Targeted therapies for the treatment of Mature T cell lymphoma

Hayder Saeed, MD
Associate Member

Moffitt Cancer Center

Objectives

- WHO classification of mature T cell lymphoma
- CD30 in mature T cell lymphoma
- CHOEP
- ECHELON-2 trial
- Belinostat
- Prelatrexate
- Romidepsin
- Duvelisib
- Azacitidine
- Cellular therapies

WHO classification of T cell lymphoma

ALCL:

- ALK-ALCL bearing TP63 rearrangements, loss of TP53 and/or overexpression of IL-2Rα are associated with poor outcomes.
- DUSP22 rearrangement have not been confirmed to be a good prognostic marker.

Nodal T-Follicular helper cell lymphoma

- New family of terminology is proposed to signify them as disease entities
- nTFHL-AI: acquisition of TET2 and DMNT3a mutations
- nTFHL-F, nTFHL-NOS are less well studied

ENKTL

- The qualifier “nasal-type” dropped from its name in WHO-HAEM5 in accordance with the recognized presentation of this disease at various extranodal sites.

Nodal EBV-positive T and NK-cell lymphoma

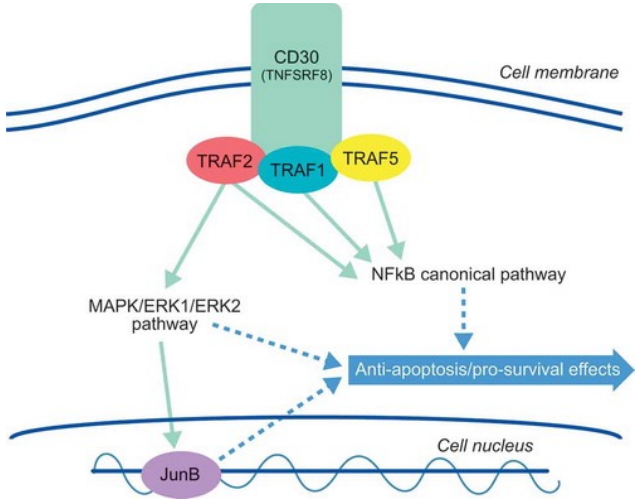
- Occurs mostly in East Asians, and is now recognized as a distinct entity in WHO-HAEM5; previously it was subsumed as a subtype under the entity of PTCL-NOS.

Anaplastic large cell lymphoma	
ALK-positive anaplastic large cell lymphoma	Anaplastic large cell lymphoma, ALK-positive
ALK-negative anaplastic large cell lymphoma	Anaplastic large cell lymphoma, ALK-negative
Breast implant-associated anaplastic large cell lymphoma	(Same)
Nodal T-follicular helper (TFH) cell lymphoma	
Nodal TFH cell lymphoma, angioimmunoblastic-type	Angioimmunoblastic T-cell lymphoma
Nodal TFH cell lymphoma, follicular-type	Follicular T-cell lymphoma
Nodal TFH cell lymphoma, NOS	Nodal peripheral T-cell lymphoma with TFH phenotype
Other peripheral T-cell lymphomas	
Peripheral T-cell lymphoma, not otherwise specified	(Same)
EBV-positive NK/T-cell lymphomas	
EBV-positive nodal T- and NK-cell lymphoma	*Not previously included*

Alaggio 2022

CD30 in T cell lymphoma

- CD30 is a 120 kDa transmembrane glycoprotein receptor. An 85 kDa soluble CD30 form (sCD30) can also be detected in vivo in inflammatory states and in CD30-expressing malignancies, which may be an independent predictor of prognosis in patients with CD30-expressing lymphomas.
- CD30 activation promotes a diverse range of effects including cell proliferation, differentiation, survival, or apoptosis, with specific effects likely to be dependent on the cell type, activation status, or cell transformation status
- CD30 expression is minimal in healthy adults but is most prominent in activated B cells, T cells, and NK cells, although it accounts for less than 1% of circulating activated lymphocytes
- Studies have shown that viral infection can increase the percentage of CD30-expressing activated peripheral blood cells from 0.1% at baseline up to 95% within 3 days
- Distinguishing between CD30-expressing neoplastic cells and CD30 expression in non-neoplastic activated lymphocytes is a key challenge.



