

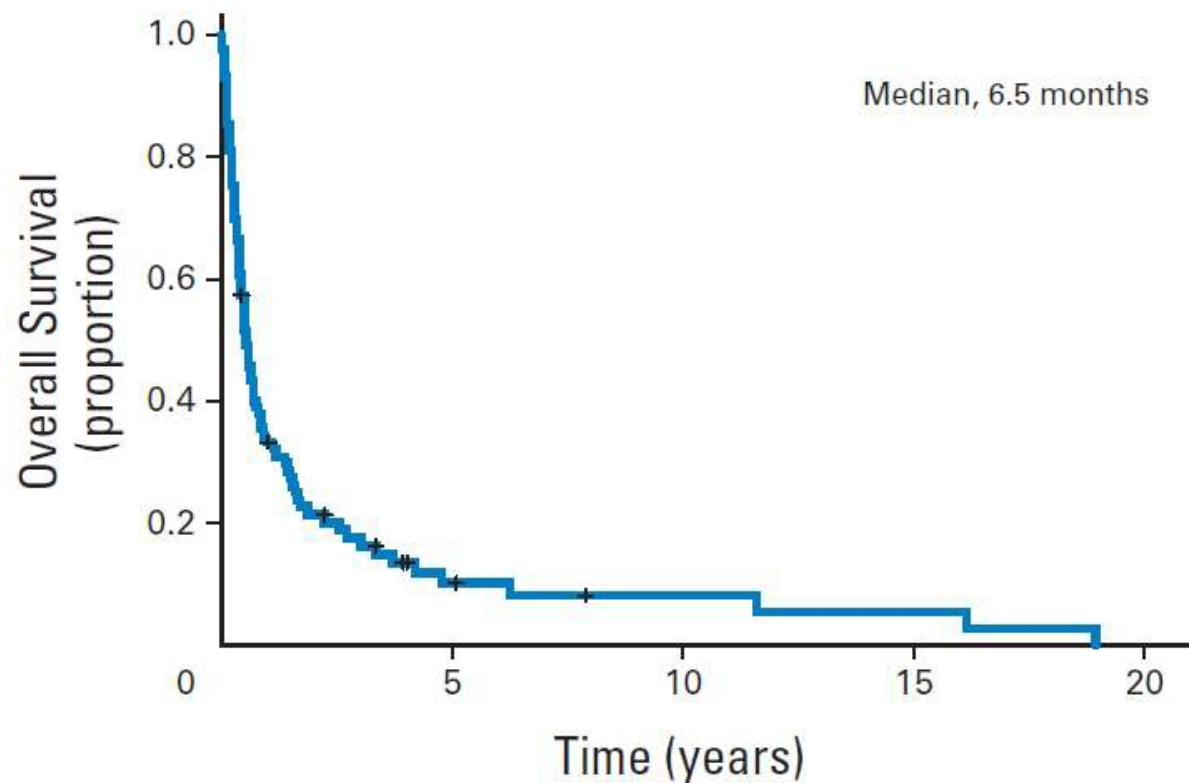
Relapsed-refractory T-cell lymphomas

Dr Chong Lip Leong

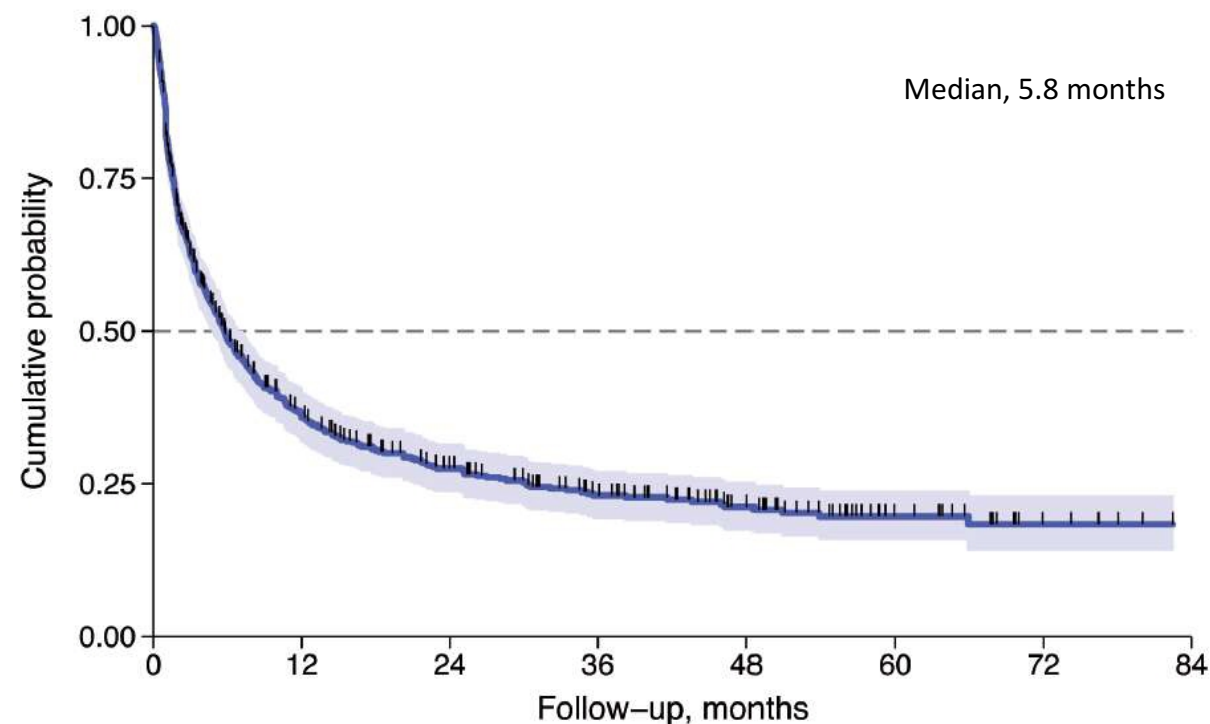
Consultant, Dept of Haematology TTSH

Poor outcome in relapsed / refractory PTCLs

BCCA cohort (1976 – 2010)¹



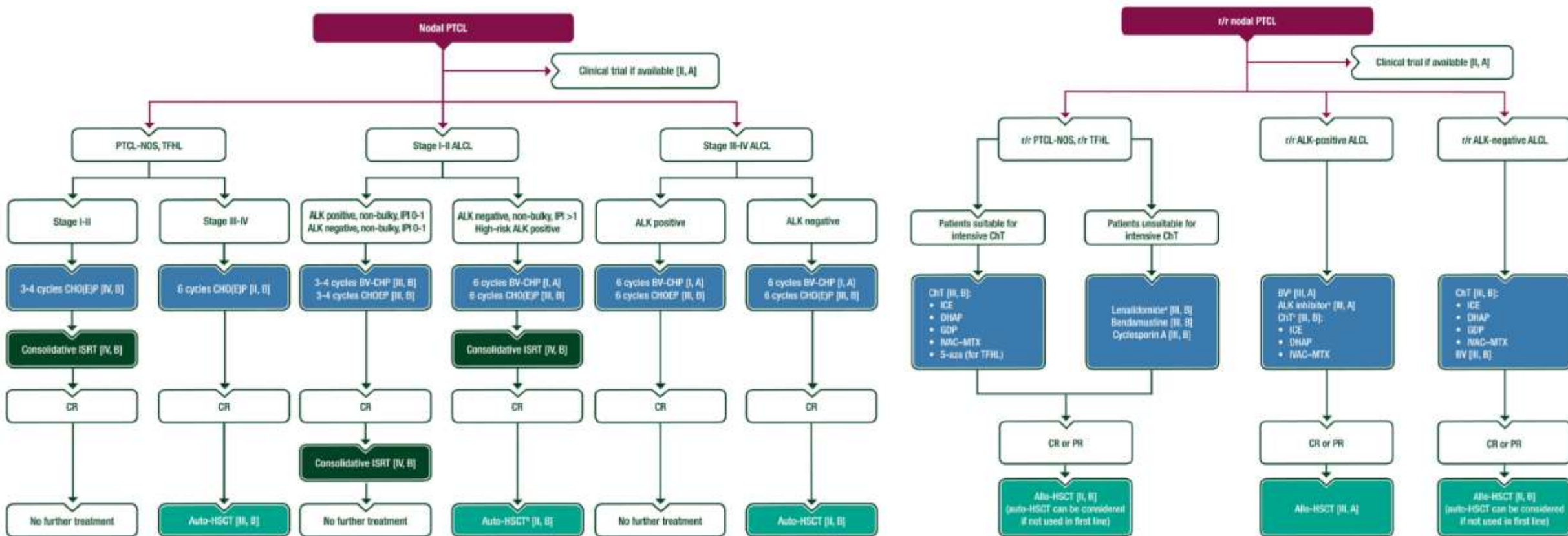
Intl T-cell project (2006 – 2016)²



¹Mak V et al. Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. *J Clin Oncol* 2013;31(16):1970-6.

²Bellei M et al. The outcome of peripheral T-cell lymphoma patients failing first-line therapy: a report from the prospective, International T-Cell Project. *Haematologica* 2018;103(7):1191-1197.

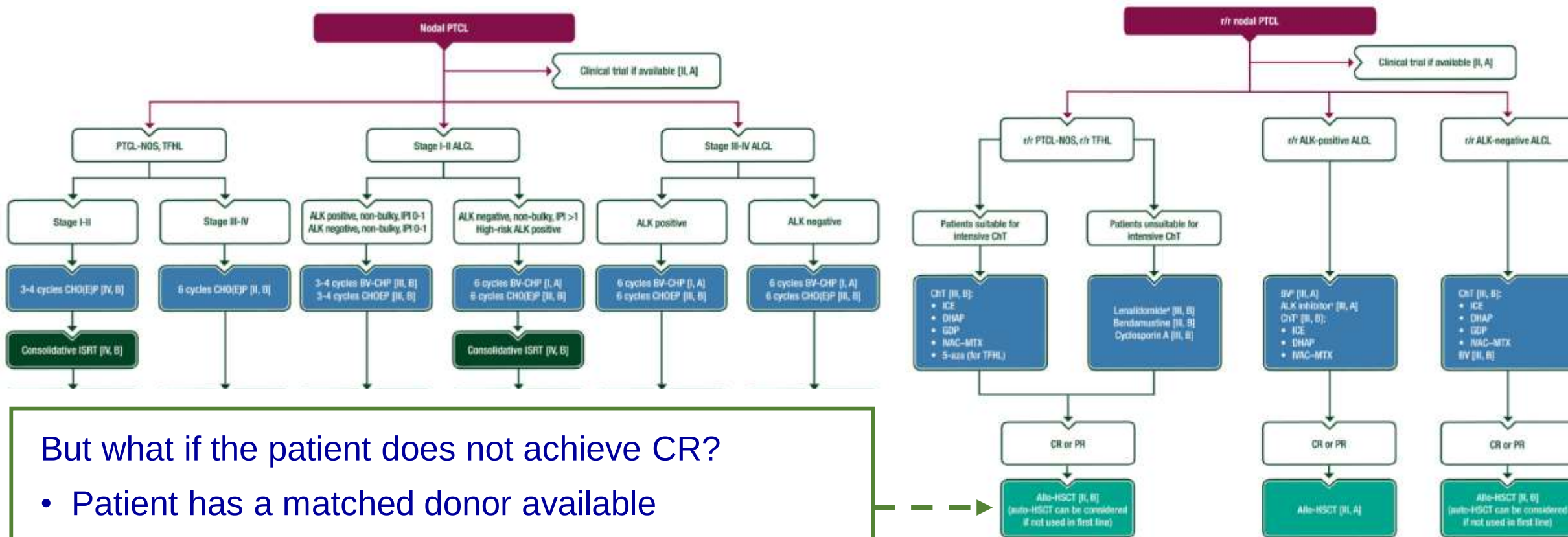
EHA-ESMO 2025 guidelines for nodal PTCL, TFHL and ALCL



¹d'Amore F et al. Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015;26 Suppl 5:v108-15.

