Precision Medicine In AML: The Goals of MyeloMATCH

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knowledge changing life

MEDICAL COLLEGE OF WISCONSIN

Disclosures

- Research Funding: Jazz Pharmaceuticals
- Pharmaceutical Consulting: Abbvie, Kura Oncology, MERCK, Curio Science, Celgene, Incyte Corporation, Nkarta Biotechnology
- I will be discussing the off-label use of medications and will indicate when that is the case

Topics of the Day

- Background
  - What is meant by “precision medicine?”
  - How should we think about Acute Myeloid Leukemia treatment?
  - What is MyeloMATCH?
- Current Standards of Care
  - Who, When and Why
- Where are we falling short?
- What can we do to address these unmet needs?

In the Ideal….

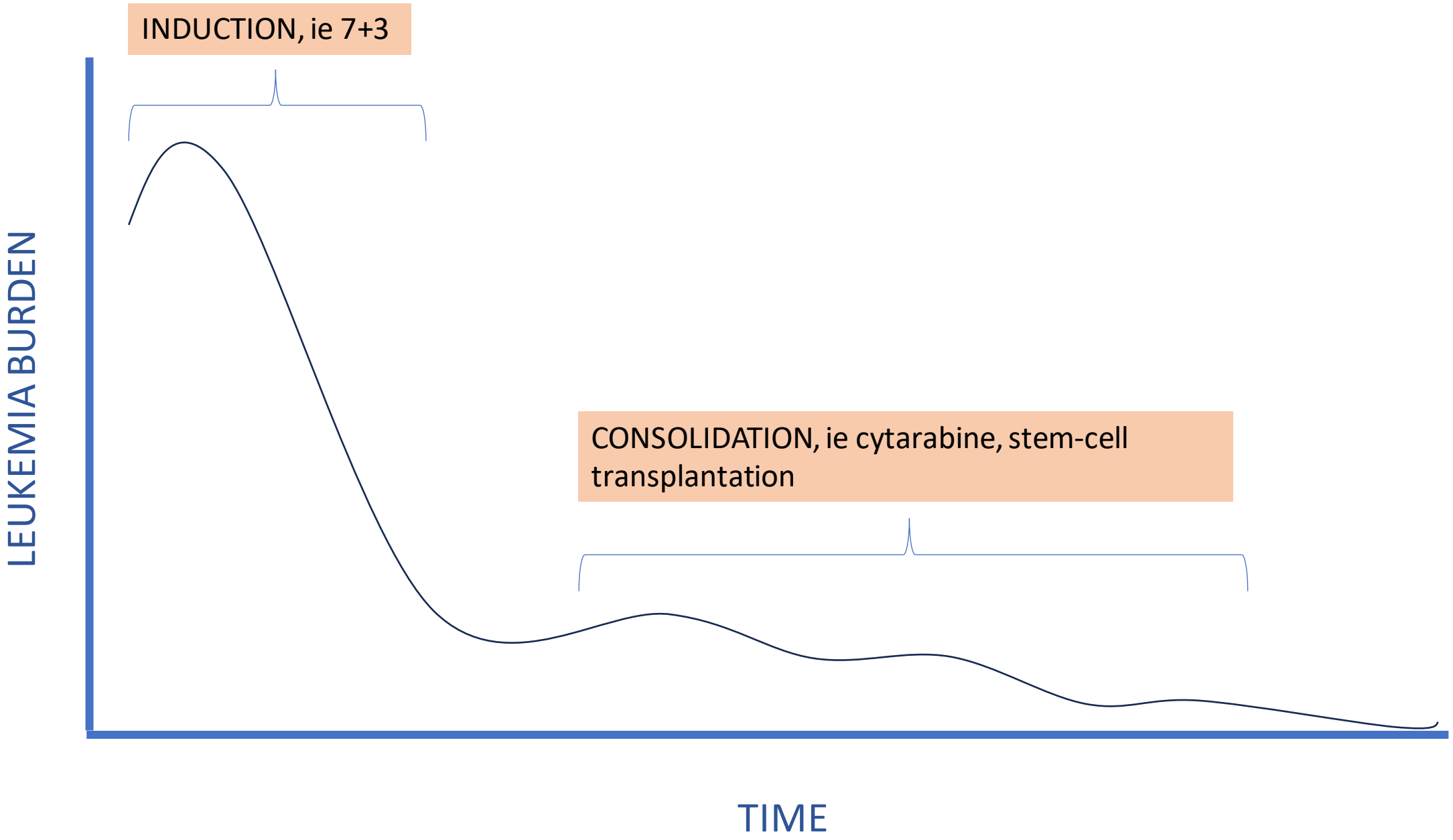
Precision Medicine is defined as:
"A form of medicine that uses information about a person's own genes or proteins to prevent, diagnose, or treat disease"

In Reality: for most of the history of hematology, the available therapeutic options, rather than disease or even patient characteristics, have dictated treatment for AML

https://www.cancer.gov/publications/dictionaries/cancer-terms/def/precision-medicine

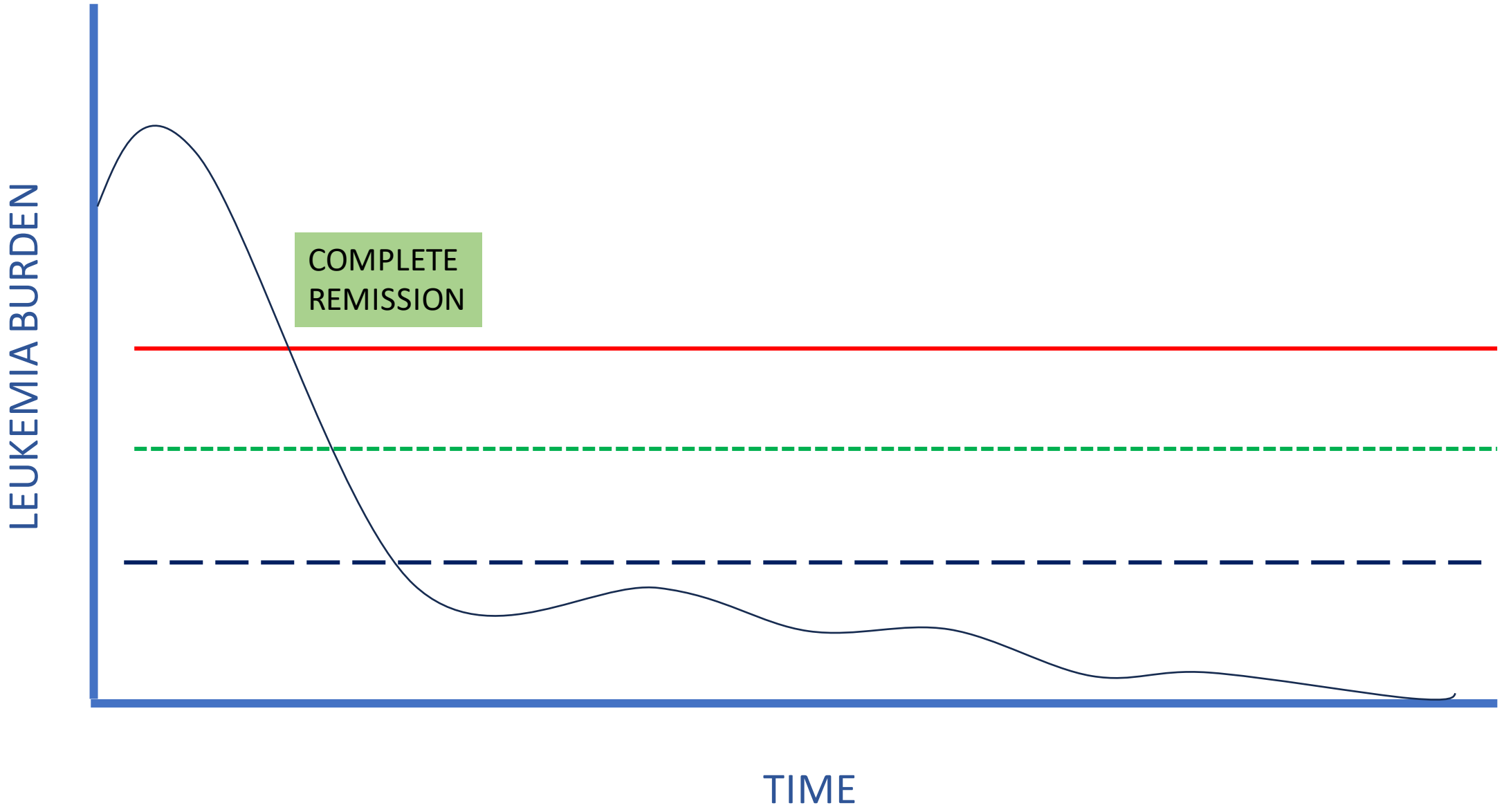
The Traditional Framework for AML Therapy

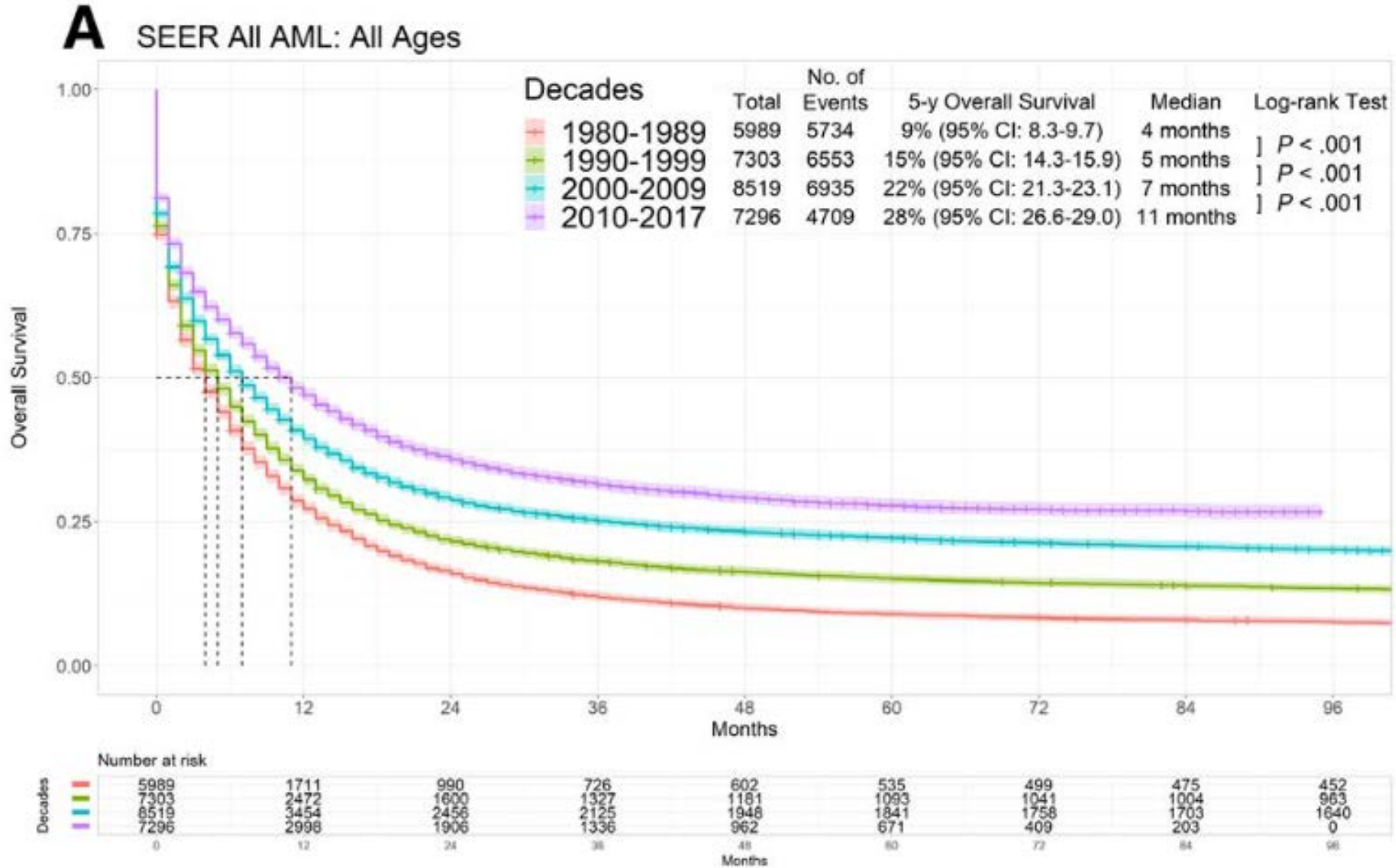
- Induction – Eliminate the bulk of the leukemic clone
- Consolidation – Eliminate remaining leukemic cells
  - Cytotoxic Chemotherapy
  - Cellular Therapy in the form of a stem-cell transplant
- Measurable Residual Disease
  - Detectable disease present after Induction and Consolidation


INDUCTION, ie 7+3
CONSOLIDATION, ie cytarabine, stem-cell transplantation
LEUKEMIA BURDEN
TIME

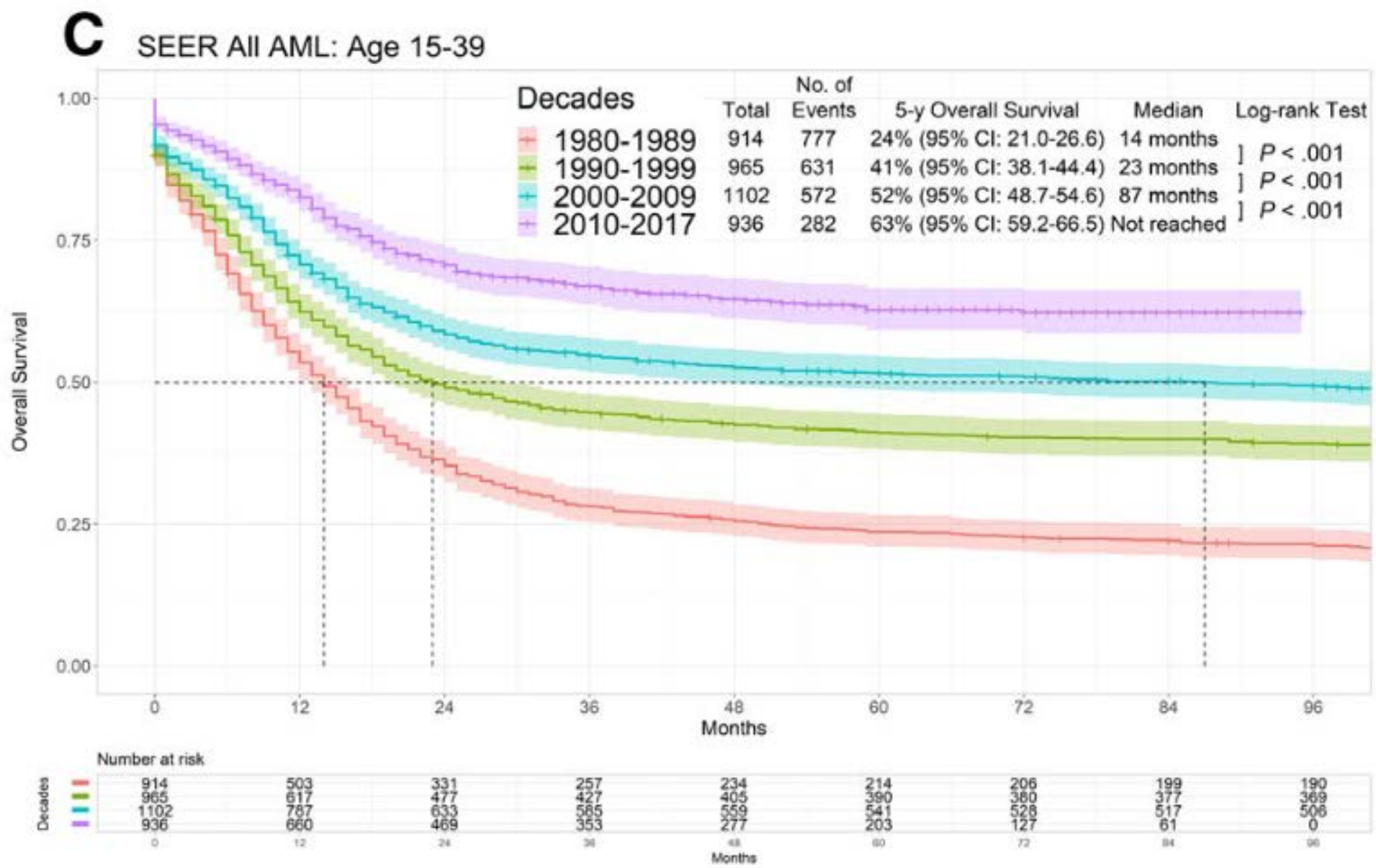
The Traditional Framework for AML Therapy

- Induction – Eliminate the bulk of the leukemic clone – Goal is
- Complete Remission
  - Morphologically with less than 5% leukemia cells in the marrow, count recovery
- Measurable Residual Disease
  - Detectable disease present after therapy using highly sensitive techniques
    - Generally measured after induction and first cycle of consolidation
    - Can be very informative prior to stem-cell transplant
  - Measured with molecular sequencing or flow cytometry

