FACULTÉ
DE MÉDECINE &
SCIENCES DE LA SANTÉ

Mise à jour sur les syndromes myélodysplasiques

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Juin 2021

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Classification génomique

- Bersanelli et al, JCO 2021

Mutation TP53 et valeur pronostique

- Hasse et al., Leukemia, 2019
- Bernard E et al, Nat Genet, 2020

Perte du Y et valeur pronostique

- Ouseph et al, haematologica 2021

Therapy-related MDS

- Kuendgen et al, Leukemia 2021

Whole genome sequencing, RNA-SEq

- Stengel et al, Blood Adv, 2021
- Duncavage et al, NEJM 2021

Optical Genome Mapping

- Yang et al, MedRxiv 2021 (not reviewed, preprint)

Clinical Trials results

- Cluzeau et al, JCO 2021
- Sallman et al, JCO 2021

Classification from genomic features

Matteo Bersanelli et al JCO 2021
(2,043 patients)

Recurrently mutated genes (47 genes) and chromosomal abnormalities have been identified in myelodysplastic syndromes (MDS).

Objective: We aim to integrate these genomic features into disease classification and prognostication.

Results:
Identification of 8 distinct subtypes according to specific genomic features.

Classification from genomic features

8 distinct subtypes:

0: without specific genomic profiles
1: patients with SF3B1 with co-existing mutations in other genes (ASXL1 and RUNX1) characterized by anemia associated with mild neutropenia and thrombocytopenia, multilineage dysplasia, and higher marrow blast percentage with respect to group 6
6: patients with ring sideroblasts and isolated SF3B1 mutations (except for co- mutation patterns including TET2, DNMT3A, and JAK/STAT pathway genes) characterized by isolated anemia, normal or high platelet count, single or multilineage dysplasia, and low percentage of marrow blasts
3: SRSF2 and concomitant TET2 mutations
5: SRSF2 mutations with co-existing mutations in other genes (ASXL1, RUNX1, IDH2, and EZH2). Patients present two or more cytopenias, multilineage dysplasia, and excess blasts
4: U2AF1 mutations associated with 20q deletion and chromosome 7 abnormalities
2: TP53 mutations and/or complex karyotype
7: patients with AML-like mutation patterns (DNMT3A, NPM1, FLT3, IDH1, and RUNX1 genes).

