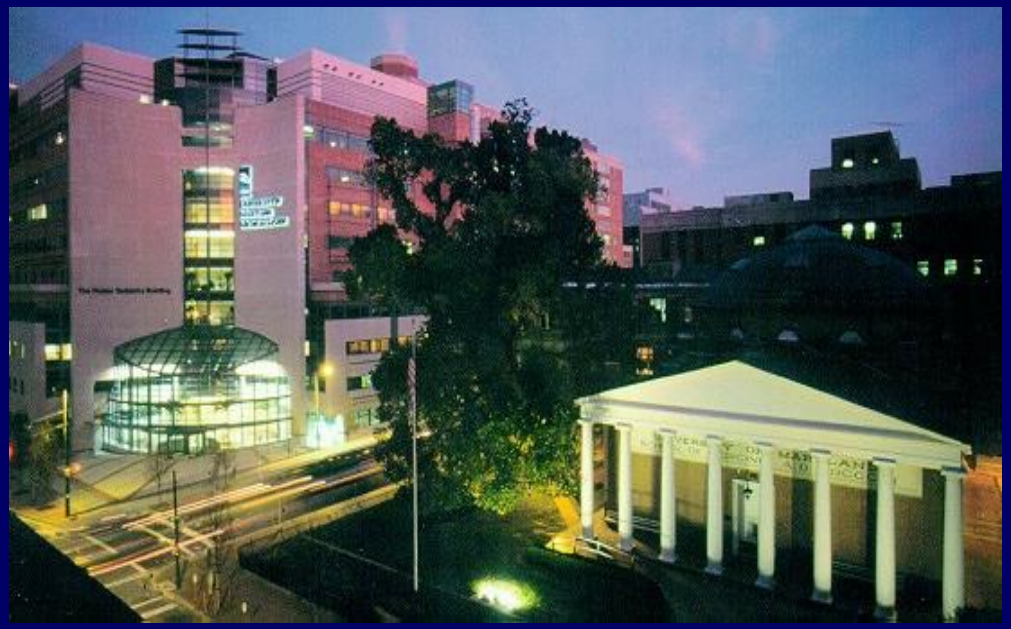
Navigating Higher-Risk Myelodysplastic Syndromes



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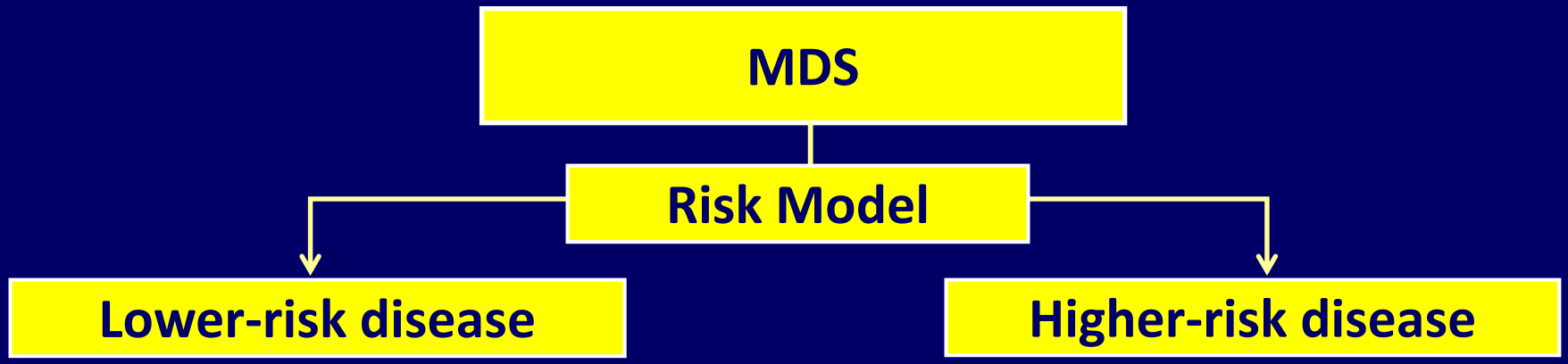
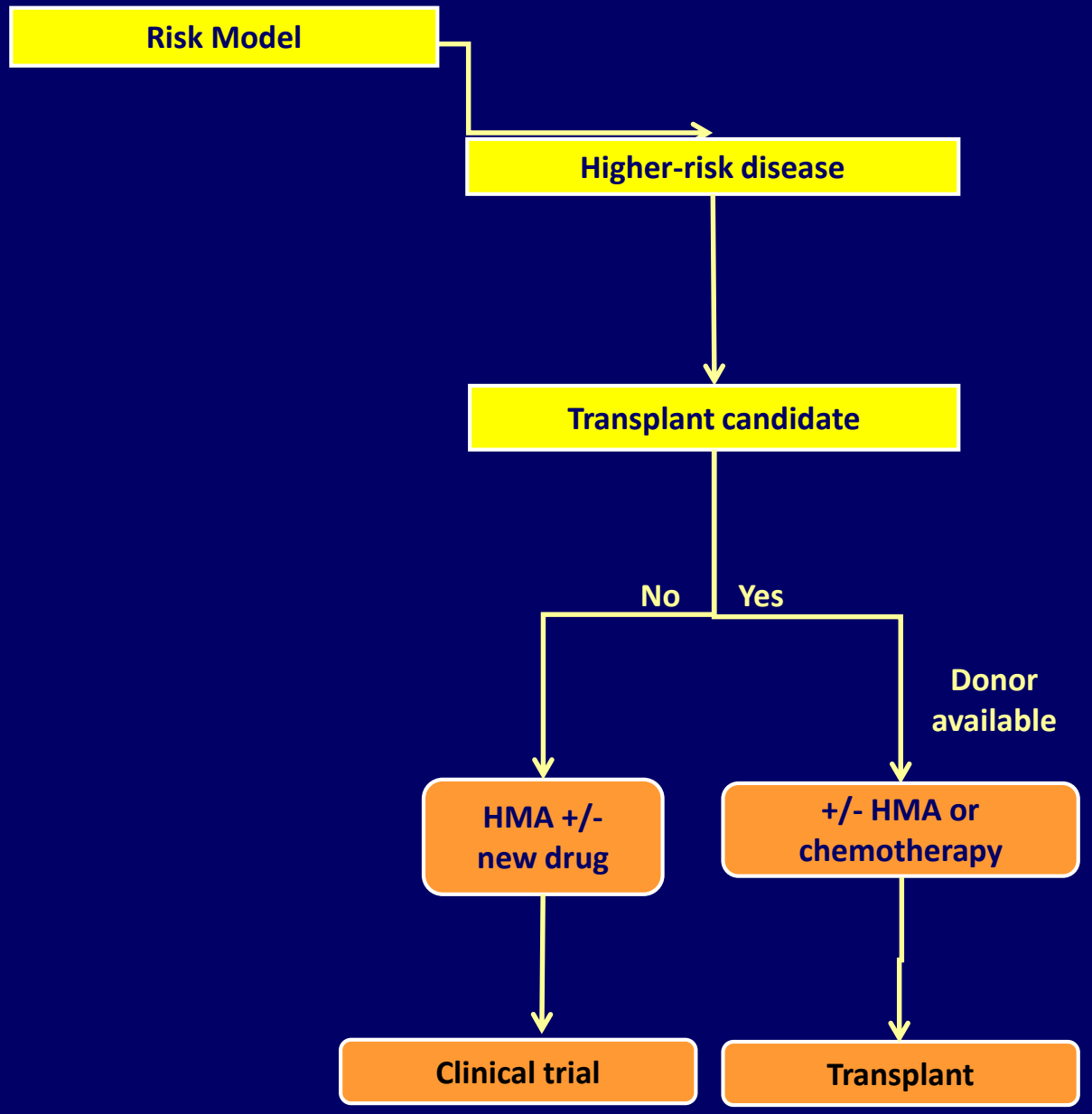
MDS Goals of Treatment



