2020

Progetto
Ematologia
Romagna

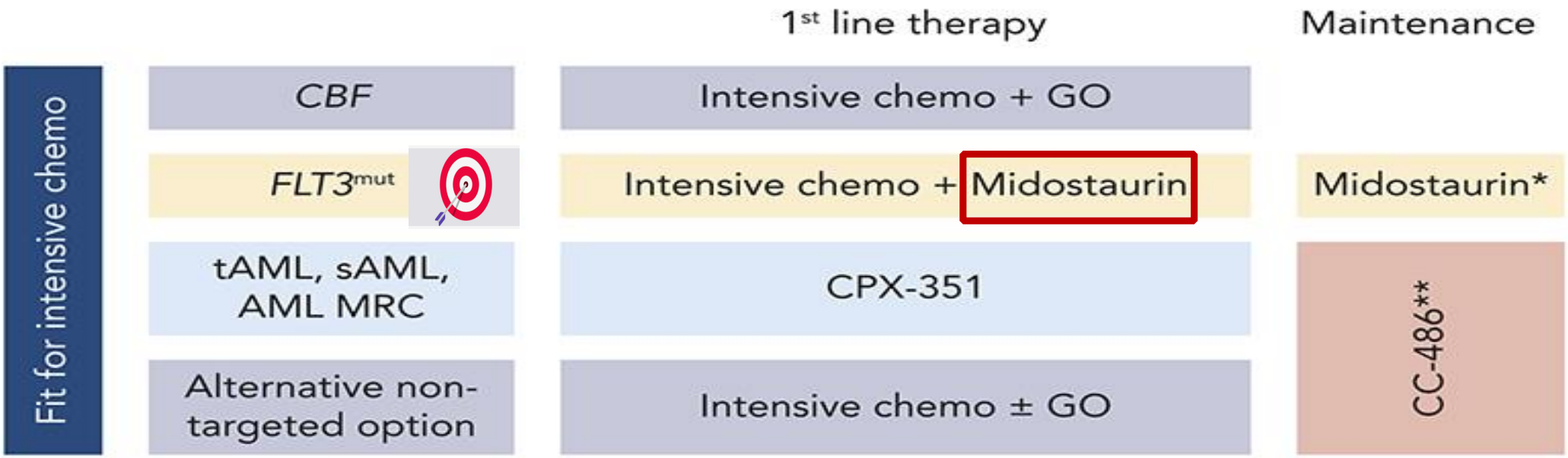
I nuovi farmaci

Cristina Papayannidis, MD, PhD

Disclosures

Advisory Boards: Novartis, Abbvie, Janssen, Pfizer, Amgen
Honoraria: Pfizer, Amgen, Astellas, Abbvie

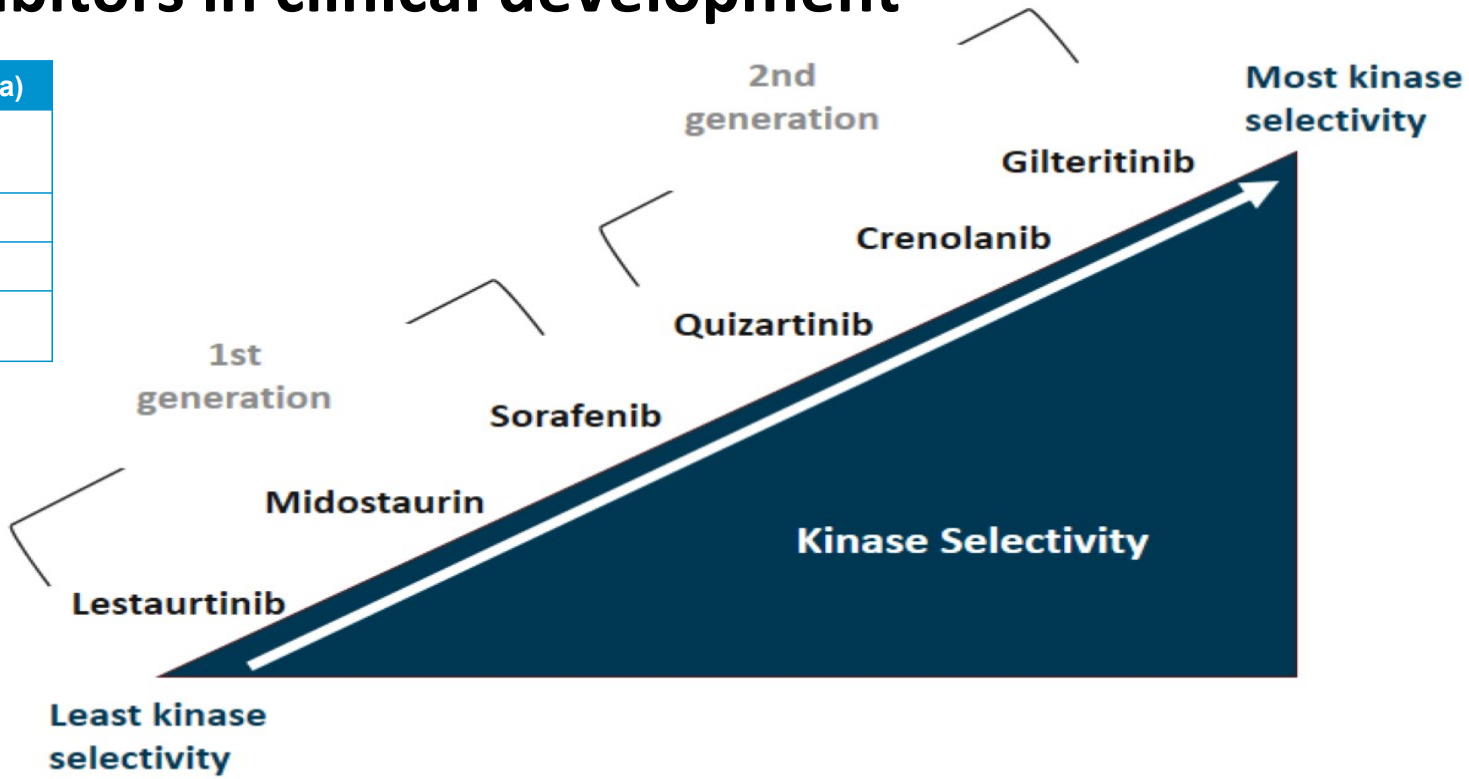
Current approach to newly diagnosed fit AML patients



Courtney D. DiNardo, Andrew H. Wei. Blood, 2020

Other FLT3 inhibitors in clinical development

	IC_{50} (plasma)
Midostaurin (PKC412)	~1000 nM
Quizartinib (AC220)	18 nM
Crenolanib	48 nM
Gilteritinib (ASP2215)	43 nM



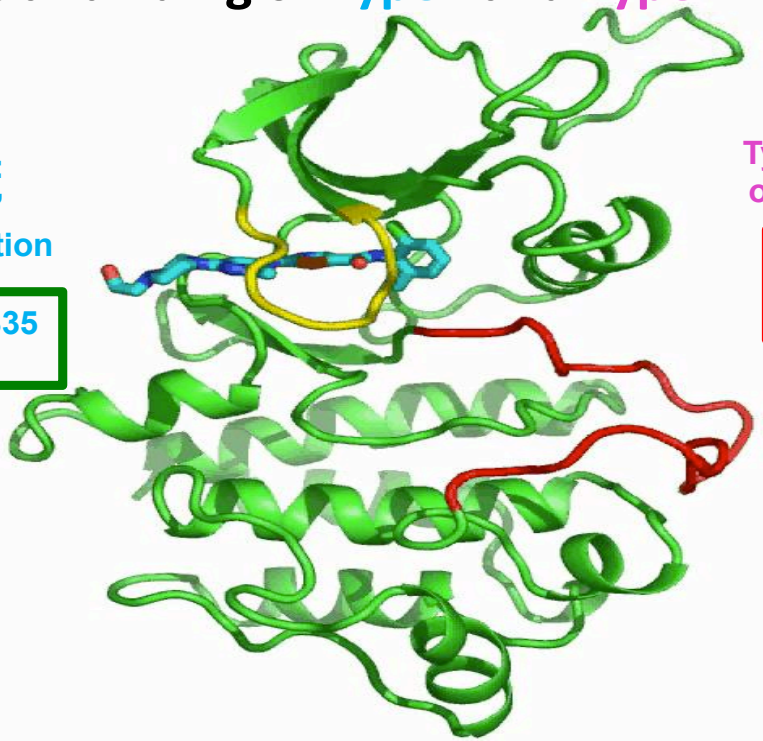
Zarrinkar PP, et al. *Blood*. 2009;114:2984-2992; Galanis A, et al. *Blood*. 2014;123:94-100; Lee LY, et al. *Blood*. 2017;129:257-260; Garcia JS, Stone RM. *Hematol Oncol Clin N Am*. 2017;31:663-680.

Differential binding of Type I and Type II Inhibitor kinase

Type I Inhibitor:
Binds "DFG-in"
ACTIVE conformation

Active against D835 mutations

Midostaurin
Crenolanib
Gilteritinib

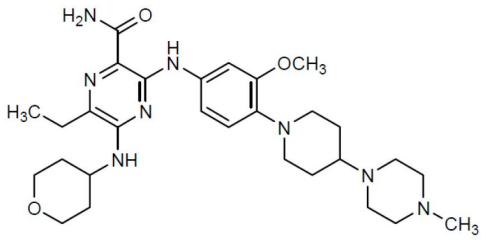


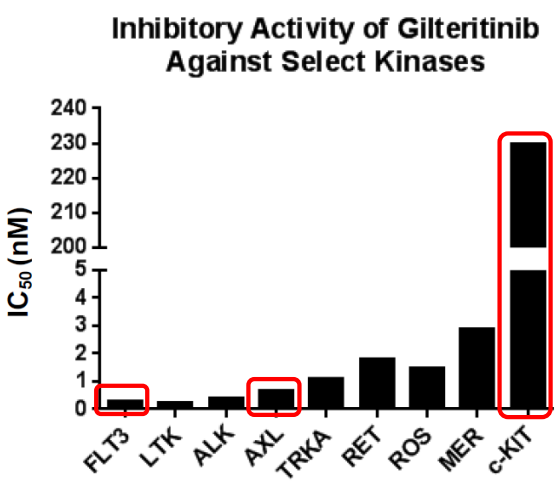
Quizartinib
Type II Inhibitor: Binds "DFG-out" INACTIVE conformation

Not active against D835 mutations

Quizartinib
Sorafenib

Gilteritinib





Active against the tyrosine kinase domain mutations that confer resistance to quizartinib and sorafenib:

FLT3 receptor subtype	Gilteritinib IC_{50}
Wild type	5 nM
Molm14 (ITD)	1.8 nM
TF/ITD	1.4 nM
Ba/F3 ITD	0.7 nM
Ba/F3 D835Y	0.5 nM
Ba/F3 D835H	1.9 nM
Ba/F3 D835V	0.7 nM
Ba/F3/ITD F691L	17.6 nM

Lee et al. *Blood*. 2017;129:257

Gilteritinib: where do we stand now?

