Managing patients with T cell Lymphoma: ongoing challenges

Kate Cwynarski

Consultant Haematologist

Department of Haematology, UCLH, London

Honorary Associate Professor UCL

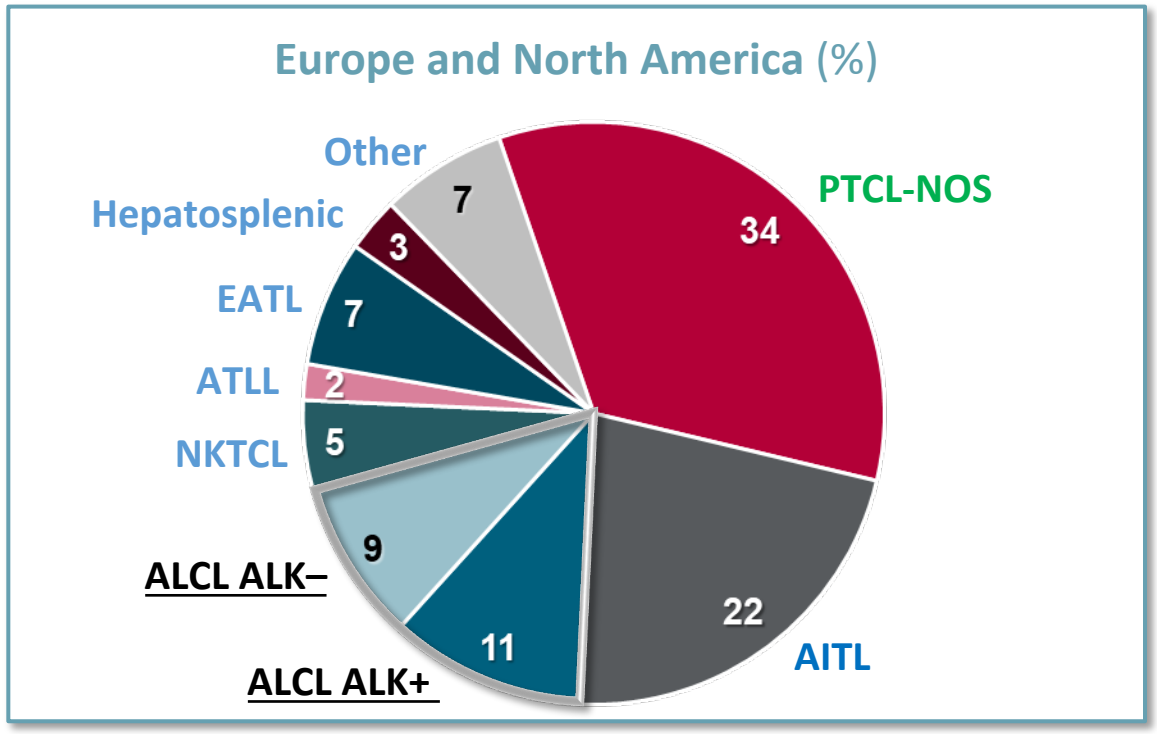
Chair UK T cell Lymphoma Group

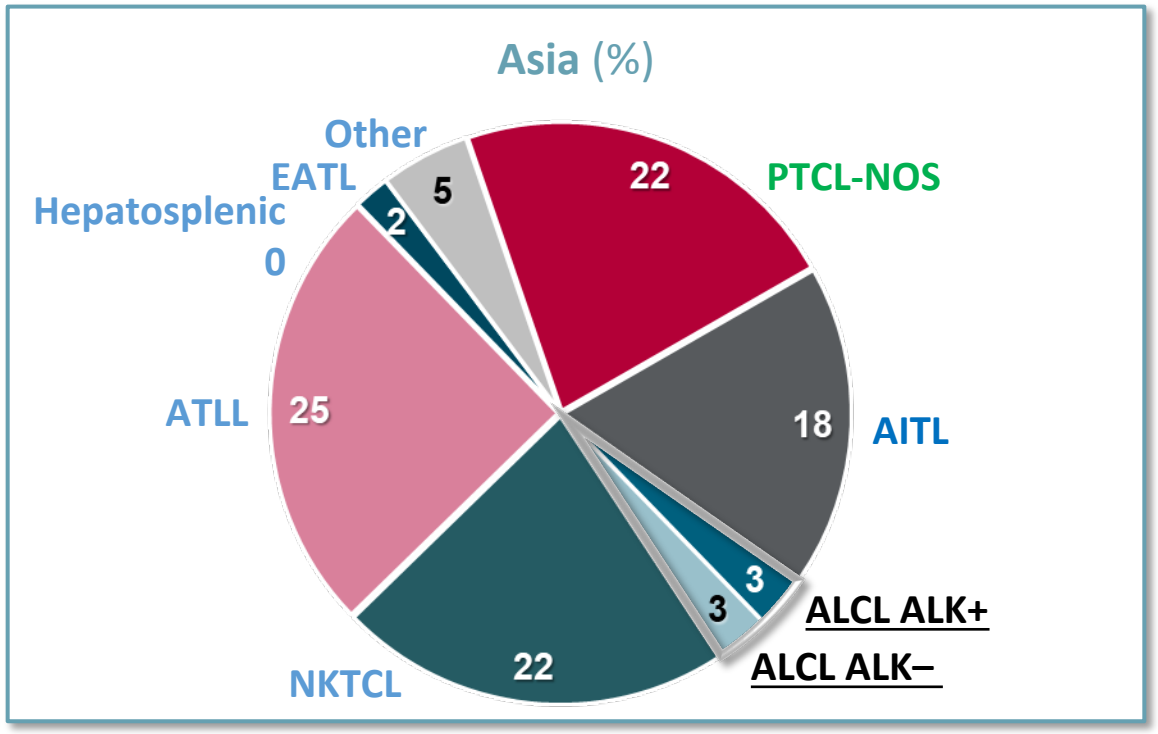
Disclosures

- Consulting/Advisory Role: Roche, Takeda, Celgene, Atara, Gilead, KITE, Janssen, Incyte, Abbvie, Sobi
- Speakers' Bureau: Roche, Takeda, KITE, Gilead,
- Conferences/Travel support: Roche, Takeda, KITE, Janssen

Distribution of Major T-cell and NK-cell Neoplasms by Geographic Region

PTCL: UK ~1400 patients/year

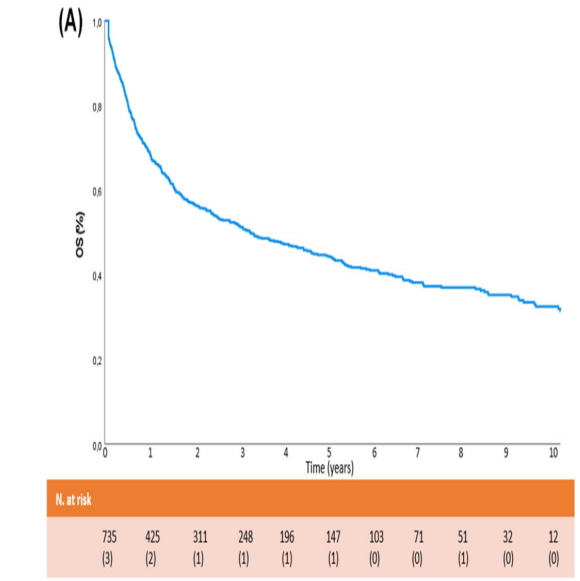


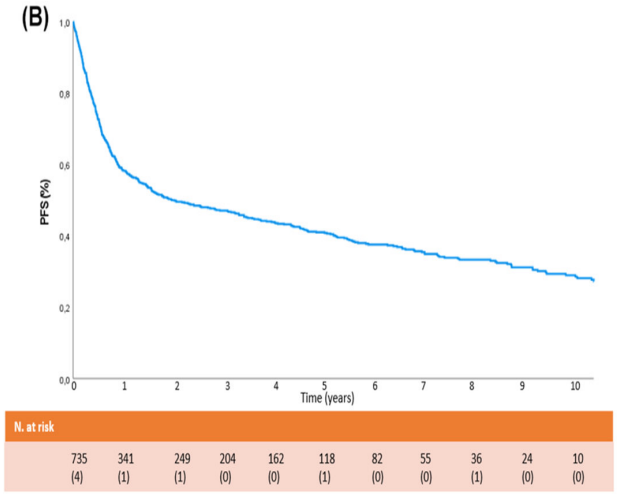


AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ALK anaplastic lymphoma kinase; ATLL, adult T-cell leukemia / lymphoma; EATL, enteropathy-associated T-cell lymphoma; NHL, non-Hodgkin lymphoma; NK, natural killer; NKTCL, natural killer / T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma - not otherwise specified.

1. Hildyard CAT, et al. *Clin Med Insights Blood Disord.* 2017;10:1179545X17705863.

The majority of patients with PTCL will relapse





Subtype	OS		PFS	
	5 year (95% CI)	10 year (95% CI)	5 year (95% CI)	10 year (95% CI)
PTCL-NOS	**31** (26–36)	**23** (18–28)	**26** (17–35)	**18** (9–27)
AITL	**44** (31–57)	**31** (26–36)	**39** (33–45)	**24** (14–34)
NK TCL	**45** (37–53)	**32** (23–41)	**40** (32–48)	**28** (20–36)
ALCL, ALK–	**49** (37–61)	**40** (34–46)	**42** (33–51)	**36** (29–43)
ALCL, ALK+	79 (65–93)	69 (62–76)	71 (60–82)	63 (53–73)

Civallero M *et al*, International Prospective T-cell Project. Br J Haem 2024

Is there a chemotherapy regimen ‘better’ than CHOP?

Strategies to improve induction efficacy in mature T-cell lymphomas

ALTERNATIVE CHEMO BACKBONES

CHOP VS GEM-P	NEGATIVE
CHOP VS CMED	INCONCLUSIVE
DA-EPOCH	SMALL PTS N°

CHOP + X STRATEGY

CHOP VS CHP-BV

CHOP VS CHOP + ALEMTUZUMAB

CHOP VS CHOP + HDACi

CHOP VS CHOP + DMAs

CHOP VS CHOP + DUVELISIB

CHOP + PRALATREXATE

CHOP + BORTEZOMIB

CHOP + LENALIDOMIDE

NOVEL NON-CHEMO BACKBONES

Demethylating agents (DMAs and
HDACi-BASED REGIMENS
IN THF-NTCL

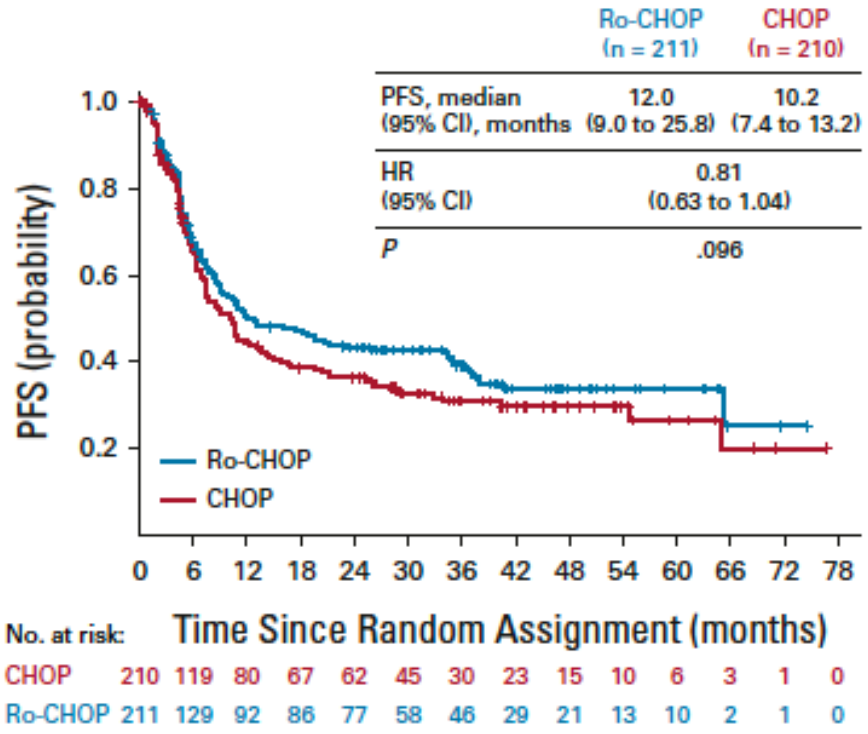
Avilés A. *Med Oncol*, 2008; Maeda Y. *Haematologica*, 2017; Gleeson M. *Lancet Haematol*, 2018

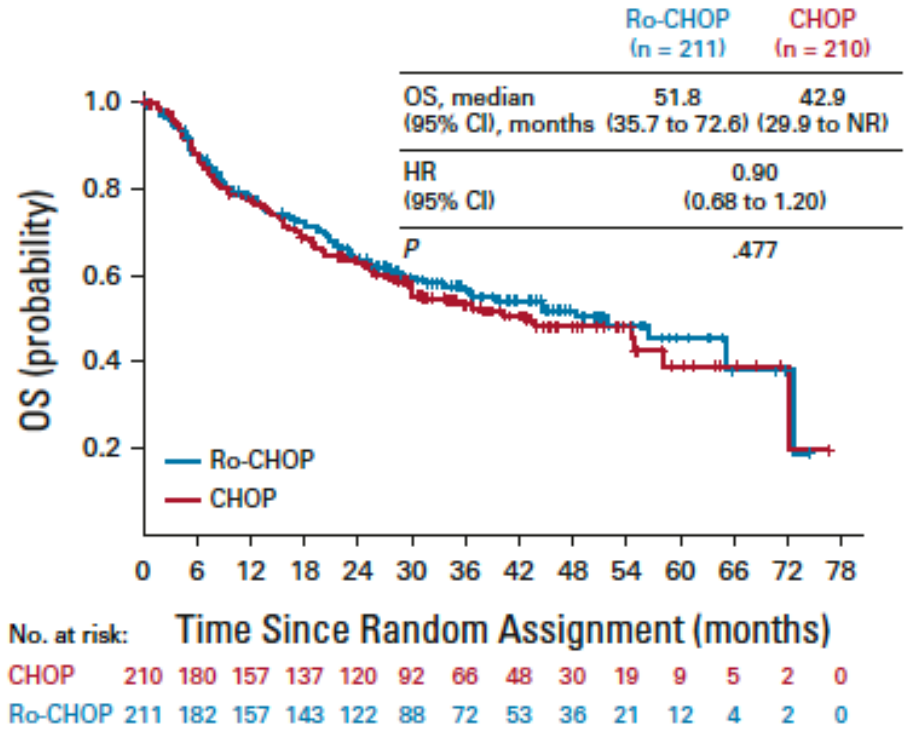
Romidepsin Plus CHOP Versus CHOP in Patients With Previously Untreated Peripheral T-Cell Lymphoma: Results of the Ro-CHOP Phase III Study (Conducted by LYSA)

Emmanuel Bachy, MD, PhD[1,2]; Vincent Camus, MD[3]; Catherine Thieblemont, MD, PhD[4]; David Sibon, MD, PhD[5];

J Clin Oncol 40:242-251.

Similar outcome after CHOP +/- Romidepsin in PTCL-NOS

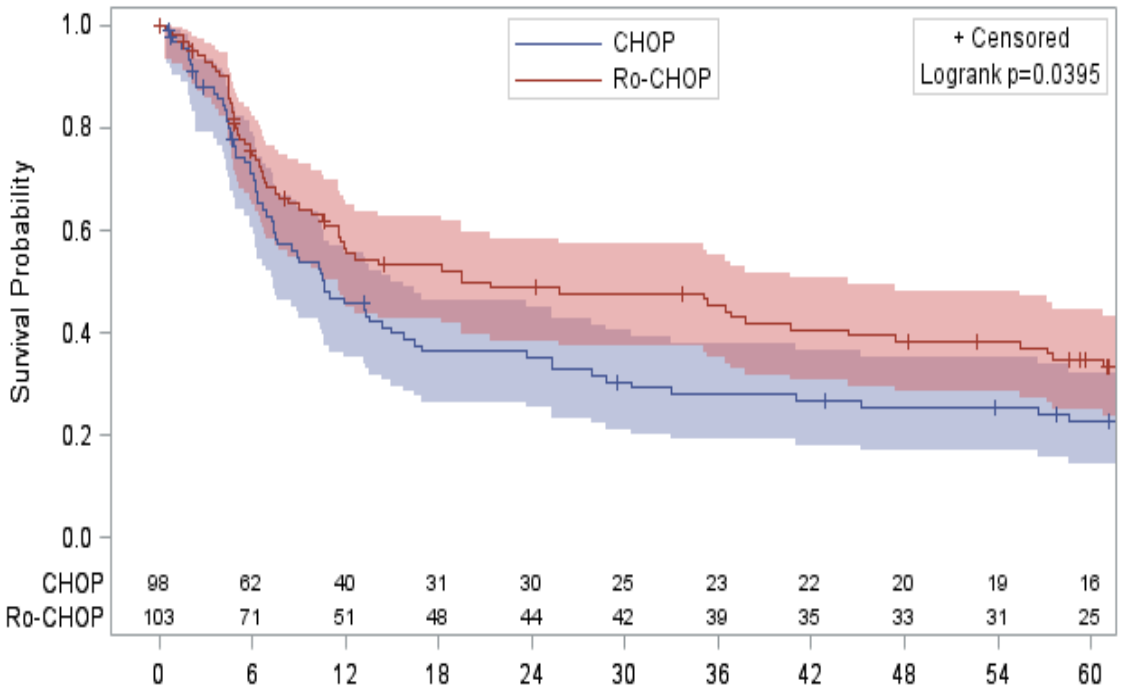




98 centres from 9 countries in Europe, Asia, and Australia.

