AML- Aktuelles in der First-line

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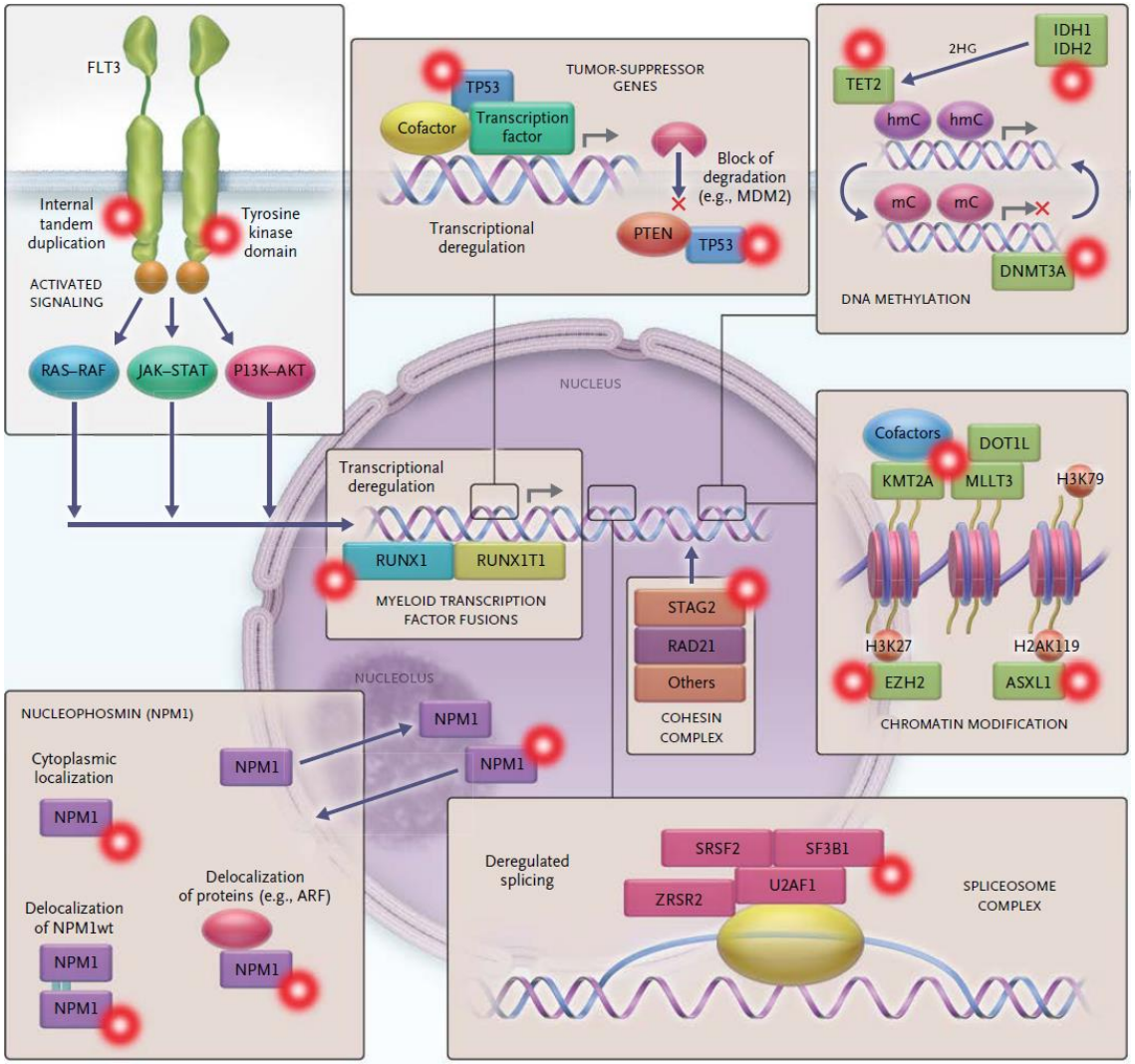
AML STUDY GROUP

Genomic landscape of de novo AML



Döhner et al. NEJM 2015

Commonly mutated functional gene categories:

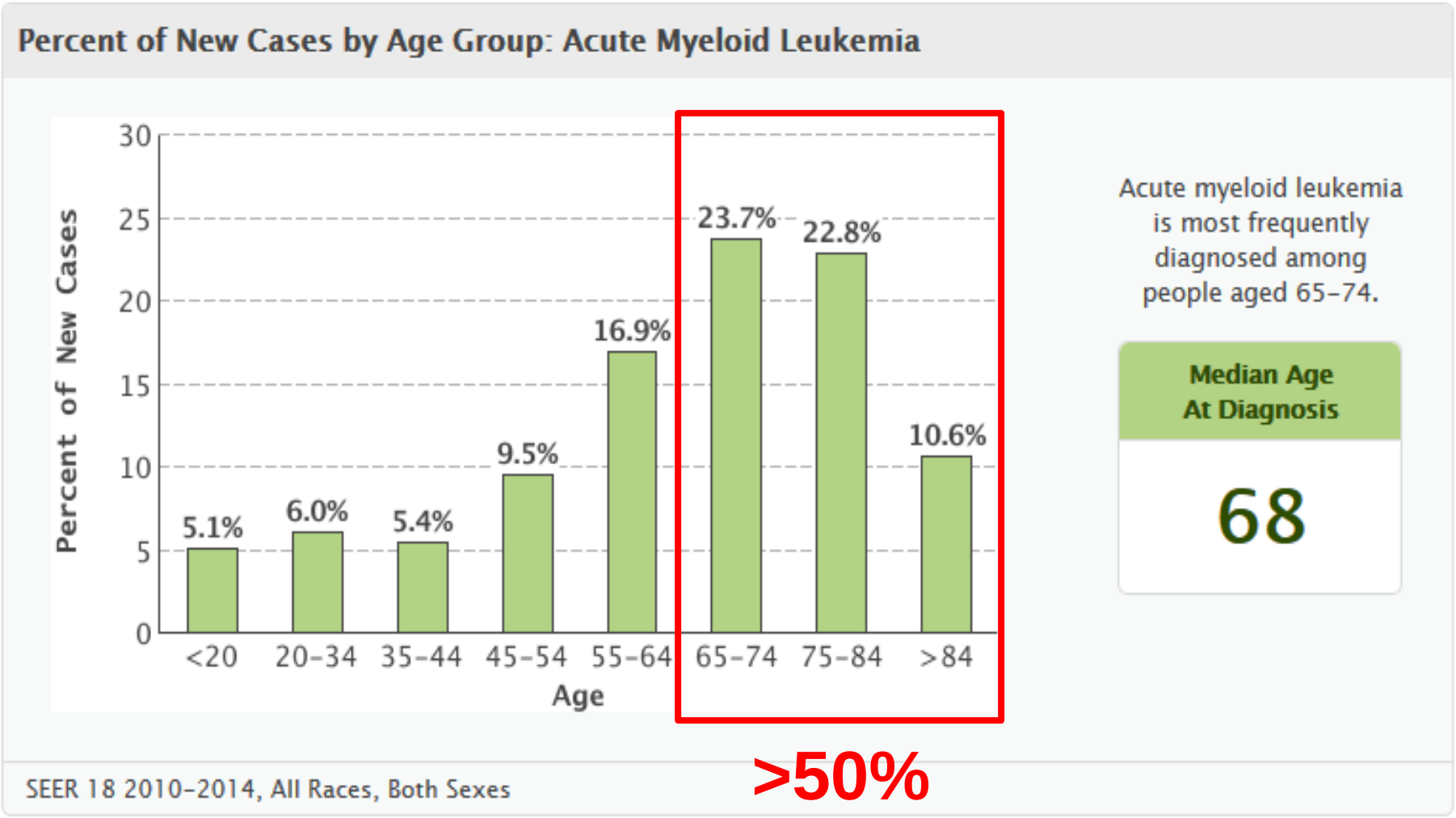
(1) signaling genes
(2) transcription factors
(3) NPM1
(4) spliceosome complex
(5) Cohesion complex
(6) chromatin modification
(7) DNA methylation
(8) tumor-suppressors

