Strategies for Treating AML

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New York, NY

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Welcome and Introductions

Strategies for Treating AML

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers

someday is today®

Eytan M. Stein, MD has disclosed he is a member of the Advisory Boards for Agios Pharmaceuticals, Celgene, and Seattle Genetics.

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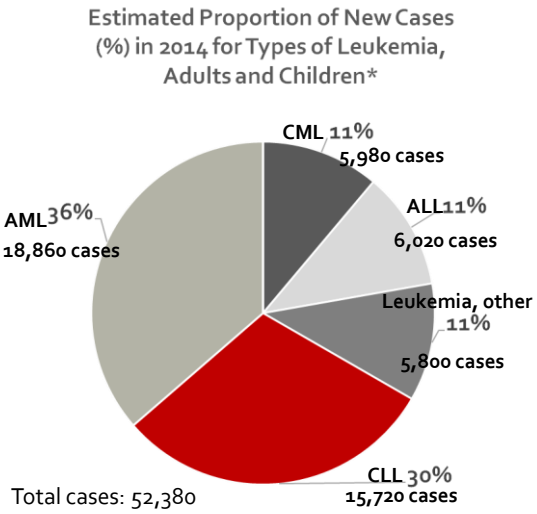
1884

Acute Myeloid Leukemia

Eytan M. Stein, MD
Assistant Attending Physician
Leukemia Service
Memorial Sloan Kettering Cancer Center

Leukemia – United States



- Acute Myeloid Leukemia
  - Projected incidence of 18,860 cases in the United States in 2014
  - Approximately 10,500 patients will succumb to their disease

*Total is less than 100% due to rounding in the calculation of individual percentages.

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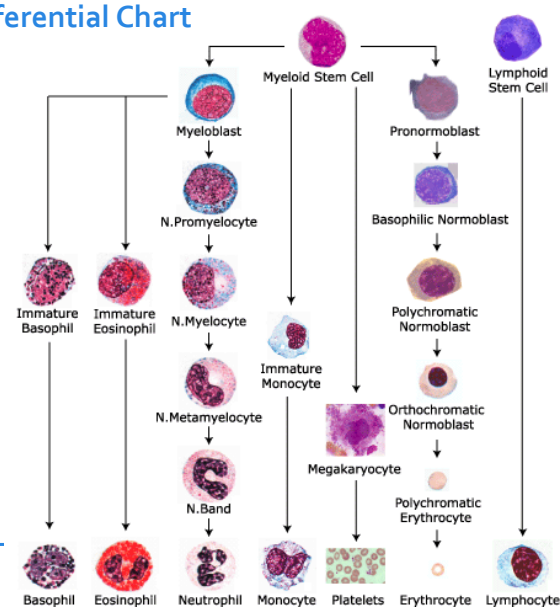
Cancer Facts & Figures, 2014. American Cancer Society; 2014. http://www.lls.org/sites/default/files/file_assets/facts.pdf.

Hematopoiesis

Maturation and Differential Chart



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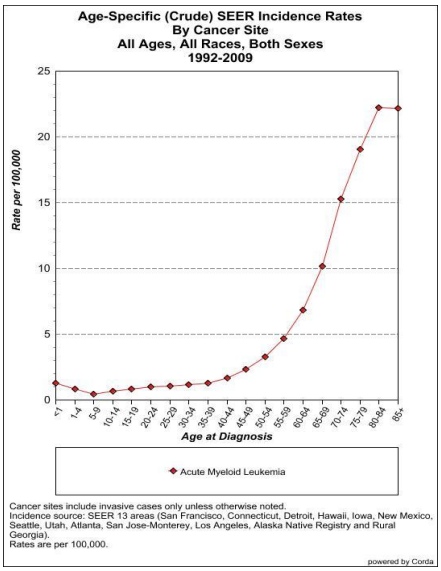
Basic Facts

- Most patients diagnosed over age 60
- Median age of 66 years at diagnosis
- Rapidly rising incidence over age 50
  - De Novo
  - Secondary
    - MDS/MPN
    - Therapy-related



www.seer.cancer.gov

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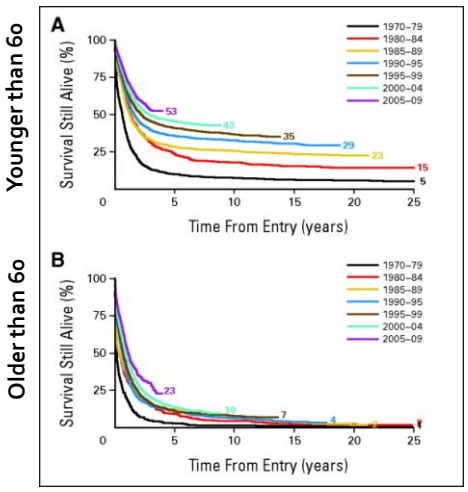
Overall Survival in AML