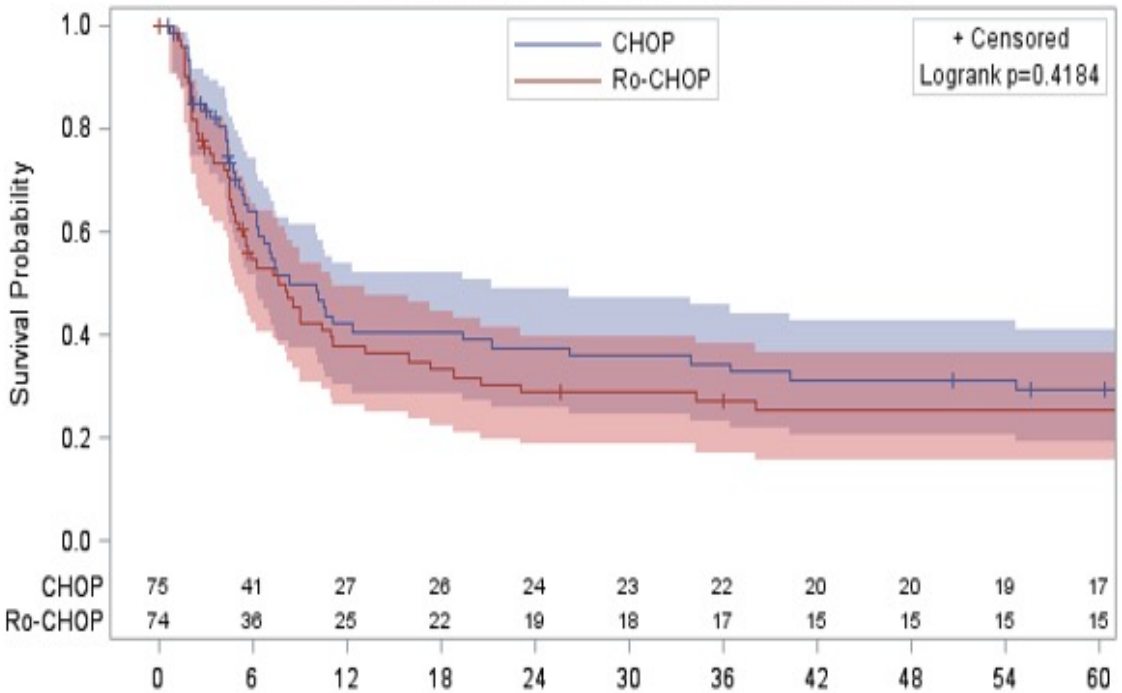
Superior PFS in patients with PTCL-TFH vs patients with non-TFH diagnosis

PTCL-TFH



	No. of Subjects	Event	Censored	Median Survival
CHOP	98	72.4 % (71)	27.6 % (27)	10.6 (7.4 ; 14.9)
Ro-CHOP	103	63.1 % (65)	36.9 % (38)	19.5 (11.5 ; 44.4)

PTCL non-TFH



	No. of Subjects	Event	Censored	Median Survival
CHOP	75	64 % (48)	36 % (27)	8.3 (6.2 ; 21.3)
Ro-CHOP	74	70.3 % (52)	29.7 % (22)	8.1 (4.8 ; 11)

Camus V *et al*, JCO 2024

Is there a chemotherapy regimen ‘better’ than CHOP?

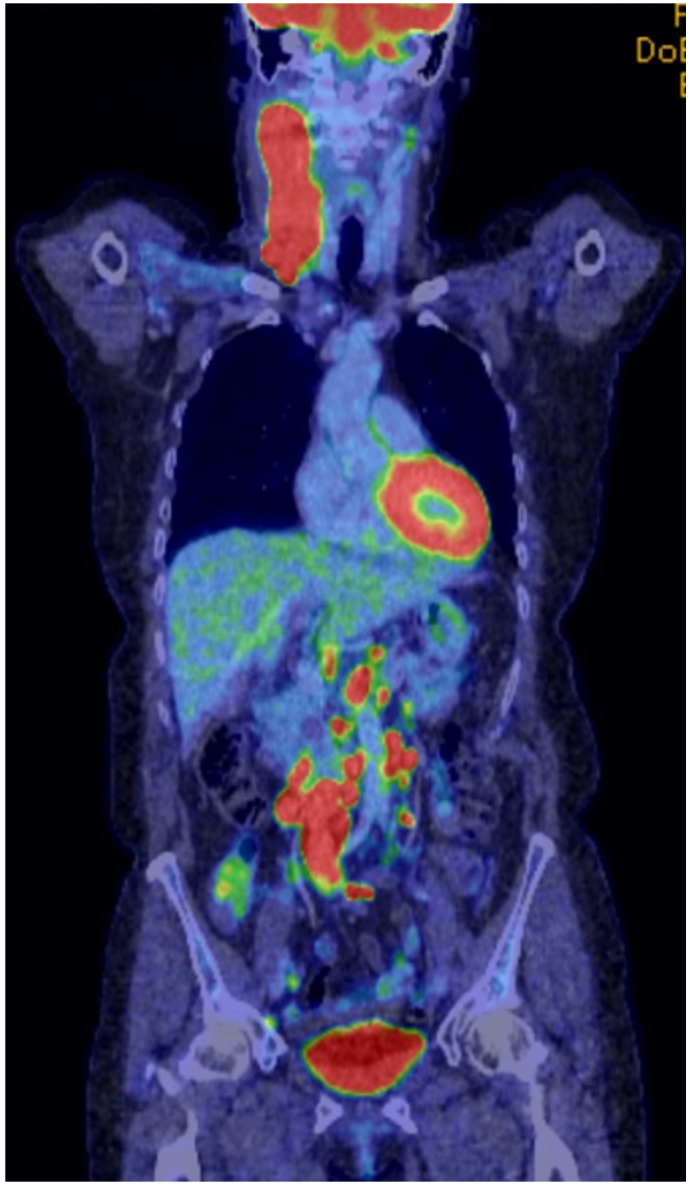
For ALL: NO

but

Can understanding biology identify new therapeutic targets?

Patient management Case 1

61 years
Angioimmunoblastic/TFH T-cell lymphoma
Rash/fatigue/widespread LN April 2017

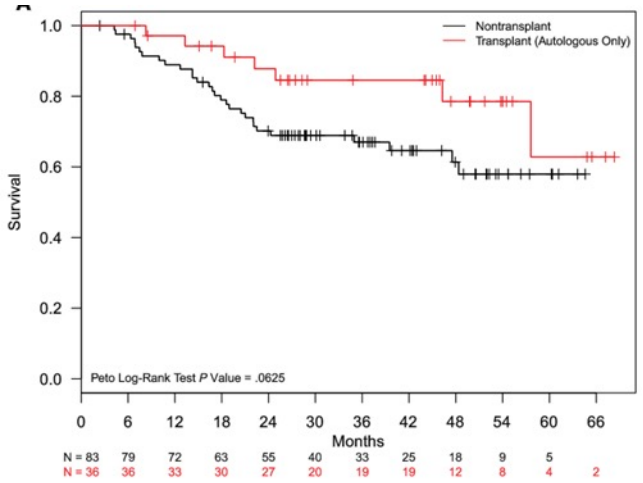


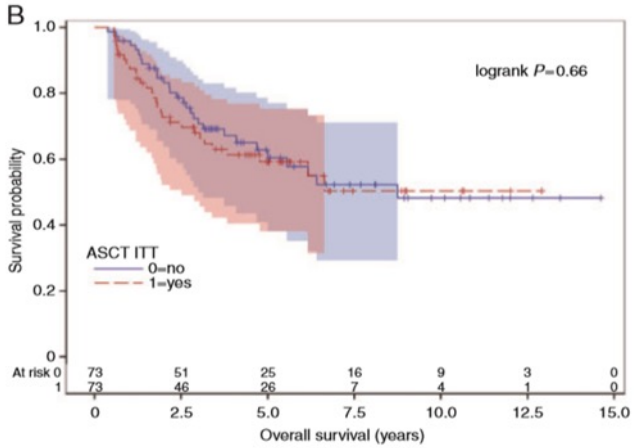
April 2017- Staging PET

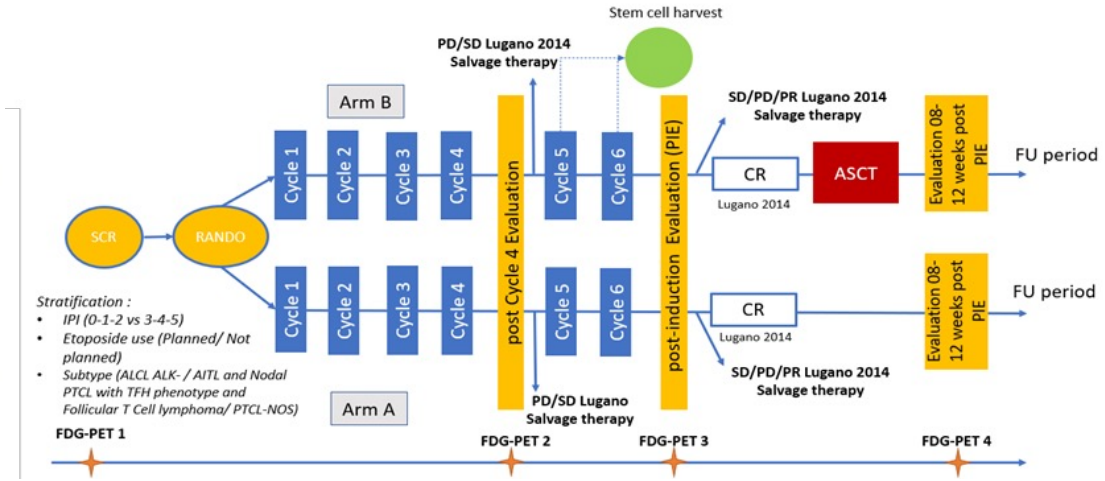
Are you planning to perform ASCT in CR1?

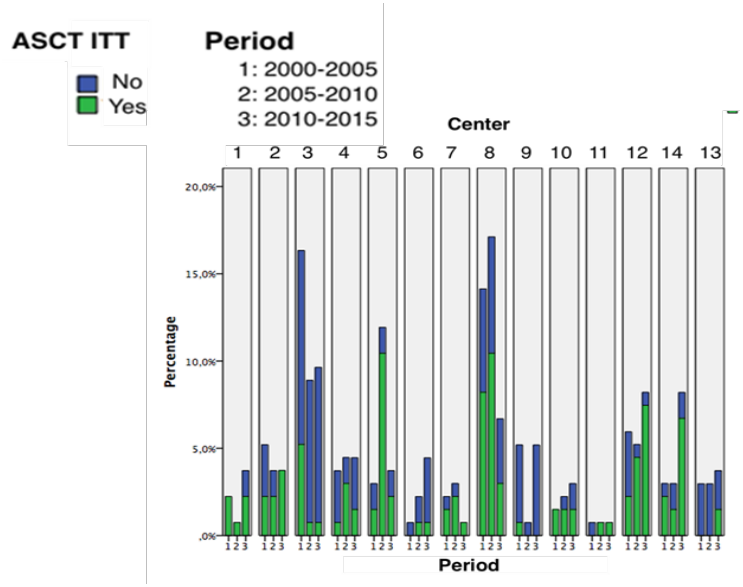
- A Definitely ‘YES’
- B Discuss ‘YES’
- C Undecided
- D Discuss ‘NO’
- E Definitely ‘NO’

Is there a role for consolidation auto-SCT in CR1?









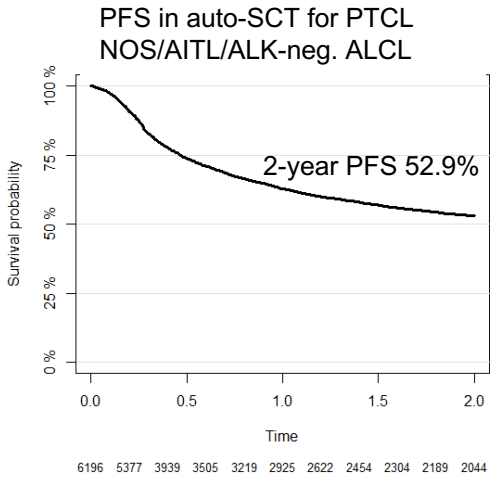
- Widely adopted
- Conflicting prospective and retrospective data
- No randomised data
- Key determinant may be induction response rather than ASCT itself

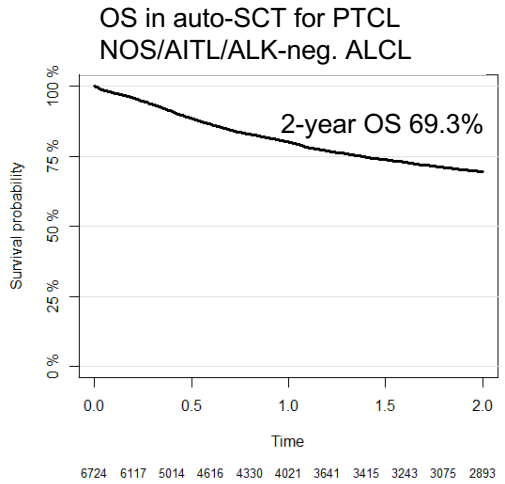
Fossard et al. Ann Onc 2018; 29: 715–723 Park et al Cancer 2019;125(9):1507-1517

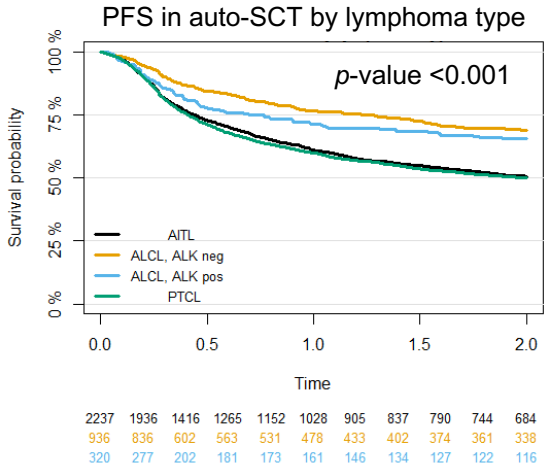
UPDATED ANALYSIS OF THE EBMT LYMPHOMA WORKING PARTY
Different outcomes of major T-cell lymphoma entities following auto-SCT

auto-SCT n=7099

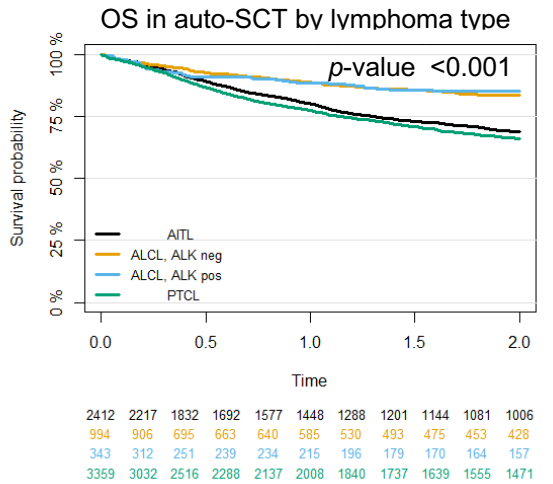
PTCLNOS	3359
AITL	2412
ALK-ALCL	994
ALK+ALCL	343







2-year PFS:
ALCL,ALK-neg. 69%
ALCL,ALK-pos. 65.5%
AITL 50.7%
PTCL NOS 50.1%

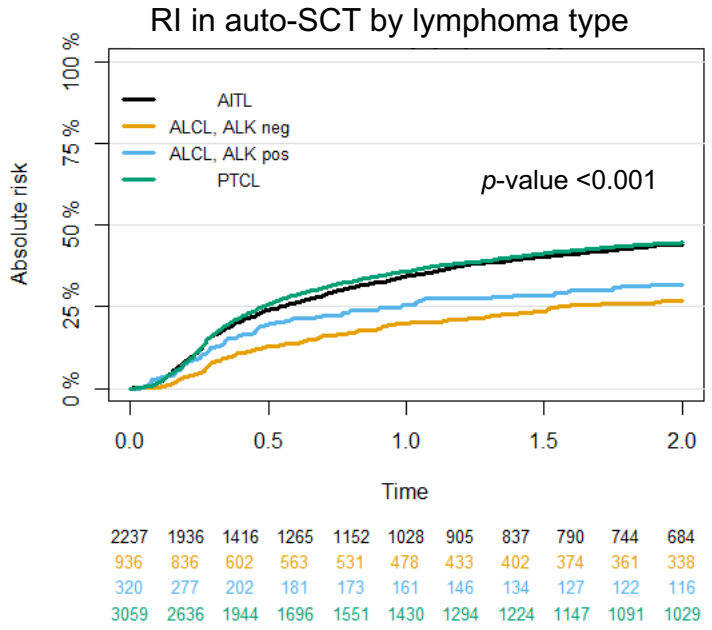


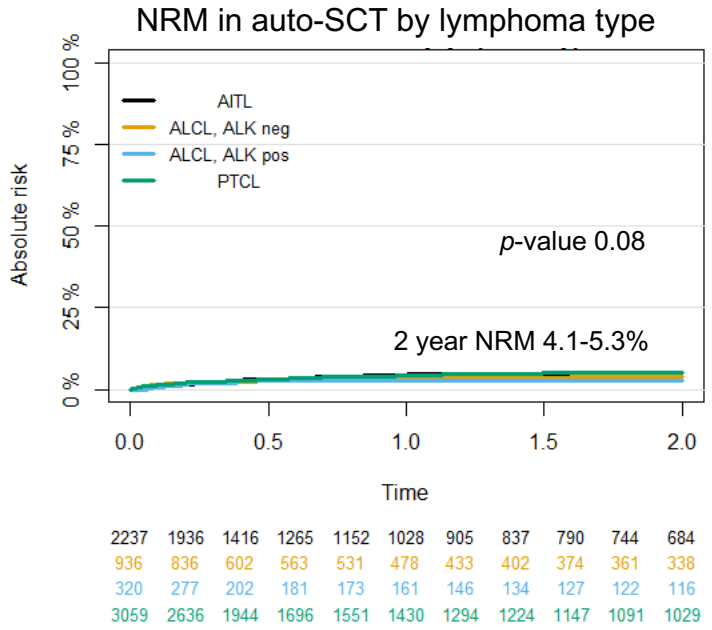
2-year OS:
ALCL,ALK-pos. 85.3%
ALCL,ALK-neg. 83.8%
AITL 68.9%
PTCL NOS 66.0%

Shumilov E *et al*, EHA 2024

Different relapse incidence (RI) and similar non-relapse mortality (NRM) in major T-cell lymphoma entities after auto-SCT

2-year RI:
PTCL, NOS 44.5%
AITL 44.2%
ALCL,ALK-pos. 31.8%
ALCL,ALK-neg. 26.9%





Shumilov E *et al*, EHA 2024

Is there a role for consolidation transplant in PTCL?

- There are no randomized clinical trials
  - Although LYSA group are conducting a prospective randomized trial
- There is retrospective evidence *for* and *against*.
- There are few prospective trials, with diverse subtype inclusion.
- The relapse risk remains high with CHOP/CHOP-like chemotherapy alone
  - thus it is *considered* in most subtypes (with the exception of low IPI ALK$^+$ ALCL)

Fox *et al*, Guidelines for the management of mature T- and natural killer-cell lymphomas. BSH Guideline 2022

Am I planning to perform ASCT in CR1?

