ADVANCES IN ACUTE MYELOID LEUKEMIA (AML)

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WELCOMING REMARKS

Advances in Acute Myeloid Leukemia (AML)

Lizette Figueroa-Rivera
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The Leukemia & Lymphoma Society

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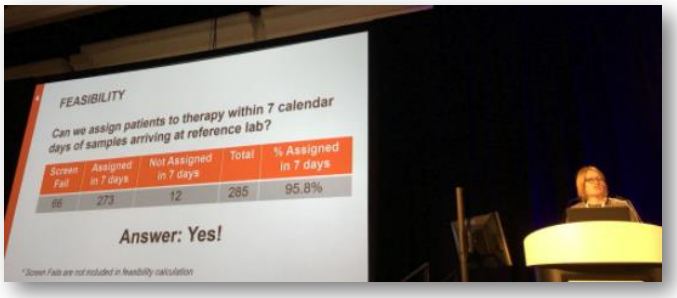
WELCOMING REMARKS

Advances in Acute Myeloid Leukemia (AML)

Amy Burd

LLS's Vice President of Research Strategy

Lead Beat AML Master Trial



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DISCLOSURES

Advances in Acute Myeloid Leukemia (AML)

AbbVie, Jazz: Grant Support

RUNX1 Foundation, Incyte, Pfizer: Honoraria/Consultation Fee

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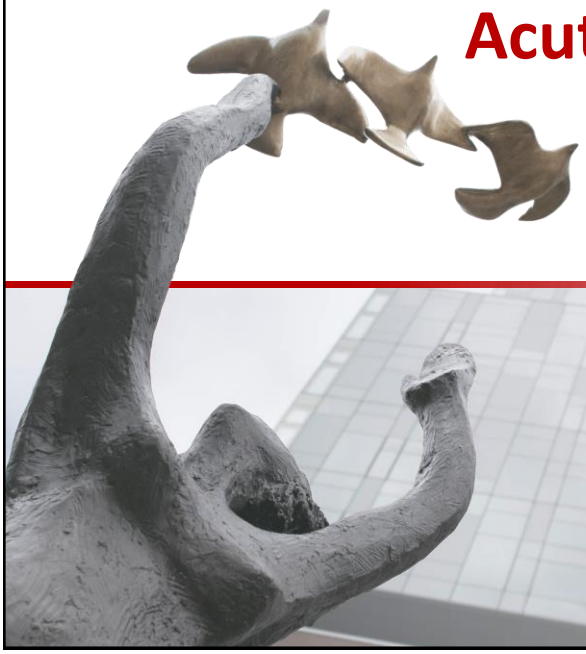

Acute Myeloid Leukemia

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Division of Hematology

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Symptoms of acute myeloid leukemia

- Constitutional symptoms
  - Fatigue, fever, chills, night sweats, weight loss
- Symptoms due to anemia
  - Fatigue, chest pain, SOB especially with exertion, light headedness
- Symptoms due to neutropenia / immunosuppression
  - Infections, mouth sores, fever
- Symptoms due to thrombocytopenia / coagulopathy
  - Petechiae, epistaxis, oral bleeding, bruising, intracranial bleeding, GI bleed
- Symptoms due to hyperleukocytosis / leukostais
  - Headache, visual changes, cranial nerve deficits, AMS, chest pain, SOB

The presentation of acute leukemia is highly variable and requires a high index of suspicion

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Lab abnormalities concerning for acute myeloid leukemia:

- Hyperleukocytosis
- Pancytopenia
- Circulating blasts or other immature forms
- Concerning symptoms/history AND CBC differential taking unusually long to result
- Acute myeloid leukemia can present with a low WBC, high WBC or “normal” WBC

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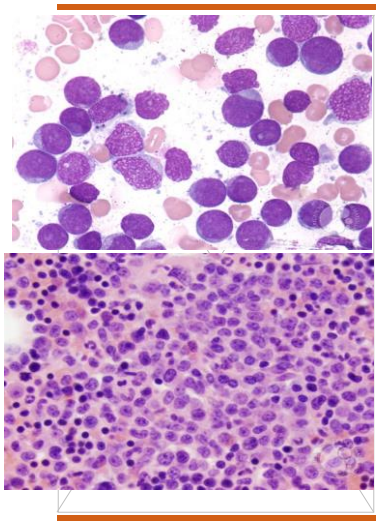
Acute Myeloid Leukemia