Karube 2021

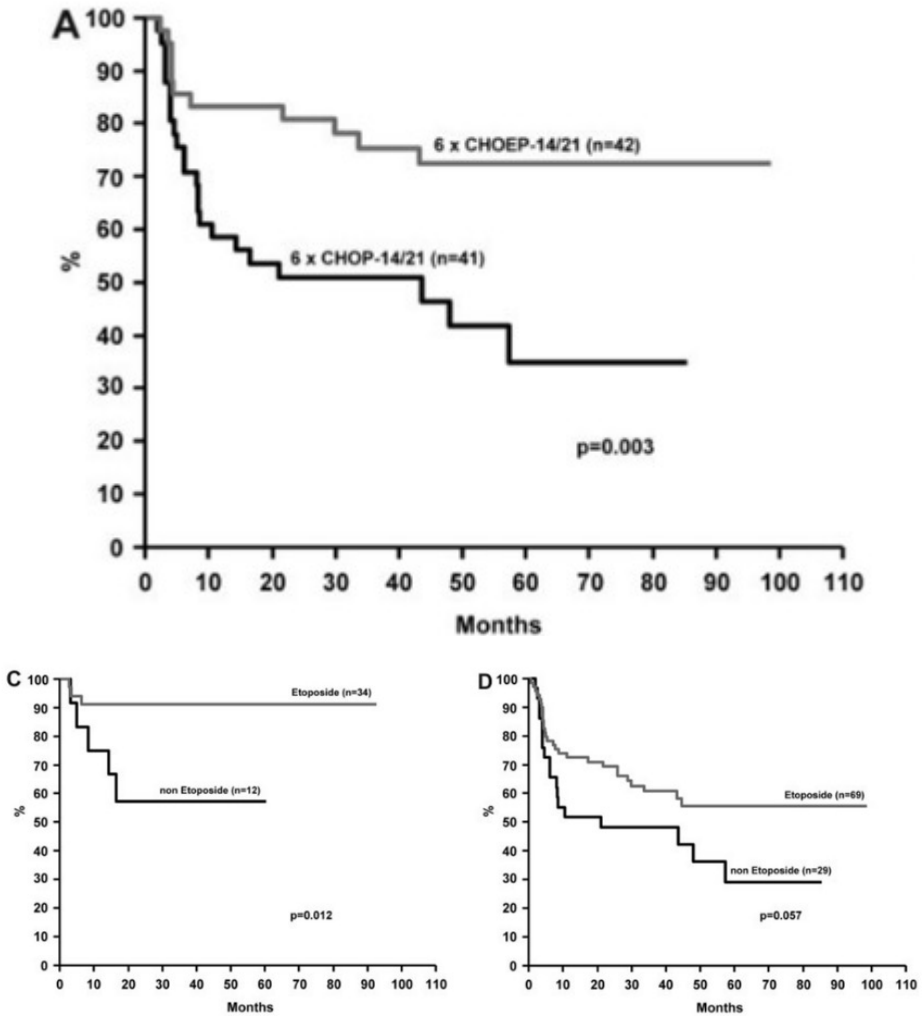
CD30 in T cell lymphoma

Reference	Method	CD30 antibody	CD30+ % cell cutoff	PTCL-NOS	AITL	ATLL	ENKTL	ALK− ALCL	ALK+ ALCL	EATL	CTCL/MF
Karube et al. 2008 (N = 319) [45]	FCM	NR	>70% 20–70%	5% 11%	0 32%	15% 24%	0 64%	58%* 35%*		– –	9%/– 9%/–
Savage et al. 2008 (N = 490) [33]	IHC	NR	>0% ≥80%	32% 5%	– –	– –	– –	100% –	100% –	– –	– –
Asano et al. 2011 (N = 47) [49]	IHC	Ber-H2	>30%	51%†	–	–	–	–	–	–	–
Duvic 2011 (N = 106) [50]	IHC	NR	>10%	–	–	–	–	–	–	–	–/11%‡
Weisenburger et al. 2011 (N = 217) [51]	IHC	NR	>20%	32%	–	–	–	–	–	–	–
Sabattini et al. 2013 (N = 192) [40]	IHC	Ber-H2	0: no staining 1+: >0% to <25% 2+: 25–50% 3+: >50–75% 4+: >75%	36% 13% 21% 13% 18%	51% 21% 12% 10% 0	– – – – –	20% 10% 30% 10% 30%	– – – – –	– – – – –	0 0 22% 0 78%	–/41% –/47% –/6% –/0 –/6%
Bossard et al. 2014 (N = 376) [44]	IHC	Ber-H2	0: <5% 1+: 5–24% 2+: 25–49% 3+: 50–75% 4+: >75%	42% 26% 9% 10% 13%	37% 47% 10% 5% 0	44% 11% 33% 11% 0	54% 7% 11% 14% 14%	0 0 0 0 100%	0 0 5% 2% 93%	50% 0 0 7% 43%	– – – – –
Lamarque et al. 2016 (N = 46) [52]§	IHC	NR	<5% 5–24% 25–49% 50–75% >75%	10% 10% 30% 30% 20%	0% 100% 0% 0% 0%	100% 0% 0% 0% 0%	– – – – –	0 0 0 0 100%	0 0 20% 20% 60%	0% 100% 0% 0% 0%	14%/– 0/– 0/– 14%/– 71%/–
Wang et al. 2017 (N = 122) [35]	IHC	NR	0: no staining 1+: >0% to <25% 2+: 25–50% 3+: >50–75% 4+: >75%	– – – – –	– – – – –	– – – – –	30% 38% 18% 10% 5%	– – – – –	– – – – –	– – – – –	– – – – –
Kawamoto et al. 2018 (N = 97) [37]	FCM and IHC	Ber-H2	≥1% ≥10% ≥20%	– – –	– – –	– – –	57% 55% 44%	– – –	– – –	– – –	– – –

