

MYELODYSPLASTIC NEOPLASMS (MDS)



MDS FOUNDATION FAMILY FORUM

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Quote of the Day

**“Difficult roads can lead to
beautiful destinations”**

Kia Wynn
Survivor

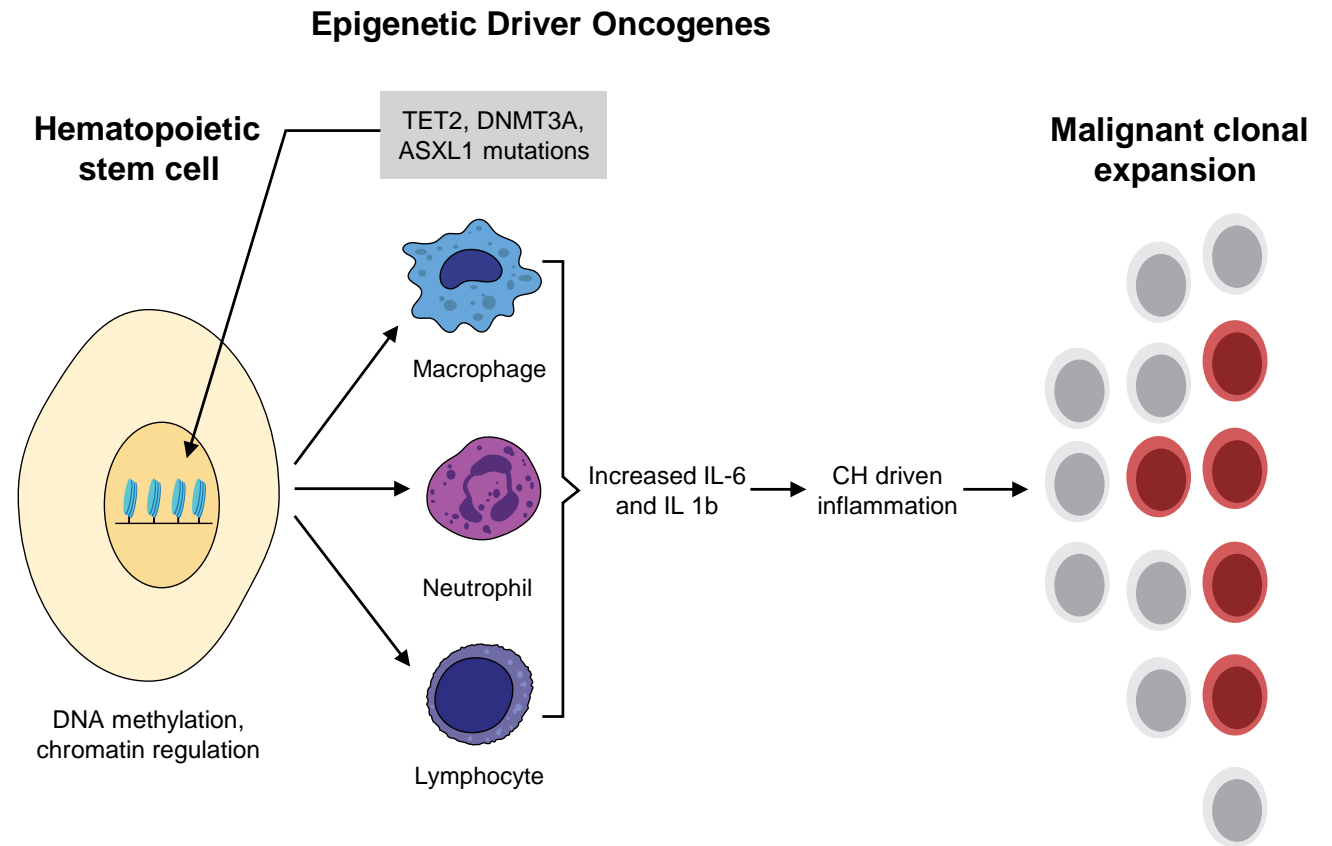


OUTLINE

- Introduction to MDS
- Diagnosis and risk stratification
- Treatment of lower risk MDS and higher risk MDS
- Survivorship
- Future Directions/Challenges

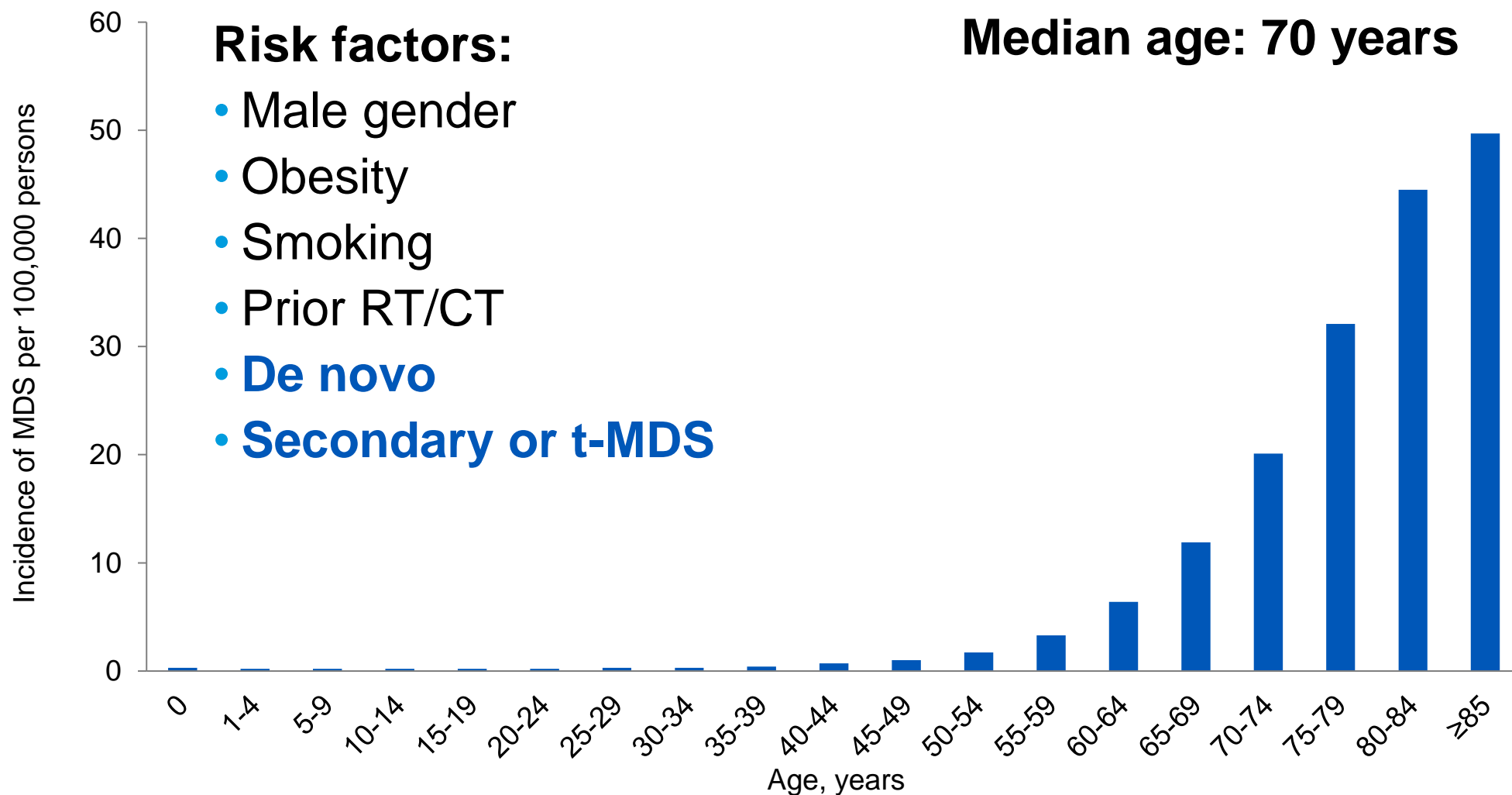
DEFINITION-MDS

- Group of blood cancers in which the bone marrow does not produce healthy blood cells.
- Clonal disease: Mutations drive and shape MDS
- Risk for transformation to acute leukemia



Redrawn from presenter-supplied original; no source supplied.

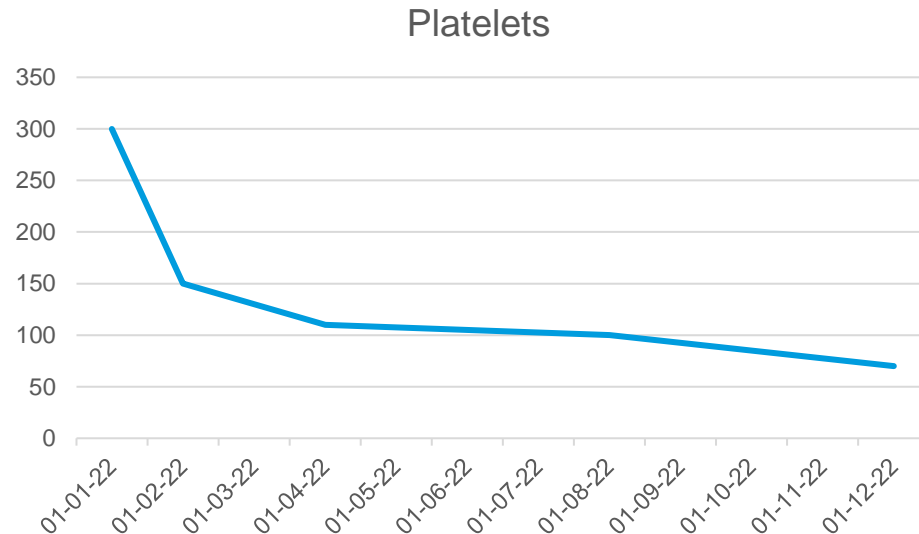
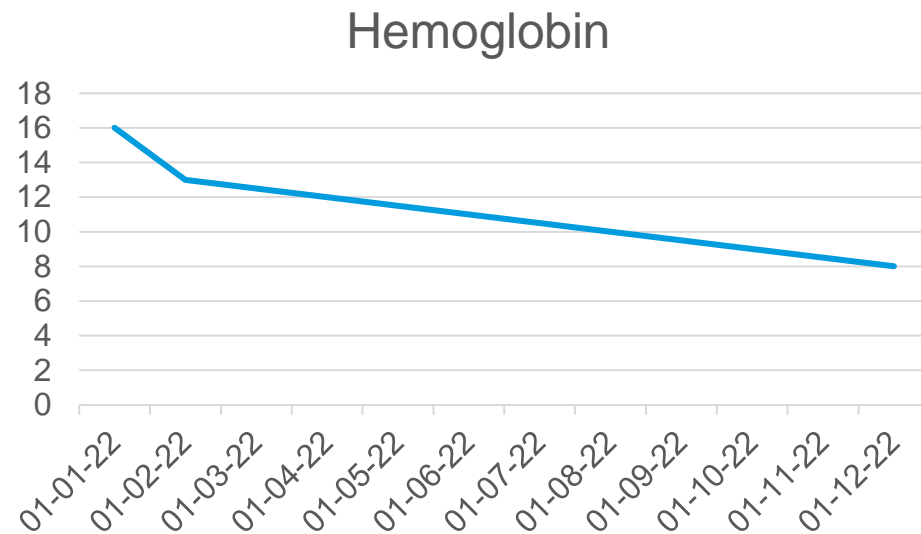
MDS INCIDENCE PER AGE