- Clonal malignant bone marrow disorder
- >20% blasts of total cells of bone marrow aspirate (from 500 cell differential count)
  - Exceptions: presence of t(8;21), inv(16), t(15;17) or myeloid sarcoma
- Leukemic cells must be of myeloid origin as demonstrated by presence of Auer rods, MPO+ or presence of sufficient myeloid markers recognized by immunophenotyping (ex. CD33, CD34, CD38, etc)
  - 20% of AML will co-express lymphoid markers (CD7, CD9, CD2)

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AML Risk factors

- Increasing age**
- **10% Familial cases**
- Down's syndrome (both ALL and AML)
- Exposures
  - Pesticides
  - Benzene
  - Ionizing radiation
  - Chemotherapy for other cancers
    - Alkylating agents (cylophosphamide, melphalan)
    - Topo II inhibitors (anthracyclines, etoposide, mitoxantrone)

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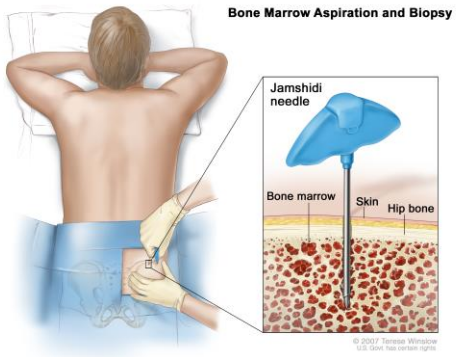
Diagnosis

- Core biopsy
- Aspirate
- Flow cytometry
- Karyotype (1-2 weeks)
- FISH (2 days)
  - t(15;17), t(8;21), inv(16)
- Myeloid molecular panel



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ELN Risk Stratification

Table 5. 2017 European LeukemiaNet risk stratification by genetics[a]

Risk Category[b]	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* without *FLT3*-ITD or with *FLT3*-ITD$^{low(c)}$ Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD$^{high(c)}$ Wild type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD$^{low(c)}$ (w/o adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*[d] Cytogenetic 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* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* -5 or del(5q); -7; -17/abn(17p) Complex karyotype,[e] monosomal karyotype[f] Wild type *NPM1* and *FLT3*-ITD$^{high(c)}$ Mutated *RUNX1*[g] Mutated *ASXL1*[g] Mutated *TP53*[h]

Dohner et al. Blood. 2017 129:424-447

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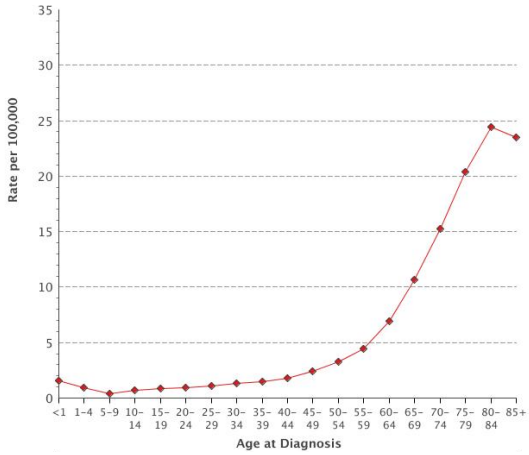
AML is more common with increasing age.



SEERS Database, 2003-2012

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Treatment decisions

- Age
  - ≥60 considered older AML population
- Performance status – ECOG PS
  - 0 is fully functional, 4 is completely bed-bound
- Medical comorbidities
  - Especially cardiac, renal and liver function
- Risk stratification by karyotype and mutation
  - Might consider intensive chemotherapy in older patient with favorable risk AML which is potentially curable with chemotherapy
- Patient preference

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Treatment options – Healthy <75 Induction

