ISTITUTO DI EMATOLOGIA "L. e A. SERAGNOLI"
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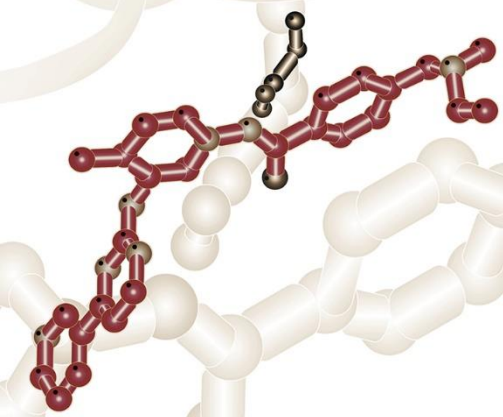
SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna
Policlinico S. Orsola-Malpighi



New Drugs in Hematology

President: Pier Luigi Zinzani
Co-President: Michele Cavo
Honorary President: Sante Tura

Bologna,
Royal Hotel Carlton
October 1-3, 2018

BOLOGNA, ROYAL HOTEL CARLTON

State-of-the-art: from genomic knowledge to targeted therapy in leukemias

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

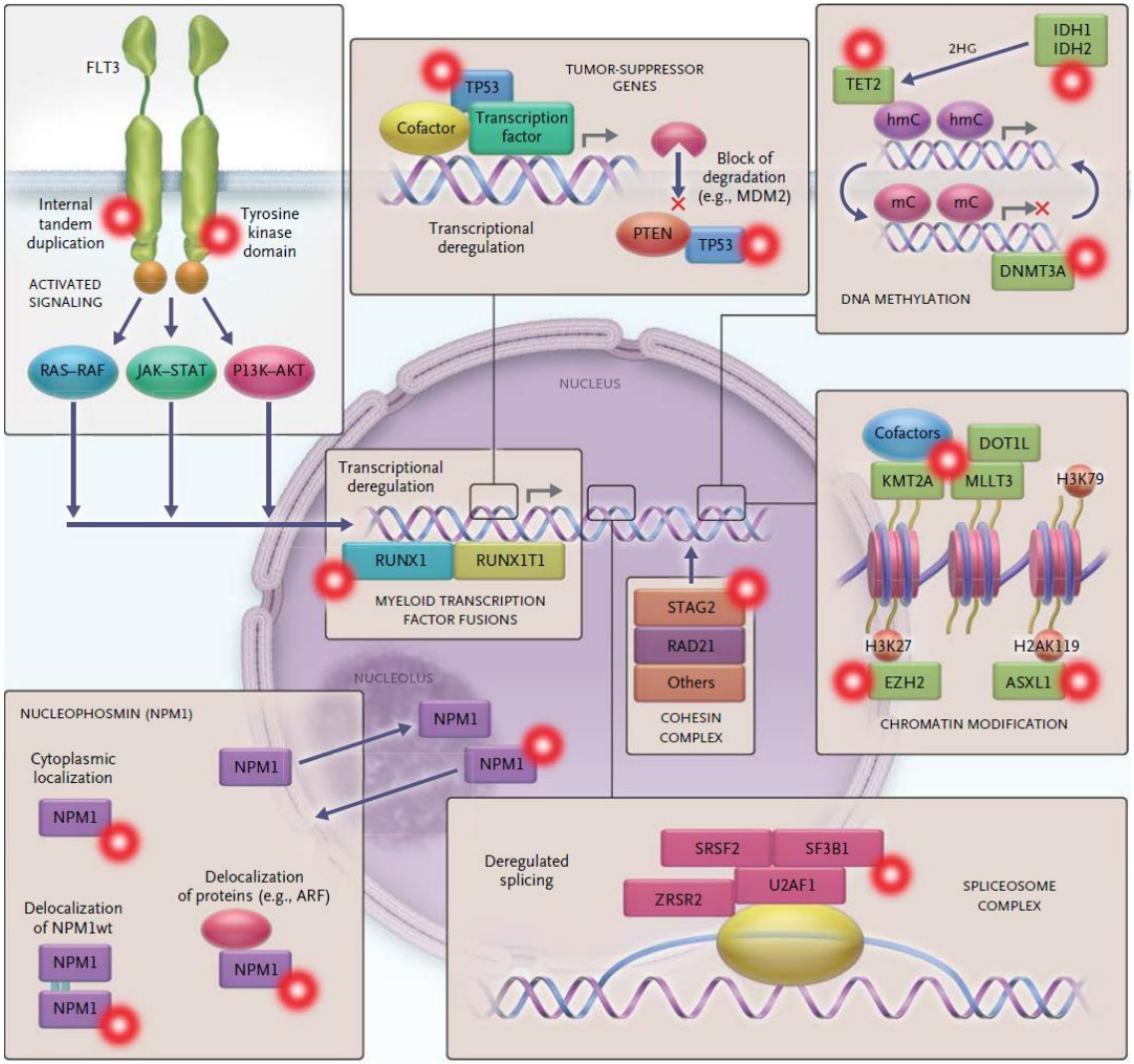
Lars Bullinger
Charité University Medicine Berlin

AML STUDY GROUP

Disclosures of NAME SURNAME

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen					x		x
Bayer Oncology	x				x		
Bristol-Myers Squibb					x	x	
Jazz Pharmaceuticals					x	x	
Novartis			x		x	x	
Pfizer					x		
Sanofi	x				x		

Genomic landscape of de novo AML



Commonly mutated functional gene categories:

(1) signaling genes
(2) transcription factors
(3) NPM1
(4) spliceosome complex
(5) Cohesion complex
(6) chromatin modification
(7) DNA methylation
(8) tumor-suppressors