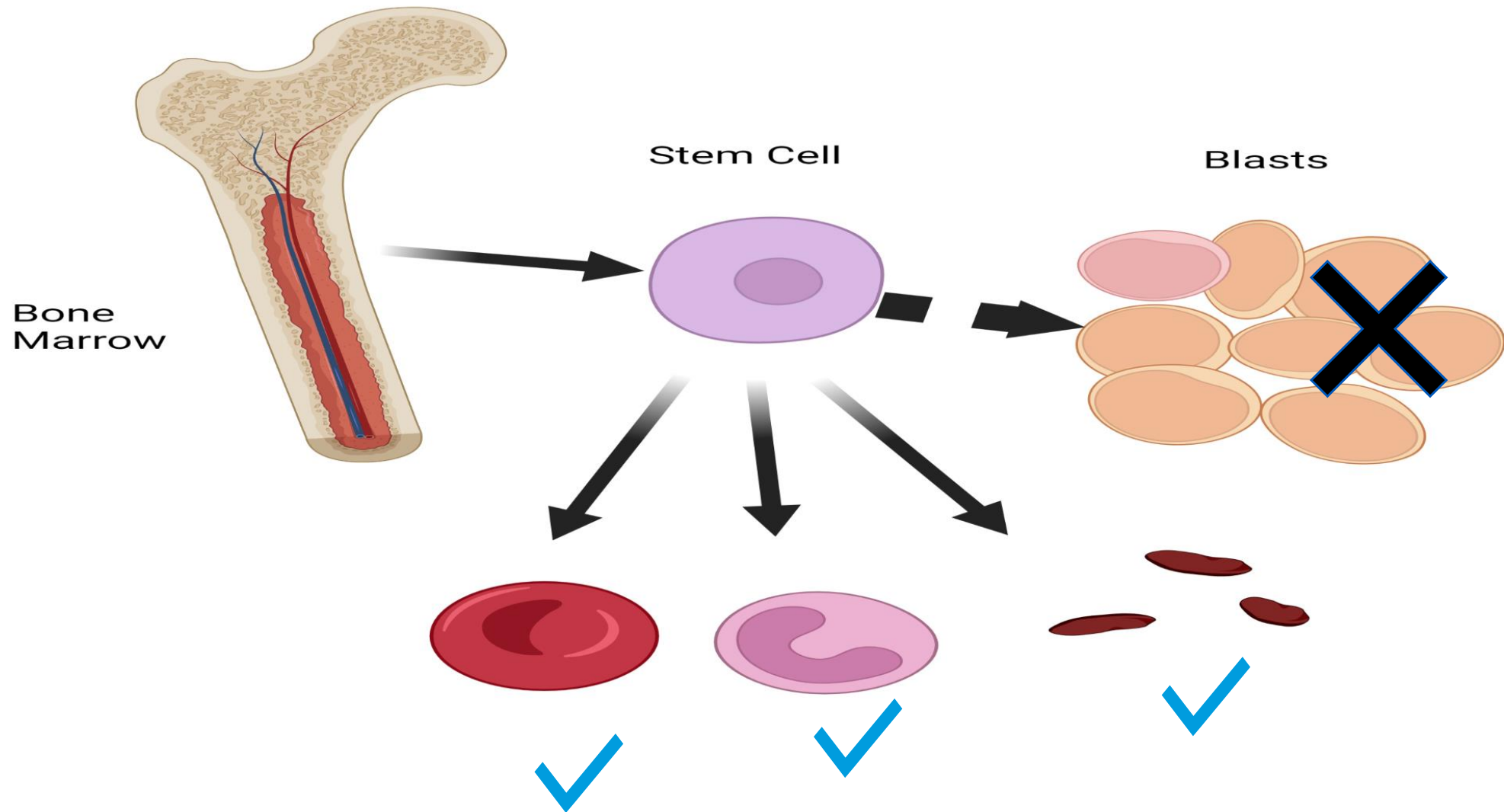
Redrawn from Ma X. Am J Med 2012; Zeidan Blood Reviews 2019

MDS CASE: ANEMIA

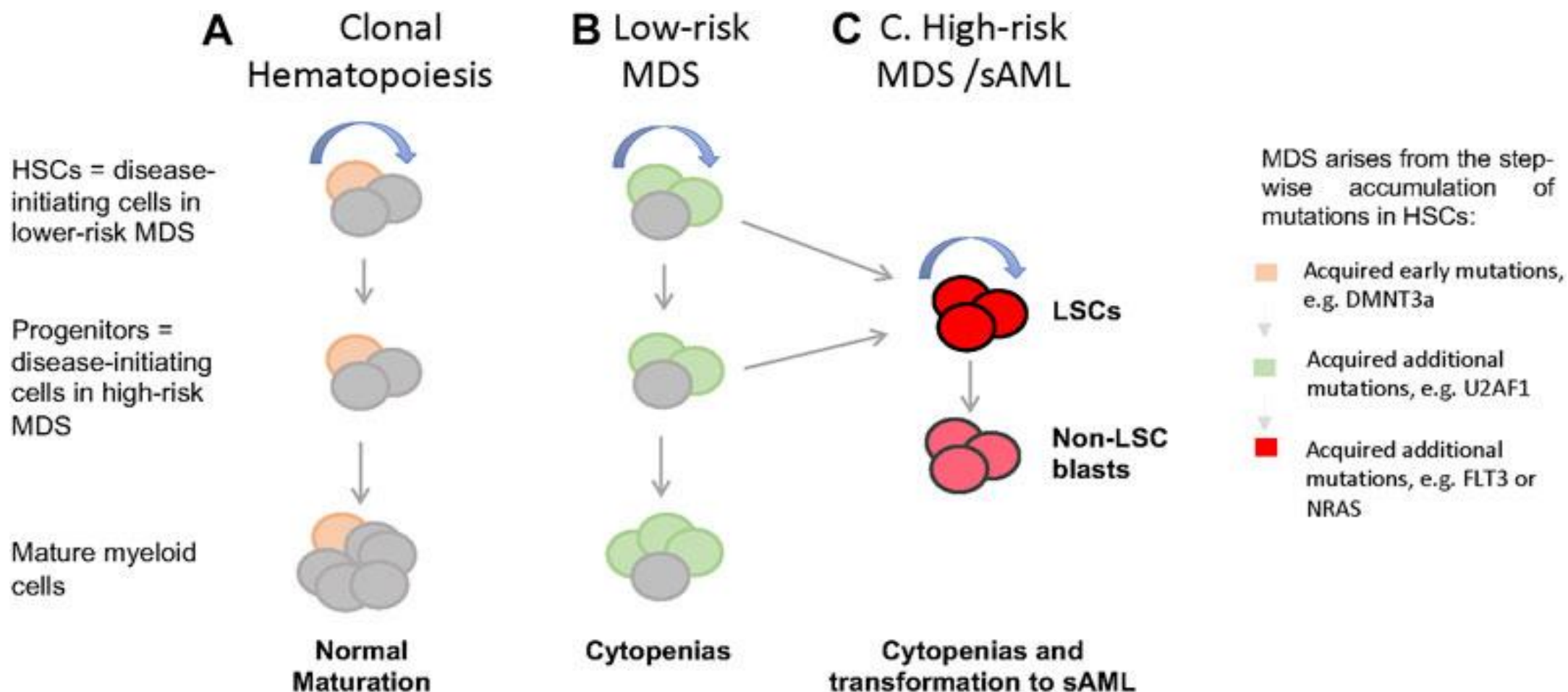
- Mr. H is 70 yo male with worsening anemia and thrombocytopenia over the past year.
- He feels tired, dizzy, and noted bruises in arms



WHAT HAPPENS IN MDS?



FROM CLONAL HEMATOPOIESIS TO MDS





DIAGNOSTIC APPROACH

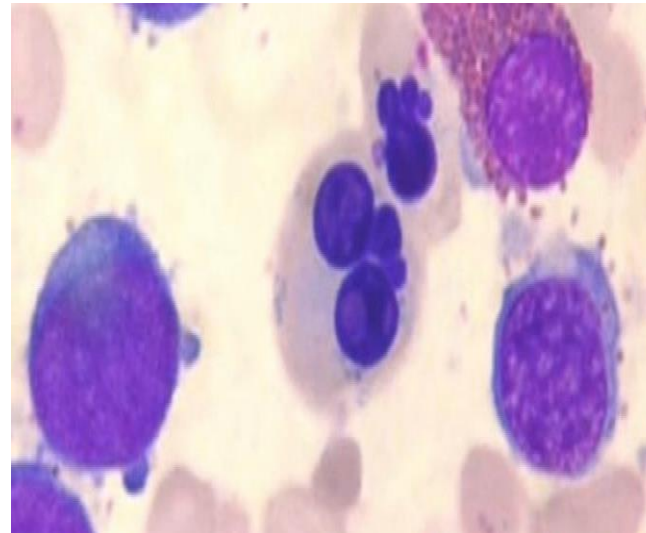
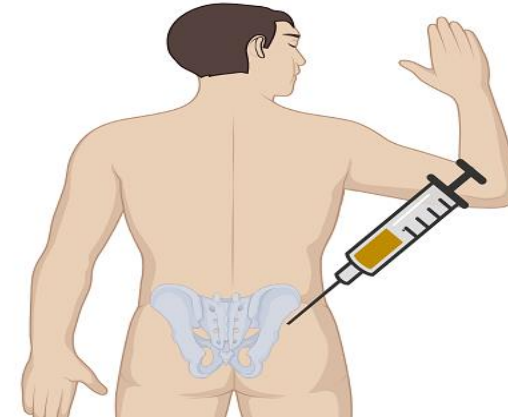
MDS DIAGNOSTIC APPROACH

- H & P: Family or personal history of cancer
- Persistent/Progressive cytopenia
- Not explained by other causes: Chronic blood loss, autoimmunity, infections



MDS WORK UP

- Laboratory studies: CBC diff, LDH, peripheral smear, reticulocyte counts
- Iron studies, B12, folate
- Thyroid function
- HIV, Hepatitis serology, ANA
- Bone marrow biopsy:
- Morphology, chromosome analysis, FISH, molecular studies
- Genetic studies for inherited MDS







RISK STRATIFICATION

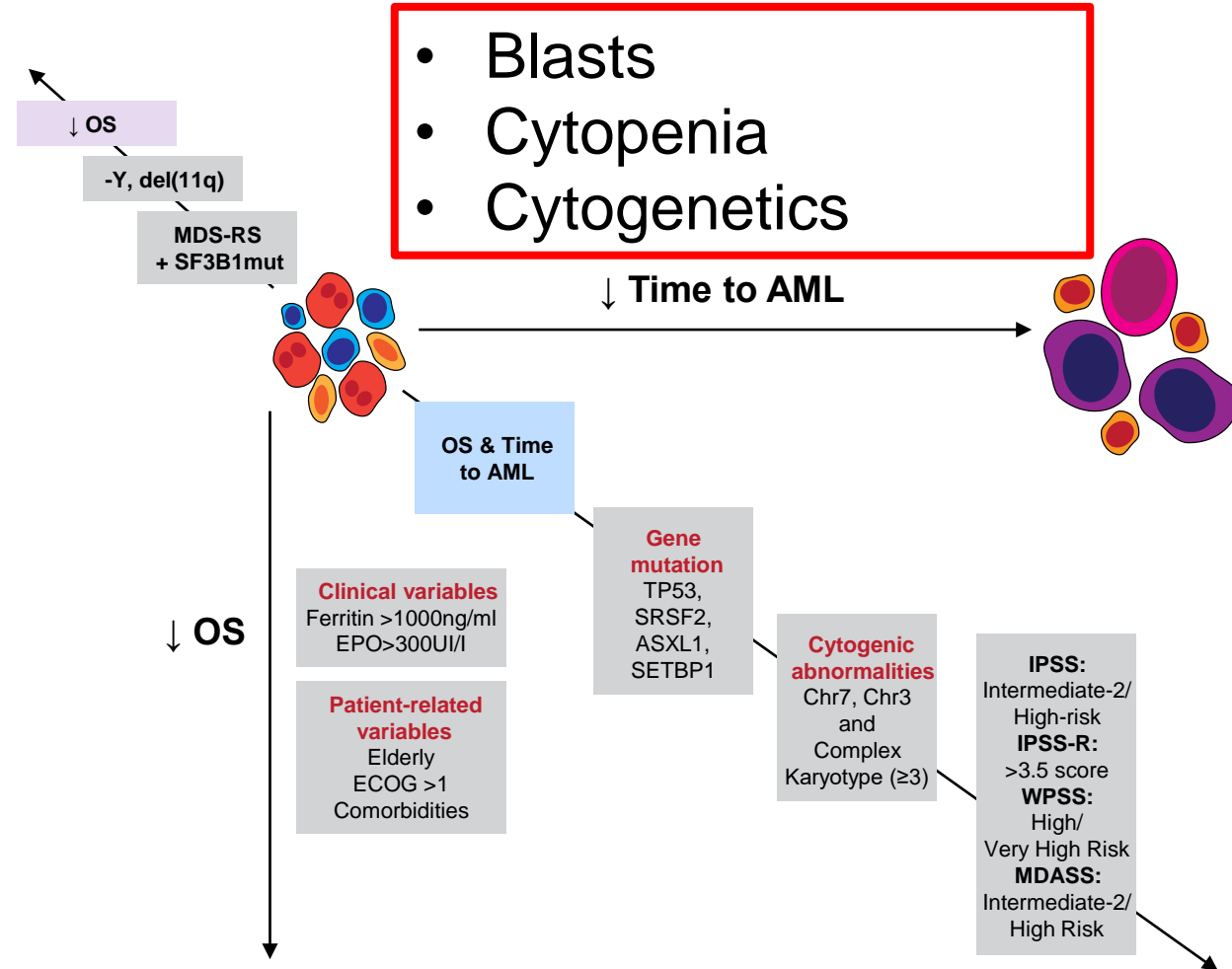
IPSS-R GUIDED TREATMENT: LOW VS. HIGH RISK