- "7+3" standard treatment: 3 days of anthracycline (daunorubicin 60-90mg/m2 or idarubicin 12mg/m2) and 7 days of continuous cytarabine (100-200 mg/m2/day).
- Patients are in the hospital for 4-6 weeks to monitor for complications of disease/therapy: neutropenic fever/infection, nausea/vomiting, diarrhea, mucositis, dehydration
- Undergo day 14 marrow biopsy to assess for residual disease (>5-10% blasts in hypocellular marrow)
- If no residual disease, await count recovery (typically occurs day 21-35)
- If residual disease, undergo a course of reinduction – 5+2, 7+3, HiDAC, amongst others

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7+3 outcomes

- A second bone marrow biopsy occurs at time of count recovery or by day 35 of induction if no count recovery
  - Used to determine if patient is in a complete remission
- Remission rate
  - 60-70% for young patients
  - 30-40% for elderly patients
- Remission rate is highly influenced by cytogenetics, mutational status
- Treatment related mortality of 10-15%
  - Average, varies significantly by age, co-morbidities and PS

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Treatment for less fit, elderly patients

- Hypomethylating agents(**HMAs**- decitabine OR azacitdine)
  - Can be given as outpatient
  - **Venetoclax + HMA** approved Nov 2018 for ≥ 75 or younger if comorbidities and cannot tolerate intensive induction
- Low dose cytarabine + venetoclax or glasdegib
- IDH inhibitors
- Clinical trial(s)
  - Immunotherapy
  - Targeted therapy
- Best supportive care
  - Transfusions, antibiotics, IVF, Hydrea for count control
- Hospice

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VIALE-A: study design (Phase III)

Eligibility

Inclusion

- Patients with newly diagnosed confirmed AML
- Ineligible for induction therapy defined as **either**
  - ≥75 years of age
  - 18 to 74 years of age with at least one of the co-morbidities:
    - CHF requiring treatment or Ejection Fraction ≤50%
    - Chronic stable angina
    - DLCO ≤ 65% or FEV1 ≤ 65%
    - ECOG 2 or 3

Exclusion

- Prior receipt of any HMA, venetoclax, or chemotherapy for myelodysplastic syndrome
- Favorable risk cytogenetics per NCCN
- Active CNS involvement

Treatment

Randomization 2:1 N=433*

- **VEN + Inj AZA (N=286)**: Venetoclax 400 mg PO, daily, days 1–28 + Azacitidine 75 mg/m² SC /IV days 1–7
- **PBO + Inj AZA (N=145)**: Placebo daily, days 1–28 + Azacitidine 75 mg/m² SC /IV days 1–7

Endpoints

Primary

- Overall survival

Secondary

- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

Randomization Stratification Factors: Age (<75 vs. ≥75 years); Cytogenetic Risk (intermediate, Poor); Region

Venetoclax dosing ramp-up: Cycle 1 ramp-up Day 1: 100 mg, Day 2: 200 mg, Day 3 - 28: 400 mg; Cycle 2 → Day 1-28: 400 mg

2 patients were not stratified by cytogenetic risk. They were excluded from efficacy analysis but included in the safety analysis. 6 patients who did not receive treatment were excluded from the safety analysis set.

DiNardo CD, et al. Oral presentation at EHA 2020. Abstract LB2601

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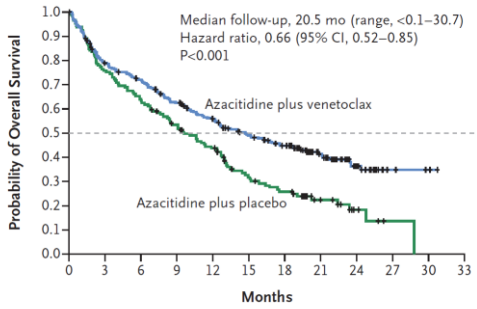
VIALE-A: key efficacy results

Key efficacy data (N=431*)

	VEN + Inj AZA (n=286)	Placebo + Inj AZA (n=145)
Median duration of follow-up, months (range)	20.5 (<0.1–30.7)	
Median number of treatment cycles (range)	7.0 (1.0–30.0)	4.5 (1.0–26.0)
Efficacy endpoints†		
Median OS, months (95% CI)	14.7 (11.9, 18.7)	9.6 (7.4, 12.7)
	HR=0.66 (0.52, 0.85); p<0.001	
CR/CRi rate, %	66.4	28.3
Median time to CR/CRi, months (range)	1.3 (0.6–9.9)	2.8 (0.8–13.2)

Overall survival (N=431)



No. at Risk

Azacitidine plus venetoclax	286	219	198	168	143	117	101	54	23	5	3	0
Azacitidine plus placebo	145	109	92	74	59	38	30	14	5	1	0	0

DiNardo CD, et al. *N Eng J Med* 2020; 383:617-29

*Two of the 433 patients who underwent randomization were not stratified according to cytogenetic risk. They were excluded from the efficacy analysis but included in the safety analysis.

