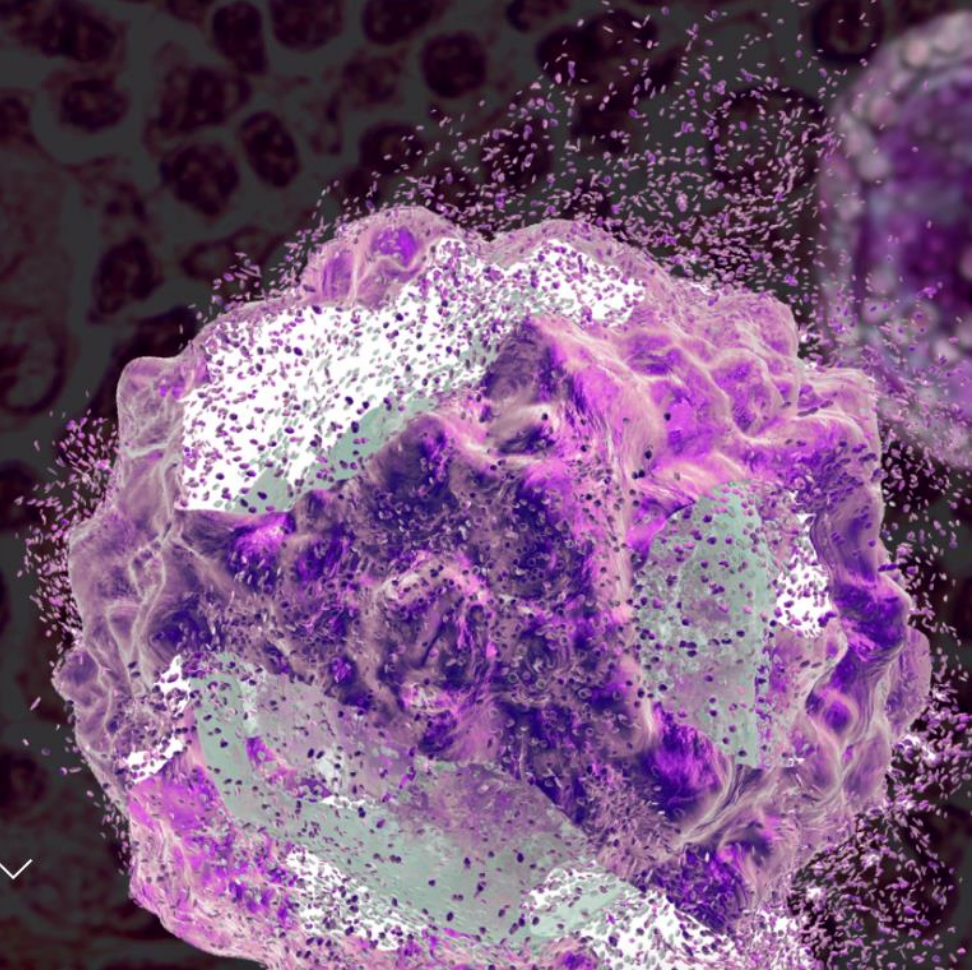
APTOSE BIOSCIENCES

Precision Oncology for Therapies of Tomorrow

Aptose Biosciences is a science-driven clinical-stage biotechnology company developing first-in-class targeted agents to address the unmet clinical need in chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and other hematologic malignancies.



KOL Symposium on CG-806 FLT3 / BTK Inhibitor for Acute Myeloid Leukemia

Rafael Bejar MD, PhD

Chief Medical Officer, Aptose Biosciences

MEETING HOST

APTOSE BIOSCIENCES

Introduction of KOLs for AML

Eytan M. Stein, MD

Hematologic Oncologist

Memorial Sloan Kettering Cancer Center

Clinical Expertise

Acute and Chronic Leukemias, Myelodysplastic Syndromes, Myeloproliferative Neoplasms

Developing Novel Therapies for AML, including AG-120 IDH-1 Inhibitor

Led Development of IDH2 Inhibitor, Enasidenib

Publications in Nature, Nature Medicine, The New England Journal of Medicine, Blood, Leukemia, OIthers

Brian J. Druker, MD

Collaborator & Chair of SAB

Key Role in Dev't of Gleevec

Member, National Academy of Medicine, National Academy of Sciences & American Academy of Arts & Sciences

Winner of Karnofsky Award, Lasker "America's Nobel" Award

Winner of Japan Prize in Healthcare and Medical Technology and the Tang Prize in Biopharmaceutical Science

Winner of the prestigious Sjöberg Prize

Leader of Inter-institutional Beat AML Initiative

Aaron Goldberg, MD, PhD

Hematologic Oncologist

Memorial Sloan Kettering Cancer Center

ASH Fellow Scholar Award in Clinical Research

Advancing Science through Pfizer Investigator Research Exchange (ASPIRE) Oncology/Hematology Clinical Research Award

ASCO Young Investigator Award

Franklyn Ellenbogen Prize in Hematology-Oncology, Weill Cornell Medical College

Clinical Expertise

Acute and Chronic Leukemias, Myelodysplastic Syndromes, Myeloproliferative Neoplasms

AGENDA

- **Eytan Stein, MD**
  - AML in the Age of Targeted Therapies
- **Aaron Goldberg, MD, PhD**
  - FLT3 Inhibitors: Recent Advances and Emerging Challenges
- **Rafael Bejar, MD, PhD**
  - Introduction to CG-806
- **Brian Druker, MD**
  - Evolution of Kinase Inhibitors
  - Perspectives of CG-806 with AML
- **Summary with Q&A**

Eytan M. Stein, MD

Hematologic Oncologist

Memorial Sloan Kettering Cancer Center

AML in the Age of Targeted Therapies

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Memorial Sloan Kettering Cancer Center

Treatment of Acute Myeloid Leukemia in the Age of Targeted Therapies

Eytan M. Stein, MD

Assistant Attending Physician

Director, Program for Drug Development in Leukemia

Leukemia Service, Department of Medicine
Memorial Sloan Kettering Cancer Center

New York, New York

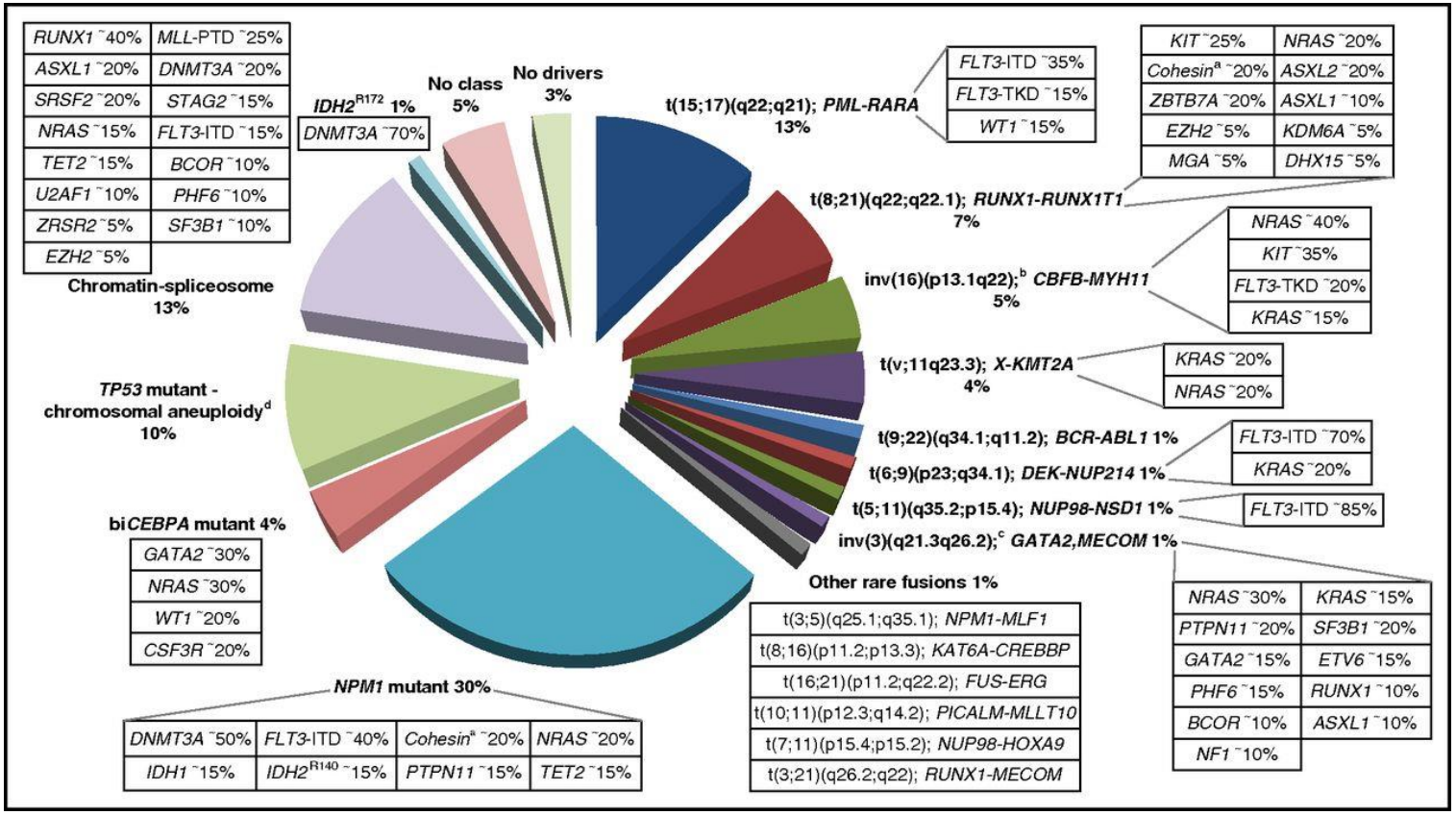
Disclosures

- **Advisory Board Participation:** Abbvie, Agios, Aptose, Astellas, Celgene, Bayer, Pfizer, PTC Therapeutics, Daiichi-Sankyo, Novartis, Syros.

- **Equity (Founder)**: Auron Therapeutics

- **Research Funding:** Agios, Amgen, Celgene, Bayer, Biotheryx, Syndax, Syros.

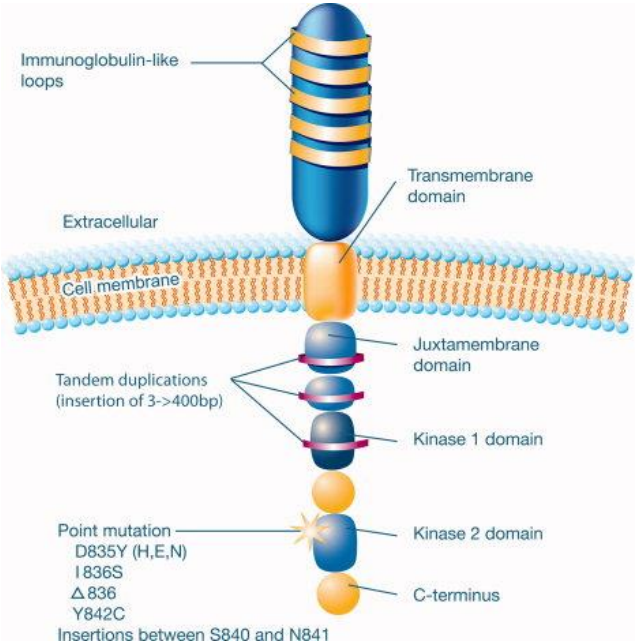
Cyto/Molecular Heterogeneity of Acute Myeloid Leukemia



Dohner, Blood, 2017

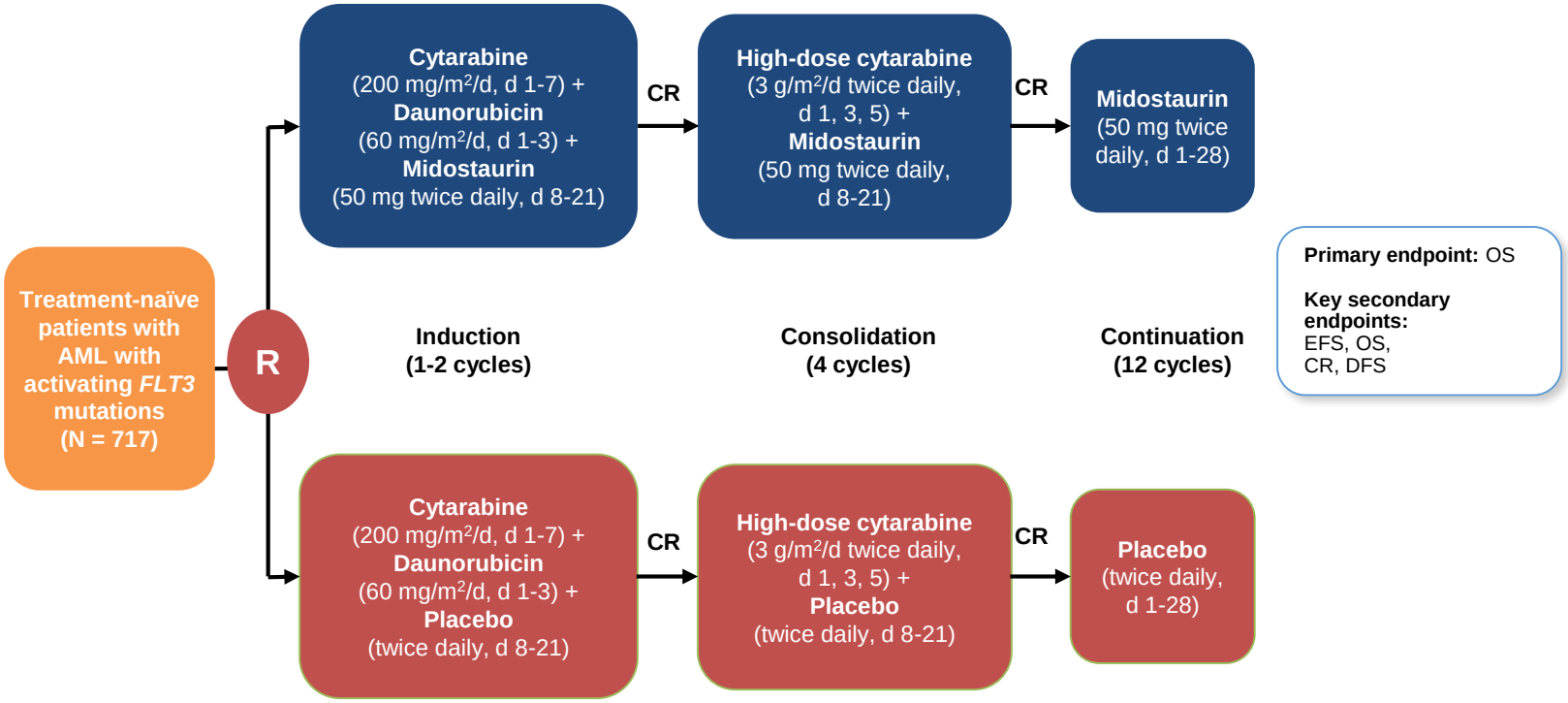
FLT3 Inhibitors

- **FLT-3 ITD found in 30% of cytogenetically normal AML**
- **Constitutive activation of FLT-3 receptor**
- **Confers a poor prognosis**
- **Multiple attempts to target FLT-3**



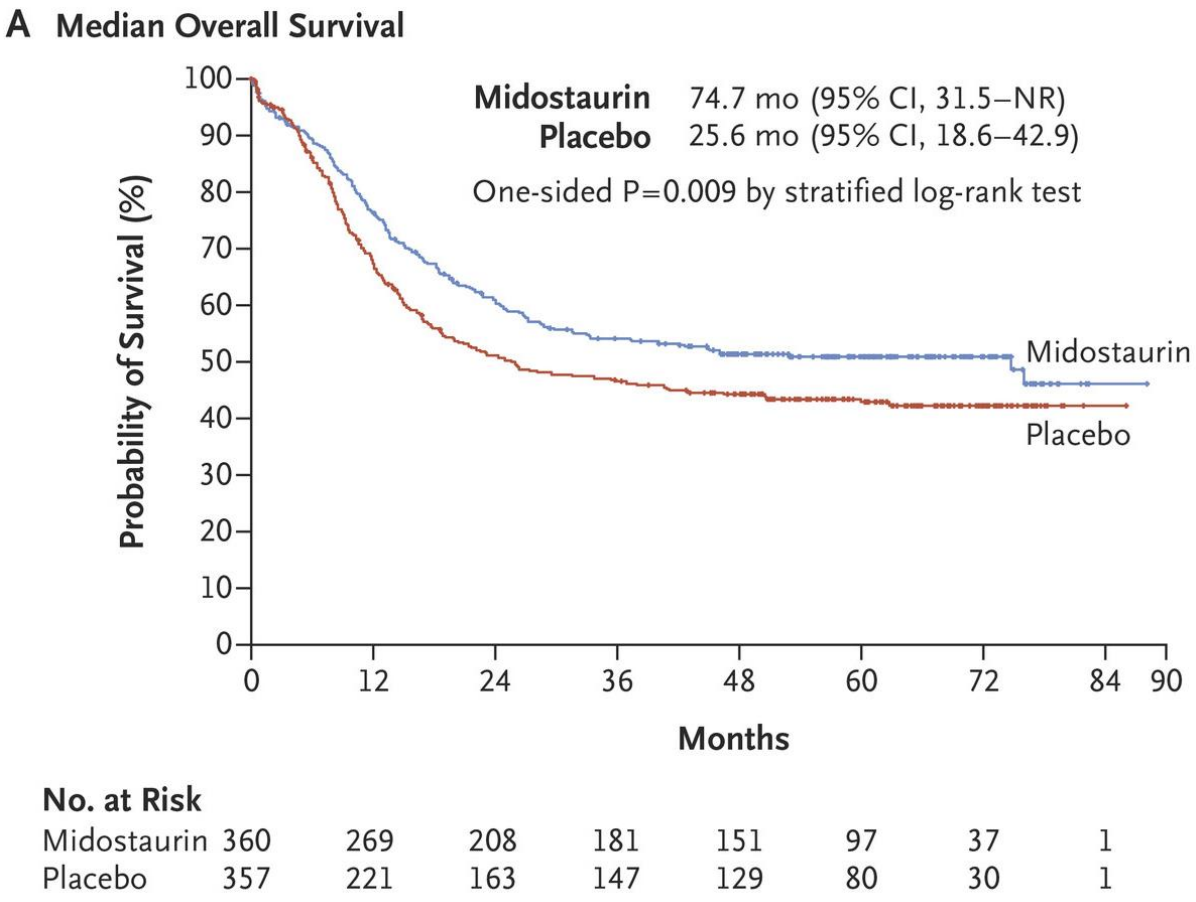
Cancer; pages 3293-3304, 11 FEB 2011 DOI: 10.1002/cncr.25908

Phase 3 RATIFY Study: Chemotherapy ± Midostaurin in Newly Diagnosed AML



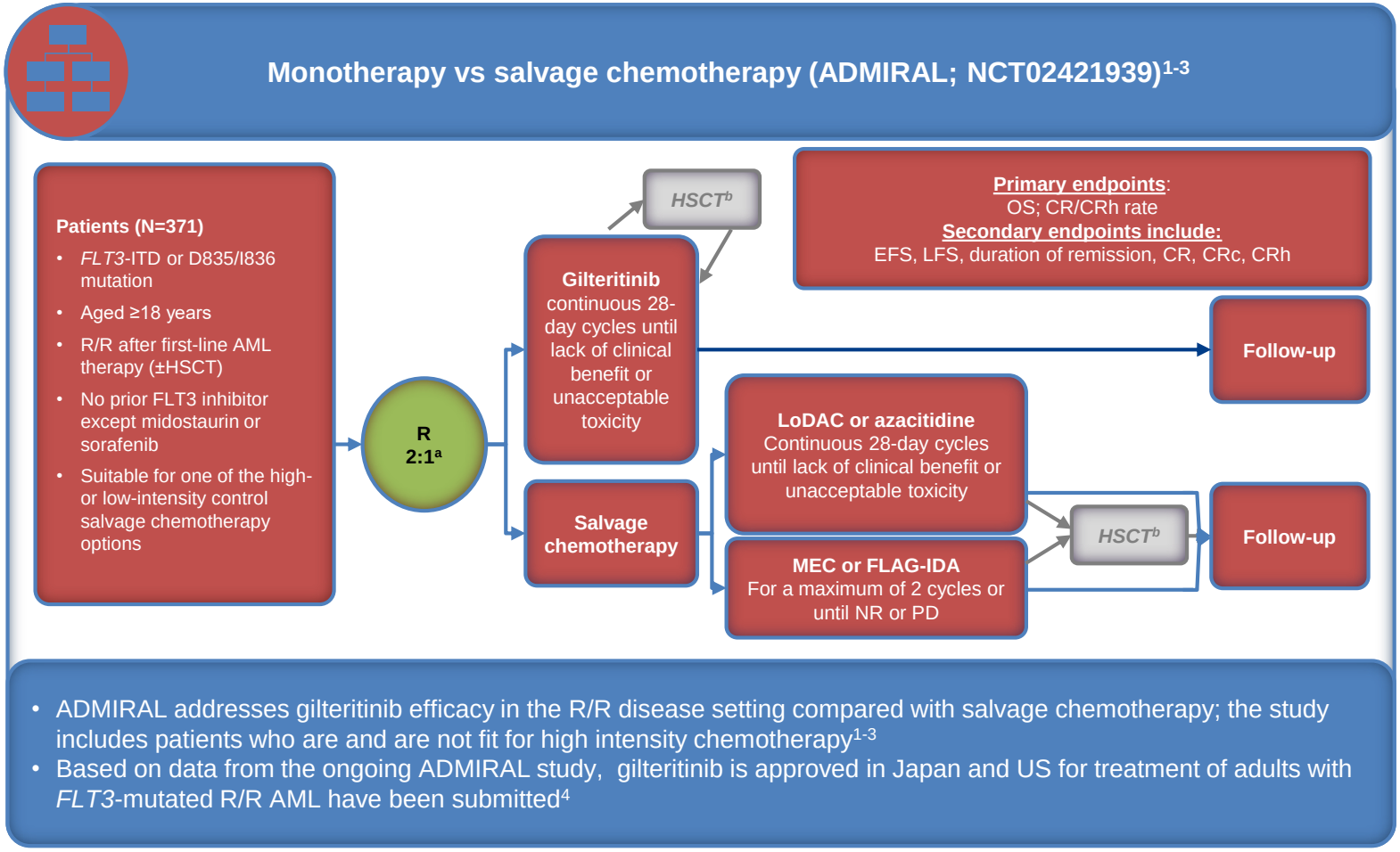
1 Stone RM et al. *N Engl J Med*. 2017;377:454-464.

RATIFY – Overall Survival



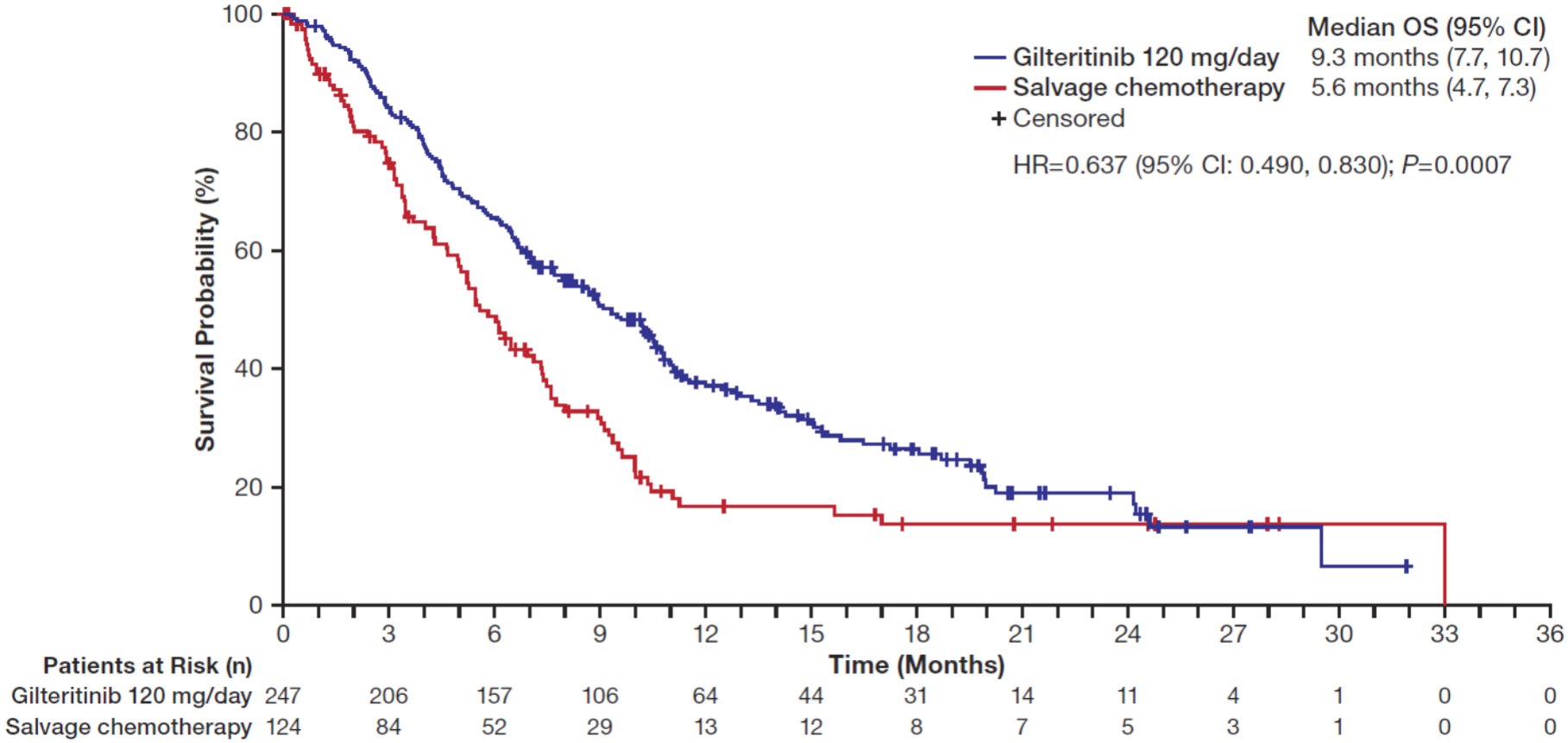
Stone RM et al. *N Engl J Med*. 2017;377:454-464.

