CAR-T藥事照護案例分享

花蓮慈濟醫院 王雅賢 藥師

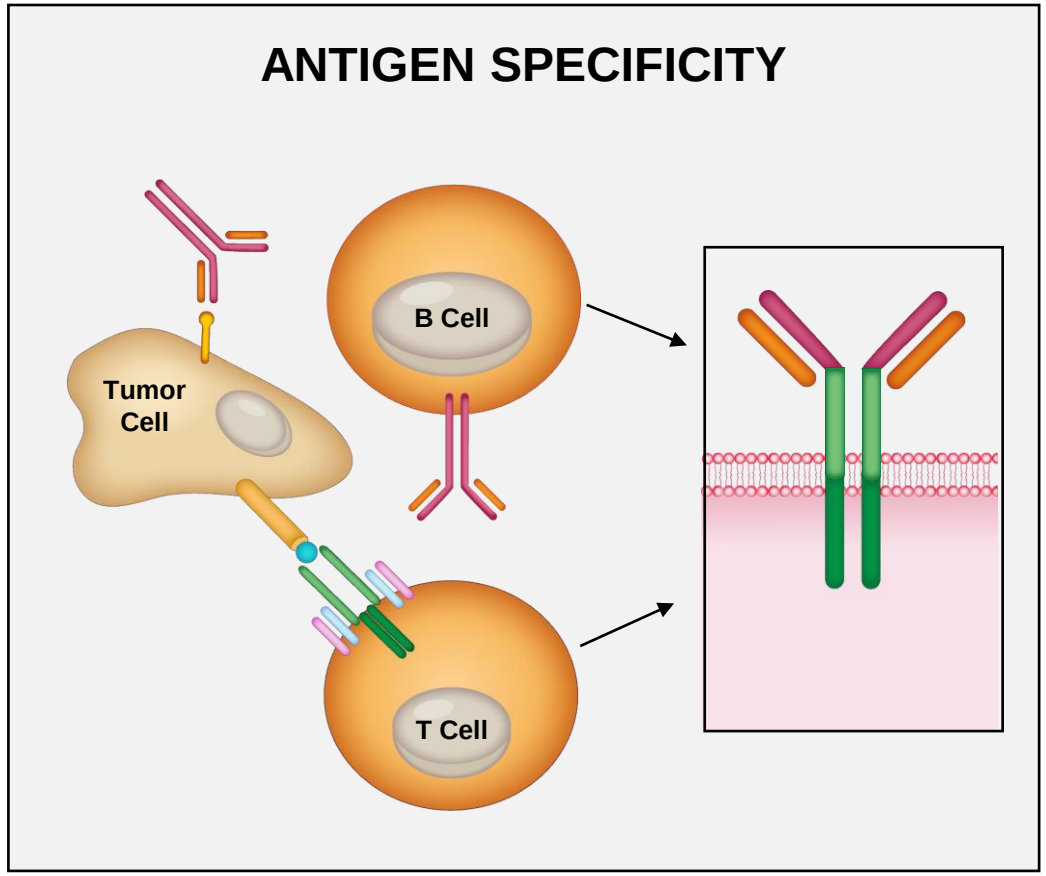
2024.11.17

佛教慈濟醫療財團法人
花蓮慈濟醫院
Hualien Tzu Chi Hospital,
Buddhist Tzu Chi Medical Foundation

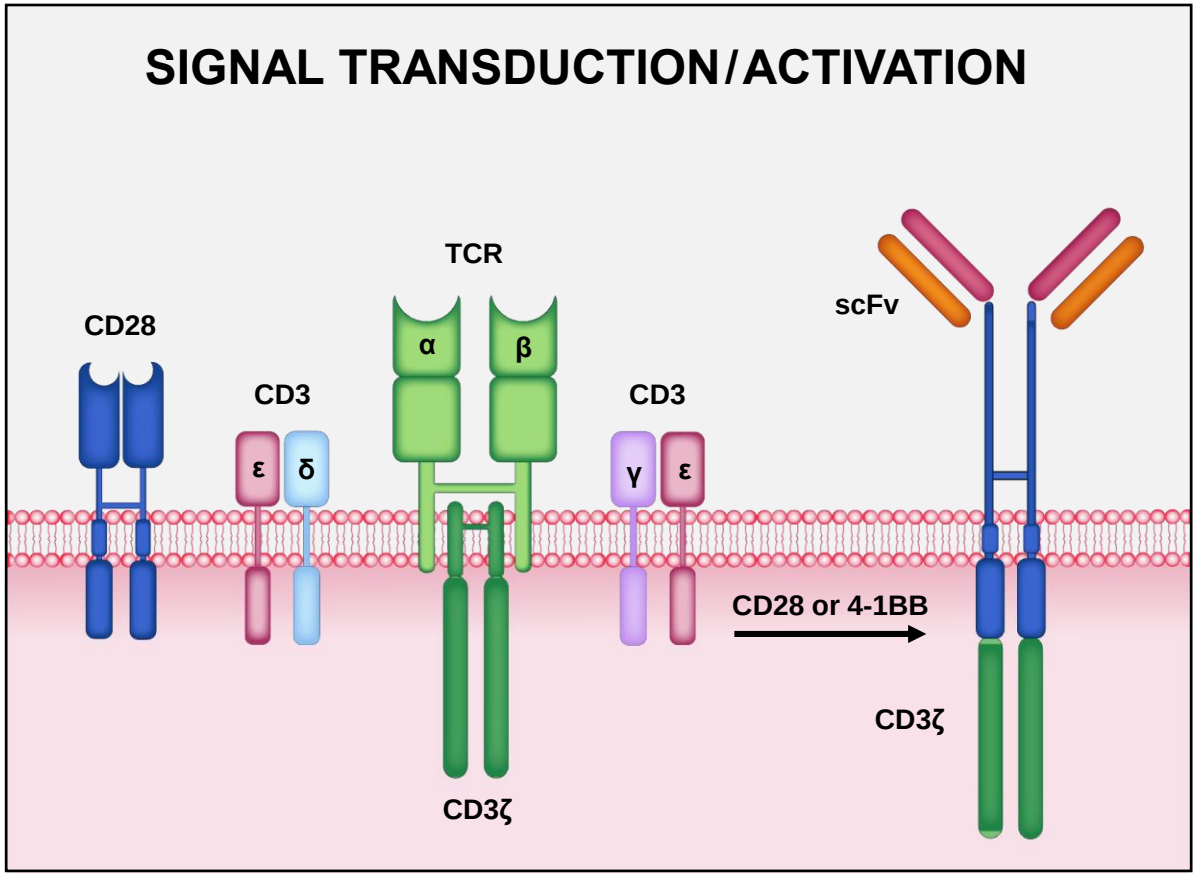
報告大綱

1. CAR-T介紹與流程簡介
2. 花蓮慈濟醫院治療經驗分享
3. 藥師在CAR-T治療扮演角色

Chimeric Antigen Receptor (CAR) T cell therapy



CAR heavy and light chain chains are components of the B-cell receptor



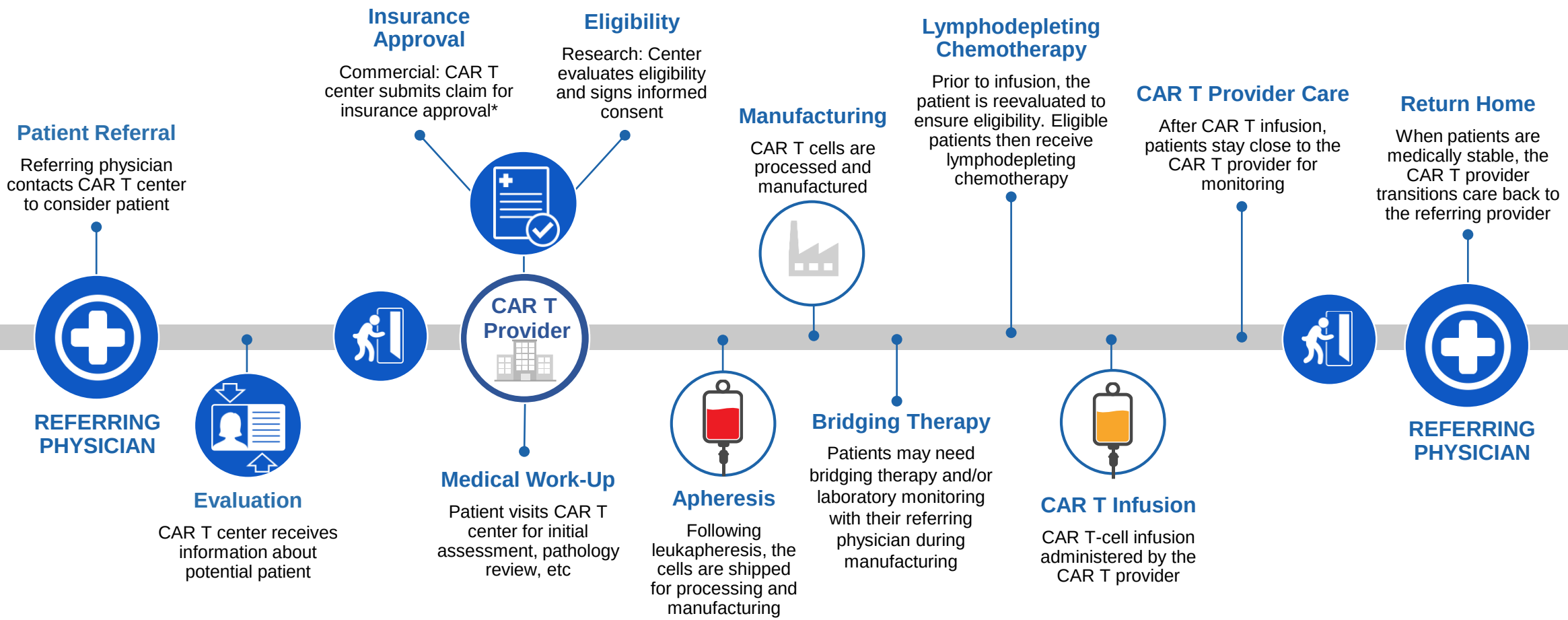
CARs integrate key components of intracellular TCR signaling and costimulatory domains

Miller JF, Sadelain M. *Cancer Cell.* 2015;27(4):439-449.

Tisa-Cel (Tisagenlecleucel, Kymriah®)

- 患有難治型、移植後復發、第二次或二次以上復發之B細胞急性淋巴性白血病（ALL）的25歲以下兒童和年輕成人病人
- 經兩線或兩線以上全身治療後之復發性或難治性瀰漫性大B細胞淋巴瘤（DLBCL）的成人病人
- 經兩線或兩線以上全身治療後之復發性或難治性濾泡性淋巴瘤（FL）成人病人

CAR-T治療高度個人化，流程的每個步驟都牽涉治療成果關鍵



CAR T WORKING GROUP

花蓮慈濟醫院治療經驗分享

佛教慈濟醫療財團法人
花蓮慈濟醫院
Hualien Tzu Chi Hospital,
Buddhist Tzu Chi Medical Foundation

CAR-T date	2023.5	2024.1	2024.4	2024.8	2024.9	2024.10