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What happens after patient is in a complete remission?

- Defined as <5% blasts in the bone marrow, ANC >1000 and platelets >100,000
- Without additional consolidation treatment, relapse will inevitably occur within months.
- Considerations:
  - Age
  - Risk stratification with cytogenetics and mutations
  - Has the patient recovered from induction?
  - Can the patient tolerate additional therapy?
- ***Major decision branch point: chemotherapy alone versus stem cell transplant?***

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Post-remission therapy in AML

- Favorable-risk AML patients typically do not require allogeneic stem cell transplant in CR1 because they may be cured with chemotherapy alone.(some caveats to this).
- High-dose cytarabine 3g/m^2 q 12 hours on days 1,3,5 of 28 day cycle, given for 3-4 cycles.
- Treatment given inpatient but patients are discharged on day 5-6.
  - Receive labs and transfusion support as outpatient
  - May be re-admitted with neutropenic fever or other complications

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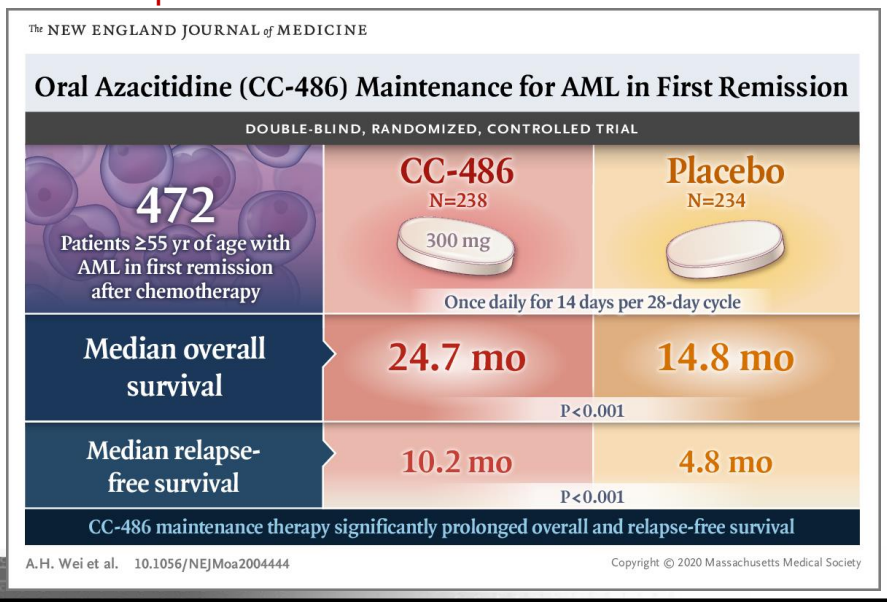
Maintenance therapy in AML after induction/consolidation IF transplant is NOT an option



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Indications for allogeneic stem cell transplant in AML

- Intermediate or High-risk disease
- Failure to achieve remission after initial induction therapy
- Relapsed disease
- Patients over age 60 with good PS and available donor
  - May receive reduced intensity conditioning
- Other requirements for transplant
  - Suitable donor: HLA matched sibling, HLA matched unrelated donor, haploidentical donor, cord blood
  - Acceptable organ function
  - Social support / caregiver

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Long term follow up (non transplant)

- Monitor for long term toxicities
  - Cardiac (anthracycline)
  - Neurologic (cytarabine)
- Encourage patients to have routine health maintenance and other chronic medical conditions addressed by PCP or other specialists as appropriate
- Monitor for relapse
  - Regular CBC
  - Bone marrow biopsy if cytopenias or circulating blasts
  - **Emerging role of Measurable residual disease (MRD) in AML**