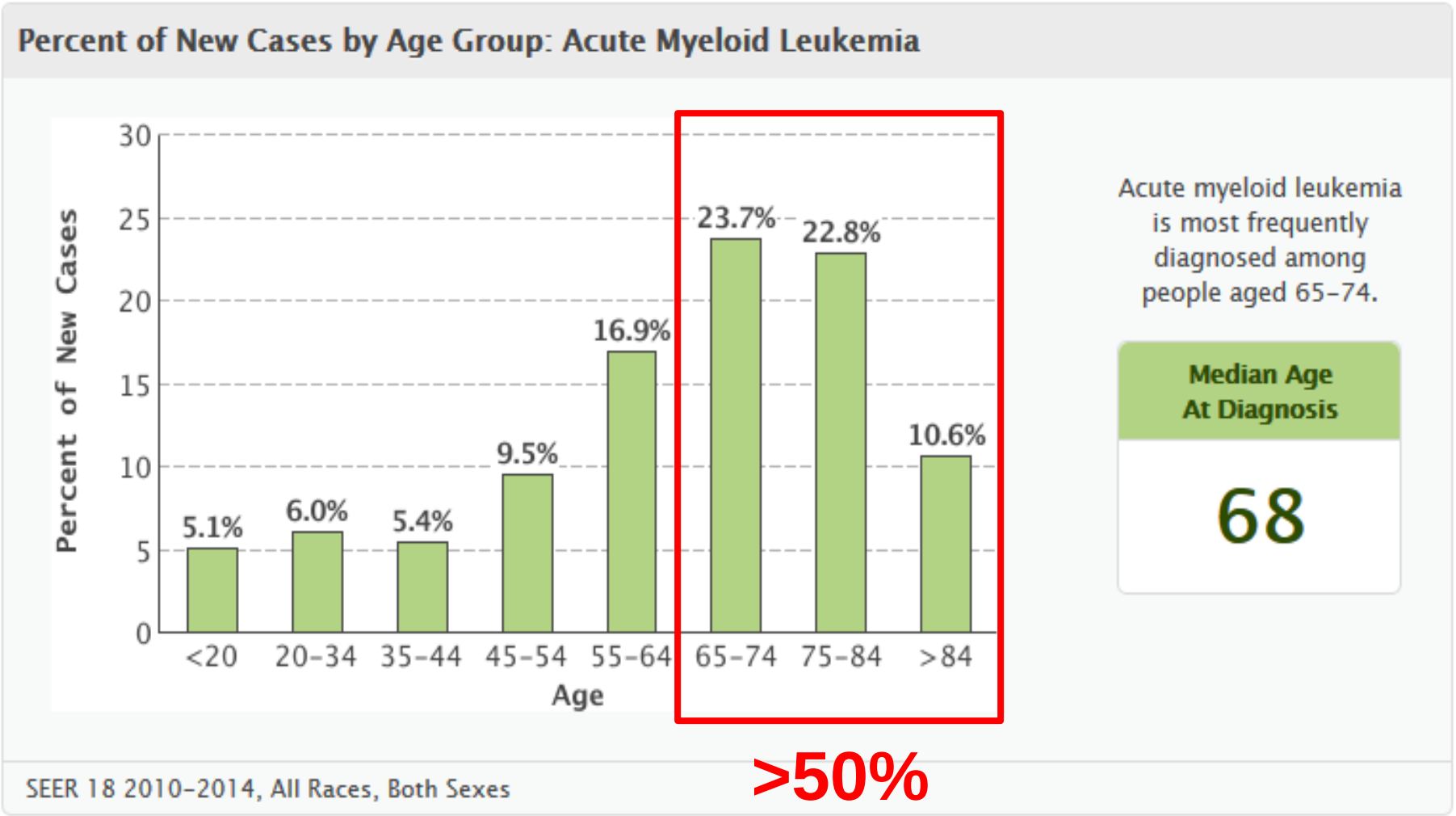
Döhner et al. NEJM 2015

2017 ELN recommendations

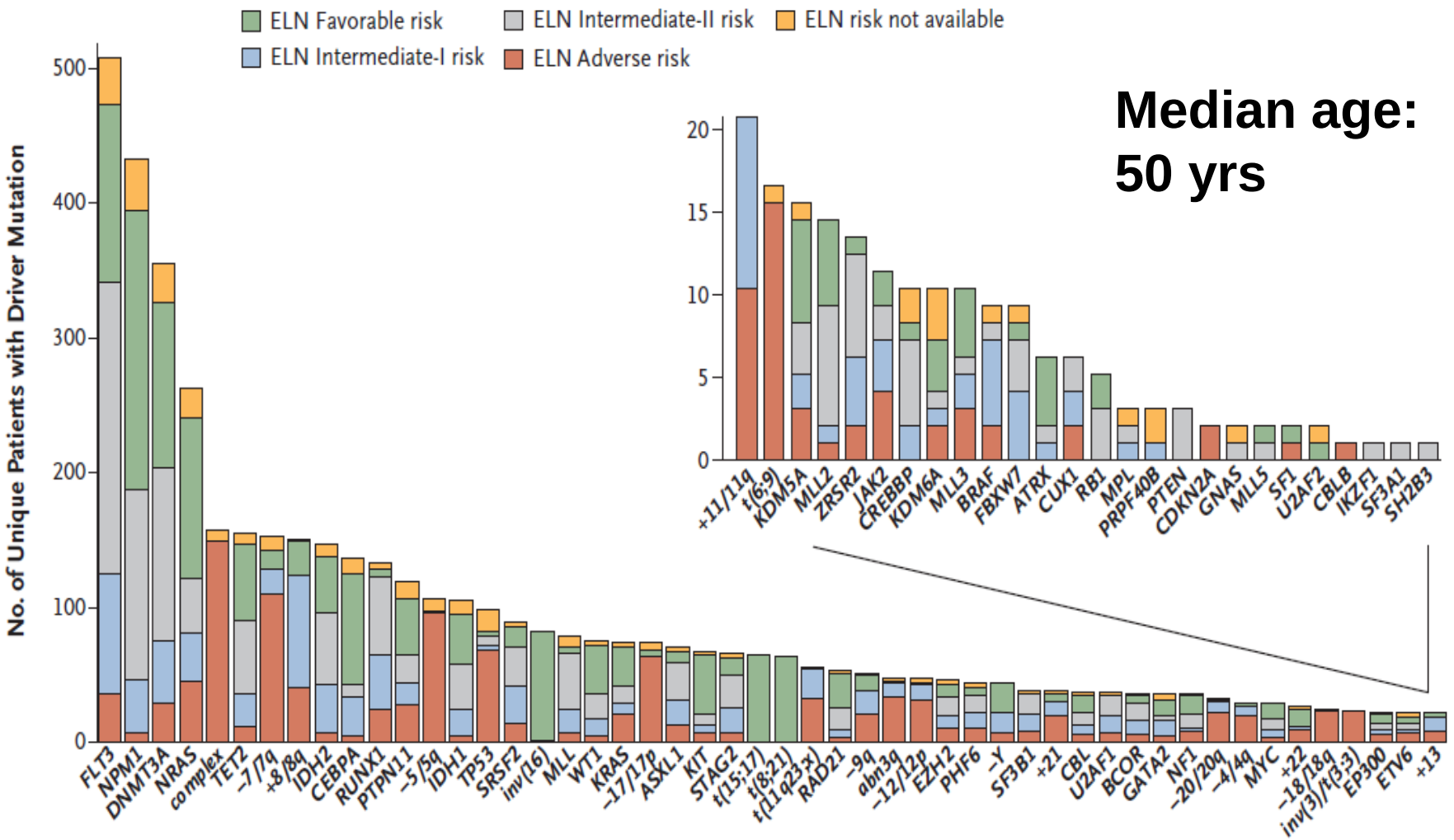
Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

