 (32%)	0.24
Therapy-relatedness, n / N (%)	358	95 / 358 (27%)	34 / 142 (24%)	61 / 216 (28%)	0.39
Prior HMA Treatment, n / N (%)	358	42 / 358 (12%)	22 / 142 (15%)	20 / 216 (9.3%)	0.093
Cytogenetics					
Monosomal KT, n / N (%)	358	229 / 358 (64%)	75 / 142 (53%)	154 / 216 (71%)	**<0.001**
Complex KT, n / N (%)	357	323 / 357 (90%)	123 / 141 (87%)	200 / 216 (93%)	0.10
Complex/Monosomal, n / N (%)	358	322 / 358 (90%)	122 / 142 (86%)	200 / 216 (93%)	**0.048**
inv(3)/t(3;3), n / N (%)	358	36 / 358 (10%)	20 / 142 (14%)	16 / 216 (7.4%)	**0.047**
5qdel.5del, n / N (%)	358	151 / 358 (42%)	40 / 142 (28%)	111 / 216 (51%)	**<0.001**
7del., n / N (%)	358	129 / 358 (36%)	40 / 142 (28%)	89 / 216 (41%)	**0.013**
17del.17pabn., n / N (%)	358	89 / 358 (25%)	21 / 142 (15%)	68 / 216 (31%)	**<0.001**
Mutations					
AML Ontogeny, n / N (%)	358				**<0.001**
De novo		89 / 358 (25%)	59 / 142 (42%)	30 / 216 (14%)	
Secondary		79 / 358 (22%)	41 / 142 (29%)	38 / 216 (18%)	
TP53		181 / 358 (51%)	40 / 142 (28%)	141 / 216 (65%)	
***TP53,* n / N (%)**		181 / 358 (51%)	40 / 142 (28%)	141 / 216 (65%)	**<0.001**
***TP53* VAF, n / N (%)**	172				>0.99
<10%		9 / 172 (5.2%)	2 / 42 (4.8%)	7 / 130 (5.4%)	
>10%		136 / 172 (79%)	37 / 42 (88%)	99 / 130 (76%)	
***FLT3*, n / N (%)**	358	21 / 358 (5.9%)	13 / 142 (9.2%)	8 / 216 (3.7%)	**0.039**
FLT3-ITD, n / N (%)	358	11 / 358 (3.1%)	6 / 142 (4.2%)	5 / 216 (2.3%)	0.039
FLT3-TKD, n / N (%)	358	11 / 358 (3.1%)	7 / 142 (4.9%)	4 / 216 (1.9%)	0.039
***GATA2*, n / N (%)**	296	5 / 296 (1.7%)	4 / 93 (4.3%)	1 / 203 (0.5%)	**0.035**
***IDH*, n / N (%)**	358	33 / 358 (9.2%)	17 / 142 (12%)	16 / 216 (7.4%)	0.19
***NRAS/KRAS*, n / N (%)**	358	49 / 358 (14%)	31 / 142 (22%)	18 / 216 (8.3%)	**<0.001**
***RAS* pathway, n / N (%)**	261	94 / 261 (36%)	43 / 76 (57%)	51 / 185 (28%)	**<0.001**
Splicing factor mutations, n / N (%)	339	64 / 339 (19%)	29 / 126 (23%)	35 / 213 (16%)	0.15

Table 2. Baseline Demographic and Disease Characteristics of Patients with AML with Very High-Risk Cytogenetics, Stratified by Cytogenetic Subgroup (CK/MK vs. inv(3)/t(3;3))

