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Optimized Use of Targeted Therapeutics in AML

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Friday, July 21, 2023

Objectives

- Summarize FDA approved targeted agents for AML
- Review promising agents in the pipeline for AML
- Algorithm for treatment of AML

CPX-351
Midostaurin
G. O.
Enasidenib
Venetoclax
Glasdegib
Gilteritinib
Ivodisdenib
Onureg
Olutasidenib

Bone Marrow transplantation first employed

GO removed from market

1973 — 1977 — 2000 — 2010 — **2017** — **2022**

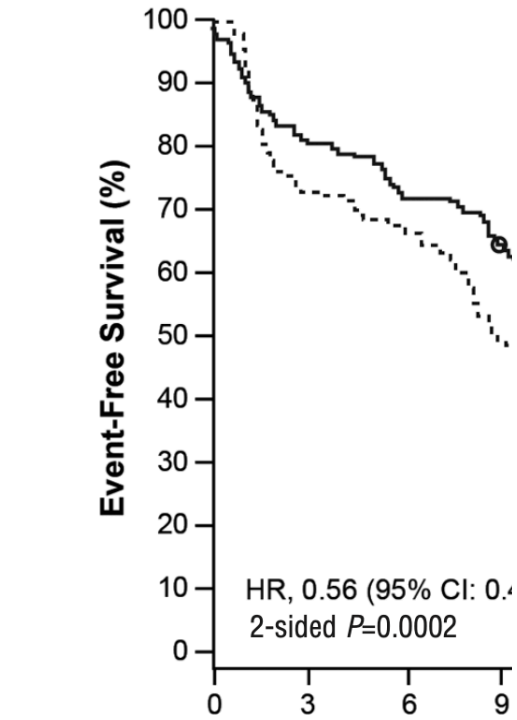
Cytarabine & Daunorubin (7&3 protocol for AML)

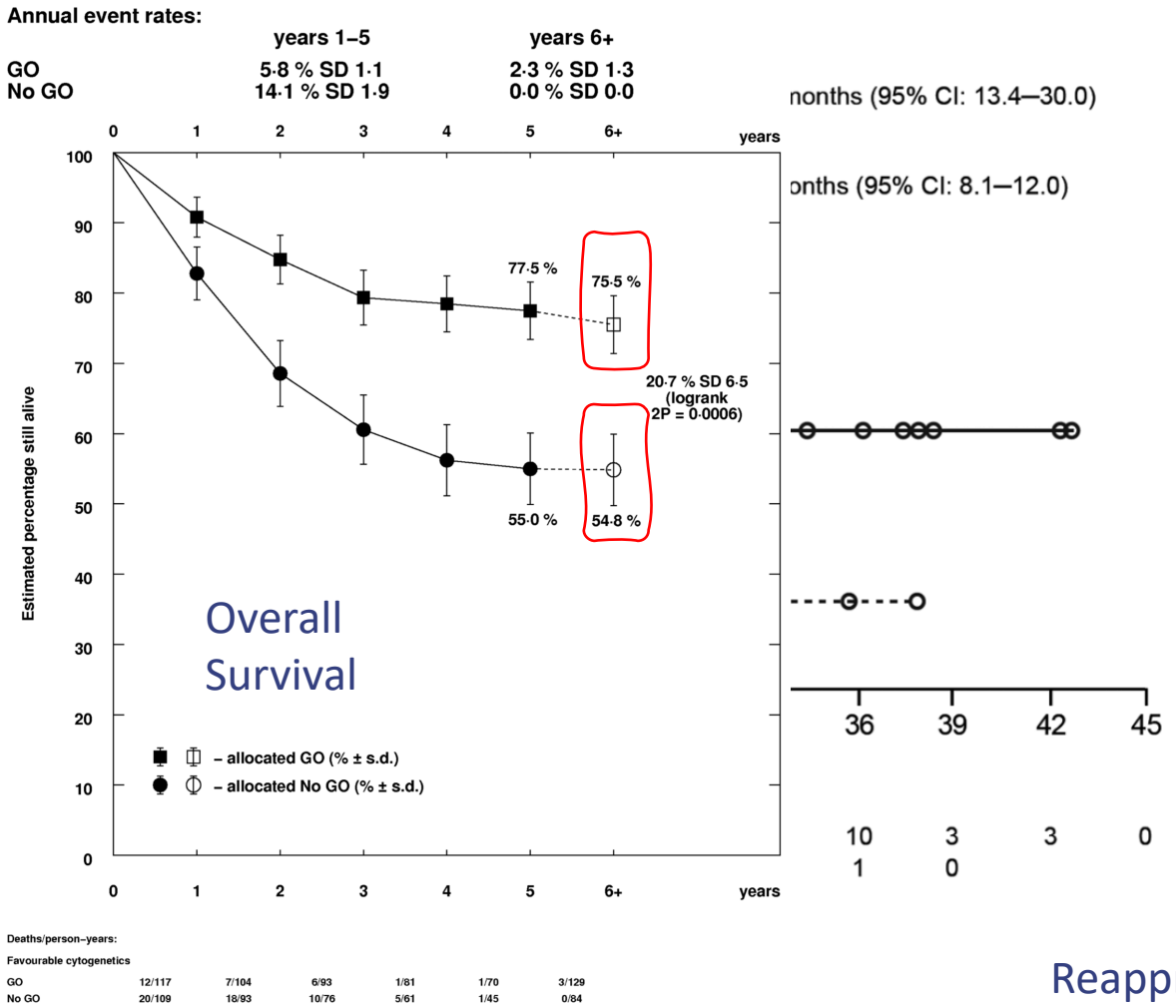
FDA Approval of G.O.

G.O. = gemtuzumab ozogamicin

Gemtuzumab Ozogamicin (GO) for De-novo AML (ALFA-0701)

Most benefit in **favorable** cytogenetic risk group



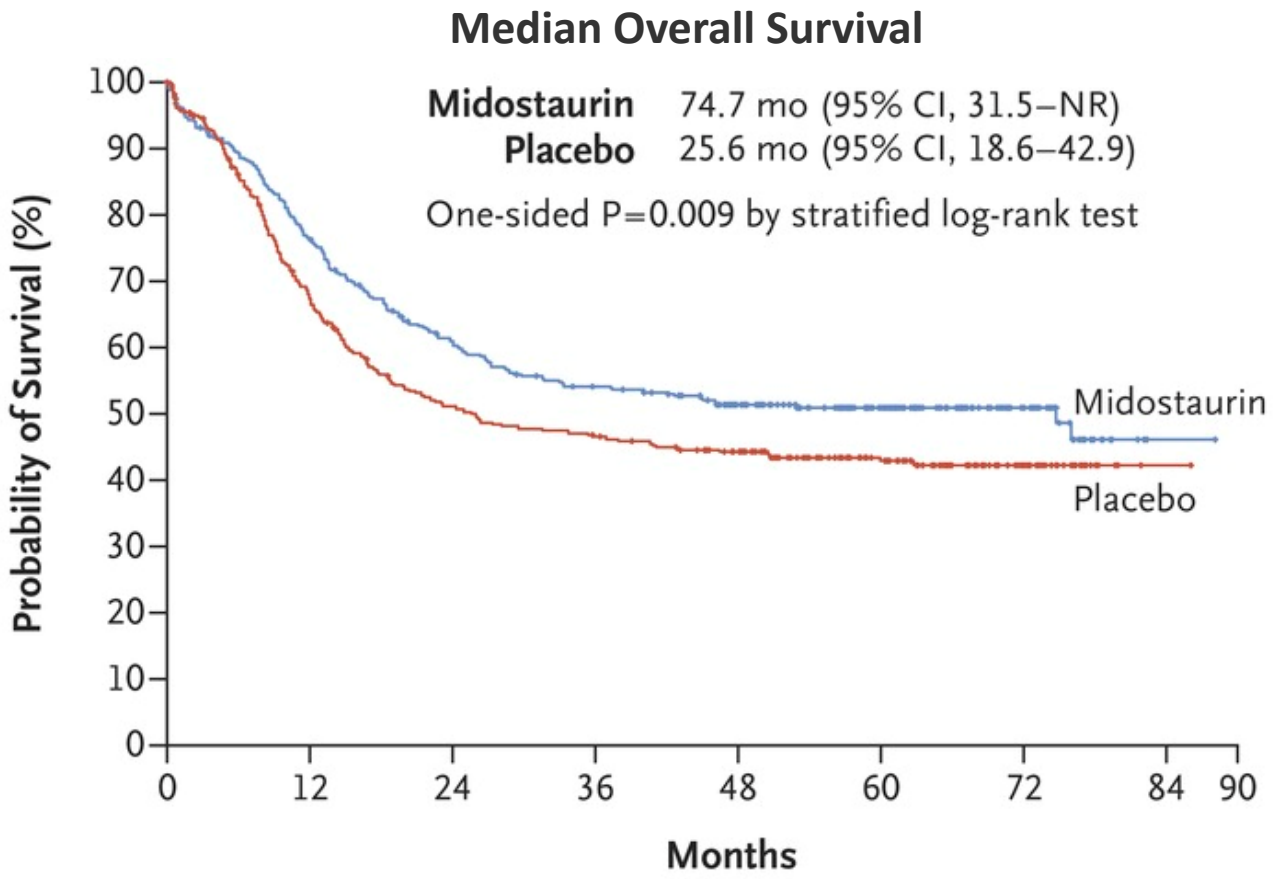


- 7+3 (DA) +/- GO
- Final analysis confirmed benefit in EFS for GO.
- CR/CRp 75% (No GO) vs. 81% (GO), P= NS
- VOD 6/131 (5%) at median 9 days

