New developments in AML

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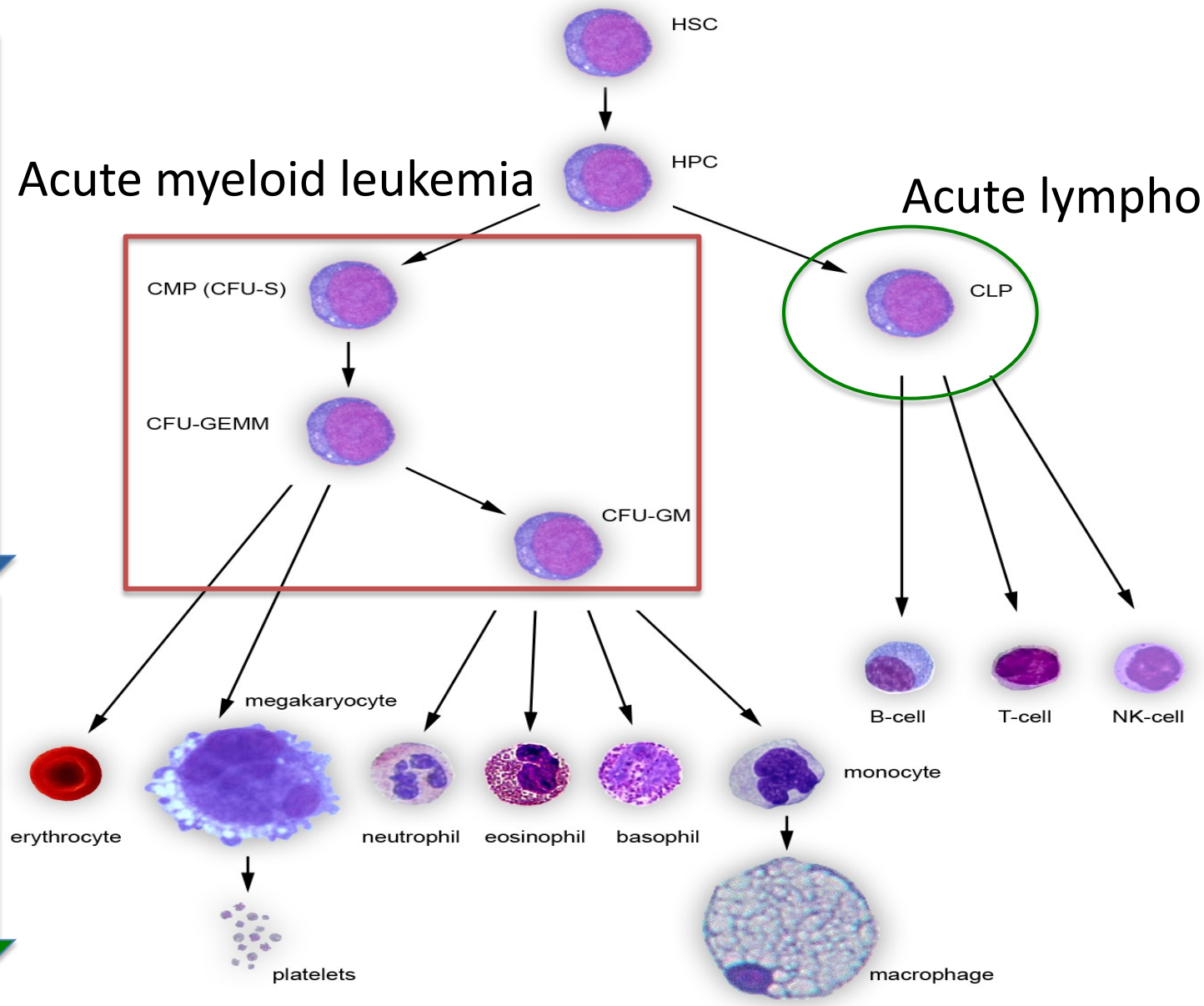
Blood cancers and cell of origin

Stem and progenitor cells (ability to regenerate)

Mature cells (terminally differentiated)



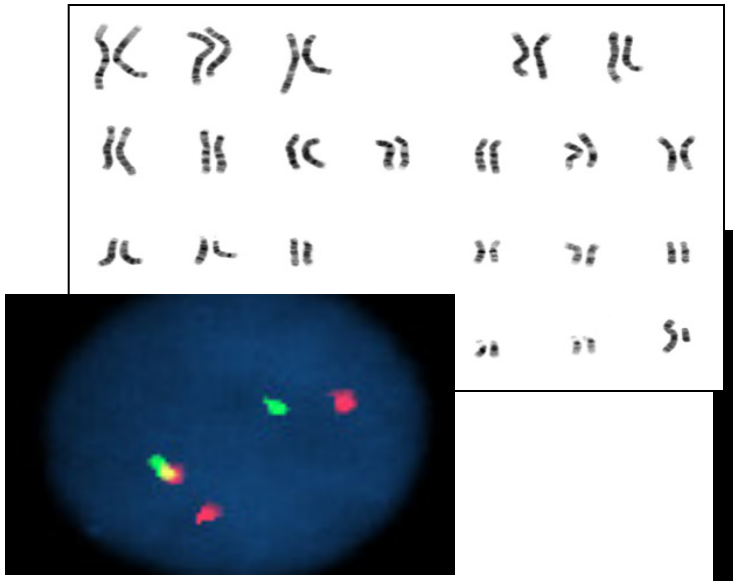
http://daley.med.harvard.edu/assets/Willy/hematopoiesis.jpg

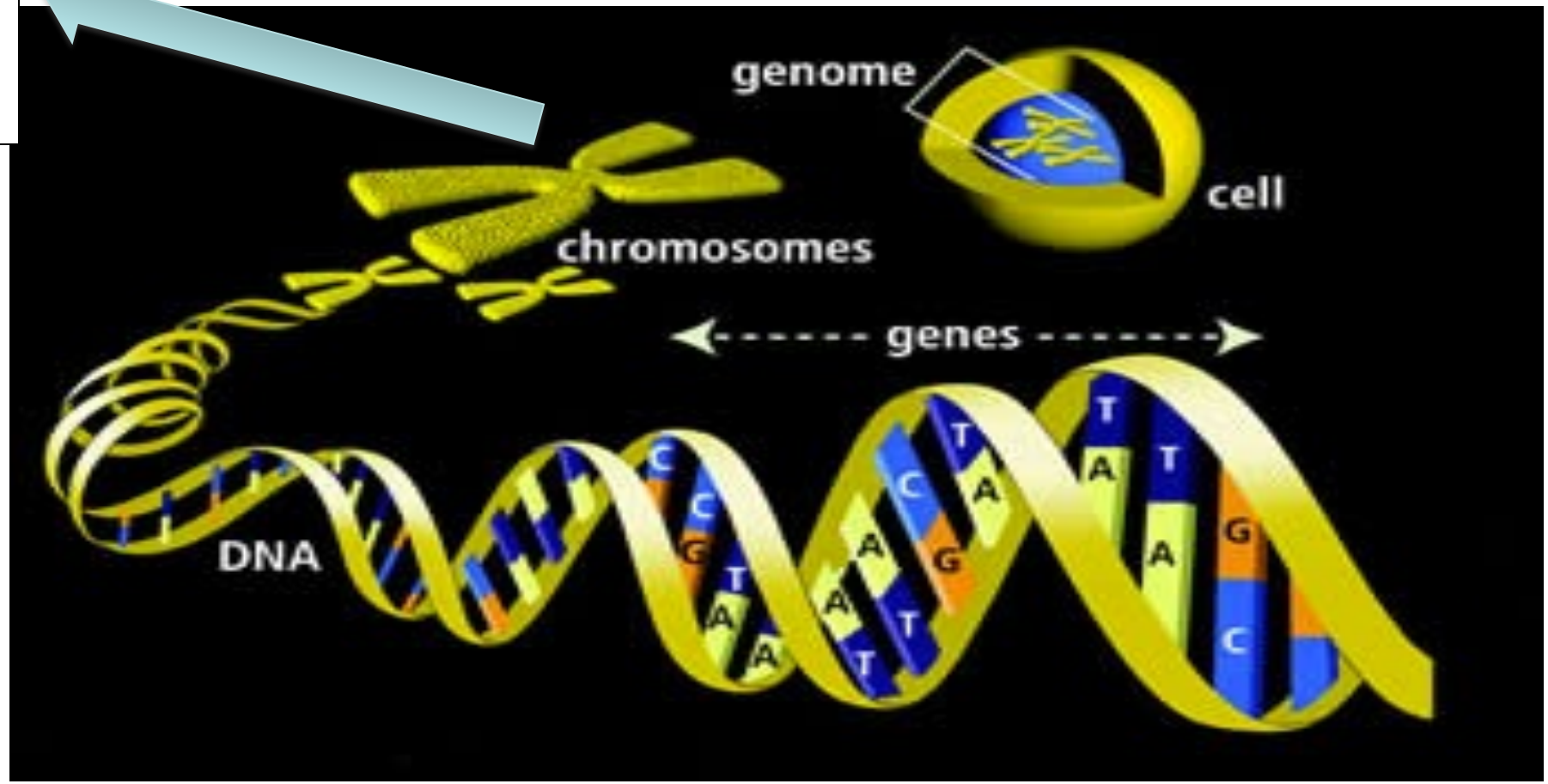
AML a disease of recurrent genetic mutations

- Prognostic
- Targets for therapy

Large chromosomal changes

Cytogenetics/FISH





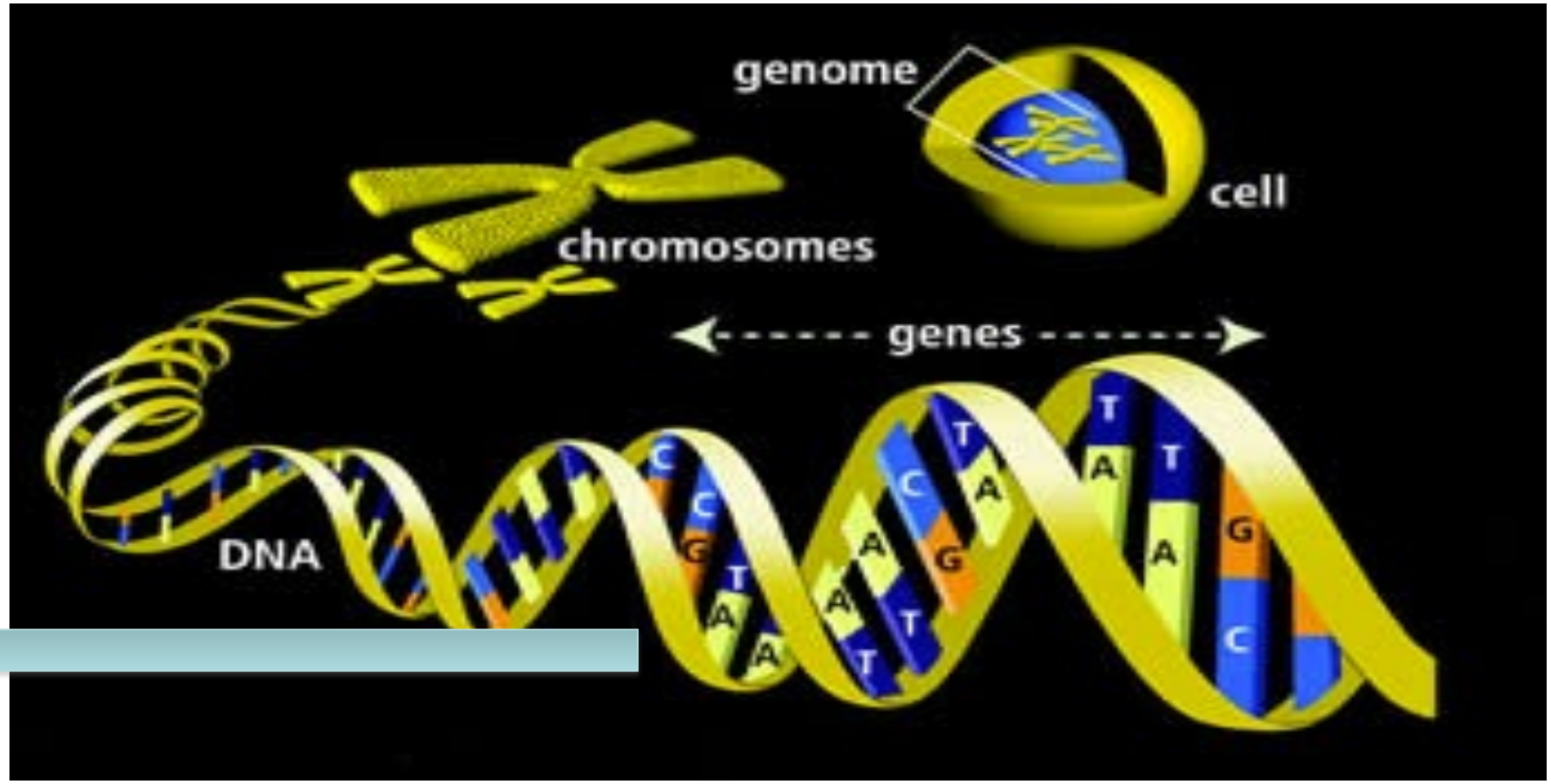
Mutations, small insertions, deletions (Molecular)

PCR (FLT3 ITD)

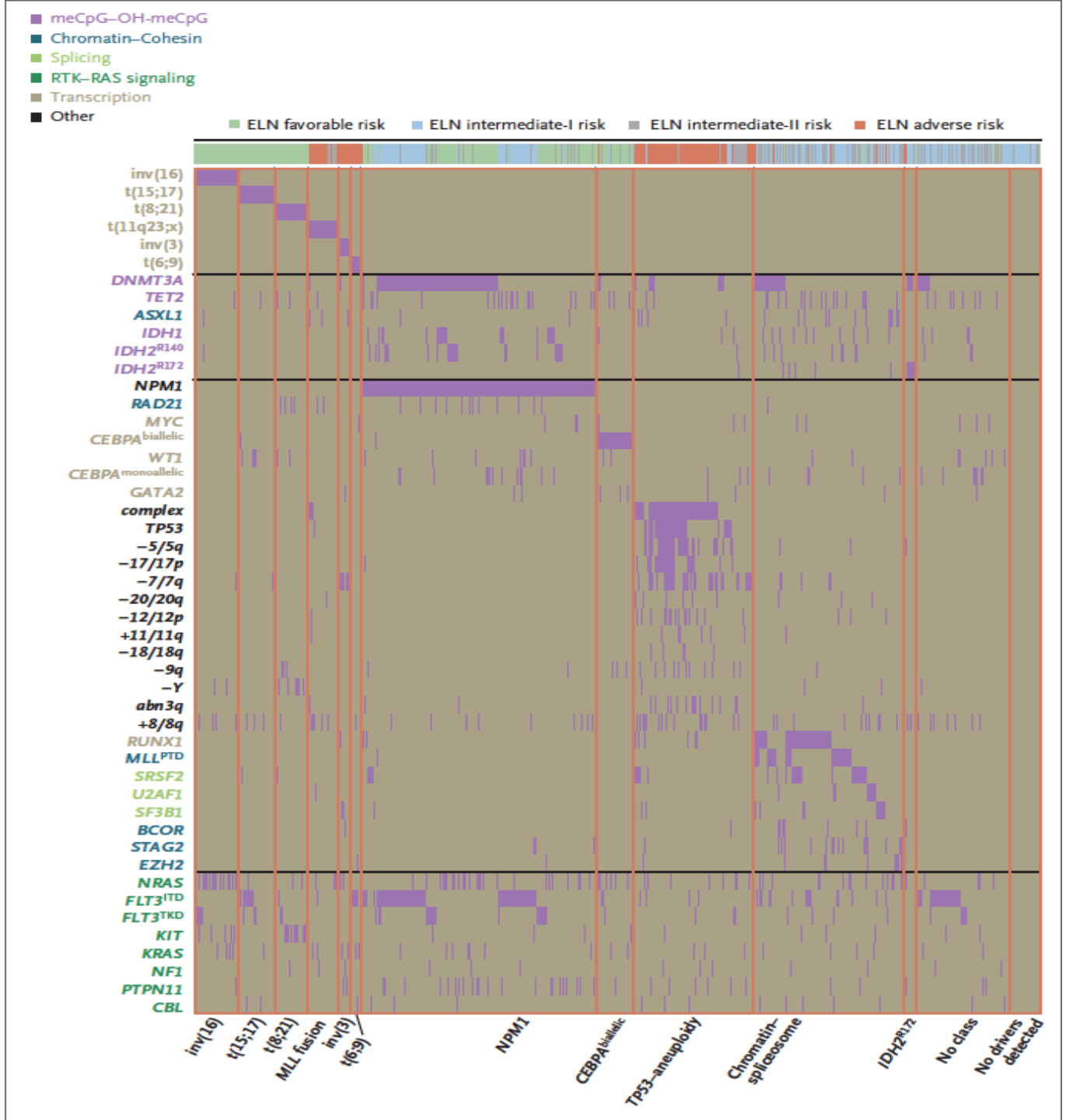
Next generation sequencing

ATACAGGCT

TATGTCCGA

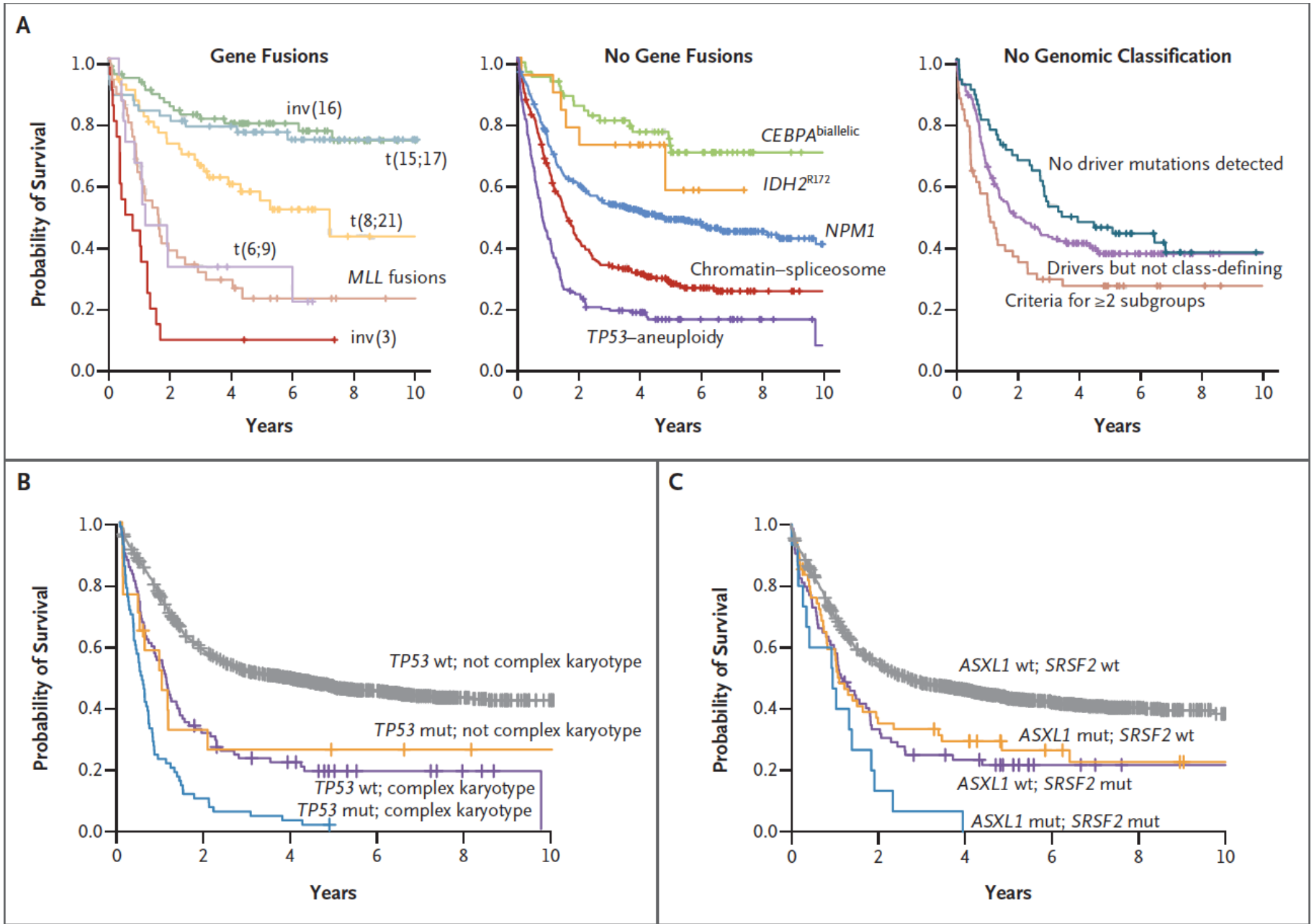


Mutations in AML



Pappaemmanuil et al. NEJM 2016

Prognostic impact of mutations (mostly with chemo)



