Module 14: Systemic Mastocytosis and Myelofibrosis

Systemic Mastocytosis — Dr Hunter

Myelofibrosis — Dr Yacoub

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We would like to do a “best paper or presentation of the year” activity. Please suggest one “paper of the year” and 2 other worthy papers based on the value in treatment of current and future patients.

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Systemic Mastocytosis: An Overview and Review of Therapeutic Advances

Anthony Hunter, MD
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Systemic Mastocytosis Classification

- Spectrum of clonal/neoplastic diseases of mast cells
  - Characterized by pathologic mast cell accumulation in tissues
  - Mast cell activation with related symptoms

Primary mast cell disorders
Mastocytosis (systemic and cutaneous)
Monoclonal mast cell activation syndrome
Secondary mast cell disorders
Allergic disorders
Physical urticarias
Mast cell activation associated with chronic inflammatory or neoplastic disorders
Idiopathic mast cell disorders
Idiopathic anaphylaxis
Idiopathic urticaria (also called chronic spontaneous urticaria)
Idiopathic histaminergic angioedema
Idiopathic mast cell activation syndrome

Table 1 | WHO classification of mastocytosis[3,5,17,20] and estimated prevalence

Variants and subvariants		Predominant age group	Estimated prevalence (%)	Individuals with *KIT*^{D816V} mutation (%)
Cutaneous mastocytosis		–	0.01	–
MPCM[a]	Polymorphic form of MPCM	Children	0.005	20[b]
	Monomorphic form of MPCM	Children and adults	0.01	30 (children)[b] and 80 (adults)
Diffuse CM	–	Children	0.0001	<10[b]
Mastocytoma of skin	–	Children	0.02	Not known
Systemic mastocytosis		–	0.005	–
Non-advanced SM	Bone marrow mastocytosis	Adults	0.002	80
	Indolent SM	Adults	0.005	90
	Smouldering SM	Adults	0.0005	95
	Well-differentiated SM subsets	Adults	<0.0001	<5[c]
Advanced SM	SM with an associated haematological neoplasm	Adults	0.001	95
	Aggressive SM	Adults	0.0001	80
	Mast cell leukaemia	Adults	<0.0001	70
	Well-differentiated subsets of advanced SM	Adults	<0.0001	<5[c]
MCS	–	Adults	<0.0001	<5
MCS-like SM[d]		Adults	<0.0001	50
Extracutaneous mastocytoma[e]	–	Adults	<0.0001	Not known

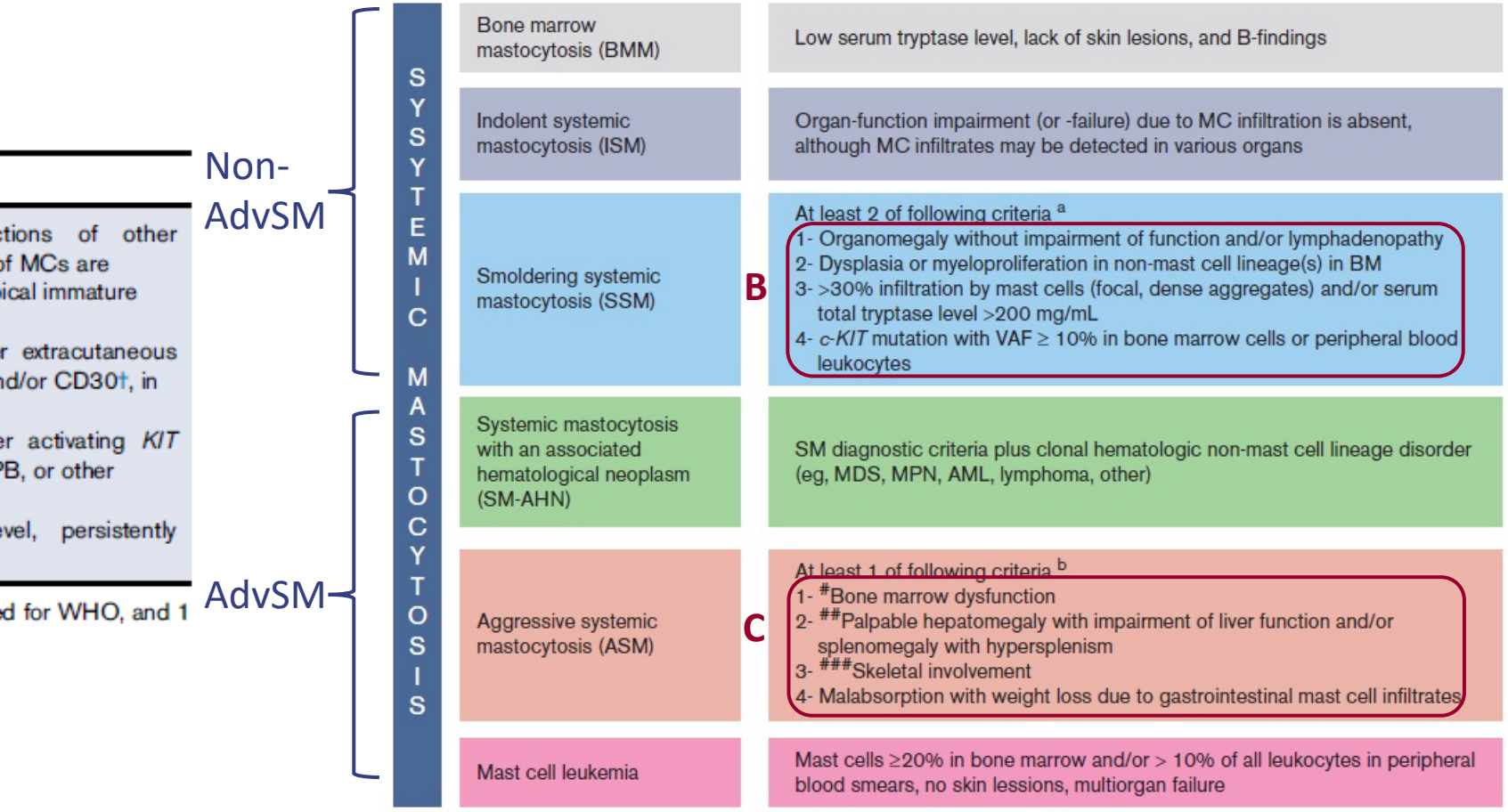
Akin, C *et al.* . *Nat Rev Dis Primers* 2025; 11(1):30. Khoury JD, et al. *Leukemia* 2022; 36(7):1703-1719

Diagnosis of Systemic Mastocytosis

Table 1. Diagnostic criteria of SM

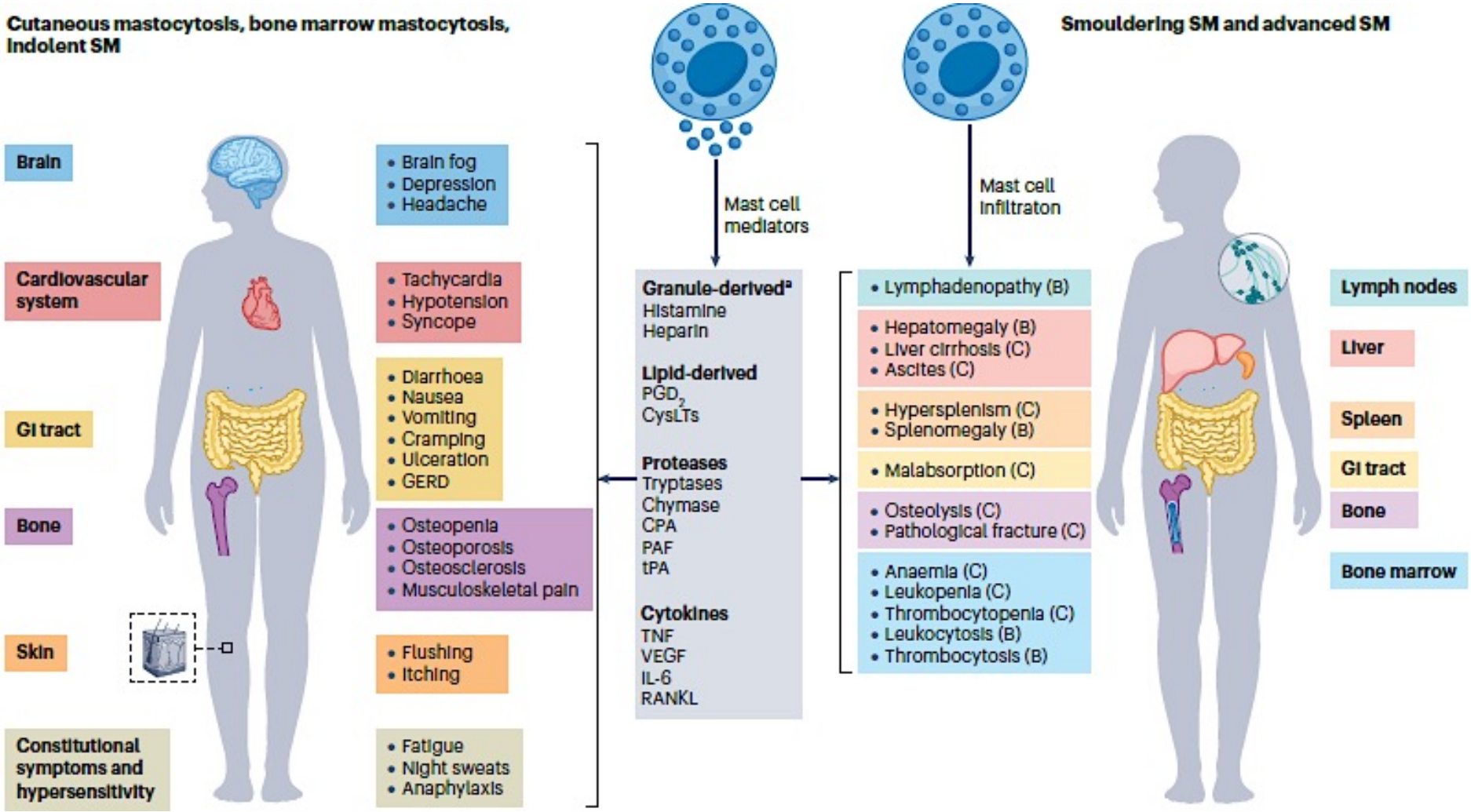
Major criterion	Minor criteria
Multifocal dense infiltrates of MCs (>15 MCs in aggregates) in BM biopsies and/or in sections of other extracutaneous organ(s)*	1. In BM biopsy or in sections of other extracutaneous organs >25% of MCs are spindle shaped or have an atypical immature morphology 2. MCs in the BM, PB, or other extracutaneous organs express CD25, CD2, and/or CD30†, in addition to MC markers 3. *KIT* D816V mutation or other activating *KIT* mutation detected in the BM, PB, or other extracutaneous organs‡ 4. Elevated serum tryptase level, persistently >20 ng/mL†,§

For the diagnosis of SM, 1 major + 1 minor or >3 minor criteria needed for WHO, and 1 major or >3 minor criteria needed for ICC classification.



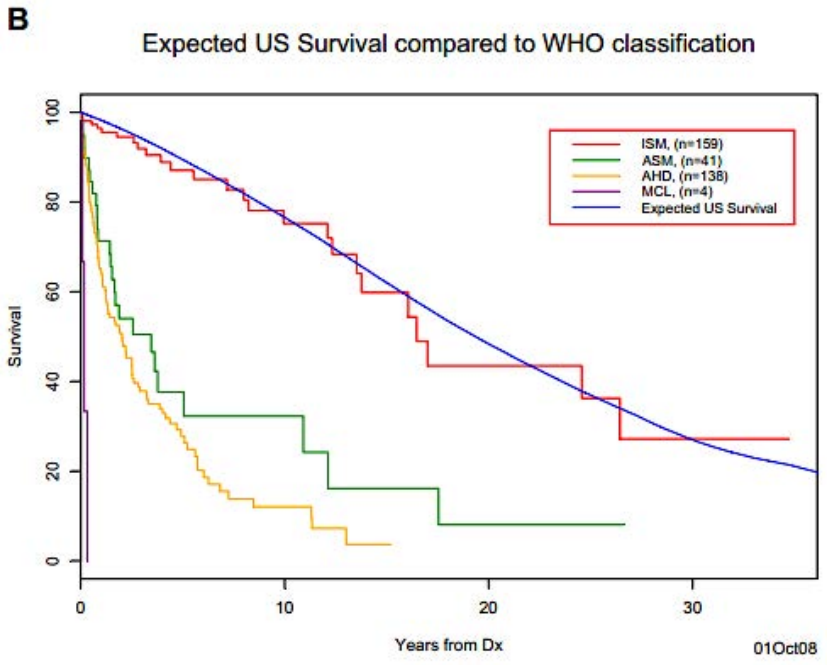
Ustun C, et al. *Blood Adv* 2025; 9(9):2048-2062. Khoury JD, et al. *Leukemia* 2022; 36(7):1703-1719. Arber DA, et al. *Blood* 2022; 140(11):1200-1228

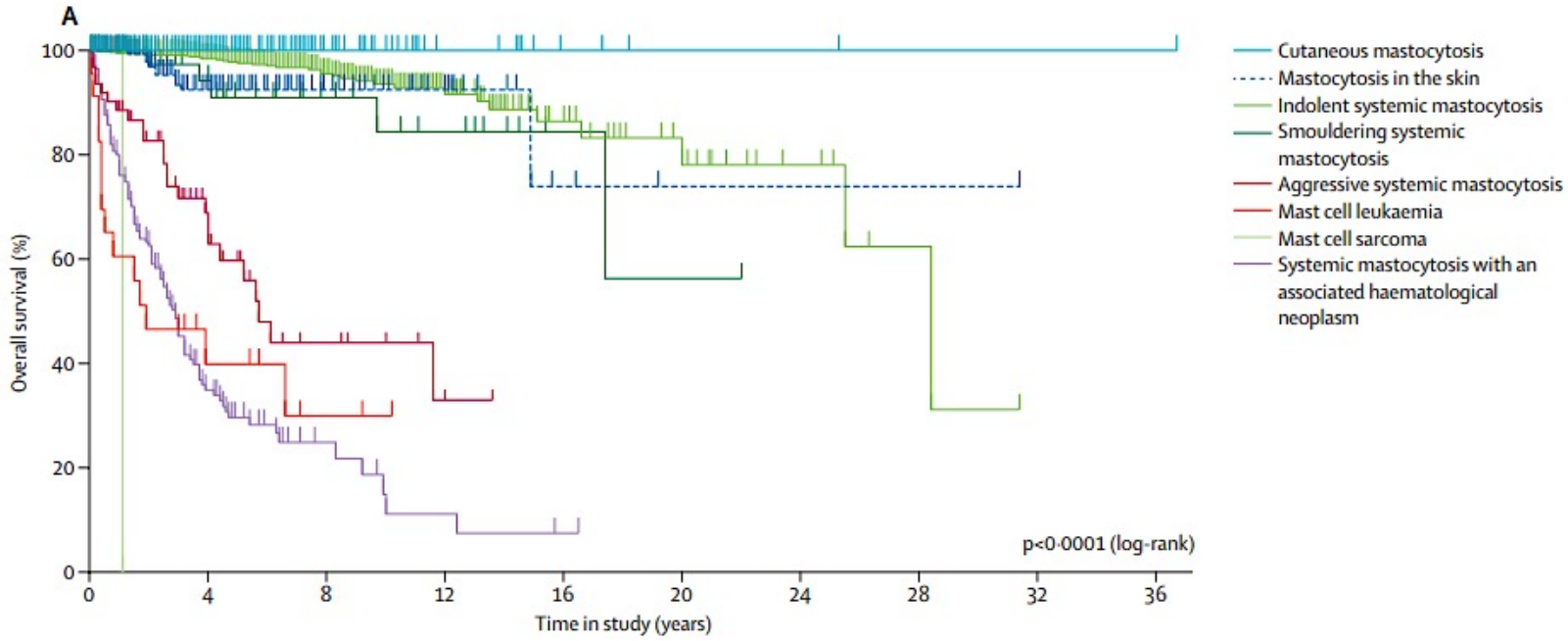
SM Displays Spectrum of Clinical Features with High Degree of Interpatient Variability



Akin, C *et al.* . *Nat Rev Dis Primers* 2025; 11(1):30

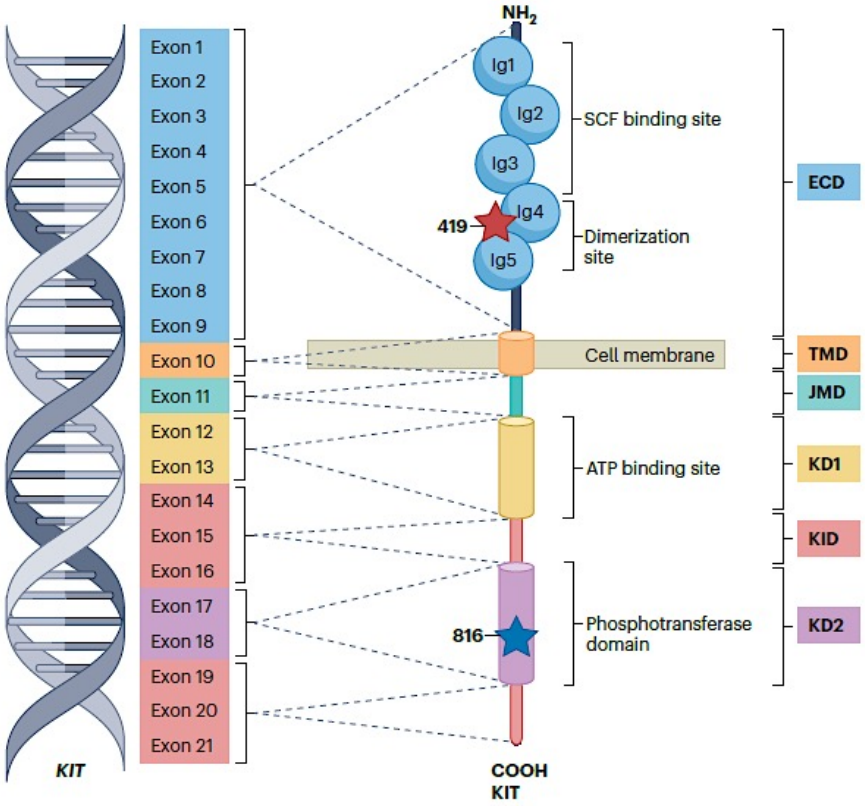
Survival of Systemic Mastocytosis by Subtype

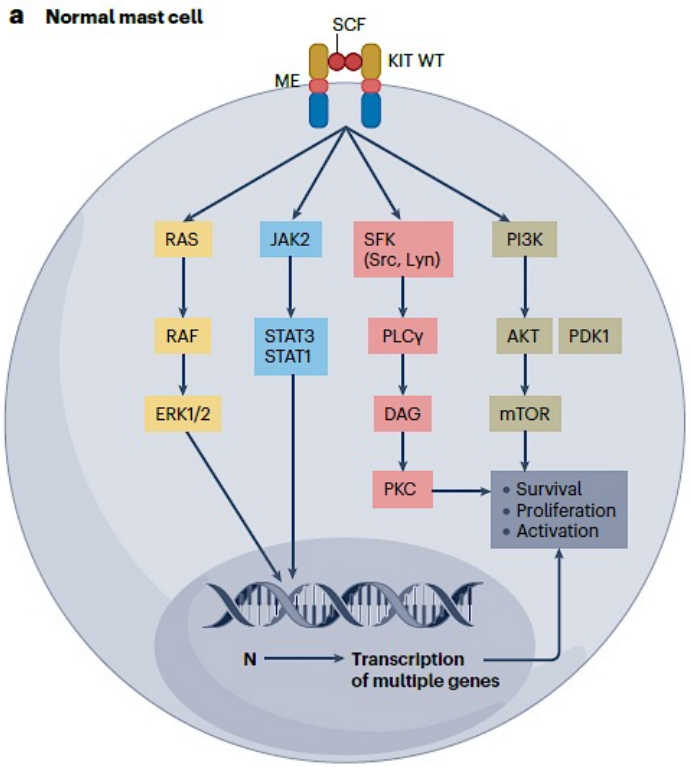


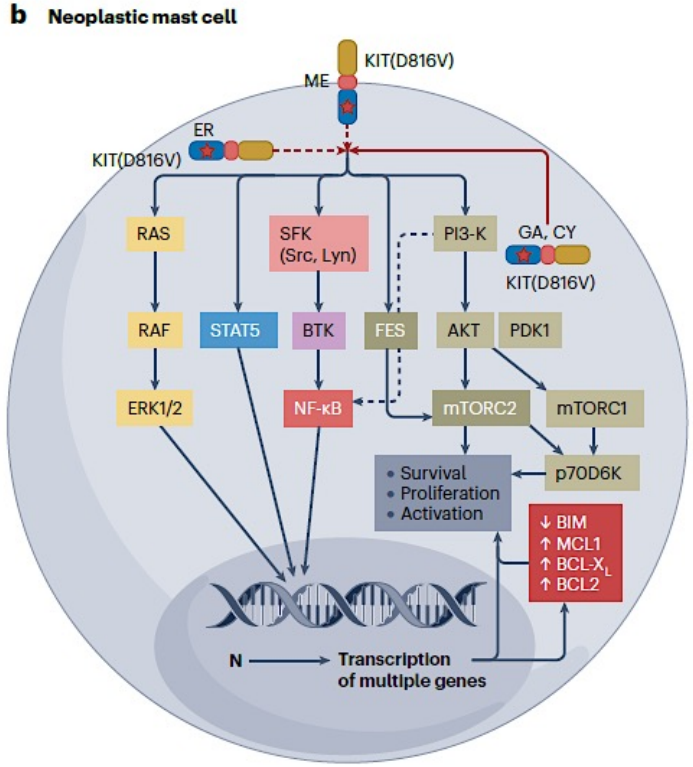


Lim KH, et al. *Blood* 2009;113(23):5727-5736. Sperr WR, et al. *Lancet Haematol* 2019;6(12):e638

Activating Mutations in *KIT* Are a Key Biologic Feature of Systemic Mastocytosis







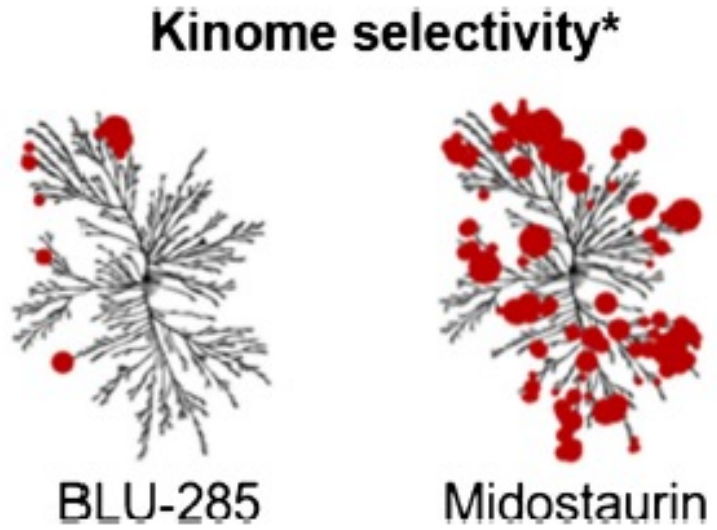
****KIT* mutations, predominantly D816V, are present in >90% of patients with SM**

- Requires high-sensitivity testing (ddPCR or ASO), VAF threshold of 0.01%-0.03%

Akin, C *et al.* . *Nat Rev Dis Primers* 2025; 11(1):30. Nagata H, et al. *PNAS* 1995;92:10560-10564. Longley B, et al. *Nat Genet* 1996; 12:312-314

KIT Inhibitors Have Changed the Treatment Paradigm in SM

- Logical therapy given high prevalence and key role of *KIT* in disease biology.
- Midostaurin approved for treatment of AdvSM in 2017
  - Broad kinase activity, less favorable toxicity profile
  - Lower response rates with more stringent criteria
- Newer generation of KIT inhibitors are more selective and potent:

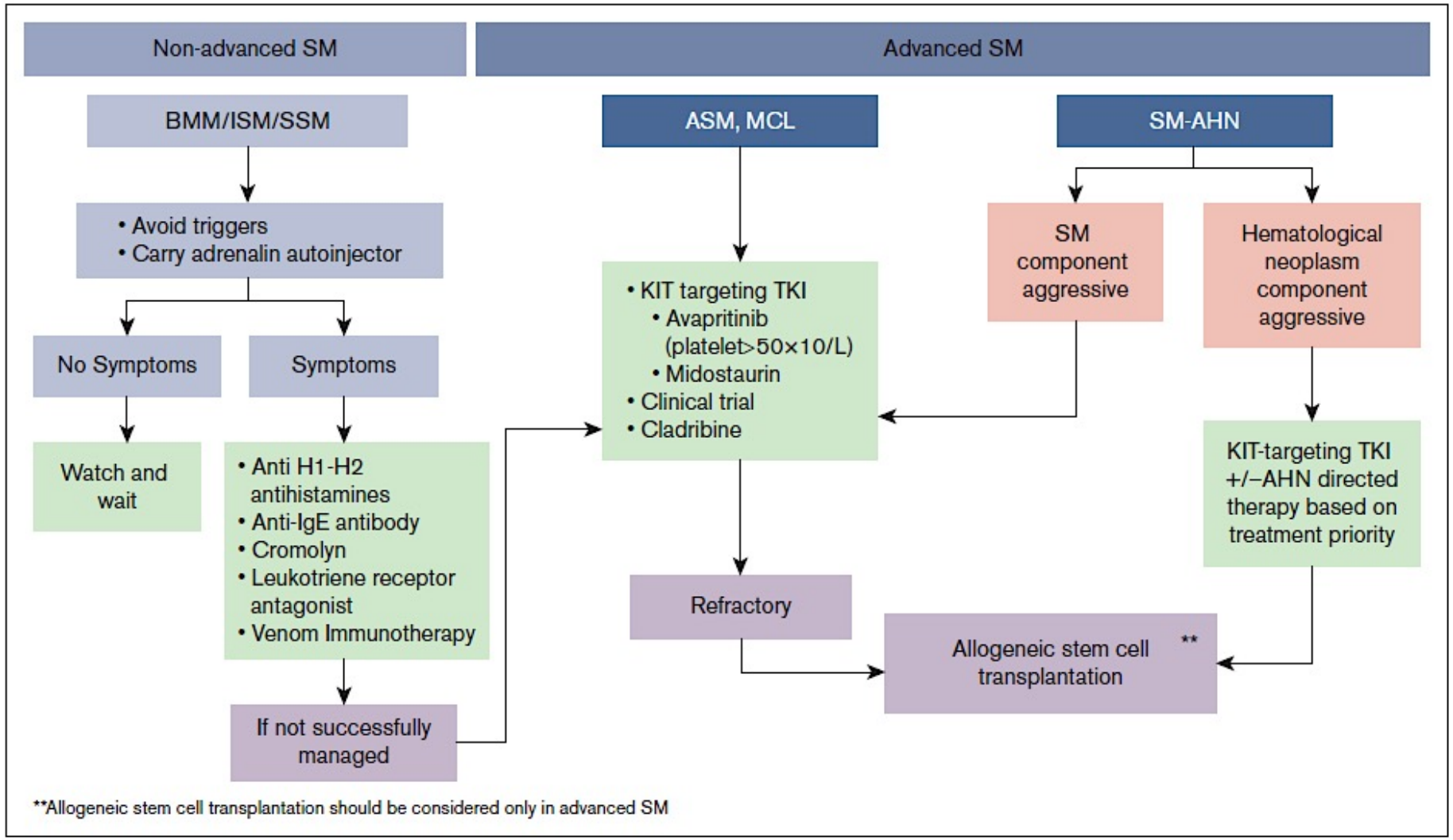


Kinase Inhibition Profile (IC_{50})

Compound	KIT V560G/D 816V (HMC 1.2)	WT KIT	PDGFRα	PDGFRβ	CSF1R	FLT3	KDR	CNS Penetration	Approval in NonAdv SM	Approval in Adv SM
Avapritinib	13	114	53	10	249	305	>1000	+	+	+
Bezuclastinib	14	121	>10,000	>10,000	>10,000	>1000	>1000	**-**	**-***	**-***
Elenestinib	6	355	21	6	161	345	>1000	-	-	-

Guarnieri A. et al. Abstract P257 Molecular Cancer Therapeutics, 2021. 20(12_Supplement), P257-P257.
DeAngelo DJ, et al. *Blood* 2024;144(Supplement 1):659. Below S, et al. *Curr Hematol Malig Rep* 2021;16(5):464-472

Treatment Framework in SM



Ustun C, et al. *Blood Adv* 2025; 9(9):2048-2062.

Avapritinib in Advanced SM

- Phase 1 (EXPLORER trial): dose escalation and expansion (n = 86)
  - Avapritinib 200mg daily as optimal dose
  - Substantial activity demonstrated

- Phase 2 (PATHFINDER): single-arm, phase 2 study in patients with AdvSM
  - AdvSM patients (n = 107; 83 were response evaluable) with or without prior therapy; plts > 50
  - Primary Endpoint: Overall response rate
  - Led to approval of avapritinib in AdvSM in 2021

DeAngelo DJ, et al. *Nat Med* 2021;27(12):2183-2191. Gotlib J, et al. *Nat Med*2021;27(12):2192-2199

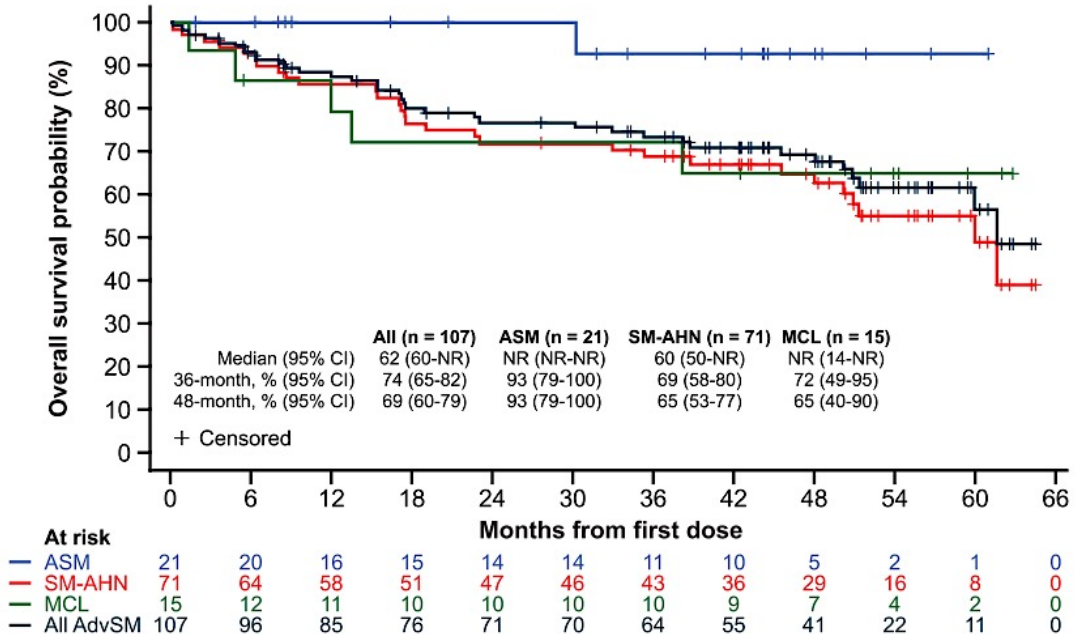
Avapritinib Demonstrates Efficacy in Advanced SM

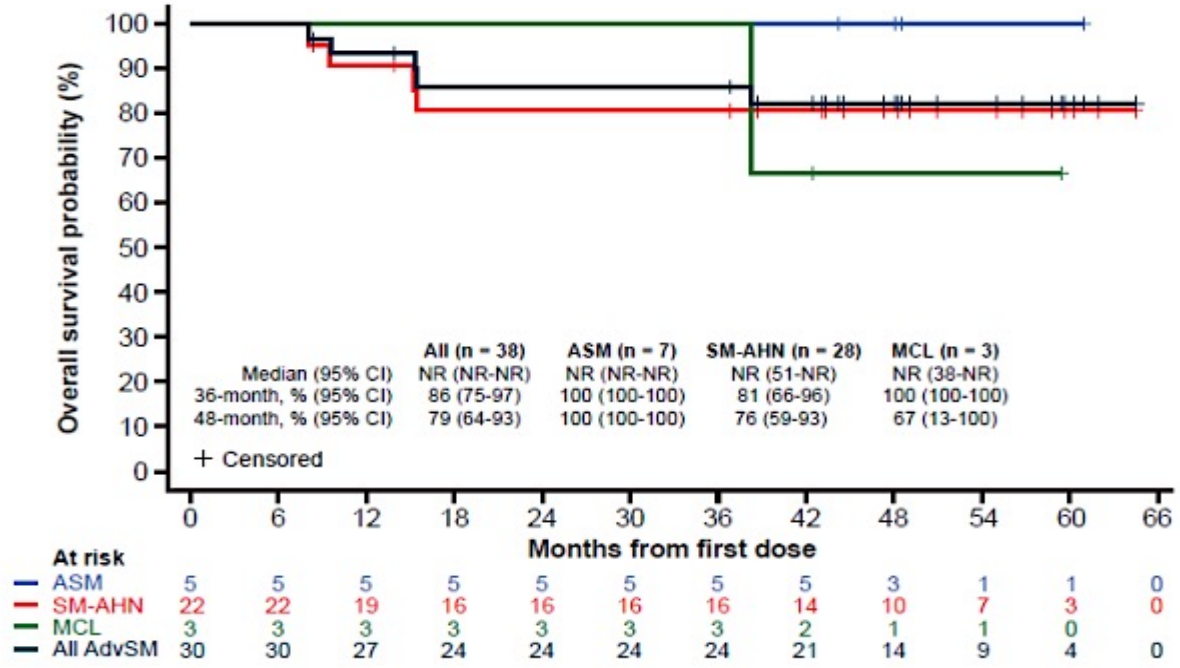
Best confirmed response, n (%)	All response-evaluable				Patients with ≥1 prior systemic therapy (n = 53)	Treatment-naïve patients (n = 30)
		AdvSM subtype				
	All (n = 83)	ASM (n = 13)	SM-AHN (n = 55)	MCL* (n = 15)		
ORR†	**61 (73)**	10 (77)	41 (75)	10 (67)	**35 (66)**	**26 (87)**
95% CI	**63-83**	46-95	61-85	38-88	**52-79**	**69-96**
Best response						
CR/CRh‡	**25 (30)**	4 (31)	18 (33)	3 (20)	**12 (23)**	**13 (43)**
CR	**14 (17)**	1 (8)	10 (18)	3 (20)	**6 (11)**	**8 (27)**
CRh	**11 (13)**	3 (23)	8 (15)	0	**6 (11)**	**5 (17)**
PR‖	**32 (39)**	6 (46)	19 (35)	7 (47)	**19 (36)**	**13 (43)**
CI	**4 (5)**	0	4 (7)	0	**4 (8)**	**0**
SD	**13 (16)**	3 (23)	7 (13)	3 (20)	**10 (19)**	**3 (10)**
PD¶	**2 (2)**	0	1 (2)	1 (7)	**2 (4)**	**0**
NE#	**7 (8)**	0	6 (11)	1 (7)	**6 (11)**	**1 (3)**

- Responses deepened over time
  - Time to response: 2.3 months
  - Time to CR/CRh: 9.3 months
- Median duration of response: 58 months (not reached in treatment-naïve patients)
- Improvements in bone density observed with long-term follow up

Gotlib J, et al. *Nat Med*2021;27(12):2192-2199. Gotlib J, et al. *Blood Adv* 2026; 2025017519. Reiter A, et al. *Blood* 2025; 145 (Supplement 1): 1022

Overall Survival with Avapritinib Compares Favorably to Historical Outcomes





Disease progression observed in 21 patients (6 AML); 19 of whom had an AHN

Safety of Avapritinib in AdvSM

Table 3. TEAEs and TRAEs of safety population (N = 107)

	Any-cause TEAEs*		Treatment-related AEs	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any, n (%)	107 (100)	95 (89)	103 (96)	73 (68)
Non-hematological AEs in ≥15%, n (%)				
Periorbital edema†	61 (57)	6 (6)	59 (55)	6 (6)
Peripheral edema†	51 (48)	2 (2)	42 (39)	2 (2)
Diarrhea	38 (36)	5 (5)	16 (15)	1 (<1)
Nausea	29 (27)	1 (<1)	13 (12)	0
Arthralgia	28 (26)	2 (2)	7 (7)	0
Vomiting	25 (23)	2 (2)	9 (8)	1 (<1)
Face edema†	24 (22)	0	23 (21)	0
Fatigue	24 (22)	3 (3)	14 (13)	2 (2)
COVID-19	22 (21)	4 (4)	-	-
Epistaxis	20 (19)	0	6 (6)	0
Hair color changes	18 (17)	0	18 (17)	0
Pruritus	19 (18)	0	5 (5)	0
Rash	18 (17)	1 (<1)	7 (7)	1 (<1)
Abdominal pain	16 (15)	1 (<1)	2 (2)	0
Constipation	16 (15)	1 (<1)	4 (4)	0
Headache	16 (15)	0	8 (7)	0
Hematological AEs in ≥15%, n (%)				
Thrombocytopenia†	62 (58)	33 (31)	55 (51)	33 (29)
Anemia†	58 (54)	35 (33)	35 (33)	17 (16)
Neutropenia†	36 (34)	32 (30)	30 (28)	27 (25)
Blood alkaline phosphatase increased	17 (16)	3 (3)	9 (8)	2 (2)
Blood creatinine increased	16 (15)	1 (<1)	3 (3)	
AEs of special interest in ≥1%, n (%)				
Cognitive effects†	36 (34)	9 (8)	30 (28)	6 (6)
Cognitive disorder	21 (20)	5 (5)	19 (18)	5 (5)
Memory impairment	10 (9)	0	9 (8)	0
Confusional state	7 (7)	2 (2)	2 (2)	0
Delirium	3 (3)	2 (2)	0	0
Intracranial bleeding†	4 (4)	2 (2)	4 (4)	2 (2)
Subdural hematoma	2 (2)	2 (2)	2 (2)	2 (2)
Intracranial hemorrhage	2 (2)	0	2 (2)	0
AEs leading to death, n (%)	10 (9)‡		1 (<1)¶	

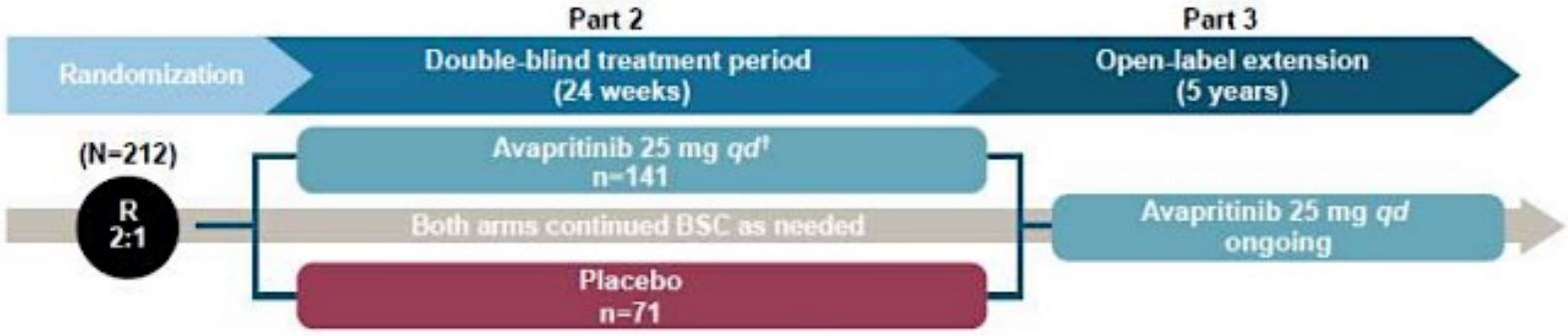
- 19% discontinued due to treatment-related AEs
- 78% had dose reductions due to treatment-related AEs

Gotlib J, et al. *Nat Med*2021;27(12):2192-2199. Gotlib J, et al. *Blood Adv* 2026; 2025017519

Avapritinib in ISM: PIONEER Study

Screening Period

- BSC medications optimized for 2–3 months
  - Antihistamines, cromolyn, anti-IgE antibody, leukotriene inhibitors, corticosteroids etc.
- Eligibility
  - Age ≥18 years
  - ISM confirmed by central pathology review
  - Uncontrolled moderate to severe (TSS ≥28) symptoms after at least 2 BSC medications

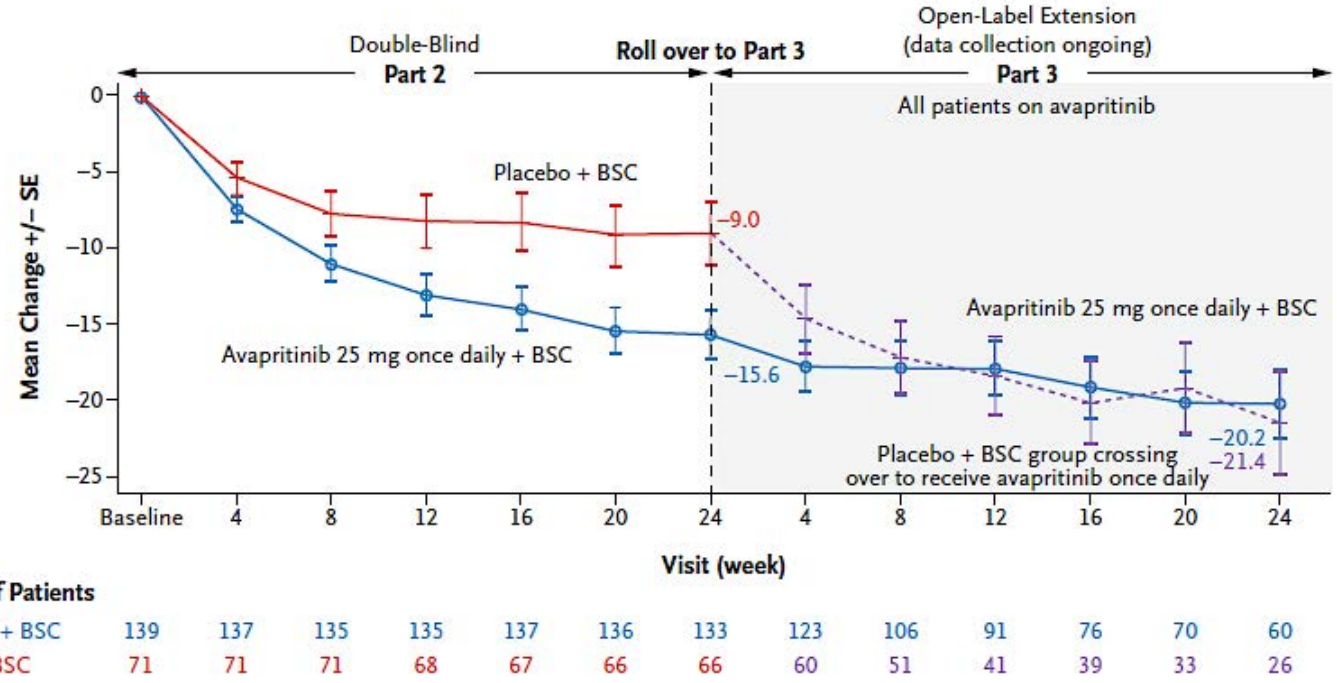


Primary endpoint
Mean change in TSS from baseline to Week 24

Key secondary endpoints
Proportion of patients achieving the following from baseline to Week 24:
- ≥50% reduction in serum tryptase levels and *KIT* D816V VAF in peripheral blood (or below level of detection [<0.02%] for patients with a detectable mutation at baseline)
- ≥50% and ≥30% reduction in ISM-SAF TSS
- ≥50% reduction in BM core biopsy MC burden (or no aggregates for patients with aggregates)

Gotlib J, et al. *NEJM Evid* 2023; 2(6)

Avapritinib Demonstrates Substantial Symptom Reduction in ISM: Approved 2023



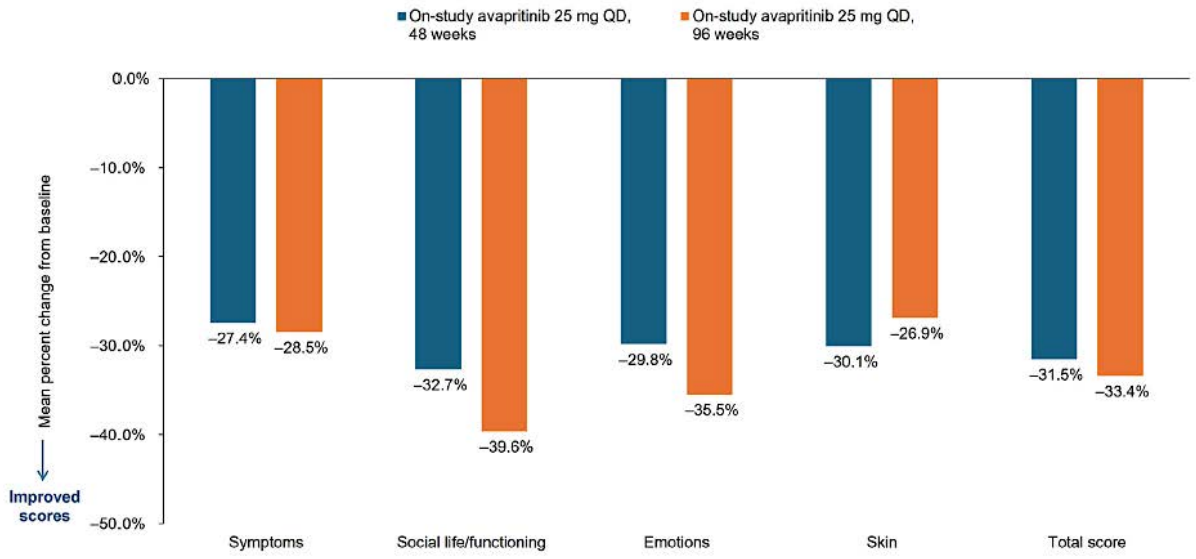
	Avapritinib	Placebo
>50% reduction in tryptase	54%	0%
>50% reduction in *KIT* D816 VAF	68%	6%
>50% reduction in BM MC's	53%	23%
>50% reduction in TSS	25%	10%

Gotlib J, et al. *NEJM Evid* 2023; 2(6)

Avapritinib Demonstrates Favorable Safety Profile in ISM and Improved QoL

TABLE I. Safety summary of patients who received avapritinib 25 mg (N = 207)*

Parameter	Randomized, placebo-controlled part 2†		OLE‡
	Avapritinib 25 mg QD (n = 141)	Placebo (n = 71)	Patients receiving avapritinib 25 mg QD (N = 207)
Median length of follow-up (mo)	5.6	5.6	24.4
Any grade TRAEs, n (%)	77 (55)	32 (45)	140 (68)
Most common TRAEs (≥5% of patients), n (%)			
Peripheral edema	9 (6)	1 (1)	22 (11)
Headache	11 (8)	7 (10)	17 (8)
Nausea	9 (6)	6 (8)	17 (8)
Periorbital edema	9 (6)	2 (3)	17 (8)
Diarrhea	4 (3)	2 (3)	12 (6)
Fatigue	6 (4)	2 (3)	11 (5)
Dizziness	4 (3)	5 (7)	7 (3)
Any grade ≥3 TRAEs, n (%)	3 (2)	2 (3)	12 (6)
Any treatment-related serious AEs, n (%)	0 (0)	0 (0)	2 (<1)
Gastric hemorrhage	–	–	1 (<1)
Peripheral edema	–	–	1 (<1)
TRAEs leading to discontinuation, n (%)§	2 (1)	1 (1)	5 (2)

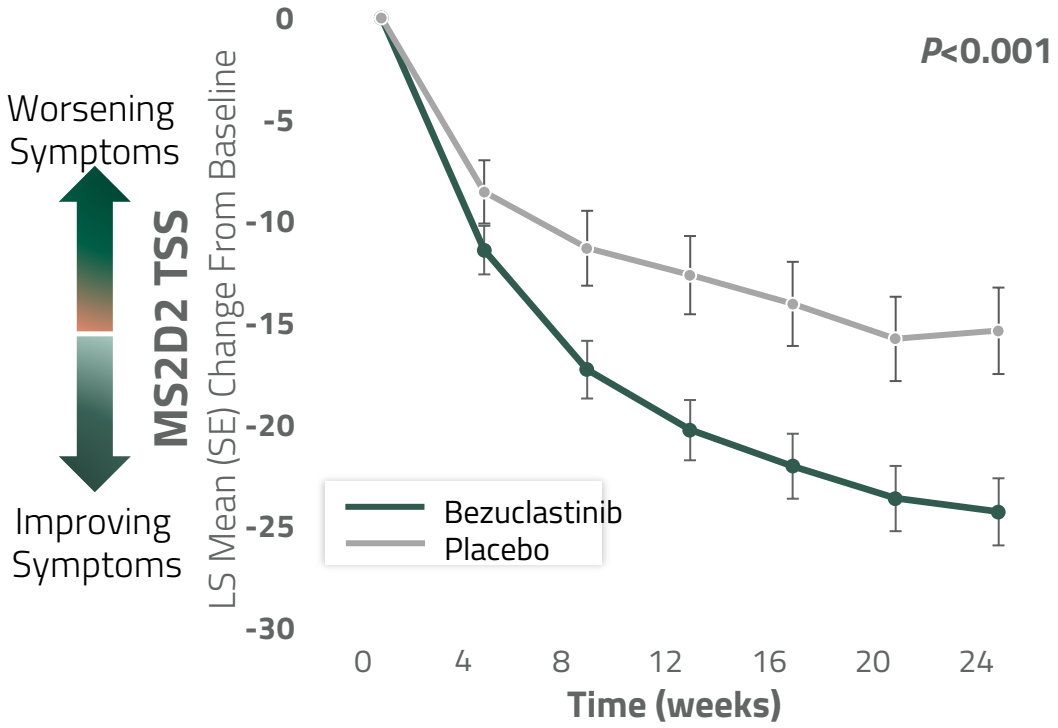


Anaphylaxis events: 2.8% vs. 4.2%

Castells M, et al. *J Allergy Clin Immunol Prac* 2025; 13(8):2194-2196. Pongdee T, et al. *World Allergy Org J* 2026; 19(4):101352

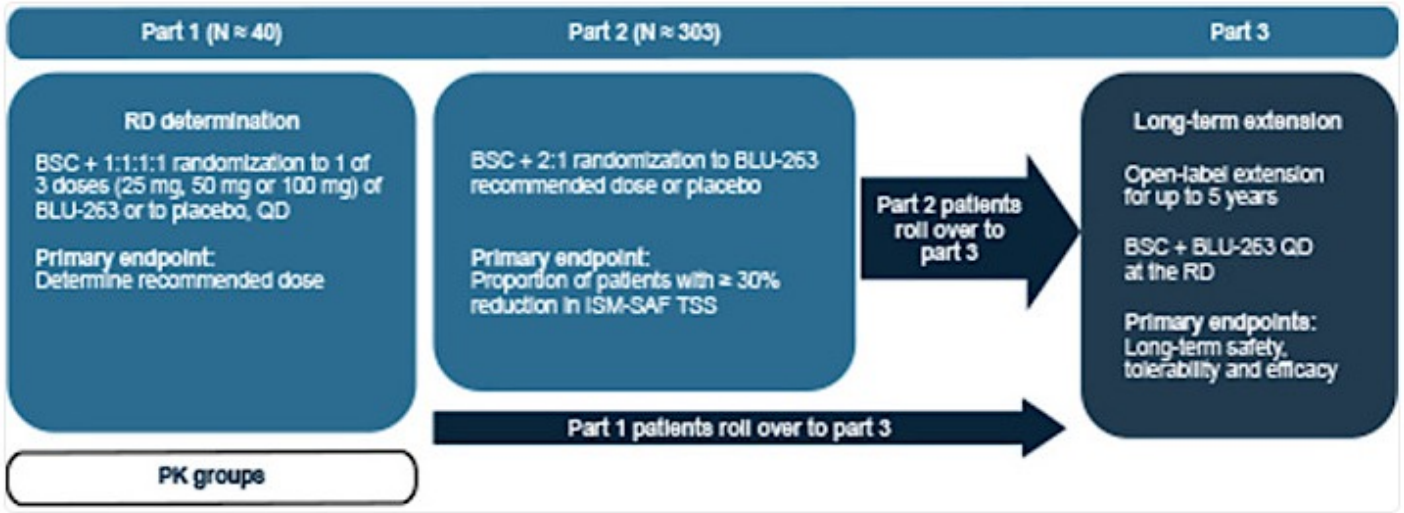
Bezuclastinib Demonstrates Efficacy in AdvSM and non-AdvSM

- SUMMIT study: Randomized phase 2, placebo-controlled study in symptomatic, non-AdvSM
- APEX study: Open-label, phase 2 study in AdvSM
  - ORR: 57%; 80% response by pure pathologic response criteria
- Potential approval late 2026, both manuscripts in development



Elenestinib, a Second-Generation KIT Inhibitor Under Investigation in SM

- HARBOR: phase 2/3 study in ISM
  - Symptom improvement across dose cohorts in Part 1 (75mg dose selected)
  - Reductions in tryptase, and *KIT* D816V VAF
- AZURE: phase ½ study in AdvSM
  - Monotherapy and in combination with azacitidine



Castells M, et al. AAAAI/WAO Joint Congress 2025; Tashi T, et al. *Blood* 2023; 142(Supplement 1): 76; DeAngelo DJ et al. *Blood* 2022 (1 Suppl):6877-6878

Summary

- Systemic mastocytosis represents a spectrum of clonal mast cell diseases with highly variable clinical course
- Improved diagnostic capabilities and increased awareness in recent years
- Given the high prevalence of *KIT*D816V mutations, KIT inhibitors have emerged to change the treatment paradigm in advanced and non-advanced SM
  - Avapritinib has demonstrated considerable efficacy
  - 2nd generation KIT inhibitors, bezuclastinib and elenestinib, are under investigation
- Still considerable room for improvement, particularly in SM-AHN patients

QUESTIONS?

Module 14: Systemic Mastocytosis and Myelofibrosis

Systemic Mastocytosis — Dr Hunter

Myelofibrosis — Dr Yacoub

Myelofibrosis: Innovations and Challenges

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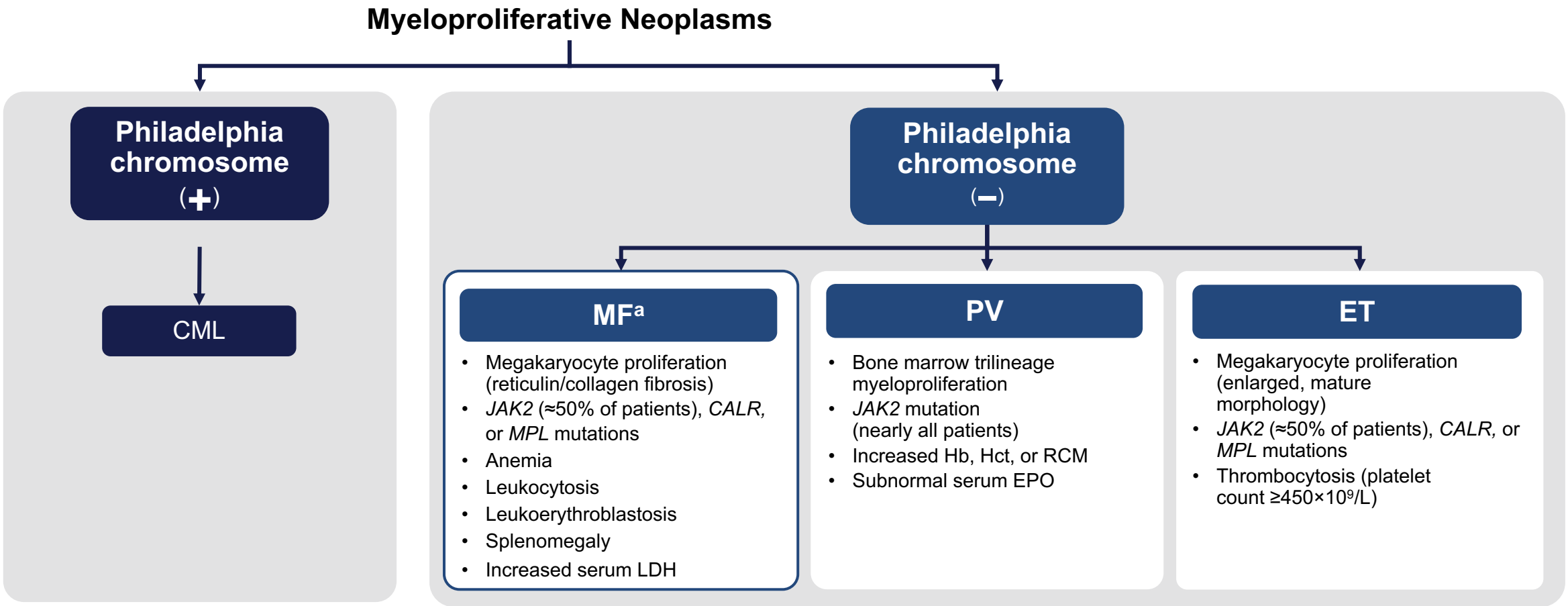
Disclosures

Consulting Agreements	Blueprint Medicines, GSK, Incyte Corporation, Karyopharm Therapeutics, Novartis, PharmaEssentia, Protagonist Therapeutics, Servier Pharmaceuticals LLC, Takeda Pharmaceuticals USA Inc
Contracted Research	CTI BioPharma, a Sobi Company, Stemline Therapeutics Inc

Introduction: Myelofibrosis (MF)



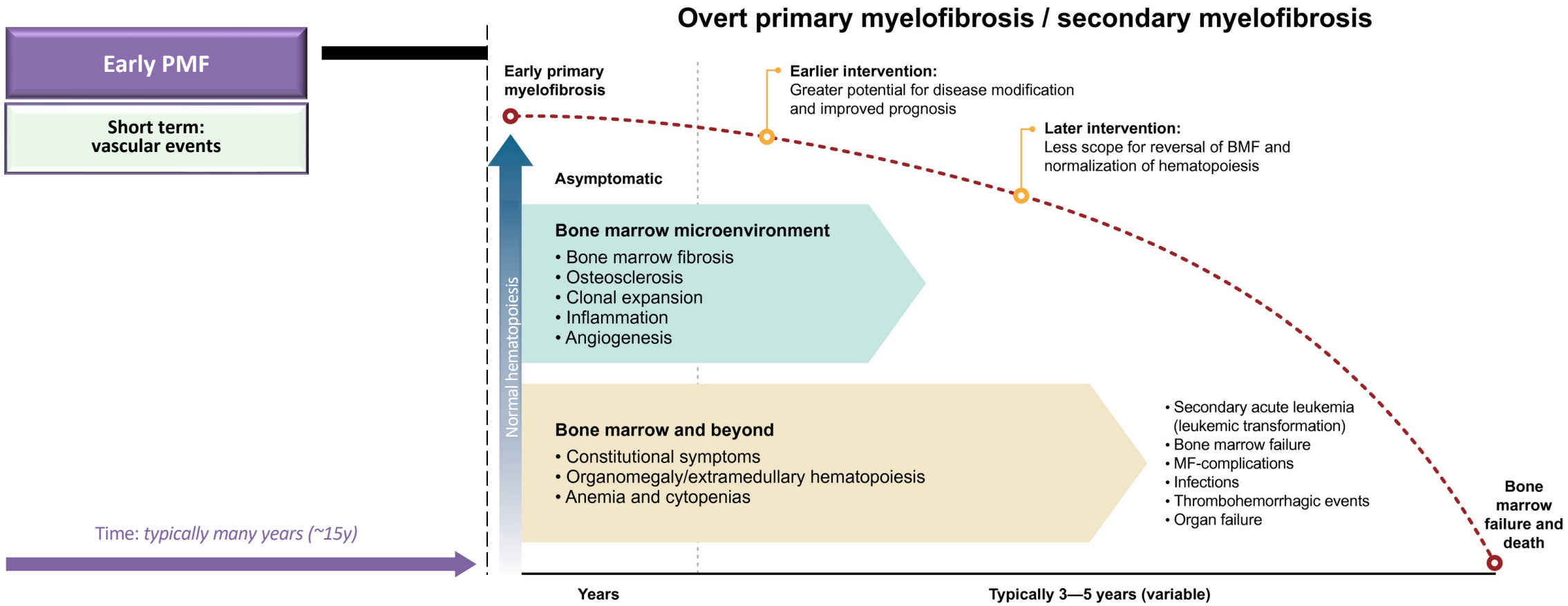
BM, bone marrow; CALR, calreticulin; CML, chronic myeloid leukemia; EPO, erythropoietin; ET, essential thrombocythemia; Hb, hemoglobin; Hct, hematocrit; JAK, Janus kinase; LDH, lactate dehydrogenase; MPL, myeloproliferative leukemia; MPN, myeloproliferative neoplasm; PV, polycythemia vera; RCM, red cell mass.

[a] MF includes primary MF, post-PV MF, and post-ET MF.

Arber DA, et al. *Blood*. 2016;127(20):2391-2405.