Characteristic	N	Overall, N = 358 (100%)	CK/MK, N = 322 (90%)	inv(3)/t(3;3), N = 36 (10%)	p-value
Age at diagnosis, Median (Range)	358	67 (22, 92)	67 (22, 92)	65 (30, 87)	0.44
Age at diagnosis, n / N (%)	358				0.30
< 60		98 / 358 (27%)	87 / 322 (27%)	11 / 36 (31%)	
> 75		76 / 358 (21%)	72 / 322 (22%)	4 / 36 (11%)	
60<= age <=75		184 / 358 (51%)	163 / 322 (51%)	21 / 36 (58%)	
Sex, n / N (%)	358				>0.99
Male		199 / 358 (56%)	179 / 322 (56%)	20 / 36 (56%)	
Female		159 / 358 (44%)	143 / 322 (44%)	16 / 36 (44%)	
Antecedent MN, n / N (%)	358	106 / 358 (30%)	98 / 322 (30%)	8 / 36 (22%)	0.34
Therapy-relatedness, n / N (%)	358	95 / 358 (27%)	84 / 322 (26%)	11 / 36 (31%)	0.55
Prior HMA Treatment, n / N (%)	358	42 / 358 (12%)	36 / 322 (11%)	6 / 36 (17%)	0.41
Allogeneic SCT, n / N (%)	358	20 / 358 (5.6%)	19 / 322 (5.9%)	1 / 36 (2.8%)	0.71
Cytogenetics					
Monosomal KT, n / N (%)	358	229 / 358 (64%)	206 / 322 (64%)	23 / 36 (64%)	>0.99
Complex KT, n / N (%)	357	323 / 357 (90%)	308 / 322 (96%)	15 / 35 (43%)	**<0.001**
inv(3)/t(3;3), n / N (%)	357	36 / 357 (10%)	0 / 321 (0%)	36 / 36 (100%)	**<0.001**
5qdel.5del, n / N (%)	358	151 / 358 (42%)	145 / 322 (45%)	6 / 36 (17%)	**0.001**
7del., n / N (%)	358	129 / 358 (36%)	112 / 322 (35%)	17 / 36 (47%)	0.15
17del.17pabn., n / N (%)	358	89 / 358 (25%)	84 / 322 (26%)	5 / 36 (14%)	0.15
Mutations					
AML Ontogeny, n / N (%)	358				**<0.001**
De novo		89 / 358 (25%)	77 / 322 (24%)	12 / 36 (33%)	
Secondary		79 / 358 (22%)	63 / 322 (20%)	16 / 36 (44%)	
TP53		190 / 358 (53%)	182 / 322 (57%)	8 / 36 (22%)	
***TP53*, n / N (%)**	358	181 / 358 (51%)	174 / 322 (54%)	7 / 36 (19%)	**<0.001**
***TP53* VAF, n / N (%)**	172				0.35
<10%		10 / 172 (5.8%)	9 / 165 (5.5%)	1 / 7 (14%)	
>10%		162 / 172 (94%)	156 / 165 (95%)	6 / 7 (86%)	
***FLT3*, n / N (%)**	358	21 / 358 (5.9%)	18 / 322 (5.6%)	3 / 36 (8.3%)	0.46
FLT3-ITD, n / N (%)	358	11 / 358 (3.1%)	8 / 322 (2.5%)	3 / 36 (8.3%)	0.088
FLT3-TKD, n / N (%)	358	11 / 358 (3.1%)	10 / 322 (3.1%)	1 / 36 (2.8%)	>0.99
***IDH*, n / N (%)**	358	33 / 358 (9.2%)	31 / 322 (9.6%)	2 / 36 (5.6%)	0.56
***NRAS*, n / N (%)**	358	31 / 358 (8.7%)	26 / 322 (8.1%)	5 / 36 (14%)	0.22
***NRAS/KRAS*, n / N (%)**	358	49 / 358 (14%)	40 / 322 (12%)	9 / 36 (25%)	0.068
***RAS* pathway, n / N (%)**	261	94 / 261 (36%)	79 / 236 (33%)	15 / 25 (60%)	**0.014**
***SF3B1*, n / N (%)**	358	24 / 358 (6.7%)	13 / 322 (4.0%)	11 / 36 (31%)	**<0.001**
Secondary Splicing, n / N (%)	339	64 / 339 (19%)	50 / 304 (16%)	14 / 35 (40%)	**0.002**
***NF1*, n / N (%)**	223	23 / 223 (10%)	18 / 204 (8.8%)	5 / 19 (26%)	**0.032**
***WT1*, n / N (%)**	355	8 / 355 (2.3%)	2 / 319 (0.6%)	6 / 36 (17%)	**<0.001**

Table 3. Response and Transplantation Rates in Patients with AML with Very High-Risk Cytogenetics, Stratified by Induction Therapy (IC vs. HMA plus venetoclax)

Characteristic	N	Overall, N = 358 (100%)	IC, N = 142 (40%)	HMA+VEN, N = 216 (60%)	p-value
Response Pattern, n / N (%)	**302**		132	170	
CR		122 / 302 (40%)	66 / 132 (50%)	56 / 170 (33%)	
CRh/CRi		42 / 302 (14%)	5 / 132 (3.8%)	37 / 170 (22%)	
MLFS		28 / 302 (9.3%)	5 / 132 (3.8%)	23 / 170 (14%)	
PR		1 / 302 (0.3%)	0 / 132 (0%)	1 / 170 (0.6%)	
PD		109 / 302 (36%)	56 / 132 (42%)	53 / 170 (31%)	
cCR (CR + CRh/CRi), n / N (%)		**164 / 302 (54%)**	**71 / 132 (54%)**	**93 / 170 (55%)**	**0.908**
Proceeded to alloHSCT, n / N (%)	358	110 / 358 (31%)	76 / 142 (54%)	34 / 216 (16%)	**<0.001**

Figure Legends

Figure 1. Mutational landscape stratified by cytogenetic phenotype. Comprehensive depiction of the clonal architecture and mutational distribution at diagnosis. Mutations are displayed in ranked bar plots by frequency and are stratified by vHR cytogenetic subgroups: CK/MK and chromosome 3-related abnormalities. Statistical comparisons were performed using Fisher's exact test. Asterisks on top of the bars denote statistical significance: $p < 0.05$ (*). Among patients harboring CK and/or MK, the five most frequent mutations were: *TP53* (54%, n=174), *TET2* (15.8%, n=51), *DNMT3A* (12.4%, n=40), *RUNX1* (10.9%, n=35), and *ASXL1* (10.2%, n=33). In contrast, among those harboring inv(3)(q21q26.2)/t(3;3)(q21;q26.2), the most common mutations included: *SF3B1* (30.6%, n=11), *NF1* (26.3%, n=5), *TP53* (19.4%, n=7), *WT1* (16.7%, n=6), and *PTPN11* (15.6%, n=5).

Figure 2. Patient outcomes by cytogenetic profile and treatment received. Kaplan-Meier estimates are shown for patients stratified by cytogenetic status (Panel A) and for those with very high-risk (vHR) AML based on treatment received (Panel B). Panel A: Patients with vHR cytogenetics (blue) had inferior survival compared to those without (red); median OS: 8.1 months (95% CI: 6.2–10) vs. 31 months (95% CI: 25–44), respectively. Panel B: Among vHR AML patients, median OS was 11 months (95% CI: 9.0–18) for those treated with intensive chemotherapy (IC; red) vs. 6.5 months (95% CI: 5.7–8.1) for those treated with HMA plus venetoclax (HMA+ven; blue).

