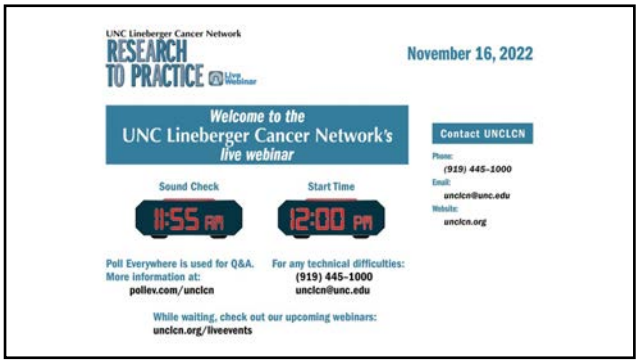
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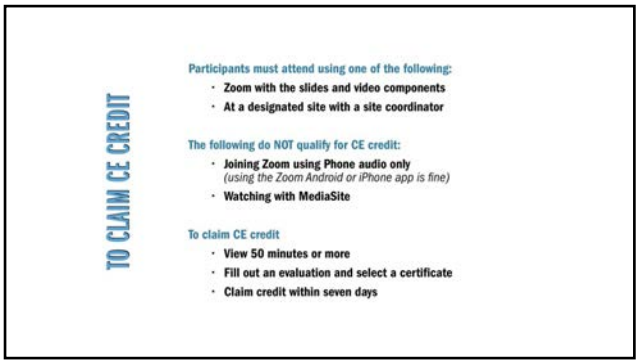
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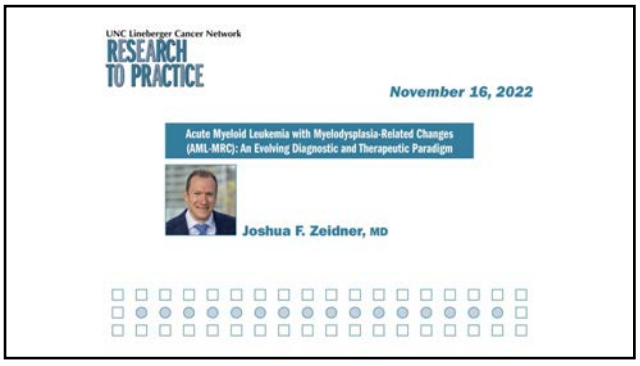
UNC Lineberger Cancer Network
RESEARCH TO PRACTICE
November 16, 2022
Acute Myeloid Leukemia with Myelodysplasia-Related Changes (AML-MRC): An Evolving Diagnostic and Therapeutic Paradigm
Joshua F. Zeidner, MD

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OUR PRESENTER

Joshua F. Zeidner, MD

Joshua F. Zeidner, MD, is an Associate Professor of Medicine at the University of North Carolina School of Medicine, Lineberger Comprehensive Cancer Center.

Dr. Zeidner is the inaugural Director of Clinical Cancer Research Commercial Integration at Lineberger Comprehensive Cancer Center and serves as the Section Chief of Leukemia Research and Associate Chief of Research within the Division of Hematology at University of North Carolina.

Dr. Zeidner's research focuses on drug development, early phase clinical trials, and innovative therapeutic strategies in acute myeloid leukemia and myelodysplastic syndromes with a particular interest in immunotherapy and apoptotic pathways.

He has designed and developed multiple Phase I-II studies in AML and serves as Principal Investigator on a multitude of cutting edge studies in AML and MDS.

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DISCLOSURES

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Acute Myeloid Leukemia with Myelodysplasia-Related Changes (AML-MRC): An Evolving Diagnostic and Therapeutic Paradigm

Joshua Zeidner, MD
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Disclosures

- Honoraria/Advisory Boards: AbbVie, Bristol Myers Squibb, Daiichi Sankyo, Genentech, Gilead, Immunogen, Servier, Shattuck Labs
- Consulting: AbbVie, Foghorn, Gilead, Servier
- Research Funding: AbbVie, Arog, Astex, Gilead, Merck, Stemline, Takeda