Reapproved September 2017

S Castaigne, C Pautas, C Terré, et. Al. Lancet 2012; 379: 1508–16; RK Hills, S Castagigne, FR Appelbaum, et al. *Lancet Oncol*. 2014 August ; 15(9): 986–996; J Lambert, C. Pautas, C. Terre, et al. Haematologica 2019 Vol. 104(1):113-119

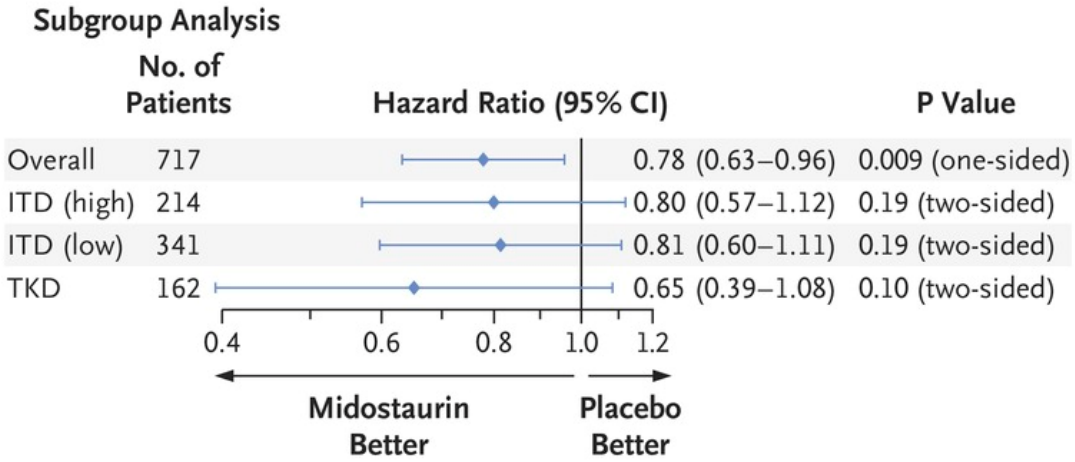
Midostaurin for Newly dxd. *FLT3*-mutated AML (RATIFY)



No. at Risk

Midostaurin	360	269	208	181	151	97	37	1
Placebo	357	221	163	147	129	80	30	1

CR 59% vs. 54%, P= NS



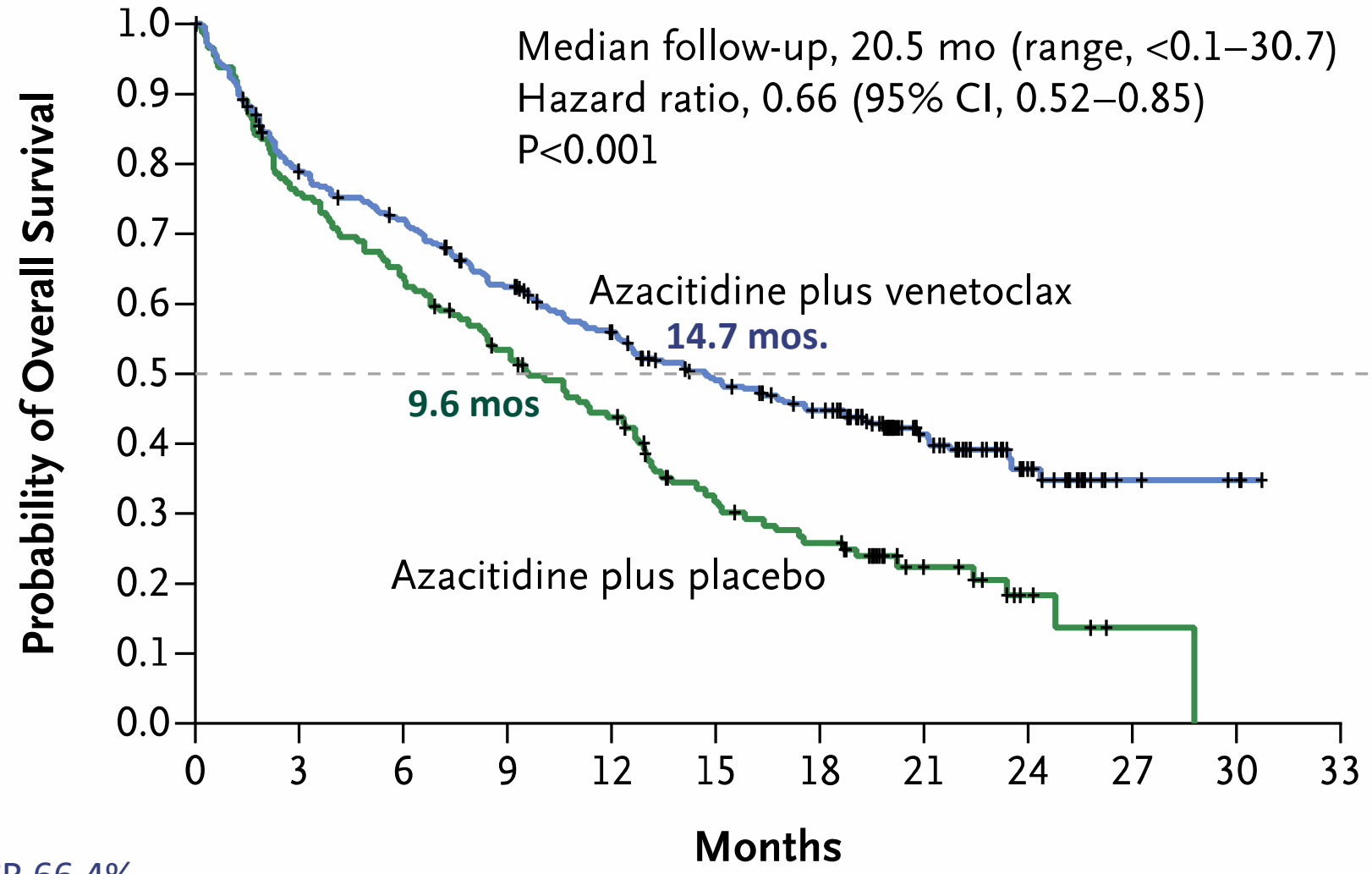
Approved April 2017

-Patients: 18-59 y/o with newly dxd. FLT3-mutated, de-novo AML

-7+3 induction, followed by HiDAC consolidation x 4 +/- Mido/Placebo (50mg BID on D8-21), and maintenance x 12 mos.

RM Stone, SJ Mandrekar, BL Sanford, et al. N Engl J Med 2017; 377:454-464

Azacitidine +/- Venetoclax for Patients with Newly dx. AML, age ≥ 75 or with Pre-existing Conditions Precluding Induction



