Update on T-cell Lymphomas

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T cell lymphomas- Heterogenous and Challenging to Diagnose

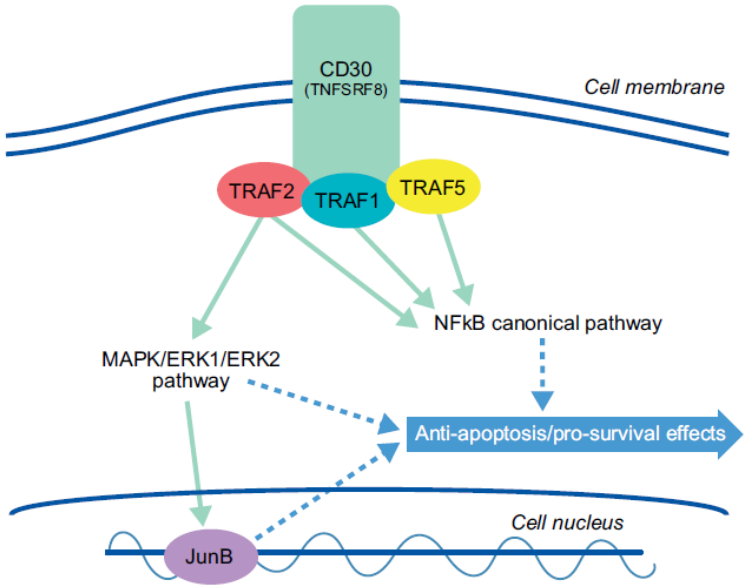
WHO classification	Proposed cell of origin
T-cell prolymphocytic leukemia	Unknown T cell with mature phenotype, possible intermediary between cortical thymocyte and mature T cell
T-cell large granular lymphocytic leukemia	CD8+ αβ T cell (rarely γδ T cell)
Chronic lymphoproliferative disorder of NK cells	Mature NK cell
Aggressive NK-cell leukemia	Activated NK cell
Systemic EBV-positive T-cell lymphoma of childhood	Cytotoxic CD8+ T cell or activated CD4+ T cell
Chronic active EBV infection of T- and NK-cell type, systemic form	CD4+ T cell, cytotoxic CD8+ T cell, NK cell (rarely γδ T cell)
Hydroa vacciniforme–like lymphoproliferative disorder	Skin-homing cytotoxic T/NK cell
Severe mosquito bite allergy	Activated NK cell
Adult T-cell leukemia/lymphoma	CD4+ T cell
Extranodal NK-/T-cell lymphoma, nasal type	Activated NK cell, less commonly cytotoxic T cell
Enteropathy-associated T-cell lymphoma	Intestinal intraepithelial T cell
Monomorphic epitheliotropic intestinal T-cell lymphoma	Intestinal intraepithelial T cell
Intestinal T-cell lymphoma, NOS	Heterogeneous, usually cytotoxic T cell
Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract	Mature peripheral T cell
Hepatosplenic T-cell lymphoma	γδ T cell, less commonly cytotoxic αβ T cell
Subcutaneous panniculitis-like T-cell lymphoma	Mature cytotoxic αβ T cell
Mycosis fungoides	Mature skin-homing CD4+ T cell
Sézary syndrome	Circulating memory T cell
Lymphomatoid papulosis	Activated skin-homing T cell
Primary cutaneous anaplastic large cell lymphoma	Activated skin-homing T cell
Primary cutaneous γδ T-cell lymphoma	Activated mature γδ T cell
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma	Skin-homing CD8+ T cell
Primary cutaneous acral CD8+ T-cell lymphoma	Skin-homing CD8+ T cell
Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder	Skin-homing CD4+ T cell with TFH phenotype
PTCL, NOS	Activated, mature T cell
Angioimmunoblastic T-cell lymphoma	CD4+ TFH cell
Follicular T-cell lymphoma	CD4+ TFH cell
Nodal PTCL with TFH phenotype	CD4+ TFH cell
Anaplastic large cell lymphoma, ALK positive	Activated mature cytotoxic T cell
Anaplastic large cell lymphoma, ALK negative	Activated mature cytotoxic T cell
Breast implant–associated anaplastic large cell lymphoma	Activated mature cytotoxic T cell

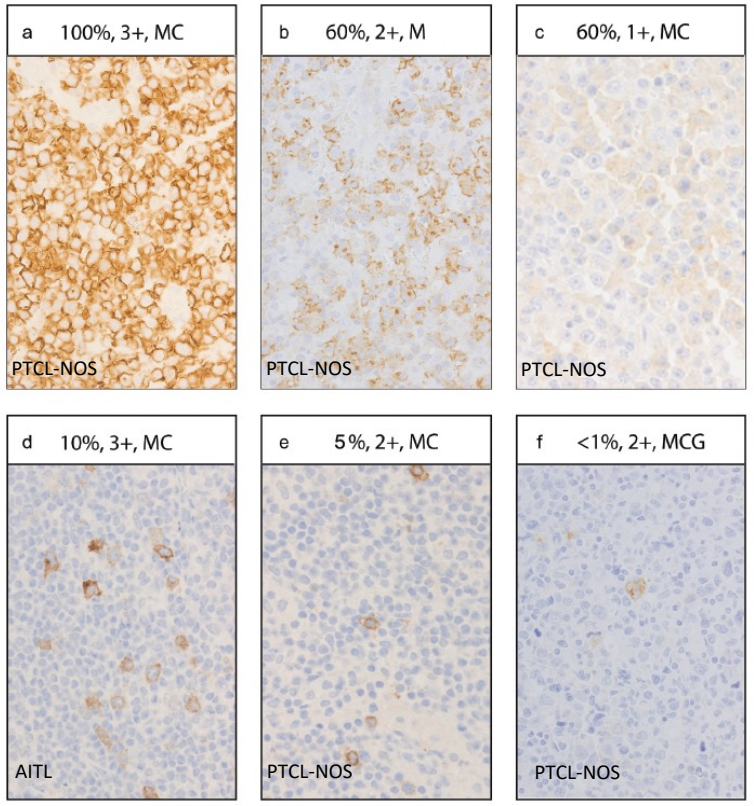
- **28 subtypes**
- **Derived post-thymic T lymphocytes**
- **International T-cell Lymphoma Project: diagnosis consensus in 74-81% Alk – sALCL, PTCL-NOS, AITL**
- **10% - initially misdiagnosed or unclassifiable**
- **rash changed Dx in 6% of all cases**
- **HTLV(+) -> 39% of PTCL-NOS reclassified to ATLL**
- **TCR rearrangements: false (+) in infection, autoimmune**
- **TCR rearrangements: false (-) low tumor burden, sampling**

Stuver, Robert et al. “Current Treatment of Peripheral T-cell Lymphoma.” *Oncology (Williston Park, N.Y.)* vol. 36,5 (2022): 293-305.

PTCLs of Different Histologies Differ Immunophenotypically and Molecularly

CD 30 Expression in PTCL Subtypes





MCG, cell membrane, cytoplasm and Golgi body staining

IHC Score	PTCL-NOS	AITL	ATLL	ENKTL	ALK-ALCL	ALK+ ALCL	EATL
0: <5%	42%	37%	44%	54%	0	0	50%
1+: 5–24%	26%	47%	11%	7%	0	0	0
2+: 25–49%	9%	10%	33%	11%	0	5%	0
3+: 50–75%	10%	5%	11%	14%	0	2%	7%
4+: >75%	13%	0	0	14%	100%	93%	43%