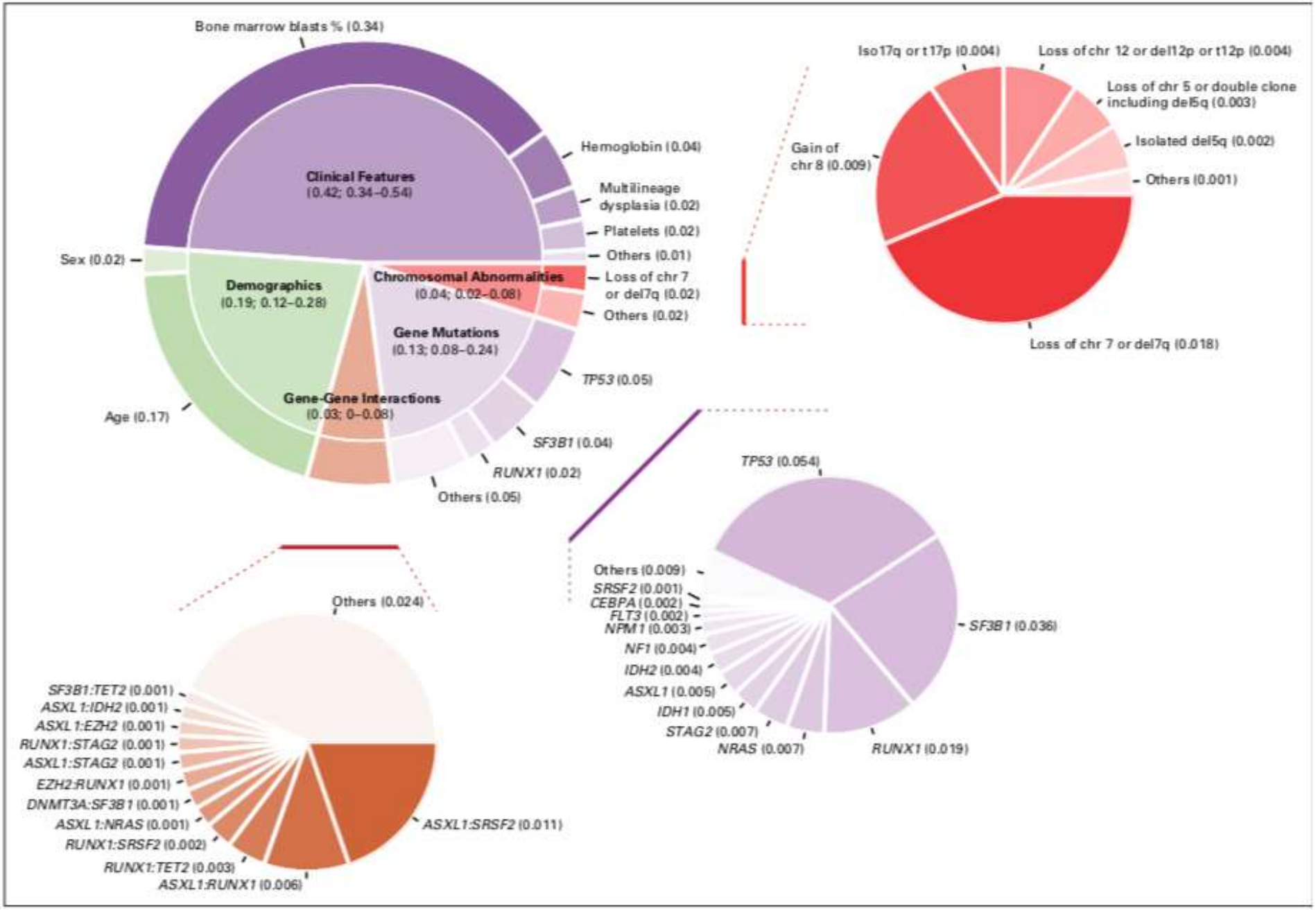

FIG 3. Fraction of explained variation that was attributable to different prognostic factors for overall survival.

Classification from genomic features

MDS with 5q deletion are clustered into two distinct groups according to the number of mutated genes and/or presence of TP53 mutations

Different probability of survival for each groups.
Groups 1 and 6 characterized by SF3B1 mutations show better survival with respect to groups 2, 3, 4, 5, and 7
Group 2 (patients with TP53 mutations and complex karyotype) and MDS with AML–like mutations show the poorest outcome

Response to treatments:
- Genomic features **do not** identify different probability of survival after hypomethylating agents.
- Genomic features able to significantly stratify post-transplantation outcome : groups defined by TP53 mutation and/or complex karyotype (group 2) and by U2AF1 mutations (group 4) are associated with a high rate of transplantation failure

Classification from genomic features

A total of **14 genes** are associated with **worse** prognosis if mutated, whereas **one gene** (SF3B1) is associated with **better outcome**

Co-occurrence of genes mutations and exclusion

We define a **novel prognostic model** that generates personally tailored predictions of survival.

EUROMDS Project: Personalized prediction of clinical outcome in patients with myelodysplastic syndrome according to genomic and clinical features.

https://mds.itb.cnr.it/#/mds

Classification génomique

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Mutation TP53 caryotype complexe et valeur pronostique

- Hasse et al., Leukemia, 2019
- Bernard E et al, Nat Genet, 2020

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- Ouseph et al, haematologica 2021

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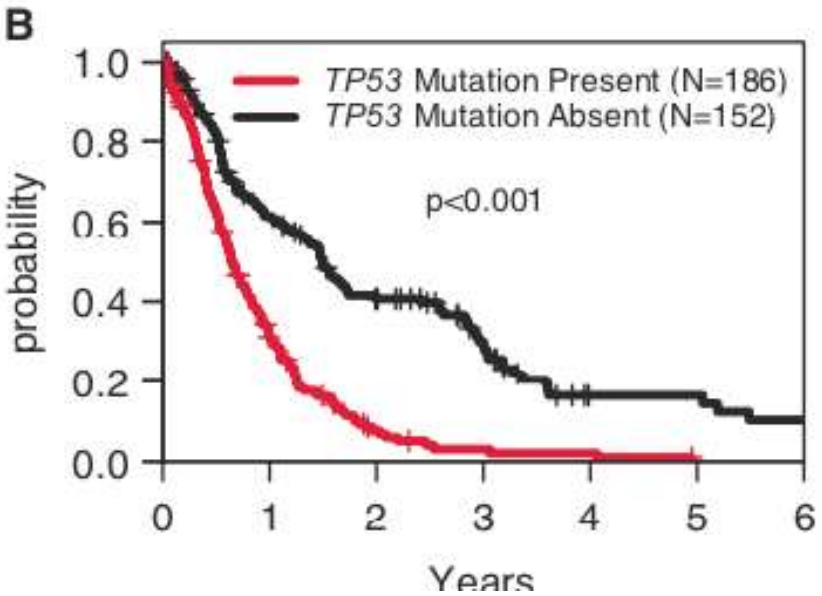
TP53, complexité, pronostic

Hasse et al, Leukemia, 2019 (International Working Group for MDS Molecular Prognostic Committee)

Objective: Risk stratification of CK-MDS

Results.
Dans les CK:
Mutations were underrepresented with the exception of TP53 mutations, identified in 55% of patients.

