Bridging to Transplant
in the Modern Era of AML Treatment

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Faculty Disclosure

Dr. James Foran has received honoraria as a consultant for Revolution Medicines, Inc. and honoraria related to formal advisory activities from Bristol-Myers Squibb Company, Novartis AG, Pfizer Inc. and SERVIER. His institution has received grant support related to research activities from AbbVie Inc., Actinium Pharmaceuticals, Inc., Aprea Therapeutics, Aptose Biosciences, Boehringer Ingelheim GmbH, H3 Biomedicine Inc., Kura Oncology, Inc., Takeda Oncology, Trillium Therapeutics Inc., and Xencor.

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Planning Committee Disclosures

The individuals listed below from MediCom Worldwide, Inc. reported the following for this activity: Joan Meyer, RN, MHA, Executive Director, Isabelle Vacher, Vice President of Educational Strategy, Wilma Guerra, Program Director, and Andrea Mathis, Project Manager, have no relevant financial relationships.

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Learning Objectives

Upon completion of this educational activity, participants should be able to:

- Address clinician- and patient-specific barriers to transplantation in older patients with relapsed or refractory AML
- Utilize appropriate strategies for bridging older patients with relapsed or refractory AML to transplant after discussing the risks and benefits with older patients and their families
- Refer appropriate older patients residing in Florida and Georgia to geographically available clinical trials evaluating bridging strategies from relapsed or refractory AML to transplant, providing information and resources that address specific concerns about trial participation

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Introduction

- Although AML is one of the most common types is leukemia and although it can occur in patients younger than 45 year, it is most often seen in older patients
- Florida has a population approaching 20 million, and people over 60 make up nearly 23 percent of that population
- The average age of people when they are first diagnosed with AML is about 68, so it is not surprising that the incidence of AML in Florida is one of the highest in the country

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Introduction (cont)

- Since allogeneic transplant is the only curative option for AML patients, including elderly patients, the major challenge is how to bridge these individuals to transplant while obtaining remission, but also while maintaining good condition and avoiding severe complications
- This program will focus on the current guidance regarding the treatment of older AML patients and the available clinical trials in Florida and the Southeastern region that investigating ways to bridge these patients to transplant

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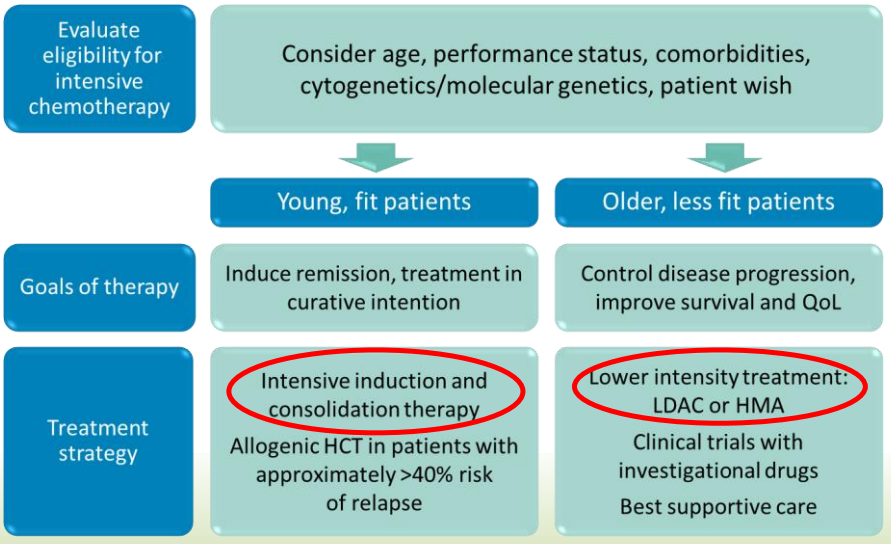
Algorithm of AML Therapy (*circa* 2017)



Döhner H, et al. *Blood.* 2017;129(4):424-447.

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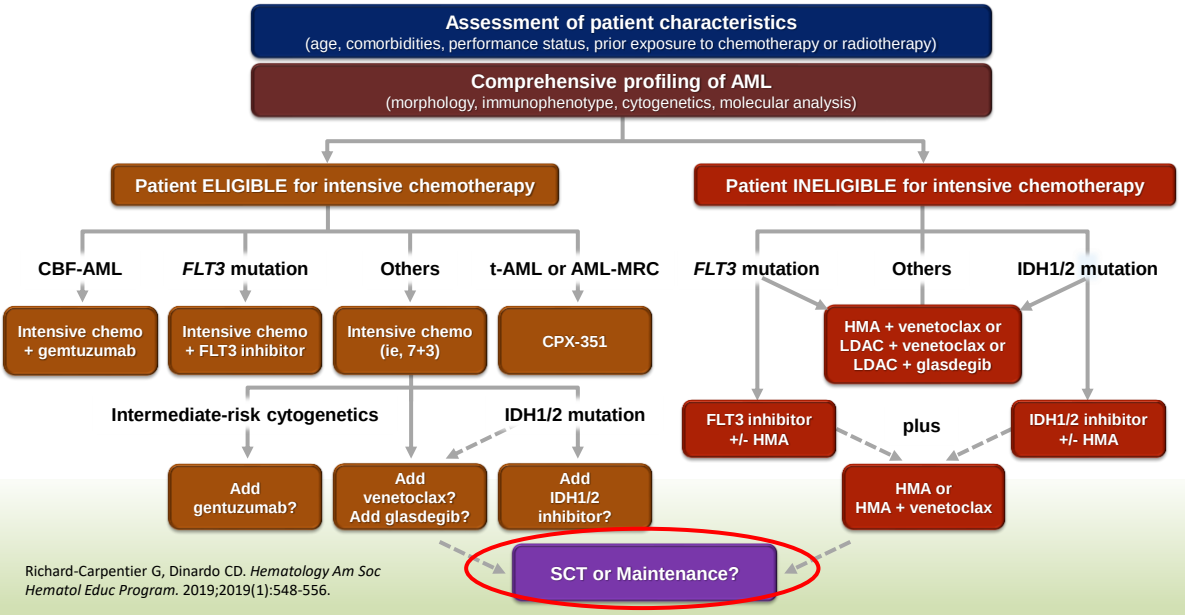
Evolving Diagnostic and Treatment Paradigm for Newly Dx AML



Richard-Carpentier G, Dinardo CD. *Hematology Am Soc Hematol Educ Program.* 2019;2019(1):548-556.

