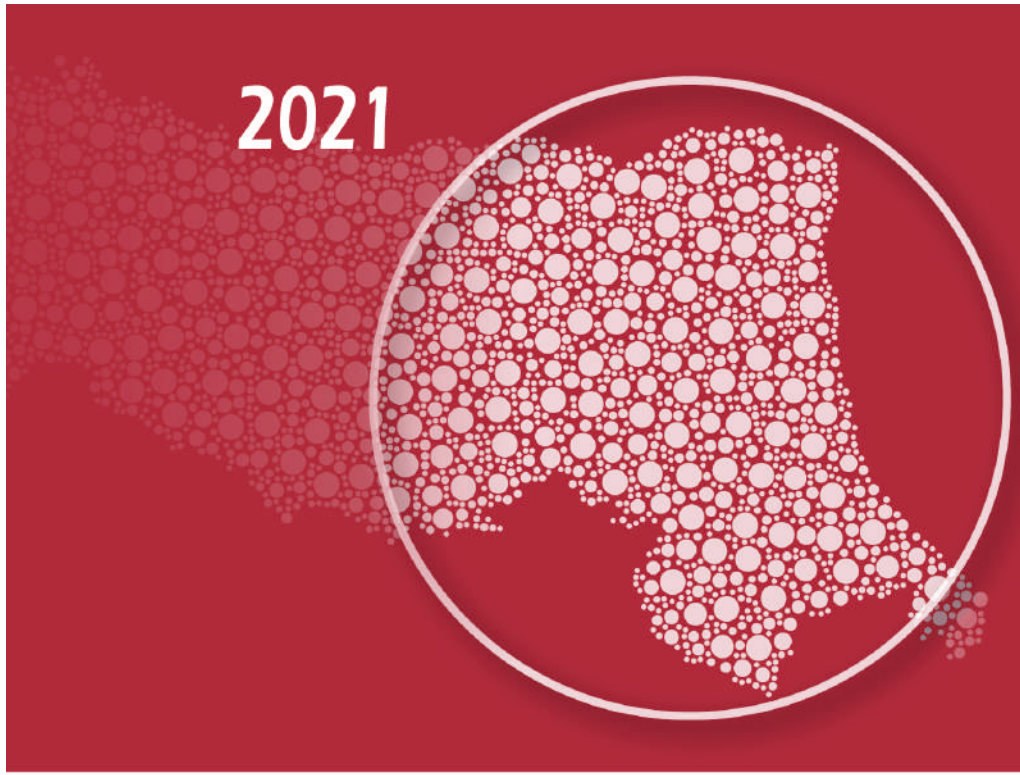


Progetto Ematologia Romagna

DALLO STUDIO DEL GENOMA UNA TERAPIA SENZA CITOTOSSICI IN ONCOEMATOLOGIA: PROMESSA O REALTÀ?

LEUCEMIA ACUTA MIELOIDE

Cristina Papayannidis, MD, PhD

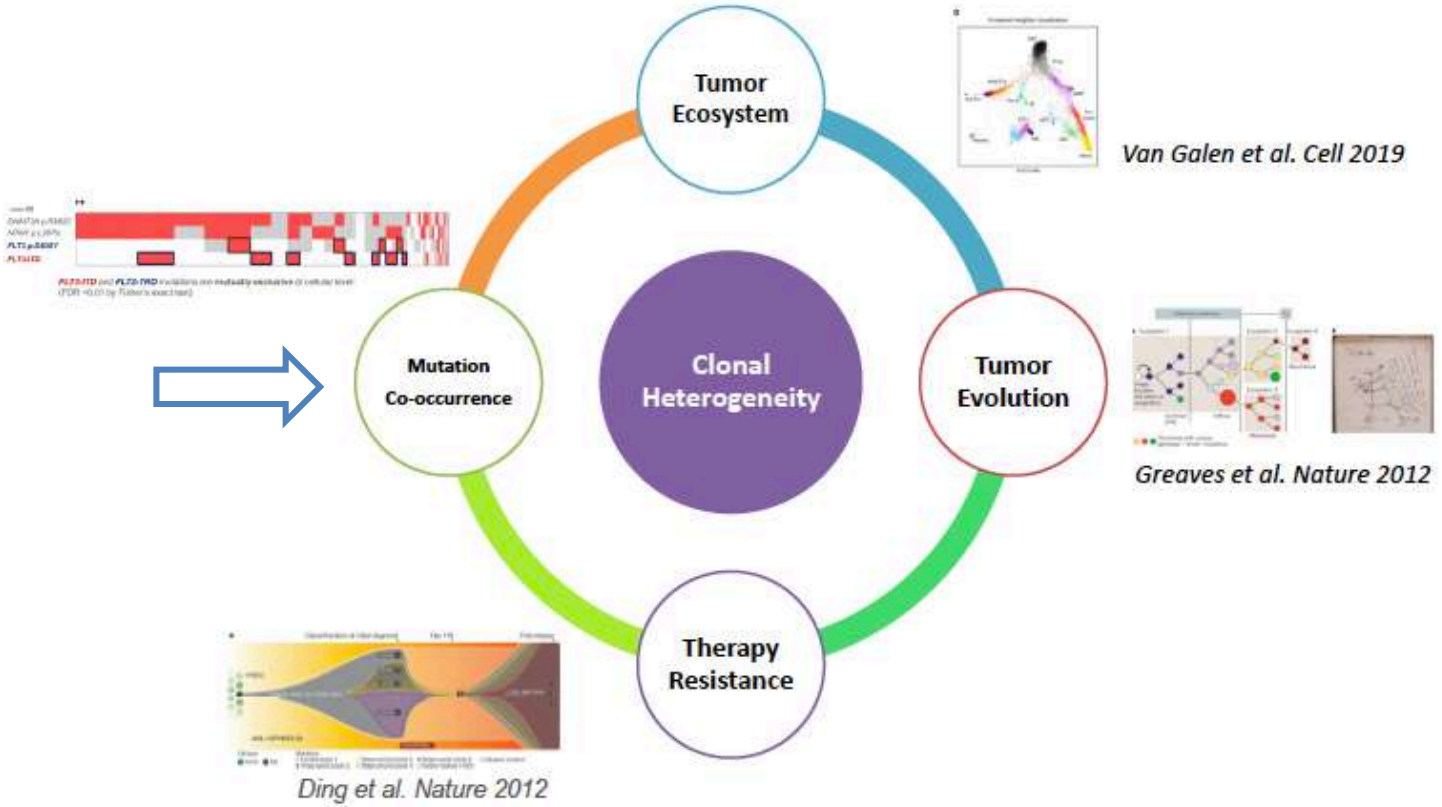
Disclosures

Honoraria: Novartis, Amgen, Pfizer, Astellas, Abbvie

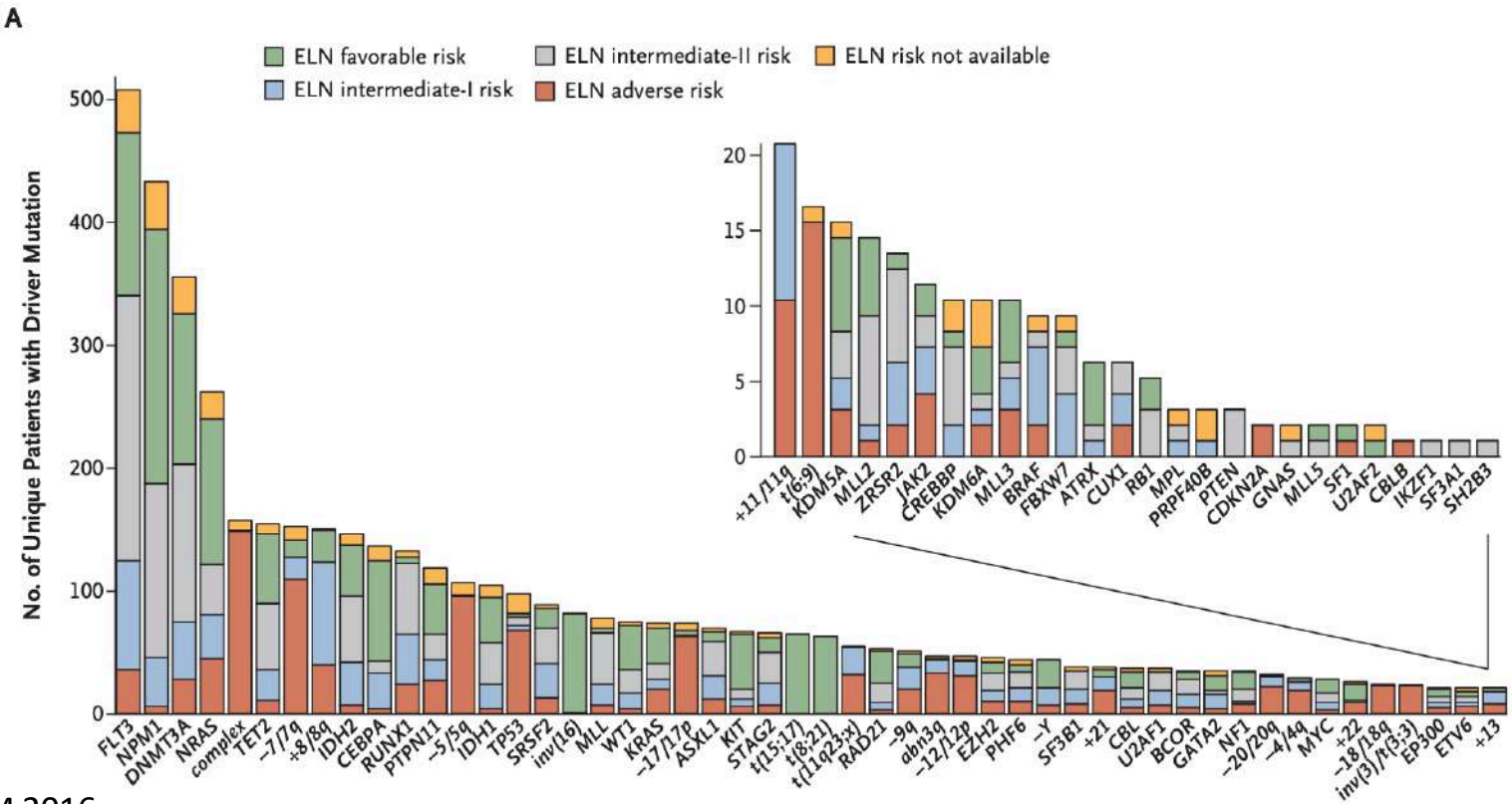
Advisory Board: Novartis, Janssen, Amgen, Pfizer, Abbvie

…Promessa **e** realta’

