“HIGHLIGHTS” IN EMATOLOGIA
Il Brutto: Le Leucemie Secondarie

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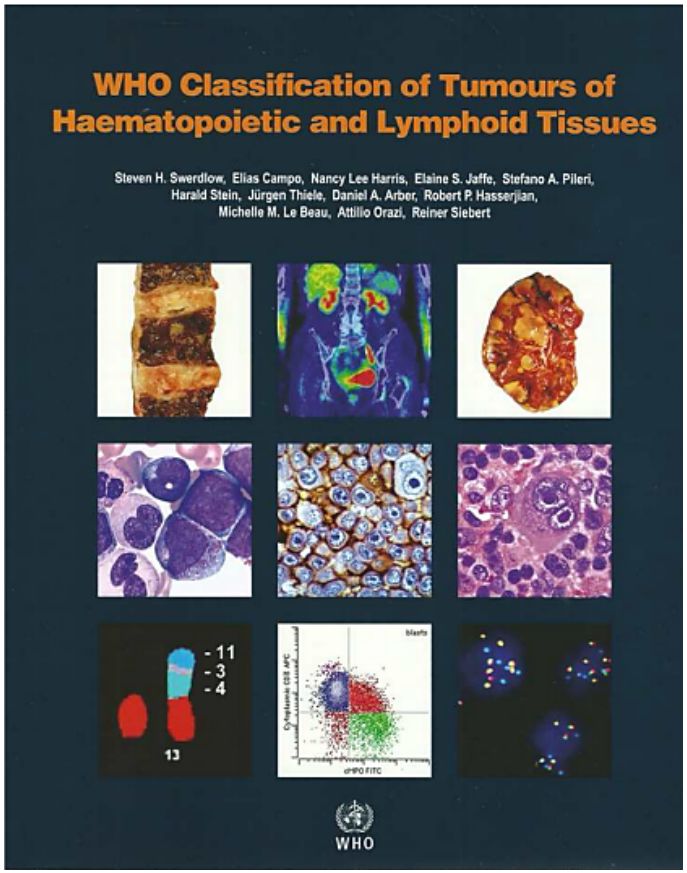
Agenda

- Biologic considerations
- Therapeutic approach

WHO Classification (2016)



MDS, myelodysplastic syndrome; WHO, World Health Organization

AML categories:

- **AML with recurrent genetic abnormalities**
- **AML with myelodysplasia-related changes (MRC)**
- **Therapy-related AML/MDS**
- **AML not otherwise specified (NOS)**
- **Myeloid sarcoma**
- **Myeloid proliferations related to Down syndrome**

Arber DA, et al. Blood. 2016;127(20):2391-2405

WHO 2016 AML Classification

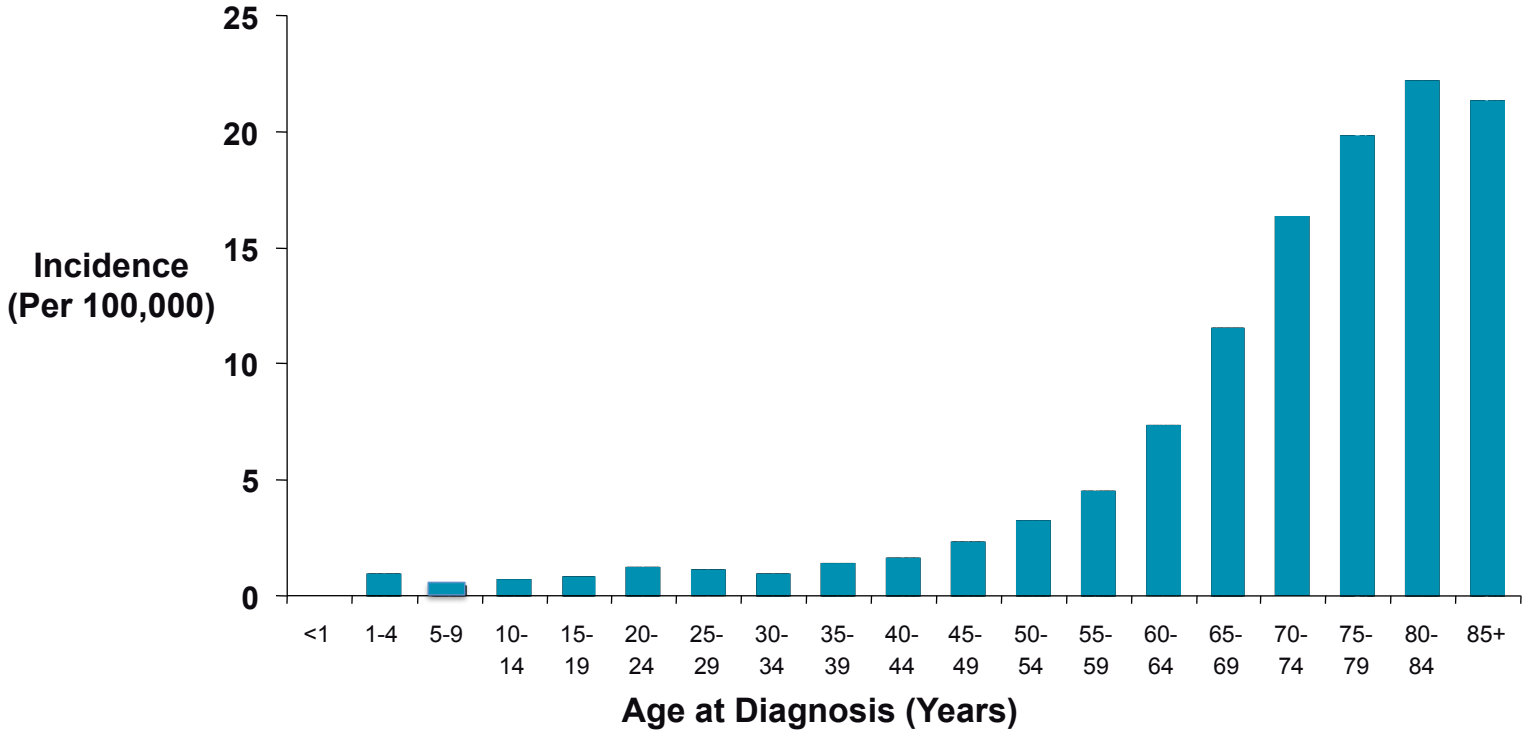
AML with MDS related changes:

- **50% dysplasic cells in 2 lines**
- **History of MDS**
- **MDS-related cytogenetics (except del9q)**

Cytogenic Abnormalities
Complex karyotype (3 or more abnormalities)
Unbalanced abnormalities
–7/del(7q)
del(5q)/t(5q)
i(17q)/t(17p)
–13/del(13q)
del(11q)
del(12p)/t(12p)
idic(X)(q13)
Balanced Abnormalities
t(11;16)(q23.3;p13.3)
t(3;21)(q26.2;q22.1)
t(1;3)(p63.3;q21.2)
t(2;11)(p21;q23.3)
t(5;12)(q32;p13.2)
t(5;7)(q32;q11.2)
t(5;17)(q32;p13.2)
t(5;10)(q32;q21.2)
t(3;5)(q25.3;q35.1)

Arber DA, et al. *Blood.* 2016;127(20):2391-2405..