Aza/veneto., N= 286; CCR 66.4%

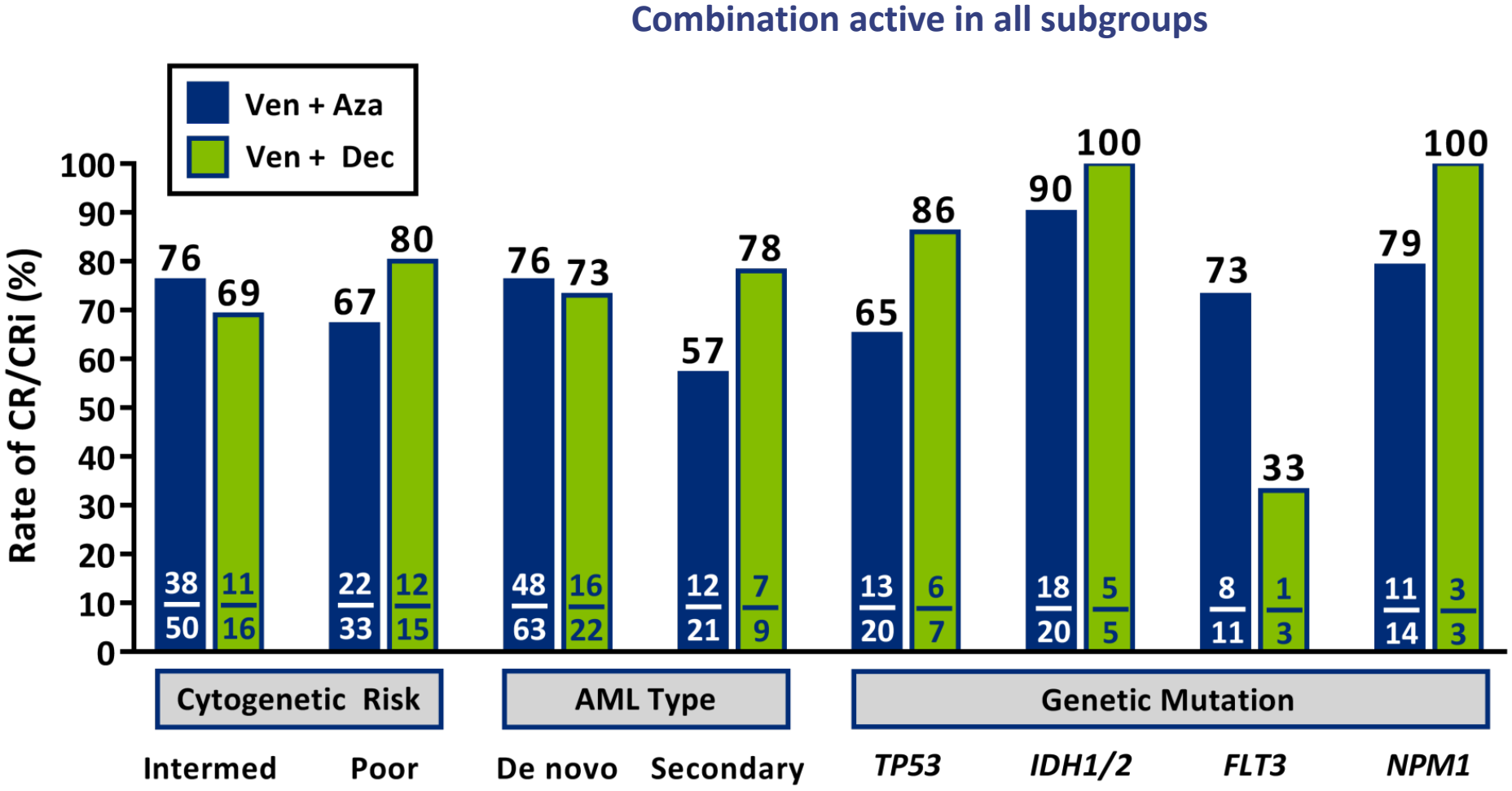
Aza/placebo, N= 145; CCR 28.3%

CCR= composite complete remission (CR+CRi)

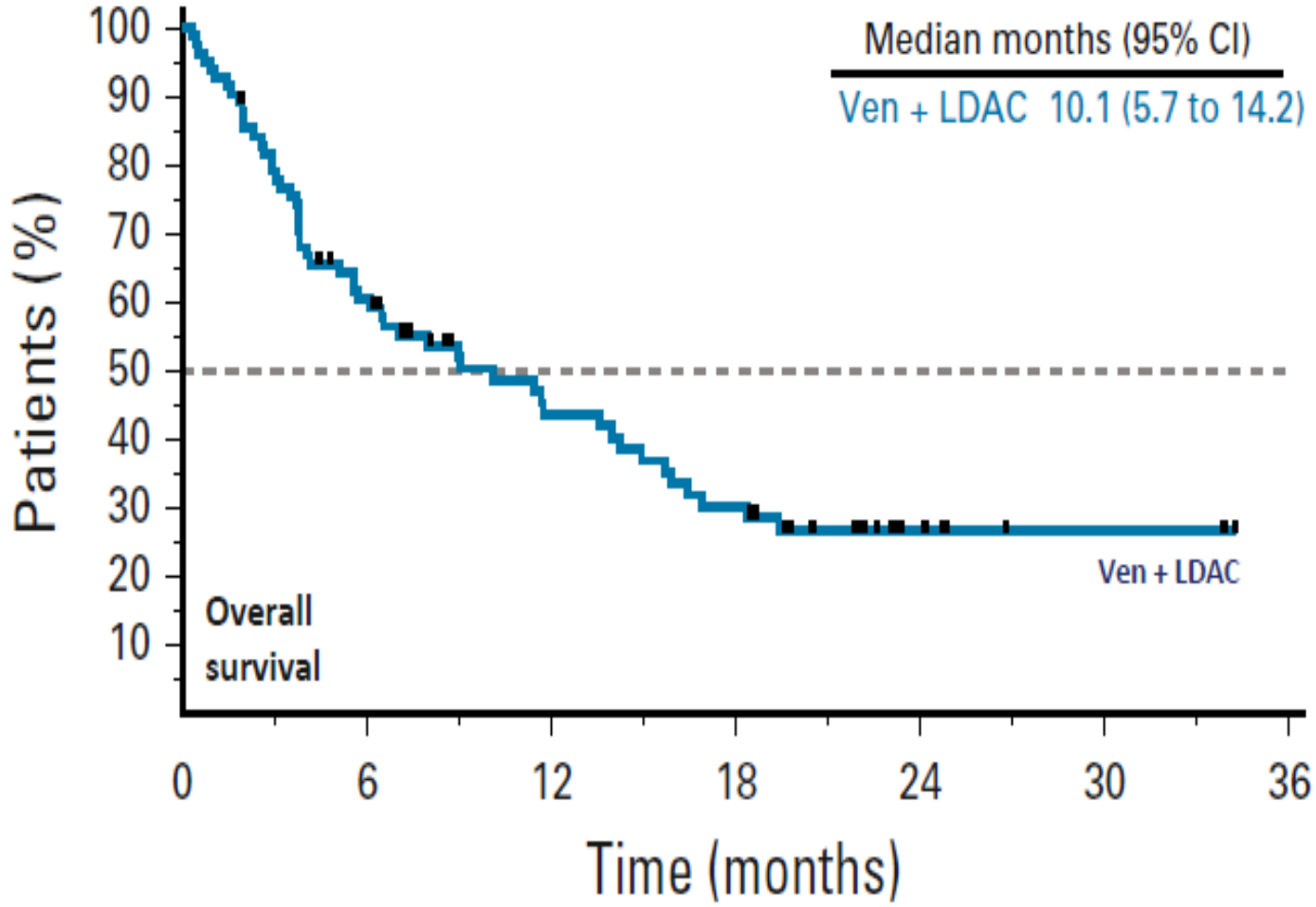
Approved November 2018, pending VIALE-A results

C.D. DiNardo, B.A. Jonas, V. Pullarkat, et al. NEJM 2020; 383: 617-29.

Response (CR/CRi) by Patient Subgroups



Venetoclax with Low-Dose Cytarabine for Newly dxd. AML



Phase IB/II

No prior HMA

- CR/CRi = 62%
- Median OS 13.5 mos.

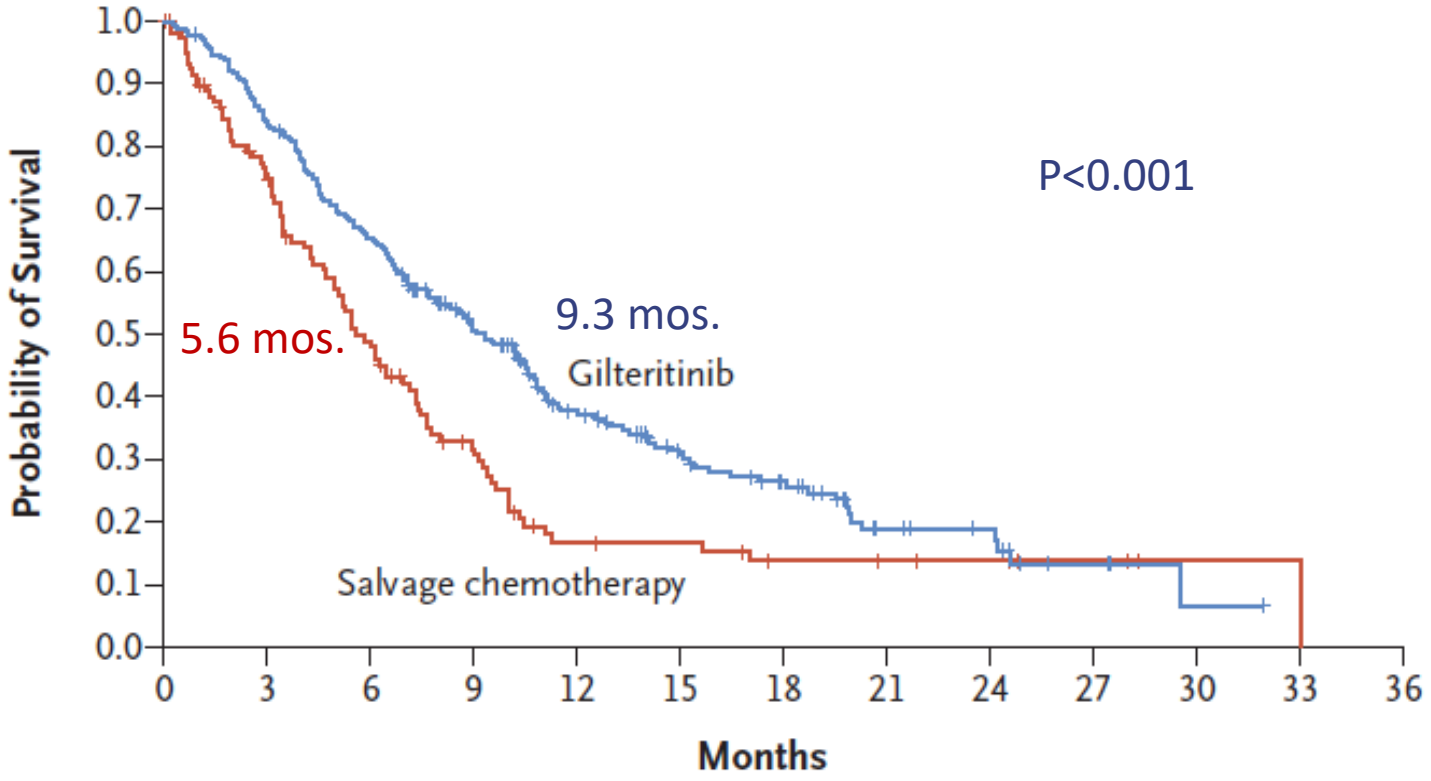
Prior HMA:

- CR/CRi = 33%
- Median OS = 4.1 mos.