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Goals of Therapy: AML in Older Adults

Intensive Therapy
- Fitter patients
- Finite, curative intent
- Consolidation strategy – favors AlloBMT if adverse risk

Low Intensity Therapy
- Improve survival, but non-curative
- Lower remission rates historically – better with AZA/Ven
- Indefinite duration of therapy – until intolerance or failure

➢ *Some patients may become eligible for curative therapy*

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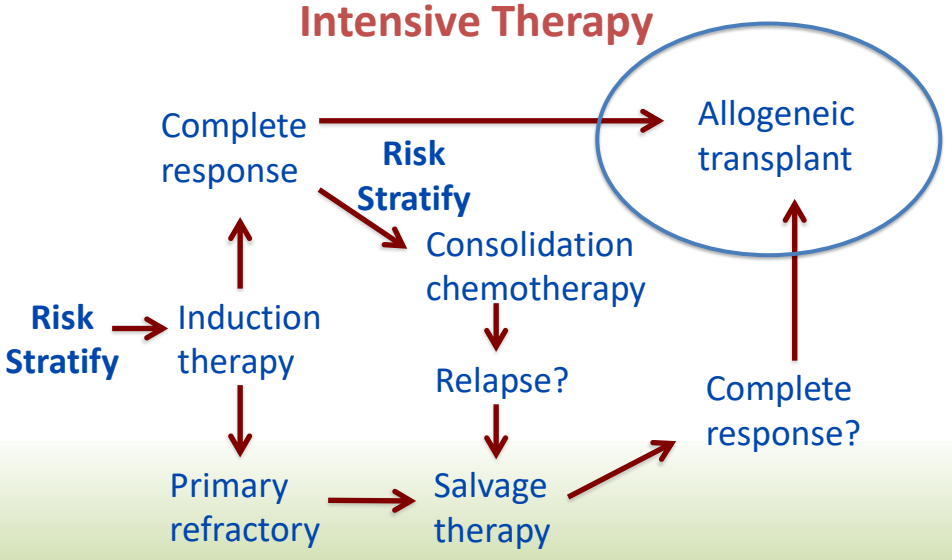
Modern Treatment Paradigm of AML

Intensive Therapy



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AlloBMT in 1st Remission of AML
Impact in Higher Risk Groups

- *FLT3* mutation after induction with 7+3 and Midostaurin
- Secondary AML after CPX-351 (Vyxeos™)
- *TP53* mutations after decitabine induction
- Low intensity therapy (ie, not curative intent)

- ***A Bridge to Transplant***

(ie, induction as a bridge to AlloBMT with curative intent, when standard therapy itself does not provide long-term DFS for most)

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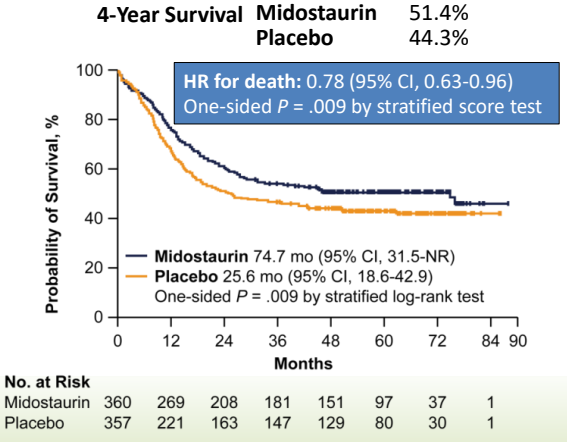
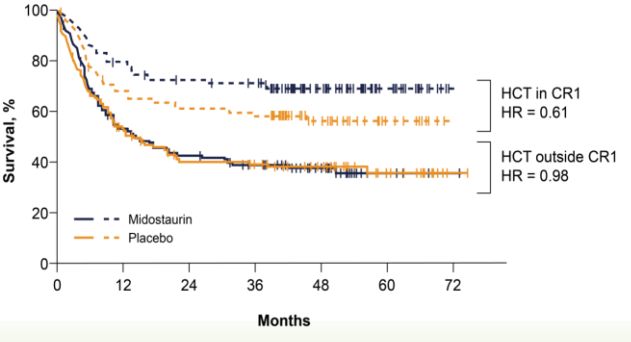
FLT3 Mutation ~30% Younger, 15% Older Patients
RATIFY Study - Overall Survival

All Patients[1]



Transplanted Patients[2]



1. Stone RM, et al. *N Engl J Med*. 2017;377:454-464.
2. Stone RM, et al. *Blood.* 2015;126(23):6.

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CPX-351 in High-Risk/Secondary AML: Phase 3 Trial Design

Key Eligibility
- Previously untreated
- Aged 60-75 years
- Able to tolerate intensive therapy
- PS 0-2

CPX-351
n = 153

Stratifications
- Therapy-related AML
- AML with history of MDS ± prior HMA therapy
- AML with history of CMML
- De novo AML with MDS karyotype
- Aged 60-69 years
- Aged 70-75 years

7+3
n = 156

Reinduction
CPX-351
days 1 and 3
***or* 5+2**

Induction
(1-2 cycles)

Patients in CR or Cri:
Consolidation
(1-2 cycles)

Follow-Up
- Death *or*
- 5 years

Primary endpoint: OS

Induction
- CPX-351 44 mg/100 mg/m^2 IV days 1, 3, and 5
- Cytarabine 100 mg/m^2/d x 7 + daunorubicin 60 mg/m^2/d x 3

Consolidation
- CPX-351 29 mg/65 mg/m^2 IV days 1 and 3
- Cytarabine 100 mg/m^2/d x 5 + daunorubicin 60 mg/m^2/d x 2

Lancet JE, et al. *J Clin Oncol*. 2018;36(26):2684-2692.

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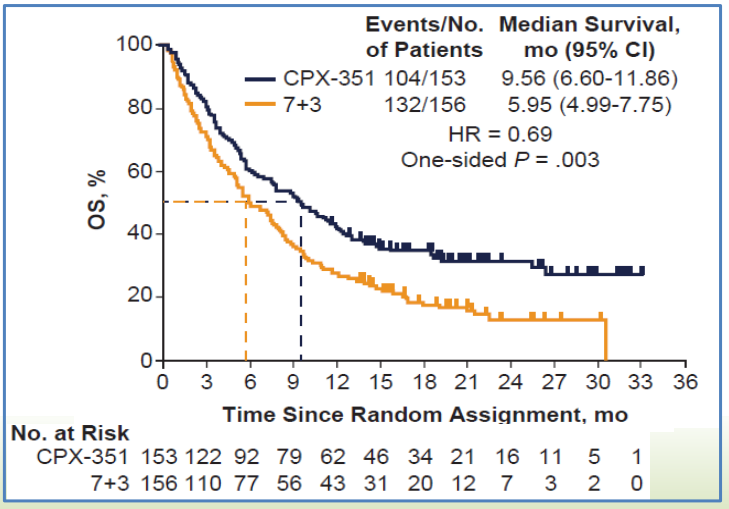
CPX-351 vs 7+3: Improvement in OS, EFS, and Remission Rate



Overall remission rate was also significantly higher:
CPX-351 47.7%
7+3 33.3%
***(P* = .016)**

Lancet JE, et al. *J Clin Oncol*. 2018;36(26):2684-2692.

