

New and Emerging Therapies for Myelodysplastic Syndromes

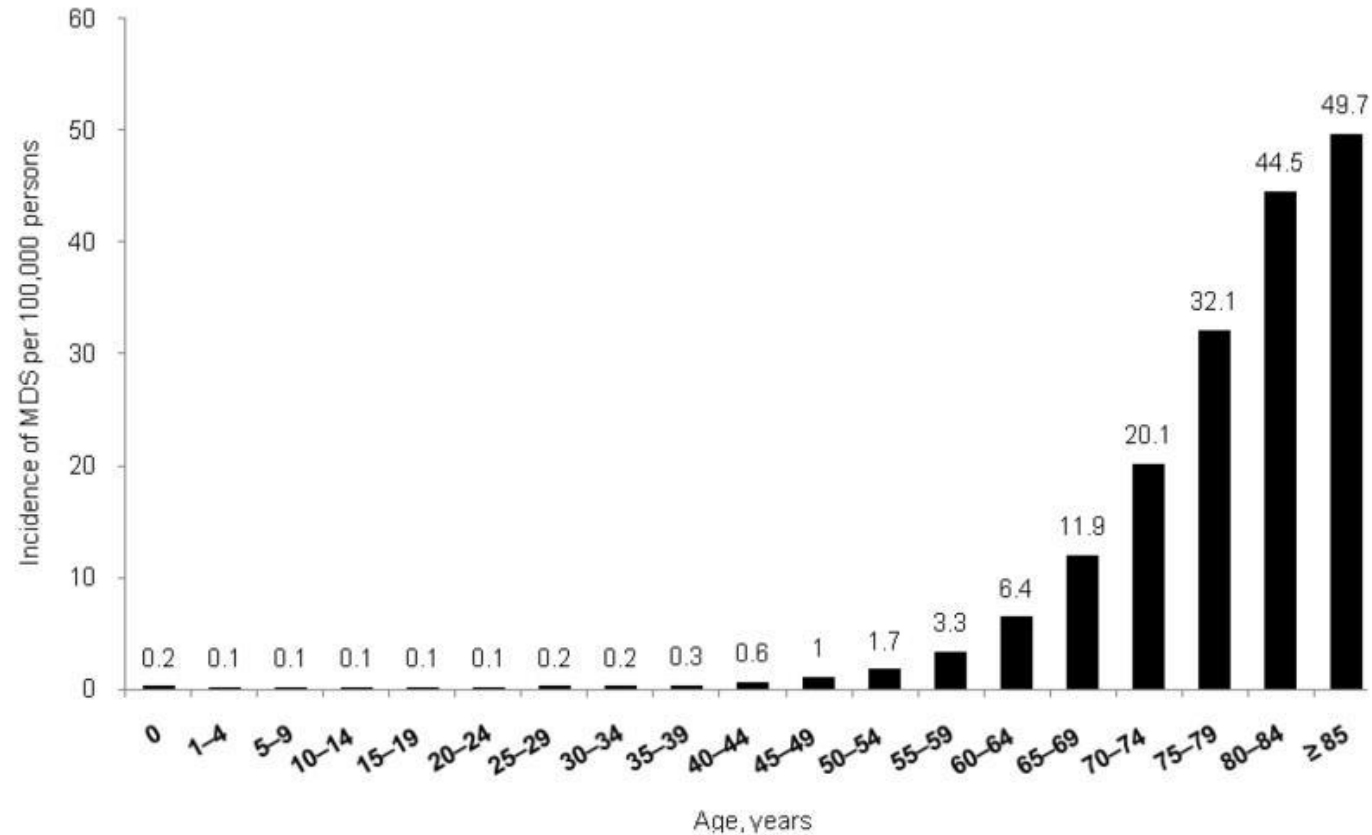
Andrew M. Brunner, MD

Massachusetts General Hospital Cancer Center

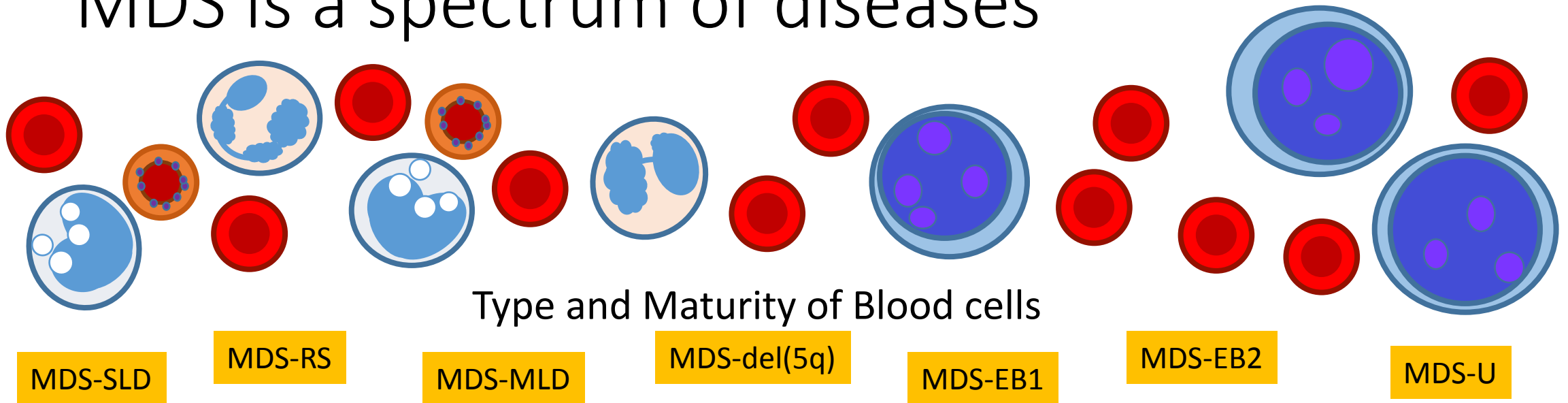
July 21, 2018

Myelodysplastic Syndromes - MDS

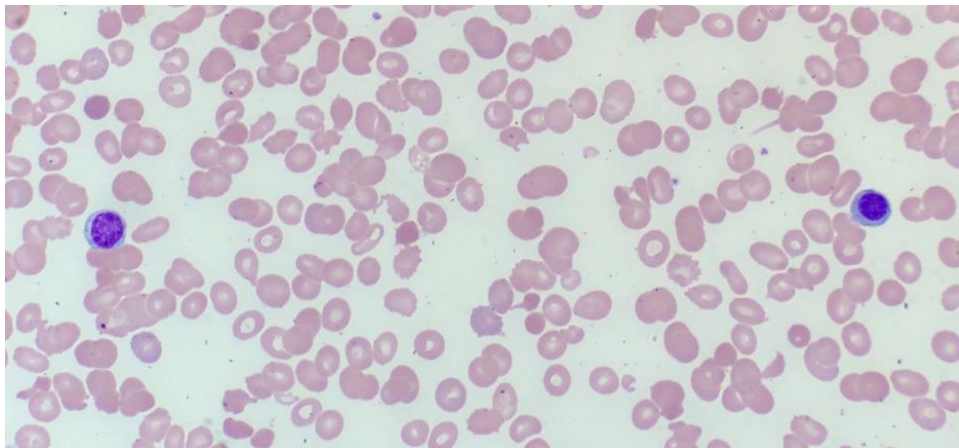
- Bone marrow cancers characterized by dysplasia, clonality, and ineffective hematopoiesis
- Disease of older individuals
- Slightly more common among men than women
- Survival varies months to years depending on subtype



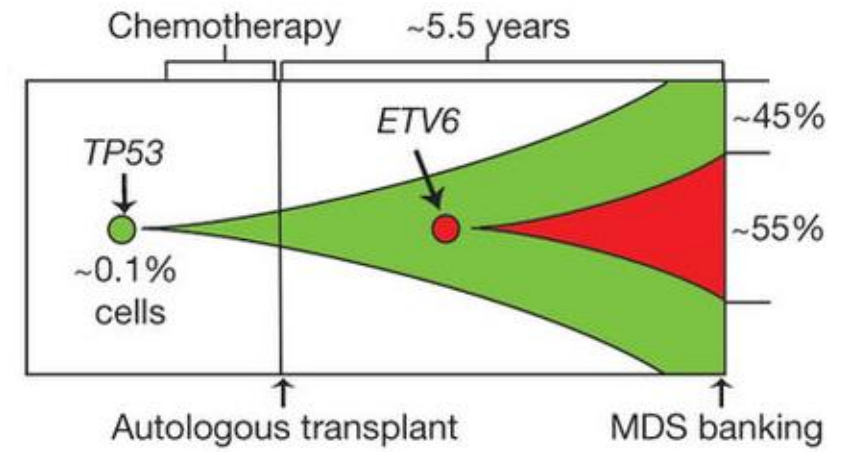
MDS is a spectrum of diseases



Type and Maturity of Blood cells



Variation in Blood Counts



Wong T et al. Nature. 2015 Feb 26; 518(7540): 552-555.

Variation in Driver Mutations

MDS treatment is based on disease risk

Risk Stratification by IPSS or IPSS-R
Blood Counts, Blasts, and Karyotype

Risk of Serious or Life-threatening
Complication related to MDS:
Infection
Bleeding

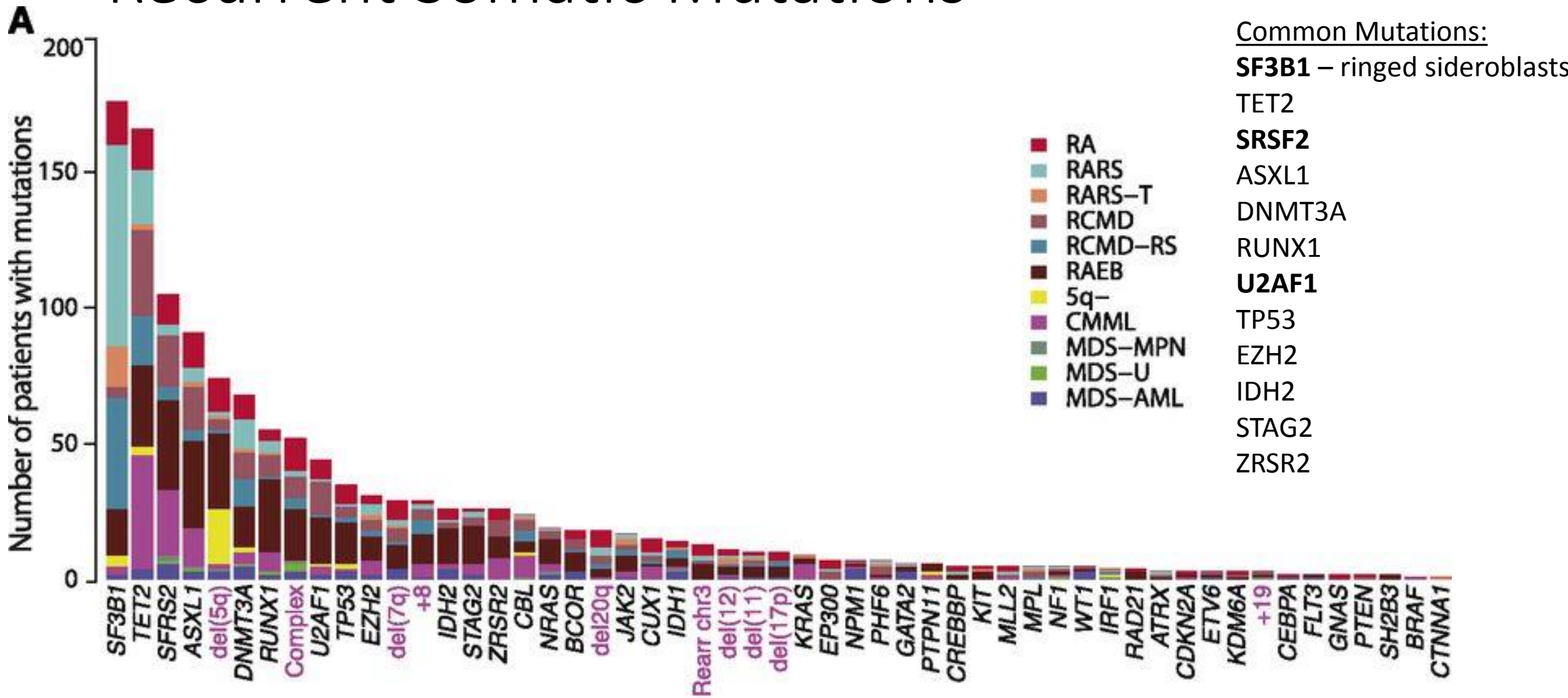
Risk of Progression to Acute
Myeloid Leukemia

IPSS and IPSS-R Risk do not always match the risk of the WHO disease subtype

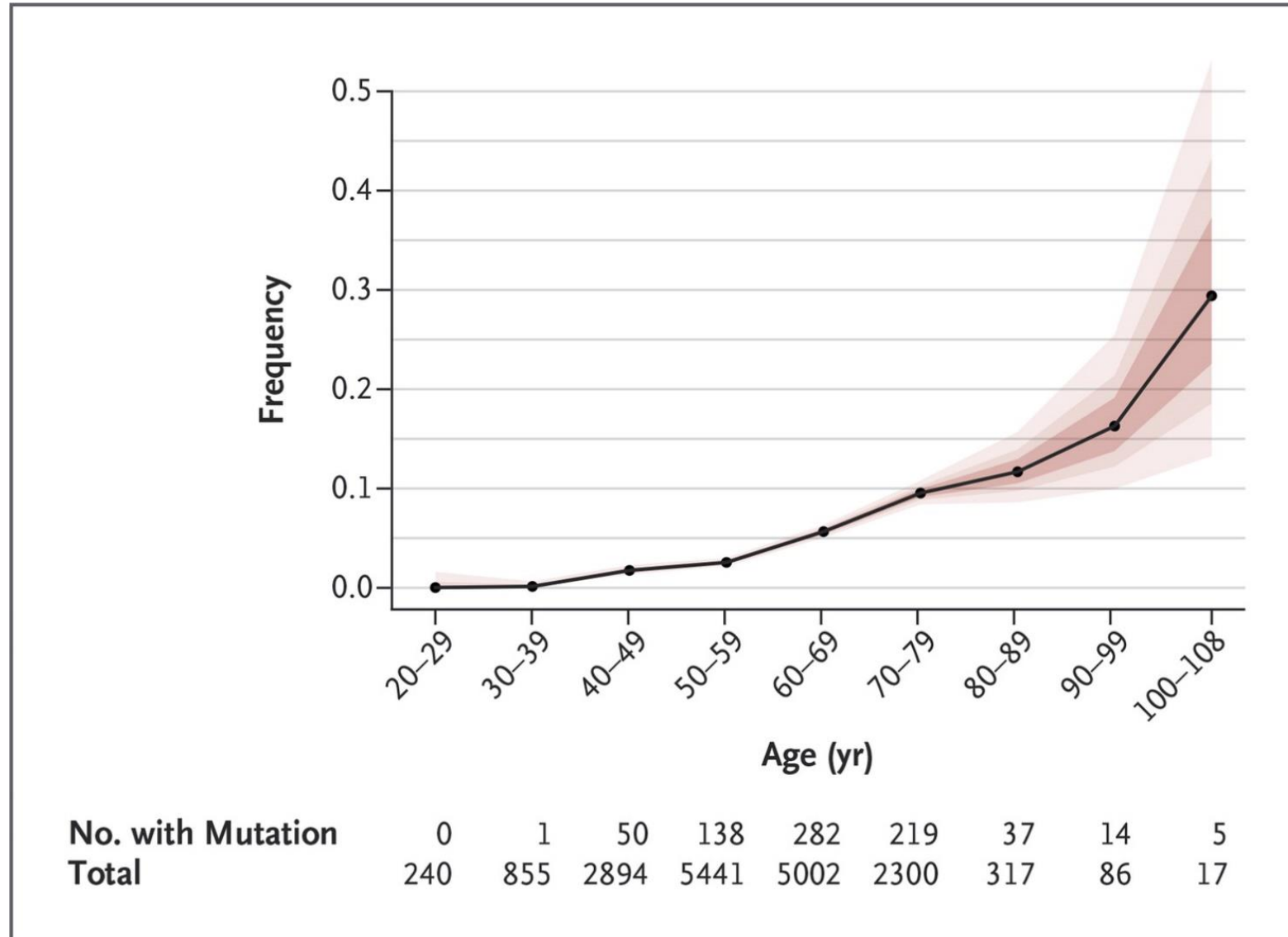
Updates in Estimating Disease Risk

- New understanding about mutations in MDS
- Competing risks in often older patients
- Changes in MDS risk over time

