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Metronomic decitabine with venetoclax offers a patient-centered frontline therapeutic approach for *TP53*-mutated complex-karyotype myeloid neoplasms

Short title: Metronomic decitabine for *TP53*-mutated complex-karyotype myeloid neoplasms: Patient-centered approach

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Author contributions: *LFW and RPL contributed equally to this work. LFW performed clinical data collection, data analysis, and manuscript preparation. RPL performed molecular data collection, data analysis, and manuscript preparation. JP performed clinical data collection. PHI provided guidance on data analysis and manuscript preparation. AA and VPSK performed patient data collection using internal databases and manuscript preparation. ABD provided bioinformatics guidance on karyotype analysis using CytoGPS R package. HLL assisted with data analysis. ZA and PP provided access to and expert guidance on using the CytoGPS tool for karyotype parsing. ABD, AED, IG, TJ, TK, GP, BDS, JAW, and LG performed manuscript preparation. ML led conceptualization, developed patient database of *TP53*mut/CK patients, provided significant guidance on clinical and scientific analyses, and assisted with manuscript preparation. GG led and oversaw all components.

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Key words: metronomic dose, decitabine, venetoclax, acute myeloid leukemia, *TP53* mutations, complex karyotype

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Main Text

Myeloid neoplasms (MNs) which harbor both a complex karyotype (CK) and *TP53* mutations (*TP53*mut) represent a subset of disease with dismal prognosis, and no effective therapeutic options exist. CK, defined as ≥ 3 chromosomal abnormalities, is found in 10-12% of acute myeloid leukemia (AML) and 10-30% of myelodysplastic syndrome (MDS) cases[1]. *TP53* mutations are uniquely frequent amongst CK MNs, occurring in 70-80% of CK-AML and 55% of CK-MDS[2, 3], compared with only 2.1% of cases without CK[4]. The co-occurrence of *TP53*mut and CK identifies a disease subtype with particularly poor outcomes[2, 3]. Clinically, *TP53*mut/CK MNs patients present with cytopenias, infections, bleeding complications, and prolonged or recurrent hospitalizations. Standard cytotoxic chemotherapy is poorly tolerated and provides limited overall-survival benefit[5]. As previously shown by us and others, relapse rates remain extremely high even after allogeneic hematopoietic stem cell transplant (HSCT)[6]. Although we continue to consider HSCT for highly selected patients with *TP53*mut/CK MN who achieve stringent remission, our institutional approach has shifted toward strategies that emphasize survival, tolerability, and quality of life. In a disease with limited survival, maximizing time outside of the hospital is an important patient-centered endpoint. Indeed, qualitative studies assessing factors important to leukemia patients and caregivers identify hospitalization burden and infectious complications as key considerations[7, 8].

Metronomic, low dose decitabine (LoDec) refers to decitabine administered at non-cytotoxic doses of 0.1-0.2 mg/kg once or twice weekly. At these doses, decitabine loses its cytotoxic properties but retains the ability to irreversibly bind and deplete DNA methyltransferase 1[9]. LoDec has shown benefit in several MNs, including MDS and AML[10, 11]. Recently, LoDec has shown clinical activity in *TP53*mut MDS and AML[12]. However, the role of LoDec plus venetoclax (ven) in the frontline treatment of *TP53*mut/CK MNs remains incompletely defined. We aimed to characterize the outcomes of patients with newly diagnosed *TP53*mut/CK MNs who received first-line therapy with metronomic decitabine.

We performed a retrospective chart review of all patients ≥18 years with newly diagnosed *TP53*mut/CK MN (MDS or AML) admitted to the inpatient leukemia service at Johns Hopkins (JH) between 2018 and 2024. The study was approved by the JH Institutional Review Board. Diagnoses of AML and MDS were made using the International Consensus Classification (ICC) and World Health Organization (WHO) definitions. CK was defined as ≥3 cytogenetic abnormalities present on conventional karyotype at the time of initial diagnosis. *TP53*mut were identified by targeted next-generation sequencing (NGS). Monoallelic *TP53* mutation was defined as a single *TP53* mutation without deletion of chromosome 17 or 17p13 on cytogenetics. Biallelic

TP53 mutation was defined as two or more *TP53* mutations on NGS, a single *TP53* mutation with loss of chromosome 17 or 17p13, or variant allele frequency (VAF) ≥50%. Patients were grouped by frontline therapy, with a focus on hypomethylating agent (HMA)-based regimens: LoDec/ven (venetoclax 400mg once WEEKLY), standard azacitidine plus venetoclax (Aza/VEN, azacitidine 75 mg/m² for 7 days +/- venetoclax 400 mg/DAY), or standard decitabine (StdDec, 20 mg/m² for 5-10 days). For inclusion in the study, patients must have completed at least one cycle of therapy. Patients not falling into one of these HMA treatment groups were categorized as "other treatment".