2017 European LeukemiaNet Guidelines

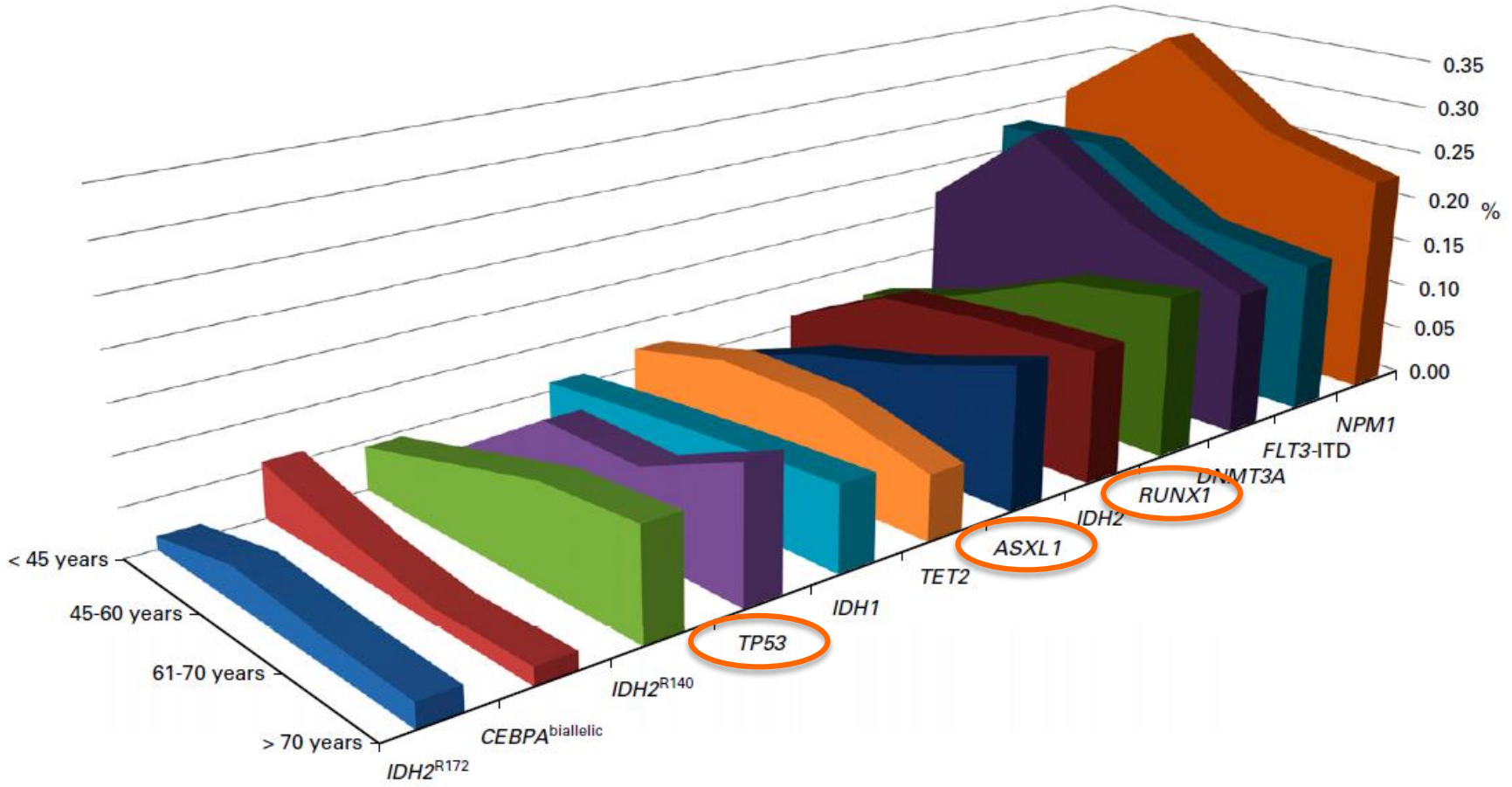
Risk Category	Genetic Lesion
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1* inv(16)(p13.1q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD or ***FLT3*-ITD^{low}** Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and ***FLT3*-ITD^{high}** Wild type *NPM1* without ***FLT3*-ITD** t(9;11)(p21.3;q23.3); *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 (≥3), monosomal karyotype Wild type *NPM1* and ***FLT3*-ITD^{high}** Mutated *RUNX1* Mutated *ASXL1* Mutated *TP53*

Döhner H, et al. Blood. 2017;129(4):424-447.

AML incidence increases with age



Age-related frequency of gene mutations



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

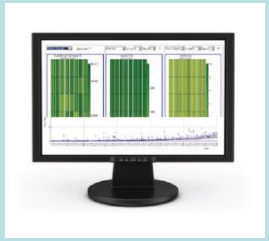
Age distribution: <45 yrs, n=2,228; 45-60 yrs, n=3,392; 61-70 yrs, 2,517; **>70 yrs, n=2,485**

Bullinger et al. J Clin Oncol 2017

NGS-based routine AML diagnostics

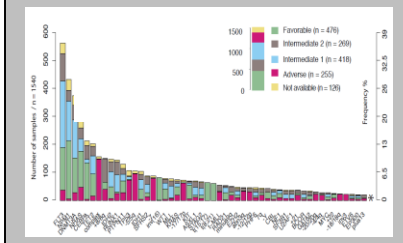
Targeted Re-Sequencing in routine AML diagnostics

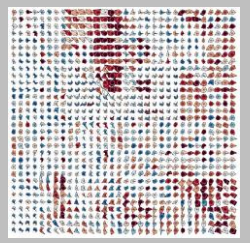
e.g. with the aid of Illumina sequencing technology (MiSeq)
=> „Myeloid Panel“



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

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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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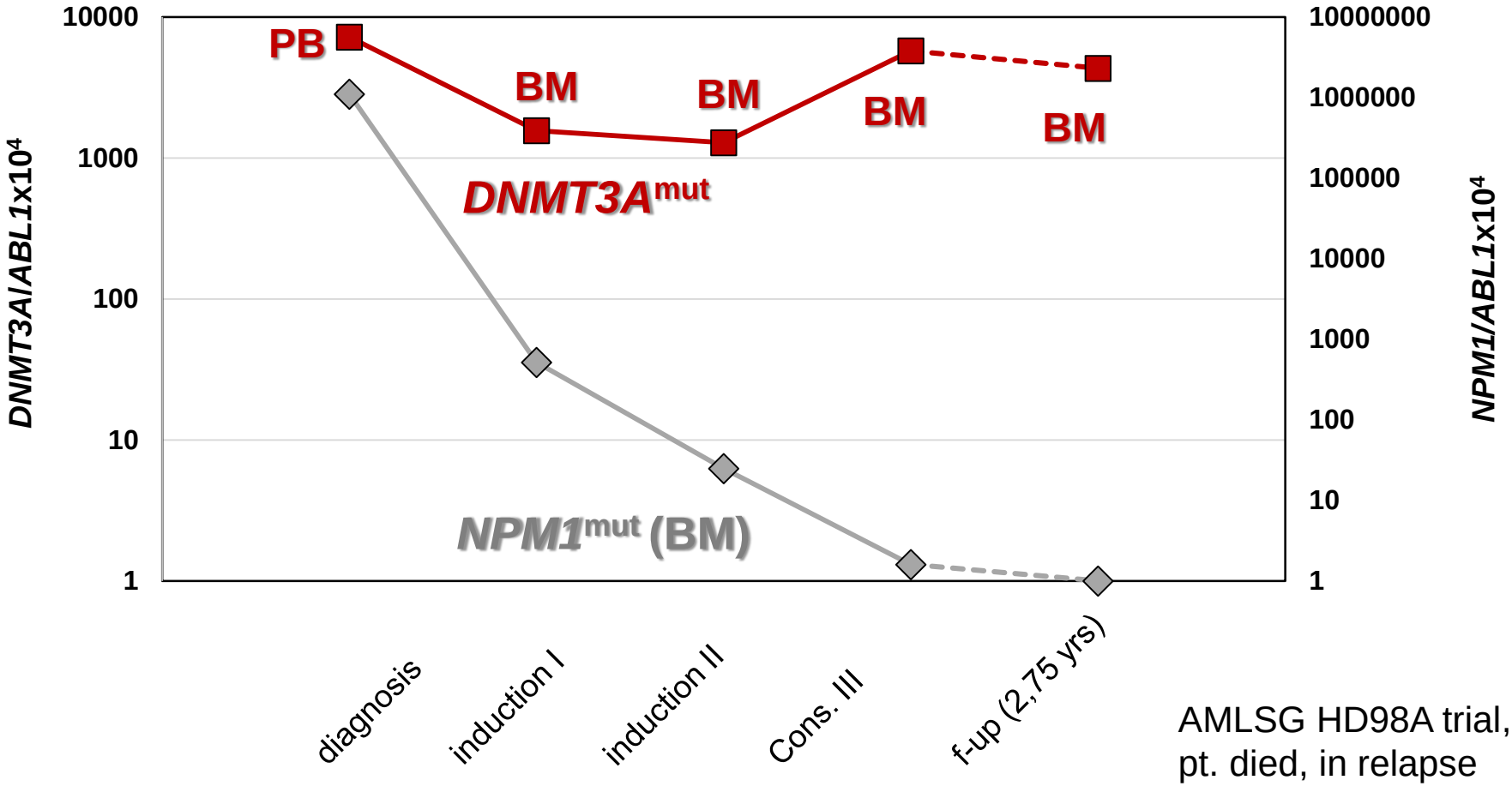
AMLSG-BiO [NCT01252485]

