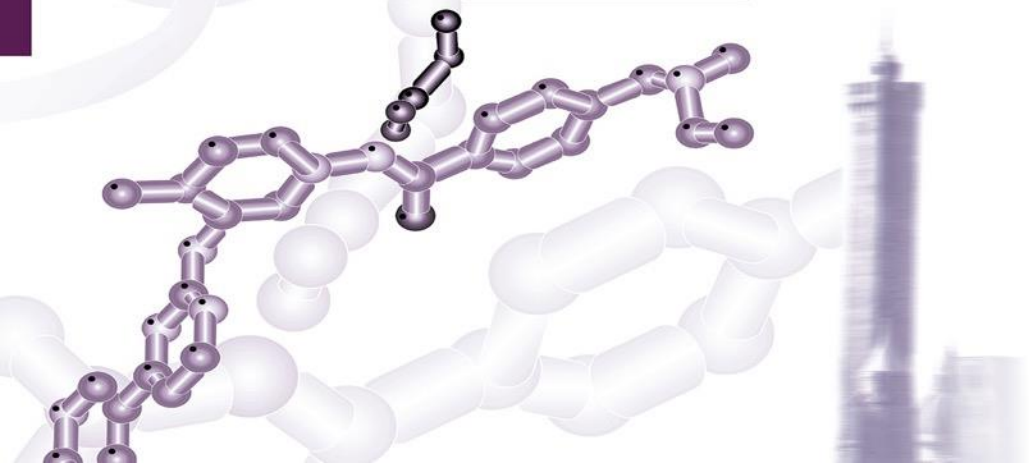
ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI MEDICINA SPECIALISTICA, DIAGNOSTICA E SPERIMENTALE

POLICLINICO DI SANT'ORSOLA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna



New Drugs in Hematology

President: Pier Luigi Zinzani
Co-President: Michele Cavo

Bologna,
Royal Hotel Carlton
May 18-20, 2022

FLT3 inhibitors for AML

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University of Pennsylvania

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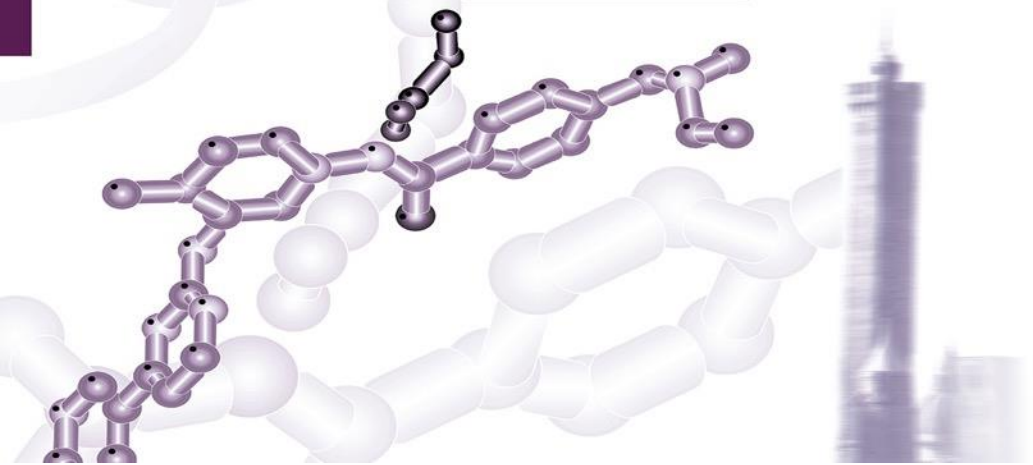

New Drugs in Hematology

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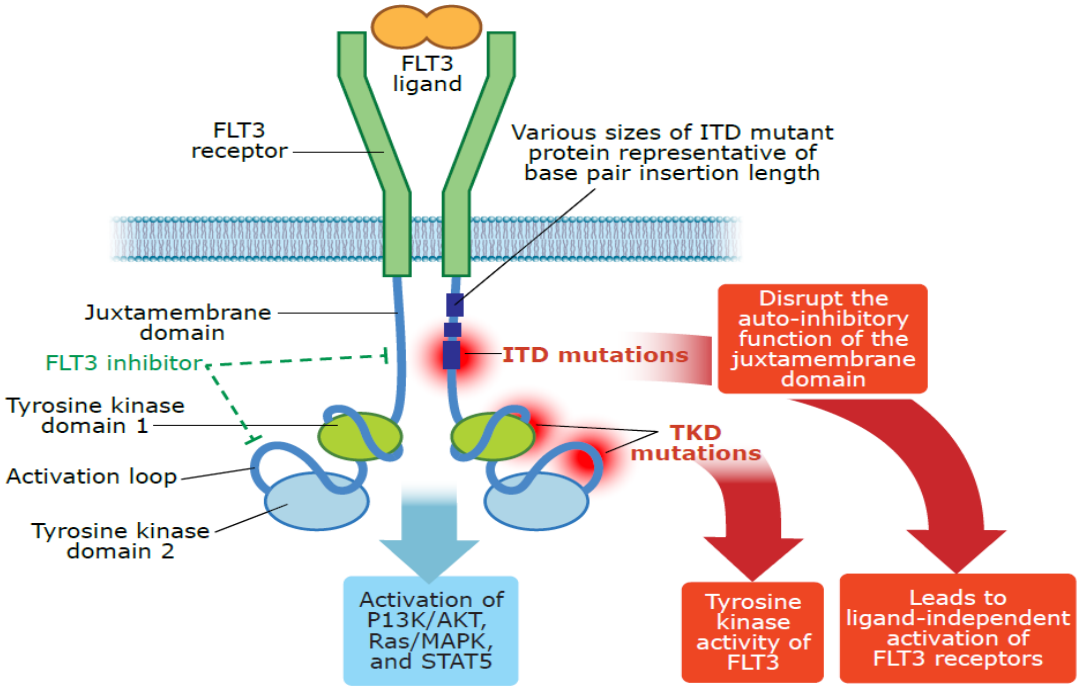
Disclosures of Alexander Perl

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie	x		x			x	
Actinium	x					x	
Astellas	x		x			x	
BerGenBio						x	
BMS						x	
Daiichi Sankyo	x		x			x	
Forma			x				
FujiFilm	x						
Genentech						x	
Immunogen						x	
LLS/Beat AML							DSMC
Syndax	x					x	

https://commons.wikimedia.org/w/index.php?curid=63857561
https://www.lambocars.com/