Clonal heterogeneity in AML



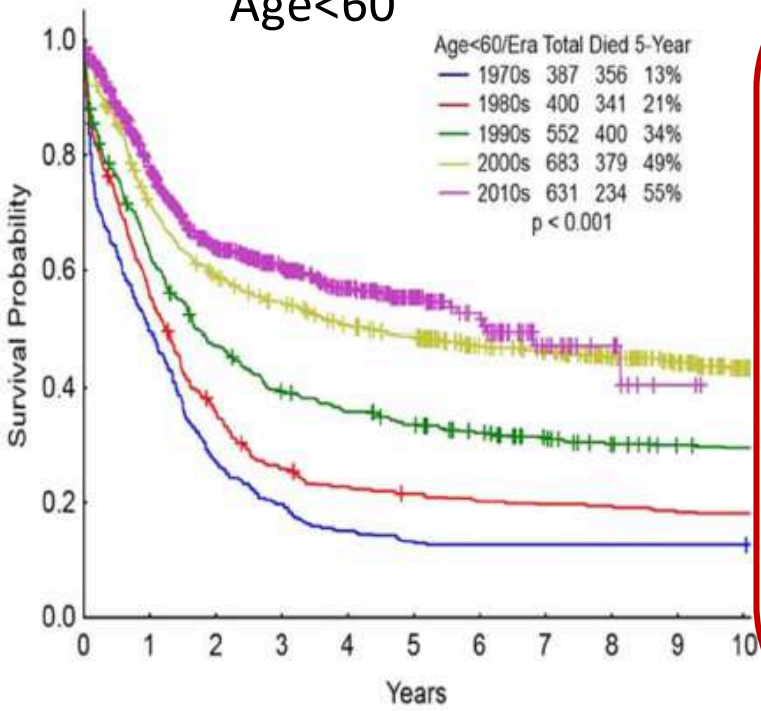
Landscape of driver mutations in AML



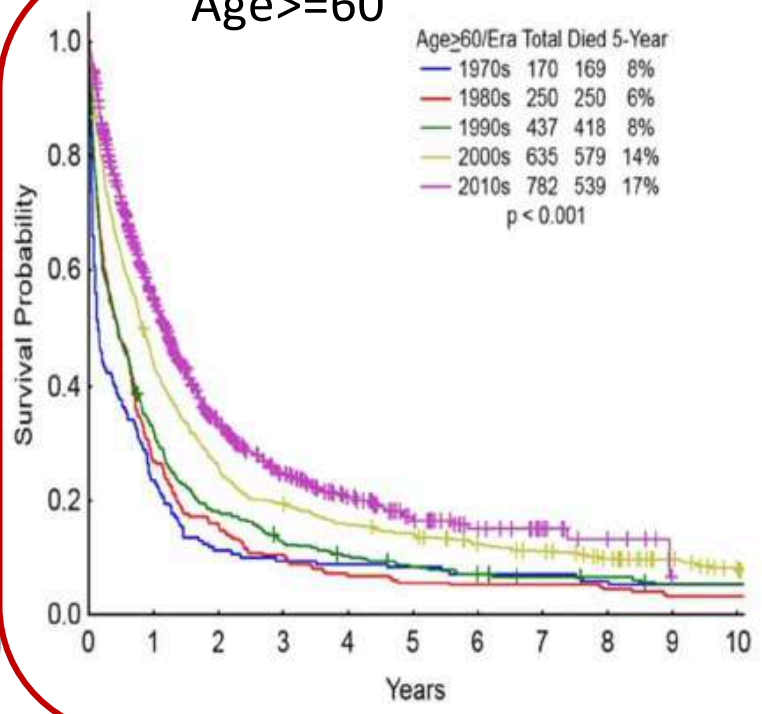
Papaemmanuil E, NEJM 2016

Can we improve AML survival with a targeted approach?

Age<60



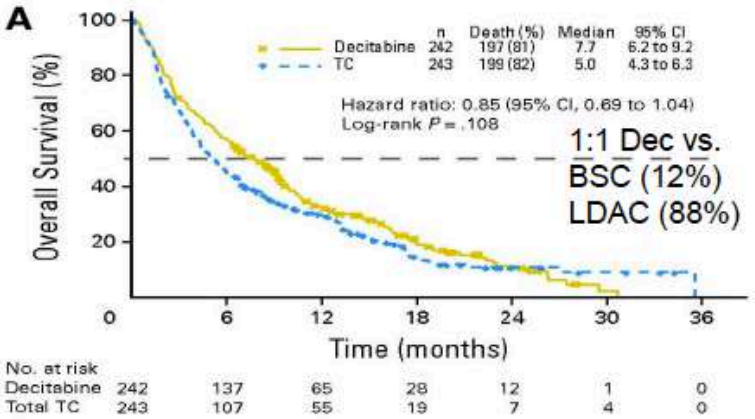
Age>=60



Kantarjian H et al, Blood Cancer Journal 2021

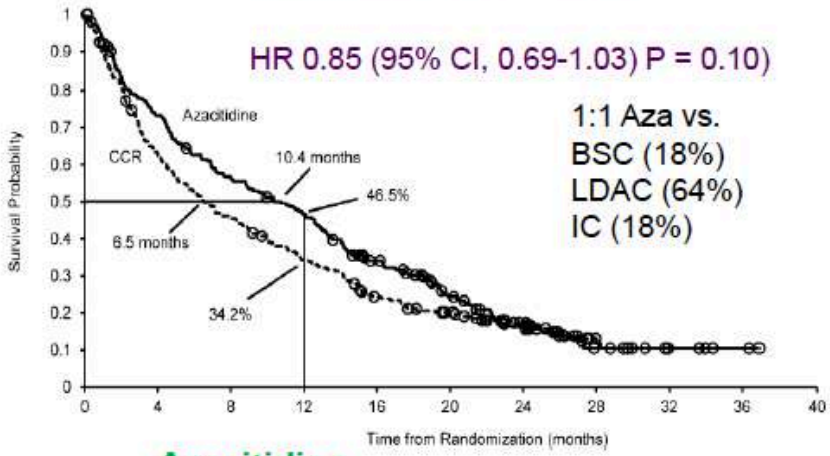
HMAs for Older Unfit AML Patients: Active but suboptimal

DACO-016 (N=485)



Decitabine
CR+CRi, 28%
CR, 16%
Median OS 7.7 months
Median time to best response 4.3 months

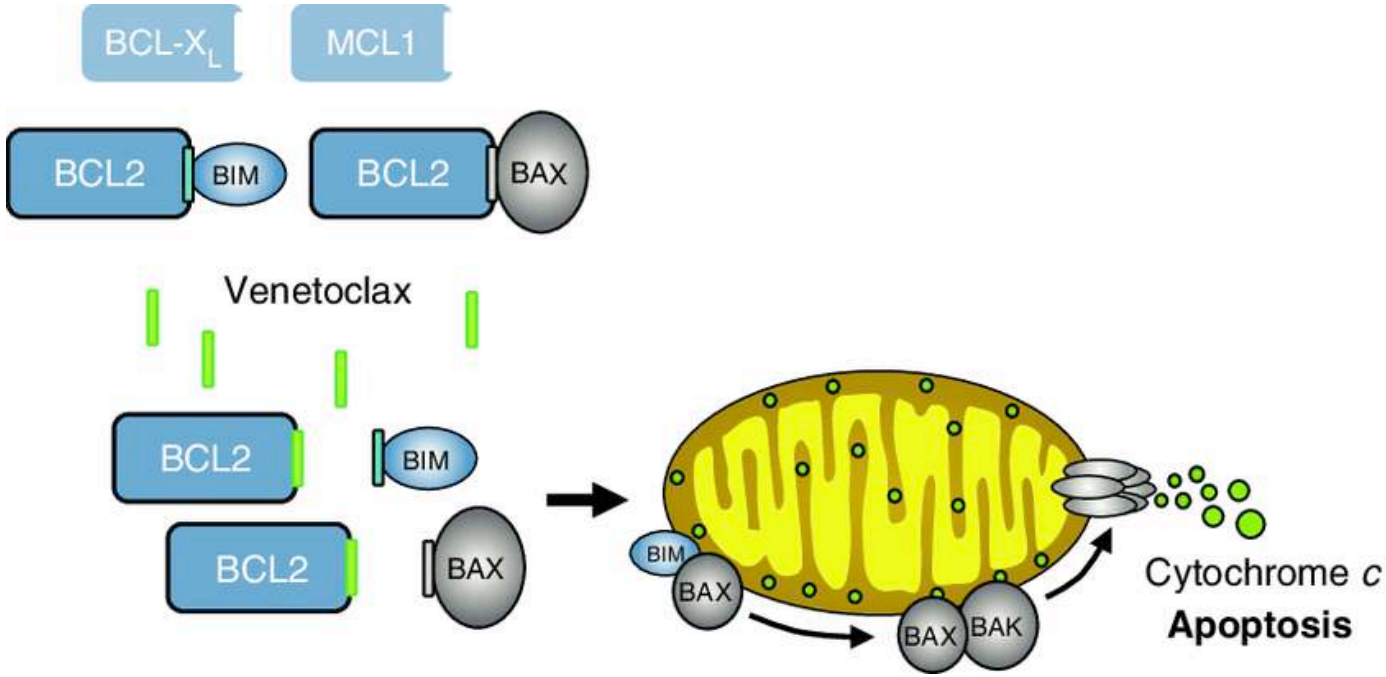
AZA-AML-001 (N=488)



Azacitidine
CR+CRi, 28%
CR, 20%
RBC TI (39%), platelet TI (41%)
Median OS 10.4 months

Kantarjian H et al, JCO 2012
Dombret H et al, Blood 2015

Venetoclax: a new player



Konopleva M et al, Cancer Discovery 2016

VIALE-A Study Design

Eligibility

Inclusion

- Patients with newly diagnosed confirmed AML
- Ineligible for induction therapy defined as **either**
  - ≥75 years of age
  - 18 to 74 years of age with at least one of the co-morbidities:
    - CHF requiring treatment or Ejection Fraction ≤50%
    - Chronic stable angina
    - DLCO ≤ 65% or FEV1 ≤ 65%
    - ECOG 2 or 3

Exclusion

- Prior receipt of any HMA, venetoclax, or chemotherapy for myelodysplastic syndrome
- Favorable risk cytogenetics per NCCN
- Active CNS involvement

Treatment

Randomization 2:1
N=433*

Venetoclax + Azacitidine (N=286)
Venetoclax 400 mg PO, daily, days 1–28 +
Azacitidine 75 mg/m² SC /IV days 1–7

Placebo + Azacitidine (N=145)
Placebo daily, days 1–28
+ Azacitidine 75 mg/m² SC /IV days 1–7

Endpoints

Primary

- Overall survival

Secondary

- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

Randomization Stratification Factors: Age (<75 vs. ≥75 years); Cytogenetic Risk (intermediate, Poor); Region

Venetoclax dosing ramp-up: **Cycle 1 ramp-up** Day 1: 100 mg, Day 2: 200 mg, Day 3 - 28: 400 mg
Cycle 2 Day 1-28: 400 mg

DiNardo C et al, NEJM 2020

VIALE-A: responses

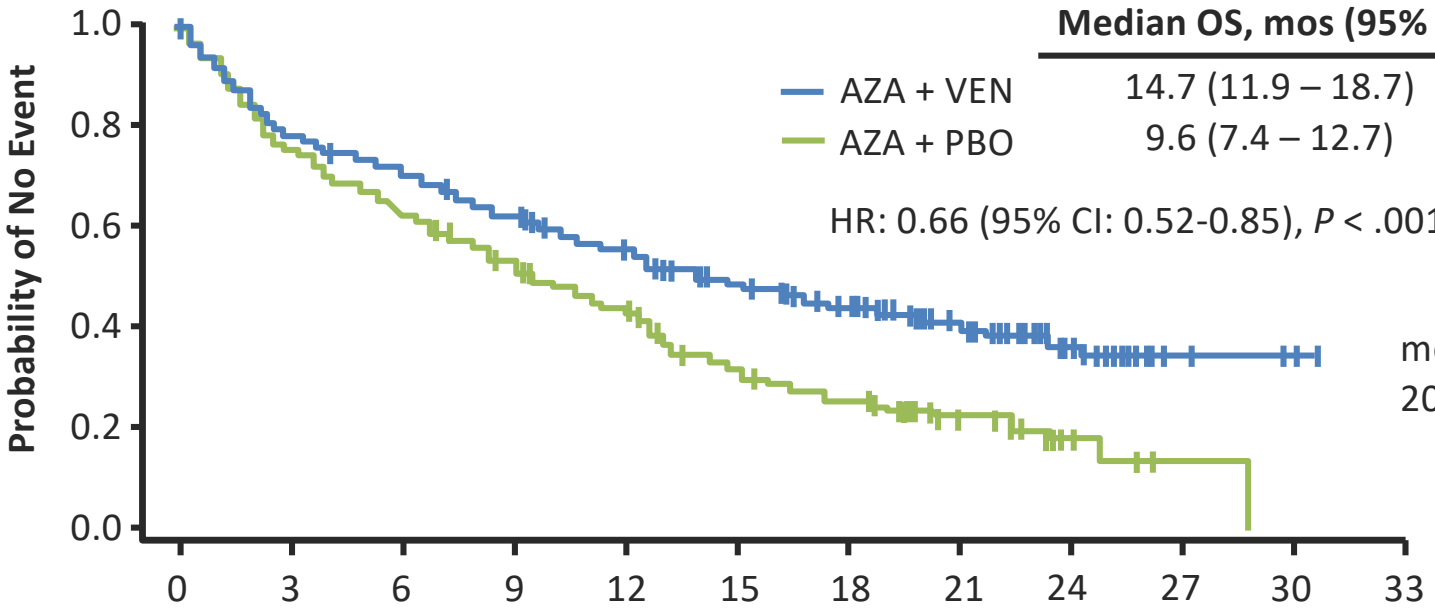
	Aza + Ven (n = 286)	Aza + Pbo (n = 145)	P value
CR + CRi rate (95% CI), %	66.4 (60.6-71.9)	28.3 (21.1-36.3)	<.001
CR + CRi by start of cycle 2 (95% CI), %	43.4 (37.5-49.3)	7.6 (3.8-13.2)	<.001
CR rate (95% CI), %	36.7 (31.1-42.6)	17.9 (12.1-25.2)	<.001
Transfusion independence* (95% CI), %			
▪ RBC	59.8 (53.9-65.5)	35.2 (27.4-43.5)	<.001
▪ Platelets	68.5 (62.8-73.9)	49.7 (41.3-58.1)	<.001
CR + CRi rate in subgroups (95% CI), %			
▪ IDH1/2	75.4 (62.7-85.5)	10.7 (2.3-28.2)	<.001
▪ FLT3	72.4 (52.8-87.3)	36.4 (17.2-59.3)	.021
▪ NPM1	66.7 (46.0-83.5)	23.5 (6.8-49.9)	.012
▪ TP53	55.3 (38.3-71.4)	0	<.001
EFS (95% CI), mo	9.8 (8.4-11.8)	7.0 (5.6-9.5)	<.001