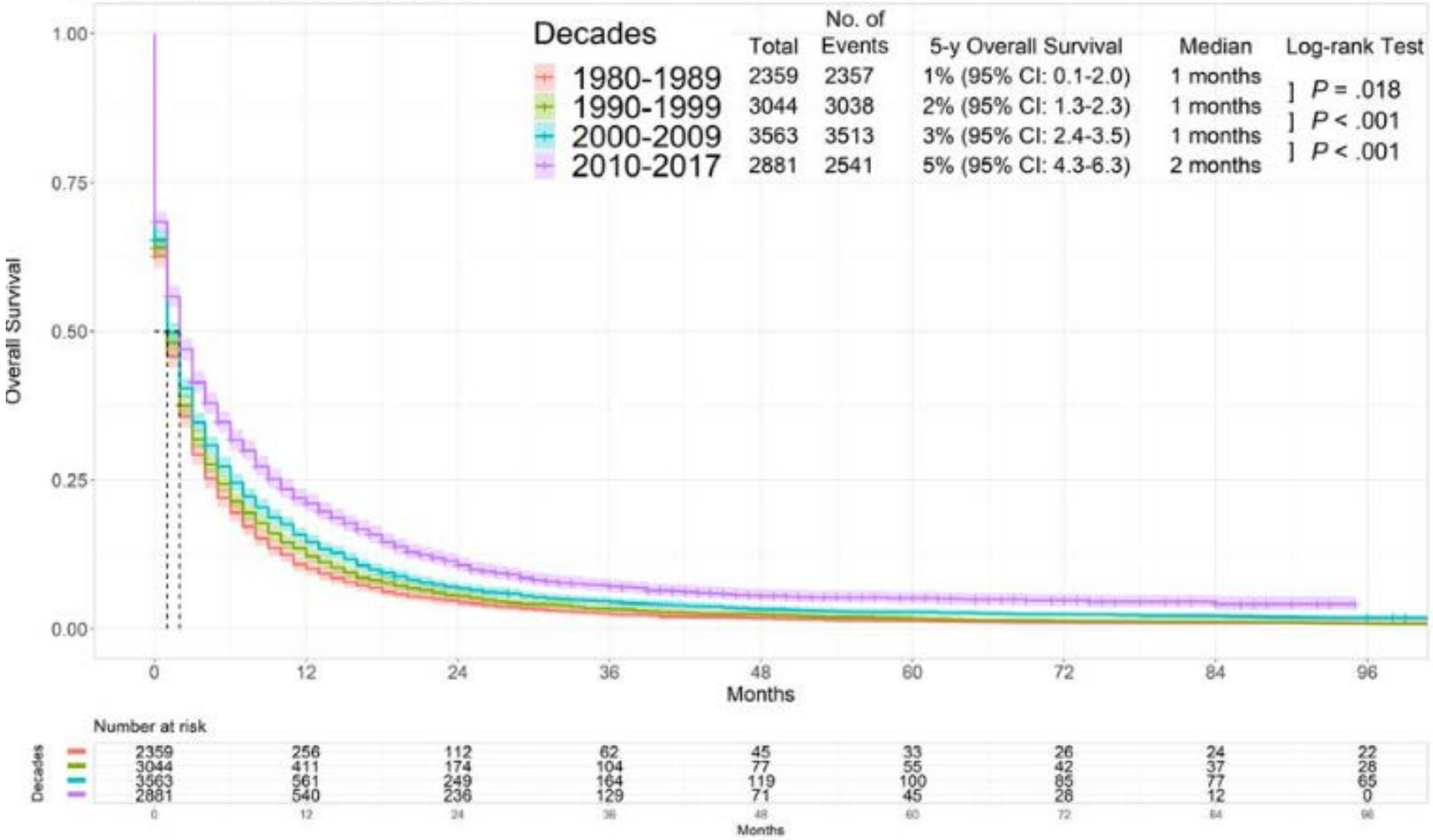

LEUKEMIA BURDEN
COMPLETE
REMISSION
TIME



Short et al., Cancer 2021;127:2049-2061


C
SEER All AML: Age 15-39
Decades
No. of
Total
Events
5-y Overall Survival
Median
Log-rank Test
1980-1989 914 777 24% (95% CI: 21.0-26.6) 14 months
1990-1999 965 631 41% (95% CI: 38.1-44.4) 23 months
2000-2009 1102 572 52% (95% CI: 48.7-54.6) 87 months
2010-2017 936 282 63% (95% CI: 59.2-66.5) Not reached
P < .001
P < .001
P < .001
Overall Survival
1.00
0.75
0.50
0.25
0.00
0
12
24
36
48
60
72
84
96
Months
Number at risk
Decades
914 503 331 257 234 214 206 199 190
965 617 477 427 405 390 380 377 369
1102 787 633 585 559 541 528 517 506
936 660 469 353 277 203 127 61 0
Months

F SEER All AML: Age ≥70



ERA	REGIMEN: Newly-Diagnosed Patients	POPULATION	EXPECTATIONS
1970s-2000	Anthracycline – Based (7+3)	Fit	CR rates: 60%-70% Med OS: Highly Variable
	Hypomethylating Agent	Older, Less-Fit	CR rates 17% Med OS: 10 mo
2017	Midostaurin + 7 + 3	FLT-3mut + Fit + Young	CR rates: 59% Med OS: 74 months
	CPX-351	Older, High-Risk	CR rates: 47% Med OS: 9.5 mo
	Gemtuzumab + Cytotoxic Agents	Fit + Fav/Inter Cytogenetics	CR rates: 70% Med OS: 27 mo
2018-2023	Azacitadine + Venetoclax	Older, Less-Fit	CR/CRi Rates: 66% Med OS: 14 mo
	Cytarabine + Glasdegib	Older, Less-Fit	CR: 17% Med OS: 8.8 mo
	Cytarabine + Venetoclax	Older, Less-fit	CR/Cri: 54% Med OS: 10 mo

What is required to improve our outcomes?

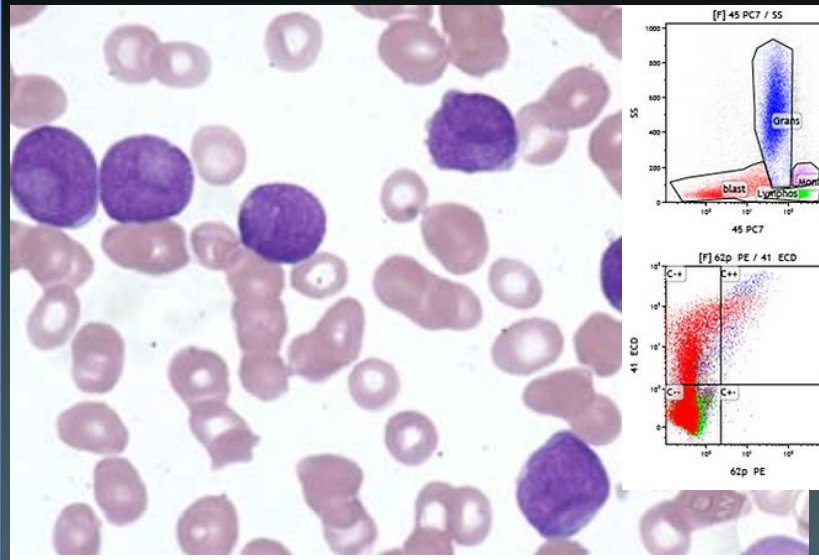
Disease Understanding

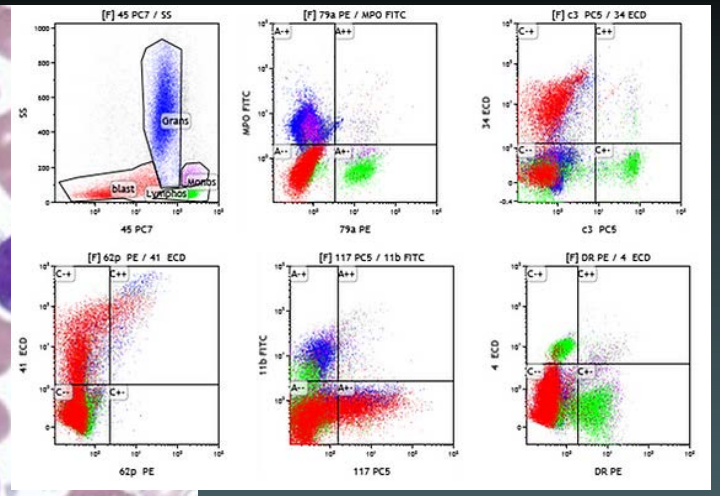
Accurate Disease Characterization

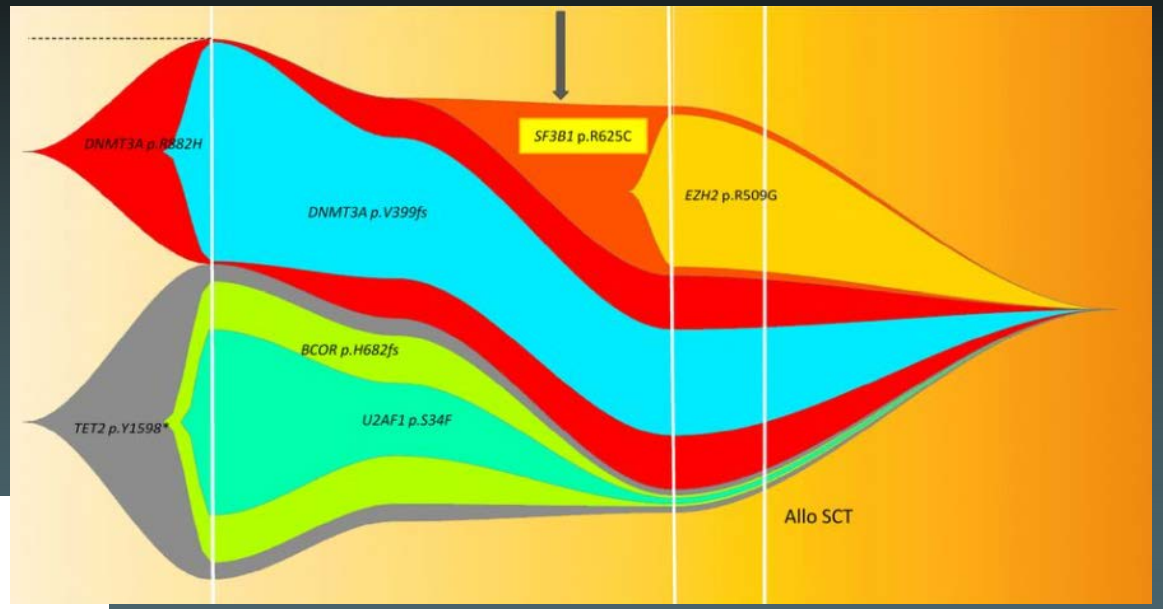
Rationally Designed Therapies

Reproducible Assessment of Fitness

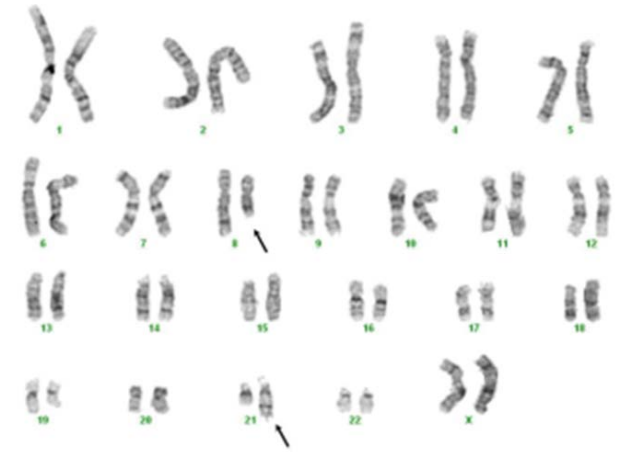
Robust Platform for Efficacy Evaluation







It is not easy to see what should be done to prevent symptoms of the kind described in this paper. Faced by a patient with a duodenal ulcer who is known to be a moderate drinker and who has had a number of acute complications of his ulcer, the surgeon must choose whether or not to operate. If he does not do so he



CYTOGENETIC STUDIES IN ACUTE LEUKAEMIA

BY

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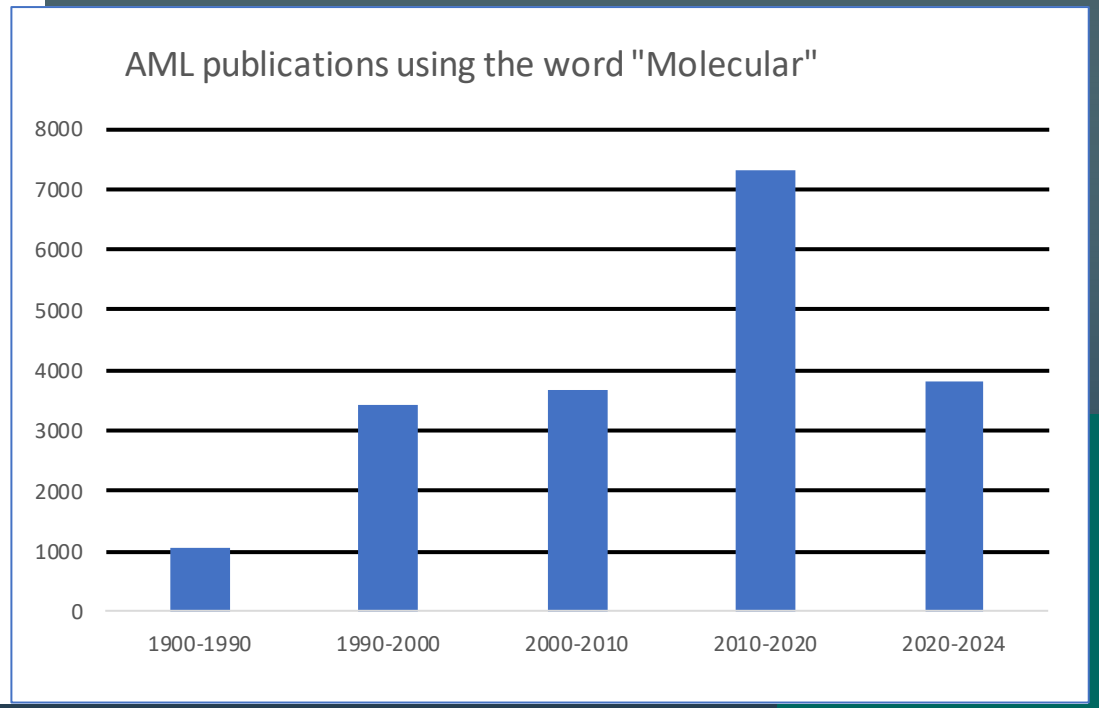
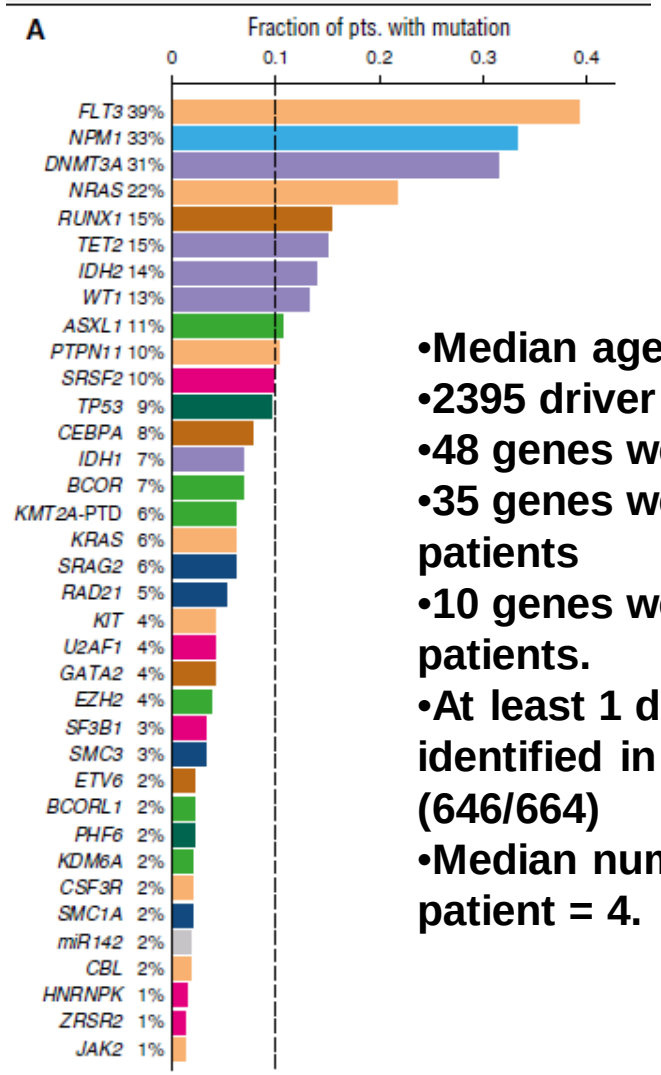
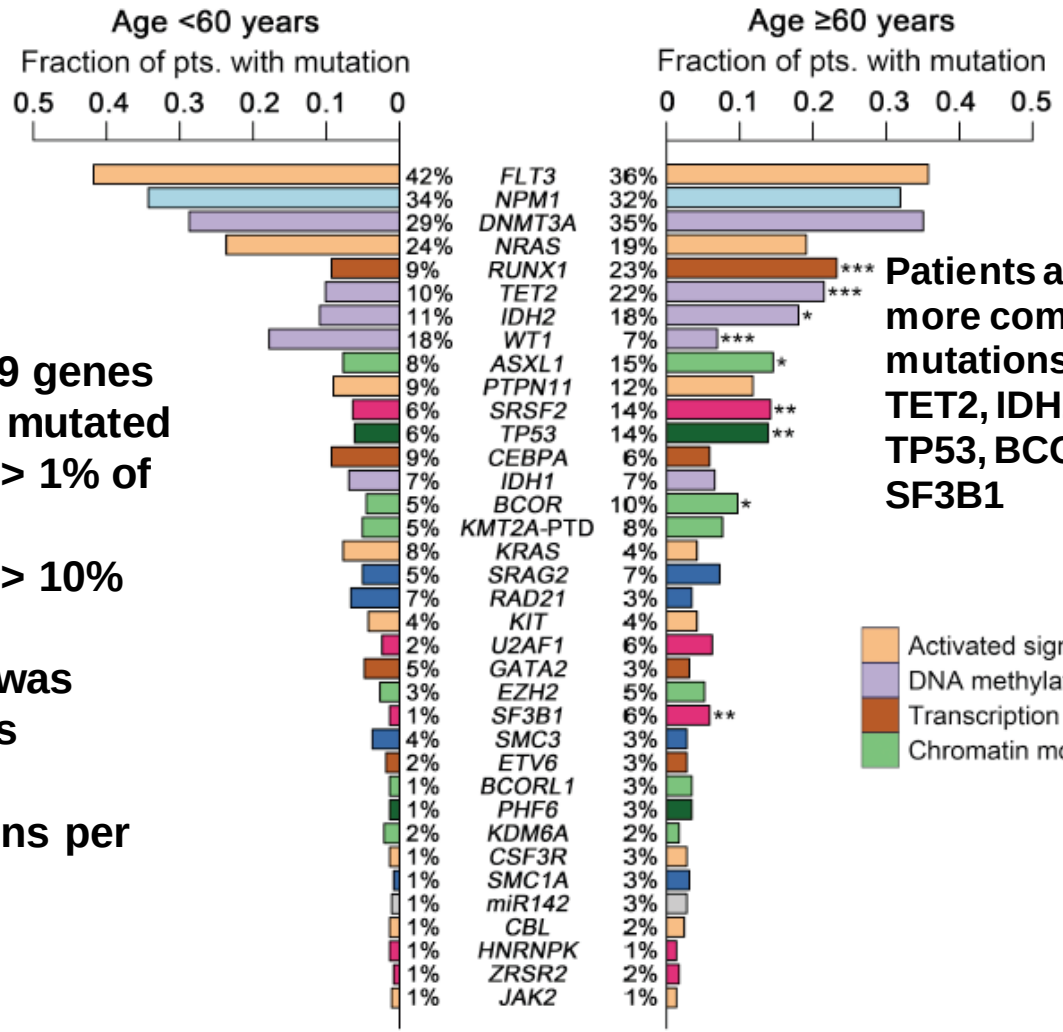
Abnormalities of the chromosomes of leukaemic cells in human acute leukaemia have now been the subject of several reports (Ford *et al.*, 1958b; Baikie *et al.*, 1959; Ford, 1960; Sandberg *et al.*, 1960). It would appear that in about half the cases reported some abnormality has been found, including aberrations of chromosome number, morphology, and sometimes both of these. Among the reported cases no two appear to have had an identical abnormality. In this respect, and as regards



Mutational Profile in AML (664 Patients)