MRD of *DNMT3A*^{mut}-R882H and *NPM1*^{mut}

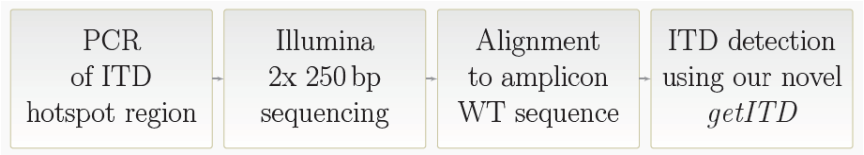


AMLSG HD98A trial,
pt. died, in relapse

Gaidzik et al. Leukemia 2018

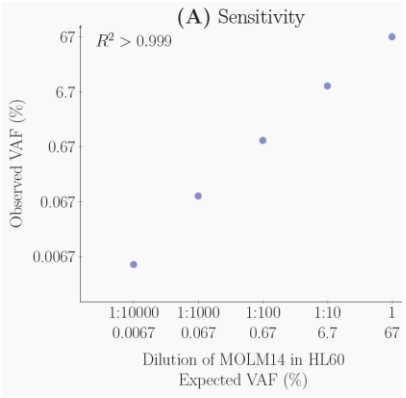
Next-Generation-Sequencing based *FLT3*-ITD MRD monitoring

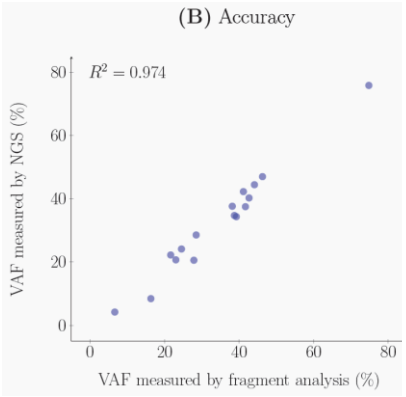
MRD Assay



FLT3-ITD Detektion

Test Performance





Blätte et al. ASH 2018, manuscript in revision.

FLT3-ITD Mutations

⇒ ***FLT3*-ITD mutations in approximately 25% of patients**

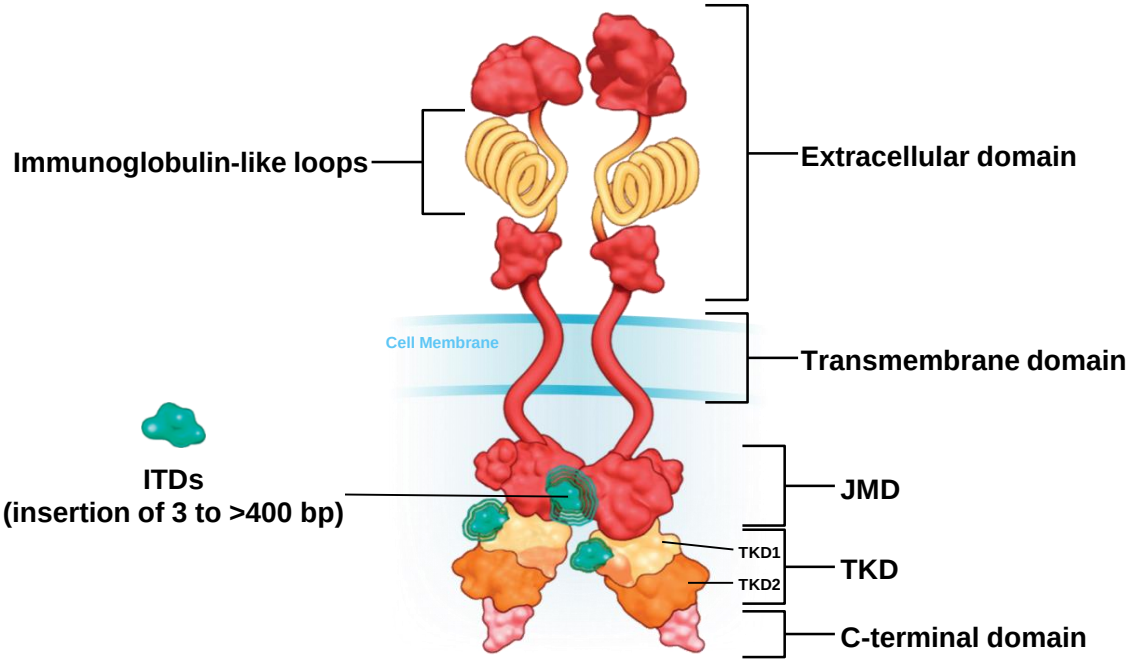


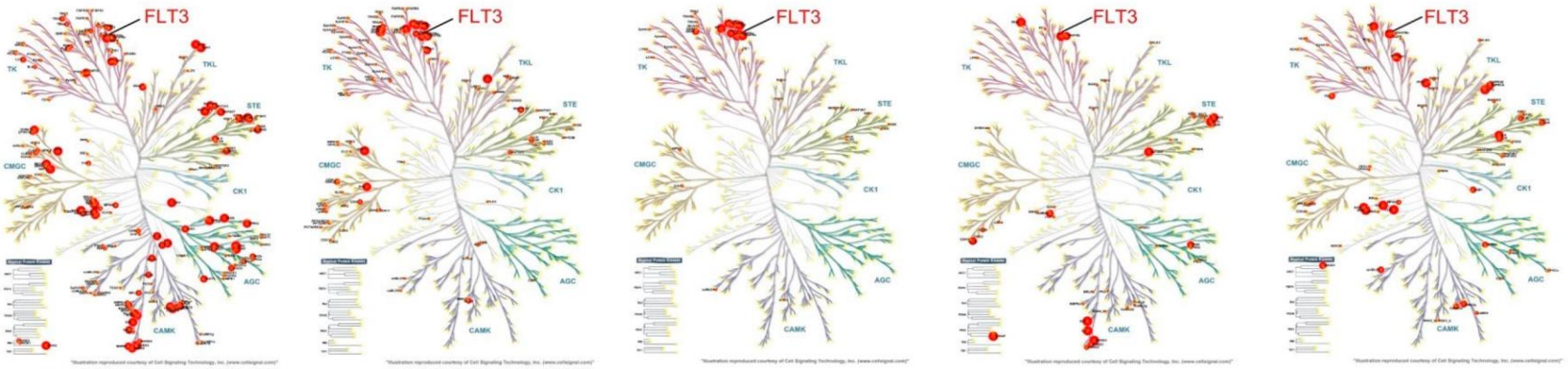
Figure adapted from Taylor & Francis Ltd, http://www.tandfonline.com: Patnaik MM. *Leuk Lymph*. 2017:1-14.

⇒ **driver mutation associated with high leukemic burden and poor prognosis (high risk of relapse, decreased response to salvage therapy, short OS)**

References: 1. Schneider F, et al. *Ann Hematol*. 2012;91(1):9-18. 2. Santos FP, et al. *Cancer*. 2011;117(10):2145-2155. 3. Kainz B, et al. *Hematol J*. 2002;3(6):283-289. 4. Kottardis PD, et al. *Blood*. 2001;98(6):1752-1759. 5. Patel JP, et al. *N Engl J Med.* 2012;366(12):1079-1089. 6. Levis M. *Hematol Am Soc Hematol Educ Program*. 2013;2013:220-226. 7. Ravandi F, et al. *Leuk Res.* 2010;34(6):752-756.
8. Tallman MS. *Hematol Am Soc Hematol Educ Program*. 2005:143-150.