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Objectives

- To describe the diagnostic work-up and criteria of AML
- To describe the different subclassifications of AML based on the World Health Organization (WHO) and International Consensus Classification (ICC)
- To list prognosis, treatment options and emerging therapies for AML-MRC

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Case #1

- A 66 year old male with a past medical history significant for hypertension and and well controlled diabetes mellitus-2 presents to his Primary Care Physician after gradual worsening symptoms of fatigue, lethargy, anorexia, and weight loss over 1-2 months.
- CBC with differential performed revealing:
  - WBC: 2.2x10^9/L, Hemoglobin: 7.8 g/dL, Platelets: 31x10^9/L
  - Absolute Neutrophil Count (ANC): 0.6x10^9/L
- Peripheral blood smear reviewed revealing dysplastic granulocytes and immature cells
- Referred to Hematologist/Oncologist and bone marrow biopsy performed
  - Hypercellular marrow (>95%) with 28% myeloblasts
  - Flow cytometry reveals myeloid immunophenotype- CD34, CD33, CD13, MPO positive

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Case #1 Question

- Despite increasing symptoms over the past 1-2 months, patient has a good ECOG PS (ECOG PS = 1).
- No evidence of tumor lysis syndrome or other complications
- **What is the best next step in the management of this patient?**
  - A) 7+3 induction chemotherapy
  - B) Azacitidine + Venetoclax
  - C) CPX-351 induction therapy
  - D) Provide transfusion support and supportive care while awaiting further diagnostic information

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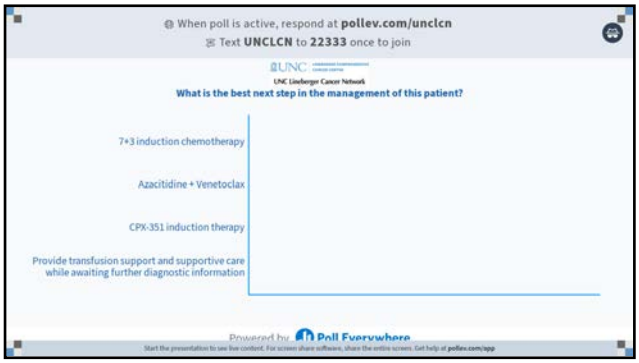

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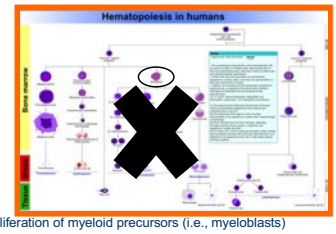
What is AML?



- Clonal proliferation of myeloid precursors (i.e., myeloblasts)
  - Reduced capacity for differentiation
  - Reduced capacity for cell death

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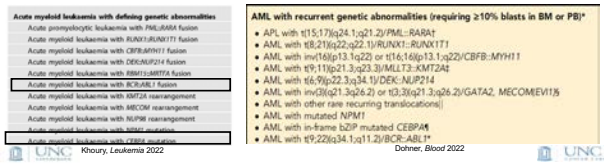
Diagnosis of AML

- Has evolved-> Increasingly incorporating genomic abnormalities into definition
- Traditionally defined as ≥20% myeloblasts in PB or BM
  - Dx dependent on immunophenotype of **myeloblasts** by flow cytometry
  - Updated 2022 criteria (WHO & ICC) recognize the subjectivity of blast %
  - **MDS/AML** category of 10-19% blasts (ICC)

WHO Classification versus ICC/ELN Criteria



Khoury, *Leukemia* 2022

Dohner, *Blood* 2022

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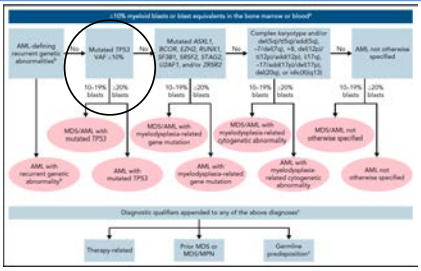
Classification of AML



Dohner, *Blood* 2022

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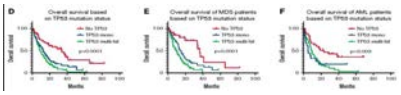
TP53 Mutated AML