Early PMF

Short term:
vascular events



Mughal TI, et al. *Int J Gen Med.* 2014

Pemmaraju, et al. 2022

MF Management Goals

Reduce Splenomegaly

Improve Symptoms

Improve Survival

Management goals may evolve over time and may vary based on risk

Treatment of MF Based on Risk and Symptoms/Signs

Lower Risk
- MIPSS-70: ≤3
- MIPSS-70+ Version 2.0: ≤3
- DIPSS-Plus: ≤1
- DIPSS: ≤2
- MYSEC-PM: <14

Low Risk
Intermediate-1

- Observation, ruxolitinib (if symptomatic) or clinical trial
- Management of cytopenias
- Allogeneic HSCT (selected patients)

Projected Median OS 5 years

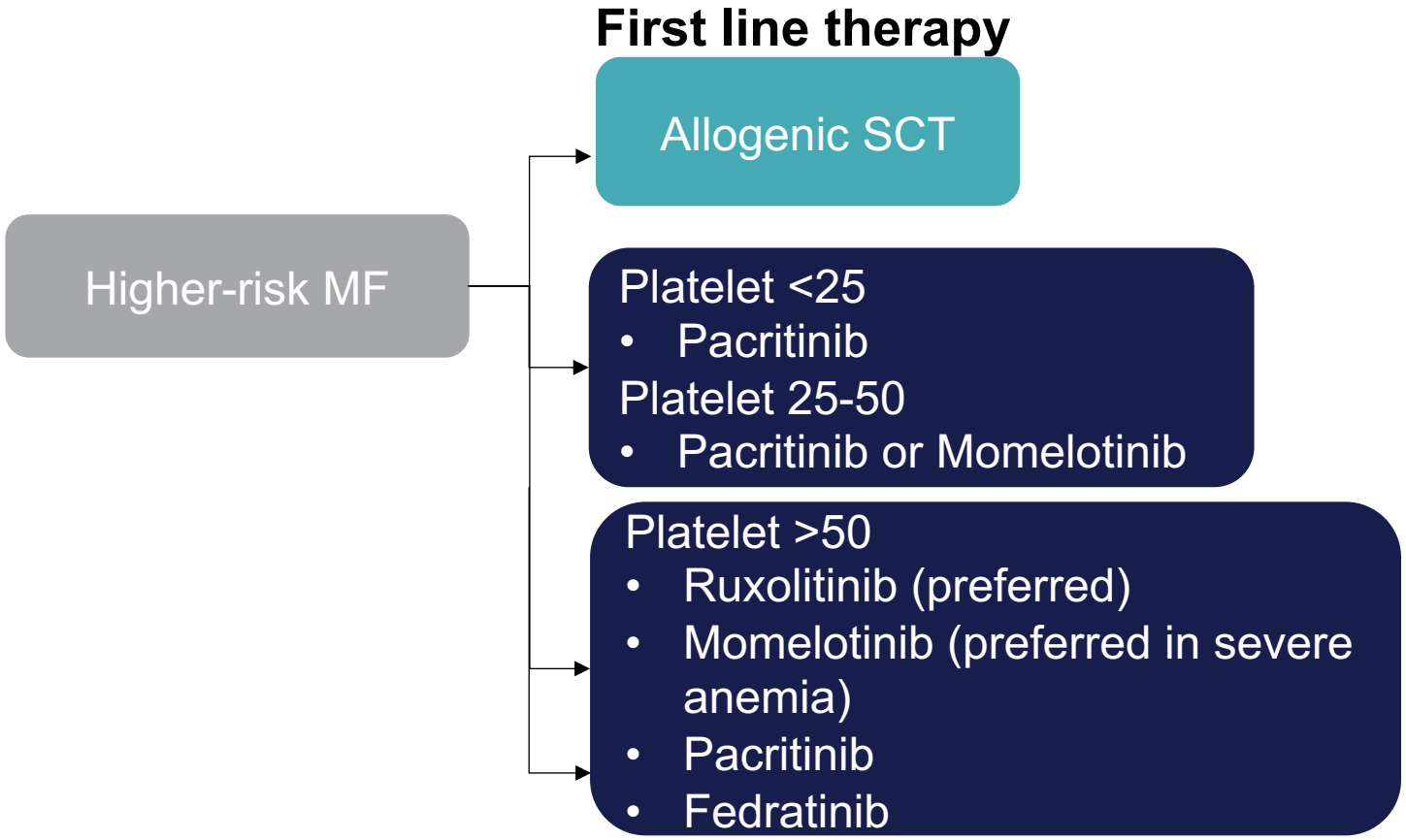
Higher Risk
- MIPSS-70: ≥4
- MIPSS-70+ Version 2.0: ≥4
- DIPSS-Plus: >1
- DIPSS: >2
- MYSEC-PM: ≥14

Intermediate-2
High Risk

- Allogeneic HSCT
- Ruxolitinib, or fedratinib, momelotinib or pacritinib (platelet <50x10^9), or clinical trial
- Anemia, thrombocytopenia (<50X10^9) clinical trial

Adapted from National Comprehensive Cancer Network (NCCN). Myeloproliferative Neoplasms (Version 1.2020), https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf.

Therapeutic Approaches for Higher-Risk MF



Beyond First line Therapy

Other JAK-I

Fedratinib
Preferred for preserved Plts and Hgb, need for rapid SVR

Pacritinib
Preferred for low Plts, Cytopenic MF

Momelotinib
Preferred for Anemia

Supportive care

- Luspatercept off label for anemia
- Danazol for Anemia
- Low dose prednisone
- HU for very proliferative disease

1. NCCN Guidelines Myeloproliferative Neoplasms. V2.2022. https://www.nccn.org/. Accessed April 28,2022.
2. Yacoub, A. MPN-MDS US Focus Meeting 2022

COMFORT-I and-II Studies: Ruxolitinib for MF

COMFORT-I[1]

- PMF or PPV-MF, or PET-MF (N=309)
- Intermediate-2 or high risk by IWG-MRT
- Palpable spleen ≥5 cm
- Platelet count ≥100 x 10^9/L
- *JAK2-V617F* positive or negative

1:1 RANDOMIZE

- Ruxolitinib 15 or 20 mg twice daily
- Placebo

COMFORT-II[2]

Patients with PMF, PPV-MF, or PET MF with ≥2 IWG risk factors (N=219)

Best available therapy (BAT) arm: patients with PD eligible for crossover to ruxolitinib

Ruxolitinib arm: patients with PD eligible for extension phase

2:1 RANDOMIZE

- Ruxolitinib 15 or 20 mg twice daily (n=146)
- Best available therapy (n=73)

1. Verstovsek S et al. *N Engl J Med*. 2012;366:799-807. **2.** Harrison C et al. *N Engl J Med.* 2012;366:787-798.

Long-Term Results With Ruxolitinib

1 SPLEEN VOLUME REDUCTION[2,3]
(SVR >35% by imaging or >50% palpation)

- 60% at any time
- 42% at 24 weeks
- Median duration of response: 3.2 years
- Dose 10 mg BID or high is more effective

- Why are these results important?
  - Reduction of spleen-related symptoms
  - Reversal of weight loss
  - Baseline splenomegaly is a surrogate of increased mortality (1.14-fold higher risk of death for each additional 5 dL)
  - Reduction in splenomegaly is proportionately associated with improved survival

2 SYMPTOM BURDEN REDUCTION[3]
(>50% reduction in TSS)

- 46% at 24 weeks

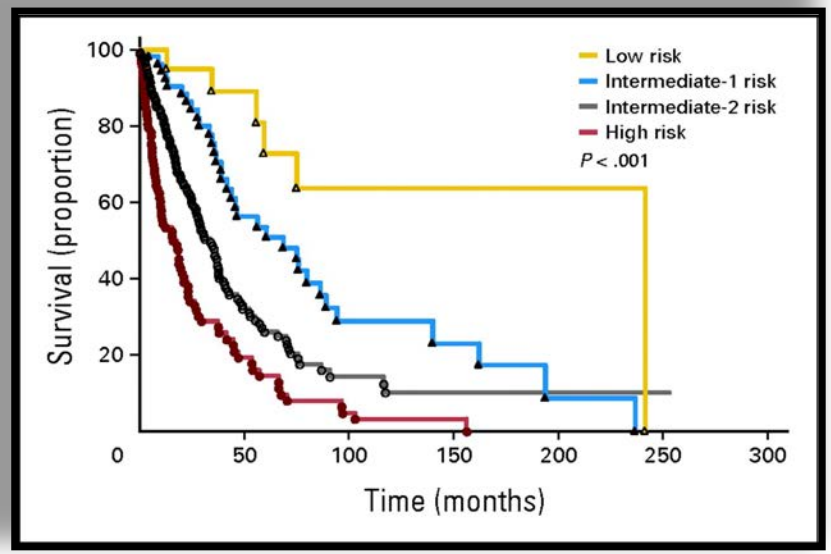
3 OVERALL SURVIVAL

. . .

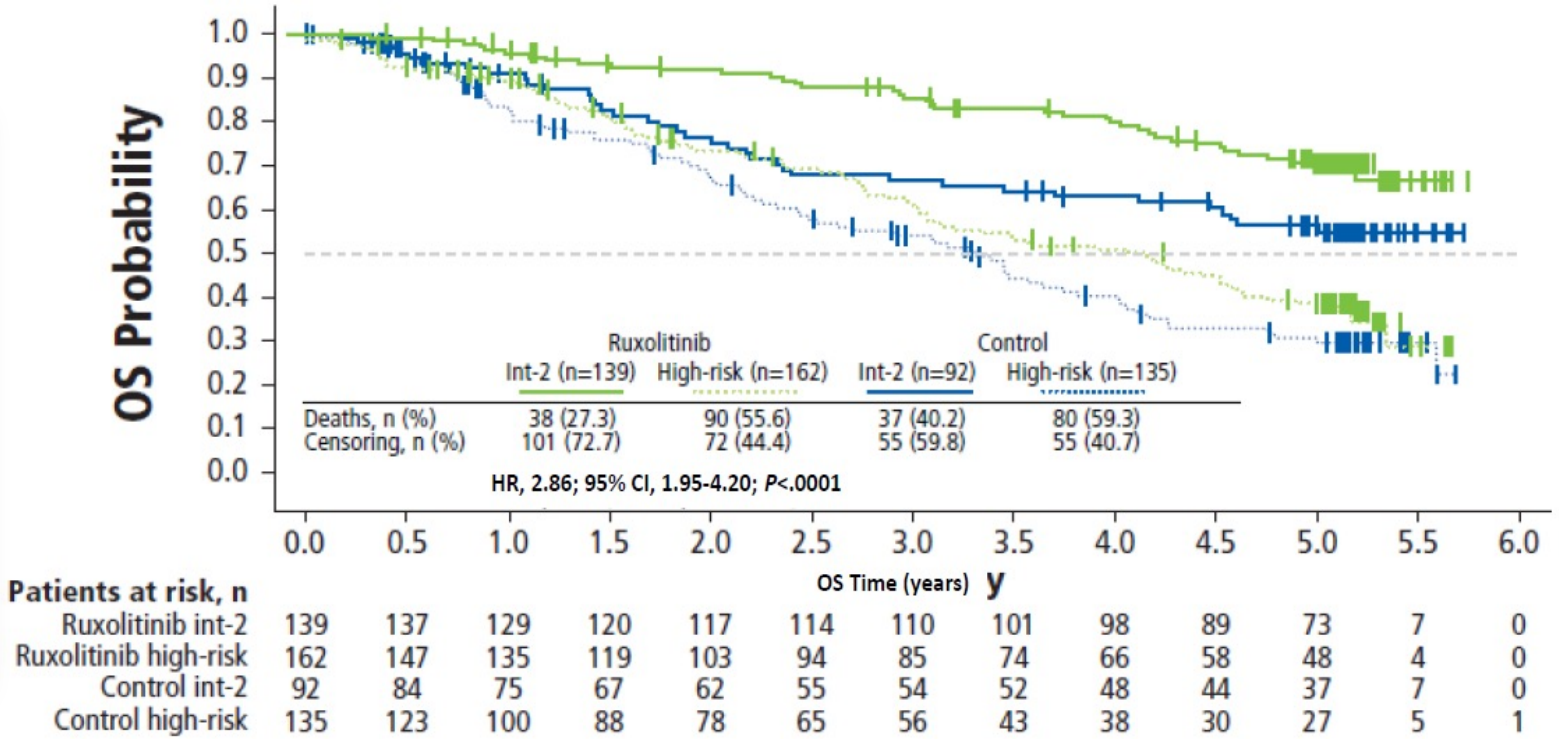
1. Yacoub, A. MPN-MDS US Focus Meeting. 2. Verstovsek S, et al. *J Hematol Oncol*. 2017;10(1):55. 3. Verstovsek S, et al. *N Engl J Med*. 2012;366(9):799-807.

Long-Term Survival in Patients Treated With Ruxolitinib for MF: COMFORT-I and –II Pooled Analyses

- Among patients randomized to ruxolitinib, patients with int-2 MF had a longer OS than those with high-risk MFa (HR high risk vs int-2: 2.86; 95% CI, 1.95-4.20; P<.0001)
- Median OS
  - Int-2: not reached (estimated 8.5 years)
  - High-risk: 4.2 years



[a] Per International Prognostic Scoring System (IPSS).
Gangat N et al. J Clin Oncol. 2011 Feb 1;29(4):392-7.



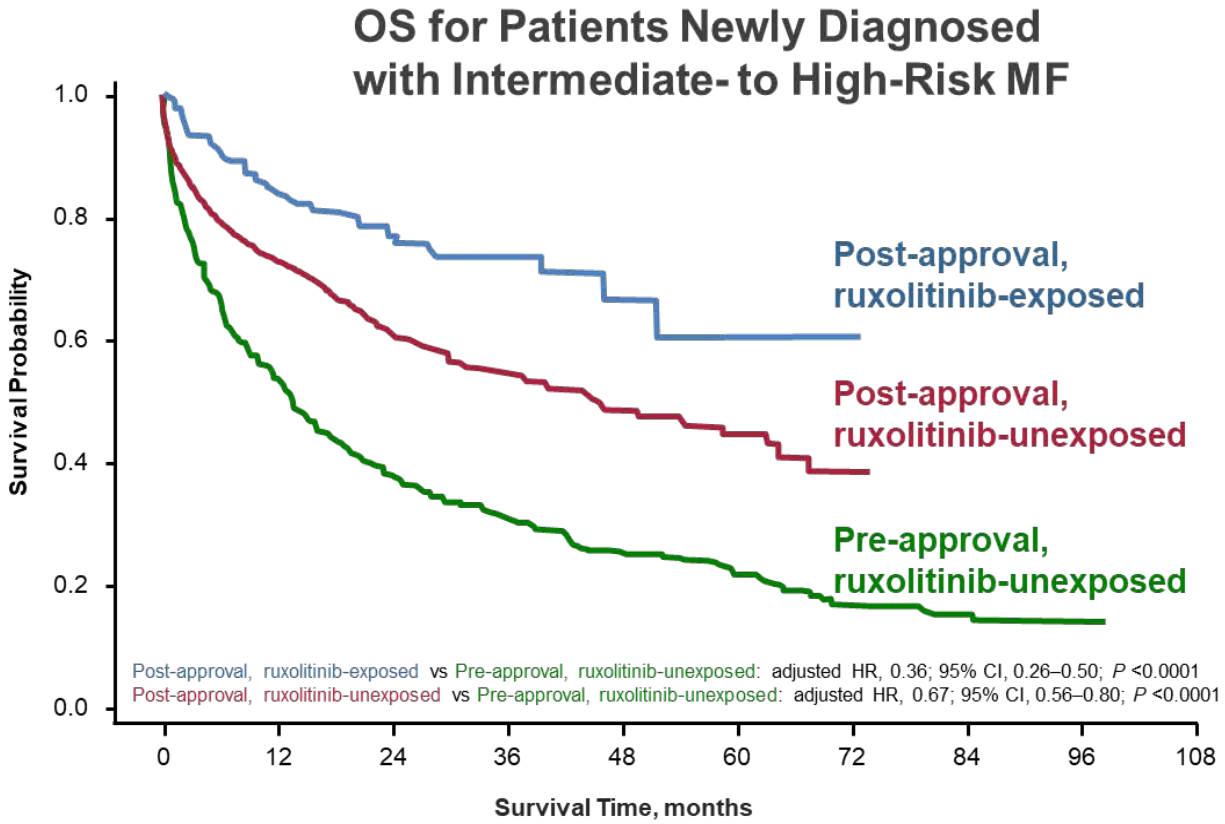
Verstovsek S, et al. *J Hematol Oncol*. 2017;10(1):156.

Real-World Survival in higher-risk MF: Impact of Ruxolitinib Approval

Mortality was lowest and OS was longest among ruxolitinib-exposed patients

	Group 1 Pre-approval Ruxolitinib-Unexposed (n=278)	Group 2 Post-approval Ruxolitinib-Unexposed (n=1127)	Group 3 Post-approval Ruxolitinib-Exposed (n=272)
Patients with valid death dates, n (%)	119 (42.8)	382 (33.9)	54 (19.9)
1-yr survival rate (95% CI), %	55.6 (49.4–61.3)	72.5 (69.5–75.2)	82.3 (76.7–86.7)

Medicare FFS Claims Database (Parts A/B/D)



Verstovsek S, et al. *Ann Hematol*. 2022.

Fedratinib in MF

- Approved in August 2019
- JAKARTA: Phase 3 study of fedratinib (400 or 500 mg/d) vs placebo in patients with int-2 or high-risk MF with splenomegaly

Endpoint Confirmed at Week 24	Fedratinib		Placebo	P value
	400 mg	500 mg		
No of patients	96	97	96	
≥35% reduction in spleen volume	36%	40%	1	< .001
No of patients	91	91	85	
≥50% reduction in the TSS	36%	34%	7%	≤ .001

- Recommended dose: 400 mg once a day
- The most common AEs: anemia, gastrointestinal symptoms
- Boxed warning: encephalopathy, can be fatal

Pardanani A, et al. *JAMA Oncol*. 2015;1:643-651.

Pacritinib Development

PERSIST-1: Pacritinib versus Best Available Therapy (BAT) to treat myelofibrosis

Key Eligibility Criteria

- PMF, PET-MF, or PPV-MF
- Intermediate- or high-risk disease
- Palpable spleen ≥5 cm
- No exclusion for baseline platelet levels; stratified for platelet counts <100,000/μL and <50,000/μL
- No exclusion for baseline Hgb levels
- No prior treatment with JAK2 inhibitors

[a] Cross-over from BAT allowed after progression or after Week 24 assessment

PERSIST-2 Study Design

Key Eligibility Criteria

- Primary or secondary MF
- Platelet count ≤100 × 10^9/L
- Prior JAK2 inhibitor therapy allowed

Randomization

- 1:1:1 pacritinib vs pacritinib vs BAT
- N=311 (221 completed 24 weeks on study)

- Pacritinib 400 mg QD
- Pacritinib 200 mg BID
- BAT (including ruxolitinib)

Coprimary Endpoints[a]

- ≥35% SVR at week 24
- ≥50% TSS reduction at week 24

FDA announces full clinical hold Feb 8, 2016
Interim survival results, bleeding and CV events
FDA removes hold Jan 5, 2017

SVR_{35}[a]: pacritinib, 18%; BAT, 3% (including RUX) (*P* = .001); TSS reduced ≥50%[a]: pacritinib, 25%; BAT, 14% (*P* = .08)

PERSIST-2: Baseline Characteristics and BAT Received

Key Baseline Characteristics in ITT-Efficacy Population[1,2]	PAC 200 mg BID (n = 74)	BAT (n = 72)
Median age, years ≥65 years, %	67 62	69 71
Male, %	65	54
MF diagnosis: PMF, PPV-MF, PET-MF, %	74, 19, 7	60, 22, 18
DIPSS score[a]: Int-1, Int-2, High, %	19, 51, 30	18, 51, 31
Median spleen length, cm[a]	15	13
JAK2^{V617F} positive, %	80	71
JAK2^{V617F} allele burden, median	30	25
Platelet count <50 × 10^9/L, %	42	44
Hemoglobin <10 g/dL, %	59	57
RBC transfusion dependence[b]: dependent, independent, indeterminate, %	19, 50, 30	19, 51, 29
Prior JAK1/2 inhibitors, % Prior ruxolitinib	45 42	47 46

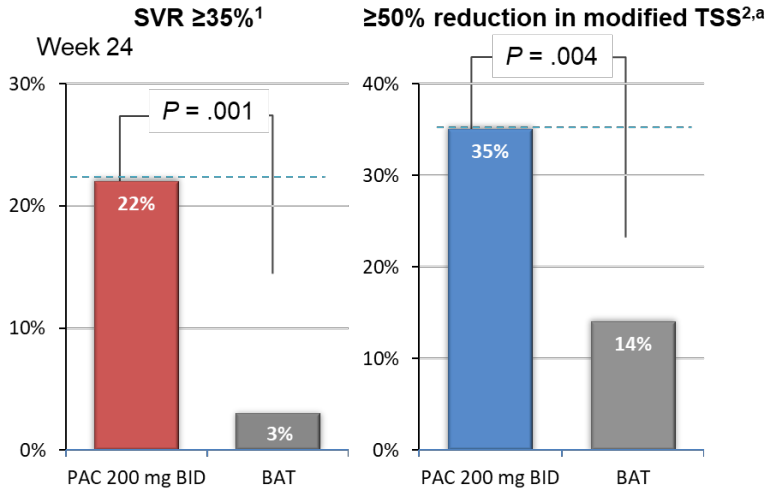
- Of the BAT patients who received ruxolitinib, 93% began treatment at ≤10 mg BID, including 64% at ≤5 mg BID[3]

BAT Received in >2 Patients, %[1]	BAT (n = 98)
Ruxolitinib[c]	45
Hydroxyurea	19
Watch-and-wait only	19
Prednisone/prednisolone	13
Danazol	5
Thalidomide	3

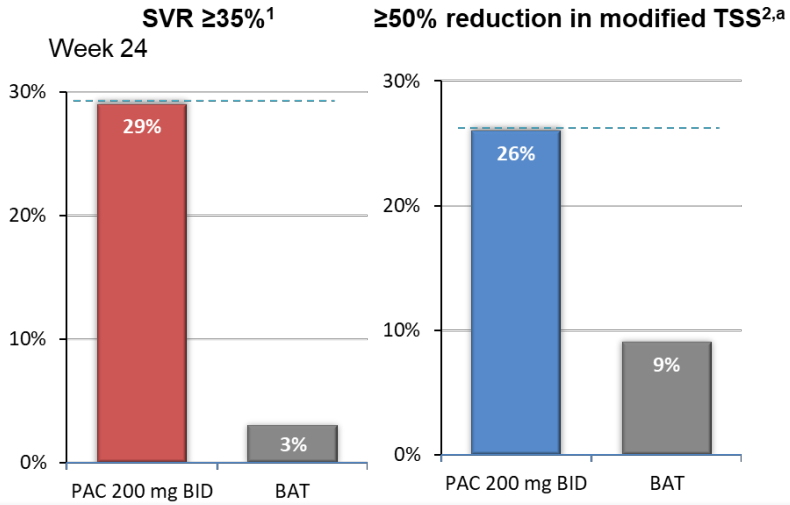
Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652-659

PERSIST-2: highlights

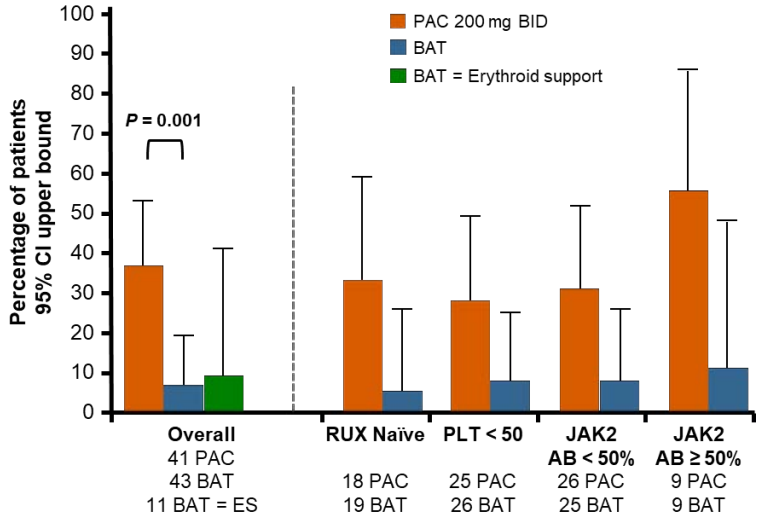
ITT population



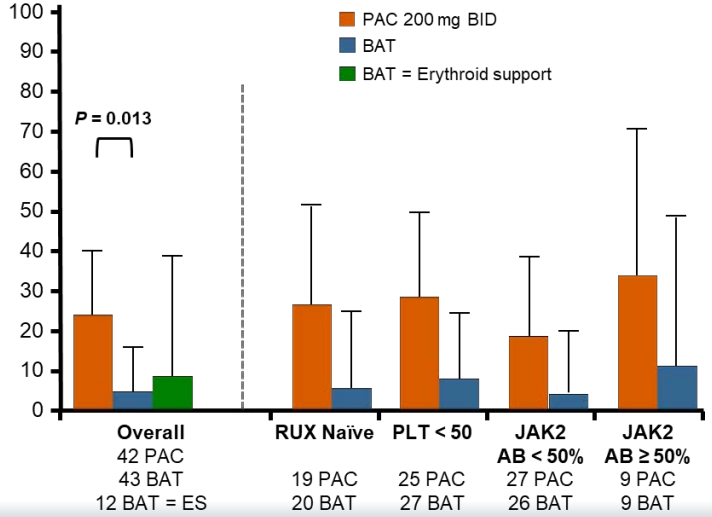
Patients with platelets <50 × 10⁹/L



Rate of TI (Gale Criteria)



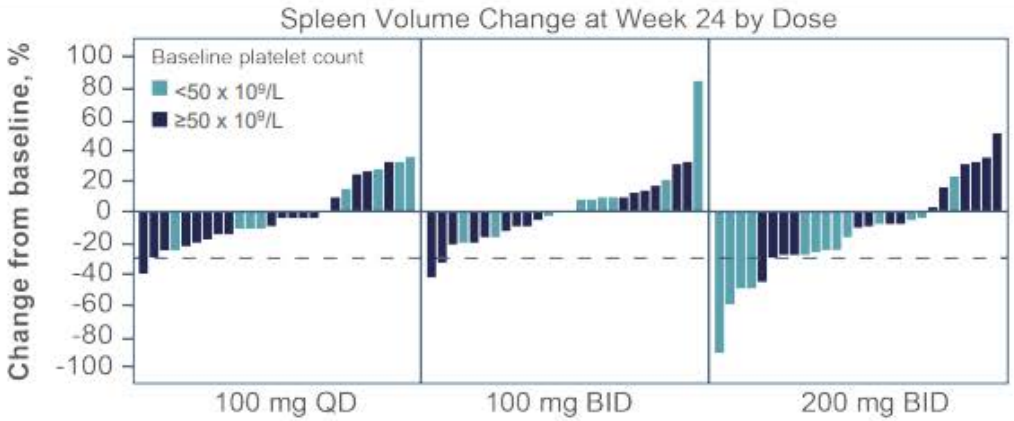
Rate of TI (SIMPLIFY Criteria)

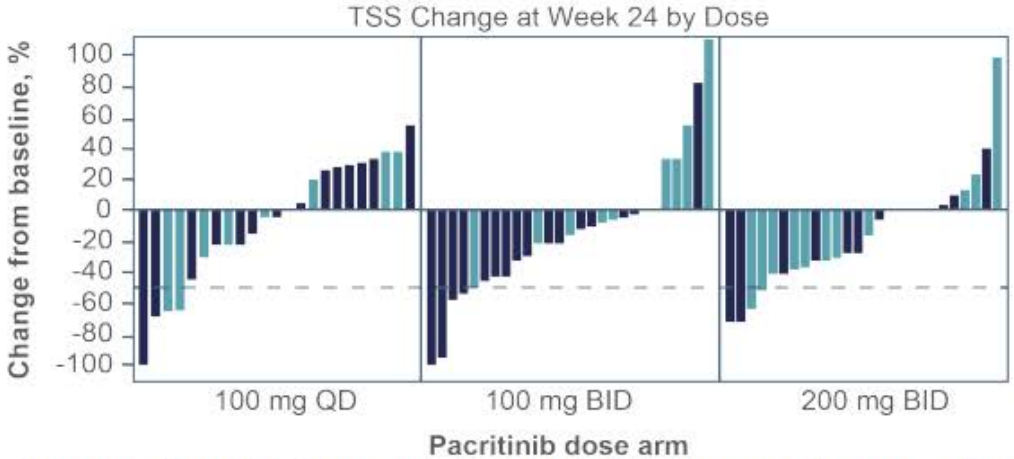


Mascarenhas J, et al. *JAMA Oncol.* 2018;4:652-659

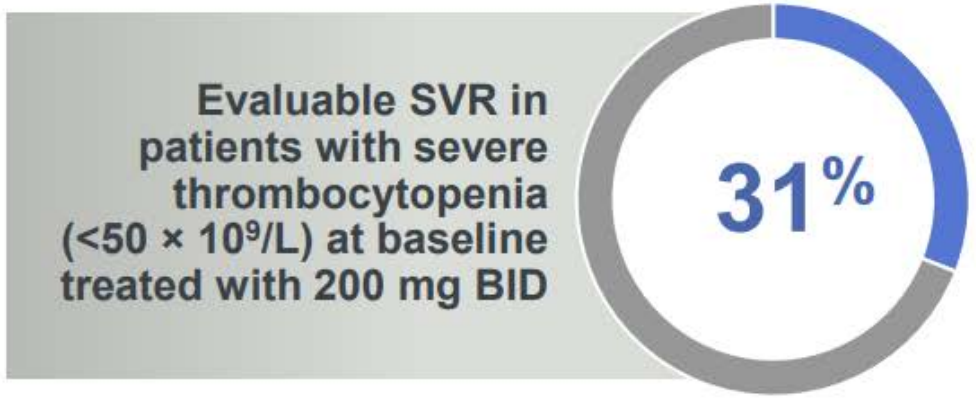
Oh ST. Blood Adv. 2023;7:5835-5842.

PAC203: Greatest efficacy of Pacritinib at 200 mg BID in Advanced Myelofibrosis

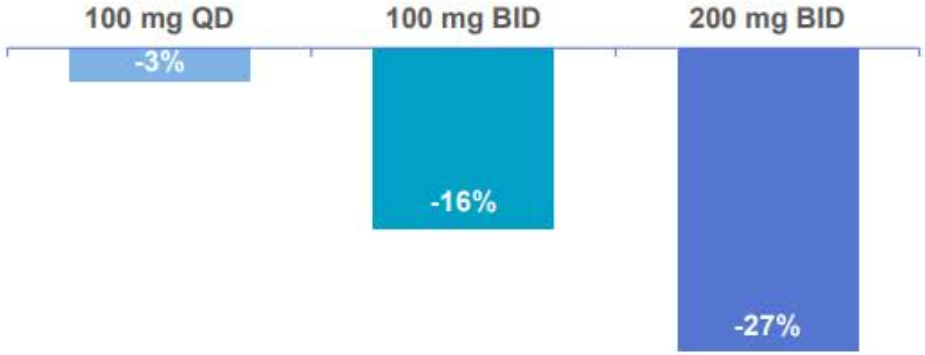




Note: One patient with 302% increase from baseline TSS score represented by truncated bar to fit to scale (far right bar in 100 mg BID).



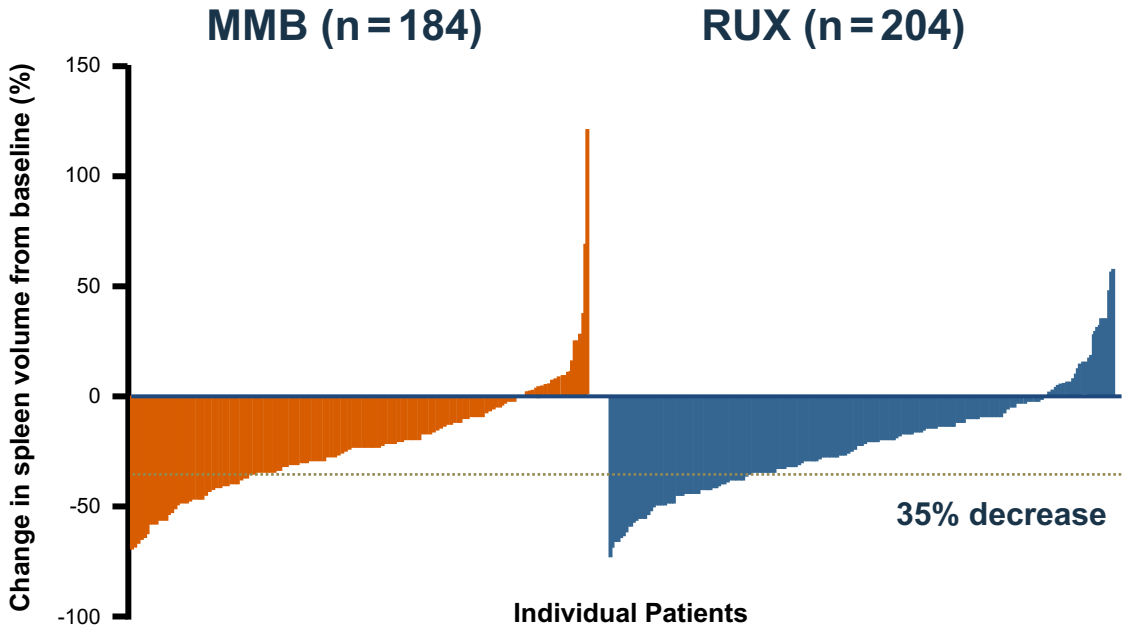
TSS analyzed as a continuous variable:
Deeper reductions with 200 mg BID



- The 200 mg BID arm had the highest rates of SVR ≥ 35% (200 mg BID: 9.3%; 100 mg BID: 1.8%; 100 mg QD: 0.0%) and TSS ≥ 50% (200 mg BID: 7.4%; 100 mg BID: 5.5%; 100 mg QD: 5.8%).[1]
- Pharmacokinetic and pharmacodynamic data support testing pacritinib 200 mg BID in the pivotal randomized PACIFICA phase 3 trial.[1]
- Pacritinib demonstrated clinical benefit and was well tolerated in advanced myelofibrosis patients, including those with severe thrombocytopenia.[1]

1. Gerds et al., *Blood Adv*, 2020; 2. Gerds et al., ASH 2019 #667; NCT03165734

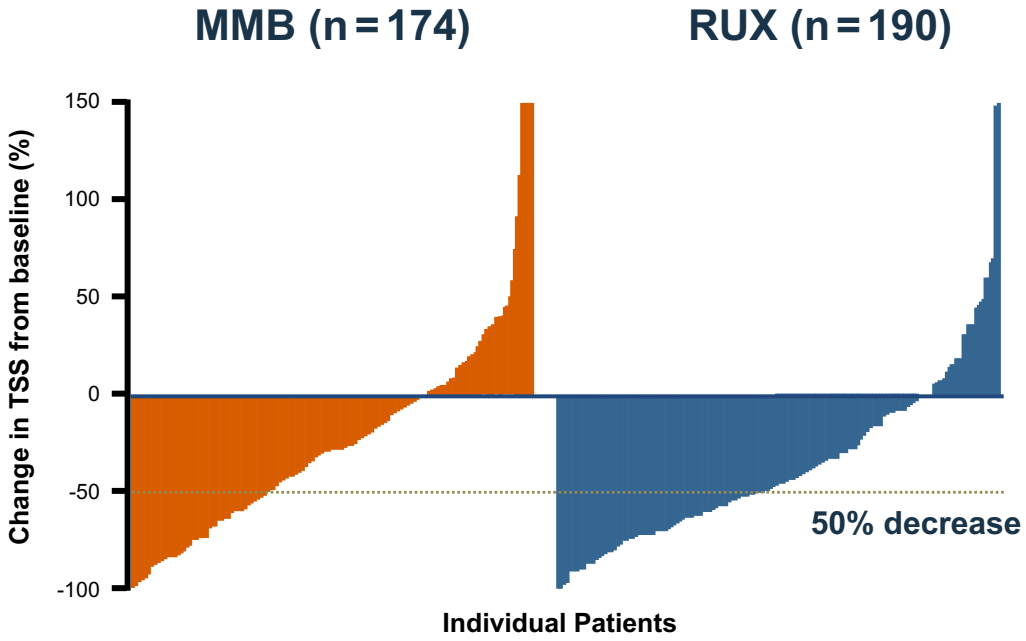
SIMPLIFY-1: Momelotinib First Line



SRR

26.5% (57 of 215) 29.0% (63 of 217)

Proportion difference of 0.09 (95% CI, 0.02 to 0.16) *P* = 0.011



TSS response rate

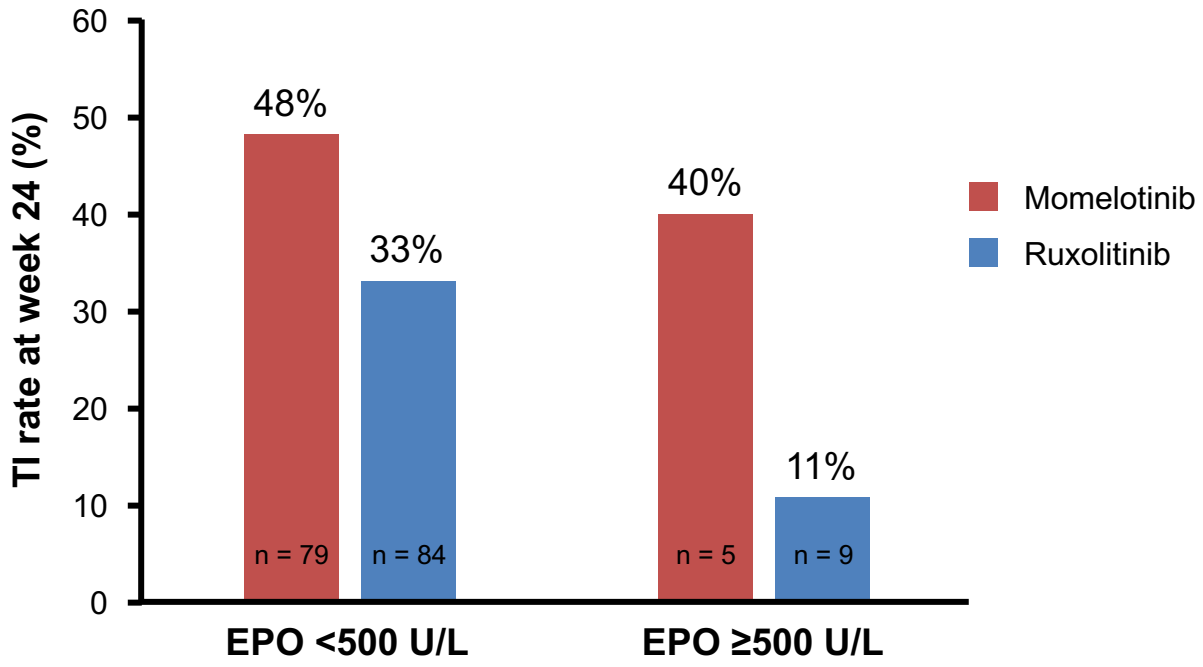
28.4% (60 of 211) 42.2% (89 of 211)

Noninferiority proportion difference of 0.09 (95% CI, -0.08 to 0.08) *P* = 0.98

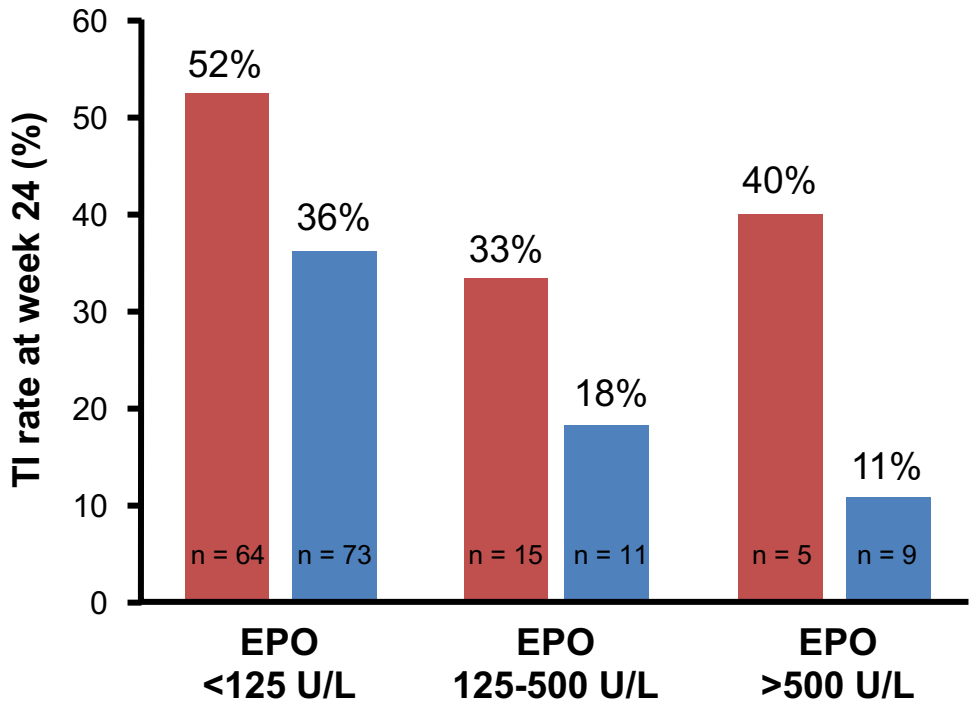
Momelotinib was noninferior for spleen reduction but NOT noninferior for symptom improvement

Mesa RA. *J Clin Oncol.* 2017;35:3844-3850.

SIMPLIFY-1: Patients With Hb ≤10 g/dL Achieving TI Stratified by EPO Level



	EPO ≤500 U/L	EPO ≥500 U/L
OR (95% CI) for momelotinib vs ruxolitinib	**2.34** (1.19-4.61)	**6.30** (0.40-99.84)



	EPO <125 U/L	EPO 125-500 U/L	EPO >500 U/L
OR (95% CI) for momelotinib vs ruxolitinib	**2.31** (1.12-4.76)	**3.35** (0.49-23.09)	**6.25** (0.39-99.15)

Oh ST, et al. ASH 2025

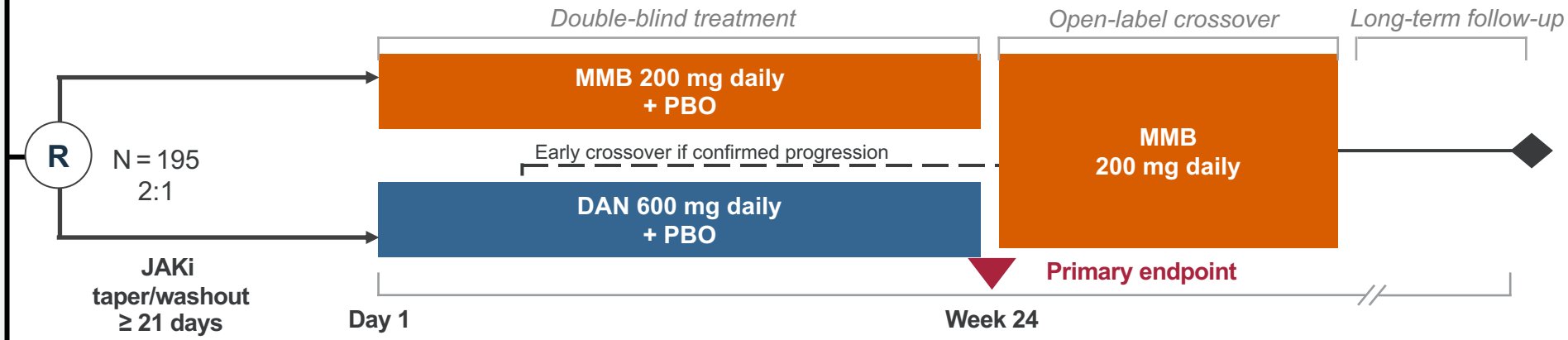
MOMENTUM: Momelotinib vs Danazol in Symptomatic, Anemic, JAKi-Experienced Patients

Previously treated with JAKi

- Symptomatic (TSS ≥ 10)
- Anemic (Hgb < 10 g/dL)
- Platelets ≥ 25 x 10^9/L

Stratification

- TSS
- Palpable spleen length
- Transfused units in prior 8 weeks
- Study site

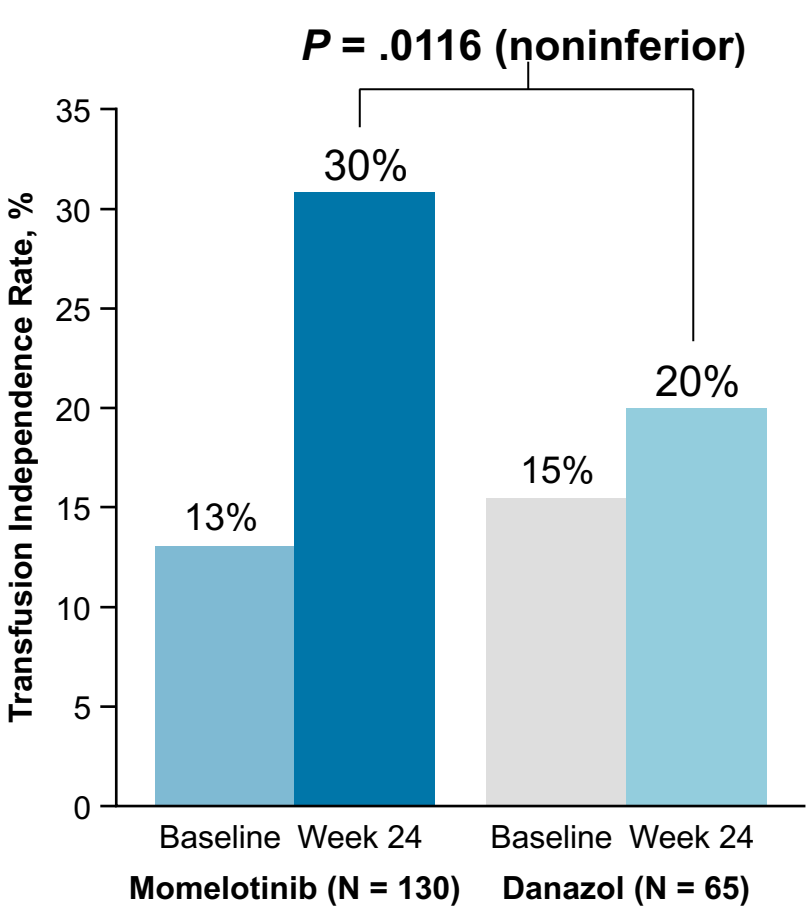


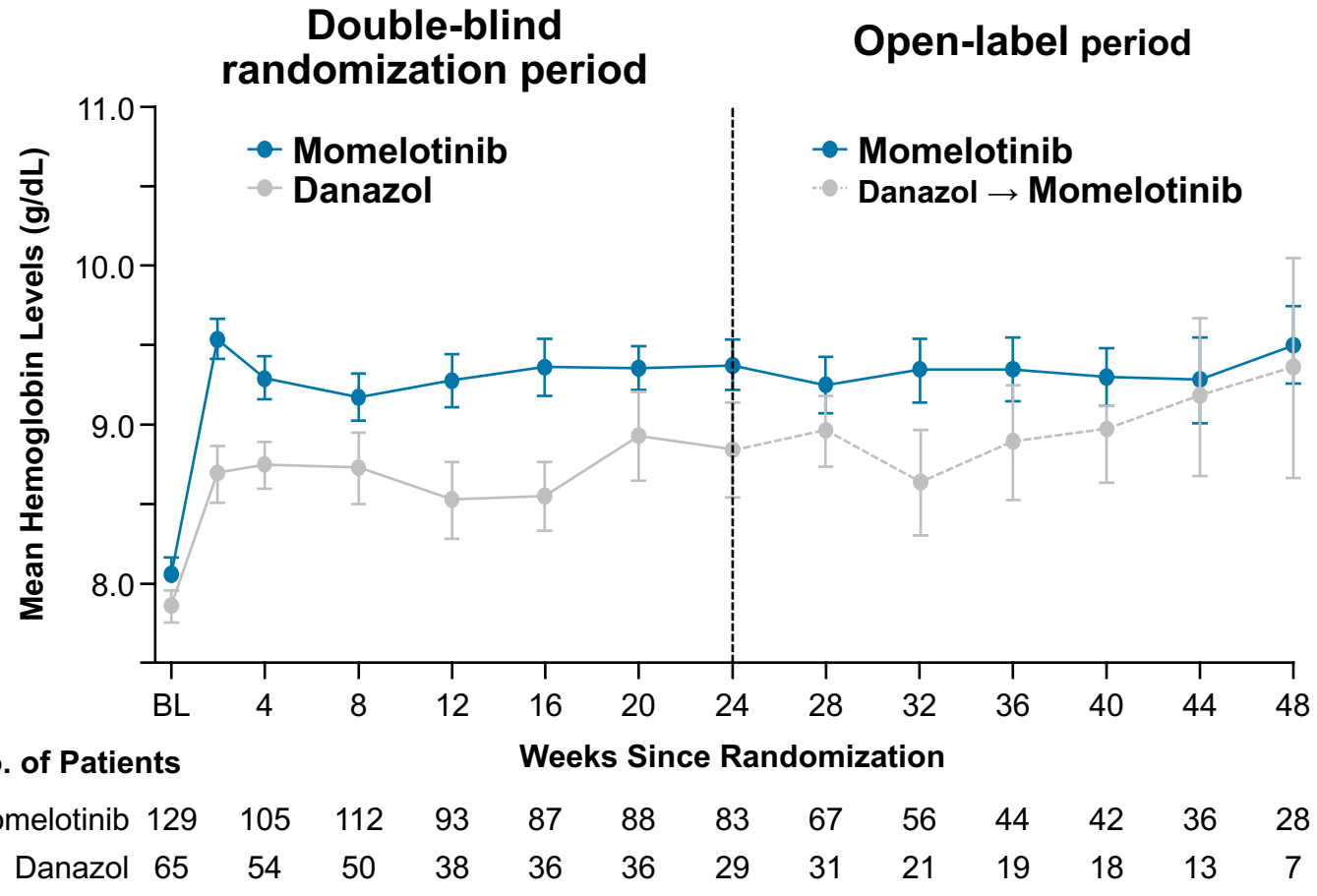
Summary of Primary and Key Secondary Efficacy Endpoint Analyses at Week 24

Endpoints	Test order	Criterion for significance	Momelotinib group (n = 130)	Danazol group (n = 65)	*P* value
TSS response rate	1	Superiority (P ≤ 0.05)	32 (25%)	6 (9%)	Two-sided 0.0095 (superior)
Transfusion independence rate	2	Noninferiority	39 (30%)	13 (20%)	One-sided 0.0116 (non-inferior)
Splenic response rate (≥ 25% reduction)	3	Superiority (P ≤ 0.05)	51 (39%)	4 (6%)	Two-sided < 0.0001 (superior)
Absolute TSS change from baseline	4	Superiority (P ≤ 0.05)	-11.5	-3.9	Two-sided 0.0014 (superior)
Splenic response rate (≥ 35% reduction)	5	Superiority (P ≤ 0.05)	29 (22%)	2 (3%)	Two-sided 0.0011 (superior)
Rate of zero transfusions to week 24	6	Superiority (P ≤ 0.05)	46 (35%)	11 (17%)	Two-sided 0.0012 (superior)

Verstovsek S. *Lancet*. 2023;401:269-280.

Momelotinib vs Danazol: MOMENTUM – Transfusion Independence at Week 24, Mean Hemoglobin Over Time





Verstovsek S, et al. EHA 2022. Abstract S195; Mesa R, et al. ASCO 2022. Abstract 7002; Verstovsek S, et al. Lancet 2023;401(10373):269-80.

JAKi	Ruxolitinib	Fedratinib	Pacritinib	Momelotinib
Approval	2011	2019	2022	2023
Targets	JAK1, JAK2	JAK2, JAK1, FLT3, TYK2,	JAK2, IRAK1, FLT3, ACVR1	JAK1, JAK2, ACVR1
Indication	Intermediate1, Intermediate2, high-risk MF platelets ≥50k	Intermediate-2 high-risk MF platelets ≥50k	Intermediate high-risk MF platelets <50k	MF patients with anemia Plt >25
Dose	10 BID 15 BID 20 BID	400 daily	200 BID	200 once daily
Risk of withdrawal	high	low	low	possible
Clinical practice points	Hematologic toxicities	Hematologic GI toxicities Monitor and replace thiamine	Less cytopenia High GI toxicities Monitor QTc Monitor for bleeding	Less cytopenia-inducing Rare peripheral neuropathy

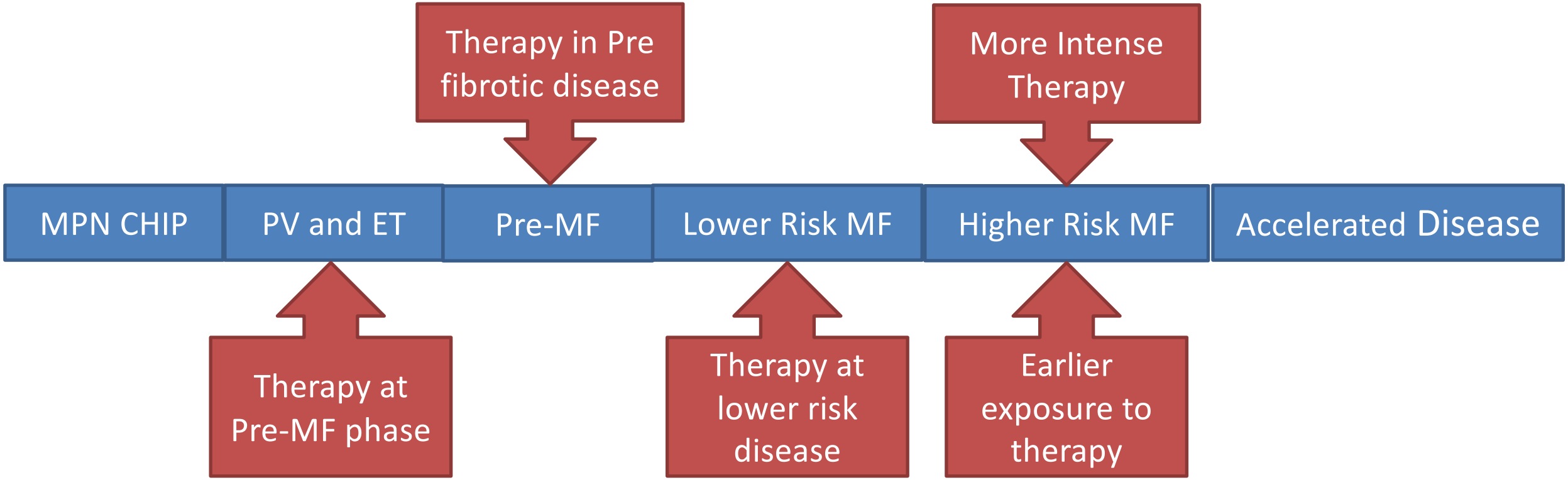
Earlier Intervention, New Paradigm

Therapeutic clinical trials in myelofibrosis (MF) have predominantly focused on higher-risk disease:

- Patients at higher risk of morbidity and mortality due to their diseases.
- May accept a higher risk/benefit ratio
- Intervention may be more impactful
- Study endpoints target regularly measurable disease parameters including:
  - Splenic volume reduction
  - Symptom burden reduction
  - PFS and OS
  - Disease / response surrogates: Fibrosis, driver mutation VAF reduction

Author's Opinion

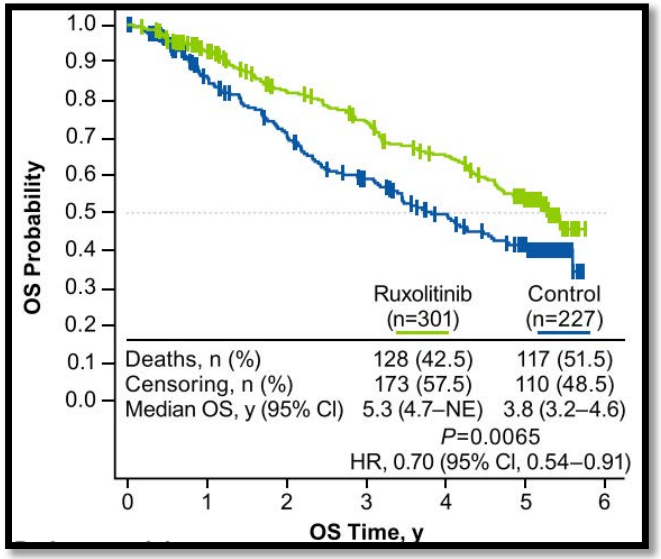
Opportunities for Early Intervention



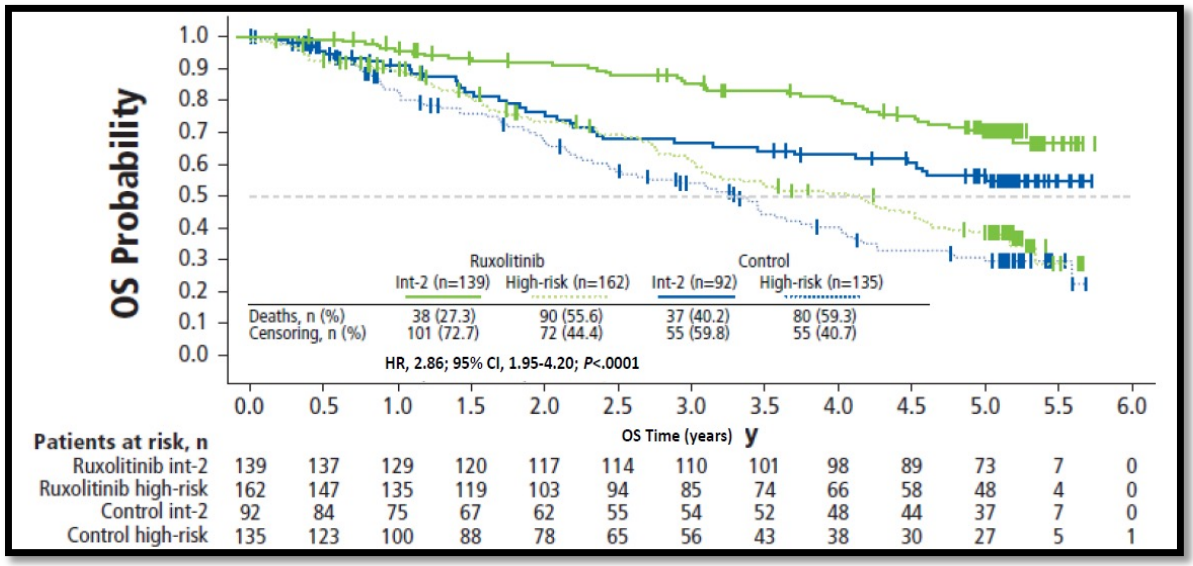
Yacoub. SOHO 2022
Yacoub, et al. CLML 2024

Early Intervention: COMFORT Studies

- **Patients randomized to Ruxolitinib, Median OS difference was 1.5 years (5.3 vs. 3.8m HR 0.7, *P*=0.0065), despite cross over at median of around 9 months.**

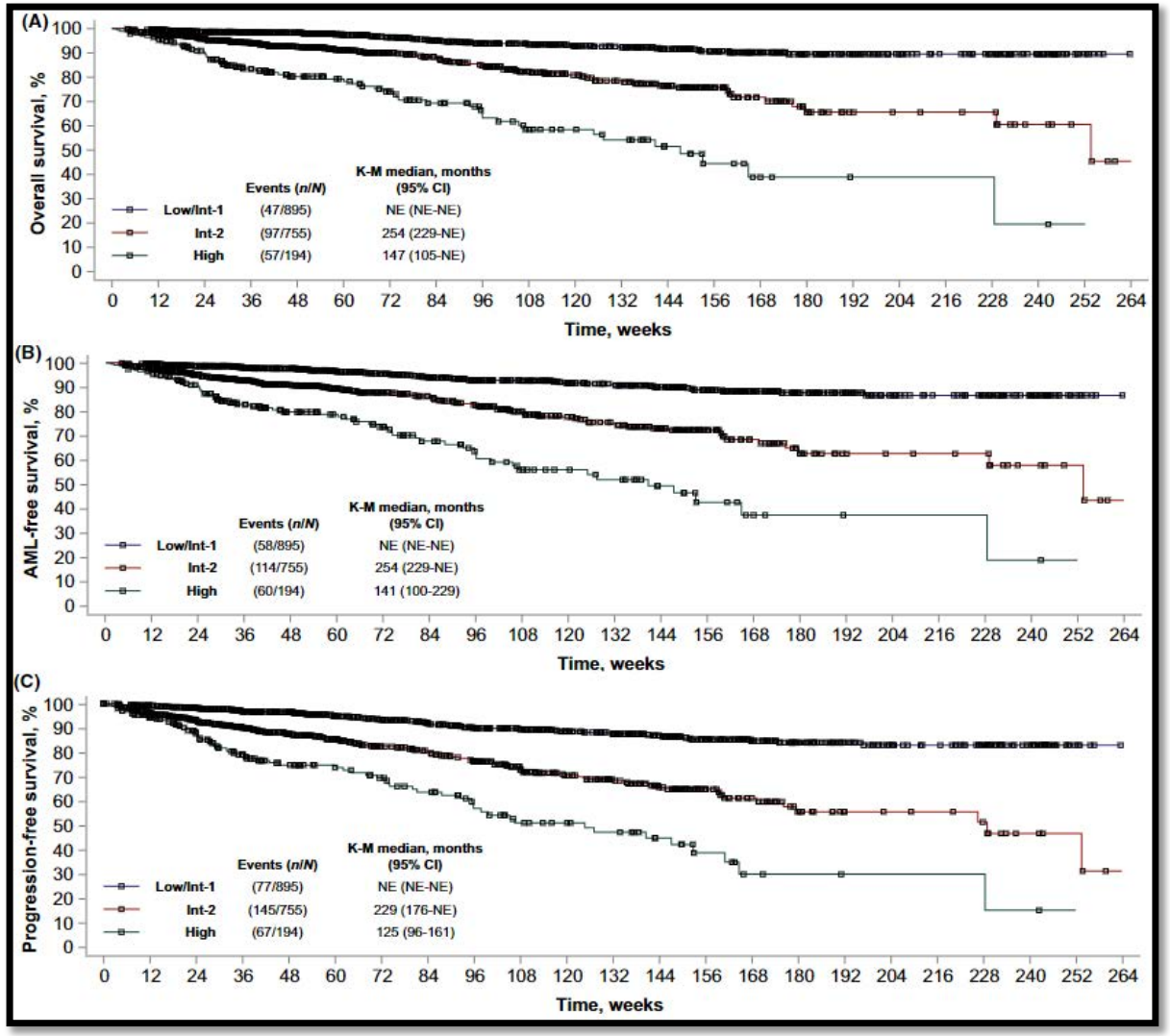


- **Among patients randomized to ruxolitinib, patients with int-2 MF had a longer OS than those with high-risk MFa (HR high risk vs int-2: 2.86; 95% CI, 1.95-4.20; P<.0001)**
- **Median OS**
  - Int-2: not reached (estimated 8.5 years)
  - High-risk: 4.2 years



Verstovsek S, et al. *J Hematol Oncol*. 2017.