Gilteritinib – Phase III ADMIRAL Study



- ADMIRAL addresses gilteritinib efficacy in the R/R disease setting compared with salvage chemotherapy; the study includes patients who are and are not fit for high intensity chemotherapy[1-3]
- Based on data from the ongoing ADMIRAL study, gilteritinib is approved in Japan and US for treatment of adults with *FLT3*-mutated R/R AML have been submitted[4]

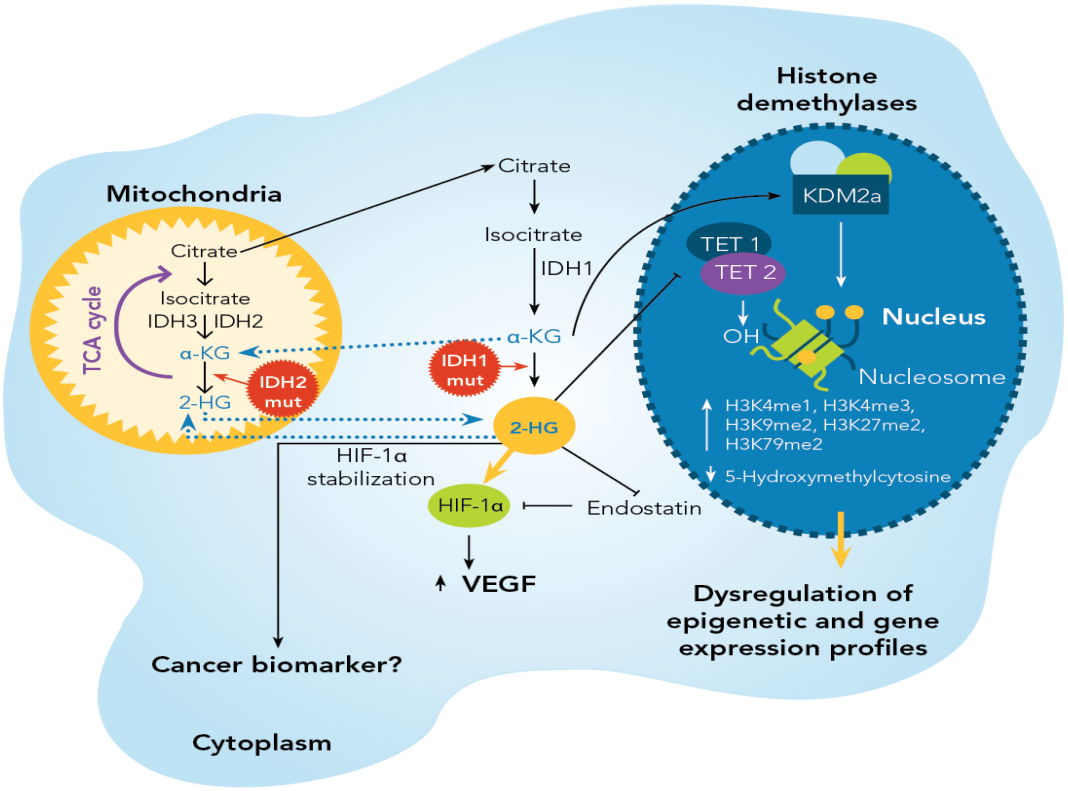
ADMIRAL: Overall Survival (ITT Population: N=371)



Perl A, NEJM, 2019

IDH1 and IDH2

Pathogenesis of IDH Mutant AML



- **IDH1 in cytoplasm and IDH2 in mitochondria**
- **Cancer-associated IDHm produces 2-hydroxyglutarate (R-2-HG)**

Prensner and Chinnaiyan Nature, 2011

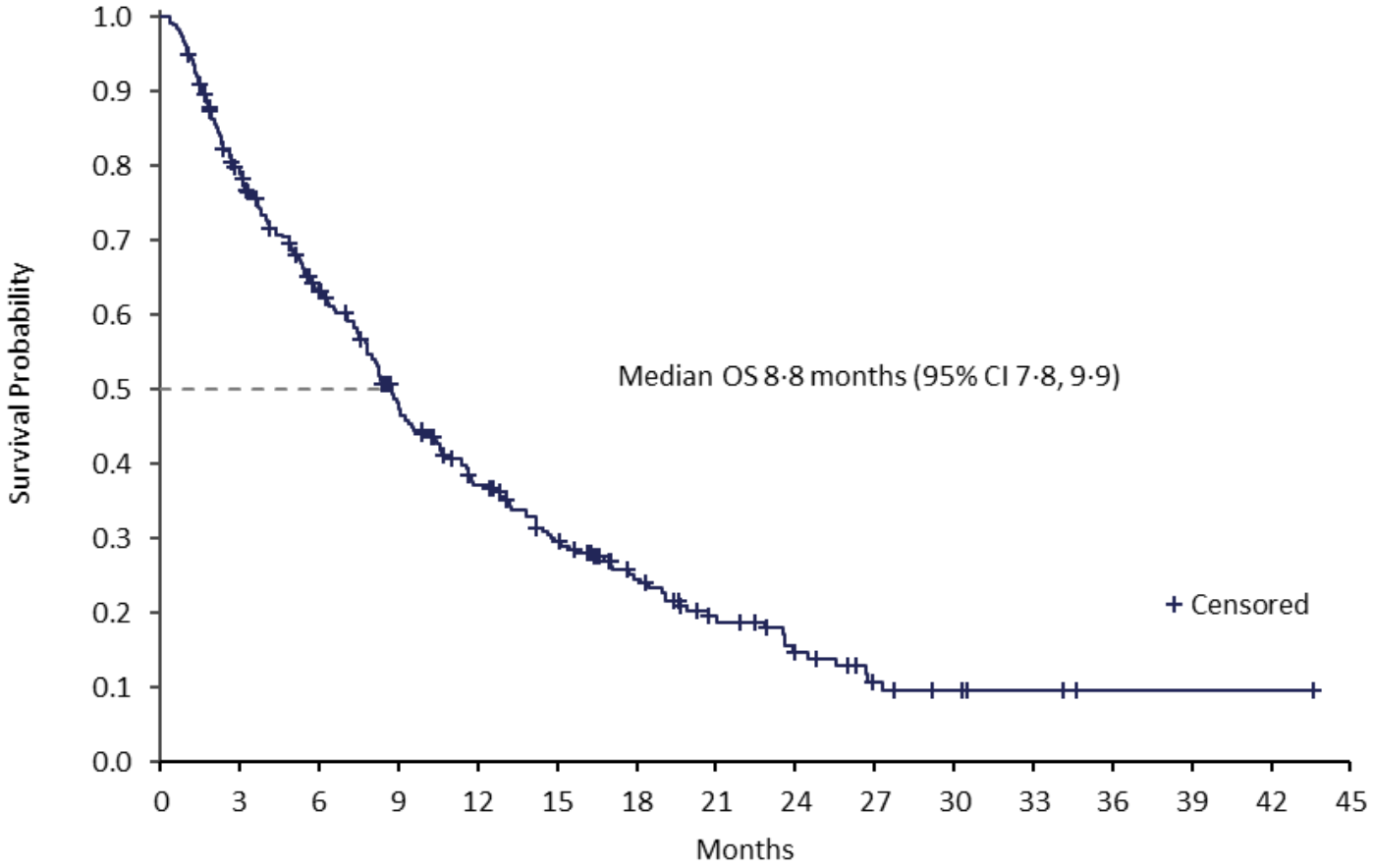
ENAsidenib (IDH2)

Efficacy of Enasidenib in R/R AML

	Relapsed/Refractory AML	
	Enasidenib 100 mg/day (n=214)	**All patients (N=280)**
Overall response rate (ORR),* % (n/N)	**38.8% (83/214)**	**39.6% (111/280)**
[95%CI for ORR]	[32.2%, 45.7%]	[33.9%, 45.6%]
CR + CRi/CRp rate, % (n/N)	29.0% (62/214)	27.9% (78/280)
Best response		
Complete remission (CR), n (%)	42 (19.6)	53 (18.9)
[CR rate 95%CI]	[14.5%, 25.6%]	[14.5%, 24.0%]
CR with incomplete count recovery (CRi/CRp), n (%)	20 (9.3)	25 (8.9)
Partial remission, n (%)	9 (4.2)	17 (6.1)
Morphologic leukemia-free state, n (%)	12 (5.6)	16 (5.7)
Stable disease,† n (%)	98 (45.8)	122 (43.6)
Progressive disease,‡ n (%)	19 (8.9)	26 (9.3)
Not evaluable, n (%)	3 (1.4)	4 (1.4)
Time to first response, months, median (range)	1.9 (0.5-9.4)	1.9 (0.5-9.4)
Duration of response, months, median [95%CI]	5.6 [3.8, 7.4]	5.6 [4.6, 6.5]
Time to best response, months, median (range)	3.7 (0.6-14.7)	3.7 (0.5-14.7)
Time to CR, months, median (range)	3.7 (0.7-14.7)	3.8 (0.5-14.7)
Overall survival, months, median [95%CI]	8.8 [7.7, 9.6]	8.8 [7.8, 9.9]
Event-free survival,§ months, median [95%CI]	4.7 [3.7, 5.6]	4.6 [3.7, 5.6]

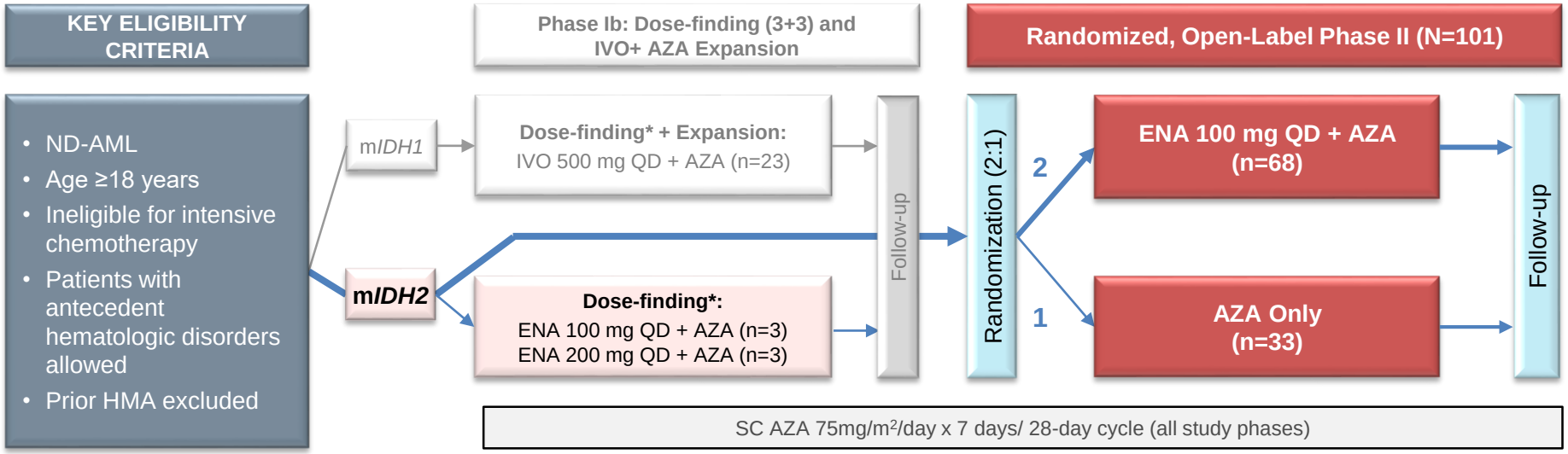
Stein EM, Dinardo CD, *Blood,* December 2018

Overall Survival – All R/R Patients



Stein EM, Dinardo CD, et al, Blood 2017

Newly Diagnosed IDH2 Mutant AML – Aza ± Enasidenib



Primary Endpoint: ORR

Key Secondary Endpoints: CR rate, safety, overall survival (OS), event-free survival (EFS)

Dinardo CD, ASH, 2019

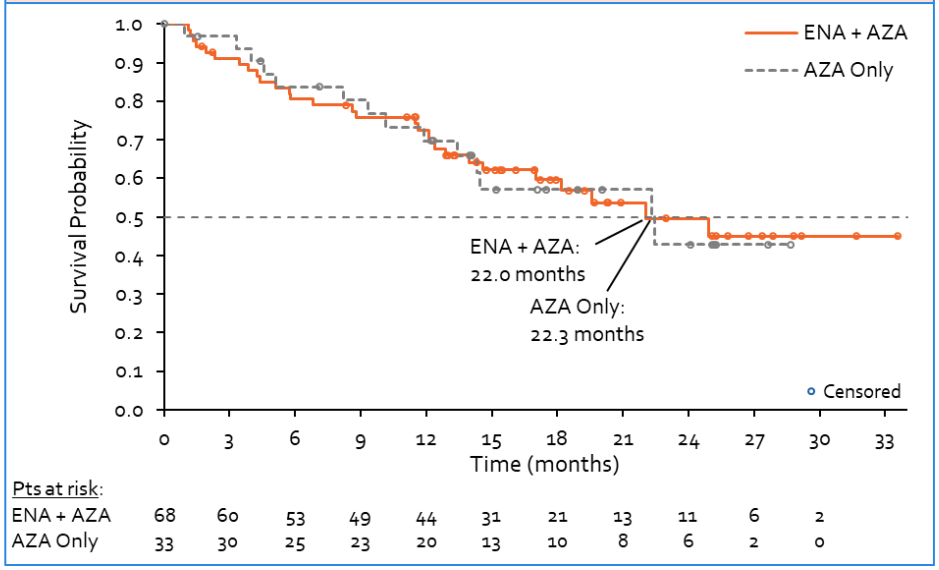
RESPONSE

	ENA + AZA (n=68)	AZA Only (n=33)
Overall response (CR, CRi/CRp, PR, MLFS), n (%)	**48 (71)**	**14 (42)**
[ORR 95%CI]	[58, 81]	[26, 61]
***P* value**	**0.0064**	
CR, n (%)	36 (53)	4 (12)
[CR rate 95%CI]	[41, 65]	[3, 28]
***P* value**	**0.0001**	
CRi/CRp, n (%)	7 (10)	4 (12)
PR, n (%)	3 (4)	4 (12)
MLFS, n (%)	2 (3)	2 (6)
Stable disease, n (%)	13 (19)	13 (39)
Disease progression, n (%)	2 (3)	1 (3)
Not evaluable / Missing, n (%)	5 (7)	5 (15)
Time to first response, months, median (range)	1.9 (0.7–9.0)	2.0 (0.8–5.8)
Time to CR, months, median (range)	5.5 (0.7–19.5)	3.7 (3.0–4.1)
Duration of response, months, median [95%CI]	24.1 [11.1, NR]	12.1 [2.8, 14.6]

Dinardo CD, ASH, 2019

SURVIVAL

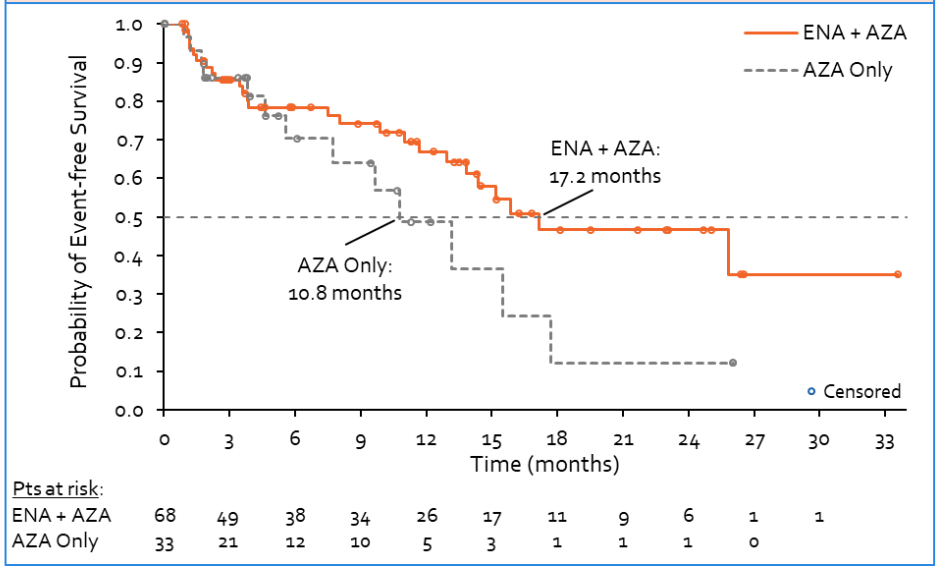
Overall survival



Pts at risk:

ENA + AZA	68	60	53	49	44	31	21	13	11	6	2
AZA Only	33	30	25	23	20	13	10	8	6	2	0

Event-free survival



Pts at risk:

ENA + AZA	68	49	38	34	26	17	11	9	6	1	1
AZA Only	33	21	12	10	5	3	1	1	1	0	

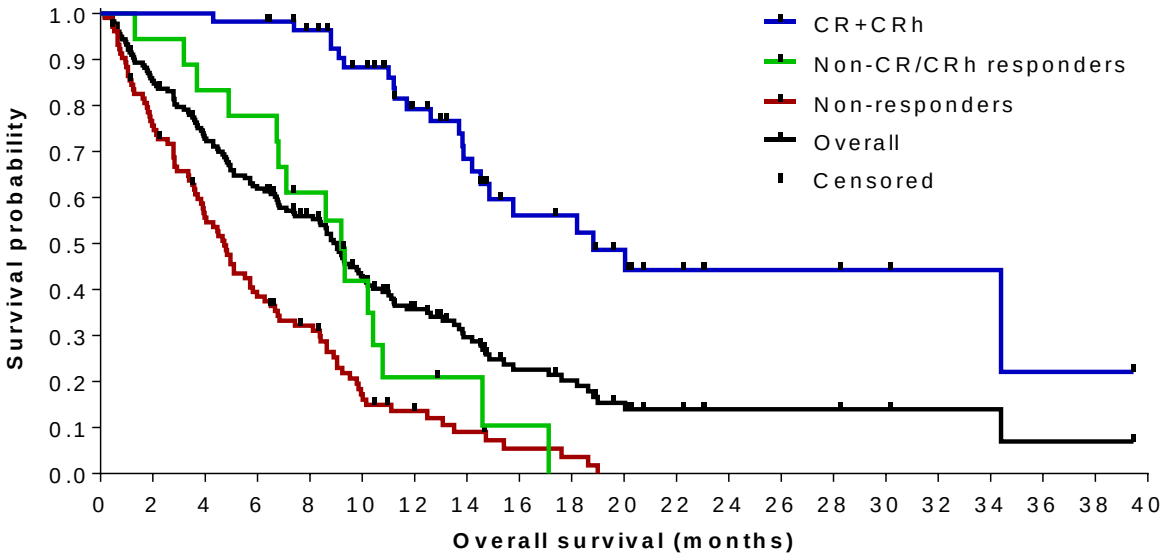
IVOsidenib (IDH1 inhibitor)

Ivosidenib – Response and Response Duration

Response	Primary Efficacy Population (N=125)	Relapsed or Refractory AML (N=179)
CR or CRh		
No. of patients	38	54
% (95% CI)	30.4 (22.5–39.3)	30.2 (23.5–37.5)
Median time to CR or CRh (range) — mo	2.7 (0.9–5.6)	2.0 (0.9–5.6)
Median duration of CR or CRh (95% CI) — mo	8.2 (5.5–12.0)	6.5 (5.5–11.1)
CR		
No. of patients	27	39
% (95% CI)	21.6 (14.7–29.8)	21.8 (16.0–28.6)
Median time to CR (range) — mo	2.8 (0.9–8.3)	2.8 (0.9–8.3)
Median duration of CR (95% CI) — mo	9.3 (5.6–18.3)	9.3 (5.6–12.5)
Overall response		
No. of patients	52	70
% (95% CI)	41.6 (32.9–50.8)	39.1 (31.9–46.7)
Median time to first response (range) — mo§	1.9 (0.8–4.7)	1.9 (0.8–4.7)
Median duration of response (95% CI) — mo	6.5 (4.6–9.3)	6.5 (4.6–9.3)

CD Dinardo, EM Stein, S deBotton et. al. N Engl J Med 2018.

Overall Survival by Best Response in R/R AML 500 mg (n=179)



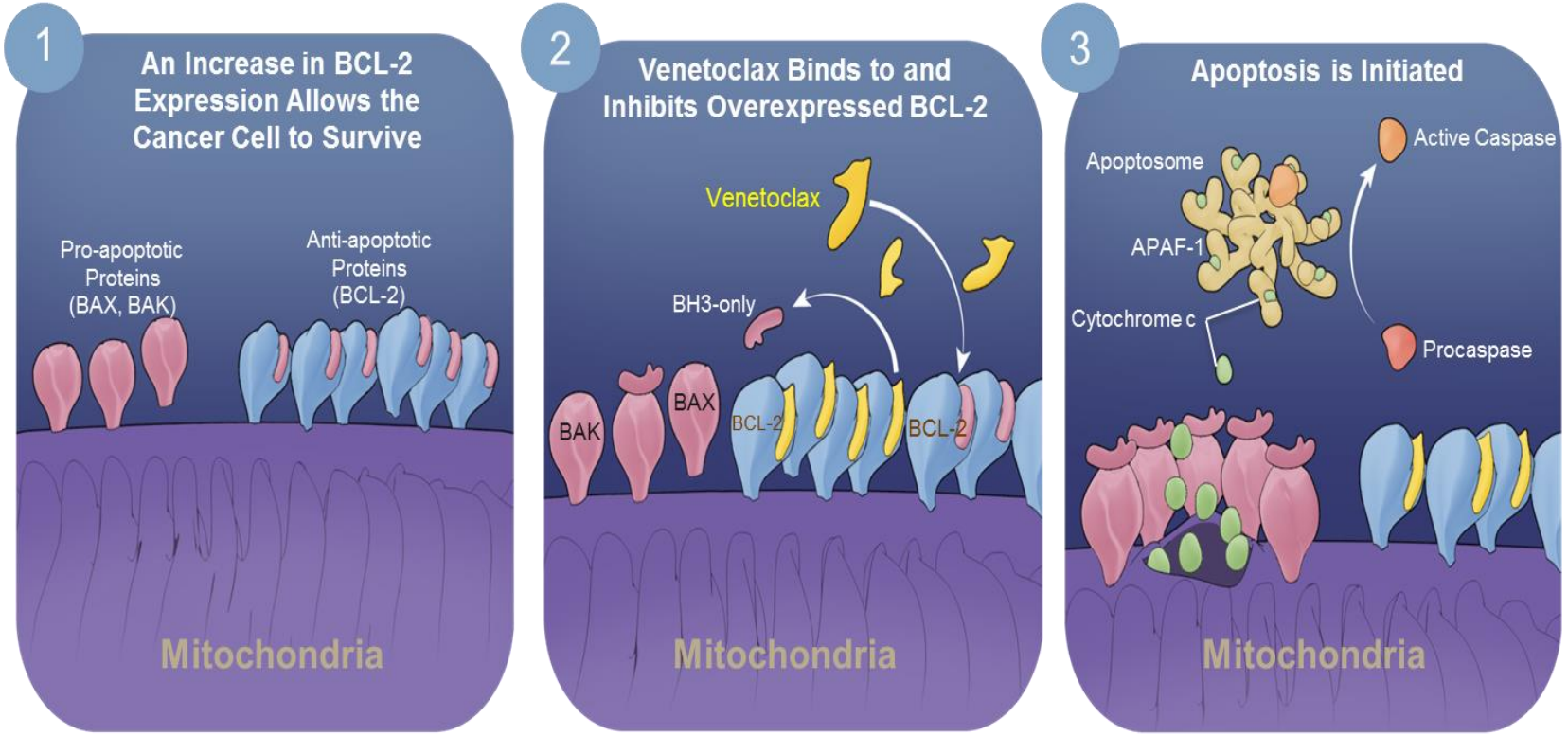
Number of patients at risk:

CR+CRh	57	57	57	56	50	43	32	25	16	15	11	7	4	4	4	3	2	2	1	1
Non-CR/CRh responders	18	17	15	14	10	6	3	2	1	0										
Non-responders	104	77	55	38	29	15	9	6	3	2	0									

	Months
Overall survival, median [95% CI]	
CR+CRh	18.8 [14.2, NE]
Non-CR/CRh responders	9.2 [6.7, 10.8]
Non-responders	4.7 [3.7, 5.7]
All	9.0 [7.1, 10.0]
Overall follow-up, median (range)	15.3 (0.2–39.5)

Pollyea D, et al, ASCO 2018

Target 🎯 – BCL-2


1
An Increase in BCL-2 Expression Allows the Cancer Cell to Survive
Pro-apoptotic Proteins (BAX, BAK)
Anti-apoptotic Proteins (BCL-2)
Mitochondria
2
Venetoclax Binds to and Inhibits Overexpressed BCL-2
Venetoclax
BH3-only
BAK
BAX
BCL-2
BCL-2
Mitochondria
3
Apoptosis is Initiated
Apoptosome
APAF-1
Cytochrome c
Active Caspase
Procaspase
Mitochondria