European Experience



Burnett A et al. JCO 2011;29:487-494

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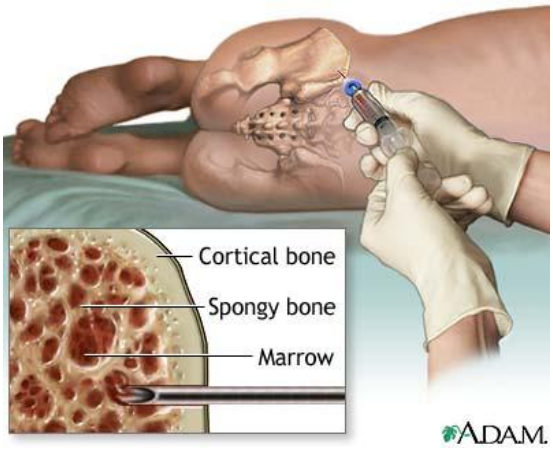

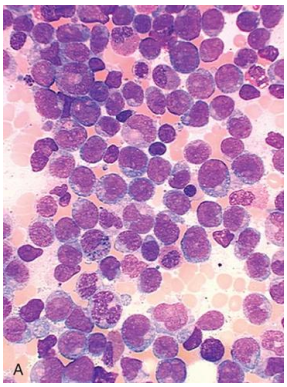

M1 → M7

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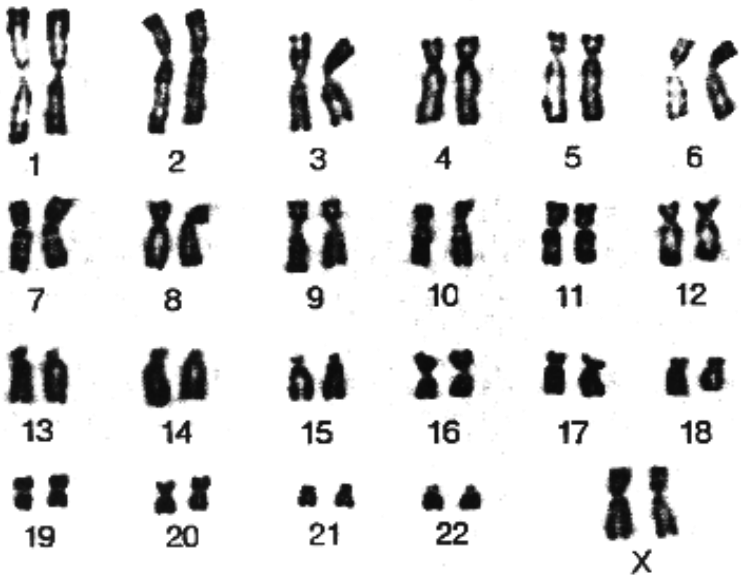

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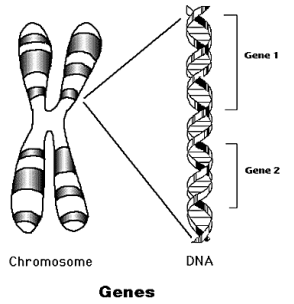
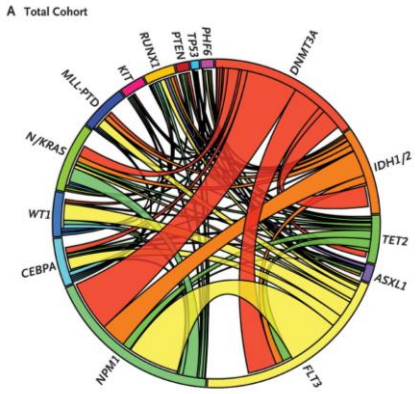
Where Have we Made Definite Progress?



FLT-3
NPM 1
CEBPα
C-KIT
IDH-1
IDH-2
TET-2
DNMT
ASXL1



Patel J, NEJM 2011

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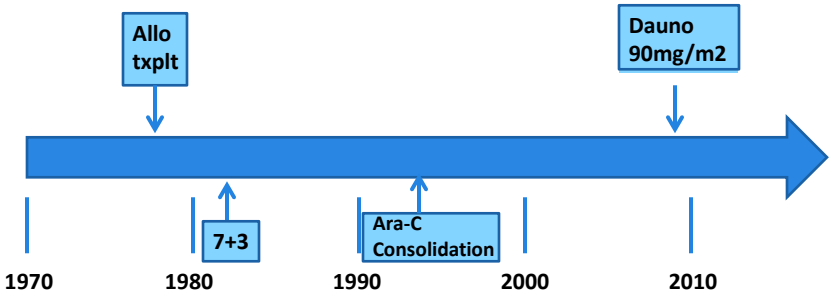
Advances in the Treatment of AML



