What's New in the Upfront Treatment of AML?

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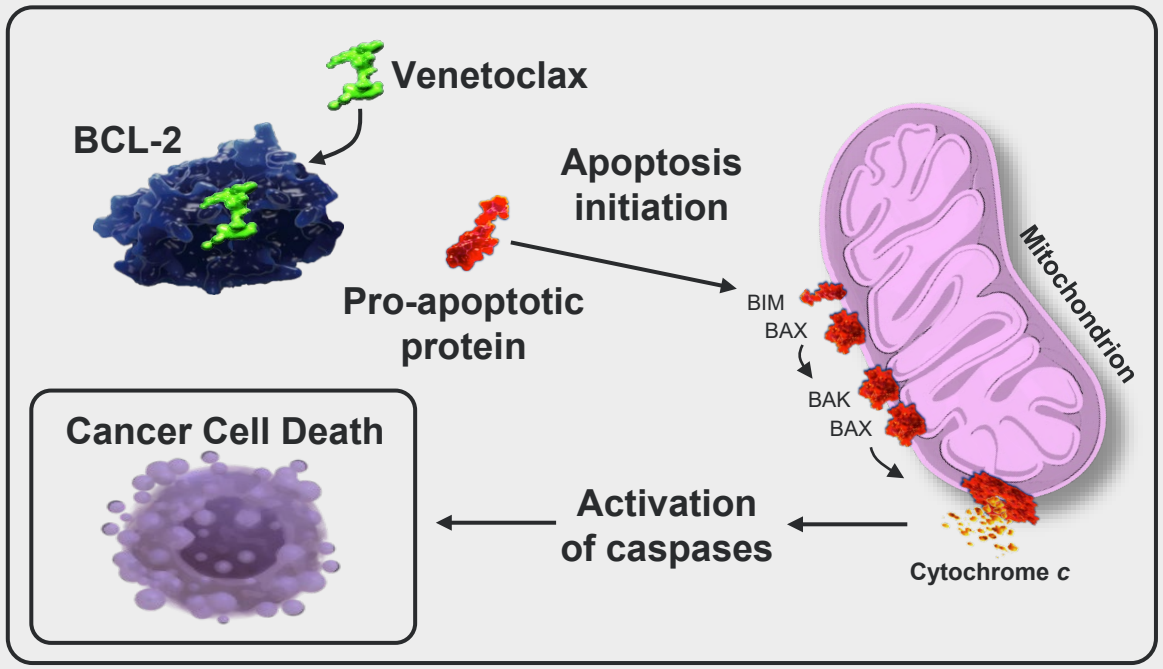
Outline

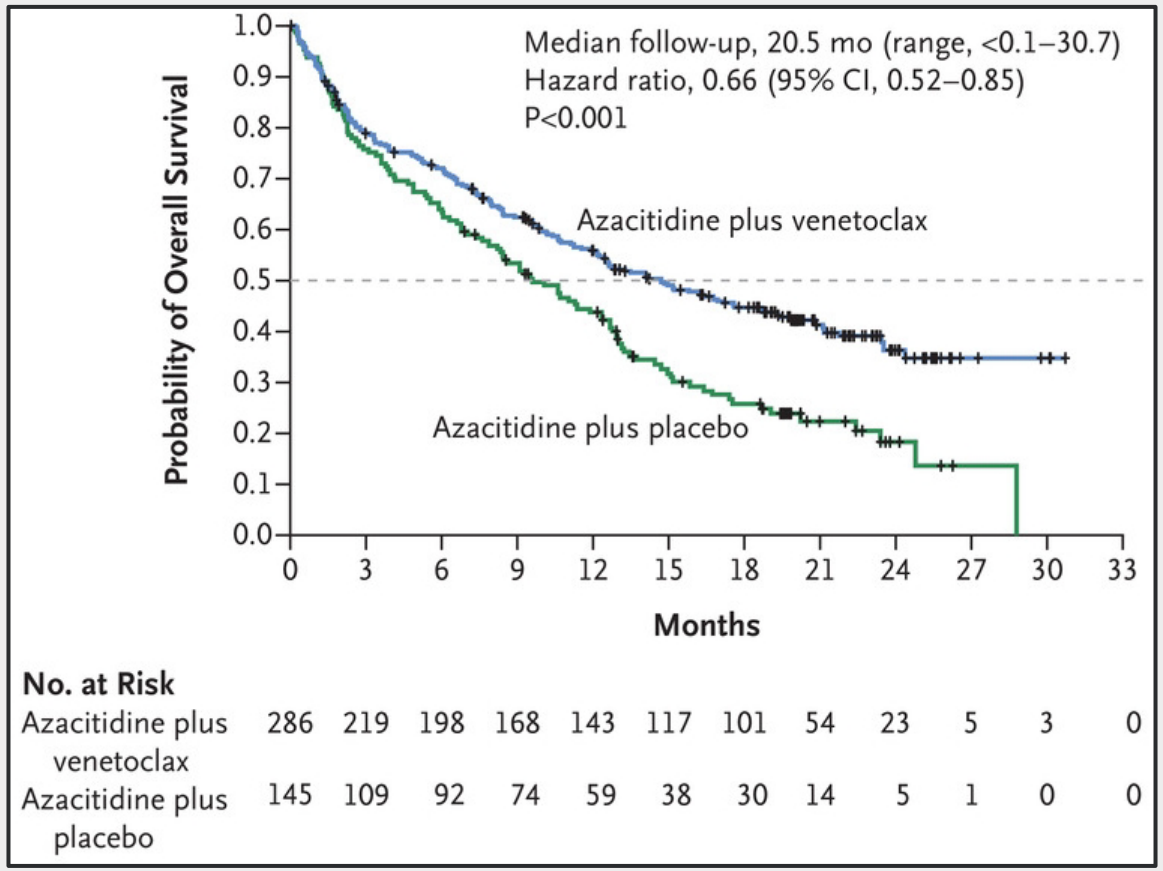
- **Abstract 371:** *Phase I/II study of azacitidine with venetoclax and magrolimab in patients with newly diagnosed older/unfit or high-risk acute myeloid leukemia and relapsed/ refractory AML* (Naval Daver).
- **Abstract 700:** *Phase 3, open-label, randomized study of gilteritinib and azacitidine vs. azacitidine for newly diagnosed* FLT3*-mutated acute myeloid leukemia in patients ineligible for intensive induction chemotherapy* (Eunice S. Wang).
- **Abstract 696:** *A triplet combination of azacitidine, venetoclax and gilteritinib for patients with* FLT3*-mutated acute myeloid leukemia: Results from a phase I/II study* (Nicholas J. Short).
- **Abstract 697:** *A global, randomized, double-blind, phase 3 study of ivosidenib + azacitidine versus placebo + azacitidine in patients with newly diagnosed acute myeloid leukemia with an* IDH1 *mutation* (Pau Montesinos).