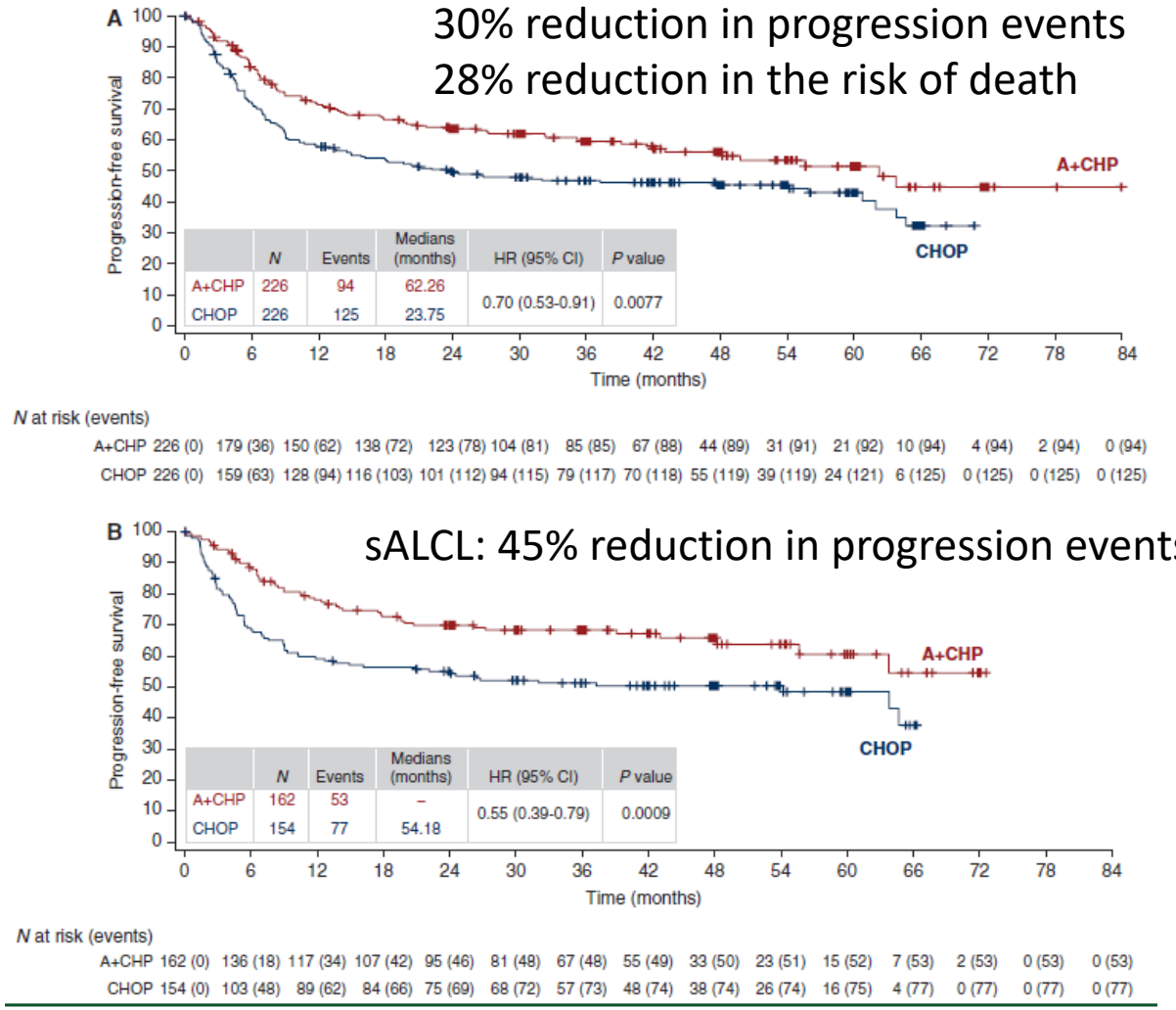
Stuver *Oncology 2022 Bossard Blood 2014 Karube Exp Rev Hematol 2021*

CD30 positive PTCLs- brentuximab improves OS

ECHELON-2 Trial: BV-CHP vs CHOP, 5-year follow up

CD30 >= 10%,ALCL 70%

Primary Endpoint: PFS



	ALL		ALCL		AITL		PTCL-NOS	
	BV-CHP	CHOP	**BV-CHP**	**CHOP**	**BV-CHP**	CHOP	**BV-CHP**	CHOP
5 yr PFS	**51% HR 0.70 p=0.007**	43%	**61% HR 0.55 p=0.0009**	**48%**	**27%**	48%	**27%**	26%
Median PFS	**62 m**	24m						
5 yr OS	**70% HR 0.72 p=0.04**	61%	**76% HR 0.66 p=0.05**	**69%**	**68%**	63%	**46%**	36%
Median OS	**NR**	NR						

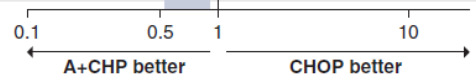
- **not powered to compare BV-CHP versus CHOP among non-ALCL histologic subtypes**

Horwitz S, O'Connor OA, Pro B, et al. The ECHELON-2 Trial: 5-year results of a randomized, phase III study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma. *Ann Oncol*. 2022;33(3):288-298

ECHELON-2 Trial: 5-year follow up

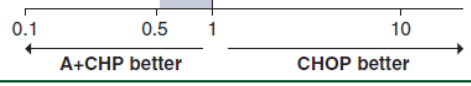
PFS Subgroup Analysis

ITT subgroups	Event/*N* A+CHP	Event/*N* CHOP	Hazard ratio (95% CI)
PFS per investigator	94/226	125/226	0.70 (0.53-0.91)
IPI score			
0-1	14/52	27/48	0.42 (0.22-0.81)
2-3	59/141	79/145	0.72 (0.51-1.01)
4-5	21/33	19/33	1.14 (0.61-2.15)
Age, years			
<65	51/157	74/156	0.64 (0.45-0.92)
≥65	43/69	51/70	0.68 (0.45-1.04)
Sex			
Male	60/133	79/151	0.84 (0.60-1.17)
Female	34/93	46/75	0.44 (0.28-0.69)
Baseline ECOG status			
0	36/84	56/93	0.63 (0.41-0.96)
1	38/90	50/86	0.61 (0.40-0.93)
2	20/51	19/47	0.99 (0.52-1.88)
Disease stage			
I	3/12	2/9	2.15 (0.22-20.88)
II	12/30	18/37	0.93 (0.43-1.99)
III	26/57	36/67	0.63 (0.37-1.05)
IV	53/127	69/113	0.66 (0.46-0.95)
Disease indication			
ALK-positive sALCL	7/49	16/49	0.40 (0.17-0.98)
ALK-negative sALCL	46/113	61/105	0.58 (0.40-0.86)
ATLL	2/4	2/3	0.69 (0.10-4.94)
AITL	19/30	12/24	1.41 (0.64-3.11)
EATL	1/1	2/2	Not estimable
PTCL-NOS	19/29	32/43	0.79 (0.43-1.43)
sALCL	53/162	77/154	0.55 (0.39-0.79)
Non-sALCL	41/64	48/72	0.96 (0.63-1.47)



OS Subgroup Analysis

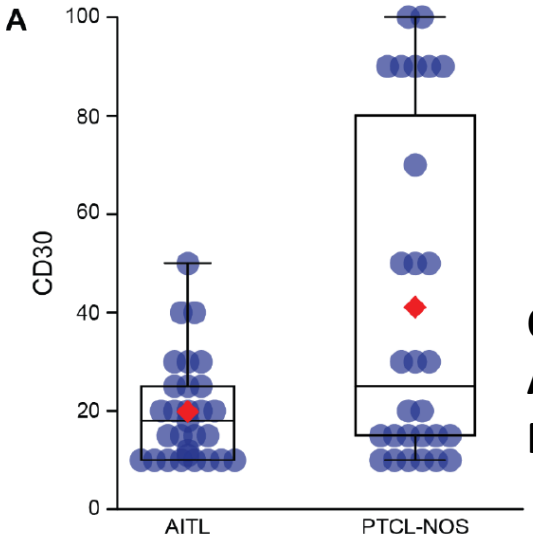
ITT subgroups	Event/*N* A+CHP	Event/*N* CHOP	Hazard ratio (95% CI)
Overall survival	68/226	89/226	0.72 (0.53-0.99)
IPI score			
0-1	8/52	13/48	0.58 (0.24-1.39)
2-3	40/141	59/145	0.61 (0.41-0.91)
4-5	20/33	17/33	1.23 (0.64-2.34)
Age, years			
<65	37/157	44/156	0.79 (0.51-1.23)
≥65	31/69	45/70	0.62 (0.39-0.98)
Sex			
Male	41/133	59/151	0.73 (0.49-1.08)
Female	27/93	30/75	0.68 (0.40-1.16)
Baseline ECOG status			
0	25/84	38/93	0.59 (0.35-0.99)
1	25/90	38/86	0.54 (0.33-0.90)
2	18/51	13/47	1.42 (0.69-2.93)
Disease stage			
I	2/12	2/9	1.34 (0.12-14.81)
II	7/30	14/37	0.66 (0.26-1.68)
III	18/57	22/67	0.70 (0.37-1.33)
IV	41/127	51/113	0.73 (0.48-1.10)
Disease indication			
ALK-positive sALCL	5/49	10/49	0.48 (0.16-1.40)
ALK-negative sALCL	34/113	39/105	0.71 (0.44-1.12)
ATLL	2/4	3/3	0.70 (0.11-4.27)
AITL	12/30	8/24	1.01 (0.40-2.55)
EATL	1/1	2/2	Not estimable
PTCL-NOS	14/29	27/43	0.75 (0.37-1.48)
sALCL	39/162	49/154	0.66 (0.43-1.01)
Non-sALCL	29/64	40/72	0.76 (0.46-1.23)



The PFS and OS analyses for key prespecified subgroups were generally consistent with the overall study results

Horwitz S *Ann Oncol*. 2022;33(3):288-298

Does CD30 Expression Correlate with CR Rate in PTCL-NOS and AITL Patients Treated with BV-CHP?