- A Definitely ‘YES’
- B Discuss ‘YES’
- C Undecided
- D Discuss ‘NO’
- E Definitely ‘NO’

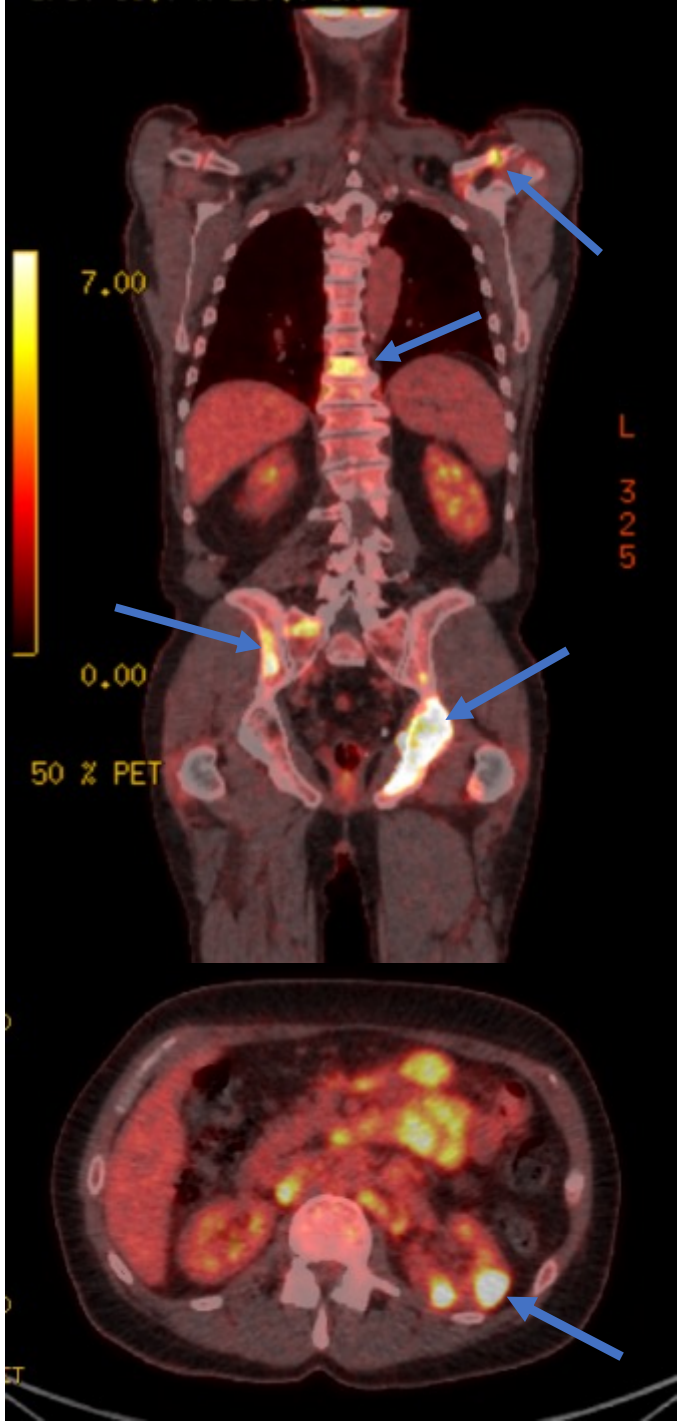
Case 2

42 year old female
Fevers, nighty sweats, bony pain
PET: Widespread bony involvement and left renal mass
Stage IVB ALK –ve ALCL

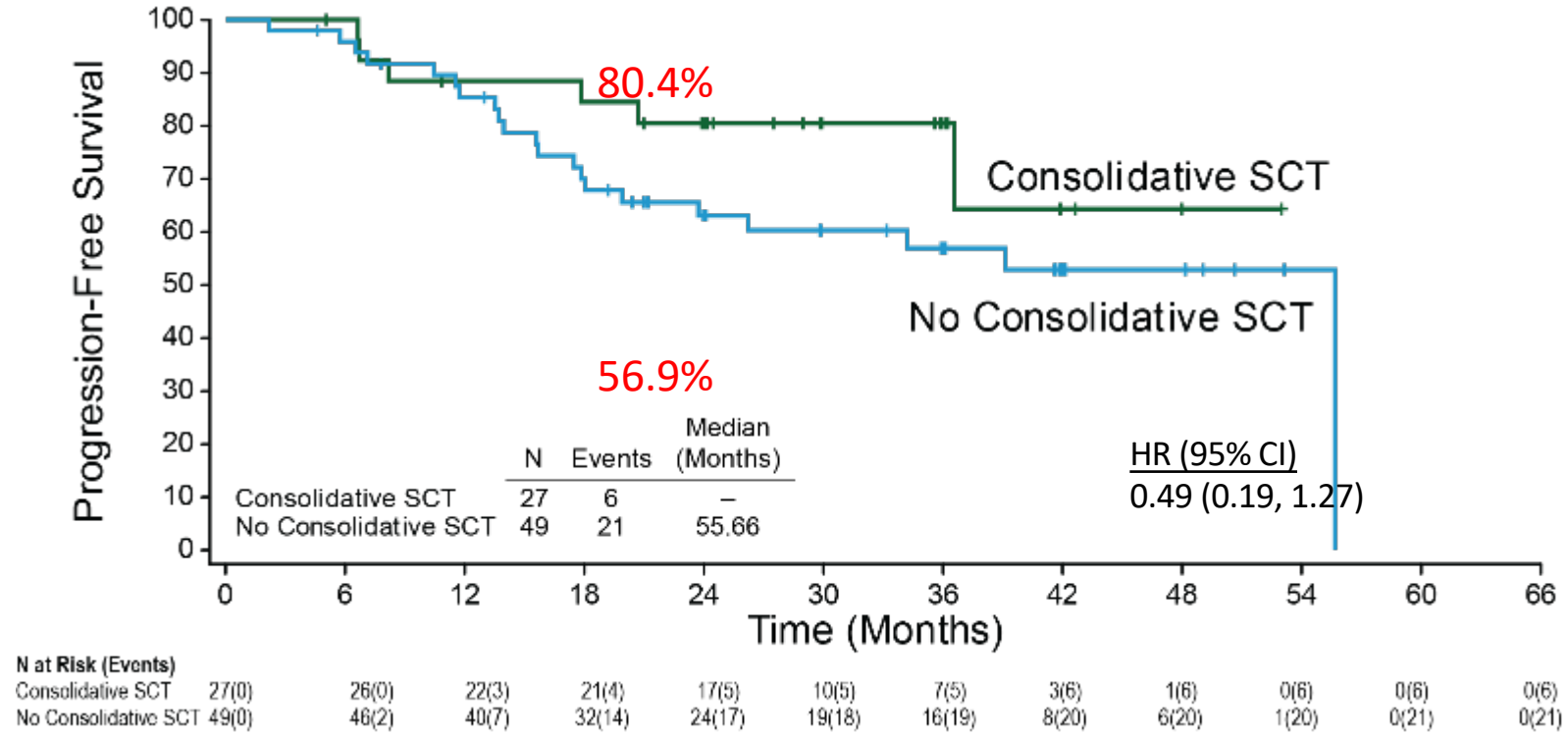
- PS=2, LDH 890, 2 extranodal sites
- No significant co-morbidity

- BV-CHP therapy planned with curative intent

- Do we consider ASCT in CR1 in ALK negative ALCL?



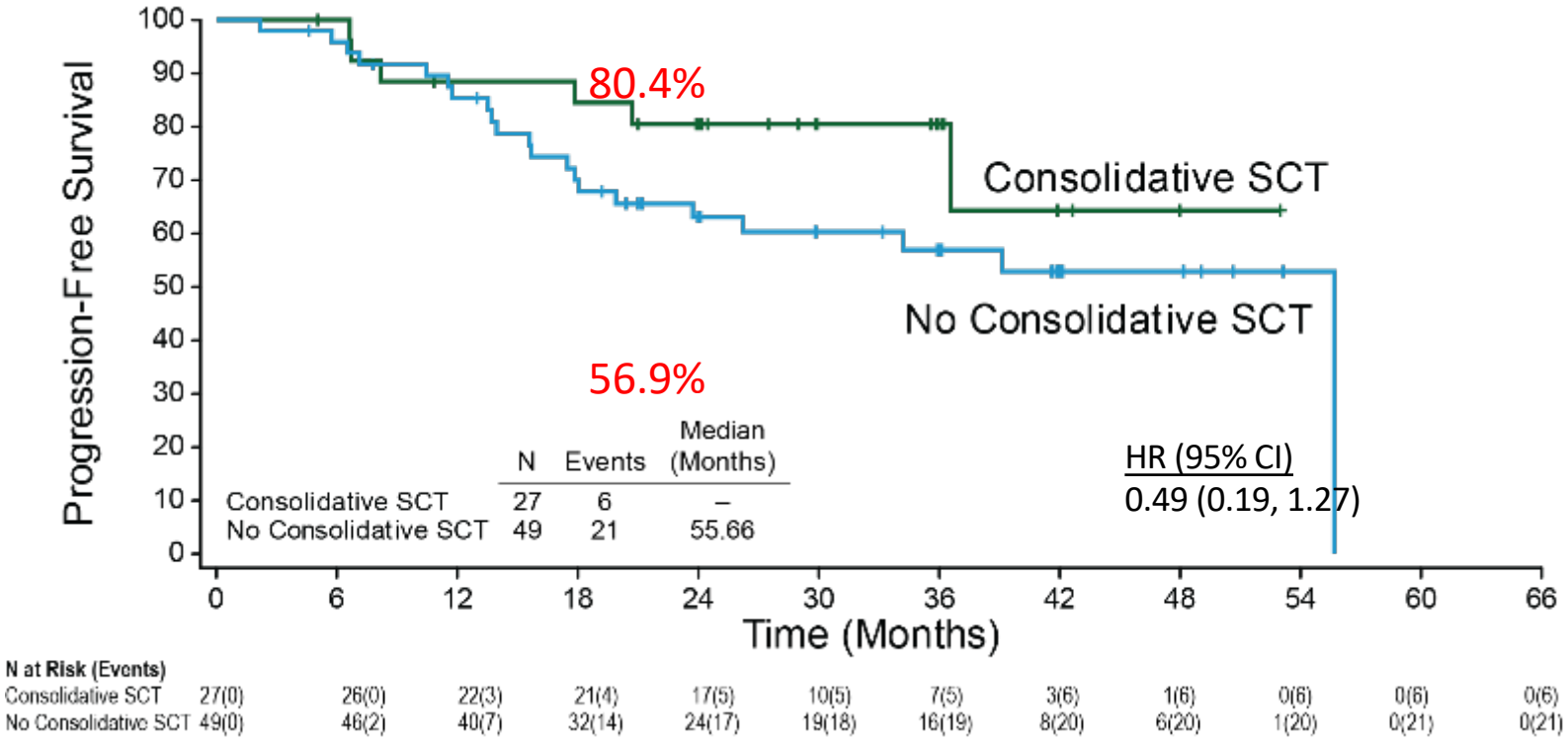
Consolidative SCT After BV-CHP in ALK–ALCL Patients? Focusing on patients in CR at EOT in ECHELON-2 trial



ITT – Yes
All: n=50 (44%)
Asia: 2/15 (13%)
Non-Asia: 48/98 (49%)

Savage *et al,* Blood Advances 2022

Consolidative SCT After BV-CHP in ALK–ALCL Patients? Focusing on patients in CR at EOT in ECHELON-2 trial



ITT – Yes
All: n=50 (44%)
Asia: 2/15 (13%)
Non-Asia: 48/98 (49%)

Only 9% of ALCL (n=214) patients proceeded to ASCT consolidation
Martinez-Calle et al, Adv Ther. 2021

Savage *et al,* Blood Advances 2022

Case 2

42 year old female
Fevers, nighty sweats, bony pain
PET: Widespread bony involvement and left renal mass
Stage IVB ALK –ve ALCL

- PS=2, LDH 890, 2 extranodal sites
- No significant co-morbidity

- 6 x BV-CHP completed

- BEAM ASCT

- Remains in complete metabolic remission 5 years

UK BSH Guideline Recommendation 2022

Consider BEAM ASCT in CR1:

ALK- ALCL

or

ALK+ ALCL with high -risk features

IPI ≥2

+/-

age >40 years

Relapsed ALCL: Brentuximab (or chemo) with aim of allo-SCT (or ASCT)

Fox C *et al*, Br J Haematol 2022

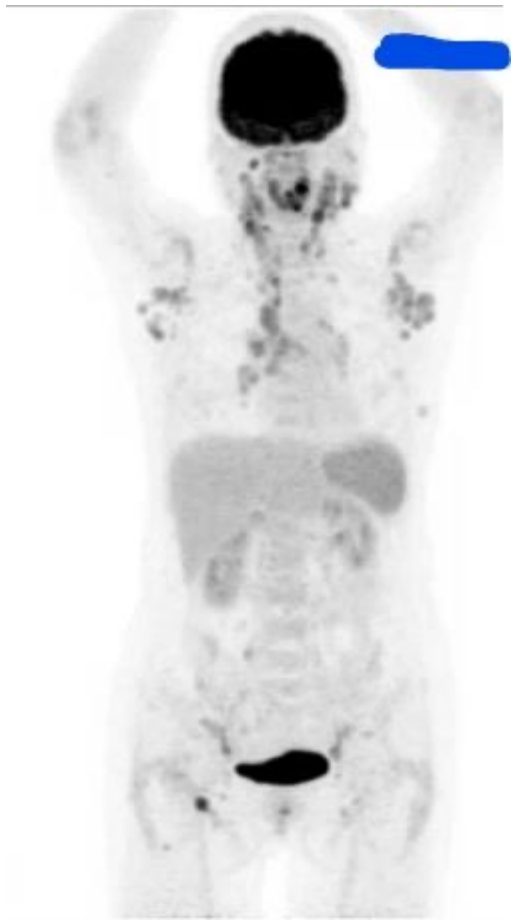
Patient management Case 1

61 years

Angioimmunoblastic/TFH T-cell lymphoma

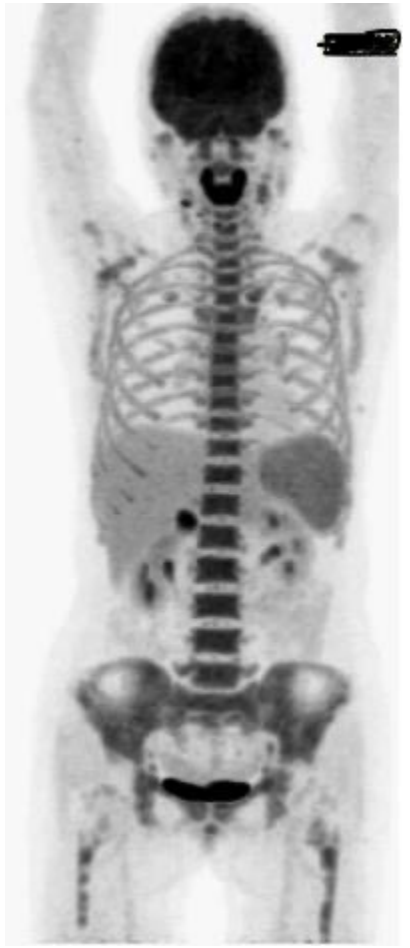
- Rash/fatigue/widespread LN April 2017
- PR to 4# CHOP
- PD after 6# CHOP Dec 2017

PRE CHOP



April 2017-
Staging PET

POST CHOP



December 2017-
EOT PET

Are you planning to perform allo-SCT in CR2?

- A Definitely ‘YES’
- B Discuss ‘YES’
- C Undecided
- D Discuss ‘NO’
- E Definitely ‘NO’

MAJORITY OF PATIENTS WITH TCL WILL RELAPSE

Ro-CHOP study (n=421): Heterogeneity of 2nd line treatments

	2L Set N=251	
Chemotherapy		
DHAOX	23	(9.2%)
DHAP	13	(5.2%)
ESHAP	18	(7.2%)
GDP	8	(3.2%)
ICE	17	(6.8%)
Gemcitabine/Gemox	21	(8.4%)
Bendamustine	21	(8.4%)
Other	130	(51.8%)
Brentuximab Vedotin (in combination with 2L chemotherapy)	31	(12.4%)
Transplant type		
Allogeneic	14	(5.6%)
Autologous	21	(8.4%)

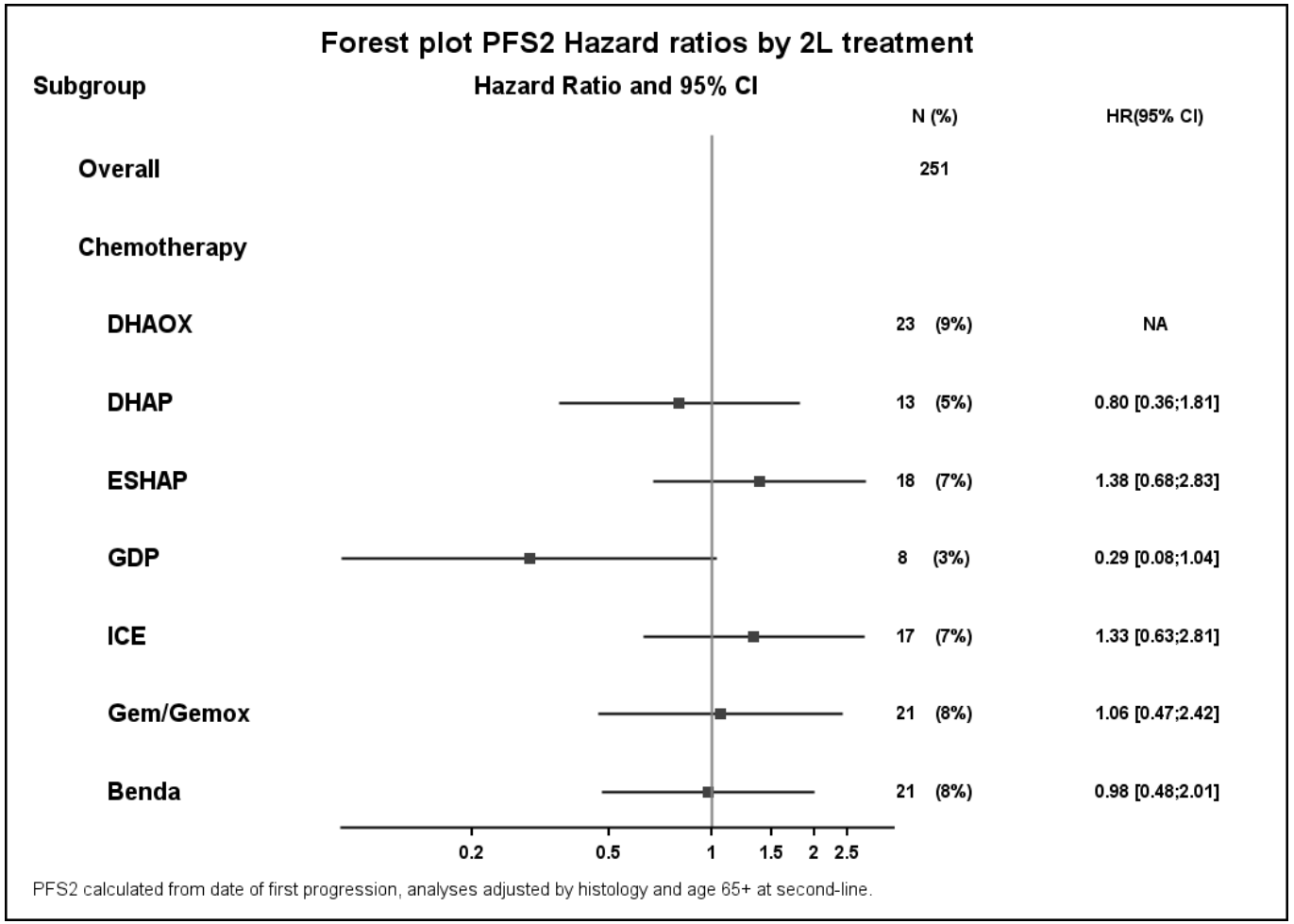
Other 2L treatment administered to ≥2 patients	**Treatment arm**		**2L set**
	Ro-CHOP N=115	CHOP N=136	N=251
Brentuximab-vedotin single-agent	5 (4.3%)	3 (2.2%)	8 (3.2%)
Romidepsin	0 (0%)	7 (5.1%)	7 (2.8%)
Azacytidine	3 (2.6%)	2 (1.5%)	5 (2%)
Bendamustine –cytarabine	3 (2.6%)	0 (0%)	3 (1.2%)
GEMOX- bendamustine	1 (0.9%)	2 (1.5%)	3 (1.2%)
Ifosfamide-VP16	2 (1.7%)	1 (0.7%)	3 (1.2%)
IVOX	1 (0.9%)	2 (1.5%)	3 (1.2%)
Methotrexate	1 (0.9%)	2 (1.5%)	3 (1.2%)
Lenalidomide	2 (1.7%)	1 (0.7%)	3 (1.2%)
Brentuximab-vedotin-nivolumab	1 (0.9%)	1 (0.7%)	2 (0.8%)
GEMOX-nivolumab	0 (0%)	2 (1.5%)	2 (0.8%)
R-GEMOX	1 (0.9%)	1 (0.7%)	2 (0.8%)
Radiotherapy	1 (0.9%)	1 (0.7%)	2 (0.8%)
Cyclophosphamide	1 (0.9%)	1 (0.7%)	2 (0.8%)
Cyclophosphamide - VP16	0 (0%)	2 (1.5%)	2 (0.8%)

GDP: gemcitabine, dexamethasone, cisplatin; ESHAP: etoposide, methylprednisolone, high-dose cytarabine and cisplatin; DHAP: etoposide, methylprednisolone, high-dose cytarabine and cisplatin; ICE: Ifosfamide, carboplatin, etoposide; GEMOX: gemcitabine, oxaliplatine; IVOX: ifosfamide, etoposide, oxaliplatin.