On November 28, 2018, **FDA approved** gilteritinib for treatment of adult patients who have **relapsed or refractory acute myeloid leukemia (AML)** with a FLT3 mutation as detected by an FDA-approved test.

EMA approved the drug in October 2019. **Italian AIFA approval** has been recently obtained.

Gilterinib vs chemotherapy in R/R FLT3+ AML

Key eligibility criteria

- Adults with AML refractory to, or relapsed after, first-line AML therapy ± HSCT
- *FLT3* mutation (*FLT3*-ITD, or *FLT3*-TKD D835/I836) in blood or bone marrow

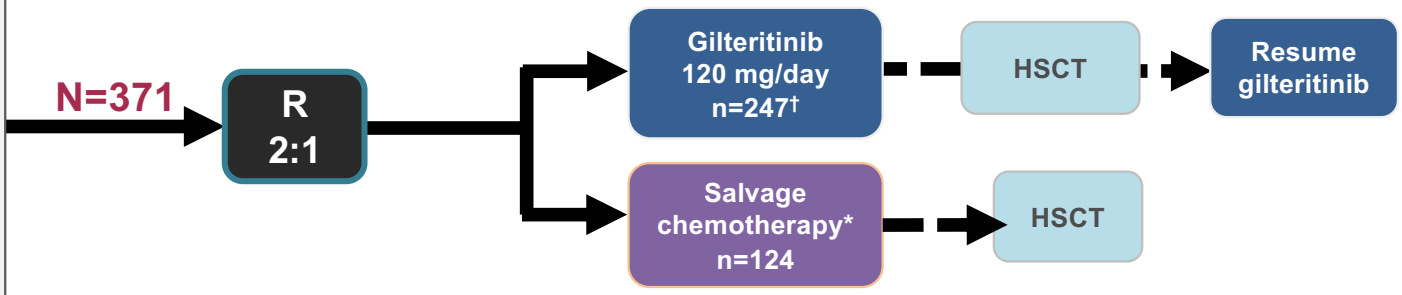
Stratification factors

- Response to first-line AML therapy
  - >6 months versus ≤6 months[2]
- Preselected chemotherapy
  - High versus low intensity

Co-primary endpoints‡

- OS
- CR/CRh recovery rate**

Between October 2015 and February 2018, 625 patients were screened and 371 were randomised in the trial



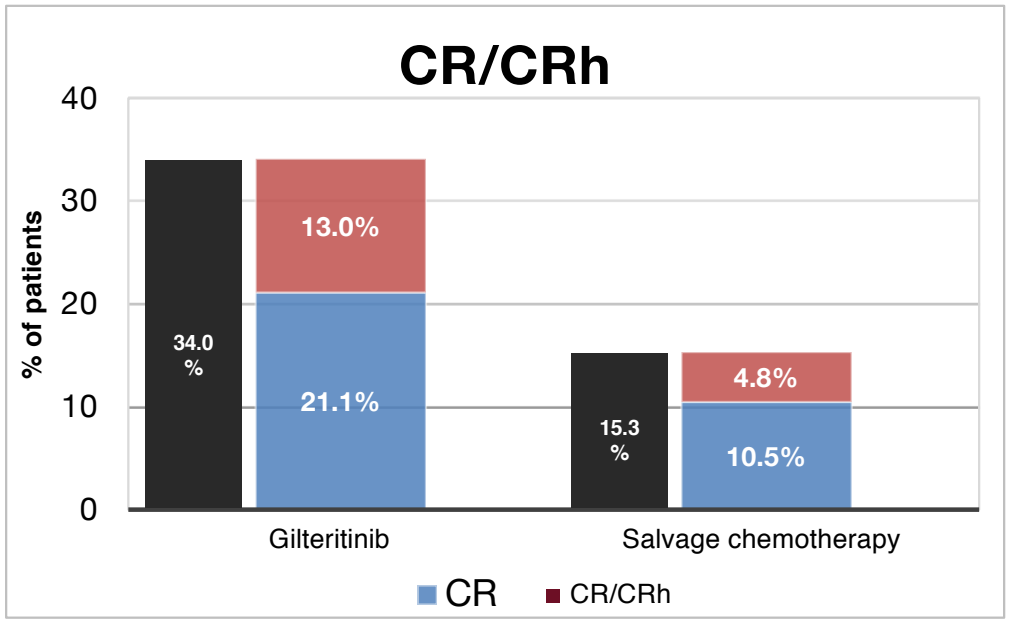
*The salvage chemotherapy regimen was selected prior to randomisation from the following options:

- **High-intensity regimens (1–2 cycles):** MEC or FLAG-IDA
- **Low-intensity regimens†:** Low-dose cytarabine or azacitidine

1. Perl AE, Martinelli G, Cortes JE, et al. *N Engl J Med.* 2019;381:1728–1740; 2. ADMIRAL study protocol. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1902688/suppl_file/nejmoa1902688_protocol.pdf. Accessed April 2020.

Abbreviations: AML, acute myeloid leukaemia; CR/CRh; complete remission/compete remission with partial haematological recovery; FLAG-IDA fludarabine, cytarabine, granulocyte colony-stimulating factor and idarubicin; HSCT, haematopoietic stem cell transplantation; ITD, internal tandem duplication; MEC, mitoxantrone, etoposide and cytarabine; MHRA, Medicines and Healthcare products Regulatory Agency; OS, overall survival; R, randomisation; TKD, tyrosine kinase domain.

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)

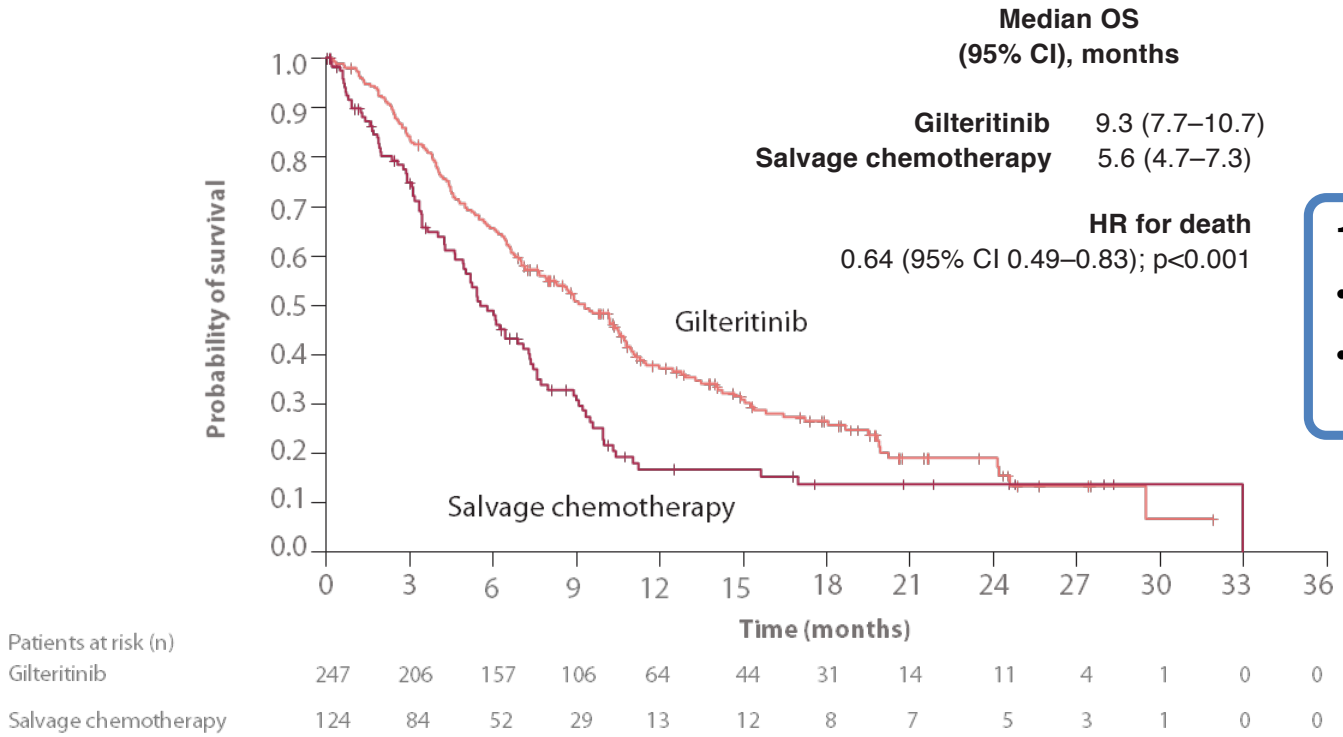
CR/CRh rate was a co-primary endpoint of the study and was analysed based on the response analysis dataset at first interim in the gilteritinib arm only

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

Abbreviations: CI, confidence interval; CR, complete remission; CRh, CR with partial haematological recovery; FLT3, Fms-like tyrosine kinase-3; m+, mutation positive; R/R, relapsed or refractory.

Adapted from Perl AE, Martinelli G, Cortes JE, et al. *N Engl J Med.* 2019;381:1728–1740.

Median OS: 9.3 months (Gilteritinib) vs 5.6 months (chemo)



12-month OS

- Gilteritinib: 37%
- Salvage chemotherapy: 17%

Perl AE, Martinelli G, Cortes JE, et al. *N Engl J Med.* 2019;381:1728–1740.

Abbreviations: CI, confidence interval; HR, hazard ratio. OS, overall survival.

*Median duration of follow up for OS 17.8 months. Two-sided p-values were determined according to the log-rank test; the Kaplan–Meier method, combined with the Greenwood formula, were used to determine OS and corresponding 95% CIs.