•**Practice changing treatments in AML: 4**

Thomas ED, N Engl J Med. 1979 Mayer, N Engl J Med. 1994, Fernandez H,N Engl J Med, 2009

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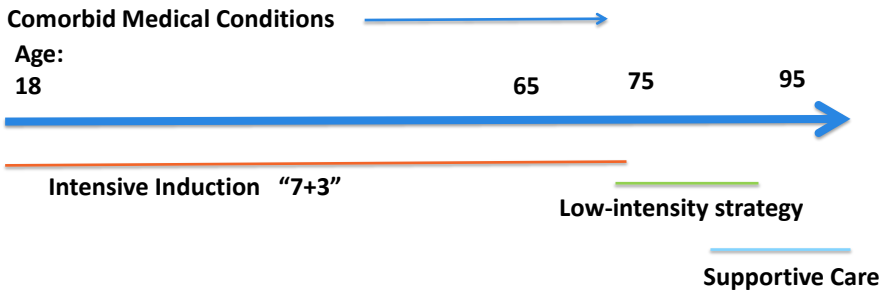
Current Paradigms for Treating Newly Diagnosed AML



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When Does 7+3 Not Equal 10?

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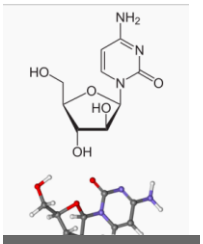

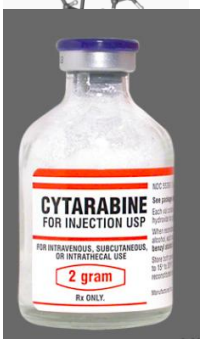

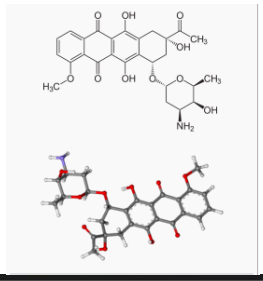

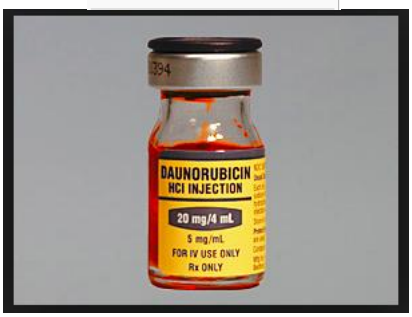

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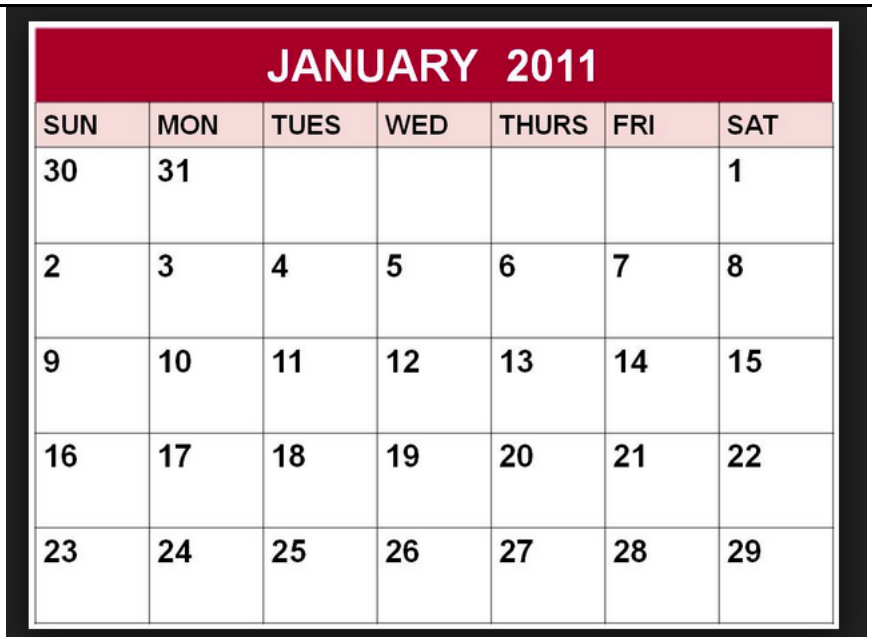

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After Complete Remission…

Risk Status (Live or Die)	Chromosomal Abnormalities	
Better-Risk	inv (16) or t(16;16) t(8;21)	Chemotherapy
Intermediate-Risk	Normal Cytogenetics (46 XX or 46 XY) Trisomy 8 t(9:11)	???
Poor-Risk	Inv (3) or translocation (3;3) More than 3 chromosomal abnormalities Deletions of chromosome 5 or 7 t(6;9) t(9;22)	Allogeneic Transplant