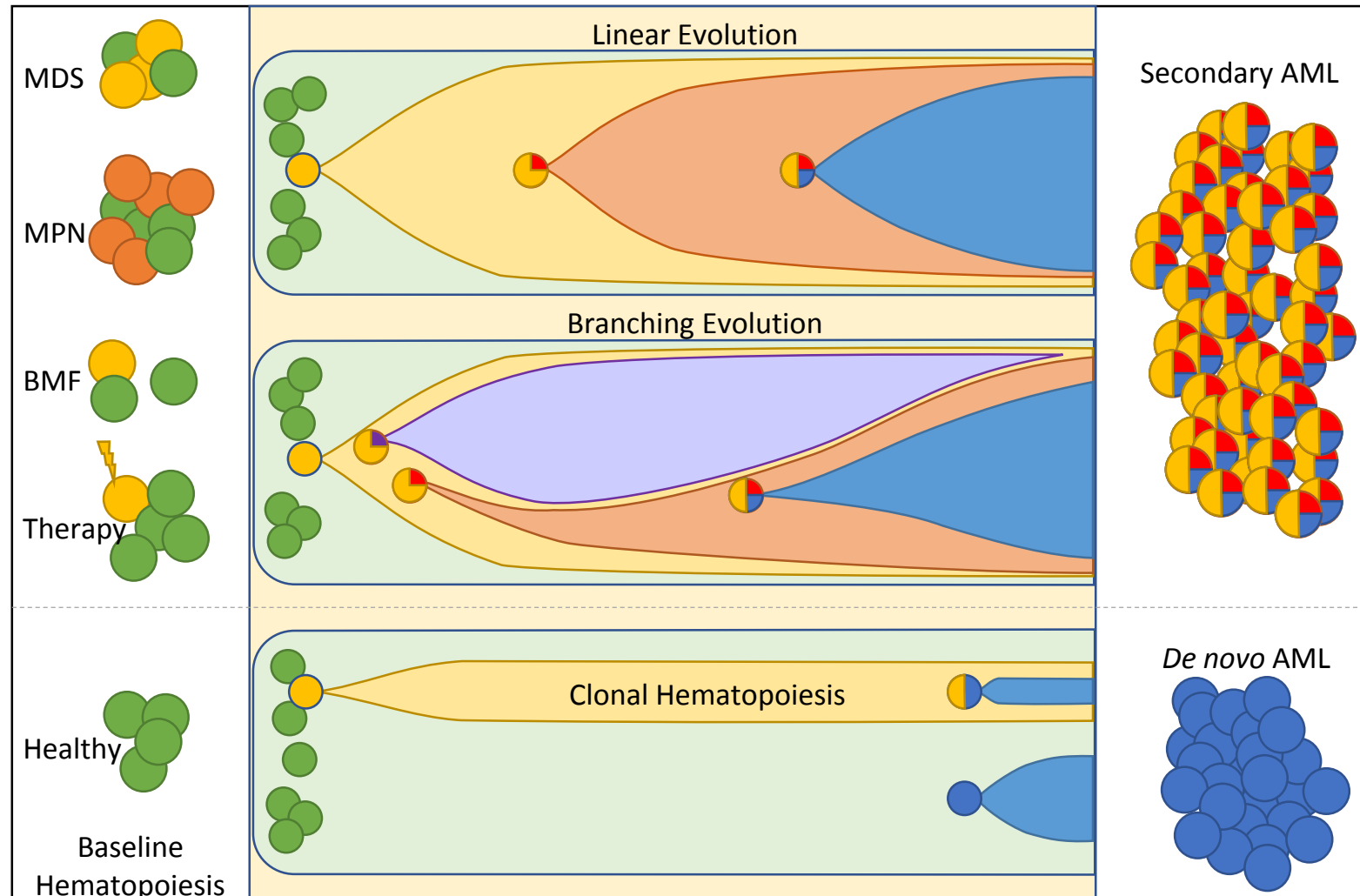
Recurrent Somatic Mutations



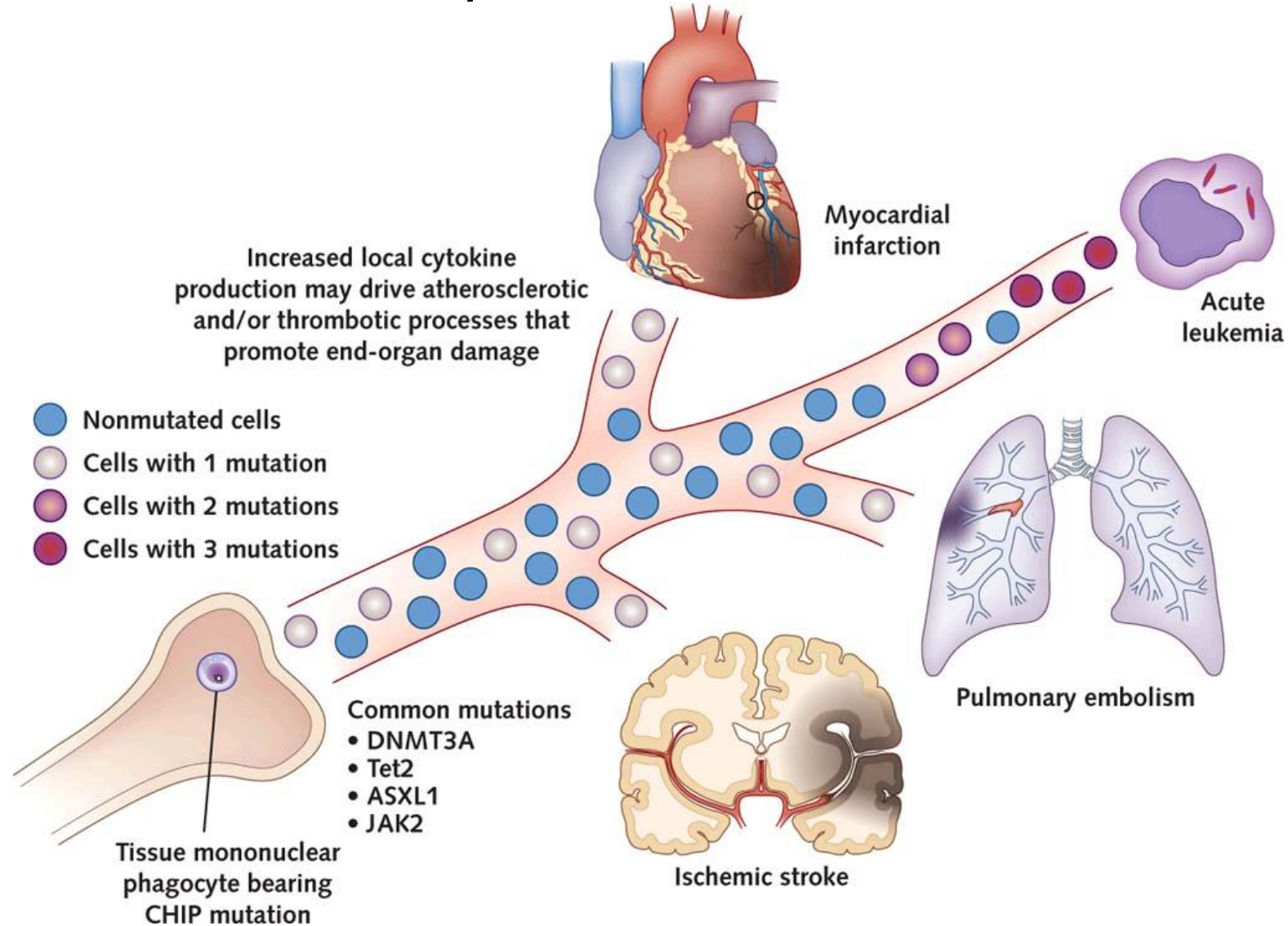
Mutations are common – and not all MDS!



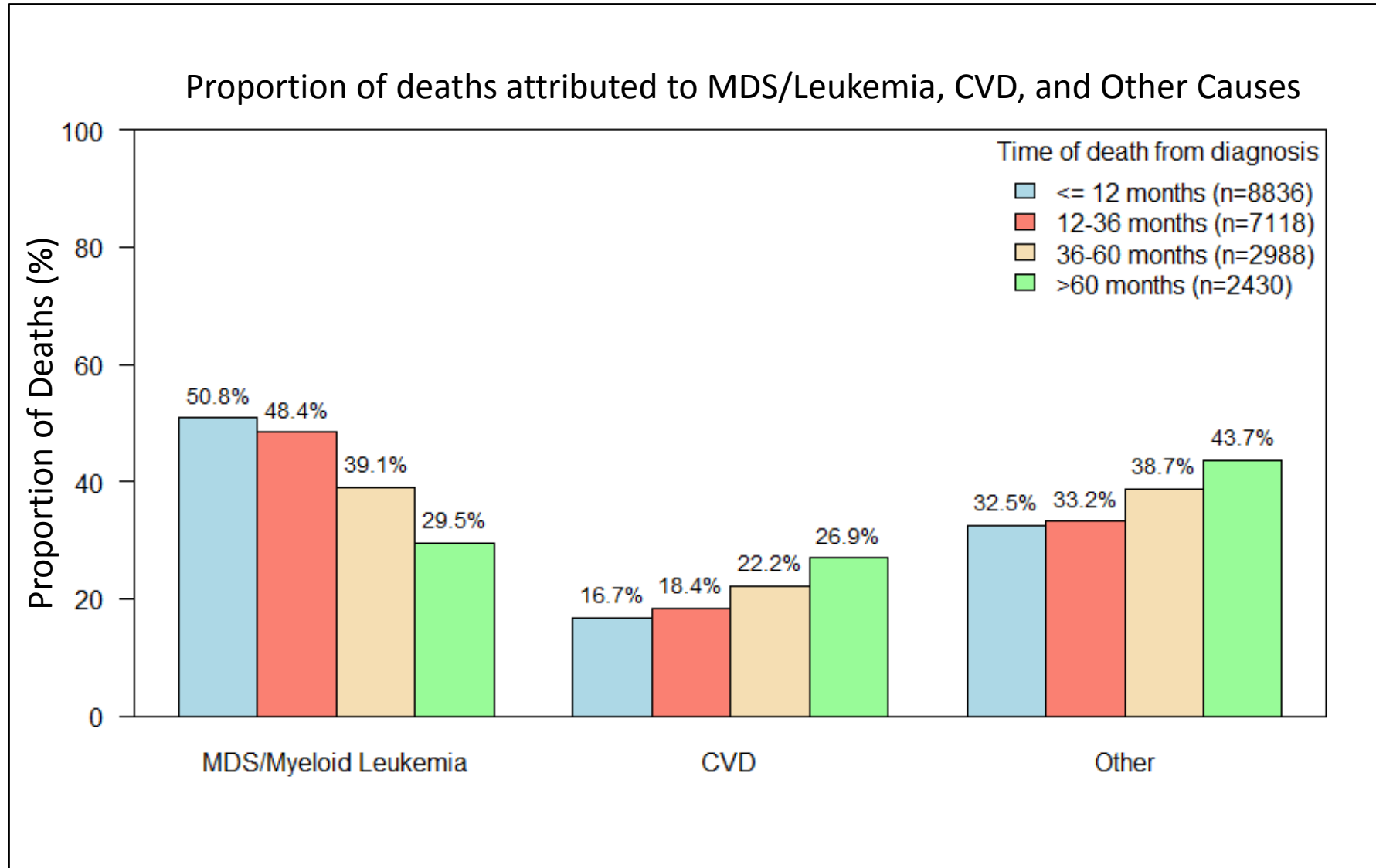
Mutations add to diagnosis and prognosis (and treatment?)