Döhner et al. Blood 2017

AML incidence increases with age



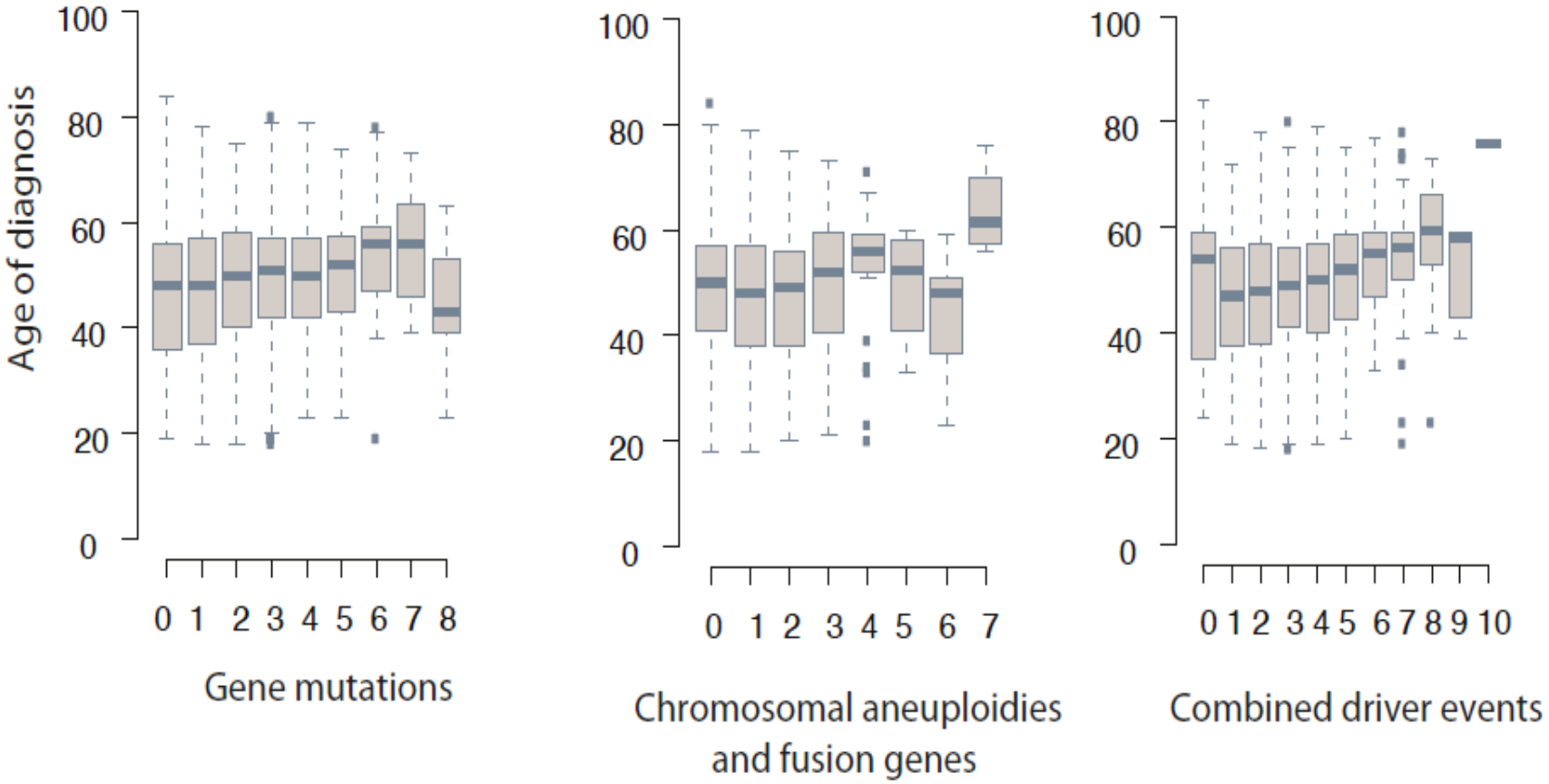
Genomic landscape of adult AML



Median age: 50 yrs

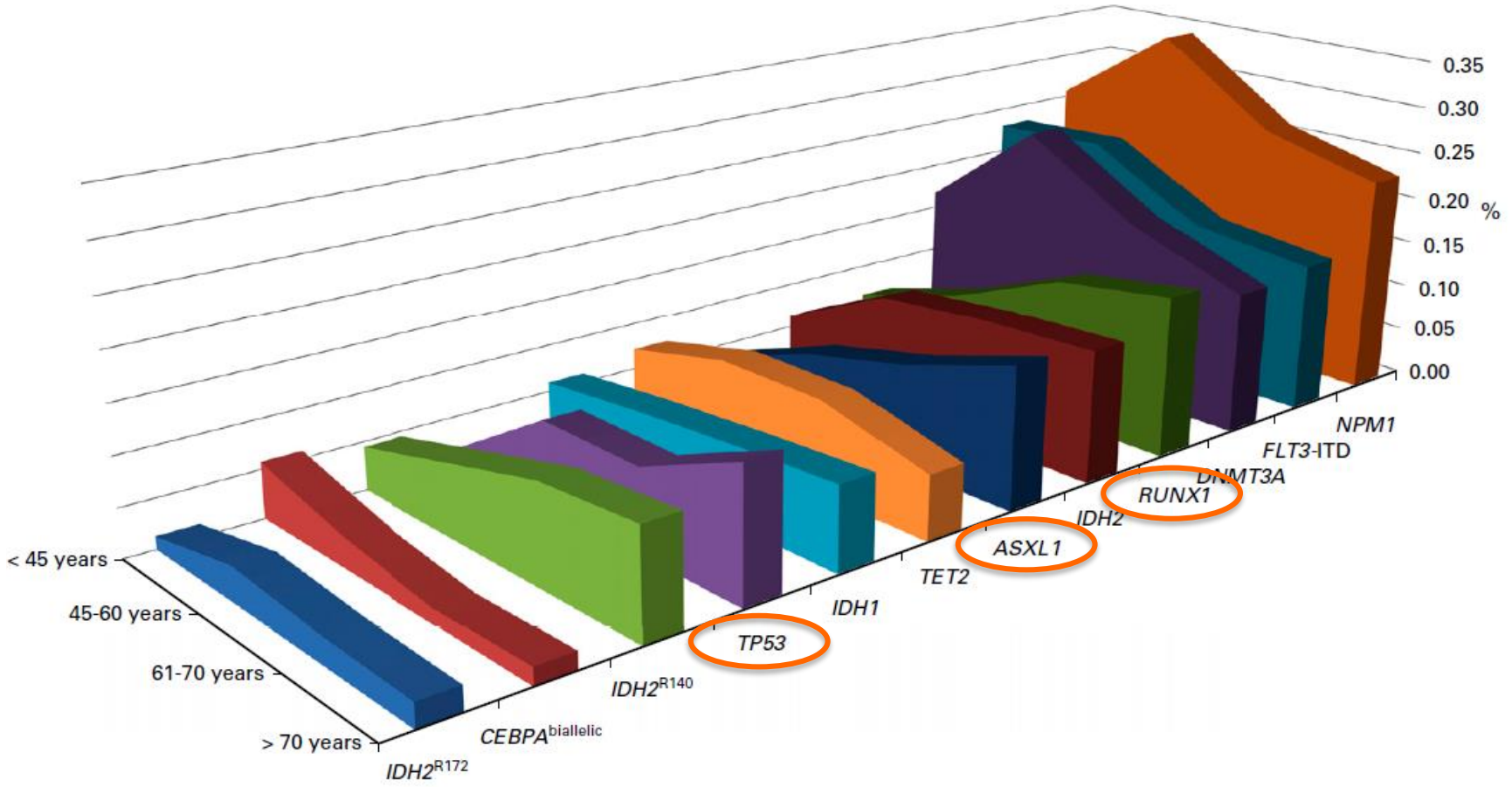
Papaemmanuil, Gerstung, Bullinger et al. N Engl J Med 2016

Number of driver mutations increases with age



Papaemmanuil, Gerstung, Bullinger et al. N Engl J Med 2016

Age-related frequency of gene mutations

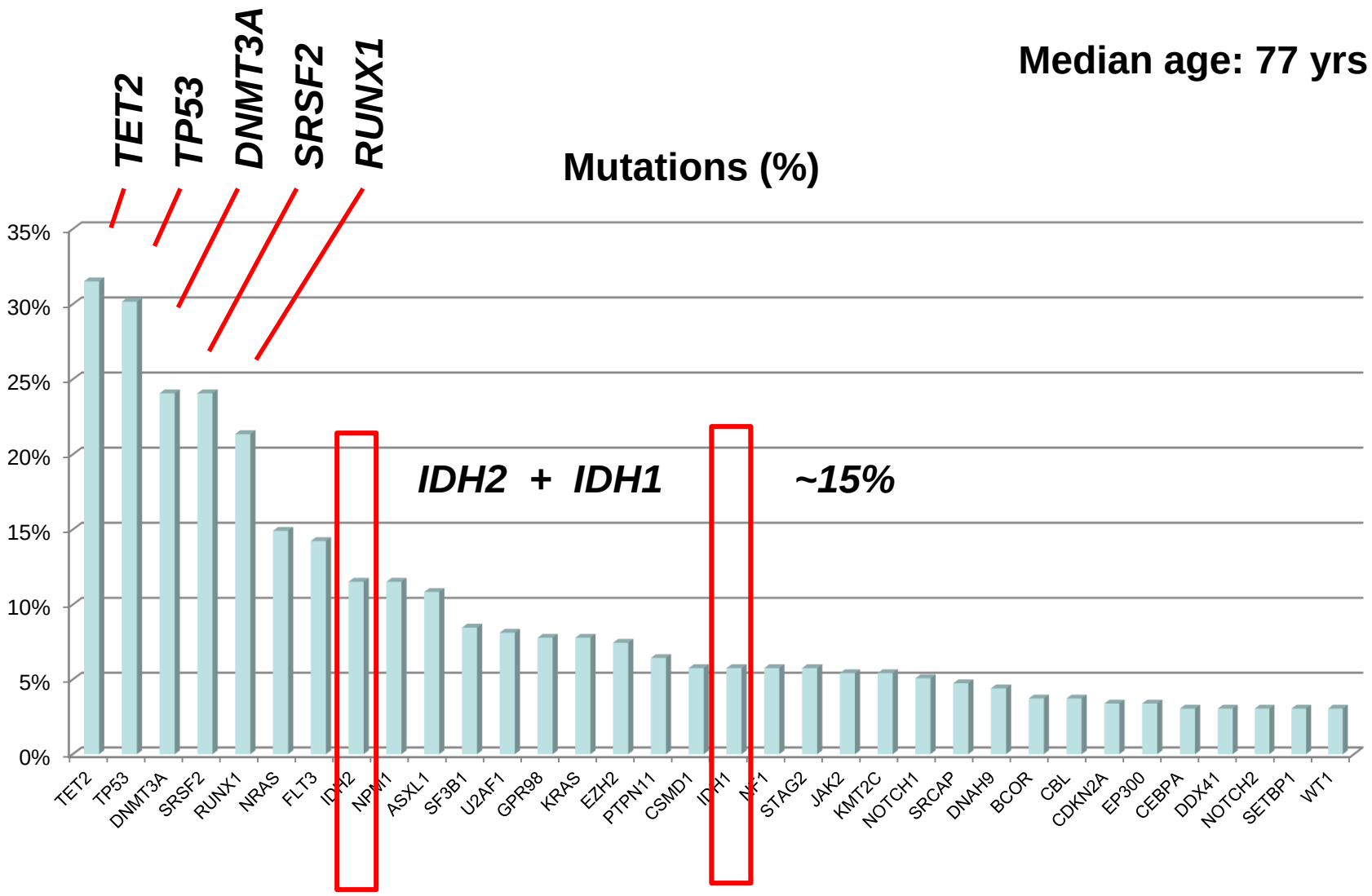


Analysis based on 10,622 AML patients from the AMLSG data base

Age distribution: <45 yrs, n=2,228; 45-60 yrs, n=3,392; 61-70 yrs, 2,517; **>70 yrs, n=2,485**

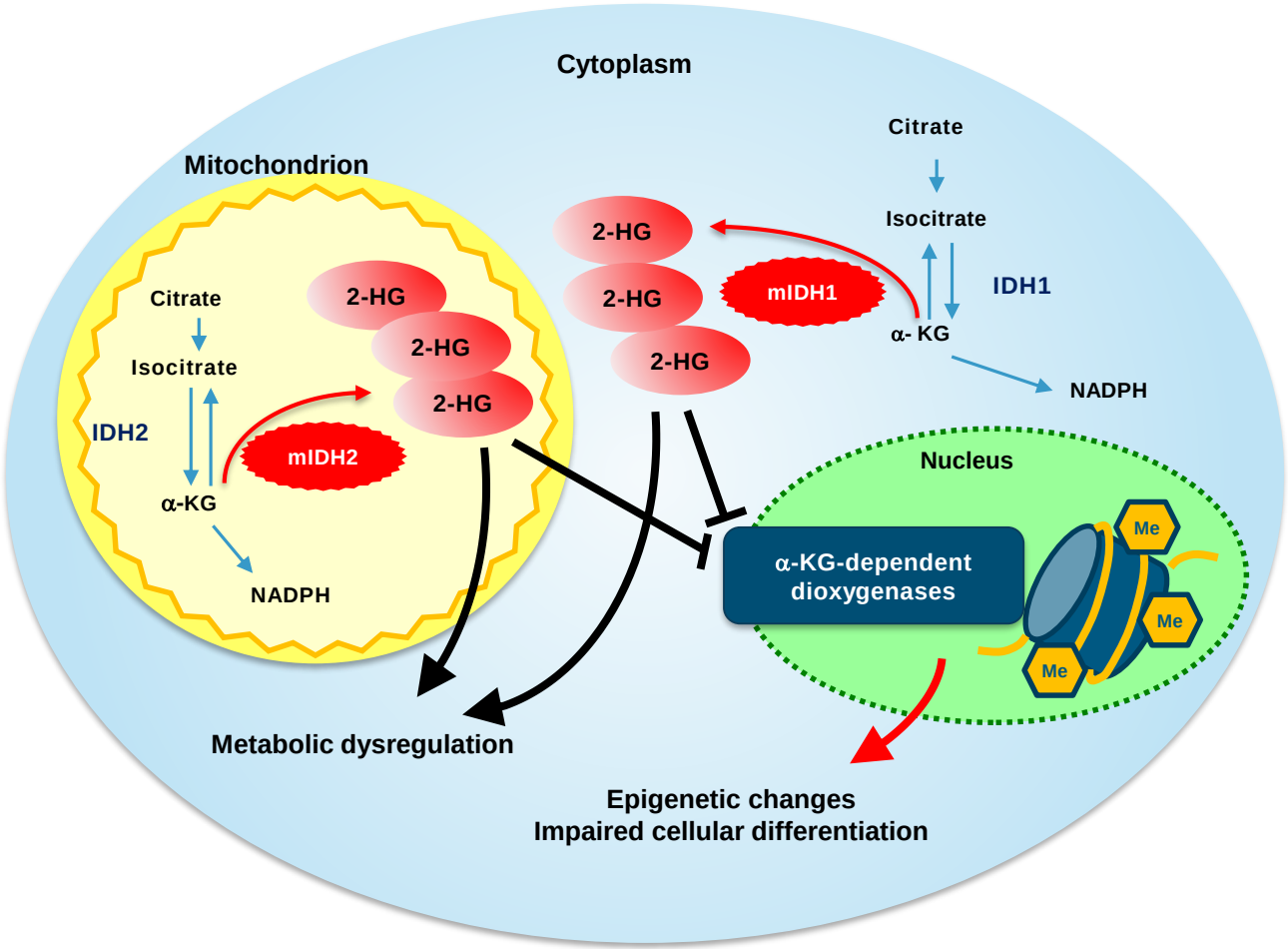
Bullinger et al. J Clin Oncol 2017

Mutational landscape in AML ≥70yrs (n=295)



