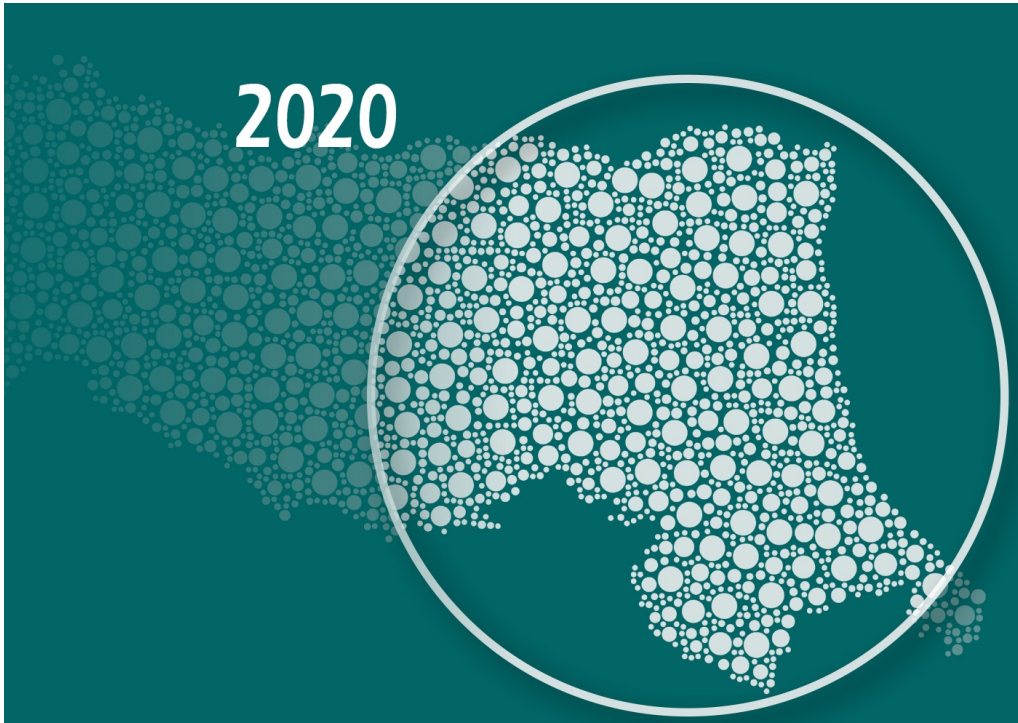


Progetto
Ematologia
Romagna

La terapia con anti-BCL2: nuovi target nelle leucemie acute mieloidi

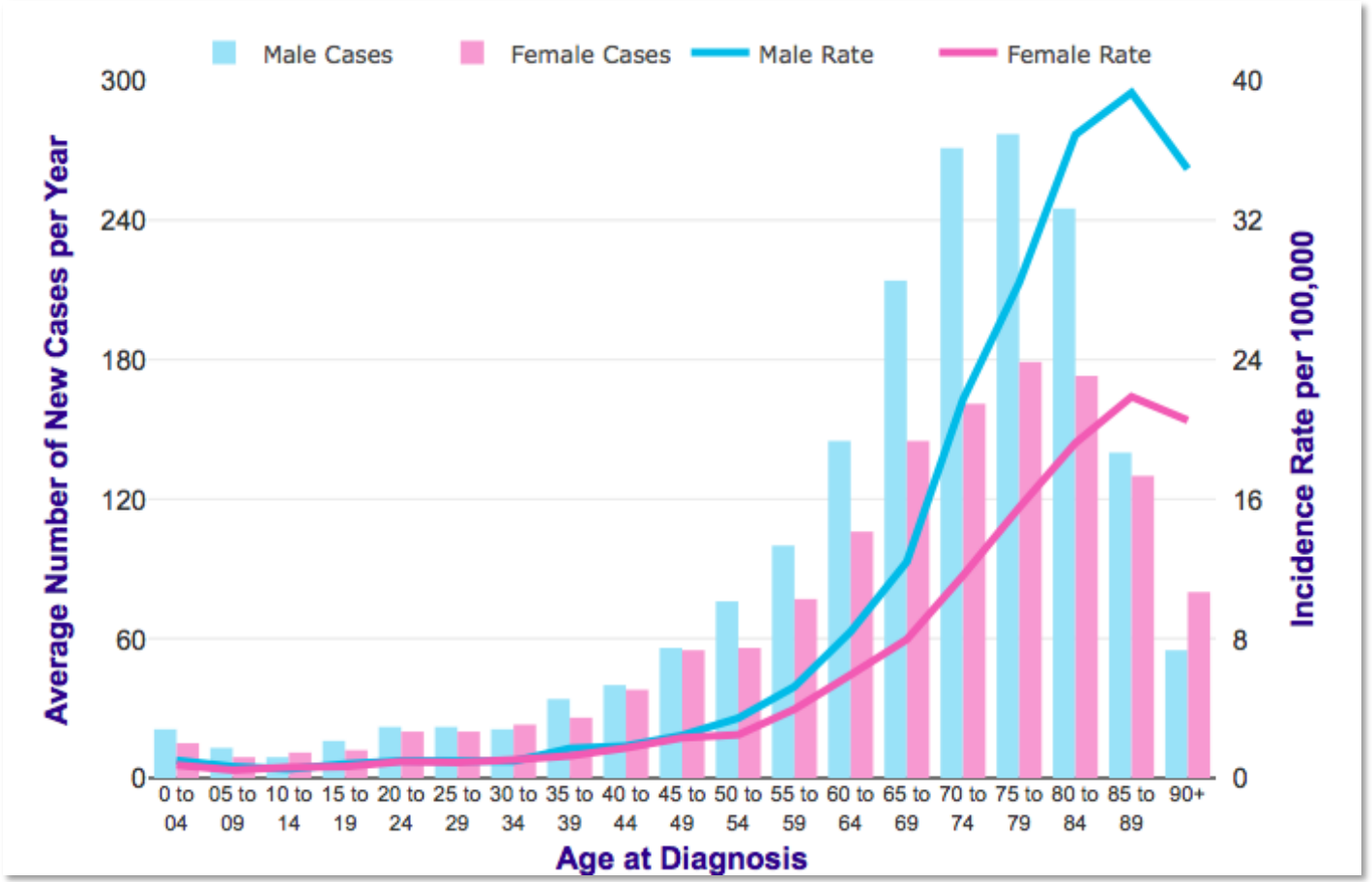
Antonio Curti

CONFLITTO DI INTERESSI

Partecipazione ad Advisory Board e Congressi:

- AbbVie
- Pfizer
- Novartis

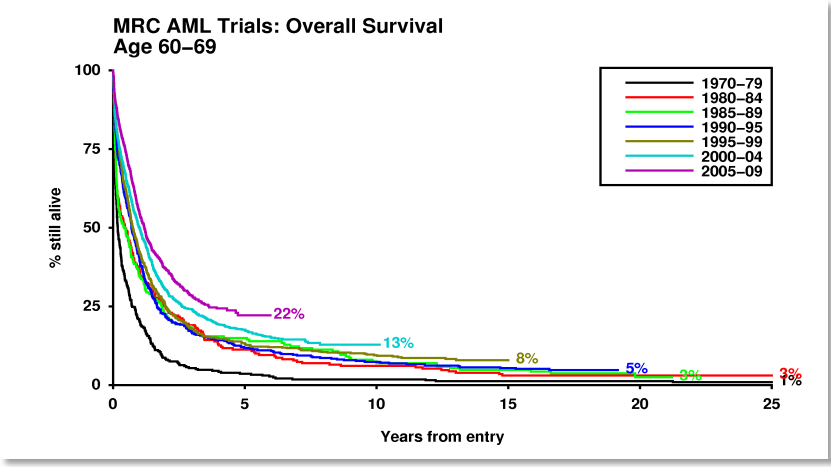
AML incidence and prevalence



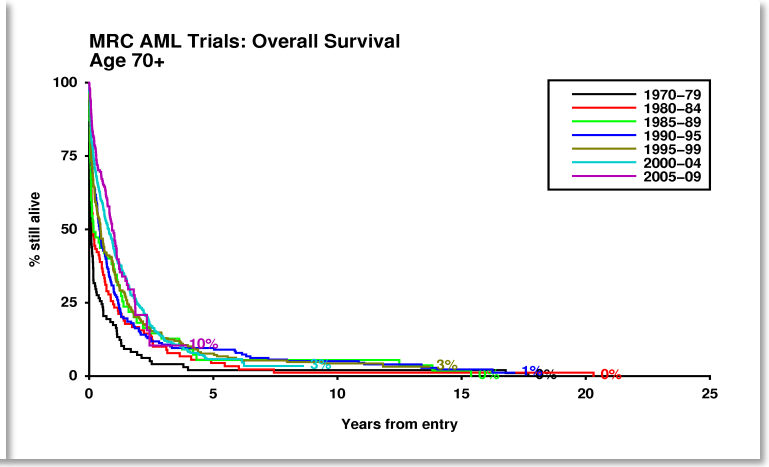
Outcome of older AML

MRC/NCRI AML trials by year

Intensive CTx[1]