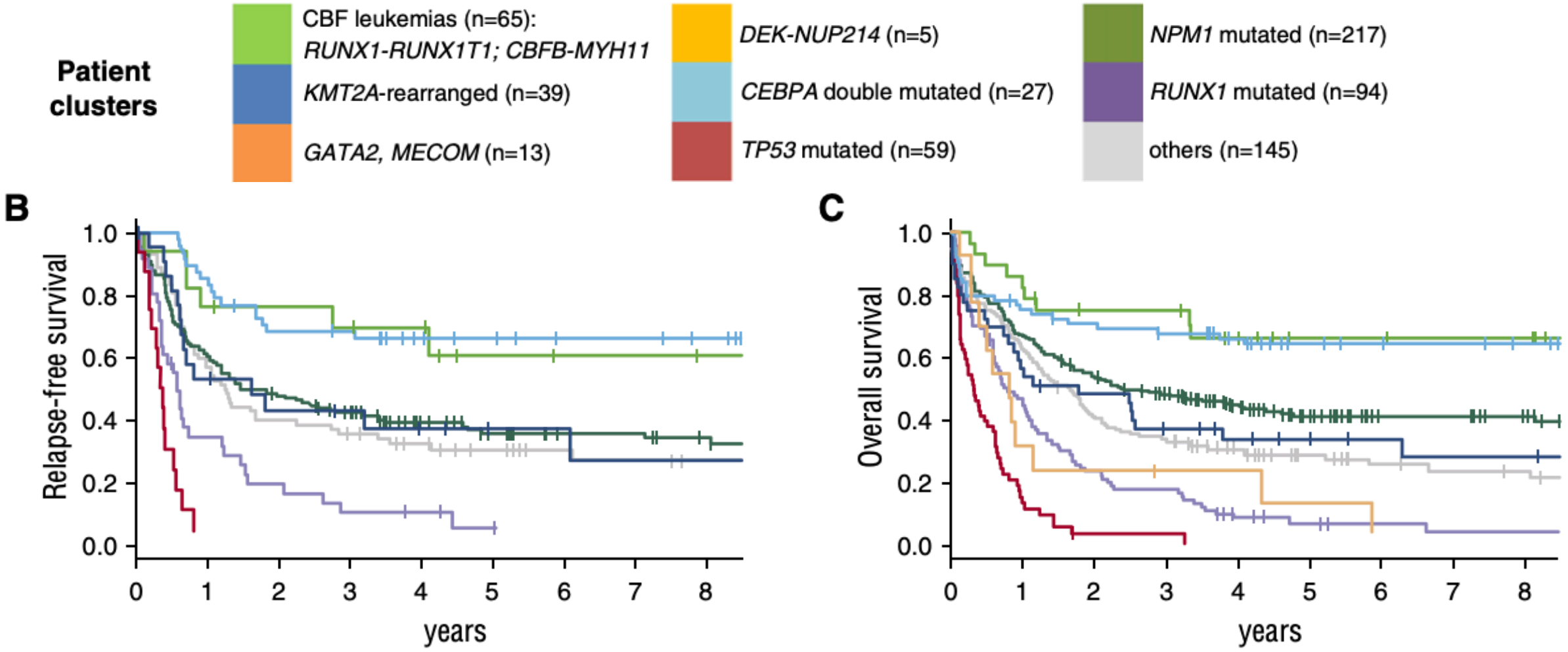
- **Median age: 57 yrs**
- **2395 driver mutations in 59 genes**
- **48 genes were recurrently mutated**
- **35 genes were mutated in > 1% of patients**
- **10 genes were mutated in > 10% patients.**
- **At least 1 driver mutation was identified in 97% of patients (646/664)**
- **Median number of mutations per patient = 4.**



Patients aged > 60 yr more commonly had mutations in RUNX1, TET2, IDH2, SRSF2, TP53, BCOR, and SF3B1

Metzeler KH, et al. Blood 2016; 128 (5): 686-696

Outcomes by cytogenetic/molecular clusters



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What is required to improve our outcomes?

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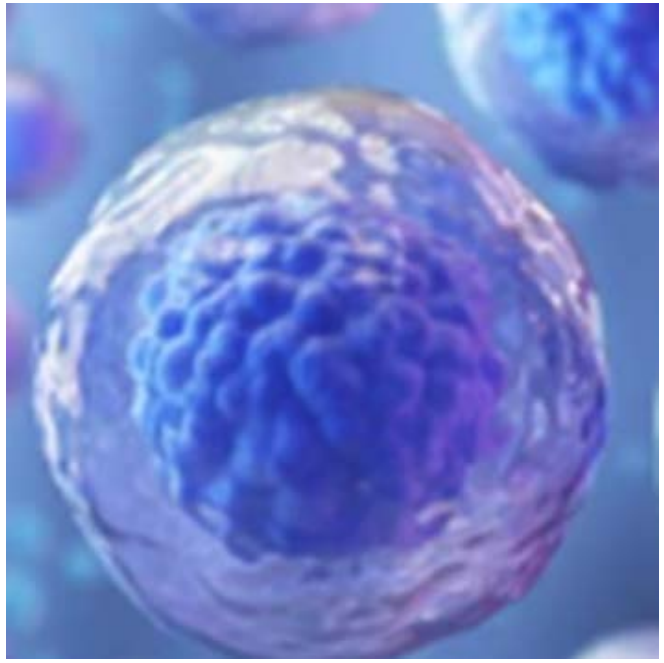
Rationally Designed Therapies

Reproducible Assessment of Fitness

Robust Platform for Efficacy Evaluation

Predisposition Syndromes

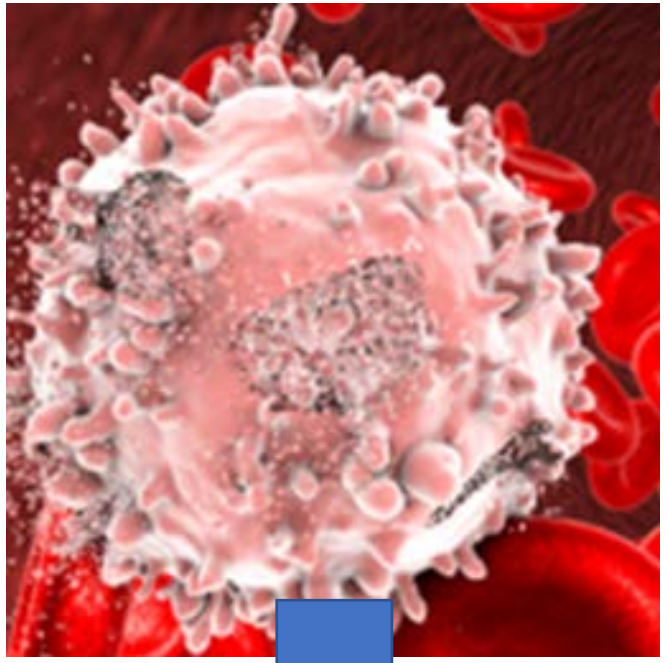
Environmental Exposures



Structural Alterations

Leukemogenic Mutations

Permissive Hematopoietic Niche



Abnormal Phenotype

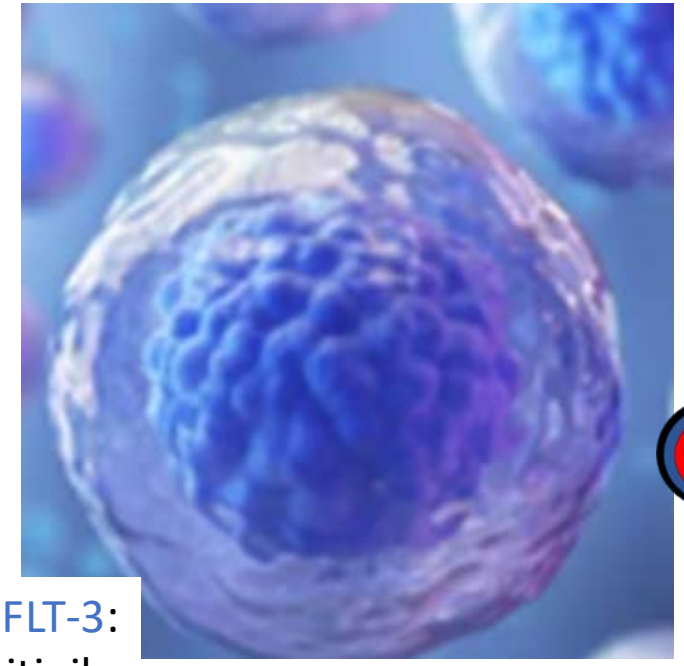
Differentiation Block

Aberrant Proliferative Capacity

Failure of Apoptosis

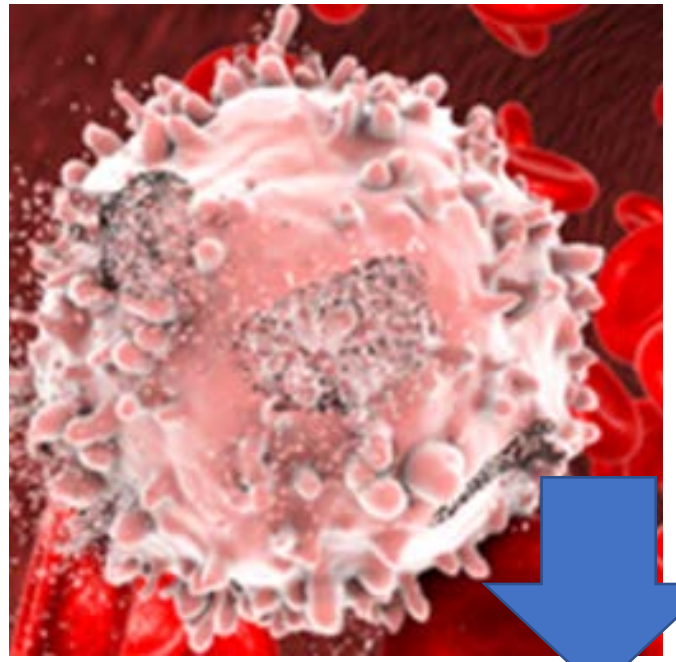
Predisposition Syndromes

Environmental Exposures



Structural Alterations

Leukemogenic Mutations



Inhibitors of FLT-3: Midostaurin, Gilteritinib, Quizartinib

Hedgehog Pathway Inhibitor: Glasdegib

Inhibitors of Isocitrate Dehydrogenase: Enasidenib, Ivosidenib, Olutasidenib

Inhibitors Menin Pathway: Revumenib, Ziftomenib, JNJ-75276617 BN-104; DSP-5336

Permissive Hematopoeitic Niche

Antibody Conjugates, i.e. Gemtuzumab Ozagamicin → Abnormal Phenotype

Differentiation: ATO/ATRA → Differentiation Block

Cytotoxic Agents, i.e., 7+3 and CPX-351 → Aberrant Proliferative Capacity

BCL2 Inhibition: Venetoclax → Failure of Apoptosis

Challenges to Drug Development in AML

- Rare Disease
- Potential targets must be identified rapidly based on clinical presentation.
- Overall Survival has been the primary endpoint for full approval of new agents in AML.
- Lack of prospective data proving the predictive value of an MRD assay
- The definition of eligibility for curative intensive therapy has been elusive
- Absence of coordinated national approach
- Most patients, at most centers, are not offered investigational options or are ineligible for the trials that exist

National Cancer Institute

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

myeloMATCH

Myeloid Malignancies Molecular Analysis for Therapy Choice

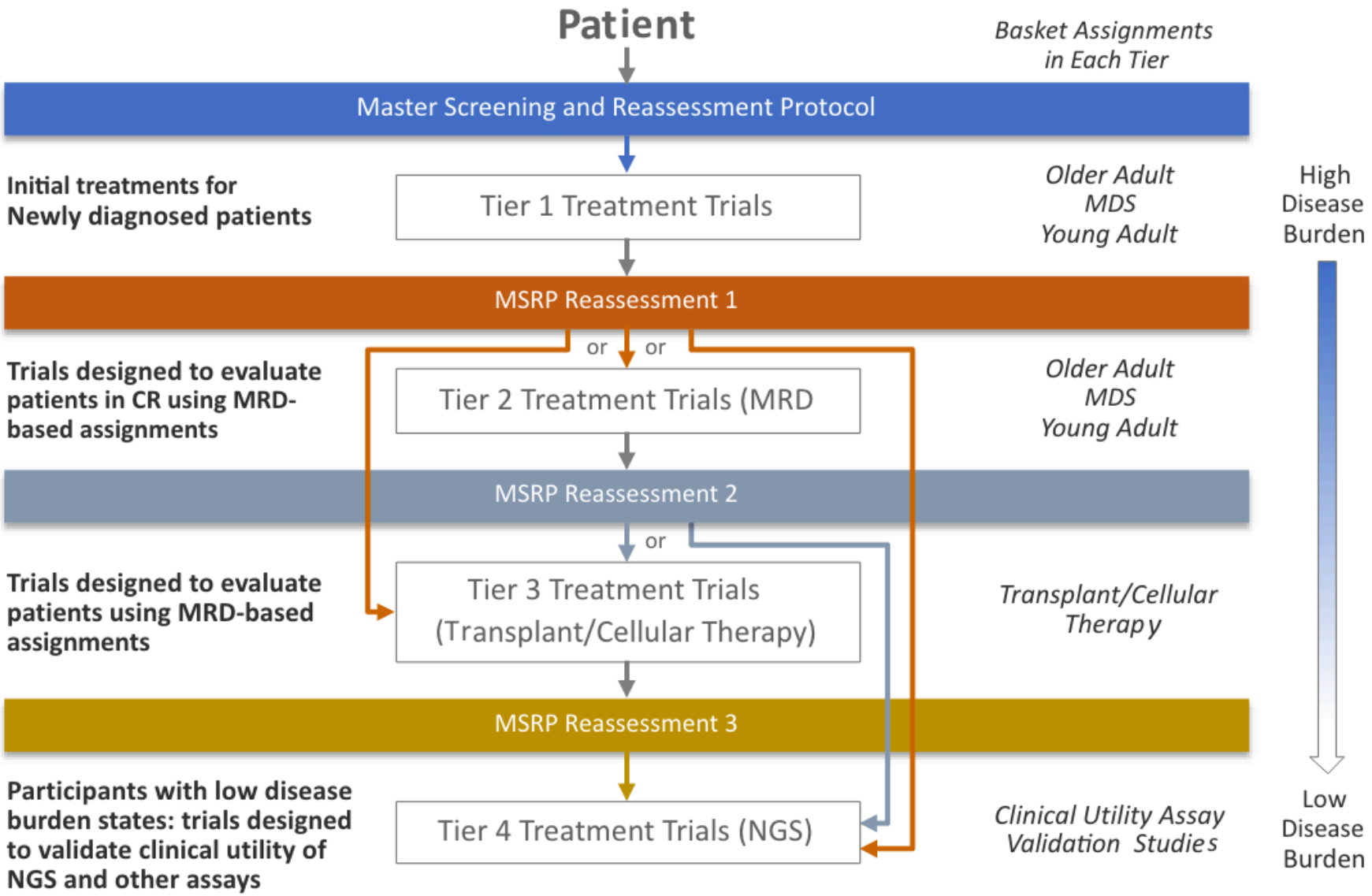
NCI National Clinical Trials Network

Leadership: Richard F. Little, M.D.
CTEP, NCI

myeloMATCH Aims

- Create a portfolio of rationally designed treatment substudies
  - Patients enroll sequentially over their entire treatment journey
  - Scientific data is generated at every stage
- Create an efficient operational model which attracts
  - Industry partners
  - NCTN sites
- Develop the careers of young investigators
  - Promoting leadership throughout the clinical trial portfolio and laboratory program.
- Efficiently test and promulgate innovative standards of care for AML
  - Outcomes to provide therapeutic clarity

MyeloMATCH MSRP Schema



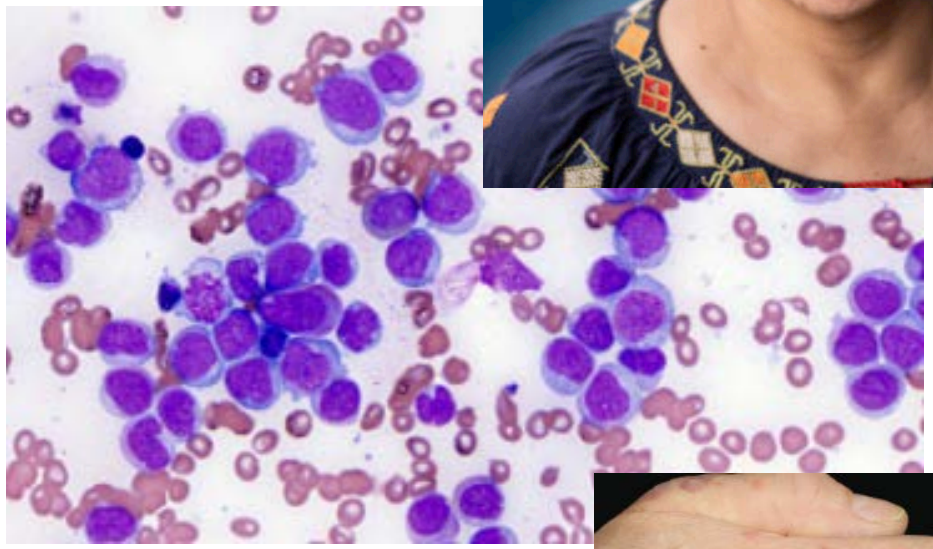
Little, Richard et al., Blood (2022) 140 (Supplement 1): 9057–9060.