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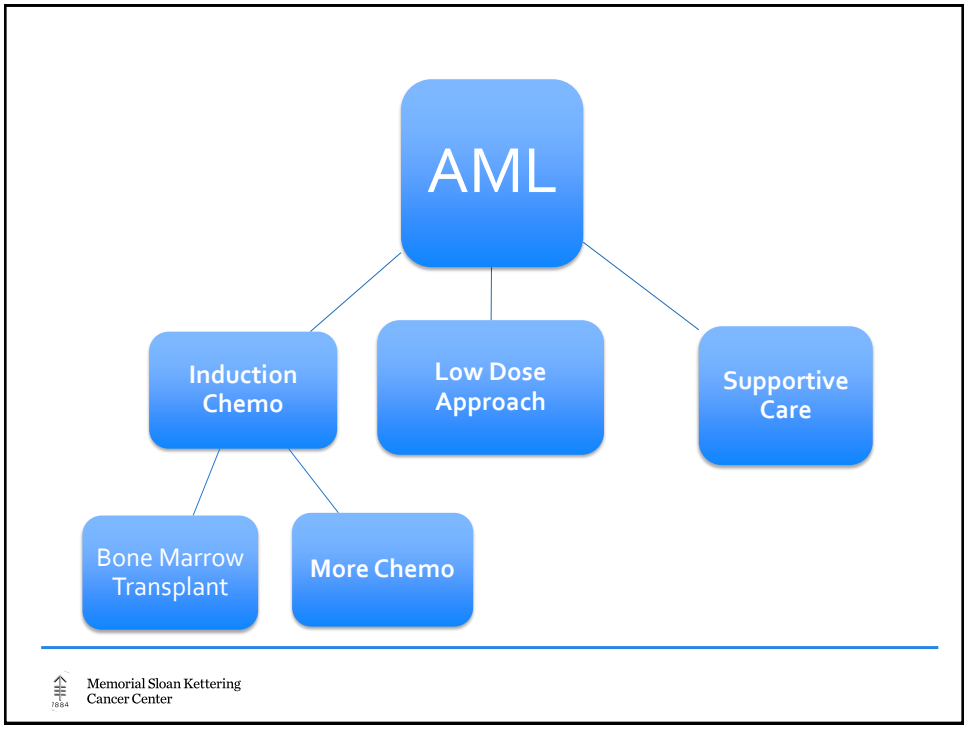
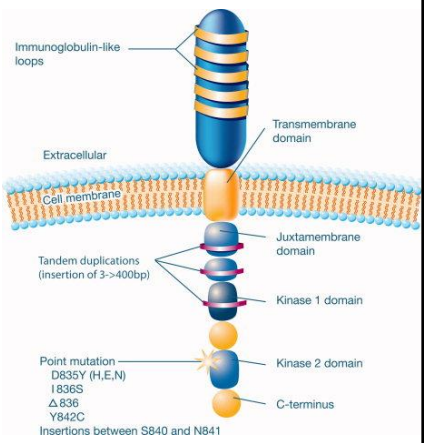


New Directions to Treat AML

FLT3 Inhibitors in the Treatment of Acute Myeloid Leukemia

- FLT-3 ITD found in 30% of cytogenetically normal AML
- Constitutive activation of FLT-3 receptor
- Confers a poor prognosis
- Multiple attempts to target FLT-3



Cancer; pages 3293-3304, 11 FEB 2011 DOI: 10.1002/cncr.25908

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ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

A Phase III Randomized Double-blinded Study Of Chemotherapy +/- Midostaurin (PKC412) In Newly Diagnosed Adults aged 18-60 with *FLT3* Mutated Acute Myeloid Leukemia (AML)

Richard M. Stone, Sumithra Mandrekar, Ben L Sanford, Susan Geyer, Clara D. Bloomfield, Konstanze Dohner, Christian Thiede, Guido Marcucci, Francesco Lo-Coco, Rebecca B. Klisovic, Andrew Wei, Jorge Sierra, Miguel A. Sanz, Joseph M. Brandwein, Theo de Witte, Dietger Niederwieser, Frederick R. Appelbaum, Bruno C. Medeiros, Martin S Tallman, Jurgen Krauter, Richard F. Schlenk, Arnold Ganser, Hubert Serve, Gerhard Ehninger, Sergio Amadori, Richard A. Larson, and Hartmut Dohner

