7th Annual

LEAD2025

Enriching Experiences for Women in Hematology & Oncology

Clinical Updates in Acute Leukemias

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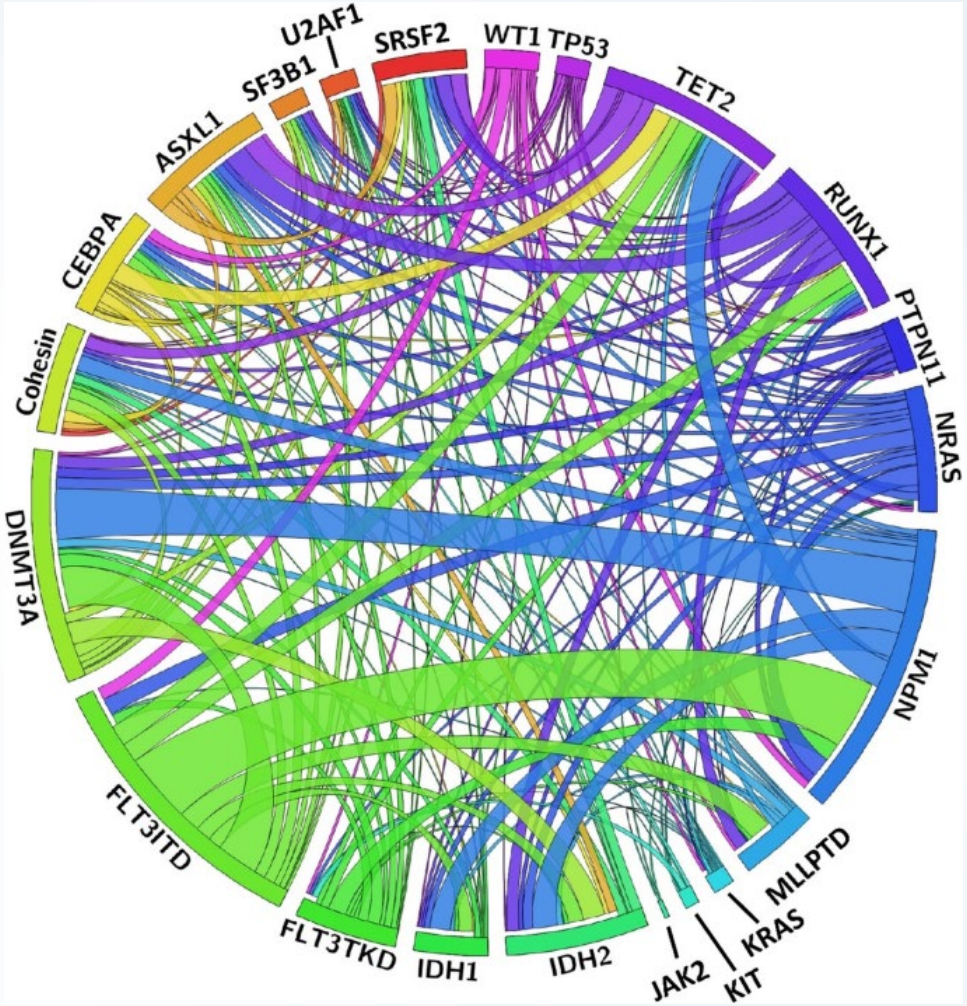
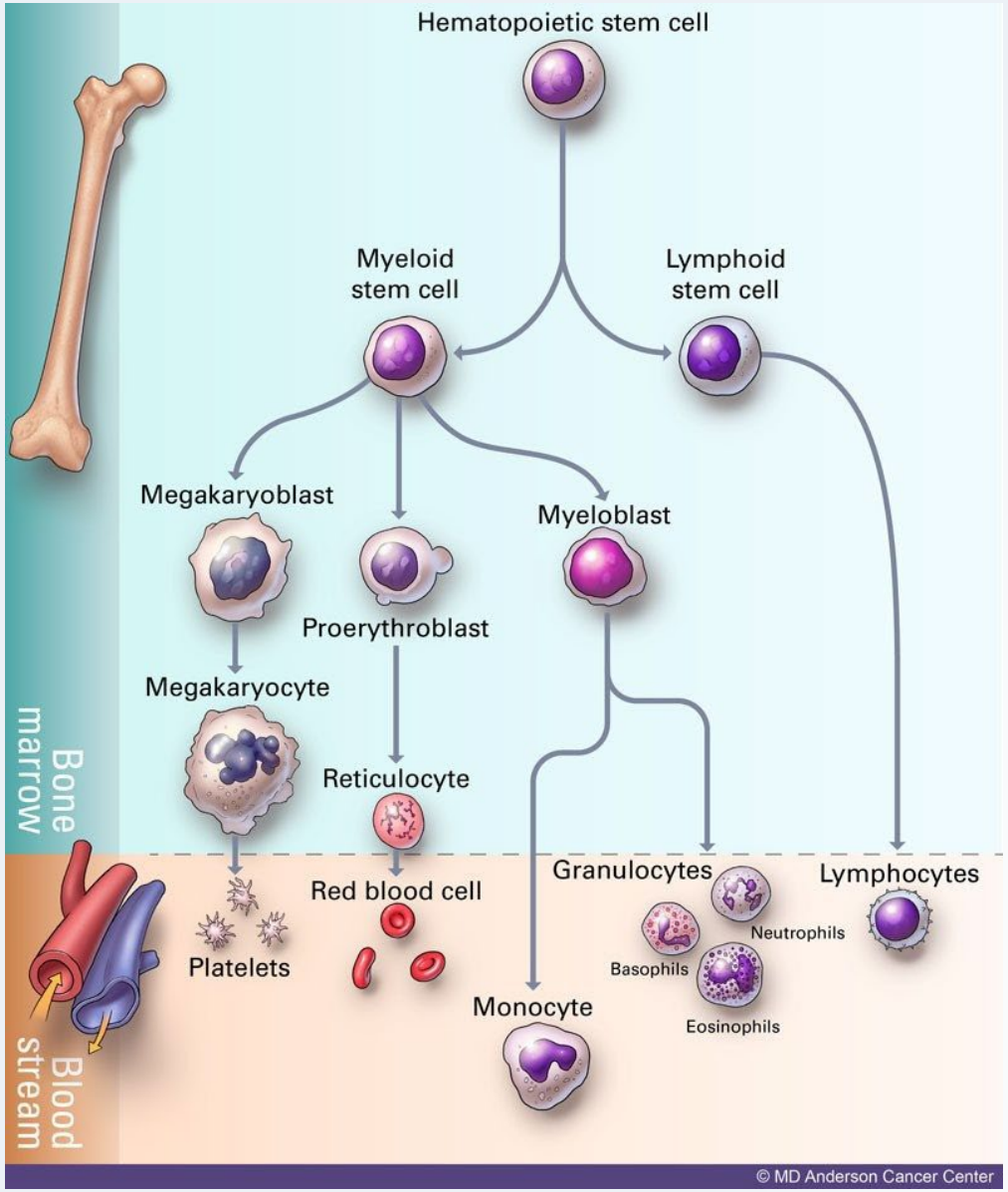
Agenda: Acute Leukemias