- Median age (range): 76 yrs (49-91)

*defined as ≥ 56 days with no RBC or platelet transfusion between first and last day of treatment

DiNardo C et al, NEJM 2020

VIALE-A: OS



median follow-up of 20.5 months

No. at Risk												
Aza + Ven	286	219	198	168	143	117	101	54	23	5	3	0
Aza + Pbo	145	109	92	74	59	38	30	14	5	1	0	0

DiNardo C et al, NEJM 2020

VIALE-A: safety

Table 2. Adverse Events.*

Event	Azacitidine–Venetoclax Group (N=283)		Azacitidine–Placebo Group (N=144)	
	All Grades†	≥Grade 3‡	All Grades†	≥Grade 3‡
	number of patients (percent)			
All adverse events	283 (100)	279 (99)	144 (100)	139 (97)
Hematologic adverse events	236 (83)	233 (82)	100 (69)	98 (68)
Thrombocytopenia	130 (46)	126 (45)	58 (40)	55 (38)
Neutropenia	119 (42)	119 (42)	42 (29)	41 (28)
Febrile neutropenia	118 (42)	118 (42)	27 (19)	27 (19)
Anemia	78 (28)	74 (26)	30 (21)	29 (20)
Leukopenia	58 (21)	58 (21)	20 (14)	17 (12)
Nonhematologic adverse events				
Nausea	124 (44)	5 (2)	50 (35)	1 (1)
Constipation	121 (43)	2 (1)	56 (39)	2 (1)
Diarrhea	117 (41)	13 (5)	48 (33)	4 (3)
Vomiting	84 (30)	6 (2)	33 (23)	1 (1)
Hypokalemia	81 (29)	30 (11)	41 (28)	15 (10)
Peripheral edema	69 (24)	1 (<1)	26 (18)	0
Pyrexia	66 (23)	5 (2)	32 (22)	2 (1)
Fatigue	59 (21)	8 (3)	24 (17)	2 (1)
Decreased appetite	72 (25)	12 (4)	25 (17)	1 (1)
Infections	239 (84)	180 (64)	97 (67)	74 (51)
Pneumonia	65 (23)	56 (20)	39 (27)	36 (25)
Serious adverse events§	235 (83)	232 (82)	105 (73)	102 (71)
Febrile neutropenia	84 (30)	84 (30)	15 (10)	15 (10)
Anemia	14 (5)	14 (5)	6 (4)	6 (4)
Neutropenia	13 (5)	13 (5)	3 (2)	3 (2)
Atrial fibrillation	13 (5)	10 (4)	2 (1)	2 (1)
Pneumonia	47 (17)	46 (16)	32 (22)	31 (22)
Sepsis	16 (6)	16 (6)	12 (8)	12 (8)

DiNardo C et al, NEJM 2020

U.S. National Library of Medicine
ClinicalTrials.gov

Gimema AML 2320

Prospective and retrospective observational evaluation of **real world** outcome of unfit AML patients treated with the combination of Venetoclax plus HMAs, under the italian law no.648/96

Italian observational study of patients with AML treated with small Molecule inhibiting BCL-2 **(AVALON)**

How can we improve these results?

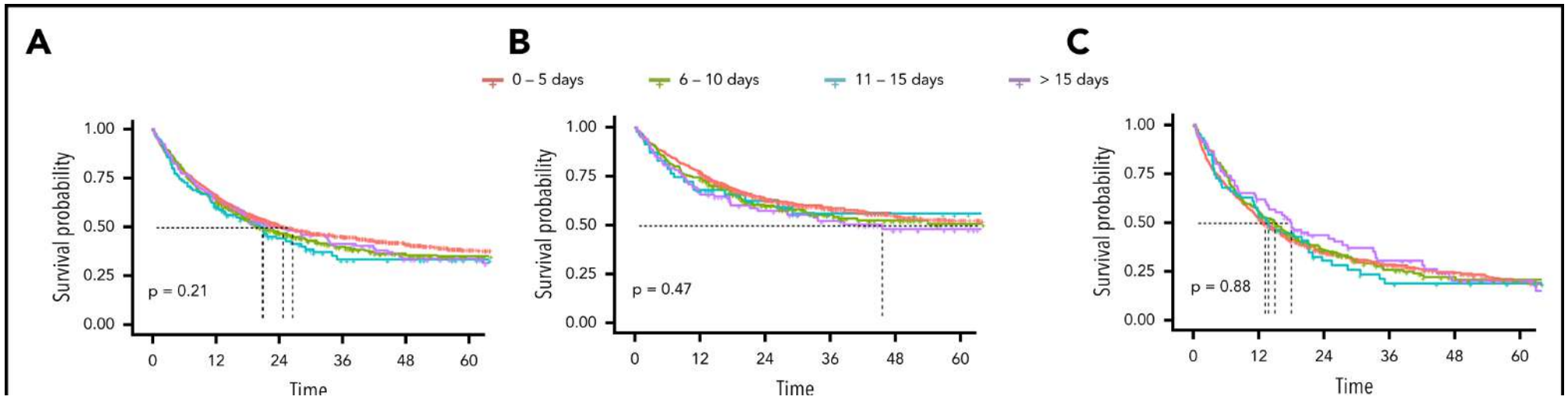
Table 2 Combination regimens with venetoclax under investigation in AML.

Doublet Venetoclax backbone	Triplet Venetoclax + HMA backbone
HMA (eg, AZA, DEC)	FLT3 inhibitor (eg, midostaurin, gilteritinib, quizartinib)
LDAC	IDH1/2 inhibitor (eg, ivosidenib, enasidenib)
FLT3 inhibitor (eg, midostaurin, gilteritinib, quizartinib)	APR-246 (TP53 target)
IDH1/2 inhibitor (eg, ivosidenib, enasidenib)	MCL1 inhibitor (CYC065, AMG 176)
MDM2 antagonist (eg, idasanutlin)	Immune therapies (CD123 ADC, CD70 antibody, PD-1 inhibitors, TIM-3 inhibitors, CD47 antibodies)
CDK9 inhibitor[a] (eg, alvocidib, voruciclib)	
MCL1 inhibitor (S64315, AZD5991)	

ADC antibody-drug conjugate, *AML* acute myeloid leukemia, *AZA* azacitidine, *CDK* cyclin-dependent kinase, *DEC* decitabine, *FLT3* FMS-like tyrosine kinase 3, *HMA* hypomethylating agent, *IDH* isocitrate dehydrogenase, *LDAC* low-dose cytarabine, *MCL1* myeloid cell leukemia-1, *MDM2* mouse double minute 2, *PD-1* programmed cell death protein 1, *TIM-3 T* cell immunoglobulin and mucin domain-containing protein 3.
[a]Data from Bogenberger et al.[24] and Luedtke et al.[25].

Daver N et al, Blood Cancer Journal 2020

To wait or not to wait for the results of genetic tests?

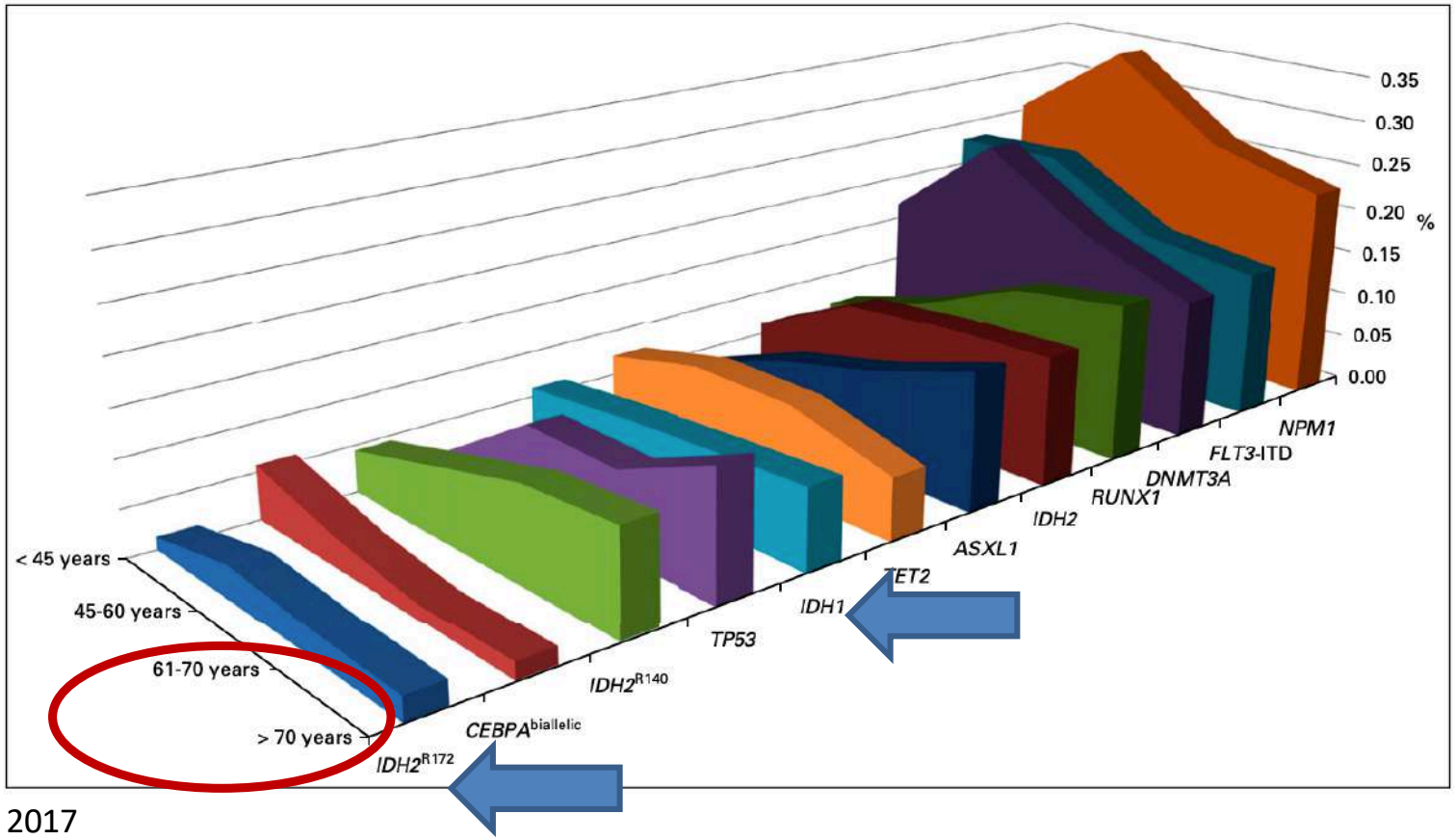


All patients | Patients<= 60 y | Patients> 60 y

Minor treatment delay to incorporate mutational data into treatment decision is safe