CD 30 expression

AITL: 10- 30%, median 18%

PTCL-NOS: 10% to 100%, median 25%

Supplementary Table S1: CR and PR rates by CD30 expression in patients with AITL or PTCL-NOS in the A+CHP arm

	CD30	Patients *N*	Complete remission *n* (%)	Partial remission *n* (%)	*P* value, CR rates for CD30 above vs below median [a]
AITL	CD30 > median	14	8 (57)	1 (7)	
	CD30 ≤ median[b]	15	8 (53)	3 (20)	0.84
	CD30 = 10%	8	5 (63)	0	
PTCL-NOS	CD30 > median	14	8 (57)	2 (14)	
	CD30 ≤ median[b]	14	10 (71)	2 (14)	0.44
	CD30 = 10%	6	4 (67)	2 (33)	

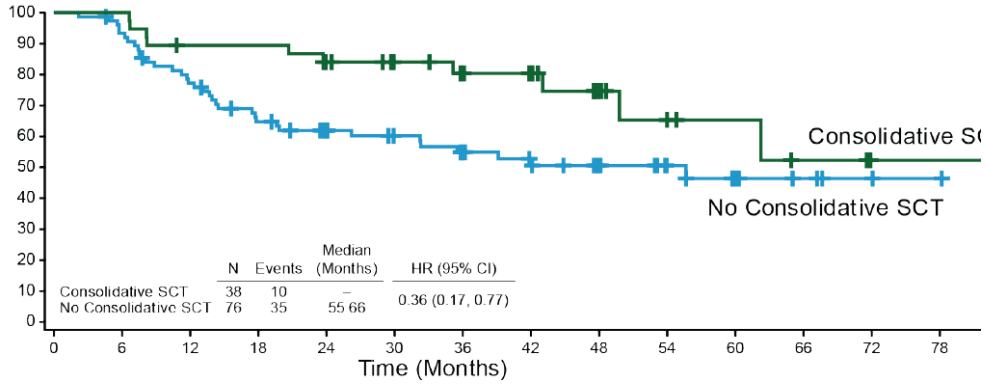
Level of CD30 expression did not correlate with CR

- responses were observed across the range of CD30 expression
- BV-CHP median time to BV re-treatment: 15 m, ORR 59% CR 38%
- CHOP median time to BV re-treatment: 8 m, ORR 50% CR 30%

Horwitz S *Ann Oncol*. 2022;33(3):288-298

BV-CHP Take Home Points

PFS HR 0.36, 64% reduction in PFS event risk with ASCT post BV-CHP

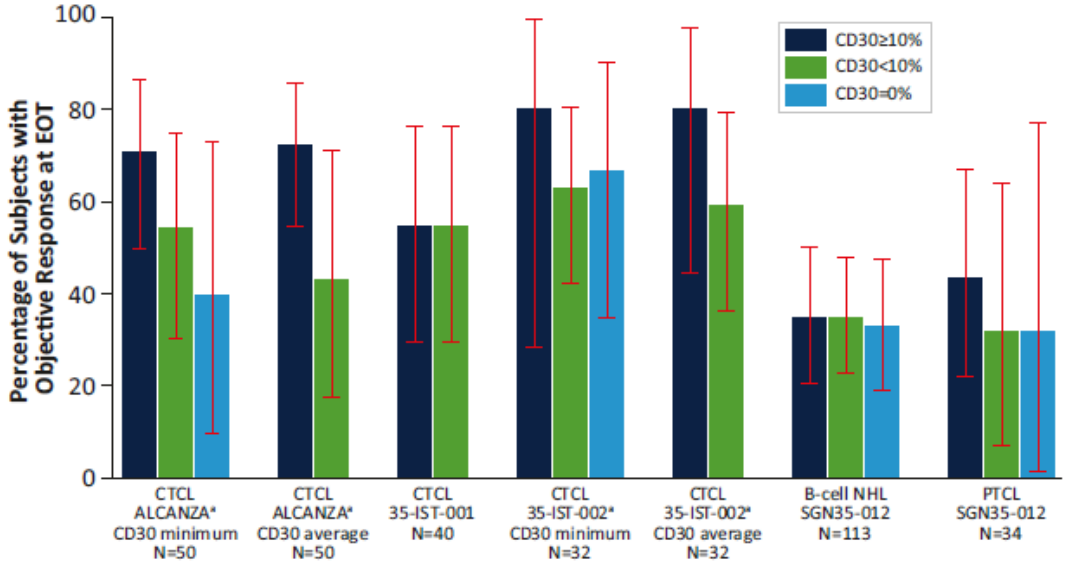


- **Trial population CD30 >= 10% or greater**
- **CD30 1% to 9%- BV-CHP benefit unproven**
- **CD30 expression level has not been shown to predict response**
- **NCT04569032: BV-CHP in treatment-naive PTCL with less than 10% CD30 expression**
- **Trial not powered to show BV-CHP superiority in subtypes other than sALCL**
- **Exploratory analysis of CR pts who underwent ASCT improved 3-year PFS rate (76.1% vs 53.3%; HR, 0.38; 95% CI, 0.18-0.82), but this population was small**
- **BV-CHP for all CD30 +; BV – CHEP for those who need more intensive induction**

How do we improve outcomes in CD30 negative PTCL?

CD30 Expression by IHC Does Not Predict BV Response- Analysis of 5 BV Monotherapy Trials

Objective response rate at end of treatment by baseline CD30 expression
N=275



Response to BV and duration of response were not associated with CD30 expression level above or below 10%
BV-CHP in <10% CD30 expression NCT04569032

Jagadeesh The Oncologist 2022

Etoposide addition to anthracycline based regimens

	CHOP	CHOEP
NHL-B1 <60 yo	**3 yr EFS 51%**	**3 yr EFS 75.4% p= .003**
NHLB1+NHLB2 (>60 yo)	**3 yr EFS 51%**	**70.5% p=.004**
	OS 75.2%	**OS 81.3% P=.285**

- CHOEP: improved EFS, NOT OS
- CHOEP: increased infections, transfusions and hospitalizations in >60 yo
- **With ALK + sALCL exclusion-> EFS significance is lost (*P* = .057)**

N=41 (PTCL, AITL)	ORR/CR	ORR/CR <60 up	2 yr PFS/OS	2 yr PFS/OS <60
DA-R-EPOCH	78%/61%	94%/70%	53%/73%	82%/66%

Maeda Haematologica 2017, Wunderlich Annals Oncol 2003, Pfreundschuh Blood 2004

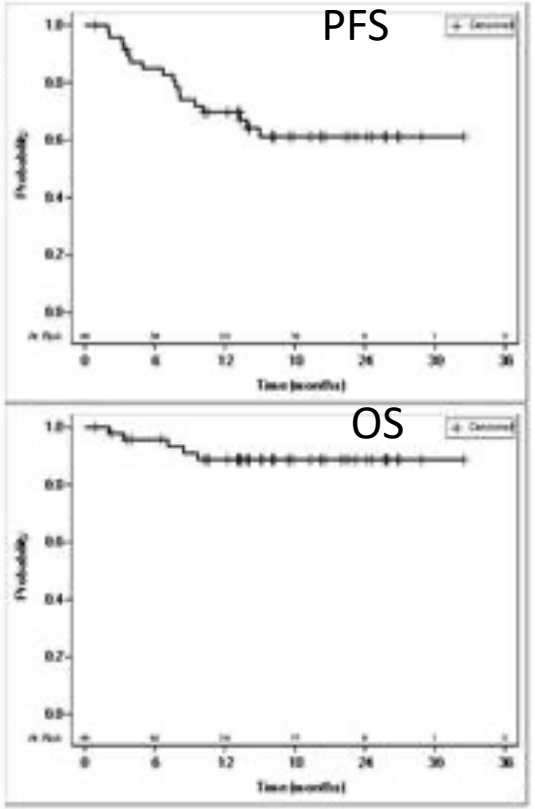
BV+ CHEP (cyclophosphamide, doxorubicin, etoposide, and prednisone) followed by BV consolidation in patients with CD30-expressing peripheral T-cell lymphomas: Phase II Trial