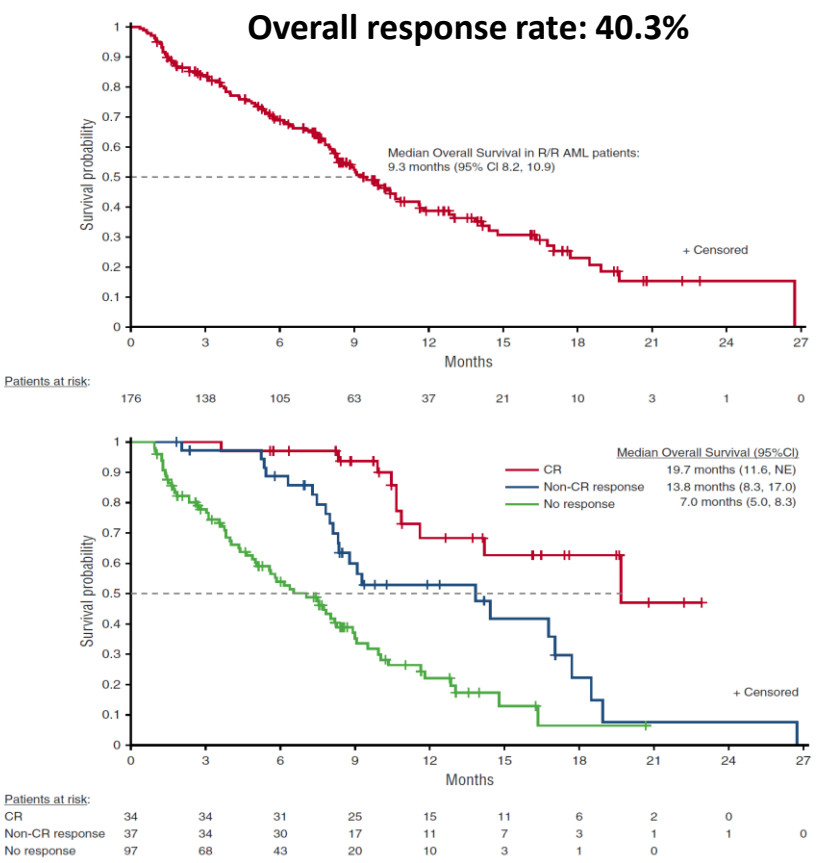
Hoyos et al. EHA 2018

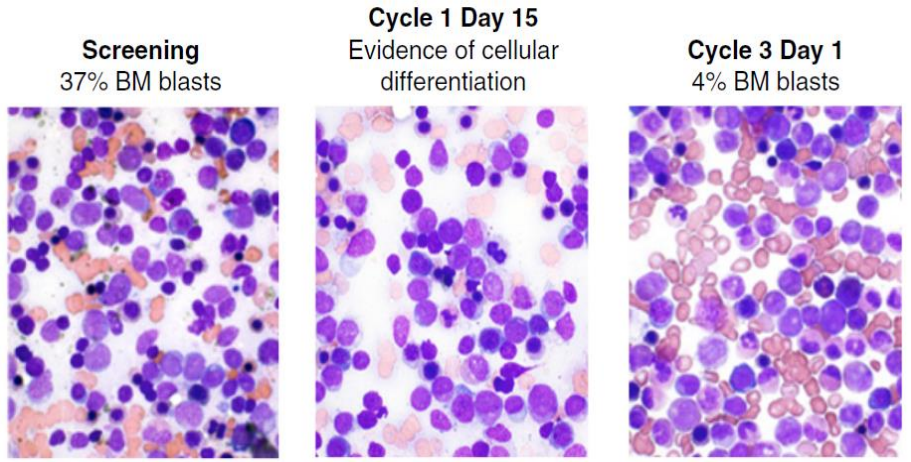
IDH1 and *IDH2* - therapeutic target structure

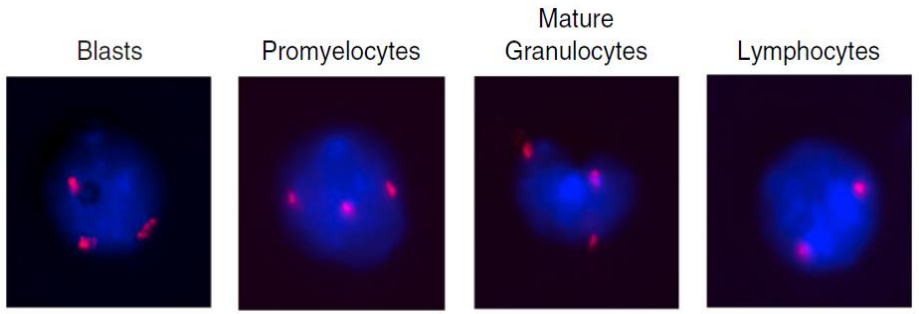


2-HG, 2-hydroxyglutarate; mIDH, mutant IDH

Enasidenib (AG-221) in *IDH2*^{mut} relapsed or refractory AML





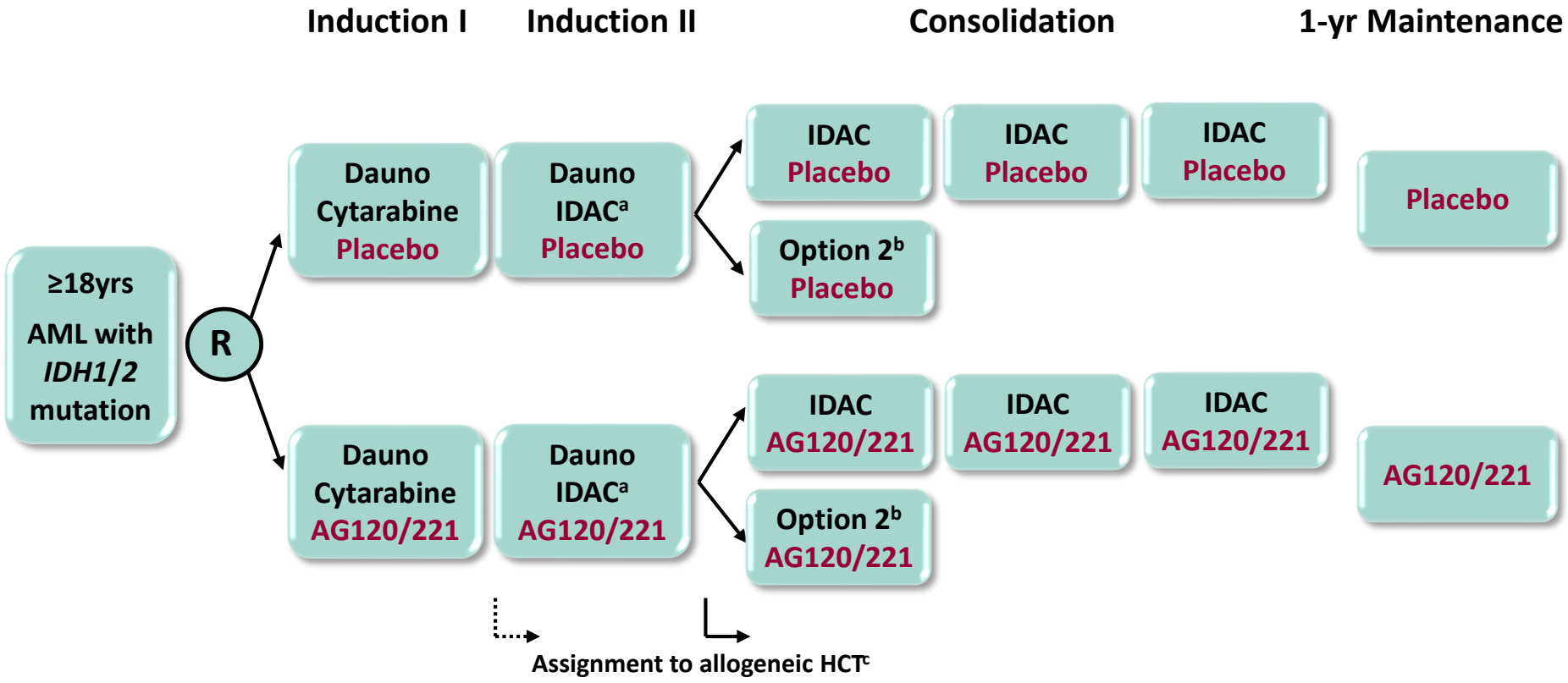


Stein et al. Blood 2017

Ivosidenib (AG-120) and Enasidenib (AG-221) clinical development program

	Phase I/II	Phase III
≥2nd r/r AML		**Phase III: AML-004 (IDHENTIFY)** Enasidenib *vs*. CCR N=280
Frontline ineligible for intensive chemotherapy	**Phase I/II AML-005** Azacitidine + ivosdenib Azaciditine +/- enasidenib N=175	**Phase III: AG120-C-009 (AGILE)** Azacitidine +/- ivosidenib N=392
Frontline eligible for intensive chemotherapy	**Phase I: AG-221-120-C-001** Ivosidenib/enasidenib + intensive Cx N=90	**HOVON 150 / AMLSG 29-18** Ivosidenib/enasidenib + intensive Cx N=~800