Participants: ALLIANCE/CALGB, AMLSG, CETLAM, ECOG, EORTC, GIMEMA, NCIC, OSHO, PETHEMA, SAL, SWOG

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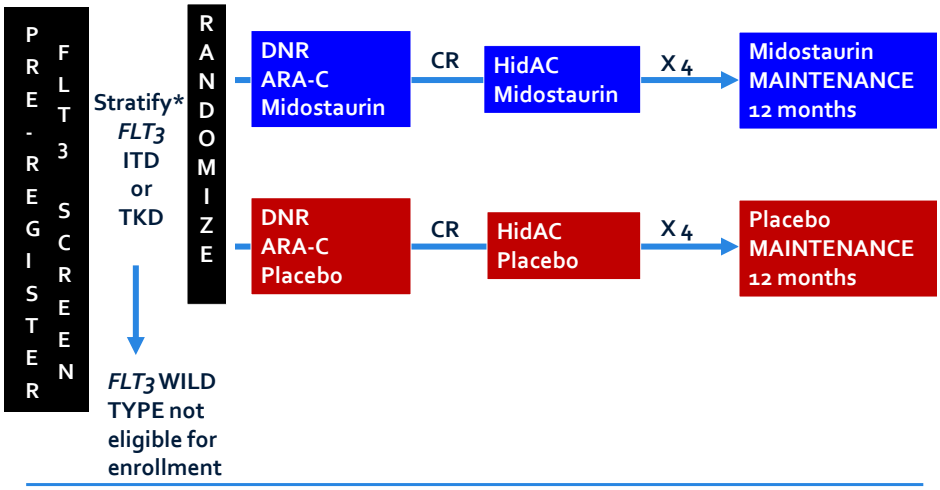
Schema



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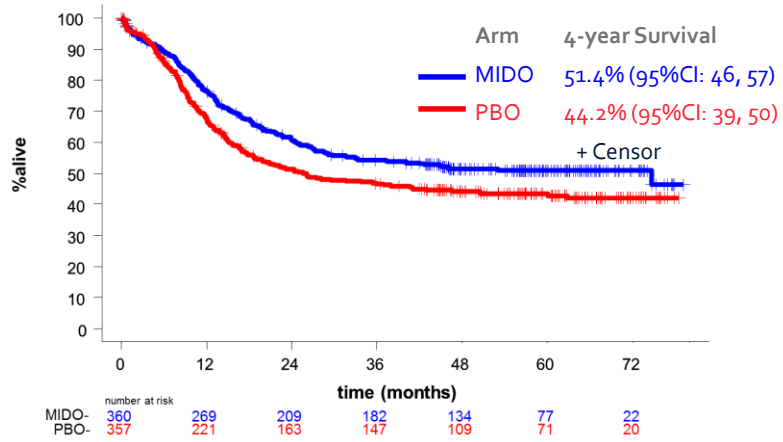
Overall Survival (Primary Endpoint)

23% Reduced Risk of Death in the Mido Arm



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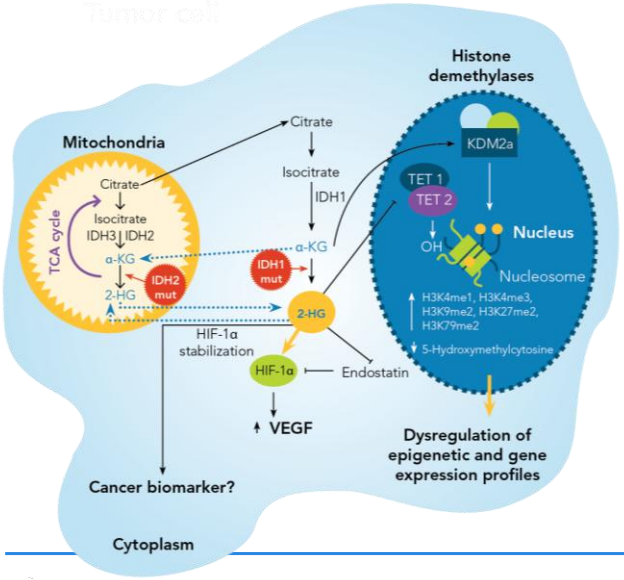
IDH in AML



- IDH is a critical metabolic enzyme in the citric acid cycle
- IDH1 in cytoplasm and IDH2 in mitochondria
- Cancer-associated IDHm produces 2-hydroxyglutarate (2-HG) and blocks normal cellular differentiation

Prensner and Chinnaiyan Nature, 2011

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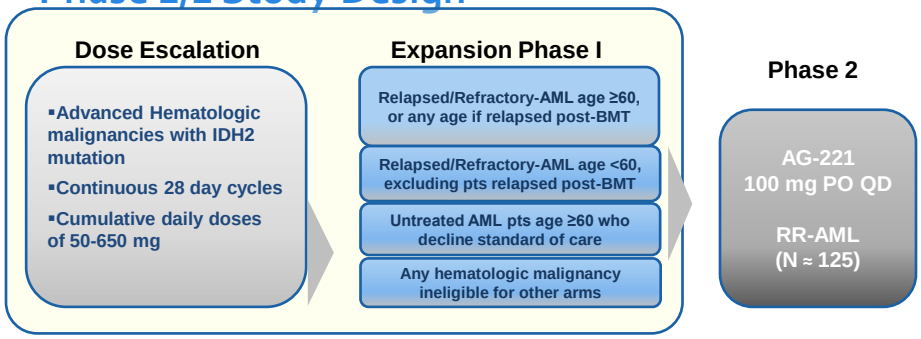
Phase 1/2 Study Design