We identified 137 patients with new diagnosis of *TP53*mut/CK MN admitted to our inpatient leukemia service between 2018 and 2024. Of these patients, 91 received one of the treatments of interest: 20 received first-line LoDec/ven, 54 received Aza/VEN, and 17 received StdDec. Among the remaining 46 patients, 15 proceeded directly to hospice/comfort care and 31 received other therapies including clinical-trial regimens and intensive chemotherapy [Supplementary Figure 1]**.**

Baseline patient characteristics are shown in Supplementary Table 1. Across treatment groups, patients were similar with respect to age (p=0.20), sex (p=0.30), and ECOG score (p=0.13). Diagnosis distribution varied across treatment groups (p=0.022), with AML more frequent in the Aza/VEN group (78%) compared with the LoDec/ven (55%) and StdDec (47%) groups, while MDS/AML was more common in the StdDec group (47%). Patients treated with LoDec/ven had higher comorbidity burden, as reflected by Charlson comorbidity index (CCI), consistent with physician selection of a less intensive approach for very frail individuals (median CCI 8.0, IQR 7.0–9.0 LoDec/ven vs. 6.0, IQR 5.0–7.0 Aza/VEN vs. 6.0, IQR 6.0–7.0 StdDec, p=0.013). A notable feature at presentation was "disease-related fever," defined as temperature >38°C without clinical, laboratory, or radiographic evidence of infection, supporting the concept that *TP53*mut/CK MNs are systemic diseases associated with inflammation, cytokine activation, and immune dysregulation[13]. Disease-related fever was similarly distributed across all treatment groups (15% LoDec/ven, 20% Aza/VEN, 35% StdDec, p=0.40). Baseline cytogenetic analysis showed frequent losses of chromosomes 5, 7, and 17 and gains of chromosome 8, 21 and 22 [Supplementary Figure 2A]. NGS features including type of *TP53* lesions and co-occurring somatic mutations, were consistent with prior reports[14] [Supplementary Figure 2B].

Because patients treated with LoDec/ven often did not undergo serial bone marrow assessment required for formal response classification of treatment, we evaluated clinically meaningful patient-centered outcomes, including transfusion independence, hospitalization burden, and neutropenic fever burden. Transfusion independence was defined as at ≥ 4weeks without red blood cell or platelet transfusion. LoDec/ven had similar rates of transfusion

independence when compared with Aza/VEN and StdDec (45% LoDec/ven vs. 29.1% Aza/VEN vs. 47% StdDec, Fisher's exact p=0.28) [Figure 1A]. Hospitalization burden was assessed as both total days admitted after diagnosis and the proportion of days alive spent in the hospital. Patients treated with LoDec/ven had the lowest hospitalization burden by days (median 17 days, IQR: 12.2–25.5 LoDec/ven vs. 30 days, IQR: 13.2–41.5 Aza/VEN vs. 36 days, IQR: 26–65 StdDec, Kruskal–Wallis p=0.0079) [Figure 1B]. When normalized to survival time the median proportion of days alive spent hospitalized was also the lowest in LoDec/ven group (7.5%, IQR: 5.8%–13.2% LoDec/ven vs. 34.5%, IQR: 14.3%–54.5% Aza/VEN vs. 17.0%, IQR: 8.0%–40.0% StdDec, Kruskal–Wallis p=0.0012) [Figure 1C]. Episodes of neutropenic fever were defined as temperature of ≥38°C in the setting of ANC ≤500 cells/uL. Neutropenic fever burden (median number of neutropenic fever episodes per 100 days alive) was different across the three treatment groups (media 0.44 for LoDec/ven; 1.39 for Aza/VEN and 0.53 for StdDec, Kruskal-Wallis p=0.032) with fewer episode in the LoDec/ven group compared to Aza/VEN (Wilcoxon p=0.0115) [Figure 1D].