Figure 3. OS by treatment regimen in patients with AML-vHRC aged 60–75 and in those undergoing alloHSCT. Kaplan-Meier estimates are shown for patients aged 60–75 (Panel A), all transplanted patients (Panel B), and transplanted patients aged 60–75 (Panel C), stratified by induction regimen: intensive chemotherapy (IC, red) vs. hypomethylating agent plus venetoclax (HMA+ven, blue). Panel A: Median OS was similar between IC (7.7 months; 95% CI: 5.7–11) and HMA+ven (6.6 months; 95% CI: 5.6–9.0); $p = 0.43$. Panel B: Among all alloHSCT recipients, median OS did not differ by induction regimen (35 months [95% CI: 21–64] for IC vs. 25 months [95% CI: 19–NR] for HMA+ven; $p = 0.56$). Panel C: Among alloHSCT recipients aged 60–75, median OS was 16 months (95% CI: 12–51) for IC and 27 months (95% CI: 18–NR) for HMA+ven ($p = 0.57$).

Figure 4. OS by treatment regimen in patients with AML-vHRC stratified by *TP53* mutation status. Kaplan-Meier estimates are shown for patients with *TP53mt* (Panel A), *TP53* wild-type (Panel B), and *TP53mt* patients aged 60–75 (Panel C), stratified by induction regimen: intensive chemotherapy (IC, red), versus HMA with venetoclax, (HMA+ven, blue). Panel A: In *TP53mt* AML, median OS was similar between IC (8.1 months; 95% CI: 5.6–12) and HMA+ven (5.8 months; 95% CI: 4.8–7.6); $p = 0.17$. Panel B: *TP53mt* status greatly impacted survival in AML with vHR cytogenetics, with a median of 12 months (95% CI: 9.3-17) in *TP53* wild-type cases vs. 6.2 months (95% CI: 5.2–7.8) in those harboring *TP53mt*; $p<0.0001$). Panel C: In *TP53* wild-type AML, median OS was significantly longer with IC (16 months; 95% CI: 10–30) compared to HMA+ven (8.6 months; 95% CI: 6.4–15); $p = 0.0036$.

Figure 5. OS in AML-vHRC by cytogenetic subgroup and treatment received. Kaplan-Meier estimates are shown for patients with vHR AML based on cytogenetic subgroup (Panel A), and stratified by cytogenetic pattern among those treated with intensive chemotherapy (IC; Panel B) or HMA plus venetoclax (HMA+ven; Panel C). Patients with CK/MK are shown in red, those with inv(3)(q21q26.2)/t(3;3)(q21;q26.2) in blue. Panel A: Median OS was 6.8 months (95% CI: 5.7–18) for inv(3)(q21q26.2)/t(3;3)(q21;q26.2) vs. 8.3 months (95% CI: 7.2–10) for CK/MK; p=0.18. Panel B: Among IC-treated patients, median OS was 12 months (95% CI, 9.0–22) for CK/MK vs. 10 months (95% CI: 95% CI, 5.6–35) for inv(3)(q21q26.2)/t(3;3)(q21;q26.2); p=0.071. Panel C: Among HMA+ven–treated patients, median OS was 6.6 months (95% CI: 5.6–8.5) for CK/MK vs. 6.2 months (95% CI: 2.9-20) for inv(3)(q21q26.2)/t(3;3)(q21;q26.2); p=0.49.

Figure 6. Multivariable analysis of overall survival in AML-vHRC. Covariates included age at diagnosis, disease ontogeny (secondary vs. de novo), vHRC subgroup (inv(3)(q21q26.2) or t(3;3)(q21;q26.2) vs. CK/MK), induction therapy (HMA+ven vs. IC), *TP53* mutation status, and allogeneic transplant as a time-dependent variable. Inferior survival was independently associated with older age (HR 1.02; 95% CI: 1.01–1.03; $p = 0.0003$), secondary AML (HR 1.91; 95% CI: 1.48–2.47; $p < 0.0001$), inv(3)(q21q26.2)/t(3;3)(q21;q26.2) (HR 2.12; 95% CI: 1.44–3.14; $p = 0.0002$), and *TP53* mutation (HR 2.07; 95% CI: 1.58–2.72; $p < 0.0001$). Transplant was associated with improved survival (HR 0.42; 95% CI: 0.29–0.60; $p < 0.0001$). Induction regimen was not significantly associated with survival.