In TP53 mutated patients:
- fewer co-mutated genes
- more del(5q) chromosomal abnormality
- more monosomal karyotype
- more high complexity (more than 4)



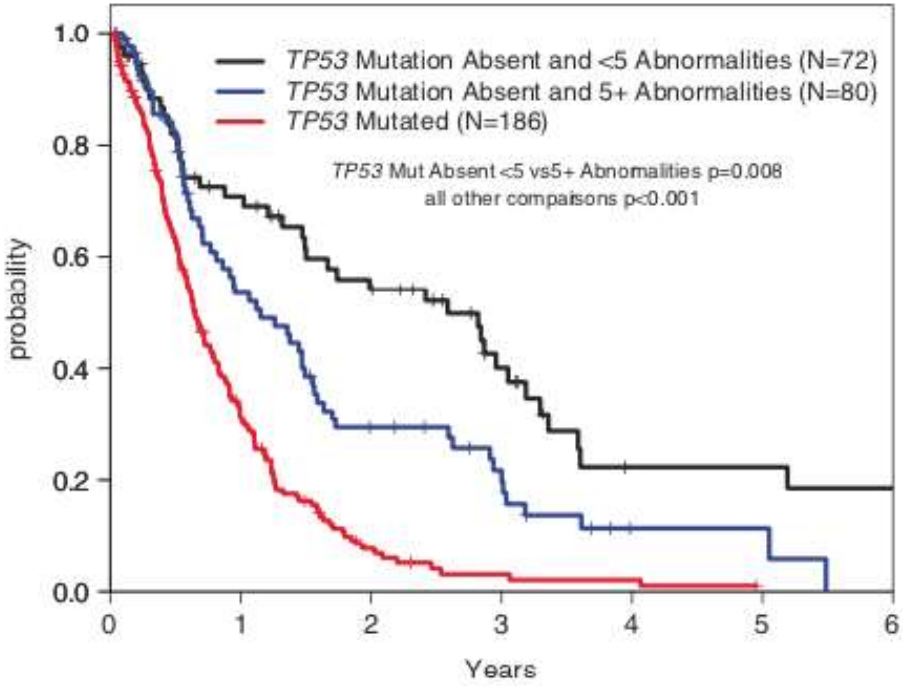


Fig. 4 Overall survival stratified by *TP53* mutation and high complexity status

In CK-MDS patients: Overall survival by TP53 mutation

TP53, complexité, pronostic

Discussion (Hasse et al 2019)

>>> TP53 mutation status remained the most frequently occurring risk factor not currently considered by existing prognostic scoring systems.

Assessment of just HC (high complexity, more than 4 abn.) and TP53 mutation status constitutes a relatively simple means of identifying the roughly 20% of CK-MDS patients predicted to have an OS that resembles that of IPSS-R **intermediate risk** patients.

As a consequence, TP53 mutant CK-MDS could be considered a distinct subtype of disease with common genetic, clinical, and therapy-related features. **Cytogenetics alone** appears **insufficient** for the evaluation of CK-MDS patients and routine testing for TP53 mutations should be considered in this population.

TP53, complexité, pronostic

Discussion (Hasse et al 2019)

1. The number and type of mutations in TP53 had less impact on OS. (voir article suivant Bernard E Nat Med 2020)
Less than 15% of the cohort carried more than one TP53 mutation, and this was not associated with any difference in survival compared to those harboring only 1 mutation

2. However, cytogenetic abnormalities predicted to cause copy number loss at the TP53 locus had **no** prognostic impact regardless of TP53 mutations status, suggesting that **loss of a TP53 allele by cytogenetic analysis might not be biologically equivalent to a TP53 point mutation in CK-MDS**

TP53 allelic state

Bernard E et al, Nat Med, 2020,
(International Working Group for Prognosis in MDS)
(cohorte de 3,324 patients)

Objective: biological and clinical implications of *TP53* allelic state in MDS ?

4 groupes:

- Monoallelic TP53 mutation
- Multiple TP53 mutation (probably no residual TP53)
- Multiple TP53 mutation + TP53 deletion (probably no residual TP53)
- Multiple TP53 mutation + cnLOH TP53 (probably no residual TP53)

