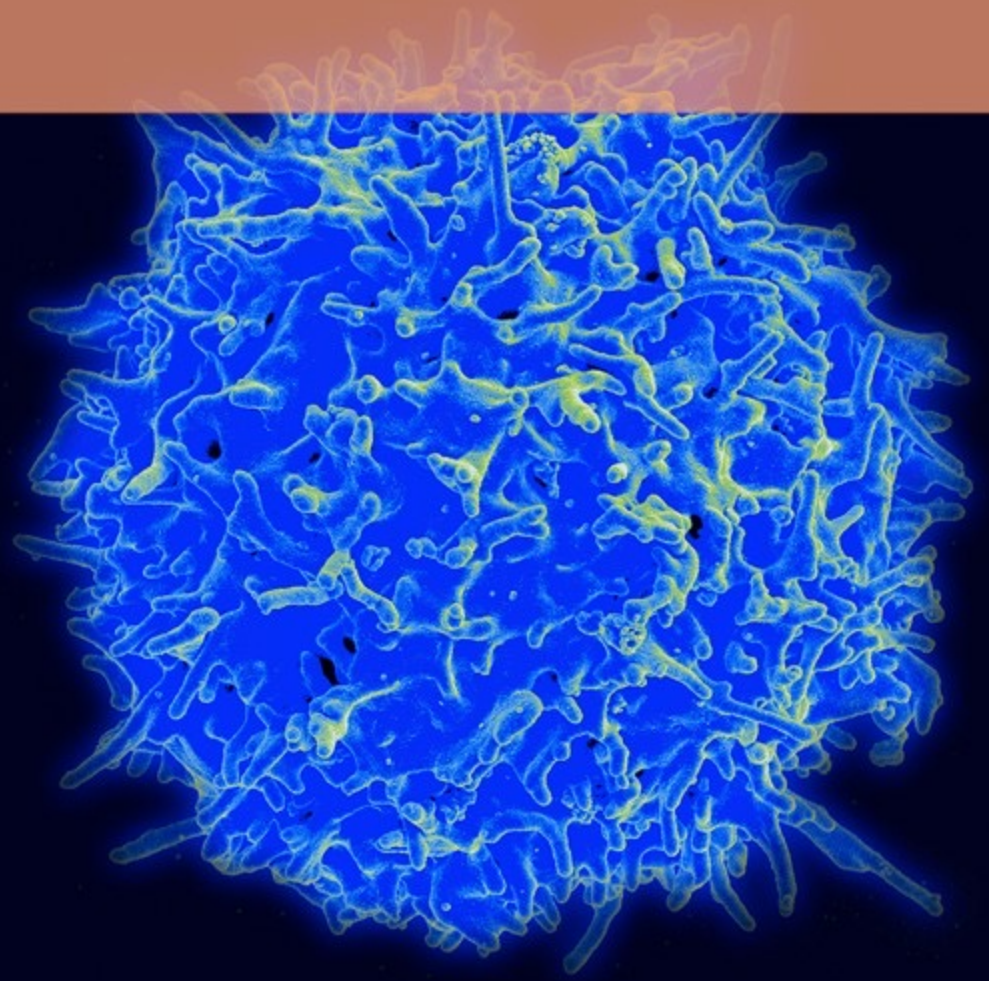
Yale SCHOOL OF MEDICINE

T-cell Lymphomas

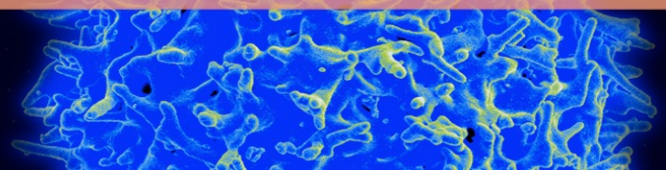
Novel approaches and challenges



Francine Foss, M.D.
Professor of Medicine and Dermatology
Yale University School of Medicine
New Haven, CT, USA