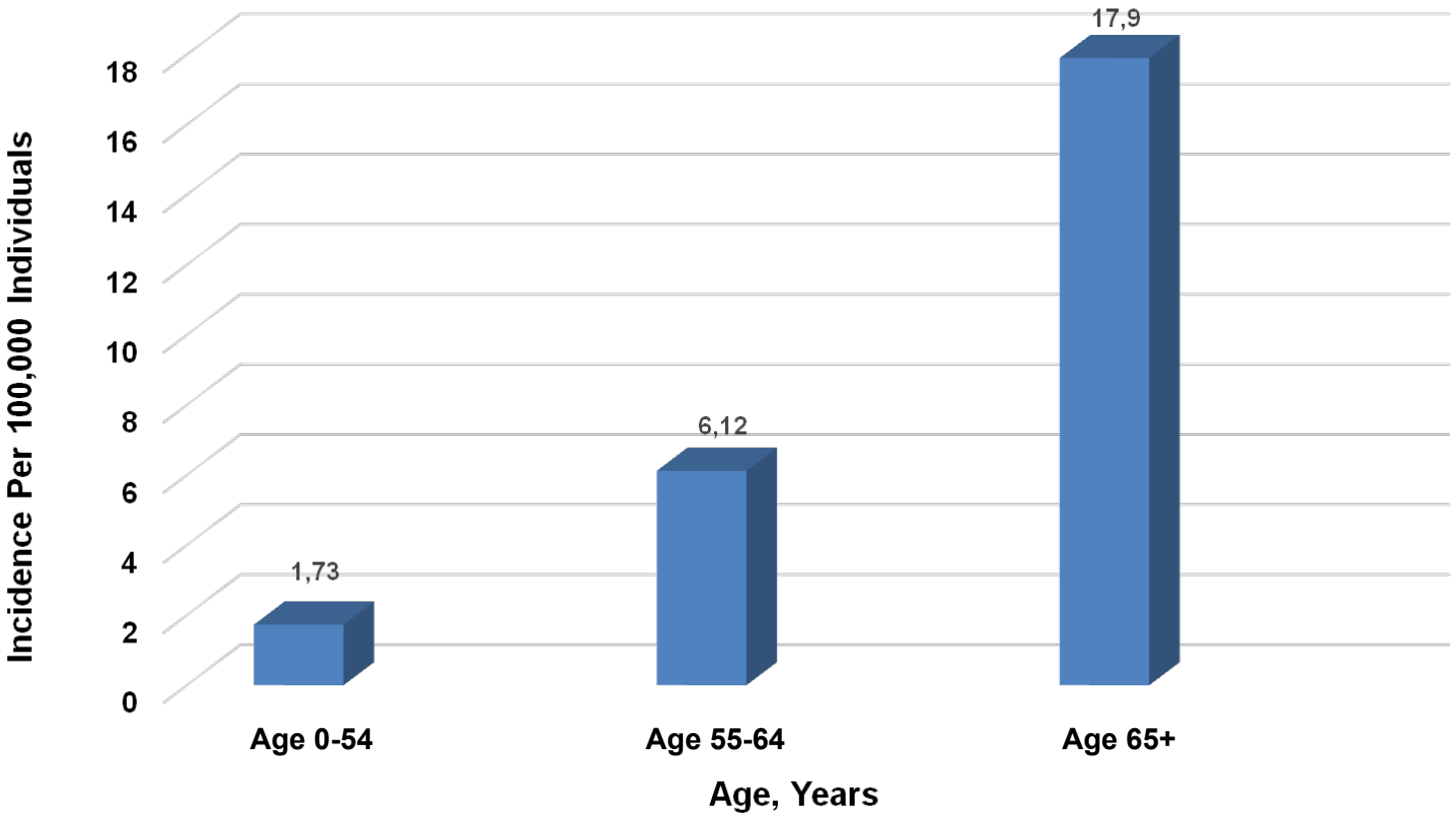
AML is Primarily a Disease of Older Adults



AML, acute myeloid leukemia

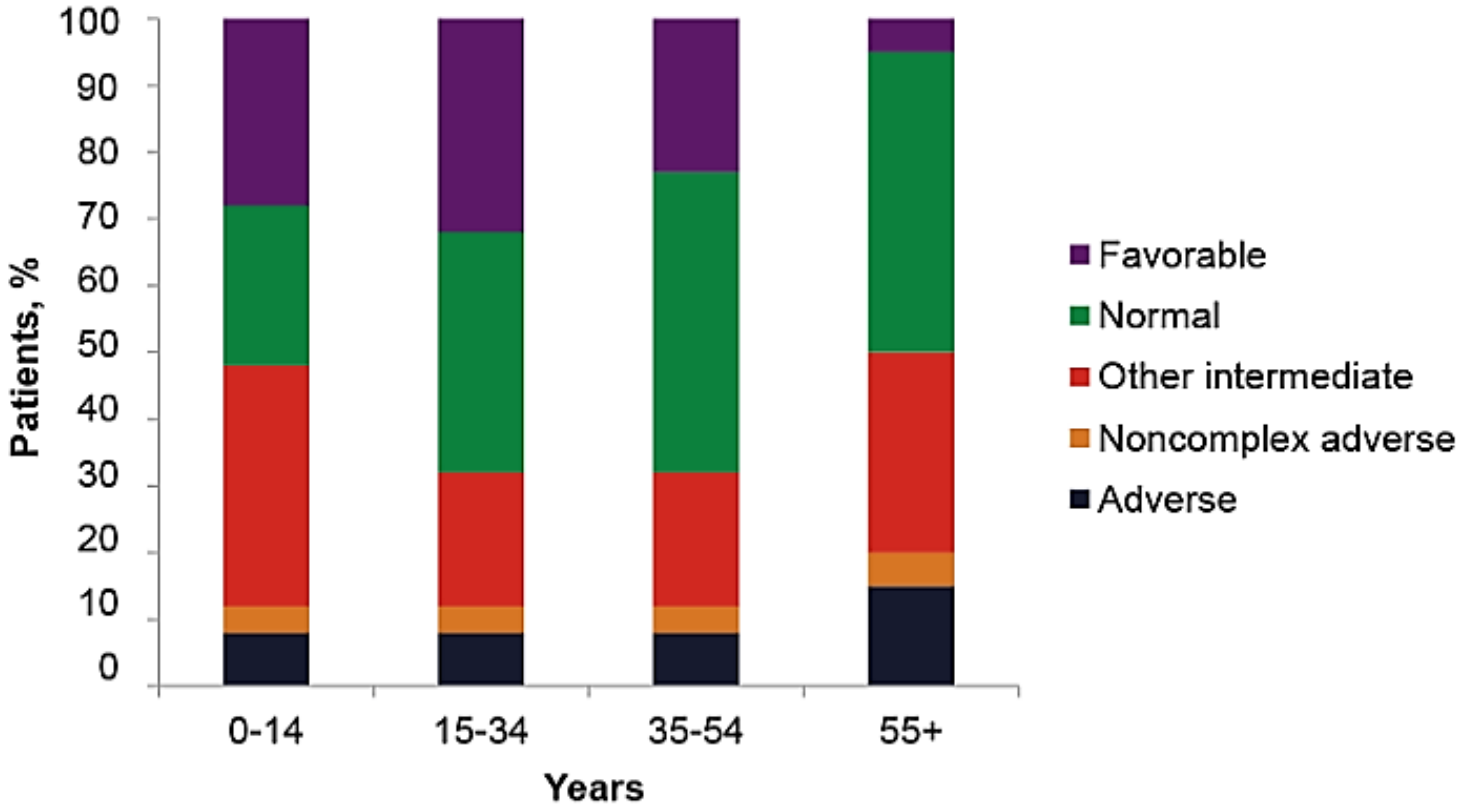
SEER Cancer Statistics Review. 1975-2000. http://seer.cancer.gov/csr/1975_2000/results_merged/sect_13_leukemia.pdf. Accessed 23 May 2018.

Incidence of AML and Age in Italy



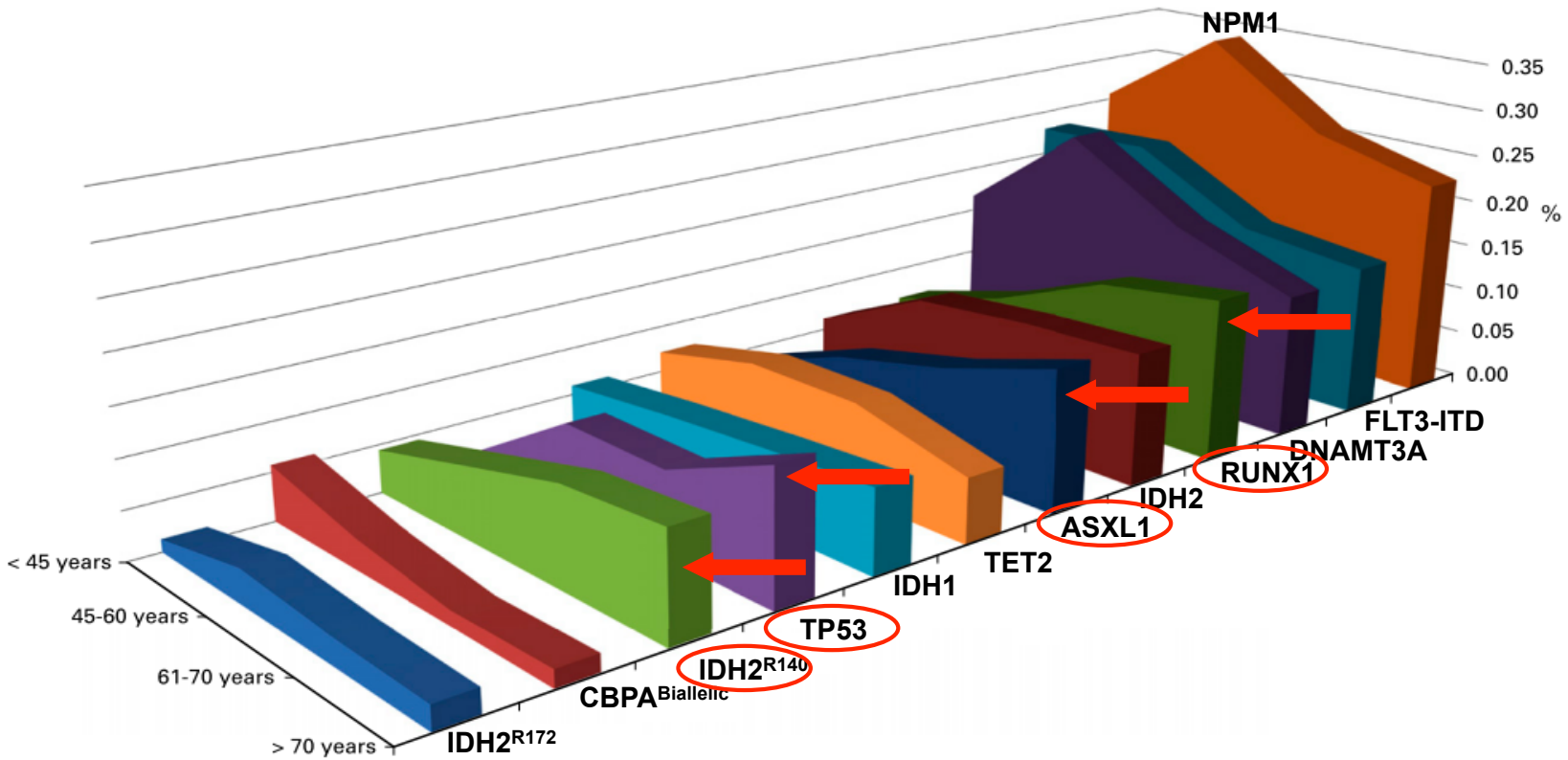
AIRTUM Working Group, et al. Epidemiol Prev. 2016;40(1 Suppl 2):1-20

