

# AALL15P1

A Group-Wide Pilot Study to Test the Tolerability and Biologic Activity of the Addition of Azacitidine (IND#133688, NSC# 102816) to Chemotherapy in Infants with Acute Lymphoblastic Leukemia (ALL) and KMT2A (MLL) Gene Rearrangement.

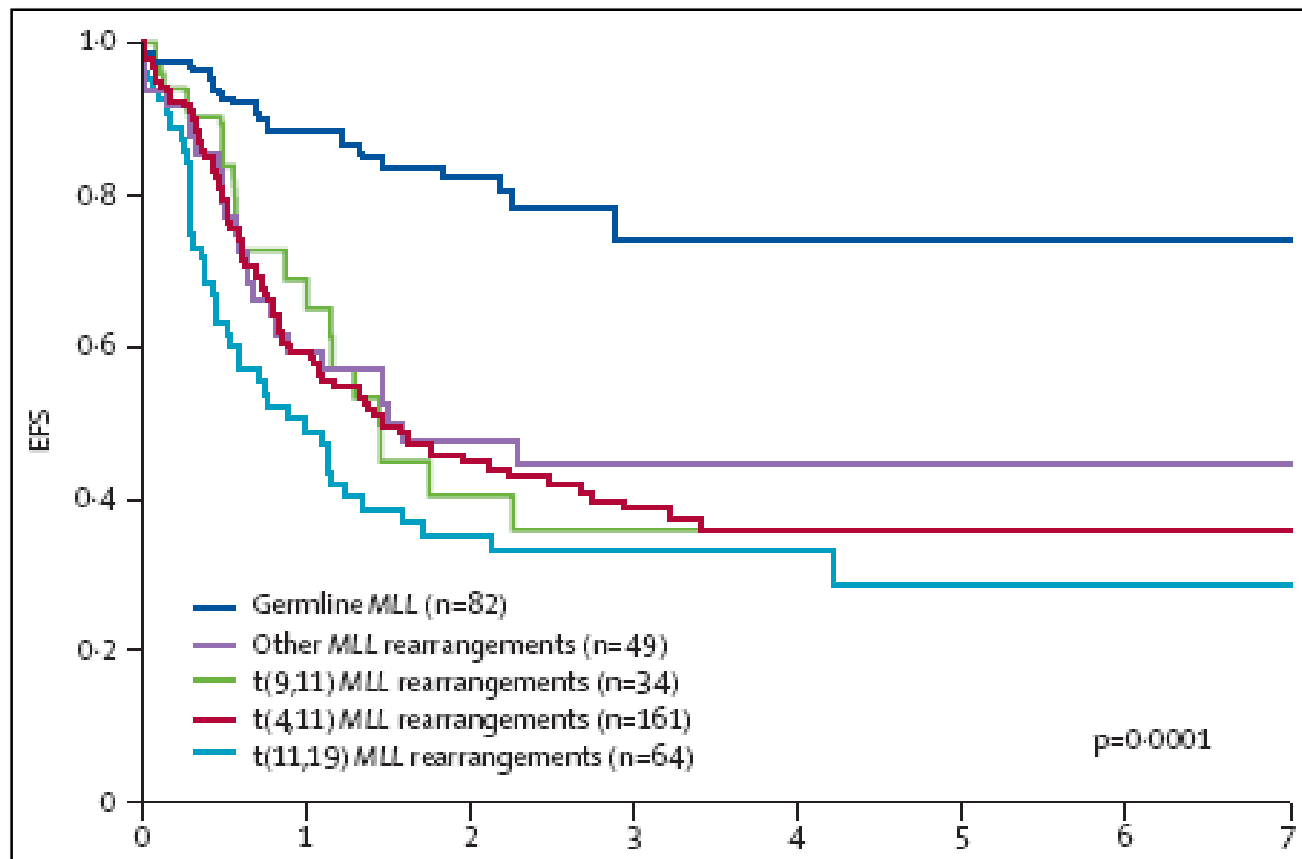
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Study Chair: Erin Guest, M.D.  
Prepared By: Paul Gibson and Kaniska Young Tai

# Background

Approximately 75-80% of infant ALL cases contain the KMT2A mutations (previously Mixed Lineage Leukemia or MLL) and the survival rate for these patients remains poor.

# MLL Rearrangement EFS



MLL or KMT2A rearrangements are involved in the development of acute leukemia, particularly in infants.

