The Betsy Poon Pharmacy Education Series

2024 COG Fall Meeting

CHILDREN'S ONCOLOGY GROUP

Practical Considerations for Children's Oncology Group (COG) Clinical Trials

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Conflicts of Interest/Disclosures

NAME	COMPANY	RELATIONSHIP
Olga Militano, PharmD,	Nothing to disclose	N/A

Reviewers

Timothy Jacobs (CPE committee): co-owner of Medicine Shoppe Pharmacy (store #1072)
Elizabeth Bisaccia: salary/honoraria/royalties - CE synergy
Melissa Sandley: consultant fees (including advisory boards) – Jazz Pharmaceuticals

All of the relevant financial relationships listed for the individual(s) have been mitigated.

Learning Objectives

- Describe recent advances in the management of infant acute lymphoblastic leukemia [ALL]: potential for targeted therapy

- Recognize opportunities to optimize clinical trial management of asparaginase in infants with ALL

- Summarize emerging data and recommendations as they pertain to open COG studies

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Off-label Use Disclosure: This session does include a discussion of off-label treatment and investigational agents not approved by the FDA for use in the US.

ABBREVIATIONS

- ALL – acute lymphoblastic leukemia
- AML – acute myeloid leukemia
- B-ALL – B-cell acute lymphoblastic leukemia
- CAL-PEG- calaspargase pegol
- COG – Children's Oncology Group
- CPIC- Clinical Pharmacogenetics Implementation Consortium
- EFS – event-free survival
- FDA- Food and Drug Administration
- HR- high risk
- IM- intramuscular
- INR- International Normalized Ratio
- IR – intermediate risk
- IV- intravenous
- KMT2A-r – KMT2A rearranged
- KMT2A-wt – KMT2A wild type
- LR- low risk
- MRD- minimal residual disease
- NG – nasogastric
- NUDT15 - nudix hydrolase 15
- OS- overall survival
- PEG - pegaspargase
- P-gp – P-glycoprotein
- PK - pharmacokinetics
- PO – oral
- RP2D – recommended Phase 2 dose
- SAA – serum asparaginase activity
- SR- standard risk
- TPMT - thiopurine S-methyltransferase

Advances in Management of Infant ALL

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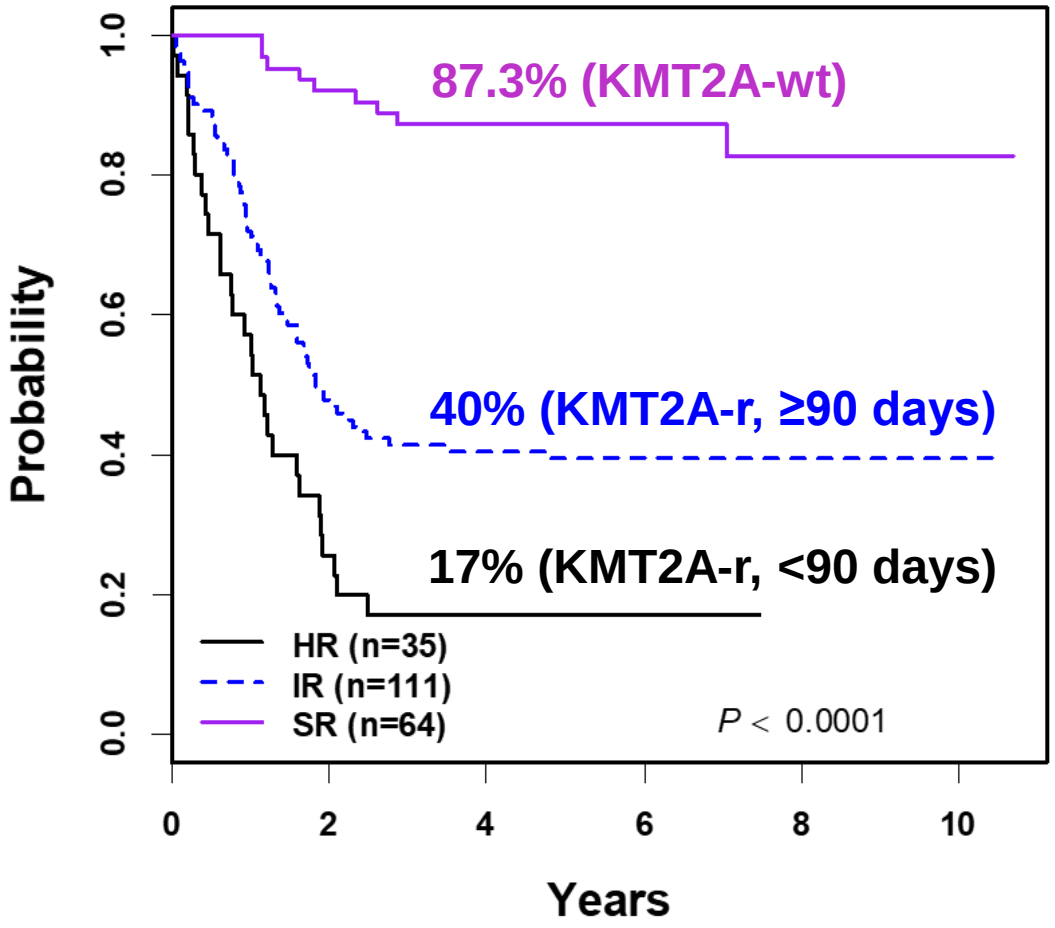
Infant ALL – Historical Perspective

- ALL diagnosed in infants < 1 year of age is difficult to treat
- Independent risk factors associated with an inferior outcome include presence of a ***KMT2A* rearrangement**, hyperleukocytosis at presentation, age less than 6 months at diagnosis, and poor response to initial prednisone therapy
- *KMT2A* rearrangements are present in ALL cells of up to 80% of infants and are associated with chemoresistance and high rates of relapse
- Intensification of conventional chemotherapy has been successful in KMT2A germline (non-rearranged) infant ALL
- 5 year EFS for infants with KMT2A rearranged ALL remains dismal at ~40%
- Most relapses occur during treatment: 2/3 occur within 1 year and 90% within 2 years after diagnosis

Kotecha RS et al . *Blood Cancer J.* 2014;4:e200
Pieters R et al. *J Clin Oncol.* 2019;37(25):2246-2256

Infant ALL EFS by Risk Group



Historical Controls

	INTERFANT-06[1] (4-year EFS)	INTERFANT-99[2] (4-year EFS)	COG AALL0631[3,4] (5-year EFS)
LR/SR	75.7%	74.5%	87.3%
MR/IR	45.7%	45.5%	40%
HR	23.2%	18.6%	17%