AG-120/AG-221 vs placebo + chemotherapy for *IDH1*^{mut}/*IDH2*^{mut} AML – AMLSG 29-18



Patients in CR/CRi after two cycles of induction proceed to AMLSG/HOVON-specific consolidation therapy; assignment to allogeneic hematopoietic cell transplantation (HCT) according to the local institutional or cooperative group prognostic algorithm; HCT can be performed at any time point following one induction cycle

[a] IDAC, intermediate-dose cytarabine; age-adapted dosing

[b] HOVON consolidation: autologous HCT; or mitoxantrone / etoposide

[c] Assignment based on patient- and disease-related factors

Expected start Q3/2018

HOVON

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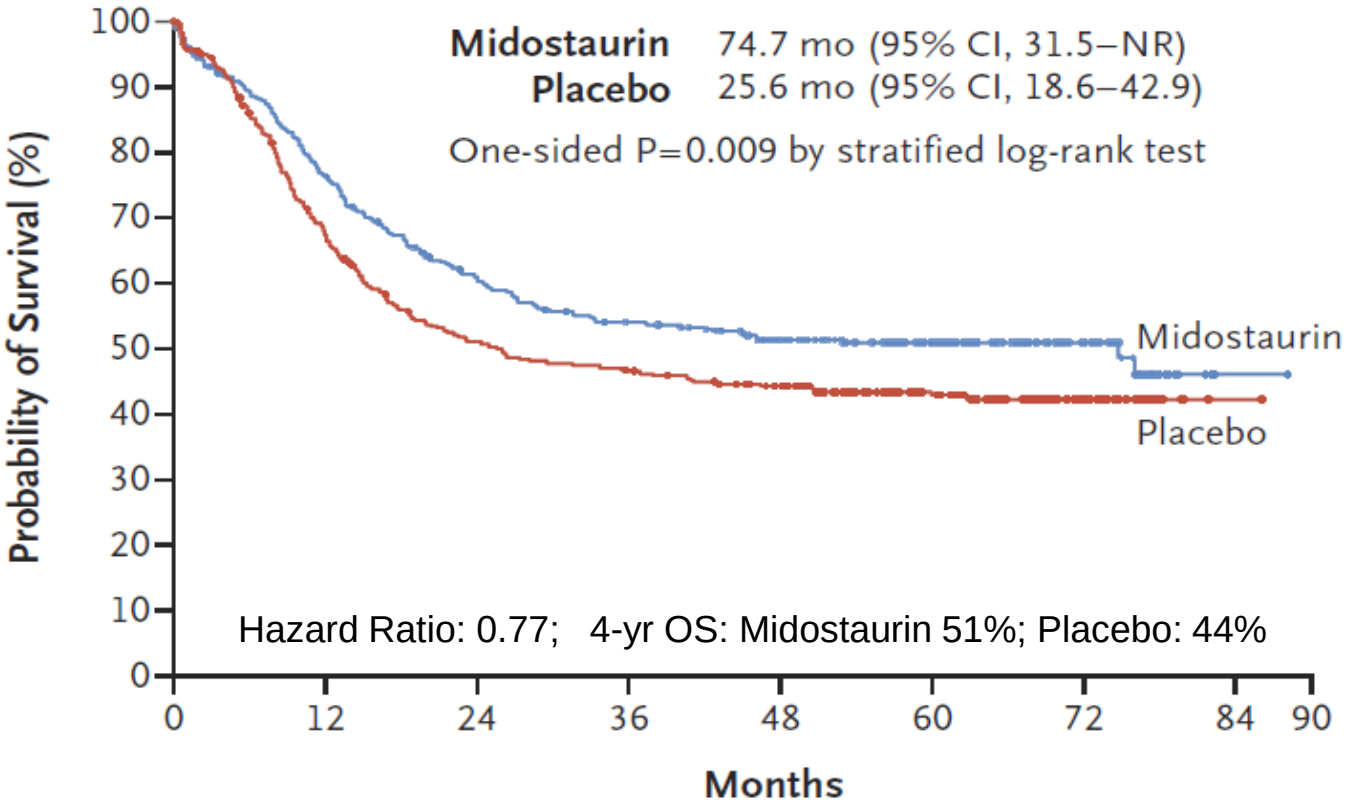
AML with *FLT3* mutation – midostaurin plus chemotherapy (RATIFY)

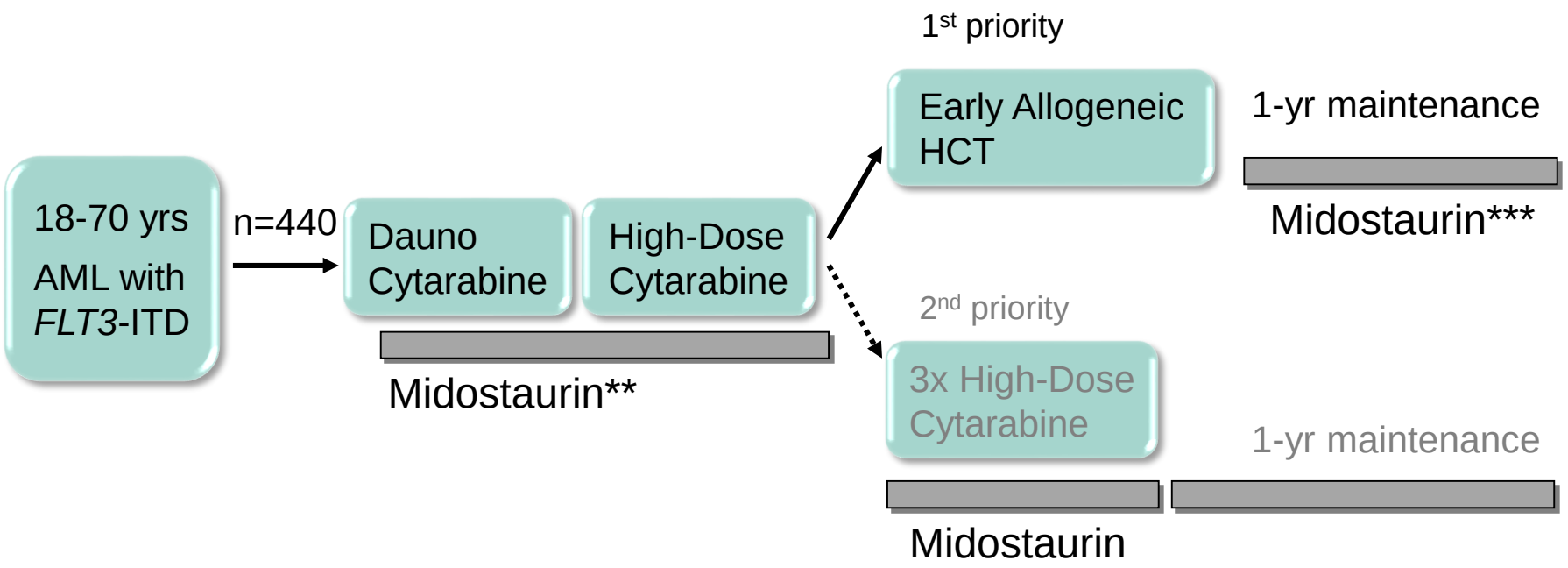


No. at Risk

Midostaurin	360	269	208	181	151	97	37	1
Placebo	357	221	163	147	129	80	30	1

Stone et al. NEJM 2017

Midostaurin plus chemotherapy for AML with *FLT3*-ITD – AMLSG 16-10



* Adult patients 18 – 70 years

** Continuous dosing of midostaurin (start on day 8; except days of chemotherapy)

*** Midostaurin given also after allogeneic HCT (start d+30)

ClinicalTrials.gov: NCT01477606 (active)

