

Clinical interrogation of *TP53* aberrations and its impact on survival in patients with myeloid neoplasms

by Jayastu Senapati, Sanam Loghavi, Guillermo Garcia-Manero, Guilin Tang, Tapan Kadia, Nicholas Short, Hussein A. Abbas, Naszrin Arani, Courtney D. DiNardo, Gautam Borthakur, Naveen Pemmaraju, Betul Oran, Elizabeth Shpall, Uday Popat, Richard Champlin, Sherry Pierce, Sankalp Arora, Ghayas Issa, Musa Yilmaz, Keyur Patel, Koichi Takahashi, Guillermo Montalban-Bravo, Danielle Hammond, Fadi G. Haddad, Farhad Ravandi, Hagop M. Kantarjian, and Naval G. Daver

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Clinical interrogation of TP53 aberrations and its impact on survival in patients with myeloid neoplasms

Jayastu Senapati⁺
Short¹, Hussein A
Pemmaraju¹, Bett
Arora³, Ghayas Iss
Danielle Hammor
¹ Department of L
² Department of C
USA.
³ Department of C
CAA.
⁴ Department of S
Cancer Center, He* These authors c
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- Abbas¹, Naszrin A
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Shpall⁴, Uday Popat⁴, Richard

Keyur Patel¹, Koichi Takahash

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|r Center, Houston,
|e authors contribut
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Elizabeth Shpa
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¹Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.

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1}Department of Leul
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³Department of Can
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* These authors con
Running Title: *TP53*
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y of Texas MD Ar Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, 1
Department of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, 1
Department of Cancer Medicine, The U ²Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX,

SSA.
Department of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX,
JSA.
Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson
Cancer Center, Hous ³Department of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX,

 4 Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson

Corresponding author:

³Depa
USA.
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4Depa
*** The
Runn Keyw
<u>Corre</u>
Depa**
Profe
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The L JSA.
Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson
Cancer Center, Houston, TX, USA.
These authors contributed equally
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Imail Cancer Center, Houston, TX, USA.

These authors contributed equally
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<u>Corresponding author:</u>

Naval G. Daver

Professor of Medicine,

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<u>Corresponding author:</u>
Naval G. Daver
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Department of Leukemia,
The University of Texas MD Reywords: *TP53*, MDS, AML. Venetoclax, allogeneic stem cell transpl
Corresponding author:
Naval G. Daver
Professor of Medicine,
Department of Leukemia,
The University of Texas MD Anderson Cancer Center,
1515 Holcombe Bl Reywords: 77.53, MDS, AML. Venetoclax, allogeneic stem cell transplantation

Corresponding author:

Naval G. Daver

Professor of Medicine,

Department of Leukemia,

The University of Texas MD Anderson Cancer Center,

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Email: <u>ndaver@</u>
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 Funding: The study was supported by University of Te

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 Funding: The study was supported by University of Texas MD Anderson SPOF

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Author COI:

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committee member for Pacyc Pharmaceuticals, Ryvu Therapeutics, and PTC Therapeutics; has been a board of directors or advisory
committee member for Pacyclex Pharmaceuticals, Novartis, CytomX, and Bio Ascend; and has been a
consultant for Gatamara Bi committee member for Pacyclex Pharmaceuticals, Novartis, CytomX, and Bio Ascend; and has been a
consultant for Catamaran Bio, AbbVie, PPD Development, Protagonist Therapeutics, and Janssen. NP has
received Consultancy/Scie consultant for Catamaran Bio, AbbVie, PPD Development, Protagonist Therapeutics, and Janssen. NP has
received Consultancy/Scientific Advisory Board/Speaking from Pacylex Pharmaceuticals, Astellas,
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Morphpsys. GCl has been a consu CancerNet, Harhorside Press, Karyopharm, Aptitude Health, Medscape, Magdalen Medical Publishing,
Morphpsys. GCl has been a consultant for Novartis, Kura Oncology, and NuProbe and received research
funding from Celgene, Kur Morphpsys. GCI has been a consultant for Novartis, Kura Oncology, and NuProbe and received research funding from Celgene, Kura Oncology, Syndax, Merck, Cullinan, and Novartis. MY has received research funding from DaichiSa funding from Celgene, Kura Oncology, Syndax, Merck, Cullinan, and Novartis. MY has received research funding from DaiichiSankyo and Pfizer. HMK has received research funding from AbbVie, Amgen, Ascentage Pharma, BMS, Daiic funding from DaiichiSankyo and Pfizer. HMK has received research funding from AbbVie, Amgen,
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relevant funding from Karyopham Therapeutical. Therapeutical disclosures and New York have not authors have no
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Author contribution:

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Abstract:

In myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) with TP53 aberrations, In invectory plustic syntheme (MDS) and active invector leader invertive (MDI) with TP53 aberrations, dissecting the interaction amongst patient, disease and treatment factors are important for therapeutic decisions and p decisions and prognostication. This retrospective analysis included patients with newly diagnosed MDS
(>5% blasts) and AML with *TP53* mutation(s) treated at MD Anderson Cancer Center. We factored
patient age, *TP53* aber (>5% blasts) and AML with *TP53* mutation(s) treated at MD Anderson Cancer Center. We factored patient age, *TP53* aberration burden, therapy intensity and use of venetoclax in the AML subgroup, and allogeneic hematopoiet (55% blasts) and AML With TF53 mutation₁) related at MD Anderson Cancer Center. We factored patient age, *TP53* aberration burden, therapy intensity and use of venetoclax in the AML subgroup, and allogeneic hematopoieti patient age, *n* 35 doctractor bateder, therapy intensity and use of venetoclax in the Kine subgroup, that
allogeneic hematopoietic stem cell transplantation (HSCT) to interrogate outcomes. *TP53* was annotated
as high-ris allogeneic hematopoietic stem cent ransplantation (HSCT) to metrogate outcomes. TF53 was annotated
as high-risk (TP53^{¹⁸) if >1 mutation, one mutation + allelic deletion or a single mutation with variant
allele frequenc} as high-risk (*IP*53^{HR}) if >1 mutation, one mutation + allelic deletion or a single mutation with variant allele frequency (VAF) ≥40%; *TP53* low risk (*TP53^{LE}*) included a single *TP53* mutation VAF <40%. 413 patient allele frequency (VAF) ≥40%; TP53 low risk (TP53⁻⁻") included a single TP53 mutation VAF <40%. 413
patients (291 AML, 122 MDS) at a median age of 69.4 years were included, 350 (85%) with TP53th (253
AML [87%], 97 [79% patients (291 AML, 122 MDS) at a median age of 69.4 years were included, 350 (85%) with *TP53*⁴⁶ (253 AML [87%], 97 [79%] MDS). Overall response (OR) rate was 53% in AML and 62% in MDS. OR and composite complete response Entry, 21 (1997), 1982), 1982), 1982), 1982), 1982), 1983 in a particular political response (CRc) rates was similar in patients with AML irrespective of treatment intensity, but higher when treated with venetoclax. At a intensity, but higher when treated with venetoclax. At a median follow-up of 77 months, median OS was
superior in patients with MDS than AML (10.8 versus 5.9 months). On multivariate analysis (MVA) MDS
had lower hazards of superior in patients with MDS than AML (10.8 versus 5.9 months). On multivariate analysis (MVA) MDS
had lower hazards of death compared to AML, as was $TP53^{18}$ and HSCT. In the AML cohort, $TP53^{18}$ and
HSCT were favorabl superior in patients with MDS than AML (10.8 versus 5.9 months).
had lower hazards of death compared to AML, as was $TP53^{LR}$ and l
HSCT were favorable on MVA, though venetoclax did not improve s
AML and burden of *TP53* ab HSCT. In the AML cohort, $TP53^{LR}$ and urvival. Both the diagnosis of MDS or nalysis and HSCT consistently led to had lower hazards of death compared to AML, as was $TP53^{\circ\circ}$ and HSCT. In the AML cohort, $TP53^{\circ\circ}$ and
HSCT were favorable on MVA, though venetoclax did not improve survival. Both the diagnosis of MDS or
AML and burde AML and burden of *TP53* aberrations dictated outcomes in our analysis and HSCT consistently led to
improved survival outcomes.
 AML and burden of TP53 aberrations dictated outcomes in our analysis and HSCT consistently led to
improved survival outcomes. improved survival outcomes.

Introduction:

ר a c t s (c i k c l c re myeloid leukemia (AML), though the outcomes of most patients with adverse-risk AML remain
dismal ¹⁻⁵. AML with *TP53* aberrations has particularly dismal outcomes due to resistance to various
treatments, including cyt acute must be variable my many metallicularly dismal outcomes due to resistance to various
treatments, including cytotoxic chemotherapy, epigenetic therapies, and apoptosis-inducing therapies
such a venetoclax ²⁶⁻⁸. Rece dismal ⁻⁻. AML with *TP53* aberrations has particularly dismal outcomes due to resistance to various
treatments, including cytotoxic chemotherapy, epigenetic therapies, and apoptosis-inducing therapies
such a venetoclax such a venetoclax 268 . Recent attempts to improve the outcomes of patients with *TP53* mutated (*TP53^{mut}*) AML have failed to improve survival, however extensive efforts are ongoing to leverage non-
chemotherapy-based such a venetoclax ^{2,6-9}. Recent attempts to improve the outcomes of patients with *IP53* mutated (*TP53^{mut}*) AML have failed to improve survival, however extensive efforts are ongoing to leverage non-
chemotherapy-bas ($IP53^{\text{min}}$) AML have failed to improve survival, however extensive efforts are ongoing to leverage non-
chemotherapy-based approaches to improve outcomes in these patients 3^{12} . Mutation-agnostic agents
including ven chemotherapy-based approaches to improve outcomes in these patients ²¹²². Mutation-agnostic agents
including venetoclax, in combination with low-intensity therapy have failed to improve outcomes of
patients with $TP53^{mit}$ mateurs with $TP53^{\text{mult}}$ AML $^{12\cdot16}$. However, whether these outcomes are homogenously dismal regardless
of the type of $TP53$ aberrations, treatment intensity, or type of therapy needs to be better understood.
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Despite allogene Despite allogeneic hematopoietic stem cell transplantation (HSCT) being the only potentially curative
Despite allogeneic hematopoietic stem cell transplantation (HSCT) being the only potentially curative
option for patient option for patients with *TP53* mutated AML, post-HSCT survival remains generally poor. In addition, the
impact of baseline *TP53* mutational burden and concomitant cytogenetics on HSCT outcomes remains
poorly defined.
Pr option for patients with TF53 mutated AML, post-HSCT survival reliants generally poor. In addition, the
impact of baseline TP53 mutational burden and concomitant cytogenetics on HSCT outcomes remains
poorly defined.
Previo impact or baseline *F153* mutational burden and concomitant cytogenetics on HSCT outcomes remains
poorly defined.
Frevious studies have annotated the allelic status of *TP53* using the mutational burden [variant allele
fr Previous studies
fraction (VAF)]
made importan
however, the in
aberrations is n
minimizing or e
mutated myelo
outcomes irresp
Routine laborat
bulk next-gener
can be used to i Previous studies have annotated the uniterated of *PF53* using the mutational butch (VAF) and *TP53* allelic loss (*TP53*¹⁰¹³) through cytogenetic assessment ¹⁷⁻¹⁹. These studies have made important contributions in co fraction (VAF)] and *TP53* allelic loss (*TP53*⁰⁰²) through cytogenetic assessment ¹⁷. These studies have made important contributions in correlating the burden of *TP53* aberrations with clinical outcomes; however, th

made important contributed is in conclading the butden of 1755 aberrations with clinical outcomes,
however, the interplay of blast burden and treatment regimens in conjunction with the burden of *TP53*
aberrations is not w however, the interplay of blast burden and treatment regimens in conjunction what the burden of TP53
aberrations is not well known and needs further characterization. A number of studies have suggested
minimizing or even o minimizing or even obviating the need for blast cutoffs in distinguishing TP53 mutated AML from TP53
mutated myelodysplastic neoplasms (MDS) with increased blasts, mostly due to their similarly poor
outcomes irrespective o mutated myelodysplastic neoplasms (MDS) with increased blasts, mostly due to their similarly poor
mutated myelodysplastic neoplasms (MDS) with increased blasts, mostly due to their similarly poor
outcomes irrespective of b outcomes irrespective of blast percentage and need for inclusion in clinical trials ²⁰⁻²⁴.
Routine laboratory methods such as conventional karyotyping, fluorescent *in situ* hybridization (FISH), bulk next-generation se outcomes irrespective of blast percentage and need for inclusion in clinical trials ²⁰-²⁴.
Routine laboratory methods such as conventional karyotyping, fluorescent *in situ* h
bulk next-generation sequencing (NGS), and Routine aboratory methods such as conventional karyotyping, morescent in situ hybridization (FISH),
bulk next-generation sequencing (NGS), and array-specific comparative genomic hybridization (aCGH)
can be used to infer th bulk next-generation sequences (NGS), and array-specific compressions, which along with patient age, fitness, blood and/or bone marrow (BM) blast percentage, can be used for prognostication and to guide treatment decisioncan be used to infer the allelic status and the burden of TF53 aberrations, which along with patient age,
fitness, blood and/or bone marrow (BM) blast percentage, can be used for prognostication and to guide
treatment deci freatment decision-making. In view of evolving data dissecting the outcomes of patients with TP53
mutated MDS and AML based solely on the burden of TP53 aberrations, we attempted to more
comprehensively study the outcomes treatment decision-making. In view of evolving data dissecting the outcomes of patients with TP53
mutated MDS and AML based solely on the burden of TP53 aberrations, we attempted to more
comprehensively study the outcomes mutation at MD and AML based solely on the burden of TP53 aberrations, we attempted to more
comprehensively study the outcomes of patients with newly diagnosed MDS and AML with TP53
mutation at MD Anderson Cancer Center (M comprehensively study the outcomes of patients with newly diagnosed MDS and AML with TP53
mutation at MD Anderson Cancer Center (MDACC) incorporating not just TP53 burden, but also age,
pathologic diagnosis (MDS vs. AML), mutation at MD Anderson Cancer Center (MDACC) incorporating not just T 53 burden, but also age, pathologic diagnosis (MDS vs. AML), treatment intensity, use of venetoclax and HSCT. The primary $\frac{5}{100}$

Methods:

boyective of the study was to compare the outcomes of patients with MDS and AML with TP53
mutations and then to focus on factors affecting outcomes of patients in the AML cohort.
Methods:
Patients and treatment
We perform Methods:

Patients and treatment

We performed a retrospective analysis of adult patients (218 years) with newly diagno

25% blasts) and AML as per World Health Organization 2016 criteria²⁵ at MDACC harborin

7P53 mutati We performed a retros

25% blasts) and AML as

7753 mutation +/- conc

percentage, cytogenetic

first remission, were ol

Institutional Review Bo

consent was obtained fr

Assessment of 7753 abe

7753 mutation analysis

Ne 25% blasts) and AML as per World Health Organization 2016 criteria²⁵ at MDACC harboring a pathogenic
25% mutation +/- concurrent deletion. Baseline parameters, including complete blood counts, BM blast
percentage, cytog 25% blasts) and AML as per World Health Organization 2016 criteria²⁴ at MDACC harboring a pathogenic TP53 mutation +/- concurrent deletion. Baseline parameters, including complete blood counts, BM blast percentage, cyto The sum and the vector of the sum that intensity, are of frontline venetoclax and HSCT in first remission, were obtained from the electronic medical records. The study was approved by the Institutional Review Board and co

TP53 mutation analysis:

First remission, were obtained from the electronic medical records. The study was approved by the
Institutional Review Board and conducted in accordance with the declaration of Helsinki. Informed
consent was obtained from Institutional Review Board and conducted in accordance with the declaration of Helsinki. Informed

consent was obtained from all participants.
 Assessment of TP53 aberrations
 TP53 mutation analysis:

Next-generation Institutional Review Board and participants.
 Institutional Review Board and Conduct And Conduct And Conducted in and conduct and conduct and conduct and conducted in the detection of NAF 22%, as described previously and Example 18 Material and particle particle

Assessment of *TP53* aberrations

TP53 mutation analysis:

Next-generation sequencing (NGS) was p

interrogating the entire exonic or hotspot

presentation) frequently mutated in ノコ バ ド く フ ノ ミ Masessment of *H* 35 aberrations

TP53 mutation analysis:

Next-generation sequencing (N

interrogating the entire exonic

presentation) frequently mutat

detection of VAF ≥2%, as describ

TP53 allelic loss/deletion:

Alle interrogating the entire exonic or hotspot regions of 28, 53 or 81 genes (depending on the time of
presentation) frequently mutated in myeloid malignancies, including *TP53*, with a lower limit of
detection of VAF ≥2%, as

TP53 allelic loss/deletion:

Annotation of TP53 aberrations:

presentation) frequently mutated in myeloid malignancies, including TP53, with a lower limit of detection of VAF ≥2%, as described previously and detailed in the supplement ^{26,27}.
 TP53 allelic loss/deletion:

Allelic presentation) frequently mataked in invertor manghanteles, including TP53, with a lower limit of detection of VAF \geq 2%, as described previously and detailed in the supplement ^{26,27}.
TP53 allelic loss/deletion:
Alleli detection of VAF ≥2%, as described previously and detailed in the supplement ^{20,27}.
 TP53 allelic loss/deletion:

Allelic loss/deletion at the TP53 locus was studied using a combination of convention

and aCGH. Alleli 「ノミノハ」 (ミート) Annotation at the TP53 locus was studied using a combination of conventional karyotyping, FISH
and aCGH. Allelic loss/deletion was defined as described previously and detailed in the supplement^{28,29}.
Annotation of TP53 and aCGH. Allelic loss/deletion was defined as described previously and detailed in the supplement

Annotation of TP53 aberrations:

We classified our patient population based on the burden of *TP53* aberrations into *TP5* ノ ヽ (こ (ミ [Trefaxed our patient population based on the burden of Trips doctrations into Trips for this (TP53th) and TP53th with a focus on clinical relevance. Multihit TP53 aberrations included patients with >1 mutation, one (*TP53*^{em}) and *TP53*^{em} with a focus on clinical relevance. Multihit *TP53* aberrations included patients with >1 mutation, one *TP53* mutation + deletion, and a *TP53* mutation + copy neutral loss of heterozygosity \sim 1 mutation, one TF53 mutation + deletion, and a TF53 mutation + copy neutral loss of heterozygosity
(cnLOH) (assessed either through a-CGH or with high VAF (\geq 40%) as a surrogate)¹⁹. Thus, our *TP53*^{HR}
group in (cnLOH) (assessed either through a-CGH or with high VAF (≥40%) as a surrogate)¹⁹. Thus, our *TP53*^{-m}
group included patients with documented multihit status (**Group 1**: > 1 *TP53* mutation with VAF ≥2%,
[Supplemental group included patients with documented matrim status (Group 1: > 1 TP53 mutation with VAF \geq 2%, [Supplemental Figure 1]; Group 2: One *TP53* mutation [VAF \geq 2%] and concurrent 17p.13 deletion, and 6 $[500]$ supplemental Figure 1]; Group 2: One TP53 mutation $[VAT \simeq 2\%]$ and concurrent 17p.13 deletion, and