²d'Amore F et al. Peripheral T- and natural killer-cell lymphomas: ESMO-EHA Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2025;36(6):626-644.

EHA-ESMO 2025: what the guidelines do not say...?



But what if the patient does not achieve CR?

- Patient has a matched donor available
- Low predicted NRM (good KPS, low HCT-CI)

*Based on expert opinion only

¹Damaj G et al. Allogeneic HCT in peripheral T-cell lymphoma: recommendations from the EBMT Practice Harmonisation and Guidelines Committee. *Lancet Haematol* 2025;12(7):e542-e554.

²Boo YL and Koh LP. Hematopoietic Stem Cell Transplantation in T Cell and Natural Killer Cell Lymphomas: Update on Recent Advances. *Transplant Cell Ther* 2021;27(7):571-588.

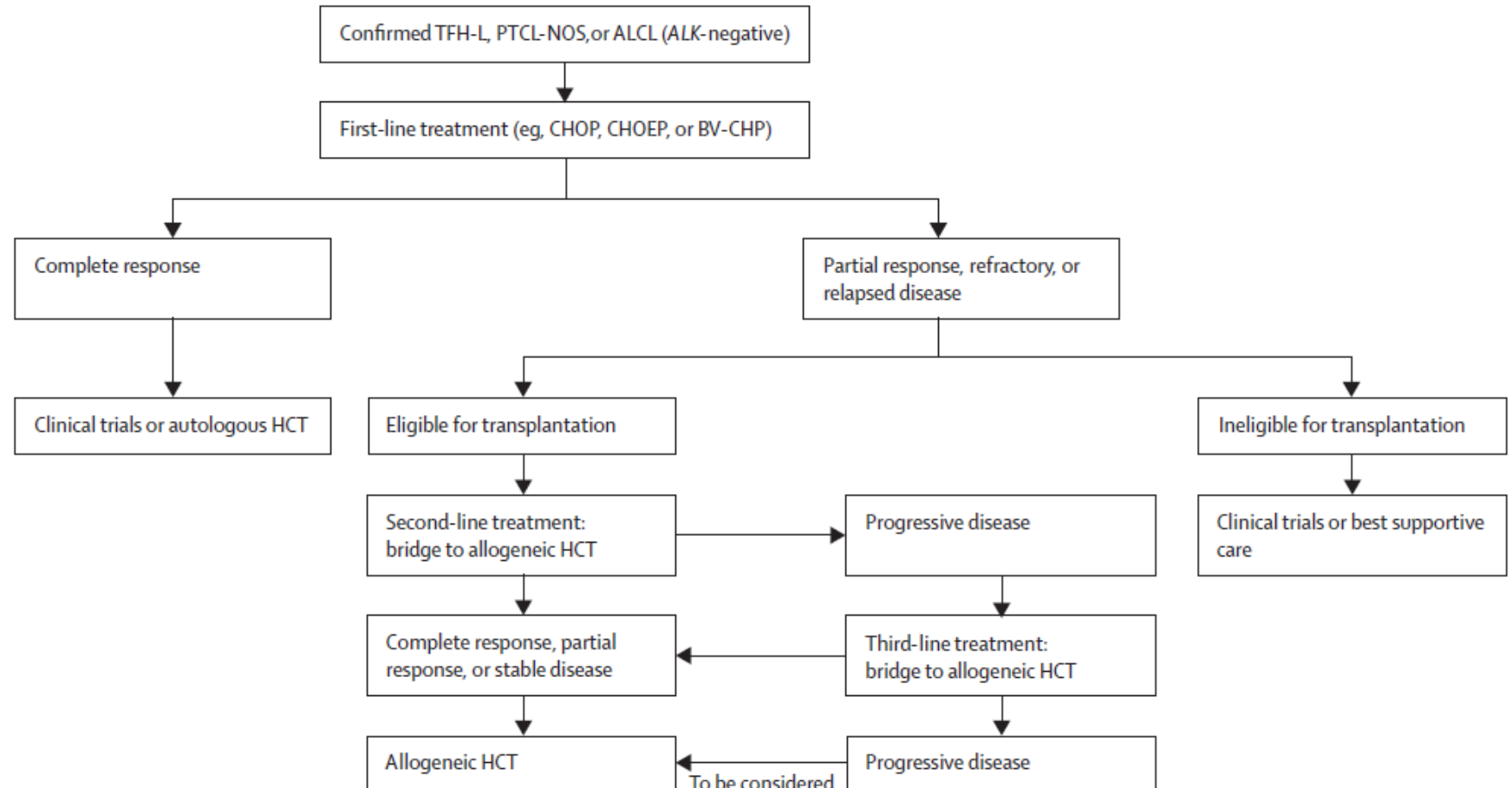
Allo-HSCT if R/R disease or failure to achieve CR1