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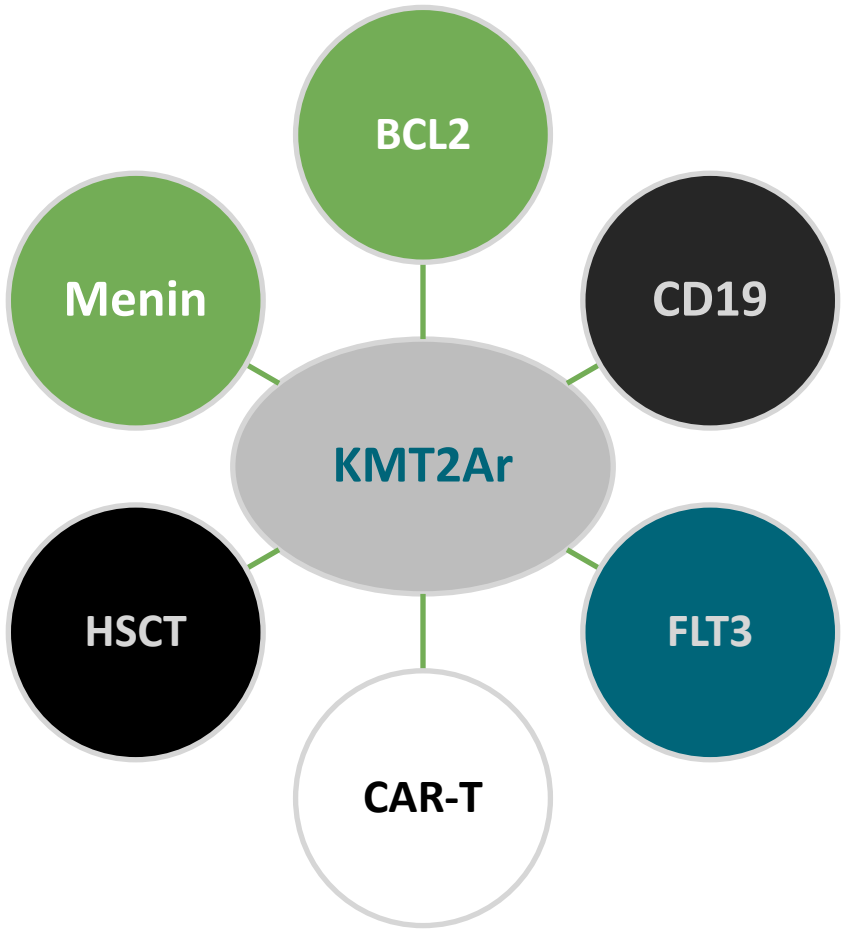
[1]Pieters *et al.* JCO 2019, [2]Pieters *et al.* Lancet 2007, [3]Brown *et al.* Leukemia 2021, [4]Guest *et al.* Haematologica 2022

Targeting KMT2A-r ALL



- B-cell lymphoma 2 (BCL-2) family proteins regulate the intrinsic mitochondrial apoptosis pathway with BCL-2 a key antiapoptotic regulator
  - High expression of BCL-2 has been identified in *KMT2A*-rearranged ALL
  - Attractive target with objective responses after treatment with venetoclax in infant *KMT2A*-rearranged patient-derived xenografts

Khaw SL et al. Blood. 2016;128(10):1382-1395

Venetoclax in Infant ALL

- Selective orally bioavailable inhibitor of BCL-2 protein (anti-apoptotic)
- Has demonstrated cytotoxic activity in tumor cells that overexpress BCL-2
- Pediatric PK trials revealed that weight-based dosing resulted in venetoclax plasma concentrations similar to adults
- Crosses blood brain barrier
- Favorable results in combination chemotherapy trials in pediatric and adult ALL and AML

Venetoclax Dosing in Infant ALL

- Dosing of venetoclax will follow the adult recommended dose of 600 mg equivalent in combination with cytotoxic chemotherapy
- Exposure was most comparable to adults when administered for 14 days of a 28-day cycle.

AALL2321 Proposed Venetoclax dosing (subject to change)

Age	Adult dose equivalent of 600 mg venetoclax (mg/kg)	Approximate dose reduction compared to RP2D in adults
0 – < 1 month	2.1	75% reduction
1 – < 3 months	4.3	50% reduction
3 – < 6 months	5.3	37% reduction
6 – < 12 months	7.9	7% reduction
≥ 12 months	10	20% dose increase*

*Accommodates increased liver to body size ratio in toddlers compared to adults

Venetoclax Administration and Toxicity

- Provided in a sachet formulation for clinical trials in children (mix with apple juice, water or soft foods)
- Can be administered PO or NG
- Drug interactions:
  - ↓ venetoclax by at least 75% when used concomitantly with the strong and ↓50% when used with moderate CYP3A4/5 inhibitor
  - Avoid P-gp inhibitors
  - Monitor warfarin INR
- Toxicity:
  - Anemia
  - Nausea, diarrhea
  - Fatigue
  - Infection
  - Neutropenia/thrombocytopenia
  - Hypertension
  - Electrolyte abnormalities
  - Autoimmune hemolytic anemia
  - Tumor lysis syndrome

Blinatumomab for KMT2Ar Infant ALL

- Bispecific single-chain antibody construct that binds cytotoxic T-cells through CD3 receptors and B cells through CD19 receptors, engaging the immune system to eradicate both B-ALL blasts and normal B cells
- FDA approved for patients ≥ 1 month of age with MRD+, relapsed/refractory, or as part of frontline consolidation therapy B-cell ALL

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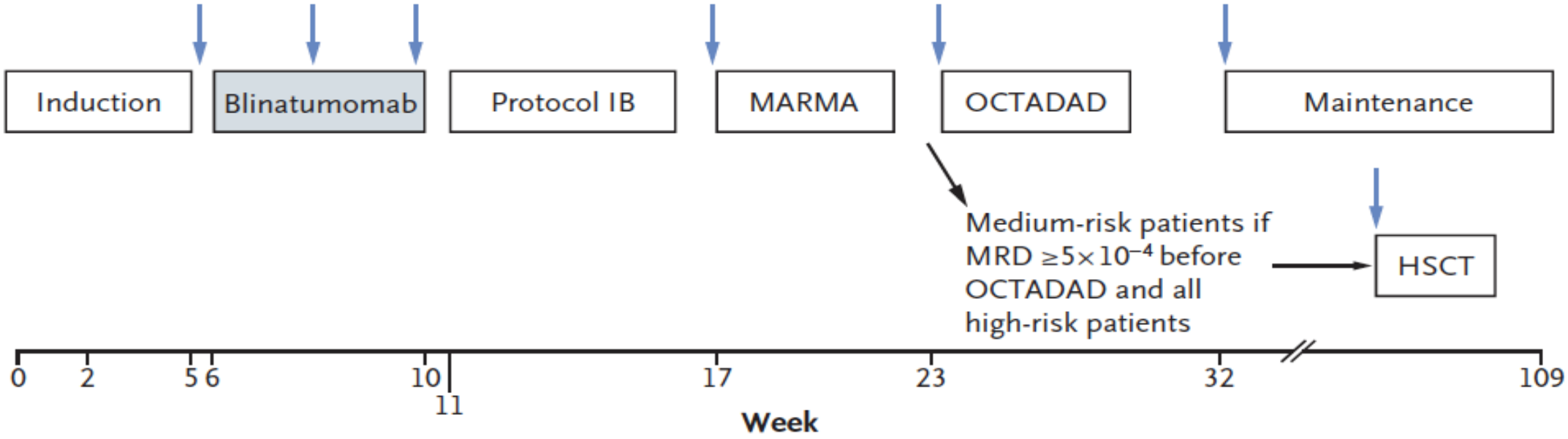
https://www.blincytohcp.com/mechanism-of-action

