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WELCOMING REMARKS
BREAKTHROUGHS AND PROGRESS: ACUTE MYELOID LEUKEMIA (AML)

Lizette Figueroa-Rivera, MA
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LEUKEMIA & LYMPHOMA SOCIETY

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FACULTY
BREAKTHROUGHS AND PROGRESS: ACUTE MYELOID LEUKEMIA (AML)

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LEUKEMIA & LYMPHOMA SOCIETY®

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Stanford MEDICINE | Division of Hematology
Department of Medicine

LEUKEMIA & LYMPHOMA SOCIETY®

BREAKTHROUGHS AND PROGRESS:
ACUTE MYELOID LEUKEMIA

Gabriel N. Mannis, MD
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Division of Hematology, Stanford University
May 29, 2025

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Disclosures

Consultancy: Abbvie, Servier, Stemline

Scientific Advisory Committees: Abbvie, Astellas, BMS/Celgene, Genentech, Immunogen, Orbital, Rigel, Servier, Stemline, Wugen

Research Funding: Aptose, Astex, Blossom Hill, BMS/Celgene, Gilead, Glycomimetics, Jazz, Menarini-Stemline, Syndax, ImmuneOnc

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Agenda

- **Historical Perspective**
- **AML for Beginners**
- **Cool New Stuff in AML!**

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Historical Perspective

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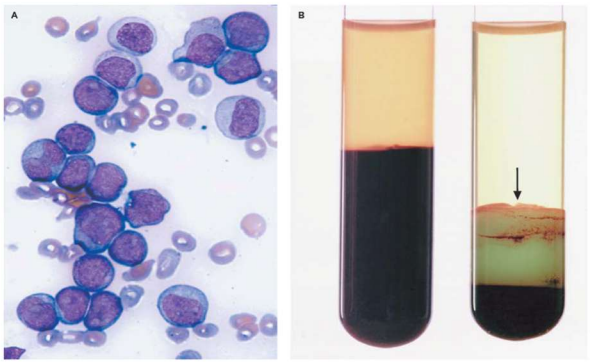
AML History

Peter Cullen (1811)

- Described a 35 year-old man with fever and abdominal pain
- Treated with blood-letting
- Serum described as milky white in color
- Likely the 1st published report of leukemia



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AML History

Rudolf Virchow (1847)

- Father of cell theory (“*omnis cellula e cellula”*)
- Also known for Virchow’s node, Virchow’s triad, standardizing autopsies
- Coined the term “leukämie”

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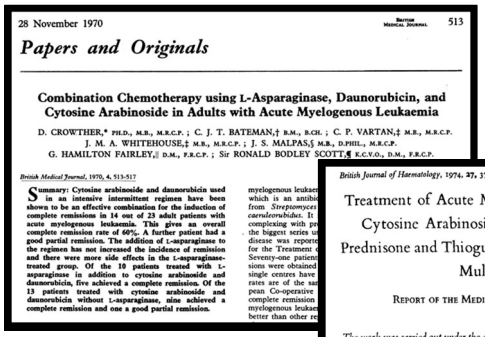
AML History



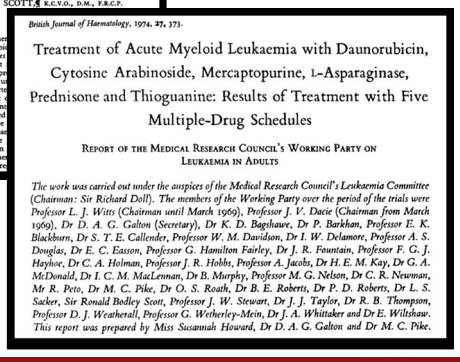
28 November 1970 — Papers and Originals — 513

Combination Chemotherapy using L-Asparaginase, Daunorubicin, and Cytosine Arabinoside in Adults with Acute Myelogenous Leukaemia

D. CROWTHER,* PH.D., M.B., M.R.C.P. ; C. J. T. BATEMAN,† B.M., B.CH. ; C. P. VARTAN,‡ M.B., M.R.C.P. ; J. M. A. WHITEHOUSE,‡ M.B., M.R.C.P. ; J. S. MALPAS,§ M.B., D.PHIL., M.R.C.P. ; G. HAMILTON FAIRLEY,‖ D.M., F.R.C.P. ; Sir RONALD BODLEY SCOTT,¶ K.C.V.O., D.M., F.R.C.P.

British Medical Journal, 1970, 4, 513-517

Summary: Cytosine arabinoside and daunorubicin used in an intensive intermittent regimen have been shown to be an effective combination for the induction of complete remissions in 14 out of 23 adult patients with acute myelogenous leukaemia. This gives an overall complete remission rate of 60%. A further patient had a good partial remission. The addition of L-asparaginase to the regimen has not increased the incidence of remission and there were more side effects in the L-asparaginase-treated group. Of the 10 patients treated with L-asparaginase in addition to cytosine arabinoside and daunorubicin, five achieved a complete remission. Of the 13 patients treated with cytosine arabinoside and daunorubicin without L-asparaginase, nine achieved a complete remission and one a good partial remission.



British Journal of Haematology, 1974, **27**, 373.

Treatment of Acute Myeloid Leukaemia with Daunorubicin, Cytosine Arabinoside, Mercaptopurine, L-Asparaginase, Prednisone and Thioguanine: Results of Treatment with Five Multiple-Drug Schedules

REPORT OF THE MEDICAL RESEARCH COUNCIL'S WORKING PARTY ON LEUKAEMIA IN ADULTS

The work was carried out under the auspices of the Medical Research Council's Leukaemia Committee (Chairman: Sir Richard Doll). The members of the Working Party over the period of the trials were Professor L. J. Witts (Chairman until March 1969), Professor J. V. Dacie (Chairman from March 1969), Dr D. A. G. Galton (Secretary), Dr K. D. Bagshawe, Dr P. Barkhan, Professor E. K. Blackburn, Dr S. T. E. Callender, Professor W. M. Davidson, Dr I. W. Delamore, Professor A. S. Douglas, Dr E. C. Easson, Professor G. Hamilton Fairley, Dr J. R. Fountain, Professor P. G. J. Hayhoe, Dr C. A. Holman, Professor J. R. Hobbs, Professor A. Jacobs, Dr H. E. M. Kay, Dr G. A. McDonald, Dr I. C. M. MacLennan, Dr B. Murphy, Professor M. G. Nelson, Dr C. R. Newman, Mr R. Peto, Dr M. C. Pike, Dr O. S. Roath, Dr B. E. Roberts, Dr P. D. Roberts, Dr L. S. Sacker, Sir Ronald Bodley Scott, Professor J. W. Stewart, Dr J. J. Taylor, Dr R. B. Thompson, Professor D. J. Weatherall, Professor G. Wetherley-Mein, Dr J. A. Whittaker and Dr E. Wiltshaw. This report was prepared by Miss Susannah Howard, Dr D. A. G. Galton and Dr M. C. Pike.