- TP53 mutation- distinct genomic entity recognized by WHO and ICC
- Approximately 10% of MDS/AML- highly associated with complex karyotype
- Not all TP53 mutations created "equal"
- **Biallelic/Multi-Hit**
  - ≥2 TP53 mutations, mutation + loss of 17p, LOH at 17p, and/or high VAF (>50%)
  - Outcomes worse in MDS
- Harmonization of MDS (≥10% blasts) and AML w/ TP53 mutations
  - ICC category of MDS/AML w/ TP53 mutation- equally poor outcomes

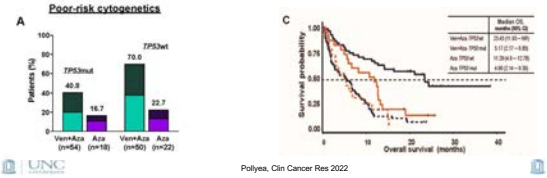


Weinberg, Blood Adv 2022

20

TP53 Mutated AML- Poor Outcomes w/ Aza/Ven

- High unmet need- poor outcomes w/ intensive chemo and Aza/Ven
- Identification of TP53 mutation critical for tailoring Tx
- Clinical trials imperative for TP53 mut MDS/AML



Pollyea, Clin Cancer Res 2022

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Risk Stratification of AML in 2022

Table 6. 2022 European LeukemiaNet (ELN) risk classification by genetics at initial diagnosis[a]

Risk Category[b]	Genetic Abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*[c] • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*[c] • Mutated *NPM1*[d,e] without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*
Intermediate	• Mutated *NPM1*[d,e] with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD • t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*[c] • 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[f] • t(9;22)(q34.1;q11.23)/*BCR::ABL1* • t(5;16)(p11.p13)/*RBA::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,[g] monosomal karyotype[g] • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2* • Mutated *TP53*[h]

Dohner, *Blood* 2022

22

Secondary AML versus AML-MRC

- **Secondary AML:** therapy-related AML (t-AML) or AML from preexisting myeloid neoplasm
- **AML-MRC:** WHO-defined subgroup- 2016 definition
  - AML from preexisting MDS/CMML
  - AML with specific MDS-related cytogenetic abnormalities
  - AML with multilineage dysplasia
    - ≥50% dysplasia in ≥2 lineages in diagnostic BM Bx
    - No *NPM1* or biallelic *CEBPA* mutation
- 25-30% of newly dx AML pts classified as AML-MRC
- Poor outcomes with conventional therapy

Arber, *Blood* 2016; Richardson, *Curr Hematol Malig Rep* 2021

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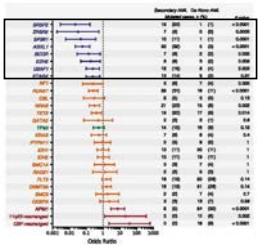
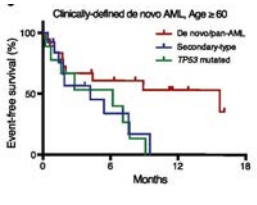
Mutations Highly Specific for Secondary AML





Lindsley, *Blood* 2015

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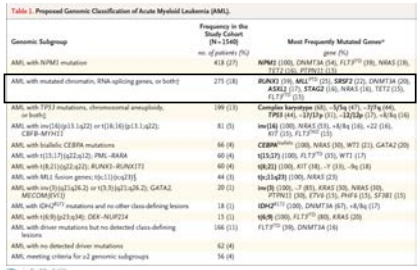
Genomic Classes of AML



- Subgroup associated with older age, worse prognosis and features of AML-MRC

Pappaemannuil, *N Engl J Med* 2016

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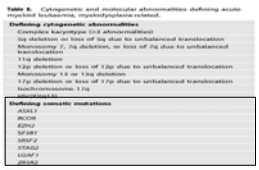
Updated AML-MRC Classification in 2022

- Now termed AML-MR (WHO), AML w/ MDS-related cytogenetics or AML w/ MDS-related gene mutations (ICC)
  - No longer includes multilineage dysplasia as diagnostic criteria
- Both WHO and ICC incorporate mutations into criteria for AML-MRC



