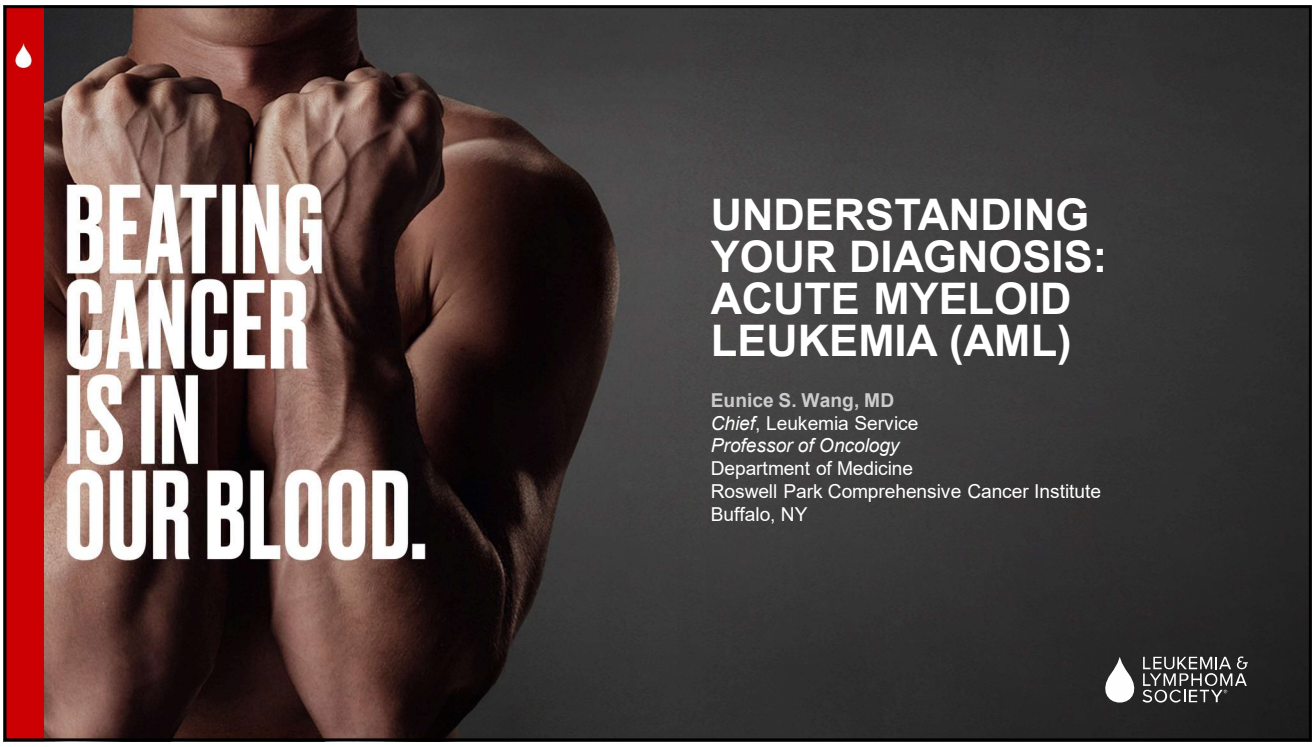


UNDERSTANDING YOUR DIAGNOSIS: ACUTE MYELOID LEUKEMIA (AML)

Eunice S. Wang, MD
Chief, Leukemia Service
Professor of Oncology
Department of Medicine
Roswell Park Comprehensive Cancer Institute
Buffalo, NY

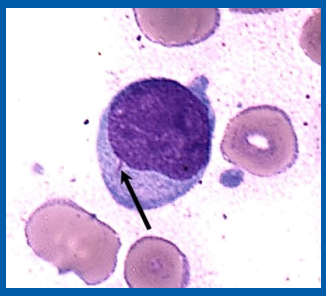
LEUKEMIA & LYMPHOMA SOCIETY®

DISCLOSURES

Understanding Your Diagnosis: Acute Myeloid Leukemia (AML)

Eunice S. Wang, MD, has affiliations with AbbVie, Agios, Amgen, Astellas, Daiichi, Gilead, Jazz, Macrogenics, Pfizer, Stemline (*Consultant*); Astellas, Jazz, Novartis, Pfizer, Stemline (*Speakers Bureau*).

Understanding Acute Myeloid Leukemia



ROSWELL PARK COMPREHENSIVE CANCER CENTER

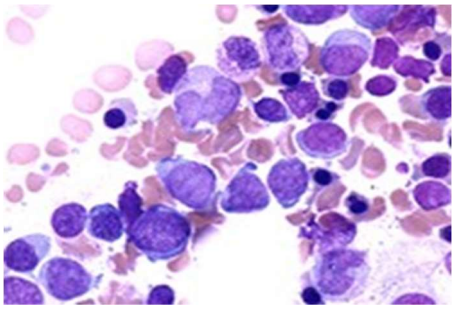
Eunice S. Wang MD
Chief, Leukemia Service

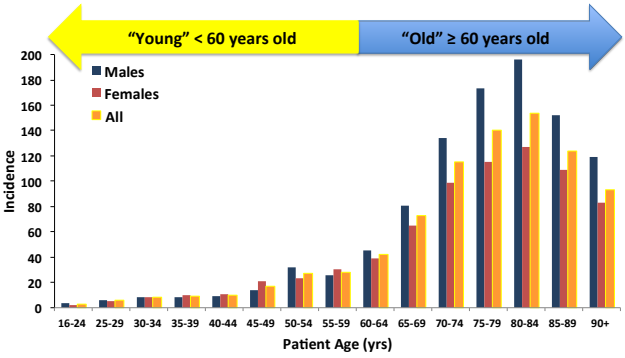
Understanding AML: 2020

- Diagnosis and Time to treatment
- Improving Venetoclax therapy
- Combination approaches
- New agents on the horizon

Acute Myeloid Leukemia: Biology

Disease of older adults (median 67-70 years)
Biologically diverse (karyotype, mutations, antigens)
Clinically aggressive disease with survival in weeks-months

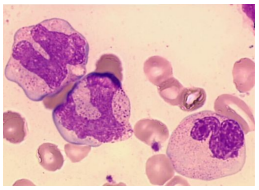




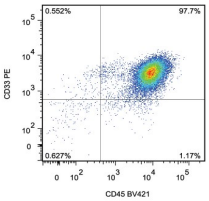
Lee et al Blood 129(2): 257, 2017.

