

# EMERGING OPTIONS FOR CANCER TREATMENT (PART 2)

*Presented by:*

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# Evolving Therapies for Acute Myeloid Leukemia Stem Cell Part 2

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St. Joseph's

8/20/2020



# About Me...



[https://www.nola.com/living/2017/10/new\\_orleans\\_nicknames\\_the\\_good.html](https://www.nola.com/living/2017/10/new_orleans_nicknames_the_good.html);

<https://tulanehealthcare.com/>



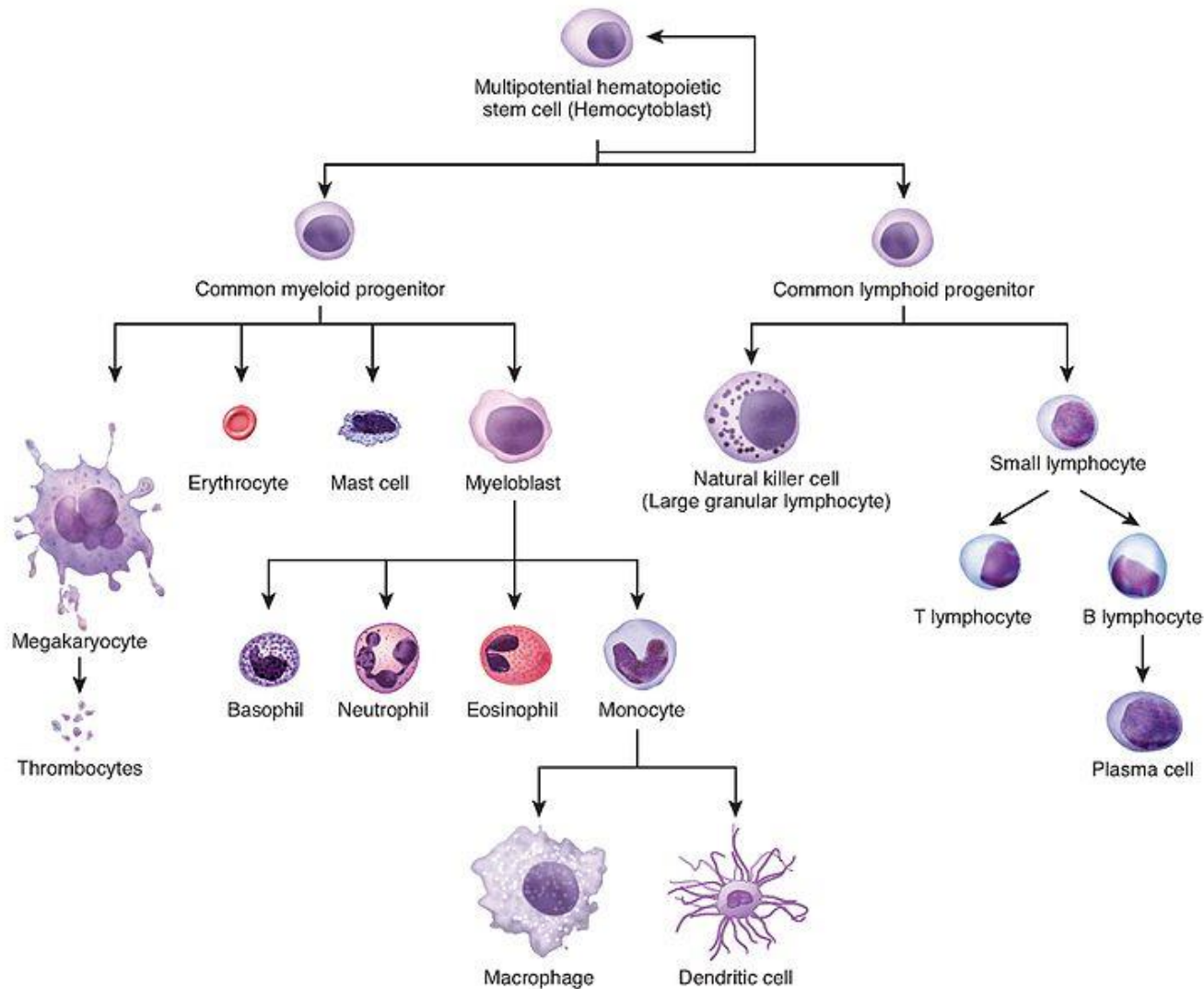
<https://www.bannerhealth.com/locations/tucson/university-of-arizona-cancer-center-tucson-Campbell;>