- ICC also includes +8 and del(20q) cytogenetics & *RUNX1* mutation as MDS-defining
- Critical to obtain all diagnostic information-> Tx decisions based on classification
- AML-MRC defining mutations now considered adverse-risk by ELN

Khoury, Leukemia 2022; Arber, Blood 2022

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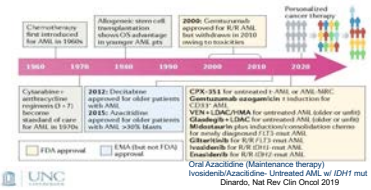
Diagnostic Algorithm of AML

- **Diagnostic BM Bx->** Manual aspirate differential
  - Cytogenetics/FISH-> turnaround time varies between 24 hours-1 week
  - Next Generation Seq (NGS) Panel
    - Essential to classify and risk stratify AML patients
    - Turnaround time- 1-2 weeks



- No longer a one-size fits all Treatment Paradigm
- Moving towards a Personalized Precision Medicine Based Tx Approach in AML
- Genomic profile provides prognostic information & Tx decisions in frontline & R/R AML

Oral Azacitidine (Maintenance therapy)
Ivosidenib/Azacitidine- Untreated AML w/ *IDH1* mut
Dinardo, Nat Rev Clin Oncol 2019

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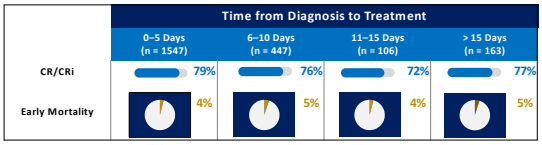
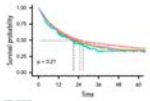
Can you Wait for Diagnostic Testing in AML?

- Retrospective database from international AML Registry (n=2,263)





- Clinical outcomes are similar in all four subgroups including younger and older patients
- Waiting for full diagnostic testing is feasible for most newly diagnosed AML cases

Rollig, *Blood* 2020

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Question #2- Case

- 66 yo M with newly diagnosed AML
- Cytogenetics reveal monosomy 7
- NGS mutational panel: *ASXL1* mutation

What is the most accurate ELN Risk Group and WHO Classification for this patient?

A) Favorable-risk; AML with MDS-Related Changes
B) Intermediate-risk; AML without maturation
C) Adverse-risk; AML Not Otherwise Specified
D) Adverse-risk; AML with MDS-Related Changes

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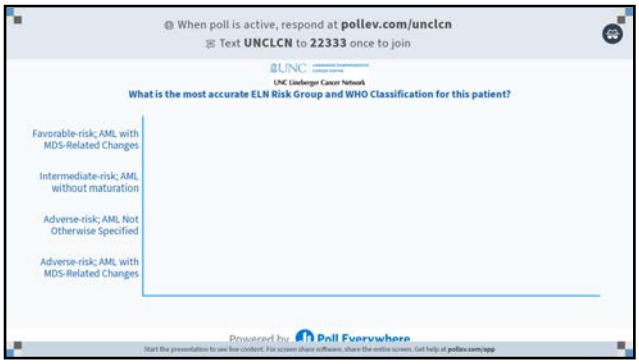

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Question #3- Case

What is the optimal frontline regimen for this patient?

A) 7+3 induction therapy
B) CPX-351 induction therapy
C) Azacitidine + Venetoclax
D) Hypomethylating agents alone
E) Clinical Trial

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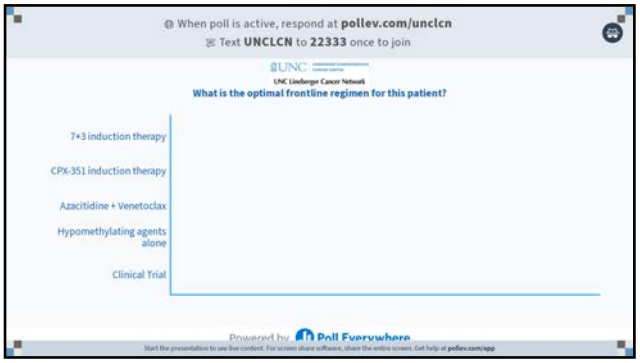