Median age 66 yrs

Camus V *et al*, JCO 2024

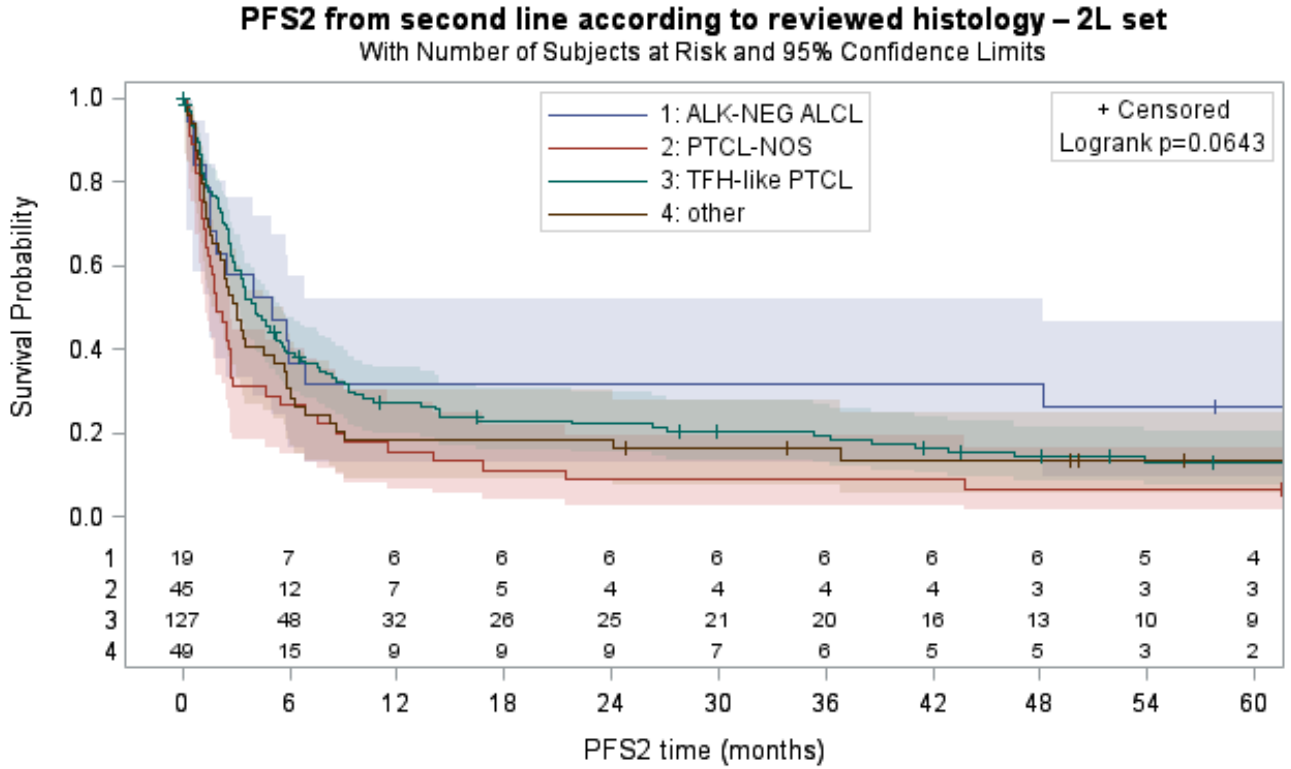
PFS2 according to main 2L approaches: We will continue to use GDP



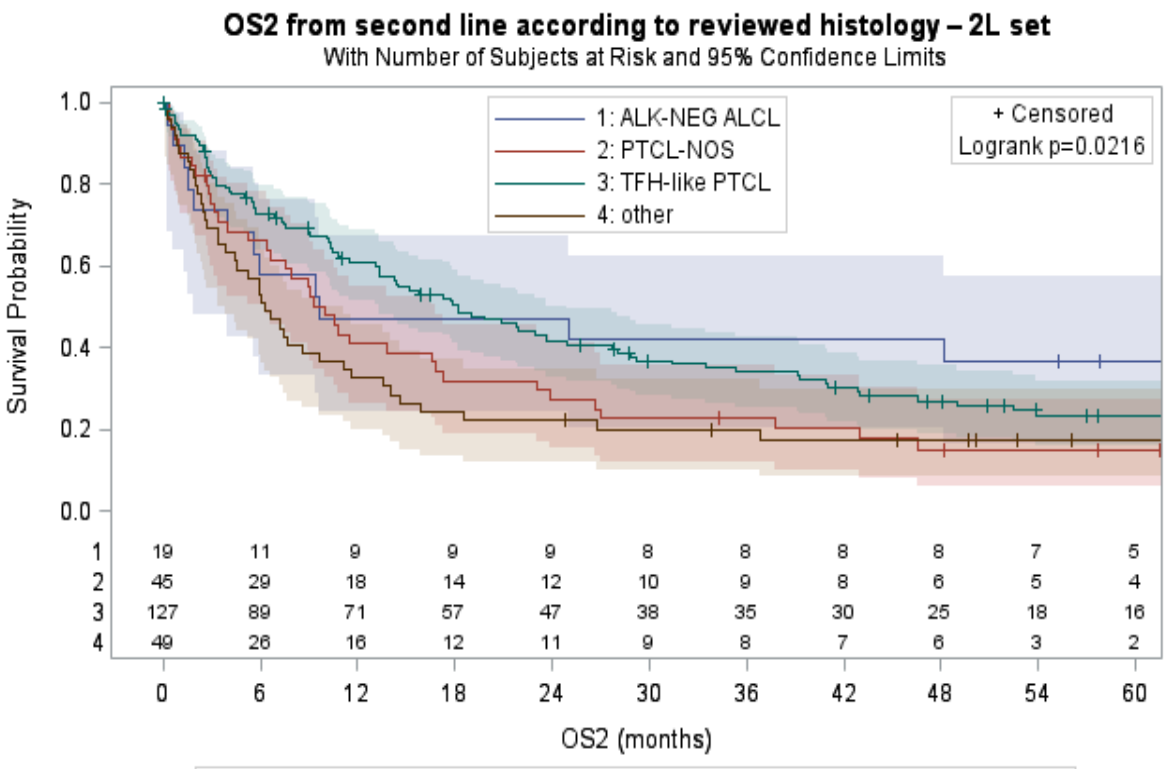
GDP: gemcitabine, dexamethasone, cisplatin; ESHAP: etoposide, methylprednisolone, high-dose cytarabine and cisplatin; DHAP: etoposide, methylprednisolone, high-dose cytarabine and cisplatin; ICE: Ifosfamide, carboplatin, etoposide; GEMOX: gemcitabine, oxaliplatine; IVOX: ifosfamide, etoposide, oxaliplatin; Benda: bendamustine single agent; Gem: gemcitabine

Camus V…..Bachy E ICML 2023

PFS2/OS2: PFS and OS after the first progression and 2nd line treatment by histological subtype



	No. of Subjects	Event	Censored	Median Survival
ALK-NEG ALCL	19	78.9 % (15)	21.1 % (4)	5 (1.5 ; 48.2)
PTCL-NOS	45	93.3 % (42)	6.7 % (3)	1.9 (1.3 ; 2.7)
TFH-like PTCL	127	82.7 % (105)	17.3 % (22)	4.1 (3.2 ; 5.6)
other	49	85.7 % (42)	14.3 % (7)	3 (2 ; 5.2)



	No. of Subjects	Event	Censored	Median Survival
ALK-NEG ALCL	19	63.2 % (12)	36.8 % (7)	9.6 (1.8 ; NA)
PTCL-NOS	45	84.4 % (38)	15.6 % (7)	10 (6.4 ; 16.8)
TFH-like PTCL	127	70.1 % (89)	29.9 % (38)	18.2 (13.3 ; 24.9)
other	49	81.6 % (40)	18.4 % (9)	6.2 (3.8 ; 9.7)

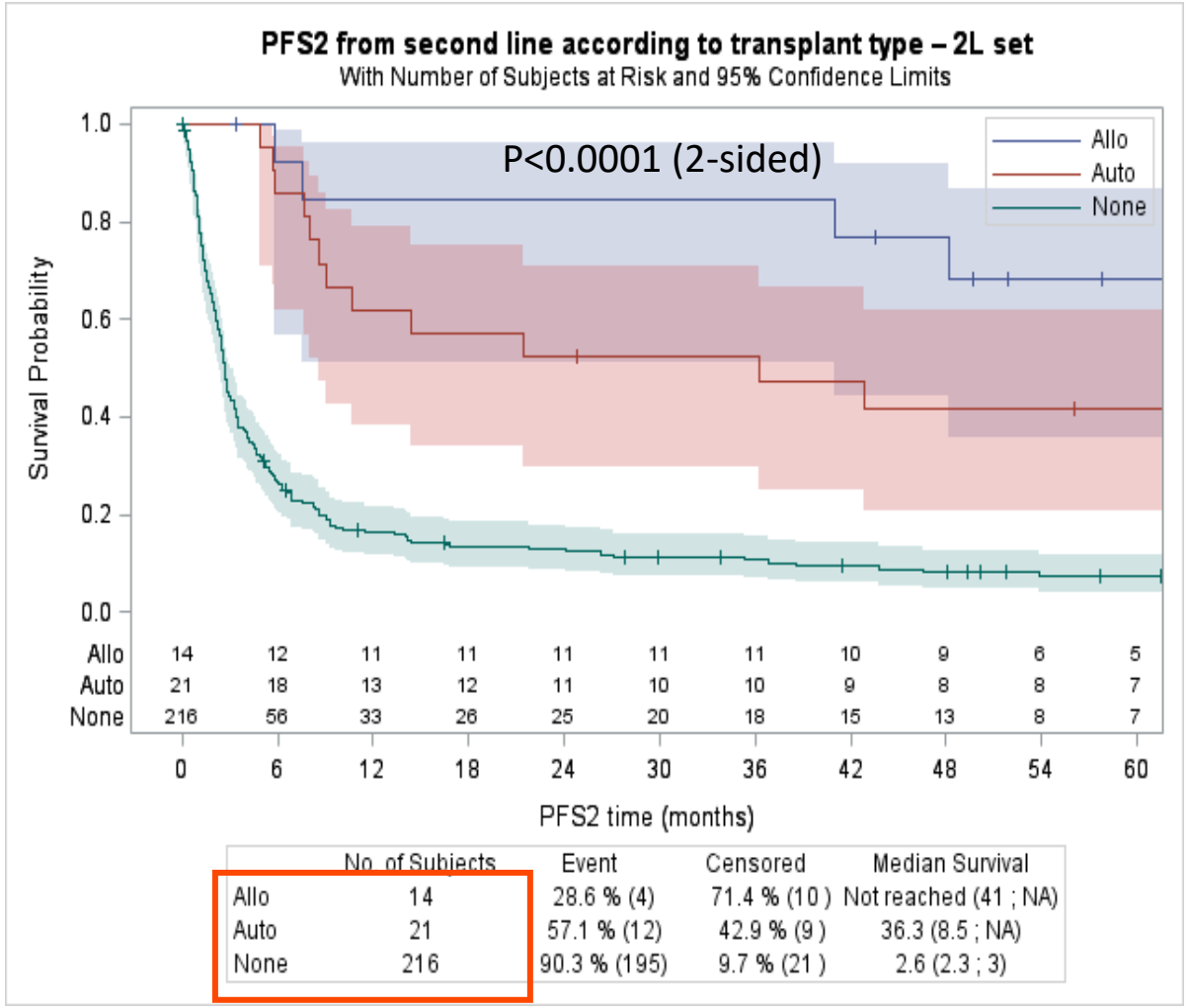
Median PFS2 : 3.3 months
Median OS2: 11.5 months

Camus V *et al,* JCO 2024

PFS2 according to transplant status

	Transplant type						2L set	
	Allo		Auto		None			
	N=14		N=21		N=216		N=251	
Age at enrollment (years) (CRF)								
Median	52.5		55.0		66.0		65.0	
Min ; Max	28 ; 68		33 ; 70		35 ; 81		28 ; 81	
Sex								
Male	11	(78.6%)	13	(61.9%)	136	(63.0%)	160	(63.7%)
Ann Arbor Stage								
III-IV	12	(85.7%)	19	(90.5%)	199	(92.1%)	230	(91.6%)
IPI group								
>=2	11	(78.6%)	18	(85.7%)	192	(88.9%)	221	(88.0%)
Histological diagnosis in class (reviewed)								
PTCL-NOS	1	(7.1%)	3	(14.3%)	41	(19.0%)	45	(17.9%)
TFH-like PTCL	8	(57.1%)	9	(42.9%)	110	(50.9%)	127	(50.6%)
ALK-NEG ALCL	3	(21.4%)	2	(9.5%)	14	(6.5%)	19	(7.6%)
Other	1	(7.1%)	6	(28.6%)	42	(19.4%)	49	(19.5%)
Missing	1		1		9		11	

Auto (8%) and allo-SCT (6%) may grant durable remissions in a highly selected subset of patients



Camus V *et al*, JCO 2024

Different outcomes of major T-cell lymphoma entities post-allo-SCT n=1292 (>50% for PTCL-NOS; 1/3 for AITL)

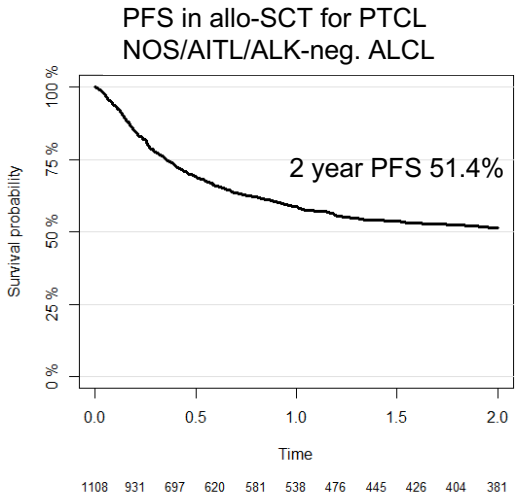
Conditioning regimen
-RIC 53%
-MAC 47%

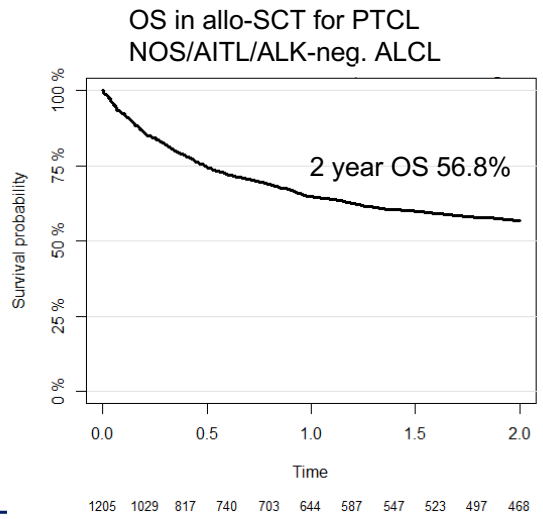
Donor type
-MRD 45%
-UD 55%/mMUD 7

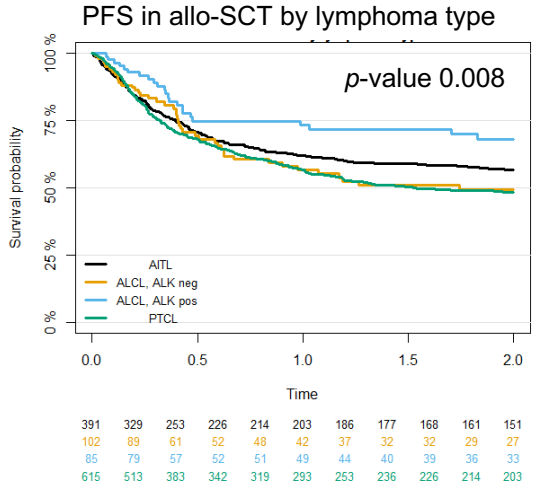
Remission status at allo-SCT
-**CR1/PR1 52%**
-CR2/PR2 and beyond 20%
-SD/PD 19%

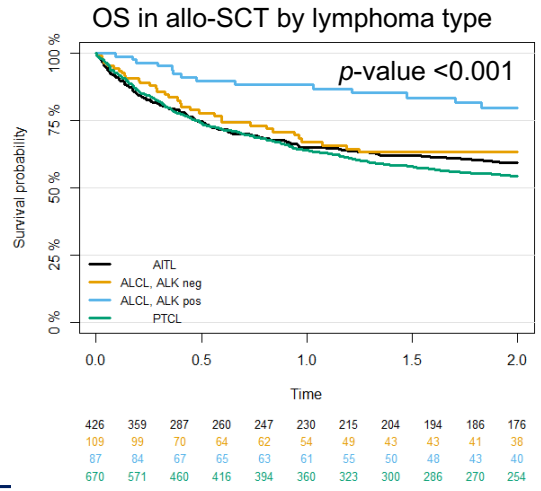
Median age 51 (43-59)

No of Rx lines prior to allo-SCT
-one line 18%
-two lines 33%
-**≥ three therapy lines 49%**