Early Intervention: JUMP Study

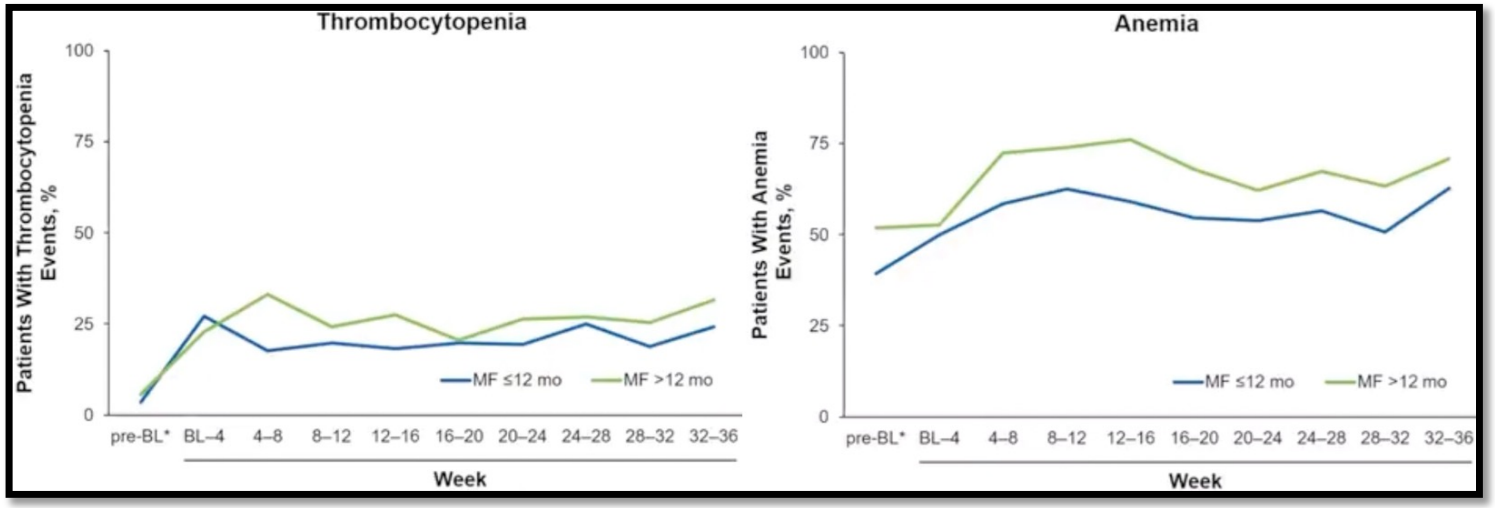


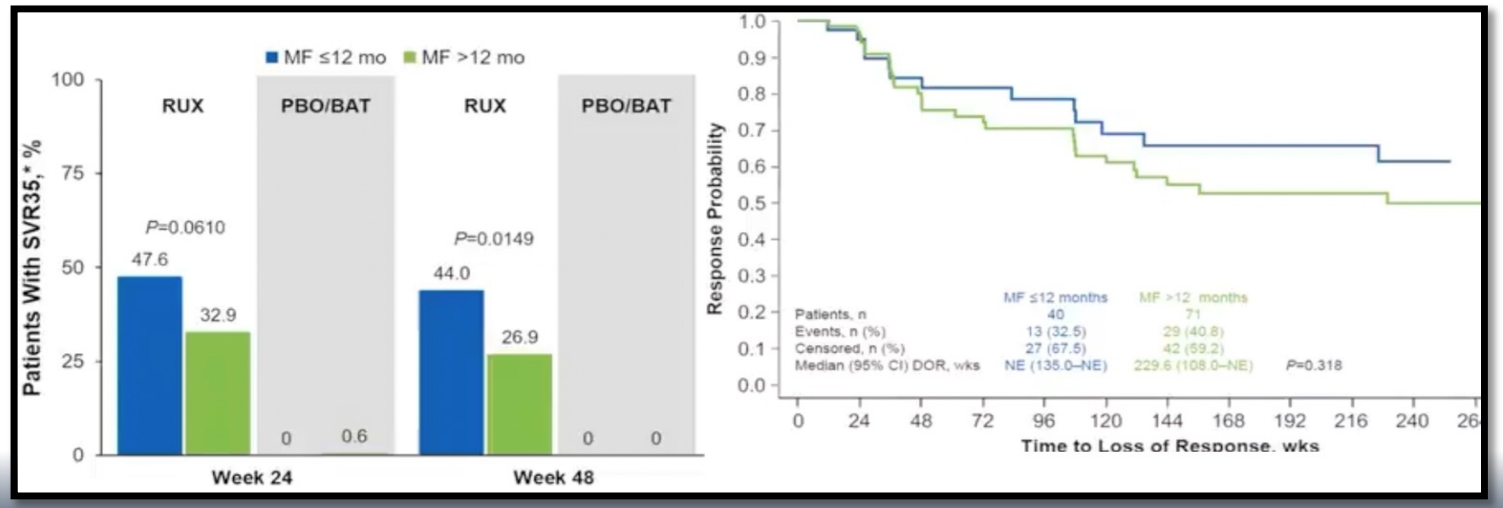
Al-Ali HK, et al. Br J Haematol. 2020

Early Intervention: Since diagnosis

Subgroup analysis of patients enrolled on COMFORT studies:

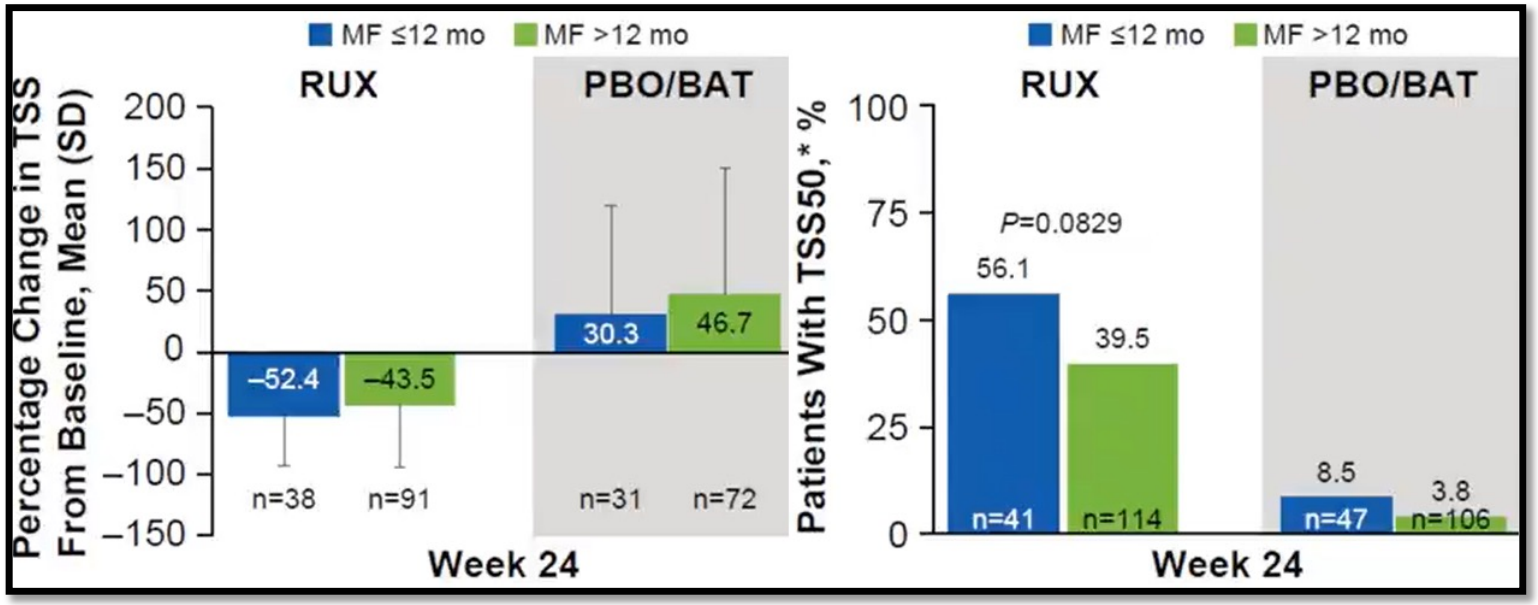
Ruxolitinib therapy since diagnosis: ≤ 12 month vs. > 12 month



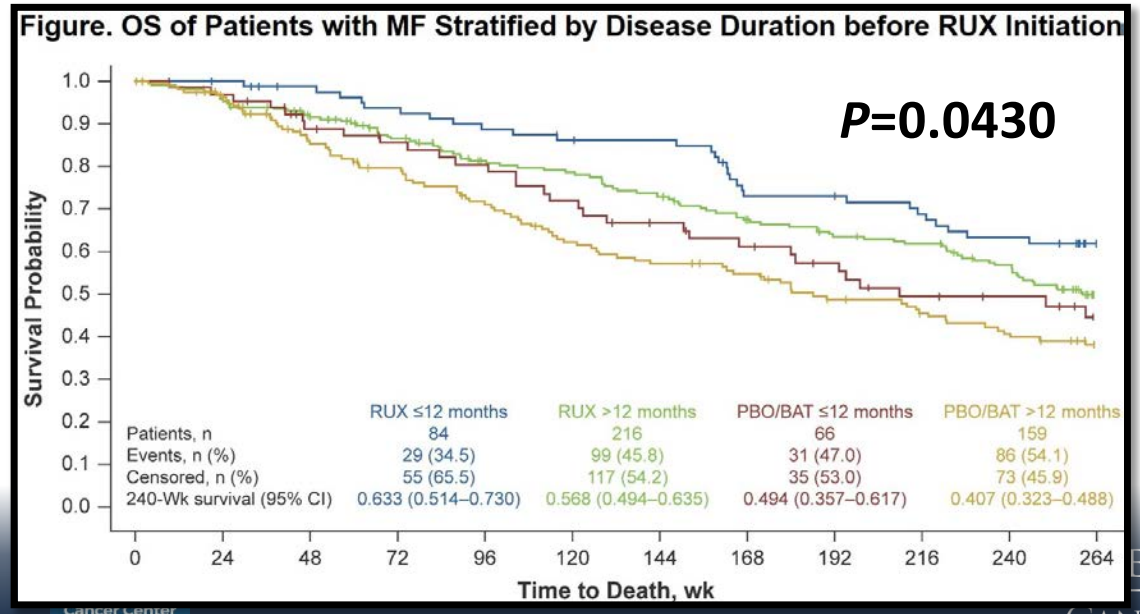


Verstovsek S et al. Cancer. 2023

Early Intervention: Since diagnosis



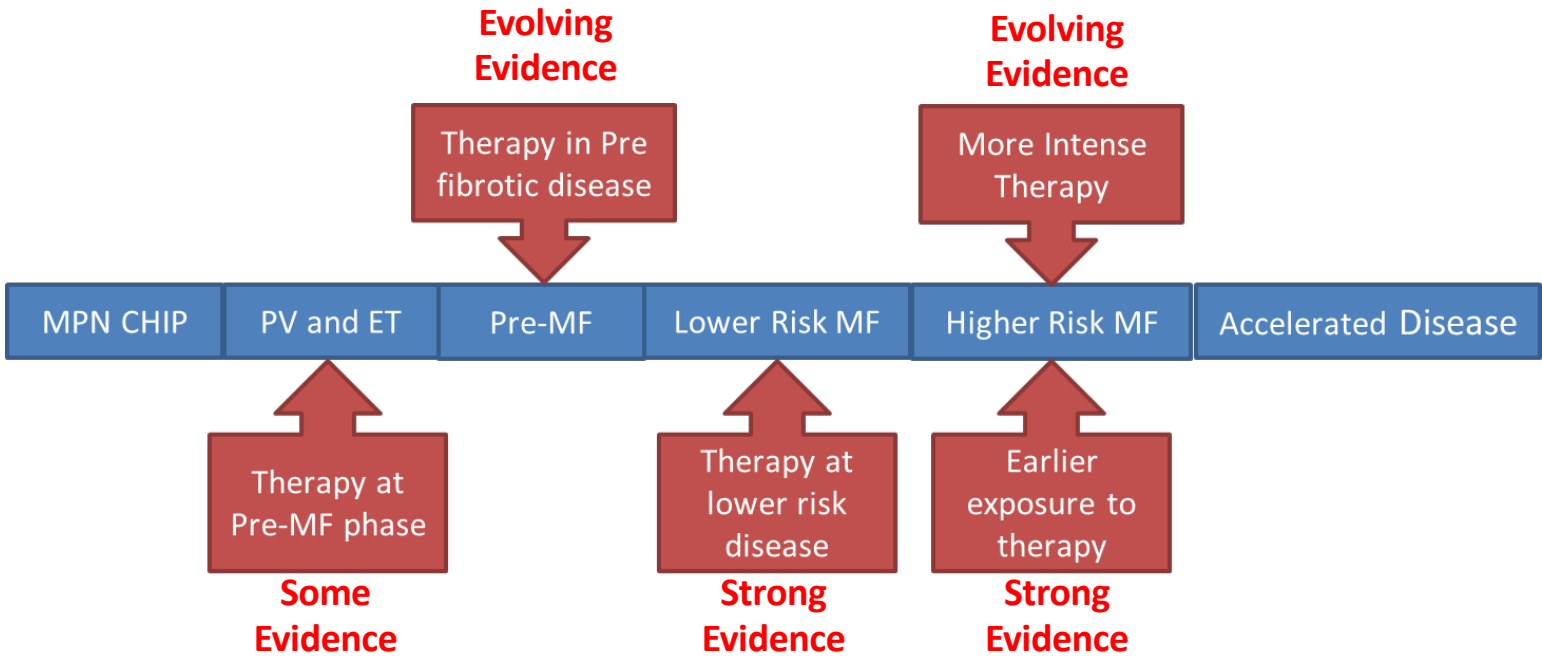
Factor	OR (95% CI)
Disease duration (≤12 vs >12 mo)	2.075 (1.117–3.898)* (*P*=0.022).
Study (COMFORT I vs COMFORT II)	1.547 (0.898–2.684)
Age	1.019 (0.987–1.053)
Sex (male vs female)	0.354 (0.195–0.631)
Risk (high vs intermediate)	0.477 (0.247–0.904)
Baseline hemoglobin level	1.015 (1.000–1.030)
Baseline platelet count	1.002 (1.001–1.004)
Baseline white blood cell count	1.005 (0.988–1.022)
Baseline spleen volume	1.000 (1.000–1.000)
MF subtype	
Post–PV vs primary MF	0.982 (0.509–1.871)
Post–ET vs primary MF	0.847 (0.390–1.806)



Verstovsek S et al. Cancer. 2023

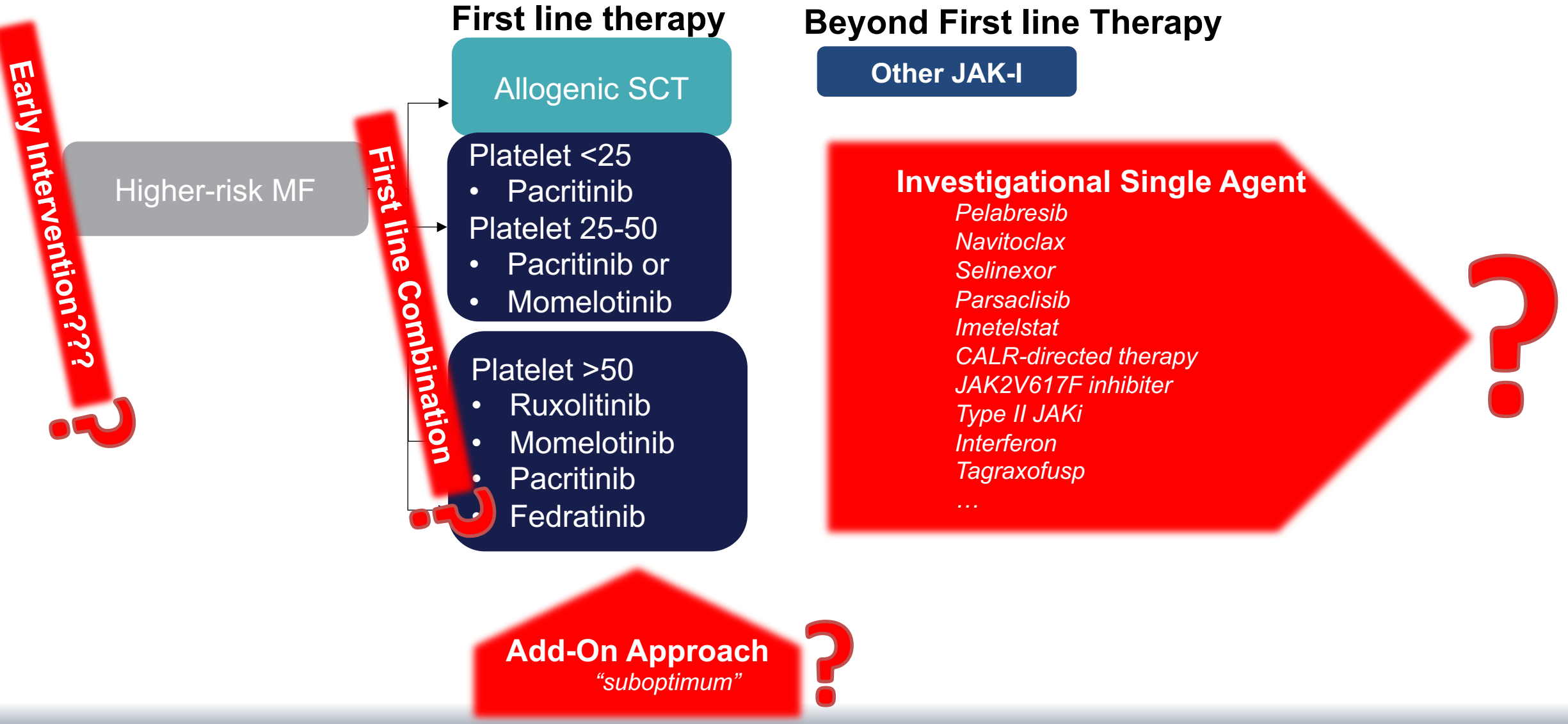
Level of Evidence of Early Intervention

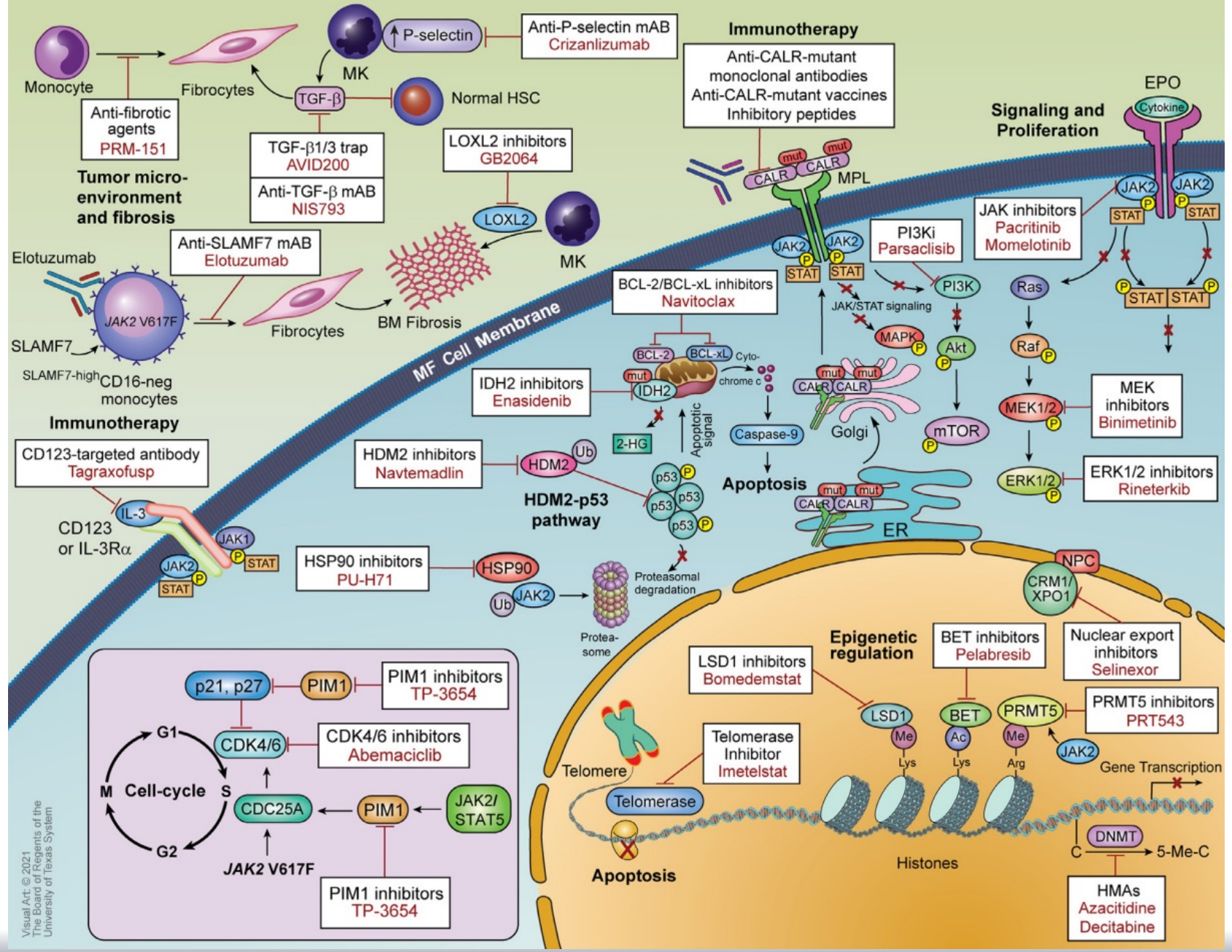
- Early intervention is recognized as a new frontier in managing MF
- Challenges continue to exist in identifying the target patients, appropriate disease stage, methods of intervention, and definitions of endpoints and outcomes.



Author's Opinion

Investigational Approaches for Higher-Risk MF





~~Ruxolitinib with Parsaclisib (PI3K δ i)~~
~~Ruxolitinib with Navitoclax (BCL-X_L i)~~
Ruxolitinib with Pelabresib (BET i)
Ruxolitinib and Luspatercept

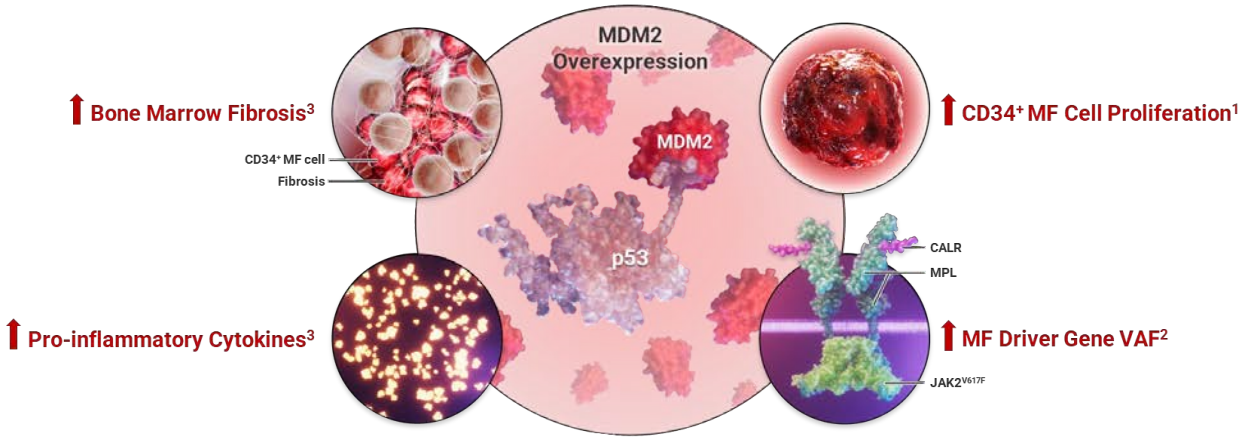
Ruxolitinib and Selinexor
Ruxolitinib and KRT-232
Imetelstat

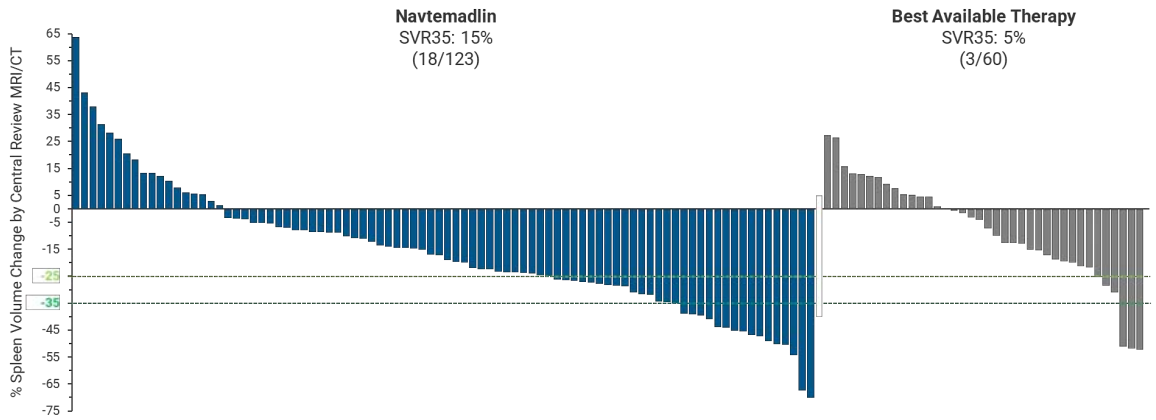
Ruxolitinib and CALRi

Momelotinib and Luspatercept
Pacritinib and Tagraxofusp
Elritercept With Ruxolitinib
Nuvisertib with Momelotinib

Chifotides HT et al. *Clin Lymphoma Myeloma Leuk.* 2022;22(4):210-223.

A Phase 3 Randomized, Double-blind, Add-on Study Evaluating the Safety and Efficacy of Navtemadlin and Ruxolitinib in JAK Inhibitor-naïve Patients With Myelofibrosis Who Have a Suboptimal Response to Ruxolitinib Treatment





Enrollment

MF Patients Who are JAK Inhibitor-naïve

Run-in Period

Rux Monotherapy
≥ 18 weeks of treatment on a stable Rux dose[1]

Assessment

Suboptimal Response

Spleen or TSS Responders *or* Refractory Non-responders

End-of-Study

Randomized

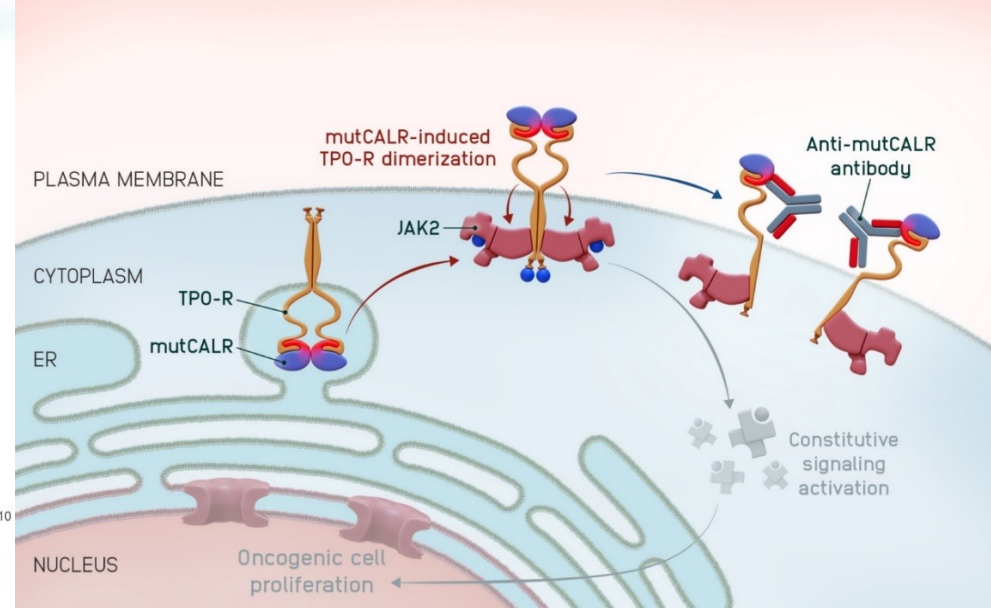
Add-on Period (Blinded)

Arm 1 — **Navtemadlin + Ruxolitinib**

Arm 2 — **Placebo + Ruxolitinib**

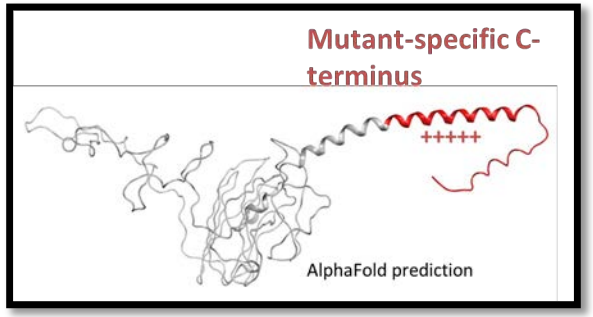
Safety and Efficacy of the Mutant Calreticulin–Specific Monoclonal Antibody INCA033989 as Monotherapy or in Combination With Ruxolitinib in Patients With Myelofibrosis: Preliminary Results From Dose Escalation of Two Global Phase 1 Studies

John Mascarenhas,[1] Haifa Kathrin Al-Ali,[2] Vikas Gupta,[3] Haris Ali,[4] Francesca Palandri,[5] Francesco Passamonti,[6] Raajit Rampal,[7] Aaron Gerds,[8] Tania Jain,[9] Sanjay Mohan,[10] Steffen Koschmieder,[11] Caroline McNamara,[12] Andrew Perkins,[13] Bethan Psaila,[14] Vincent Ribrag,[15] William Shomali,[16] Rosa Ayala Diaz,[17] Mikkel Helleberg Dorff,[18] Claire Harrison,[19] Stephen Oh,[20] Frank Stegelmann,[21] Alessandro Maria Vannucchi,[22] Abdulraheem Yacoub,[23] Jason Gotlib,[16] Jyoti Nangalia,[24] Chenwei Tian,[25] Betty Lamothe,[25] Erin Crowgey,[25] Tatiana Zinger,[25] Evan Braunstein,[25] David M. Ross[26]



- Fully human IgG1
- Fc-silent
- Selective binding to mutCALR

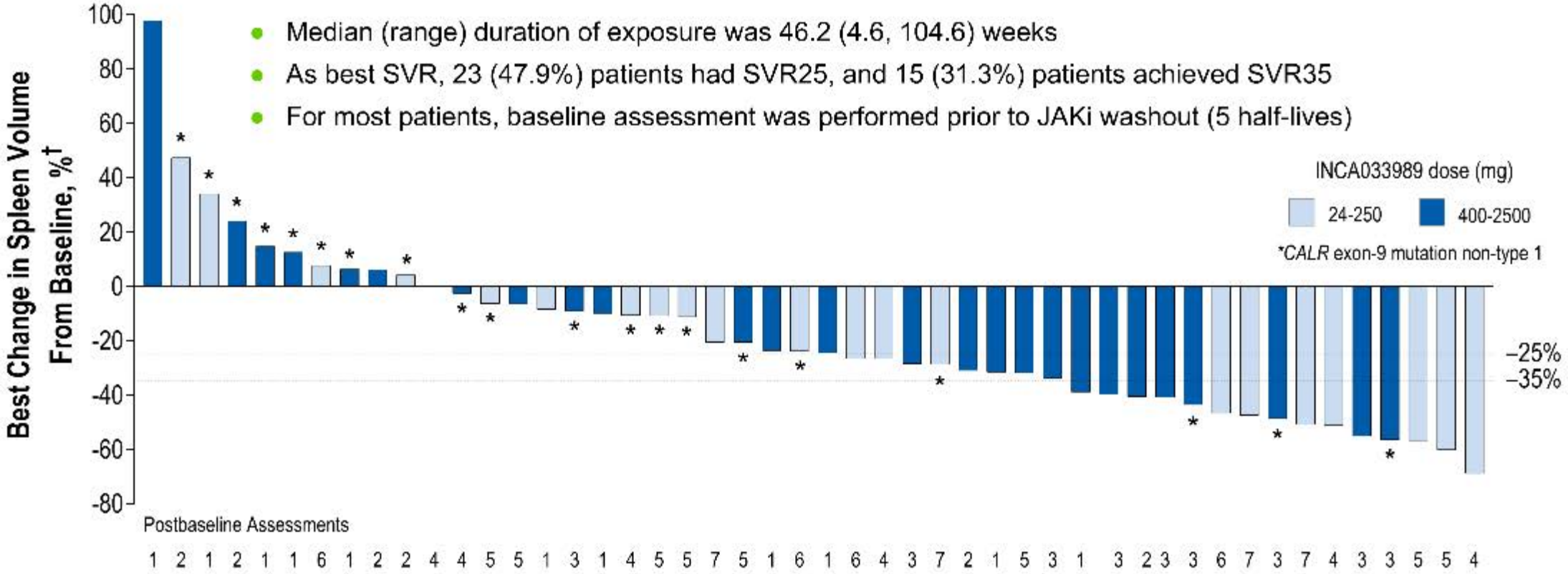
- Excellent safety profile



52-bp deletion (Type 1)
5 bp-insertion (Type 2)

Mascarenhas JO, et al. ASH 2025;Abstract 484

Spleen Volume Reductions Observed With INCA033989 Monotherapy



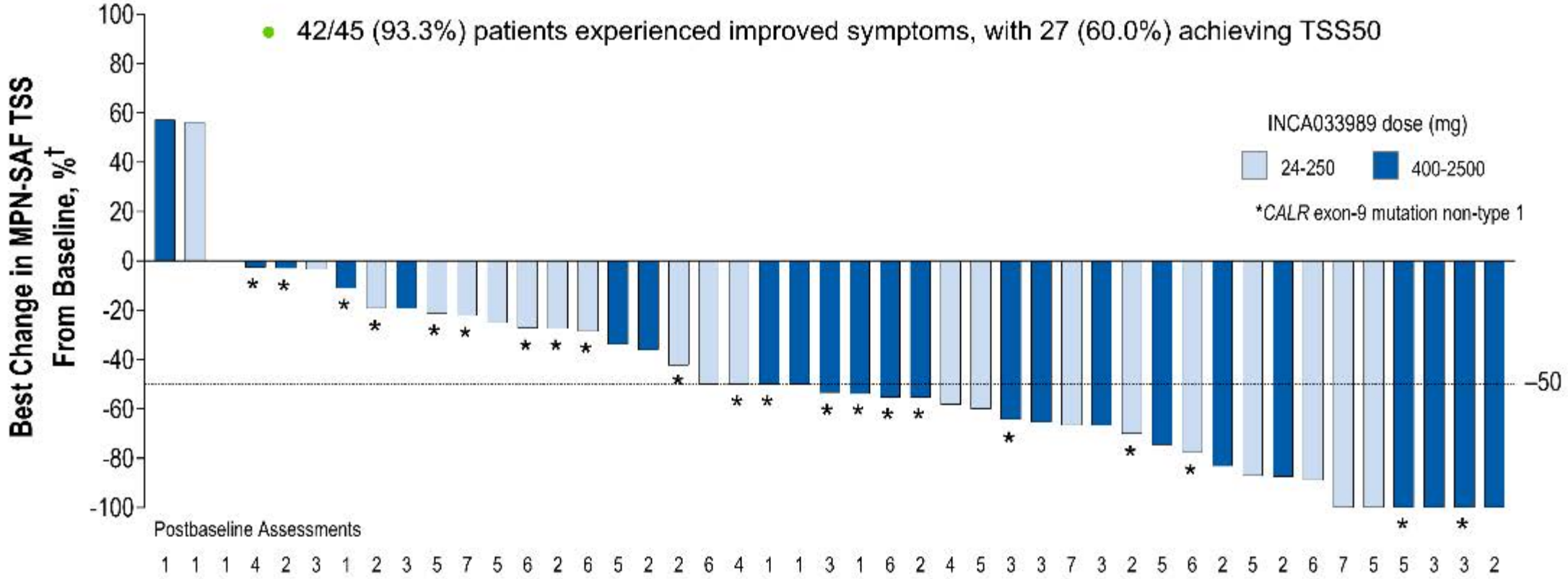
SVR at Week 24 (N=36)

	Total	No Prior JAKi	R/R or Intolerant to JAKi‡
SVR25, n/N (%)	15/36 (41.7)	5/7 (71.4)	10/29 (34.5)
SVR35, n/N (%)	12/36 (33.3)	4/7 (57.1)	8/29 (27.6)

†N=48; 4 patients excluded due to lack of postbaseline assessments but remain on study. Postbaseline assessments performed every 12 weeks. ‡R/R or intolerant to JAKi, including 7 patients with incomplete data (6 of 7 known prior JAKi treatment ≥12 weeks).
JAKi, Janus kinase inhibitor; R/R, relapsed/refractory; SVR25, spleen volume reduction ≥25%; SVR35, spleen volume reduction ≥35%.

Mascarenhas JO, et al. ASH 2025;Abstract 484

Most Patients Experienced Symptom Improvements With INCA033989 Monotherapy



TSS50 at Week 24 (N=33)

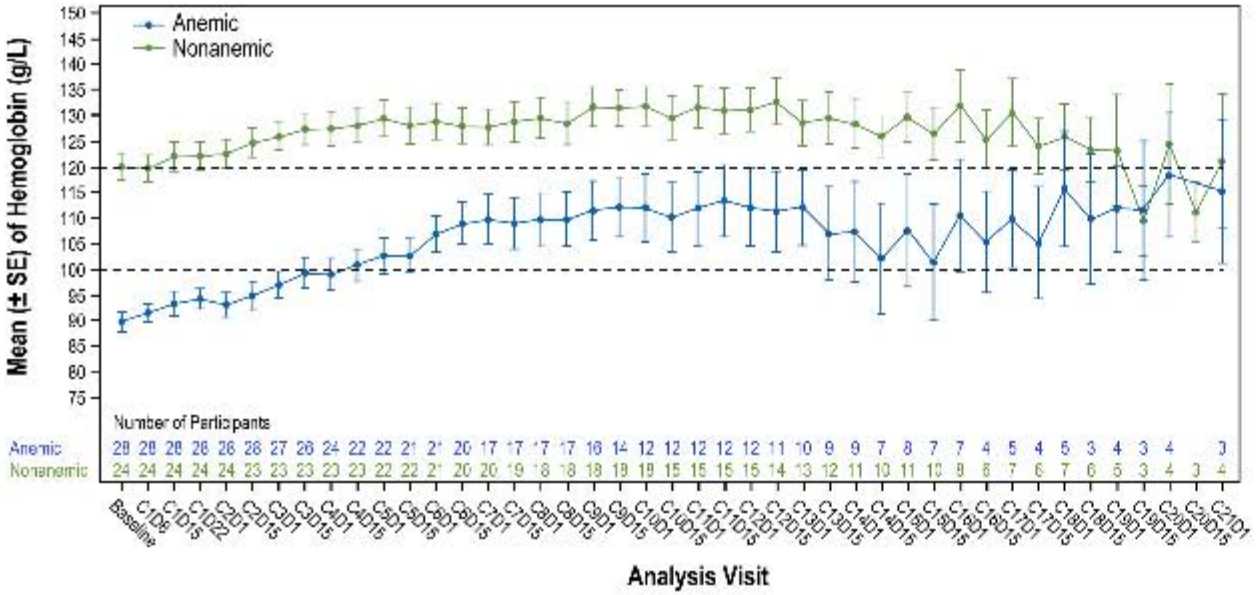
	Total	No Prior JAKi	R/R or Intolerant to JAKi†
TSS50, n/N (%)	13/33 (39.4)	3/5 (60.0)	10/28 (35.7)

†N=45; 7 patients excluded due to lack of postbaseline assessment. Postbaseline assessments performed every 12 weeks. ‡R/R or intolerant to JAKi, including 7 patients with incomplete data (6 of 7 known prior JAKi treatment ≥12 weeks).
JAKi, Janus kinase inhibitor; MPN-SAF, Myeloproliferative Neoplasm-Symptom Assessment Form; R/R, relapsed/refractory; TSS, total symptom score; TSS50, ≥50% reduction in MPN-SAF TSS.

Mascarenhas JO, et al. ASH 2025;Abstract 484

Most Patients Experienced Robust Anemia Improvements With INCA033989 Monotherapy

Mean Hemoglobin During Study by Anemic Status*



Best Anemia Response in Evaluable Patients

Variable	Total (N=25)	TDA (n=5)	Non-TDA (n=20)
Best anemia response, n (%)			
Major response	10 (40.0)	1 (20.0)	9 (45.0)
Minor response	4 (16.0)	2 (40.0)	2 (10.0)
Stable anemia	8 (32.0)	1 (20.0)	7 (35.0)
Progressive anemia	2 (8.0)	1 (20.0)	1 (5.0)
Missing†	1 (4.0)	0	1 (5.0)

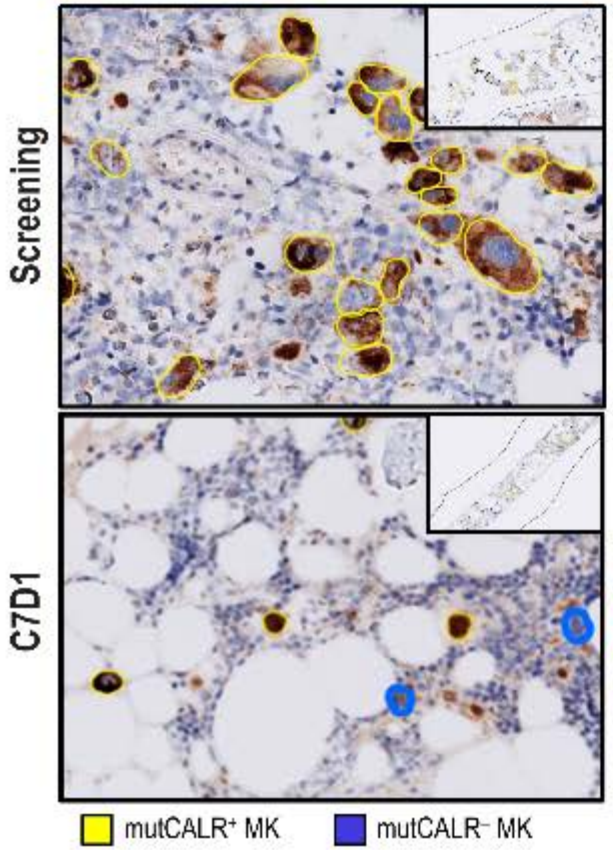
- At baseline, median (range) hemoglobin among patients with anemia was 92 (70, 108) g/L
- Anemia response occurred in 14/25 (56%) of evaluable‡ anemic patients; most patients achieved a major response

*Criteria for baseline anemia and response based on Tefferi A. *Blood*. 2024;114:1813. Major and minor anemia responses were according to IWG-ELN response criteria. Dotted lines indicate anemia threshold (100 g/L) and lower limit of normal (120 g/L). †Patient who terminated treatment before 12 weeks. ‡3/28 anemic patients were not evaluable for response due to missing data at 12 weeks.
IWG-ELN, International Working Group–European LeukemiaNet; TDA, transfusion-dependent anemia.

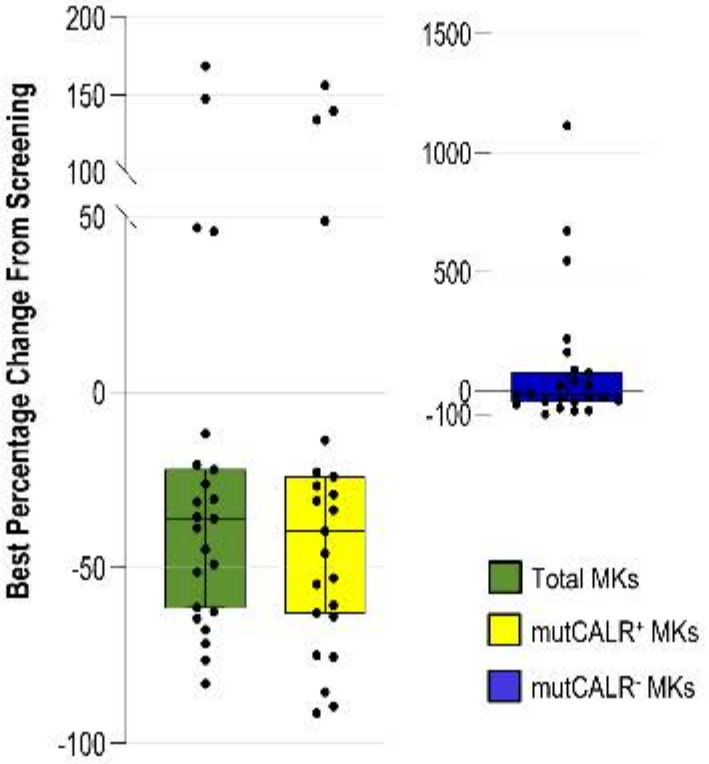
Mascarenhas JO, et al. ASH 2025;Abstract 484

Improvement in Bone Marrow Pathology With INCA033989

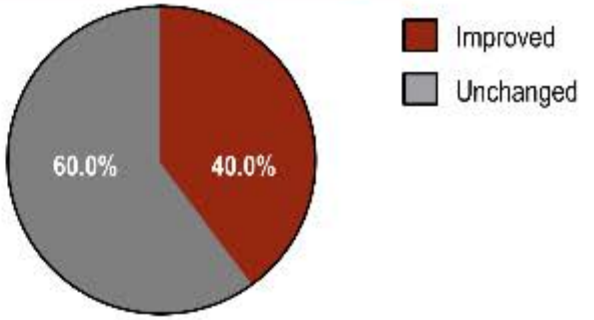
mutCALR IHC



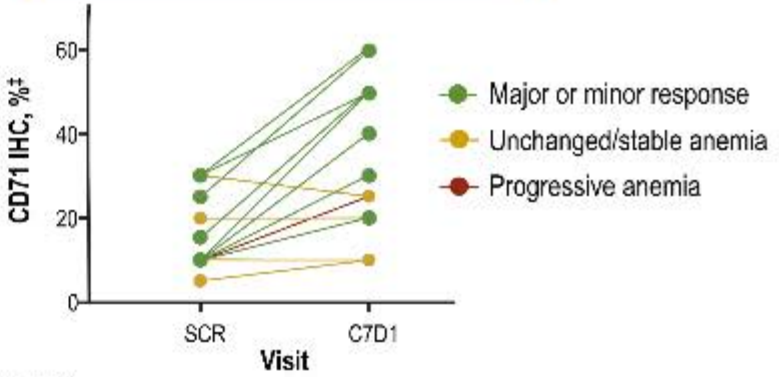
Patients With MF (n=23)*



Fibrosis Grade† (n=30)



Erythroid Progenitors (Anemic Patients, n=14)



- Reduction of total and mutCALR+ MK in MF is accompanied by increase of wild-type (mutCALR−)

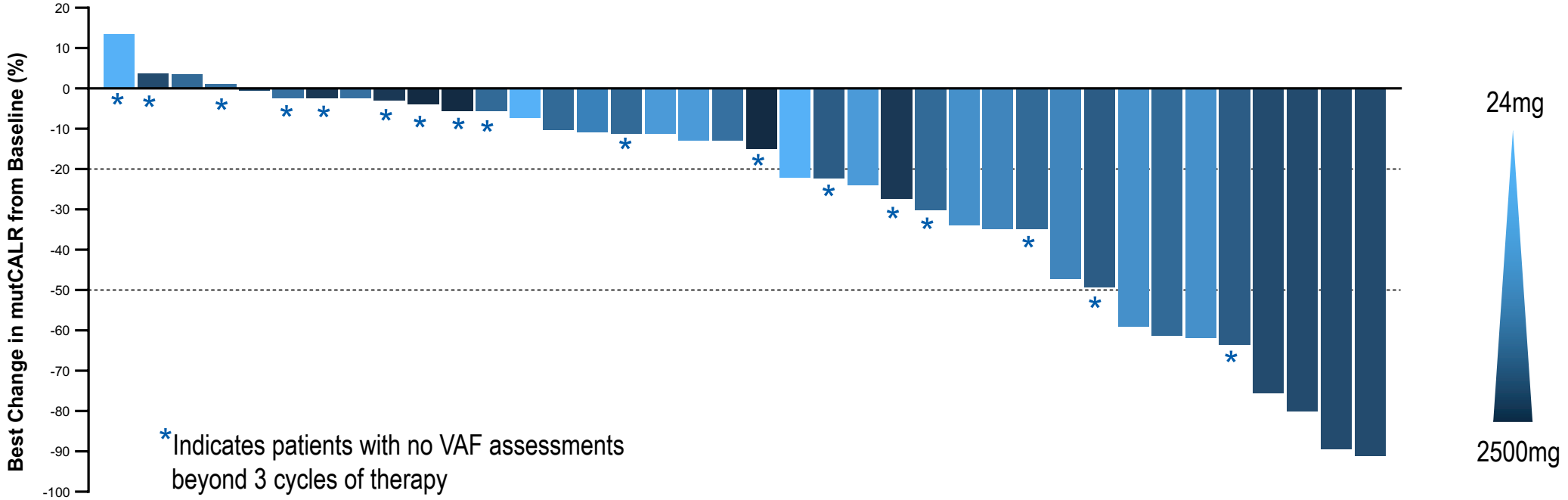
*1 patient with 0 mut*CALR* MK at screening is not shown. Bone marrow mutCALR IHC quantitative assessment of mutCALR+ and mutCALR− MK were conducted by pathologist at screening and at timepoints on-treatment (primarily 3 or 6 cycles). †Fibrosis grade was centrally assessed for all patients with available screening and C7D1 samples. "Improved": decreased by ≥1 grade; "Unchanged": stable. ‡CD71 IHC was centrally assessed by a single pathologist; data includes all patients with baseline anemia and available CD71 IHC for screening and C7D1 (n=14).

C, cycle; D, day; IHC, immunohistochemistry; MF, myelofibrosis; MK, megakaryocytes; mut*CALR*, mutations of calreticulin; SCR, screening; SVR35, spleen volume reduction ≥35%.

Mascarenhas JO, et al. ASH 2025;Abstract 484

Molecular Responses are Rapid and Frequent

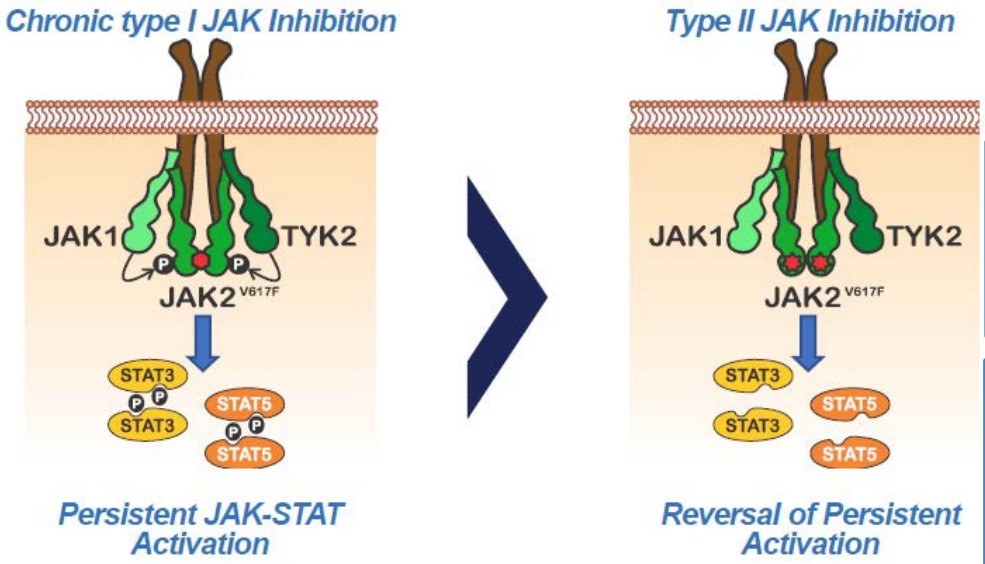
- A reduction in mut*CALR* VAF from baseline occurred in 34/38 (89%) evaluable patients
  - 18/38 (47%) achieved >20% best reduction in VAF
  - 8/38 (21%) achieved >50% best reduction in VAF
- All 18 molecular responders all achieved >20% VAF reduction by the end of 6 cycles of therapy
- Of the 18 molecular responders, 16 (89%) achieved a hematological response of durable CR or PR



Dotted lines represent 20% and 50% VAF thresholds. 1 cycle = 28 days or 2 doses. CALR, calreticulin; VAF, variant allele frequency.

Mascarenhas JO, et al. EHA 2025;Abstract LBA4002

Novel JAK2 V617F inhibition



- All current JAK2 inhibitors are Type I inhibitors that bind the active conformation
- Type II JAK2 inhibition overcomes ruxolitinib persistent MPN cells

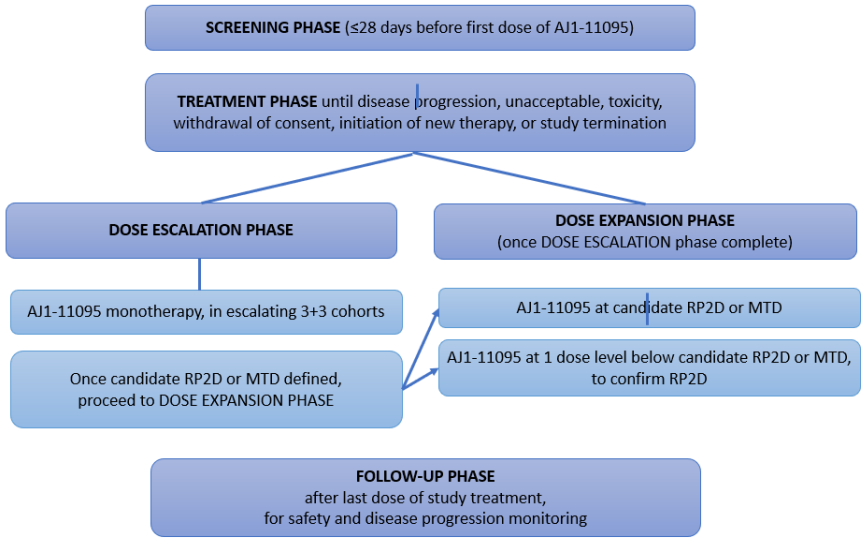
AJ1-11095 BACKGROUND

AJX-101: A Multicenter, Open-Label, Phase 1 Study of AJ1-11095 Administered as Oral Monotherapy in Patients with Myelofibrosis Who Have Been Failed by a Type 1 JAK2 Inhibitor

AJX-101 CLINICAL TRIAL DESIGN

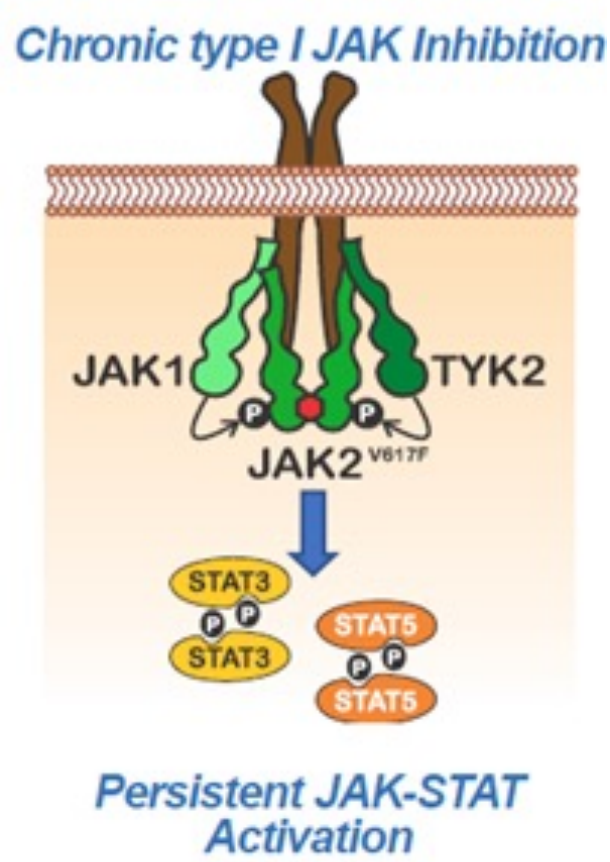
- Phase 1, multicenter, open-label dose escalation and expansion study
- US only initially, then expanding to other regions
- ***First patient enrolled October 2024***

- **Starting dose** of AJ1-11095: **25 mg once daily**
- Dose escalation: conventional 3+3 design
- Subsequent doses determined by a modified Fibonacci sequence and informed by all available safety/tolerability and pharmacokinetics data
- Dose limiting toxicities (DLTs) are defined within the protocol & determined during the first 28-day cycle of treatment
- AE grading: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v. 5.0



Mascarenhas JO. MPN Education Foundation

Novel JAK2 V617F inhibition



INCB 160058-101: Multicenter Study of INCB160058 (selective *JAK2V617F inhibitor)* in Participants With Myeloproliferative Neoplasms

Conclusions

- Significant advances in the understanding of MPN biology has led to many novel and promising therapeutic agents in investigation in Myelofibrosis
- First line therapy for MF will likely be re-defined by the ongoing clinical trials
- Correlative studies, and clinical and molecular predictors are needed to better guide future clinical trial design
- Advocacy for clinical trial enrolment is a must to advance the therapeutic field forward

Thank you

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The University of Kansas Cancer Center
Email: ayacoub@kumc.edu
Cell phone: 314-882-7124

QUESTIONS?

Module 15: Targeted Therapies for NSCLC

Therapeutic Approaches Targeting HER2 and RET — Dr Bazhenova

Therapeutic Approaches Targeting ALK and ROS1 — Dr Langer

Faculty

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Lecanto, Florida

Module 15: Targeted Therapies for NSCLC

Therapeutic Approaches Targeting HER2 and RET — Dr Bazhenova

Therapeutic Approaches Targeting ALK and ROS1 — Dr Langer

Module 15: Targeted Therapies for NSCLC

We would like to do a “best paper or presentation of the year” activity. Please suggest one “paper of the year” and 2 other worthy papers based on the value in treatment of current and future patients.

UC San Diego Health

Therapeutic Approaches Targeting HER2 and RET

Lyudmila Bazhenova, MD, FASCO
Professor of Medicine
Lung Cancer Unit Leader
Director Hematology Oncology training program
UC San Diego Moores Cancer Center.