Age/ gender	53 Male	70 Female	13 Female	31 Female	76 Male	61 Female
Disease	R/R DLBCL	R/R DLBCL	R/R ALL	R/R ALL	R/R DLBCL	R/R DLBCL

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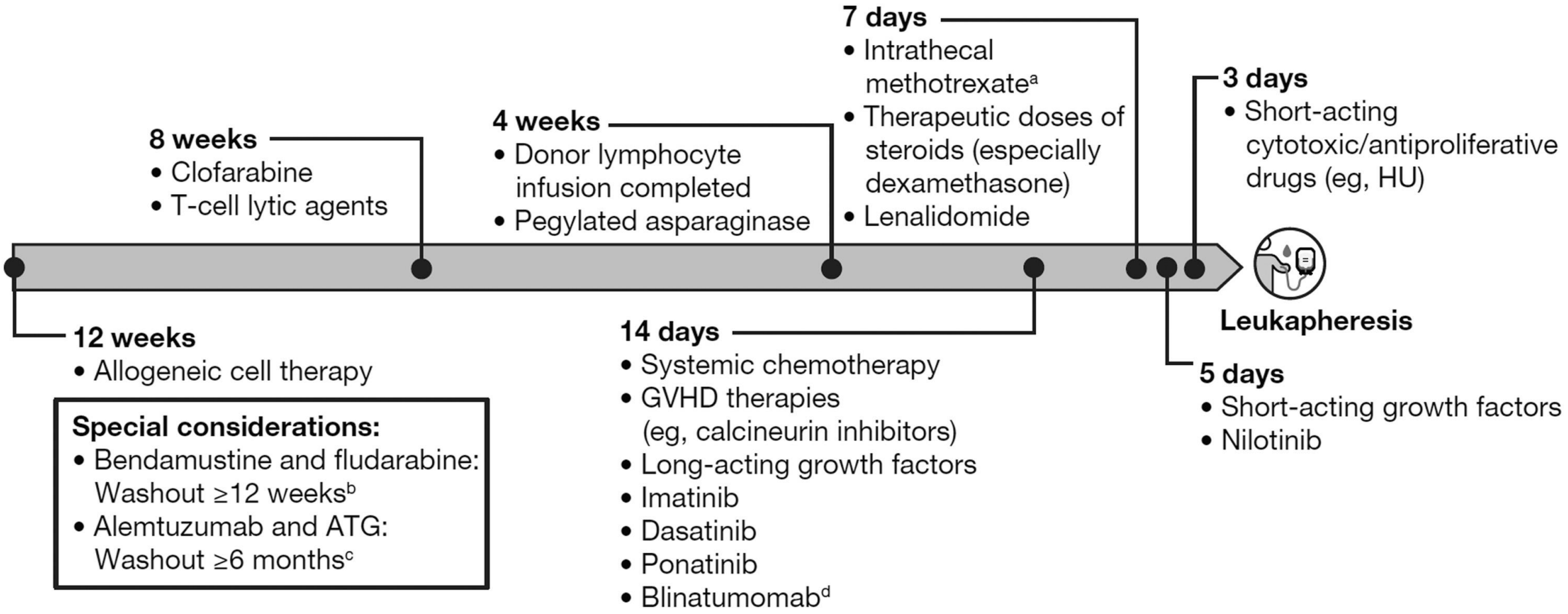
Disease	R/R DLBCL	R/R DLBCL	R/R ALL	R/R ALL	R/R DLBCL	R/R DLBCL
Prior therapies	1. R-CODOX-M/ R-IVAC (II), CR 2. allo-MUD-PBSCT relapse 55 months post-HSCT	1. R-COP, RB-Copanlisib, +local RT, PR 2. R-ESHAP, CR2 3. auto-PSBCT relapse 31 months post-HSCT	1. FRALLE 2000 B2 protocol, relapse 2. haplo- HSCT, CR relapse 25 months post-HSCT 1. Blinatumomab, refractory 2. Inotuzumab, CRi	1. GRAALL induction, refractory 2. N1+FLAG, consolidation Inotuzumab + Bloc MTX, CR 3. allo-MUD-PBSCT, relapse 6 months post-HSCT 4. Inotuzumab,PR 5. Blinatumomab, CHR	1. R2-COP, CR1 2. R-ESHAP(III), CR2 relapse, duration of remission: 15 months	1. R-CHOP(6), CR1 relapse, duration of remission: 9 months 1. Pola-RICE(III), PR
Prior lines of therapies	2	3	4	5	2	2