<https://www.modernhealthcare.com/article/20150226/NEWS/150229916/banner-uahn-merger-in-arizona-signals-future-of-academic-medical-centers>

# Overview

- Definition of Acute Myeloid Leukemia (AML)
- Clinical Presentation
- Diagnostic Criteria
- Classification
- Treatment
- Targeted Therapies
- AML in the Elderly

# What is AML?



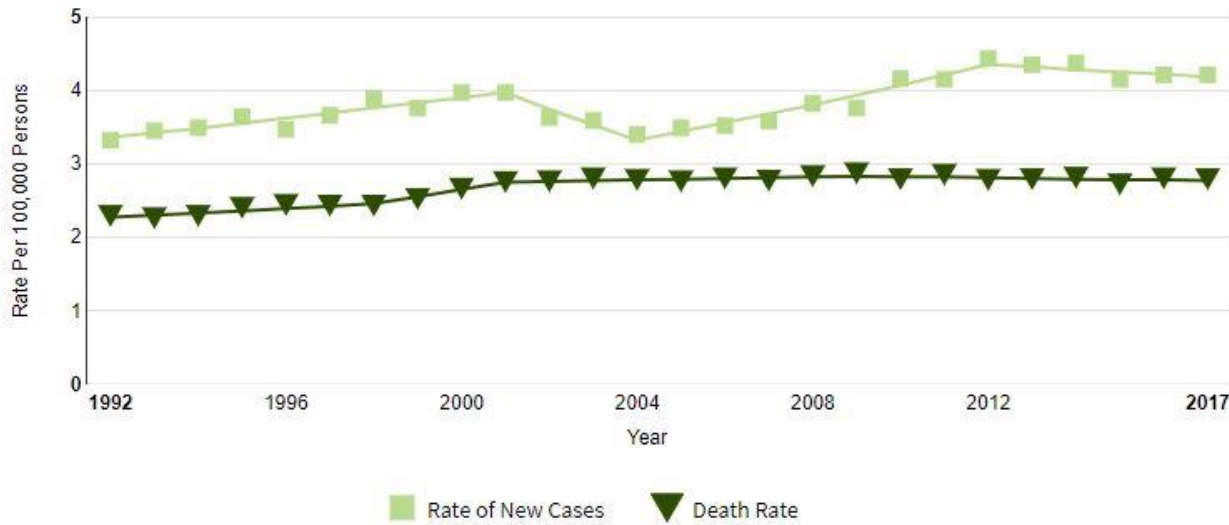
# Incidence

## At a Glance

Estimated New Cases in 2020	19,940
% of All New Cancer Cases	1.1%

Estimated Deaths in 2020	11,180
% of All Cancer Deaths	1.8%

<b>5-Year Relative Survival</b>
<b>28.7%</b>
2010-2016





# AML, Age-Adjusted SEER Incidence Rates, 2012-2016

Age at Diagnosis	All Races		
	Both Sexes	Males	Females
All ages	4.3	5.2	3.5
Under 65	2.0	2.1	1.9
65 and over	20.1	26.9	15.2
All ages (WHO world std) <sup>b</sup>	3.2	3.8	2.8

# Risk Factors

- Idiopathic
- Chemicals
- Irradiation
- Chemotherapy – history of use of alkylators (i.e. cyclophosphamide, melphalan) or topoisomerase II inhibitors (i.e. anthracyclines, etoposide)
- Immunosuppression
- Pre-existing hematological diseases

