



中山醫學大學附設醫院

兒癌診療指引

(Acute Lymphoid Leukemia)

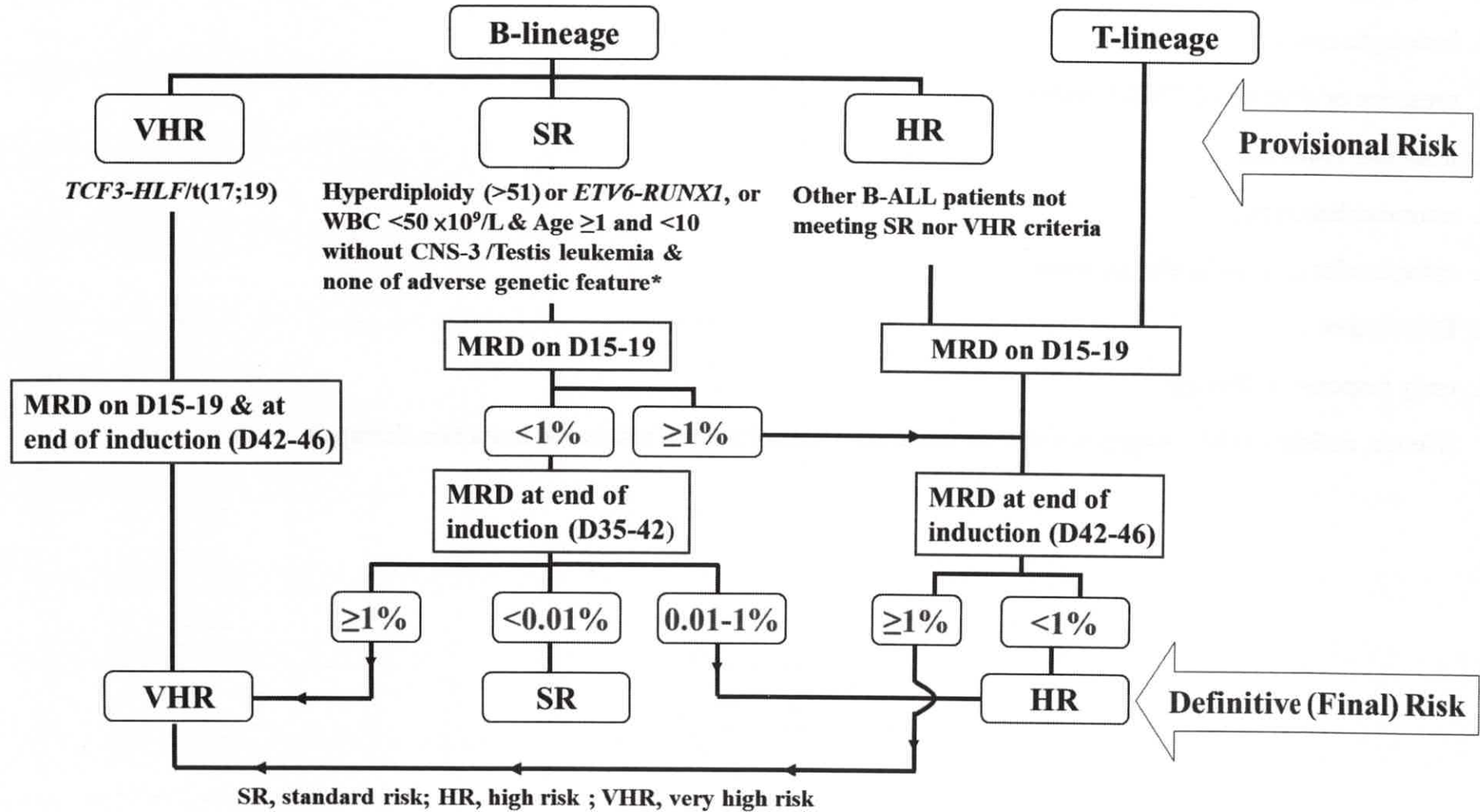
本臨床指引參考TPOG與兒童癌症多專科醫療團隊編修

2026/04/13 Version 6.0
2025/10/20 Version 6.0
2024/11/25 Version 5.0
2023/11/27 Version 5.0
2022/11/28 Version 5.0
2021/11/25 Version 4.0
2020/11/26 Version 3.0
2020/04/09 Version 3.0
2019/07/24 Version 2.0
2018/07/04 Version 1.0

癌症委員會主任委員	癌症委員會執行長	癌症中心主任	抗癌藥物安全小組	團隊負責人
危光川	黃明志	李良駁	翁德甫	翁德甫

目錄

一、	Risk classification	2
二、	Classification.....	3
三、	Treatment Plans.....	6
四、	DROP OFF CRITERIA	32
五、	Post-treatment Evaluation.....	32
六、	Evaluation Criteria.....	33
七、	復發評估.....	33
八、	追蹤評估.....	35
九、	Reference	36
十、	完治率定義.....	39





一、 Risk classification

Patients are classified into one of three categories (standard-risk, high-risk, or very high-risk) based on

1. the presenting age
2. leukocyte count
3. presence or absence of CNS-3 status
4. testicular leukemia
5. immunophenotype,
6. cytogenetics and molecular genetics
7. DNA index
8. early response to therapy.

(Hence, definitive risk assignment will be made after completion of remission induction therapy)



二、 Classification

Criteria for standard risk ALL

1. B-lymphoblastic ALL with DNAindex ≥ 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:
 - (1.) CNS 3 status (5 WBC/ μL of cerebrospinal fluid with morphologically identifiable blasts or cranial nerve palsy).
 - (2.) Overt testicular leukemia(evidenced by ultrasonogram).
 - (3.) 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).
 - (4.) Poor early response (1%lymphoblasts on day 15 of remission induction,% lymphoblasts by immunologic or molecular methods on remission date).

*hyperdiploidy: >51 chromosomes or DNA index (DI) ≥ 1.16 or identified by RNA-seq. If results are not accordant each other, the evidence priority are RNA-seq $>$ DNA Index $>$ karyotype.

#hypodiploidy: DNA index <0.95 or <44 chromosomes or identified by RNA-seq.



Criteria for very high risk ALL

1. All non-hyperdiploid B-ALL with MRD2 $\geq 1\%$.
2. Hyperdiploid B-ALL with MRD2 $\geq 1\%$ and MRD remaining positive ($\geq 0.01\%$) 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 $\geq 0.1\%$ after early intensification, no matter the MRD results afterward.
6. TCF3-HLF/t(17;19).