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Options for relapsed AML

- Most relapses will occur within 12 months of first remission, but may occur later (typically considered “cured” 5 years from last definitive treatment without relapse).
- Treatment:
  - **Clinical trial (MANY new targeted agents**)
  - If good candidate, intensive salvage chemotherapy
  - Hypomethylating agent
  - IDH inhibitors – Ivosidenib and Enasidenib
  - FLT3 inhibitor – Gilteritinib
  - CD33 monoclonal antibody - mylotarg
- If the patient is able to obtain CR2 and is a good candidate, should evaluate for allogeneic stem cell transplantation

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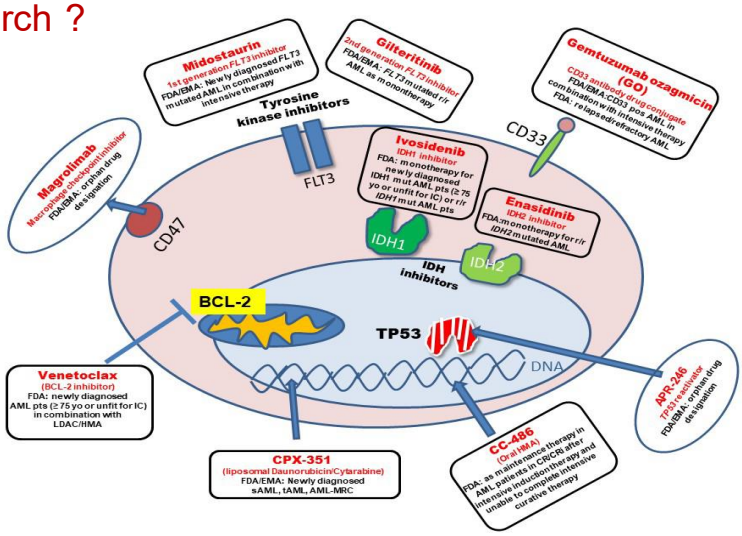
What's new in AML research ?

- **<u>Always</u>** ask your doctor about clinical **trials-they are NOT meant as a last resort option.**



Felicitas Thol, What to use to treat AML: the role of emerging therapies, Hematology Am Soc Hematol Educ Program, 2021,

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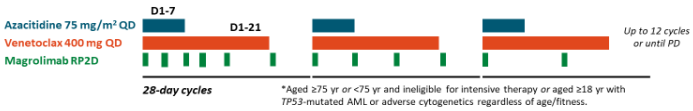
Go bigger ? Triplet therapy building on Aza+Ven in high risk AML

- Patients with AML harboring *TP53* mutations have poor outcomes[4]
- Magrolimab is an anti-CD47 antibody with promising activity when used in combination with AZA in *TP53* WT and mutated AML[5]

Azacitidine + Venetoclax + Magrolimab in AML: Study Design

- Open-label phase Ib/II trial
  - Phase Ib: adult patients with R/R AML only; phase II: patients with ND* or R/R AML (venetoclax-naive and experienced cohorts)



- No DLTs observed in phase Ib (n = 6); magrolimab RP2D established at 1 mg/kg C1D1, C1D4; 15 mg/kg C1D8; 30 mg/kg C1D11 and subsequent doses
- Primary objectives: determine MTD and RP2D, CR/CRi rate; secondary objectives: ORR (CR/CRi + PR + MLFS), DoR, EFS, OS, MRD negative rate, 4- and 8-wk mortality, number of patients transitioning to transplant

Daver. ASH 2021. Abstr 371.

Slide credit: clinicaloptions.com

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FLT3 AML –new trials in upfront and R/R FLT3 AML

Quizartinib/Venetoclax/Decitabine in *FLT3*-Mutated AML: Study Design

- Ongoing, single-arm, open-label phase I/II trial

All: Patients with *FLT3*-mutated disease

- **R/R cohort**: R/R AML or high-risk MDS (≥10% blasts; n = 23)
- **ND cohort**: newly diagnosed with AML and ineligible for intensive chemo (n = 5)

Induction (1 Cycle): **Quizartinib** 30-40 mg/day on Days 1-28 + **Venetoclax** 400 mg/day on Days 1-21 (Days 1-14 for patients with BM blasts ≤5% or hypoplastic BM) + **Decitabine** 20 mg/m² on Days 1-10, all given in one 28-day cycle

Consolidation (Up to 12 Cycles): **Quizartinib** 30-40 mg/day on Days 1-28* + **Venetoclax** 400 mg/day on Days 1-14† + **Decitabine** 20 mg/m² on Days 1-5, all given in 28-day cycles

*Quizartinib duration reduced to 14 days in patients with prolonged count recovery.
†Venetoclax duration reduced to 7-10 days for patients in CR based on count recovery durations.