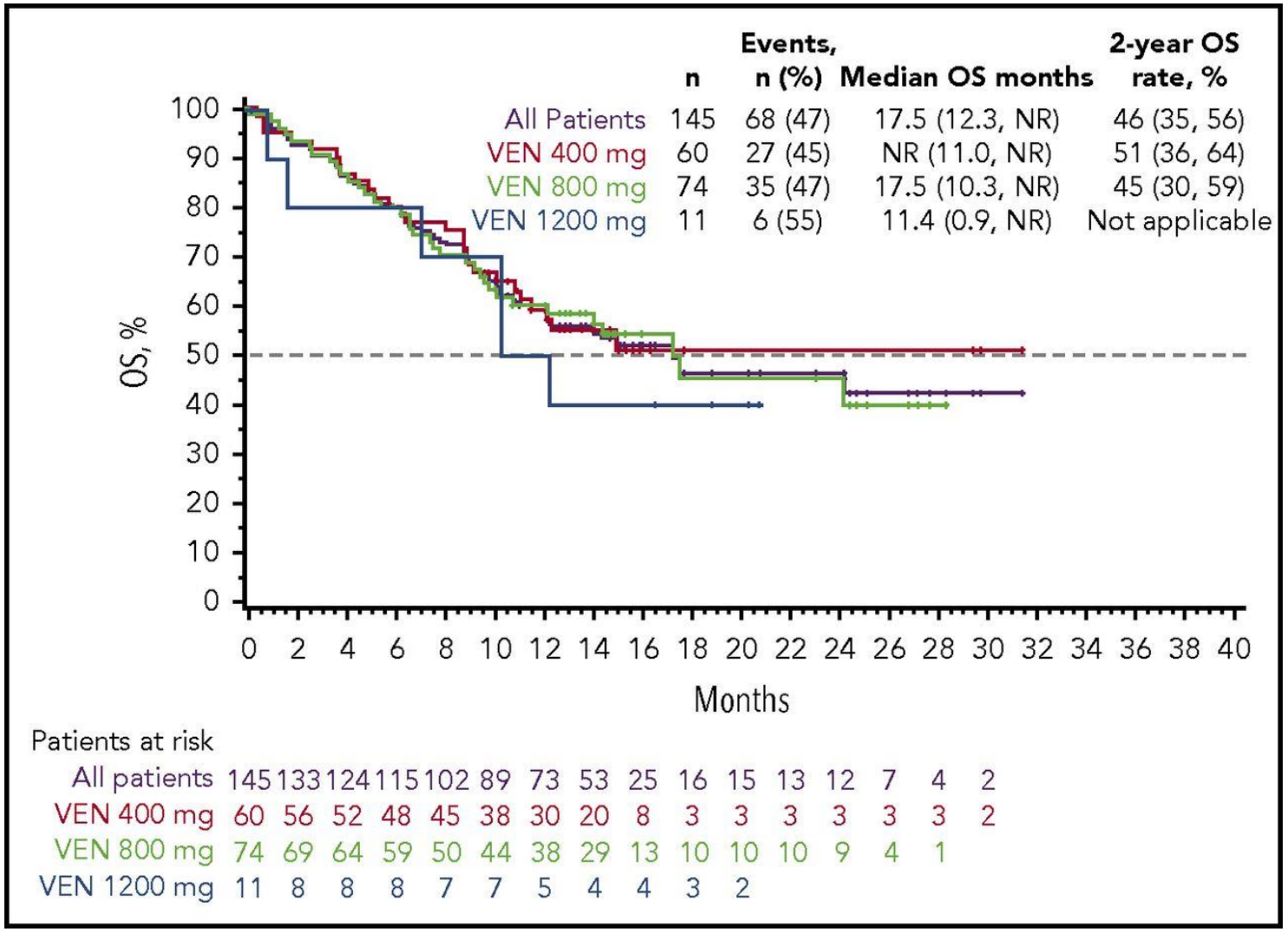
"Unfit" Patients – HMA/Venetoclax

Table 5. Efficacy outcomes by subgroups

Subgroup	Evaluable for response/OS, n (%)	CR + CRi, n (%)	n for Median duration of CR + CRi	Median duration of CR + CRi, mo (95%CI)	Median OS, mo (95%CI)
All patients	145	97 (67)	97	11.3 (8.9, NR)	17.5 (12.3-NR)
Cytogenetic risk					
Intermediate	74 (51)	55 (74)	55	12.9 (11, NR)	NR (17.5-NR)
Poor	71 (49)	42 (60)	42	6.7 (4.1, 9.4)	9.6 (7.2-12.4)
Age					
≥75 y	62 (43)	40 (65)	40	9.2 (6.4, 12.5)	11 (9.3-NR)
<75 y	83 (57)	57 (69)	57	12.9 (9.2, NR)	17.7 (14.2-NR)
AML					
De novo	109 (75)	73 (67)	73	9.4 (7.2, 11.7)	12.5 (10.3-24.4)
Secondary	36 (25)	24 (67)	24	NR (12.5, NR)	NR (14.6-NR)
Mutations*					
FLT3†	18 (12)	13 (72)	13	11 (6.5, NR)	NR (8-NR)
IDH1 or 2‡	35 (24)	25 (71)	25	NR (6.8, NR)	24.4 (12.3-NR)
NPM1	23 (16)	21 (91)	21	NR (6.8, NR)	NR (11-NR)
TP53	36 (25)	17 (47)	17	5.6 (1.2, 9.4)	7.2 (3.7-NR)

Courtney D. DiNardo et al. Blood 2019;133:7-17

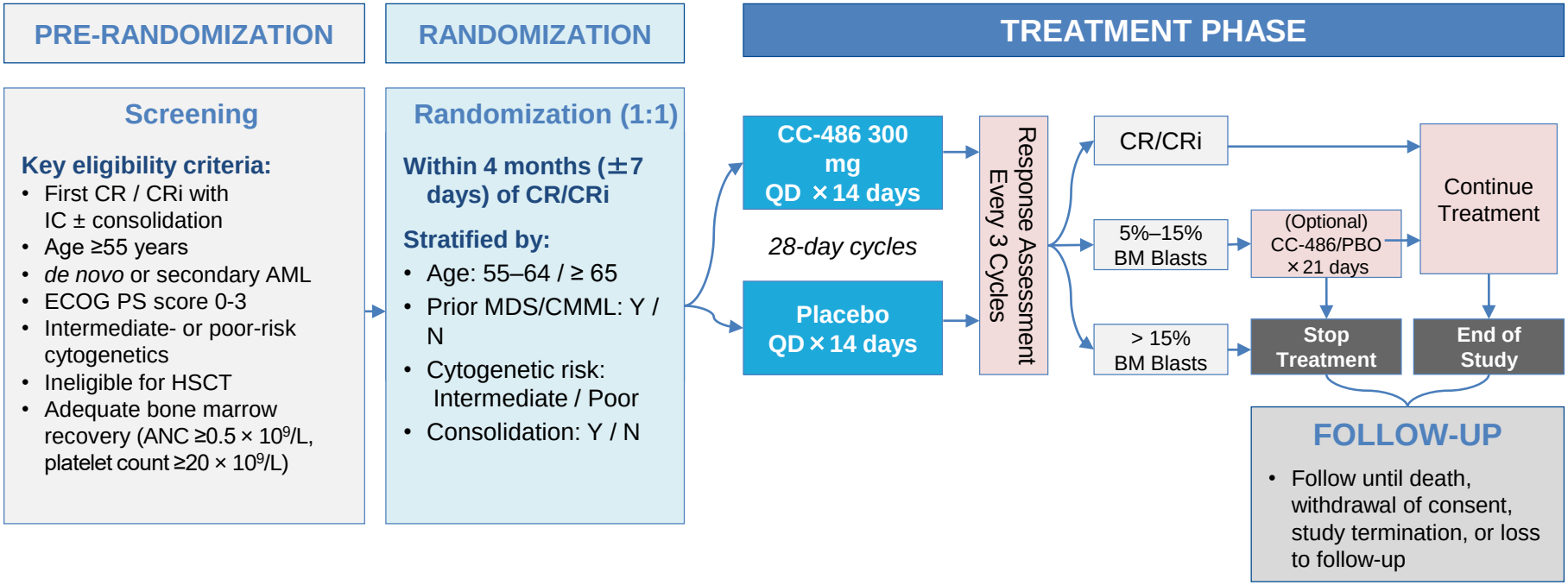
"Unfit" Patients – HMA/Venetoclax



Courtney D. DiNardo et al. Blood 2019;133:7-17

Maintenance - QUAZAR AML-001: Study design

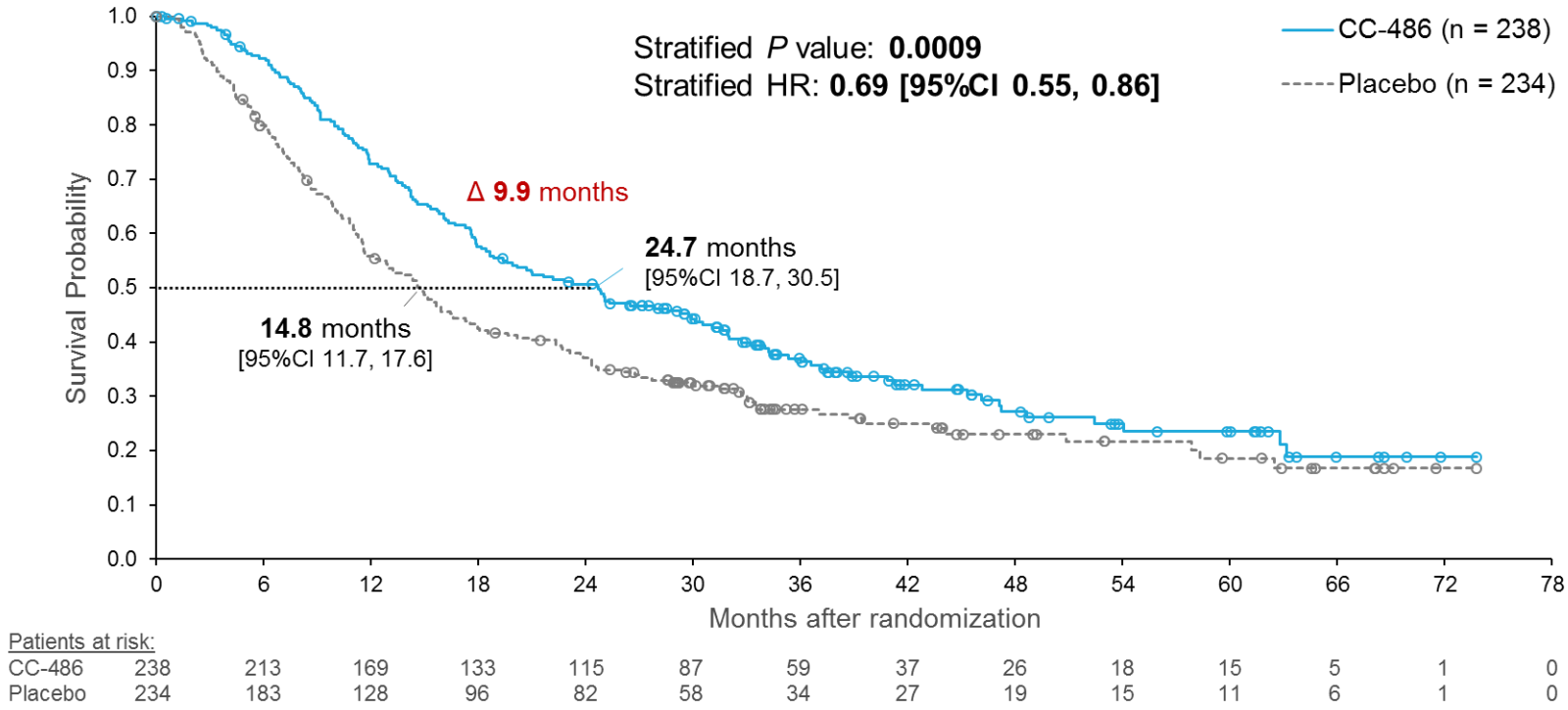
International, multicenter, placebo-controlled, double-blind, randomized, phase III study that enrolled patients from 148 sites in 23 countries (NCT01757535)



Wei A, ASH 2019

Primary endpoint: Overall Survival from randomization

- Median follow-up: 41.2 months



Patients at risk:

CC-486	238	213	169	133	115	87	59	37	26	18	15	5	1	0
Placebo	234	183	128	96	82	58	34	27	19	15	11	6	1	0

Wei A, ASH 2019

Thank You!

steine@mskcc.org

Aaron Goldberg, MD, PhD

Hematologic Oncologist

Memorial Sloan Kettering Cancer Center

FLT3 Inhibitors:

Recent Advances and Emerging Challenges

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Memorial Sloan Kettering Cancer Center

FLT3 Inhibition in Acute Myeloid Leukemia: Recent Advances and Emerging Challenges

Aaron D. Goldberg, MD, PhD
Assistant Attending Physician
Leukemia Service

February 5, 2020

Disclosures

- **Consulting/Advisory Board Participation:**
  - Abbvie, Aptose, Celgene, Daiichi-Sankyo
- **Research Funding:**
  - Abbvie, Aprea, Arog, Daiichi-Sankyo, Pfizer

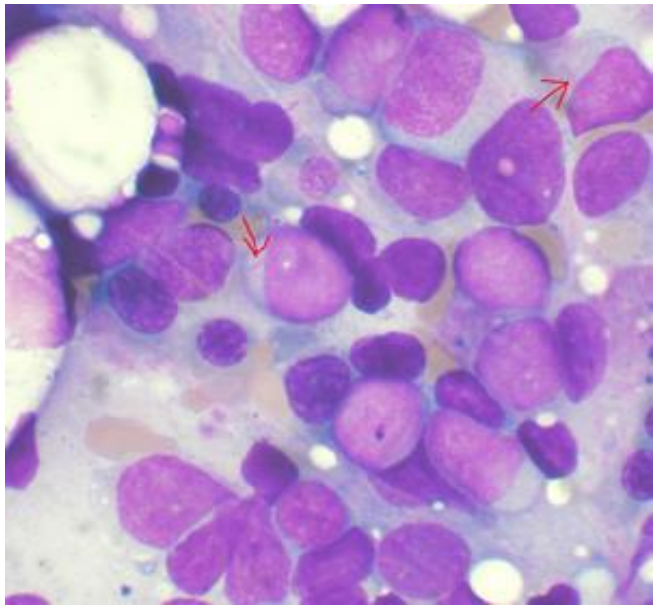
Acute Myeloid Leukemia Is a Deadly Cancer of the Blood and Bone Marrow

Profound Clinical Consequences

- Patients experience abnormal blood counts, a weakened immune system, leading to infections, weakness, bleeding, and transfusion dependence
- AML can be diagnosed at any age, but median age at diagnosis is 68

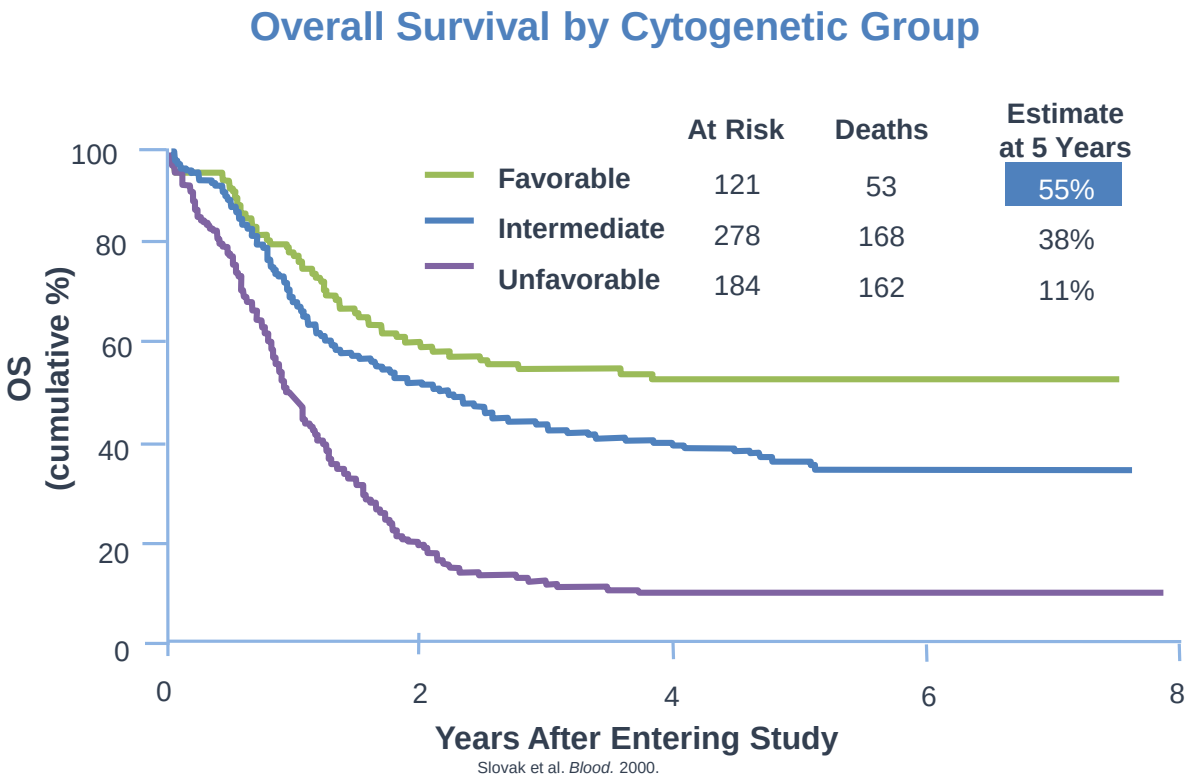
Poor Prognosis

- AML progresses rapidly and can be difficult to treat
- ~21,450 people will be diagnosed with AML this year
- ~10,920 deaths from AML will occur this year
- The 5-year survival rate for patients with AML is approximately 28.3%.



https://www.lls.org/leukemia/acute-myeloid-leukemia
https://www.cancer.org/cancer/acute-myeloid-leukemia/about/what-is-aml.html

AML Is a Deadly Disease in Even "Favorable" Subtypes

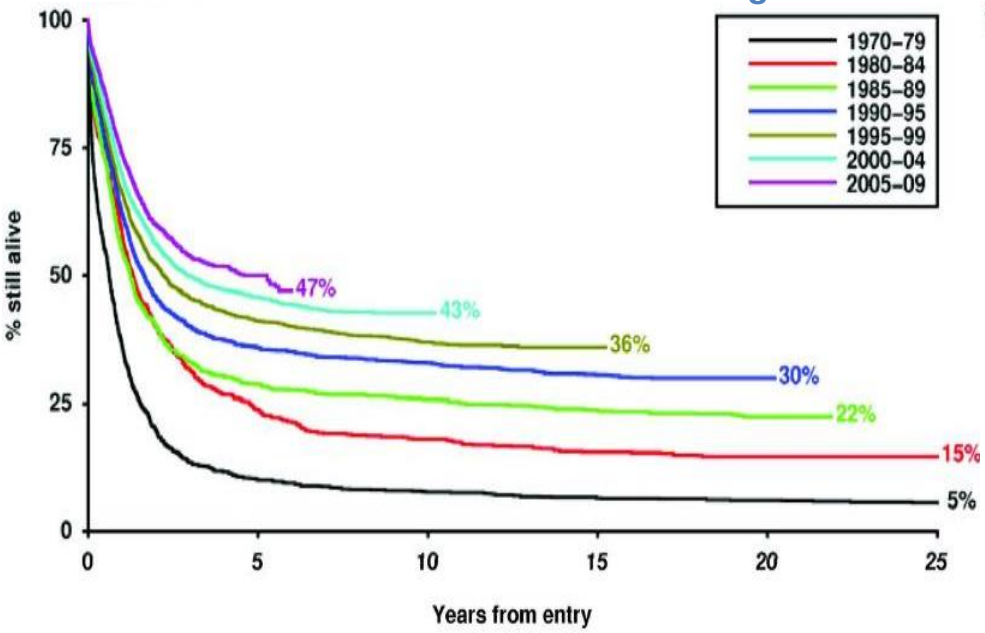


Slovak et al. *Blood.* 2000.

Older adults with AML have a particularly poor prognosis

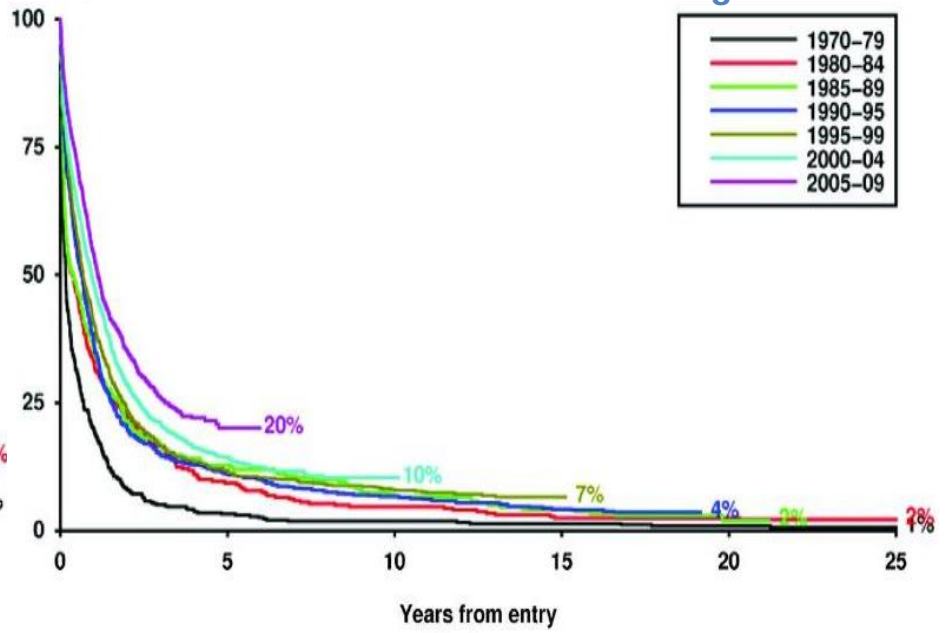
Younger Patients

MRC AML Trials: Overall Survival Age 15-59



Older Patients

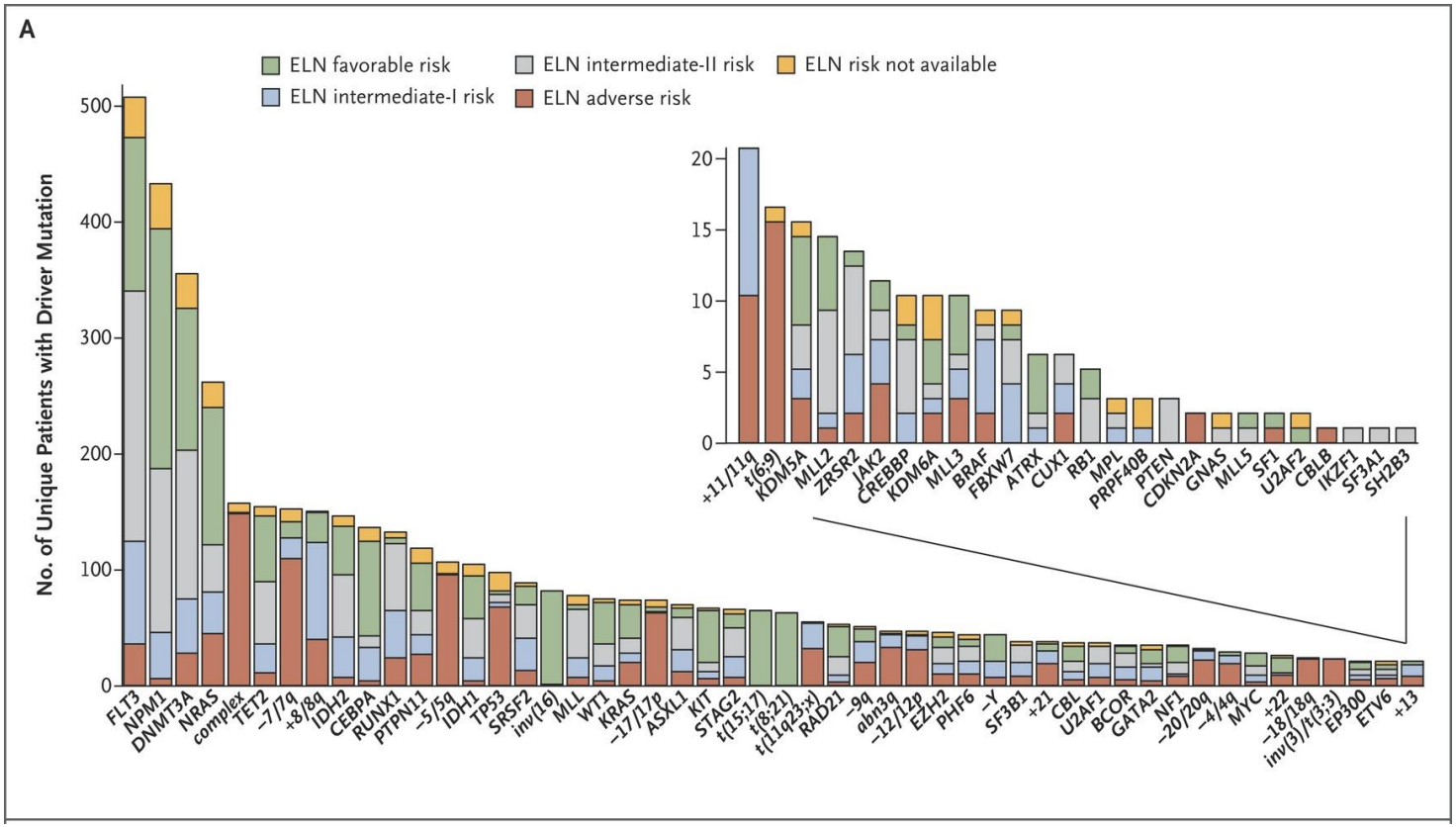
MRC AML Trials: Overall Survival Age 60+



Burnett AK. *Hematology.* 2012;2012:1-6.

FLT3 activation is the most common abnormality in AML

Found in 25-37% of patients



Papaemmanuil E et al. N Engl J Med 2016;374:2209-2221.