Rollig C et al, Blood 2020

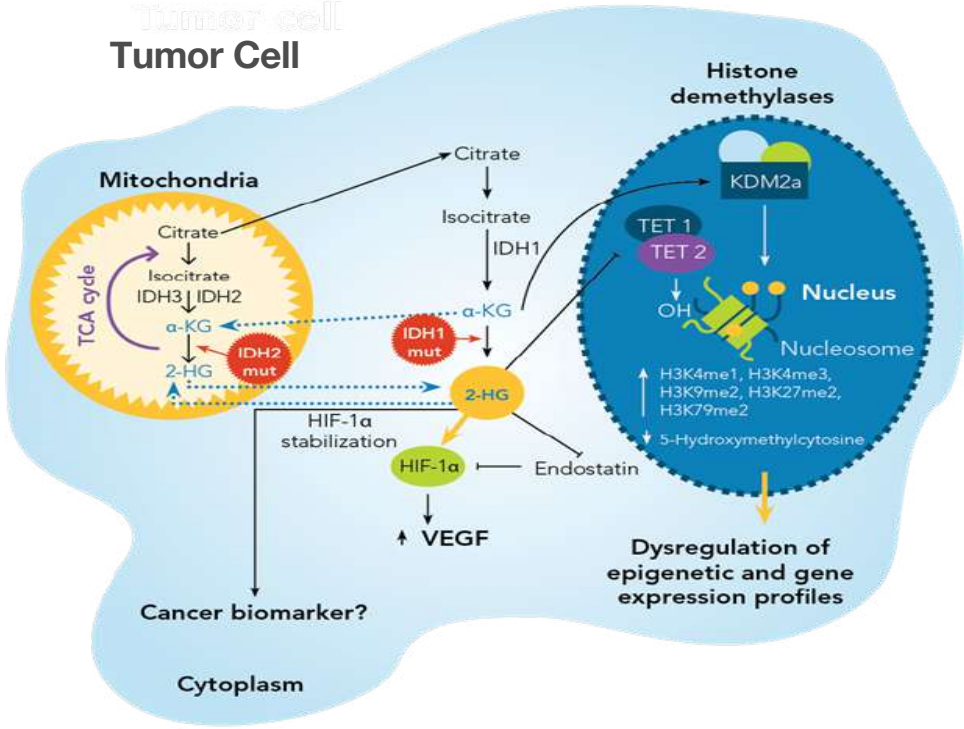
Age-related recurring gene mutations:



Bullinger L et al, JCO 2017

IDH Mutations as a Target in AML

- IDH = isocitrate dehydrogenase, a critical enzyme of the citric acid cycle
- *IDH*m are gain of function mutations
  - IDH1 R132, IDH2 R140, IDH2 R172
- IDHm produces 2-HG, which alters DNA and histone methylation and blocks cellular differentiation
- Enasidenib (AG-221) is a selective, oral, potent inhibitor of mutant IDH2 enzyme.
- Ivosidenib (AG-120), is a selective, oral, potent inhibitor of mutant IDH1 enzyme.



DiNardo CD et al. *Leukemia*. 2016;30:980-984.
Prensner JR, Chinnaiyan AM. *Nat Med*. 2011;17:291-293.

original reports

Mutant Isocitrate Dehydrogenase 1 Inhibitor Ivosidenib in Combination With Azacitidine for Newly Diagnosed Acute Myeloid Leukemia

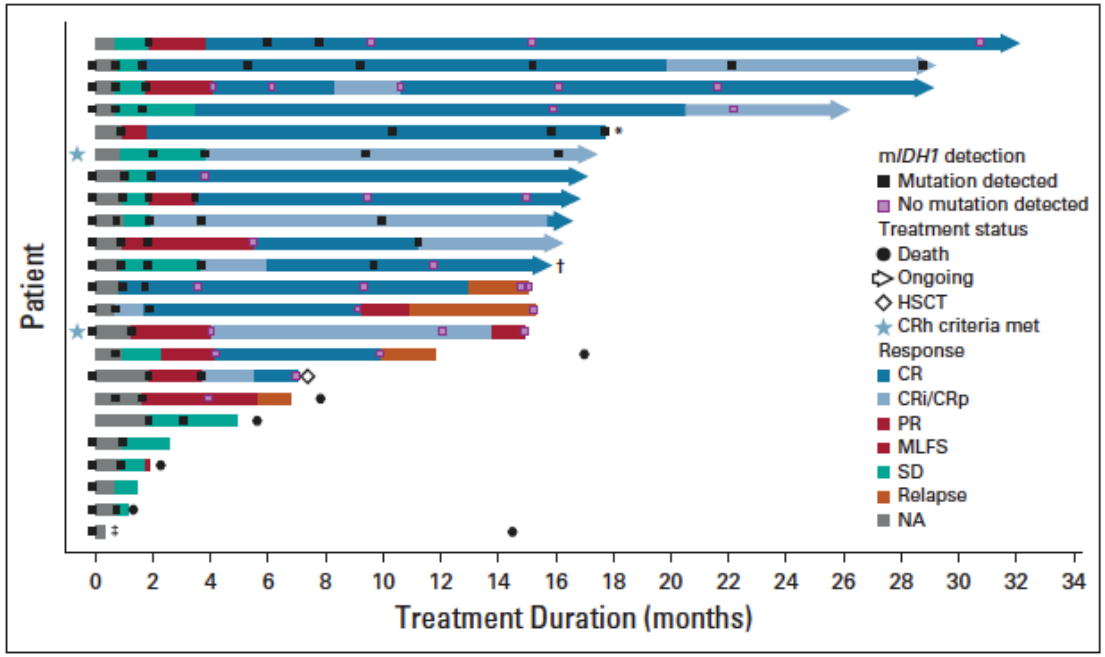
Courtney D. DiNardo, MD[1]; Anthony S. Stein, MD[2]; Eytan M. Stein, MD[3]; Amir T. Fathi, MD[4]; Olga Frankfurt, MD[5]; Andre C. Schuh, MD[6]; Hartmut Döhner, MD[7]; Giovanni Martinelli, MD[8]; Prapti A. Patel, MD[9]; Emmanuel Raffoux, MD[10]; Peter Tan, MBBS[11]; Amer M. Zeidan, MBBS[12]; Stéphane de Botton, MD, PhD[13]; Hagop M. Kantarjian, MD[1]; Richard M. Stone, MD[14]; Mark G. Frattini, MD, PhD[15]; Frederik Lersch, RN[16]; Jing Gong, PhD[15]; Diego A. Gianolio, PhD[17]; Vickie Zhang, PhD[17]; Aleksandra Franovic, PhD[18]; Bin Fan, PhD[17]; Meredith Goldwasser, ScD[17]; Scott Daigle, MS[17]; Sung Choe, PhD[17]; Bin Wu, PhD[17]; Thomas Winkler, MD[17]; and Paresh Vyas, MD, PhD[19]

TABLE 1. Baseline Demographic and Disease Characteristics (N = 23)

Characteristic	Measure
Median age, years (range)	76.0 (61.0-88.0)
Age ≥ 75 years	12 (52.2)
Male/female, No.	11/12
Median mutant *IDH1* VAF in BMMCs, % (range)[a]	42 (17-48)
ECOG PS at baseline	
0	5 (21.7)
1	14 (60.9)
2	4 (17.4)
Disease history	
De novo AML	15 (65.2)
Secondary AML	8 (34.8)
Antecedent myelodysplastic syndrome	2 (8.7)
Antecedent myeloproliferative neoplasm	2 (8.7)
Treatment related	4 (17.4)
IDH1 mutation type	
R132C	16 (69.6)
R132H	4 (17.4)
R132L	3 (13.0)
Cytogenetic risk status by investigator	
Intermediate	15 (65.2)
Poor	5 (21.7)
Failure/missing	3 (13.0)

JCO 2020

Response Category	Response
CR + CRh,[a] No. (%) [95% CI]	16 (69.6) [47.1 to 86.8]
Median time to CR/CRh, months (range)	2.8 (0.8-11.5)
Median duration of CR/CRh, months [95% CI]	NE [12.2 to NE]
CR, No. (%) [95% CI]	14 (60.9) [38.5 to 80.3]
Median time to CR, months (range)	3.7 (0.8-15.7)
Median duration of CR, months [95% CI]	NE [9.3 to NE]
CRh,[a] No. (%)	2 (8.7)
ORR,[b] No. (%) [95% CI]	18 (78.3) [56.3 to 92.5]
Median time to response, months (range)	1.8 (0.7-3.8)
Median duration of response, months [95% CI]	NE [10.3 to NE]
Best response,[c] No. (%)	
CR	14 (60.9)
CRi/CRp	2 (8.7)
MLFS	2 (8.7)
SD	4 (17.4)
NA	1 (4.3)



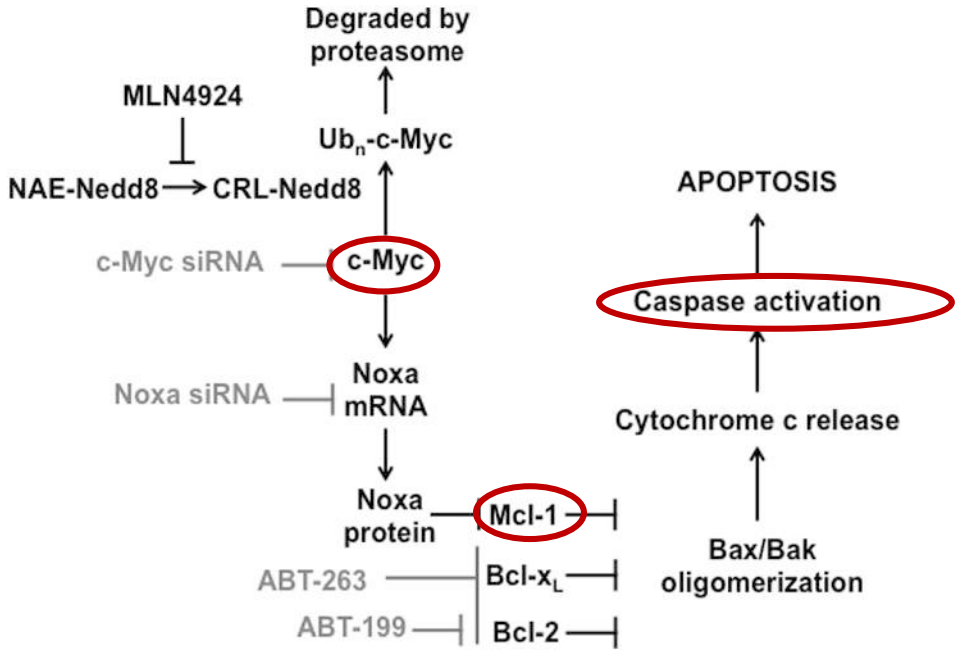
JCO 2020

Cell Death and Differentiation (2015) 22, 2133–2142

www.nature.com/cdd

MLN4924 induces Noxa upregulation in acute myelogenous leukemia and synergizes with Bcl-2 inhibitors

KLB Knorr[1], PA Schneider[2], XW Meng[1,2], H Dai[1,2], BD Smith[3], AD Hess[3], JE Karp[3] and SH Kaufmann*[,1,2]



PEVENAZA: study design

Randomized, open-label, controlled, phase 2 study (NCT04266795)[1]

- Adults ≥18 years
- Morphologically confirmed newly diagnosed AML (WHO criteria 2008)
- Considered unfit for treatment with cytarabine and anthracycline induction due to age and/or comorbidities

N~150

Stratification:
- Age (18 to <75 years vs ≥75 years)
- AML subtype (*de novo* vs secondary)