Group 3: *TP53* single hit mutations with VAF ≥40% ²⁷. The *TP53*²³ group included patients with a single mutation with a VAF <40% and no concurrent 17p.13 deletion.
Response and outcomes
Response and outcomes
Respons Response and outcomes
Response was annotated per the European LeukemiaNet (ELN
International Working Group criteria for MDS ³¹. Best respon
prior to HSCT. Overall response (OR) included a combinatio
remission with incomp Response was annotated
International Working Gl
prior to HSCT. Overall r
remission with incomplet
and CR and BM CR for MI
relapse, transformation t
(OS) was calculated from
follow-up.
Statistical analysis
Mann-Whitney U te Response was annotated per the European LeukemiaNet (ELN) 2017 guidelines for AML²⁰ and the 2006
International Working Group criteria for MDS³³. Best response after frontline therapy was recorded,
prior to HSCT. Overal International Working Group criteria for MDS "". Best response after frontline therapy was recorded,
prior to HSCT. Overall response (OR) included a combination of complete remission (CR), complete
remission with incomplet prior to HSCT. The HSCT. The HSCT. The HSCT. The HSCT. The tem ission with incomplete counts recovery (CRi) and morphological leukemia free state (MLFS) for AML, and CR and BM CR for MDS. Relapse-free survival (RFS) was ca

remines and BM CR for MDS. Relapse-free survival (RFS) was calculated from the time of best response to
relapse, transformation to AML (for MDS patients) or death. We did not censor for HSCT. Overall survival
(OS) was calc relapse, transformation to AML (for MDS patients) or death. We did not censor for HSCT. Overall survival
(OS) was calculated from the time of therapy initiation to death from any cause and censored at last
follow-up.
Stati (OS) was calculated from the time of therapy initiation to death from any cause and censored at last

follow-up.

Statistical analysis

Mann-Whitney U test and a 2-sided Fisher T test were used to compare continuous and ca (OS) was calculated from the time of the
Mann-Whitney U test and a 2-sided Fisher T test were used to compare continuous and categorical
baseline vari Statistical

Statistical

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9 3 1 (Gran vin her die komme van die voorvan die van die v Mann-Whitney U

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analysis was done

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9.3.1 (GraphPad S

solution. baseline variables. A P value of <0.05 was considered significant. Survival data were calculated using the Kaplan Meier test and compared using the Mantel Cox log-rank test. Follow up was calculated using reverse Kaplan Me baseline variables. A P value of sells was considered significant. Survival data were circulated using reverse Kaplan Meier method. Cox proportional hazard was used to study disease and treatment factors associated with OS reverse Kaplan Meier method. Cox proportional hazard was used to study disease and treatment factors
associated with OS through univariate (UVA) and multivariate analysis (MVA). For MVA, factors
biologically relevant on th reverse Imperial interatmental in proportional and interatmental and the state of State State State State State
State State State (INT) model as a predictive decision-making tool for survival at 1-year. Propensity score
an associally relevant on the UVA model and/or those with P<0.1 were used. We used a classification and regression tree (CRT) model as a predictive decision-making tool for survival at 1-year. Propensity score analysis was do regression tree (CRT) model as a predictive decision-making tool for survival at 1-year. Propensity score
analysis was done by comparing logit of propensity scores from baseline covariates and using a caliper
width of sigm

Results:

analysis was done by comparing logit of propensity scores from baseline covariates and using a caliper
width of sigma 0.1 with an optimal selection algorithm. Analysis was done using GraphPad Prism version
9.3.1 (GraphPad analysis must satisfy comparing logit of propensity scales from baseline consing GraphPad Prism version
9.3.1 (GraphPad Software, Boston, MA) and the Lumivero (New York, NY) (2023) XLSTAT statistical
solution.
Results:
We when the sigma disc must are planet as a statement of sigma must an optimal selection.

S. S.1 (GraphPad Software, Boston, MA) and the Lumivero (New York, NY) (2023) XLSTAT statistical

solution.

Nesults:

We identified 4 solution.

Results:

We identified 413 unique patients with newly diagnosed AML (291 [70.5%]) and MDS (122 [29.5%])

harboring a known pathogenic 7P53 mutation with available cytogenetic (CTG) data between January

2013 to Results:
We ident
harboring
2013 to J
69.4 year
age was Narboring a known pathogenic *TP53* mutation with available cytogenetic (CTG) data between January 2013 to July 2022. Baseline characteristics are summarized in **Table 1.** The median age at diagnosis was 69.4 years (range harboring a known pathogenic 7733 mutation with available cytogenetic (CTG) data between January
2013 to July 2022. Baseline characteristics are summarized in **Table 1.** The median age at diagnosis was
69.4 years (range, 2013 to July 2022. Baseline characteristics are summarized in Table 1. The median age at diagnosis was
69.4 years (range, 18.2-90.4 years); 321 patients (78%) were ≥ 60 years. In the AML group, the median
age was 70 y Frange was 70 years (range, 20.1-87 years). The median age in the MDS cohort was 69 years (range 18.2-1900) were very statents (79%) were $\frac{1}{2}$

TP53 allelic status:

91.4 years). The median BM aspirate and provides in the MDS constant that is (20%) and the median BM blasts at diagnosis.
 1953 allelic status:
 1953 allelic status:
 1953 allelic status:
 19753 allelic status:
 PERTURE (47.4) MARTLE 10 MARTLE 10 MARTLE 10 MARTLE 17.53
 PP53 allelic status:
 210 SPS patients (18%) had a complex karyotype (CK
 2 patients (15%) had $TP53^{\text{LR}}$ [38 patients (13%)
 (Supplemental Figure 1 [Fi 立ち こうくく くうしょう トライ・ドラ 358 patients (87%) had a complex karyotype (CR) including 350 patients (46%) with 1735 deletion. Only 2 patients (15%) had 7P53¹⁸ [38 patients (13%) with AML and 25 patients (20%) with MDS, p=0.07]
(**Supplemental Figure**

2 patients (15%) had 7*F53*^{L8} [38 patients (13%) with AML and 25 patients (20%) with MDS, $p=0.07$]
(**Supplemental Figure 1 [Figure S1]**). The median VAF in the patients with *TP53*^{L8} was 21% (range, 2%-33%) and 45/63 63 patients (15%) had *TP53*¹¹ [38 patients (13%) with AML and 25 patients (20%) with MDS, $p=0.07$]
(**Supplemental Figure 1 [Figure S1]**). The median VAF in the patients with *TP53^{LR}* was 21% (range, 2%-33%) and 45/6 (Supplemental Figure 1 [Figure S1]). The median VAF in the patients with *TP53*⁻" was 21% (range, 2%-33%) and 45/63 patients (71%) had a VAF ≥10%. The median *TP53*^{LR} VAF was 20% (range, 2%-37%) in the MDS group and 2 39%) and 45/63 patients (71%) had a VAF ≥10%. The median *IP53*³⁶ VAF was 20% (range, 2%-37%) in the MDS group and 23% (range, 2%-39%) in the AML group, *P*=0.40. In the T*P53¹⁸* group 37 patients (59%) had a complex MDS group and 23% (range, 2%-39%) in the AML group, $P=0.40$. In the $IP53$ ¹⁸ group 37 patients (59%) had a complex karyotype (20 of 38 [53%] with $TP53$ ¹⁸ AML and 17 of 25 [68%] with TP53¹⁸ MDS).
A total of 350 patien had a complex karyotype (20 of 38 [53%] with *IP53*³⁶ AML and 17 of 25 [68%] with IP53³⁶ MDS).
A total of 350 patients (85%) had a *TP53^{HR}* aberration, of whom 111 patients (32%) had multip
mutations (Group 1). Among ノ 「 = = = (ニ (ニ = = = = = A total of 350 patients (85%) had a *IP53*³⁶⁶ aberration, of whom 111 patients (32%) had multiple *IP53*
mutations (Group 1). Among these, 65 patients (59%) had a VAF sum of ≥50% (43 with AML and 35 with
MDS) and 47 (41 MDS) and 47 (41%) had a VAF sum <50% (35 with AML and 12 with MDS). There was no difference in OS
based on *TP53* VAF sum in the full cohort or the AML and MDS cohorts, when analyzed separately
(Figure 52). Based on this, based on *TP53* VAF sum in the full cohort or the AML and MDS cohorts, when analyzed separately (**Figure S2).** Based on this, all patients with multiple *TP53* mutations were considered to have multihit *TP53* status irre based on *H* 53 VAF sum in the full cohort of the AML and MDS collone, when analyzed separately (Figure 52). Based on this, all patients with multiple *TP53* mutations were considered to have multihit *IP53* status irrespe (Figure 32). Based on this, all patients with multiple Tr. 35 mutations were considered to have multime TP53 status irrespective of the VAF sums, for subsequent analysis. The $TP53$ ^{tim} cohort also included 112 (32%) pati TP53 status irrespective of the VAF sums, for subsequent analysis. The TP53^h cohort also included 112 (32%) patients with a single TP53 mutation and a TP53 deletion [Group 2; median TP53 VAF:33% (range, 2%-93%);71/112 ((32x) patients with a single TF53 mutation and a TF53 deletion [Group 2; median TF53 vAT:33% (range, 2%-93%);71/112 (63%) with *TP53* VAF <40%]. and 127 patients (36%) with a single *TP53* mutation 240% (Group 3; median 2% 35%);12/112 (63%) with TP53 VAF seosy. and 127 patients (36%) with a single TP53 matation 25%
(Group 3; median TP53 VAF :69% (range, 40%-97%)]. We validated the VAF cutoff for patients with single
a TP53 mutation in the [Group 3; median *H* 53 VAF:69% (range, 40%-97%)]. We validated the VAF clubri for patients with single
a TP53 mutation in the AML cohort using decision trees from a CRT model. A TP53 VAF >37.5% (very
close to our VAF cuto close to our VAF cutoff of 40% for calling *TP53*^{HR}) had the best discriminatory power to predict OS at 1 year and was associated with OS < 1 year in 78% patients (**Figure 53**). Further details are in the supplement (**Fi**

Treatment and response outcomes:

close to our VAF cutoff of 40% for calling $TP53$ "") had the best discriminatory power to predict OS at 1
year and was associated with OS < 1 year in 78% patients (Figure S3). Further details are in the
supplement (Figure year and was associated with OS < 1 year in 78% patients (righte 35). Further details are in the supplement (Figure **S4-55**).

