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What is the standard for high-risk MDS, what hasn't worked, and what seems promising?

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Presentation Roadmap

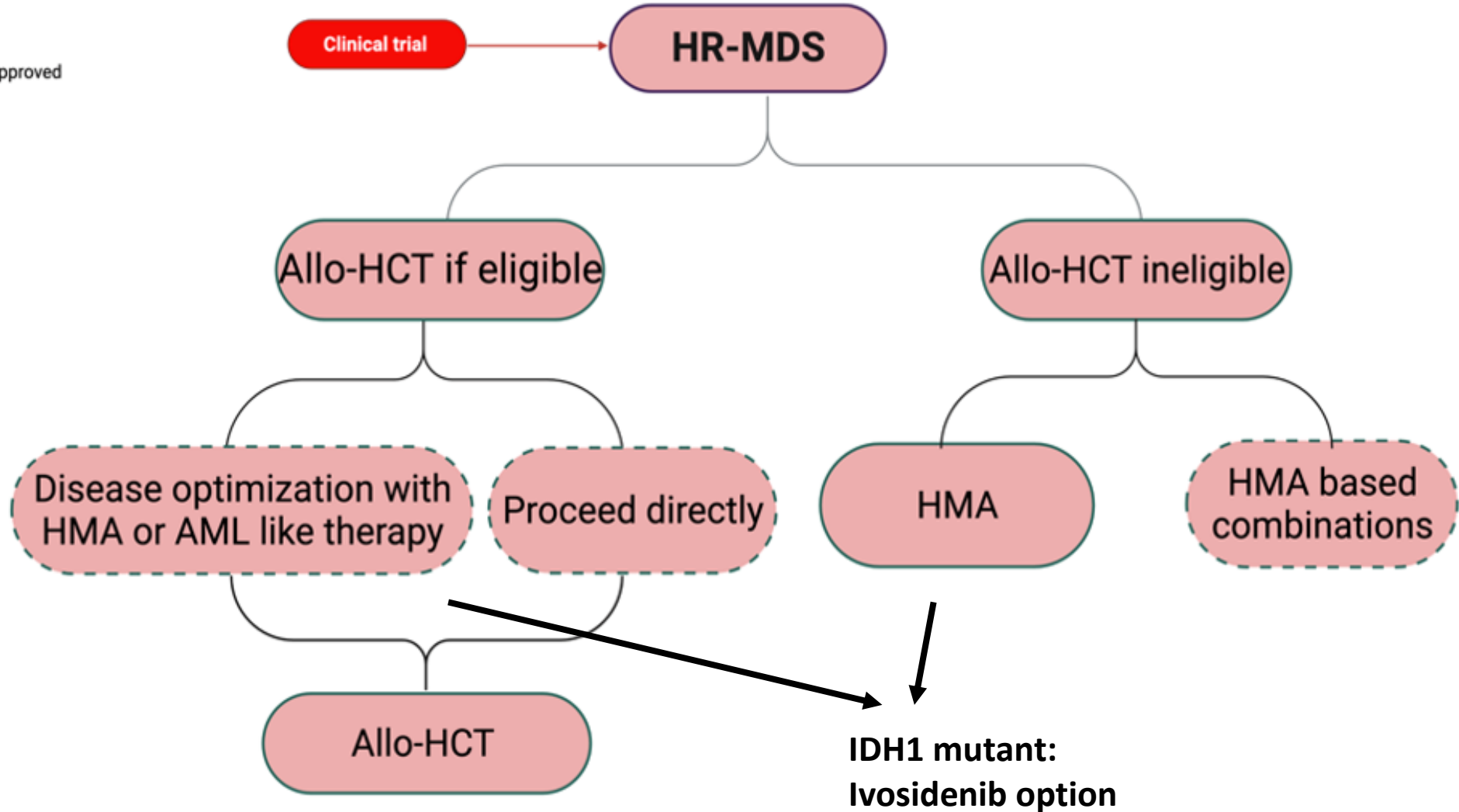
1. General Treatment Algorithm/ Approach to HR-MDS
2. What has worked...
 - Hypomethylating Agent Therapy
 - Allogeneic Transplantation (separate talk)
3. What has not worked... (many trials!)
4. The path forward.

Approach for HR-MDS

MDS diagnosis according to WHO/ICC criteria

- Approved therapy
- - - Clinically used, not approved

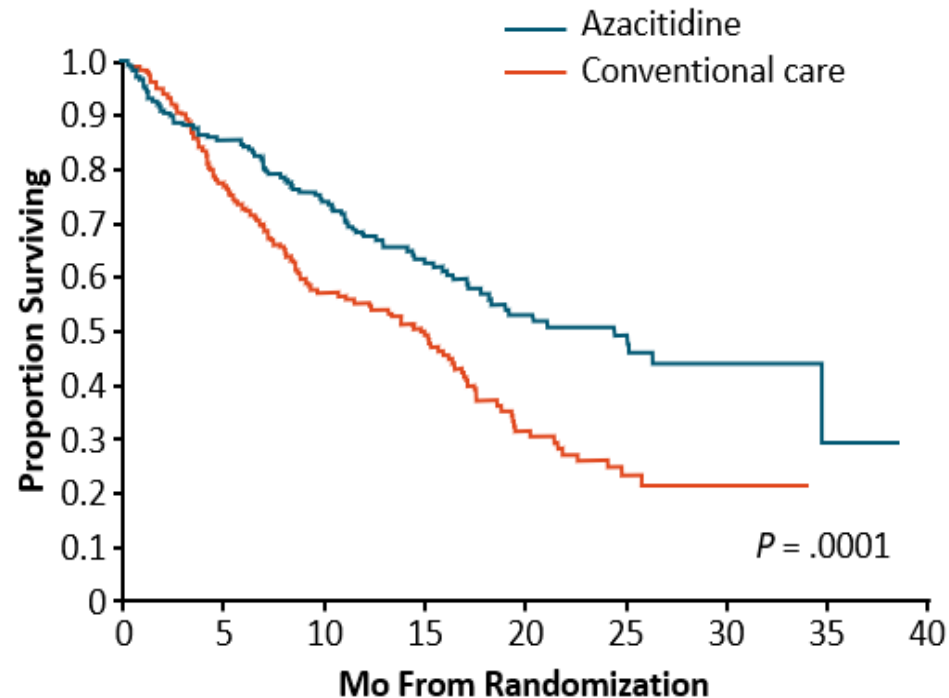
Consider clinical trial at all stages



What has worked...