Criteria for high risk 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

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

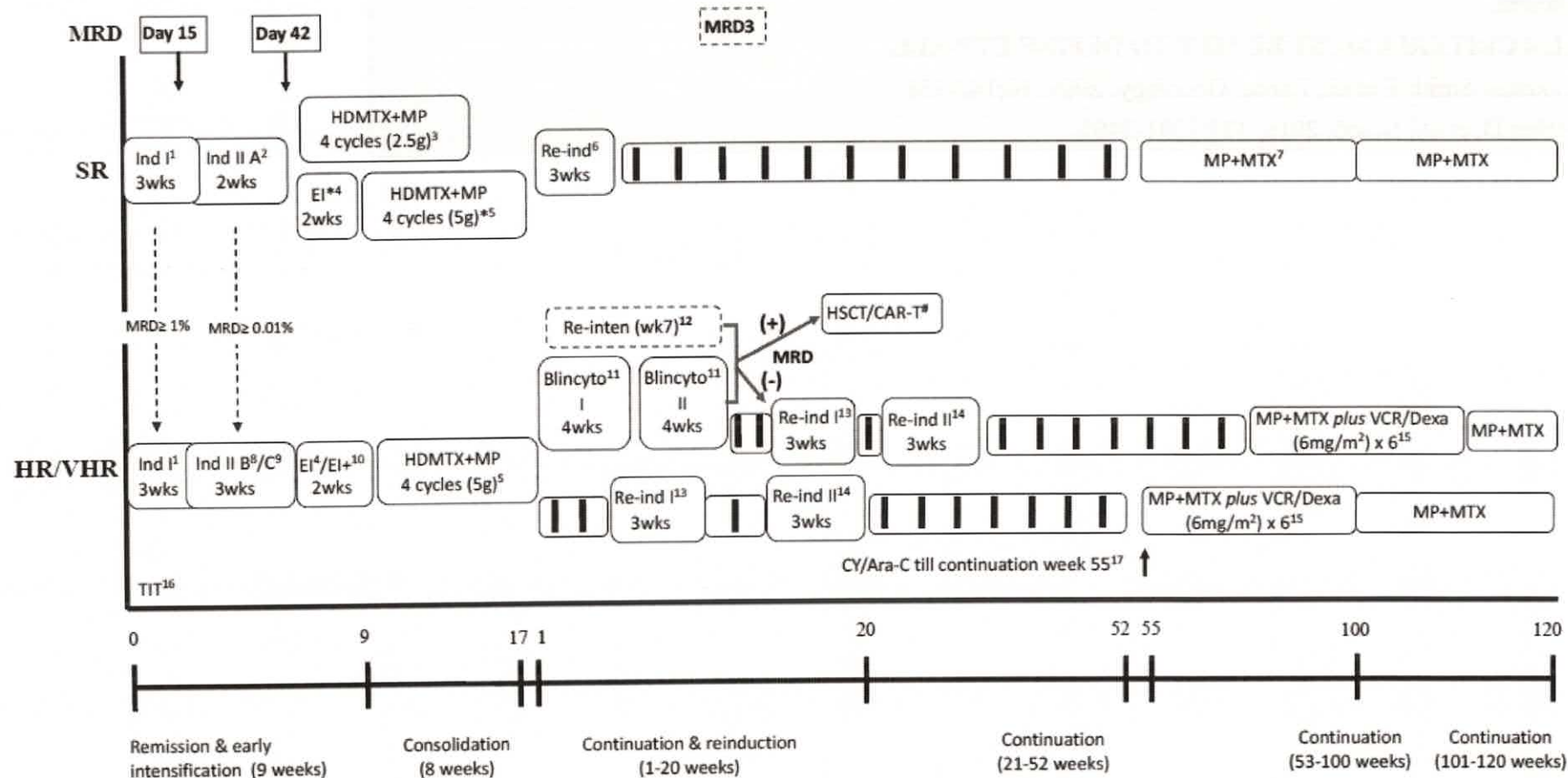
1. Coustan-Smith E et al., Lancet Oncology. 2009; 10:147-156
2. Arber D, et al., Blood. 2016; 127:2391-2405.