CD30 >= 1%

BV-CHEP q 21 d X 6

BV 1.8 mg/kg d1
CHP d1
Etop 100 mg/m2 D1-3
GCSF proph
N=48
St III-IV 43 (90%)
IPI 3-4 19 (39%)
CD>=30% 32 (67%)

ASCT
No ASCT → BV 1.8 mg/m2 q 3 wks X 10



	ALL N=46	ALCL N=16	Non-ALCL N=30	PTCL-NOS N=11	AITL N=18	tTFH N=2	CD30 <10% N=15	CD30 >=10% N=31
ORR	91%	94%	90%	82%	94%	100%	93%	90%
CR	80%	**94%**	**73%**	**55%**	**82%**	**100%**	**67%**	**87%**
18m PFS	**61%**	**81%**	**49%**				**48%**	**67%**
18m OS	**89%**							

	ASCT N=24	No ASCT N=19
BV con	20	13
1 yr PFS	**82%**	**48%**

Neuropathy 67%
G3+ AE neutropenia 37.5%
Febrile neutropenia 23%

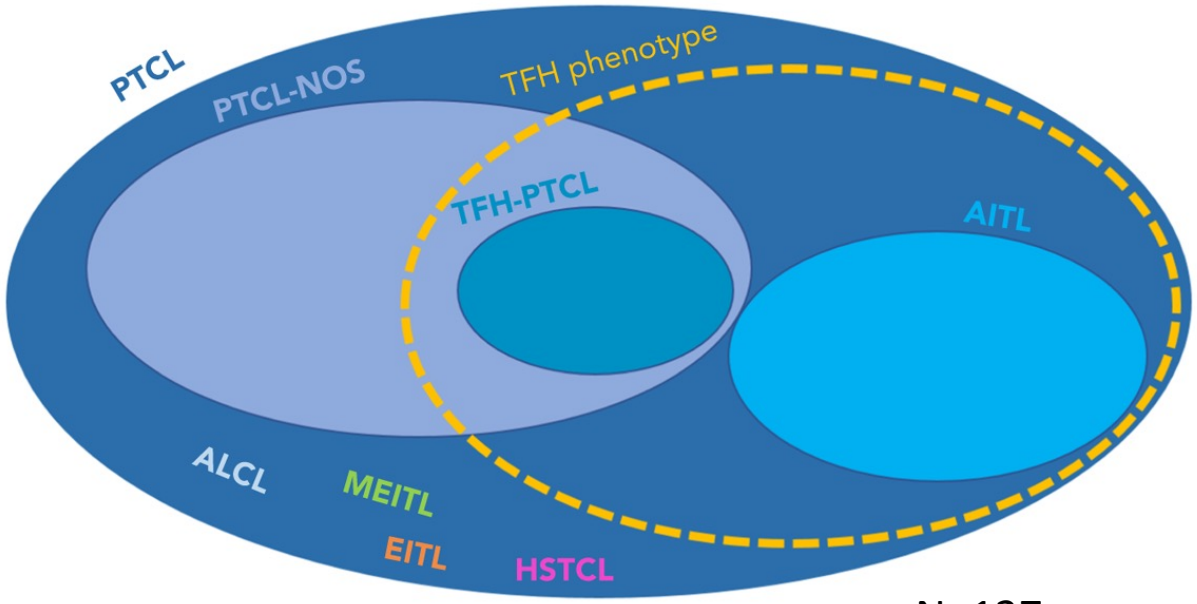
Herrera AF Blood. 2019, Herrera Blood. 2021

Is It Prime Time for Epigenetic Therapies? Can they improve outcomes in tTFH

T follicular helper phenotype TCL (tTFH) has unique biology and predicts response to histone deacetylase inhibitors in R/R PTCL

tTFH enriched in epigenetic modifier mutations:

TET2 (50%-80%), ***DNMT3A*** (20%-30%), and ***IDH2*** **(**20%-30%), ***RHOA*** G17V 70%



TFH PHENOTYPE CD4+

Strong expression of at least two of TFH markers, namely

-CD10,
-CD279 (PD-1),
-CXCL13,
-ICOS,
-CXCR5,
-BCL6

by immunohistochemistry and/or flow cytometry

R/R PTCL-NOS vs AITL + TFH-PTCL receiving HDACi

N=127

Non-TFH vs TFH phenotype	P value
ORR to HDACi and HDACi combinations 29% (19% CR) vs 56% (29% CR)	.003
Logistic regression model TFH independent predictive factor of ORR to HDACi	.009

Ghione Blood Adv 2020

Romidepsine-CHOP vs CHOP: Phase III

- Romidepsine: HDAC inhibitor, ORR 25%, CR 15%, more effective in tTFH

PTCL-NOS, AITL, Alk-ALCL, EATCL, HSTCL, SPTCL
No SCT planned
St IV -66%

421
1:1

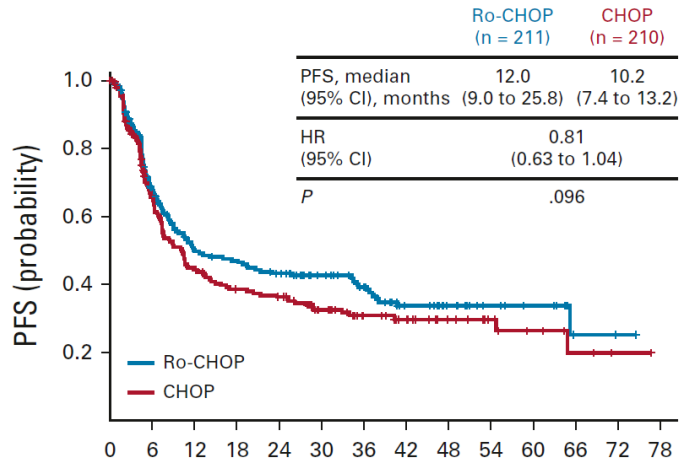
Romi-CHOP X6
Romi 12 mg/m2 D 1,8

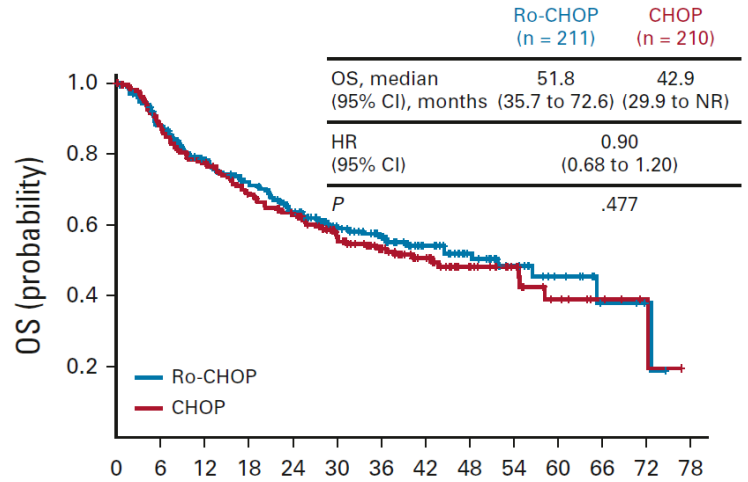
ORR 63% CR 41%

Primary endpoint: PFS

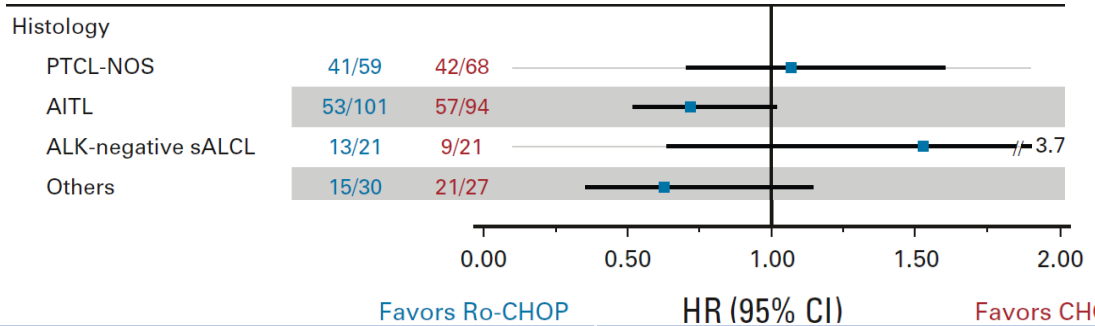
CHOP x6

ORR 60% CR 37% p=0.1





Exploratory analysis of PFS in tTFH lymphomas



Ro-CHOP n=103	CHOP n=98
Median PFS 19.5 m	Median PFS 10.6 m
HR 0.69 (0.48-1.00) p= 0.046	

