

高雄榮民總醫院 急性淋巴性白血病診療原則

2025年02月24日第一版

兒童癌症醫療團隊擬訂

注意事項：這個診療原則主要作為醫師和其他保健專家診療癌症病人參考之用。假如你是一個癌症病人，直接引用這個診療原則並不恰當，只有你的醫師才能決定給你最恰當的治療。

修訂指引

- 本診療原則依下列參考資料制定版本
 - 台灣兒童癌症研究群(TPOG)
 1. TPOG-ALL-2021_0801
 2. TPOG-Infant ALL-2022
 3. 2025年2月發布關於TPOG-ALL-2021
Blinatumomab使用修訂及TPOG-Infant ALL-2022
(202502 Revision)

會議討論

上次會議：2024/02/26

本共識與上一版的差異

上一版	新版
1. 增加infant ALL治療更新指引(PPT. 44、PPT. 45)	1. 新增blincyto的使用時機(PPT. 32、PPT. 33) 2. 修改infant ALL治療更新指引(PPT. 45的療程表有修改，主要差異在blincyto的使用；增加PPT. 46)

Risk Classification

Patients are classified into one of three categories (**standard-, high-, or very high-risk**) based on Presenting age, Leukocyte count, Presence or absence of CNS-3 status or testicular leukemia, Immunophenotype, Cytogenetics and molecular genetics, DNA index, and early response to therapy. Hence, definitive risk assignment will be made after completion of remission induction therapy. The criteria and the estimated proportion of patients in each category are provided below.

Criteria for Standard-risk(SR) ALL

1. B-lymphoblastic ALL with DNA index ≥ 1.16 [or hyperdiploidy (51-68)], *TEL-AML1* fusion, or age 1 to 9.9 years and presenting WBC $< 50,000/\text{mm}^3$. AND
2. Must **not** have:
 - ✓ CNS 3 status ($\geq 5 \text{ WBC}/\mu\text{L}$ of cerebrospinal fluid with morphologically identifiable blasts or cranial nerve palsy).
 - ✓ Overt testicular leukemia (evidenced by ultrasonogram).
 - ✓ Adverse genetic features: t(9;22) or *BCR-ABL1* fusion; t(1;19) with *E2A-PBX1* fusion; rearranged *MLL* (as measured by FISH and/or PCR); or hypodiploidy (< 44 chromosomes).
 - ✓ Poor early response ($\geq 1\%$ lymphoblasts on day 15 of remission induction (**MRD1**), $\geq 0.01\%$ lymphoblasts by immunologic or molecular methods on remission date(**MRD2**)).

Criteria for High-risk(HR) ALL

1. Other B-ALL patients not meeting standard-risk nor very high-risk criteria.
2. Other T-ALL patients not meeting very high-risk criteria

Criteria for Very High-risk(VHR) ALL

1. All non-hyperdiploid B-ALL with MRD₂ ≥1%.
2. Hyperdiploid B-ALL with MRD₂ ≥1% and MRD remaining positive (≥0.01%) after consolidation
3. Re-emergence of leukemic lymphoblasts by MRD (at any level) in patients previously MRD negative (<0.01%)
4. Persistently detectable MRD at lower levels
5. All T-ALL with MRD ≥0.1% after early intensification, no matter the MRD results afterward
6. TCF3-HLF/t(17;19).

Criteria for ETP

Classification of ETP-ALL requires the following criteria:

Criteria 1. Unequivocal diagnosis of T-ALL as defined by:

CD3-positive (surface, or cytoplasmic only)

CD7-positive

Myeloperoxidase (MPO)-negative

Criteria 2.

CD1a-negative AND CD8-negative

Criteria 3.

Dim CD5.

Definition of “dim”: mean fluorescence intensity (MFI) at least 10-fold lower than that of normal T lymphocytes (use residual normal T cells in the sample to calculate) AND/OR <75% CD5-positive blasts

Criteria 4.

Expression of stem-cell associated antigens (CD34, CD133, CD117 and/or HLA-Dr) AND/OR expression of myeloid-associated antigens (CD13, CD33, CD15 and/or CD11b). Positivity with any one of these markers is sufficient.

ALL 4 CRITERIA MUST BE MET TO DEFINE ETP-ALL

[Dr. D-C Liang personal communication with Dr. Campana]

兒癌-ALL

Treatment Plans

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Summary of Induction/Early Intensification/Consolidation

B-ALL

Pro-Risk	Sub-group	MRD1	Up-grade	Ind II	EOI BM Date	MRD2	Final Risk	Early Inten	Consolidation (HD-MTX)	Continuation, week 1		
SR	<0.1%		A	D35-42		<0.01%	SR	No	2.5 g/m ²	Reinduction		
						0.01-0.99%	HR	EI	5.0 g/m ²	Blincyto or reintensification [#]		
						≥1%*	VHR	EI+				
	0.1-0.99%		A	D35-42		<0.01%	SR	EI	5.0 g/m ²	Reinduction		
						0.01-0.99%	HR	EI	5.0 g/m ²	Blincyto or reintensification [#]		
						≥1%*	VHR	EI+				
	1-4.99%	HR	B	D42-46		<0.01%	HR	EI	5.0 g/m ²	DEX+EPI+VCR+6MP+ASP		
						0.01-0.99%	HR	EI	5.0 g/m ²	Blincyto or reintensification [#]		
						≥1%*	VHR	EI+				
		≥5%	HR			<0.01%	HR	EI+	5.0 g/m ²	DEX+EPI+VCR+6MP+ASP		
						0.01-0.99%	HR	EI+	5.0 g/m ²	Blincyto or reintensification [#]		
						≥1%*	VHR					

Blincyto, blinatumomab; EOI, end of induction; Ind, induction; Inten, intensification; Pro-risk, provisional risk.

*VHR in Hyperdiploid ALL: MRD2 ≥1% and MRD remaining positive (≥0.01%) after consolidation.

[#]Reintensification will be given: 1). after consolidation for MRD2 ≥1% (VHR) and 2). after reinduction I for HR patients with MRD ≥0.01% on continuation week 7,

Blincyto 使用期間 dasatinib 需繼續使用，Blincyto 最後 1 天予 TIT。不併用 C/T 及 ruxolitinib。

MRD3 at continuation week 7 for patients with MRD2 ≥0.01%; optional MRD4 for patients who completion of Blincyto or reintensification; further MRD for persistent MRD ≥0.01%.

[Blincyto 後將導致 CD19 消失，後續若仍進行 flow MRD F/U 時，務必告知檢查單位使用 Blincyto 的病史，以另行尋找 markers 或其他 MRD 檢測方法。]

Treatment Plans

B-ALL (continued)

Pro-Risk	Sub-group	MRD1	Ind II	EOI BM Date	MRD2	Final Risk	Early Inten	Consolidation (HD-MTX)	Continuation Week 1
HR	<5%	B	D42-46	<0.01%	HR	EI	5.0 g/m ²	DEX+EPI+VCR+6MP+ASP	
				0.01-0.99%	HR	EI	5.0 g/m ²	Blincyto or reintensification [#]	
				≥1%	VHR	EI+			
	≥5%	C	D42-46	<0.01%	HR	EI+	5.0 g/m ²	DEX+EPI+VCR+6MP+ASP	
				0.01-0.99%	HR	EI+	5.0 g/m ²	Blincyto or reintensification [#]	
				≥1%	VHR				
	t(9;22) [‡]	<1%	B	D42-46	<0.01%	HR	No	5.0 g/m ²	Blincyto* or DEX+EPI+VCR+6MP+ASP
					0.01-0.99%	HR	EI	5.0 g/m ²	Blincyto or reintensification [#]
					≥1%	VHR			
		≥1%	B	D42-46	<0.01%	HR	EI	5.0 g/m ²	Blincyto* or DEX+EPI+VCR+6MP+ASP
					0.01-0.99%	HR	EI	5.0 g/m ²	Blincyto or reintensification [#]
					≥1%	VHR			
VHR	Any	C	D42-46	Any	VHR	EI+	5.0 g/m ²	Blincyto or reintensification [#]	

Blincyto, blinatumomab; EOI, end of induction; Ind, induction; Inten, intensification; Pro-risk, provisional risk.

*For patients with MRD2 <0.01%, Blincyto could be sponsored by CCF。

[#]Reintensification will be given: 1). after consolidation for MRD2 ≥1% (VHR) and 2). after reinduction I for HR patients with MRD ≥0.01% on continuation week 7.

[‡]Dasatinib 80 mg/m²/day will start after Dx and continue to the end of therapy.

Blincyto 使用期間 dasatinib 需繼續使用，Blincyto 最後 1 天予 TIT。不併用 C/T 及 ruxolitinib。

MRD3 at continuation week 7 for patients with MRD2 ≥0.01%; optional MRD4 for patients who completion of Blincyto or reintensification; further MRD for persistent MRD ≥0.01%.