HMA= Hypomethylating agent

A. Wei, SA. Strickland, J-A Hou, et al. J Clin Oncol. 2019; 37:1277-1284

Gilteritinib for R/R AML - Admiral trial



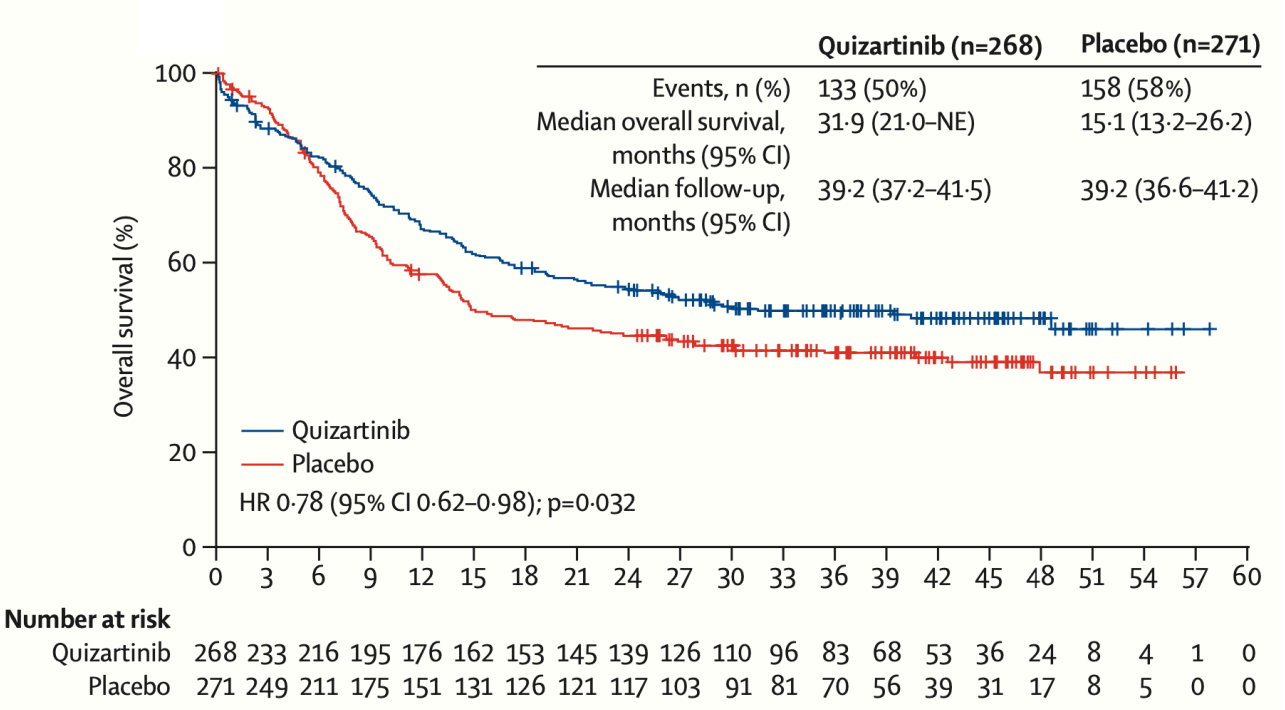
No. at Risk													
Gilteritinib	247	206	157	106	64	44	31	14	11	4	1	0	0
Salvage chemotherapy	124	84	52	29	13	12	8	7	5	3	1	0	0

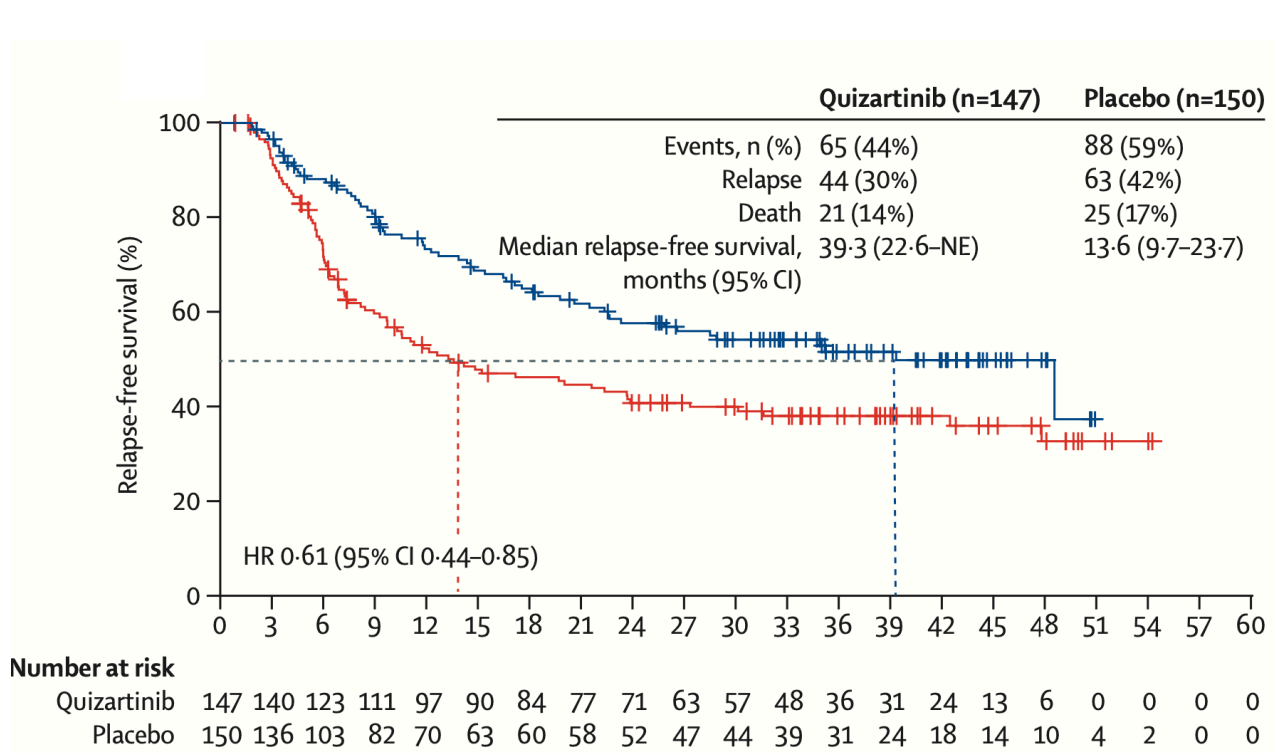
-CR+CRh 34% for gilteritinib and 15.3% for chemotherapy
-Triplet combinations showing CRc rates > 70% (trials ongoing)

Approved November 2018

Perl, Martinelli, Cortes. NEJM 2019 ; 381:1728-40

Quizartinib for Newly dxd. *FLT3*-ITD+ AML (QuANTUM-First)



