Acute Myeloid Leukemia: Prognostication, Targeting and Sequencing Therapies

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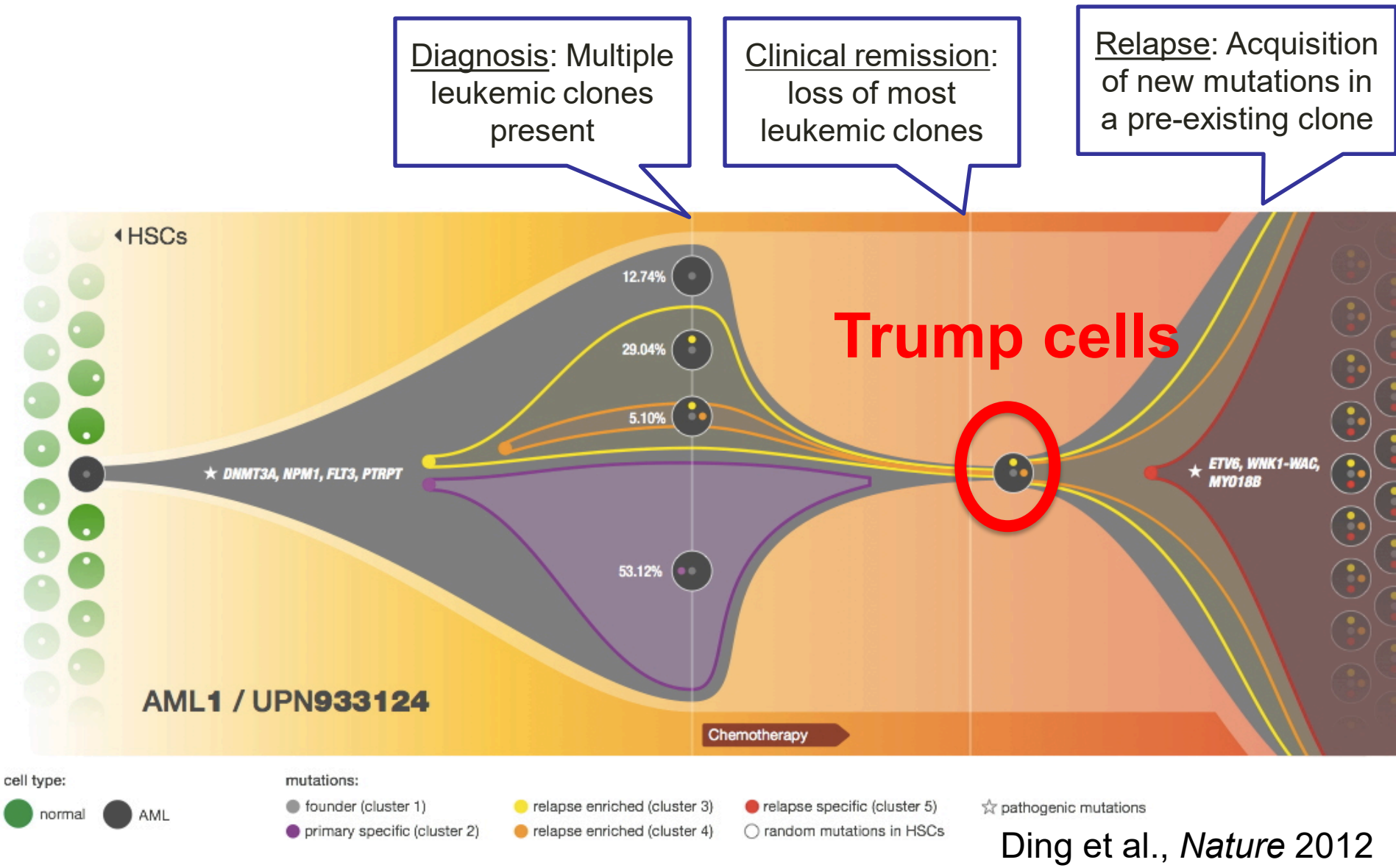
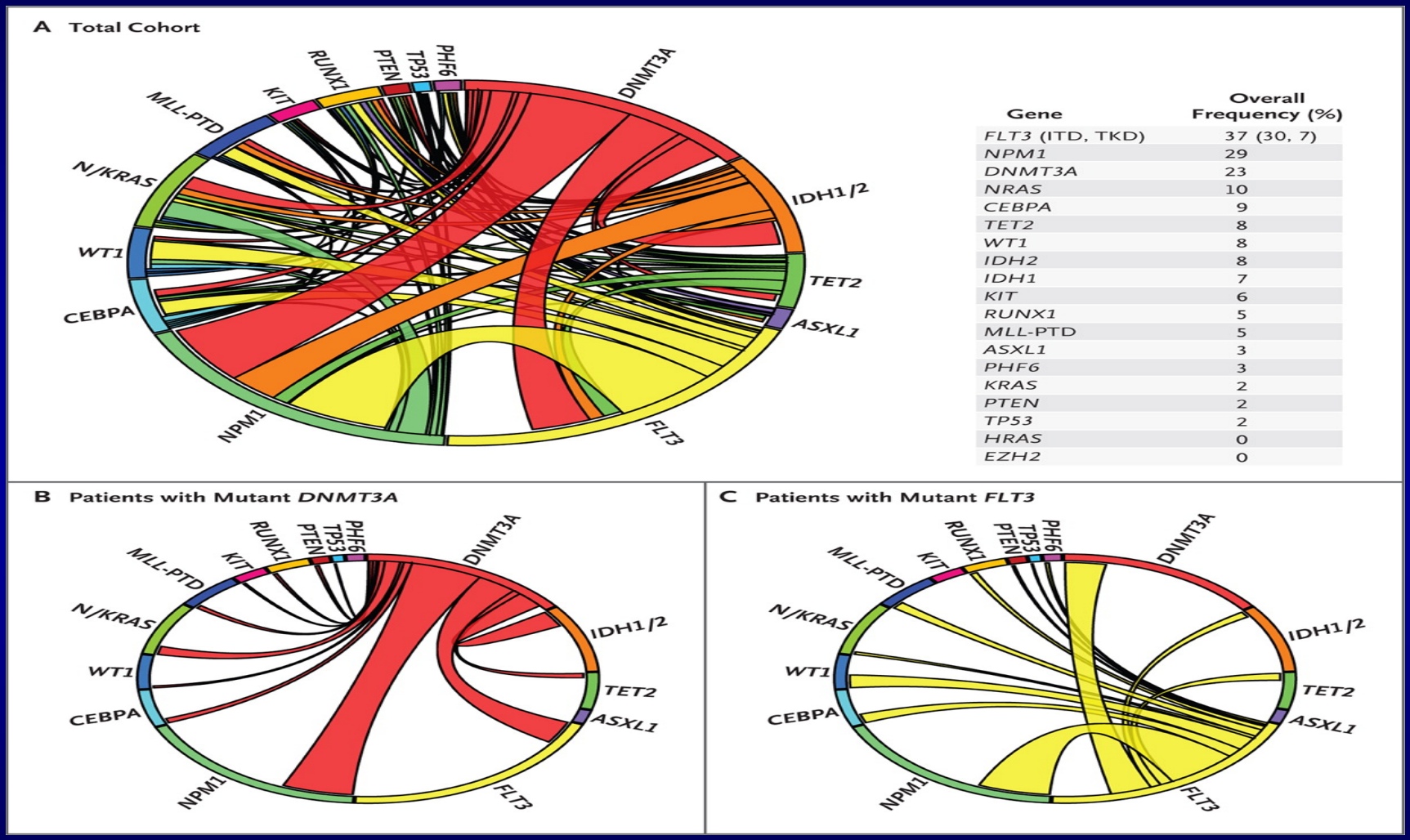
Targeting Founder/Driver Mutations