“7+3”

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AML History

FDA Drug Approvals in AML, 1970s-2017:

- Gemtuzumab ozogamicin (2000)
- Withdrawn from market in 2010

"Boulevard of Broken Dreams"

Sekeres and Steensma, *JCO* 2012

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AML History

FDA Drug Approvals in AML, 2017-2024:

04/28/17: **Midostaurin** (Rydapt; FLT3 inhibitor)

08/01/17: **Enasidenib** (IDHIFA; IDH2 inhibitor)

08/03/17: **Liposomal 7+3** (CPX-351/Vyxeos)

09/01/17: **Gemtuzumab ozogamicin** (Mylotarg; CD33 Antibody-Drug conjugate)

07/20/18: **Ivosidenib** (Tibsovo; IDH1 inhibitor)

11/21/18: **Venetoclax** (Venclexta; BCL2 inhibitor) + HMA/LDAC

11/21/18: **Glasdegib** (Daurismo; Hedgehog pathway inhibitor) + LDAC

11/28/18: Gilteritinib (Xospata; FLT3 inhibitor)

06/01/20: Oral azacitidine (Onureg; maintenance therapy)

05/25/22: Ivosidenib + azacitidine

12/02/22: Olutasidenib (Rezlildhia; IDH1 inhibitor)

07/20/23: Quizartinib (Vanflyta; FLT3 inhibitor)

11/15/24: Revumenib (Revuforj; Menin inhibitor)

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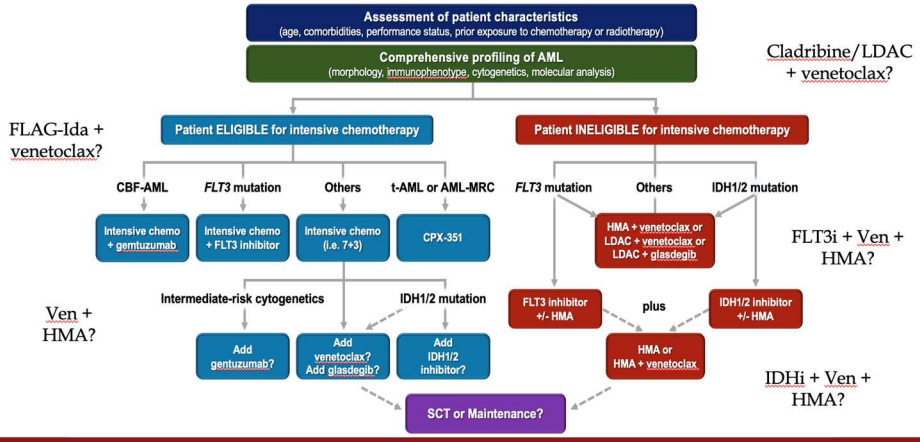
AML History

Treatment Paradigm for AML in 2025:



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AML for Beginners

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AML for Beginners

- What is AML?
- How did I get this?
- Is it curable?
- How is it treated?
- What can *I* do to help fight this?
- What other questions should I be asking?

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AML for Beginners

- What is AML?

Acute

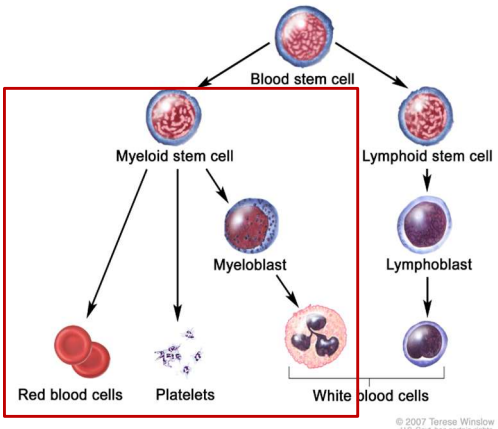
- Symptoms usually come on quickly (2-3 months or less)
- Treatment often initiated urgently

Myeloid

- Refers to the subtype of blood cell

Leukemia

- Cancer of blood cells
- Most commonly defined by >20% "blasts" in the blood or bone marrow



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AML for Beginners

- What is AML?

White cells

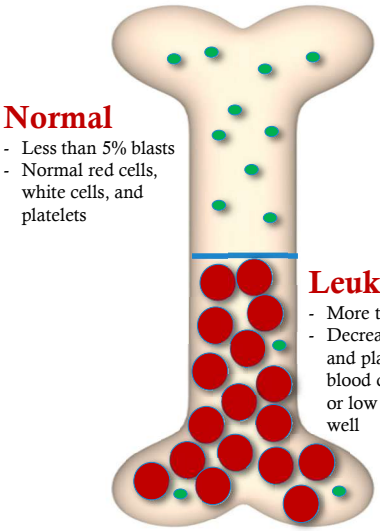
- Your immune cells
- Help fight infection
- Neutrophils are key

Red cells

- Oxygen-carrying cells

Platelets

- Help form clots and prevent bleedi



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AML for Beginners

- What is AML?

White cells

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- Help fight infection
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Red cells

- Oxygen-carrying cells

Platelets

- Help form clots and prevent bleeding

LEUKEMIA → Fever, Infection, Anemia

LEUKEMIA → Fatigue, Trouble breathing

LEUKEMIA → Easy bruising, Bleeding

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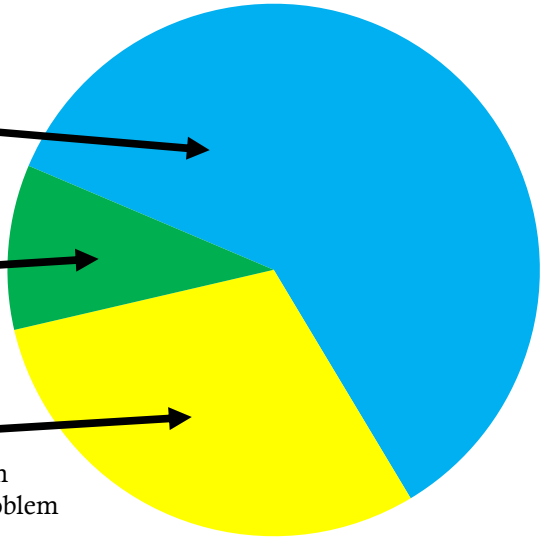
AML for Beginners

- How did I get this?