Karube 2021

CHOEP

- Although there have been no randomized studies comparing CHOP and CHOEP regimens in PTCLs, a number of retrospective or phase 2 prospective studies have suggested a benefit of CHOEP. Due to the increased toxicity of CHOEP, this regimen is usually preferred in patients less than 60 years old.
- The effect is more pronounced in ALCL-ALK+ve patients versus other types of T cell lymphoma.
- CHOEP did not offer any benefit in the Asian population, several studies including a meta-analysis confirmed that.



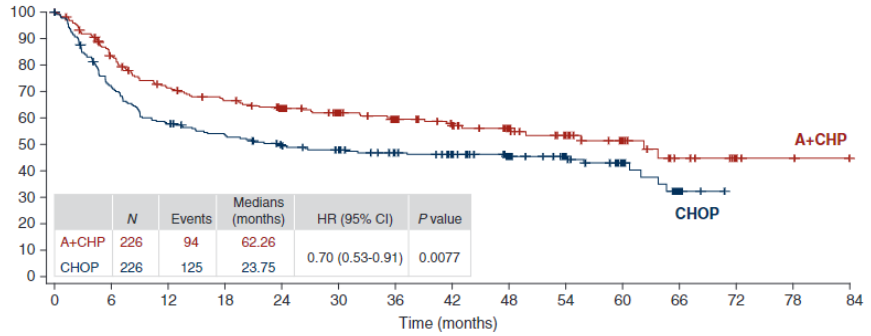
Schmitz 2010, Deng 2019

ECHELON-2

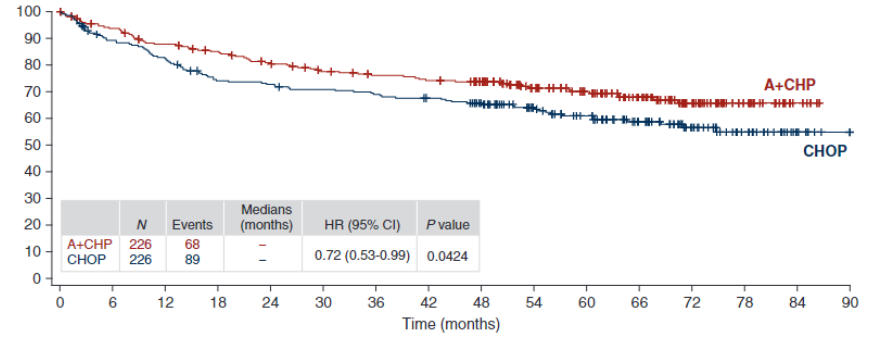
- ECHELON-2 is a double-blind, double-dummy, randomized,placebo-controlled, active-comparator phase III study.
- Included Previously untreated CD30-positive PTCL (CD30 detected in >10% of neoplastic cells by local review)
- Eligible histologies included:
  - ALK+ve ALCL
  - ALK-ve ALCL
  - PTCL-NOS
  - AITL
  - ATLL
  - EATL
  - HS TCL

Patients were randomized to BV-CHP or CHOP.

- BV CHP improved PFS and OS in ITT.
- Retreatment with BV is possible and beneficial



	N	Events	Medians (months)	HR (95% CI)	P value
A+CHP	226	94	62.26	0.70 (0.53-0.91)	0.0077
CHOP	226	125	23.75		



	N	Events	Medians (months)	HR (95% CI)	P value
A+CHP	226	68	–	0.72 (0.53-0.99)	0.0424
CHOP	226	89	–		

Table 1. Response to first brentuximab vedotin treatment after frontline therapy

	Overall	sALCL	PTCL-NOS	AITL	EATL
A+CHP					
N	29	19	5	5	0
Objective response rate, *n* (%)	17 (59)	12 (63)	3 (60)	2 (40)	NA
Complete remission, *n* (%)[a]	11 (38)	8 (42)	2 (40)	1 (20)	NA
Partial remission, *n* (%)[a]	6 (21)	4 (21)	1 (20)	1 (20)	NA
CHOP					
N	54	39	10	4	1
Objective response rate, *n* (%)	27 (50)	23 (59)	3 (30)	1 (25)	0 (0)
Complete remission, *n* (%)[a]	16 (30)	12 (31)	3 (30)	1 (25)	0
Partial remission, *n* (%)[a]	11 (20)	11 (28)	0	0	0