- AML
  - Molecularly Targeted Therapies
    - Menin Inhibitors
    - FLT3 mutated AML
  - Recommendations for less intensive therapies
    - ELN 2024 risk stratification
    - Advancement of all-oral regimens
- ALL
  - Blinatumomab expanded use in consolidation
  - Obe-cel approval



Hou et al, JBS, 2020



What is acute leukemia ?

- Diagnosed with bone marrow biopsy, flow cytometry, genetic testing including cytogenetics, FISH, and targeted NGS

Acute myeloid leukemia

- >20% myeloblasts in the bone marrow or peripheral blood, or molecularly defined with 10-20% blasts

Acute lymphoblastic leukemia

- Dense infiltration of lymphoid blasts >25%, defined by B or T markers

Case 1: R/R KMT2a AML

64yo F with RR AML with KMT2Ar who experienced relapse after induction with CPX-351 and subsequent salvage with azacitidine/venetoclax.

- Initial diagnosis with t(9;11)
- Subsequent confirmation of KMT2Ar at most recent relapse

ASH image bank

KMT2a Rearrangements ~5-10% of AML and ALL, higher in infant leukemia

Revumenib: First menin inhibitor approved for KMT2Ar Leukemia

FDA approves revumenib for relapsed or refractory acute leukemia with a KMT2A translocation

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On November 15, 2024, the Food and Drug Administration approved revumenib a menin inhibitor, for relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (KMT2A) translocation in adult and pediatric patients 1 year and older.

Full prescribing information for Revuforj will be posted on Drugs@FDA.

Aldoss I, et al. JCO, 2025

Revumenib: Efficacy and Safety

Parameter	Efficacy population (n=57)
ORR, n (%)	36 (63)
CR+CRh rate, n (%)	13 (22.8)
95% CI	12.7–35.8
CRc, n (%)	25 (43.9)
95% CI	30.7-57.6
Negative MRD status, n (%)	
CR+CRh	7/10 (70)
CRc	15/22 (68.2)

All terms, n (%)	TEAE (N=94)	TEAE grade ≥3 (N=94)
Nausea	42 (44.7)	
Febrile neutropenia	36 (38.3)	35 (37.2)
Edema	30 (31.9)	
Diarrhea	35 (30.2)	
Vomiting	29 (30.9)	
Differentiation syndrome	26 (27.7)	15 (16.0)
QTc prolongation	24 (25.5)	13 (13.8)
Anemia	21 (22.3)	