Disclosures

Advisory Committees	AbbVie Inc, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Genentech, a member of the Roche Group, Janssen Biotech Inc, Lilly, Merck, Natera Inc, Nuvalent, Pfizer Inc, Revolution Medicines Inc, Summit Therapeutics, Taiho Oncology Inc
Nonrelevant Financial Relationships	Alliance for Clinical Trials in Oncology Foundation

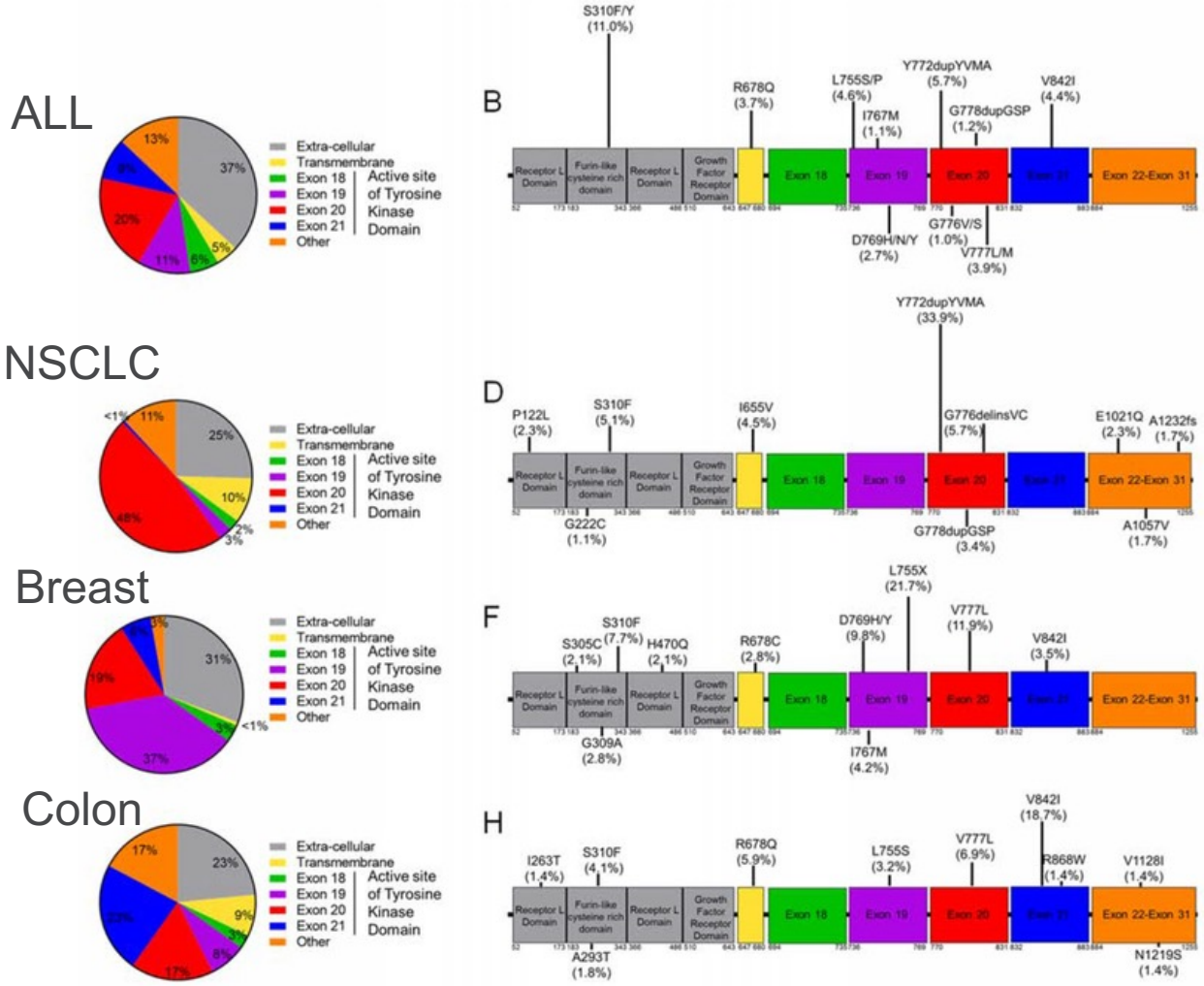
UC San Diego Health

HER 2 alterations

What Is "*HER2*+" Lung Cancer?

HER2 in NSCLC	Frequency
Protein overexpression	59%
Overexpression (IHC 2+/ 3+)	15-30%
Overexpression (IHC 3+ only)	2-6%
Amplification (FISH) GCN to CEP 17 >=2	2-6%
Mutations	1-5%

- **TKD mutations:** ~ 50% to 60%
  - **Exon 20 insertions** (most common): Y772_A775dup (aka ins YVMA)
  - Other rare TKD mutations: L755P in exon 19, etc
- **Trans/juxtamembrane domain mutations:** ~ 5% to 10% G660D, V659E, etc
- **Extracellular domain mutations**: ~10% to 20% S310F, S310Y, etc



Robichaux et al Cancer cell 2020

ECD = extracellular domain; TMD = transmembrane domain.

Pillai RN, et al. *Cancer*. 2017;123(21):4099-4105. Liu S, et al. *J Clin Oncol*. 2010;28(25):4006-4012. Nakamura H, et al. *Cancer*. 2005;92(6):1033-1037. Bansal P, et al. *Front Oncol*. 2016;6:112. Heinmoller P, et al. *Clin Cancer Res*. 2003;9(14):5238-5243. Menard S, et al. *Ann Oncol*. 2001;12(Suppl 1):S15-S19. Peters S, et al. *Transl Lung Cancer Res*. 2014;3(2):84-88. Rothschild SI. *Cancer* (Basel). 2015;7(2):930-949. Hyman DM, et al. *Nature*. 2018;554(7691):189-194.

UC San Diego Health

Two major approaches with FDA approval in NSCLC

ADC

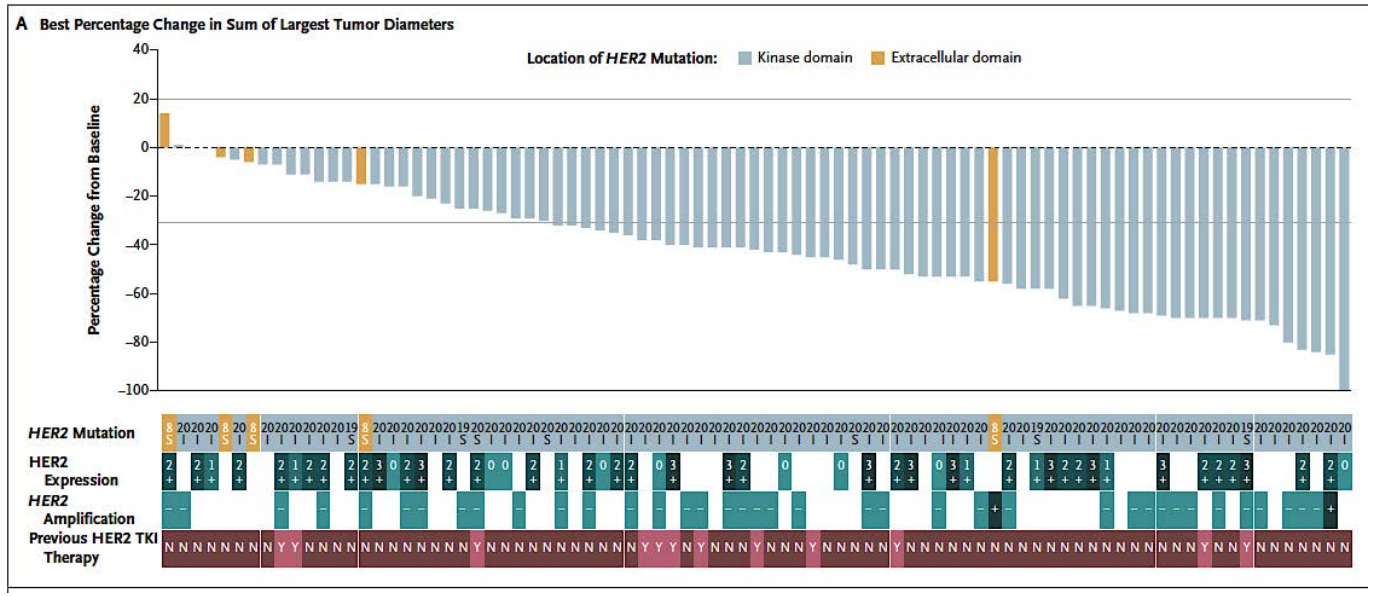
- Trastuzumab deruxtecan (T-DXd)
  - HER2 mt
  - HER2 3+ overexpressing after failure of platinum doublet

TKI

- Sevabertinib
- Zongertinib

Trastuzumab Deruxtecan in *HER2* mt NSCLC (DESTINY LUNG 01)

T-DXd is a Humanized anti-HER2 IgG1 mAB with a topoisomerase I inhibitor payload, cleavable linker and DAR of ≈8



mPFS 8.2 months (95% CI, 6.0 to 11.9)
mOS 17.8 months (95% CI, 13.8 to 22.1)

Table 2. Response to Trastuzumab Deruxtecan as Assessed by Independent Central Review.

Response Assessment	Patients (N=91)
Confirmed objective response*	
No. of patients	50
Percentage of patients (95% CI)	55 (44–65)
Best response — no. (%)	
Complete response	1 (1)
Partial response	49 (54)
Stable disease	34 (37)
Progressive disease	3 (3)
Response could not be evaluated	4 (4)
Disease control†	
No. of patients	84
Percentage of patients (95% CI)	92 (85–97)
Median time to response (range) — mo‡	1.5 (1.2–9.3)
Median duration of response (95% CI) — mo‡	9.3 (5.7–14.7)

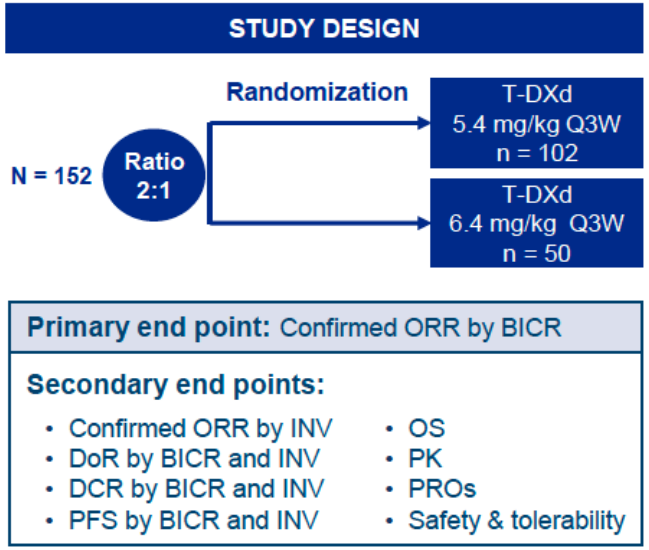
Li BT et al. *N Engl J Med.* 2021;386:241-251.

UC San Diego Health

Randomized phase II trial (DESTINY LUNG 02)

Key Eligibility criteria

- Stage IV
- Activating HER 2 mutations
- 2L +
- ECOG 0-1



Response by BICR	T-DXd 5.4 mg/kg N=102	T-DXd 6.4 mg/kg N=50
Confirmed ORR % (CI)	49 (39-59)	56 (41.3-70))
mDOR, Months	16.8 (6.4-NE)	NE (8.3-NE)
mPFS	9.9 (7.4-NE)	15.4 (8.3-NE)
mOS	19.5 (13.6 –NE)	NE (12.1-NE)

Patients, investigators and study staff are blinded to dose level
The study was not powered to statistically compare two arms.

Adjudicated Drug related ILD

	T-DXd 5.4 mg/kg N=101	T-DXd 6.4 mg/kg N=50
Any Grade n(%)	13 (12.9%)	14 (28%)

K Goto et al ESMO 2022, Goto et al JCO 2023

TABLE 3. Most Common (≥20% of patients) Treatment-Emergent Adverse Events in Patients With Human Epidermal Growth Factor Receptor 2–Mutant Metastatic Non–Small-Cell Lung Cancer Treated With T-DXd

	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 101),[a] No. (%)		T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 50),[a] No. (%)	
Preferred Term	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Nausea	68 (67.3)	4 (4.0)	41 (82.0)	3 (6.0)
Neutropenia[b]	43 (42.6)	19 (18.8)	28 (56.0)	18 (36.0)
Fatigue[b]	45 (44.6)	8 (7.9)	25 (50.0)	5 (10.0)
Decreased appetite	40 (39.6)	2 (2.0)	25 (50.0)	2 (4.0)
Anemia[b]	37 (36.6)	11 (10.9)	26 (52.0)	8 (16.0)
Vomiting	32 (31.7)	3 (3.0)	22 (44.0)	1 (2.0)
Constipation	37 (36.6)	1 (1.0)	16 (32.0)	0
Leukopenia[b]	29 (28.7)	5 (5.0)	17 (34.0)	8 (16.0)
Thrombocytopenia[b]	28 (27.7)	6 (5.9)	14 (28.0)	5 (10.0)
Diarrhea	23 (22.8)	1 (1.0)	18 (36.0)	2 (4.0)
Alopecia	22 (21.8)	0	17 (34.0)	0
Transaminases increased[b]	22 (21.8)	3 (3.0)	10 (20.0)	0

CNS activity of T-DxD

Response	Patients, No. (%)							
	T-DXd 5.4-mg/kg dose group in DESTINY-Lung02 trial (n = 102)			T-DXd 6.4-mg/kg dose group pooled from DESTINY-Lung01 and DESTINY-Lung02 trials (n = 141)			Combined groups	
	With measurable BMs (n = 14)	With prior treatment (n = 8)	Without prior treatment (n = 6)	With measurable BMs (n = 30)	With prior treatment (n = 14)	Without prior treatment (n = 16)	With prior treatment (n = 22)	Without prior treatment (n = 22)
Intracranial confirmed objective response	7 (50)	4 (50)	3 (50)	9 (30)	3 (21)	6 (38)	7 (32)	9 (41)
Intracranial confirmed ORR (95% CI), %[a,b]	50 (23-77)	50 (16-84)	50 (12-88)	30 (15-49)	21 (5-51)	38 (15-65)	32 (14-55)	41 (21-64)
CR	3 (21)	0	3 (50)	0	0	0	0	3 (14)
PR	4 (29)	4 (50)	0	9 (30)	3 (21)	6 (38)	7 (32)	6 (27)
SD	6 (43)	3 (38)	3 (50)	13 (43)	7 (50)	6 (38)	10 (45)	9 (41)
PD	1 (7)	1 (13)	0	4 (13)	3 (21)	1 (6)	4 (18)	1 (5)
NE	0	0	0	2 (7)	0	2 (13)	0	2 (9)
Missing data	0	0	0	2 (7)	1 (7)	1 (6)	1 (5)	1 (5)
Intracranial disease control	13 (93)	7 (88)	6 (100)	22 (73)	10 (71)	12 (75)	17 (77)	18 (82)
Intracranial DCR (95% CI), %[a,b]	93 (66-100)	88 (47-100)	100 (54-100)	73 (54-88)	71 (42-92)	75 (48-93)	77 (55-92)	82 (60-95)
Intracranial DOR, median (95% CI), mo[c,d]	9.5 (3.6-NE)	7.1 (3.6-NE)	9.5 (NE-NE)	4.4 (2.9-10.2)	4.4 (2.9-NE)	5.6 (2.9-NE)	4.6 (2.9-NE)	6.8 (2.9-NE)
Time to intracranial progression, median (range), mo	NA	2.8 (1.3-10.9)	NE (NE-NE)	NA	2.6 (1.2-6.9)	5.6 (0.6-14.0)	2.7 (1.2-10.9)	5.6 (0.6-14.0)
Time since prior brain radiotherapy, median (range), mo*	NA	9.2 (7.2-23.9)	NA	NA	0.9 (0.6-0.9)	NA	7.2 (0.6-23.9)	NA

Abbreviations: BM, brain metastasis; CR, complete response; DCR, disease control rate; DOR, duration of response; NA, not applicable; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan.

* Denominator for percentage is the number of patients in the full analysis set who had at least 1 target lesion at baseline, per blinded independent central review.

[b] Based on Clopper-Pearson method for single proportion.

[c] Calculated as time from first response in brain until progression in brain.

[d] Based on Kaplan-Meier analysis and computed with the Brookmeyer-Crowley method.

* For patients with confirmed best overall response in brain (CR, PR).

Janne et al JAMA network open 2025

Efficacy of sevabertinib in patients with HER2 mutations

	COHORT D Previously treated Naïve to HER2 therapy	Cohort E Prior HER2 ADC	Cohort F Treatment naive
N	81	55	73
ORR BICR	64%	38%	71%
DOR 95% (CI)	9.2 (6.3, 13.5)	8.5 (5.6, 16.4)	11 (8.1 NE)
PFS	8.3 (6.9, 12.3)	5.5 (0.3 to 8.3)	Not mature

Le X et al. *NEJM*. 2025: Le et al ESMO 2025

Efficacy of zongertinib in patients with HER2 mutations

	COHORT 1 Previously treated Naïve to HER2 therapy	Cohort 5 Prior HER 2 ADC	Cohort 2 Treatment Naive
N	75	31	74
ORR BICR	71%	48%	76%
DOR 95% (CI)	14.1 (6.9-NE)	5.3	15.2 (9.8 – NE)
PFS	12.4 (8.2 NE)	6.8	14.4 (11.1-NE)

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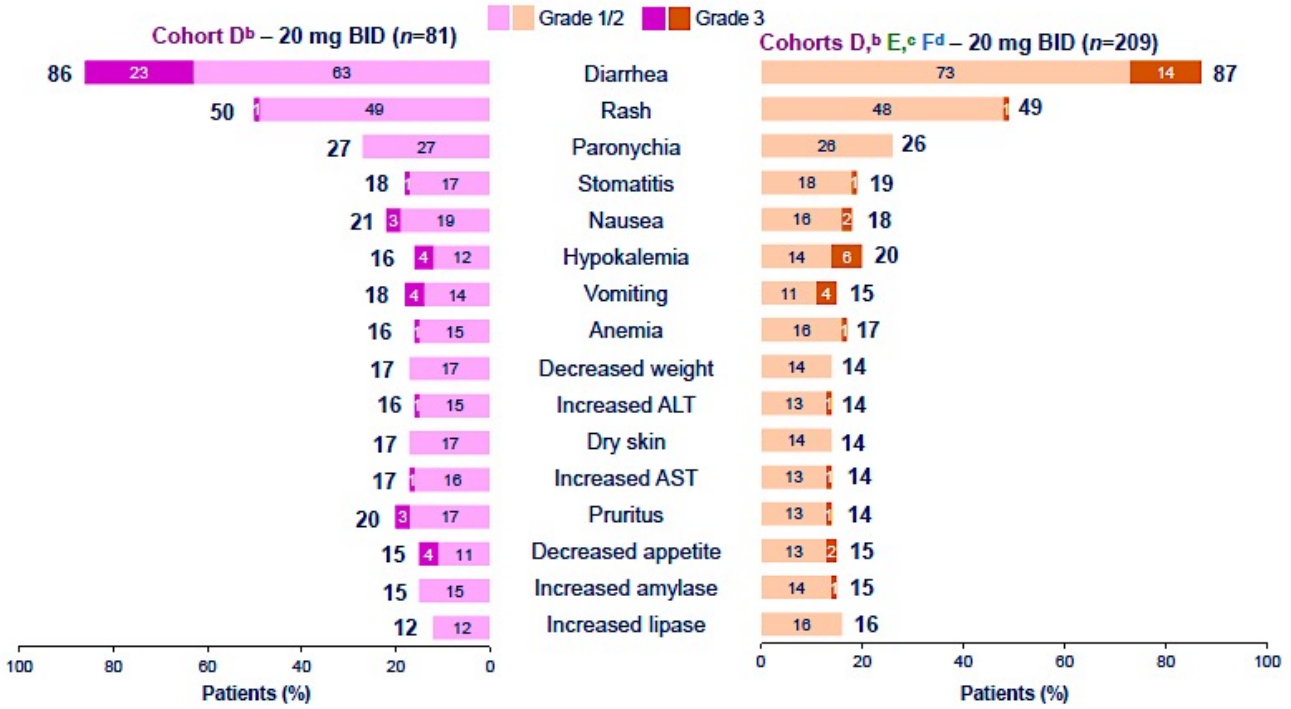
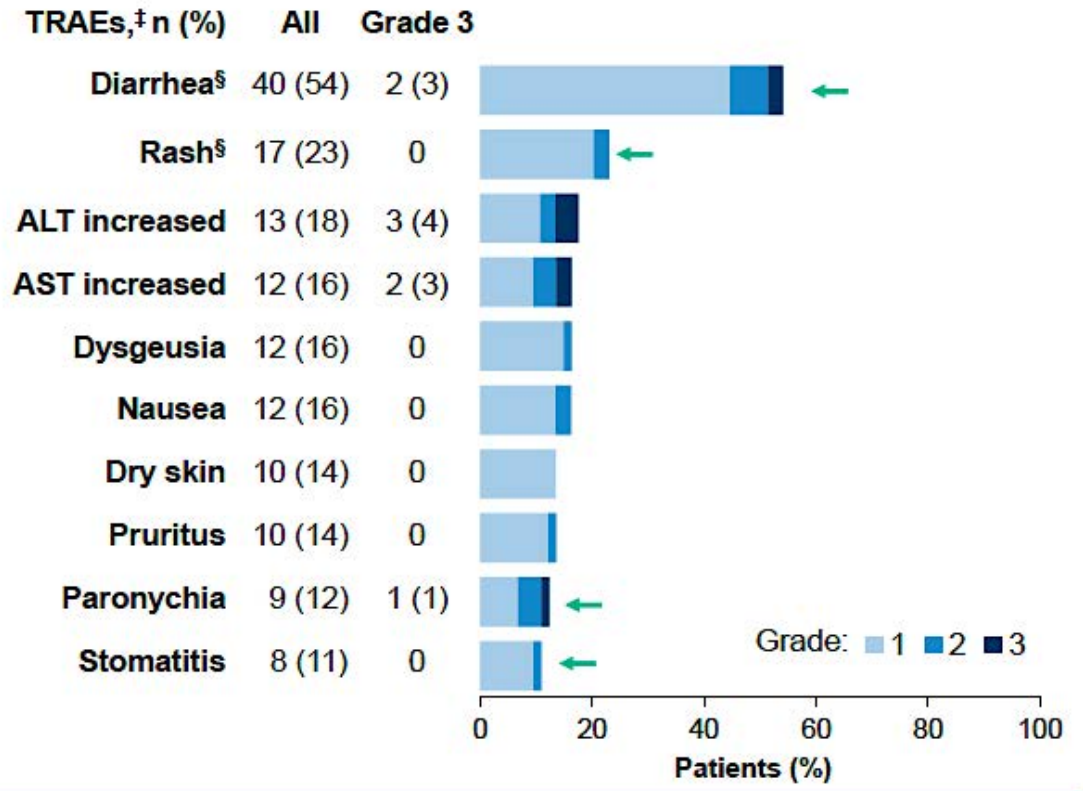
Heymach JV et al. *NEJM*. 2025;392:2321-33, Sanjay Popat, ESMO 2025., Heymach et al NEJM 2026

Side effect profile

Sevabertinib all cohorts



Zongertinib 1L



Le et al ESMO 2025

Sanjay Popat, ESMO 2025

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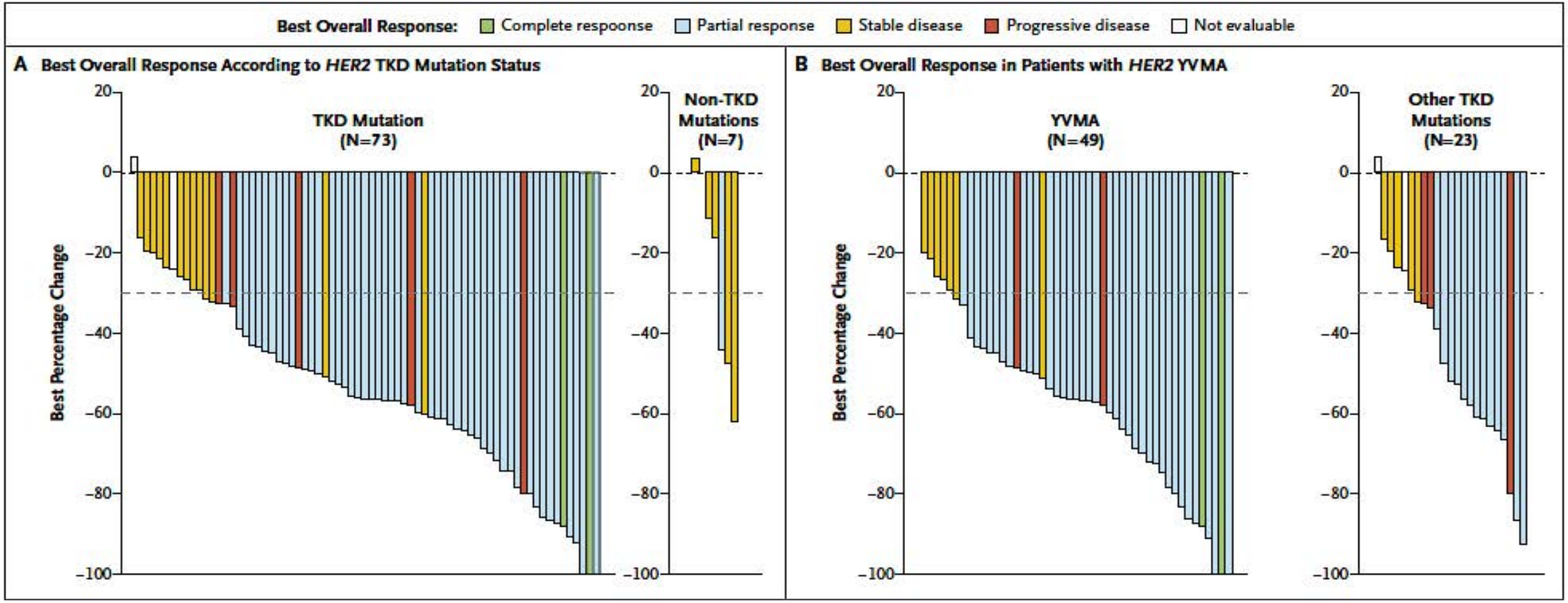
Does the type of the mutation matter?

Sevabertinib



ORR 71%
mPFS 9.6m

ORR 78%
mPFS 12.2m

ORR
mPFS 7m

Le X et al. *NEJM*. 2025

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Does the type of the mutation matter?

Zongertinib

Cohort 3. Non TKD mutation, pretreated, naïve to HER2 therapy
(*S310F, V659E, S310Y, P1199S, D277Y, S113F, G660D)*

Response assessment RECIST, version 1.1	Cohort 3 (N = 20)
Objective response — no. (%)	6 (30)
95% CI	15–52
Complete response — no. (%)	0
Partial response — no. (%)	6 (30)
Disease control — no. (%)	13 (65)
95% CI	43–82
Stable disease — no. (%)	7 (35)
Progressive disease — no. (%)	6 (30)
Not evaluable — no. (%)	1 (5)

COHORT 1 Previously treated Naïve to HER2 therapy
N=75
ORR 71%
mDOR 14.1 (6.9-NE)
mPFS 12.4 (8.2 NE)

Heymach et al NEJM 2025

Zongertinib CNS activity

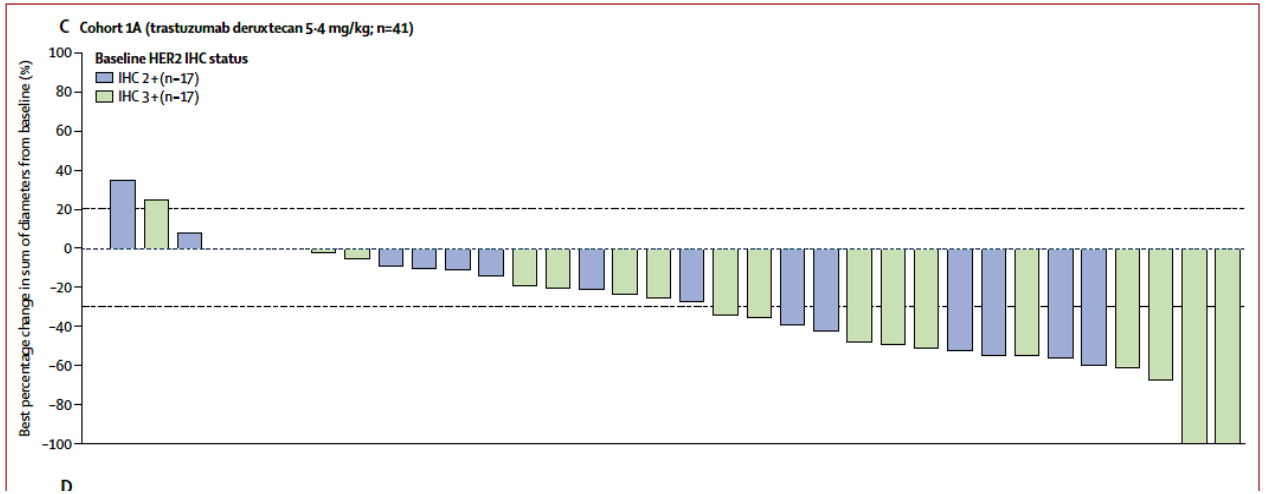
Confirmed Intracranial Response in Patients with Active Brain Metastases Treated with Zongertinib 120 mg in Beamion LUNG-1 Cohort 4, as Assessed by Blinded Independent Central Review. TKD mutation

Intracranial Response Assessment	Any line, 120 mg (N = 30)	First-line, 120 mg (N = 8)
RANO-BM criteria		
Objective response		
Total no. of patients — no. (%)	14 (47)	4 (50)
95% CI	30–64	22–79
Complete response — no. (%)	2 (7)	0
Partial response — no. (%)	12 (40)	4 (50)
Disease control		
Total no. of patients — no. (%)	26 (87)	6 (75)
95% CI	70–95	41–93
Stable disease — no. (%)	12 (40)	2 (25)
Not evaluable — no. (%)	4 (13)	2 (25)

Ruiter G et al. WCLC 2025, Heymach et al, NEJM 2026

T-DXd in HER2-overexpressing lung cancer (IHC 2+/3+)

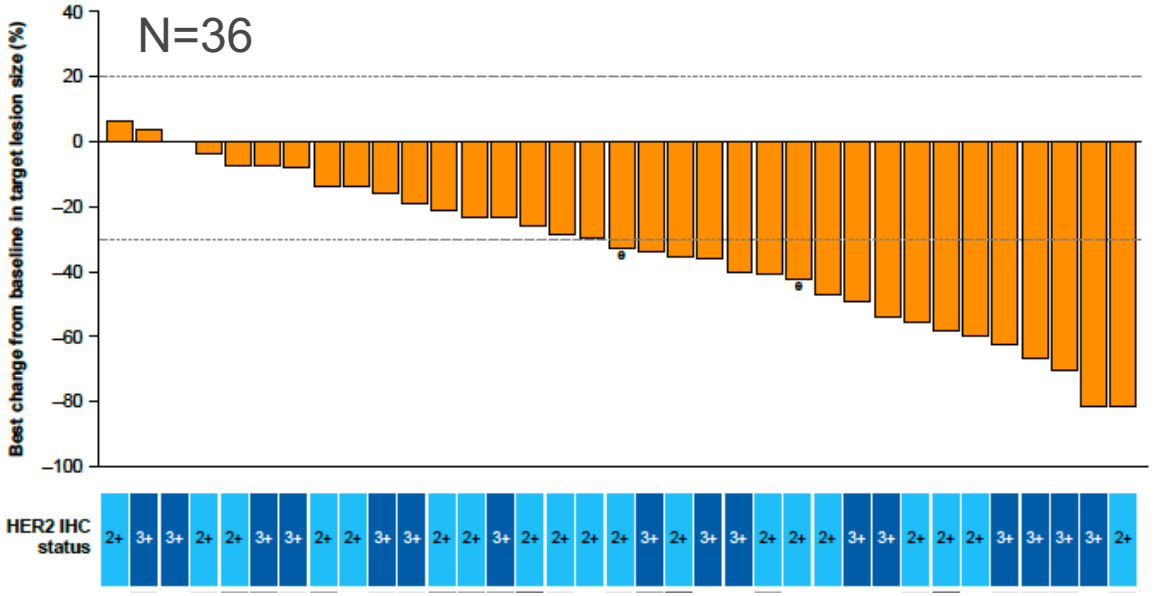
Destiny Lung 01
N=41



ORR 34% (95% CI 20.1 -50.6) combined 2+ and 3+
mDOR 6.2 months (4.2-9.8)
mPFS 6.7 months (95% CI (4.2–8.4)
mOS: 11.2 months (95% CI, 8·4–not evaluable)

Smit al Lancet Oncology 2024

Destiny Lung 03



ORR 44.4 (16) 27.9-61.9) combined 2+ and 3+
mDOR 11.0 (5.5-16.7)
mPFS 8.2 months (6.7–11.1)
mOS:17.1 months (11.6–23.8)

Planchard et al JCO 2025

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Ongoing 1L studies with T-DXD, zongertinib, sevabertinib

BEAMION LUNG-2 Phase III Trial Design of 1L Zongertinib

Estimated enrollment N = 270

- Advanced and/or metastatic non-squamous NSCLC
- Documented HER2 mutation in the TKD as per local laboratory results
- No prior systemic treatment for locally advanced or metastatic disease
- ≥1 lesion evaluable by RECIST v1.1
- Eligible to receive cisplatin/pemetrexed or carboplatin/pemetrexed + pembrolizumab
- Life expectancy ≥12 weeks at start of treatment
- ECOG PS 0-1

R

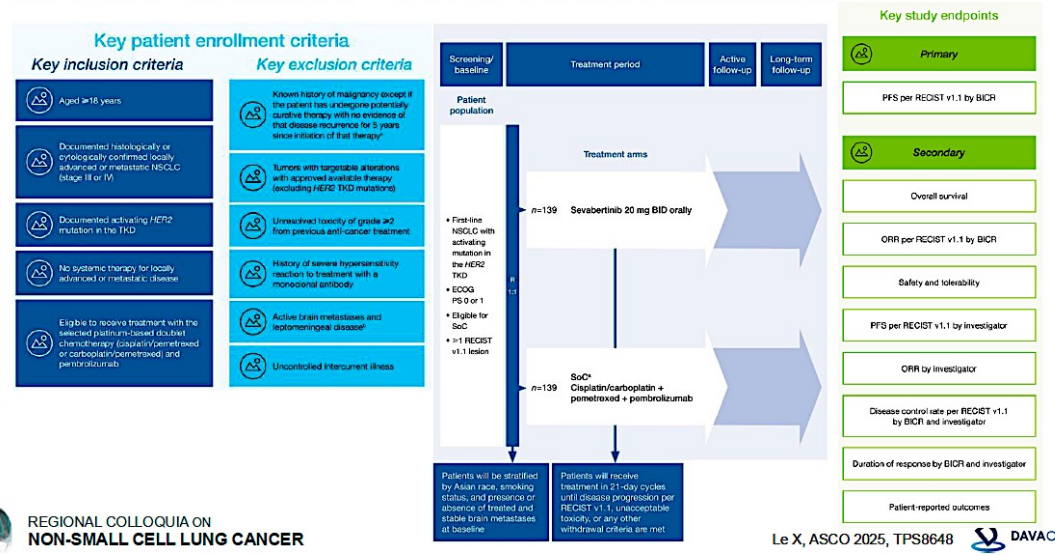
120 mg zongertinib once daily orally in 21-day cycles

Standard of care

Primary endpoint: PFS

Secondary endpoints: OR, OS, DOR, QoL, safety

SOHO-02: Randomized Phase III Trial with 1L Sevabertinib



REGIONAL COLLOQUIA ON NON-SMALL CELL LUNG CANCER

Le X, ASCO 2025, TPS8648

DAVAOncology

DESTINY-Lung04: Randomized Phase III Trial of 1L T-Dxd

Patient population (N≈264)

- Unresectable, locally advanced (not amenable to curative therapy), or metastatic nonsquamous NSCLC with *HER2* exon 19 or 20 mutations[a]
- Naive to systemic therapy in the locally advanced or metastatic setting
- No known other targetable oncogenic mutations/alterations

Randomization 1:1

Arm 1: T-DXd[b]

Arm 2: Standard of care[b]
platinum[c] (cisplatin or carboplatin)
+ pemetrexed
+ pembrolizumab

"The results might determine whether T-DXd could extend to the first-line setting," potentially revolutionizing the treatment landscape from the point of diagnosis.

ESMO 2023

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Summary

- HER2 mutation and over expressions are targetable alterations therefore testing is important
- Three FDA approved agents: sevabertinib, zongertinib, Trastuzumab deruxtecan
- CNS activity has been confirmed with zongertinib and T-DXd
- Several unanswered questions.
  - Impact of the specific HER2 mutation on treatment selection
  - How to best sequence TKIs and ADCs
  - CNS activity
  - Use of TKIs as single-agent vs combination

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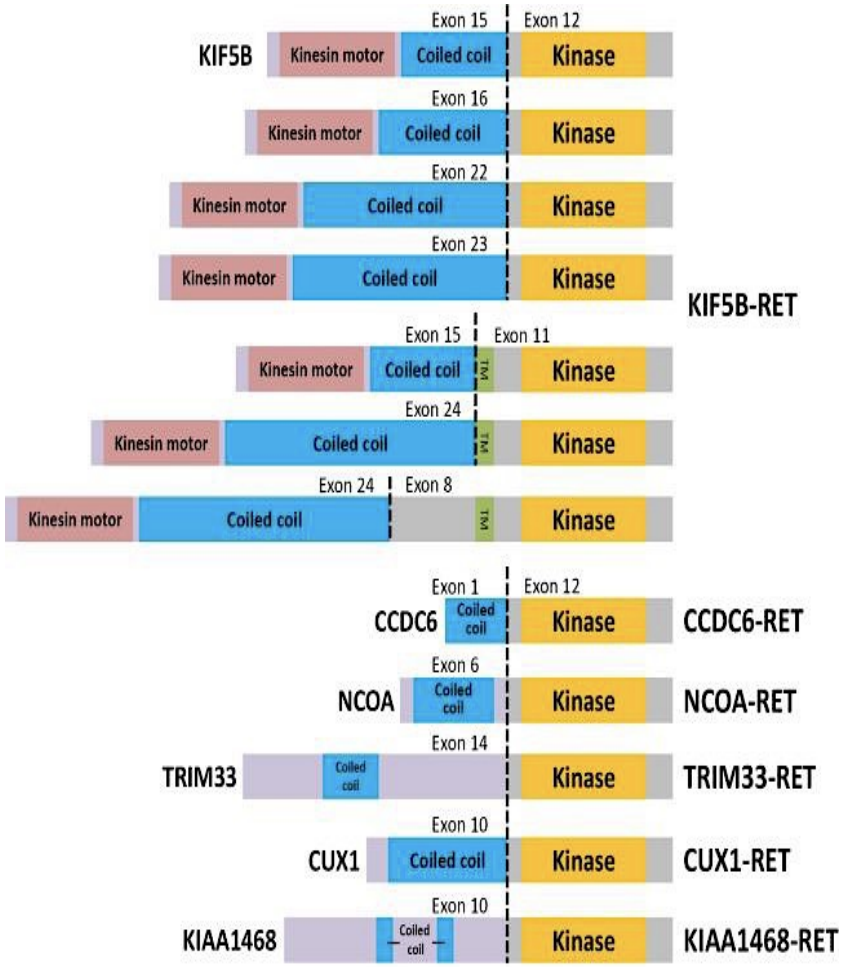
RET rearranged NSCLC

RET Alterations

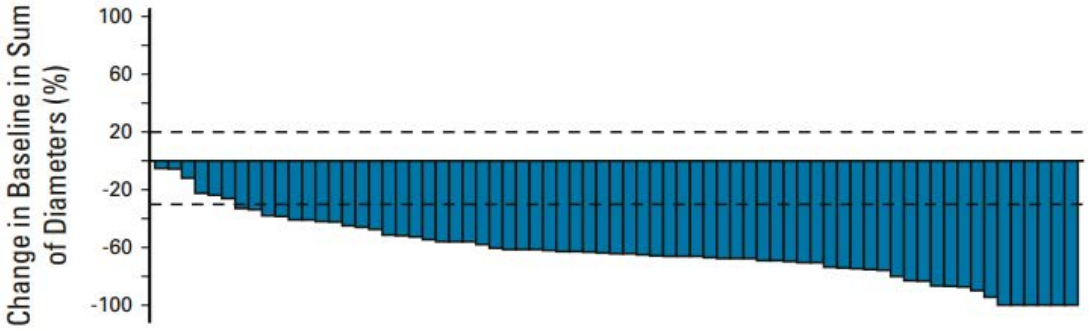
- RET (REarranged during Transfection) can be altered in two distinct ways
  - Point mutations found predominantly in MTC
  - Fusions seen in papillary thyroid cancer and NSCLC
    - Many known fusion partners
    - Intact tyrosine kinase domain fused with upstream partner.
    - KIF5B is the most common fusion partner in lung cancer
      - Other partners are CCDC6, *NCOA4*, and *TRIM33*
    - Typically, do not occur concurrently with alterations in *EGFR*, *ALK*, *ROS1*, *BRAF*, or *KRAS*
- Frequency in lung cancer: 1-2 % overall



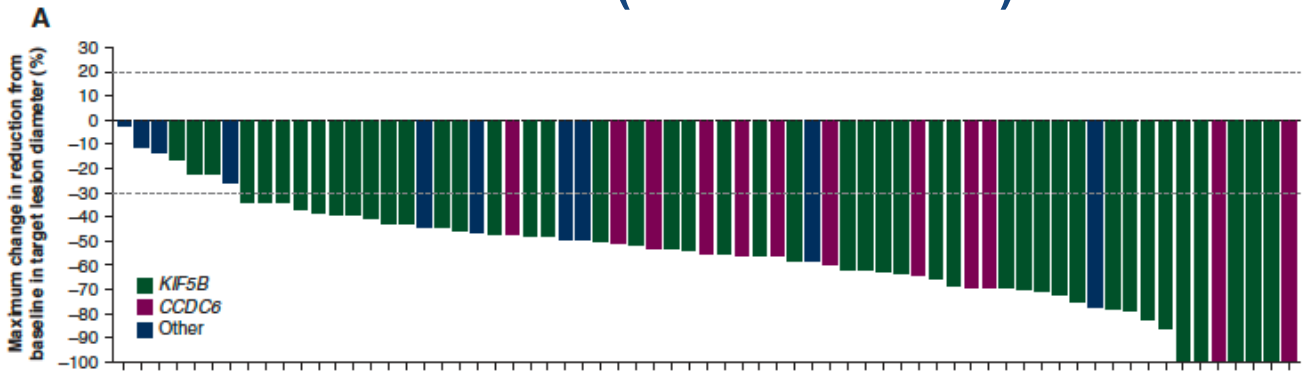
Ju YS et al. *Genome Res*. 2012;22:436-445. Drilon A et al. *Cancer Discov*. 2013;3:630-635. Wang R et al. *J Clin Oncol.* 2012;30:4352-4359; Kohno T et al. *Cancer Sci.* 2013;104:1396-1400.

Efficacy of Selective RET Inhibitors in NSCLC

Selpercatinib (treatment naïve)



Pralsetinib (treatment naïve)

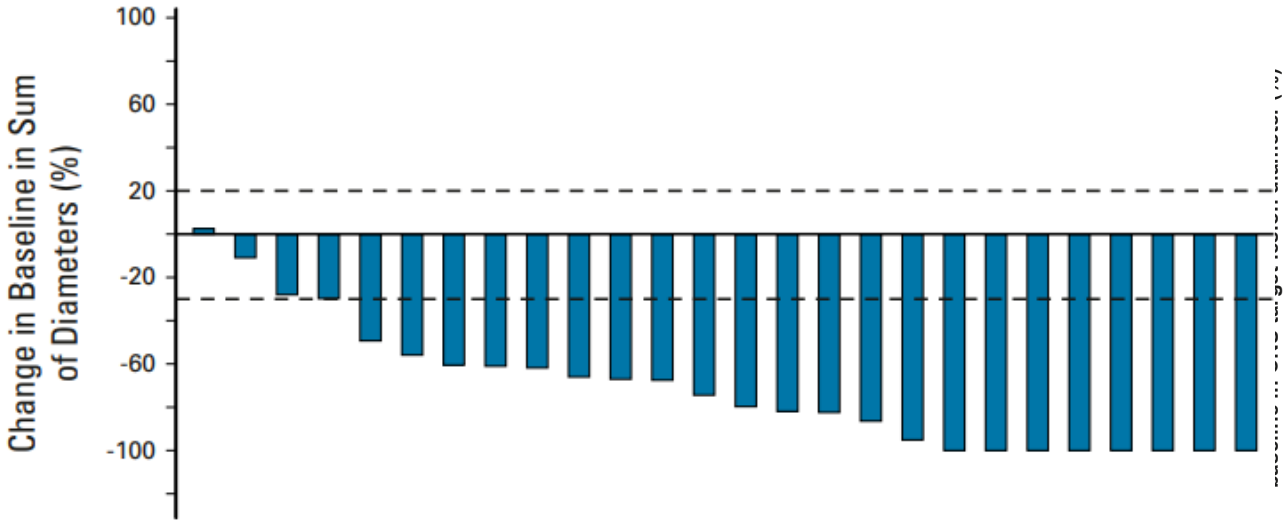


	Platinum pretreated N = 247				Treatment Naïve N = 69		
	IRC ORR % (95% CI)	mDOR, months (95% CI)	mPFS, months (95% CI)	Intracranial ORR (95% CI)	IRC ORR % (95% CI)	mDOR, months (95% CI)	mPFS,months (95% CI)
Selpercatinib[1-4]	61 (55, 67)	28.6 (20.4, NE)	24.9 (19.3, NE)	85 (65 -96)	84 (73, 92)	20.2 (13.0, NE)	22.0 (13.8, NE)
	N=130 for ORR, N=141 for PFS and OS				N=106 for ORR N=116 for PFS and OS		
Pralsetinib[5,6,7]	63 (54-71)	31.8 (15.1-40.4)	16.4 (11.4 -23.5)	56 (21-86)	78 (69-86)	13.4 (9.4-21.7)	12.1 (9.2-16.6)

1. Drilon A et al. *J Clin Oncol.* 2023;41(2):385-394. 2. Drilon A et al, *N Engl J Med.* 2020;383(9):813-824. 3. Besse B et al. *J Clin Oncol* 2021;39(no. 15_suppl):9065-9065. 4. Drilon A et al. *Ann Oncol*. 2022;33:S43. 5. Gainor JF et al. *Lancet Oncol*. 2021;22(7):959-969. 6. Griesinger F et al. *Ann Oncol.* 2022 ;33(11):1168-1178.7 Besse et al JCO 2026

CNS Activity in Measurable CNS Metastases

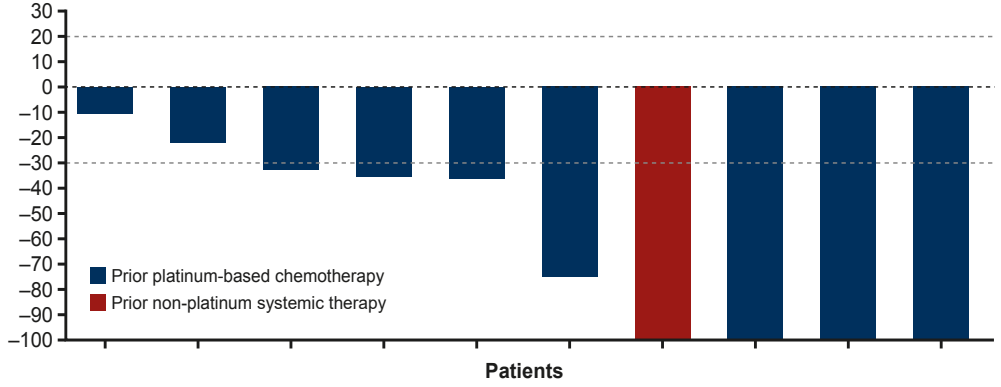
Selpercatinib (treatment naive)



- icORR 85% (22/26; 95% CI, 65 - 96)
- Seven patients (27%) with intracranial CR

Drilon A et al. *J Clin Oncol.* 2023;41(2):385-394.

Pralsetinib



- icORR 70% (7/10; 95% CI, 35 - 93)
- Three patients (30%) with intracranial CR

Griesinger F et al. *Ann Oncol.* 2022 ;33(11):1168-1178.

Adverse Events

Selpercatinib

Preferred or Composite Terms	Any Causality (N = 796)		Related to Treatment (N = 796)	
	Any Grade[a]	Grade ≥ 3	Any Grade	Grade ≥ 3[b]
Patients with ≥ 1 AE	795 (99.9)	572 (71.9)	756 (95.0)	307 (38.6)
Edema	386 (48.5)	6 (0.7)	246 (30.9)	5 (0.6)
Diarrhea	374 (47.0)	40 (5.0)	217 (27.3)	16 (2.0)
Fatigue	365 (45.9)	25 (3.1)	221 (27.8)	17 (2.1)
Dry mouth	344 (43.2)	0	304 (38.2)	0
Hypertension (AESI)	326 (41.0)	157 (19.7)	224 (28.1)	105 (13.2)
AST increased	292 (36.7)	70 (8.8)	229 (28.8)	50 (6.3)
ALT increased	284 (35.7)	91 (11.4)	227 (28.5)	72 (9.0)
Abdominal pain	268 (33.7)	20 (2.5)	88 (11.1)	3 (0.4)
Constipation	261 (32.8)	6 (0.8)	115 (14.4)	2 (0.3)
Rash	261 (32.8)	5 (0.6)	159 (20.0)	5 (0.6)
Nausea	248 (31.2)	9 (1.1)	98 (12.3)	3 (0.4)
Blood creatinine increased	227 (28.5)	15 (1.9)	123 (15.4)	2 (0.3)
Headache	220 (27.6)	11 (1.4)	76 (9.5)	3 (0.4)
Cough	184 (23.1)	0	19 (2.4)	0
Dyspnea	179 (22.5)	25 (3.1)	26 (3.3)	1 (0.1)
Vomiting	178 (22.4)	14 (1.8)	54 (6.8)	3 (0.4)
ECG QT prolongation (AESI)	168 (21.1)	38 (4.8)	130 (16.3)	27 (3.4)
Arthralgia	165 (20.7)	2 (0.3)	43 (5.4)	1 (0.1)

Drilon A et al. *J Clin Oncol.* 2023;41(2):385-394.

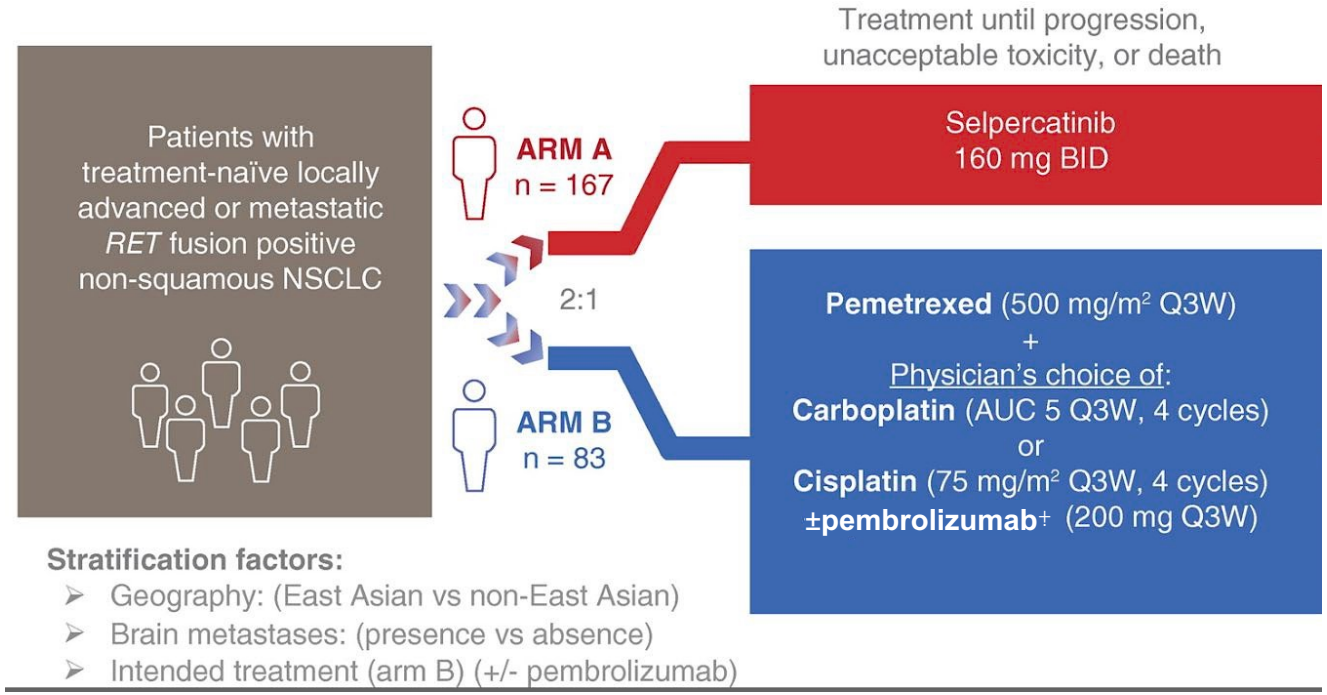
Pralsetinib

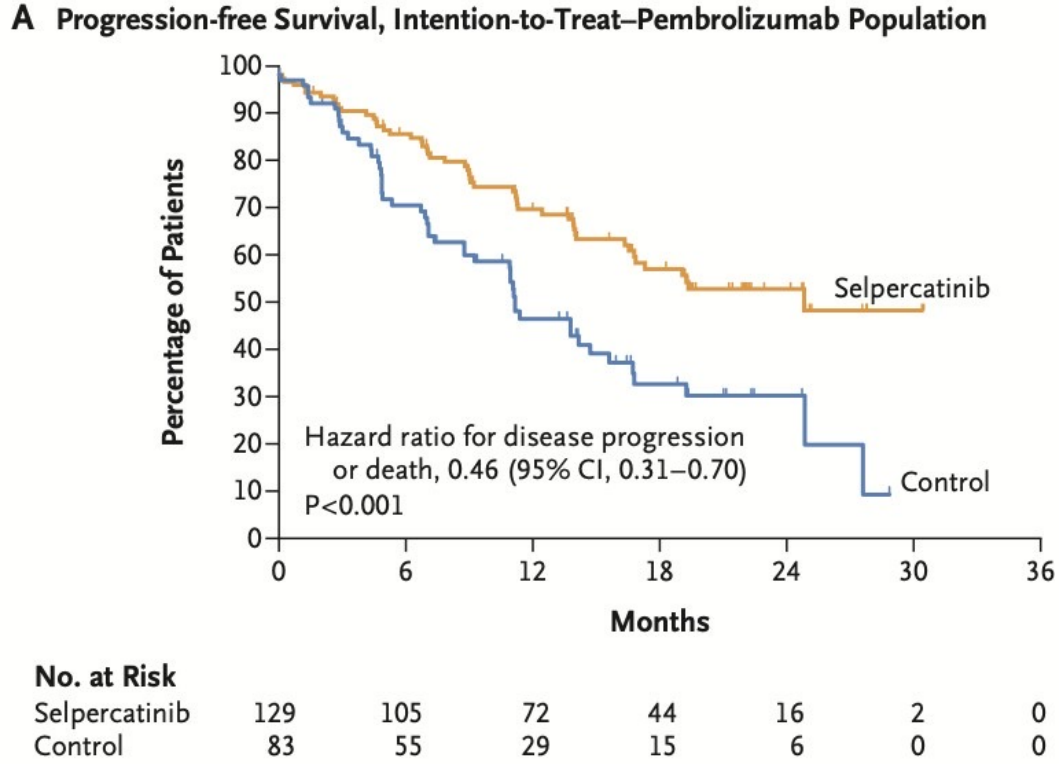
Treatment-related AE, *n* (%)	All (*n* = 281)	
	Any grade	Grade 3-4
Neutropenia	128 (46)	57 (20)
Leukopenia	96 (34)	22 (8)
Increased aspartate aminotransferase	114 (41)	8 (3)
Anaemia	108 (38)	35 (12)
Increased alanine aminotransferase	84 (30)	6 (2)
Constipation	73 (26)	2 (1)
Fatigue	70 (25)	5 (2)
Increased blood creatine phosphokinase	49 (17)	18 (6)
Hypertension	71 (25)	34 (12)
Taste disorder	39 (14)	0
Lymphopenia	42 (15)	24 (9)
Hyperbilirubinaemia	34 (12)	2 (1)
Thrombocytopenia	45 (16)	11 (4)
Oedema	49 (17)	0
Increased blood creatinine	41 (15)	1 (<1)
Diarrhoea	39 (14)	2 (1)
Dry mouth	35 (12)	0
Hyperphosphataemia	30 (11)	0
Pneumonitis	34 (12)	6 (2)
Increased blood alkaline phosphatase	25 (9)	3 (1)

Griesinger F et al. *Ann Oncol.* 2022 ;33(11):1168-1178.

ESTABLISHED IN 1812 NOVEMBER 16, 2023 VOL. 389 NO. 20

First-Line Selpercatinib or Chemotherapy and Pembrolizumab in *RET* Fusion–Positive NSCLC



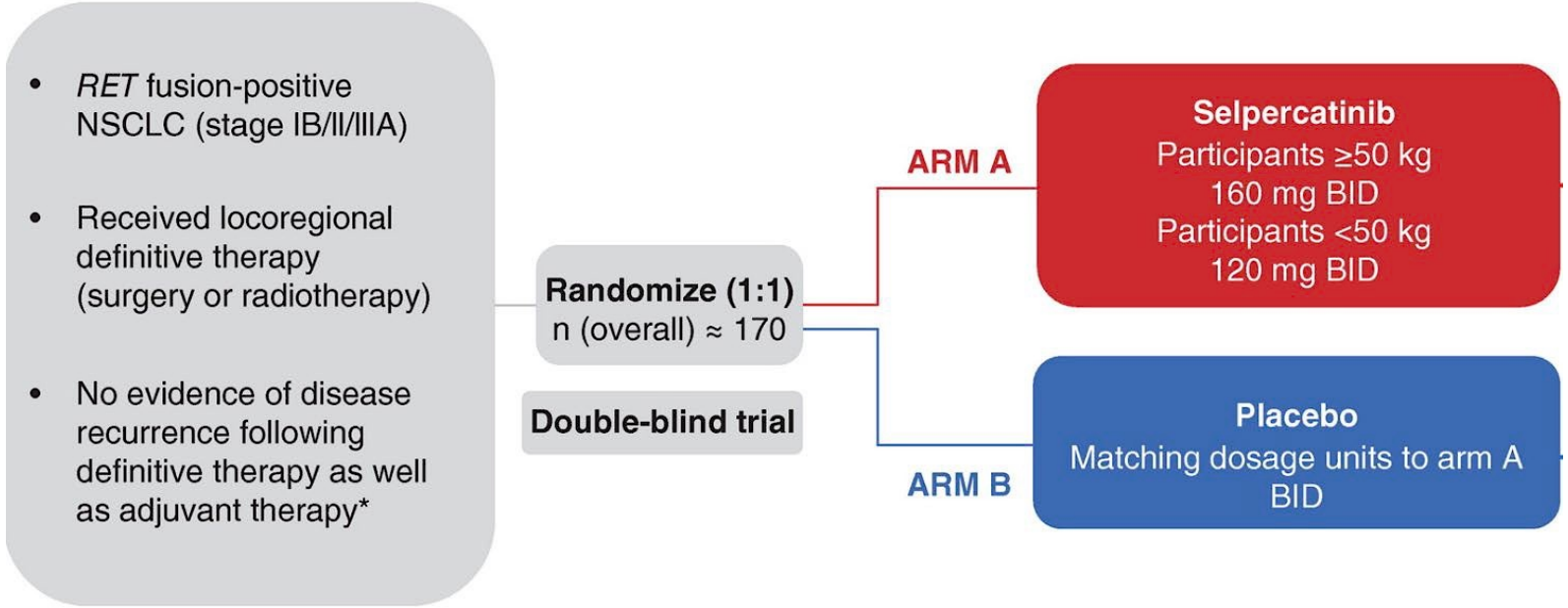


	Selpercatinib	Chemo + Pembro
PFS	24.8 mo	11.2 mo
ORR	84%	65%
DoR	24.2 mo	11.5 mo

UC San Diego Health

Zhou. NEJM. 2023;389:1839; Solomon. Future Oncology 2021;17:763-773

Libretto 432



EFS benefit has been reported for selpercatinib as adjuvant therapy in early stage RET fusion-positive NSCLC

February 16, 2026

Selpercatinib demonstrated a highly statistically significant and clinically meaningful improvement in reducing the risk of disease recurrence or death

Results from the LIBRETTO-432 trial build on previous results for selpercatinib in advanced NSCLC and reinforce the value of genomic testing at diagnosis and across all stages of disease

INDIANAPOLIS, Feb. 16, 2026 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced positive topline results from the Phase 3 LIBRETTO-432 clinical trial of Retevmo (selpercatinib) as adjuvant therapy versus placebo. The study met its primary endpoint, demonstrating a highly statistically significant and clinically meaningful improvement in investigator-assessed event-free survival (EFS) in patients with early-stage (II-IIIA) *rearranged during transfection (RET)* fusion-positive non-small cell lung cancer (NSCLC).

Overall survival results trended in favor of selpercatinib, but were immature at the time of this analysis with few events observed. The overall safety profile of selpercatinib in LIBRETTO-432 was generally consistent with previously reported trials in the selpercatinib development program.

Detailed results will be presented at an upcoming medical congress, submitted to a peer-reviewed journal, and discussed with health authorities globally.

https://investor.lilly.com/news-releases/news-release-details/lillys-retevmo-selpercatinib-delivers-substantial-event-free

UC San Diego Health

Summary

- RET fusions are targetable in NSCLC
- Selective RET inhibitors appear to be effective and well tolerated
  - Pralsetinib, selpercatinib
  - Both with extracranial and intracranial activity
- Drugs that address RET inhibitor resistance are in development

QUESTIONS?