# Clinical Presentation

- Low blood cell counts without symptoms
- Bleeding or clotting
- Type “B” symptoms: Unexplained fevers, appetite changes, fatigue, etc.
- Enlarged dental gums
- Skin changes

- Enlarged dental gums



<https://ipj.quintessenz.de/ipj/content/2006-02/poster311/abb1.jpg>

- Skin Changes

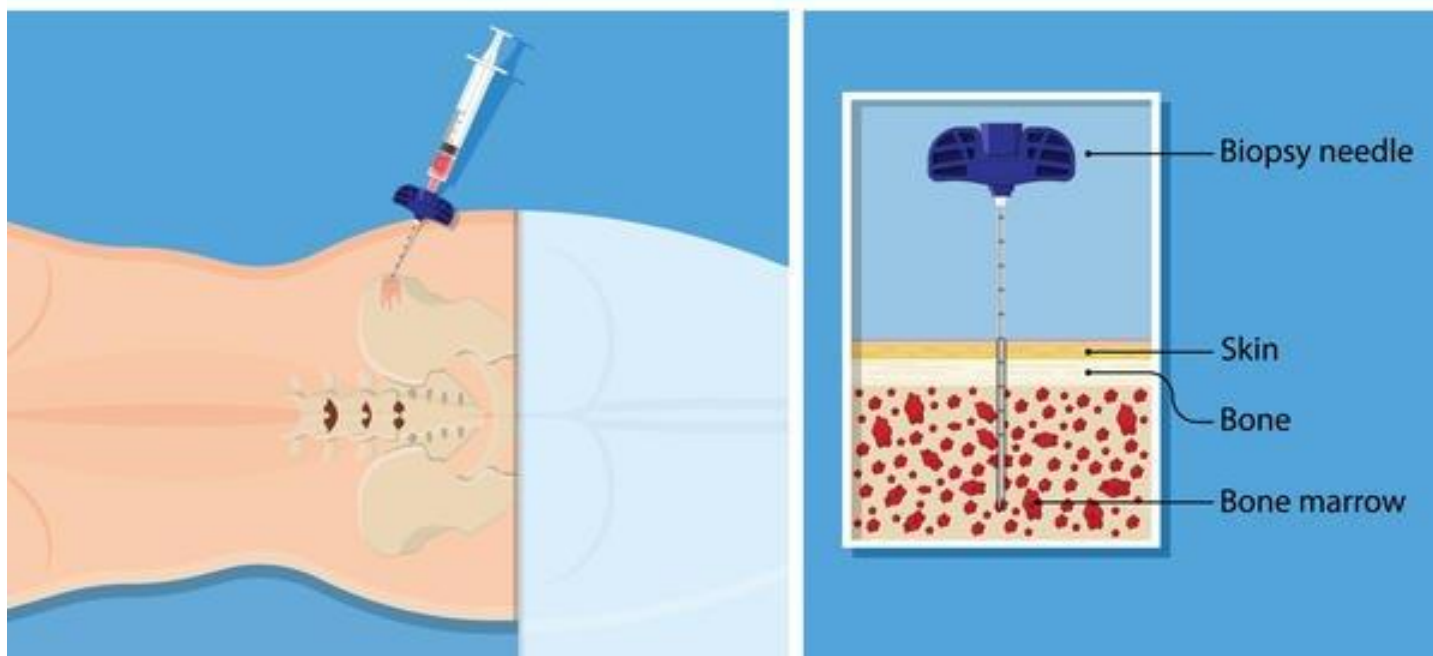


<http://medicalpicturesinfo.com/wp-content/uploads/2011/09/Leukemia-cutis-2.jpg>

# Diagnostic Tests for Acute Myeloid Leukemia


- Various blood tests including blood count and genetic and molecular testing of the leukemia
- Bone marrow biopsy