The median duration of CR+CRh was 6.4 months (95% CI, 3.4 to not reached)

Aldoss I, et al. JCO, 2025

Menin inhibitors: Multiple agents, Open Questions

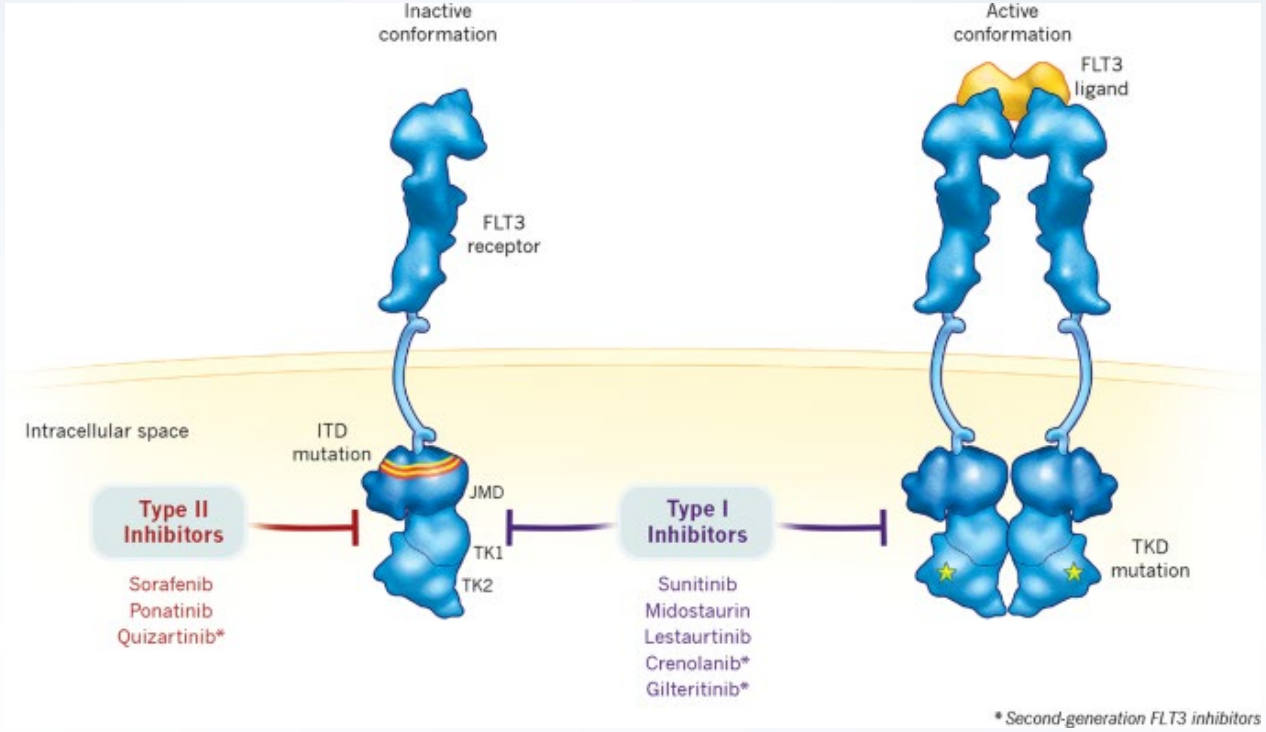
Agent	KMT2A – R/R AML	KMT2A – ND AML	NPM1 – R/R AML	NPM1 – ND AML
Revumenib	AUGMENT-101 monotherapy → FDA-approved (Nov 15, 2024) for R/R acute leukemia with KMT2A-t	AZA+VEN+revumenib; phase I signal; randomized phase 3 HO177 ongoing.	AUGMENT-101 NPM1 cohort → sNDA Priority Review; PDUFA Oct 25, 2025.	AZA+VEN+revumenib in older/unfit; HO177 includes NPM1.
Ziftomenib	KOMET-001 monotherapy (phase 1/2) with activity in KMT2A-r cohort.	KOMET-007 + 7+3/other SOC combos; early strong activity; expansion ongoing.	KOMET-001 NPM1 cohort → NDA Priority Review; PDUFA Nov 30, 2025.	KOMET-007 + 7+3 (ND AML, NPM1-mut): promising early efficacy.
Bleximenib	First-in-human mono (cAMeLot-1) + phase 1b combos (±VEN/±AZA).	Triplet bleximenib+VEN+AZA: phase 3 underway in ND, IC-ineligible AML.	Included in mono/combination R/R AML programs (phase 1/1b).	Phase 3 bleximenib+VEN+AZA vs placebo+VEN+AZA
Enzomenib	Phase 1/2 monotherapy (NCT04988555) in R/R AML (KMT2A-r / NPM1).	—	Same phase 1/2 includes R/R NPM1-mut AML cohorts; early responses.	—