Pappaemmanuil et al. NEJM 2016

Update to AML risk stratification

Table 5. 2017 ELN risk stratification by genetics

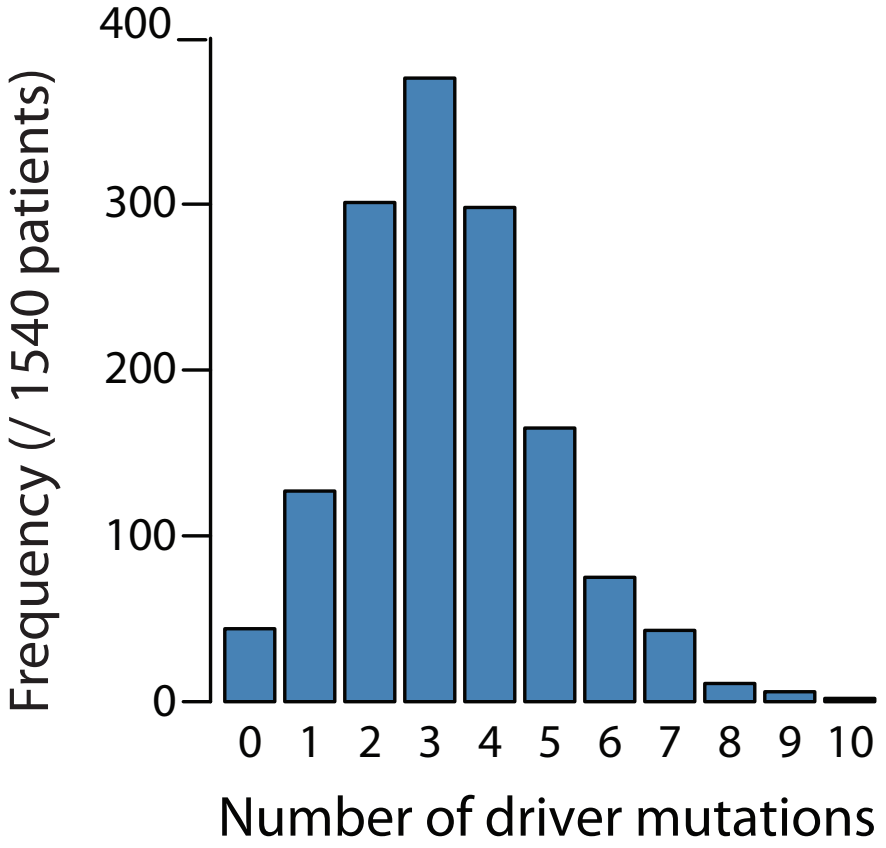
Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *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*#

Table 6. 2022 European LeukemiaNet (ELN) risk classification by genetics at initial diagnosis[a]

Risk Category[b]	Genetic Abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*[b,c] • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*[b,c] • Mutated *NPM1*[b,d] without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*[e]
Intermediate	• Mutated *NPM1*[b,d] with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*[b,f] • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged[g] • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11;p13)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*, *MECOM(EVI1)* • t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged • -5 or del(5q); -7; -17/abn(17p) • Complex karyotype,[h] monosomal karyotype[i] • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2*[j] • Mutated *TP53*[k]

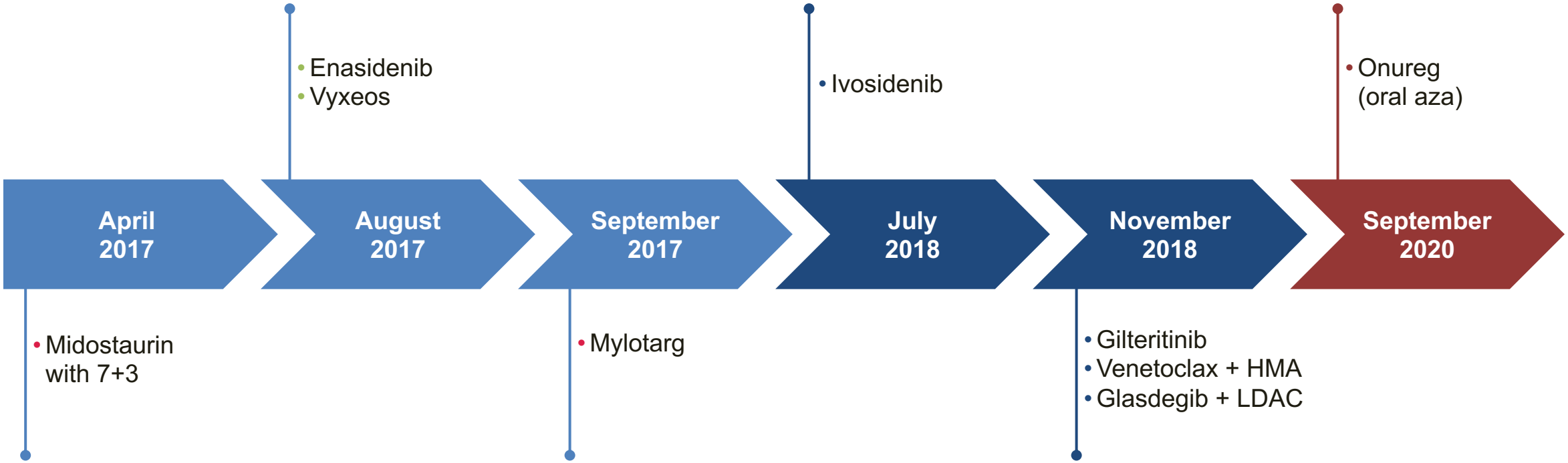
Most leukemias have multiple mutations

- This makes assessing risk a little harder
- Targeted treatment is also more challenging
- ***Need better combinations***



Pappaemmanuil et al. NEJM 2016

We have made progress – 9 drugs approved in AML since 2017!

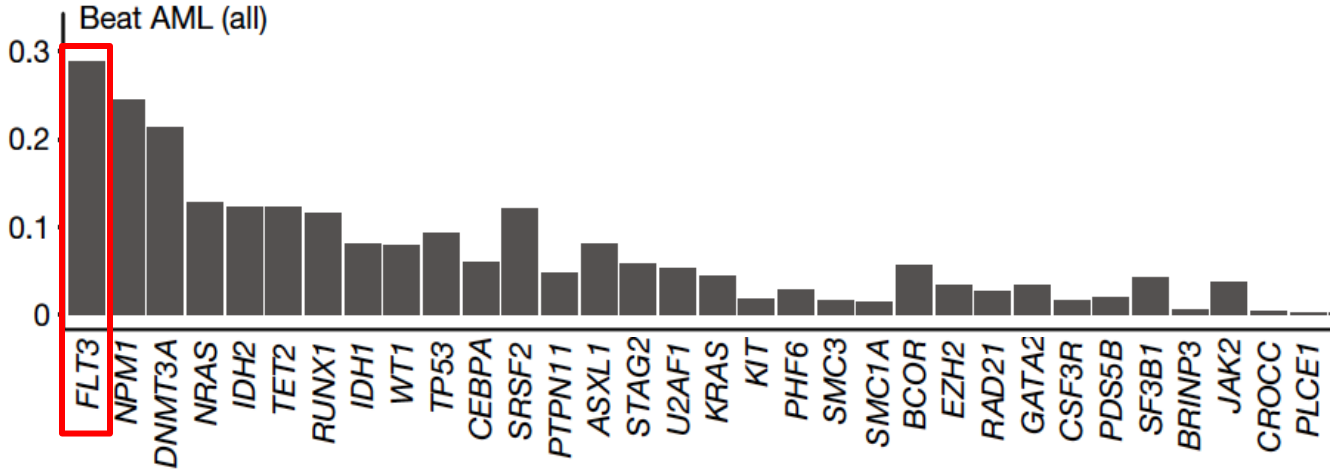


Next challenge: how best to mix and match for different types of AML patients

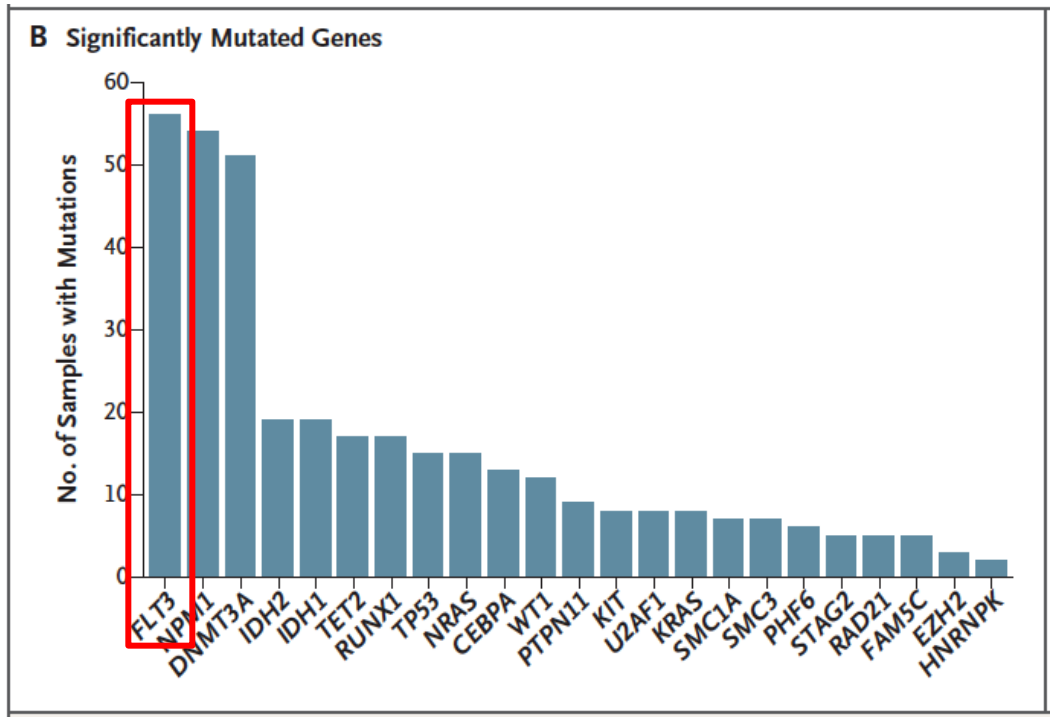
FLT3 inhibitors

- Slow down leukemia cell growth

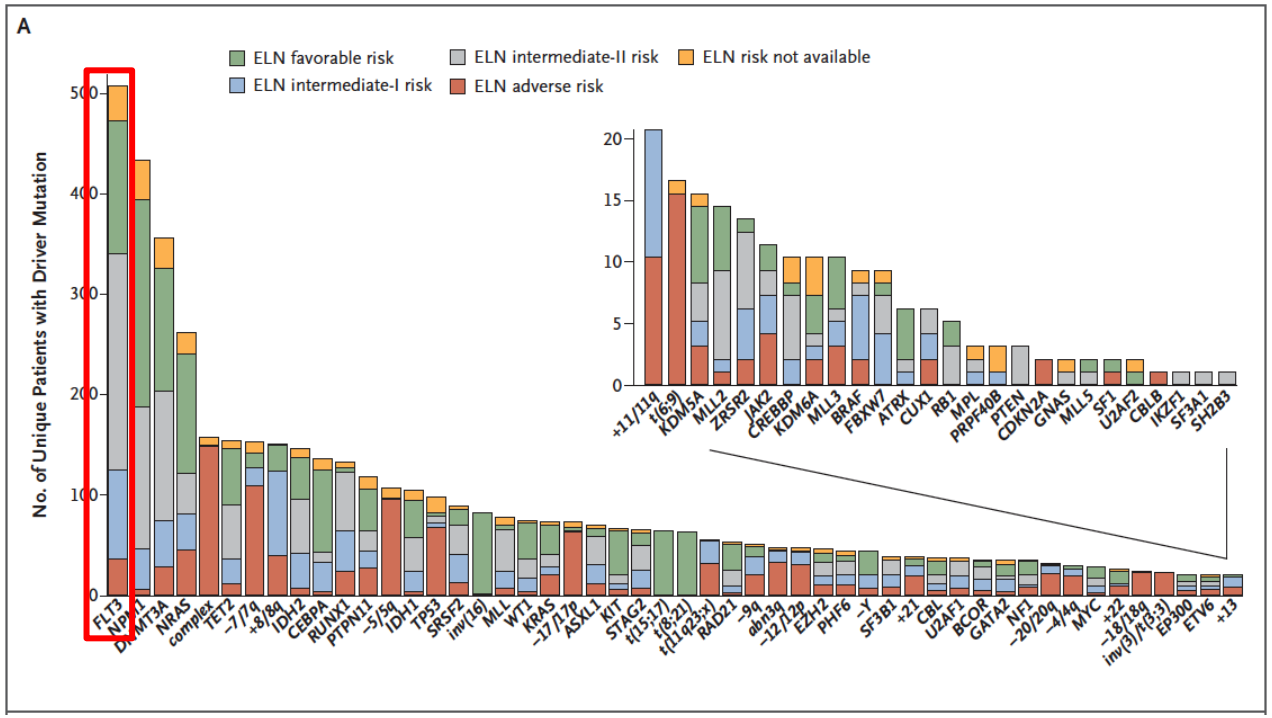
FLT3 is the most common mutation in AML



Tyner et al. Nature 2018

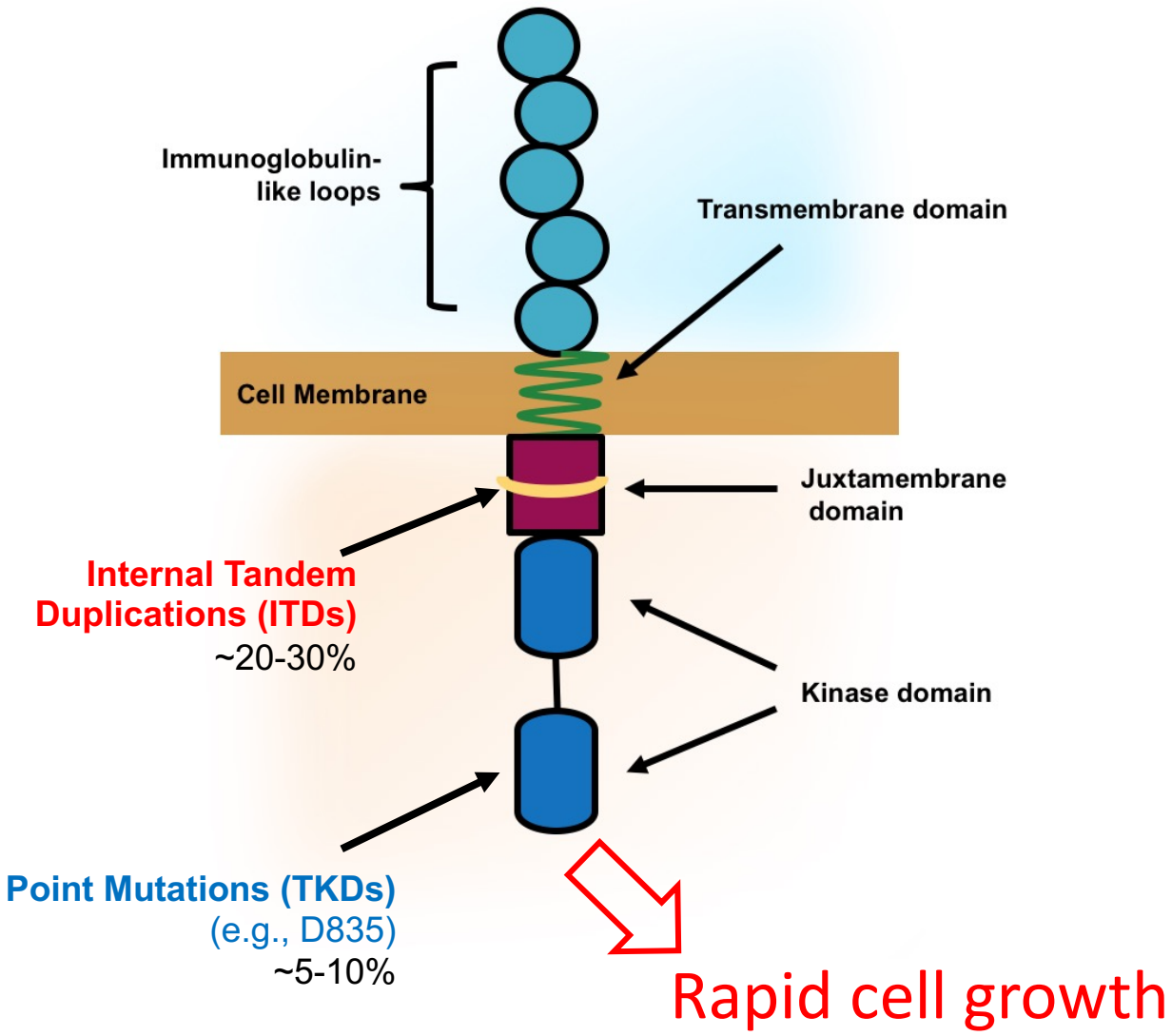


TCGA. NEJM 2013



Pappaemmanuil et al. NEJM 2016

FLT3 mutations drive leukemia cell growth



- Many inhibitors of FLT3 developed
- FLT3 inhibitors block leukemia cell growth
- Can often get rapid responses

Fletcher L., *et al.*, Cancer Manag Res, 2020.