Figure 1

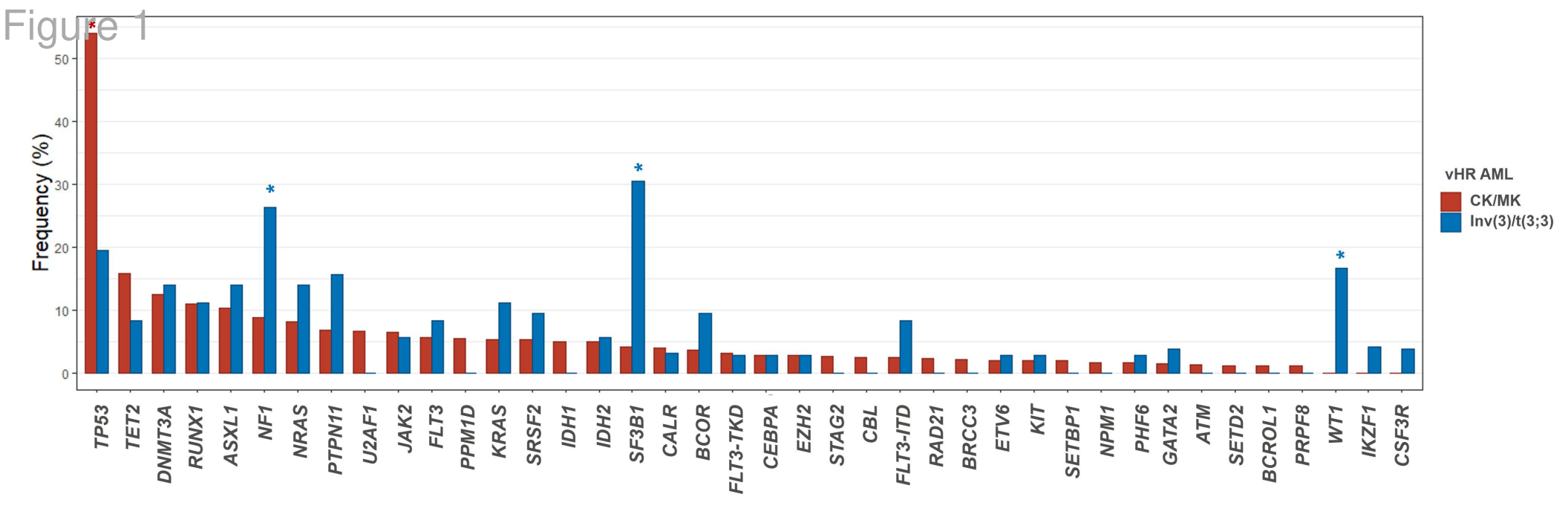

Frequency (%)
0
10
20
30
40
50
*
*
*
*
vHR AML
CK/MK
Inv(3)/t(3;3)
TP53
TET2
DNMT3A
RUNX1
ASXL1
NF1
NRAS
PTPN11
U2AF1
JAK2
FLT3
PPM1D
KRAS
SRSF2
IDH1
IDH2
SF3B1
CALR
BCOR
FLT3-TKD
CEBPA
EZH2
STAG2
CBL
FLT3-ITD
RAD21
BRCC3
ETV6
KIT
SETBP1
NPM1
PHF6
GATA2
ATM
SETD2
BCROL1
PRPF8
WT1
IKZF1
CSF3R