The chart on the right shows that there are different KMT2A rearrangements with varied prognosis inferior to the Germline MLL (see the line).

# AALL 15P1: Primary Aim

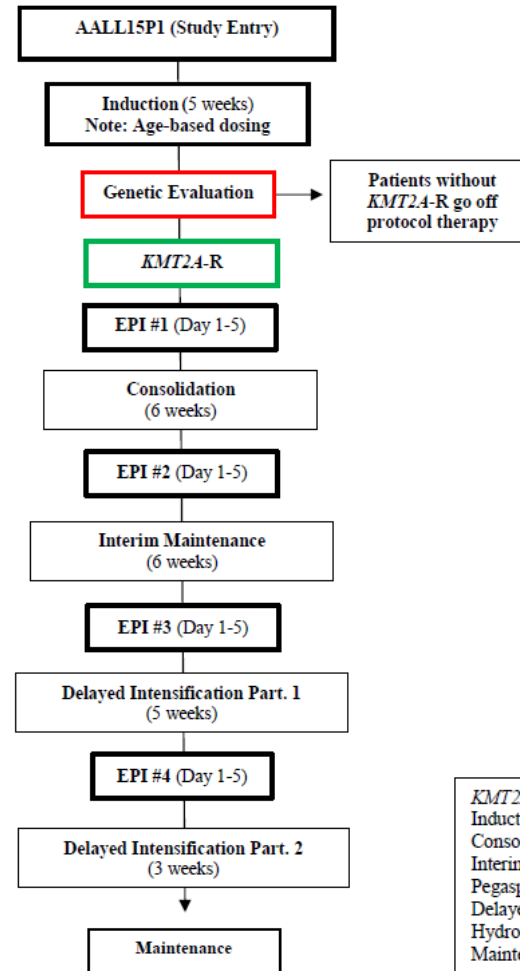
To evaluate the tolerability of azacitidine in addition to Interfant-06 standard chemotherapy in infants with newly diagnosed ALL with *KMT2A* gene rearrangement (*KMT2A*-R).

# Azacitidine

It is a demethylating agent as well as an antimetabolite chemotherapy agent.

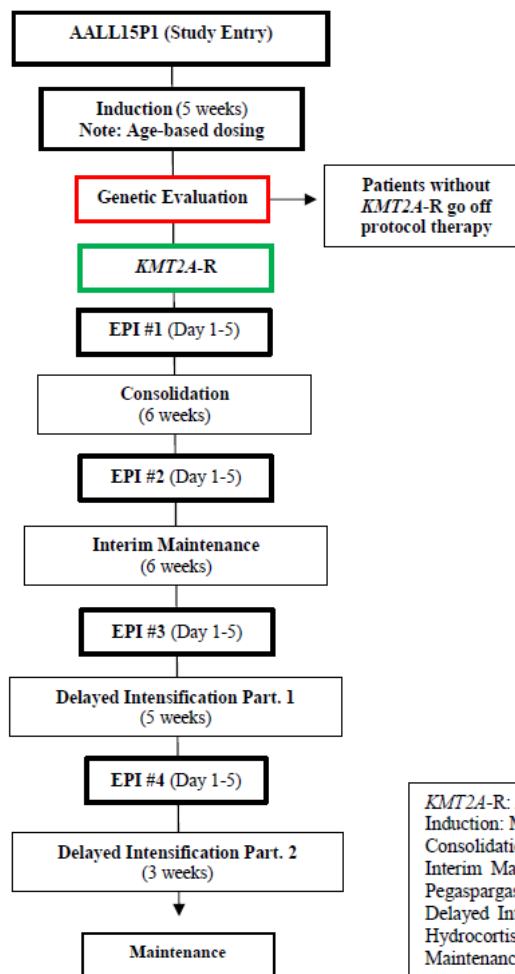
The rationale for this protocol was that low-dose azacitidine as an epigenetic priming agent could reverse aberrant DNA methylation, overcome drug resistance, and improve the cytotoxic effect of the chemotherapy medications (a pre-treatment).