[Blincyto 後將導致 CD19 消失，後續若仍進行 flow MRD F/U 時，務必告知檢查單位使用 Blincyto 的病史，以另行尋找 markers 或其他 MRD 檢測方法。]

兒癌-ALL

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Treatment Plans

T-ALL

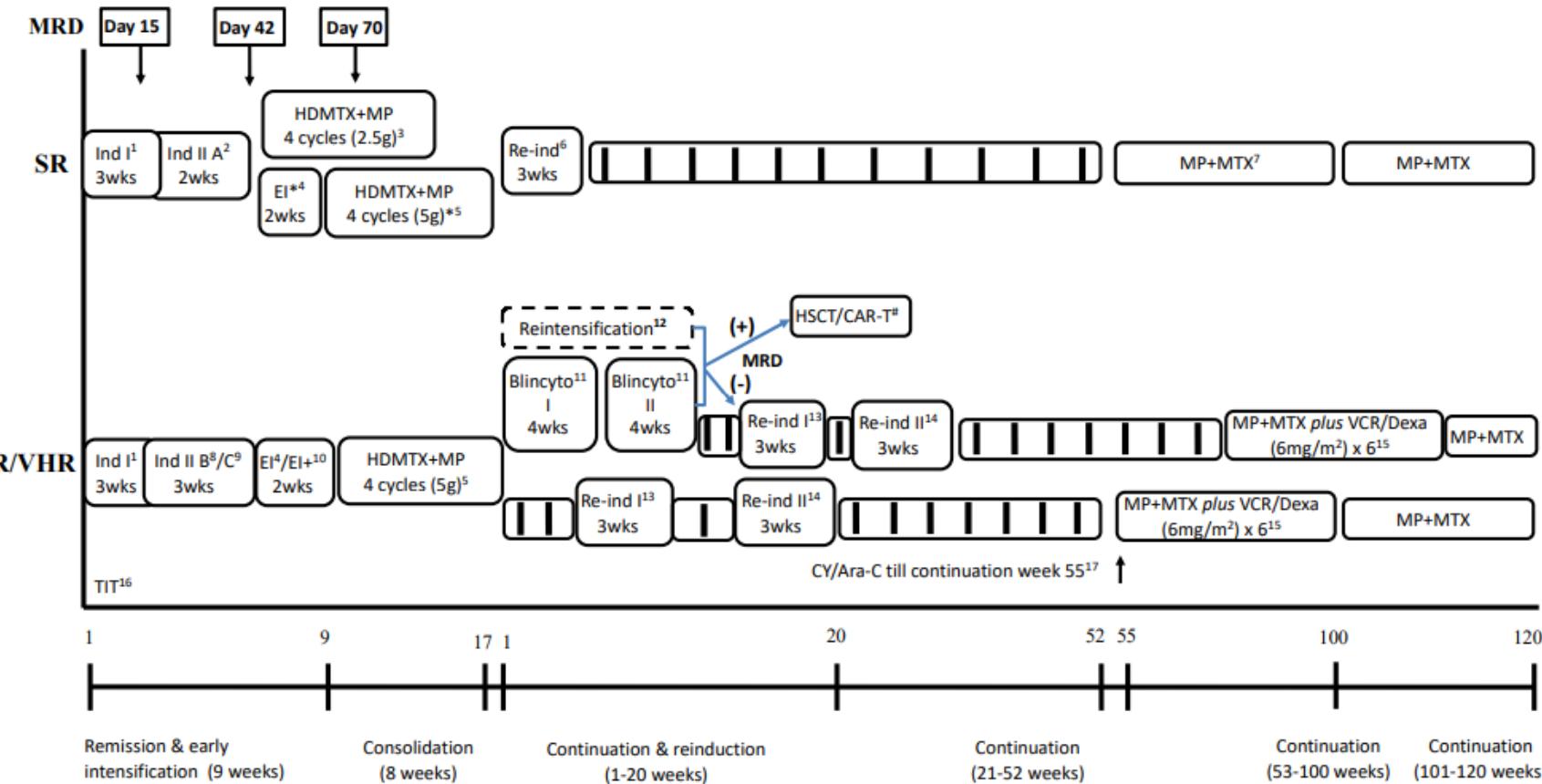
Pro-Risk	MRD1	Ind II	EOI BM Date	MRD2	Risk	Early Inten	MRD3 (D65-70)	Final Risk	Tx options
Non-ETP	Any	C	D42-46	<0.01%	HR	EI+	No	HR	Dasatinib plus C/T or Nelarabine-based or HD-Ara-C-based
				≥0.01%	HR	EI+	<0.01%	HR	
							0.01-0.99%	HR	
							≥0.1%	VHR	
ETP	Any	C	D42-46	<0.01%	HR	EI+	<0.01%	HR	V-EI
							0.01-0.99%	HR	
							≥0.1%	VHR	
				≥0.01%	HR	V-EI	<0.01%	HR	V-EI
							0.01-0.99%	HR	
							≥0.1%	VHR	

EOI, end of induction; ETP, early T precursor; Ind, induction; Inten, intensification; Pro-risk, provisional risk。

MRD3 after EI/EI+ for patients with MRD2 ≥0.01% and all ETP; further MRD for persistent MRD ≥0.01%。

Treatment Plans

Schema of TPOG-ALL-2021, B-ALL



Treatment Plans

5. SR revisions

- A. Final SR with MRD1 0.1-1% & MRD2 <0.01%
 - (1). Addition of 1 cycle of EI (CY/Ara-C/Asp)
 - (2). 5 g/m² MTX, not 2.5 g/m² in consolidation
- B. Final SR
 - (1). Move reinduction treatment immediate to the end of consolidation to reduce the risk of allergic reaction to asparaginase
 - (2). Omission of pulse-therapy of VCR/Dexa after 1-year of continuation therapy

6. HR revisions

A. MRD1 <5%

- (1). Addition of 1 cycle of Induction II-B (CY/Ara-C/6MP/Asp)
- (2). Addition of 1 cycle of EI (CY/Ara-C/Asp)

B. MRD1 ≥5%

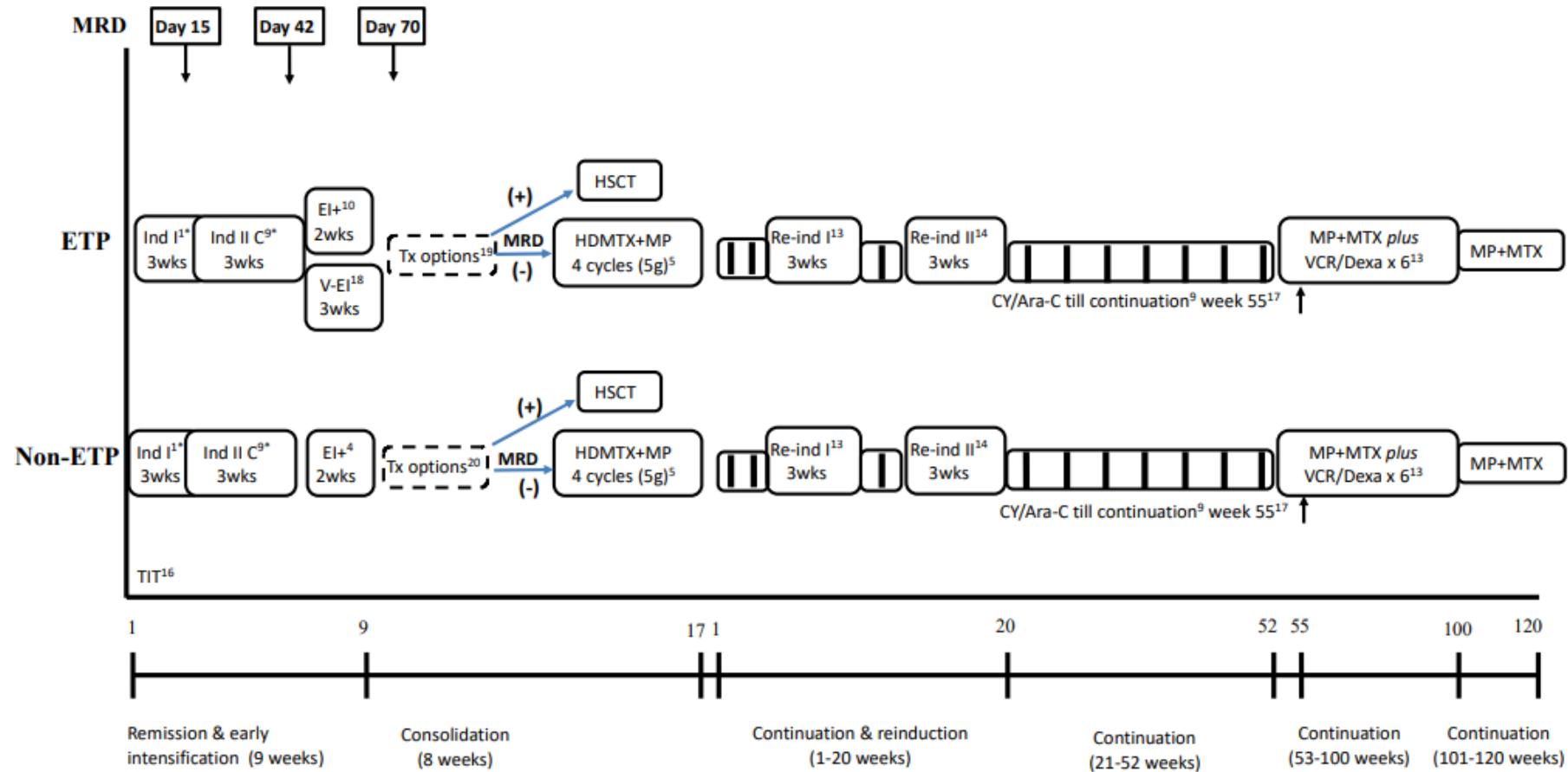
- (1). Addition of 1 cycle of Induction II-C (CY/Ara-C/6MP/Asp plus Bortezomib)
- (2). Addition of 1 cycle of EI+ (CY/Ara-C/Asp plus Bortezomib)

C. Final HR

- (1). Omission of the courses of CY/Ara-C after week 55 in HR/VHR (as St. Jude Total 17)
- (2). The frequency of VCR/Dexa pulse therapy will be decreased from every 4 weeks to every 8 weeks after 1-year of continuation therapy in HR/VHR; and Dexa will be decreased to 6 mg/m²/day at the 2nd year of continuation.