Figure 2

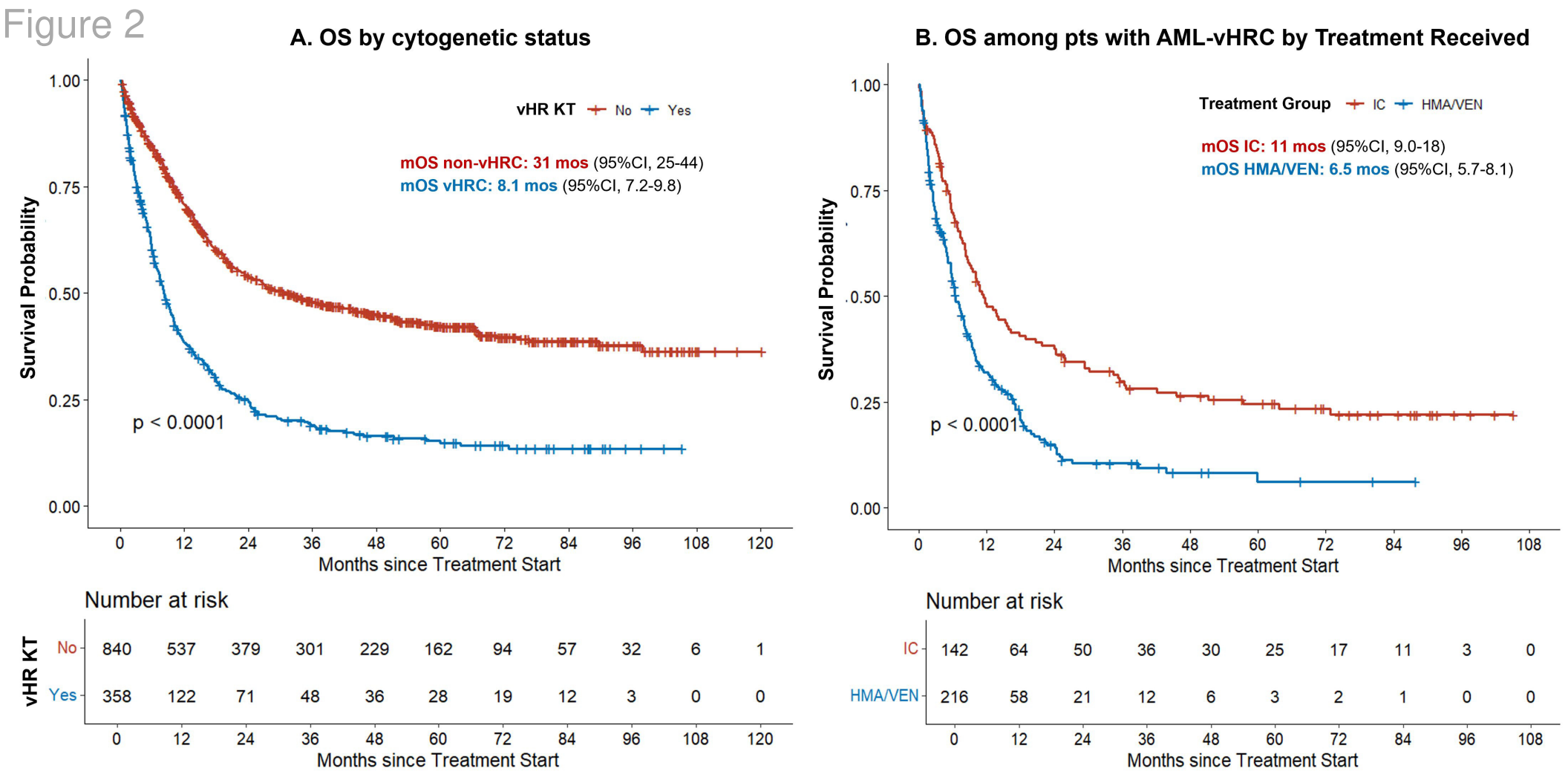

A. OS by cytogenetic status
vHR KT No Yes
mOS non-vHRC: 31 mos (95%CI, 25-44)
mOS vHRC: 8.1 mos (95%CI, 7.2-9.8)
p < 0.0001
Survival Probability
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72 84 96 108 120
Months since Treatment Start
Number at risk
vHR KT
No 840 537 379 301 229 162 94 57 32 6 1
Yes 358 122 71 48 36 28 19 12 3 0 0
0 12 24 36 48 60 72 84 96 108 120
Months since Treatment Start
B. OS among pts with AML-vHRC by Treatment Received
Treatment Group IC HMA/VEN
mOS IC: 11 mos (95%CI, 9.0-18)
mOS HMA/VEN: 6.5 mos (95%CI, 5.7-8.1)
p < 0.0001
Survival Probability
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72 84 96 108
Months since Treatment Start
Number at risk
IC 142 64 50 36 30 25 17 11 3 0
HMA/VEN 216 58 21 12 6 3 2 1 0 0
0 12 24 36 48 60 72 84 96 108
Months since Treatment Start

Figure 3

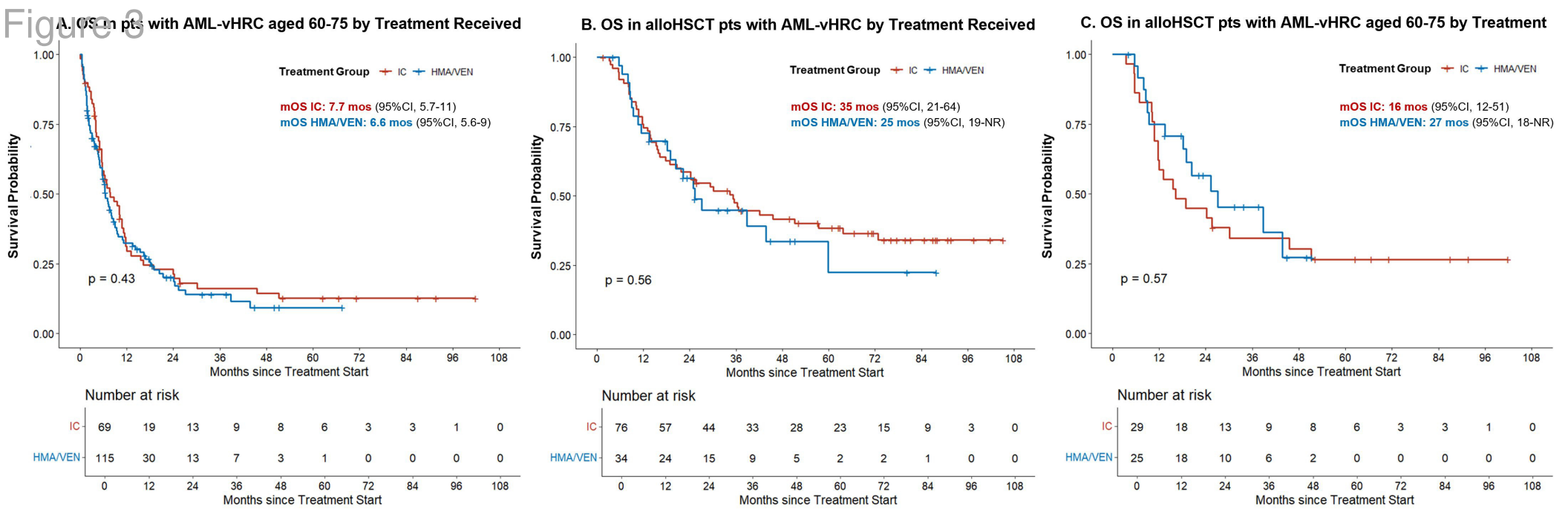
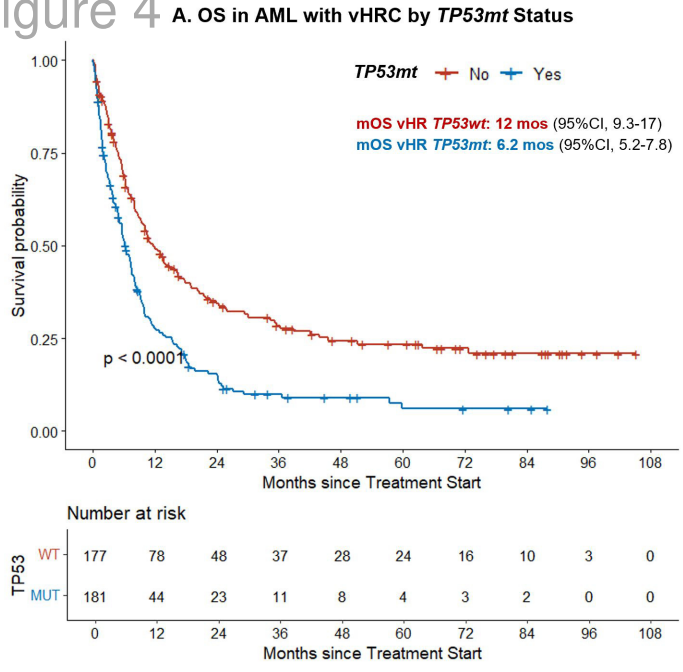
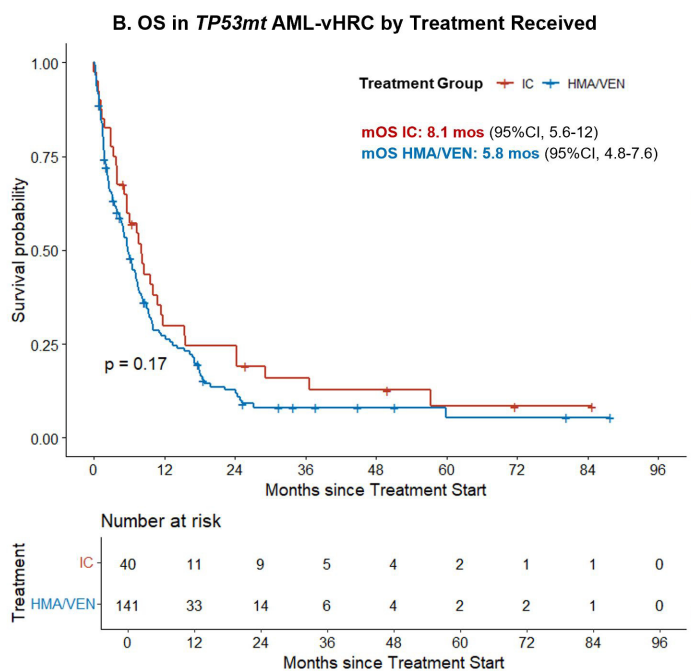