No intensive CTx[1]



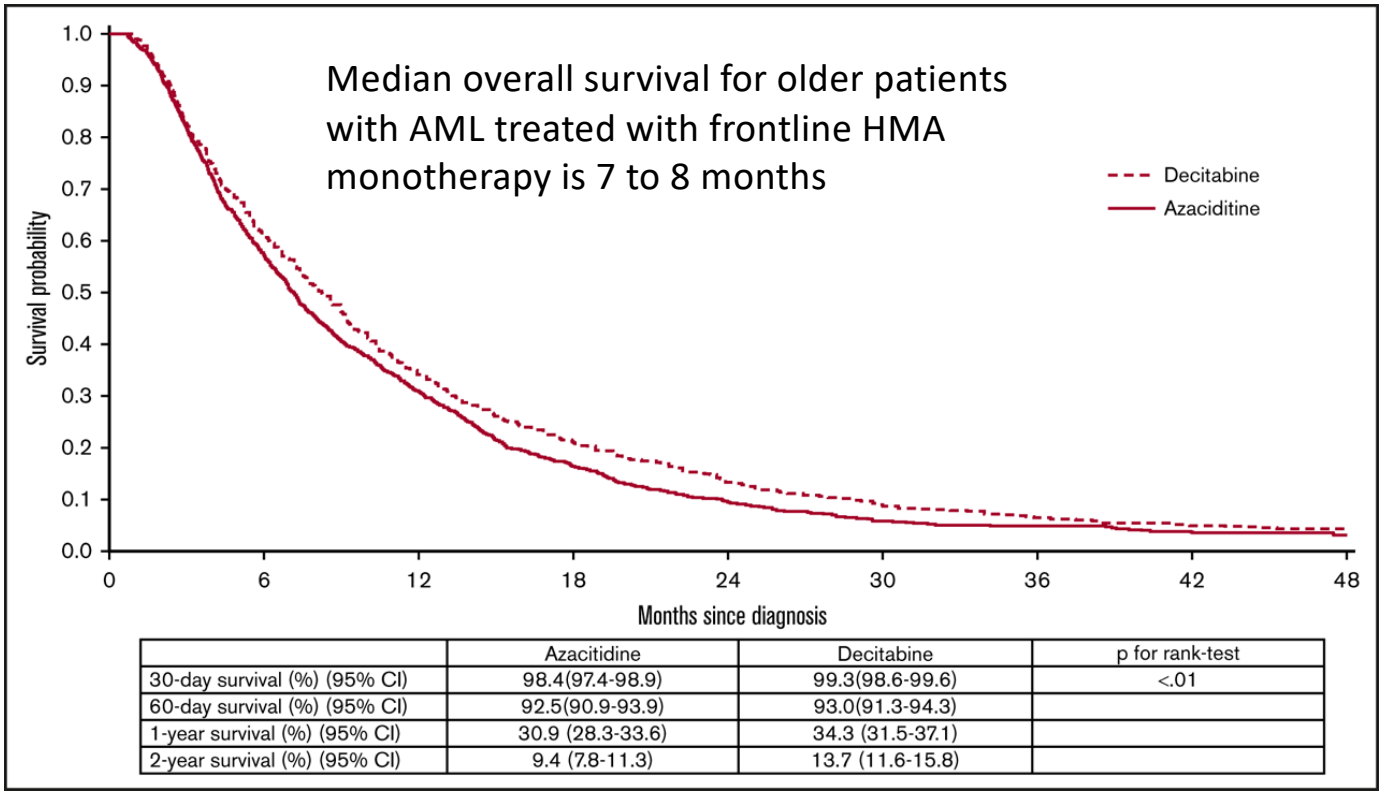
AML: acute myeloid leukemia; MRC: Medical Research Council; NCRI: National Cancer Research Institute; CTx: chemotherapy

1. Images courtesy of AK Burnett

Challenges of traditional therapy in the elderly population

- CR difficult to achieve
  - CR not long-lasting if achieved
- What does it actually mean to be fit vs unfit?
  - Selecting appropriate patients for treatment
- Challenges related to induction therapy in older pts
  - High toxicity/low tolerability
  - Lack of care-giver support
- Many patients not offered therapy due to unsatisfactory treatment options

Clinical outcomes of older patients with AML receiving hypomethylating agents: a large population-based study in the United States on 2263 patients



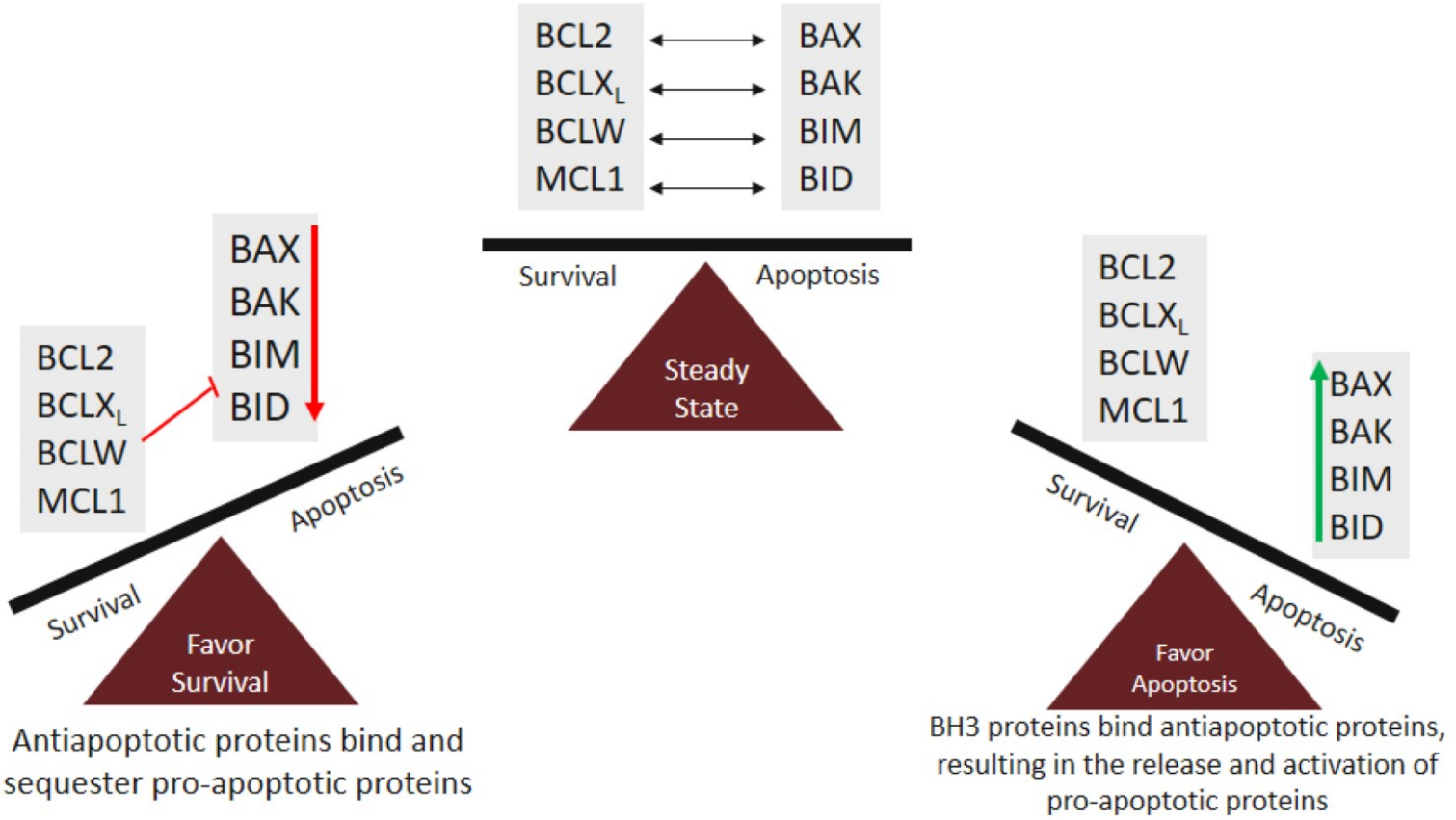
	Azacitidine	Decitabine	p for rank-test
30-day survival (%) (95% CI)	98.4(97.4-98.9)	99.3(98.6-99.6)	<.01
60-day survival (%) (95% CI)	92.5(90.9-93.9)	93.0(91.3-94.3)	
1-year survival (%) (95% CI)	30.9 (28.3-33.6)	34.3 (31.5-37.1)	
2-year survival (%) (95% CI)	9.4 (7.8-11.3)	13.7 (11.6-15.8)	