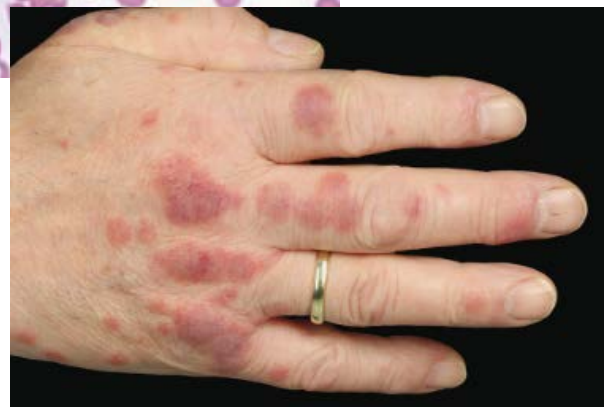
Topics for the Day

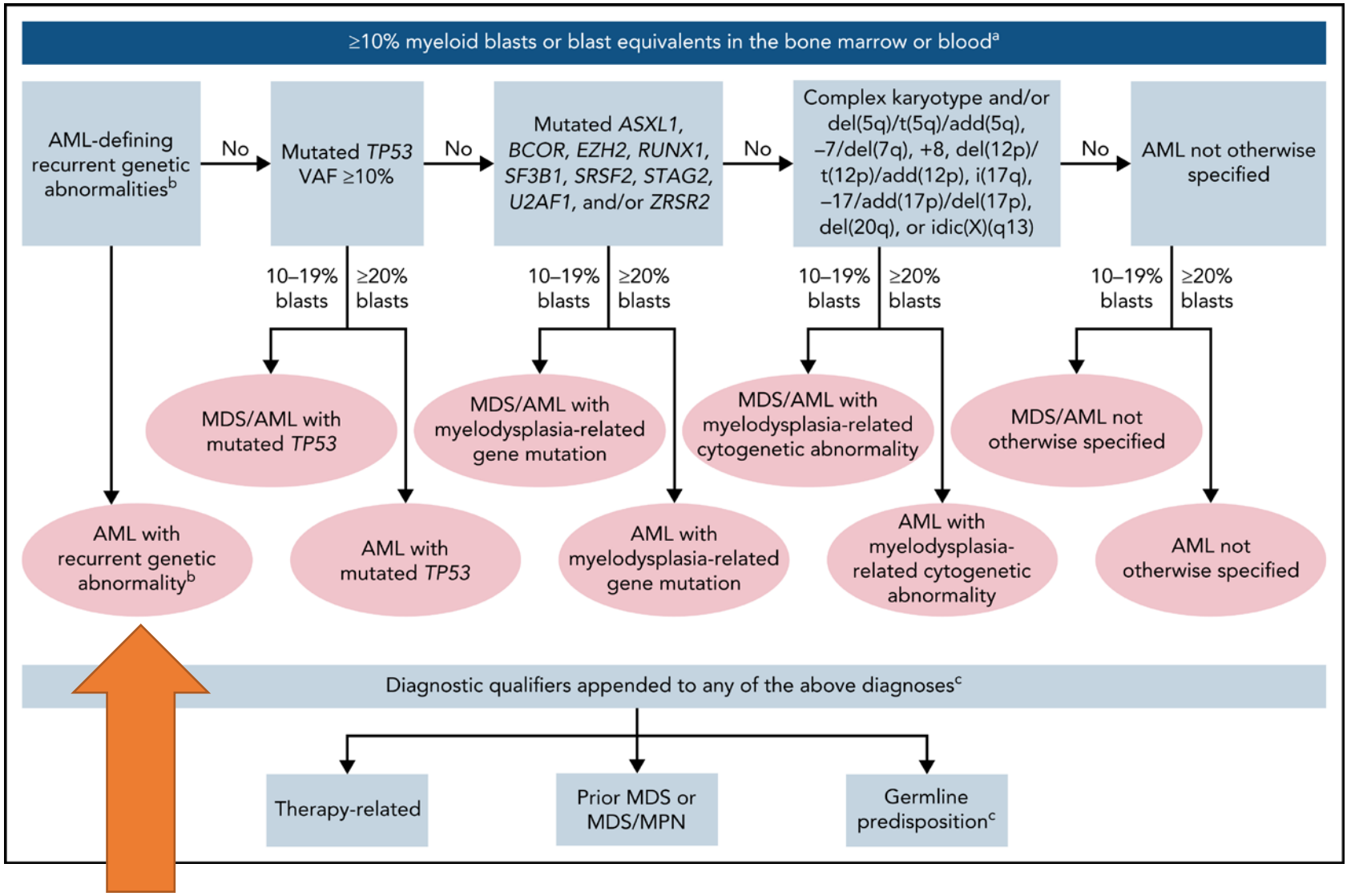
- Definitions
  - Precision Medicine
  - myeloMATCH
- Current State of Therapeutic Options
  - Younger, Fit
  - Older or Frail
- Hurdles and Potential for this Strategy
- Discussion

- 58-year-old woman
- History of well-controlled hypothyroidism
- Presents with night sweats, mild cough, new rash

WBC	24 X 10^3/uL
HGN	9.3 g/dL
PLTS	67 X 10^3/uL
Circulating Blasts	70%
Chromosomes	t(9;11)(p21;q23) KMT2A/MLLT3
Molecular Mutation	KRAS c.436G>A, p.Ala146Thr VAF: 10.2% KRAS c.38G>A, p.Gly13Asp VAF: 7.0%







Döhner et al., Diagnosis and management of AML in adults: Blood, 2022

2022 ELN risk classification by genetics at initial diagnosis*

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*†,§ without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*‖
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*†,¶ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged# • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11.2;p13.3)/*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, and/or ZRSR2*‡‡ • Mutated *TP53*§

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MCW Acute Myeloid Leukemia:2024

Fit, Induction-eligible candidate

Clinical trial available? Appropriate? If not, then

Favorable-risk Cytogenetics

Gemtuzumab Ozagomicin 3mg/m2 D1,4,7
Daunorubicin 60mg/m2 D1-3
Cytarabine 200mg/m2 D1-7
See Castaigne et al., Lancet 2012

MRD Follow UP

Intermediate-risk Cytogenetics

FLT3 STATUS

unmutated

Daunorubicin 60-90mg/m2 D1-3
Cytarabine 100mg/m2 CI D1-7
See Fernandez et al., NEJM 2009;
Luskin et al., Blood. 2016

Consider Gemtuzumab

mutated

Daunorubicin 60mg/m2 D1-3#
Cytarabine 200mg/m2 CI D1-7
Midostaurin 50mg PO BID D8-21
OR Quizartinib 40mg PO D8-21
See Stone et al., NEJM 2017
Erba et al., LANCET 2023

Adverse-risk Cytogenetics

Prioritize clinical trial enrollment given poor long-term outcomes

Ages 60-75 years
Therapy-related AML,
secondary AML,
MDS-related karyotype

Liposomal daunorubicin and cytarabine (CPX-351, Vyxeos) 44mg/m2 & 100 mg/m2 IV d1,3,5
See Lancet et al, JCO 2018

IDH2 mutated? – Discuss Data on IDH1/2 inhibitor

Under 60
Monosomal karyotype negative

Idarubicin 12mg/m2 D1-3
Cytarabine 200mg/m2 CI D1-7
See Lee et al., JCO 2017

OR

Daunorubicin 60-90mg/m2 D1-3
Cytarabine 100mg/m2 CI D1-7
See Fernandez et al., NEJM 2009;
Luskin et al., Blood. 2016

If possible, clinical trial of VEN + Intensive Chemotherapy

Other

Cladribine 5mg/m2 IV D 2-6
Cytarabine 2mg/m2 IV D 2-6
Mitoxantrone 10mg/m2 D 2-4
Filgrastim d 1-6
See Jaglal et al, Leukemia Research 2014

Intermediate/Adverse-risk Cytogenetics and NO transplant: Discuss MRD follow up and /or Maintenance therapy X 2 years

Study	Arms				Comments
E1900 Fernandez et al., NEJM 2009; Luskin et al., Blood. 2016 Mar 24;127(12):1551-8	Daunorubicin 45mg/m2 d1-3 + 100mg/m2 Cytarabine CI d1-7		Daunorubicin 90mg/m2 d1-3 + 100mg/m2 Cytarabine CI d1-7		Ages 17-60 yrs Data after Median F/U: 80.1 mo for survivors 90mg/m2 of daunorubicin vs 45mg/m2 benefits AML patients with favorable and intermediate cytogenetics and with FLT3-ITD, NPM1, and DNMT3A mutations.
	n:330		n:327		
	CR:	4-y OS:	CR:	4-y OS:	
All Patients	59%	31%	71%	39%	
Karyotype					
Favorable Risk	84%	46%	80%	64%	
Intermediate Risk	56%	35%	77%	45%	
Adverse Risk	44%	14%	57%	19%	

Lee et al. JCO 2017	Idarubicin (12mg/m2 d1,2,3) + cytarabine (200 mg/m2) d1-7 (Control arm)		Daunorubincin 90mg/m2 (d1,2,3) + cytarabine (200 mg/m2) d1-7		Ages: 15-65 years Powered for non-inferiority No difference between Idarubicin and Daunorubicin arms with regard to CR, OS. High-dose daunorubicin was more effective than idarubicin for patients with FLT-ITD mutation
	N=149		N=150		
	CR/CRi	4-y OS	CR/CRi	4-yr OS	
All Patients	80.5%	51.1%	74.7%	54.7%	
Cytogenetic Risk Group					
Good	88.9%	85.2	100%	90.7	
Intermediate	84.5%	53.1	75.3%	49	
Poor, monosomal karyotype neg	58.3%	25.0	61.3%	40.8	
Poor, monosomal karyotype pos	44.4%	0	30.0%	24.0	

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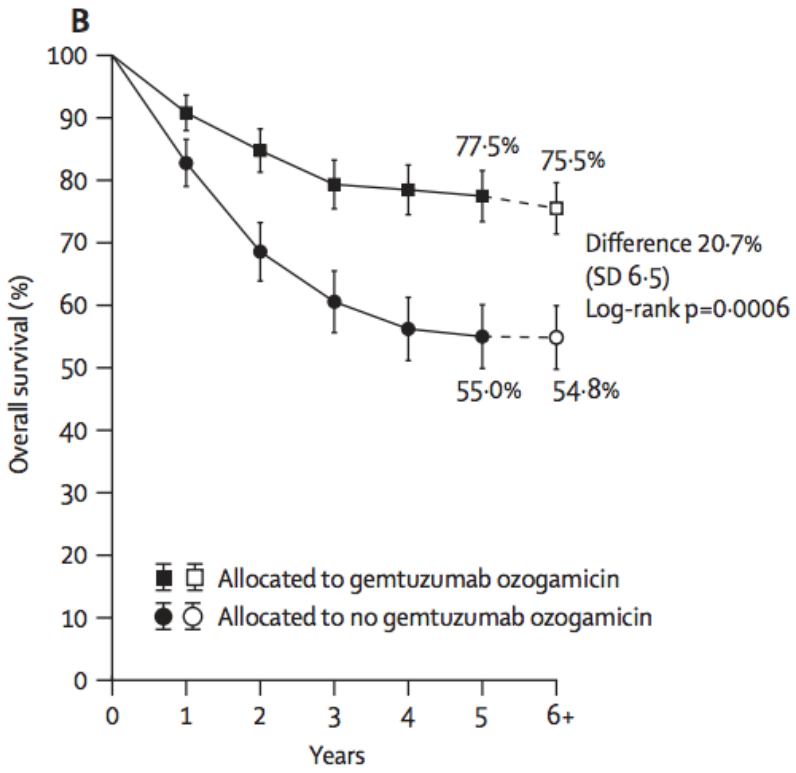
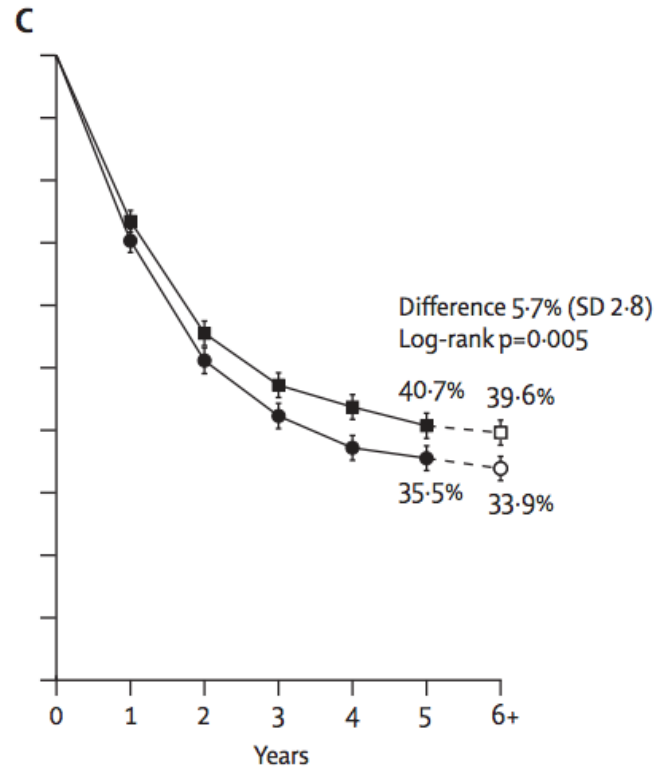
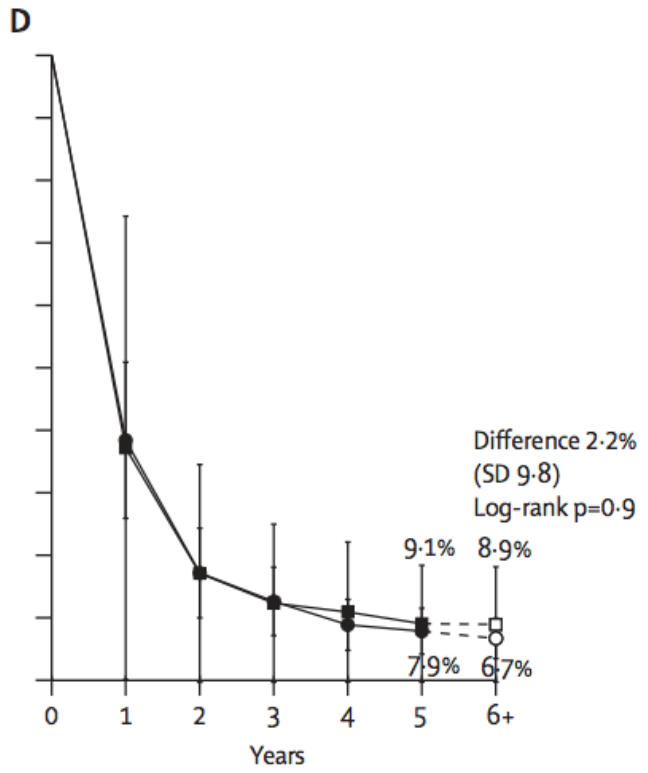
Meta Analysis of Gemtuzumab combination therapy



Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	5·8% SD 1·1	2·3% SD 1·3
No gemtuzumab ozogamicin	14·1% SD 1·9	0·0% SD 0·0



Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	22·4% SD 1·0	2·7% SD 0·9
No gemtuzumab ozogamicin	26·2% SD 1·1	4·9% SD 1·3

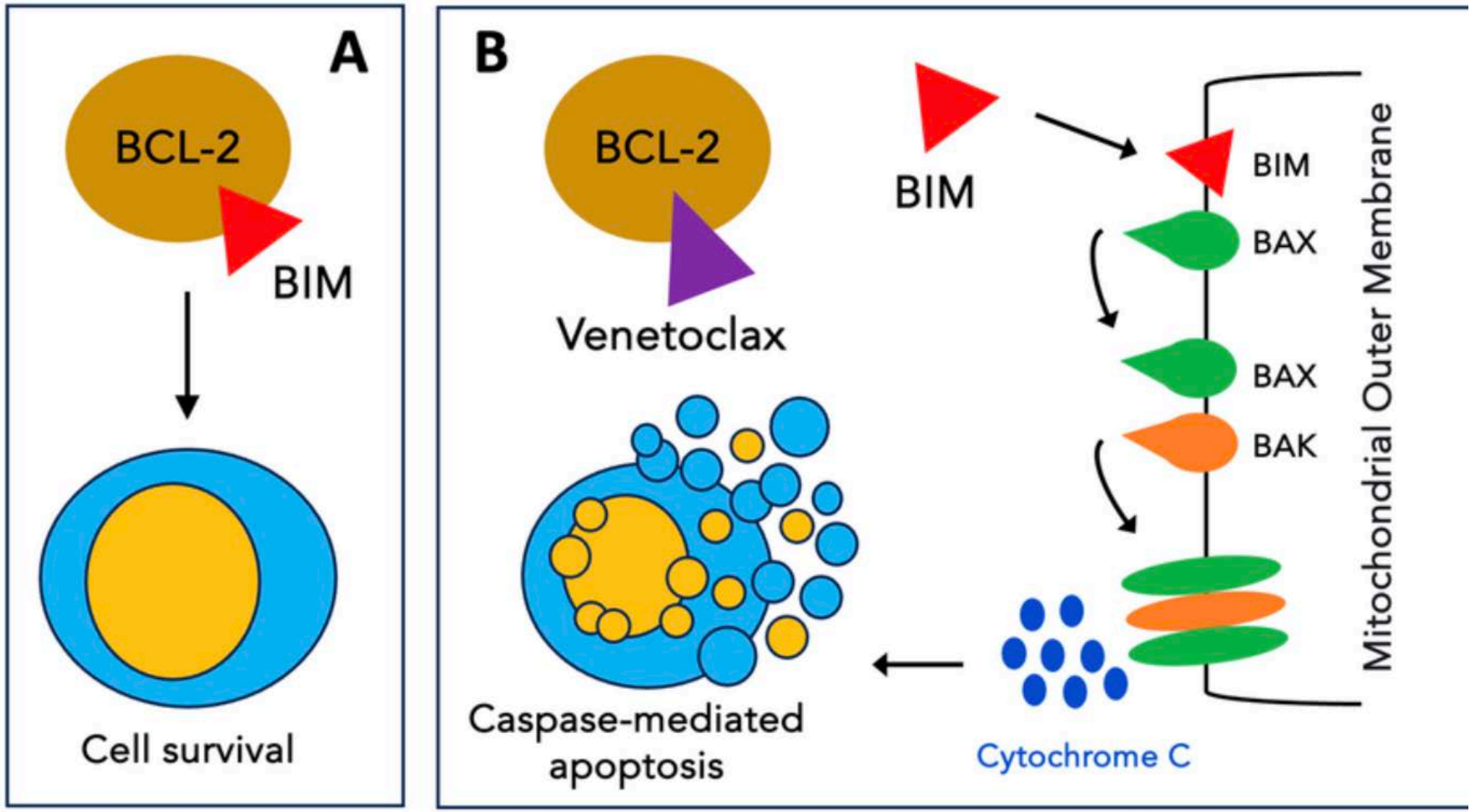


Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	73·8% SD 4·6	2·4% SD 2·4
No gemtuzumab ozogamicin	76·7% SD 4·8	21·1% SD 10·5

Hills et al., Lancet Oncol. 2014 Aug;15(9):986-96. doi: 10.1016/S1470-2045(14)70281-5. Epub 2014 Jul 6

Unanswered Questions

- What about adding venetoclax to cytotoxic induction?
- Could a menin inhibitor be utilized here alongside the cytotoxic backbone?
- How best follow her MRD? What do we do with persistent MRD?
- Is the cytotoxic backbone even necessary?



Rahme et al., Journal of Clinical Medicine, Jan 2024

Why BCL2 inhibition in AML?

Preclinical data	• Upregulated BCL-2 → evasion of apoptosis • Increased BCL-2 expression → worse prognosis
CALBG Study 2000s	• BCL-2 antisense oligonucleotide + intensive chemotherapy
Venetoclax	• BH3 mimetic, BCL-2 selective inhibitor • Monotherapy in R/R AML: Overall response rate of 19%

Dinardo, NEJM 2020; DiNardo, Blood 2020; Konopleva, Blood 2018; Michaelis, Blood 2020; Marcucci, JCO 2005

Regimen	Trial	Citation
Daunorubicin Cytarabine + Venetoclax	Phase II; Conducted in China N=33; CCR: 91% Ages 18-60 years No TRM	Wang et al., Lancet Haematol. 2022 Jun;9(6):e415-e424. doi: 10.1016/S2352-3026(22)00106-5. Epub 2022 May 2. PMID: 35512726
Cladribine, Idarubicin, Cytarabine + Venetoclax	Phase II; MD Anderson N=50; Up to age 65 years CCR: 94% TRM 1/50	Kadia et al., Lancet Haematol. 2021 Aug;8(8):e552-e561. doi: 10.1016/S2352-3026(21)00192-7.
Fludarabine Cytarabine Idarubicin + Venetoclax	Phase I; MD Anderson ND AML, N=29 Up to age 65; CCR: 96% 60-day mortality: 4%	DiNardo et al., J Clin Oncol. 2021 Sep 1;39(25):2768-2778. doi: 10.1200/JCO.20.03736. Epub 2021 May 27.
Daunorubicin Cytarabine + Venetoclax	Phase Ib Conducted in Australia ND AML, Ages 63-80 CR/CRI 97% in denovo AML	Chua et al., J Clin Oncol . 2020 Oct 20;38(30):3506-3517. doi: 10.1200/JCO.20.00572. Epub 2020 Jul 20.

Multiagent Chemotherapy + Venetoclax

- MD Anderson team investigated Fludarabine, Cytarabine, Idarubicin backbone with Venetoclax
- Newly Diagnosed AML
- Phase II, single-arm study
- Endpoint: ORR
- N=45 patients

TABLE 2 Response outcomes

Parameter[a]	All patients (*N* = 45)	ELN favorable[c] (*N* = 8)	ELN intermediate (*N* = 18)	ELN adverse (*N* = 19)
Overall response[b]	98 (44 [90–100])	100 (8 [74–100])	94 (17 [77–99])	100 (19) [90–100]
Composite CR	89 (40 [75–96])	88 (7 [32–99])	89 (16 [61–98])	89 (17 [63–98])
Complete response	73 (33)	63 (5)	72 (13)	79 (15)
CRh	11 (5)	25 (2)	11 (2)	5 (1)
CRi	4 (2)	-	6 (1)	5 (1)
MLFS	9 (4)	13 (1)	6 (1)	11 (2)
No response	1 (2)	-	1 (6)	-
MRD-negative (MFC)	93 (37/40 [78–98])	100 (7/7 [NA])	88 (14/16 [57–97])	94 (16/17 [63–99])
Duration of response	NR (-)	NR (-)	NR (17-NR)	NR (11-NR)

[a]All variables presented as median (range) or % (*N*/).