Missense mutations were the most common, occurring in 361 patients (87%), followed by frameshif Supplement (Figure 34-33).
Missense mutations were tl
42 patients (10%), nonsense
Treatment and response or
Overall, 319 patients (77%
patients (82%) with MDS.
therapy, 201 (86%) of whon A 2 patients (10%), nonsense in 31 patients (7%) and splice site mutations in 10 patients (2%) (Figure S6).

Treatment and response outcomes:

Overall, 319 patients (77%) were treated on a clinical trial, 219 (75%) patient Freatment and response outcomes:

Overall, 319 patients (77%) were treated on a clinical trial, 219 (75%) patients with AML and 100

patients (82%) with MDS. In the AML group, 234 patients (80%) were treated with low-inten patients (82%) with MDS. In the AML group, 234 patients (80%) were treated with low-intensity
therapy, 201 (86%) of whom received hypomethylating agent (HMA)-based therapy. Amongst these 234
8 patherapy, 201 (86%) of whom received hypomethylating agent (HMA)-based therapy. Amongst these 234 8

patients, 81 (35%) received venetoclay and 213 patients, 812 (74%) patients were \leq 60 years and only 9 patients (15%) received concurrent venetoclax (Table S1).
Amongst patients with AML, an OR was attained in 155 patie wears and only 9 patients (15%) received concurrent venetoclax (Table S1).

Amongst patients with AML, an OR was attained in 155 patients (53%) and a composite complete

response (CRc) [CRc=CR+CRi] in 129 (44%) (Figure S7) years and only 9 patients (15%) received concurrent venetoclax (Table 31).

Amongst patients with AML, an OR was attained in 155 patients (53%)

response (CRc) [CRc=CR+CRi] in 129 (44%) (Figure S7). Thirty-one patients

20

ノ 「 ニ ノ i ̄ g (r r Materian: (CRC) [CRC=CR+CRi] in 129 (44%) (Figure S7). Thirty-one patients (11% of full AML group and
20% of responders) proceeded to HSCT in first remission. The median age of the transplanted patients at
AML diagnosis wa response (ene) [crce=crecting in 129 (44%) (Figure 97). Thirty-one patients (11% of full Amle group and 20% of responders) proceeded to HSCT in first remission. The median age of the transplanted patients at AML diagnosis 2008 of responders) proceeds to HSCT (Figure S8A).

The most common treatment in the MDS group was HMA, used in 114 patients (93%) and cumulatively

The most common treatment in the MDS group was HMA, used in 114 patients The most common treatment in the MDS gro
8 patients (6%) had received venetoclax as p
62%), of whom 43 patients (30%) had a CR (
proceeded to an HSCT. Twenty-two patients
responders and 6 patients amongst them had
TP53 ab | ג (ה ב ב)
| ג ה ב ד ה ב (ד ה ב)

TP53 aberration status and survival outcomes:

(95% C.I. 2.5-5.6 months) and 5.9 months respectively (95% C.I. 5.3-7.3 months); for patients with MDS 8 patients (6%) had received venetoclax as part of frontline therapy. An OR was attained in 76 patients (62%), of whom 43 patients (30%) had a CR (Figure 57). Overall, 23 responders (20% of full MDS group) proceeded to an 8 patients (62%), of whom 43 patients (30%) had a CR (Figure 57). Overall, 23 responders (20% of full MDS group)
proceeded to an HSCT. Twenty-two patients (18%) transformed to an AML, 16 of whom were
responders and 6 patie (62%), of whom 43 patients (50%) had a CR (Figure S7). Overall, 23 responders (20% of full MDS group)
proceeded to an HSCT. Twenty-two patients (18%) transformed to an AML, 16 of whom were
responders and 6 patients amongst proceeded to a HSCT (Figure S8B).
 PP53 aberration status and survival outcomes:

The median follow-up of the whole cohort was 77.8 months (95% CI 77-90 months); 78 months for AML

and not reached for the MDS group. The **TP53 aberration status and survival outcomes:**
The median follow-up of the whole cohort was 77.8 months (95% CI 77-90 months)
and not reached for the MDS group. The median RFS and OS in the patients with ,
(95% C.I. 2.5-ユーニ ミ (t l l (・ l)

and not reached for the MDS group. The median RFS and OS in the patients with AML was 4.7 months
(95% C.I. 2.5-5.6 months) and 5.9 months respectively (95% C.I. 5.3-7.3 months); for patients with MDS
the median RFS and OS (95% C.I. 2.5-5.6 months) and 5.9 months respectively (95% C.I. 5.3-7.3 months); for patients with MDS
the median RFS and OS were 5.9 months (95% C.I. 3.9-7.7 months) and 10.8 months (95% C.I. 9.1-11.9
months) respectivel The median RFS and OS were 5.9 months (95% C.I. 3.9-7.7 months) and 10.8 months (95% C.I. 9.1-11.9 months) respectively (Figure 1).

In the full cohort, the median OS was significantly longer in patients with $7P53^{18}$ c months) respectively (**Figure 1).**

In the full cohort, the median OS was significantly longer in patients with $TP53^{th}$ compared with $TP53^{th}$

(12.1 months versus 6.8 months, P<0.001) while there was no significant diff In the full cohort, the median O
(12.1 months versus 6.8 month
 $TP53^{\text{HR}}$ (Figure 2A, S9A). Stratifyi
compared to the $TP53^{\text{HR}}$ (14.3 vs
 $TP53^{\text{HR}}$ groups (11.6 months in G
rank for trend 0.67) (Figure S9B)
5.4 months In the full cohort, the median OS was significantly longer in patients with $IP53^{10}$ compared with $IP53^{10}$
(12.1 months versus 6.8 months, P<0.001) while there was no significant difference between type of
 $IP53^{18}$ (F TP53^{tiR} (Figure 2A, S9A). Stratifying by diagnosis, in the MDS cohort, OS was significantly better in TP53^{LR}
compared to the TP53^{LR} (14.3 vs. 9.3 months, P= 0.06 (Figure 2B) There was no difference amongst the 3
TP5 *TP53*^{III} (Figure 2A, S9A). Stratifying by diagnosis, in the MDS cohort, OS was significantly better in *IP53*^{III}
compared to the *TP53*^{II}⁸ (14.3 vs. 9.3 months, P= 0.06 (Figure 2B) There was no difference amongst compared to the *IP53*th (14.3 vs. 9.3 months, P= 0.06 (Figure 2B) There was no difference amongst the 3

TP53^{HR} groups (11.6 months in Group 1 versus 10.1 months in Group 2 and 8.4 months in Group 3, p log-

rank for TP53^{III} groups (11.6 months in Group 1 versus 10.1 months in Group 2 and 8.4 months in Group 3, p log-
rank for trend 0.67) (Figure S9B). Patients with TP53^{LR} AML had a better OS of 10.4 months compared to
5.4 months rank for trend 0.67) (Figure S9B). Patients with *TP53*^{LIA} AML had a better OS of 10.4 months compared to 5.4 months in patients with *TP53*^{LIR} AML (P= <0.01) (Figure 2C). The median OS was slightly better in Group 2 5.4 months in patients with TP53^{HR} AML (P= <0.01) (Figure 2C). The median OS was slightly better in Group 2 TP53^{HR} at 6.9 months compared with 5.6 months (Group 3) and 4.4 months (Group 1) (P= for trend 0.02). Despite Group 2 TP53^{hrm} at 6.9 months compared with 5.6 months (Group 3) and 4.4 months (Group 1) (P= for
trend 0.02). Despite statistical significance the absolute durations of response were short and dismal in
g

MDS vs AML survival outcomes

all 3 *TP53*^{tin} sub-groups (Figure S9C). Twenty of 38 (53%) patients with AML *TP53*th had a CK (without *TP53* deletion) and an inferior survival of 8.2 months, compared to the remainder *TP53th* patients with AML TP53 deletion) and an inferior survival of 8.2 months, compared to the remainder TP53¹¹ patients with AML who did not have a CK (12.7 months, P= 0.04). The median TP53 VAF was not different between the 2 groups (25% ver 2 groups (25% versus 22%, P=0.63) (Figure **S10A)**. Though limited by very small patient numbers, there was no different in OS in the MDS $TP53^{L8}$ group based on CK (Figure **S10B).**

MDS vs AML survival outcomes

In patie Example 125% versus 22%, P=0.63) (Figure 2304). Findely minited by very small patient numbers, there was no different in OS in the MDS $TP53^{16}$ group based on CK (Figure S10B).

MDS vs AML survival outcomes

In patients was no different in OS in the MDS *TP53*^{LR} group based on CK (Figure S10B).

MDS vs AML survival outcomes

In patients with MDS, there was no difference in median OS based on 5-1

versus 11.6 months, P=0.21). However, OS In patients with MDS, irrespective of blast
percentage, compared to AML (Figure S11). Amongst patients with TP53¹⁸, there was a significant
difference in OS between the MDS and AML group (9.3 and 5.4 months respectively, percentage, compared to AML (Figure **S11).** Amongst patients with $TP53^{\text{th}}$, there was a significant difference in OS between the MDS and AML group (9.3 and 5.4 months respectively, P=0.001), however there was no signif percentage, compared to AML (Figure S11). Amongst patients with *IP53th*, there was a significant difference in OS between the MDS and AML group (9.3 and 5.4 months respectively, P=0.001), however there was no significan

there was no significant difference in OS between *TP53*^{LR} MDS and AML (14.3 versus 10.5 months respectively, P=0.83) (Figure 512). We then selected the patients with *TP53*^{LR} AML (n=23) and MDS (n=16) who underwent HS there was no significant difference in OS between *TP53*¹⁸ MDS and AML (14.3 versus 10.5 months
respectively, P=0.83) (Figure **S12)**. We then selected the patients with *TP53*¹⁸ AML (n=23) and MDS
(n=16) who underwent respectively, P=0.83) (Figure S12). We then selected the patients with $1P53$ ¹⁸ AML (n=23) and MDS
(n=16) who underwent HSCT; the median survival was similar at 12.6 months and 15.4 months
respectively, P= 0.73 (Figure (netable 13). The numbers in the *TP53*¹⁸ HSCT arms were too small for a salient

emparison.