- Primary endpoint: RP2D of quizartinib in combination with venetoclax + decitabine
- Key secondary endpoint: CR, CRi, MRD, OS

Yilmaz. ASH 2021. Abstr 370.

Slide credit: clinicaloptions.com

Gilteritinib + Venetoclax for R/R AML: Study Design

- Multicenter, open-label, single-arm phase Ib trial

Patients with R/R AML with *FLT3*^{wt} or *FLT3*^{mut}, ≥1 prior line of therapy, WBC count ≤25 x 10⁹/L at study drug initiation, and ECOG PS 0-2 (N = 54)

Dose-Escalation Phase (*FLT3*^{wt} and *FLT3*^{mut}): Gilt 80 mg + Ven 400 mg (n = 7); Gilt 120 mg + Ven 400 mg (n = 8) — *DLT monitoring*

Dose-Expansion Phase (*FLT3*^{mut} Only): Gilt 120 mg (RP2D) + Ven 400 mg (n = 46) — *DLT monitoring*

Patients followed monthly post treatment for max. 1 yr after last treatment dose

- Primary endpoint: mCRc (CR + CRp + CRi + MLFS)
- Secondary endpoints: CR + CRh, DoR of mCRc
- Exploratory endpoints: OS in *FLT3*^{mut} subgroups, allelic burden of *FLT3* mutations

Daver. ASH 2021. Abstr 691.

Slide credit: clinicaloptions.com

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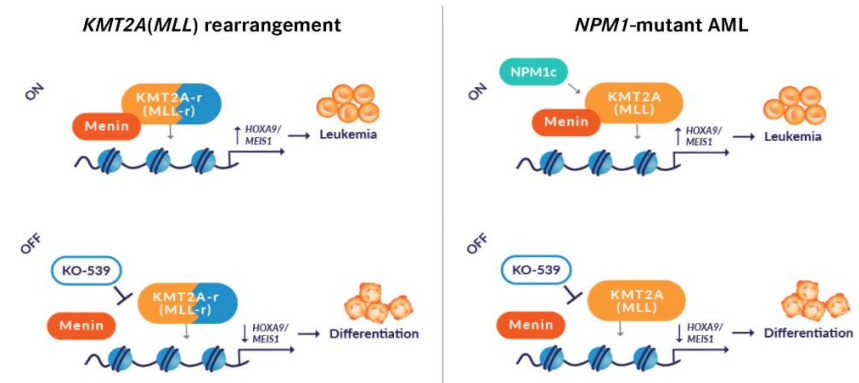
New exciting pathway targets-MENIN-inhibitors

FIGURE. Targeting Menin-MLL Interactions



Targeting the menin-KMT2A(MLL) interaction to reverse epigenetic dysregulation in MLL-rearranged AML

A central role for menin-KMT2A(MLL) interaction in epigenetic dysregulation in *NPM1*-mutant AML

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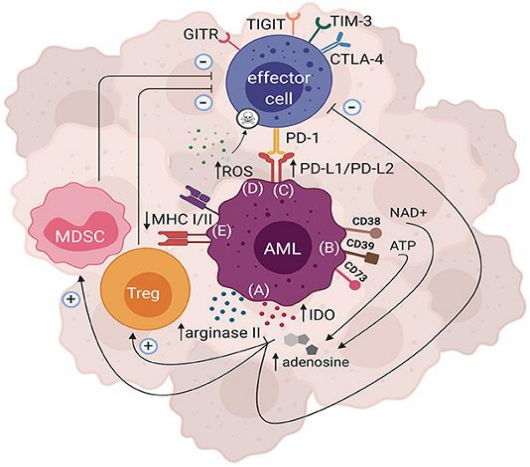
CAR-T therapy in AML-big challenges to overcome

While complete ablation of CD19-expressing B cells, both cancerous and healthy, is clinically tolerated, ***the primary challenge limiting the use of CAR T cells in myeloid malignancies is the absence of a dispensable antigen, as myeloid antigens are often co-expressed on normal hematopoietic stem/progenitor cells (HSPCs), depletion of which would lead to intolerable myeloablation***.