Washout periods prior to leukapheresis



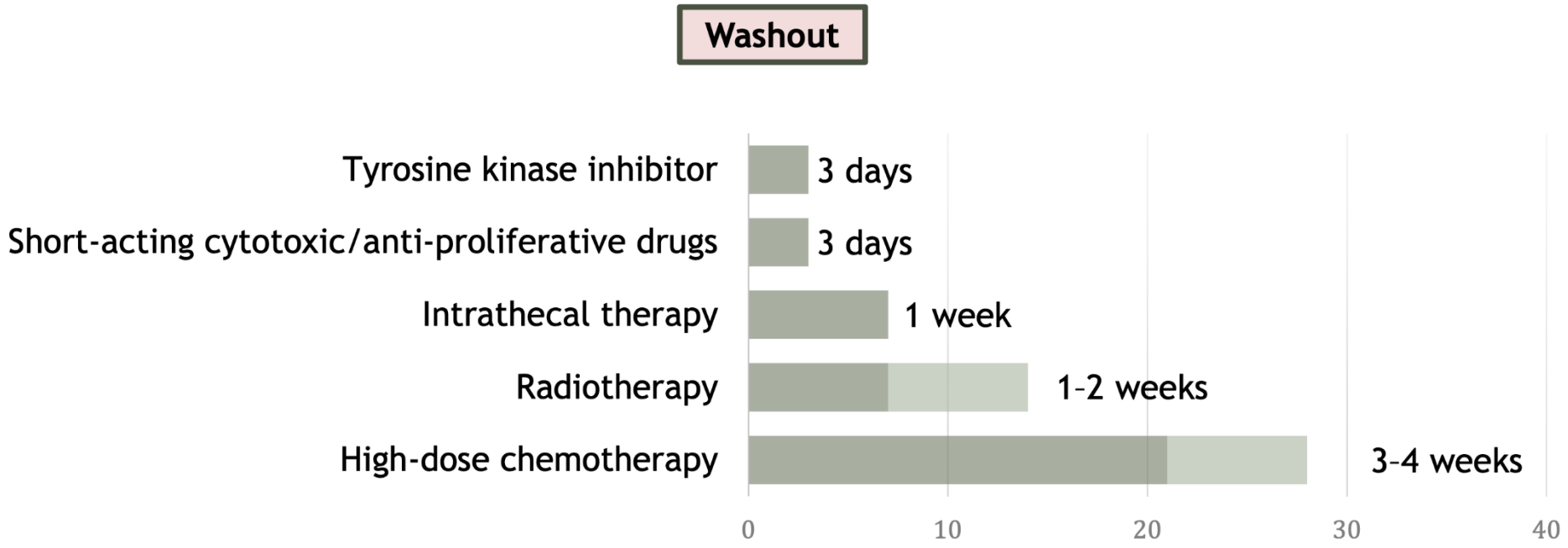
Cytotherapy. 2022 Sep;24(9):869-878.

Age/ gender	53 Male	70 Female	13 Female	31 Female	76 Male	61 Female
Disease	R/R DLBCL	R/R DLBCL	R/R ALL	R/R ALL	R/R DLBCL	R/R DLBCL
Bridging therapy	• R-BOEMS (I), PD; • PBGR (Polatuzumab, Bendamustin, Obinutuzumab, Lenalidomide) + XRT, PR	• Polatuzumab-RB, good PR • Lenalidomide +acalabrutinib, CR3	Inotuzumab, CRi	• Blinatumomab, relapse • Venetoclax+ Blinatumomab, refractory	ARR-GemOx(I)+ ARR(III), PR	modified iR2 (ibrutinib, rituximab, lenalidomide) +XRT, late CR2

Disease	When to consider bridging therapy	Choices for bridging therapy
NHL	Bulky disease (≥10 cm), > 1 extranodal site involved, stage 3–4 disease, bone marrow involvement, elevated pretreatment LDH, CRP	Rituximab ± chemotherapy (gemcitabine, etoposide, cisplatin, cytarabine, bendamustine, oxaliplatin) Polatuzumab (± bendamustine, rituximab) Single agent: lenalidomide, BTK inhibitor, Tafasitamab[a] ± Steroids ± XRT
B cell ALL	Bone marrow blasts > 5%, extramedullary disease, CNS disease[b]	Chemotherapy (single agent or combination): vincristine, doxorubicin/idarubicin, mercaptopurine, methotrexate, fludarabine, cytarabine, cyclophosphamide Single agent: TKI, hydroxyurea, inotuzumab ozogamicin, blinatumomab[c] ± Steroids

EJHaem. 2022 Jan; 3(Suppl 1): 39–45.

Washout periods of bridging therapy



P.J. Hayden, et al. Ann Oncol. 2022; 33(3):259-275

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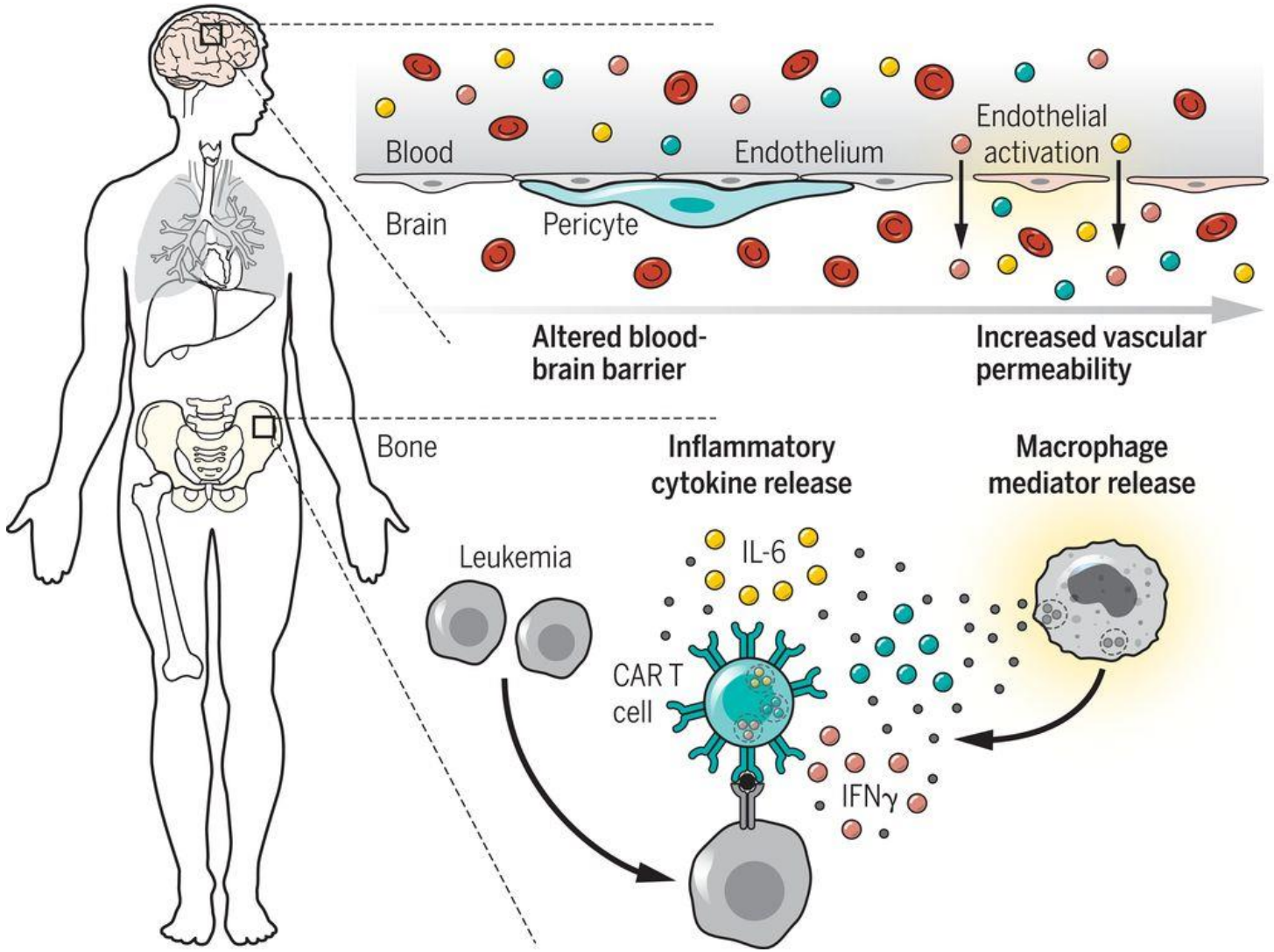
Disease	R/R DLBCL	R/R DLBCL	R/R ALL	R/R ALL	R/R DLBCL	R/R DLBCL
Lympho-Depleting regimen	FLU 25 mg/m^2/day + CYC 250 mg/m^2/day		Fludarabine 30mg/m^2/day + Endoxan 500mg/m^2/day	FLU 30 mg/m^2/day + CYC 500 mg/m^2/day	FLU 25 mg/m^2/day + CYC 250 mg/m^2/day	
Cell dose	5.2 x10^8 CAR+ viable T cells	4.0 x10^8 CAR+ viable T cells	3.5 x 10^6/kg viable T-cells	1.5 x10^8 CAR+ viable T cells	3.0 x10^8 CAR+ viable T cells	3.8 x10^8 CAR+ viable T cells
CRS	Grade 2; D+2 - D+4 Fever, hypotension, Cervical edema	Grade 1; D+3-D+7 Cervical edema	Grade 1; D+4-D+5 Fever	Grade 2; D+3-D+21 Fever, hypotension, Cervical edema	Grade 1; D+2-D+6 Fever	Grade 1; D+2-D+7 Fever, cervical and facial edema