Bad Luck (60%)

- Blood stem cells acquire random mutations as we age

Inherited (~10%)

- >90% of cases are not passed down to other family members

Environment (30%)

- Prior chemotherapy/radiation
- Pre-existing bone marrow problem (MDS, chronic leukemia)

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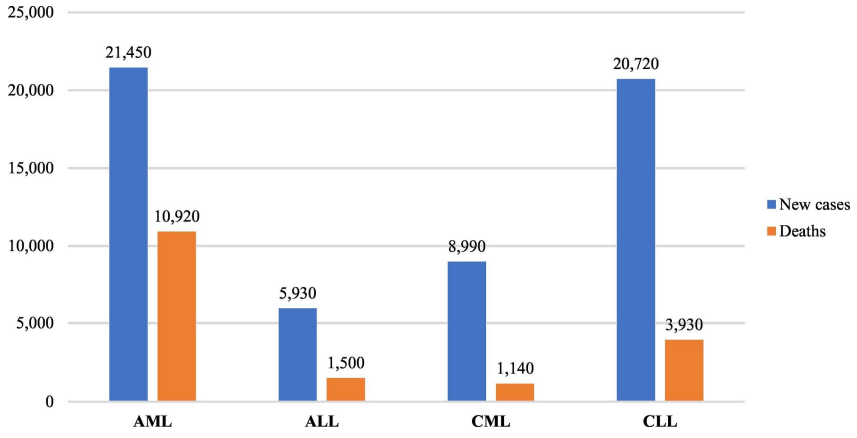
AML for Beginners

- AML by the numbers



Shallis et al, *Blood Rev, 2019 Jul, (36)70-87.*

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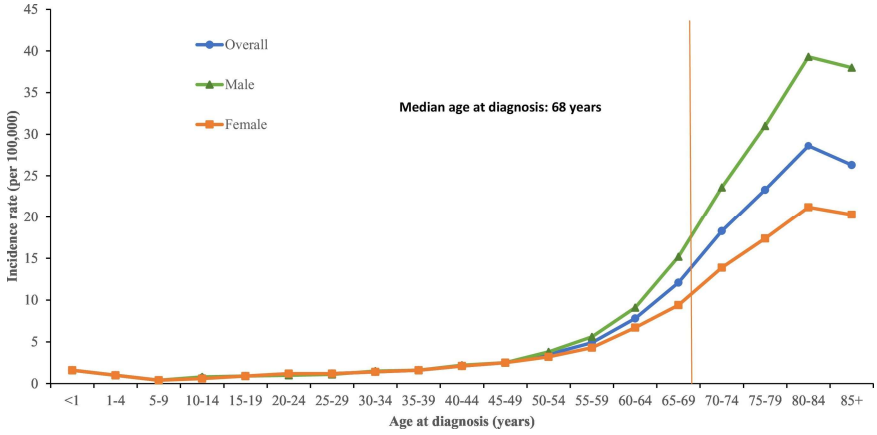
AML for Beginners

- AML by the numbers



Shallis et al, *Blood Rev, 2019 Jul, (36)70-87.*

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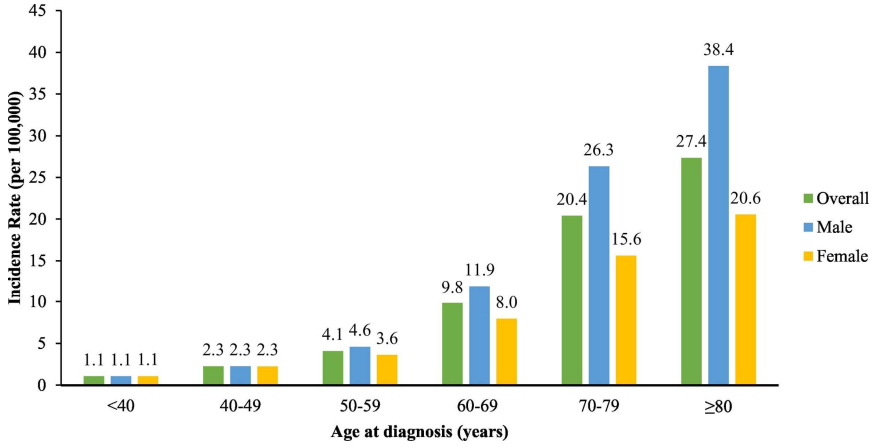
AML for Beginners

- AML by the numbers



Shallis et al, *Blood Rev, 2019 Jul, (36)70-87.*

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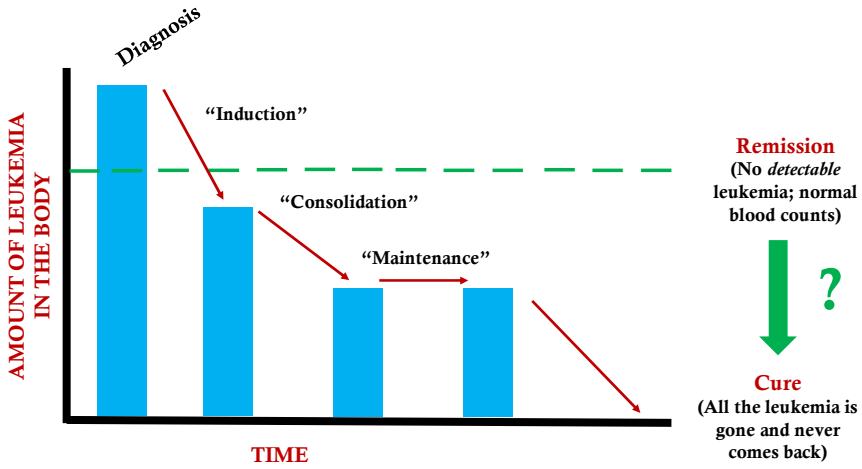
AML for Beginners

- Is it curable?



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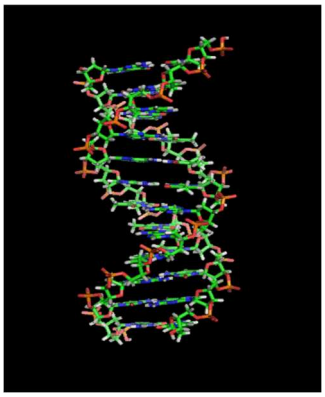
AML for Beginners

- Is it curable?

AGE

Older patients are less likely to be curable

GENETICS



Certain chromosome and gene changes are less likely to be curable

If not curable, the goal is typically to live as well as possible, for as long as possible

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AML for Beginners

- What's my prognosis?
  - Disease biology
  - Age
  - Other health issues
  - Social determinants

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AML for Beginners

- What's my prognosis?

Risk Category	Genetic Abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11* • Mutated *NPM1*[a] without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*
Intermediate	• Mutated *NPM1*[a] with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD • t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A* • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23;q34.1)/*DEK::NUP214* • t(v;11q23.3)/*KMT2A*-rearranged • t(9;22)(q34.1;q11.2)/*BCR::ABL1* • t(8;16)(p11;p13)/*KAT6A::CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2,MECOM(EVI1)* • t(3q26.2;v)/*MECOM(EVI1)*-rearranged • -5 or del(5q); -7; -17/abn(17p) • Complex karyotype, monosomal karyotype • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2* • Mutated *TP53*

Potentially curable with intensive chemotherapy alone

????