AZA-001: Survival with Azacitidine vs CCR

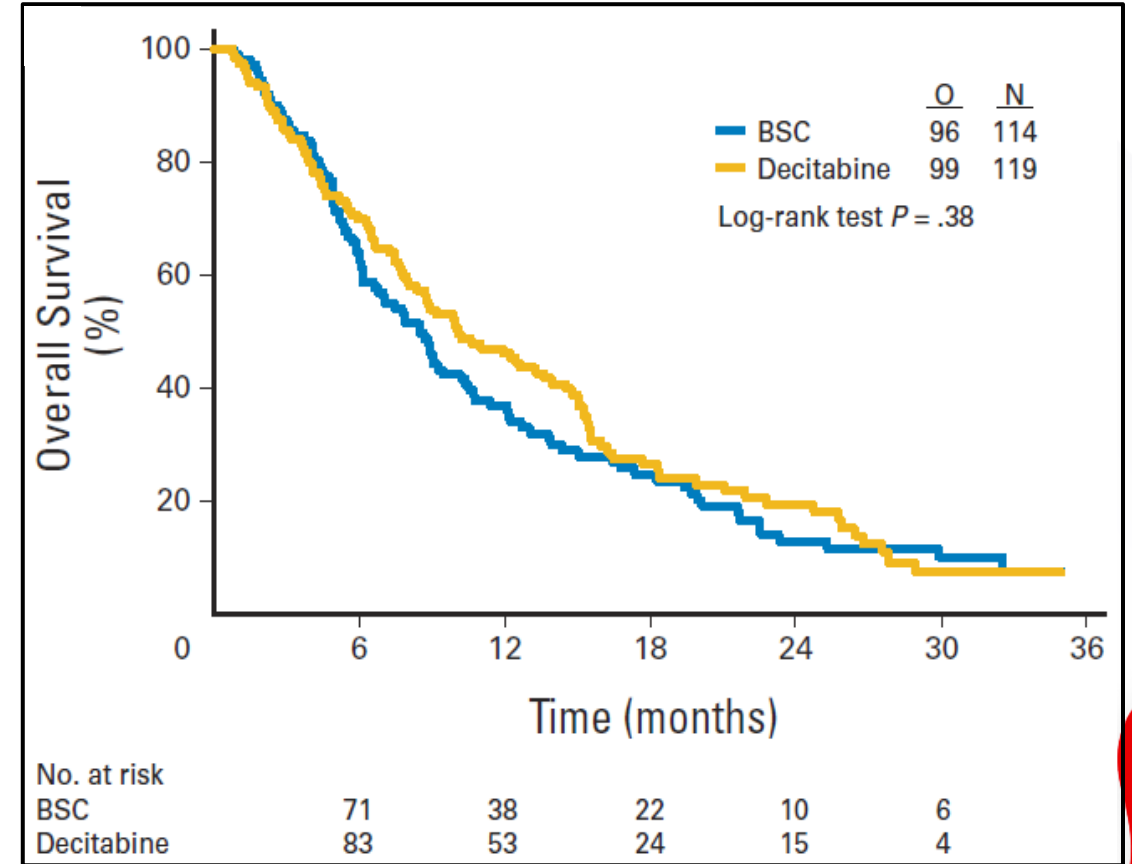
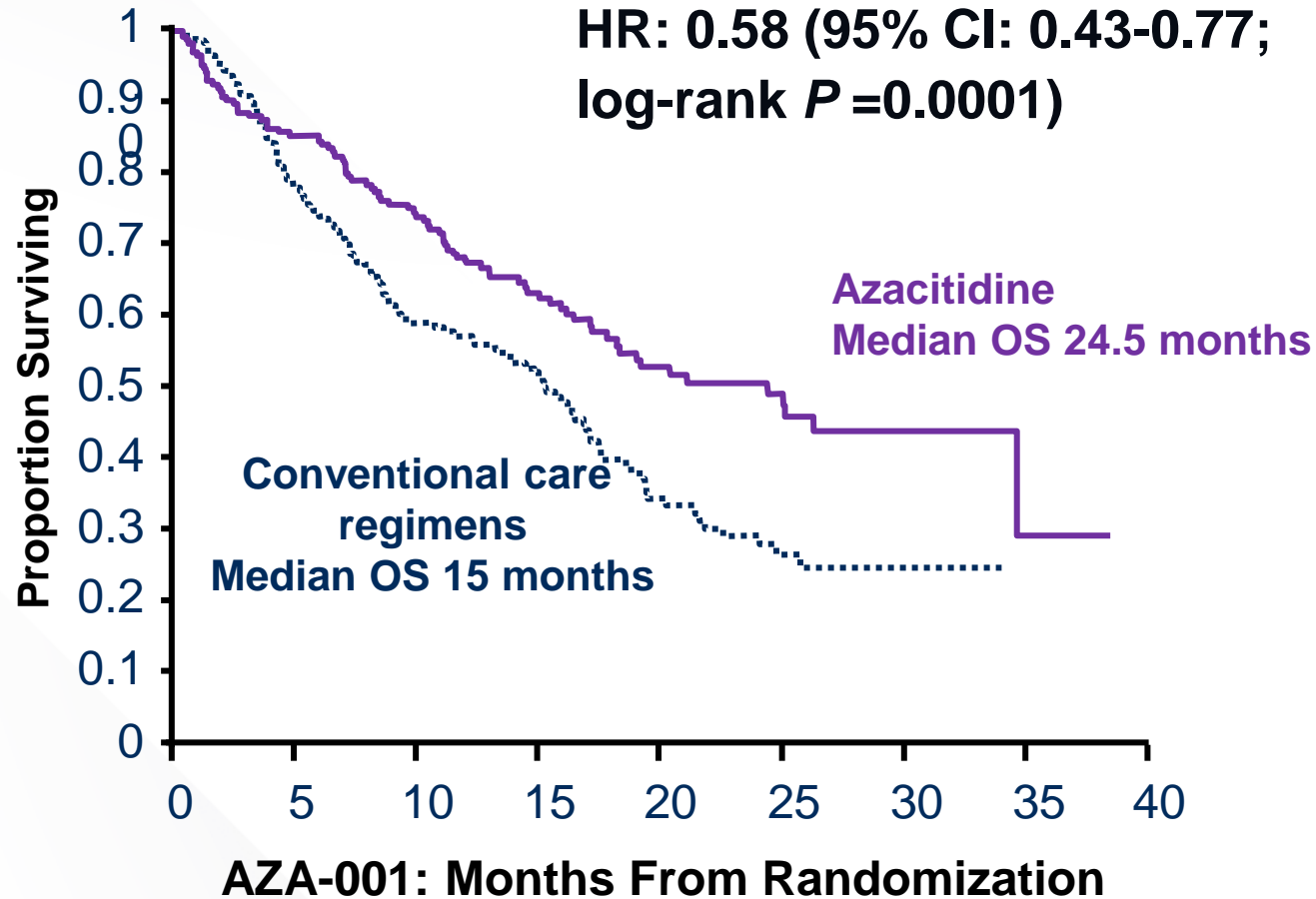


Patients at Risk, n		0	5	10	15	20	25	30	35	40
Azacitidine	179	152	130	85	52	30	10	1	0	0
Conventional care	179	132	95	69	32	14	5	0	0	0

Fenaux. Lancet Oncol. 2009;10:223

- **Phase III AZA-001 study (N = 358)**
 - Subset analysis in patients >75 yr of age (n = 87; ~1/4 of randomized patients)
- **2-yr OS superior with azacitidine ($P = .0003$)**
 - Azacitidine: 55%
 - Conventional care: 15%
- **No significant difference in the rate of bleeding or infections**

Hypomethylating agents (HMAs) remain the standard of care for HR-MDS



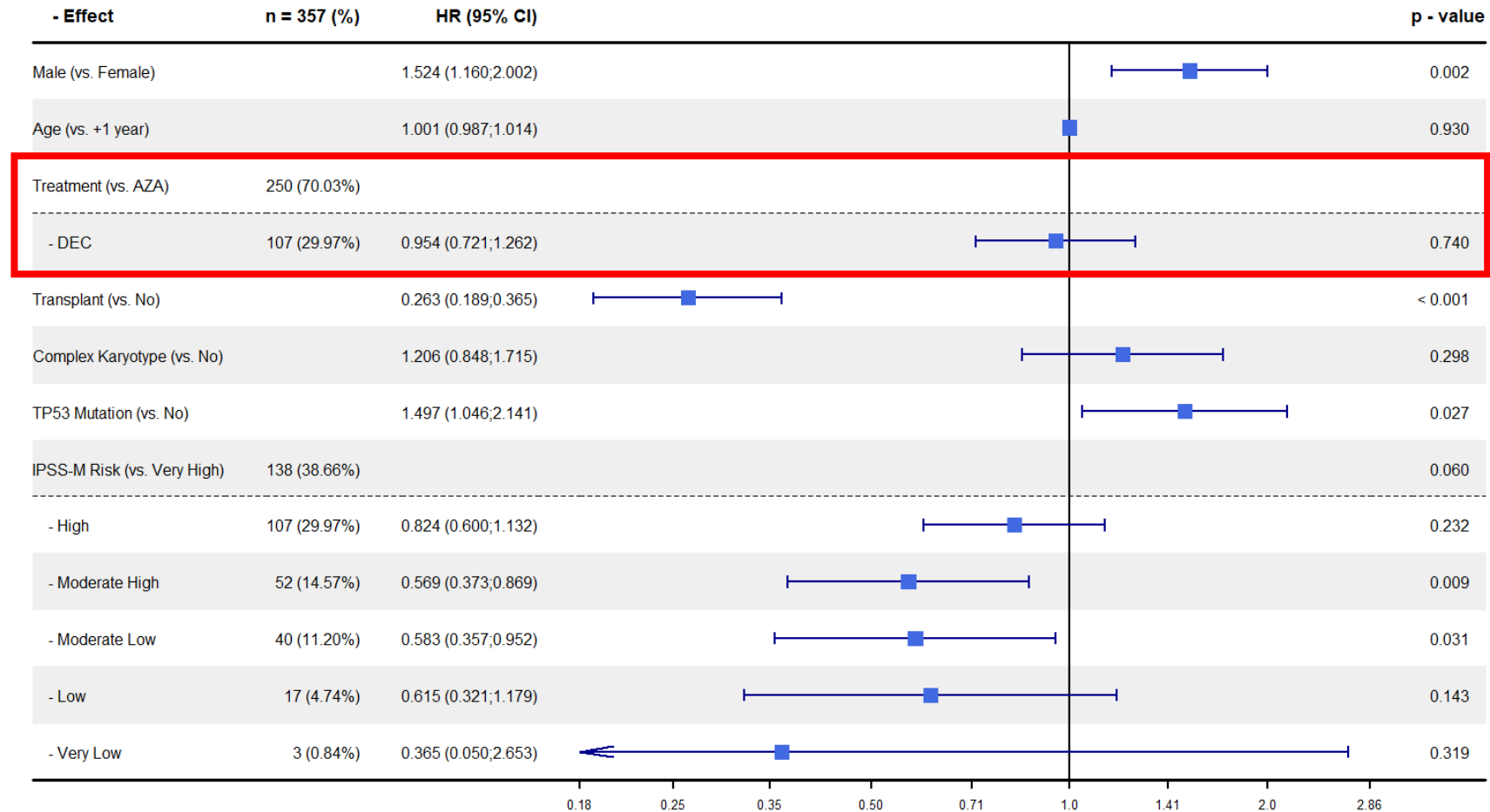
EORTC-06011: Overall Survival with Decitabine Treatment vs BSC (n=233)