Interfant Blinatumomab Pilot

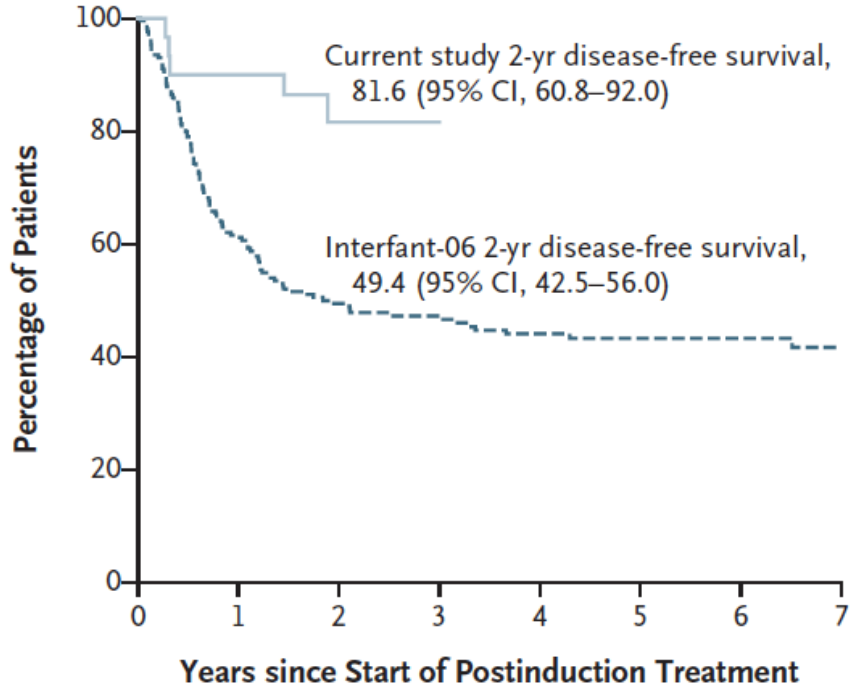


- Phase 2 pilot study of feasibility, safety, and tolerability of the addition of 1 cycle of blinatumomab to the Interfant-06 backbone in 30 infants with *KMT2A*-r ALL
- Feasibility - All completed 4 weeks of blinatumomab at 15 mcg/m^2/day
- Toxicity - Well tolerated overall; No neurologic toxicities, CRS = 1 patient (Grade 1)

van der Sluis IM *et al.* NEJM 2023;388:1572-1581

Interfant Blinatumomab Pilot Results

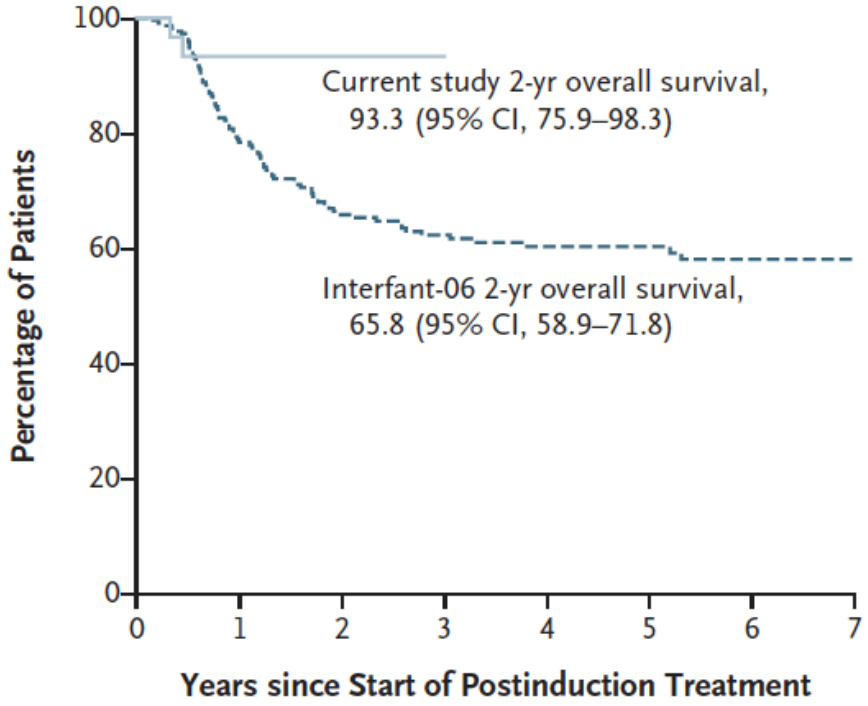
Disease-free Survival, Current Study vs. Interfant-06



No. at Risk (censored)

Current study	30 (0)	27 (0)	16 (9)	5 (20)	1 (24)	0 (25)	0 (25)	0 (25)
Interfant-06	214 (0)	129 (2)	91 (16)	77 (26)	59 (39)	44 (53)	32 (65)	20 (76)

Overall Survival, Current Study vs. Interfant-06



No. at Risk (censored)

Current study	30 (0)	28 (0)	18 (10)	6 (22)	1 (27)	0 (28)	0 (28)	0 (28)
Interfant-06	214 (0)	165 (3)	119 (24)	98 (39)	78 (56)	59 (75)	40 (92)	26 (106)

The number of relapses was low; however, all the patients who had a relapse had CNS involvement at relapse

van der Sluis IM *et al.* New England Journal of Medicine 2023

Caveats of Blinatumomab Administration in Infants

- Blinatumomab 24, 48, 72 and 96 hour bags are most commonly used in infants
  - FDA permitted the use of 72 and 96 hour bags for certain COG trials that allow for collection of infectious toxicity data related to bag duration during blinatumomab cycles
- 7-day blinatumomab bags are for infants with BSA ≥ 0.4 m^2
  - Lack of safety data in infants with BSA < 0.4 m^2
  - Do not use an in-line filter during the administration of 7-day IV bag
- Infusion rates and volumes for dilution are important due to risk of fluid overload
  - Infusion rate ≤ 5 mL/hr is preferred in infants

blincyto_pi_hcp_english.pdf (amgen.com)