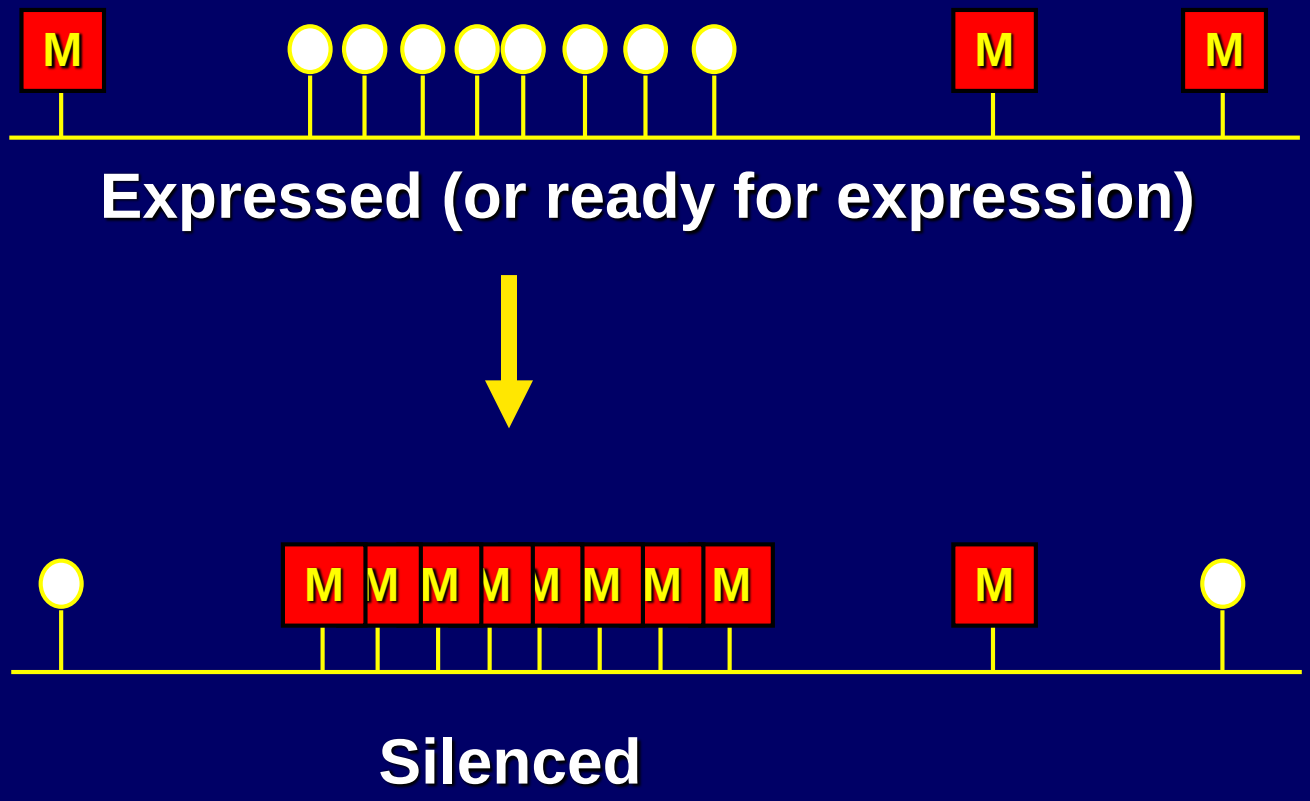
- Improve blood counts
- Decrease symptoms
- Improve quality of life

- Change natural history
- Prevent progression to AML
- Improve overall survival

Management of Higher-risk MDS

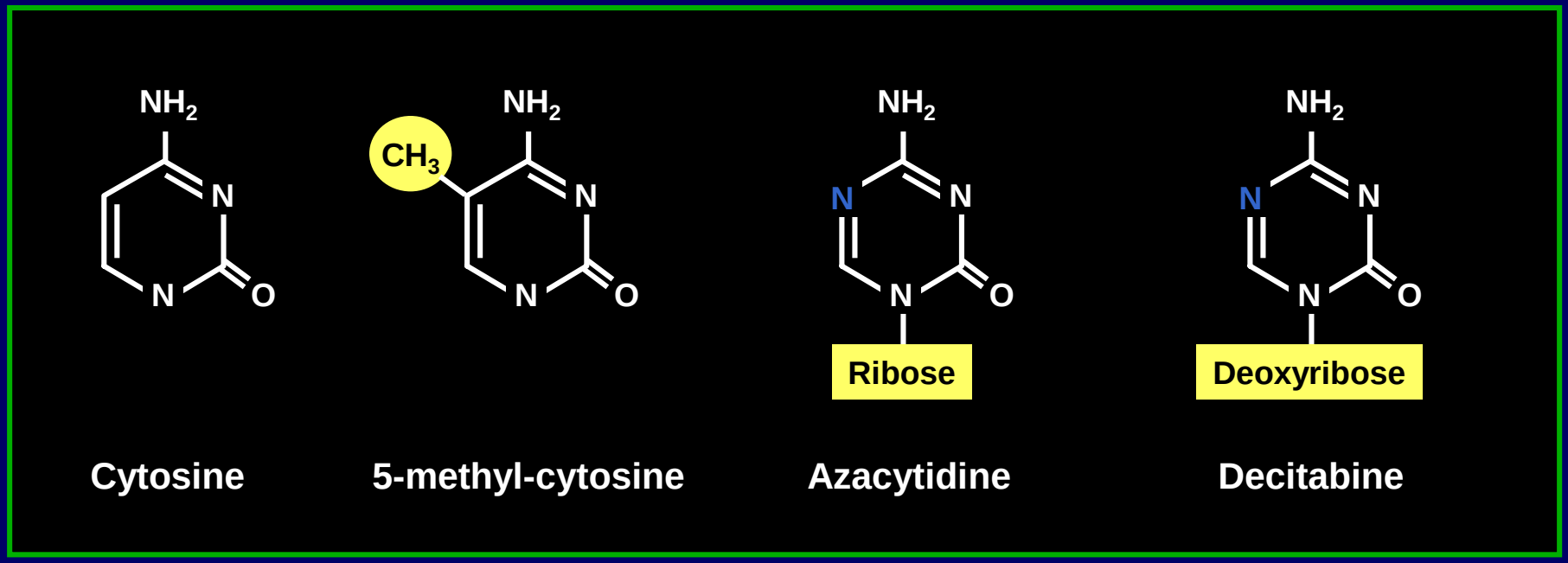


Gene hypermethylation in MDS



Adapted from of Issa, JP

Hypomethylating cytosine analogs



Santini V, Kantarjian, HM, Issa, JP. Ann Intern Med 2001, Apr 3;134(7):573-86.