TP53 allelic state

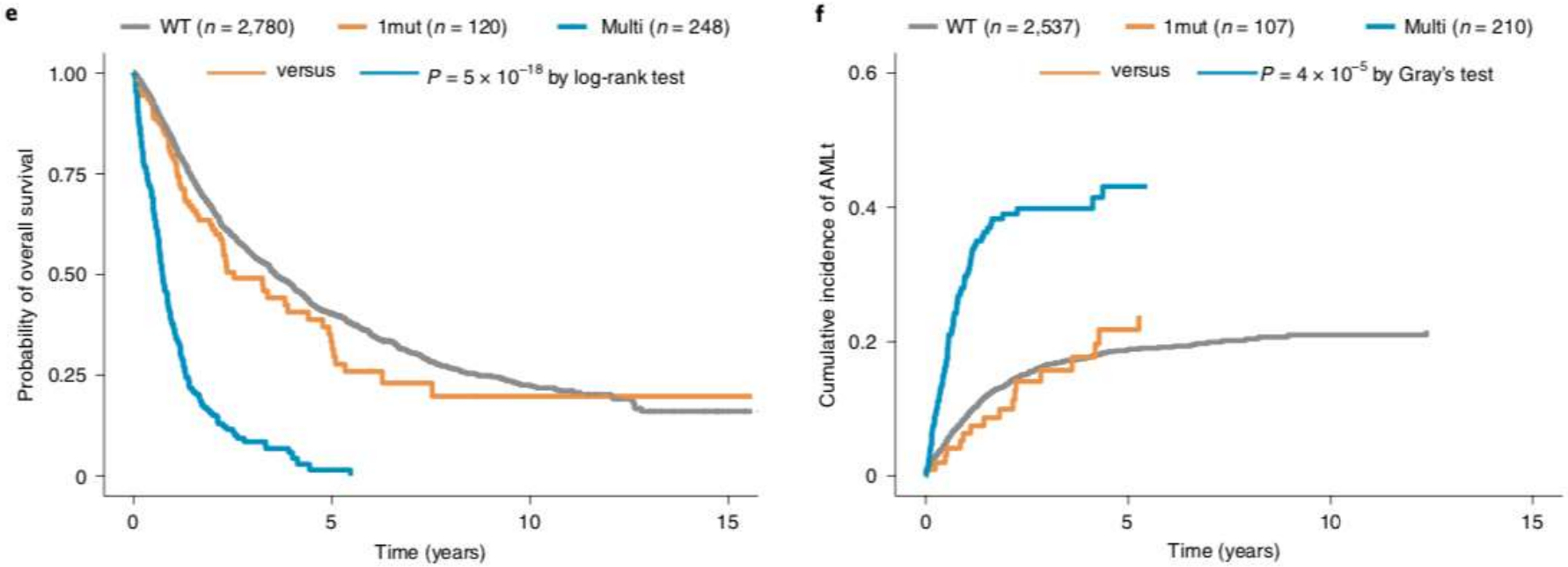
One-third of *TP53*-mutated patients had monoallelic mutations whereas two-thirds had multiple hits (multi-hit) consistent with biallelic targeting.

Established associations with complex karyotype, few co-occurring mutations, high-risk presentation and poor outcomes were specific to multi-hit patients only.

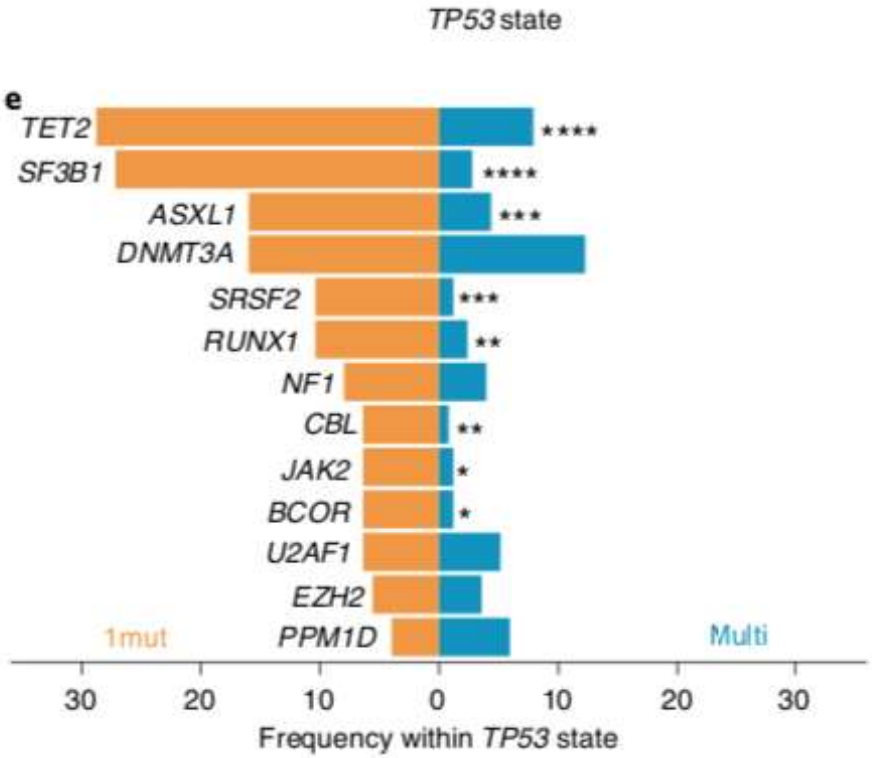
TP53 multi-hit state predicted risk of death and leukemic transformation independently of the Revised International Prognostic Scoring System (IPSS-R).

Surprisingly, monoallelic patients did not differ from *TP53* wild-type patients in outcomes and response to therapy.

TP53 allelic state



TP53 allelic state



TP53 allelic state

Bernard E et al, Nat Genet, 2020

Different evolutionary trajectories between multi-hit and mono- allelic patients emerged from our data.

In multi-hit state, *TP53* mutations were predominantly in the dominant clone with complex karyotypes and few other mutations, reflecting early truncal events in MDS pathogenesis.

In contrast, monoallelic *TP53* mutations were frequently subclonal and co-occurred with mutations from a broad range of genes, to include genes associated with both a favorable (*SF3B1*) or poor (*ASXL1*, *RUNX1*, *CBL*) prognosis.

TP53 allelic state

Bernard E et al, Nat Genet, 2020,

implication of *TP53* allelic state in response to therapy.

For HMA and lenalidomide, patients with monoallelic *TP53* mutations had evidence of longer survival compared to multi-hit patients

a trend for improved survival of monoallelic patients compared to multi-hit patients following HSCT

Our findings imply that diagnostic and prognostic precision in MDS requires the assessment of *TP53* allelic state.