What is the true CR rate with AZA? 7-32%

Multicenter VALIDATE Analysis: No difference in clinical outcomes between injectable AZA and Dec (N=919)

- No difference in response rates of OS between AZA and DEC monotherapy (Hazard ratio [HR]: 0.95, 95% CI: 0.72 – 1.26; p=0.740) in adjusted analyses

- Other factors (e.g., *TP53* mutations, complex karyotype) are more relevant to outcomes than the type of HMA used.



Oral HMAs in MDS

Single agent uncombined (CC-486) > Oral AZA > AML Maintenance Approval

Combined with cytidine deaminase inhibitor > **MDS Approval**

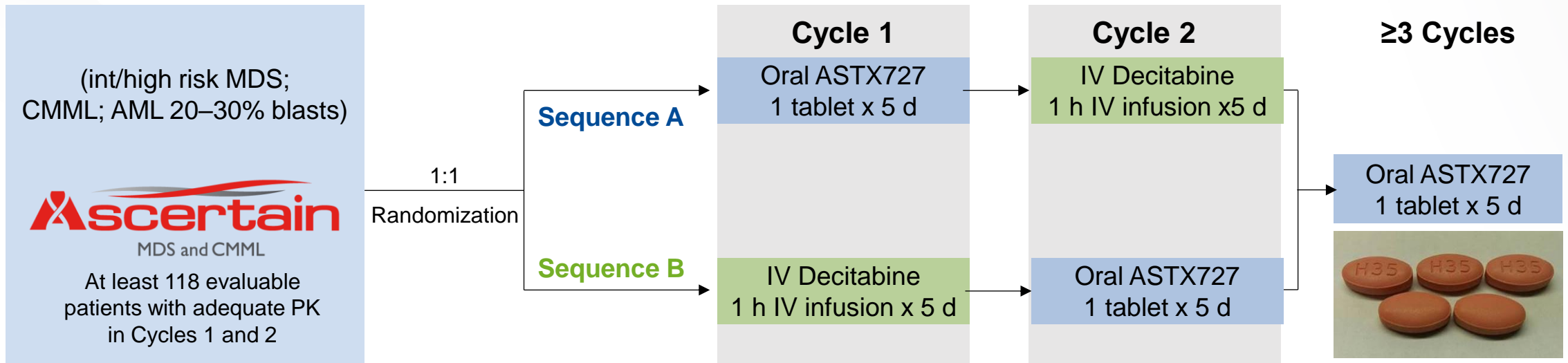
Decitabine-Cedazuridine (ASTX727) > DAC-C

It is very important to note these are **not the same**! They Cannot be used interchangeably!

*Different Pharmacokinetics!

ASTX727 Phase 3 Study (ASCERTAIN) in MDS/CMML

Trial Design: Randomized Cross-Over



Major entry criteria

- Candidates for IV decitabine
- ECOG PS 0–1
- Life expectancy of ≥ 3 months
- Adequate Organ Function
- One prior cycle of HMA is allowed

Primary endpoint

- Total 5-d decitabine AUC equivalence (Oral/IV 90% CI between 80% and 125%)

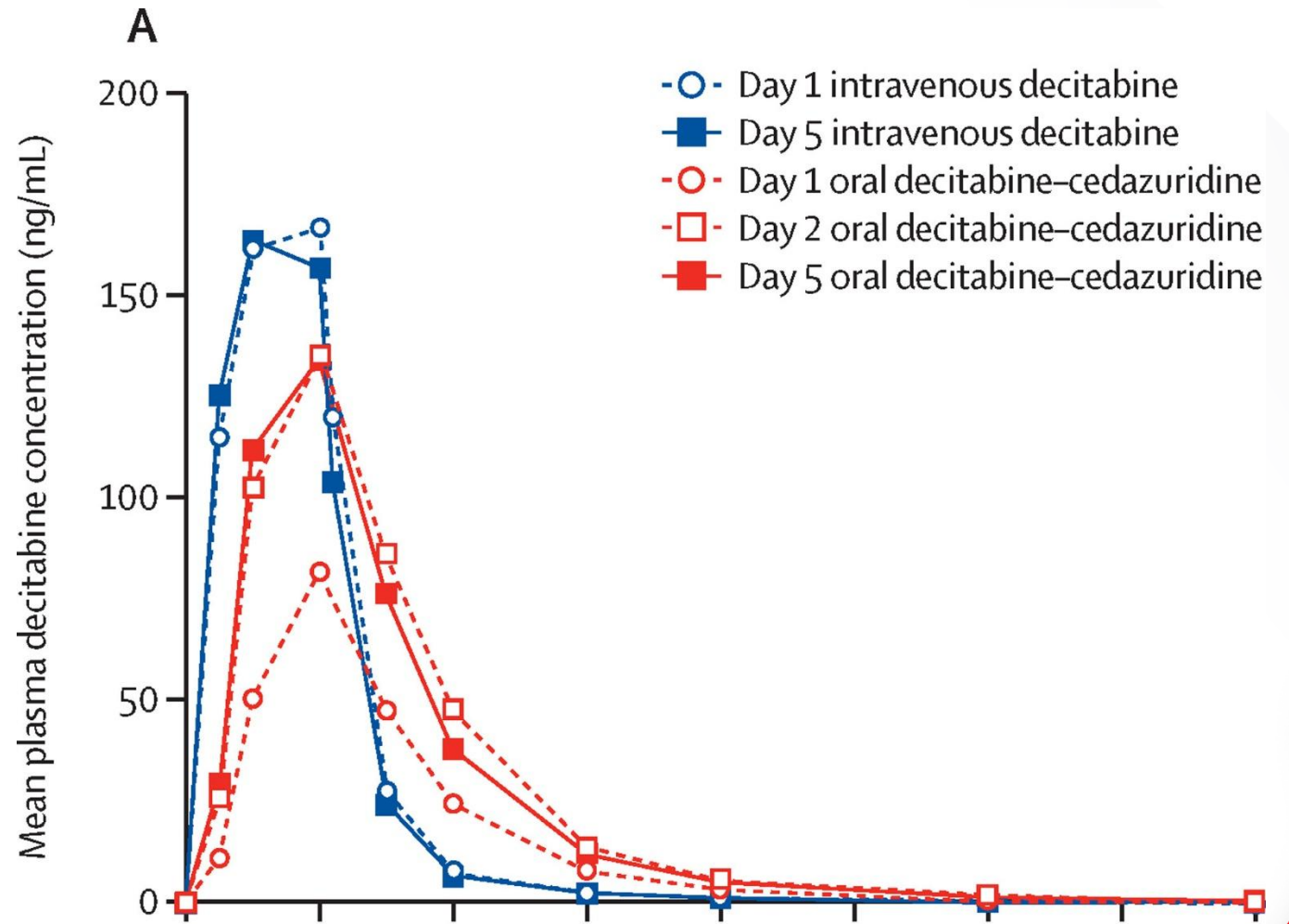
Secondary endpoints

- Efficacy: Response rate; Transfusion independence; duration of response; Leukemia-free and overall survival
- Safety of ASTX727
- Max LINE-1 demethylation

Oral HMA: Decitabine and Cedazuridine (Inqovi)

