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Treatment Algorithm in the Molecular Era for AML

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EMORY WINSHIP CANCER INSTITUTE
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Disclosures

Syndax Pharmaceuticals-served on advisory board panel on menin inhibition in leukemia

Objectives

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

1973 — Cytarabine & Daunorubin (7&3 protocol for AML)

1977 — Bone Marrow transplantation first employed

2000 — FDA Approval of G.O.

2010 — GO removed from market

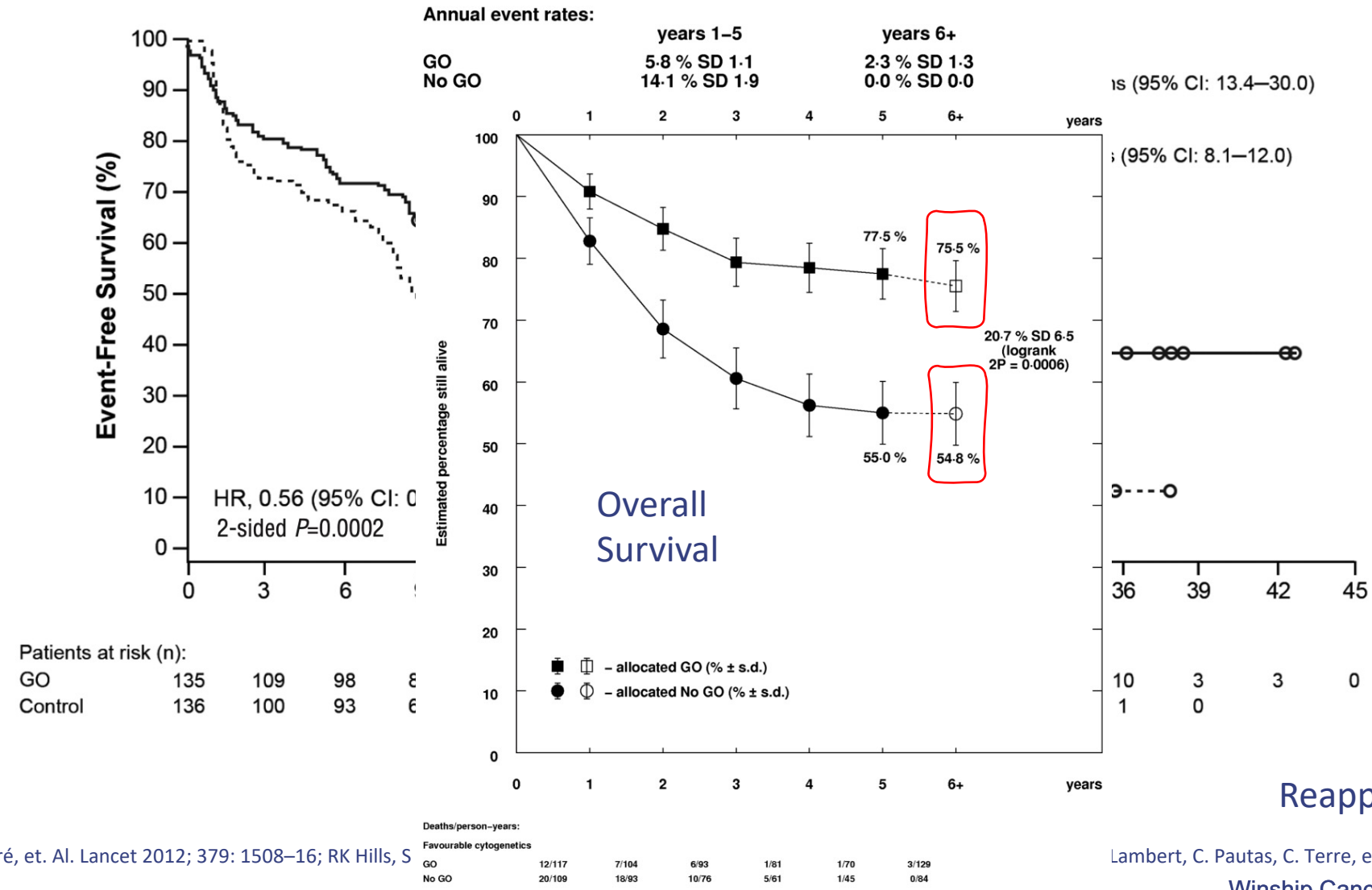
2017-2018 — CPX-351, Midostaurin, GO, Enasidenib, Venetoclax, Glasdegib, Gilteritinib, Ivodisdenib

