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FOR KIDS WITH CANCER
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AALL1631

International Phase 3 trial in Philadelphia chromosome-positive Acute Lymphoblastic Leukemia (*Ph+ALL*) testing imatinib in combination with two different cytotoxic chemotherapy backbones

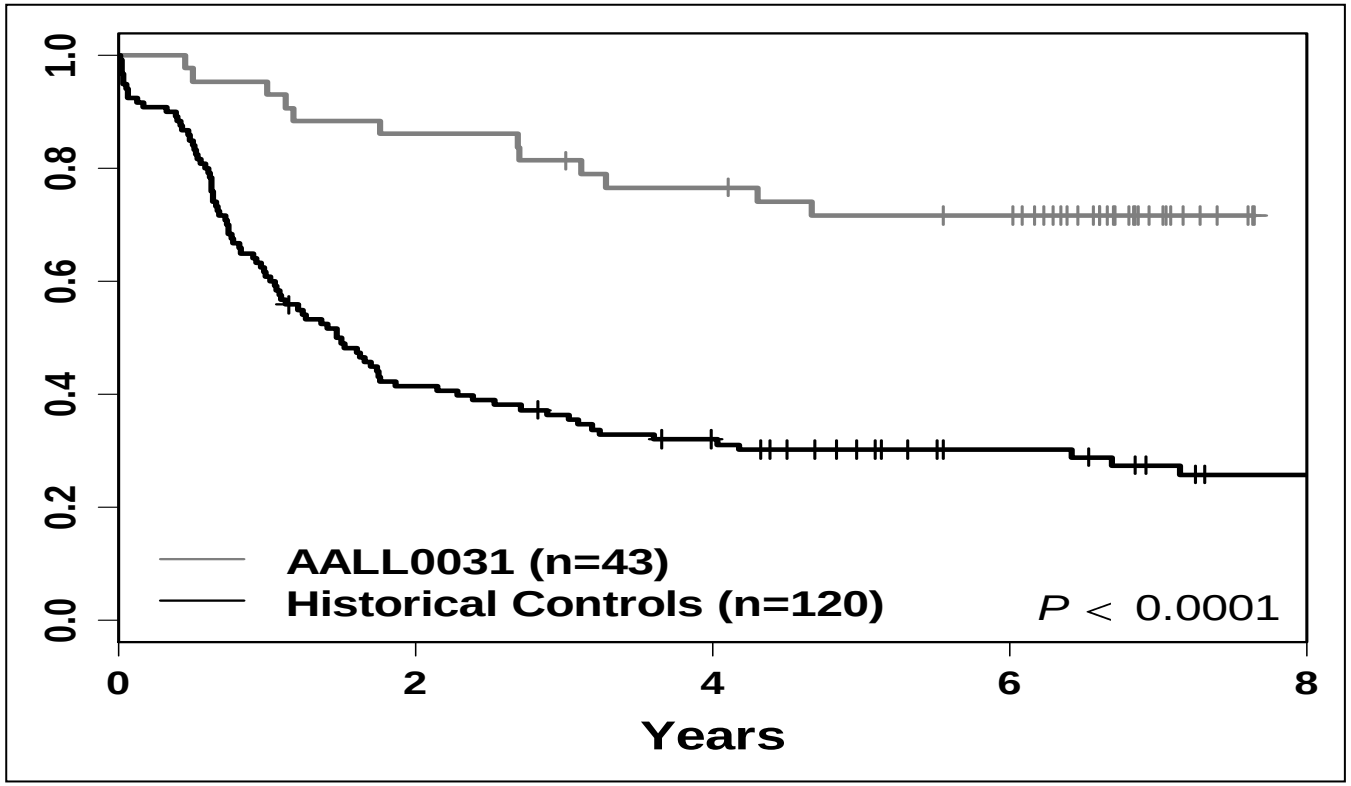
JULY 28, 2019

Study Chair: Lewis Silverman, M.D.
Prepared by: Paul Gibson and Kaniska Young Tai

AALL 1631: Primary Aim

To compare disease-free survival (DFS) of Standard Risk (SR) pediatric Ph+ ALL treated with continuous imatinib combined with either a high-risk COG ALL chemotherapy backbone or the more intensive EsPhALL chemotherapy backbone.