Cytogenetic Categories and Age in AML



Grimwade D, et al. Blood. 2001;98(5):1312-1320

Age-Related Frequency of Selected Recurring Gene Mutations



Bullinger L, et al. J Clin Oncol. 2017;35(9):934-946

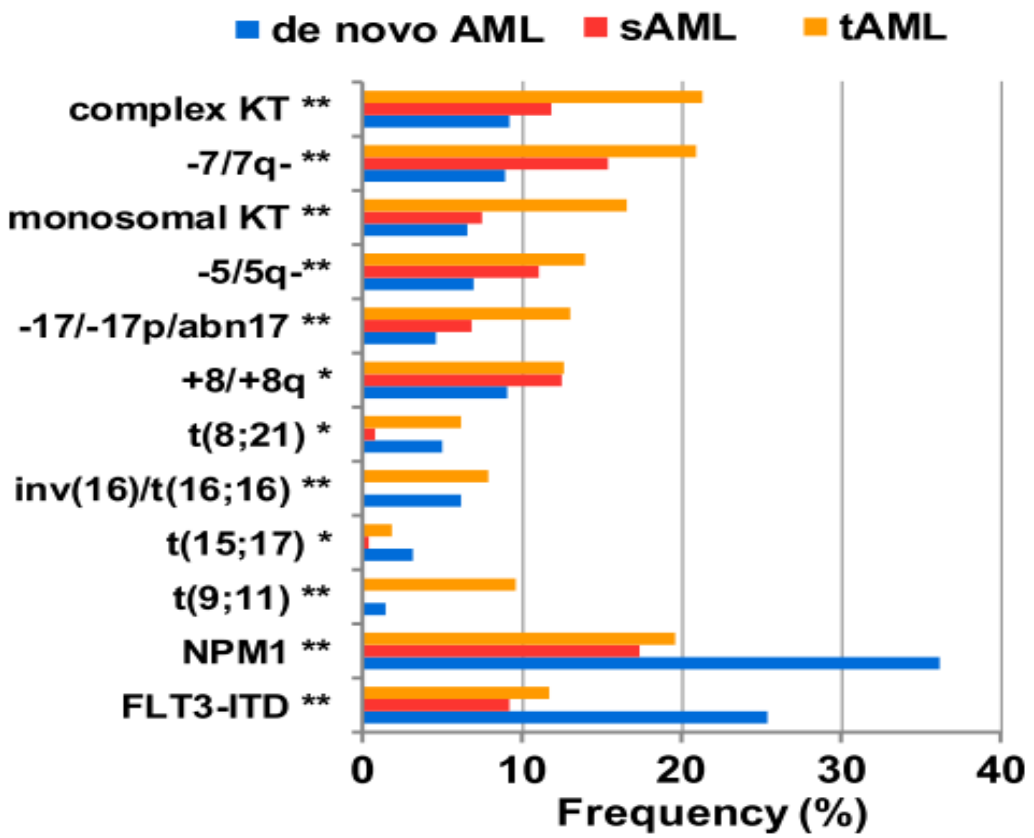
- Can AML ontogeny be mutationally defined?
- Is there any relationship between ontogenic models and age?

Ontogenic Models in AML: 3 Distinct Categories

- ***De novo* AML:** Arises in absence of identified exposure or prodromal stem cell disorder
- **Secondary AML (sAML):** Transformation of AHD
- ***Therapy*-related AML (tAML):** Late complication in individuals with exposure to leukemogenic agents

AHD, antecedent hematologic disorder

Frequency of Cytogenetic Aberrations in *De Novo*, sAML, and tAML



Heuser M. Hematology Am Soc Hematol Educ Program. 2016;2016(1):24-32

AML Ontogeny Can Be Mutationally Defined

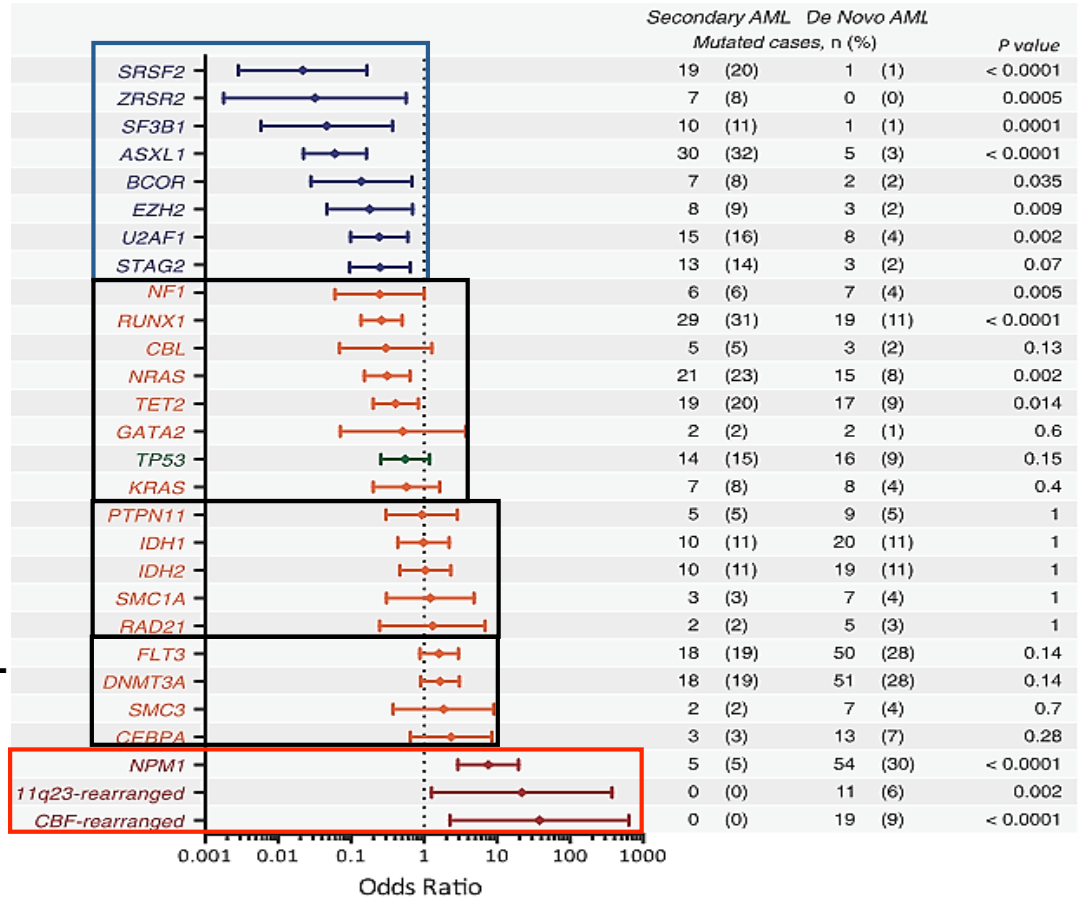
Association with sAML with >95% specificity