PROS

- Predictive and prognostic

CONS

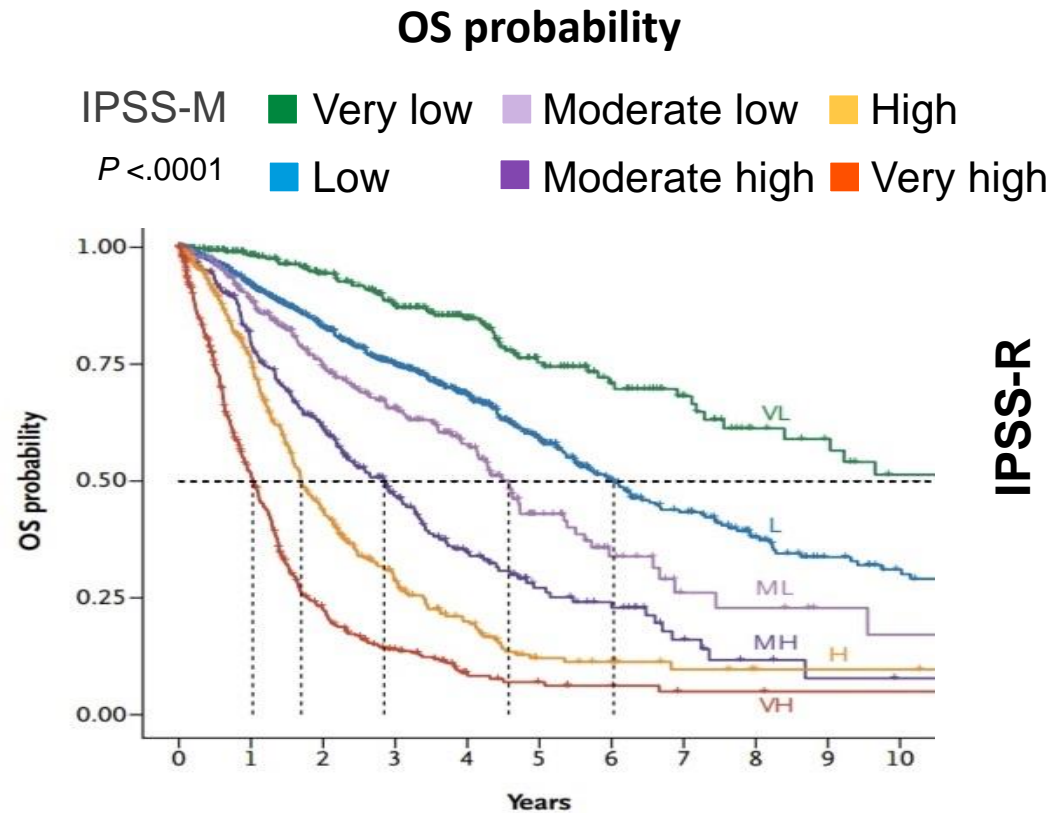
- Does not consider other factors: transfusion dependence, molecular status, comorbidities
- Not predictive of outcomes in IR-MDS



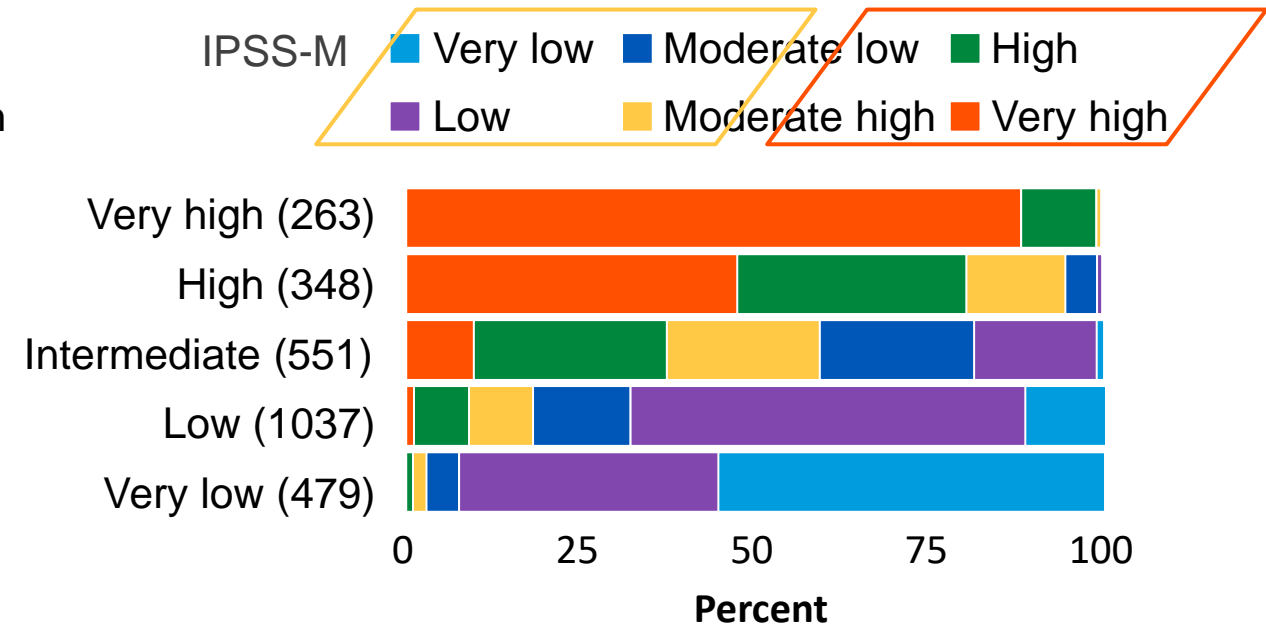
Redrawn from Benton et al AJH 2018, Chen-Liang TH J Clin Med 2021

IPSS-M:

- Variables: Blood counts, blasts, CG, gene mutations



IPSS-R

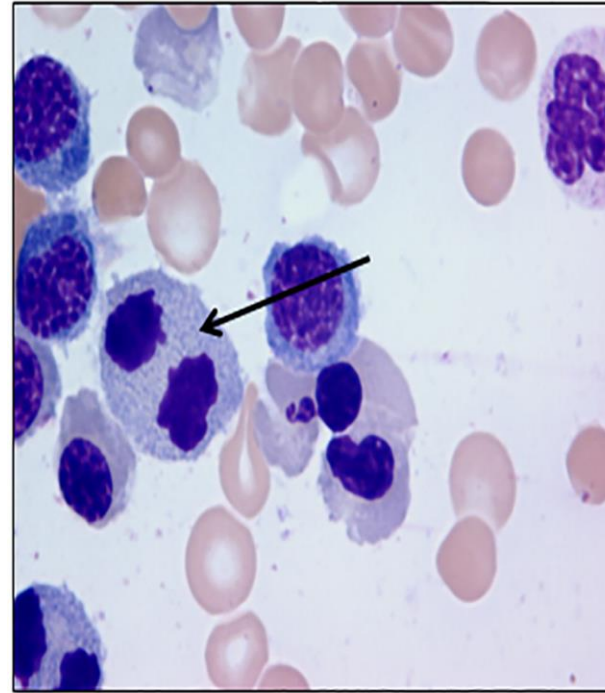


Redrawn from <https://mds-risk-model.com/>
Bernard. NEJM 2022

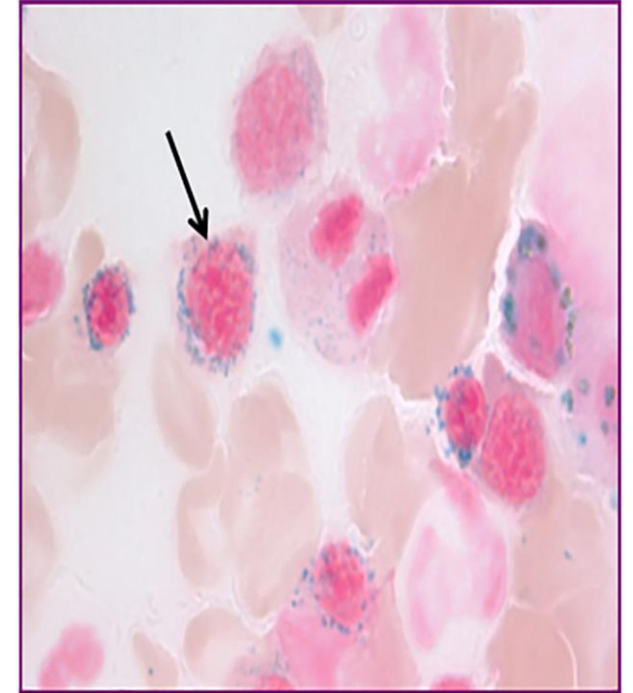
MDS CASE

- Bone marrow biopsy: MDS-ring sideroblasts
- Cytogenetics: Normal
- Molecular studies: SF3B1
- IPSS-M Category: Very Low Risk
- Treatment?

(A)



(B)



TREATMENT

TREATMENT PRINCIPLES

- Risk Oriented Treatment → IPSS-R, IPSS-M
- Chemotherapy only? → Growth factors, immunotherapy, clinical trials
- Goals: Survival, quality of life → Outcomes, transfusion independence, PRO
- Transplant cures MDS → Transplant modalities, supportive care