COG AALL0031: Imatinib Improves Outcome in Ph+ ALL



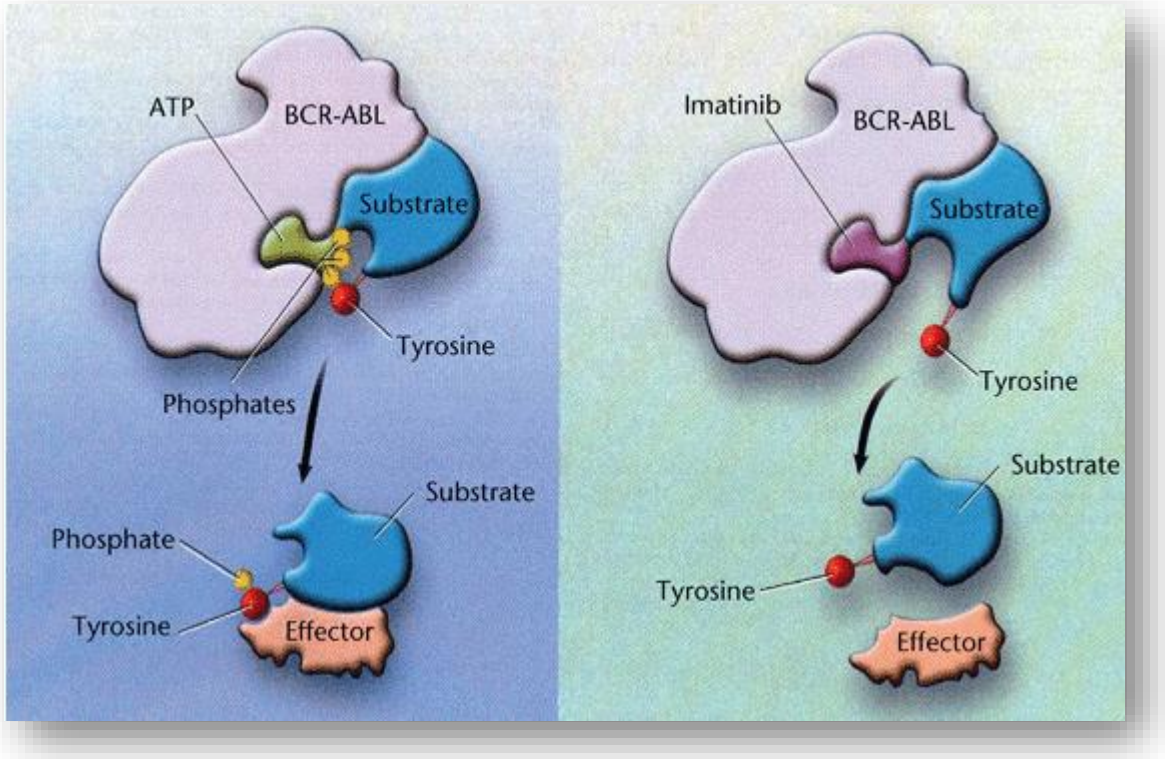
Schultz KR, JCO 27: 571, 2009; data updated Feb 2013

Philadelphia Chromosome Positive ALL (PH+ ALL) has historically been associated with a dismal outcome

The advent of imatinib brought new hope to this patient group

AALL 0031: Combined imatinib with very intensive/toxic chemo backbone

What is Imatinib?



https://www.researchgate.net/figure/The-presumed-mechanism-of-action-of-imatinib-The-phosphorylation-of-a-substrate-is-shown_fig3_229483289

Imatinib is a tyrosine-kinase inhibitor

Imatinib works by stopping the Bcr-Abl tyrosine-kinase. This can slow growth or result in apoptosis