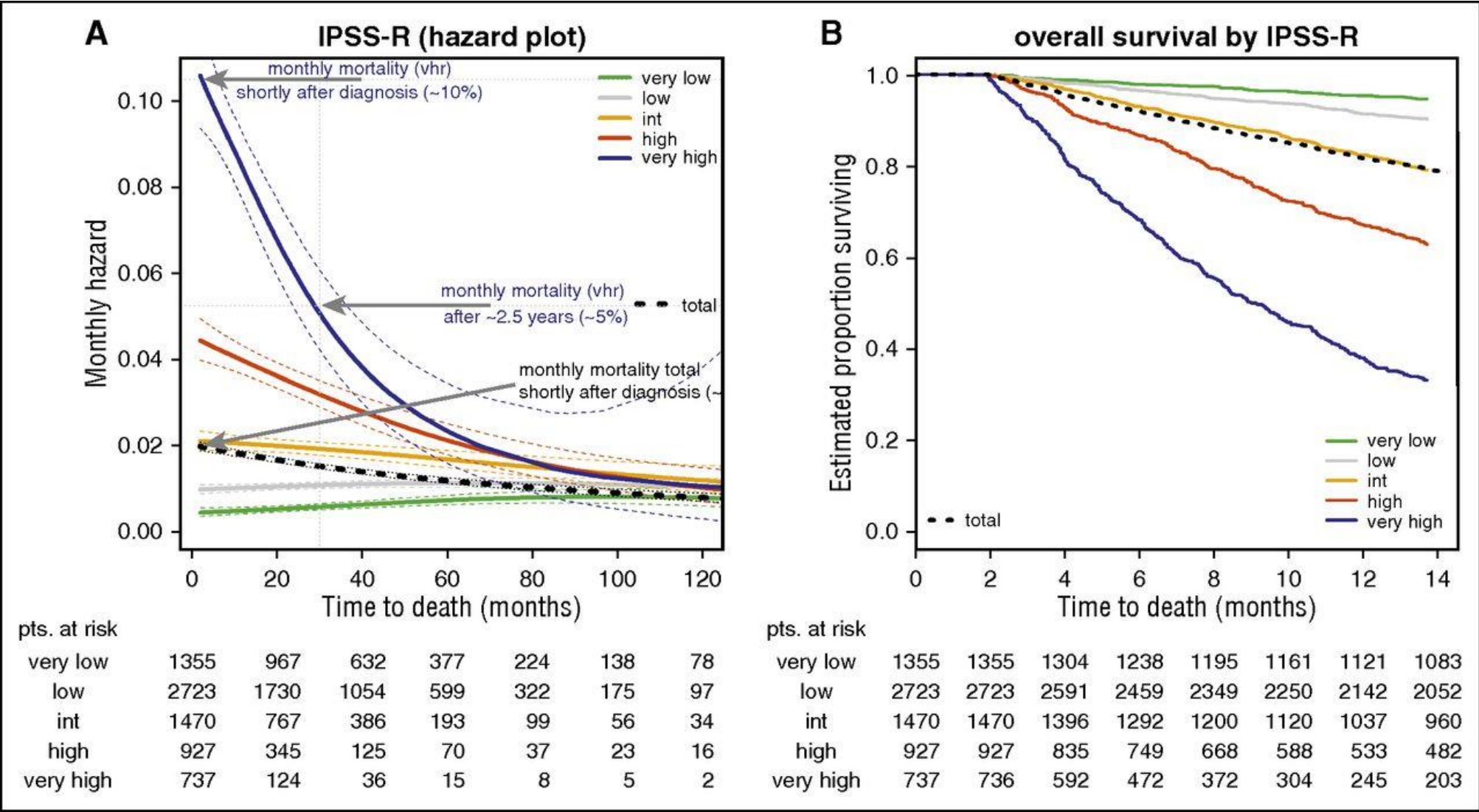
Mutations in Healthy Persons and Heart Disease



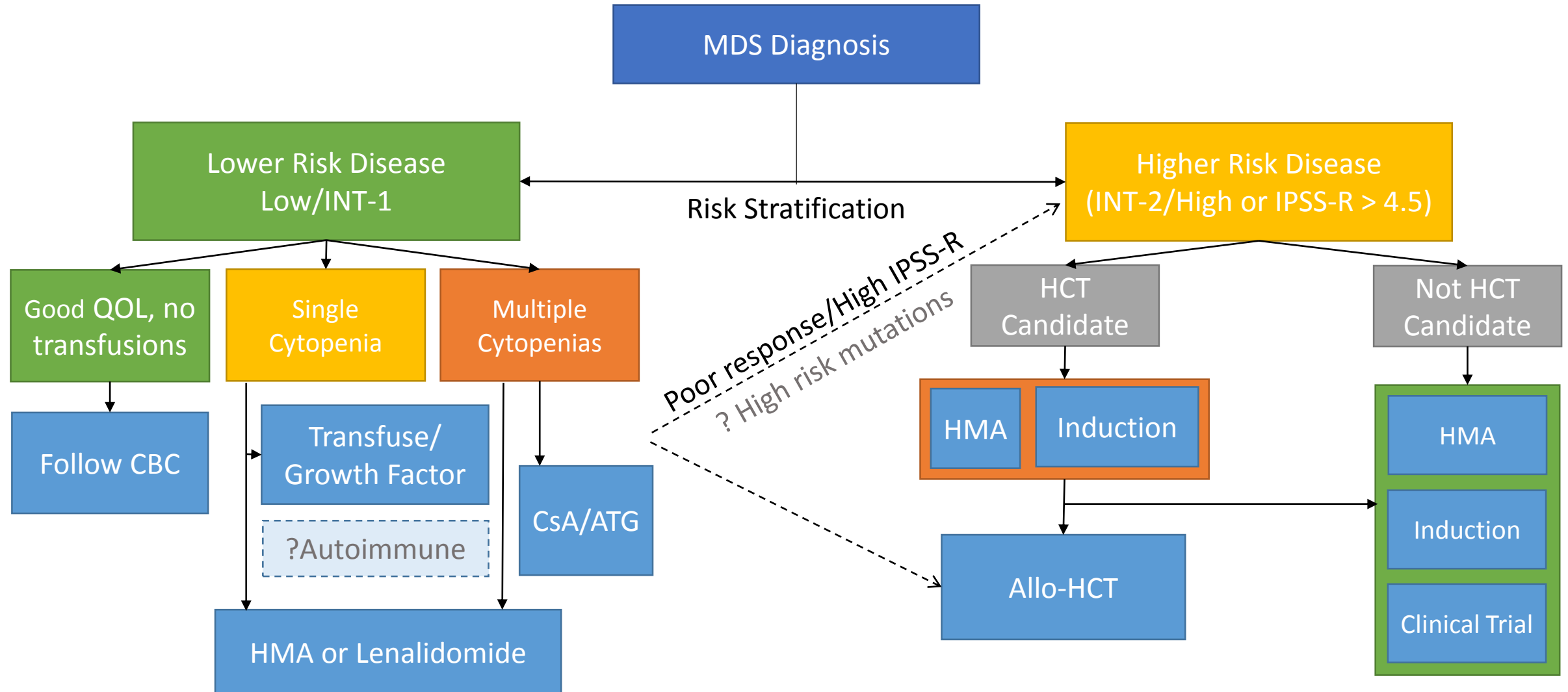
Competing Risks in MDS



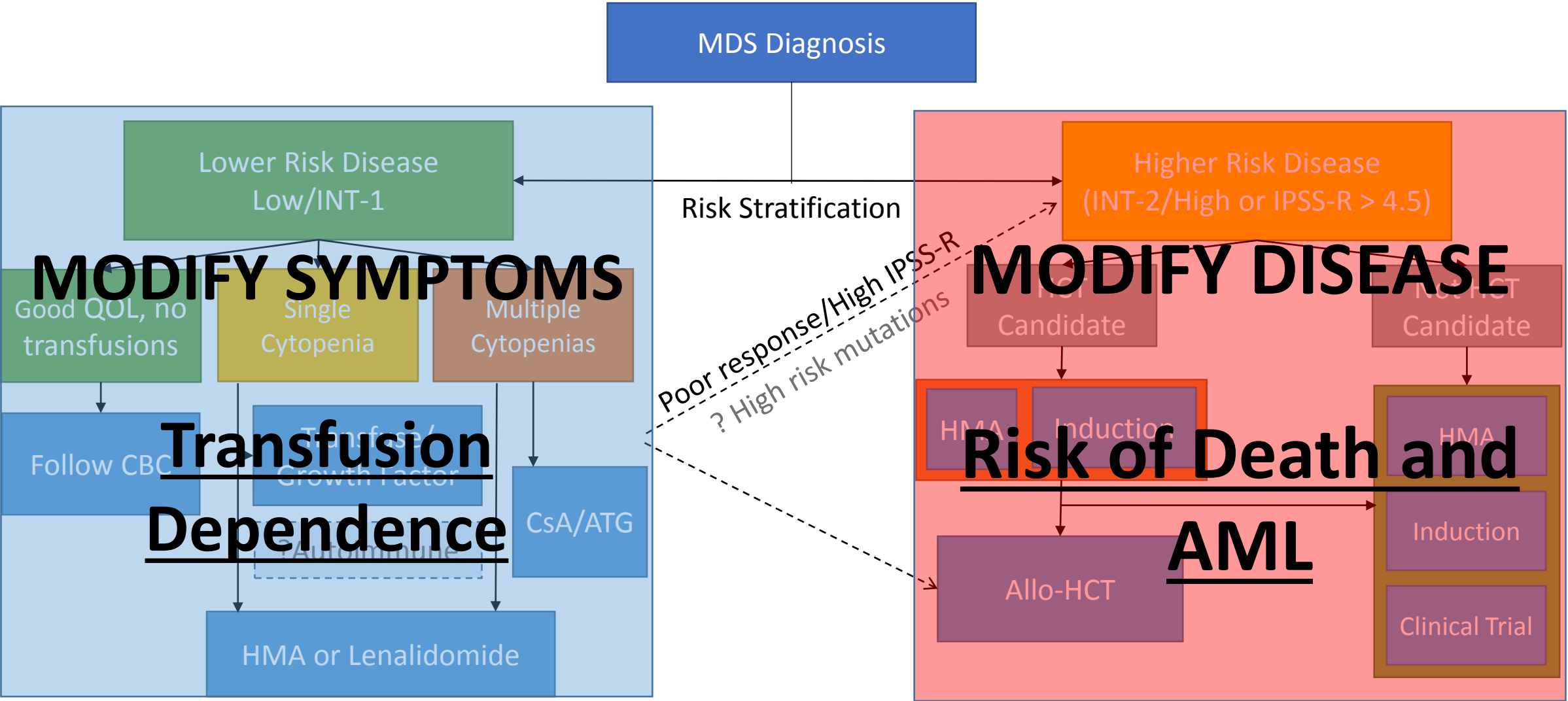
Disease Risk: Fixed or Fluctuating?