Treatment Plans

Schema of TPOG-ALL-2021, T-ALL



7. Ph+ALL revisions

- A. Ph+ALL is not designated as provisional VHR
- B. Dasatinib will be given ASAP after Dx of Ph+ALL and continue to the end of therapy
- C. In consolidation, dasatinib should be held 24 hours before start of infusion and until clearance of MTX
- D. MRD1 <1%
 - (1). Addition of 1 cycle of Induction II-B (CY/Ara-C/6MP/Asp)
- E. MRD1 ≥1%
 - (1). Addition of 1 cycle of Induction II-B (CY/Ara-C/6MP/Asp)
 - (2). Addition of 1 cycle of EI (CY/Ara-C/Asp)

8. T-ALL revisions

- A. Any MRD1
 - (1). Addition of 1 cycle of Induction II-C (CY/Ara-C/6MP/Asp plus Bortezomib)
- B. MRD2
 - (1). ETP with MRD2 $\geq 0.01\%$: Addition of 1 cycle of V-EI (Venetoclax/VCR/Dexa/Asp)
 - (2). All other T-ALL: Addition of 1 cycle of EI+ (CY/Ara-C/Asp plus Bortezomib)
- C. HSCT should be considered for all T-ALL with MRD3 (after EI/EI+) $\geq 0.1\%$

8. T-ALL revisions

- A. Any MRD1
 - (1). Addition of 1 cycle of Induction II-C (CY/Ara-C/6MP/Asp plus Bortezomib)
- B. MRD2
 - (1). ETP with MRD2 $\geq 0.01\%$: Addition of 1 cycle of V-EI (Venetoclax/VCR/Dexa/Asp)
 - (2). All other T-ALL: Addition of 1 cycle of EI+ (CY/Ara-C/Asp plus Bortezomib)
- C. HSCT should be considered for all T-ALL with MRD3 (after EI/EI+) $\geq 0.1\%$

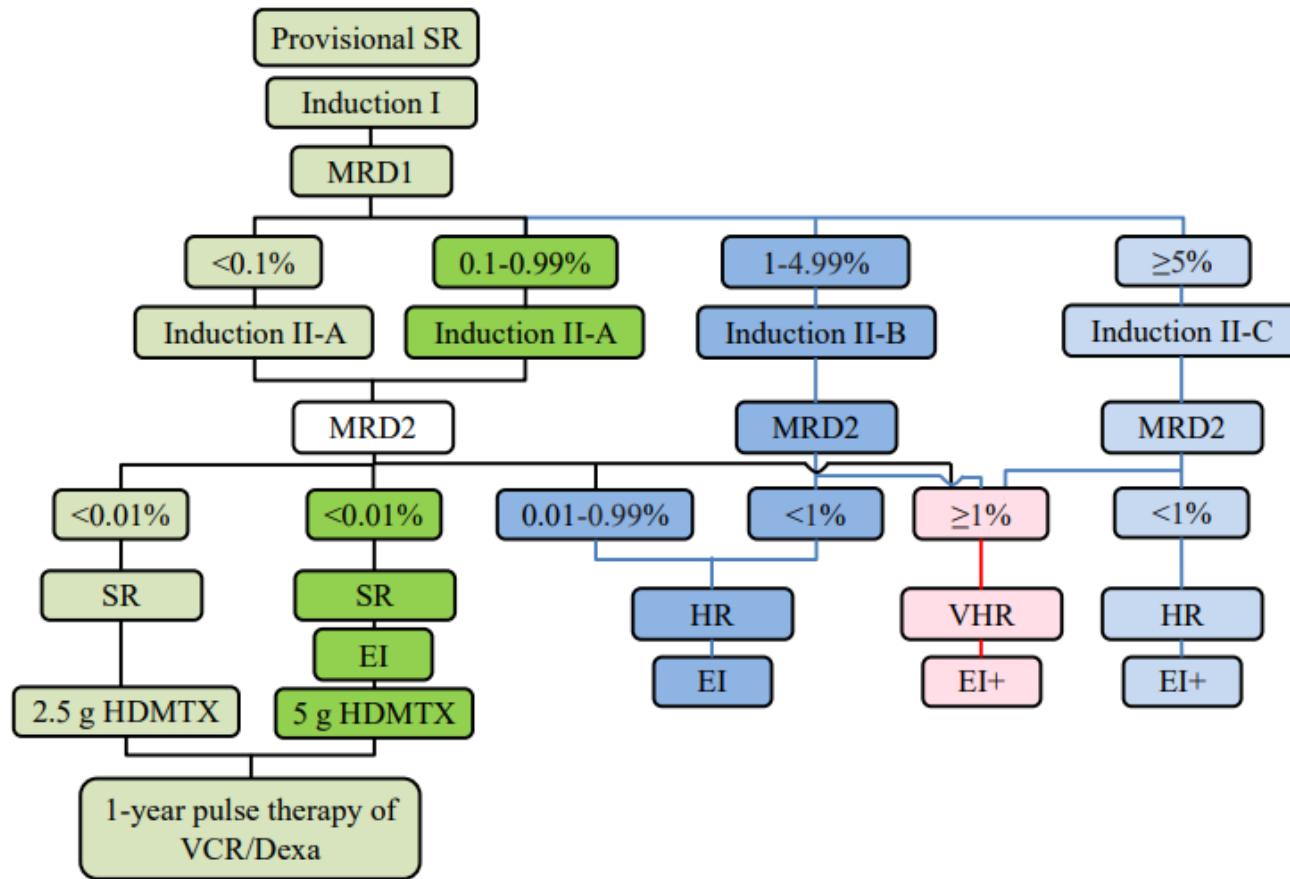
9. Ph-like ALL (Mar. 2021 修改) :

- A. 加入 ruxolitinib 治療建議：*CRLF2-R* 及 *JAK2-R* 或 *EPOR-R* 者，且於 $MRD1 \geq 5\%$ or $MRD2 \geq 1\%$ 者，可申請 compassionate use。The dose is $50 \text{ mg/m}^2/\text{dose}$ PO BID (max 200 mg/day), 2 weeks on and 2 weeks off, starting on the day of Early Intensification。
- B. 加入 dasatinib 治療建議：patients with ABL class chimeric fusions (e.g., *ABL1*, *ABL2*, *CSF1R*, *PDGFRA* or *PDGFRB*) are known to be responsive to dasatinib. The dose is $80 \text{ mg/m}^2/\text{day}$, starting on the day when the aberration is identified regardless of MRD level. 實務上，可依 MRD 結果申請健保事前審查。