Gilteritinib for relapsed/refractory AML

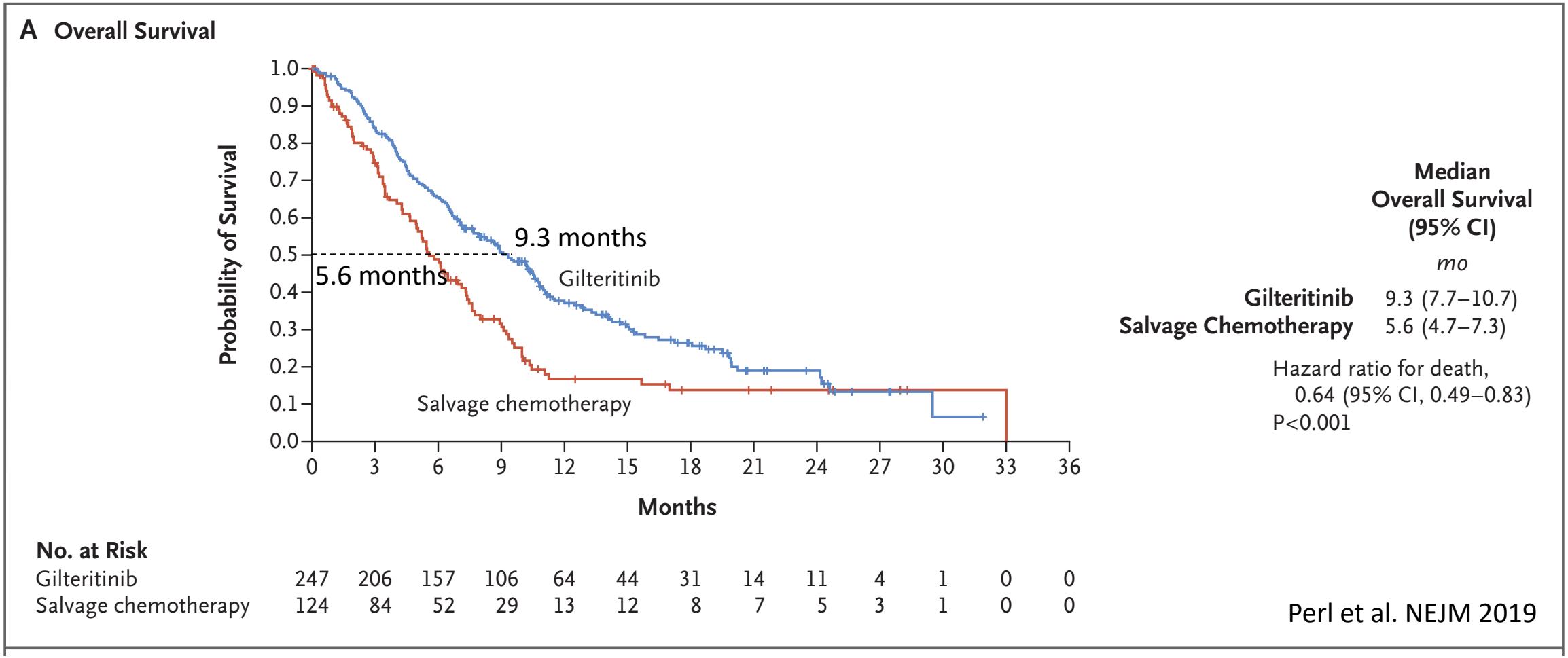
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Gilteritinib or Chemotherapy for Relapsed or Refractory *FLT3*-Mutated AML

A.E. Perl, G. Martinelli, J.E. Cortes, A. Neubauer, E. Berman, S. Paolini, P. Montesinos, M.R. Baer, R.A. Larson, C. Ustun, F. Fabbiano, H.P. Erba, A. Di Stasi, R. Stuart, R. Olin, M. Kasner, F. Ciceri, W.-C. Chou, N. Podoltsev, C. Recher, H. Yokoyama, N. Hosono, S.-S. Yoon, J.-H. Lee, T. Pardee, A.T. Fathi, C. Liu, N. Hasabou, X. Liu, E. Bahceci, and M.J. Levis

Gilteritinib superior to chemotherapy, but eventually leukemia cells become resistant



Combine FLT3 inhibitors with chemotherapy to kill residual leukemia cells?

FLT3 inhibitors with chemotherapy

The NEW ENGLAND JOURNAL *of* MEDICINE

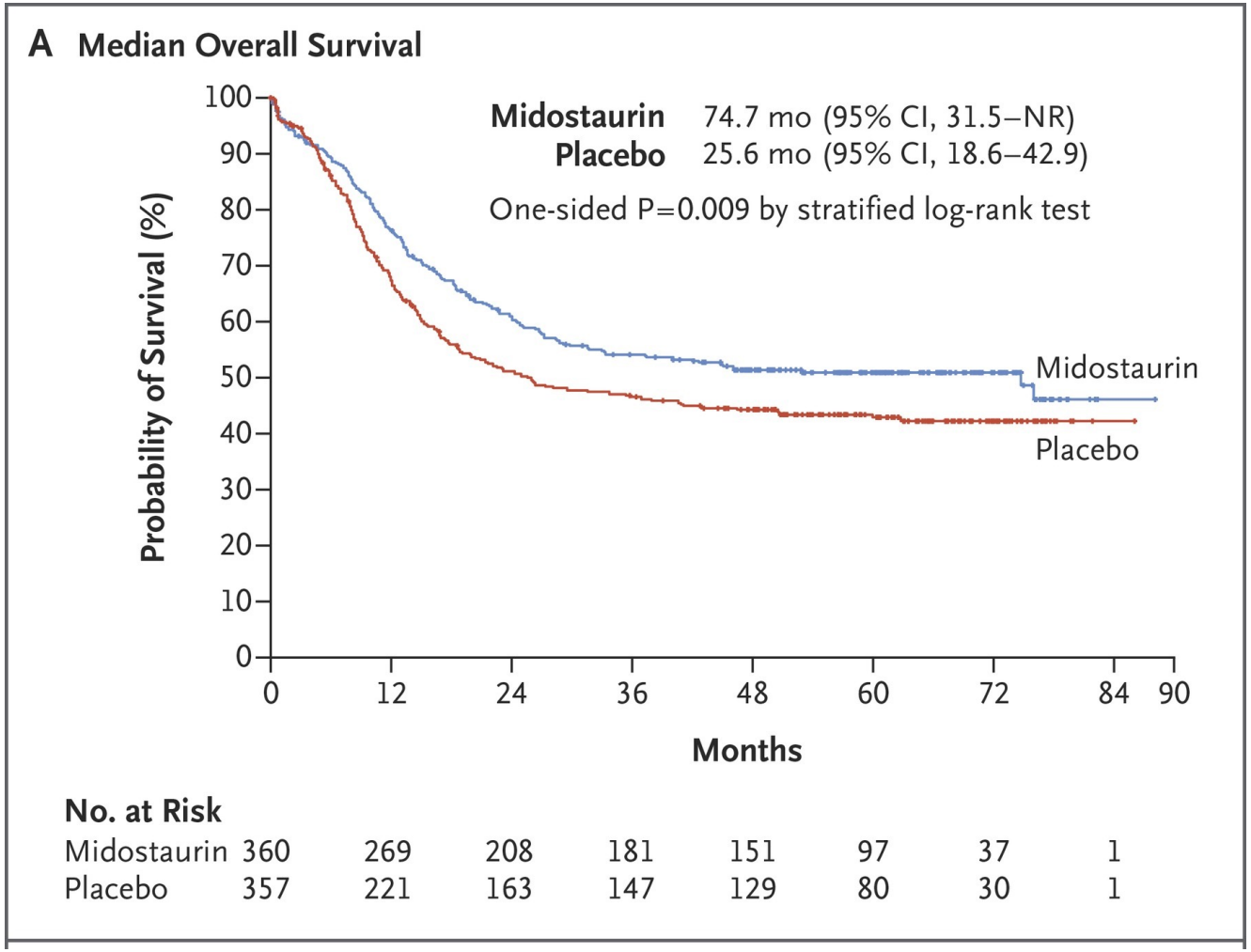
ORIGINAL ARTICLE

Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a *FLT3* Mutation

R.M. Stone, S.J. Mandrekar, B.L. Sanford, K. Laumann, S. Geyer, C.D. Bloomfield, C. Thiede, T.W. Prior, K. Döhner, G. Marcucci, F. Lo-Coco, R.B. Klisovic, A. Wei, J. Sierra, M.A. Sanz, J.M. Brandwein, T. de Witte, D. Niederwieser, F.R. Appelbaum, B.C. Medeiros, M.S. Tallman, J. Krauter, R.F. Schlenk, A. Ganser, H. Serve, G. Ehninger, S. Amadori, R.A. Larson, and H. Döhner

RATIFY trial for FLT3 ITD and TKD

- Midostaurin is a FLT3 inhibitor
- Multikinase inhibitor (first generation)
- Less potent than gilteritinib and other FLT3 inhibitors



Stone et al. NEJM 2017

More potent FLT3 inhibitors work better with chemotherapy?

More FLT3 inhibitors being tested in combination

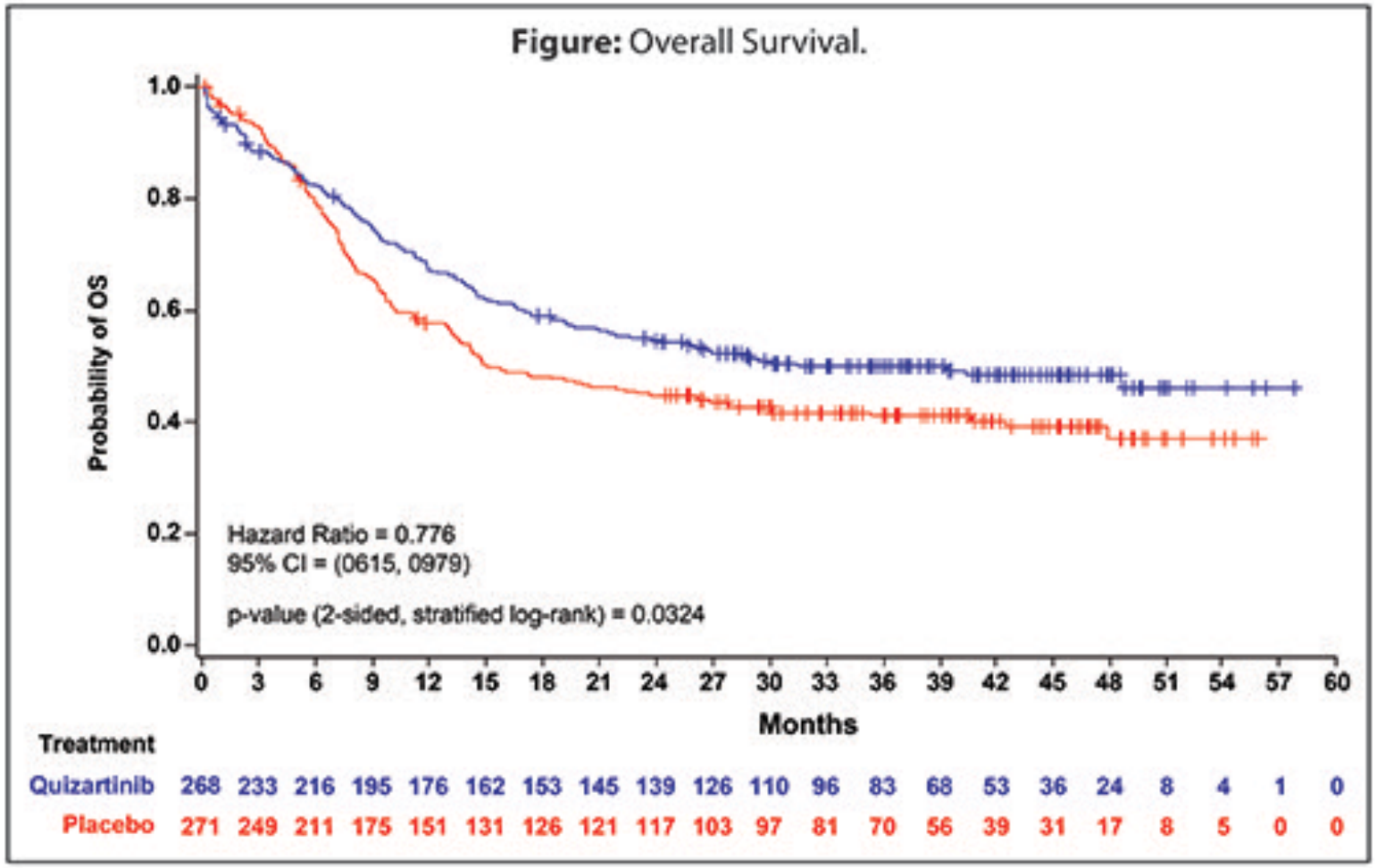
- 7+3 + quizartinib
  - Started prior to approval of midostaurin
  - Results reported at EHA 2022

- 7+3 + gilteritinib vs midostaurin
  - Phase 1 reported – high CR rate
  - Phase 3 ongoing

- 7+3 + crenolanib vs midostaurin
  - Phase 2 reported – high CR rate
  - Phase 3 ongoing

7+3 with Quizartinib

- Improved OS
- Only for FLT3 ITD mutations
- Similar side effects seen with previous trials
  - Neutropenia
  - QTc prolongation
- Submitted to FDA



Erba et al. EHA 2022 Abstract 100

What about FLT3 inhibitors and hypomethylating agents?

Key Eligibility Criteria
- Newly diagnosed *FLT3*$^{mut+}$ AML
- Not eligible for intensive induction chemotherapy

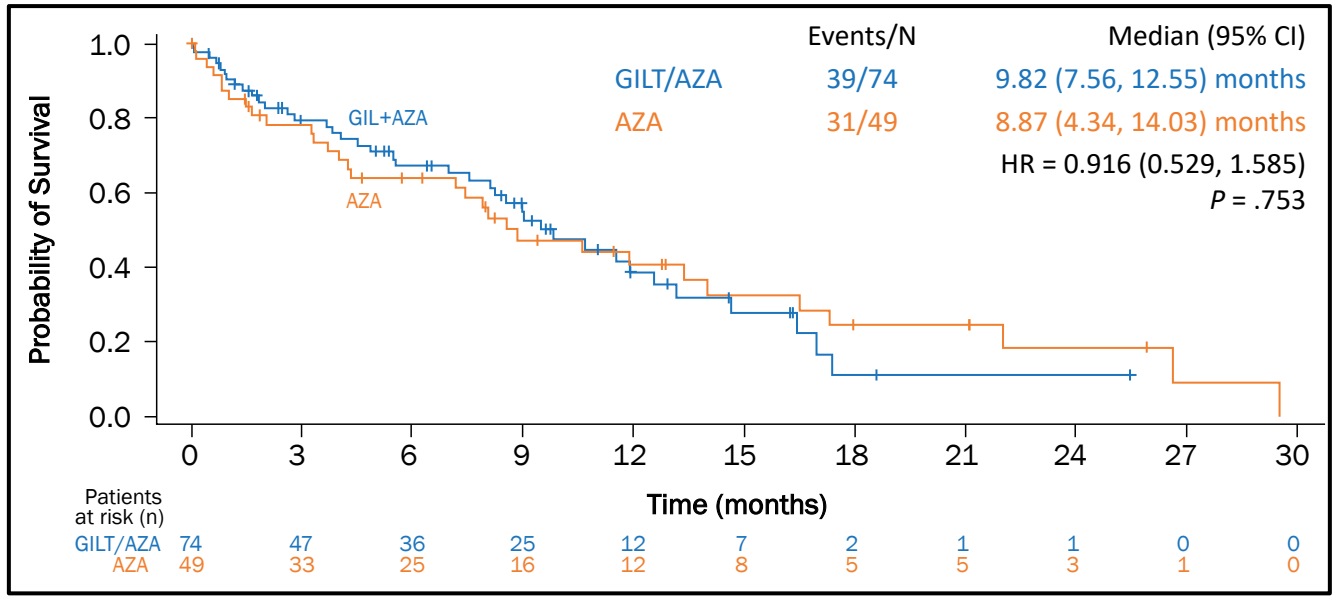
Administered over 28-day cycles

RANDOMIZED 2:1*

- **Gilteritinib** 120 mg PO daily on days 1 to 28
- **Gilteritinib + Azacitidine** Gilt 120 mg PO daily, days 1 to 28, Aza 75 mg/m^2 IV or SUBQ daily, days 1 to 7
- **Azacitidine (Aza)** 75 mg/m^2 IV or SUBQ daily, days 1 to 7

Wang et al. ASH 2021 Abstract 700

No significant OS difference observed with GILT+AZA vs. AZA



Median follow-up: 9.76 months for GILT/AZA and 17.97 months for AZA

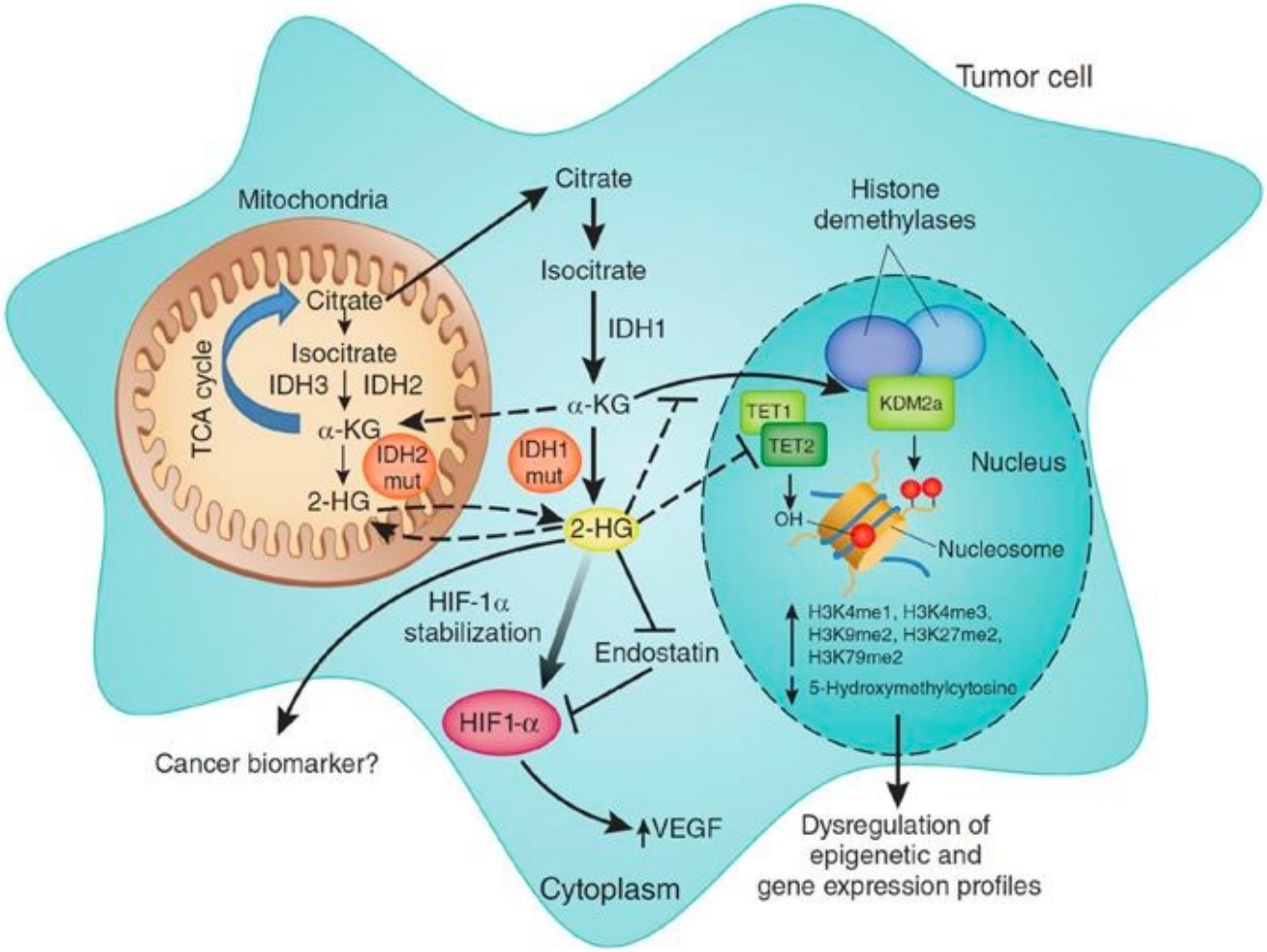
Unclear why the combination did not perform better than azacitidine alone