# Bone Marrow Aspiration and Biopsy



<https://www.oncolink.org/cancer-treatment/procedures-diagnostic-tests/biopsy-procedures/bone-marrow-aspiration-and-biopsy>

# WHO 2016 Classification of AML: AML and Related Neoplasms

- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- AML, NOS
- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic/monocytic leukemia
- Pure erythroid leukemia
- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
- Transient abnormal myelopoiesis
- Blastic plasmacytoid dendritic cell neoplasia 

Roboz G, MD Anderson Board Review 2017



# WHO 2016 Classification of AML: AML with recurrent genetic abnormalities

- t(8;21)(q22;q22.1); RUNX1-RUNX1T1
- inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
- Acute promyelocytic leukemia with PML-RARA
- t(9;11)(p21.3;q23.3); MLLT3-KMT2A
- t(6;9)(p23;q34.1); DEK-NUP214
- inv(3)(q21.3q26.2) or (3;3)(q21.3;q26.2); GATA2,MECOM(EVI1)
- AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); RBM15-MKL1
- AML with biallelic mutations of CEBP
- Provisional entity: AML with BCR-ABL1
- Provisional entity: AML with mutated RUNX1

Roboz G, MD Anderson Board Review 2017

## FAB classification of acute myeloblastic leukaemia

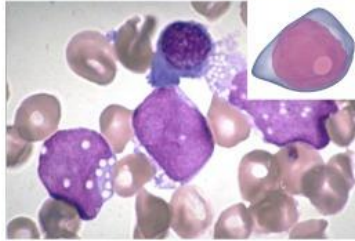


Photo courtesy of: Acute myeloid leukemia pathophysiology, 2012

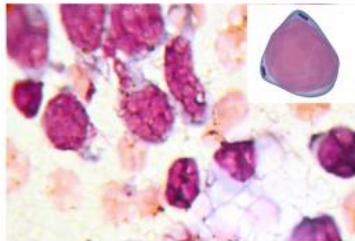
### M0 Acute myeloblastic leukaemia with minimal differentiation

#### Morphology:

Can resemble LLA-L2 blasts. Medium-sized blasts, rounded nucleus, fine chromatin, basophilic non-granular cytoplasm, prominent nucleoli.

#### Immunophenotype

- CD13 +
- CD33 +
- CD11b +
- CD11c +
- CD14 +
- CD15 +



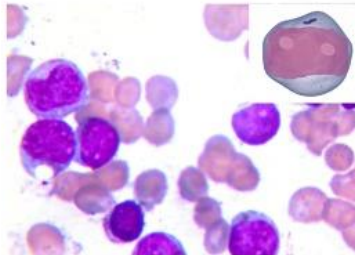
### M1 Acute myeloblastic leukaemia without maturation

#### Morphology:

Medium-sized blasts with high nucleocytoplasmic (n:c) ratio, rounded nuclei with immature, dispersed chromatin with one or more prominent nucleoli. Blasts can show fine azurophilic granulation or isolated Auer rods in the cytoplasm in 5% to 10% of cases

#### Immunophenotype

- MPO +
- CD13 +
- CD33 +
- CD117+
- CD34 +/-



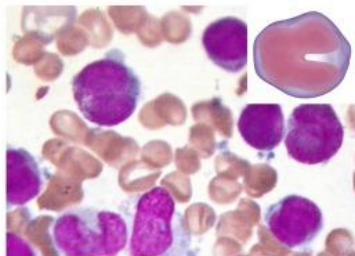
### M2 Acute myeloblastic leukaemia with maturation

#### Morphology:

Small to medium-sized blasts with high nucleocytoplasmic (n:c) ratio and rounded nuclei sometimes located in a corner of the cytoplasm. The nucleus shows dispersed, immature chromatin with one or more nucleoli. The cytoplasm is basophilic and can contain traces of primary azurophilic granulation or isolated Auer rods.