Key Endpoints:

- **Safety, tolerability, MTD (maximum tolerated dose) DLTs (dose limiting toxicities**
- **Response rates as assessed by local investigator per IWG (International Working Group) criteria**
- **Assessment of clinical activity**

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Response

	RR-AML (n = 159)	Untreated AML (n = 24)	MDS (n = 14)	All (N = 209)
Overall Response (CR, CRp, CRi, mCR, PR)	**59 (37%)** [95%CI: 30%, 45%]	**10 (42%)** [22%, 63%]	**7 (50%)** [23%, 77%]	**79 (38%)** [31%, 45%]
CR	**29 (18%)** [95%CI: 13%, 25%]	**4 (17%)** [5%, 37%]	**3 (21%)** [5%, 51%]	**37 (18%)** [13%, 24%]
CRp	1 (1%)	1 (4%)	1 (7%)	3 (1%)
CRi	3 (2%)	0	0	3 (1%)
mCR	9 (6%)	1 (4%)	3 (21%)	14 (7%)
PR	17 (11%)	4 (17%)	0	22 (11%)
SD	72 (45%)	9 (38%)	6 (43%)	96 (46%)
PD	10 (6%)	1 (4%)	0	11 (5%)
Not evaluable	18 (11%)	4 (17%)	1 (7%)	23 (11%)

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Antileukemic Activity and Tolerability of ASP2215 ≥80 mg in FLT3 Mutation-Positive Subjects with Relapsed or Refractory Acute Myeloid Leukemia: Results from a Phase 1/2, Open-Label, Dose-Escalation/Dose-Response Study

Jessica K. Altman[1]; Alexander E. Perl[2]; Jorge Cortes[3]; Mark Levis[4]; Catherine Smith[5]; Mark Litzow[6]; Maria R. Baer[7]; David Claxton[8]; Harry Erba[9]; Stan Gill[10]; Stuart Goldberg[11]; Joseph Jurcic[12]; Richard A. Larson[13]; Charles Liu[10]; Ellen Ritchie[14]; Briana Sargent[10]; Gary Schiller[15]; Alexander Spira[16]; Stephen Strickland[17]; Raoul Tibes[18]; Celalettin Ustun[19]; Eunice S. Wang[20]; Robert Stuart[21]; Claudia Baldus[22]; Christoph Röllig[23]; Andreas Neubauer[24]; Giovanni Martinelli[25]; Erkut Bahceci[10]

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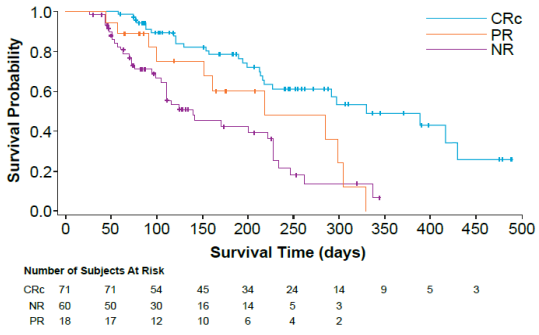
Overall Survival by Response in FLT3+ Subjects Treated with ≥80 mg Gilteritinib

- Across all FLT3+ subjects treated with gilteritinib ≥80 mg:
  - Median duration[a] of response was 111 (range: 8–383) days
  - Median time to best response[b] was 32 (range: 26–364) days
  - Median overall survival was 218 (range: 12–430) days



[a] Duration of response was calculated from the first observed response of PR or better.
[b] Time to best response was only evaluated for subjects who achieved best response of PR or better.

