Is it time to consider Triplet Therapy in Older Adults with FLT3-mutated AML

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Objectives

Understand the role of triplet induction therapy for FLT3-mutated AML in older adults

Background

Acute Myeloid Leukemia (AML) is the most common leukemia among adults

- Approximately 4.2 new cases per 100,000 population
- Median age of diagnosis is 65 years

Characterized by mutations in genes involved in hematopoiesis

- These mutations promote clonal expansion of undifferentiated myeloid “blasts” which expand in the peripheral blood and bone marrow
- Congenital mutations associated with AML diagnosis in younger adults

Vakiti A. *StatPearls. 2022.*

Background

Nucleophosmin 1 (NPM1)	**FMS-like Tyrosine Kinase 3 (FLT3)**	Runt-related Transcription Factor (RUNX1)
Isocitrate Dehydrogenase (IDH)	Tumor Protein 53 (TP53)	Lysine Methyltransferase 2A (KMT2A-rearrangement)

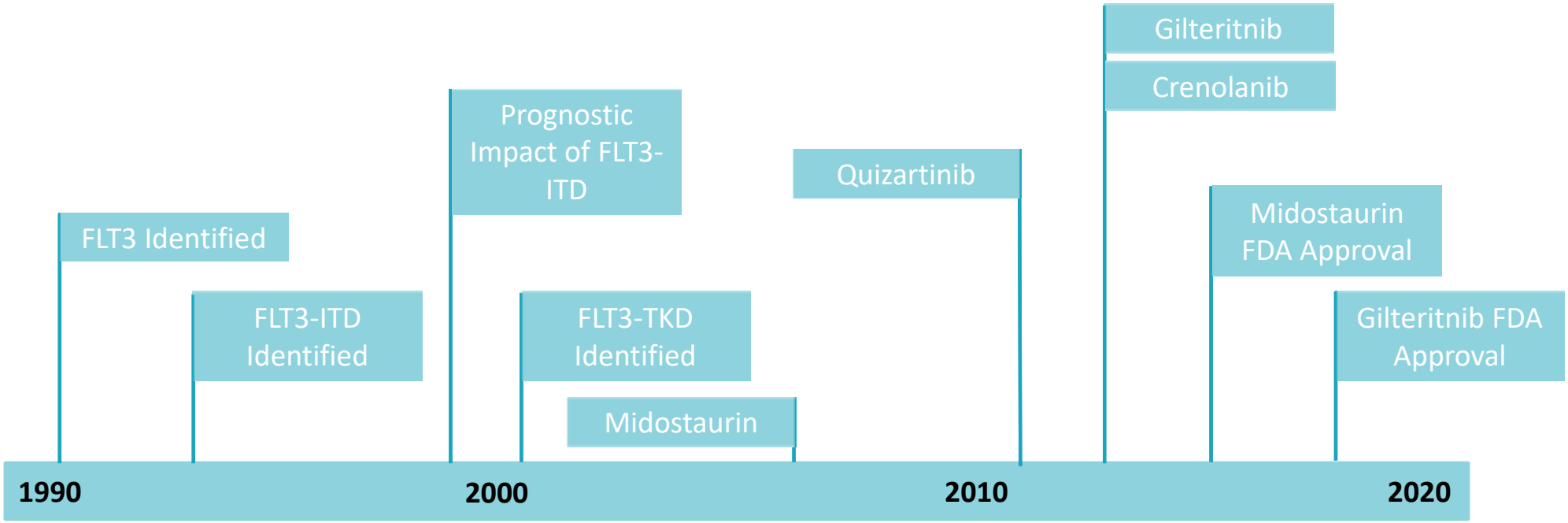
Vakiti A. *StatPearls. 2022.*

FMS-like Tyrosine Kinase 3 (FLT3)

Most frequent genetic alternation and poor prognostic factor in AML	• Approximately 30% of AML cases • European LeukemiaNet (ELN) 2022 reclassified FLT3-AML as **intermediate** risk
Type III Receptor Tyrosine Kinase which plays a role in hematopoietic stem cell proliferation and survival	• Present on both normal stem cells and myeloid blasts
Two major types of FLT3 mutations:	• Internal tandem duplication mutation in the juxtamembrane domain (FLT3-ITD) • point mutations or deletion in the tyrosine kinase domain (FLT3-TKD)
Both mutant FLT3 molecules are activated through ligand-independent dimerization and trans-phosphorylation	• Downstream activation of pathways involving PI3K, RAS and STAT5