- FDA Approval in 2020 →
Key Trial: ASCERTAIN

Trial based on
pharmacokinetics



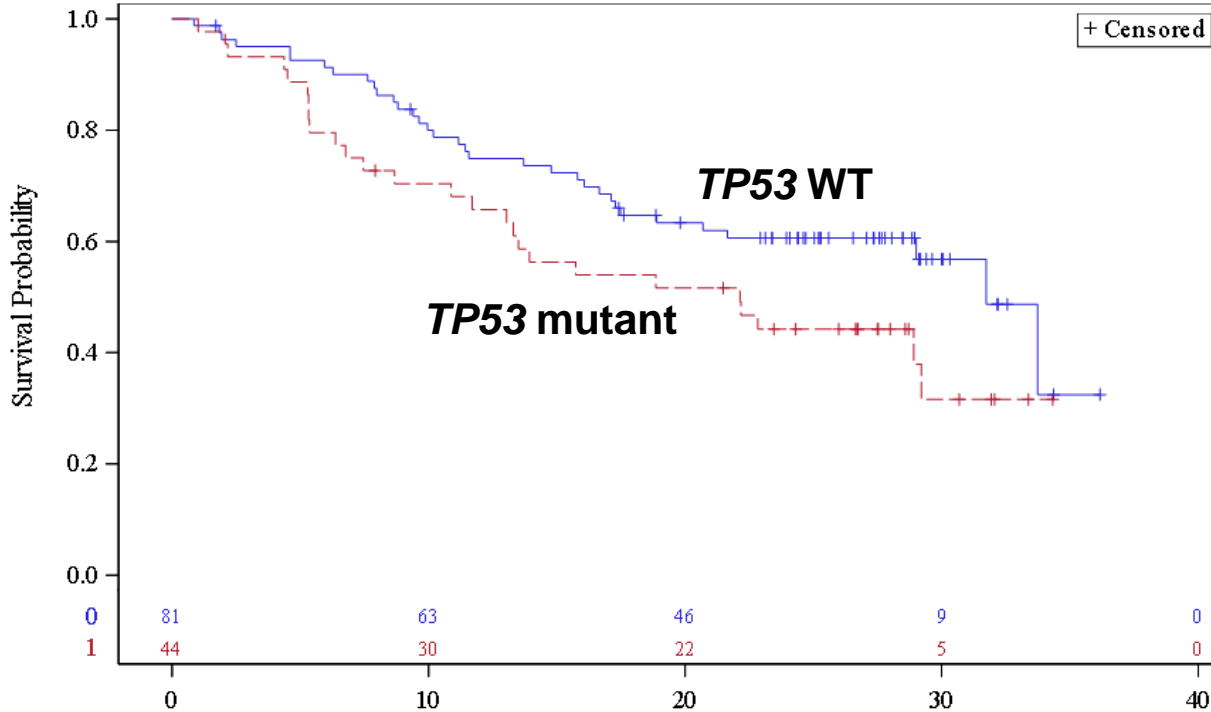
Efficacy

Response category	Treated Patients (N=133), n (%)	95% CI
Complete response (CR)	29 (22)	(15.1,29.8)
Partial response (PR)	0	
Marrow CR (mCR)	43 (32.3%)	(24.5,41.0)
mCR with hematologic improvement	22 (16.5%)	(10.7,24.0)
Hematologic improvement (HI)	10 (7.5%)	(3.7,13.4)
HI-erythroid	2 (1.5%)	(0.2,5.3)
HI-neutrophils	1 (0.8%)	(0.0,4.1)
HI-platelet	7 (5.3%)	(2.1,10.5)
Overall response (CR + PR + mCR + HI)	82 (61.7)	(52.8,69.9)
Progressive Disease	6 (4.5%)	(1.7,9.6)
No Response	28 (21.1%)	(14.5, 29.0)
Non-evaluable	17 (12.8%)	(7.6, 19.7)

Oral decitabine OS and LFS in $TP53^{mut}$ Patients

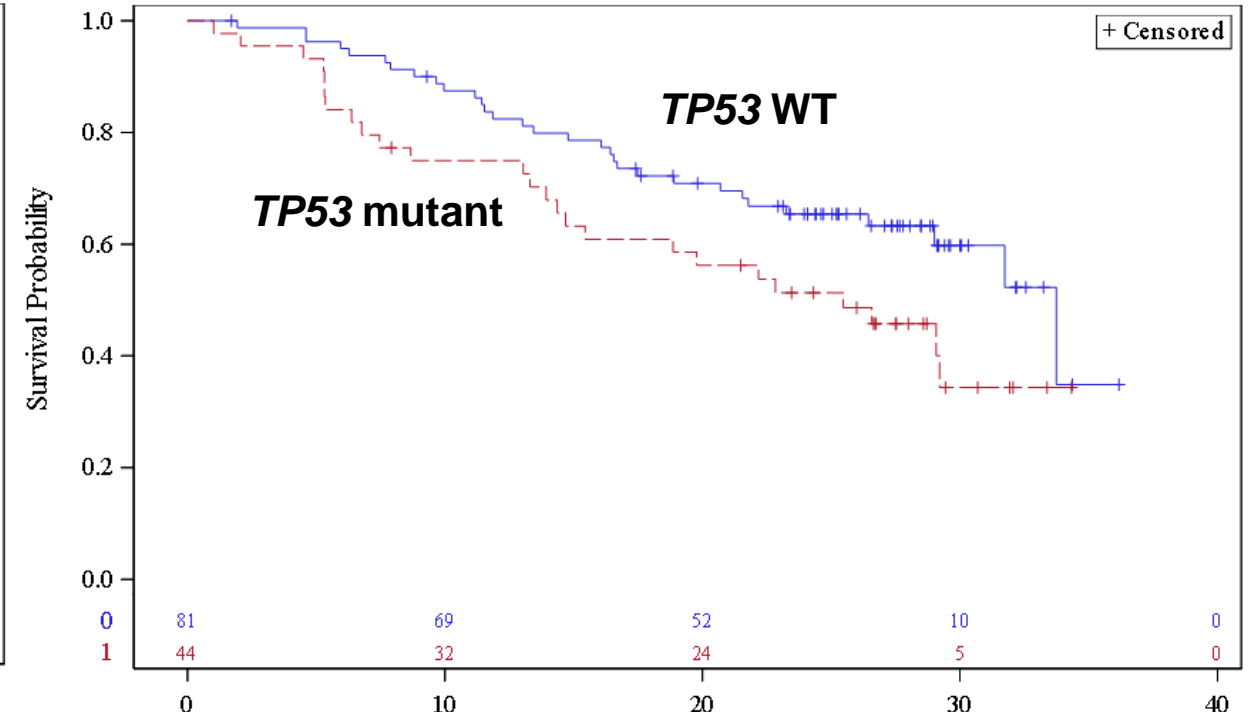
Leukemia-Free Survival

Product-Limit Survival Estimates
With Number of Subjects at Risk



Overall Survival

Product-Limit Survival Estimates
With Number of Subjects at Risk

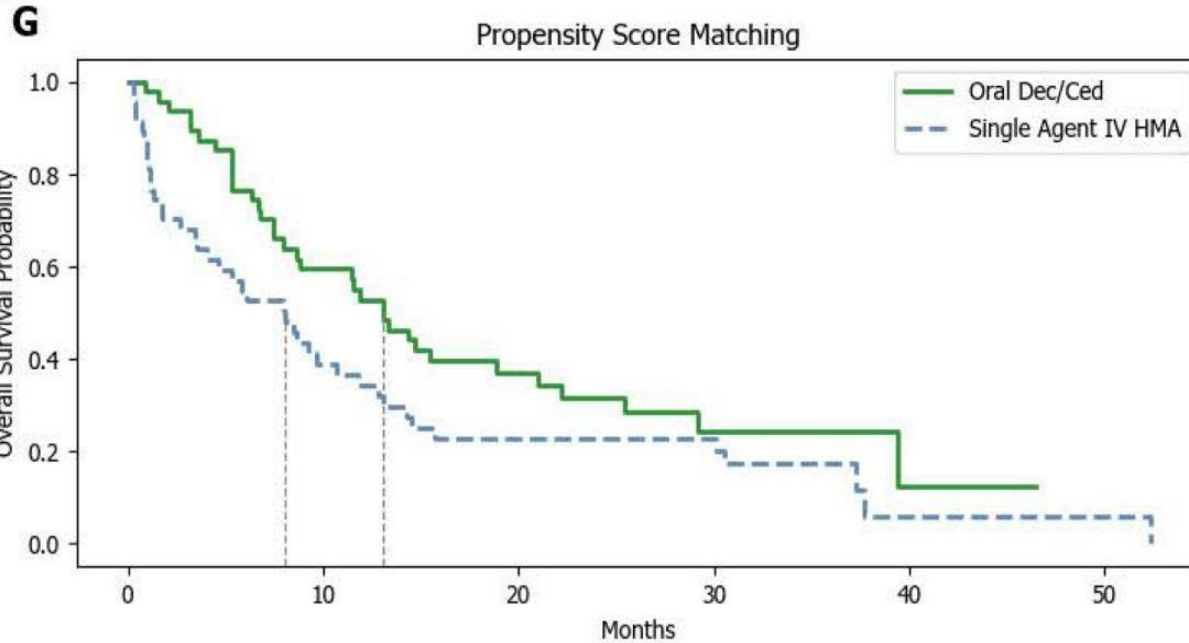


LFS: WT 31.7 months (21.7, NE)
Mut 22.1 months (11.7, 29.2)