2020-2023 — Azacitidine, Olutasidenib, Quizartinib

GO = gemtuzumab ozogamicin

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

Most benefit in **favorable** cytogenetic risk group

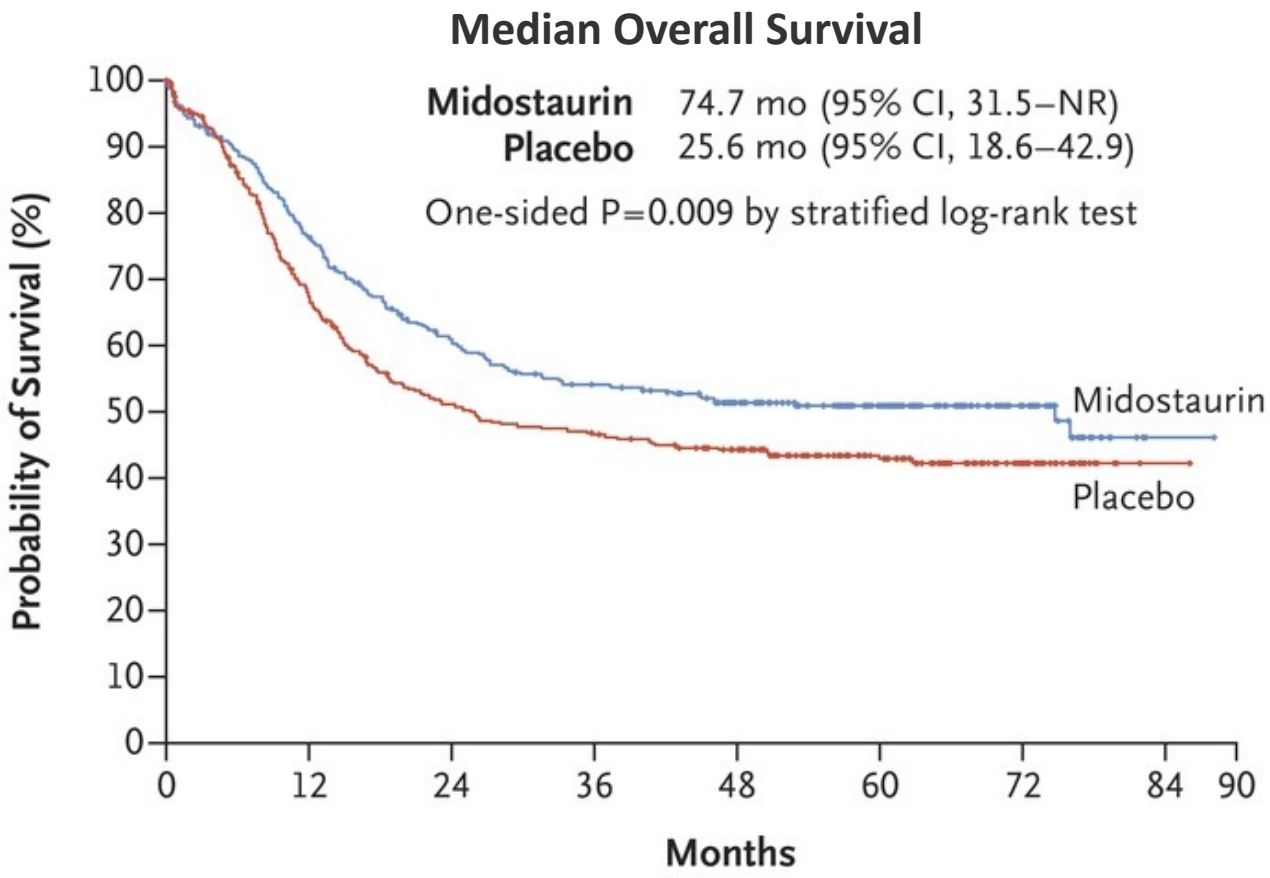


- 7+3 (DA) +/- GO
- Final analysis confirmed benefit in EFS for GO.
- CR/CRp 75% (No GO) vs. 81% (GO), P= NS
- VOD 6/131 (5%) at median 9 days

Reapproved September 2017

S Castaigne, C Pautas, C Terré, et. Al. Lancet 2012; 379: 1508–16; RK Hills, S Lambert, C. Pautas, C. Terre, et al. Haematologica 2019 Vol. 104(1):113-119

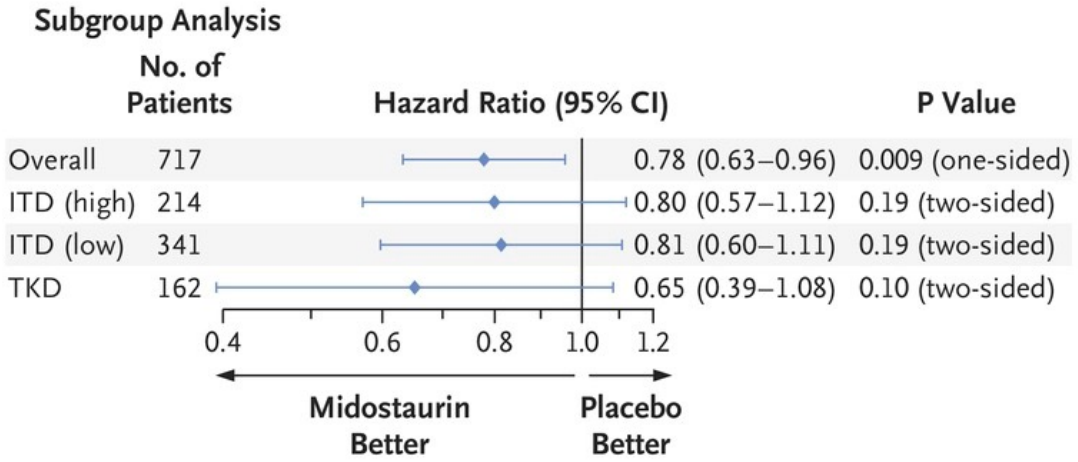
Midostaurin for Newly dxd. *FLT3*-mutated AML (RATIFY)