Mutated FLT3: the target



Incidence

- *FLT3*-ITD 20-25%
- *FLT3*-TKD 5-10%

Clinical features

- Leukocytosis
- High marrow blast percent
- Proliferative disease

Genetic associations

- Diploid karyotype
- *NPM1* mutation
- t(6;9)
- t(15;17)

Frequently sub-clonal

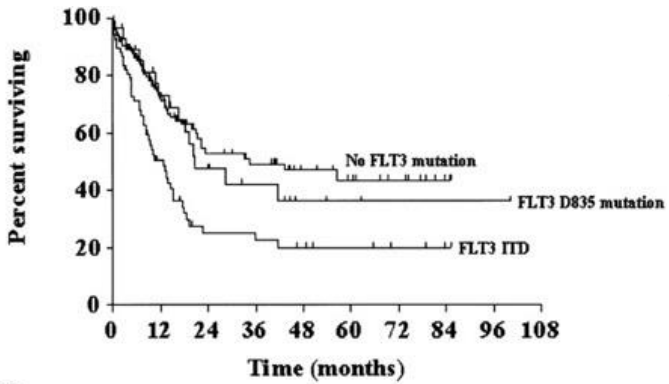
- gained at relapse/progression
- Sometimes lost at relapse/progression

ITD= internal tandem duplication, first described in 1996
TKD= tyrosine kinase domain, first described in 2001

figure courtesy of Ashkan Emadi

Targeting FLT3: a history

Untreated AML, age <60 y

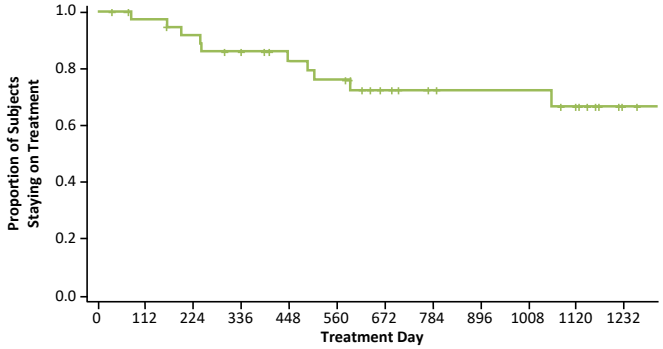


Number at risk

No FLT3 mutation	125	67	31	26	16	12	8	3	0
FLT3 D835 mutation	28	18	11	7	3	2	1	1	1
FLT3 ITD	67	25	10	9	7	5	3	1	0

20 years of therapy advancement

Untreated FLT3^{mut+} AML, All ages (median 59 years, range 23-77) 75% FLT3-ITD+

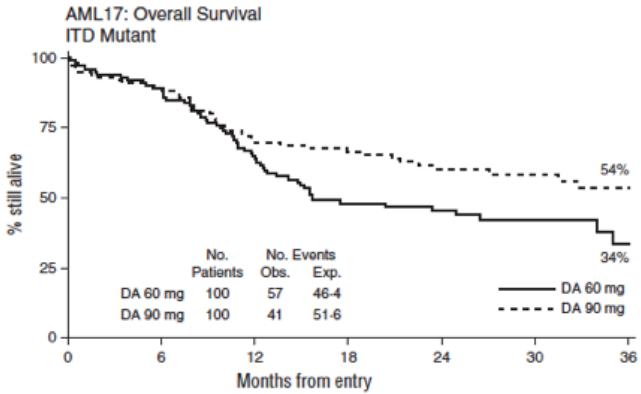


Number of subjects at risk 38 37 35 33 32 30 29 27 25 24 23 20 17 15 14 13 13 13 13 12 10 6 4 3

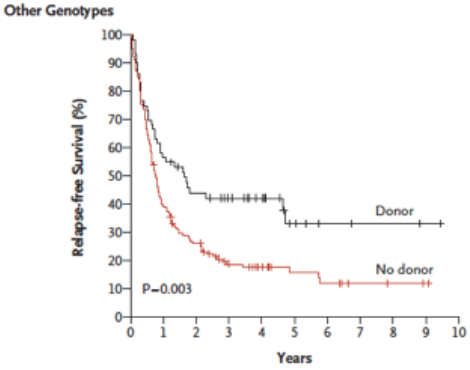
Fröhling S et al. *Blood*. 2002;100:4372-4380
Pratz KW, et al. ASH 2020, abstract #24

Improving cure of FLT3^{mut+} AML: what have we learned?

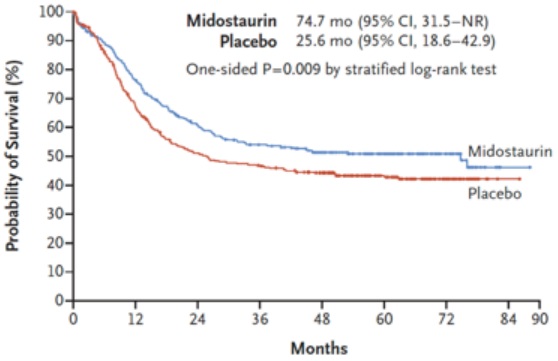
High dose daunorubicin



First remission AlloHSCT



FLT3 inhibitors



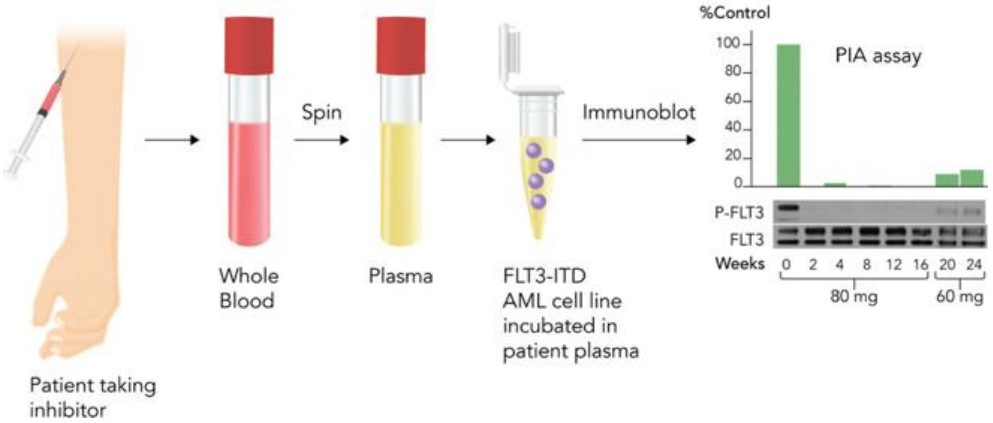
Burnett AK, et al. *Blood. 2016 Jul 21;128(3):449-52*
Schlenk RF, et al. N Engl J Med. 2008 May 1;358(18):1909-18.
Stone RM, et al. *N Engl J Med*. 2017 Aug 3;377(5):454-464