- Demonstrated efficacy as leading class of agents for r/r KMT2Ar and NPM1m AML
- Under investigation for upfront inclusion in these populations

Case 2: FLT3m AML

33yo F with no PMH presents with pancytopenia:
WBC: 32 k/uL Hg: 6.9 g/dL, Plt: 12 k/uL; 96% blasts on smear

Mutations in FLT3-ITD, NPM1, IDH1, TET2

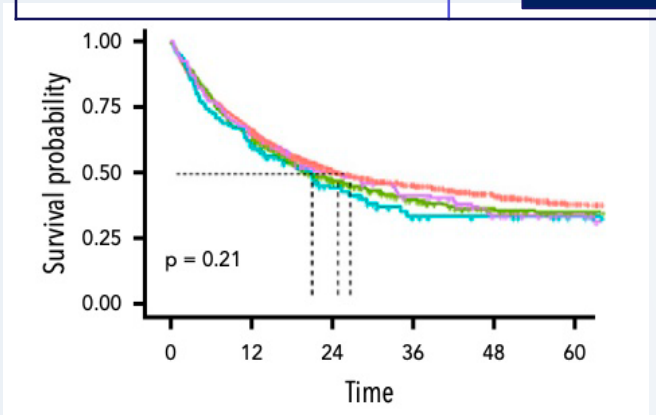


FLT3: Abnormalities in 25% of AML

Can you Wait for Diagnostic Testing in AML?

- **Retrospective database from international AML Registry (n=2,263) of pts receiving intensive chemo**

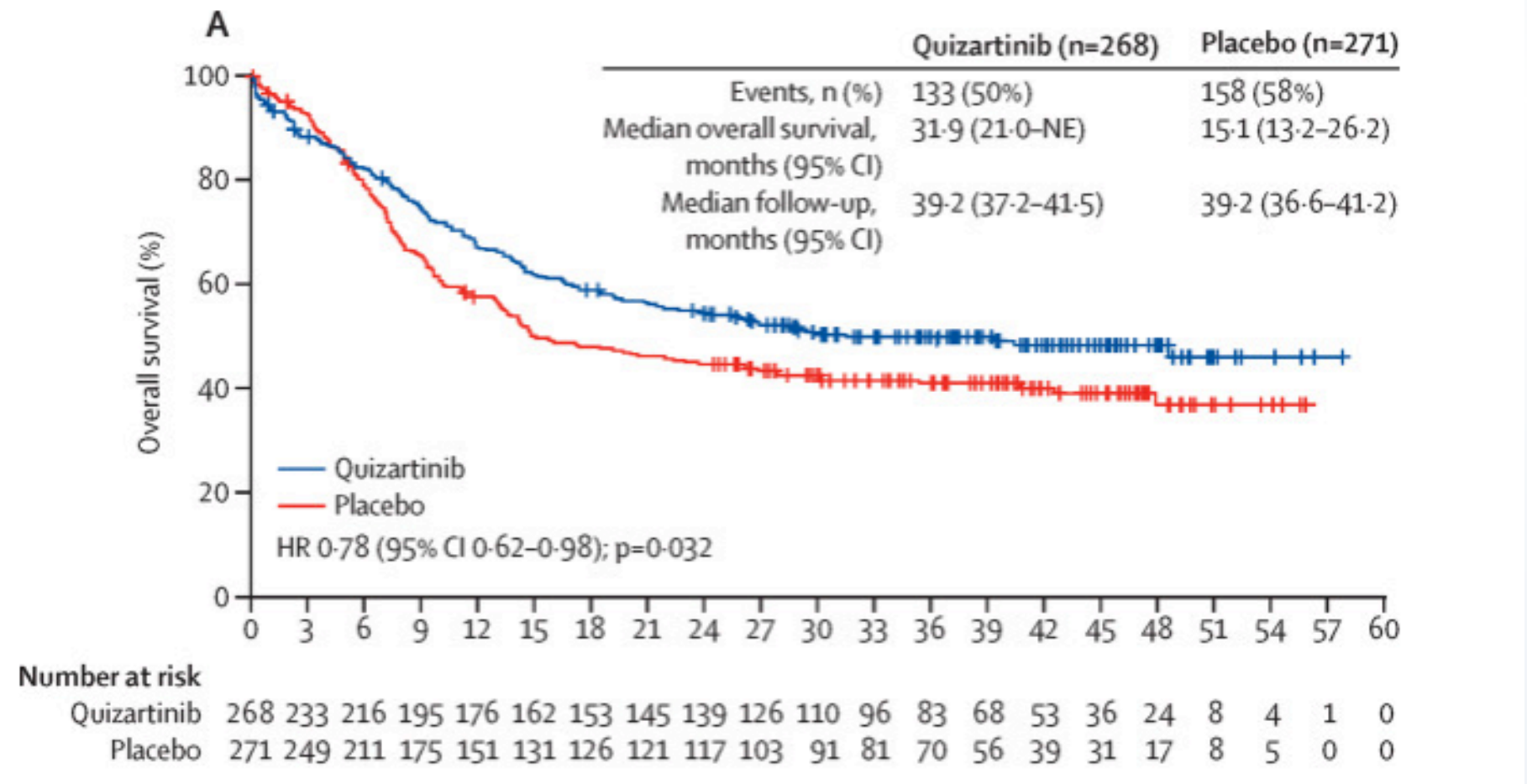
	Time from Diagnosis to Intensive Chemo			
	0–5 Days (n = 1547)	6–10 Days (n = 447)	11–15 Days (n = 106)	> 15 Days (n = 163)
CR/CRi	79%	76%	72%	77%
Early Mortality	4%	5%	4%	5%