HCT consolidation in first-line treatment (figure 1)

- Consider clinical trials whenever possible
- In transplant-eligible patients with complete metabolic response, autologous HCT consolidation should be considered
- For patients with ALK-positive anaplastic large cell lymphoma, autologous HCT is an option for those with high-risk features who have had a complete metabolic response; however, its role is challenged by BV (brentuximab vedotin) in combination with CHP (cyclophosphamide, doxorubicin, and prednisone) or CHEP (cyclophosphamide, doxorubicin, etoposide, and prednisone) regimens
- There is currently no indication for consolidative allogeneic HCT in patients in first complete response
- For patients who are not in complete response, treatment should be regarded a failure and allogeneic HCT should be considered

Patients with refractory or relapsed peripheral T-cell lymphoma

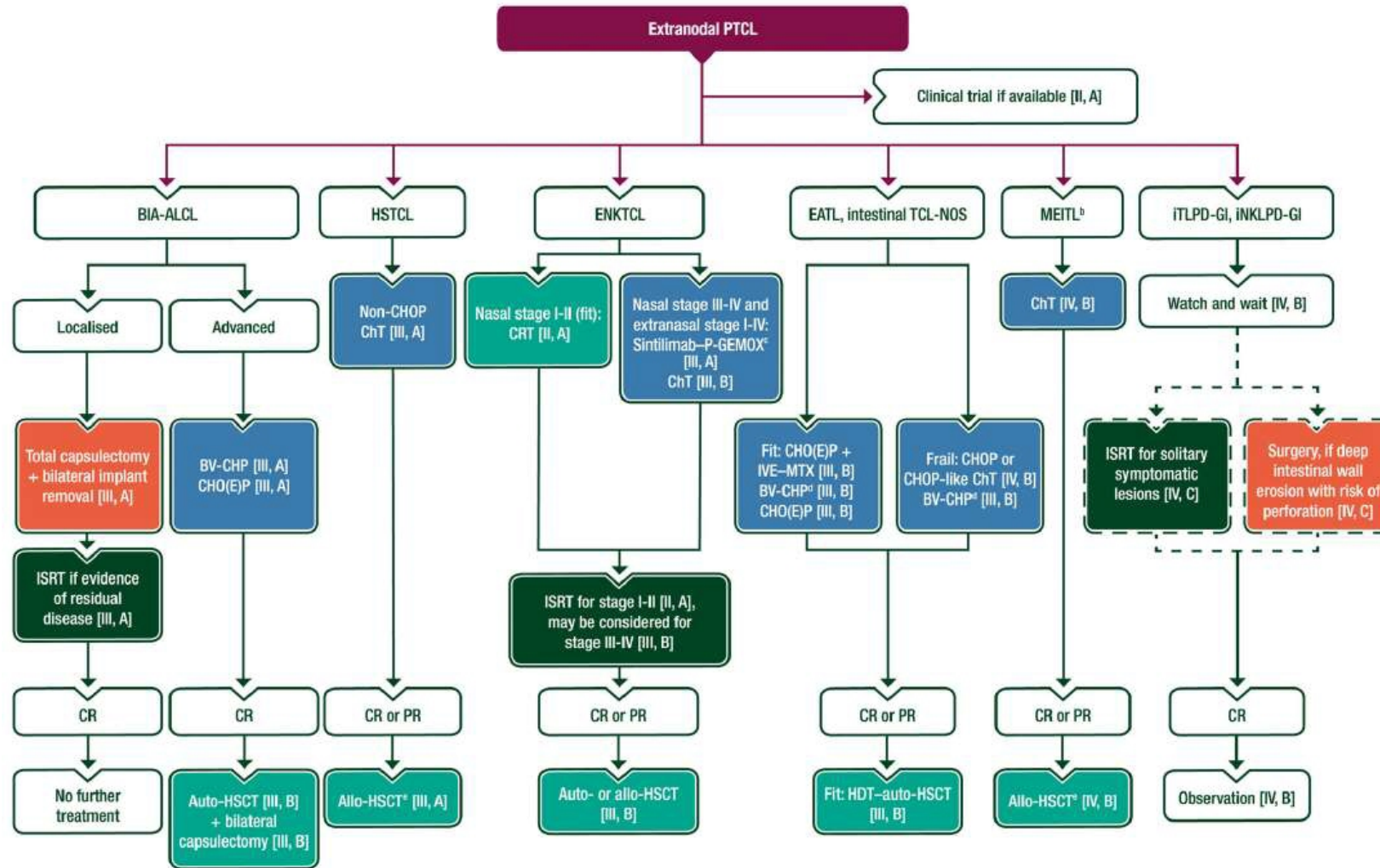
- Allogeneic HCT is the treatment of choice in all eligible patients:
 - With insufficient response or refractory to first-line therapy
 - With relapsed disease after first complete response regardless of prior treatment, including autologous HCT
- In allogeneic HCT ineligible patients, autologous HCT might be considered in those patients who have relapsed disease after first complete response and have reached another metabolic complete response



¹Damaj G et al. Allogeneic HCT in peripheral T-cell lymphoma: recommendations from the EBMT Practice Harmonisation and Guidelines Committee. *Lancet Haematol* 2025;12(7):e542-e554.