How to diagnose AML

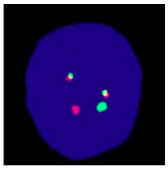
Morphology



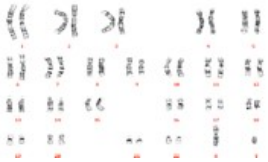
Flow Cytometry



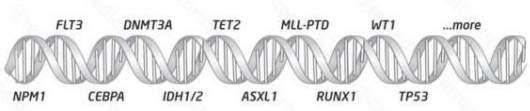
FISH



Cytogenetics

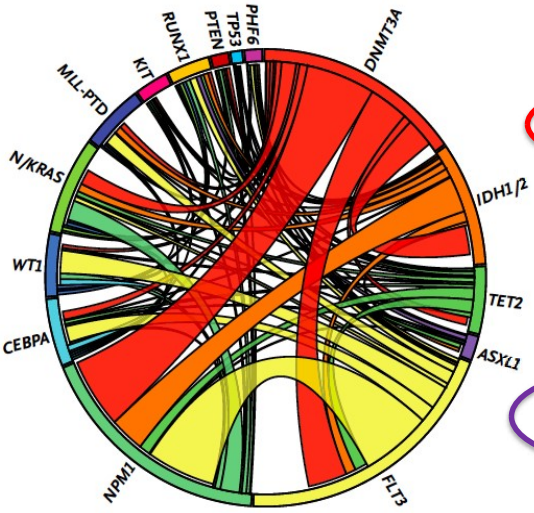


Mutation Profiling



- Risk stratification
- Drug targeting
- Disease monitoring

AML is characterized by many mutations



Gene	Overall Frequency, %
FLT3 (ITD, TKD)	37 (30,7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPA	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6

Gene	Overall Frequency, %
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0

ROSWELL PARK COMPREHENSIVE CANCER CENTER

Papaemmanuil E et al NEJM 374(23): 2209-221, 2016

7

History of AML Therapy

Cytosine Arabinoside (NSC-63878) and Daunorubicin (NSC-83142) Therapy in Acute Nonlymphocytic Leukemia [1,2,3]

Jerome W. Yates, H. James Wallace, Jr., Rose Ruth Ellison, and James F. Holland [4]

Roswell Park Memorial Institute, Buffalo, NY

US FDA approvals

All-trans retinoic acid (ATRA) FDA approved for APL

Gemtuzumab FDA approved and subsequently removed from market in 2010

1. First FLT3 inhibitor midostaurin US FDA approved
2. First IDH2 inhibitor enasidenib US FDA approved
3. Liposomal cytarabine/daunorubicin US FDA approved
4. Gemtuzumab Ozogamicin re-US FDA approved

1973 1977 1995 2000 2017 2018

1. Ivosidenib is FDA approved in 2018 for relapsed or refractory AML with a susceptible IDH1 mutation

2. AZA+VEN and LDAC+Ven approved for older AML (Nov 21 2018)

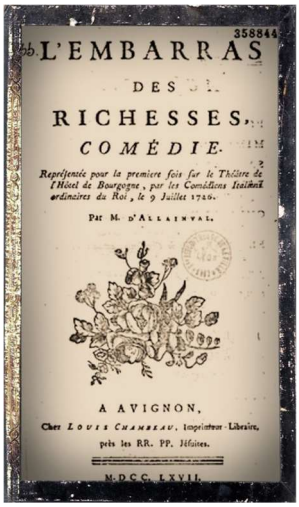
3. LDAC+glasdegib approved for older AML (Nov 21 2018)

7+3 =  **1973 to 2017 (44 years!)**

ROSWELL PARK COMPREHENSIVE CANCER CENTER

8

AML Therapy: Many new drugs



Attributed to John Ozell's translation of a French play (1738); Translated in 1725 as <u>The Plague of Riches</u>

Definition: Generally used to describe an abundance of something, (typically positive) with the idea that there are so many of these good things that it's difficult to pick just one.

8 Drugs approved for AML in last 2 years
Midostaurin, Enasidenib, CPX-351, Gemtuzumab
Ivosidenib, Gilteritinib, Glasdegib, Venetoclax

Therapy for AML patients based on mutations

Newly diagnosed AML and not fit for intensive chemotherapy and/or age ≥ 60 years

No actionable mutations

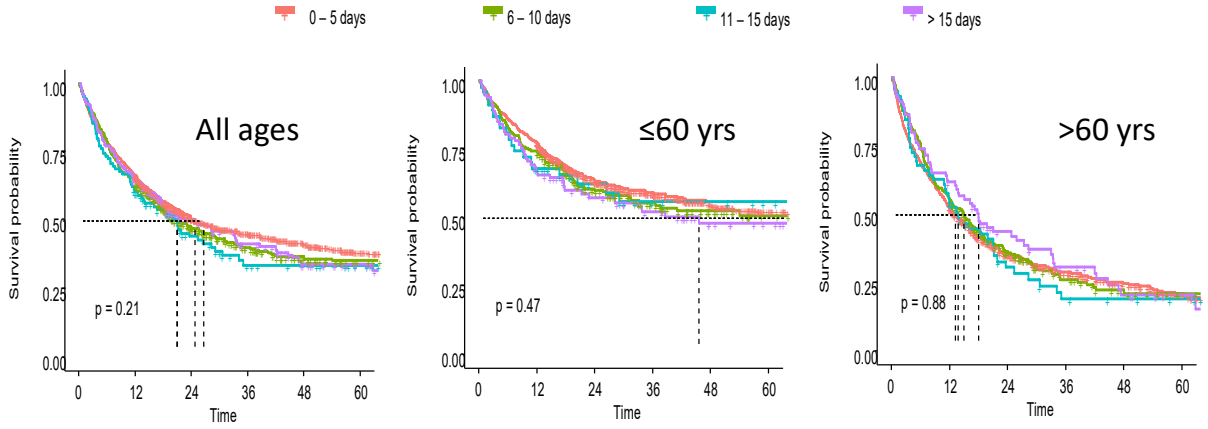
- Venetoclax + decitabine
- Venetoclax + azacitidine
- Venetoclax + LDAC
- Aza or decitabine (HMA)
- Glasdegib + LDAC
- LDAC alone
- GO (CD33+)
- Best supportive care

Actionable mutation

- Ivosidenib (IDH1 mutant)
- Enasidenib (IDH2 mutant)
- Sorafenib + HMA (FLT3 mutant)
- Aza or decitabine
- Venetoclax + HMA/LDAC

Safe to wait for genetic information to start AML therapy

2263 patients with newly dx AML from 46 centers across Germany
Time from diagnosis to intensive induction did NOT affect outcome or survival



Röllig et al ASH 2019. Abstr 13.