Treatment Plans

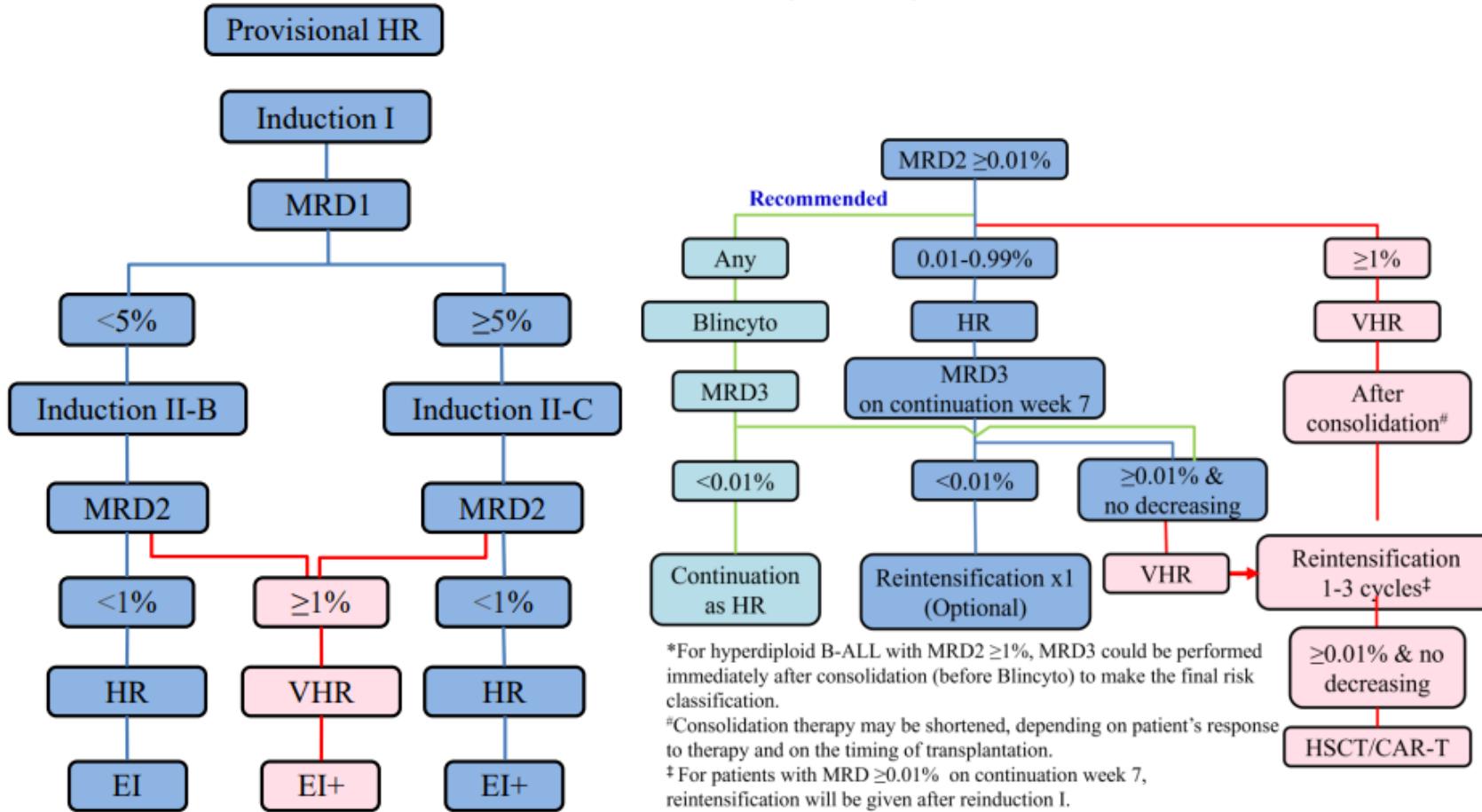
◎ Schema of TPOG-ALL-2021 精簡版

TPOG-ALL-2021, B-ALL, SR

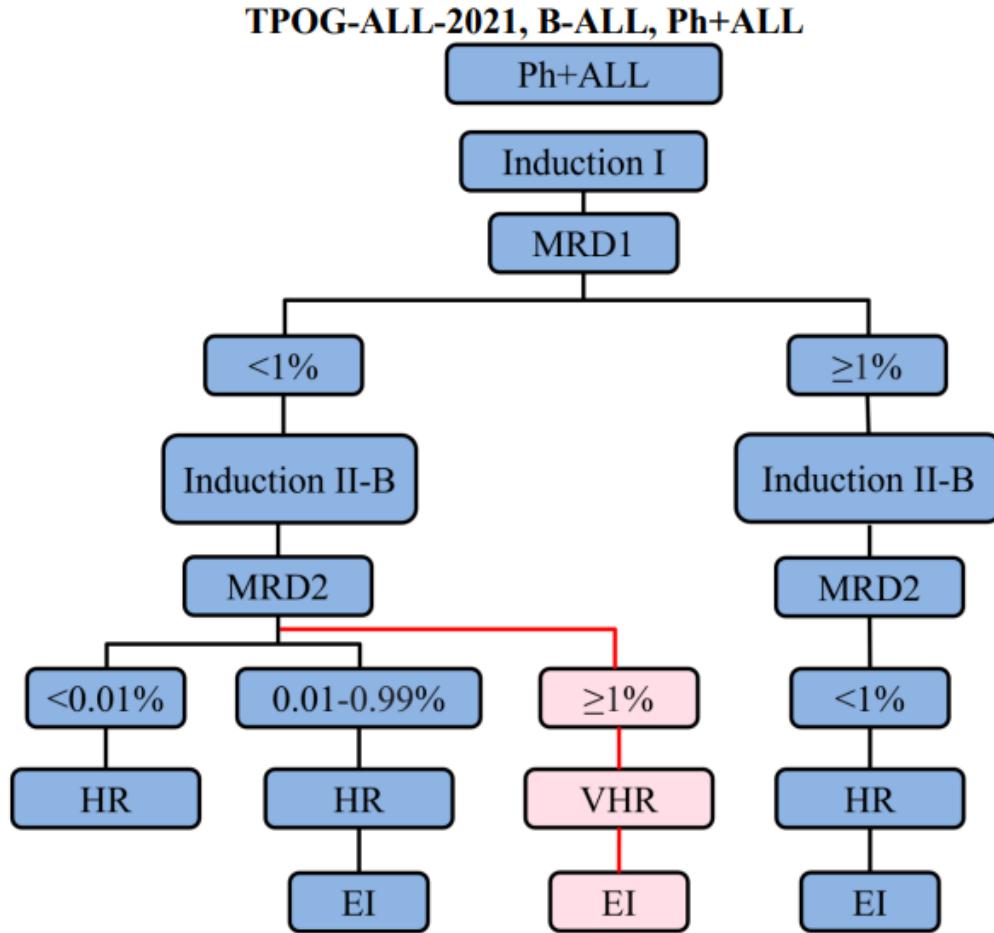


◎Schema of TPOG-ALL-2021精簡版

TPOG-ALL-2021, B-ALL, HR



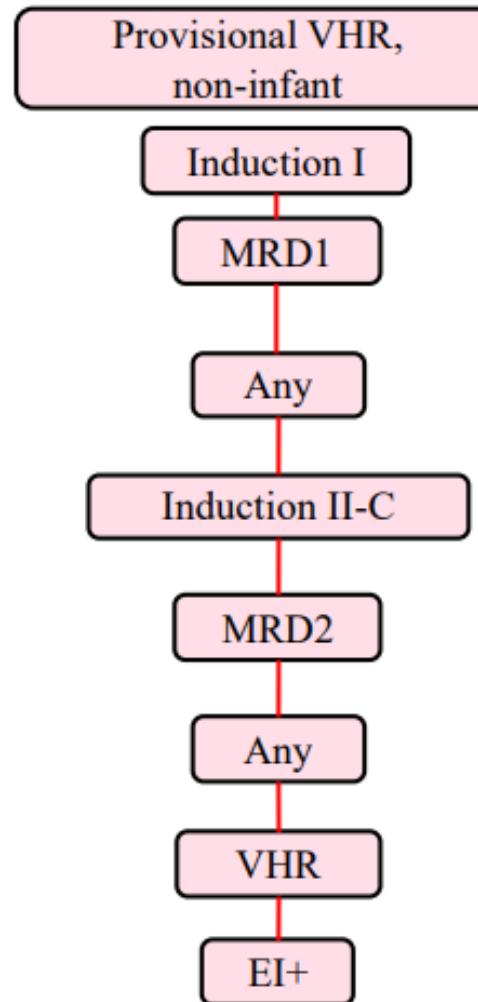
◎Schema of TPOG-ALL-2021精簡版



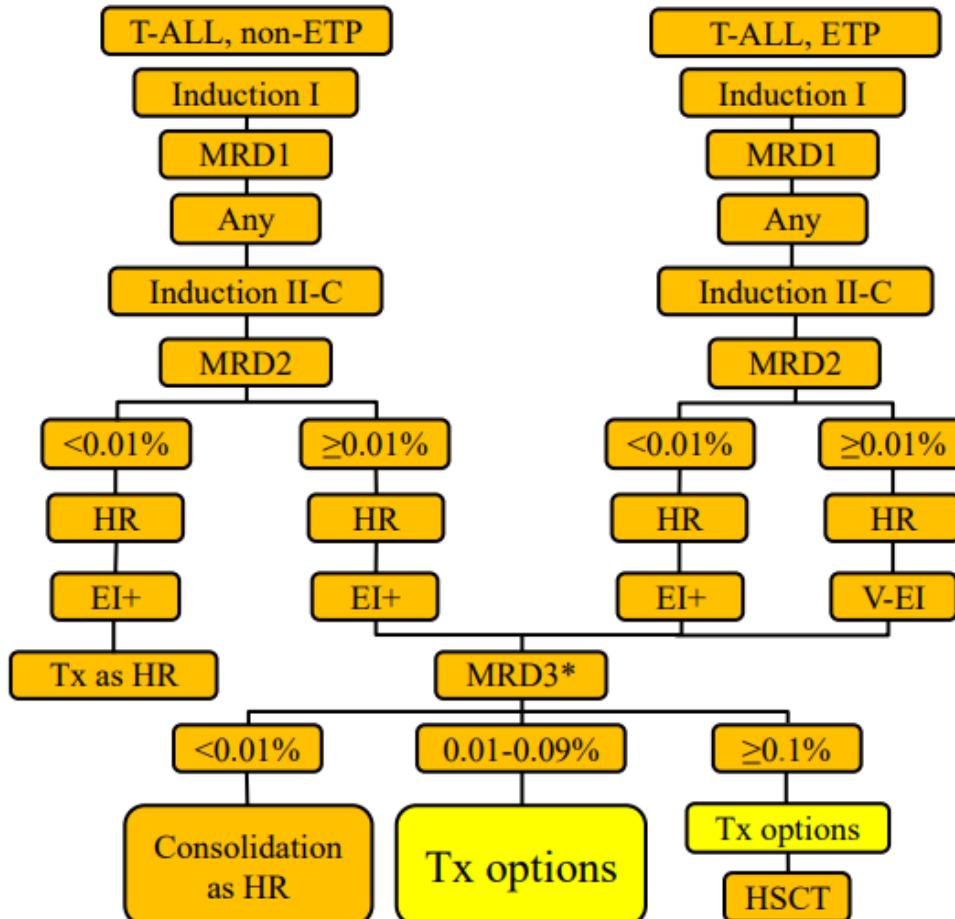
Dasatinib 80 mg/m²/day will start after Dx and continue to the end of therapy.