#### Immunophenotype

- MPO +
- CD34 +/-
- CD13 +
- CD15 +
- HLA-DR +/-
- Sudan black +
- CD117 +/-



### M3 Promyelocytic leukaemia

#### Morphology:

Abundant, intensely azurophilic granulation. The nucleus is usually monocytic in appearance (reniform) and is either irregular or bilobed with a deep cleft. Scarcely basophilic cytoplasm due to the proliferation of azurophilic granulation. Some atypical promyelocytes also contain elongated or splinter-shaped crystalline cytoplasmic inclusions specific to this type of leukaemia. These usually form clumps, but differ from Auer rods in that they show a tubular substructure on electronic microscopy.

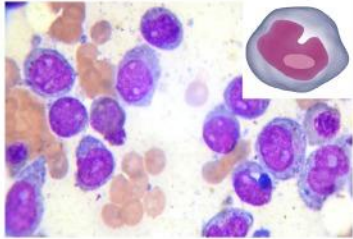
#### Immunophenotype

- CD13 +
- CD33 +
- HLA-DR -
- CD34 -

Ladines-Castro W, et al. Revista Medica del Hospital General de Mexico 2016

FAB classification of acute myeloblastic leukaemia

**M4** Acute myelomonocytic leukaemia

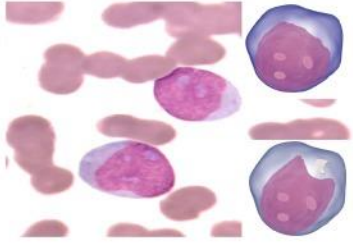


**Morphology:**  
Large blasts, moderate nucleocytoplasmic (n:c) ratio and variable basophilia. The nucleus may be rounded, kidney-shaped or irregular. Nucleoli are usually prominent.

**Immunophenotype**

- CD13 +
- CD15 +
- CD33 +
- CD11b +
- CD11c +
- CD14 +
- CD64 +
- CD4 +

**M5** Acute monocytic leukaemia



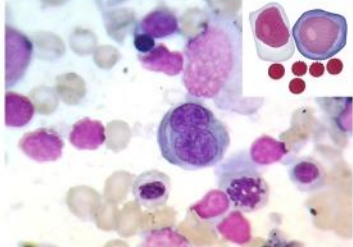
**M5a acute monoblastic leukaemia:**  
Large blasts with rounded nucleus and dispersed, immature chromatin (1-3 nucleoli) and moderately large and intensely basophilic cytoplasm. The cytoplasm may show some Auer rods and/or prolongations and granulations.

**M5b acute monocytic leukaemia**  
Promonocytes have a rounded or kidney-shaped nucleus with a less basophilic cytoplasm that is more highly granulated than monoblasts and contains some vacuoles. A finding of erythrophagocytosis together with monocytic blasts suggests a t(8;16) translocation.

**Immunophenotype**

- CD14 +
- CD68 +
- CD4 +
- CD11c +
- HLA-DR +
- CD64 +

**M6** Acute erythroid leukaemia



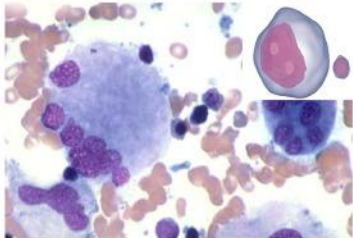
**M6a erythroid leukaemia with proliferation of mixed blasts:**  
Over 50% erythroid precursors and around 30% myeloblasts. Morphology of erythrocytes in peripheral blood is greatly changed, with schistocytes, "pincer" or mushroom-shaped cells, and spiculated echinocyte and acanthocyte cells.

**M6b pure erythroid leukaemia:**  
Erythroids make up 80% of bone marrow cells, with less than 3% myeloid cells. Erythrocytes in peripheral blood consist of macrocytes, basophilic stippling, Howell-Jolly bodies or Cabot rings.