Potency and selectivity of FLT3 inhibitors

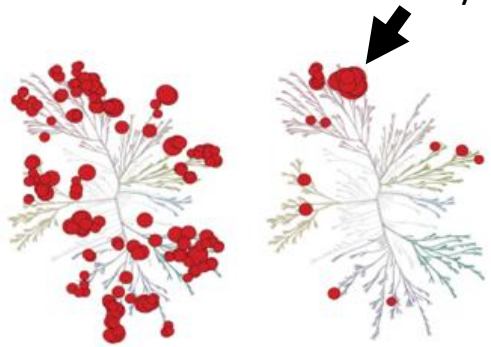
		IC_{50} (medium)	IC_{50} (plasma)	Single agent clinical activity	Kinase inhibition
1st gen	Lestaurtinib	2 nM	700 nM	-	**Type 1**
	Midostaurin	6 nM	~1000 nM	-	**Type 1**
	Sorafenib	3 nM	~265 nM	+/-	**Type 2**
2nd gen	Quizartinib	1 nM	18 nM	+	**Type 2**
	Crenolanib	2 nM	48 nM	+	**Type 1**
	Gilteritinib	3 nM	43 nM	+	**Type 1**

Type 2 inhibitors: resistance due to FLT3-D835
Type 1 inhibitors: active against FLT3-D835, limited potential for on-target resistance

The plasma inhibitory activity (PIA) assay for FLT3



Class 3 RTK's:
FLT3, KIT, CSF1R, PDGFRA/B

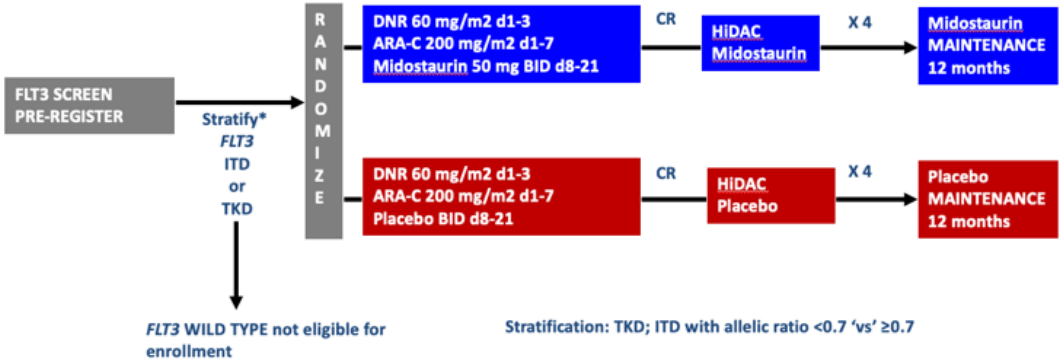


Midostaurin **Quizartinib**

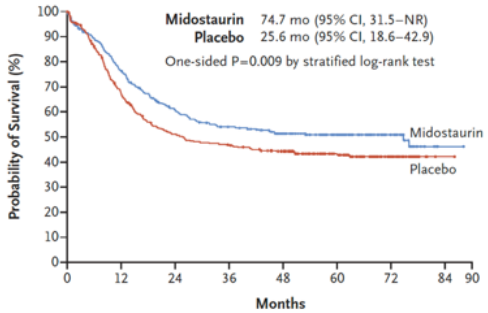
Pratz KW, et al. Blood 2010;115(7):1425-32
Zarrinkar PP, et al. Blood. 2009 Oct 1;114(14):2984-92
Galanis A, et al. Blood 2014 Jan 2;123(1):94-100
Levis M, Perl AE. Blood Adv. 2020 Mar 24;4(6):1178-1191
Smith CC, et al. Nature. 2012 Apr 15;485(7397):260-3
Tarver TC, et al. Blood Adv. 2020 Feb 11;4(3):514-524

Early use of FLT3 inhibition improves survival

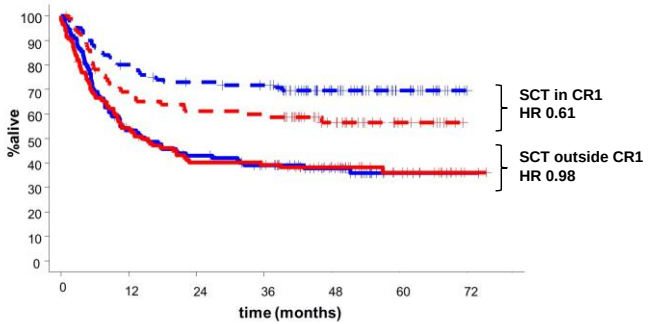
Newly diagnosed, FLT3^{mut+}, given with intensive induction, age <60 (midostaurin)



RATIFY



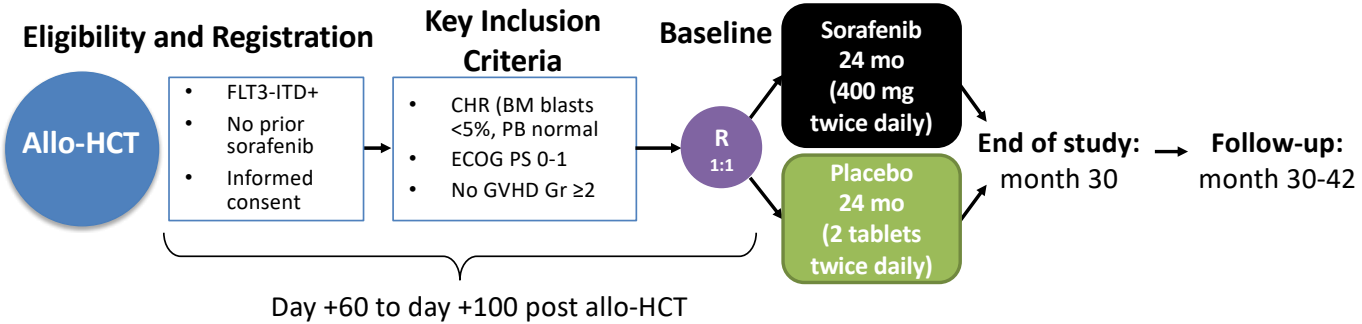
Transplanted patients (57% of study)