# Experimental Study Schema



*KMT2A-R*: *KMT2A* gene- Rearrangement      EPI: Azacitidine Epigenetic Therapy  
 Induction: Methotrexate, Prednisolone, Daunorubicin, Cytarabine, Dexamethasone, Vincristine, Pegaspargase, and Hydrocortisone  
 Consolidation: Cyclophosphamide, Mesna, Mercaptopurine, Cytarabine, Methotrexate, and Hydrocortisone.  
 Interim Maintenance: Mercaptopurine, High-dose Methotrexate, Leucovorin, Methotrexate/Hydrocortisone, High-dose Cytarabine, and Pegaspargase.  
 Delayed Intensification: Dexamethasone, 6-Thioguanine, Vincristine, Daunorubicin, Pegaspargase, Cyclophosphamide, Cytarabine, and Hydrocortisone  
 Maintenance: Mercaptopurine, Methotrexate, Hydrocortisone, and Cytarabine

# Experimental Study Schema

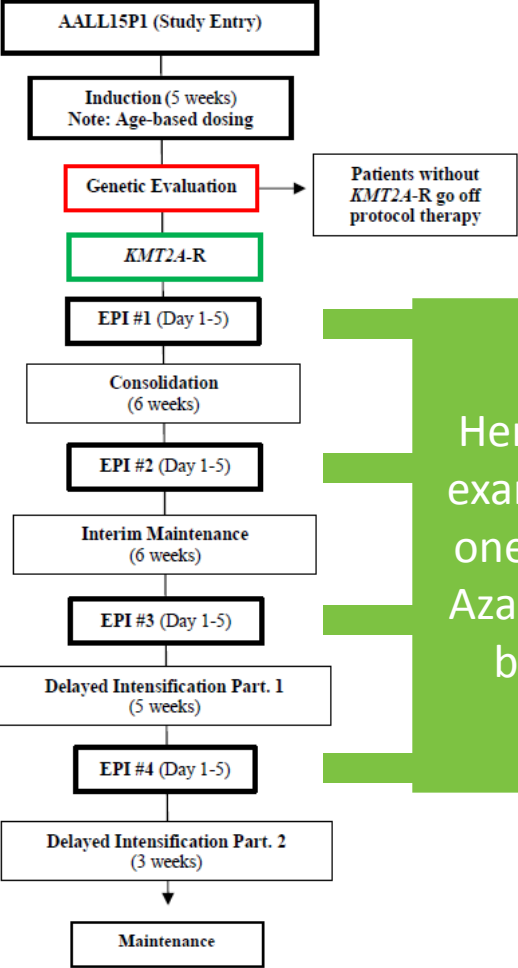


Four cycles of Azacitidine given as a “priming agent” in the EPI blocks for the upcoming phase.

Begin each Azacitidine EPI Block when peripheral counts recover with ANC  $\geq 500/\mu\text{L}$  and platelets  $\geq 50,000/\mu\text{L}$ , and resolution of any toxicity.

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 Maintenance: Mercaptopurine, Methotrexate, Hydrocortisone, and Cytarabine

# Azacitidine



Here is an example of one of the Azacitidine blocks

CHILDREN'S ONCOLOGY GROUP

THIS PROTOCOL IS FOR RESEARCH PURPOSES ONLY, SEE PAGE 1 FOR USAGE POLICY

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4.3 Azacitidine EPI BLOCK #1

4.3.1 Therapy Delivery Map – Azacitidine EPI BLOCK #1

Following Induction therapy and the recovery of peripheral blood cell counts, azacitidine will be administered as a pre-treatment prior to Consolidation therapy, for 5 days. Azacitidine therapy is 5 days.

Patient COG ID number

DOB

Patients with *KMT2A-R* M3 marrow, start EPI Block #1 immediately following the completion of Induction therapy. Patients with *KMT2A-R* M1 or M2 marrow, start EPI Block #1 when ANC  $\geq 500/\mu\text{L}$  and platelets  $\geq 50,000/\mu\text{L}$ , and resolution of mucositis and/or diaper area dermatitis to  $\leq$  Grade 2 (whichever occurs later). Treatment details and criteria to start are in [Section 4.3.3](#). This Therapy Delivery Map is two (2) pages in length.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Azacitidine (AZA) IND# 133688	IV over 10-40 mins	2.5 mg/kg/dose	1-5	Note: Infusion must be completed within 45 minutes of vial reconstitution.

Ht

cm

Wt

kg

BSA

m<sup>2</sup>

Date Due	Date Given	Day	Azacitidine _____mg	Studies
			Enter actual dose administered below	
		1	_____mg	a-d
		2	_____mg	
		3	_____mg	e
		4	_____mg	e
		5	_____mg	d-e
		6	Continue to Consolidation ( <a href="#">Section 4.4</a> ) on Day 6 irrespective of ANC and platelet counts.	