A. OS in pts with AML-vHRC aged 60-75 by Treatment Received
Treatment Group IC HMA/VEN
mOS IC: 7.7 mos (95%CI, 5.7-11)
mOS HMA/VEN: 6.6 mos (95%CI, 5.6-9)
p = 0.43
Survival Probability
Months since Treatment Start
Number at risk
IC 69 19 13 9 8 6 3 3 1 0
HMA/VEN 115 30 13 7 3 1 0 0 0 0
B. OS in alloHSCT pts with AML-vHRC by Treatment Received
Treatment Group IC HMA/VEN
mOS IC: 35 mos (95%CI, 21-64)
mOS HMA/VEN: 25 mos (95%CI, 19-NR)
p = 0.56
Survival Probability
Months since Treatment Start
Number at risk
IC 76 57 44 33 28 23 15 9 3 0
HMA/VEN 34 24 15 9 5 2 2 1 0 0
C. OS in alloHSCT pts with AML-vHRC aged 60-75 by Treatment
Treatment Group IC HMA/VEN
mOS IC: 16 mos (95%CI, 12-51)
mOS HMA/VEN: 27 mos (95%CI, 18-NR)
p = 0.57
Survival Probability
Months since Treatment Start
Number at risk
IC 29 18 13 9 8 6 3 3 1 0
HMA/VEN 25 18 10 6 2 0 0 0 0 0

Figure 4


A. OS in AML with vHRC by TP53mt Status
TP53mt No Yes
mOS vHR TP53wt: 12 mos (95%CI, 9.3-17)
mOS vHR TP53mt: 6.2 mos (95%CI, 5.2-7.8)
p < 0.0001
Survival probability
Months since Treatment Start
Number at risk
TP53
WT 177 78 48 37 28 24 16 10 3 0
MUT 181 44 23 11 8 4 3 2 0 0


B. OS in TP53mt AML-vHRC by Treatment Received
Treatment Group IC HMA/VEN
mOS IC: 8.1 mos (95%CI, 5.6-12)
mOS HMA/VEN: 5.8 mos (95%CI, 4.8-7.6)
p = 0.17
Survival probability
Months since Treatment Start
Number at risk
Treatment
IC 40 11 9 5 4 2 1 1 0
HMA/VEN 141 33 14 6 4 2 2 1 0