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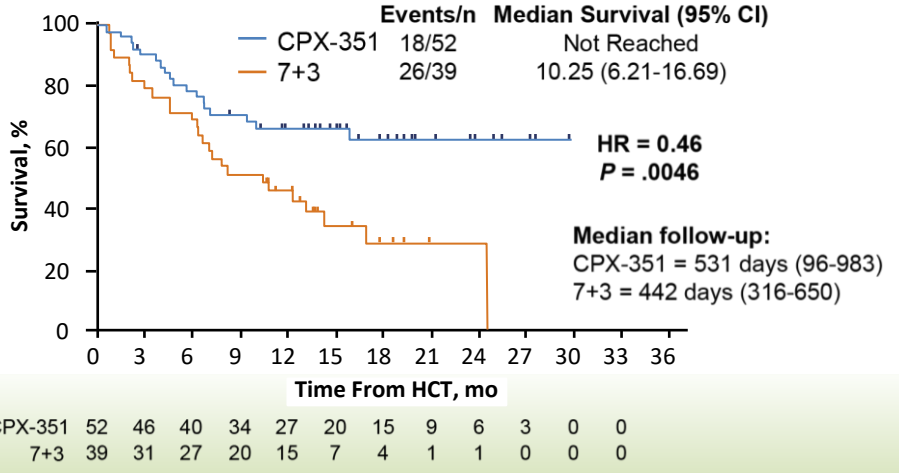
CPX-351 vs 7+3:
Survival From Time of Transplant

- **Landmark analysis shows significant OS improvement with CPX-351 from time of HCT**



Lancet JE et al. *J Clin Oncol*. 2018;36(26):2684-2692.

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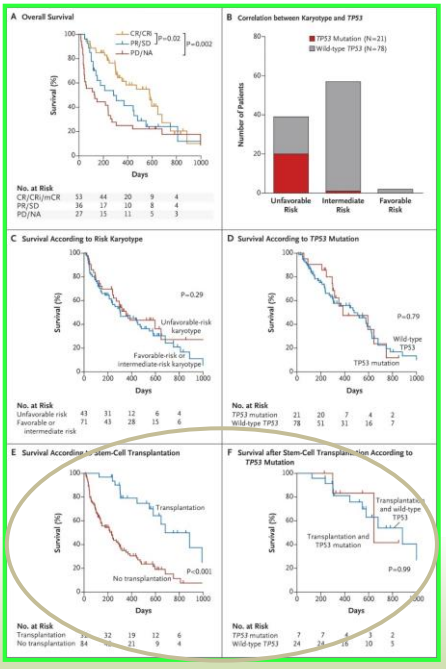

10-Day Decitabine

N=116, median age 74 yrs

- 13% CR, 33% CRi
- Higher RR in unfavorable genetic subgroups
  - **Esp. *TP53$_{mut}$***
- Median OS
  - 11.6 months [Adverse]
  - 10 months [Favorable/Intermediate risk]
- ***Survival advantage for those who were able to proceed to allogeneic HCT***

Blum W, et al. *Proc Natl Acad Sci.* 2010;107:7473-7478.
Welch JS, et al. *N Engl J Med.* 2016;375:2023-2036.

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Older Adults with AML
Low Intensity Therapy

- Most not candidates for intensive therapy
- Survival advantage of LDAC and HMA therapy (esp. azacitidine) over supportive care
- Addition of venetoclax (with AZA), or glasdegib (with LDAC) improves overall survival
- Problems:
  - Not curative
  - Cytopenias and supportive care
  - Many still do not achieve remission

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VIALE-A: Phase 3 randomized study of AZA/Venetoclax vs AZA/Placebo

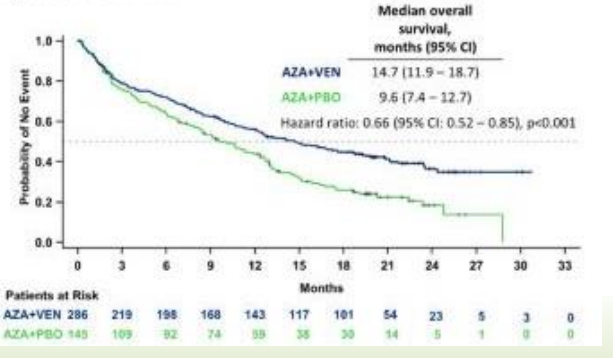
- AML *ineligible* for intensive therapy, or age >75 yrs
- N=431 patients
- Median age 76 years (range 49-91)

Table: Patient responses in treatment groups

	AZA+VEN (n=286)	AZA+PBO (n=145)	p-value
CR + CRi rate, % (95% CI)	66.4 (60.6-71.9)	28.3 (21.1-36.3)	<0.001
CR+CRi by initiation of cycle 2, % (95% CI)	43.4 (37.5-49.3)	7.6 (3.8-13.2)	<0.001
CR rate, % (95% CI)	36.7 (31.1-42.6)	17.9 (12.1-25.2)	<0.001
TI, % (95% CI)			
Red blood cells	59.8 (53.9-65.5)	35.2 (27.4-43.5)	<0.001
Platelets	68.5 (62.8-73.9)	49.7 (41.3-58.1)	<0.001
CR+CRi rates in molecular subgroups, % (95% CI)			
IDH1/2	75.4 (62.7-85.5)	10.7 (2.3-28.2)	<0.001
FLT3	72.4 (52.8-87.3)	36.4 (17.2-59.3)	0.021
NPM1	66.7 (46.0-83.5)	23.5 (6.8-49.9)	0.012
TP53	55.3 (38.3-71.4)	0	<0.001
Event free survival, months (95% CI)	9.8 (8.4–11.8)	7.0 (5.6–9.5)	<0.001

AZA+VEN: Azacitidine+Venetoclax; AZA+PBO: Azacitidine+Placebo; CR: Complete remission; CRi: CR with incomplete marrow recovery; CRh: CR with partial hematologic recovery; TI: Transfusion independence (defined as ≥ 56 days with no RBC or platelet transfusion between first and last day of treatment)

Figure. Overall survival



New Standard of Care in Older Adults with AML

DiNardo CD, et al. EHA 2020, LB2601.