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IV](#) and the COG Member website for Supportive Care Guidelines.

Since this is a study drug, it will be given at the tertiary centres only

**Azacitidine:**  
**Intravenous (IV) over 10-40 mins**  
Days: 1-5  
Dose: 2.5 mg/kg/dose  
Note: Infusion must be completed within 45 minutes of vial reconstitution

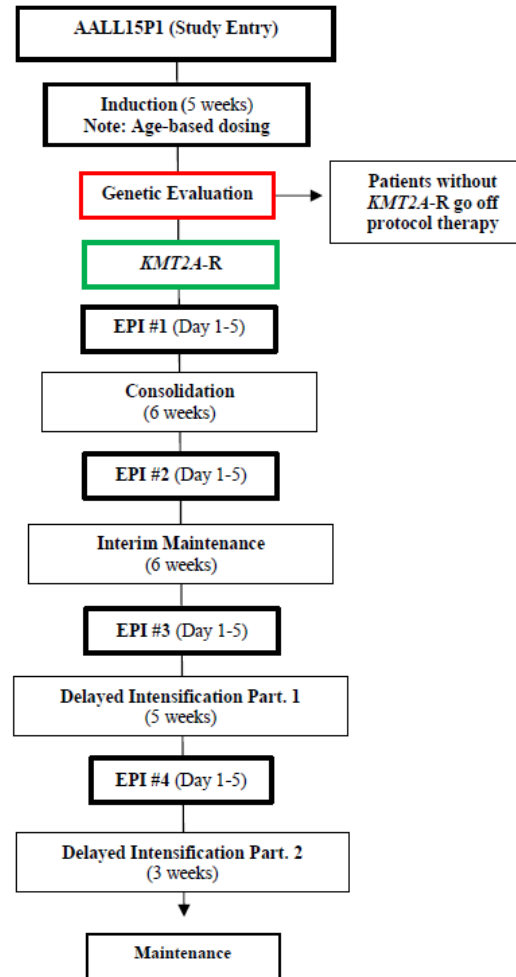


# Azacitidine: Dose Modifications

Dose-Limiting Toxicity (DLT) evaluation period consists of the first three courses of azacitidine in combination with chemotherapy (EPI#1 through DI Part 1) and until the patient meets counts requirements to begin the fourth course of azacitidine (EPI #4).

During the evaluation period, the patient will be seen at the tertiary centre. If a patient who is having toxicity symptoms arrives at your centre for assessment, please contact the tertiary team for guidance and possible transfer.

# Experimental Study Schema



# Consolidation

## 4.4.1 Therapy Delivery Map - CONSOLIDATION

All patients will receive the same Consolidation therapy with regards to agents and schedule. Non-IT drugs are dosed based on age on Day 1 of Consolidation and BSA, as outlined below. IT doses are based on age on the day of administration. Consolidation therapy is 6 weeks (42 days) duration.