OS: WT 33.7 months (29.0, NE)
Mut 25.5 months (14.4, NE)

NE – not estimatable

Propensity score matching of TP53-mut HR-MDS who received oral DEC-C vs injectable HMAs



Characteristic	IV/SQ HMA	Oral Dec/Ced	p
n	47	47	
Age, median [IQR]	71 [64,77]	69.0 [63.0,75.0]	0.36
TP53 VAF, median [IQR]	20 [7,34]	10 [5,24]	0.122
BM blast, median [IQR]	4[2,7]	5 [2,8]	0.343
ECOG PS 0, n (%)	14 (29.8)	15 (31.9)	0.759
ECOG PS 1, n (%)	28 (59.6)	29 (61.7)	
ECOG PS 2, n (%)	5 (10.6)	3 (6.4)	
IPSSR, median [IQR]	6.5 [4.0,8.0]	5.8 [4.5,7.4]	0.648

	At risk					
Single Agent IV HMA	47	17	9	8	1	1
Oral Dec/Ced	47	27	14	6	1	0

	Oral Dec-C months (95%CI)	IV/SQ HMA months (95%CI)	p
mOS	13.1 (8.4-21.3)	8.0 (5.2-13.0)	0.047

What we don't actually know about HMA therapy...

- How do HMAs work?
- What are the mechanisms of resistance?
- Biomarkers of response

What this means:

- Everyone is treated with an HMA
- Almost all combination studies are with an HMA backbone

Allogeneic Transplantation

AlloSCT continues to improve

Don't write anyone off unless they have a clear contraindication

Controversies surrounding AlloSCT

Should we reduce disease burden before transplant?

What blast cutoff is best before proceeding to transplant?

Should we transplant patients with multi-hit TP53 mutations & complex karyotype?

What is the best conditioning regimen for alloBMT?

Should we proceed with a haplo donor if MUD search is delayed?

Should we defer transplant if patients remain MRD positive?

Should we use maintenance therapy post transplant?

What has not worked...



Combinations: Some Recent Disappointing results

- Eprenetapopt (APR-246) + AZA
- Magrolimab+AZA (ENHANCE trial)
- Pevonidostat+AZA v. AZA (PANTHER trial)
- Sabatolimab+HMA vs. HMA+placebo (STIMULUS trial)

Most Recent:

- Tamibarotene+ AZA v. Placebo+ AZA (SELECT-MDS-1 Phase 3 trial)

On a bad day...

- HMA + Lenalidomide
- HMA + Vorinostat
- HMA + volasertib
- HMA + Eltrombopag
- HMA + romiplostim
- HMA + Pracinostat
- HMA + Durvalumab
- HMA + Pevonedistat
- HMA + APR246
- HMA + Magrolimab
- HMA+ Sabatolimab
- HMA+ Tamibarotene



Why? Bad Disease? Bad Drugs? Or Bad Trials?

Bad disease

Biological and molecular heterogeneity of the disease

>85-90% of pts have ≥ 1 mutation

More than 45 mutations, none specific to MDS

Only 5-6 mutations seen >10% cases

Average number of mutations per patient is 2-4

'Bad' Drugs

- Poor understanding of mechanisms of response/resistance
- Enthusiasm too early in the process

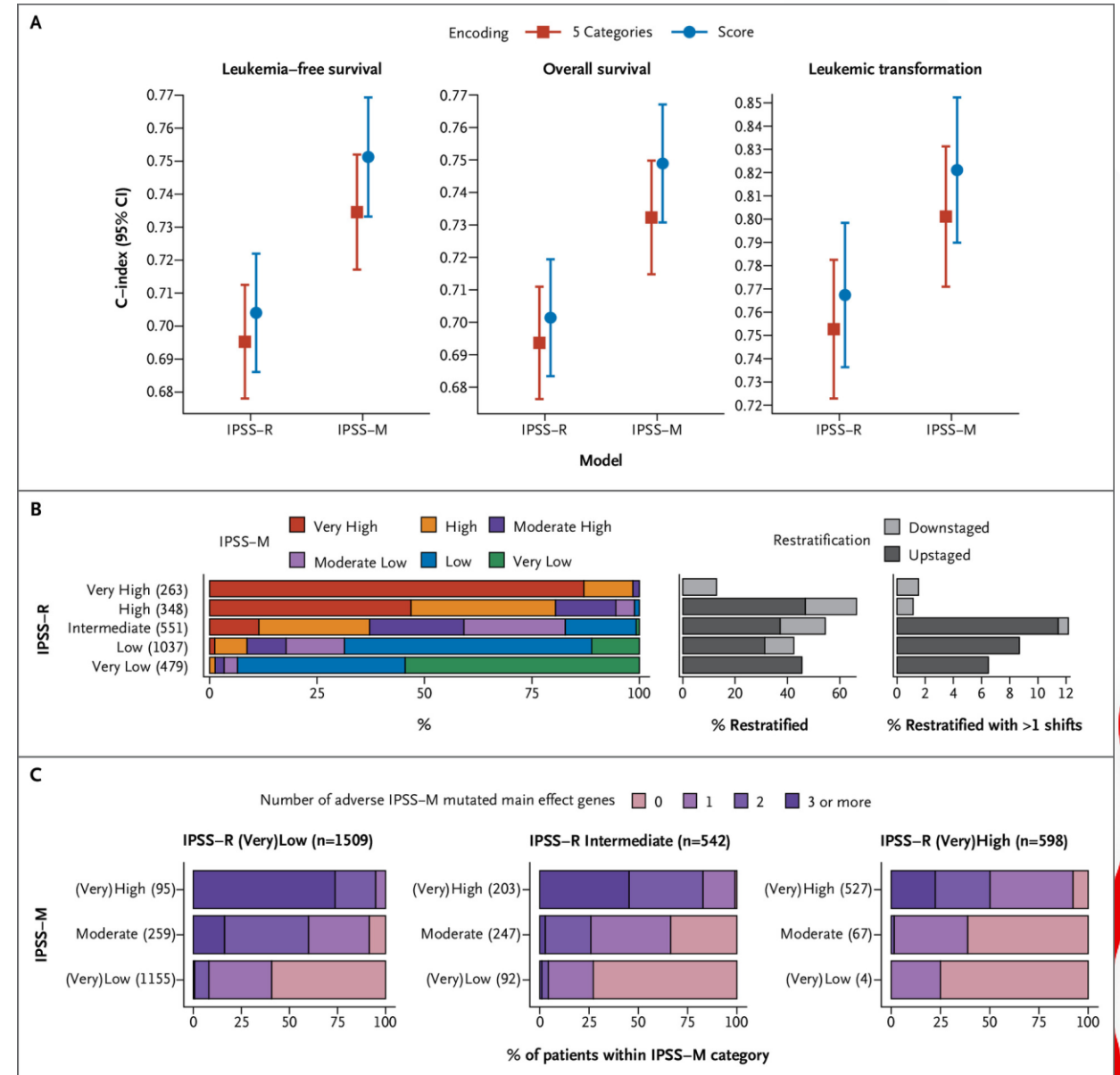
'Bad' Trials

- Classification of disease into risk groups
- Older, frail patients, limited social support, live far from tertiary centers where trials are typically conducted- trouble enrolling real world patients
- Selected patients enrolled in phase 1/2 trials leads to results that rarely successfully translate to randomized phase 3 trials and the general population
- Rethinking response criteria

Moving target with Prognostication of High Risk MDS: WHO-HAEM5 vs. ICC 2022 vs. IPSS-R Vs. IPSS-M