- CRS--Cytokine release syndrome



Neurotoxicity
Delirium
Aphasia
Seizures
Cerebral edema
Intracranial hemorrhage

Hemodynamic instability
Tachycardia
Hypotension
Capillary leak syndrome

Organ dysfunction
AST and ALT elevation
Hyperbilirubinemia
Respiratory failure

發生率30% -100%

1–14 天內可能發生

中位數在輸注後 7 天

.June CH, O'Connor RS, Kawalekar OU, Ghassemi S, Milone MC. *Science*. 2018;359(6382):1361-1365.

CRS: Clinical Signs and Symptoms

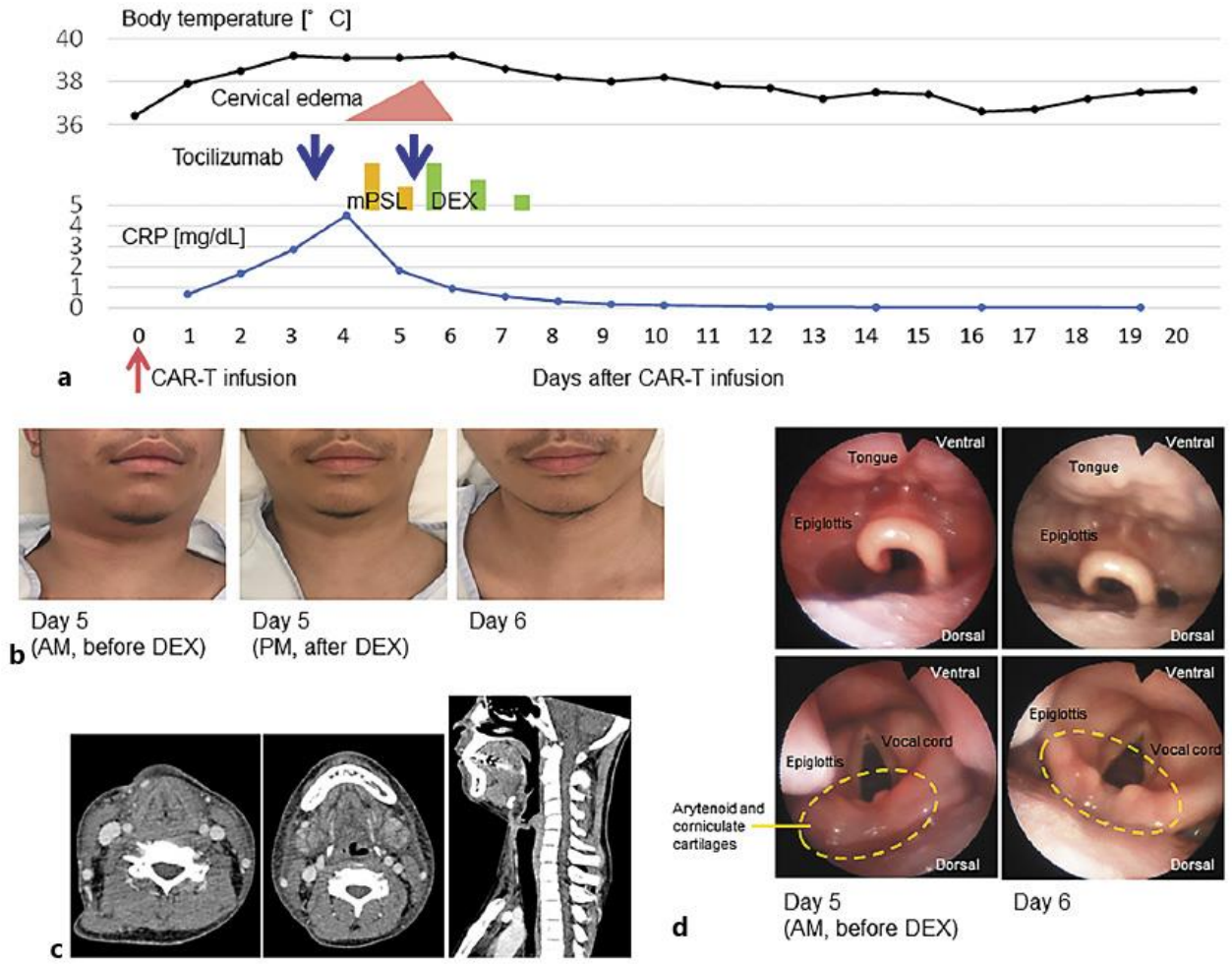
The hallmark presenting sign of CRS is fever that occurs after infusion of immune effector cells

Organ System	Symptoms and Findings Can Include
Constitutional	Fever ± rigors, malaise, fatigue, anorexia, myalgias, arthralgias, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late),
Coagulation	Elevated D-dimer, hypofibrinogenemia ± bleeding, disseminated intravascular coagulation
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Headache, mental status changes, confusion, delirium, word-finding difficulty or frank aphasia, hallucinations, tremor, altered gait, seizures

Lee DW, Gardner R, Porter DL, et al. *Blood*. 2014;124(2):188-195.