Patient COG ID Number      DOB

Following completion of Azacitidine Block 1 (EPI#1), begin Consolidation therapy on Day 6 irrespective of peripheral blood cell counts. Details and criteria to start are in [Section 4.4.3](#). This Therapy Delivery Map is two (2) pages in length.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Cyclophosphamide (CPM)	IV over 30-60 min	<div>Age</div> <div>Dose</div> <div>&lt; 6 mo      670 mg/m<sup>2</sup>/dose</div> <div>≥ 6 mo &amp; &lt; 12 mo      750 mg/m<sup>2</sup>/dose</div> <div>≥ 12 mo      1000 mg/m<sup>2</sup>/dose</div>	1 & 29	Must have ANC ≥ 500/μL and platelets ≥ 30,000/μL to receive Day 29 CPM. Refer to <a href="#">Section 4.4.3</a> for admin guidelines.
Mesna	IV over 15min	<div>Age</div> <div>Dose</div> <div>&lt; 6 mo      134 mg/m<sup>2</sup>/dose</div> <div>≥ 6 mo &amp; &lt; 12 mo      150 mg/m<sup>2</sup>/dose</div> <div>≥ 12 mo      200 mg/m<sup>2</sup>/dose</div>	1 & 29	Administer at 0, 4 and 8 hours from the start of CPM infusion. Refer to <a href="#">Section 4.4.3</a> for admin guidelines.
Mercaptopurine (MP)	PO or NG	<div>Age</div> <div>Dose</div> <div>&lt; 6 mo      40 mg/m<sup>2</sup>/dose</div> <div>≥ 6 mo &amp; &lt; 12 mo      45 mg/m<sup>2</sup>/dose</div> <div>≥ 12 mo      60 mg/m<sup>2</sup>/dose</div>	1-28	Refer to <a href="#">Section 4.4.3</a> and <a href="#">Section 5.7</a> for admin guidelines.
Cytarabine (ARAC)	IV push or SubQ	<div>Age</div> <div>Dose</div> <div>&lt; 6 mo      50 mg/m<sup>2</sup>/dose</div> <div>≥ 6 mo &amp; &lt; 12 mo      56 mg/m<sup>2</sup>/dose</div> <div>≥ 12 mo      75 mg/m<sup>2</sup>/dose</div>	3-6, 10-13, 17-20, & 24-27	Refer to <a href="#">Section 4.4.3</a> for admin guidelines.
Cytarabine (IT ARAC)	IT	<div>Age (yr)</div> <div>Dose</div> <div>&lt; 1      15 mg</div> <div>≥ 1      20 mg</div>	10	
Intrathecal Hydrocortisone (IT HC)	IT	<div>Age (yr)</div> <div>Dose</div> <div>&lt; 1      12 mg</div> <div>≥ 1      16 mg</div>	10 & 24	
Intrathecal Methotrexate (IT MTX)	IT	<div>Age (yr)</div> <div>Dose</div> <div>&lt; 1      6 mg</div> <div>≥ 1      8 mg</div>	24	

More total doses of Cytarabine in this study's Consolidation phase

Date Due	Date Given	Day	CPM mg	MESNA mg    mg    mg	MP mg	ARAC mg	IT ARAC mg	IT HC mg	IT MTX mg	Studies
		1	mg	mg    mg    mg						b-c
		3			mg	mg				
		4				mg				
		5				mg				
		6				mg				
		10				mg	mg	mg		b, d
		11				mg				
		12				mg				
		13				mg				
		17				mg				
		18				mg				
		19				mg				
		20				mg				
		24				mg		mg	mg	b, d
		25				mg				
		26				mg				
		27				mg				
		28								
		29	mg	mg    mg    mg						a-c
		42								b, e-g
		43	If M1 marrow is achieved, continue to azacitidine EPI Block #2 ( <a href="#">Section 4.5</a> ) on Day 43 or when ANC ≥ 500/μL and platelets ≥ 50,000/μL, and resolution of mucositis and diaper area dermatitis to ≤ Grade 2 (whichever occurs later).							

# Consolidation

Sepsis is a concern for these patients due to:

- Increased numbers of myelosuppressive agents during the consolidation phase
- These patients are infants!

# Maintenance

Oral Chemo starting dose based on AGE on Day 1 of  
Maintenance Cycle 1

<b><u>Mercaptopurine: Oral (PO) or Nasogastric (NG)</u></b>	
Days: Days 1-84	
Dose: Age based dosing	
<u>Age</u>	<u>Dose</u>
≥ 6 mo & < 12 mo	38 mg/m <sup>2</sup> /dose
≥ 12 mo	50 mg/m <sup>2</sup> /dose

<b><u>Methotrexate: Oral (PO)</u></b>	
Days: Once weekly, omit during week 1.	
Dose: Aged based dosing	
<u>Age</u>	<u>Dose</u>
≥ 6 mo & < 12 mo	15 mg/m <sup>2</sup> /dose
≥ 12 mo	20 mg/m <sup>2</sup> /dose

Dose escalation in Maintenance based on ANC

# Summary

To be enrolled on this study, the patient must have a KMT2A gene rearrangement

To evaluate the tolerability of azacitidine in addition to Interfant-06 standard chemotherapy in infants

Azacitidine is used as an epigenetic priming agent that could reverse aberrant DNA methylation, overcome drug resistance, and improve the cytotoxic effect of the chemotherapy medications

In the Maintenance phase, the starting dose is based on the patient's age at the start of the cycle!

# Certificate of Completion

This certificate is awarded to

\_\_\_\_\_

name

for the completion of the POGO AALL15P1 educational training module



PEDIATRIC ONCOLOGY GROUP OF ONTARIO

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date

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signature