Azacitidine and Venetoclax for Unfit AML Patients



Treatment	Overall Response Rate
Azacitidine	28.3%
Azacitidine/venetoclax	66.4%

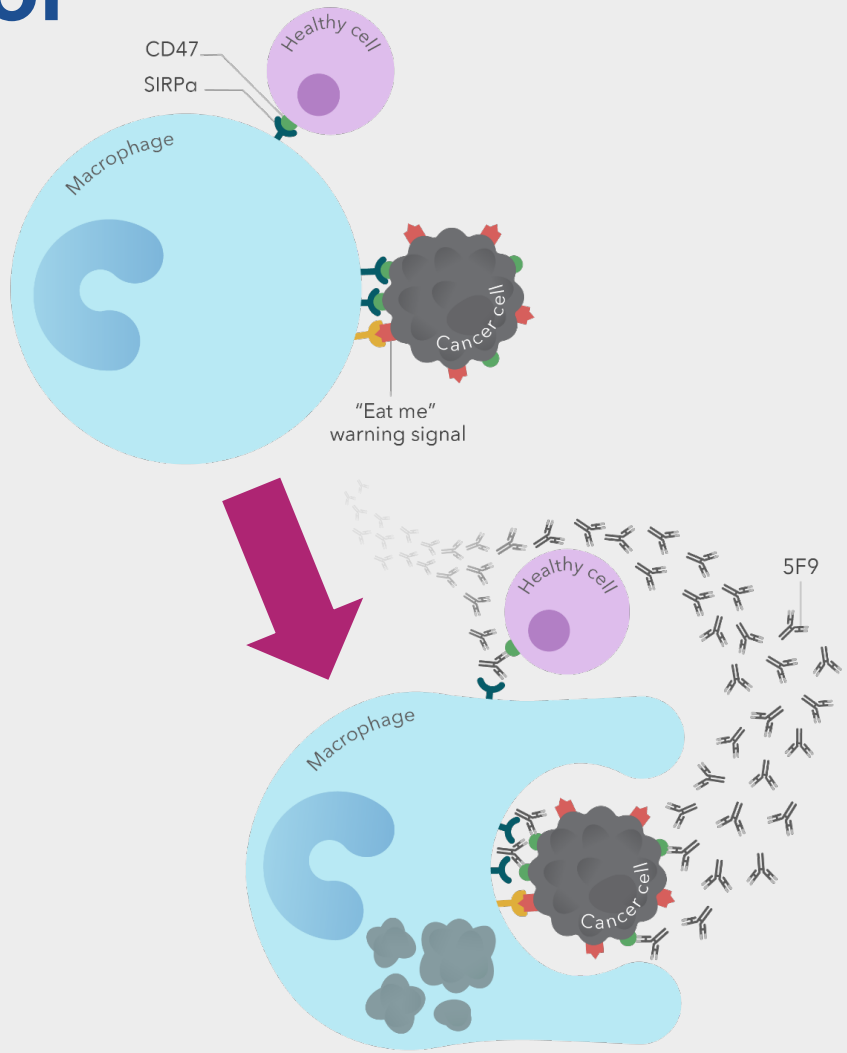
Overall Survival After Azacitidine/Venetoclax vs Azacitidine



DiNardo CD *et al. New Engl J Med* 2020; 383:617-629.

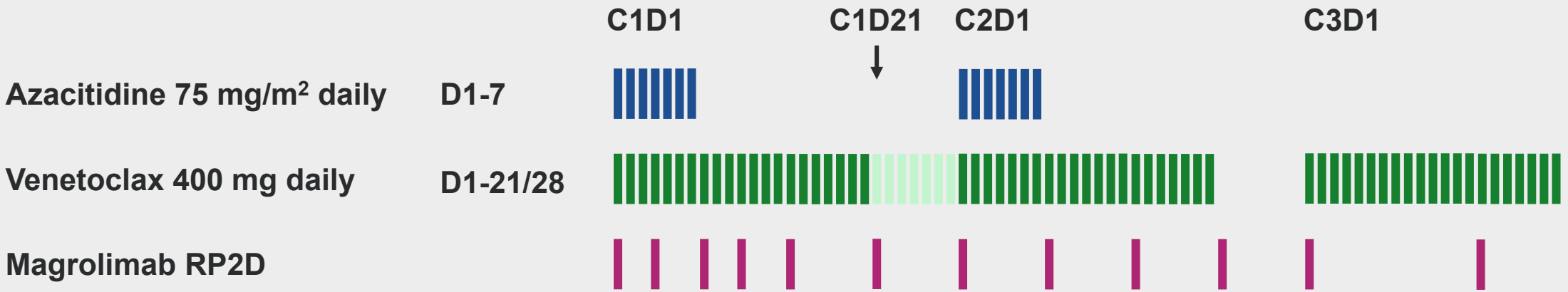
Magrolimab: An Anti-CD47 Macrophage Immune Checkpoint Inhibitor

- CD47 is overexpressed on multiple cancers, including AML.
- CD47 provides a “do not eat me” signal, leading to macrophage immune evasion.
- Magrolimab, an IgG4 anti-CD47 mAb, eliminates tumor cells through macrophage phagocytosis.
- Synergizes with azacitidine via induction of pro-phagocytic signals, such as calreticulin.
- Azacitidine/magrolimab has shown encouraging activity in single-arm studies in frontline *TP53*^{wt} and *TP*53^{mut} AML.
- Intravascular hemolysis can occur due to expression of CD47 on mature RBC’s.
- HMA/venetoclax produces responses in 30-40% of *TP53*^{mut} AML patients with median OS of 5-7 months.