Horwitz 2022

Belinostat

- T-cell lymphomas (TCLs) have have marked epigenetic dysregulation, which partially explains their sensitivity to histone deacetylase (HDAC) inhibitors.
- The identification of pathogenetic features affecting DNA methylation (TET2, IDH1/2, DNMT3) or histone remodeling in TCL may portend sensitivity to drugs affecting this biology.
- Belinostat is a pan-HDAC inhibitor, inhibiting class I, II and IV HDAC isoforms with nanomolar potency
- Its approval was based on the Phase II BELIEF trial.
- Enrolled patients with relapsed PTCL. Prior therapies 2 (1-8)
- ORR (25%), CR (11%)
- Median DOR; 14 mo (4.5-29mo)
- Median OS: 7.9 mo (6-13mo)
- Toxicity profile, manageable

PTCL subtype by central review	
PTCL-NOS	77 (64.2)
AITL	22 (18.3)
ALCL	
ALK negative	13 (10.8)
ALK positive	2 (1.7)
Enteropathy-associated TCL	2 (1.7)
Extranodal NK TCL, nasal type	2 (1.7)
Hepatosplenic TCL	2 (1.7)

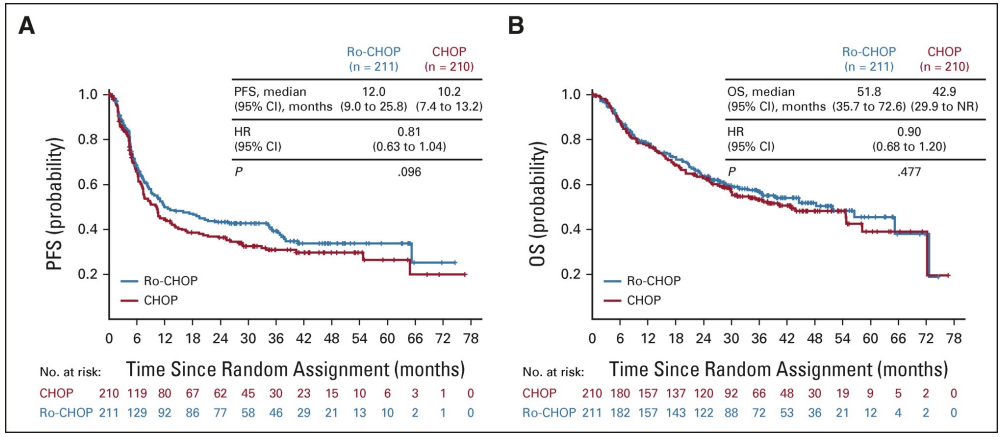
Pretreatment Characteristic	ORR by IRC No. (%)	95% CI
PTCL subtype by central review		
PTCL-NOS	18 of 77 (23.3)	14.5 to 34.4
AITL	10 of 22 (45.5)	24.4 to 67.8
ALCL		
ALK negative	2 of 13 (15.3)	1.9 to 45.4
ALK positive	0 of 2 (0.0)	0.0 to 84.2
Enteropathy-associated TCL	0 of 2 (0.0)	0.0 to 84.2
Extranodal NK TCL, nasal	1 of 2 (50.0)	1.3 to 98.7
Hepatosplenic TCL	0 of 2 (0.0)	0.0 to 84.2

	NCI CTCAE Grade		
MedDRA Preferred Term	All Grades No. (%)	1 to 2 No. (%)	3 to 4 No. (%)
SAEs (> two patients)	61 (47.3)	20 (15.5)	45 (34.9)
Pneumonia	9 (7.0)	1 (0.8)	7 (5.4)
Pyrexia	7 (5.4)	7 (5.4)	0 (0)
Infection	4 (3.1)	0 (0)	4 (3.1)
Anemia	3 (2.3)	0 (0)	3 (2.3)
Increased blood creatinine	3 (2.3)	3 (2.3)	0 (0)
Multiorgan failure	3 (2.3)	0 (0)	0 (0)
Thrombocytopenia	3 (2.3)	0 (0)	3 (2.3)

