THE UNIVERSITY OF CHICAGO MEDICINE

# Differences between Secondary Leukemia and Therapy-related Leukemia

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# Differences between Secondary Leukemia and Therapy-related Leukemia

Is this just a matter of definitions?

FIFTH

INTERNATIONAL SYMPOSIUM ON SECONDARY LEUKEMIA AND LEUKEMOGENESIS

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## Disclosures of Richard A. Larson, MD

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| Ariad | | | | | | | DSMB |
| Astellas | X | | | | | | |
| BristolMyers | | | | | | | DSMB |
| Celgene | X | | X | | | | DSMB |
| CVS | | | X | | | | |
| Daiichi Sankyo | X | | | | | | |
| Erytech | X | | X | | | | |
| Novartis | X | | X | | | | |
| Pfizer | | | X | | | | |

# Secondary leukemia & t-MN

- Do these syndromes have distinct clinical features?
- Does it matter?
- What are the features that overlap?

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- Do these syndromes have distinct clinical features?
- Does it matter?
- What are the features that overlap?
- Moving from morphology to genetic subclassification for better treatment decisions.

# Secondary leukemia & t-MN


All roads lead to Rome.

# What does WHO mean that t-MN is a distinct entity?

- WHO combines patients with morphologic features of MDS, MDS/MPN, and AML.
- Any patient who has previously received a DNA-damaging agent for a previous non-myeloid disorder.
- No arbitrary limits on the duration or intensity of exposure.
- No minimum or maximum limits on the latency period.

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- No arbitrary limits on the duration or intensity of exposure.
- No minimum or maximum limits on the latency period.
- Since t-MN overlaps with primary myeloid neoplasms, these patients should be treated according to their cytogenetic and molecular features and clinical risk factors (ideally on front-line clinical trials).

# Why retain therapy-related myeloid neoplasms as a distinct subgroup?

- To highlight an increasingly common, late complication of cytotoxic chemotherapy and radiation.
- To learn about the effect of mutagenic exposures on humans.
- To identify patients at risk and monitor them for early intervention.
- To discover the pathways of leukemogenesis that will likely apply to primary MDS and *de novo* AML as well as to t-MN.

# Areas of confusion and debate in defining “therapy-related” myeloid neoplasms

- What exposures are leukemogenic?
- Is there a minimum dose or exposure required to be leukemogenic?
- Is there a minimum latency? How quickly can leukemia develop after exposure?
- Is there a maximum latency? When does the risk of leukemia drop to the population baseline?

# Which exposures are leukemogenic?

- Alkylating agents
- Topoisomerase II inhibitors
  - Doxorubicin, etoposide, teniposide, mitoxantrone, actinomycin D
- Antimetabolites
  - Thiopurines (azathioprine, mercaptopurine, thioguanine)
  - Mycophenolate mofetil
  - Fludarabine
- Radiotherapy
  - Large fields containing active marrow; low doses
- Autologous hematopoietic stem cell transplantation
  - Genotoxic and proliferative stress

# Are these exposures also leukemogenic?

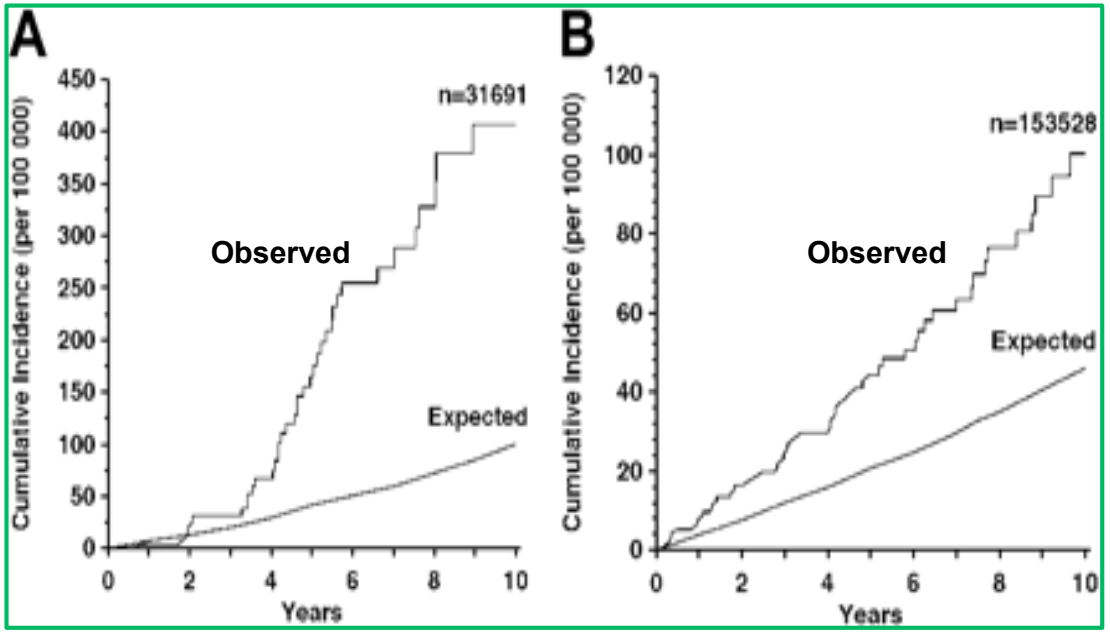
- Other chemotherapy agents
  - Hydroxyurea, vinca alkaloids, L-asparaginase, interferon
  - Methotrexate
  - Radio-isotopes ($^{131}$I, $^{32}$P, Bexxar, Strontium-89)
- Hematopoietic growth factors
  - G-CSF (severe congenital neutropenia; adjuvant chemotherapy)
  - Androgens
- Environmental exposures
  - Smoking
  - Benzene-associated hematotoxicity
  - Radiation accidents (Chernobyl); Radon gas
  - Cosmic rays (commercial jet pilots; astronauts)
  - Diet (flavanoids)
  - Electromagnetic fields

# Therapy-related myeloid neoplasms after only methotrexate exposure

| Age/ Sex | Primary disease | Dysplasia | BM Cellularity | BM Blasts | Cytogenetics | Survival |
|---|---|---|---|---|---|---|
| 78F | RA | Mega | 30% | 2% | del(11)(q23q25) | 20+ mos |
| 63F | SLE | Trilineage | 80% | 14% | del(5q),-7,t(12;17) | 3 mos |
| 86F | RA | Trilineage | 70% | 22% | del(5q),-7 | 4 mos |
| 66M | RA | Gran; Mega | 60% | 6% | 46,XY → -7 | 20+ mos |
| 51F | RA, SLE | Gran; Mega | 70% | 10-22% | 46,XX | 7 mos |
| 58M | Psoriasis | Gran; Mega | 80% | 55% | +8 | 14 mos |
| 67F | RA | Gran; Mega | 75% | 35% | Complex | 18 mos |
| 58F | RA | Trilineage | 50% | 5% | +8 | 2+ mos |
| 72F | RA | Ery; Mega | 70% | 13% | 46,XX | 1+ mos |