IDH inhibitors

- Promote leukemia cell maturation (differentiation)

IDH1/2 mutations interfere with DNA methylation

- IDH mutations cause production of 2-HG instead of α-KG
- 2-HG inhibits TET2 and methylation of DNA
- This blocks normal maturation of white blood cells
- Drugs developed to block the mutated IDH1 or IDH2 proteins



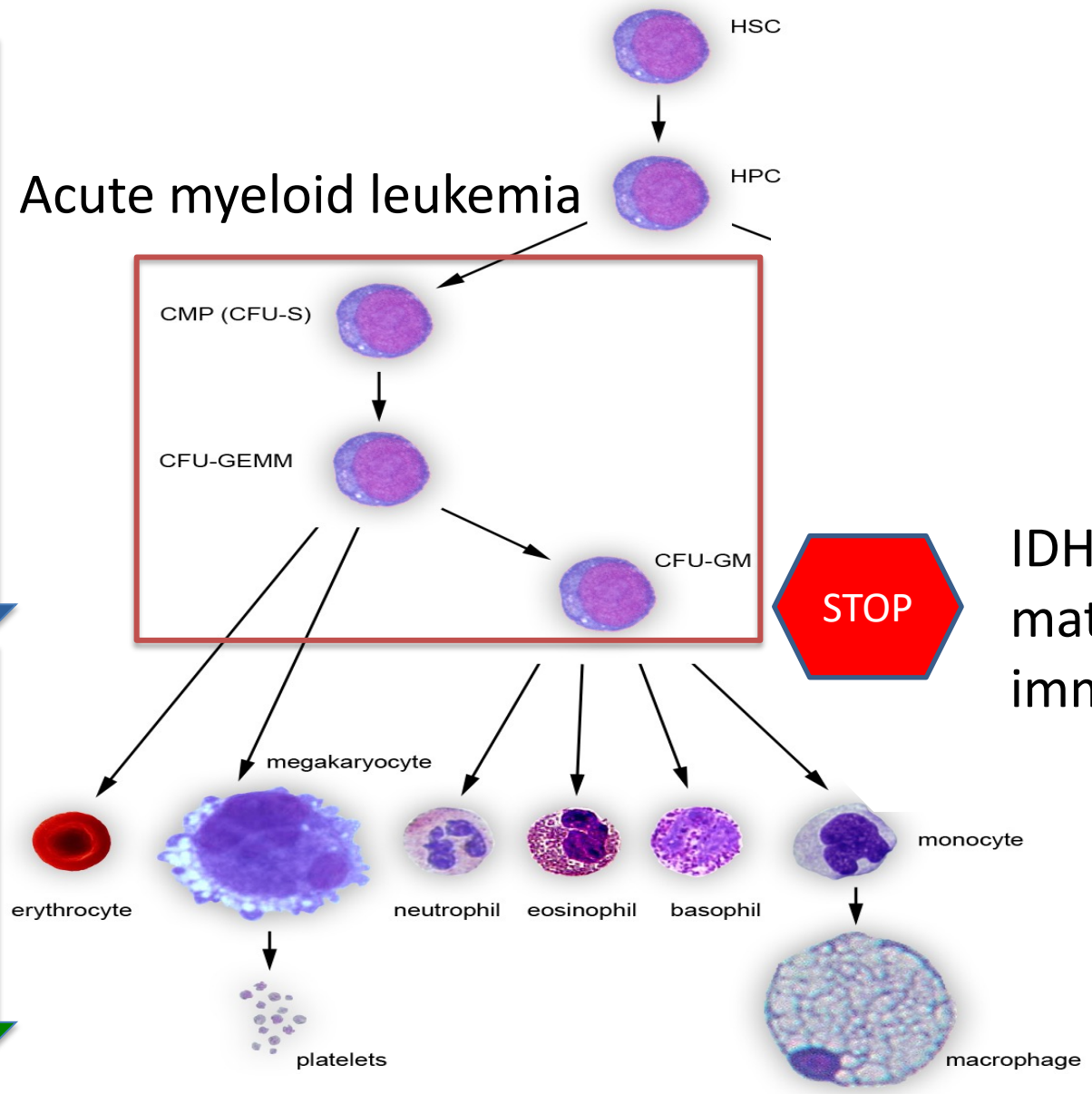
Prensner JR and Chinnaiyan AM. Nature Medicine 2011

IDH mutations block maturation

Stem and progenitor cells (ability to regenerate)

Mature cells (terminally differentiated)

Acute myeloid leukemia



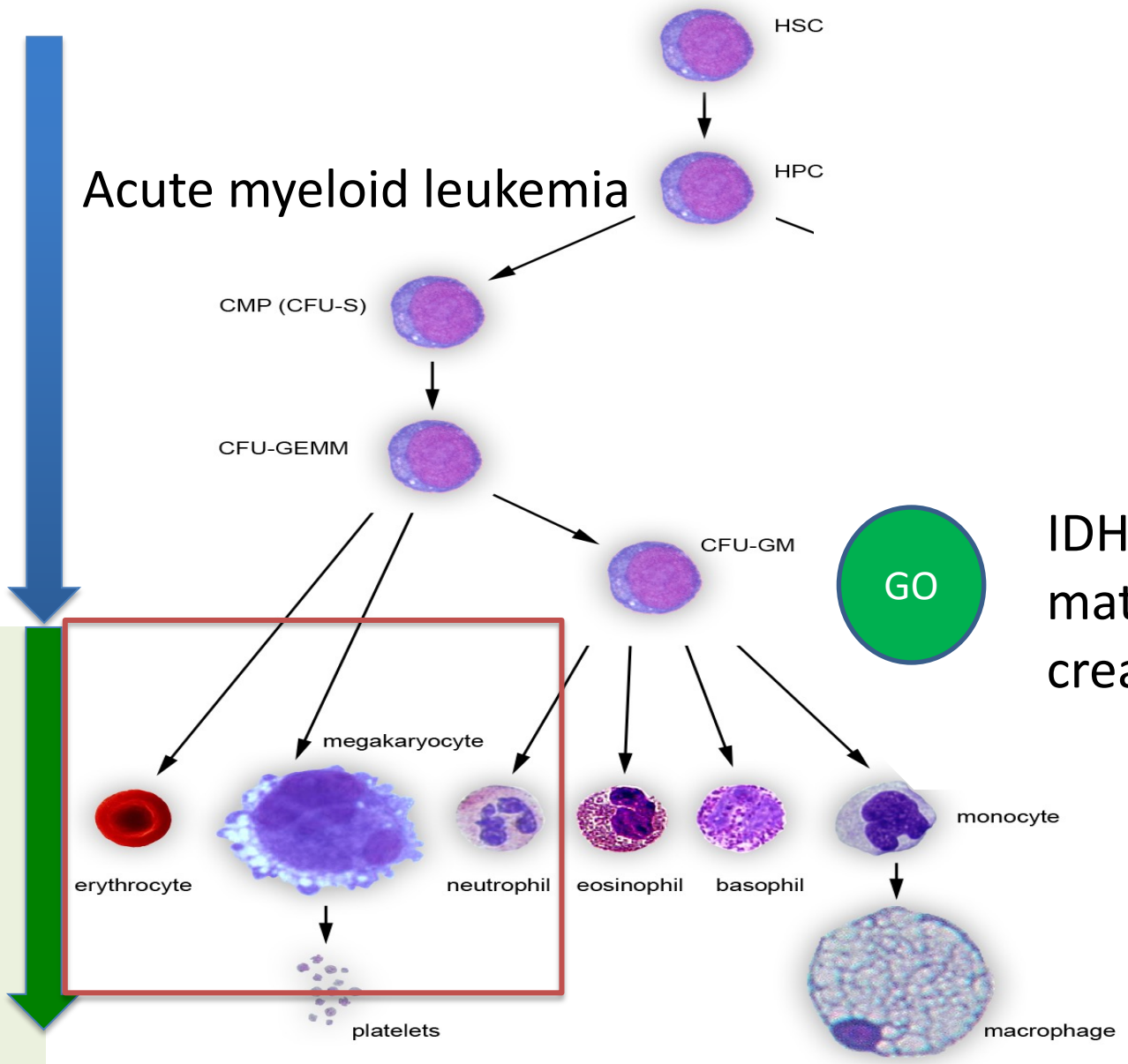
IDH mutations prevent maturation, leading to immature blasts

http://daley.med.harvard.edu/assets/Willy/hematopoiesis.jpg

IDH inhibitors release the blockade

Stem and progenitor cells (ability to regenerate)

Mature cells (terminally differentiated)



IDH inhibitors allow maturation to resume, creating mature cells

http://daley.med.harvard.edu/assets/Willy/hematopoiesis.jpg

Enasidenib – IDH2 inhibitor

Leukemia
https://doi.org/10.1038/s41375-019-0472-2

ARTICLE

Acute myeloid leukemia

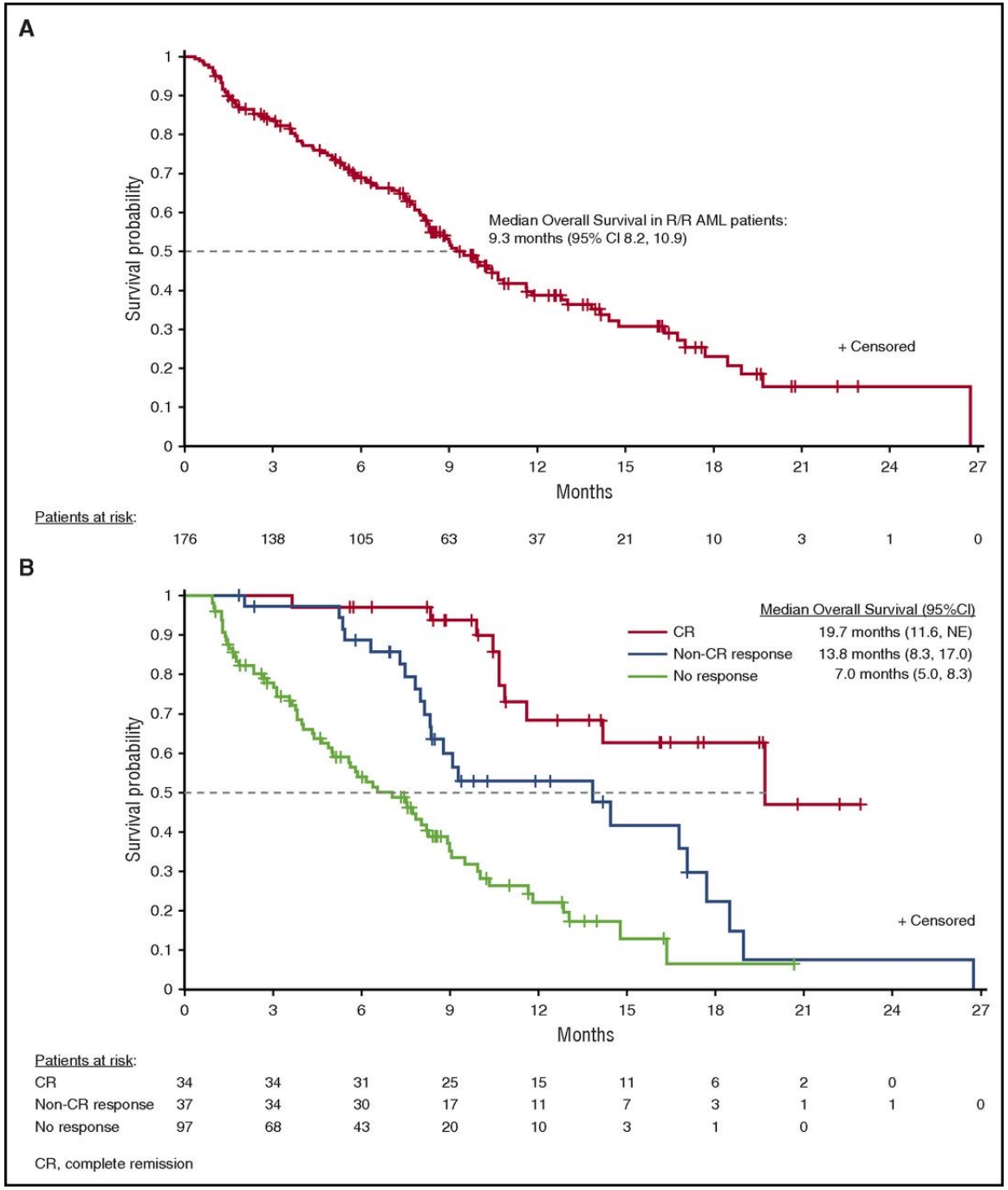
Enasidenib, an inhibitor of mutant IDH2 proteins, induces durable remissions in older patients with newly diagnosed acute myeloid leukemia

Daniel A. Pollyea[1] · Martin S. Tallman[2] · Stéphane de Botton[3,4] · Hagop M. Kantarjian[5] · Robert Collins[6] · Anthony S. Stein[7] · Mark G. Frattini[8] · Qiang Xu[8] · Alessandra Tosolini[8] · Wendy L. See[8] · Kyle J. MacBeth[8] · Samuel V. Agresta[9] · Eyal C. Attar[9] · Courtney D. DiNardo[5] · Eytan M. Stein[2,10]

Received: 28 January 2019 / Revised: 22 March 2019 / Accepted: 25 March 2019

Enasidenib in R/R AML (IDH2 inhibitor)

- Enasidenib improves survival
- CR/CRh ~30%
- Improved production of blood cells
- Much less toxic than chemotherapy



Stein et al. Blood 2017

- Very tolerable overall
- Elevated bilirubin
- **IDH differentiation syndrome**
  - 15-20% of patients
  - Tends to occur 1-2 months into therapy

Table 2 Enasidenib-related adverse events reported in ≥10% of patients

Adverse event	Patients with newly diagnosed AML $N = 39$	
	All grades *n* (%)	Grade ≥3
Hyperbilirubinemia	12 (31)	5 (13)
Nausea	9 (23)	0
Decreased appetite	7 (18)	1 (3)
Fatigue	7 (18)	1 (3)
Thrombocytopenia	7 (18)	3 (8)
Rash	7 (18)	0
Anemia	6 (15)	5 (13)
IDH differentiation syndrome	5 (13)	4 (10)[a]
Dysgeusia	4 (10)	0
Electrocardiogram QT prolongation	4 (10)	1 (3)
Peripheral neuropathy	4 (10)	0
Tumor lysis syndrome	4 (10)	3 (8)
Vomiting	4 (10)	0

[a]The only treatment-related grade 5 event was cardiac tamponade, which was retrospectively adjudicated by the Differentiation Syndrome Review Committee to have potentially been related to IDH differentiation syndrome

Ivosidenib – IDH1 inhibitor

The NEW ENGLAND JOURNAL of MEDICINE

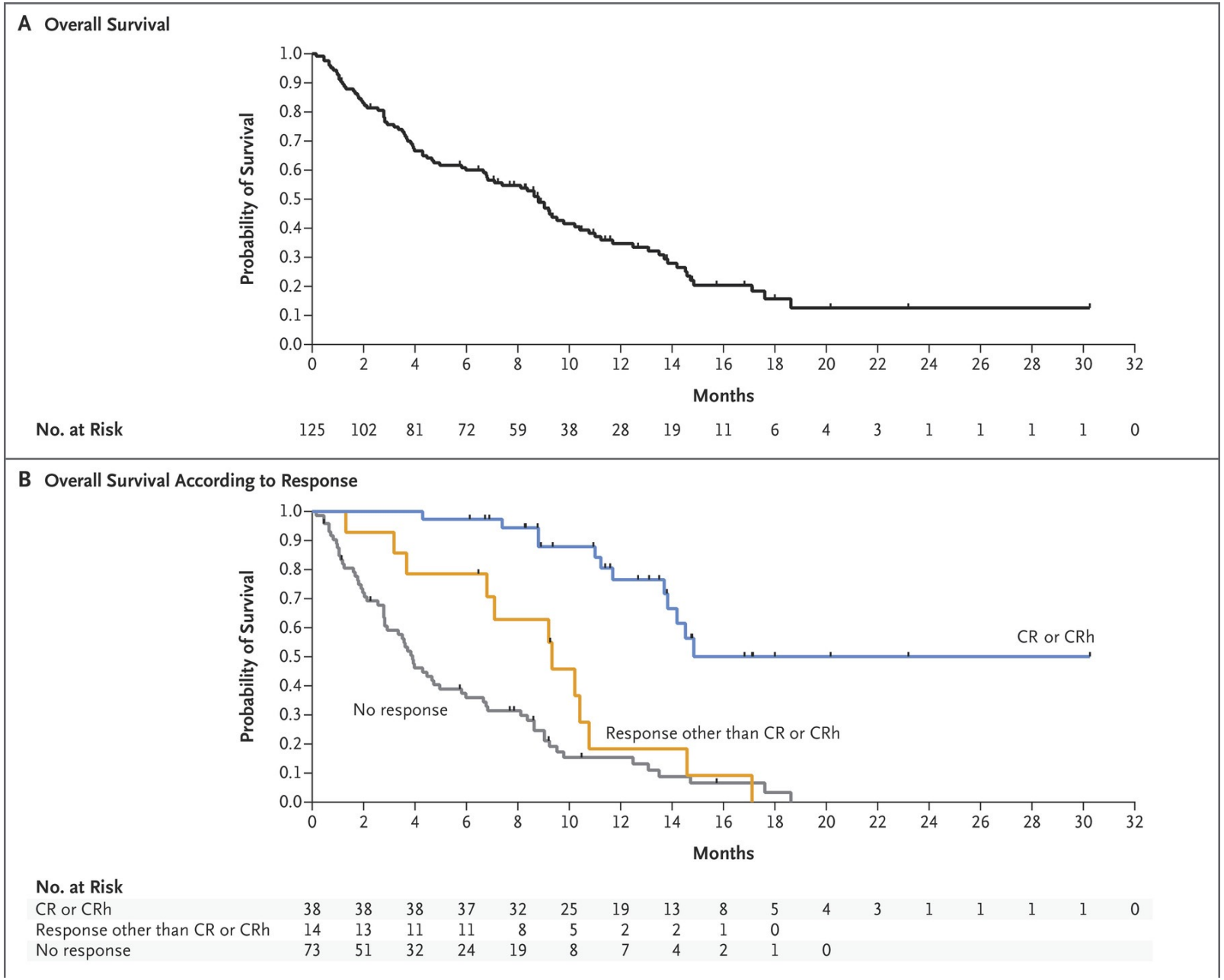
ORIGINAL ARTICLE

Durable Remissions with Ivosidenib in *IDH1*-Mutated Relapsed or Refractory AML

C.D. DiNardo, E.M. Stein, S. de Botton, G.J. Roboz, J.K. Altman, A.S. Mims, R. Swords, R.H. Collins, G.N. Mannis, D.A. Pollyea, W. Donnellan, A.T. Fathi, A. Pigneux, H.P. Erba, G.T. Prince, A.S. Stein, G.L. Uy, J.M. Foran, E. Traer, R.K. Stuart, M.L. Arellano, J.L. Slack, M.A. Sekeres, C. Willekens, S. Choe, H. Wang, V. Zhang, K.E. Yen, S.M. Kapsalis, H. Yang, D. Dai, B. Fan, M. Goldwasser, H. Liu, S. Agresta, B. Wu, E.C. Attar, M.S. Tallman, R.M. Stone, and H.M. Kantarjian

Ivosidenib in R/R AML (IDH1 inhibitor)