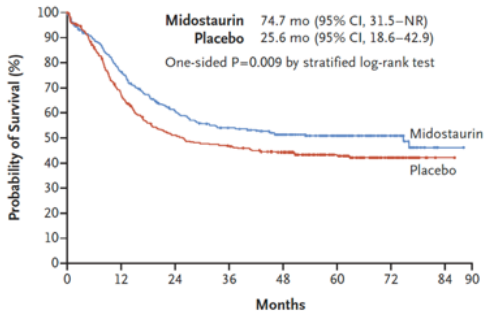
Stone RM, et al. *N Engl J Med*. 2017 Aug 3;377(5):454-464

FLT3 inhibition improves relapse-free survival after HSCT

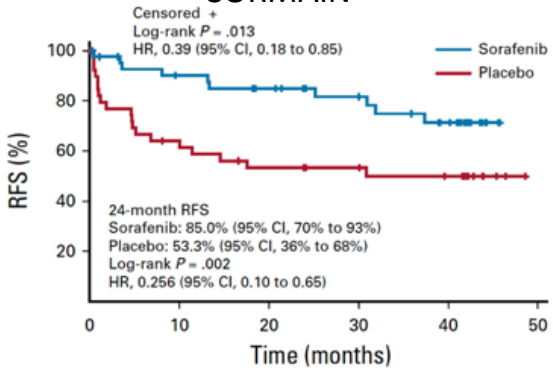
FLT3-ITD+ at diagnosis, in CR after alloHSCT



RATIFY



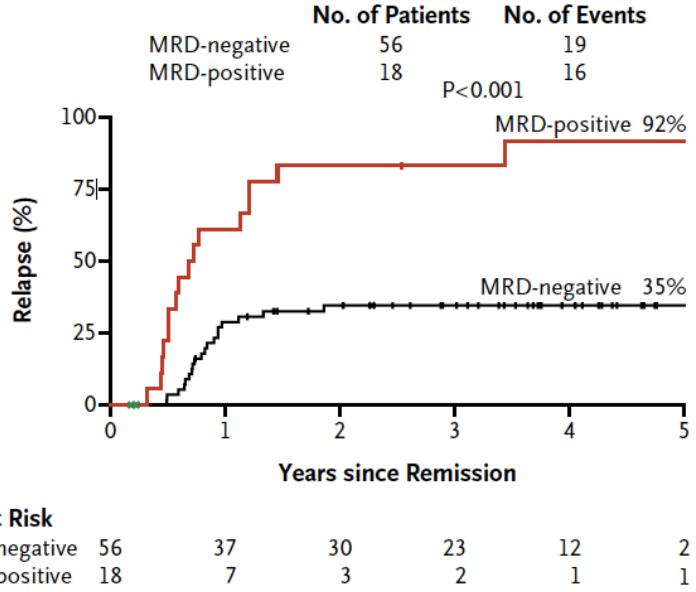
SORMAIN



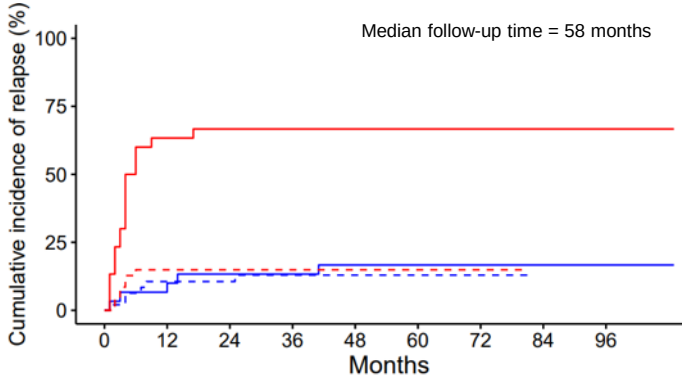
Stone RM, et al. *N Engl J Med*. 2017 Aug 3;377(5):454-464
Burchert A, et al. *J Clin Oncol.* 2020 Sep 10;38(26):2993-3002

Role of MRD in *FLT3*-ITD+ AML

FLT3-ITD+ patients: MRD status using peripheral blood RT-PCR for NPM1 mutation after two induction cycles



FLT3-ITD+ patients: MRD status Pre-HSCT in BM (n=69) or PB (n=9) using getITD (NGS for *FLT3*-ITD with 0.001% LLD)



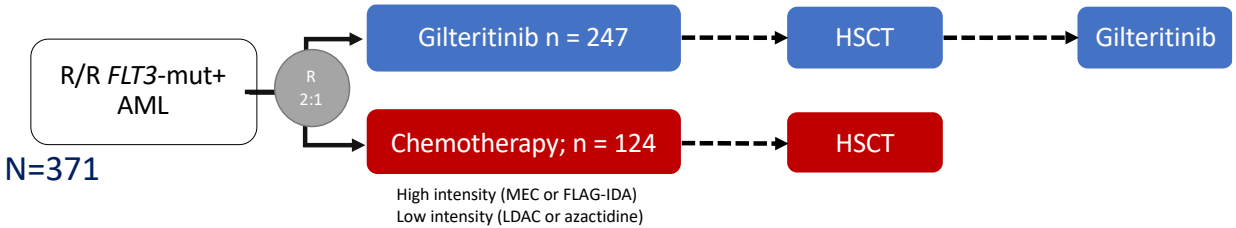
n= 78; 48 MRD(-) for *FLT3*-ITD
median follow up =58 months
83% *NPM1+*
14% had FLT3 inhibitor pre-HSCT

Ivey A, et al. *N Engl J Med.* 2016 Feb 4;374(5):422-33
Loo S, et al. ASH 2021 #2364
Blätte TJ, et a. *Leukemia*. 2019 Oct;33(10):2535-2539

Gilteritinib: ADMIRAL study

Key Eligibility Criteria:

- Refractory to initial induction or untreated first relapse after prior CRc
  - Prior frontline midostaurin or sorafenib allowed
- Central laboratory-confirmed *FLT3*-ITD or *FLT3*-TKD (D835/I836) by PCR
- ECOG performance status ≤2
- Normal liver, renal function
- QTcF ≤450 msec by central ECG reading