Module 15: Targeted Therapies for NSCLC

Therapeutic Approaches Targeting HER2 and RET — Dr Bazhenova

Therapeutic Approaches Targeting ALK and ROS1 — Dr Langer

Penn Medicine
Abramson Cancer Center

Division of Hematology & Oncology

Targeting ALK and ROS1 in NSCLC: State-of-the-Art - 2026

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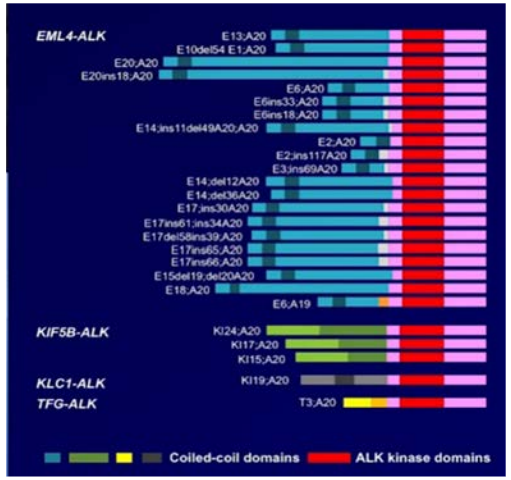
Disclosures

Advisory Committees	Oncocyte, Summit Therapeutics; Consulting Agreements: Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Caris Life Sciences, Fosun Pharma, Genentech, a member of the Roche Group, Gilead Sciences Inc, Guardant Health, Jazz Pharmaceuticals Inc, Merck, Novartis, Novocure Inc, Onyx Pharmaceuticals, an Amgen subsidiary, Pfizer Inc, Regeneron Pharmaceuticals Inc, Takeda Pharmaceuticals USA Inc
Contracted Research (Institutional Support)	Advangene, Amgen Inc, AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, FUJIFILM Pharmaceuticals USA Inc, Genentech, a member of the Roche Group, Guardant Health, Inovio Pharmaceuticals Inc, Lilly, Merck, Navire, Novocure Inc, Pfizer Inc, Takeda Pharmaceuticals USA Inc, Trizell
Data and Safety Monitoring Boards/Committees	Incyte Corporation, Summit Therapeutics
Research Colloquia	Aptitude Health
Nonrelevant Financial Relationships	Valor (VA)

ALK+ NSCLC in brief

1. Incidence of *ALK* rearrangements: 5-7% of all NSCLC*



*** Over 50.000 new cases/year worldwide**

2. Testing for *ALK* rearrangements is mandatory

COLLEGE of AMERICAN PATHOLOGISTS

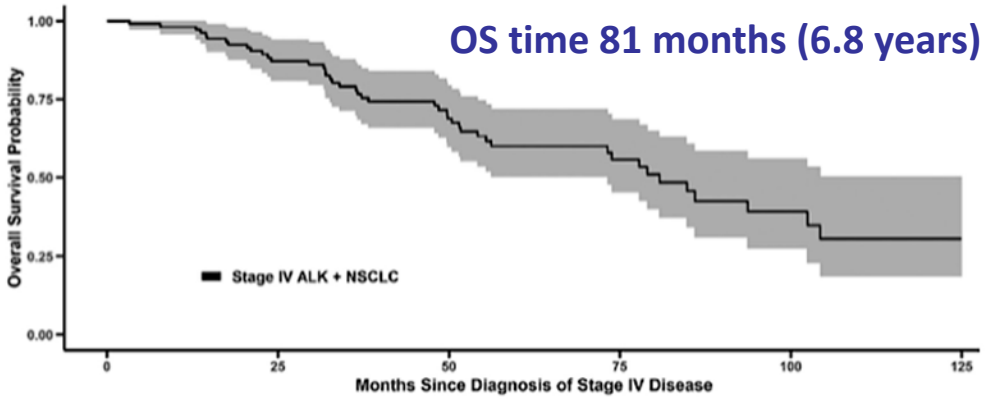
IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
Conquering Thoracic Cancers Worldwide

AMP ASSOCIATION FOR MOLECULAR PATHOLOGY

Molecular Testing Guideline for Selection of Lung Cancer Patients – Revision
2016 Draft Recommendations

Strong Recommendation: Physicians must use *EGFR* and *ALK* molecular testing for lung adenocarcinoma patients at the time of diagnosis for patients presenting with advanced stage disease or at progression in patients who originally presented with lower stage disease but were not previously tested.

3. ALK-Is are extending survival in *ALK+* NSCLC



4. No role for IT as single agent or in combination with ALK-Is

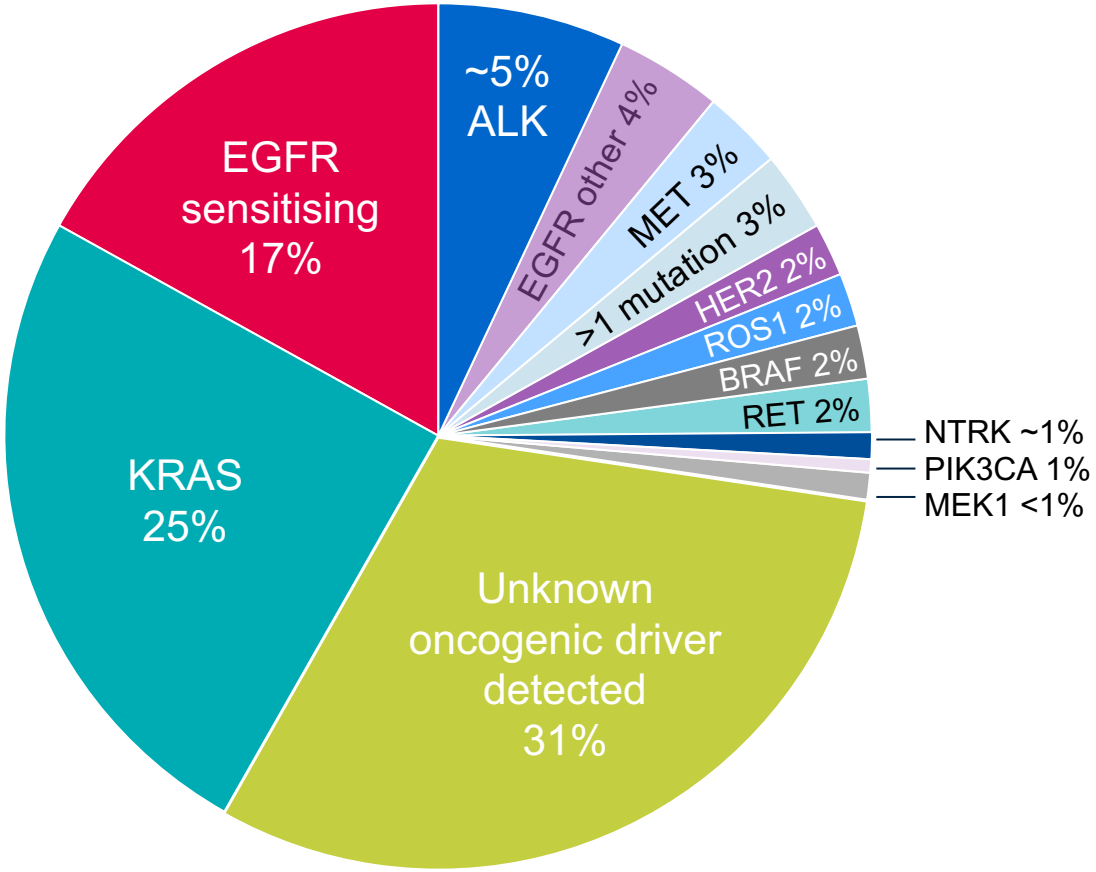
	EGFR	*ALK*	*ROS1*	*BRAF*	*KRAS*
Targeted therapy	**80%**[a]	**83%**	*77%*	*64%*	*54%*[b]
ICI	**11%**	**4%**	**14%**	**24%**	**57%**[c]
					25%
ICI + targeted therapy	*75%*[d]	*81%*[d]			
Chemotherapy + ICI	***81%***[a]	**NA**			***41%***

Penn Medicine
Abramson Cancer Center

1. Goodman, A. The ASCO Post. June 25, 2017, 2. Lindeman NI et al. Arch Pathol Lab Med 2018 Mar;142(3):321-346. 3. Pacheco JM et al. J Thorac Oncol . 2019 Apr;14(4):691-700 4. Calles A, et al.Am Soc Clin Oncol Educ Book . 2020 May:40:372-384.

ALK is an oncogenic driver mutation for a distinct subset of NSCLC

Driver mutations in lung cancer[1]



Patients tend to be…

Younger[2–4]

Median age ~52 years versus ~70 years for other types of NSCLC

Never or light smokers[3,5,6]

~70% patients with *ALK*+ NSCLC have never smoked

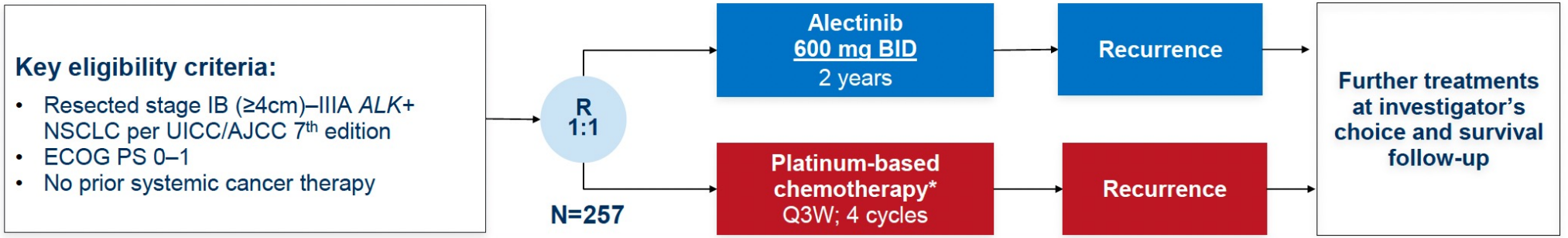
Advanced disease at presentation[7–9]

- Pleural/pericardial effusion
- Multiple lesions/sites
- Symptomatic
- CNS metastases – high propensity
- Poor prognosis without TKIs

1. Tsao, et al. J Thorac Oncol 2016;
2. Chia, et al. Clin Epidemiol 2014;
3. Camidge, et al. Lancet 2012;
4. SEER Cancer Stat Fact Sheets Lung and Bronchus Cancer
5. Tao, et al. Thorac Cancer 2017
6. Kayaniyil, et al. Curr Oncol 2016;
7. Solomon, et al. N Engl J Med 2014;
8. Soria, et al. Lancet 2017;
9. Peters, et al. N Engl J Med 2017

ALINA: phase III, open-label superiority study

- **Alectinib**, an ALK inhibitor, is an approved **standard-of-care** for patients with **resected or advanced *ALK*+ NSCLC**[1–3]
  - Alectinib has **demonstrated efficacy and delayed disease progression in the CNS**[1–3]
  - Long-term data show alectinib is tolerable and has a manageable safety profile[1–3]
- **ALINA** is the only **positive phase III trial** of an ALK inhibitor in **resectable, stage IB–IIIA** (UICC/AJCC 7th edition), *ALK*+ NSCLC[2–4]
  - The primary analysis showed a **significant DFS benefit** with alectinib vs chemotherapy (**HR: 0.24**; 95% CI 0.13–0.43; p<0.0001)[2,3]



Here, we present updated data from the ALINA study with a median follow-up of 4 years
All patients in the alectinib arm had completed 2 years of treatment with ≥1 year of follow-up

NCT03456076. Crossover was not permitted prior to disease recurrence. *Cisplatin + pemetrexed, cisplatin + vinorelbine or cisplatin + gemcitabine; cisplatin could be switched to carboplatin in case of intolerability. †Stratification by patient race recorded in the interactive voice/web response system. 1. Alecensa Prescribing Information Genentech Inc. 2024; 2. Solomon et al. ESMO 2023 (LBA2); 3. Wu et al. N Engl J Med 2024; 4. Ahn et al. ESMO Asia 2023 (LBA1). *ALK*, anaplastic lymphoma kinase; AJCC, American Joint Committee on Cancer; BID, twice daily; CI, confidence interval; CNS, central nervous system; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ITT, intention to treat OS, overall survival; Q3W, every 3 weeks; R, randomisation; UICC, Union for International Cancer Control

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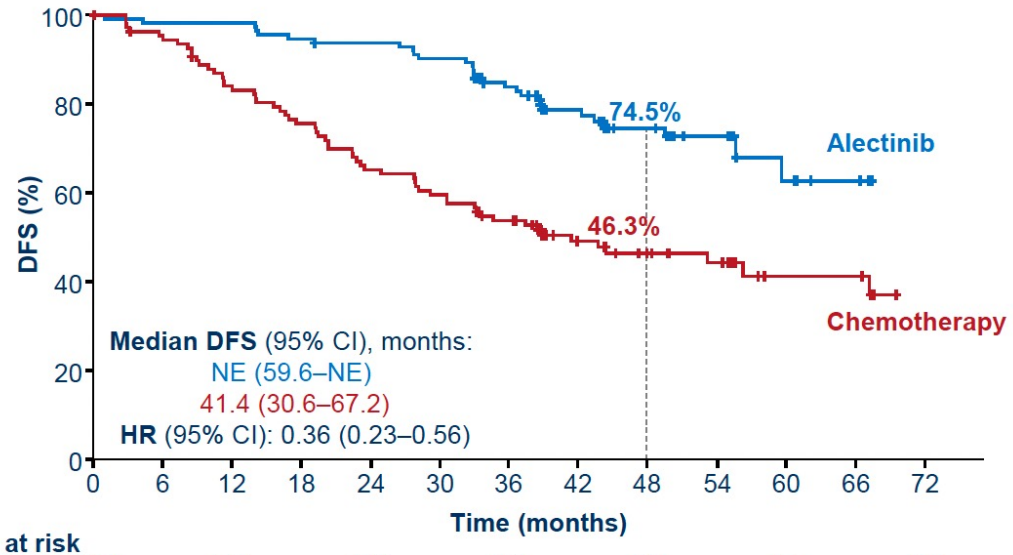
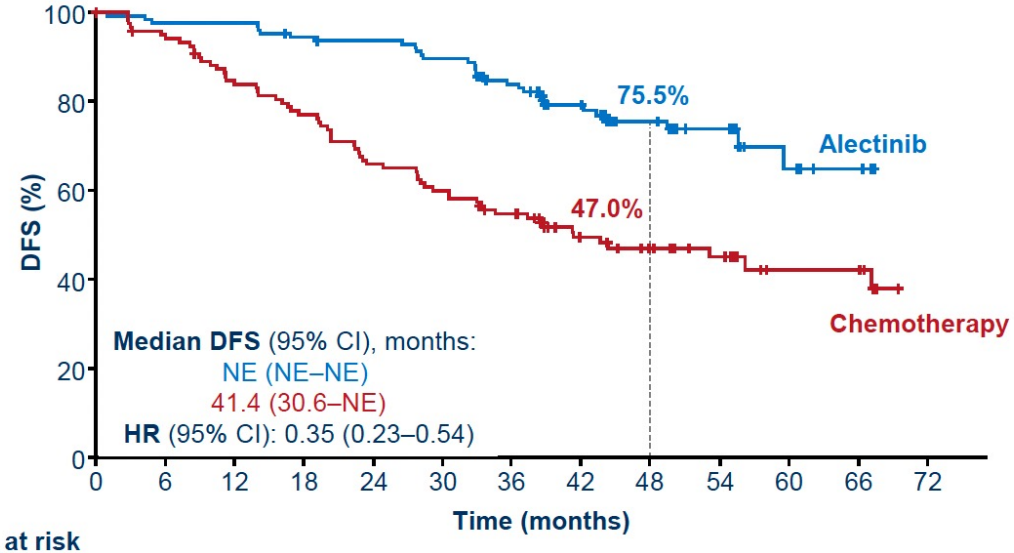
ALINA: Disease-free survival

DFS in stage II–IIIA*



No. at risk							
Alectinib	116	111	105	87	43	12	NE
Chemo	115	88	69	54	28	11	NE

DFS in stage IB–IIIA (ITT)*



No. at risk							
Alectinib	130	123	116	97	48	13	NE
Chemo	127	98	77	61	33	12	NE

Median follow-up (ITT): alectinib, 48.0 months; chemotherapy, 47.4 months

DFS benefit was sustained with alectinib versus chemotherapy in the stage II–IIIA and stage IB-IIIA (ITT) populations

Data cut-off: 8 December 2024. DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurred first
*Per UICC/AJCC 7th edition. Chemo, chemotherapy; NE, not estimable

Prof. Rafal Dziadziuszko

BERLIN 2025 ESMO congress

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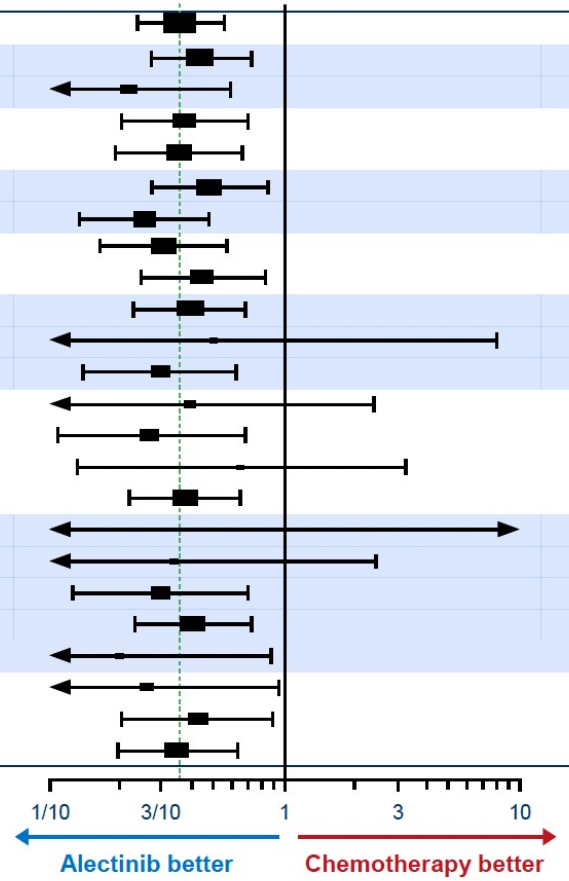
Disease-free survival subgroup analysis (ITT)

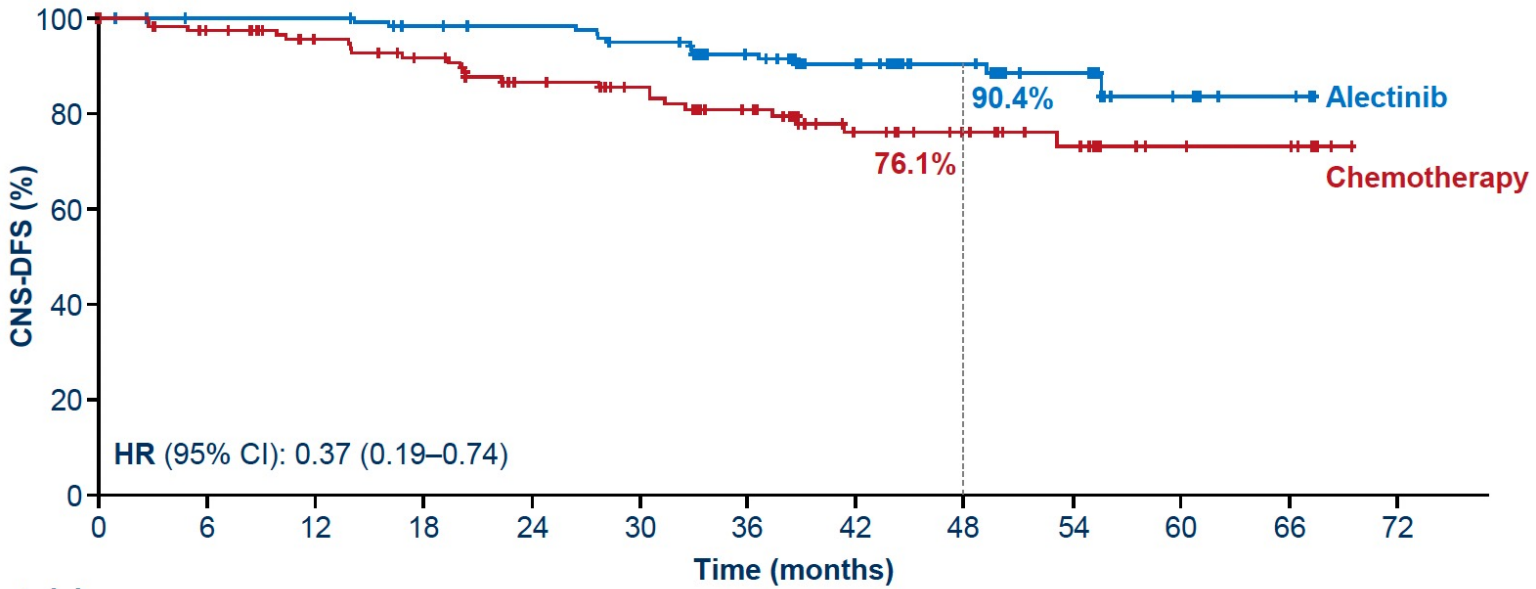
Subgroup		No. events / patients	HR (95%CI)
All patients		94 / 257	0.36 (0.24–0.56)
Age, years	<65	67 / 196	0.44 (0.27–0.72)
	≥65	27 / 61	0.22 (0.08–0.59)
Sex	Male	50 / 123	0.38 (0.20–0.70)
	Female	44 / 134	0.36 (0.19–0.65)
Race (IxRS)	Asian	49 / 143	0.48 (0.27–0.86)
	Non-Asian	45 / 114	0.25 (0.13–0.48)
ECOG performance status at baseline	0	47 / 137	0.31 (0.17–0.57)
	1	47 / 120	0.45 (0.25–0.83)
Tobacco use history	Never	52 / 154	0.40 (0.23–0.69)
	Current	3 / 8	0.50 (0.03–7.99)
	Previous	39 / 95	0.30 (0.14–0.63)
Stage per AJCC 7th edition (eCRF)	Stage IB	5 / 26	0.40 (0.07–2.41)
	Stage IIA	25 / 81	0.27 (0.11–0.69)
	Stage IIB	6 / 10	0.66 (0.13–3.29)
	Stage IIIA	58 / 140	0.38 (0.22–0.65)
Stage per AJCC 8th edition (eCRF)	Stage IB	1 / 11	<0.01 (0.00–NE)
	Stage IIA	4 / 15	0.34 (0.05–2.46)
	Stage IIB	27 / 85	0.30 (0.13–0.70)
	Stage IIIA	53 / 133	0.41 (0.23–0.72)
	Stage IIIB	9 / 13	0.20 (0.04–0.88)
Regional lymph node status	N0	12 / 39	0.26 (0.07–0.95)
	N1	31 / 88	0.43 (0.20–0.89)
	N2	51 / 130	0.35 (0.20–0.64)



Prof. Rafal Dziadziuszko

Data cut-off: 8 December 2024. eCRF, electronic case report form; IxRS, interactive voice response system

CNS disease-free survival in the ITT population



No. at risk							
Alectinib	130	124	117	98	49	13	NE
Chemo	127	99	80	61	33	13	NE

Median follow-up (ITT): alectinib, 48.0 months; chemotherapy, 47.4 months

A clinically meaningful CNS-DFS benefit was maintained in the IB–IIIA* (ITT) population

Prof. Rafal Dziadziuszko

Data cut-off: 8 December 2024. CNS-DFS defined as time from randomisation to the first documented recurrence of disease in the CNS or death from any cause, whichever occurred first. *Per UICC/AJCC 7th edition

Other key trials of alectinib in stage I–III NSCLC

NAUTIKA-1

NCT04302025

Phase II study in **resectable stage IB–IIIA NSCLC,** which includes a cohort of patients receiving **perioperative alectinib**[1]

HORIZON-1

NCT05170204

Phase III, open-label, randomised cohort of patients with **unresectable stage III, *ALK*+ NSCLC** receiving **alectinib** vs durvalumab following chemoradiotherapy

1. Lee et al. WCLC 2023 (Abs EP02.04)

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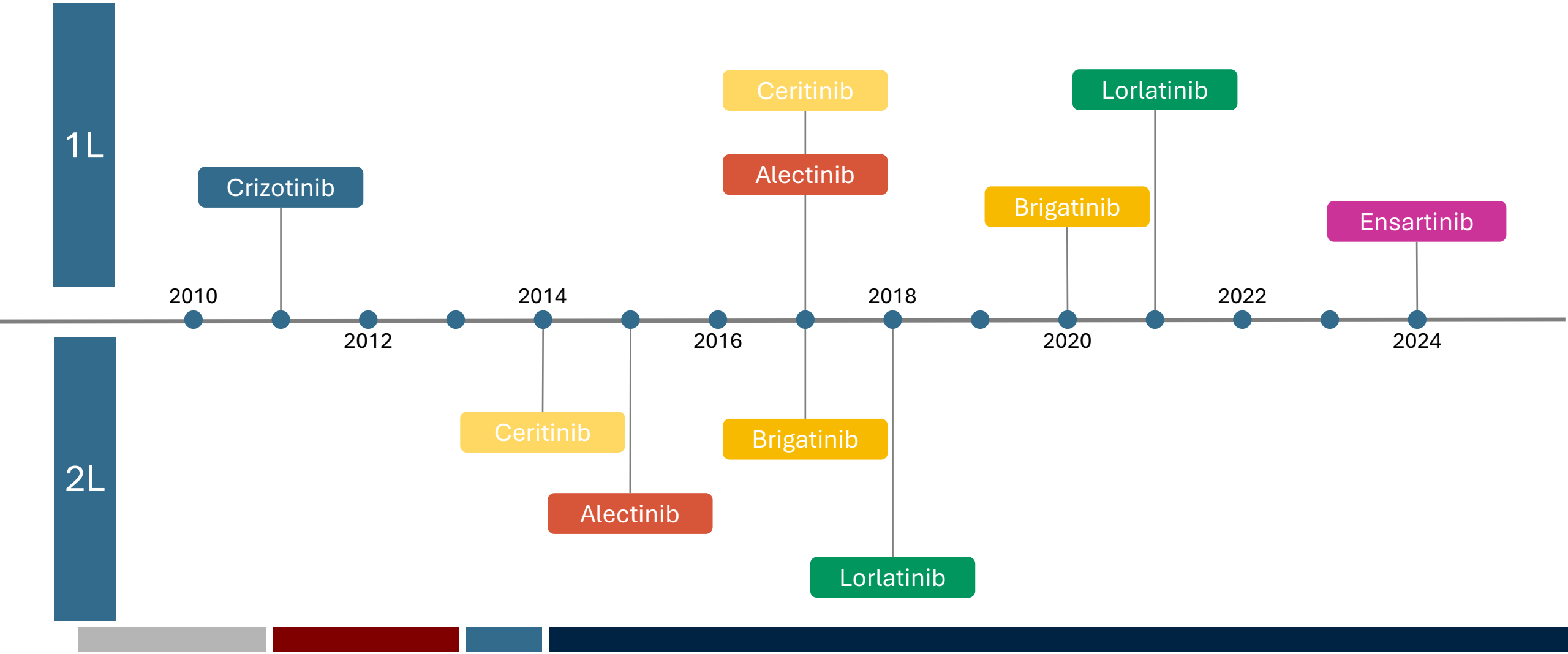
How do we manage advanced/metastatic *ALK*+ NSCLC?



XALKORI (crizotinib) US PI; XALKORI (crizotinib) SmPC; ZYKADIA (ceritinib) US PI; ZYKADIA (ceritinib) SmPC; TECENTRIQ (atezolizumab) US PI; TECENTRIQ (atezolizumab) SmPC; ALUNBRIG (brigatinib) US PI; ALUNBRIG (brigatinib) SmPC; LORBRENA (lorlatinib) US PI; LORVIQUA (lorlatinib) SmPC; ENSACOVE (ensartinib) US PI

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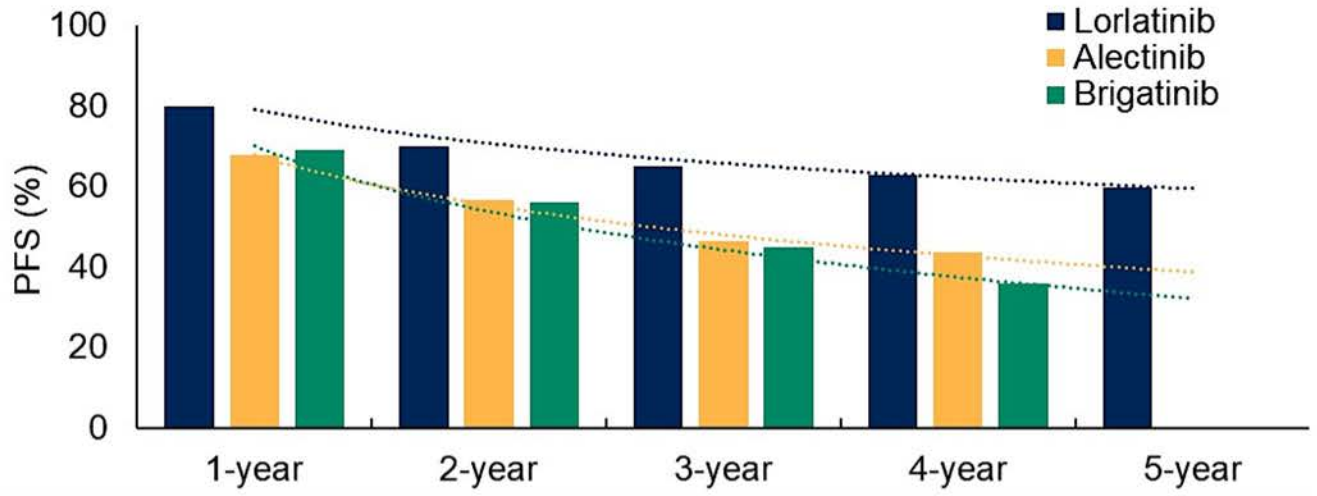
Efficacy of Next-Generation ALK TKIs for 1L Treatment of ALK+ NSCLC

	ALECTINIB (Global ALEX[1,2])	BRIGATINIB (ALTA-1L[3,4])	ENSARTINIB* (eXalt-3[5])	LORLATINIB (Interim CROWN[6,7])
Comparator	Crizotinib	Crizotinib	Crizotinib	Crizotinib
N	ALEC: 152 CRZ: 151	BRIG: 137 CRZ: 138	ENSAR: 143 CRZ: 147	LOR: 149 CRZ: 147
PFS, median (BIRC)	**ALEC: 34.8 mos** CRZ: 10.4 mos **HR 0.43 (0.32–0.58)**	**BRIG: 24.0 mos** CRZ: 11.0 mos **HR 0.48 (0.35-0.66)**	**ENSAR: 25.8 mos** CRZ: 12.7 mos **HR 0.51 (0.35-0.72)**	**LOR: NR** CRZ: 9.6 mos **HR 0.27 (0.18-0.39)**
Median follow-up for PFS above	ALEC: 18.6 mos CRZ: 17.6 mos	BRIG: 40.4 mos CRZ: 15.2 mos	ENSAR: 23.8 mos CRZ: 20.2 mos	LOR: 36.7 mos CRZ: 29.3 mos
CNS mets at baseline	ALEC: 42% CRZ: 38%	BRIG: 29% CRZ: 30%	ENSAR: 33% CRZ: 39%	LOR: 26% CRZ: 27%
PFS in pts with brain mets	ALEC: 25.4 mos^ CRZ: 7.4 mos^ **HR 0.37 (0.23-0.58)**	BRIG: 24.0 mos CRZ: 5.6 mos **HR 0.25 (0.14-0.46)**	ENSAR: 11.8 mos CRZ: 7.5 mos **HR 0.55 (0.30-1.01)**	LOR: NR CRZ: 7.2 mos **HR 0.21 (0.10-0.44)**
PFS in pts without brain mets	ALEC: 38.6 mos^ CRZ: 14.8 mos ^ **HR 0.46 (0.31-0.68)**	BRIG: 24.0 mos CRZ: 13.0 mos **HR 0.62 (0.43-0.91)**	ENSAR: NR CRZ: 16.6 mos **HR 0.40 (0.23-0.70)**	LOR: NR CRZ: 11.0 mos **HR 0.29 (0.19-0.44)**
ORR	ALEC: 83%^ CRZ: 76%^	BRIG: 74% CRZ: 62%	ENSAR: 74% CRZ: 67%	LOR: 77% CRZ: 58%

^By investigator assessment. **Investigational (not FDA-approved)*

[1]Peters S, et al. *N Engl J Med*. 2017;377(9):829-838. [2]Mok T, et al., *Ann Oncol*. 2020; [3] Camidge DR, et al. *N Engl J Med*. 2018;379(21):2027-2039. [4]Camidge DR, et al. *J Thorac Oncol*. 2021;16(12):2091-2108. [5]Horn L, et al. *JAMA Oncol*. 2021;7(11):1617-1625. [6] Shaw AT, et al. *N Engl J Med*. 2020;383(21):2018-2029. [7]Solomon BJ, et al. Presented at: AACR;2022. Abstract CT223.

Evaluating CROWN in the context of ALK treatment landscape: systemic efficacy



	Median PFS	1-year PFS (%)	2-year PFS (%)	3-year PFS (%)	4-year PFS (%)	5-year PFS (%)
Lorlatinib[1-3]	**Not reached at 60.2 mos**	80	70	63	63	60
Alectinib[4]	**34.8 mos**	67.8	56.6	46.4	43.7	N/A
Brigatinib[5-7]	**30.8 mos**	69	56	45	36	N/A

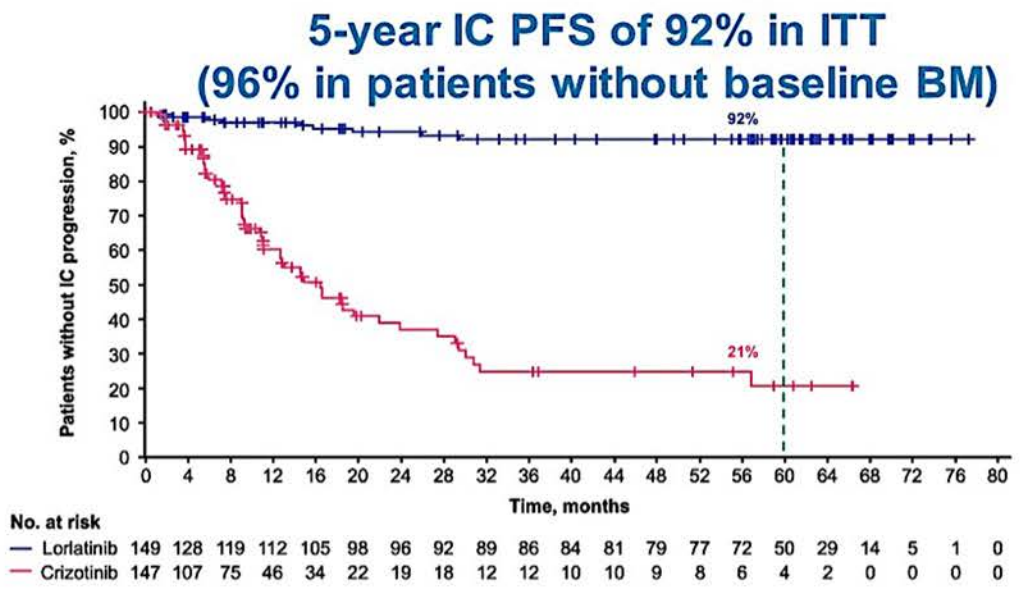
**PFS results per investigator assessment in CROWN, global ALEX (alectinib), and ALTA-1L (brigatinib) trials. N/A, not available; mos, months*

1. Shaw AT et al., N Engl J Med 2020;383:2018-29
2. Solomon BJ et al., Lancet Respir Med 2023;11(4):354-66
3. Solomon BJ et al., ASCO 2024
4. Mok T et al., Ann Oncol 2020;31(8):1056-64
5. Camidge DR et al., N Engl J Med 2018; 379:2027-39
6. Camidge DR et al., J Clin Oncol 2020;38(31):3592-603
7. Camidge DR et al., J Thorac Oncol 2021;16(12):2091-108

PRESENTED BY: Jessica J. Lin (jjlin1@mgb.org)

Evaluating CROWN in the context of ALK treatment landscape: CNS efficacy

- **Brain metastases are common** at initial diagnosis (25-40%) and cumulatively (>70% at 5 years)[1-2]
- Despite CNS activity of 2G ALK TKIs, **CNS relapses** occur
  - **1L Alectinib**: 12-month cumulative incidence rate for CNS progression 9.4%[3]
  - **1L Brigatinib**: 3-year intracranial PFS rate 57%[4]

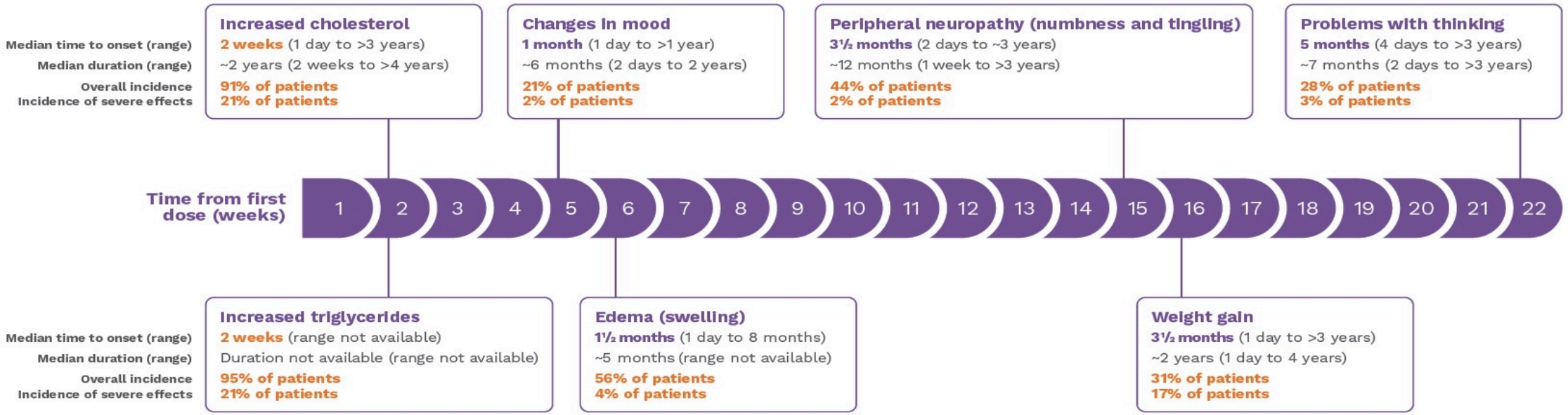


	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	9	65
Time to IC progression, median (95% CI), months	NR (NR-NR)	16.4 (12.7-21.9)
HR (95% CI)	**0.06 (0.03-0.12)**	

1. Gainor JF et al., JCO Precis Oncol 2017:PO.17.00063; 2. Pacheco JM et al., J Thorac Oncol 2019;14(4):691-700
3. Peters S et al., N Engl J Med 2017;377(9):829-38; 4. Camidge DR et al., J Thorac Oncol 2021;16(12):2091-108

PRESENTED BY: Jessica J. Lin (jjlin1@mgb.org)

Timing and Incidence of Most Common Adverse Reactions Based on Data from the CROWN and Phase I/2 Trials

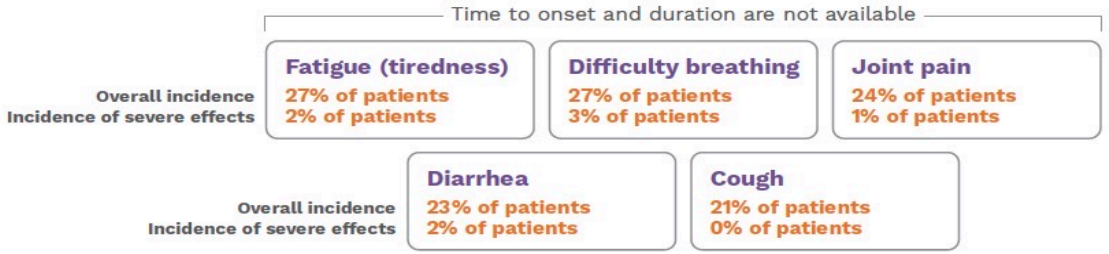


UNDERSTANDING THE TIMELINE

- Data that are from the Lorlatinib Prescribing Information are in orange; data from published medical journal articles are in black
- **Median** is a statistics term. It is the middle value in a set of measurements
- **Changes in mood** include, for example, depression and irritability
- **Problems with thinking** include, for example, forgetfulness and confusion
- **Severe side effects** are medically significant and may mean that you will have to go to the hospital or stay longer in the hospital. They can make daily self-care difficult. Some severe side effects are life-threatening and should be treated right away

In some patients in the CROWN trial, Lorlatinib dosing was adjusted or stopped to manage side effects

- Lorlatinib was stopped for a period of time in 49% of patients, the Lorlatinib dose was reduced in 21% of patients, and Lorlatinib was completely stopped in 7% of patients



Patient Guide to Common Side Effects of Lorlatinib
- PP-LOR-USA-0557-LORBRENA-Patient-AE-Timeline-Digital
- https://www.lorbrena.com/files/PP-LOR-USA-0557-LORBRENA-Patient-AE-Timeline-Digital.pdf

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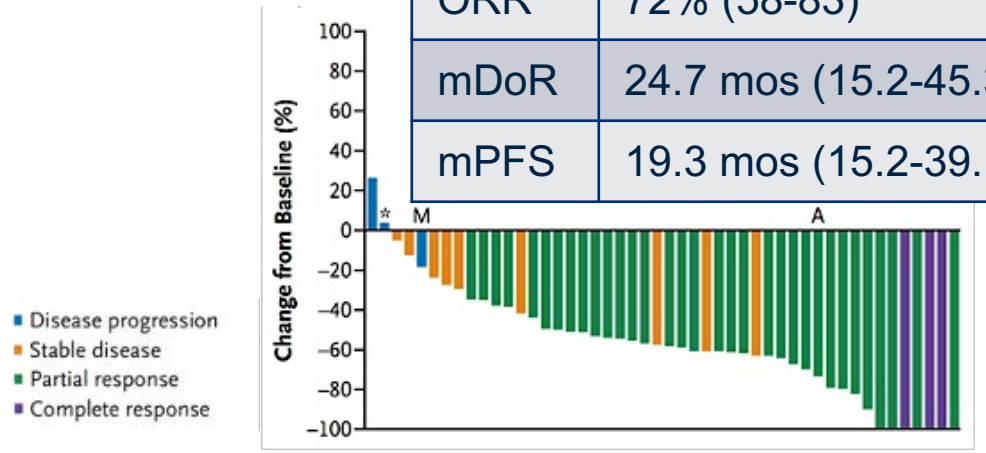
ALK Inhibition: Conclusions

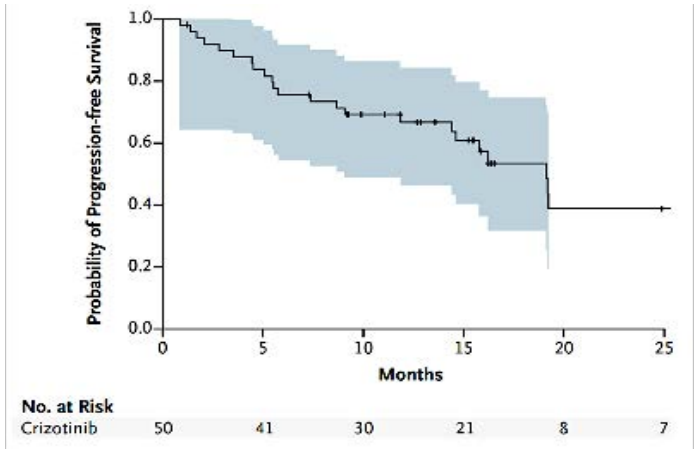
- Alk fusions: 3-8% of all NonSq NSCLC
  - Younger pts; minimal or no smoking hx; aggressive clinical course
  - High propensity for CNS invasion
- TKIs: standard of care
  - LTS: previously < 12-18 mos, now 6-8+ yrs
  - US: Alectinib vs Lorlatinib: latter appears to have better PFS, potentially more CNS penetrance; but clearly heightened toxicity
- Salvage Tx: depends on initial choice of TKI and subsequent NGS testing
  - Final common pathway: Pem/Carbo +/- Bev
  - CPIs: marginal, if any activity
- Clear role in Adjuvant setting (Optimal Duration and Need for DDP in question)

Standard 1L ROS1 TKIs
Crizotinib and Entrectinib: Systemic Efficacy

Crizotinib

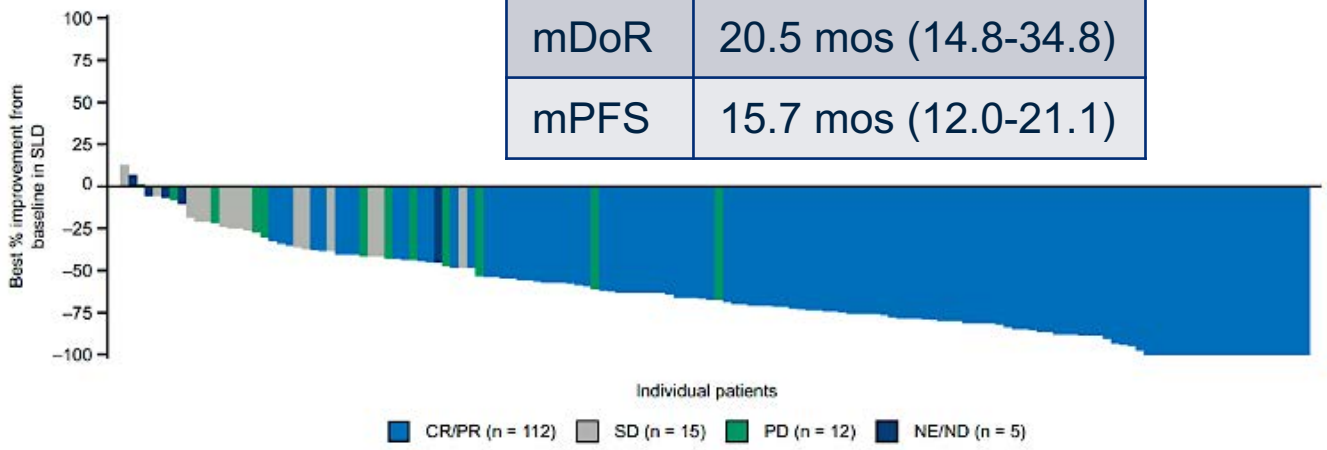
ORR	72% (58-83)
mDoR	24.7 mos (15.2-45.3)
mPFS	19.3 mos (15.2-39.1)

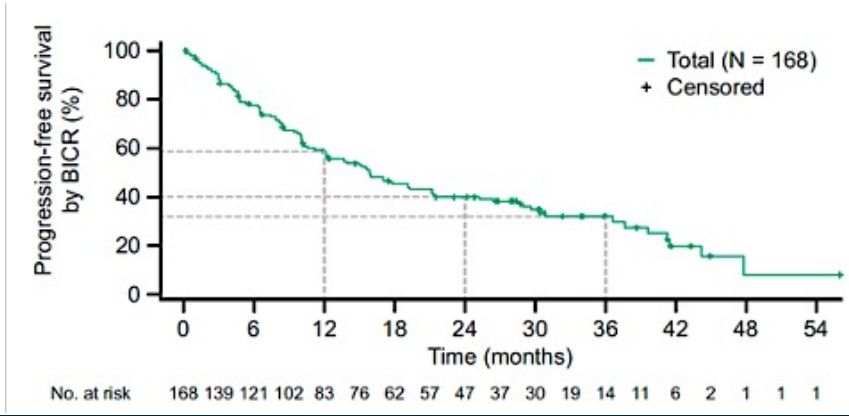




Entrectinib

ORR	68% (60-75)
mDoR	20.5 mos (14.8-34.8)
mPFS	15.7 mos (12.0-21.1)





Shaw AT, et al. *N Engl J Med*. 2014;371:1963-71.

Shaw AT, et al. *Ann Oncol*. 2019;30:1121-6. Drilon A, et al. *JTO Clin Res Rep*. 2022;3:100332.

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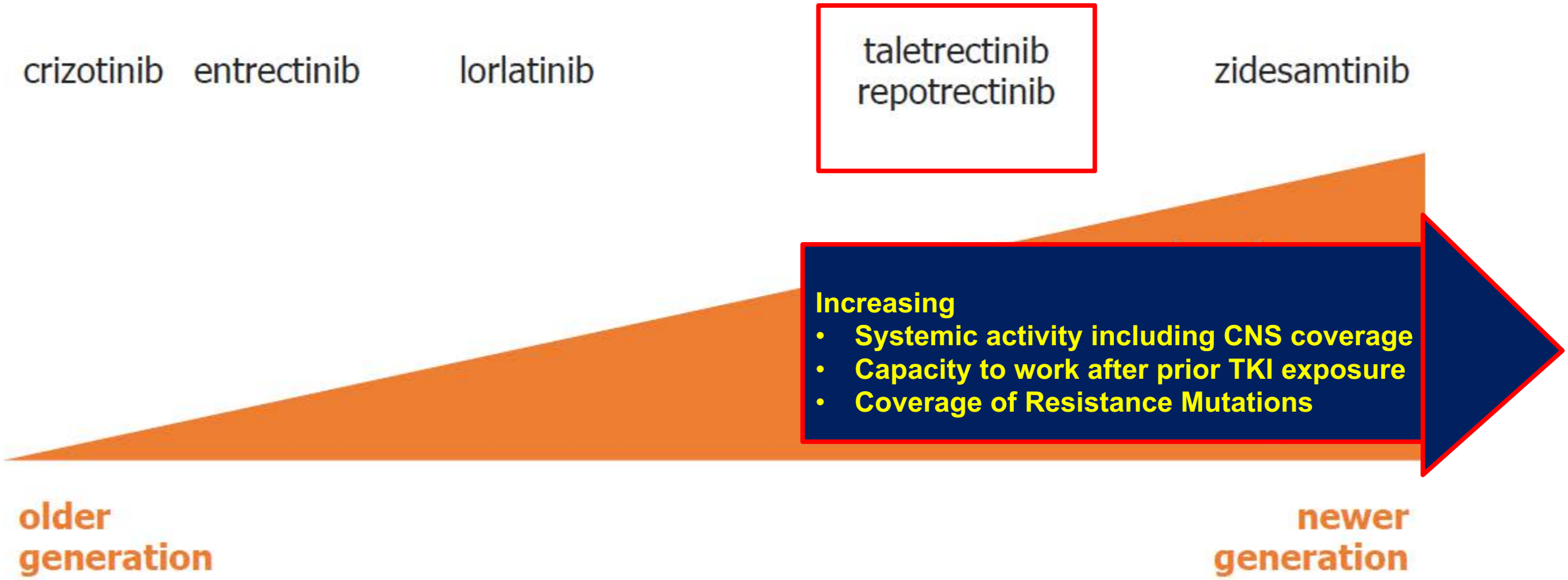
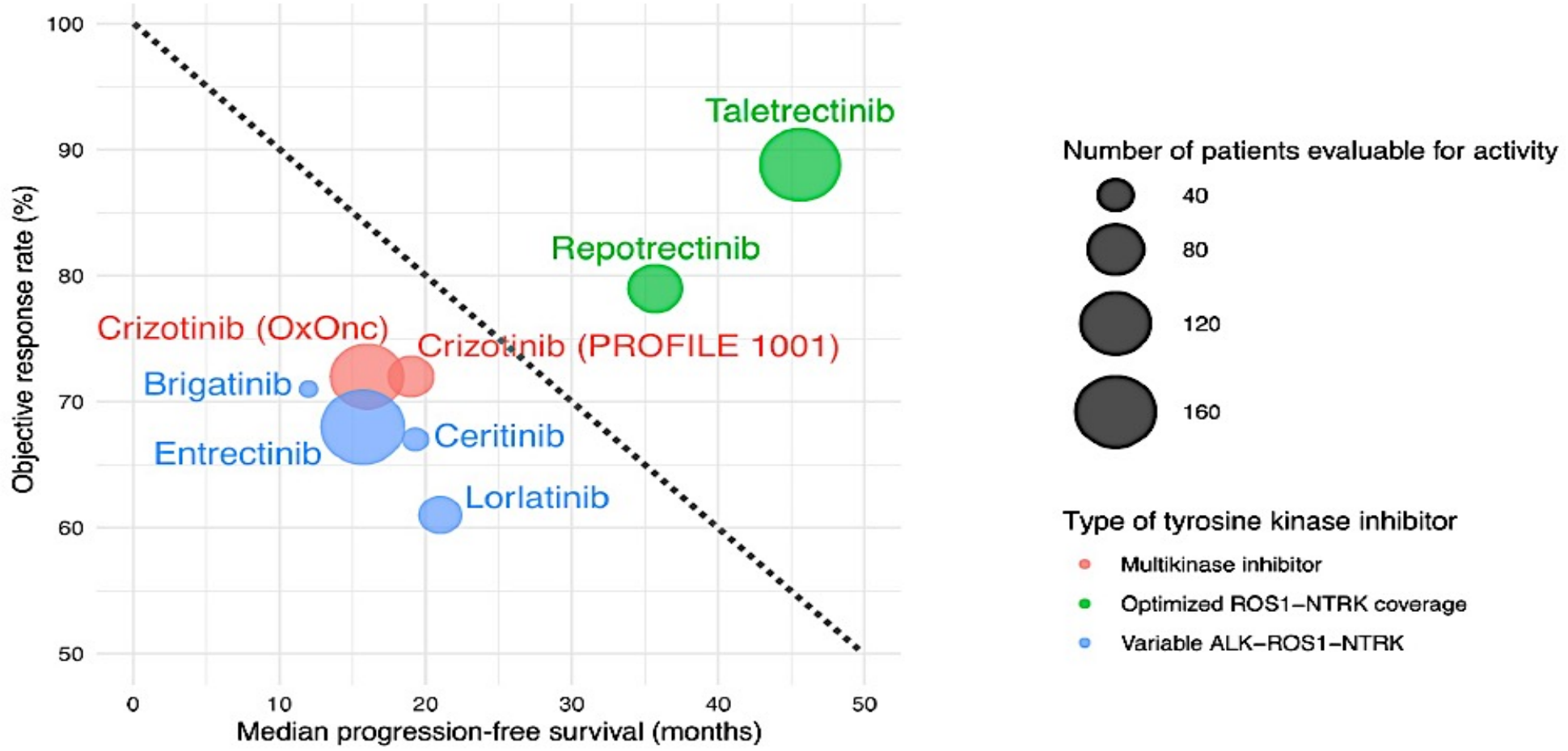
Evolving Specificity of ROS1 Inhibitors over Time



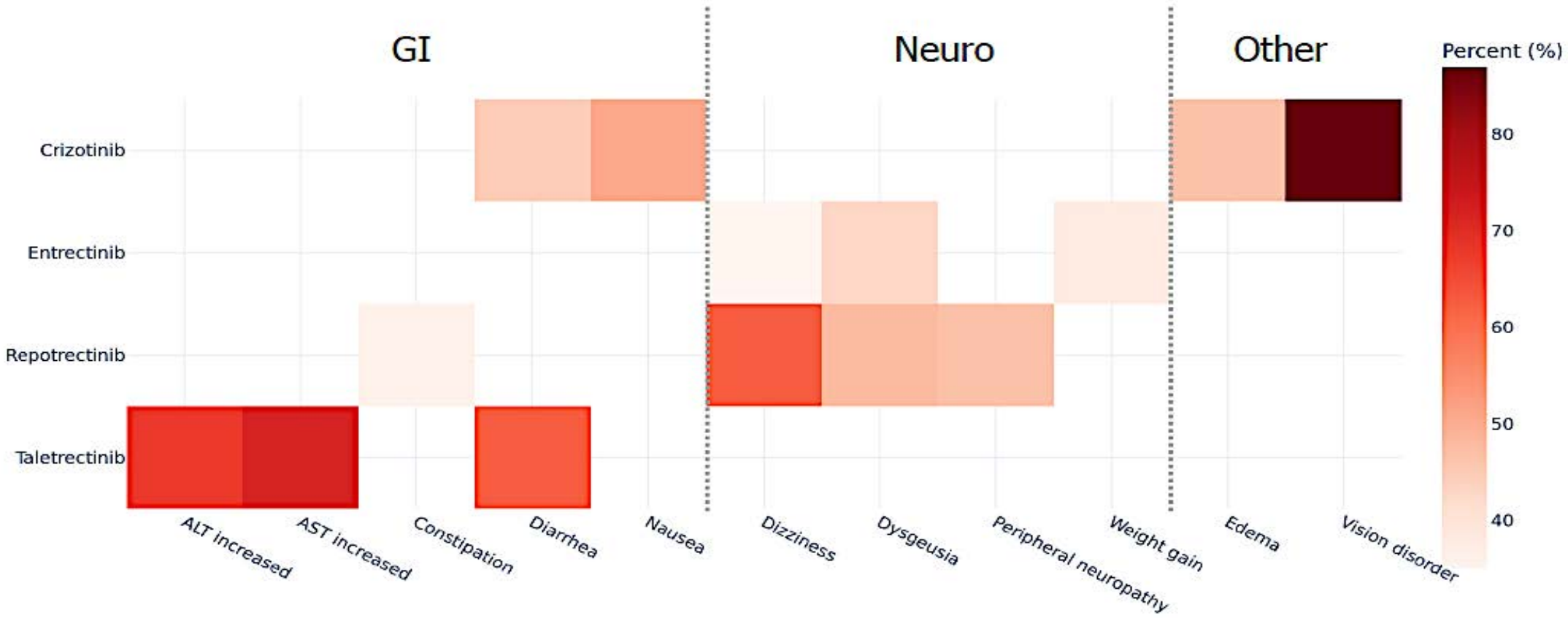
only includes ROS1 TKIs with regulatory approval in 1 or more regions, breakthrough designation, or guidelines listing

Activity of TKIs in TKI-Naïve ROS1 (+) mNSCLC



Desilets et al, Cancer 2025

Differential Safety Profiles of ROS1 TKIs

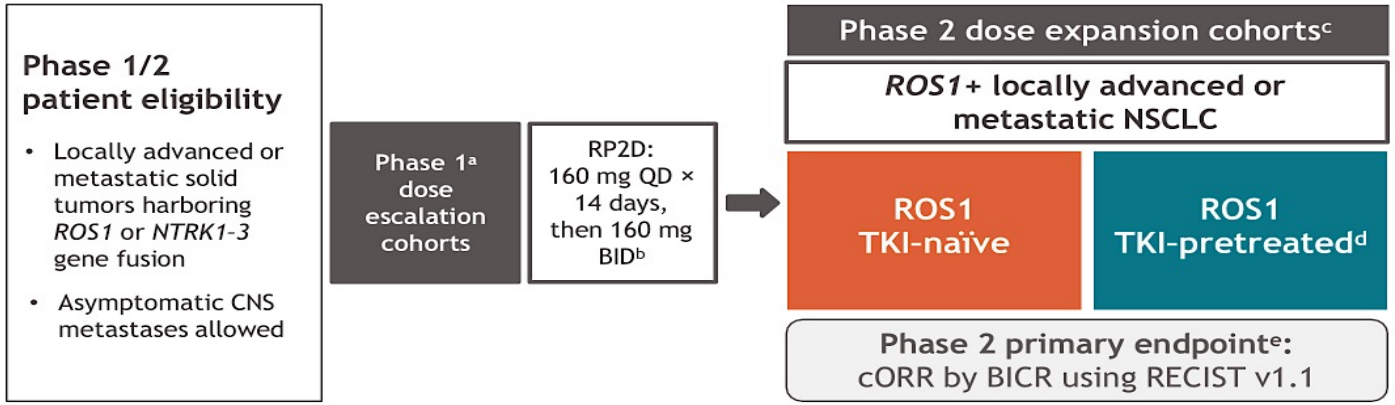


Perol et al, JCO 2025; Drilon et al, NEJM 2024; Dziadziuskszko et al, JCO 2021; Shaw et al, Ann Oncol 2019

Repotrectinib – TRIDENT-1

Introduction and study design

- Repotrectinib is a next-generation ROS1 and TRK TKI approved for treatment of adult patients with locally advanced or metastatic *ROS1*+ NSCLC and adult or pediatric patients (≤ 12 y) with locally advanced or metastatic *NTRK*+ solid tumors based on results from the TRIDENT-1 trial (NCT03093116)[1,2]
- Here, we report long-term follow-up from TRIDENT-1 (median follow-up, ≥ 42 months) in patients with *ROS1*+ NSCLC



- **Primary efficacy population** included patients pooled from phase 1/2[f] who initiated repotrectinib at any dose prior to October 15, 2021
- **Expanded efficacy population** included patients pooled from phase 1/2[f] who initiated repotrectinib at any dose before March 29, 2023
- **Safety population** included all patients treated at the RP2D

Data cutoff date: September 3, 2024.