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



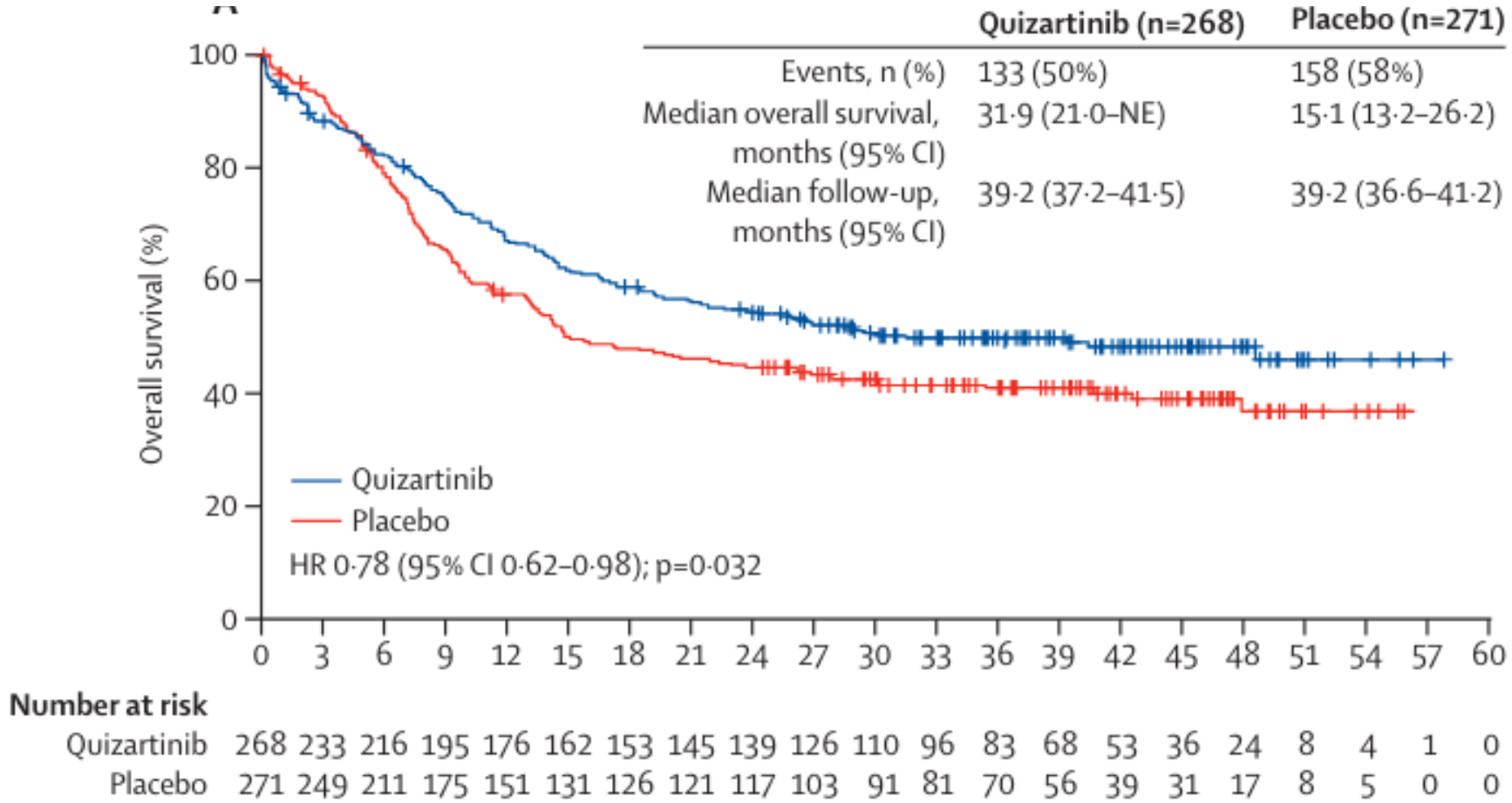
Approved April 2017

-Patients: 18-59 y/o with newly dxd. FLT3-mutated (ITD and TKD), 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

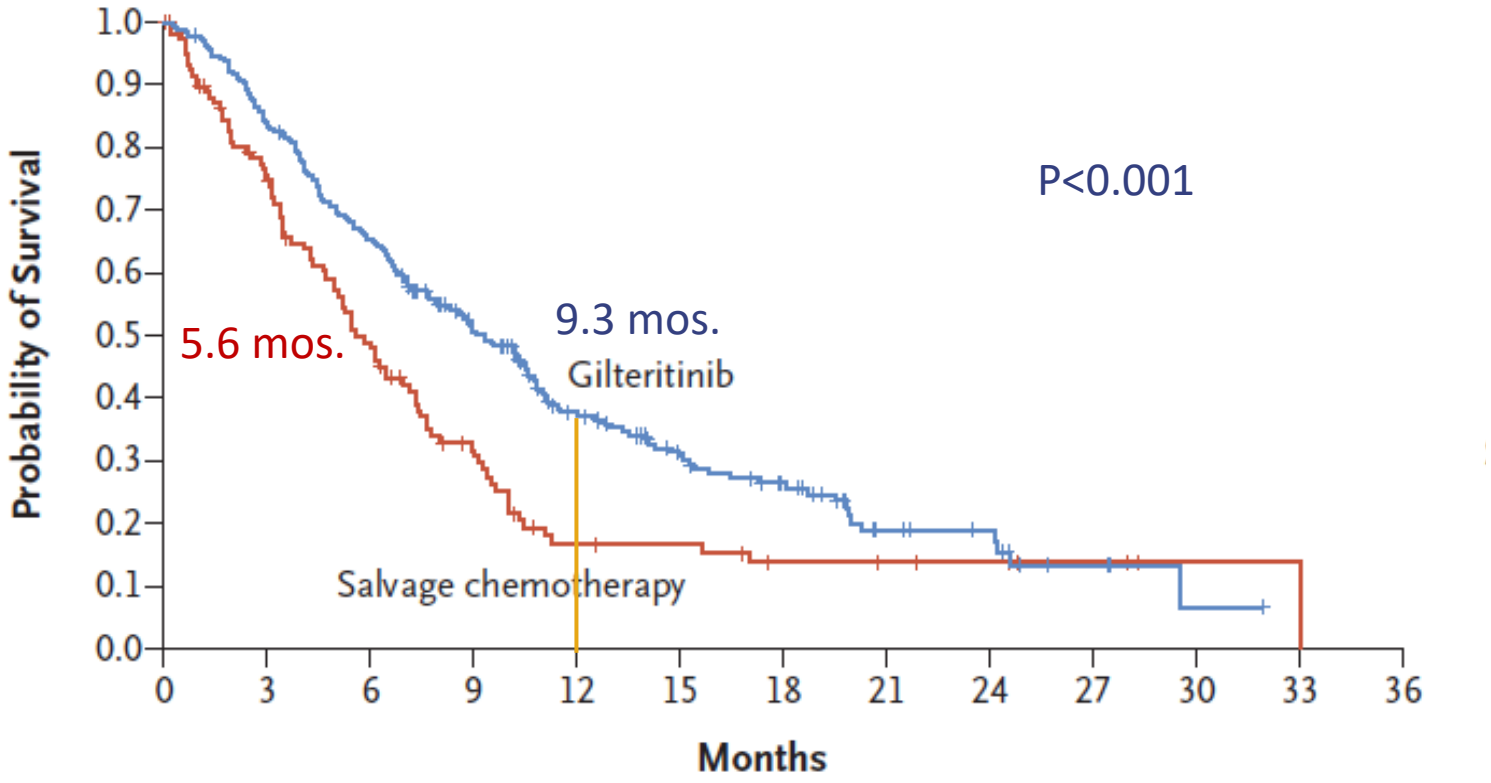
Quizartinib for Newly Diagnosed AML with *FLT3* ITD (QUANTUM-First)



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.