FLT3 Inhibitors in Clinical Development

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

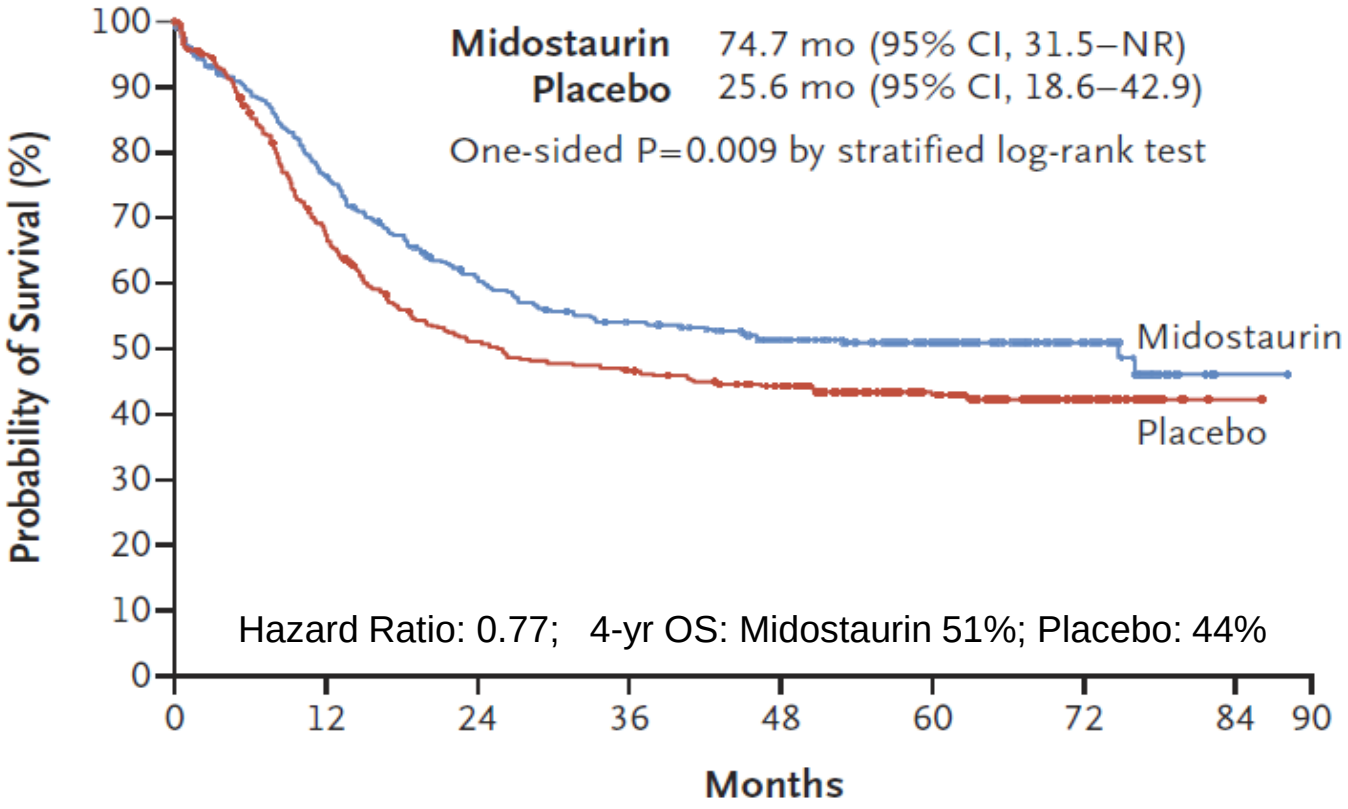


Midostaurin	Sorafenib	**Quizartinib**	**Crenolanib**	**Gilteritinib**
1000 nM	265 nM	**18 nM**	**35 nM**	**0.29 nM**

- **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. Staudt D, et al. Int J Mol Sci. 2018;19(10).

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

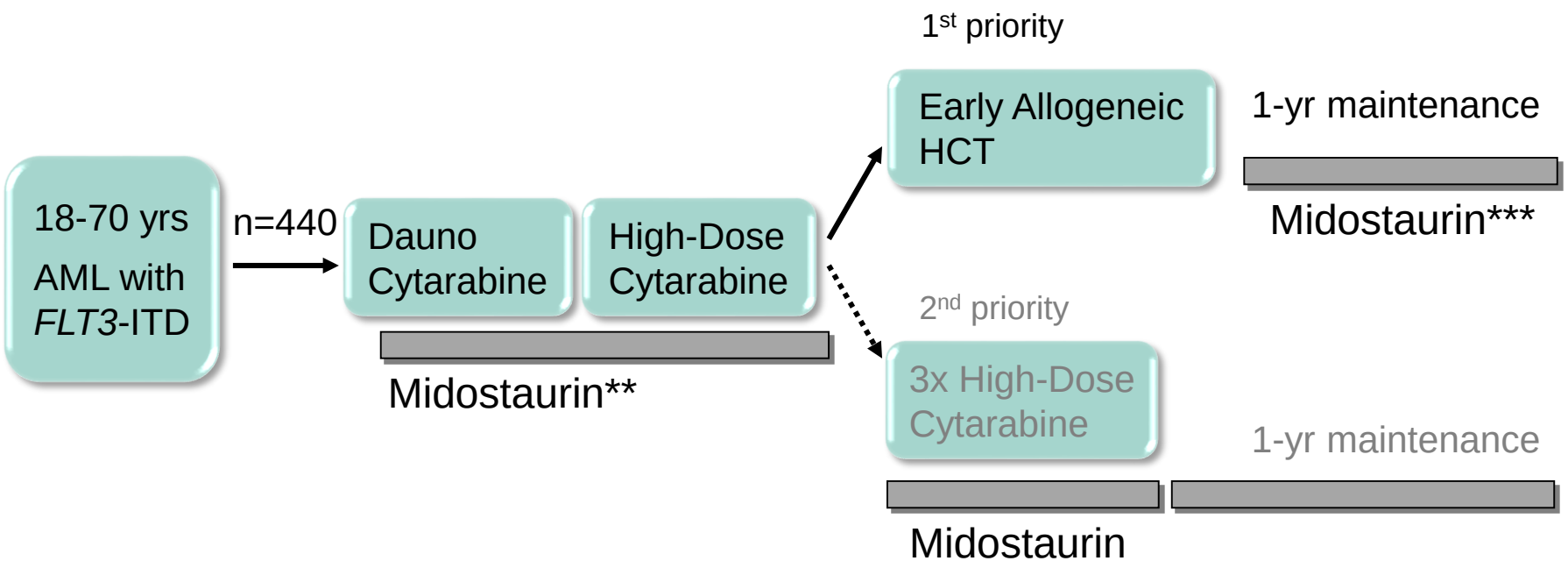


No. at Risk

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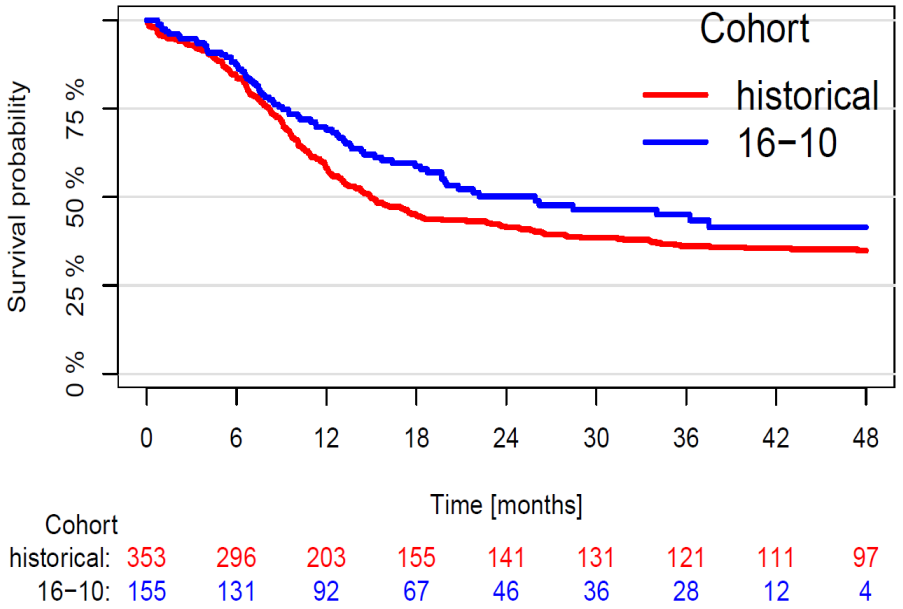
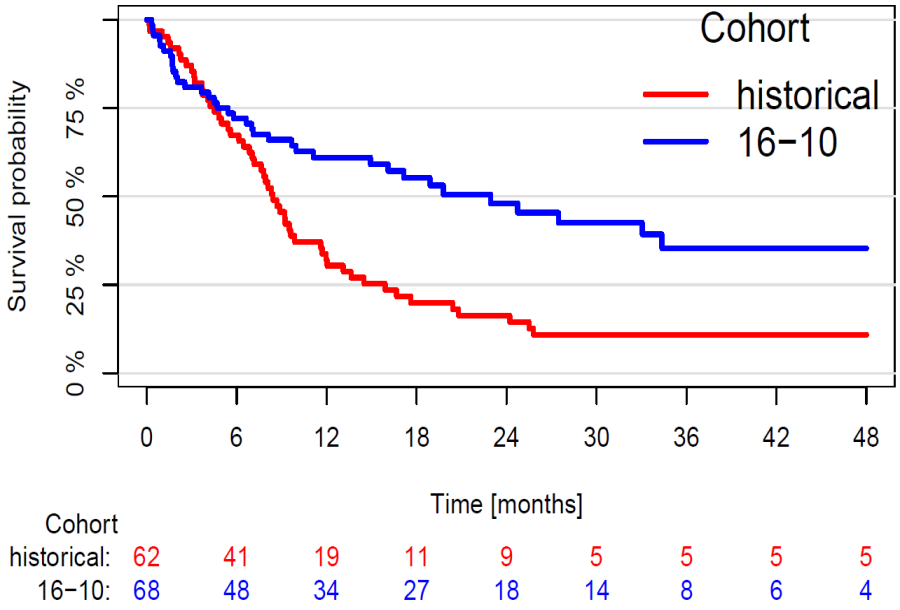
AMLSG 16-10 vs historical control - Propensity Score Weighting Analysis*