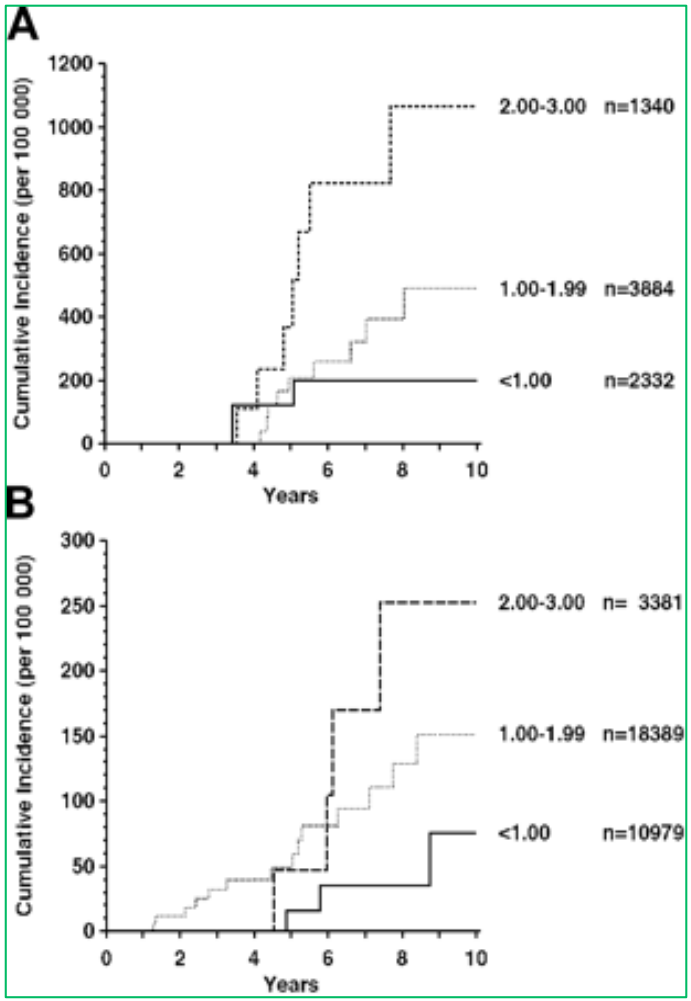
Data provided by Dr. John Anastasi, University of Chicago

# Therapy-related myeloid leukemia after solid organ transplantation




(A) Heart, lung or both; (B) Cadaver kidney.
Incidence of t-AML vs age, sex,
& location matched controls.