FLT3 activation is the most common abnormality in AML

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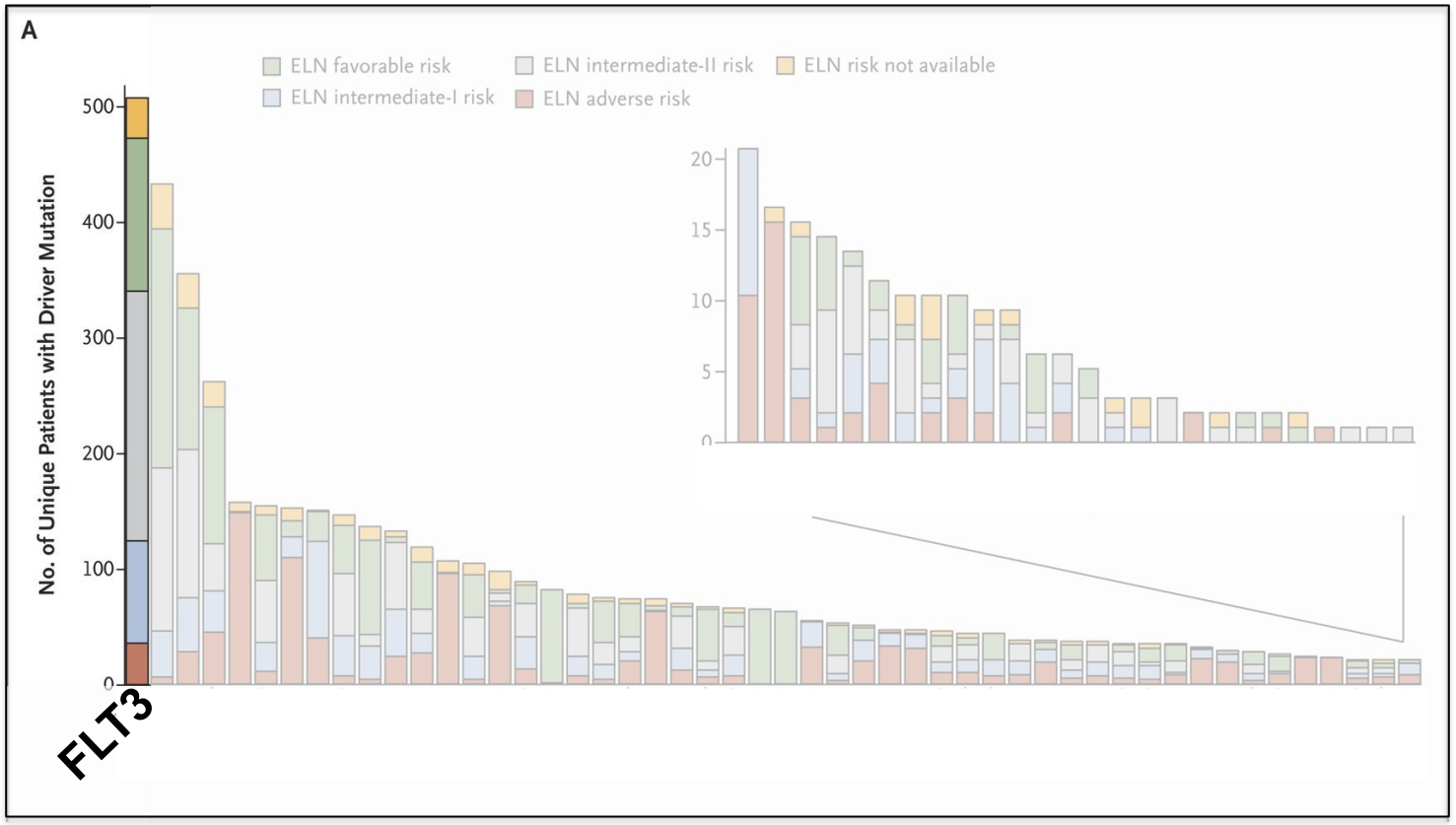
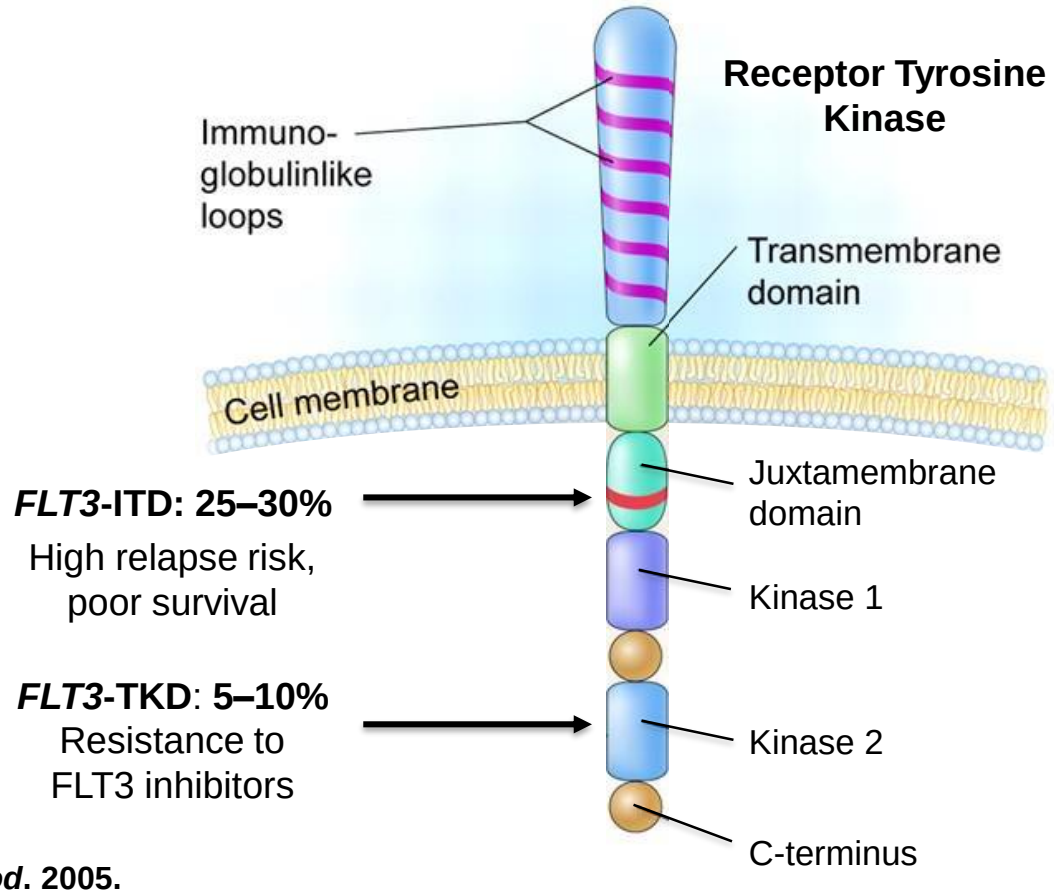


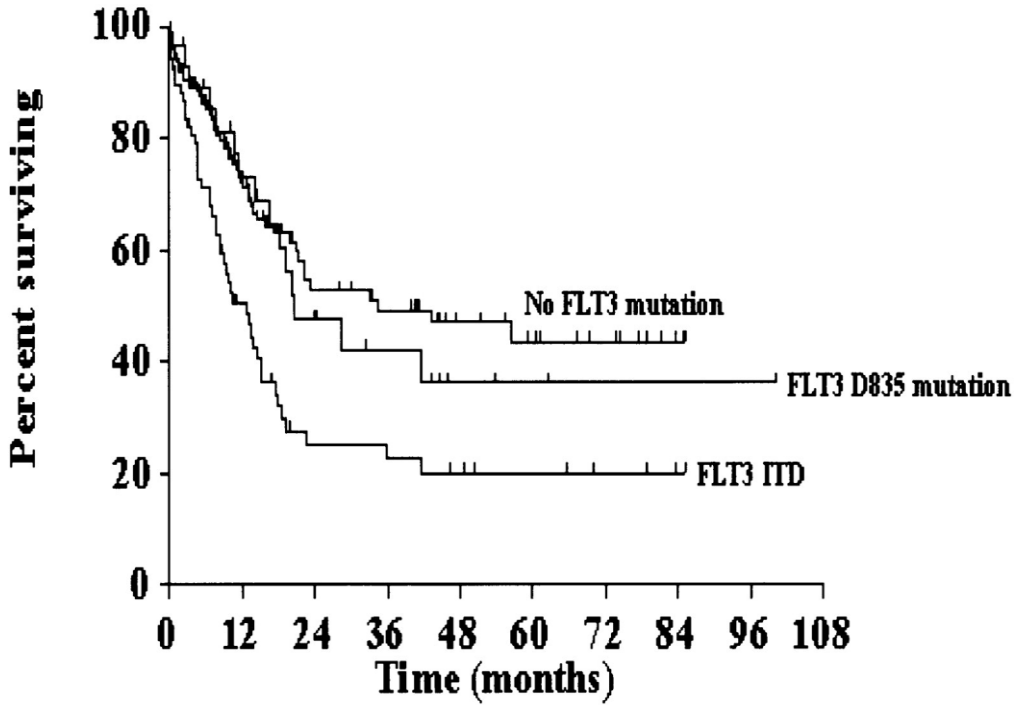
Papaemmanuil E et al. N Engl J Med 2016;374:2209-2221.

FLT3 Mutations in Acute Myeloid Leukemia

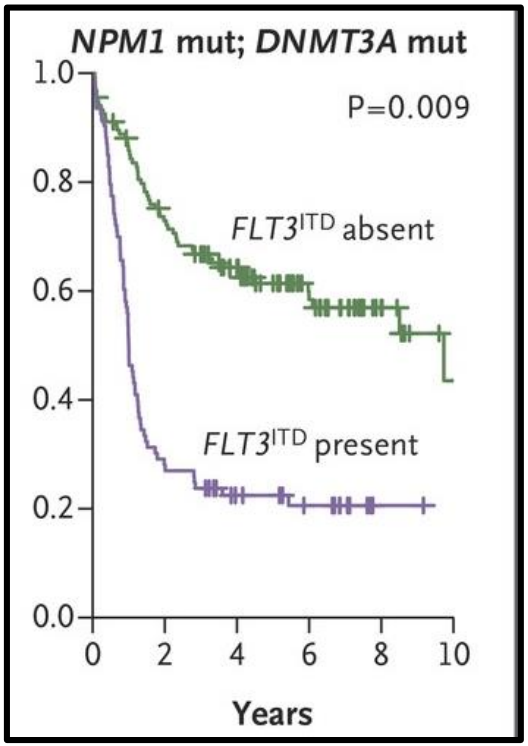


Litzow MR. *Blood*. 2005.

FLT3-ITD mutations are poor prognostic markers in AML



Fröhling et al. Blood 2002



Papaemmanuil E et al. NEJM 2016

Current FLT3 Inhibitors in AML

Agent	Midostaurin	Gilteritinib*	Quizartinib
Dosing	Twice daily	Once daily	Once daily
FDA approved	Yes - 2017	Yes - 2018	No – approved in Japan 2019
Newly dx or R/R	Newly dx	R/R	R/R
Monotherapy or combination with chemo	Combination with chemotherapy	Monotherapy	Monotherapy
FLT3-ITD or TKD	FLT3-ITD and TKD	FLT3-ITD and TKD	FLT3-ITD only
Adverse effects	Nausea, vomiting, diarrhea	CK elevation, LFTs	QT prolongation

*Gilteritinib: only FLT3 inhibitor currently FDA approved in R/R AML with FLT3 mutations

Memorial Sloan Kettering Cancer Center

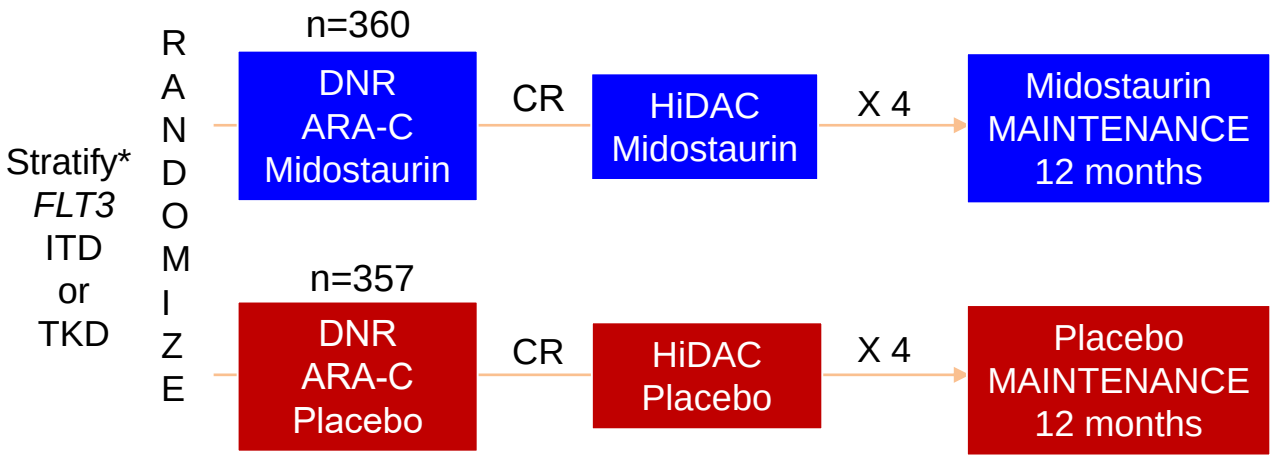
Newly diagnosed FLT3+ AML: FLT3 inhibitors + chemotherapy

RATIFY (C10603) Trial

Schema

FLT3-ITD or _FLT3_-TKD positive AML (N=717)

- Age, ≥18 to 59 years
- Newly diagnosed
- ≥5% *FLT3* allelic frequency



*Stratification: TKD; ITD with allelic ratio <0.7 ‘vs’ ≥0.7

Stone RM et al. *N Engl J Med*. 2017;377:454-464.

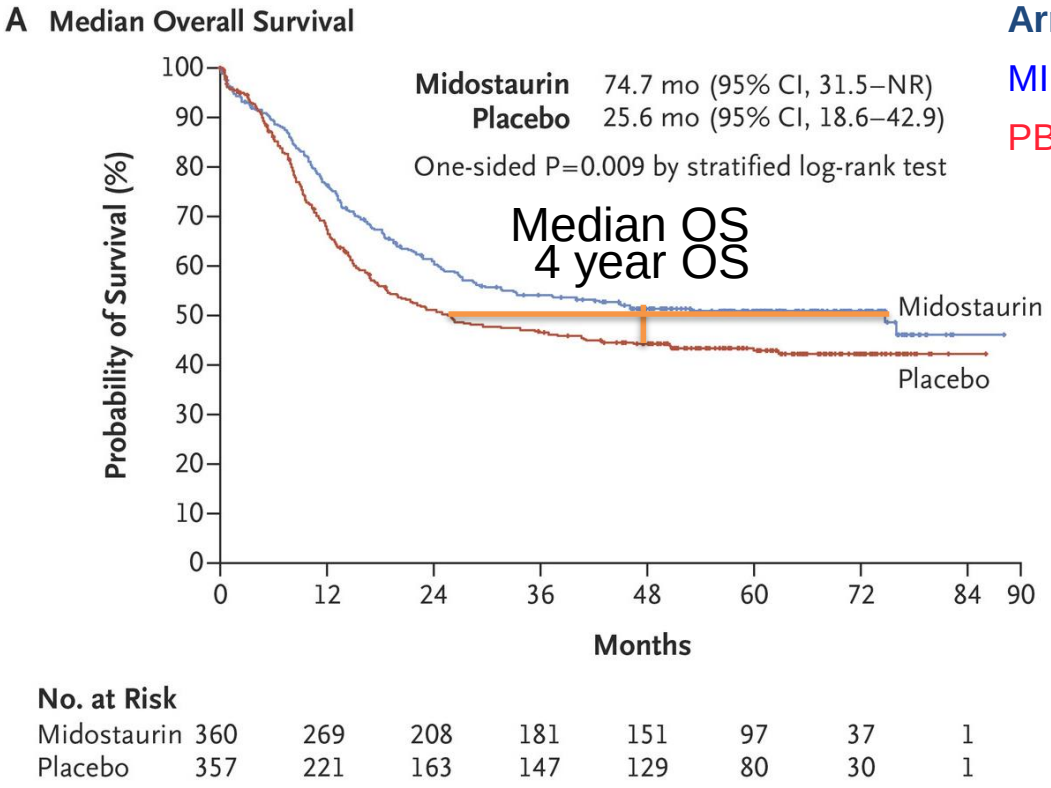
RATIFY – Remission Rates

Table 3. Summary of Complete Remission.*

Variable	Midostaurin Group (N=360)	Placebo Group (N=357)	P Value†
Protocol-specified complete remission — no. (%)	212 (59)	191 (54)	0.15
Kaplan–Meier estimate of time to complete remission — days			
Median	35	35	
Range	20–60	20–60	

Stone RM et al. *N Engl J Med*. 2017;377:454-464.

RATIFY: Overall Survival (Primary Endpoint)



Arm	4-year OS
MIDO	51.4% (95%CI: 46, 57)
PBO	44.2% (95%CI: 39, 50)

Stone RM et al. *N Engl J Med*. 2017;377:454-464.

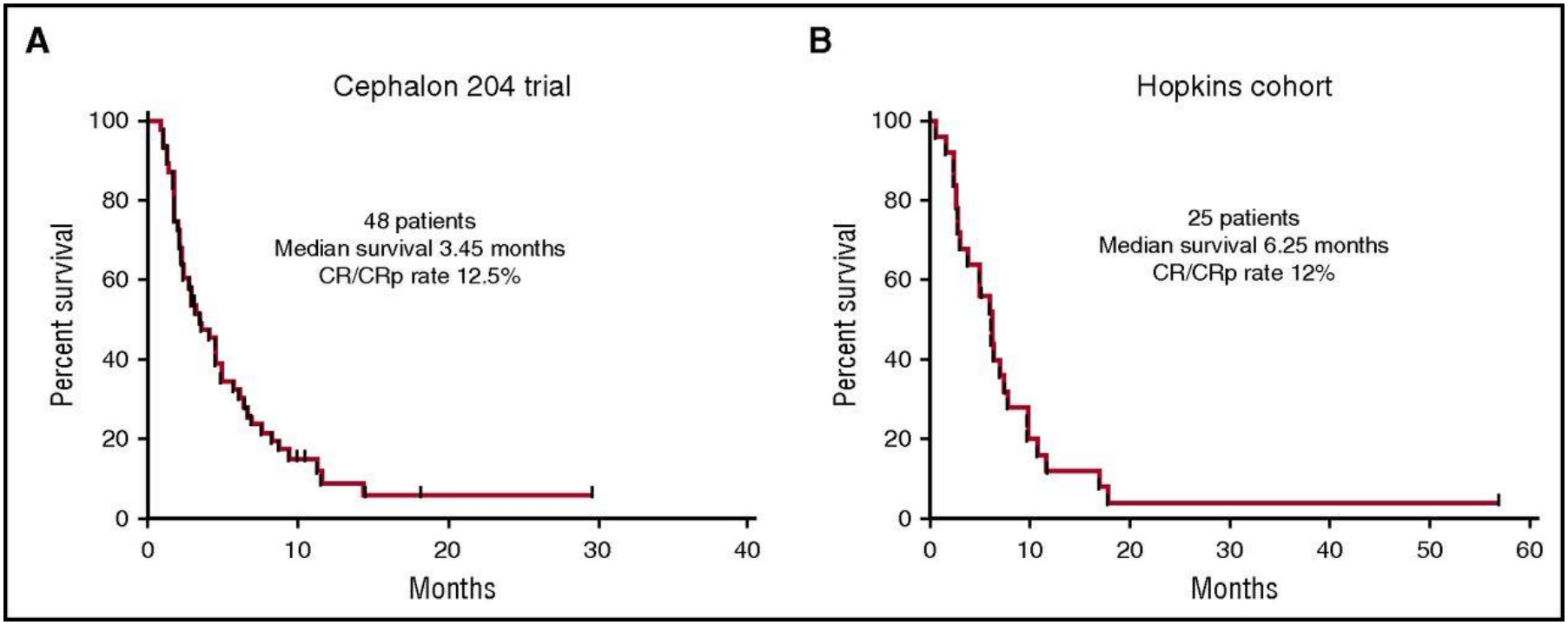
Limitations of midostaurin and opportunities in newly diagnosed FLT3 mutant AML

- Midostaurin approved in combination with intensive chemotherapy in newly diagnosed FLT3+ AML
- Age of inclusion 59 and younger – median age of AML diagnosis is 68
- Marginal benefit in OS over chemotherapy alone – 4 year OS 51.4%
- Midostaurin is a multitargeted (dirty) TKI and among least potent FLT3 inhibitors
- More potent FLT3 inhibitors (crenolanib, gilteritinib) combined with chemotherapy promising in phase II studies – phase III studies randomizing chemo + midostaurin vs chemo + novel FLT3i are ongoing

Memorial Sloan Kettering Cancer Center

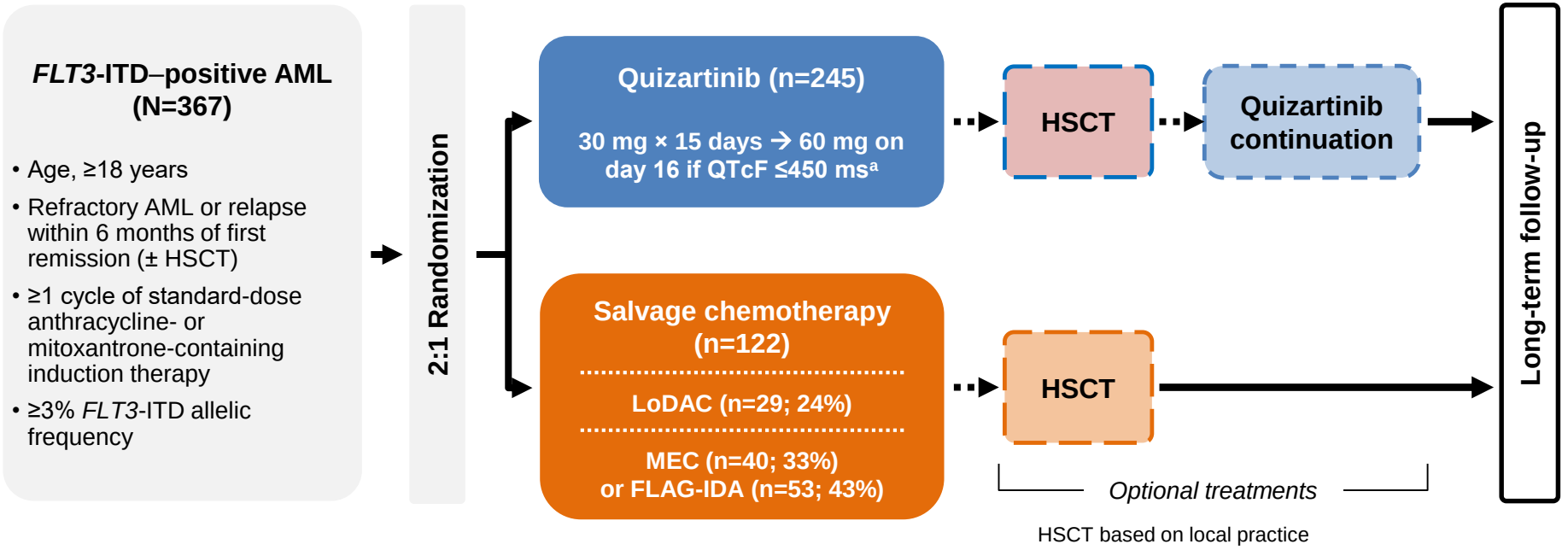
Relapsed / refractory AML – quizartinib and gilteritinib

Relapsed and refractory FLT3 mutant AML has a very poor prognosis



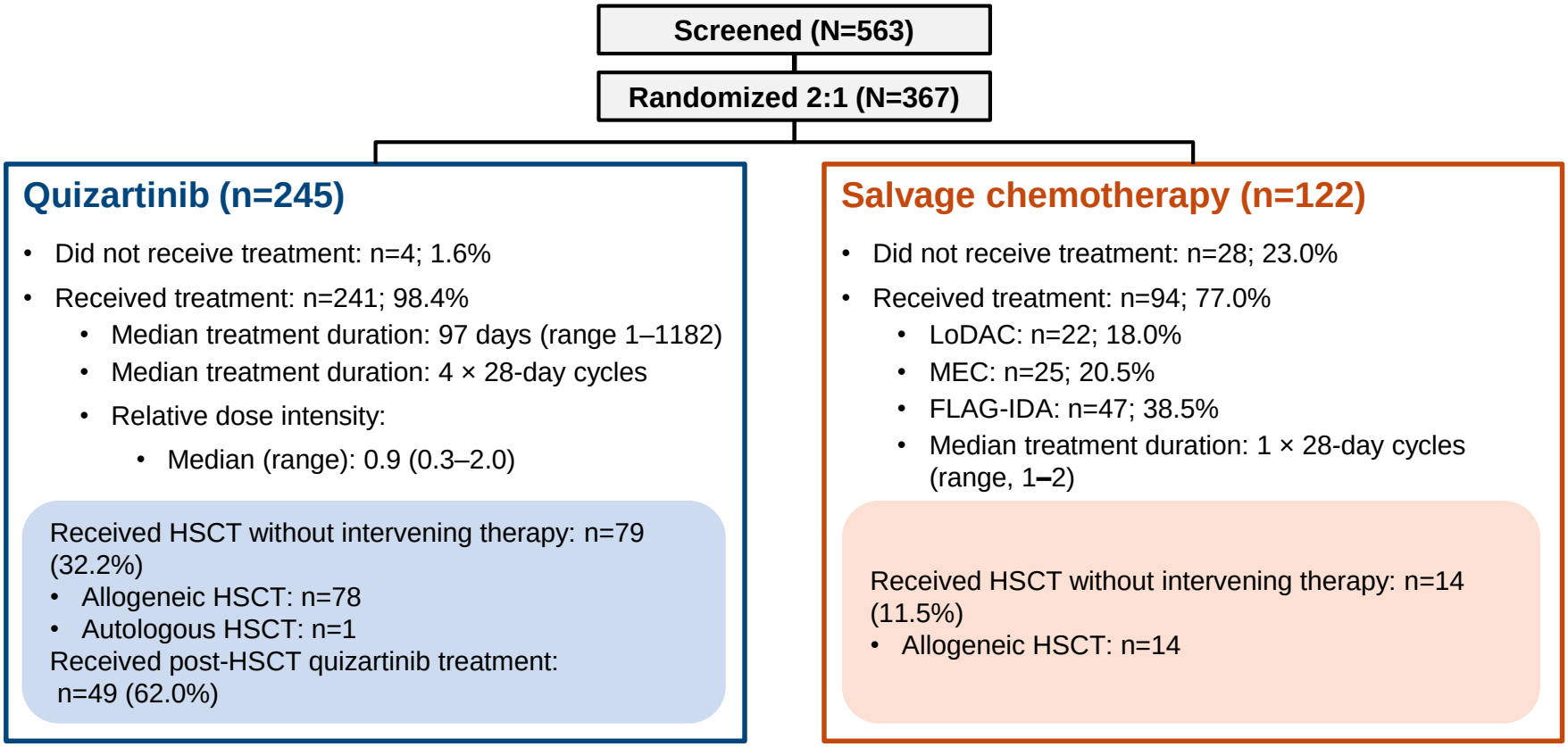
Pratz and Levis, How I treat FLT3-mutated AML, Blood, 2017

QuANTUM-R: Phase 3, Open-label Study of Single-agent Quizartinib vs Salvage Chemotherapy in R/R *FLT3*-ITD–positive AML



Cortes J, ASH 2018

QuANTUM-R: CONSORT Diagram



[a]Received allogeneic HSCT without intervening nonprotocol-specified AML therapy.