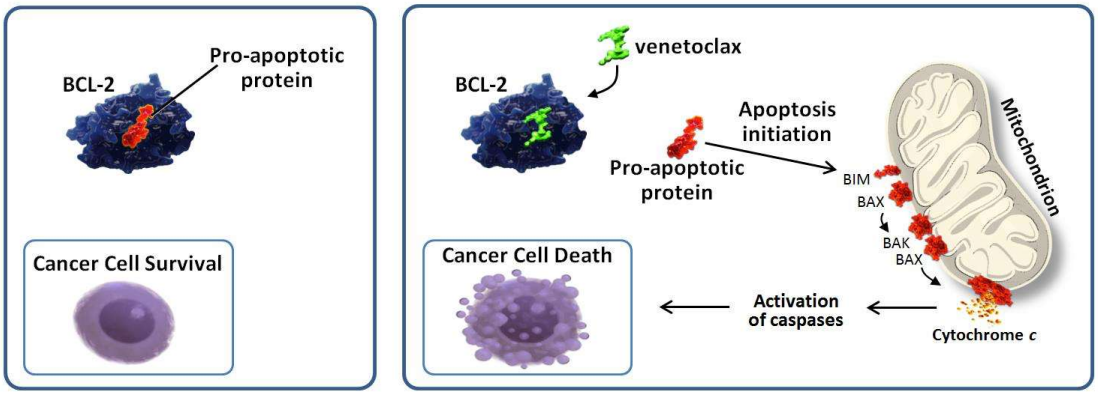
Novel combinations to improve outcomes

Backbone Chemo

Novel agents

Combinations tailored to individual patients

Venetoclax: BCL-2 inhibitor



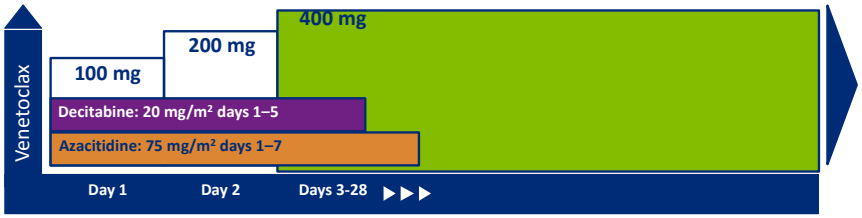
Cancer cells evade cell death through overexpression of BCL-2 which sequesters pro-apoptotic proteins

Venetoclax is a potent small molecule BCL-2 inhibitor which binds to BCL-2, "freeing" pro-apoptotic proteins which then initiate cell death

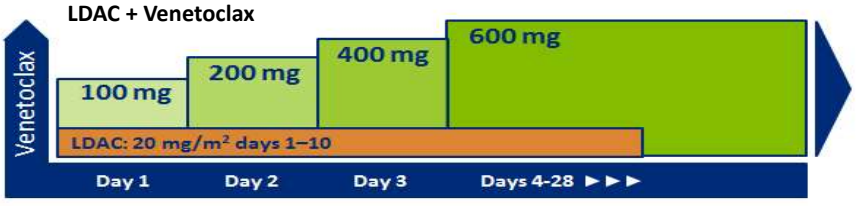
Venetoclax + Chemo for Older Patients

Indicated for:
- Newly Dx AML
- Age ≥ 75 yrs
  OR
- ECOG 2-3
- Cardiac, lung, liver or renal disease

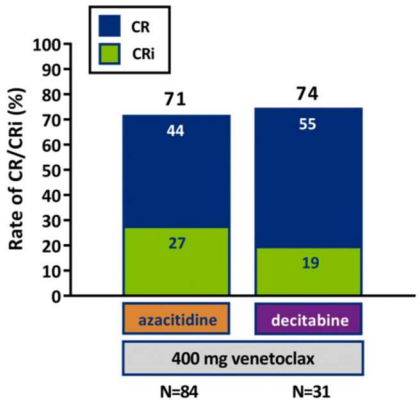
HMA + Venetoclax

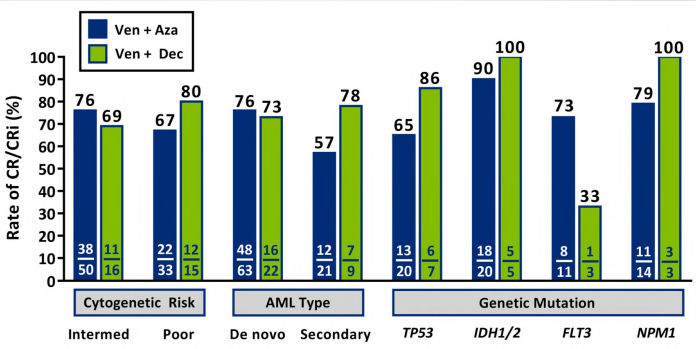


LDAC + Venetoclax



Venetoclax + Chemo: High response rate

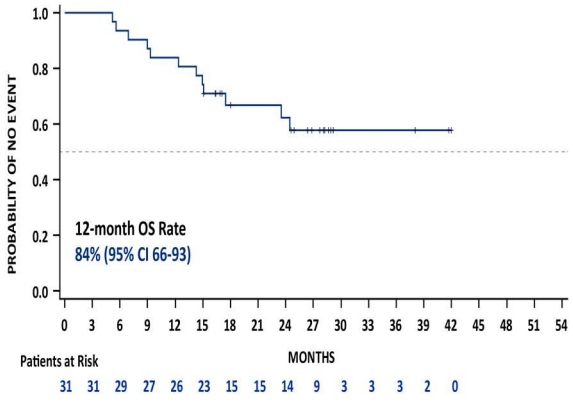




	Ven + Aza	Ven + Dec
Time to CR		
median (range)	1.2 (0.7–5.5)	1.9 (0.9–4.6)
No. of treatment cycles for these patients		
median (range)	6.0 (1–32)	6.0 (1–29)