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

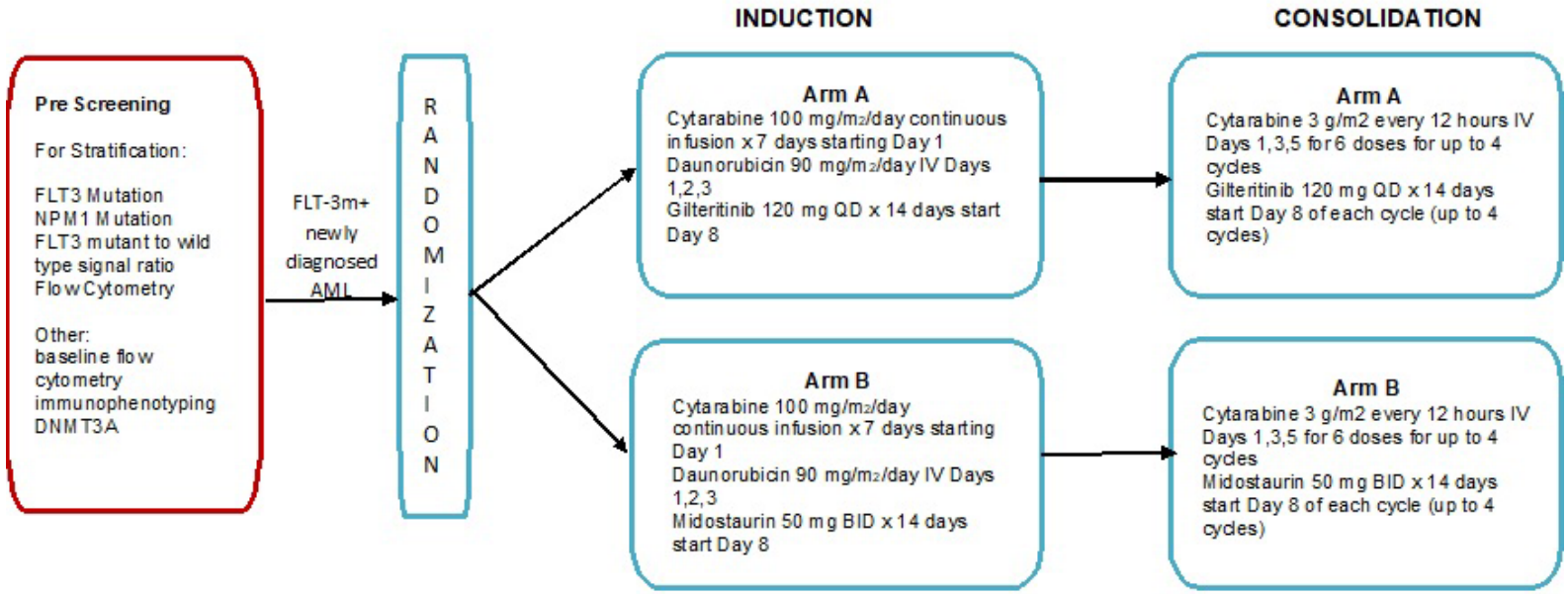
Saturday, December 5, 2020: 7:30 AM

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

Phase II Randomized Trial of Gilteritinib Vs Midostaurin in Newly Diagnosed FLT3+ AML



Selina M. Luger et al, Blood, 2019

FF-10101: a new FLT3 inhibitor

616.ACUTE MYELOID LEUKEMIA: NOVEL THERAPY, EXCLUDING TRANSPLANTATION | NOVEMBER 13, 2019

FF-10101 Retains Potent Inhibitory Activities Against Resistant Mutations to FLT3 Inhibitors, Newly Identified in Random Mutagenesis Screens

Yuichi Ishikawa, MD PhD, Koichi Saito, PhD, Naomi Kawashima, MD PhD, Michie Morimoto, Hidetoshi Murao, PhD, Daisuke Terada, Takeshi Yamaura, Shinji Hagiwara, PhD, Hitoshi Kiyoi, MD PhD

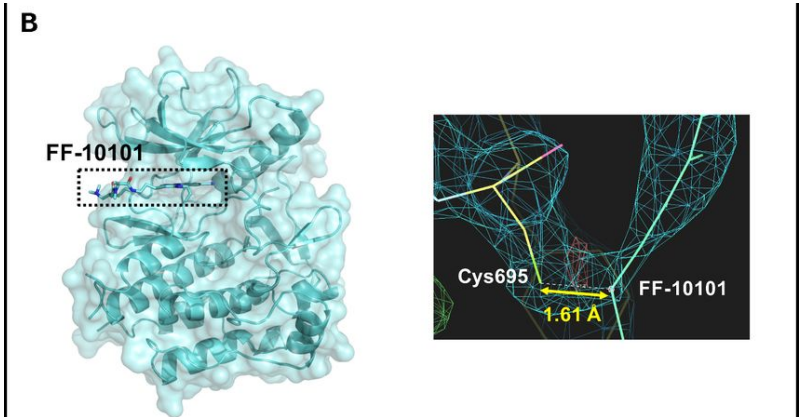


Table. Growth inhibitory profile of FLT3 inhibitors in 32D cells with FLT3 mutations

	GI50, nM ± SD (fold change)				
	FF-10101	Gilteritinib	Quizartinib	Crenolanib	Midostaurin
FLT3-ITD	0.25±0.033 (1.0)	2.3±0.51 (1.0)	0.60±0.11 (1.0)	3.2±0.47 (1.0)	5.7±1.6 (1.0)
FLT3-ITD+D698N	0.73±0.15 (2.9)	27±9.1 (12)	0.99±0.17 (1.7)	19±2.8 (5.9)	47±5.7 (8.2)
FLT3-ITD+N676T	0.73±0.27 (2.9)	9.4±4.7 (4.1)	6.6±2.2 (11)	19±4.8 (5.9)	83±25 (15)
FLT3-ITD+C695W	29±3.8 (120)	5.4±3.8 (2.3)	1.2±0.27 (2.0)	5.0±0.71 (1.6)	20±3.1 (3.5)

Mean GI50 ± SD values from 3 independent experiments are shown.

ASH 2019

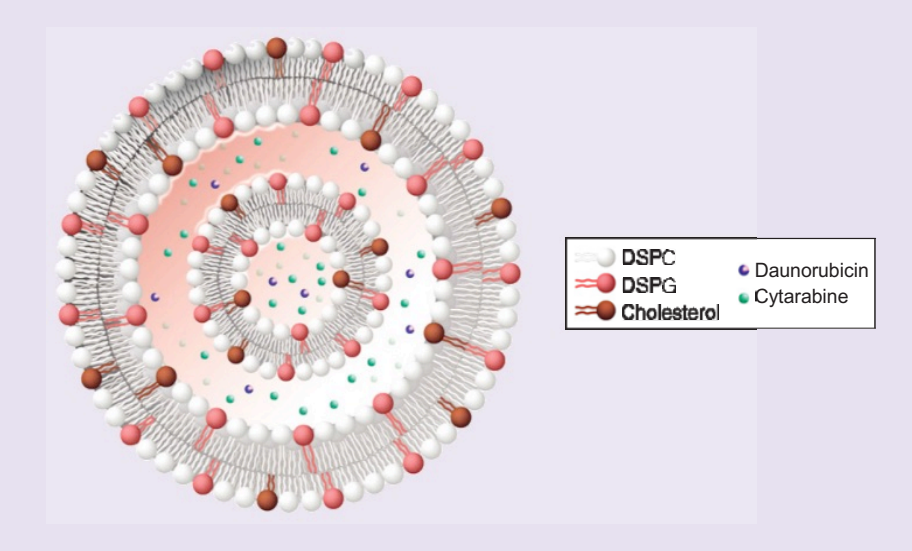
Current approach to newly diagnosed fit AML patients

		1st line therapy	Maintenance
Fit for intensive chemo	*CBF*	Intensive chemo + GO	
	FLT3^{mut}	Intensive chemo + Midostaurin	Midostaurin*
	tAML, sAML, AML MRC 	CPX-351	CC-486**
	Alternative non-targeted option	Intensive chemo ± GO	

Courtney D. DiNardo, Andrew H. Wei. Blood, 2020

DRUG DELIVERY: Advanced Nanoscale Liposomal Technology

CPX-351 has been specifically developed to control the delivery and distinct individual pharmacokinetics of daunorubicin and cytarabine to optimise efficacy



- **Facilitate intracellular delivery of anticancer drugs**
- **Prolong retention time of cytotoxic compounds Intracellularly.**
- **Minimize off-target effects**

First dual-drug advanced liposomal formulation

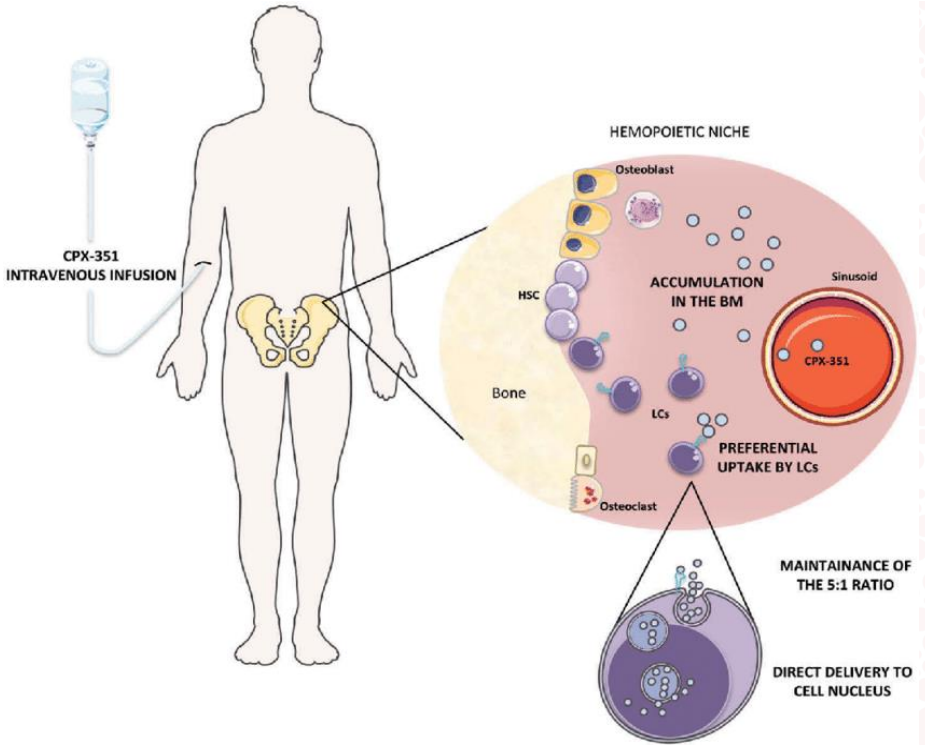
5:1 synergistic molar ratio of cytarabine to daunorubicin