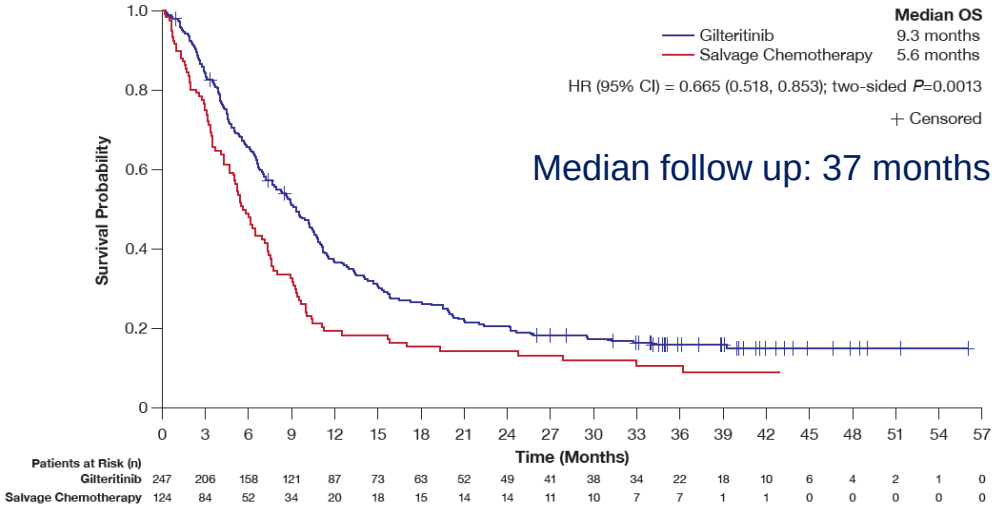


N=371

CR/CRh

34%

15.3%



Median follow up: 37 months

Gilteritinib Side effects:

- Cytopenias
- Abnormal LFTs
- GI irritation
- Elevated CPK
- Monitor QT
- Potential for differentiation syndrome
- Rare but serious: pancreatitis, PRES, cardiomyopathy, bowel injury

Perl AE, et al. N Engl J Med. 2019 Oct 31;381(18):1728-1740

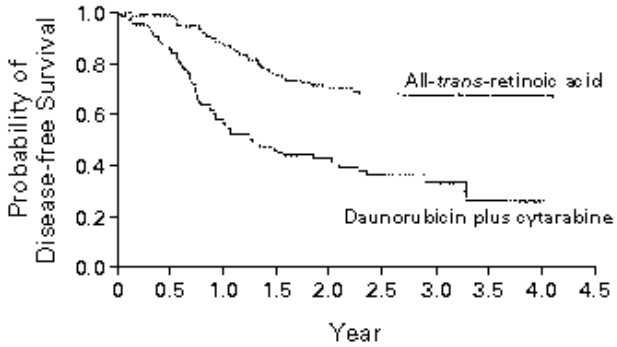
Perl AE, et al. *Blood* 2022 [in press]

The burning question in *FLT3*-ITD+ AML….

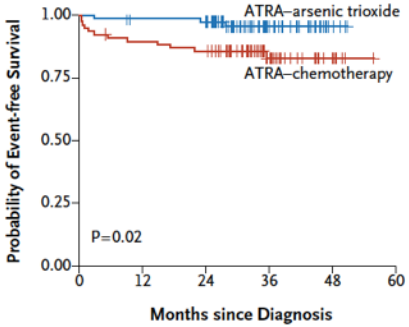
If a drug like midostaurin incrementally improves survival, will results with more potent, selective FLT3 inhibitors be transformative?

APL over the years

Tallman, NEJM 1997



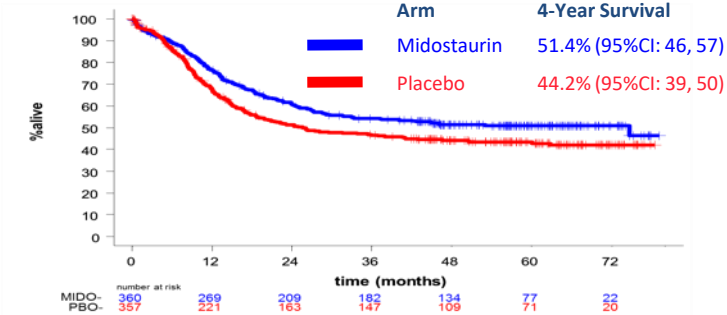
Lo Coco, NEJM 2013



Frontline quizartinib, crenolanib, or gilteritinib?