**Thiopurines select for mismatch repair-deficient clones.**



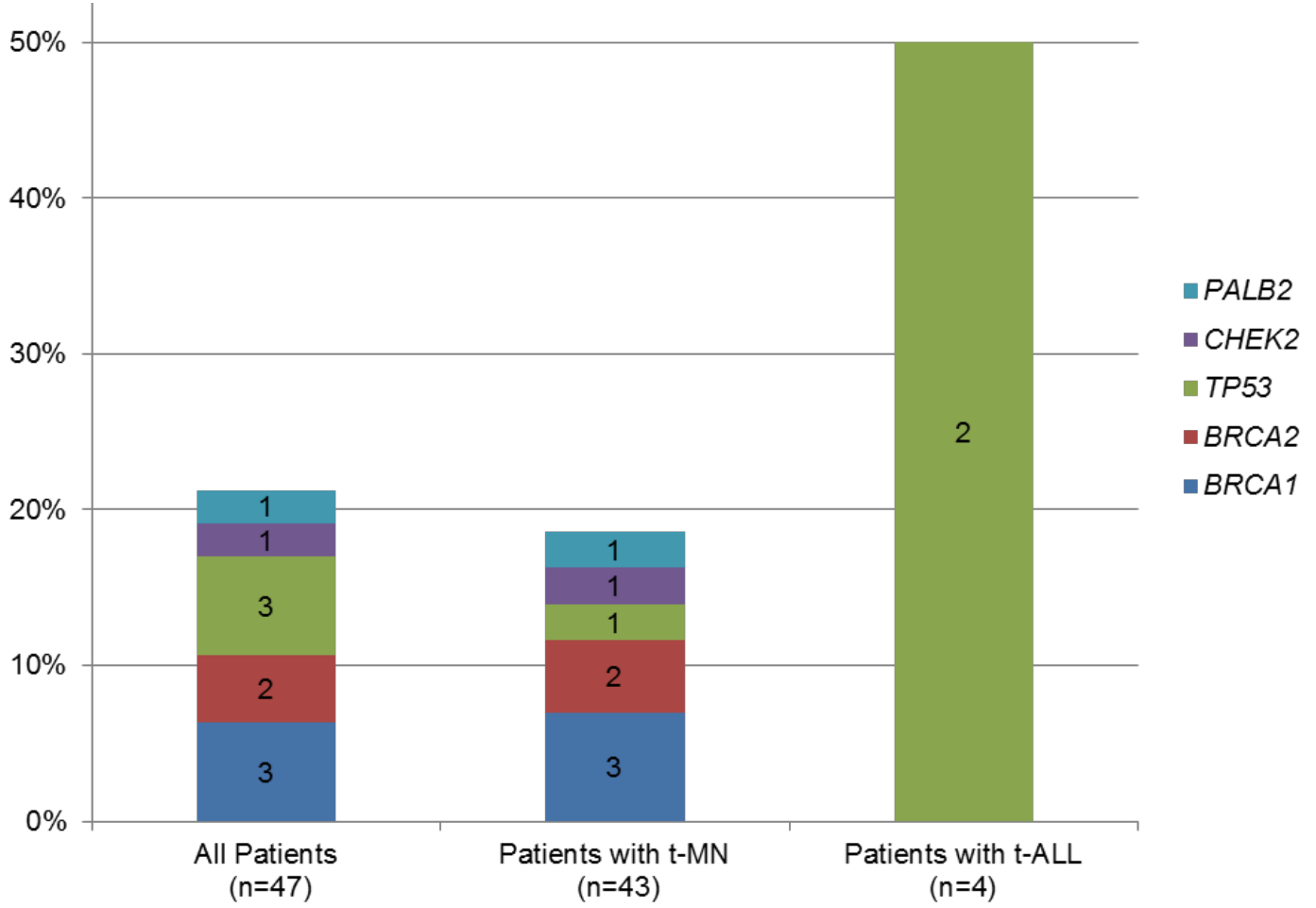

Azathioprine doses (mg/kg/d)
given during the first year post-transplant



Offman et al. Blood 2004; 104: 822

# Inherited mutations in breast cancer susceptibility genes

47 patients with therapy-related leukemia after treatment for breast cancer



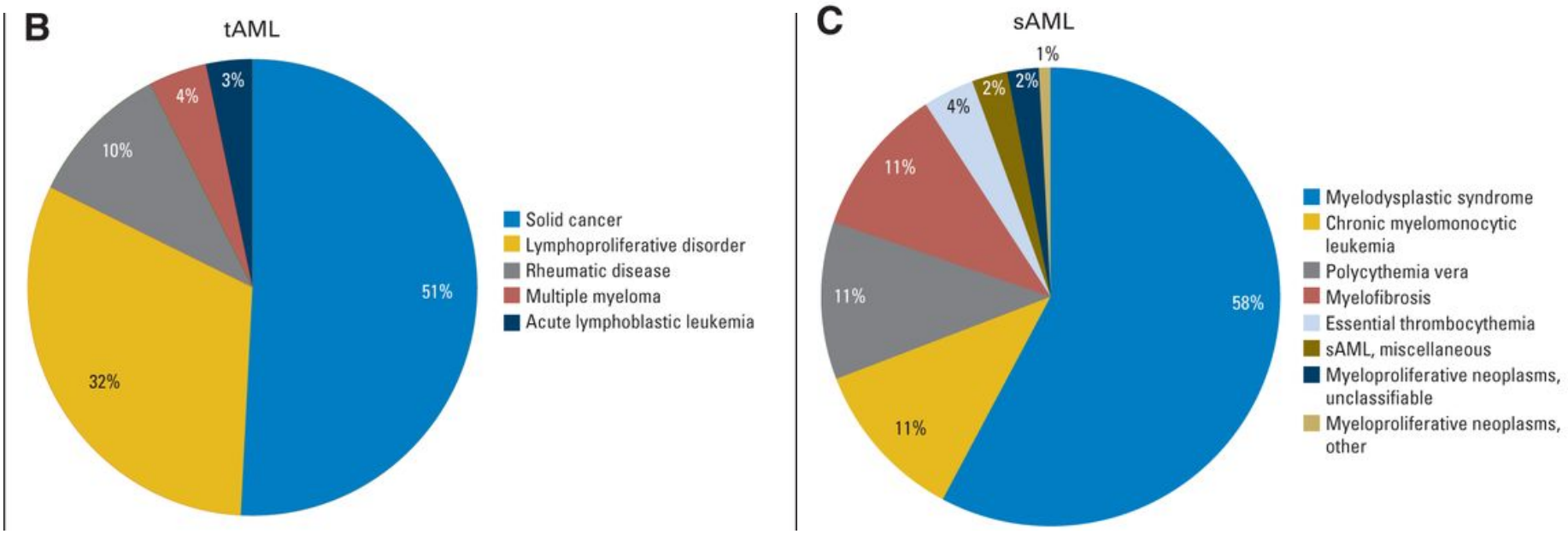

Churpek et al. Cancer 2016; 122: 304

# What is “Secondary” Leukemia?

- AML that follows previously diagnosed MDS
- AML with myelodysplasia-related changes
- AML that follows a myelodysplastic/myeloproliferative disorder, such as CMML
- Terminal blast phase of primary myelofibrosis or other myeloproliferative neoplasm (but not CML)
- AML that follows aplastic anemia or other antecedent hematologic disorder
- AML that follows chemo-radiotherapy (i.e., t-MN) or occupational exposures (e.g. benzene)