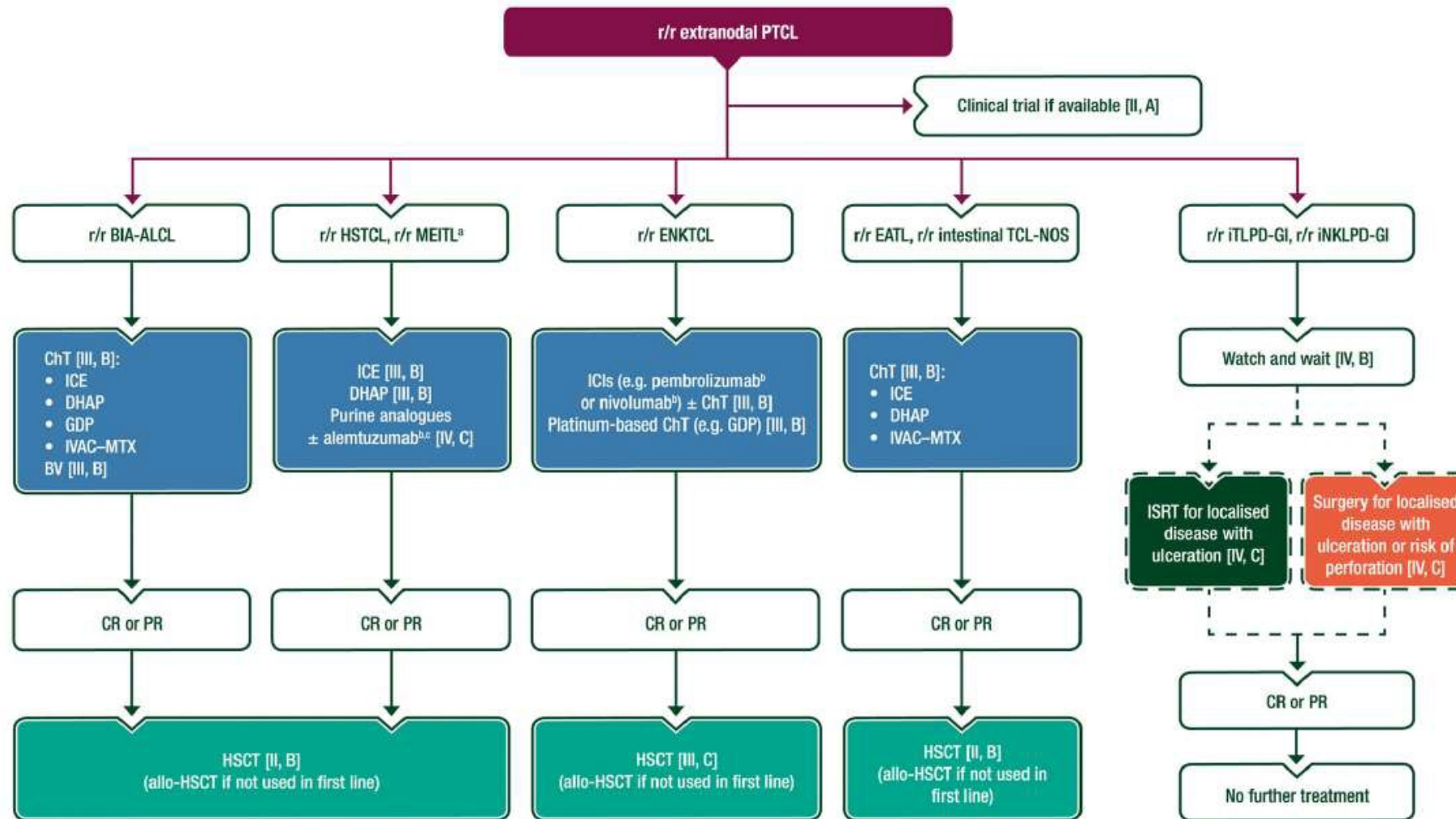
²Boo YL and Koh LP. Hematopoietic Stem Cell Transplantation in T Cell and Natural Killer Cell Lymphomas: Update on Recent Advances. *Transplant Cell Ther* 2021;27(7):571-588.

It is important to get it right the first time



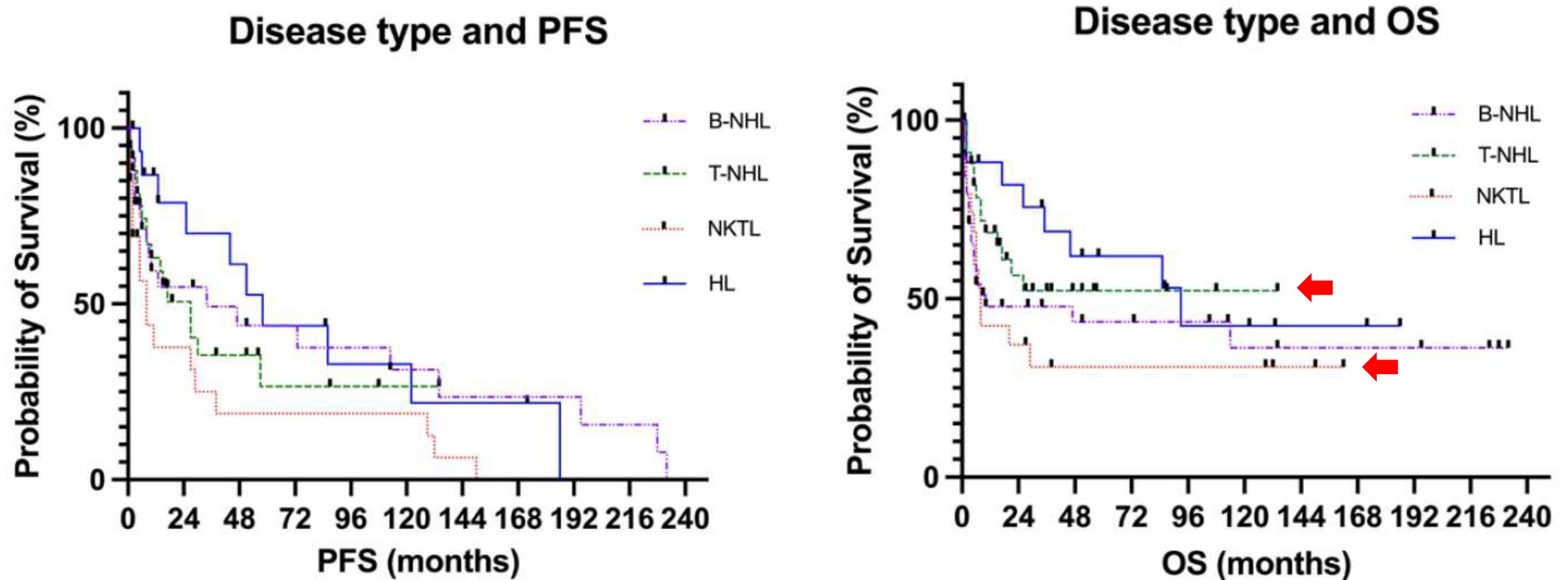
¹d'Amore F et al. Peripheral T- and natural killer-cell lymphomas: ESMO-EHA Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2025;36(6):626-644.

R/R disease: every path leads to allo-HSCT (provided fit)



¹d'Amore F et al. Peripheral T- and natural killer-cell lymphomas: ESMO-EHA Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2025;36(6):626-644.

Allo-HSCT can cure some patients with R/R lymphomas



¹Loke WSJ et al. Long-term survival and clinical implications of allogeneic SCT in relapse/refractory lymphoma: A 20-year Singapore experience. *Ann Acad Med Singap* 2024;54(1):5-16.