Amer M. et al, Blood Adv, 2020

New emerging and promising options

- Optimizing intensive chemotherapy
  - GO instead of anthracyclines
  - Liposomal formulation (CPX-351)
- Different strategies
- New agents +/- HMAs
  - Ivosidenib/Enasidenib
  - Glasdegib
  - Venetoclax

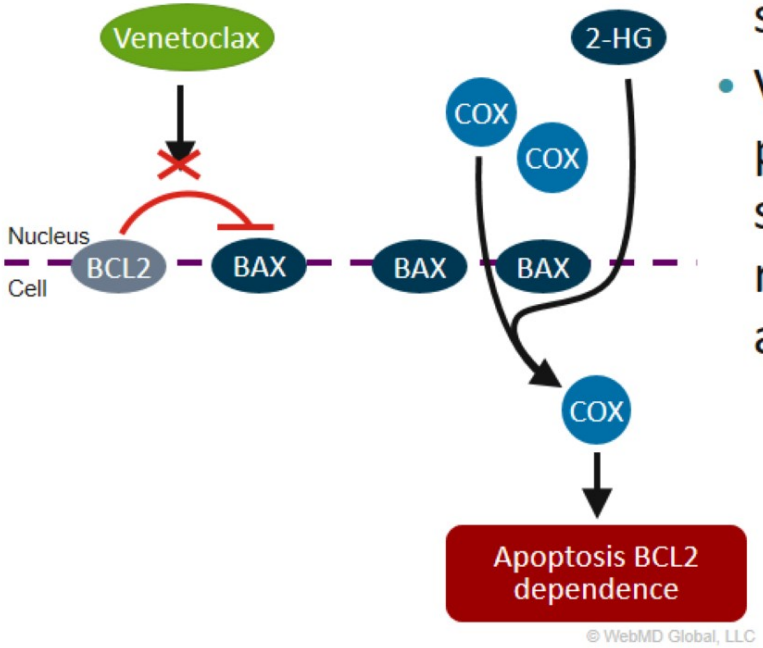
Cells Use the BCL-2 Family of Proteins to Decide Whether to Die or to Survive



Antiapoptotic proteins bind and sequester pro-apoptotic proteins

BH3 proteins bind antiapoptotic proteins, resulting in the release and activation of pro-apoptotic proteins

Venetoclax Mechanism of Action



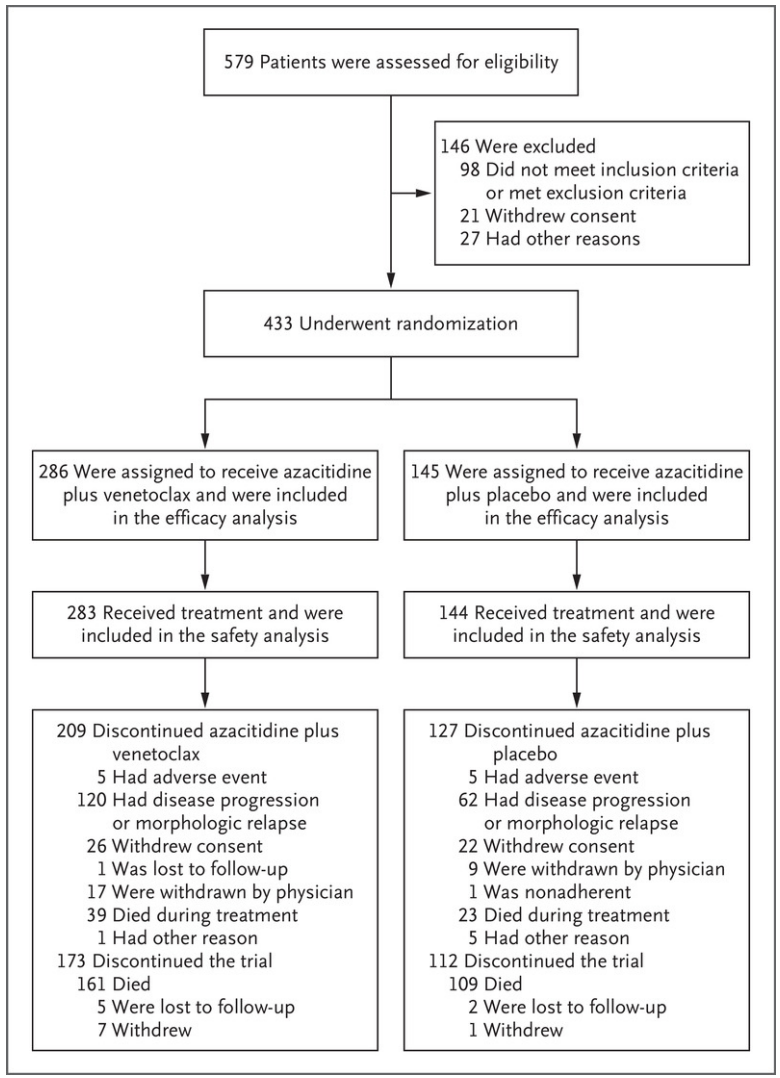
- Venetoclax is a highly selective, BCL2 inhibitor.
- Venetoclax binds to BCL2, proapoptotic proteins such as BIM and BAX are released, and induction of apoptosis is facilitated

Buege MJ, et al. *Cancers (Basel)*. 2018;10. pii: E187.

FDA Approval of Venetoclax For AML in Adults With Older Age or Comorbidities

Location	Indication
United States	• In combination with azacitidine or decitabine or LDAC for the treatment of newly-diagnosed AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy[a] • This indication is approved under accelerated approval based on response rates. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials
Ex-US/EMA	Granted orphan designation by EC for the treatment of AML

a. VENCLEXTA® PI 2018; b. EMA website. Orphan designation: venetoclax.



Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia (VIALE-A Study)

Enrolment: total 431 patients (286 in the azacitidine–venetoclax group and 145 in the azacitidine–placebo).

Median age: 76 years in both groups (range, 49 to 91)