Unadjusted overall survival (OS), defined as time from diagnosis to death, was significantly different between the three treatment groups (log-rank p=0.012). Patients treated with LoDec/ven had a median OS of 211.5 days, which was intermediate between that of Aza/VEN (90 days) and StdDec (371 days). Pairwise Kaplan–Meier analyses demonstrated a trend towards difference in OS between LoDec/ven and Aza/VEN (log-rank p=0.06) but not between LoDec/ven and StdDec (log-rank p=0.40) [Figure 2A]. However, given differences in baseline characteristics and treatment selection, these comparisons should be interpreted descriptively.

Despite higher baseline CCI scores in the LoDec/ven group, 30-day mortality was statistically similar across treatment groups (5.0% LoDec/ven, 9.3% Aza/VEN, and 11.8% StdDec; Fisher's exact p=0.78). In contrast, 90-day mortality was significantly lower for patients treated with LoDec/ven compared to Aza/VEN (15% LoDec/ven vs. 51.9% Aza/VEN v, pairwise Fisher's exact p=0.007) [Figure 2B]. These findings suggest that standard-dose HMA-based regimens, including Aza/VEN, may be associated with substantial early toxicity in this frail, high-risk population despite being conventionally considered "low-intensity".

We and others have previously published that patients with *TP53*mut/CK MNs have exceedingly high relapse rates even if they achieve a very stringent complete remission and they proceed to HSCT [6]. In the present cohort only three successfully proceeded to HSCT. Two received Aza/VEN and one received StdDec; none survived beyond 14 months.

In myeloid neoplasms, both *TP53* mutations and complex karyotypes are markers of unfavorable risk. When present together, they define a group of diseases that are universally fatal.

Optimal management for these patients remains a critical unmet need driven not only by intrinsic chemoresistance but also by substantial treatment-related toxicities. Notably, more than half of patients treated with Aza/VEN did not survive beyond 90 days despite management at an academic tertiary referral center and despite Aza/VEN being considered a low-intensity regimen. Metronomic decitabine has shown activity in relapsed/refractory AML[9] and in frontline treatment of *TP53*mut MNs[12]. Here, by focusing specifically on newly diagnosed *TP53*mut/CK MNs, we show that LoDec/ven is clinically active (45% achieved TFI) and relatively well tolerated (90-day mortality of 15% even in frail patients). Importantly, LoDec/ven maximized time outside the hospital and resulted in fewer episodes of neutropenic fevers with potential downstream reduction in financial burden[15].

These findings support LoDec/ven as a clinically active and less toxic strategy for this highly vulnerable population. Because formal response assessments were not performed uniformly, some patients may have achieved deeper remissions than captured by transfusion independence alone, including responses that might otherwise have supported consideration of HSCT had comorbidity burden been lower. In addition to being retrospective, this study is constrained by small sample sizes in treatment groups, limiting feasibility of multivariable analysis. In the absence of effective *TP53*-directed therapies, prospective randomized studies are needed to confirm whether upfront therapy with LoDec/ven improves patient-centered outcomes and reduces the current heterogeneity in physician-directed management.