三、 Treatment Plans

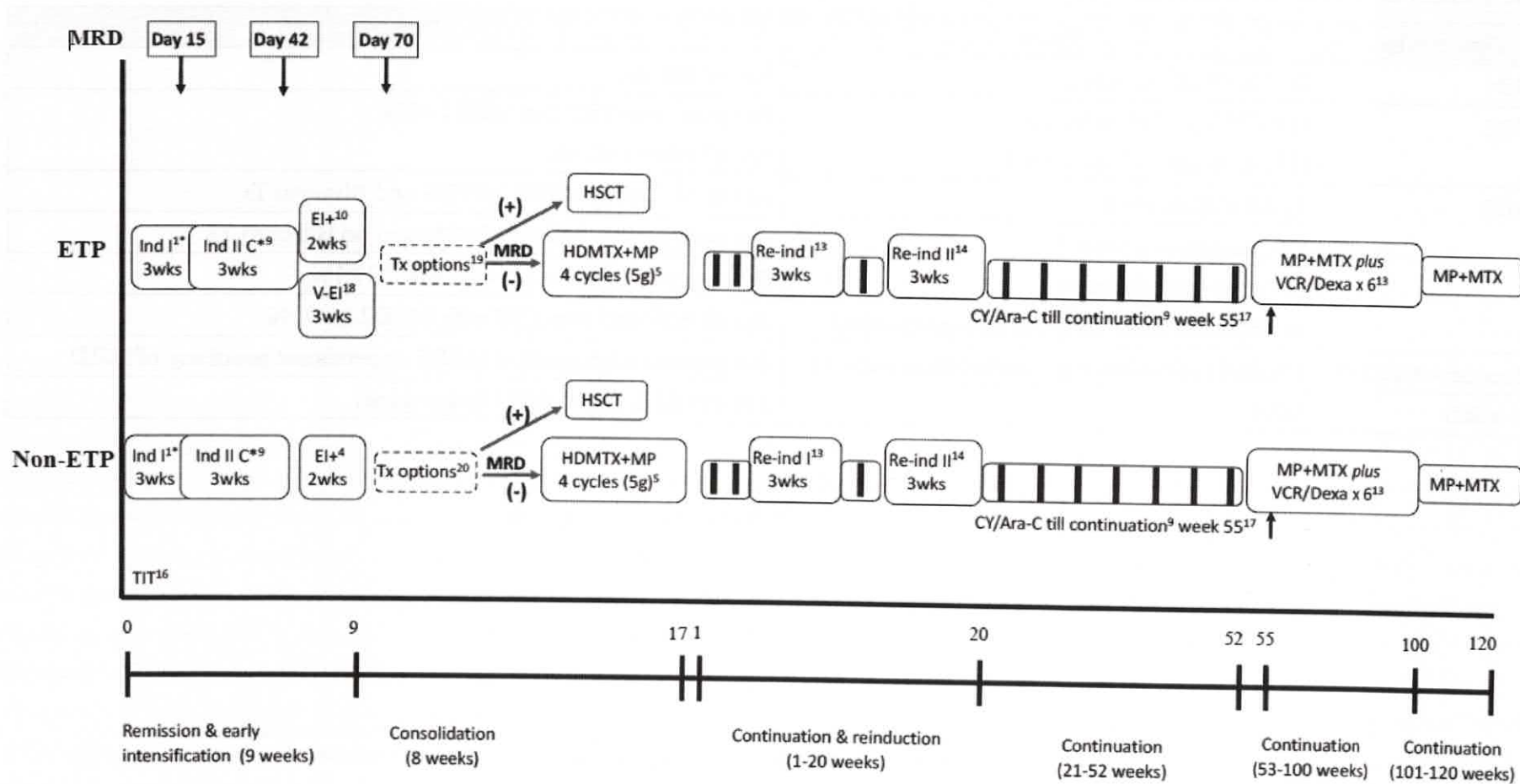
Schema of TPOG-ALL-2021

Treatment Schema of TPOG-ALL-2021, B-ALL





Treatment Schema of TPOG-ALL-2021, T-ALL



**Time Points of MRD Measurement on TPOG-ALL-2021**

Time Points	Dates	Patients
MRD1	D15-D19 (of induction)	For all patients
MRD2	D35-D42 (end of induction)	For provisional SR and MRD1 <1%
	D42-D46 (end of induction)	For all other patients
MRD3	1) After Blincyto II	For B-ALL with MRD2 $\geq 0.01\%$ and Blincyto Tx
	2) Continuation week 7	For B-ALL with MRD2 $\geq 0.01\%$ and no Blincyto Tx
	3) *After consolidation	For hyperdiploid B-ALL with MRD2 $\geq 1\%$
	4) D65-D70 (after early intensification/ <i>plus</i>)	For all ETP and non-ETP with MRD2 $\geq 0.01\%$
Subsequent MRD(s)	Clinical evaluation, e.g., continuation week 17	For patients with positive MRD3 or persistent positivity of MRD
F/U MRD	Q3M	For Ph+ALL (<i>BCR-ABL1</i> fusion gene)

**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	C	<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，後續若仍以 flow MRD F/U 時，務必告知檢查單位使用 Blincyto 病史，以尋找其他 markers 或改 MRD 檢測方法。

**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%	H	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 (Max 140 mg) 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 $\geq 0.01\%$; optional MRD4 for patients who completion of Blincyto or reintensification; further MRD for persistent MRD $\geq 0.01\%$.

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	
				$\geq 0.01\%$	HR	EI+	<0.01%	HR	
							0.01-0.09%	HR	Dasatinib plus C/T or HD-Ara-C-based or Nelarabine-based therapy
							$\geq 0.1\%$	VHR	
ETP	Any	C	D42-46	<0.01%	HR	EI+	<0.01%	HR	V-EI
							0.01-0.09%	HR	
							$\geq 0.1\%$	VHR	
				$\geq 0.01\%$	HR	V-EI	<0.01%	HR	V-EI
							0.01-0.09%	HR	
							$\geq 0.1\%$	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 $\geq 0.01\%$ and all ETP; further MRD for persistent MRD $\geq 0.01\%$



Induction therapy

Induction treatment will begin with prednisone, vincristine, epirubicin, L-asparaginase and triple intrathecal treatment, followed by cyclophosphamide/cytarabine/L-asparaginase/mercaptopurine.

It could be an acceptable practice to give steroids in patients with large leukemic burden (WBC >100,000/mm³; large organs especially mediastinum) to reduce the risk of massive tumor lysis syndrome. If steroids should be used alone, it is limited to 1-3 days and the first day of steroid administration will be recorded as the day 1 of induction therapy.

**INDUCTION THERAPY FOR B-ALL****Induction I (first 3 weeks) for B-ALL**

Wk 1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
	PRED VCR EPI TIT*	PRED	PRED L-ASP(1)	PRED	PRED L-ASP(2)	PRED	PRED L-ASP(3)
Wk 2	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
	PRED VCR EPI#	PRED	PRED L-ASP(4)	PRED	PRED L-ASP(5)	PRED	PRED L-ASP(6)
Wk 3	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
	PRED VCR TIT BMA,MRD1	PRED	PRED L-ASP(7)	PRED	PRED L-ASP(8)	PRED	PRED L-ASP(9)

Agent	Dosage & Route	Doses	Schedule
Prednisone (PRED)	40/60 mg/ m ² /day, PO (TID)	84	Days 1-28
Vincristine (VCR)	1.5 mg/ m ² /day, (Max 2), IV	3	Days 1, 8, 15
Epirubicin (EPI)	20 mg/ m ² /day, IV	2	Days 1, 8#
L-asparaginase(L-Asp)	6,000 U/ m ² /day, IM	9	Days 3, 5, 7, 10, 12, 14, 17, 19, 21
Dasatinib (for Ph+ALL)	80 mg/ m ² /day (Max 140 mg), PO	Daily	Starting after Dx
Triple intrathecal therapy (TIT)	Days 1*, 15 The additional TITs on Days 8, 11 will be given according to risk group/CNS status. See Summary of Intrathecal Therapy on TPOG-ALL-2021.		



For infants without KMT2A-rearrangement: vincristine, 0.05 mg/kg for age <6 months and 1.5 mg/ m² for age ≥6 months; other drugs (except prednisolone): 2/3, 3/4 and full dose for age <2, 2-6 months and 6-12 months.

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

*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 MD1 <0.1%; but it is suggested to be given on weeks 3/4 in SR with MRD1 ≥0.1%.

Induction II-A for B-ALL

	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Wk 4	PRED VCR TIT#	PRED	PRED	PRED	PRED	PRED	PRED
	Day 29	Day 30	Day 31	Day 32	Day 33	Day 34	Day 35
Wk 5	PRED Taper	PRED Taper	PRED Taper	PRED T aper	PRED Taper	PRED Taper	PRED Taper

Agent	Dosage & 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) /day, IV	1	Day 22
Triple intrathecal therapy (TIT)#	The TIT will be given according to risk group/CNS status. See Summary of Intrathecal Therapy on TPOG-ALL-2021.		