Median follow-up: 20.5 months

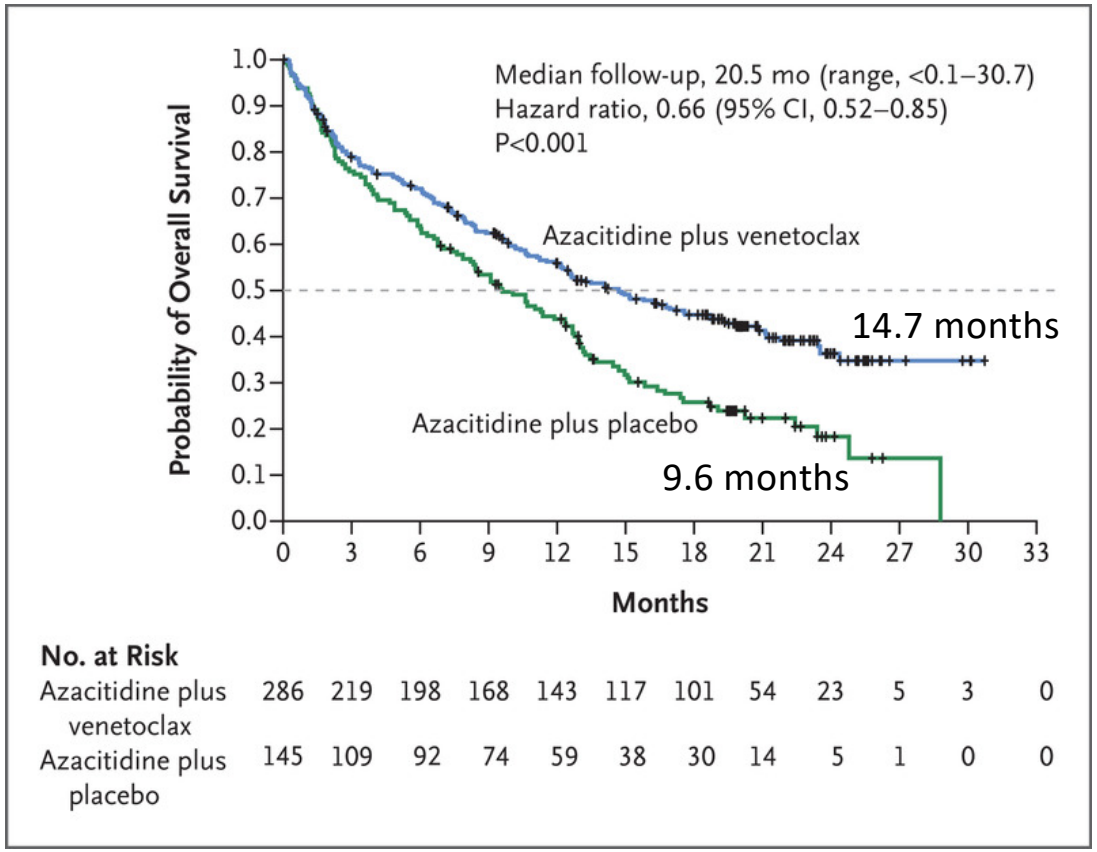
Median overall survival: 14.7 months in the azacitidine–venetoclax group and 9.6 months in the control group (P<0.001).

Incidence of complete remission: 36.7% vs 17.9% (P<0.001)

Incidence of composite complete remission: 66.4% vs. 28.3% (P<0.001)

DiNardo C et al, N Engl J Med 2020; 383:617-629

Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia (VIALE-A Study)



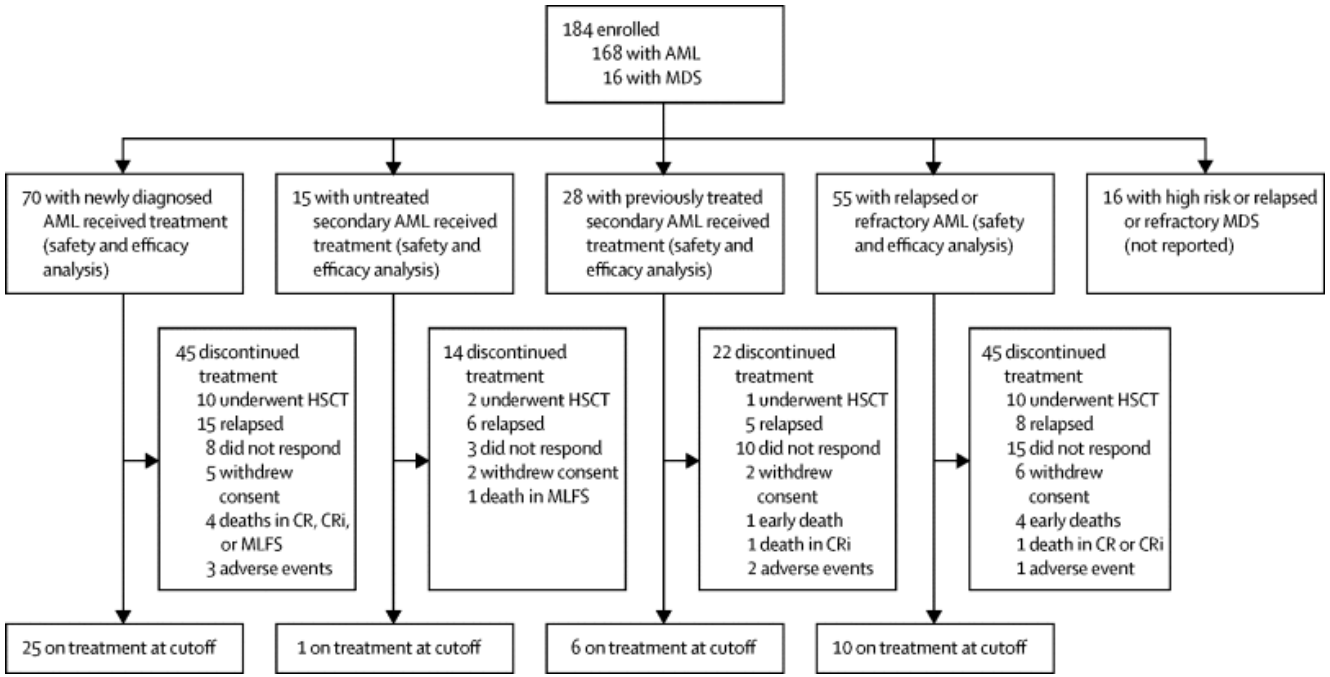
DiNardo C et al, N Engl J Med 2020; 383:617-629

Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia (VIALE-A Study)

Treatment	Neutropenia	Febrile neutropenia	Infections
VEN-AZA	42	42	84
AZA	28	19	67

The incidence of febrile neutropenia was higher in the venetoclax–azacitidine group than in the control group.

10-day decitabine with venetoclax for newly diagnosed intensive chemotherapy ineligible, and relapsed or refractory acute myeloid leukaemia: a single-centre, phase 2 trial



Treatment schedule

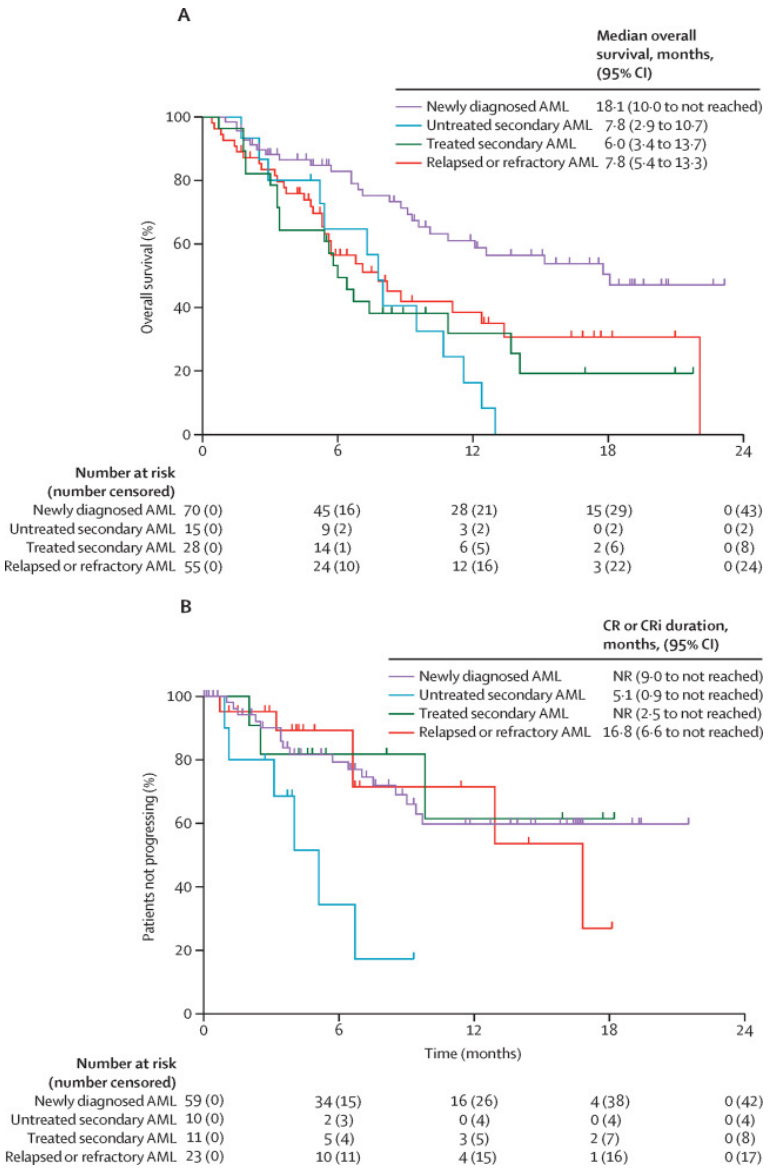
Induction:

- decitabine 20 mg/m^2 for 10 days
- venetoclax 400 mg daily

Consolidation:

- decitabine 20 mg/m^2 for 5 days
- venetoclax 400 mg daily

DiNardo C et al, Lancet Haematol. 2020 Oct;7(10):e724-e736



10-day decitabine with venetoclax for newly diagnosed intensive chemotherapy ineligible, and relapsed or refractory acute myeloid leukaemia: a single-centre, phase 2 trial

Enrolment: total 168 AML patients

Median age: 71 (range, 65-76)

Median follow-up: 16 months

Median overall survival: 18.1 months in newly diagnosed AML, 7.8 months in untreated secondary AML, 6.0 months in treated secondary AML and 7.8 months in R/R AML

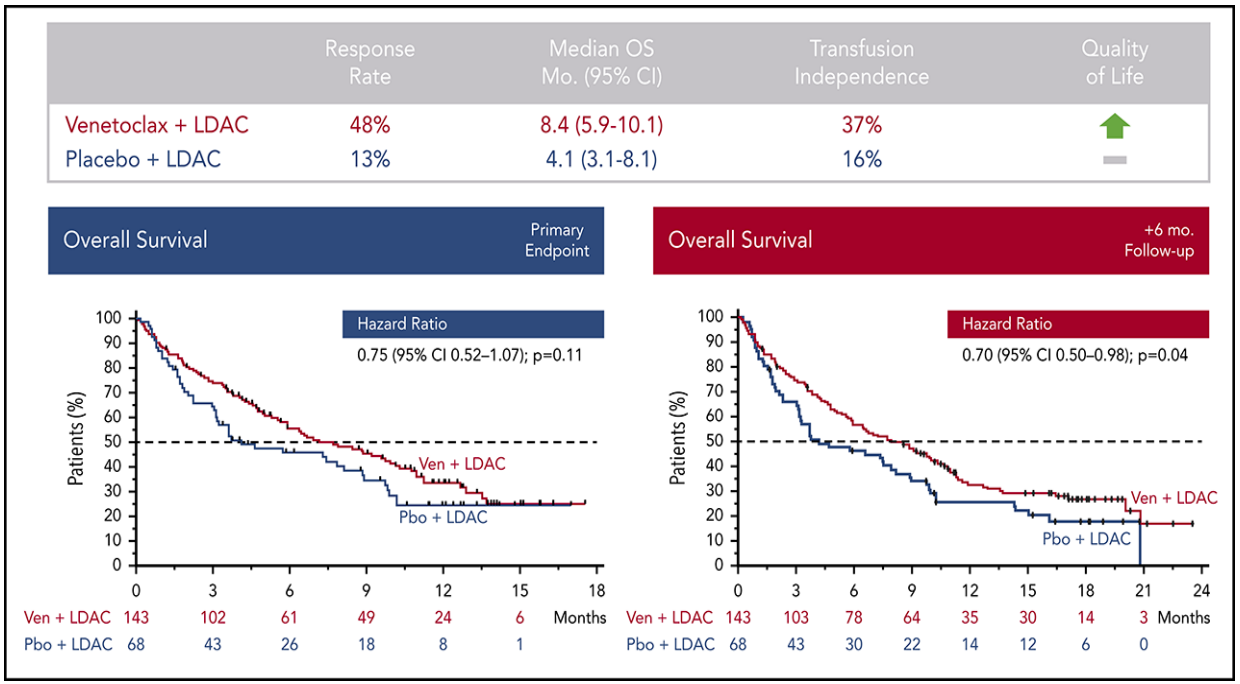
ORR:
89%in newly diagnosed AML,
80% in untreated secondary AML
61% in treated secondary AML
62% in R/R AML

Incidence of composite complete remission: 66.4% vs. 28.3% (P<0.001)

DiNardo C et al, Lancet Haematol. 2020 Oct;7(10):e724-e736

Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial

	Response Rate	Median OS Mo. (95% CI)	Transfusion Independence	Quality of Life
Venetoclax + LDAC	48%	8.4 (5.9-10.1)	37%	↑
Placebo + LDAC	13%	4.1 (3.1-8.1)	16%	–



Total 211 elderly AML Patients
Median age: 76 years (range, 36-93 years)
Previous treatment:
-38% secondary AML
-20% had received prior HMAs

Key Points

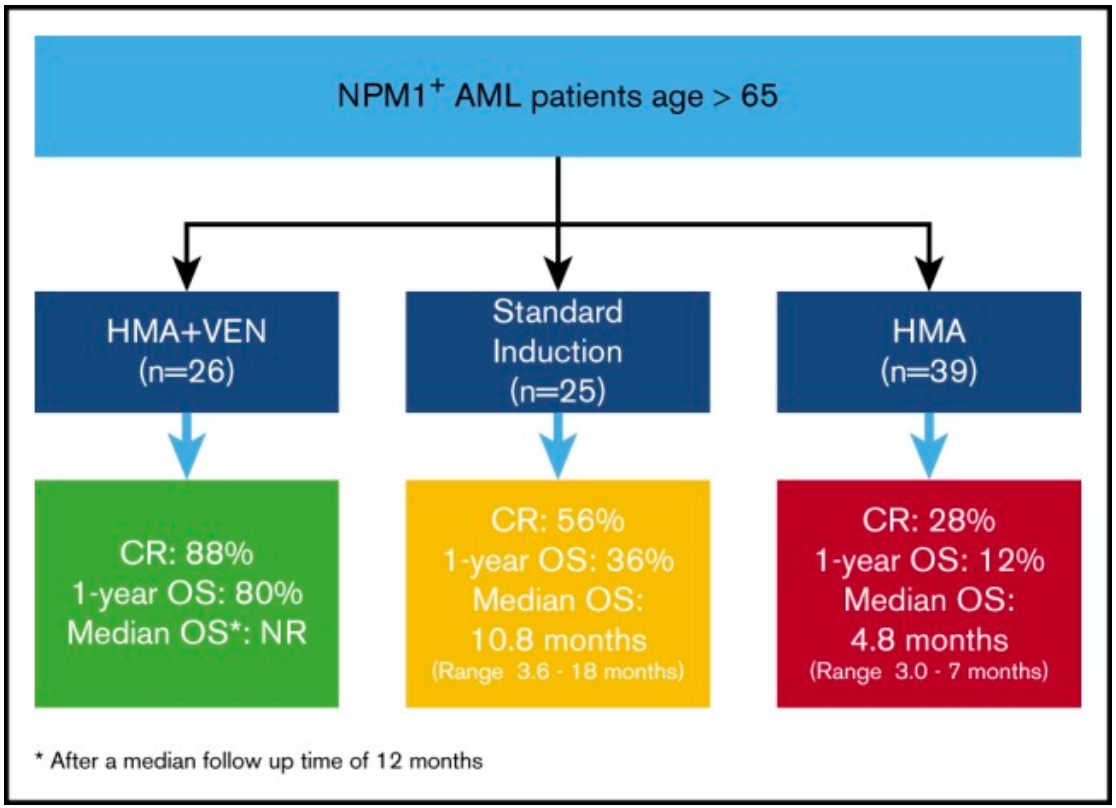
Venetoclax plus LDAC improves response rate, transfusion independence, and patient-reported outcomes

•Median OS for patients receiving venetoclax plus LDAC was 8.4 months vs 4.1 months for those receiving LDAC alone.