LOW-RISK MDS

Watchful waiting

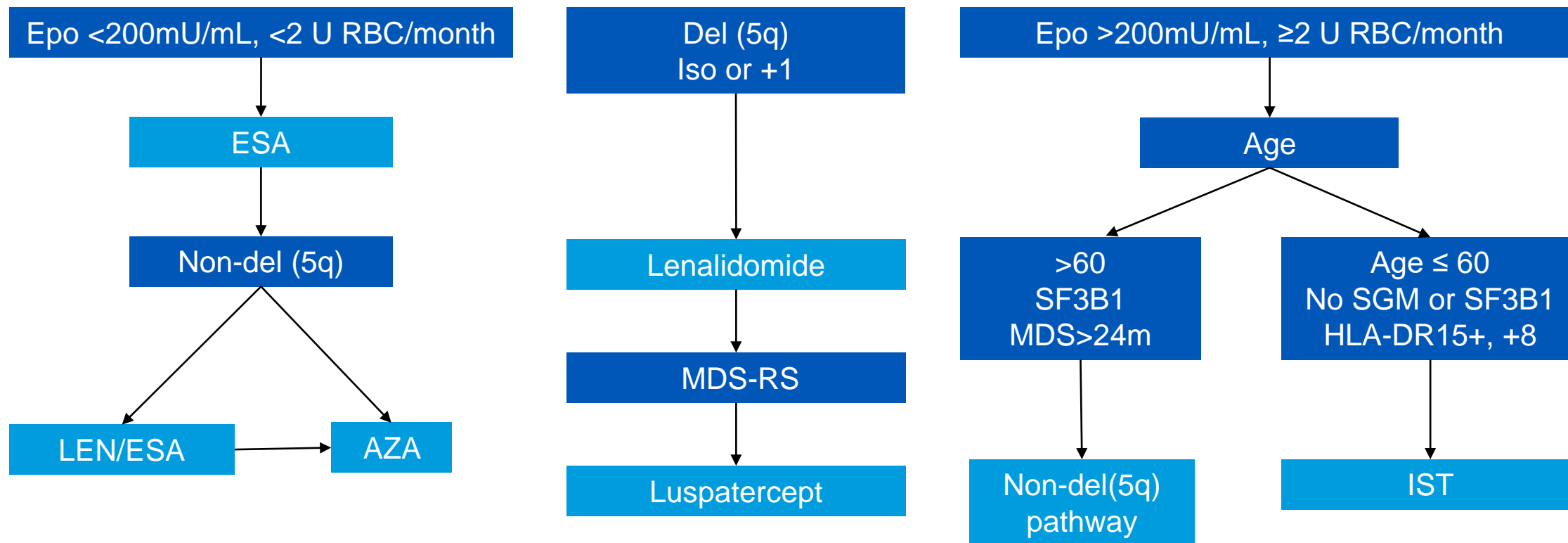


**Treatment of anemia/thrombocytopenia:
PRBC, ESA, luspatercept, platelets**

ESA: EPO or DAR for LR-MDS without 5q, EPO <500

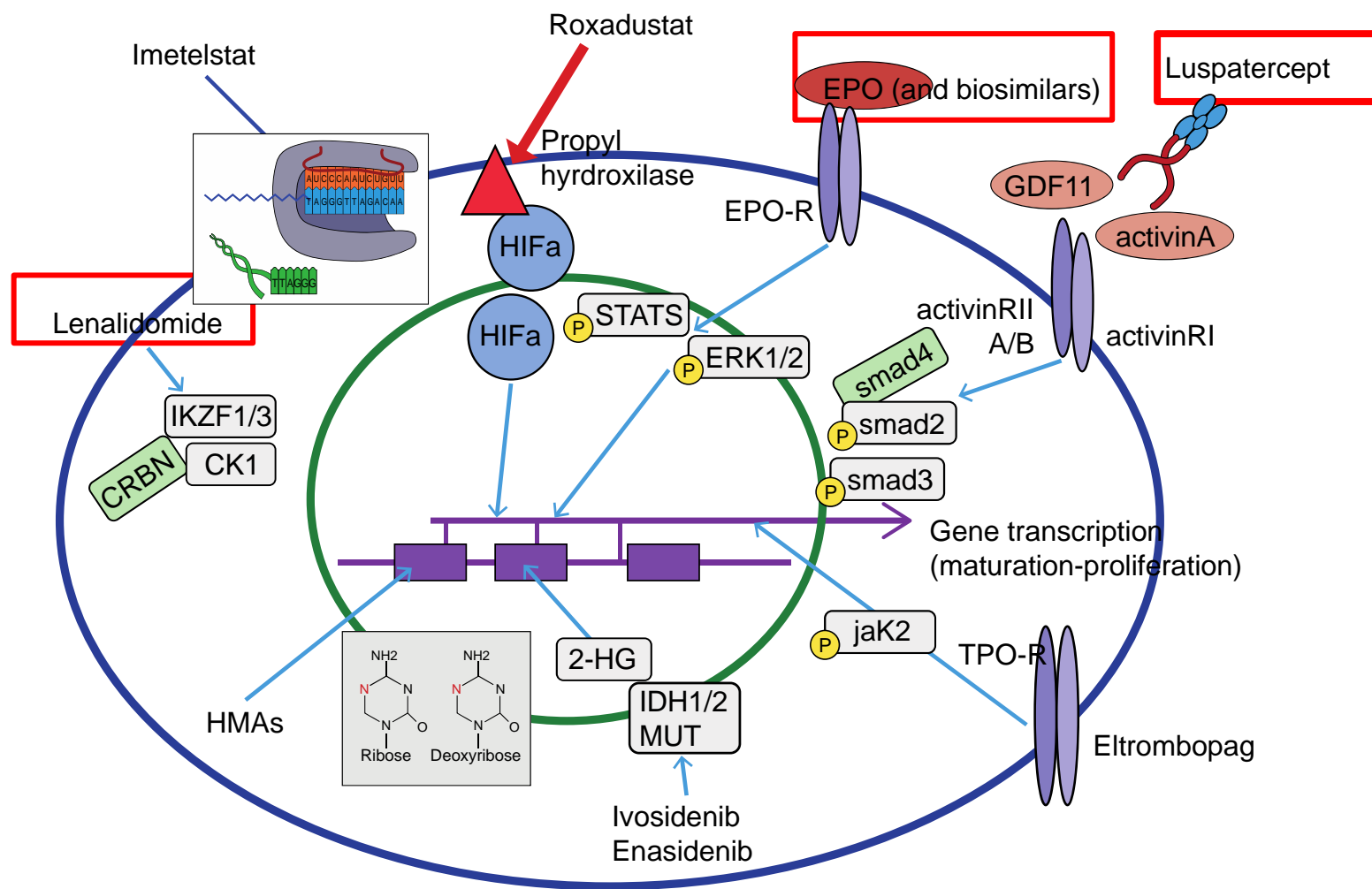
Multiple cytopenia/Hypoplastic MDS: ATGAM, HMA

LOW RISK MDS



Redrawn from Volpe et al, Clin Lymphoma, Myeloma and Leukemia 2021

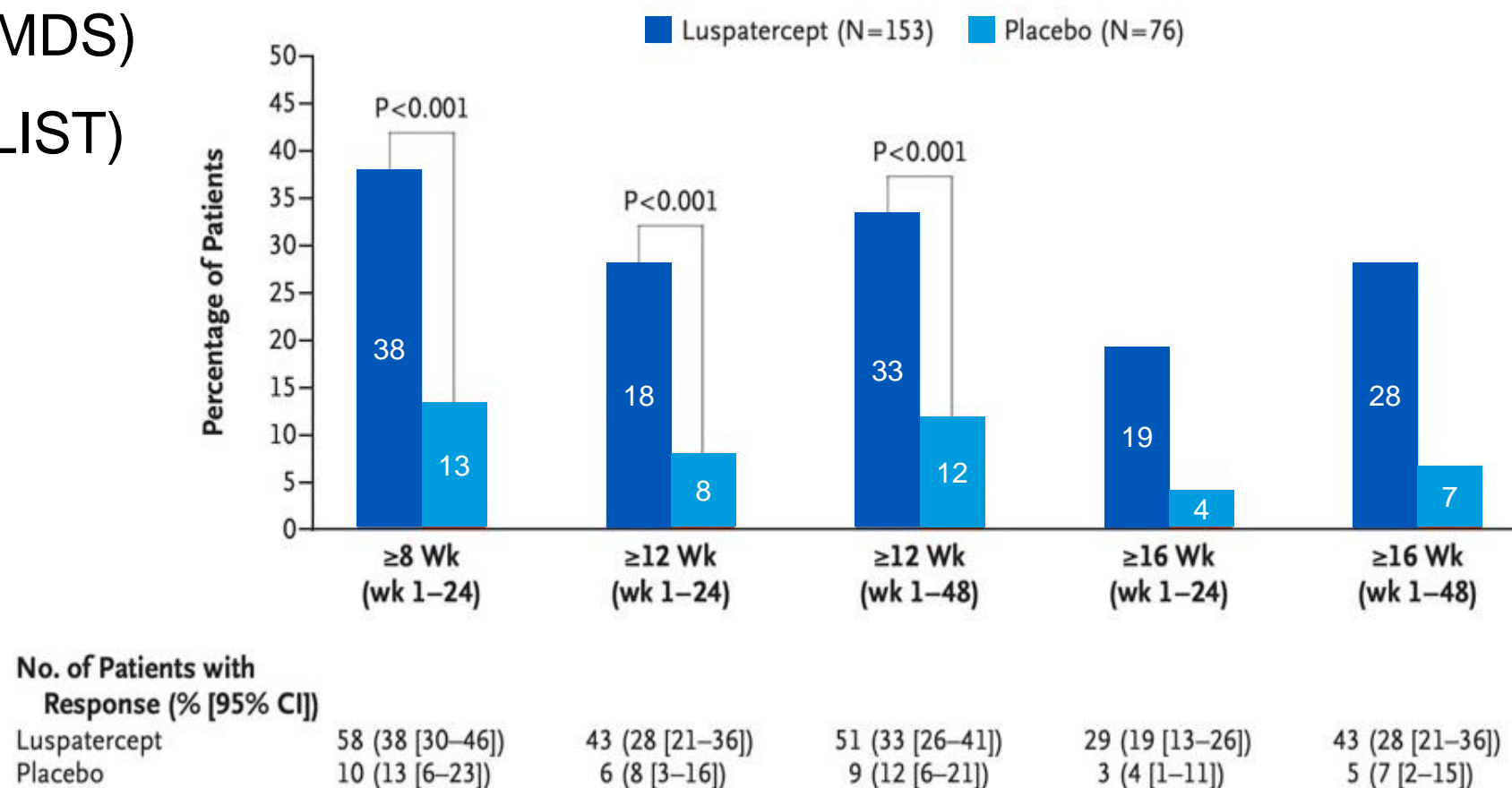
NOVEL THERAPEUTIC AGENTS IN LR-MDS



Redrawn from Santini V. Hemato 2022

LUSPATERCEPT IN MDS (MEDALIST)