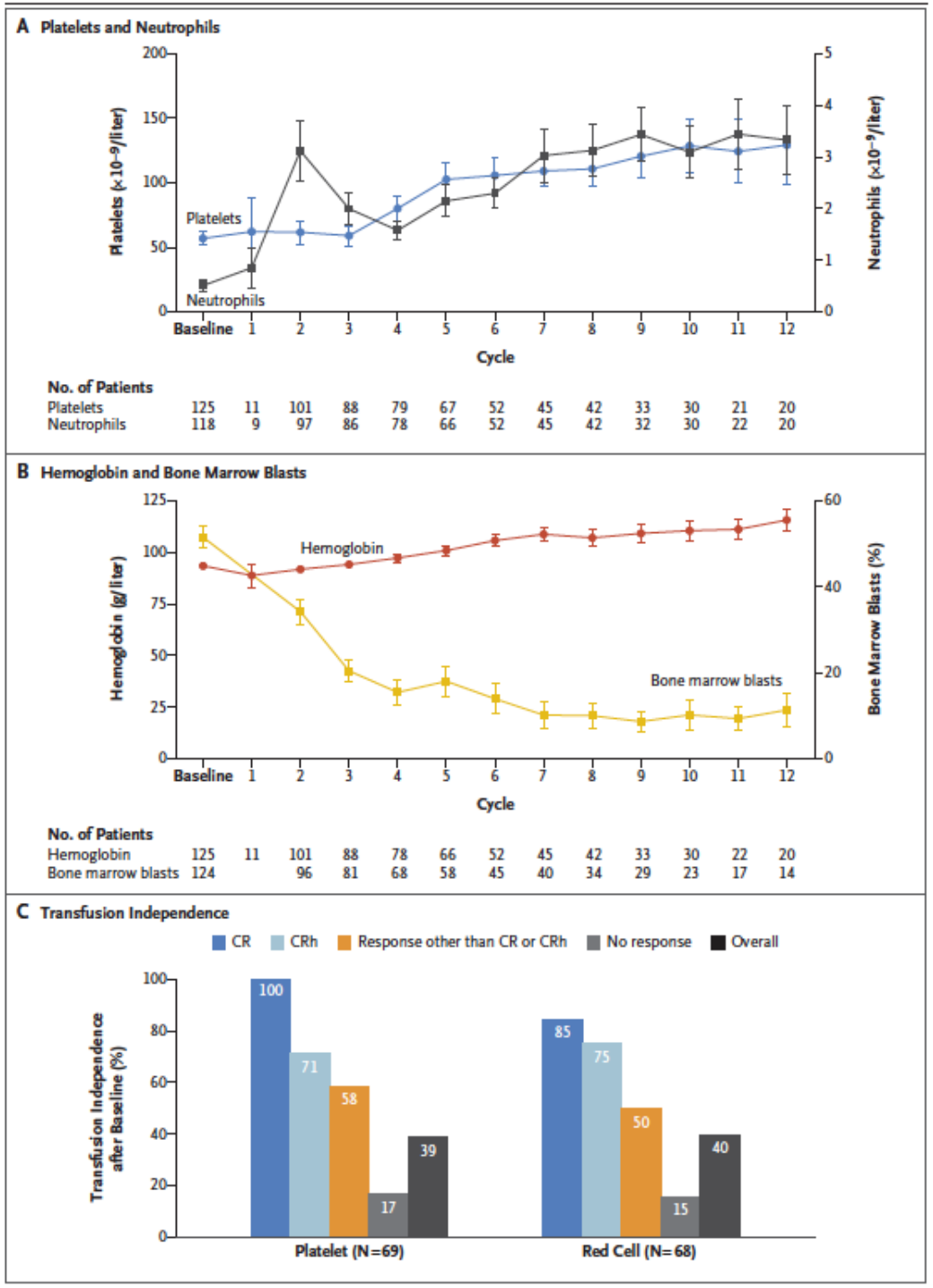
- Ivosidenib also improves survival
- CR/CRh rate ~30%
- Good toxicity profile



DiNardo et al. NEJM 2018

Differentiation effect

- Bump in neutrophils between month 1-2
  - Correlates with IDH differentiation syndrome
- Slow decrease in blasts and rise in Hg
- Many patients achieved transfusion independence



How to improve responses with IDH inhibitors?

- Combine with chemotherapy
  - Frequently found with NPM1 mutations
  - Enasidenib and ivosidenib both being tested with 7+3
  - Reduce relapse?

- Combine with hypomethylating agents
  - Increased response rates with azacytidine: CR rates >50%
  - Aza + enasidenib
    - LLS study on Beat AML trial
  - Aza + ivosidenib (NEJM)
    - LLS study on Beat AML trial

Azacitidine + Ivosidenib

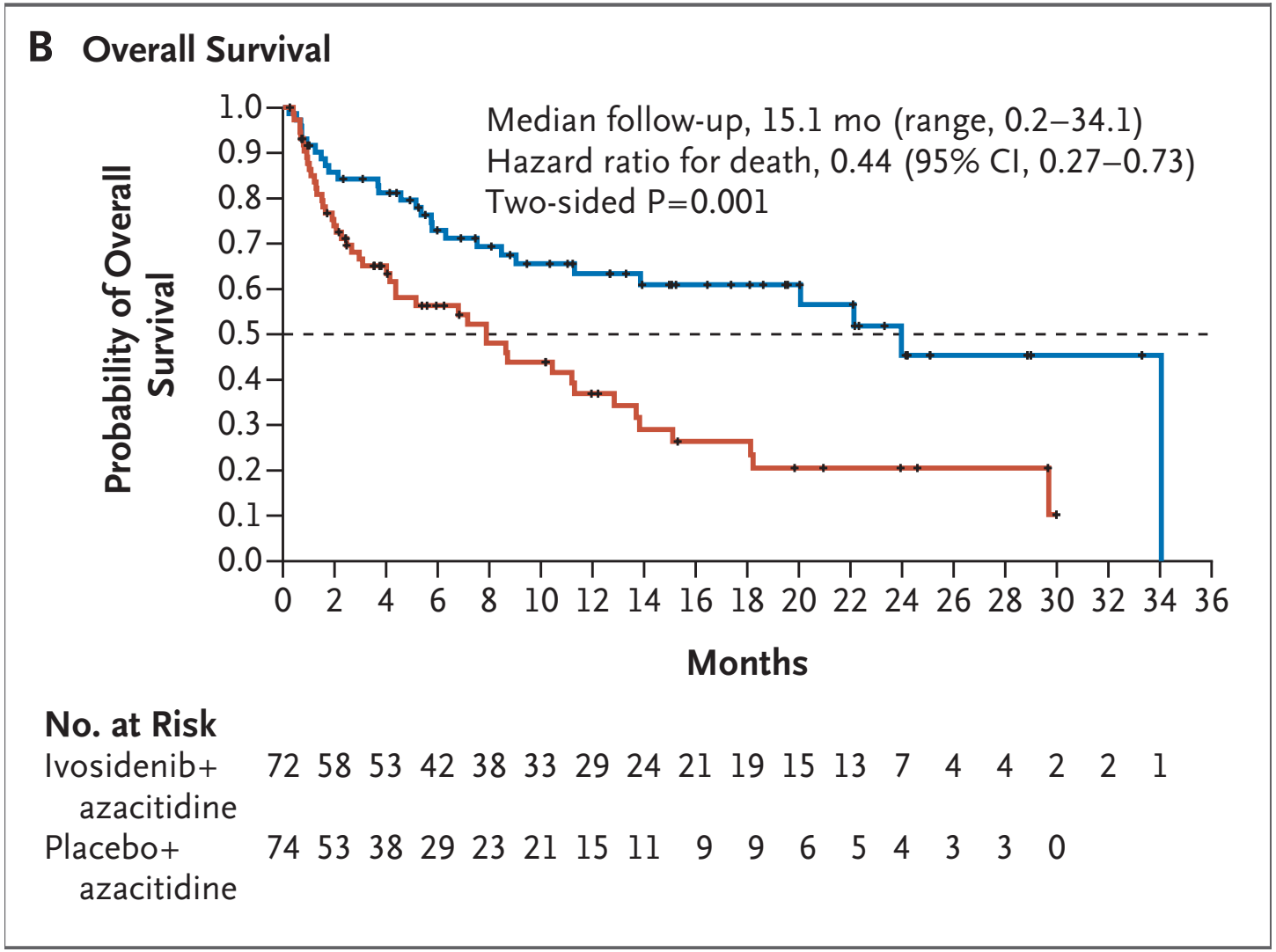
ORIGINAL ARTICLE

Ivosidenib and Azacitidine in *IDH1*-Mutated Acute Myeloid Leukemia

Pau Montesinos, M.D., Ph.D., Christian Recher, M.D., Ph.D., Susana Vives, M.D., Ewa Zarzycka, M.D., Jianxiang Wang, M.D., Giambattista Bertani, M.D., Michael Heuser, M.D., Rodrigo T. Calado, M.D., Ph.D., Andre C. Schuh, M.D., Su-Peng Yeh, M.D., Scott R. Daigle, M.S., Jianan Hui, Ph.D., Shuchi S. Pandya, M.D., Diego A. Gianolio, Ph.D., Stephane de Botton, M.D., Ph.D., and Hartmut Döhner, M.D.

Improved overall survival

- CR in 53% of patients with aza + ivo
- Differentiation syndrome in 14%
- Median survival of 24 months



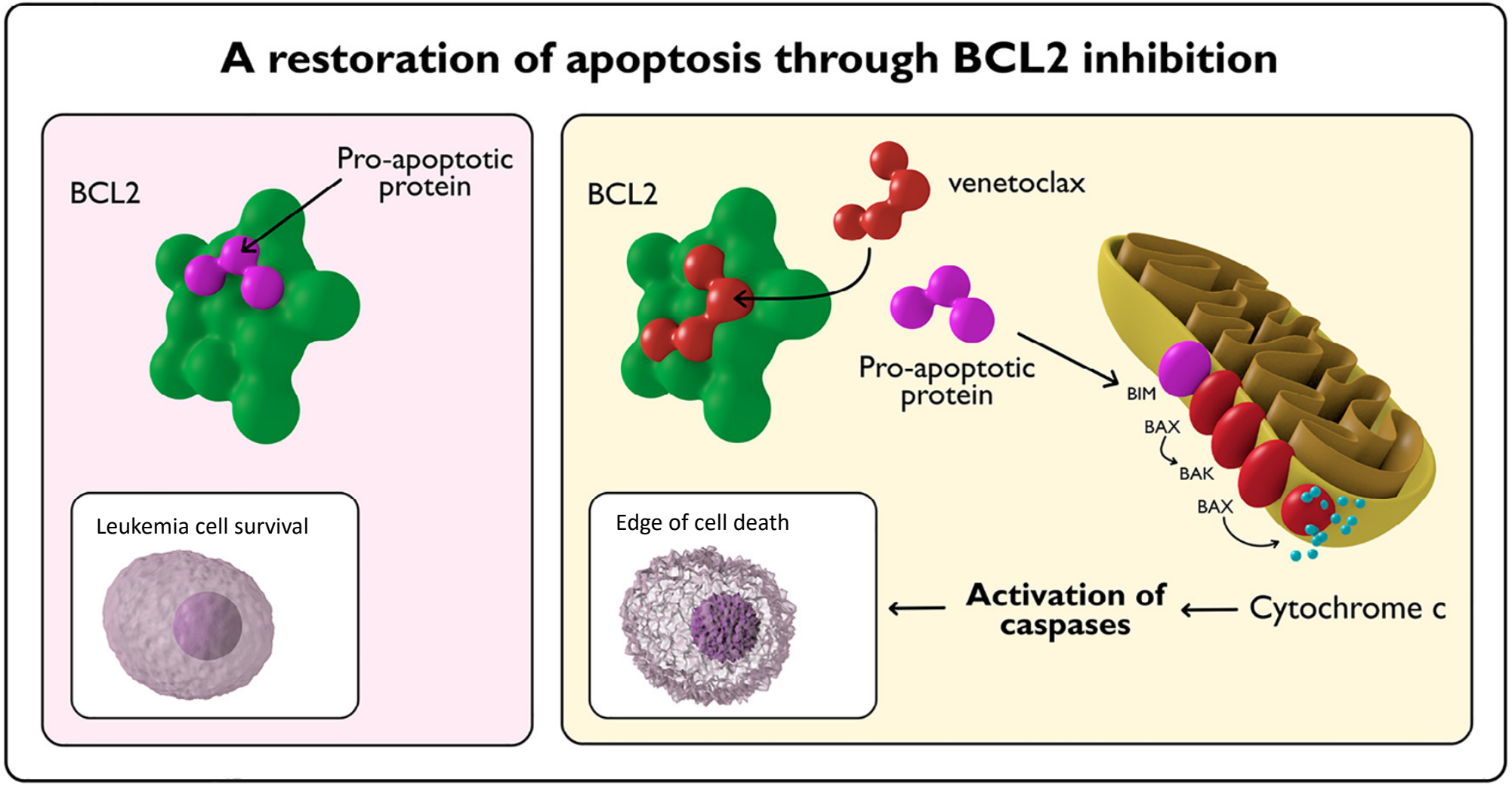
Similar responses found with enasidenib + aza

- Few different studies
- Combination has improved response
- Different approaches to combination

Venetoclax

- Sensitize leukemia cells to other drugs

Venetoclax – makes AML cells more prone to die



Mihalyova et al. Exp Hem 2018

AML cells have increased BCL2

Inhibiting BCL2 primes leukemia cells to die

VIALE-A trial – landmark trial in AML treatment

The NEW ENGLAND JOURNAL of MEDICINE

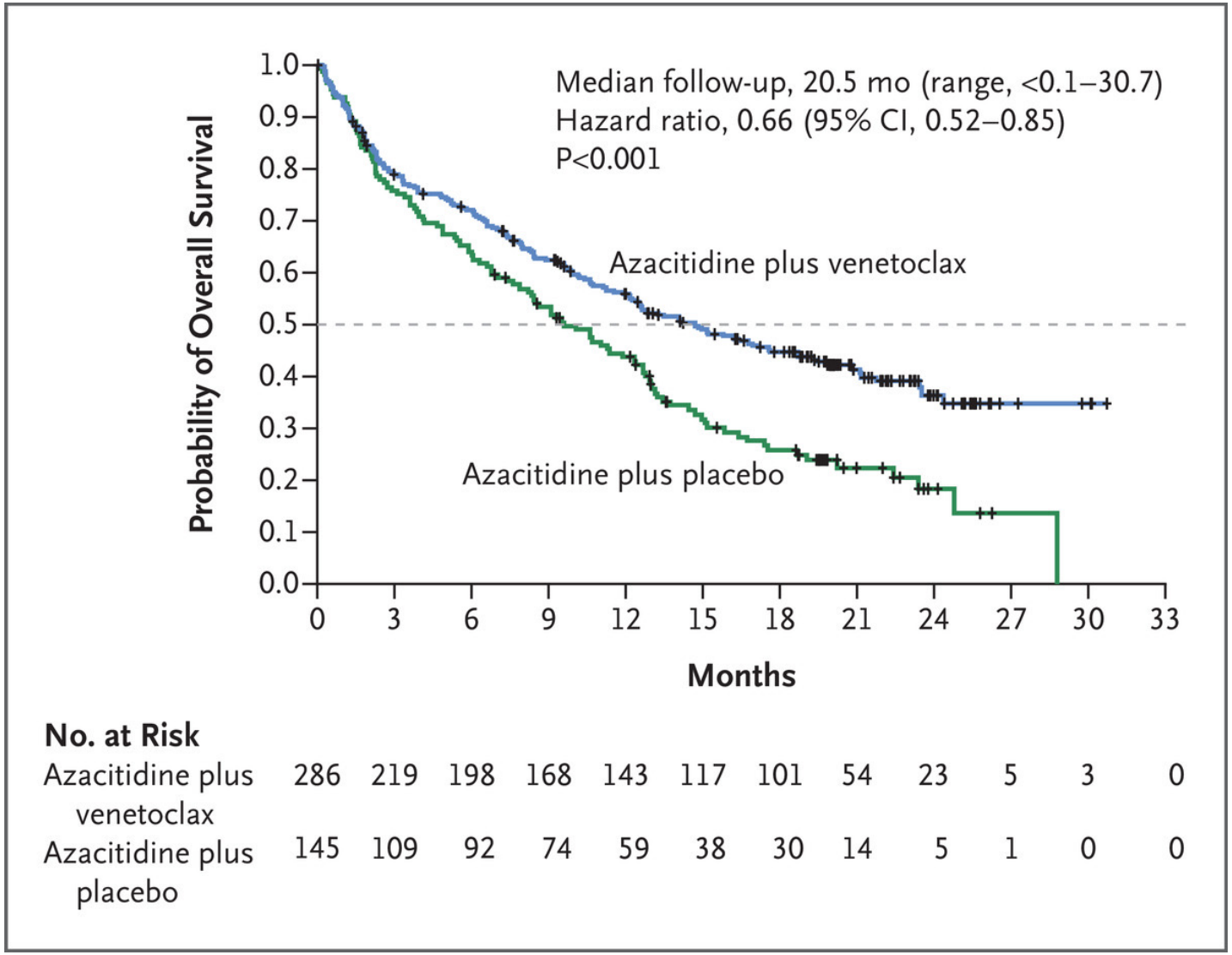
ESTABLISHED IN 1812 AUGUST 13, 2020 VOL. 383 NO. 7

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

VIALE-A trial results

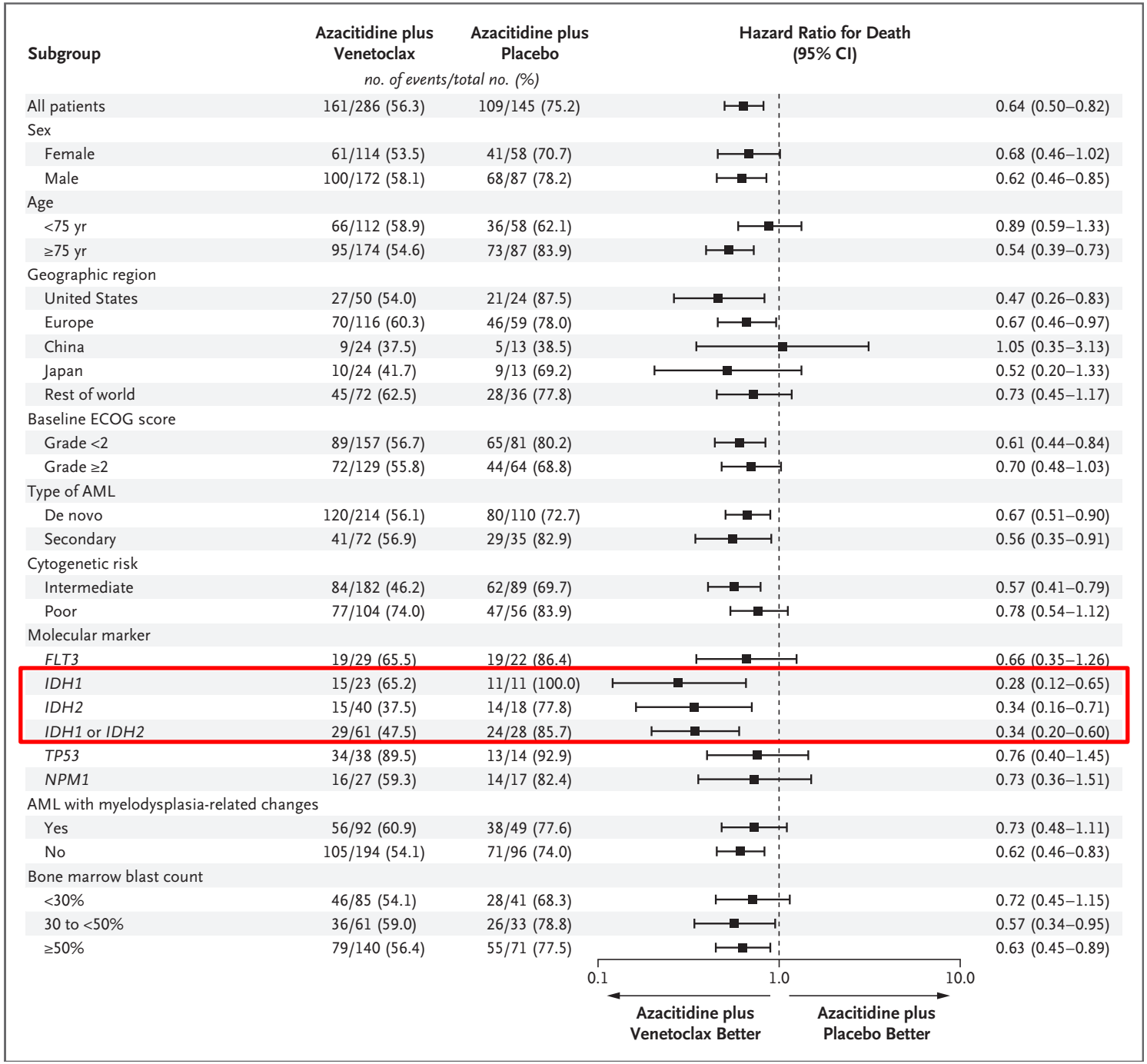
- High response rates
- Works for multiple types of AML
- Side effects of cytopenias (low blood counts)



CD DiNardo et al. N Engl J Med 2020;383:617-629.