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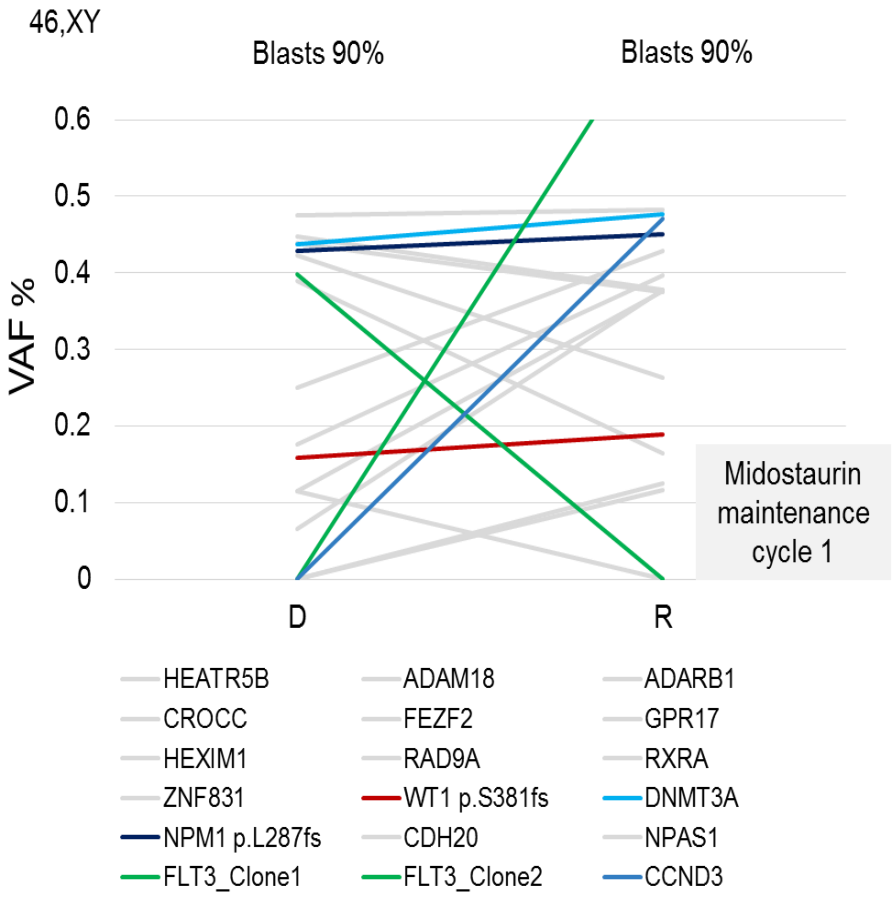
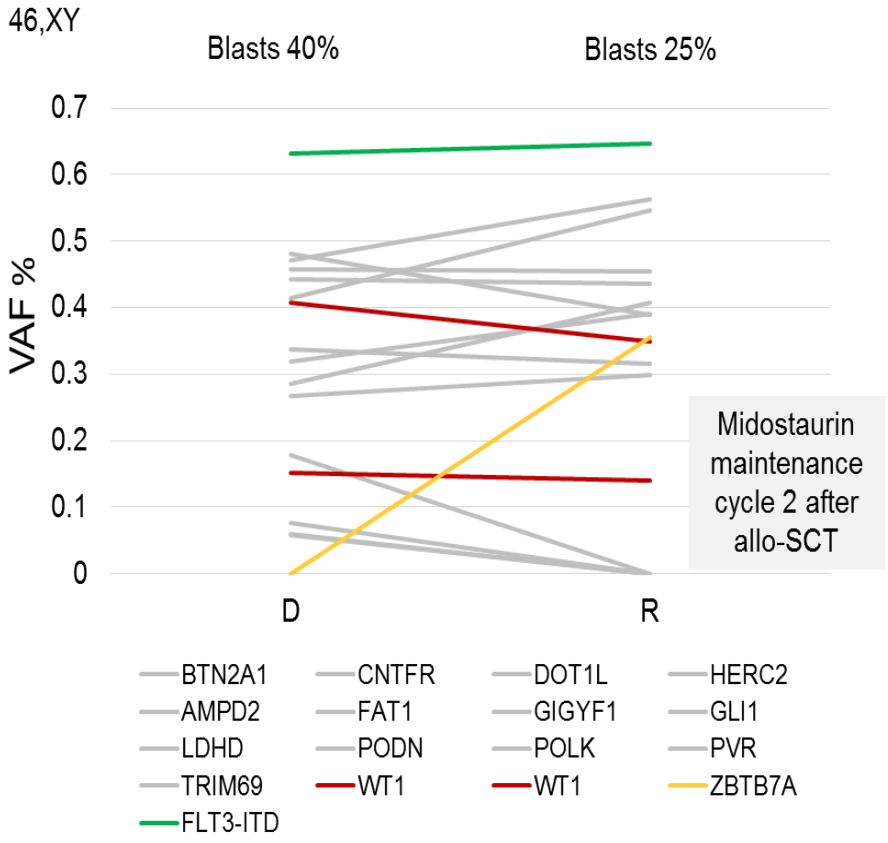
*Propensity score weighting
on age, gender, WBC, marrow blasts, *NPM1* mutations

Resistance to FLT3 inhibition

Patterns of clonal evolution – persistence of FLT3 at relapse





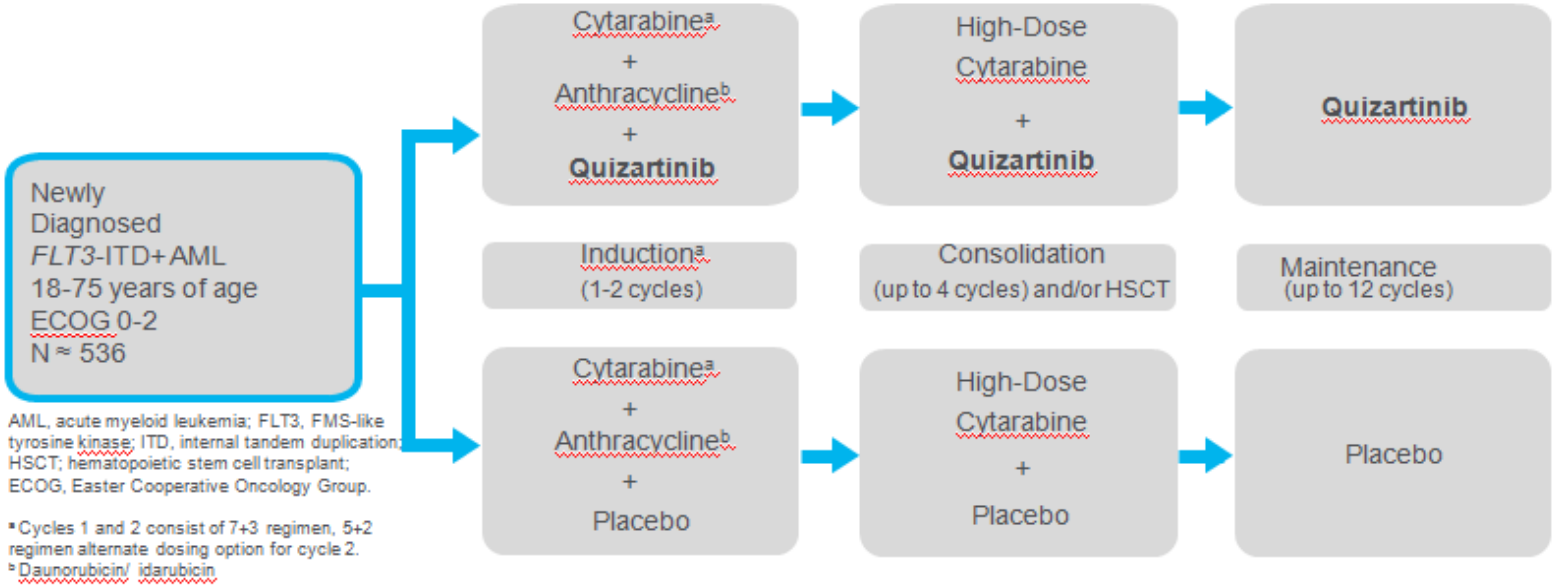
BM = Bone Marrow D = Diagnosis; R = Relapse; VAF = Variant Allele Frequency

Schmalbrock et al. ASH 2017, Manuscript in preparation.