Ding et al., *Nature* 2012

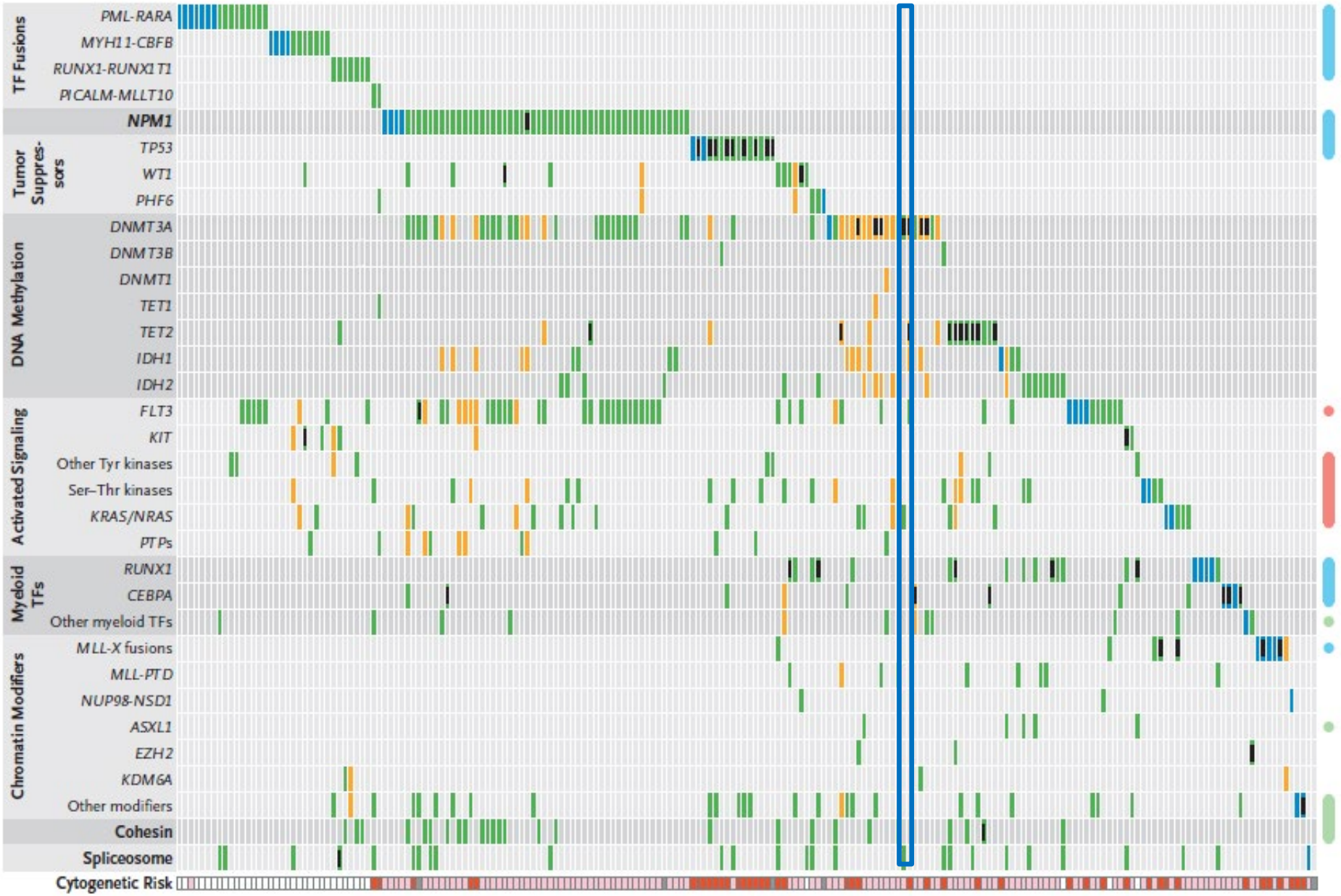
Mutational Complexity of Acute Myeloid Leukemia (AML)



Gene	Overall Frequency (%)
FLT3 (ITD, TKD)	37 (30, 7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPA	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0

Patel JP et al. N Engl J Med 2012;366:1079-1089.

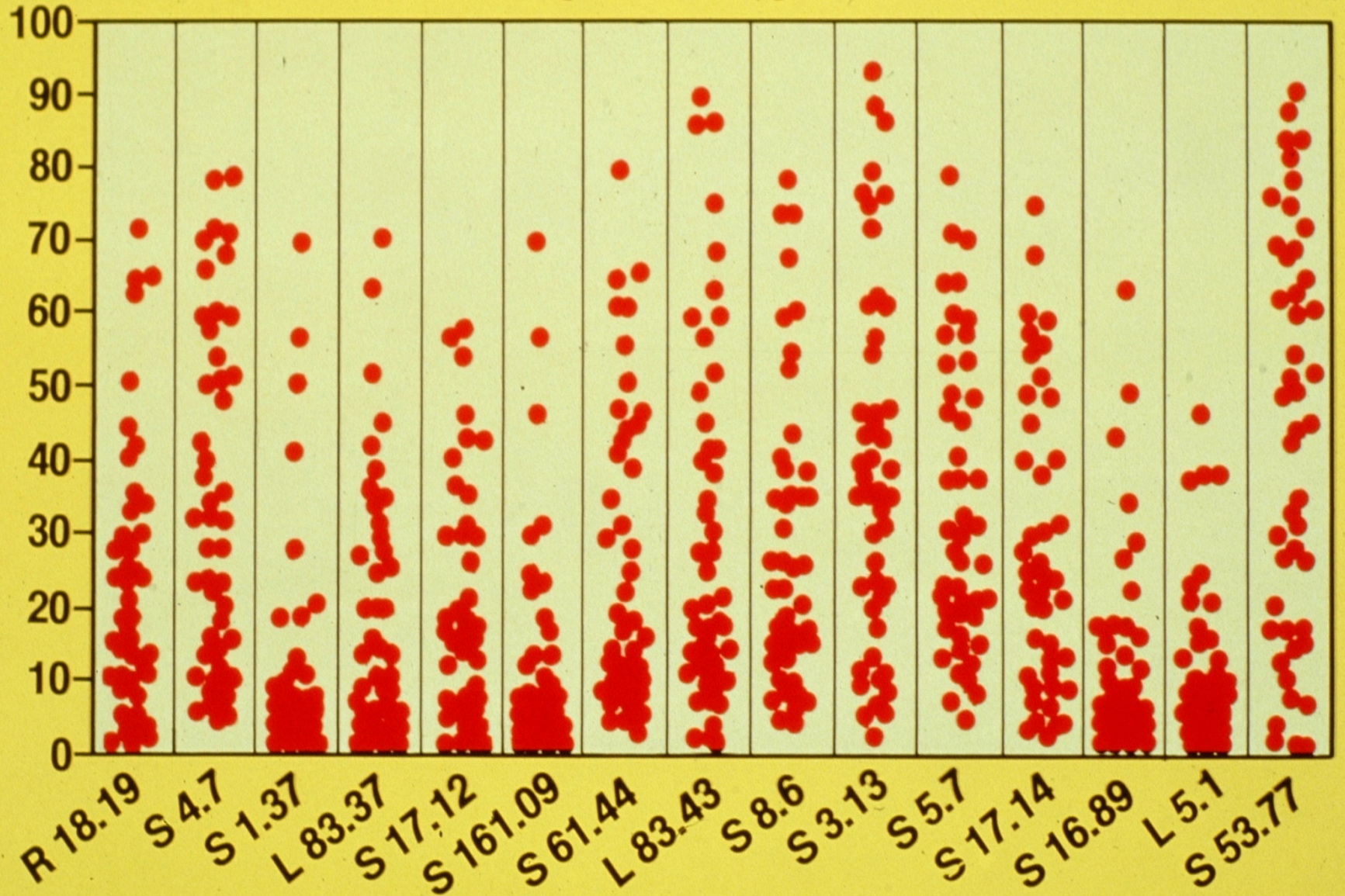
AML : It's (genomically) complicated!