For infants without KMT2A-rearrangement: vincristine, 0.05 mg/kg for age <6 months and 1.5 mg/ m² for age ≥6 months

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

**Induction II-B for B-ALL**

Wk 4	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
	PRED VCR TIT#	PRED	PRED L-ASP(10)	PRED	PRED L-ASP(11)	PRED	PRED L-ASP(12)
Wk 5	Day 29	Day 30	Day 31	Day 32	Day 33	Day 34	Day 35
	PRED Taper CY MP TIT	PRED Taper Ara-C MP	PRED Taper Ara-C MP	PRED Taper Ara-C MP	PRED Taper Ara-C MP	PRED Taper MP	PRED Taper MP
Wk 6	Day 36	Day 37	Day 38	Day 39	Day 40	Day 41	Day 42
	MP	Ara-C MP	Ara-C MP	Ara-C MP	Ara-C MP	Ara-C MP	MP

Agent	Dosage & Route	Doses	Schedule
Prednisone (PRED)*	40/60 mg/ m ² /day, PO (TID)	84	Days 1-28
Vincristine (VCR)	1.5 mg/ m ² /day (Max. 2), IV	1	Day 22
L-asparaginase (L-Asp)	6,000 U/ m ² /day, 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 /day, IV 30 mins	8	Days 30-33, 37-40
6-mercaptopurine (MP)	30 mg/ m ² /day, PO	14	Days 29-42
Dasatinib (for Ph+ALL)	80 mg/ m ² /day (Max 140 mg), PO	Daily	Starting after Dx
TIT	Day 29. ‡The additional TIT on Day 22 will be given according to risk group/CNS status. See Summary of Intrathecal Therapy on TPOG-ALL-2021.		



For infants without KMT2A-rearrangement: vincristine, 0.05 mg/kg for age <6 months and 1.5 mg/ m² for age ≥6 months; other drugs (except prednisolone): 2/3, 3/4 and full dose for age <2, 2-6 months and 6-12 months.

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

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.

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

	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Wk 4	PRED VCR TIT	PRED	PRED L-ASP(10)	PRED	PRED L-ASP(11)	PRED	PRED L-ASP(12)
	Day 29	Day 30	Day 31	Day 32	Day 33	Day 34	Day 35
Wk 5	PRED Taper CY MP TIT	PRED Taper Ara-C MP Bort(1)	PRED Taper Ara-C MP	PRED Taper Ara-C MP	PRED Taper Ara-C MP Bort(2)	PRED Taper MP	PRED Taper MP
	Day 36	Day 37	Day 38	Day 39	Day 40	Day41	Day42
Wk 6							



Agent	Dosage & Route	Doses	Schedule
Prednisone (PRED)*	40/60 mg/ m ² /day, PO (TID)	84	Days 1-28
Vincristine (VCR)	1.5 mg/ m ² /day, (Max. 2), IV	1	Day 22
L-asparaginase (L-Asp)	6,000 U/ m ² /day, 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 /day, IV 30 mins	4	Days 30-33
6-mercaptopurine (MP)	30 mg/ m ² /day, PO	7	Days 29-35
Bortezomib (Bort)	1.3 mg/ m ² /day, IV	2	Days 30, 33
TIT	Day 29 ‡The additional TIT on Day 22 will be given according to risk group/CNS status. See Summary of Intrathecal Therapy on TPOG-ALL-2021		

For infants without KMT2A-rearrangement: vincristine, 0.05 mg/kg for age <6 months and 1.5 mg/ m² for age ≥6 months; bortezomib, 0.043mg/kg/dose; other drugs (except prednisolone): 2/3, 3/4 and full dose for age <2, 2-6 months and 6-12 months.

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

Suggested criteria to start D29 C/T:

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

**INDUCTION THERAPY FOR T-ALL****Induction I (first 3 weeks) for T-ALL**

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Wk 1	DEXA VCR EPI TIT*	DEXA	DEXA L-ASP(1)	DEXA	DEXA L-ASP(2)	DEXA	DEXA L-ASP(3)
	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Wk 2	DEXA VCR TIT EPI#	DEXA	DEXA L-ASP(4)	DEXA	DEXA L-ASP(5)	DEXA	DEXA L-ASP(6)
	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
Wk 3	DEXA VCR TIT BMA, MRD1	DEXA	DEXA L-ASP(7)	DEXA	DEXA L-ASP(8)	DEXA	DEXA L-ASP(9)

Agent	Dosage & 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 (L-Asp)	6,000 U/ m ² , IM	9	Days 3, 5, 7, 10, 12, 14, 17, 19, 21
Triple intrathecal therapy (TIT)	Days 1*, 8‡, 15 ‡The 2nd TIT could be done 1 week after the first TIT or twice a week if possible. The additional TIT on Day 11 will be given according to risk group/CNS status. See Summary of Intrathecal Therapy on TPOG-ALL-2021.		

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

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

Induction II-C* for T-ALL

Wk 4	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
	DEXA Taper VCR TIT	DEXA Taper	DEXA Taper L-ASP(10)	DEXA Taper	DEXA Taper L-ASP(11)	DEXA Taper	DEXA Taper L-ASP(12)
Wk 5	Day 29	Day 30	Day 31	Day 32	Day 33	Day 34	Day 35
	CY MP TIT	Ara-C MP Bort(1)	Ara-C MP	Ara-C MP	Ara-C MP Bort(2)	MP	MP
Wk 6	Day 36	Day 37	Day 38	Day 39	Day 40	Day41	Day42

Agent	Dosage & 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 (L-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 /day, IV 30 mins	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.

INTRATHECAL THERAPY DURING INDUCTION THERAPY

As a traumatic lumbar puncture at diagnosis may result in a poorer outcome and the need for extra intrathecal therapy subsequently, all diagnostic lumbar punctures will be performed by experienced personnel, preferably under general anesthesia or deep sedation.

Triple intrathecal chemotherapy (TIT) will be administered immediately after cerebrospinal fluid is collected at the disappearance of blast from PB, no later than D10. 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 is used with dosages based on age as follows

Age(months)	Methotrexate (mg)	Hydrocortisone (mg)	Ara-C (mg)	Volume (ml)
<3	3	6	9	4
3-12	6	12	18	6
12-23	8	16	24	8
24-35	10	20	30	10
36	12	24	36	12

Frequency and total number of triple intrathecal treatments for remission induction is based on the patient's risk of CNS relapse, as follows:

1. Patients with any of the following features will receive totally 5 weekly TIT during induction therapy:



- Philadelphia chromosome
- Hypodiploidy (<44)
- WBC $\geq 100,000/\text{mm}^3$ at diagnosis (4 times for SR)
- t(1;19)/E2A-PBX1
- T-cell ALL

2. Patients with any of the following features will receive TIT twice a week for 2 weeks followed by weekly TIT for 2 weeks (totally 6 TIT during induction therapy):