Eligibility

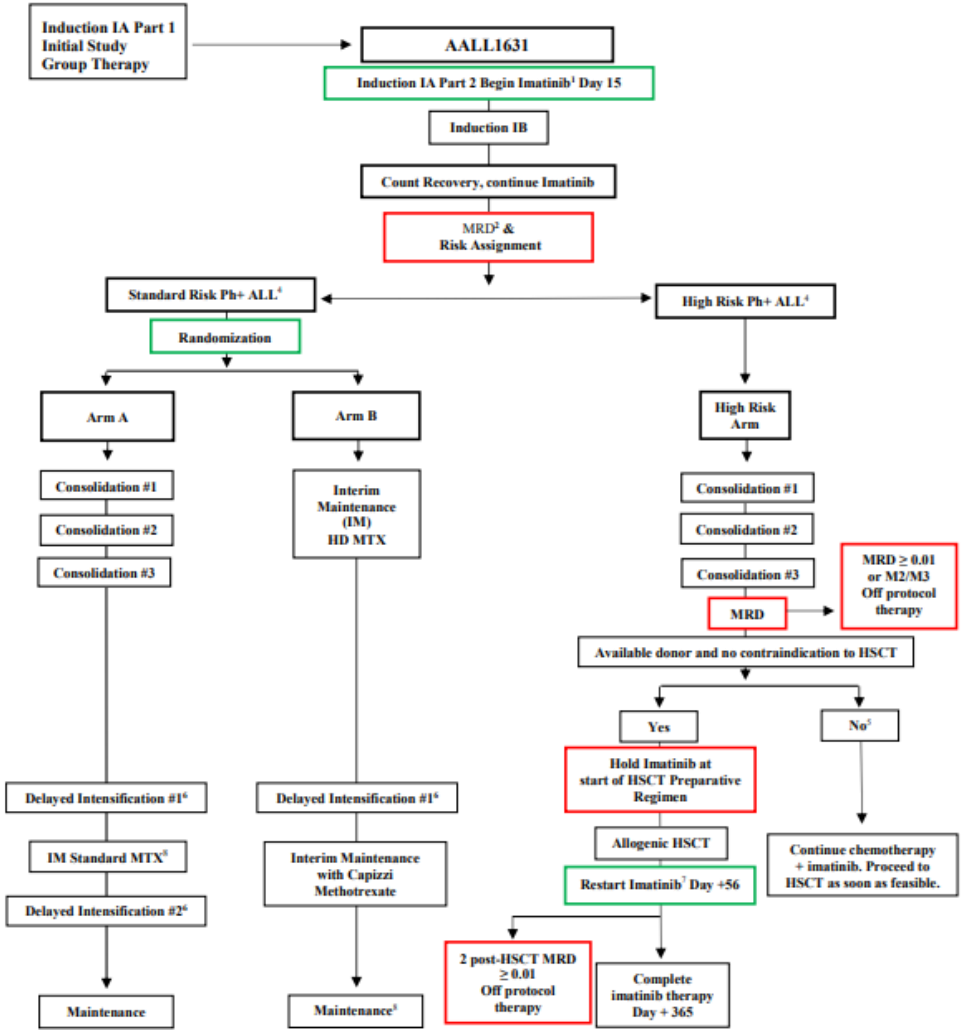
Enrolled on AALL 08B1 or APEC or have available marrow to ship for probe creation.

Has not received more than 14 days of multi-agent Induction therapy beginning with the first dose of vincristine.

Must have previously started Induction therapy, which includes vincristine, a corticosteroid, pegaspargase, with or without anthracycline, and/or other standard cytotoxic chemotherapy.

May have started imatinib prior to study entry but has not received more than 14 days of imatinib.

Study Schema



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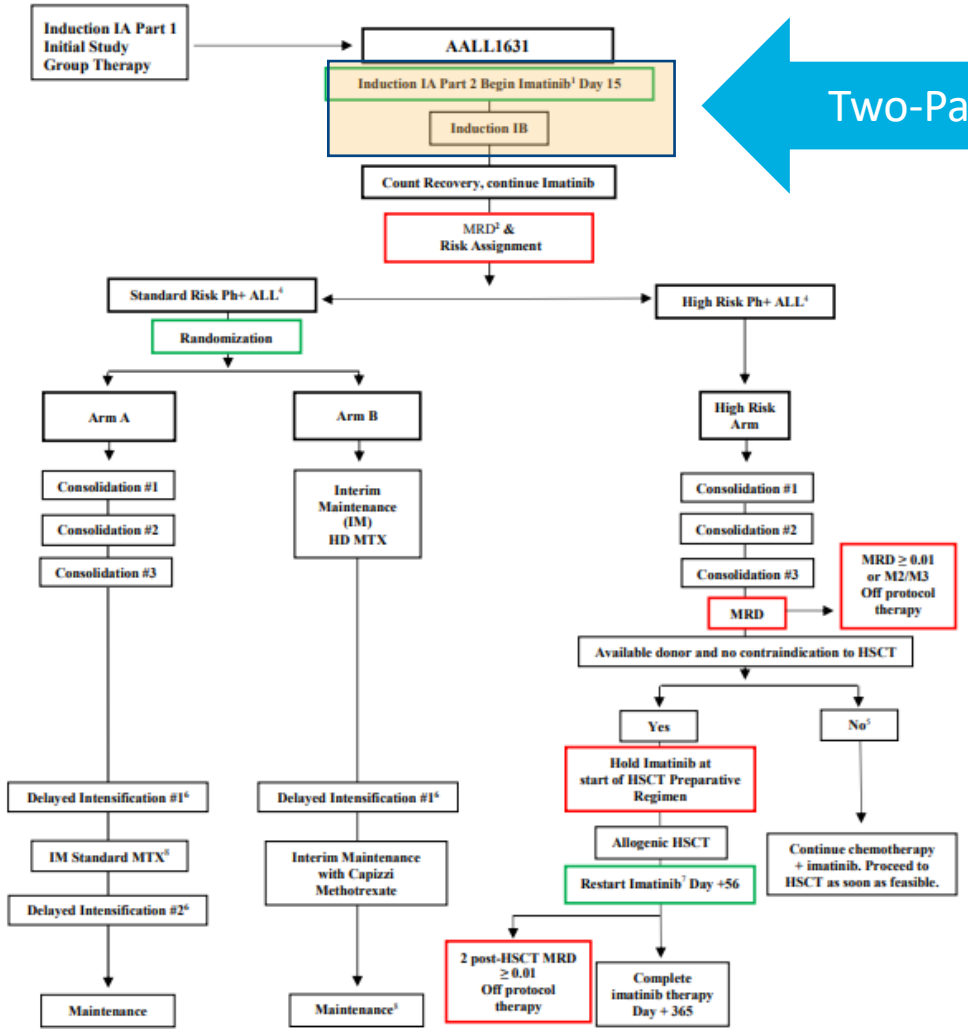
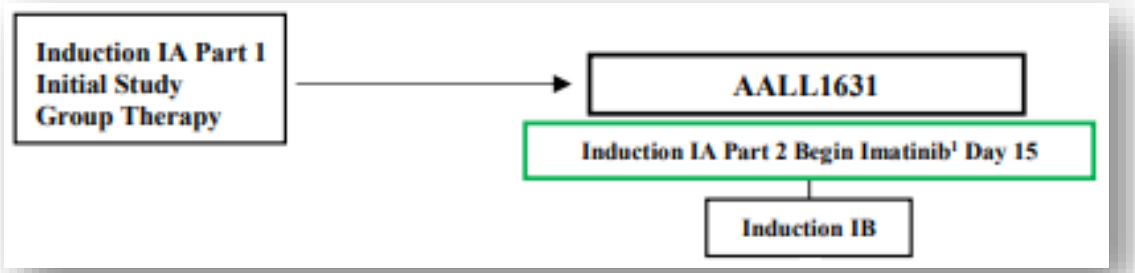
Two-Part Induction (1A & 1B)