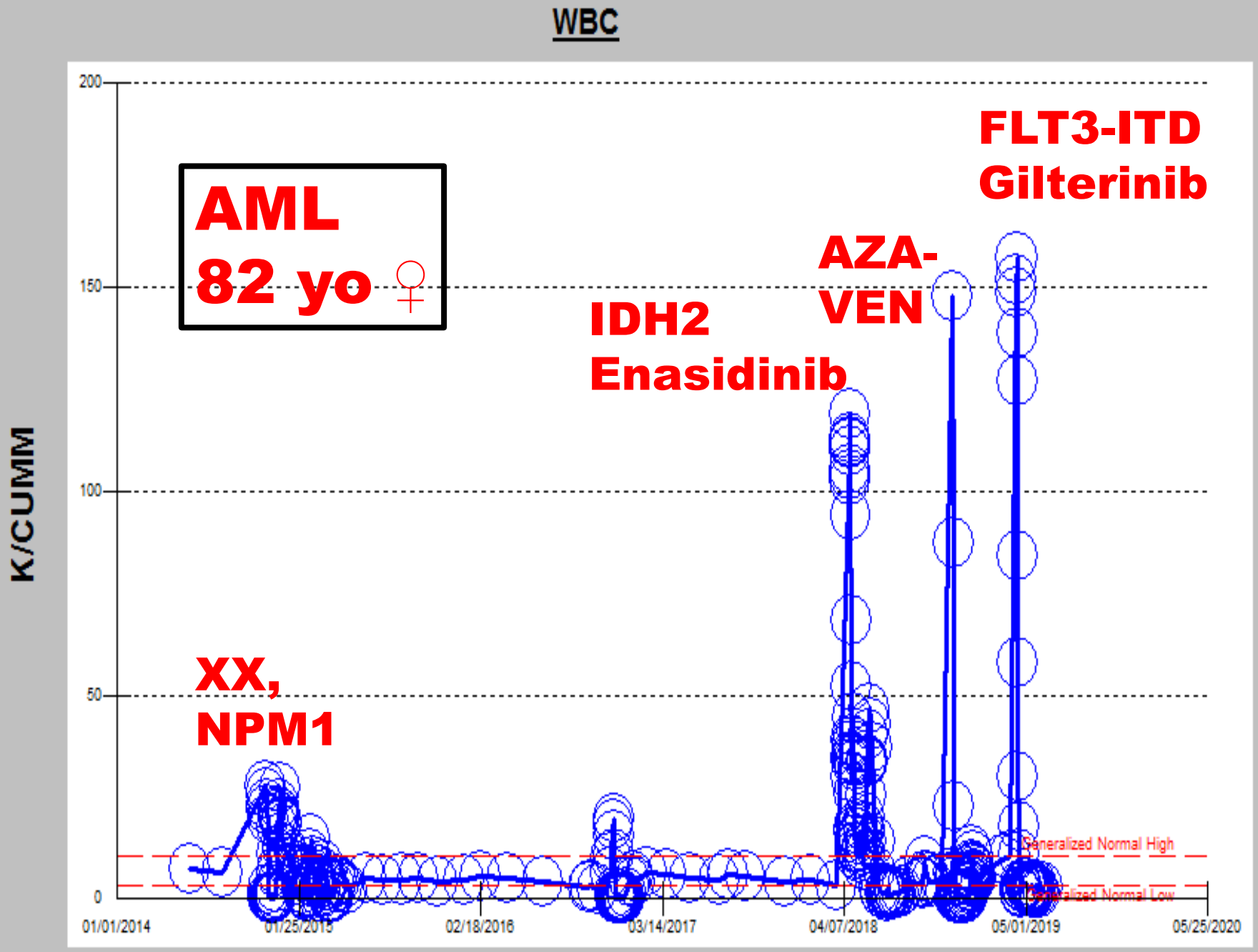
The Cancer Genome Atlas Research Network

Acute Myelogenous Leukemia

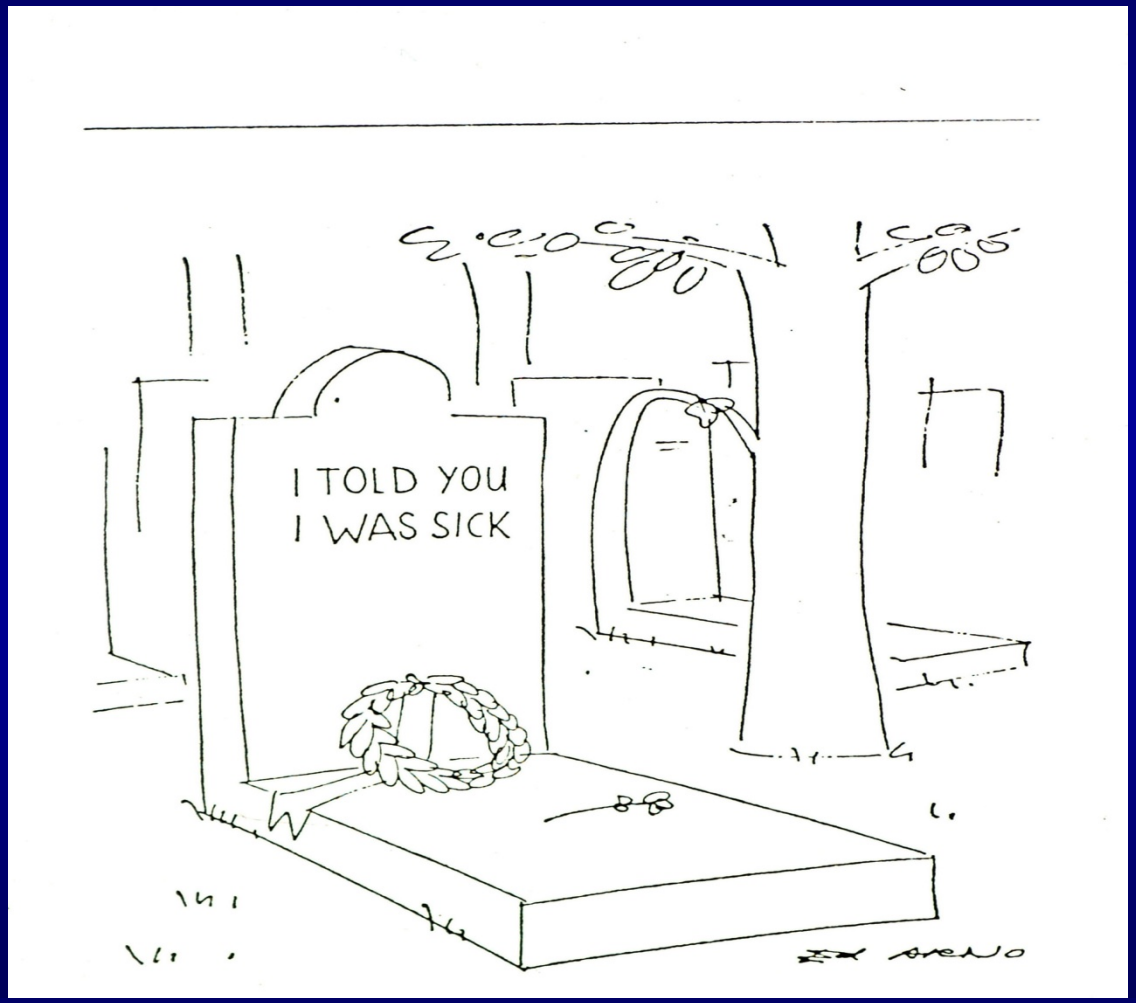
(All Cases)



A BRIEF EXAMPLE OF THE IMPORTANCE OF REPEATING MOLECULAR TESTING FOR FLT-3 IN RELAPSED PATIENTS


WBC
K/CUMM
200
150
100
50
0
AML
82 yo ♀
XX,
NPM1
IDH2
Enasidinib
AZA-
VEN
FLT3-ITD
Gilterinib
Generalized Normal High
Generalized Normal Low
01/01/2014
01/25/2015
02/18/2016
03/14/2017
04/07/2018
05/01/2019
05/25/2020