Potentially curable only with transplant after achieving remission

Khoury et al, *Leukemia, 2022*

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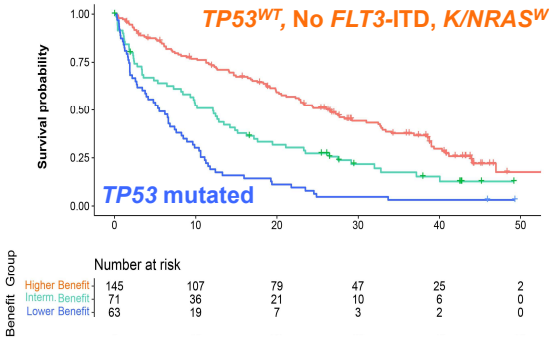
AML for Beginners

- What's my prognosis if not treated with intensive chemotherapy?



"Molecular Prognostic Risk Signature"
mPRS

- **Favorable (52%): 24 months**
- **Intermediate (25%): 12 months**
- **Poor (23%): 6 months**

TP53^{WT} and *FLT3*-ITD or *K/NRAS* mutated

Dohner et al, *ASH*, 2023
Bataller, *Blood Adv*, 2024

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AML for Beginners

- How is it treated?

FIT	UNFIT
CURABLE	INCURABLE
ACTIONABLE TARGET	NO ACTIONABLE TARGET

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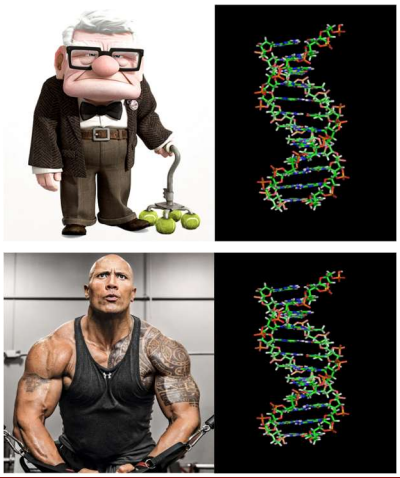
AML for Beginners

- How is it treated?



Lower intensity treatment

- Fewer potential side effects
- Mostly outpatient treatment
- Repeat cycles every month until it stops working
- Consideration of bone marrow (aka stem cell transplant) in a select few

Higher intensity treatment

- More potential side effects
- Usually ~1 month in the hospital
- Generally only up to 3-4 cycles of treatment
- Consideration of bone marrow (aka stem cell) transplant in most patients

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AML for Beginners

- What to expect with treatment

Low red blood cells (anemia) Low platelets	→ Frequent blood and platelet transfusions
Low white blood cells	→ Preventative antibacterial, antiviral, antifungal medications
Nausea / Diarrhea /Constipation Fatigue Hair loss Anxiety / Depression Fertility issues	→ Supportive medications, Palliative Care/Symptom Management referral, Fertility specialists
Frequent blood draws Bone marrow biopsies	→ PICC line or Port placement

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AML for Beginners

- What can I do on my own to maximize my chances of success during treatment?

Stay active!

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AML for Beginners

- What can I do on my own to maximize my chances of success during treatment?

Eat!

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AML for Beginners

- What can I do on my own to maximize my chances of success during treatment?

Train your brain!

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AML for Beginners

- What else should I be asking?
  - What is the standard treatment, and what alternatives are there?
  - If the initial treatment does not work, do I have back-up options?
  - Can I get a second opinion?
  - What clinical trials available?

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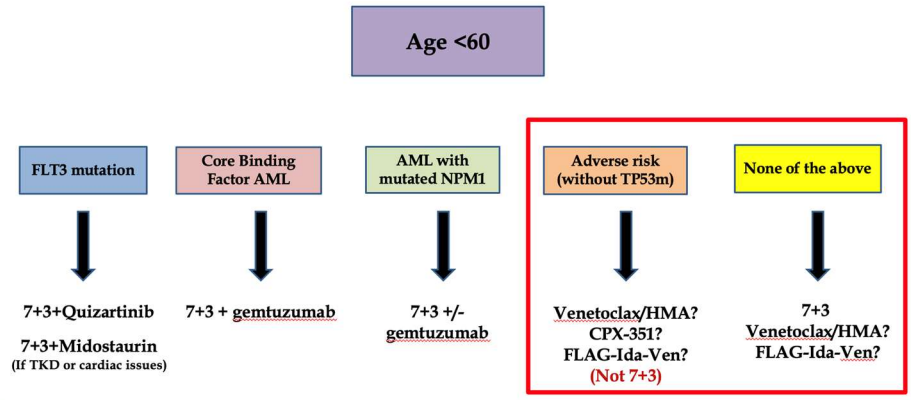
AML for Beginners

- Standard treatment paradigm, newly diagnosed AML in 2025 ("FIT")



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AML for Beginners

- Standard treatment paradigm, newly diagnosed AML in 2025 ("UNFIT")

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AML for Beginners

- What if my leukemia comes back or doesn't respond to initial treatment?

1) Test for targetable mutations

- FLT3
- IDH
- NPM1 / KMT2A

2) Check for clinical trial availability

3) Change mechanism

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Cool New Stuff in AML!

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Cool New Stuff in AML!

- Paradigm shift?
- All oral treatment?
- Menin inhibitors
- Triplets
- Novel cell therapy approaches

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Paradigm Shift?

PARADIGM: A Phase 2 Randomized Study Comparing Venetoclax and Azacitidine to Induction Chemotherapy for Newly Diagnosed Fit Adults with Acute Myeloid Leukemia

DF/HCC SITES:

Massachusetts General Hospital - *(Lead Site and Coordinating Center)*
Beth Israel Deaconess Medical Center
Dana Farber Cancer Institute

OTHER SITES:

City of Hope National Medical Center
Levine Cancer Institute/Atrium Healthcare
Ohio State University Comprehensive Cancer Center
University of California Davis Comprehensive Cancer Center
University of Pennsylvania Abramson Cancer Center
Stanford Cancer Institute, Stanford University

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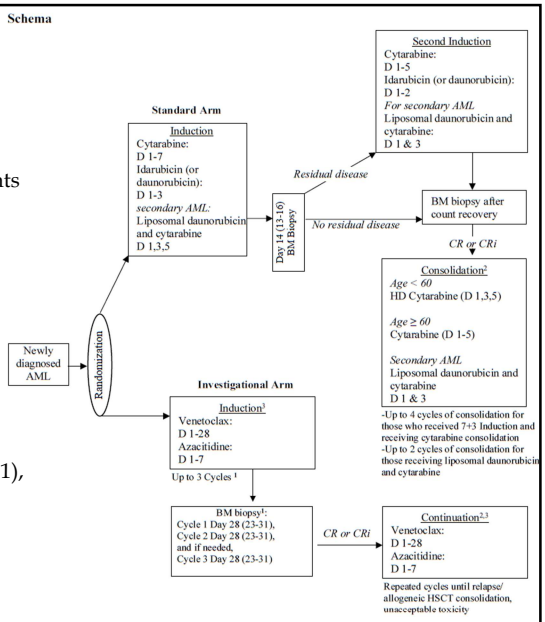
Paradigm Shift?