Venetoclax-based therapy followed by transplant

- 31 of 304 patients (10%) treated with venetoclax + chemo underwent transplant
-
- **Over two thirds (68%,** 21 of 31) patients were alive 12 months after transplant
- **55%** (17/31) of all patients undergoing transplant have remission of ≥12 months after transplant
- **71%** (12/17) of those patients remained in remission for ≥ 2 years



Pratz K et al, ASH 2019

Adding Venetoclax to intensive AML chemotherapy

- Single-center, phase Ib/II trial with FLAG-IDA plus venetoclax

Adult, fit patients with AML; ECOG PS ≤ 2; AML or high-risk MDS (≥ 10% blasts); satisfactory organ function

Phase Ib: Dose escalation
Filgrastim 5 mcg/kg D1-7* + Fludarabine 30 mg/m² IV D2-6 + Idarubicin 6 mg/m² D4-6 + Cytarabine + Venetoclax† (N = 16 R/R AML)

*Or peg-filgrastim 6 mg x 1 after D5
†3-level dosing of cytarabine + venetoclax: 1) CYT 2 g/m² D2-6 /VEN 200 mg D1-21; 2) CYT 1.5 g/m² D2-6 /VEN 200 mg D1-14; 3) CYT 1.5 g/m² D2-6 /VEN 400 mg D1-14

Phase II: Dose expansion
Filgrastim 5 mcg/kg D1-7* + Fludarabine 30 mg/m² IV D2-6 + Idarubicin 6 mg/m² D4-6 + Cytarabine 1.5 g/m² IV D2-6 + Venetoclax 400 mg D1-14 (N = 14 ND, 26 R/R‡ AML)

‡Including the 16 R/R AML patients from phase I

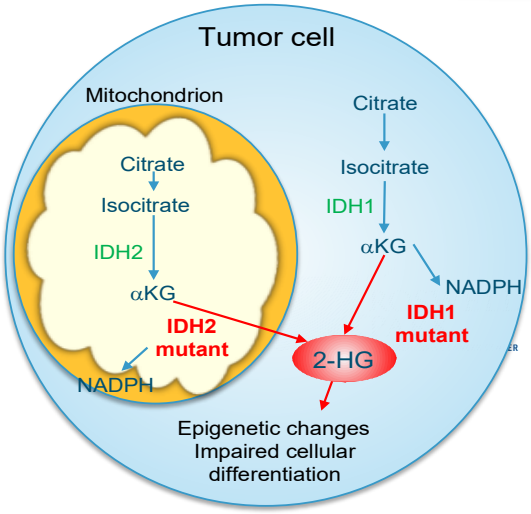
Consolidation
Filgrastim 5 mcg/kg D1-7* + Fludarabine 30 mg/m² IV D2-6 + Cytarabine 1.5 g/m² IV D2-6 + Venetoclax 400 mg D1-14

Maintenance (if no ASCT)
Venetoclax 400 mg D1-14 up to 1 year

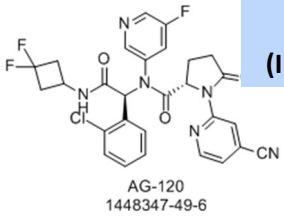
Aboudalle. ASH 2019. Abstr 176.

IDH mutations in AML

- **Isocitrate dehydrogenase (IDH)** is a critical enzyme regulating tumor metabolism
- IDH mutations promote AML development
- *IDH* mutations infrequent in AML
  - *IDH1* mut found in 6-9% of AML
  - *IDH2* mut found in 8-12% of AML

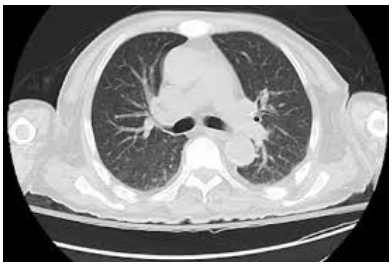


IDH1 and IDH2 inhibitors in AML



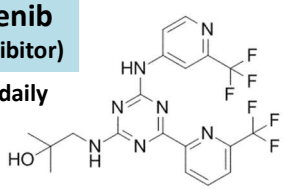
Ivosidenib
(IDH1 inhibitior)

500 mg daily



Enasidenib
(IDH2 inhibitor)

100 mg daily



Differentiation Syndrome

New onset or worsening of fever, rapid weight gain or swelling in legs, respiratory symptoms, fluid in lungs or surrounding the heart, ;ow blood pressure, kidney problems

DiNardo CD, et al. NEJM. 2018;378(25):2386-2398.; Stein EM, et al. Blood. 2017;130(6):722-731.

Enasidenib + Azacitidine for newly dx IDH2 mutant AML

- Randomized phase I/II study
  - Phase I portion consisted of 3 + 3 dose-finding for enasidenib + azacitidine

Randomized 2:1

Adult patients with mutant *IDH2* ND AML, ineligible for intensive CT and no history of treatment with hypomethylating agents (N = 101)

Enasidenib 100 mg QD **+**
Azacitidine 75 mg/m^2/day SQ x 7 days/28-day cycle
(n = 68)

Azacitidine Monotherapy
75 mg/m^2/day SQ x 7 days/28-day cycle
(n = 33)

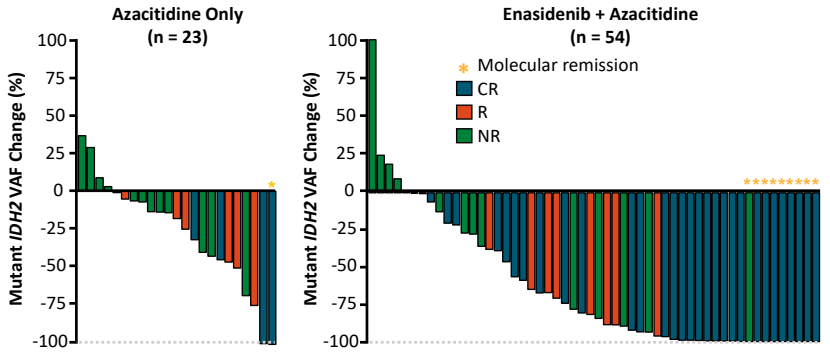
- Results: Higher response rates with combination therapy
- Safety: Combination therapy was tolerated well by patients