Association with sAML with <95% specificity

Neutrality

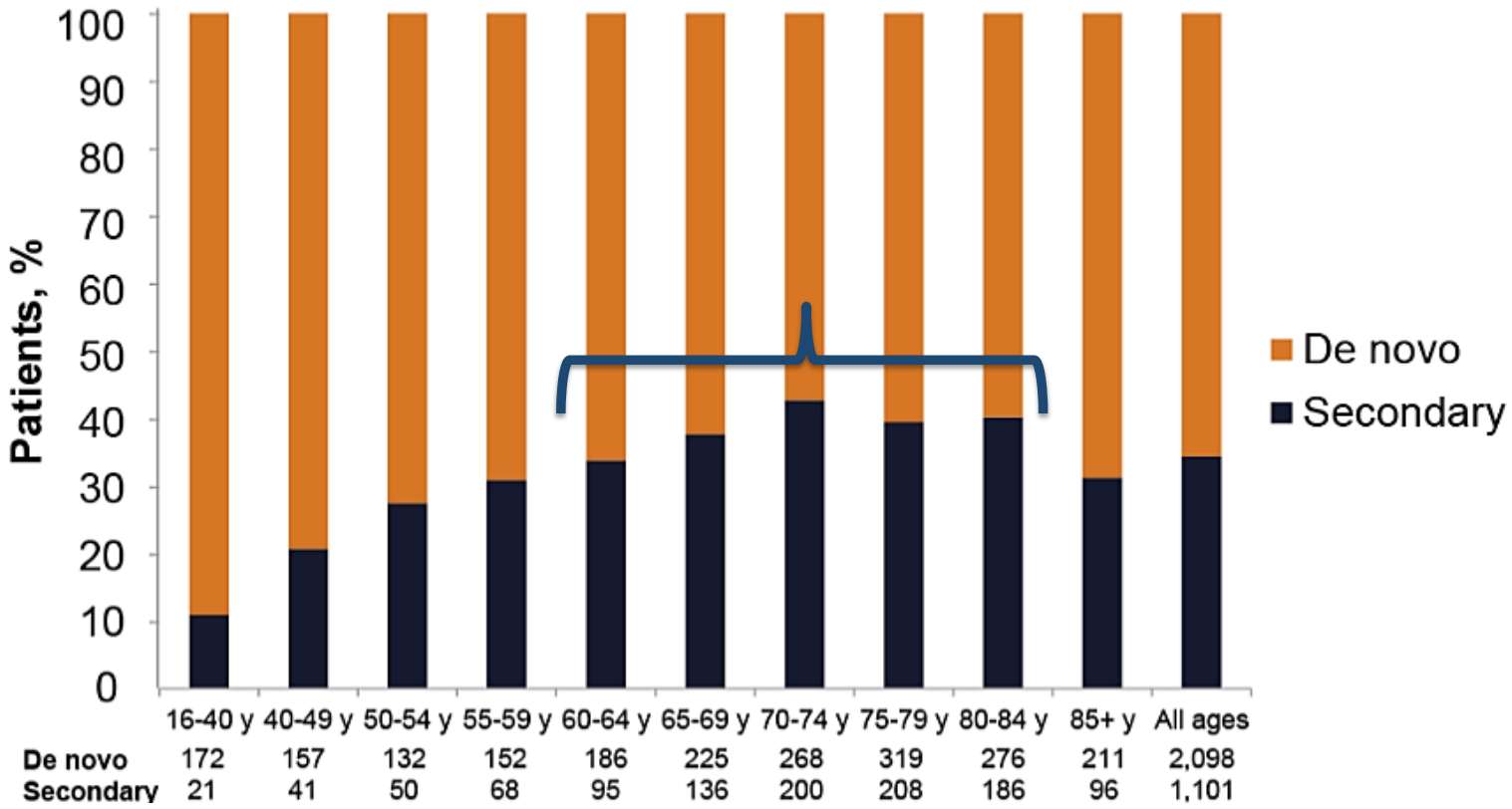
Association with *de novo* AML with <95% specificity

Association with *de novo* AML with >95% specificity



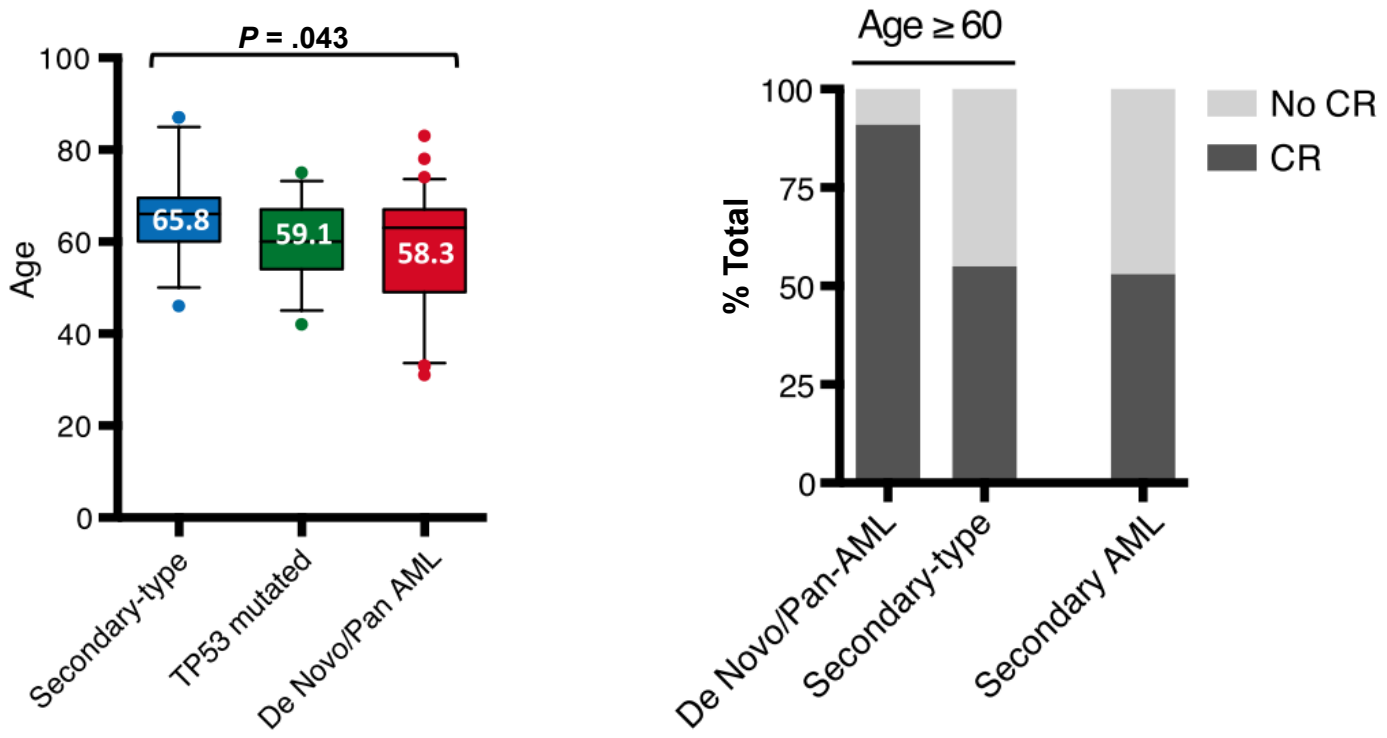
Lindsley RC, et al. Blood. 2015;125(9):1367-1376

