Haematological malignancies proffered papers discussion abstracts 2850 and 2860

Michele Ghielmini

Oncology Institute of Southern Switzerland

Bellinzona, Switzerland

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Disclosure slide

Roche
Cellgene
Mundipharma
Janssen

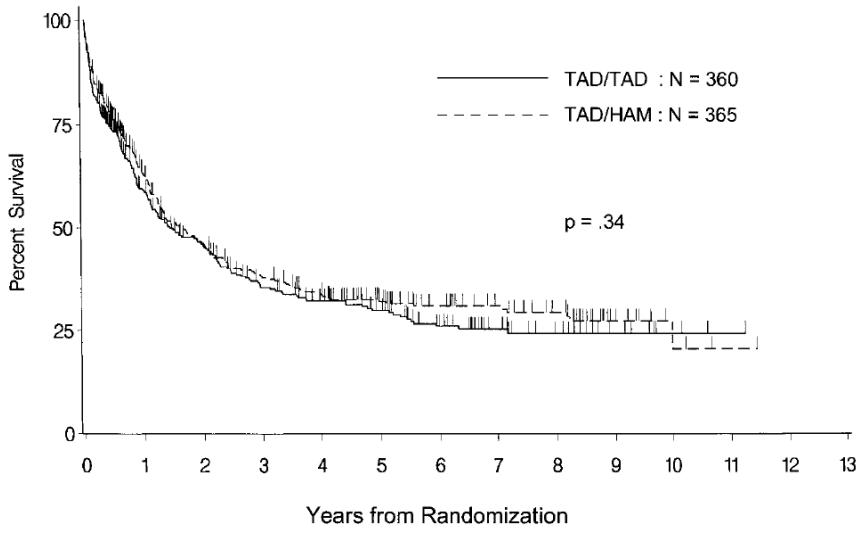
Gilead
Bayer
Millenium
Servier

High-dose vs. low-dose Ara-C in AML is a recurrent question

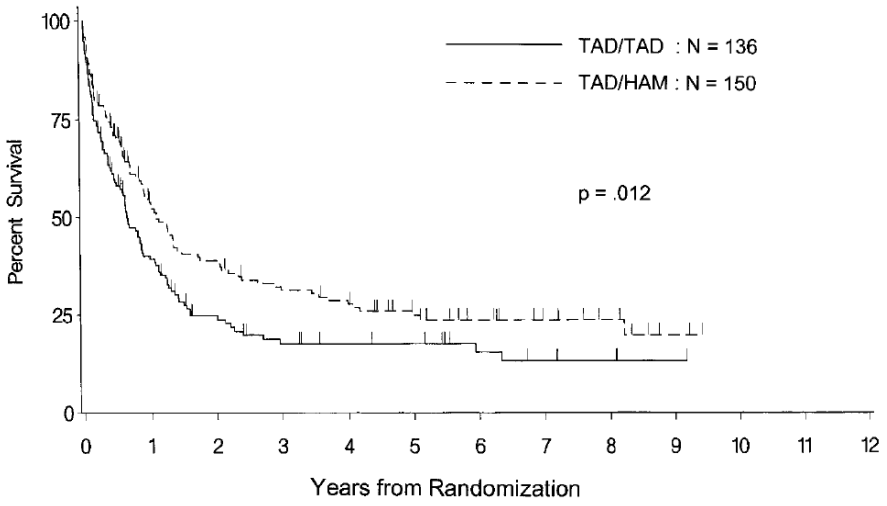
n = 725 Double induction without (TAD/TAD) or with HD AraC (18 g/m2)

OS

All patients



High-risk patients



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Büchner et al, Blood 1999

Consolidation after HD Ara-C induction

n = 202 , ICE induction , consolidation with either ICE (AraC 24 g/m2) or IcE (0.5 g/m2)