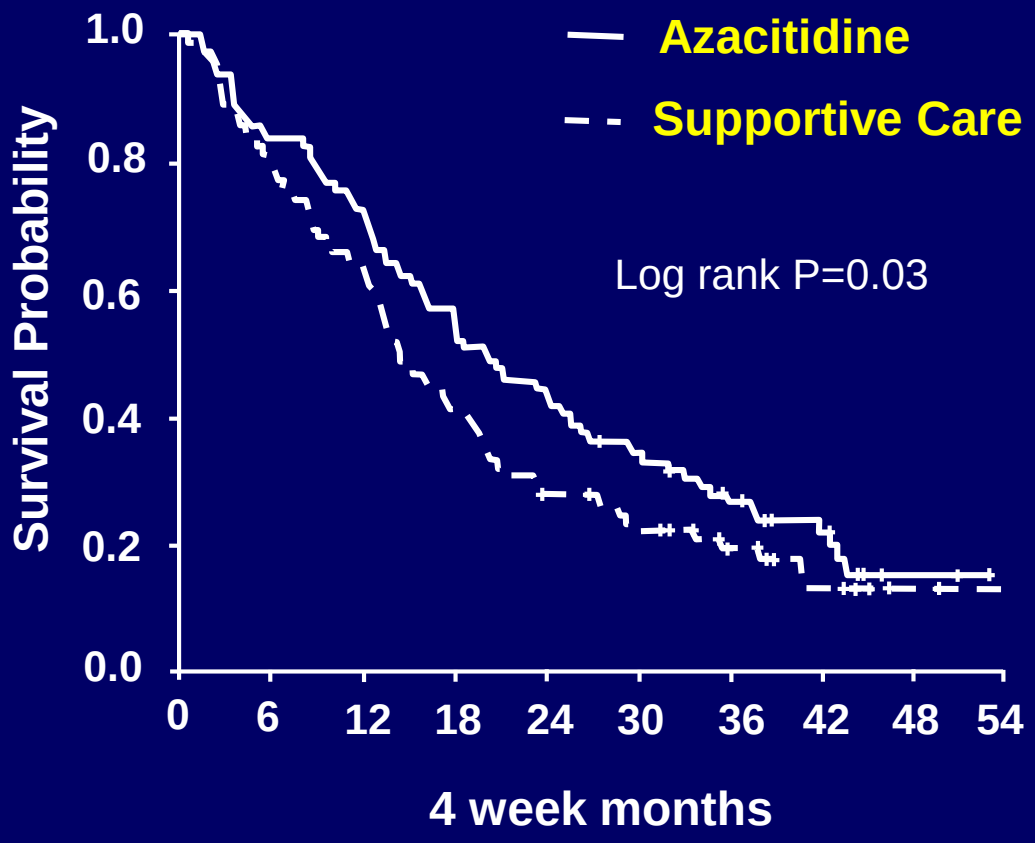
First randomized study of azacitidine in patients with MDS

75 mg/m^2/d SC x 7 days every 4 weeks

Responses (after 4 cycles)

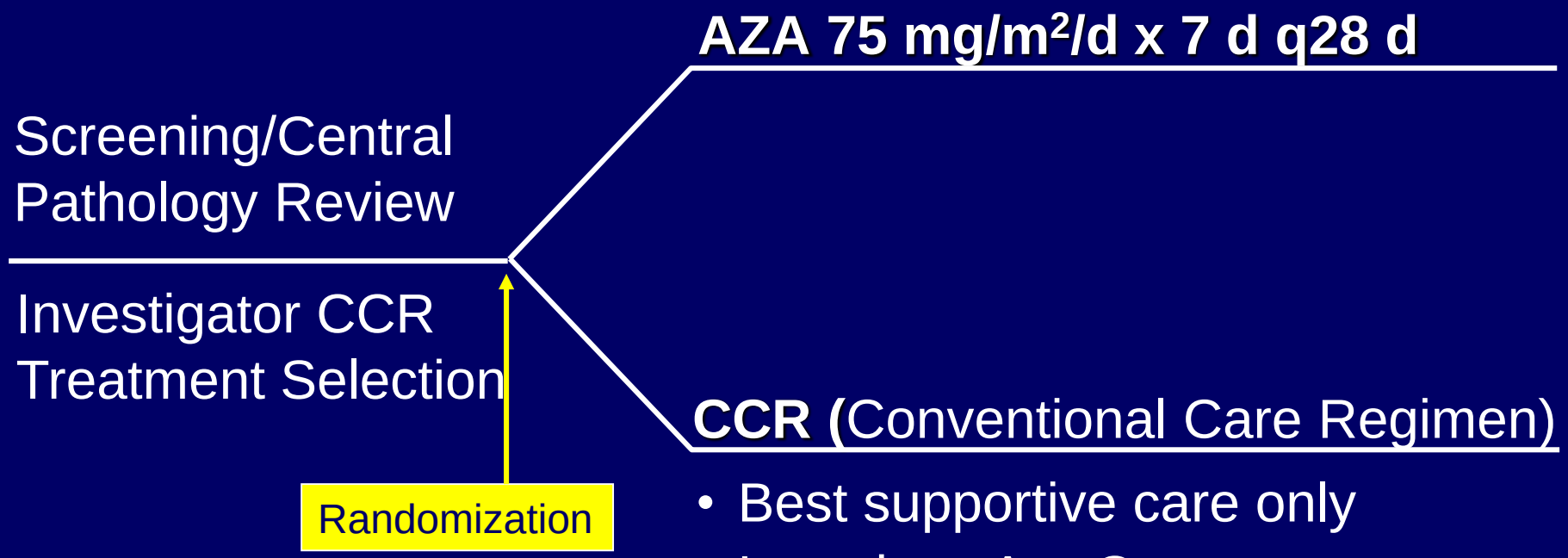
Complete remission - 7%
Partial remission - 16%
Improved - 37%