- CNS-2 status (<5 WBC/ μL of CSF with blasts)
- CNS-3 status (≥ 5 WBC/ μL of CSF with blasts or cranial nerve palsy)
- Traumatic lumbar puncture with blasts

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

Early Intensification (EI)

SR BCP-ALL with MRD1 0.1-0.99% (from Day 43)

HR BCP-ALL

-Ph-negative, MRD1 <5% and MRD2 <1%

-Ph+ALL with either MRD1 $\geq 1\%$ or MRD2 $\geq 0.01\%$

	Day 50	Day 51	Day 52	Day 53	Day 54	Day 55	Day 56
Wk 8	CY TIT	Ara-C	Ara-C L-Asp(1)	Ara-C	Ara-C L-Asp(2)		L-Asp(3)
Wk 9	Day 57	Day 58	Day 59	Day 60	Day 61	Day 62	Day 63
		Ara-C	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 /day, IV 30 mins	8	Days 51-54, 58-61
L-asparaginase (L-Asp)	6,000 U/m ² IM	3	Days 52, 54, 56
Dasatinib#	80 mg/m ² /day (Max 140 mg), PO	Daily	Starting after Dx
TIT		1	Day 50

For infants without *KMT2A*-rearrangement, doses of each drug: 2/3, 3/4 and full dose for age <2, 2-6 months and 6-12 months.

*EI will start on week 7 or earlier for SR patients with Induction II-A

#For Ph+ALL

Suggested criteria to start EI:

Day 50 chemotherapy could be given earlier if the patient has early count recovery (WBC $\geq 1,500/\text{mm}^3$ with ANC $\geq 300/\text{mm}^3$ or APC $\geq 500/\text{mm}^3$, and platelet count $\geq 75 \times 10^9/\text{L}$). G-CSF is suggested if the treatment is delayed.

Early Intensification *plus* (EI+)

HR BCP-ALL : Ph-negative, MRD1 $\geq 5\%$ or MRD2 $\geq 1\%$

T-ALL : -all non-ETP, -ETP with MRD2 $< 0.01\%$

	Day 50	Day 51	Day 52	Day 53	Day 54	Day 55	Day 56
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)
	Day 57	Day 58	Day 59	Day 60	Day 61	Day 62	Day 63
Wk 9		Ara-C	Ara-C	Ara-C	Ara-C		



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

For infants without KMT2A-rearrangement: bortezomib, 0.043mg/kg/dose; other drugs: 2/3, 3/4 and full dose for age <2, 2-6 months and 6-12 months.

Suggested criteria to start EI+:

Day 50 chemotherapy could be given earlier if the patient has early count recovery (WBC $\geq 1,500/\text{mm}^3$ with ANC $\geq 300/\text{mm}^3$ or APC $\geq 500/\text{mm}^3$, and platelet count $\geq 75 \times 10^9/\text{L}$). G-CSF is suggested if the treatment is delayed.

Venetoclax-Early Intensification (V-EI)

ETP with MRD2 $\geq 0.01\%$

Agent	Dosage & Route	Doses	Schedule
Vincristine (VCR)	1.5 mg/m ² /day (Max. 2), IV	2	Days 1, 15
Dexamethasone (Dexa)	8 mg/m ² /day, PO (TID)	45	Days 1-8, 15-21
Venetoclax	240 mg/m ² , PO QD (Max. 400)	21	Days 1-21
L-asparaginase (L-Asp)	6,000 U/m ² , IM	6	Days 8, 10, 12, 15, 17, 19
TIT			Day 1

For infants: vincristine: 0.05 mg/kg for age <6 months and 1.5 mg/m² for age ≥ 6 months.

Venetoclax dosing for pediatric age and weight groups based on pharmacokinetics and CYP3A ontogeny for children aged <2 years. (Badawi MA, ASH 2020, Abstract #1009)(Section 6.0 TREATMENT MODIFICATIONS)



Doses of other drugs (except vincristine, dexamethasone, bortezomib) will be reduced to 2/3 in patients younger than 2 months and 3/4 in those 2 to 6 months of age. Full dose will be given for patients older than 6 months.

V-EI could be given earlier if the patient has early count recovery ($WBC \geq 1,500/mm^3$ with $ANC \geq 300/mm^3$ or $APC \geq 500/mm^3$, and platelet count $\geq 75 \times 10^9/L$). G-CSF is suggested if the treatment is delayed.

Consolidation Therapy (SR, HR, VHR)

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Wk 1	MTX 6-MP TIT	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP
	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Wk 2	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP
	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
Wk 3	MTX 6-MP TIT	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP
	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Wk 4	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP
	Day 29	Day 30	Day 31	Day 32	Day 33	Day 34	Day 35
Wk 5	MTX 6-MP TIT	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP
Wk 6	Day 36	Day 37	Day 38	Day 39	Day 40	Day 41	Day 42



	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP
	Day 43	Day 44	Day 45	Day 46	Day 47	Day 48	Day 49
Wk7	MTX						
	6-MP TIT	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP
Wk8	Day 50	Day 51	Day 52	Day 53	Day 54	Day 55	Day 56
	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP	6-MP

SR with MRD1 <0.1%	HR/VHR & SR with MRD1 0.1-0.99%
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)
Dasatinib should be held 24 hours before start of infusion and until clearance of MTX. (~5 days/course)	

For infants without KMT2A-rearrangement, doses of each drug: 2/3, 3/4 and full dose for age <2, 2-6 months and 6-12 months.

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 $\geq 50 \times 10^9/\text{L}$.

TMP-SMZ should not be hold during MTX treatment.

**Reintensification: Regimen-A**

Agent	Dosage & Route	Doses	Schedule
Dexamethasone (Dexa)	20 mg/ m ² /day PO or IV (TID)	18	Days 1-6
Cytarabine (Ara-C)	2 g/ m ² , 3-hr IV Q12 hrs	4	Days 1-2
Etoposide (VP-16)	100 mg/ m ² , 1-hr IV Q12 hrs	5	Days 3-5
L-asparaginase (L-Asp)	25,000 U/ m ² IM	1	Day 6
TIT	Age-dependent	1	Day 5

Reintensification: Regimen-B

Agent	Dosage & Route	Doses	Schedule
Clofarabine	25 mg/ m ² /day, 2-hr IV	5	Days 1-5
Etoposide (VP-16)	100 mg/ m ² /day, 2-hr IV	5	Days 1-5
Cyclophosphamide (CY)	300 mg/ m ² /day, 30-60 mins IV	5	Days 1-5
Dexamethasone (Dexa)	8 mg/ m ² /day PO (TID)	15	Days 1-5

For infants without KMT2A-rearrangement, doses of each drug (except dexamethasone): 2/3, 3/4 and full dose for age <2, 2-6 months and 6-12 months.