1:1

Pevonedistat
20 mg/m² IV (days 1, 3, and 5)
Venetoclax
400 mg by mouth (days 1–28 until remission; subsequently days 1–21, or 1–28 if tolerated)
Azacitidine
75 mg/m² IV or SC (days 1–7, or days 1–5, 8, and 9)

Venetoclax
400 mg by mouth (days 1–28 until remission; subsequently days 1–21, or 1–28 if tolerated)
Azacitidine
75 mg/m² IV or SC (days 1–7, or days 1–5, 8, and 9)

Until unacceptable toxicity, relapse, PD, or death

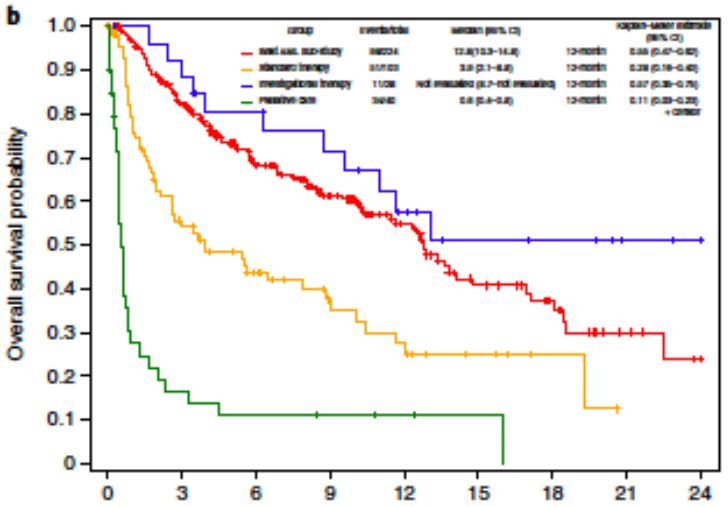
IV, intravenous; PD, progressive disease; SC, subcutaneous; WHO, World Health Organization.

1. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT04266795.

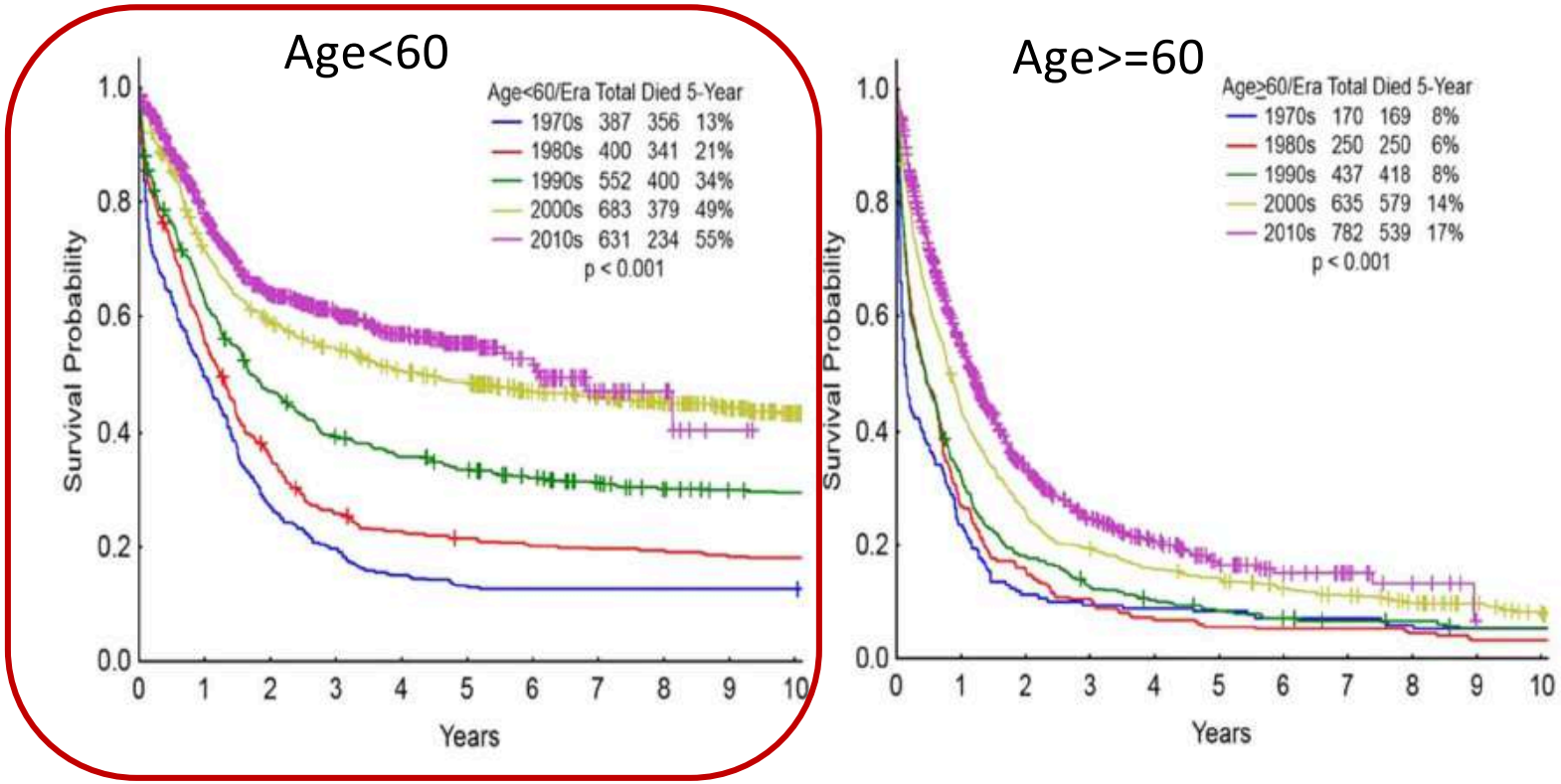
LETTERS
https://doi.org/10.1038/s41591-020-1089-8
nature medicine

Precision medicine treatment in acute myeloid leukemia using prospective genomic profiling: feasibility and preliminary efficacy of the Beat AML Master Trial

Amy Burd[1,18], Ross L. Levine[2,18], Amy S. Ruppert[3], Alice S. Mims[3], Uma Borate[4], Eytan M. Stein[2], Prapti Patel[5], Maria R. Baer[6], Wendy Stock[7], Michael Deininger[8], William Blum[9], Gary Schiller[10], Rebecca Olin[11], Mark Litzow[12], James Foran[13], Tara L. Lin[14], Brian Ball[2], Michael Boyiadzis[15], Elie Traer[4], Olatoyosi Odenike[7], Martha Arellano[9], Alison Walker[3], Vu. H. Duong[6], Tibor Kovacsovics[8], Robert Collins[5], Abigail B. Shoben[3], Nyla A. Heerema[3], Matthew C. Foster[16], Jo-Anne Vergilio[17], Tim Brennan[17], Christine Vietz[17], Eric Severson[17], Molly Miller[3], Leonard Rosenberg[1], Sonja Marcus[1], Ashley Yocum[1], Timothy Chen[1], Mona Stefanos[1], Brian Druker[4,18] and John C. Byrd[2,18]✉



Can we improve AML survival with a targeted approach?



Kantarjian H et al, Blood Cancer Journal 2021

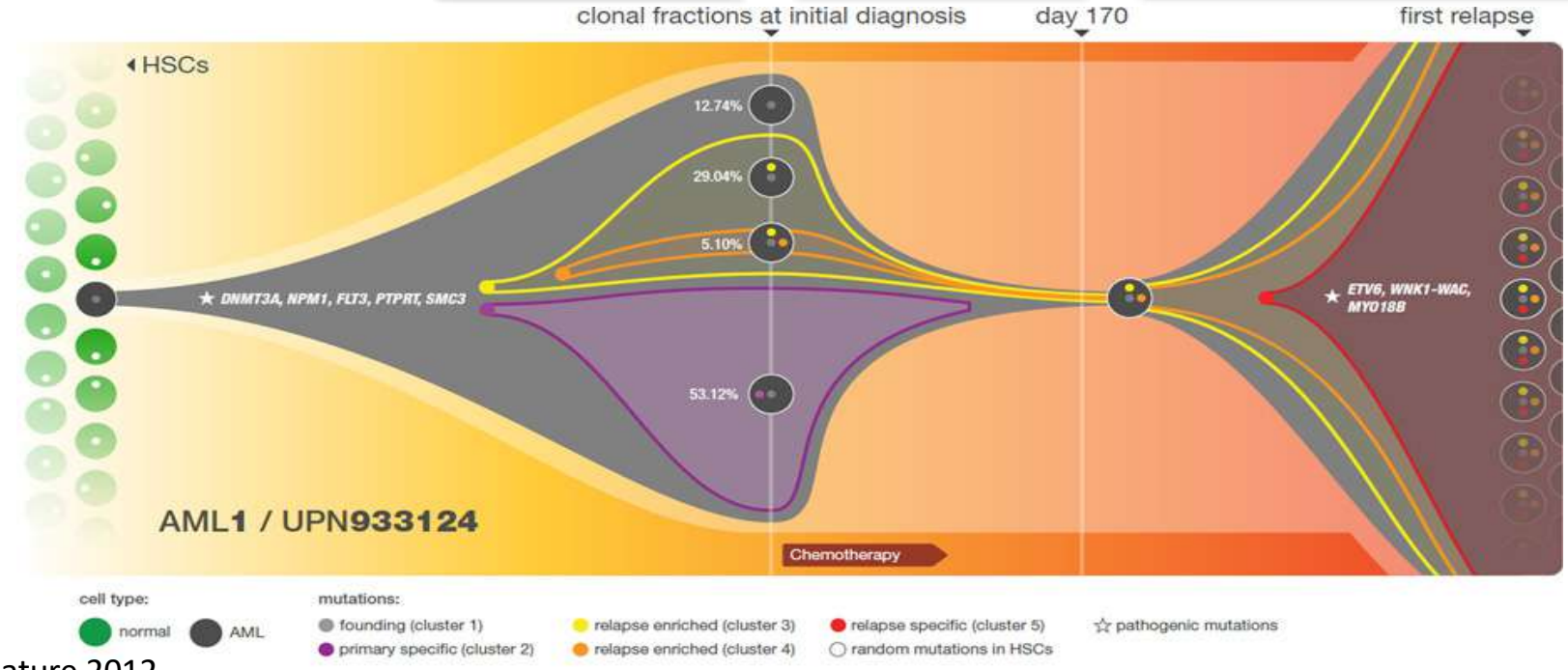
Chemotherapy and clonal evolution in AML

Genetic mapping demonstrates how clonal evolution can result in an AML clone that is genetically distinct at relapse compared with diagnosis