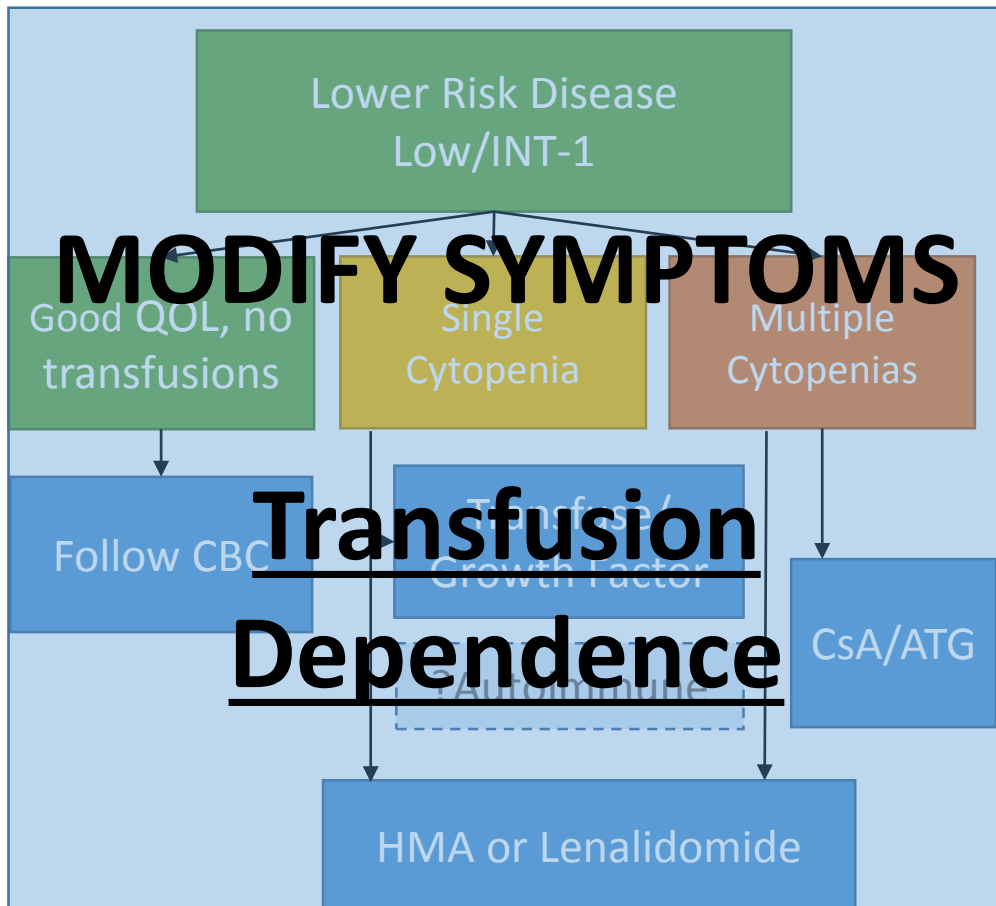
MDS Management



MDS Management



MDS Management



Specific Cytopenia

5q- Syndrome

EPO Level

Transfusion Dependence

Neutropenia

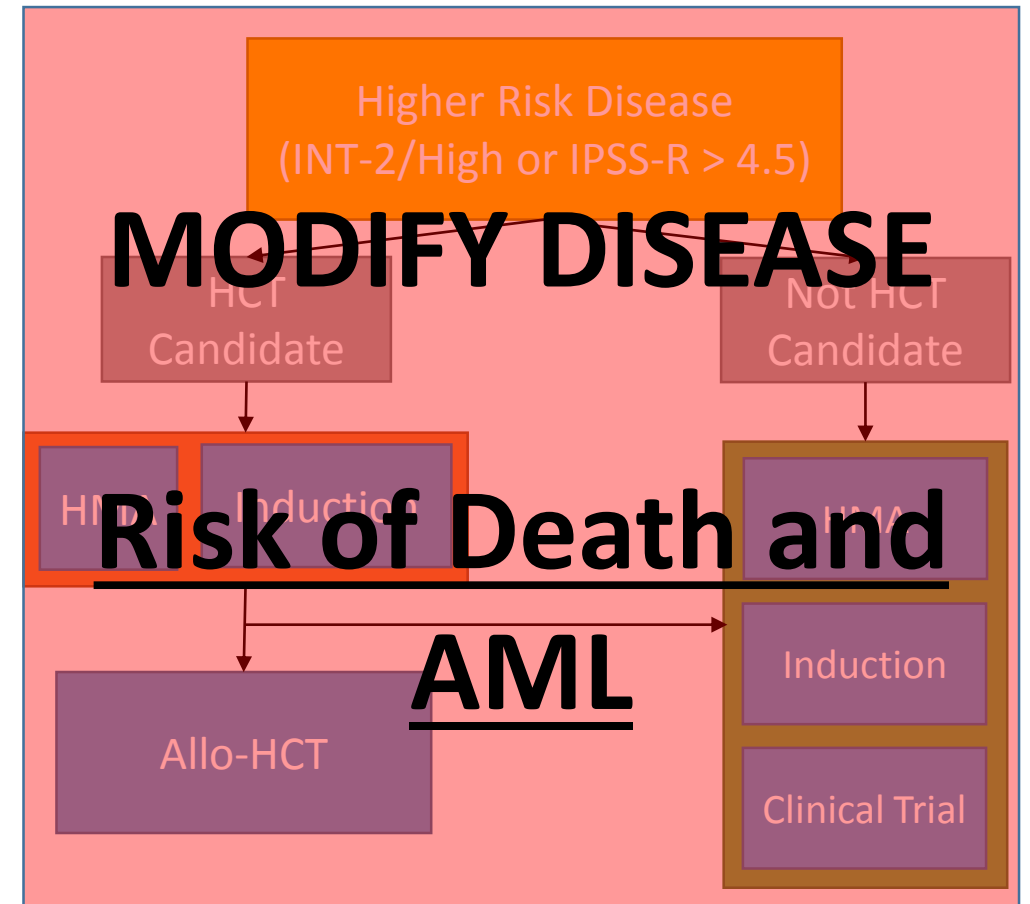
Hypoplastic MDS/AA

MDS Management

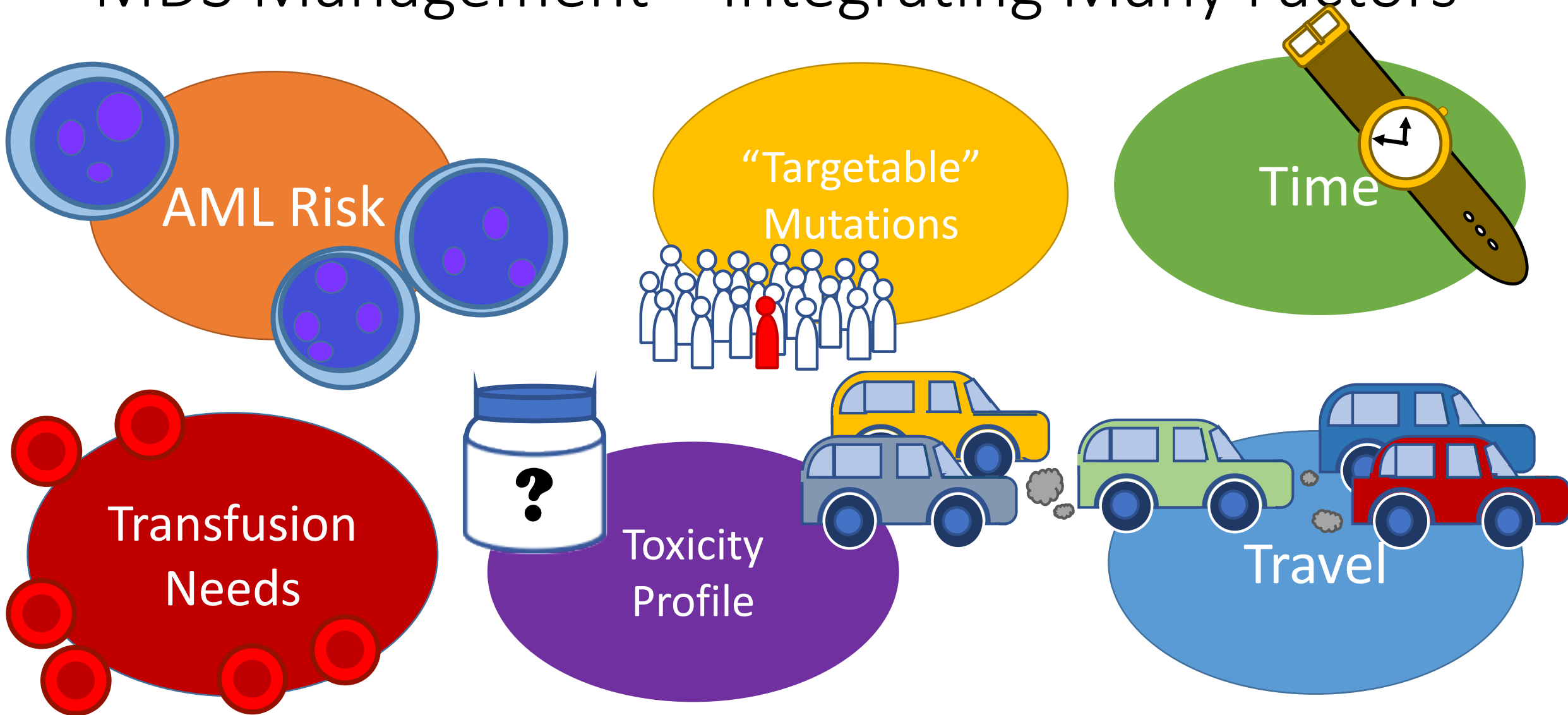
More Immediate Risk of Death Due to Disease
or AML

Transplant Candidacy

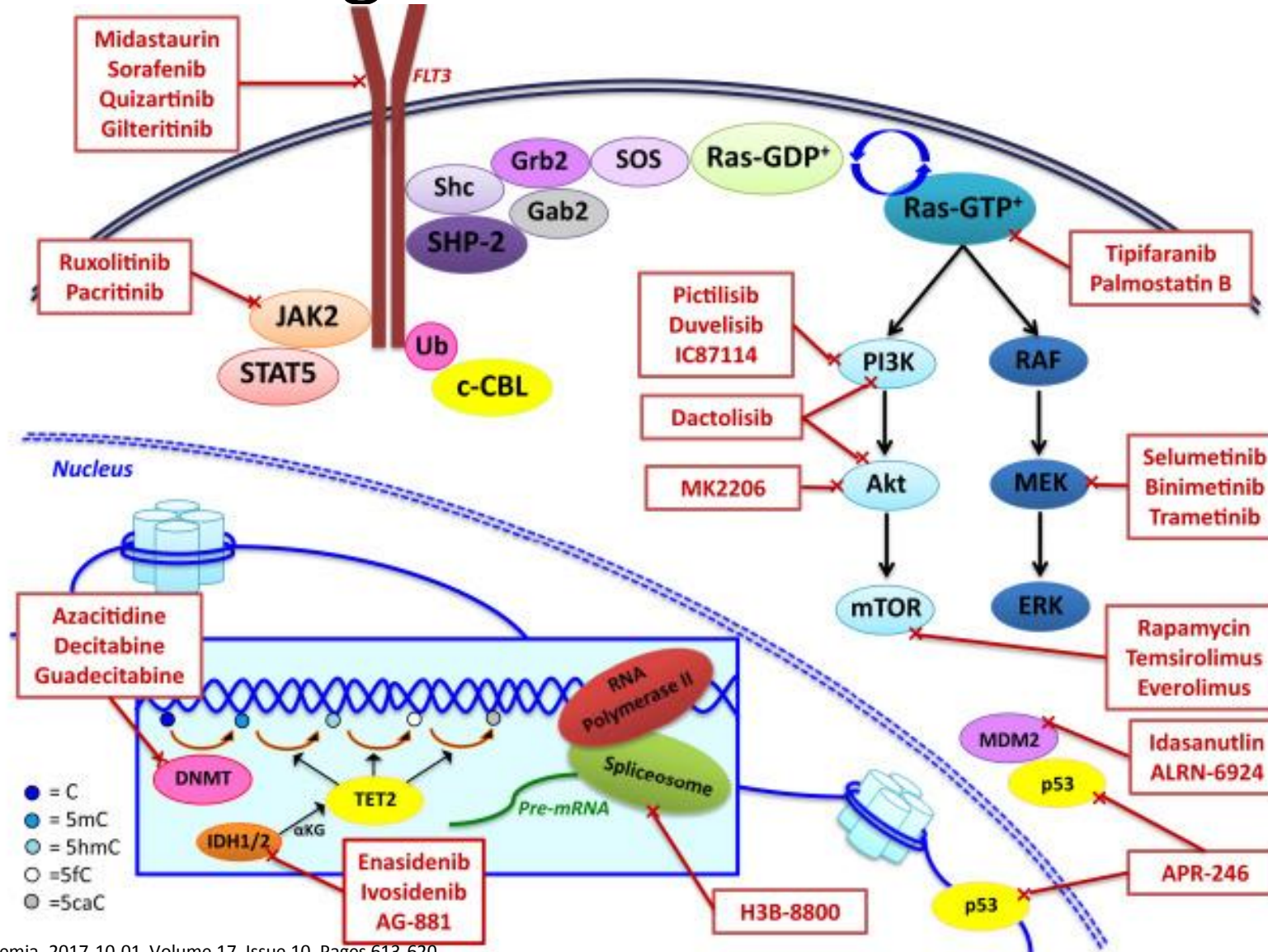
Chemotherapy



MDS Management – Integrating Many Factors

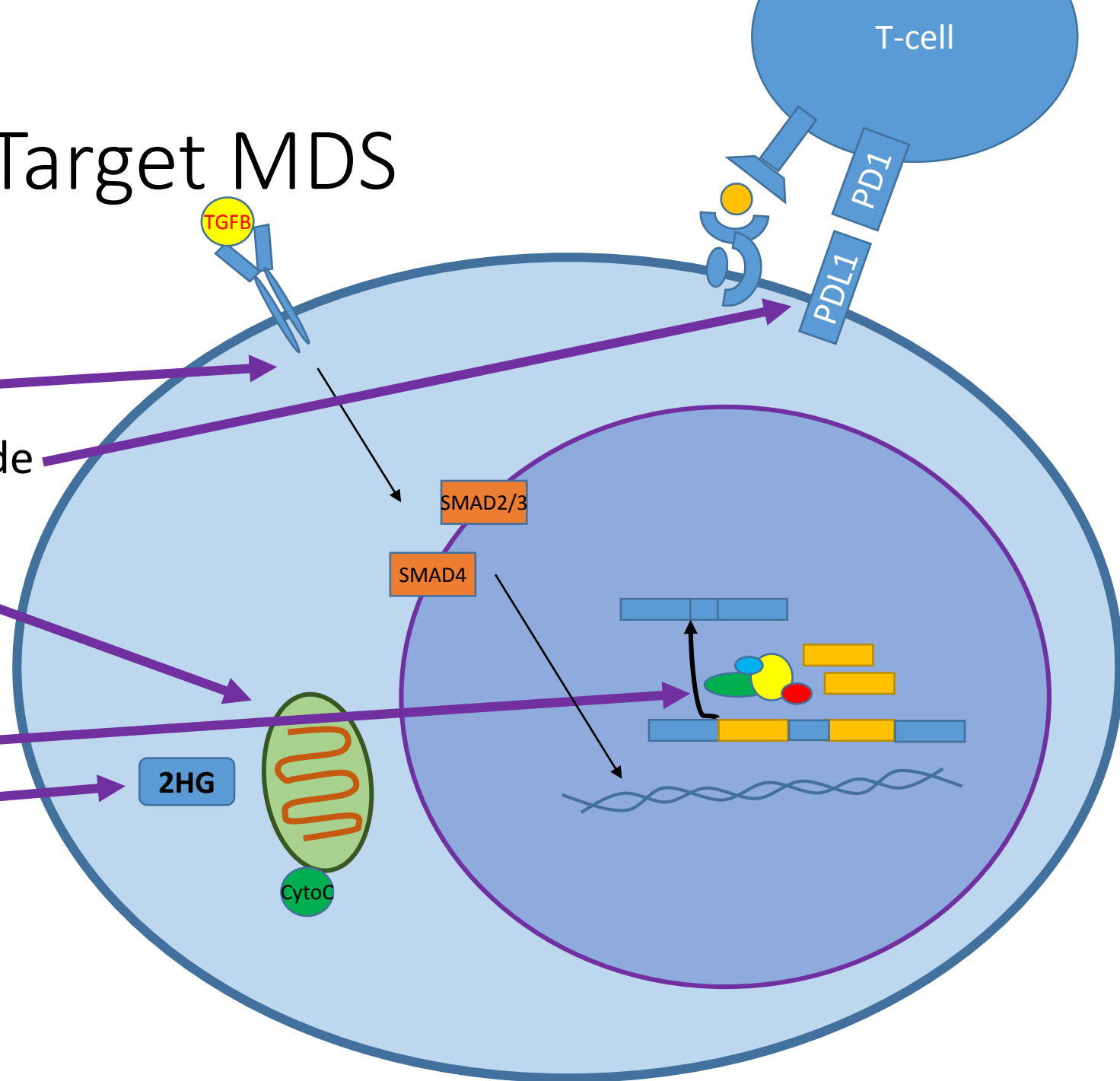


Therapeutic Targets in MDS



New Therapies to Target MDS

- Pathway Driven
 - TGF- β pathway
 - Immune Checkpoint Blockade
 - Apoptosis – Bcl2
- Mutation Driven
 - Spliceosome mutations
 - Mutated IDH enzymes