# Danish National Population-based Study

## (2000-2013: 2249 patients had *de novo* AML)



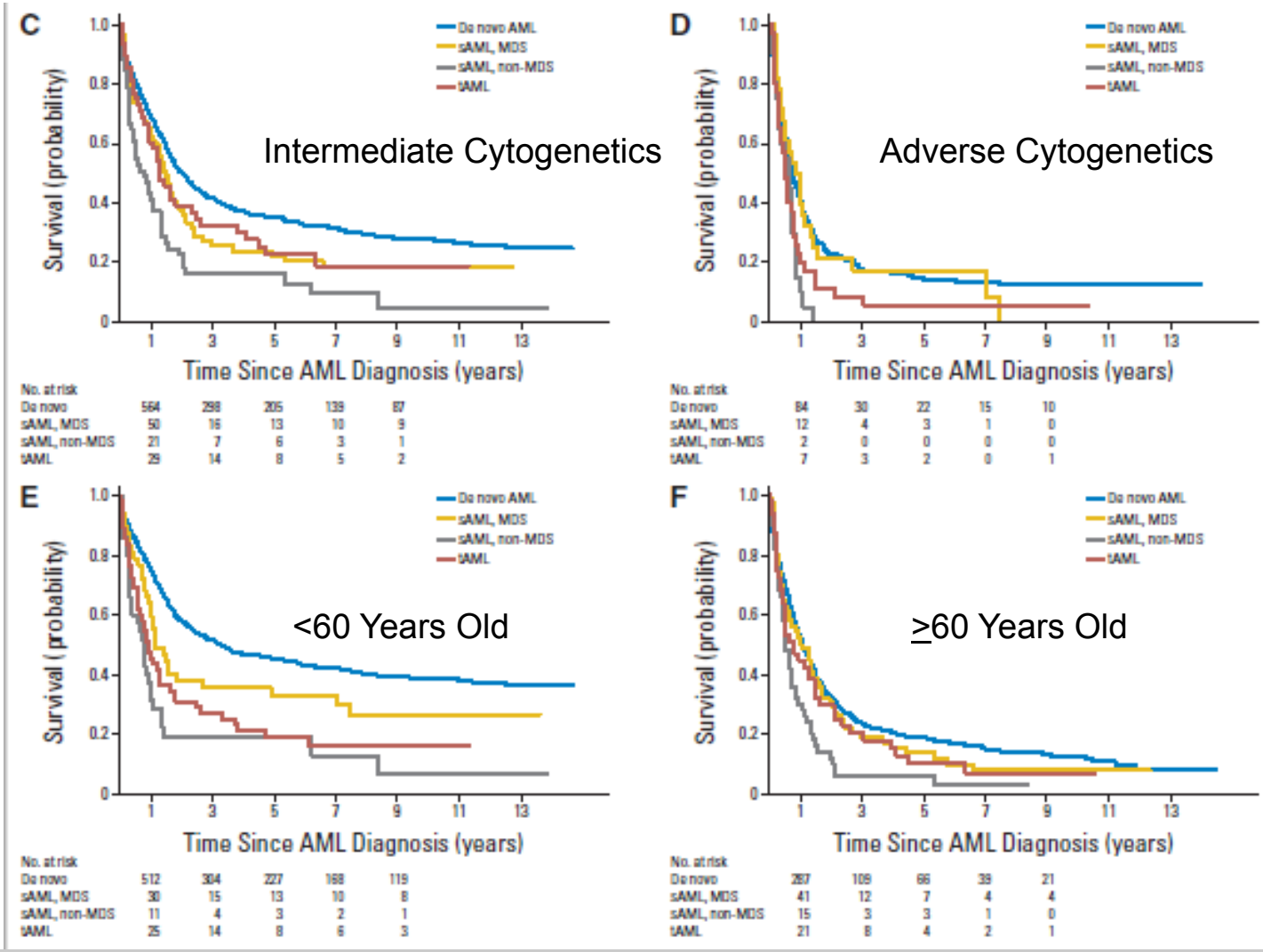

t-AML
N=203

Secondary AML
N= 603



Ostgard et al. J Clin Oncol 2015; 33: 3641

# Danish National Population-based Study: Survival after intensive therapy

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# UK's population-based Haematological Malignancy Research network 2004-2015

| Malignancy | No. of patients | Median age (yrs) | Incidence/ 100,000 | 5-Yr Survival |
|---|---|---|---|---|
| All AML: | 1411 | 71 | 4.39 | 15% |
| AML with Myelodysplasia-related changes | 197 | 77 | 0.61 | 3% |
| t-AML | 61 | 72 | 0.19 | 3% |
| All MDS: | 1194 | 76 | 3.72 | 28% |
| MDS with Excess Blasts | 458 | 75 | 1.43 | 10% |
| MDS/MPN | 296 | 77 | 0.92 | 17% |

Roman et al. Cancer Epidemiol 2016; 42:186

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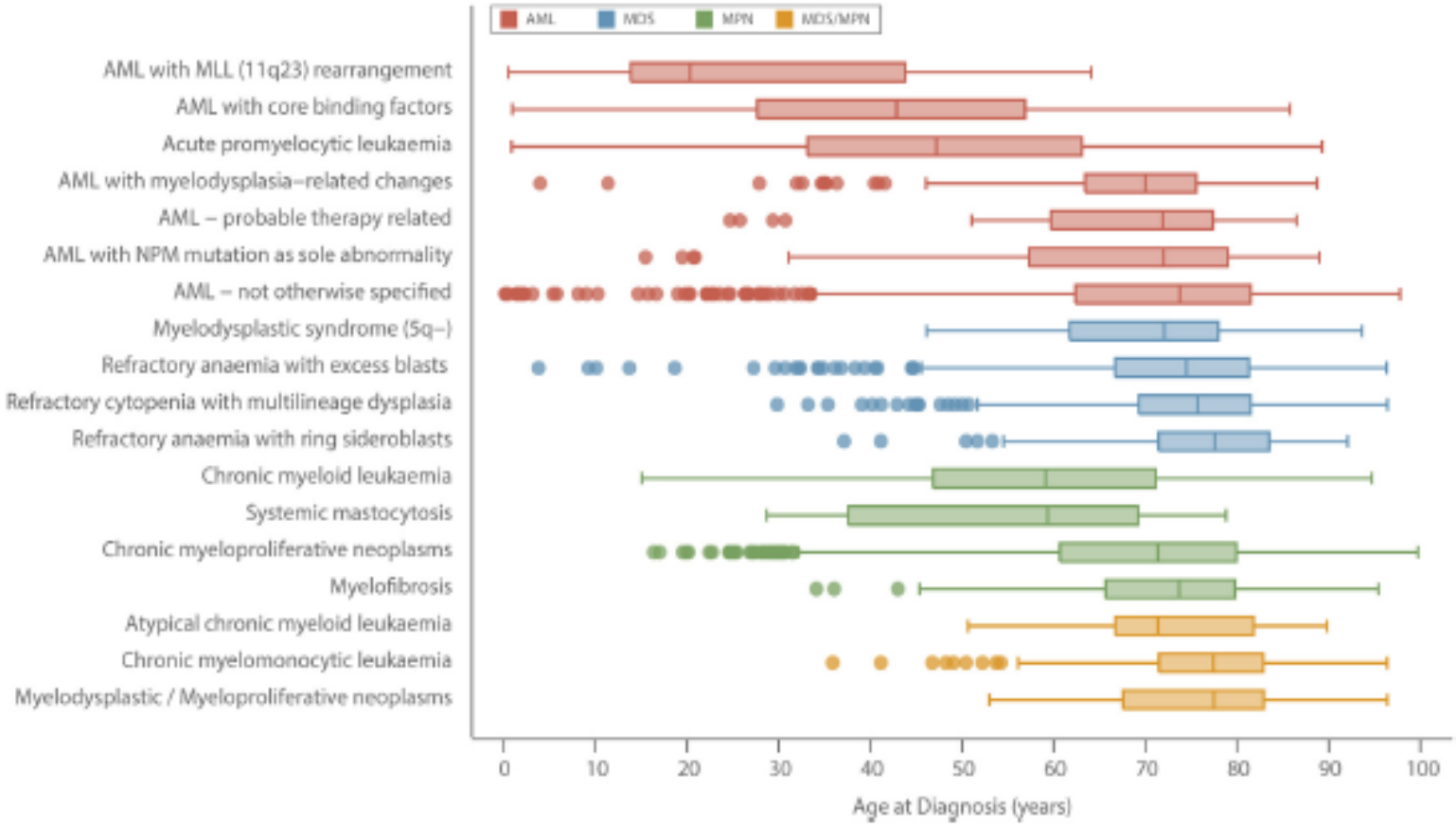