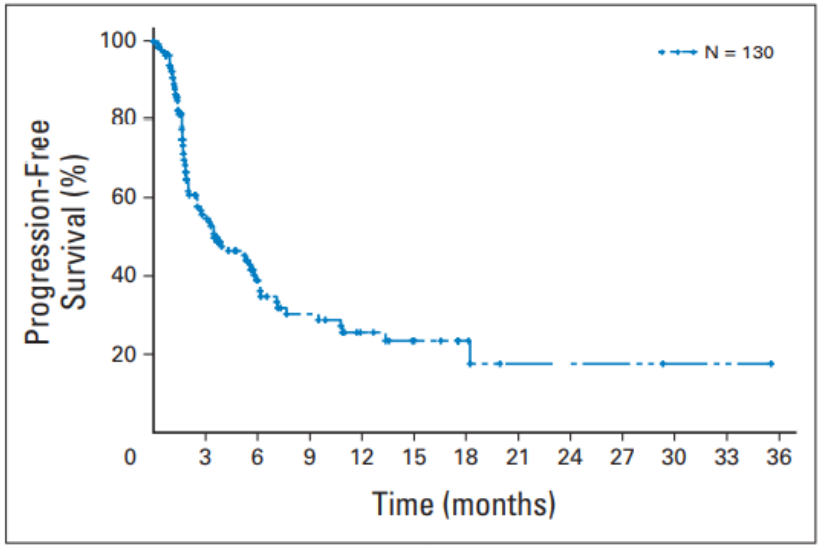
O'Connor 2013

Romidepsin

- Romidepsin is a potent, bicyclic class 1 selective histone deacetylase (HDAC) inhibitor.
- 131 patients with RR PTCL were enrolled.
- Prior therapies 2 (1-8)
- ORR (25%), CR (13%)
- Median DOR; 16.6 mo (0.1-34 mo)
- Toxicity profile, significant for cytopenia
- FDA approval was withdrawn after failure of the randomized ph3 to show benefits over SOC CHOP.



Coiffier 2012, Bachy 2021



	All Events				Drug-Related Events			
	All Grades		Grade ≥ 3		All Grades		Grade ≥ 3	
Event	No.	%	No.	%	No.	%	No.	%
Nausea	77	59	3	2	71	54	2	2
Infections SOC*	72	55	25	19	24	18	8	6
Asthenia/fatigue	72	55	11	8	68	52	7	5
Thrombocytopenia	53	41	32	24	52	40	30	23
Vomiting	51	39	6	5	44	34	5	4
Diarrhea	47	36	3	2	30	23	2	2
Pyrexia	46	35	7	5	22	17	5	4
Neutropenia	39	30	26	20	38	29	24	18
Constipation	39	30	1	1	19	15	0	
Anorexia	37	28	2	2	34	26	2	2
Anemia	32	24	14	11	27	21	7	5
Dysgeusia	27	21	0		27	21	0	
Cough	23	18	0		2	2	0	
Headache	19	15	0		14	11	0	
Abdominal pain	18	14	3	2	8	6	0	
Dyspnea	17	13	3	2	7	5	1	1
Leukopenia	16	12	8	6	16	12	8	6
Chills	14	11	1	1	6	5	0	
Hypokalemia	14	11	3	2	7	5	2	2
Peripheral edema	13	10	1	1	3	2	0	
Decreased weight	13	10	0		10	8	0	
Stomatitis	13	10	0		9	7	0	
Tachycardia	13	10	0		6	5	0	

Pralatrexate

- Pralatrexate is an antifolate that was designed to be efficiently internalized by the reduced folate carrier (RFC). In addition, because it is a superior substrate for folylpoly glutamyl synthetase, pralatrexate is more effectively polyglutamylated and retained, minimizing extrusion via natural efflux pumps.
- 115 patients with RR PTCL were enrolled.
- Prior therapies 3 (1-13)
- ORR (29%), CR (10%)
- ORR in AITL (8%)
- Median DOR; 10.1 mo
- Median OS 14.1 Mo
- Toxicity profile, significant for G3 cytopenia (14%), G3 Mucositis (18%)

O'Connor 2011

Duvelisib

- Duvelisib (DUV), a dual PI3K-δ,γ inhibitor
- The phase 2 trial PRIMO is ongoing
- It is given as 75 mg BID for the first 2 months then dose decrease to 25 mg BID afterwards to minimize autoimmune toxicity.

Table 1. Response Rates

	ORR n (%)	CR* n (%)	Time to Response (days)	mDOR (days)	mPFS (days)
	Expansion Phase, n=78				
IRC Assessment Range 95% CI	39 (50.0%)	25 (32.1%)	53 15-114 N/A	233 1+, 420+ 90, NC	107 1+, 469+ 57, 188
Subtypes (n, %)					
PTCL NOS (42, 53.8%)	22 (52.4%)	12 (28.6%)			
ALCL (11, 14.1%)	1 (9.1%)*	1 (9.1%)			
AITL (21, 26.9%)	14 (66.7%)	10 (47.6%)			
Other (4, 0.5%)	2 (50%)	2 (50%)			

*4 patients had unknown response

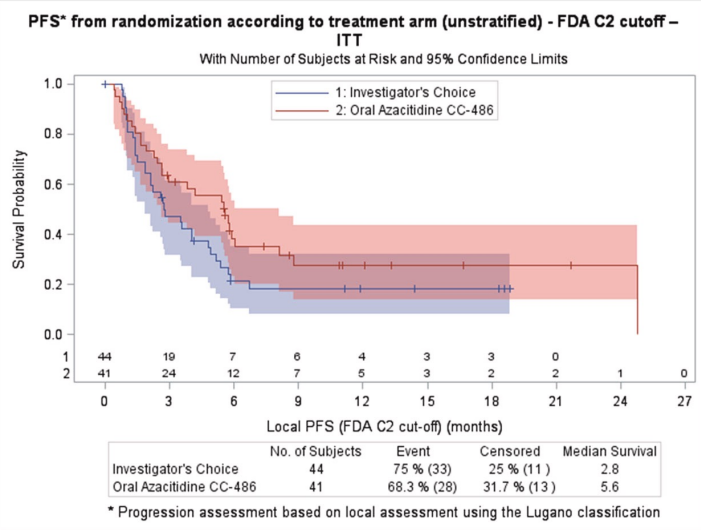
Table 2. Selected ≥ Grade 3 Adverse Events (n=78)