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

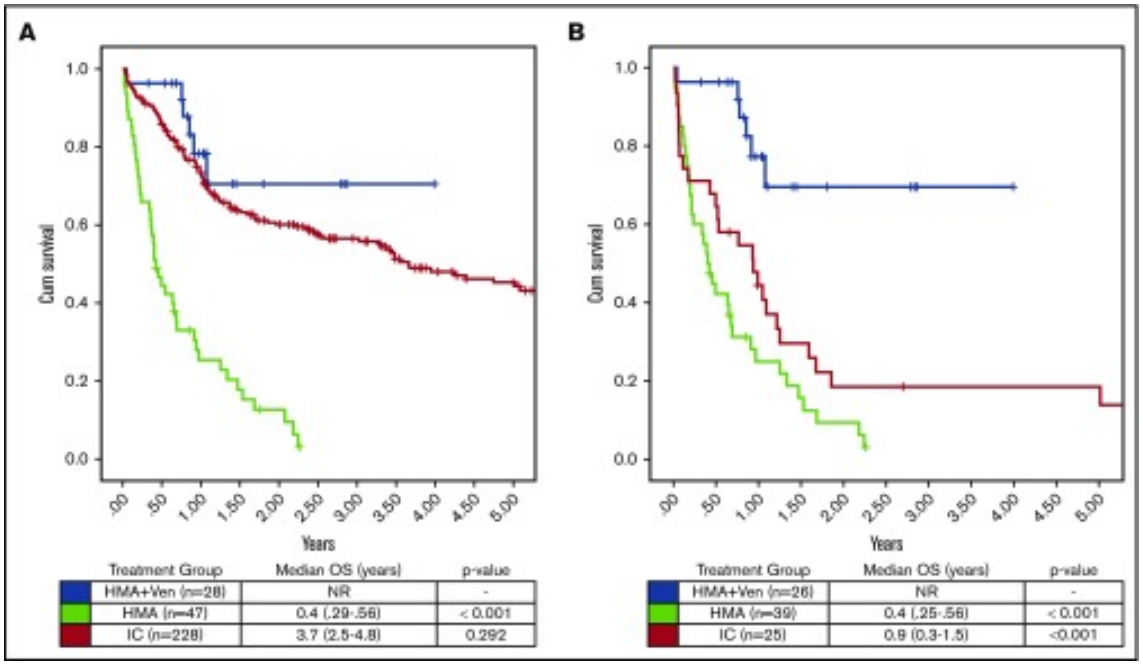
Wei A et al, Blood, 2020

Outcomes of Older Patients With NPM1-mutated AML: Current Treatments and the Promise of Venetoclax-Based Regimens

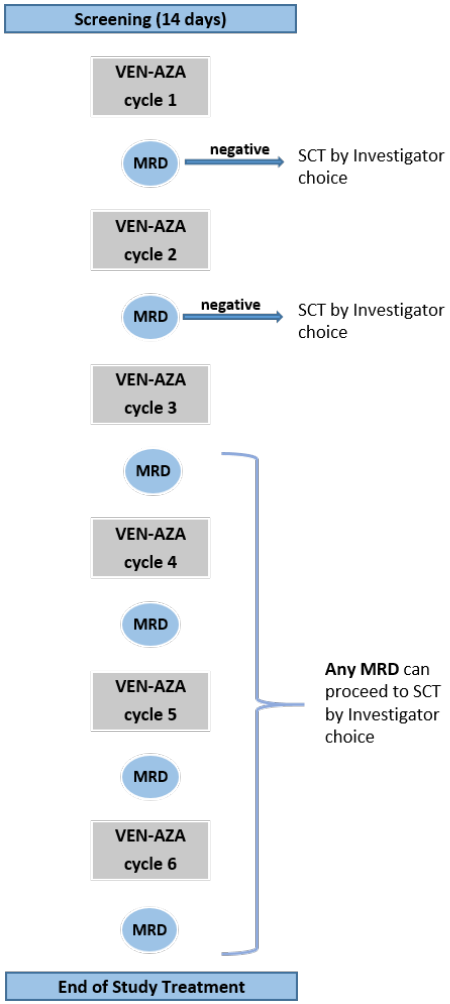


Blood Adv. 2020 Apr 14;4(7):1311-1320

OS by treatment group in *NPM1*$^{+}$patients treated with HMA + VEN, HMA, and IC



Blood Adv. 2020 Apr 14;4(7):1311-1320



A MULTICENTRIC PHASE 2 STUDY OF VENETOCLAX AND AZACITIDINE FOR THE MANAGEMENT OF MOLECULAR RELAPSE/PROGRESSION IN ADULT NPM1-MUTATED ACUTE MYELOID LEUKEMIA

Type of study: phase 2 non-randomized, interventional, open-label, multicentric trial (GIMEMA)

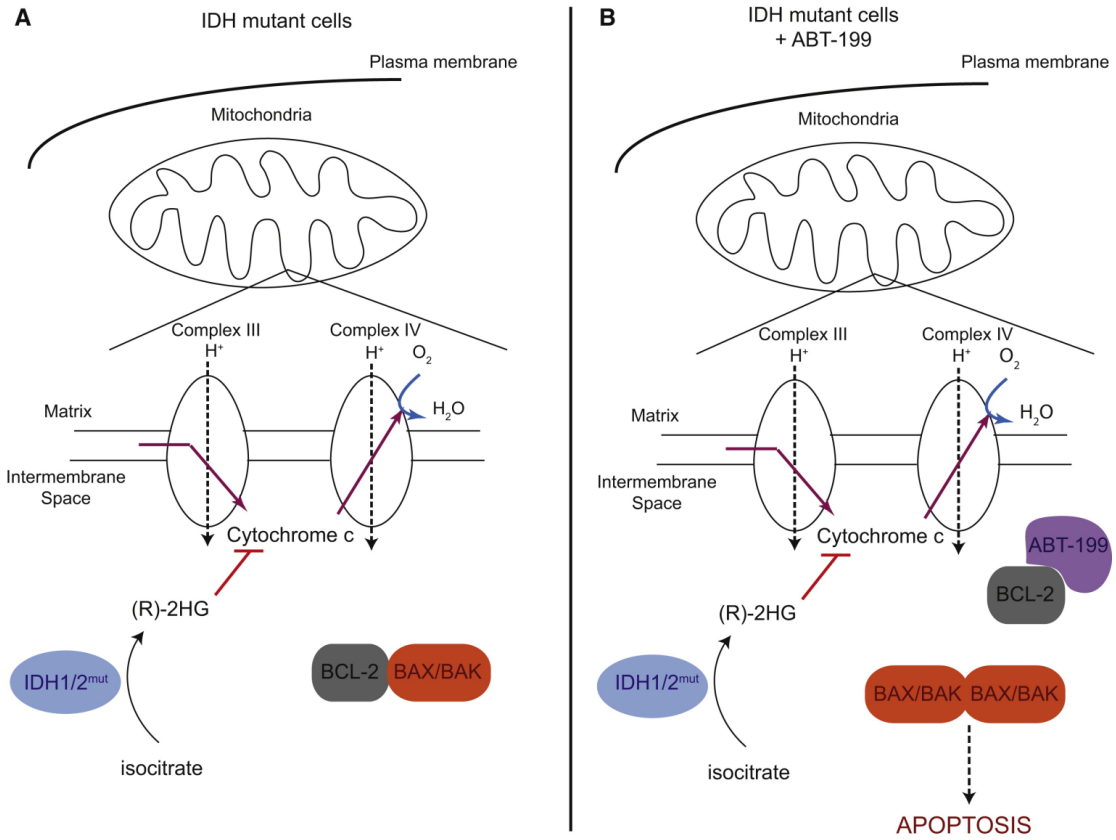
Primary objective: to evaluate efficacy of VEN-AZA as a bridge-to-transplant therapy for preventing morphological relapse in adult $NPM1^{mut}$ AML patients who experience molecular relapse or progression during treatment or follow-up

Treatment: venetoclax 400 mg orally QD on Days 1 – 28 plus azacitidine 75 mg/m2 SC daily for 7 days (schedule 1-7 or 5-2-2)

Enrollment: the trial will include 25 GIMEMA Italian Hematology centers and 35 subjects will be enrolled