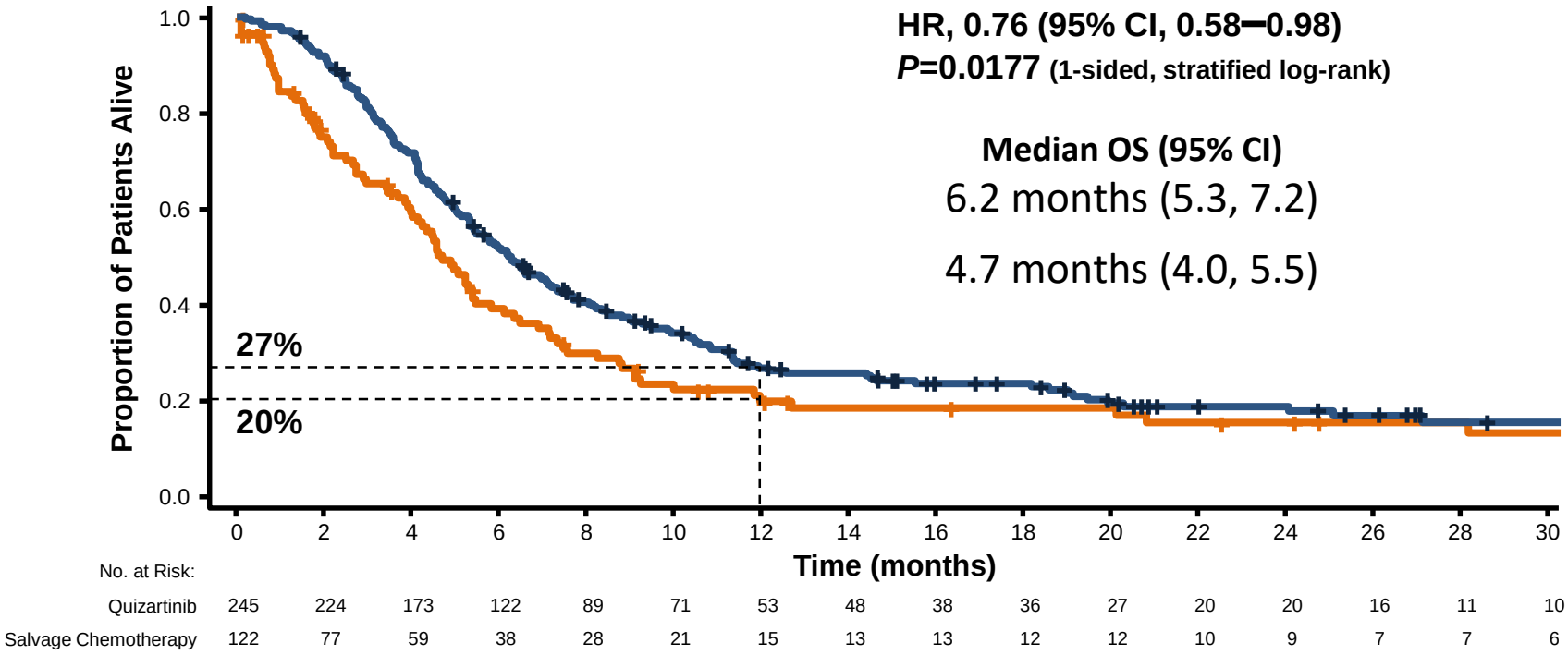
Cortes J, ASH 2018

R/R FLT3+ AML - Quizartinib

Characteristic	Quizartinib n = 245	Salvage Chemotherapy n = 122
Best response, n		
CRc[a]	118 (48%)	33 (27%)
CR	10 (4%)	1 (1%)
CRp	9 (4%)	0
CRi	99 (40%)	32 (26%)
PR	52 (21%)	4 (3%)
ORR (CRc + PR)	170 (69%)	37 (30%)
No response	62 (25%)	45 (37%)
Not evaluable	13 (5%)	40 (33%)
Time to first CRc		
Median (range)	4.9 (3.7-19.7) wks	4.0 (2.0-14.9) wks
Duration of CRc		
Median (95% CI)	12.1 (10.4-27.1) wks	5.0 (3.3-12.6) wks

Cortes J, ASH 2018

R/R FLT3+ AML - Quizartinib



- **Approved in Japan**
- **Not approved by US FDA**

Mechanisms of resistance to quizartinib

Table 1 | Summary of FLT3 kinase domain mutations in patients relapsed on AC220

Subject number	Sex	Age (years)	Prior therapy	Karyotype at enrolment	Karyotype at relapse	Blasts in relapse sample (%)	New mutation at relapse	ITD$^+$ clones with mutation	Weeks on study
1009-003	F	75	7+3	45~54,XX,+3,+6,+7, +8,+13,+14,+21, +22[cp15]/46,XX[5]	52,XX,+3,+6,+7,+8, +10,+12,+13[cp7]/46, XX[14]	90	D835F	6/15	12
1011-006	M	70	7+3, low-dose cytarabine	Normal	ND	10	D835Y	4/15	8
1011-007	F	56	7+3, HAM	Normal	46,XX,del(11) (p?13p?15) [12]/46,XX[9]	80	F691L D835V	4/24 5/24	11
1005-004	F	60	Cytarabine and mitoxantrone	Normal	Normal	92	F691L	9/22	19
1005-006	M	43	7+3, MEC, allogeneic stem cell transplant	6,XY,t(1;15)(p22;q15)	ND	59	D835Y	8/17	6
1005-007	F	59	7+3, HDAC	Normal	ND	39	D835V	9/21	23
1005-009	M	68	Cytarabine and mitoxantrone	Normal	ND	58	D835Y	8/14	19
1005-010	M	52	7+3, HDAC, mitoxantrone and etoposide	46,XY,t(4;12)(q26;p11.2), t(8;14)(q13;q11.2)	ND	22	F691L	6/18	20

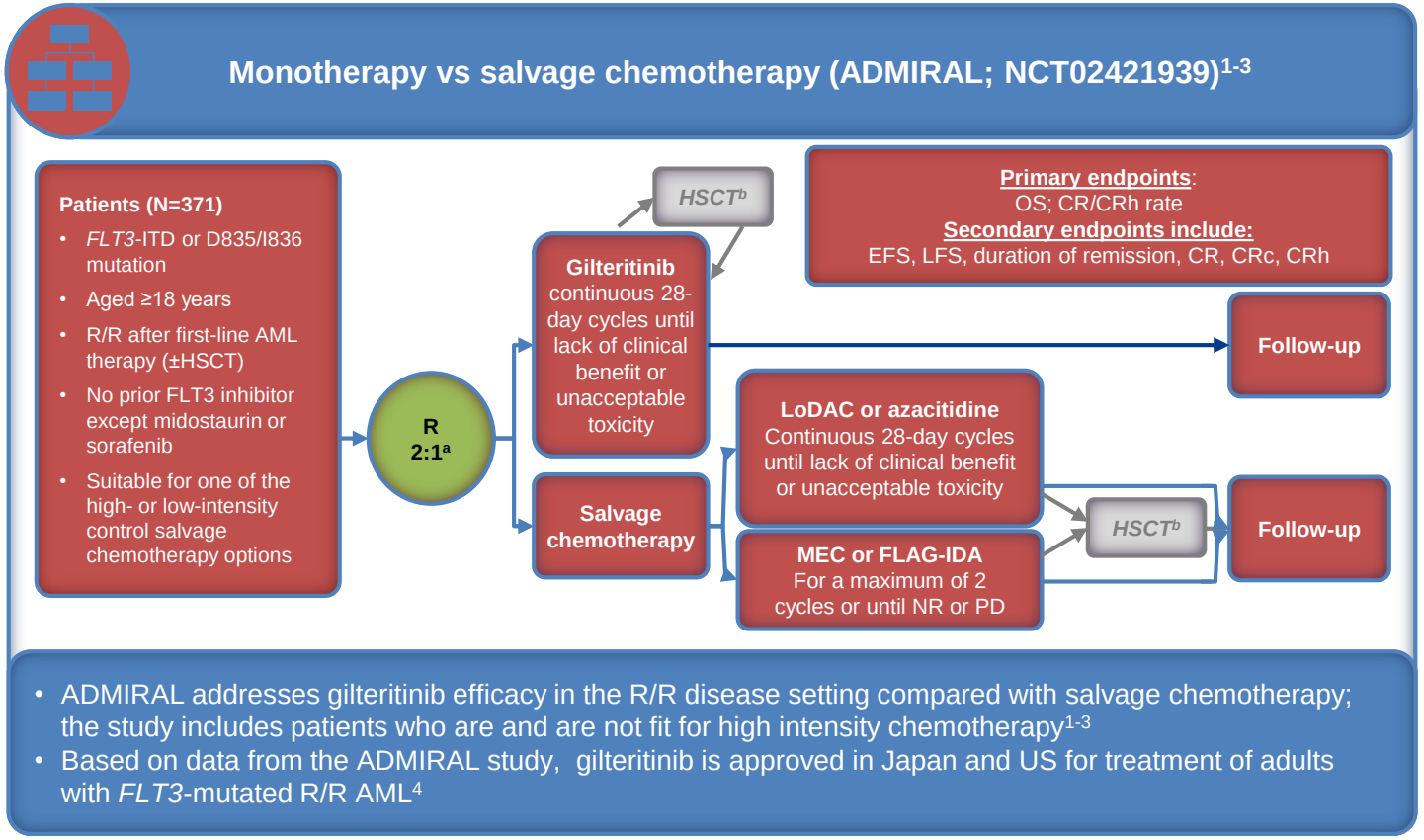
All patients achieved morphological bone marrow blasts of ≤5% at best response. 7+3, low-dose cytarabine for 7 days plus 3 days anthracycline; HAM, high-dose cytarabine plus mitoxantrone; HDAC, high-dose cytarabine; MEC, mitoxantrone, etoposide, cytarabine. ND, not done.

FLT3 kinase mutations

- Acquired FLT3 TKD mutations validate FLT3 inhibition
- Deep sequencing shows polyclonal resistance
- Crenolanib and gilteritinib: both active against FLT3-D835

Smith CC et al. Nature 2012

Gilteritinib – Phase III ADMIRAL Study



Perl et al. NEJM 2019

Response Outcomes (ITT Population: N=371)

Response Parameter*	Gilteritinib (n=247)	Salvage Chemotherapy (n=124)
CR, n (%)	**52 (21)**	**13 (11)**
CRh, n (%)	32 (13)	6 (5)
CRi, n (%)	63 (26)	14 (11)
CRp, n (%)	19 (8)	0 (0)
CRc, n (%)	**134 (54)**	**27 (22)**
CR/CRh, n (%)	**84 (34)**	**19 (15)**
PR, n (%)	33 (13)	5 (4)
ORR, n (%)	167 (68)	32 (26)
NR, n (%)	66 (27)	43 (35)
Mean time to achieve CRc (SD), months	2.3 (1.9)	1.3 (0.5)
Median DoR† (95% CI), months	11.0 (4.6, NE)	1.8 (NE, NE)
Allogeneic HSCT, n (%)	**63 (26)**	**19 (15)**

*Response was not evaluable in 14 patients (6%) in the gilteritinib arm and in 49 patients (40%) in the salvage chemotherapy arm.
†Duration of remission includes duration of CRc, duration of CR/CRh, duration of CR, duration of CRp, and duration of response (CRc + PR).
Abbreviations: CR, complete remission; CRc, composite complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery;
CRp, complete remission with incomplete platelet recovery; DoR duration of remission; HSCT, hematopoietic stem cell transplantation; ITT, intention-to-treat; NE, not estimable; ORR, overall response rate; PR, partial remission; SD, standard deviation.

ADMIRAL: Overall Survival (ITT Population: N=371)

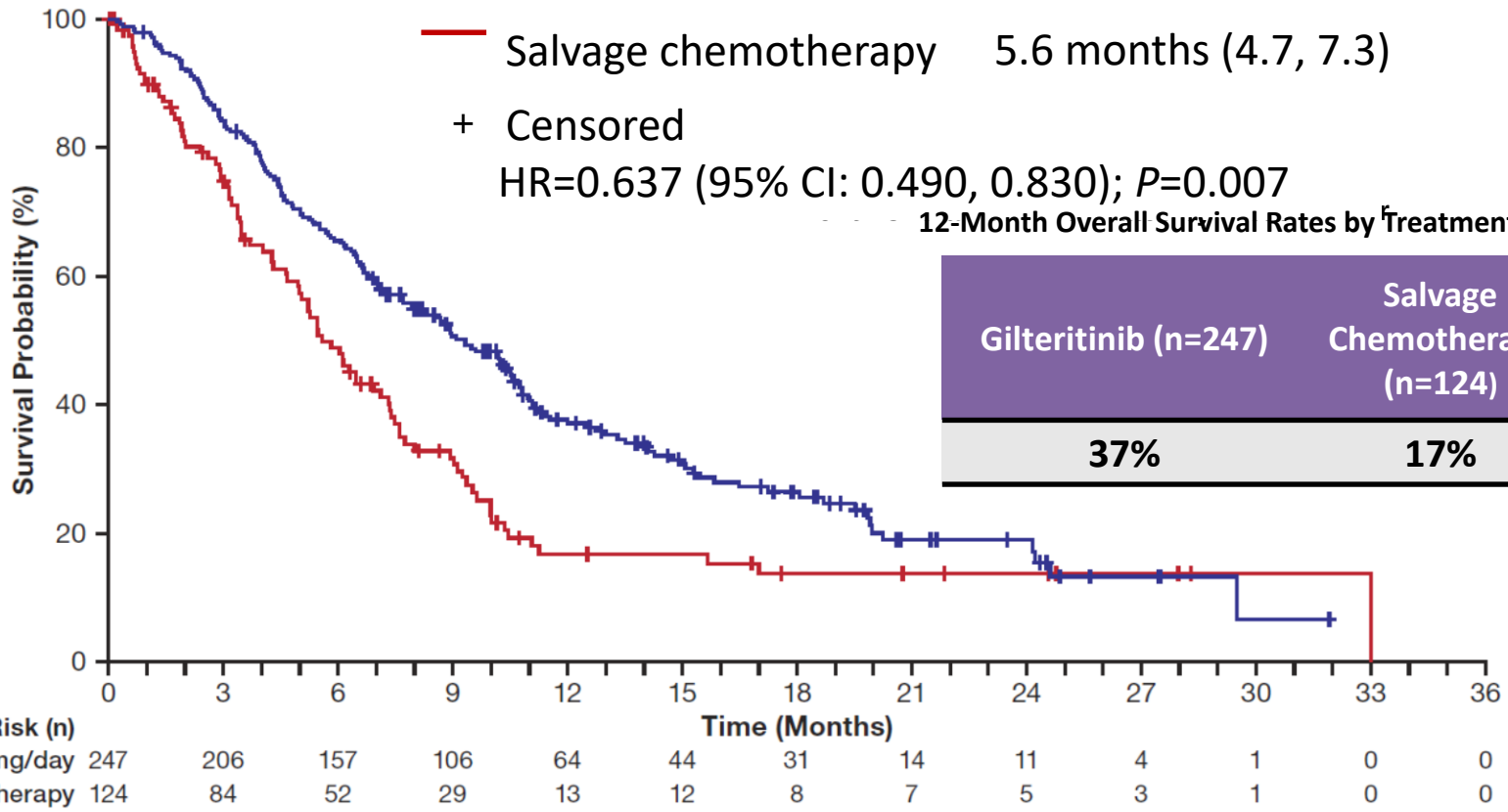
Median OS (95% CI)

Gilteritinib 120 mg/day 9.3 months (7.7, 10.7)

Salvage chemotherapy 5.6 months (4.7, 7.3)

\+ Censored

HR=0.637 (95% CI: 0.490, 0.830); *P*=0.007



12-Month Overall Survival Rates by Treatment Arm

Gilteritinib (n=247)	Salvage Chemotherapy (n=124)
37%	17%

Perl et al. NEJM 2019

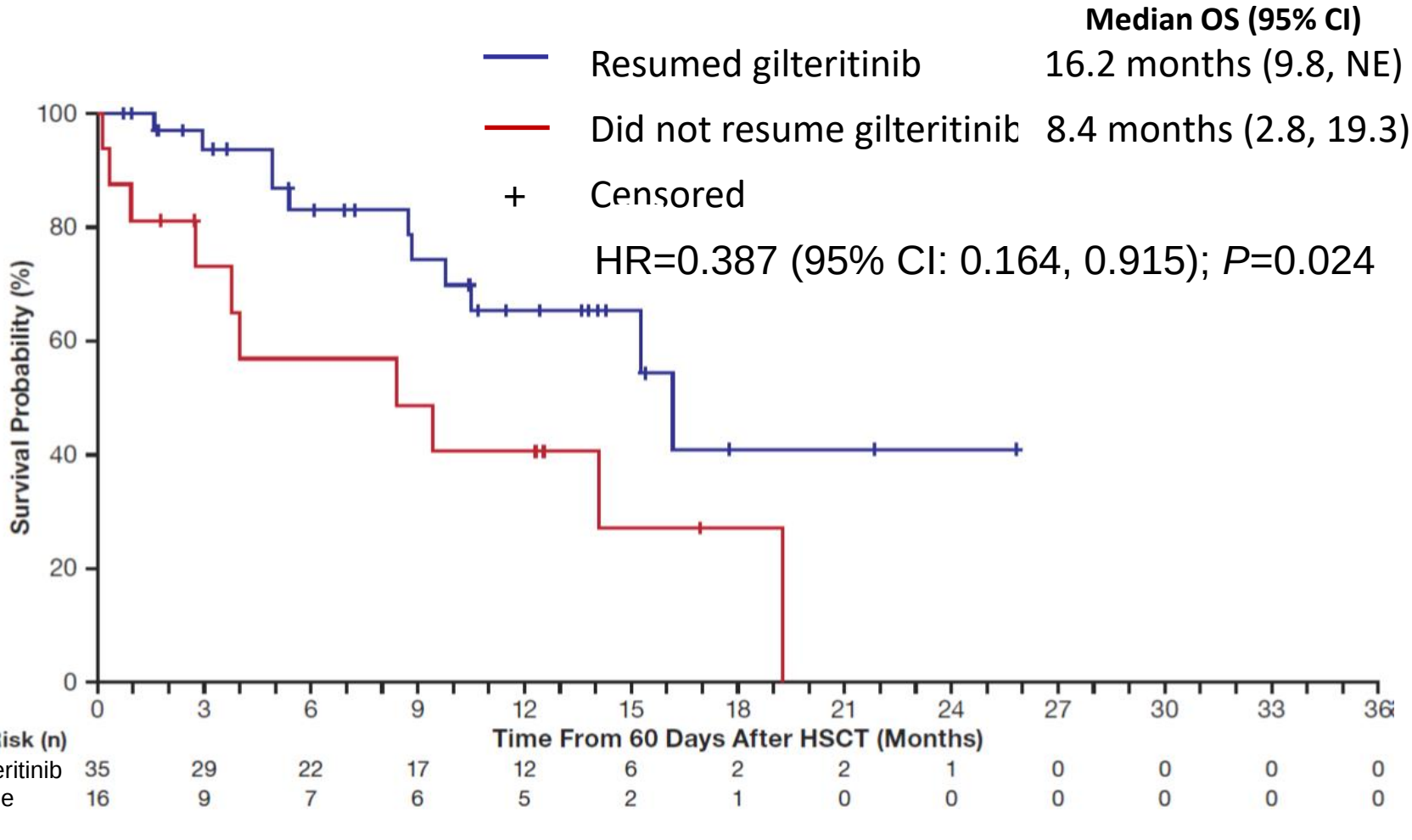
Patients at Risk (n)

Gilteritinib 120 mg/day	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

Two-sided *P*-values were determined according to the log-rank test; the Kaplan-Meier method in combination with the Greenwood formula were used to determine overall survival and corresponding 95% confidence intervals.

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival.

Post-HSCT Survival in the Gilteritinib Arm: Effect of Maintenance Therapy (Landmark Analysis From Day 60 Post-HSCT; n=51)



Perl et al. NEJM 2019

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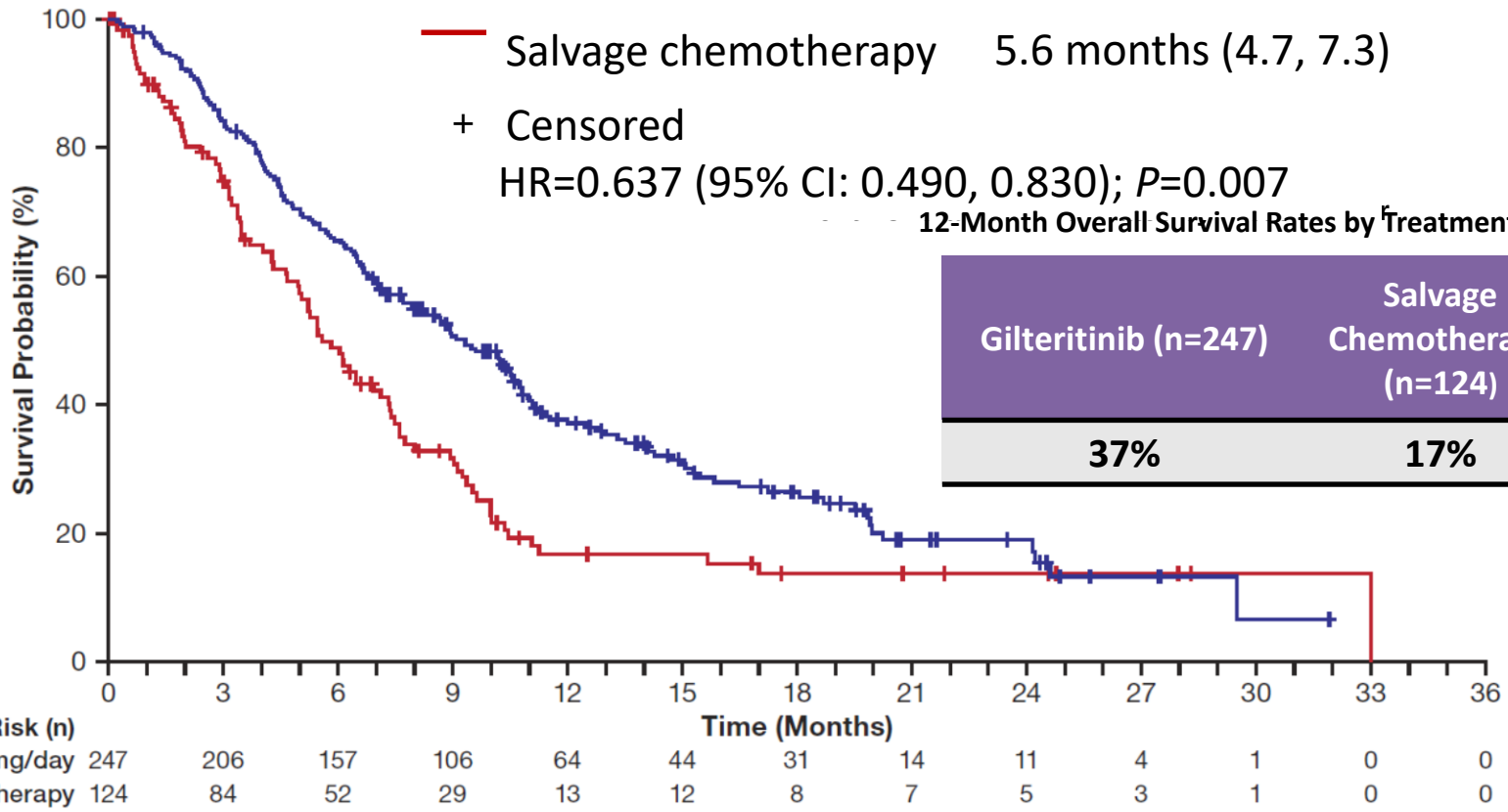