- Clinical outcomes are similar in all four subgroups including younger and older patients
- Waiting for full diagnostic testing is feasible for most newly diagnosed AML cases

Rollig, *Blood* 2020

QuANTUM FIRST: Quizartinib approval July 2023 for induction, consolidation, and maintenance

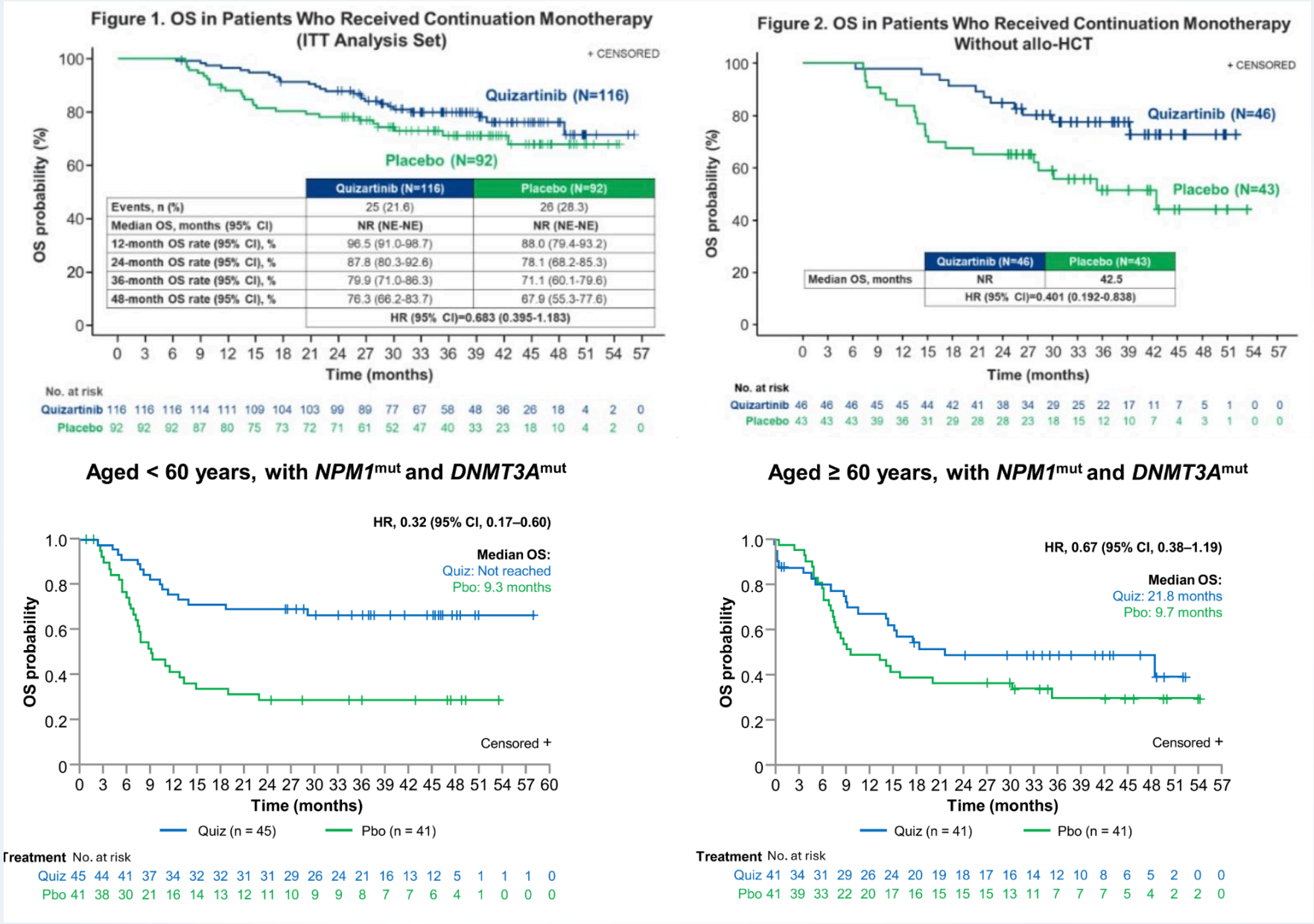


Erba et al, Lancet, 2023

Quizartinib: Updated analyses

EHA 2024: Improved OS for patients on maintenance Quizartinib

EHA 2025: Increased sensitivity to quizartinib for patients with *NPM1, FLT3-ITD,* and *DNMT3A* mutations