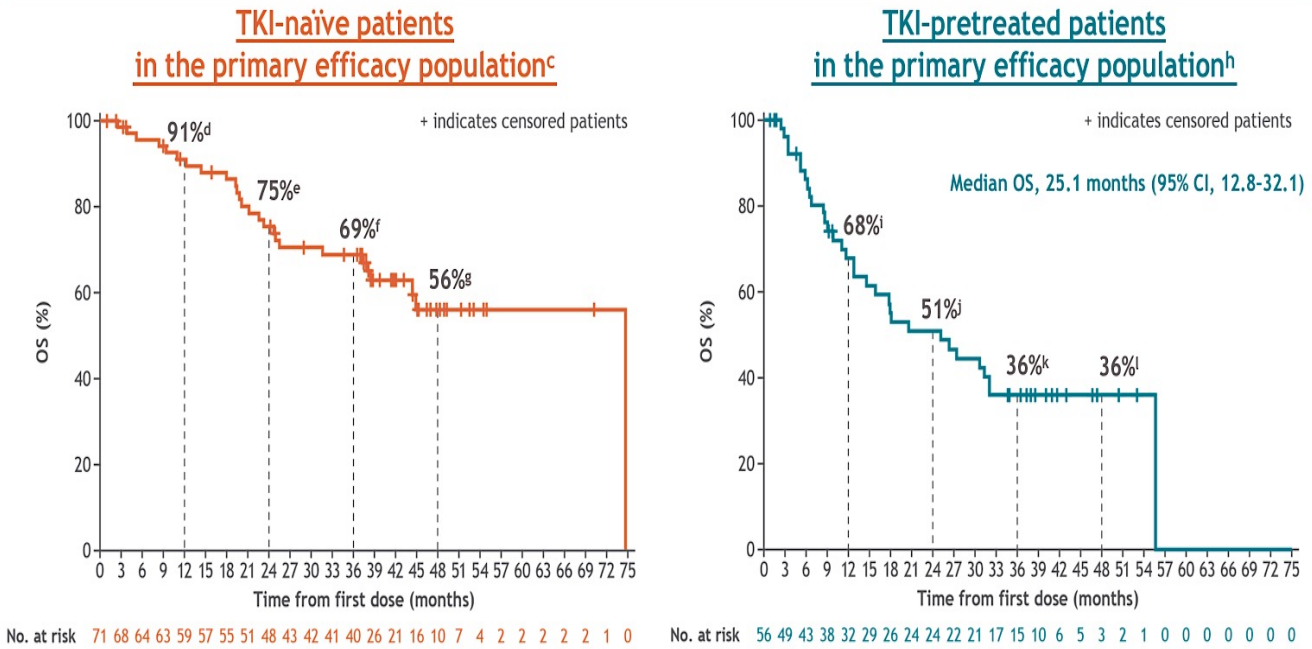
[a]Phase 1 primary endpoints: DLT, MTD, RP2D. Phase 1 secondary endpoints: safety and tolerability, PK, food effect on PK, preliminary ORR per BICR, CBR, CYP3A induction potential. [b]Based on tolerability. [c]Study design includes 2 additional cohorts of patients with *ROS1* fusions (1 prior ROS1 TKI with 1 prior platinum-based chemo and 2 prior ROS1 TKIs with no prior chemo) and 2 cohorts of patients with *NTRK* fusions (TRK TKI-naïve and TRK TKI-pretreated) not presented here. [d]Herein, ROS1 TKI-pretreated refers to the cohort of patients with 1 prior ROS1 TKI and no prior chemo. [e]Phase 2 secondary endpoints: DOR, CBR, TTR, cORR in TKI-pretreated patients harboring *ROS1* G2032R, and PFS by RECIST v1.1, OS, icORR by modified RECIST v1.1 in patients with measurable brain metastases, safety, and patient-reported outcomes. [f]Patients from phase 1 received 40 mg QD to 160 mg QD.

1. AUGTYRO® (repotrectinib) [package insert]. Princeton, NJ: Bristol Myers Squibb; June 2024.
2. AUGTYRO® [repotrectinib] {summary of product characteristics}. Dublin, Ireland: Bristol-Myers Squibb Pharma EEIG; January 2024.

Repotrectinib – TRIDENT-1

TRIDENT-1 long-term follow-up: repotrectinib in *ROS1*+ NSCLC

OS in patients with *ROS1*+ locally advanced or metastatic NSCLC[a,b]



- **In the expanded efficacy population**,[m] median OS was 74.6 months (95% CI, 44.4-NE) for TKI-naïve patients (n = 121) and 20.5 months (95% CI, 17.8-31.4) for TKI-pretreated patients (n = 107)

[a]Among patients in the primary efficacy population treated at the RP2D, median OS was NE (95% CI, 38.0-NE) for TKI-naïve patients (n = 63) and 20.5 months (95% CI, 12.8-32.1) for TKI-pretreated patients (n = 53). [b]Among 1L treatment-naïve patients in the TKI-naïve cohort of the primary efficacy population (n = 51), median OS was NE (95% CI, 38.0-NE). [c]Number of events = 26 (37%). [d]95% CI, 81-96. [e]95% CI, 63-84. [f]95% CI, 56-79. [g]95% CI, 41-69. [h]Number of events = 32 (57%). [i]95% CI, 53-79. [j]95% CI, 36-64. [k]95% CI, 23-49. [l]95% CI, 23-49. [m]Median follow-up was 37.7 months for TKI-naïve patients and 34.8 months for TKI-pretreated patients.

WCLC '25: MA02.03 – Repotrectinib in Patients With ROS1 Fusion-Positive (ROS1+) NSCLC: Long-Term Follow-Up From the Phase 1/2 TRIDENT-1 Trial. Cho BC, et al

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Taletrectinib

Taletrectinib: Efficacy Outcomes in TKI-naïve ROS1+ NSCLC

Efficacy	TKI-naïve (n=54)
cORR: prior chemo, yes / no, n/N (%)	9/10 (90.0) / 37/44 (84.1)
Median TTR,[c] mo (95% CI)	1.4 (1.3–1.4)
IC efficacy	**(n=9)[d]**
IC-ORR, % (95% CI)	66.7 (29.9–92.5)

Taletrectinib: Efficacy Outcomes in TKI-pretreated ROS1+ NSCLC

Efficacy	TKI-pretreated (n=47)
cORR: prior chemo, yes / no, n/N (%)	15/19 (78.9) / 14/28 (50.0)
Median TTR,[c] mo (95% CI)	1.4 (1.4–1.6)
IC efficacy	**(n=16)[d]**
IC-ORR, % (95% CI)	56.3 (29.9–80.3)

Toxicity Profile: With 5 months of additional follow-up,[1] no new safety signals were identified

- **Rates of neurologic TEAEs were low and limited to Grade 1 or 2** Dysgeusia: 15.2% Grade 1; 4.1% Grade 2 Dizziness: 15.2% Grade 1; 2.3% Grade 2

- **2.3% of patients discontinued treatment due to treatment-related AEs. No patients in TRUST-II discontinued treatment due to increased ALT or AST**

Zidesamtinib

ARROS-1: A Global First-in-Human Phase 1/2 Clinical Trial of Zidesamtinib in Advanced *ROS1*-Positive NSCLC and Other Solid Tumors (NCT05118789)

ZIDESAMTINIB DESIGN GOALS:

- ROS1 Activity
- \+
- ROS1 Mutant Activity
- \+
- Brain Penetrance
- \+
- Avoiding TRK

PHASE 1: Zidesamtinib dose escalation (25 – 150 mg QD) in ROS1 TKI pre-treated patients with advanced *ROS1*+ solid tumors

PHASE 2: Zidesamtinib 100 mg QD (RP2D)

ARROS-1 PHASE 2 PATIENT POPULATION	PRIOR ROS1 TKI	PRIOR CHEMO/I-O
ROS1+ NSCLC	ROS1 TKI-naïve [a]	≤ 1
	1 prior ROS1 TKI [b]	None
		1 [c]
	≥ 2 Prior ROS1 TKIs [d]	≤ 1
Any *ROS1*+ Solid Tumor [e]	Any	Any

PHASE 2 OBJECTIVES

- **Primary:** ORR by blinded independent central review (BICR)
- **Secondary:** Additional efficacy measures (DOR, TTR, CBR, PFS, OS), intracranial activity, overall safety and tolerability, confirmation of PK profile, PROs

Zidesamtinib is an investigational product and has not been approved by the FDA or any other health authority.

BICR, blinded independent central review; CBR, clinical benefit rate; DOR, duration of response; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PRO, patient reported outcomes; QD, once daily; RP2D, recommended phase 2 dose; TKI, tyrosine kinase inhibitor; TRK, tropomyosin-related kinase; TTR, time to response.

[a] Open for enrollment; [b] Either crizotinib or entrectinib; [c] Platinum-based chemotherapy with or without immunotherapy; [d] With initial TKI of either crizotinib or entrectinib; [e] Exploratory cohort, currently enrolling; Includes NSCLC who do not qualify for any of the other cohorts.

Patient Populations

Data cut-off: March 21, 2025

Total Enrolled: N = 514
Any *ROS1*+ solid tumor, any dose
Phase 1 + Phase 2 pooled

Pivotal Safety Population: N = 432
Advanced *ROS1*+ NSCLC
Received zidesamtinib at 100 mg QD

Pivotal Efficacy Population:
ROS1 TKI Pre-treated
with measurable disease by BICR
Treated by May 31, 2024
(≥ 6 months DOR follow up)
n = 117

Preliminary Data
TKI-Naïve
with measurable disease by BICR
Treated by August 31, 2024
n = 35

Zidesamtinib

ARROS-1: Objective Response in ROS1 TKI Pre-treated Patients

Advanced *ROS1*+ NSCLC RECIST 1.1 by BICR	Any prior ROS1 TKI (range 1 – 4) ± chemotherapy	1 prior ROS1 TKI (crizotinib or entrectinib) ± chemotherapy
ORR, % (n/N) [95% CI]	44% (51/117) [34, 53]	51% (28/55) [a] [37, 65]
CR, % (n/N)	1% (1/117)	2% (1/55)

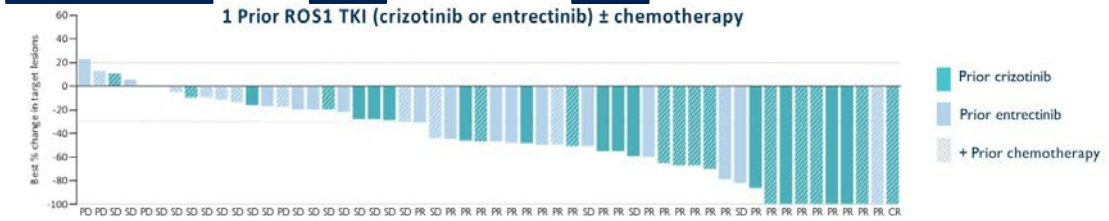
herapy: ORR = 68 | 40 | ior entrectinib only ± chemother | 68 | % (9/27).

18 m PFS %

Responses were also observed in patients previously treated with:

- **≥2 prior ROS1 TKIs ± chemotherapy**: ORR = 38% (22/58; 95% CI: [26, 52])
- **Prior repotrectinib: ORR = 47% (8/17)**, DOR range 3.5 to 17.2 months
- **Prior taletrectinib: ORR = 43% (3/7)**, DOR range 5.2 to 7.0+ months

1 Prior ROS1 TKI (crizotinib or entrectinib) ± chemotherapy



Data cut-off: March 21, 2025. CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease.

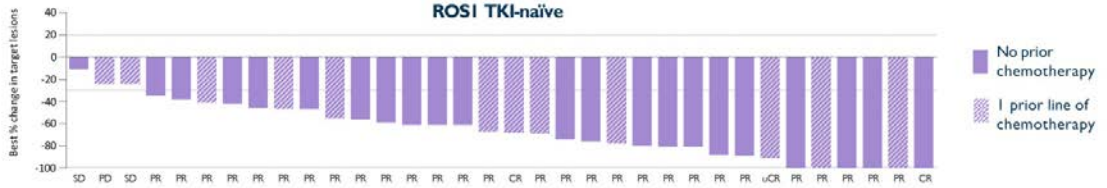
ARROS-1 Preliminary Data: TKI-Naïve Patients with Advanced *ROS1*+ NSCLC

TKI-naïve advanced *ROS1*+ NSCLC Analysis by BICR	Response-evaluable n = 35
ORR, % (n/N)	89% (31/35)
CR, % (n/N)	9% (3/35) [a]
% **DOR ≥ 6 months** [95% CI] [b]	96% [76, 99]
% **DOR ≥ 12 months** [95% CI] [b]	96% [76, 99]
DOR range	1.9+ to 13.9+ months

[a] Includes 1 unconfirmed CR following confirmed partial response (PR).
[b] Analyses of DOR based on Kaplan-Meier estimates.

TKI-naïve advanced *ROS1*+ NSCLC Analysis by BICR	Measurable intracranial lesions n = 6
IC-ORR, % (n/N)	83% (5/6)
IC-CR, % (n/N)	67% (4/6)
IC-DOR	No CNS progression events among intracranial responders
IC-DOR range	4.6+ to 11.1+ months

ROS1 TKI-naïve



Data for patients treated with zidesamtinib 100 mg QD by August 31, 2024 in the Phase 2 portion of ARROS-1 with a data cut-off of March 21, 2025. Patients may have received up to 1 prior line of chemotherapy.

Zidesamtinib

All Treatment-Emergent Adverse Events (TEAEs) in ≥15% of Patients Treated with Zidesamtinib 100 mg QD (N = 432) [a]

Preferred or grouped term	Any Grade	Grade ≥ 3
Peripheral edema [b]	36%	0.7%
Constipation	17%	0%
Blood CPK increased	16%	3.5%
Fatigue [c]	16%	0.7%
Dyspnea [d]	15%	3.0%

[a] Patients received at least 1 dose of zidesamtinib at 100 mg QD with median duration of exposure of 5 months (range: 0, 32).
[b] Includes terms peripheral edema, peripheral swelling, edema, generalized edema.
[c] Includes terms fatigue, asthenia, malaise.
[d] Includes terms dyspnea, dyspnea exertional, orthopnea

Dose reduction due to TEAEs: 10% (43/4

- Most common (>2 patients): peripheral (n=8), blood CPK increased (n=4), periph sensory neuropathy (n=4), arthralgia (n= paraesthesia (n=3)

Discontinuation due to TEAE: 2% (10/43

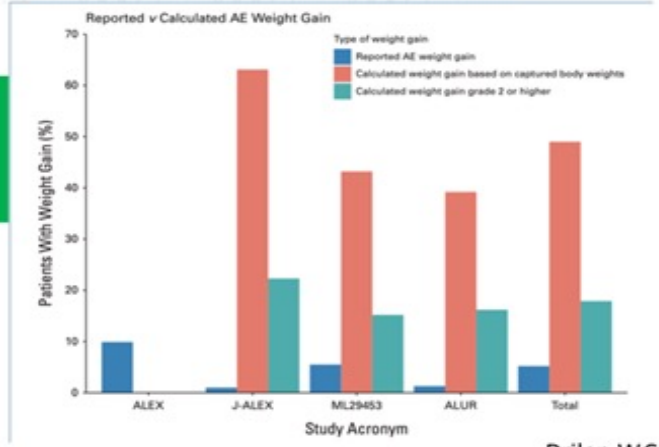
- Most common (>2 patients): pneumonia

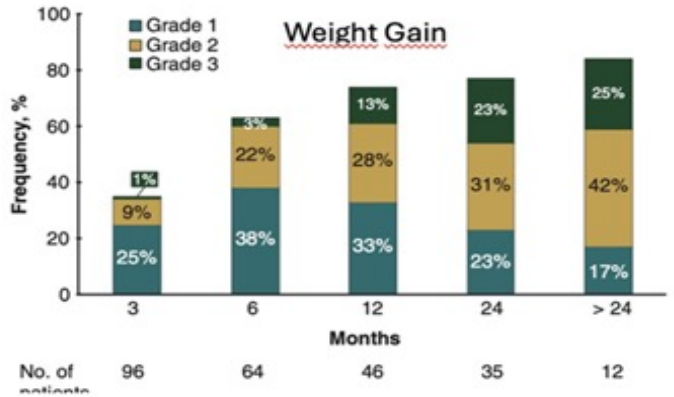
The only treatment-related adverse event of patients was peripheral edema (29%)

Treatment-Related Adverse Events (TRAEs) in ≥ 10% of Patients All Treated (N = 104)

Preferred Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Any Grade n (%)
Oedema peripheral	15 (14%)	5 (5%)	-	20 (19%)
ALT increased	11 (11%)	-	-	11 (11%)
AST increased	11 (11%)	-	-	11 (11%)
Weight increased	7 (7%)	3 (3%)	1 (1%)	11 (11%)

Weight gain was mainly grade 1-2; < 15% of pts
Remember: gr 2 weight gain ≥ 10%



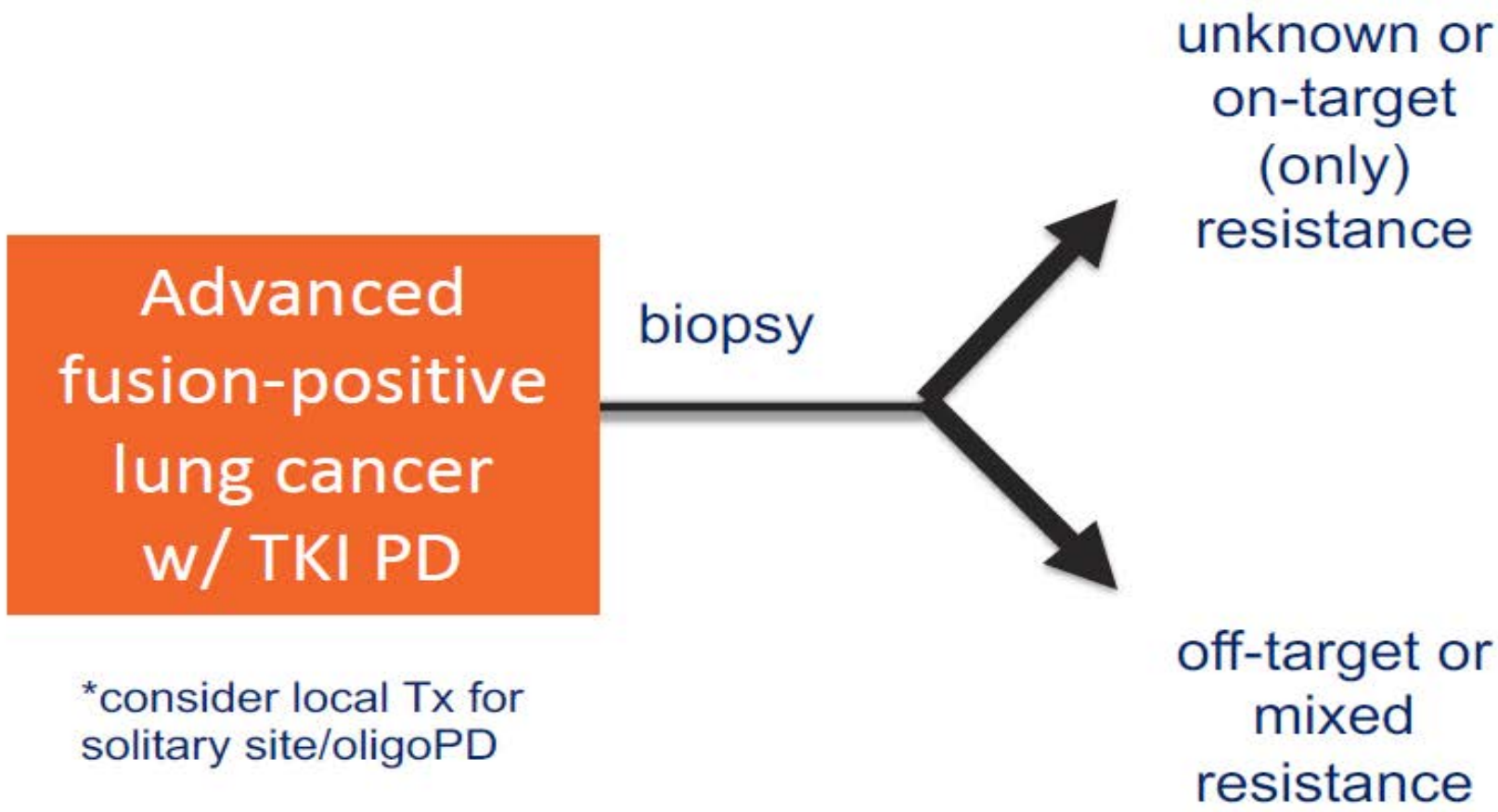


Dingemans, WCLC 2025

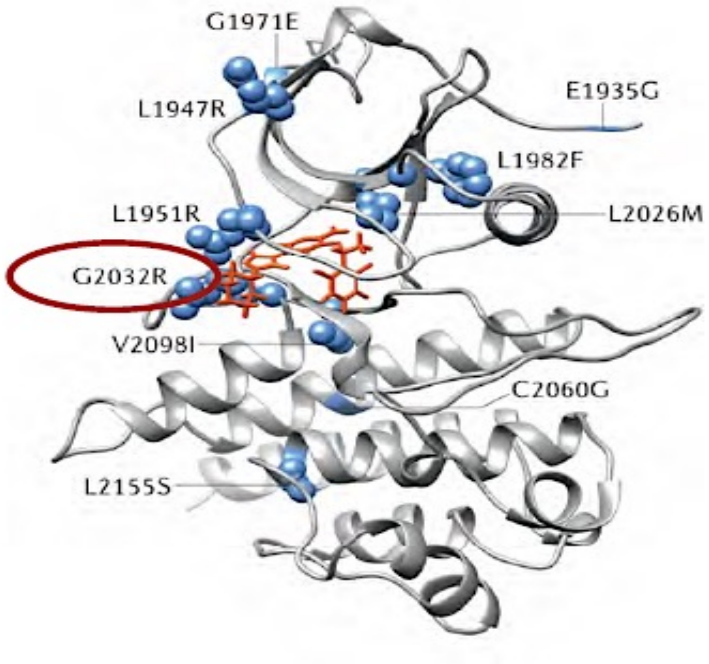
Drilon WCLC 2025; Besse, ESMO 2024; Liu Ann Oncol 2020; Sikkema JCO 2024

wclc.iaslc.org

Selecting Tx for ROS1 TKI Pre-treated Pts



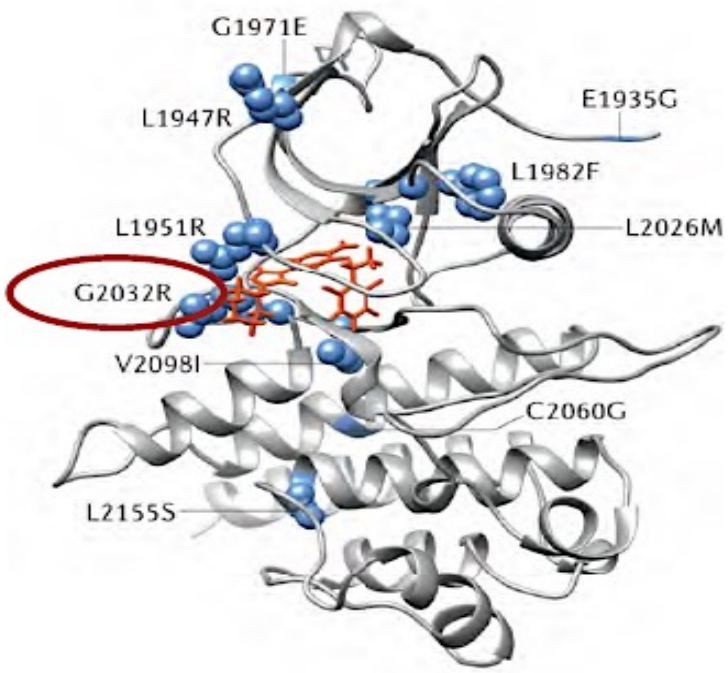
Acquired ROS1 Mutation Coverage Correlates with Activity TKI Pre-treated Pts



	ORR	PFS	ROS1^{G2032R}
lorlatinib (post crizotinib)	35%	8.5 mo	0%
repotrectinib (post crizotinib, entrectinib, ceritinib)	38%	9 mo	59%
taletrectinib (post crizotinib, entrectinib)	56%	9.7 mo	62%
zidesamtinib (post crizotinib, entrectinib)	51%	not reached	83%

ilon et al, Nat Rev Clin Oncol 2017; Drilon et al, WCLC 2025; Perol et al, JCO 2025; Drilon et al, NEJM 2024; Shaw et al, Lancet Oncol 2019

Activity of Zidesamtinib in ROS1 TKI-Exposed mNSCLC



- **≥2 prior ROS1 TKIs ± chemotherapy:**
  ORR = 38% (22/58; 95% CI: [26, 52])
- **Prior repotrectinib: ORR = 47% (8/17),**
  DOR range 3.5 to 17.2 months
- **Prior taletrectinib: ORR = 43% (3/7),**
  DOR range 5.2 to 7.0+ months

ilon et al, Nat Rev Clin Oncol 2017; Drilon et al, WCLC 2025; Perol et al, JCO 2025; Drilon et al, NEJM 2024; Shaw et al, Lancet Oncol 2019

Strategies for Off-Target or Polclonal Resistance ROS1 TKI-Exposed mNSCLC

Treatment Choices

Plat. Doublet Naïve	Plat. Doublet Treated
platinum doublet inclusive therapy	standard chemotherapy
*transformation may modify chemotherapy choice	*transformation may modify chemotherapy choice
investigational therapy	ADC therapy
	investigational therapy

	ORR	Durability
IO Monotherapy	**ORR 13-17%**	**TTD 2.1-2.4 months**
Immunotarget, Ann Oncol 2019	17% (n=7)	-
Choudhury et al, JTO CRR 2021	13% (n=16) all PD-L1	2.1 mo TTD 2.4 mo TTD PD-L1 high
Chemo + IO	**ORR 29-83%**	**TTD/PFS 5.8-24.3 months**
Huang et al, JCO PO 2023	83% 1L (n=6) 29% later line (n=14)	24.3 mo PFS 5.8 mo mPFS
Coudhury et al, JTO CRR 2021	83% (n=6)	10.0 mo TTD
Chemo alone	**ORR 78%**	**PFS 23 months**
Drilon et al, Ann Oncol 2016	78% (n=10)	23 mo PFS

ROS1 Inhibition: Conclusions

- ROS1 fusions: ~ 2% of all NonSq NSCLC
  - Younger pts; minimal or no smoking hx; aggressive clinical course
  - High propensity for CNS invasion
- TKIs: standard of care
  - LTS: previously < 12-18 mos, now > 4-5+ yrs
  - Crizotinib and Entrectinib: “historic interest”
  - US: Taletrectinib > Repotrectinib: Both have RR% ~ 80-90% in Tx-naïve pts, CNS penetrance, mPFS 3-4 yrs
  - Zidesamtinib: “may” be superior
- Salvage Tx: depends on initial choice of TKI and subsequent NGS testing
  - Final common pathway: Pem/Carbo +/- Bev
  - CPIs: marginal, if any activity

QUESTIONS?

Module 16: Acute Myeloid Leukemia (AML)

Current Management Approaches for FLT3- and IDH-Mutated AML — Dr DiNardo

Current and Future Role of Menin Inhibitors for Patients with AML — Dr Erba

Faculty

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Module 16: Acute Myeloid Leukemia (AML)

Current Management Approaches for FLT3- and IDH-Mutated AML — Dr DiNardo

Current and Future Role of Menin Inhibitors for Patients with AML — Dr Erba

Module 16: Targeted Treatment of AML

We would like to do a “best paper or presentation of the year” activity. Please suggest one “paper of the year” and 2 other worthy papers based on the value in treatment of current and future patients.

American Society *of* Hematology

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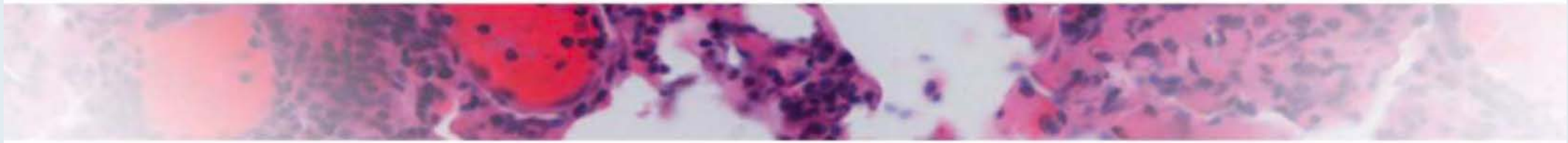


Results from PARADIGM - A phase 2 randomized multi-center study comparing azacitidine and venetoclax to conventional induction chemotherapy for newly diagnosed fit adults with AML

Amir T. Fathi[1], Alexander E. Perl[2], Geoffrey G. Fell[3], Brian A. Jonas[4], Brittany K. Ragon[5], Alice S. Mims[6], Uma Borate[6], Gabriel N. Mannis[7], Karen Quillen[8], Maximilian Stahl[3,9], Paul Koller[10], Andrew S. Artz[10], Monzr M. Al Malki[10], Guido Marcucci[10], Mary Linton B. Peters[8], Timothy A Graubert[1], Peter Westervelt[1], Philip C. Amrein[1], Hanno R. Hock[1], Andrew M. Brunner[1], Gabriela Hobbs[1], Rupa Narayan[1], Michelle H. Lee[1], Brandon J. Aubrey[1], Alyssa L. Watson[1], Richard Hao[1], Shilton Dhaver[1], Michael R. Grunwald[5], Yi-Bin Chen[1], Andrew H. Matthews[2], Brent L. Wood[11], Chris S. Hourigan[12], Donna S. Neuberg[3], Areej El-Jawahri[1], Ibrahim Aldoss[10]

Fathi AT et al. ASH 2025;Abstract 6.

PARADIGM: Conclusions

- The study met its primary endpoint in this IC-eligible population.
- Aza-Ven improves EFS versus conventional IC.
- Aza-Ven leads to higher rates of OR and CCR, when compared to IC.
- A greater proportion of Aza-Ven patients successfully proceeded to HCT following response on trial.
- Aza-Ven was associated with less early mortality, improved QOL and symptom burden during initial therapy, with less time in the hospital and ICU.
- These data support the use of Aza-Ven in functionally fit patients with intermediate or adverse-risk, *FLT3*-wildtype AML.

Fathi AT et al. ASH 2025;Abstract 6.

Current Management Approaches for FLT3 and IDH Mutant AML

Courtney DiNardo, MD MSCE

Department of Leukemia

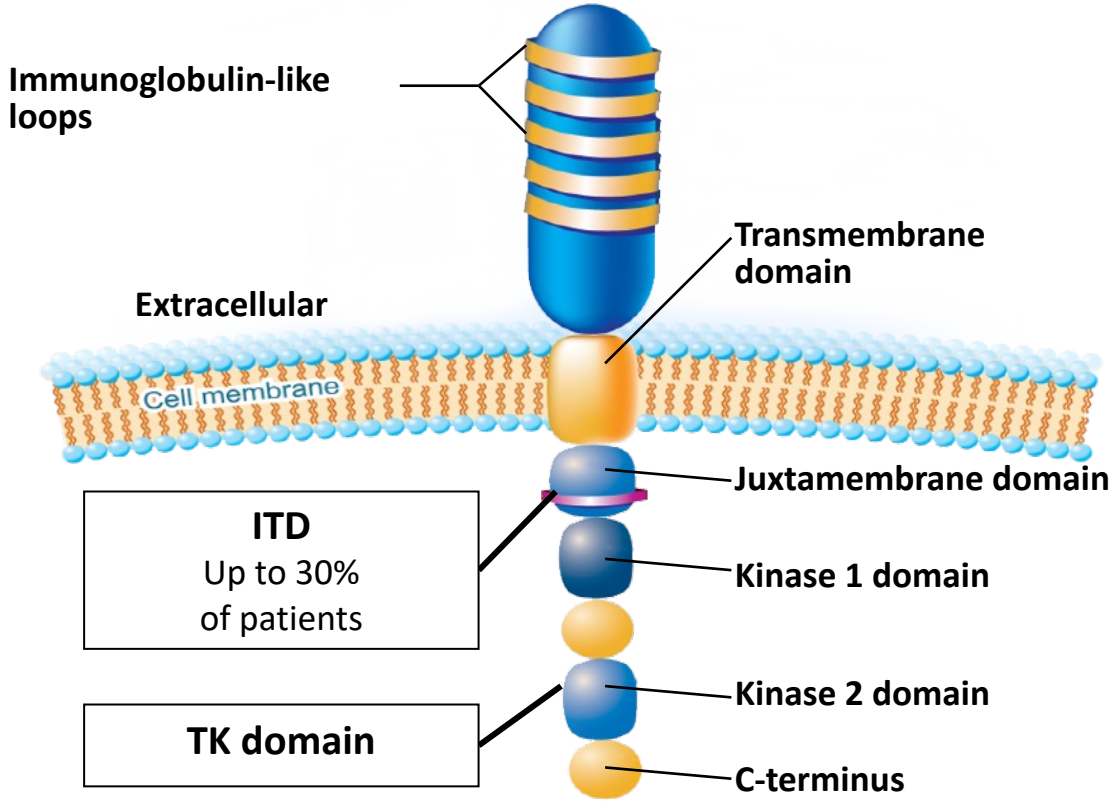
MD Anderson Cancer Center

Disclosures

Advisory Committees	Astellas, Bristol Myers Squibb, Kura Oncology
Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Genmab US Inc, Molecular Partners, Rigel Pharmaceuticals Inc, Servier Pharmaceuticals LLC
Contracted Research	AbbVie Inc, Astex Pharmaceuticals, Auron Therapeutics, Remix Therapeutics, Rigel Pharmaceuticals Inc, Servier Pharmaceuticals LLC, SillaJen, SystImmune Inc

Characteristics of FLT3 Mutations in AML

- *FLT3-ITD* in ~25% and *FLT3-TKD* in ~10% AML
- More frequent in younger pts, *de novo* AML and diploid cytogenetics
- Leads to constitutive activation of FLT-3 receptor
- *FLT3-ITD* independent predictor of poor prognosis; often associated with more proliferative disease

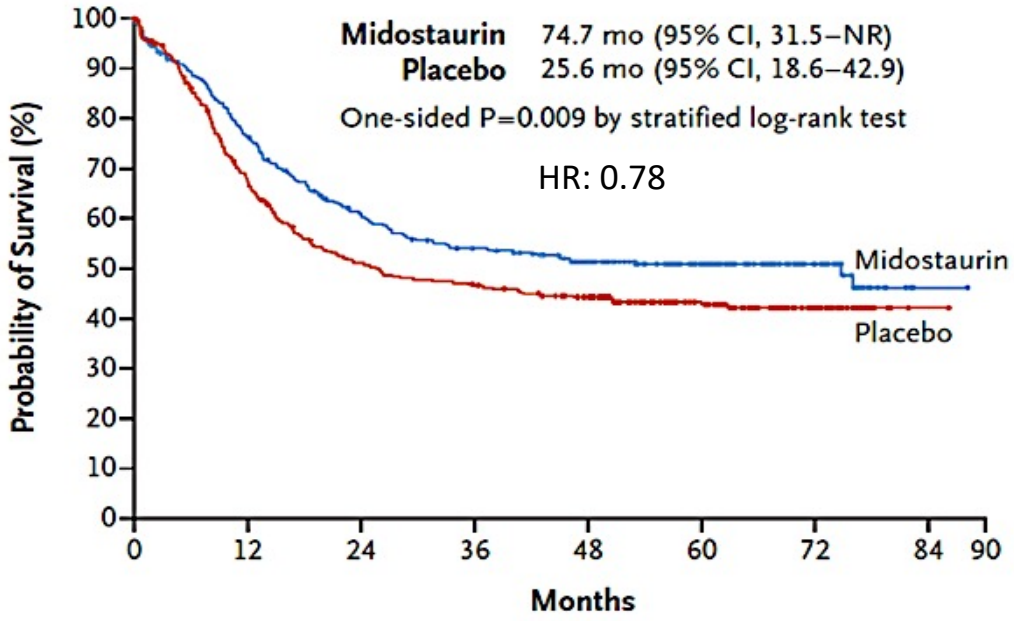


Activated proliferation and pro-survival pathways

- Litzow MR et al, Blood 2015

Approved Regimens for Newly Dx FLT3-Mutated AML

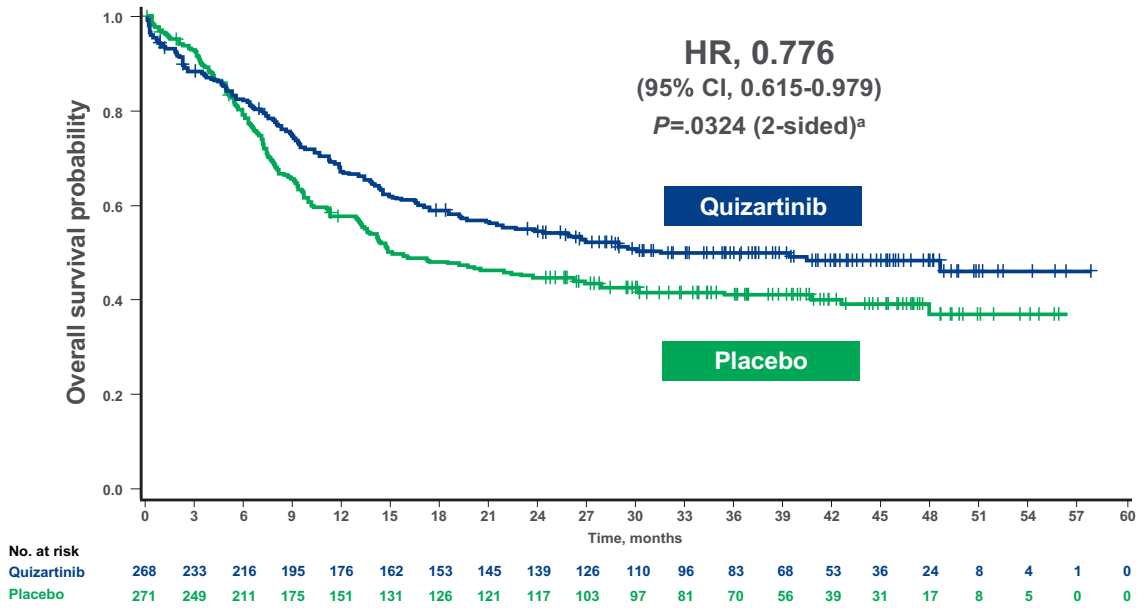
	CR
Midostaurin	68%
Placebo	61%



FLT3-ITD and FLT3-TKD mutations, age < 60 yrs

- 60-day mortality: not reported

	CR	CR/CRi
Quizartinib	54.9%	71.6
Placebo	55.4%	64.9



FLT3-ITD only, and age < 75 yrs

- 60-day mortality: quizartinib 7.5%, placebo 4.9% (mostly infections)

Stone RM, et al. *N Engl J Med.* 2017 Aug 3;377(5):454-464
Erba HP, et al. *Lancet*. 2023 May 13;401(10388):1571-1583

Quick Review of FLT3 Inhibitors

Midostaurin
(Type 1 – TKD and ITD)

- **Approved in Newly Dx Fit AML in combo w/ chemotx**
- **GI effects/nausea/diarrhea, transaminitis, rash**

Quizartinib
(Type 2 – FLT3-ITD only)

- **Approved in Newly Dx Fit AML in combo with chemotx**
- **QTC prolongation**, potential ventricular arrhythmias, myelosuppression, transaminitis

Gilteritinib
(Type 1 – TKD and ITD)

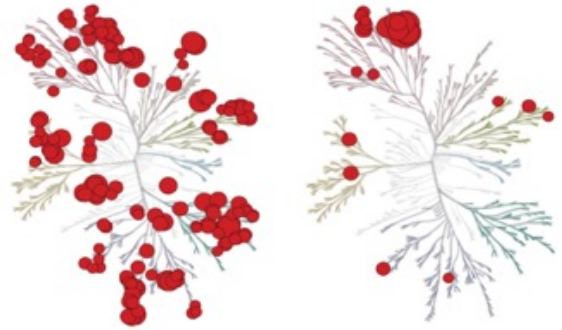
- **Approved in R/R AML as monotherapy**
- QTc prolongation, myelosuppression, and **transaminitis**

Important Differences of FLT3 inhibitors

		First generation	Second generation
		Lack specificity for FLT3	More specific and potent
Type I	Pure ATP-competitive* Active on ITD+ and TKD+	Sunitinib Lestaurtinib Midostaurin	Gilteritinib Crenolanib
Type II	Maintain the inactive conformation† Active on ITD+ only	Sorafenib Tandutinib	Quizartinib Ponatinib Pacritinib Ibrutinib

**blue and green compounds are clinically used in the US for FLT3-mutated AML*

2nd GEN:
More potent and selective:
FLT3, KIT, CSF1R, PDGFRA/B



Midostaurin **Quizartinib**

*Bind to the ATP-binding site when the receptor is in the active conformation.

†Interact with a hydrophobic region immediately adjacent to the ATP binding site that is only accessible when the receptor is in the inactive conformation; prevent receptor activation. As most TKD (D835) mutations favor the active conformation, Type II inhibitors are usually ineffective on TKD-positive cells.

Larrosa-Garcia M, et al. *Mol Cancer Ther*. 2017;16:991-1001
Smith CC, et al. Nature. 2012 Apr 15;485(7397):260-3
Whartenby K, et al. PNAS. 2005 Nov 15;102(46):16741-6
Levis M, Perl AE. Blood Adv. 2020 Mar 24;4(6):1178-1191

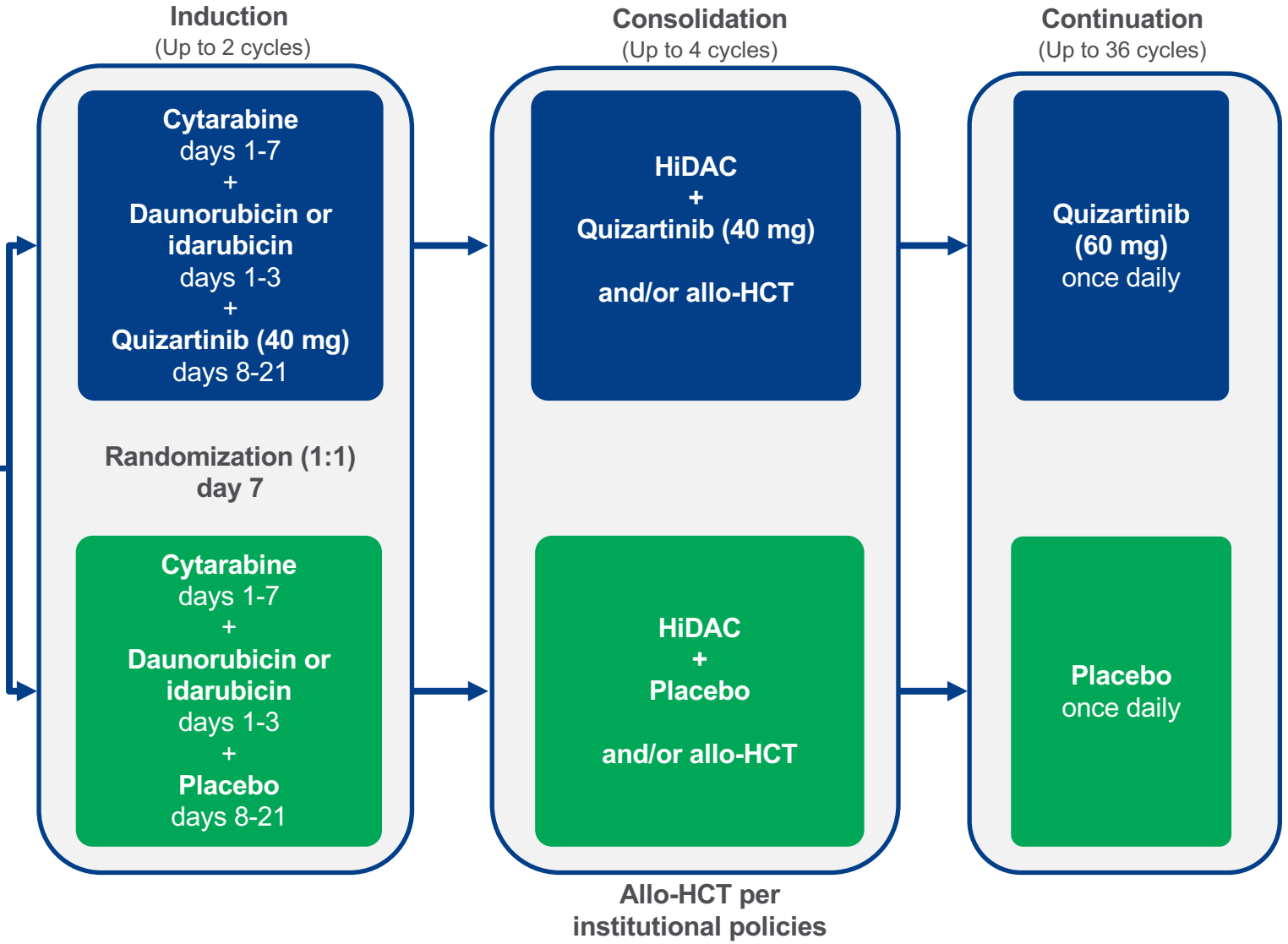
QuANTUM-First Phase 3 Trial: Quizartinib Plus Standard Induction Chemotherapy Followed by Single-Agent Quizartinib –

Enrollment dates: September 2016 to August 2019
trial designed and started before midostaurin approval, so randomization is to placebo

- Newly diagnosed ***FLT3*-ITD+** AML
- 18-75 years of age
- ≥3% *FLT3*-ITD allelic frequency

Selected endpoints

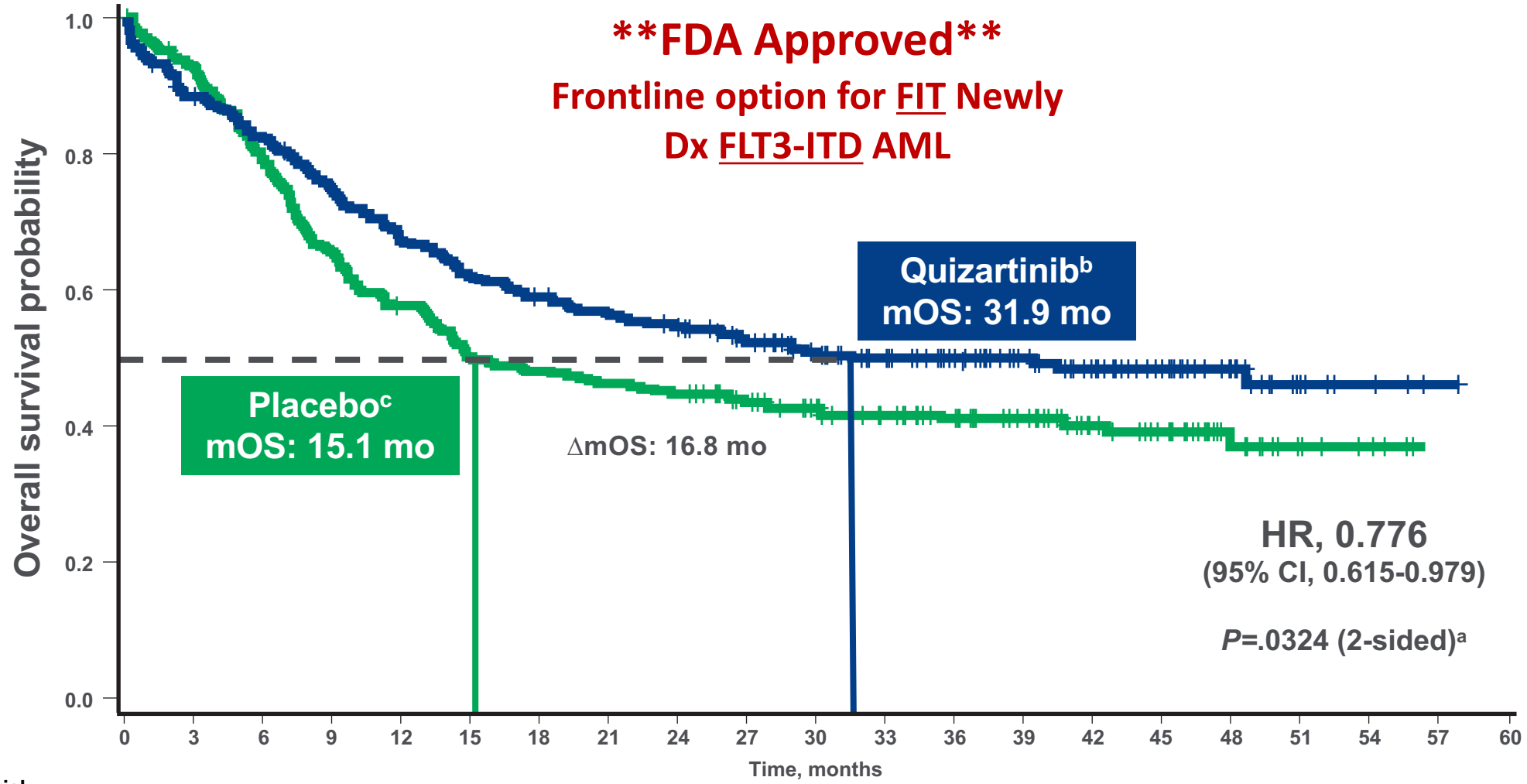
- **Primary endpoint**: OS
- **Secondary endpoints**: EFS, CR/CRc, Safety
- **Exploratory endpoints**: RFS, DoCR



AML, acute myeloid leukemia; CR, complete remission; CRc, composite complete remission; DoCR, duration of complete remission; EFS, event-free survival; HiDAC, high-dose cytarabine, OS, overall survival; RFS, relapse-free survival;

Erba HP et al, Lancet 2023

Primary Endpoint: Overall Survival

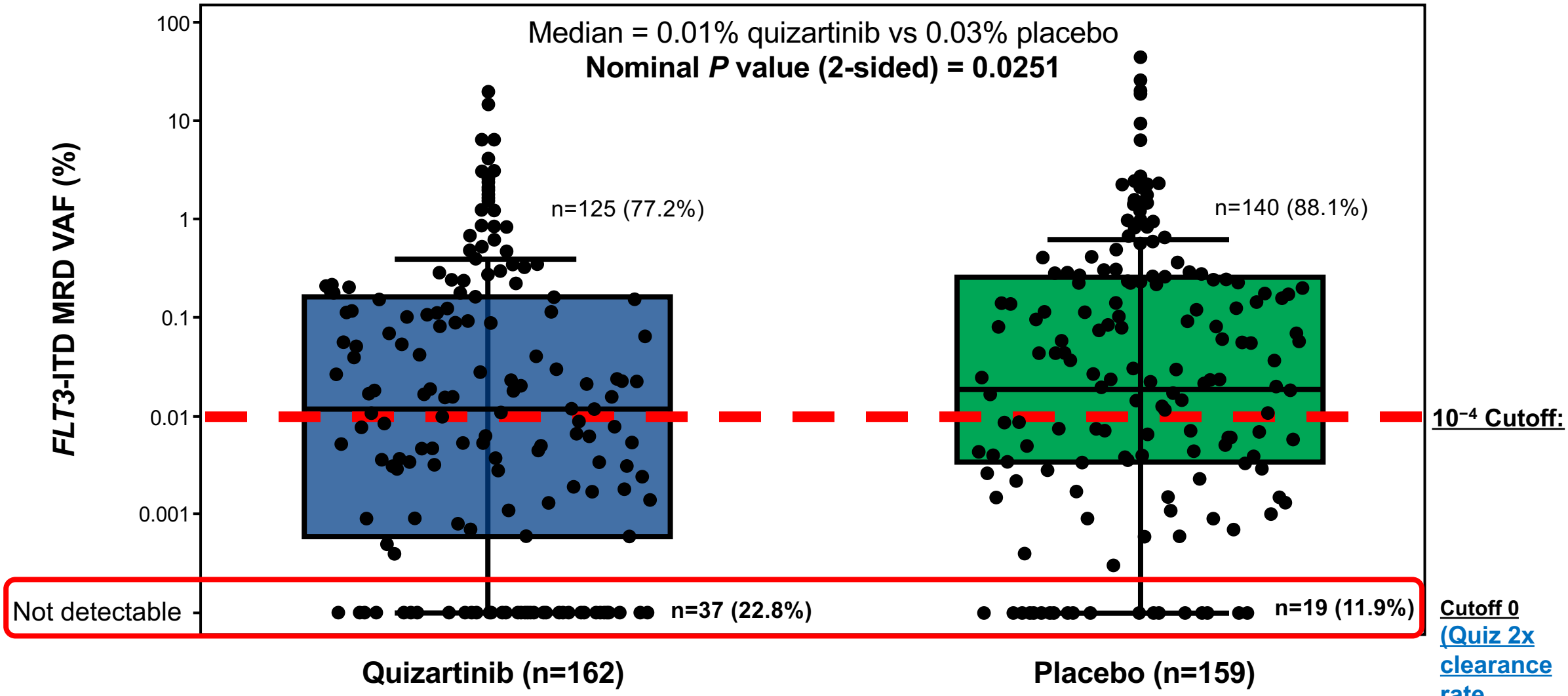


HR, hazard ratio; mOS, median overall survival.
[a] *P* value was calculated using a stratified log-rank test. [b] Median follow-up time for quizartinib arm, 39.2 months. [c] Median follow-up time for placebo arm, 39.2 months.

Erba HP et al, Lancet 2023

Quizartinib Treatment Is Associated with 3-Fold Lower Level of *FLT3*-ITD MRD, Among CRc Patients by the End of Induction

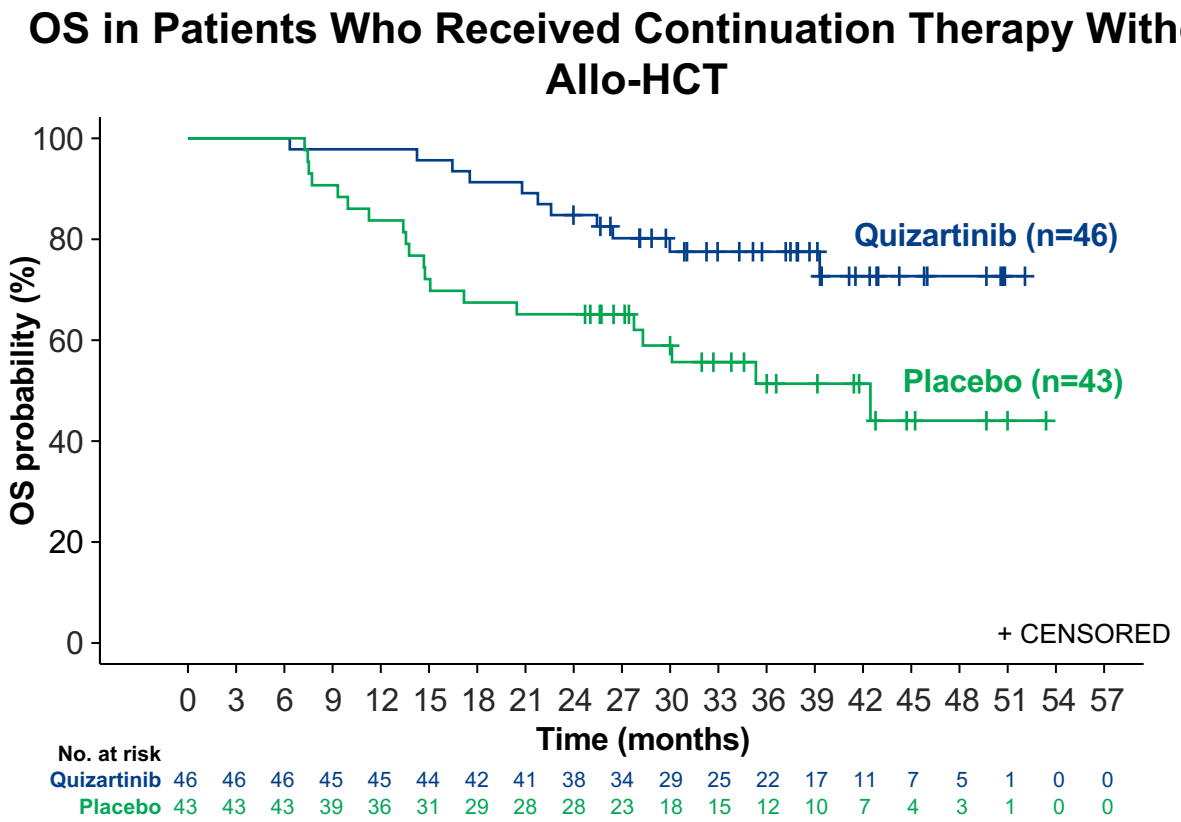
Post hoc analysis.



10^{-4} cutoff chosen for analysis per ELN and FDA cutoff

Erba HP et al, Lancet 2023

Impact of QUIZ maintenance in patients without SCT in CR1



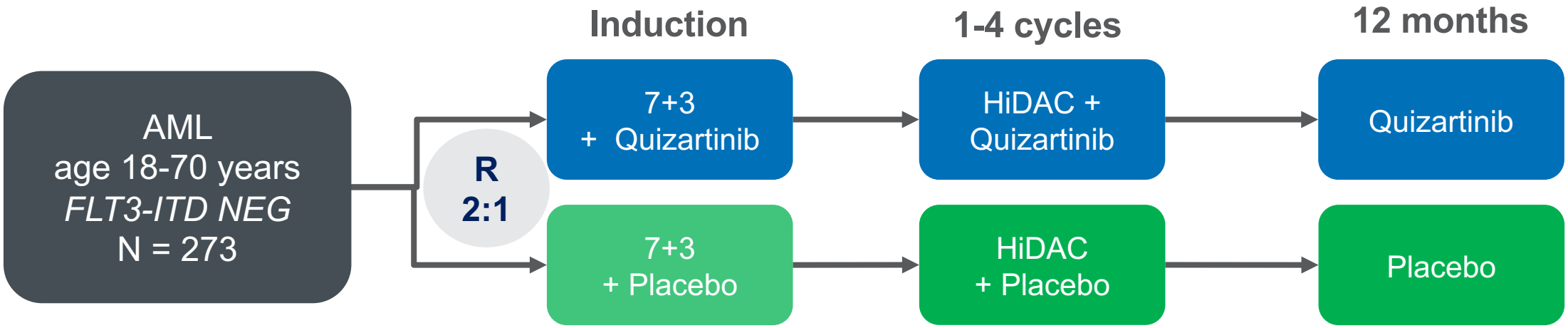
- Similar number of patients without allo-SCT in both groups were able to reach continuation phase (**about 60-70% of non-SCT** pts)

Allo-HCT, allogeneic hematopoietic cell transplantation; CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival.

Sekeres M et al, EHA 2024 S142; Levis MJ et al. Blood Adv 2026

PETHEMA-QUIWI Study

Quizartinib for Newly Diagnosed Adult Patients with FLT3-WILD TYPE AML?!?



Primary endpoint: EFS

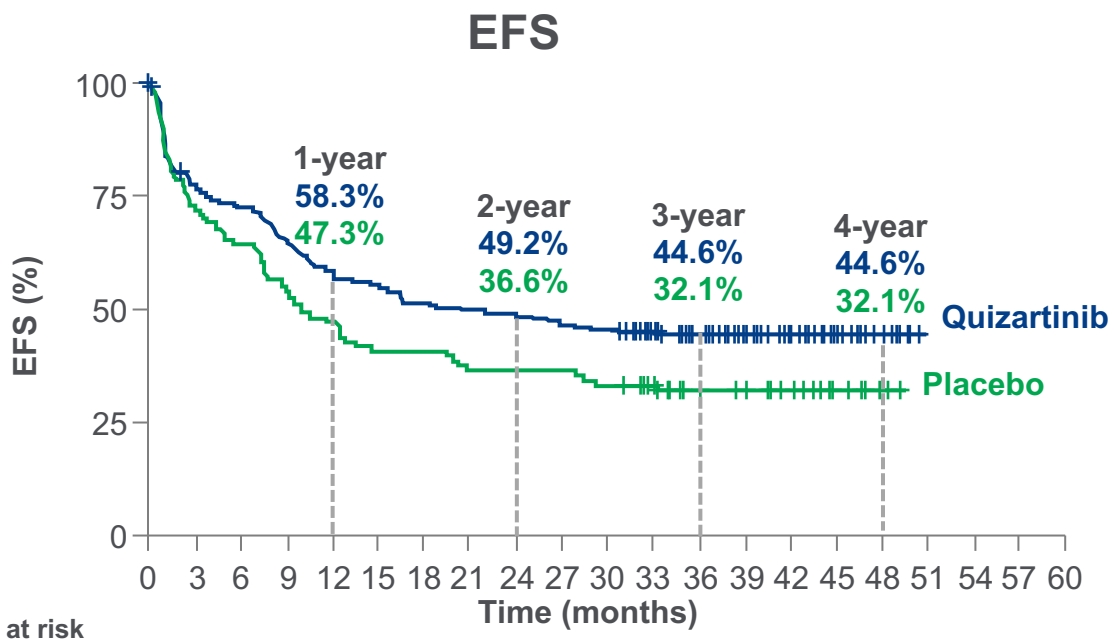
Secondary endpoint: OS

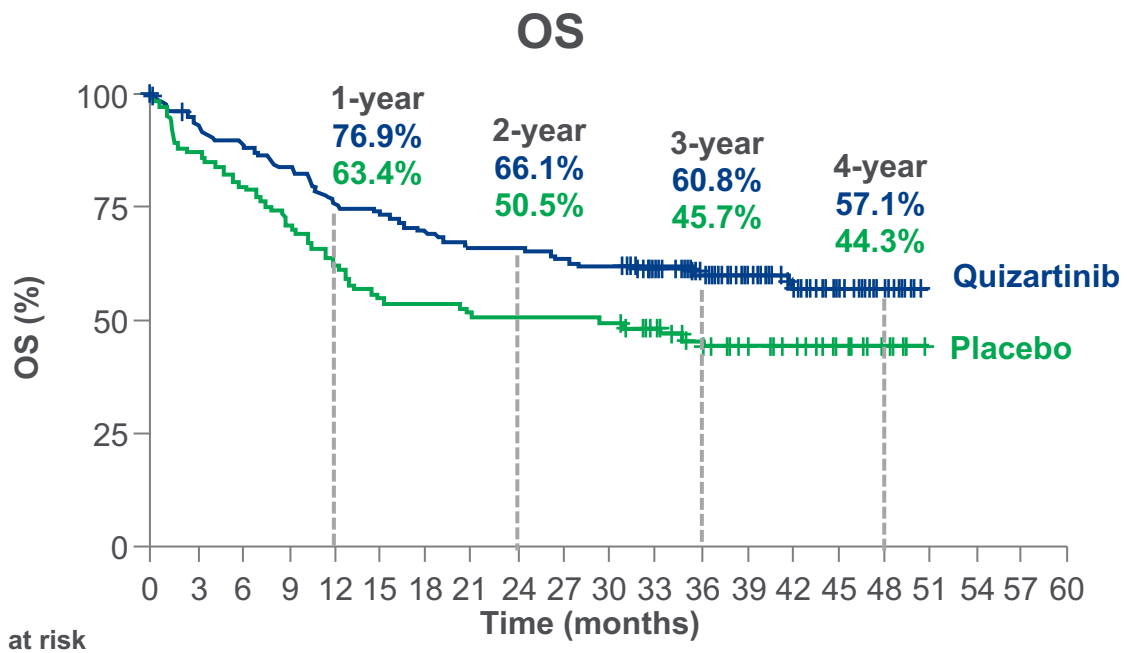
Stratification Factor: age < or ≥ 60 yrs

- AlloHCT at discretion of physician
- Maintenance Post-HCT

Montesinos, P et al., J Clin Oncol 2025

QUIWI: Efficacy Results: EFS and OS





	Quizartinib (n = 180)	Placebo (n = 93)
Events, n (%)	98 (54.4)	63 (67.7)
Median EFS, months	**18.8**	**9.9**
	HR, 0.72 (95% CI, 0.53-1.00); P=0.045	

	Quizartinib (n = 180)	Placebo (n = 93)
Events, n (%)	72 (40.0)	51 (54.8)
Median OS, months	**NR**	**29.3**
	HR, 0.63 (95% CI, 0.44-0.91); P=0.01	

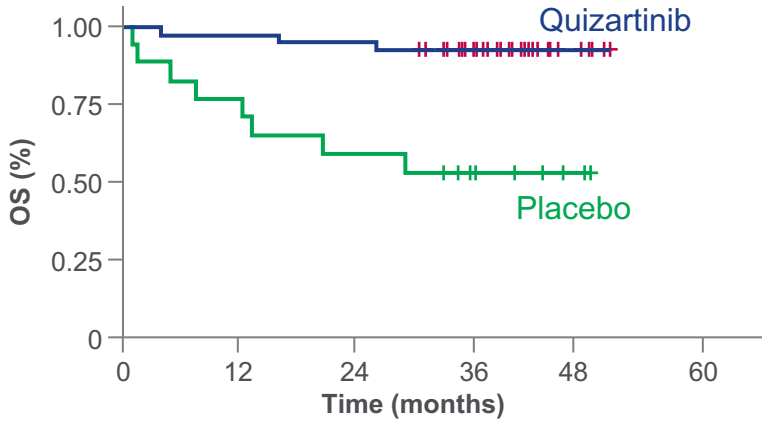
Median follow-up: 39.4 months.