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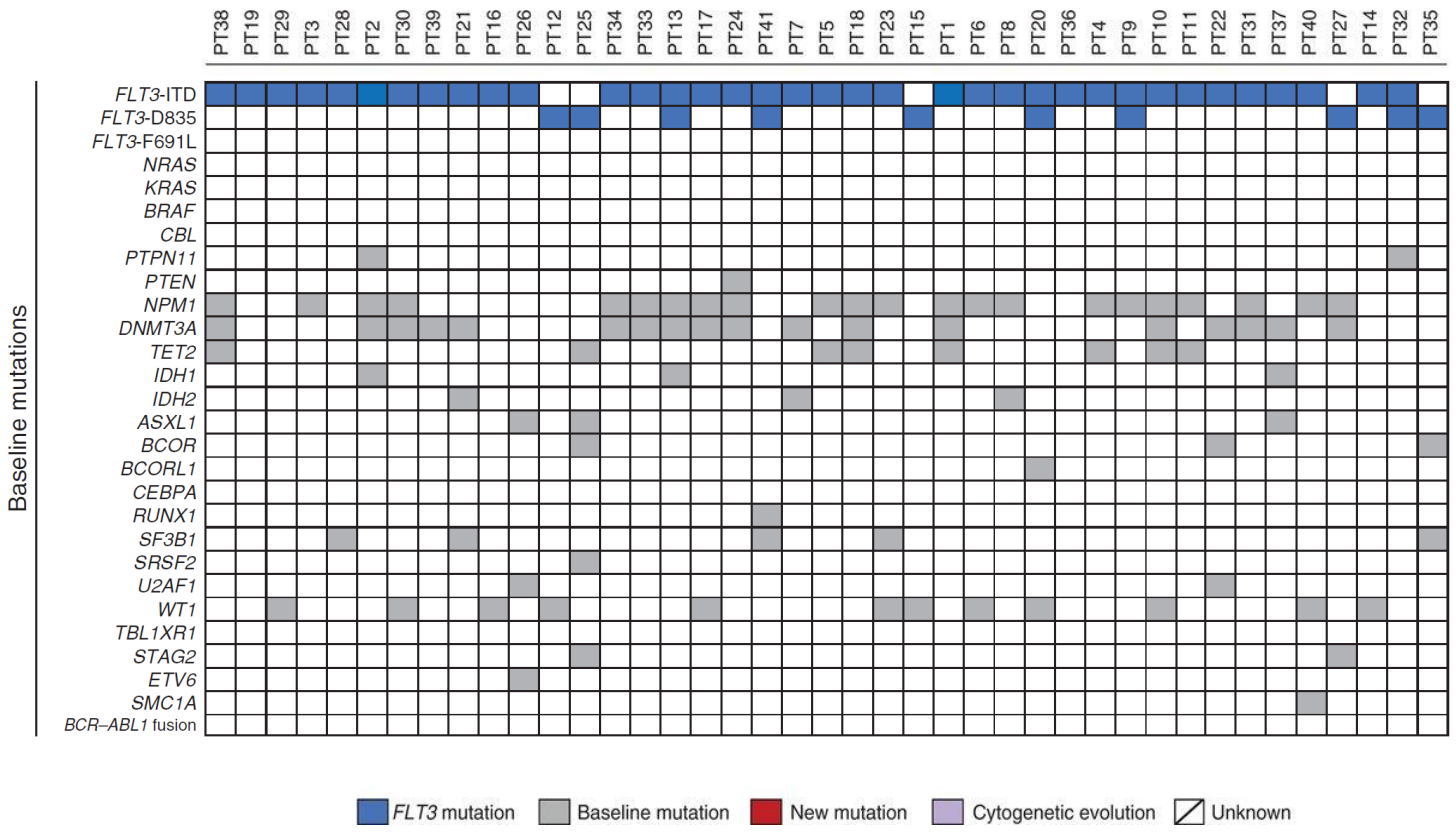
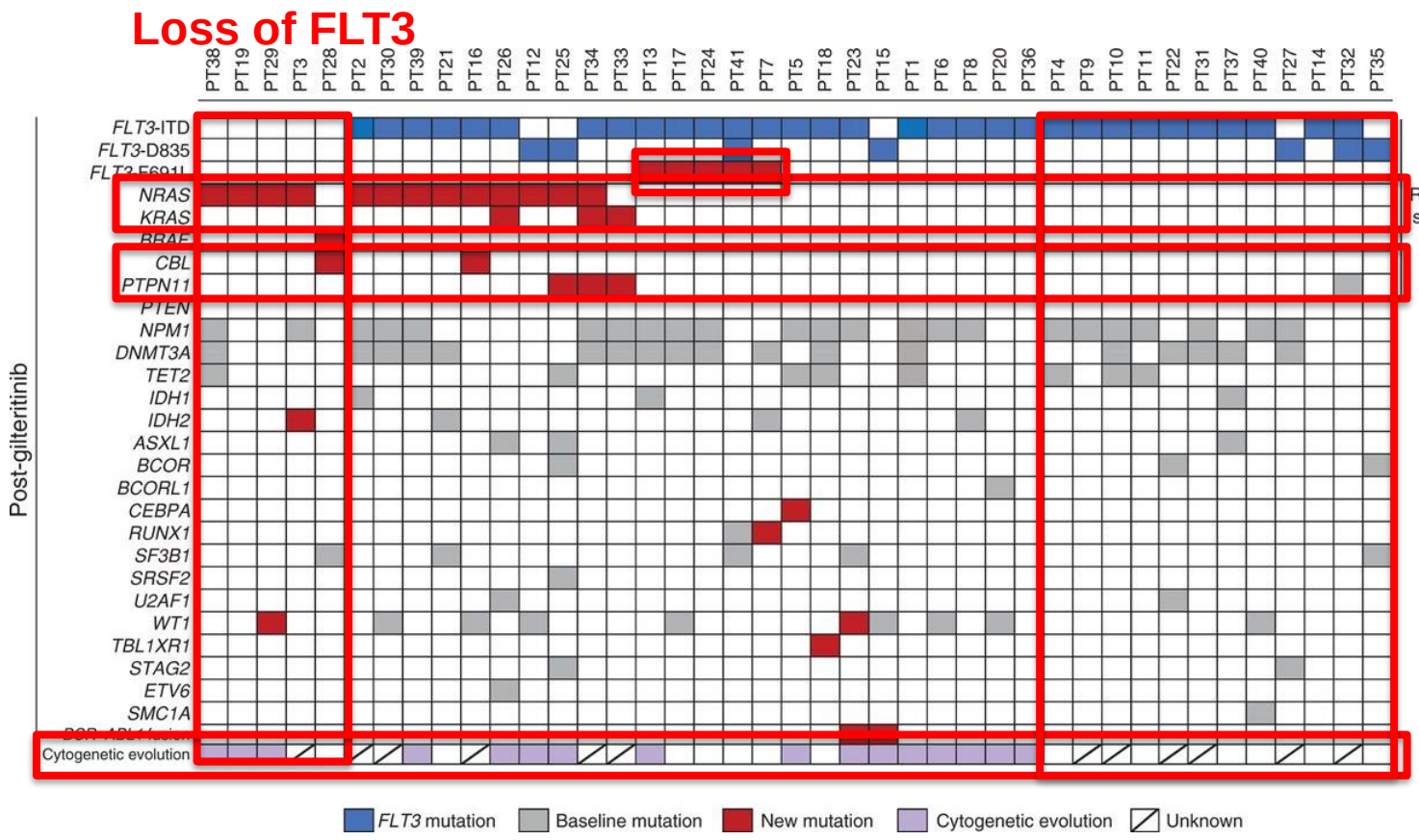
Multiple mechanisms of gilteritinib resistance



Cytogenetic evolution

McMahon CM et al. Cancer Discovery. 2019

Multiple mechanisms of gilteritinib resistance



FLT3-F691L

Other RAS mechanisms

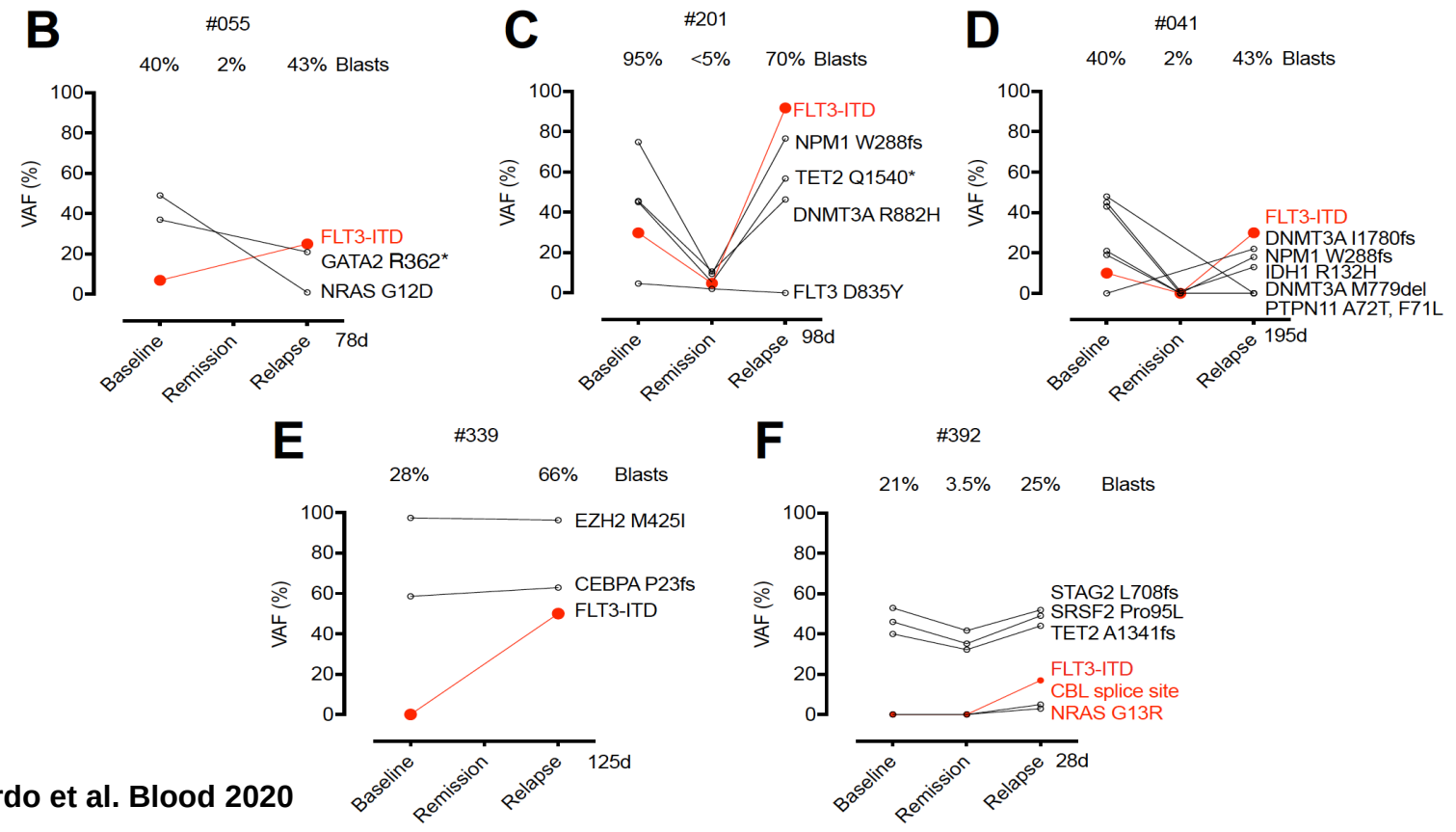
pathway

New mutations were acquired in 23/41 (56.1%) subjects at time of progression of gilteritinib

Cytogenetic evolution

McMahon CM et al. Cancer Discovery. 2019

FLT3-ITD: key mechanism of resistance to front-line venetoclax combinations



Dinardo et al. Blood 2020

FLT3 inhibition in AML --- next steps

- Outcomes have improved --- but most patients with AML and particularly FLT3 mutated AML still die of their disease
- FDA approved FLT3 inhibitors include midostaurin (untreated AML in combination with chemotherapy) and gilteritinib (R/R AML as monotherapy); quizartinib approved in Japan (R/R AML as monotherapy)
- Current FLT3 inhibitors are NOT curative – multiple mechanisms of resistance – even responding patients will eventually progress – median OS for gilteritinib treated R/R AML patients is 9.3 months
- Development of FLT3 inhibitors for FLT3 mutated AML patients who fail gilteritinib represents an urgent clinical need
- Ideal drug for gilteritinib failures: potent FLT3 inhibitor, target FLT3-ITD and FLT3-TKD, target multiple mechanisms of FLT3 resistance, active in setting of RAS mutations; potentially synergize with venetoclax

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Sankyo, Pfizer

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CONQUER CANCER FOUNDATION of the American Society of Clinical Oncology
YOUNG INVESTIGATOR AWARD

AMERICAN SOCIETY OF HEMATOLOGY
Clinical Fellow
Scholar Award

1884
Memorial Sloan Kettering
Cancer Center

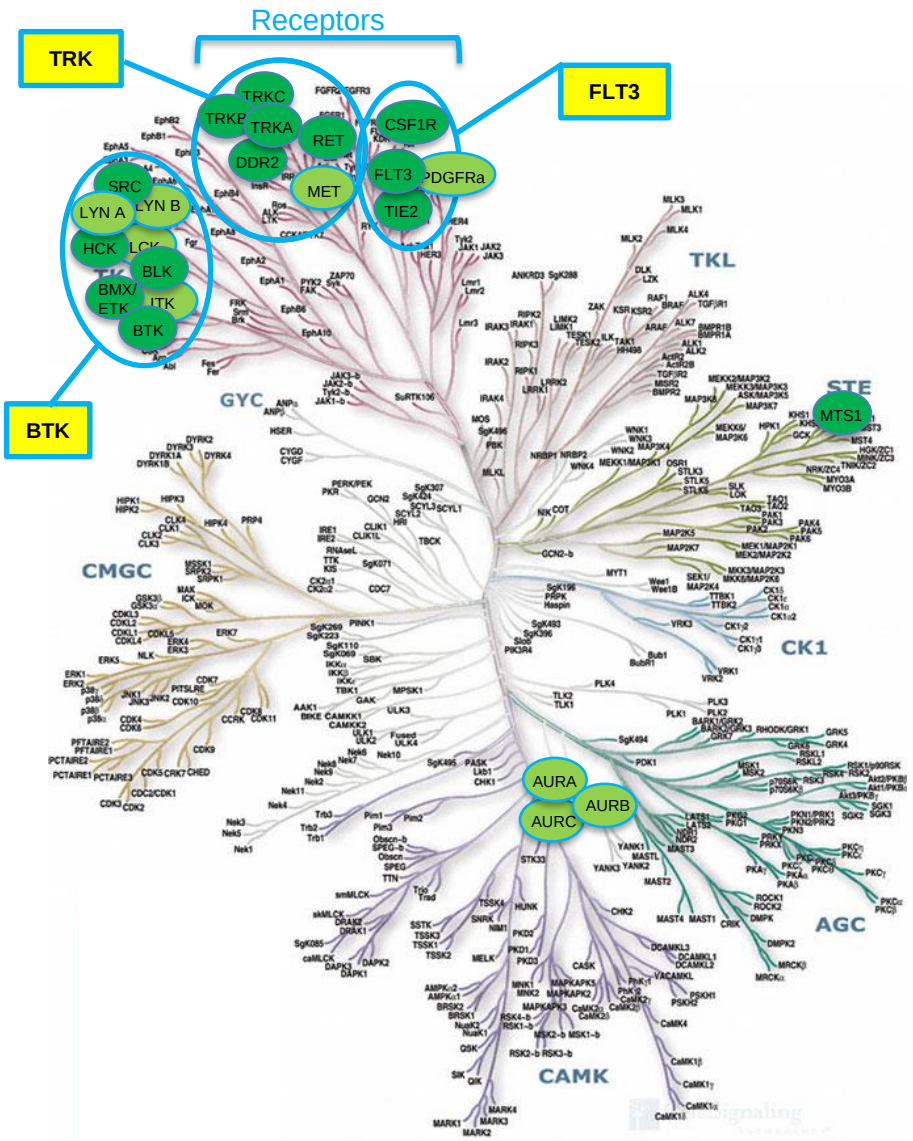
Rafael Bejar MD, PhD
Chief Medical Officer, Aptose Biosciences

CG-806

1st-in-Class Oral FLT3 / rBTK Inhibitor

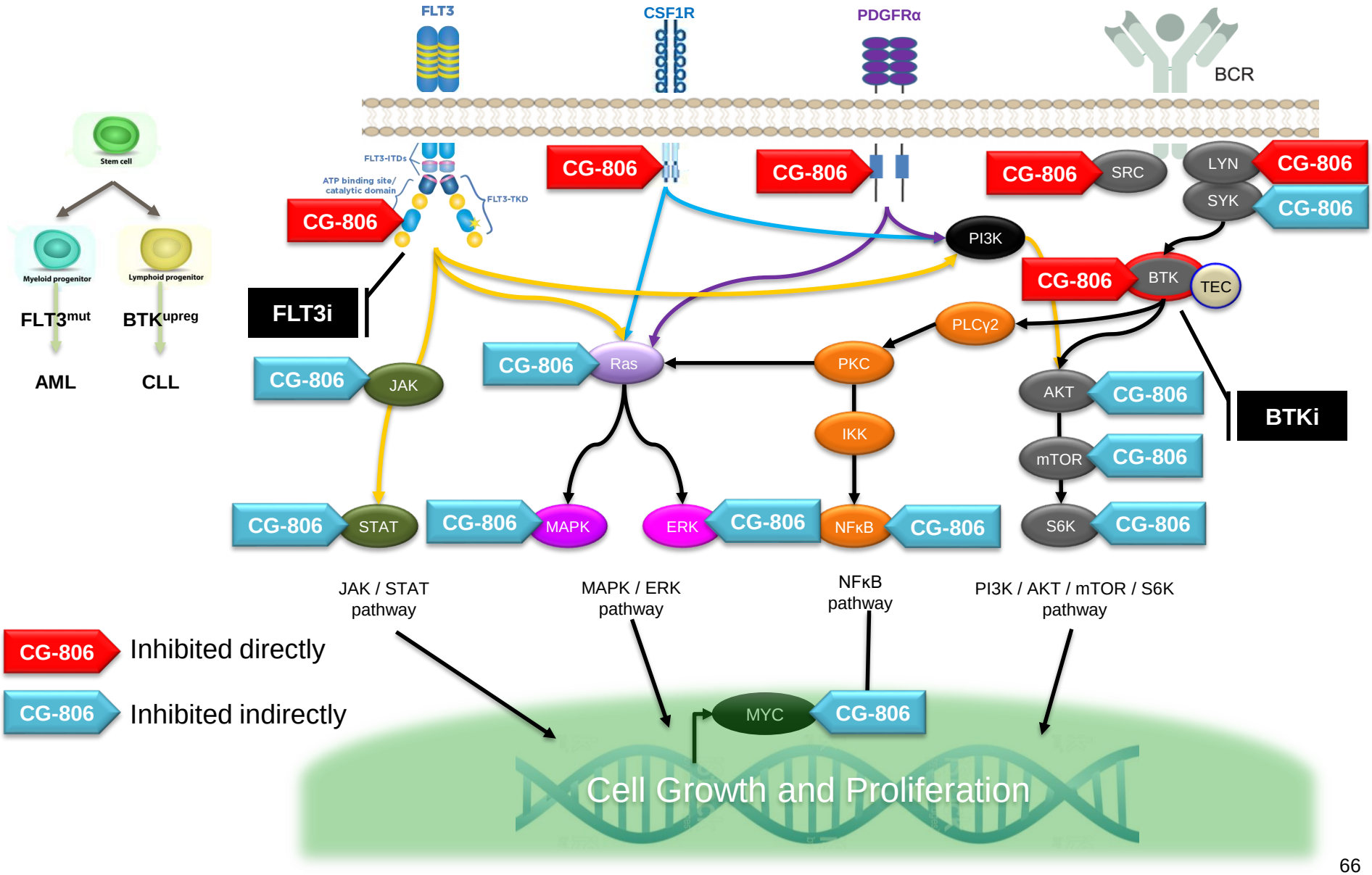
1. Non-covalent “reversible” inhibitor with unique kinome targeting profile
2. Potent inhibitor of all forms of BTK (WT / C481S) driver kinase
3. Potent inhibitor of all forms of FLT3 (WT / ITD or TKD mutated) driver kinase
4. Suppresses multiple signaling pathways essential for cancer cell survival
5. Precision spares safety targets & pathways associated with toxicity
6. Ongoing trial Ph1a/b for CLL & NHL B-cell malignancies
7. Planning trial Ph1a/b for AML/MDS myeloid malignancies

“Cluster-Selective Kinase Inhibitor”: CG-806 Potently and Selectively Inhibits Clusters of Related Kinases



- **Mutation Agnostic**
  - Inhibits all forms of FLT3
  - Inhibits all forms of BTK
  - Simultaneously suppresses multiple signaling pathways
- **Robust Safety Profile**
  - NOT a “dirty” kinase inhibitor
  - Avoids kinases that impact safety
  - No drug-related AEs seen to date
- **Inhibits Clusters of Kinases that Drive Hematologic Malignancies**
  - FLT3 cluster → AML & MDS
  - BTK cluster → CLL & NHL

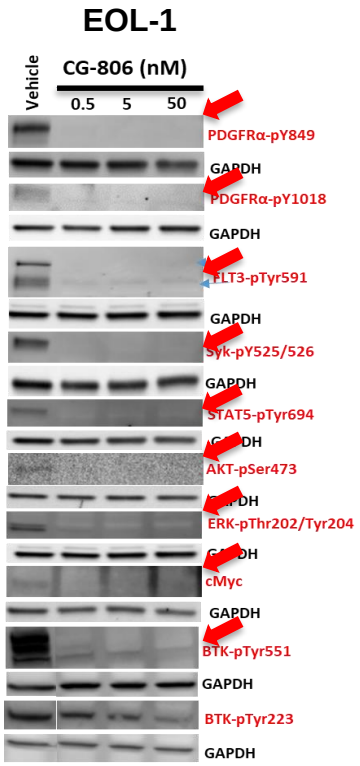
CG-806 Suppresses Key Oncogenic Targets and Pathways in Myeloid & Lymphoid Malignancies

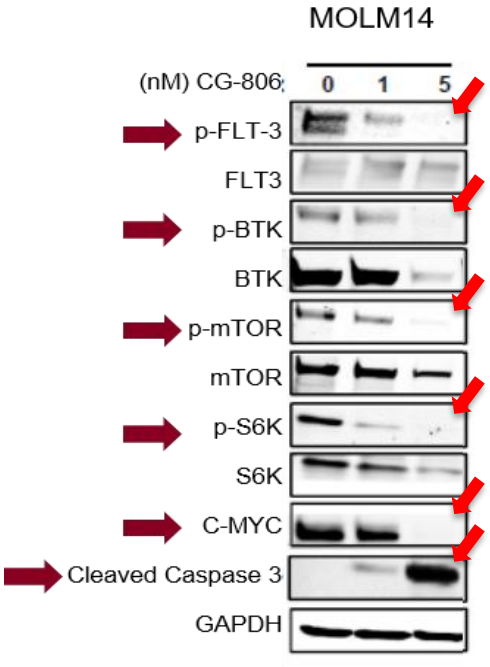


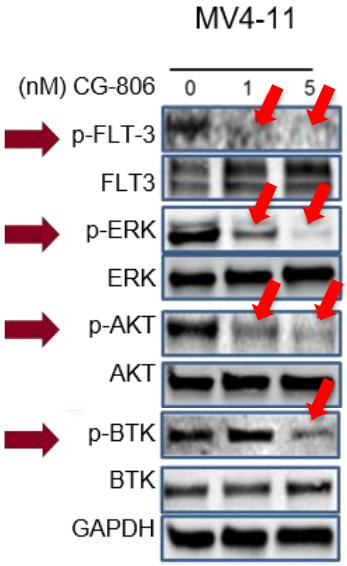
CG-806 is More Than Just FLT3 or BTK Inhibitor: Suppress Initiation and Transmission of Oncogenic Signaling

CG-806 Potently Inhibits:
- **FLT3 / BTK Driver Kinases**
- **Oncogenic Signaling Pathways**

FLT3 / CSF1R / PDGFRα Receptors
TRK / RET / MET Receptors
BTK / AURK Intracellular Kinases
BCR Pathway (SYK/SRC/LCK/LCK)
AKT Pathway (SYK/PI3K/AKT/mTOR/S6K)
JAK/STAT Pathway
ERK Pathway
MYC Pathway







CG-806 Phase 1 Clinical Development Plan

Developing CG-806 for R/R-CLL/NHL and R/R-AML/MDS

But AML patients are acutely ill and do not wish to dose sub-therapeutically

1st
Perform Phase 1a/b in Patients with R/R-CLL / NHL

- Define safety, tolerance, PK, PD and RP2D in CLL/NHL patients
- Seek a dose that delivers a likely "therapeutic exposure" for AML

Pending FDA Approval

2nd
Perform Phase 1a/b : Relapsed/Refractory AML/MDS

- Seek responses in AML/MDS patients
- Define safety, tolerance, PK, PD and RP2D

CG-806 in Phase 1a/b Clinical Trial for Treatment of Patients with R/R-CLL/NHL

Dose Level 1 (150mg BID for 28d) Completed

Only One Patient Required in Dose Level 1

- **R/R-CLL/SLL** with TP53 mutation ; Heavily pretreated
- **Challenging Case with TP53 mutation – No DLTs and completed Cycle 6**

Dose Level 2 (300mg BID for 28d) Completed

Only One Patient Required in Dose Level 2

- **R/R-CLL** with unmutated IGHV ; Heavily pretreated
- Marrow involvement with neutropenia and thrombocytopenia
- **Highly complicated disease to manage – No DLTs and completed Cycle 4**

Dose Level 3 (450mg BID for 28d) Dosing Ongoing

Three Patients Required in Dose Level 3 – Three patients on study

CG-806 Delivered Evidence Safety, Target Engagement and Clinical Activity at Dose Level 2 (300mg BID)

Evidence of Safety with No Unexpected Toxicities

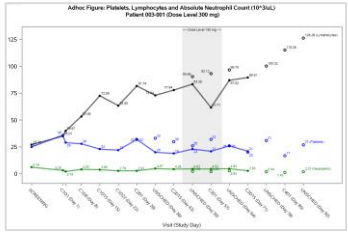
- No myelosuppression ; stabilized platelets and neutrophils
- No drug-related SAEs ; No dose-limiting toxicities

Evidence of Target Engagement with ↓P-BTK

- 100% inhibition of P-BTK in PBMC : ELISA Assay
- Inhibition of P-BTK, P-SYK, others : PIA Assay

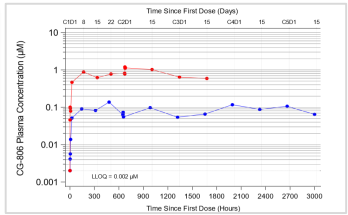
Evidence of Clinical Activity in R/R CLL

- **Marked lymphocytosis**
  - BTK inhibition in patients leads to CLL cell exfiltrated from lymphoid tissues
  - Observed immediately upon initiation of dosing in Cycle 1