Second line therapy for PTCL

SECOND-LINE THERAPY AND SUBSEQUENT THERAPY (INTENTION TO PROCEED TO TRANSPLANT)

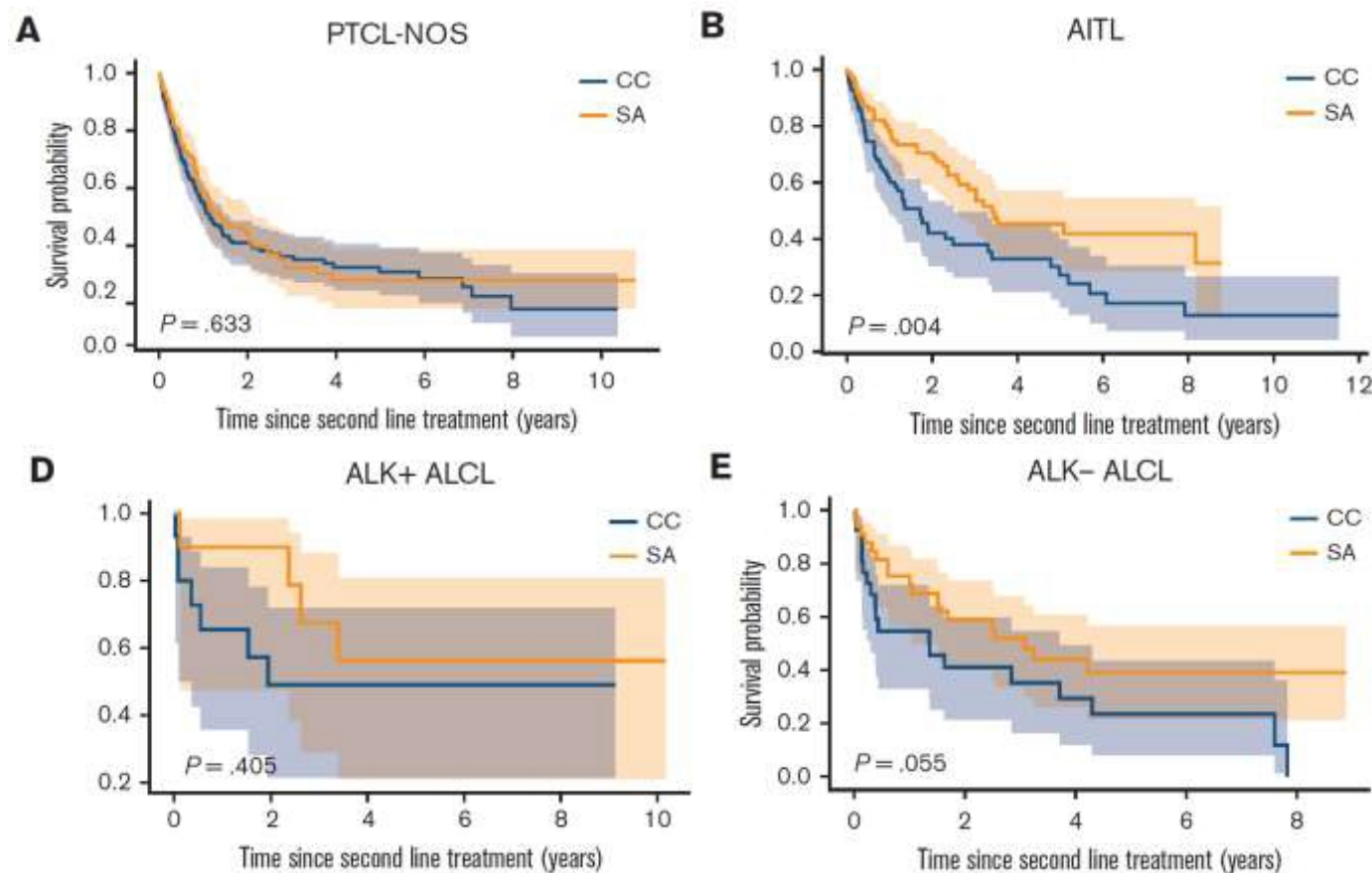
Preferred regimens (regimens in alphabetical order)

- Clinical trial
- Single agents (alphabetical order)
 - ▶ Belinostat
 - ▶ Brentuximab vedotin for CD30+ PTCL^{e,h}
 - ▶ Duvelisib^{e,j}
 - ▶ Pralatrexate
 - ▶ Romidepsin
- Combination regimens (alphabetical order)
 - ▶ DHA (dexamethasone and cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin)
 - ▶ ESHA (etoposide, methylprednisolone, and cytarabine) + platinum (cisplatin or oxaliplatin)
 - ▶ GDP (gemcitabine, dexamethasone, and cisplatin)
 - ▶ GemOx (gemcitabine and oxaliplatin)
 - ▶ ICE (ifosfamide, carboplatin, and etoposide)

Other recommended regimens (alphabetical order by category)

- Single agents
 - ▶ Bendamustine^e
 - ▶ Gemcitabine
 - ▶ Lenalidomide^e
 - ▶ Ruxolitinib (category 2B)
- Combination regimens
 - ▶ Duvelisib^e and romidepsin
 - ▶ GVD (gemcitabine, vinorelbine, and liposomal doxorubicin)^q
 - ▶ Brentuximab vedotin and bendamustine for CD30+ PTCL^{e,h} (category 2B)

Global PETAL consortium (n = 1240)²



¹NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for T-cell Lymphomas V.2.2025.

²Han JX et al. Global outcomes and prognosis for relapsed/refractory mature T-cell and NK-cell lymphomas: results from the PETAL consortium. *Blood Adv* 2025;9(3):583-602.

Second line therapy for PTCL

Table 3. Approved novel agents for the treatment of relapsed/refractory peripheral T-cell lymphomas: global perspective.

Agent	Type of agent	Study phase	Country approval	PTCL subtype(s)	ORR/CR %	Median DoR in months	Median PFS in months	Median OS in months
Pralatrexate ⁵¹	DHFR inhibitor	II	USA/Canada	PTCL/tMF	29/11	10.1	3.5	14.5
Brentuximab vedotin ⁶⁶	ADC CD30	II	Global	ALCL	86/57	12.6 ^a	13.3	Not reached*
Romidepsin ^{50,71, b*}	HDAC inhibitor	II	USA/Canada (de-listed)	PTCL AITL	25/15 27/19	17 ^b -	4 -	11.3 -
Belinostat ⁷²	HDAC inhibitor	II	USA	PTCL AITL	26/11 45.5	13.6 -	1.6 -	7.9 -
Chidamide ⁷³	HDAC inhibitor	II	China	PTCL AITL	28/14 50/40	9.9	2.1	21.4
Forodesine ¹¹³	PNP inhibitor	II	Japan	PTCL	25/10	10.4	1.9	15.6
Mogamulizumab ^{114,c}	CCR4 antibody	II	Japan	CCR4 ⁺ PTCL ^c (2014)	34/17	NR	2.0	14.2
Crizotinib ⁶⁷	ALK inhibitor	II	USA 1-21 yr	ALK ⁺ ALCL	88/81	NR	NR	NR

Singapore

X

ALCL, CTCL

No subsidy

X

X

X

X

No subsidy

¹Ngu HS and Savage KJ. Past, present and future therapeutic approaches in nodal peripheral T-cell lymphomas. *Haematologica* 2023;108(12):3211-3226.