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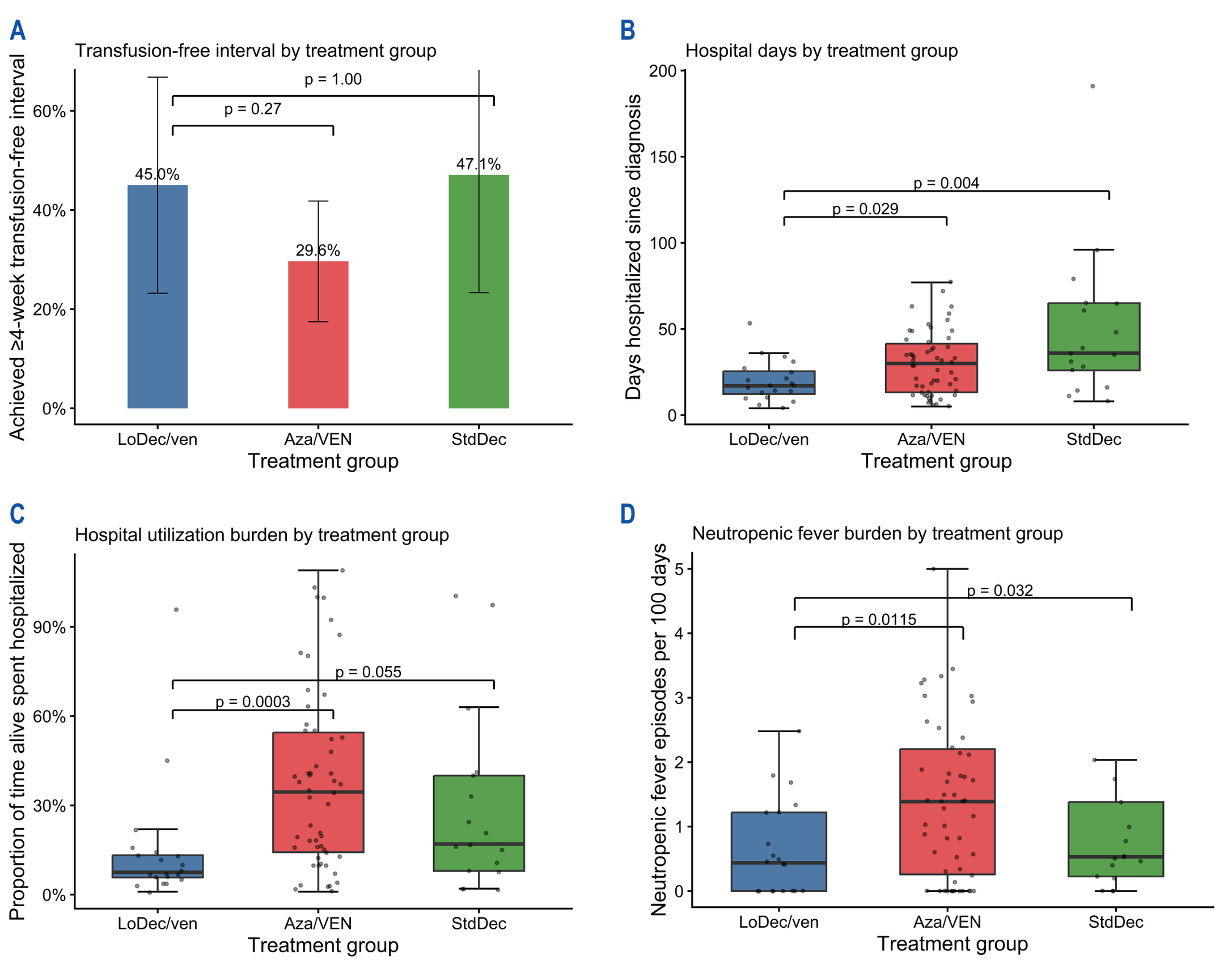
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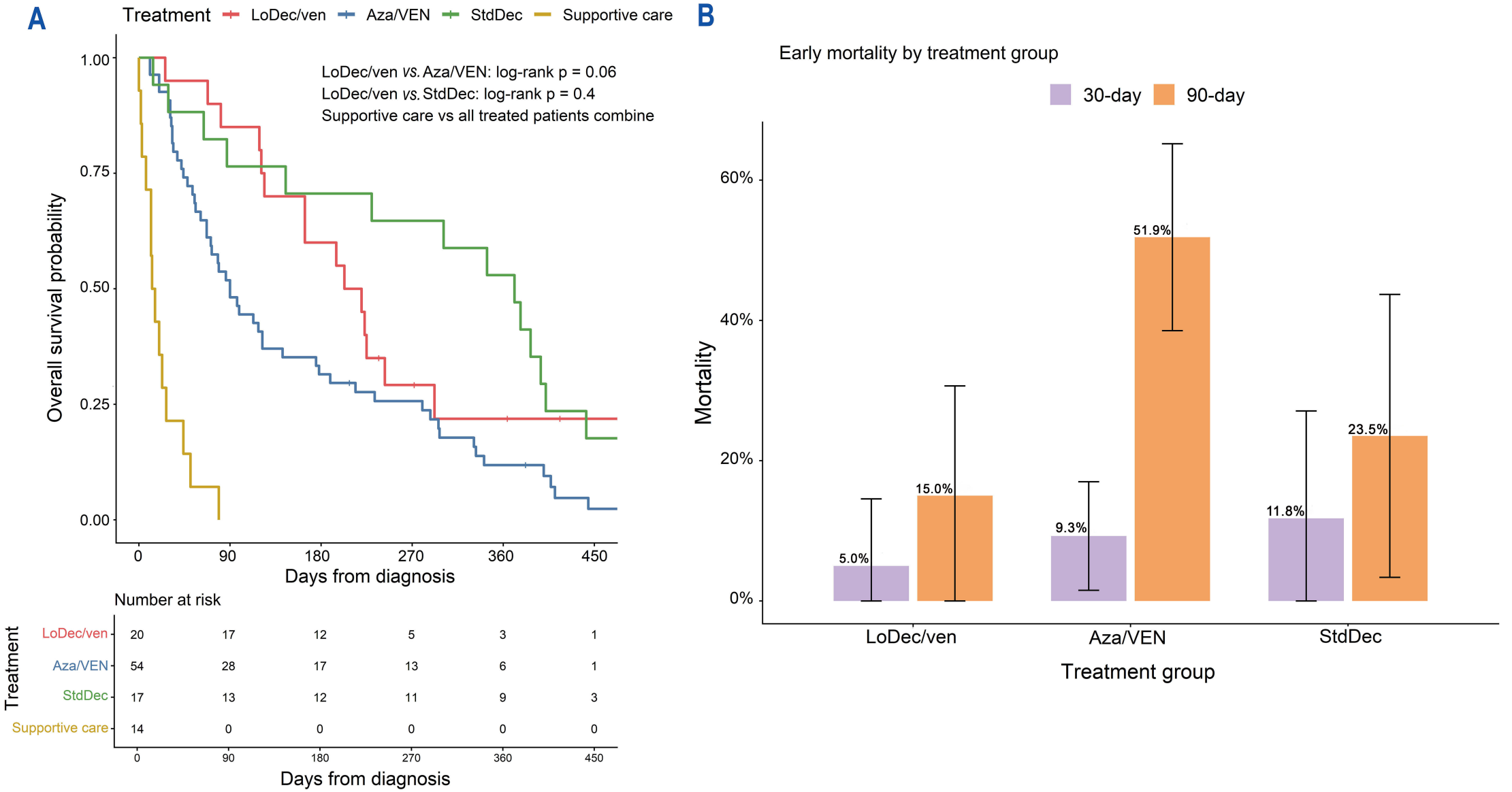
Figure Legends