Ro-CHOP did not improve PFS, ORR, OS
Increased grade 3 TAEs- cytopenias

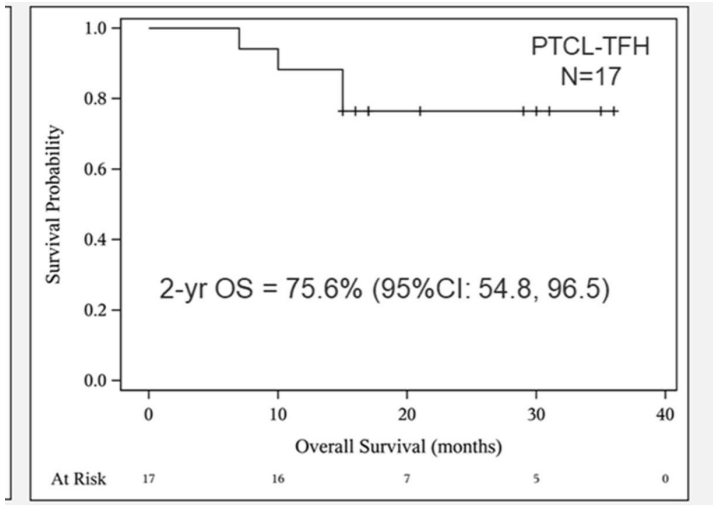
Bachy JCO 2021

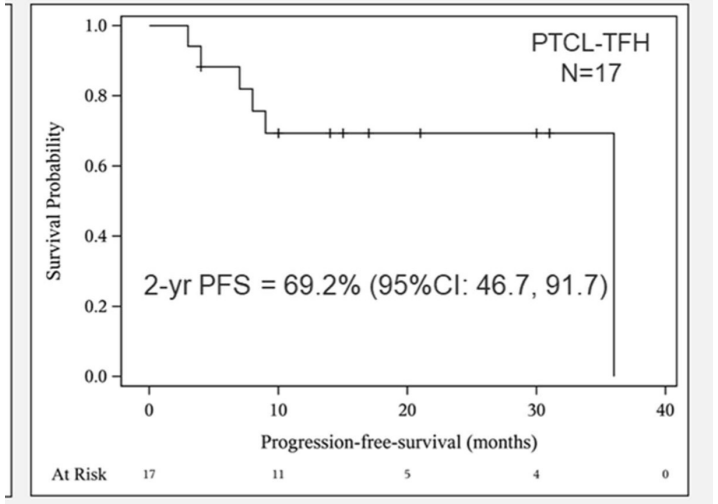
Azacitidine-CHOP in Upfront Treatment of PTCL: Phase II Study

Azacitidine: DNMT inhibitor, single agent activity in R/R PTCL: ORR 53%, CR 26%, ORR 75% in AITL

Primary endpoint: CR rate
PTCL-TFH 17/20 (85%)
St III-IV 90%
CD30 <5% - 76%

	ALL N=20	tTFH N=17
EOT ORR and CR	77%	**88%**
2 yr PFS	66%	**69%**
2 yr OS	68%	**76%**





- **Median PFS 36 m**
- **CR did not correlate with CD30 expression**
- ***TET2* - associated with CR, favorable PFS, OS (p<0.05)**
- **DNMT3A mutations: adverse OS (p=0.028),** emergence of DNMT3A mutant clones in early relapse

Ruan ASH Blood 2021 NCT03542266

Romidepsine-Lenalidomide for Untreated PTCL: Chemo-Free Regimen

Untreated PTCL
>60 yo
NON-SOC candidates
N=29
AITL 55%
PTCL-NOS 38%
Median age 75
St III-IV 66%

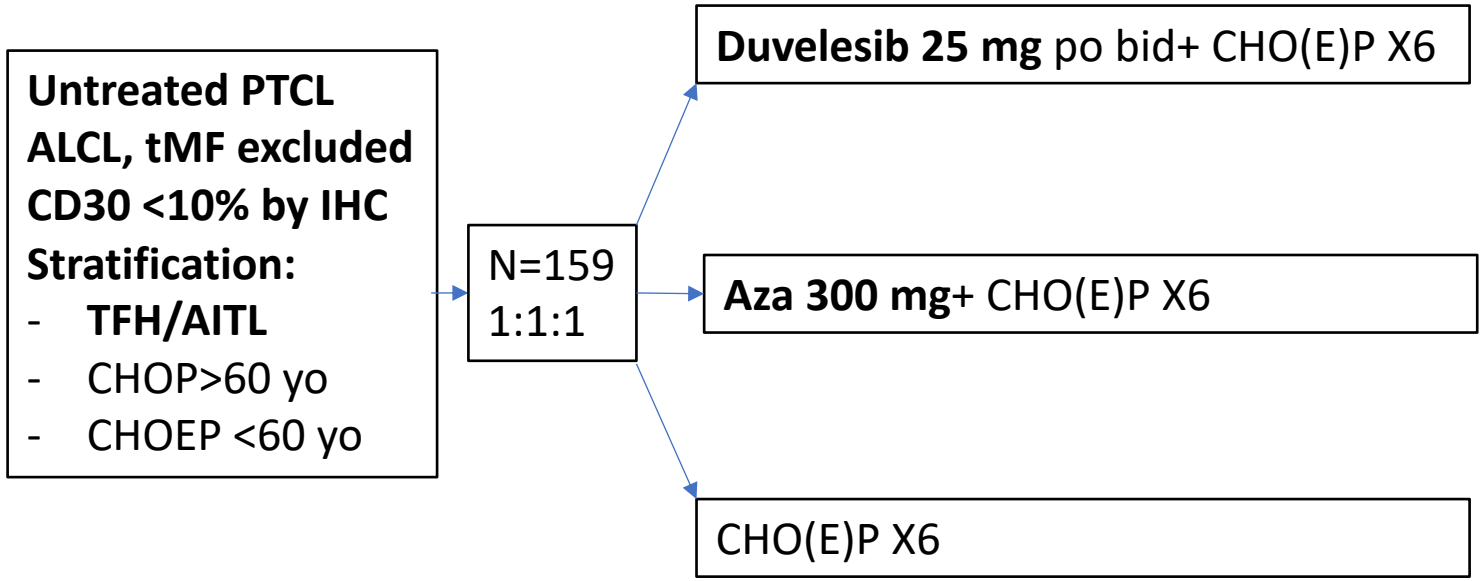
Romi 10 mg/m2 D1,8,15
Len 25 mg po D 1-21
Q 21 days

N=20 evaluable
ORR 75%
CR 38%
Median DOR for CR 14.3 m
1 yr PFS 54% OS 76%
3 yr PFS 36.2 % OS 51%
Median DOR 4.2 m
N=2 -> ASCT
N=4 -> subsequent therapy

romidepsin and lenalidomide combination is feasible and effective as initial PTCL therapy for patients who are not candidates for cytotoxic chemotherapy

Ruan JCO ASCO 2021

Alliance A059102: A randomized phase II U.S. intergroup study of CHO(E)P versus CC-486-CHO(E)P versus duvelisib-CHO(E)P in previously untreated, CD30-negative, peripheral T-cell lymphomas.



