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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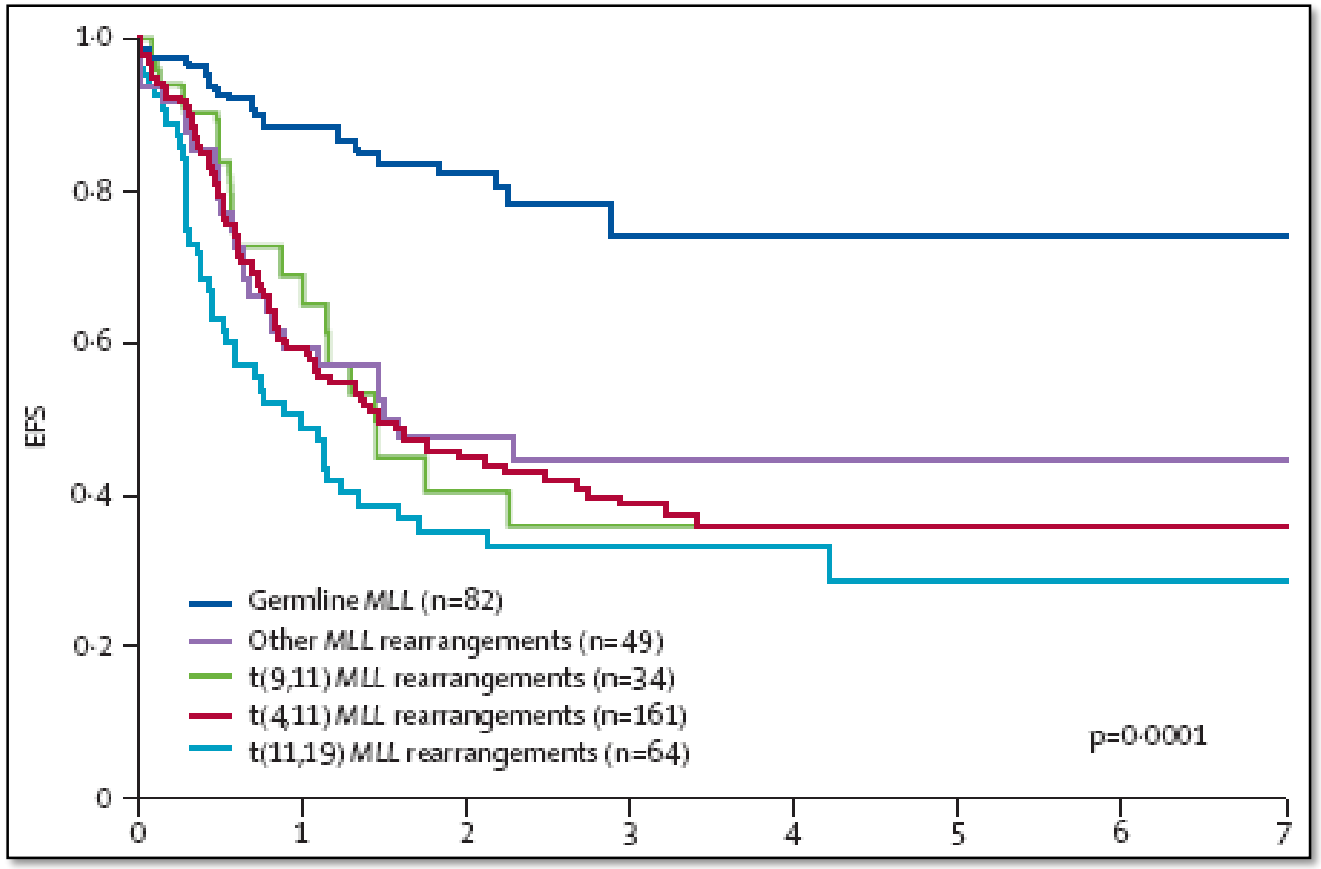
Background

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).