[b]95% Credible intervals per Protocol-defined primary efficacy outcome (95% credible interval estimation assumed ORR follows a prior distribution of beta of (1.4, 0.6). 95% Exact confidence intervals presented for other response outcomes. Response variables reported as % (N [95%CI]) when credible interval or confidence interval included.

[c]ELN favorable risk patients were composed of *NPM1* or biallelic *CEBPA* mutations, no patients with favorable risk cytogenetics were enrolled on study.

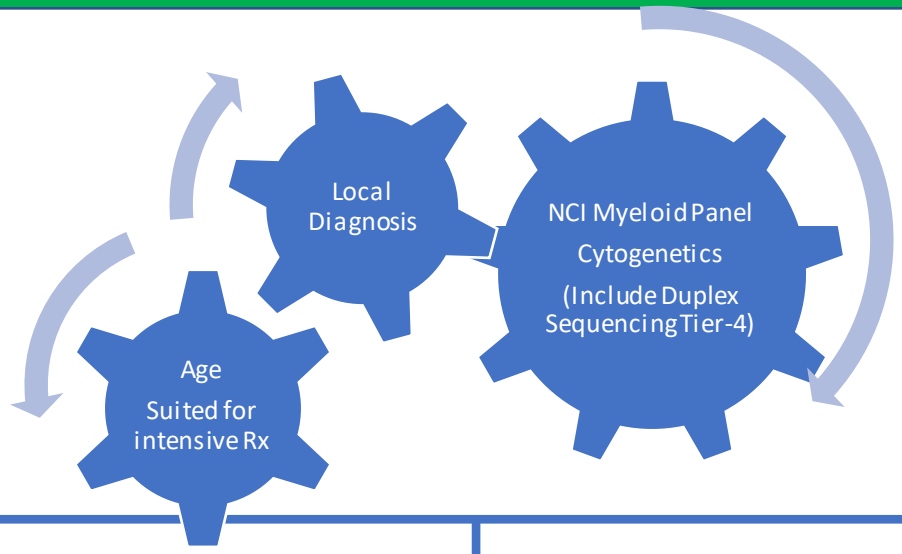
DiNardo et al, Am J Hematol.2022;97:1035–1043

What would this patient’s treatment look like on myeloMATCH?

myeloMATCH option

Patient would be consented and registered

Master Screening Protocol MATCHBox



TIER 1

Older Basket → **Younger Basket**

MDS

MyeloMATCH: Menu of Assays (<72 hours TAT)

- At diagnosis (risk classification, therapy targets)
  - Rapid cytogenetics/FISH/CGAT
  - Flow cytometry
  - Rapid NGS (Ion Torrent™)
- MRD assessment
  - Multicolor flow cytometry (outcome, MRD eraser assignment)
  - Duplex sequencing-potentially better than flow?
- Clonal heterogeneity (understanding clonal selection and response)
  - Single cell DNA, RNA, protein

Integral studies
Integrated studies

All assays performed in CLIA certified labs in FHCRC, Frederick National Laboratory, and UCLA Children's Hospital

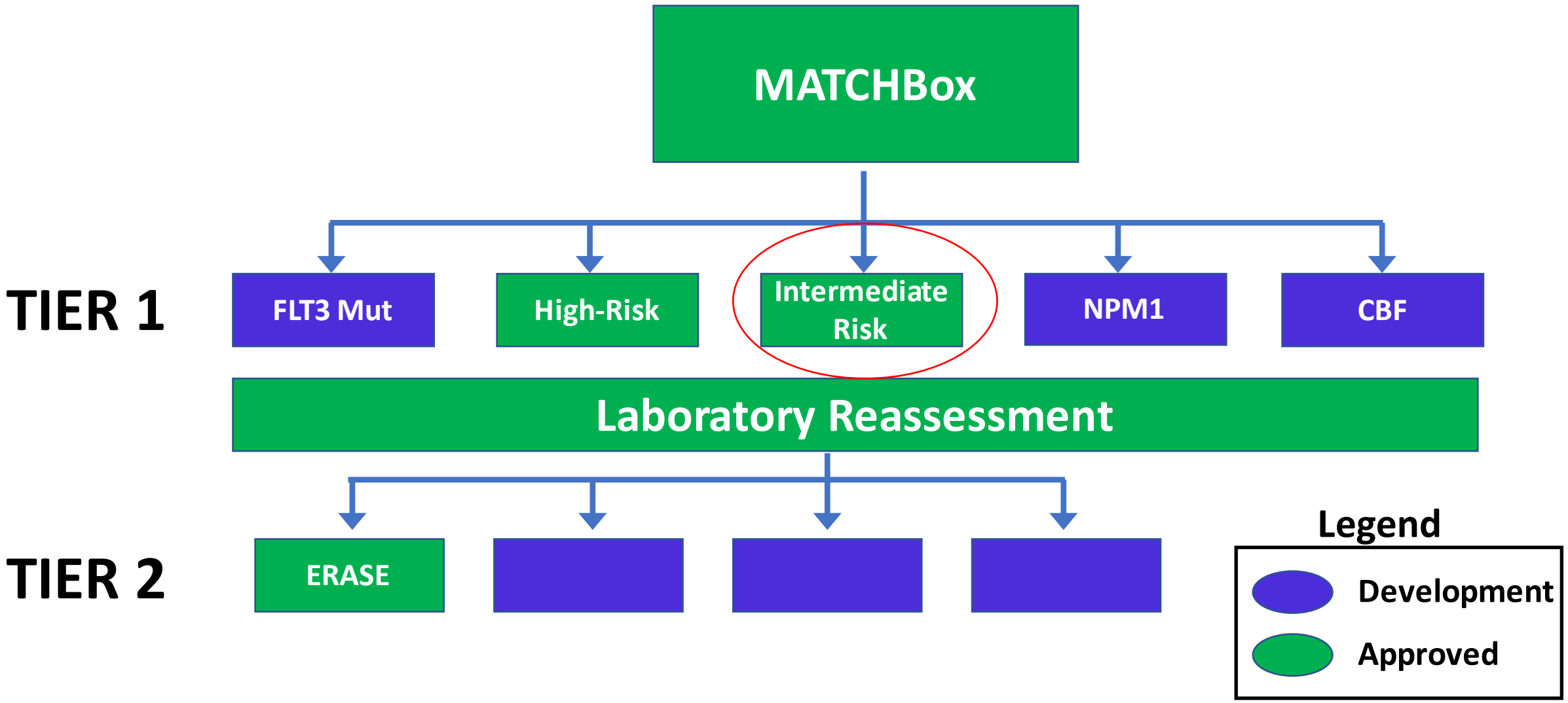
MyeloMATCH: NCI Myeloid Gene Assay version 2

DNA hotspots				
ABL1	*ANKRD26*	*BRAF*	*CBL*	*CSF3R*
DDX41	*DNMT3A*	*FLT3*	*GATA2*	*HRAS*
IDH1	*IDH2*	*JAK2*	*KIT*	*KRAS*
MPL	*MYD88*	*NPM1*	*NRAS*	*PPM1D*
PTPN11	*SETBP1*	*SF3B1*	*SMC1A*	*SMC3*
SRSF2	*U2AF1*	*WT1*		
DNA Full Gene				
ASXL1	*BCOR*	*CALR*	*CEBPA*	*ETV6*
EZH2	*IKZF1*	*NF1*	*PHF6*	*PRPF8*
RB1	*RUNX1*	*SH2B3*	*STAG2*	*TET2*
TP53	*ZRSR2*			
RNA Fusion Driver Genes				
ABL1	*ALK*	*BCL2*	*BRAF*	*CCND1*
CREBBP	*EGFR*	*ETV6*	*FGFR1*	*FGFR2*
FUS	*HMGA2*	*JAK2*	*KMT2A (MLL) +PTDs*	*MECOM*
MET	*MLLT10*	*MLLT3*	*MYBL1*	*MYH11*
NTRK3	*NUP214*	*NUP98*	*PDGFRA*	*PDGFRB*
RARA	*RBM15*	*RUNX1*	*TCF3*	*TFE3*
BAALC	*MECOM*	*MYC*	*SMC1A*	*WT1*

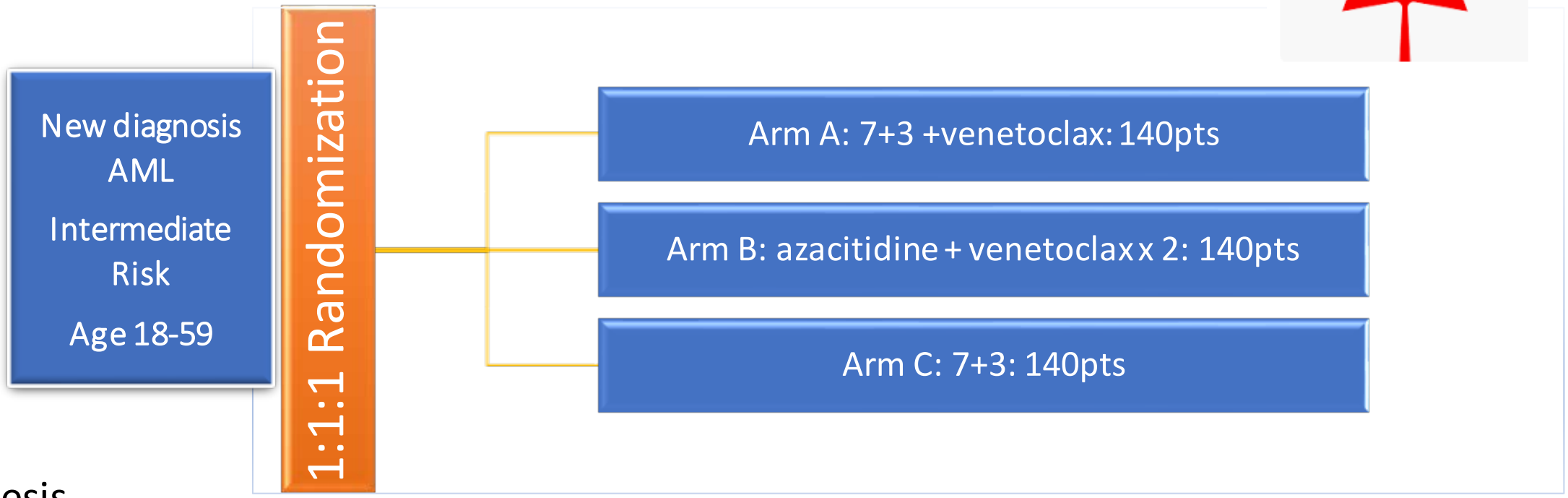
- Platform: Ion Torrent™ Genexus™ System
  - 45 DNA genes and 35 fusion driver genes
  - Includes 28/30 (93.3%) genes mutated with >=3% frequency in AML.
  - Includes 36/50 (72%) genes mutated with >1% frequency in AML.
  - Includes 779 unique fusions reported in AML
  - Can detect FLT3-ITD up to 120bp
- Can detect all genetic alterations needed for
  - WHO classification of AML, except inv 3
  - NCCN/ELN risk stratification, except inv 3

Slide courtesy of Rich Little, Harry Erba

First Generation Studies in the Younger Basket



MM1YA-CTG01
Study co-chairs: Sarit Assouline and Lynn Savoie



Hypothesis

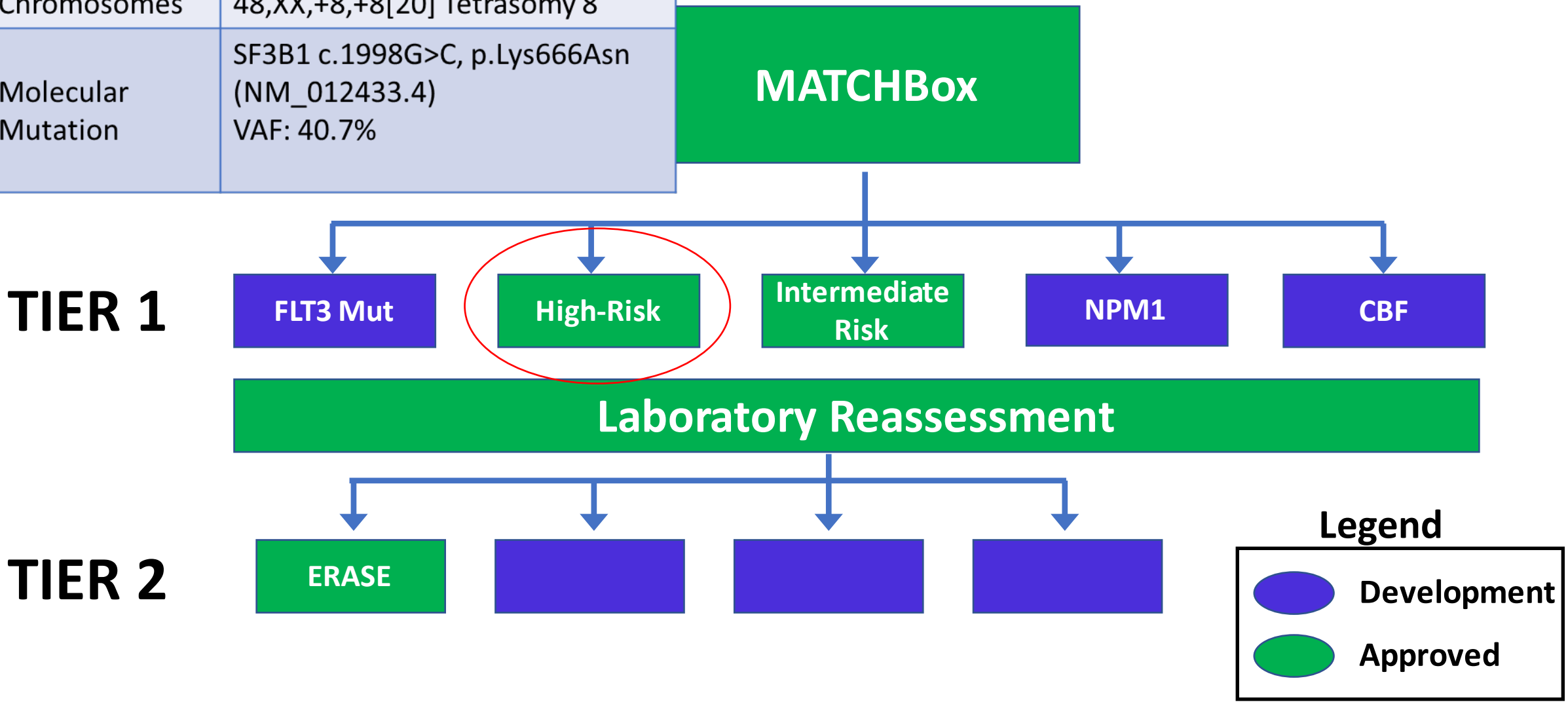
- The addition of venetoclax to chemotherapy will increase MRD negative complete response (CR) in newly diagnosed AML patients fit for induction chemotherapy with intermediate risk disease

Primary objective

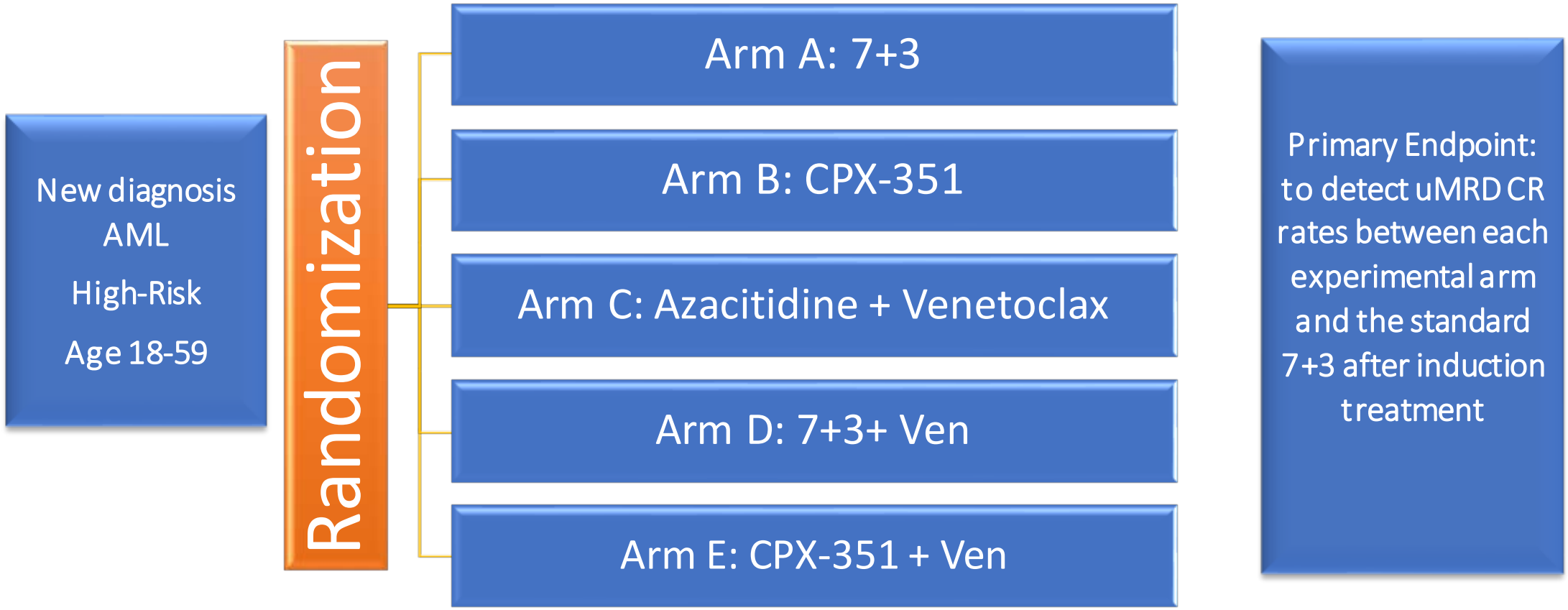
- MRD negative (by FLOW Cytometry) complete response rate (CR) after standard induction, standard induction with venetoclax, or two cycles of venetoclax + azacitidine