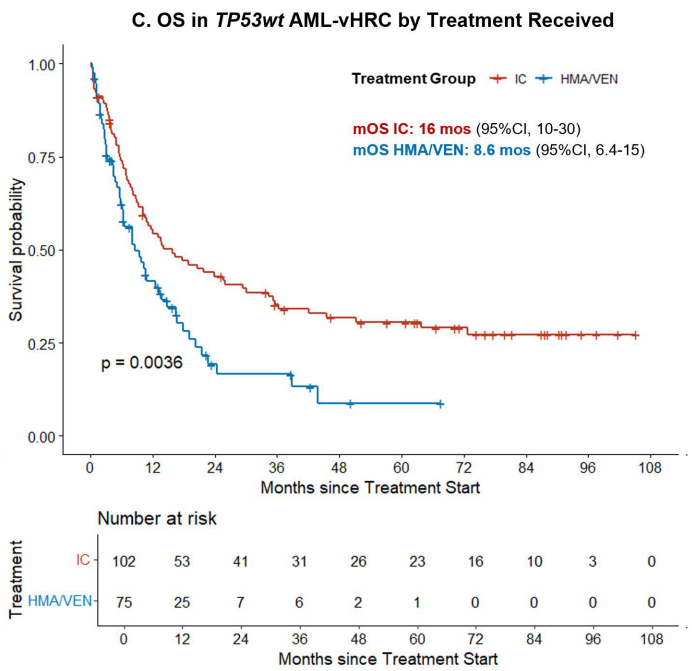
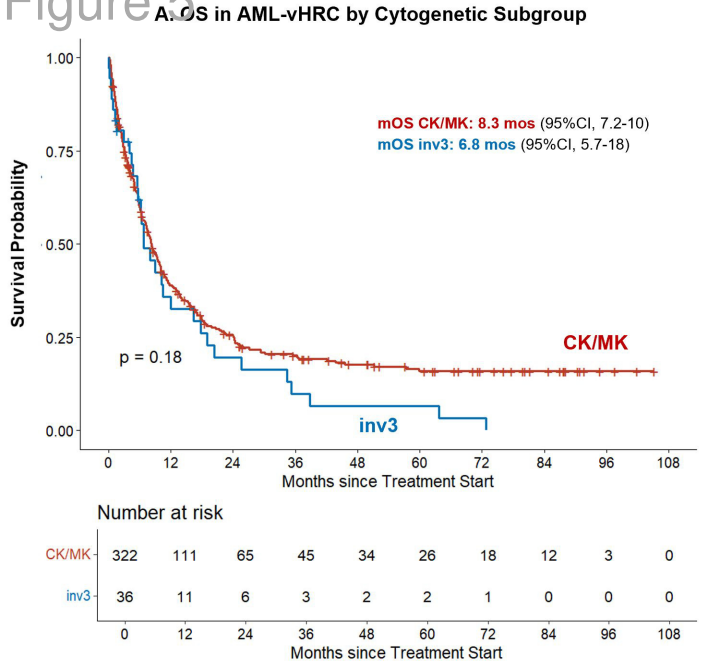
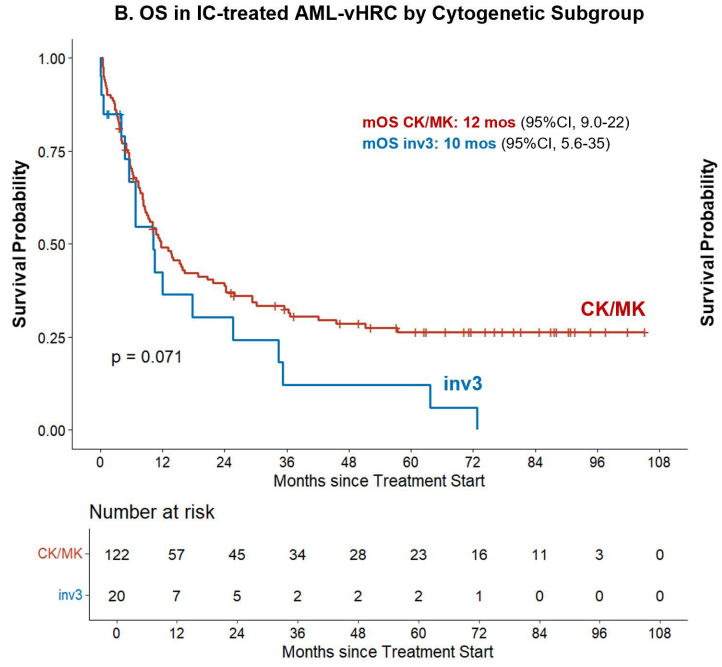

C. OS in TP53wt AML-vHRC by Treatment Received
Treatment Group IC HMA/VEN
mOS IC: 16 mos (95%CI, 10-30)
mOS HMA/VEN: 8.6 mos (95%CI, 6.4-15)
p = 0.0036
Survival probability
Months since Treatment Start
Number at risk
Treatment
IC 102 53 41 31 26 23 16 10 3 0
HMA/VEN 75 25 7 6 2 1 0 0 0 0

Figure 5


A. OS in AML-vHRC by Cytogenetic Subgroup
mOS CK/MK: 8.3 mos (95%CI, 7.2-10)
mOS inv3: 6.8 mos (95%CI, 5.7-18)
p = 0.18
CK/MK
inv3
Survival Probability
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72 84 96 108
Months since Treatment Start
Number at risk
CK/MK 322 111 65 45 34 26 18 12 3 0
inv3 36 11 6 3 2 2 1 0 0 0
0 12 24 36 48 60 72 84 96 108
Months since Treatment Start


B. OS in IC-treated AML-vHRC by Cytogenetic Subgroup
mOS CK/MK: 12 mos (95%CI, 9.0-22)
mOS inv3: 10 mos (95%CI, 5.6-35)
p = 0.071
CK/MK
inv3
Survival Probability
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72 84 96 108
Months since Treatment Start
Number at risk
CK/MK 122 57 45 34 28 23 16 11 3 0
inv3 20 7 5 2 2 2 1 0 0 0
0 12 24 36 48 60 72 84 96 108
Months since Treatment Start