Figure 1. Patient-Centered Outcomes. 1A, Transfusion-free interval according to active treatment group. Proportion of actively treated patients with *TP53*mut/CK achieving a transfusion-free interval of ≥ 4 weeks. Rates were 45.0% for LoDec/ven, 29.6% for Aza/VEN, and 47.1% for StdDec. Pairwise comparisons showed no significant differences in achievement of a transfusion-free interval between LoDec/ven and Aza/VEN (Fisher's exact p=0.27), or between LoDec/ven and StdDec (Fisher's exact p=1.00). Error bars represent 95% confidence intervals for proportions. **1B**, Days admitted to hospital according to active treatment group. Boxplots with individual data points showing total days admitted to hospital from diagnosis in actively treated patients with *TP53*mut/CK MNs. Median days admitted were 17.0 days (IQR, 12.2–25.5) for LoDec/ven, 30.0 days (IQR, 13.2–41.5) for Aza/VEN, and 36.0 days (IQR, 26.0–65.0) for StdDec. In pairwise comparisons, LoDec/ven was associated with significantly fewer hospital days than both Aza/VEN (Wilcoxon p=0.029) and StdDec (Wilcoxon p=0.004).**1C**, Proportion of time alive spent admitted to hospital according to active treatment group. Boxplots with individual data points showing the proportion of time alive from diagnosis spent admitted to hospital in actively treated patients with *TP53*mut/CK MNs. Median proportions were 7.5% (IQR, 5.8–13.2%) for LoDec/ven, 34.5% (IQR, 14.3–54.5%) for Aza/VEN, and 17.0% (IQR, 8.0–40.0%) for StdDec. In pairwise comparisons, LoDec/ven was associated with a lower proportion of time alive spent in the hospital than Aza/VEN (Wilcoxon p=0.0003), or StdDec (Wilcoxon p=0.055). **1D**, Neutropenic fever burden by treatment group. Boxplots with individual patient values showing neutropenic fever burden, normalized to follow-up time, among actively treated patients with *TP53*mut/CK MNs. Neutropenic fever burden (median number of neutropenic fever episodes per 100 days alive) was differed across the three treatment groups (media 0.44 for LoDec/ven; 1.39 for Aza/VEN and 0.53 for StdDec, Kruskal-Wallis p=0.032) with fewer episode in the LoDec/ven group compared to Aza/VEN (Wilcoxon p=0.0115) The y-axis is truncated at 5 episodes per 100 days for visualization.