Trials with Excessive Toxicity in Infants

- P9407, 1996-2006 (n=68, cohorts 1+2)
  - Excessive infection-related induction mortality (10/17, 58.8% infants ≤90 days; 7/51, 13.7% infants >90 days)
  - Study halted and induction amended twice
  - Modifications to multiple agents to reduce mortality rates
  - All 3 cohorts received L-asparaginase 6000 U/m^2/dose
- AALL0631, 2008-2012 (n=26, cohort 1)
  - Utilized P9407 cohort 3 induction, changed from L-asparaginase to pegaspargase 2,500 IU/m^2/dose, single dose, no age-based dose reductions
  - Study halted due to excessive induction mortality (4/26, 15.4%)
  - All deaths infection-related

Salzer W, et al. Pediatr Blood Cancer 2012; Salzer W, et al. Pediatr Blood Cancer 2015; Brown P, et al. Leukemia 2021

Trials with Safe Asparaginase Dosing in Infants

- AALL15P1, 2017-2019 (n=78)[1]
  - Age-based dose reductions of pegaspargase implemented due to the excessive induction mortality on predecessor study AALL0631:
    - 1250 IU/m^2/dose <7 days (50% dosing)
    - 1750 IU/m^2/dose 7 days to <6 months (70% dosing)
    - 2000 IU/m^2/dose 6-11 months (80% dosing)
    - 2500 IU/m^2/dose ≥ 12 months of age
  - Dosing strategy well tolerated
  - Therapeutic serum asparaginase activity levels 7 days post-dose
- MLL-10, 2011-2015 (n=90)[2]
  - L-asparaginase 10,000 U/m^2/dose induction, 6000 U/m^2/dose post-induction
  - Age-based dose reductions based on findings of excessive toxicity from AALL0631
  - Dose reduced by 1/3 infants <2 months and by 1/4 infants 2-3 months
  - Dosing strategy well tolerated

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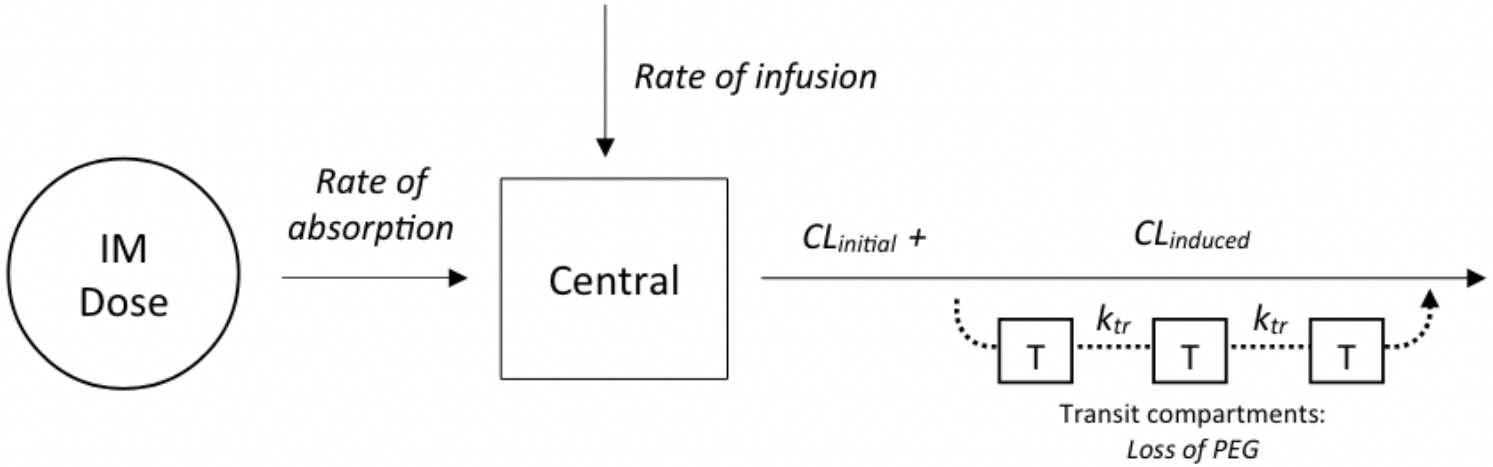
[1]Guest, et al. Blood 2022;140 (Supplement 1): 3256–3257.
[2]Tomizawa D, et al. Blood 2020;136 (16): 1813–1823

Population PK of Pegaspargase Activity

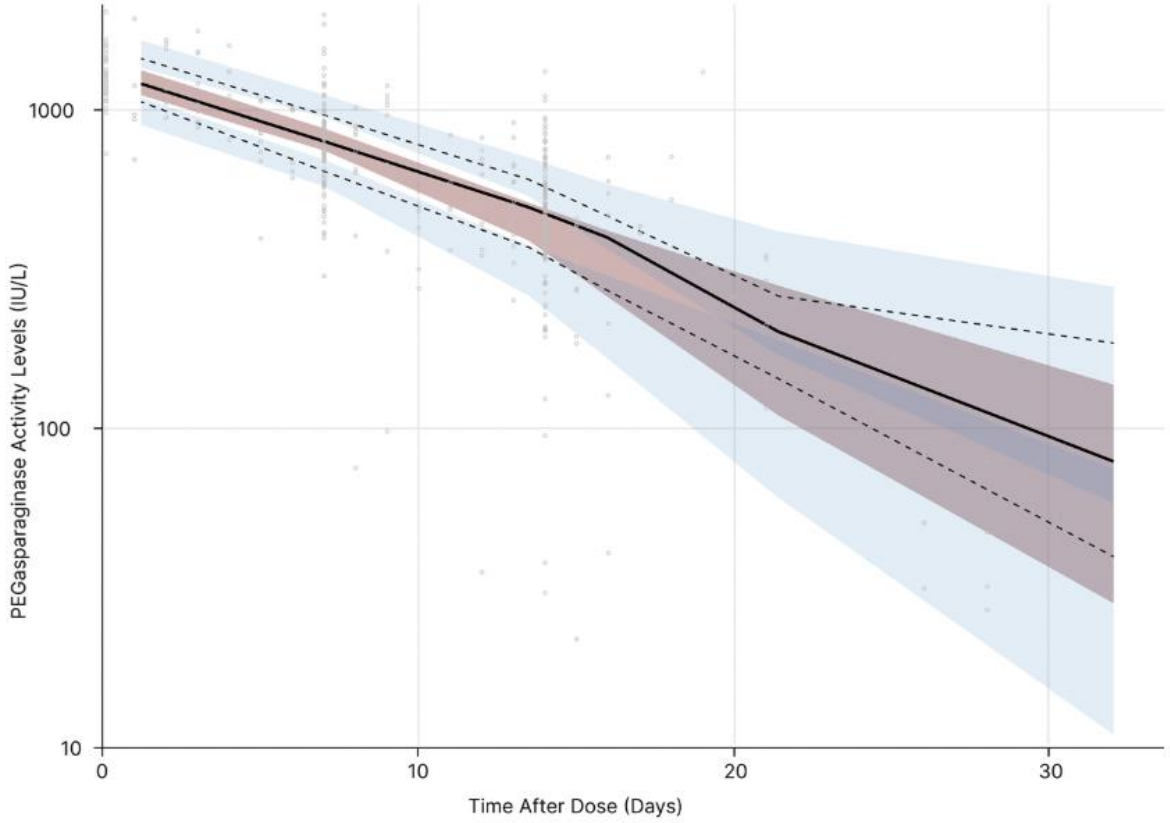
- No difference between infants and older children (68 subjects; 6.6 months (range 2.5-9.4), ~50% were < 6 months of age
- Doses ranged from 400-3600IU/m^2