Total - 60%



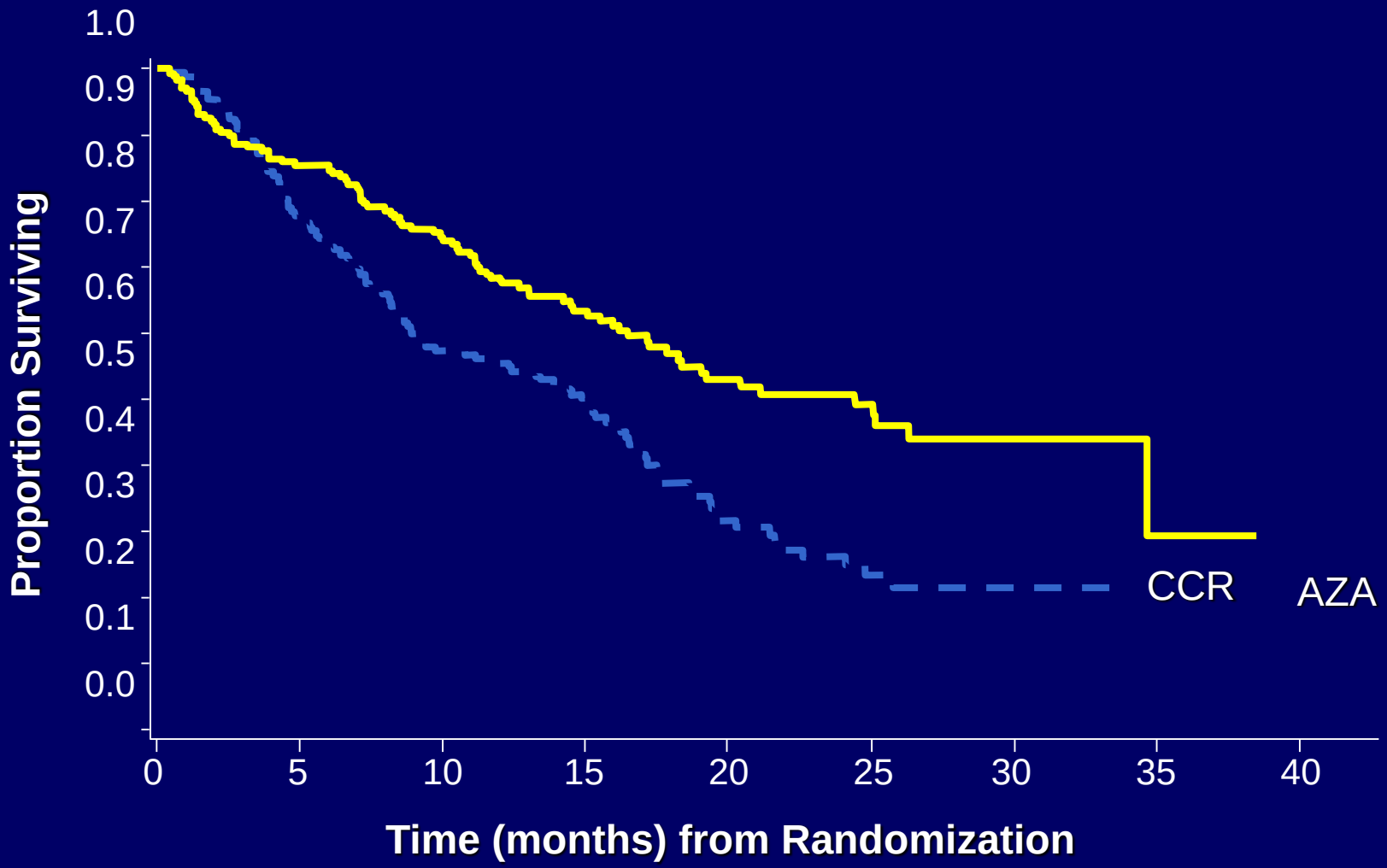
Silverman et al. *J Clin Oncol*. 2002;20:2429

Azacitidine survival study in higher-risk MDS



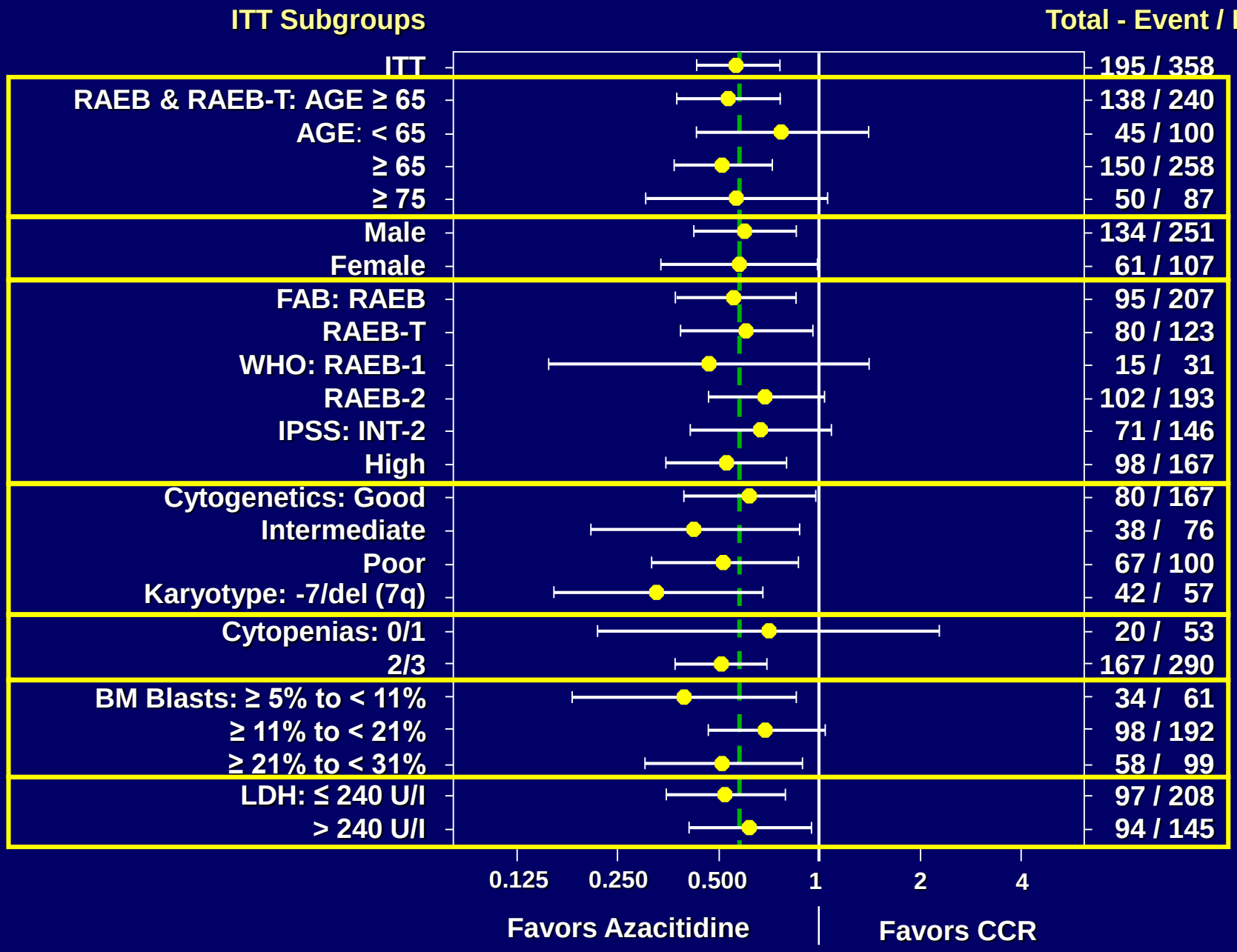
Fenaux P, et al. Lancet Onc 2009;10:223

Overall Survival in higher-risk: Azacitidine vs CCR



Fenaux P, et al. Lancet Onc 2009;10:223

Azacitidine survival benefit by disease categories



Azacitidine treatment

- Subcutaneous or intravenous injections daily for 7 [or 5(+2)] days every 28 days
- Median cycles to first response: 2-3
- Response may require 4-6 cycles
- Do NOT need a complete response for benefit
- Responders need to continue treatment to sustain response.