SGN-CD33A Plus Hypomethylating Agents: A Novel, Well-Tolerated Regimen with High Remission Rate in Frontline Unfit AML

Amir T. Fathi, MD[1], Harry P. Erba, MD, PhD[2], Jeffrey E. Lancet, MD[3], Eytan M. Stein, MD[4], Roland B. Walter MD, PhD, MS[5], Daniel J. DeAngelo, MD, PhD[6], Stefan Faderl, MD[7], Anand Jillella, MD[8], Farhad Ravandi, MD[9], Anjali S. Advani, MD[10], Dale Bixby, MD, PhD[11], Tibor Kovacsovics, MD[12], Megan M. O'Meara, MD[13], Dana A. Kennedy, PharmD[13], Anthony S. Stein, MD[14]

[1]Massachusetts General Hospital Cancer Center, [2]University of Alabama-Birmingham, [3]Moffitt Center, [4]Memorial Sloan Kettering Cancer Center, [5]Fred Hutchinson Cancer Research Center, [6]Dana-Farber Cancer Institute , [7]Hackensack University Medical Center, [8]Winship Cancer Institute-Emory University School of Medicine, [9]MD Anderson – University of Texas, [10]Cleveland Clinic, [11]University of Michigan Comprehensive Cancer Center, [12]Huntsman Cancer Institute-University of Utah, [13]Seattle Genetics, Inc., [14]Gehr Family Center for Leukemia Research, City of Hope

ASH 2015, Orlando, FL, December 5 - 8, 2015, Abstract No. 454

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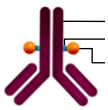
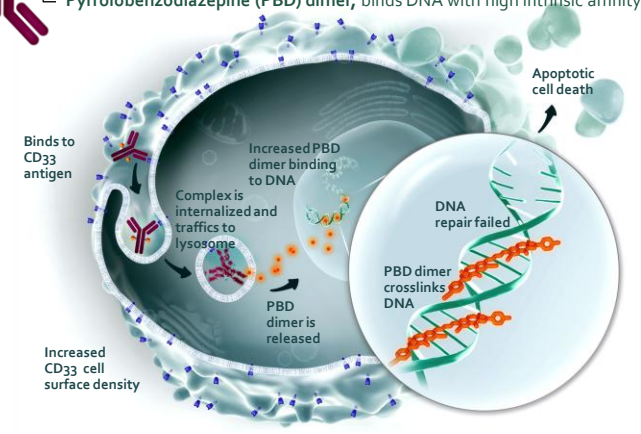
Vadastuximab Talirine (SGN-CD33A; 33A)

Proposed Mechanism of Action in Combination with HMA



Anti-CD33 antibody, engineered cysteines to enable uniform site-specific conjugation
Cleavable dipeptide linker, highly stable in circulation
Pyrrolobenzodiazepine (PBD) dimer, binds DNA with high intrinsic affinity



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Best Clinical Response per Investigator

Efficacy Evaluable Patients	Azacitidine (N=11)	Decitabine (N=12)	Total (N=23)
CR	3	3	6
CRi (n)*	2	1	3
CRi (p)**	3	3	6
Resistant Disease	3	5	8
Remission Rate	73%	58%	65%

* CRi (n)= CR with platelets ≥100k, incomplete neutrophil recovery
** CRi (p)= CR with ANC ≥1000, incomplete platelet recovery

- **Time to remission ~2 cycles**
- **Durability and survival in patients with CR/CRi**
  - **14/15 (93%) alive at last follow-up**
  - **13/15 (87%) maintain remission (range, 0.7+ to 33.6 weeks)**
- **Responses achieved in higher-risk patients**
  - **Underlying myelodysplasia (80%, n=10)**
  - **Adverse cytogenetics (89%, n=9)**

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A Phase 1b Study of Venetoclax (ABT-199/GDC-0199) in Combination with Decitabine or Azacitidine in Treatment-Naive Patients with Acute Myelogenous Leukemia Who Are ≥65 Years and Not Eligible for Standard Induction Therapy

Courtney DiNardo*[1], Daniel Pollyea*[2], Keith Pratz[3], Michael Thirman[4], Anthony Letai[5], Andrew Wei[6], Martha Arellano[7], Mark Frattini[8], Brian Jonas[9], Joel Leverson[10], Ming Zhu[10], Martin Dunbar[10], Nancy Falotico[10], Rachel Kirby[10], Suresh Agarwal[10], Mack Mabry[10], Jalaja Potluri[10], Rod Humerickhouse[10], Hagop Kantarjian[1], Marina Konopleva[1]

[1]University of Texas MD Anderson Cancer Center, Houston, TX; [2]University of Colorado School of Medicine, Aurora, CO; [3]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; [4]University of Chicago Medical Center, Chicago, IL; [5]Dana-Farber Cancer Institute, Boston, MA; [6]The Alfred Hospital, Melbourne, Victoria, Australia; [7]Emory University, Atlanta, GA; [8]Columbia University Medical Center, New York, NY; [9]UC Davis Comprehensive Cancer Center, Sacramento, CA; [10]AbbVie Inc., North Chicago, IL

*Both authors contributed equally to this work.