DiNardo. ASH 2019. Abstr 643

Enasidenib + Azacytidine for newly dx IDH2 mutant AML

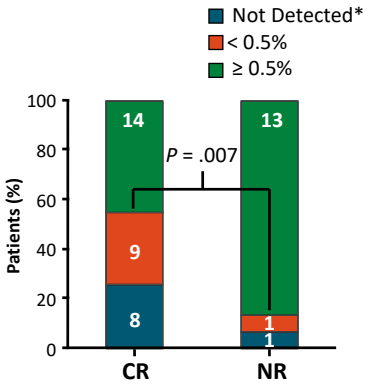
- Enasidenib + azacitidine showed significantly greater reduction in maximal mutant *IDH2* VAF suppression from baseline vs azacitidine alone: median reductions -83.4% vs -17.7%, respectively (*P* = .0008)

Enasidenib + Azacitidine vs Azacitidine Monotherapy
Maximum Mutant *IDH2* VAF Reductions From Baseline



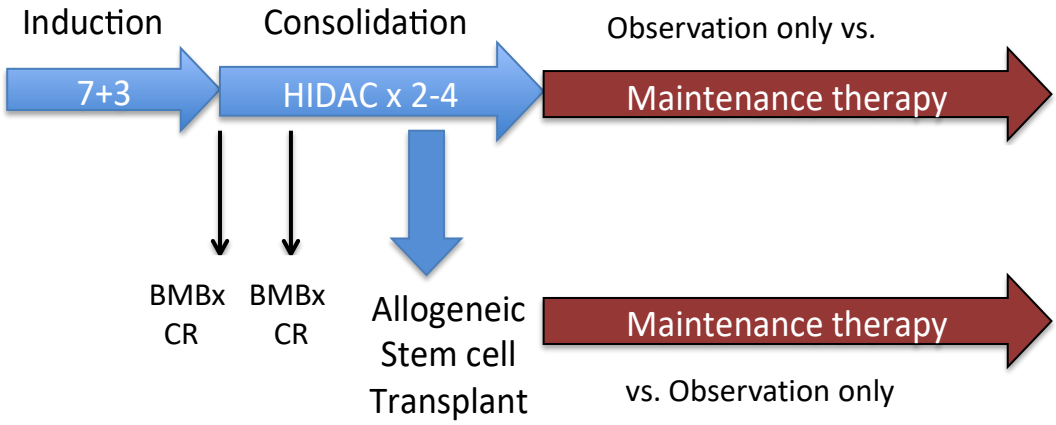
*Mutant *IDH2* VAF below the limit of detection (0.02% to 0.04%)
Data cutoff: August 19, 2019.
Mutant *IDH2* VAF in bone marrow mononuclear cells were assessed by digital PCR.

ENA + AZA:
Mutant *IDH2* VAF Clearance

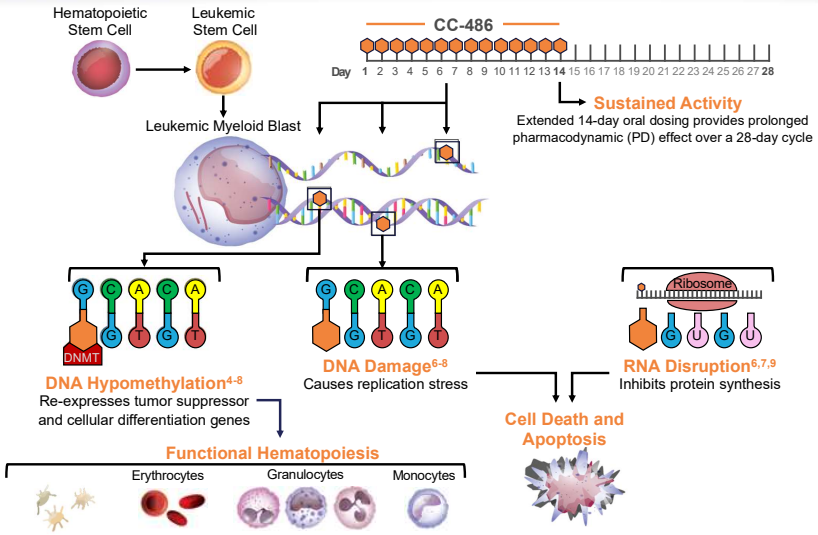


DiNardo. ASH 2019. Abstr 643

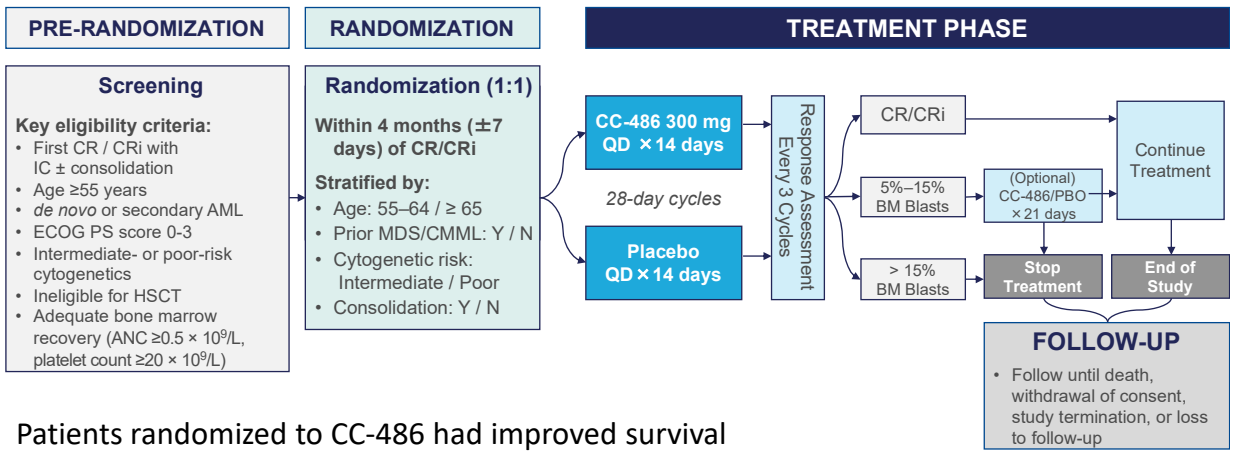
Maintenance therapy for AML



Oral azacitidine: First drug for AML maintenance?