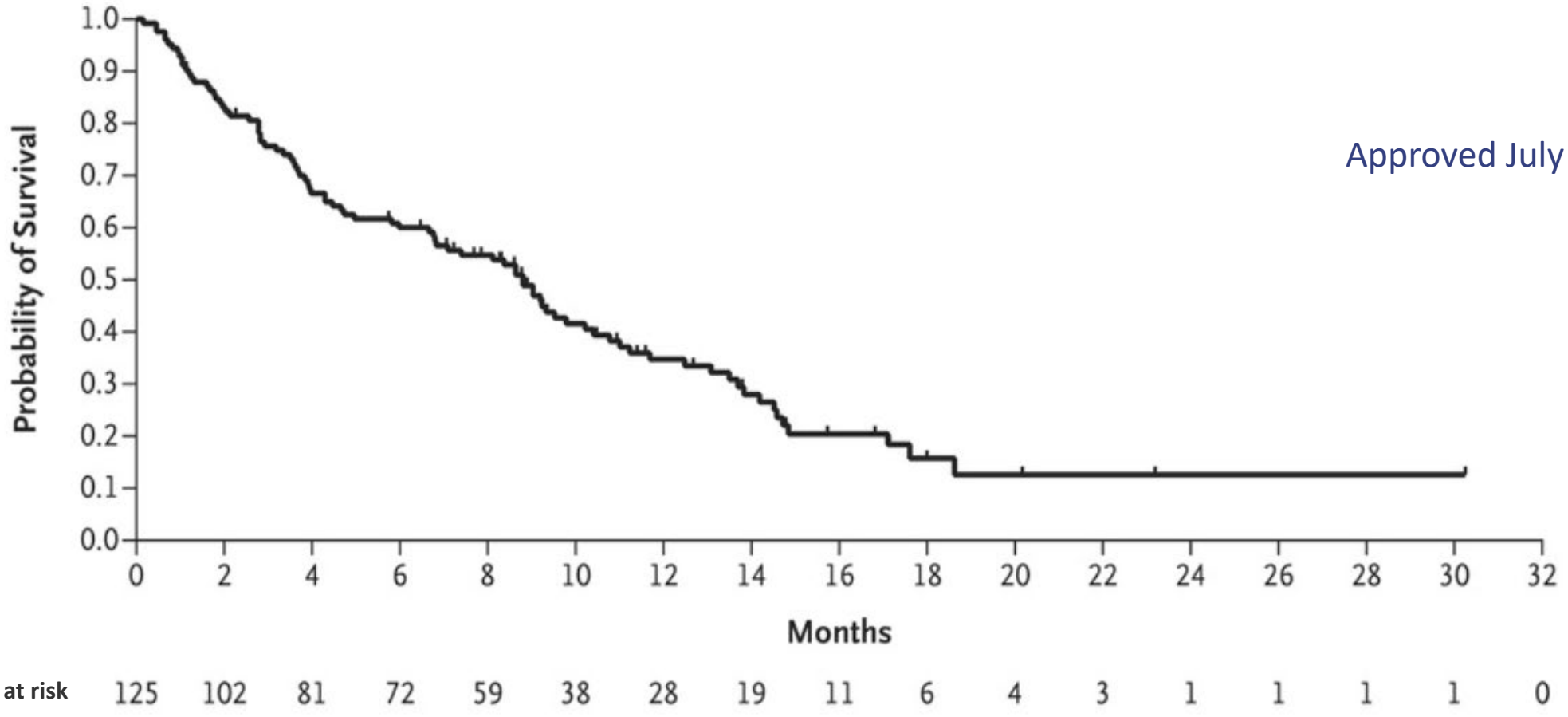


- 7+3 + Quizartinib (n= 268) or placebo (n=271) 40mg/day days 8-21, consolidation/transplant, and maintenance x 3 years.
- Median patient age 56 (18-75) years)
- CRc 71.6% for quizartinib vs. 64.9% for placebo. CR 54.9% vs. 55.4% respectively.

Quizartinib, Venetoclax, & Decitabine for R/R or Newly dxd. *FLT3*-mutated AML

- N= 21
- 9/13 (69%) pts with R/R AML achieved CRc.
- 4/4 pts with newly dx AML achieved CRc.
- 60-day mortality 0% in front-line cohort.
- Grade ≥ 3 non-heme toxicities included lung infections (N=9), neutropenic fever (N=6).

Ivosidenib for *IDH1*-mutated R/R and Newly Diagnosed AML



Approved July 2018

Single agent

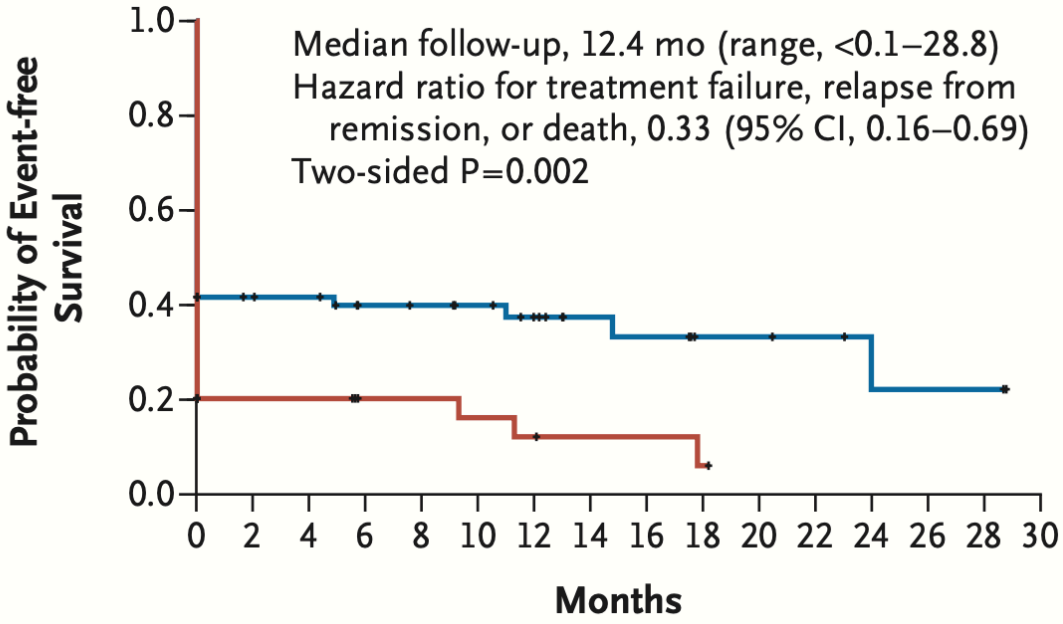
-R/R AML: ORR, 41.6%, CR/CRi, 30.4%

-CR in newly dx AML (N= 28), 43%

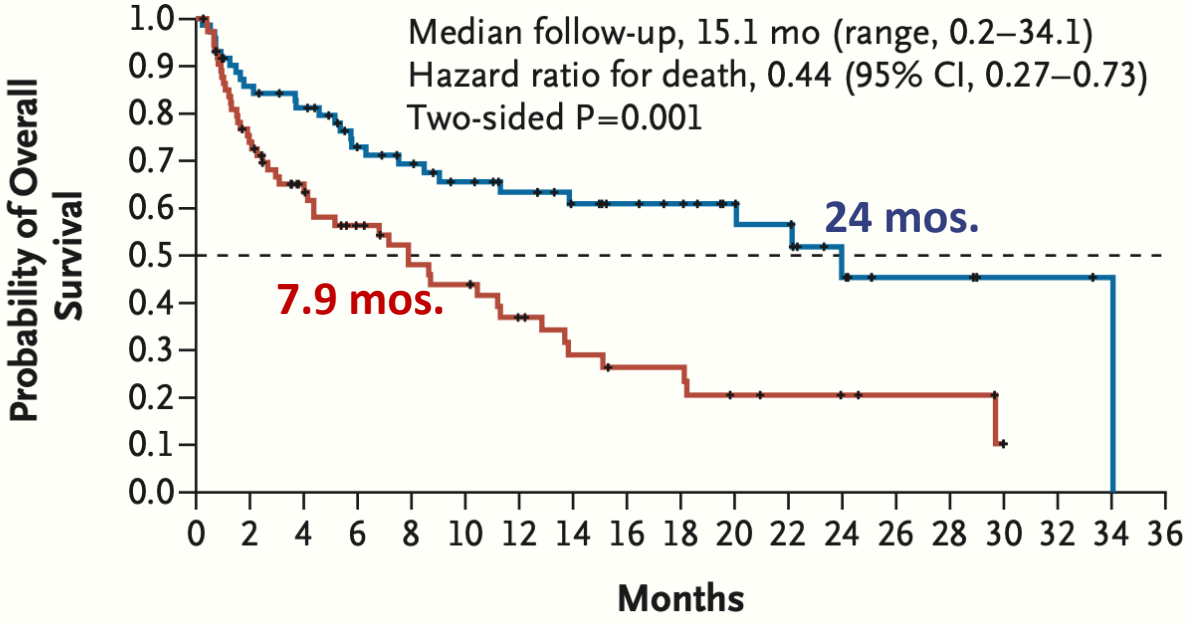
Differentiation syndrome in 15-25%

CD DiNardo, EM Stein, S de Botton, et al. N Engl J Med 2018; 378:2386-2398

Ivosidenib Combined with Azacitidine for Newly Diagnosed AML



No. at Risk																
Ivosidenib+ azacitidine	72	26	25	20	19	17	13	9	8	5	5	4	2	2	2	0
Placebo+ azacitidine	74	8	8	5	5	4	3	2	2	1	0					