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ManagingAML

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Outcomes after stem cell transplant in older patients with acute myeloid leukemia treated with venetoclax-based therapies

Keith Pratz[1], Courtney D. DiNardo[2], Martha Arellano[3], Anthony Letai[4], Michael Thirman[5], Vinod Pullarkat[6], Gail J. Roboz[7], Pamela S. Becker[8], Wan-Jen Hong[9], Qi Jiang[10], John Hayslip[10], Jalaja Potluri[10], Daniel A. Pollyea[11]

[1]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA; [2]MD Anderson Cancer Center, Houston, TX, USA; [3]Department of Hematology and Oncology, Emory University School of Medicine, Atlanta, GA, USA; [4]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [5]University of Chicago Medical Center, Chicago, IL, USA; [6]Department of Hematology and Hematopoietic Cell Transplantation and Gehr Family Center for Leukemia Research, City of Hope National Medical Center, Duarte, CA, USA; [7]Weill Medical College of Cornell University and New York-Presbyterian Hospital, New York, NY, USA; [8]Clinical Research Division, Fred Hutchinson Cancer Research Center and Division of Hematology, Department of Medicine, University of Washington School of Medicine, Seattle, WA, USA; [9]Genentech, Inc., South San Francisco, CA, USA; [10]AbbVie Inc., North Chicago, IL, USA; [11]University of Colorado School of Medicine, Aurora, CO, USA

American Society of Hematology (ASH) – 61st Annual Meeting
Orlando, FL, USA ● December 7, 2019

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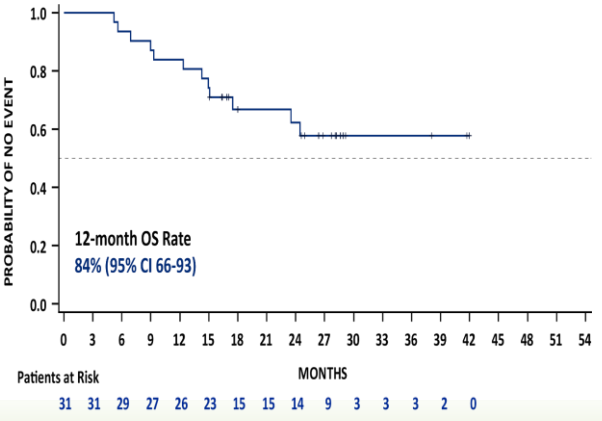
Outcomes of SCT in Patients After VEN-based Regimens

- **10%** 31 of 304 patients received SCT
  - 26/31 in CR/CRi
- **68%** (21/31) of patients remained alive at 12 months post-transplant
- **55%** (17/31) of all patients that had SCT had posttransplant remission of ≥12 months
  - **71%** (12/17) of those patients remained in remission for ≥2 years

VEN-based regimens, even in patients deemed unfit for intensive induction, may provide a path to curative SCT



Pratz K, et al. *Blood.* 2019;134(Supplement_1):264.

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Older Adults with AML
Allogeneic Transplantation in 1st Remission

- Results of E2906 phase III study support the use of intensive induction therapy for patients age ≥ 60 years who are fit for treatment[1]
  - Median survival almost 14 months, evidence of prolonged LFS
    - High risk of relapse remains a significant barrier to curative therapy
- Allogeneic transplantation with **Bu-Flu-ATG** reduced intensity conditioning (RIC) is feasible in *older adults* in first remission
  - 48% survival and 42% DFS at 2-years in phase 2 study[2]
    - Low rates of acute GVHD (10%) & transplant-related mortality (15%)
- Prospective study of AlloBMT in remission in patients age ≥60 years
  - Embedded in E2906 phase III trial
    - Incorporated upfront from time of diagnosis and induction therapy

Foran JM, et al. *Blood.* 2019;134(Supplement_1):115.
Devine SM, et al. *J Clin Oncol.* 2015;33:4167-4175.

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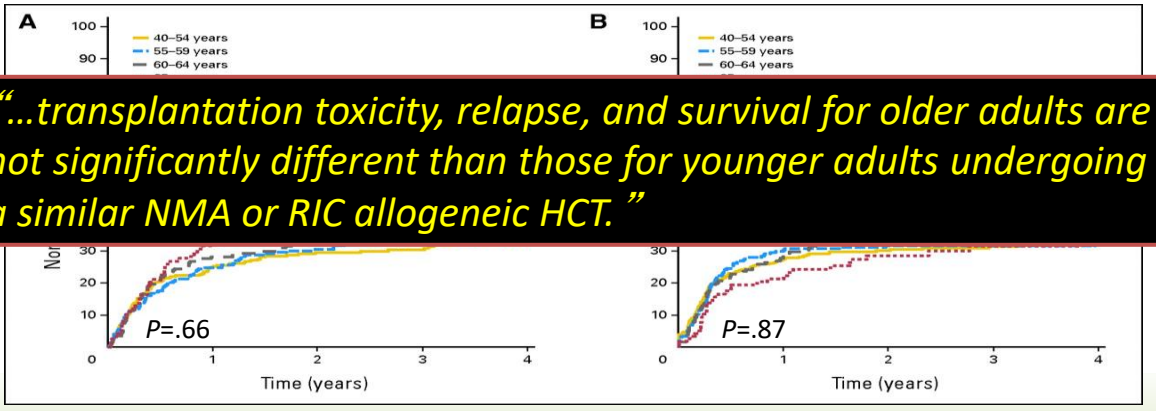
RIC/NMA AlloHCT for AML in CR1 in Patients Age >40 Years
Non-Relapse Mortality and Relapse



"…transplantation toxicity, relapse, and survival for older adults are not significantly different than those for younger adults undergoing a similar NMA or RIC allogeneic HCT."

McClune BL, et al. *J Clin Oncol.* 2010;28:1878-1887.

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Older Adults with AML
AlloBMT with Reduced Intensity Conditioning

- Significantly lower non-relapse mortality, and improvement in overall survival with RIC[1]
- No independent impact of age on outcomes from age 40-74 yrs[2]
- Feasibility of RIC with busulfan-fludarabine alloBMT in prospective study in patients age 60-74 yrs[3]
  - Age alone is not a barrier to consideration allogeneic BMT
  - Older patients have as much to gain and as much to lose
- *Patient-centered decision based on disease risk, together with evaluation at BMT center*

1. Gooley TA, et al. *N Engl J Med.* 2010;363:2091-2101.
2. McClune BL, et al. *J Clin Oncol.* 2010;28:1878-1887.
3. Devine SM, et al. *J Clin Oncol.* 2015;33:4167-4175.

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E2906 Allogeneic BMT Analysis: Patient Flow

Induction (n=727)
- Establish BMT eligibility, initiate donor search
- 2013 Amendment – include age ≥70 years

CR, CRi, MLFS (n=360)
* Centrally Confirmed

HLA Matched Donor

Donor (n=135)
(Sibling 42%, URD 58%)

No Donor (n=225)

Protocol RIC Allo BMT (n=61)
- Bu-Flu +/- ATG

Foran JM, et al. EHA 2018. Abstract S857.