#Suggested criteria to start reintensification:

WBC $\geq 1000/\text{mm}^3$ with ANC $\geq 300/\text{mm}^3$ and platelet count $\geq 50 \times 10^9/\text{L}$

Continuation Treatment (120 weeks)

Post-remission continuation treatment begins after the completion of consolidation, provided that the WBC $\geq 1500/\text{mm}^3$, ANC $\geq 300/\text{mm}^3$, and platelet count $50 \times 10^9/\text{L}$ as well as no evidence of Grade 3 or 4 mucositis. Continuation treatment (120 weeks) differs according to the risk classification & the use of blinatumomab.

**CONTINUATION TREATMENT OF SR****Weeks 1-3: Reinduction for SR**

Agent	Dosage & Route	Doses	Schedule
Dexamethasone (Dexa)	10 mg/m ² /day PO (TID)	45	Days 1-8, 15-21
Vincristine (VCR)	1.5 mg/ m ² /week IV (Max. 2 mg)	3	Days 1, 8, 15
Epirubicin (EPI)	30 mg/ m ²	1	Day 1
L-asparaginase (L-Asp)*	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 & Route	Schedule
6-mercaptopurine (6MP)	50 mg/ m ² /day, PO (QD)	Start wk4 to the end
Methotrexate (MTX)	40 mg/ m ² /day, Day 1, IV or IM	Wk4-7,9-11,13-15,17-19,21-23, 25-27,29-31,33-35,37-39,41-43, 45-47,49-120
Vincristine (VCR)#	2.0 mg/ m ² /dose (Max 2), Day 1, IV	Wk1,2,3,8,12,16,20,24,28,32,36,40,44,48
Dexamethasone (Dexa)#	8 mg/ m ² /day, Days 1-5, PO (TID)	Wk1,3,8,12,16,20,24,28,32,36, 40,44,48
TIT	Age-dependent	Wk1,6,11,16,24,(28),32,(36),40,(44),48

For infants without KMT2A-rearrangement: vincristine, 0.05 mg/kg for age <6 months and 1.5 mg/ m² for age ≥6 months; other drugs (except dexamethasone): 2/3, 3/4 and full dose for age <2, 2-6 months and 6-12 months.

*First dose of L-Asp will be given at day 3 (after 2 days of Dexa) to reduce the risk of allergy.

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

(TIT) will be given on weeks 28, 36, 44 in (1) SR with ≥100 x 10⁹/L & CNS-1 (2) SR with CNS-2/TLP with blasts.

**CONTINUATION TREATMENT OF HR/VHR****Weeks 1 to 6 and 10 to 16**

Agent	Dosage & Route	Schedule
Dexamethasone (Dexa)	12 mg/m ² /day, Day 1-5, PO (TID)	Wk1,4,14
Epirubicin (EPI)	30 mg/ m ² /dose, Day 1, IV	Wk1,4,11,14
Vincristine (VCR)	2.0 mg/ m ² /dose, (Max 2), Day 1, IV	Wk1,4,11,14
6-mercaptopurine (6MP)	40 mg/ m ² /day, PO	Wk1-6,10-16
L-asparaginase (L-Asp)*	10,000 U/ m ² /dose, Day 1, IM	Wk1-6,10-16
TIT	Age-dependent	Wk (3), 12
Dasatinib#	80 mg/m ² /day (Max 140 mg), PO	Continue to the end

For infants without KMT2A-rearrangement: vincristine, 0.05 mg/kg for age <6 months and 1.5 mg/m² for age ≥6 months; other drugs (except dexamethasone): 2/3, 3/4 and full dose for age <2, 2-6 months and 6-12 months.

*L-Asp on week 1 will be given at day 3 (after 2 days of DEX) to reduce the risk of allergy.

(TIT) for patients with T-ALL, WBC ≥100,000/mm³, t (1;19), hypodiploidy <44, CNS-2, CNS-3 or traumatic lumbar puncture with blasts at Dx.

#For Ph+ALL

**Reinduction I for HR/VHR**

Agent	Dosage & Route	Doses	Schedule
Dexamethasone (Dexa)	12 mg/ m ² /day, PO (TID)	45	Days 1-8, 15-21
Vincristine (VCR)	1.5 mg/ m ² /dose, (Max 2), IV	3	Days 1, 8, 15
Epirubicin (EPI)	30 mg/ m ² /dose, IV	2	Days 1, 8
L-asparaginase (L-Asp)	6,000 U/ m ² /dose, thrice weekly, IM	9	Days 1, 3, 5, 7, 10, 12, 14, 17, 19
TIT	Age-dependent	1	Day 1
Dasatinib#	80 mg/ m ² /day (Max 140 mg), PO		

For infants without KMT2A-rearrangement: vincristine, 0.05 mg/kg for age <6 months and 1.5 mg/m² for age ≥6 months; other drugs (except dexamethasone): 2/3, 3/4 and full dose for age <2, 2-6 months and 6-12 months.

Reinduction II for HR/VHR

Agent	Dosage & Route	Doses	Schedule
Dexamethasone (Dexa)	12 mg/ m ² /day PO (TID)	45	Days 1-8, 15-21
Vincristine (VCR)	1.5 mg/ m ² /week IV (Max. 2 mg)	3	Days 1, 8, 15
L-asparaginase (L-Asp)	6,000 U/ m ² /dose, thrice weekly IM	9	Days 1, 3, 5, 7, 10, 12, 14, 17, 19
TIT	Age-dependent	1	Day 1
Dasatinib#	80 mg/ m ² /day (Max 140 mg), PO		

For infants without KMT2A-rearrangement: vincristine, 0.05 mg/kg for age <6 months and 1.5 mg/ m² for age ≥6 months; other drugs (except dexamethasone): 2/3, 3/4 and full dose for age <2, 2-6 months and 6-12 months.

#For Ph+ALL

**Continuation Treatment: week 21 to end of therapy**

Agent	Dosage & Route	Schedule
6-mercaptopurine (6MP)	50 mg/ m ² /day, PO	Wk21,22,25,26,29,30,33,34,37,38,41,42,45,46,49,50,52-54,56-120
Methotrexate (MTX)	40 mg/ m ² /dose, Day 1, IV or IM	Wk21,22,25,26,29,30,33,34,37,38,41,42,45,46,49,50,52-54,57-63,65-71, 73-79,81-87,89-95,97-120
Vincristine (VCR)‡	2.0 mg/ m ² /dose, (Max 2), Day 1, IV	Wk24,28,32,36,40,44,48,56,64,72,80,88,96
Dexamethasone (Dexa)‡	1st year: 12 mg/ m ² /day, Days 1-5, PO, TID 2nd year (since wk56): 6 mg/ m ² /day, Days 1-5, PO, TID	Wk24,28,32,36,40,44,48,56,64,72,80,88,96
Cyclophosphamide (CY)†	300 mg/ m ² /dose, Day 1, IV	Wk23,27,31,35,39,43,47,51,55
Cytarabine(Ara-C)†	300 mg/ m ² /dose, Day 1, IV	Wk23,27,31,35,39,43,47,51,55
TIT	Age-dependent	Wk24,28,32,36,40,44,48,(56),(64), (72),(80)
Dasatinib#	80 mg/m ² /day (Max 140 mg), PO	Continue to the end

mg/m² for age \geq 6 months; other drugs (except dexamethasone): 2/3, 3/4 and full dose for age <2, 2-6 months and 6-12 months.