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Talking to your AML treatment team about what matters to you

When in doubt-ASK.

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Talking to your team about AML therapy questions

- Treatment side effects
- Quality of life
- Financial impact on your life/family
- CLINICAL TRIALS
- Second opinion-to do or not to do ?

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AML in the era of COVID19

The good, the bad , the ugly

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COVID 19 in AML-vaccine recommendations

- People ages 12 years and older who are moderately or severely immunocompromised **should receive a total of 4 doses** of COVID-19 vaccine. The 4 doses are made up of a primary series of 3 doses of an mRNA COVID-19 vaccine, plus 1 booster of an mRNA COVID-19 vaccine (4th dose).

Primary Series COVID-19 Vaccine	Age Group	Number of Doses to Complete Primary Series and Timing	Booster and Timing
Pfizer-BioNTech	12+ years	3 doses 2nd dose given 3 weeks (21 days) after 1st dose 3rd dose given at least 4 weeks (28 days) after 2nd dose	1 booster Given at least 3 months after 3rd dose
Moderna	18+ years	3 doses 2nd dose given 4 weeks (28 days) after 1st dose 3rd dose given at least 4 weeks (28 days) after 2nd dose	1 booster Given at least 3 months after 3rd dose

*Although mRNA vaccines are preferred for people 18 years and older, J&J/Janssen COVID-19 vaccine may be considered in some situations.

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33 https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html?s_cid=10483:immunocompromised%20and%20covid%20vaccine:sem.ga:p:RG:GM:gen:PTN:FY21

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In summary

- AML in a treatable and in specific situations curable blood cancer
- Treatments are extremely varied depending on the type of AML and the patient, as are the side effects, response and survival rates with these treatments.
- CLINICAL TRIALS are an option at diagnosis and every stage of the disease- ask questions about these to your team. Multiple resources available about available trials close to you.
- Quality of life is ALWAYS important –up to you as a patient how to define your expectations to align with your goals.
- We are a TEAM-we will never stop looking for a cure.

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- **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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Monday to Friday, 10 a.m. to 7 p.m. ET
Email: **www.LLS.org/ContactUs**
All email messages are answered within one business day.

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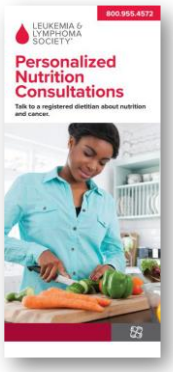

NUTRITION CONSULTATIONS
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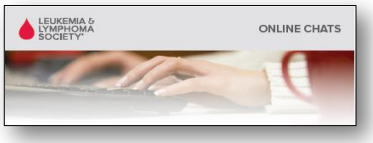

Online Chats
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Education Videos
View our free education videos on disease, treatment, and survivorship. To view all patient videos, please visit **www.LLS.org/EducationVideos**.

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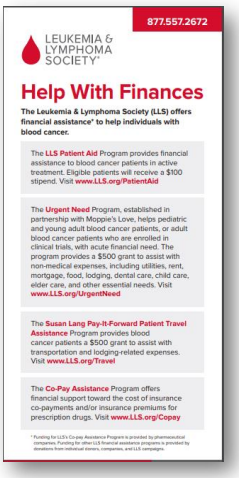
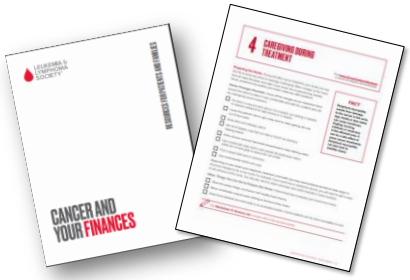


The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancer: **www.LLS.org/Finances**



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

LEUKEMIA & LYMPHOMA SOCIETY®

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THANK YOU
We have one goal: A world without blood cancers
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