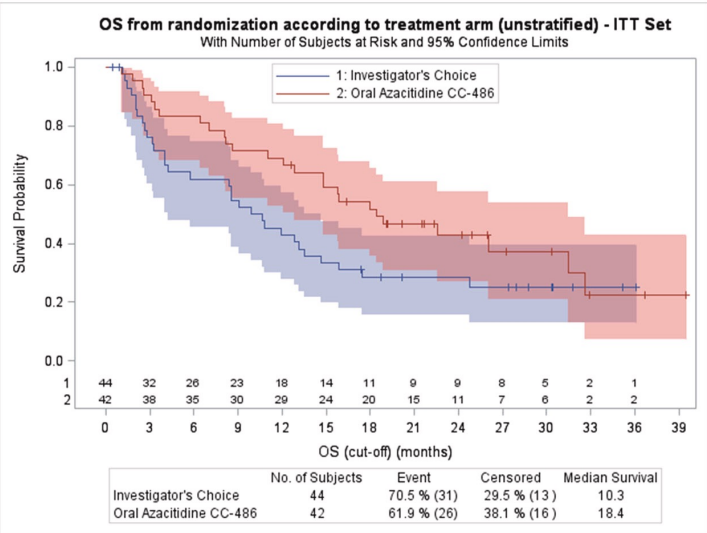
Subjects with any TEAE resulting in treatment discontinuation	14 (17.9%)
Adverse Event	**Patients Number (%)**
Neutropenia	30 (38.5%)
ALT/AST	19 (24.4%) / 17 (21.8%)
Rash	6 (7.7%)
Lymphocyte count decreased	6 (7.7%)
Sepsis	5 (6.4%)

Brammer 2021

Oral azacitidine

- ORACLE study (NCT03593018), a phase III trial comparing CC-486, an oral form of 5-azacytidine, to single agent treatment chosen by the investigator.
- Eighty-six patients with relapsed/refractory AITL or nodal follicular helper T-cell lymphoma were randomized between CC-486 (n=42) and investigator's choice (gemcitabine, n=24, bendamustine n=16, romidepsin n=4)
- The primary endpoint was analyzed after a follow-up of 14.4 months.
- Median PFS in the CC-486 arm was 5.6 (95%CI, 2.66-8.11) months vs 2.8 (95%CI, 1.87-4.83) months in the standard arm (stratified log-rank test p=0.0421), with a hazard ratio of 0.634 (95%CI, 0.38; 1.07), which did not reach the required significance of p<0.025.

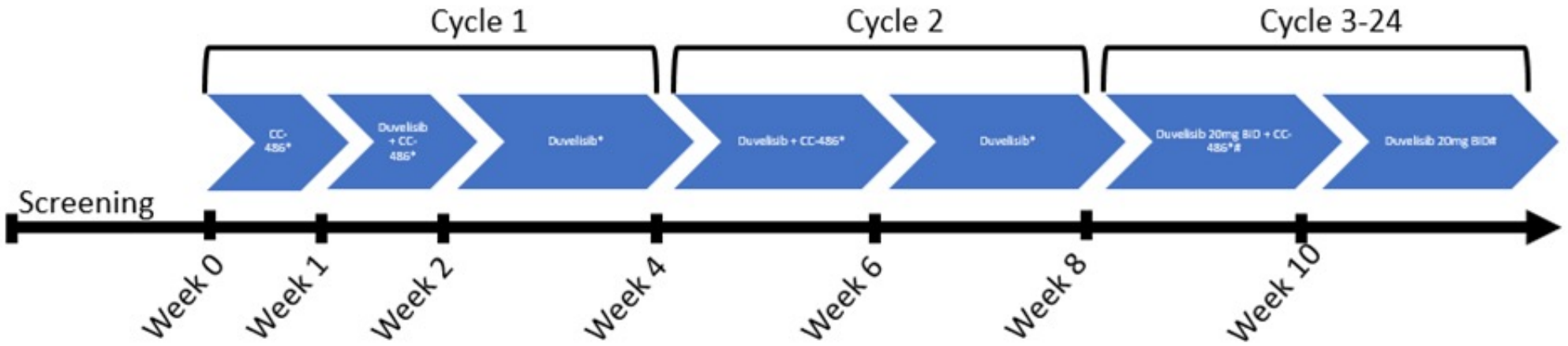




Dupuis 2022

Duvelisib and oral azacitidine

- We have a phase 1 study using duvelisib in combination with oral azacytidine in rr PTCL