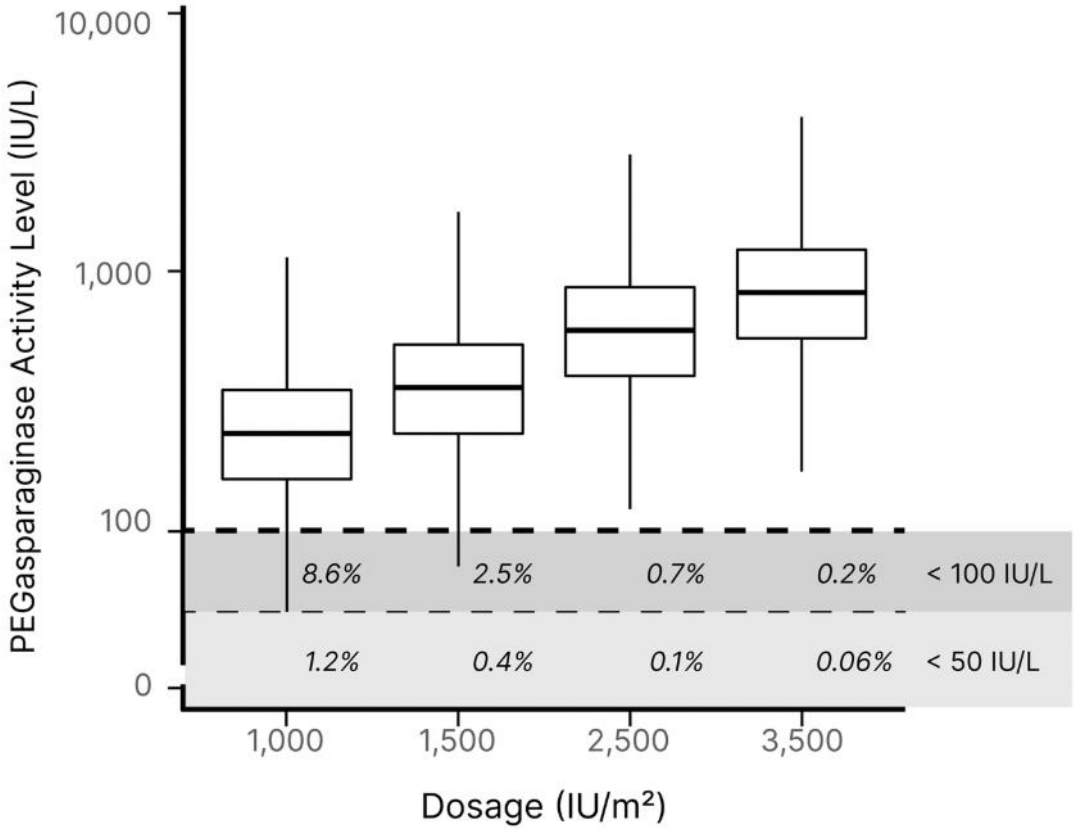


Brigitha et al. Pharmaceutical Research.2024;41:711-720

Population PK of Pegaspargase Activity

97.5% of patients had a SAA level >=0.1 IU/ml at 14 days with 1500 IU/m^2 dosing





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Brigitha et al. Pharmaceutical Research. 2024;41:711-720

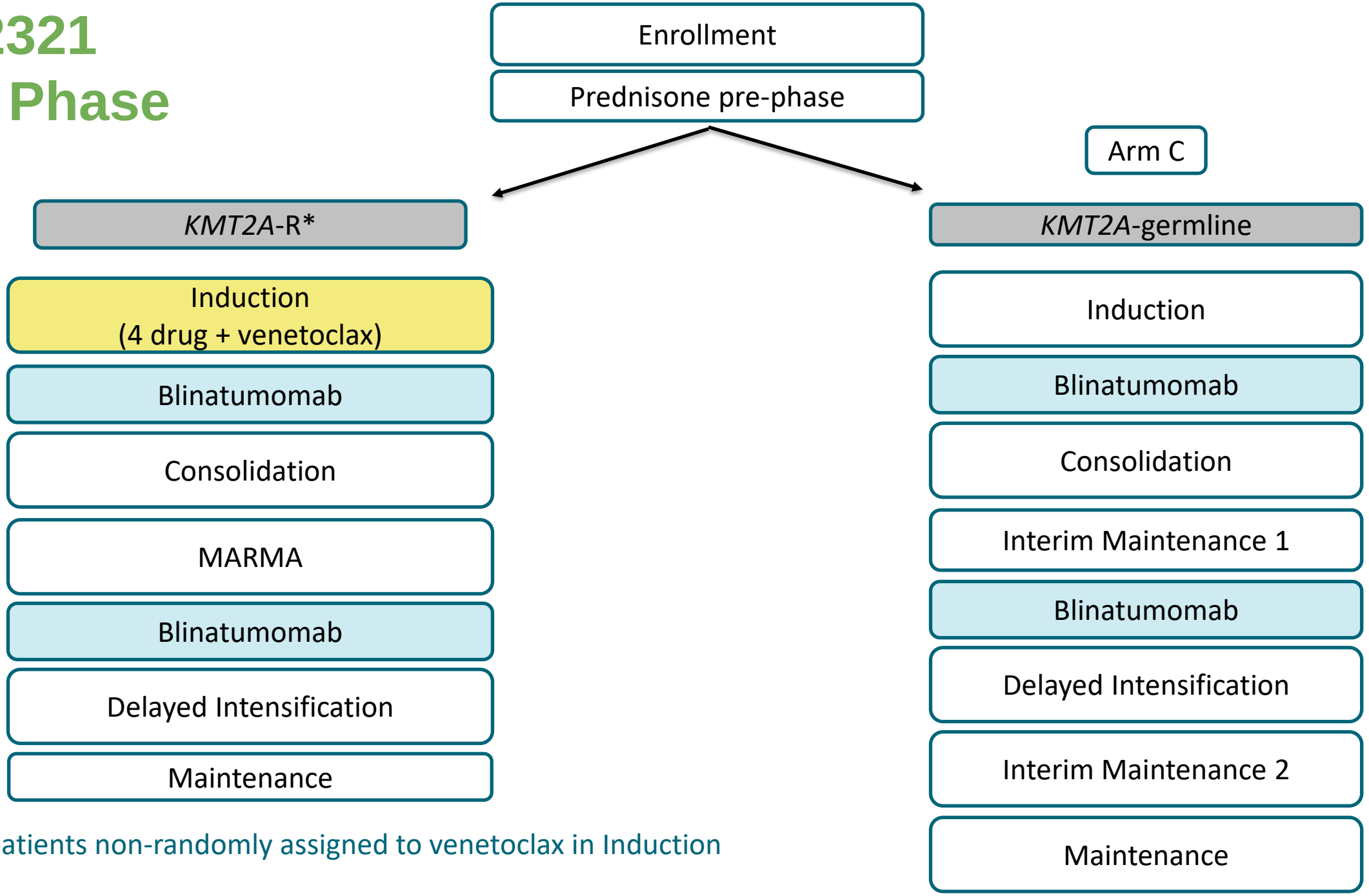
AALL2321:A Phase 2 Study of Blinatumomab in Combination with Chemotherapy for Infants with Newly Diagnosed ALL with Randomization of *KMT2A-R* Patients to Addition of Venetoclax