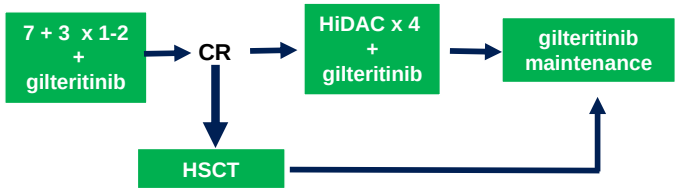
FLT3^{mut+} AML over the years

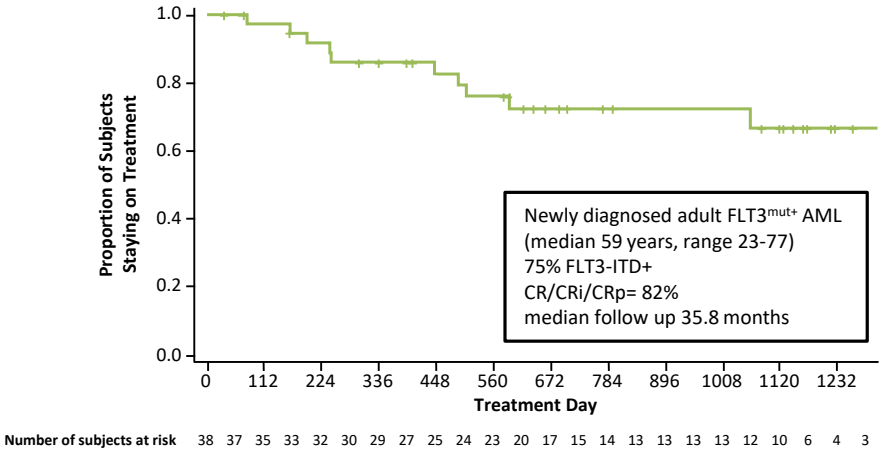
Stone (RATIFY) NEJM 2017

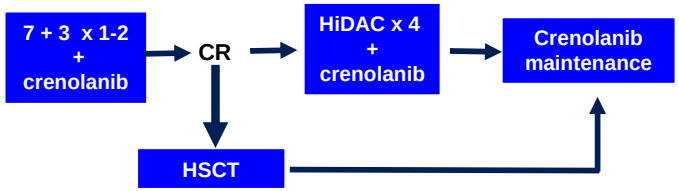


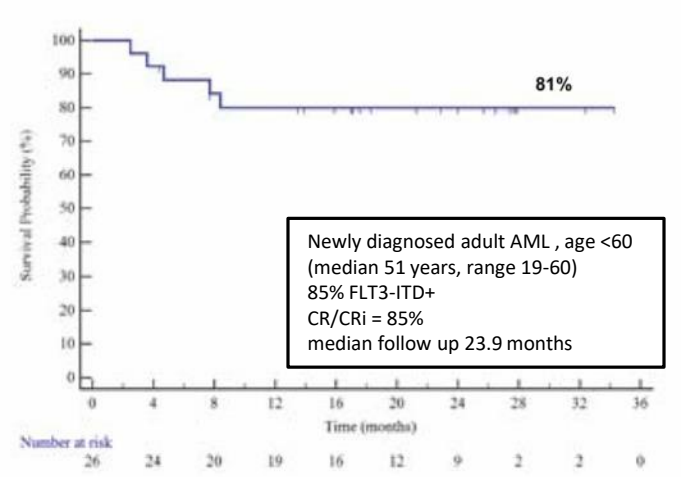
TBD

Combining 2nd Gen. FLT3 inhibitors with intensive chemotherapy



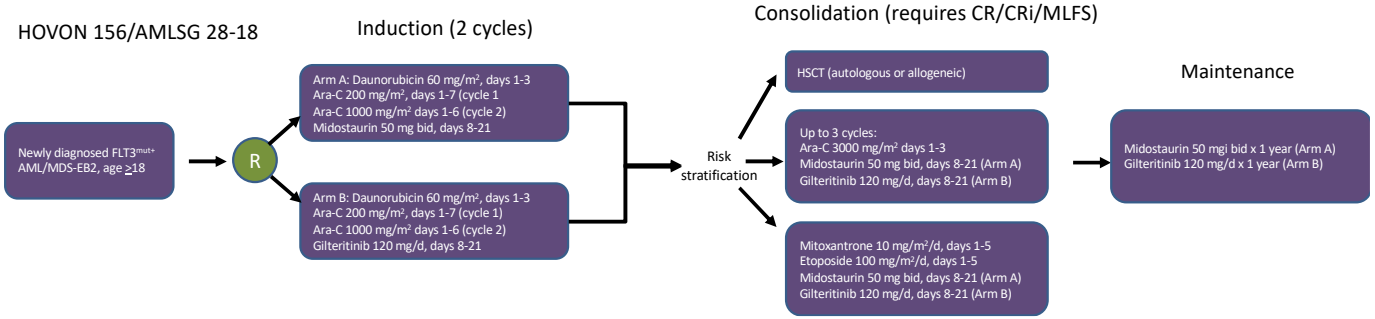




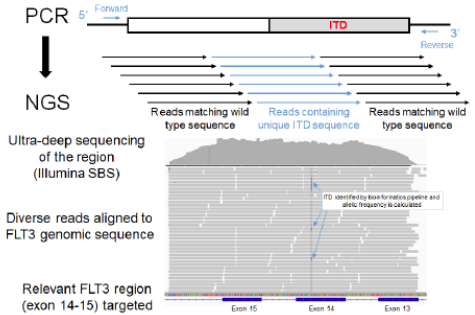


Pratz KW, et al. ASH 2020, abstract #24
Walter RB et al. EHA abstracts 2018

Frontline randomized trials of 2nd gen. FLT3 inhibitors + intensive chemo



MRD assay for FLT3-ITD burden



Trial	Phase (N)	Control	Maintenance	Primary endpoint	status	Clinicaltrials.gov
Quantum-FIRST (quizartinib)	3 (539)	Placebo	1-3 years	EFS→ OS	Complete: Quizartinib IMPROVED OS (data not yet public)	NCT02668653
ARO-021 (crenolanib)	3 (510)	Midostaurin	1 year	EFS	Ongoing (US)	NCT03258931
PrECOG 0905 (gilteritinib)	2 (170)	Midostaurin	None	$FLT3^{mut}$(-) CRc	Ongoing (US)	NCT03836209
HOVON 156/AMLSG 28-18 (gilteritinib)	3 (768)	Midostaurin	1 year	EFS	Ongoing (Europe)	NCT04027309

Levis MJ, et al. Blood. 2020 Jan 2;135(1):75-78.
https://hovon.nl/en/trials/ho156 (accessed 5/15/21)
Erba H, et al. EHA Annual Congress 2022, abstract S100

How does QuANTUM First differ from RATIFY?

RATIFY (midostaurin/placebo)

- multikinase inhibitor, limited single agent activity
- adults up to age 60
- *FLT3*-ITD or *FLT3*-TKD
- enrolled 2008-2011
- no maintenance post-HSCT
- no MRD data
- OS in each arm for *FLT3*-ITD+ patients was not reported

QuANTUM First (quizartinib/placebo)

- selective/potent FLT3 inhibitor, active as single agent
- adults up to age 75
- *FLT3*-ITD+ only
- enrolled 2016-2019
- included maintenance post-HSCT
- collected MRD data
- primary endpoint is OS in FLT3-ITD+

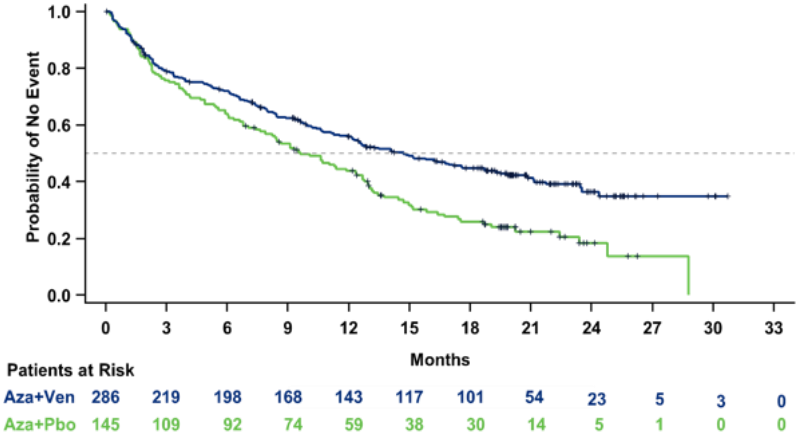

The Future
NEXT EXIT

The NEW ENGLAND JOURNAL of MEDICINE

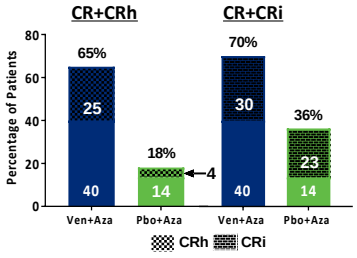
ESTABLISHED IN 1812 AUGUST 13, 2020 VOL. 383 NO. 7

Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

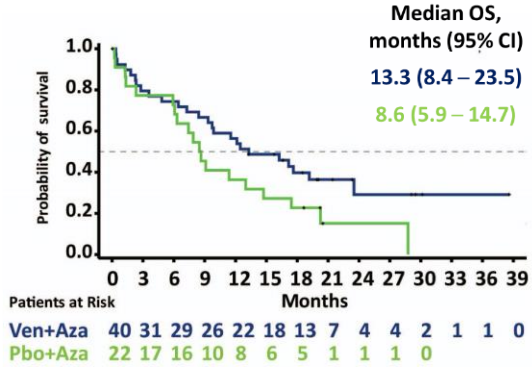
C.D. DiNardo, B.A. Jonas, V. Pullarkat, M.J. Thirman, J.S. Garcia, A.H. Wei, M. Konopleva, H. Döhner, A. Letai, P. Fenaux, E. Koller, V. Havelange, B. Leber, J. Esteve, J. Wang, V. Pejsa, R. Hájek, K. Porkka, Á. Illés, D. Lavie, R.M. Lemoli, K. Yamamoto, S.-S. Yoon, J.-H. Jang, S.-P. Yeh, M. Turgut,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



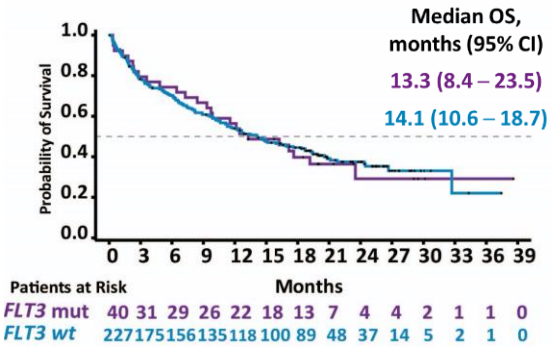
Ven+ AZA: Response and Overall survival in patients with *FLT3* mutation



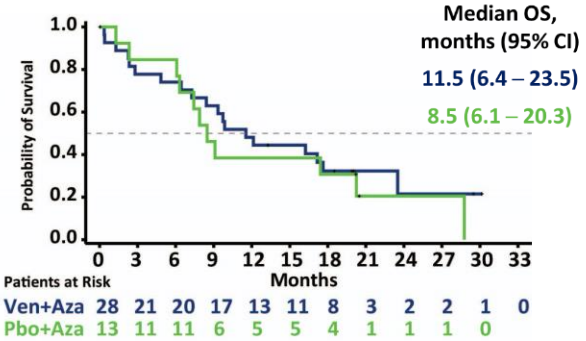
A. FLT3mut



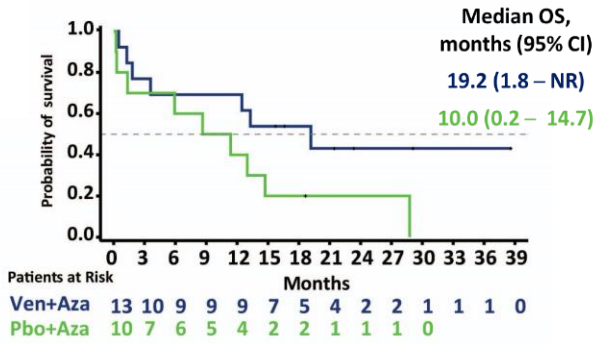
B. FLT3mut vs. wt in Ven+Aza



C. FLT3-ITD



D. FLT3-TKD



Konopleva M, et al. Clin Cancer Res 2022 [in press, epub]

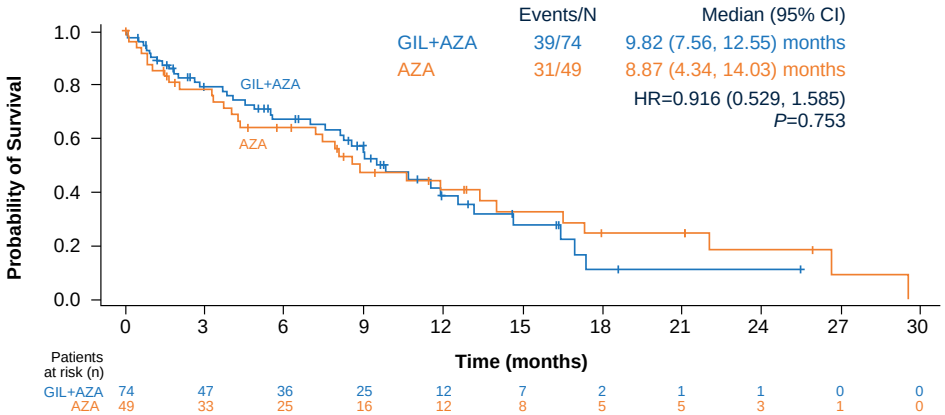
Phase 3: Gilteritinib + AZA vs. AZA alone (LACEWING) – Overall Survival

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

RANDOMIZED 2:1[a]

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

Primary endpoint: OS
Key secondary endpoint: EFS
Other secondary endpoints: Response, safety/ tolerability
Exploratory endpoint: PK