First Generation Studies in the Younger Basket

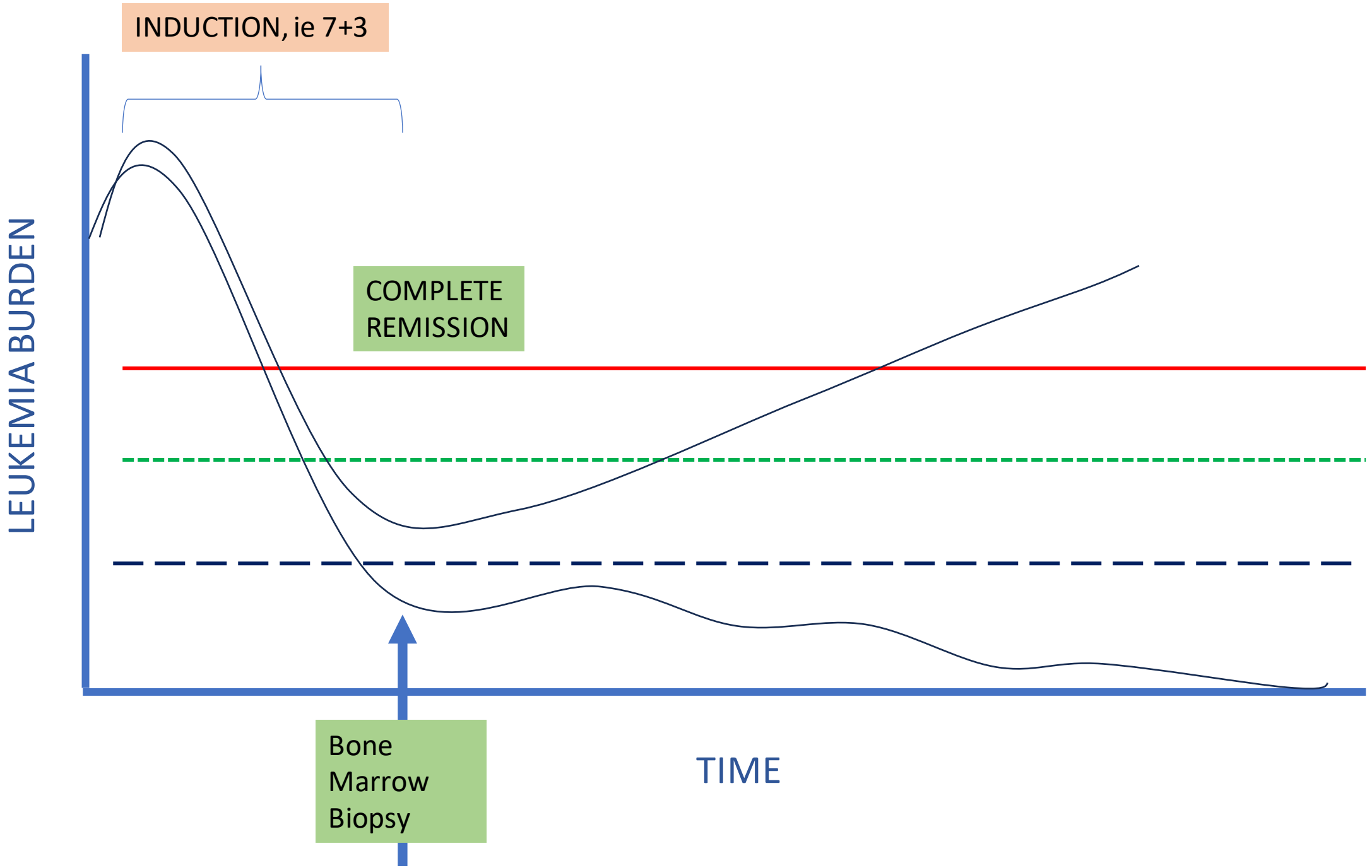
Chromosomes	48,XX,+8,+8[20] Tetrasomy 8
Molecular Mutation	SF3B1 c.1998G>C, p.Lys666Asn (NM_012433.4) VAF: 40.7%



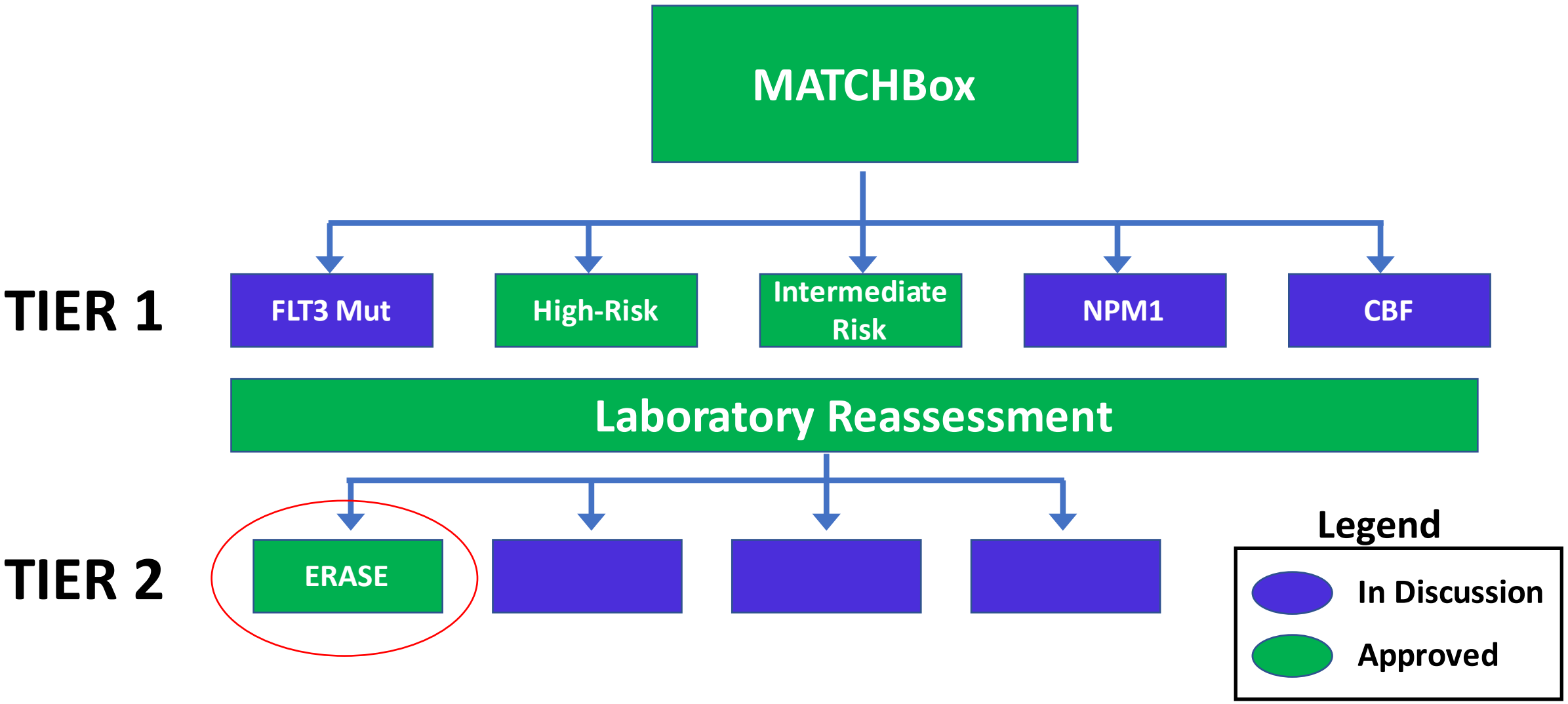
MM1YA-S01
Study co-chairs: Paul Shami and Tara Lin



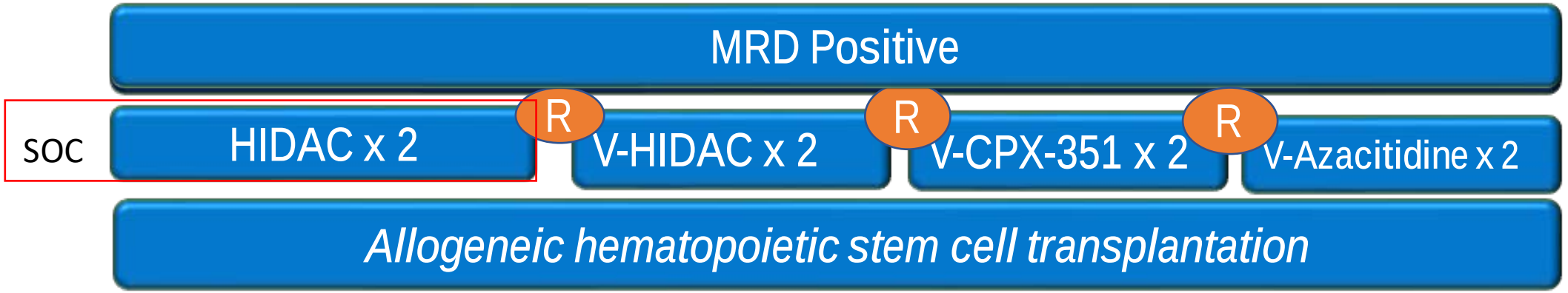
Sample size: 268 (60 +7 per arm)


INDUCTION, ie 7+3
LEUKEMIA BURDEN
COMPLETE
REMISSION
Bone
Marrow
Biopsy
TIME

First Generation Studies in the Younger Basket



MM2YA-EA01
Study co-chairs: Ehab Atallah and Rita Assa

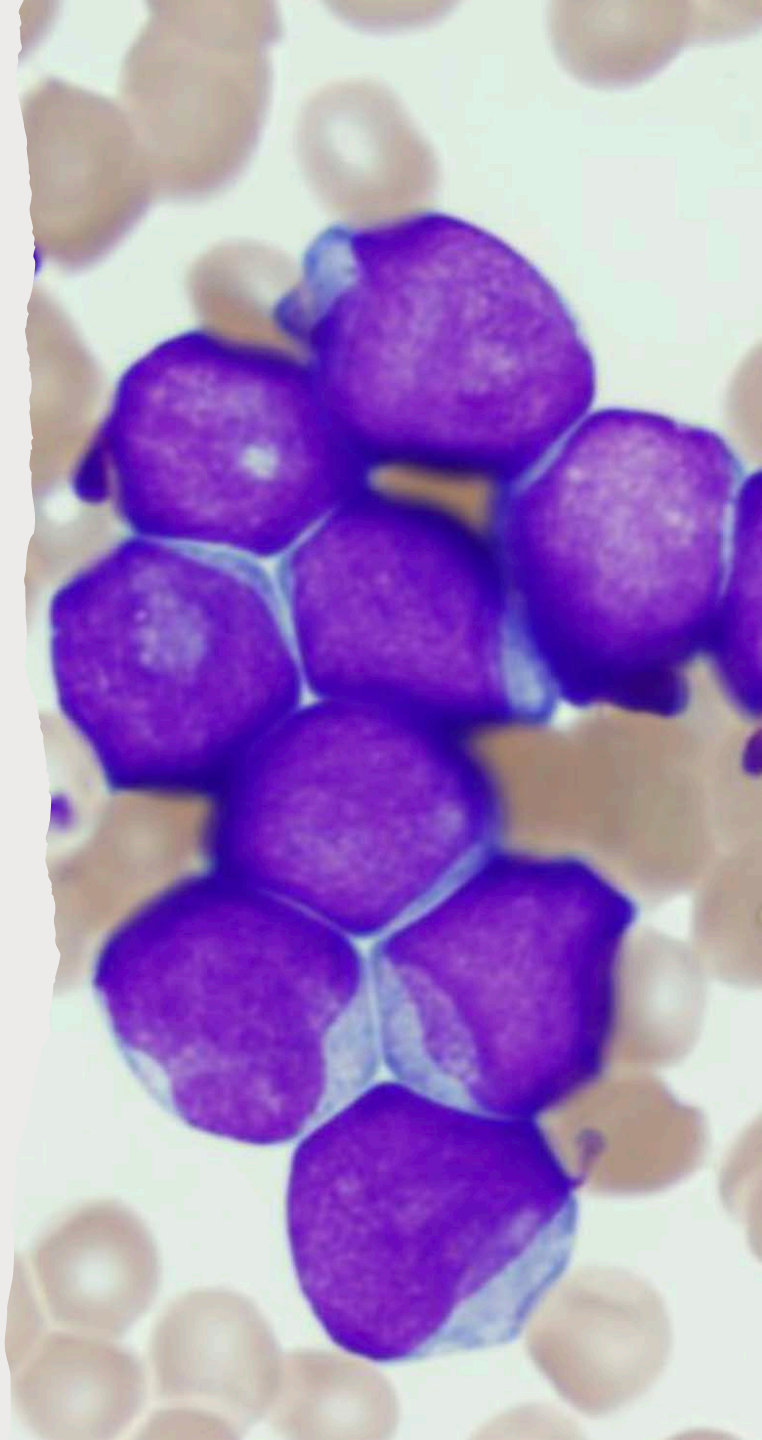


Specific Hypothesis: The inclusion of venetoclax in post remission therapy will lead to better MRD –ve CR rates amongst patients with MRD+ve disease after initial induction therapy compared to standard post- remission treatment.

Topics for the Day

- Definitions
  - Precision Medicine
  - myeloMATCH
- Current State of Therapeutic Options
  - Younger, Fit
  - Older or Frail
- Hurdles and Potential for this Strategy
- Discussion

- 74-yo man referred from emergency department of hospital in Appleton Wisconsin
- Hypertension, hyperlipidemia
- Smoked: ages 20-50
- H/O renal cell carcinoma with left-sided nephrectomy 19 years ago
- Presents with fatigue, night sweats, cough
- Complete blood count concerning for leukocytosis, anemia, thrombocytopenia and circulating blasts
- History of Chronic Obstructive Pulmonary Disease (COPD)



- Peripheral Blood:
  - WBC: 23.20 X 10^3/uL
  - Hgn: 7.5 gm/dL
  - Platelet Count: 36 X 10^3/uL
  - 37% circulating myeloid blasts
- Flow-cytometry with aberrant immunophenotype
- Bone Marrow Biopsy confirms Acute Myeloid Leukemia
- FISH: No recurrent cytogenetic mutations
- NPM-1mut, FLT3 ITD

Fit for Intensive therapy?

Acute Myeloid Leukemia : 2024

Clinical trial available? Appropriate? If not, then…

Likely To Respond to cytotoxic therapy? Fit for Intensive therapy? Curable with cytotoxic therapy alone? If not, then…

FLT-3 Mutated	IDH1 or IDH2 mutated	No targetable Mutations
Venetoclax + Azacitidine or Decitabine DiNardo, NEJM 2020	Venetoclax + Azacitidine or Decitabine DiNardo, NEJM 2020	Venetoclax + Azacitidine or Decitabine DiNardo, NEJM 2020
Azacitidine + Sorafenib Ohanian et al., Am J Hematology 2018; 93:1136-1141	Ivosidenib or Enasidenib monotherapy Dinardo et al., Blood 2017; Stein et al, Blood 2015	HMA Exposed/Refractory
		Venetoclax + Low-Dose Cytarabine Wei et al., JCO, 2020
	Ivosidenib + Azacitidine Montesitos et al., NEJM 2022	Glasdegib + Low-Dose Cytarabine – over 75 years of age Cortes, Blood 2016

Complete Remission (+/- MRD) AND No significant comorbidities: Discuss Reduced-Intensity Allogeneic Stem Cell Transplant

Why BCL2 inhibition in AML?

Preclinical data	• Upregulated BCL-2 → evasion of apoptosis
CAL	
Venetoclax	• Monotherapy in R/R AML: Overall response rate of 19%
Azacitadine	• Non-specific, but some anti-MCL-1 activity

ORIGINAL ARTICLE

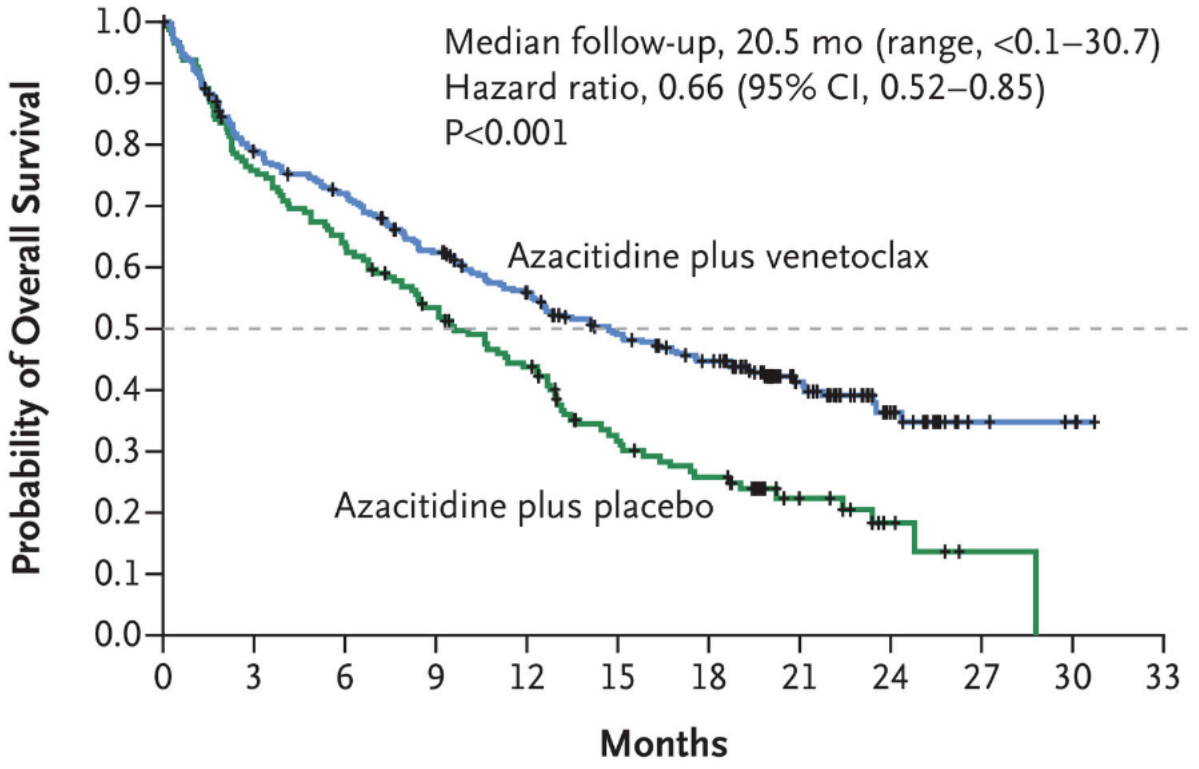
Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

Courtney D. DiNardo, M.D., Brian A. Jonas, M.D., Ph.D., Vinod Pullarkat, M.D., Michael J. Thirman, M.D., Jacqueline S. Garcia, M.D., Andrew H. Wei, M.B., B.S., Ph.D., Marina Konopleva, M.D., Ph.D., Hartmut Döhner, M.D., Anthony Letai, M.D., Ph.D., Pierre Fenaux, M.D., Ph.D., Elizabeth Koller, M.D., Violaine Havelange, M.D., Ph.D., et al.