Chao MP *et al. Front Oncol* 2019; 9:1380.
Sallman DA *et al. Blood* 2020; 136(Suppl 1):330.

Phase 1b/2 Study of Azacitidine, Venetoclax, and Magrolimab
Treatment Schema



Phase 1 (Dose Finding)

- R/R AML
- ≥ 18 yrs
- ECOG PS ≤ 2
- Adequate organ function
- WBC ≤ 15 × 10^9/L

Phase 2 Cohorts

1. **Frontline**
   - ≥ 75 yrs or
   - < 75 yrs, ineligible for intensive therapy
   - ≥ 18 yrs with *TP53*^{mut} or adverse risk CG, regardless of "fitness"
2. **R/R venetoclax-naïve (Salvage 1 and 2)**
3. **R/R prior venetoclax (Salvage 1 and 2)**

RP2D Determination

- Phase 1b (n=6): no DLTs
- Magrolimab RP2D:
  - 1 mg/kg on C1D1, C1D4
  - 15 mg/kg on C1D8
  - 30 mg/kg on C1D11 and subsequent doses

Daver N *et al. Blood* 2021; 138 (Suppl 1):371.

Phase 1b/2 Study of Azacitidine, Venetoclax, and Magrolimab

Response Rates for Frontline Cohort (n=25)

Outcome	*TP53* mutated (n=14)	*TP53* wild type (n=11)
ORR, n (%) CR/CRi CR CRi MLFS/PR	12 (86) 9 (64) 9 (64) 0 3 (21)	11 (100) 10 (91) 7 (64) 3 (27) 1 (9)
MRD neg by FCM	5/9 (55)	4/9 (45)
CCyR, n (%)	4/9 (44)	5/6 (83)
No response, n (%)	2 (14)	0
TT 1st response, mo	0.7 (0.6-1.9)	0.7 (0.7-1.5)
TT best response, mo	1.5 (0.7-3.2)	1.1 (0.7-2.9)
Med TT ANC > 500, days	28 (20-41)	
Med TT Plt > 50K, days	24 (18-41)	
8-wk mortality	0	0

Daver N *et al. Blood* 2021; 138 (Suppl 1):371.

Phase 1b/2 Study of Azacitidine, Venetoclax, and Magrolimab
Treatment-Related Adverse Events

- No discontinuations due to TRAEs
- Grade 1-2 infusion reactions in 3/48 patients (6%), prevented with dexamethasone premedication in subsequent doses
- Grade 1-2 hyperbilirubinemia in 2 patients (4%) due to hemolysis
- Anemia
  - D1-2 Hgb decrease > 2 gm: 9 patients (19%); > 3 gm: 3 patients (6%)
  - D4-5 Hgb decrease > 2 gm: 3 patients (6%); > 3 gm: 0
  - No patients had Hgb decrease > 2 gm after 2nd dose of magrolimab
- No immune-related adverse events

Daver N *et al. Blood* 2021; 138 (Suppl 1):371.