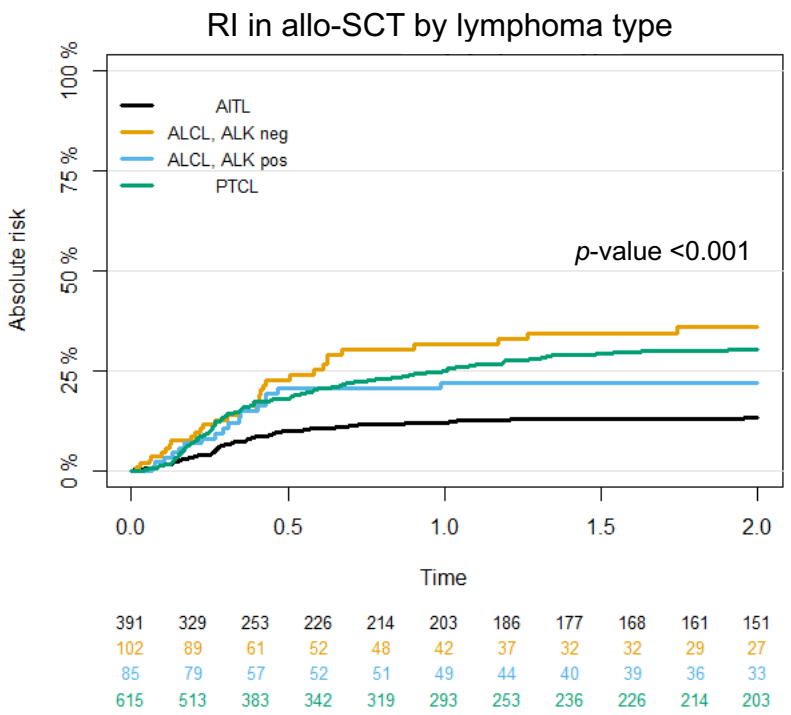
2-year PFS:
ALCL ALK-pos. 68%
AITL 56.6%
ALCL ALK-neg. 49.4%
PTCL NOS 48.3%

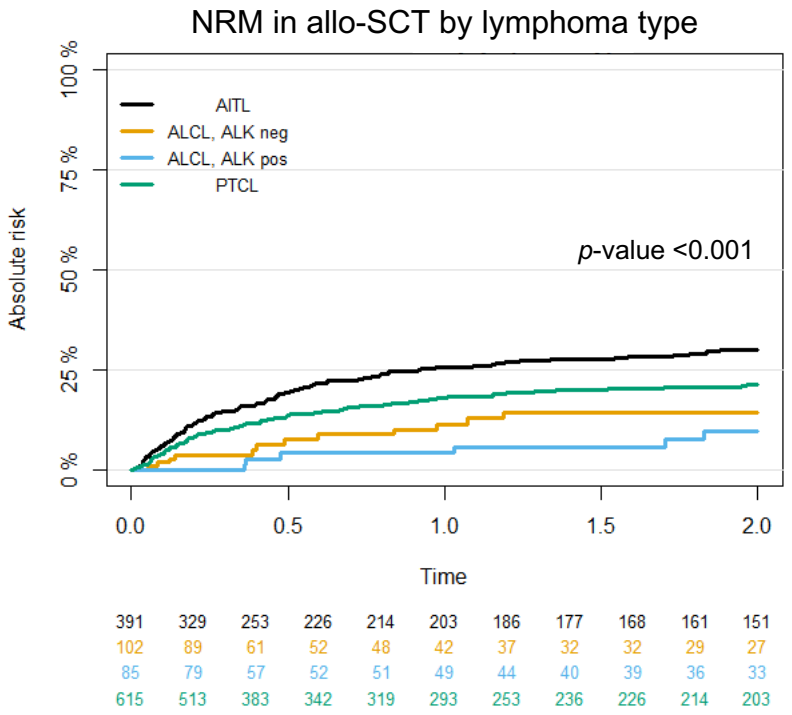
2-year OS:
ALCL ALK-pos. 79.9%
ALCL,ALK-neg. 63.3%
AITL 59.4%
PTCL, NOS 53.3%

Shumilov E *et al*, EHA 2024

RI and NRM in major T-cell lymphoma entities following allo-SCT

2-year RI:
ALCL ALK-neg. 36.2%
PTCL NOS 30.3%
ALCL ALK-pos. 23.2%
AITL 13.4%





2-year NRM:
AITL 30.0%
PTCL NOS 21.4%
ALCL ALK-neg. 14.4%
ALCL ALK-pos. 11.6%

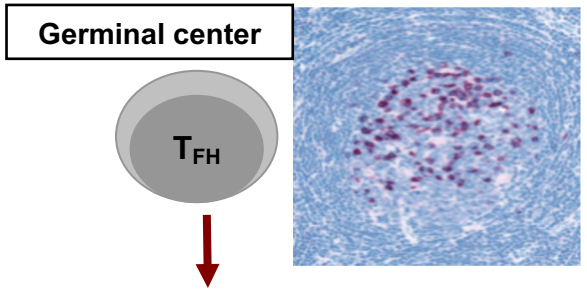
Shumilov E *et al*, EHA 2024

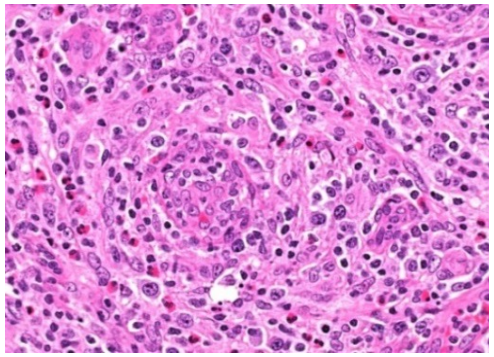
Are you planning to perform allo-SCT in CR2?

- A Definitely ‘YES’
- B Discuss ‘YES’ – but manage expectations
- C Undecided
- D Discuss ‘NO’
- E Definitely ‘NO’

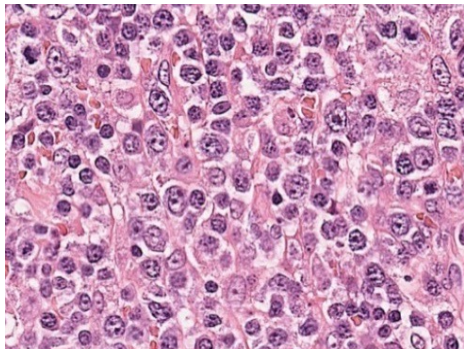
(Nodal) Follicular Helper T-cell lymphomas

- ✓ Occur in Elderly
- ✓ Frequent autoimmunity
- ✓ Frequent extranodal involvment
- ✓ Poor prognosis
- ✓ Few therapeutic progresses

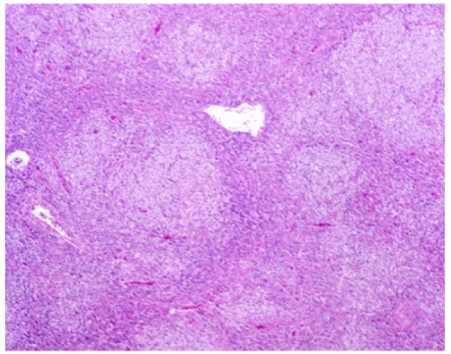




Angioimmunoblastic type



NOS



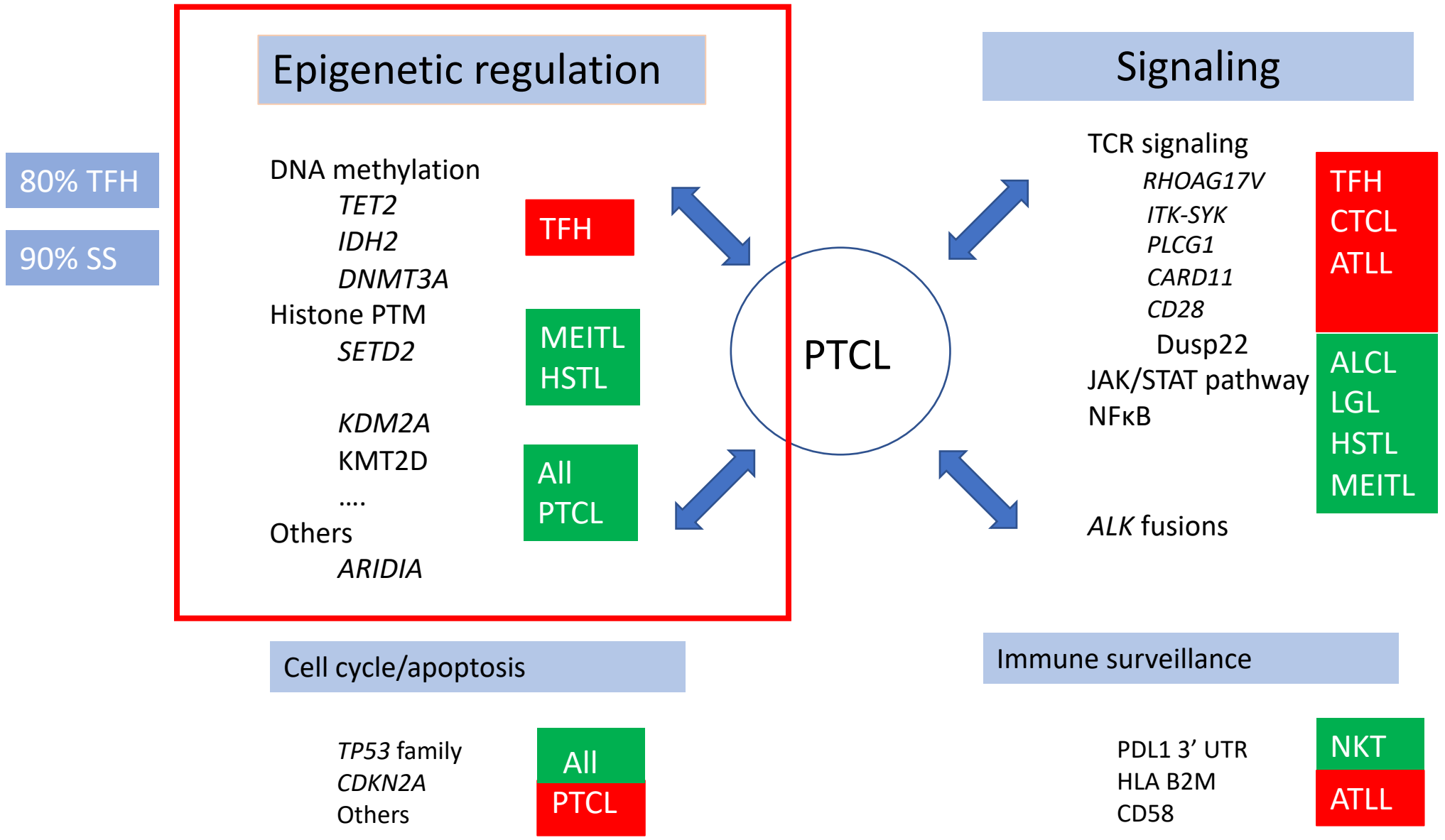
follicular type

Microenvironment

Frequency

Campo *et al*. Blood 2022; Alaggio *et al*. Leukemia 2022

Pathways involved in PTCL oncogenesis



Lemonnier F EHA 2024

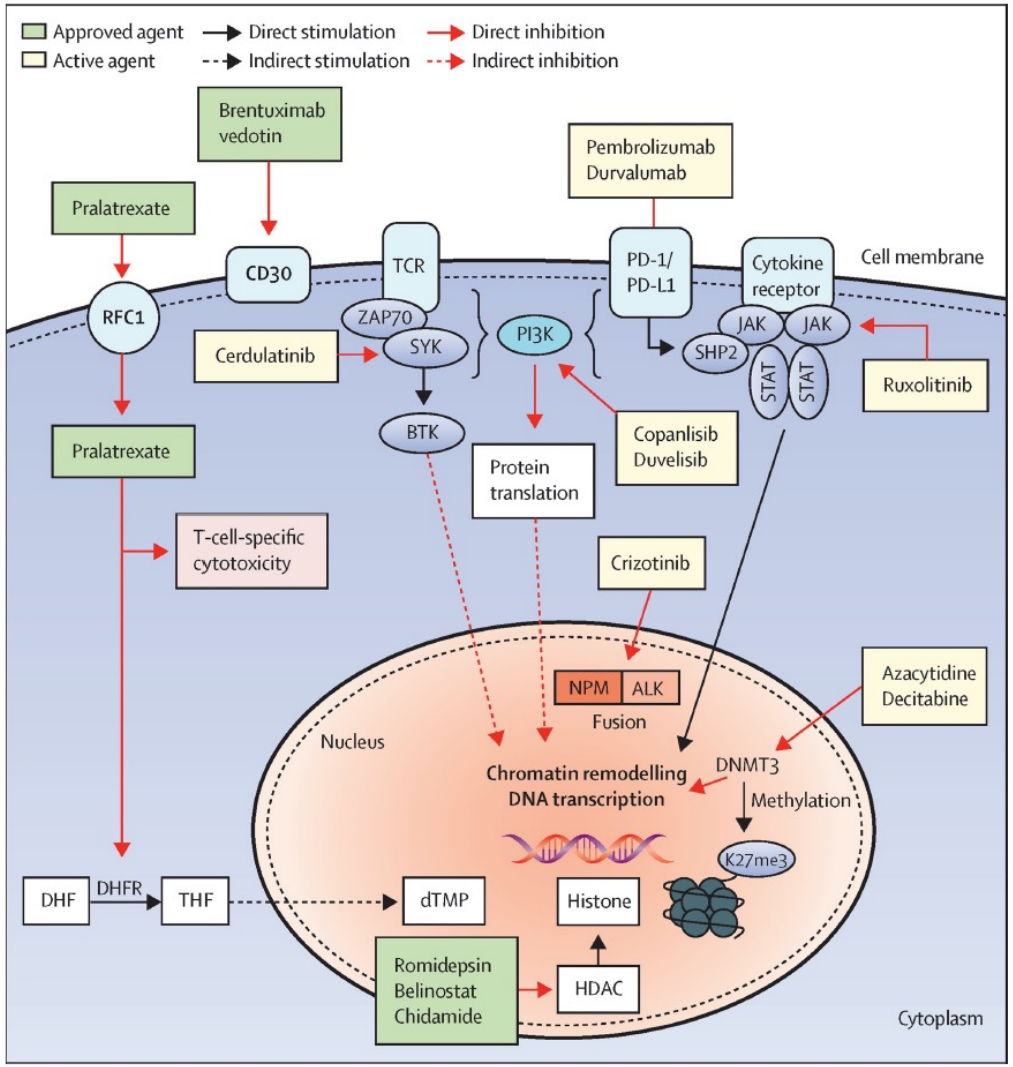
Potentially targetable intracellular signals in PTCL

Pi3K
Copanlisib
PRIMO trial — Duvelisib
Tenalisib
Linperlisib

JAK: Ruxolitinib
Golidocitinib

ALK inhibitors:
UK access? — Crizotinib
Alectinib

EZH1/EZH2 inhibitors:
VALENTINE trial — Valemetostat



SYK/(JAK)
Cerdulatinib

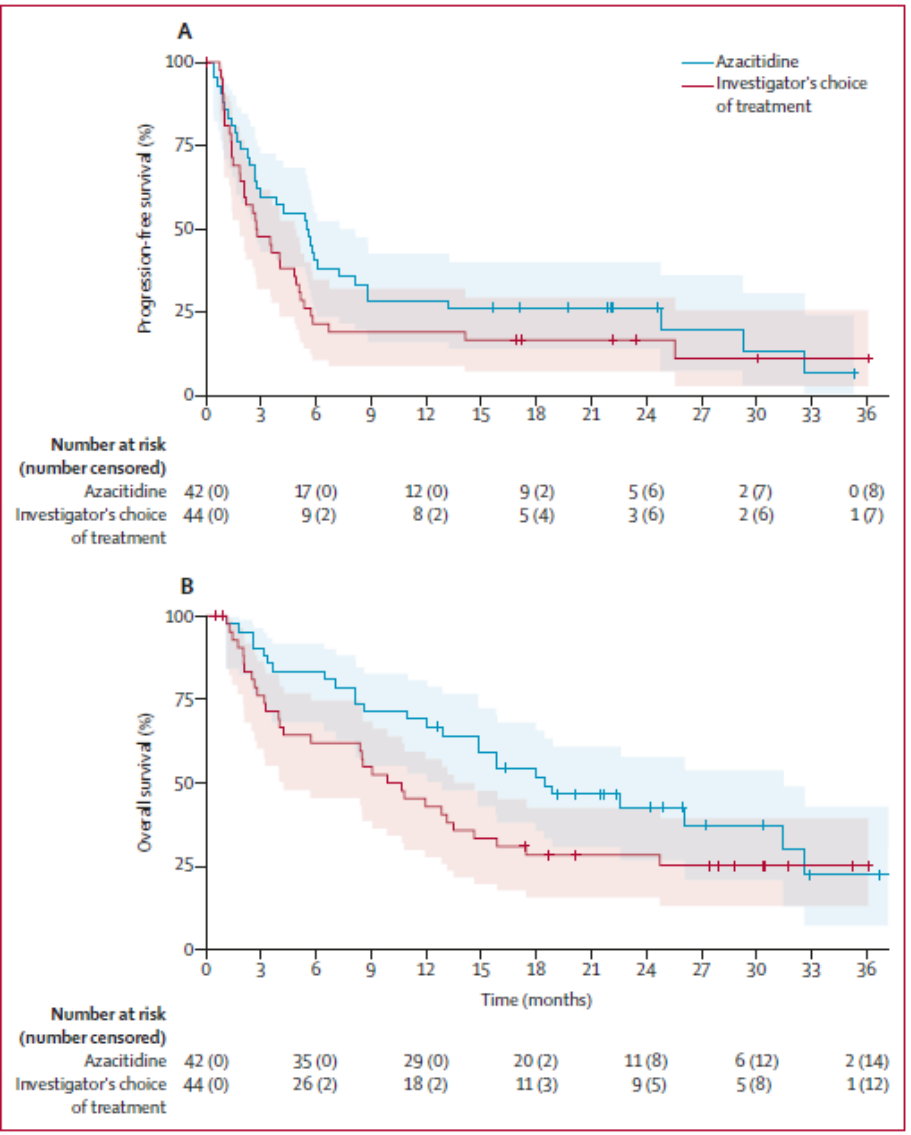
BCL2:
Venetoclax

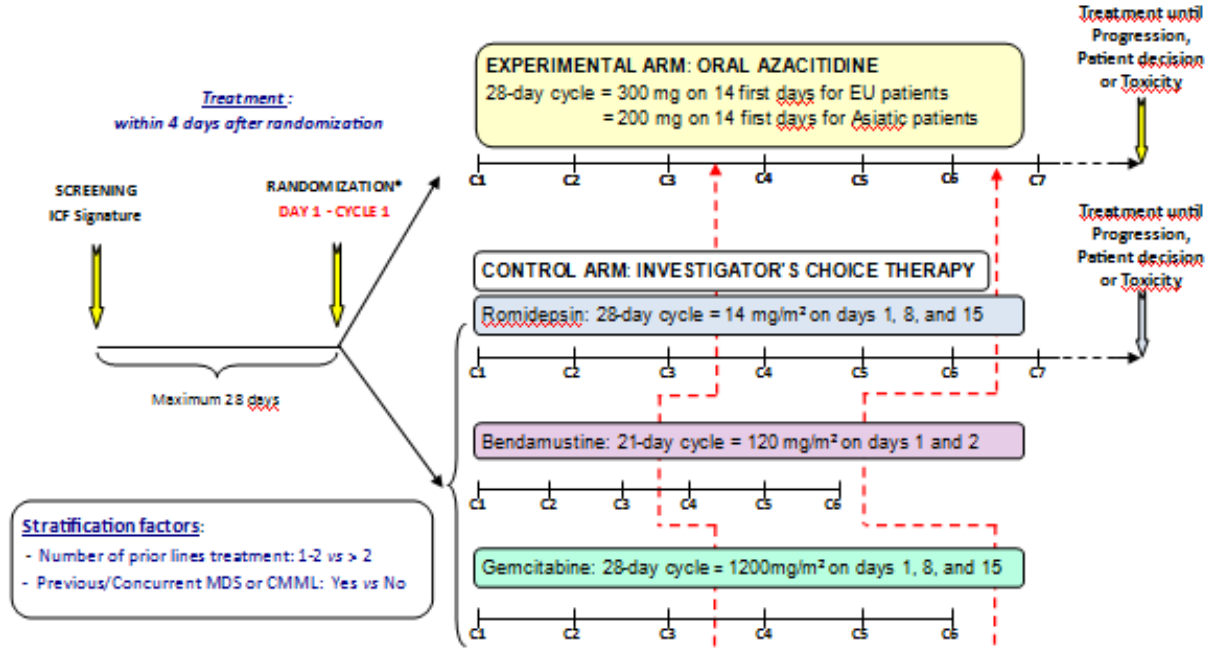
Hypomethylators
Azacytidine — Trial: ORACLE
Decitabine