Consolidation
- Maintenance decitabine randomization

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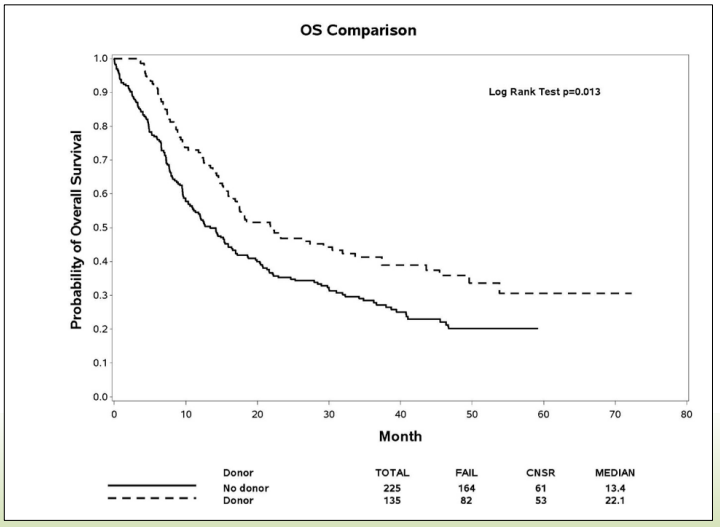
Overall Survival of Patients Achieving CR, CRi, or MLFS According to HLA-Matched Donor Status: Primary Analysis



Overall Survival	
Donor	22.1 mos
No Donor	13.4 mos
	***P*=.013**

Median Follow-up 37.7 months

Foran JM, et al. EHA 2018. Abstract S857.

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Reasons to Evaluate for Allogeneic Transplantation in Older Patients

- Provides significant reduction in risk of relapse
  - Limitations of consolidation chemotherapy strategies
    - Focus on intermediate- and higher-risk groups
- Improved outcomes in *Modern Era*
  - High resolution/molecular HLA typing for URDs
  - Reduced intensity conditioning in older adults
  - Improvements in supportive care
    - *Older adults represent increasing proportion BMT recipients
- Increased availability of donor [unrelated and alternative]
  - Haplo-identical donors with novel immunosuppression (PTCy)

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Selection at BMT Center

- Patient-centered evaluation
  - Discussion and decision together with BMT physicians
- Balance disease risks with risks/benefits of allogeneic BMT
  - Leukemia: disease risk and status
  - Patient: eligibility, HCTCI, psychosocial assessment, consent
  - System: donor availability, caregiver strategy/support, insurance
- Strict national standards, recognized indications[1]
  - FACT [Foundation for Accreditation of Cellular Therapy], every 3 years
  - Stem Cell Therapeutic Outcomes Database[2]

1. Majhail NS, et al. 2015;21:1863-1869. 2. * http://bloodcell.transplant.hrsa.gov

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Collaborative Care for Older Adults with AML

- More patients diagnosed and initiating practice in the community setting
  - Allow patients to receive treatment close to home
    - Consider transplant early in course of disease
- Relapse remains the greatest challenge
  - Goal of therapy : disease control, bridge to AlloHCT
    - Targeted therapy if candidate
- Value of clinical trials that allow access to BMT
  - Goal of improving OS in relapsed AML

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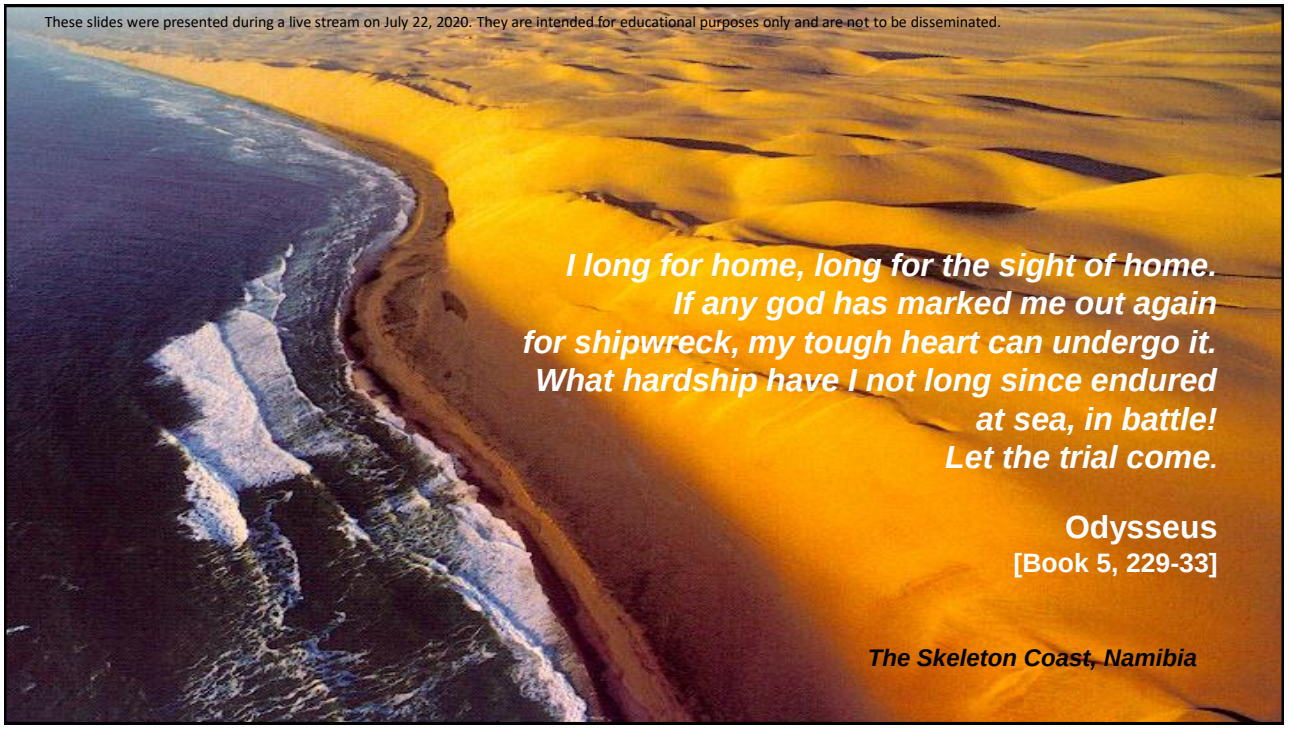

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End of Life Care for AML
Palliative and Supportive Care

- Difficult clinical management issues
  - Limitation in hospice care due to transfusion support
  - Inpatient care for infection, supportive care
  - Infection
  - Require continuation of care until end of life
- Care remains with primary oncologist
- Value of therapies that lessen transfusion burden and restore hematopoiesis, even if not curative