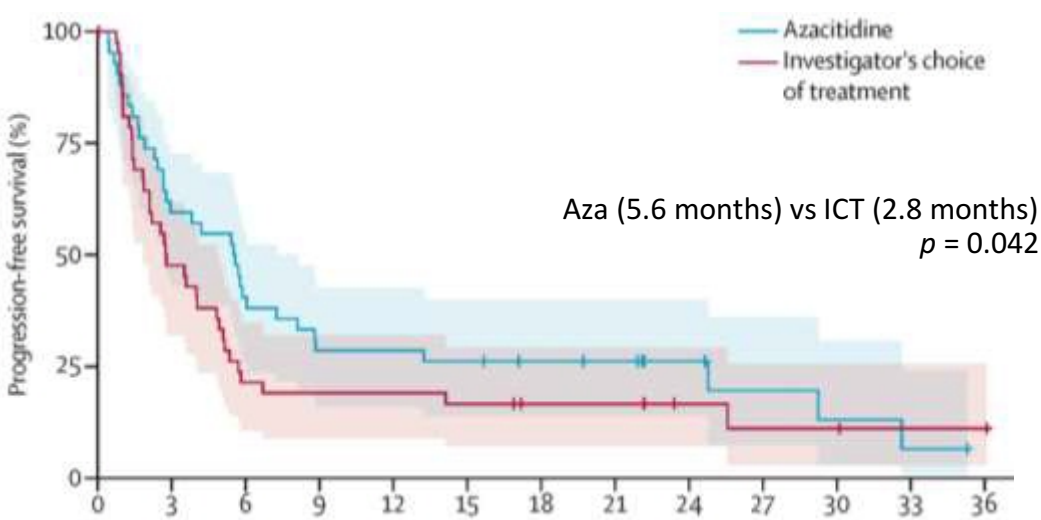
²Singapore Cancer Drug List: <https://www.moh.gov.sg/managing-expenses/schemes-and-subsidies/medishield-life/cancer-drug-list/>

Second line therapy for nodal TFH lymphomas

Table 4. Selected novel agent/combination therapy in relapsed/refractory peripheral T-cell lymphomas.

Agents Study	Target	Phase	PTCL subtype (N)	ORR/CR %	Median DoR in months	Median PFS in months
Alisertib ⁸⁹ vs. Investigators' choice ^a Lumiere	Aurora kinase	III	PTCL (271 total) ^c	33/18 45/27	7.4 5.6	3.8 3.5
Lenalidomide ⁸²	Immunomodulatory Anti-angiogenic	II	PTCL (54) AITL (26)	22/11 31/15	3.6 3.5	2.5 4.6
Duvelisib ⁸⁹	PI3K $\gamma\delta$	II	PTCL (78) AITL (21)	50/32 67/48	7.8 NR	3.6 NR
Cerdulatinib ⁹¹	Dual JAK/SYK	II	PTCL (65) TFHL (29)	35 52	NR 12.9	NR 4.6
Ruxolitinib ⁴⁹	JAK1/2	II	PTCL (53)	25	8.4	2.8
			Cohort 1 JAK/STAT ⁺	33	7.5	NR
			Cohort 2 pSTAT3 ⁺	29	14.7	NR
			Cohort 3 unselected	12	Not reached	NR
Golidocitinib JAKPOT8 ⁹²	JAK1	I/II	PTCL (51) AITL (20)	43/22 60	Not reached	NR
Tipifarnib ⁹⁰	Farnesyltransferase	II	CXCL12 3'UTR (12) AITL (11) ^d	42/25 45/27	NR NR	NR
Azacitidine ⁷⁶ vs. Investigators' choice ^b ORACLE	DNMT1	III	TFHL (86 total)	33/12 43/23	NR NR	5.6* 2.8
Valemetostat ⁷⁸	EZH2	I	PTCL (45) AITL	56/24 70.6	NR NR	NR NR
Combination therapies						
Romidepsin + azacitidine ⁹⁵	HDAC + DNMT1	II TN/RR	PTCL (25) TFHL (15)	61/43 80/60	20.3 NR	8.0 8.9
Romidepsin + duvelisib ⁵³	HDAC + PI3K $\gamma\delta$	I	PTCL (55) TFHL (19)	58/42 68/58	8.1 NR	6.9 NR
Romidepsin + pralatrexate ¹¹⁵	HDAC + DHFR	I	PTCL (14)	71/29	NR	NR

ORACLE (oral Azacitidine vs ICT)



Single agent for TFHL (AITL)

ORR 31 – 71 %, CR 15 – 48 %

Combination therapy for TFHL (AITL)

ORR 70 – 80 %, CR 60 %

¹Ngu HS and Savage KJ. Past, present and future therapeutic approaches in nodal peripheral T-cell lymphomas. *Haematologica* 2023;108(12):3211-3226.

²Dupuis J et al. Oral azacitidine compared with standard therapy in patients with RR TFH lymphoma (ORACLE): an open-label randomised, phase 3 study. *Lancet Haematol* 2024;11(6):e406-e414.

Treatment for specific subtypes of T-cell lymphoma

Subtype	Suggested second line treatment ^{1,2}
TFHL (AITL)	Azacitidine, romidepsin*, duvelisib, or combination treatment
ALCL	If CD30+, consider brentuximab re-treatment in late relapse <u>ALK+ ALCL</u> : crizotinib, alectinib, brigatinib, ceritinib, lorlatinib
T-PLL	Alemtuzumab (if not given in first line), pentostatin
ATLL	Brentuximab (if CD30+), mogalizumab (if CCR4+), lenalidomide
ENKTL	Immune checkpoint inhibitors (eg. pembrolizumab, nivolumab)

*withdrawn from USA and Canada

¹NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for T-cell Lymphomas V.2.2025.

²d'Amore F et al. Peripheral T- and natural killer-cell lymphomas: ESMO-EHA Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2025;36(6):626-644.

POLAR: Pembrolizumab + Olaparib for R/R PTCL

Recruiting ⓘ

Pembrolizumab and Olaparib Treatment for Relapsed or Refractory Peripheral T-Cell Lymphoma (POLAR)

ClinicalTrials.gov ID ⓘ NCT06160843

Sponsor ⓘ National Cancer Centre, Singapore

Information provided by ⓘ National Cancer Centre, Singapore (Responsible Party)