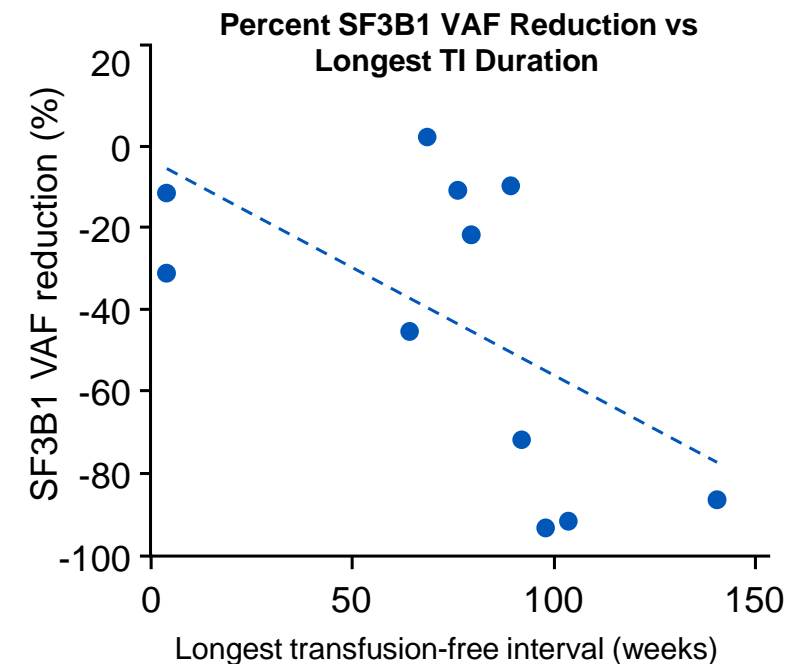
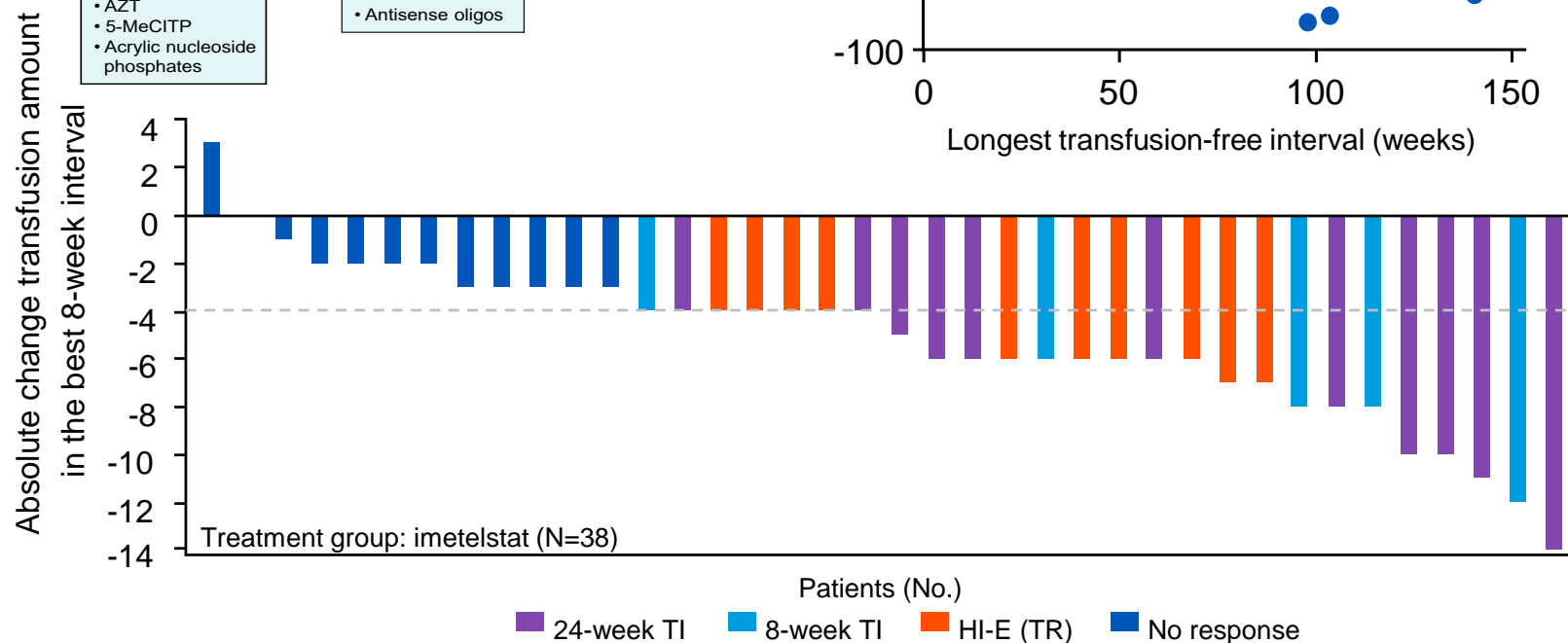
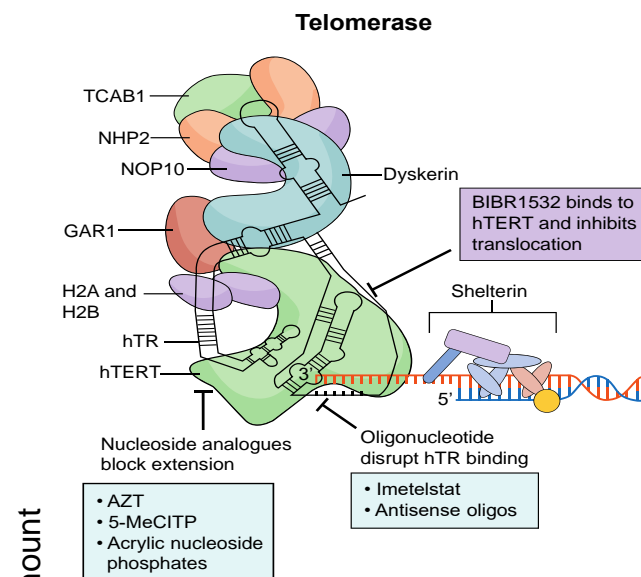
- Phase 2 (PACE-MDS)
- Phase 3 (MEDALIST)



Redrawn from Fenaux, NEJM 2020

IMETELSTAT

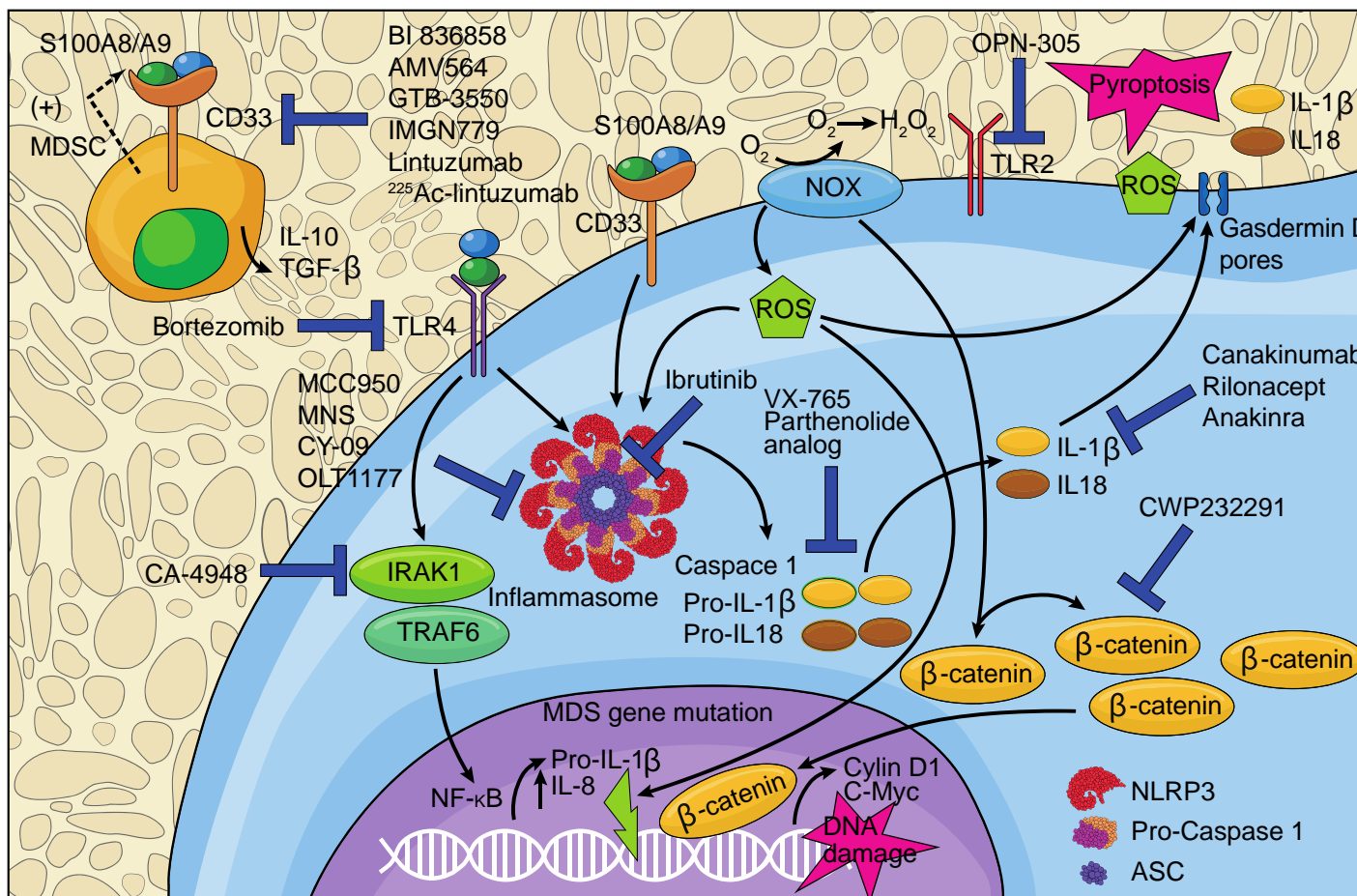
- Telomerase inhibitor
- >50% reduction hTERT expression and decrease of SF3B1 mutational burden
- Response duration >1 year
- Phase III randomized trial results pending



Redrawn from Steensma D, JCO 2021, Gao, Nature Reviews Cancer, 2022

INFLAMMATION IN MDS

- Inflammation shapes MDS
- Agents:
 1. Canakinumab: mAb IL-1 β
 2. R289 IRAK1/4 inhibitor
- Studies in LR MDS, alone and in combination



Redrawn from Chakraborty S, BCJ, 2021

SEQUENTIAL LR-MDS TREATMENT?