- **Duvelisib:** gdPI3K inhibitor, 50% ORR, higher in tTFH
- **Azacitidine:** hypomethylating agent, 75% ORR in tTFH
- **CC-486, oral azacytidine:** Aza - CHOP 75% ORR with a higher ORR in tTFH
- **Primary endpoint:** CR rate by the Lugano 2014 criteria
- **Correlatives: TFH phenotype**, cell free DNA to predict outcomes

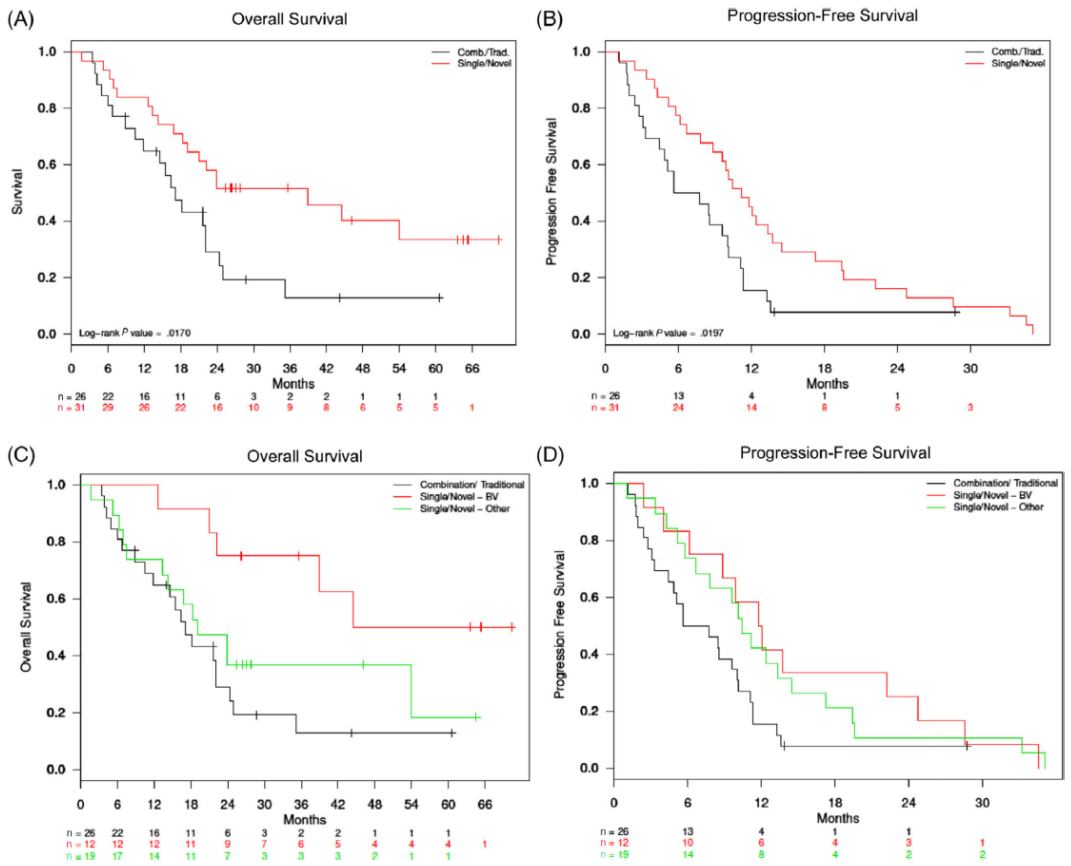
Mehat-Shah ASCO 2022, Brammer Blood 2021, Ruan Blood 2021

R/R PTCL- IS MORE CHEMO BETTER?
Epigenetic therapies take center stage

Single agents vs combination chemotherapy in T cell lymphoma: Results from the Comprehensive Oncology Measures for Peripheral T-cell lymphoma treatment (COMPLETE) registry

- **R/R PTCL median OS 6 m, ORR around 30% to approved therapies, CR rates <50%**
- Analyzed: PTCL-NOS, ALTL, AITL, EATL, HSTCL, NKT
- Pralatrexate (16%), romidepsin (23%), BV (39%), belinostat, bendamustine, alisertib, denileukin diftitox, or lenalidomide
- **R/R s/p 1 prior systemic Tx**
- **Primary endpoint: best response to treatment**, BV cohort analyzed separately
- Median f/u= 2 yrs

	Single Agent N=31	Combination Chemo N=26	p
CR %	**41**	19	0.02
PFS months	**11.2**	6.7	0.02
OS months	**39**	17	0.02
SCT	**26**	8	0.07
Gr 3-4 AEs %	**65**	81	0.17



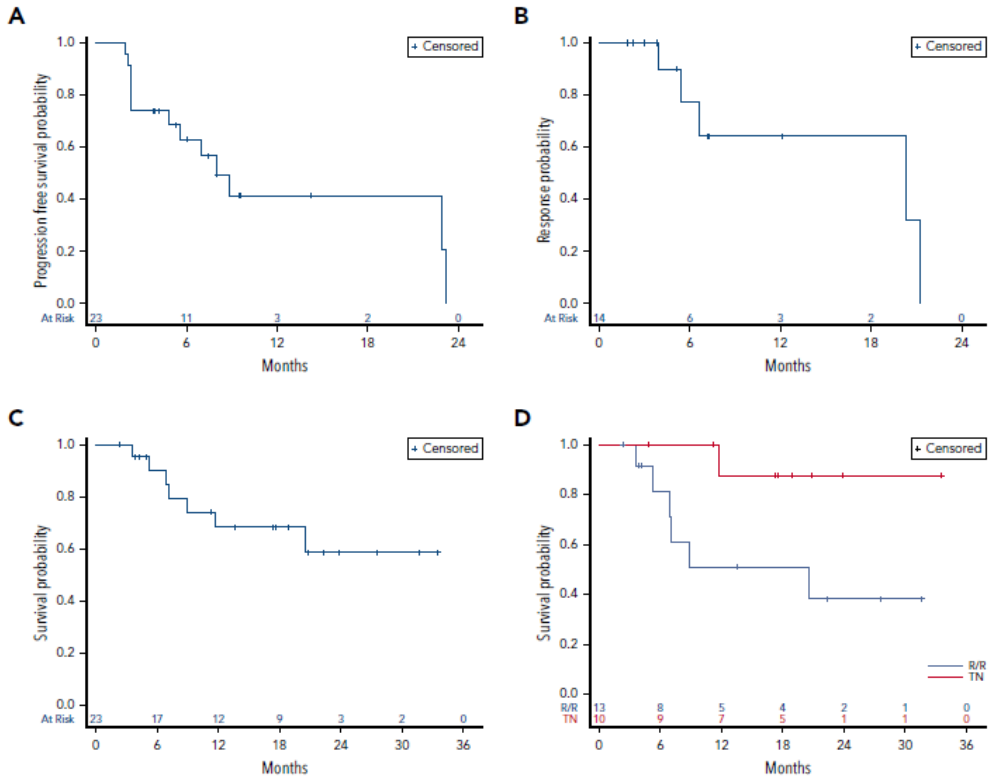
	BV	Single	Combination Chemo
CR rate %	**58**	29	19
Median OS months	**44.5**	19	17
Median PFS months	**12**	10	7

Stuver 2019 Am J Hematol

Combined oral 5-azacytidine and romidepsin are highly effective in patients with PTCL: a multicenter phase 2 study

- azacytidine 300 mg po daily d 1 – 14+ romidepsin 14 mg/m2 d 8, 15, and 22 q 35 d 35 days.

	ALL N=23	tTFH vs Other N=15 N=8	Tx Naïve N=10	R/R N=13
ORR	**61%**	**80% vs 25%**	**70%**	**54%**
CR	**48%**	**60% vs 12.5%**	**50%**	**38%**
PFS median	**8 m**	**8.9 vs 2.3 m HR 0.3 p=.05**	**NR**	**8 m (p=.58)**
DOR	**20 m**		**NR**	**13.5 (p=.62)**
Median OS	**NR**	**NR vs 9.4 m HR 0.2 p=.03**	**NR**	**20.6**



	TET2 mut N=16	TET2 wt N=5
ORR	**11 (69%)**	2 (40%)
CR	**9 (53%)**	1 (20%)

Higher response rates in tTFH and treatment naïve, TET2 mutants

- Responders: enriched in DNA methylation, histone methylation and acetylation mutations