WHAT MOST PROGNOSTIC CLASSIFICATIONS TELL US



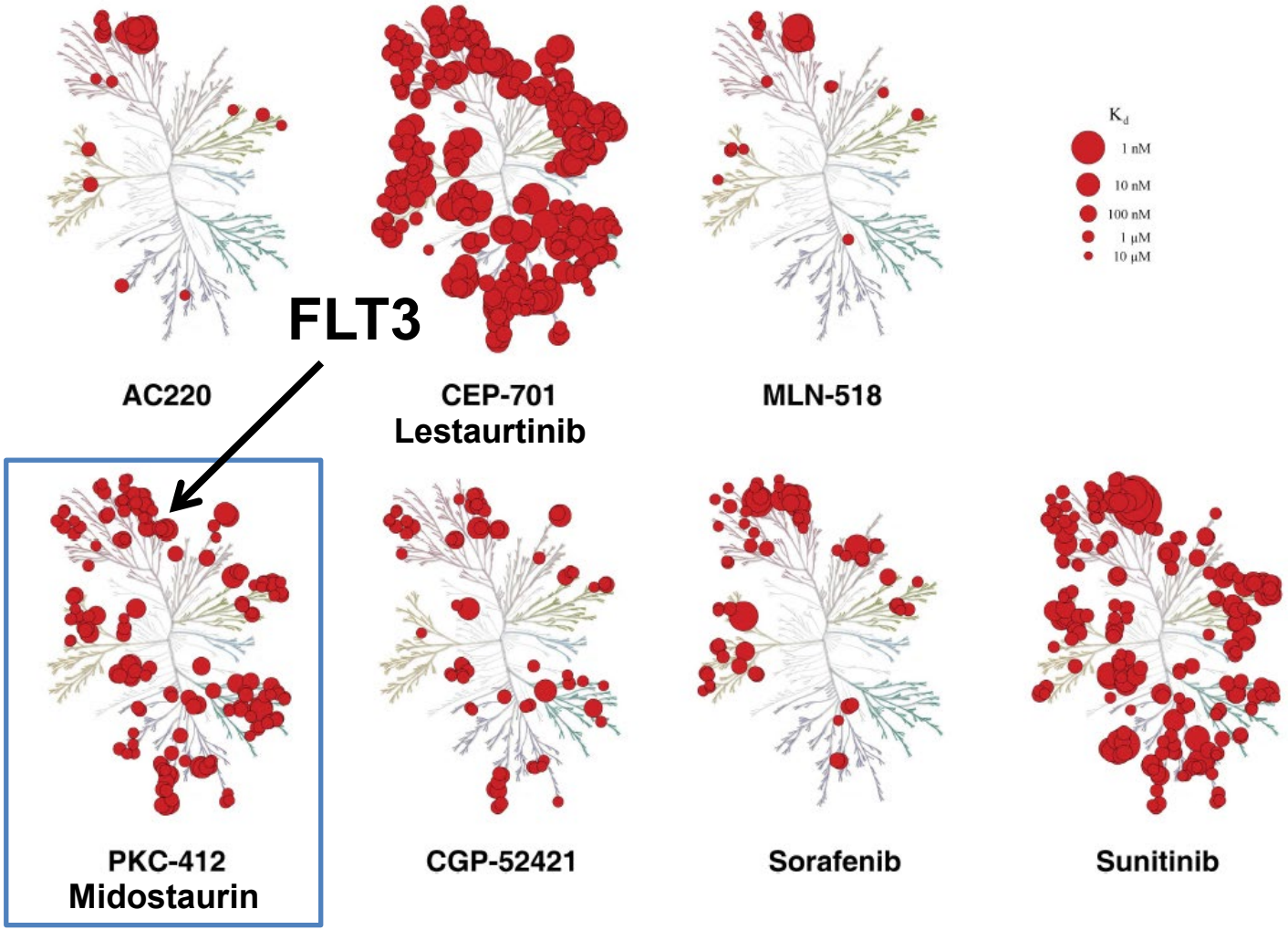
Prognostic ≠ Predictive

Recently Approved Drugs for AML

- Gentuzumab ozogamicin (CBF AML – inv16, t(8;21))
- Vyxeos – 2^0 AML, MDS associated
- Venetoclax + low dose cytarabine or azacytidine or decitabine (age > 75, comorbidities)
- Midostaurin (FLT3 – newly diagnosed)
- Gilteritinib (FLT3 - relapsed)
- 5-azacytidine ("unfit" for intensive therapy)
- Enasidenib (IDH2 mutated)
- Ivosidenib (IDH1 mutated)
- Glasdegib (hedgehog inhibitor)

Meaning that you have to have rapid access to molecular/cytogenetic results to rationally apply these “targeted” therapies…

FLT3 Inhibitors in AML



Zarrinkar et al. Blood 2009.

A Phase III Randomized Double-blinded Study Of Chemotherapy +/- Midostaurin (PKC412) In Newly Diagnosed Adults aged 18-60 with *FLT3* Mutated Acute Myeloid Leukemia (AML)

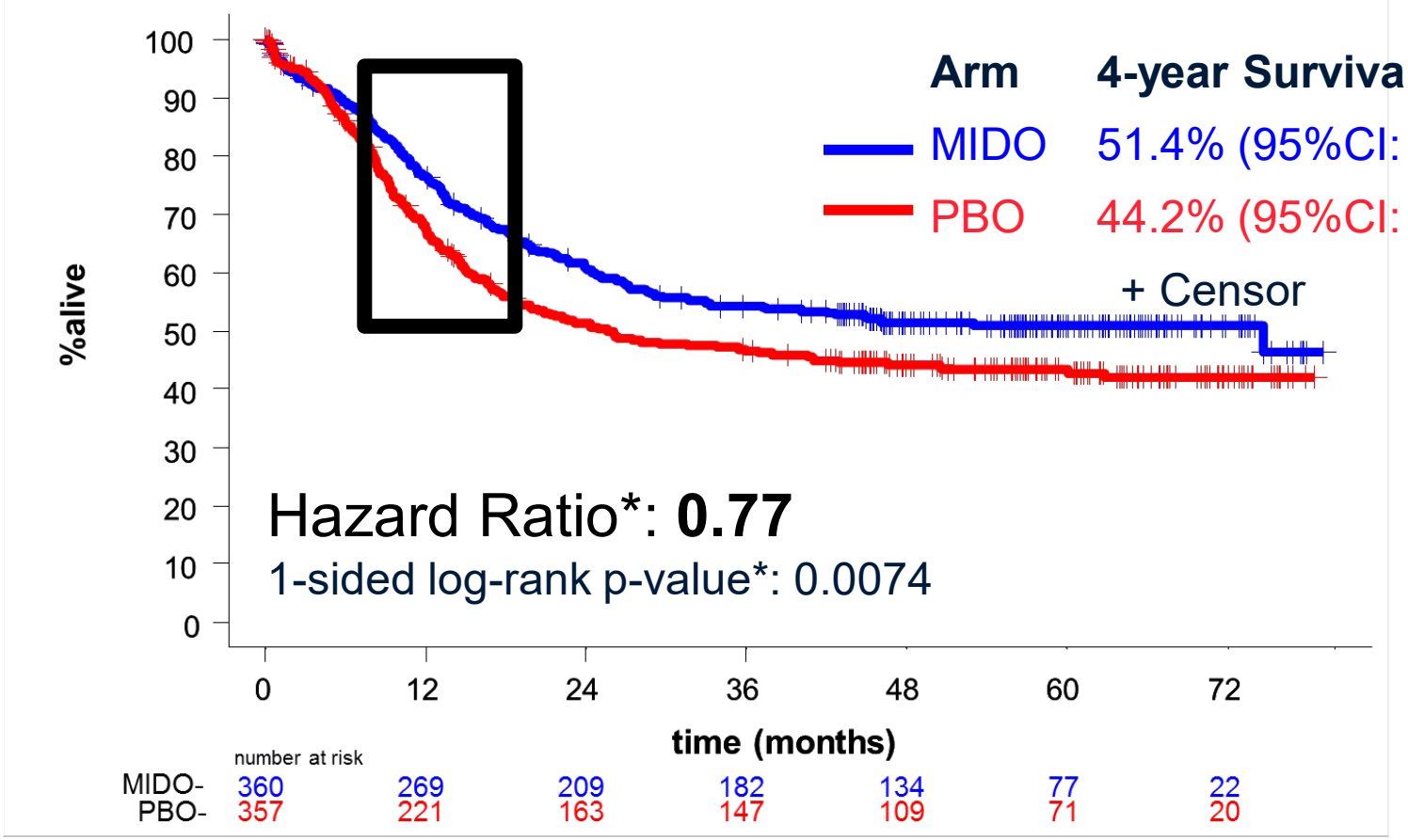
Richard M. Stone, Sumithra Mandrekar, Ben L Sanford, Susan Geyer, Clara D. Bloomfield, Konstanze Dohner, Christian Thiede, Guido Marcucci, Francesco Lo-Coco, Rebecca B. Klisovic, Andrew Wei, Jorge Sierra, Miguel A. Sanz, Joseph M. Brandwein, Theo de Witte, Dietger Niederwieser, Frederick R. Appelbaum, Bruno C. Medeiros, Martin S Tallman, Jurgen Krauter, Richard F. Schlenk, Arnold Ganser, Hubert Serve, Gerhard Ehninger, Sergio Amadori, Richard A. Larson, and Hartmut Dohner

Participants: ALLIANCE/CALGB, AMLSG, CETLAM, ECOG, EORTC, GIMEMA, NCIC, OSHO, PETHEMA, SAL, SWOG

CTEP sponsored, Novartis provided drug and sponsored outside North America, and Alliance (formerly CALGB) chaired study, collected data and performed analysis

Overall Survival (Primary Endpoint)

23% reduced risk of death in the Mido arm



- **Median OS**: Mido 74.7 (31.7-NE); PBO 25.6 (18.6-42.9) months

NE: not estimable

* controlled for FLT3 subtype (TKD, ITD-Low, ITD-High)

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PHARMA DESIGNED-DOMINATED CLINICAL TRIALS

- Focused trials designed primarily for drug approval rather than addressing the questions which clinicians would consider to be clinically important
- Complicated and inefficient processes which affect the ability of U.S. cooperative groups to implement studies

The example of trials of FLT3 inhibiton in AML

FLT3 Inhibitors	Selectivity	Targets	Phases of Development	Toxicity
Sunitinib (SU11248)	Non-selective	c-KIT, KDR PDGFR, and FLT3	Phase II [26]	Decreased appetite, headache, GI symptoms
Lesta (CE				ns, sepsis, l infarction
Tand (CT5				weakness
Quiz (AC				longation
Sora				igue, diarrhea
Mido (PK				ke symptoms, es, unusual or bruising
Gilteritinib (ASP2215)	Selective	FLT3/AXL	Phase I/II [50] Phase III [ongoing]	Diarrhea, fatigue, high liver function tests (LFT)

Simultaneous, separate trials are in progress in newly diagnosed patients using 7 & 3 (midostaurin) with or without quizartinib, crenolanib, gilteritinib, sorafenib….