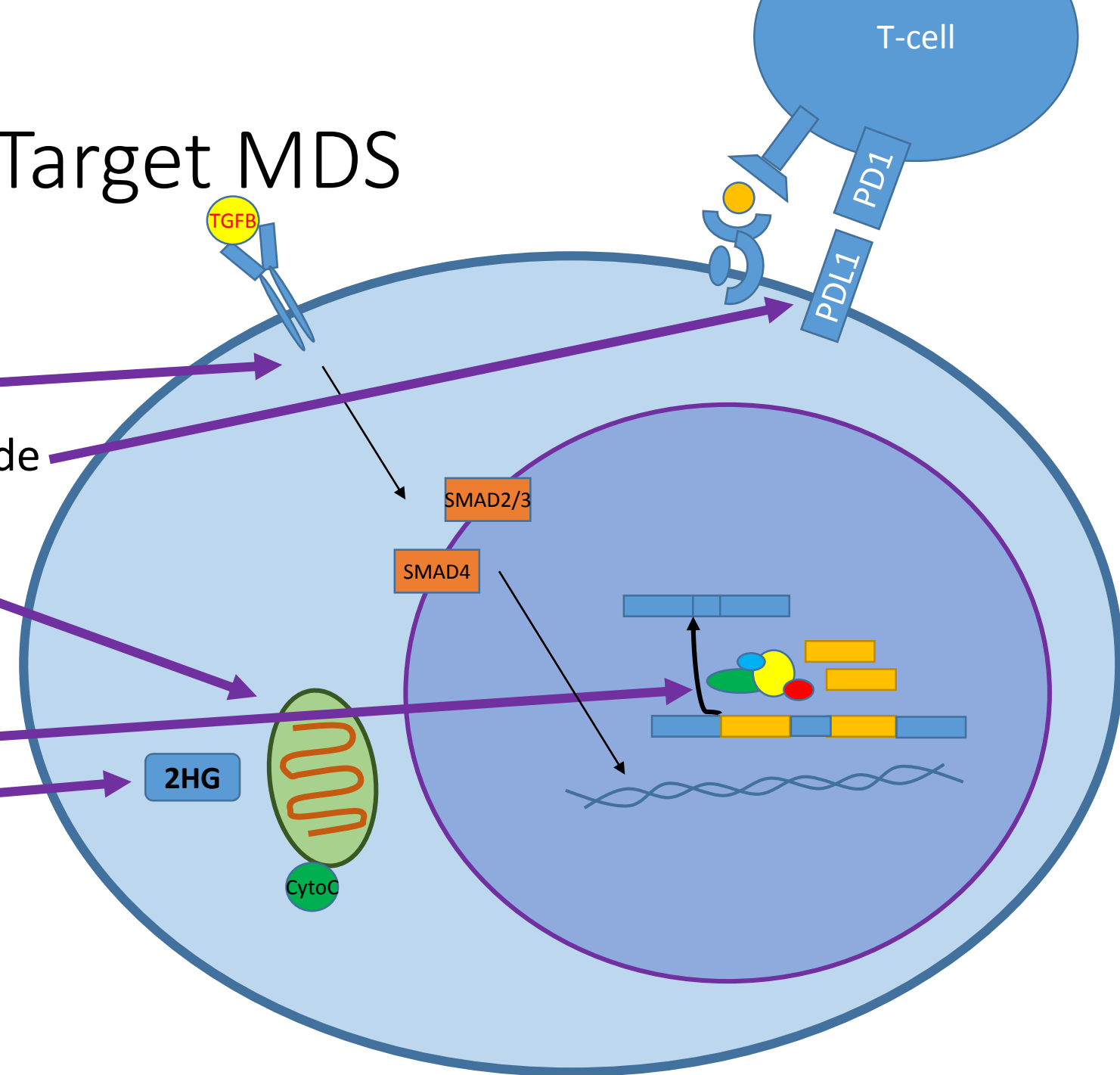
New Therapies to Target MDS

- Pathway Driven

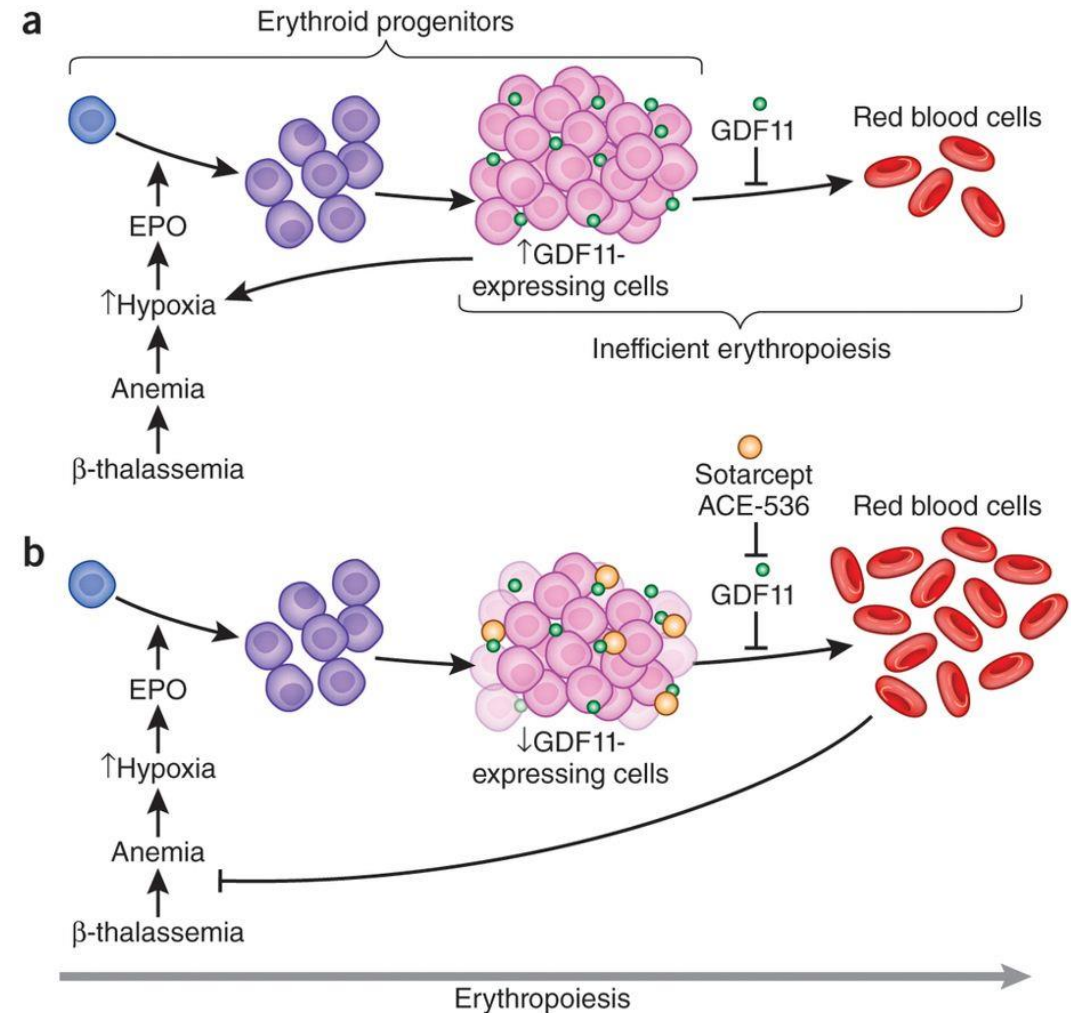
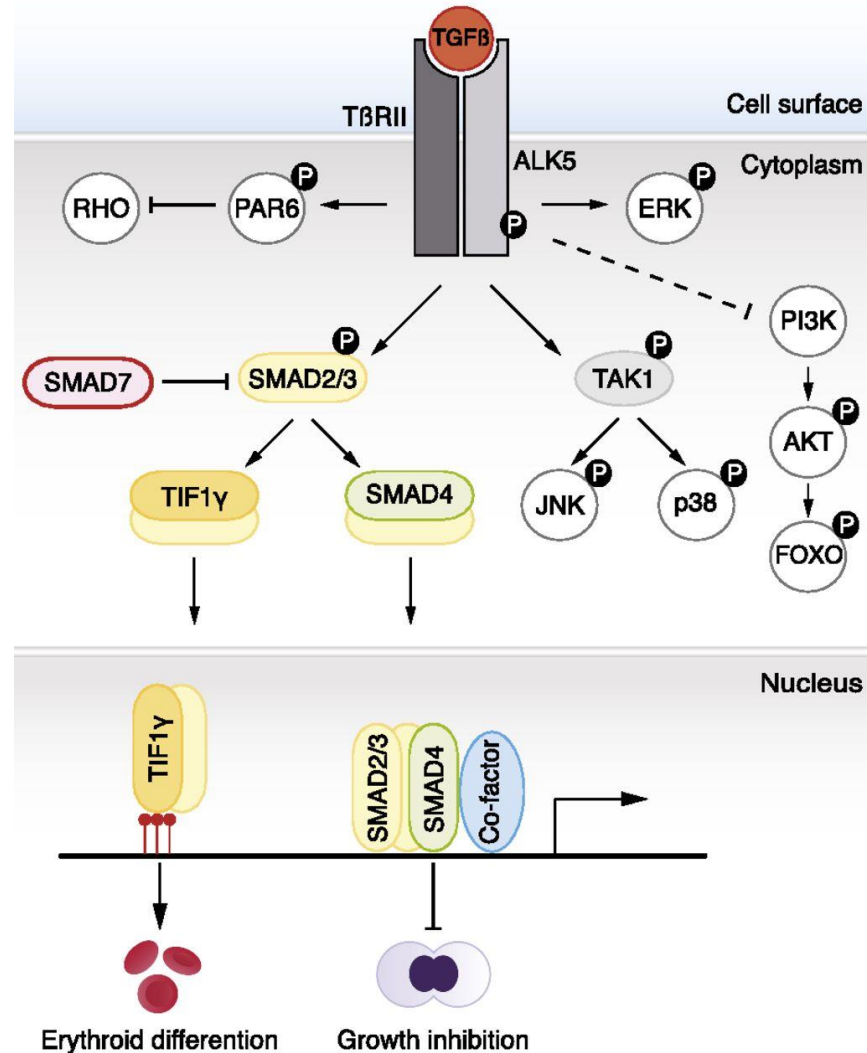
- **TGF- β pathway**
- Immune Checkpoint Blockade
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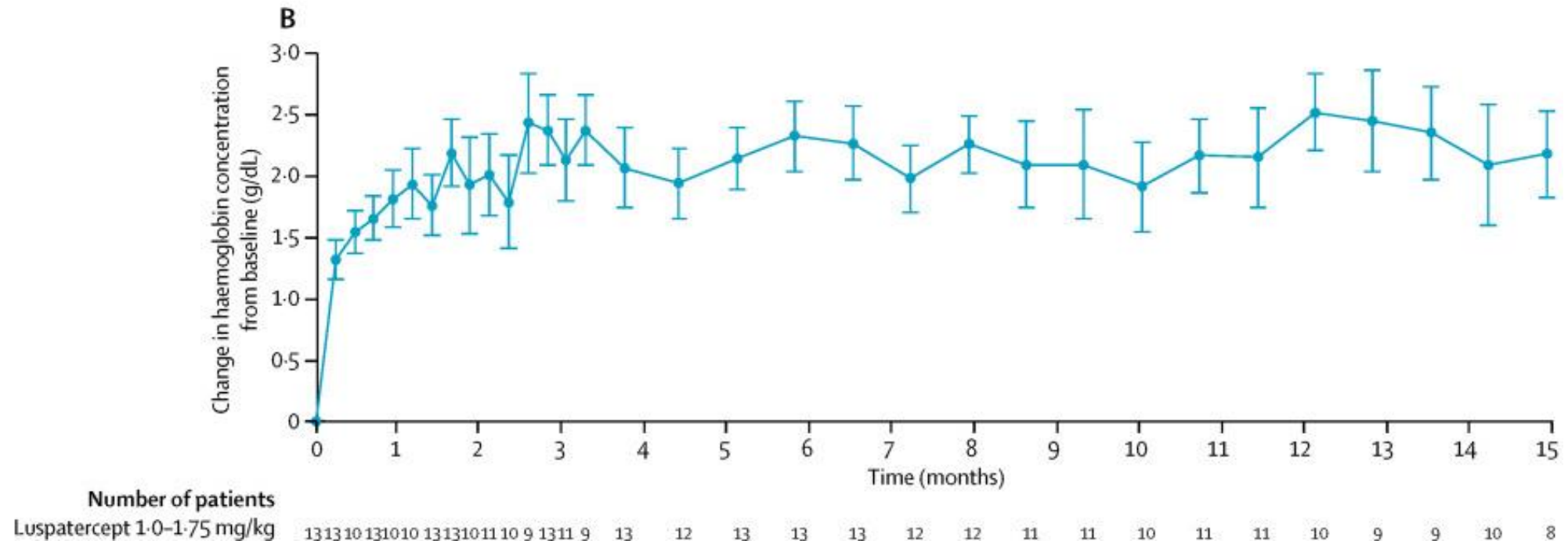
TGF- β Ligand Traps and Erythropoiesis



Paulson RF. Nature Medicine volume20, pages334–335 (2014)

Luspatercept

- Activin receptor IIB protein, TGFB family member ligand trap
- EPO >500 or intolerant of ESAs, no prior HMA