All genetic subtypes benefit

- But some more than others…
- IDH1/2 mutations have higher response rates and longer duration of remission
- TP53 has good response rate but response doesn't last very long
- FLT3 mutations have shorter duration of response

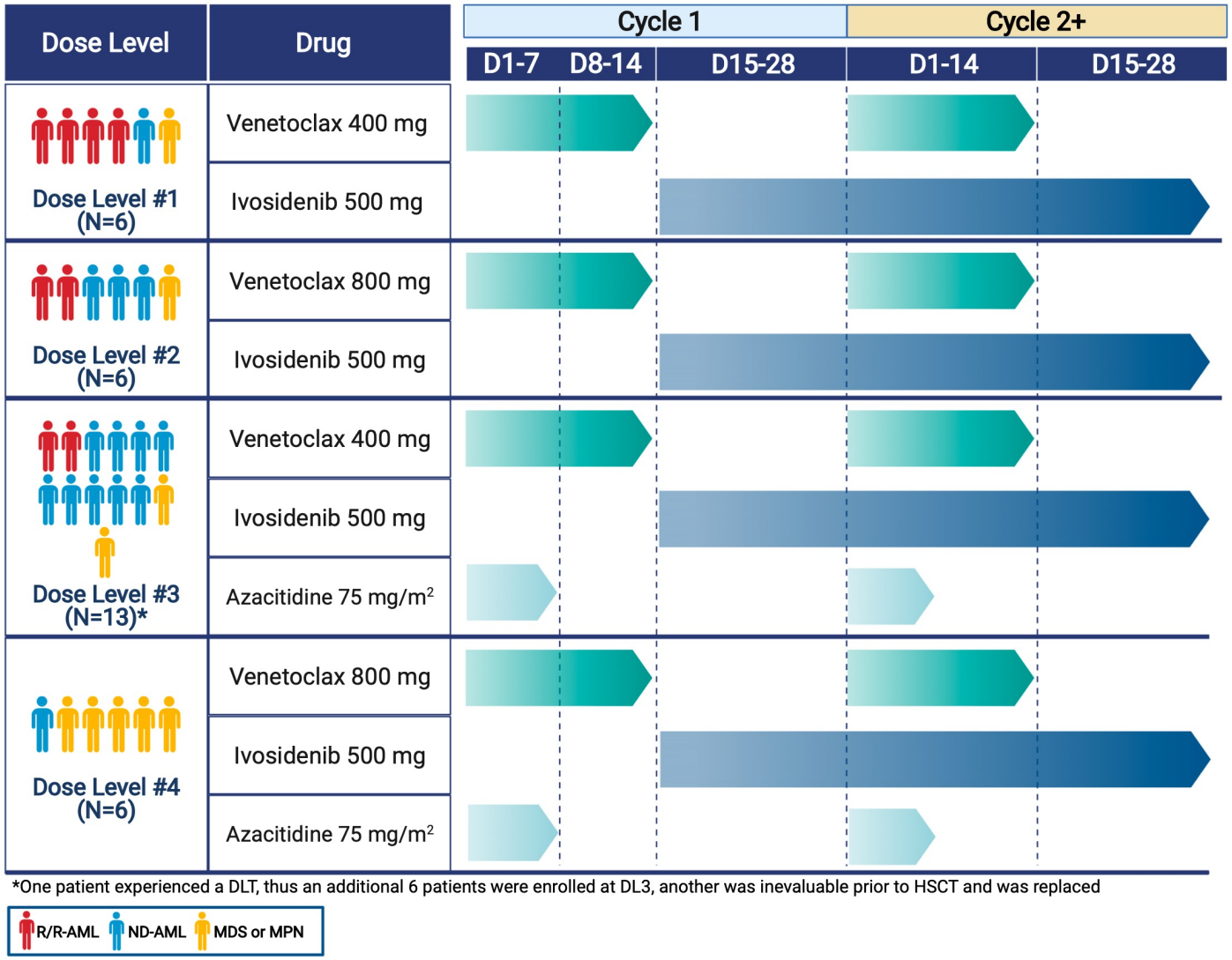


Subgroup	Azacitidine plus Venetoclax	Azacitidine plus Placebo	Hazard Ratio for Death (95% CI)
	no. of events/total no. (%)		
All patients	161/286 (56.3)	109/145 (75.2)	0.64 (0.50–0.82)
Sex			
Female	61/114 (53.5)	41/58 (70.7)	0.68 (0.46–1.02)
Male	100/172 (58.1)	68/87 (78.2)	0.62 (0.46–0.85)
Age			
<75 yr	66/112 (58.9)	36/58 (62.1)	0.89 (0.59–1.33)
≥75 yr	95/174 (54.6)	73/87 (83.9)	0.54 (0.39–0.73)
Geographic region			
United States	27/50 (54.0)	21/24 (87.5)	0.47 (0.26–0.83)
Europe	70/116 (60.3)	46/59 (78.0)	0.67 (0.46–0.97)
China	9/24 (37.5)	5/13 (38.5)	1.05 (0.35–3.13)
Japan	10/24 (41.7)	9/13 (69.2)	0.52 (0.20–1.33)
Rest of world	45/72 (62.5)	28/36 (77.8)	0.73 (0.45–1.17)
Baseline ECOG score			
Grade <2	89/157 (56.7)	65/81 (80.2)	0.61 (0.44–0.84)
Grade ≥2	72/129 (55.8)	44/64 (68.8)	0.70 (0.48–1.03)
Type of AML			
De novo	120/214 (56.1)	80/110 (72.7)	0.67 (0.51–0.90)
Secondary	41/72 (56.9)	29/35 (82.9)	0.56 (0.35–0.91)
Cytogenetic risk			
Intermediate	84/182 (46.2)	62/89 (69.7)	0.57 (0.41–0.79)
Poor	77/104 (74.0)	47/56 (83.9)	0.78 (0.54–1.12)
Molecular marker			
FLT3	19/29 (65.5)	19/22 (86.4)	0.66 (0.35–1.26)
IDH1	15/23 (65.2)	11/11 (100.0)	0.28 (0.12–0.65)
IDH2	15/40 (37.5)	14/18 (77.8)	0.34 (0.16–0.71)
IDH1 or *IDH2*	29/61 (47.5)	24/28 (85.7)	0.34 (0.20–0.60)
TP53	34/38 (89.5)	13/14 (92.9)	0.76 (0.40–1.45)
NPM1	16/27 (59.3)	14/17 (82.4)	0.73 (0.36–1.51)
AML with myelodysplasia-related changes			
Yes	56/92 (60.9)	38/49 (77.6)	0.73 (0.48–1.11)
No	105/194 (54.1)	71/96 (74.0)	0.62 (0.46–0.83)
Bone marrow blast count			
<30%	46/85 (54.1)	28/41 (68.3)	0.72 (0.45–1.15)
30 to <50%	36/61 (59.0)	26/33 (78.8)	0.57 (0.34–0.95)
≥50%	79/140 (56.4)	55/71 (77.5)	0.63 (0.45–0.89)

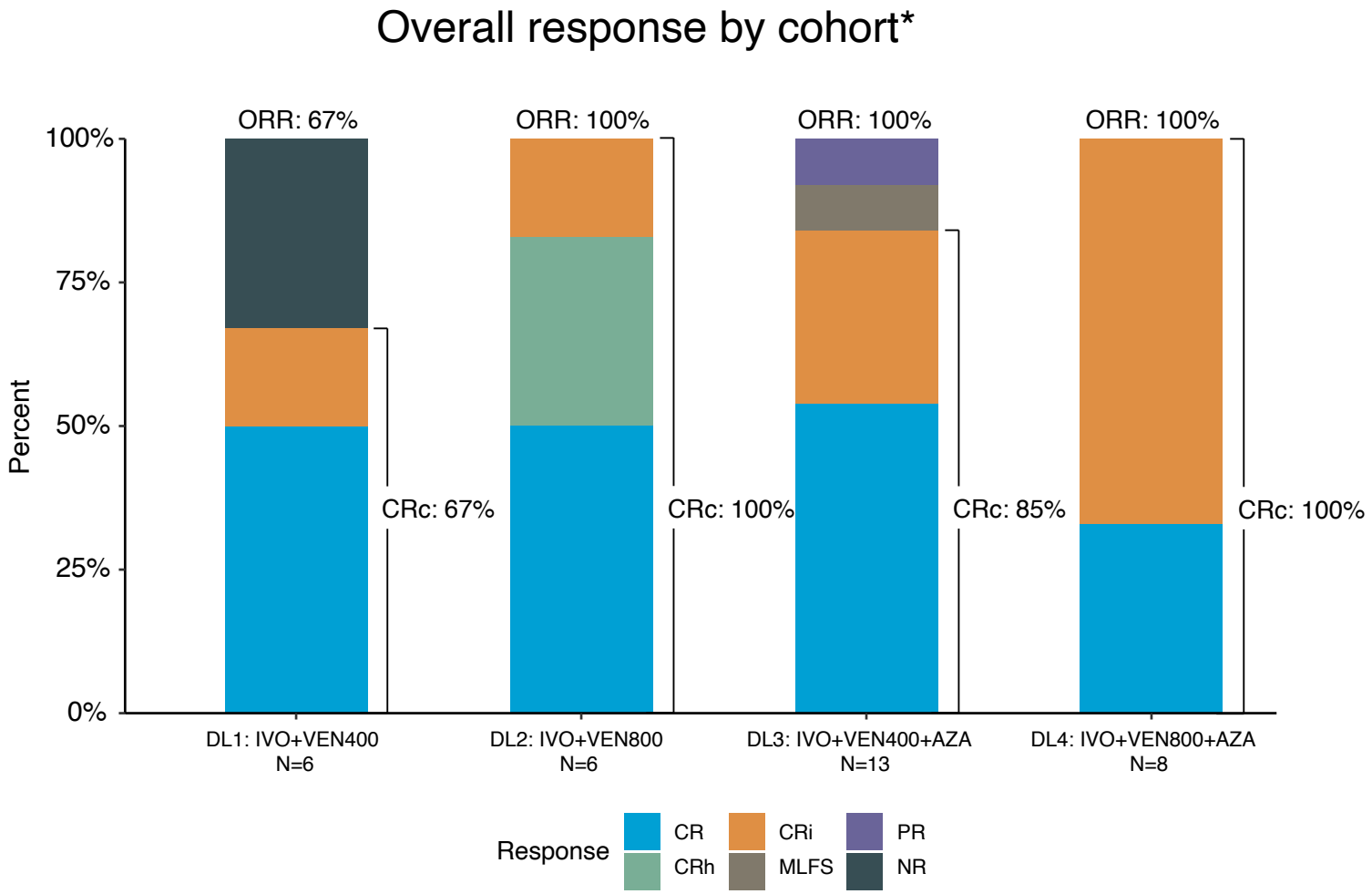
If IDH mutated AML is more sensitive to aza + ven and also responds to IDH inhibitors…

- What if you put them all together…
- Triplets

Azacitidine + Ivosidenib + Venetoclax



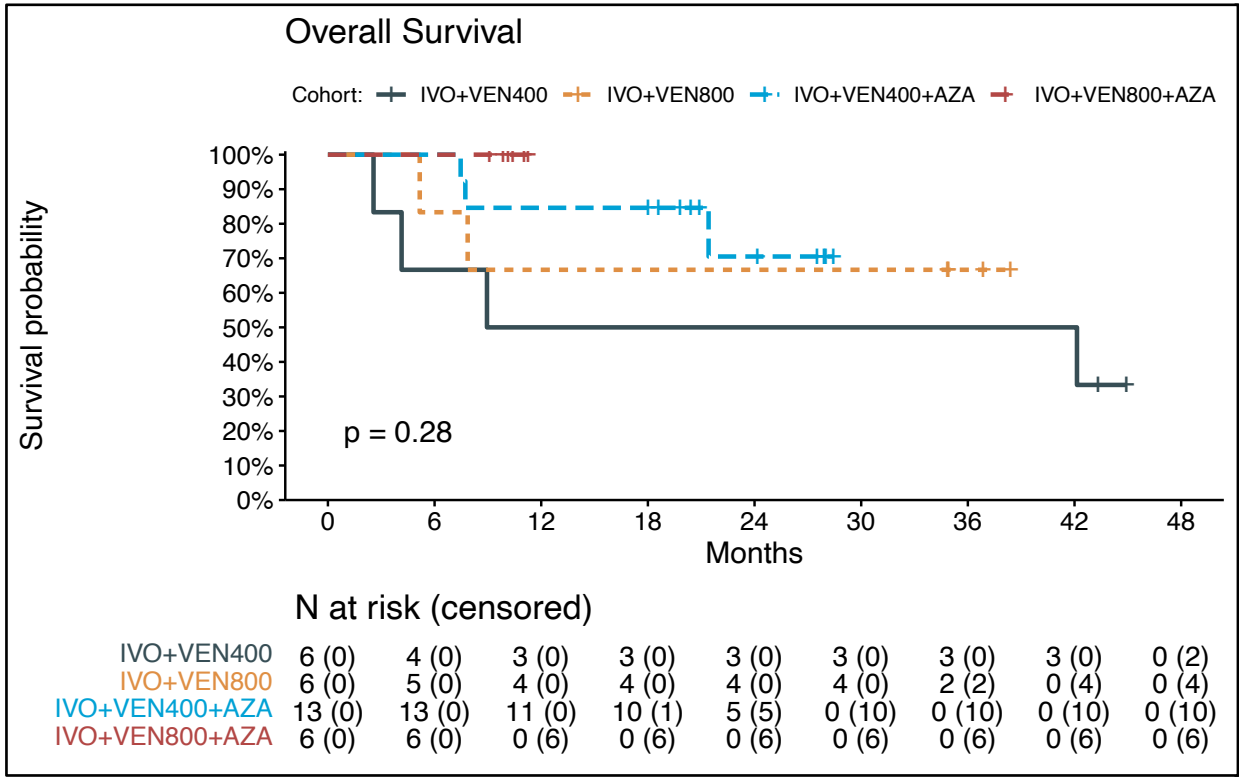
Azacitidine + Ivosidenib + Venetoclax response



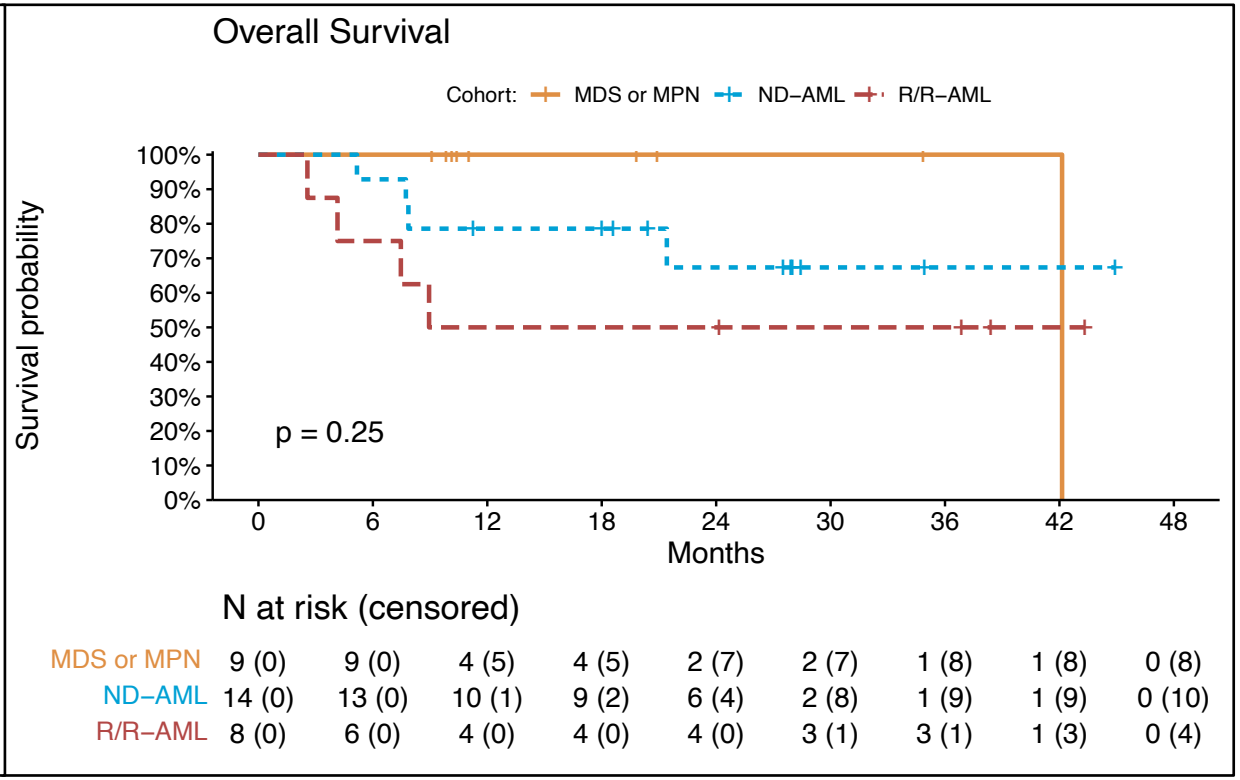
*CRc: CR+CRh+CRi

Azacitidine + Ivosidenib + Venetoclax survival

Overall survival by cohort



Overall survival by disease



Survival by dose level

Survival*	DL#1 (N=6)	DL#2 (N=6)	DL#3 (N=13)	DL#4 (N=6)
Median EFS	7.9 (0-NR)	8.7 (7-NR)	NR (23-NR)	NR (-)
Median OS	26 (3-NR)	NR (5-NR)	NR (21-NR)	NR (-)
12-month EFS	50% (20%)	50% (20%)	77% (12%)	NA
12-month OS	50% (20%)	67% (19%)	85% (10%)	NA

Survival by disease

Survival*	MDS or MPN (N=9)	ND-AML (N=14)	R/R-AML (N=8)
Median EFS	NR (14-NR)	36.4 (23-NR)	6 (2-NR)
Median OS	42.1 (-)	NR (21-NR)	9 (8-NR)
12-month EFS	89% (11%)	71% (12%)	50% (18%)
12-month OS	100% (-)	79% (11%)	50% (18%)

*Outcomes reported as median (95%CI) or % (standard error)

Other triplets

- Early studies with enasidenib + aza + ven (IDH2) are promising

<u>FLT3 inhibitors</u>

- Gilteritinib + azacytidine + venetoclax
  - Initial study at MD Anderson
  - Viceroy study will open soon

- Gilteritinib + decitabine + venetoclax
  - LLS BeatAML Study

Combinations with venetoclax and HMA are showing good response rates but low blood counts are challenging

Need to balance efficacy and toxicity with triplet therapies

Don’t overlook doublets – Gilteritinib + Venetoclax

- Gilteritinib + venetoclax combination
  - Daver et al. ASH Abstract 333 -2020
  - Heavily pre-treated with TKI
  - Very high response rate
  - Low blood counts were common!