Ongoing: QuANTUM-FIRST - Phase 3 Trial in Newly Diagnosed *FLT3*-ITD Mutated AML

Quizartinib **A**dvancement into the **N**ext Generation of **T**rials for **U**nmet Needs in A**ML**

A Phase 3, Randomized, Double-Blind, Placebo-controlled Study of Quizartinib (AC220) Administered in Combination With Induction and Consolidation Chemotherapy, and Administered as Maintenance Therapy in Subjects 18 to 75 Years Old With Newly Diagnosed **FLT3-ITD (+) Acute Myeloid Leukemia**



AML, acute myeloid leukemia; FLT3, FMS-like tyrosine kinase; ITD, internal tandem duplication; HSCT; hematopoietic stem cell transplant; ECOG, Easter Cooperative Oncology Group.

[a] Cycles 1 and 2 consist of 7+3 regimen, 5+2 regimen alternate dosing option for cycle 2.
[b] Daunorubicin/ idarubicin

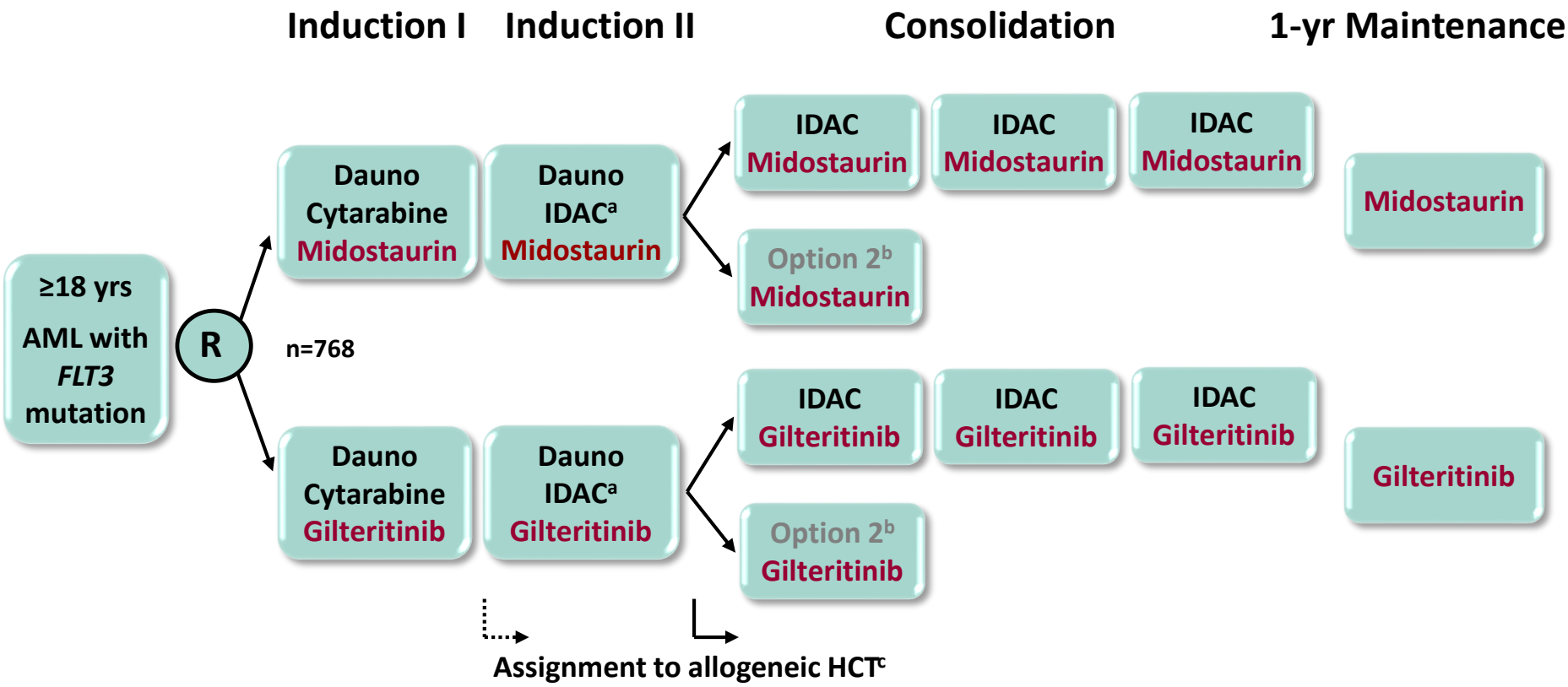
Primary Endpoint: Event-free Survival (EFS)

Secondary Endpoints:

- Overall Survival (OS)
- Complete Remission (CR)
- Composite Complete Remission (CRc)
- CR with no evidence of minimal residual disease (MRD)

Location: North America, Europe, Asia/Other Regions | **ClinicalTrials.gov Identifier:** NCT02668653