We propose that biallelic *TP53* should be distinguished from monoallelic *TP53* mutations in future revisions of IPSS-R and in correlative studies of treatment response.

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Perte du Y

Madhu M. Ouseph Heamatologica 2021

Objective

As MDS is predominantly observed in older people, it is difficult to separate age-associated loss of Y (LOY) from disease-associated LOY.

> ? Whether the proportion of metaphases with LOY is associated with the incidence of myeloid neoplasia-associated genomic alterations

Results

In our series, marrow samples **with ≥75% (percentage of metaphases) LOY** had :

- a high likelihood of morphological diagnosis of myeloid neoplasia, most commonly MDS.
- a higher likelihood of **progression** to a morphological diagnosis **of MDS** on follow-up.
- a high prevalence (>80%) of somatic mutations associated with myeloid neoplasia, especially MDS.


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•Sallman et al, JCO 2021

Therapy-related MDS

Kuendgen et al, Leukemia 2021
(2087 t-MDS)

Objective:
Currently: WHO: 1 subgroup: therapy-related myelodysplastic syndromes (t-MDS) are categorized together with therapy-related acute myeloid leukemia (AML) and t-myelodysplastic/myeloproliferative neoplasms, independently of blast count and morphologic features such as cellularity or dysplasia.

- **To evaluate classification and prognostication tools used for primary MDS (**FAB and WHO-classification, IPSS-R, and WPSS-R)

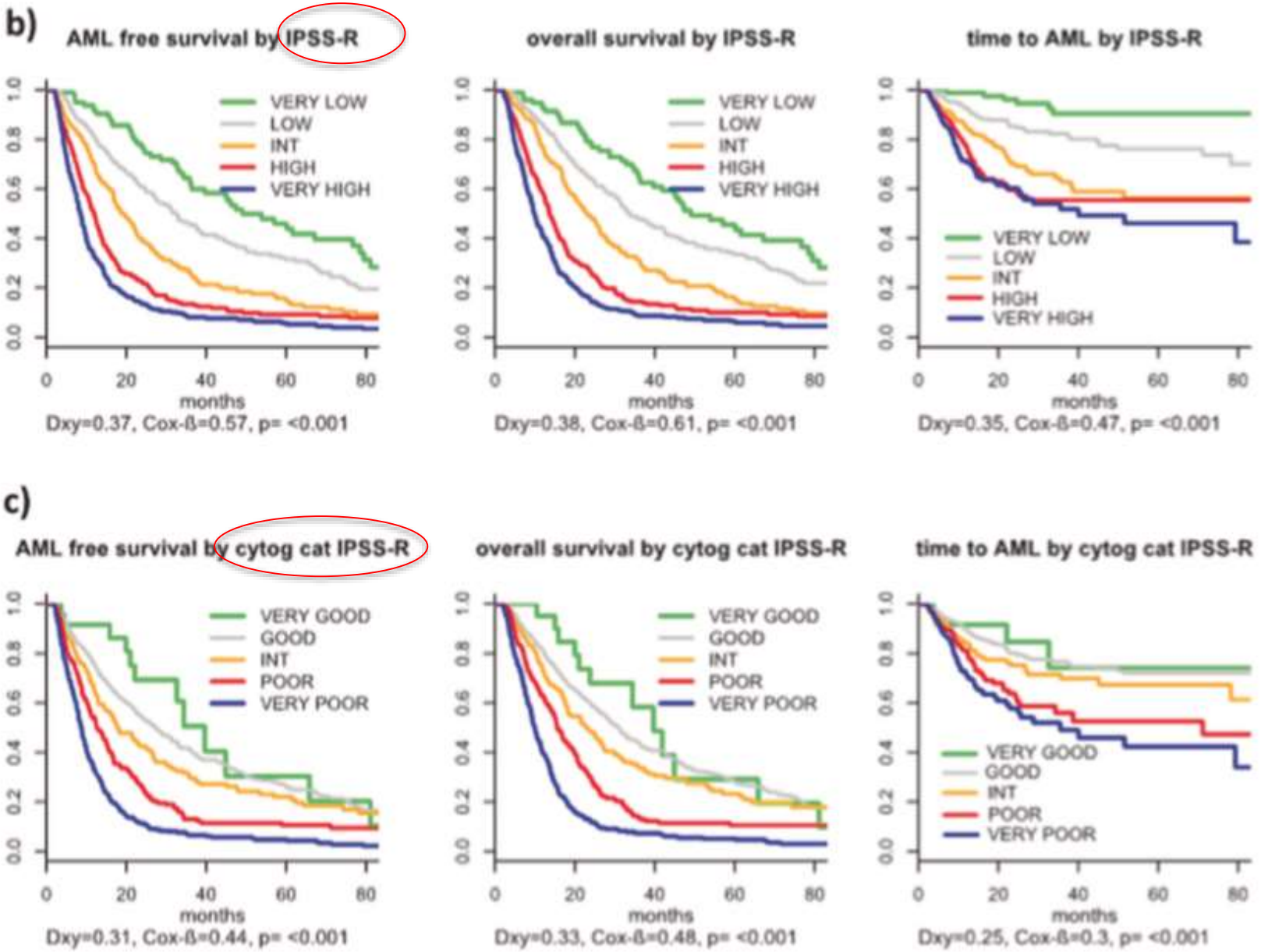

Fig. 1 Outcome of patients with t-MDS according to different tools for classification and prognosis. a outcome according to WHO 2016, **b** outcome according to IPSS-R, **c** Outcome according to cytogenetic IPSS-R risk categories.