Decitabine- ADOPT study

- Decitabine 20 mg/m2 IV daily x for 5 days; 28-day cycles
- Overall response rate 32% (17% complete remission and 15% marrow complete remission)
- Overall improvement rate 51%, including 18% improvement in blood counts.
- Similar response rates in all risk categories.
- 82% of patients who improved showed responses by the end of cycle two.
- Survival advantage not yet demonstarted for decitabine, likely due to inferior study designs.

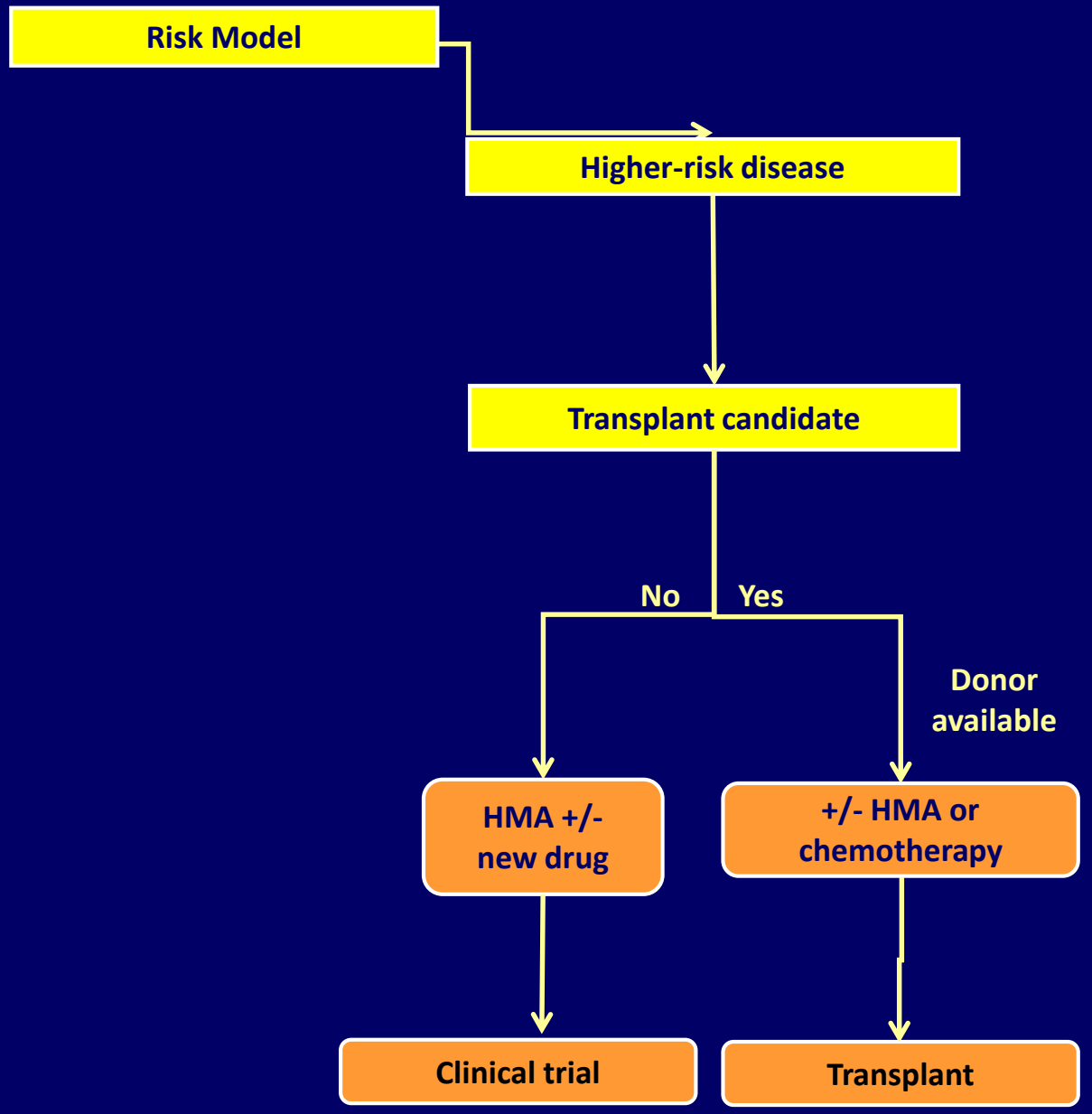
Steensma et al. J Clin Oncol 27:3842-8, 2009

Testing new treatments

- Test with azacitidine or decitabine to try to increase response rates and duration.

- Test in patients who do not respond to azacitidine or decitabine, or lose response to azacitidine or decitabine