Sekeres et al, EHA 6/2024; Levis et al, EHA, 2025

ELN 2024: Genetic Risk Classification for Patients Receiving Less Intensive Regimens

Genetic marker	Median OS, mo	Reference
Favorable-risk group		
Mutated *NPM1* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	39	4
Mutated *IDH2* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	37	4
Mutated *IDH1** (*TP53*^{wt})	29	6,17
Mutated *DDX41*	>24	3,13
AML with MR gene mutations (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	23	4
Intermediate-risk group		
AML with MR gene mutations (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})	13	4
Other cytogenetic and molecular abnormalities (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})	12	4
Adverse-risk group		
Mutated *TP53*	5-8	3,4,7,10,14-16

Distinct risk profile for patients treated on less intensive regimens compared to earlier risk classifications for those treated with intensive chemotherapy regimens

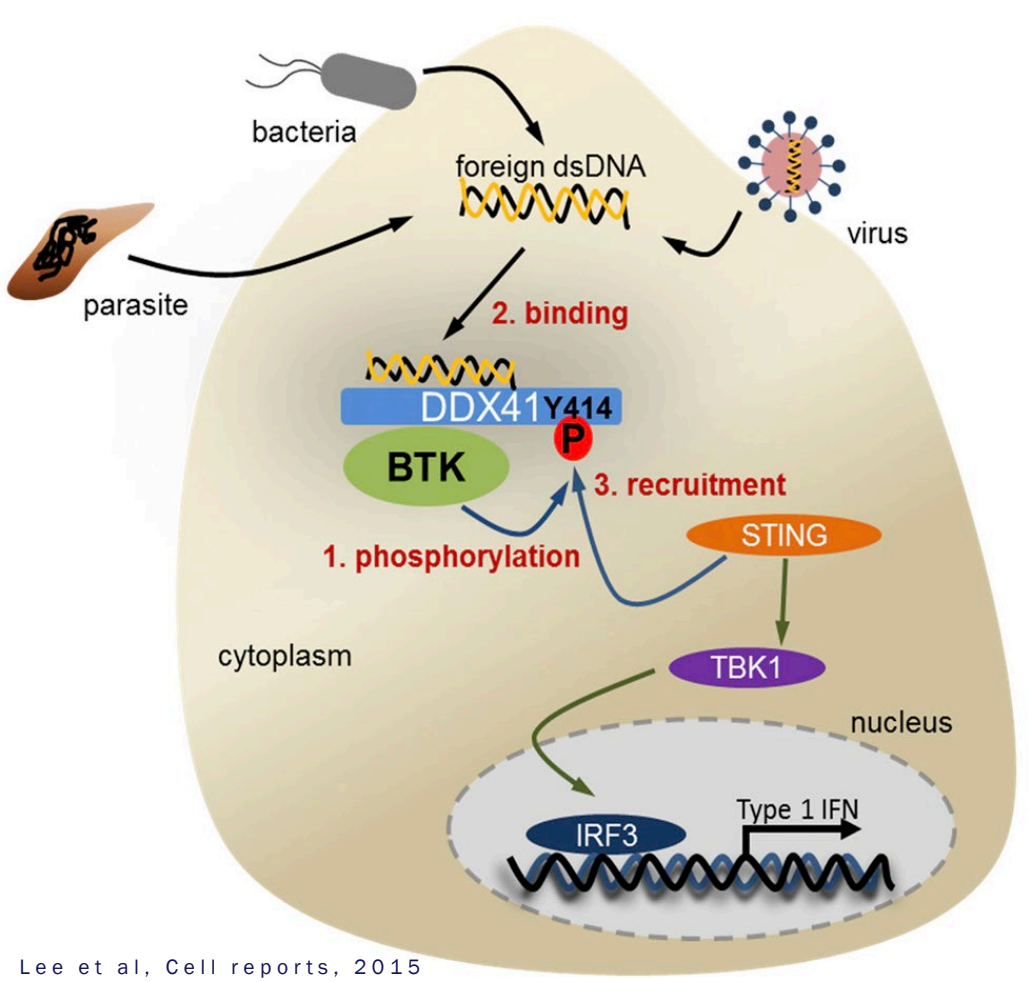
Dohner et al, Blood 2024

Case 3:

76yo M with HTN, CAD with new diagnosis of AML.
WBC 2k/uL, Hg 8.5g/dL,
Plts 25k/uL

He lives 3 hours from a treatment center for leukemia.