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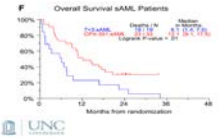
CPX-351

- Liposomal formulation of cytarabine and daunorubicin
- Initial activity & safety noted in newly diagnosed older AML pts
- **Randomized Phase 2 Study**: CPX-351 vs. 7+3 in newly diagnosed AML pts 60-75 years
  - Not restricted to specific risk groups
  - CR rates = 67% vs. 51%, p=0.07
  - Median OS = 14.7 months vs. 12.9 months; lower 60-day mortality with CPX-351



CR rates in Secondary AML: 58% vs. 32%

Lancet, Blood 2014

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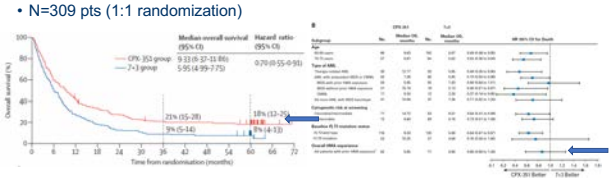
RP3 Study of CPX-351 vs. 7+3 in Newly Dx AML-MRC

- Eligibility: Therapy-related AML, AML from MDS/CMML, AML-MRC (cytogenetics)
- Age: 60-75 years, fit for intensive chemo
- N=309 pts (1:1 randomization)



- CR rates = 48% vs. 33%, p=0.016

Lancet, *Lancet Haematol* 2021

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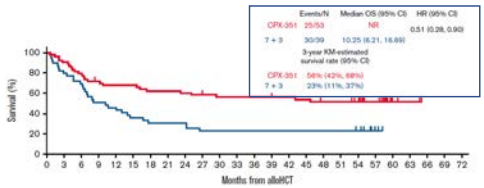
CPX-351 and Allogeneic Stem Cell Transplant



- CPX-> improved outcomes at time of AlloBMT vs. 7+3
- Lower incidence of non-relapse mortality
- Higher rates of alloBMT in CPX (higher CR rates)

Uy, Blood Adv 2022

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CPX-351 SOC for AML-MRC

- CPX-351 FDA-approved for management of AML-MRC, therapy-related AML, or AML from preexisting MDS/CMML in 2017
- No age restriction by label but landmark study only conferred benefit in **60-75 yrs**
  - Best outcomes in pts who achieve CR followed by alloBMT
- Studies ongoing in other pt populations
- 7+3 not a useful comparator- dismal outcomes in control group
  - Unclear how CPX compares with Azacitidine + Venetoclax- NCT04801797 (PI: Fathi, MGH)
- Evolving definition of AML-MRC-> which genomic subgroups truly benefit from CPX?
  - **TP53 mutations do not appear to benefit from CPX**
- CPX moves the needle slightly- outcomes still poor in AML-MRC

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How Do We Improve Outcomes in AML-MRC?

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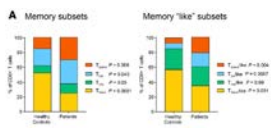
Immune System is Dysfunctional in AML

- Multiple immune aberrations exist in AML at Dx-> immune suppression, exhaustion, and senescence
  - Dysfunctional T effector cells
  - Increased expression of coinhibitory molecules and decreased expression of co-stimulatory genes
  - Increased Tregs
  - Dysfunctional and deficient NK cells
  - Tolerogenic dendritic cells and antigen presenting cells



- ↑ % of senescent and exhausted T cells at diagnosis-> functionally impaired
- Dysfunctional immune state reversible in CR but persists in pts without response to induction chemo

Ustun, Blood 2011; Kanakry, Blood 2010; Knaus, JCI Insight 2018

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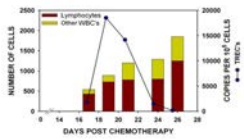
Early Lymphocyte Recovery (ELR)-> Enriched for Tregs