Primary Objectives:

- To evaluate the safety and tolerability of venetoclax in addition to a standard chemotherapy backbone and two cycles of blinatumomab in infants (aged 365 days or less at diagnosis) with newly diagnosed *KMT2A*-R ALL.

- To determine in a randomized manner if the addition of venetoclax to induction chemotherapy improves end of induction MRD-negative remission rates in infants with *KMT2A*-R ALL.

AALL2321 Safety Phase



**KMT2A*-R patients non-randomly assigned to venetoclax in Induction

AALL2321 Expansion Phase

(when Arm B assigned to Cohort 1)

Enrollment

Prednisone pre-phase

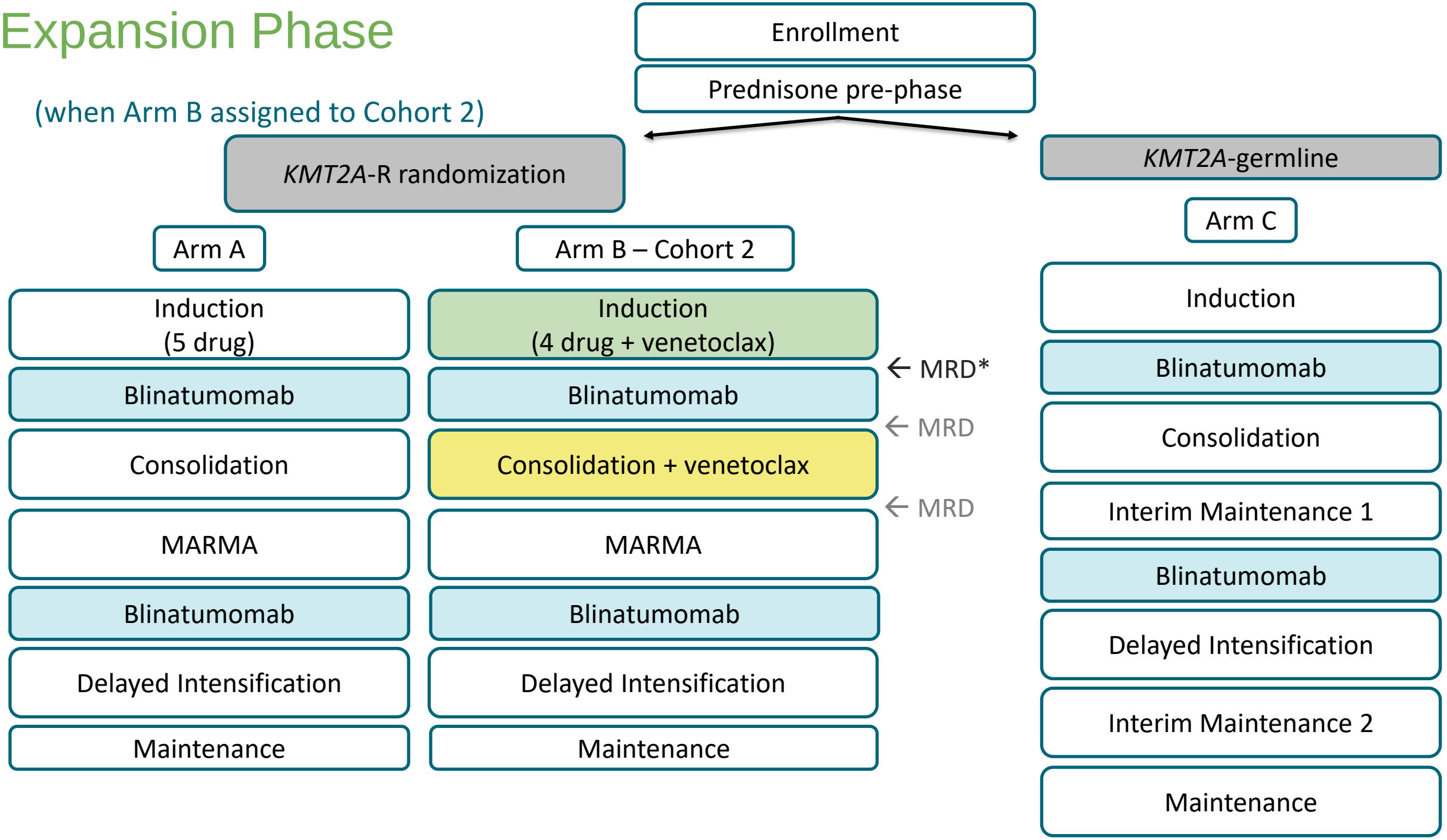
KMT2A-R randomization

KMT2A-germline

Arm A	Arm B – Cohort 1		Arm C
Induction (5 drug)	Induction (4 drug + venetoclax)	← MRD*	Induction
Blinatumomab	Blinatumomab	← MRD	Blinatumomab
Consolidation	Consolidation	← MRD	Consolidation
MARMA	MARMA + venetoclax		Interim Maintenance 1
Blinatumomab	Blinatumomab		Blinatumomab
Delayed Intensification	Delayed Intensification		Delayed Intensification
Maintenance	Maintenance		Interim Maintenance 2
			Maintenance