Incidence of sAML Increases With Age



Juliusson G, et al. Blood. 2012;119(17):3890-3899

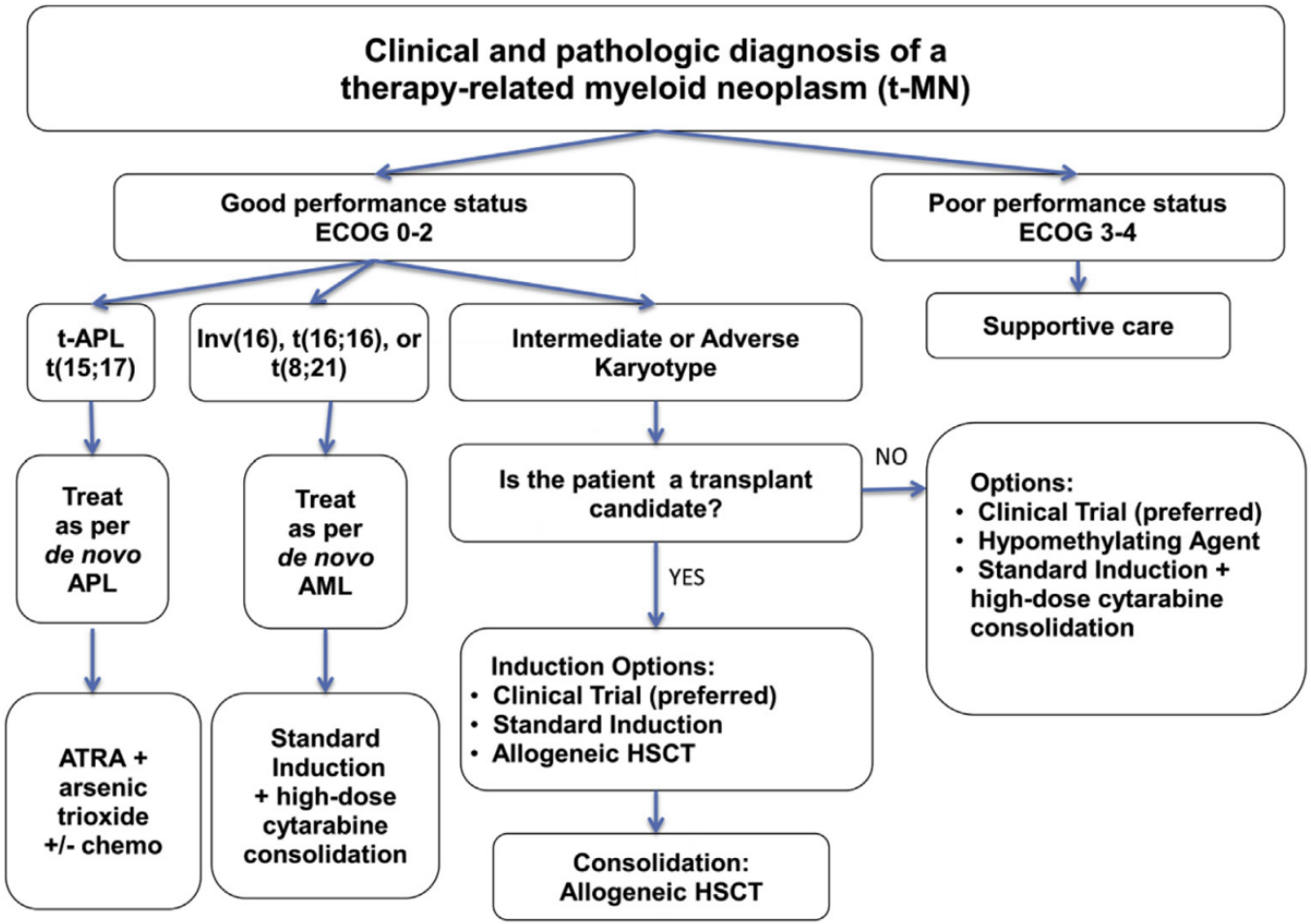
Even in Clinically-Defined *De Novo* AML, sAML-Like Features Are Associated With Age



CR, complete response

Lindsley RC, et al. Blood. 2015;125(9):1367-1376

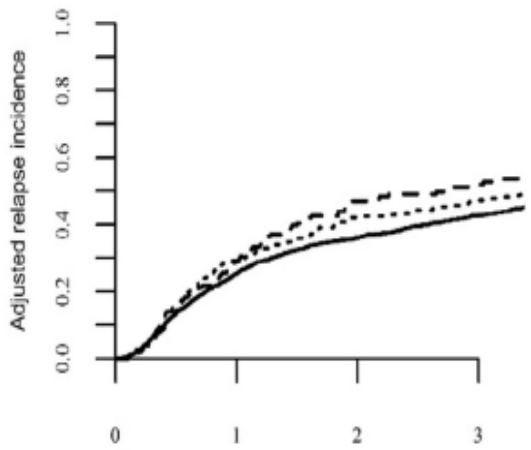
Algorithm for the treatment of t-MN



Churpek & Larson, BPRCH 2013

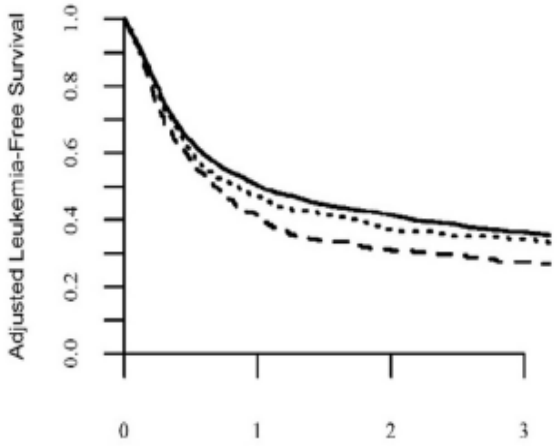
Transplant outcome based on disease type before SAML

RI



Previous diagnosis	number of at-risk patients			
— MDS/ MPN	3960	1540	1041	751
- - OMHD	467	186	121	89
··· ST	537	250	189	153

LFS



Previous diagnosis	number of at-risk patients			
— MDS/ MPN	3960	1540	1041	751
- - OMHD	467	186	121	89
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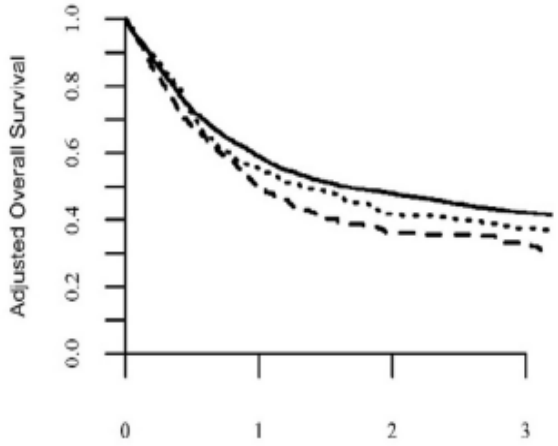
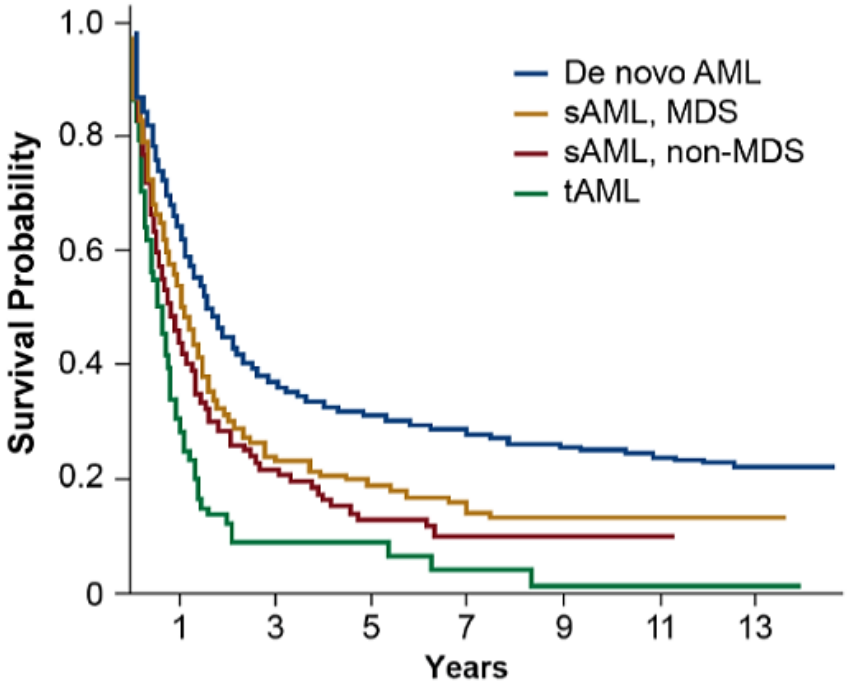
OS



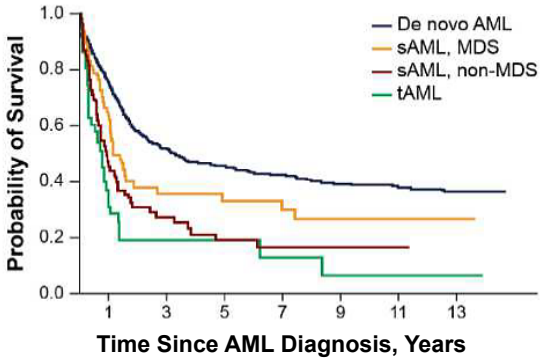
Previous diagnosis	number of at-risk patients			
— MDS/ MPN	3960	1794	1191	866
- - OMHD	467	218	135	102
··· ST	537	287	212	170