Phase 1b/2 Study of Azacitidine, Venetoclax, and Magrolimab
Summary

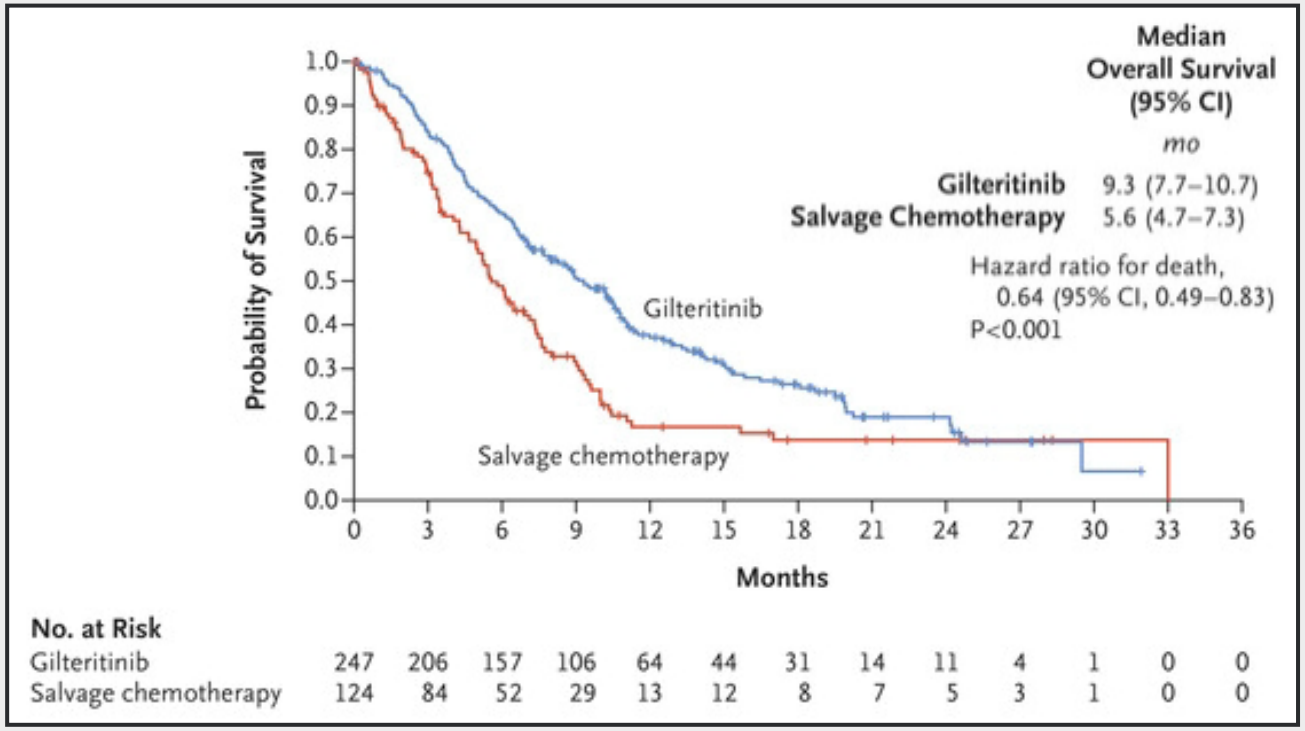
- TRAEs in > 5% included increased bilirubin; Hgb must be monitored closely after Doses 1 and 2 of magrolimab
- Encouraging response rates seen:
  - Frontline *TP53*^{mut} AML CR rate = 64%, ORR = 86%
  - Frontline *TP53*^{wt} AML CR rate = 64%, ORR = 100%
  - R/R venetoclax-naïve AML CR/CRi = 63%; prior venetoclax-exposed AML CR/CRi = 20%
- Ongoing studies:
  - Phase 3 trial of azacitidine/magrolimab vs azacitidine/placebo in higher risk MDS
  - Phase 3 trial of azacitidine/magrolimab vs azacitidine/venetoclax or 7+3 chemotherapy in *TP53*-mutated AML
  - Phase 2 trial of magrolimab with azacitidine/venetoclax, MEC, and oral azacitidine

Daver N *et al. Blood* 2021; 138 (Suppl 1):371.

Gilteritinib: A Selective *FLT3* Inhibitor

- *FLT3* mutations are seen in ~30% of AML patients.
- In general, presence of a *FLT3*-ITD mutation adversely affects survival.
- Gilteritinib is a selective inhibitor with activity against *FLT3*-ITD and TKD mutations.
- Gilteritinib produces CR/CRi in 34% of patients with R/R *FLT3*-mutated AML with improved OS compared to salvage chemotherapy.

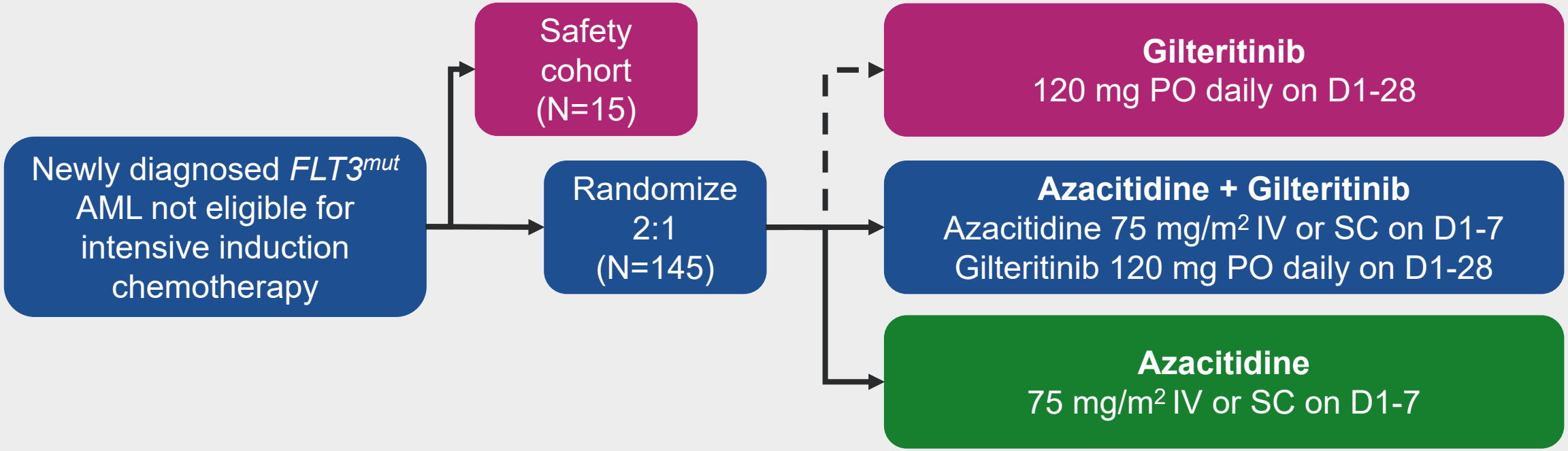
Overall Survival



Perl AE *et al. New Engl J Med* 2019; 381:1728-1740.