OS all patients

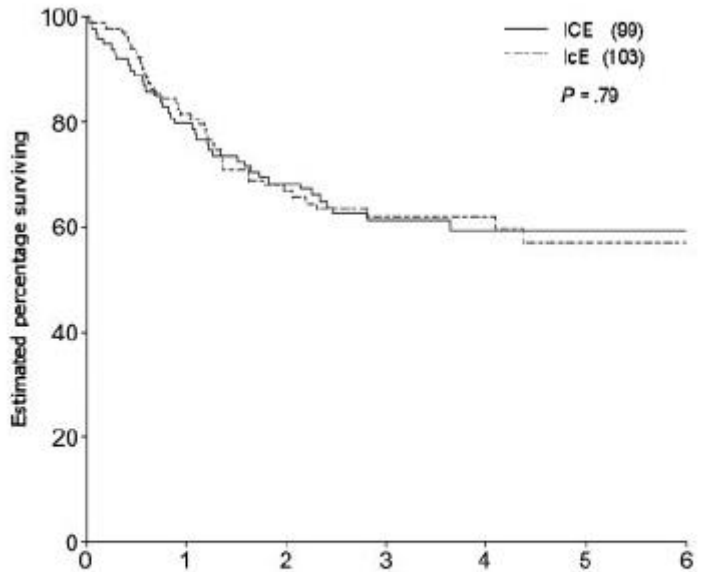
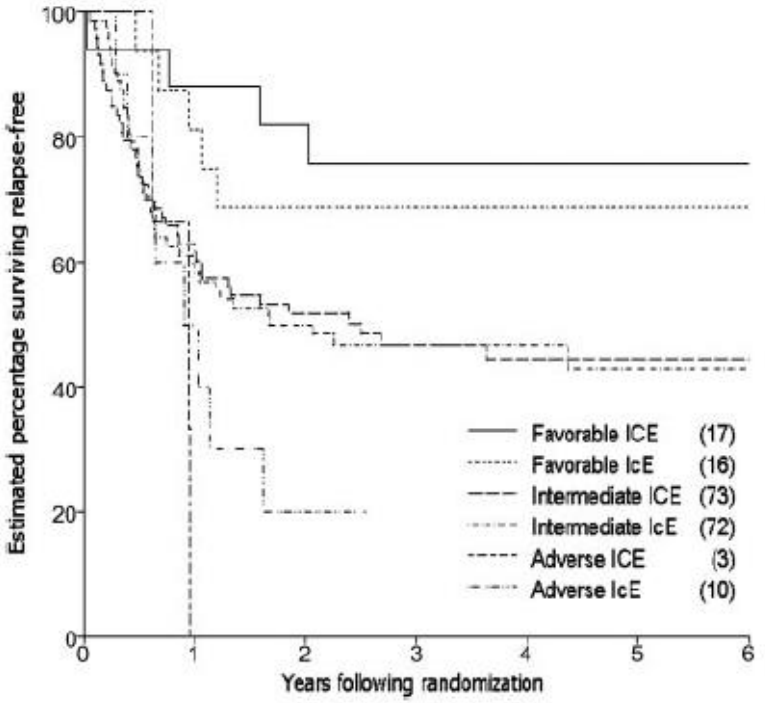


Figure 4. Survival following consolidation randomization.

PFS by risk



Bradstock et al, Blood 2005

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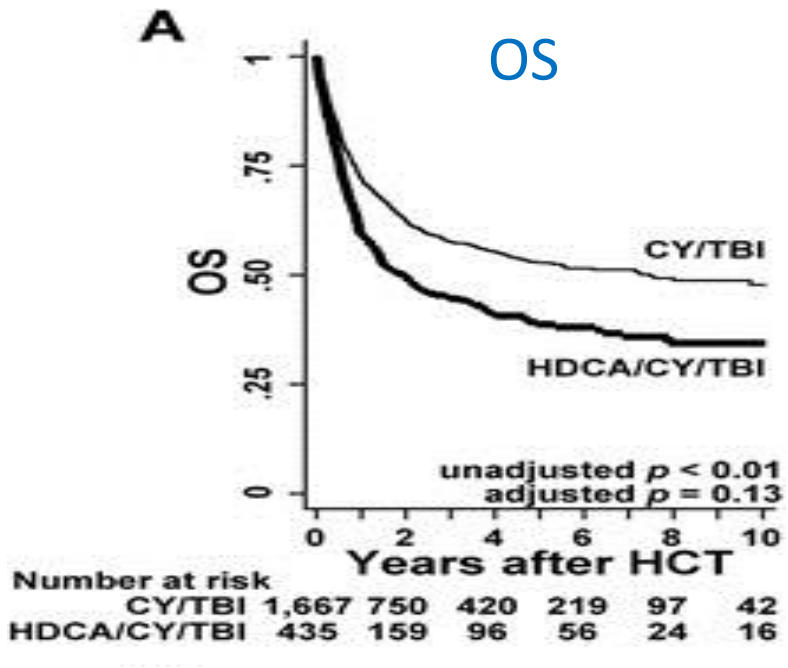
HD Ara-C to intensify conditioning