AML is polyclonal at diagnosis

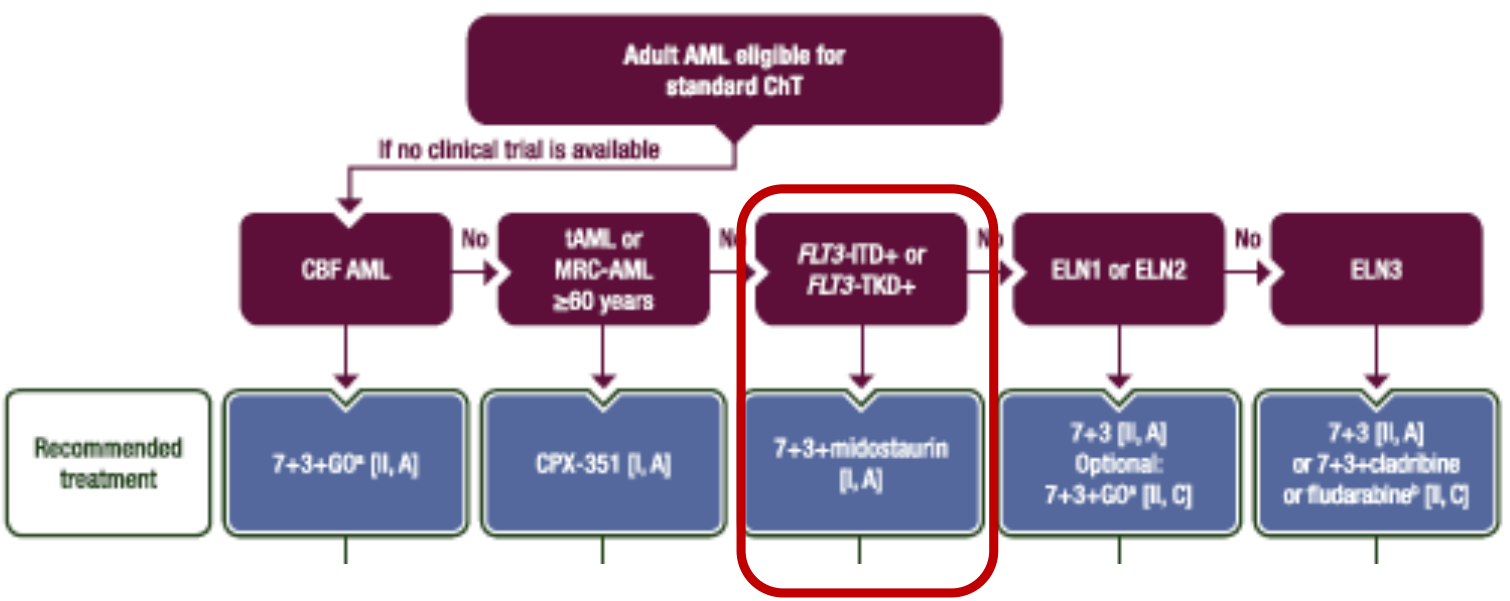
Chemotherapy eliminates almost all disease

A subclone acquires additional mutations that drive relapse



Ding et al, Nature 2012

Adult fit patients therapy: a still chemo-based approach



Heuser M et al, Annals of Oncology 2020

24 A Phase 1 Study of Gilteritinib in Combination with Induction and Consolidation Chemotherapy in Patients with Newly Diagnosed AML: Final Results

Program: Oral and Poster Abstracts
Type: Oral
Session: 616. Acute Myeloid Leukemia: Novel Therapy, excluding Transplantation: Novel combination therapies in treatment of newly diagnosed AML
Hematology Disease Topics & Pathways:
Adult, Diseases, Therapies, Combinations, Study Population, Clinically relevant, Myeloid Malignancies

Saturday, December 5, 2020: 7:30 AM

***Keith W. Pratz, MD[1]**, Mohamad Cherry, MD, MS[2], Jessica K. Altman, MD[3], Brenda W. Cooper, MD[4], Jose Carlos Cruz, MD[5], Joseph G. Jurcic, MD[6], Mark Levis, MD, PhD[1], Tara Lin, MD[7], Alexander E. Perl, MD[8], Nikolai A. Podoltsev, MD, PhD[9], Gary J. Schiller, MD[10], Jason E. Hill, PhD[11*], Angela James, PhD[11*], Qiaoyang Lu, MS[11*] and Ramon V. Tiu, MD[12*]*

Response Parameter,[a] n (%)	*FLT3*$^{mut+}$ Patients who Received 120 mg/d (N=38)[b]
CR	15 (39.5)
CRp	1 (2.6)
CRi	15 (39.5)
CRc	31 (81.6)

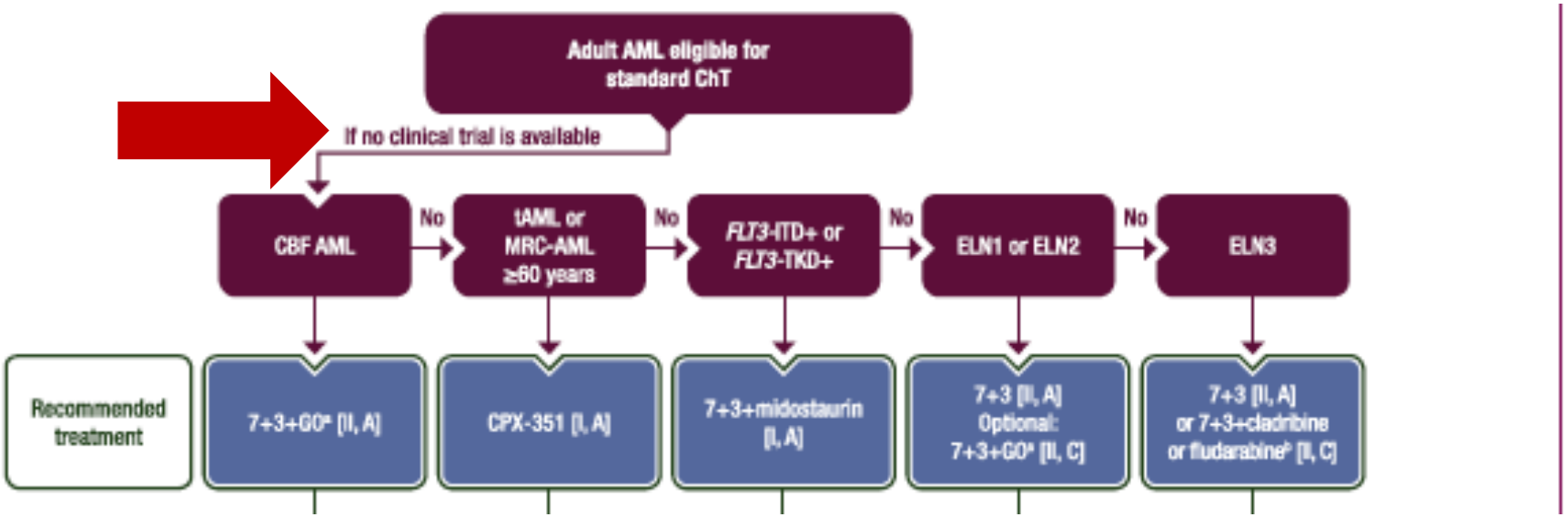
ASH 2020

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	A Study of **Gilteritinib** Versus **Midostaurin** in Combination With Induction and Consolidation Therapy Followed by One-year Maintenance in Patients With Newly Diagnosed Acute Myeloid Leukemia or Myelodysplastic Syndromes With Excess Blasts-2 With FLT3 Mutations Eligible for Intensive Chemotherapy	• Acute Myeloid Leukemia • Myelodysplastic Syndrome With Excess Blasts-2	• Drug: **Gilteritinib** • Drug: **Midostaurin**	• Erasmus MC Rotterdam, Netherlands
2	☐	Recruiting	**Gilteritinib** vs **Midostaurin** in FLT3 Mutated Acute Myeloid Leukemia	• Acute Myeloid Leukemia	• Drug: **Gilteritinib** • Drug: **Midostaurin** • Drug: Daunorubicin • Drug: Cytarabine	• HonorHealth Research Institute Scottsdale, Arizona, United States • University of California, San Francisco-Fresno (University Oncology Associates) Clovis, California, United States • UCLA Los Angeles, California, United States • (and 37 more...)

Adult fit patients therapy

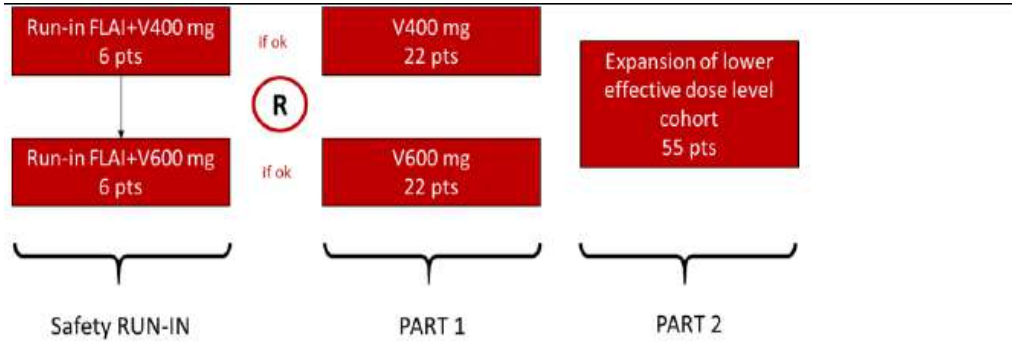


Heuser M et al, Annals of Oncology 2020

Current GIMEMA trial: AML 1718 for intermediate and high risk AML patients

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche FRANCO MANDELLI

PROTOCOL TITLE:	A SAFETY RUN-IN AND PHASE 2, OPEN-LABEL, MULTICENTRE, STUDY INVESTIGATING SAFETY, TOLERABILITY AND EFFECTIVENESS OF VENETOCLAX ADD IN COMBINATION AT FLUDARABINE, CYRATABINE AND IDARUBICINE IN INDUCTION THERAPY OF NEW ONSET NON-M3 ACUTE MYELOID LEUKEMIA
SHORT NAME:	V-FIRST
PROTOCOL NUMBER:	AML1718
VERSION NUMBER:	2.0
EUDRACT NUMBER:	2018-000392-33
CLINICAL TRIAL NUMBER	NCT03455504
TEST PRODUCT:	VENETOCLAX
SPONSOR:	Fondazione GIMEMA Franco Mandelli Onlus
DATE FINAL:	February, 18th 2020



original reports

Venetoclax Combined With FLAG-IDA Induction and Consolidation in Newly Diagnosed and Relapsed or Refractory Acute Myeloid Leukemia

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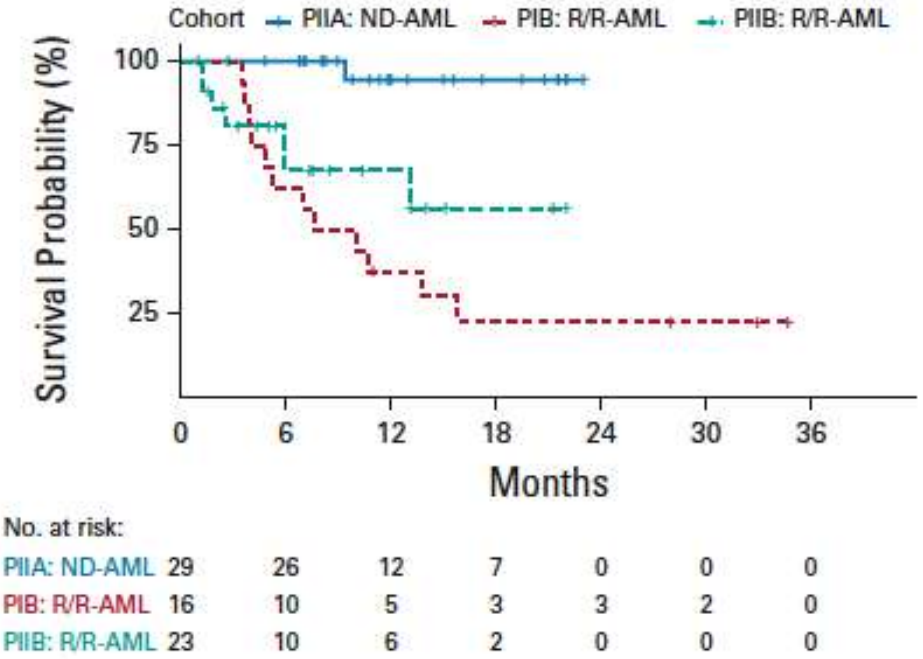
Parameter	Phase IIA ND-AML (n = 29)	Phase IB R/R-AML (n = 16)	Phase IIB R/R-AML (n = 23)
Age, years	45 (20-65)	51 (20-73)	47 (22-66)
Sex (male)	13	10	14
VEN dose level			
Dose level −1 (VEN 200 mg, D1-21)	—	8	—
Alternate dose level −1 (VEN 200 mg, D1-14)	—	5	—
Dose level 0 (VEN 400 mg, D1-14)	29	3	23
Median No. of prior therapies	—	2 (1-6)	1 (1-3)
Prior HSCT	—	7	7
Median duration of prior CR, months	—	15.1 (2.3-44)	12.6 (2.7-70)
Salvage 1	—	8	19
Salvage 2	—	3	3
Salvage 3 or greater	—	5	1
Median blast (%) at enrollment[a]	41 (4-85)	63 (6-94)	46 (1-89)
Extramedullary leukemia	3	—	1
AML type			
de novo AML	17	—	—
sAML	5	—	—
ts-AML	2	—	—
t-AML	5	—	—
R/R-AML	—	16	23
ELN risk group			
Favorable	5	6	6
Intermediate	13	2	3
Adverse	11	8	14