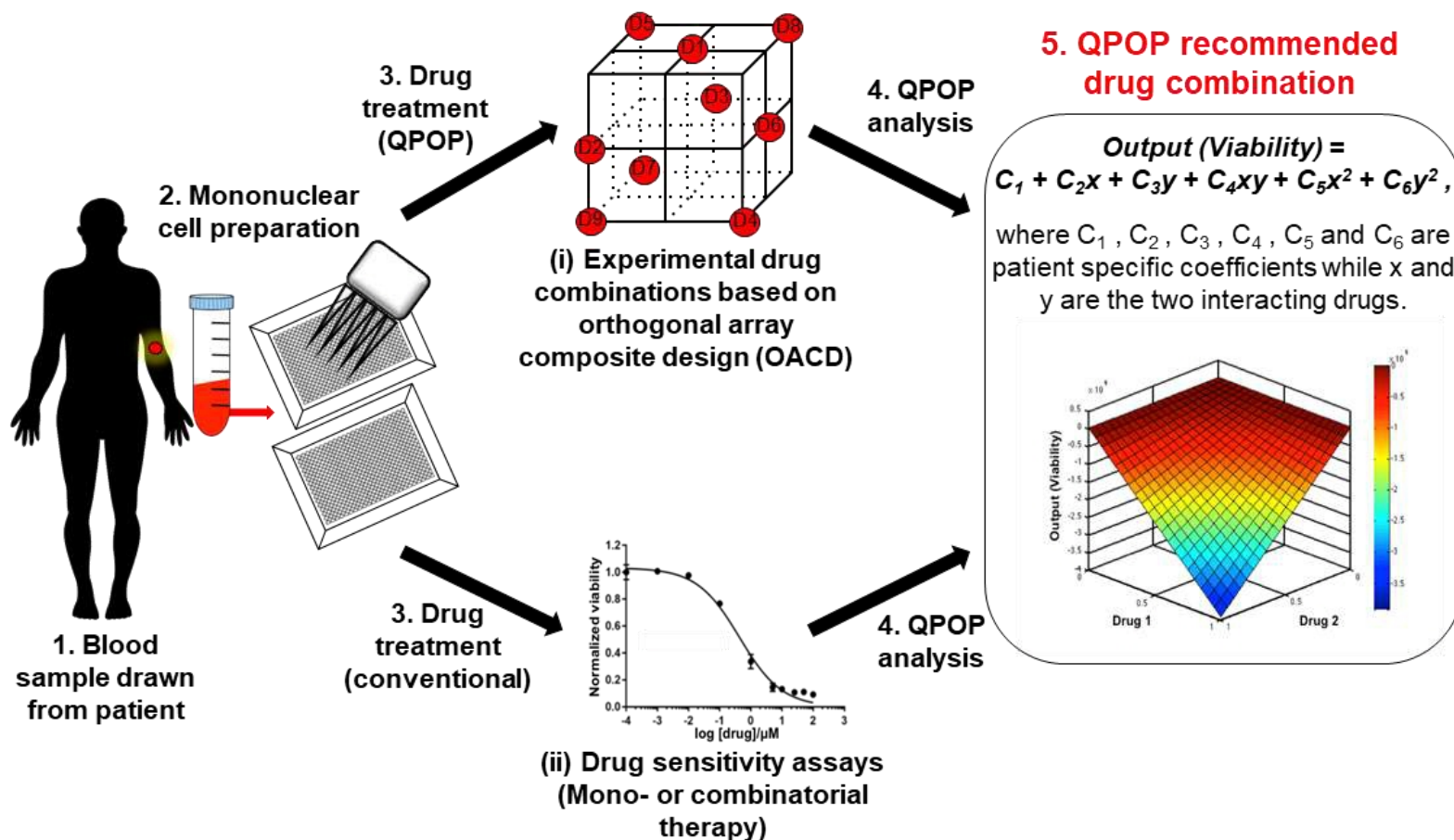
Last Update Posted ⓘ 2024-07-03

- IV Pembrolizumab 200 mg every 3 weeks
- PO Olaparib 300 mg bd
- Continue until disease progression, or unacceptable toxicity, up to 35 cycles

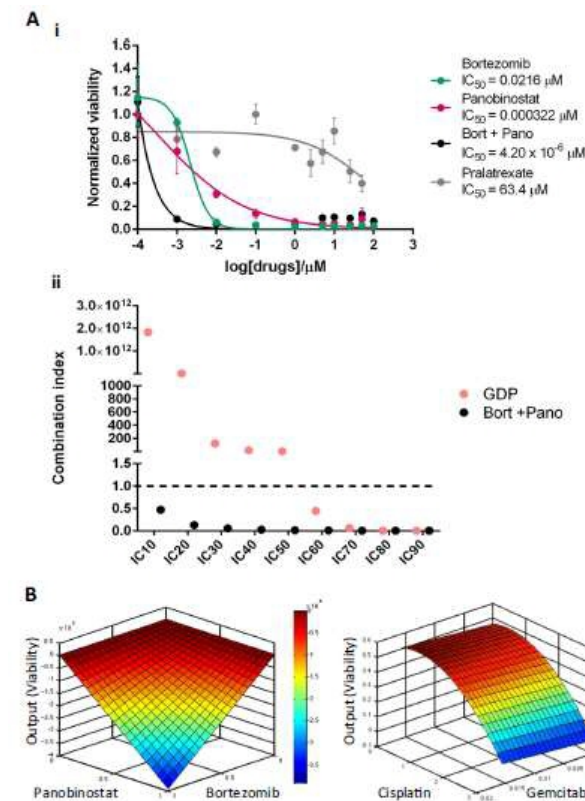
<https://clinicaltrials.gov/study/NCT06160843?term=POLAR&locStr=Singapore&country=Singapore&rank=1>

Restricted, Sensitive - Normal

QPOP: an ex-vivo drug sensitivity testing platform



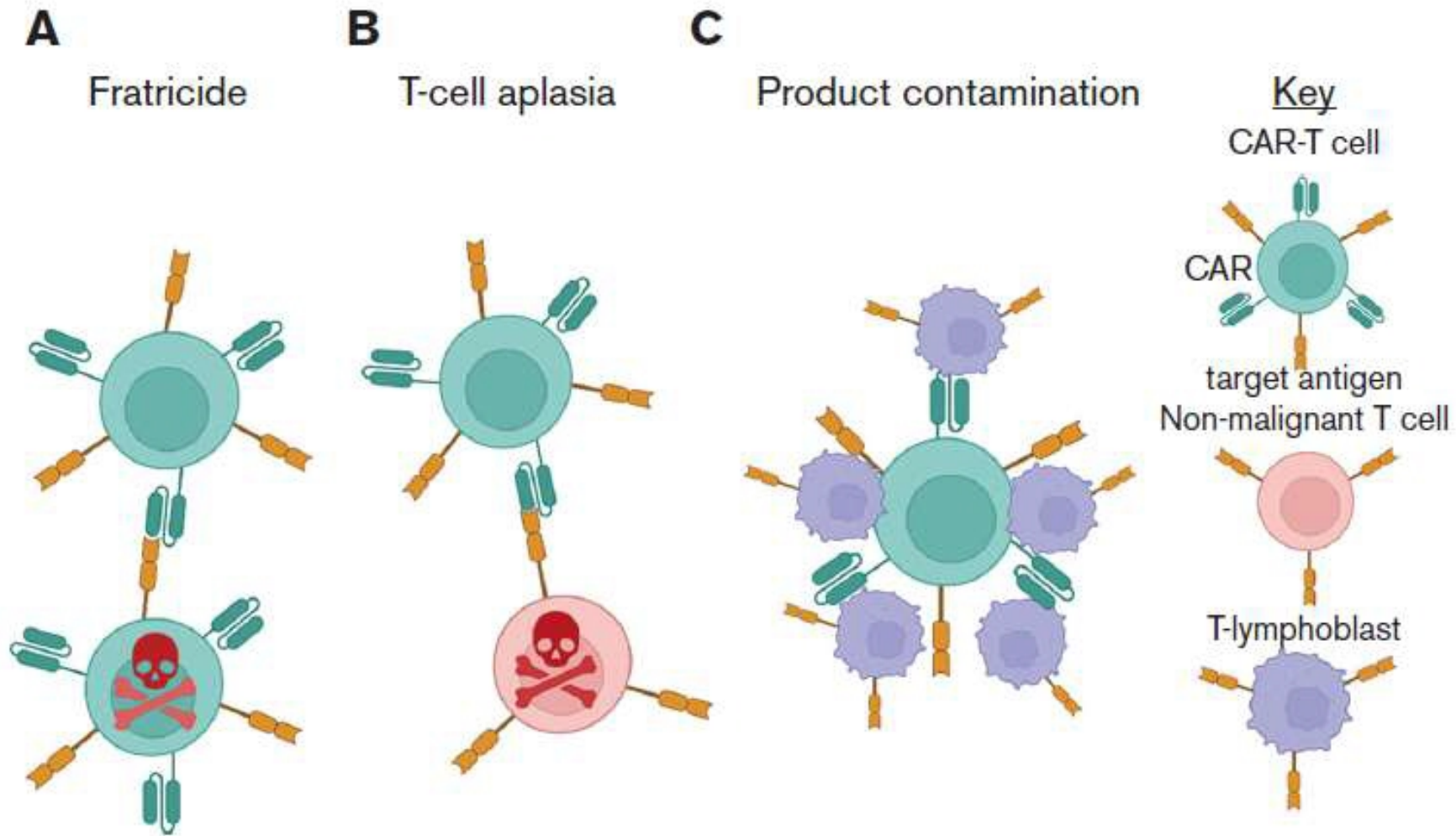
55 yr old with r/r HSTCL



¹Goh J et al. An ex vivo platform to guide drug combination treatment in relapsed/refractory lymphoma. *Sci Transl Med* 2022;14(667):eabn7824.