Two-Part Induction



Enlarged View

Induction 1A

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/m^2/day **Maximum dose: 800 mg**	Daily	Administer doses > 600 mg/day, twice daily. See Section 4.2.3 for additional details. Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
PrediSO(LO)ONE (PRED)	PO	60 mg/ m^2/day	15-28	Total daily dose: ~~60 mg/ m^2~~, divided BID. Refer to Section 4.2.3 for admin guidelines.
VinCRIStine (VCR)	IV over 1 min	1.5 mg/ m^2/dose **Maximum dose: 2 mg**	15 & 22	Or infusion via minibag as per institutional policy.
DAUNOrubicin* (DAUN)	IV over 1-15 mins	25 mg/ m^2/dose	15 & 22	May be infused over the course of 1 hour. Refer to Section 4.2.3 for admin guidelines. *Should **not** be given to patients who began Induction IA on or as per DFCI Consortium protocol.
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) — Dose 1-1.99 — 8mg 2-2.99 — 10mg ≥3 — 12mg	29 ***CNS3 also on 15 & 22**	Refer to Section 4.2.3 for admin guidelines. **Note age-based dosing.**

Induction 1B

SIMILAR to HR B-cell Consolidation

4.3.1 Therapy Delivery Map – Induction IB

Induction Therapy IB is for all patients. Begin Induction IB no sooner than 4 days from Induction IA. Induction IB is 5 weeks (35 days).

Patient COG number _____ DOB _____

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
Imatinib	PO	340 mg/m^2/day **Maximum dose: 800 mg**	Daily	Administer doses > 600 mg/day, twice daily. See Section 4.3.3 for additional details. Imatinib is given daily without interruption Hold only for toxicity (Section 5.7)
Cyclophosphamide (CPM)	IV over 30-60 min	1000 mg/ m^2/dose	1 & 28	
Mercaptopurine (MP)	PO	60 mg/ m^2/day	1-28	Refer to Section 4.3.3 for admin guidelines. See Section 5.11 for suggested starting dose based on TPMT and NUDT15 status.
Cytarabine (ARAC)	IV over 1-30 min or SubQ	75 mg/ m^2/dose	1-4, 8-11, 15-18, & 22-25	Refer to Section 4.3.3 for admin guidelines. Must have **ANC ≥ 300/µL** and **platelets ≥ 30,000/uL** to start each 4-day Cytarabine block beginning on Days 8, 15, and 22
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) / Dose 1-1.99 / 8 mg 2-2.99 / 10 mg ≥ 3 / 12 mg	8 & 22	**Note: Age based dosing**