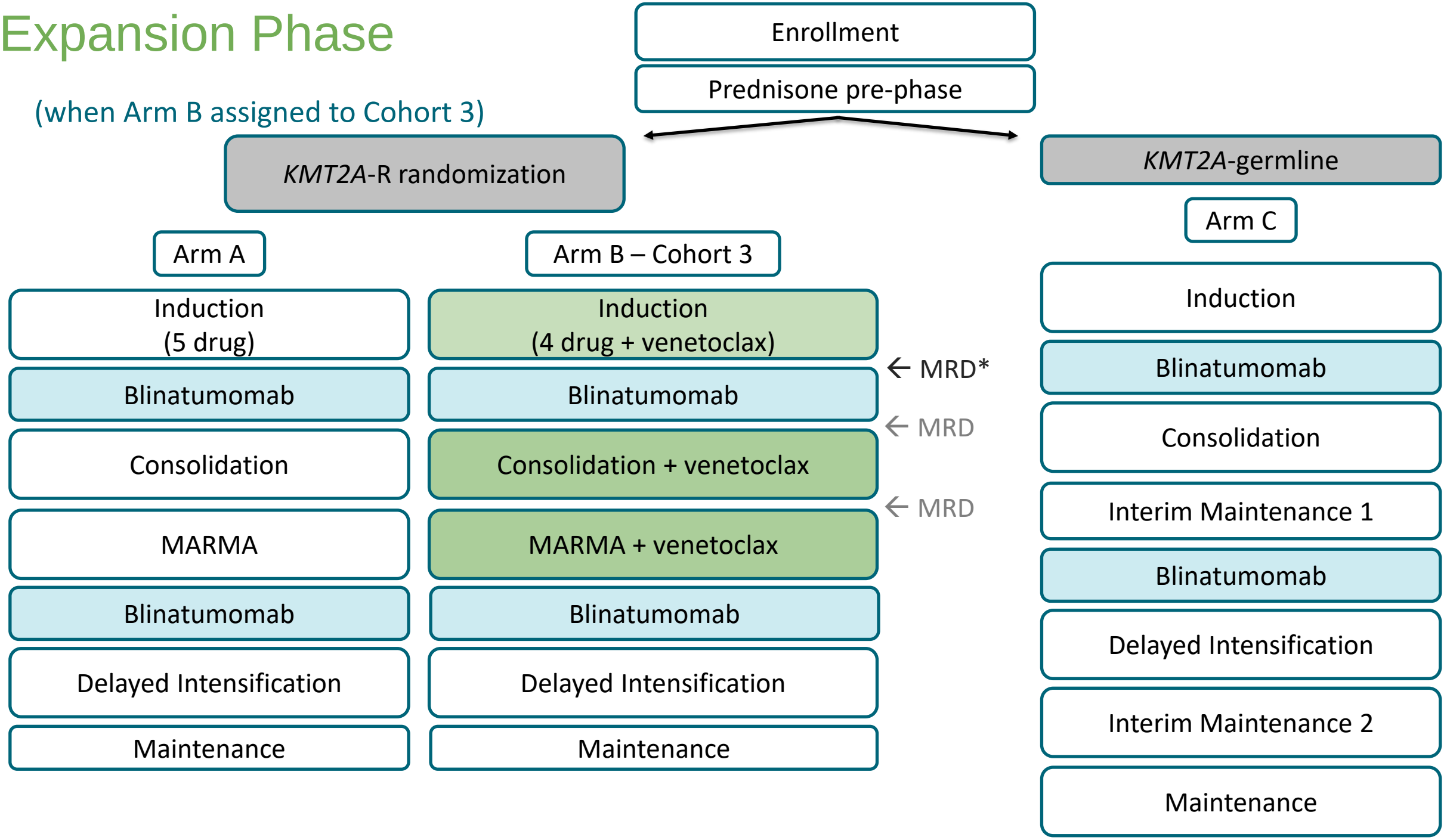
Expansion Phase

(when Arm B assigned to Cohort 2)



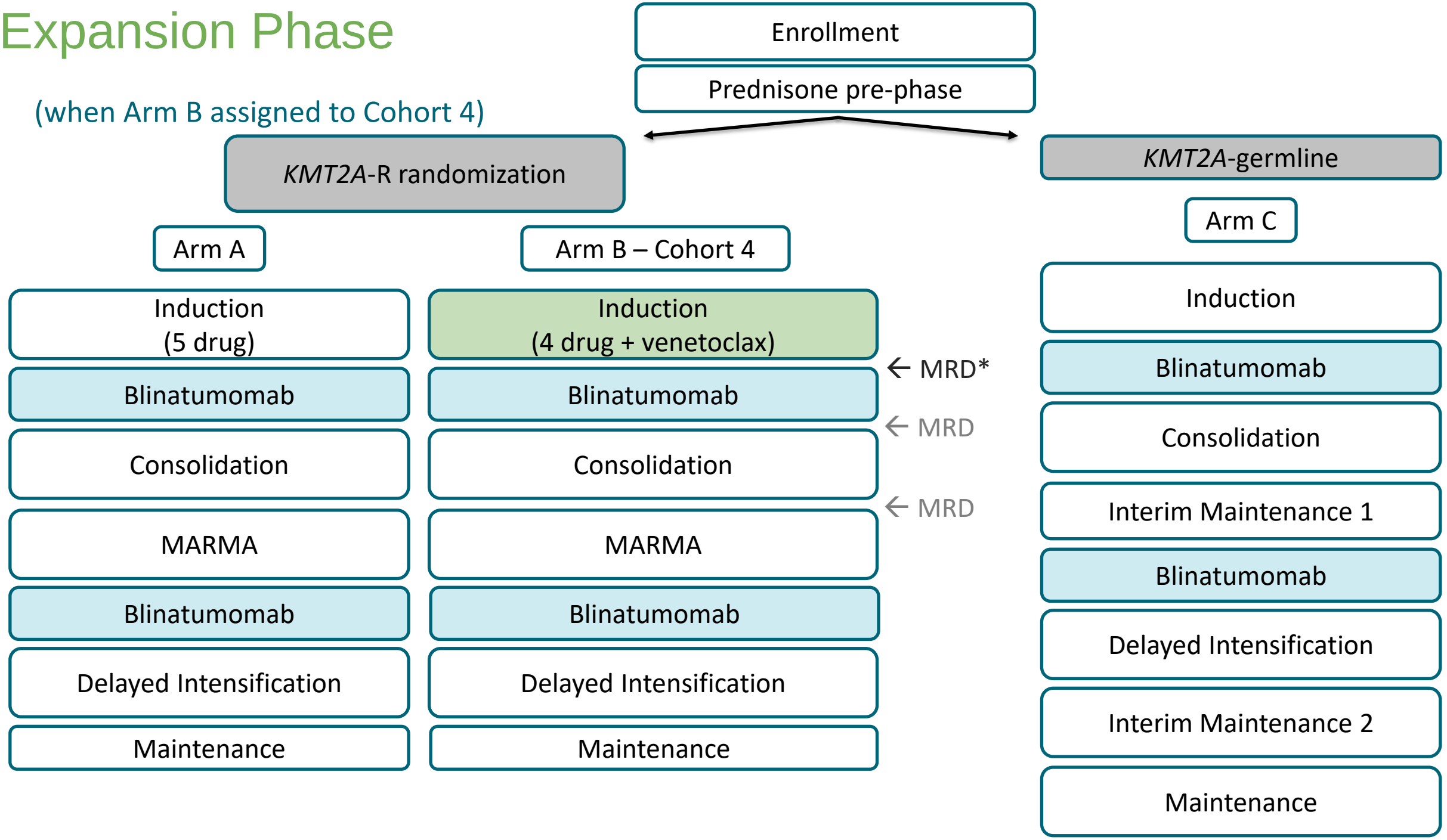
Expansion Phase

(when Arm B assigned to Cohort 3)