**Immunophenotype**

- CD13 +
- CD33 +
- CD15 +
- Glycophorin A +
- Glycophorin C +

**M7** Acute megakaryocytic leukaemia



**Morphology:**  
Highly immature, polymorphic blasts. The nucleus is eccentric with dispersed, reticulated chromatin and 1-3 prominent nucleoli. The cytoplasm is non-granular, basophilic, and very similar in appearance to platelets, with pseudopods or granulations. Micromegakaryocytes and fragments of megakaryoblasts are seen in peripheral blood (giant platelets, some highly degranulated).

**Immunophenotype**

- CD41 +
- CD61 +
- CD42 +
- CD13 +
- CD33 +
- CD34 +

Ladines-Castro W, et al. Revista Medica del Hospital General de Mexico 2016

# Major Prognostic Factors

- Leukemia genetics and molecular findings
- Patient age
- Organ involvement of Leukemia
- Associated other blood diseases
- Very high blood cell counts
- Prior chemotherapy

# Treatment

- Induction chemotherapy
- Consolidation chemotherapy
- Allogeneic stem cell transplant (with some exceptions)

# Induction Chemotherapy

- “7+3”: 7 days of cytarabine + 3 days of Daunorubicin
- Additional targeted therapy based on prior molecular testing is added if found

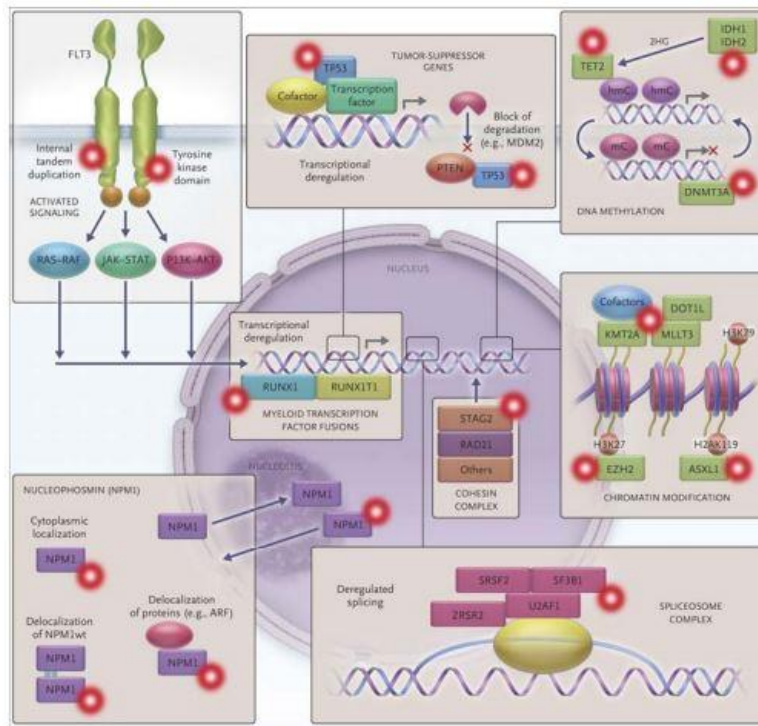
# Consolidation Chemotherapy

- Consolidation chemotherapy is given once a leukemia patient is proven to be in remission on bone marrow biopsy after completing induction chemotherapy
- Helps extend patient's survival
- Most patients will proceed to undergo an allogeneic stem cell transplantation