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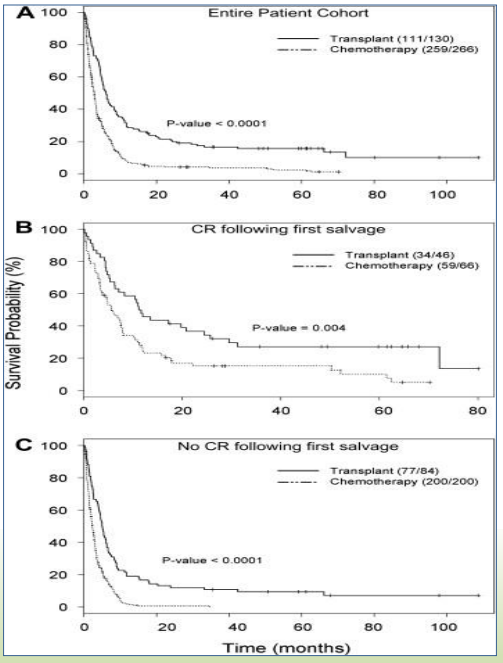

Quantifying the Survival Benefit for Allogeneic HCT in Relapsed AML

- No prospective study in relapse
- MDACC Retrospective Study 1st Relapse, 1995-2004
- **OS Advantage in all subgroups**

Armistead PM, et al.
Biol Bone Marrow Transplant. 2009;15:1431-1438.

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AML: Intensive Strategies in Relapse

- Goal is to achieve CR2
  - No clear "best" 1st-line salvage chemotherapy
  - Very few long-term survivors esp. if relapse <6-12 mo
    - Ara-C efficacy vs poor in early relapse
  - CR <u>not</u> good surrogate for survival in relapse studies

➔ Targeted agents appear superior to salvage regimen to establish CR / disease control

➔ Goal is bridge to allogeneic transplantation

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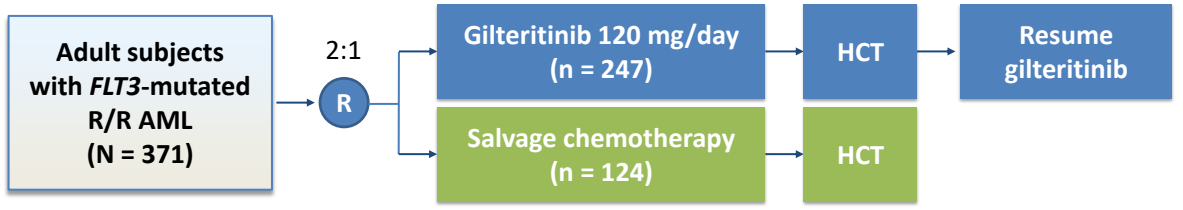
ADMIRAL Trial: Phase 3 Study



- **Primary endpoints:** OS, CR/CRh rate
- **Key secondary endpoints:** EFS, CR rate

Perl AE, et al. *N Engl J Med*. 2019;381:1728-1740.

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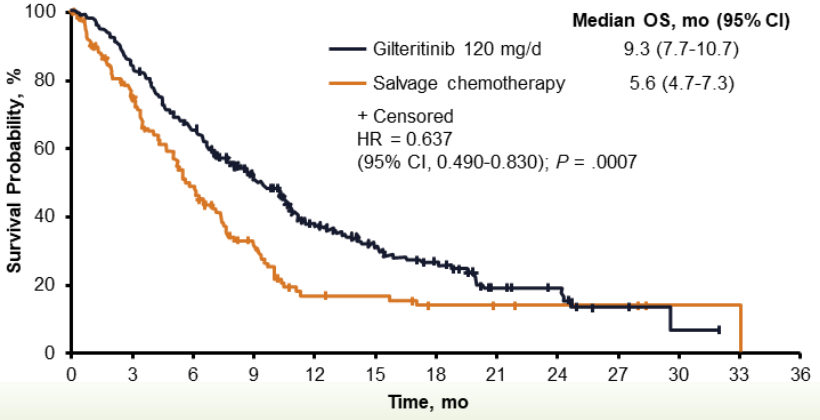
ADMIRAL Trial: Gilteritinib vs Salvage Chemotherapy in Relapsed AML

Overall, results showed improved OS and response with gilteritinib vs chemotherapy



No. at Risk

Gilteritinib 120 mg/d	247	206	157	106	64	44	31	14	11	4	1	0	0
Salvage chemotherapy	124	84	52	29	13	12	8	7	5	3	1	0	0

Perl AE, et al. *N Engl J Med*. 2019;381:1728-1740.

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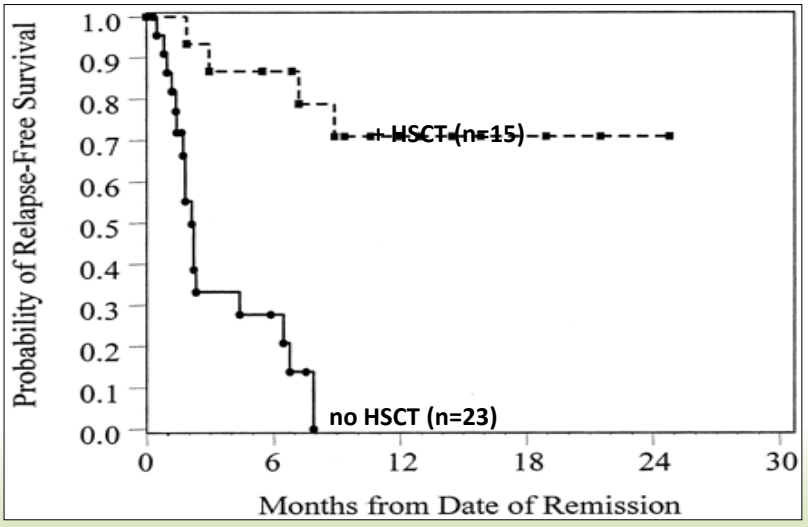
Relapse-Free Survival Following Gemtuzumab Ozogamicin



Sievers EL, et al. *J Clin Oncol.* 2001;19:3244-3254.