CI, confidence interval; EFS, event-free survival; HR, hazard ratio; NR, not reached; OS, overall survival
Montesinos P, et al. ASH 2024. Abstract 1512.

Montesinos, P et al., J Clin Oncol 2025

OS Benefit with Quizartinib was Observed across most of the Assessed Subgroups including *NPM1*^{mut}, *DNMT3A*^{mut} and *FLT3*-TKD^{mut}

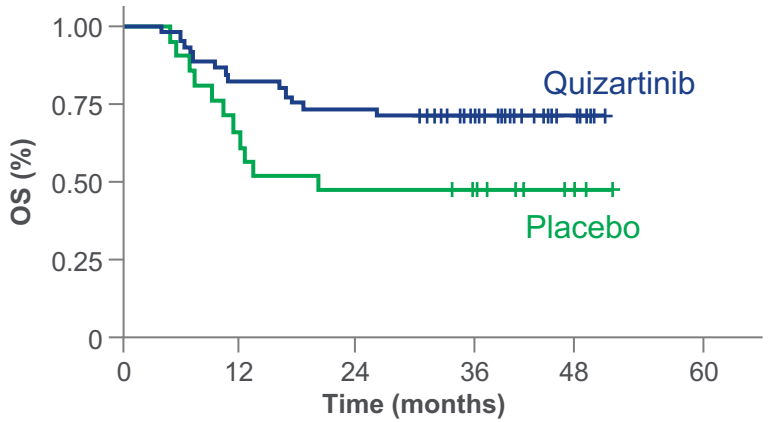
OS in patients with *NPM1* mutation



No. at risk						
Quizartinib	40	39	38	28	5	0
Placebo	17	13	10	7	1	0

	Quizartinib	Placebo
Number of events	3/40	8/17
3-years OS	92%	53%
	HR, 0.123 (95% CI, 0.033-0.467); *p*=2e-04	

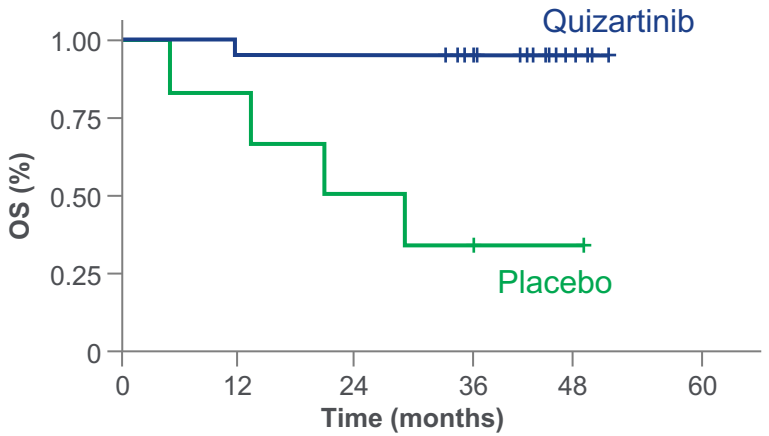
OS in patients with *DNMT3A* mutation



No. at risk						
Quizartinib	45	37	33	25	4	0
Placebo	21	14	10	9	1	0

	Quizartinib	Placebo
Number of events	13/45	11/21
3-years OS	71%	48%
	HR, 0.458 (95% CI, 0.205-1.024); p=0.051	

OS in patients with *FLT3*-TKD mutation



No. at risk						
Quizartinib	20	19	19	14	3	0
Placebo	6	5	3	2	0	0

	Quizartinib	Placebo
Number of events	1/20	4/6
3-years OS	95%	33%
	HR, 0.057 (95% CI, 0.006-0.514); p=5e-04	

OS benefits with Quiz *vs*. PBO were observed across most assessed subgroups, including *NPM1*^{mut} and *DNMT3A*^{mut}; *FLT3*-TKD^{mut}; *IDH2*^{mut} (3-years OS 72% and 47%, respectively; HR, 0.503 [0.204, 1.24])

Martínez-Cuadrón D, et al. ASH 2024. Abstract 2895; Montesinos P et al, JCO 2025

“FLT3-like” Gene Expression Predicts Outcome with Quizartinib

- 80 / 180 cases (~ 45-50%) of FLT3 WT were “FLT3-like” and benefitted from QUIZ
- Enrichment of NPM1, DNMT3A, and FLT3-TKD mutations in “FLT3-like” patients
- Expands potential of patients who may benefit from IC + QUIZ : FLT3m 30% + FLT3-like 30-35%: 60-65%

HR/p Value	Not FLT3-like QUIZ vs NO	FLT3-like QUIZ vs NO
EFS	1.07/.8	0.45/.009
RFS	0.88/.76	0.37/.01
OS	1.22/.62	0.41/.01

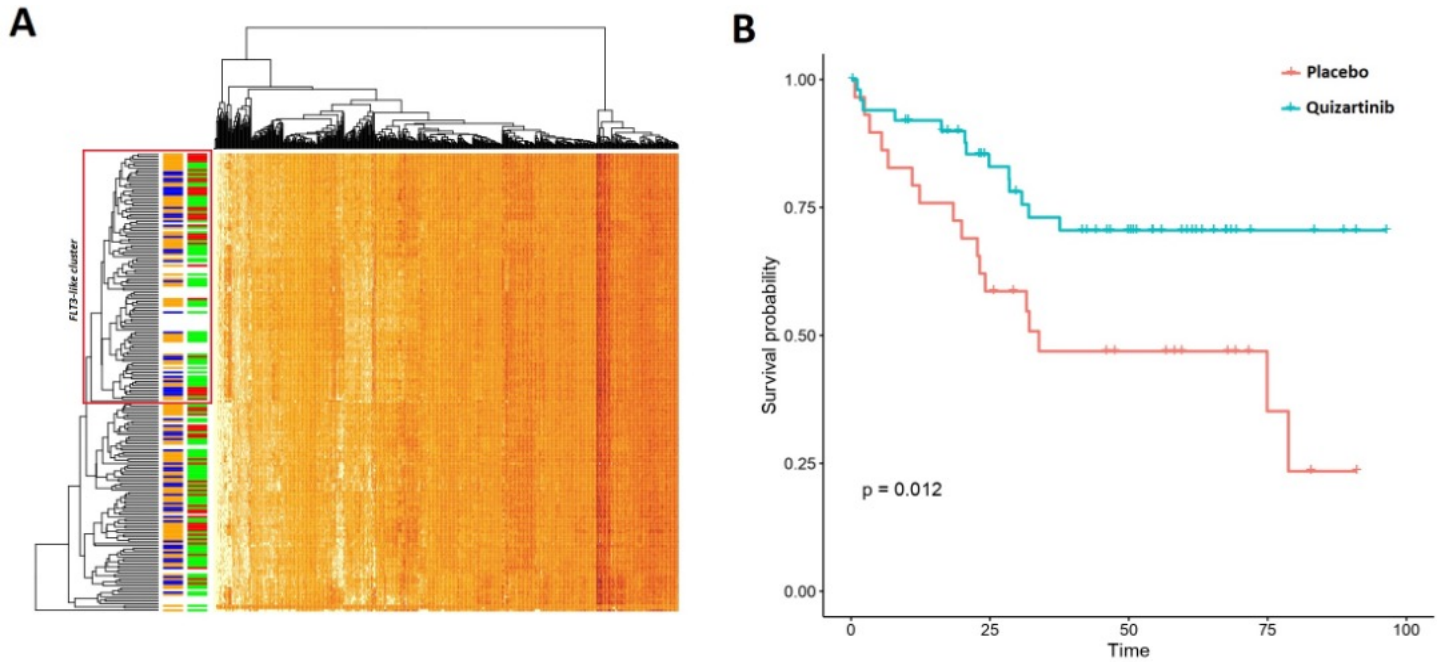
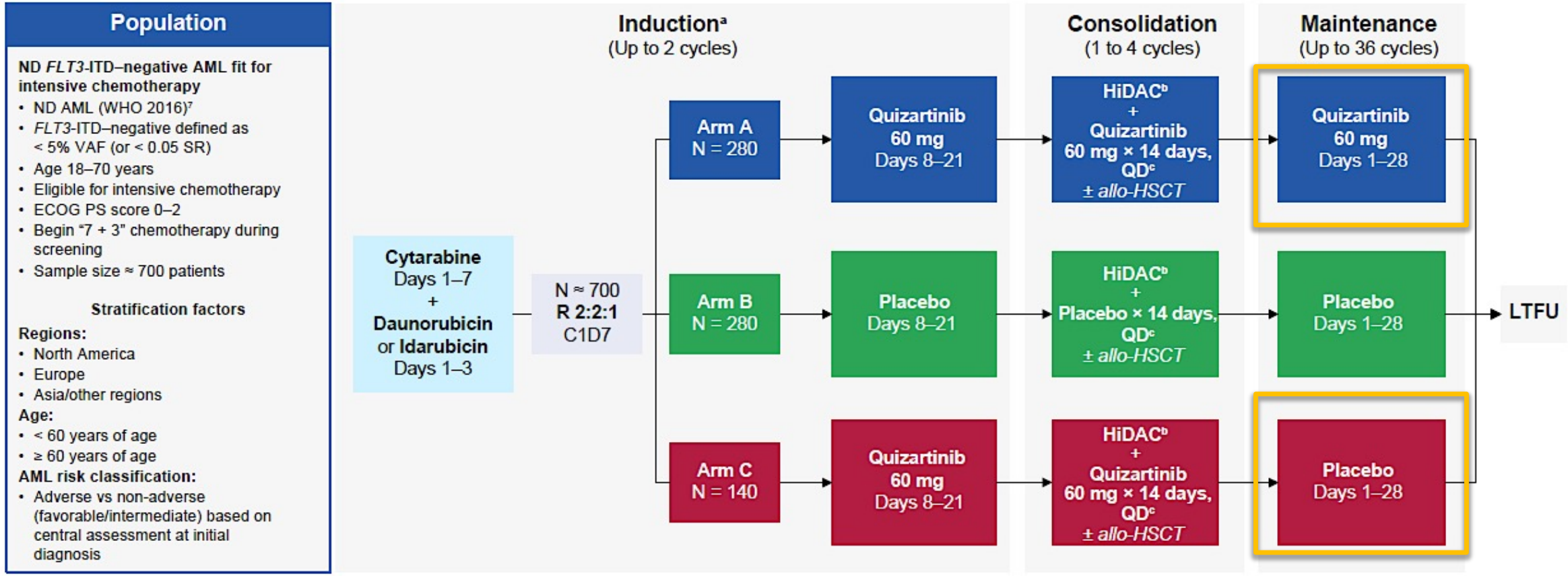


Figure 1. A) Heatmap representing the 595-signature in the 206 patients available for analysis. The top dendogram represents the hierarchical clustering of genes in the signature. The left side dendrogram represents the hierarchical clustering of samples according to the gene expression signature. Two colored row bars are represented. The left one represents the treatment arm in the clinical trial: quizartinib (orange), placebo (blue) and screening failure due to FLT3-mutation (white). The right one represents the status of patients at last follow-up: alive (green), death (red) and screening failure due to FLT3 mutation (white). The FLT3-like cluster is highlighted in the red box, an it is characterized by an enrichment in FLT3 mutant AML cases (71.1% of all FLT3-mutated cases). B) Kaplan-Meier plot representing the overall survival of patients in the FLT3-like cluster, indicating a superiority of quizartinib over placebo in this group.

Mosquera-Orgueira. Blood 142: abst 974; 2023

Phase 3 QuANTUM-WILD trial design for Newly Dx AML

Primary Endpoint: OS (Arm A vs Arm B)

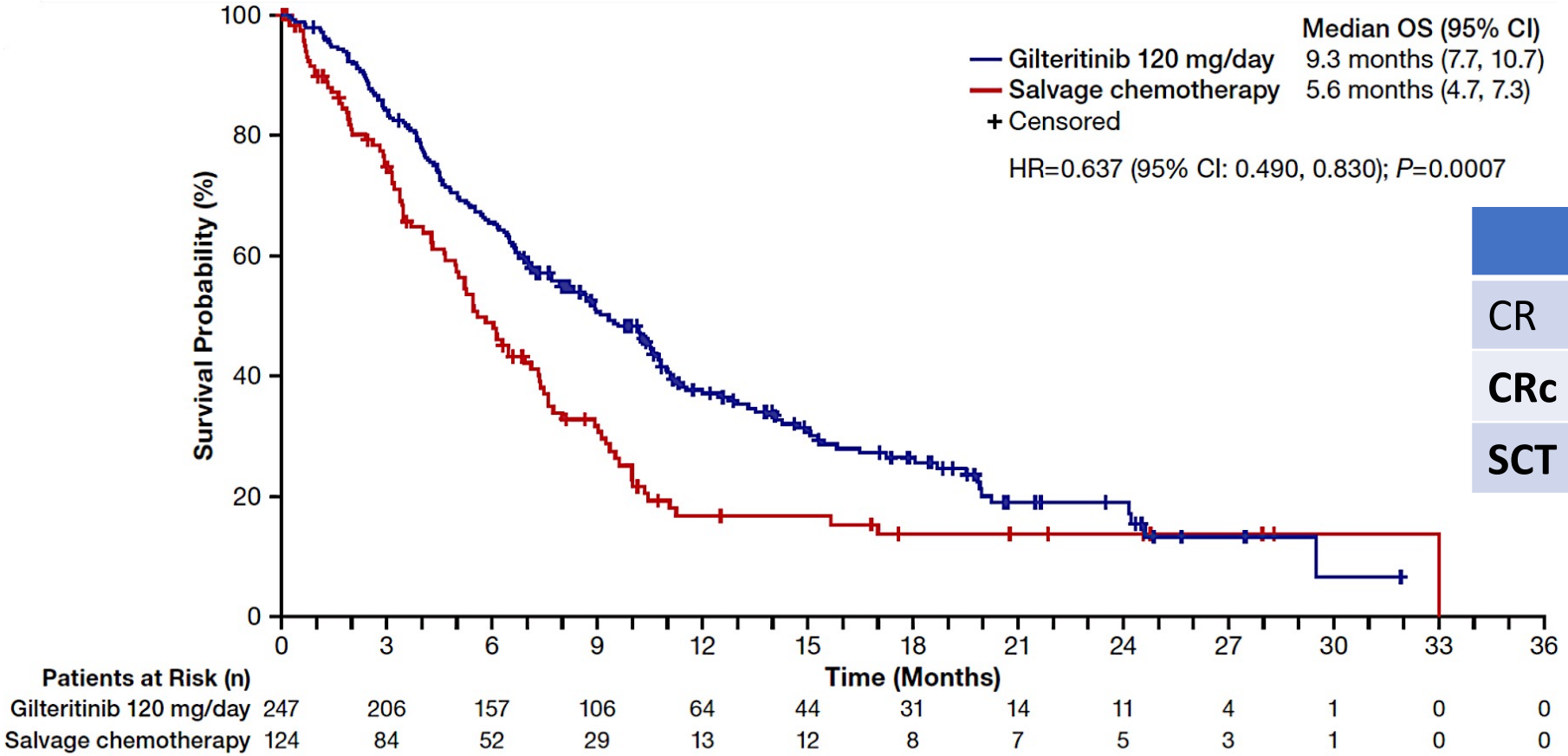


A vs C: Randomization to quiz vs placebo maintenance

Courtesy of Courtney DiNardo, MD, MSCE

ADMIRAL Phase 3 RCT: Overall survival (n=371)

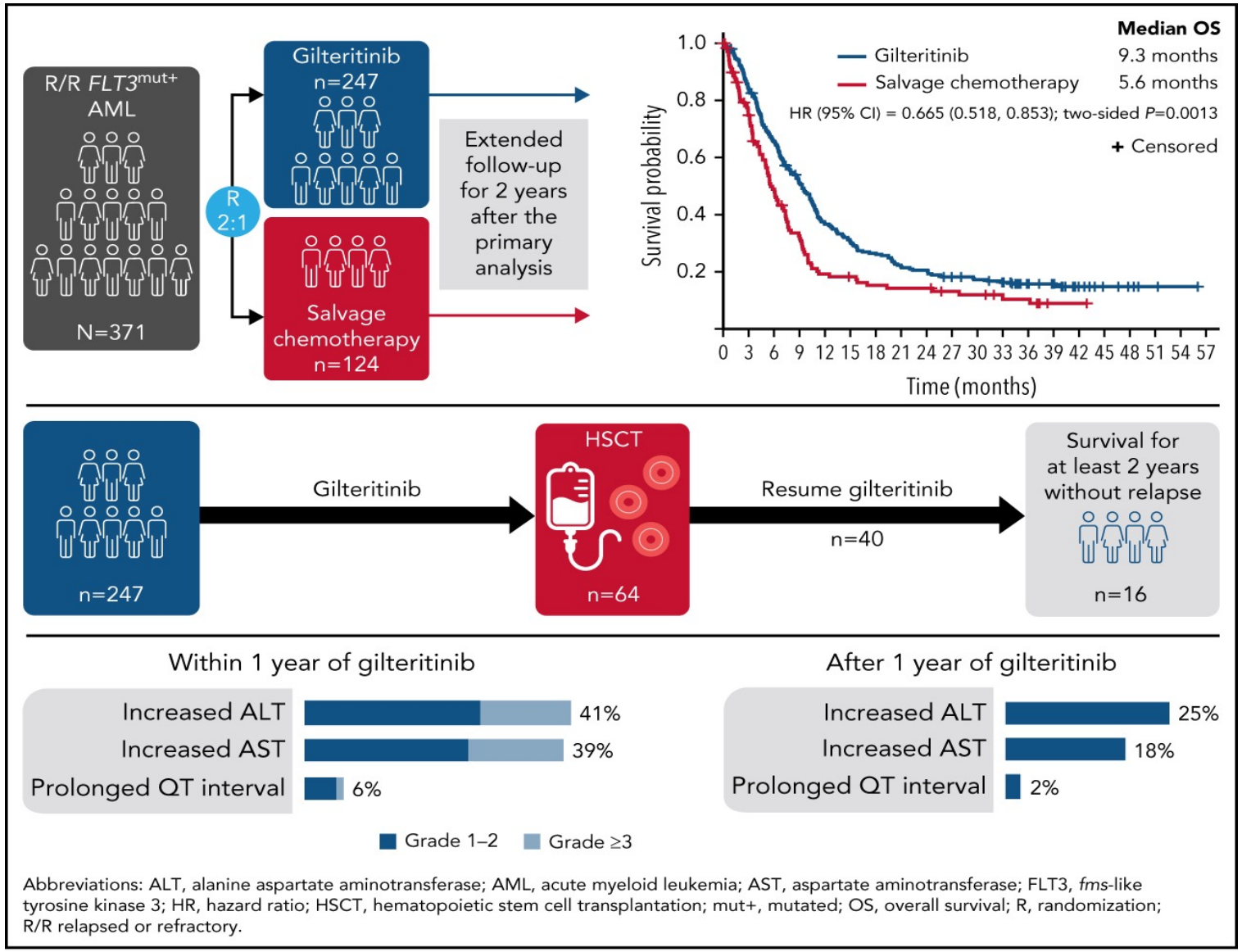
Gilteritinib monotherapy vs SOC salvage (MEC, FLAG-IDA, azacitidine, LDAC)



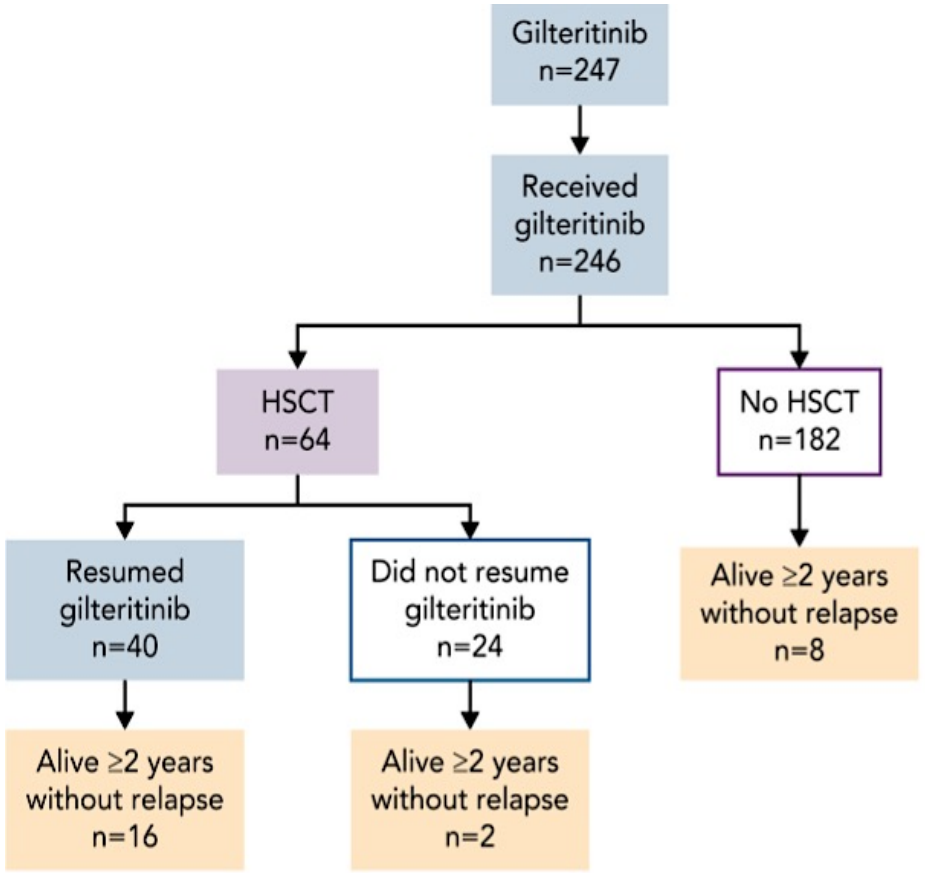
	GILT	Chemotx
CR	21%	11%
CRc	**54%**	**22%**
SCT	**26%**	**15%**

Perl A et al NEJM 2019

ADMIRAL Trial: Long-term follow up



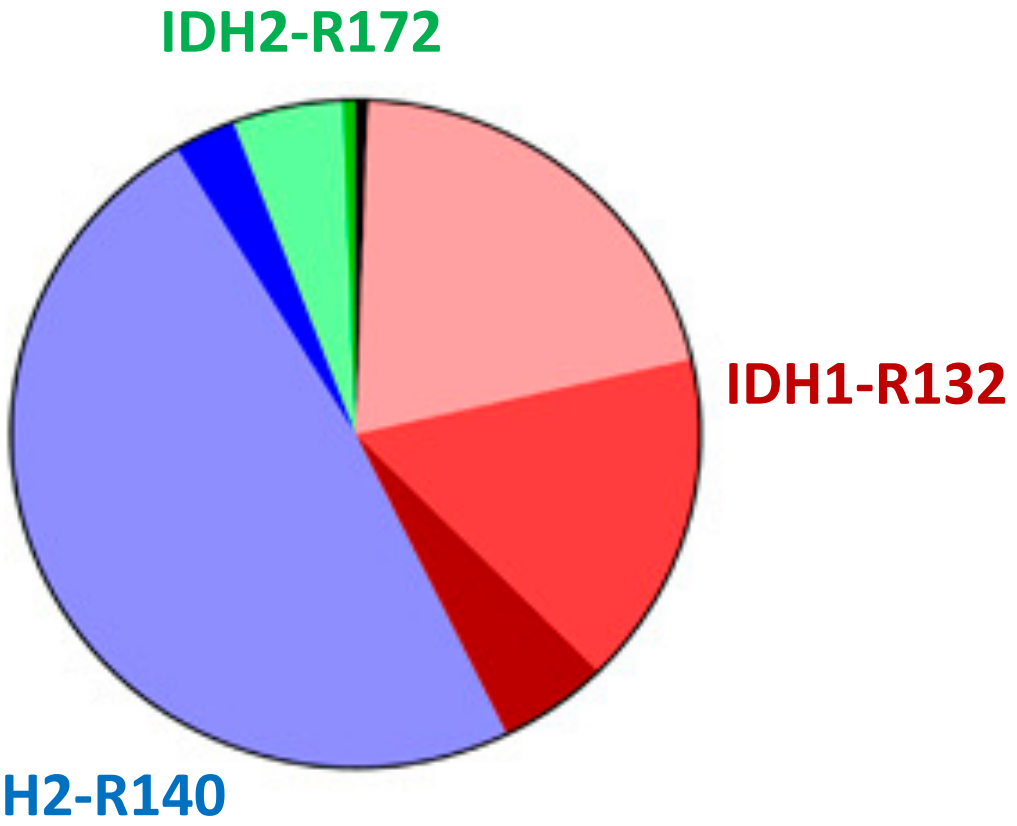
Abbreviations: ALT, alanine aspartate aminotransferase; AML, acute myeloid leukemia; AST, aspartate aminotransferase; FLT3, *fms*-like tyrosine kinase 3; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; mut+, mutated; OS, overall survival; R, randomization; R/R relapsed or refractory.



Perl AE et al, Blood 2022

Characteristics of IDH mutations in AML

- **IDH mutations occur in ~ 20% of AML**
  - Most (~85%) occur in *de novo,* diploid or +8 AML
  - IDH1 in ~8-10% AML, IDH2 in ~ 12-15% AML
  - **↑ prevalence with ↑ patient age (~ 25% of older "unfit" AML)**
  - **Often sustained platelet count**
- **Hot-Spot mutations in enzyme active site**
  - **IDH1-R132 (~40%), IDH2-R140 (~55%) or IDH2-R172 (~5%)**
- **Can be acquired at progression**
  - ~10-15% of AML from MDS
  - **~20-25% of AML from MPN**

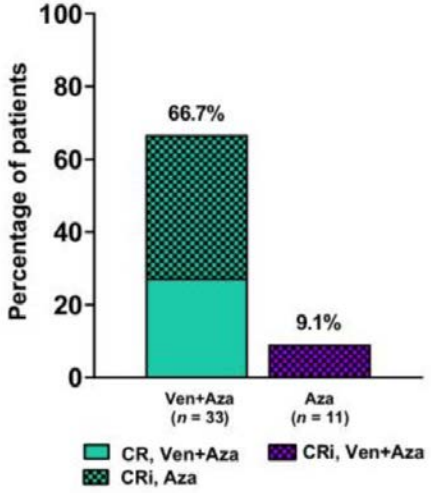


Dang L. Trends in Mol Med, 2010

Chou et al, Leukemia 2011

Molenaar et al, Leukemia 2015

Long-term follow up of *IDH1*^{MUT} AML with HMA-based doublet therapy

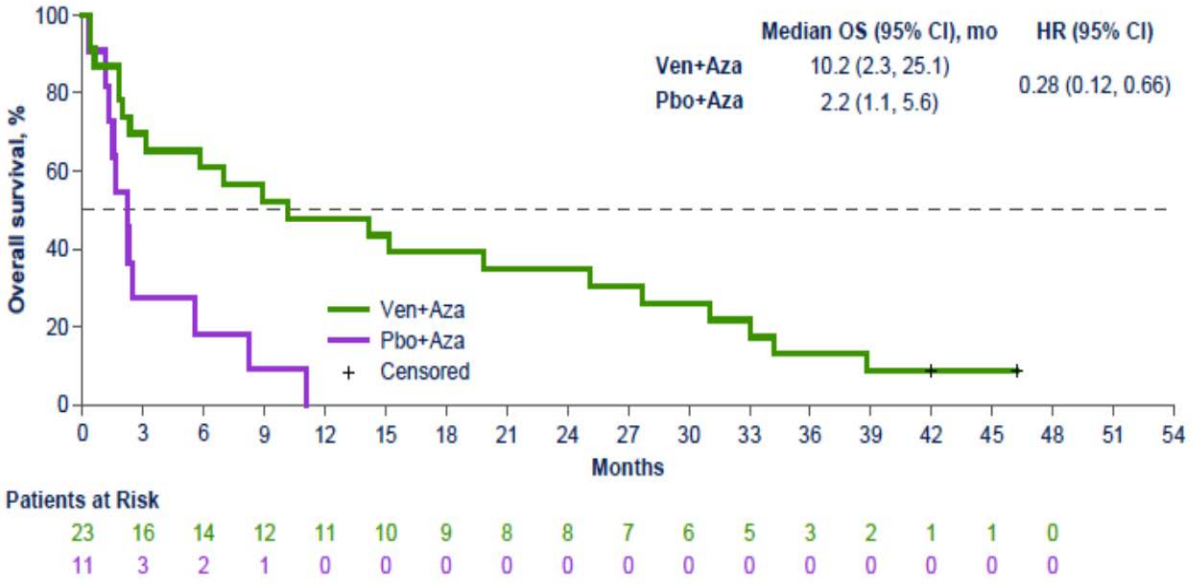


VIALE-A[1]

AZA ± VEN

↓

Median OS: 10.2 months
CRc: 66.7%

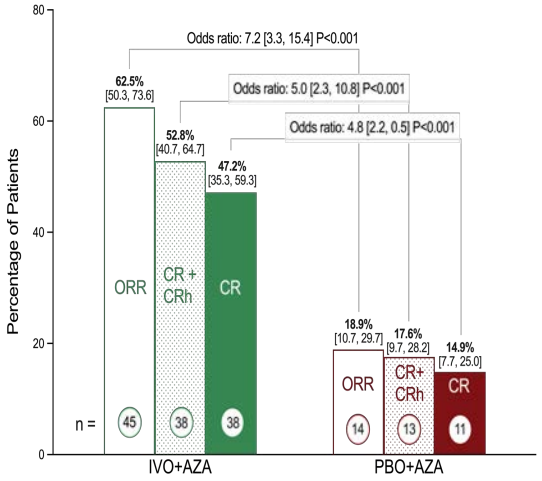


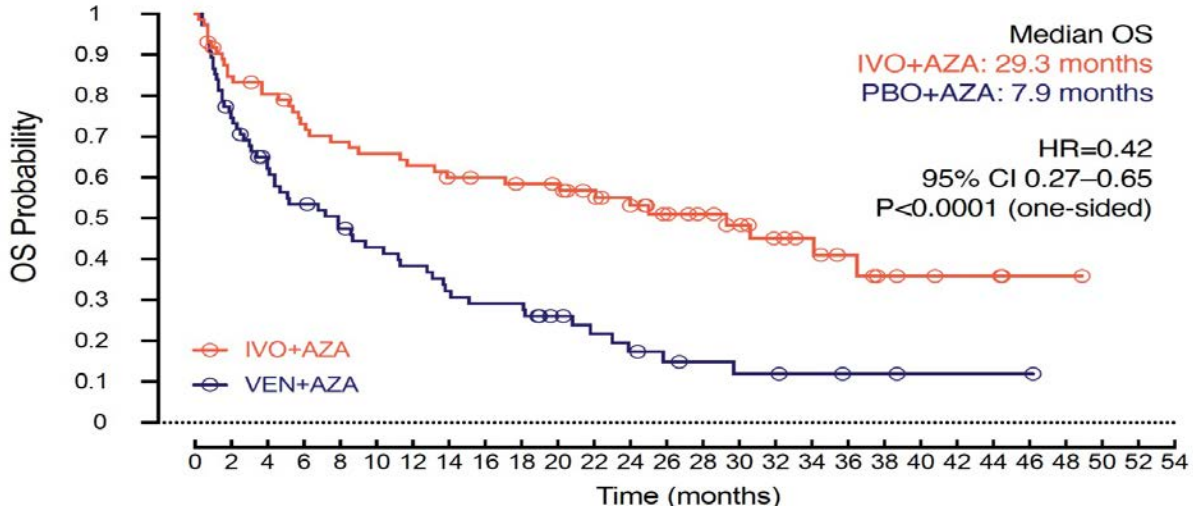
AGILE[2]

AZA ± IVO

↓

Median OS: 29.3 months
CRc: 52.8%

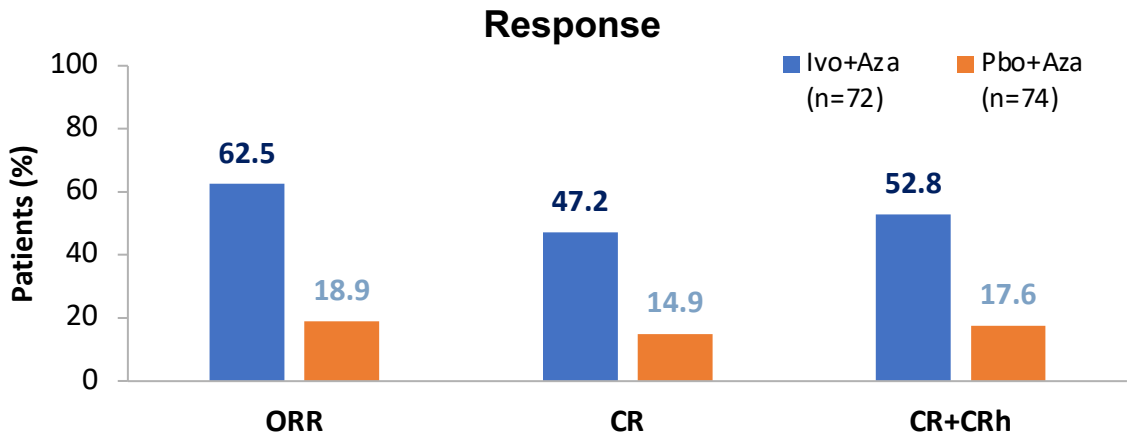


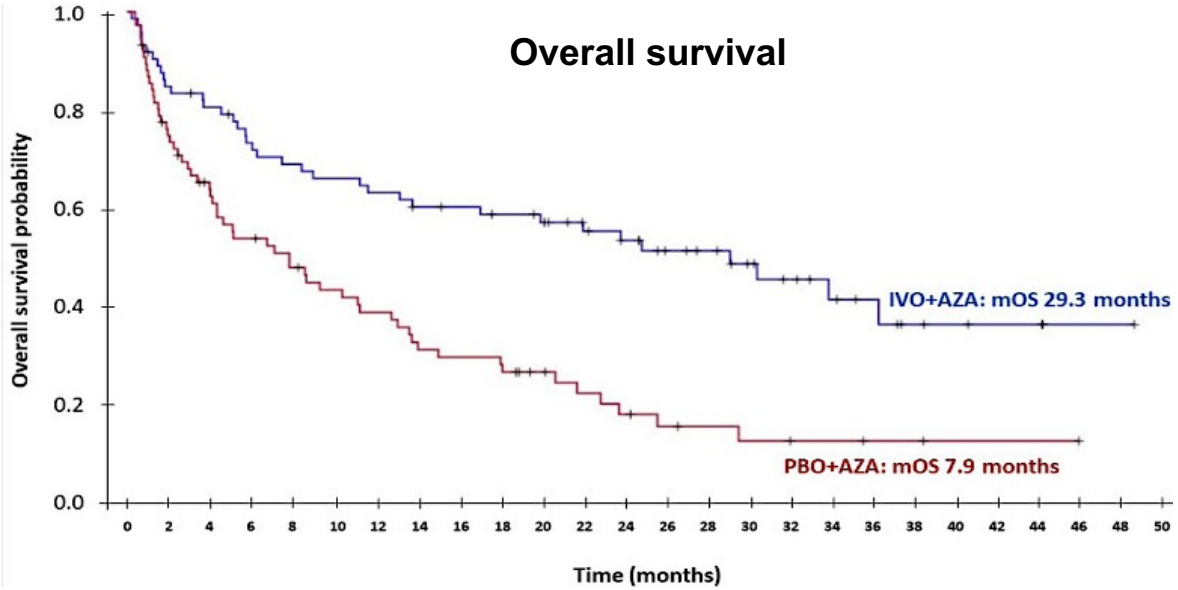


[1]Pollyea et al., Clin Cancer Research 2022; Pratz et al., AJH 2024
[2]Montesinos et al., NEJM 2022; Dohner et al., EHA 2023; Montesinos et al. Blood Advances 2025

AGILE: Ivosidenib+Aza vs Pbo+Aza in ND *IDH1*^{mut} AML

Randomized, Ph3 trial in patients with untreated AML and an IDH1 mutation (N=146)





Grade ≥3 AEs in ≥20% of patients in either arm, n (%)	Ivo+Aza (n=71)	Pbo+Aza (n=73)
Hematologic AEs	50 (70)	47 (64)
Anemia	18 (25)	19 (26)
Febrile neutropenia	20 (28)	25 (34)
Neutropenia	19 (27)	12 (16)
Thrombocytopenia	17 (24)	15 (21)
Non-hematologic AEs		
Pneumonia	16 (23)	21 (29)
Infections	15 (21)	22 (30)

Other safety events, n (%)	Ivo+Aza (n=71)	Pbo+Aza (n=73)
Differentiation syndrome (any grade) Grade ≥3	10 (14) 3 (4)	6 (8) 3 (4)
QT interval prolonged on ECG (any grade) Grade ≥3	14 (20) 7 (10)	5 (7) 2 (3)
Discontinuation as a result of AEs	19 (27)	19 (26)

- Aza, azacitidine; ECG, electrocardiography; Ivo, ivosidenib; mut, mutated; ND, newly diagnosed.

Montesinos P, *et al. N Engl J Med* 2022; **386:**1519–1531; Dohner H et al, EHA Hemasphere 2023 ;Montesinos et al. Blood Advances 2025

Olutasidenib and Ivosidenib

- Olutasidenib has a smaller molecular weight
- Binds both protein units in the dimer (2:1)
- CNS penetration

- Ivosidenib has a larger molecular weight
- Binds at one of the 2 allosteric sites

Different binding kinetics:

- Ivosidenib has slower & tighter binding; greater inhibition of mutant **and** wild-type, with longer half-life
- Olutasidenib binds more quickly and more transiently (quick off-rate)

Reinbold R et al, Nat Commun 2022

Olutasidenib and Ivosidenib Data in R/R AML

***NOTE:** This is a summary of data from independent trials, not a head-to-head comparison within a single study.

PARAMETERS	OLUTASIDENIB[1]	IVOSIDENIB[2,3]
Composite complete remission *(CR + CRh)*	**35%**	**33%**
Median duration of CR/CRh (95% CI)	**25.3 months (13.5, NR)**	**8.2 months (5.6, 12)**
Complete remission rate (CR)	**32%**	**25%**
Median duration of CR	**28.1 months**	**10.1 months**
Overall response rate *(CR + CRh + CRi + PR + MLFS)*	**48%**	**42%**
Median duration of overall response	**15.5 months**	**6.5 months**

Response rates are quite similar, but duration of remissions favor OLUTA

1. de Botton S, et al. *Blood Adv.* 2023;bloodadvances.2022009411; Cortes J et al. J Hematol Oncol 2025;18(1):102. 2. Ivosidenib. Prescribing information. 3. DiNardo CD, et al. *N Engl J Med.* 2018;378:2386-2398.

Olutasidenib and Ivosidenib Baseline Demographics and Disease Characteristics in Approval R/R AML Study Populations

	OLUTASIDENIB[1,2] N=147	IVOSIDENIB[3,4] N=174
Age, median (range)	71 (32-87)	67 (18-87)
Cytogenetic risk, n (%)		
Favorable	6 (4)	–
Intermediate	107 (73)	104 (60)
Poor	25 (17)	**47 (27)**
Missing/unknown	9 (6)	23 (13)
Comutations, n (%)*		
NPM1	31 (21)	44 (26)
FLT3	15 (10)	11 (7)
TP53	9 (6)	**21 (13)**

	OLUTASIDENIB[1,2] N=147	IVOSIDENIB[3,4] N=174
Prior AML therapy outcome, n (%)		
Primary refractory	46 (31)	64 (37)
Untreated relapse	81 (55)	65 (37)
Refractory relapse	20 (14)	**45 (26)**
Prior regimens, median (range)	2 (1-7)	2 (1-6)
Prior Venetoclax, n (%)	**12 (8)**	0
Prior HSCT, n (%)	17 (12)	**40 (23)**
ECOG PS, n (%)		
0	45 (31)	36 (21)
1	76 (52)	97 (56)
2	23 (16)	39 (22)
3	0 (0)	2 (1)

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

*For ivosidenib, comutation analysis based on Choe et al. (2020), which had a baseline of 167 samples (ie, denominator=167).

1. de Botton S, et al. *Blood Adv.* 2023;bloodadvances.2022009411. 2. Olutasidenib. Prescribing information. 3. Ivosidenib. Prescribing information.
4. Choe S, et al. *Blood Adv.* 2020;4(9):1894-1905.

Olutasidenib 5-Year Results - TEAEs

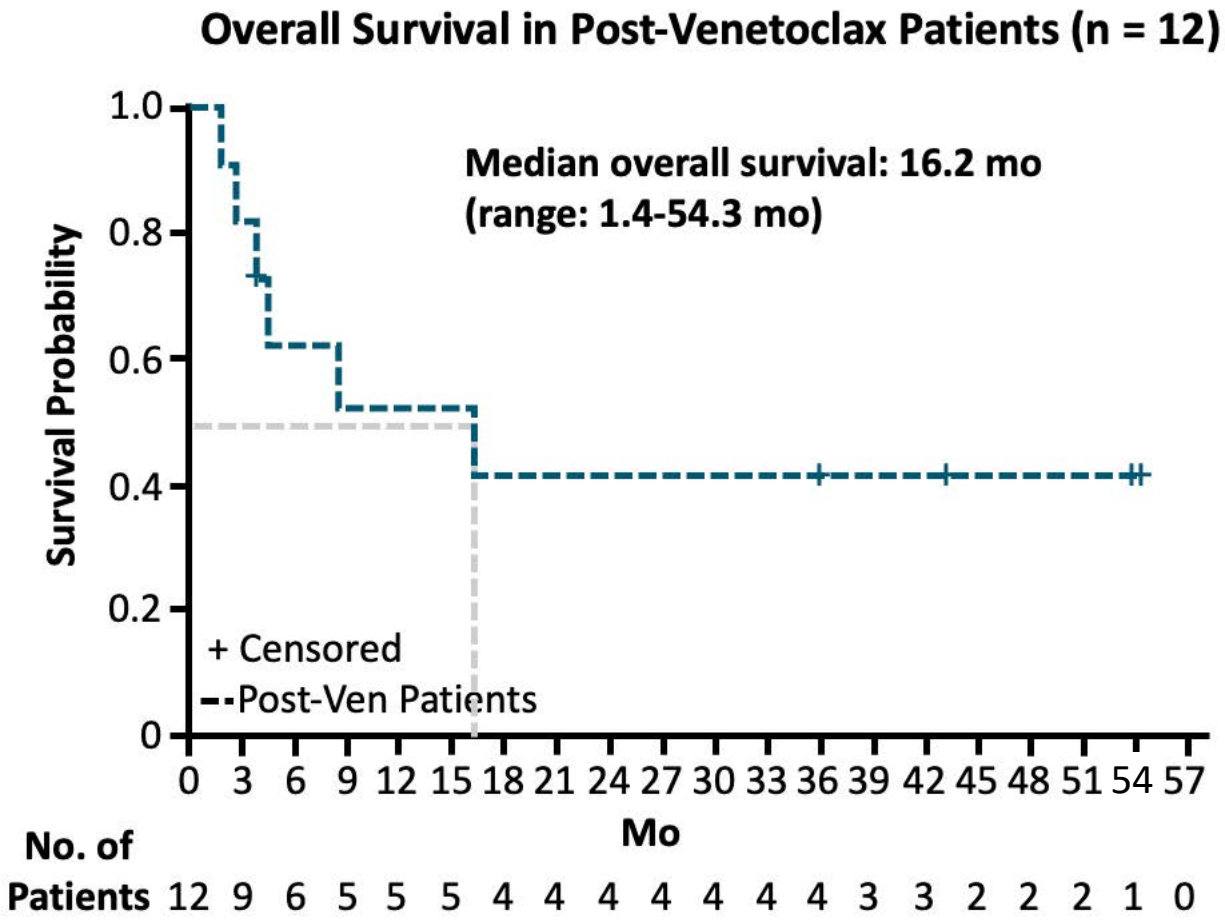
TEAEs	By Year 3 (*N* = 153) *n* (%)	By Year 5 (*N* = 153) *n* (%)	New Events by Year 5, *n*
Nausea	58 (38)	59 (39)	1
Constipation	40 (26)	41 (27)	1
RBC count decreased	40 (26)	40 (26)	0
WBC count increased	38 (25)	38 (25)	0
Pyrexia	36 (24)	36 (24)	0
Fatigue	35 (23)	35 (23)	0
Febrile neutropenia	33 (22)	33 (22)	0
Hypokalemia	30 (20)	33 (22)	3
Diarrhea	31 (20)	32 (21)	1
Platelet count decreased	30 (20)	32 (21)	2
Dyspnea	31 (20)	31 (20)	0
Asthenia	25 (16)	30 (20)	5

RBC, red blood cell; TEAEs, treatment emergent adverse events; WBC, white blood cell

Cortes J et al. *J Hematol Oncol* 2025;18(1):102.

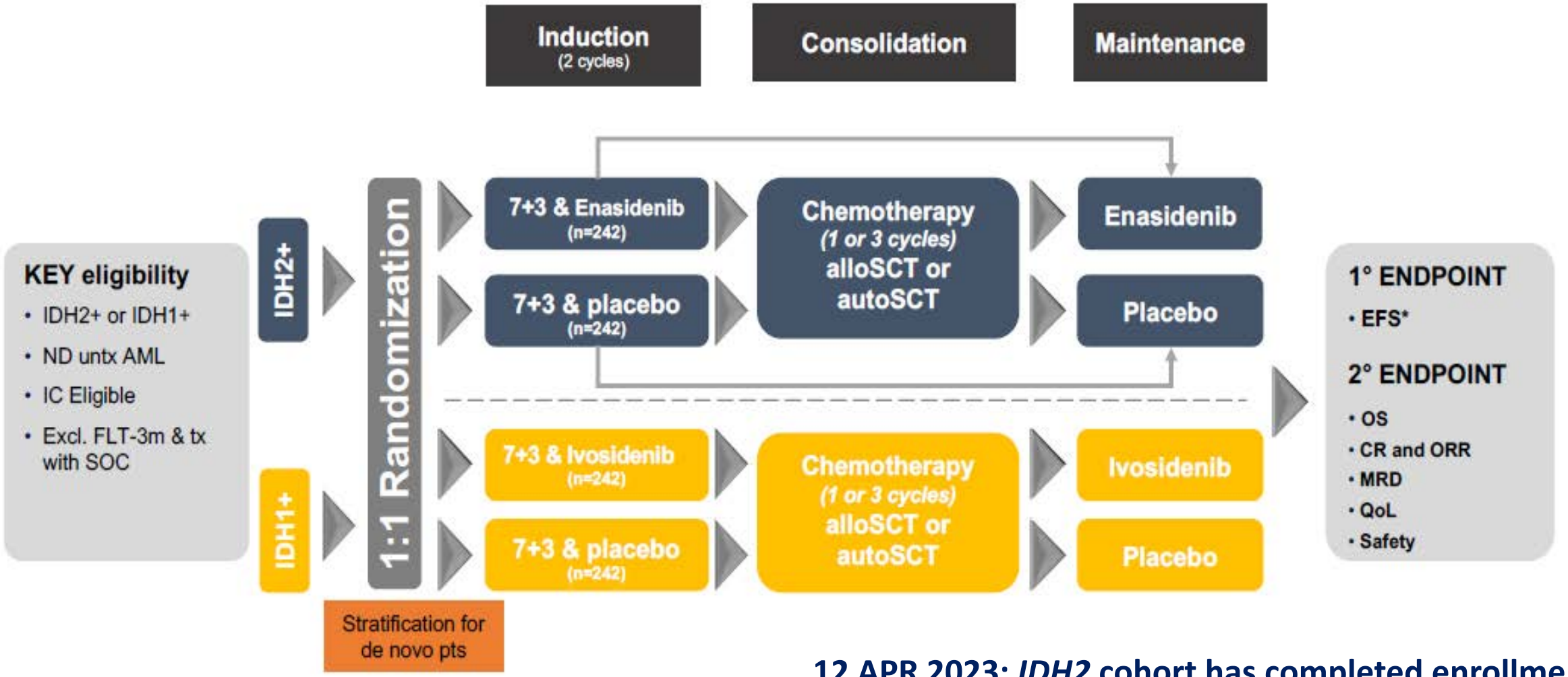
Post-Venetoclax Olutasidenib Outcomes

- In 12 pts R/R to venetoclax (median duration of previous venetoclax therapy of 6.7 mo), olutasidenib yielded:
  - **CR/CRh**: 33%
  - **Median time to CR/CRh:** 2.4 mo (1-2.8)
  - **Median duration of CR/CRh:** not reached (range: 4.8-50.6 mo)
- **ORR:** 50%; CR: 25%; CRh: 8%; CRi: 17%
  - Median time to ORR: 1.7 mo
  - Median duration of ORR: NR (1.2-52.5 mo)



Abaza. Am J Hematol. 2024;99:606. Cortes. EHA 2024; Abstract P614. Cortes. EHA 2024; Abstract 6528.

Randomized Phase III HOVON 150 / AMLSG 29-18 Trial



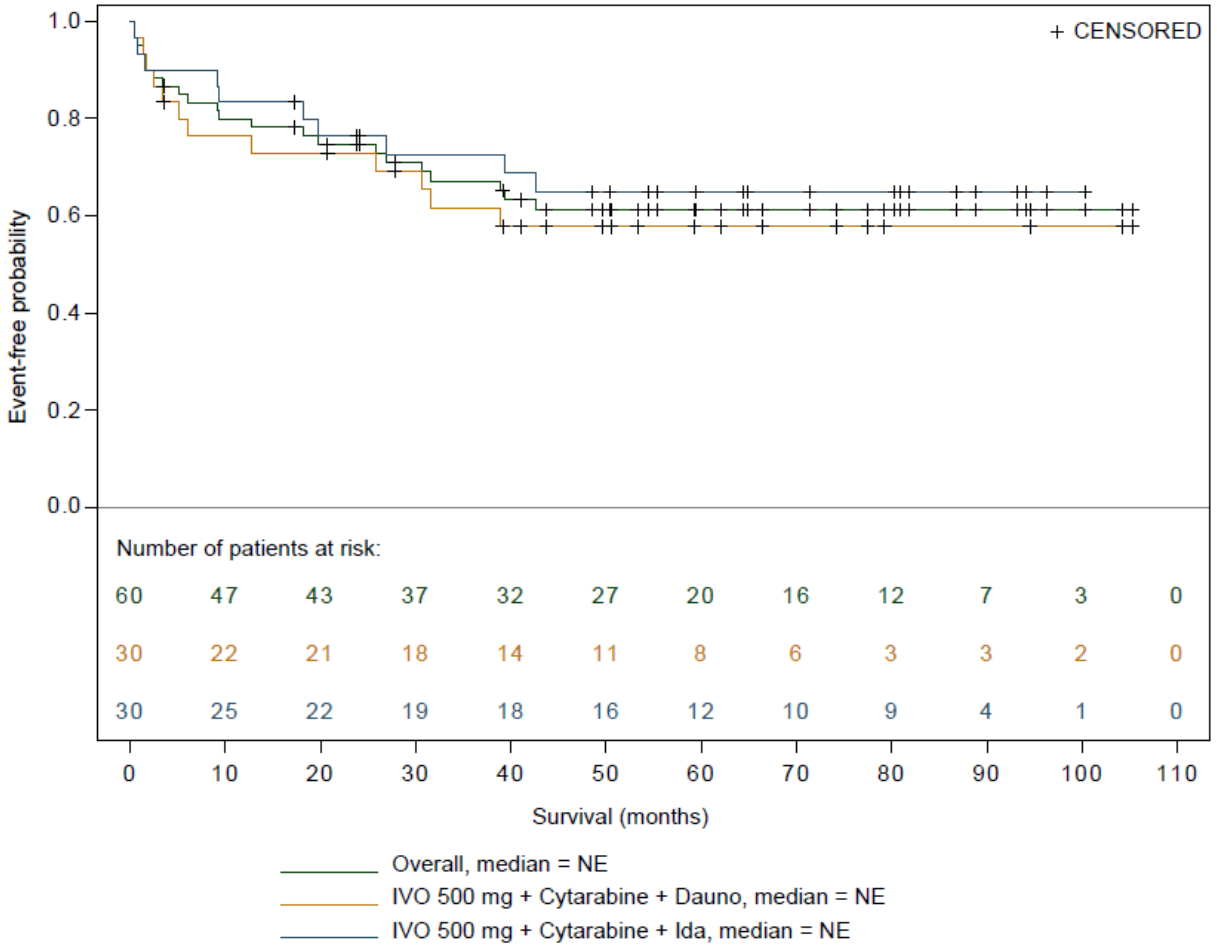
12 APR 2023: *IDH2* cohort has completed enrollment
17 SEPT 2024: *IDH1* cohort has completed enrollment

- Study design provided courtesy of HOVON and AMSLG chairs.

Courtesy of Courtney DiNardo, MD, MSCE

7+3+IVO in ND IDH1^{mut} AML: 3-year overall survival was 67%

Overall survival[b]: IVO cohorts



Data cutoff: 16 January 2025

	IVO 500 mg + Cytarabine + Dauno (n=30)	IVO 500 mg + Cytarabine + Ida (n=30)	Total (N=60)
OS probability,[a] %			
12 months	76	83	80
24 months	73	76	75
36 months	62	73	67
48 months	58	65	61
60 months	58	65	61
OS duration, mo, median (95% CI)	NE (25.8–NE)	NE (39.4–NE)	NE (39.4–NE)
Sensitivity analysis, median (95% CI)	30.6 (6.1–NE)	NE (39.4–NE)	42.6 (25.8–NE)
12-month EFS, %	41	58	49

- **29 pts (48%) underwent HSCT**; 13 (22%) after induction, 14 (23%) after consolidation, 2 (3%) during maintenance
- **19 pts (32%) received IVO maintenance** (median time maintenance 19.4 mo, and 10 pts still on study survival f/u)

[a]Calculated using Kaplan-Meier estimate of survival function.
[b]OS sensitivity analyses censored patients at their time of HSCT, or the last dose date + 28 days if the HSCT date is not available.

Stein EM et al, ASH 2025

AE Profiles and Clinical Expectations of IDH Inhibitors as monotherapy in R/R AML

Treatment-Related TEAEs, Grade 3/4, n (%)	**Enasidenib (IDH2i)** 100 mg/d (n = 153)[1]	**Ivosidenib (IDH1i)** 500 mg/d (n = 179)[2]	**Olutasidenib** (IDH1i) 150 mg BID (n = 153)[3]
	CR = 20% **CRc = 26%** **mOS= 9mo** **(~20mo if CR)**	**CR = 25%** **CRc = 33%** **mOS= 9mo** **(~20mo if CR)**	**CR = 32%** **CRc = 35%** **mOS= 12mo** **(NR if CR, 18mo OS 78%)**
Hyperbilirubinemia	**13 (8)**	NR	2 (1)
Prolonged QT interval	---	**14 (8)**	1 (<1)
IDH differentiation syndrome	**11 (7)**	**7 (4)**	**12 (7)**
Anemia	10 (7)	4 (2)	7 (5)
Thrombocytopenia	8 (5)	3 (2)	6 (4)
Tumor lysis syndrome	5 (3)	---	3 (2)
Decreased appetite	3 (2)	---	---
Leukocytosis	2 (1)	3 (2)	7 (5)
Hepatic AESI (transaminitis)	---	----	**23 (15)**

NR, not reported; TEAEs, treatment-emergent adverse events.

1. Stein EM, et al. Blood. 2017;130:722-731; 2. DiNardo CD, et al. N Engl J Med. 2018;378:2386-2398; 3. De Botton S, et al. Blood Adv. 2023;7:3117-3127.

QUESTIONS?