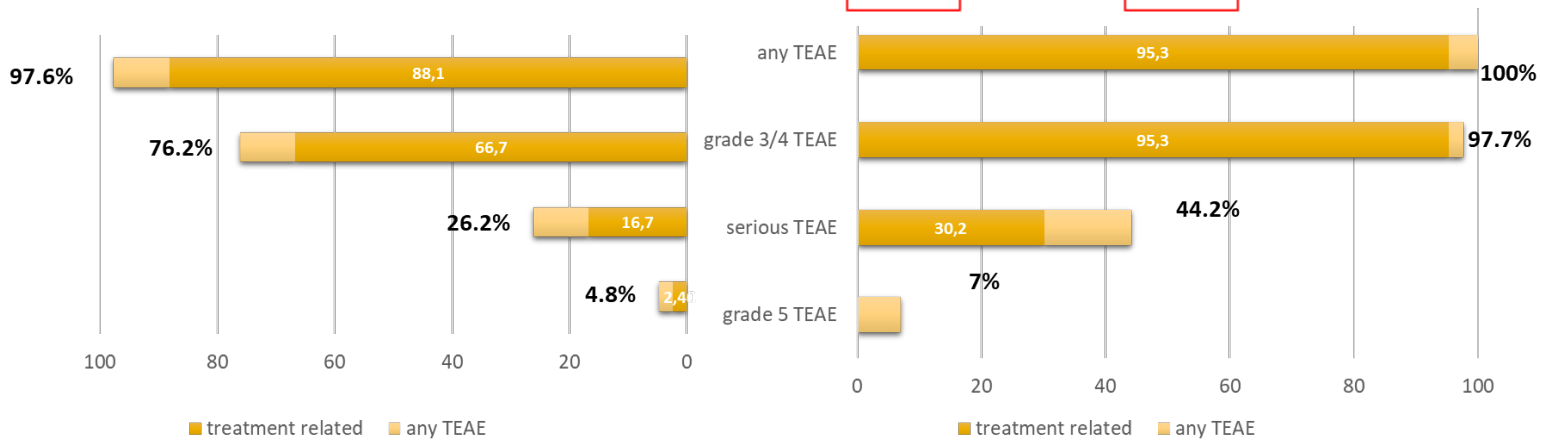
HDAC: — Trial: ROMICAR
Romidepsin
Belinostat
Chidamide

ICML 2023

Hypomethylating agent Azacitidine in R/R TFHL: ORACLE study







Dupuis *et al*. Lancet Haematol. 2024

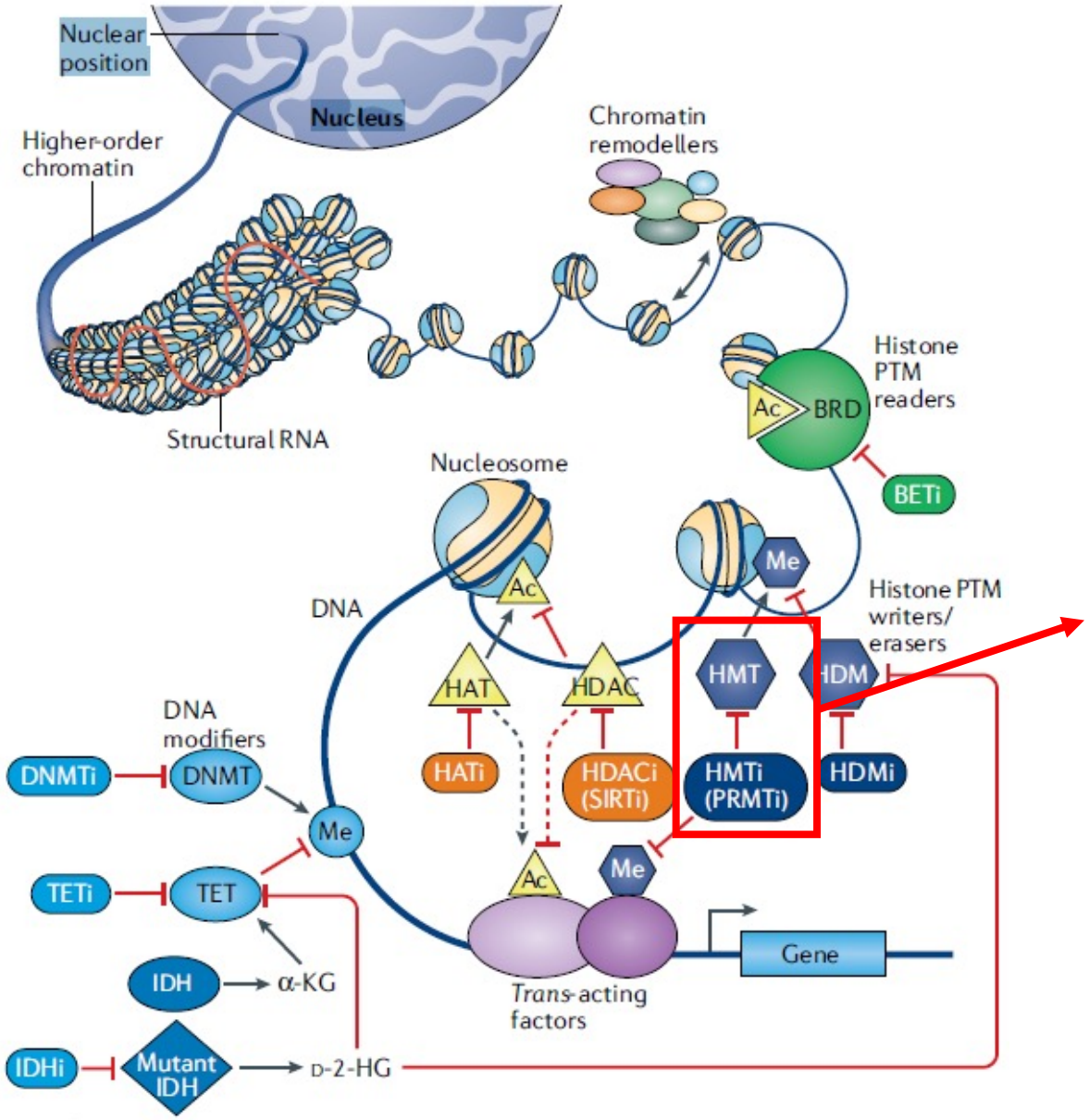
Global differences in approval of drugs for relapsed/refractory PTCL

	U.S.(FDA)	Canada (HC)	Europe (EMA)
Pralatrexate	Approved 2009	Approved 2018	Not approved for marketing
Romidepsin	Approved 2012 (withdrawn)*	Approved 2013 (withdrawn)*	Not approved for marketing
Brentuximab Vedotin	Approved 2011 (relapsed ALCL)	Approved 2013 (relapsed ALCL)	Approved 2011 (relapsed ALCL)
Belinostat	Approved July 2014	Withdrawn	Not approved for marketing
Crizotinib	Approved Jan 2021 (ALK-pos, 1-≤21 y)	Not approved	Not approved

* Withdrawn due to negative Ro-CHOP *vs* CHOP study

Zinzani PL. ICML 2023

Other epigenetic targeting approach



EZH1/EZH2

Valemetostat

VALENTINE-PTCL01: global, multicenter, open-label, single-arm, Phase 2 trial of valemetostat in R/R PTCLs

Eligibility Criteria

- ≥ 18 years
- Confirmed PTCL diagnosis (WHO 2016 classification[1])
- ECOG PS score ≤ 2
- ≥ 1 prior line of systemic therapy

  Patients with ALCL received prior brentuximab vedotin treatment

R/R PTCL

N = 133

N = 119 with PTCL histology confirmed by central pathology

Valemetostat

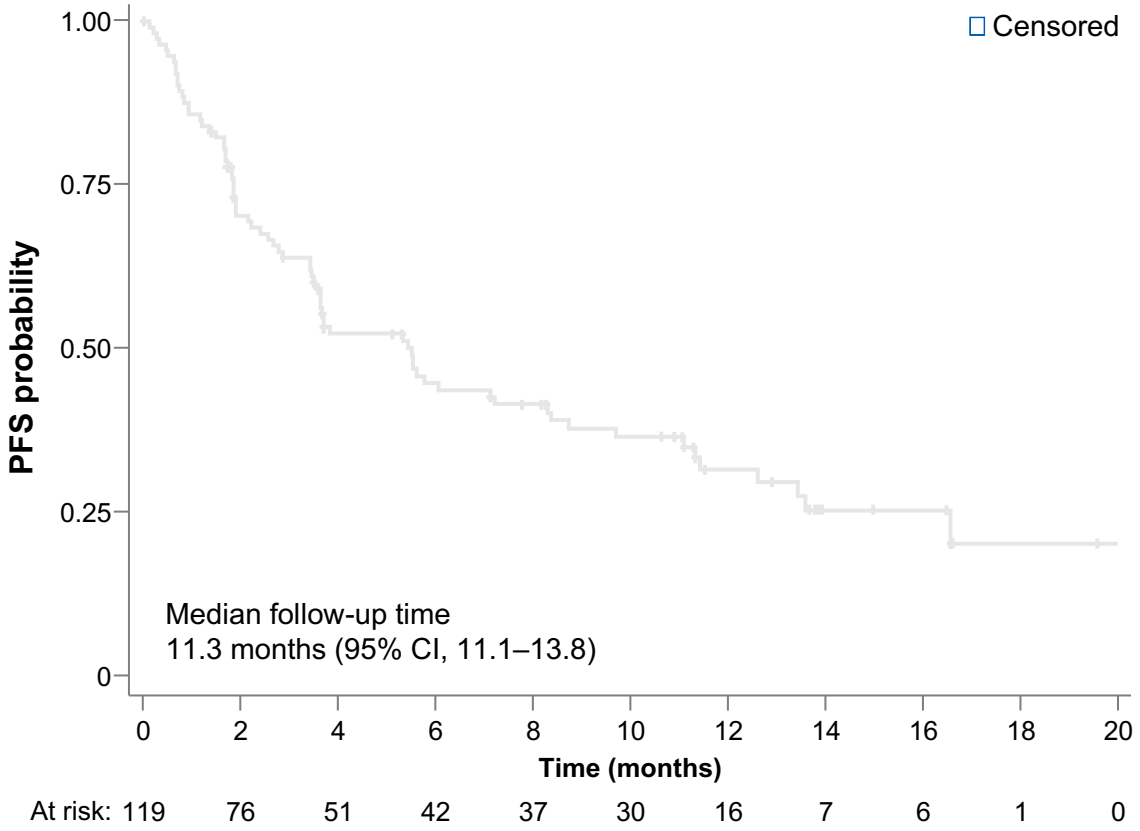
200 mg/day

Continuous 28-day cycles until PD or unacceptable toxicity

Progression-Free Survival and Overall Survival

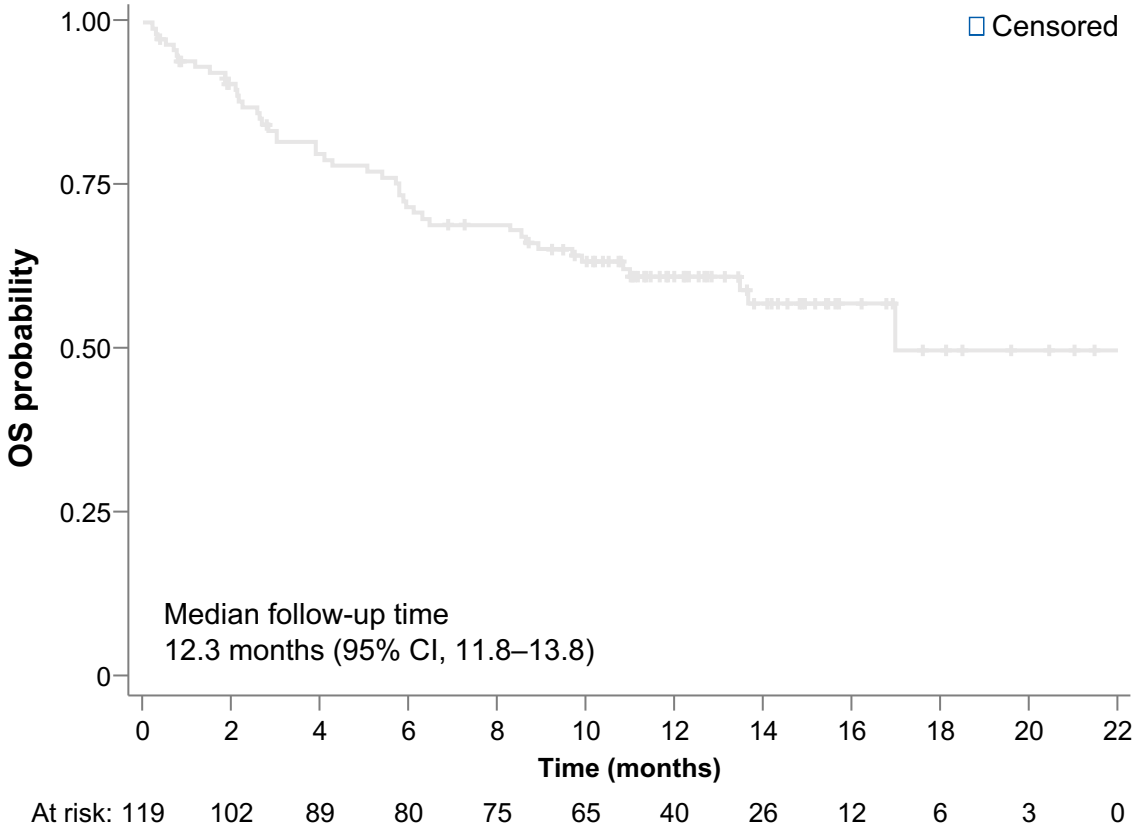
PFS[a]

(N = 119)
Median 5.5 months (95% CI, 3.5–8.3)



OS

(N = 119)
Median 17.0 months (95% CI, 13.5 months to NE)



Data cutoff: May 5, 2023.
[a] PFS evaluated by BICR CT-based assessment.

Zinzani PL *et al*, Lancet Onc 2024

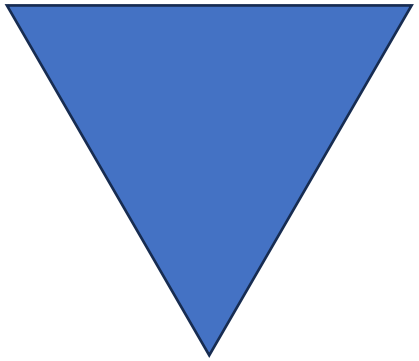
Moving to combination

Epigenetic targeting drugs

romidepsin
azacitdine
valemetostat
belinostat
chidamide
others

Signaling targeting drugs

duvelisib
cerdulatinib
ruxolitinib
golidocitinib
others



others

cellmod
checkpoint inhibitors:anti PD1
chemotherapy
brentuximab vedotin
others

Moving to combination

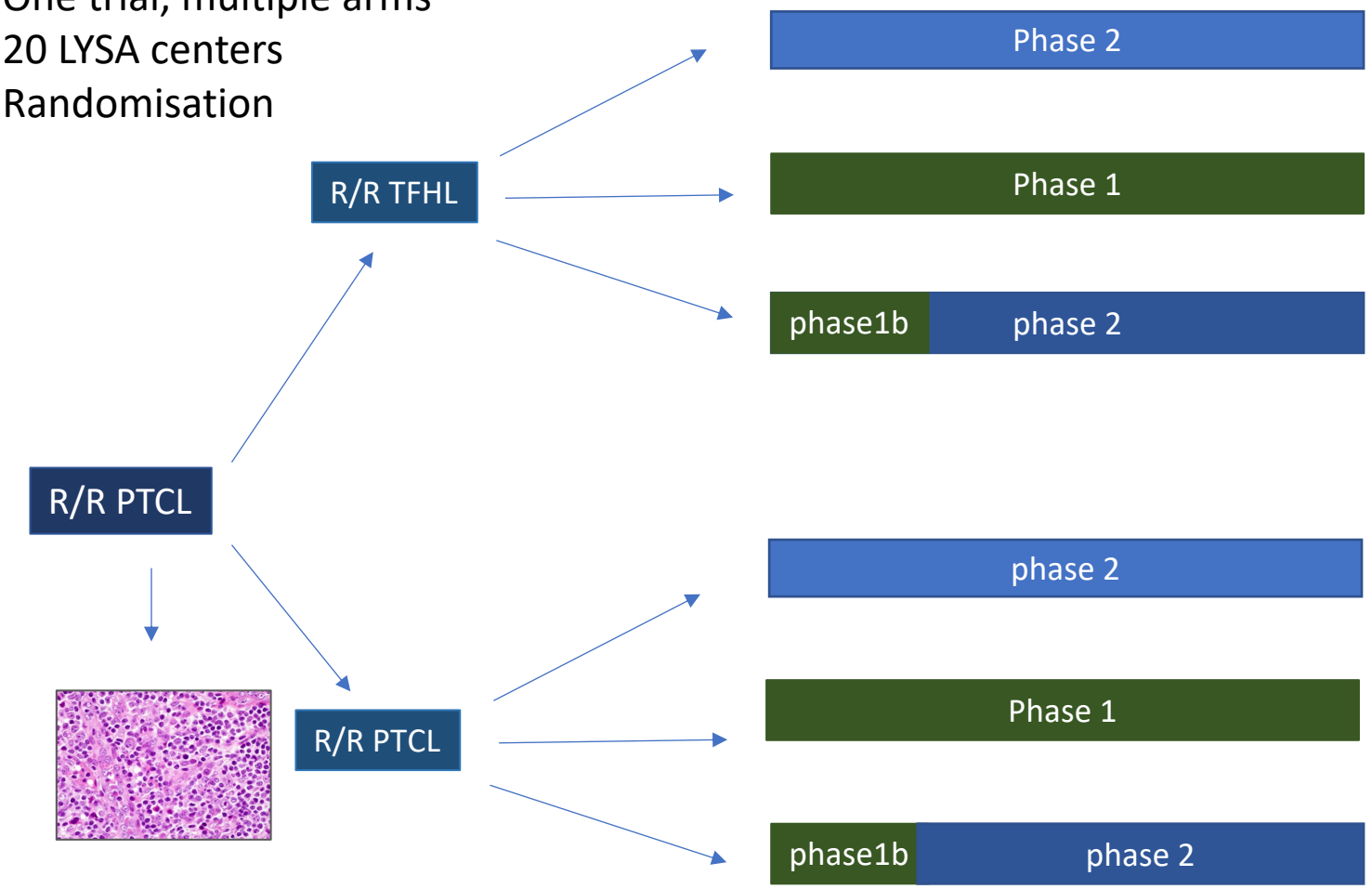
Romidepsin+ duvelisib

Histology	Treated	Evaluable	ORR N (%)	CR N (%)	Bridged to Allo SCT N (%)
PTCL	**55**	**53**	**31 (58)**	**22 (42)**	**15 (28)**
PTCL NOS	20	19	10 (53)	6 (32)	3 (16)
AITL/TFH	19	19	13 (68)	11 (58)	7 (37)
PC γδ	3	3	1 (33)	1 (33)	1 (33)
ALCL	3	3	3 (100)	2 (67)	2 (66)
HSTCL	2	2	1 (50)	0	1 (50)
Aggr epidermotropic CD8+	2	2	1 (50)	1 (50)	0
Other TCL	6	5	2 (40)	1 (20)	1 (20)