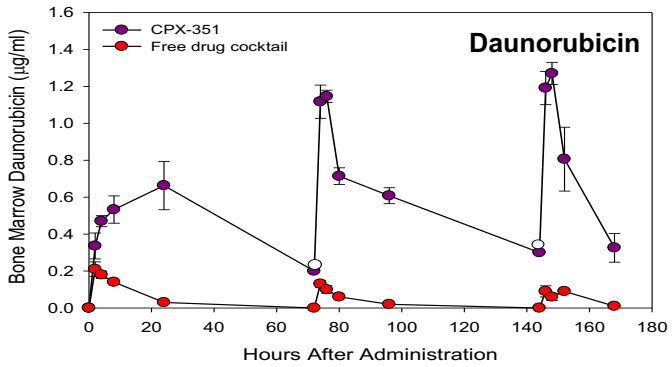
1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin

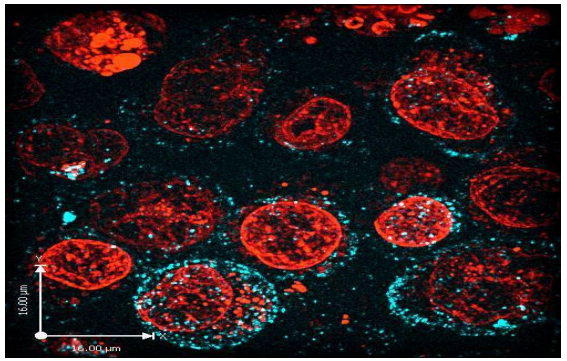
100 nm bilamellar liposomes

Mayer, et al., Mol Cancer Ther, 5:1854-1863, 2006
Tolcher AW and Mayer LD. Future Oncol 2018 ;14(13):1317-1332

CPX-351 Accumulates in Bone Marrow at High Concentrations and is Preferentially Taken Up by Leukemia Cells





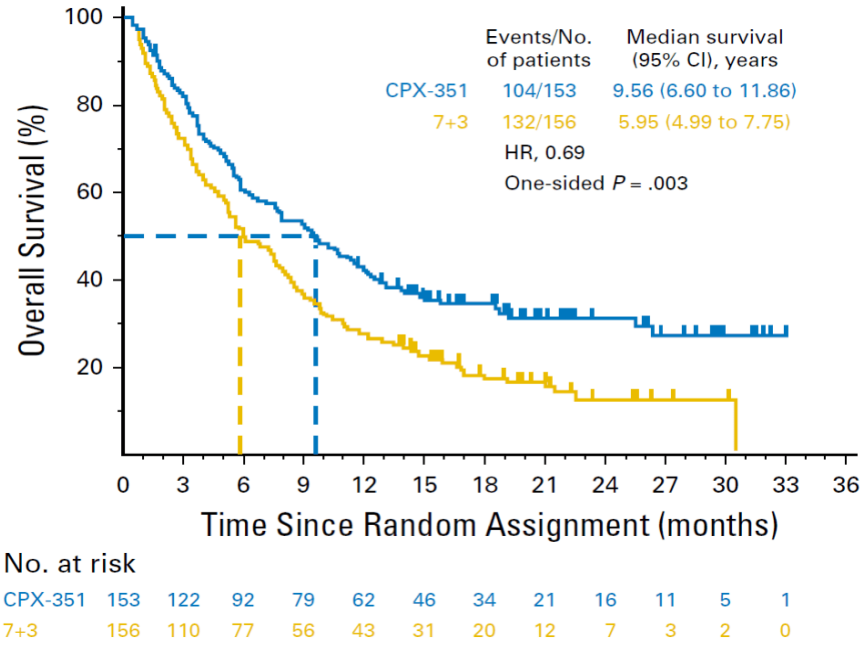


1. P. Tardi et al. Leukemia Research 33 (2009) 129–139
2. Lim, et. al., Leukemia Research 34 (2010) 1214–1223

CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia

CR 47.7% vs 33.3%

A

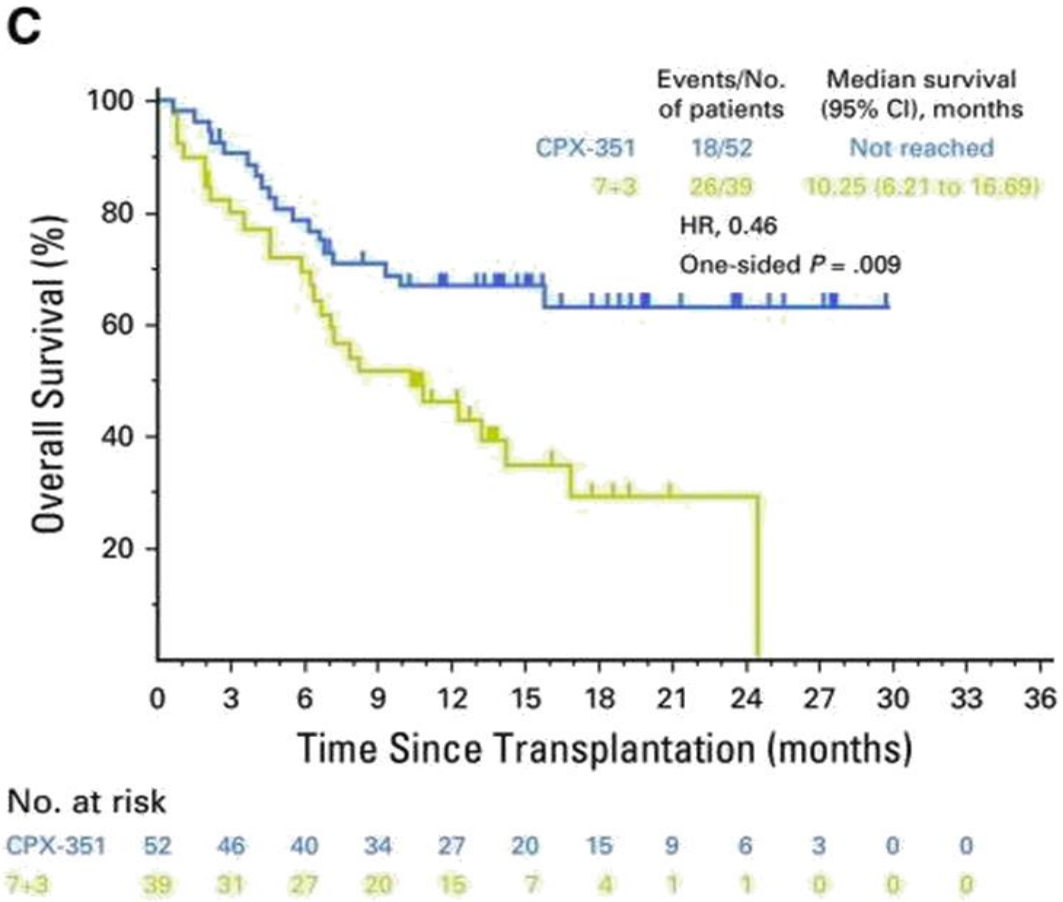


Increased CR rate, Overall and Disease Free Survival among:

-Therapy related Myeloid Neoplasm
- AML with MDS-related changes

The increase in OS in the whole study population is 20% when compared to standard “3+7”

Lancet JL et al. J Clin Oncol. 2018; 36: 2684–2692.



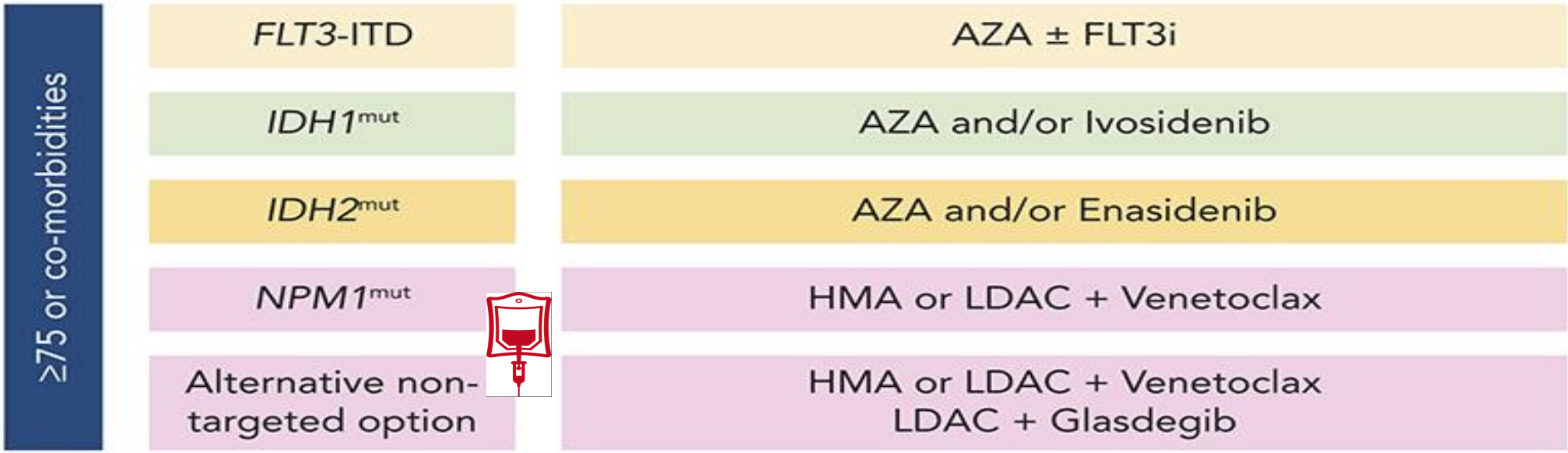
The improvement in survival is even more evident in patient undergoing to allogeneic stem cell transplantation.

Lancet JL et al. J Clin Oncol. 2018; 36: 2684–2692.