Phase 3 Trial of Azacitidine and Gilteritinib vs Azacitidine

Study Design

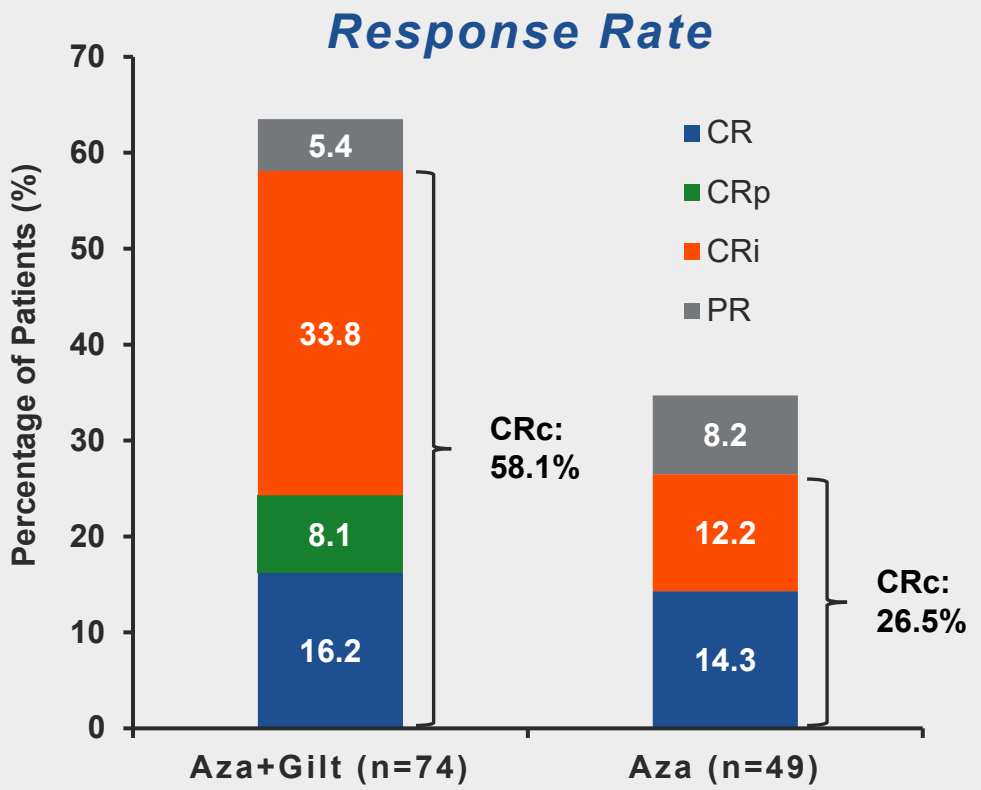


Primary endpoint: Overall survival
Key secondary endpoint: Event-free survival
Other secondary endpoints: Response, safety, tolerability
Exploratory: Pharmacokinetics

Wang ES *et al. Blood* 2021; 138 (Suppl 1):700.

Phase 3 Trial of Azacitidine and Gilteritinib vs Azacitidine
Patient Outcomes

Outcome	Azacitidine + Gilteritinib (n=74)	Azacitidine (n=49)	HR (95% CI)	*P*
Median OS (95% CI), mo	9.82 (7.56, 12.55)	8.87 (4.34, 14.03)	0.916 (0.529, 1.585)	0.753
Median OS by *FLT3* mutation status, mo ITD ITD allelic ratio ≥ 0.5 ITD allelic ratio < 0.5	 11.5 (n=60) 10.7 (n=35) 11.5 (n=25)	 8.1 (n=42) 4.3 (n=24) 13.4 (n=18)	—	—
Median EFS, mo	0.03	0.03	1.175 (0.764, 1.807)	0.459



Wang ES et al. *Blood* 2021;138 (Suppl 1):700.

Phase 3 Trial of Azacitidine and Gilteritinib vs Azacitidine
Summary

- No difference in OS with azacitidine/gilteritinib or azacitidine alone was seen.
- Factors contributing to lack of OS difference include:
  - Confounding effects from use of subsequent therapy.
  - Higher proportion of patients with ECOG ≥ 2 in the azacitidine/gilteritinib arm.
  - Differences in follow-up duration due to study design change.
- CRc rate was significantly higher in the azacitidine/gilteritinib arm, although CR rates were similar.
- Patients with *FLT3*-ITD allelic ratio ≥ 0.5 may have greater benefit from azacitidine/gilteritinib.
- Incidence of grade ≥ 3 AEs were similar between the arms.

Wang ES *et al. Blood* 2021; 138 (Suppl 1):700.

Phase 1/2 Trial of Azacitidine, Venetoclax, and Gilteritinib

Study Design

Eligibility

- R/R *FLT3*-mutated AML, high-risk MDS, or CMML
- Newly diagnosed *FLT3*-mutated AML unfit for intensive chemotherapy

Induction

Azacitidine
75 mg/m^2 IV or SC on D1-7

Venetoclax*
D1-28 (bone marrow on D14**)

Gilteritinib
80-120 mg on D1-28

Consolidation

Azacitidine
75 mg/m^2 IV or SC on D1-5

Venetoclax*
400 mg on D1-7

Gilteritinib
80-120 mg on D1-28

*Ramp-up during Cycle 1: 100 mg on D1, 200 mg in D2, 400 mg on D3+

**If < 5% blasts on D14, venetoclax held (both cohort) and gilteritinib held (frontline only)

Primary endpoints: Gilteritinib MTD (phase 1), CR/CRi rate (phase 2)

Secondary endpoints: CR rate, MRD negativity rate, response duration, OS, safety

MTD Determination

- Gilteritinib 120 mg (n=4)
  - 1 DLT (grade 4 myelosuppression)
  - Best response was MLFS
- Gilteritinib 80 mg (n=6)
  - No DLTs
  - 3 CR/CRi
  - 80 mg was determined to be RP2D

Short NJ *et al. Blood* 2021; 138 (Suppl 1):696.

Phase 1/2 Trial of Azacitidine, Venetoclax, and Gilteritinib
Patient Outcomes for Frontline Patients

Outcome	Frontline Patients (N=14)
ORR, n (%) CR CRi MLFS	14 (100) 13 (93) 0 1 (7)
MRD negativity, % Flow cytometry PCR	 75 86
30-day mortality	0
Median OS*, mo	9.5
6-month OS, %	92%

*3 deaths: 1 in CR (2 months), 1 post-SCT (7 months), 1 post-relapse (9.5 months)

Short NJ *et al. Blood* 2021; 138 (Suppl 1):696.