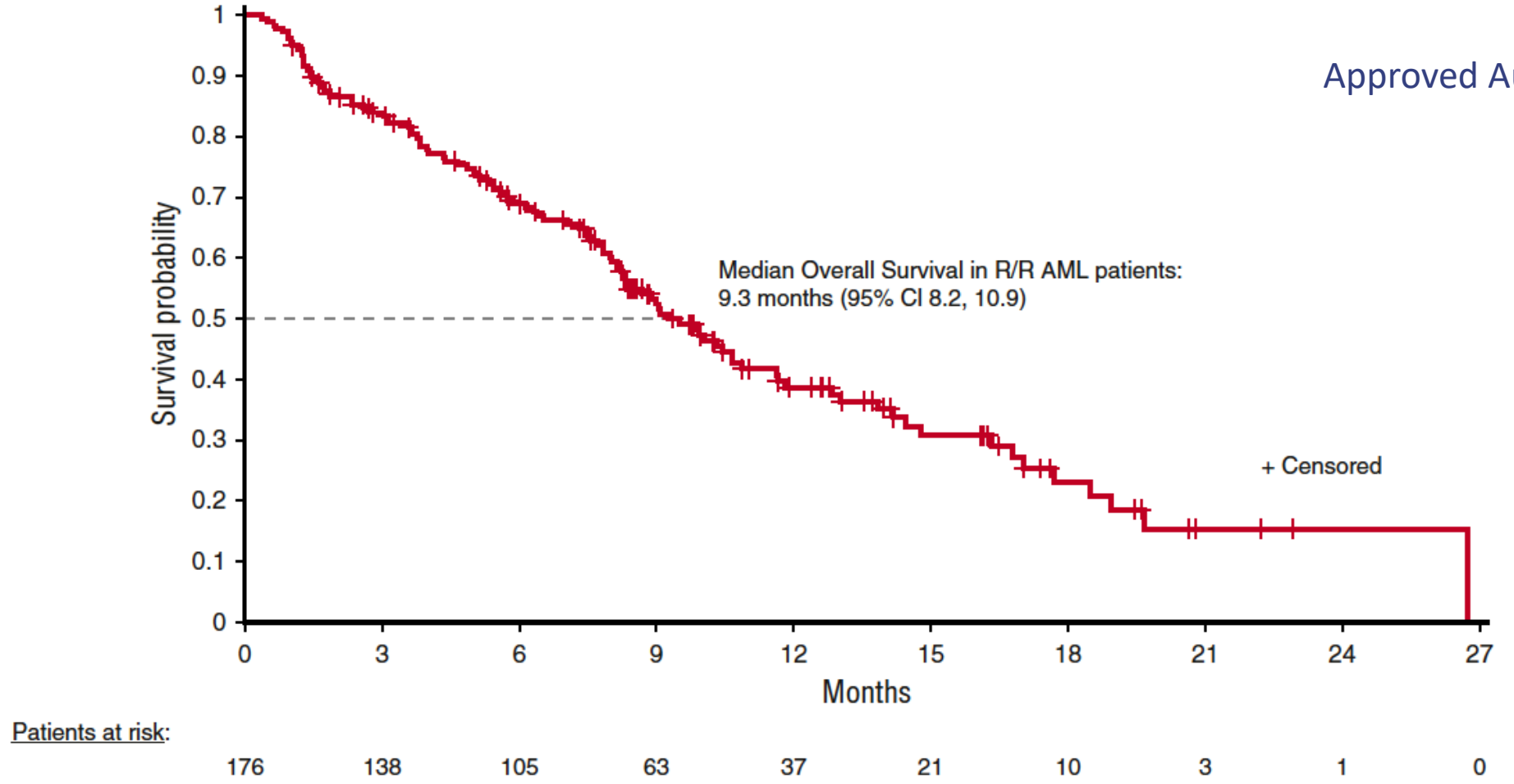


No. at Risk																	
Ivosidenib+ azacitidine	72	58	53	42	38	33	29	24	21	19	15	13	7	4	4	2	2	1
Placebo+ azacitidine	74	53	38	29	23	21	15	11	9	9	6	5	4	3	3	0		

- CR + CRh 53% with ivo/aza vs. 18% with placebo/aza
- CR 47% (38% by 24 weeks) with ivo/aza vs. 15% (11% by 24 weeks) with placebo/aza
- Triplets (IVO +AZA+VEN) ongoing.

Enasidenib for Relapsed/Refractory *IDH2*-mutated AML

Approved August 2017

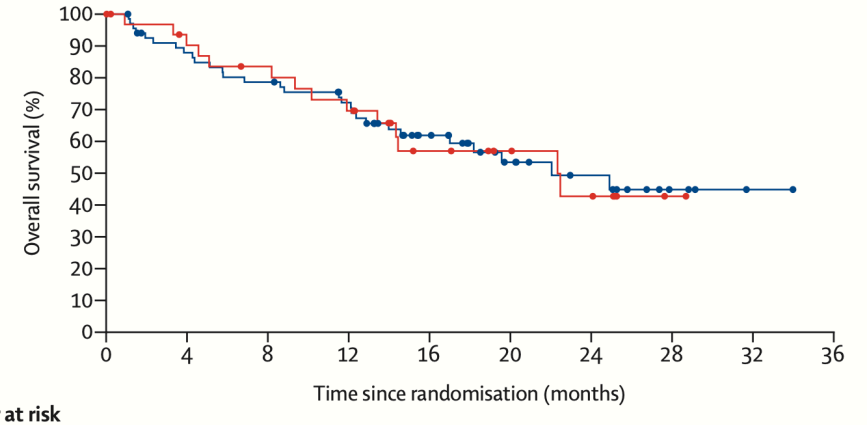


-CR+ CRi in R/R AML = 33%

Stein, Dinardo, Pollyea, et al. Blood 2017;130(6):722-731

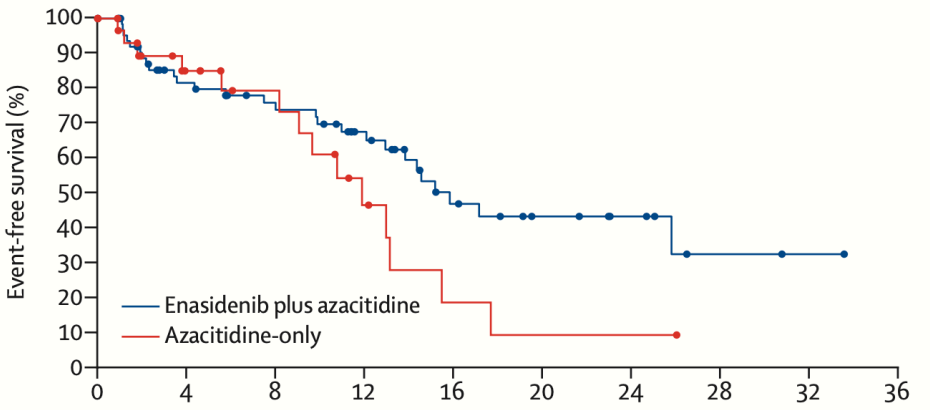
Enasidenib and Azacitidine for Patients with Newly dxd. *IDH2*-mutated AML (AG221-AML-005)

	Enasidenib plus azacitidine (n=68)	Azacitidine only (n=33)
Events	29 (43%)	14 (42%)
Censored	39 (57%)	19 (58%)
Median overall survival, months	22·0 (95% CI 14·6–NR)	22·3 (95% CI 11·9–NR)
Hazard ratio	0·99 (95% CI 0·52–1·87)	
Log-rank p value	0·97	



Number at risk (number censored)										
Enasidenib plus azacitidine	68 (0)	57 (3)	51 (3)	44 (6)	28 (16)	16 (25)	11 (29)	4 (35)	1 (38)	0 (39)
Azacitidine only	33 (0)	27 (3)	24 (4)	20 (4)	12 (9)	9 (12)	6 (13)	1 (18)	0 (19)	..