- 20 AML pts undergoing intensive induction therapy
- Serially assessed for T cell subsets during ELR (WBC >0.2x10^9/L above nadir)
- Predominance of actively proliferating (high Ki67) Tregs during ELR irrespective of response



- **Hypothesis**: Immune modulation at the time of ELR after induction chemo may mitigate dysfunctional immune phenotype & improve clinical activity of chemo

Kanakry, Blood 2011

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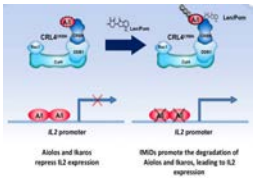
Pomalidomide

- Pomalidomide- 2nd generation IMiD approved for multiple myeloma



- IMiD's = protean immune-stimulation
- Potentiates co-stimulation of T cells
- Down-regulates co-inhibitory receptors
- Inhibits Tregs
- Enhances NK cell activity
- Inhibits angiogenesis

- Hypothesis: Pomalidomide at ELR will mitigate immune dysfunctional phenotype and increase clinical activity of induction chemotherapy

Gandhi AK, Br J Haematol 2013; Zeidner JF, Curr Drug Tar 2017

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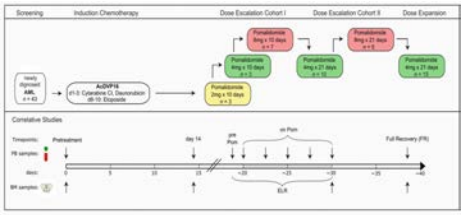
NCI-9524: Phase 1 Study of Induction Chemo Followed by Pomalidomide in Newly Dx AML



- Eligibility: Newly Dx AML or HR-MDS (>10% blasts)
- 18-65 years, excluded favorable-risk cytogenetics

Zeidner, Leukemia 2020

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Consort Diagram

Zeidner, Leukemia 2020

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Patient Characteristics

Patient Characteristics	High-Risk MDS (N=4)	AML (N=39)	Total (N=43)
Age- Median (Range)	50 (35-63)	54 (21-65)	54 (21-65)
Age ≥60 Years	1 (25%)	11 (28%)	12 (28%)
Male/Female	2/2	16/23	18/25
BM Blast %- Median (Range)	17% (15-18%)	55% (11-95%)	54% (11-95%)
Peak WBC- Median (Range)	3.1 (0.9-5.3)	12.7 (1.0-227.3)	6.1 (0.9-227.3)
Secondary AML AML w/ MDS-Related Changes	N/A N/A	14 (36%) 13 (33%)	14 (33%) 13 (30%)
SWOG Cytogenetic Risk Favorable Intermediate	 0 1 (25%)	 0 23 (59%)	 0 24 (56%)
Unfavorable	3 (75%)	14 (36%)	17 (40%)
Unknown	0	2 (5%)	2 (5%)
NPM1 mutations	0	8 (21%)	8 (19%)
FLT3-ITD Mutations	0	4 (10%)	4 (9%)

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Safety Data

- Median time to Pom = 21 days (Range: 15-30 days)
  - Cohort 2: DLT's: 8 mg x 21 days = Grade 3 hepatitis and Grade 4 respiratory failure
  - MTD = 4 mg x 21 days
- Most common toxicities = rash (16%), hepatitis (14%), mucositis (14%)
- 14 pts (33%) discontinued Pom early
- Median time to full hematologic recovery 38 days

Non-Hematologic Adverse Events

Adverse Event	2 mg x 10 days (n=3)	4 mg x 10 days (n=3)	8 mg x 10 days (n=7)	4 mg x 21 days (n=25)	8 mg x 21 days (n=5)
Infectious Febrile neutropenia Lung infection Sepsis		 1 1	3	5 1	1
Electrolytes Hypokalemia				1	
Hepatic ALT elevation AST elevation				1	 1 1
Pulmonary Hypoxia Respiratory Failure				1	1
Renal AKI				1	
General Fatigue Maculopapular Rash				1 5	1

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Clinical Activity of AcDVP16 + Pomalidomide