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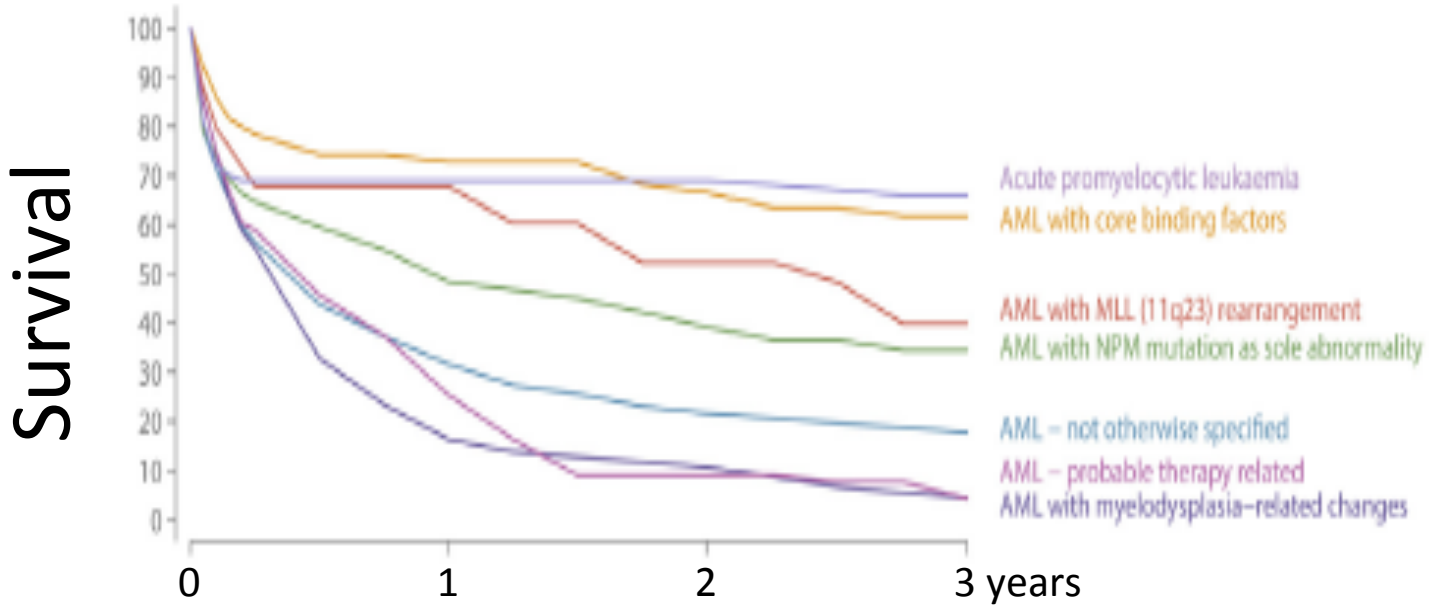
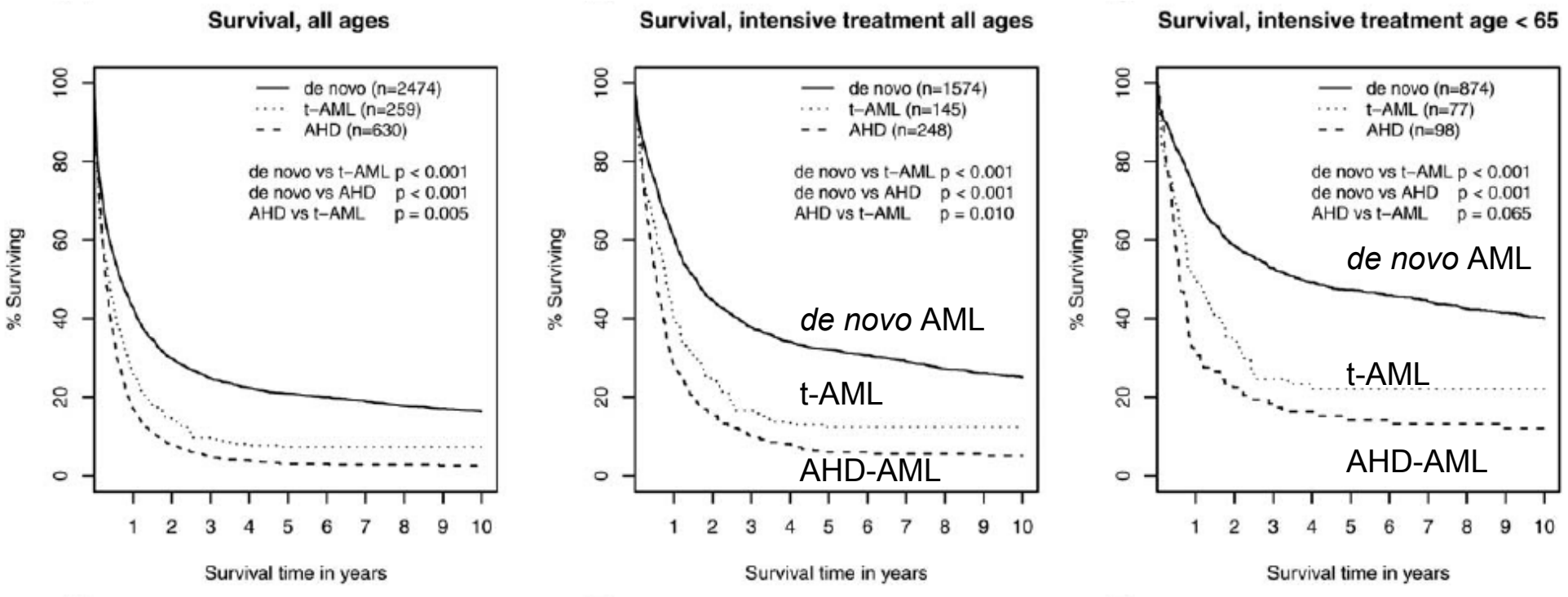



Patients with t-AML and AML with myelodysplasia-related changes had equally poor outcomes.



Roman et al. Cancer Epidemiol 2016; 42:186

# Secondary AML in the Swedish Registry, 2015




*De novo* AML = 2472 (73%)
AHD- AML = 630 (19%) [Antecedent hematologic disorder = 440 with prior MDS + 226 prior MPN]

t-AML = 259 (8%)