Erba HP, Montesinos P, Kim Hee-Je, et al. Lancet 2023; 401:1571-83

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

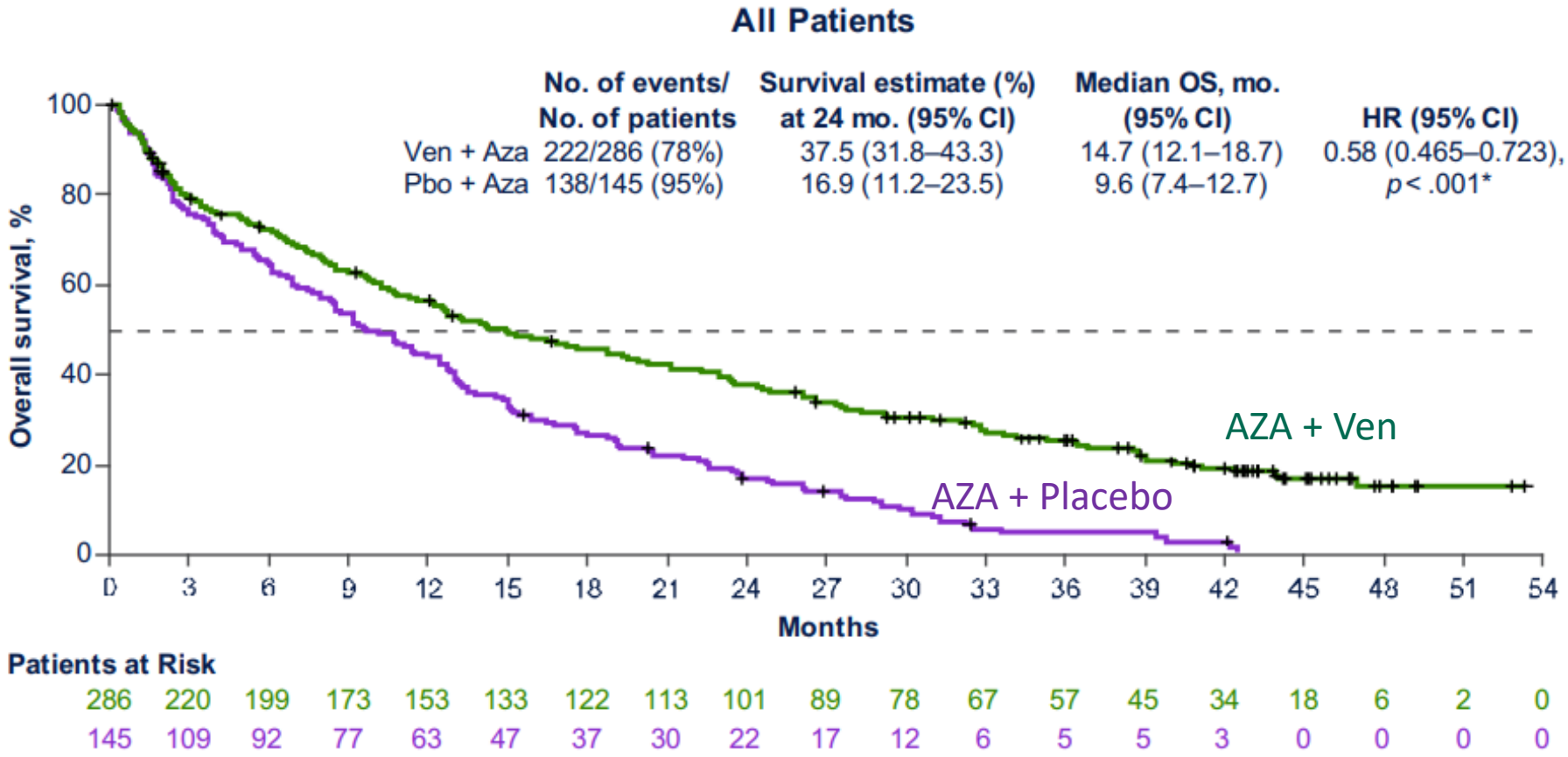
-CR+CRh 34% for gilteritinib and 15.3% for chemotherapy
-One-year OS 37% vs. 17%.
-Triplet combinations showing CRc rates > 70% (trials ongoing)

Morpho- Post-SCT maintenance if MRD+

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

Long Term Follow-up on VIALE-A

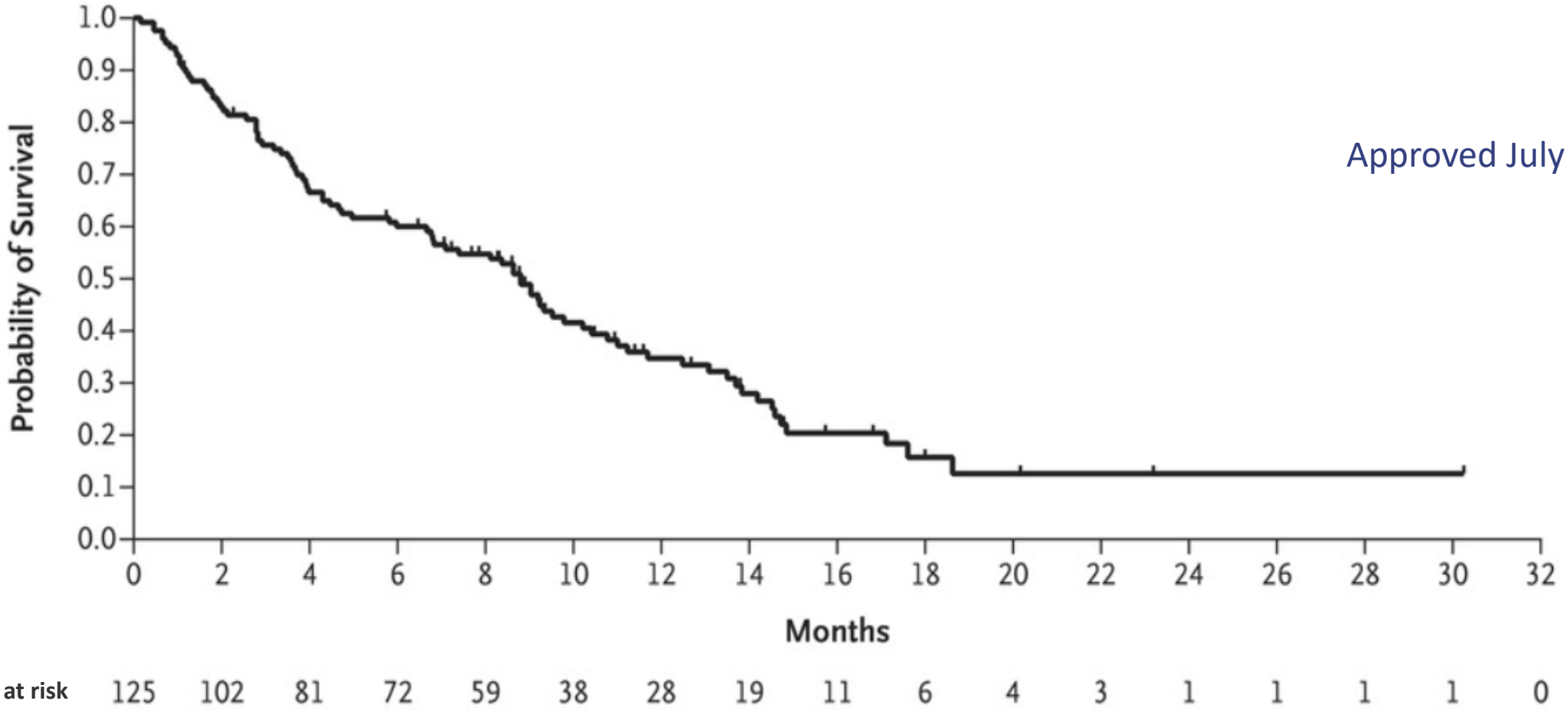
Median f/u 43.2 mos. (< 0.1-53.4)