Take home messages (fit patients)

- A **molecular analysis** must be performed at diagnosis in order to assess FLT3 mutational status, before starting treatment
- **Midostaurin** + 3+7 is the standard of care for FLT3+ patients
- Randomized trials are comparing Midostaurin with **other FLT3 inhibitors** (Gilteritinib) in combination with standard chemotherapy
- **CPX-351** is approved for tAML and MRC-AML
- **GO** is approved in combination with standard of care (major benefit in good and intermediate AML risk)

Current approach to newly diagnosed unfit AML patients



Courtney D. DiNardo, Andrew H. Wei. Blood, 2020

Venetoclax+ HMAs: new standard of care for elderly or unfit patients

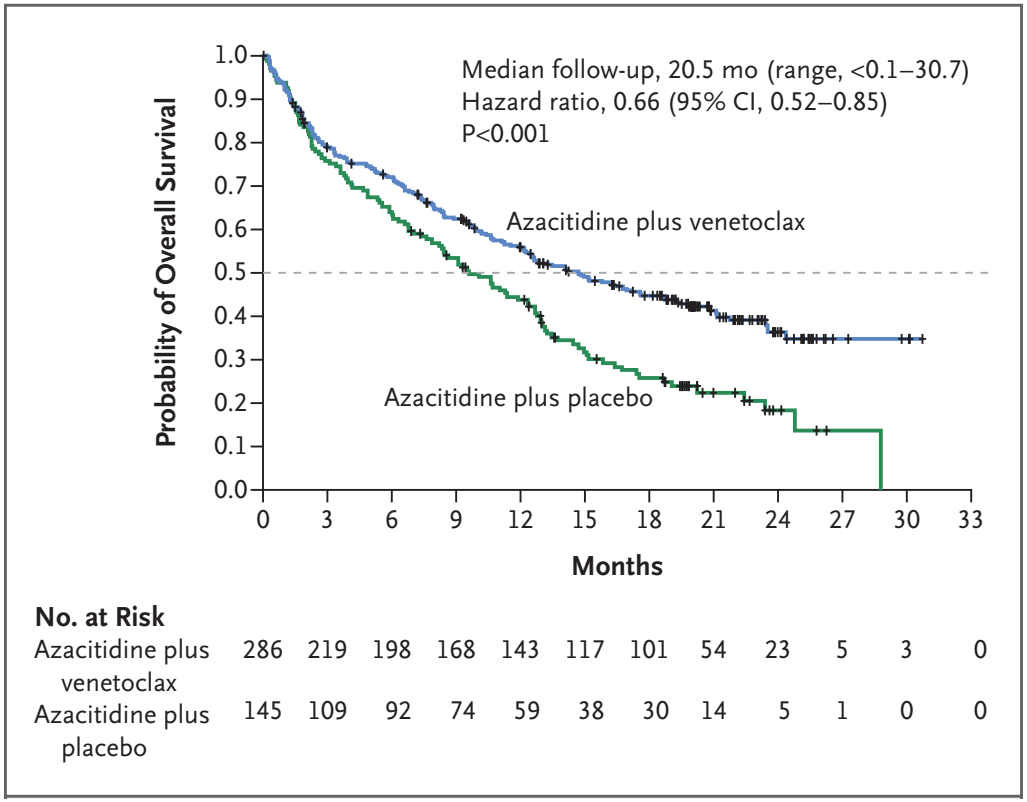


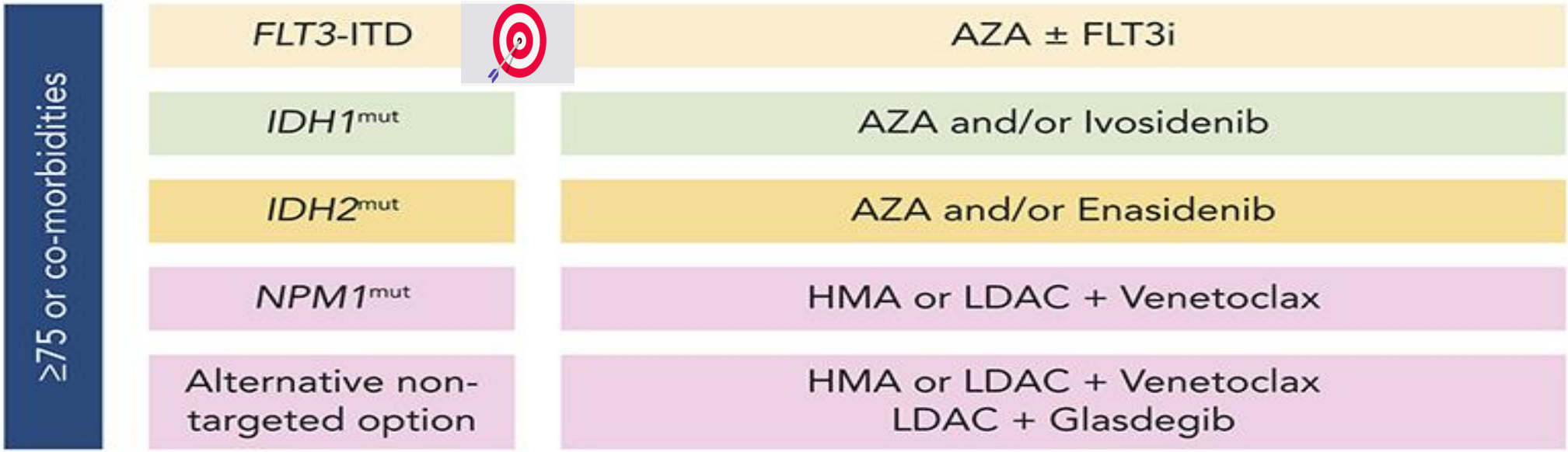
Table: Patient responses in treatment groups

	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)	<0.001
CR+CRi by initiation of cycle 2, % (95% CI)	43.4 (37.5-49.3)	7.6 (3.8-13.2)	<0.001
CR rate, % (95% CI)	36.7 (31.1-42.6)	17.9 (12.1-25.2)	<0.001
TI, % (95% CI)			
Red blood cells	59.8 (53.9-65.5)	35.2 (27.4-43.5)	<0.001
Platelets	68.5 (62.8-73.9)	49.7 (41.3-58.1)	<0.001
CR+CRi rates in molecular subgroups, % (95% CI)			
IDH1/2	75.4 (62.7-85.5)	10.7 (2.3-28.2)	<0.001
FLT3	72.4 (52.8-87.3)	36.4 (17.2-59.3)	0.021
NPM1	66.7 (46.0-83.5)	23.5 (6.8-49.9)	0.012
TP53	55.3 (38.3-71.4)	0	<0.001
Event free survival, months (95% CI)	9.8 (8.4–11.8)	7.0 (5.6–9.5)	<0.001

AZA+VEN: Azacitidine+Venetoclax; AZA+PBO: Azacitidine+Placebo; CR: Complete remission; CRi: CR with incomplete marrow recovery; CRh: CR with partial hematologic recovery; TI: Transfusion independence (defined as ≥ 56 days with no RBC or platelet transfusion between first and last day of treatment)

DiNardo C et al, NEJM 2020

Current approach to newly diagnosed unfit AML patients



Courtney D. DiNardo, Andrew H. Wei. Blood, 2020

ASH 2018

2736 Multicenter, Open-Label, 3-Arm Study of Gilteritinib, Gilteritinib Plus Azacitidine, or Azacitidine Alone in Newly Diagnosed *FLT3* Mutated ($FLT3^{mut+}$) Acute Myeloid Leukemia (AML) Patients Ineligible for Intensive Induction Chemotherapy: Findings from the Safety Cohort

Program: Oral and Poster Abstracts
Session: 616. Acute Myeloid Leukemia: Novel Therapy, excluding Transplantation: Poster II
Hematology Disease Topics & Pathways:
Diseases, Leukemia, AML, Therapies, Non-Biological, Myeloid Malignancies, pharmacology

Sunday, December 2, 2018, 6:00 PM-8:00 PM
Hall GH (San Diego Convention Center)

Jordi Esteve, MD, PhD[1], Rik Schots[2], Teresa Bernal Del Castillo, MD, PhD[3*], Je-Hwan Lee, MD, PhD[4], Eunice S. Wang, MD[5], Shira Dinner, MD[6], Mark D. Minden, MD, PhD[7], Olga Salamero, MD[8*], Jorge Sierra, MD[9], Goichi Yoshimoto, MD, PhD[10*], Kamel Laribi, MD[11*], Janusz Halka, MD[12*], Pau Fernandez[13*], Shufang Liu[14*], Elizabeth Shima Rich, MD, PhD[14] and Erkut Bahceci, MD[14]*

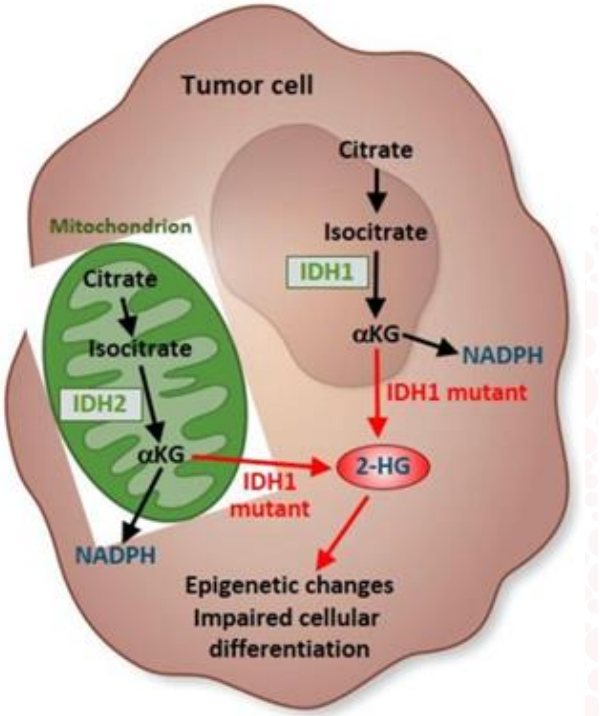
15 adult patients enrolled, median age 76 (65-86)
9 pts: 80 mg/daily; 6 pts 120 mg/daily
8/15 pts: treatment duration>6 months
Grade>=3 AEs in >=25% of the pts: febrile neutropenia (n=6); anemia (n=5), neutropenia (n=5),thrombocytopenia (n=4)
CCR 67% (4 CR + 6 CRi)

Current approach to newly diagnosed unfit AML patients

≥75 or co-morbidities	
FLT3-ITD	AZA ± FLT3i
IDH1^{mut}	AZA and/or Ivosidenib
IDH2^{mut}	AZA and/or Enasidenib
NPM1^{mut}	HMA or LDAC + Venetoclax
Alternative non-targeted option	HMA or LDAC + Venetoclax LDAC + Glasdegib

Courtney D. DiNardo, Andrew H. Wei. Blood, 2020

IDH1-2 AML



- Isocitrate dehydrogenase (IDH) is a critical enzyme of the citric acid cycle
- IDH mutations occur in a spectrum of solid and hematologic tumors
- IDH1 in AML are significantly associated with normal karyotype and *NPM1* mutation
- Orally administered, small molecule–targeted inhibitors of mutant IDH1 (**Ivosidenib**) and IDH2 (**Enasidenib**) target mutant IDH enzymes and block production of the 2-hydroxyglutarate oncometabolite.