* The dose of the drug will be according to dose escalation schedule.
# Duvelisib dose will be 25mg BID starting cycle 3 and beyond unless the dose level is at -1 then it will be kept at 15mg/BID

Saeed 2022

BV and Gem

- Patients with confirmed CD30+ (≥5%) PTCL with measurable disease who failed or were refractory to 1-3 systemic therapy (excluding G and Bv) were enrolled (N=71)
- TFH-PTCL (34 ; 47.9%) [including AITL (27 ; 38%) and other nodal PTCL-TFH (7 ; 9.9%)] ;
- ALK- ALCL (14 ; 27%)
- PTCL-NOS (9 ; 13%)
- ALK+ ALCL (5 ; 7%)
- EATL (2 ; 2.8%)
- Other entities (7 ; 9.9%).
- ORR (46%), CR (19%)

Figure 1A (n=71)

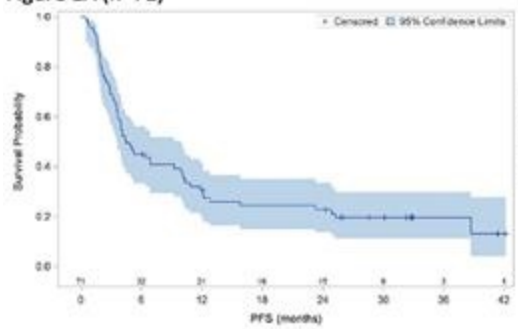


Figure 1B (non ALCL pts)

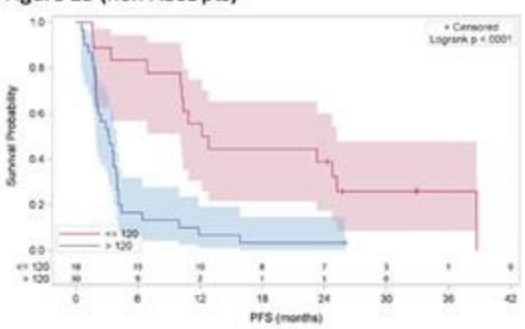


Table 1 CD30 evaluation in non-ALCL pts

	Baseline serum sCD30 (ELISA) (n=48)		p	CD30 on tumor cells (IHC) (n=44)		p
	≤120 ng/mL	>120 ng/mL		≤10%	>10%	
n	18	30		13	31	
ORR	77.8%	13.3%	*<0.001*	46.2%	38.7%	*0.65*
PFS	12.5 m (10.1-25.2)	3.2 m (2.0-4.0)	*<0.001*	4.1 m (1.7-10.3)	4.1 m (3.1-10.9)	*0.53*
OS	29.6 m (13.4-39.3)	7.3 m (3.9-10.8)	*<0.001*	9.0 m (5.0-25.5)	13.4 m (7.3-29.6)	*0.44*
n	14	4		6	12	
DOR	24.0 m (10.4-38.7)	10.9 m (6.4-15.8)	*0.019*	10.3 m (4.9-NA)	17.7m (10-25.2)	*0.32*

NA : non achieved, m : months

TRBC1 CARTs

First in Human Study of AUTO4, a TRBC1-Targeting CAR T-Cell Therapy in Relapsed/Refractory TRBC1-Positive Peripheral T-Cell Lymphoma

- Pan T-cell depletion is highly toxic and there are few or no T-cell lymphoma-specific antigen targets that discriminate malignant from normal T cells.
- The British group recently described a targeting strategy based on the mutually exclusive expression of T cell receptor beta-chain constant domains 1 and 2 (TRBC1 and TRBC2) (Maciocia, PM. et al, Nat Med 2017) which can spare a proportion of the normal T cell compartment.
- Tumor biopsies from n=73 patients were screened for TRBC1, 36% were TRBC1+.
- Four flat dose levels of AUTO4 were explored: 25 x 106, 75 x 106, 225 x 106, and 450 x 106 CAR T cells were administered as a single dose.
- The PTCL subtypes treated were PCTL NOS (n=5), AITL (n=4), and CD30+ ALCL (n=1).
- Nine patients were evaluable for response at Month 1:
  - n=5 were in complete metabolic response (CMR) by PET-CT, though one patient was in CMR after bridging at the time of lymphodepletion,
  - 1 patient achieved a PR, and 3 patients did not respond.
  - One patient was not evaluable at Month 1 by PET-CT due to COVID19 infection.
  - Three of the 4 patients at the 450x106 cell dose achieved a CMR at Month 1. With longer follow-up, 2/4 patients at the 450x106 cell dose maintained a CMR at 6 and 9 months, respectively.