We performed Cox regression analysis accounting for MDS or AML diagnosis, age (</260 years), *TP3*

status (*TP53¹⁸*, versu respectively, $P= 0.73$ (Figure S13). The numbers in the $IP53$ ²⁶ HSCT arms were too small for a salient
comparison.
We performed Cox regression analysis accounting for MDS or AML diagnosis, age (\langle 260 years), TP3
stat Comparison.
We perform
status (*TP53[†]*
had significa:
with AML, al
other covari:
comparison (
TP53^{HR} versu
difference o
incidentally t
matched aga We performed Cox regression analysis accounting for MDS or AWL diagnosis, age ($\sqrt{2}$ CO years), TTS
status ($TP53^{18}$) ersus $TP53^{18}$), CTG (CK or not), use of venetoclax and HSCT; on MVA patients with MDS
had significan status (*TP53*^{III}</sup> versus *TP53*^{III}), CTG (CK or not), use of venetoclax and HSCT; on MVA patients with MDS
had significantly reduced risk of death (Hazard ratio [hr]=0.76, 95% Cl 0.61-0.94) compared to patients
with A with AML, along with *TP53*^{LR} (hr=0.66, 95% CI 0.48-0.89) and HSCT (hr=0.42, 95% CI 0.30-0.57) while
other covariates were not significant (**Table 2).** We subsequently performed a propensity matched
comparison of patien with AML, along with *IP53*ⁿ (hr=0.66, 95% CI 0.48-0.89) and HSCI (hr=0.42, 95% CI 0.30-0.57) while
other covariates were not significant (**Table 2)**. We subsequently performed a propensity matched
comparison of patients comer covariates were not significant (Table 2). We subsequently performed a propensity matched
comparison of patients in the MDS cohort to the AML cohort, including age (continuous), *TP53* status
(*TP53th*, extains 105 comparison of patients in the MDS conort to the AML cohort, including age (continuous), 77.53 status
(TP53th) ersuss TP53th), attainment of OR and HSCT as variables; amongst 23 matched pairs there was no
difference of (*TP53*⁻ wersus *TP53*⁻), attainment of OR and HSCI as variables; amongst 23 matched pairs there was no difference of median OS between the 2 groups (17.3 versus 13.9 months respective, P= 0.69); incidentally this matc incidentally this matching selected 23 patients in each group who had undergone an HSCT. We thus
matched again discounting the patients who had undergone HSCT and maintaining the other variables;
all 99 non-transplanted p matched again discounting the patients who had undergone HSCT and maintaining the other variables;
all 99 non-transplanted patients in the MDS group could be adequately matched to 99/260 non-
transplanted patients in the all 99 non-transplanted patients in the MDS group could be adequately matched to 99/260 non-
transplanted patients in the AML group. The median OS was significantly shorter in the AML compared
to the MDS group; 5.3 versus to the MDS group; 5.3 versus 9.3 months respectively, $P=0.001$ (Figure 3). Finally, we used the full dataset of 413 patients (AML + MDS) and proceeded with a CRT using the diagnosis (MDS vs AML), age \geq /< 60 years and dataset of 413 patients (AML + MDS) and proceeded with a CRT using the diagnosis (MDS vs AML), age \ge /< 60 years and *TP53* aberration status; the primary decision node was *TP53* status, with a 75% 10 \ge /< 60 years and *TP53* aberration status; the primary decision node was *TP53* status, with a 75%
10 $\frac{2}{5}$ < 60 years and TP53 aberration status; the primary decision node was TP53 status, with a 75%

HSCT, TP53 status and outcomes in AML and MDS

mortality within 1 year in patients with *TP53*¹¹¹. The *TP53* status predicted survival at 1 year more
strongly than the diagnosis of MDS or AML (Figure **S14**).
HSCT, *TP53* status and outcomes in AML and MDS
A total of **HSCT, TP53 status and outcomes in AML and MDS**
A total of 32 patients (11%) (9 of 38 [24%] patients with
P =0.02) with AML at a median age of 61.3 years (ran
median of 3.7 months of therapy (range, 2.1-7.4 months
2-year ■ ノ F r s a \ \ a r t A total of 32 patients (11%) (9 of 38 [24%] patients with *TP53*²³ and 23 of 253 [9%] patients with *TP53*²⁸, $P = 0.02$) with AML at a median age of 61.3 years (range, 20-73.6 years) could proceed to HSCT at a median P =0.02) with AML at a median age of 61.3 years (range, 20-73.6 years) codic proceed to fisch at a median of 3.7 months of therapy (range, 2.1-7.4 months) leading to a median survival of 14 months and 2-year OS of 32%; th 2-year OS of 32%; this was significantly superior to a landmark comparison of patients <70 years who attained a response but did not undergo HSCT (14 versus 9.4 months, p log-rank 0.001) (Figure 4A-B).
When comparing the 2) Figure 2020 and this dignition, γ is a land to a statistically significant improvement in OS (12.6 versus 9 months, $P = 0.009$). Amongst the patients with AML who underwent an HSCT, 17 (7 TP53^{LR} and 16 TP53^{LR}) h attained a response but dia not undergo HSCT (14 versus 3.4 montais, p log tame 0.001) (Figure 4A b).
When comparing the TP53^{H8} AML, again HSCT led to a statistically significant improvement in OS (12.6
versus 9 months, When comparing the *IP53*^{-*} AML, again HSC1 led to a statistically significant improvement in OS (12.6 versus 9 months, *P*= 0.009). Amongst the patients with AML who underwent an HSCT, 17 (7 *TP53^{LR}*) and a best resp versus 9 months, P= 0.009). Amongst the patients with AML who underwent an HSC1, 17 (7 TP53^{us} and 16 TP53^{H8}) had a best response of MRD negative CRc before HSCT, and the other 15 patients (3 TP53^{us} and 12 TP53¹¹⁸) 16 *TP53*¹¹⁶) had a best response of MRD negative CRc before HSCT, and the other 15 patients (3 *TP53*²¹⁶) and 12 *TP53¹¹⁸*) were positive for MRD by flow cytometry (13 CRc, 1 MLFS and 1 stable disease). The median O

and 12 *IP53*¹⁸) were positive for MRD by flow cytometry (13 CRc, 1 MLFS and 1 stable disease). The
median OS of patients with MRD negative before HSCT was 29.5 months compared to 10.0 months for
those who were MRD posi those who were MRD positive before HSCT (p<0.001). Selecting only patients with TP53^{^{HR}, the median OS was 26.4 months who were MRD negative compared to 9.5 months who were MRD positive before HSCT (p=0.003) (Figure 4C-} those who were MRD positive before HSC1 (p<0.001). Selecting only patients with IP53^{**}, the median OS was 26.4 months who were MRD negative compared to 9.5 months who were MRD positive before HSCT (p=0.003) (Figure 4C-D) HSCT (p=0.003) (Figure 4C-D).

In the MDS group 23 patients (18.8%) (median age of 63.4 years, range 18.2-76 years) underwent an

HSCT [7 of 25 (28%) patients with $7PS3^{18}$ and 16 of 97 (16%) patients with $7PS3^{18}$] wit HSCT (p=0.003) (Figure 4C-D).
In the MDS group 23 patient:
HSCT [7 of 25 (28%) patients \
17.3 months and 2-year OS o
(range 2.9-17.7 months). On a
patients who had a response
versus 12.4 months, P=0.02) i
comparator group IN SCT [7 of 25 (28%) patients with $7PS3^{18}$ and 16 of 97 (16%) patients with $7PS3^{18}$] with a median OS of
17.3 months and 2-year OS of 32%. The median time to HSCT post therapy initiation was 5.4 months
(range 2.9-17. HSCT | *I* of 25 (28%) patients with *IP53*ⁿ and 16 of 97 (16%) patients with *IP53*ⁿⁿ] with a median OS of
17.3 months and 2-year OS of 32%. The median time to HSCT post therapy initiation was 5.4 months
(range 2.9-(range 2.9-17.7 months). On a landmark analysis comparing transplanted patients to non-transplanted
patients who had a response and <70 years of age at diagnosis, HSCT significantly improved OS (17.3
versus 12.4 months, P= (range 2.12.4 months, P=0.02) (Figure 4E-F). On selecting only 7P53^{HR} patients in the transplanted OS (17.3 versus 12.4 months, P=0.02) (Figure 4E-F). On selecting only 7P53^{HR} patients in the transplanted and comparato particular who had a response and surface and the response and the transplanted and comparator group, again transplanted patients had a superior OS (15.5 versus 11.9 months, P=0.05) on landmark analysis.

Assessment of fac versus 12.4 months, P=0.02) (Figure 4E-F). On selecting only 7P53^h patients in the transplanted and
comparator group, again transplanted patients had a superior OS (15.5 versus 11.9 months, P=0.05) on
landmark analysis.

Assessment of factors affecting survival in AML

comparator and the AML cohort we analyzed disease and treatment related factors that affected the rates of HSCT and survival.
Focusing on the AML cohort we analyzed disease and treatment related factors that affected the r Assessment of fact
Focusing on the AM
of HSCT and surviva
Venetoclax, treatm Focusing on the AML continues and all cohort we are achieved that a factor of HSCT and survival.