Cervical Edema as Local Cytokine Release Syndrome

--Cervical Edema Extending to the Larynx as Local Cytokine Release Syndrome Following Chimeric Antigen Receptor T-Cell Therapy in a Boy with Refractory Acute Lymphoblastic Leukemia



Case Rep Oncol. 2022;15(1):257-262. doi:10.1159/000522669

Cervical Edema as Local Cytokine Release Syndrome

-- Cervical Local Cytokine Release Syndrome Following Chimeric Antigen Receptor T-cell Therapy in Patients With Relapsed or Refractory Diffuse Large B-cell Lymphoma

A. At the emergence of local cytokine release syndrome (CRS) on day five post-CAR-T cell infusion.
B. After the resolution of local CRS.

CAR-T輸注後第五天　　CAR-T輸注後第八天緩解

Cureus. 2023 May 11;15(5):e38905. doi: 10.7759/cureus.38905

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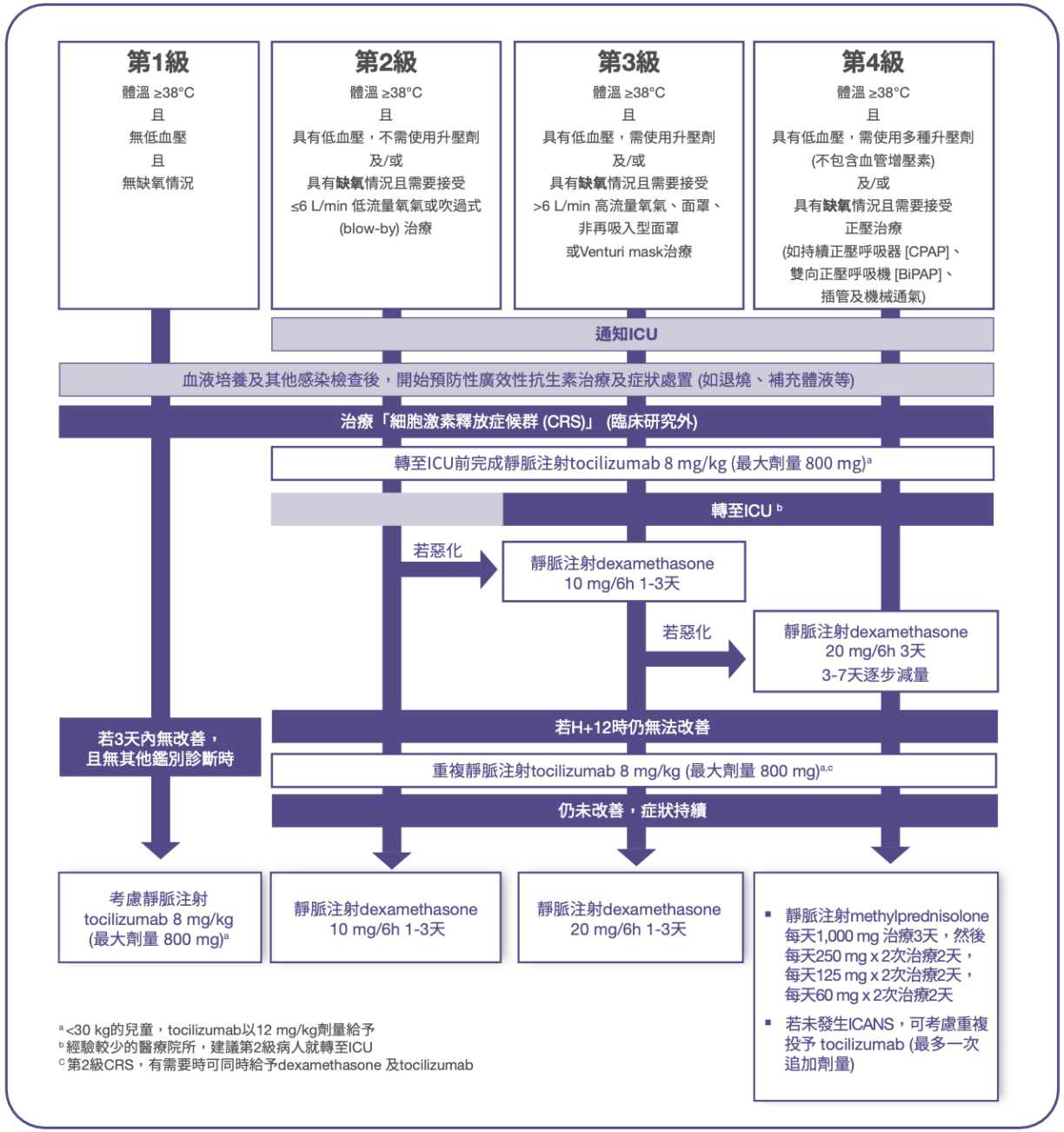
CRS	Grade 2; D+2 - D+4 Fever, hypotension, Cervical edema	Grade 1; D+3-D+7 Cervical edema	Grade 1; D+4-D+5 Fever	Grade 1; D+2-D+10 Fever, Cervical edema	Grade 1; D+2-D+6 Fever, , cervical and facial edema	Grade 1; D+2-D+7 Fever, cervical and facial edema
CRS manage ment	One dose of tocilizumab on D+3	Three doses of tocilizumab On D+3, 4, 7		• Four doses of tocilizumab on D+2,4,6,10	Three doses of tocilizumab on D+2,3,6	• Five doses of tocilizumab on D+2,3,4 • 2 doses of dexamethasone on D5,7

圖四、CRS之分級及處置流程 [8]



[a] <30 kg的兒童，tocilizumab以12 mg/kg劑量給予
[b] 經驗較少的醫療院所，建議第2級病人就轉至ICU
[c] 第2級CRS，有需要時可同時給予dexamethasone 及tocilizumab