Japanese allo-transplant registry

CY-TBI	1’667
HD AC/Cy-TBI	435

Arai et al, J. Hematol. Oncol. 2015

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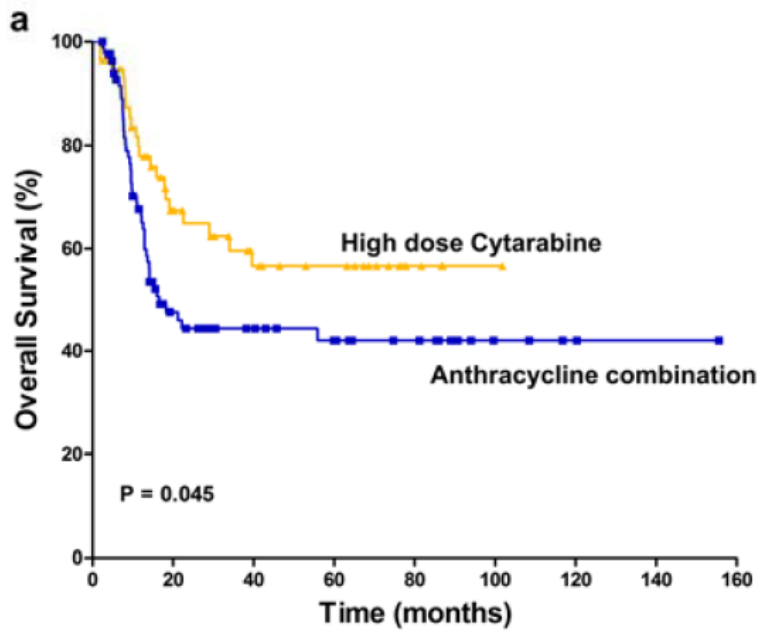
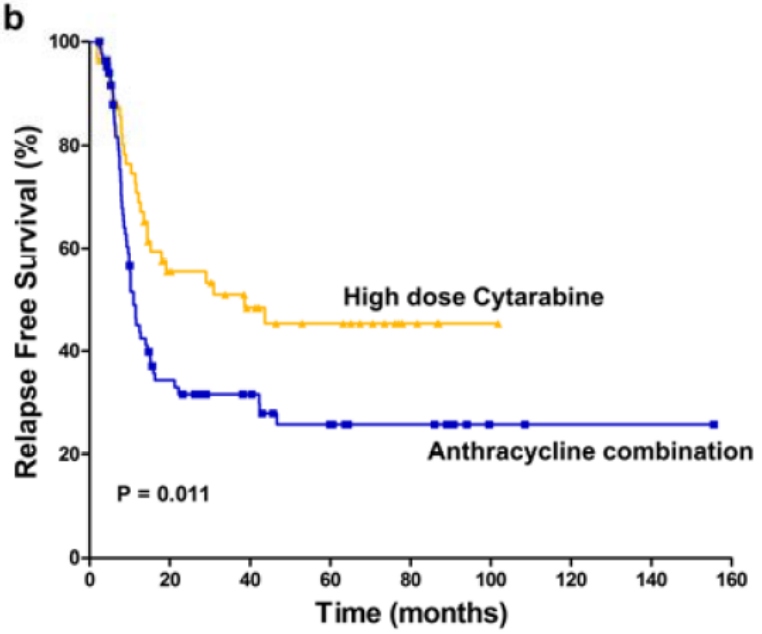
Consolidation with HD Ara-C (3 g/m^2) or iD Ara-C (1 g/m^2) + Anthracycline





Korean registry

HD Ara-C	58
iD Ara-C/Anthra	87

Kim et al, Ann Hematol 2015

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The present study

- Population: children and adults
- Sample size: 170 recruited, 90 analyzed, 79 completed treatment
- Toxicity: comparable
- Design: standard induction (7+3), consolidation HD vs. iD Ara-C (both doses are high!)
- Relapse rate: high in both arms (55% vs. 51%)
- OS: significantly better for 18 g/m^2

How to interpret the present study

- Response rate and response duration similar
- Survival different
- Too early, interim analysis only
- No sufficient power as yet to draw any conclusion

Myelodysplastic Syndromes (MDS)

- Heterogeneous disorders of hemopoietic stem cells
- Causes ineffective hemopoiesis
- Increased risk of transformation to AML