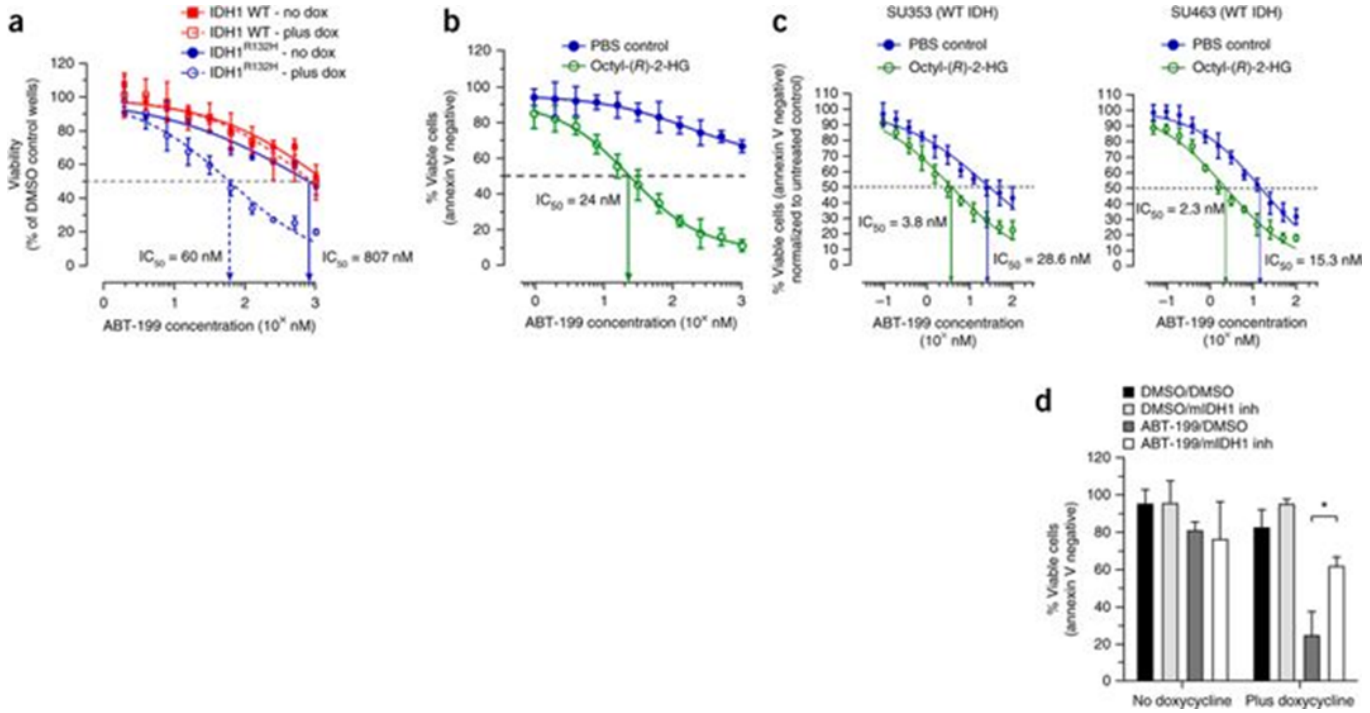
Total study duration: 2 years of enrollment, with 12 months of follow up.

IDH1/2 Mutations and BCL-2 Dependence: An Unexpected Chink in AML's Armour

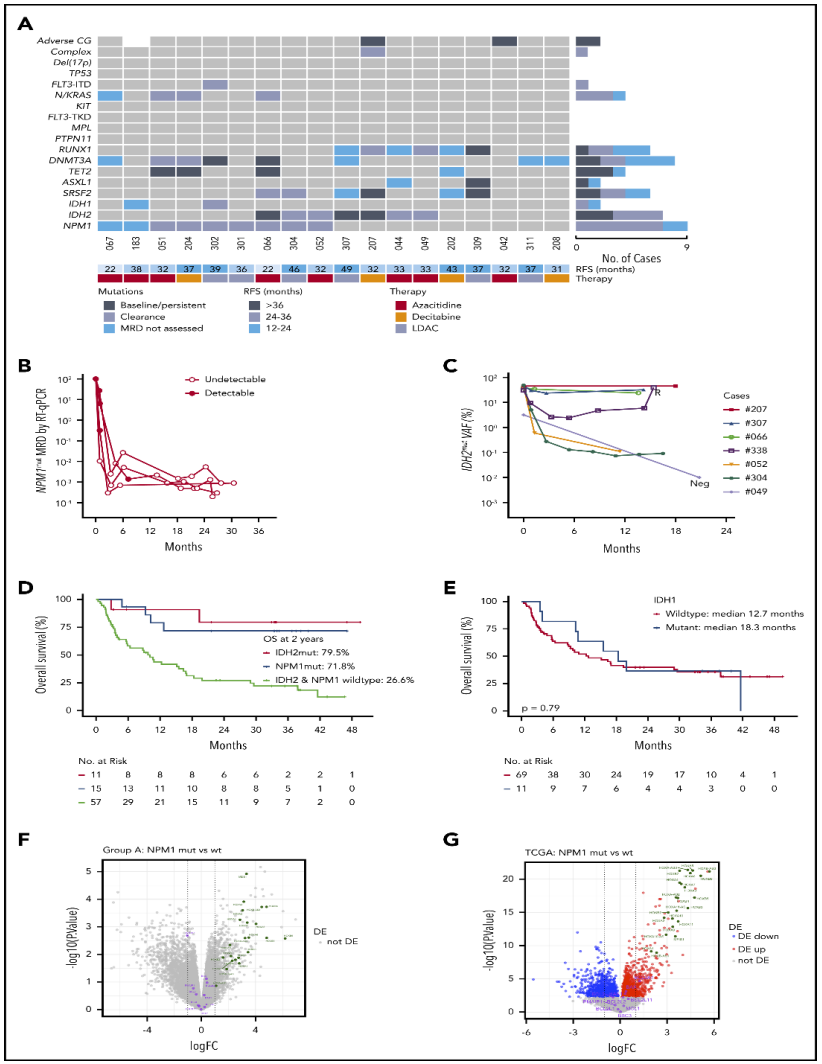


Cancer Cell 27, March 9, 2015

Isocitrate dehydrogenase 1 and 2 mutations induce BCL-2 dependence in acute myeloid leukemia



Chan SM, Nat Med. 2015 Feb;21(2):178-84.



Molecular patterns of response and treatment failure after frontline venetoclax combinations in older patients with AML

Key Points

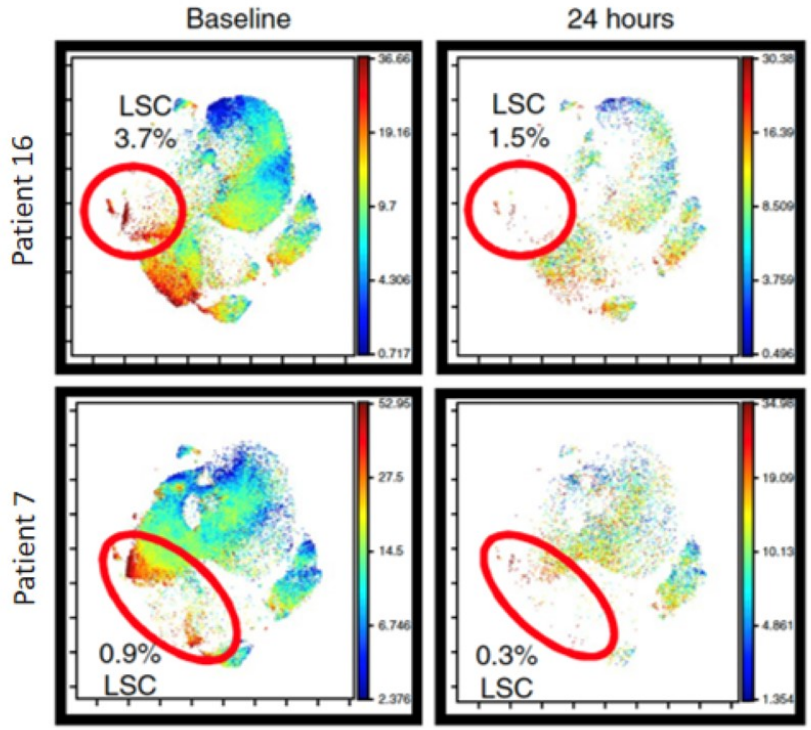
Adaptive resistance is often associated with TP53 abnormalities or kinase activation, particularly FLT3 internal tandem duplication.

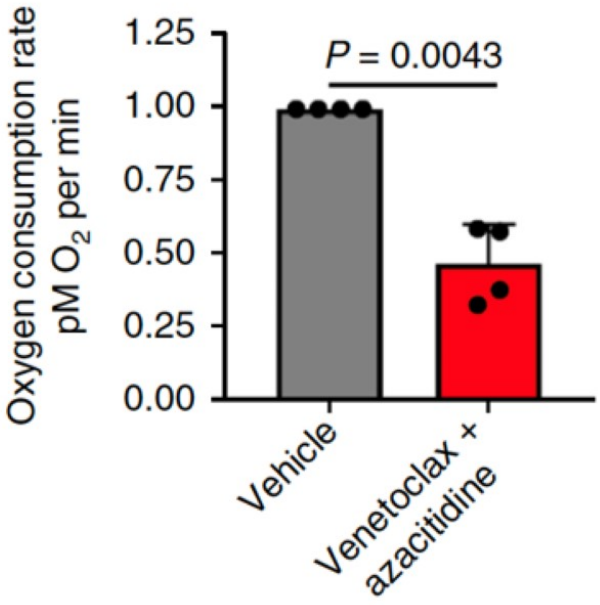
High response rates and durable remissions were typically associated with *NPM1* or *IDH2* mutations

NPM1 mutation is associated with excellent survival prospects and durable molecular remission after venetoclax-based combination therapy.