More intensive Cytarabine (every week)

Must have ANC ≥ 300/µL and platelets ≥ 30,000/µL to start each four-day Cytarabine block beginning on Days 8, 15, and 22

Cyclophosphamide on Day 1 AND 28

No PEG

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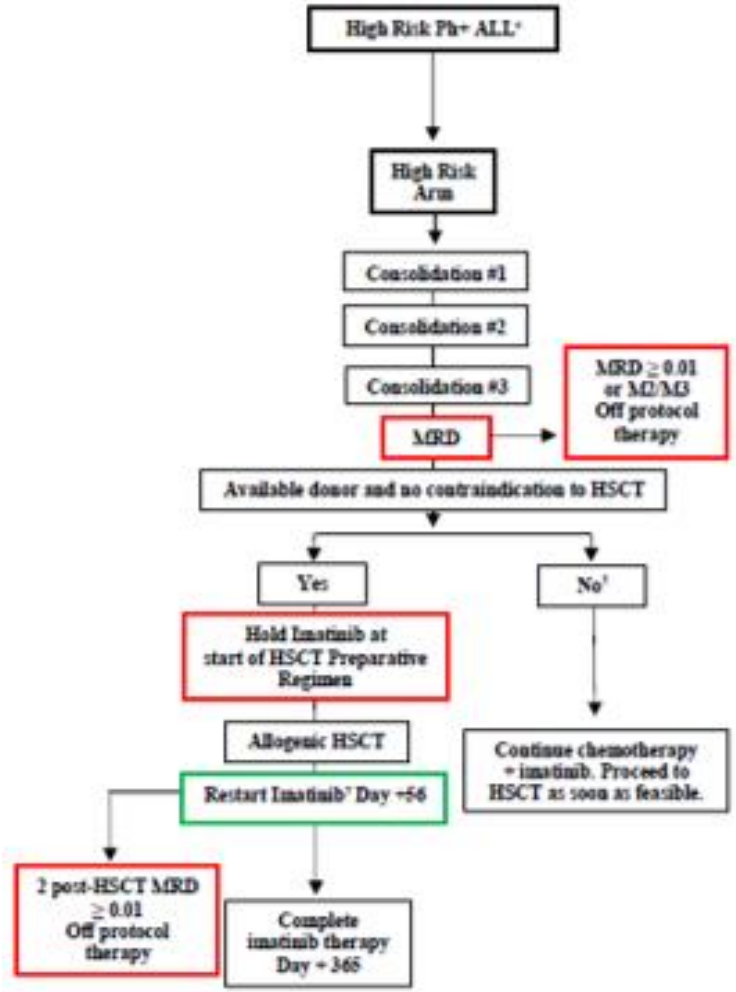
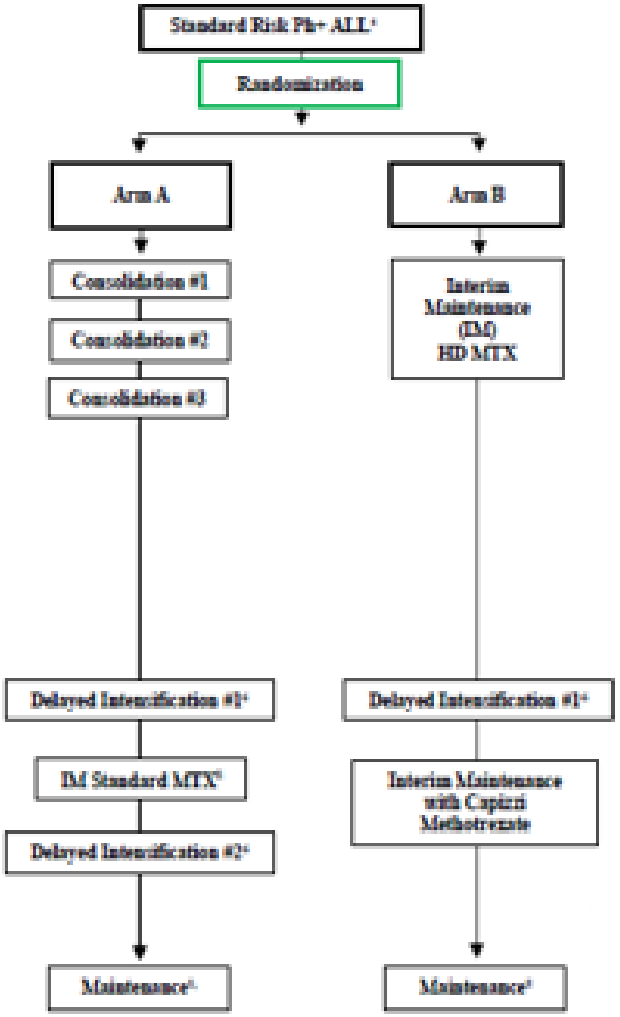
High Risk Arm