Oral azacitidine (CC-486): First drug for AML maintenance?



Patients randomized to CC-486 had improved survival

Low dose Decitabine can also be used as maintenance

Stratified by: age ≥ 70 yrs, unfavorable cytogenetics, induction therapy

AML patients ≥ 60 yrs of age with BM biopsy-confirmed CR/CRi after consolidation therapy* (N = 120)

Decitabine 20 mg/m^2 on Days 1-3 Q4W for 1 yr (n = 59)

Observation (n = 61)

Follow-up:

- ***CBC Q1M for 1 yr, then Q3M***
- ***BM biopsy Q3M for 2 yrs after randomization***

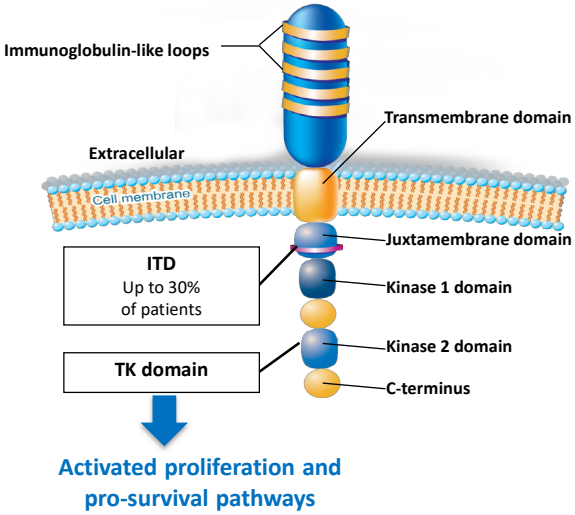
*Cytarabine after 7+3 induction, or clofarabine after clofarabine induction.

- Primary endpoint: disease-free survival (relapse or death from any cause)
- Trend to improved survival in FLT3 negative AML patients receiving decitabine

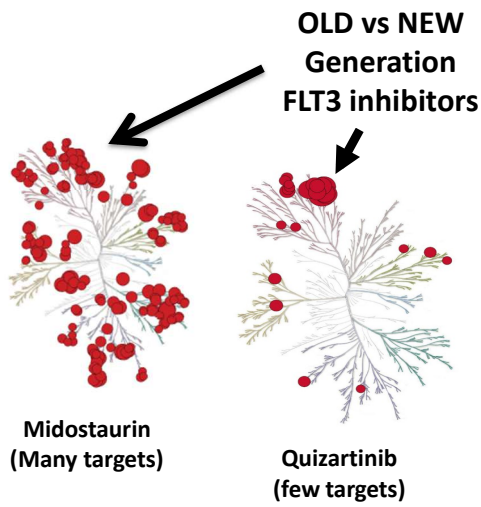
Foran. ASH 2019. Abstr 115.

FLT3 mutations in AML

- *FLT3-ITD* occurs in ~25-37% of AML
- *FLT3-TKD* occurs in ~10% of AML
- More frequent in younger patients, *de novo* AML and diploid cytogenetics
- Associated with resistance to 7+3
- Increased risk of relapse
- Many FLT3 inhibitors developed



FLT3 inhibitors for AML

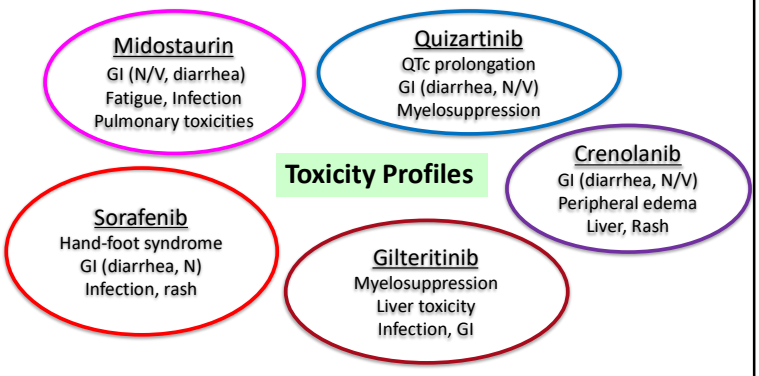


	Targets	FLT3 inhibitory dose
Lestaurtinib	FLT3, JAK2, TrkA	700 nM
Midostaurin*	FLT3, KIT, PKC, PDGFR, VEGFR	1000 nM
Sorafenib*	FLT3, KIT, PDGFR, RAF, VEGFR	265 nM
Quizartinib	FLT3, KIT, PDGFR, RET	18 nM
Crenolanib	FLT3, PDGFR	48 nM
Gilteritinib*	FLT3, AXL	43 nM

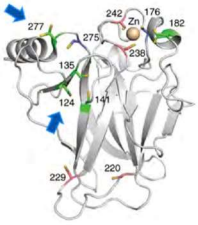
**FDA approved drugs*

Best FLT3 inhibitor is context dependent

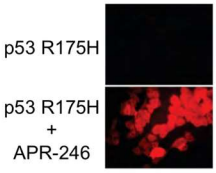
Clinical setting	Standard of care
Newly diagnosed FLT3^{mut}	Midostaurin plus 7+3
Older newly diagnosed FLT3^{mut}	Sorafenib plus Azacitidine
FLT3^{mut} after transplant	Sorafenib
Relapsed FLT3^{mut}	Gilteritinib