JCO 2021

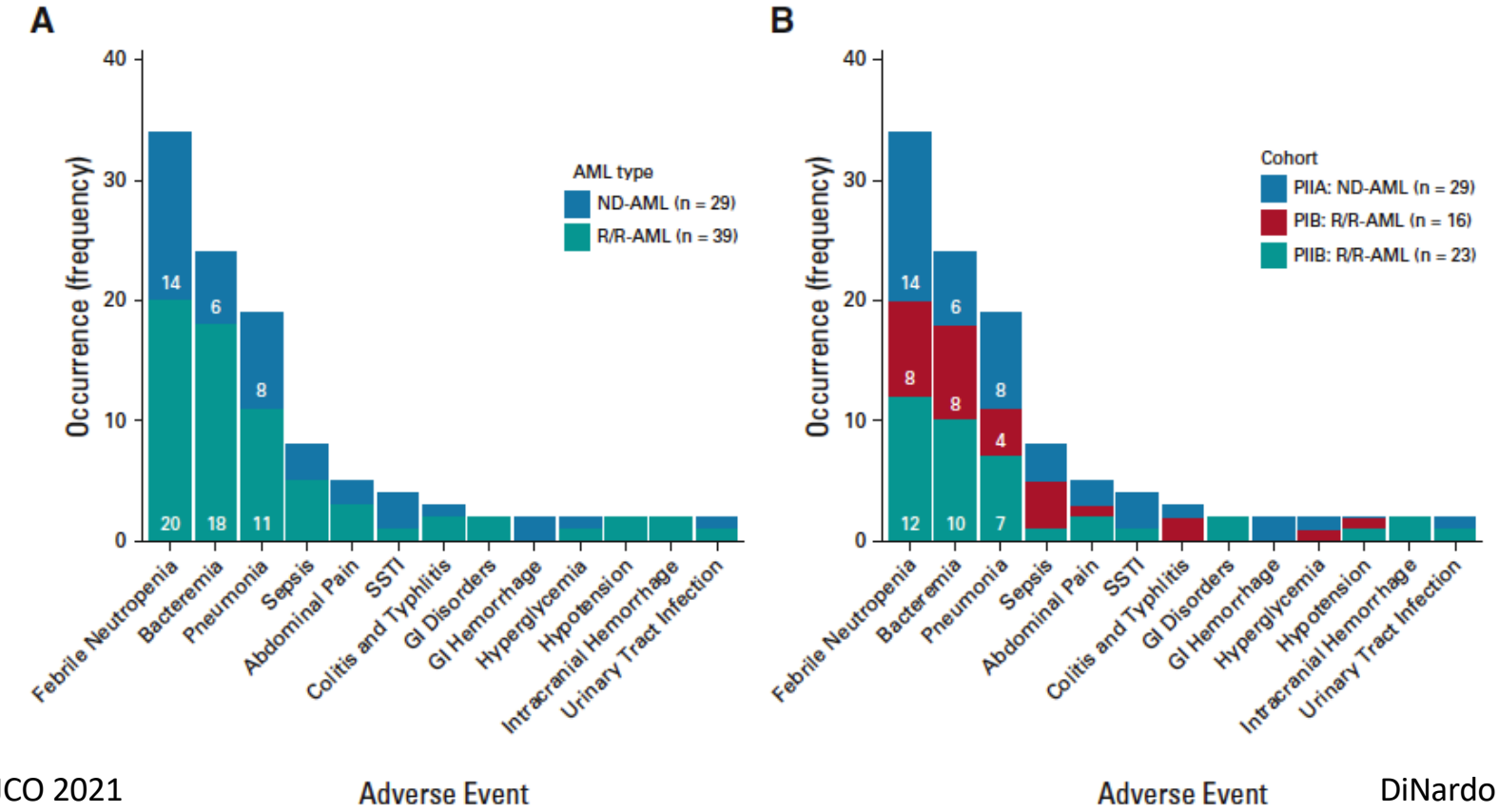
Outcome	All (N = 68)	Phase IIA ND-AML (n = 29)
ORR, No. (% [CI])	56 (82 [71 to 91])	28 (97 [85 to 99])[a]
CRc (CR + CRi + CRh), No. (% [95% CI])	52 (76 [65 to 86])	26 (90 [73 to 98])
CR, No. (%)	37 (53)	20 (69)
CRh, No. (%)	10 (15)	5 (17)
CRi, No. (%)	5 (7)	1 (3)
MRD⁻ CR (flow cytometry), No. (% [95% CI])	43 (83 [70 to 92])	25 (96 [80 to 99])
MLFS	4	2
No response	12	1
DOR (median, months)	NR	NR
EFS		
Median, months (95% CI)	18 (10.1 to NE)	NR
6-month, % (95% CI)	70 (59 to 81)	89 (78 to 100)
12-month, % (95% CI)	56 (44 to 71)	85 (72 to 100)
OS		
Median, months (95% CI)	NR	NR
6-month, % (95% CI)	81 (71 to 91)	100
12-month, % (95% CI)	70 (58 to 83)	94 (84 to 100)

B

Median f-up: 12 months



DiNardo C et al, JCO 2021

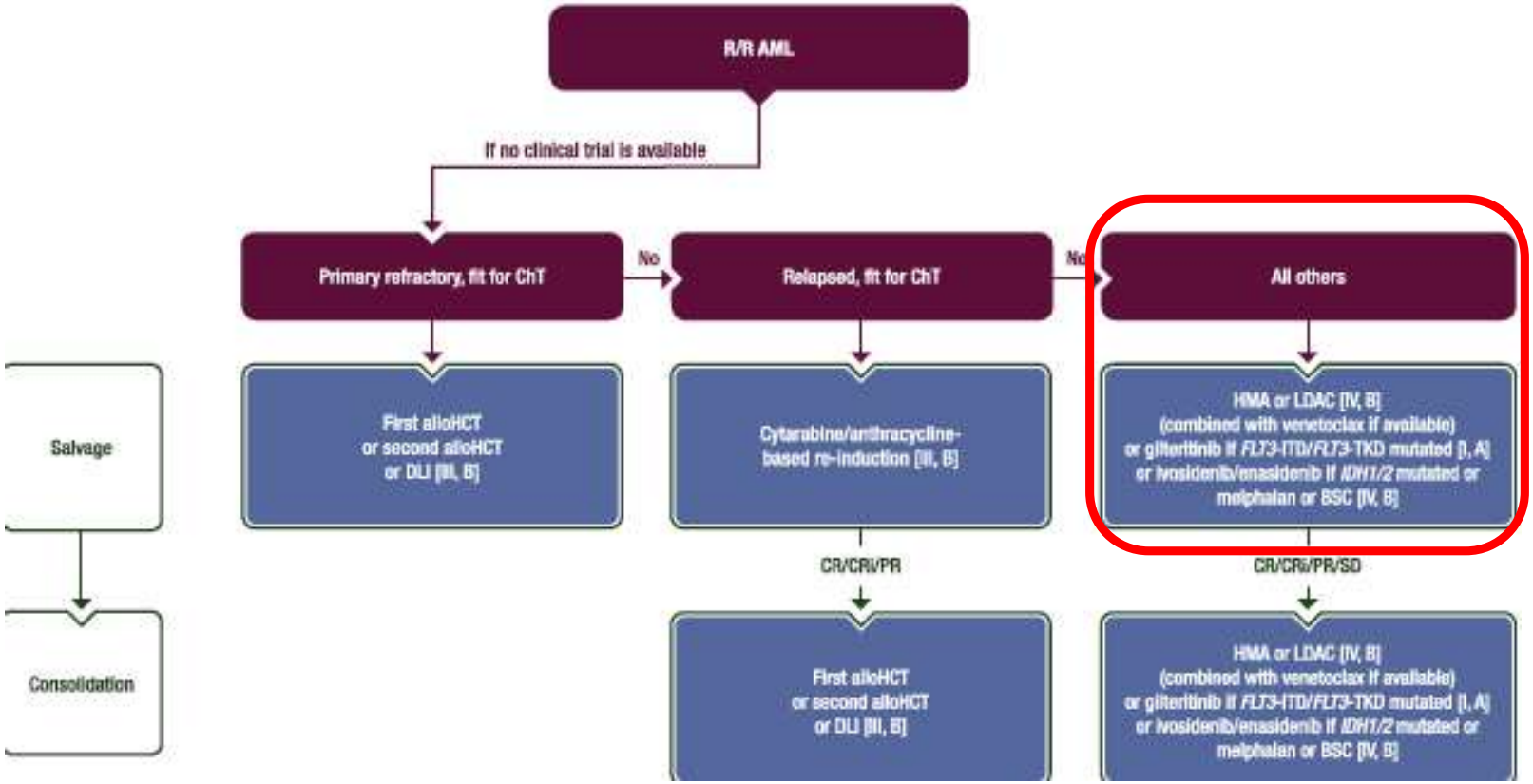


DiNardo C et al, JCO 2021

DiNardo C et al, JCO 2021

- Three deaths in CR (all R/R AML) due to systemic mucormycosis with typhlitis, SBO, perforated fistula (> Day 100), HLH complicating *E. coli* and RSV infection with no response to HLH therapy (> Day 100), and lung aspergilloma and respiratory hemorrhage (Day 51)

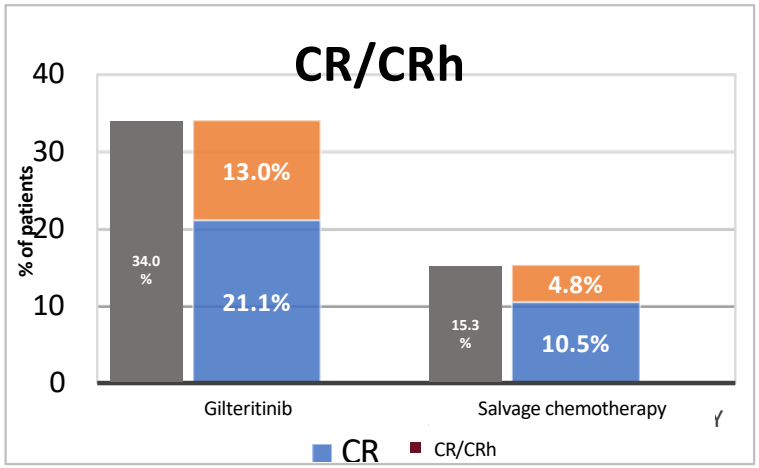
R/R patients therapy: targeted therapy in specific subsets



Heuser M et al, Annals of Oncology 2020

Gilteritinib vs chemo: better CR rate

CR/CRh: 34% (Gilteritinib) vs 15.3% (chemo)



The CR/CRh rate was 34.0% in the gilteritinib arm and 15.3% in the salvage chemotherapy arm (treatment difference: 18.6%; 95% CI: 9.8–27.4)

CR/CRh rate was a co-primary endpoint of the study and was analysed based on the response analysis dataset at first interim in the gilteritinib arm only