ESA

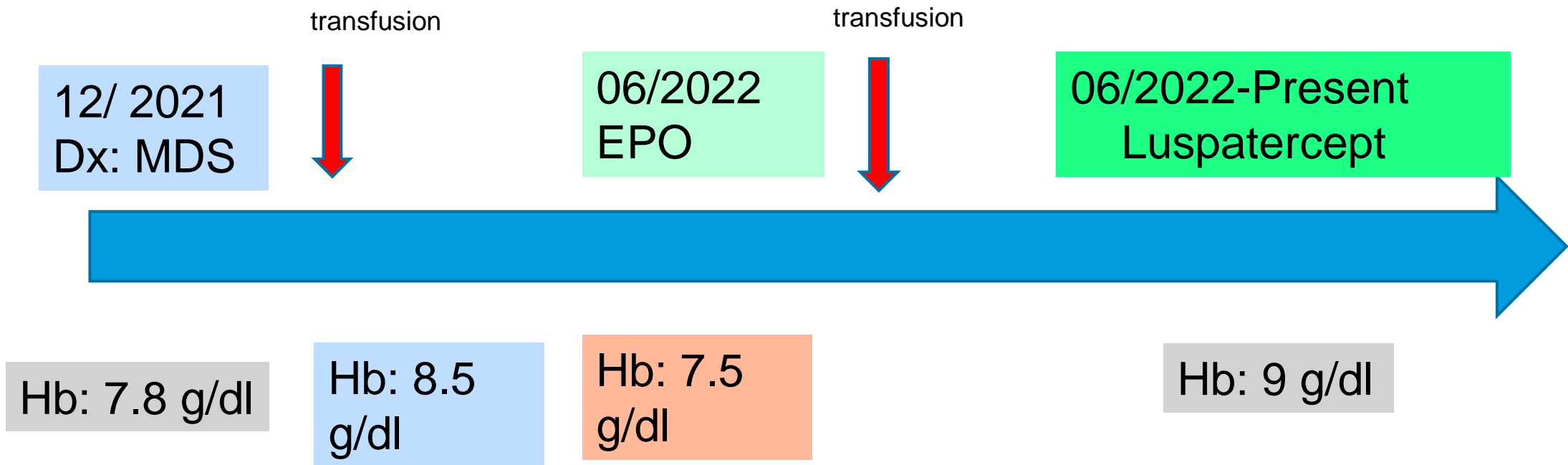
IMETELSTAT

LUSPATERCEPT: RA-RS

LENALIDOMIDE in 5q-

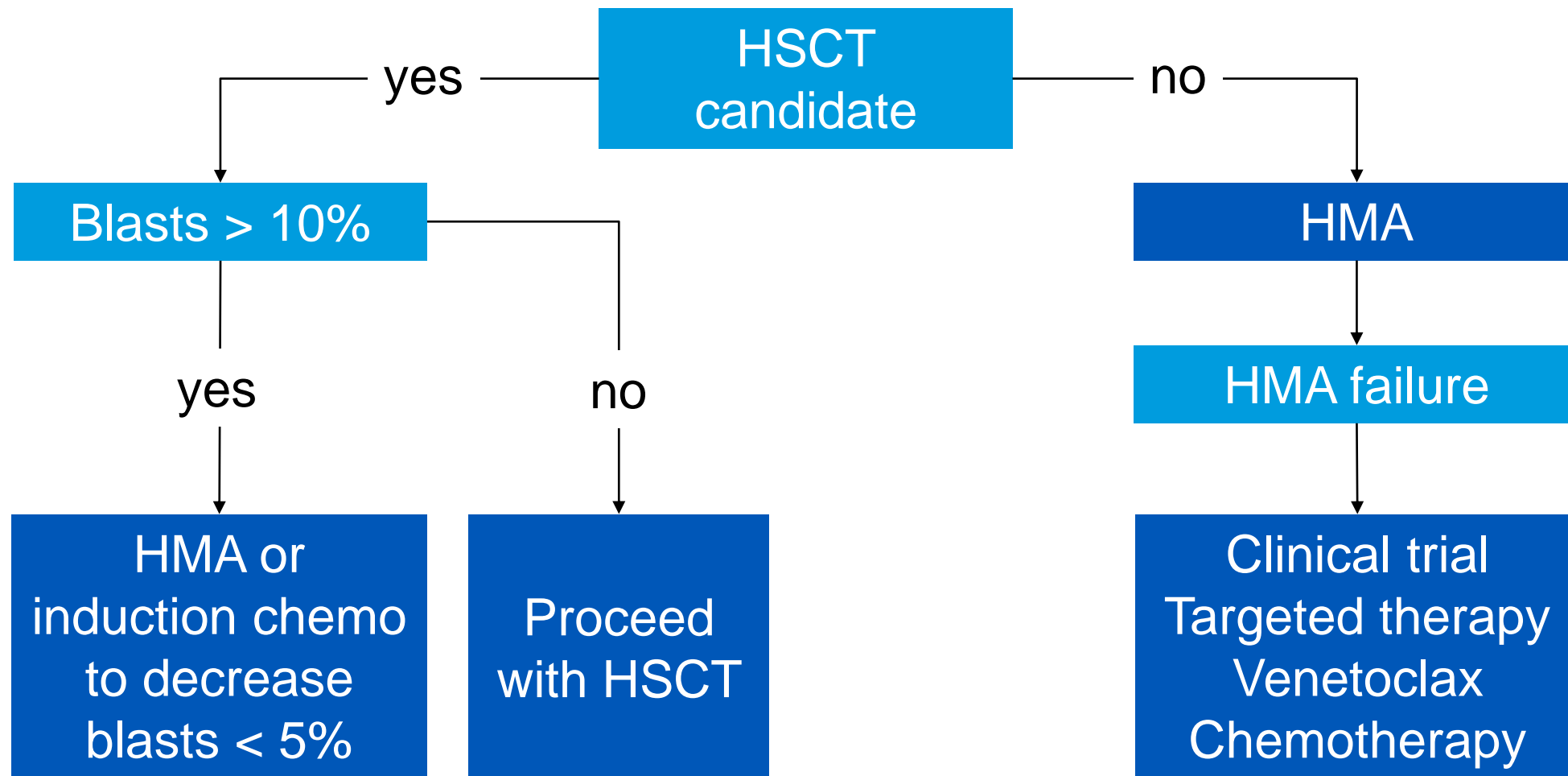
Canakinumab,
IRAK1/4
combinations

MDS CASE TREATMENT TIMELINE



HIGH RISK MDS

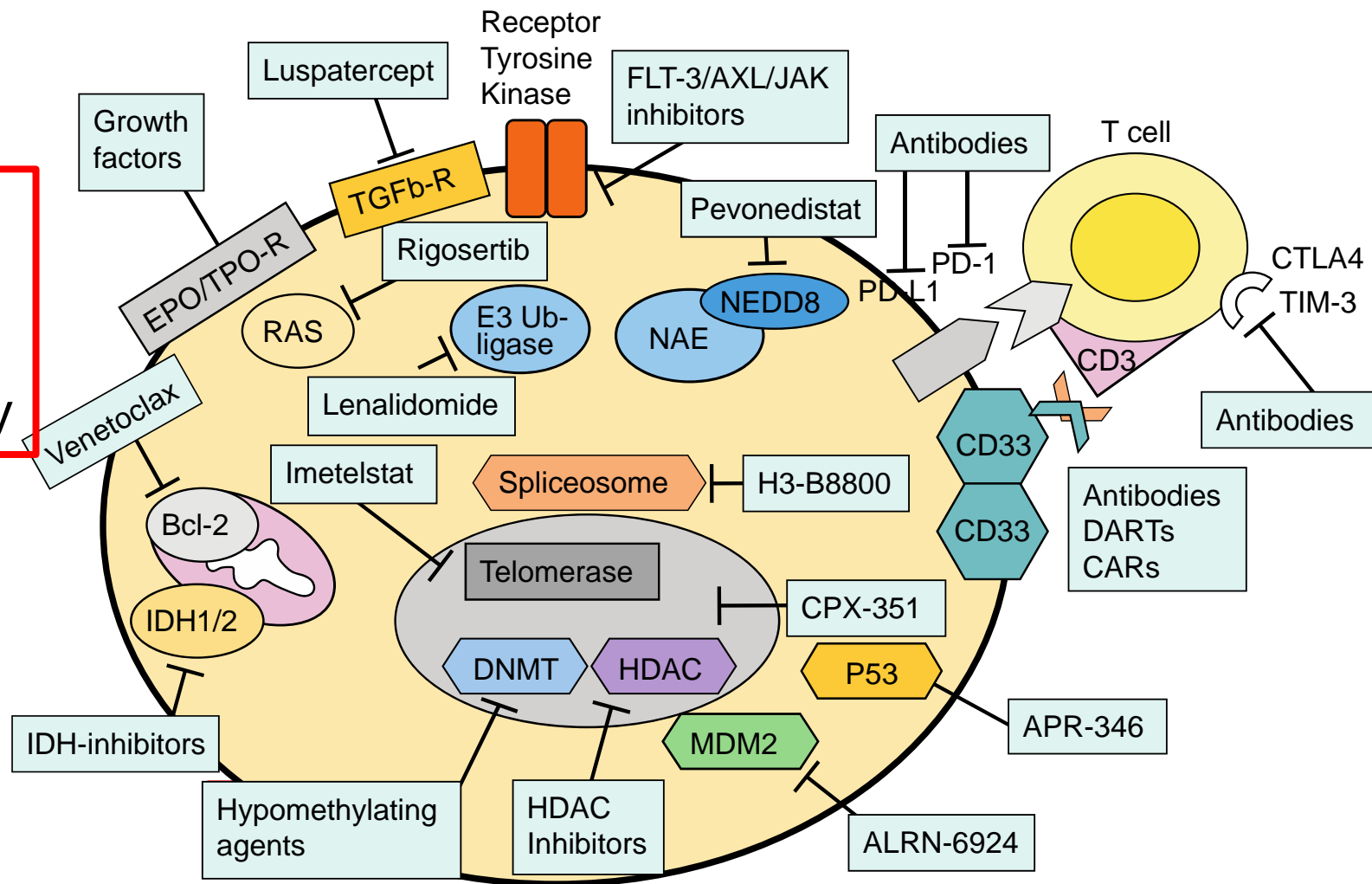
MANAGEMENT OF HIGH RISK MDS



Redrawn from Volpe V. Clin Lymphoma and Leukemia 2022

THERAPEUTIC OPTIONS IN HR-MDS

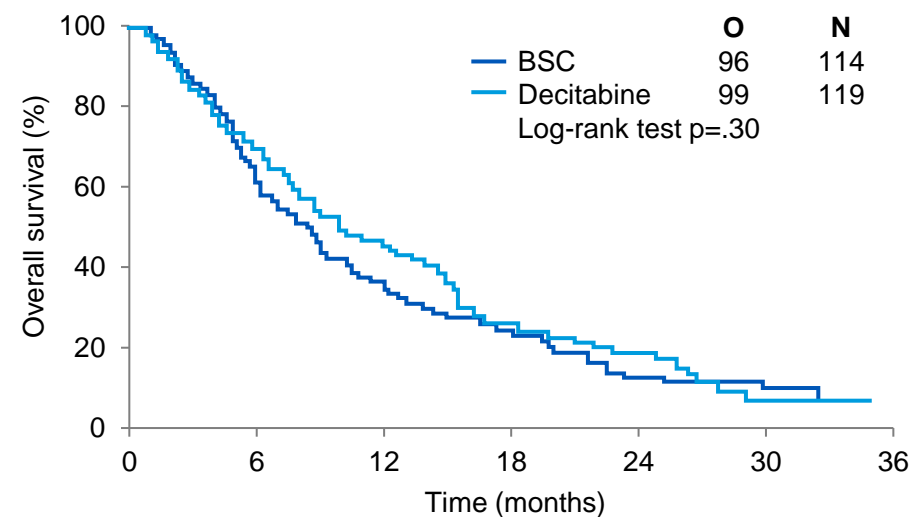
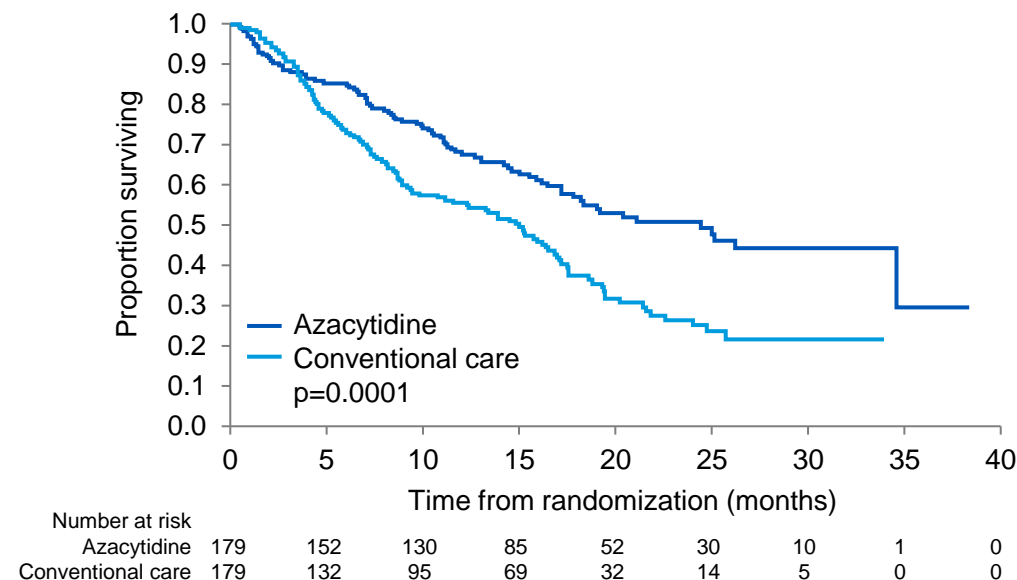
- HMA
- Targeted Therapies
- Immunotherapy