Module 16: Acute Myeloid Leukemia (AML)

Current Management Approaches for FLT3- and IDH-Mutated AML — Dr DiNardo

Current and Future Role of Menin Inhibitors for Patients with AML — Dr Erba

Menin Inhibitors In Acute Myeloid Leukemia: Current and Future

Harry P. Erba, MD PhD
Professor, Medicine
Director, Leukemia Program
Division of Hematologic Malignancies and Cellular Therapy
Duke University
Durham, NC

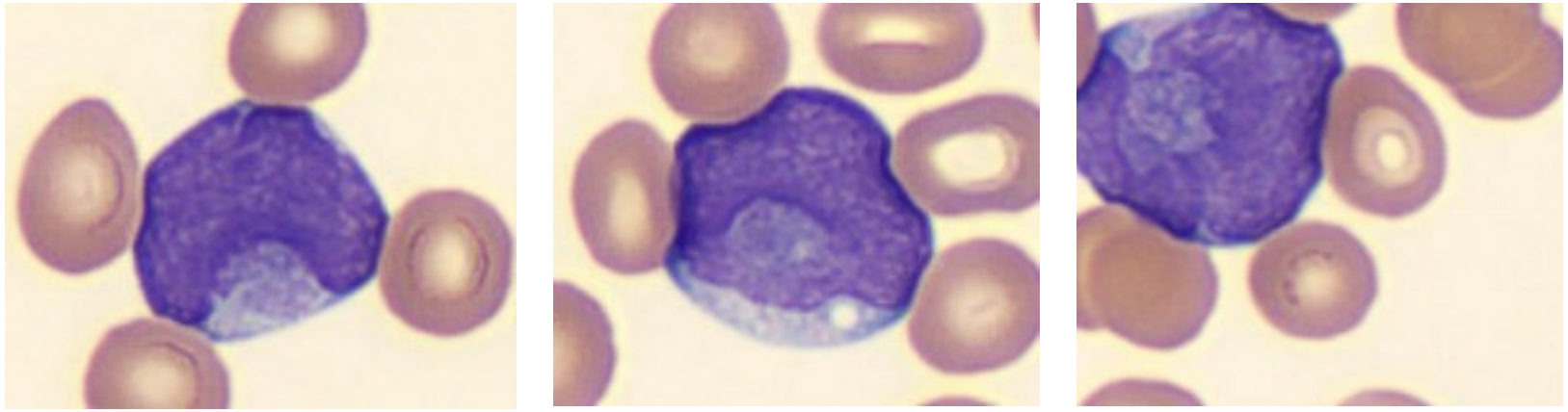
DukeHealth

Disclosures

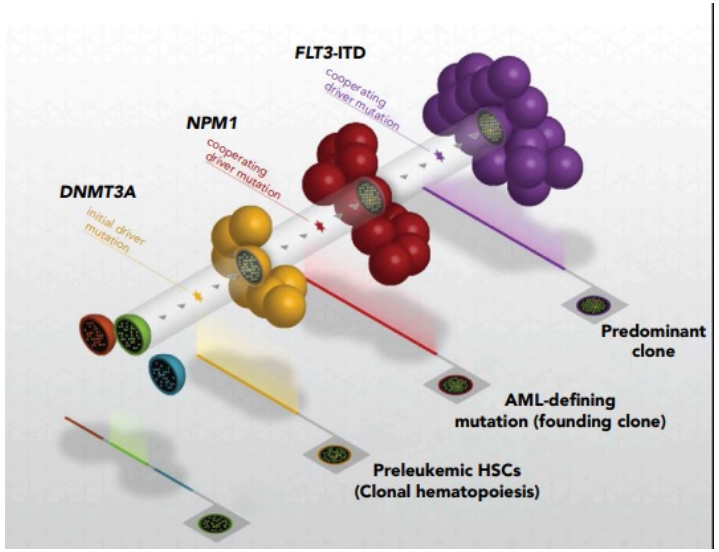
Advisory Committees	Daiichi Sankyo Inc, GlycoMimetics Inc, Kura Oncology, Sumitomo Pharma America
Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, GlycoMimetics Inc, Kura Oncology, Schrödinger, Servier Pharmaceuticals LLC, Stemline Therapeutics Inc, Sumitomo Pharma America, Taiho Oncology Inc
Contracted Research	Agios Pharmaceuticals Inc, ALX Oncology, Aptose Biosciences Inc, Ascentage Pharma, AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Gilead Sciences Inc, ImmunoGen Inc, Kura Oncology, MacroGenics Inc, Novartis, Oryzon, Rigel Pharmaceuticals Inc, Sumitomo Pharma America, Taiho Oncology Inc
Speakers Bureaus	AbbVie Inc, Incyte Corporation, Jazz Pharmaceuticals Inc, Kura Oncology, Servier Pharmaceuticals LLC, Syndax Pharmaceuticals

Features of *NPM1*m AML

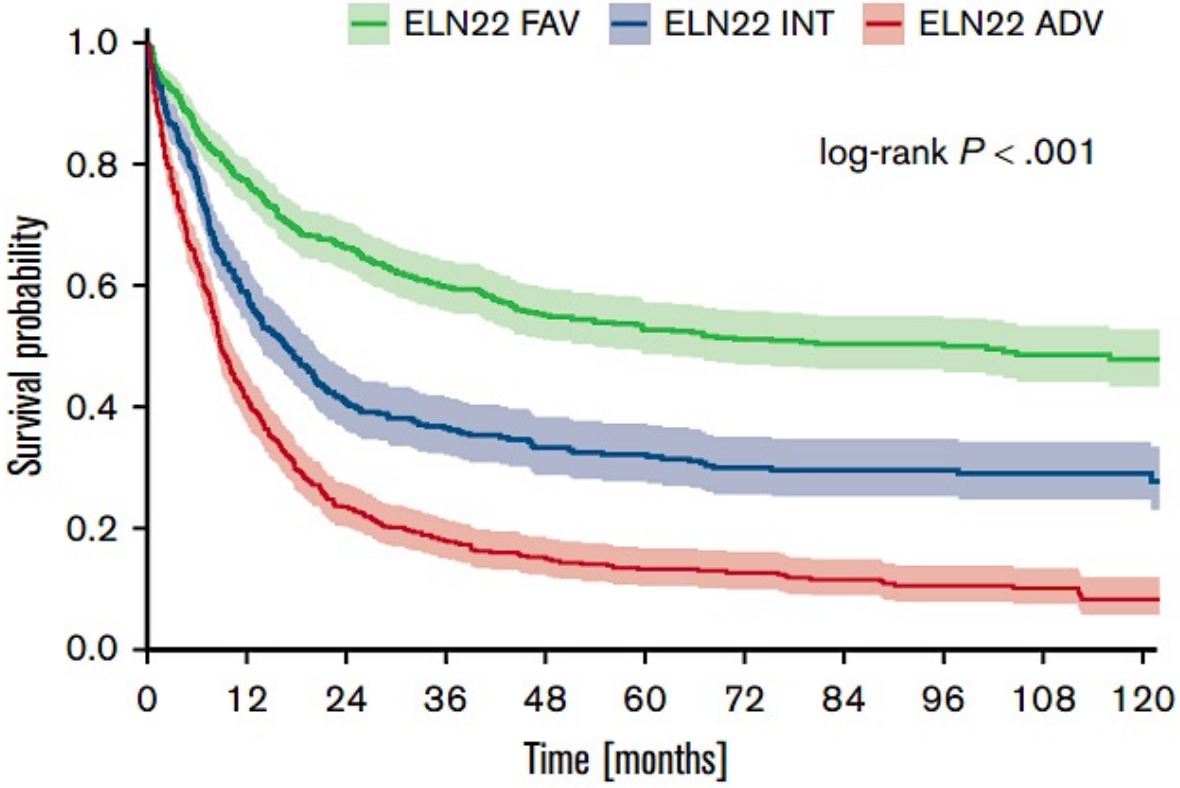
1. One of the three most common genetic lesions in adult AML (30-35%)
2. Typically associated with normal karyotype (85% of *NPM1*m cases)
3. An AML driver mutation, not observed in clonal hematopoiesis
4. Genetically-defined AML per ICC-2022 (>10% blasts) and WHO 2022 (regardless blast %)
5. Frequently co-occurs with mutant *FLT3*, *DNMT3A, IDH1,* and *IDH2*
6. Myeloid immunophenotype with decreased/absent expression of CD34 and HLA-Dr
7. Deep invaginations of the nuclear envelope (fish mouth or cup-like nuclei)

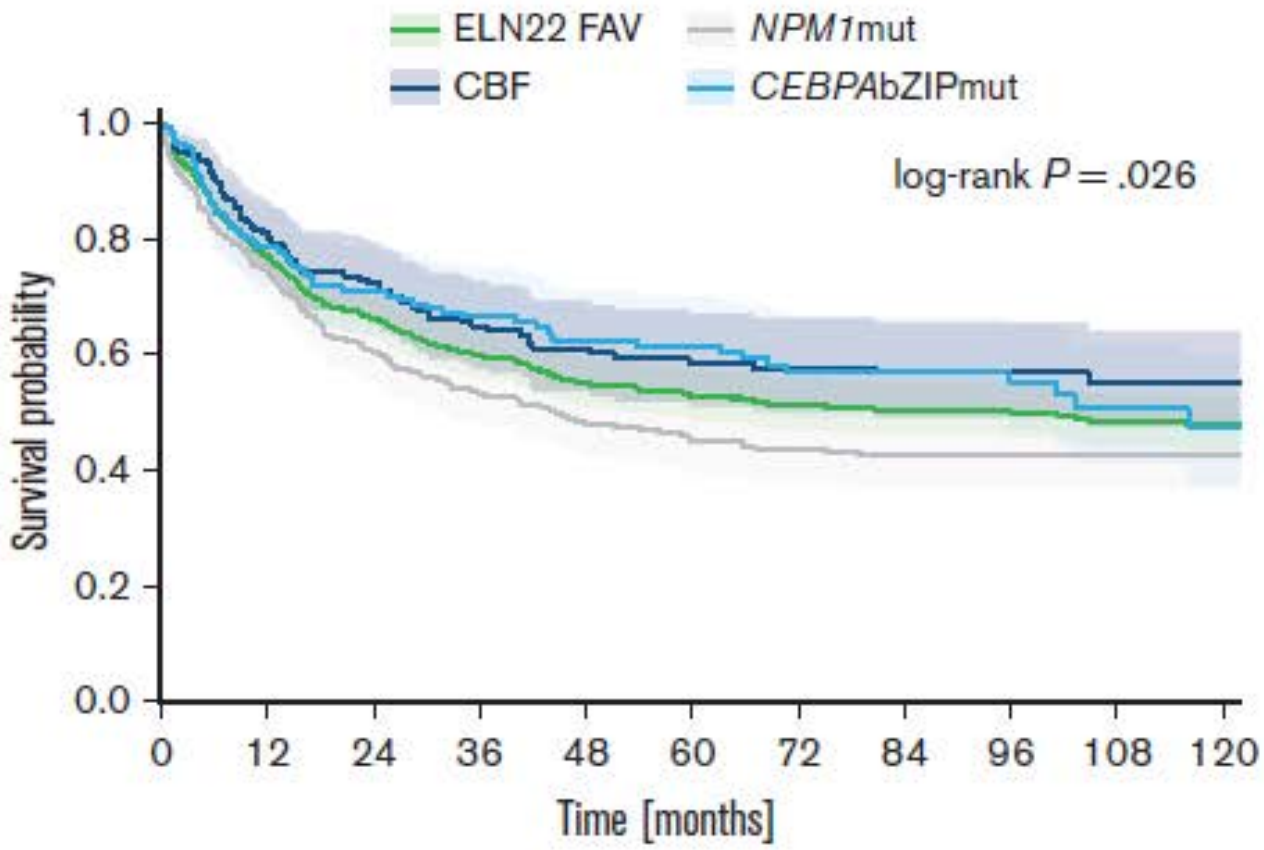


Falini B, et al. *Blood* 2020; 136: 1707



Overall Survival of Adults with Acute Myeloid Leukemia (SAL Registry)

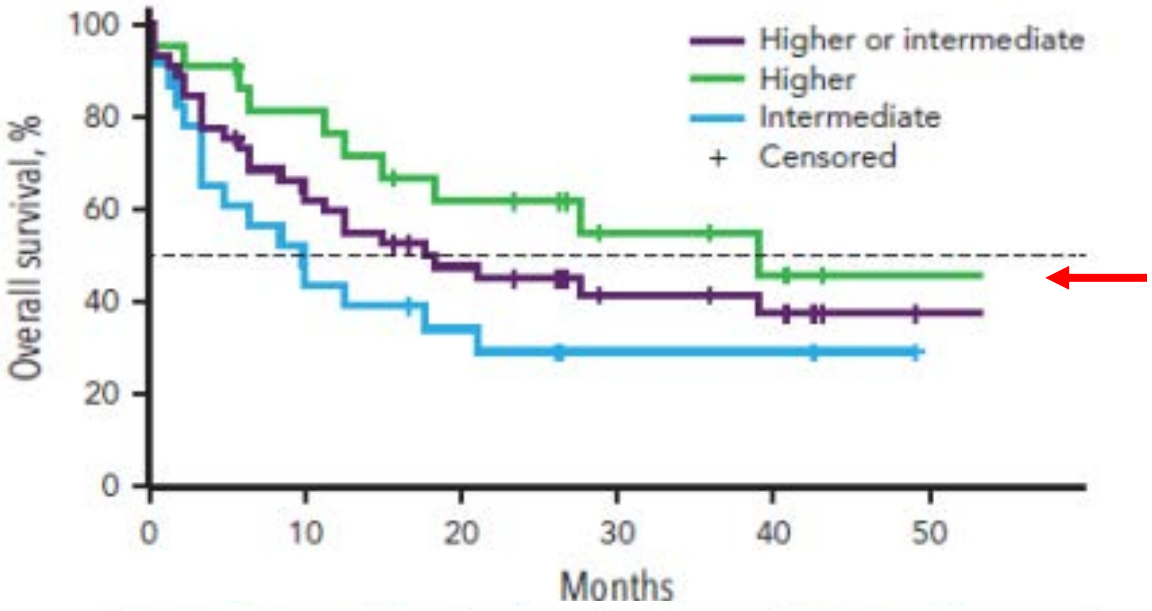




1570 adults received cytarabine plus anthracycline/mitoxantrone induction followed by high dose cytarabine based consolidation, +/- auto or allo HSCT

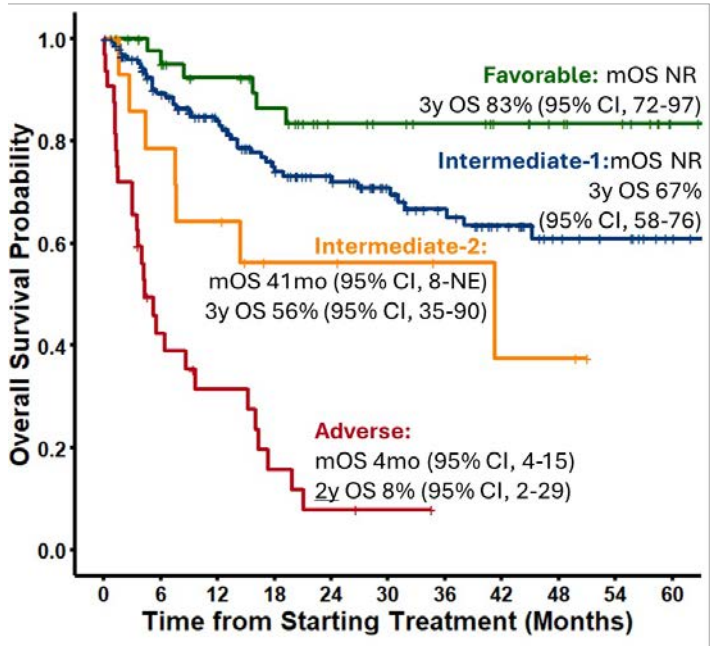
Ruhnke L, et al. *Blood Adv.* 2025; 9(6): 1392

Venetoclax in Combination with HMA or Intensive Chemotherapy is Effective in *NPM1* Mutated AML



NPM1 mutated: Benefit group	N	Events	Median OS, months (95% CI)
Higher or intermediate	45	26	18.3 (9.9, NR)
Higher	22	10	39.0 (12.5, NR)
Intermediate	23	16	9.9 (3.4, 21.1)

Higher benefit: *TP53*^{WT}, no *FLT3* ITD, *NRAS*^{WT}, *KRAS*^{WT}

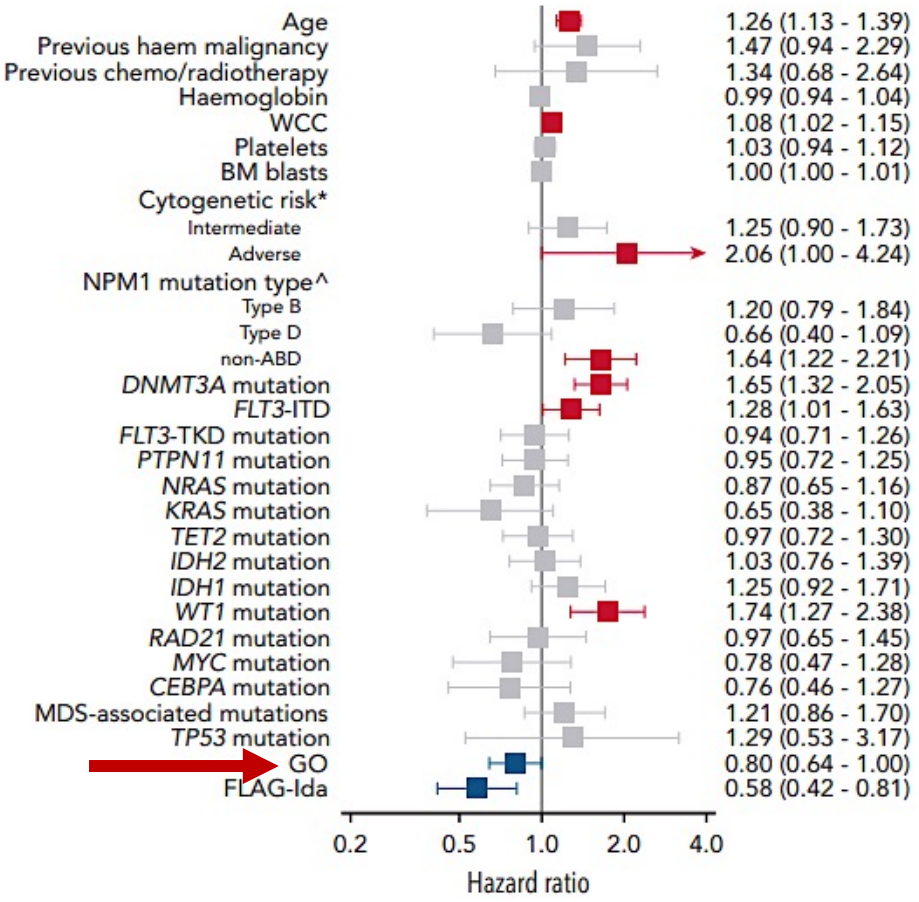


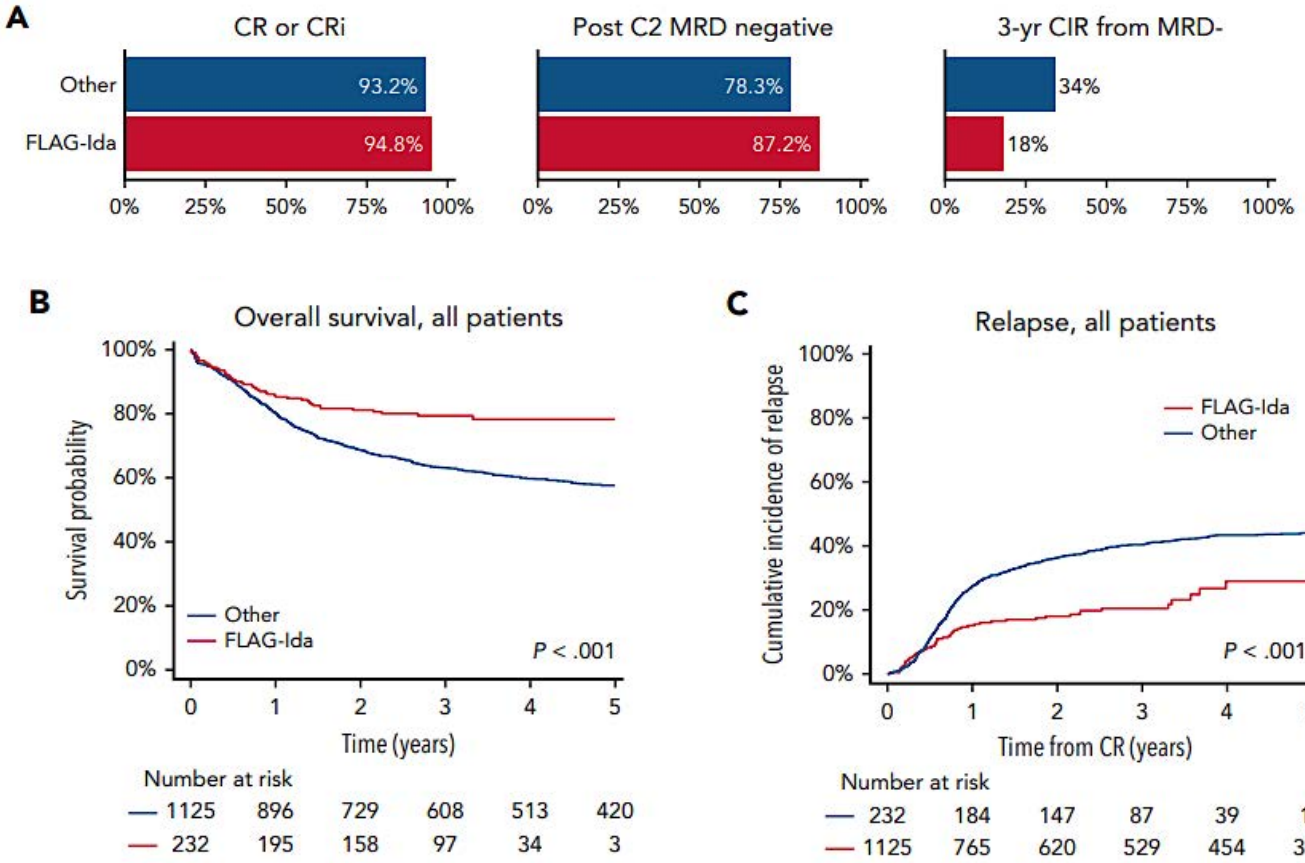
- **Adverse:** *TP53*^{mut} or *MECOM*r
- **Intermediate-2:** -5/del(5q), -7, -17, or abn(17p)
- **Favorable:** **diploid** cytogenetics **and** *NPM1*^{mut} **or** *CEBPA*^{bZIP}
- **Intermediate-1:** all others

FLAG-IDA + VEN
CLIA + VEN
CPX-351 + VEN

Dohner H, et al. *Blood* 2024; 144(21): 2211 1311; Jen W-Y, et al. EHA 2025

FLAG-IDA and Gemtuzumab are Associated with Higher Rate of MRD Negative Remission, Improved Survival and Lower Cumulative Incidence of Relapse in Younger *NPM1*m AML Patients





Othman J, et al. *Blood* 2024; 144(7): 714-728

Rel/Ref *NPM1*m AML Patients (MDACC Retrospective)

Table 2. Response rates by line and type of salvage therapy

	All therapies		HI		LI		LI + venetoclax	
	NPM1c	*NPM1*^{wt}	*NPM1c*	*NPM1*^{wt}	*NPM1c*	*NPM1*^{wt}	*NPM1c*	*NPM1*^{wt}
All lines (N)	206	1516	68	459	109	762	24	201
CR (%)	49 (24)*	224 (15)	32 (47)†	95 (21)	7 (6)	87 (11)	7 (29)	34 (12)
CRi (%)	53 (26)*	272 (18)	11 (16)	73 (16)	31 (28)*	117 (15)	10 (42)	56 (20)
CR/CRi (%)	102 (50)†	496 (33)	43 (63)†	168 (37)	38 (34)	194 (26)	17 (71)*	90 (32)
S1 (N)	132	953	52	313	63	443	13	140
CR (%)	42 (32)*	178 (19)	28 (48)†	82 (26)	6 (10)	56 (13)	5 (38)	27 (19)
CRi (%)	32 (24)	175 (18)	8 (19)	49 (16)	18 (29)*	71 (18)	5 (38)	37 (26)
CR/CRi (%)	74 (56)†	353 (37)	36 (67)*	131 (42)	24 (38)	127 (29)	10 (76)*	64 (45)

Median OS for NPM1m vs NPM1wt	NPM1m had no impact on risk of relapse or death
After salvage 1	7.8 vs 6.0 mos
After salvage 2	5.3 vs 4.1 mos
After salvage 3	3.5 vs 3.6 mos

Issa GC, et al. *Blood Adv.* 2023;7(6):933.

KMT2A-r Is a Stable Driver of Leukemogenesis with over 100 Fusion Partners [1-3]

Pediatric acute leukemia

AML	ALL
Infant: 35%-60%[2] Pediatric: ~10%-15%[1,2]	Infant: >80%[3] Pediatric: 5%-6%[3]

Adult acute leukemia

AML	ALL	MPAL
~10%[2]	15%[3]	1%-3%[4]

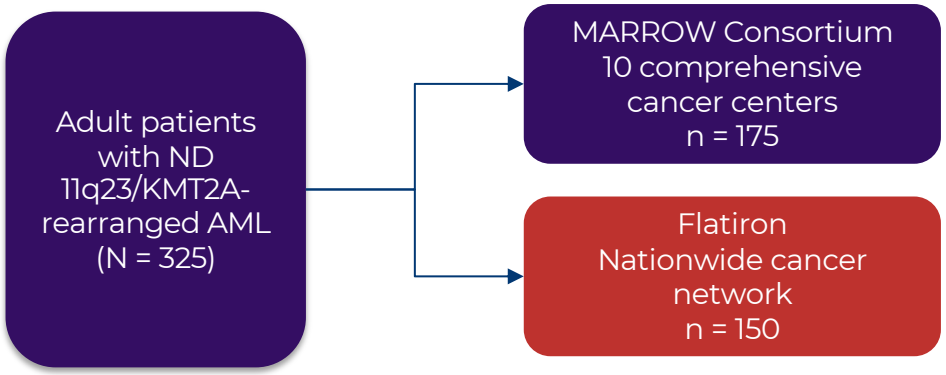
- The median age at diagnosis for *KMT2A*-r AML is lower than for all AML (52 vs. 68 years)[5,6]

1. Issa GC, et al. *Leukemia*. 2021;35:2482-2495. 2. Conneely SE, Rau RE. *Cancer Metastasis Rev*. 2020;39(1):189-209.
3. Górecki M, et al. *Biomedicines*. 2023;11:821. 4. George BS, et al. *Biomedicines*. 2022;10(8):1974.
5. Issa GC, et al. *Blood Cancer J*. 2021;11:162. 6. Appelbaum FR, et al. *Blood*. 2006;107:3481-3485.

Clinical Characteristics and Outcomes of Adults With *KMT2Ar* AML

Baseline demographics	All N = 325	MARROW Consortium n = 175	Flatiron n = 150	*P*-value*
Median age, yr (range)	55 (18-79)	50 (18-79)	62 (20-84)	<0.001
Age ≥60 yrs, n (%)	132 (41%)	48 (27%)	84 (56%)	<0.001
Non-Hispanic black, n (%)	32 (11%)	16 (10%)	16 (13%)	0.12
Hispanic, n (%)	32 (11%)	20 (12%)	12 (11%)	0.63
t(9;11), n (%)	147 (45%)	68 (39%)	79 (63%)	0.01

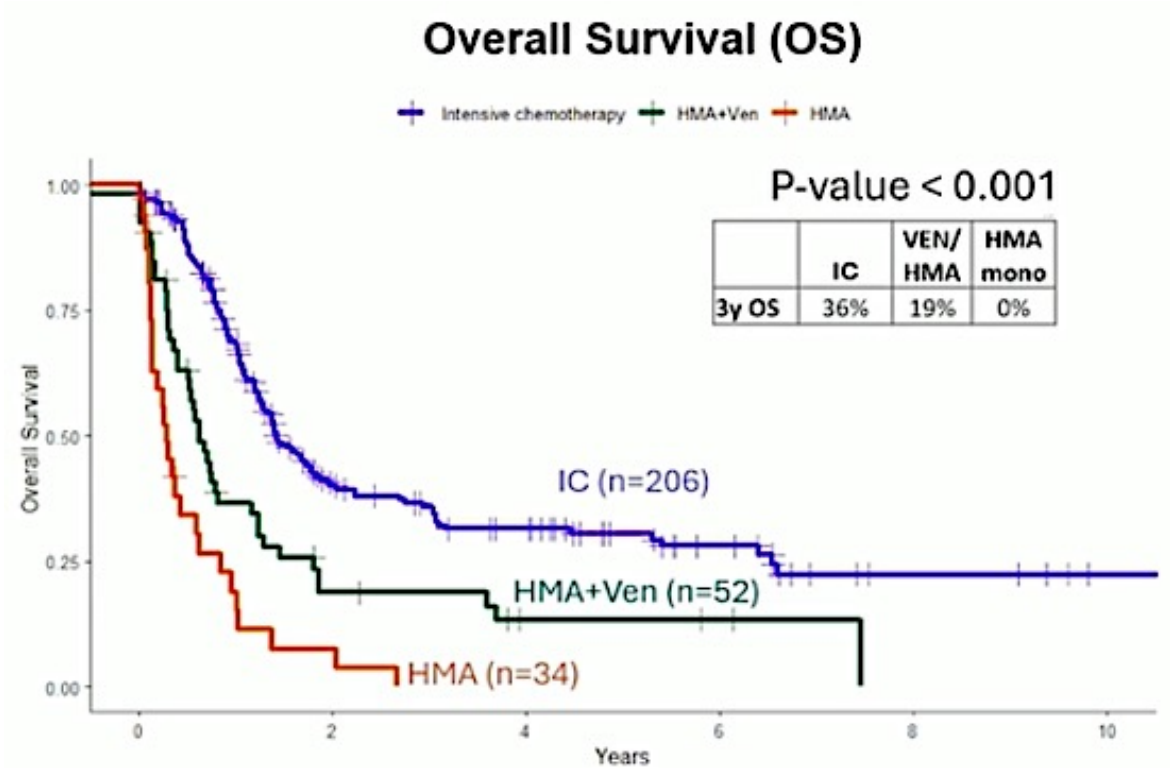
Independent and combined analyses of data from patients with 11q23/KMT2A-r AML in 2 datasets

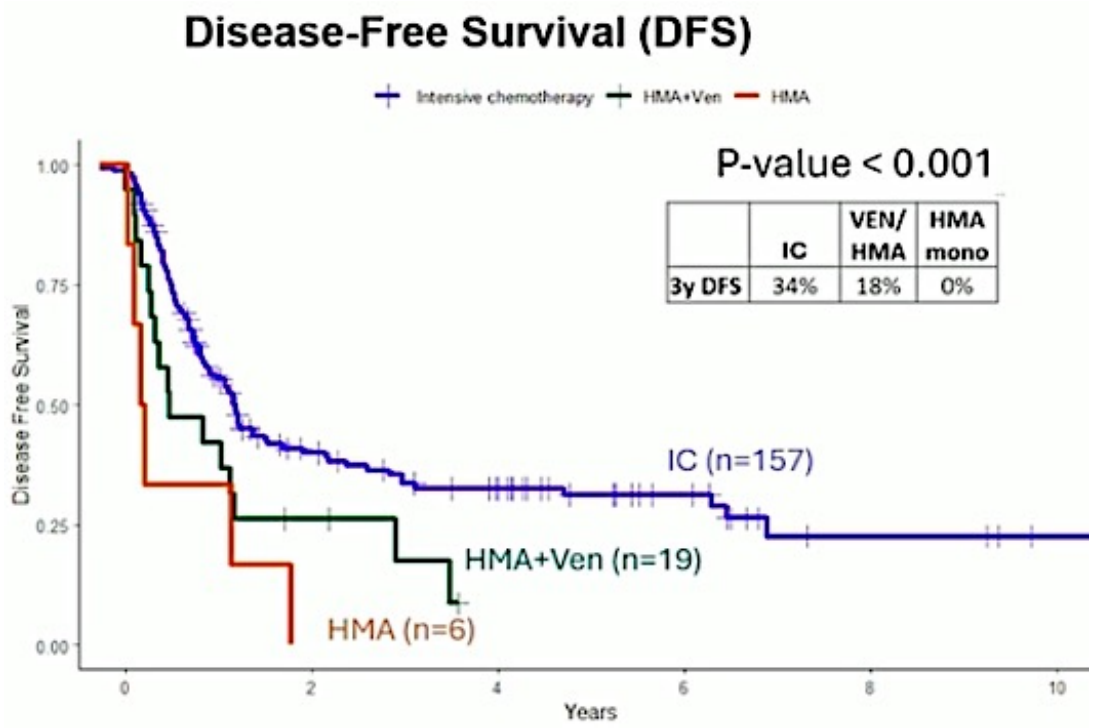


Molecular profile	All N = 325
NRAS	23%
KRAS	21%
TP53	13%
FLT-TKD/FLT3-ITD	12%/10%
TET2	11%

McMahon C, et al. ASH 2025. Abstract 292.

Outcomes of Adults With *KMT2A*r AML





	IC N = 214	VEN/HMA N = 54	HMA mono N = 35	P-value
CRc	75%	37%	20%	<0.001

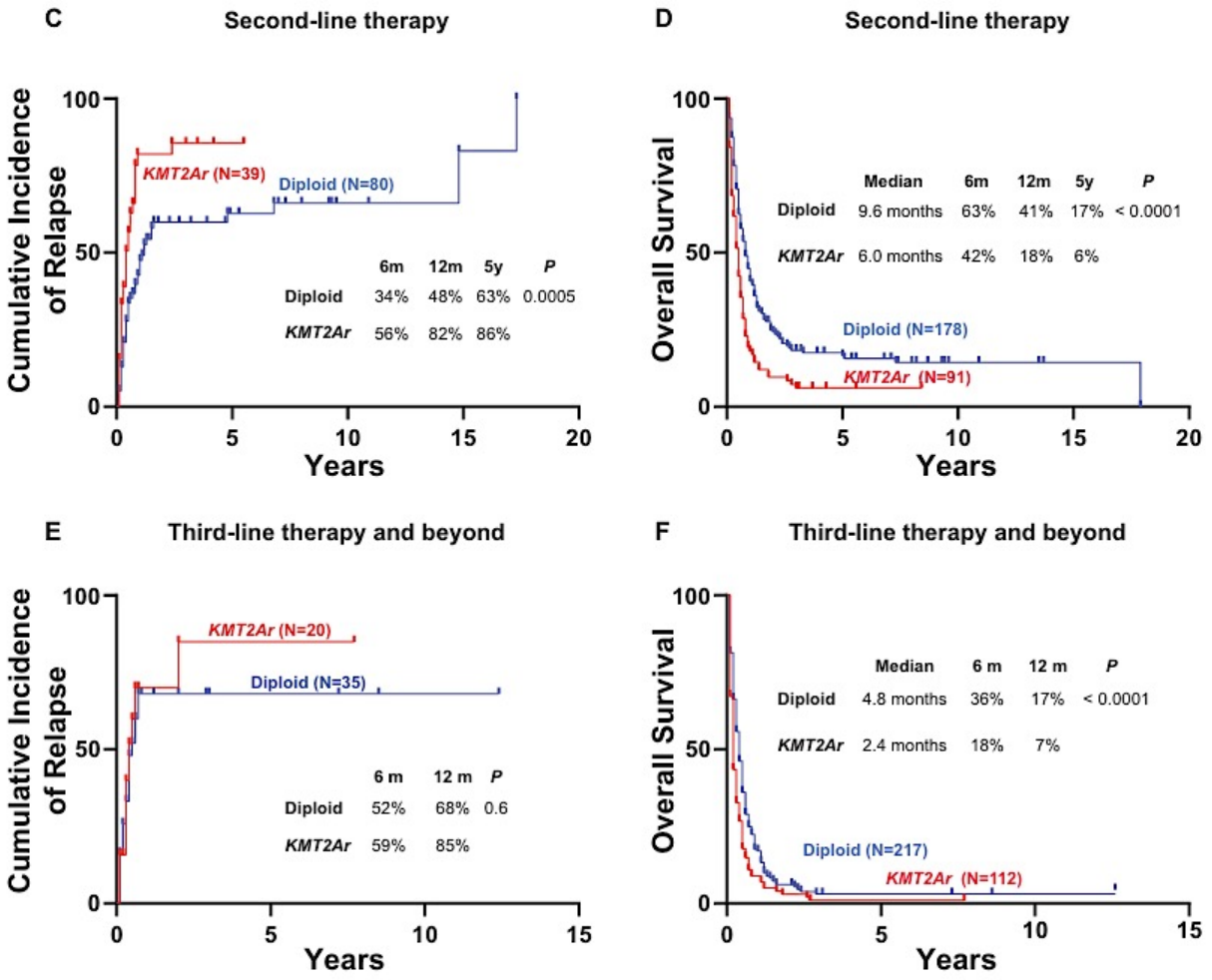
- Survival outcomes improved with IC vs VEN/HMA or HMA monotherapy in patients with *KMT2A*r AML

McMahon C, et al. ASH 2025. Abstract 292.

Patients with Relapsed/Refractory *KMT2A*r AML have Poor Outcome

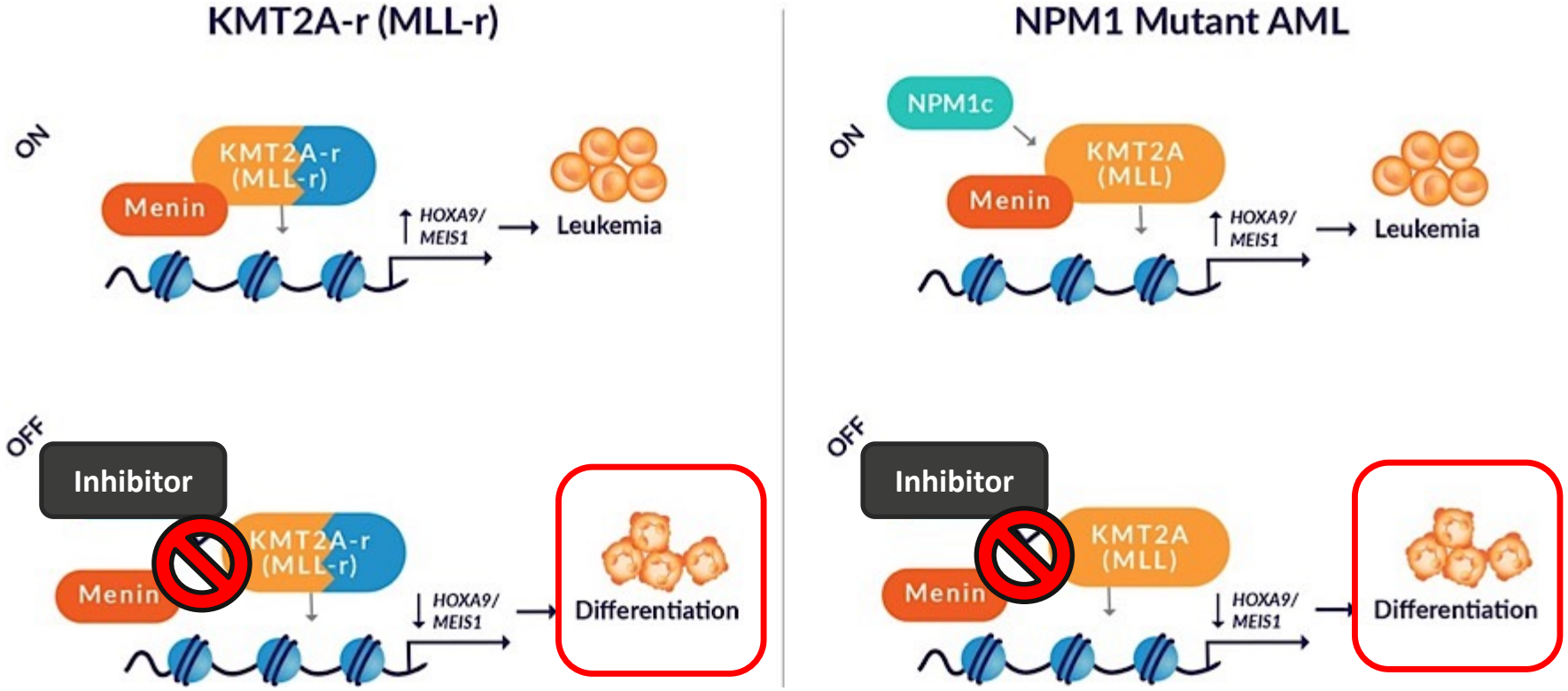
- In a retrospective analysis, 112 adult patients with R/R *KMT2A*r AML were identified and compared with 217 age-matched patients with a normal karyotype

112 patients with R/R KMT2Ar after ≥3 lines of therapy	
Response to SOC therapies	
9%	CR + CRi
91%	No response
Survival outcomes	
2.4 mo	Median OS
7%	1-y OS
Relapse	
85%	1-y CIR



Issa GC, et al. *Blood Cancer J.* 2021;11:162.

Menin Inhibitors are Active in *KMT2Ar* and *NPM1m* AML

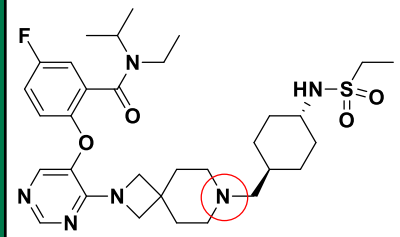
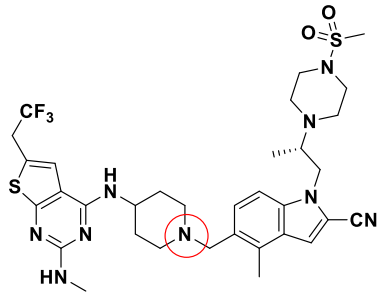
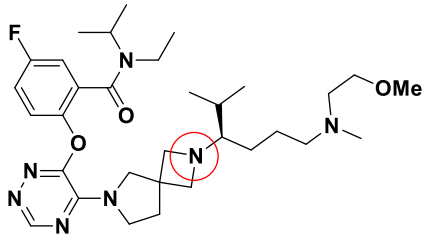
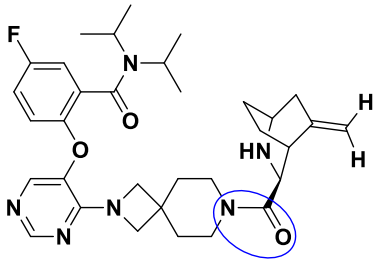


Targeting the menin-KMT2A(MLL) interaction to reverse epigenetic dysregulation in *MLL*-rearranged AML

A central role for menin-KMT2A(MLL) interaction in epigenetic dysregulation in *NPM1*-mutant AML

Kühn MW, et al. *Cancer Discov*. 2016;6(10):1166-1181; Thorsteinsdottir U, et al. *Mol Cell Biol*. 2001;21(1):224-234
Patel SS, et al. *Curr Hematol Malig Rep*. 2020;15(4):350-359; Brunetti L, et al. *Cancer Cell*. 2018;34(3):499-512

Menin inhibitors are not the same with differences in chemical structure and physiochemical properties

	Revumenib	Ziftomenib	Bleximenib	Enzomenib
Structure*				
	Tertiary amine bond	Tertiary amine bond	Tertiary amine bond	**Amide bond**

*National Center for Biotechnology Information (2024). PubChem Compound Summary for CID 132212657, 138497449, 156498110, 146430058

- Each menin inhibitor has a different chemical structure and different physiochemical properties such as polar surface area, lipophilicity, and basicity that may impact safety and efficacy[1,2]
- Enzomenib was specifically and intentionally designed to have low lipophilicity and basicity, which preliminary clinical data from the ongoing phase 1 trial has shown results in rapid clearance and minimal to no accumulation[4]

Daver N, et al. ASH 2025

Chemical Property*	**Polar Surface Area[1,2,3]**	**Lipophilicity[1,2]**	**Basicity[1,2]**
Target Value	PSA > 75	ClogP <3.0	Pka <7.4
Enzomenib	**89.8**	**2.9**	**6.68**
Revumenib	106.9	3.13	9.27
Bleximenib	85.6	3.63	9.48
Ziftomenib	119.7	5.88	8.85

**Numeric values derived from ChemDraw based on NIH CID*

1. Hughes, J., et. Al (2008) Biorg Med. Chem. Lett., 18, 17, 4872-4875
2. Yukawa T., Naven R. (2020) ACS Med. Chem. Lett., 11, 203-209
3. The surface area of a compound associated with polar atoms
4. Zeidner et al, ASH 2024

Menin inhibitors: A New Class of Acute Leukemia Therapeutics Agents

- **Revumenib is approved for patients with relapsed/refractory (R/R) *KMT2A*r AML and for patients with R/R NPM1m AML; Ziftomenib is only approved for patients with R/R *NPM1*m AML**
- **The safety profile for both agents includes differentiation syndrome (DS) and QTc interval prolongation**
- **CR+CRh is 21-23% and MEN1 mutations are reported in 35-40% of patients receiving revumenib, likely contributing to a short duration of CR-CRh of 4.5 to 6.3 months**

	Revumenib[1]		Ziftomenib[2]
Genetic subtype	*KMT2Ar*	*NPM1m*	*NPM1m*
CR + CRh	21.2% (22/104)	23.1% (15/65)	21.4% (24/112)
CR-CRh Duration	6.4 months	4.5 months	5 months
Differentiation Syndrome	Any Grade: 33%, G3: 12%	Any Grade: 18%, Gr3: 12%	Any Grade 26%, G3: 13%
QTc Interval Prolongation	Any Grade: 36%, Gr ≥3: 17%		Any Grade: 12%, Gr ≥3: 8%
Dose Modification Required for Strong CYP 3A4 Inhibitor	YES		NO

1. Revumenib (Revuforj) FDA prescribing information; 2. Ziftomenib (Komzifti) FDA prescribing information

Enzomenib Monotherapy Safety Profile

- **Wide therapeutic window with no DLTs seen at any dose levels (n = 116)**
- **No treatment-related deaths**
- **Enzomenib has been well tolerated**
  - Differentiation syndrome (DS):
    - Any grade DS was reported in 12.9% and Gr ≥3 in 7.8%
    - No mortality or permanent discontinuations of enzomenib due to DS
    - No DS prophylaxis or ramp-up used with enzomenib
  - QTc interval prolongation:
    - Any cause QTc interval prolongation of any grade was reported in 11 patients (9.5%)
    - Any cause Grade 3 QTc interval prolongation was reported in 3 patients (2.6%) and none were considered related to enzomenib treatment
    - No permanent discontinuations of enzomenib due to QTc interval prolongation

Daver N, et al. ASH 2025

Enzomenib Monotherapy in Rel/Ref Acute Leukemia: Response Rates

***KMT2A*r AL (n = 39)**

- Optimal RP2D as monotherapy is 300 mg po bid (n=15)
- At RP2D
  - Overall Response rate (CR/CRh/CRi/MLFS) 73.3%
  - Composite CR rate (CR/CRh/CRi) 60%
  - CR + CRh rate 40%

***NPM1*m AML (n = 25)**

- Dose optimization is ongoing at 200, 300 and 400 mg po bid and initial activity is similar across dose levels

	NPM1m		
Response Category* * Pts who achieved CRh and CRi or MLFS were counted as CRh	**200 mg BID (n = 10)**	**300 mg BID (n = 7)**	**400 mg BID (n = 8)**
Overall Response rate (CR/CRh/CRi/MLFS)	**60% (6/10)**	**57.1% (4/7)**	**37.5% (3/8)**
Composite CR rate (CR/CRh/CRi)	**50% (5/10)**	**42.9% (3/7)**	**37.5% (3/8)**
CR/CRh rate	**50% (5/10)**	**42.9% (3/7)**	**37.5% (3/8)**

- The efficacy analysis population (n = 64) did not include < 200 mg BID enzomenib (n = 16), prior menin inhibitor (n = 11), BM blasts < 5% (n = 4)

Daver N, et al. ASH 2025

Bleximenib Menin Inhibitor Monotherapy in R/R Acute Leukemia

Most Common Related TEAEs with Bleximenib 90/100 mg BID vs 150 mg BID Dose

TEAE, n (%)*	150 mg BID (n=33)		90/100 mg BID (n=31)	
	All grade	Grade ≥3	All grade	Grade ≥3
Total	**28** (84.8)	**12** (36.4)	**17** (54.8)	**7** (22.6)
DS	**6** (18.2)	**3** (9.1)	**6** (19.4)	**2** (6.5)
Neutropenia	**6** (18.2)	**5** (15.2)	**1** (3.2)	**1** (3.2)
Thrombocytopenia	**4** (12.1)	**3** (9.1)	**3** (9.7)	**3** (9.7)
Nausea	**6** (18.2)	**0**	**4** (12.9)	**0**
Vomiting	**5** (15.2)	**1** (3.0)	**0** (0)	**0**
AST or ALT increase	**4** (12.1)	**0**	**1** (3.2)	**0**

**Occurring in ≥10% pts relative to 150 mg BID dose level (all grades)*

Key Observations

- Safety profile optimized with bleximenib 90/100 mg BID dose level
  - Bleximenib discontinuations due to related TEAEs at 90/100 mg BID: 6.5%
- Dose modifications and discontinuations occurred more frequently at bleximenib 150 mg BID due to AEs
- ≥Grade 3 related neutropenia more commonly reported with bleximenib 150 mg BID

Searle E, et al. ASH 2025

Bleximenib Menin Inhibitor Monotherapy in R/R Acute Leukemia: Differentiation Syndrome (DS)

AE, n (%)	All-dosed population (n=146)		90/100 mg BID (n=31)	
	All grade	Grade ≥3	All grade	Grade ≥3
DS	21 (14.4)	10 (6.8)	6 (19.4)	2 (6.5)

- Median time to onset: 8 days
- some pts experienced recurrent DS
- Most initial cases of DS occurred in Cycle 1
- Most common signs/symptoms (n≥3) of DS include:
  - Leukocytosis
  - Elevated ferritin
  - Dyspnea
  - Hypotension
  - Increased body weight
  - Bone pain

Searle E, et al. ASH 2025

Key Observations

Majority of DS events observed were low grade

DS observed similarly across *KMT2A* and *NPM1*

2 fatal cases of DS observed (all-dosed)

DS mitigation measures

Temporary **interruption** of bleximenib with initiation of **hemodynamic monitoring**

Systemic **corticosteroids** +/- hydroxyurea

Supportive care as indicated

Consider **resuming bleximenib** when signs/symptoms resolve to Grade 1 or baseline

Bleximenib Menin Inhibitor Monotherapy in R/R Acute Leukemia: ITT Efficacy in Dosing Subgroups – R/R *KMT2Ar* or *NPM1m* AML

Efficacy Parameter	Bleximenib 45 mg BID (n=11)	Bleximenib 90/100 mg BID (n=21)	Bleximenib 150 mg BID (n=20)
ORR (≥PR), n (%)	**4** (36.4)	**10 (47.6)**	**11** (55.0)
Best response			
Composite CR (CR/CRh/CRi), n (%)	**2** (18.2)	**8 (38.1)**	**8** (40.0)
CR/CRh, n (%)	**2** (18.2)	**7 (33.3)**	**8** (40.0)
Median time to first response, months (range)	**1.5** (1.0–1.9)	**1.4 (0.9–4.7)**	**1.0** (0.9–2.1)
Pts proceeded to allogeneic HCT (%)	**1** (9%)	**3 (14.3%)**	**2** (10%)

Best overall response by mutation, n (%)	Bleximenib 90/100 mg BID cohort	
	KMT2Ar (n=9)	*NPM1m* (n=12)
cCR, n (%)	**4** (44.4)	**4** (33.3)
CR/CRh , n (%)	**3** (33.3)	**4** (33.3)

All dosed population:

- Median follow-up 6.5 months (N=146; 0.07–25.9)
- Median duration of CR/CRh = 6 mos (95% CI: 1.9–NE)

Searle E, et al. ASH 2025

Duration of Response and Overall Survival in Rel/Ref *NPM1* AML with Menin Inhibitor Monotherapy

Rel/Ref NPM1m AML

Menin Inhibitor	Duration of CR/CRh	Median OS
Revumenib 160-270 mg bid	4.4 mos	4.0 mos
Ziftomenib 600 mg qd	4.6 mos	6.6 mos
Enzomenib 300 mg bid	5.7 mos	8.5 mos
Bleximenib 200-300 mg bid	6.0 mos	Not reported

Arellano M et al Blood 2025; Wang E et al JCO 2025; Watts J et al ASH 2025; Searle E et al ASH 2024

Rel/Ref KMT2Ar AML

Menin Inhibitor	Duration of CR/CRh	Median Overall Survival
Revumenib 160-270 bid	6.4 mos	8.0 mos
Enzomenib 300 mg BID	12.5 mos	11.8 mos
Bleximenib 100 mg BID	6.0 mos	Not reported

Issa G et al JCO 2024; Watts J et al ASH 2025; Searle E et al ASH 2024

VEN/HMA Plus Menin Inhibitor for Rel/Ref *KMT2A*r or *NPM1*m AML

Agent (# pts)	Bleximenib + Ven/Aza	Revumenib + Ven/DEC-C (SAVE)	Ziftomenib + Ven/Aza (K-007)	Enzomenib + Ven/Aza
Trial	Phase 1	Phase 1	Phase 1	Phase 1
Number Pts	N=125	N =33	N=83	N=22
Start Menin Inhib	C1 D4	C1 D1	C1 D8	C1 D1
DS	6% (5 Gr3)	9% (1 Gr3)	1%	10% (no Gr3)
QTc prolongation	4%	64%; 9% ≥Gr3	0%	10% (no Gr 3)
CR	Not reported	39%	27%/6%	Not reported
CR/CRh	40.9%	48%	NPM 40%/KMT2A 22%	Not reported
CRc (CR/CRh/CRi)	59.1%	60%	NPM 48%/KMT2A 28%	50%
ORR	81.8%	82%	NPM 65%/KMT2A 41%	77%
Median DOR	Not reported	Not reached (F/u 9 mo)	NPM1: 10 mos	Not reported
Median OS	Not reported	Not reached	NPM1: 13.7 mos	Not reported

Wei et al EHA 2025; Issa et al ASH 2024; Issa G et al ASH 2025; Watts J et al ASH 2025

Safety of Ziftomenib plus 7+3 in Newly Diagnosed AML: Grade ≥3 in ≥10% of Patients

n (%)	*NPM1*-m 600 mg (n=49)	*KMT2A*-r 600 mg (n=33)	All Patients 600 mg (N=82)
Grade ≥3	**42 (86)**	**29 (88)**	**71 (87)**
Febrile neutropenia	25 (51)	20 (61)	45 (55)
Platelet count decreased	23 (47)	12 (36)	35 (43)
Anemia	16 (33)	8 (24)	24 (29)
Neutrophil count decreased	14 (29)	6 (18)	20 (24)
White blood cell count decreased	10 (20)	7 (21)	17 (21)
Sepsis	8 (16)	5 (15)	13 (16)
Lymphocyte count decreased	5 (10)	4 (12)	9 (11)

29 Patients (35%) had Grade ≥3 ziftomenib-related adverse events:

- **Most common (≥10%) were febrile neutropenia (15%), decreased platelet count (15%), anemia (11%), and decreased neutrophil count (11%)**
- **1 case of differentiation syndrome (*KMT2A*-r, Gr3), which was successfully managed**
- **2 cases of investigator-assessed QTc prolongation (both *KMT2A*-r, Gr3)***

Erba H, et al. EHA 2025 Abstract S136

Ziftomenib plus 7+3 in Newly Diagnosed AML: Neutrophil and Platelet Recovery in CRc Responders

Median days (range), Cycle 1	*NPM1*-m 600 mg (n=41)	*KMT2A*-r 600 mg (n=24)	All Patients 600 mg (n=65)
ANC ≥0.5 × 10^9/L	28 (19–66)	32 (20–63)	31 (19–66)
ANC ≥1.0 × 10^9/L	30.5 (20–88)	33 (20–63)	**32 (20–88)**
Platelets ≥50 × 10^9/L	27 (18–105)	31.5 (20–63)	27 (18–105)
Platelets ≥100 × 10^9/L	28 (20–105)	32 (20–63)	**29 (20–63)**

- Time to neutrophil and platelet recovery was comparable to that for intensive chemotherapy regimens[1,2]

1. Lancet JE et al. *J Clin Oncol.* 2018; 36(26):2684-92; 2. Erba HP et al. *Lancet.* 2023; 401(10388):1571-83.

Erba H, et al. EHA 2025 Abstract S136

Ziftomenib plus 7+3 in Newly Diagnosed *NPM1m* and *KMT2Ar* AML

n (%)	*NPM1*-m 600 mg (n=44)	*KMT2A*-r 600 mg (n=27)	All Patients 600 mg (N=71)
CRc	**41 (93)**	**24 (89)**	**65 (92)**
ORR	**43 (98)**	**24 (89)**	**67 (94)**
CR	37 (84)	20 (74)	57 (80)
CRh	1 (2)	0	1 (1)
CRi	3 (7)	4 (15)	7 (10)
MLFS	2 (5)	0	2 (3)
PR	0	0	0
NR	1 (2)	2 (7)	3 (4)
NE	0	1 (4)	1 (1)
CR MRD-negativity, n/N (%)[b]	**24/34 (71)**	**14/16 (88)**	**38/50 (76)**
CRc MRD-negativity, n/N (%)[b]	**26/38 (68)**	**15/18 (83)**	**41/56 (73)**
Median time to CR MRD-negativity, weeks (range)	4.7 (2–17)	4.4 (3–12)	4.5 (2–17)
Median time to CRc MRD-negativity, weeks (range)	4.7 (2–17)	4.1 (3–12)	4.3 (2–17)

***NPM1*m:** Median follow-up = **24.9 weeks**

- **Median DOR = not reached**
  - **Median OS = not reached**
  - 2 *NPM1*-m patients received HSCT
  - 96% (47/49) of pts alive on-study

***KMT2A*r:** Median follow-up = **15.7 weeks**

- **Median DOR = 25.6 weeks**
- **Median OS = not reached**
- 6 *KMT2A*-r pts received HSCT.
- 88% (29/33) of pts alive on-study

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VEN/HMA plus Menin Inhibitor for Newly Diagnosed *KMT2A*r or *NPM1*m AML

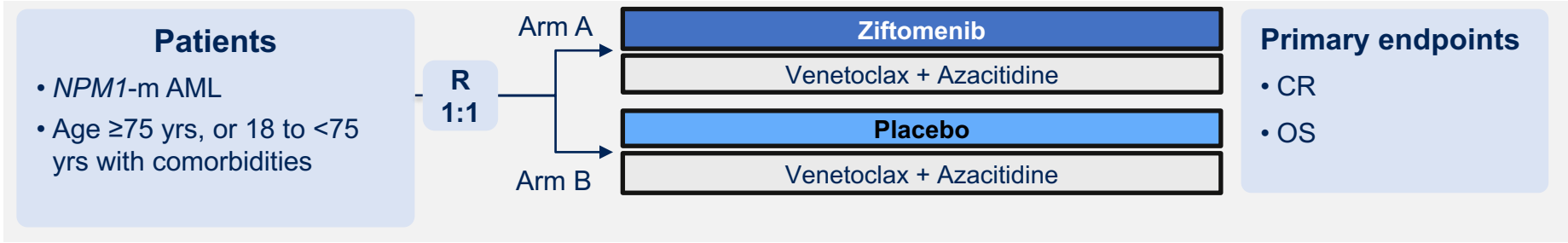
	AZA/VEN + Revumenib (D1-28)		ASTX727/VEN + Revumenib (D1-28)		AZA/VEN + Ziftomenib (D8)	AZA/VEN + Bleximenib (D4)	
Trial	Beat AML[1]		SAVE[2]		KOMET-007[3]	ALE1002[4]	
Population	Newly Dx AML ≥60 years NPM1m, KMT2Ar		Newly Dx AML or MPAL >18 years unfit NPM1m, KMT2Ar, NUP98r		Newly Dx AML >18 years unfit NPM1m	Newly Dx AML >18 years unfit NPM1m, KMT2Ar	
Therapeutic Dose(s)	220 mg BID; 270 mg BID Dose-adjusted with azoles		220 mg BID; 270 mg BID Dose-adjusted for azoles		600 mg daily	100 mg BID	
Subtype	KMT2Ar n=9	NPM1m n=34	KMT2Ar n=7	NPM1m n=14	NPM1m n=34	KMT2Ar n=4	NPM1m n=16
ORR	100%	85%	86%	86%	89%	75%	94%
CR/CRh	78%	68%	86%	79%	78%	75%	75%
CR	78%	65%	86%	71%	73%	NR	NR
DS (any)	19%		19%		3%	NR	

1- Zeidner, J Clin Oncol 2025; 2-Jen, Blood [ASH] 2025; 3-Roboz, Blood [ASH] 2025; 4-Wei, HemaSphere [EHA] 2025

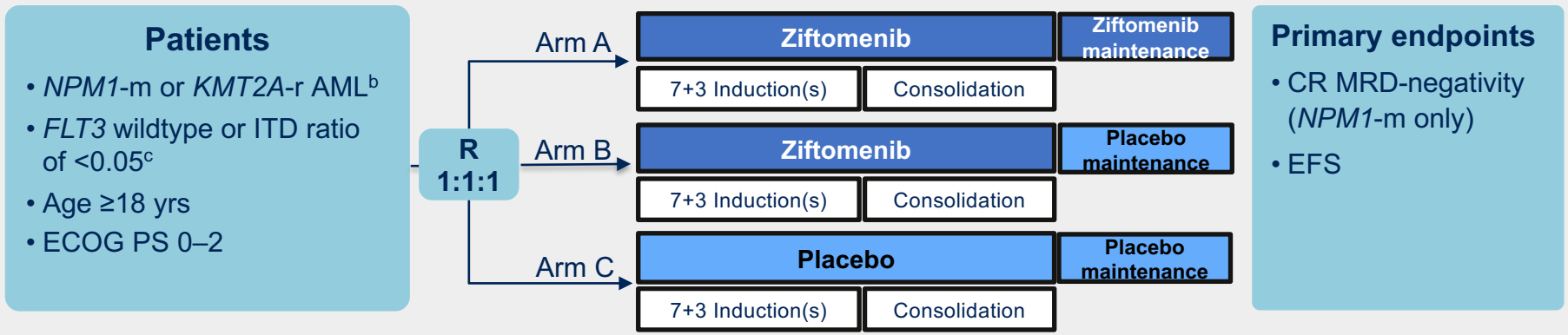
Ziftomenib Phase 3 Newly Diagnosed AML Combination Studies

- **Two independently powered, registration-enabling, randomized phase 3 studies in fit and unfit newly diagnosed AML (N=1300)**

KOMET-017-NIC: Non-intensive therapy[a] – Ziftomenib + venetoclax/azacitidine combo



KOMET-017-IC: Intensive therapy[a] – Ziftomenib and 7+3 combo



[a]HSCT allowed on both studies. [b]Excluding partial tandem duplication. [c]Unless ineligible for *FLT3*-targeted therapy.

Currently enrolling as of September 2025 (NCT07007312)

CR, complete remission; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HSCT, hematopoietic stem cell transplant; ITD, internal tandem duplication; MRD, measurable residual disease; OS, overall survival.

Menin Inhibitors in Acute Myeloid Leukemia: Current Knowledge and Future Challenges

- Menin inhibitor monotherapy is active in *KMT2A*r and *NPM1*m AML.
  - However, CR+CRh rates are generally low, and duration of response is short
- *NPM1*c *and KMT2A*r mutations drive leukemogenesis through Menin-KMT2A directed expression of HOX and MEIS1
  - *NPM1* mutations may be acquired following other leukemogenic driver mutations
  - Menin mutations and other pathways lead to resistance
- Toxicity management:
  - QT prolongation observed with revu-, zifto-, and blexi-, but not enzomenib
  - Differentiation syndrome common to all Menin inhibitors, but can be difficult distinguishing DS from disease progression/lack of response
  - Myelosuppression should be expected based on preclinical data
- Addition of Menin inhibitors to current intensive and less intensive therapy may improve outcomes

QUESTIONS?

Thank you for joining us!
Your feedback is very important to us.

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