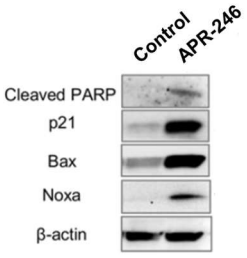
APR-246: New drug for p53 mutant AML



APR-246 binds covalently to p53…

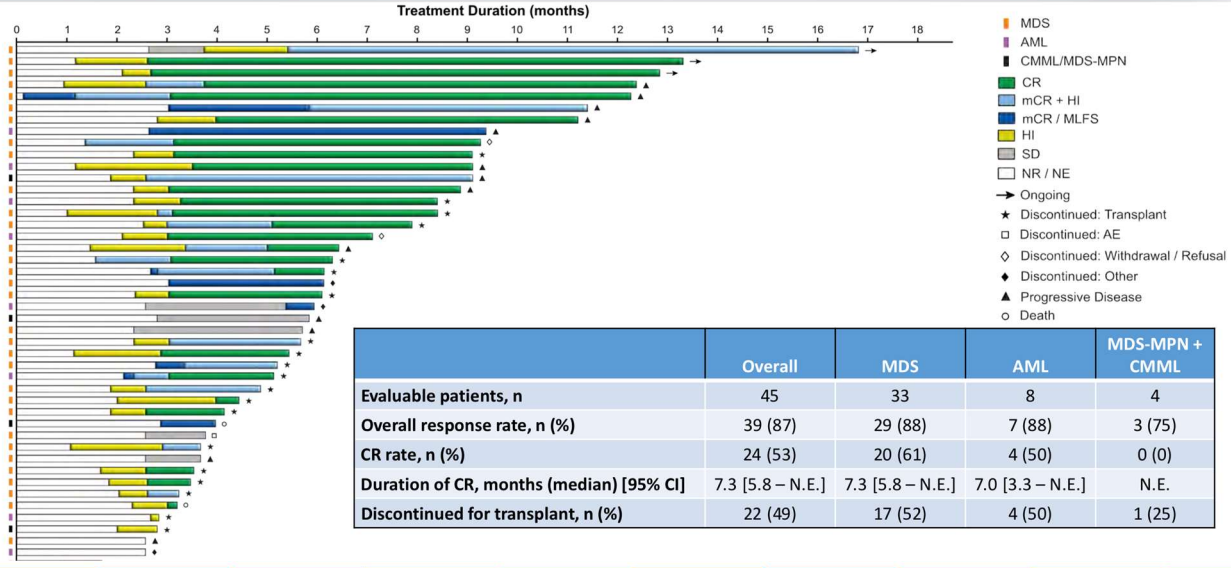


…restores wt p53 conformation & activity…



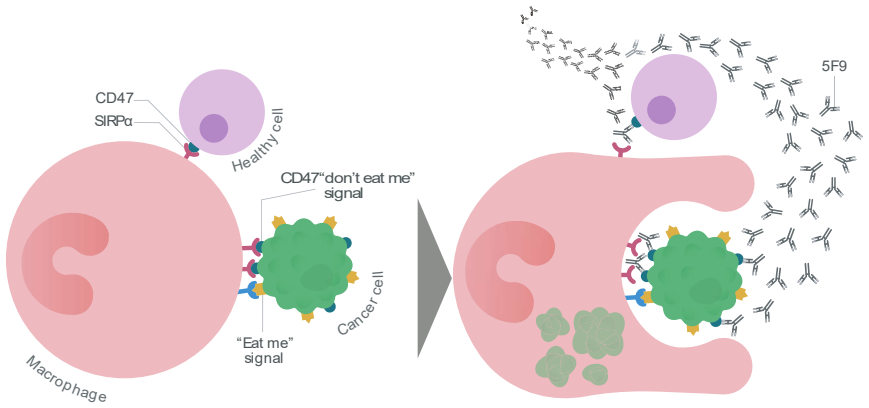
…and triggers cell cycle arrest and apoptosis

APR-246: New drug for p53 mutant AML

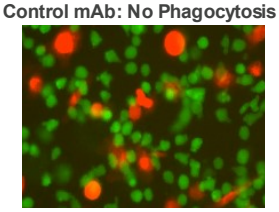


	Overall	MDS	AML	MDS-MPN + CMML
Evaluable patients, n	45	33	8	4
Overall response rate, n (%)	39 (87)	29 (88)	7 (88)	3 (75)
CR rate, n (%)	24 (53)	20 (61)	4 (50)	0 (0)
Duration of CR, months (median) [95% CI]	7.3 [5.8 – N.E.]	7.3 [5.8 – N.E.]	7.0 [3.3 – N.E.]	N.E.
Discontinued for transplant, n (%)	22 (49)	17 (52)	4 (50)	1 (25)

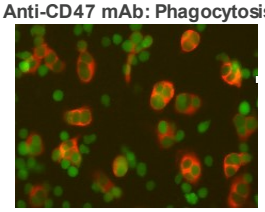
Anti-CD47: Telling immune cells to "eat" AML cells