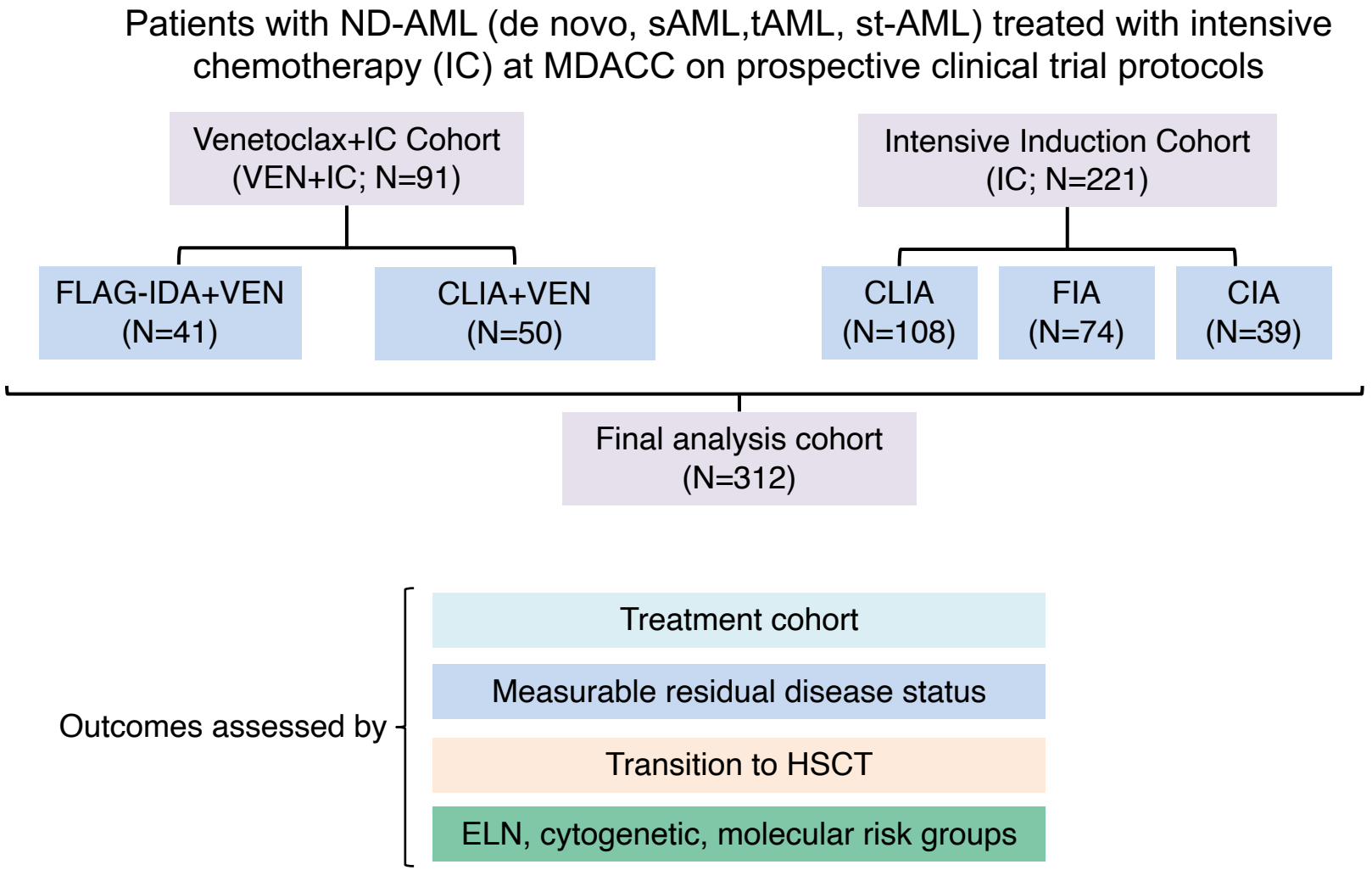
Table. Summary of Best Response to Ven 400 mg Plus Gilteritinib 120 mg in Dose Escalation and Expansion Cohorts

Characteristic	Mutant FLT3 (n=37)[a]
Response, n (%)	
mCRc	31 (83.8)
CR	3 (8.1)
CRi	3 (8.1)
CRp	5 (13.5)
MLFS	20 (54.1)
CR/CRh	7 (18.9)
CRh	4 (10.8)
PR	0
Resistant disease	4 (10.8)
Disease progression	1 (2.7)
Discontinued with no response data	1 (2.7)
Early mortality, n (%)	
≤30 days	0
≤60 days	5 (13.5)

[a]Two on-treatment patients did not have the first disease assessment at the cutoff date and are not included in efficacy analysis

CR, complete remission, CRi, CR with incomplete blood count recovery; CRp, CR with incomplete platelet recovery; *FLT3*, FMS-like tyrosine kinase 3; MLFS, morphologic leukemia-free state; PR, partial remission

Can even use ven with intensive chemotherapy



DiNardo et al. Am J Hematol. 2022

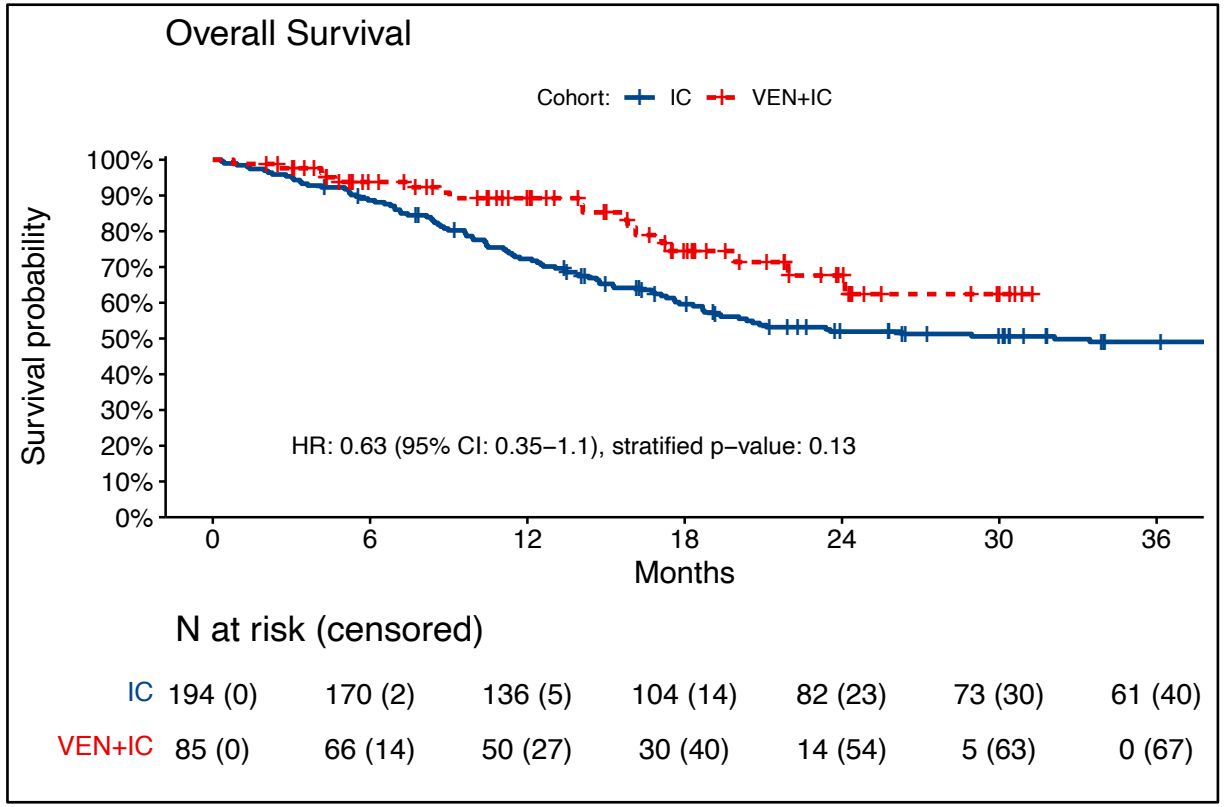
Venetoclax + intensive chemotherapy overall survival

Overall survival	IC N = 194	VEN N = 85	p-value
OS, months	**32**	**NR**	
HR: 0.63 (95% CI: 0.35-1.1)			0.13
2017 ELN Risk			
Favorable	NR	NR	
HR: 1.4 (95% CI: 0.45-4.2)			0.58
Intermediate	NR	NR	
HR: 0.39 (95% CI: 0.04-3.8)			0.42
Adverse	17	NR	
HR: 0.31 (95% CI: 0.10-0.90)			**0.029**

OS favored VEN+IC vs. IC though without a significant benefit in the entire cohort

- ELN adverse-risk patients benefited most from addition of VEN

OS between cohorts



Combinations galore with venetoclax

- Improving responses to targeted drugs and chemotherapy
- Being tested with Vyxeos, etc.
- But, toxicity is an issue
- Makes normal blood stem cells more sensitive as well

Maintenance chemotherapy

- Suppression of leukemia cells after treatment

Maintenance therapy in AML

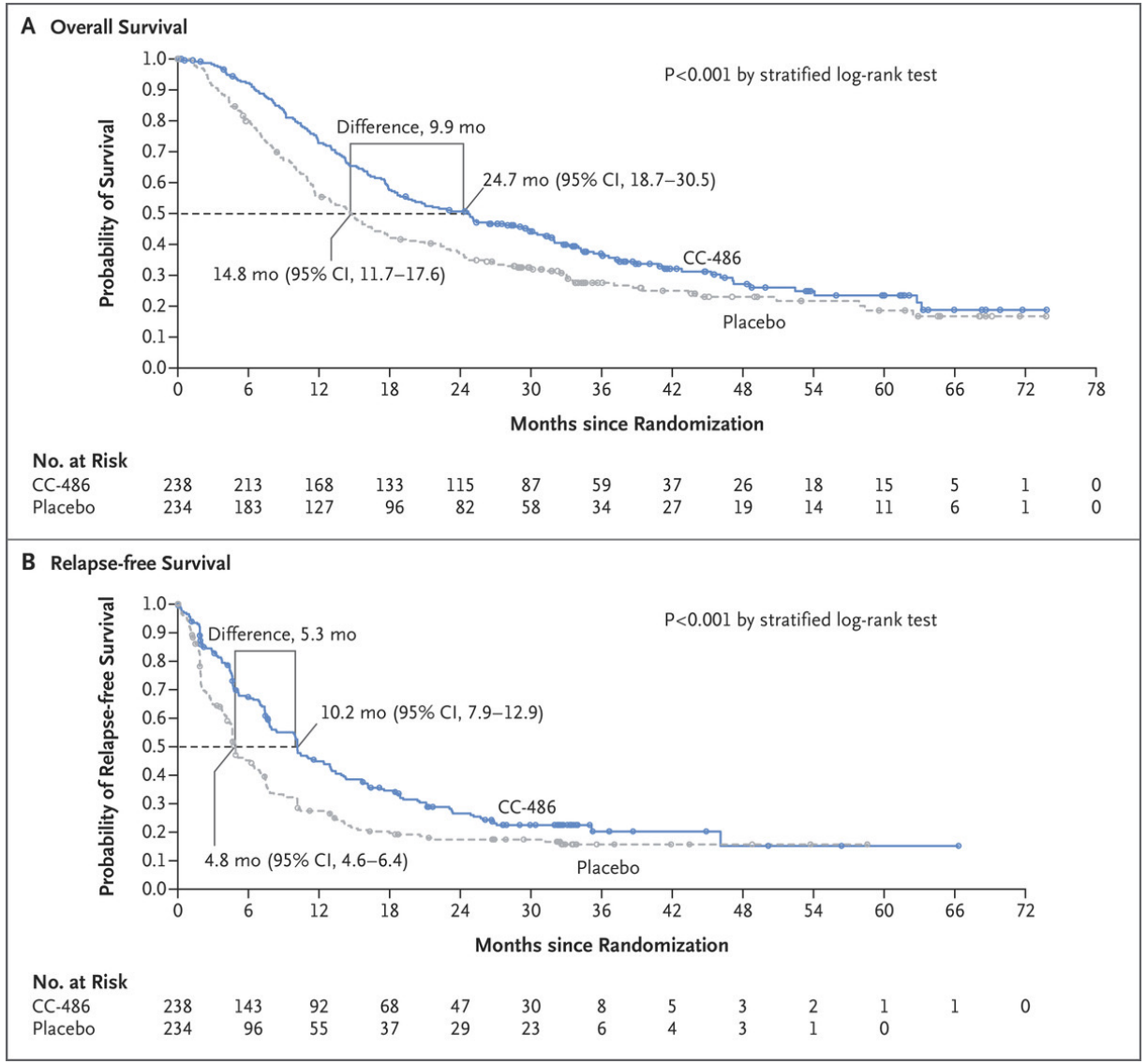
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission

A.H. Wei, H. Döhner, C. Pocock, P. Montesinos, B. Afanasyev,* H. Dombret, F. Ravandi, H. Sayar, J.-H. Jang, K. Porkka, D. Selleslag, I. Sandhu, M. Turgut, V. Giai, Y. Ofran, M. Kizil Çakar, A. Botelho de Sousa, J. Rybka, C. Frairia, L. Borin, G. Beltrami, J. Čermák, G.J. Ossenkoppele, I. La Torre, B. Skikne, K. Kumar, Q. Dong, C.L. Beach, and G.J. Roboz, for the QUAZAR AML-001 Trial Investigators†

Onureg maintenance therapy



AH Wei et al. N Engl J Med 2020;383:2526-2537.

Univariate analysis

Subgroup	No. of Patients		2-Yr Survival		2-Yr Survival Difference (95% CI)
	CC-486	Placebo	CC-486	Placebo	
			%		*percentage points*
Overall	238	234	50.6	37.1	13.5 (4.5 to 22.5)
Age					
≥55 to <65 yr	66	68	61.3	45.1	16.2 (−0.9 to 33.4)
≥65 yr	172	166	46.7	33.9	12.8 (2.3 to 23.3)
≥75 yr	28	24	51.9	24.8	27.1 (0.7 to 53.4)
Sex					
Male	118	127	47.8	39.0	8.8 (−3.7 to 21.4)
Female	120	107	53.4	34.8	18.6 (5.7 to 31.5)
WHO AML classification					
AML with recurrent genetic abnormalities	39	46	50.0	47.0	3.0 (−18.6 to 24.5)
AML with myelodysplasia-related changes	49	42	43.5	29.8	13.8 (−6.3 to 33.8)
AML not otherwise specified	148	145	53.8	35.6	18.1 (6.8 to 29.5)
ECOG performance-status score					
0 or 1	217	217	50.9	38.0	13.0 (3.5 to 22.4)
2 or 3	21	17	47.6	25.5	22.1 (−8.2 to 52.4)
History of MDS or CMML					
Yes	22	17	66.7	31.4	35.3 (4.9 to 65.7)
No	216	217	49.0	37.5	11.5 (2.1 to 20.9)
Cytogenetic risk at induction					
Intermediate	203	203	54.1	40.4	13.6 (3.9 to 23.4)
Poor	35	31	30.3	15.5	14.8 (−5.6 to 35.2)
Consolidation after induction					
Yes	186	192	50.8	39.2	11.6 (1.4 to 21.7)
No	52	42	50.0	27.4	22.6 (3.2 to 42.0)
Consolidation cycles					
1 or 2	180	179	50.8	37.6	13.3 (2.9 to 23.7)
3	6	13	50.0	61.5	−11.5 (−59.5 to 36.4)
Response at randomization					
Complete remission	183	177	49.7	36.7	13.0 (2.7 to 23.3)
Complete remission with incomplete blood count recovery	50	44	55.1	38.6	16.5 (−3.8 to 36.8)
MRD status at randomization					
Positive	103	116	39.5	22.0	17.5 (5.3 to 29.8)
Negative	133	111	58.6	51.7	6.9 (−5.8 to 19.5)

AH Wei et al. N Engl J Med 2020;383:2526-2537.