Falchi Blood. 2021

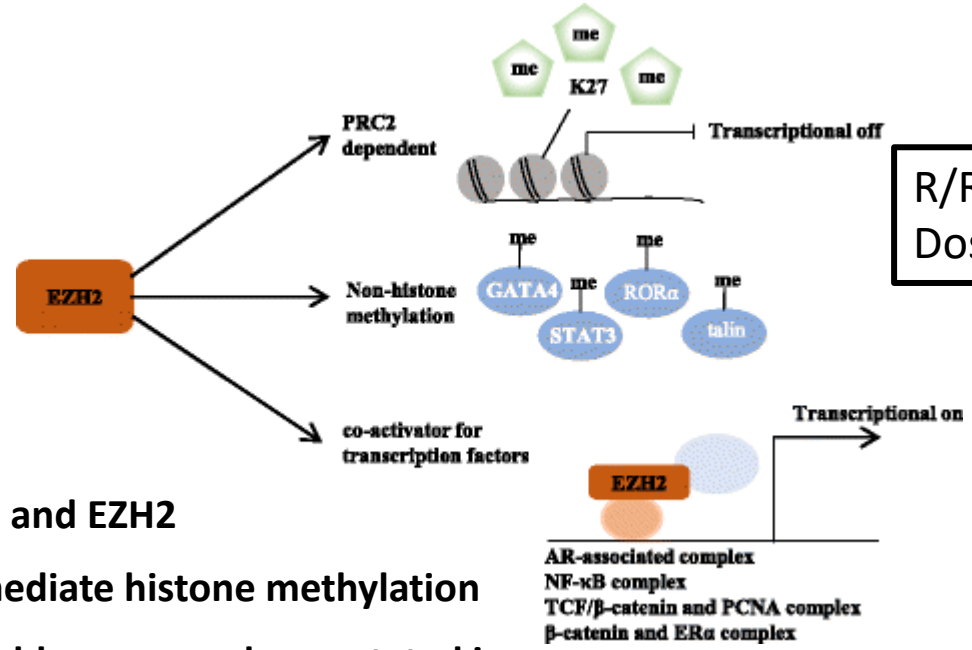
A real-world experience of combined treatment with romidepsin and azacitidine in patients with peripheral T-cell lymphoma.

- N=17 (11 AITL, 2 ATLL, 2 TFH PTCL, 1PTCL NOS, 1 TFH+DLBCL)
- ORR 76% and CR 52%
- 4 pts- bridge to allo SCT

A Randomized, Phase IIB, Multicenter, Trial of Oral Azacytidine Plus Romidepsin versus Investigator's Choice in Patients with R/R PTCL NCT04747236

Kalak ASCO 2022

EZH2 Inhibitor Valmetostat Phase ½ Study



R/R NHL
Dose escalation

200 mg po qd
Dose expansion

ATLL
(Japan)

PTCL
(US)

EZH1 and EZH2

- **mediate histone methylation**
- **highly expressed or mutated in PTCLs**

	ALL PTCL (n=44)	AITL (n=17)	PTCL-NOS (n=20)	ATLL (n=25)
ORR	55%	**65%**	50%	**48%**
CR	27%	**47%**	20%	**20%**

ATLL- median DOR NR
PTCL Median DOR 56 wks

Gan Biomarker Research 2018, Yoshimitsu Blood (ASH) 2021, Mehat-Shah Chicago Lymphoma Symposium, Foss Blood (ASH)2021

Romi-Len Combinations in R/R TCL: Phase I

Romi and Len are synergistic in vitro: induce of apoptosis through generation of reactive oxygen species, caspase activation, and downregulation of PI3K/AKT and MAPK/ERK pathways

MTD:
Romi 14 mg/m2 d1,8, 15
Len 25 mg d 1-21
TCL n= 27

- **ORR 50%**
- **CR 13%**
- **CRs: MF 1, ATLL 1, AITL 1**
- **Median PFS: 4.8 m, OS 18 m**
- **Allo – 3 pts**

All AITL responded
Allo SCT 6 pts- chemo-free SCT bridge

MTD:
Romi 1 mg/m2 d1,8
Len 10 mg d 1-14
Carfilzomib 36 mg/m2 D 1, 8
TCL n=16

- **ORR 50%**
- **CR 31%**
- **CRs: PTCL-NOS 1, AITL 4**
- **Median EFS: 3 m, OS 22 m**

Mehta-Shah Am J Haem 2021

Targeted Therapies and Combinations in PTCL

- PI3K inhibitors
- Jak inhibitors

Duvelesib in R/R PTCL: Phase II PRIMO trial

- **Duvelesib:** gamma delta PI3K inhibitor, changes macrophage distribution from immunosuppressive to immunostimulatory xenografts and changes serum cytokine profile
- median age of 66.5 years, median 3 lines of Tx
- Dose-optimization (N=33): 75 mg bid- ORR 54% 25 mg po bid - ORR 35%
- Dose expansion (N=78): 75 mg BID X 2 cycles -> 25 mg BID
- ALT/AST increased 24-21%
- **LFT elevation most common reason for d/c**

	ORR	CR
ALL (78)	50%	32%
PTCL NOS (42)	52%	29%
AITL (21)	**67%**	**48%**
ALCL (11)	9%	9%

5 patients bridged to transplant

Brammer ASH Blood 2021
Horwitz Blood 2018

Romidepsine-Duvelisib in R/R PTCL and CTCL: Phase 1

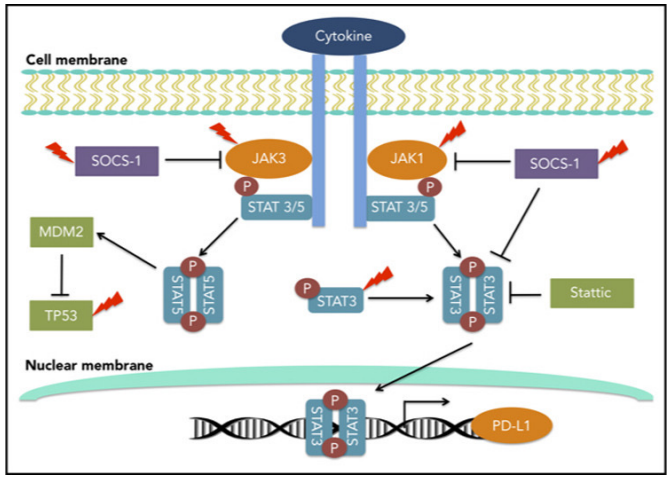
- MTD of Duvalesib 75mg BID + Romi 10 mg/m2 on days 1, 8, 15 q 28 days; 10 pt Duvalesib lead in only
- **4/10 transaminitis in lead-in, 4/29 all**
- **PTCL n=52 ORR 58%, CR 42%**
- **PTCL-NOS n=19 ORR 53% CR 32%**
- **AITL ORR n=19 68% CR 58%**
- CTCL ORR n=11 was 36% - all PR
- 43% proceeded to allo-SCT
- median PFS 6.9 m (PTCL) and 5.5 m (CTCL)
- median DOR 8.1 m

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)
CTCL	**11**	**11**	**4 (36)**	**0**	**0**
MF	7	7	2 (29)	0	0
LCT	*3*	*3*	*0*	*0*	*0*
SS	4	4	2 (50)	0	0
LCT	*1*	*1*	*0*	*0*	*0*
Overall	**66**	**64**	**35 (55)**	**22 (34)**	**15 (23)**

Horwitz Blood 2018
Horwitz ICML 2021

Ruxolitinib in R/R PTCL: a Biomarker Driven Phase 2 Trial

JAK/STAT pathway mutations and pathway activation are common in T cell lymphomas



endpoint: CBR*
R/R PTCL n=45
R/R MF=7

1. activating JAK and/or STAT mutations
2. ≥30% pSTAT3 expression by IHC
3. Neither/insufficient

Ruxolitinib
20 mg po bid

1 CBR 53%

2 CBR 45%

3 CBR 13%

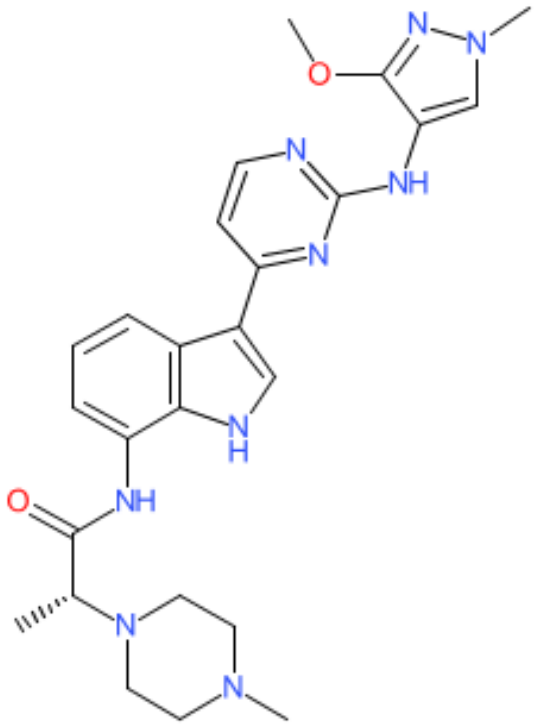
- 8 pts CBR >12 m
- MAPK activation in <25% cells correlated with response