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Pathogenesis of MDS

MDS are associated with:

- Genetic alterations (→ epigenetic)
- Repression of apoptosis
- Deregulation of the microenvironment

Epigenetics

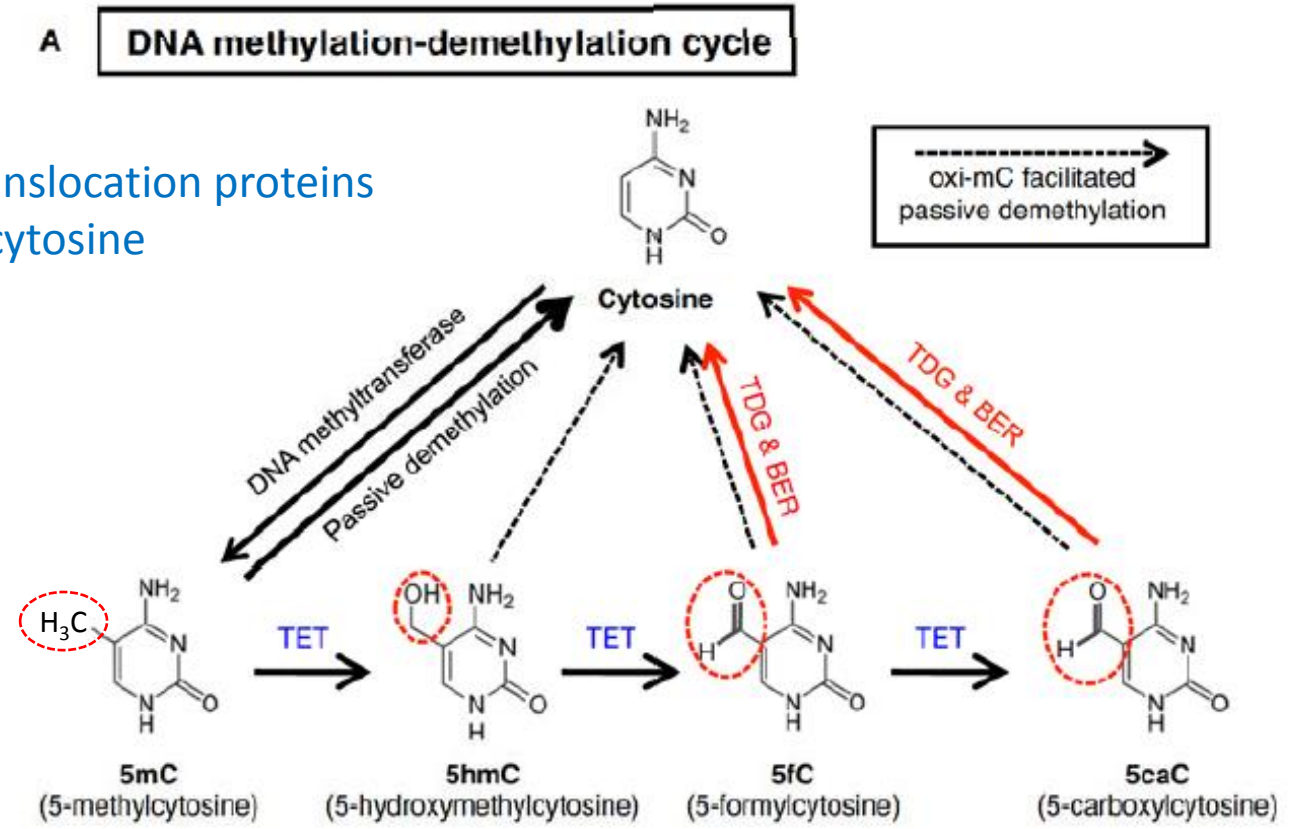
«Changes in gene expression that are not due to alterations in DNA sequence”

Holliday, Science, 1987

- DNA methylation
- Histone modification
- RNA interference (mostly due to micro-RNA)