#For Ph+ALL

‡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

†Omission of CY/Ara-C after continuation week 55

(TIT) will be given on weeks 56, 64, 72, 80 for patients with T-ALL, WBC \geq 100,000/mm³, t(1;19), hypodiploidy <44, CNS-2, CNS-3 or traumatic lumbar puncture with blasts at Dx.

Intrathecal therapy during continuation: see Section 4.4, Summary of Intrathecal Therapy on TPOG-ALL-2021.

**Blinatumomab (Blincyto) (first 10 weeks of continuation therap)**

Wk	Tx Schedule	Dose	
		BW < 45 kg	BW ≥45 kg
1	Blincyto I, week 1	5 mcg/ m ² /day, Max. 9 mcg	9 mcg/day
2	Blincyto I, week 2	15 mcg/ m ² /day, Max. 28 mcg	28 mcg/day
3	Blincyto I, week 3	15 mcg/ m ² /day, Max. 28 mcg	28 mcg/day
4	Blincyto I, week 4 TIT	15 mcg/ m ² /day, Max. 28 mcg	28 mcg/day
5	OFF		
6	OFF		
7	Blincyto II, week 1	15 mcg/ m ² /day, Max. 28 mcg	28 mcg/day
8	Blincyto II, week 2	15 mcg/ m ² /day, Max. 28 mcg	28 mcg/day
9	Blincyto II, week 3	15 mcg/ m ² /day, Max. 28 mcg	28 mcg/day
10	Blincyto II, week 4 TIT & BM MRD	15 mcg/m ² /day, Max. 28 mcg	28 mcg/day

Indications

1. B-ALL with MRD2 (+), if Blincyto is approved by National Insurance Program (NIP)
2. All Ph+ALL, regardless of MRD2 data
3. B-ALL with persistent MRD (+) after continuation week 7 could try the NIP-approval of Blincyto, if Blincyto is not yet used before
4. Optional use: patients with unfavorable genetics features, e.g., hypodiploid, BCR-ABL1-like, ETV6-RUNX1-like, AMP21, MEF2D-R, TCF3-HLF and Down syndrome, even though their MRD2 are negative.

(Ref: Blood Cancer Discov 2021; 2: 326-337 & St. Jude Total 17)



四、 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.

五、 Post-treatment Evaluation

1. Postprandial blood sugar, albumin, amylase, lipase BiW during L-asparaginase therapy
2. Sodium QW in induction therapy (watching for SIADH)
3. Chemical profile, if needed, esp. within 48 hours after chemotherapy is started.
4. BUN and creatine before and after HDMTX
5. CBC
6. Plasma MTX level after HDMTX therapy



六、 Evaluation Criteria

1. Complete remission: M1 marrow status with restoration of normal hematopoiesis and normal performance status.
2. These findings must persist for a least one month. Induction failure: $\geq 5\%$ leukemic blasts in marrow after 42 days of remission induction treatment confirmed by flow cytometry based MRD.
3. Bone marrow relapse: $\geq 25\%$ leukemic blasts in marrow
4. CNS relapse: ≥ 5 WBC/ μL of CSF with definite blasts on cytopspin preparation
5. Testicular relapse: Isolated testicular relapse must be confirmed pathologically; in the event of bone marrow relapse, combined testicular relapse can be based on testicular enlargement (documented by sonogram) without biopsy.

七、 復發評估

1. Induction failures
2. Patients who do not attain complete remission (5% leukemic blasts in bone marrow) after remission induction, consolidation treatment and reintensification treatment will be removed from the protocol. Those who do not achieve a remission after induction therapy, but subsequently attain complete remission after consolidation or reintensification treatment, are candidates for allogeneic hematopoietic stem cell transplantation.
3. Hematologic relapse
4. Patients with 25% lymphoblasts in marrow aspirate will become eligible for relapse protocols.
5. Extramedullary relapse (except CNS relapse)



6. Patients with any form of extramedullary relapse (testes, ovarian, etc) except that of CNS will become eligible for relapse protocols.
7. Extramedullary relapse (CNS relapse)
8. Patients with overt CNS relapse (i.e. $5 \text{ WBC}/\mu\text{L}$ of CSF with blasts) will remain on the protocol.
9. Emergence of CSF Lymphoblasts During Remission Requiring CNS Radiation: Preventive cranial irradiation will not be given prophylactically to patients with CNS leukemia at diagnosis or to those with high-risk leukemia. Only patients with immunologically proven leukemic lymphoblasts in CSF (regardless of cell count) during hematologic remission will receive therapeutic CNS irradiation after receiving a second remission induction followed by 1-2 cycles of reintensification (reinduction) to consolidate bone marrow remission after induction



八、 追蹤評估

檢查項目 \ 時程	化療前	化療後第 1 年	化療後第 2 年	化療後第 3 年	化療後第 4 年後
Physical Examination	◎	每隔 2 週	每隔 1 個月	每隔 1 個月	每隔 6 個月
CBC	◎	每隔 2 週	每隔 1 個月	每隔 1 個月	每隔 6 個月
LDH	◎	每隔 1 至 3 個月	每隔 1 至 3 個月	每隔 1 至 3 個月	-
	備註：If Initial LDH High:每隔 1 個月檢測；Initial LDH Low :每隔 3 個月檢測				
Bone Marrow Examination	◎	每隔 3 至 6 個月	每隔 3 至 6 個月	每隔 3 至 6 個月	-
	備註： Standard Risk 每隔 6 個月 High Risk 每隔 3~6 個月 Very High Risk 每隔 3 個月				
Cardia Echo/EKG	◎	每 1 年檢測一次，追蹤 5 年			



九、 Reference

*TPOG-ALL2013 21, rev.2021.1.17 47 PROTOCOLS FOR CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA FOR CHILDHOOD CANCER FOUNDATION OF TAIWAN BY TAIWAN PEDIATRIC ONCOLOGY GROUP, 2021.1.17