- Least benefit in *TP53*, *KRAS, NRAS, FLT3 ITD*
- 30-day death in 7% (A+V) vs. 9% (A + PBO)
- Backbone for triplet combinations

C.D. DiNardo, B.A. Jonas, V. Pullarkat, et al. NEJM 2020; 383: 617-29.
Pratz KW, Jonas BA, Pullarkat V, et. Al. AJH 2024. DOI:10:100002/ajh.27246

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



Approved July 2018

Single agent

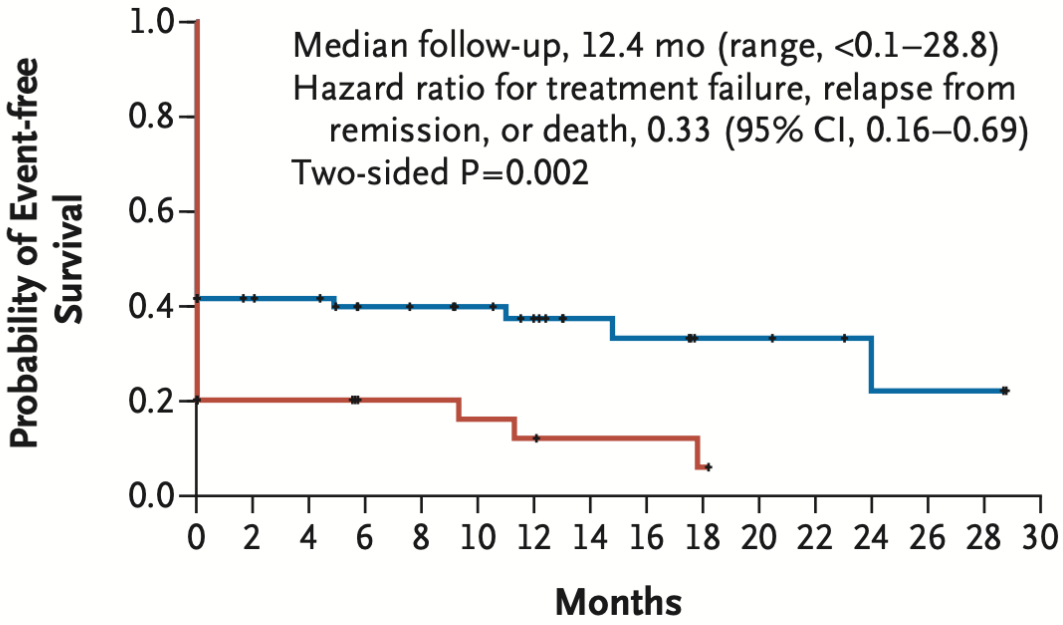
-R/R AML: ORR, 41.6%, CR/CRi, 30.4%

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

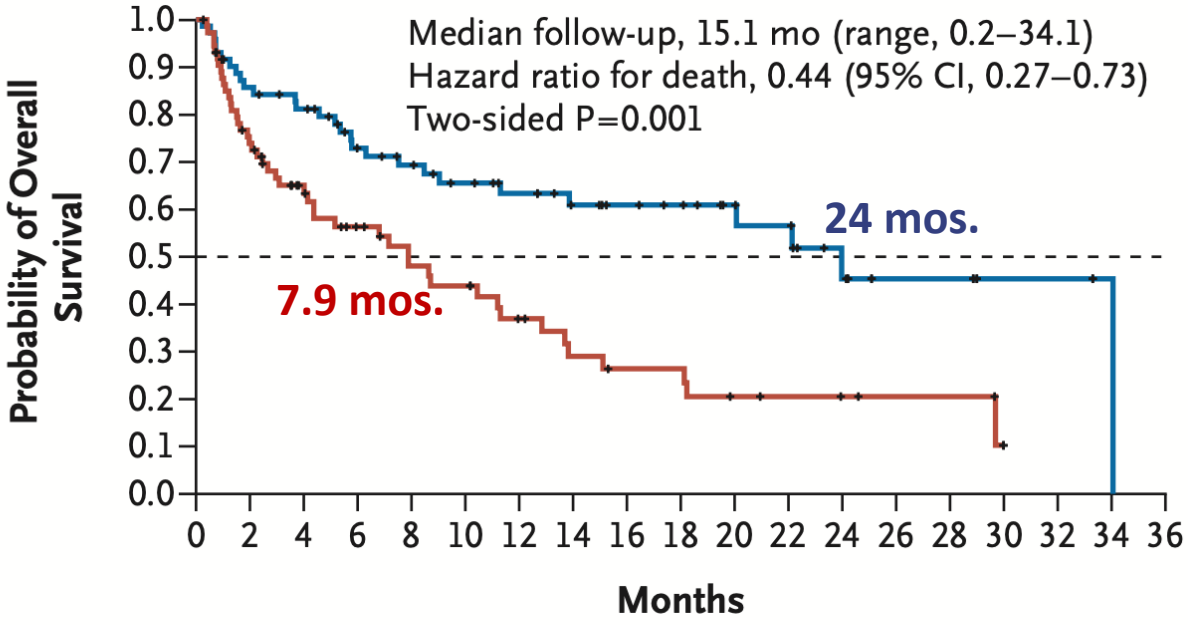
Differentiation syndrome in 15-25%

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					