S. Sengsayadeth et al. BBMT 24 (2018) 1406–1414

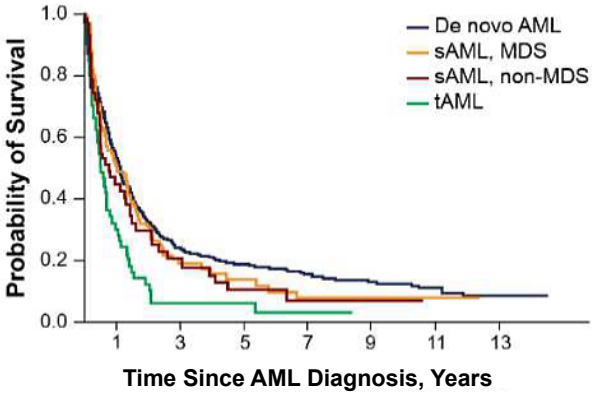
Poor Outcome of sAML and t-AML



Patients <60 Years



Patients ≥60 Years

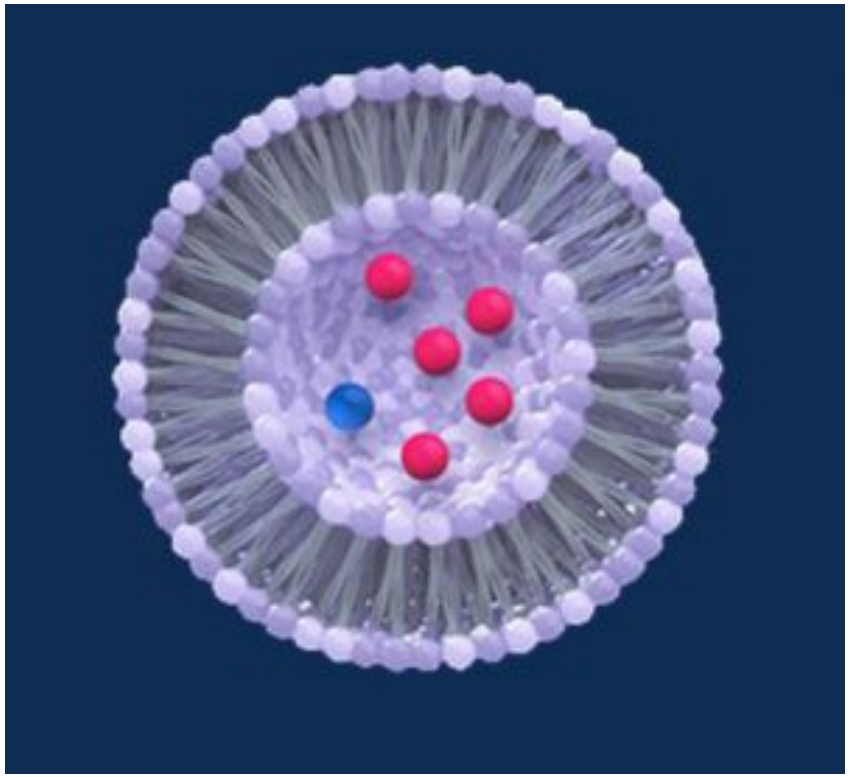


Granfeldt Østgard LS, et al. J Clin Oncol. 2015;33(31):3641-3649

Drug	FDA Approval/ Orphan Drug Designation for AML[1]	FDA Indication for AML[1]	EMA Approval /Orphan Drug Designation for AML[2]	EMA Indication for AML[2]
GO (fractionated) plus 3+7	2017	Newly diagnosed or R/R CD33-positive AML	None	None
GO (fractionated) single agent		R/R CD33-positive AML	None	None
CPX-351	2017	Newly diagnosed tAML or AML-MRC	2012 (orphan)	None
Midostaurin (plus 3+7)	2017	Newly diagnosed FLT3-mut+	2005 (orphan)	Newly diagnosed FLT3-mut+
Enasidenib	2017	R/R IDH2-mut	2016 (orphan)	None

1. US Food and Drug Administration. http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Accessed May 18, 2017
2. 2. European Medicines Agency. European Public Assessment Reports. Accessed March 3, 2017. 3. Döhner H, et al. *Blood*. 2017:129:424-447.

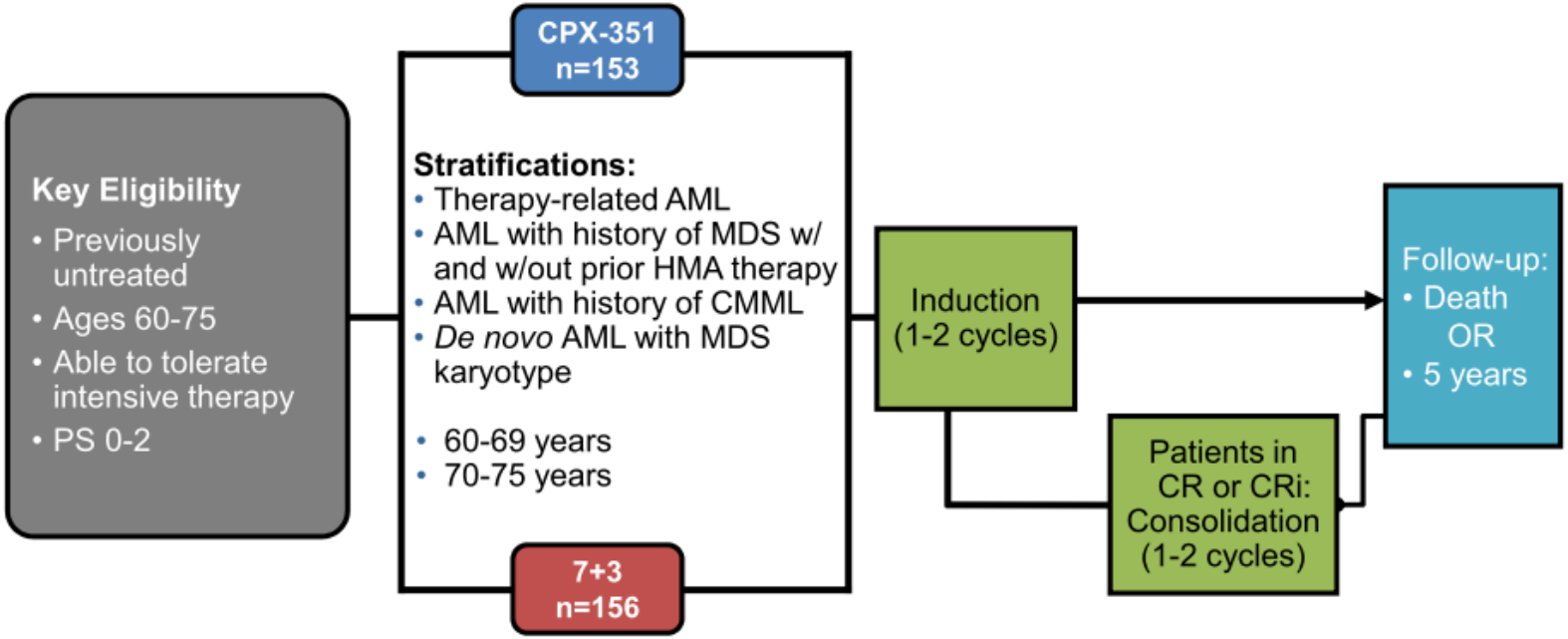
CPX-351 Uses a Nano-Scale Delivery Complex



- ✓ 100-nm bilamellar liposomes
- ✓ 5:1 molar ratio of cytarabine to daunorubicin
- ✓ 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin

Lancet JE, et al. ASCO 2016. Abstract 7000.