◎Schema of TPOG-ALL-2021精簡版

TPOG-ALL-2022, B-ALL, VHR



TPOG-ALL-2021, T-ALL



Tx options

ETP: V-EI

Non-ETP:

1. Dasatinib if drug sensitivity could be confirmed.
2. Nelarabine-based therapy
3. High-dose Ara-C-based

MRD3* for all ETP & non-ETP with MRD2 ≥0.01%

兒癌-ALL

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Treatment Plans

◎Induction I (1-3 weeks)

Induction I (first 3 weeks) for B-ALL

	Day1	Day2	Day3	Day4	Day5	Day6	Day7
Wk 1	PRED	PRED	PRED L-ASP (1)	PRED	PRED L-ASP (2)	PRED	PRED L-ASP (3)
	Day8	Day9	Day10	Day11	Day12	Day13	Day14
	PRED	PRED	PRED L-ASP (4)	PRED	PRED L-ASP (5)	PRED	PRED L-ASP (6)
	Day15	Day16	Day17	Day18	Day19	Day20	Day21
Wk 3	PRED	PRED	PRED L-ASP (7)	PRED	PRED L-ASP (8)	PRED	PRED L-ASP (9)
	PRED	PRED	PRED L-ASP (7)	PRED	PRED L-ASP (8)	PRED	PRED L-ASP (9)
	BMA, MRD1						

*Delayed TIT until the disappearance of blast from PB, but no later than D10.

#The second dose of epirubicin on day 8 may be delayed in SR patients who has cleared circulating blasts and has severe neutropenia, or in any risk group patient who is sick with infection. The second dose of epirubicin could be omitted in SR with MRD1 <0.1%; but it is suggested to be given on weeks 3/4 in SR with MRD1 ≥0.1%.

Agent	Dosage and Route	# Doses	Schedule
Prednisone (PRED)	40/60 mg/m ² /day, PO (tid)	84	Days 1-28
Vincristine (VCR)	1.5 mg/m ² (max 2), IV	3	Days 1, 8, 15
Epirubicin (EPI)	20 mg/m ² , IV	2	Days 1, 8 [#]
L-asparaginase (ASP)	6,000 U/m ² , IM	9	Days 3, 5, 7, 10, 12, 14, 17, 19, 21
Dasatinib [‡]	80 mg/m ² /day	Daily	Starting after Dx
Triple intrathecal therapy (TIT)			Days 1*, 15

PRED: 40 mg/m²/day for SR and 60 mg/m²/day for HR.

[‡]For Ph+ALL.

Treatment Plans

Induction II-A

BCP-ALL

-SR, MRD1 <1%

Induction II-A for B-ALL

	Day22	Day23	Day24	Day25	Day26	Day27	Day28
Wk 4	PRED VCR	PRED	PRED	PRED	PRED	PRED	PRED
Wk 5	Day29 PRED Taper	Day30 PRED Taper	Day31 PRED Taper	Day32 PRED Taper	Day33 PRED Taper	Day34 PRED Taper	Day35 PRED Taper

Agent	Dosage and Route	# Doses	Schedule
Prednisone (PRED)*	40/60 mg/m ² /day, PO (tid)	84	Days 1-28
Vincristine (VCR)	1.5 mg/m ² (max 2), IV	1	Day 22

*40 mg/m²/day for SR and 60 mg/m²/day for HR.

兒癌-ALL

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Treatment Plans

Induction II-B

BCP-ALL

- t(12;21)/HD ≥1%

-Other SR, MRD1 1-5%

-HR, MRD1 <5%

-*Dasatinib for Ph+ALL

Induction II-B for B-ALL

	Day22	Day23	Day24	Day25	Day26	Day27	Day28
Wk 4	PRED	PRED	PRED	PRED	PRED	PRED	PRED
	VCR	L-ASP (10)		L-ASP (11)			L-ASP (12)
Wk 5	Day29	Day30	Day31	Day32	Day33	Day34	Day35
	PRED	PRED	PRED	PRED	PRED	PRED	PRED
	Taper	Taper	Taper	Taper	Taper	Taper	Taper
	CY	Ara-C	Ara-C	Ara-C	Ara-C		
	MP	MP	MP	MP	MP	MP	MP
Wk 6	Day36	Day37	Day38	Day39	Day40	Day41	Day42
	Ara-C	Ara-C	Ara-C	Ara-C	Ara-C		
	MP	MP	MP	MP	MP	MP	MP

Agent	Dosage and Route	# Doses	Schedule
Prednisone (PRED)*	40/60 mg/m ² /day, PO (tid)	84	Days 1-28
Vincristine (VCR)	1.5 mg/m ² (max 2), IV	1	Day 22
L-asparaginase (ASP)	6,000 U/m ² IM	3	Days 24, 26, 28
Cyclophosphamide (CY)	1,000 mg/m ² IV 1 hr	1	Day 29‡
Cytarabine (Ara-C)	75 mg/m ² /dose IV 30 mins, QD	8	Days 30-33, 37-40
6-mercaptopurine (MP)	30 mg/m ² /dose	14	Days 29-42
Dasatinib#	80 mg/m ² /day	Daily	Starting after Dx

*40 mg/m²/day for SR and 60 mg/m²/day for HR.

#For Ph+ALL.

‡Suggested criteria to start D29 C/T:

- WBC ≥1000/mm³ with ANC ≥300/mm³. G-CSF is suggested if the treatment is delayed.
- Following Day 29 treatment, cytarabine and mercaptopurine may be delayed or omitted (after Day 35) if patient develops febrile neutropenia or Grade 3 or 4 mucositis.
- Doses may be completely omitted if the patient is beyond Day 35 of remission induction (i.e., 50% or more doses of mercaptopurine and cytarabine have been given), to allow early bone marrow recovery, on-time (Days 42-46) bone marrow examination, MRD detection and early initiation of continuation therapy or early intensification therapy.

Treatment Plans

Induction II-C (=Induction B plus Bort) for B-ALL

	Day22	Day23	Day24	Day25	Day26	Day27	Day28
Wk 4	PRED VCR	PRED	PRED L-ASP (10)	PRED	PRED L-ASP (11)	PRED	PRED L-ASP (12)
Wk 5	Day29	Day30	Day31	Day32	Day33	Day34	Day35
	PRED Taper CY	PRED Taper	PRED Taper	PRED Taper	PRED Taper	PRED Taper	PRED Taper
	MP	Ara-C MP Bort (1)	Ara-C MP	Ara-C MP	Ara-C MP Bort (2)	MP	MP
	Day36	Day37	Day38	Day39	Day40	Day41	Day42
Wk 6							

Agent	Dosage and Route	# Doses	Schedule
Prednisone (PRED)*	40/60 mg/m ² /day, PO (tid)	84	Days 1-28
Vincristine (VCR)	1.5 mg/m ² (max 2), IV	1	Day 22
L-asparaginase (ASP)	6,000 U/m ² IM	3	Days 24, 26, 28
Cyclophosphamide (CY)	1,000 mg/m ² IV 1 hr	1	Day 29 [#]
Cytarabine (Ara-C)	75 mg/m ² /dose IV 30 mins, QD	8	Days 30-33
6-mercaptopurine (MP)	30 mg/m ² /dose	7	Days 29-35
Bortezomib (Bort)	1.3 mg/m ² IV	2	Days 30, 33

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*40 mg/m²/day for SR and 60 mg/m²/day for HR.

[#]Suggested criteria to start D29 C/T:

- WBC \geq 1000/mm³ with ANC \geq 300/mm³. G-CSF is suggested if the treatment is delayed.

Treatment Plans

Induction I (first 3 weeks) for T-ALL

	Day1	Day2	Day3	Day4	Day5	Day6	Day7
Wk 1	DEXA	DEXA	DEXA	DEXA	DEXA	DEXA	DEXA
	VCR		L-ASP (1)		L-ASP (2)		L-ASP (3)
	EPI						
	TIT*						
Wk 2	Day8	Day9	Day10	Day11	Day12	Day13	Day14
	DEXA	DEXA	DEXA	DEXA	DEXA	DEXA	DEXA
	VCR		L-ASP (4)		L-ASP (5)		L-ASP (6)
Wk 3	Day15	Day16	Day17	Day18	Day19	Day20	Day21
	DEXA	DEXA	DEXA	DEXA	DEXA	DEXA	DEXA
	VCR		L-ASP (7)		L-ASP (8)		L-ASP (9)
	TIT						
	BMA,						
	MRD1						

Agent	Dosage and Route	# Doses	Schedule
Dexamethasone Dexa) [#]	10/8 mg/m ² /day, PO (tid)	63	Days 1-21
Vincristine (VCR)	1.5 mg/m ² (max 2), IV	3	Days 1, 8, 15
Epirubicin (EPI)	20 mg/m ² , IV	2	Days 1, 8
L-asparaginase (ASP)	6,000 U/m ² , IM	9	Days 3, 5, 7, 10, 12, 14, 17, 19, 21
TIT			Days 1*, 15

*Delayed TIT until the disappearance of blast from PB, but no later than D10.