Expansion Phase

(when Arm B assigned to Cohort 4)



Calaspargase Pegol Protocol Updates

Frontline Infant ALL (AALL2321)

- Calaspargase pegol will be the only formulation used
  - Servier to provide calaspargase pegol to sites outside of US
- Age –based dosing (similar to pegaspargase on AALL15P1) will be utilized, with required real-time serum asparaginase activity monitoring to assure achievement of target SAA levels (≥ 0.1 IU/mL) at 14 days
- Include monitoring rule to guard against subtherapeutic SAA levels
- Planned dose escalation if monitoring rules triggered after DSMC review to ensure balancing safety and efficacy

Relapsed infant ALL (AALL2121)

- Will ONLY utilize calaspargase pegol (all patients will be older than 1 month)
- Will receive one dose at the FDA approved dosing (2,500 units/m^2)
- Servier to provide calaspargase pegol to sites outside the US

Audience Response Question 1

Which of the following are true regarding the upfront COG AALL2321 trial in development:

A. Due to safety concerns all patients will receive Erwinia formulations of asparaginase
B. AALL2321 will randomize patients to receive or not receive blinatumomab
C. AALL2321 will utilize age-based dosing of calaspargase pegol with real-time monitoring of SAA levels.
D. Infants with both germline and KMT2A-R Infant ALL will be eligible for the randomization to venetoclax

Late Breaking News

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Late Breaking Updates/Future Directions

- Blinatumomab consolidation in B-cell ALL
  - Blinatumomab received FDA approval for Philadelphia chromosome negative [Ph(-)] B-cell ALL in consolidation phase of multiphase chemotherapy
  - Interim results of ALL1731 demonstrated blinatumomab when added to chemotherapy produces significantly superior outcomes compared to chemotherapy alone ($p < 0.0001$)
- Oral Leucovorin
  - Maximum oral leucovorin dose for saturable absorption increased to 50 mg/dose in COG chemotherapy administration guidelines
- Asparaginase toxicity
  - Interim analysis of AALL1732 asparaginase toxicity data in Induction and Consolidation was accepted as oral presentation at SIOP 2024

AALL1731 Blinatumomab Consolidation

- AALL1731 Data Safety Monitoring Committee (DSMC) has performed a planned interim analysis and recommended that the blinatumomab randomization be permanently closed
- ALL1731 interim analysis:
  - Blinatumomab randomized groups have 3-year disease-free survival (DFS) of 96% vs 87.9% on the non-blinatumomab arms.
    - SR-average patients randomized to the blinatumomab containing arm (Arm B) have a three-year DFS of 97.5% vs 90.2% on the non-blinatumomab containing arm (Arm A).
    - SR-High patients on the blinatumomab containing arm (Arm D) have a 3-year DFS of 94.1% vs 84.8% on the non-blinatumomab containing arm (Arm C).
- SR-Average (Avg)/SR-High randomization is closed and SR-Avg/SR-High patients completing Callback #2 will be non-randomly assigned to treatment with blinatumomab on Arm B or Arm D

https://cogmembers.org/prot/aall1731/AALL1731Mem7_12_24.pdf

AALL1731 Recommendations

The overall recommendations of the Study Committee are as follows:

Patients currently in Induction or Consolidation therapy	May continue on protocol therapy. SR-Avg/SR-High patients completing Callback #2 will be non-randomly assigned to treatment with blinatumomab on Arm B or Arm D.
SR-Avg and SR-High patients receiving treatment on Arm A or Arm C and not yet in Maintenance.	Patients assigned to Arm A or Arm C (standard arms without Blinatumomab) may continue on protocol therapy with the addition of 1-2 cycles of non-sequential blinatumomab, as detailed below.
SR-Avg and SR-High patients in Maintenance	No change
SR-Avg and SR-High patients receiving treatment on Arm B or Arm D	No change

Investigational blinatumomab will continue to be provided by NCI/CTEP for patients registered on AALL1731 Arms A, B, C, and D prior to study closure

https://cogmembers.org/prot/aall1731/AALL1731Mem7_12_24.pdf

Blinatumomab Consolidation Results: Clinical Trials Implications

- Blinatumomab consolidation became the new standard of care for Ph(-) SR-average, SR-high, and HR B-ALL patients
- AALL1732 (High Risk trial) temporary closed to accrual to undergo amendment to include blinatumomab consolidation in addition to inotuzumab
  - The Study Committee recommends the addition of two non-sequential cycles of commercial blinatumomab as a medical intervention to be incorporated after Consolidation and prior to the start of Maintenance therapy in HR B-ALL, similar to the AALL1731 SR-High Arm D regimen. There are no data to support the addition of blinatumomab for patients who are already in Maintenance or have completed protocol therapy
- AALL2321 (frontline infant ALL trial) will include blinatumomab in all therapy arms (investigational supply provided by CTEP)

https://cogmembers.org/prot/aall1731/AALL1731Mem7_12_24.pdf
https://cogmembers.org/prot/aall1732/AALL1732Mem7_18_24.pdf
Litzow, MR et al. N Engl J Med. 2024;391:320-33

AALL1732: Calaspargase vs Pegaspargase Toxicity

- Interim Analysis Comparison of Pegaspargase (PEG) and Calaspargase-pegol (CALPEG) during Induction and Consolidation (initial 13 weeks of therapy)
- Age ≥ 10 years
- Toxicities examined: pancreatitis, thrombosis, hepatotoxicity*
- No significant toxicity difference

Toxicity at Induction	PEG (N=1291) (%)	CALPEG (N=420) (%)	P-value
Composite Toxicity Outcome	156 (12.1)	46 (11)	0.533
Pancreatitis	21 (1.6)	11 (2.6)	0.192
Thrombosis	24 (1.9)	10 (2.4)	0.506
Hepatotoxicity	125 (9.7)	34 (8.1)	0.331

Toxicity at Consolidation	PEG (N=1033) (%)	CALPEG (N=286) (%)	P-value
Composite Toxicity Outcome	97 (9.4)	29 (10.1)	0.703
Pancreatitis	42 (4.1)	11 (3.9)	0.867
Thrombosis	11 (1.1)	4 (1.4)	0.638
Hepatotoxicity	50 (4.8)	15 (5.2)	0.780

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*transaminitis, hyperbilirubinemia

Unpublished. Abstract Accepted to SIOP 2024

Audience Response Question 2

Which of the following is True regarding blinatumomab use for B-Cell ALL:

A) Blinatumomab is FDA approved as part of multiphase consolidation therapy for Ph (+) B-cell ALL

B) Based on interim results of AALL1731 trial, blinatumomab consolidation became the new standard of care for Ph(-) SR-average, SR-High, and HR B-cell ALL in pediatric patients

C) 72 hour and 96 hour bags of blinatumomab are NOT permitted to be used on COG ALL trials

D) AALL1732 study committee recommends 2 sequential cycles of investigational blinatumomab as medical intervention after Consolidation therapy

Question & Answer Session

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