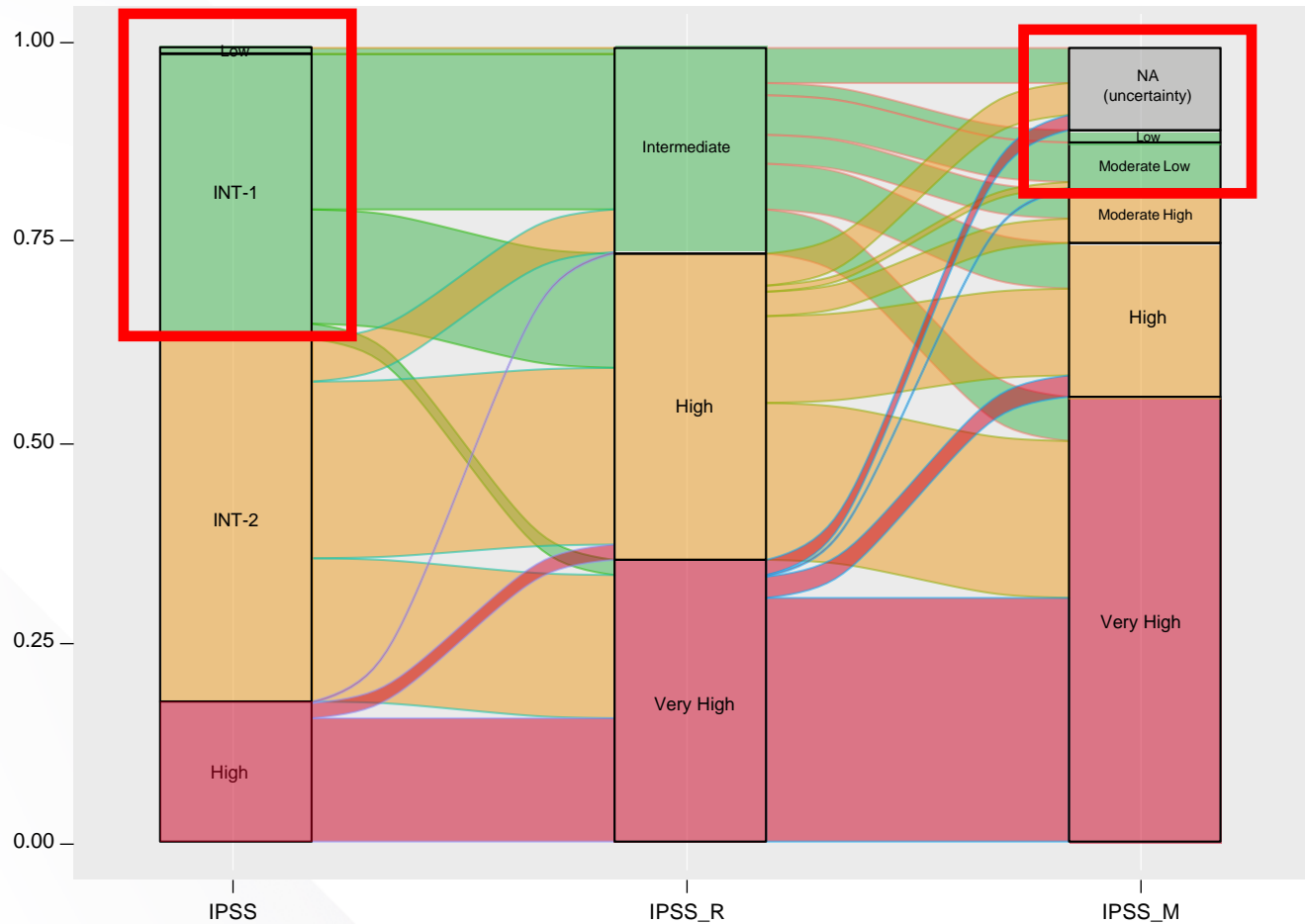
- 46% re- stratified
- 74% upstaged
- 26% down-staged
- Marked differences in outcomes were observed between IPSS-M categories within each IPSS-R stratum
- Cumulative contribution of the prognostic mutations

Bernard E, et al NEJM evidence 2022



Risk re-stratification of HR-MDS patients in STIMULUS MDS 1 and 2 trials

Pooled MDS1 & MDS2 – IPSS vs IPSS-R vs. IPSS-M



- Upstaging was observed from derived former IPSS criteria to IPSS-R
- Comparing IPSS-R and IPSS-M
 - Of patients with IR IPSS-R, 22.2% and 21.5% were upstaged to HR and vHR IPSS-M, respectively
 - 51.2% of patients with HR IPSS-R were upstaged to vHR IPSS-M
 - 86.5% of patients with vHR IPSS-R remained vHR and 7.6% were downstaged to HR IPSS-M

STIMULUS MDS-1: IPSS-R VH, H, Int ($\geq 5\%$ blasts)
STIMULUS MDS-2: IPSS-R VH, H, Int (Score > 3.5)

Differences in Classification Systems

MDS WHO Classification

MDS w. Biallelic TP53 inactivation

MDS with Increased Blasts

MDS IB-1

Peripheral Blood: 2-4%

Bone Marrow: 5-9%

MDS IB-2

Peripheral Blood: 5-19%

Bone Marrow: 10-19%

MDS with Fibrosis (MDS IB+ F)

MDS ICC Classification

MDS with Excess Blasts

MDS EB

Peripheral Blood: 2-9%

Bone Marrow: 5-9%

MDS/ AML

Peripheral Blood: 10-19%

Bone Marrow: 10-19%

This will also be important for response assessment

WHO 2016	WHO 2022	ICC
MDS with single lineage dysplasia (MDS-SLD)	Not included MDS with low blasts (MDS-LB) < 5% BM and <2% PB	MDS, not otherwise specified with single lineage dysplasia (MDS, NOS-SLD)
MDS with multi-lineage dysplasia (MDS-MLD)	MDS with low blasts (MDS-LB) < 5% BM and <2% PB	MDS, not otherwise specified with multi-lineage dysplasia (MDS, NOS-MLD)
MDS with ring sideroblasts • With single lineage dysplasia (MDS-RS-SLD) • With multi-lineage dysplasia (MDS-RS-MLD)	MDS with low blasts and mutated <i>SF3B1</i> or MDS with ring sideroblasts (if ≥ 15% RS and <i>SF3B1</i> wild-type)	MDS with mutated <i>SF3B1</i>
MDS with isolated del(5q)	MDS with low blasts and isolated 5q deletion (MDS-5q)	MDS with del(5q)
MDS unclassifiable	Not included	Not included
Not included	Not included	MDS, not otherwise specified without dysplasia (e.g., monosomy 7/del(7q)) ^a
MDS excess blasts-1 (MDS-EB1; 5–9% bone marrow blasts)	MDS with increased blasts-1 (MDS-IB1; 5–9% bone marrow and/or 2–4% peripheral blood blasts)	MDS excess blasts (5–9% bone marrow and/or 2–9% peripheral blood blasts)
MDS excess blasts-2 (MDS-EB2; 10–19% bone marrow or peripheral blood blasts or Auer rods)	MDS with increased blasts-2 (MDS-IB2; 10–19% bone marrow or 5–19% peripheral blood blasts or Auer rods)	MDS/AML (10–19% bone marrow or peripheral blood blasts)
AML-defining genetics ^b	AML-defining genetics independent of bone marrow and peripheral blood blast count	AML-defining genetics with ≥10% bone marrow and peripheral blood blasts
AML (≥20% bone marrow and peripheral blood blasts)	AML (≥20% bone marrow and peripheral blood blasts)	AML (≥20% bone marrow and peripheral blood blasts)
Not included	MDS with biallelic <i>TP53</i> inactivation (Two or more <i>TP53</i> mutations, or 1 mutation with evidence of <i>TP53</i> copy number loss or cnLOH)	MDS with mutated <i>TP53</i> (Multi-hit <i>TP53</i> mutation, or <i>TP53</i> mutation (VAF > 10%) and loss of 17p) and MDS/AML with mutated <i>TP53</i> (Any somatic <i>TP53</i> mutation (VAF > 10%))
Not included	MDS, hypoplastic (MDS-h)	Not included
Not included	MDS with fibrosis (MDS-f)	Not included
Not included	Clonal hematopoiesis (CHIP, CCUS) ^c	Pre-malignant clonal cytopenias and CCUS ^c

AML response criteria??

MDS response criteria??

Harmonization of Systems

Example:

The TITAN Study-A collaborative, world-wide effort to collect and analyze clinical and genomic information from real-world patients affected by myeloid neoplasms.