Horwitz *et al*. Nature Medicine 2024

Planned plaTform trial

One trial, multiple arms
20 LYSA centers
Randomisation



Biopsy
viable
congelation

Primary objective:
- mPFS based on investigator assessment

Secondary objectives:
- ORR
- CR
- OS
- Safety
- duration of response
- comparison with a synthetic arm

Exploratory objectives
- identification of biomarkers of response
- Comprehensive studies on PDXs
- identifying new drugs and combinations

Evaluation: Lugano 2014

Phase 2
PFS 3.7=> 7.4 months
One sided α= 0.05
Power=0.8
N=31 patients/arm

Phase 1
Boin method
target toxicity rate for the MTD is 0.3
N=18 patients

(further) Patient management Case 1

Angioimmunoblastic/TFH T-cell lymphoma

- Rash/fatigue/widespread LN April 2017
- PR to 4# CHOP
- PD after 6# CHOP Dec 2017

ROMICAR Jan 2018 to CMR

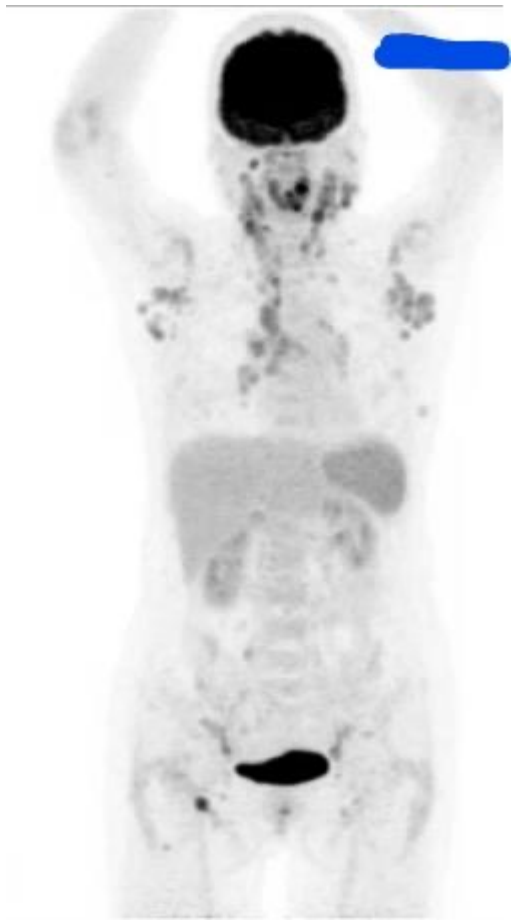
- Refused allo-SCT
- PD March 2019 (13 months Rx on ROMICAR)

Lenalidamide for 36 months

Valemostat April 2022 for > 18 months

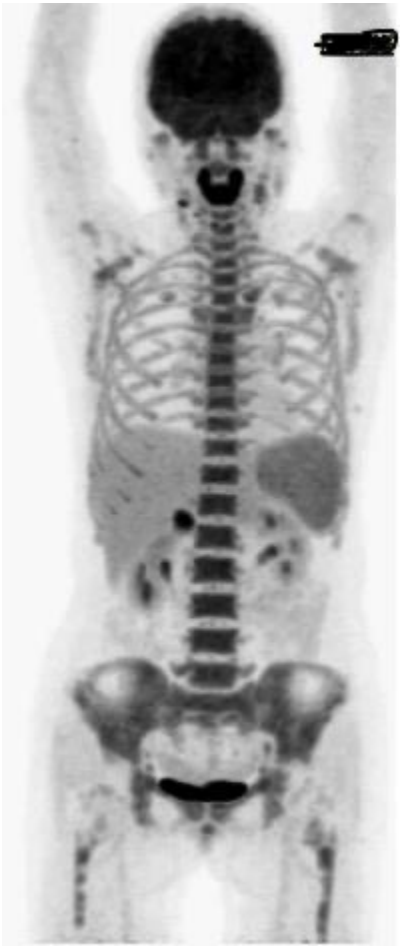
AUTO-4 (TRB1+ve)

PRE CHOP



April 2017-
Staging PET

POST CHOP



December 2017-
EOT PET

Engaging the immune system to treat PTCLs

Checkpoint inhibitors:

- NKTCL, hyperprogressions seen in PTCL

Tumor associated macrophage (TAM) activation:

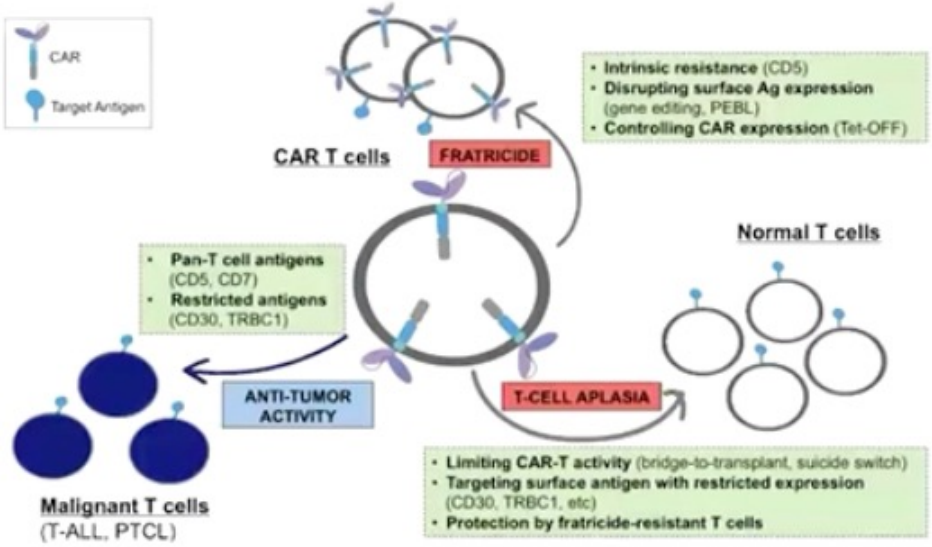
- anti CD47

CAR-T

- Targets: Pan-T(CD5-CD7)/restricted (CD30, TRBC1)
- Fratricide killing
- T-Cell aplasia

Bispecific antibodies

- antiCD30/CD16a (AFM13). NK targeting towards the tumor



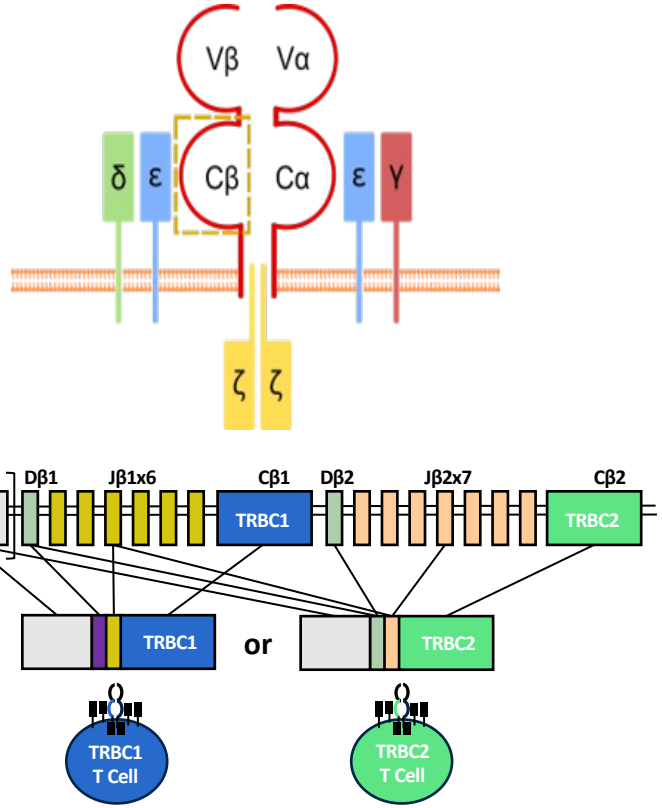
From: Scherer et al. Front Oncol. 2019; 9: 126. doi: 10.3389/fonc.2019.00126

- **PTCL has not benefited from immunotherapy**
- **Pan T-cell depletion is highly toxic**
- **Few/no tumour-specific antigen targets in PTCL**

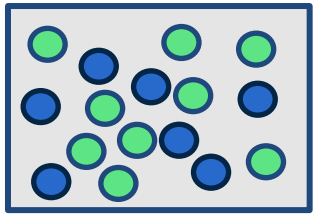
TRBC1 (or TRBC2) as a Target in PTCL

Structure of the T Cell Receptor or TCR

PTCL are clonal and express either TRBC1 or TRBC2



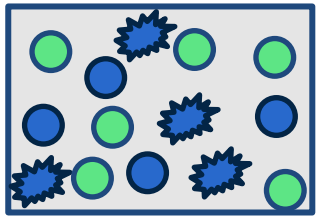
Healthy T Cells



Contain mixture of

- TRBC1+ cells
- TRBC2+ cells

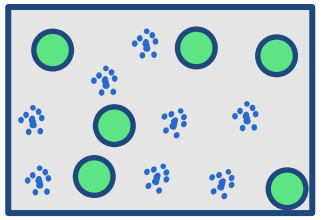
TRBC1+ T cell lymphoma



TRBC1+ tumour cell

TRBC1 CAR

TRBC2+ normal T cells retained
(immunity maintained)



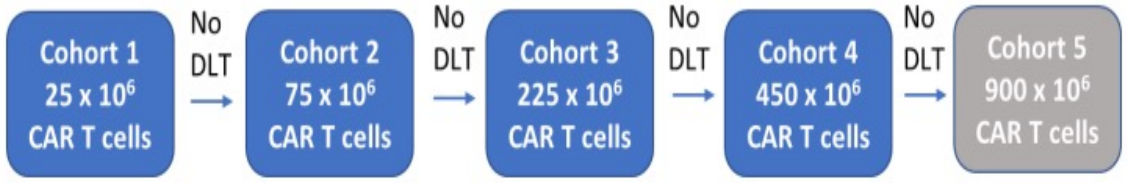
TRBC1+ cells killed
(tumour & healthy)

Maciocia et al., Nat Med 2017

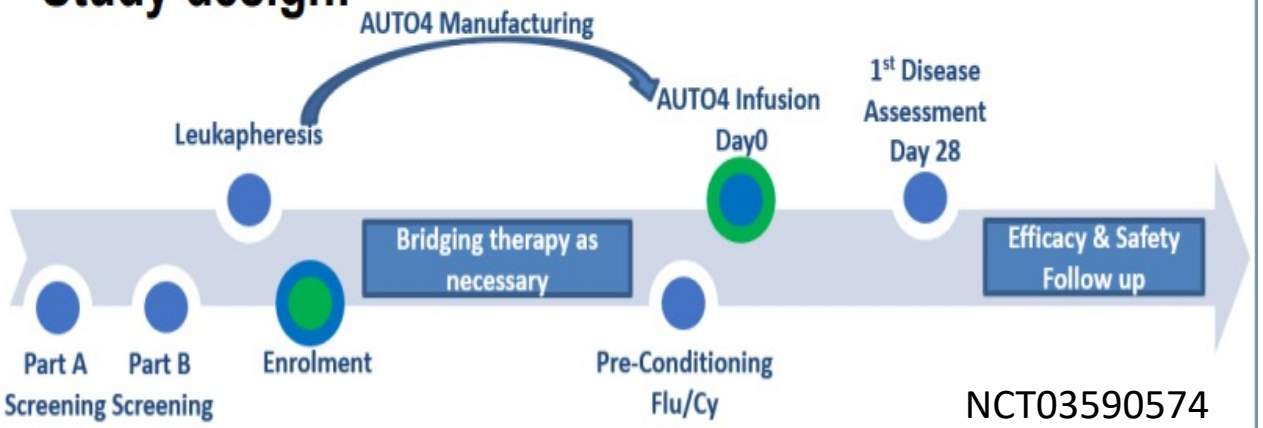
Current Landscape of CAR-T cells for T cell Lymphomas

TRBC1 Directed CARs

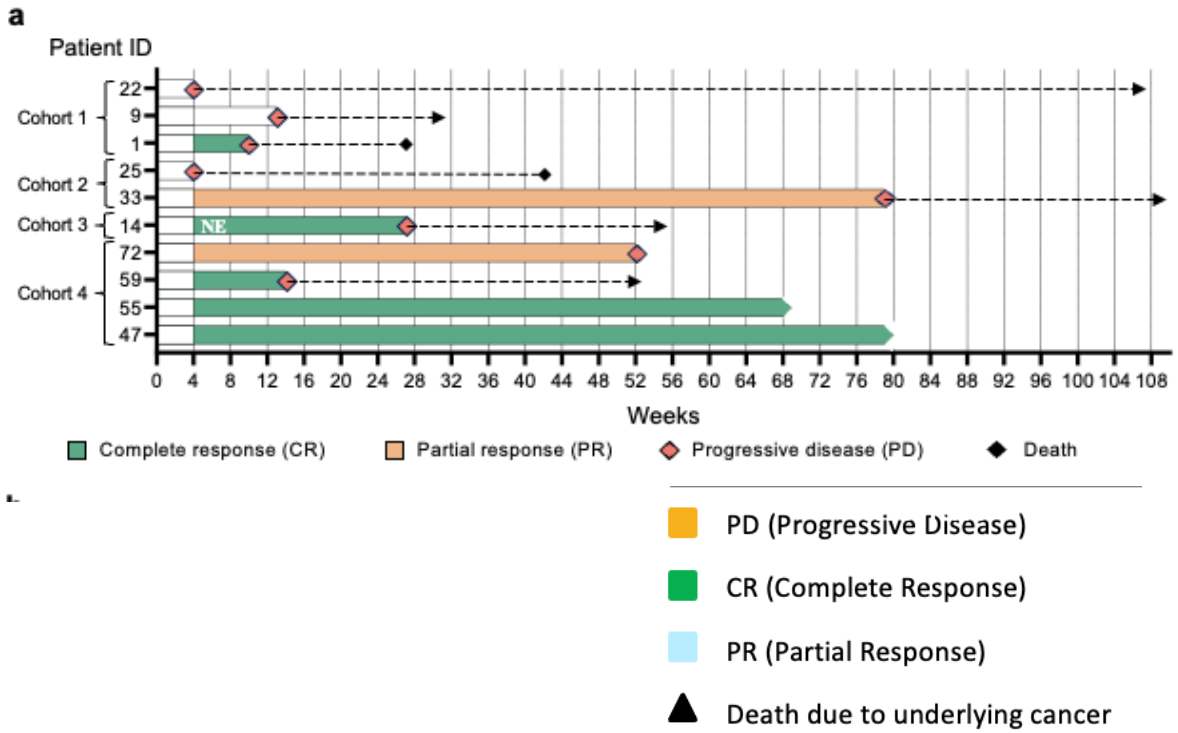
- **Phase I dose escalation:**



- **Study design:**



NCT03590574



N=10
Median prior lines = 3 (1-5)
Advanced stage = 70%
Bridging received = 70%

CRS = 40% of pts (25% grade 3)
No ICANS

4/4 patients at 450x10^6 cell dose achieved a response
2/4 remain in CMR beyond 12 months

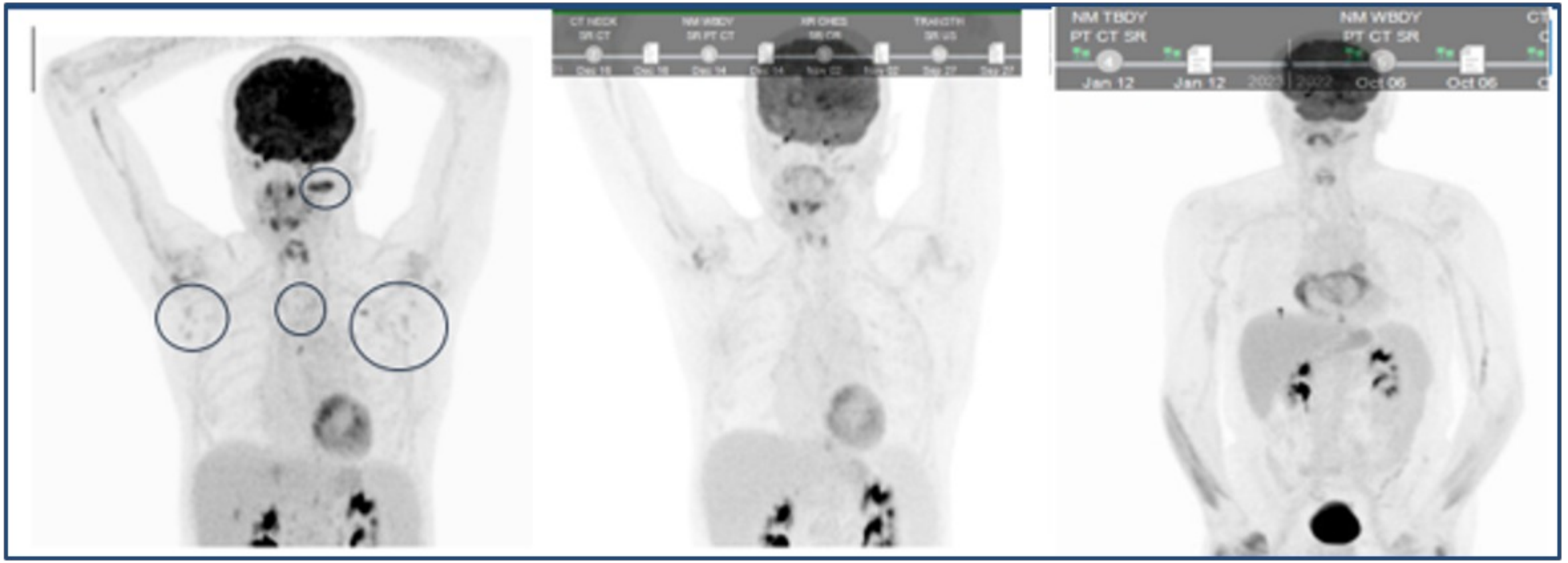
Cwynarski et al. Nature Medicine 2024

PET-CT in Responding Patients at 450Mio Cell Dose

Patient 055 (63 y.o. man, AITL)