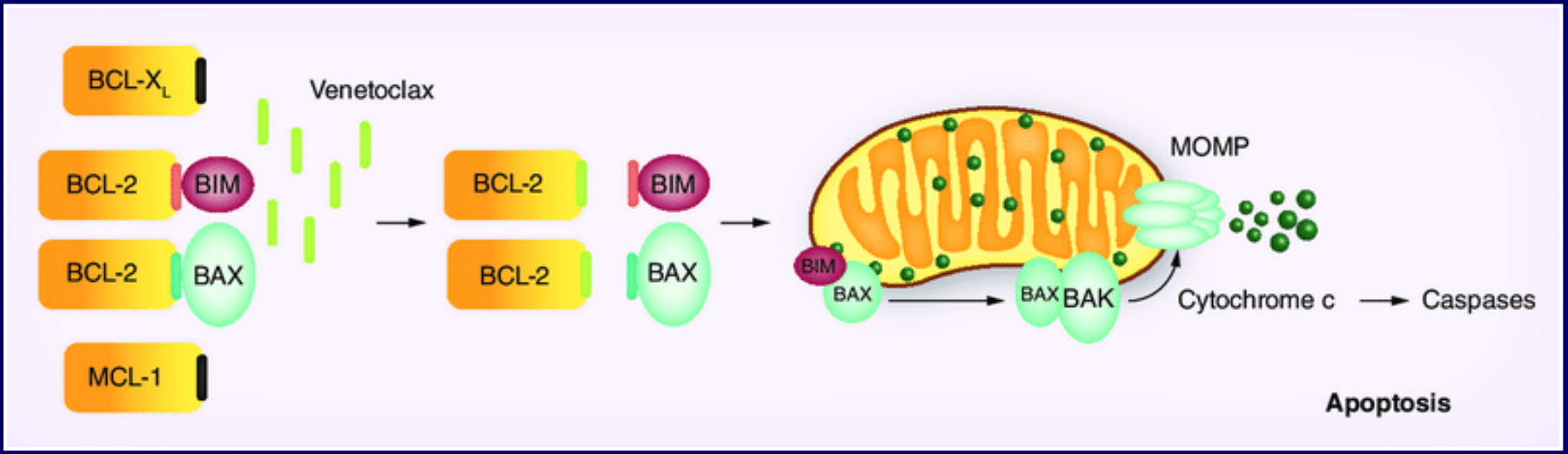
Management of Higher-risk MDS



New treatments for myelodysplastic syndromes

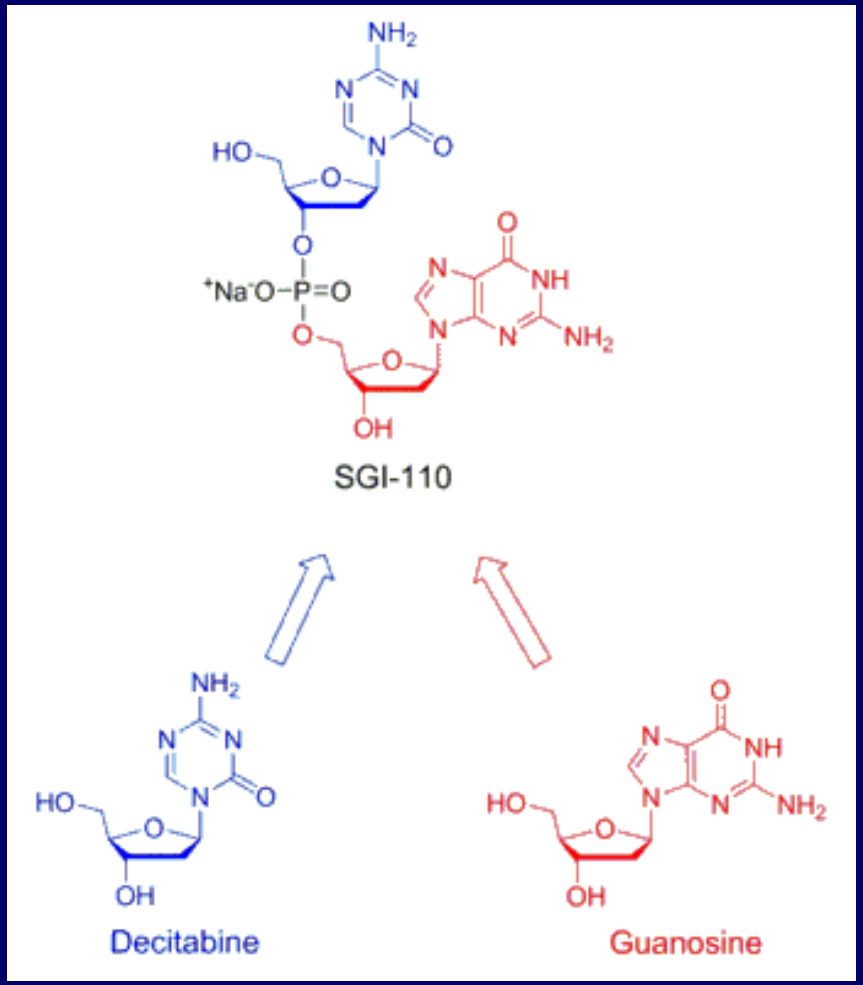
- Enhance programmed cell death
  -- Venetoclax
- New hypomethylating agent
  – Guadecitabine (SGI-110)
- Inhibit cell signaling
  – Rigosertib
- Inhibit mutation signaling
  – IDH1, IDH2
  – Spliceosome
- Immunotherapy
  – Atezolizumab
  – BITE antibody

Venetoclax



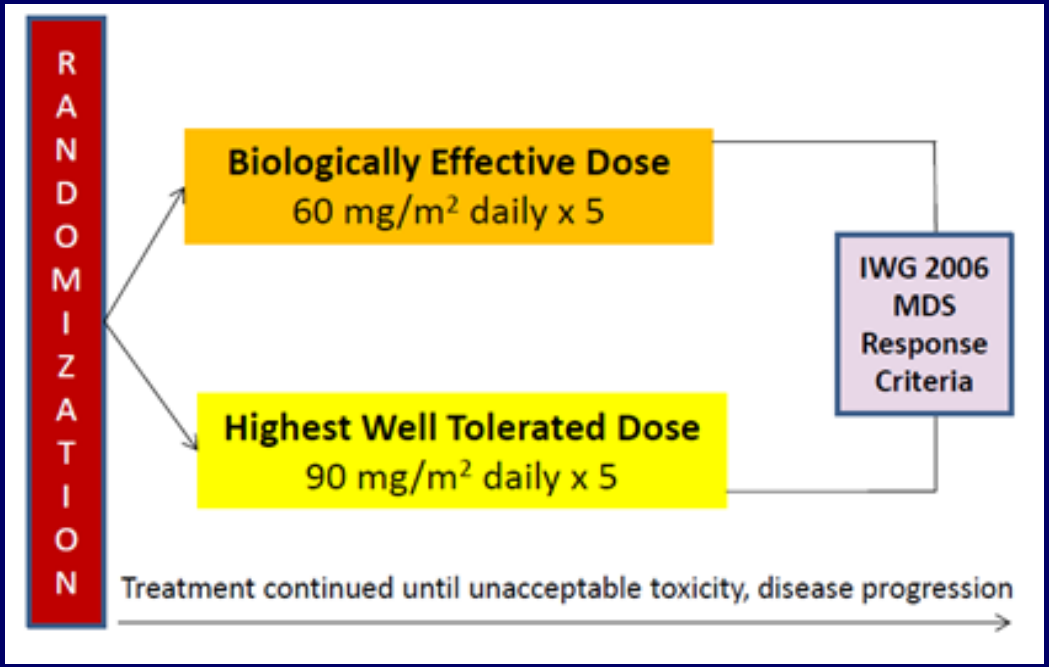
- Recently FDA-approved for use with azacitidine or decitabine in newly diagnosed AML patients who are older and/or unfit for chemotherapy, with significantly higher response rate.
- Clinical trial with azacitidine in higher-risk MDS – data analysis in progress.