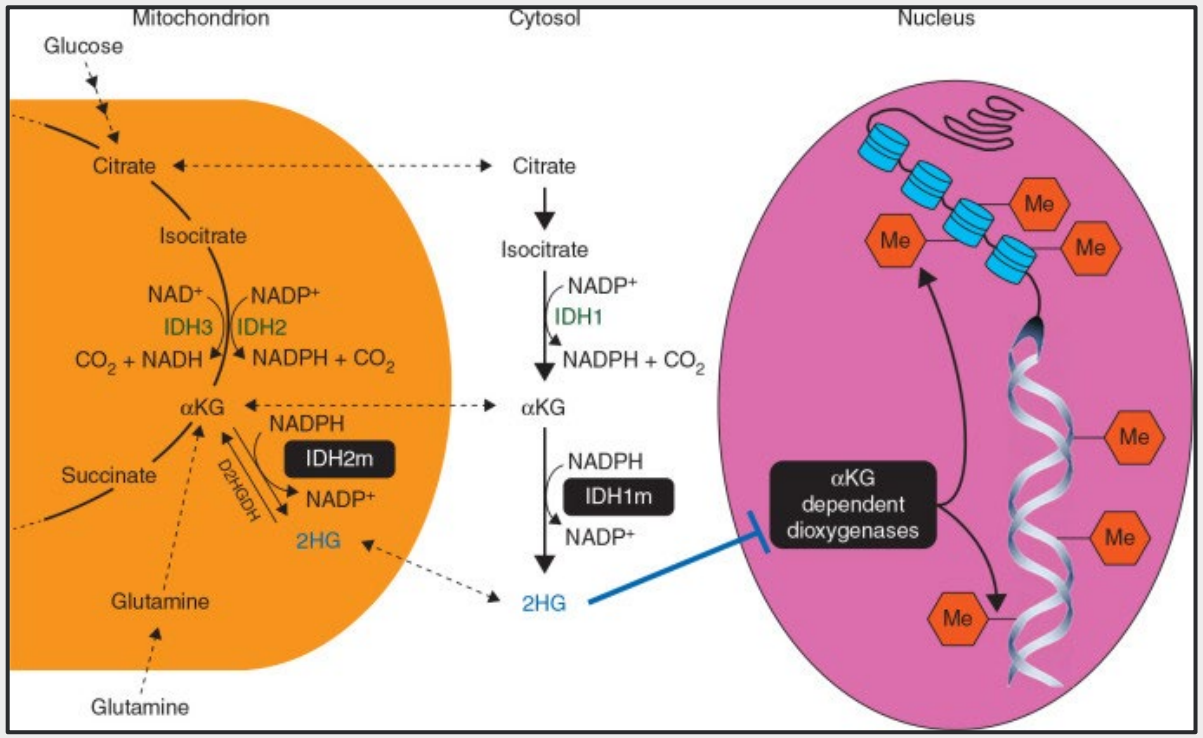
Phase 1/2 Trial of Azacitidine, Venetoclax, and Gilteritinib
Summary

- Azacitidine, venetoclax, gilteritinib produces high CRc rates in *FLT3*-mutated AML
  - 100% in newly diagnosed patients; 69% in R/R patients
  - CR rate was 93% in newly diagnosed patients with 86% MRD-negative
- Myelosuppression is common but manageable with mitigation strategies:
  - Use of gilteritinib 80 mg daily
  - Day 14 marrow evaluation in Cycle 1 to determine course duration of venetoclax and gilteritinib
  - Attenuation of azacitidine and venetoclax doses in consolidation

Short NJ *et al. Blood* 2021; 138 (Suppl 1):696.

Ivosidenib: A Targeted Inhibitor for Newly Diagnosed and Relapsed/Refractory *IDH1*-Mutated AML