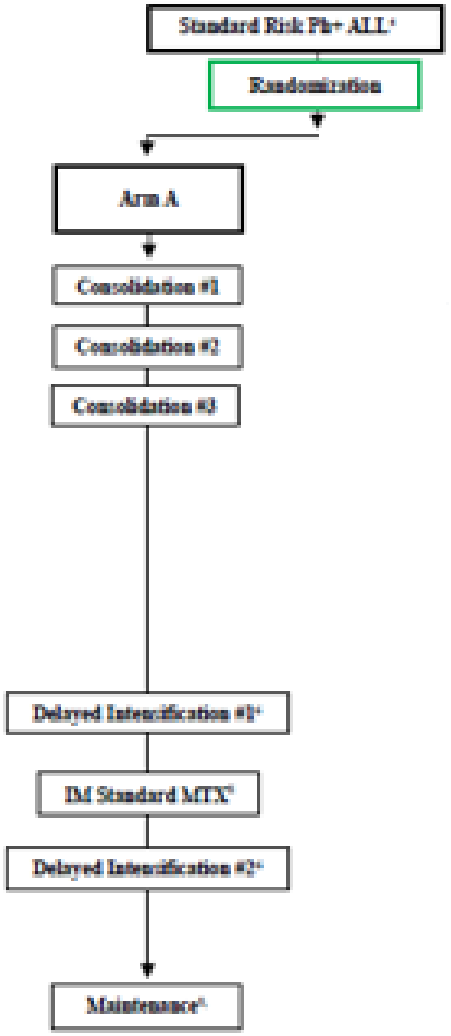
The High Risk Arm therapy will be given mostly in the tertiary centres.

However, these patients may present at the Satellite setting for CBC count checks, fever and neutropenia, frequent transfusions, and other supportive care.

Standard Arm



Arm A "EsPhALL" Therapy



High risk of fever/neutropenia/sepsis:

- EsPhALL Treatment-Related Mortality: 16%!!
- AALL 0622: 5%

GSCF used at the end of each consolidation block.

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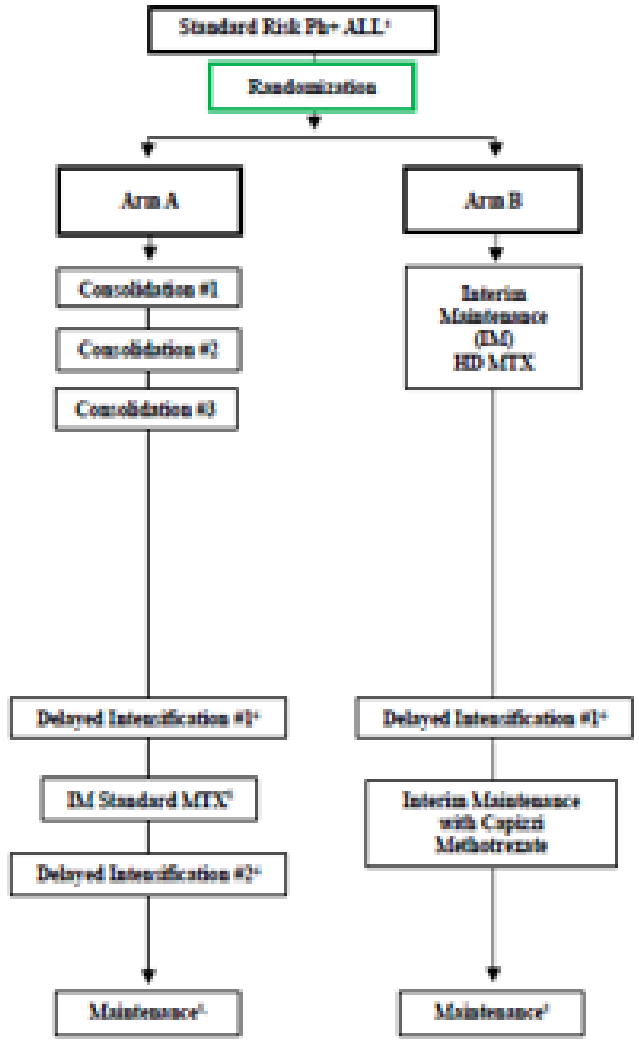
Arm A “EsPhALL” Therapy

There are two Delayed Intensifications found only in the EsPhALL arm.