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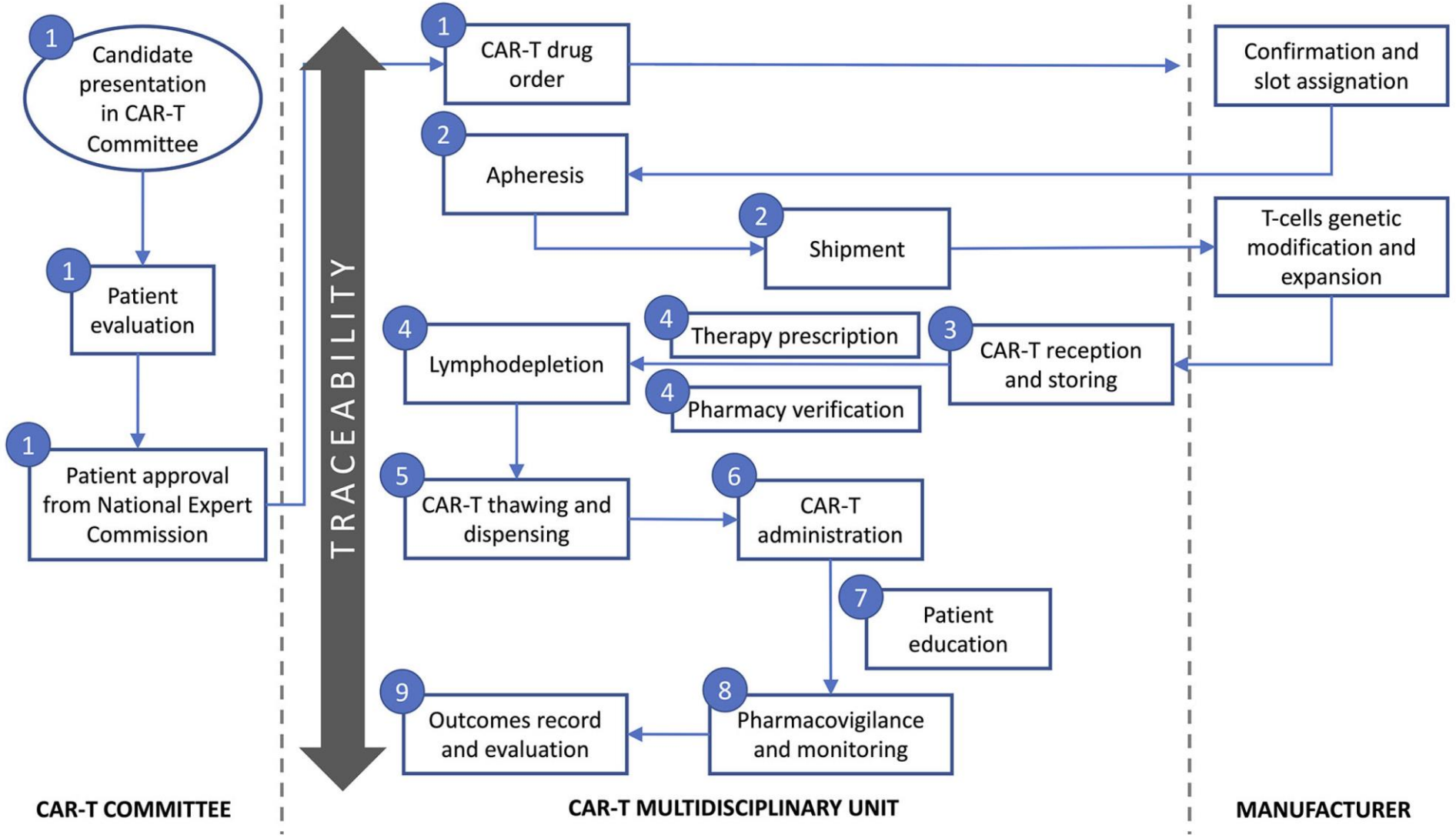
Disease	R/R DLBCL	R/R DLBCL	R/R ALL	R/R ALL	R/R DLBCL	R/R DLBCL
ICANS						
Cytopenia	ANC on D+27, platelet on D+35; G-CSF, eltrombobag support	ANC on D+15, platelet on D+10	ANC on D+10 Persisted thrombocytopenia, eltrombobag support	ANC on D+44, platelet on D+33 G-CSF, transfusion support	ANC on D+7	ANC on D+6
Hypogamma globulinemia	IVIG support	IVIG support			IVIG support	
Disease status	Relapse refractory Currently on Epcoritamab +Polatuzumab	CR	MRD (-)	Relapse on D+57	CR	

ICANS:Immune Effector Cell-associated Neurotoxicity Syndrome

P.J. Hayden, et al. Ann Oncol. 2022; 33(3):259-275

CAR-T治療流程仰賴多專科的合作



細胞治療中心

血液腫瘤科

藥學部

檢驗醫學科

Marzal-Alfaro MB, et al. *Front Oncol* 2021; 11: 636068

- 建立藥品檔案資訊、制定品管流程
- 確認病人臨床狀況與用藥合適性

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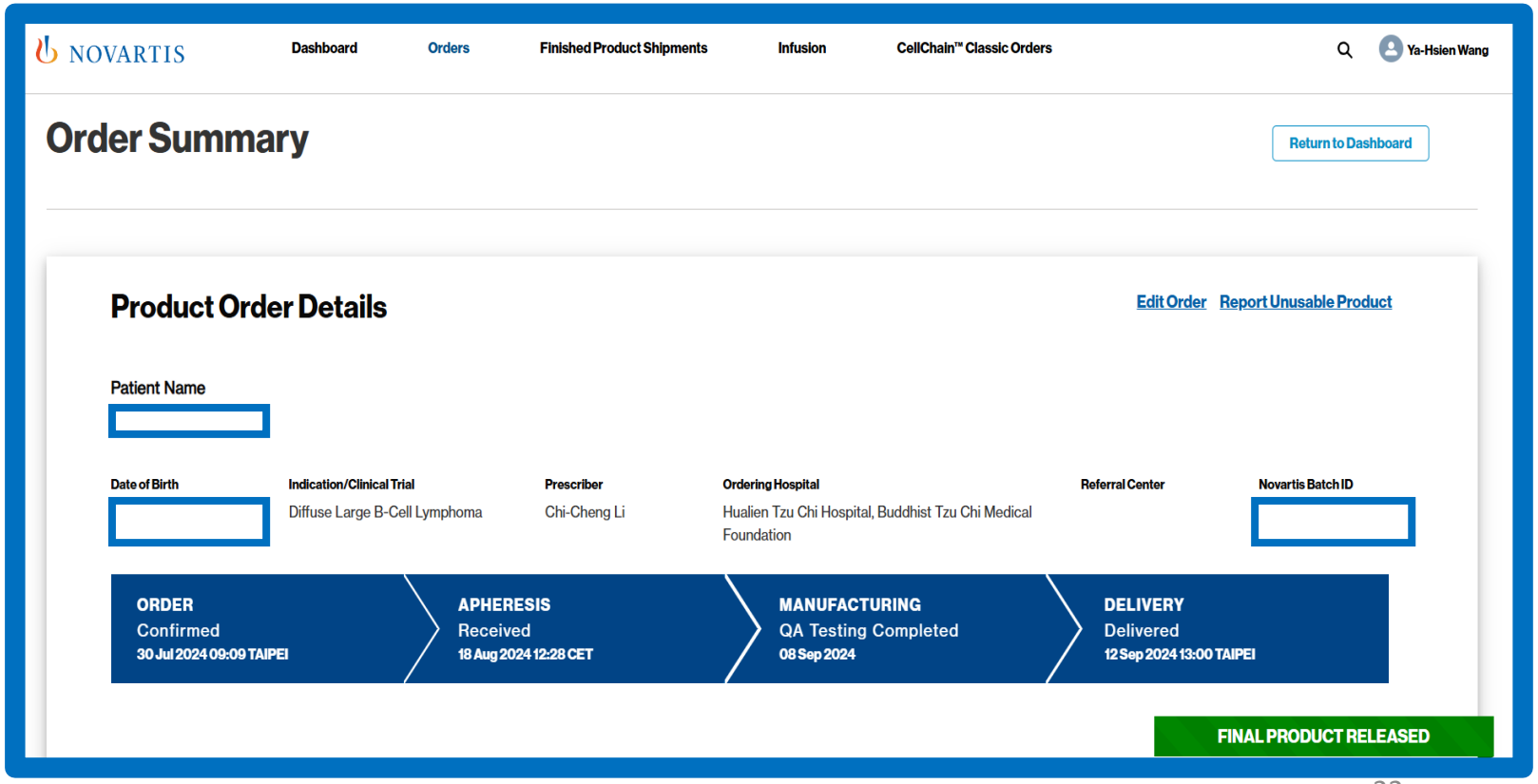
- 協助訂購藥品