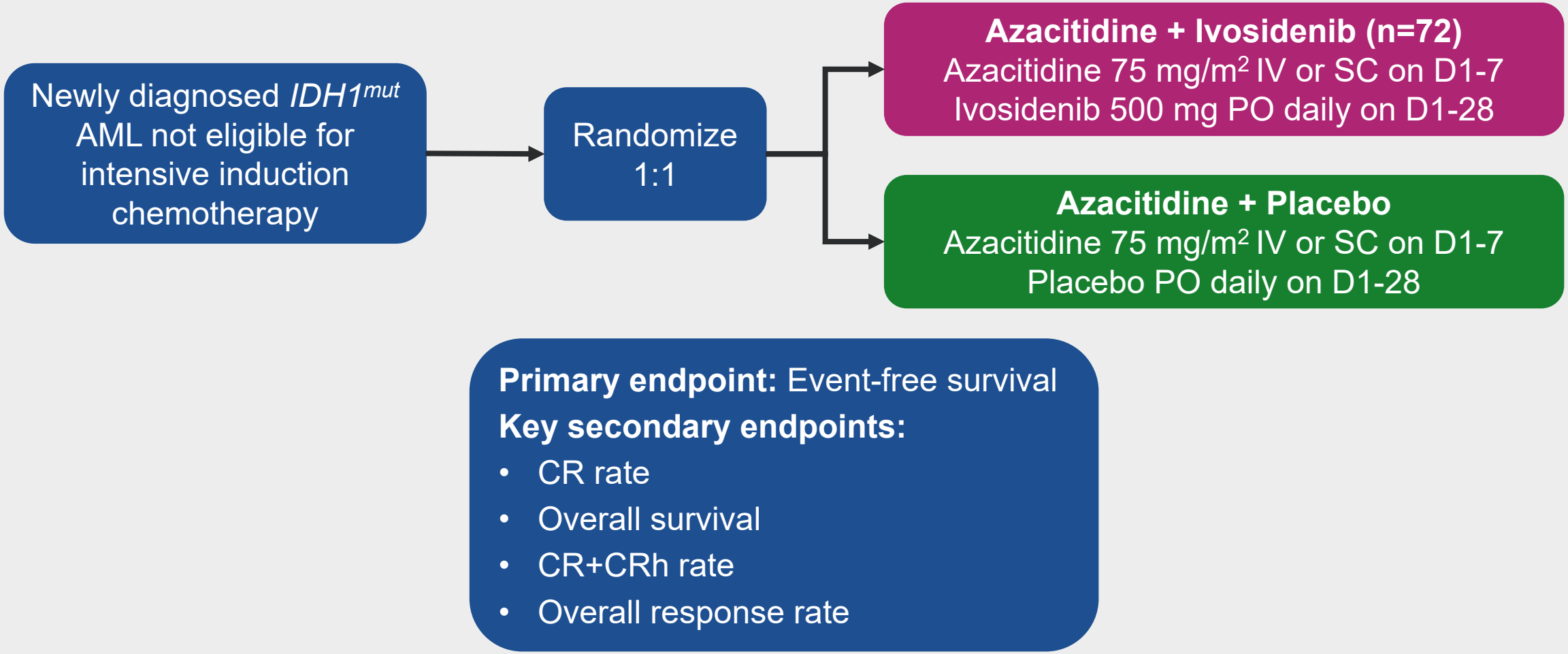
- Mutant *IDH1* (m*IDH1*) catalyzes production of the oncometabolite 2-hydroxyglutarate (2-HG)[1]
  - Leads to impaired differentiation and oncogenesis
- Ivosidenib is an oral targeted inhibitor of m*IDH1* approved for:
  - Relapsed/refractory *IDH1*-mutated AML[2]
  - Newly diagnosed *IDH1*-mutated AML in patients not candidates for intensive induction chemotherapy[3]
- Combination azacitidine/ivosidenib induces durable responses in newly diagnosed *IDH1*-mutated AML[4]
  - CR/CRi rate, 69.6%
  - 12-month OS, 82%



1. Dang L et al. *Ann Oncol* 2016; 27:599-608; 2. DiNardo CD et al. *New Engl J Med* 2018; 378:2386-2398; 3. Roboz GJ et al. *Blood* 2020; 135:463-471; 4. DiNardo CD et al. *J Clin Oncol* 2021; 39:57-65.

Phase 3 Trial of Azacitidine and Ivosidenib vs Azacitidine

Study Design



Primary endpoint: Event-free survival

Key secondary endpoints:

- CR rate
- Overall survival
- CR+CRh rate
- Overall response rate

Montesinos P *et al. Blood* 2021; 138 (Suppl 1):697.

Phase 3 Trial of Azacitidine and Ivosidenib vs Azacitidine
Patient Outcomes

Outcome	Azacitidine + Ivosidenib (n=72)	Azacitidine + Placebo (n=74)	HR (95% CI)	*P*
Event-free survival Intent to treat Median EFS in responders, mo	 – NE	 – 17.8	 0.33 (0.16, 0.69) –	 0.011 –
Median overall survival, mo	24.0	7.9	0.44 (0.27-0.73)	0.0005
ORR, n (%) (95% CI) CR CR + CRh	45 (62.5) (50.3, 73.6) 34 (47.2) (35.3, 59.3) 38 (52.8) (40.7, 64.7)	14 (18.9) (10.7, 29.7) 11 (14.9) (7.7, 25.0) 13 (17.6) (9.7, 28.2)	7.2 (3.3, 15.4) 4.8 (2.2,10.5) 5.0 (2.3, 10.8)	< 0.0001
Med response duration (95% CI), mo CR CR + CRh ORR	 NE (13.0, NE) NE (13.0, NE) 22.1 (13.0, NE)	 11.2 (3.2, NE) 9.2 (5.8, NE) 9.2 (6.6, 14.1)	–	–
Med TT 1st response (range), mo CR CR + CRh ORR	 4.3 (1.7-9.2) 4.0 (1.7-8.6) 2.1 (1.7-7.5)	 3.8 (1.9-8.5) 3.9 (1.9-7.2) 3.7 (1.9-9.45)	–	–

Montesinos P *et al. Blood* 2021; 138 (Suppl 1):697.

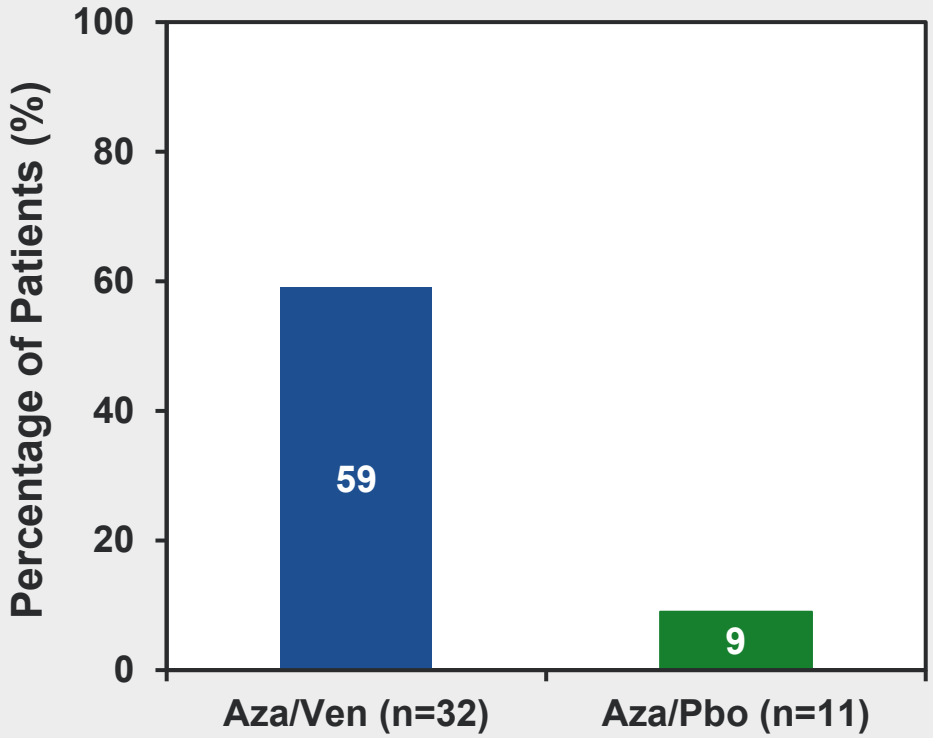
Phase 3 Trial of Azacitidine and Ivosidenib vs. Azacitidine
Adverse Events