Response Characteristics	High-Risk MDS	AML	Overall
CR CRi	3/4 (75%) 0	28/39 (72%) 2/39 (5%)	31/43 (72%) 2/43 (5%)
CR + CRi	2/4 (50%)	30/39 (77%)	33/43 (77%)
MRD negative CR/CRi	1/4 (25%)	18/39 (46%)	19/43 (44%)
Secondary AML	N/A	10/14 (71%)	10/14 (71%)
AML with MDS-Related Changes	N/A	11/13 (85%)	11/13 (85%)
<60 years ≥60 years	2/3 (67%) 1/1 (100%)	21/28 (75%) 9/11 (82%)	23/31 (74%) 10/12 (83%)
SWOG Cytogenetics Risk Favorable Intermediate	 N/A 7/1	 N/A 16/23 (70%)	 N/A 17/25 (68%)
Unfavorable	2/3 (67%)	12/14 (86%)	14/17 (82%)
Unknown	N/A	2/2 (100%)	2/2 (100%)
Allogeneic SCT	3/4 (75%)	23/39 (59%)	26/43 (60%)
60 day mortality	0	1/39 (3%)	1/43 (2%)

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Outcomes Compared with Historical Controls

CR Subsets	Historical Controls (AcDVP16)[1]	AcDVP16 + Pom[2]
Median Age	52 (20-74)	54 (21-65)
Overall CR/CRi	205/301 (68%)	30/39 (77%)
Age ≥60 years	45/79 (57%)	9/11 (82%)
Secondary AML	51/96 (53%)	10/14 (71%)
Cytogenetics		
Intermediate	133/180 (60%)	16/23 (70%)
Unfavorable	49/94 (52%)	12/14 (86%)
Non-Favorable	182/274 (66%)	30/39 (77%)
Median OS	17.2 months	33.8 months
Median DFS	15.0 months	27.1 months
Unfavorable Cytogenetics		
Median OS	8.2 months	19.7 months
Median DFS	9.2 months	8.2 months

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Summary of Phase 1 Results

- Pomalidomide is safe and feasible after induction therapy for AML
  - MTD = 4 mg x 21 days at ELR
- Addition of Pom to induction therapy-> encouraging clinical activity
  - CR rates = 77%, Median OS = 33 months w/o appreciable increase in early mortality
  - Compares favorably with historical controls of AcDVP16 induction w/o Pomalidomide
- Correlates: Pom-> Robust decrease in Aiolos expression, promoted T cell differentiation, proliferation and cytokine production
  - Pom may augment immune activation and abrogate T cell exhaustion/senescence after induction chemo

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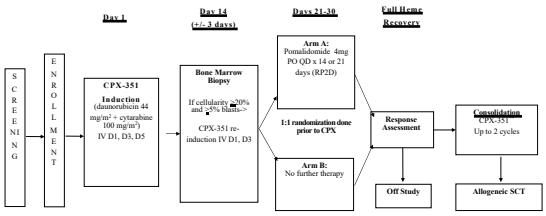
NCI-10434: Randomized Phase 2 Study of CPX-351 +/- Pom in Newly Dx AML-MRC



- **Eligibility: 18-75 years with AML-MRC or t-AML**
- **Safety Run-In** to evaluate Pom 4 mg x 14 days or 21 days

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NCI-10434: Randomized Phase 2 Study of CPX-351 +/- Pom in Newly Dx AML-MRC

- 18-75 years with newly diagnosed AML (≥20% blasts in blood or BM)
- Must meet following criteria:
  - Therapy-related AML
  - AML-MRC- incorporating 2022 WHO/ICC Guidelines with cytogenetics and/or mutations
  - Previous history of myeloid malignancy
- No prior treatment for AML other than hydroxyurea
- Fit for intensive chemo- adequate organ function
  - EF >50%, AST/ALT <5xULN, total bilirubin <1.5xULN, Creatinine clearance ≥30 ml/min

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NCI-10434: Statistical Design