El Fakih, Riad, et al. "Targeting FLT3 mutations in acute myeloid leukemia." *Cells* 7.1 (2018): 4.

INSTEAD – A SINGLE STUDY

7 & 3, HIDAC consolidation +/-

- Midostaurin
- Quizartinib
- Crenolonib
- Gilteritinib
- Sorafinib

Standard definition of FLT3 + (stratify by VAF)

Compare flow and pcr MRD

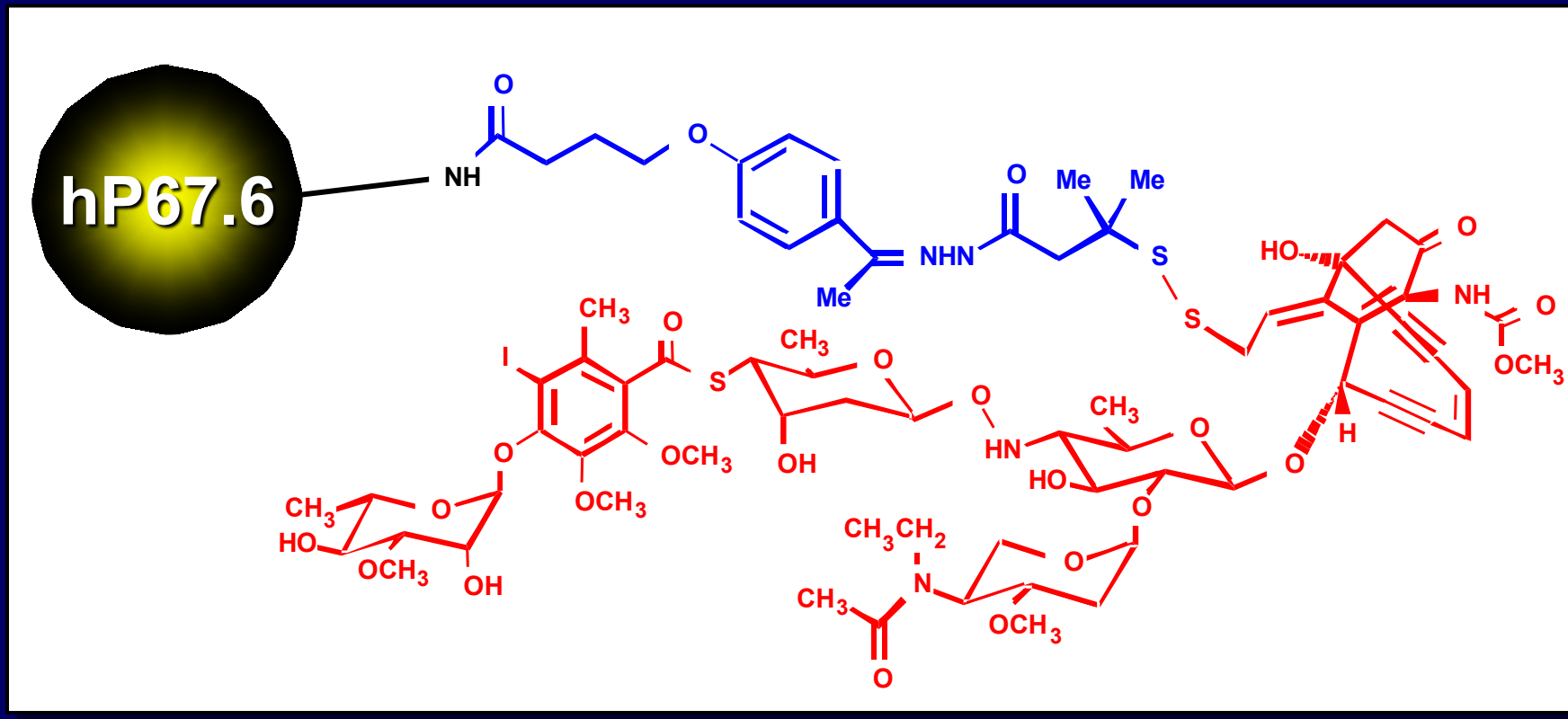
All ages

Standardize “intent to transplant” language

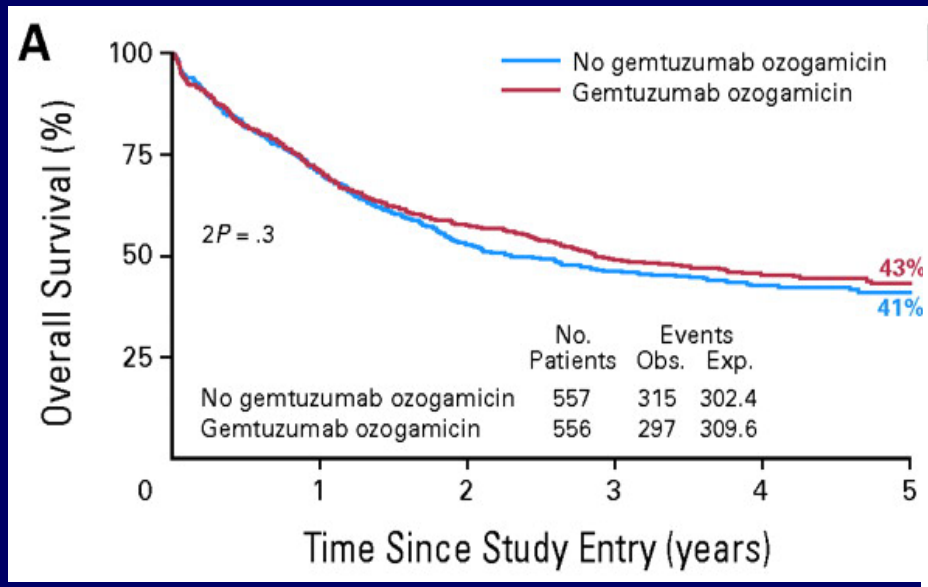
OS, ?? EFS endpoint

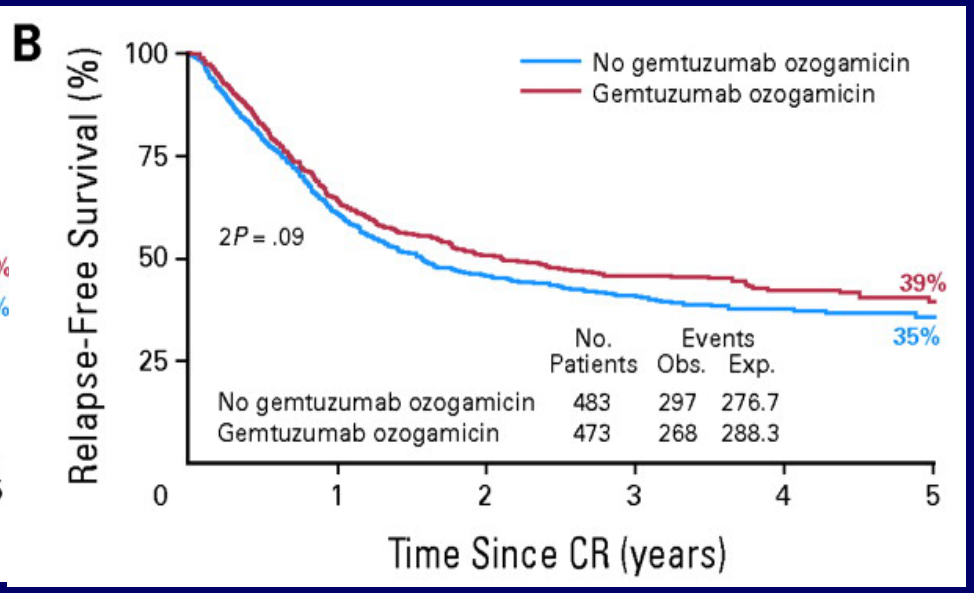
Gemtuzumab ozogamicin (GO)

Humanized murine anti CD33 monoclonal antibody (hP67.6) conjugated to NAc-calicheamicin