Therapy-related MDS

Kuendgen et al, Leukemia 2021
(2087 t-MDS)

Results:
The WHO classification for p-MDS successfully predicts **time to transformation** and **survival** of t-MDS.

FAB and WHO-classification, IPSS-R, and WPSS-R separated t-MDS patients into differing **risk groups** effectively, indicating that all established risk factors for p-MDS maintained relevance in t-MDS, with cytogenetic features having enhanced predictive power.
These data strongly argue to classify t-MDS as a separate entity distinct from other WHO-classified t-myeloid neoplasms.

Therapy-related MDS

Kuendgen et al, Leukemia 2021

Remarque

Earlier publications on t-MDS demonstrated mostly high-risk karyotypes in these patients, mainly including chromosome 5 and 7 abnormalities as well as complex karyotypes, in more than 90% of patients.

Although these features are still a hallmark of t-MDS in general, **they do not represent all patients with a history of chemo- and/or radiotherapy**.

Our data demonstrated an unexpectedly **high percentage of good-risk and normal cytogenetics,** which are concordant with other more recently published data.

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RNA-seq (WTS): Nouveaux gènes de fusion

Stengel, A.et al ., and Haferlach, C. Blood Adv (2020).
630 myelodysplastic syndrome (MDS) patients by whole transcriptome sequencing (WTS= RNA-Seq)

Objective:
comprehensive analysis of the fusion transcript landscape

Results:
In 16/630 MDS patients, 16 fusion events (15 unique fusions) were detected (3%).
Only 1 fusion was described previously (NRIP1-MECOM, n = 2).
88% (14/16) in MDS fusion were not reported.
All novel fusions were observed in 1 patient each.

New genomic alterations leading to fusion transcripts were much more common in AML (37%) than in MDS (3%).

RNA-seq (WTS): Nouveaux gènes de fusion

Stengel, A.et al ., and Haferlach, C. Blood Adv (2020).

Moreover, WTS proved to be especially a powerful tool for detection of cytogenetic cryptic aberrations, and for detection of intrachromosomal fusions, which are often missed by chromosome banding analyses, and thus illustrates the shortcomings of conventional diagnostic methods in these cases.

(A partir d'une autre étude) Significant association between gene content of chromosomes and chromosome bands and the number of genes involved in fusions was observed.
This suggests that the majority of gene fusions detected non recurrently by massively parallel sequencing methods including RNAseq are merely stochastic events and that the respective gene fusions are passengers without a role in pathogenesis.

Whole Genome Sequencing

Duncavage et al, NEJM 2021
(263 patients: AML and MDS (n=81))

Objective:
Assessing potential replacement for conventional cytogenetic and sequencing approaches by Whole-genome sequencing

Methods
WGS (60x) mais analyses de 40 genes et genome-wide CNA greater than 5 Mbp, structural variants matching 612 recurrent structural alteration in myeloid cancers

Whole Genome Sequencing

Duncavage et al, NEJM 2021

Results

17% of the patients had results that had not been detected by conventional cytogenetic analysis.

New abnormalities that were not present in the karyotype analysis or reported by FISH in 17 of 68 patients (25%).

These abnormalities included :

- cryptic or complex chromosomal rearrangements in 5 patients,
- new copy-number alterations that resulted in a complex karyotype in 4 patients,
- and identification of either a normal karyotype (in 4 patients) or 1 or 2 cytogenetic abnormalities in patients with inconclusive or unsuccessful results by cytogenetic analysis (in 4 patients)

Whole-genome sequencing detected 100% of the clinically significant abnormalities that had been identified by cytogenetic analysis and clinical FISH assays.

… temps de rendu des résultats et cout.