Response Assessment Criteria

AML

Complete Remission (CR)

Hematologic complete remission is defined as meeting all of the following response criteria:

- < 5% blasts in the bone marrow
- No blasts with Auer rods
- No extramedullary disease (e.g., CNS, soft tissue disease)
- Neutrophils $\geq 1,000/\mu\text{L}$
- Platelets $\geq 100,000/\mu\text{L}$
- Transfusion independent

MDS

Complete Remission (CR)

Requires all of the following maintained for a minimum of four weeks. When reporting the CR achievement date, report the first date when CR was achieved (not the four week date in which CR was maintained).

Bone marrow evaluation

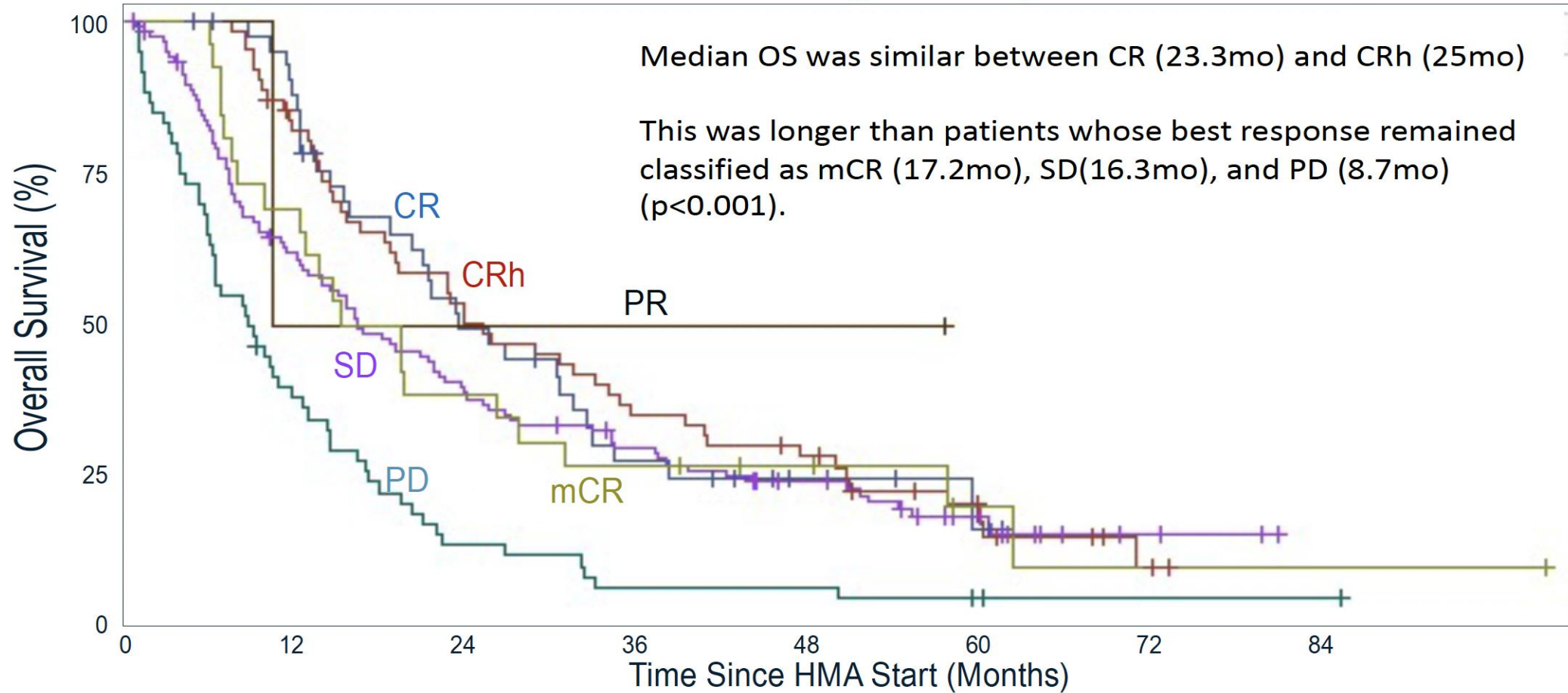
- < 5% myeloblasts with normal maturation of all cell lines

Peripheral blood evaluation:

- Hemoglobin ≥ 11 g/dL untransfused without erythropoietic support
- ANC $\geq 1000/\text{mm}^3$ without myeloid growth factor support
- Platelets $\geq 100,000/\text{mm}^3$ without thrombopoietic support
- 0% blasts in blood

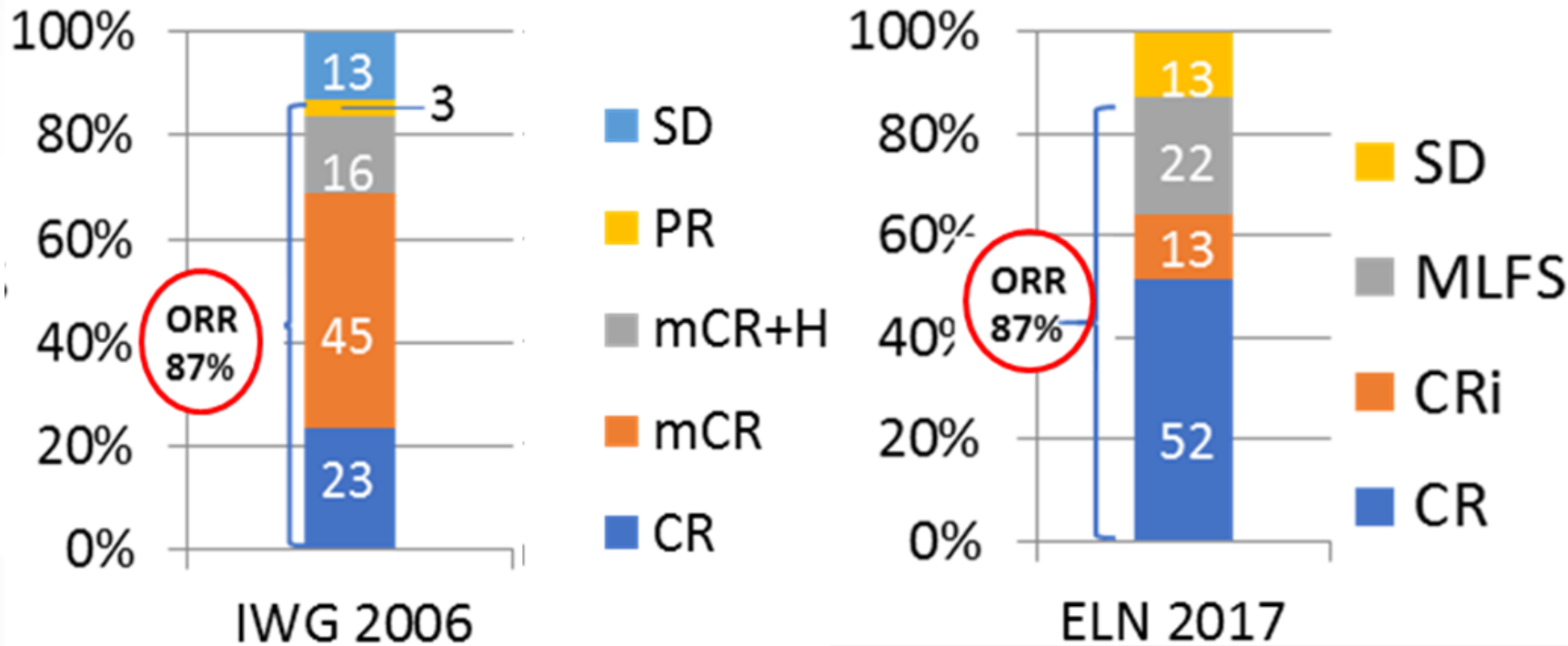
B.

Overall Survival According to Response with CRh



CR	43	11	0	
CRh	62	25	5	0
PD	60	5	1	0
PR	2	1	0	
SD	118	37	6	0
mCR	26	7	1	1

CR in MDS: Do we really need a Hb cutoff of 11 gm/dL?