*__clinical benefit rate__ = CR+PR+SD >= 6 months

Moscowitz Blood 2021, Manso BJH 2017

Golidocitinib, a selective JAK1 inhibitor, in R/R PTCL (JACKPOT8 phase 1/2 clinical trial)

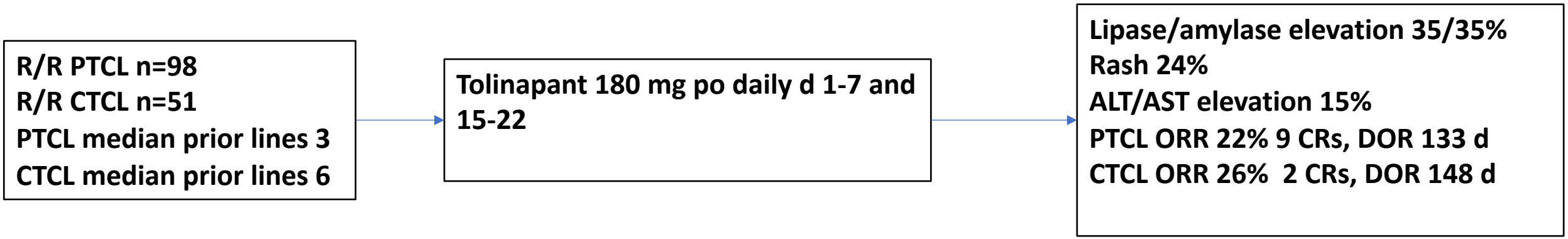
- **Golidocitinib - oral potent JAK1 specific inhibitor**
- **In Part A: dose escalation 150 mg (n=35) or 250 mg QD (n=16)**
- **PTCL-NOS 41.2%, AITL 39.2% n=49 evaluable**
- **ORR 42.9%, CR 22.4 %**
- **median DOR NR, longest DoR > 14 months**
- **Most common AEs hematologic, manageable**
- **Promising activity and manageable toxicity**
- **FDA fast track for RR PTCL**



Kim ASCO 2022, **NCT04105010**

TOLINAPANT (ASTX660) MONOTHERAPY IN R/R PTCL and CTCL: Phase 2

TOLINAPANT: oral small-molecule antagonist of cellular/X-linked inhibitors of apoptosis proteins (cIAP1/2 and XIAP), induces necroptosis in T-cell lymphoma models, induces immunomodulatory antitumoral effect



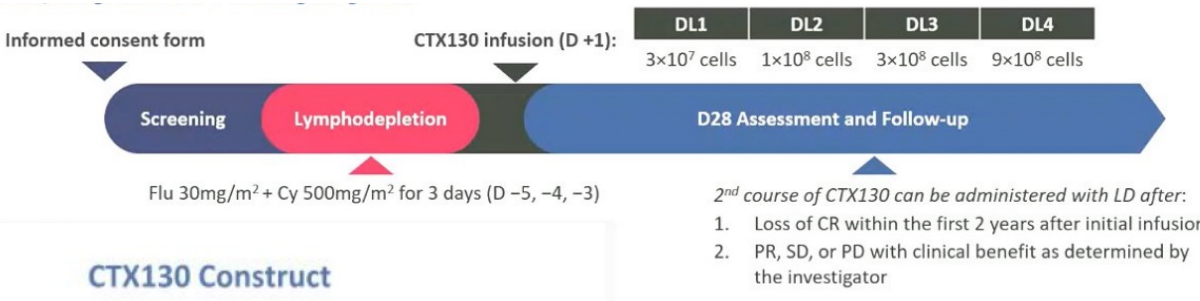
Novel mechanism of action, potential for combination therapies

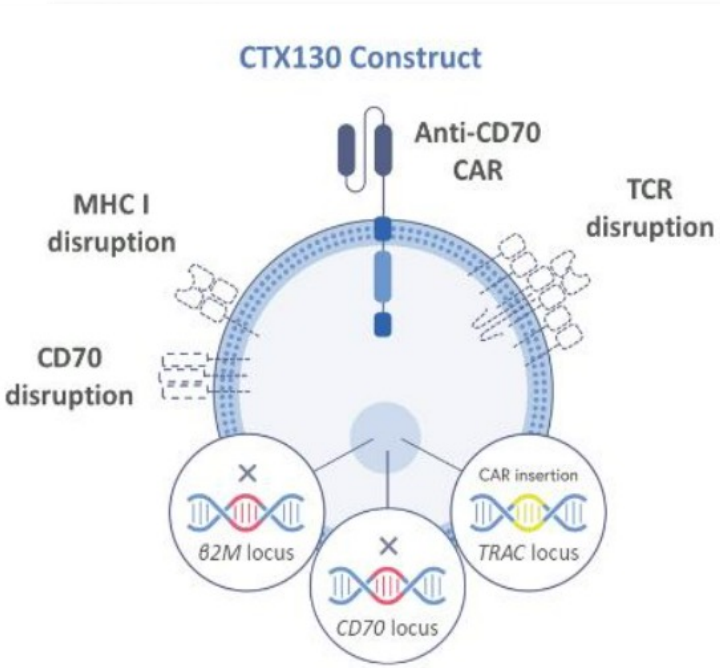
Michot Foss EHA 2022

CARs for T cell Lymphomas

THE COBALT-LYM STUDY OF CTX130: A PHASE 1 STUDY OF CD70-TARGETED ALLOGENEIC CAR T CELLS IN R/R T Cell Lymphomas

- **Challenges with CARs in TCLs**
  - poor function of donor T cells
  - fratricide
  - risk of infusing transduced malignant CAR T cells into pts
- **CD70 – highly expressed on many TCLs**
- **CTX130TM: is a first-in-class, CD70-targeting allogeneic CAR T therapy, modified with CRISPR/Cas9-editing to eliminate expression of:**
  - T-cell receptor
  - MHC I expression by β2-microglobulin disruption
  - CD70 to mitigate fratricide and enhance performance
- Median follow up 3.1 months
- **At DL ≥3: ORR 71%, CR rate 29%**
- **No DLTs, no Grade (Gr) ≥3 CRS or ICANS**
- **Gr 1-2 CRS and ICANS 47% and 20%.**





	PTCL		CTCL	
	DL≥3 N=5	Total N=8	DL≥3 N=5	Total N=10
ORR	4 (80)	5 (63)	3 (60)	4 (40)
CR	2 (40)	3 (38)	1 (20)	1 (10)
PR	2 (40)	2 (25)	2 (40)	3 (30)
DCR	4 (80)	5 (63)	5 (100)	8 (80)

Iyer, Sica et al 05/12/22 EHA Library. P. Iyer S. 06/11/22; 357126; S262, CRISPR https://sec.report/Document/0000950170-22-011518/

A Phase 1/2, Open-Label, First-in-Human, Multiple Ascending Dose Multicenter Study of MT-101 in Subjects with CD5+ Relapsed/ Refractory Peripheral T Cell Lymphoma

- Myeloid cells: up to 75% of tumor mass
- Activate, Target, Attack & Kill (ATAK) CAR myeloid cell platform: receptors combine tumor recognition with multiple proprietary innate-immune signaling domains
- The anti-CD5 CAR is incorporated into myeloid cells via mRNA transfection
- Trail candidates: PTCL-NOS, AITL, ALCL Alk-, ALCL Alk+ RR to two lines of systemic therapy

Diwanji AACR 2022, https://clinicaltrials.gov/ct2/show/record/NCT05138458

Summary

- CD30 +: brentuximab improves efficacy in upfront and relapsed CD30+ T cell lymphomas
- CD30-: etoposide can improve CR and PFS
- T follicular helper phenotype PTCL (AITL and TFH-PTCL) are more sensitive to epigenetic therapies including HDACi and hypomethylating agents
- HD therapy and ASCT in 1st CR can improve PFS and OS
- In R/R setting, greater response and survival is achieved with single agents as first retreatment, while maintaining the ability to achieve transplantation
- Multiple novel regimens for targeted PTCL treatment are under development