# Targeted Therapies

## Pathogenesis and Biology of AML

Eight functional categories of genes commonly mutated in AML



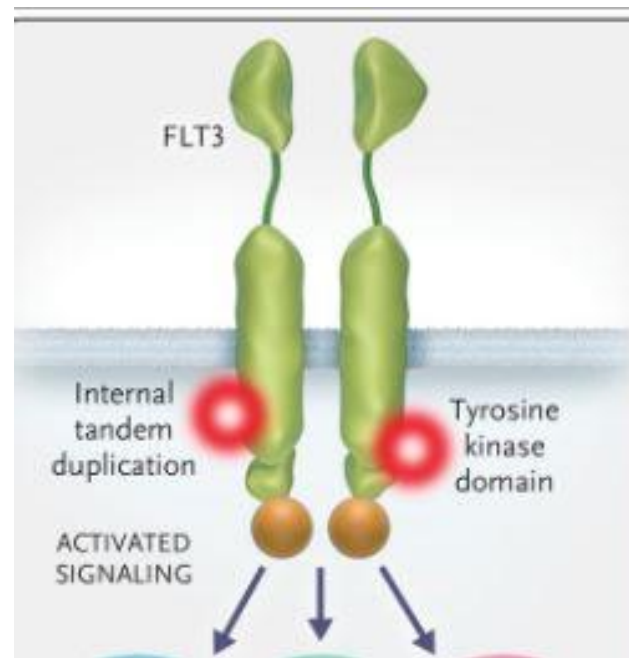
1. Activated signaling
2. Tumor suppressor
3. DNA methylation
4. Transcriptional deregulation
5. Cohesin complex
6. Chromatin modification
7. Nucleophosmin
8. Deregulated splicing

Döhner H et al. N Engl J Med 2015;373:1136-1152.



## FLT3 inhibitors

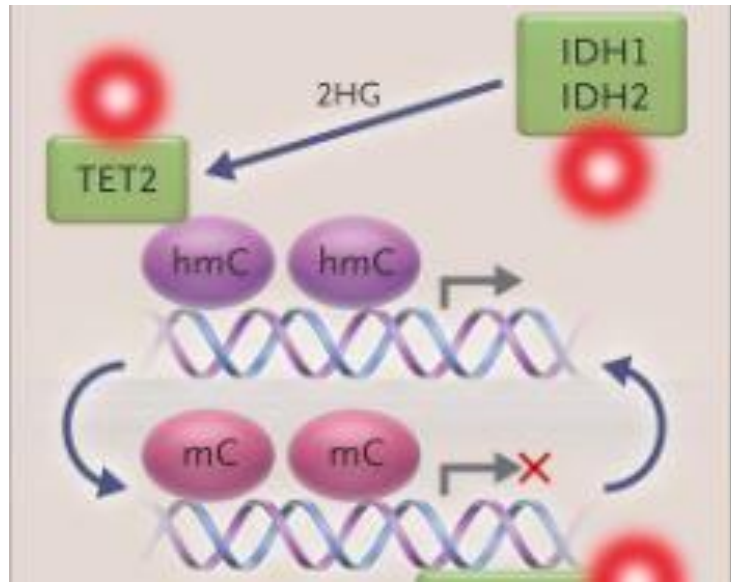
- Midostaurin – FDA approved in frontline treatment
- Gilteritinib – FDA approved in relapsed treatment



Dohner H et al. N Engl J Med 2015; 373:1136-1152

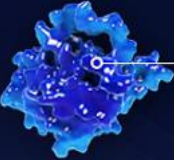
# IDH1, IDH2 inhibitors

- Enasidenib – IDH2 inhibitor
- Ivosidenib – IDH1 inhibitor



Dohner H et al. N Engl J Med 2015; 373:1136-1152


# Venetoclax



**Anti-apoptotic proteins**

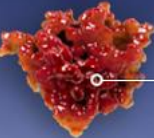
**BCL-2**  
Other members include BCL-X<sub>L</sub>, BCL-W, MCL-1, BCL-B