透過Cell Chain追蹤進度



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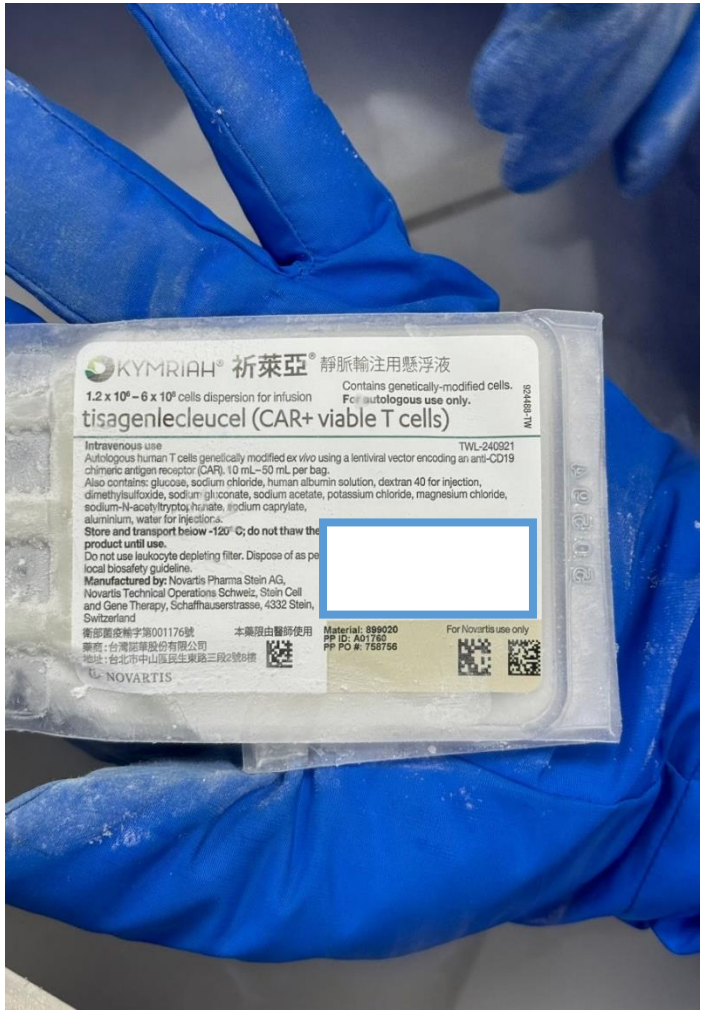
- 訂藥與製劑驗收 (核對資訊、COA)

藥品入庫與驗收



NOVARTIS

Manufacturing Site :
Novartis Pharma Stein AG
Cell and Gene Therapies
Schaffhauserstrasse 101
4332 Stein AG
Switzerland
Manufacturing licence no.: 511177-102709490
GMP certificate no.: GMP-CH-1005628

CERTIFICATE OF ANALYSIS

Batch Number: NTR7K9A

Product Name:	CTL019 tisagenlecleucel autologous T-cell suspension in Infusion bag		
Indication:	DLBCL		
PP Material Number:	899020		
FP Material Number:	768304		
LIMS ID:	20,456	**Specification:**	DP_8007488_001_R_22
		LIMS Specification Version:	v 47
Country of Destination:	TAIWAN	***Condition of storage*:**	≤ -120°C in vapor of LN2
Manufacturing Date:	20-Aug-2024		
Expiration Date:	20-May-2025		
Number of bag(s) per dose:	1 Bag(s) per Dose		

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- 確認病患治療流程、治療用藥庫存

(1) General and prophylactic order

On BMT routine
On Port-A with care
Avoid choking (due to XRT side effect), bed elevation 床頭搖高
Pain control with morphine and mouth care, for tongue/ oral ulcers

General medications:
Morphine Sulfate (15 mg) 1# TID
Morphine 5 mg SC q4h prn if oral pain
Sennoside 2# HS
Lactulose 20 cc prn if constipation

- Anti-microbial prophylaxis
  - Valaciclovir (Valtrex) 500mg 1# QD PO, to D+365 or CD4 > 200/μL
  - Baktar (SMX-TMP) 1# QD PO, to D+365 or CD4 count > 200/μL
  - Tenofovir alafenamide (Vemlidy) 25mg 1# QD PO, to D+365
- TLS prevention (if high tumor burden): not applicable
- Seizure prophylaxis (if history of CNS disease or seizure): not applicable

(2) Lymphodepleting chemotherapy order

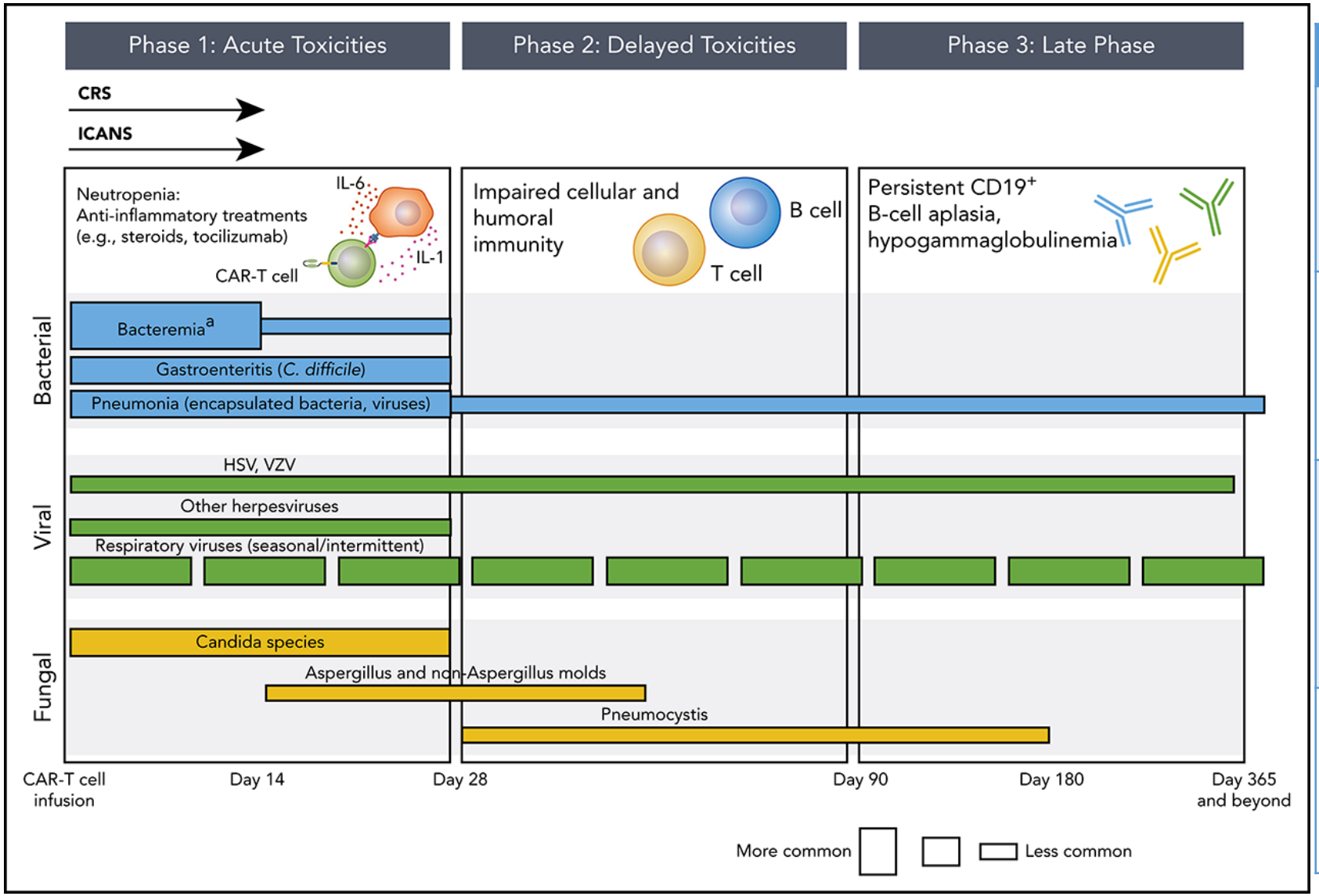
148.4 cm / 50.1 kg (adjusted BSA 1.42 m^2)

- **Regimen: FLU 25 mg/m^2/day + CYC 250 mg/m^2/d on D-5~D-3**
  - Fludarabine **35 mg** in NS 100ml IVD 30min, QD on D-5~D-3 (10/19~10/21)
  - Cyclophosphamide **350 mg** in NS 100ml IVD 30min, QD D-5~D-3 (10/19~10/21)
- Antiemetics (moderate risk)
  - **Aloxi (Palonosetron, 0.25mg) 1amp** IVD 30min before chemotherapy, QOD on D-5 and D-3 (10/19,10/21)
  - Metoclopramide 10mg 1amp IV TID on D-5 to D-3 (10/19~10/21)
- Hydration: 2.5% GS (Suntose) 1500ml QD on D-5~D0 (10/19~10/24)