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]

Median follow up: 16 months
12 month survival estimate: 82% (95% CI, 58.8% to 92.8%)

AEs>= Gr 3
Neutropenia 22%
Anemia 13%
Thrombocytopenia 13%

Differentiation syndrome 17%

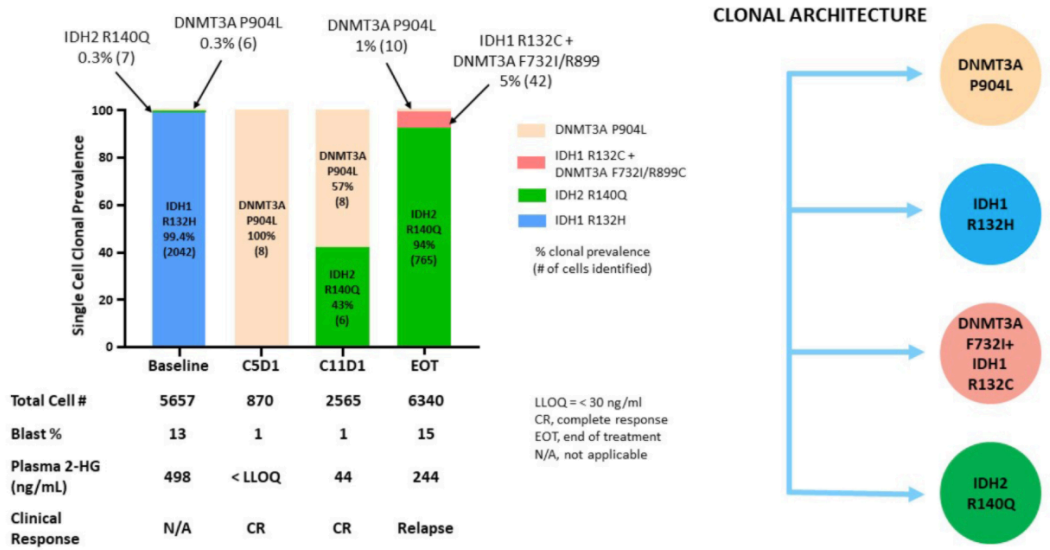
TABLE 3. Hematologic Response, Time to Response, and Response Duration (N = 23)

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)

DiNardo C et al, JCO 2020

1943 Molecular Characterization of Clinical Response and Relapse in Patients with *IDH1*-Mutant Newly Diagnosed Acute Myeloid Leukemia Treated with Ivosidenib and Azacitidine

Figure. Example of Clonal Evolution of a Baseline m*IDH2* Clone Expanding in a Pt Experiencing Relapse

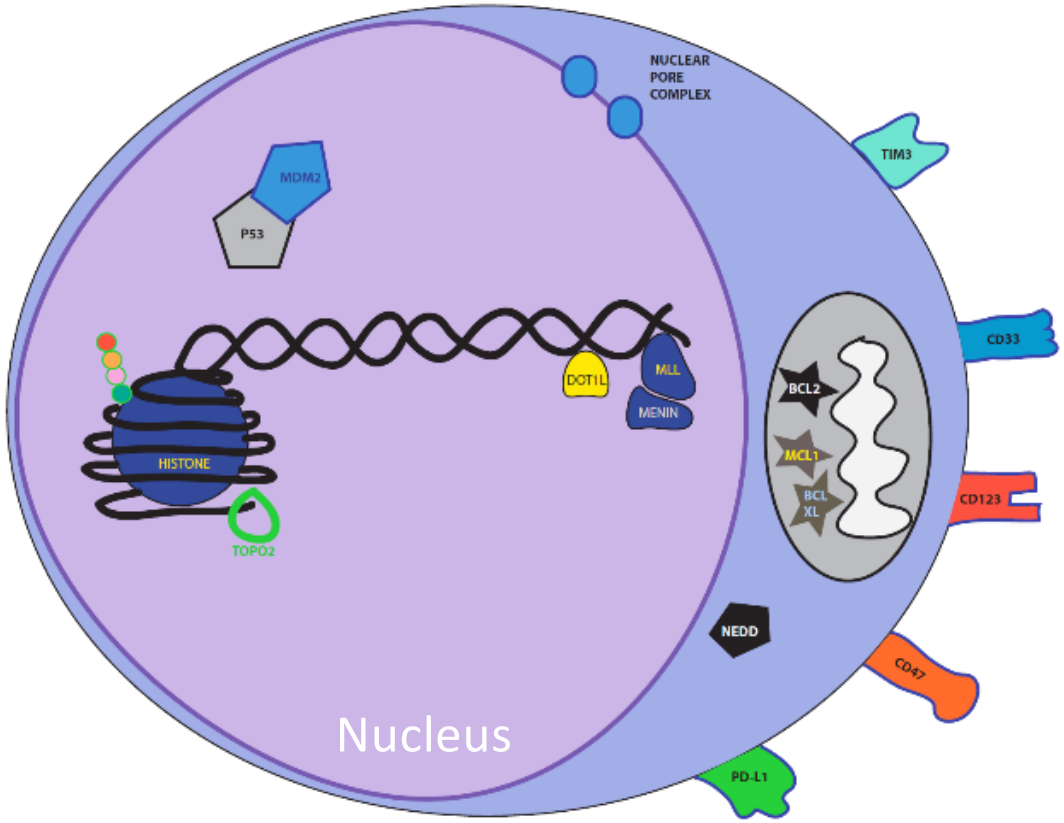


Daigle S et al, ASH 2020

Favourable	• t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* • ***NPM1*mut without *FLT3*-ITD or with *FLT3*-ITD^{low}** • Biallelic mutated *CEBPA*
Intermediate	• ***NPM1*mut and *FLT3*-ITD^{high}** • ***NPM1*wt without *FLT3*-ITD or with *FLT3*-ITD^{low} (without adverse-risk genetic lesions)** • t(9;21)(q21.3;q23.3); *MLLT3-KMT2A* • Cytogenetic abnormalities not classified as favourable 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 • ***NPM1*wt and *FLT3*-ITD^{high}** • Mutated *RUNX1* • Mutated ASXL1 • Mutated TP53

ELN AML classification 2017

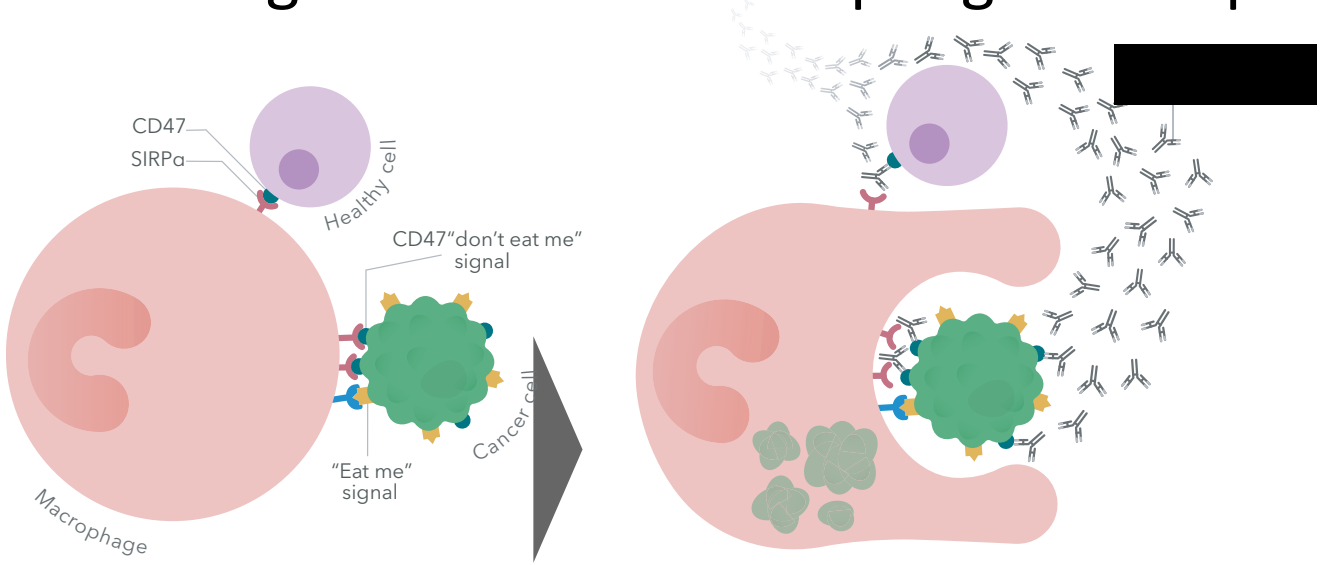
Extracellular Targets for Investigational AML Therapies



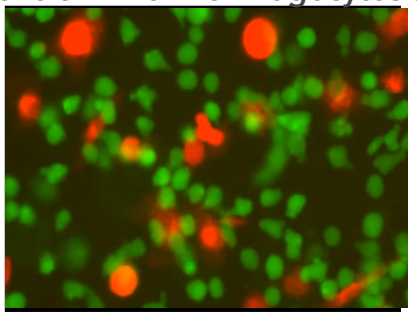
Agent	Modality
MBG453	Monoclonal Ab
AMV564	Bite
UCAR123	CAR-T
Magrolimab	Monoclonal Ab
Nivolumab	Monoclonal Ab

Adapted from Dillon

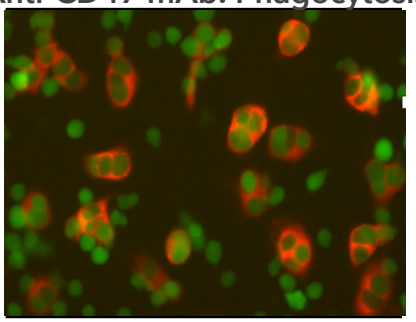
Magrolimab Is a Macrophage Checkpoint Inhibitor



Control mAb: No Phagocytosis



Anti-CD47 mAb: Phagocytosis



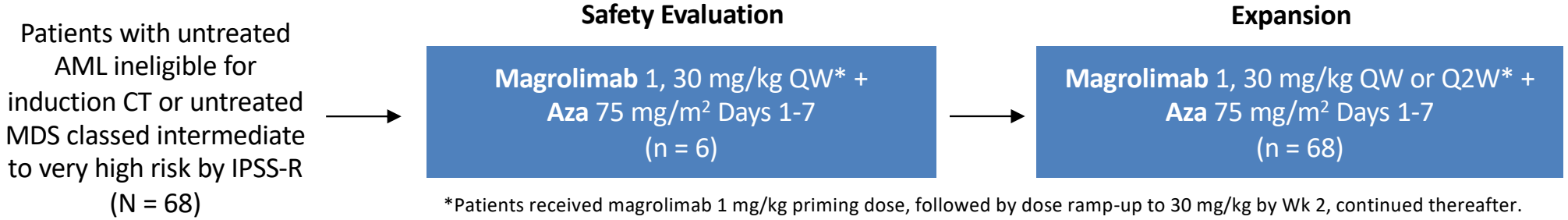
Macrophages Cancer cells

- Magrolimab is an IgG4 anti-CD47 monoclonal antibody that eliminates tumor cells through macrophage phagocytosis
- Magrolimab is being investigated in multiple cancers with >500 patients dosed

Daver. EHA 2020. Abstr S144.