Dinardo, NEJM 2020; DiNardo, Blood 2020; Konopleva, Blood 2018; Michaelis, Blood 2020; Marcucci, JCO 2005

- Median Follow-up 20.5 months
- Median OS
  - Interventional Arm: 14.7 months
  - Control Arm: 9.6 months
  - HR for death, 0.66; 95% CI, 0.52 to 0.85; P<0.001
- Complete Remission Rate/Composite Complete Remission Rate (CR + CRi)
  - Interventional Arm: 36.7%/66.4%
  - Control Arm: 17.9%/28.3%

TAKE HOME MESSAGES
- Excellent New Option
- Safe, but not risk-free
- Unknown effectiveness compared to cytotoxic therapy

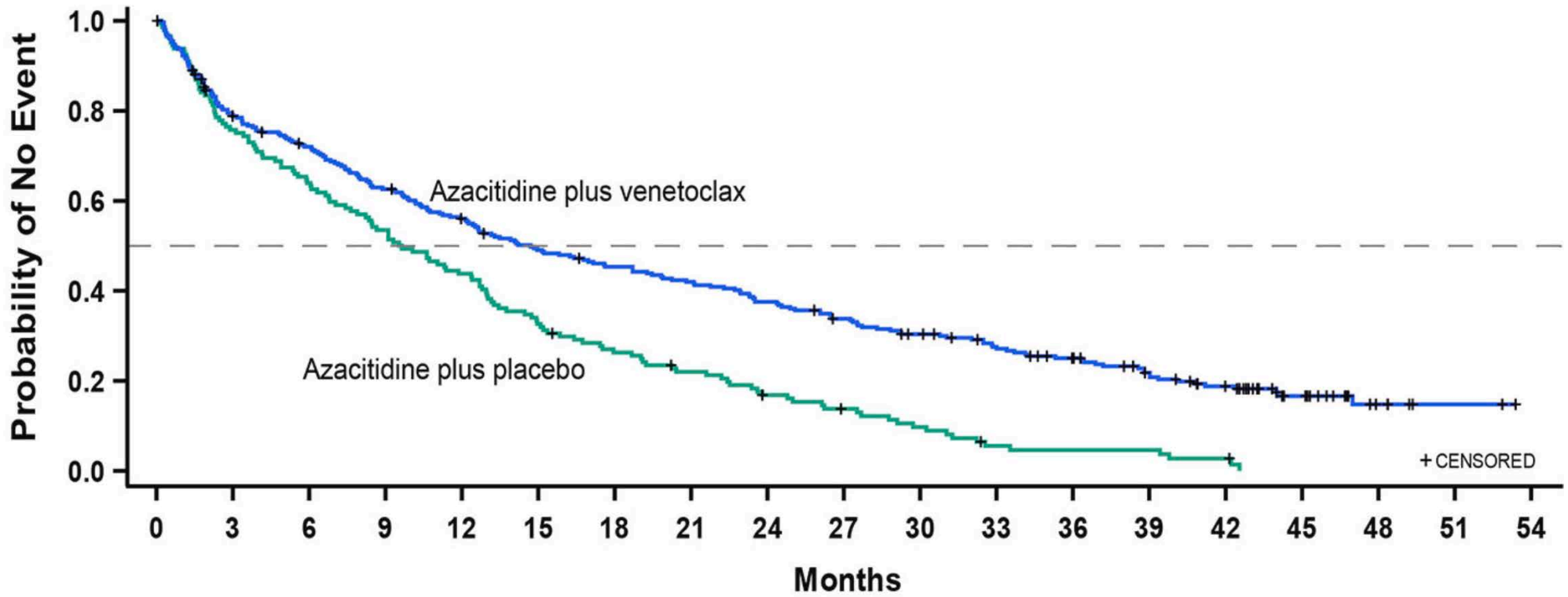


No. at Risk

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; Jonas BA et al., NEJM August 2020

Figure 1. Overall Survival

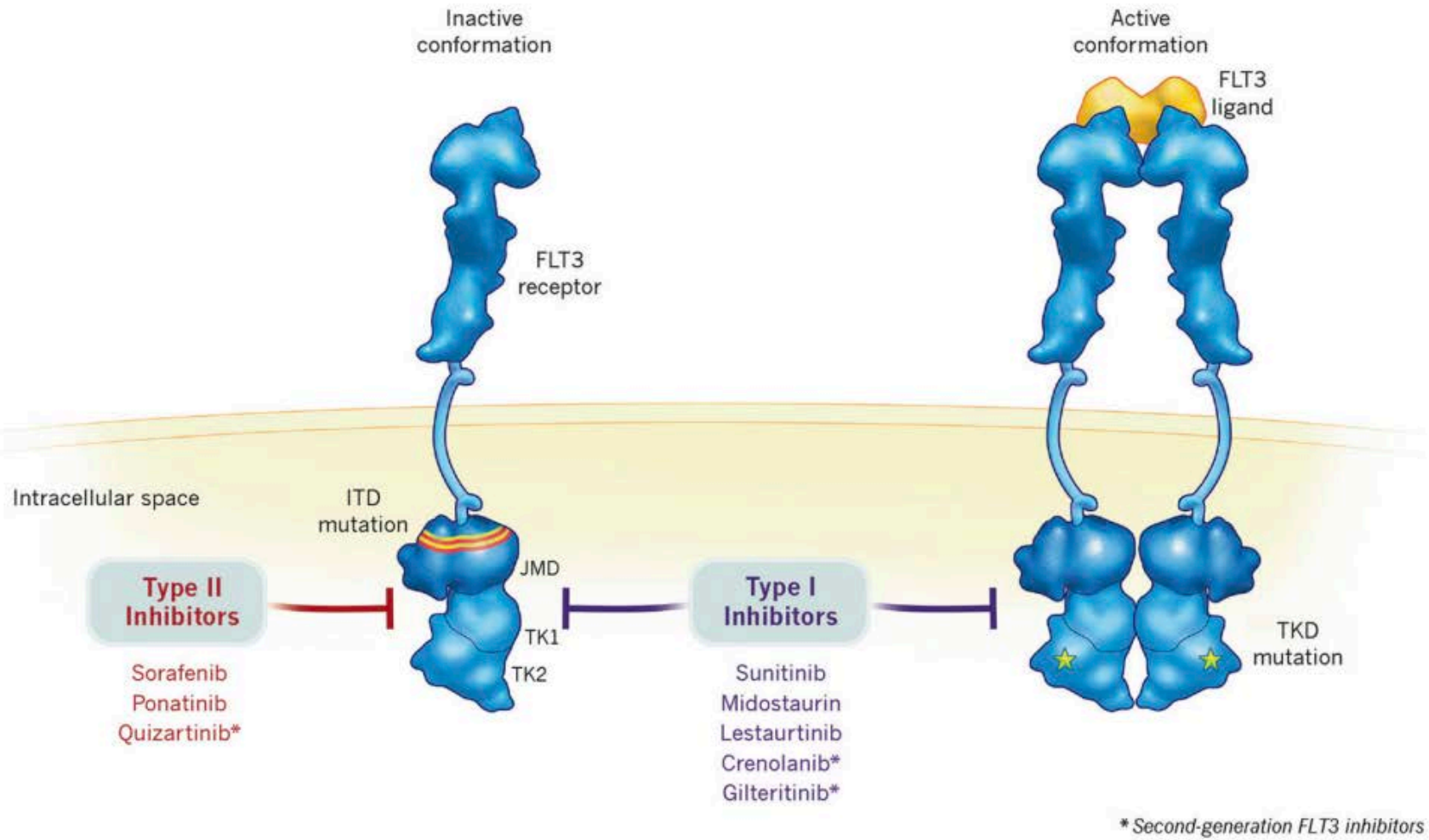


Patients at Risk

Azacitidine plus placebo	145	109	92	77	63	47	37	30	22	17	12	6	5	5	3	0			
Azacitidine plus venetoclax	286	220	199	173	153	133	122	113	101	89	78	67	57	45	34	18	6	2	0

Pratz et al., ASH 2022 Update

FLT3 inhibition

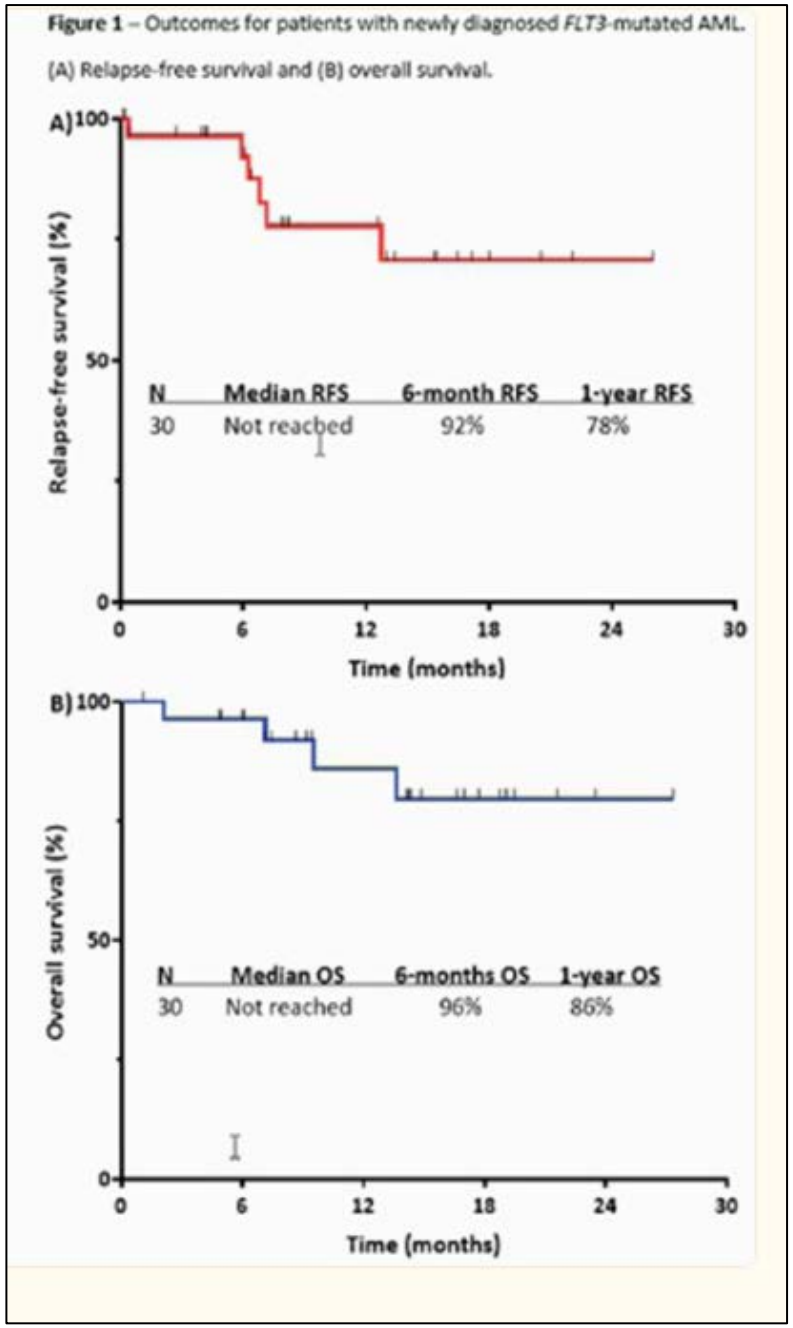


Daver et al, Nature Medicine 2019

What about triplet therapy?

- Gilteritinib plus Aza-Ven N=30
- ND FLT3mut AML
- MD Anderson team
- Phase II, FLT3mut (ITD and TKD)
- Newly Diagnosed AML, ages 18-60

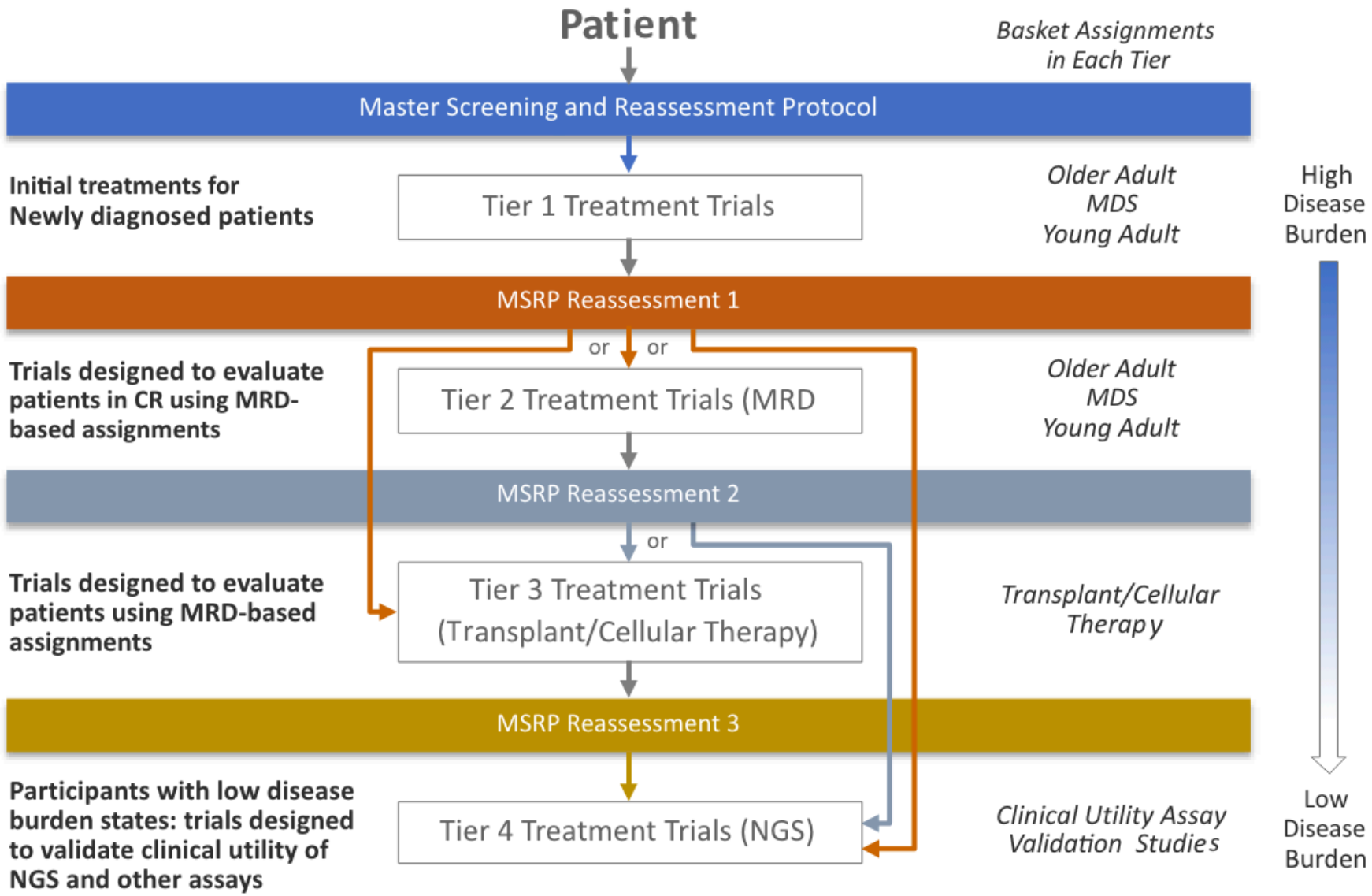
CR/CRi	29/30 (96%)
MRDneg by flow	26/30 (87%)
MRDneg by PCR	27/30 (90%)



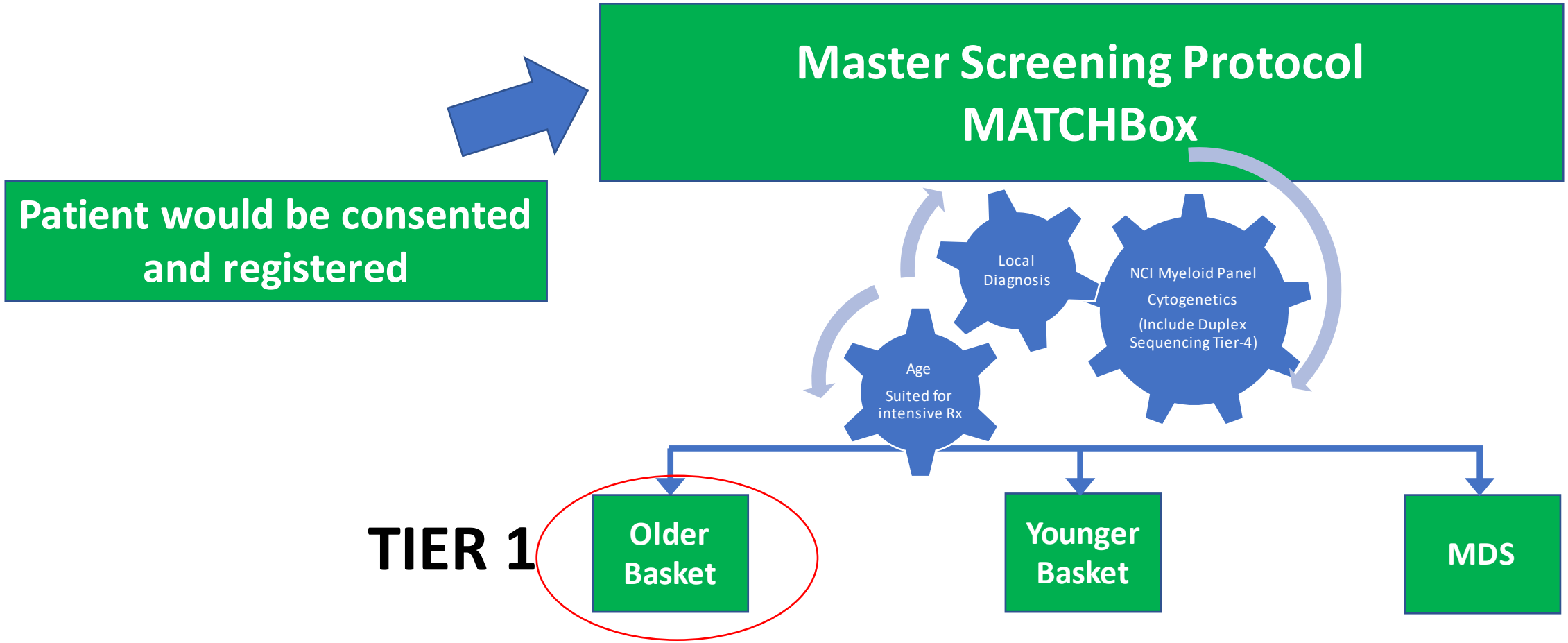
Short et al, ASH 2021; EHA 2023.

What would this patient’s treatment look like on myeloMATCH?