Hulegardh et al. Am J Hematol 2015; 90: 208

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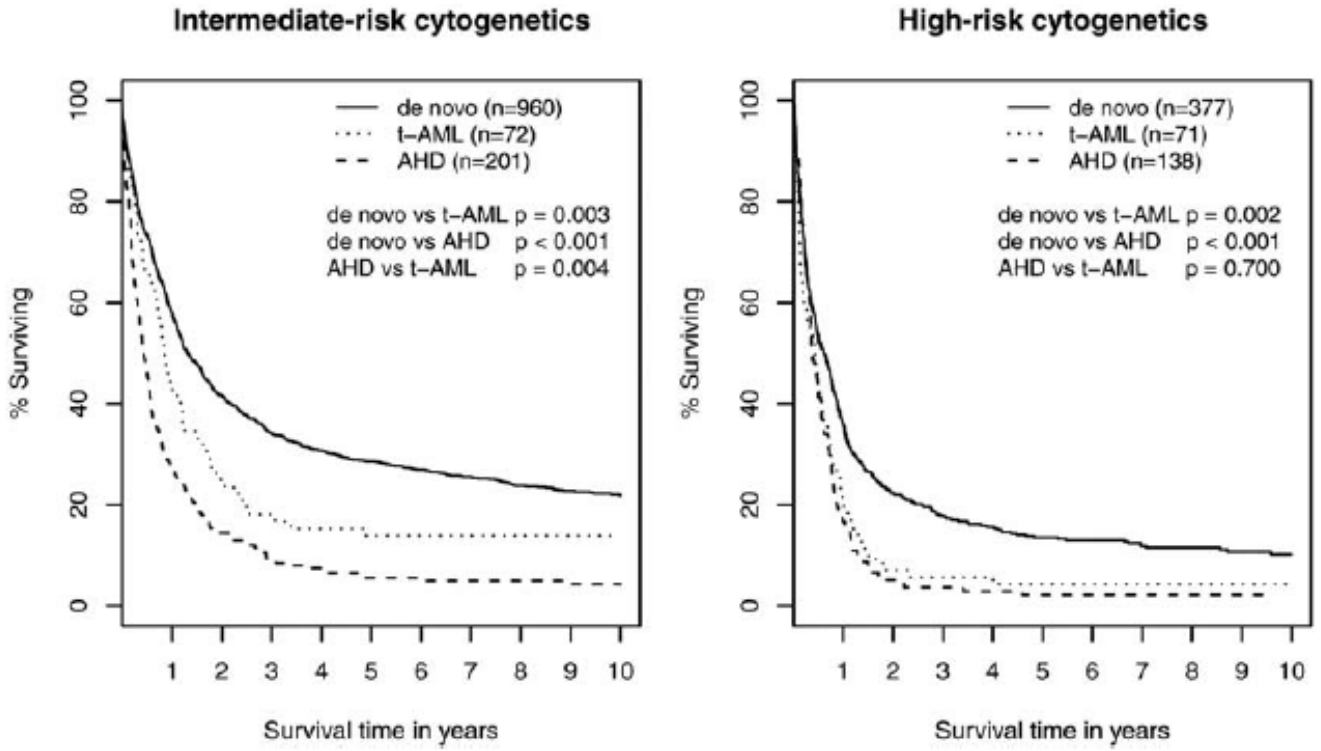


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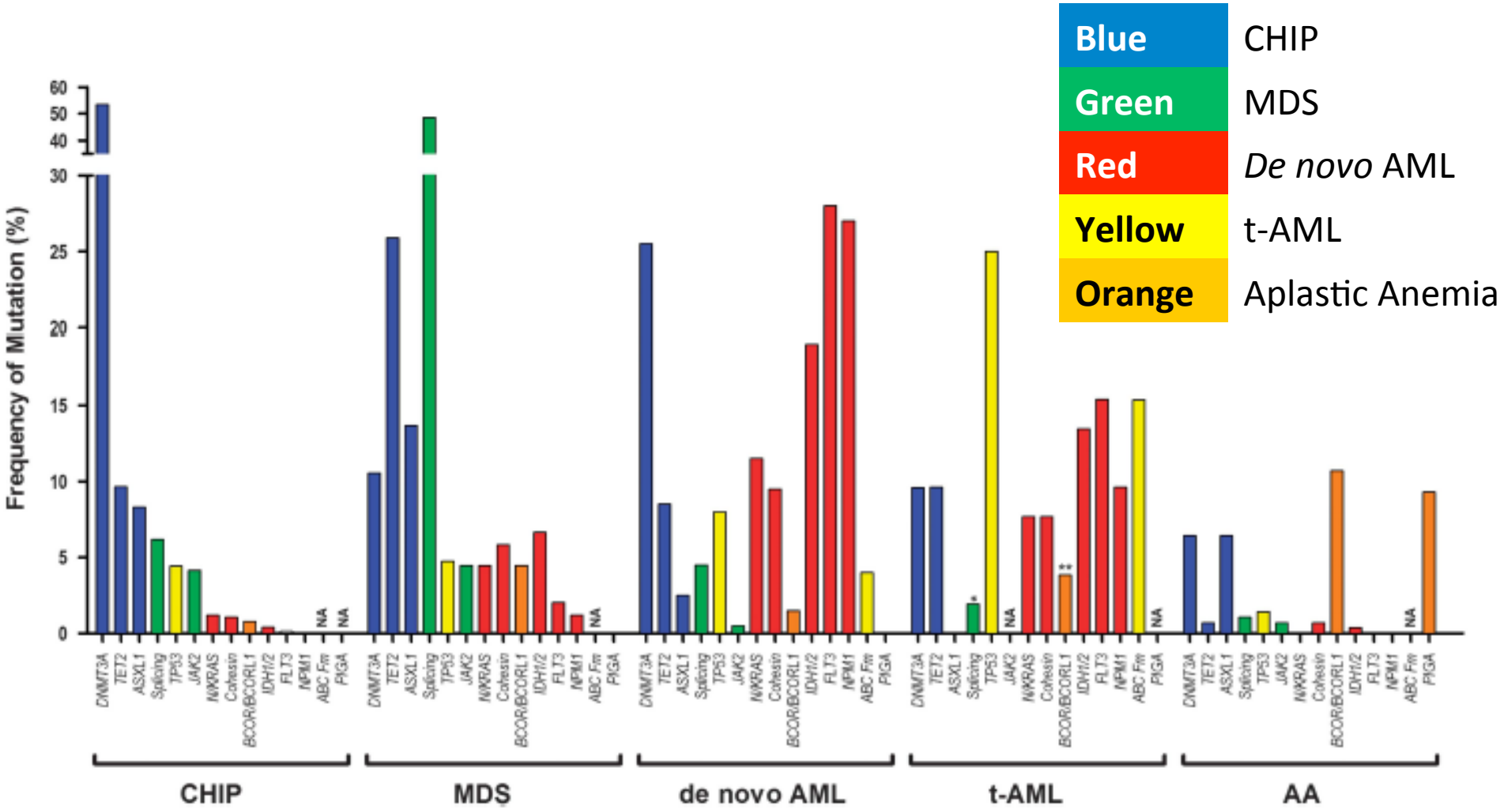
# Somatic gene mutations are enriched in clonal hematopoietic disorders




Link & Walter. Leukemia 2016; 30: 1633.