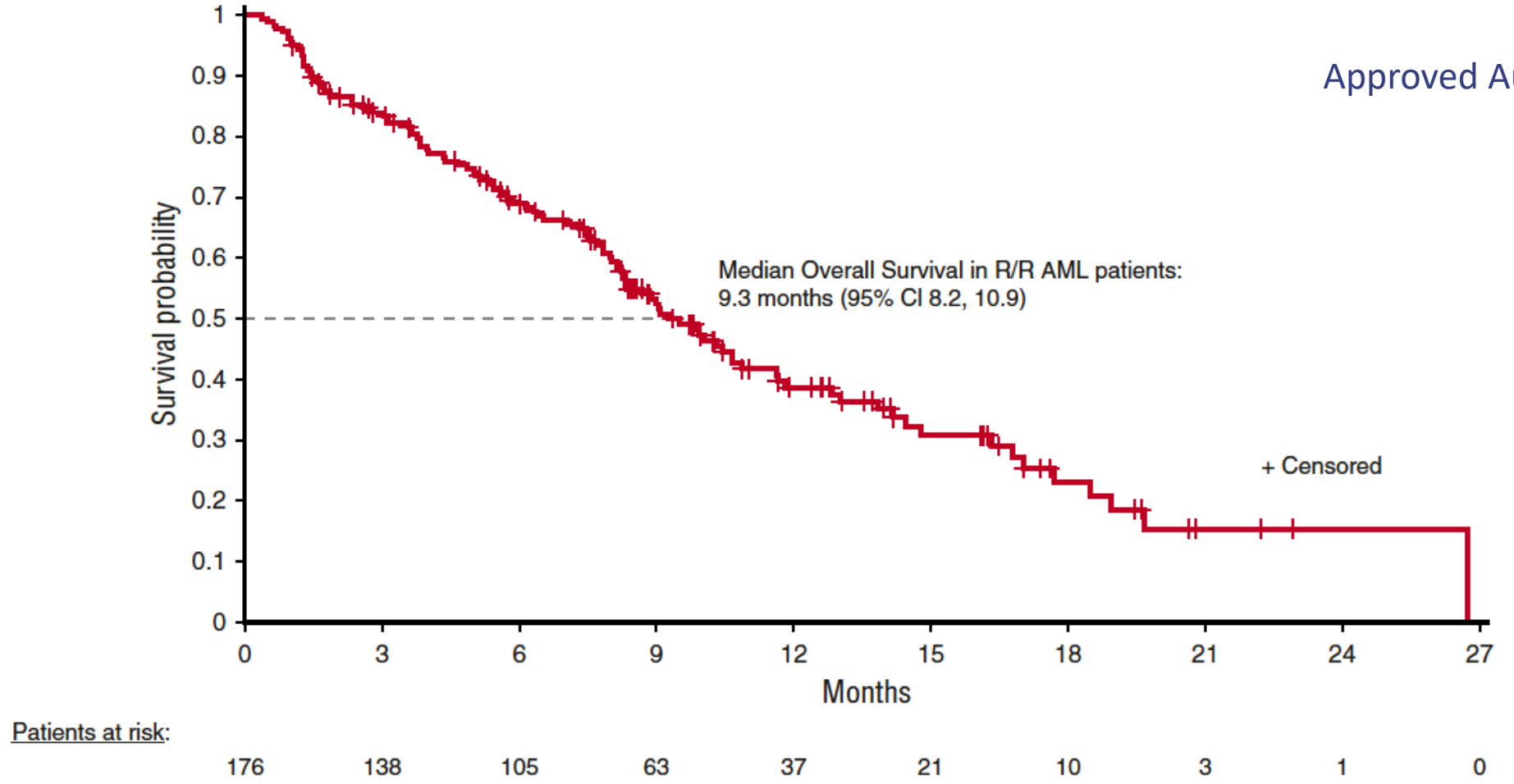


No. at Risk																	
Ivosidenib+ azacitidine	72	58	53	42	38	33	29	24	21	19	15	13	7	4	4	2	2	1
Placebo+ azacitidine	74	53	38	29	23	21	15	11	9	9	6	5	4	3	3	0		

- 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

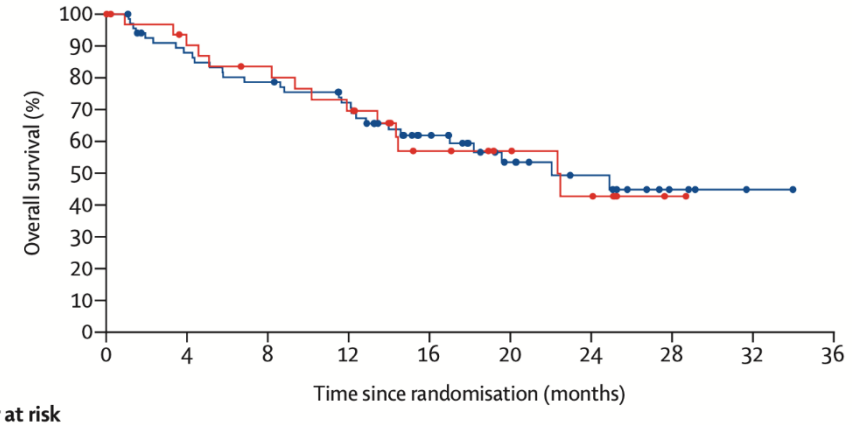


-CR+ CRi in R/R AML = 33%

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

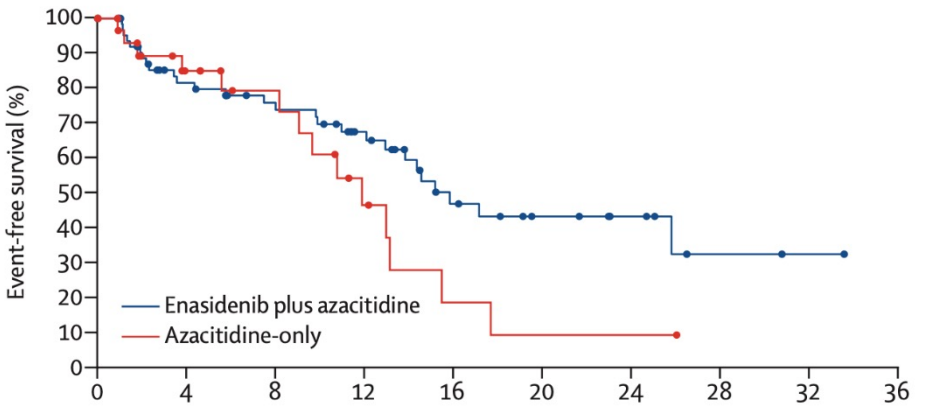
Enasidenib and Azacitidine for Patients with Newly dxd. *IDH2*-mutated AML (AG221-AML-005)

	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)	..