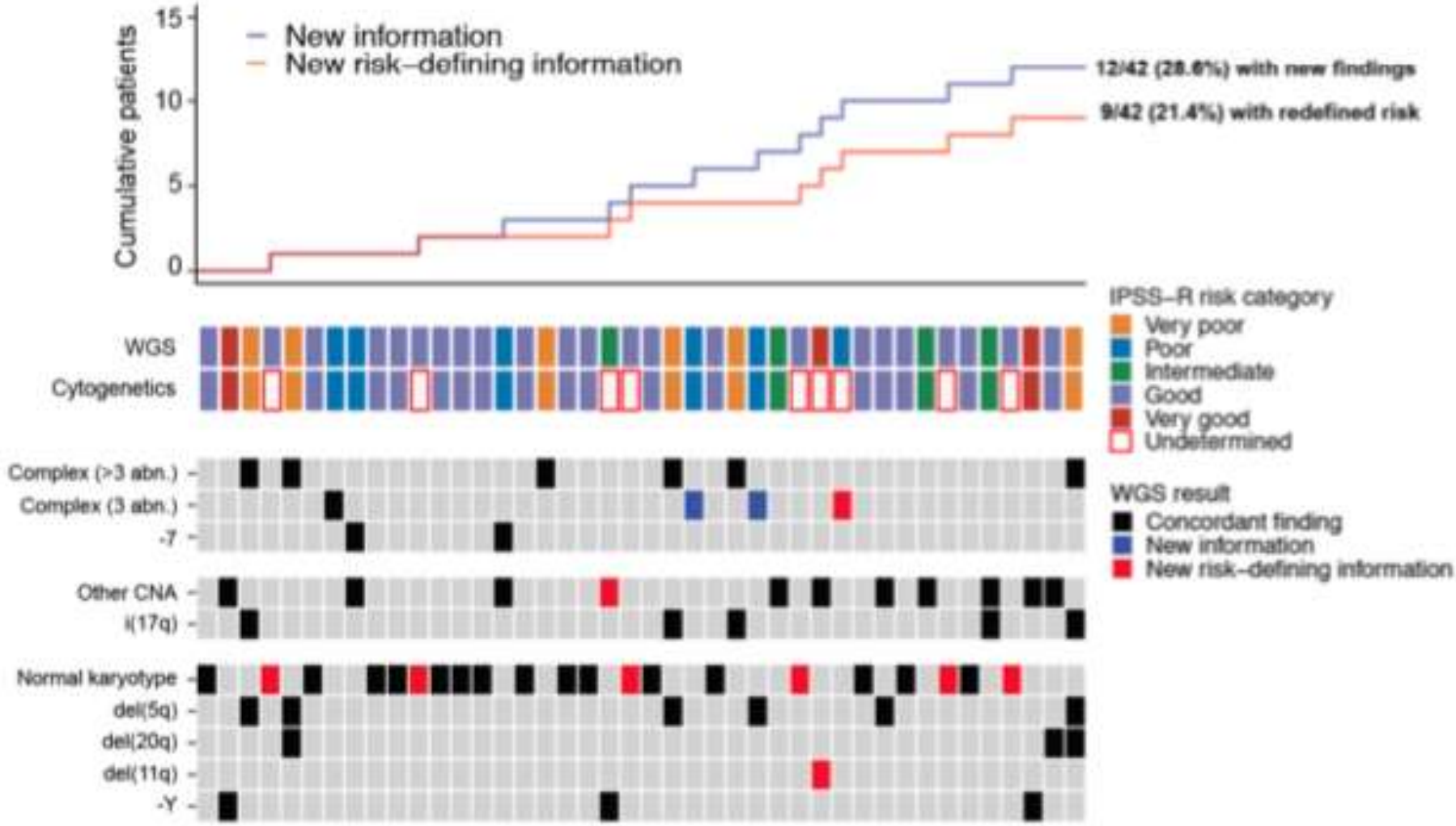

Figure S3. Diagnostic yield from prospective sequencing of MDS patients.


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Optical genome mapping (« bionano »)

Yang, H., et al MedRxiv 2021.01.13.21249611.(not reviewed, preprint)
Optical genome mapping : genome-wide detection of all types of clinically important chromosomal variants (CNVs and SVs) at a high resolution

Objective:
proof-of-principle study
12 previously well-characterized **MDS cases** using clinical BM samples

Optical genome mapping (« bionano »)

Yang, H., et al MedRxiv 2021.01.13.21249611. (not reviewed, preprint)

By OGM:

-Detection of 26 of the 28 clonal chromosomal variants (concordance rate: 93% with conventional karyotyping; 100% with chromosomal microarray)

These included copy number gains/losses, inversions, inter and intra-chromosomal translocations, dicentric and complex derivative chromosomes; the degree of complexity in latter aberrations was not apparent using standard technologies.

The 2 missed aberrations were from a single patient within a composite karyotype, below the limit of detection.

Optical genome mapping (« bionano »)

Yang, H., et al MedRxiv 2021.01.13.21249611. (not reviewed, preprint)

OGM uncovered **6 additional clinically** relevant sub-microscopic aberrations in 4 (33%) (in *TP53* and *KMT2A)* patients that were cryptic by standard-of-care technologies.

OGM is a potent single-platform assay for high- throughput and accurate identification of clinically important chromosomal variants.

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- Sallman et al, JCO 2021

Résultats d’essais cliniques

Cluzeau, T., Sebert, M., Rahmé, R., Cuzzubbo, S., Lehmann-Che, J., Madelaine, I., Peterlin, P., Bève, B., Attalah, H., Chermat, F., et al. (2021).
Eprenetapopt Plus Azacitidine in TP53-Mutated Myelodysplastic Syndromes and Acute Myeloid Leukemia: A Phase II Study by the Groupe Francophone des Myélodysplasies (GFM). J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. JCO2002342.