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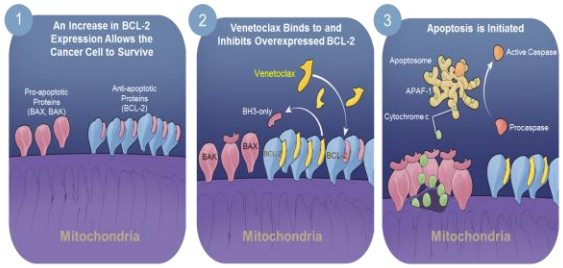
Venetoclax: Selective BCL-2 Inhibitor



- Venetoclax is a potent, orally bioavailable agent[1] with demonstrated single-agent activity in
  - AML cell lines and primary patient samples[2]
  - Heavily pretreated relapsed/refractory AML patients[3]
- Venetoclax was shown to synergize with HMA in preclinical models, suggesting that combination with HMA may be a promising approach in AML[4]
- Herein is reported an ongoing phase 1b, open-label, nonrandomized, dose-escalation trial of venetoclax in combination with DEC or AZA in older (≥65 years), treatment-naive AML patients (NCT02203773)

1. Souers A, et al. *Nat Med*. 2013;19:202-8; 2. Pan R, et al. *Cancer Discov*. 2014;4:362-75; 3. Konopleva M, et al. 56th Annual American Society of Hematology; December 6–9, 2014; Abstract 118; 4. Tsao T, et al. *Ann Hematol*. 2012;91:1861-70.

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Best Responses in All Evaluable Patients in All Cohorts

Best Response, n (%)	VEN + DEC 400 mg (n=6)	VEN + DEC 800 mg (n=12)	VEN + AZA 400 mg (n=4)	VEN + AZA 800 mg (n=12)	ITT Responses (N=34)
CR	2 (33)	2 (17)	3 (75)	5 (42)	**12 (35)**
CRi	1 (17)	6 (50)	1 (25)	4 (33)	**12 (35)**
PR	0	2 (17)	0	0	**2 (6)**
MLFS	0	1 (8)	0	0	**1 (3)**
RD	1 (17)	1 (8)	0	2 (17)	**4 (12)**
Not evaluable[a]	2 (33)	0	0	1 (8)	**3 (9)**
ORR (CR/CRi/PR) **CR+CRi**	**3 (50)** 3 (50)	**10 (83)** 8 (67)	**4 (100)** 4 (100)	**9 (75)** 9 (75)	**26 (76)** **24 (71)**

[a]Three of the 34 patients discontinued prior to the first disease assessment.

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The Future is Bright

- We increasingly understand the genetics of AML
- Novel targeted therapies are oral, well tolerated and lead to impressive response rates.
  - Inhibitors of FLT-3
  - Inhibitors of IDH1 and IDH2
  - Inhibitors of BCL-2
- Antibody-drug conjugates in combination with Decitabine or 5-aza show exciting promise

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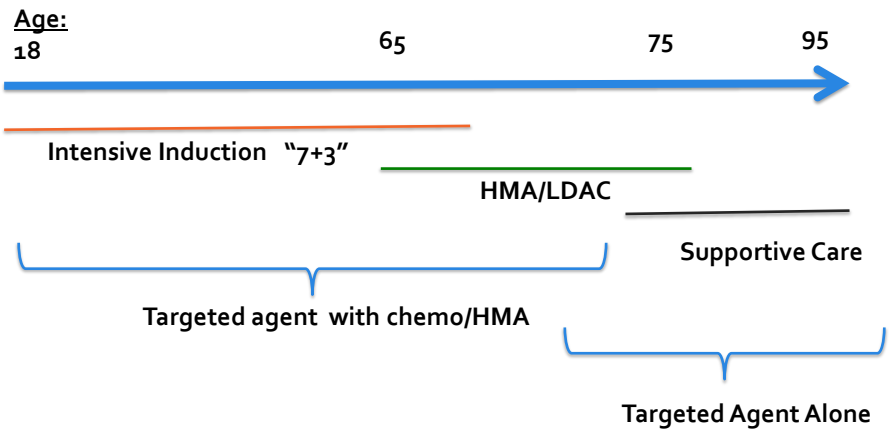
Future Paradigm for Treating Newly Diagnosed AML



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Thank You!

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Strategies for Treating AML

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Question & Answer Session

The speaker's slides are available for download at www.LLS.org/programs

Resources to Make Informed Treatment Decisions

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The Leukemia & Lymphoma Society (LLS) offers:

- **Live, Online Chats provide a friendly forum to share experiences with others.**
  - **WEBSITE: www.LLS.org/chat**
- **What to ask: For a list of suggested questions to ask about certain topics, download and print any of the following guides.**
  - **WEBSITE: www.LLS.org/whattoask**
- **Free education materials: www.LLS.org/publications**
- **Information Resource Center: Speak one-on-one with an Information Specialist who can assist you through cancer treatment, financial, and social challenges.**
  - **EMAIL: infocenter@LLS.org, TOLL-FREE PHONE: (800) 955-4572**