2 mutations found in DDX41



Lee et al, Cell reports, 2015

DDX41: Most common inherited predisposition to AML found in older individuals

All oral regimens in AML

EHA 2025 – Newly diagnosed not fit for intensive chemotherapy

- ASCERTAIN-V: Inqovi and venetoclax – 189 pts, CR/CRi of 63.4%, Rate of febrile neutropenia 49.5%
  - ➢ sNDA with FDA in progress
- Oral azacitidine and venetoclax – 13 ND pts, ORR 69%, Febrile neutropenia 21%

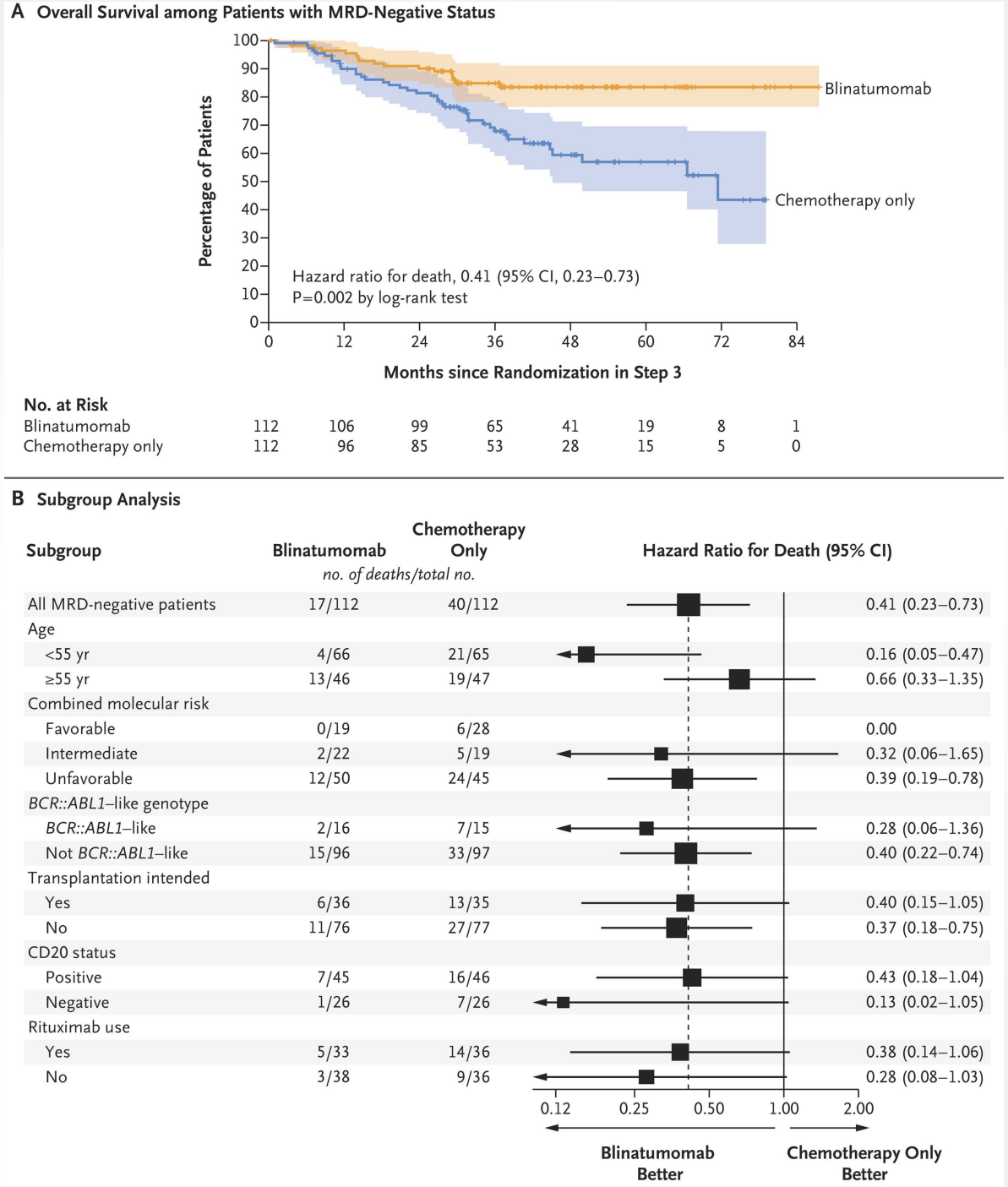
Drug	AML indication (approval context)	FDA approval date
Ivosidenib	**R/R IDH1-mut AML** (monotherapy)	July 20, 2018.
	ND IDH1-mut AML in adults ≥75 y or unfit for intensive chemo (monotherapy)	May 2, 2019.
	ND IDH1-mut AML in combination with azacitidine	May 25, 2022.
Enasidenib	**R/R IDH2-mut AML** (monotherapy)	August 1, 2017.
Olutasidenib	**R/R IDH1-mut AML** (monotherapy)	December 1, 2022.
Gilteritinib	**R/R FLT3-mut AML** (monotherapy)	November 28, 2018.
Oral azacitidine	**Maintenance** after intensive induction (CR/CRi)	September 1, 2020.