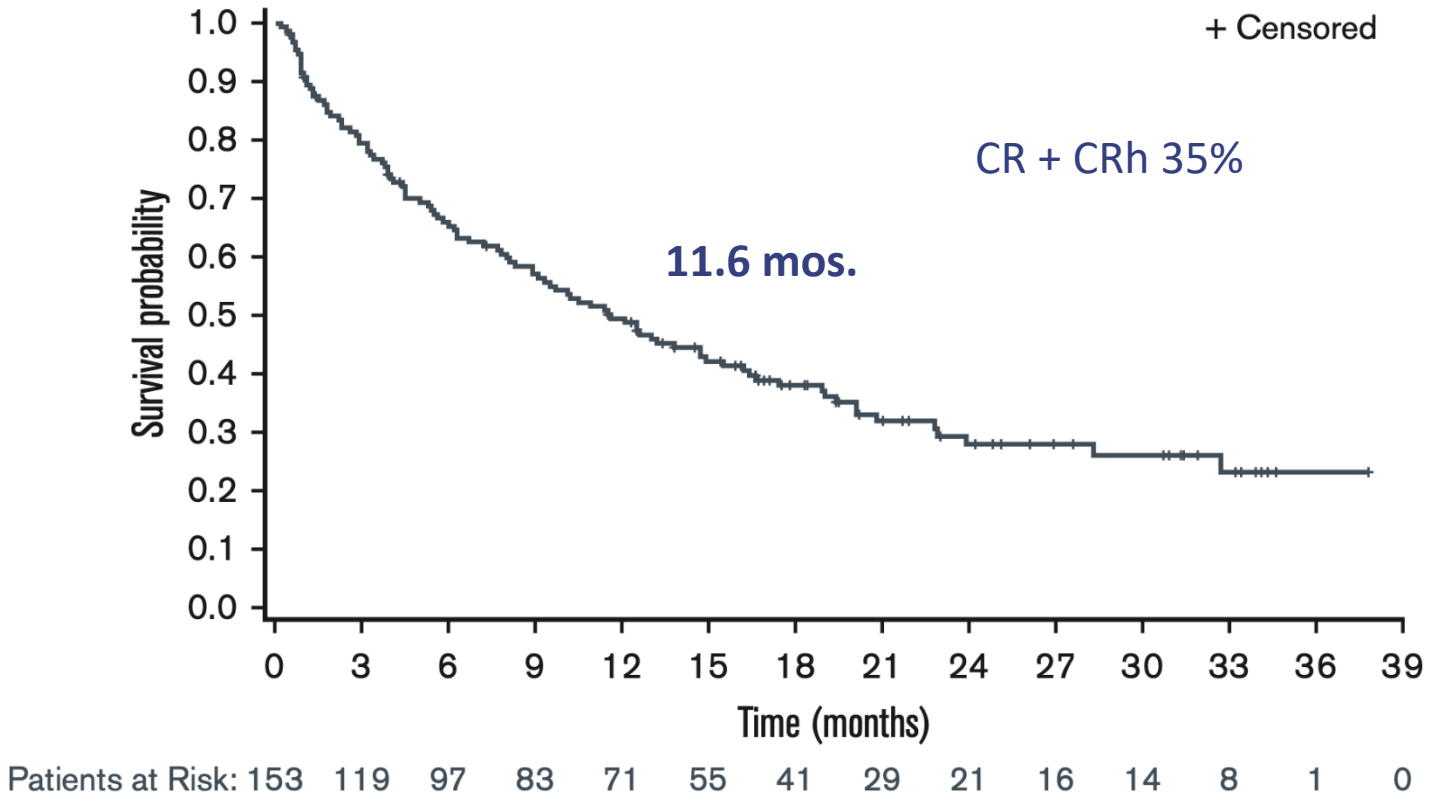
	Enasidenib plus azacitidine (n=68)	Azacitidine only (n=33)
Events	27 (40%)	14 (42%)
Censored	41 (60%)	19 (58%)
Median event-free survival, months	15·9 (95% CI 13·0–NR)	11·9 (95% CI 8·2–15·5)
Hazard ratio	0·59 (95% CI 0·30–1·13)	
Log-rank p value	0·11	



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

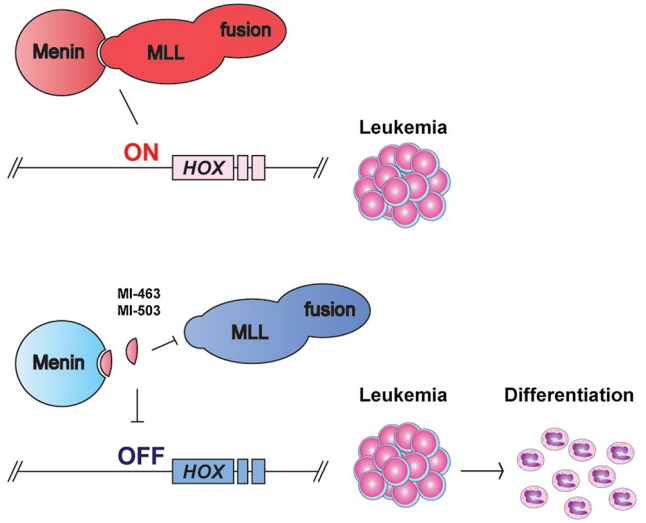
Olutasidenib (FT-2102) for *IDH1*-mutated R/R AML