GFM trial of CPX-351 for frontline treatment of MDS

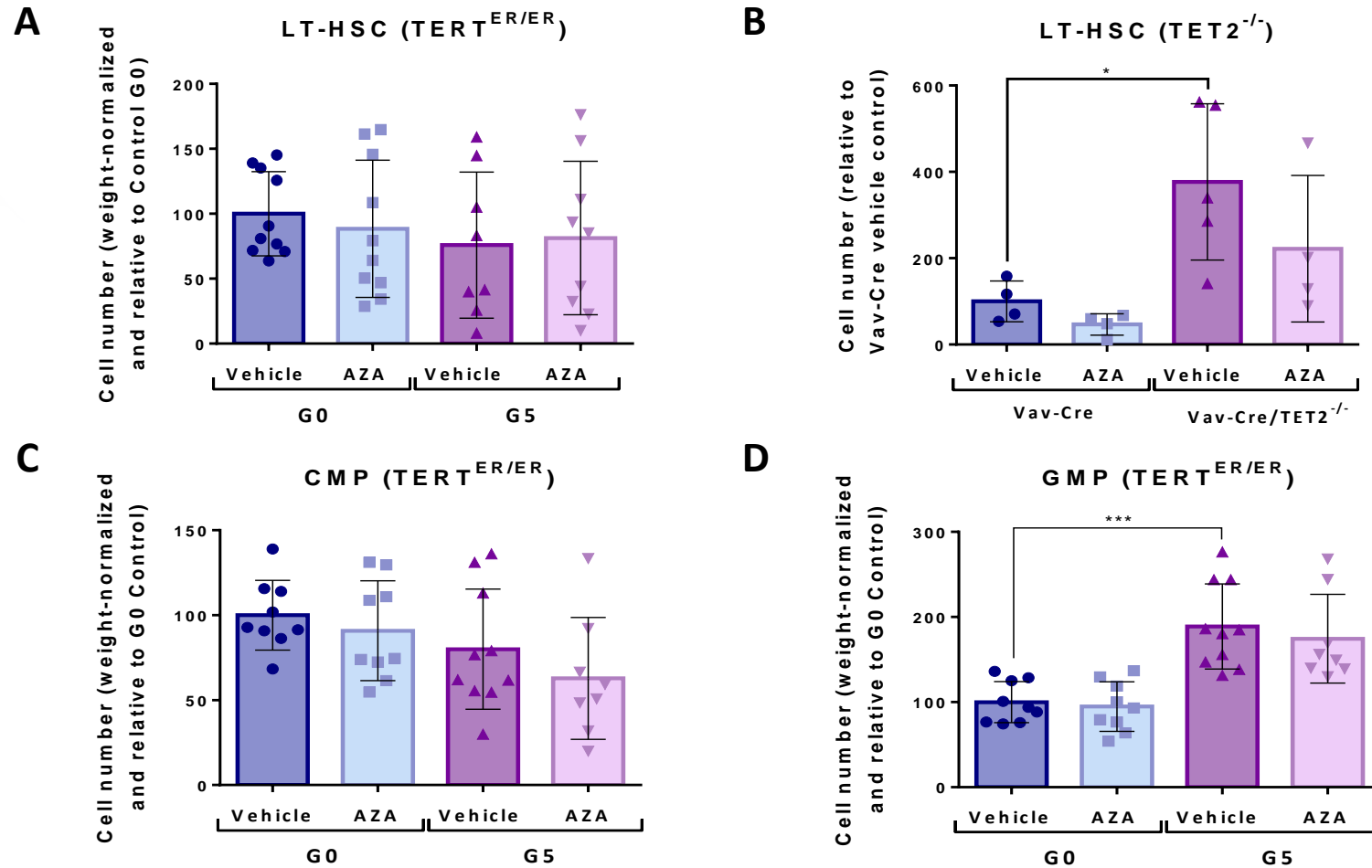
ELN 2017 criteria: CR: 52%, CRi: 13%, MLFS: 23%, SD: 13%

IWG 2006 criteria : CR: 23%, mCR: 45%, mCR + HI-P: 6%, mCR + HI-P + HI-N: 6%, mCR + HI-N: 3%, PR: 3%, SD: 13%

Discrepancy in CR rates due to Hb threshold (11 g/dL versus none)

AZA as backbone?

AZA does not eradicate the MDS HSC and does not overcome aberrant myeloid differentiation



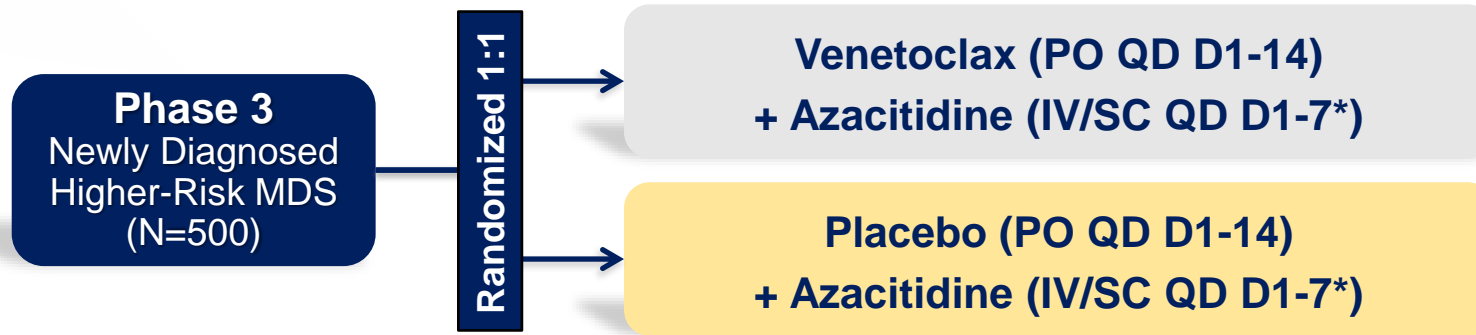
The path forward



Phase 3 VERONA Study (NCT04401748)

• Study Design and Endpoint

VERONA Study Design



*7 days within the first 9 calendar days/28 day cycle

Select Inclusion Criteria

- + ≥18 years old with newly diagnosed MDS according to 2016 WHO classification
- + <20% BM blasts
- + ECOG PS 0-2
- + IPSS-R score of >3 (Intermediate, High, Very High)
- + No planned HSCT at the time of C1D1

Select Exclusion Criteria

- Prior therapy for MDS with HMA, chemotherapy, or allo-HSCT
- Prior diagnosis of therapy-related MDS, MDS evolved from MPN, MDS/MPN including CMML, aCML, JMML, and unclassifiable MDS/MPN

End Points

Primary: **CR, OS**

Secondary:

mOR

TI

ORR

Fatigue score

Physical functioning score

Time to deterioration in physical functioning

Other Agents to Consider with MDS

- IDH-2 (5-10%): enasidenib
- IDH-1 (5%): ivosidenib, olutasidenib
- Flt-3 (15%): multiple agents
- NPM1: high dose ara-C
- TP53 (10-30%): ??

ENA Phase 2 Trial in IDH2m MDS

Cohorts:

- A (HR-MDS, failed HMA) – **28 patients**
- B (Untreated HR-MDS) – **30 patients**
- C (LR-MDS, failed ESA) – **11 patients**

	HR Treated (R/R)	HR Untreated (1L-treated)	LR (Lower Risk)
OR	42.9% (95% CI, 24.5-62.8)	43.3% (95% CI, 25.5-62.6)	55% (CR with transfusion independence)
CR	5 (42%)	5 (38%)	6 (55%)
HI	7 (58%)	6 (46%)	-
DOR	6.9 months	12.2 months	-
OS	14.9 months	25.5 months	Not reached
12-Month OS Rate	57.1% (95% CI, 41.5-78.8)	85.8% (95% CI, 73.9-99.7)	-
Grade 3+ Adverse Events (AE)	72 cases (78% of patients)	72 cases (78% of patients)	5 cases (2 related)

Key Takeaways:

✓ ENA demonstrated efficacy (43.1% OR across HR-MDS).

✓ OS

✓ Well-tolerated: no ENA-related SAEs.

✓ LR-MDS: durable response



Obrigado! Thank you!

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Do we have the right endpoints in HR-MDS?

- IWG 2006 criteria have many problems and should be phased out
- IWG 2023 eliminated problematic mCR without HI and introduced near-CR responses to reflect BM blast clearance with meaningful count recovery (CRL [including CRunilineage & CRbilineage] and CRh).
- IWG 2023 criteria have now been validated retrospectively and are being increasingly included in clinical trials to allow prospective validation and further refining.
- Clinical, genetic and treatment context all can affect the performance of trial endpoints in HR-MDS
 - For *TP53* mutated HR-MDS, event driven endpoints (EFS, OS) and early randomization rather than rates of CR are more reliable
 - In my view, bridging to alloSCT (which is a means to an end and not a benefit by itself) should not be an endpoint for clinical trial. Any benefit from more patients going to alloSCT with a therapy should be measured by EFS and OS.
 - Impact of responses before alloSCT continues to be debated, especially for patients with <10% blasts.
 - Use of MRD is provisional and needs careful investigations with longitudinal samples from prospective randomized trials
- All this might not matter as much in the absence of better drugs ...