Senetoclax, treatment intensity and outcomes in AML:

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Venetoclax, treatmen
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. \overline{a} Venetoclax, treatment intensity and outcomes in AML: A CRc and OR was attained in 21/38 (55%) and 27/38 (71%) patients with $TP53^{\text{un}}$ compared to 108/253 (43%) (P=0.16) and 128/253 (36%) (P=0.02) patients with $TP53^{\text{un}}$. On UVA, $TP53^{\text{un}}$ and use of venetoclax was ass

(43%) (P=0.16) and 128/253 (36%) (P=0.02) patients with $7P53$ ¹¹⁶. On UVA, $7P53$ ¹¹⁶ and use of venetoclax was associated with higher odds of response in AML while CK was associated with lower odds for OR. On MVA incl MVA including CTG, *TP53* status, use of venetoclax and treatment intensity as variables, *TP53^{IR}*
continued to favor odds of response compared to *TP53^{IIR}* (Odds ratio 2.415, 95% CI 0.99-4.95) along with
venetoclax (MVA including CTG, TP53 status, use of venetoclax and treatment intensity as variables, TP53¹¹
continued to favor odds of response compared to $TP53^{118}$ (Odds ratio 2.415, 95% CT 0.99-4.95) along with
venetoclax (Odds continued to favor odds of response compared to 7P53⁻⁻⁻ (Odds ratio 2.415, 95% CI 0.99-4.95) along with
venetoclax (Odds ratio 2.09, 95% CI 1.30-3.78) while other variables were not independently significant
(**Table S2**) (Table S2).

Two-hundred thirty-four (80%) patients with AML received a low-intensity therapy of whom 202 (86%)

had 7P53^{HR} (Table S3). Amongst the 57 patients treated with intensive therapy, 51 (89%) patients had

7P53 Two-hundro
had *TP53^{HR}
TP53^{HR}. An
TP53^{HR}. An
(53%) (CRc
arm, an OF
There was
were highe
9%, <i>P*=0.03
median age
years of a_l had *TP53*¹¹⁸ (**Table S3).** Amongst the 57 patients treated with intensive therapy, 51 (89%) patients had *TP53*¹¹⁸. An OR was seen in 130 patients (56%) (CRc:44%) treated with low-intensity therapy and 107/202 (53%) (had *IP53*^{ne}. **An** OR was seen in 130 patients treated with intensive therapy, 51 (89%) patients had *IP53¹⁸*. An OR was seen in 130 patients (56%) (CRc:44%) treated with low-intensity therapy and 107/202 (53%) (CRc: 4 *IP53*^m. An OR was seen in 130 patients (56%) (CRc:44%) treated with low-intensity therapy and 107/202 (53%) (CRc: 43%) patients with *TP53*^{HR} treated with low-intensity therapy. In the intensively treated arm, an OR w (53%) (CRc: 43%) patients with *TP53*" treated with low-intensity therapy. In the intensively treated arm, an OR was seen in 25/57 (44%) (CRc:44%) and in 21/51 (41%) (CRc:41%) patients with *TP53*^{IH}.
There was no differ arm, an OR was seen in 25/57 (44%) (CRc:44%) and in 21/51 (41%) (CRc:41%) patients with *IP53*⁻⁻.
There was no difference in RFS and OS based on treatment intensity (**Figure S15)**. The rates of HSCT
were higher for patie

mere was no difference in RFS and OS based on treatment intensity (Figure S15). The rates of HSC is
overe higher for patients treated with intensive therapy compared to low-intensity therapy (19% versus
9%, P=0.03) despite 9%, P=0.03) despite comparable response rates between the two arm, possibly because of the lower
median age in the intensively treated patients (56.6 years versus 72.2 years, P<0.0001). In patients <60
years of age (n=63) 9%, P=0.03) despite comparable response rates between the two arm, possibly decause of the lower-
median age in the intensively treated patients (56.6 years versus 72.2 years, P<0.0001). In patients <60
years of age (n=63 years of age (n=63), there was no difference in OS between intensive and low-intensity therapy,
irrespective of *TP53* burden (**Figure S16**).
With respect to venetoclax, overall, 90 patients (31%) had received venetoclax Frespective of *TP53* burden (**Figure S16).**
With respect to venetoclax, overall, 90 patients (31%) had received venetoclax of whom 81 patients
(90%) were treated with low-intensity therapy (**Table S4**). The rates of CRc a With respective of H 53 burden (Figure 316).
With respect to venetoclax, overall, 90 |
(90%) were treated with low-intensity th
patients treated with venetoclax contain
receive venetoclax (40%, P=0.02 and 48
 $TP53^{\text{HR}}$, ヽヽ (´´; ´; ´ * (´´ ´; ´ (90%) were treated with low-intensity therapy (**Table S4**). The rates of CRc and OR was higher in the patients treated with venetoclax containing regimens (54% and 66%) compared to those who did not receive venetoclax (40 (90%) were treated with low-intensity therapy (Table 34). The rates of CRc and OR was ingite in the patients treated with venetoclax containing regimens (54% and 66%) compared to those who did not receive venetoclax (40%, patients treated with containing regiment (streated with venetoclax (40%, P=0.02) and 48%, P=0.005 respectively). When selecting only patients with $TP53^{\text{HR}}$, again, rates of CRc and OR was higher when patients were tre $TPS3¹⁸$, again, rates of CRc and OR was higher when patients were treated with venetoclax (54% vs.
37%, P=0.02 and 63% vs. 44%, P=0.005 respectively). However, HSCT rates, RFS and OS were similar
between patients tr *IP53*⁻⁻, again, rates of CRc and OR was higher when patients were treated with venetoclax (54% vs.
37%, P=0.02 and 63% vs. 44%, P=0.005 respectively). However, HSCT rates, RFS and OS were similar
between patients treate ³⁷
37%, Person patients treated with or without venetoclax in the full AML cohort as well as *TP53*^{HR} AML group
537 (Figure S17). The 60-day mortality was similar in patients who received low-intensity therapy with or
 between patients treated with or without venetoclax in the full AML cohort as well as *IP53*⁴⁶ AML group (Figure S17). The 60-day mortality was similar in patients who received low-intensity therapy with or without venet (Figure S17). The 60-day mortality was similar in patients who received low intensity therapy with or
without venetoclax (15/81 [18%] versus 22/153 [14%], P=0.45). Characteristics and outcomes of patients
treated only wit with versus 22/21 [18] versus 22/153 [18], P=0.45, P= treated only with HMA based low-intensity therapy is described in Table S5.

Finally, the and example analysis to the inpatients with AML. On UVA, using age </260 years, *de novo*
and treatment factors affecting survival in patients with AML. On UVA, using age </260 years, *de novo*
oversus seconda and treatment factors affecting survival in patients with AML. On UVA, daing age </200 years, de novo
tersus secondary or therapy-related AML, TP53¹⁸, versus TP53¹⁸, CTG (CK versus others), use of
venetoclax and HSCT, versus secondary or therapy-related AML, *IP53*⁻⁻⁻ versus *IP53*⁻⁻, CTG (CK versus others), use of
venetoclax and HSCT, *de novo* AML and HSCT were favorable risk factors while CK was adverse. Including
these significa

Discussion

electional and HSCT, de *hovo* AML and HSCT were favorable risk factors while CK was adverse. Including
these significant factors on a stepwise multivariate Cox, *de novo* AML (hr=0.73, 95% CI 0.57-0.93), 7P53^{LR}
(hr=0.58 these significant factors on a stepwise multivariate Cox, de novo AML (hr=0.73, 95% CI 0.57-0.93), 7P53⁻⁻⁻
(hr=0.58, 95% CI 0.38-0.86) and HSCT (hr=0.40, 95% CI 0.26-0.60) continued to remain significant **(Table**
3A). (hr=0.58, 95% CI 0.58-0.69) and HSCT (hr=0.40, 95% CI 0.26-0.60) continued to remain significant (Table 3A).
 Discussion

We present a comprehensive analysis on the impact of *TP53* aberrations on outcomes among a large
 SH). MVA for factors affecting survival only in pattents who attained ORR is in Table 3B.
Discussion
We present a comprehensive analysis on the impact of *TP53* aberrations on outcome
contemporary cohort of patients with we present a comprenensive analysis on the mipact of *n D* 3 aberrations on outcomes among a large contemporary cohort of patients with *TP53* mutated AML and MDS. Our report includes well curated data at a single large contemporary contrivation pretents with TP53 mutated AML and MDS. Our report includes well curated
data at a single large academic center with >75% patients treated on clinical trials with a median follow-
up of >6 years. given by years. Importantly, we never thee to analyze the emited relevance of the TP53 allele status on
Burvival outcomes, and better define what constitutes truly high-risk TP53 mutations in MDS and AML
from a clinical st survival outcomes, and better define what constitutes truly high-risk TP53 mutations in MDS and AML
from a clinical standpoint. The focus of our analysis was to understand the interplay between MDS and
AML (based on histor AML (based on historical blast percentage cutoffs) and baseline *TP53* burden on clinical outcomes, and
to study the impact of therapeutic interventions including HSCT, intensive vs non-intensive therapy, and
venetoclax u

significant even on MVA. Though median survival was <12 months in both the MDS and AML group, in AML (based on historical blast percentage cutoffs) and baseline TP53 burden on clinical outcomes, and the impact of the impact of the baseline TP53 burden in patients with AML.
Using a machine learning algorithm, we also validated the cutoff of a single TP53 mutation (without an
allelic loss) in AML that is associated wit venetoclax use on response and survival in relation to the baseline *H* 55 burden in patients with AML
Using a machine learning algorithm, we also validated the cutoff of a single *TP53* mutation (without an
allelic loss) Using a machine learning algorithm, we also vanidated the eatter of a single TF53 matation (without an allelic loss) in AML that is associated with inferior outcomes; our present finding of 37.5% is close to the 40% report 40% reported in previous analysis.
 $7P53^{1/8}$ was associated with inferior ORR in patients with AML but not with MDS, and this remained