- TEAEs of special interest with AZA + IVO vs AZA + placebo included:
  - Grade ≥ 2 differentiation syndrome (14.1% vs 8.2%)
  - Grade ≥ 3 QT prolongation (9.9% vs 4.1%)
- Infections were less common in AZA + IVO compared to AZA + placebo (28.2% vs. 49.3%)
- There were no treatment-related deaths

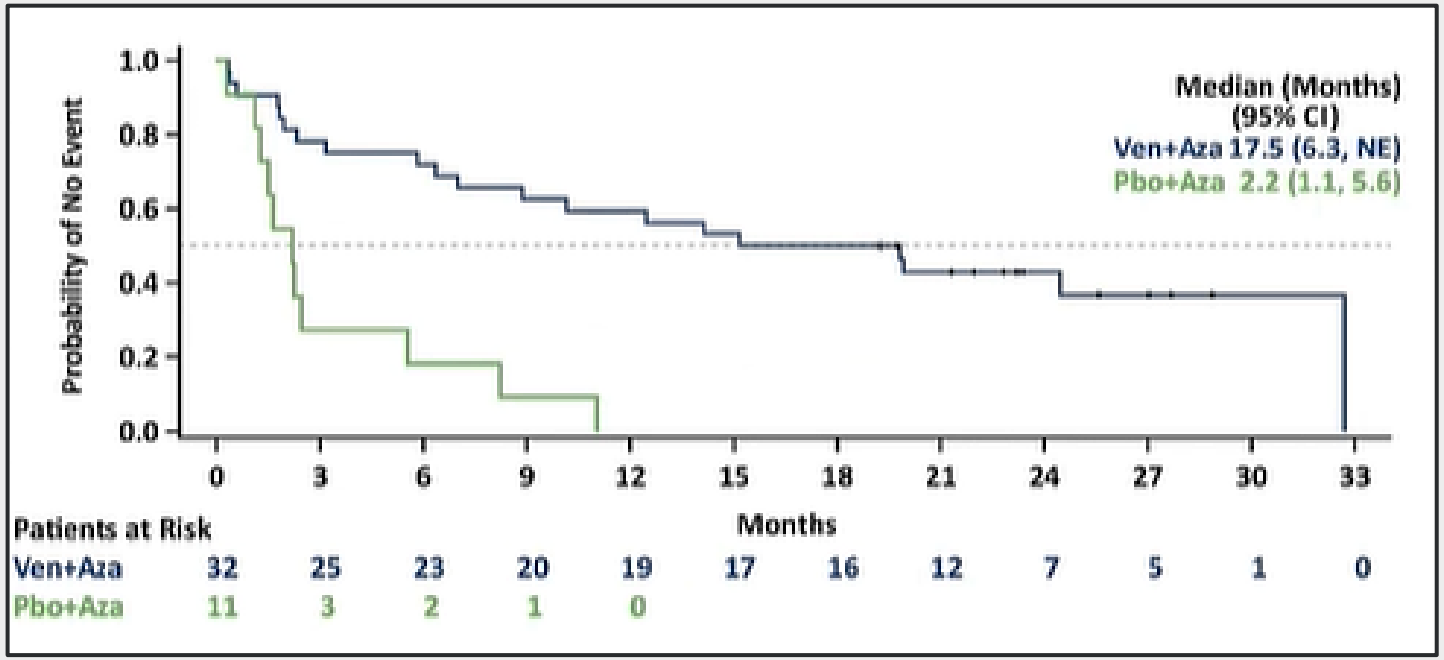
Montesinos P *et al. Blood* 2021; 138 (Suppl 1):697.

Azacitidine/Venetoclax in *IDH1*-Mutated AML

CR + CRh Rate



Overall Survival



Pollyea DA *et al. Blood* 2020; 136 (Suppl 1):461.

Phase 3 Trial of Azacitidine and Ivosidenib vs Azacitidine
Summary

- Azacitidine/ivosidenib significantly improved EFS, OS, and response compared to azacitidine/placebo in newly diagnosed *IDH1*-mutated AML patients
- Safety profile of azacitidine/ivosidenib was manageable, with fewer infections relative to azacitidine/placebo
- Open questions remain:
  - Is azacitidine/ivosidenib superior to azacitidine/venetoclax?
  - Is combination azacitidine, venetoclax, and ivosidenib superior to either doublet?

Montesinos P *et al. Blood* 2021; 138 (Suppl 1):697.

Conclusions

- The anti-CD47 mAb magrolimab produced encouraging results when combined with azacitidine/venetoclax, particularly in *TP53*-mutated AML, but careful management of treatment-associated hemolysis is required.
- The addition of the *FLT3* inhibitor gilteritinib to azacitidine did not improve survival of *FLT3*-mutated AML patients compared to azacitidine alone.
- Encouraging results were seen when gilteritinib was added to azacitidine/venetoclax, but dose modifications were required to manage myelosuppression.
- Azacitidine/ivosidenib significantly improved outcomes of *IDH1*-mutated AML patients compared to azacitidine alone.