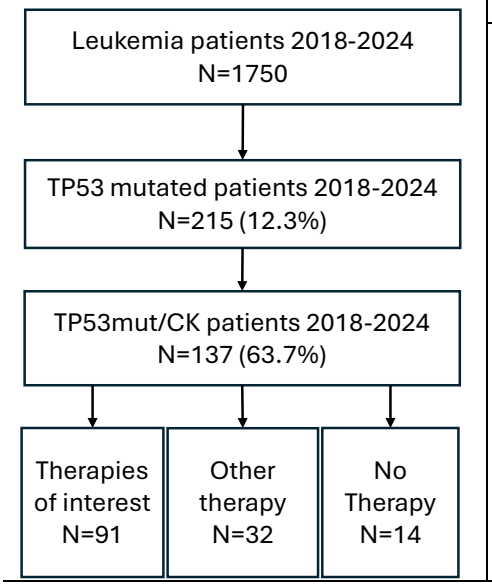
Figure 2, Survival and Mortality. 2A, Overall survival according to active treatment group. Kaplan–Meier estimates of overall survival from diagnosis in actively treated patients with *TP53*-mutated complex karyotype myeloid neoplasms, stratified by Aza/VEN, LoDec/ven, and StdDec. Median overall survival was 90.0, 211.5, and 371.0 days, respectively. Tick marks indicate censored observations. P value was calculated by log-rank test. **2B, Early mortality according to active treatment group.** Thirty-day and 90-day mortality from diagnosis in actively treated patients with *TP53*-mutated complex karyotype myeloid neoplasms treated with Aza/VEN,

LoDec/ven, or StdDec. Thirty-day mortality was 9.3%, 5.0%, and 11.8%, respectively (Fisher's exact p=0.78). Ninety-day mortality was 51.9%, 15.0%, and 23.5%, respectively (Fisher's exact p=0.0059). Error bars represent approximate 95% confidence intervals for the proportion.


A
Transfusion-free interval by treatment group
Achieved ≥4-week transfusion-free interval
60%
40%
20%
0%
p = 1.00
p = 0.27
45.0%
29.6%
47.1%
LoDec/ven
Aza/VEN
StdDec
Treatment group
B
Hospital days by treatment group
Days hospitalized since diagnosis
200
150
100
50
0
p = 0.004
p = 0.029
LoDec/ven
Aza/VEN
StdDec
Treatment group
C
Hospital utilization burden by treatment group
Proportion of time alive spent hospitalized
90%
60%
30%
0%
p = 0.055
p = 0.0003
LoDec/ven
Aza/VEN
StdDec
Treatment group
D
Neutropenic fever burden by treatment group
Neutropenic fever episodes per 100 days
5
4
3
2
1
0
p = 0.032
p = 0.0115
LoDec/ven
Aza/VEN
StdDec
Treatment group


A
Treatment
LoDec/ven
Aza/VEN
StdDec
Supportive care
LoDec/ven vs. Aza/VEN: log-rank p = 0.06
LoDec/ven vs. StdDec: log-rank p = 0.4
Supportive care vs all treated patients combine
Overall survival probability
1.00
0.75
0.50
0.25
0.00
0
90
180
270
360
450
Days from diagnosis
Number at risk
Treatment
LoDec/ven 20 17 12 5 3 1
Aza/VEN 54 28 17 13 6 1
StdDec 17 13 12 11 9 3
Supportive care 14 0 0 0 0 0
Days from diagnosis
B
Early mortality by treatment group
30-day
90-day
Mortality
60%
40%
20%
0%
5.0%
15.0%
9.3%
51.9%
11.8%
23.5%
LoDec/ven
Aza/VEN
StdDec
Treatment group