Magrolimab + Aza in Patients With MDS and AML: Study Design

- Multicenter, single-arm phase Ib study
  - Current analysis reports data from expansion phase



*Patients received magrolimab 1 mg/kg priming dose, followed by dose ramp-up to 30 mg/kg by Wk 2, continued thereafter.

- Primary endpoints: safety, efficacy
- Secondary endpoints: magrolimab PK, PD, immunogenicity
- Exploratory endpoints: CD47 receptor occupancy, immune activity markers, molecular profiling

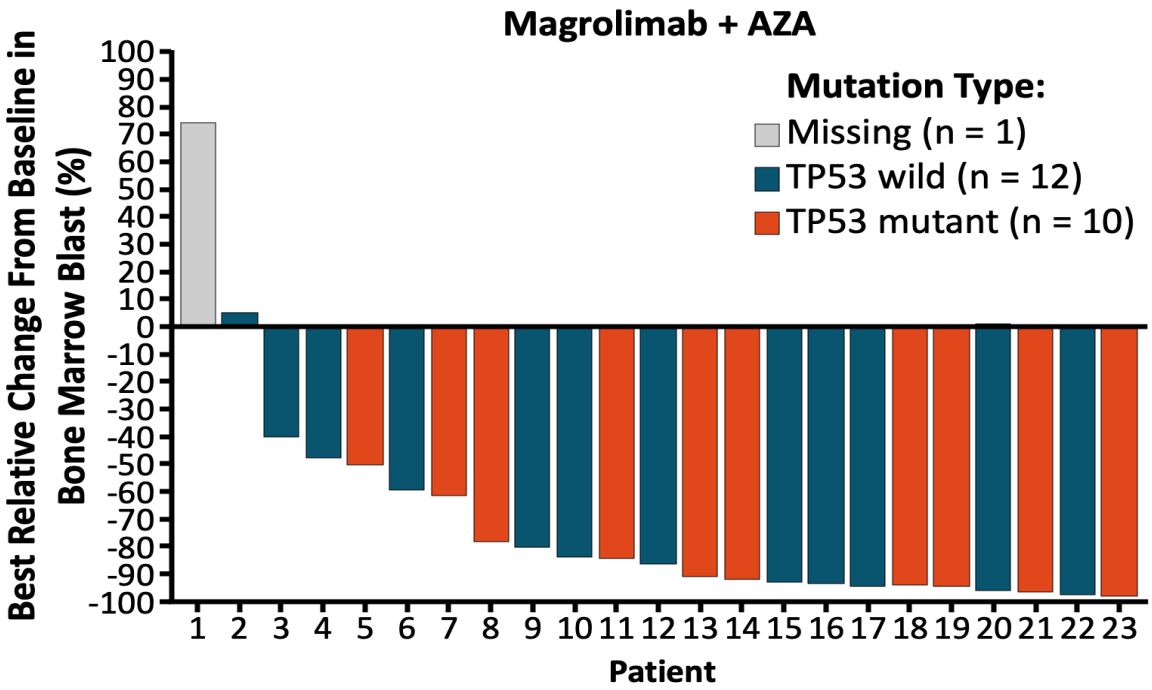
Daver. EHA 2020. Abstr S144.

AZA + MAGRO: Response

Best Overall Response, n (%)	1L AML (n = 25)
ORR	16 (64)
CR	10 (40)
CRi	4 (16)
PR	1 (4)
MLFS/marrow CR	1 (4)
SD	8 (32)
PD	1 (4)

Response per 2017 AML ELN criteria

Pts with ≥1 post-treatment response shown



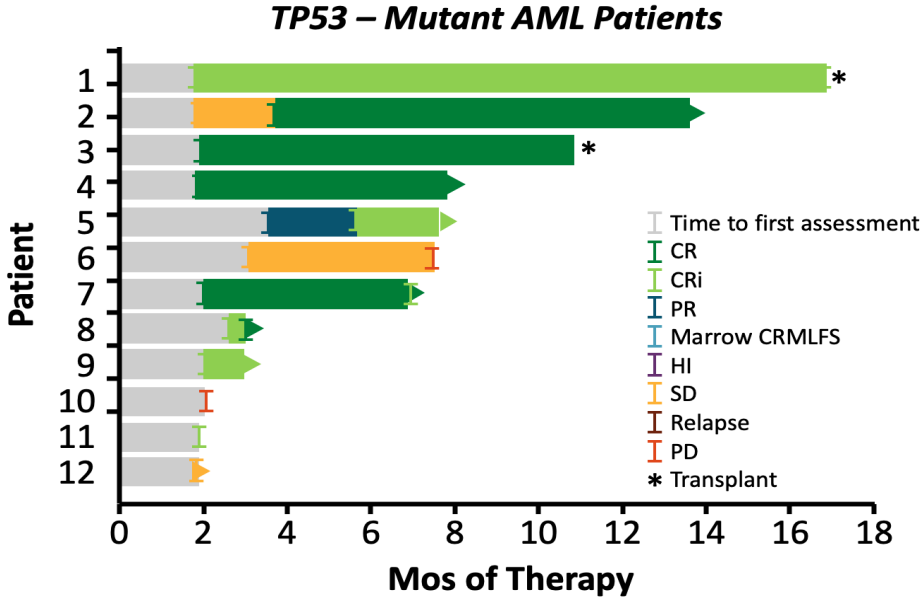
< 5% blasts imputed as 2.5%. Two patients not shown due to missing values.

Daver. EHA 2020. Abstr S144.

AZA + MAGRO: Response in Patients With TP53 Mutations

Outcome	AML *TP53* Mutant (n = 12)
ORR, n (%)	9 (75)
CR, n (%)	5 (42)
CRi/marrow CR, n (%)	4 (33)
Complete cytogenetic response, n/N (%)*	4/8 (50)
MRD negativity in responders, n/N (%)	4/9 (44)
Median DoR, mos	NR (0.03+ to 15.1+)
6-mo survival probability, %	91
Median follow-up, mos (range)	8 (1.9 to 16.9)

*Responding pt with abnormal cytogenetics at baseline

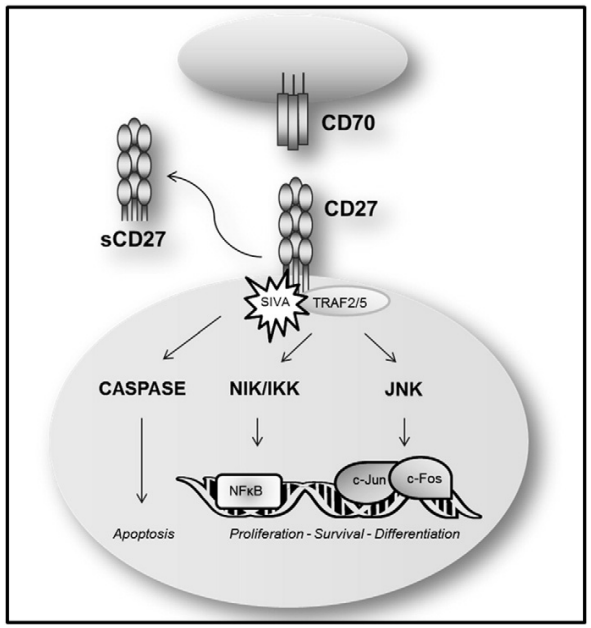


- High response rate with magrolimab + AZA; estimated 6-mo survival of 91%
- Median DoR and OS not yet reached

Daver. EHA 2020. Abstr S144.

CD70: An emerging target in cancer immunotherapy

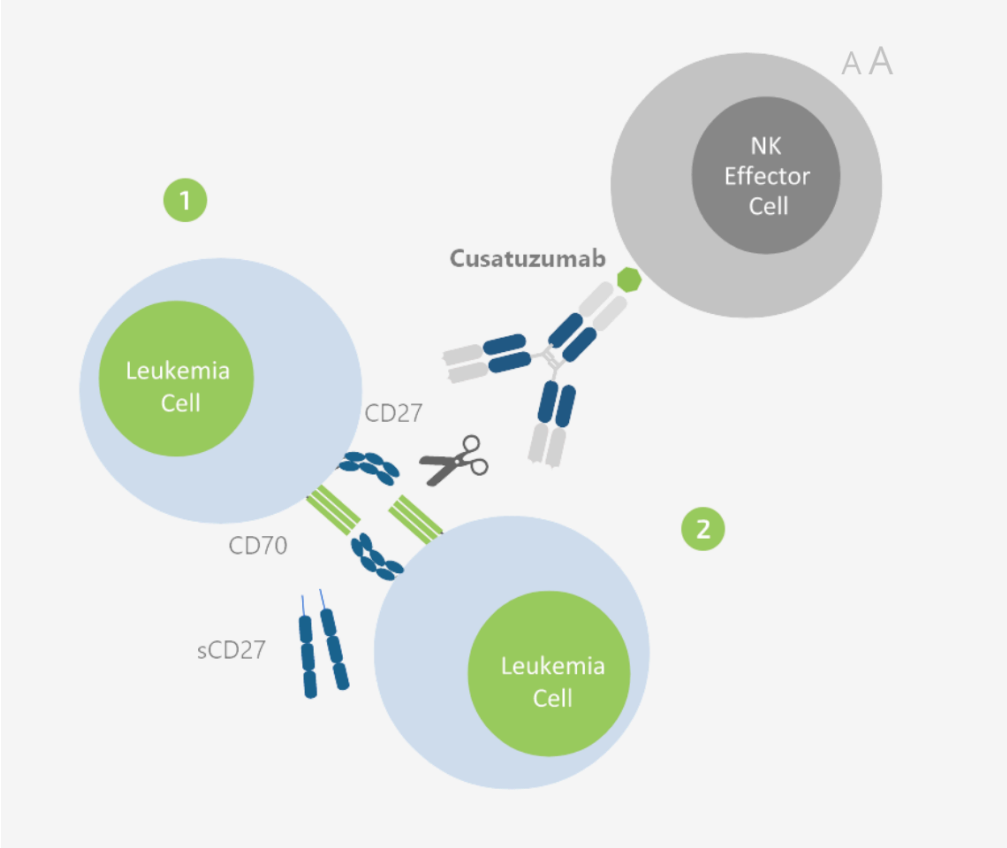
J. Jacobs [a,b,*], V. Deschoolmeester [a,b], K. Zwaenepoel [b], C. Rolfo [c,d], K. Silence [e], S. Rottey [f], F. Lardon [a], E. Smits [a,g,1], P. Pauwels [a,b,1]