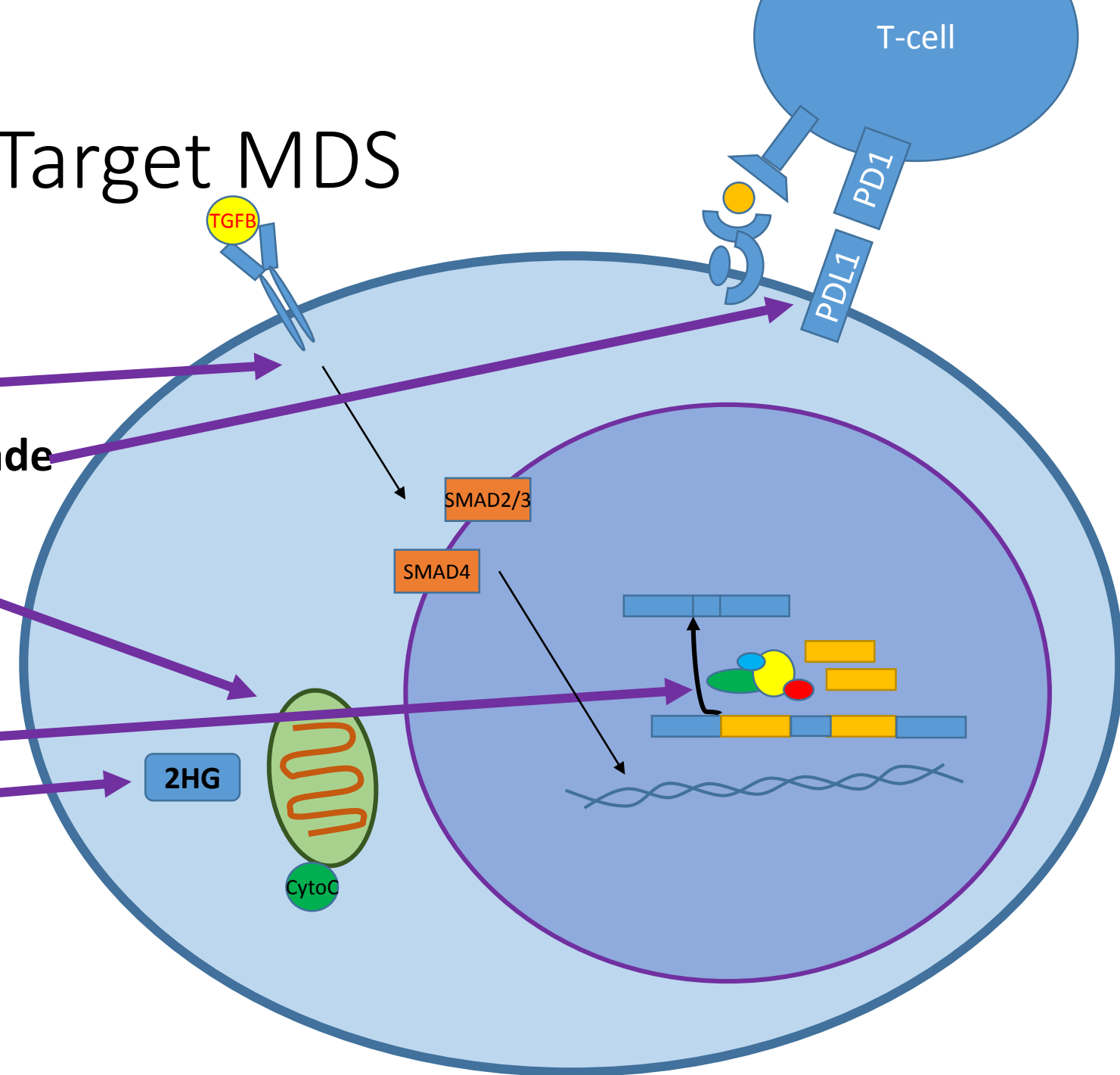
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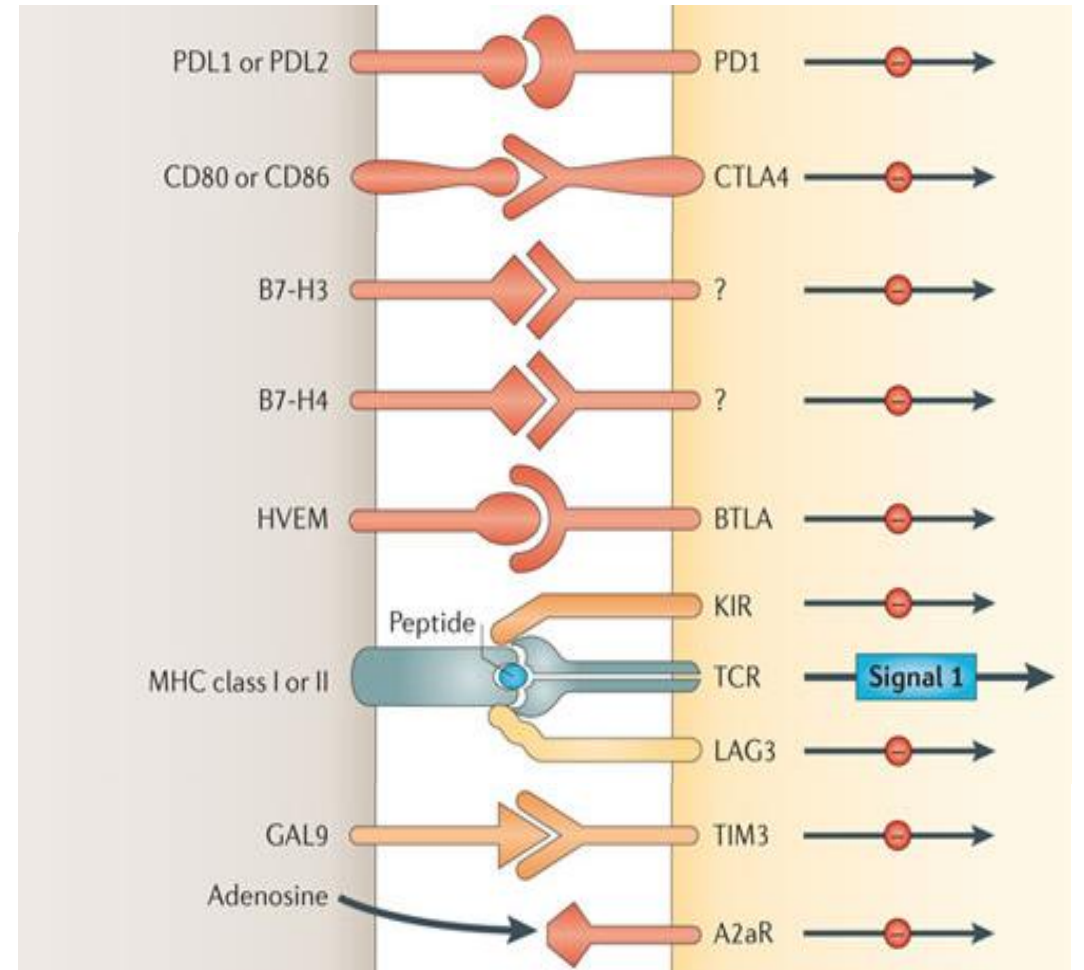
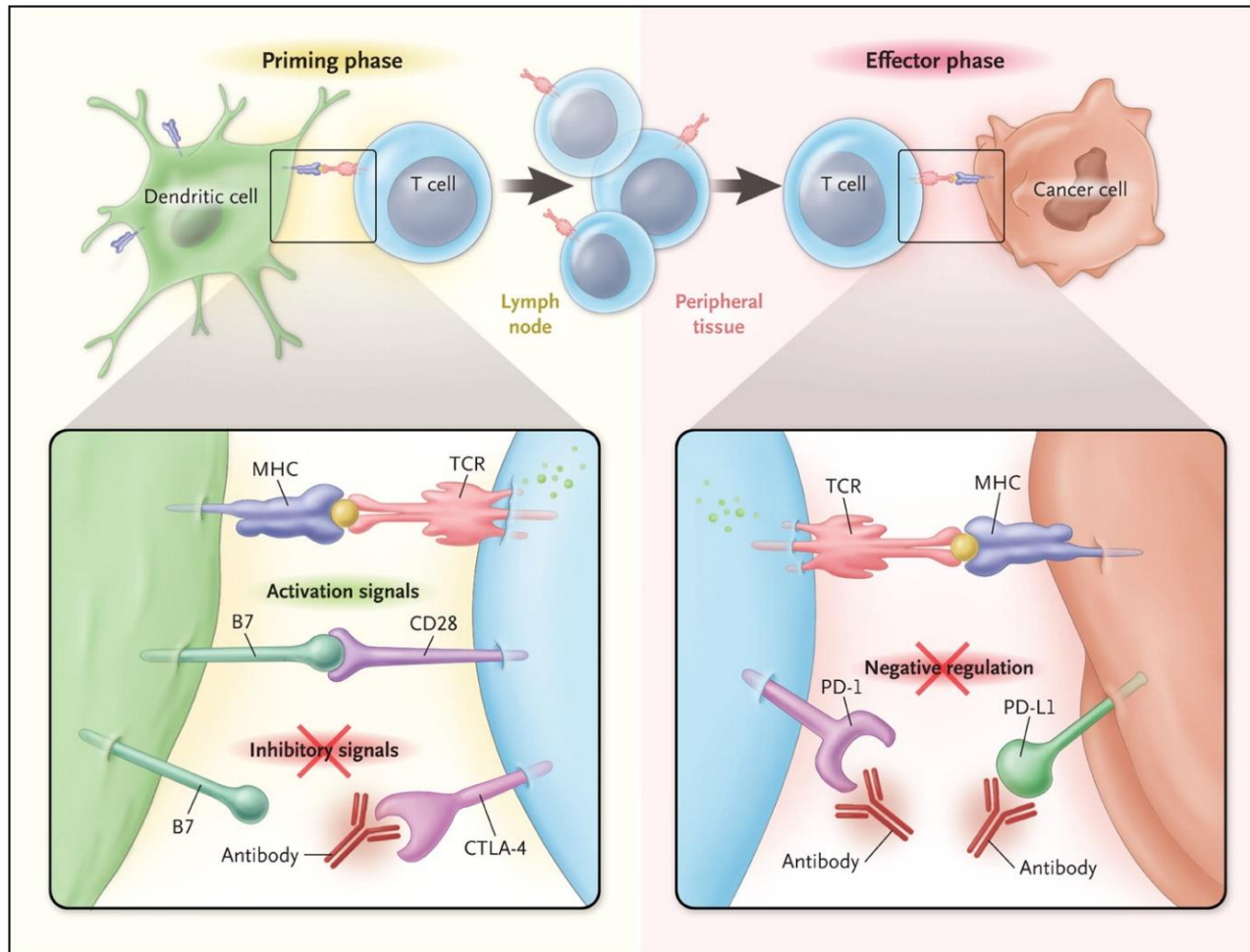
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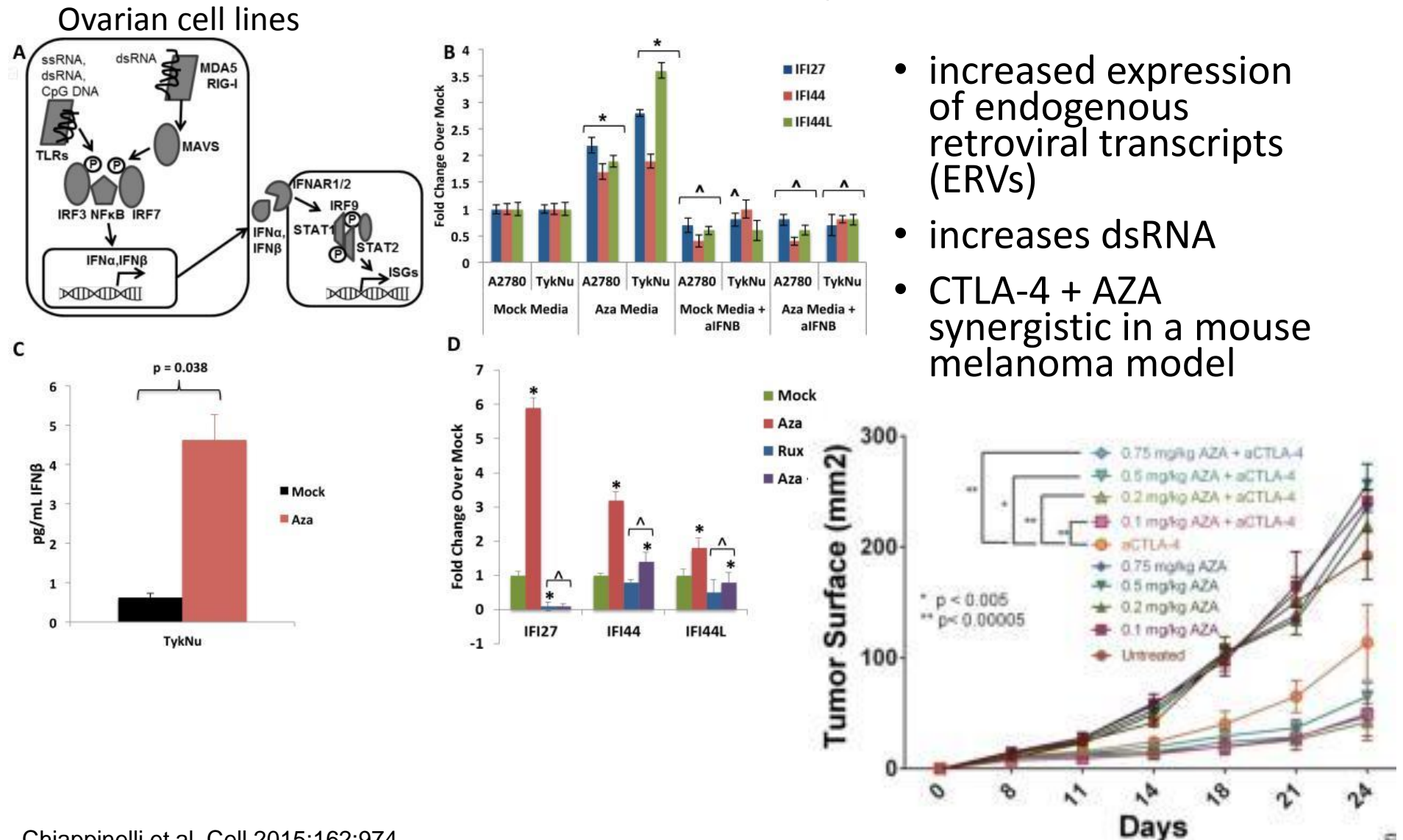
Immune Checkpoints in Cancer



Pardoll DM. Nature Reviews Cancer 2012;12, 252-264

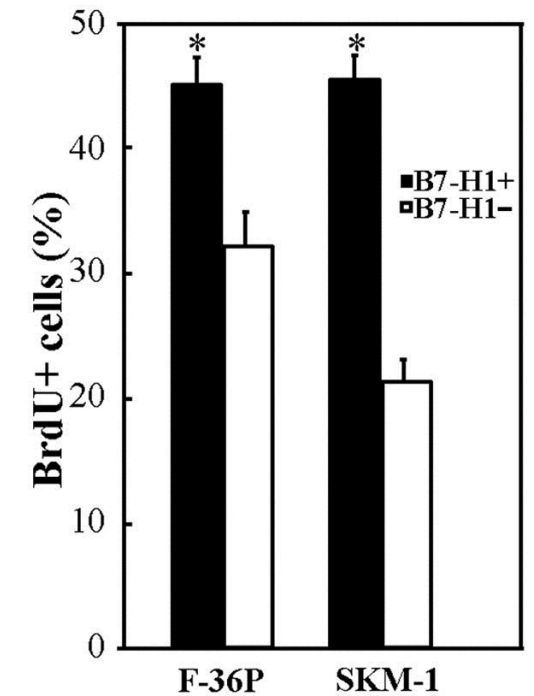
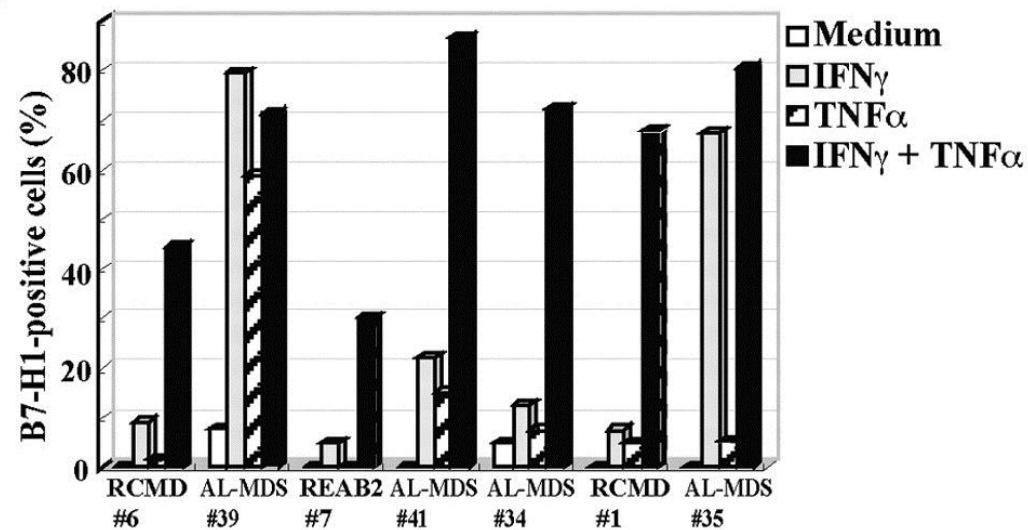
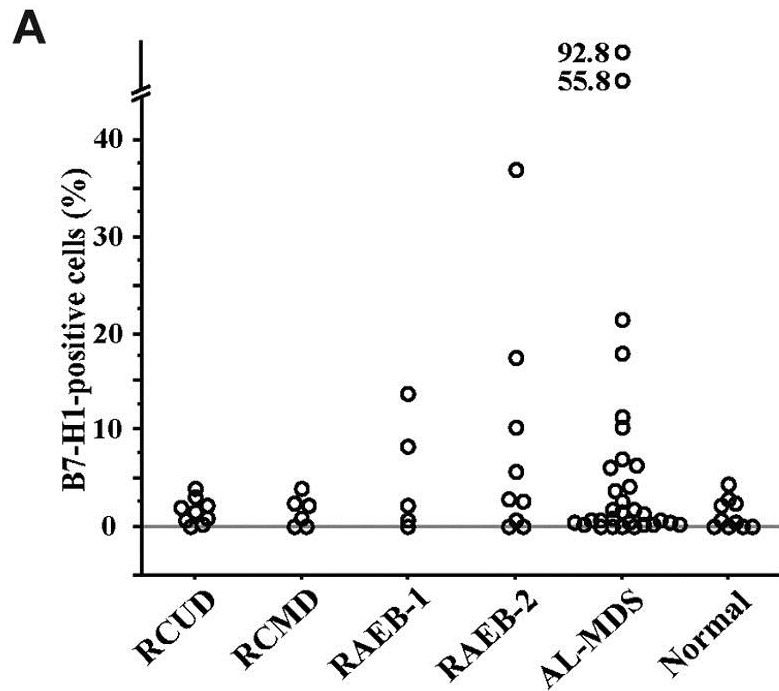
Ribas A. N Engl J Med 2012;366:2517-2519.