Control mAb: No Phagocytosis



Anti-CD47 mAb: Phagocytosis



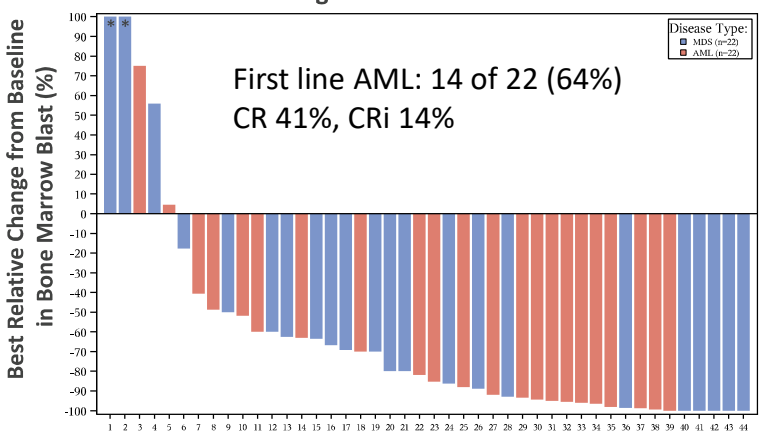
Macrophages Cancer cells

Anti-CD47: Telling immune cells to "eat" AML cells

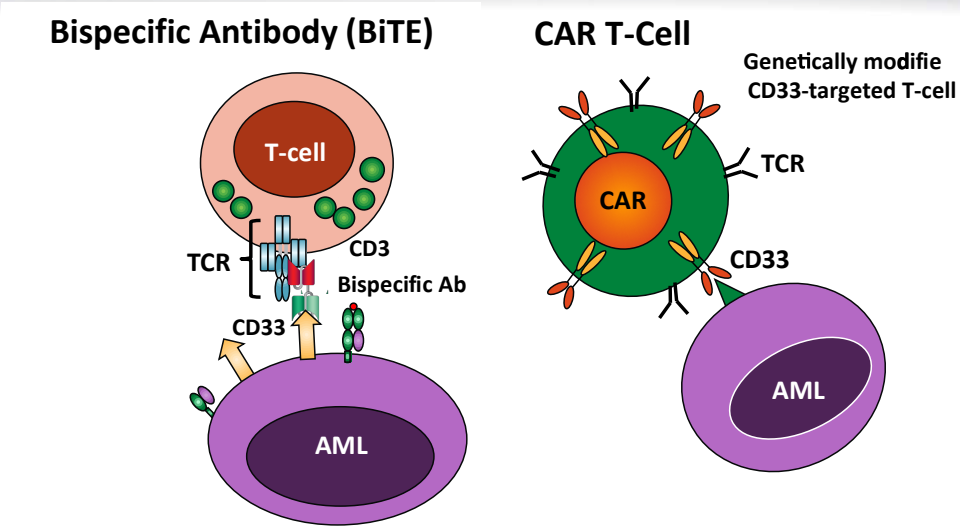
Magrolimab is a an anti-CD47 antibody

- Targets CD47 on AML cells
- Induces macrophage cells to "eat" AML cells
- Eliminates leukemic stem cells in AML models
- Azaciditine induces CD47 expression on AML blasts and increases efficacy of magrolimab

Magrolimab+AZA



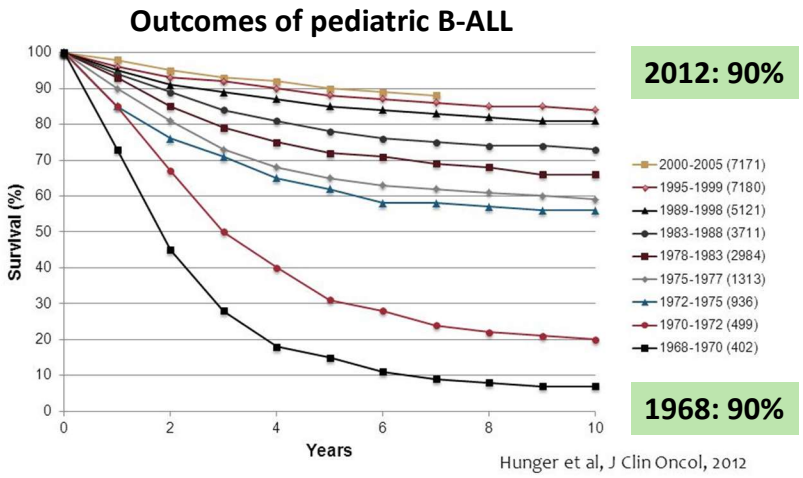
Immunotherapy for AML



Understanding AML: 2020

- Diagnosis and Time to treatment
- Improving Venetoclax therapy
- Combination approaches
- New agents on the horizon

Example of pediatric ALL



2012: 90%

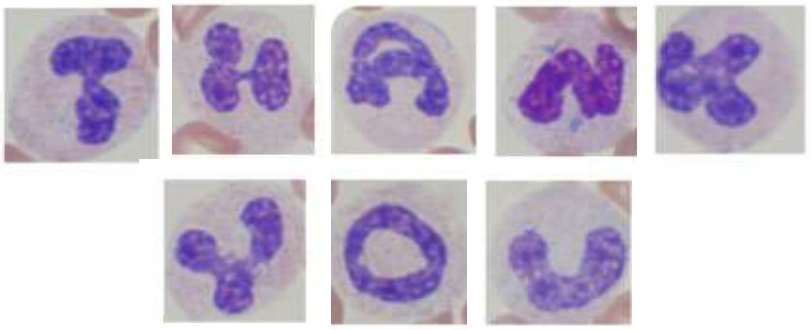
1968: 90%

Hunger et al, J Clin Oncol, 2012

Current survival rate for childhood ALL = >90%

To cure AML, we need to:

- Introduce new drugs
- Design combo Rx
- Conduct clinical trials



Q&A SESSION

Understanding Your Diagnosis: Acute Myeloid Leukemia (AML)

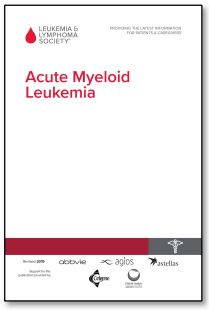
- **Ask a question by phone:**
  - Press star (*) then the number 1 on your keypad.
- **Ask a question by web:**
  - Click “Ask a question”
  - Type your question
  - Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.

LLS EDUCATION & SUPPORT RESOURCES

- **Information Specialists**

  Master’s level oncology professionals, available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.
  - **EMAIL:** infocenter@LLS.org
  - **TOLL-FREE PHONE:** 1-800-955-4572
- **Free Education Booklets:**
  - www.LLS.org/booklets
- **Free Telephone/Web Programs:**
  - www.LLS.org/programs
- **Live, weekly Online Chats:**
  - www.LLS.org/chat



LLS EDUCATION & SUPPORT RESOURCES

- **LLS Podcast, *The Bloodline with LLS***

  Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: www.thebloodline.org

- **Education Videos**

  Free education videos about survivorship, treatment, disease updates and other topics: www.LLS.org/educationvideos

- **Patti Robinson Kaufmann First Connection Program**

  Peer-to-peer program that matches newly diagnosed patients and their families: www.LLS.org/firstconnection

- **Free Nutrition Consults**

  Telephone and email consultations with a Registered Dietitian: www.LLS.org/nutrition

- **What to Ask**

  Questions to ask your treatment team: www.LLS.org/whattoask

- **Other Support Resources**

  LLS Community, discussion boards, blogs, support groups, financial assistance and more: www.LLS.org/support

BEATING CANCER IS IN OUR BLOOD.

LEUKEMIA & LYMPHOMA SOCIETY®

39

THANK YOU

We have one goal: A world without blood cancers

LEUKEMIA & LYMPHOMA SOCIETY®

40