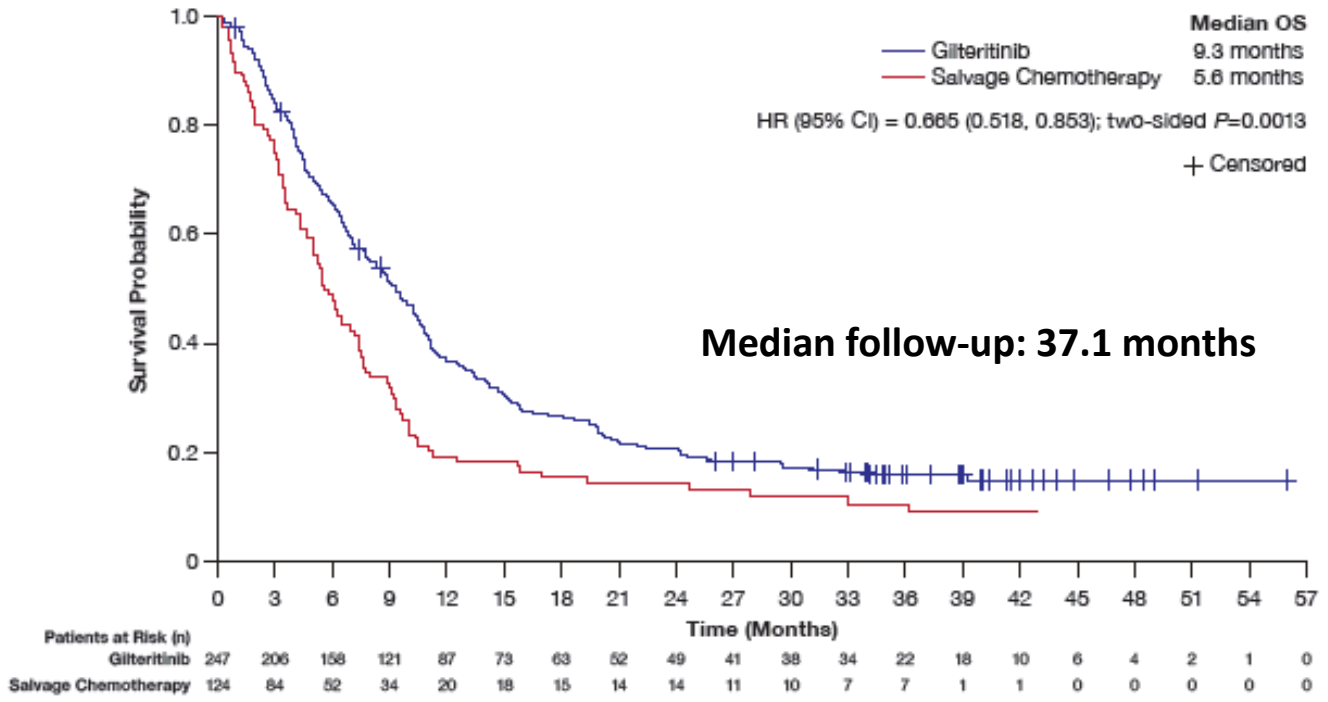
CR/CRh rate was summarised descriptively at the final analysis for both treatment arms

Perl AE et al. *N Engl J Med.* 2019;381:1728–1740.

Gilteritinib vs chemo: better OS

Transplantation rate:
25.5% (Gilt)
15.3% (chemo)

Figure 2. Overall Survival in R/R FLT3mut+ AML Patients (ITT Population; N=371)



Abbreviations: ML, acute myeloid leukemia; CI, confidence interval; *FLT3*$^{mut+}$, *FLT3*-mutation–positive; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; R/R, relapsed or refractory.

Perl A et al, EHA 2021

Patterns of Resistance Differ in Patients with Acute Myeloid Leukemia Treated with Type I versus Type II FLT3 inhibitors

Ahmad S. Alotaibi[1,●], Musa Yilmaz[1,●], Rashmi Kanagal-Shamanna[2], Sanam Loghavi[2], Tapan M. Kadia[1], Courtney D. DiNardo[1], Gautam Borthakur[1], Marina Konopleva[1], Sherry A. Pierce[1], Sa A. Wang[2], Guilin Tang[2], Veronica Guerra[1], Bachar Samra[1], Naveen Pemmaraju[1], Elias Jabbour[1], Nicholas J. Short[1], Ghayas C. Issa[1], Maro Ohanian[1], Guillermo Garcia-Manero[1], Kapil N. Bhalla[1], Keyur P. Patel[2], Koichi Takahashi[1], Michael Andreeff[1], Jorge E. Cortes[3], Hagop M. Kantarjian[1], Farhad Ravandi[1], Naval Daver[1]

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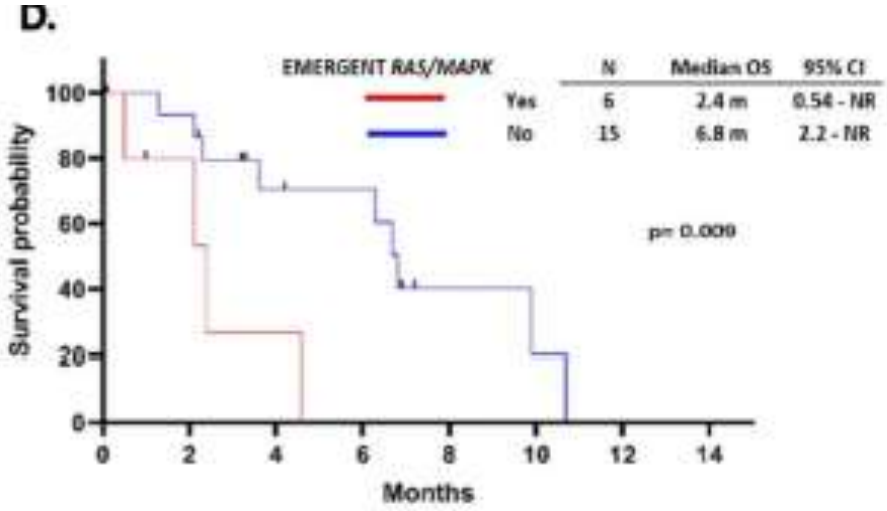
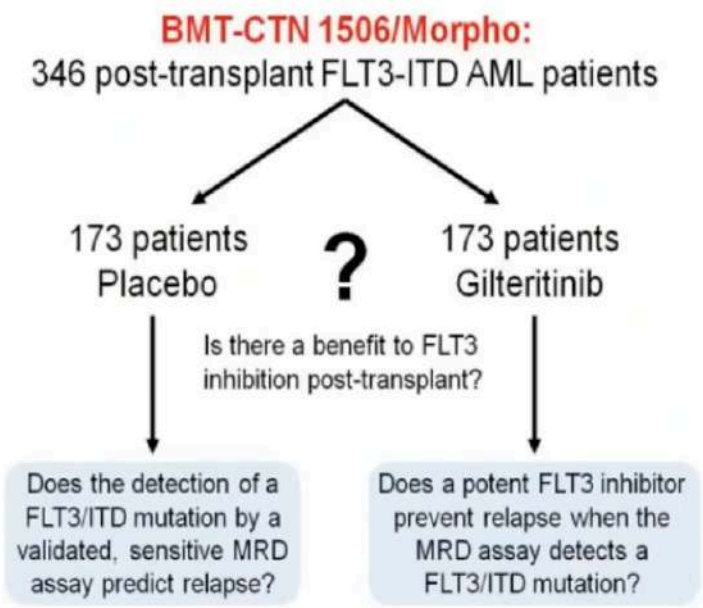
Type I FLT3-inh→ RAS/MAPK mut

Type II FLT3-inh→ FLT3 D835



Blood Cancer Discovery 2021

BMT CTN Protocol 1506: a phase III trial of Gilteritinib as maintenance therapy after allo HSCT in FLT3 ITD+ patients



AML in CR1 who are ≥30 days and ≤90 days from scheduled allogeneic HSCT.

N= 346 subjects

Randomized (1:1; stratified by conditioning regimen intensity, time from HSCT [Day 0] to randomization [30-60 days vs 61-90 days], and presence of minimal residual disease [MRD] in the pre-transplant bone marrow sample)

Oral gilteritinib (120 mg) or matching placebo for 2 years. The primary endpoint is relapse-free survival (RFS) in the two treatment arms;

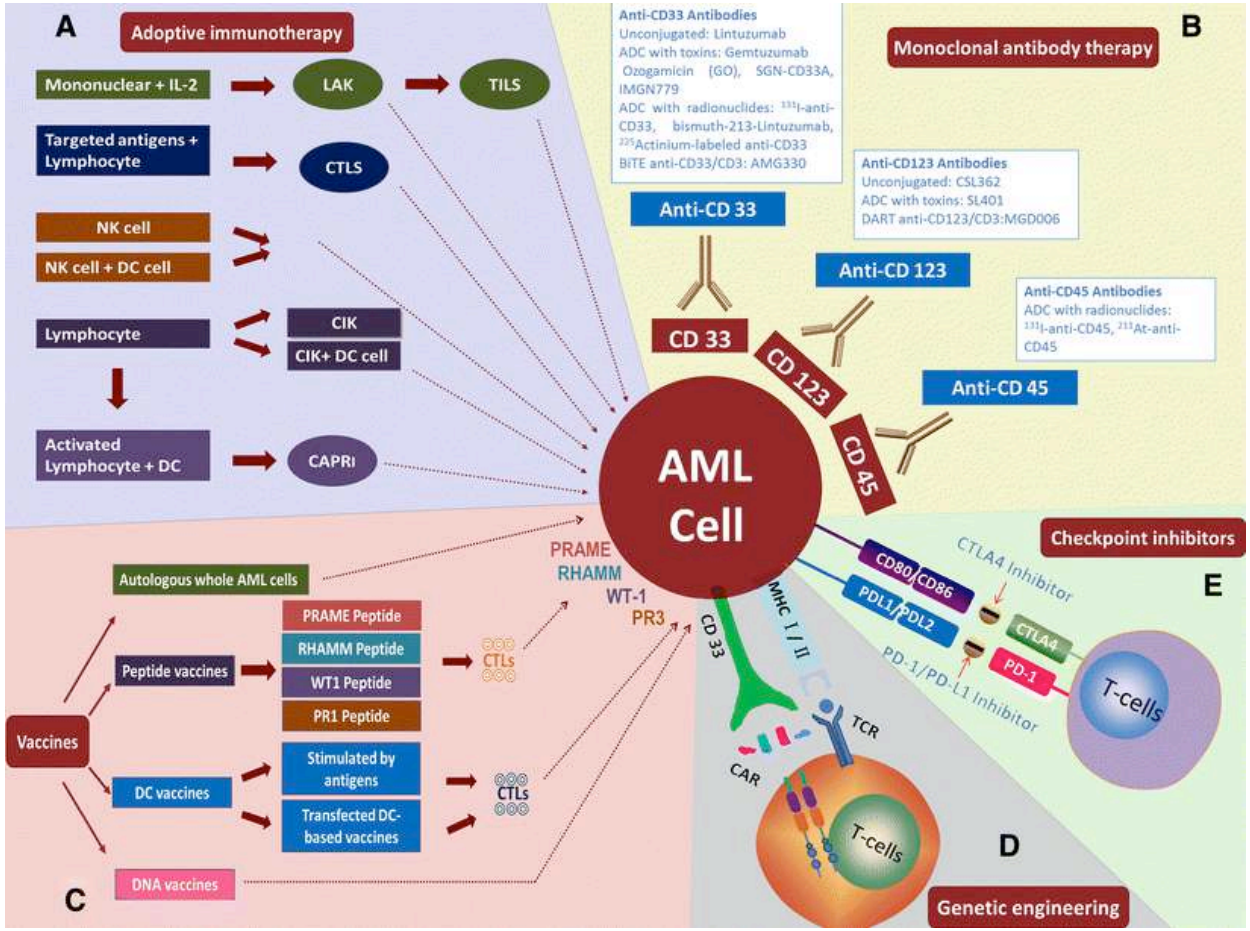
MRD status will continue to be monitored over the duration of the maintenance therapy, although investigators will be blinded to the MRD assay results

Mark J. Levis, et al 1506: A Phase 3 Trial of Gilteritinib As Maintenance Therapy after Allogeneic Hematopoietic Stem Cell Transplantation in Patients with FLT3-ITD+ AML, Blood, 2019

American Society of Hematology

- ✓ Moving to triplets
- ✓ Better understanding of mechanisms of resistance to molecular approaches
- ✓ Better understanding of new drugs' management and toxicities
- ✓ Integration between molecular and immunotherapy approaches

Immunotherapy in AML



Yang D et al, Annals of Hematology 2017

Thank you!

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