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Older Adults with Relapsed or Refractory AML:
Barriers to Transplant - Myth or Reality

- Older adults comprise majority of those with AML
  - Median age 70-72 yrs
  - Higher HCTCI (comorbidity) scores
- Lower complete remission rates
  - Tolerate salvage therapy less well, many do not receive therapy
  - Few become candidates for transplant
- Perception that older adults are not candidates for AlloBMT
  - Need for therapies for this population that are tolerable and establish disease control to allow engraftment and GvL effect
- Particularly relevant for Florida and Georgia , where the proportion of patients age >55 years is greater

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Clinical Trials in R/R AML for Older Adults

- Low intensity therapy options
- Targeted agents for select patients with targetable mutations
  - Non-cytotoxic
    - Advances in Precision Medicine
- Bridge to transplant
  - Most studies are designed to establish response, then consolidate with AlloBMT with curative intent
- clinicaltrials.gov

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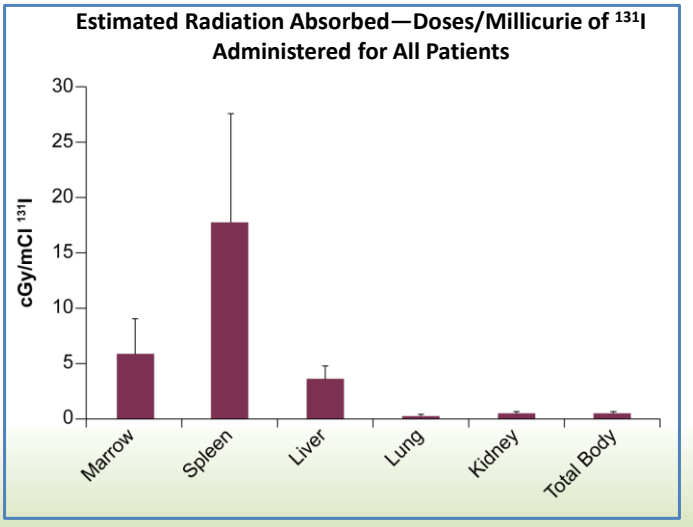
Iomab-B and CD45: Mechanisms and Biodistribution

- CD45 antigen expressed on virtually all lymphocytes and 85%-90% of acute leukemias
- Iomab-B: **combines anti-CD45 mAb that targets lympho-hematopoietic cells with γ particle–emitting radionuclide ^{131}I**
- Offers target-specific ablation as a conditioning regimen prior to HCT
- Does not bind other normal tissues; directs radiation to leukemic and immune cells



Pagel JM, et al. *Blood*. 2009;114:5444-5453.

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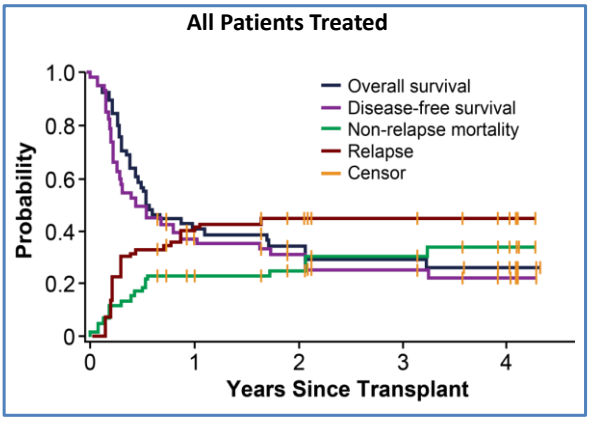
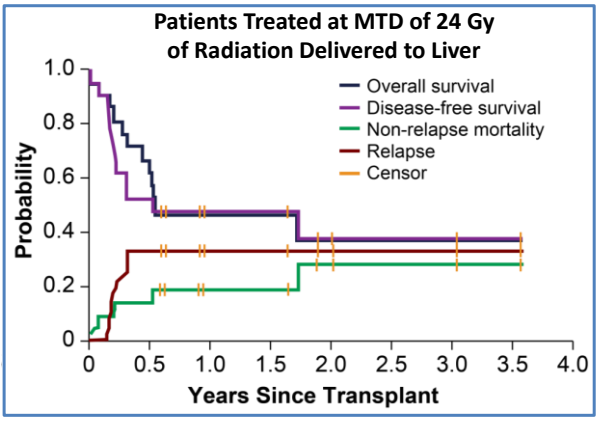
Phase 2 Study: Iomab-B + RIC in Patients >50 Years With Advanced AML and High-Risk MDS





At 1 Year, %	OS	NRM	Relapse
	41	22	40

At 1 Year, %	OS
	48

Pagel JM, et al. *Blood*. 2009;114:5444-5453.

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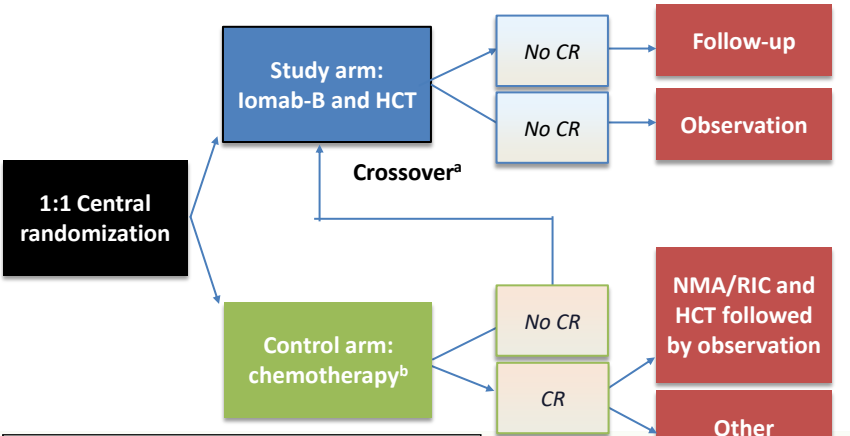
Phase 3 SIERRA Trial: Iomab-B Prior to HCT vs Chemotherapy in R/R AML

Inclusion Criteria

- Aged ≥55 y with active, R/R AML defined by:
  - Primary induction failure after ≥2 cycles of chemotherapy
  - First early relapse after remission <6 months
  - Refractory to salvage combination chemotherapy with high-dose cytarabine
  - Second or subsequent relapse
- 8/8 HCT donor match (related and unrelated)
- Karnofsky score ≥700



- **Primary endpoint:** dCR
- **Secondary endpoint**: 1-year OS

[a]Control arm patients with no CR offered crossover for ethical reasons.
[b]Physician choice of best salvage chemotherapy using approved products.

1. https://clinicaltrials.gov/ct2/show/NCT02665065. Accessed July 2020, 2020.