significant even on MVA. Though median survival was <12 months in both the MDS and $TP53^{\text{HR}}$ was associated with inferiosignificant even on MVA. Though r
mutation burden unstratified an
significantly shorter than MDS (5.5
MDS group based on the blast pe
median OS approximately 11 mo
diminutive (in som こと contrast records にっぽん *IP53*⁻⁻ was associated with inferior ORR in patients with AML but not with MDS, and this remained significant even on MVA. Though median survival was <12 months in both the MDS and AML group, in mutation burden unstrat significantly shorter than MDS (5.9 versus 10.8 months). There was no difference in survival within the MDS group based on the blast percentage either for the entire population (5-10% vs >10% both with median OS approximat significantly shorter than MDS (5.9 versus 10.8 months). There was no difference in survival within the
MDS group based on the blast percentage either for the entire population (5-10% vs >10% both with
median OS approxima Significantly shorter the entire population (5-10% vs >10% both with median OS approximately 11 months, **Figure S6)** or for the *TP53*^{HR}. Although studies have claimed diminutive (in some cases even irrelevant) effects median OS approximately 11 months, **Figure 56)** or for the $TPS3^{HR}$. Although studies have claimed diminutive (in some cases even irrelevant) effects of blast percentage defining MDS and AML on OS in patients with high bu median OS approximately 11 months, **Figure S6)** or for the *TP53*¹¹³. Although studies have claimed
diminutive (in some cases even irrelevant) effects of blast percentage defining MDS and AML on OS in
patients with high diminutive (in some cases) patients with high burden *TP53* aberrations, in our analysis with a large number of well-annotated and contemporary patients we see a statistically better survival in patients with MDS (5-19%) c patients with high burden TP53 aberrations, in our analysis with a large number of well-annotated and
contemporary patients we see a statistically better survival in patients with MDS (5-19%) compared to
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PRES^{tik} it is important to have the OS expectations clearly defined and differentiated between these 2 populations to enable critical and realistic appraisal of emerging data from phase I/II single arm studies in the TP53th it is important to have the OS expectations clearly defined and differentiated between these 2
populations to enable critical and realistic appraisal of emerging data from phase I/II single arm studies
in the righ in the right context. For example, an OS of 12 months may be considered encouraging in a study of frontline $TP53^{118}$ AML but is very similar to expected historical outcomes in frontline $TP53^{118}$ MDS. In further interr frontline *TP53*^{¹⁸</sub>. AML but is very similar to expected historical outcomes in frontline *TP53*¹¹⁸. MDS. In further interrogation towards this effect, we found on MVA that both the diagnosis (MDS or AML) as well as} frontline TP53^{HR} AML but is very similar to expected historical outcomes in frontline TP53^{HR} (MDS or AML) as
further interrogation towards this effect, we found on MVA that both the diagnosis (MDS or AML) as
well as th

well as the *TP53* allele status had an independent impact on OS. However, on the CRT analysis, the
 TP53<sup>¹¹⁸ status indeed carried more weight and had the most discriminatory role in predicting poor

survival at 1 yea</sup> *TP53*¹⁸ status indeed carried more weight and had the most discriminatory role in predicting poor survival at 1 year. Putting these into perspective, we can draw the conclusion that both the diagnosis of AML and MDS as TP53^{he} status indeed carried more weight and had the most discriminatory role in predicting poor
survival at 1 year. Putting these into perspective, we can draw the conclusion that both the diagnosis of
AML and MDS as we AML and MDS as well as the *TP53* allele status at baseline are important prognostic variables.
Our study shows important evidence in assessing *TP53* aberration burden and that patients with *TP53^{LR}*
have better outcom AML and MDS as well as the TP53 allele status at baseline are important progrids to variables.

Our study shows important evidence in assessing TP53 aberration burden and that patients v

have better outcomes in both MDS a Chcktl Nhcife Our study shows important evidence in assessing *TP53* aberration burden and that patients with *TP53*⁻⁻
have better outcomes in both MDS and AML, validated with independent statistical models. The lack of
convergence of convergence of OS of patients with high-blast MDS and AML was surprising and different from analysis
by other groups ¹⁷. Though few patients in both disease groups proceeded to HSCT, we show that
transplanted patients wi by other groups ¹⁷. Though few patients in both disease groups proceeded to HSCT, we show that
transplanted patients with MDS and AML had similar survival to each other, and led to improved OS on a
landmark analysis comp by other groups ". Though few patients in both disease groups proceeded to HSCT, we show that
transplanted patients with MDS and AML had similar survival to each other, and led to improved OS on a
landmark analysis compari landmark analysis comparing to patients who did not undergo HSCT; the independent benefit from HSCT
was also maintained on multivariate Cox regression analysis. This again underlines the need to facilitate
HSCT in patients was also maintained on multivariate Cox regression analysis. This again underlines the need to facilitate HSCT in patients with TP53 aberrations whenever feasible. Though HSCT in TP53 mutated myeloid disorders is often deb HSCT in patients with *TP53* aberrations whenever feasible. Though HSCT in *TP53* mutated myeloid
disorders is often debated, it remains the only line of management which has the potential to offer an
improved survival ove HSCT in patients with TP53 aberrations whenever reasible. Though HSCT in TP53 middled injected
disorders is often debated, it remains the only line of management which has the potential to offer an
improved survival over a improved survival over any other form of non-transplant therapy and should be the goal after some
form of BM remission is attained in a transplant eligible patient. The presence of *TP53* aberrations
should in isolation no form of BM remission is attained in a transplant eligible patient. The presence of *TP53* aberrations
should in isolation not preclude patients from an HSCT. Next, we show that treatment intensity does not
have a significa form of BM remission is attained in a transplant engible pattent. The presence of TT53 aberrations
should in isolation not preclude patients from an HSCT. Next, we show that treatment intensity does not
have a significant showe a significant bearing on long-term survival outcomes. In patients 460 years of age, intensive and
low-intensity therapy fared equivocally both in terms of response rates as well as OS. Though more
patients treated wi have intensity therapy fared equivocally both in terms of response rates as well as OS. Though more patients treated with intensive therapy proceeded to an HSCT, this was a function of the lower median age and more patient patients treated with intensive therapy proceeded to an HSCT, this was a function of the lower median
age and more patients <60 years of age in the intensive treated arm compared to the low-intensity
treatment arm, which w Fraction and more patients <60 years of age in the intensive treated arm compared to the low-intensity
treatment arm, which would have driven their therapy choice in the first place. In the context of
venetoclax, we showed and more patients and more patients and the interventional more parameterized were to class, we showed that despite the higher rates of CRc and OR in patients with AML who received were toclass along with their treatment, treatment and more than the first arm and started the first of CRC and OR in patients with AML who received
venetoclax along with their treatment, these responses were not durable and did not lead to higher
rates of HSCT o venetoclax along with their treatment, these responses were not durable and did not lead to higher rates of HSCT or improved survival.
That is of HSCT or improved survival. ventes of HSCT or improved survival.
14 rates of HSCT or improved survival.

The matrice of the analysis of this and the analyses stem from well curated
prospectively collected data. Enrollment of patients on clinical trials could however be associated with
potential selection biases secondary to t magnery of the patient and the multiment of patients on clinical trials could however be associated with
potential selection biases secondary to trial enrollment criteria, though clinical trials remain the ideal
treatment expectively detection biases secondary to trial enrollment criteria, though clinical trials remain the ideal
treatment decision for patents with high-risk AML (including *TP53^{mut}* AML) given dismal outcomes with
standard reatment decision for patents with high-risk AML (including $TP53^{\text{mut}}$ AML) given dismal outcomes with standard of care therapy. Secondly the $TP53$ allele loss call was from a combination of cytogenetic data, FISH and aCG treatment decision for patents with high-risk AML (including *TP53*¹¹⁰² AML) given dismal outcomes with standard of care therapy. Secondly the *TP53* allele loss call was from a combination of cytogenetic data, FISH and

standard of care therapy. Secondly the TF53 allele loss can was from a combination of cytogenetic data,
FISH and aCGH and might have missed some cn-LOH. Nonetheless the use of routine laboratory tools
for the annotation of FISH and action of *TP53* aberration in our patients make the interpretation of this data clinically robust and widely adaptable.
In summary, our study shows that *TP53* aberrations (mutations and/or allelic loss) is an in for the annotation of TP53 aberration in our patients make the interpretation of this data clinically
for that and widely adaptable.
In summary, our study shows that TP53 aberrations (mutations and/or allelic loss) is an i In summary, our study show
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factor that affects survival outcomes, and this impact is dependent on the burden of this aberration.
Secondly, the diagno Factor that affects survival, and the burden of the burden of the burden of the burdent of the burdent of the burden of the burdent of the burden of the Secondy, the diagnosis of MDS of AML, and the burden of TP53 aberration independently affect
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Abbreviations: HR, hazard ratio; MDS, myelodysplastic syndrome; CK, complex karyotype; HSCT, allogeneic hematopoietic stem cell transplantation Abbreviations: HR, hazard ratio; MDS, myelodysplastic syndrome; CK, complex karyotype; HSCT,
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Figure Legends

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Figure 1: Comparative relapse free survival and overall survival of the full injectory spinoline and active injectors

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The 3: Propensity matched survival outcomes between patients with myelodys

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Figure 3: Propensity matching

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Deverall survival Figure 4: Outcomes with allogeneic hematopoietic stem centralisplantation (HSCT)
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C. Overall survival in the transplanted acute myeloid leukemia cohort

D. Overall survival in the transplanted acute myeloid leukemia cohort with $TPS3^{HR}$

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Supplemental Data

Clinical interrogation of *TP53* **aberrations and its impact on survival in patients with myeloid neoplasms**

Jayastu Senapati^{1*}, Sanam Loghavi^{2*}, Guillermo Garcia-Manero¹, Guillin Tang² Tapan Kadia¹, Nicholas J. Short¹, Hussein A. Abbas¹, Naszrin Arani³, Courtney D. DiNardo¹, Gautam Borthakur¹, Naveen Pemmaraju¹, Betul Oran⁴, Elizabeth Shpall⁴, Uday Popat⁴, Richard Champlin⁴, Sherry Pierce¹, Sankalp Arora³, Ghayas Issa¹, Musa Yilmaz¹, Keyur Patel¹, Koichi Takahashi¹, Guillermo Montalban-Bravo¹, Danielle Hammond¹, Fadi G. Haddad¹, Farhad Ravandi¹, Hagop M. Kantarjian¹, Naval G. Daver¹

¹Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston.

²Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston.

³Department of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston.

⁴Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston.

* These authors contributed equally

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(Sequence of tables and figures in this supplement is according to the appearance in the manuscript)

Figure S1: Types of *TP53* aberration amongst the patients stratified based on the diagnosis of MDS or AML

Abbreviations: LR, low risk; HR, high-risk; VAF, variant allele fraction

Figure S2: Overall survival of patients with multi-hit *TP53* mutations stratified by the sum of VAFs (<50% versus ≥50%)

Figure S3: Classification and regression tree (CRT) model predicting the VAF cutoff for inferior survival at 1 year in patients with AML harboring a single-hit *TP53* mutation (n=128); **ROC AUC= 0.68**

Figure S4: Classification and regression tree (CRT) model predicting the VAF cutoff for inferior survival at 1 year in patients with AML harboring a single-hit *TP53* mutation (n=128); Depth level of 2, **ROC AUC= 0.73**

Figure S5: OS of patients with AML harboring a single *TP53* mutation stratified based on VAF cutoffs predicted from the CRT model.

Figure S6: Representation of the type of *TP53* mutation in the full patient cohort

Table S1A-B: Details of treatment regimens

A: AML cohort

Abbreviations: FLAG, fludarabine/intermediate dose cytarabine/G-CSF; IDA, idarubicin; CLIA, cladribine /idarubicin/intermediate dose cytarabine; MEC, mitoxantrone, etoposide, intermediate dose cytarabine; CLAD, cladribine; LDAC, low dose cytarabine; AZA, azacitidine; APR246, eprenetapopt; FLT3i, FMS like tyrosine kinase 3 inhibitor; GO, gemtuzumab ozogamicin; FA, fludarabine. Intermediate dose cytarabine; IA, idarubicin, intermediate dose cytarabine; CIA, clofarabine, idarubicin, intermediate dose cytarabine; 7+3, 7 days of continuous infusion cytarabine and 3 days of daunorubicin; CAT, cyclophosphamide /cytarabine/topotecan; CECA, cyclophosphamide, etoposide, carboplatin; intermediate dose cytarabine; Pembro, pembrolizumab

*These groups denote HMA monotherapy

SGN CD33A: CD33-targeting antibody-drug conjugate using a pyrrolobenzodiazepine dimer **BP1001:** Liposomal Grb2 antisense oligonucleotide

B: MDS cohort

Abbreviations: AZA, azacitidine; IPI, ipilimumab; PEMBRO, pembrolizumab; NIVO, nivolumab; APR246, eprenetapopt; CLAD, cladribine; LDAC, low dose cytarabine

CB839: Glutaminase inhibitor

FF-10501-01: Inosine-5-monophosphate dehydrogenase inhibitor

Figure S7: Response rates in the MDS and AML cohort based on the *TP53* aberration burden.

Abbreviations: CR, complete remission; CRi, CR with incomplete counts recovery; MLFS, morphological leukemia free state; NR, no response; TP53 LR, *TP53*LR; TP53 HR, *TP53*HR

Figure S8A: Sankey Diagram of patients with MDS showing age, *TP53* burden, response rates, allogeneic stem cell transplantation and survival at 1 year.

Abbreviations: MDS, myelodysplastic syndrome; OR, overall response; NR, no response, SCT, allogeneic stem cell transplnatation, OS, overall survival

Figure 8B: Sankey Diagram of patients with AML showing treatment intensity, *TP53* burden, response rates, allogeneic stem cell transplantation (SCT)* and survival at 1 year.

*Total 32 patients with AML underwent SCT, 31 patients after attainment of an OR and one patient with stable disease.

Abbreviations: AML, acute myeloid leukemia; OR, overall response; NR, no response, SCT, allogeneic stem cell transplnatation, OS, overall survival

Figure S9: OS in the *TP53*HR group based on the type of *TP53* aberrations

Figure S10: Overall survival (OS) of patients with AML or MDS and *TP53^{LR}* stratified by complex karyotype

Abbreviations: LR, *TP53*LR; w/o, without; CK, complex karyotype

Figure S11: Overall survival (OS) of patients with MDS and AML stratified by BM blast percentage

Figure S12: Comparison of OS of patients in the MDS group to the AML group stratified by the *TP53* aberration status.

Figure S13: Comparison of OS of patients with MDS versus patients with AML who had *TP53*HR and underwent an HSCT.

Figure S14: CRT decision tree showing variables affecting survival at 1 year for the full cohort; **ROC AUC 0.69**

Table S2: Logistic regression analysis of factors affecting overall response in patients with AML.

Table S3: Response rates in patients with AML based on treatment intensity.

Figure S15: Survival outcomes in patients with AML stratified by the treatment intensity.

Figure S16: Survival outcomes in patients with AML <60 years of age stratified by the treatment intensity.

Table S4: Response rates in patients with AML patients based on venetoclax exposure.

Full AML Cohort (n=291)									
Venetoclax	n	Median age	Low intensity therapy	CRC	$P -$	ORR	$P -$	HSCT	$P -$
		[IQR]	(%)	(%)	value	(%)	value	(%)	value
Yes	90	71.3 [64.7-	81 (90)	49	0.02	59 (66)	0.005	11(12)	0.69
		77.5		(54)					
No	201	68.8 [59.8-	153 (76)	80		96 (48)		21(10)	
		75.7		(40)					
AML with $TP53^{HR}$ (n=253)									
Yes	82	72.4 [65.1-	73 (89)	44		52(63)		7(9)	
		77.5		(54)	0.02		0.005		0.99
No	171	69.5 [59.8-	129 (75)	64		76 (44)		16(9)	
		75.9		(37)					

Figure S17: Survival outcomes in patients with AML stratified by venetoclax exposure.

Table S5: Baseline characteristics and outcomes of patients with AML treated with HMA based low-intensity therapy

Abbreviations: HMA, hypomethylating agent; CRc, composite complete response; ORR, overall response rate; NR, not reached; OS overall survival; RFS, relapse free revival

Supplemental Methods File

Clinical Interrogation of *TP53* **Aberrations and its Impact on Survival in Patients with Myeloid Neoplasms**

Jayastu Senapati^{1*}, Sanam Loghavi^{2*}, Guillermo Garcia-Manero¹, Guillin Tang² Tapan Kadia¹, Nicholas J. Short¹, Hussein Abbas¹, Naszrin Arani³, Courtney D. DiNardo¹, Gautam Borthakur¹, Naveen Pemmaraju¹, Betul Oran⁴, Elizabeth Shpall⁴, Uday Popat⁴, Richard Champlin⁴, Sherry Pierce¹, Sankalp Arora³, Ghayas Issa¹, Musa Yilmaz¹, Keyur Patel¹, Koichi Takahashi¹, Guillermo Montalban-Bravo¹, Danielle Hammond¹, Fadi G. Haddad¹, Farhad Ravandi¹, Hagop M. Kantarjian¹, Naval G. Daver¹

¹Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston.

²Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston.

³Department of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston.

⁴Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston.

* These authors contributed equally

1. Assessment of *TP53* **mutations:**

Next-generation sequencing (NGS) was performed using our clinically validated myeloid panels, interrogating the entire exonic or hotspot regions of 28, 53 or 81 genes (depending on the time of presentation) frequently mutated in myeloid malignancies, including TP53, as described previously^{1,2}. Sequencing libraries were prepared using 250 ng of genomic DNA and respective sequencing libraries were subjected to the Illumina MiSeq (Illumina,Inc., San Diego, CA, USA) sequencer. A minimum sequencing coverage of x250 (bidirectional true paired-end sequencing) was required to allow achieving a lower limit of detection of 2% variant allelic frequency in the background of wild-type sequence.

2. Assessment of *TP53* **allelic loss/deletion:**

Allelic loss/deletion at the TP53 locus was studied using a combination of conventional karyotyping, FISH and aCGH. Allelic loss/deletion was defined as described previously $3,4$: monosomy 17 (-17); isochromosome i(17)(q10); del(17)(pvar(variable)) with pvar centromeric to p13.1; unbalanced translocations involving 17(p), including der(var)t(var;17)(var;qvar),–17; der(var)t(var;17)(var;pvar), –17 with pvar centromeric to p13.1; der(17)t(17;var)(pvar;var)der(17)t(var;17)(var;pvar) with pvar centromeric to p13.1; der(var)t(var;17)(var;qvar) with dicentric der; der(var)t(var;17)(var;pvar) with pvar centromeric to p13.1 and dicentric der; balanced translocation and 17p13 breakpoint: t(17;var)(p13;var) or t(var;17)(var;p13) in the presence of TP53 deletion by FISH; additive material: add(17)(pvar) in the presence of TP53 deletion by FISH; dicentric chromosome dic(var;17)(var;pvar); and ring chromosome r(17)(pvarqvar) with the presence of TP53 deletion by FISH.