Roboz et al, EHA, 2025; Amaya et al, EHA, 2025; FDA

Case 4: Updates in ALL

28yo M with B-ALL with CRLF2-IGH rearrangement.

Has initiated pediatric-inspired regimen and experienced pancreatitis after second dose of pegasparaginase.



FDA approves blinatumomab as consolidation for CD19-positive Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia

On June 14, 2024, the Food and Drug Administration approved blinatumomab for adult and pediatric patients one month and older with CD19-positive Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia (Ph-negative BCP ALL) in the consolidation phase of multiphase chemotherapy.

Consideration for blinatumomab in consolidation based on outcomes from E1910 and Gimema LAL2317 studies

Case 4 continued: Updates in ALL

28yo M with B-ALL with CRLF2-IGH rearrangement.

During maintenance therapy on pediatric-inspired regimen with incorporation of blinatumomab, he experiences recurrence of MRD positive disease by flow.

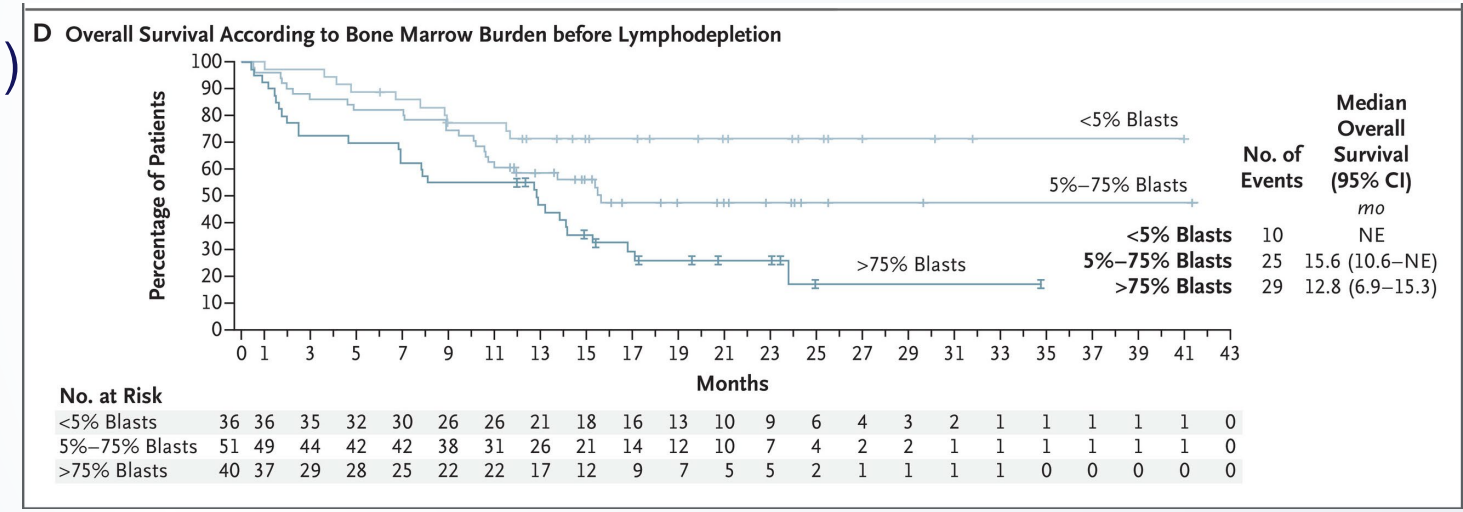
FDA approves obecabtagene autoleucel for adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia

On November 8, 2024, the Food and Drug Administration approved obecabtagene autoleucel a CD19-directed genetically modified autologous T cell immunotherapy, for adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

Obe-cel Approval

Trial Data (FELIX study, phase I/II)

- **Population:** Adult r/r B-ALL (including high disease burden, prior therapies)
- **Response:**
  - **CR/CRi rate:** ~77% (CR 55%, CRi 21%)
  - **MRD negativity:** >90% among responders
- **Durability:**
  - **Median DOR:** ~21 months (95% CI, 11.6–NE)
  - **Median OS:** ~15.6 months
- **Safety:**
  - Low severe CRS (grade ≥3 ~3%)
  - Low severe neurotoxicity (ICANS grade ≥3 ~2%)
  - Favorable tolerability



Roddie et al, NEJM, 2024