More thoughts on maintenance

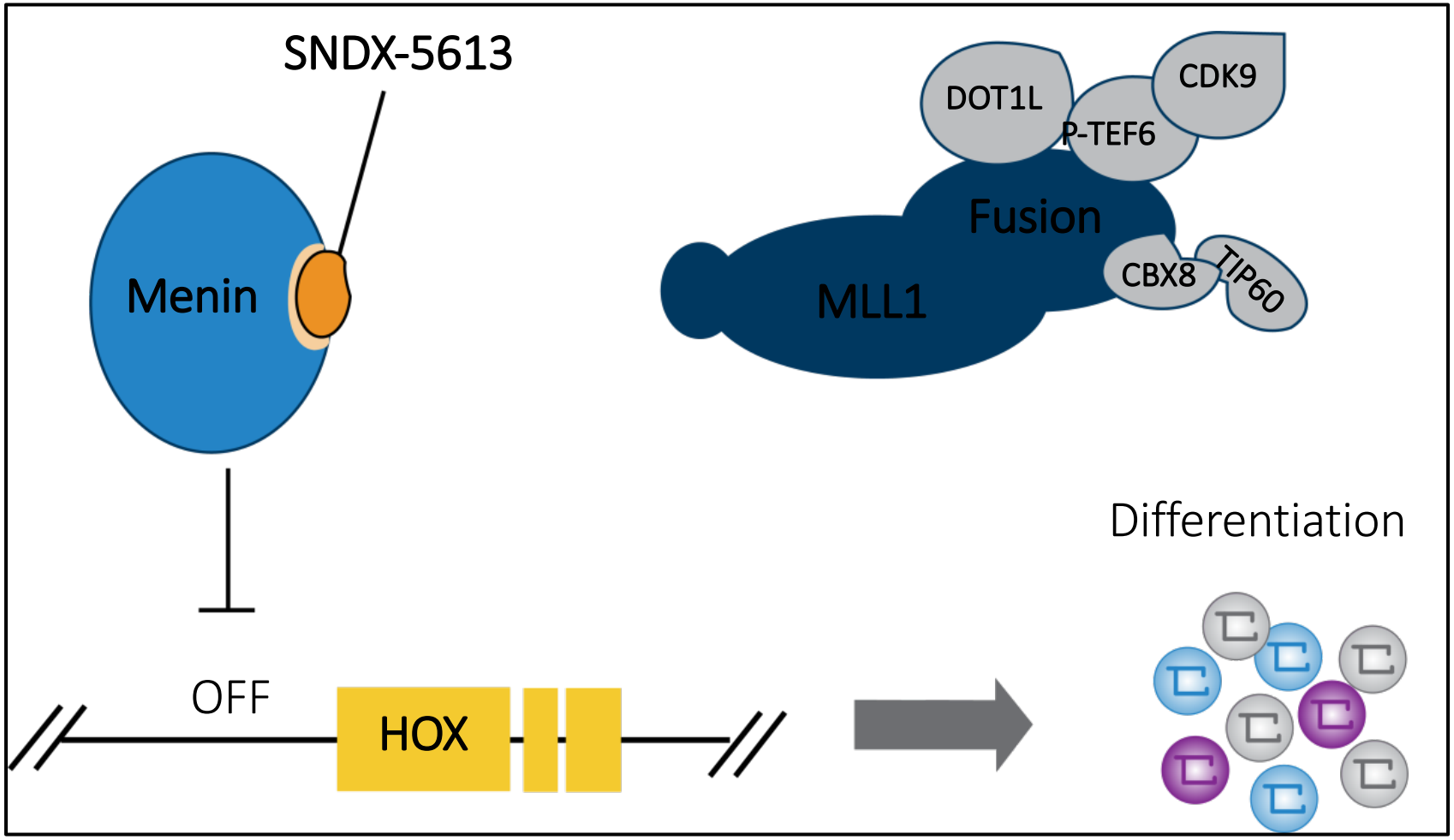
- Idea of maintenance is gaining traction again
- Onureg approved but side effects
- Gilteritinib and other FLT3 inhibitors being used as maintenance after allo SCT, low toxicity
- IDH inhibitors have very few side effects and ideal for maintenance
- Maintenance is making a comeback

New drugs of interest

- SNDX-5613
  - Menin inhibitor
  - Drives maturation in MLL rearranged and NPM1 AML
  - Early studies encouraging

- Magrolimab
  - Antibody therapy -> binds to CD47
  - Causes macrophages to eat leukemia cells
  - Has shown some promise against TP53 mutated AML

SNDX-5613 in MLL rearranged or NPM1-mutated AML

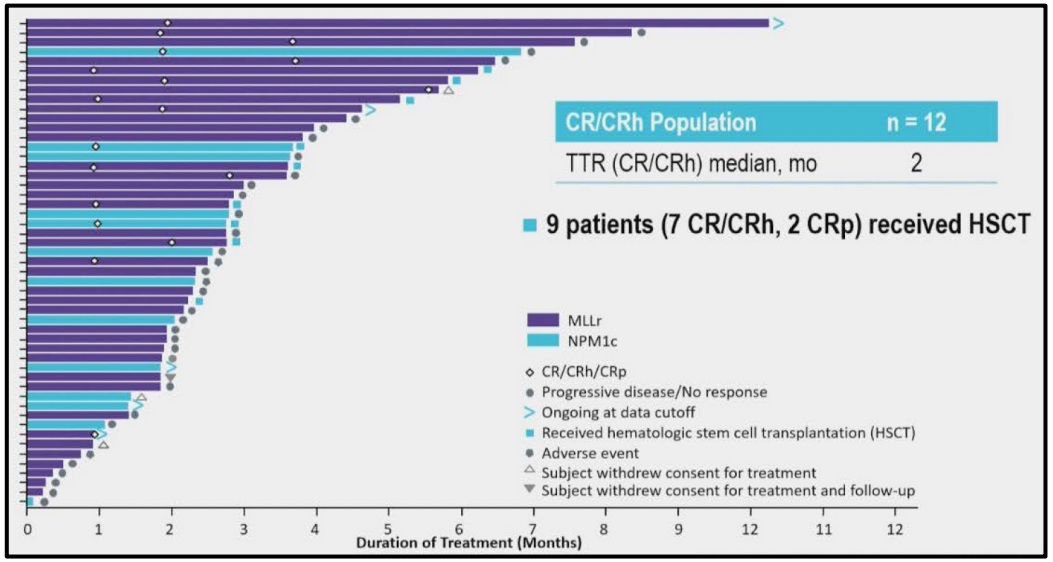


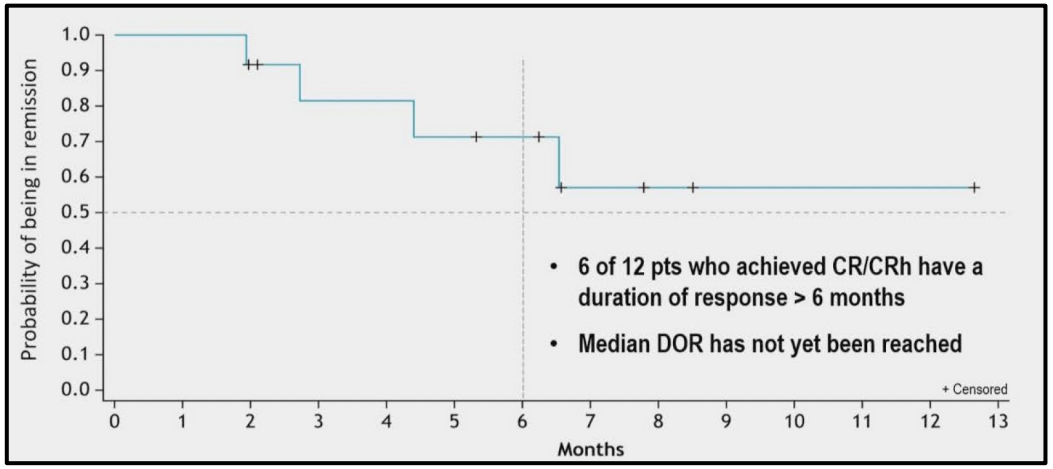
MLLr, mixed lineage leukemia-rearranged.

a. Uckelmann HJ, et al. Blood. 2018;132:546; b. Kuhl MW, Armstrong SA. Cancer Cell. 2015;27:431-433.

SNDX-5613 in MLLr or NPM1-mutated AML: Response and survival

Best Response, n (%)		Efficacy Population (n=51)
Response	Overall response rate	28 (55)
	CR	8 (16)
	CRh	4 (8)
	CRp	7 (14)
	MLFS	9 (18)
MRD neg	CRc MRD neg rate	16/51 (31)
	within CR/CRh MRD neg	11/12 (92)
	within CR/CRh/CRp MRD neg	16/19 (84)
MLLr	Overall response rate	23/38 (61)
	CR/CRh	9/38 (24)
NPM1 mut	Overall response rate	5/13 (38)
	CR/CRh	3/13 (23)

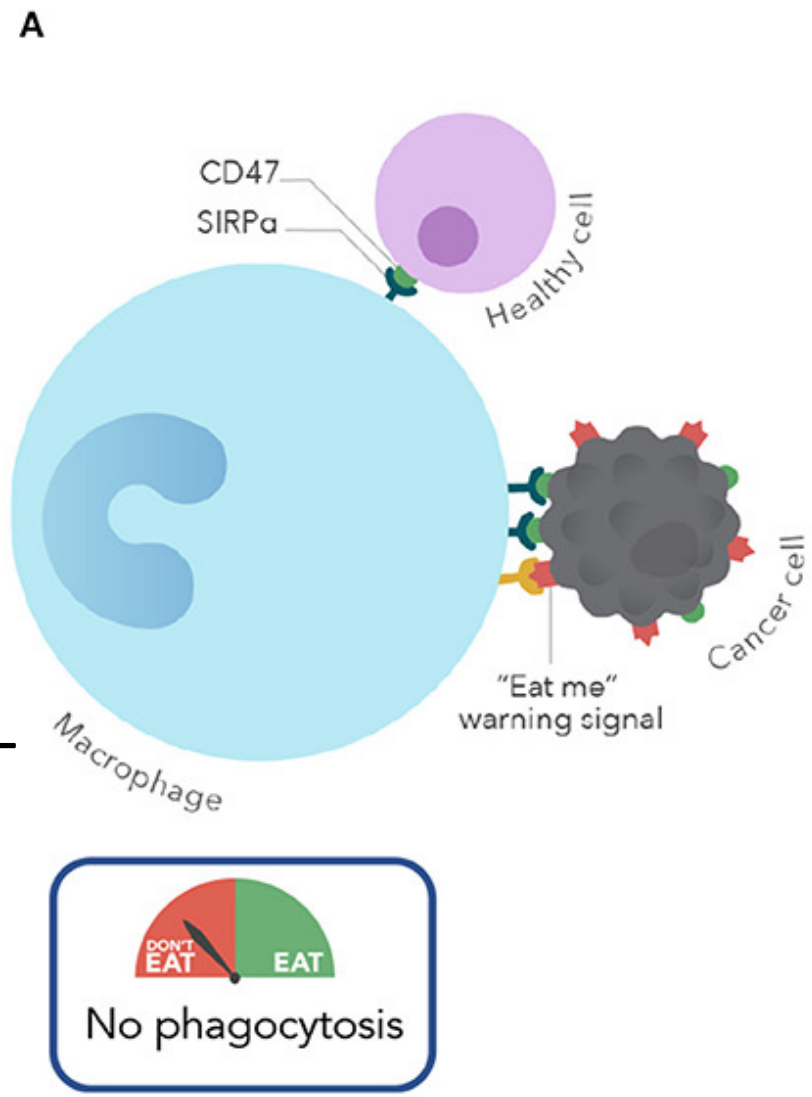


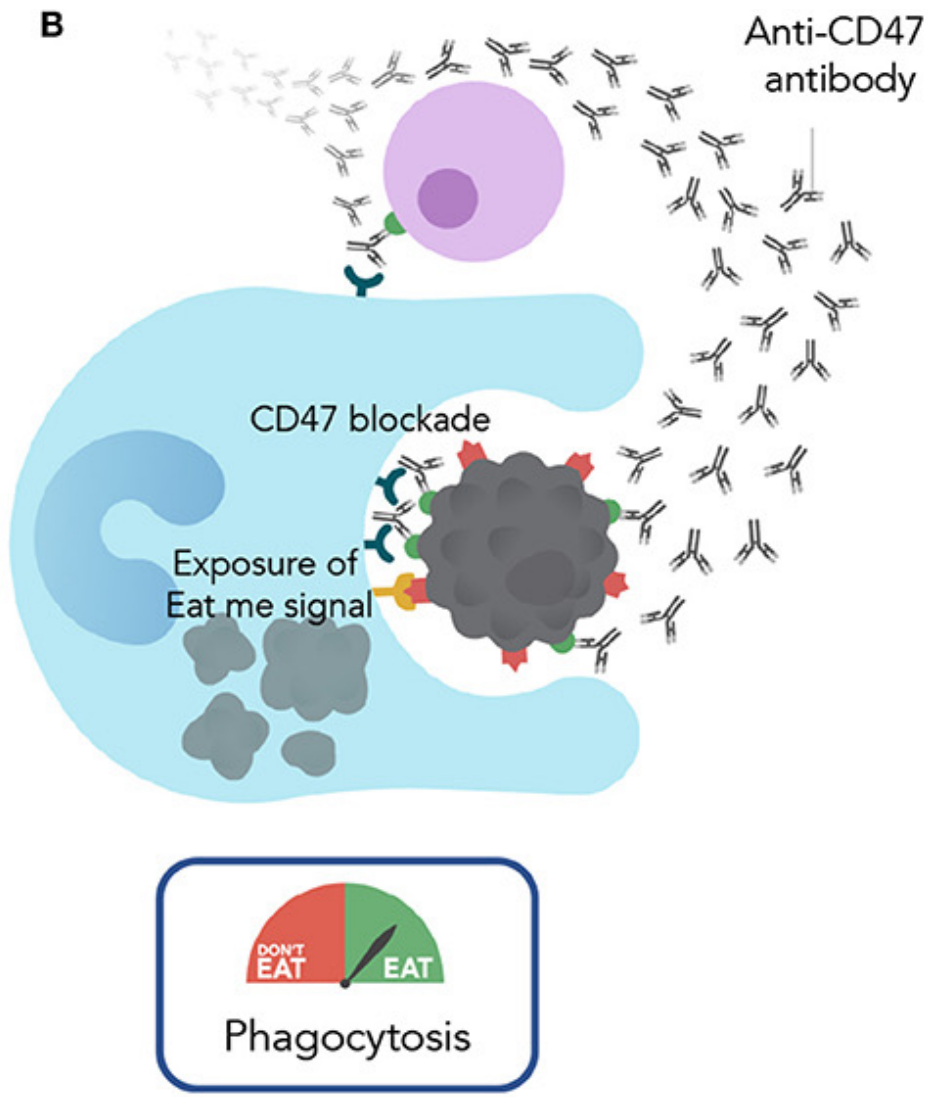


Stein E, et al. ASH 2021 Abstract 699

Magrolimab

- Antibody therapy
- Aza + magrolimab with good activity in AML
- Being tested in AML and MDS
- Combine with ven?



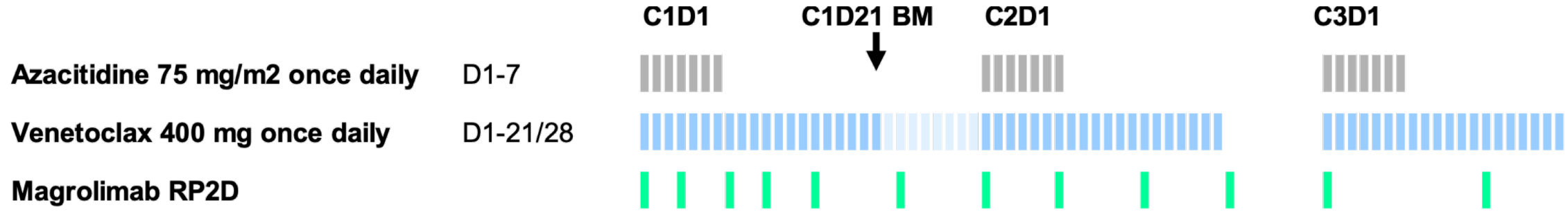


Chao et al. Front. Oncol. 2020

Azacitidine + Venetoclax + Magrolimab

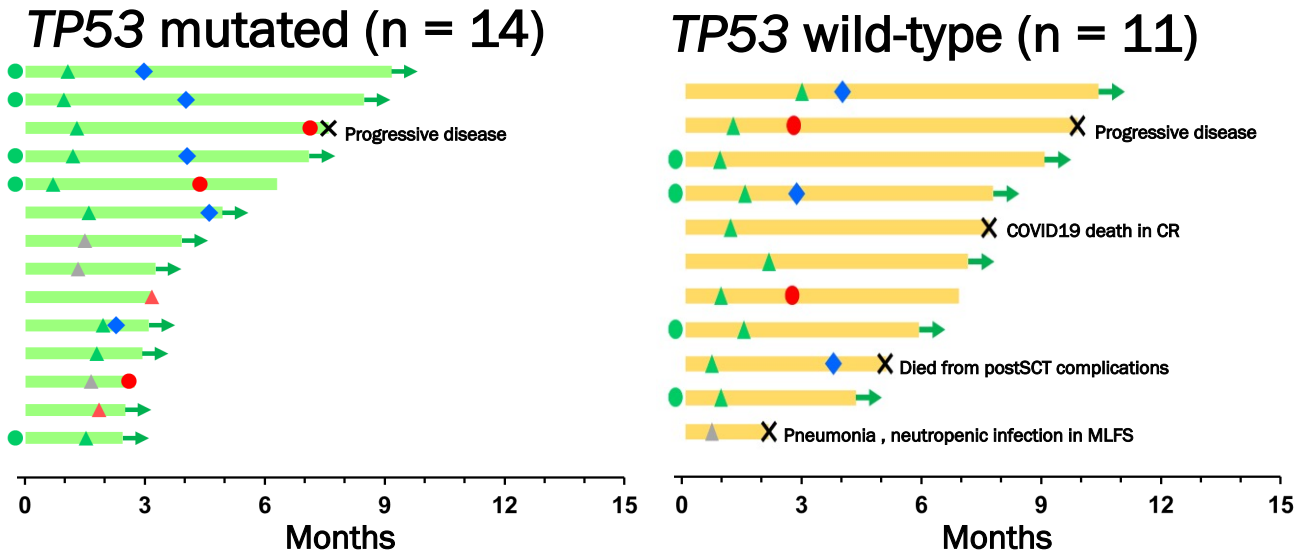
Characteristics	Frontline Cohort (n=25)		R/R Cohort (n=23)	
	TP53 mutated (n=14)	TP53 wild type (n=11)	VEN-naïve (n=8)	Prior VEN (n=15)
Age, yrs	67 [46 to 77]	71 [32 to 82]	51 [28 to 74]	70 [35 to 79]
BM blasts, %	37 (9 to 96)	33 (16 to 92)	29 (11 to 87)	57 (6 to 85)
Diagnosis				
De novo AML	4 (29)	6 (55)	4 (50)	5 (33)
Secondary AML	10 (71)	5 (45)	4 (50)	10 (67)
ELN 2017 CG				
Intermediate	2 (14)	6 (55)	2 (25)	4 (27)
Adverse	11 (86)	5 (45)	6 (75)	11 (73)
Prior therapies	0	0	2 (1 to 3)	2 (1 to 5)

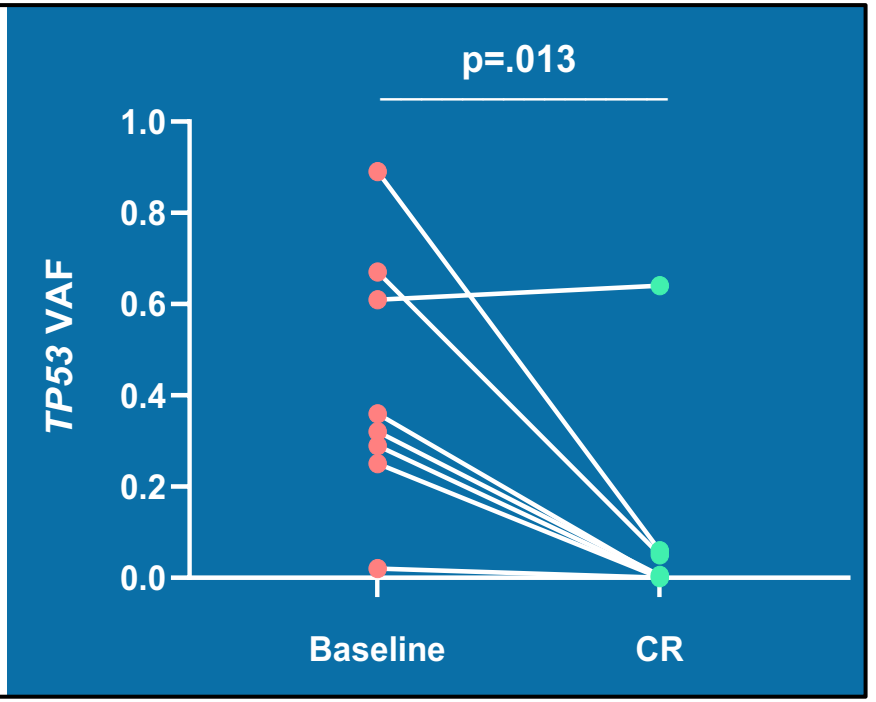
Results expressed as no. (%) or median [range], unless specified.



Daver N, et al. ASH 2021 Abstract 371.

Azacitidine + Venetoclax + Magrolimab survival





OS by Treatment	*TP53* Mutated (N=14)	*TP53* wild-type (N=11)
Median follow-up	3.9 (range: 2.4-9.2)	7.0 (range: 2.1-10.3)
6-month DOR	83%	80%
6-month OS	100%	81%

Magrolimab appears active in *TP53* AML. Longer follow-up needed to confirm early efficacy signal

Daver N, et al. ASH 2021 Abstract 371.

Thank you!!

- To all the patients, families, caregivers and support groups
- Leukemia & Lymphoma Society