DI #1

DI #2



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Delayed Intensification #2

Delayed Intensification #2 SR Ph+ ALL: Arm A (EsPhALL Arm)

4.9.1 Therapy Delivery Map – Delayed Intensification #2 Part 1 SR Ph+ ALL: Arm A (EsPhALL Arm) Begin DI #2 Part 1 therapy on Day 29 of EsPhALL Interim Maintenance or when criteria to start are met. Delayed Intensification therapy is 7 weeks (49 days).	Patient COG ID number _____ DOB _____

Treatment details and criteria to start are in Section 4.9.4. This Therapy Delivery Map is three (3) pages in length.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/ m^2/day **Maximum dose: 800 mg**	daily	Administer doses > 600 mg/day, twice daily. See Section 4.9.4 for additional details. Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) — Dose 1-1.99 — 8 mg 2-2.99 — 10 mg ≥ 3 — 12 mg	1	Refer to Section 4.9.4 for admin guidelines. **Note age-based dosing.**
Dexamethasone (DEX)	PO or IV	5 mg/m^2/day BID	1-7 & 15-21	Total daily dose: 10 mg/m^2/day divided BID Refer to Section 4.9.4 for admin guidelines.
VinCRIStine (VCR)*	IV over 1 min	1.5 mg/m^2/dose **Maximum dose: 2 mg**	8, 15, 22 & 29	*Or infusion via minibag as per institutional policy
Dexrazoxane (DXR)	IV over 5-15 min	250 mg/m^2/dose	8, 15, 22 & 29	Administer immediately prior to each Doxorubicin dose (required) Refer to Section 4.9.4 for admin guidelines.
DOXOrubicin (DOXO)	IV over 1-15 min	25 mg/m^2/dose	8, 15, 22 & 29	Slow IV push or IV bolus up to 1 hr per institutional guidelines. Refer to Section 4.9.4 for admin guidelines.
Pegaspargase (PEG-ASP)	IV over 1-2 hr	2500 IU/ m^2/dose	8	Refer to Section 4.9.4 for admin guidelines.

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Dexrazoxane

Delayed Intensification #2 SR Ph+ ALL: Arm A (EsPhALL Arm)

4.9.1 Therapy Delivery Map – Delayed Intensification #2 Part 1 SR Ph+ ALL: Arm A (EsPhALL Arm)

Begin DI #2 Part 1 therapy on Day 29 of EsPhALL Interim Maintenance or when criteria to start are met. Delayed Intensification therapy is 7 weeks (49 days).