Guadecitabine (SGI-110)



- Dinucleotide of decitabine and guanosine
- Longer half life
- Longer exposure
- Protection from degradation

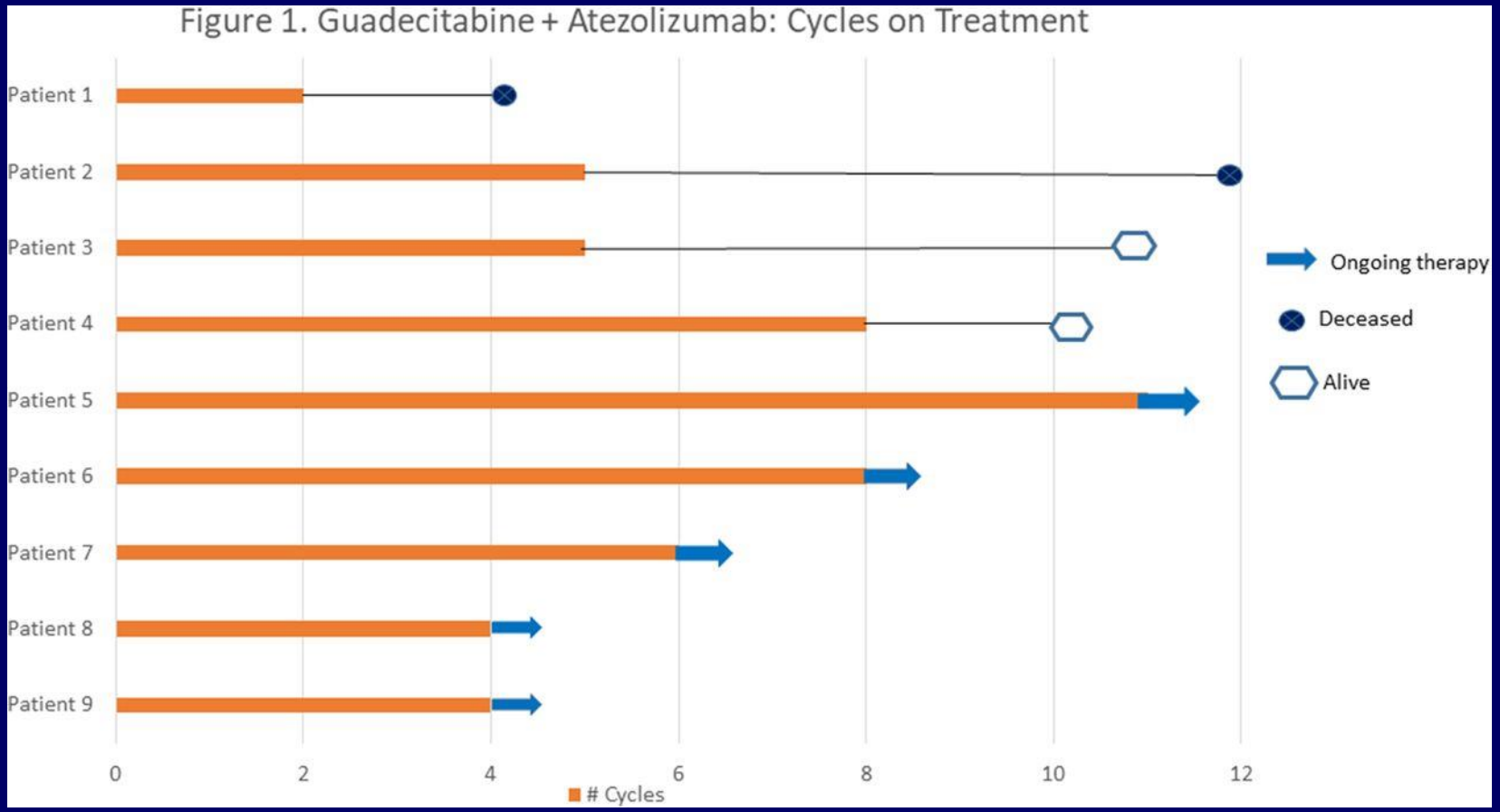
Guadecitabine – Higher-risk and previously treated



Response	Prev Treated (n=53)
CR	2 (3.8%)
Marrow CR	15/34 (44%)
HI	11 (20.8%)

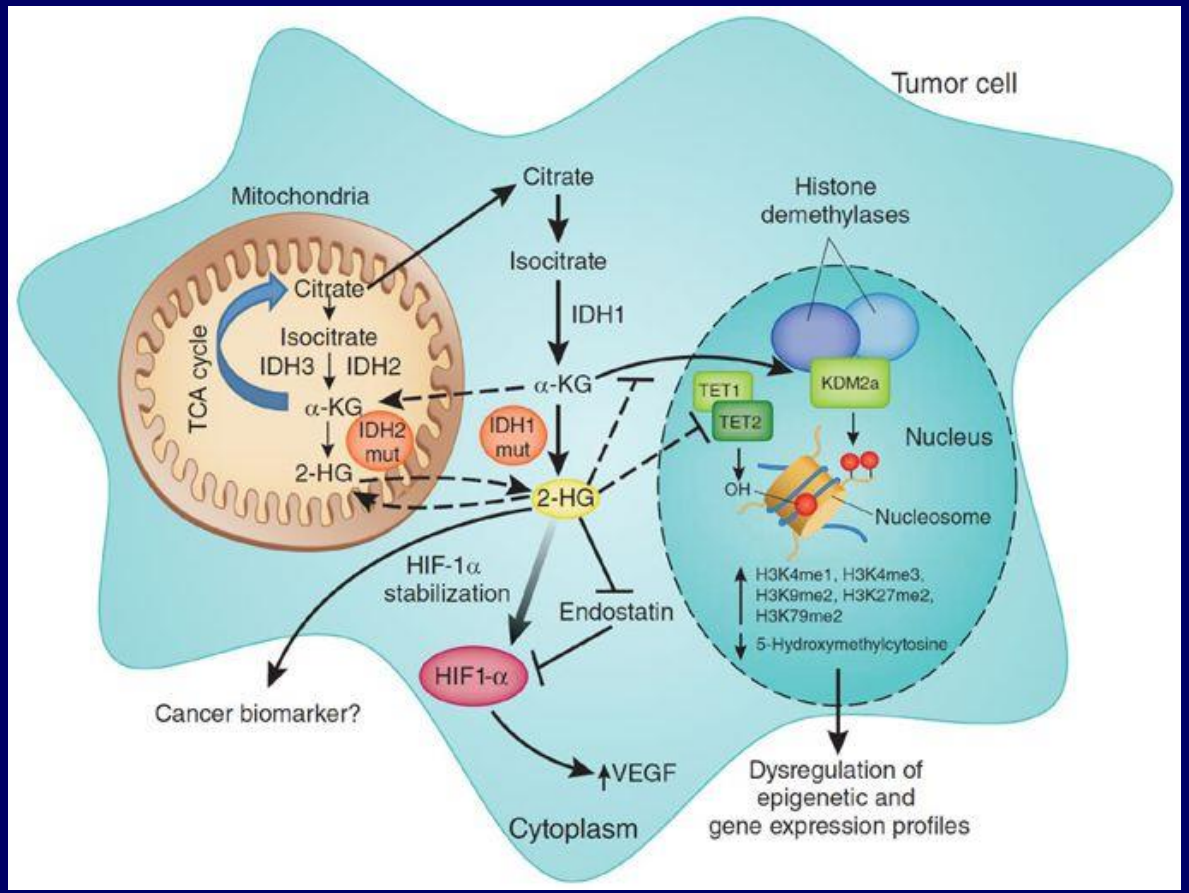
Garcia-Manero G, EHA 2016, Abstract P249