²de Mel S et al. Application of an ex-vivo drug sensitivity platform towards achieving complete remission in a refractory T-cell lymphoma. *Blood Cancer J* 2020;10(1):9.

The challenges of CAR T-cell therapy in T-cell lymphomas

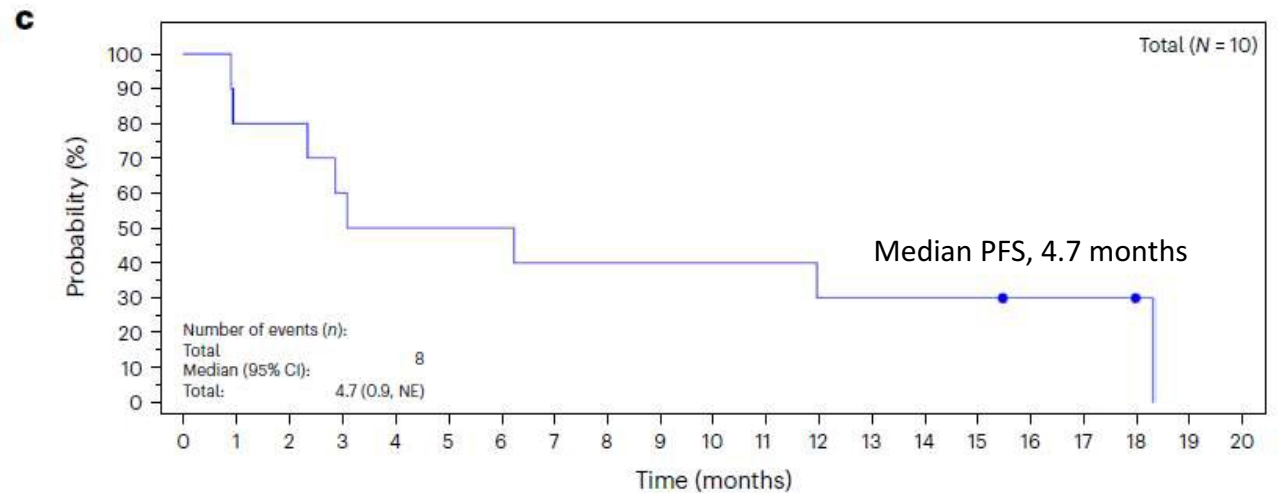
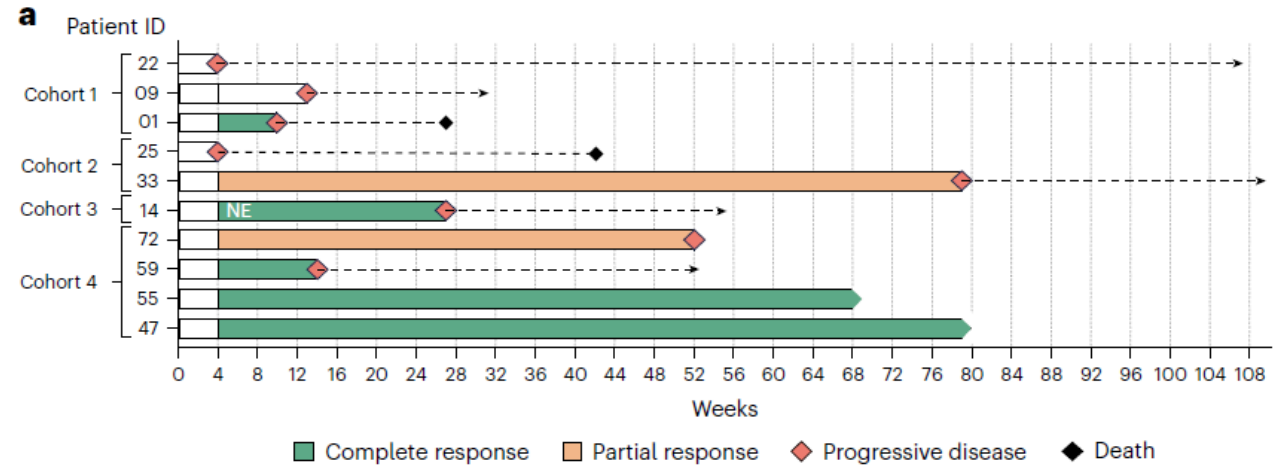


¹Maciocia N et al. CAR T-cell therapies for T-cell malignancies: does cellular immunotherapy represent the best chance of cure? *Blood Adv* 2025;9(4):913-923.

LibraT1 phase 1/2 study: CAR T-cell therapy in PTCL

- AUTO4 CAR T with TRBC1 selectivity
- Depletion of TRBC1+ autologous T-cells

Patient ID	Cohort dose	Histologic subtype	Age (years)	Sex	No. of prior lines	Prior ASCT	Bridging
22	25×10 ⁶	PTCL-NOS	34	Female	5	N	Y
01	25×10 ⁶	AITL	57	Male	2	N	Y
09	25×10 ⁶	AITL	61	Female	2	Y	N
33	75×10 ⁶	PTCL-NOS	35	Female	1	N	Y
25	75×10 ⁶	PTCL-NOS	53	Male	4	N	Y
14	225×10 ⁶	ALCL	47	Male	3	Y	Y
72	450×10 ⁶	PTCL-NOS	44	Male	2	Y	Y
55	450×10 ⁶	AITL	63	Male	3	N	Y
59	450×10 ⁶	PTCL-NOS	58	Male	3	N	N
47	450×10 ⁶	AITL	61	Male	2	N	Y



¹Macioccia PM et al. Targeting the T cell receptor β -chain constant region for immunotherapy of T cell malignancies. *Nat Med* 2017;23(12):1416-1423.

²Cwynarski K et al. TRBC1-CAR T cell therapy in peripheral T cell lymphoma: a phase 1/2 trial. *Nat Med* 2025;31(1):137-143.

Conclusion

- Relapsed T-cell lymphomas are a heterogeneous group of diseases with poor prognosis and limited advances in treatment option
- There is no standard of care for relapsed-refractory T-cell lymphomas
- Consider enrolment into a clinical trial, whenever possible
- Platinum-based regimens which are non-cross resistant to 1L Rx
- Novel agents are preferred in certain subtypes (eg. TFHL, ENKTL)
- Consolidative allogeneic HSCT may cure a subset of patients



Thank You

Tan Tock Seng Hospital • Khoo Teck Puat Hospital • Woodlands Hospital • Yishun Community Hospital • TTSH Integrated Care Hub
Institute of Mental Health • National Skin Centre • National Centre for Infectious Diseases • NHG Cancer Institute • NHG Eye Institute • NHG Heart Institute
Population Health • NHG Polyclinics • Diagnostics • Pharmacy • Community Care • NHG College • Centre for Healthcare Innovation