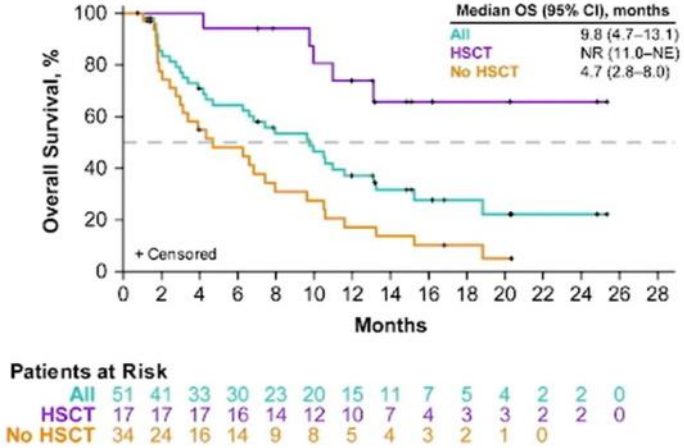


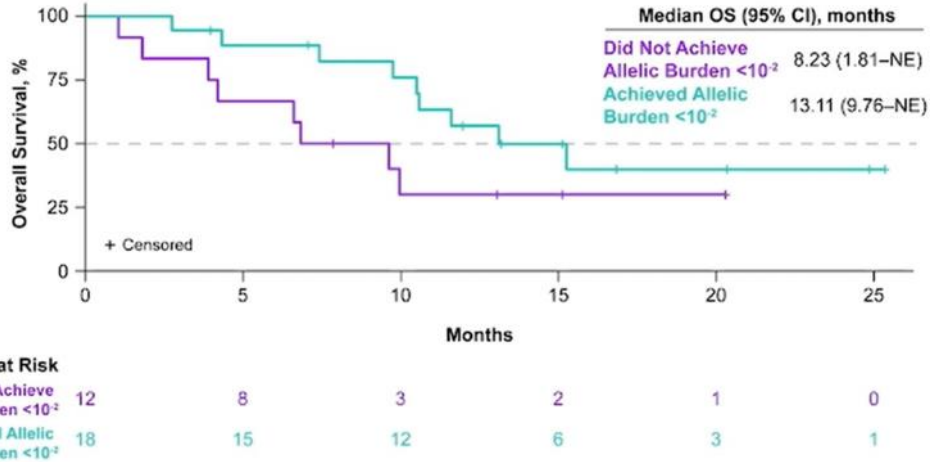
Median follow-up: 9.76 months for GIL+AZA and 17.97 months for AZA

- CAVEATS: open label, unblinded study
- higher CR/CRi/CRp rate for AZA/GILT (58%) than AZA (27%)
- AZA arm had shorter duration of study therapy and high frequency of subsequent FLT3 inhibitor use
- subgroup analysis suggests high *FLT3*-ITD:WT allelic ratio may benefit from AZA + gilteritinib

Phase 1b Study of Venetoclax + Gilteritinib in Patients With *FLT3*-Mutated R/R AML: Efficacy and Summary

OS by Transplant, Response Status, and for of mCRc Patients at RP2D Who Achieved *FLT3* Allelic Burden >10^{-2}

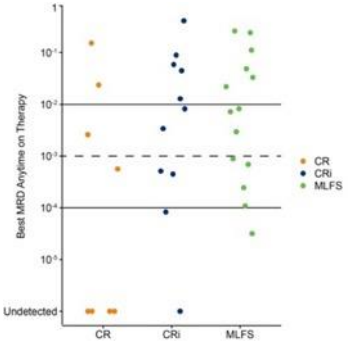




Median follow-up: 15.1 months (range, 0.8-25.3)

Best Response, n (%)	*FLT3*mut With Prior TKI (n=32)	*FLT3*-ITD (n=43)	All *FLT3*mut Patients (n=51)
mCRc	25 (78.1)	34 (79.1)	38 (74.5)
CR+CRp+CRi	10 (31.3)	17 (39.5)	19 (37.3)
MLFS	15 (46.9)	17 (39.5)	19 (37.3)

Lowest level of FLT3-ITD burden by NGS MRD assay

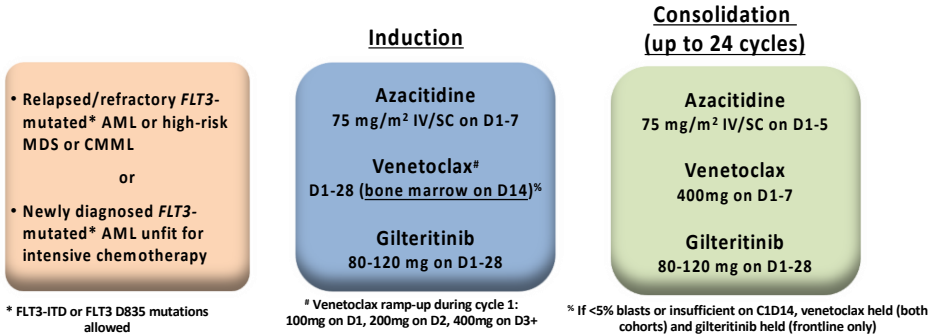


Daver N, Perl AE, et al. ASH 2021. Abstract 691.

What about triplets?!?

www.trippingovertriplets.com

Aza+Ven+Gilteritinib in FLT3-mutated AML



gilteritinib RP2D = 80 mg

Responses

Response, n (%)	Frontline N = 14	R/R N = 16
mCRc (CR/CRi/MLFS)	14 (100)	11 (69)
CR	13 (93)	3 (19)
CRi	0	2 (13)
MLFS	1 (7)	6 (37)
PR**	0	1 (6)
No response	0	4 (25)
Early death	0	0

Hematologic toxicity

Hematologic parameter	Frontline cohort		R/R cohort	
	Evaluable pts	Median [range]	Evaluable pts	Median [range]
ANC >500	n=14	38 [28-117 days]	n=6	46 [35-63 days]
ANC >1000	n=13	40 [32-53 days]	n=5	53 [46-77 days]
Platelets >50K	n=14	20 [16-84 days]	n=5	26 [13-77 days]
Platelets >100K	n=13	28 [18-43 days]	n=3	21 [17-82 days]

Short N, et al ASH 2021 #696

Conclusions

- The outcome of patients with FLT3^{mut+} AML has dramatically improved over the past 20 years
  - FLT3 targeted therapy is not yet standard for newly diagnosed *FLT3*$^{mut+}$ patients unift for intensive chemo

- Clinical development of FLT3 inhibitors has been a long journey
  - for R/R FLT3^{mut+} AML, single agent gilteritinib is currently the standard, but combinations are promising
  - for newly diagnosed *FLT3*$^{mut+}$ AML, randomized trials should identify the optimal TKI with intensive chemotherapy
  - multicenter randomized trials will clarify the role for venetoclax-based doublets or triplets in frontline or salvage settings—these have the potential to revolutionize therapeutic approach

- The natural history of *FLT3*$^{mut+}$ AML is changing through therapeutic advances
  - Hopefully, we will soon reduce frontline therapy intensity to develop more effective targeted approaches like APL