Patient COG ID number _____ DOB _____

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Imatinib	PO	340 mg/ m^2/day **Maximum dose: 800 mg**	daily	Administer doses > 600 mg/day, twice daily. See Section 4.9.4 for additional details. Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) / Dose: 1-1.99 / 8 mg; 2-2.99 / 10 mg; ≥ 3 / 12 mg	1	Refer to Section 4.9.4 for admin guidelines. **Note age-based dosing.**
Dexamethasone (DEX)	PO or IV	5 mg/m^2/day BID	1-7 & 15-21	Total daily dose: 10 mg/m^2/day divided BID Refer to Section 4.9.4 for admin guidelines.
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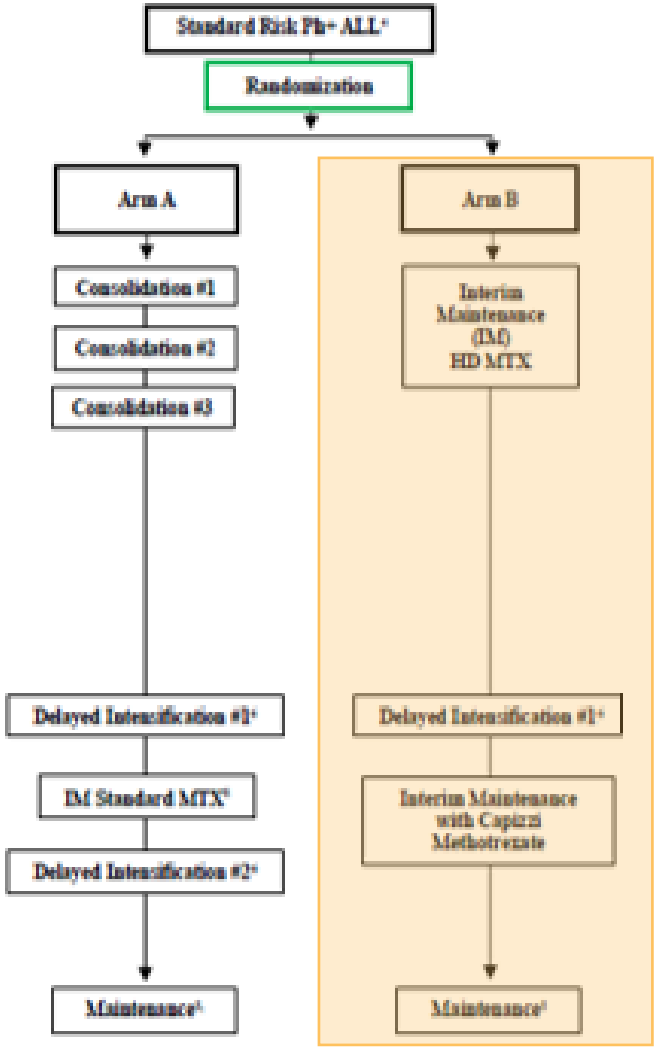
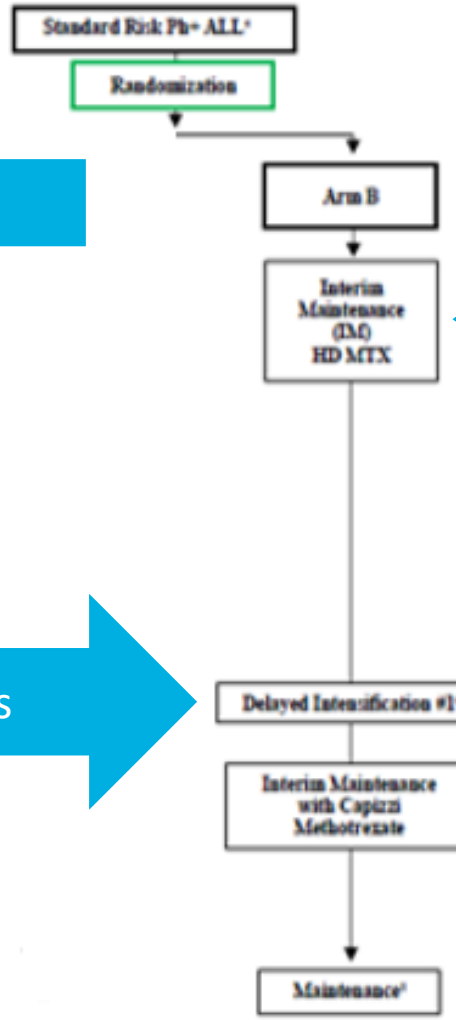
Dexrazoxane (DXR)	IV over 5-15 min	250 mg/m^2/dose	8, 15, 22 & 29	Administer immediately prior to each Doxorubicin dose (required) Refer to Section 4.9.4 for admin guidelines.
DOXOrubicin (DOXO)	IV over 1-15 min	25 mg/m^2/dose	8, 15, 22 & 29	Slow IV push or IV bolus up to 1 hr per institutional guidelines. Refer to Section 4.9.4 for admin guidelines.
Pegaspargase (PEG-ASP)	IV over 1-2 hr	2500 IU/ m^2/dose	8	Refer to Section 4.9.4 for admin guidelines.

Dexrazoxane is a cardio-protectant that is given immediately prior to the administration of the anthracycline Doxorubicin.

Standard Risk Arm B “COG” Therapy



Standard Risk Arm B “COG” Therapy



Continuous Imatinib in this Arm

Interim Maintenance #1: High Dose Methotrexate

DI: “Normal,” two Pegasparagase doses

If patient has a Pegasparagase allergy, they will be switched to Erwinia (Satellite-friendly chemotherapy)

Interim Maintenance #2: Capizzi MTX with two Pegasparagase doses

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Toxicities and Imatinib

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Imatinib	PO	340 mg/m^2/day **Maximum dose: 800 mg**	Daily	Administer doses > 600 mg/day, twice daily. See Section 4.2.3 for additional details. Imatinib is given daily without interruption. Hold only for toxicity (Section 5.7)

Section 5.7 in the full COG protocol outlines when you should hold Imatinib.

There are many parts to this section but from a Satellite perspective, there is a slight shift in practice when considering holding antineoplastics for a patient who is experiencing toxicities:

- Do not hold or reduce dose for low blood counts, unless prolonged (resulting in a > 14-day delay in next block of chemotherapy).

Holding and management of toxicities should be done in discussion with tertiary centre.

Summary

Continuous Imatinib (> 600mg goes bid)

Hold other antineoplastics with toxicities (e.g. fever) but continue with Imatinib unless parameters met as per Section 5.7 in the COG protocol.

HR: EsPhALL, persistent MRD to transplant.

SR: EsPhALL vs. COG

- Three Consolidation blocks with G-CSF post
- Two delay intensifications with Satellite-friendly chemotherapy

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