Redrawn from Platzbecker U. Blood 2019

HMA IN MDS

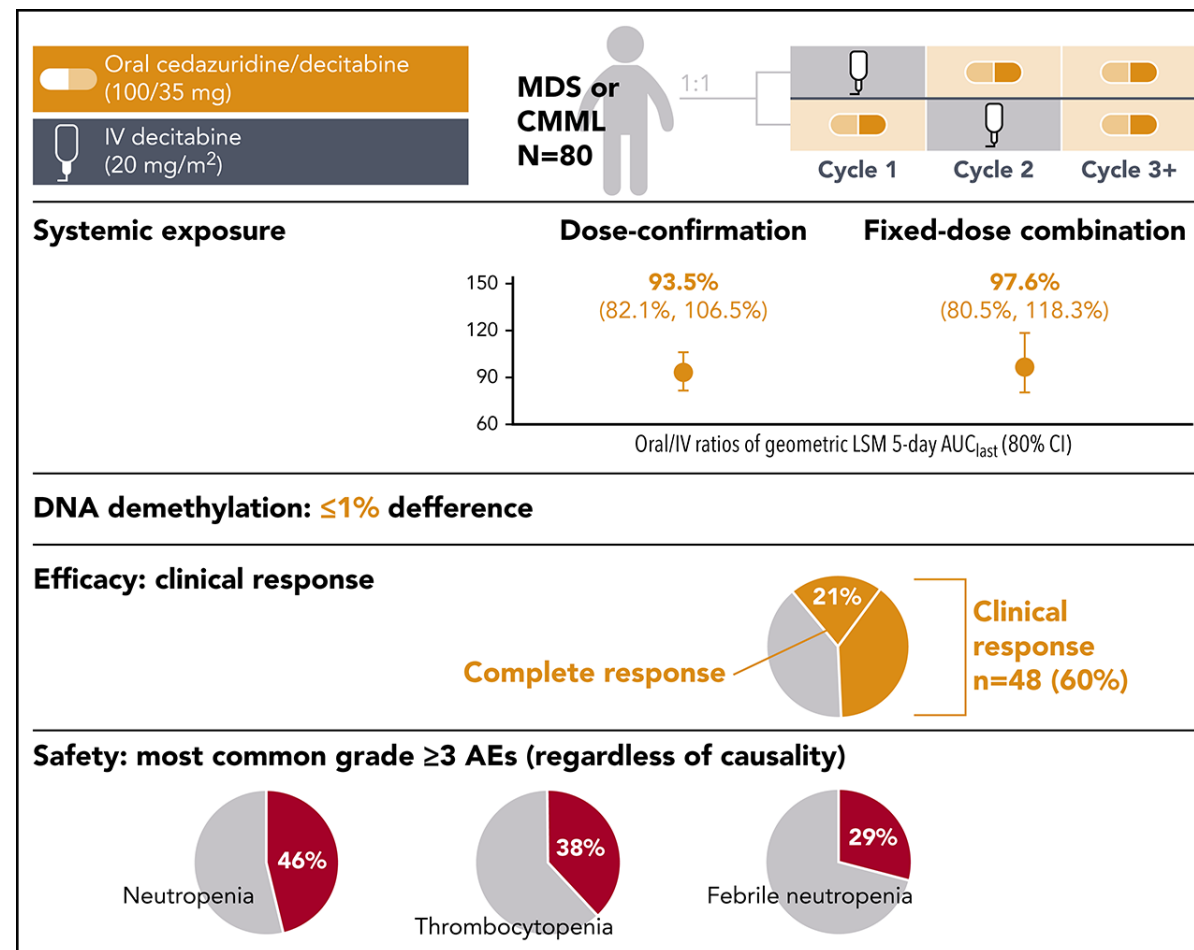
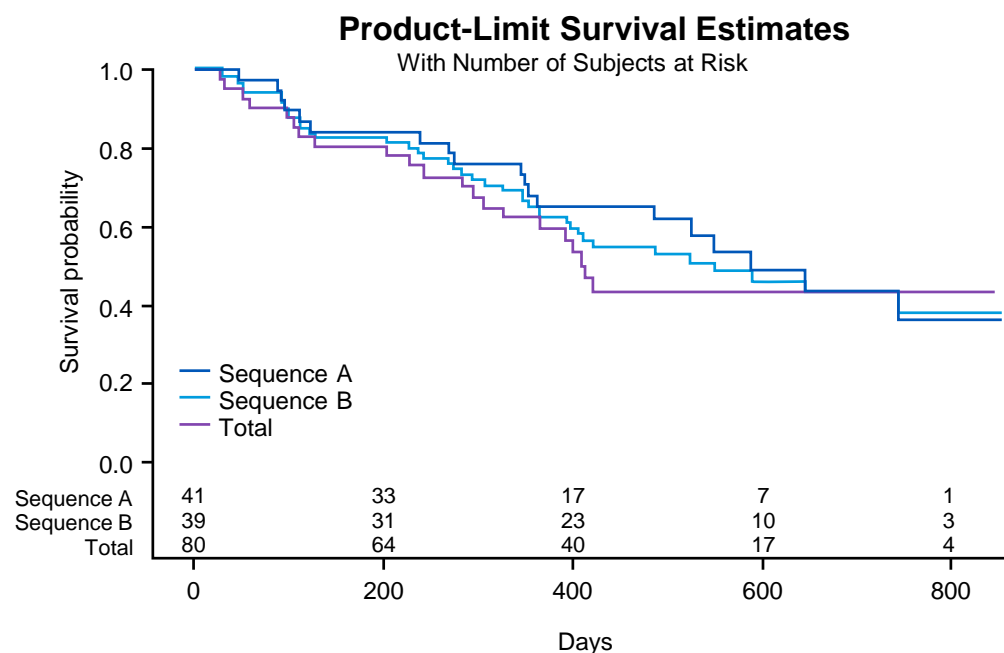
- Phase III AZA-MDS-001
mOS:24m
- Phase III DAC ORR 17% m
DOR 10.3m
- Real-World data: 10-17m
only ?



Redrawn from Fenaux et al Lancet Oncology 2009; Lubbert et al, JCO 2011; Zeidan Future Onc 2021; Hunter, Blood Adv 2021, Park, Blood 2020

ORAL DECITABINE IN MDS

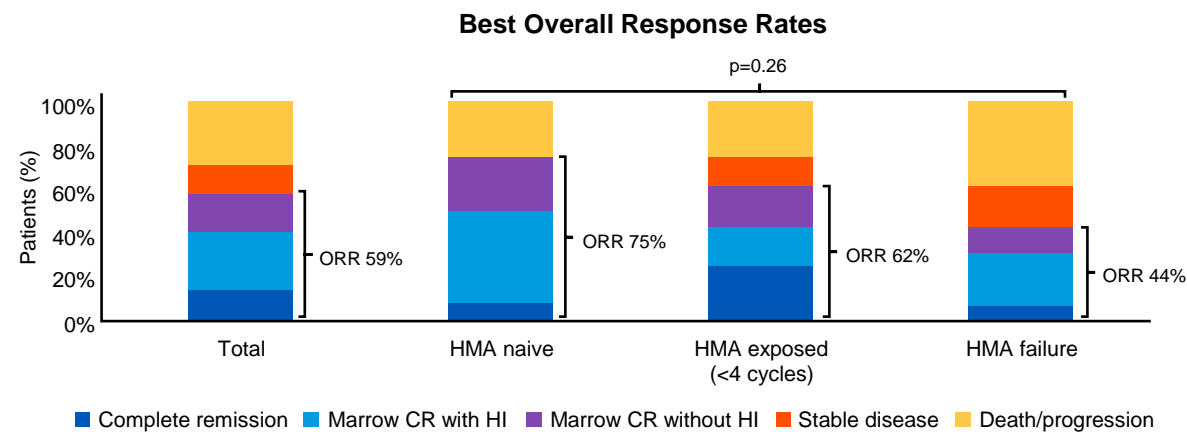
- Phase II Study in I-HR-MDS
- Equivalent to IV DAC



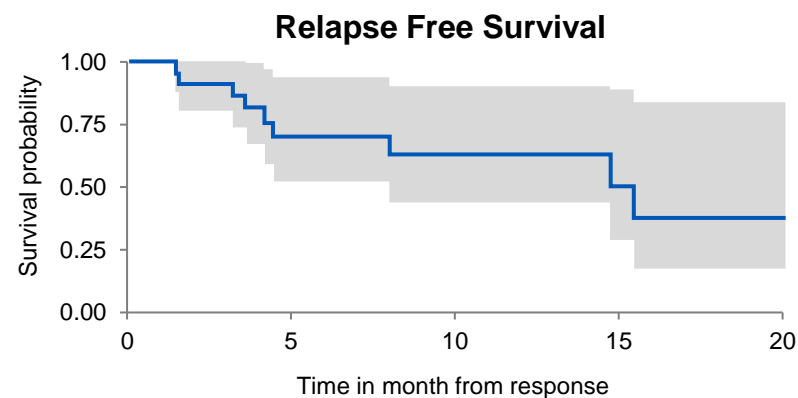
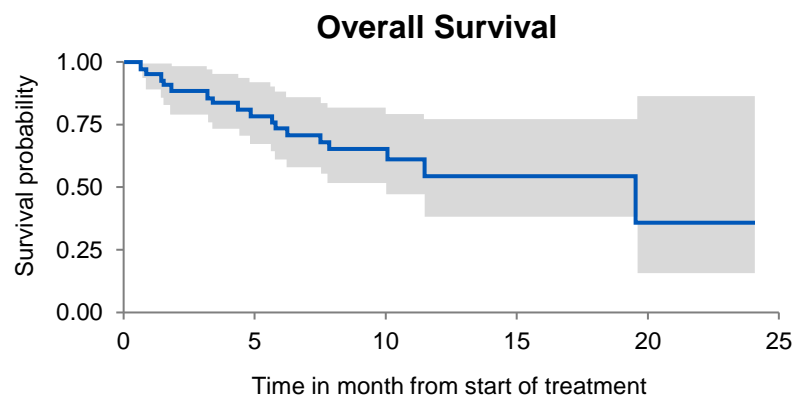
Redrawn from Garcia Manero et al , Blood 2020

HMA AND VENETOCLAX

- BCL2 overexpressed in leukemia stem cells
- ORR 77% (TN) and 40%(R/R)
- High rate of marrow remission (59%), HI (41%), and HSCT (62%)