DNMTI and Interferon Response



PD-L1 in MDS

- PD-L1 is upregulated in MDS blasts after exposure to IFN γ and TNF α



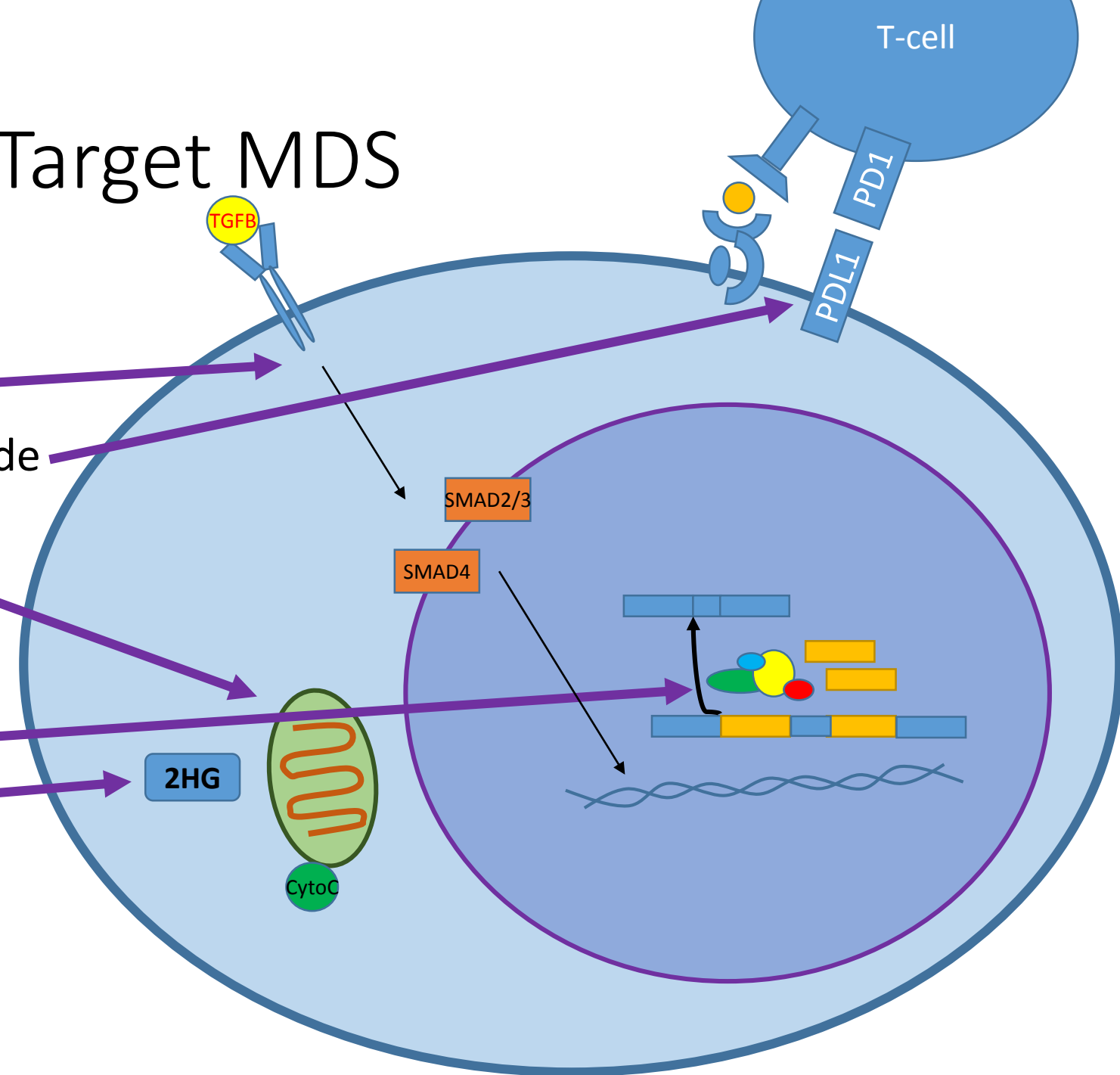
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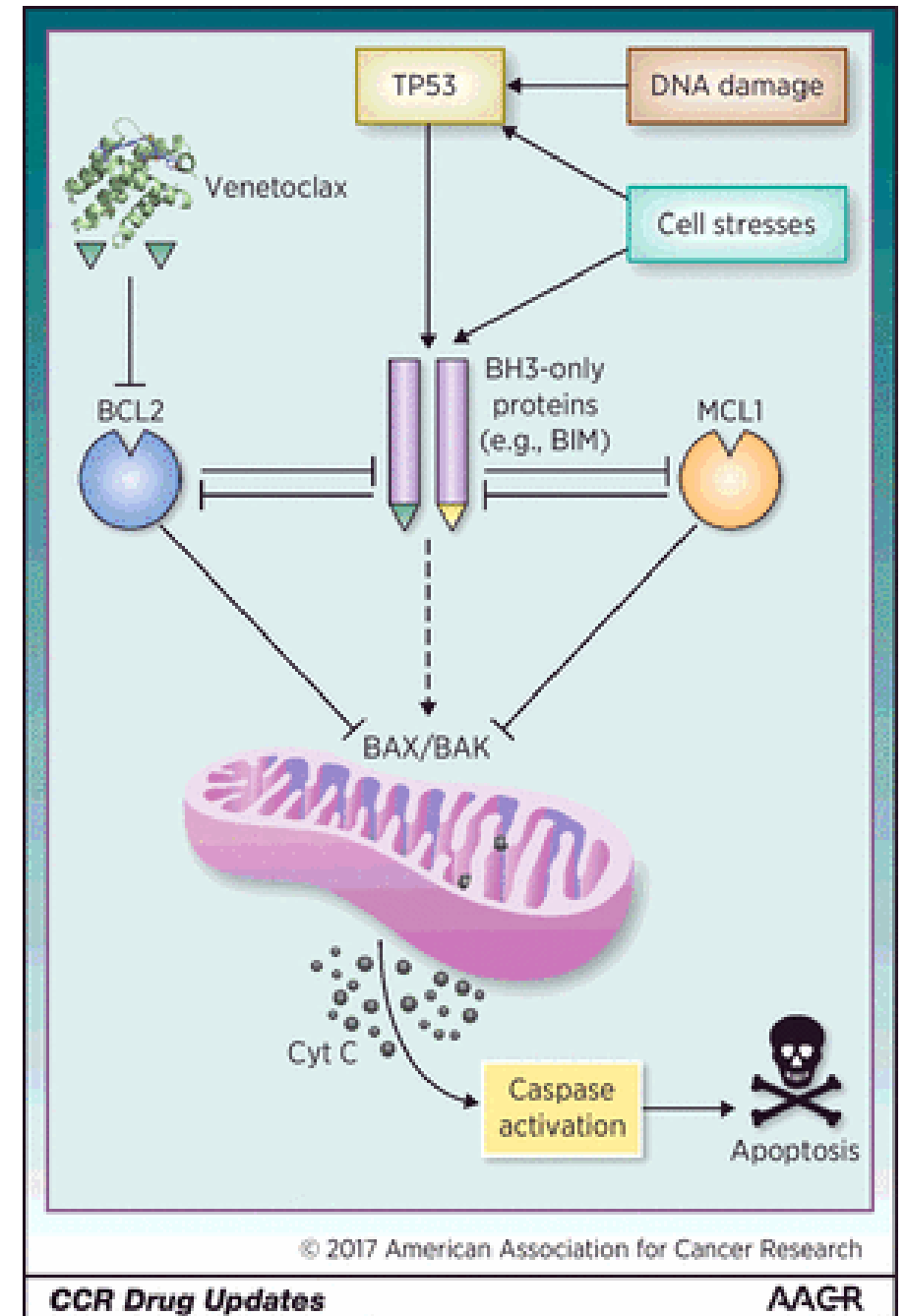
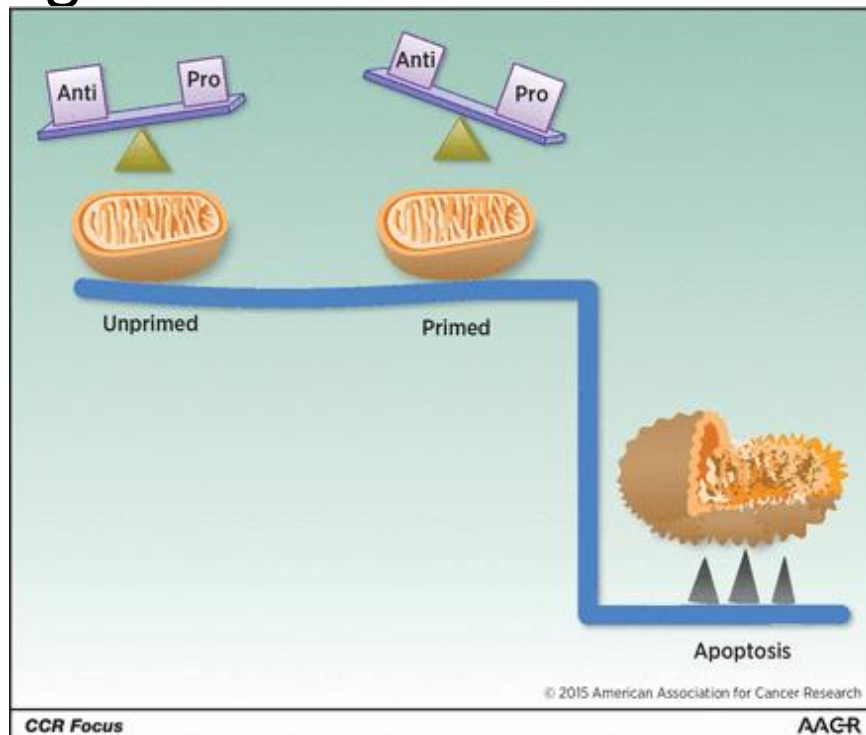
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Apoptosis in MDS

- BCL2 is a regulator of apoptosis
- “priming” apoptosis may be attractive in treating MDS