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



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: Q2 / 2019

HOVON

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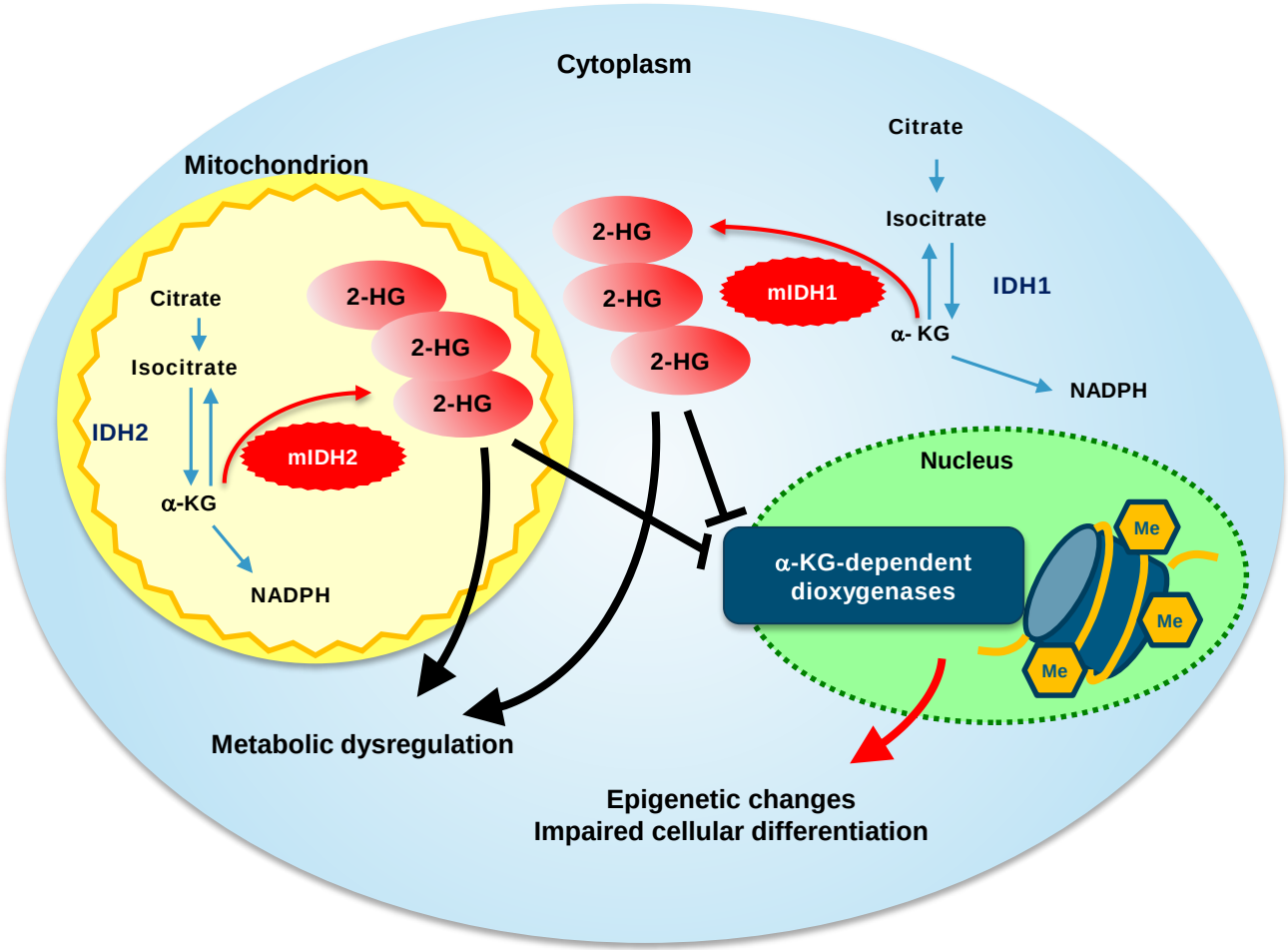
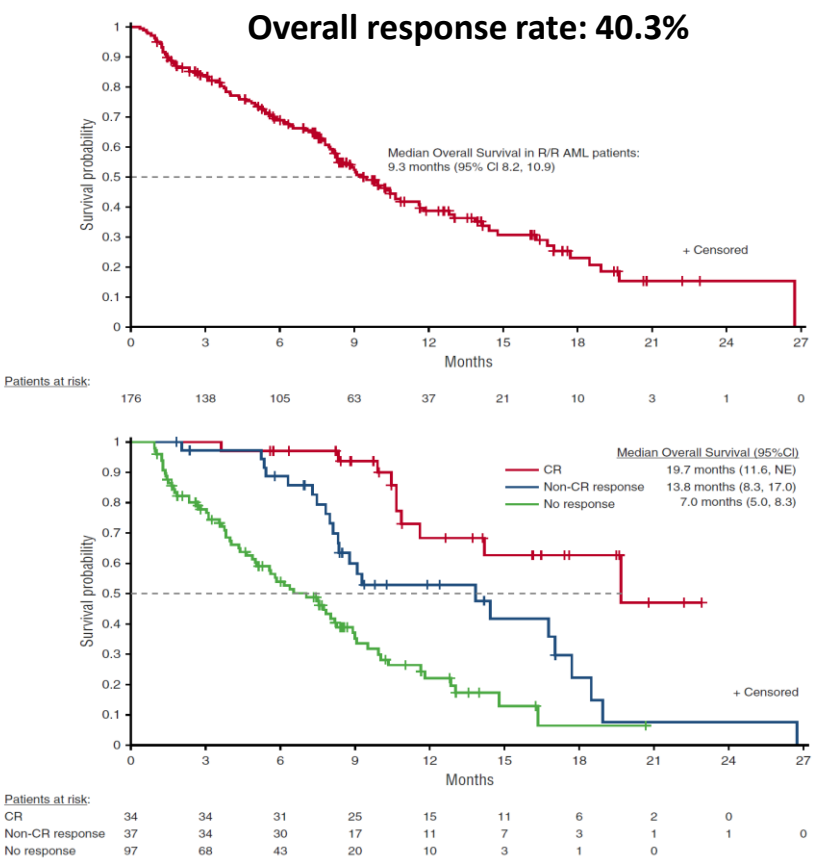
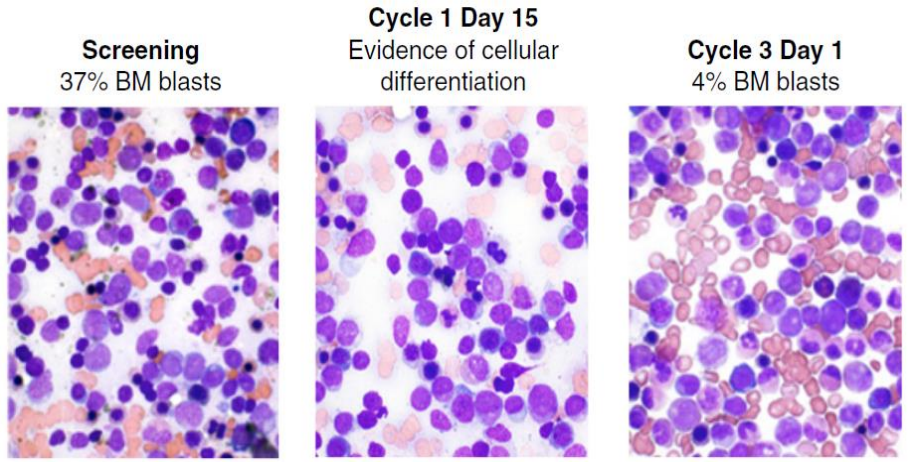
IDH1 and *IDH2* - therapeutic target structure

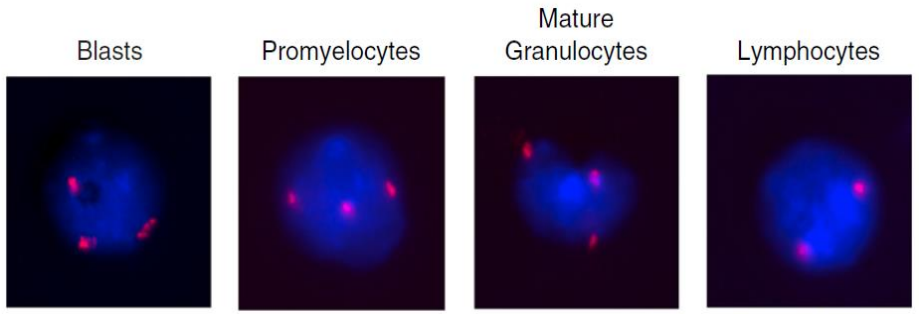


2-HG, 2-hydroxyglutarate; mIDH, mutant IDH

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





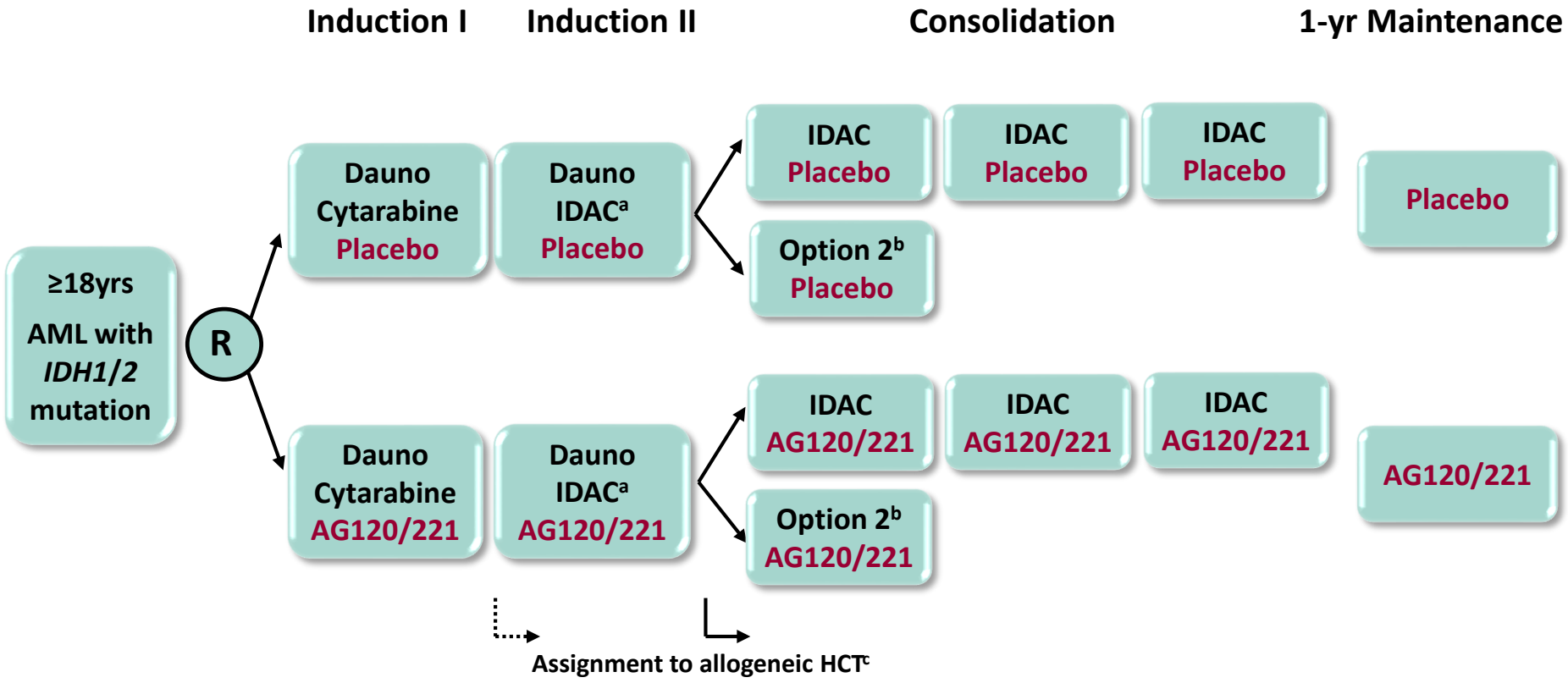


Stein et al. Blood 2017

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



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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 Q2 / 2019