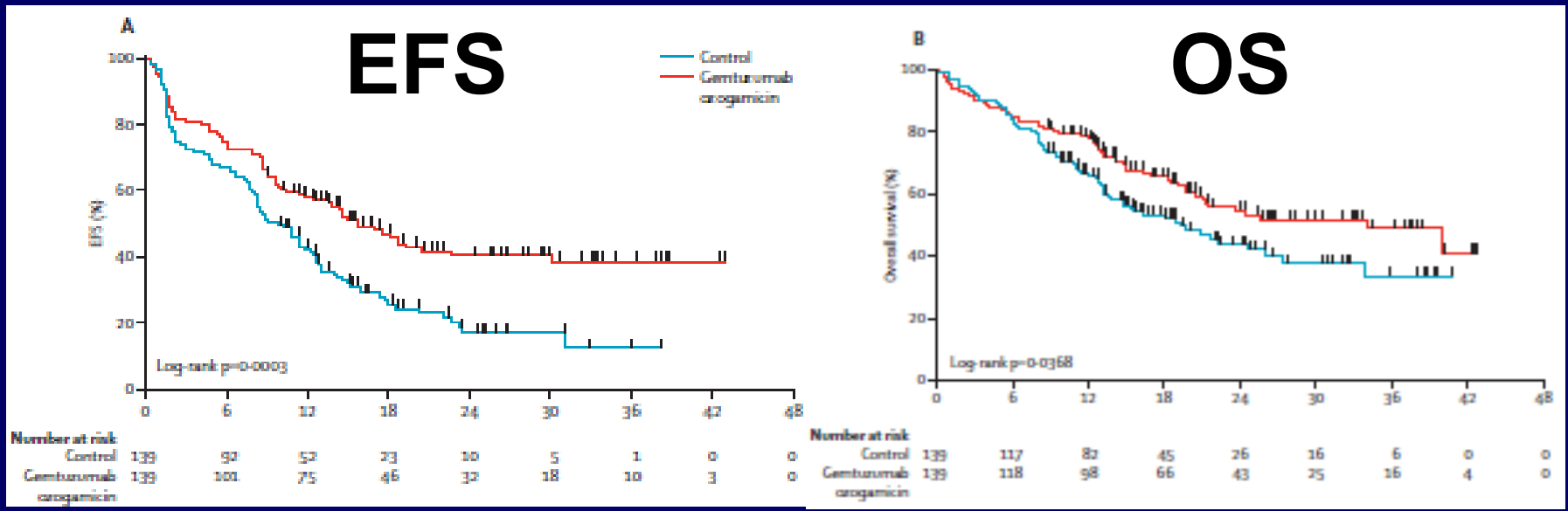
Addition of GO to Chemotherapy for Younger AML Patients Does NOT Improve OS or EFS (MRC AML 15 Trial)





Burnett et al. *J Clin Oncol* 2011;29:369

Addition of Fractionated GO to 3+7 Induction and Consolidation in Older AML Patients Improves EFS and OS

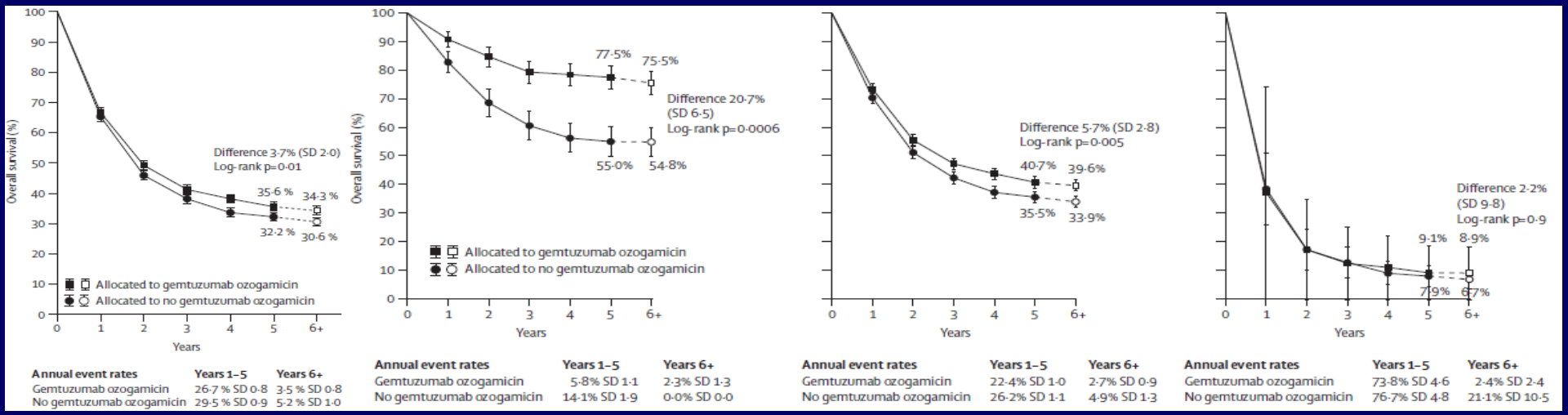


Castaigne S et al. *Lancet* 2012; 379: 1508-16.

Addition of GO to Induction Chemotherapy for AML:

A Meta-Analysis of Data from 3325 Individual Patients

All | Favorable | Intermediate | Poor Risk



Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	26·7 % SD 0·8	3·5 % SD 0·8
No gemtuzumab ozogamicin	29·5 % SD 0·9	5·2 % SD 1·0

Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	5·8% SD 1·1	2·3% SD 1·3
No gemtuzumab ozogamicin	14·1% SD 1·9	0·0% SD 0·0

Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	22·4% SD 1·0	2·7% SD 0·9
No gemtuzumab ozogamicin	26·2% SD 1·1	4·9% SD 1·3

Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	73·8% SD 4·6	2·4% SD 2·4
No gemtuzumab ozogamicin	76·7% SD 4·8	21·1% SD 10·5

Hills RK et al. *Lancet Oncol* 2014; 15: 686-96.

ARE YOU CONFUSED?

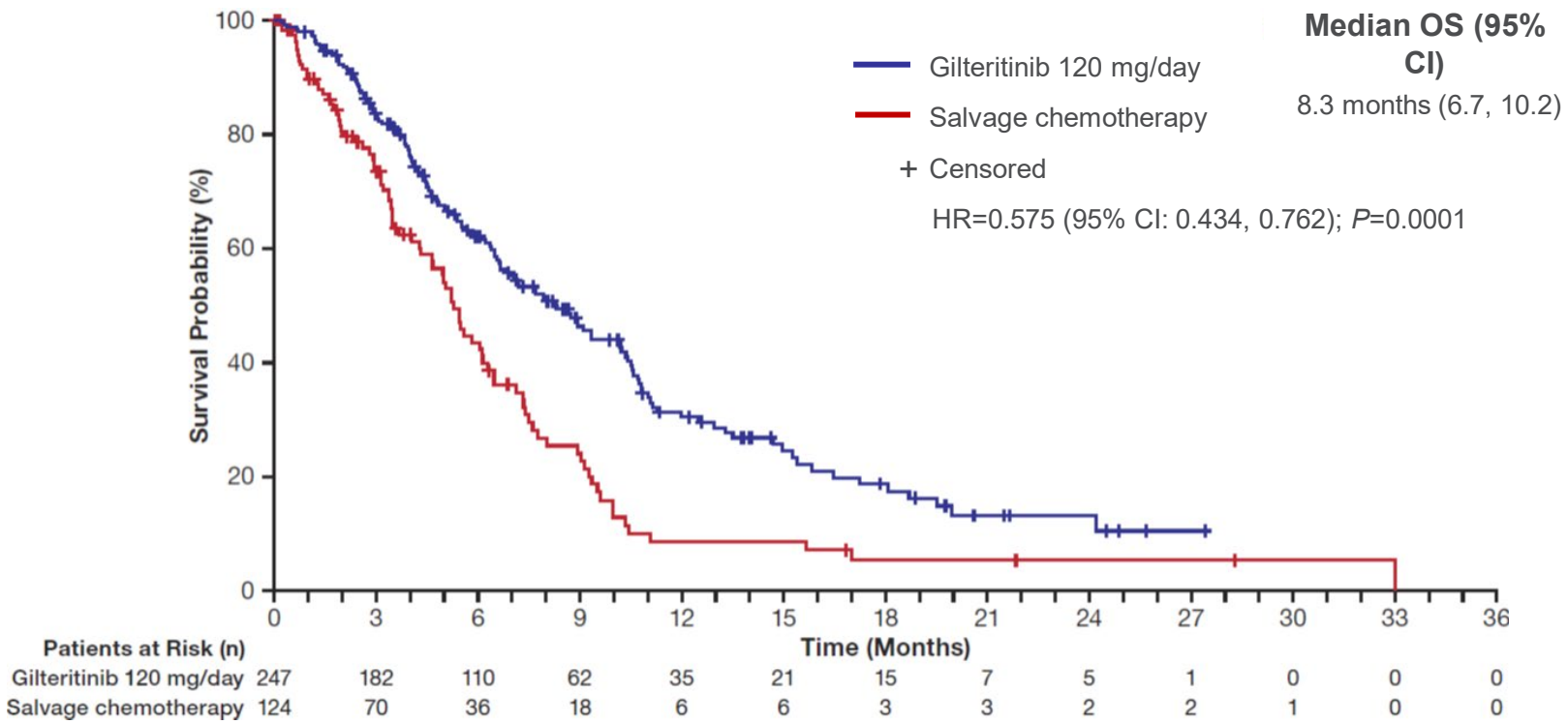
- Polymorphism assay is not routinely available
- Dose and schedule are all over the place
- We use GO in CBF leukemias à la Français – days 1, 4, 7
- Not for high risk cytogenetics
- There may be benefit in FLT3 +

Effect of gilteritinib on survival in patients with FLT3-mutated (FLT3mut+) relapsed/refractory (R/R) AML who have common AML co-mutations or a high FLT3-ITD allelic ratio.