# Two diseases or only one with progression?

- The term “secondary” leukemia implies that there is a difference between the antecedent disorder and the leukemia.
- Alternatively, secondary leukemia may be a single disease with a continuum of increasing dysplasia and decreasing myeloid  maturation, until the myeloblasts exceed 20%.
  - “Blast phase of MDS”

# Does early (t-MDS) differ from later t-MN (t-AML)?

- Are there differences at the two ends of the spectrum?
  - Percentage of blasts
  - Cytogenetic abnormalities
- Do morphological subsets make a difference in t-MDS?
- Or is t-MDS a spectrum of clinical presentations and biological features rather than multiple distinct subsets?

# Cytogenetics of t-MDS and t-AML (n=155)

| Karyotype | t-MDS (n = 86) [ <20% blasts] | t-AML (n = 69) [ ≥ 20% blasts] |
|---|---|---|
| Normal: | 10 (12%) | 6 (9%) |
| Abnormalities of chrom. 5, 7, or both (+/- others): | 64 (74%) | 38 (55%) |
| Balanced translocations: | 0 | 11 |
| t(11q23) | | 6 |
| t(8;21) | | 2 |
| inv(16) | | 2 |
| t(15;17) | | 1 |
| Other abnormalities: | 12 | 14 |
| Complex (≥ 3 abnormalities) | 41 (48%) | 35 (51%) |

ZN Singh et al. Am J Clin Pathol 2007; 127: 197-205

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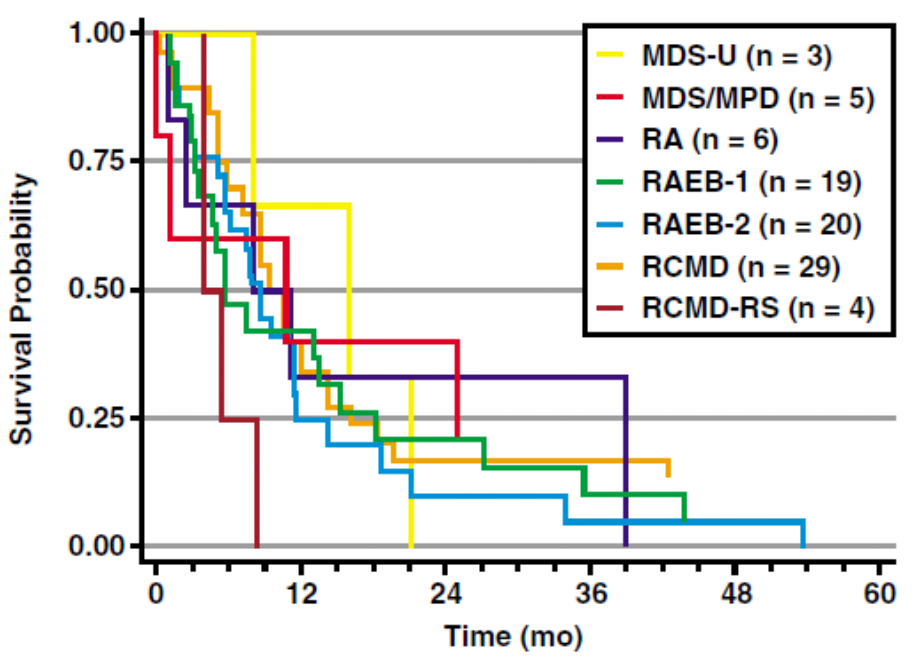
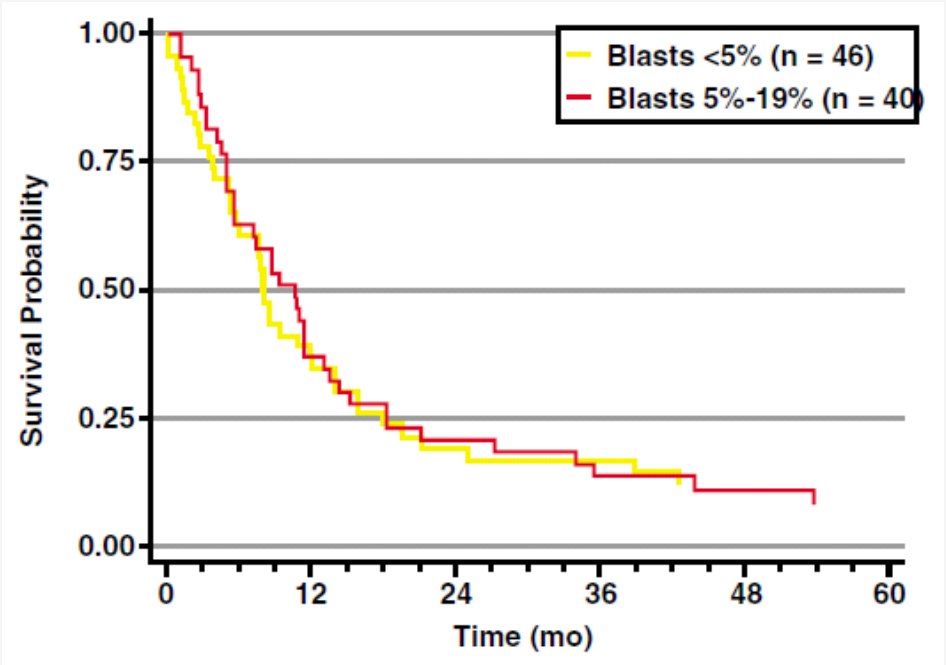
# Among patients with t-MDS, morphologic subclassification may not be clinically relevant.