Cwynaraski 2022

CTX-130

THE COBALT-LYM STUDY OF CTX130: A PHASE 1 DOSE ESCALATION STUDY OF CD70-TARGETED ALLOGENEIC CRISPR-CAS9–ENGINEERED CAR T CELLS IN PATIENTS WITH RELAPSED/REFRACTORY (R/R) T-CELL MALIGNANCIES

- CTX130TM is a first-in-class, CD70-targeting allogeneic (allo) CAR T therapy that may allow for CAR T therapy in pts whose own T cells are not ideal to manufacture auto CAR T cells.
- CD70 is a co-stimulatory protein with temporally limited expression on activated lymphocytes and is highly expressed in many TCLs.
- CTX130 is modified with CRISPR/Cas9-editing to eliminate expression of:
  - 1) T-cell receptor (TCR) by TCR alpha constant disruption
  - 2) major histocompatibility complex class I expression by β2-microglobulin disruption
  - 3) CD70 to mitigate fratricide and enhance performance.
- 4 dose levels were used. LD with Flu Cy.

Dose Level (CAR+ T Cells)	DL1 $3x10^7$	DL2 $1x10^8$	DL3 $3x10^8$	DL4 $9x10^8$	DL3+ DL4	Total
N	4	4	5	2	7	15
Age, median yrs (range)	58 (41-67)	66 (39-71)	67 (54-78)	68 (68-68)	68 (54-78)	**67 (39-78)**
ECOG PS at Screening, n (%)						
0	1 (25)	3 (75)	2 (40)	2 (100)	4 (57)	**8 (53)**
1	3 (75)	1 (25)	3 (60)	0	3 (43)	**7 (47)**
Prior lines of therapy, median n (range)	3 (1-6)	6 (3-8)	5 (1-7)	3 (2-3)	3 (1-7)	**3 (1-8)**
TCL subtype, n (%)						
PTCL	**2 (50)**	**1 (25)**	**2 (40)**	**2 (100)**	**4 (57)**	**7 (47)**
ATLL	1 (25)	1 (25)	1 (20)	0	1 (14)	**3 (20)**
AITL	0	0	1 (20)	2 (100)	3 (43)	**3 (20)**
PTCL-NOS	1 (25)	0	0	0	0	**1 (7)**
CTCL (MF or SS)	**2 (50)**	**3 (75)**	**3 (60)**	0	**3 (43)**	**8 (53)**
Skin Involvement, n (%)	3 (75)	3 (75)	4 (80)	0	4 (57)	**10 (67)**
Blood Involvement, n (%)	1 (25)	1 (25)	2 (40)	0	2 (29)	**4 (27)**
Bone Marrow Involvement, n (%)	0	0	3 (60)	0	3 (43)	**3 (20)**
ORR, n (%)	**2 (50)**	**0**	**4 (80)**	**1 (50)**	**5 (71)**	**7 (47)**
CR	1 (25)	0	2 (40)	0	2 (29)	3 (20)
PR	1 (25)	0	2 (40)	1 (50)	3 (43)	4 (27)
DCR, n (%)	**3 (75)**	**1 (25)**	**5 (100)**	**2 (100)**	**7 (100)**	**11 (73)**
SD	1 (25)	1 (25)	1 (20)	1 (50)	2 (29)	4 (27)
CRS, n (%)	1 (25)	1 (25)	4 (80)	1 (50)	5 (71)	**7 (47)**
Gr ≥3 CRS	0	0	0	0	0	**0**
ICANS, n (%)	0	0	3 (60)	0	3 (43)	**3 (20)**
Gr ≥3 ICANS	0	0	0	0	0	**0**
Gr ≥3 Infection, n (%)	1 (25)	0	0	0	0	**1 (7)**
GvHD, n (%)	0	0	0	0	0	**0**

AITL, angioimmunoblastic T-cell lymphoma; ATLL, adult T-cell leukemia/lymphoma; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; CTCL, cutaneous T-cell lymphoma; DCR, disease control rate; DL, dose level; ECOG, Eastern Cooperative Oncology Group; Gr, grade; GvHD, graft versus host disease; ICANS, immune effector cell-associated neurotoxicity syndrome MF, mycosis fungoides; NOS, not otherwise specified; PR, partial response; PS, performance status; PTCL, peripheral T-cell lymphoma; SD, stable disease; SS, Sezary syndrome; TCL, T-cell lymphoma.

Swaminathan 2022

Conclusions

- Mature T cell lymphomas are diverse biologically and can not be seen as one disease
- Understanding the rule of CD30 expression is essential for the management of T cell lymphoma
- CHOP continue to be an essential regimen for the majority of T cell lymphoma
- BV-CHP is the first regimen that changed the landscape of frontline therapy in T cell lymphoma
- Relapse/refractory T cell lymphoma has dismal prognosis
- Currently, only BV, Belinostat and Pralatrexate has FDA approval in relapse T cell lymphoma
- Newer targeted therapies using PI3Ki has the most promising activity.
- Cellular therapies are coming slowly into the T cell lymphoma space.

Thank you