mOS=19.5m
RFS= 15.4m

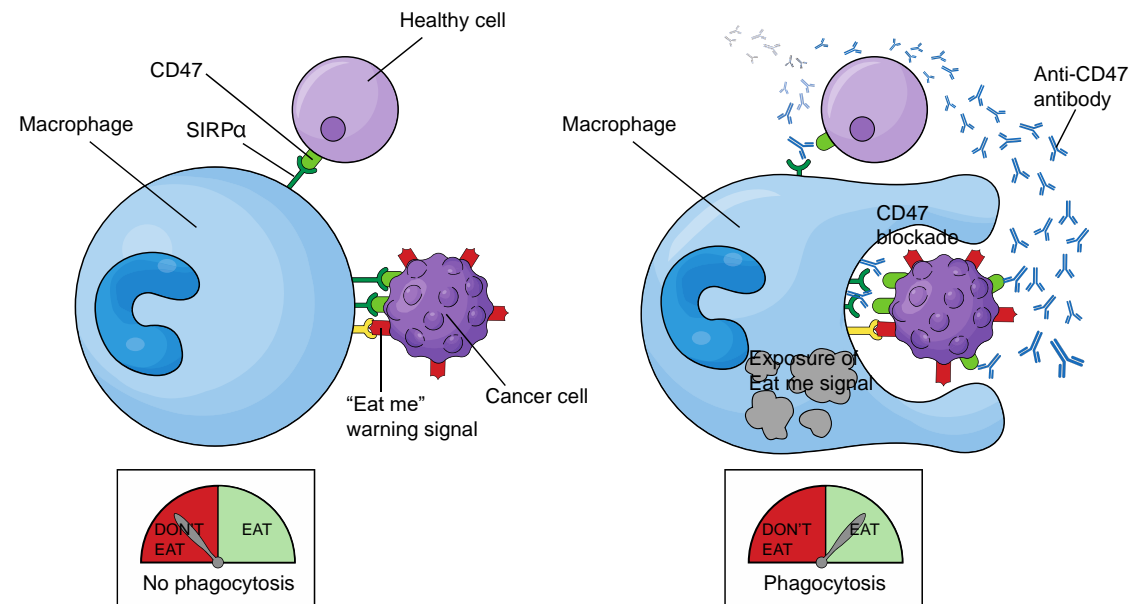


Redrawn from Brian J. et al. Blood Adv, 2020

IMMUNOTHERAPY/CELL THERAPY

MAGROLIMAB

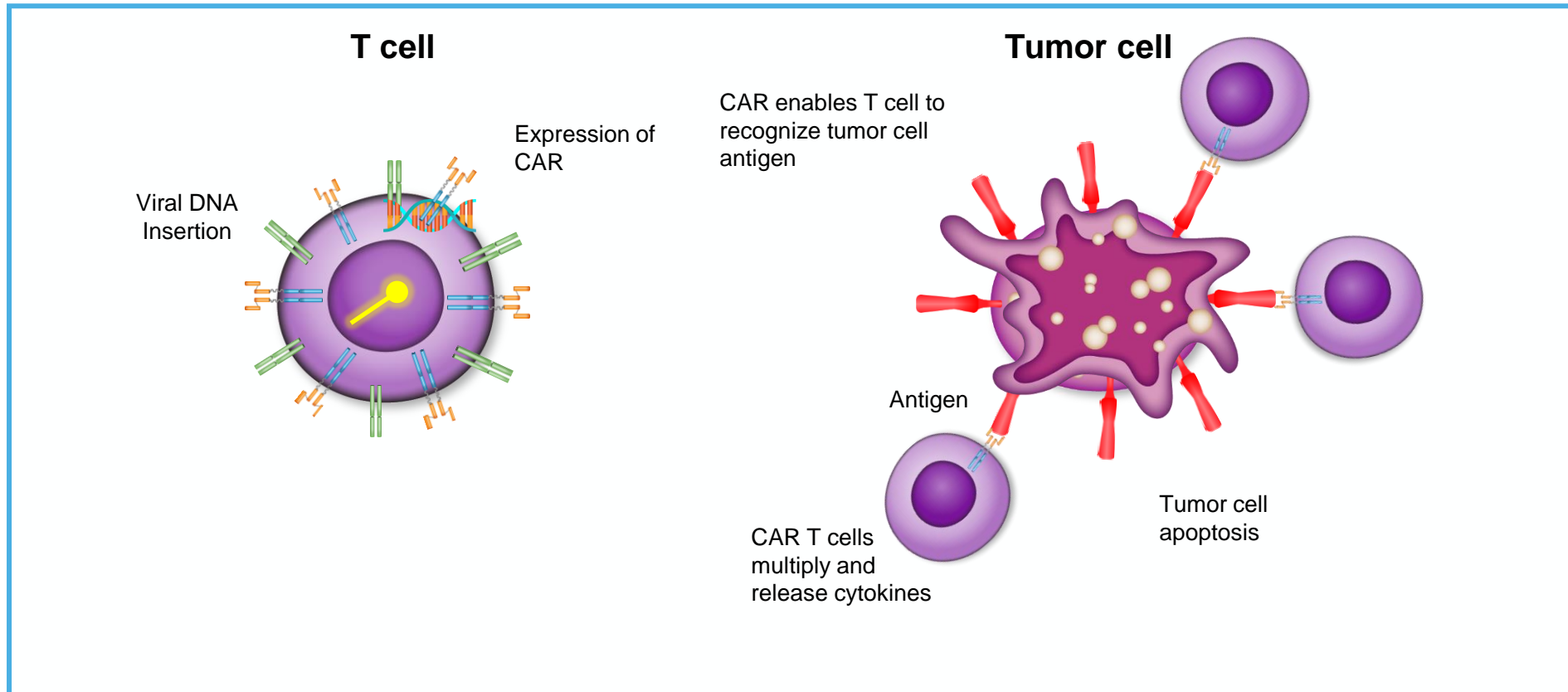
- Macrophage immune-checkpoint inhibitor, allows immune system evasion by cancer cells
- Phase 1b N=95, MDS



Outcome	All (N=95*)	TP53-wt MDS (N=61)	TP53-mut MDS (N=25)
Objective response rate, %	75	79	68
CR, % (95% CI)	33 (23, 43)	31 (20, 44)	40 (21, 61)
Marrow CR, %	32	38	20
SD w/HI, %	11	10	8
DCR, median (95% CI) mos	11.1 (7.6, 13.4)	12.9 (8.0, NR)	7.6 (3.1, 13.4)
Marrow CR with HI/Any HI, %	17/59	20/61	12/56
Converted to RBC transfusion independence, %	14	10	24
PFS, median (95% CI) mos	11.6 (9.0, 14.0)	11.8 (8.8, 16.6)	11.0 (6.3, 12.8)
OS, median (95% CI) mos	NR (16.3, NR)	NR (21.3, NR)	16.3 (10.8, NR)

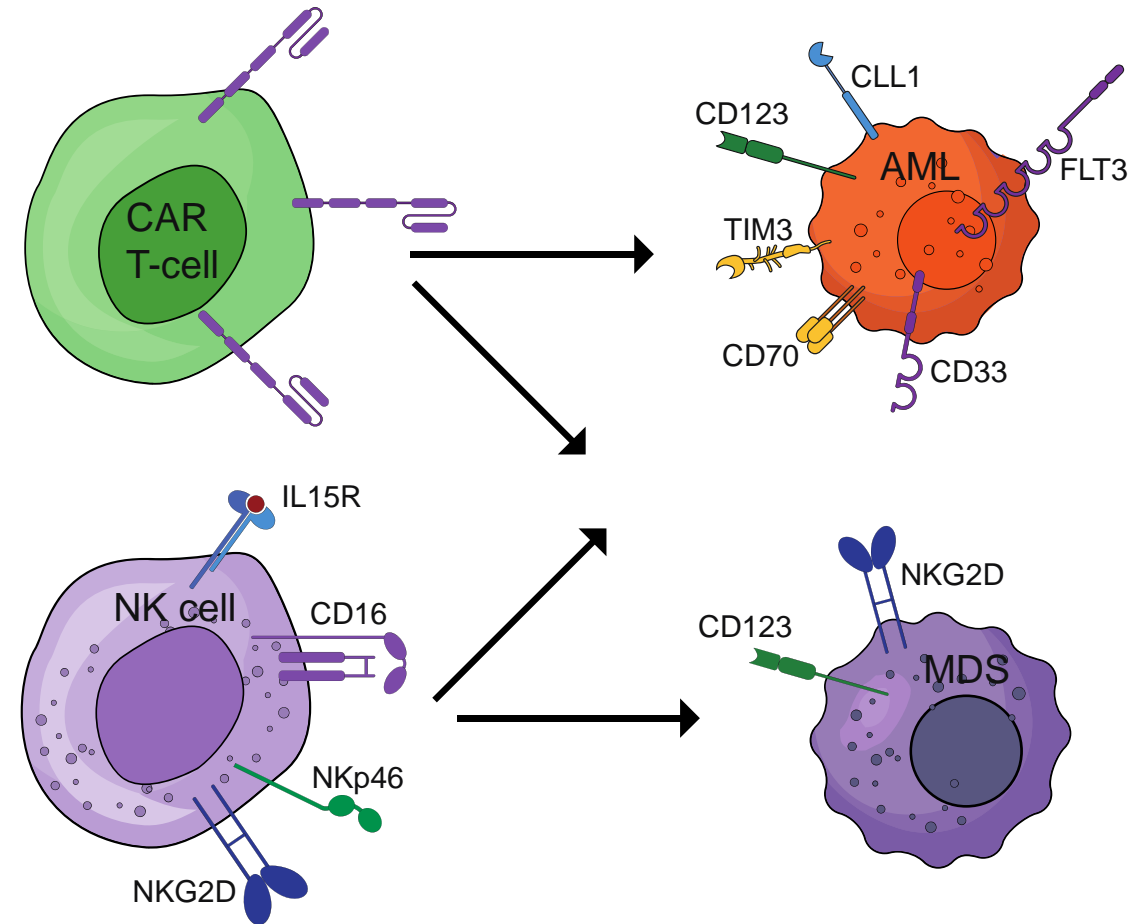
Redrawn from Sallman D, JCO 2022

CAR T Cells: Mechanism of Action



CAR T CELL THERAPY

- Ideal antigen in MDS?
- Potential targets:
 - Natural Killer group 2D
NKG2D
 - CD123



Redrawn from Kapoor S, Cancers 2021

HR-MDS TREATMENT SUMMARY

HSCT eligibility at diagnosis

Age <60, no HR mutations, IC

**HR mutations, transplant ineligible:
HMA based chemo**

Cell Therapy in R/R

Clinical trials:
Triplets,
doublets?

HIGH RISK MDS TREATMENT ASPECTS

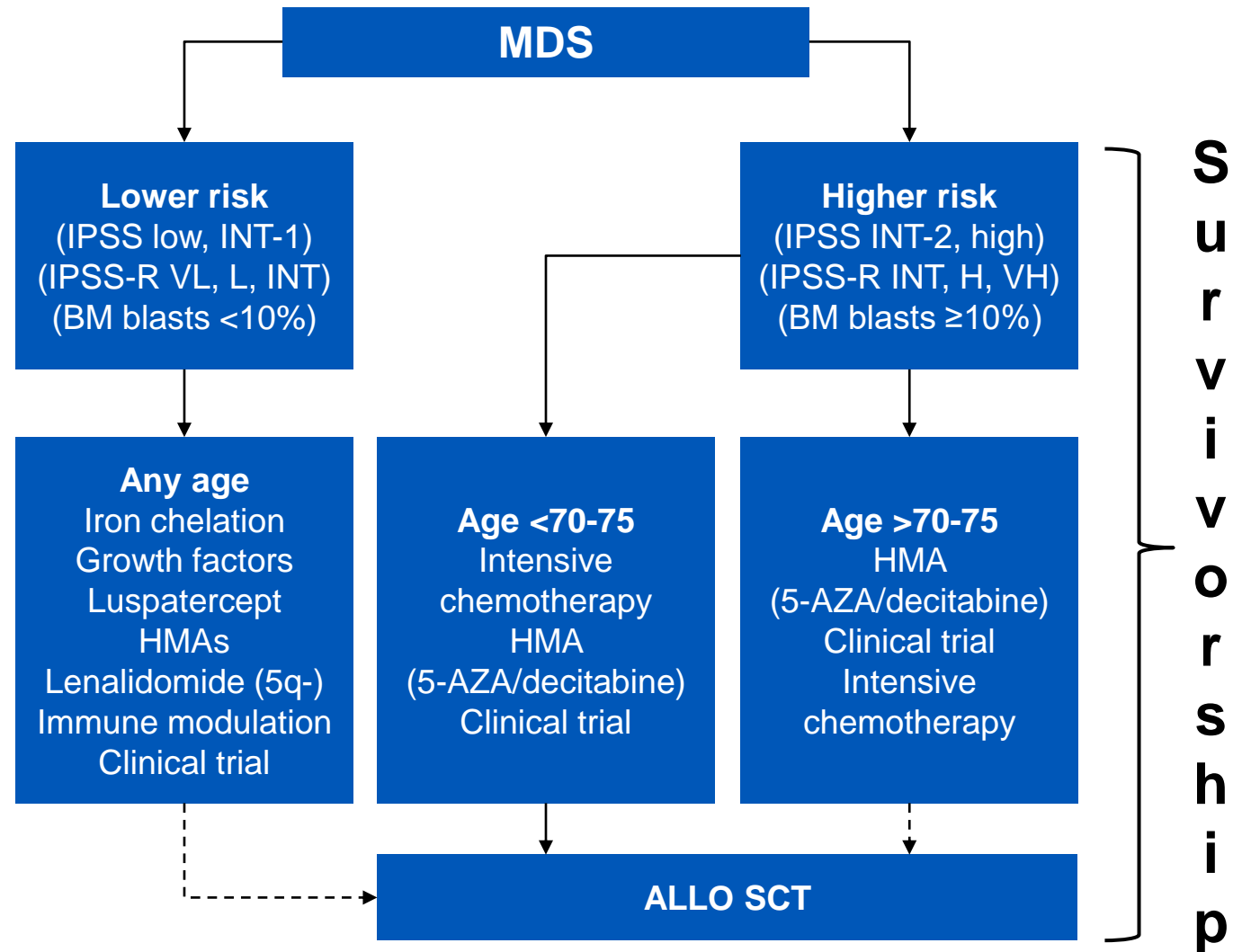
- Communication with Hematology/BMT team
- Survivorship care plan
- Complications post transplant: GVHD, infections
- IST side effects
- Transfusion aspects
- Palliative Care/End of Life



SURVIVORSHIP

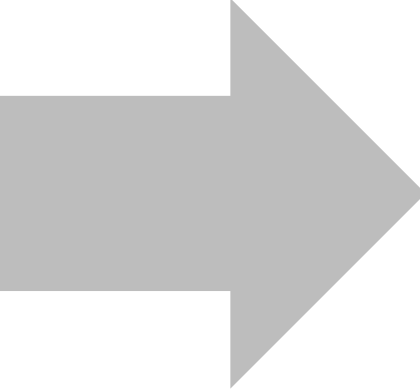
MDS SURVIVORSHIP

- “An individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life”



Redrawn from NCI, 2019; Garcia-Manero G, AJH 2021

STANDARDS OF SURVIVORSHIP CARE

- Cancer recurrence
 - Long term effects
 - Prevention and detection of late effects of cancer
 - Management of cancer related symptoms
 - Coordination of care
- 

- Survivorship Care Plan
- Survivorship Clinics
- Physician led
- Nurse led
- Group vs Individual counseling

CONCLUSIONS

- Heterogenous group of disorders with variable prognosis
- Molecular studies are key in prognosis and treatment options
- Novel treatments improve outcomes.
- Goals: Improving quality of life and survival.





QUESTIONS & DISCUSSION