Primary Objective:
- To evaluate event free survival for patients treated with venetoclax and azacytidine compared to patients treated with either 7+3 regimen or liposomal daunorubicin and cytarabine.

Key Inclusion Criteria:
- Age ≥ 18 years
- Eligible for intensive induction chemotherapy, according to their treating physician

Key Exclusion Criteria:
- Diagnosis of AML with favorable cytogenetics [t(8;21), inv(16), t(16;16)]
- Patients < 60 years old with *NPM1*-mutated AML
- Patients with *FLT3*-mutated AML (TKD or ITD).

172 subjects were enrolled in the study



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Paradigm Shift?

Secondary Objectives:

- 30-day and 60-day mortality
- The proportion of patients receiving stem cell transplantation (SCT) following induction
- Quality of life, mood, symptom burden, coping, and patients post-traumatic stress disorder as assessed by:
  - Functional Assessment of Cancer Therapy-Leukemia (FACT-Leuk)
  - Hospital Anxiety and Depression Scale (HADS)
  - Edmonton Symptom Assessment Scale (ESAS)
  - Post-Traumatic Stress Disorder Checklist (PCL) Civil Version

Secondary Objectives (Continued):

- Healthcare Utilization:
  - Days alive and spent out of the hospital
  - Number of hospital days
  - Number of hospitalizations
  - Emergency department (ED) visits
  - Admission to the ICU
  - Days in the ICU
- Overall cost of care: To cover first 6 months, excluding period of transplantation for patients who proceed to transplant.
- Incidence of neutropenic fever or neutropenic infections

Preliminary results expected later this year

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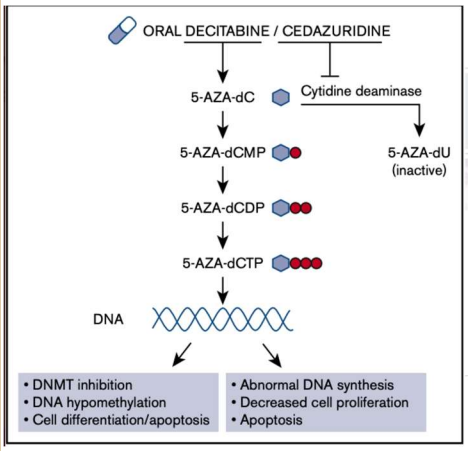
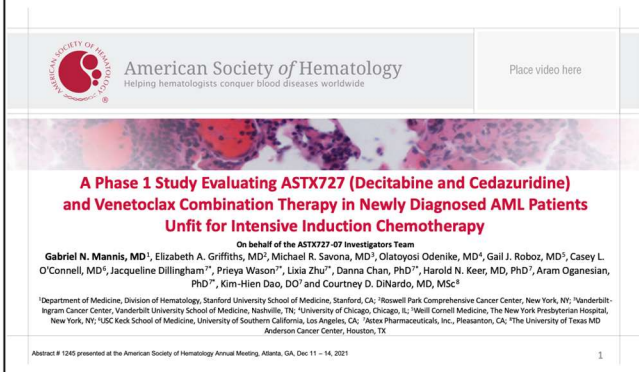
All oral treatment?



ASTX727 (Inqovi)


American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Place video here

A Phase 1 Study Evaluating ASTX727 (Decitabine and Cedazuridine) and Venetoclax Combination Therapy in Newly Diagnosed AML Patients Unfit for Intensive Induction Chemotherapy

On behalf of the ASTX727-07 Investigators Team

Gabriel N. Mannis, MD[1], Elizabeth A. Griffiths, MD[2], Michael R. Savona, MD[3], Olatoyosi Odenike, MD[4], Gail J. Roboz, MD[5], Casey L. O'Connell, MD[6], Jacqueline Dillingham[7*], Prieya Wason[7*], Lixia Zhu[7*], Danna Chan, PhD[7*], Harold N. Keer, MD, PhD[7], Aram Oganesian, PhD[7*], Kim-Hien Dao, DO[7] and Courtney D. DiNardo, MD, MSc[8]

[1]Department of Medicine, Division of Hematology, Stanford University School of Medicine, Stanford, CA; [2]Roswell Park Comprehensive Cancer Center, New York, NY; [3]Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN; [4]University of Chicago, Chicago, IL; [5]Weill Cornell Medicine, The New York Presbyterian Hospital, New York, NY; [6]USC Keck School of Medicine, University of Southern California, Los Angeles, CA; [7]Astex Pharmaceuticals, Inc., Pleasanton, CA; [8]The University of Texas MD Anderson Cancer Center, Houston, TX

Abstract # 1245 presented at the American Society of Hematology Annual Meeting, Atlanta, GA, Dec 11 – 14, 2021

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Mannis et al, *ASH* 2021

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#6504

2025 ASCO ANNUAL MEETING

An All-Oral Regimen of Decitabine-Cedazuridine Plus Venetoclax in Patients With Newly Diagnosed Acute Myeloid Leukemia Ineligible for Intensive Induction Chemotherapy: Results From a Phase 2 Cohort of 101 Patients

Amer M. Zeidan,[1] Elizabeth A. Griffiths,[2] Courtney D. DiNardo,[3] Gabriel N. Mannis,[4] Pau Montesinos,[5] Montserrat Arnan,[6] Michael R. Savona,[7] Olatoyosi Odenike,[8] James K. McCloskey,[9] Harsh V. Amin,[10] Amir T. Fathi,[11] Teresa Bernal del Castillo,[12] Gabriela Rodríguez-Macías,[13] Jane Liesveld,[14] Annie P. Im,[15] Aram Oganesian,[16] Qing Xu,[16] Margit Dijkstra,[16] Harold Keer,[16] Gail J. Roboz[17]

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All oral treatment?

- 101 patients treated
- Median age of 78
- Composite remission rate ~65%
- Of patients achieving remission, ~75% remained in remission 1 year later

Zeidan et al, *ASCO* 2025

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Menin Inhibitors

November 15, 2024

Syndax Announces FDA Approval of Revuforj® (revumenib), the First and Only Menin Inhibitor to Treat Adult and Pediatric Patients with Relapsed or Refractory Acute Leukemia with a KMT2A Translocation

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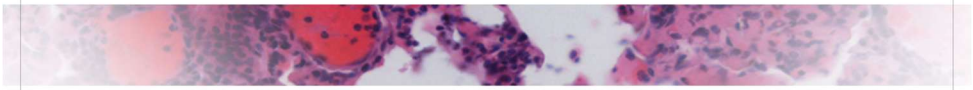
Menin Inhibitors

American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide



Updated Results and Longer Follow-up From the AUGMENT-101 Phase 2 Study of Revumenib in All Patients With Relapsed or Refractory (R/R) *KMT2Ar* Acute Leukemia

Ibrahim Aldoss, Ghayas C. Issa, James S. Blachly, Michael J. Thirman, Gabriel N. Mannis, Martha L. Arellano, John F. DiPersio, Elie Traer, C. Michel Zwaan, Neerav Shukla, Branko Cuglievan, Carolyn S. Grove, Matthew Greenwood, Christine M. McMahon, Alexander E. Perl, Richard M. Stone, Cristina Papayannidis, David S. Dickens, Maël Heiblig, Andrius Žučenka, Pau Montesinos, Ioannis Mantzaris, Tibor Kovacsovics, Paul J. Shami, Li Yu, Rebecca G. Bagley, Nicole McNeer, Eytan M. Stein

Presented at the 66th ASH Annual Meeting & Exposition; December 7–10, 2024; San Diego, CA. Oral abstract 211.