HOVON

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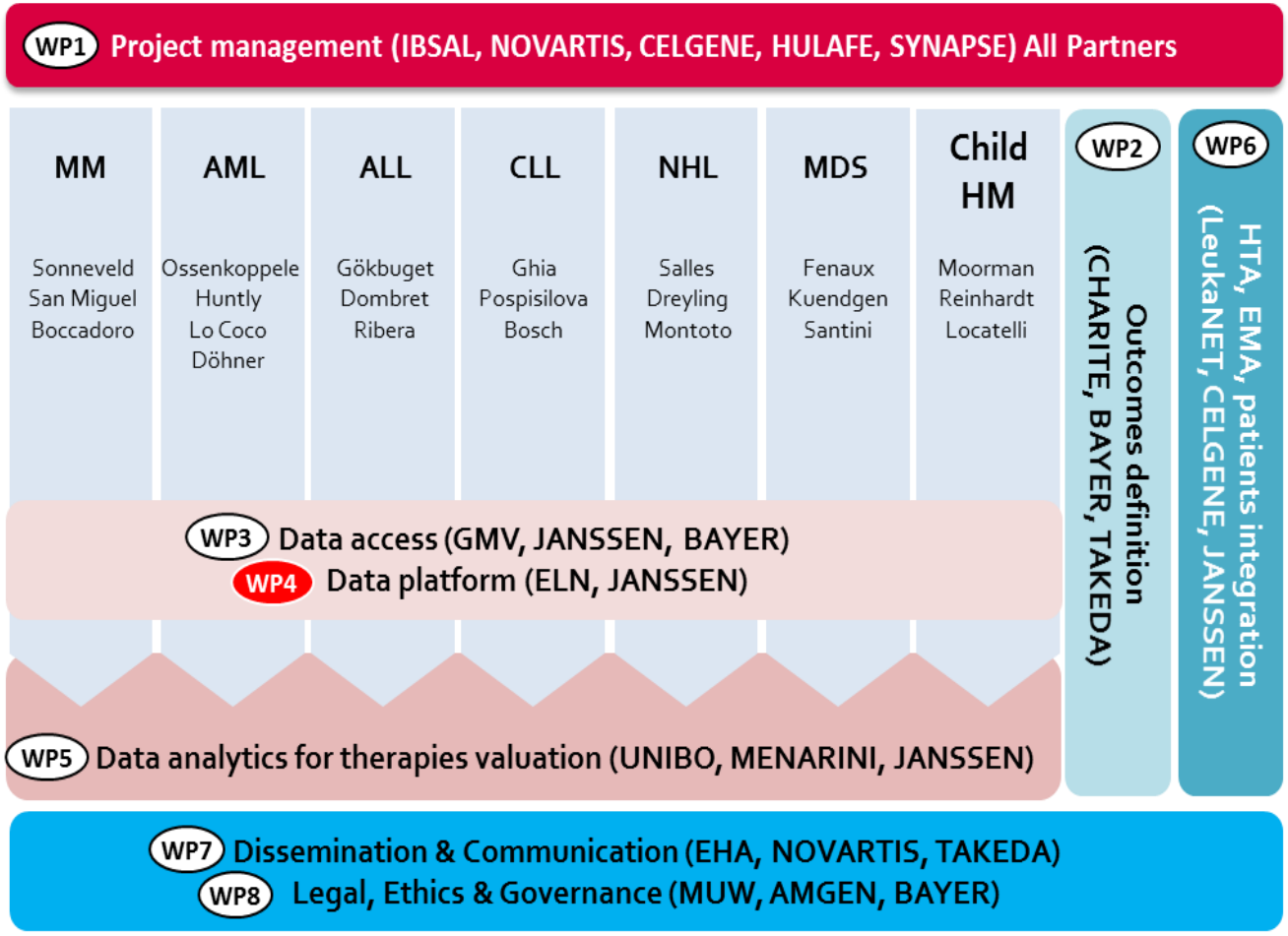
Big Data for Better Outcomes program



HARMONY

Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in HematologY

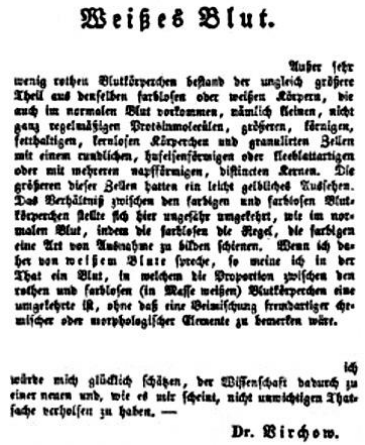
efpia

imi innovative medicines initiative

www.harmony-alliance.eu

Precision Medicine – Fiction or Reality?

Charité Season 1: 1880s



Weißes Blut.

Außer sehr wenig rothen Blutkörperchen bestand der ungleich größere Theil aus denselben farblosen oder weißen Körpern, die auch im normalen Blut vorkommen, nämlich kleinen, nicht ganz regelmäßigen Protoplasmaballen, größeren, körnigen, farbhaltigen, kernlosen Körperchen und granulirten Zellen mit einem rundlichen, hufeisenförmigen oder kleeblattartigen oder mit mehreren napfförmigen, distincten Kernen. Die größeren dieser Zellen hatten ein leicht gelbliches Aussehen. Das Verhältniß zwischen den farbigen und farblosen Blutkörperchen stellte sich hier ungefähr umgekehrt, wie im normalen Blut, indem die farblosen die Regel, die farbigen eine Art von Ausnahme zu bilden schienen. Wenn ich daher von weißem Blute spreche, so meine ich in der That ein Blut, in welchem die Proportion zwischen den rothen und farblosen (in Masse weilen) Blutkörperchen eine umgekehrte ist, ohne daß eine Beimischung fremdartiger chemischer oder morphologischer Elemente zu bemerken wäre.

würde mich glücklich schätzen, der Wissenschaft dadurch zu einer neuen und, wie es mir scheint, nicht unwichtigen Thatsache verholfen zu haben. —

Dr. Virchow.

Virchow: Leukemia diagnosis

Charité Season 2: 1940s

Folia Haematologica

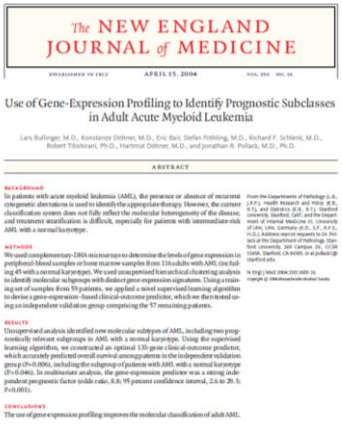
Internationales Magazin für klinische und morphologische Blutforschung.

Begründet von Prof. Dr. Artur Pappenheim †
Herausgegeben von Prof. Dr. O. Naegeli-Zürich,
Prof. Dr. Hans Hirschfeld-Berlin
und Prof. Hal Downey-Minneapolis

Hirschfeld: Modern hematology

Charité Season 3: 2010s

?



The NEW ENGLAND JOURNAL of MEDICINE

APRIL 15, 2004

Use of Gene-Expression Profiling to Identify Prognostic Subclasses in Adult Acute Myeloid Leukemia

Lars Bullinger, M.D., Konstanze Döhner, M.D., Eric Bair, Stefan Fröhling, M.D., Richard F. Schlenk, M.D., Robert Tibshirani, Ph.D., Hartmut Döhner, M.D., and Jonathan R. Pollack, M.D., Ph.D.

ABSTRACT

Bullinger: Omics based classification

Precision medicine in AML

- 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: identify gene-gene interactions to effectively combine treatment strategies to overcome mechanisms of resistance

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

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TRANSCAN

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