DiNardo C et al, Blood. 2020

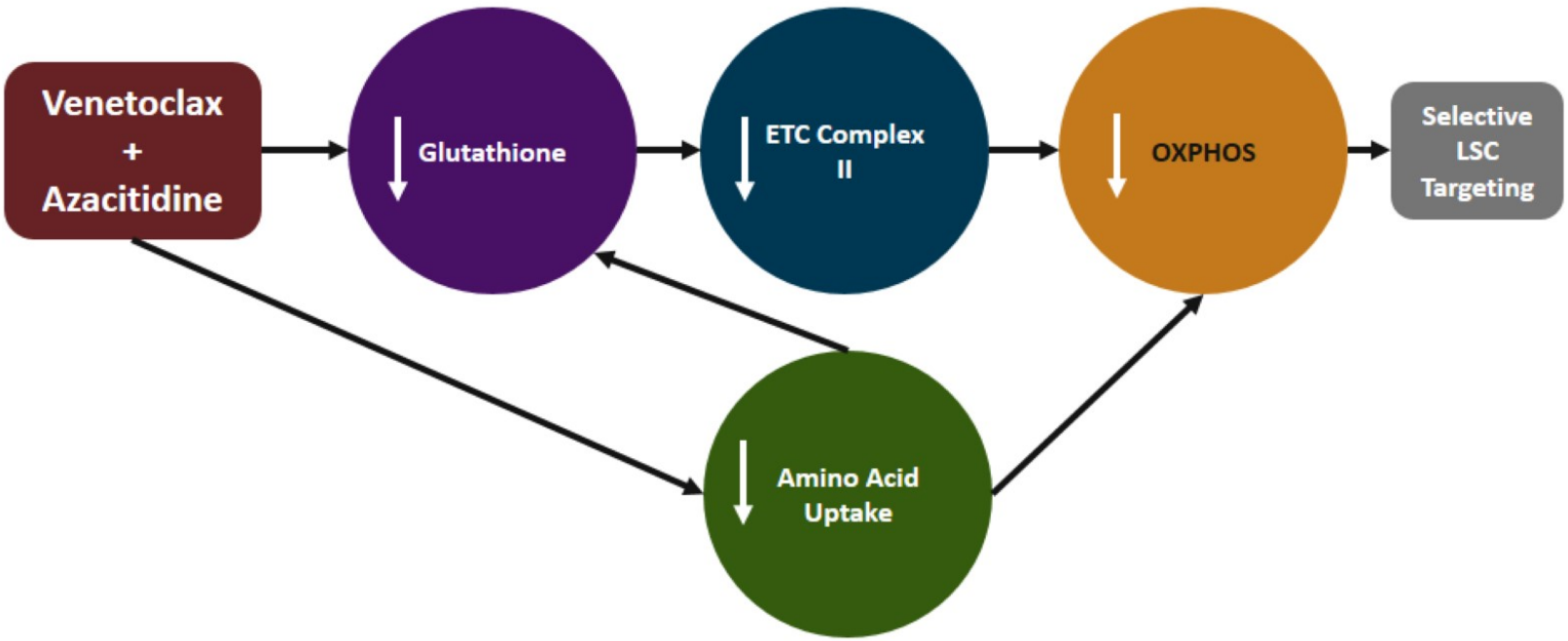
Venetoclax + AZA disrupts energy metabolism and target LSCs in AML





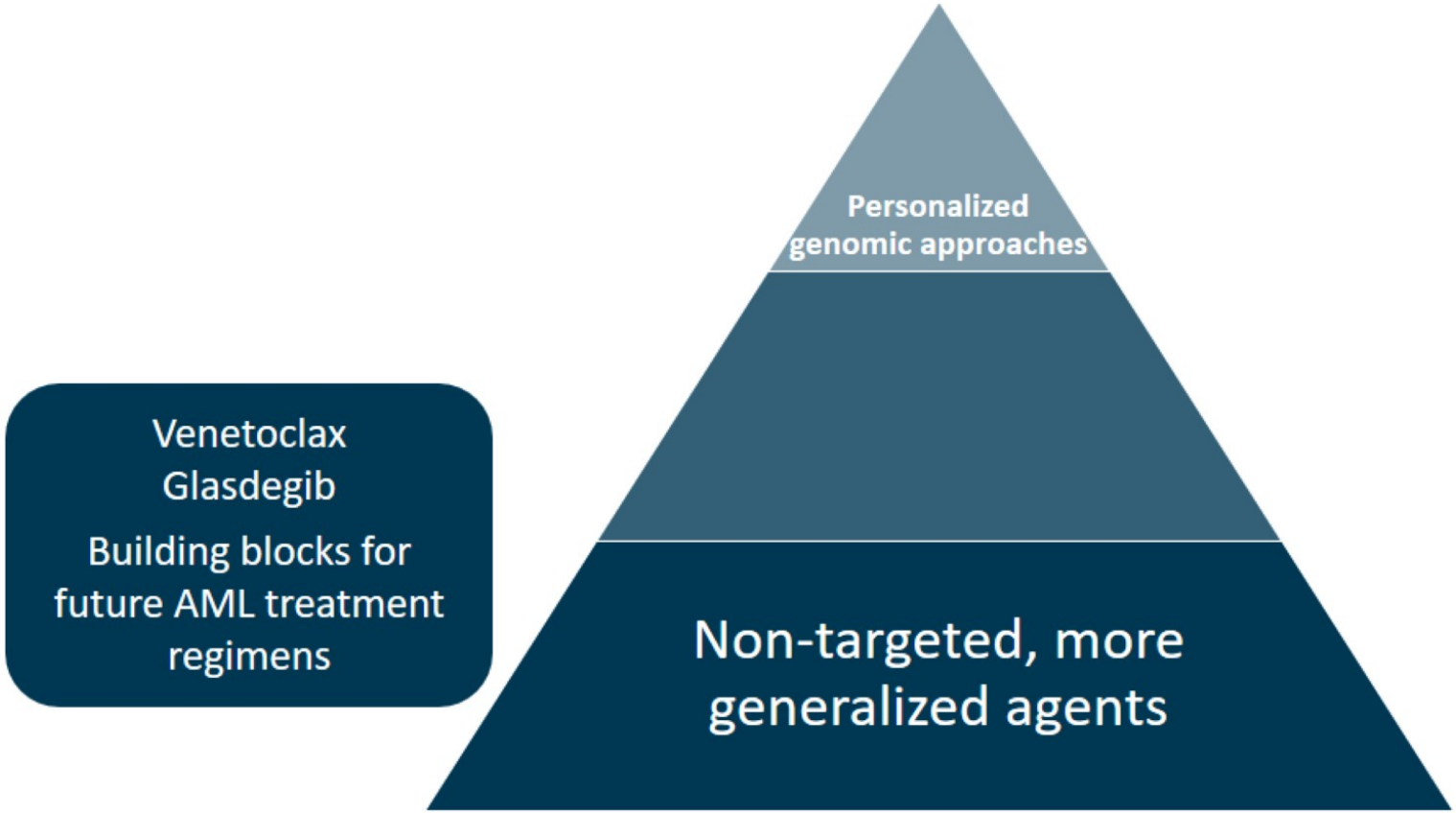
Pollyea DA, et al. *Nat Med.* 2018;24:1859-1866.

Mechanism of BCL-2 Inhibition in AML: "Leukemia Stem Cell Hypothesis"



Pollyea DA, et al. *Nat Med.* 2018;24:1859-1866.

Resurgence of Nontargeted Therapy for AML Treatment



Discussion

- Venetoclax/HMA combination is rapidly evolving as a new standard-of-care for newly diagnosed older AML patients, not eligible for intensive chemotherapy

- In terms of toxicity, Venetoclax/HMA represent a third way between intensive chemotherapy and HMA alone. A better definition of clinical fitness to venetoclax/HMA is highly warranted

- Genomic AML subsets have shown great lethal sensitivity to venetoclax/HMA, providing the rationale for exploring this association also in younger patients