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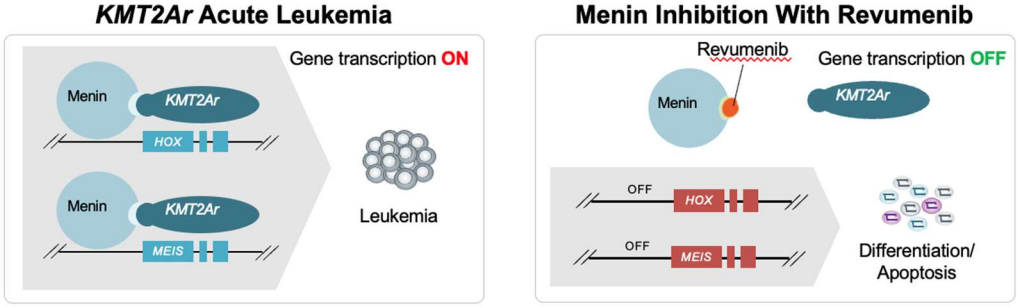
Menin Inhibitors

- Revumenib is an oral, small molecule menin inhibitor that disrupts menin-KMT2A interactions



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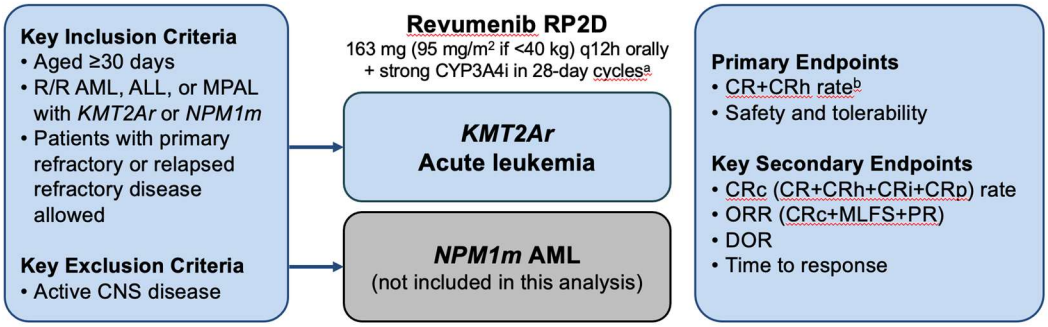
Menin Inhibitors

AUGMENT-101 Phase 2 Study Design



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Menin Inhibitors

Phase 2 *KMT2Ar*: Baseline Characteristics

Parameter	Efficacy population (n=97)[a]	Safety population (N=116)[b]
Leukemia type, n (%)		
AML	78 (80.4)	95 (81.9)
ALL	13 (13.4)	15 (12.9)
MPAL/other	6 (6.2)	6 (5.2)
Co-mutations, n (%)[c]		
FLT3-ITD	5 (5.2)	7 (6.0)
FLT3-TKD	2 (2.1)	3 (2.6)
RAS	12 (12.4)	12 (10.3)
TP53	5 (5.2)	5 (4.3)
Primary refractory, n (%)	19 (19.6)	20 (17.2)
No. of prior lines of therapy, median (range)	2 (1–11)	2 (1–11)
≥3, n (%)	41 (42.3)	51 (44.0)
Prior venetoclax, n (%)	62 (63.9)	73 (62.9)
Prior HSCT, n (%)	46 (47.4)	59 (50.9)

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Menin Inhibitors

Phase 2 *KMT2Ar*: Revumenib Efficacy

Parameter	Efficacy population (n=97)[a]
ORR, n (%)	**62 (63.9)**
CR+CRh rate, n (%)	22 (22.7)
95% CI	14.8–32.3
CRc, n (%)	41 (42.3)
95% CI	32.3–52.7
Negative MRD status, n (%)[b]	
CR+CRh	11/18 (61.1)
CRc	21/36 (58.3)

Parameter	Efficacy population (n=97)[a]
Best response, n (%)	
CR	15 (15.5)
CRh	7 (7.2)
CRi	2 (2.1)
CRp	17 (17.5)
MLFS	20 (20.6)
PR	1 (1.0)
PD	7 (7.2)
No response	21 (21.6)
Other[c]	7 (7.2)

Data cutoff: February 29, 2024.
[a]All patients who have received ≥1 dose of revumenib, have been centrally confirmed for *KMT2Ar* acute leukemia, and have ≥5% blasts in bone marrow at baseline.
[b]MRD done locally; not all patients had MRD status reported.
[c]Includes patients without postbaseline disease assessment.

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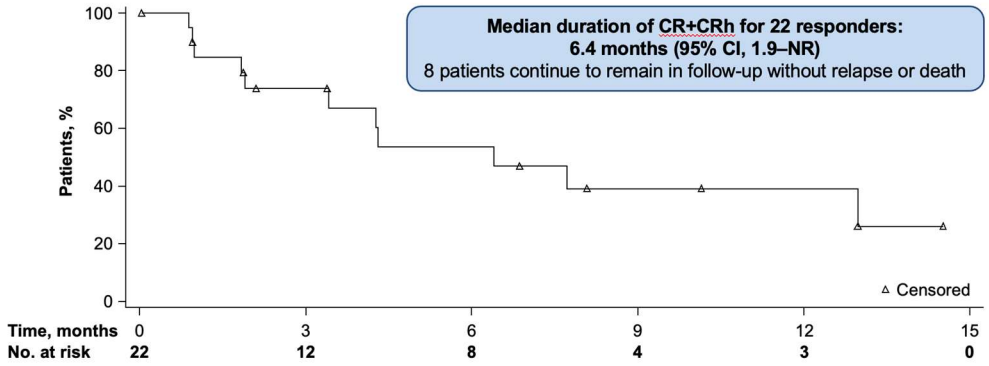
Menin Inhibitors

Phase 2 *KMT2Ar*: Duration of CR+CRh



For the 13 CR+CRh responders from the interim analysis[1] the **updated median duration of CR+CRh was 13.0 months (95% CI, 3.4–NR)**

Data cutoff: February 29, 2024.

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Menin Inhibitors

- Revumenib now approved for relapsed/refractory KMT2A-r leukemia; NPM1 approval likely coming soon
- Several other menin inhibitors already in development (ziftomenib, bleximenib, enzomenib)
- Highly active class of drugs, short duration of response as monotherapy (best used as bridge to transplant)
- Combination strategies in both the newly diagnosed and relapsed/refractory settings may increase response rates, response duration
- Differentiation syndrome, EKG changes, gastrointestinal toxicity, and low blood counts are the key side effects; newer generations of these drugs may mitigate some of these issues

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Triplets








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Triplets: Can we improve on Ven/Aza?