Guadecitabine and Atezolizumab following azacitidine/decitabine failure



O'Connell et al. ASH 2018

IDH Inhibitors



Ivosidenib (AG-120) Induced Durable Remissions and Transfusion Independence in Patients with IDH1-Mutant Relapsed or Refractory Myelodysplastic Syndrome: Results from a Phase 1 Dose Escalation and Expansion Study – DiNardo et al. ASH 2018

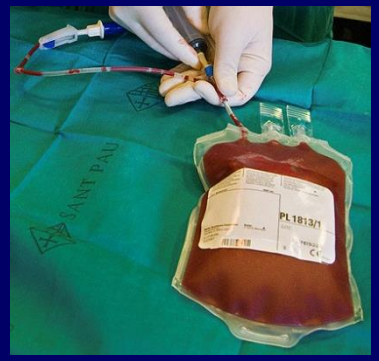
Allogeneic hematopoietic stem cell transplantation

- Only treatment currently known to be curative, but cure rate is <50%
- Has been applicable to only a minority of MDS patients because of age, other medical problems and donor availability, but non-myeloablative approach and alternative donors are increasing its applicability.

Allogeneic hematopoietic stem cell transplantation

- Procedure
  - High-dose chemotherapy/ radiation therapy
  - Transfusion of donor blood/ marrow stem cells
- Donor
  - Related - HLA-identical; haploidentical
  - Unrelated
- Sources
  - Bone marrow
  - Peripheral blood
- Conditioning
  - Myeloablative
  - Non-myeloablative
- Immunologic effects
  - Graft vs. leukemia
  - Graft vs. host

Bone marrow harvest

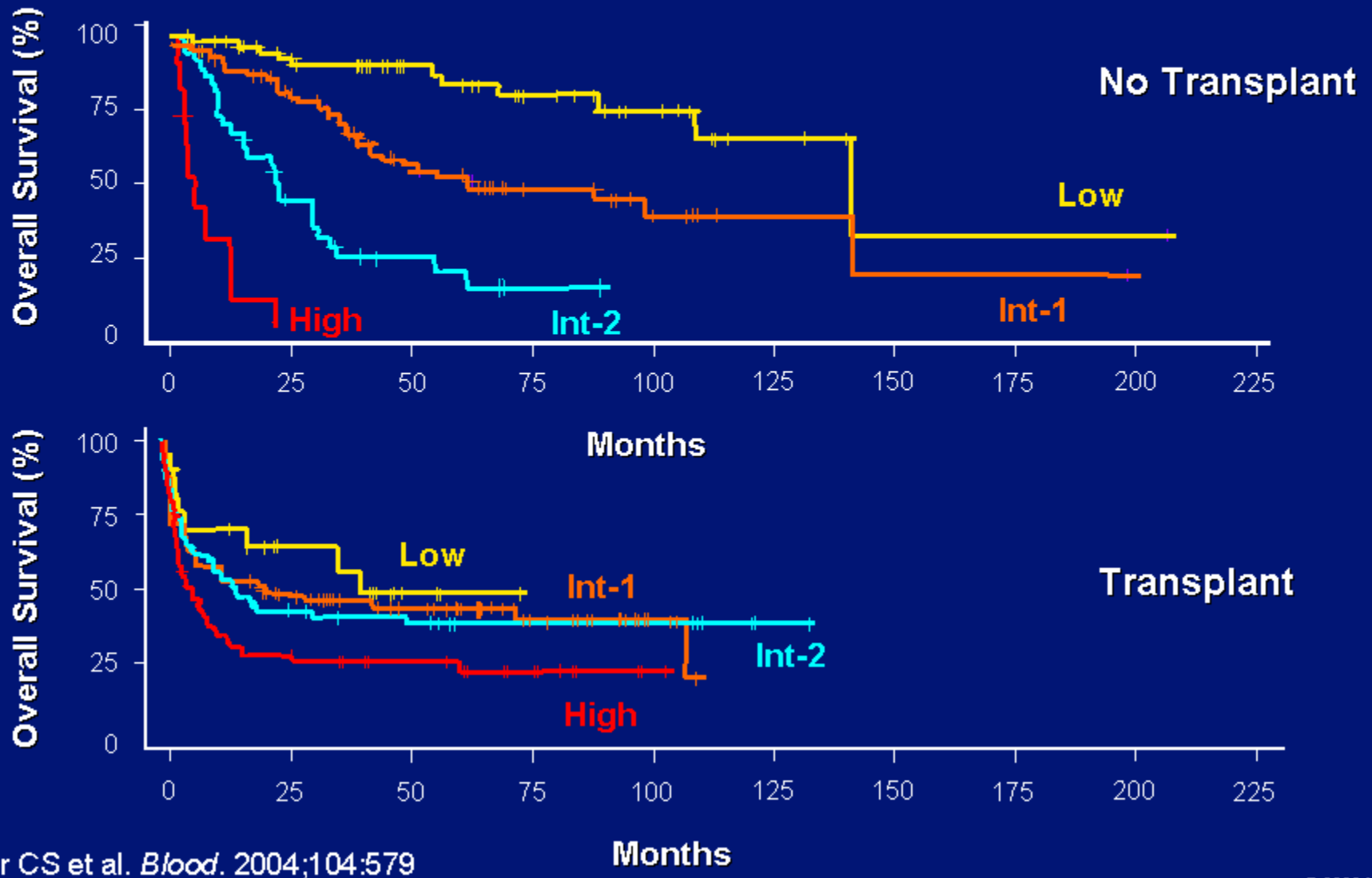


Leukapheresis

Allogeneic hematopoietic stem cell transplantation outcomes

- Acute complications
- Chronic complications
- Relapse
- Cure

Survival by IPSS risk in patients who did or did not undergo transplantation



Cutler CS et al. *Blood*. 2004;104:579

Transplant decision

- Disease
  - Risk status
  - Chromosomes
  - Mutations
- Donor
  - Matched sibling
  - Matched unrelated donor
  - Half-matched related donor
- Patient
  - Age
  - Medical problems
  - “Performance status”
  - Support system
  - Personal choice

Myelodysplastic syndromes

- Treatable, and treatments change the course of disease.
- Treatment approach depends on presentation.
- Transplant can cure, but indication depends on presentation and on patient-specific factors.
- FDA-approved treatments, all approved in the last 15 years based on recent clinical trials
- Promising new drugs based on new biological insights
- Ongoing importance of clinical trials!!!