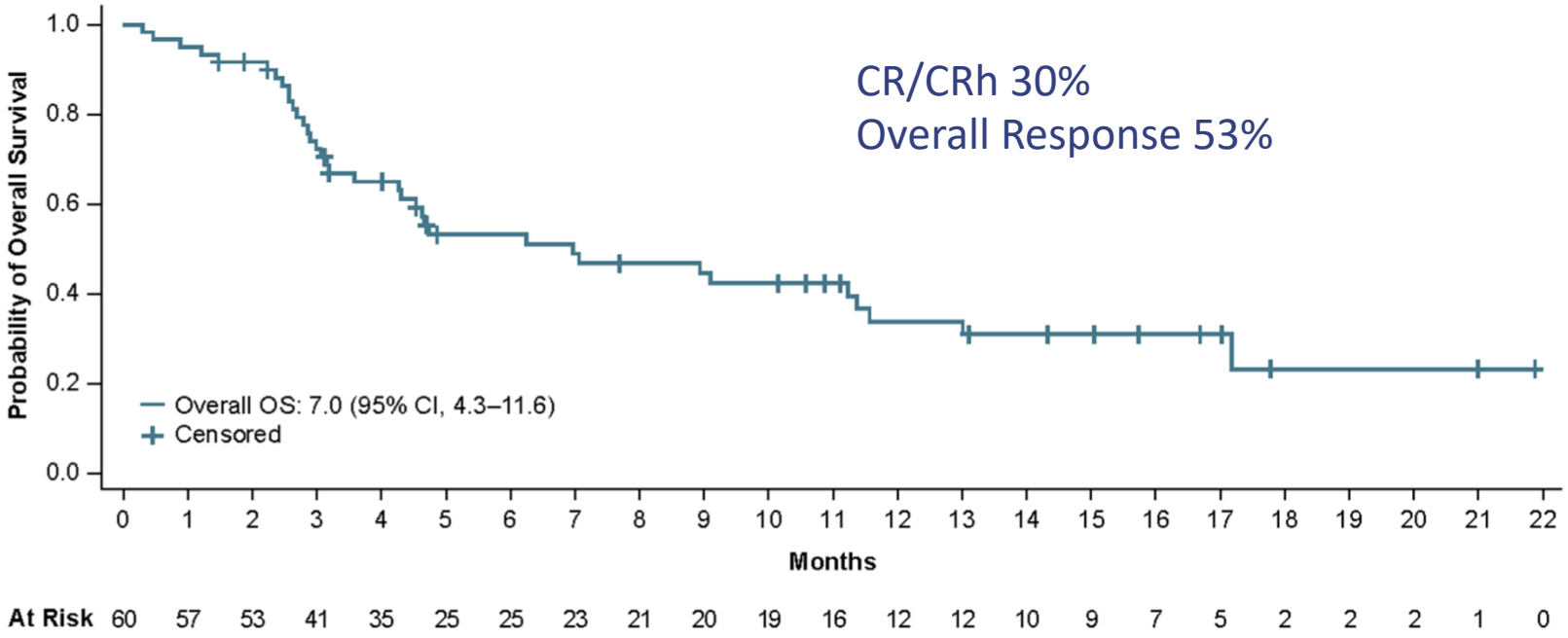


Approved December 2022

-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)



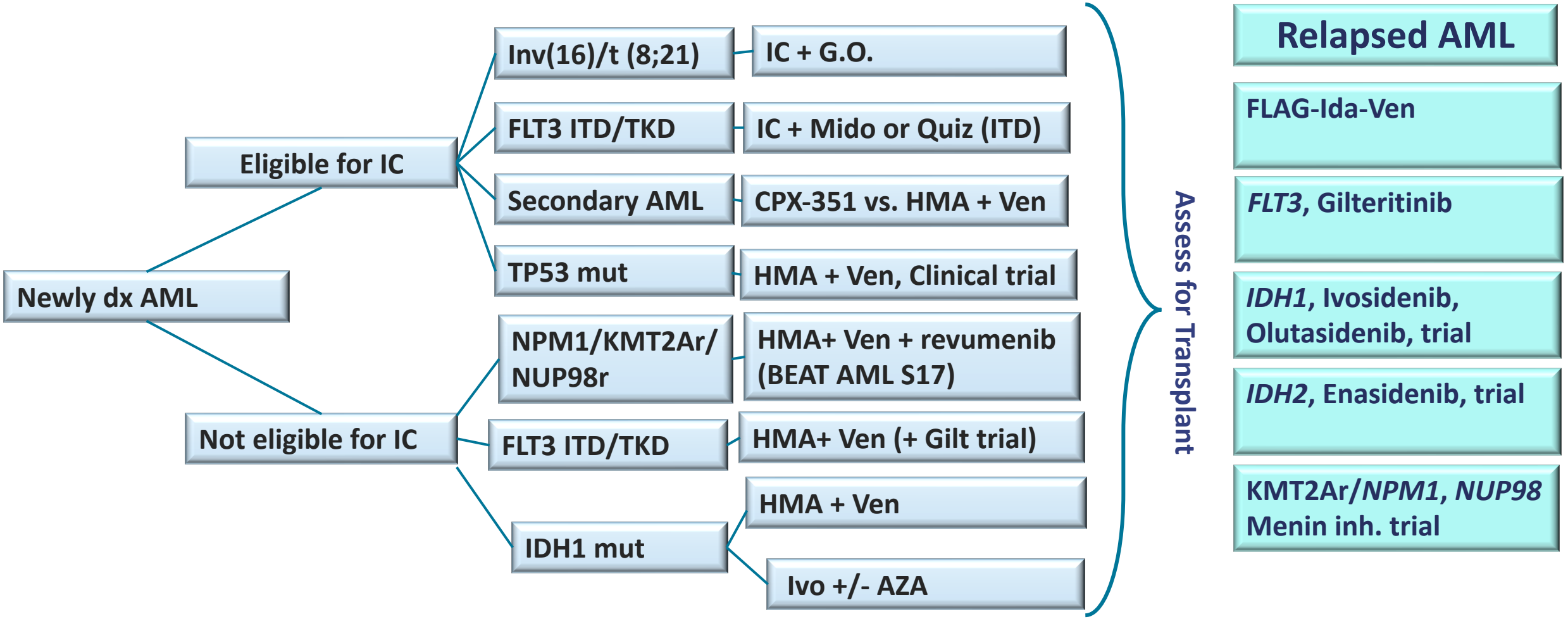


CR/CRh 30%
Overall Response 53%

-Potent, selective oral inhibitor of the menin–KMT2A interaction (*KMT2A*r, *NUP98*r, *NPM1* mut).
-BEAT AML substudy of the triplet SNDX-5613 + Azacitidine + venetoclax combination accruing at Emory.
-Other menin inhibitors 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.

Treatment Algorithm for AML



Consider clinical trial for all patients.

Coming soon, newly dx KMT2Ar/NPM1 mut AML: 2nd generation menin inhibitor combination 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

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

- Nine new targeted agents FDA approved since 2017
- HMA + Venetoclax, backbone for triplet combinations
- Clinical trials still the best option for many patients

Questions?

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