- How to avoid being just a "third wheel"
  - *Single agent activity*
  - *Synergizes with ven and/or aza*
  - *Agnostic to type of AML*
  - *Targets known resistance mechanisms*
  - *Does not add significant side effects*
  - *Easy to take/administer*

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Triplets: Can we improve on Ven/Aza?

PARTIAL ACCESS | ORIGINAL REPORTS | January 26, 2024

Azacitidine, Venetoclax, and Gilteritinib in Newly Diagnosed and Relapsed or Refractory *FLT3*-Mutated AML

Authors: Nicholas J. Short, MD, Naval Daver, MD, Courtney D. Dinardo, MD, Tapan Kadia, MD, Lewis F. Nasr, MD, MSc, Walid Macaron, MD, MSc, Musa Yilmaz, MD, SHOW ALL, and Farhad Ravandi, MD AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 42, Number 13 • https://doi.org/10.1200/JCO.23.01911

RESEARCH ARTICLES | JULY 05 2023

A Phase Ib/II Study of Ivosidenib with Venetoclax ± Azacitidine in *IDH1*-Mutated Myeloid Malignancies FREE

Curtis A. Lachowiez; Sanam Loghavi; Zhihong Zeng; Tomoyuki Tanaka; Yi June Kim; Hidetaka Uryu; Sven Turkalj; Niels Asger Jakobsen; Marlise R. Luskin; Dzifa Y. Duose; Rebecca S.S. Tidwell; Nicholas J. Short; Gautam Borthakur; Tapan M. Kadia; Lucia Masarova; George D. Tippett; Prithviraj Bose; Elias J. Jabbour; Farhad Ravandi; Naval G. Daver; Guillermo Garcia-Manero; Hagop Kantarjian; Jacqueline S. Garcia; Paresh Vyas; Koichi Takahashi; Marina Konopleva; Courtney D. DiNardo

616.ACUTE MYELOID LEUKEMIAS: INVESTIGATIONAL DRUG AND CELLULAR THERAPIES | NOVEMBER 5, 2024

Phase I/II Study of the All-Oral Combination of Revumenib (SNDX-5613) with Decitabine/Cedazuridine (ASTX727) and Venetoclax (SAVE) in R/R AML

Ghayas C. Issa, Branko Cuglievan, Naval Daver, Courtney D. DiNardo, Aziz Farhat, Nicholas J. Short, David McCall, Allison Pike, Sheila Tan, Brianna Kammerer, Aimee Marshal, Musa Yilmaz, Tapan M. Kadia, Naveen Pemmaraju, Maro Ohanian, Hussein A. Abbas, Abhishek Maiti, Alexandre Bazinet, Elias Jabbour, Koji Sasaki, Gautam Borthakur, Guillermo Montalban-Bravo, Nitin Jain, Yesid Alvarado Valero, Farhad Ravandi, Guillermo Garcia-Manero, Michael Andreeff, Hagop M. Kantarjian

PRESENTATION ID S139

Auditorium

TUSCANY STUDY OF SAFETY AND EFFICACY OF TUSPETINIB PLUS STANDARD OF CARE VENETOCLAX AND AZACITIDINE IN STUDY PARTICIPANTS WITH NEWLY DIAGNOSED AML INELIGIBLE FOR INDUCTION CHEMOTHERAPY

Dr. Gabriel Mannis (Stanford, CA, United States of America)

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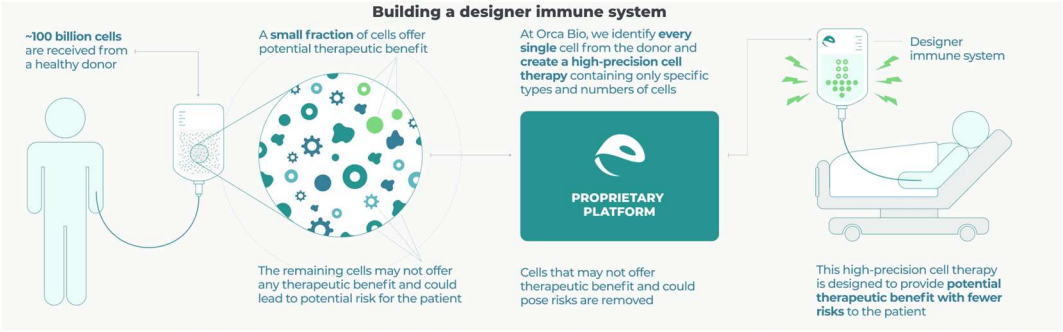
Novel cell therapy approaches: Transplant



"Engineered" stem cell product may be able to remove cells responsible for causing graft versus host disease (GVHD) without compromising the power of the donor immune system

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Novel cell therapy approaches: Transplant

Orca Bio Announces Positive Results from the Pivotal Phase 3 Study of Investigational Orca-T® Compared to Allogeneic Stem Cell Transplant for the Treatment of Hematologic Malignancies

Precision-T study met the primary endpoint of a statistically significant improvement in survival free of moderate-to-severe chronic graft versus host disease (cGvHD), showing 78% with Orca-T versus 38% with conventional allogeneic stem cell transplant (alloHSCT) at one year (HR 0.26, p<0.00001)

Overall survival with Orca-T was 94% compared to 83% with alloHSCT at one year, and the cumulative incidence of moderate-to-severe cGvHD was 13% versus 44%, respectively

"Engineered" stem cell product may be able to remove cells responsible for causing graft versus host disease (GVHD) without compromising the power of the donor immune system

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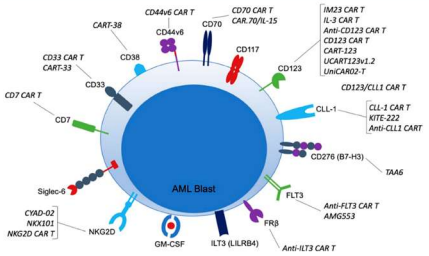
Novel cell therapy approaches: CAR T cells

Antigen Targets for Myeloid Malignancies

- **CD123: Expressed on 95% of leukemic stem cells on ~80% AML and also present in MDS and MPN**
- **CLL1: C-type lectin-like receptor expressed on up to 92% blasts and 45% leukemic stem cells in >85% AML patients**
- **CD33: Expressed in ~90% of leukemic stem cells in 85% of AML cases**
- **CD70: TNF-alpha family protein expressed on >75% leukemic blast and stem cells in 85% of AML patients but not on normal hematopoietic tissue**

MOFFITT CANCER CENTER



Marvin-Peek. Cancers. 2022.
Schorr. Front Immunol. 2022

- Need to kill AML cells but preserve normal white blood cells
- Unclear if a suitable target antigen exists in AML

Slide courtesy of Hany Elmariah

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Novel cell therapy approaches: CAR T cells

TABLE 1 | CAR T cell trials in myeloid malignancies currently recruiting.