[#]Dexa: 10 mg/m²/day for age<10; 8 mg/m²/day for age ≥10

兒癌-ALL

高雄榮民總醫院 臨床診療指引 2025年第一版

Treatment Plans

Induction II-C for T-ALL

	Day22	Day23	Day24	Day25	Day26	Day27	Day28
Wk 4	DEXA Taper VCR TIT	DEXA Taper L-ASP (10)	DEXA Taper L-ASP (11)	DEXA Taper L-ASP (12)			
Wk 5	Day29 CY MP TIT	Day30 Ara-C MP Bort (1)	Day31 Ara-C MP	Day32 Ara-C MP Bort (2)	Day33 Ara-C MP	Day34 MP	Day35 MP
Wk 6	Day36	Day37	Day38	Day39	Day40	Day41	Day42

Agent	Dosage and Route	# Doses	Schedule
Dexamethasone (Dexa)*	10/8 mg/m ² /day, PO (tid)	63	Days 1-21
Vincristine (VCR)	1.5 mg/ m ² (max 2), IV	1	Day 22
L-asparaginase (ASP)	6,000 U/m ² IM	3	Days 24, 26, 28
Cyclophosphamide (CY)	1,000 mg/m ² IV 1 hr	1	Day 29 [#]
Cytarabine (Ara-C)	75 mg/m ² /dose IV 30 mins, QD	4	Days 30-33
6-mercaptopurine (MP)	30 mg/m ² /dose	7	Days 29-35
Bortezomib (Bort)	1.3 mg/m ² IV	2	Days 30, 33
TIT	Age-dependent	2	Days 22, 29

*Dexa: 10 mg/m²/day for age<10; 8 mg/m²/day for age ≥10

[#]Suggested criteria to start D29 C/T:

- WBC ≥1000/mm³ with ANC ≥300/mm³. G-CSF is suggested if the treatment is delayed.

Treatment Plans

◎選擇induction II的A,B或C及Blincyto的使用建議請參閱下表

BCP-ALL

Pro-Risk	Subgroup	MRD1	Up-grade	Ind II	EOI BM Date	MRD2	Final Risk	Early Inten	Consolidation (HD-MTX x 4)	Continuation Week 1
SR	t(12;21)/HD	<1%		A	D35-42	<0.01%	SR	No	2.5 g/m ²	
	t(12;21)/HD	<1%		A	D35-42	≥0.01%	HR	No	5.0 g/m ² *	2 cycles of Blincyto
	t(12;21)/HD	≥1%	HR	B	D35-46	<0.01%	HR	No	5.0 g/m ²	
	t(12;21)/HD	≥1%	HR	B	D35-46	≥0.01%	HR	No	5.0 g/m ²	2 cycles of Blincyto
	Others	<1%		A	D35-42	<0.01%	SR	No	2.5 g/m ²	
	Others	<1%		A	D35-42	0.01-0.99%	HR	No	5.0 g/m ²	2 cycles of Blincyto
	Others	<1%		A	D35-42	≥1%	VHR	Yes	5.0 g/m ² *	2 cycles of Blincyto
	Others	1-5%	HR	B	D35-46	<0.01%	HR	No	5.0 g/m ²	
	Others	1-5%	HR	B	D35-46	0.01-0.99%	HR	No	5.0 g/m ²	2 cycles of Blincyto
	Others	1-5%	HR	B	D35-46	≥1%	VHR	Yes	5.0 g/m ²	2 cycles of Blincyto
	Others	≥5%	HR	C	D35-46	<0.01%	HR	Yes	5.0 g/m ²	
	Others	≥5%	HR	C	D35-46	0.01-0.99%	HR	Yes	5.0 g/m ²	2 cycles of Blincyto
	Others	≥5%	HR	C	D35-46	≥1%	VHR	Yes	5.0 g/m ²	2 cycles of Blincyto
HR		<1%		B	D35-46	<0.01%	HR	No	5.0 g/m ²	
		<1%		B	D35-46	0.01-0.99%	HR	No	5.0 g/m ²	2 cycles of Blincyto
		<1%		B	D35-46	≥1%	VHR	Yes	5.0 g/m ²	2 cycles of Blincyto
		1-5%		B	D35-46	<0.01%	HR	No	5.0 g/m ²	
		1-5%		B	D35-46	0.01-0.99%	HR	No	5.0 g/m ²	2 cycles of Blincyto
		1-5%		B	D35-46	≥1%	VHR	Yes	5.0 g/m ²	2 cycles of Blincyto
		≥5%		C	D35-46	<0.01%	HR	Yes	5.0 g/m ²	
		≥5%		C	D35-46	0.01-0.99%	HR	Yes	5.0 g/m ²	2 cycles of Blincyto
		≥5%		C	D35-46	≥1%	VHR	Yes	5.0 g/m ²	2 cycles of Blincyto
				B+Dasa	D35-46	<0.01%	VHR	No	5.0 g/m ²	2 cycles of Blincyto*
VHR	t(9;22)	<1%		B+Dasa	D35-46	≥0.01%	VHR	No	5.0 g/m ²	2 cycles of Blincyto
		<1%		B+Dasa	D35-46	<0.01%	VHR	Yes	5.0 g/m ²	2 cycles of Blincyto*
		≥1%		B+Dasa	D35-46	≥0.01%	VHR	Yes	5.0 g/m ²	2 cycles of Blincyto*
		≥1%		B+Dasa	D35-46	≥0.01%	VHR	Yes	5.0 g/m ²	2 cycles of Blincyto
	Infant with KMT2A-R	Any		C	D35-46	Any	VHR	Yes	5.0 g/m ²	2 cycles of Blincyto*

Early Intensification plus (EI+)

	Day50	Day51	Day52	Day53	Day54	Day55	Day56
Wk 8	CY TIT	Ara-C Bort (1)	Ara-C L-ASP (1)	Ara-C	Ara-C L-ASP (2) Bort (2)		L-ASP (3)
Wk 9	Day57	Day58	Day59	Day60	Day61	Day62	Day63
		Ara-C	Ara-C	Ara-C			

Agent	Dosage and Route	# Doses	Schedule
Cyclophosphamide (CY)	1,000 mg/m ² IV 1 hr	1	Day 50
Cytarabine (Ara-C)	75 mg/m ² /dose IV 30 mins, QD	8	Days 51-54, 58-61
L-asparaginase (ASP)	6,000 U/m ² IM	3	Days 52, 54, 56
TIT		1	Day 50
Bortezomib (Bort)	1.3 mg/m ² IV	2	Days 51, 54

Suggested criteria to start EI+:

Day 50 chemotherapy can be given earlier if the patient has early count recovery (WBC \geq 1,500/mm³ with ANC \geq 300/mm³ or APC \geq 500/mm³, and platelet count \geq 75 x 10⁹/L). G-CSF is suggested if the treatment is delayed.

Venetoclax-Early Intensification (V-EI)

Agent	Dosage and Route	# Doses	Schedule
Vincristine	1.5 mg/m ² /day (max 2), IV	2	Days 1, 15
Dexamethasone	8 mg/m ² /day		Days 1-8, 15-21
Venetoclax	240 mg/m ²	21	Days 1-21
L-asparaginase	6,000 U/m ² IM	6	Days 8, 10, 12, 15, 17, 19

2025新增

使用時機修正 (裴正康院士指導)²⁻⁶

1. Blincyto 的使用時間點：由 continuation week 1, 提早到 consolidation 中 high-dose MTX 兩個療程後開始。
2. Ph-negative B-ALL 連續使用 Blincyto 兩個療程後可能因 T-cell exhaustion 而導致療效不佳的疑慮。於 high-dose MTX 兩個療程後使用第一個 Blincyto 療程，然後再接續 high-dose MTX 兩個療程，接著使用第二個 Blincyto 療程。
3. 特殊分型：non-infant *KMT2A-R* 及 *ZNF384-R* 使用 Blincyto 後為避免 lineage switch, 於兩個療程後改予 venetoclax-containing reinduction regimen.
4. Ph-positive B-ALL 因併用 dasatinib，連續使用 Blincyto 兩個療程後不會因 T-cell exhaustion 而有療效不佳的疑慮。因此於 high-dose MTX 兩個療程後可連續使用兩個 Blincyto 療程，中間休息 2 周予 high-dose MTX 一個療程，Blincyto 療程完成後接續一個 high-dose MTX 療程。
5. Blincyto 療程須特別注意 CNS-directed therapy, 請留意 TIT 療程之修改 (Summary 見 p7)。

2025新增

Blinatumomab (Blincyto)

Indications (修)

1. Ph-positive ALL, regardless of MRD2 data
2. Ph-negative B-ALL with MRD2 (+), if Blincyto is approved by the National Health Insurance (NHI).
3. Ph-negative B-ALL with persistent MRD (+) after continuation week 7 could try the NHI-approval of Blincyto, if Blincyto is not yet used before.
4. **Suggested indications:** patients with unfavorable genetics features, e.g., hypodiploid, *BCR-ABL1*-like, *ETV6-RUNX1*-like, iAMP21, *KMT2A-R*, *MEF2D-R*, *TCF3-HLF*, *ZNF384-R* and Down syndrome, even though their MRD2 are negative. (Ref¹ & St. Jude Total 17)

Treatment Plans

◎Induction (5-7weeks)

T-ALL

Pro-Risk	Subgroup	MRD1	Up-grade	Ind II	EOI BM Date	MRD2	Final Risk	Early Inten	Consolidation (HD-MTX x 4)
Non-ETP		<1%		C	D35-46	<0.01%	HR	No	5.0 g/m ² *
		<1%		C	D35-46	0.01-0.99%	HR	No	5.0 g/m ²
		<1%		C	D35-46	≥1%	VHR	No	5.0 g/m ²
		≥1%		C	D35-46	<0.01%	HR	Yes	5.0 g/m ²
		≥1%		C	D35-46	0.01-0.99%	HR	Yes	5.0 g/m ²
		≥1%		C	D35-46	≥1%	VHR	Yes	5.0 g/m ²
ETP	Any			C	D35-46	Any	VHR	Yes	5.0 g/m ²

Blincyto, blinatumomab; MRD2(+)之 BCP-ALL，且通過健保事前審查者，建議於 continuation 第 1 周即開始使 Blincyto.