- **Primary Endpoint(s):**
  - 1) To establish recommended phase II dose of pomalidomide after CPX-351 induction
  - 2) To compare overall CR rates between CPX-351 + Pom vs. CPX
    - Null hypothesis: 48% CR/CRi rate with CPX-351
    - Alternative hypothesis: 77.3% CR/CRi rate with CPX-351 + Pom
    - 80% Power with one-sided type 1 error rate = 5%
    - N= 78 pts (1:1 randomization)
- **Trial Design:**
  - 1st stage = 16 pts in each arm- trial may stop for futility if one-sided p >0.52
  - Feasibility Analysis
  - Continuous Monitoring for Toxicity

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NCI-10434: Translational Correlates

- **Biomarker** analysis to assess for predictors of response to Pom
  - Comprehensive NGS mutational panel on all pre-treatment BM samples (Foundation One Heme)
  - Aiolos- transcription factor selectively ubiquinated by Cereblon during Pom administration
    - To assess whether Aiolos expression in PB and BM at baseline associated w/ CR to CPX-351 + Pom
  - Immune correlates of response by flow cytometry
    - To assess whether pre-treatment expression of T cell subsets in PB and BM associated w/ CR to CPX-351 + Pom
- **MRD Analysis**
  - All pts will have uniform flow cytometry MRD at response (Hematologics)
  - DNA Seq at response to assess depth of CR w/ CPX-351 + Pom vs. CPX-351

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AML-MRC Future Directions

- **Can addition of Venetoclax improve outcomes in AML-MRC?**
  - Aza/Ven SOC for older unfit AML
  - Older fit AML pts appear to have similar outcomes b/w CPX and Aza/Ven
  - Intensive chemo (FLAG-IDA) + Ven promising induction backbone
- **Optimal Treatment for AML-MRC after previous exposure to HMA's**
  - No SOC, intensive chemo-> dismal outcomes
  - Aza/Ven excluded pts w/ previous HMA's
  - TAGALONG Study: Phase II study of Tagraxofusp +/- Azacitidine (NCT05442216)
- **Optimal Treatment for AML-MRC <60 years?**
  - Limited data of CPX in <60 years
  - Real World Data suggests favorable outcomes w/ CPX
  - NCRI AML19- FLAG-IDA vs. CPX in newly diagnosed adverse-risk AML

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Conclusions

- Definition of AML has evolved to incorporate genomics-> more refined subclassifications
- AML treatment armantarium expanding
  - No longer a one-size fits all Tx paradigm
  - Moving closer to a Precision-Medicine based Individualized Treatment Approach
- AML-MRC- now includes both cytogenetics and molecular mutations
  - Critical to obtain diagnostic information (cytogenetics, FISH, NGS) prior to Tx initiation
- CPX-351 is SOC for fit AML-MRC pts-> outcomes are still poor
- Clinical trials are imperative for AML

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- Questions: Email: Joshua_Zeidner@med.unc.edu
- Twitter: @LeukDocJZ

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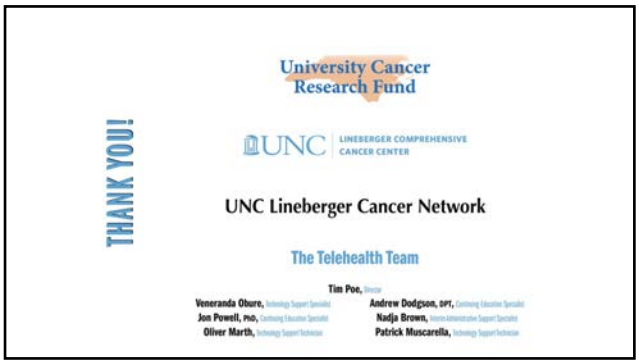
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November 30
12:00 PM
Promoting Equity in American Indian Cancer Control
Donald Warne, MD, MPH
December 7
12:00 PM
Occupational Therapy for Cancer Survivors
Farrell Wiggins, OTR/L
Alexis Petteway, OT
December 14
4:00 PM
GVHD: An Overview of Graft vs Host Disease Post Hematopoietic Stem Cell Transplant
Megan McElfresh, PA-C
January 22
12:00 PM
Overview of CCSP and All of Their Available Resources for Patients
Linnea Van Pelt, BSN, RN, CMSRN, OCN
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