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AALL 15P1: Primary Aim

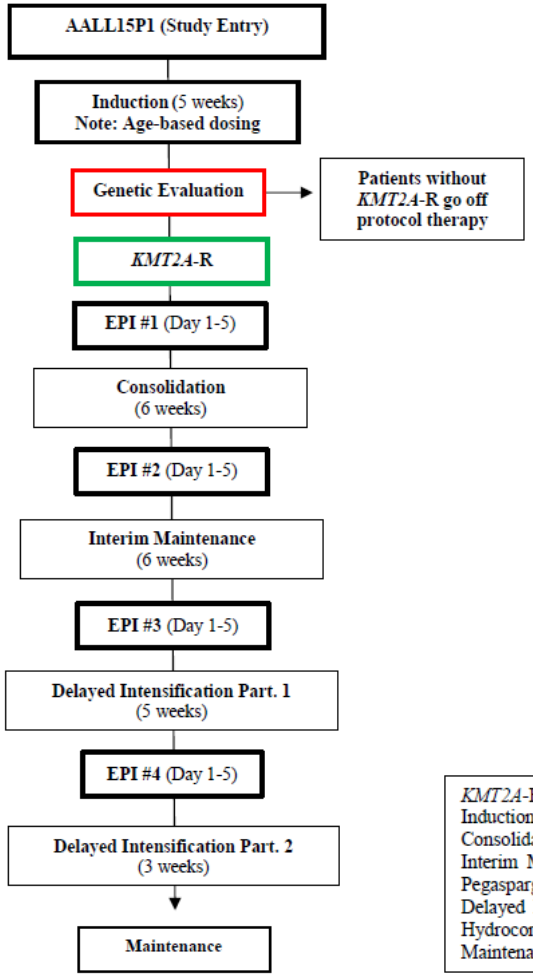
To evaluate the tolerability of azacitidine in addition to Interfant-06 standard chemotherapy in infants with newly diagnosed ALL with *KMT2A* gene rearrangement (*KMT2A*-R).

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, Predniso(lo)ne, 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

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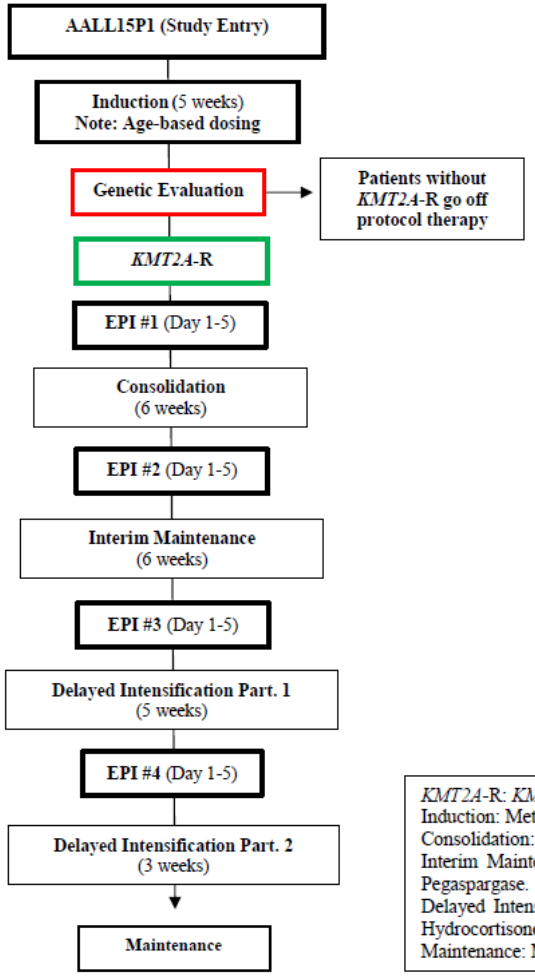
Experimental Study Schema

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 ≥ 500/µL and platelets ≥ 50,000/µL, and resolution of any toxicity.

KMT2A-R: *KMT2A* gene- Rearrangement EPI: Azacitidine Epigenetic Therapy
Induction: Methotrexate, Predniso(lo)ne, Daunorubicin, Cytarabine, Dexamethasone, Vincristine, Pegaspargase, and Hydrocortisone
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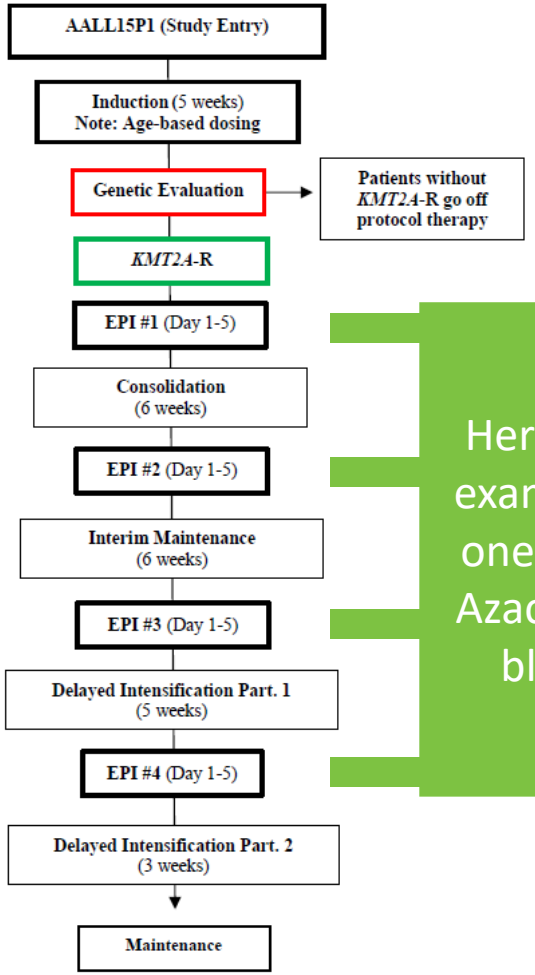
Azacitidine