Malignancy	Reference	IHC method	CD70 antibody	CD70 expression		Threshold for CD70 positivity
				$CD70^+$/total	Percentage $CD70^+$	
Hematological malignancies						
Non-Hodgkin lymphoma						
	McEarchern et al., 2008	IHC-FFPE	mAb SG-21.1 C1	71/119	60%	n.s.
	Tannir et al., 2014	IHC-FFPE000000	n.s.	82/107	77%	n.s.
Diffuse large B cell lymphoma	Lens et al., 1999	IHC-Fr	mAb 2F2	15/21	71%	20%
	Adam et al., 2006	IHC-Fr	mAb HNE5.1	4/6	67%	n.s.
Follicular lymphoma	Lens et al., 1999	IHC-Fr	mAb 2F2	6/18	33%	20%
	Adam et al., 2006	IHC-Fr	mAb HNE5.1	0/8	0%	n.s.
Mantle cell lymphoma	Lens et al., 1999	IHC-Fr	mAb 2F2	1/4	25%	20%
Burkitt lymphoma	Lens et al., 1999	IHC-Fr	mAb 2F2	1/4	25%	20%
CAEBV associated T cell lymphoma	Shaffer et al., 2012	IHC-FFPE	n.s.	1/1	100%	n.s.
Hodgkin lymphoma						
	Gruss & Kadin, 1996	IHC-?	n.s.	n.s.	96%	n.s.
	McEarchern et al., 2008	IHC-FFPE	mAb SG-21.1 C1	23/24	97%	n.s.
Leukemia						
B-cell chronic lymphocytic leukemia	Lens et al., 1999	IHC-Fr	mAb 2F2	3/6	50%	20%
	Adam et al., 2006	IHC-Fr	mAb HNE5.1	0/2	0%	n.s.
Multiple myeloma						
	McEarchern et al., 2008	IHC-FFPE	mAb SG-21.1 C1	9/22	41%	n.s.

J. Jacobs et al. / Pharmacology & Therapeutics 155 (2015) 1–10

Cusatuzumab: anti CD70 antibody



Proposed Mechanism Of Action

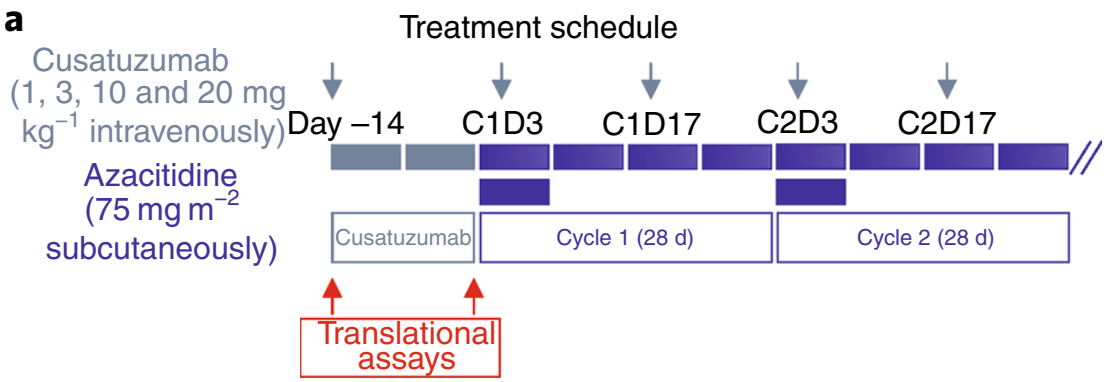
1. Blocking CD70-CD27 signaling, which leads to myeloid differentiation and stops proliferation of leukemic stem cells; and blocking release of soluble CD27, which is generated by CD70-CD27 ligation

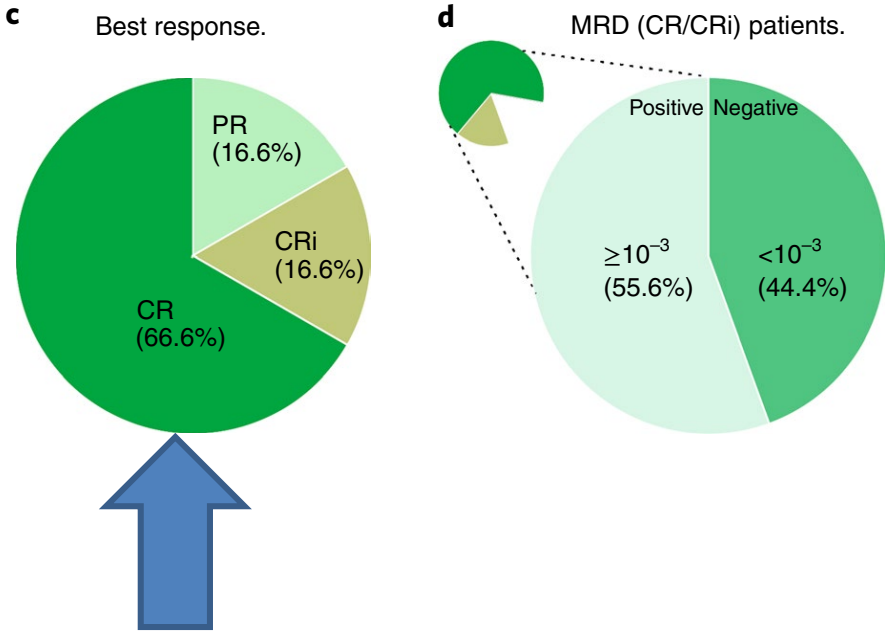
2. Killing cells via Fc-dependent complement dependent cytotoxicity and enhanced antibody-dependent cellular cytotoxicity (ADCC)

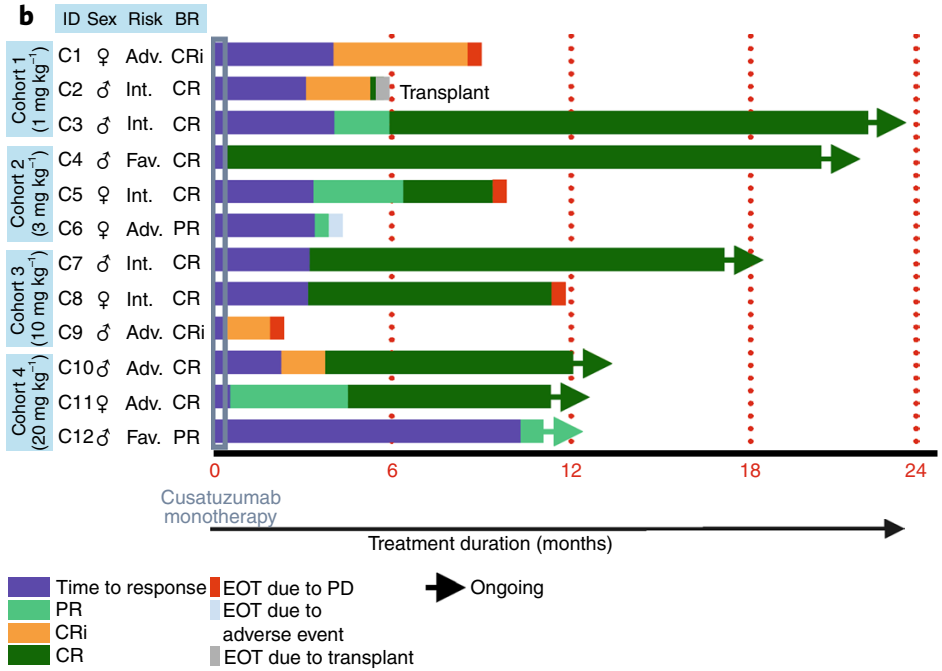
Targeting CD70 with cusatuzumab eliminates acute myeloid leukemia stem cells in patients treated with hypomethylating agents

nature medicine

Carsten Riether[1,2]✉, Thomas Pabst[1], Sabine Höpner[1,2], Ulrike Bacher[3], Magdalena Hinterbrandner[1,2,4], Yara Banz[5], Rouven Müller[6], Markus G. Manz[6], Walid H. Gharib[7], David Francisco[7], Remy Bruggmann[7], Luc van Rompaey[8], Mahan Moshir[8], Tim Delahaye[8], Domenica Gandini[8], Ellen Erzeel[8], Anna Hultberg[8], Samson Fung[8,9], Hans de Haard[8], Nicolas Leupin[8] and Adrian F. Ochsenbein[1,2]✉







Riether C. et al, Nature Medicine 2020

Near future: BCL2 + TKI ± HMA Combinations

- Gilteritinib + venetoclax[1]
  - Multiple US centers, phase 1 dose escalation; 52 patients
- Quizartinib + venetoclax[2]
  - MDACC, phase 1b/2; 32 patients
  - MRD endpoint - change in FLT-ITD allelic burden
- Quizartinib + venetoclax + decitabine[3]
  - MDACC, Phase 1/2; 52 patients
- Gilteritinib + venetoclax + azacytidine[4]
  - MDACC, phase 1/2; 42 patients

1. NCT03625505. 2. NCT03735875. 3. NCT03661307. 4. NCT04140487.

Thank you!

Prof M. Cavo

Antonio Curti
Stefania Paolini
Chiara Sartor
Jacopo Nanni
Sarah Parisi
Giovanni Marconi
Gianluca Cristiano

Francesca Bonifazi
Mario Arpinati

Emanuela Ottaviani
Valentina Robustelli
Carolina Terragna
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