(3) CAR-T cell infusion

D0 (2024/10/24)

- Dose: **3.8 x10^8** total CAR+ viable T cells, **19 ml**
- Pre-medications:
  - **Acetaminophen 500mg 1# PO** 30-60 min before CAR-T infusion



EBMT/EHA recommendation
Bacterial— Not routinely recommended. Levofloxacin or ciprofloxacin during neutropenia
Viral-- Acyclovir 800 mg BID or valacyclovir 500 mg BID for 1 year after CART infusion or CD4 count > 200/µL
Fungal— Not routinely recommended. Can be consider in patients with severe or prolonged neutropenia and on corticosteroids.
PJP— Co-trimoxazole 480 mg PO QD for 1 year after CART infusion or CD4 count > 200/µL

Blood. 2020 Aug 20;136(8):925-935.
P.J. Hayden, et al. Ann Oncol. 2022; 33(3):259-275

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- 確認病患治療流程、治療用藥庫存
- 確認解凍方式、協助給藥

花蓮

佛教慈濟醫療財團法人花蓮慈濟醫院
Hualien Tzu Chi Hospital,Buddhist Tzu Chi Medical Foundation

針劑

女

領藥號 Prescription No. 1-1

BM-01

0000537

藥名 年齡:61/4 體重:48.4 Kg 醫師:李啟誠 操作員(專):游畿嘉 總量 113/10/24 10:07

Medication 藥品名稱 用量 頻率 途徑 開藥日 儲位 包數 Quantity 總量

*1 I Tisagenlecleucel (CAR + viable T Cells) (Kymriah)
1 set ST IV 10241001
10241001 - 10241001

1 set

藥品外觀 Appearance 注意事項：D0=2024/10/24, 3.8*10(8) CAR+ viable T cell, 19ml / 注射/輸液袋 /

用法用量 Administration and Dosage

42899220

主要用途 Clinical Uses B細胞急性淋巴性白血病

注意事項及警語 Instructions & Warning [請冷藏]120℃保存/運送，解凍後30分鐘內輸注完畢

批號

【自費藥

處方期限 Use Before

CRE 1131023 :0.46(0.60-1.20 mg/dL)
eGFR 1131023 : 146.78
202.80 Other lymphomas unspecified site

調劑日期 Date Dispensed

藥物過敏史:

處方醫師 Physician

調劑藥師 Pharmacist

早上 Morning | 中午 Noon | 晚上 Night | 睡前 Bedtime | 飯前 Before meals | 飯後 After meals

花蓮市中央路三段707號 No.707, Sec.3, Chongyang Rd., Hualien City, Hualien County, Taiwan
代表號☎(03)8561825 藥物諮詢專線☎(03) 8574349 http:www.tzuchi.com.tw
正當使用合法藥物，造成嚴重疾病（住院）、障礙或死亡，得申請藥害救濟。財團法人藥害救濟基金會☎:(02) 23584097
If any serious diseases (hospitalization), disability, or death occurred under the proper use of medication, The Drug Relief fundation can be applied, Taiwan Drug Relief Foundation at (02)2358-4097

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- 確認病患治療流程、治療用藥庫存
- 確認解凍方式、協助給藥
- 安全監測、急救藥物預備

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- 不良反應通報

衛生福利部 藥品不良反應通報表 僅供藥商部內部使用

郵寄地址:100 台北市中正區愛國東路 22 號 10 樓
傳真: (02)2358-4100
通報網址: http://adr.fda.gov.tw
電子信箱: adr@tdrf.org.tw

個案編號（由通報中心填寫）:

- 綠底為必填欄位
- 接種日期請填入 YYYY(年)/ MM(月)/ DD(日)。

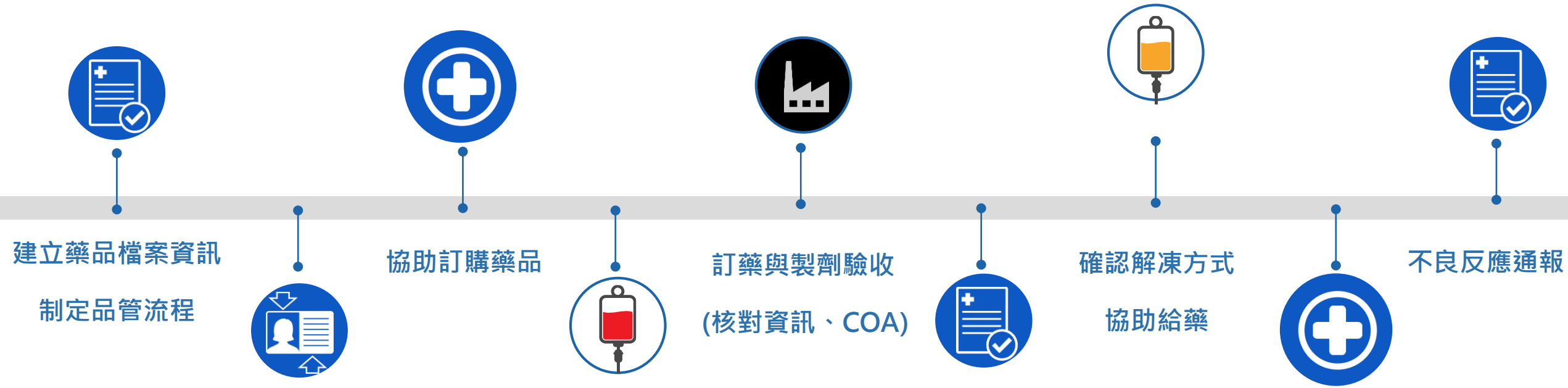
通報者資料	通報者姓名	王雅賢		
	電話	03-8561825 #13097	電子郵件信箱	a2200184@gmail.com
	通報人員身份	□醫師 ■藥師 □其他醫療人員 □廠商 □民眾 □其他		
	服務機構名稱	花蓮慈濟醫院		
	服務機構地址	花蓮市中央路三段 707 號		
	獲知藥品不良反應日期	2023 年 5 月 19 日 (請填西元年)		
	獲知藥品不良反應來源	□醫師 ■藥師 □其他醫療人員(姓名) □廠商 □民眾 □其他 □文獻，文獻名稱: (請記錄訊息來源者姓名)		

※註：若通報人員身分為民眾，則無須填寫服務機構名稱；服務機構地址請改為填寫聯絡地址。

病人資料	識別代號：	tz-112036		原通報單位識別代號：	tz-112036	
	性別	■男 □女	體重	72.2(公斤)	身高	170(公分)
	出生日期(或年齡)	1969 年 9 月 8 日(或 53 歲)				

不良反應相關資	不良反應發生日期	(請填寫_2023_年__5__月__19__日，如無請填寫未知) (請填西元年)
	不良反應嚴重性	□死亡，日期: 年 月 日，死亡原因：_____ □危及生命 □造成永久性殘疾 □胎兒先天性畸形 □導致病人住院或延長病人住院時間 ■其他具重要臨床意義之情況 □非嚴重
		(請依案件發生前後時序填寫，應包括使用藥物治療之疾病/症狀、用藥後發生不良反應之時間及部位、症狀、嚴重程度及處置。) 不良反應症狀: Grade 2 細胞激素釋放症候群（cytokine release syndrome, CRS）

藥師可參與的部分



The EBMT/EHA CAR-T Cell Handbook: Chapter 41 Role of Pharmacists

感恩聆聽