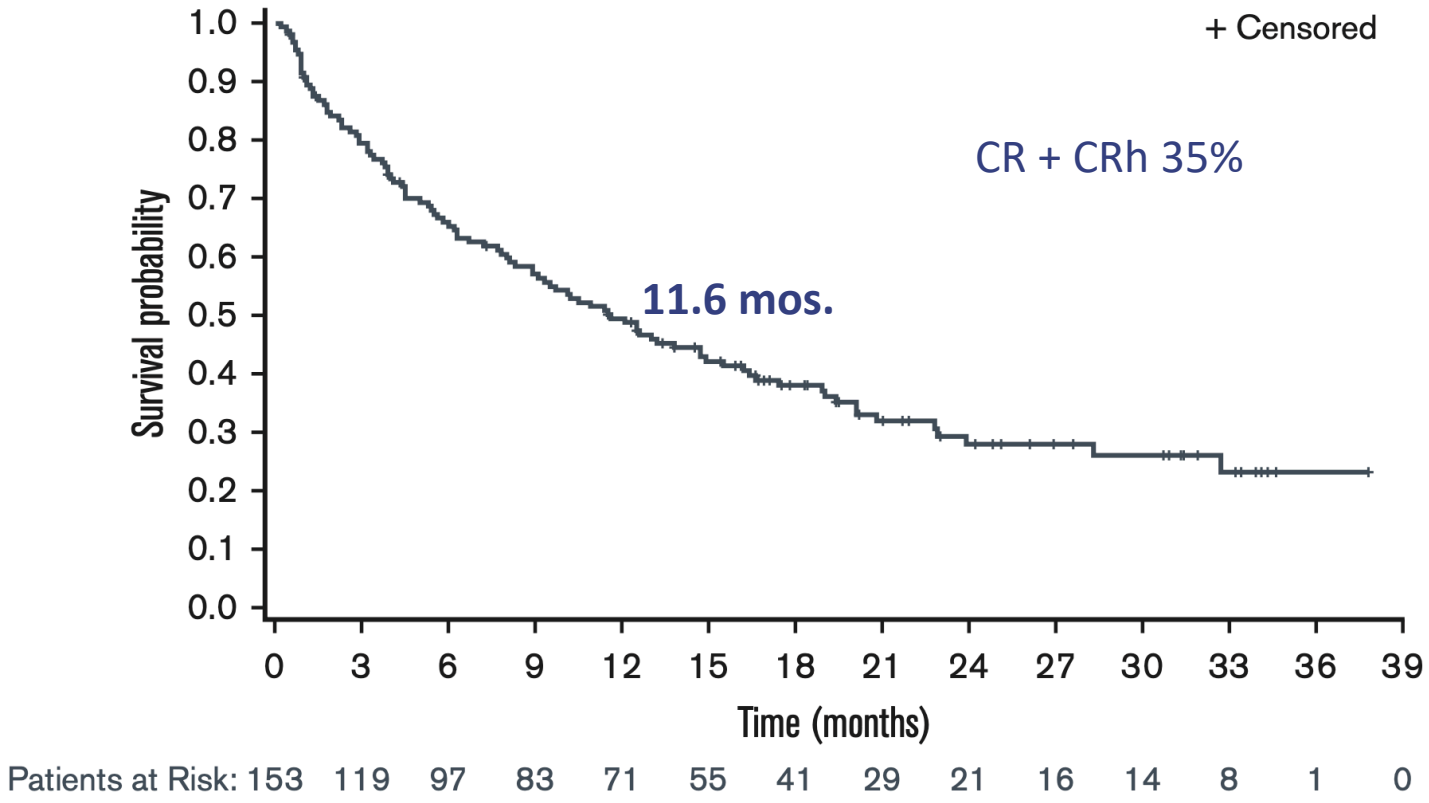
	Enasidenib plus azacitidine (n=68)	Azacitidine only (n=33)
Events	27 (40%)	14 (42%)
Censored	41 (60%)	19 (58%)
Median event-free survival, months	15·9 (95% CI 13·0–NR)	11·9 (95% CI 8·2–15·5)
Hazard ratio	0·59 (95% CI 0·30–1·13)	
Log-rank p value	0·11	



Number at risk (number censored)										
Enasidenib plus azacitidine	68 (0)	45 (12)	37 (17)	27 (23)	14 (29)	9 (33)	6 (36)	2 (39)	1 (40)	0 (41)
Azacitidine only	33 (0)	18 (11)	13 (15)	6 (17)	2 (18)	1 (18)	1 (18)	0 (19)	..	..

- Single-arm phase 1b and randomized phase 2.
- Ph 1b: enasidenib 100 or 200 mg/day in 28-day cycles + azacitidine daily for 7 days of each cycle.
- Ph 2: assigned (2:1) to enasidenib 100mg + azacitidine or azacitidine, stratified by AML type (de novo or s-AML).
- CR + CRi 39 (57%) for ENA+ AZA vs. 6 (18%) for AZA alone

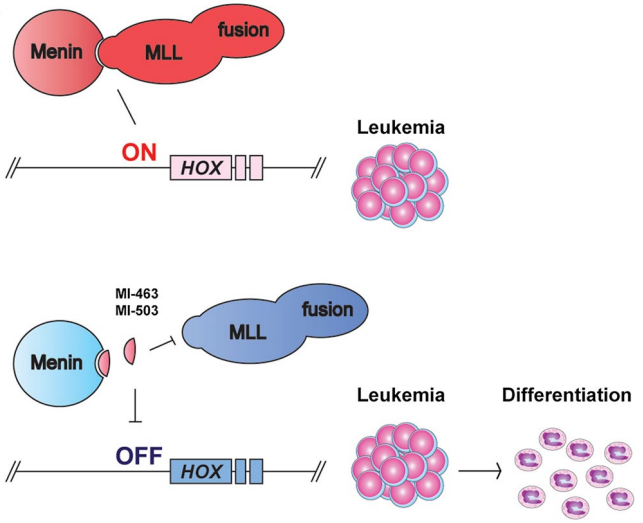
Olutasidenib (FT-2102) for *IDH1*-mutated R/R AML

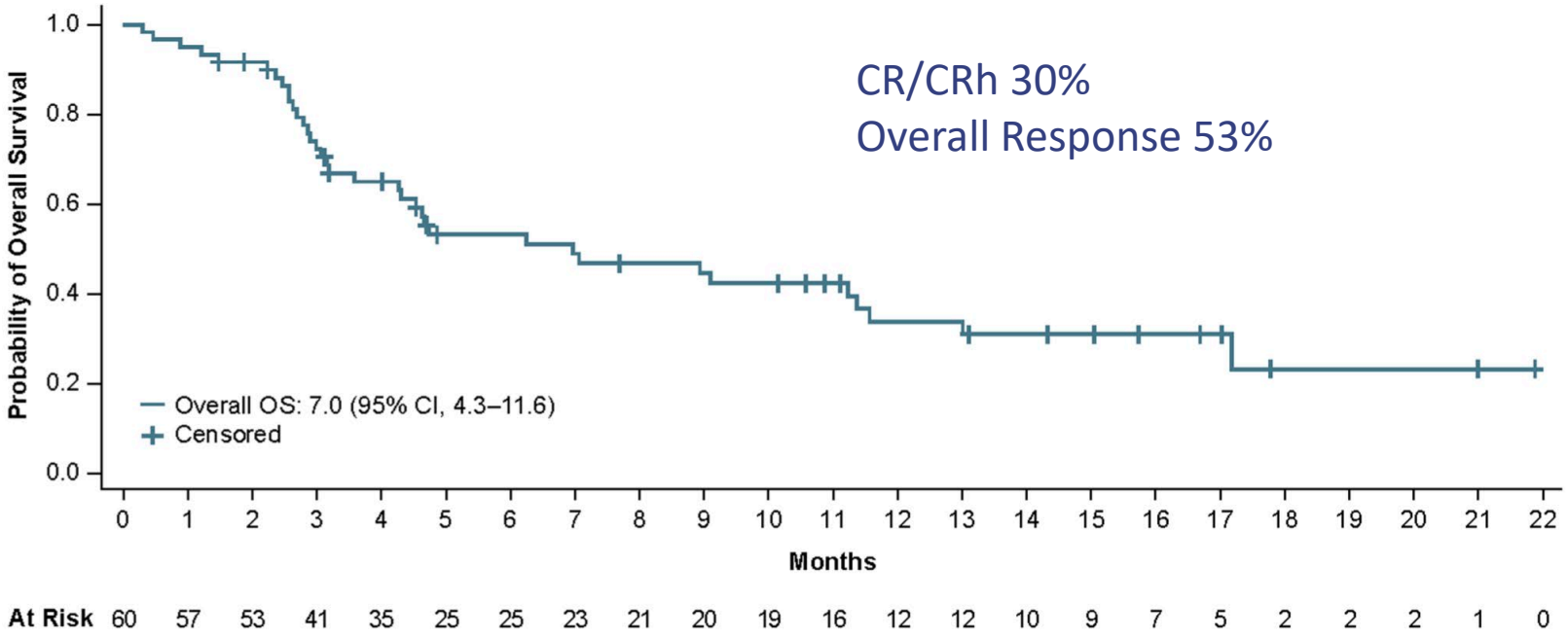


Approved December 2022

-153 IDH1 inhibitor–naive patients with mIDH1R132 R/R AML. Median age 71 (range 32-87 years).
-Olutasidenib 150 mg twice daily.
-DS in 14% (9% of ≥ Gr 3)

Augment-101: Phase 1/2 Trial of Revumenib (SNDX-5613) in Patients with R/R AML/ALL/MPAL (with *NPM1* mutation or *MLL/KMT2A* rearrangement)