M Levis, A Perl, G Martinelli, et al

- Phase 3 - Gilterinib vs chemotherapy
- CR + CRh : 34% (21% CR) vs ~ 15%
- Med OS : 9.3 vs 5.6 mos
- Survival @ 12 mos: 37% vs 16.7%
- Phase 3 in progress : 3 & 7 +/- Gil

OVERALL SURVIVAL WITH CENSORING AT TRANSPLANTATION (ITT POPULATION: N=371)



Two-sided *P*-values were determined according to the log-rank test; the Kaplan-Meier method in combination with the Greenwood formula were used to determine overall survival and corresponding 95% confidence intervals.
Abbreviations: CI, confidence interval; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; ITT, intention-to-treat; OS, overall survival.

Ivosidenib (IVO; AG-120) in mutant IDH1 relapsed/refractory acute myeloid leukemia (R/R AML): Results of a phase 1 study

Daniel A Pollyea[1], Courtney D DiNardo[2], Stéphane de Botton[3], Eytan M Stein[4], Gail J Roboz[5], Alice S Mims[6], Ronan T Swords[7], Jessica K Altman[8], Robert H Collins[9], Gabriel N Mannis[10], Geoffrey L Uy[11], Will Donnellan[12], Arnaud Pigneux[13], Amir T Fathi[14], Hua Liu[15], Bin Wu[15], Eyal C Attar[15], Martin S Tallman[4], Richard M Stone,[16] Hagop M Kantarjian[2]

[1]University of Colorado School of Medicine, Aurora, CO; [2]University of Texas MD Anderson Cancer Center, Houston, TX; [3]Institut Gustave Roussy, Villejuif, France; [4]Memorial Sloan Kettering Cancer Center, New York, NY; [5]Weill Cornell Medical College, New York, NY; [6]Ohio State University Wexner Medical Center, Columbus, OH; [7]Sylvester Comprehensive Cancer Center, Miami, FL; [8]Northwestern University, Chicago, IL;[9]UT Southwestern Medical Center, Dallas, TX; [10]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; [11]Washington University School of Medicine, St Louis, MO; [12]Sarah Cannon Research Institute, Nashville, TN; [13]CHU Bordeaux, Bordeaux, France; [14]Massachusetts General Hospital Cancer Center, Boston, MA; [15]Agios Pharmaceuticals, Inc., Cambridge, MA; [16]Dana-Farber Cancer Institute, Boston, MA

Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, June 1–5, 2018, Chicago, IL, USA

Presented By Daniel Pollyea at 2018 ASCO Annual Meeting

Response in R/R AML 500 mg (n=179)

	R/R AML 500 mg (n=179)
CR+CRh rate, n (%) [95% CI]	**57 (31.8) [25.1, 39.2]**
Time to CR/CRh, median (range) months	2.0 (0.9, 5.6)
Duration of CR/CRh, median [95% CI] months	8.2 [5.6, 12.0]
CR rate, n (%) [95% CI]	43 (24.0) [18.0, 31.0]
Time to CR, median (range) months	2.8 (0.9, 8.3)
Duration of CR, median [95% CI] months	10.1 [6.5, 22.2]
CRh rate, n (%)	14 (7.8)
Duration of CRh, median [95% CI] months	3.6 [1.0, 5.5]

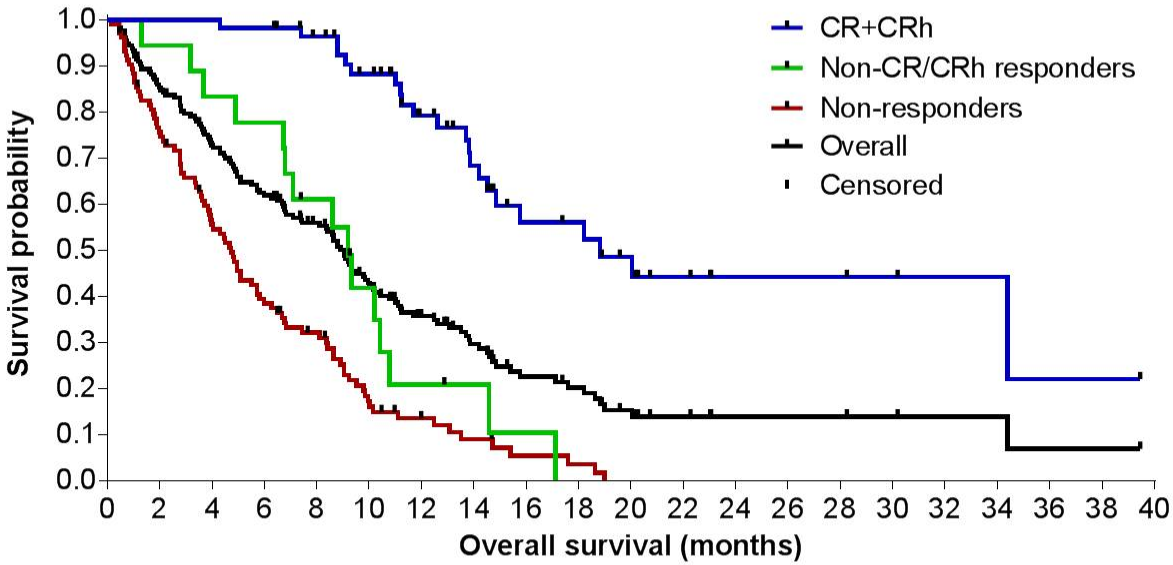
	R/R AML 500 mg (n=179)
Overall Response Rate, n (%) [95% CI]	**75 (41.9) [34.6, 49.5]**
Time to first response, median (range) months	1.9 (0.8, 4.7)
Duration of response, median [95% CI] months	6.5 [5.5, 10.1]
Best response, n (%)	
CR	43 (24.0)
CRi or CRp	21 (11.7)
MLFS	11 (6.1)
SD	68 (38.0)
PD	15 (8.4)
NA	21 (11.7)

CRh = 9 patients with investigator-assessed responses of CRi/CRp and 5 with MLFS

Among the 179 patients with R/R AML, 5 from dose escalation and 1 from dose expansion were not positive for mIDH1 by the companion diagnostic test and none of these 6 patients achieved a CR or CRh
CR+CRh was consistent across baseline age groups, including patients who were > 65 years of age
Overall response rate includes CR, CRi/CRp, MLFS and PR

Data cutoff: 10Nov2017. PD, progressive disease; PR, partial response

Overall Survival by Best Response in R/R AML 500 mg (n=179)



Number of patients at risk:

57	57	57	56	50	43	32	25	16	15	11	7	4	4	4	3	2	2	1	1
18	17	15	14	10	6	3	2	1	0										
104	77	55	38	29	15	9	6	3	2	0									

CR+CRh
Non-CR/CRh responders
Non-responders

	Months
Overall survival, median [95% CI]	
CR+CRh	18.8 [14.2, NE]
Non-CR/CRh responders	9.2 [6.7, 10.8]
Non-responders	4.7 [3.7, 5.7]
All	9.0 [7.1, 10.0]
Overall follow-up, median (range)	15.3 (0.2–39.5)

Non-CR/CRh responders include CRi, CRp, and MLFS who are not CRh
Non-responders = all others including those with best responses of SD, PD, or not evaluable