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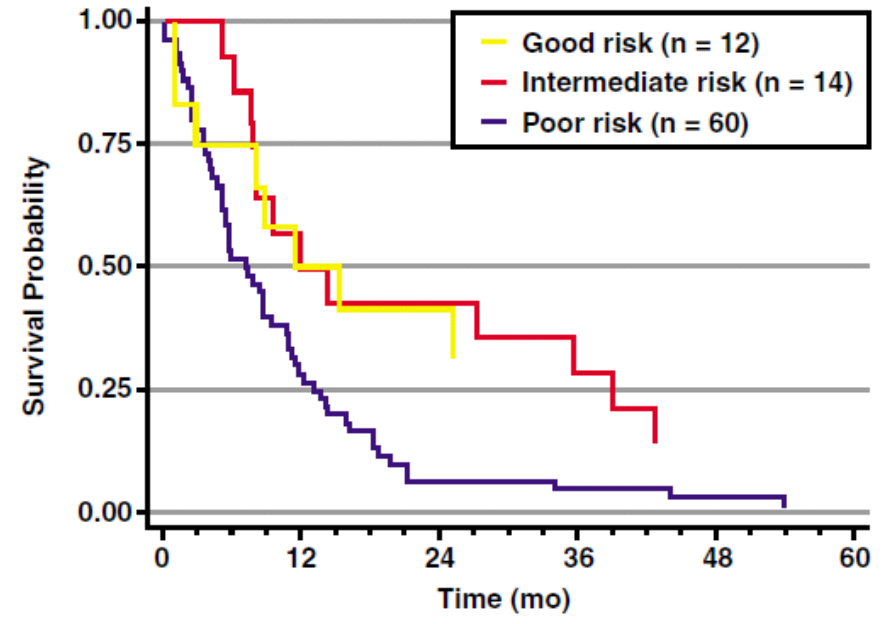
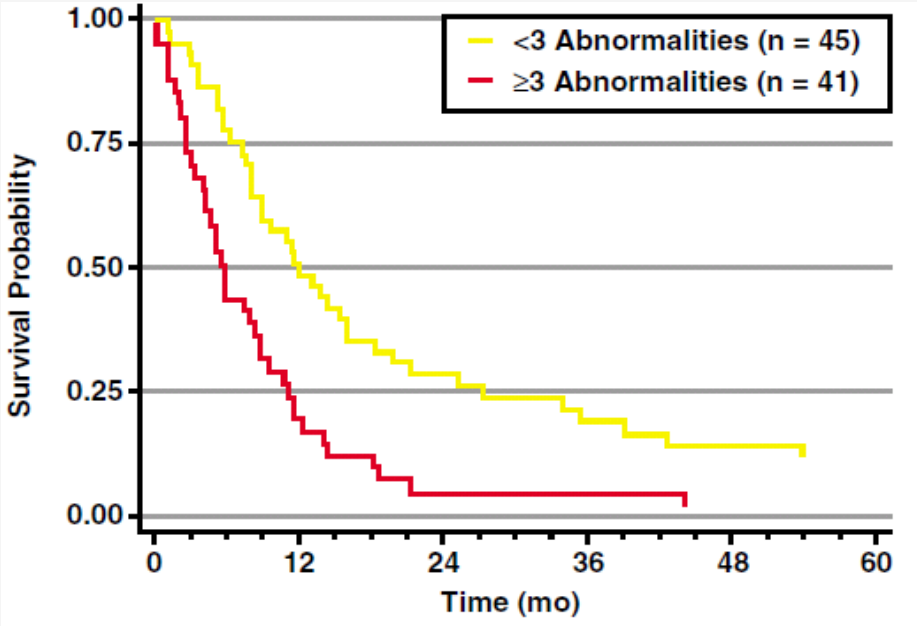
# Cytogenetic features are clinically relevant in t-MDS.

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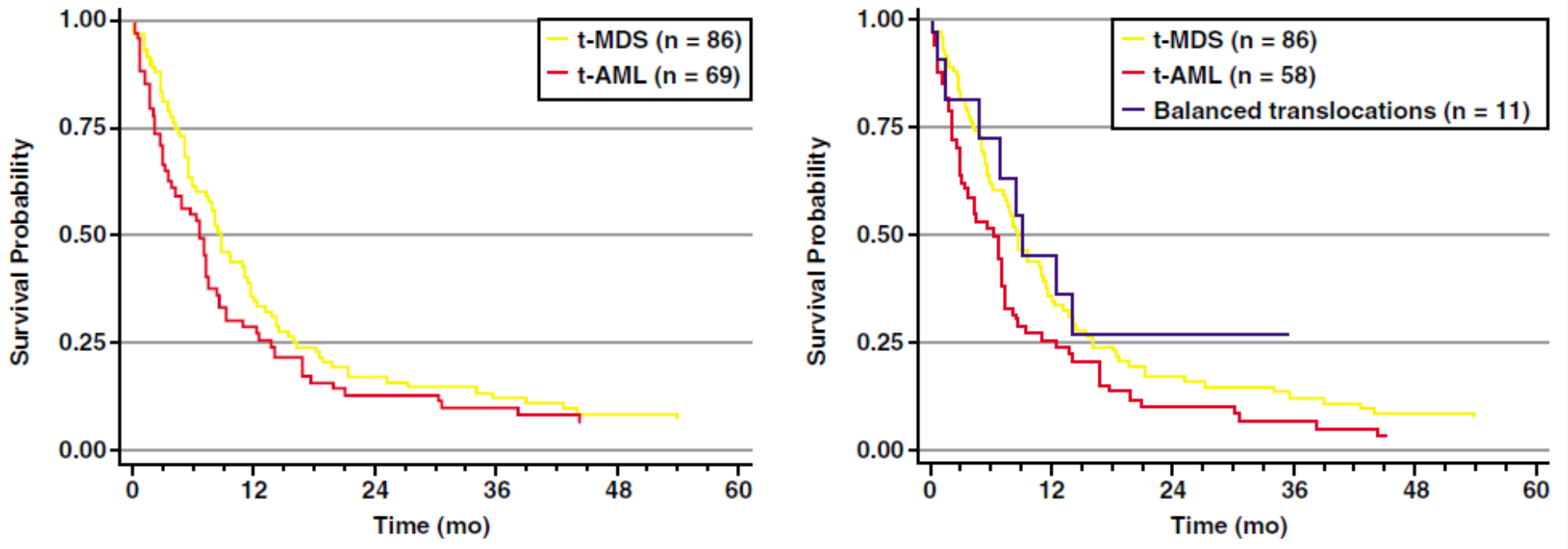
# Survival is similar for t-MDS and t-AML, except for patients with balanced rearrangements.

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# Who is at risk?

- An entirely stochastic event (happening by chance)
  - Age-related
- A mutational event or series of mutations entirely due to a specific DNA damaging agent
- Selection for a mutator phenotype (mismatch repair deficiency)
- Germline genetic factors that impact an individual's susceptibility to DNA damage
  - Hereditary cancer susceptibility: *TP53, BRCA1, BRCA2, FANC*
  - Inactivating polymorphisms
- A host susceptible to development of myeloid neoplasms regardless of exposure: *RUNX1, DDX41, CEBPA, TERC,TERT, GATA2, ANKRD26, ALA2, RPS*

# Acknowledge biologic differences; emphasize clinical similarities

- Leukemia is the terminal phase of a number of clonal hematopoietic disorders.
  - Neoplastic, malignant, progressive
- There are different initiating events – to be discovered.
- These leukemias share common clinical and biologic features.
- Unfortunately, they share poor outcomes overall.
- Move from morphology to genetic subclassification.
  - Drug development should focus on blocking common pathways of progression.

# Thank you!


Rimini
Pesaro
Ancona
Leghorn
Siena
TUSCANY
Grosseto
Elba
Corse
Bastia
Ajaccio
Monte Cristo I.
Civitavecchia
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