Kiyoi H. *Cancer Science. 2019.*

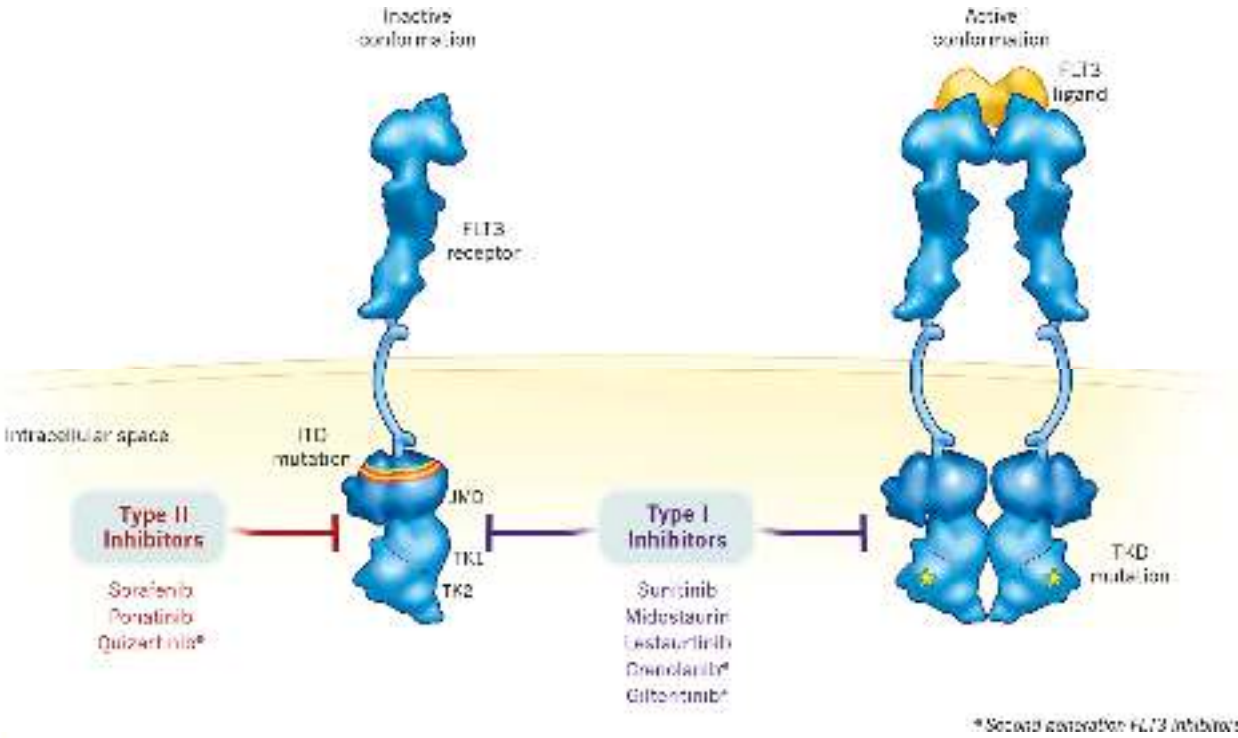
FMS-like Tyrosine Kinase 3 (FLT3)



Kiyoi H. *Cancer Science. 2019.*

FMS-like Tyrosine Kinase 3 (FLT3)

- **Type I Inhibitors:** Bind to FLT3 in the **Active** conformation; at either the activation loop or the ATP-binding pocket
  - **Active against ITD and TKD**
- **Type II Inhibitors:** Bind to FLT3 in the **Inactive** confirmation; adjacent to the ATP-binding domain
  - **Active against ITD Only**



Kiyoi H. *Cancer Science. 2019.*
Daver N. Leukemia. 2019.