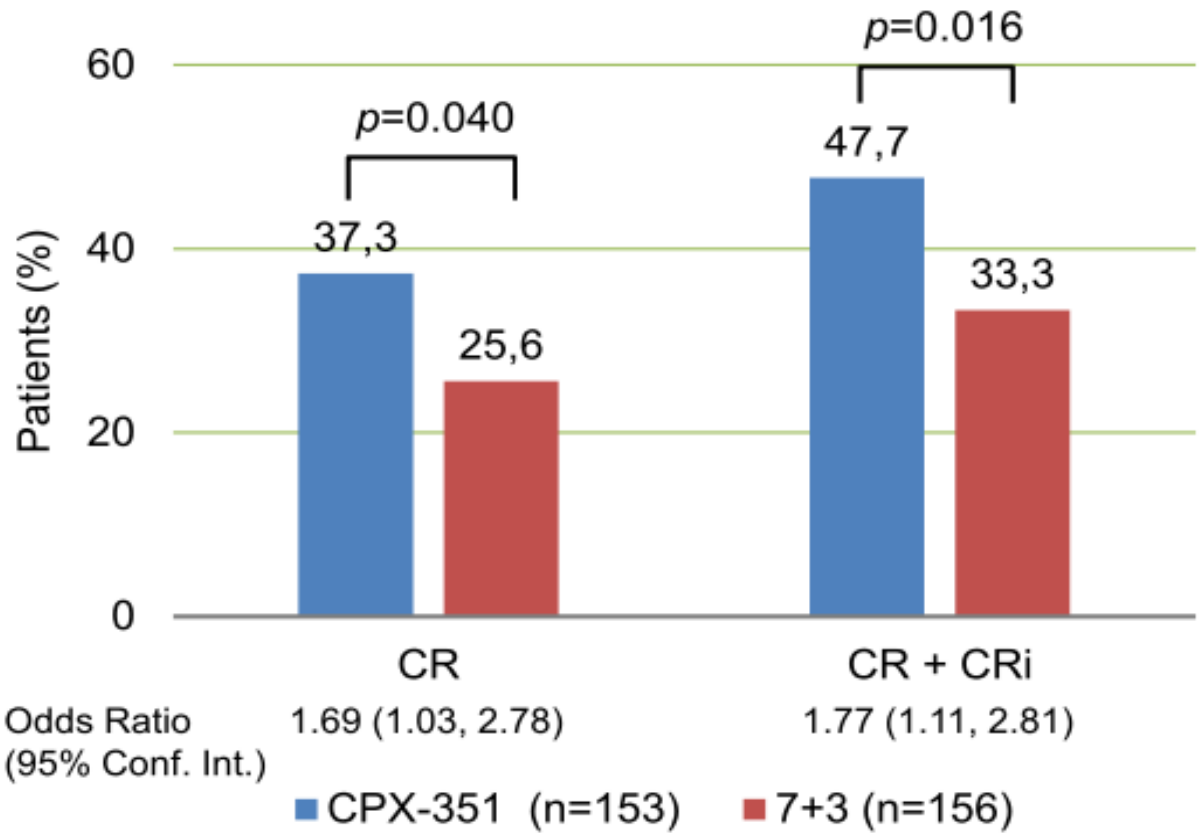
Phase 3 Study of CPX-351 vs Standard Induction in Older Patients w/ Newly Diagnosed Secondary AML (Study 301)