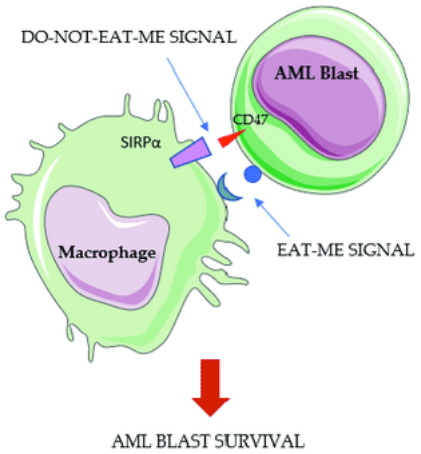


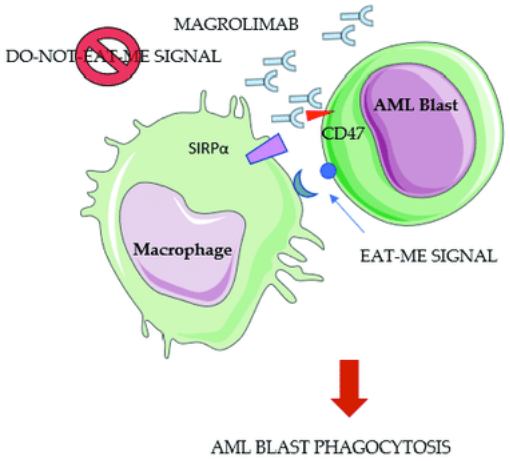
CR/CRh 30%
Overall Response 53%

-First-in-human phase 1 trial of revumenib (SNDX-5613), a potent, selective oral inhibitor of the menin–KMT2A interaction, in patients with relapsed or refractory acute leukemia.
-BEAT AML substudy of the triplet SNDX-5613 + Azacitidine + venetoclax combination opening soon at Emory.
-Other menin inhibitors also in the pipeline.

Kühn MWM, Armstrong SA. Cancer Cell 2015 27431-433. Issa GC, Aldoss I, DiPersio J, et al. Nature (2023); Vol 65. 920-925.

Magrolimab and Azacitidine in Frontline *TP53*- mutated AML



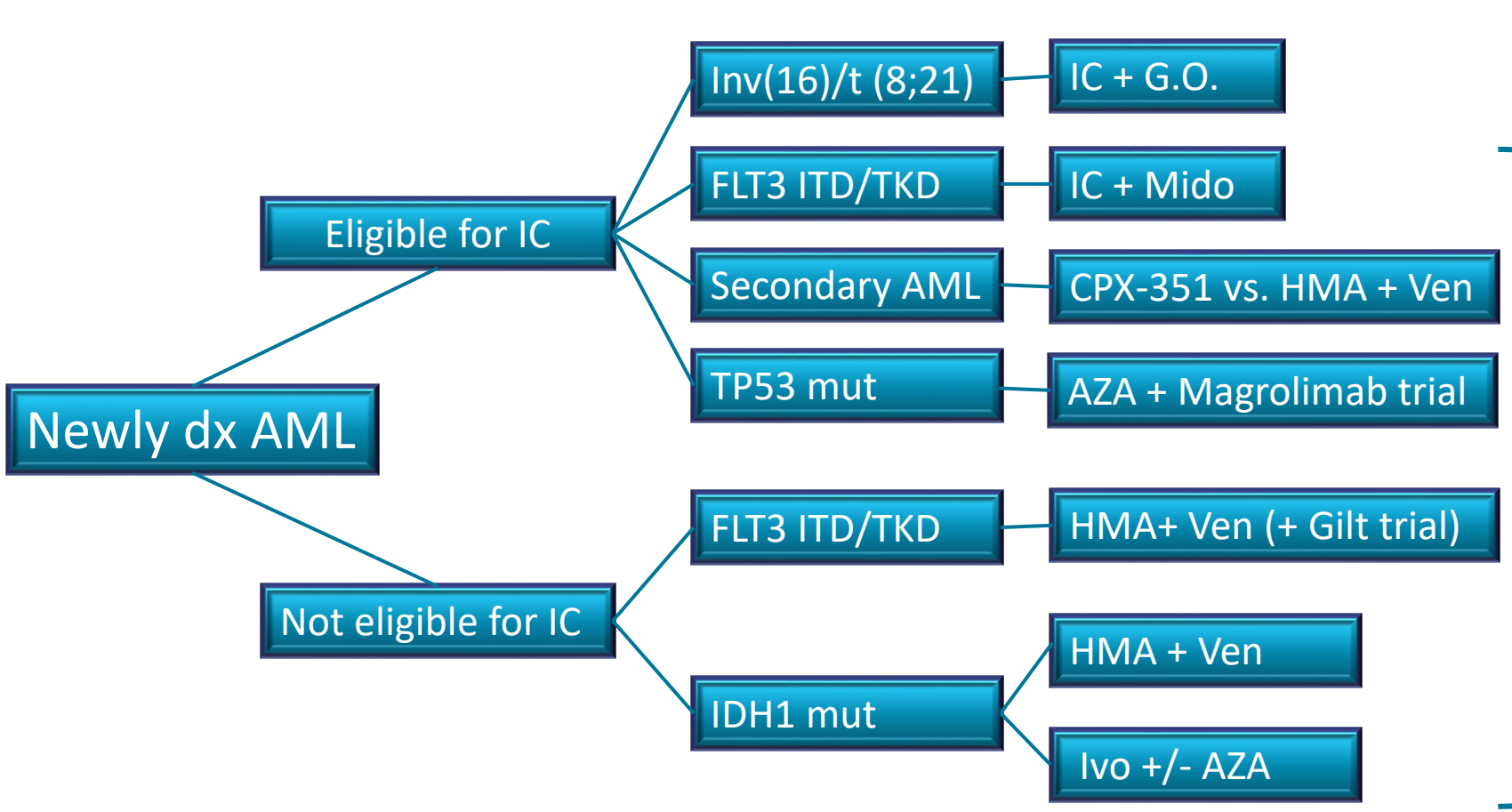


- Ph Ib in pts. With TP53 mut AML not candidates for intensive induction.
- Magrolimab IV priming dose (1 mg/kg) followed by ramp-up to 30 mg/kg QW or Q2W as maintenance and AZA on Days 1–7 of each 28-day cycle.
- N=72
- Response: CR+ CRi 41.6% (33.3% CR + 8.3% CRi) at median 2.2-3 mos.
- Median overall survival 10.8 mos at median follow up 8.3 mos.
- ENHANCE-2 randomized combinations (Aza + Magro vs. SOC) for newly dx TP53 mutated AML, ongoing

Andreozzi F, Massaro F, Wittnebel S, et al. Int Jnl of Molec Sciences 2022, 23, 3887.

Daver N, Vyas P, Kambhampati S, et al. ASCO 2022

Treatment Algorithm for AML - Emory



Assess for Transplant

Relapsed AML

- FLAG-Ida-Ven
- FLT3, Gilteritinib, HM-FLTI-101 trial
- IDH1, Ivosidenib, Olutasidenib, trial
- IDH2, Enasidenib, trial
- KMT2Ar/NPM1, Menin inh. trial
- NKX101 CAR trial

Coming soon for newly dx KMT2Ar/NPM1 mut AML: Menin inhibitor combination trial for pts. eligible and ineligible for IC

IC= Intensive Chemotherapy, Mido= midostaurin, HMA=hypomethylating agent, CBF= core binding factor, G.O.= gemtuzumab ozogamicin, AZA= azacytidine, Ivo= Ivosidenib, Gilt= gilteritinib, Ven= venetoclax

AML Trials at Emory

SNDX-5613-0700- A Study of SNDX-5613 in R/R Leukemias Including Those With an MLLr/KMT2A Gene Rearrangement or NPM1 Mutation

HM-FLTI-101- Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of HM43239 (FLT3 inh) in Patients With Relapsed or Refractory AML

XMAB14045-01- PH 1 Study to Evaluate Safety and Tolerability of XmAb14045 in Patients With CD123-expressing Hematologic Malignancies

BEAT AML- Biomarker-Based Treatment of AML. Arms: SNDX-5613 + azacytidine + venetoclax for newly dx KMT2Ar or NPM1 mutated AML

ENHANCE-2- Magrolimab combination (Magro+ aza vs. Aza + ven or 7+3) for patients with newly dx. *TP53* mutated AML.

NKX101-101- Phase I study of NKX101, an activating NK CAR, in subjects with Hematological malignancies or Dysplasias

IO-202- Phase I study of IO-202 in patients with R/R AML with monocytic differentiation and R/R CMML

TCD17197: Dose escalation study of SAR443579 in patients with R/R AML, B-cell ALL or high risk MDS

MRX-2843 in Adolescents and Adults With Relapsed/Refractory AML, ALL, or MPAL.

MRKR-10-401-01- Ph II study of donor-derived multi-tumor associated antigen specific T cells (MT-401) in patients with AML following HCT.

DF-HCC-16-593- DC/AML Fusion Cell Vaccine vs Observation in Patients Who Achieve a Chemotherapy-induced Remission

BMT-CTN-1702- Clinical Transplant-Related Long-term Outcomes of Alternative Donor Allogeneic Transplantation

CYAD-N2T-005- DEPLETHINK - LymphoDEPLEtion and THerapeutic Immunotherapy With NKR-2

SUMMARY

- Eight new targeted agents FDA approved since 2017
- Triplets may be better than doublet combinations
- Clinical trials still the best option for many patients

Questions?

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