Sallman, D.A., DeZern, A.E., Garcia-Manero, G., Steensma, D.P., Roboz, G.J., Sekeres, M.A., Cluzeau, T., Sweet, K.L., McLemore, A., McGraw, K.L., et al. (2021).
Eprenetapopt (APR-246) and Azacitidine in TP53-Mutant Myelodysplastic Syndromes. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. JCO2002341.

Résultats d'essais cliniques

Cluzeau, T. et al. (2021). JCO 2021 : AZA + APR-246

TP53-mutated (TP53m) myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) Eprenetapopt (APR-246), a novel first-in-class drug, leads to p53 protein reconformation and reactivates its proapoptotic and cell-cycle arrest functions.

Objective:
phase II study assessed the safety and efficacy of eprenetapopt in combination with AZA in untreated high or very high International Prognostic Scoring System-R TP53m MDS and AML patients.

Results:
In this very high-risk population of TP53m MDS and AML patients, eprenetapopt combined with AZA was safe and showed potentially higher ORR and CR rate, and longer OS than reported with AZA alone.

>>ongoing international phase III, multicenter, randomized study of eprenetapopt in combination with AZA versus AZA alone in patients with *TP53*-mutant MDS

Résultats d'essais cliniques

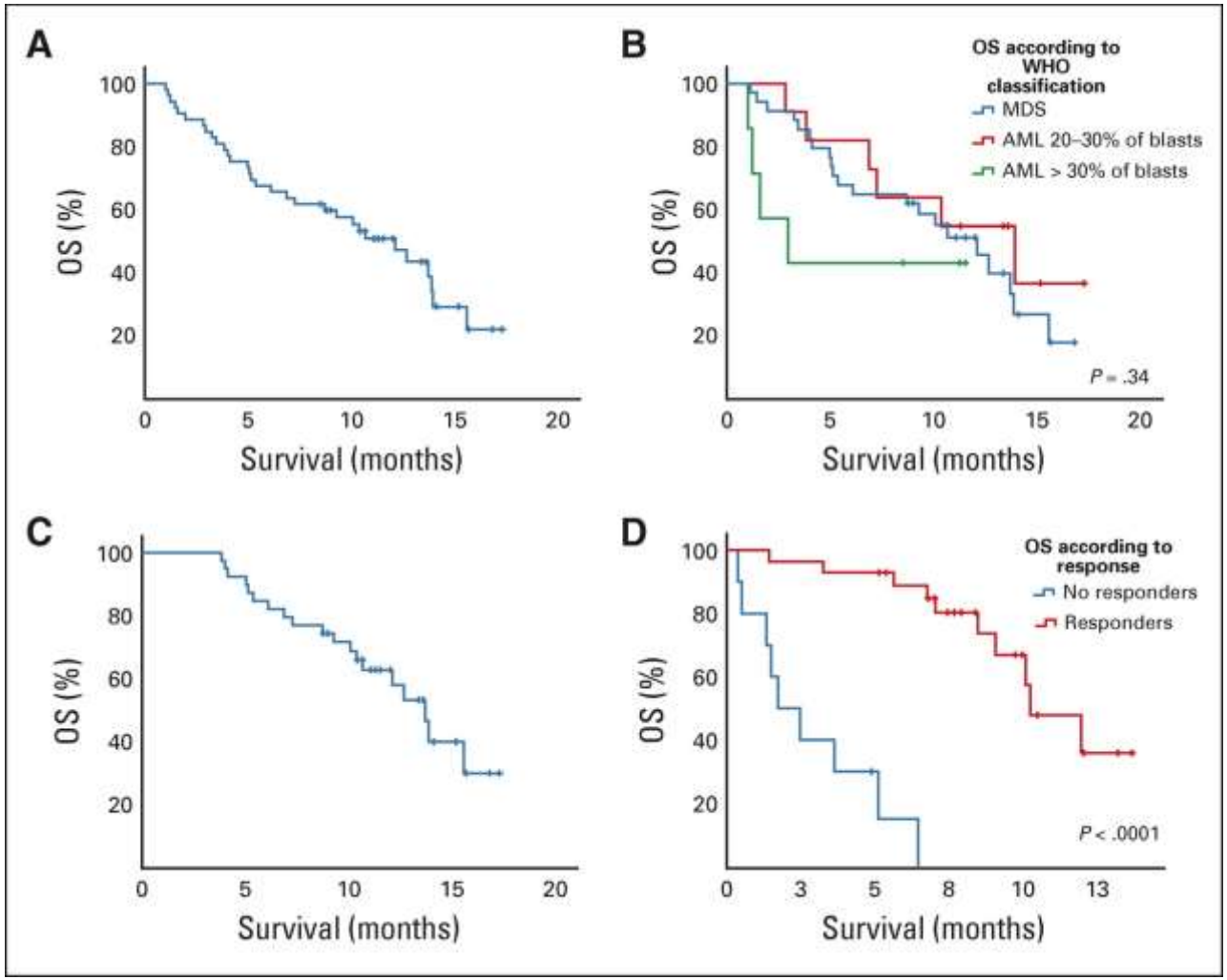

FIG 2. OS (A) in the overall population, (B) in MDS and AML, (C) in patients who received at least three cycles, and (D) in responders versus nonresponders. AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; OS, overall survival.

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