Data cutoff: 10Nov2017 NE, not estimable

Presented By Daniel Pollyea at 2018 ASCO Annual Meeting

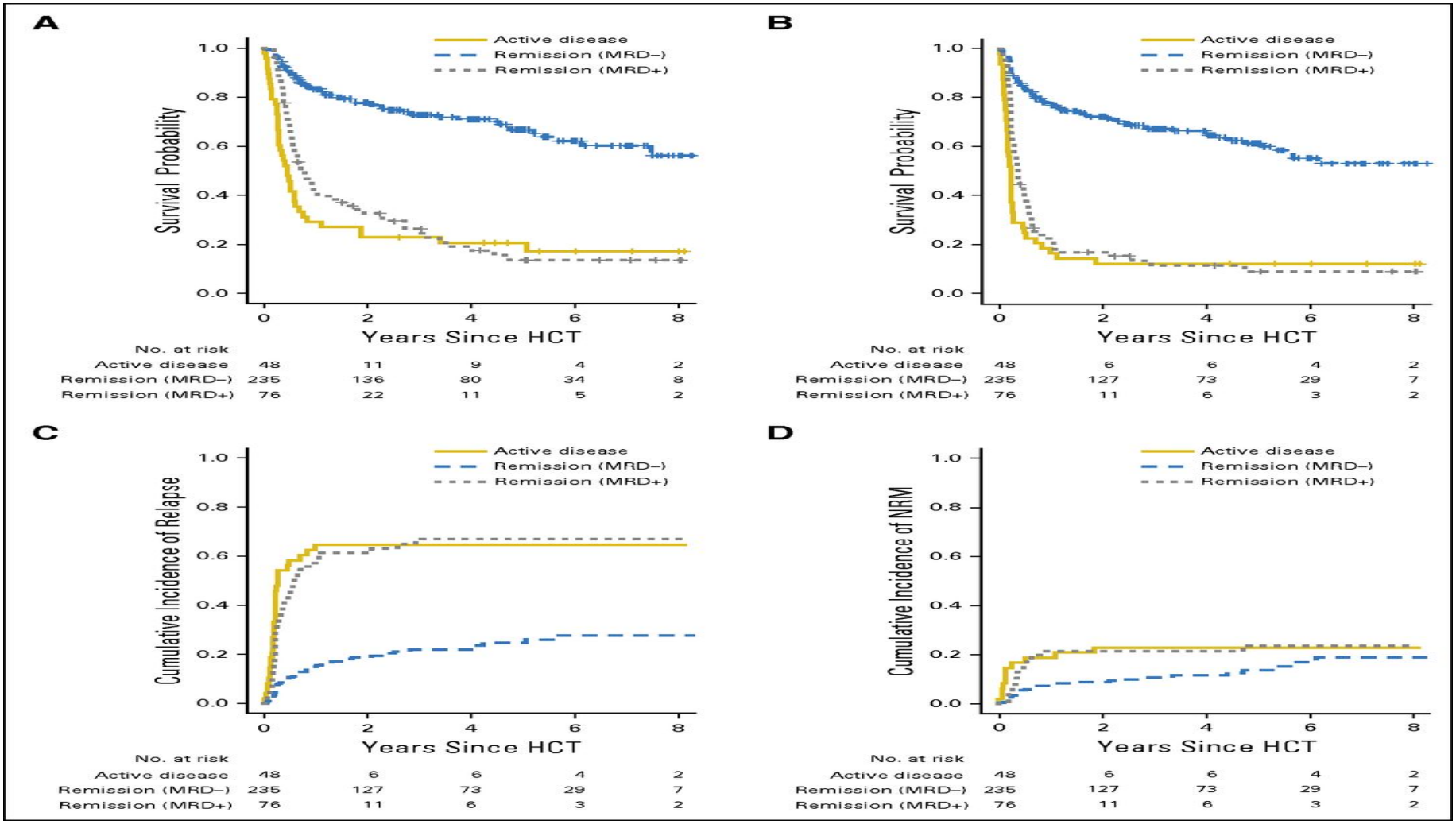
TAKE HOME – IDH1and IDH2

- Do molecular testing on all AML/MDS
- Responses can be slow
- Differentiation syndrome
- Almost certainly palliative
- Trials in combination with chemotherapy are in progress

Minimal Residual Disease

- Detectable by flow, pcr with > 10^{-4} sensitivity
- In general, predictive of relapse and inferior outcome
- Can now study the characteristics of single, sorted cells

Association between pretransplant disease status and outcome for patients with acute myeloid leukemia (AML) after myeloablative hematopoietic cell transplantation (HCT).



Daisuke Araki et al. JCO 2016;34:329-336

Response Rates

	Aza/Venetoclax	Azacytidine
CR	37%	18%
CCR	66%	28%

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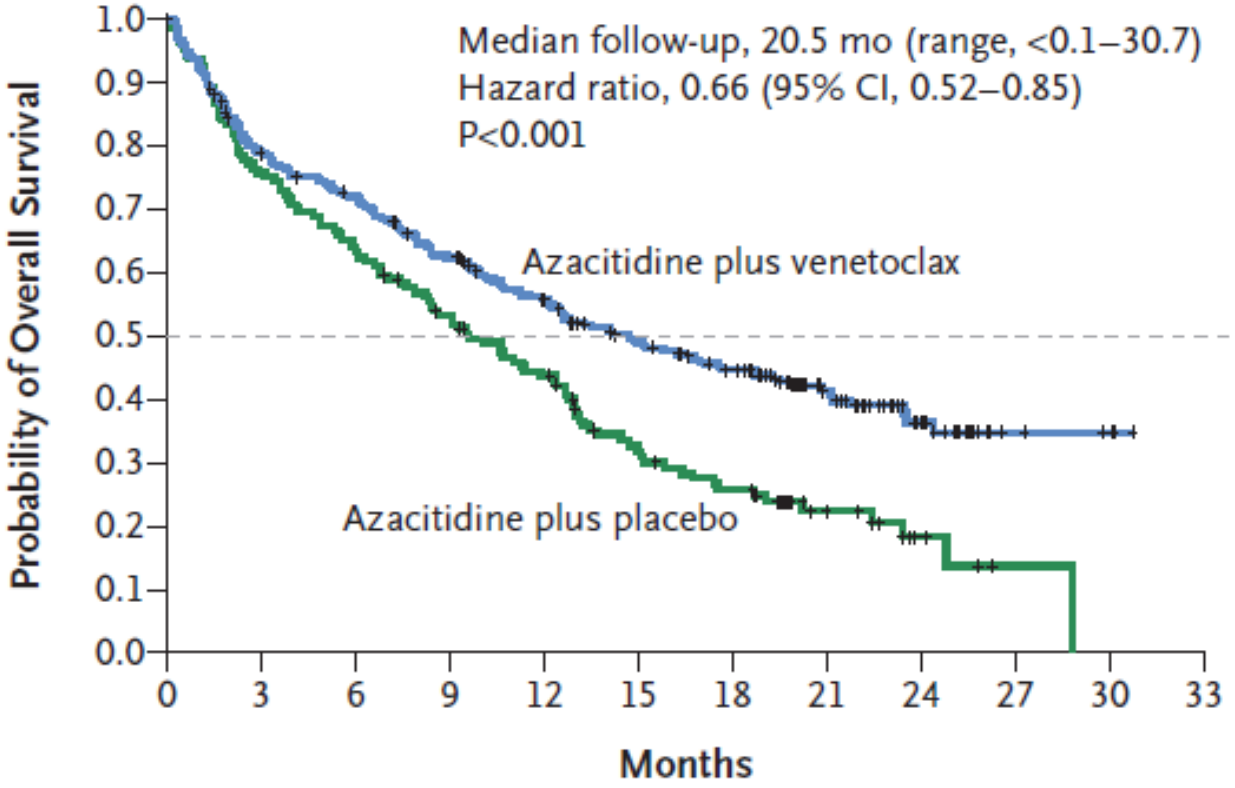
Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

C.D. DiNardo, B.A. Jonas, V. Pullarkat, M.J. Thirman, J.S. Garcia, A.H. Wei, M. Konopleva, H. Döhner, A. Letai, P. Fenaux, E. Koller, V. Havelange, B. Leber, J. Esteve, J. Wang, V. Pejsa, R. Hájek, K. Porkka, Á. Illés, D. Lavie, R.M. Lemoli, K. Yamamoto, S.-S. Yoon, J.-H. Jang, S.-P. Yeh, M. Turgut, W.-J. Hong, Y. Zhou, J. Potluri, and K.W. Pratz

Promoting Apoptosis with Venetoclax — A Benefit for Older Patients with AML

Charles A. Schiffer, M.D.



No. at Risk

Azacitidine plus venetoclax	286	219	198	168	143	117	101	54	23	5	3	0
Azacitidine plus placebo	145	109	92	74	59	38	30	14	5	1	0	0

MANY REMAINING QUESTIONS

- Definition of “unfit for chemotherapy”
- Should this replace 7 & 3 for older patients?
- Unproven in CBF AML where HIDAC is important for cure
- Untested in “proliferative” AML

<u>The principle of synergy has been established</u>

- How to build upon these results
  - In combination with FLT3, IDH inhibitors
  - In combination with standard chemotherapy

WHY ARE SOME PATIENTS CURED?

- Sufficient cytoreduction by chemotherapy
- Unique sensitivity of the clonogenic leukemia stem cell (CBF AML)
- Re-expression of genes suppressed by the CBF or other mutations
- Differentiation of leukemia: “clonal remissions"
- Recovery of immune surveillance – elimination/suppression of residual disease