DNA methylation / demethylation

TET = Ten-Eleven-Translocation proteins
Demethylate cytosine



Ko et al, Immunol. reviews 2015

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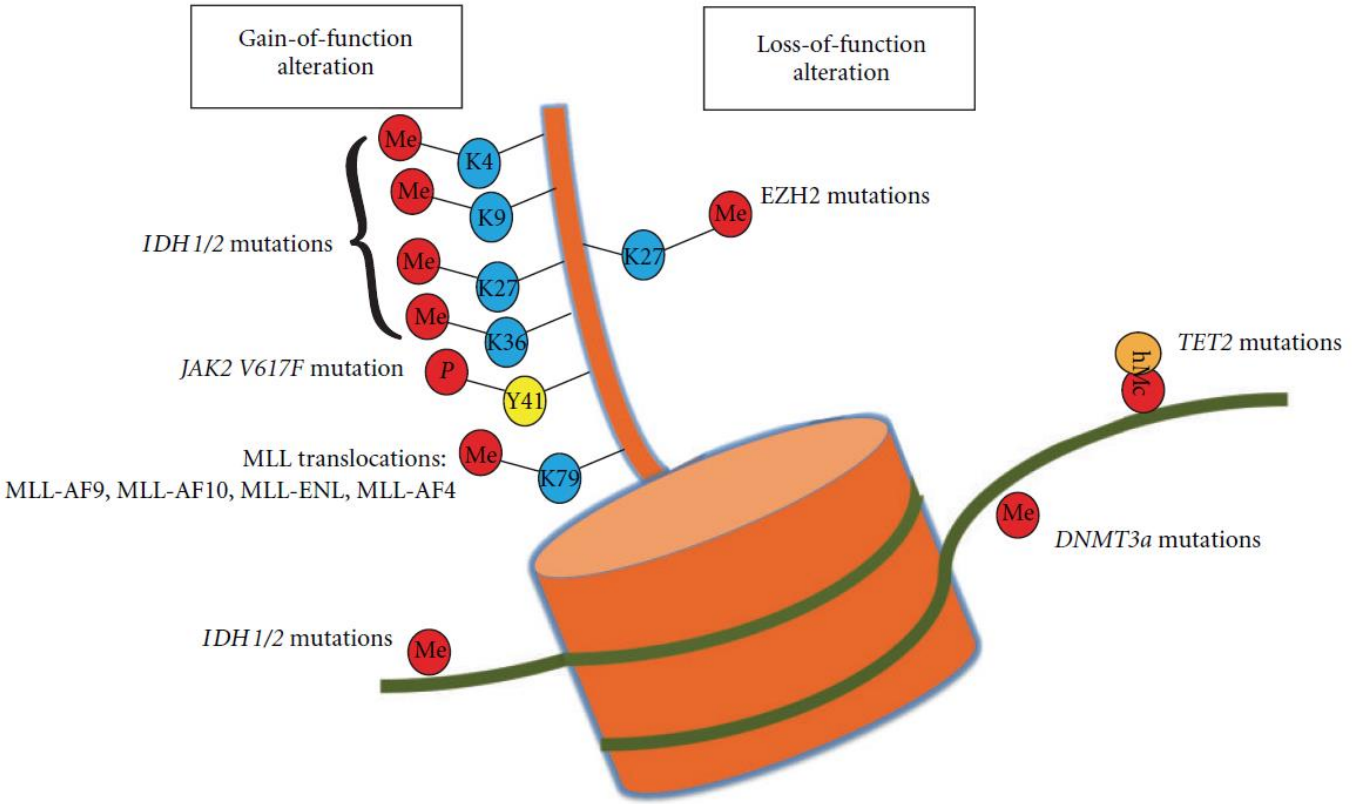
Epigenetic modifications in hematological malignancies

The mutation of some genes causes methylation or hypomethylation of potentially leukemogenic genes or change of the histone function



Fathi et al, Adv. in Hematol. 2012

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DNA methyltransferase inhibitors and MDS

Azacitidine
Decitabine

Inhibit methyltransferase → Cytosine not methylated (DNA hypomethylation) → MDS reversed

RR in MDS: 20-40%

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Prognostic factors for response

93 patients with MDS treated with azacitidine

Mutations detected	SF3B1	59/86
	TET2	29/87
	DNMT3A	12/87
	ASXL1	5/89
	JAK2	3/87

None predicted response to azacitidine

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Thepot et al, ASH 2013

The present study

- 70 newly diagnosed MDS
  treated with 5 days decitabine
- RR 52.5%
  responders survive longer
- 17% mutation in methylating machinery genes
- RR mutated 83%
  non mutated 43%

How to interpret the present study

- Demethylating agents confirm to have a (modest) activity in MDS
- This activity is (possibly) higher in the presence of mutations in genes involved with the epigenetic machinery
- The predictive role of these gene mutations must be confirmed by further studies