Supplementary Figures and Tables



Therapies of Interest	Other therapies
Metronimic decitabine • Decitabine 0.2 mg/kg/week SQ plus VEN (400 mg/week) (N=20) Standard-dose decitabine • Decitabine 20 mg/m² × 5 days IV (N=13) • Decitabine 20 mg/m² × 10 days IV (N=4) Standard-dose azacitidine • Aza, (75 mg/m² × 7 days) plus ven (400 mg/day) (N=49) • Aza, (75 mg/m² × 7 days) monotherapy (N=5)	Clinical trial (N=12) Anthracycline-based therapy (7+3) (N=10) Vyxeos (N=5) Incomplete cycle of StdDec or Aza/VEN (N=5)

Supplementary Figure 1: Patient identification process and therapies of interest.

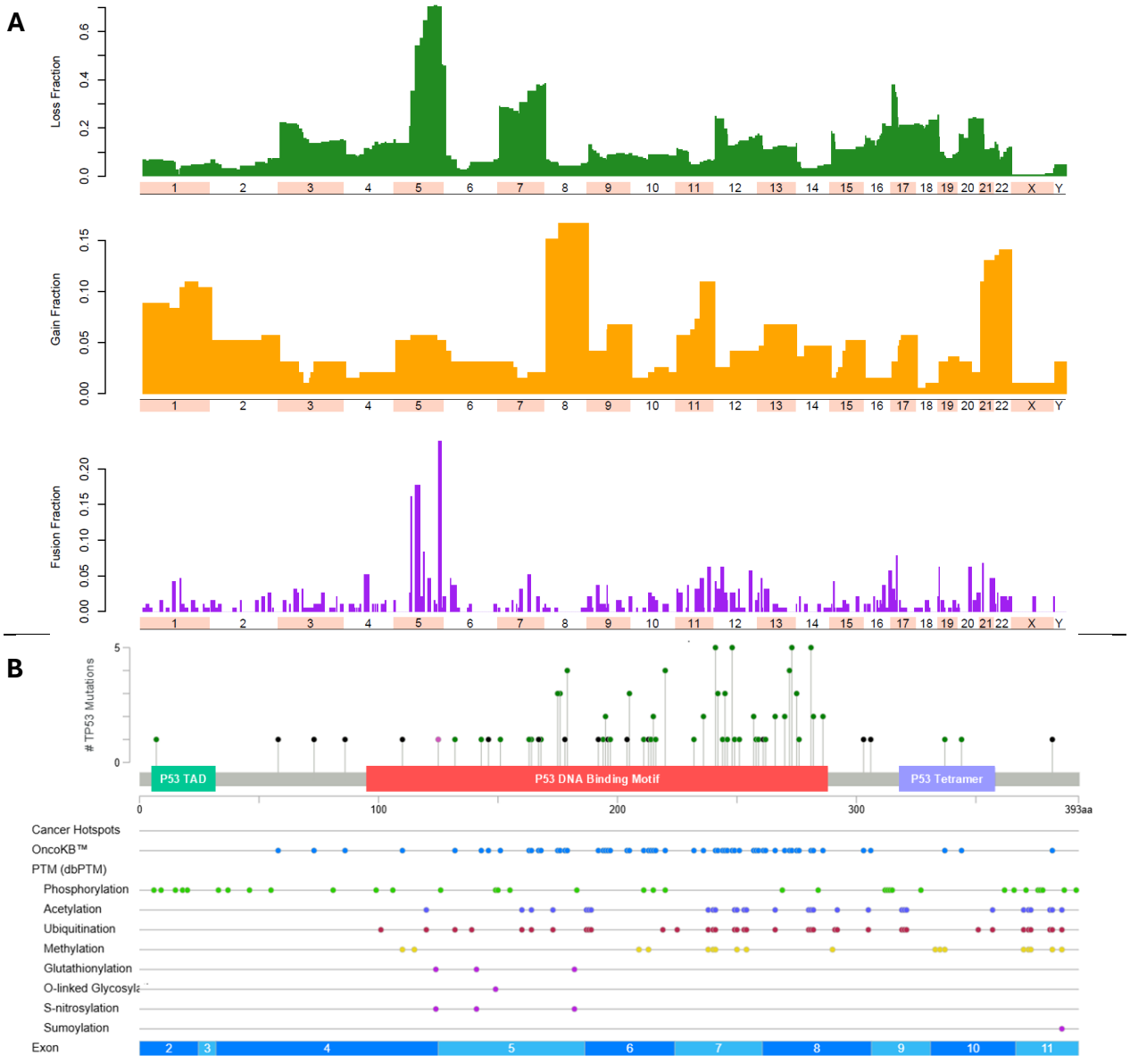
Supplementary Table 1

Characteristic	LoDec/ven N = 20[1]	Aza/VEN N = 54[1]	StdDec N = 17[1]	p-value[2]
Age at diagnosis	74 (69, 78)	71 (66, 76)	68 (64, 74)	0.2
Sex				0.3
Female	10 (50%)	17 (31%)	5 (29%)	
Male	10 (50%)	37 (69%)	12 (71%)	
ECOG performance status at diagnosis				0.7
0	1 (5.0%)	6 (11%)	0 (0%)	
1-2	14 (70%)	37 (69%)	12 (71%)	
3-4	5 (25%)	11 (20%)	5 (29%)	
Diagnosis				0.022
MDS	4 (20%)	2 (3.7%)	1 (5.9%)	
MDS/AML	5 (25%)	10 (19%)	8 (47%)	
AML	11 (55%)	42 (78%)	8 (47%)	
TP53 Allele Status				0.5
Biallelic	15 (75%)	44 (81%)	12 (71%)	
Monoallelic	5 (25%)	10 (19%)	5 (29%)	
Bone marrow blast percentage at diagnosis				0.4
<5%	2 (13%)	1 (2.2%)	0 (0%)	

Characteristic	LoDec/ven N = 20[1]	Aza/VEN N = 54[1]	StdDec N = 17[1]	p-value[2]
5-10%	3 (20%)	5 (11%)	2 (18%)	
11-20%	4 (27%)	11 (24%)	2 (18%)	
>20%	6 (40%)	29 (63%)	7 (64%)	
Unknown	5	8	6	
Peripheral blast percentage at diagnosis				0.017