Dasa, dasatinib; EOI, end of induction; HD, hyperdiploidy; KMT2A-R, KMT2A-rearrangement; Ind, induction; Inten, intensification, Pro-risk; provisional risk

*If MRD (+), the provisional standard-risk case will then be classified as high-risk or very high-risk accordingly, and will receive subsequent 3 doses of HDMTX at a higher dosage (i.e., 5 gm/m²). (These cases would have received the first HDMTX of consolidation therapy at 2.5 gm/m²)

For patients with MRD2 (-), the Blincyto could be sponsored by TPOG.

Treatment Plans

◎Induction (5-7weeks)

For infant with MLL+

Agent	Dosage and Route	Doses	Schedule
Clofarabine	25 mg/m ² /day, 2-hour IV infusion	5	Days 22-26
Etoposide	100 mg/m ² /day, 2-hour IV infusion	5	Days 22-26
Cyclophosphamide	300 mg/m ² /day, 1-hour IV infusion	5	Days 22-26

Day 22 Vincristine will be omitted for infants with MLL+

Treatment Plans

Summary of Intrathecal Therapy on TPOG-ALL-2021 (紅字為與 TPOG-ALL-2013 不同之處)

		Induction/Early intensification		Consolidation		Continuation Week 1-20		Continuation Weeks 21-120		All Phases
Risk-group	CNS Status	Days	Total	Days	Total	Weeks	Total	Weeks	Total	Total
SR	CNS-1	#, 15	2	1, 15, 29, 43	4	1, 6, 11, 16	4	24, 32, 40, 48	4	14
SR with MRD1, 0.1-0.99%	CNS-1	#, 15, 43	3	1, 15, 29, 43	4	1, 6, 11, 16	4	24, 32, 40, 48	4	15
SR with $\geq 100 \times 10^9/L$	CNS-1	#, 8, 15, 22	4	1, 15, 29, 43	4	1, 6, 11, 16	4	24, 28, 32, 36, 40, 44, 48	7	19
SR	CNS-2 or TLP with blasts	#, 8, 15, 22	4	1, 15, 29, 43	4	1, 6, 11, 16	4	24, 28, 32, 36, 40, 44, 48	7	19
HR/VHR	CNS-1	#, 15, 29, 50	4	1, 15, 29, 43	4	7, 12, 17	3	24, 28, 32, 36, 40, 44, 48	7	18
HR/VHR	CNS-2, CNS-3 or TLP with blasts	#, 8, 11, 15, 22, 29, 50	7*	1, 15, 29, 43	4	3, 7, 12, 17	4	24, 28, 32, 36, 40, 44, 48, 56, 64, 72, 80, 88, 96	11	26
Other HR/VHR with $\geq 100 \times 10^9/L$, T-ALL, t(1;19), Ph+, hypodiploidy <44	CNS-1	#, 8, 15, 22, 29, 50	6	1, 15, 29, 43	4	3, 7, 12, 17	4	24, 28, 32, 36, 40, 44, 48, 56, 64, 72, 80, 88, 96	11	25

*The first TIT will be performed after the disappearance of blasts from peripheral blood by 10 days of induction therapy. But, exception remained for patients presenting with cranial nerve palsy or other evidence of CNS disease, lumbar puncture and first TIT will be initiated on the day of Dx.

* TIT twice a week for 2 weeks followed by weekly TIT for 2 weeks (totally 6 TITs during induction therapy):

Abbreviations: SR, standard-risk; HR, high-risk; VHR, very high-risk; TLP, traumatic lumbar puncture

Treatment Plans

◎IT Chemotherapy During Induction Treatment

Leucovorin rescue (5 mg/m²/dose, max 5 mg) PO will be given at 24 and 30 hours after each triple intrathecal treatment during induction.

Follow plasma methotrexate levels (starting 24 hours after intrathecal therapy and until level becomes undetectable) in patients with renal dysfunction or extra fluid in third space, and rescue with leucovorin.

It is also important to correct hypertension and to prevent constipation during remission induction because patients with these features are at high risk of seizure (posterior reversible encephalopathy syndrome). Avoid syndrome of inappropriate antidiuretic hormone secretion from vincristine treatment.

Treatment Plans

Consolidation (TPOG ALL-2021 SR, HR, VHR)

	Day1	Day2	Day3	Day4	Day5	Day6	Day7
Wk 1	MTX 6-MP TIT	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP
Wk 2	Day8 6-MP	Day9 6-MP	Day10 6-MP	Day11 6-MP	Day12 6-MP	Day13 6-MP	Day14 6-MP
Wk 3	Day15 MTX 6-MP TIT	Day16 6-MP	Day17 6-MP	Day18 6-MP	Day19 6-MP	Day20 6-MP	Day21 6-MP
Wk 4	Day22 6-MP	Day23 6-MP	Day24 6-MP	Day25 6-MP	Day26 6-MP	Day27 6-MP	Day28 6-MP
Wk 5	Day29 MTX 6-MP TIT	Day30 6-MP	Day31 6-MP	Day32 6-MP	Day33 6-MP	Day34 6-MP	Day35 6-MP
Wk 6	Day36 6-MP	Day37 6-MP	Day38 6-MP	Day39 6-MP	Day40 6-MP	Day41 6-MP	Day42 6-MP
Wk 7	Day43 MTX 6-MP TIT	Day44 6-MP	Day45 6-MP	Day46 6-MP	Day47 6-MP	Day48 6-MP	Day49 6-MP
Wk 8	Day50 6-MP	Day51 6-MP	Day52 6-MP	Day53 6-MP	Day54 6-MP	Day55 6-MP	Day56 6-MP

SR	HR/VHR
MTX 2.5 g/m ² IV drip Days 1, 15, 29, 43	MTX 5 g/m ² IV drip Days 1, 15, 29, 43
6-MP 40 mg/m ² /day Days 1-56	6-MP 40 mg/m ² /day Days 1-56
TIT Days 1, 15, 29, 43 (8-12 hrs before HDMTX)	TIT Days 1, 15, 29, 43 (8-12 hrs before HDMTX)

Suggested criteria to start consolidation:

- WBC $\geq 1,500/\text{mm}^3$ with ANC $\geq 300/\text{mm}^3$ or APC $\geq 500/\text{mm}^3$, and platelet count $\geq 75 \times 10^9/\text{L}$. Dasatinib should be held 24 hours before start of infusion and until clearance of MTX. (~5 days)

Treatment Plans

◎ Consolidation Treatment(8 weeks)

Leucovorin rescue

Leucovorin, 15 mg/m² (IV or PO) for high-/very high-risk or 10 mg/m² (PO or IV) for standard-risk cases, will be started at 42 hours after the start of methotrexate and repeated every 6 hours for a total of three doses. The dosage of leucovorin will be increased in patients with high plasma methotrexate concentrations (>1.0μM at 42 hours) and continued until the methotrexate concentration is less than 0.10μM. Additional measures, such as hydration, hemoperfusion, or carboxypeptidase will be considered in patients with 42-hour methotrexate levels > 10μM. Patients with a history of delayed Grade 3 or 4 gastrointestinal toxicity with prior methotrexate or a history of typhlitis with any chemotherapy should have leucovorin continue for 5, rather than 3 doses; those with early toxicity should have leucovorin begin at 36 hours with subsequent methotrexate; if toxicity recurs, the baseline leucovorin dosage should also be increased.

Blood counts should be followed after high-dose methotrexate twice weekly; 6-MP dose should be reduced to half dose (20 mg/m²/day) if WBC is between 1000 to 1500/mm³, and should be held if WBC is less than 1000/mm³.

Avoid the use of concomitant Bactrim or penicillin during high-dose methotrexate treatment because they will delay methotrexate clearance.

*Alternatively, monitoring of MTX levels (starting at 30 hrs) and leucovorin rescue regimen can follow the guidelines of TPOG-ALL-2002 Protocol. Please give adequate prehydration and bolus NaHCO₃ before the infusion of high-dose MTX.