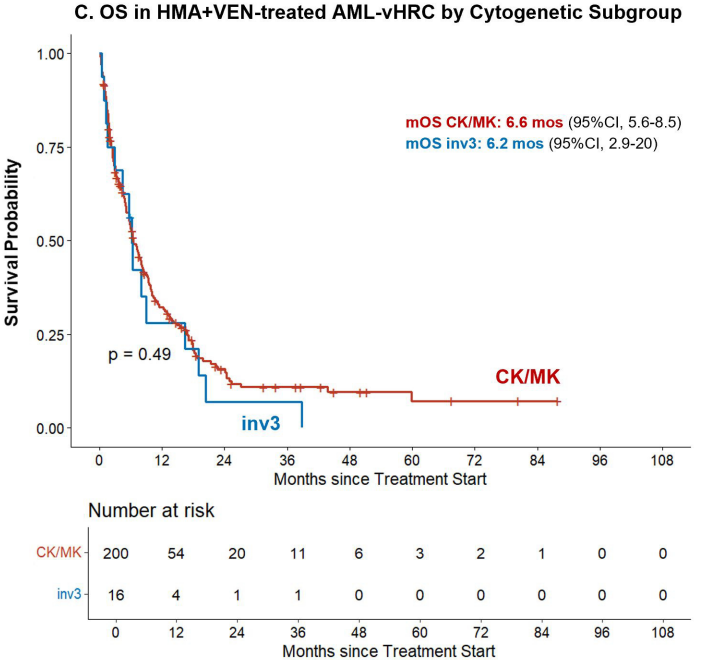
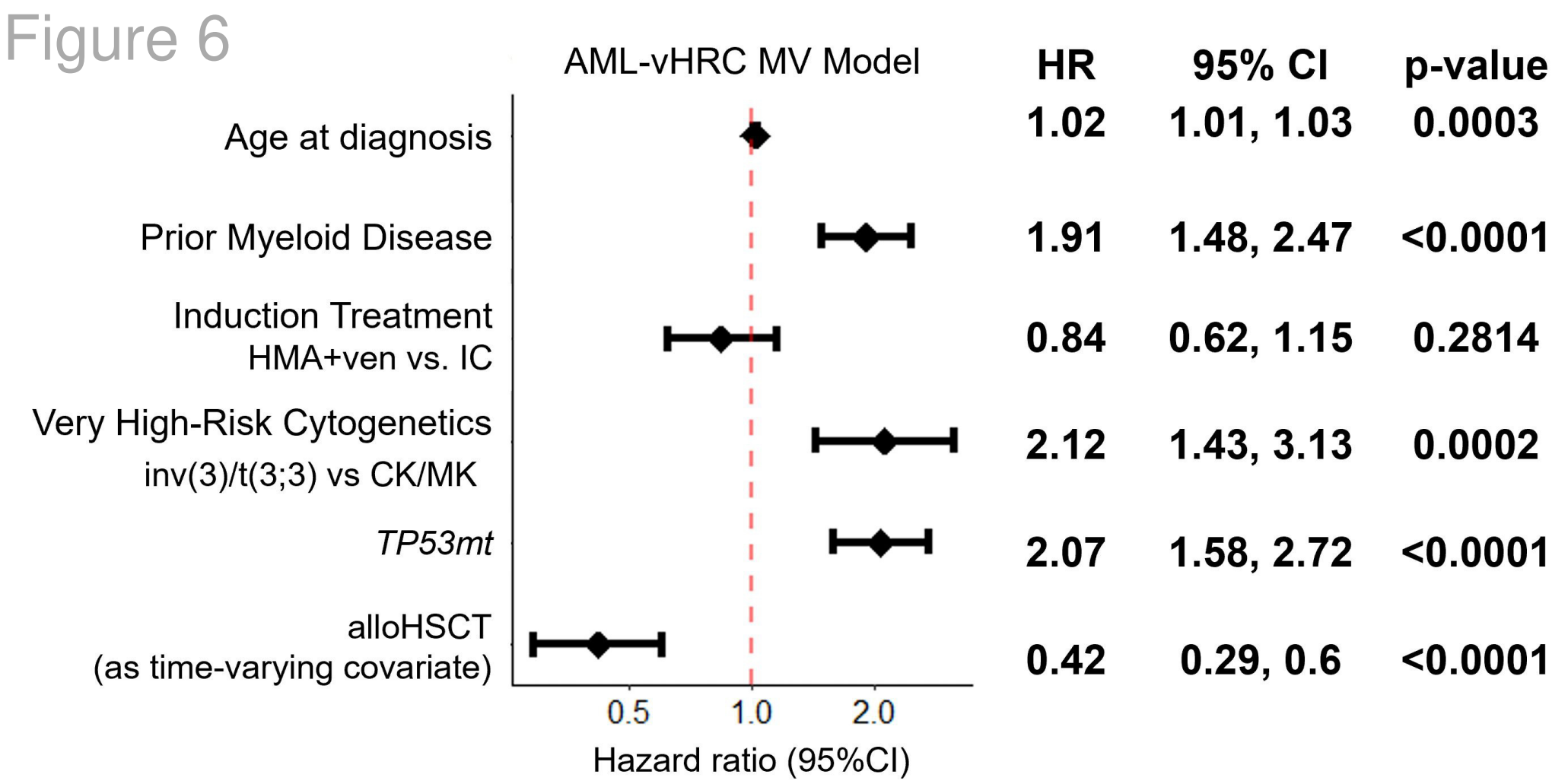

C. OS in HMA+VEN-treated AML-vHRC by Cytogenetic Subgroup
mOS CK/MK: 6.6 mos (95%CI, 5.6-8.5)
mOS inv3: 6.2 mos (95%CI, 2.9-20)
p = 0.49
CK/MK
inv3
Survival Probability
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72 84 96 108
Months since Treatment Start
Number at risk
CK/MK 200 54 20 11 6 3 2 1 0 0
inv3 16 4 1 1 0 0 0 0 0 0
0 12 24 36 48 60 72 84 96 108
Months since Treatment Start

Figure 6


AML-vHRC MV Model
HR
95% CI
p-value
Age at diagnosis
1.02
1.01, 1.03
0.0003
Prior Myeloid Disease
1.91
1.48, 2.47
<0.0001
Induction Treatment
HMA+ven vs. IC
0.84
0.62, 1.15
0.2814
Very High-Risk Cytogenetics
inv(3)/t(3;3) vs CK/MK
2.12
1.43, 3.13
0.0002
TP53mt
2.07
1.58, 2.72
<0.0001
alloHSCT
(as time-varying covariate)
0.42
0.29, 0.6
<0.0001
0.5
1.0
2.0
Hazard ratio (95%CI)