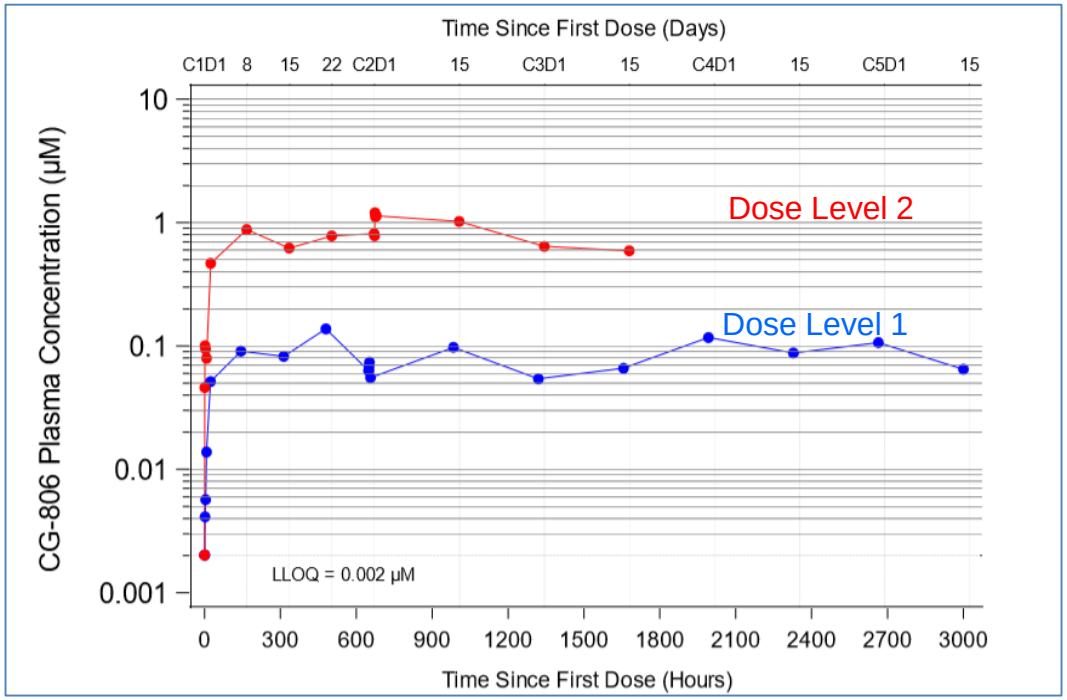


Well-behaved Steady-State Oral Pharmacokinetics

- Absorption that delivered near-uM plasma exposure levels



CG-806 Favorable Steady-State Pharmacokinetics (C_{MIN})



- Oral absorption, dose-related exposure, predictable steady-state PK
- Achieving 0.6-1µM steady state (C_{min}) levels at Dose Level 2
- Approaching active exposure in Dose Level 2
- Continue dose escalation to optimal dose
- Nearing dose for application to AML – Perhaps Dose Level 3 or 4

CG-806 : A New Class of Drugs
Only BTKi Also to Inhibit FLT3 for AML

Breadth for Difficult-to-Treat CLL and NHL Patients

- Potently inhibits WT-BTK and C481S-BTK
- Potential to treat CLL patients failing approved & investigational agents
- Potential to treat Richter's Transformation, Tx-refractory DLBCL / FL / DHL

Safety : Targets Key Oncogenic Kinases and Avoids Safety Targets

- To date: safe, well-tolerated, and no drug related AEs have been observed
- Does not inhibit TEC, EGFR or ErbB2 kinases that cause toxicities with other kinase inhibitors
- Structurally distinct : assumes unique binding mode in kinase active sites relative to competitor agents

PLUS….Under Development for AML Patients Failing Other Drugs

- Only agent that inhibits BTK and FLT3 and is being developed for CLL/NHL and AML/MDS

CG-806 Inhibits *All Forms of FLT3* More Potently than Other FLT3 Inhibitors

Mutations in the FLT3 Kinase are Clear Drivers of AML

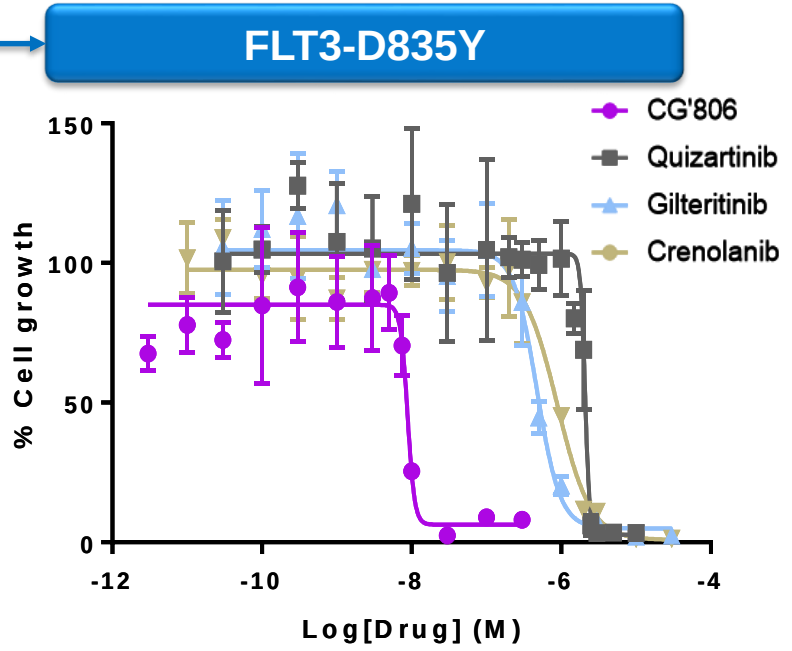
CG-806 Superior to Other FLT3-ITD Inhibitors

Drug	IC_{50} (nM)
CG-806[1]	0.8
Quizartinib[2]	8.8
Gilteritinib[3]	0.9
Crenolanib[4]	2
Midostaurin[2]	11
Nexavar[2]	79
Sutent[2]	1

CG-806 Potent (Kd) FLT3 WT/Mutants

FLT3 Proteins (Fragments)	CG-806 Kd (nM)
FLT3 WT	0.24
FLT3 ITD	3.1
FLT3 D835Y	**4.2**
D835H	2.2
D835V	7.9
R834Q	6.4
N841I	0.8
K663Q	0.55
ITD / F691L	16

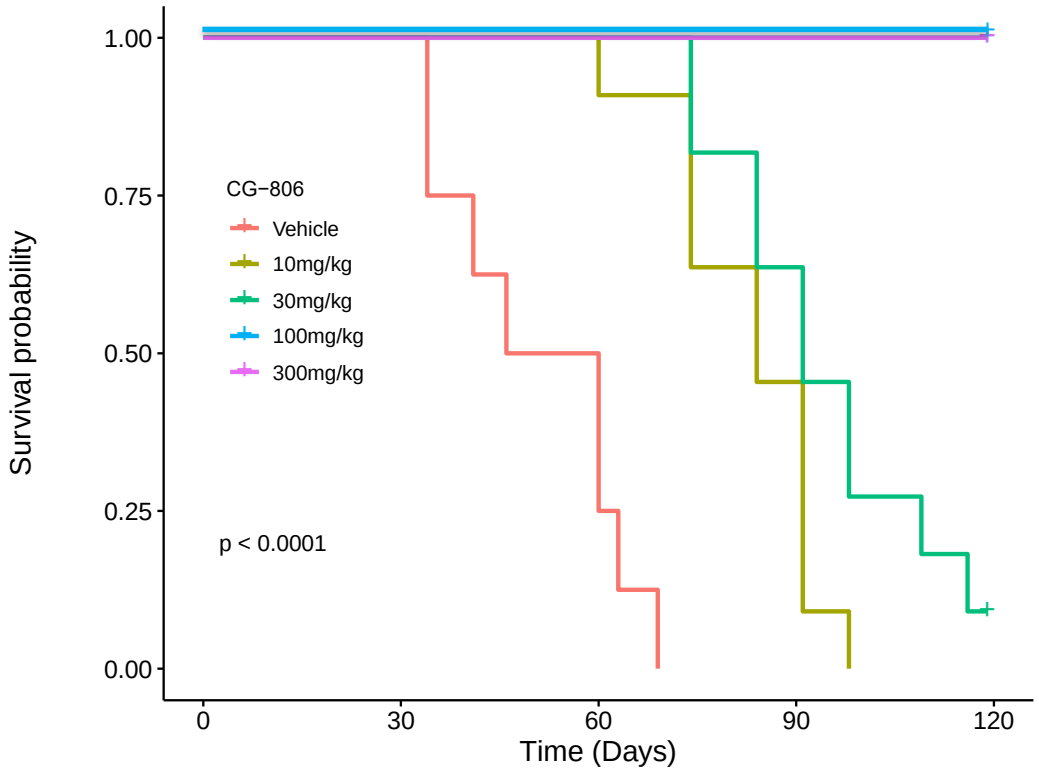
CG-806 Superior to Other FLT3 Inhibitors on AML Cells with FLT3-D835Y Mutation

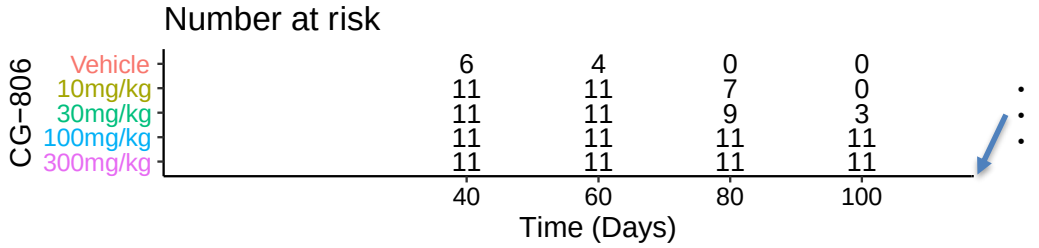


[1]Ba/F3 isogenic cells kindly provided by Dr. Michael Andreeff at MDACC

(1) Reaction Biology Corp.
(2) Blood. 2009 Oct 1; 114(14): 2984–2992
(3) J Clin Oncol 32:5s, 2014 (suppl; abstr 7070)
(4) Blood 2014 Jan 2; 123(1): 94-100 ; AACR Poster 2012
(5) ASH Oral Presentation 2016
N/A – Data not available / Not Applicable.

CG-806 Extends Survival in Dose Dependent Way in Mouse Model of AML After Oral Dosing for 28 Days

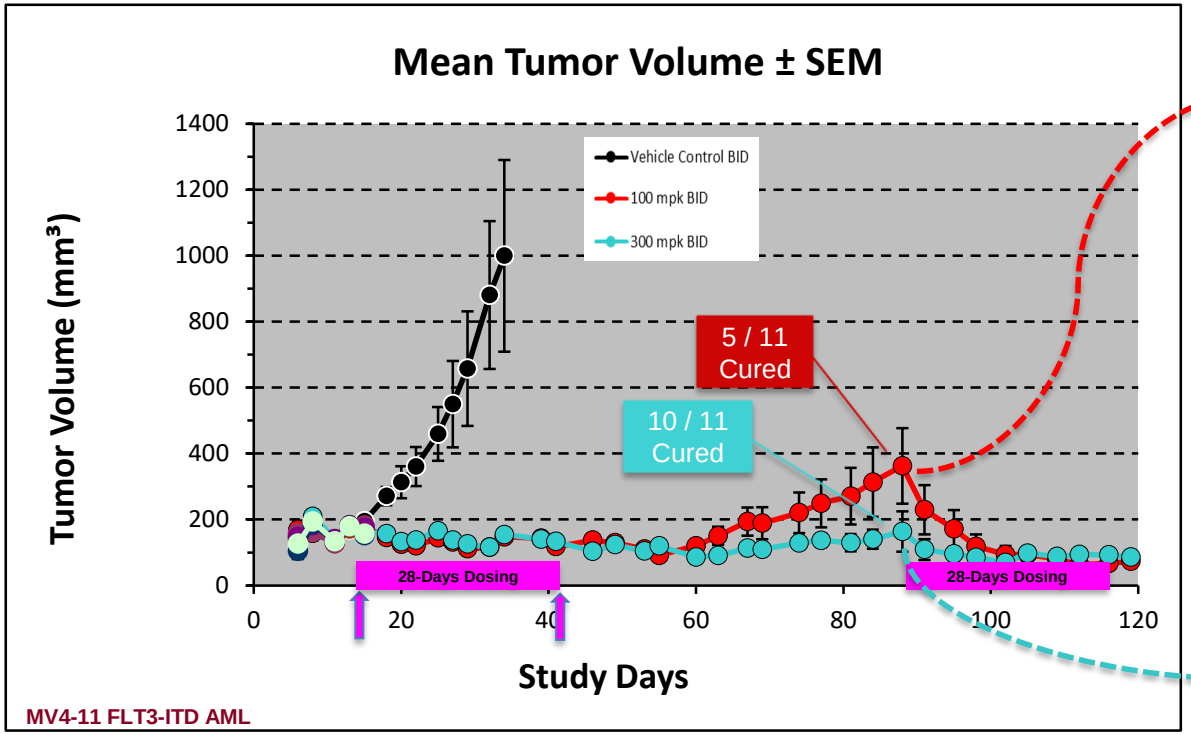


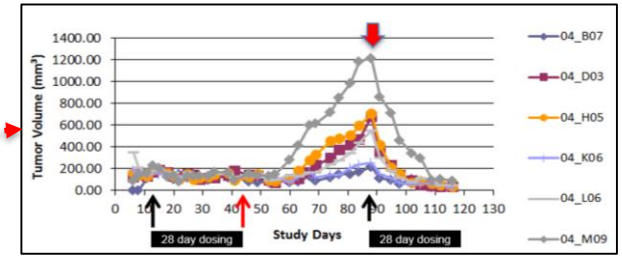


No evidence of toxicity at any dose

- Study terminated on day 119
- 11 / 11 mice survived in the 100mg/kg group
- 11 / 11 mice survived in the 300mg/kg group

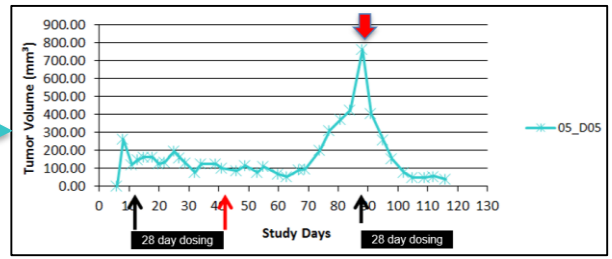
CG-806 Rapid and Sustained Antitumor Activity in Mouse Model of AML After Oral Dosing for 28 Days





100mg/kg BID
5 of 11 mice cured with 1st course

"Uncured" mice (see above) at d88 were treated with 300mg/kg BID for 2nd course of 28 days beginning d88 and those tumors responded to treatment



300mg/kg BID
10 of 11 mice cured with 1st course

"Uncured" mouse (see above) at d88 was treated with 300mg/kg BID for 2nd course of 28 days beginning d88 and that tumor responded to treatment

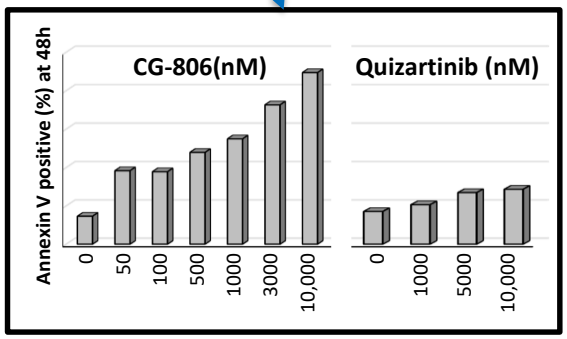
- No weight loss or toxicity at any dose level
- Significant cure rates with two highest dose levels
- Re-challenge of uncured mice with large tumors

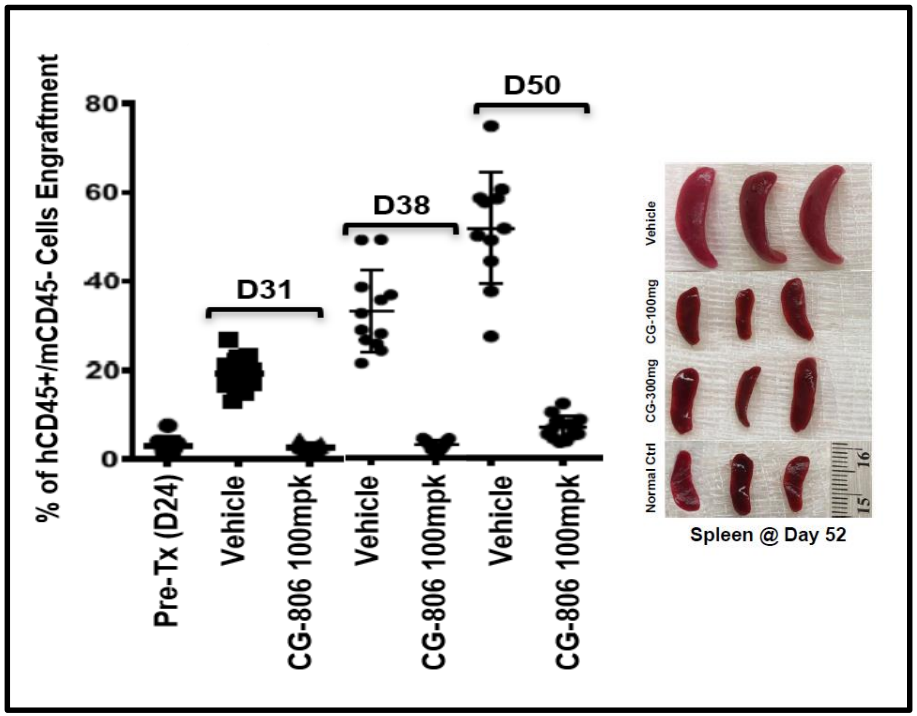
➡ Active on large tumors and no resistance observed

CG-806 Efficacy in PDX Model Against AML Patient Cells with FLT3 ITD + D835 Mutations

Patient information: AML patient (FLT3-ITD) received Sorafenib+Azacitidine Tx and experienced CR after one cycle therapy; relapsed after 3 cycles of treatment and acquired a D835 mutation (now FLT3-ITD/D835)

Patient Derived Xenograft (PDX) Model





Model implanted with FLT3 ITD+D835 mutated primary AML cells. CG-806 Tx initiated d27 (QDx5/wk Orally). hCD45+/mCD45- leukemic cells in peripheral blood were quantitated with flow cytometry.

CG-806

- Reduced leukemia cell burden
- Reduced splenomegaly
- Extended survival
- Active against patient-derived FLT3-ITD / D835 AML
- Potential to treat emerging FLT3i-resistant AML patients

Brian J. Druker, MD

Collaborator & Chair of SAB

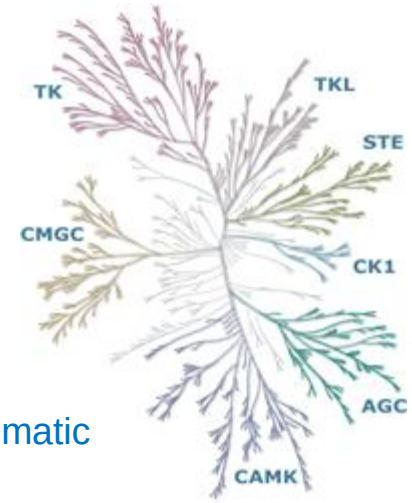
Evolution of Kinase Inhibitors and Perspectives of CG-806 with AML

APTOSE BIOSCIENCES

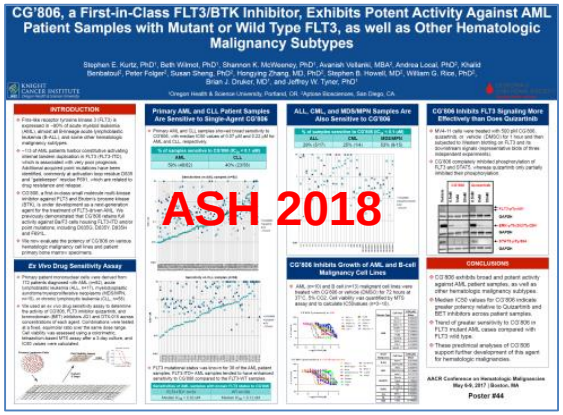
CG-806 in the Context of Kinase Inhibitors

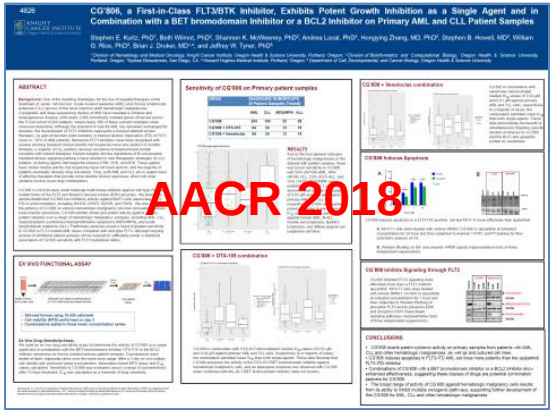
- **Protein Kinases -** >500 human protein kinases
  - **Mutated Kinases Alter Signaling Cascades – Can Lead to Cancer**
- **Over 50 Kinase Inhibitors (Kis) approved in the US**
  - Saved numerous lives and generated tremendous revenues
- **Multiple Generations of KIs Have Been Developed**
  - Trailblazer: Imatinib highly selective for Bcr-Abl
  - First Generation: Non-selective with off-target toxicities
  - Second Generation: More selective to reduce toxicities - resistance problematic
  - **Next Generation: Hits multiple targets, but avoids toxicity and rapid emergence of resistance**

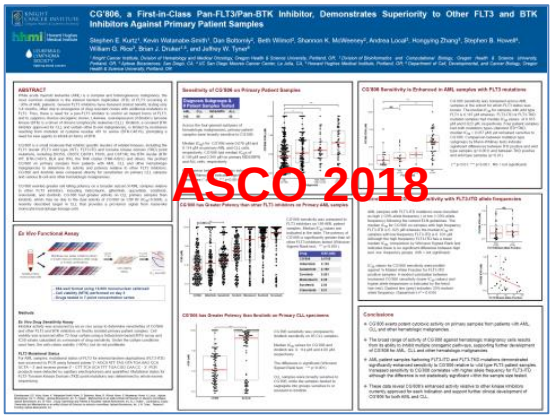
Human Kinome
Seven Major Groups

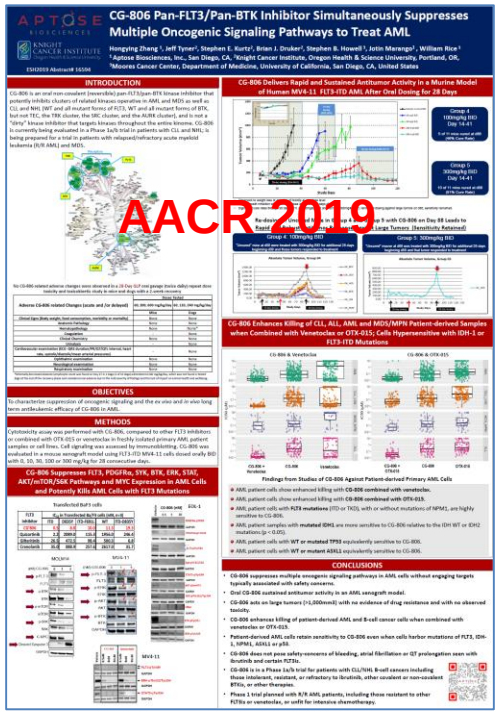


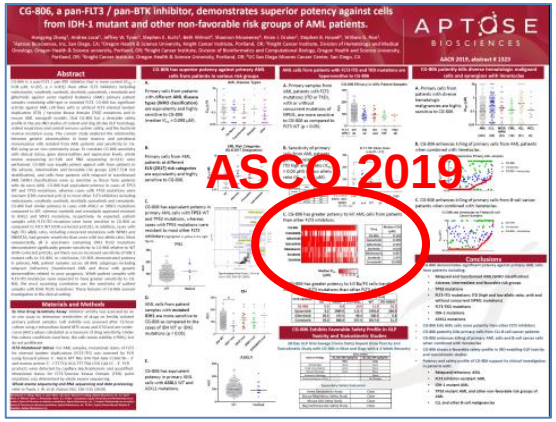
OHSU and Aptose Collaboration to Develop CG-806 as a Kinase Inhibitor for AML





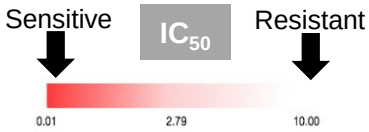


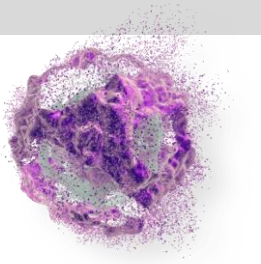


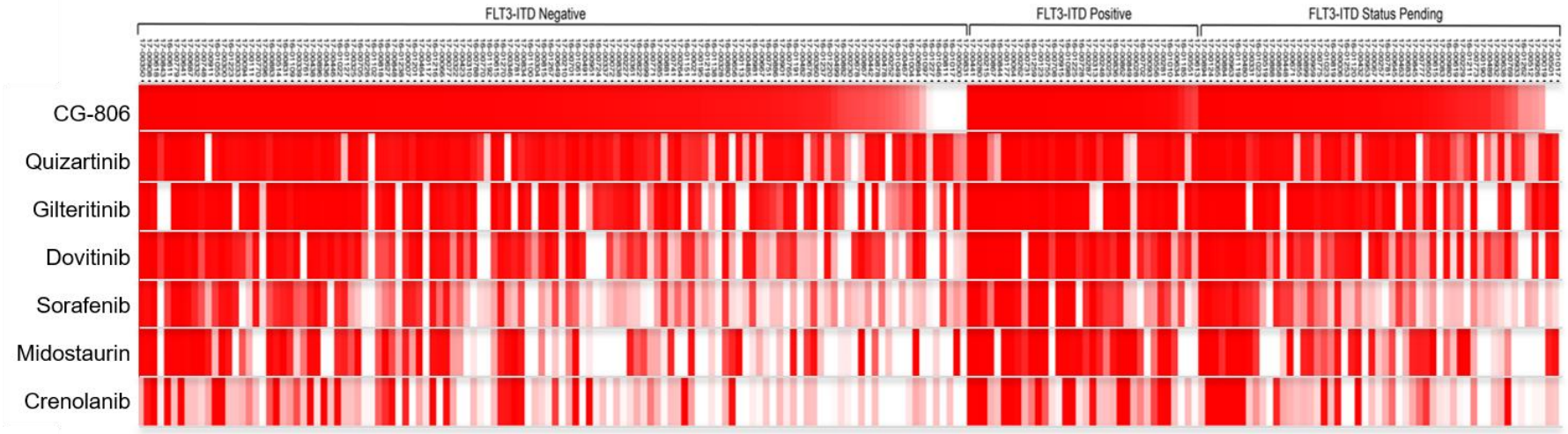


CG-806 Exerts Broad & Superior Killing Potency Compared to FLT3i on AML Patient Samples

- OHSU Measured the Ability of CG-806 and Various FLT3i's to Kill Primary Cells from >200 AML Patients IC_{50} transformed into a Heatmap of Sensitivity
- **CG-806 more potent and more broadly effective in killing primary AML cells bearing wild-type FLT3 or FLT3-ITD**