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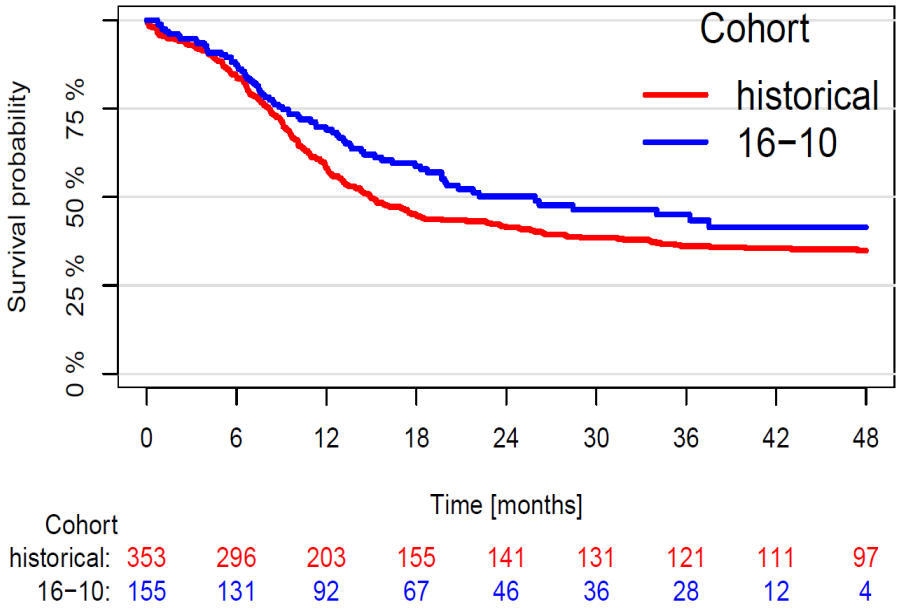
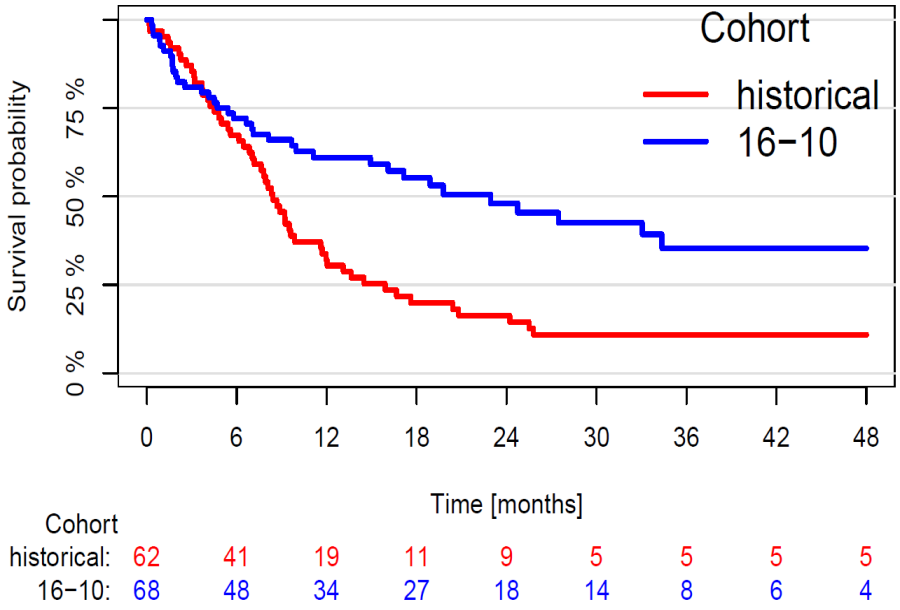
AMLSG 16-10 vs historical control - Propensity Score Weighting Analysis*

Age 18-60 years



HR = 0.70 (CI95% 0.535, 0.920)

Age 60-70 years



HR = 0.49 (CI95% 0.316, 0.753)

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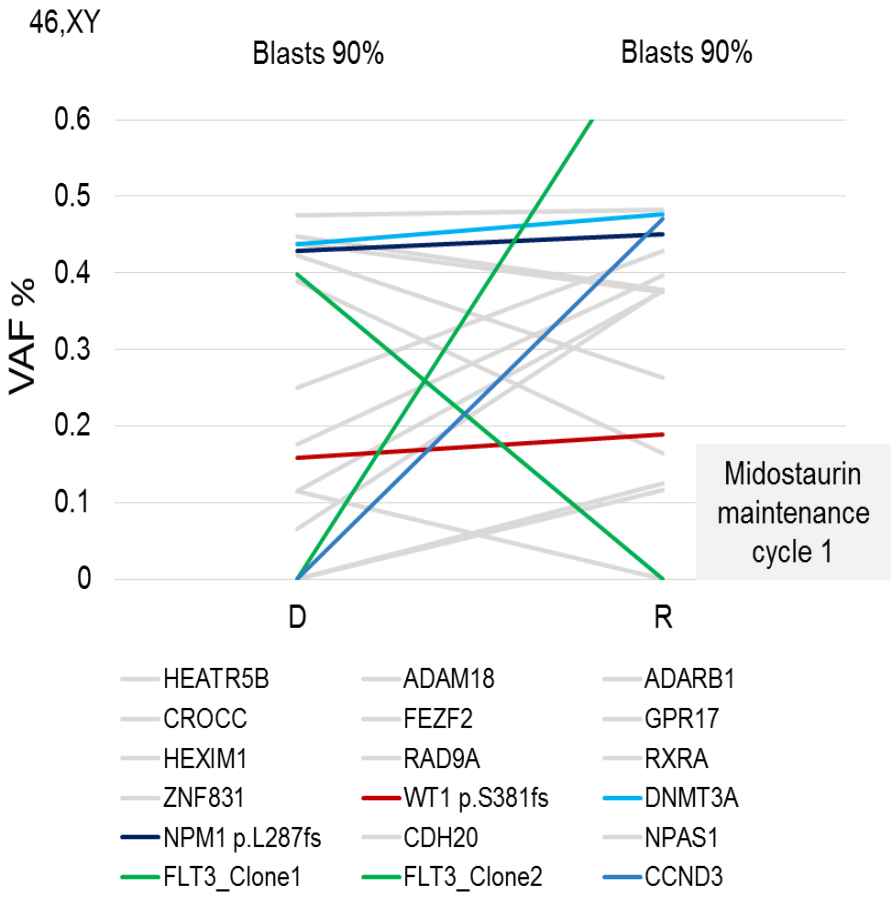
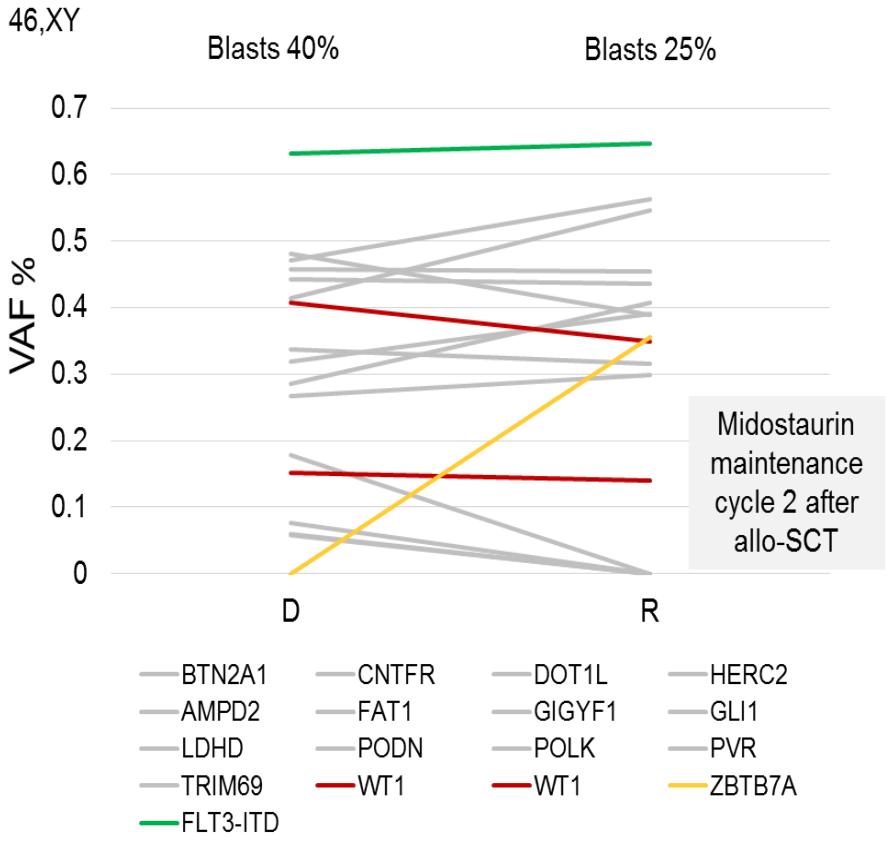
*Propensity score weighting
on age, gender, WBC, marrow blasts, *NPM1* mutations

Resistance to FLT3 inhibition

Patterns of clonal evolution – persistence of FLT3 at relapse

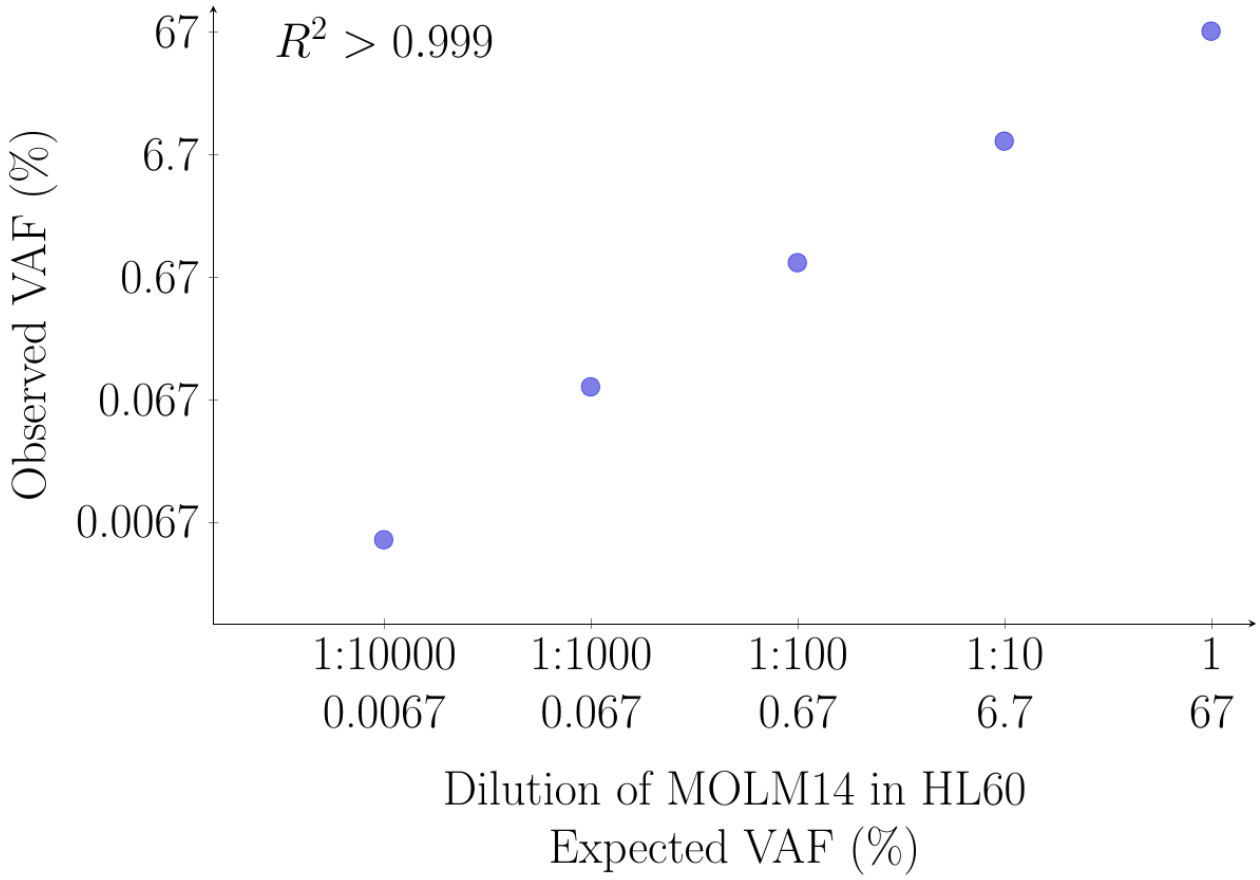




BM = Bone Marrow D = Diagnosis; R = Relapse; VAF = Variant Allele Frequency

Schmalbrock et al. ASH 2017, Manuscript in preparation.