Disease	Interventions	Identifier ID	Phase	Location
AML	CD123/CLL1 CAR T cells	NCT03631576	II/III	Fujian Medical University Union Hospital, China
	CLL-1, CD33 and/or CD123 CAR T cells	NCT04010877	I/II	Shenzhen Geno-Immune Medical Institute, China
	CD123 CAR T cells	NCT03796390	I	Hebei Yanda Ludaopei Hospital, China
	CD123 CAR T cells	NCT03585517	I	Xian Lu, China
	Muc1/CLL1/CD33/CD38/CD56/CD123 CAR T cells	NCT03222674	I/II	Zhujiang Hospital of Southern Medical University, Yunnan Cancer Hospital, Shenzhen Geno-Immune Medical Institute, China
	CD38/CD33/CD56/CD123/CD117 /CD133/CD34/Mucl CAR T cells	NCT03473457	N/A	Southern Medical University Zhujiang Hospital, China
	CD123 CAR T cells expressing EGFRt		I	Fengtai District, China
	CD44v6 CAR T cells	NCT04097301	I/II	IRCCS San Raffaele, IRCCS Ospedale Pediatrico Bambino Gesù, Italy
	CD33 CAR T cells	NCT03971799	I/II	The Children's Hospital of Philadelphia, USA
	Universal CD123 CAR T cells	NCT03190278	I	H. Lee Moffitt Cancer Center, Dana-Farber Cancer Institute, Weill Medical College of Cornell University, MD Anderson Cancer Center, USA
	CD123 CAR T cells	NCT04014881	I	Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, China
	CD123 CAR T cells	NCT03556982	I/II	307 Hospital of PLA, China
	CD123 CAR T cells expressing EGFRt	NCT02159495	I	City of Hope Medical Center, USA
	CD123 CAR T cells	NCT03766126	I	University of Pennsylvania, USA

- New "logic gated" (if/and) and "shielded" CAR T cell approaches hold promise but still not ready for prime time

Mardiana et al, *Front Oncol* 2020

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AML Summary

- AML remains a very challenging disease, but…
- Significant progress has been made in the past few years, and…
- There is a lot more on the horizon in the coming years

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Thanks!

All of my patients and their families

Stanford Hematology

Caroline Berube	Lawrence Leung
Roni Brar	Michaela Liedtke
Steve Coutre	Ravi Majeti
Robert Diep	Beth Martin
Bita Fakhri	Ann Mullaly
Peter Greenberg	Giselle Salmasi
Jason Gotlib	William Shomali
David Iberri	Tian Zhang

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ASK A QUESTION

BREAKTHROUGHS AND PROGRESS: 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.

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HOW TO CONTACT US:

To contact an **Information Specialist** about disease, treatment and support information, resources and clinical trials:
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Call: (800) 955-4572
Monday to Friday, 9 a.m. to 9 p.m. ET

Chat live online: www.LLS.org/InformationSpecialists
Monday to Friday, 10 a.m. to 7 p.m. ET
Email: www.LLS.org/ContactUs

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Work one-on-one with an LLS Clinical Trial Nurse Navigator who will help you find clinical trials and personally assist you throughout the entire clinical-trial process. Visit: www.LLS.org/Navigation

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Online Chats

Online Chats are free, live sessions, moderated by oncology social workers. To register for one of the chats below, or for more information, please visit www.LLS.org/Chat

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View our free education videos on disease, treatment, and survivorship. To view all patient videos, please visit www.LLS.org/EducationVideos

Patient Podcast

The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit www.TheBloodline.org

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LLS EDUCATION & SUPPORT RESOURCES

The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancers: www.LLS.org/Finances.

To order free materials: www.LLS.org/Booklets

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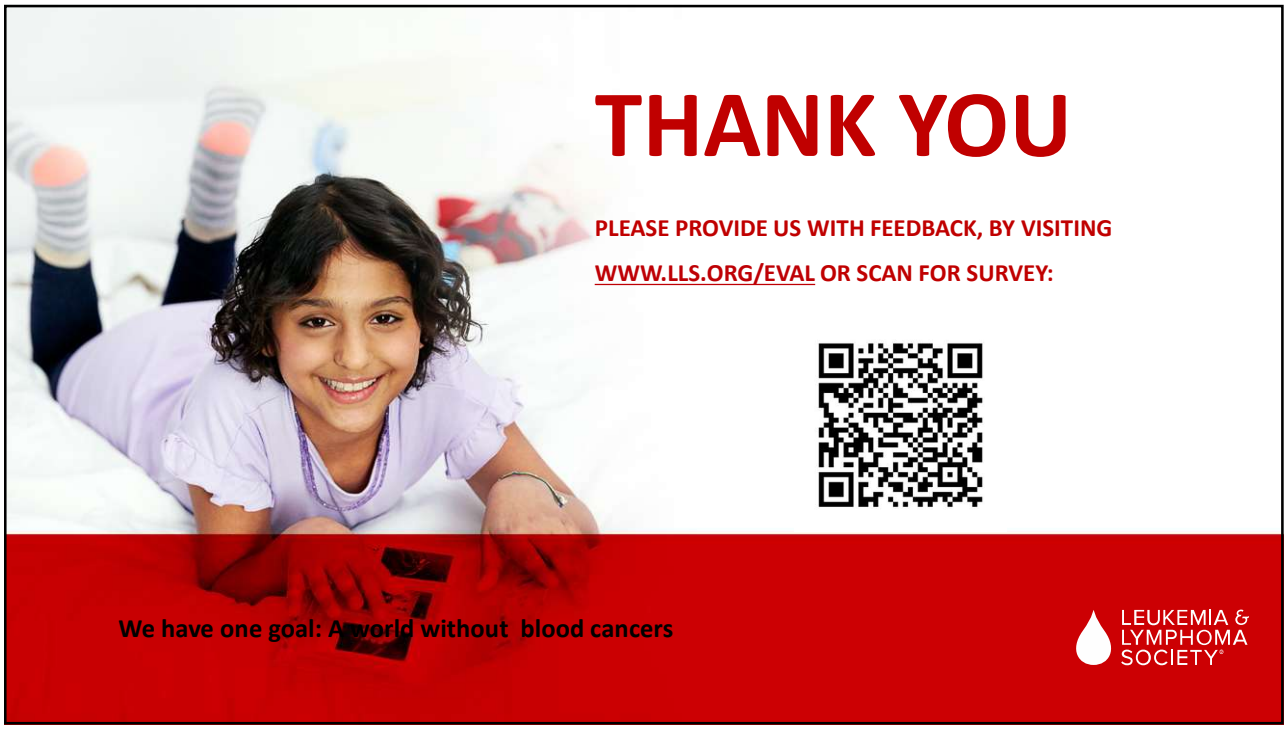
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We have one goal: A world without blood cancers
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