<5%	13 (65%)	22 (42%)	4 (31%)	
5-10%	3 (15%)	6 (11%)	5 (38%)	
11-20%	3 (15%)	5 (9.4%)	2 (15%)	
>20%	1 (5.0%)	20 (38%)	2 (15%)	
Unknown	0	1	4	
Fever at presentation	3 (15%)	11 (20%)	6 (35%)	0.4
Charlson Comorbidity Index	8.00 (7.00, 9.00)	6.00 (5.00, 7.00)	6.00 (6.00, 7.00)	0.013
Duration of first-line therapy, days	137 (60, 208)	24 (13, 62)	76 (33, 124)	<0.001

[1] Median (Q1, Q3); n (%)

[2] Kruskal-Wallis rank sum test; Fisher's exact test



Supplementary Figure 2. A) Cytogenetic aberrations across 91 patients withTP53mut CK myeloid neoplasms. Frequencies of cytogenetic losses (green), gains (yellow), and fusions (purple) are shown. The most common losses occurred on chromosomes 5, 7, and 17. The most common gains occurred on chromosomes 8, 21, 22. Chromosome 5 was most frequently involved in fusion events. Figure created with CytoGPS and associated R package. **B) Protein-level TP53 mutations from patients with TP53 mut CK myeloid neoplasms.** 107 protein-level TP53 mutations from our patient cohort are visualized using C-BioPortal Mutation Mapper. The X-axis shows the P53 protein domains. Y-axis shows frequency of each mutation within our cohort. The most common mutations were p.S241F/A/T, p.R248W/Q, p.R273H, p.D281N/V/G (5 occurrences each). Most mutations occurred within the DNA-binding motif (red). Exons 5-8 were most frequently affected. OncoKB, Precision Oncology Knowledge Base. PTM, Post-Translational Modification. P53 TAD, P53 transactivation motif (6 - 29). P53 tetramer, P53 tetramerization motif (318 - 358).