Next-Generation-Sequencing based MRD monitoring in *FLT3*-ITD AML



Blätte et al. Manuscript in preparation

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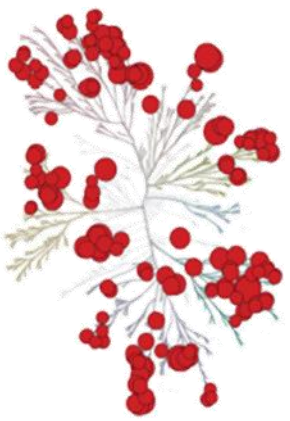
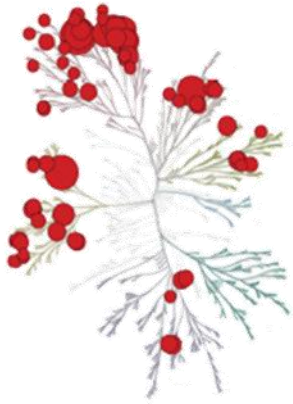
FLT3 Inhibitors in Clinical Development

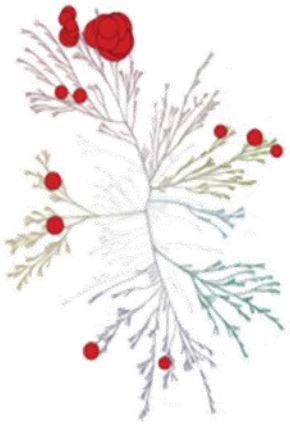
Relative selectivity and potency (IC_{50}) of TKIs against FLT3-ITD



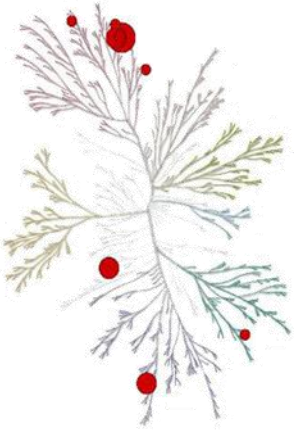
Midostaurin
1000 nM



Sorafenib
265 nM



Quizartinib
18 nM



Crenolanib
35 nM

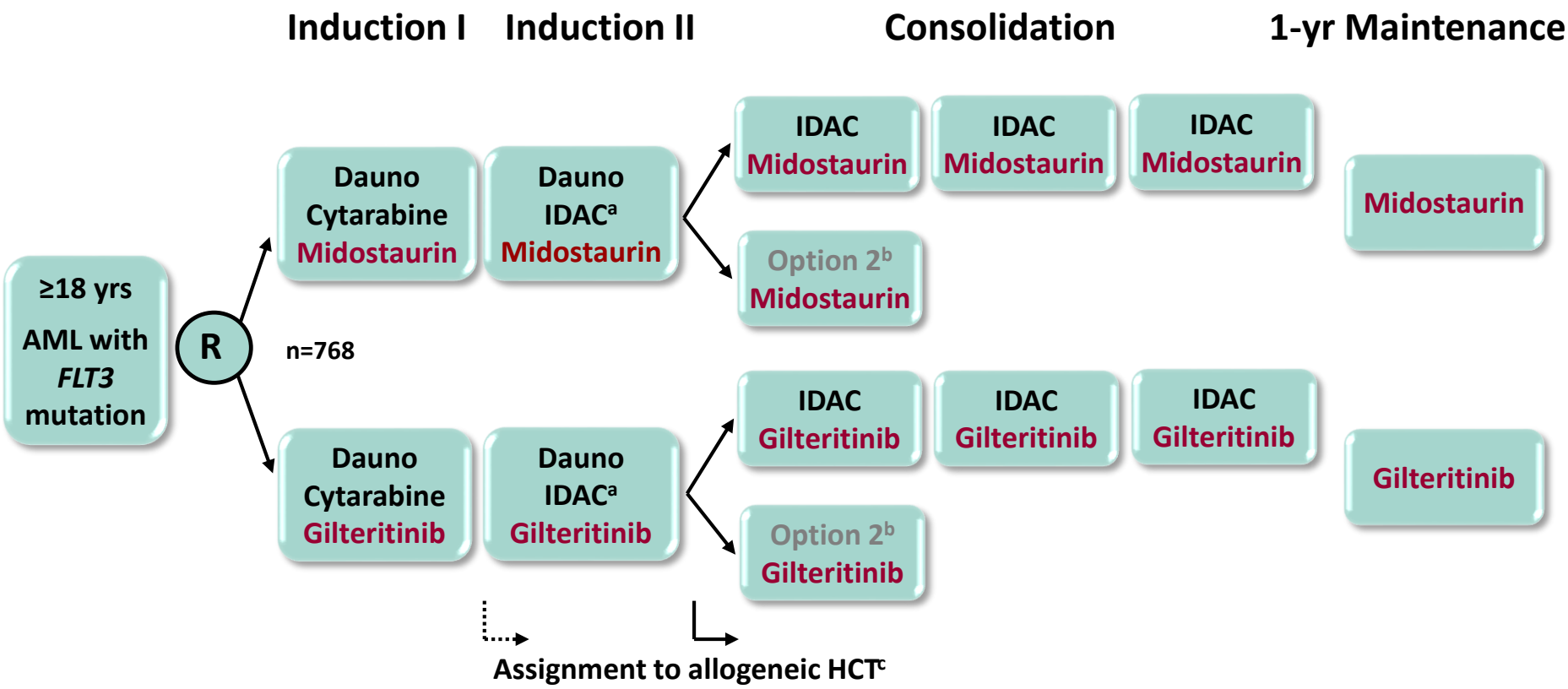
Kinase	IC_{50} (nmol/L)
FLT3	0.29
LTK	0.25
ALK	0.42
AXL	0.70
TRKA	1.1
RET	1.8
ROS	1.5
MER	2.9
c-KIT	230

Gilteritinib
0.29 nM

- **1st generation TKIs non-selective; less favorable safety profile; when used as single agent, only transient blast reductions observed**
- **2nd generation TKIs (quizartinib [AC220], crenolanib, gilteritinib [ASP2215]) more selective and more potent**

Galanis A, et al. Cancer Res. 2012;72:3660 (abstract); Karaman MW, et al. Nature Biotechnology. 2008;26(1):127-132; Zarrinkar PP, et al. Blood. 2009;114(14):2984-2992.

Midostaurin vs Gilteritinib + chemotherapy for *FLT3*^{mut} AML – AMLSG 28-18



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[a] IDAC, intermediate-dose cytarabine; age-adapted dosing

[b] HOVON consolidation: autologous HCT; or mitoxantrone / etoposide

[c] Assignment based on patient- and disease-related factors

Expected start: Q3 / 2018

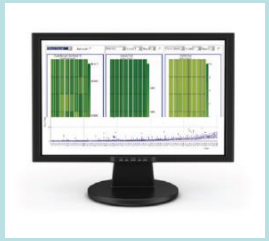
HOVON

STUDY AML GROUP

NGS-based routine AML diagnostics

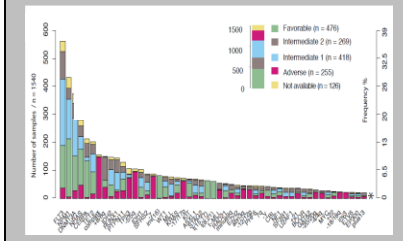
Targeted Re-Sequencing in routine AML diagnostics

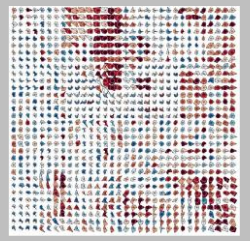
e.g. with the aid of Illumina sequencing technology (MiSeq)
=> „Myeloid Panel“



Building up databases => Linking genetic and clinical information („Knowledge Databases“)

Continuous process (data sets from older pts, targeted therapies, etc.)