Gilteritnib

Mechanism: Inhibits activated FLT3 for both ITD and TKD mutations

- Secondary Mechanisms:
  - AXL Inhibition
  - Induction of Differentiation

Dosing: 120 mg oral once daily on days 1-28 of a 28-day cycle

Warnings/Precautions:

- Differentiation Syndrome, QTc Prolongation, Pancreatitis, Posterior Reversible Encephalopathy Syndrome (PRES)

Drug Interactions:

- CYP 3A4 (major)
- P-glycoprotein/ABCB1 (minor)

Kiyoi H. *Cancer Science. 2019.*
Daver N. Leukemia. 2019.
Tian Z. *J Heme Onc. 2021.*

Triplet Combination of Azacitidine, Venetoclax and Gilteritinib

Citation	**Published November 15, 2022** Blood 2022; 140 (Supplement 1): 2007–2009. doi: https://doi.org/10.1182/blood-2022-157210
Authors	*Short N, DiNardo CD, Daver N, et al.*
Journal	**Blood** • Updated results of an Oral Abstract presented at ASH 2021

Purpose

Assess safety and efficacy of the triplet regimen of azacitidine (AZA), venetoclax (VEN) and gilteritinib (GILT) in pts with FLT3-mutated AML.

Design

Phase 1/2, single-arm, single center study conducted at 35 sites across the United States between December 2019 and June 2022

Funding and Oversight

- **Funding:** Stemline Therapeutics, Astellas and Takeda Oncology
- **Oversight:** Stemline Therapeutics, Astellas, Pfizer, AstraZeneca and Takeda Oncology

Patient Eligibility and Endpoints

Inclusion:

- 18 years of age
- The following diagnosis unfit for intensive chemotherapy:
  - Relapsed/Refractory (R/R) FLT3-AML
  - R/R High Risk FLT3-MDS/CMML
  - Newly Diagnosed (ND) FLT3-AML
- FLT3-ITD and FLT3-TKD mutations were allowed

Exclusion:

- ECOG Performance Status > 3
- Total Bilirubin > 2.5 ULN
- Creatinine Clearance < 30 mL/min

Primary Outcome

- ORR

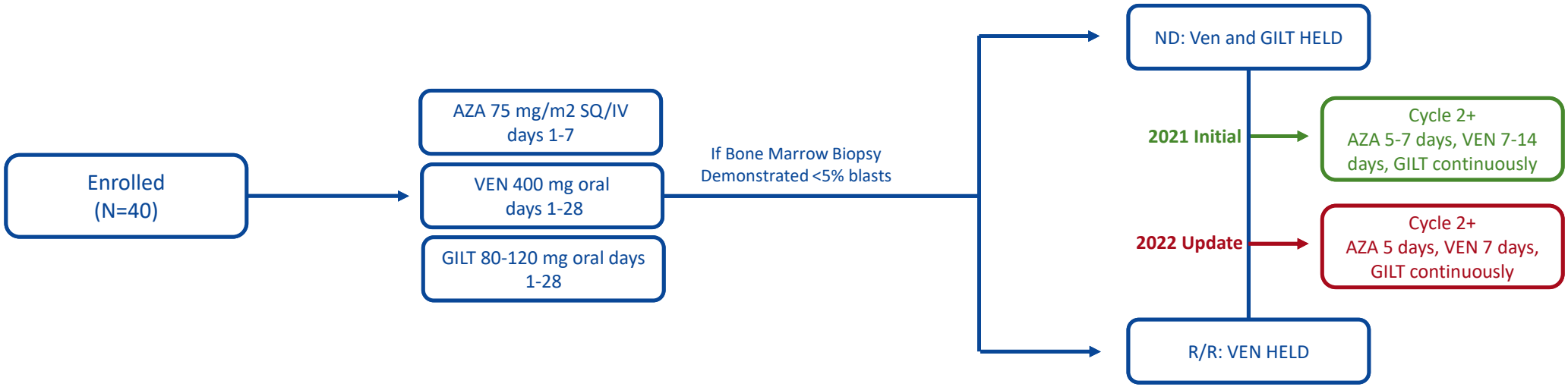
Secondary Outcomes

- Duration of response, CR/CRi, MLFS, PFS, OS, 30 and 60-day mortality

ORR = Overall Response Rate
MLFS = Morphologic Leukemia Free State
CR = Complete Response
PFS = Progression Free Survival
OS = Overall Survival
CRi: Complete Response with Incomplete Count Recovery

Methods

Phase 1/2



Baseline Characteristics

Baseline Characteristics of the Patients		
Characteristic	**Frontline (N=21)**	**Relapse/Refractory (N=19)**
Median Age (range), yrs.	68 (18-82)	68 (19-90)
Age Category (%), no.		
≥ 60 yrs.	20 (95)	15 (79)
≥ 75 yrs.	5 (24)	4 (21)
Number of Prior Therapies (range)	-	2 (1-5)
Type of FLT3 Mutation (%), no.		
ITD only	14 (67)	8 (42)
TKD only	7 (33)	7 (37)
ITD + TKD	0	4 (21)
FLT3 Allelic Ratio (range)		
ITD	0.29 (0.04-3.35)	0.61 (0.03-15.7)
TKD	0.85 (0.03-1.34)	0.59 (0.01-1.81)
Diagnosis (%), no.		
AML	21 (100)	18 (94)
MDS/CMML	0	1 (6)