Treatment Plans

Continuation Therapy of SR

Weeks 1-3: Reinduction for SR

Agents	Dosages and routes	# Doses	Schedules
Dexamethasone	10 mg/m ² /day PO (t.i.d.)	45	Days 1-8, 15-21
Vincristine	1.5 mg/m ² /week IV (max 2 mg)	3	Days 1, 8, 15
Epirubicin	30 mg/m ²	1	Day 1
L-asparaginase	6,000 U/m ² /thrice weekly IM	9	Days 3, 5, 7, 10, 12, 14, 17, 19, 21
TIT	Age-dependent	1	Day 1

Week 4 to end of therapy

Agent	Dosage and Route
6-mercaptopurine (6MP)	50 mg/m ² PO daily x 7 days, Days 1-7
Methotrexate (MTX)	40 mg/m ² IV or IM, Day 1
Vincristine (VCR)*	2.0 mg/m ² IV push (max. 2 mg), Day 1
Dexamethasone (Dexa)*	8 mg/m ² PO daily (tid) x 5 days, Days 1-5
TIT	Age-dependent

*Omission of VCR/Dexa pulse after 1-year of continuation

Treatment Plans

Reintensification: Regimen-A

Agent	Dosage and Route	Doses	Schedule
Dexamethasone	20 mg/m ² /day PO or IV (t.i.d)	18	Days 1-6
Cytarabine	2 grams/m ² , 3-hour IV q12 hrs	4	Days 1-2
Etoposide	100 mg/m ² , 1-hour IV q12 hrs	5	Days 3-5
L-asparaginase	25,000iu/m ² IM	1	Day 6
TIT	Age-dependent	1	Day 5

Reintensification: Regimen-B

Agent	Dosage and Route	Doses	Schedule
Clofarabine	25 mg/m ² /day, 2-hr IV infusion	5	Days 1-5
Etoposide	100 mg/m ² /day, 2-hr IV infusion	5	Days 1-5
Cyclophosphamide	300 mg/m ² /day, 30-60 minute IV	5	Days 1-5
Dexamethasone	8 mg/m ² /day PO daily (tid)	15	Days 1-5

Treatment Plans

Continuation therapy of HR/VHR

Weeks 1 to 6 and 10 to 16

Agent	Dosage and Route
Dexamethasone (Dexa)	12 mg/m ² PO daily (tid) x 5 days, Days 1-5
Epirubicin (EPI)	30 mg/m ² IV, Day 1
Vincristine (VCR)*	2.0 mg/m ² IV push (max. 2 mg), Day 1
6-mercaptopurine (6MP)	40 mg/m ² PO daily x 7 days, Days 1-7
L-asparaginase (ASP)	10,000 U/m ² IM, Day 1
Methotrexate (MTX)	40 mg/m ² IV or IM, Day 1
Dasatinib [#]	80 mg/m ² /day

Reinduction I for HR/VHR

Agents	Dosages and routes	# Doses	Schedules
Dexamethasone	12 mg/m ² /day PO (t.i.d.)	45	Days 1-8, 15-21
Vincristine	1.5 mg/m ² /week IV (max 2 mg)	3	Days 1, 8, 15
Epirubicin	30 mg/m ²	2	Days 1, 8
L-asparaginase	6,000 U/m ² /thrice weekly IM	9	Days 3, 5, 7, 10, 12, 14, 17, 19, 21
TIT	Age-dependent	1	Day 1
Dasatinib [#]	80 mg/m ² /day		

Treatment Plans

Reinduction II for HR/VHR

Agents	Dosages and routes	# Doses	Schedules
Dexamethasone	12 mg/m ² /day PO (t.i.d.)	45	Days 1-8, 15-21
Vincristine	1.5 mg/m ² /week IV (max 2 mg)	3	Days 1, 8, 15
L-asparaginase	6,000 U/m ² /thrice weekly IM	9	Days 3, 5, 7, 10, 12, 14, 17, 19, 21
TIT	Age-dependent	1	Day 1
Dasatinib [#]	80 mg/m ² /day		

Continuation Therapy: week 21 to end of therapy

Agent	Dosage and Route
6-mercaptopurine (6MP)	50 mg/m ² PO daily x 7 days, Days 1-7
Methotrexate (MTX)	40 mg/m ² IV or IM, Day 1
Vincristine (VCR)*	2.0 mg/m ² IV push (max. 2 mg), Day 1
Dexamethasone (Dexa)*	12 mg/m ² PO daily (tid) x 5 days, Days 1-5, at the first year; 6 mg/m ² PO daily (tid) x 5 days, Days 1-5, at the 2nd year
Cyclophosphamide (CY) [‡]	300 mg/m ² IV, Day 1
Cytarabine(Ara-C) [‡]	300 mg/m ² IV, Day 1
TIT	Age-dependent
Dasatinib [#]	80 mg/m ² /day till the end of therapy

*VCR/Dexa pulse will be decreased from q4 wks to q8 wks after 1-year of continuation. Dexa will be decreased to 6 mg/m² at the 2nd year of continuation

[#]For Ph+ALL

[‡]Omission of CY/Ara-C after continuation week 55

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TPOG-Infant ALL-2022, Risk Classification

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KMT2A	Clinical Features	Risk	MRD	Treatment Protocol
KMT2A-g		LR		TPOG-ALL-2021 (provisional HR)
KMT2A-r	No HR features	IR	MRD <0.01% after consolidation (TP4)	TPOG-Infant ALL-2022 IR
			Others	TPOG-Infant ALL-2022 IR/HSCT or CAR-T
KMT2A-r	HR features: Age <6 m or WBC ≥300,000/mm ³	HR	MRD <0.01% after consolidation (TP4)	TPOG-Infant ALL-2022 HR
			Others	TPOG-Infant ALL-2022 HR/HSCT or CAR-T

g: germline; HR: high risk; IR: intermediate risk; r: rearrangement; TP: MRD time point

注意: infant ALL treatment protocol的選擇如下

- (1). KMT2A-germline: 依TPOG-ALL-2021進行risk classification/treatment
- (2). KMT2A-rearrangement: 依TPOG-ALL-Infant-2022進行risk classification/treatment

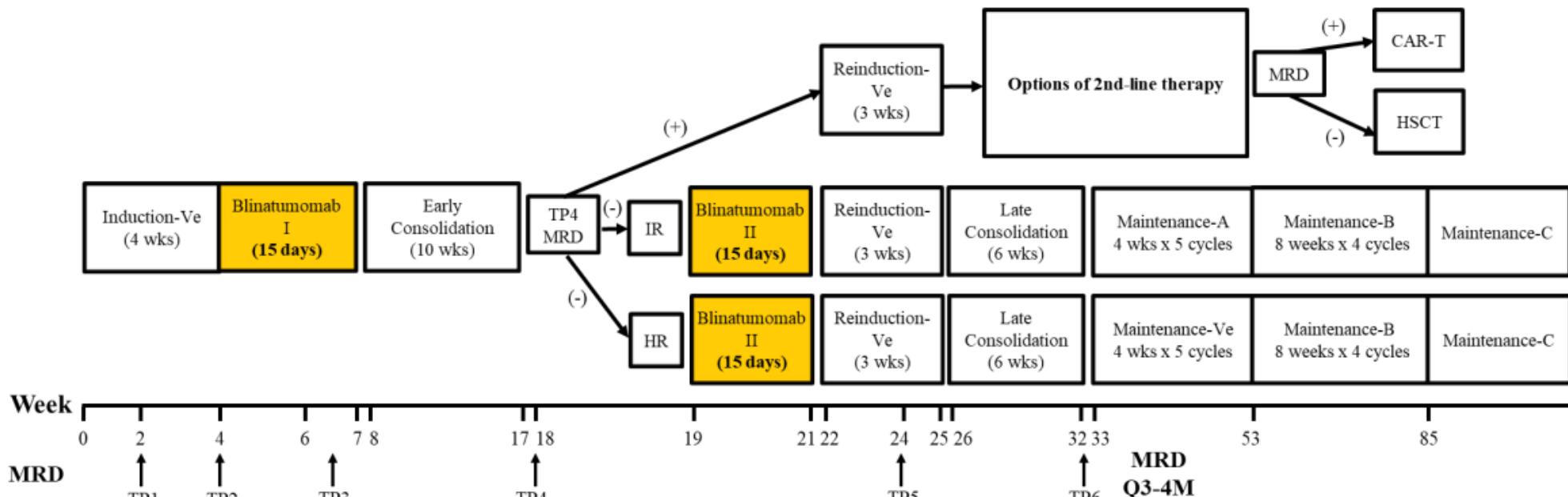
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TPOG-Infant ALL-2022, IR/HR Treatment Schema



IR, intermediate risk; HR, high risk; Ve, venetoclax

Hematopoietic Stem Cell Transplantation (HSCT)

- Patients with persistent MRD ($\geq 0.01\%$) after Early Consolidation (TP4) are suggested to receive HSCT after Re-induction course.
- Any patient who has MRD recurrence during maintenance therapy is suggested to receive HSCT after achieving another negative MRD status after salvage therapy.

2025新增

Time Points of MRD Measurement on TPOG-Infant ALL-2022

Time Points	Dates
MRD1	D15-D19 of Induction
MRD2	D35-D42 (end of Induction) (or first day of Blincyto)
MRD3	Week 7/8, after Blincyto
MRD4	Week 17/18, after Early Consolidation
MRD5	D15 of Reinduction-Ve
MRD6	Week 32, after Late Consolidation
Subsequent MRD(s)	Q3M (till 1 year after completion of therapy)

- Positive MRD level will be defined as $\geq 0.01\%$ (one or more lymphoblasts among 10^4 bone marrow mononuclear cells) by either flow MRD or ASO-IgG/TCR qPCR MRD.
- To compare/convert the data, patients using TaqMan RQ-PCR of fusion genes:
 $1\% \sim 2 \text{ log reduction}$; $0.01\% \sim 4 \text{ log reduction}$

DROP OFF CRITERIA

1. Incorrect diagnosis.
2. Patient and/or parents refuse to allow additional therapy.
3. A patient who, in the judgement of the Principal Investigator, could not or did not follow the assigned treatment, may be removed from study.
4. Patients who fail to meet all eligibility requirements of protocol (i.e., ineligible) will be taken off study, e.g., using other protocols, or not newly diagnosed patients.

癌症藥物停藥準則

骨髓及血液檢查，腫瘤有復發或變大情況，應停止或改變治療方式。