Individualized risk prediction and therapeutic decision making

Translation into the clinic

AMLSG Center

AMLSG BiO Registry

Informed Consent

- Diagnostic work-up
- Documentation of clinical data
- Biobanking

➢ Biosamples (BM/PB) sent via Courier Express

Reference Lab

Genetic Testing

Molecular genetics — within 24-48 hrs

- *PML-RARA*
- *RUNX1-RUNX1T1*
- *CBFB-MYH11*
- *MLLT3-KMT2A*
- *NPM1*
- *CEBPA*
- *FLT3*
- *IDH1/2*

within 1st Rx cycle

- *RUNX1*
- *ASXL1*
- *TP53*

Cytogenetics — within 5-7 days

AMLSG Center

Recommendation

APOLLO	+/- ATO-ATRA-Ida
AMLSG 21-13	+/- Dasatinib
AMLSG 19-13	+/- Crenolanib
AMLSG 28-18	Mido vs Gilteritinib
Novartis	+/- Midostaurin
AMLSG 29-18	+/- AG-120/-221
AMLSG 30-18	CPX-351 vs ‚3+7'
AMLSG 24-15	AZA + Vosaroxin
Conventional Care	

0 — 24 — 48-72 hrs

7 days a week

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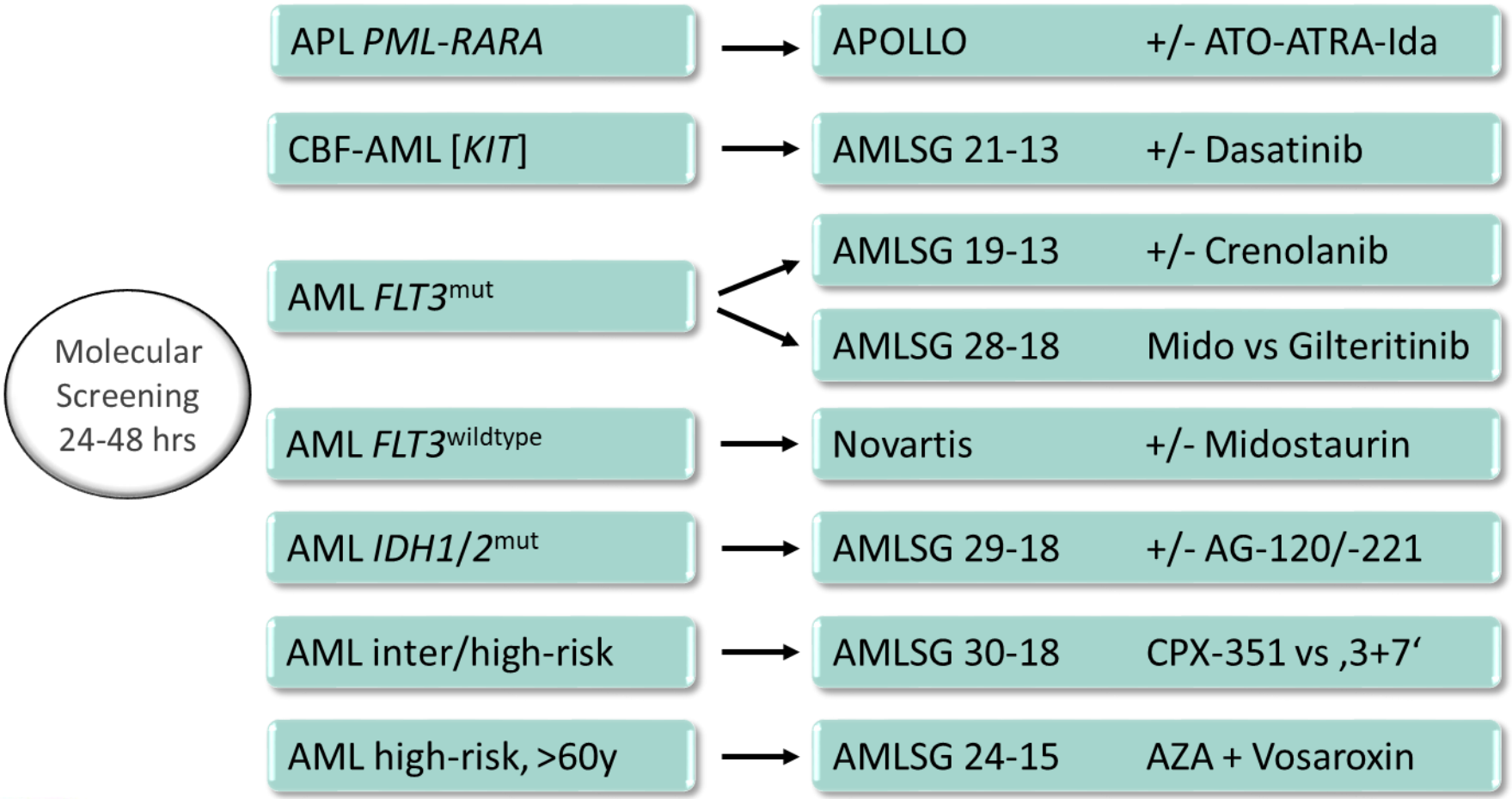
AMLSG-BiO [NCT01252485]

Genetics guided AML therapy

⇒ AMLSG 2018 portfolio – intensive therapy



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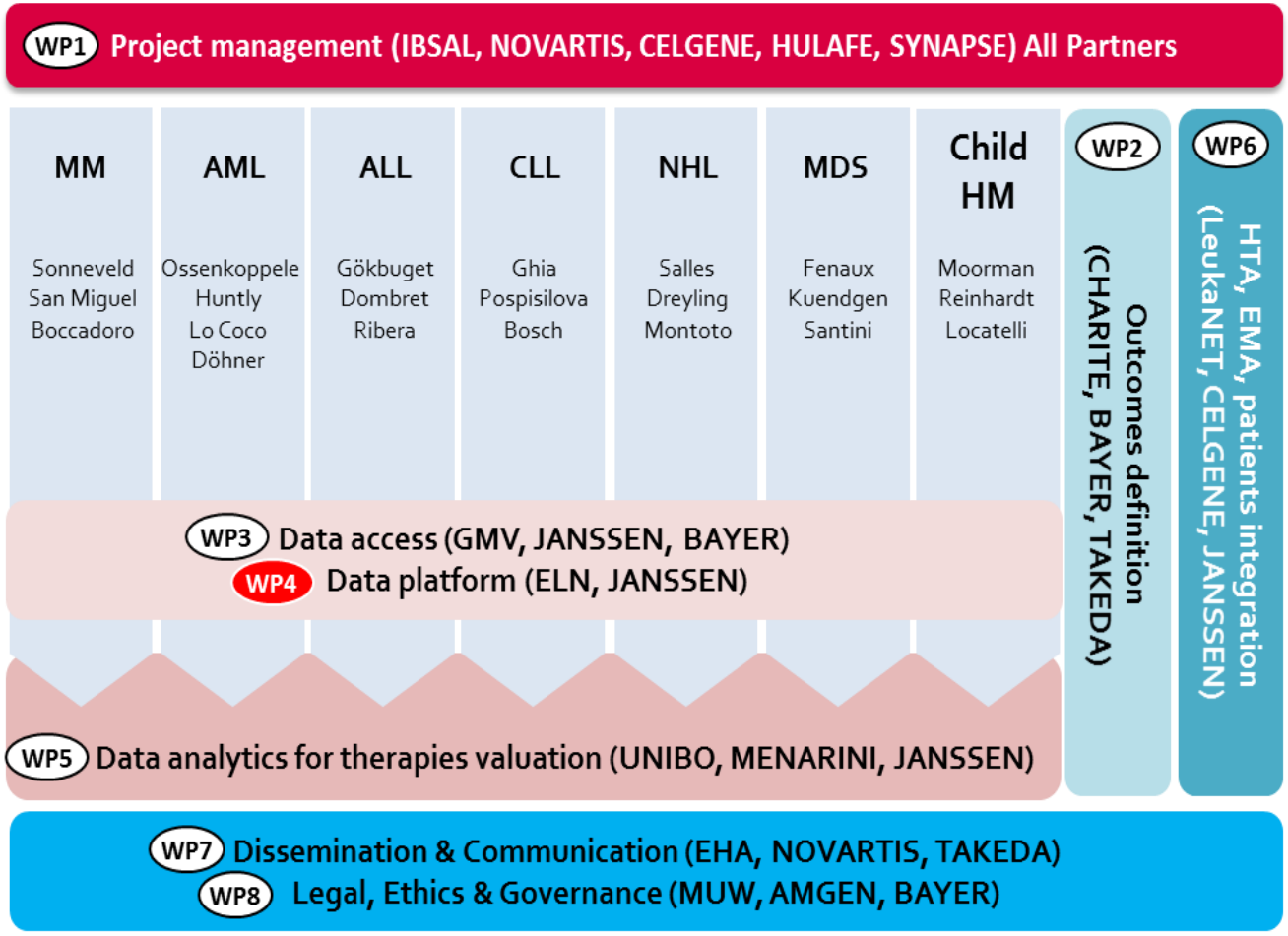
Big Data for Better Outcomes program



HARMONY

Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in HematologY

efpia

imi innovative medicines initiative

www.harmony-alliance.eu

Precision medicine in AML: hype or hope?

- We have entered a new era in leukemia genomics
- Currently, cytogenetics and *NPM1*, *CEBPA*, *FLT3*, *RUNX1*, *ASXL1* and *TP53* mutational screening are standard of care (ELN)

  ⇒ *Targeted gene panel testing*
- Explosion of knowledge starts to be translated into therapeutic benefit

  ⇒ *Building up large knowledge data bases*

  ⇒ *Novel compounds at the horizon hold promise to enter the clinic*
- Major challenge: identification of predictive biomarkers that help selecting the appropriate therapy for an individual patient

  ⇒ *Integrate biosampling, companion studies*
- **Enter your patients, younger or older, on a clinical trial!**

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Bundesministerium für Bildung und Forschung

TRANSCAN

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