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**Pro-apoptotic proteins**

**BH3-only activators**  
BID, BIM  
Other members include BAD, NOXA, PUMA



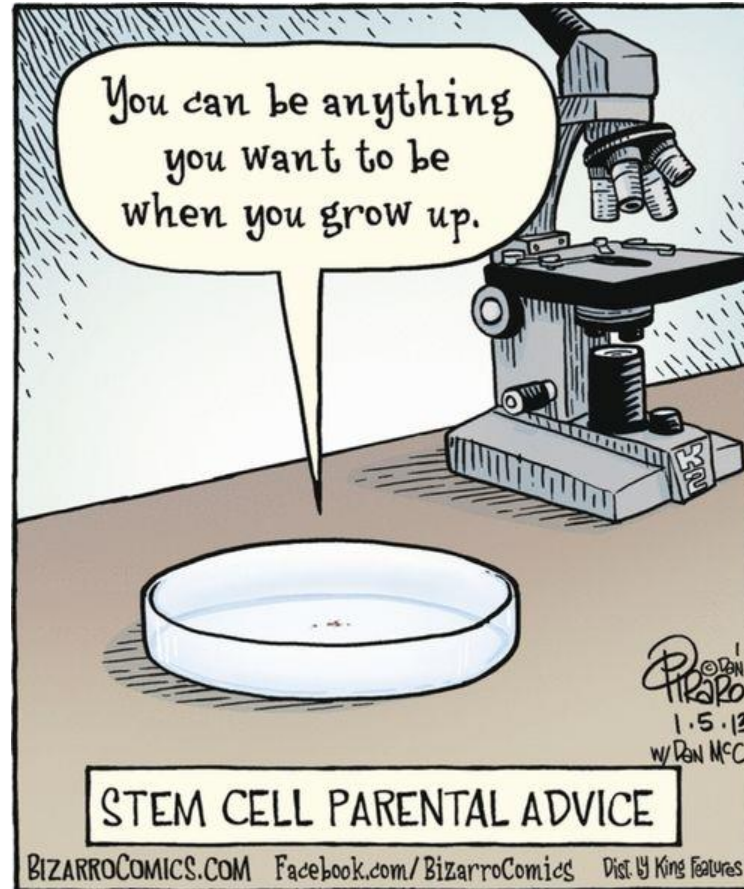
**Multi-domain effectors**  
BAX, BAK, BOK

<https://www.biooncology.com/pathways/cancer-tumor-targets/bcl-2/bcl-2-family-proteins.html>

# AML in the elderly

Age at Diagnosis	All Races		
	Both Sexes	Males	Females
<1	1.6	1.6	1.6
1-4	1.0	1.0	1.0
5-9	0.4	0.4	0.4
10-14	0.7	0.8	0.6
15-19	0.9	0.9	0.9
20-24	1.1	1.0	1.2
25-29	1.2	1.1	1.2
30-34	1.4	1.5	1.4
35-39	1.6	1.6	1.6
40-44	2.1	2.2	2.1
45-49	2.5	2.5	2.5
50-54	3.5	3.8	3.2
55-59	4.9	5.6	4.3
60-64	7.8	9.1	6.7
65-69	12.1	15.2	9.4
70-74	18.3	23.6	13.9
75-79	23.3	31.0	17.4
80-84	28.6	39.3	21.2

# Questions?



The Multidisciplinary Cancer Program with  
60+ cancer experts at Dignity Health  
*Everyone and Everything You Need In One Place*  
**Hematology Oncologists**



**Murali Kodali, MD**  
Hematologic Oncology



**Soyoung Park, MD**  
Malignant Hematologic Oncology

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**Karen Dirrigl, MS**  
Genetic Counselor



**Kimberly Brussow, MS, CGC**  
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**Kerry Tobias, DO**  
Supportive Care and  
Survivorship

**Radiation Oncology**



**Nitika Thawani, MD**  
Radiation Oncology

**Medical Oncology**



**Mital Patel, MD**  
Gastrointestinal  
Oncology

# Thank You!

For more information about cancer prevention, treatment, screening, or to request a speaker for your worksite on any cancer-related topic, **call:**  
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**PLEASE ENTER YOUR  
QUESTIONS IN THE CHAT.**





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