1. Nachman JB, Sather HN, Sensel MG et al. Augmented post-induction therapy for children with high-risk acute lymphoblastic leukemia and a slow response to initial therapy. *N.Engl.J.Med.* 1998;338:1663-1671.
2. Silverman LB, Gelber RD, Dalton VK et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01. *Blood* 2001;97:1211-1218.
3. Vora A, Mitchell CD, Lennard L et al. Toxicity and efficacy of 6-thioguanine versus 6-mercaptopurine in childhood lymphoblastic leukaemia: a randomised trial. *Lancet* 2006;368:1339-1348.
4. Mitchell CD, Richards SM, Kinsey SE et al. Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: results of the UK Medical Research Council ALL97 randomized trial. *Br.J.Haematol.* 2005;129:734-745.
5. Bostrom BC, Sensel MR, Sather HN et al. Dexamethasone versus prednisone and daily oral versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. *Blood* 2003;101:3809-3817.
6. Matloub Y, Lindemulder S, Gaynon PS et al. Intrathecal triple therapy decreases central nervous system relapse but fails to improve event-free survival when compared with intrathecal methotrexate: results of the Children's Cancer Group (CCG) 1952 study for standard-risk acute lymphoblastic leukemia, reported by the Children's Oncology Group. *Blood* 2006;108:1165-1173.
7. Pinheiro JP, Boos J. The best way to use asparaginase in childhood acute lymphatic leukaemia--still to be defined?



- Br.J.Haematol. 2004;125:117-127.
8. Wetzler M, Sanford BL, Kurtzberg J et al. Effective asparagine depletion with pegylated asparaginase results in improved outcomes in adult acute lymphoblastic leukemia: Cancer and Leukemia Group B Study 9511. *Blood* 2007;109:4164-4167.
 9. Hijiya N, Franklin J, Rytting M et al. A phase I study of clofarabine in combination with cyclophosphamide and etoposide: A new regimen in pediatric patients with refractory or relapsed acute leukemia. *ASCO Meeting Abstracts* 2007;25:9529.
 10. Flotho C, Coustan-Smith E, Pei D et al. Genes contributing to minimal residual disease in childhood acute lymphoblastic leukemia: prognostic significance of CASP8AP2. *Blood* 2006;108:1050-1057.
 11. Flotho C, Coustan-Smith E, Pei D et al. A set of genes that regulate cell proliferation predicts treatment outcome in childhood acute lymphoblastic leukemia. *Blood* 2007;110:1271-1277.
 12. Flotho C, Coustan-Smith E, Pei D et al. Genes contributing to minimal residual disease in childhood acute lymphoblastic leukemia: prognostic significance of CASP8AP2. *Blood* 2006;108:1050-1057.
 13. Holleman A, Cheok MH, den Boer ML et al. Gene-expression patterns in drug-resistant acute lymphoblastic leukemia cells and response to treatment. *N.Engl.J.Med.* 2004;351:533-542.
 14. Lugthart S, Cheok MH, den Boer ML et al. Identification of genes associated with chemotherapy crossresistance and treatment response in childhood acute lymphoblastic leukemia. *Cancer Cell* 2005;7:375-386.
 15. *TPOG-ALL2013, rev.2018.5.25 47 PROTOCOLS FOR CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA FOR CHILDHOOD CANCER FOUNDATION OF TAIWAN BY TAIWAN PEDIATRIC ONCOLOGY GROUP, 2018.5.25



16. Cheng Q, Yang W, Raimondi SC et al. Karyotypic abnormalities create discordance of germline genotype and cancer cell phenotypes. *Nat.Genet.* 2005;37:878-882.
17. Cheng C, Pounds SB, Boyett JM et al. Statistical significance threshold criteria for analysis of microarray gene expression data. *Stat Appl.Genet.Mol.Biol.* 2004;3:Article36.
18. Pounds S, Cheng C. Robust estimation of the false discovery rate. *Bioinformatics.* 2006;22:1979-1987.
19. Benjamini Y, Krieger AM, Yekutieli D. Adaptive linear step-up procedures that control the false discovery rate. *Biometrika* 2006;93:491-507.
20. Pounds S, Cheng C. Robust estimation of the false discovery rate. *Bioinformatics* 2006;22:1979-1987.
21. Pounds S, Cheng C. Sample size determination for the false discovery rate. *Bioinformatics* 2005;21:4263-4271.
22. Holleman A, Cheok MH, den Boer ML et al. Gene-expression patterns in drug-resistant acute lymphoblastic leukemia cells and response to treatment. *N.Engl.J.Med.* 2004;351:533-542.
23. Cheng C. Microarray gene co-expression analysis and validation by a sequential clustering algorithm [abstract]. Joint Statistical Meetings of the American Statistical Association 2007;Salt Lake City, UT:
24. De Pauw B, Walsh T, Donnelly J et al. Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clinical Infectious Diseases* 2008;46:1813-1821.
25. Manabe A, Ohara A, Hasegawa D et al. Significance of the complete clearance of peripheral blasts after 7 days of prednisolone treatment in children with acute lymphoblastic leukemia: the Tokyo Children's Cancer Study Group Study L99-15. *Haematologica* 2008; 93:1155-1160.



26. Kishi S, Yang W, Boureau B et al. Effects of prednisone and genetic polymorphisms on etoposide disposition in children with acute lymphoblastic leukemia. *Blood* 2004;103:67-72.
27. Kishi S, Griener J, Cheng C et al. Homocysteine, Pharmacogenetics, and Neurotoxicity in Children With Leukemia. *J Clin Oncol* 2003;21:3084-3091.
28. Blanco JG, Edick MJ, Hancock ML et al. Genetic polymorphisms in CYP3A5, CYP3A4 and NQO1 in children who developed therapy-related myeloid malignancies. *Pharmacogenetics* 2002;12:605-611.
29. Relling MV, Yang W, Das S et al. Pharmacogenetic Risk Factors for Osteonecrosis of the Hip Among Children With Leukemia. *J Clin Oncol* 2004;22:3930-3936.
30. Mullighan CG, Goorha S, Radtke I et al. Genome-wide analysis of genetic alterations in TPOG-ALL2013, rev.2018.5.25 60 acute lymphoblastic leukaemia. *Nature* 2007;446:758-764.

十、 完治率定義

癌別	完治率定義
急性淋巴性 白血病	將疾病分為標準危險群(standard risk)、高危險群(high risk)及最高危險群(very high risk)的療程為 2.5 年，依 TPOG ALL-2013 治療計畫分為引導期(5 週)、鞏固期(8 週)、再引導期(3 週/1-2 次)、維持期(120 週)等階段，完成引導期即算完成治療。