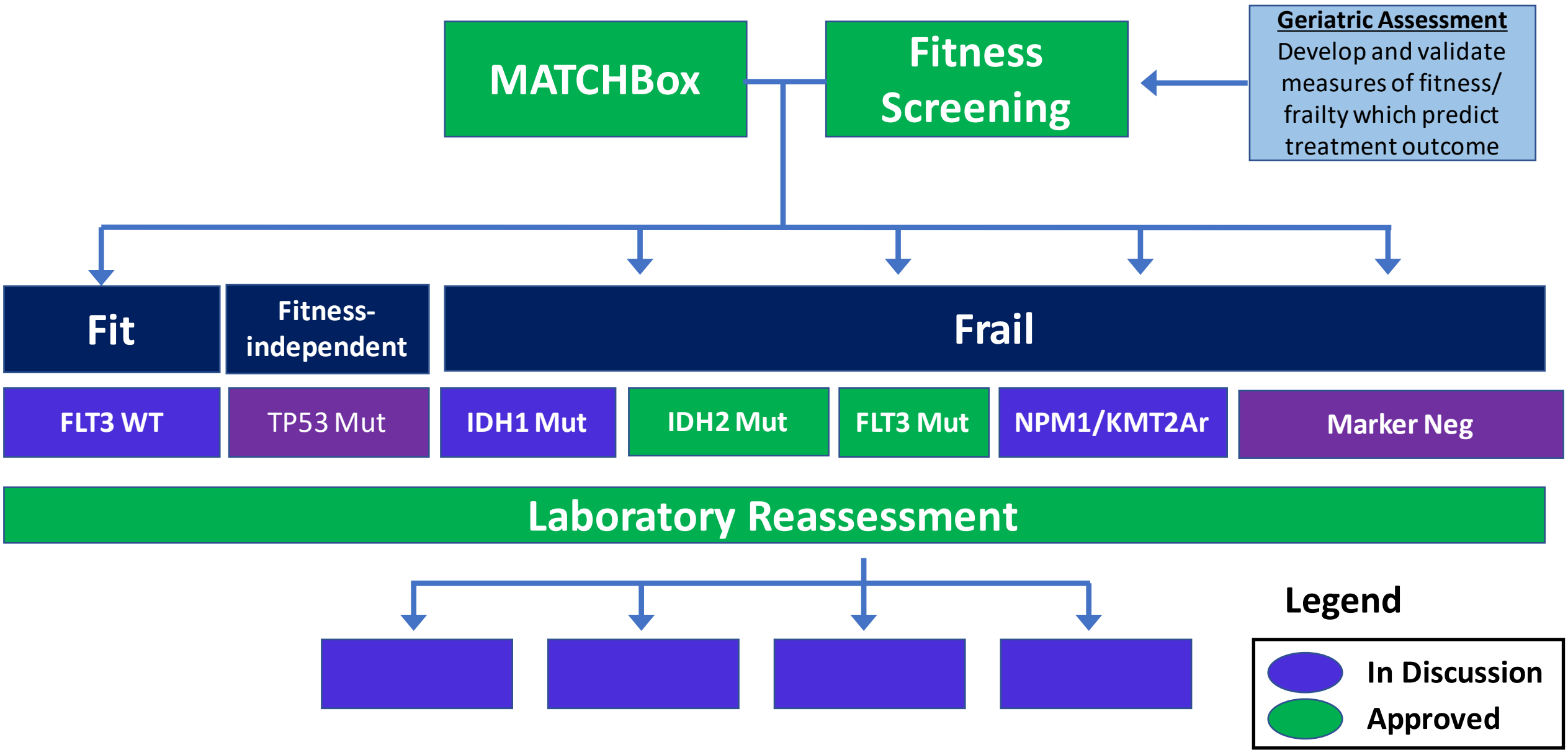
MyeloMATCH MSRP Schema



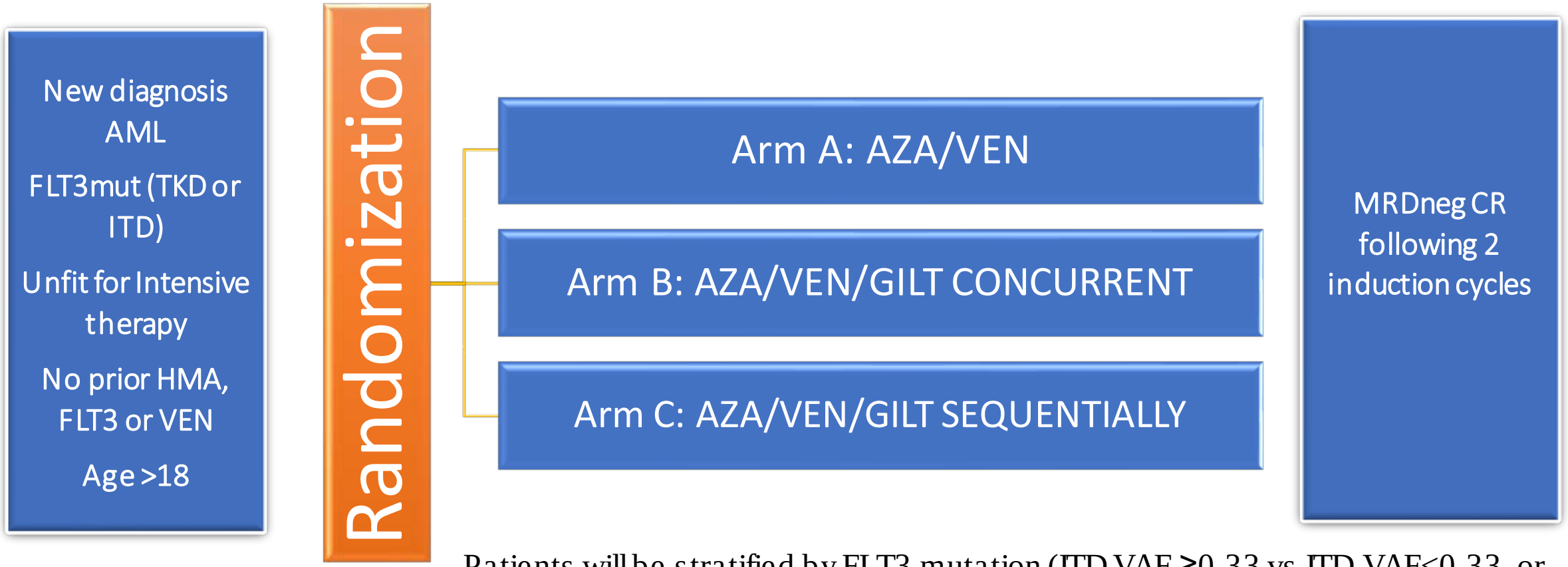
myeloMATCH option



First Generation Studies in the Older Basket

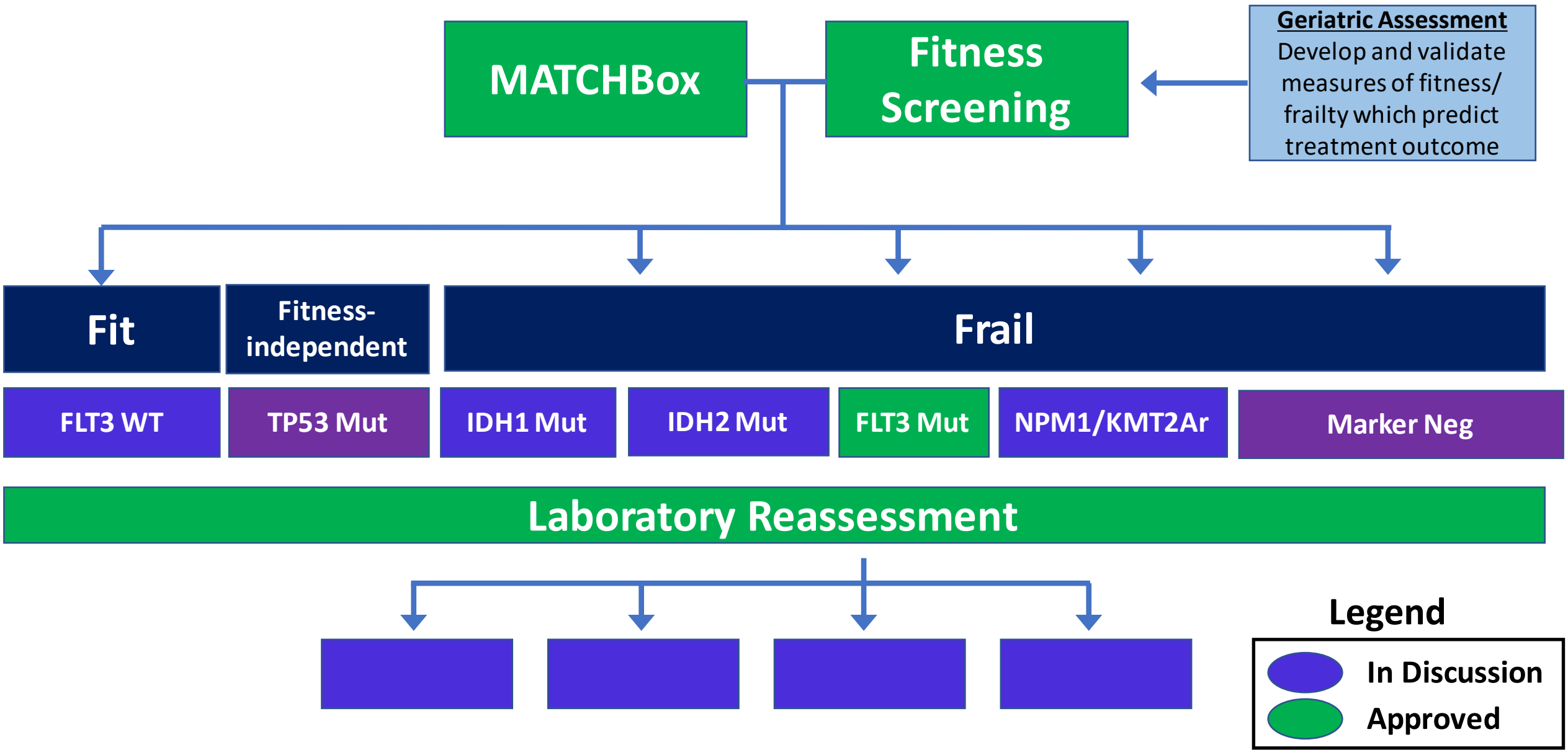


MM1OA-EA02
Study co-chairs: Jessica Altman, Alexander Perl



Patients will be stratified by FLT3 mutation (ITD VAF ≥0.33 vs ITD VAF<0.33, or TKD) and age (<70. ≥ 70 years)
N=147

First Generation Studies in the Older Basket



What about the patients for whom there is no trial?

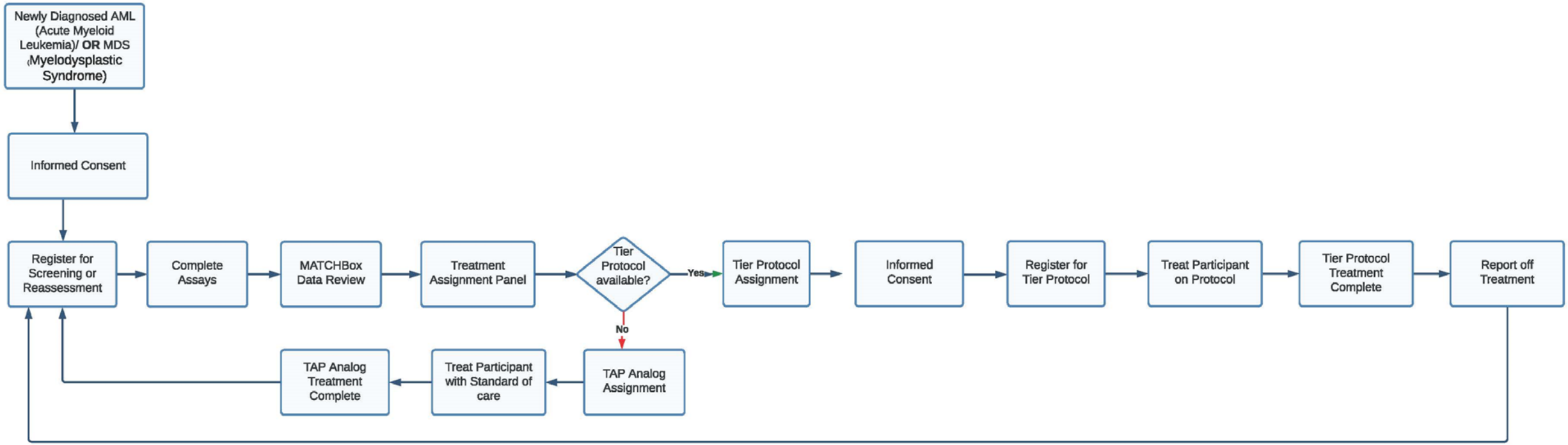
Tier Advancment Pathway (TAP)

Screening and Reassessment (MSRP): To evaluate the feasibility of MATCHBox generating all data needed for assignment to a myeloMATCH clinical trial or Tier Advancement Pathway (TAP) within 72 hours of MDNet receipt of all required specimens for initial therapy and within 10 days for subsequent therapy.

Tier Advancement Pathway (TAP): To enable participants who are not matched to an investigational myeloMATCH treatment substudy to receive standard of care while remaining on the MSRP to maintain access to later tiers of treatment substudies.

MyeloMATCH Treatment Options

Updated Aug 03, 2023



What is the current status of the platform?

MyeloMATCH: Current Status

- 20 MyeloMATCH-specific and CTEP-wide CRADAs with industry collaborators in place to support clinical sub-studies
- FDA CDRH approved MyeloMATCH MSRP IDE on 14 DEC 2023.
- FDA CDER gave the IND “safe to proceed” on 10 JAN 2024.
- Activated May of 2024
- More than 200 people currently enrolled
- 11 additional concepts are currently in development
  3-Older AML basket; 3-MDS basket; 3-Younger AML basket; 2-Transplant basket

What Can We Learn…

- Is the platform feasible?
- Which induction arm leads to highest rate of MRDu CRs?
- What are the comparative toxicities?
- Can we confirm MRDneg CR as a reliable surrogate for event-free survival and overall survival?
- What disease features, other than molecular signature and chromosome, impact outcome? What patient features?
- Can we accrue at sites outside of large leukemia centers?

Short et al., JAMA Oncol. 2020; Jongen-Laverencic et al., Molecular minimal residual disease in acute myeloid leukemia, NEJM 2018; Hourigan et al., JCO 2020

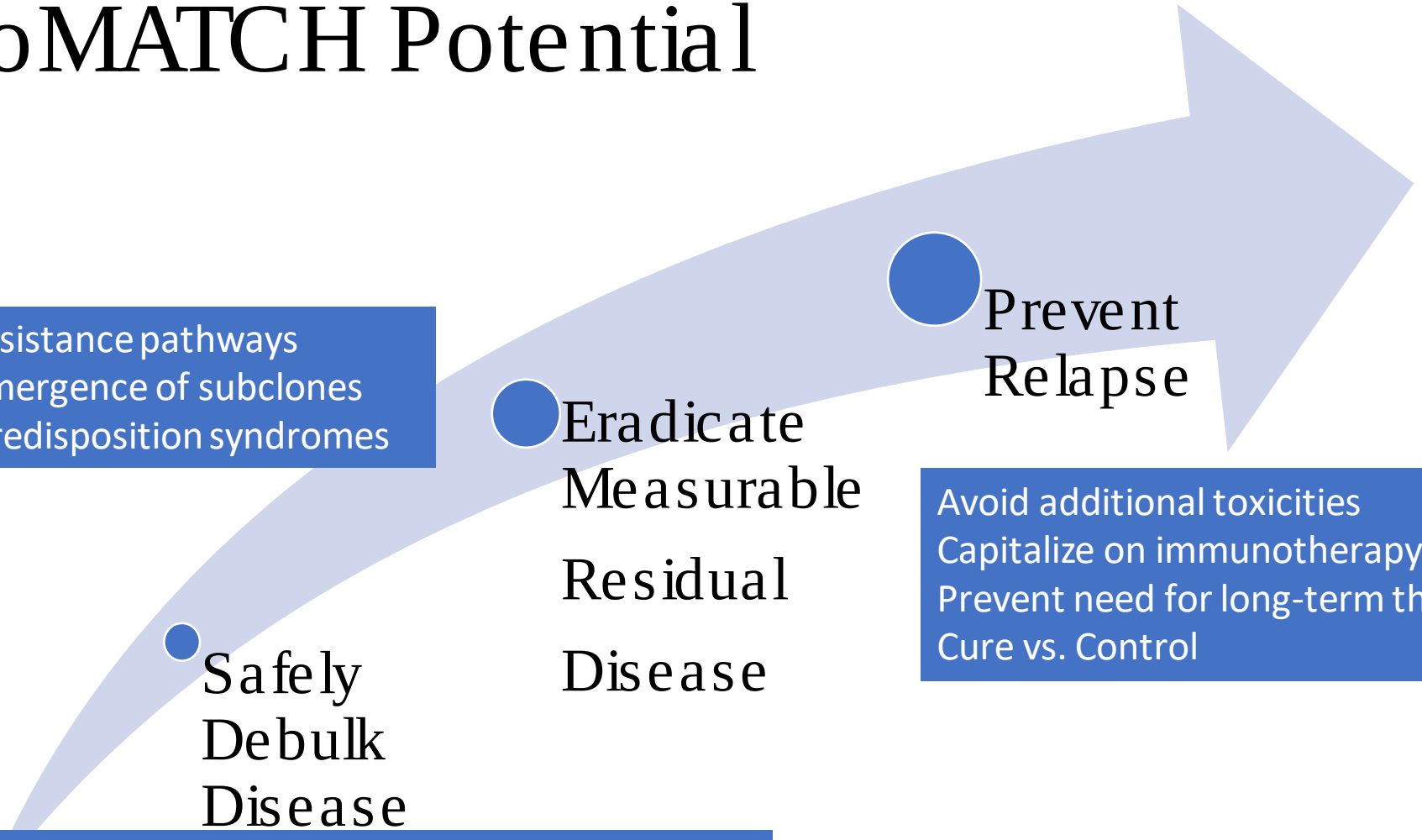
MyeloMATCH Hurdles

- Immense Logistical Feat
  - Collaboration amongst the cooperative groups
  - Collaboration with pharmaceutical partners
  - Working with FDA
- Challenges facing the sites
- Dealing with a dynamic environment

- Even if the logistics all go perfectly…

  - Not enough drugs for the targets
  - Not enough studies for the patients
  - Not enough patients enrolled on the trials

MyeloMATCH Potential



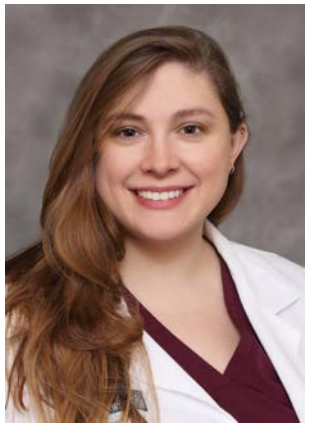
Leukemia Faculty and APPs







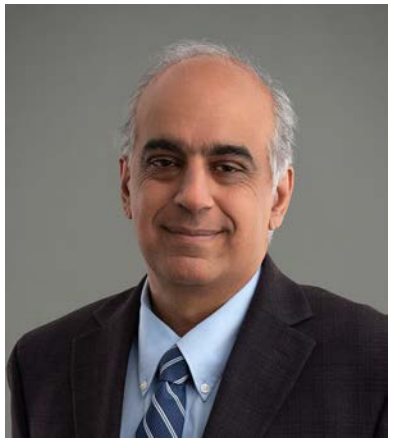


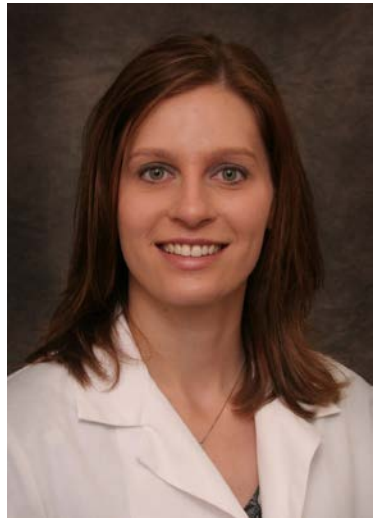



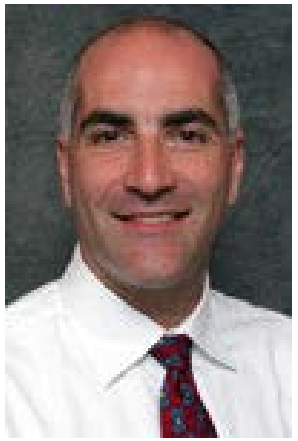

Malignant Hematology Faculty and Staff

- Transplant and Cellular Therapy





Thanks so much for the invitation to speak

Very happy to take any questions

NCI myeloMATCH Leadership Team

Rich Little; Jerry Radich; Percy Ivy; Rich Stone; Mark Litzhow; Harry Erba; Geoff Uy; Ehab Atallah; Toyosi Odenike; Selina Lugar; Patrick Stiff; Steve Gore and many many many others

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