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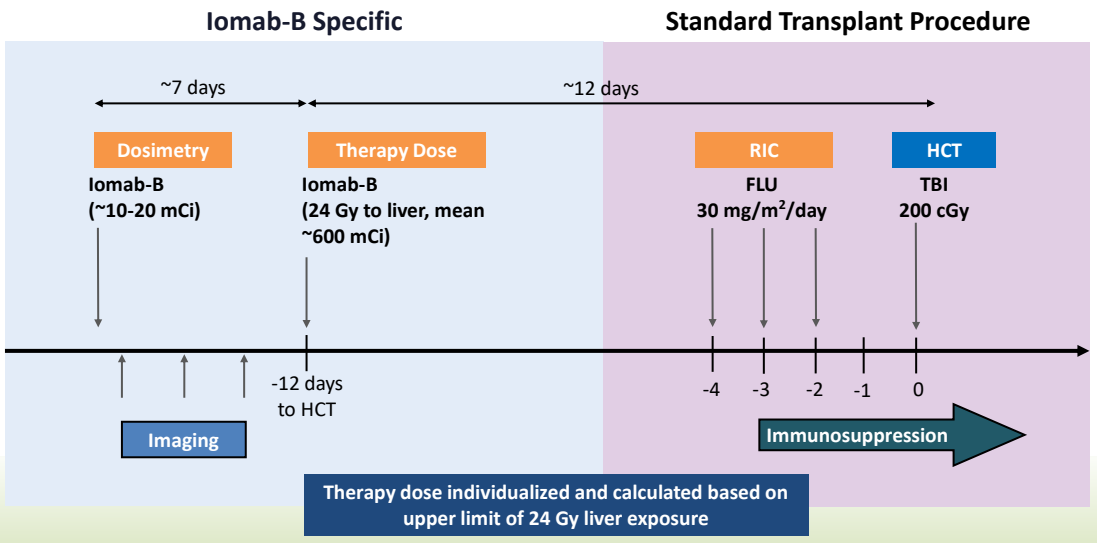
SIERRA: Iomab-B Treatment Schedule



Agura E, et al. *Blood.* 2018;132(Supplement 1):1017.

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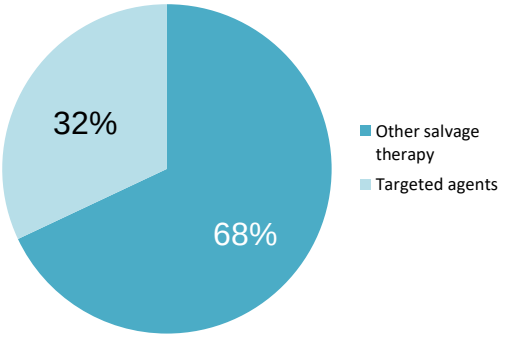
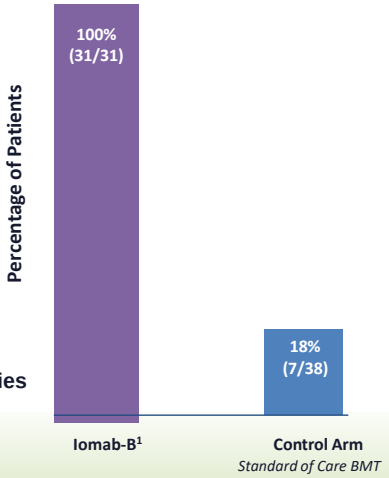
SIERRA: Post-Conditioning HCT Rate

Therapies After Enrollment: Control Arm



HCT Rate After Iomab-B vs SOC Control



- **12/38 patients (32%) in the control arm received targeted therapies**
- **11/12 patients (92%) received venetoclax + HMA or LDAC**
- **3/11 patients (27%) of venetoclax patients went to SOC HCT**

Gyurkocza B, et al. Presented at: TCT 2020. Abstract 285.

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SIERRA: Results at 50% Enrollment

	Randomized to Study Arm (N=37)	Randomized to Conventional Care (N=38)	
	Received Therapeutic Dose of Iomab-B, transplanted 100% (N=31/31)	Achieved CR and received standard of care transplant 18% (N=7/38)	Did not Achieve CR (N=31/38)[a] Crossed over, Iomab-B therapy and transplanted 100% (N=20/20)[a]
Days to ANC engraftment	15 (9-22)[b]	18 (13-82)[c]	14 (10-37)[d]
Days to platelet engraftment	20 (4-39)[b]	22 (9-35)[c]	19 (13-38)[d]
Days to HCT (post randomization)	30 (23-50)	67 (51-86)	64 (44-161)[e]

- Despite high blast counts,100% evaluable patients receiving therapeutic Iomab-B successfully engrafted[c,e]
- 7/38 (18%) of patients achieved a CR on the control arm and received a SOC HCT
- 31/38 (82%) of patients did not achieve a CR and 20/31 (65%) of patients crossed over to receive Iomab-B + HCT
- If randomized to conventional care arm, time to HCT after cross over to Iomab-B is consistent with SOC transplant

[a] 1 patient had unfavorable dosimetry. [b] 5 patients ineligible for transplant. [c] ANC engraftment data not available (n = 2); platelet engraftment data not available (n = 3). [d] n = 2 patients, platelet engraftment data not available. [e] 1 patient at 161 days had delayed transplant due to infection and respiratory failure, received Iomab-B and transplant when stable.

Gyurkocza B, et al. TCT 2020. Abstract 285.

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SIERRA: 100 Days Post-Transplant NR

	Randomized to Study Arm (N=37)	Randomized to Conventional Care (N=38)	
	Received Iomab-B therapeutic dose, transplanted (N=31)	Achieved CR and received standard of care transplant (N=7)	Did not Achieve CR Crossed over to Iomab-B arm and transplanted (N=20)
100-Day Non-Relapse Transplant Related Mortality	**2/31** (6%)	**2/7** (29%)	**2/20** (10%)
Dose Delivered to Bone Marrow	15.5 (4.6-32) Gy 616 (366-1027) mCi	n/a	14.4 (6.3-30) Gy 560 (313-1008) mCi

- Lower 100-day non-relapse transplant related mortality rates observed in Iomab-B arm and cross over than control patients
- Iomab-B delivers high amounts of radiation to the site of disease but is well tolerated with minimal extramedullary toxicities due to its targeted mechanism of action

Low 100-day non-relapse transplant related mortality observed with Iomab-B

Gyurkocza B, et al. TCT 2020. Abstract 285.

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SIERRA: Summary

- 77% of all enrolled patients were able to receive transplant
  - Only 18% in the control arm achieved remission and were transplanted conventionally
- 100% engraftment and low TRM after Iomab-B/HCT (despite high pre-transplant median blast count of ~30%)
- Low rate of mucositis, febrile neutropenia, and sepsis with Iomab-B
- Update: patients not responding to venetoclax/HMA are now eligible for SIERRA

Gyurkocza B, et al. TCT 2020. Abstract 285.

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Therapy of R/R AML in Older Adults
Conclusions

- Need for options for older adults
  - Few are eligible for or receive intensive salvage therapy
  - Targeted therapy available for only minority, not curative
- Area of need
- Iomab-B clinical trial option
  - Potential for anti-AML efficacy
  - Increased donor availability
  - Experience in non-ablative AlloBMT for older patients
- Clinicaltrials.gov for options for patients in Florida/SE

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Resources

- HRSA Blood Stem Cell Website: https://bloodstemcell.hrsa.gov/
- SIERRA Trial: https://clinicaltrials.gov/ct2/show/NCT02665065

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