Baseline Characteristics

Baseline Characteristics of the Patients		
Characteristic	**Frontline (N=21)**	**Relapse/Refractory (N=19)**
Previous FLT3 Inhibitor (%), no.	-	5 (26)
Previous HSCT (%), no.	-	5 (26)
Previous HMA + VEN (%), no.	-	8 (42)
Cytogenetics (%), no.		
Adverse Risk	13 (62)	8 (42)
Diploid	3 (14)	7 (37)
Other	5 (24)	4 (21)

Results

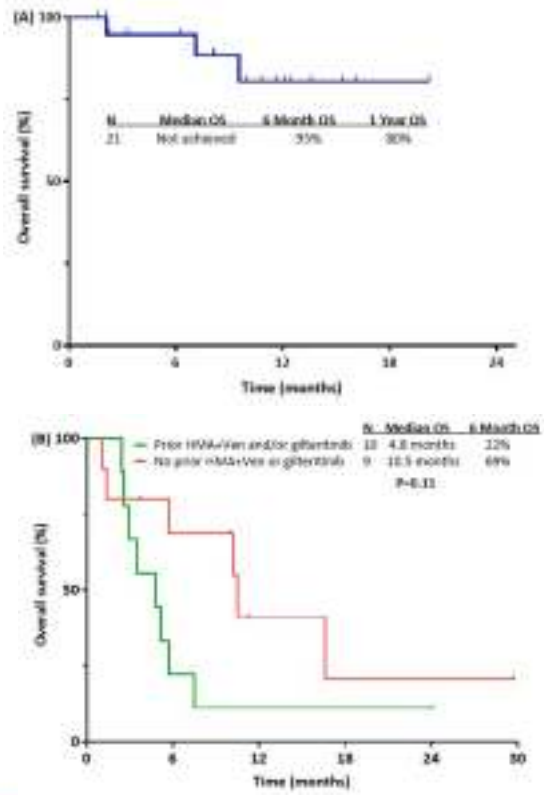
Median duration of follow-up of 14.1 months

Primary Outcome

- ORR (CR + CRi + MLFS)
  - R/R: 74%
  - ND: 100%*

Secondary Outcomes

- CR
  - R/R: 4 patient (21%)
  - ND: 20 patients (95%)
- DOR
  - R/R: 9.0 months**
  - ND: 6.8 months
- OS
  - R/R: 5.8 months
  - ND: 1-year OS rate of 80%
- 30/60 Day Mortality
  - R/R: 0%/13%**
  - ND: 0%/0%



*All patients achieved marrow remission by day 14
**From original study, Not updated in 2022 update

Safety

Specific safety outcomes not yet reported

GILT 80 mg daily chosen as phase 2 dose given significant myelosuppression with 120 mg dose

Subsequent cycles of therapy required shorter duration of AZA and VEN secondary to toxicity and cytopenias

Author's Conclusion

The combination of AZA, VEN and GILT was effective in treatment of patients with FLT3-AML

GILT 80 mg dose provided improved safety profile and was selected as the dose to move forward for future studies

- Myelosuppression was still common at this lower dose resulting in need to hold/delay subsequent AZA/VEN administration

Impact on Clinical Practice

Patients in the R/R setting had better response without prior AZA/VEN exposure	• Addition of GILT to patients who have already received HMA/VEN might not provide the clinical benefit needed for sustained response
8 patients (20%) proceeded to HSCT in remission	• Questions the overall performance status of patients enrolled in this trial • Would consider this treatment in patients who were transplant ineligible
Limited safety and tolerability data reported	• Incidence of infection, treatment delays and cause of treatment delays important factor in decision to utilize this regimen in unfit, older adults • Subsequent cycles resulted in a frequency reduction of AZA and VEN administration

Other Clinical Considerations

Infection prophylaxis?	GILT dose reduction for toxicity?	Duration of therapy?
• Does Triplet therapy require additional prophylaxis over HMA/VEN doublet?	• No formalized dose reduction for GILT doses under 80 mg	• Phase 2 study in ND FLT3-AML assessed reductions in VEN dose to 14-21d