Here is an example of one of the Azacitidine blocks

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Page 1 of 2

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 ≥ 500/µL and platelets ≥ 50,000/µL, and resolution of mucositis and/or diaper area dermatitis to ≤ 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** _____**m²**

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 (Section 4.4) 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

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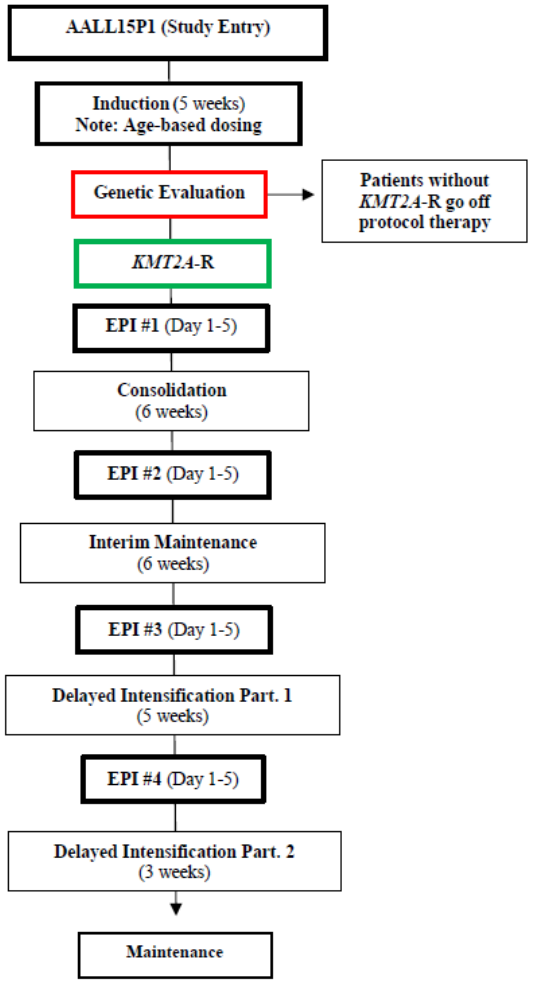
Azacitidine: Dose Modifications

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 criteri
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	Age < 6 mo ≥ 6 mo & < 12 mo ≥ 12 mo	Dose 670 mg/m²/dose 750 mg/m²/dose 1000 mg/m²/dose	1 & 29	Must have ANC ≥ 500/µL and platelets ≥ 30,000/µL to receive Day 29 CPM. Refer to Section 4.4.3 for admin guidelines.
Mesna	IV over 15min	Age < 6 mo ≥ 6 mo & < 12 mo ≥ 12 mo	Dose 134 mg/m²/dose 150 mg/m²/dose 200 mg/m²/dose	1 & 29	Administer at 0, 4 and 8 hours from the start of CPM infusion. Refer to Section 4.4.3 for admin guidelines.
Mercaptopurine (MP)	PO or NG	Age < 6 mo ≥ 6 mo & < 12 mo ≥ 12 mo	Dose 40 mg/m²/dose 45 mg/m²/dose 60 mg/m²/dose	1-28	Refer to Section 4.4.3 and Section 5.7 for admin guidelines.
Cytarabine (ARAC)	IV push or SubQ	Age < 6 mo ≥ 6 mo & < 12 mo ≥ 12 mo	Dose 50 mg/m²/dose 56 mg/m²/dose 75 mg/m²/dose	3-6, 10-13, 17-20, & 24-27	Refer to Section 4.4.3 for admin guidelines.
Cytarabine (IT ARAC)	IT	Age (yr) < 1 ≥ 1	Dose 15 mg 20 mg	10	
Intrathecal Hydrocortisone (IT HC)	IT	Age (yr) < 1 ≥ 1	Dose 12 mg 16 mg	10 & 24	
Intrathecal Methotrexate (IT MTX)	IT	Age (yr) < 1 ≥ 1	Dose 6 mg 8 mg	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
				Enter calculated dose above and actual dose administered below						
		1	___mg	___mg ___mg ___mg	___mg					b-c
		3				___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 (Section 4.5) 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).							

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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

Mercaptopurine: Oral (PO) or Nasogastric (NG)
Days: Days 1-84
Dose: Age based dosing

Age	Dose
≥ 6 mo & < 12 mo	38 mg/m^2/dose
≥ 12 mo	50 mg/m^2/dose

Methotrexate: Oral (PO)
Days: Once weekly, omit during week 1.
Dose: Aged based dosing

Age	Dose
≥ 6 mo & < 12 mo	15 mg/m^2/dose
≥ 12 mo	20 mg/m^2/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!

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