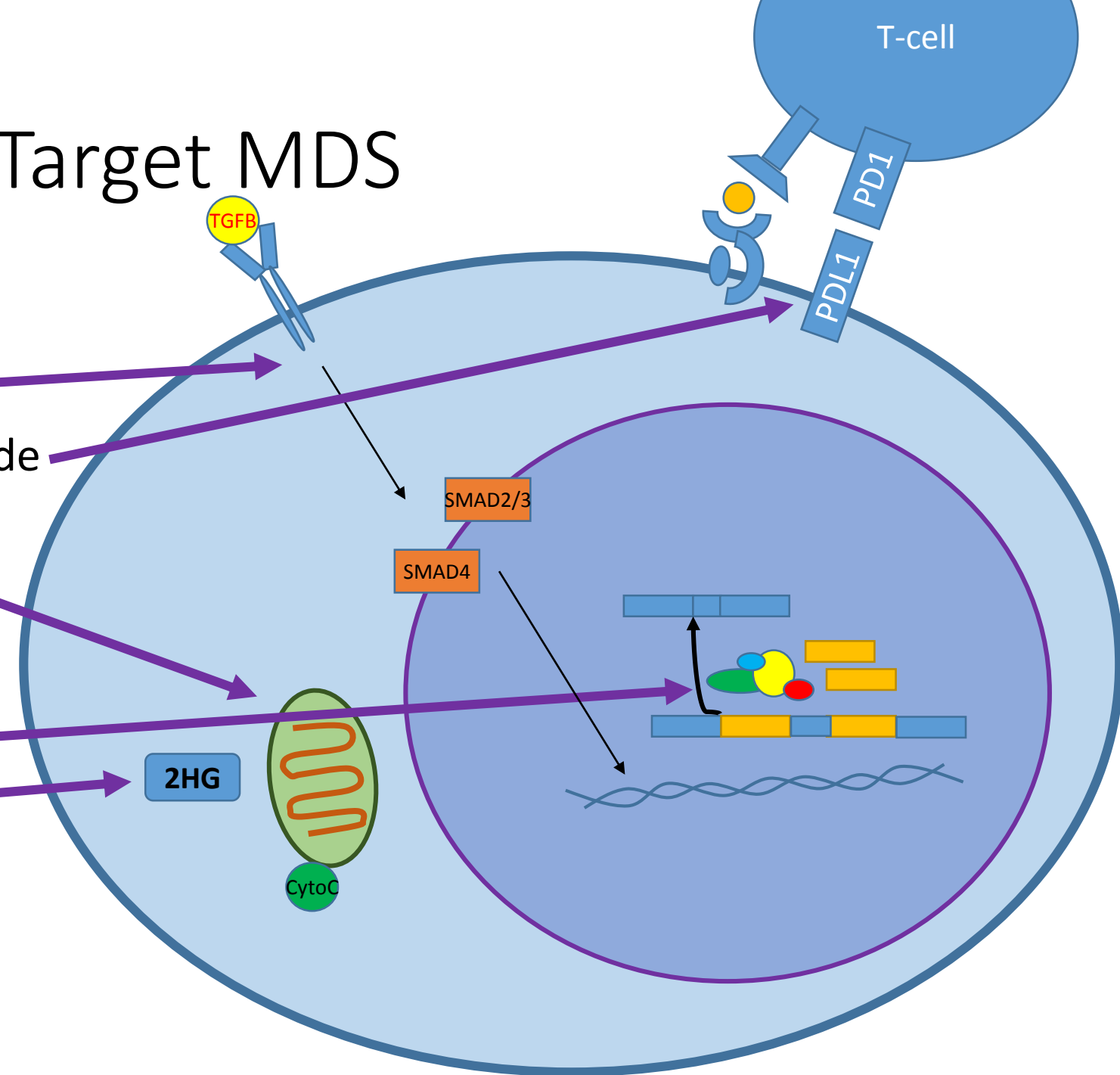
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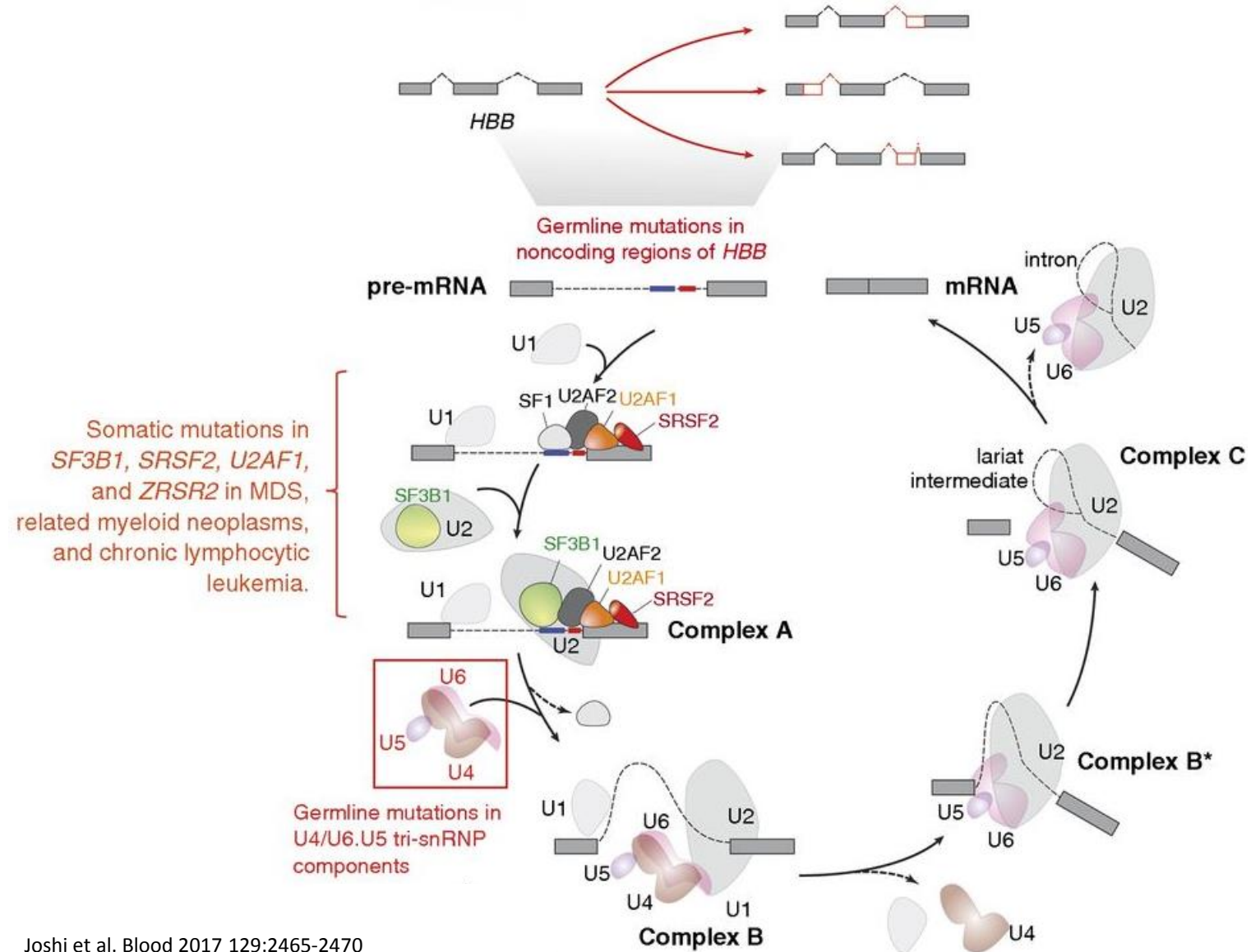
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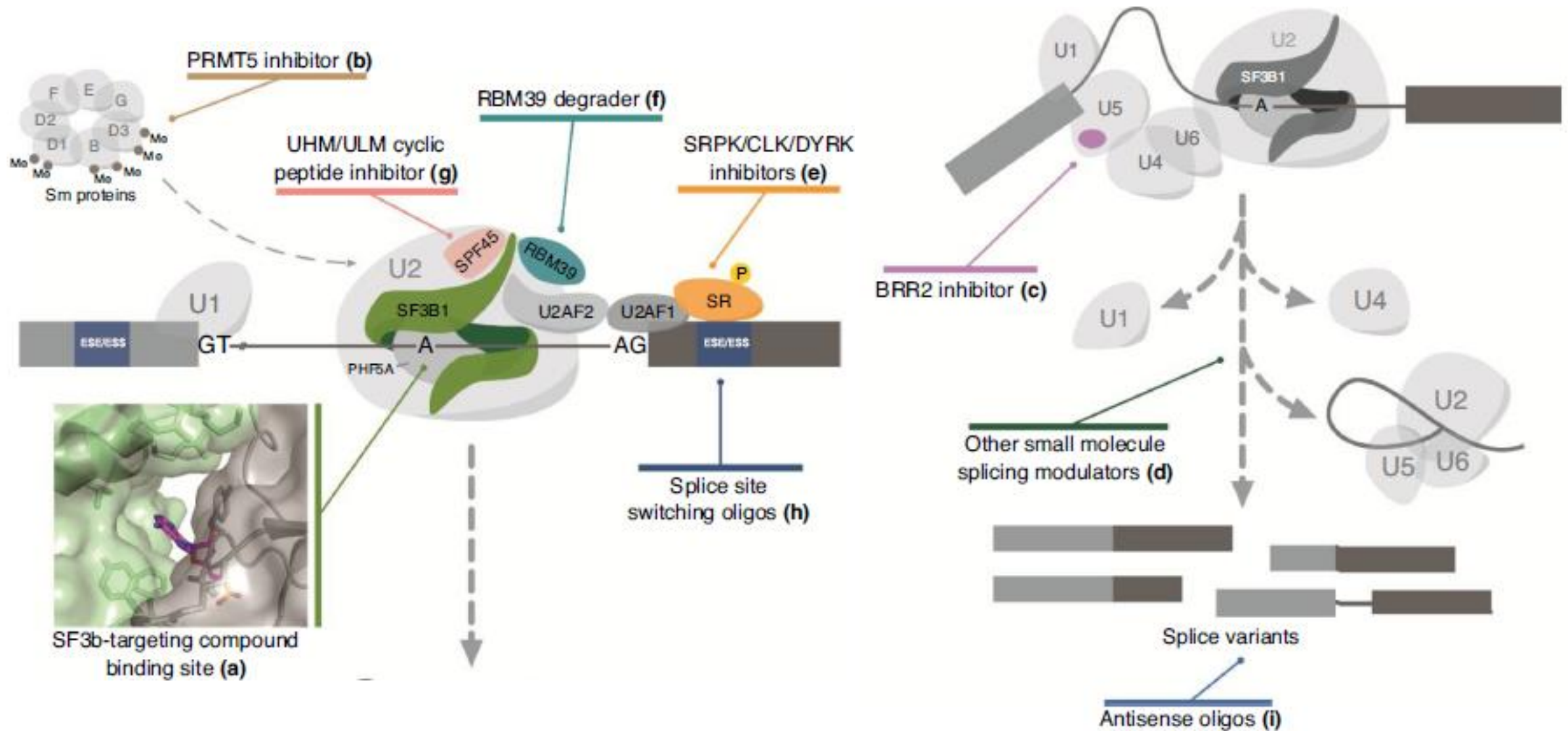
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Spliceosome mutations in MDS



Possible Spliceosome Targets



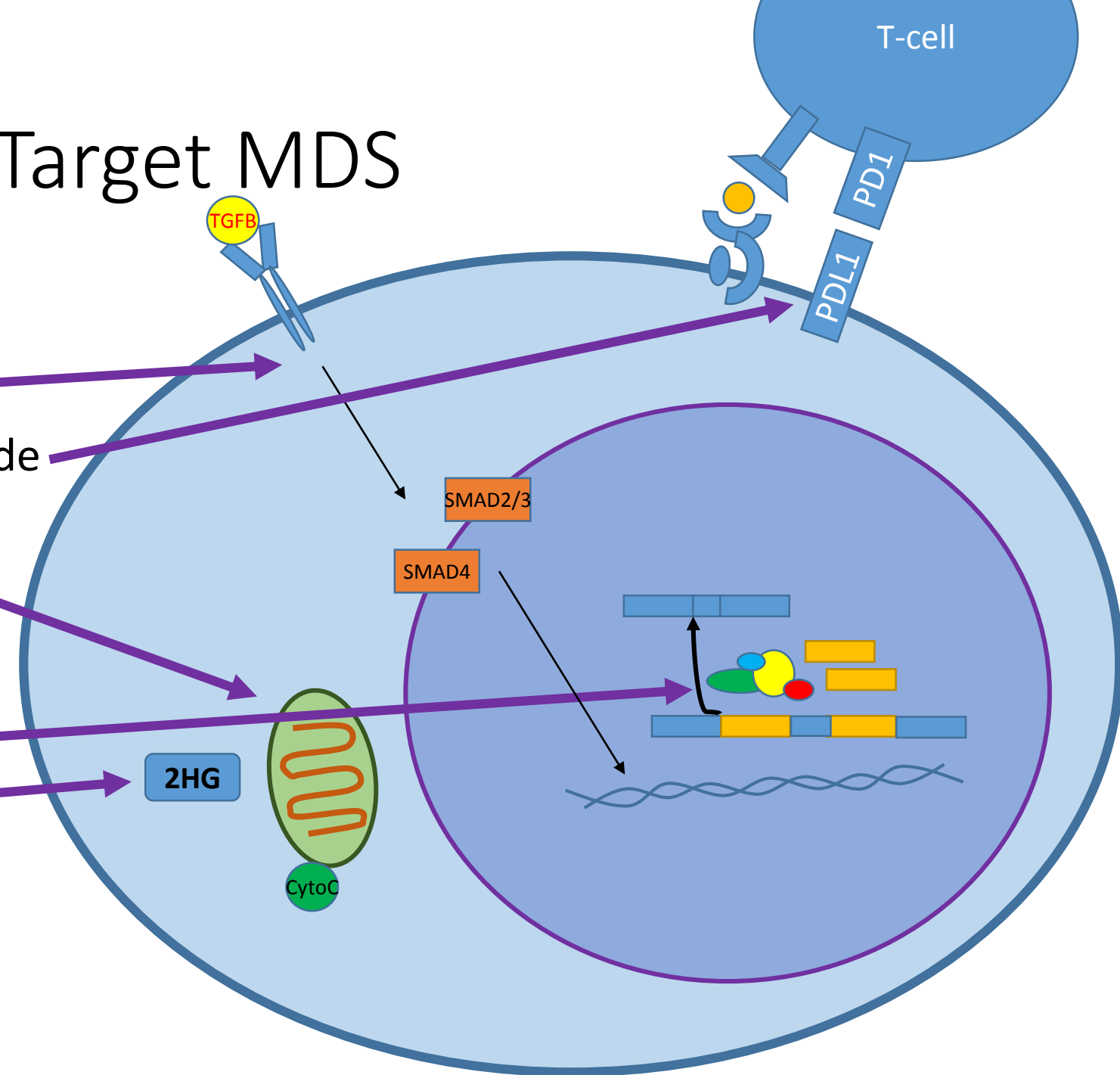
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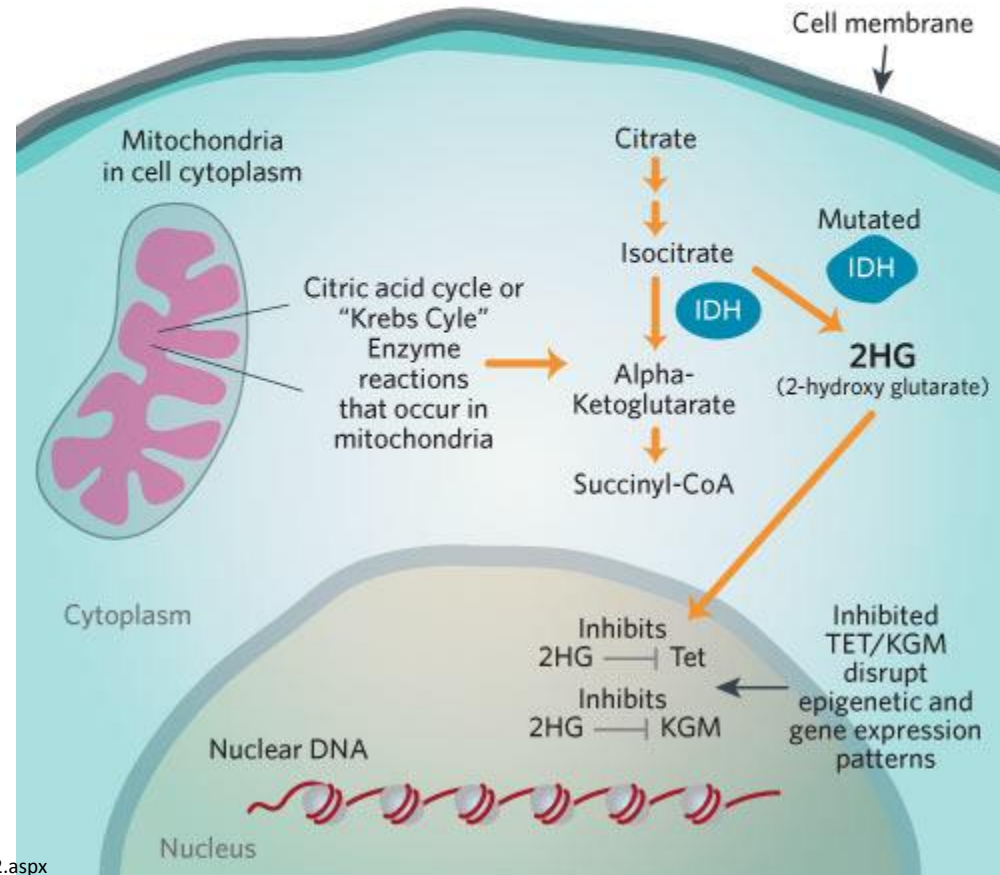
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Targeting mutated IDH proteins

Cellular Metabolism Proteins: IDH1 and IDH2



Conclusions

- Our understanding of MDS has grown significantly
- This knowledge may help us to identify new targets for treatment
- A number of therapies are in development and have exciting potential
- New targets continue to be identified
- Questions? abrunner@partners.org