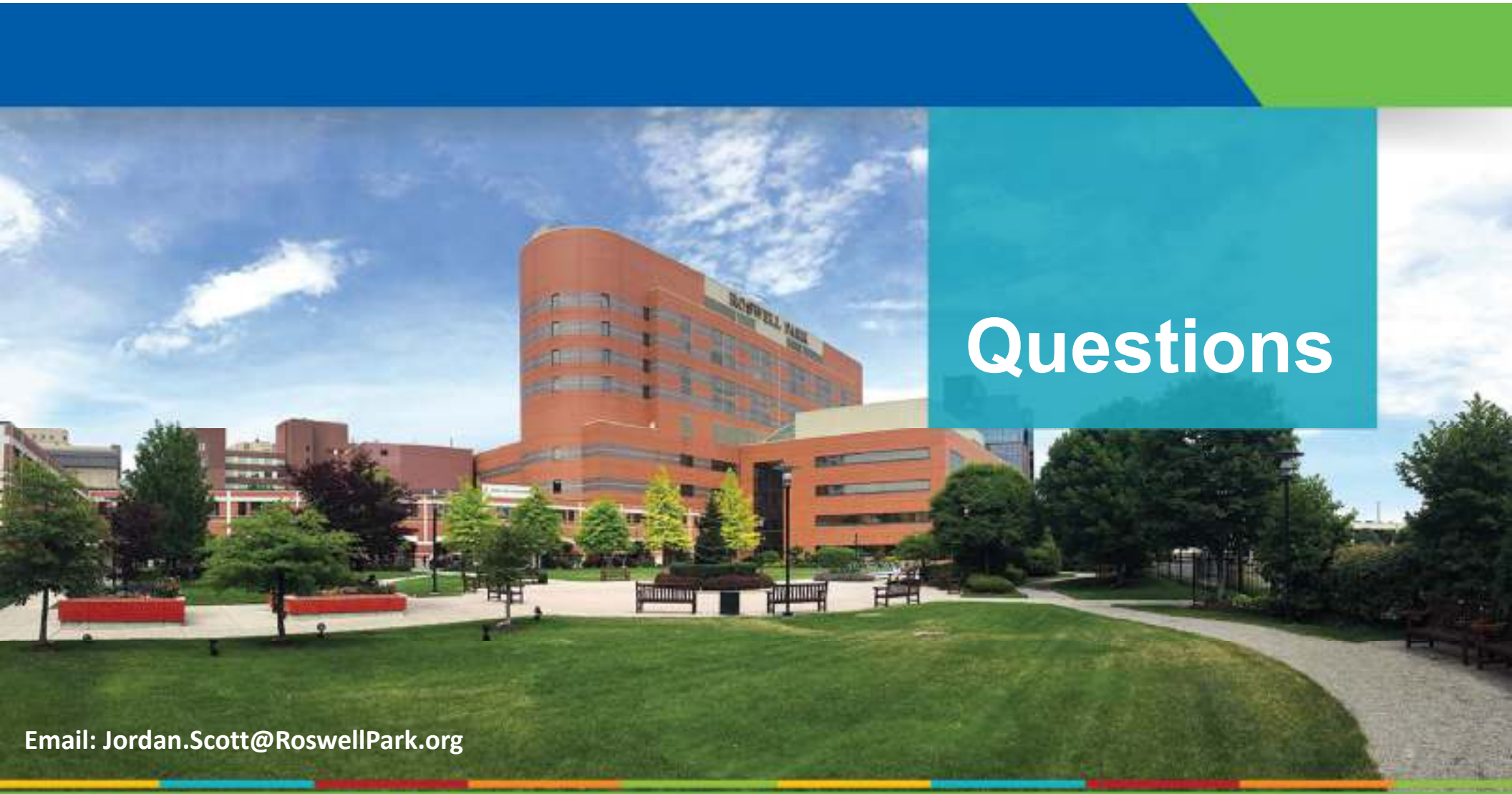
Maiti A. *Blood Cancer Journal,* 2021.

Summary

3. AZA, VEN and GILT is an option for FLT3-AML induction in older adults who may not tolerate standard high dose induction chemotherapy

Safety and Tolerability of the regimen remains a question in this patient population

Dose reduction in the GILT to 80 mg daily can mitigate some of the bone marrow suppression noted with triplet induction therapy



Questions

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