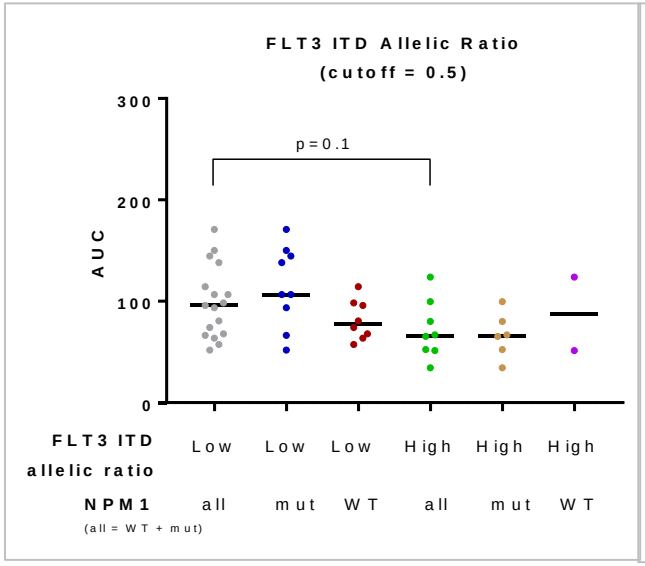


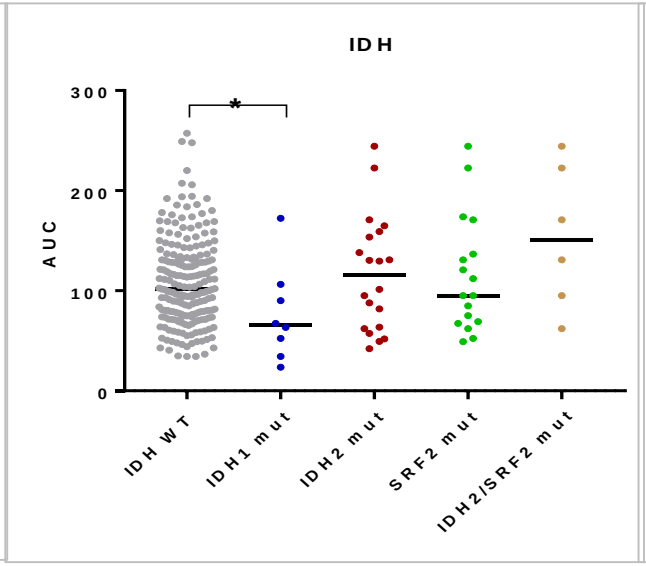


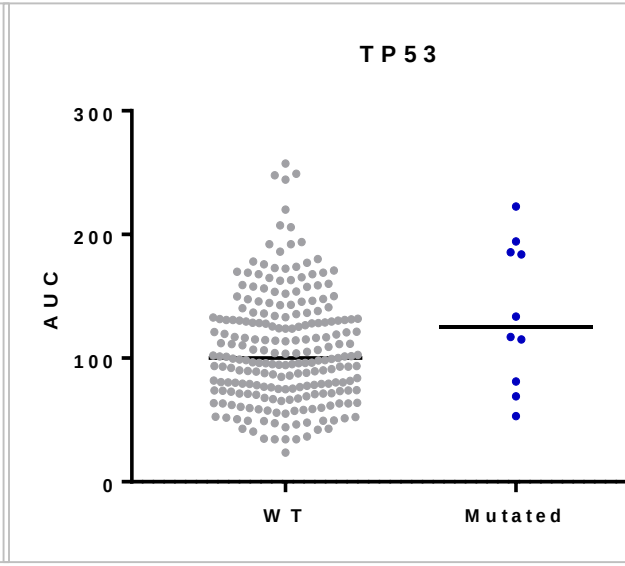


Sensitivity of AML Patients Samples to CG-806: AACR 2019

Maintains Potency in Samples with FLT3, IDH1, NPM1, p53, N-RAS and ASXL1 Mutations

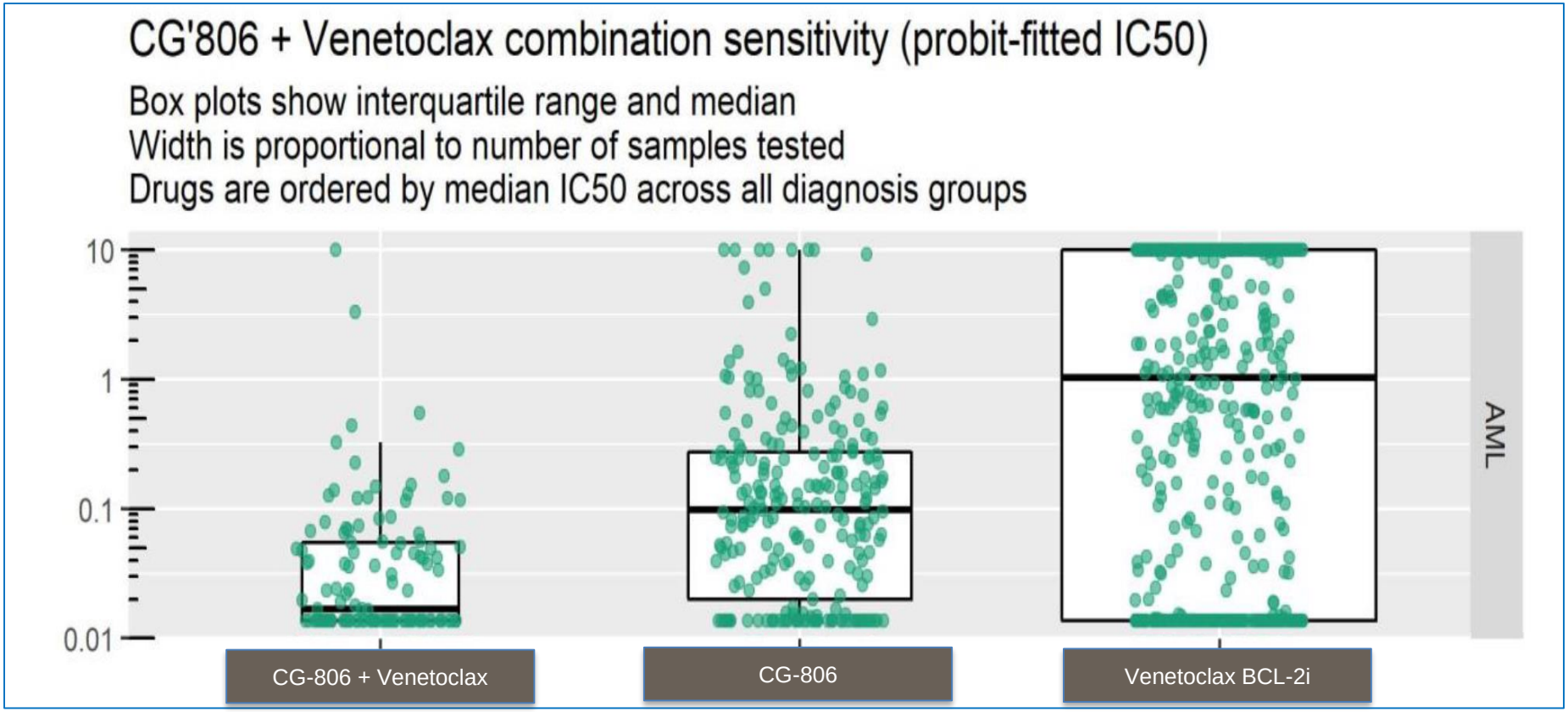






- Sensitivity of AML patient samples generally related to FLT3 ITD high allelic ratio (IC50 = 0.03 µM) vs. low allelic ratio (IC50 = 0.11 µM)
- AML patient samples with mutated IDH1 are more sensitive to CG-806 relative to the IDH WT or IDH2 mutations ($p < 0.05$)
- AML patient samples with TP53 WT and TP53 mutations equivalently sensitive to CG-806
  - AML patient samples with TP53 mutations were resistant to most other FLT3 inhibitors
- AML patient samples with NRAS WT and NRAS and ASXL1 WT and ASXL1 mutations equivalently sensitive to CG-806

CG-806 Combines Successfully with Venetoclax to Kill Primary AML Patient Samples



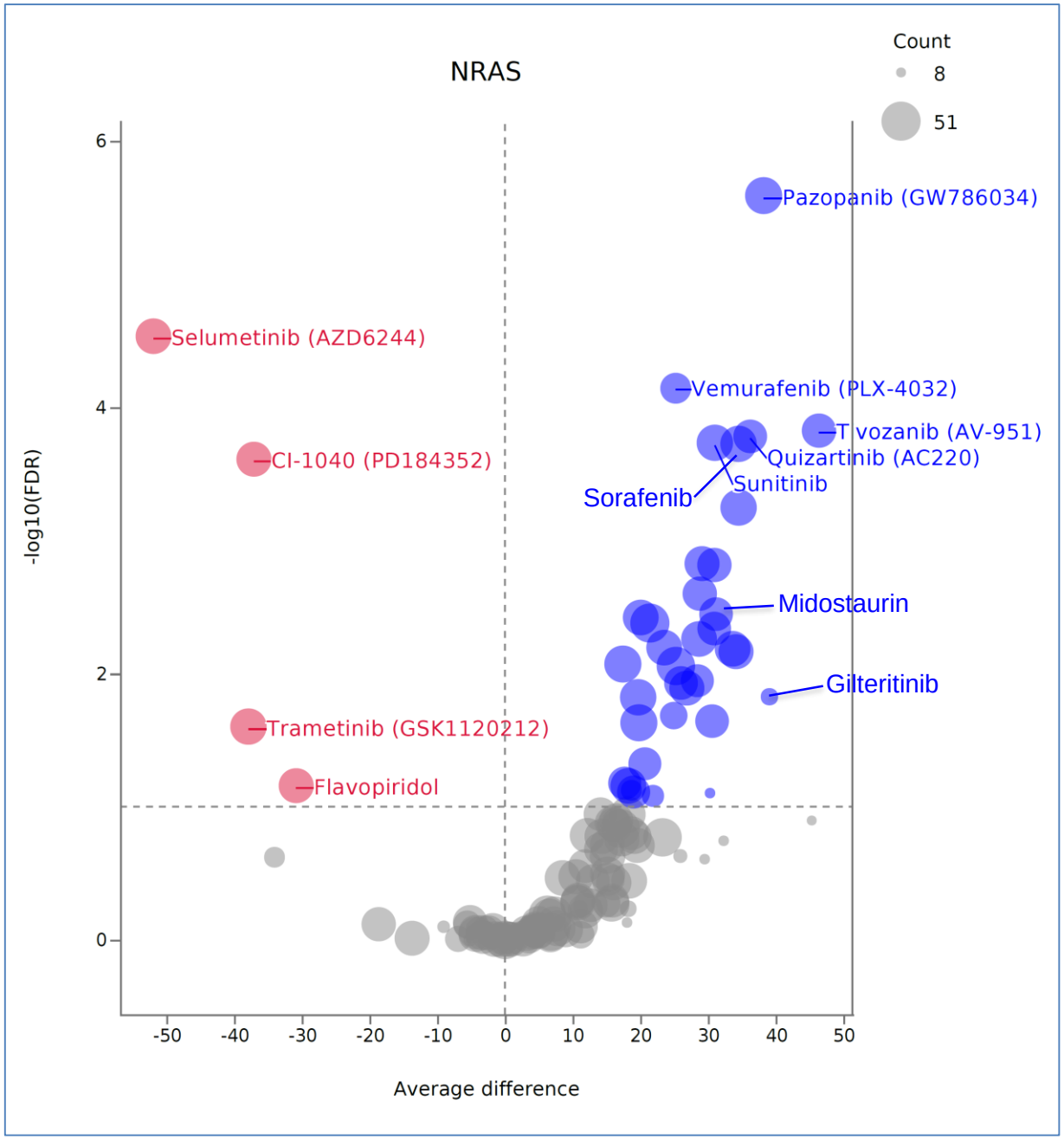
CG-806 as a Kinase Inhibitor for AML

- **CG-806 Preclinical Profile Meets "NextGen KI" Profile**
  - Strong efficacy and safety, while avoiding rapid emergence of drug resistance
  - Hits multiple "operative" targets/pathways but avoid targets that compromise safety
  - If the preclinical safety profile of CG-806 continues in humans, CG-806 has the potential to be among the best in class
- **CG-806 May Become a Highly Differentiated Agent for AML / MDS**
  - CG-806 is more than a FLT3 inhibitor
  - Suppresses FLT3, JAK/STAT, RAS, MAPK, ERK, AKT, BTK (SRC, SYK, LCK)
  - Safe and well tolerated to date

Rafael Bejar MD, PhD
Chief Medical Officer, Aptose Biosciences

SUMMARY OF CG-806 APPLICATION TO AML

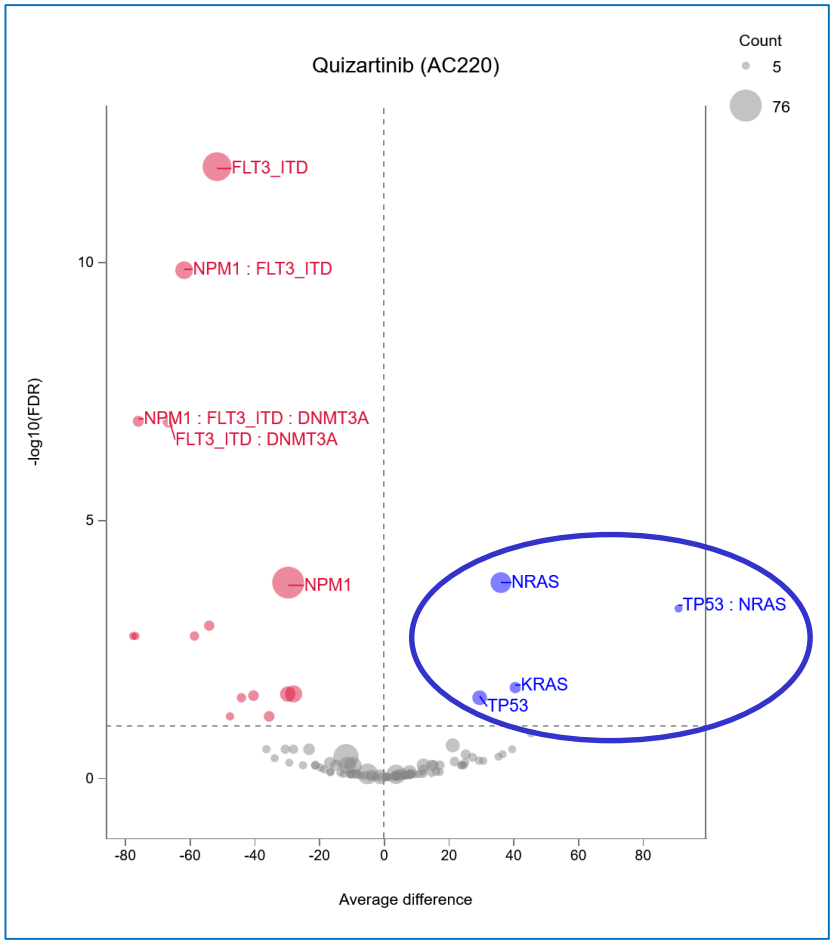
APTOSE BIOSCIENCES


NRAS
Count
8
51
Pazopanib (GW786034)
Selumetinib (AZD6244)
Vemurafenib (PLX-4032)
Tivozanib (AV-951)
Quizartinib (AC220)
CI-1040 (PD184352)
Sunitinib
Sorafenib
Midostaurin
Gilteritinib
Trametinib (GSK1120212)
Flavopiridol
-log10(FDR)
Average difference
6
4
2
0
-50
-40
-30
-20
-10
0
10
20
30
40
50

AML Patient Genes Engendering Sensitivity or Resistance Quizartinib vs Gilteritinib

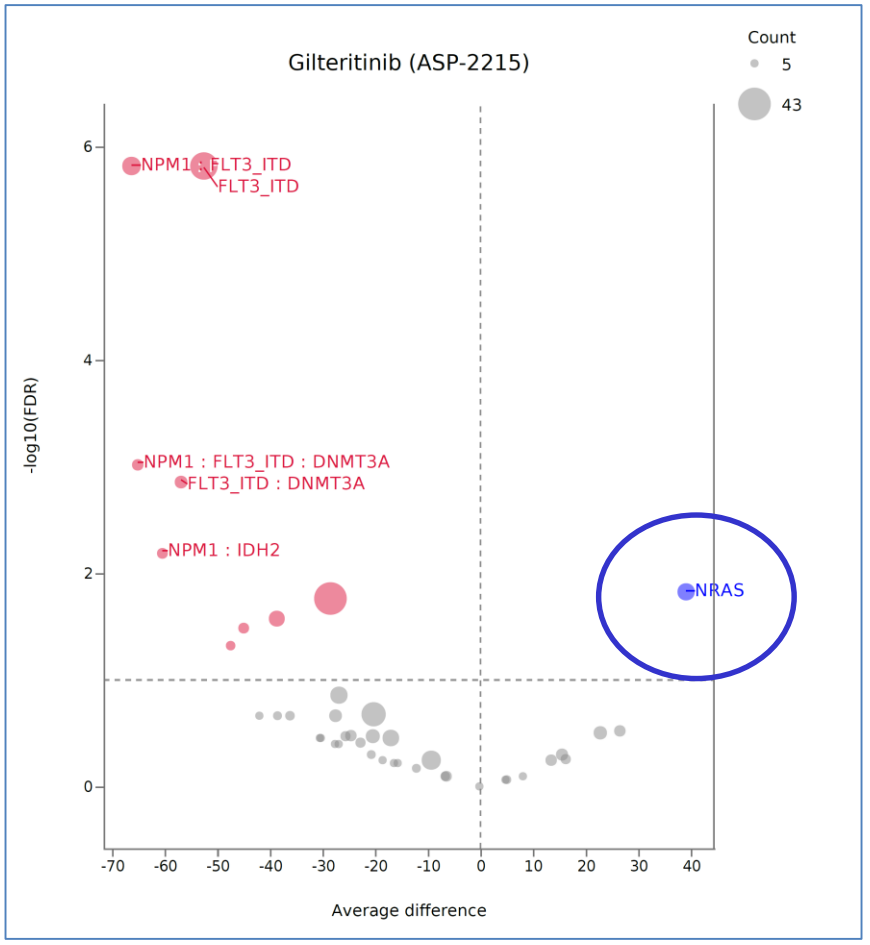
Volcano plot showing mutations significantly associated with sensitivity (red) or resistance (blue) to Quizartinib alone.

- ":" indicates co-occurring mutations
- Horizontal dashed line indicates significance threshold

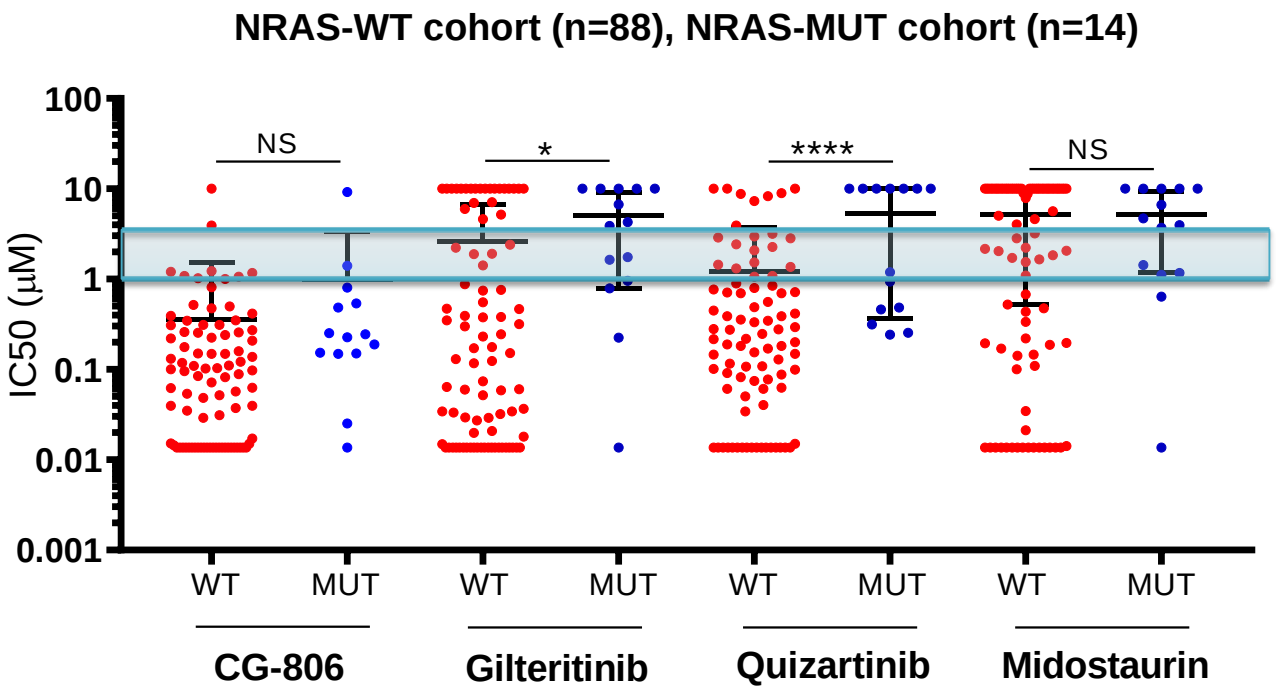


Volcano plot showing mutations significantly associated with sensitivity (red) or resistance (blue) to Gilteritinib alone.

- ":" indicates co-occurring mutations
- Horizontal dashed line indicates significance threshold

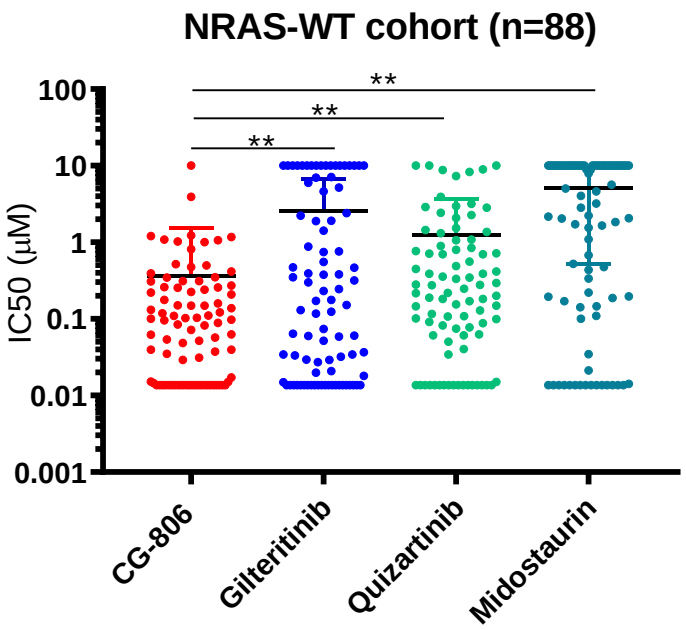


Unlike other FLT3 inhibitors, CG-806 retains high potency in patient samples carrying NRAS mutations

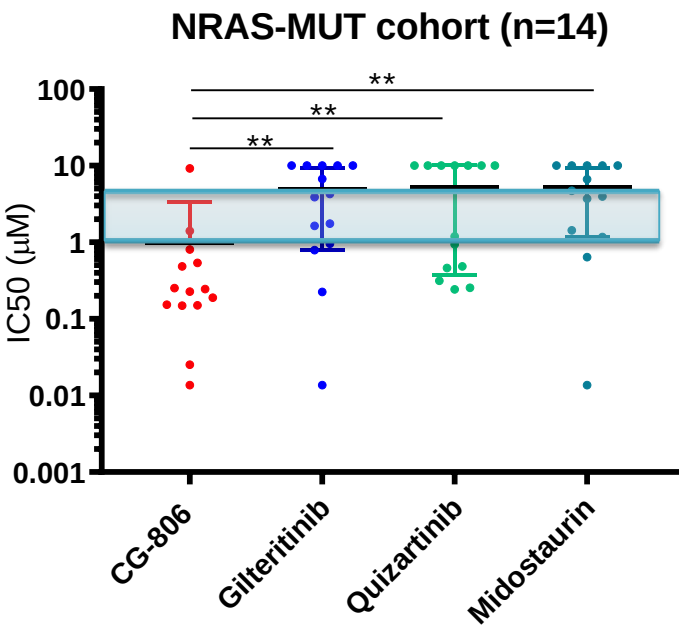


	CG-806/WT	CG-806/MUT	Gilteritinib/WT	Gilteritinib/MUT	Quizartinib/WT	Quizartinib/MUT	Midostaurin/WT	Midostaurin/MUT
Mean	0.3598	0.9902	2.592	5.016	1.232	5.278	5.131	5.247

CG-806 is significantly superior to other FLT3 inhibitors in both NRAS-wildtype and NRAS-mutant patient samples



	CG-806	Gilteritinib	Quizartinib	Midostaurin
Mean	0.3598	2.592	1.232	5.131



	CG-806	Gilteritinib	Quizartinib	Midostaurin
Mean	0.9902	5.016	5.278	5.247

CG-806 in AML Summary

- **Medical Need for New Agents to Control R/R-AML**
  - Patients are failing all current therapies
  - Seek to control AML resistant to other FLT3i and venetoclax
  - Seek to treat AML with mutations in IDH-1, TP53, RAS
  - Seek to treat “unfit” patient with AML
- **CG-806 Potently Inhibits All Known Forms of FLT3**
  - Potently suppresses multiple oncogenic signaling pathways
  - Avoids targets traditionally associated with toxicity
- **Human PK Exposures Nearing Therapeutic Range at Dose Levels 3**
- **Plan to Submit IND Amendment as Soon as Possible**
  - Provided PK and Safety Data supportive
- **Attractiveness for Clinical and Commercial Success Driven by:**
  - FLT3 is a validated target
  - Combinatorial optionality
  - Potential cornerstone of therapy as oral targeted agent
  - Broad applicability but unlikely to require genomic/biomarker-guided patient selection

CG-806

Ideal drug for gilteritinib failures:

- √ – potent FLT3 inhibitor,
- √ – target FLT3-ITD and FLT3-TKD
- √ – target multiple mechanisms of FLT3 resistance
- √ – active in setting of RAS mutations
- √ – potentially synergize with venetoclax

Thank You!

APTOSE BIOSCIENCES