- **Primary Endpoint:** Overall survival

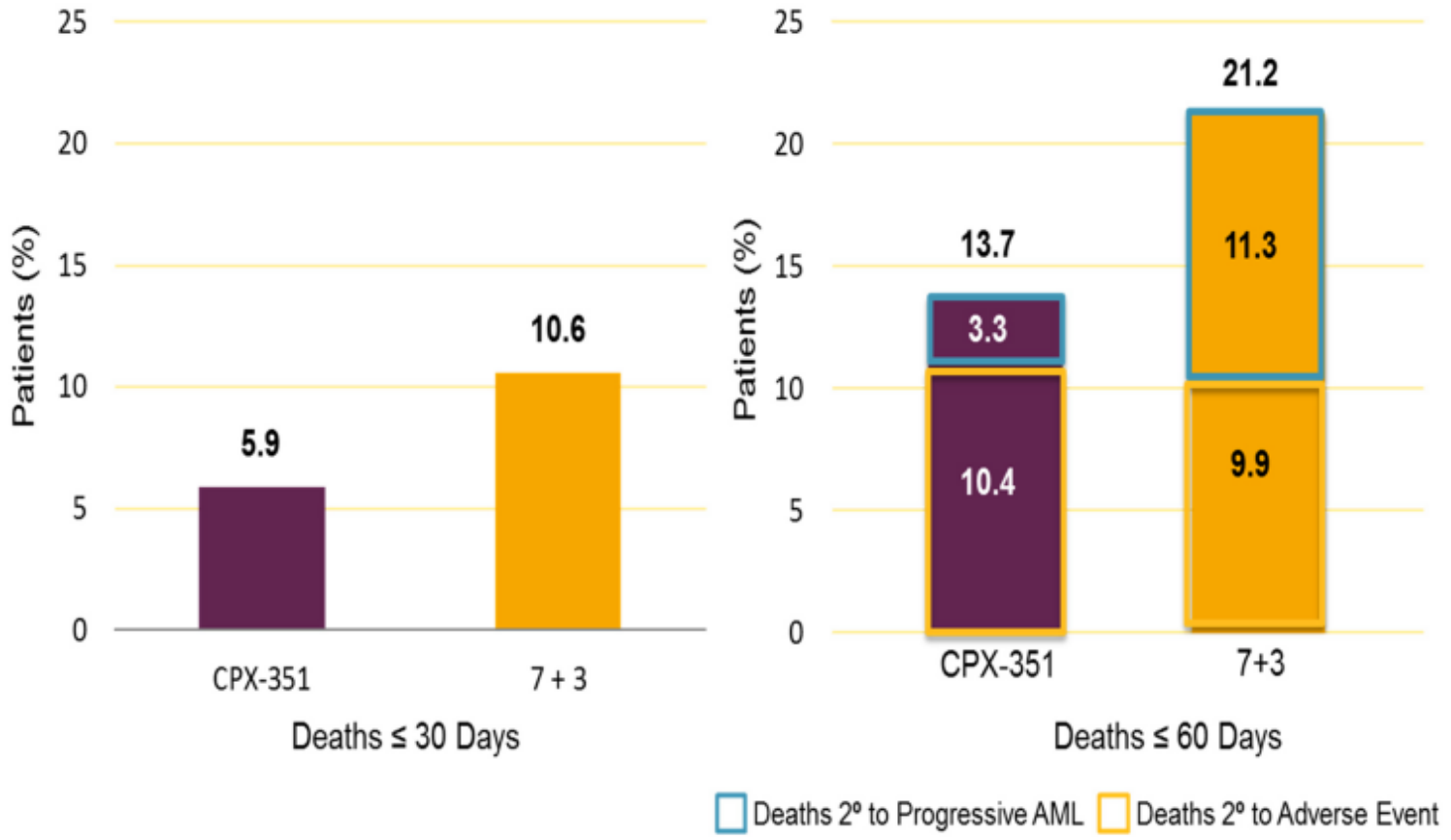
Lancet JE, et al. JCO 2018

Response Rate



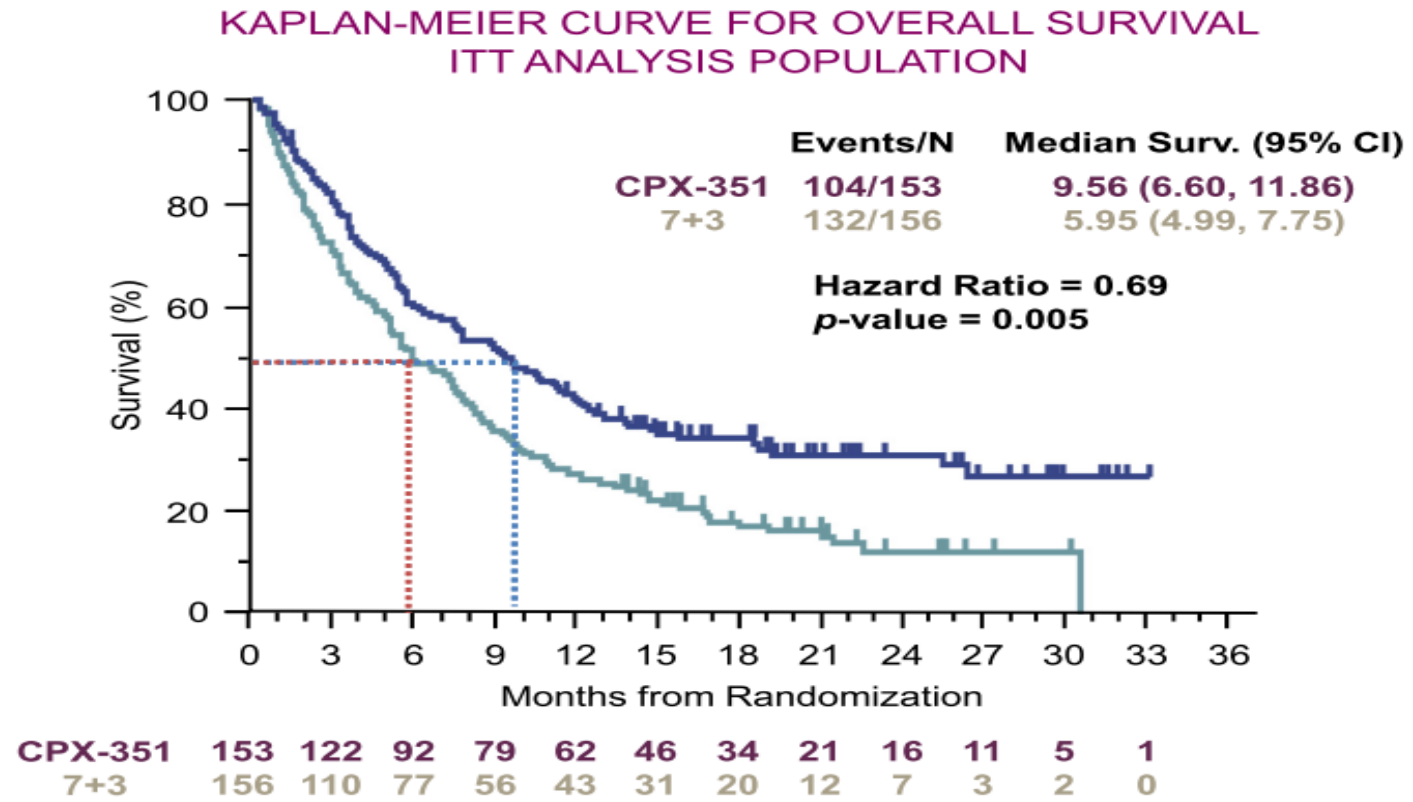
Lancet JE, et al. JCO 2018

30-Day & 60-Day Mortality Rates



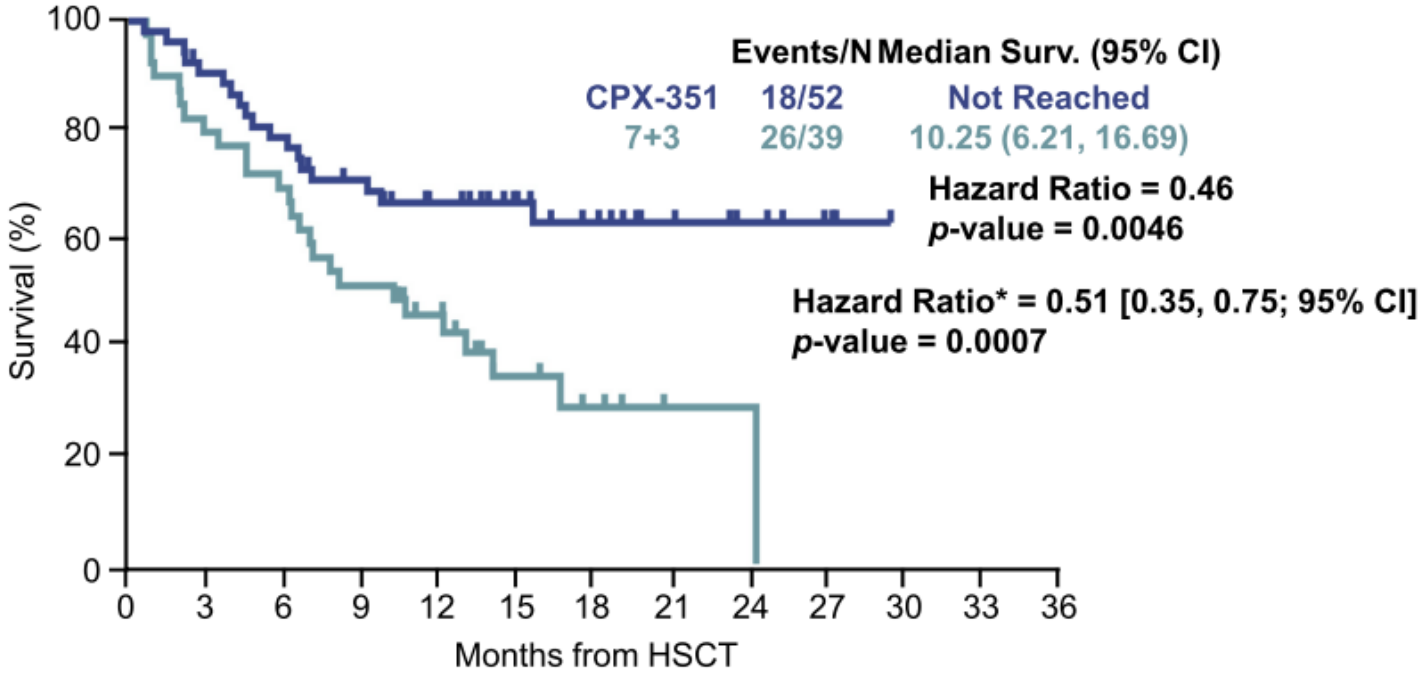
Lancet JE, et al. JCO 2018

Overall Survival Greater in the CPX-351 Arm Compared to the 7+3 Arm in Phase 3 Study 301



Lancet JE, et al. JCO 2018

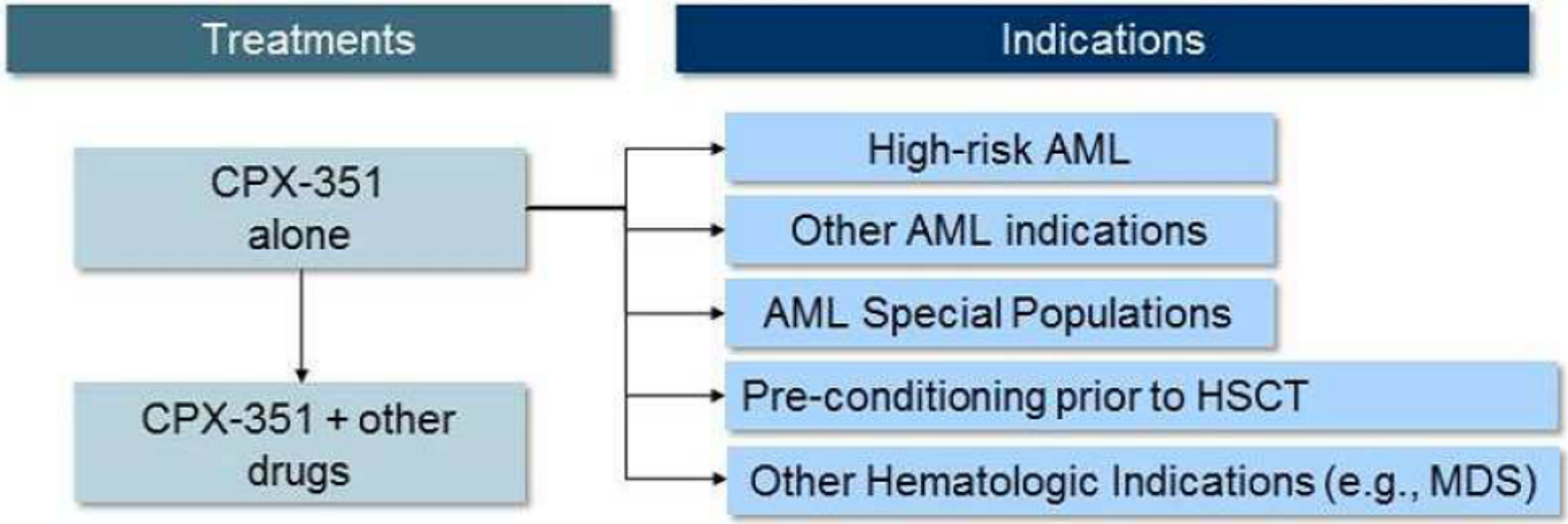
KAPLAN-MEIER CURVE FOR OVERALL SURVIVAL LANDMARKED AT STEM CELL TRANSPLANT ITT ANALYSIS POPULATION



Lancet JE, et al. JCO 2018

CPX-351 life cycle development

Extend use to other AML and hematologic malignancies



Conclusions-1

- sAML among the most difficult disease to treat
- For patients who achieve an initial CR, ASCT represents the best chance for long-term OS
- Need of continued development of novel agents

Conclusions-2

- The current list of disease-relevant genes is likely to expand
- More chances to capture AML heterogeneity at a single-cell level
- Advances in (personalized) treatment
  - Novel therapies

CLINICAL TRIALS IN THE «GENOMIC ERA»

- *Patients' selection*

  Relationship between mutations, malignancy and response to novel agents

- *Basket clinical trials*

  Pooling together different cancers per their genomic pattern irrespective of their histologic origin (Histology-agnostic randomized trials)

- *Umbrella clinical trials*

  Multiple targeted agents/drugs for a single histology (Beat AML – Master Clinical Trial)

- *Adaptive clinical trials*

  Use of multiple interim analysis to adapt key features based on predefined rules