CHOP → PD
ICE →PD
Duvelisib→PD

Baseline | **M1 (DS=2)** | **M18 (DS=1)**

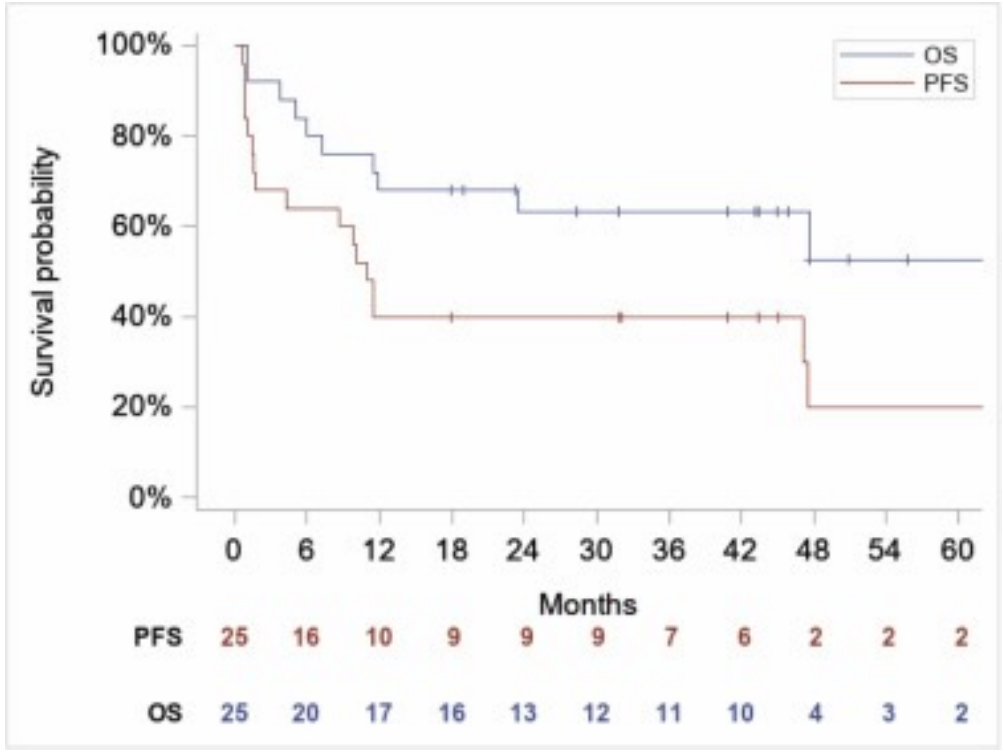


DS, Deauville score

Cwynarski et al. Nature Medicine 2024

ALK inhibition in ALK+ ALCL

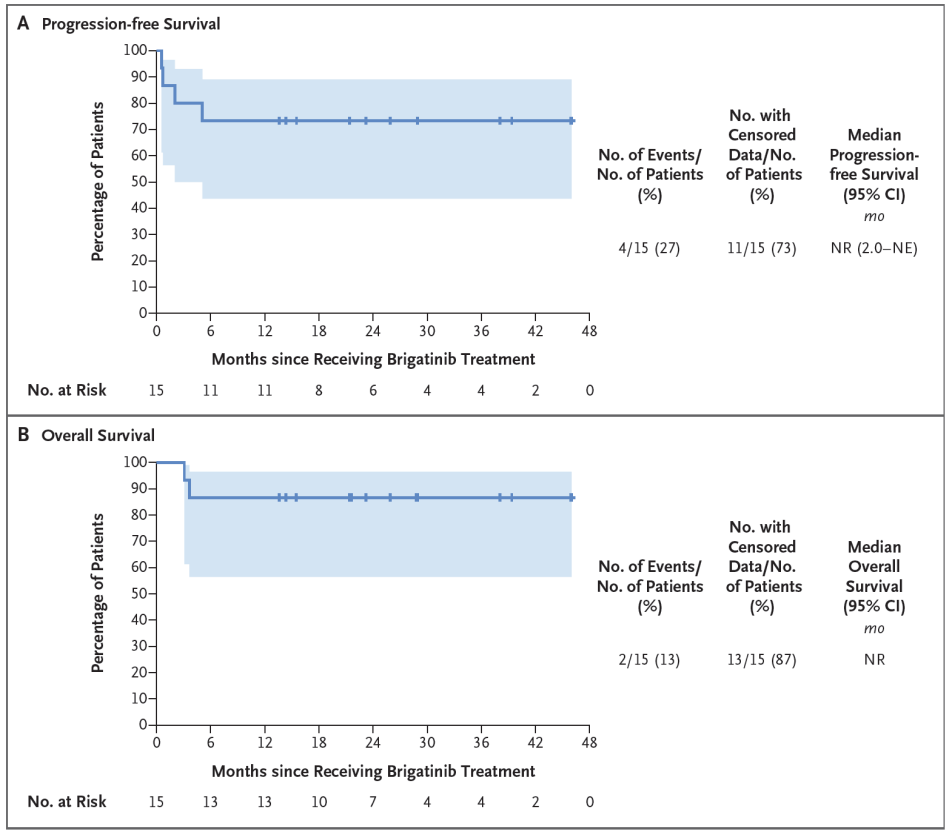
Crizotinib



ORR 64%

Brugieres et al. Eur J Cancer 2023

Brigatinib



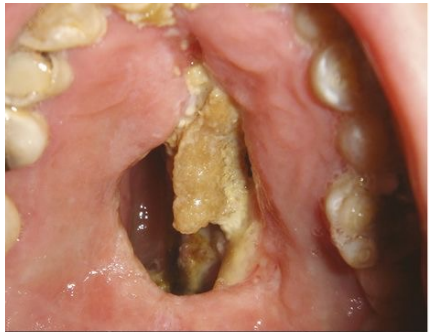
ORR 92%

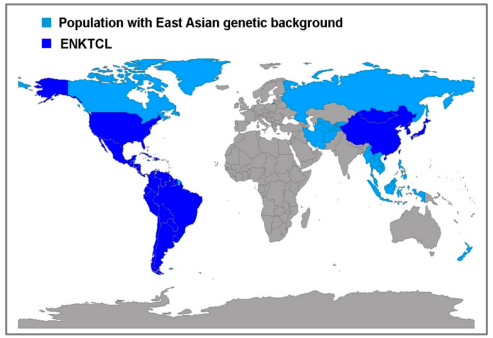
Veleanu, Lamant, Sibon. NEJM 2024

DETERMINE TRIAL

Rarer entities: Extranodal NK/T-cell lymphoma

- EBV driven disease
- Staging critical (inc MRI)
- Baseline PINK-E score refines clinical outcomes
- Anthracycline resistance
- Limited stage
  - Combined chemoradiotherapy
  - Early high dose radiotherapy key
  - EBV PCR prognostic





Age > 60 years
Stage III/IV
Non-nasal primary localisation
Distant lymph node involvement
Detectable plasma EBV DNA

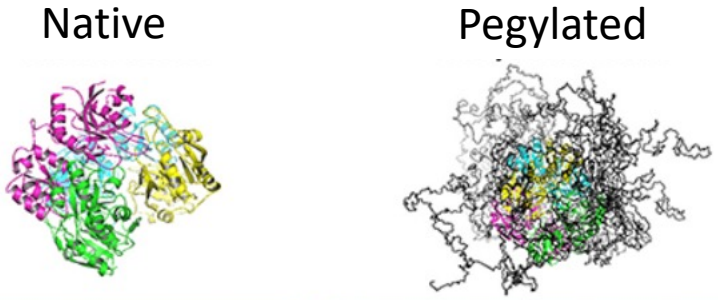
Points	Risk	3-yr OS
0	LOW	81%
1		
2	INT	55%
3	HIGH	21%
4		
5		

KimJ et al Hematol Oncol 2018 Dec 20;11(1):140

Eric Tse, and Yok-Lam Kwong Blood 2013;121:4997-5005

Extranodal NK/T-cell lymphoma - advanced

- Non-anthracycline platinum-based chemotherapy, +/- asparaginase
- L-asparaginase vs PEG-asparaginase
- Commonly used regimens
  - *SMILE*
  - DDGP
  - GELOX
  - AspMetDex
- Role of HSCT unclear
  - AlloSCT in CR1 for high-risk patients preferred
- Anti-PD-1/PD-L1 mAbs active



CNS-PINK

Extranodal involvement ≥ 2
PINK score INT/HIGH

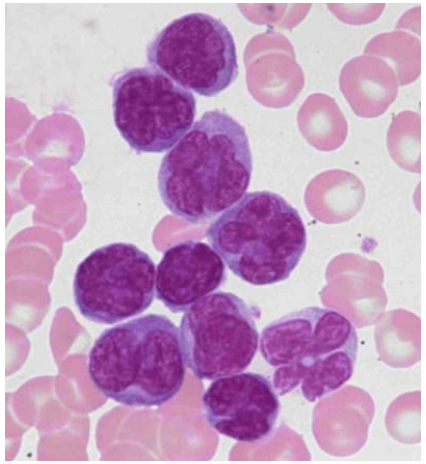
Points	Risk	2-yr CNS relapse
0	LOW	4.10%
1		
2	HIGH	22.80%

KimJ et al Blood 2020 Nov 26;136(22):2548-2556

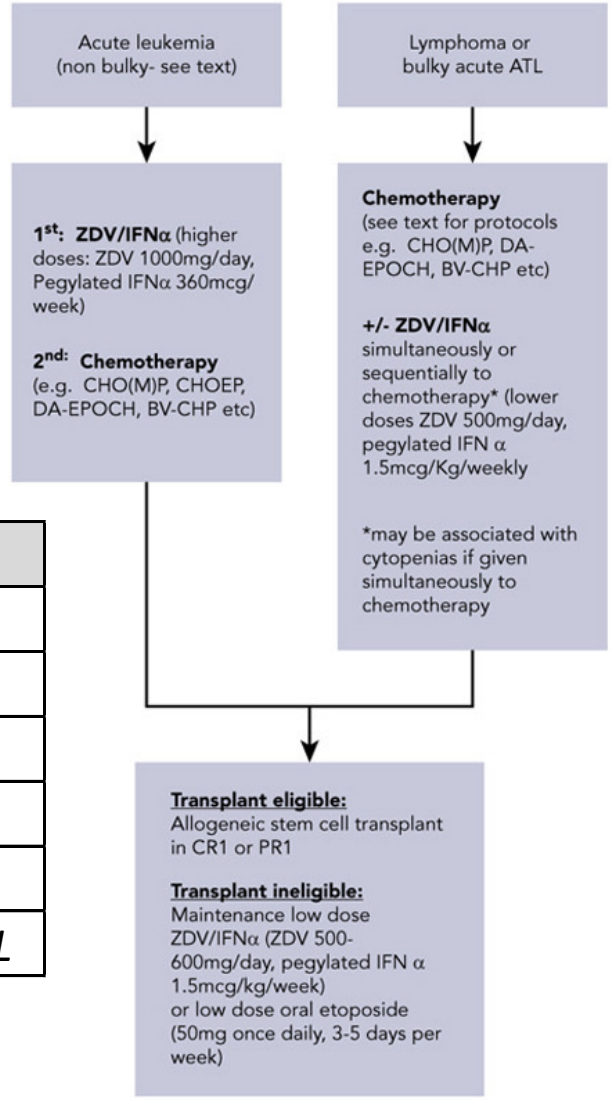
Adult T-cell leukaemia/lymphoma

- HTLV1 driven disease
- First-degree relatives/partner screening important
  - Involve national HTLV service

  http://www.htlv.eu/
- Heavily immunocompromised
- Poor clinical outcomes for lymphoma type
- CHOP +/- AZT/IFN-α
- High CNS risk
- Early alloSCT performed in CR key



Shimoyama classification
Smouldering
Chronic
Lymphoma
Acute
Primary cutaneous tumoural ATL

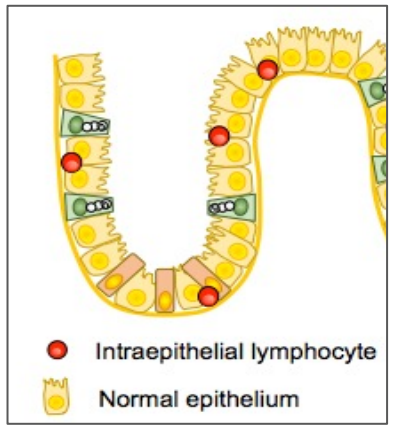


Cook et al Blood 2021 Jan 28;137(4):459-470

https://imagebank.hematology.org/image/63381/adult-tcell-leukemialymphoma-marrow

Aggressive Intestinal T-cell lymphoma

- EATL (previously EATL-I)
  - Enteropathy associated
  - Complex relationship with various stages of Coeliac disease
- MEITL (previously EATL-II)
  - No association with enteropathy



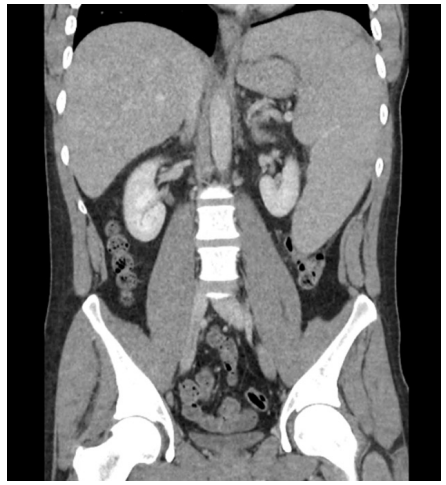
- 50% present with bowel perforation
- Performance status, malabsorption, malnutrition hamper chemo delivery
- Very poor clinical outcomes
- CHOP/CHOP vs SNLG/Newcastle

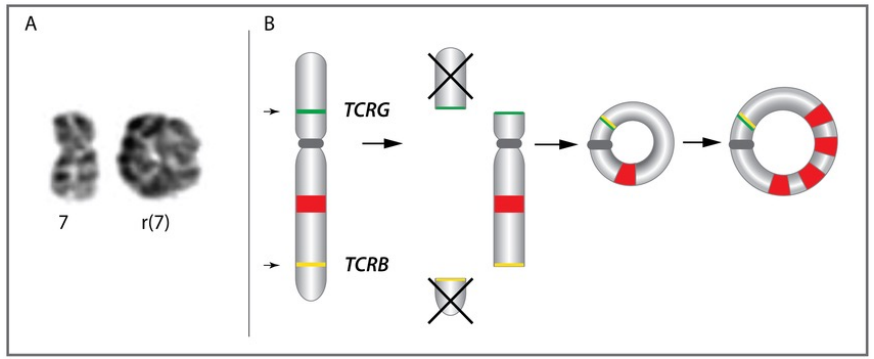
SNLG protocol	D1	D21	D42	D49	D70	D77	D98	AutoSCT
	CHOP	IVE	MTX	IVE	MTX	IVE	MTX	

n=11

D'Amore et al J Clin Oncol. 2012 Sep 1;30(25):3093-9
Philips et al Bone Marrow Transplant. 2020 Apr;55(4):840

Hepatosplenic T-cell lymphoma





Isochromosome 7q abnormality, Expression γδ-TCR

- Very rare
- Average age older than previously thought
- Case reports:linked with immune suppression
- Invove Liver, spleen and bone marrow
- Median survival 11 months
  - 5-year survival 20%
- Intensive multiagent non-anthracycline-based chemotherapy regimens often used
  - ICE, IVAC
- Aim for allogeneic stem cell transplant where possible

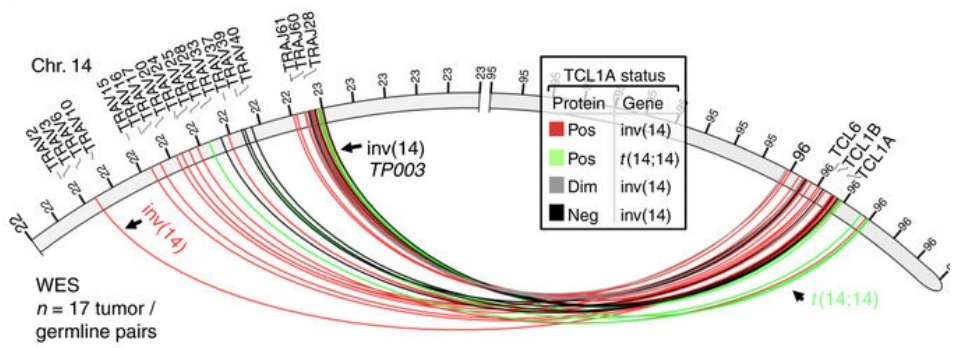
Ferreiro *et al* PLoS One 2014 Jul 24;9(7):e102977

T-prolymphocytic leukaemia

- Lymphocytosis, splenomegaly, low volume lymphadenopathy
- Up to 30% are asymptomatic
- 90% show rearrangement *TCL1A* or *MTCP1* locus
- Active T-PLL: IV Alemtuzumab
  - Pentostatin
- Risk of opportunistic infection
  - ACV, septrin, Azole, CMV PCR
- Consider alloSCT in CR1
- Alemtuzumab retreatment possible; recheck sCD52 status

Major criteria	Minor criteria (at least 1 required)
• >5 × 10^9/L cells of T-PLL phenotype in peripheral blood or bone marrow	• Abnormalities involving chromosome 11 (11q22.3; *ATM*)
• T-cell clonality (by PCR for TRB/TRG, or by flow cytometry)	• Abnormalities in chromosome 8: idic(8)(p11), t(8;8), trisomy 8q
• Abnormalities of 14q32 or Xq28 OR expression of *TCL1A/B*, or *MTCP1**	• Abnormalities in chromosome 5, 12, 13, 22, or complex karyotype
	• Involvement of T-PLL specific site (eg, splenomegaly, effusions)

* Cases without TCL1A, TCL1B, or MTCP1 rearrangement or their respective overexpression are collected as TCL1-family negative T-PLL.



Staber *et al* Blood 2019 Oct 3;134(14):1132-1143

Shrader et al Nat Commun. 2018 Feb 15;9(1):697

Conclusions

- R/R PTCL is an area of unmet need
- Innovative Rx approaches inc disease biology/molecular mechanisms
- Novel treatment platforms are urgently required
- The ‘one fits all’ approach does NOT work in PTCL
- The key for future development in PTCL treatment is:
  - Identify and target the specific subtypes
  - International collaboration

Acknowledgements

Matt Ahearne
Christopher Fox
Jessica Okosun
Jesca Boot
Dan Hodson

Gloria Iacoboni
Eleni Tholouli
Tobias Menne
David Irvine

Martin Pule
Paul Maciocia
Teresa Marafioti
Wolfram Brugger
P. Lao-Sirieix
Mathieu Ferrari
Silvia Basilico et al

CAR-T teams
UCLH, London, UK
VHIO Vall d'Hebron, Spain
Manchester Royal Infirmary, UK
Freeman Hospital, Newcastle, UK
QE Univ Hosp, Glasgow, UK