18th Annual New Orleans Summer Cancer Meeting

WHO classification of T cell Lymphomas



Legend: Most common Less common Rare

Leukemic

- T-cell PLL
- **T-cell LGL leukemia**
- *Chronic LPDs of NK cells*
- Aggressive NK-cell leukemia
- **ATLL**
- Systemic EBV+ T-cell lymphoma of childhood
- Hydroa vacciniforme-like lymphoproliferative disorder

Nodal

- PTCL-NOS
- AITL (angioimmunoblastic)
- Follicular T-cell lymphoma
- Nodal PTCL with TFH phenotype
- ALCL, ALK-positive
- ALCL, ALK-negative

Cutaneous

- MF/Sezary Syndrome
- Primary cutaneous CD30+ LPD
- LyP, pcALCL
- Primary cutaneous $\gamma\delta$ TCL
- Primary cutaneous CD8+ aggressive epidermotropic cytotoxic TCL
- Primary cutaneous acral CD8+ TCL
- Primary cutaneous CD4+ small/medium T-cell LPD

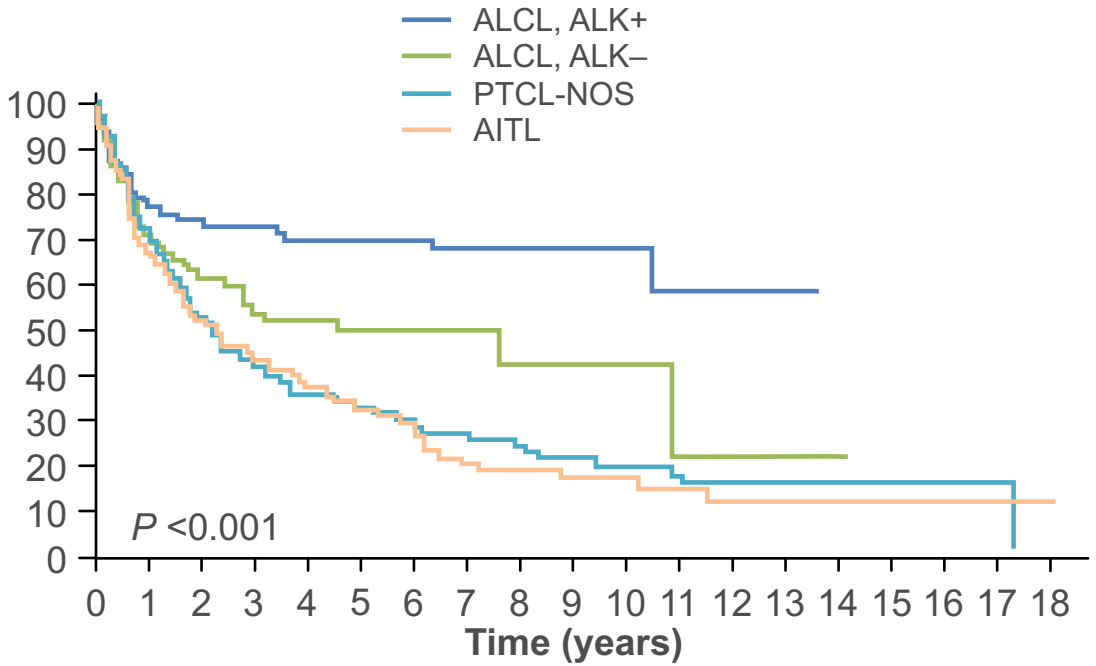
Extranodal

- Extranodal NK/TCL, nasal type
- Enteropathy-associated TCL
- Monomorphic epitheliotropic intestinal T-cell lymphoma
- Indolent T-cell proliferative disorder of the GI tract
- Subcut. panniculitis-like TCL
- Hepatosplenic TCL
- Breast implant-associated ALCL

Courtesy of L. de Level Swerdlow. WHO Classification of Tumours, revised 4th edition, Vol. 2 (2017)

Outcomes for PTCL-then and now

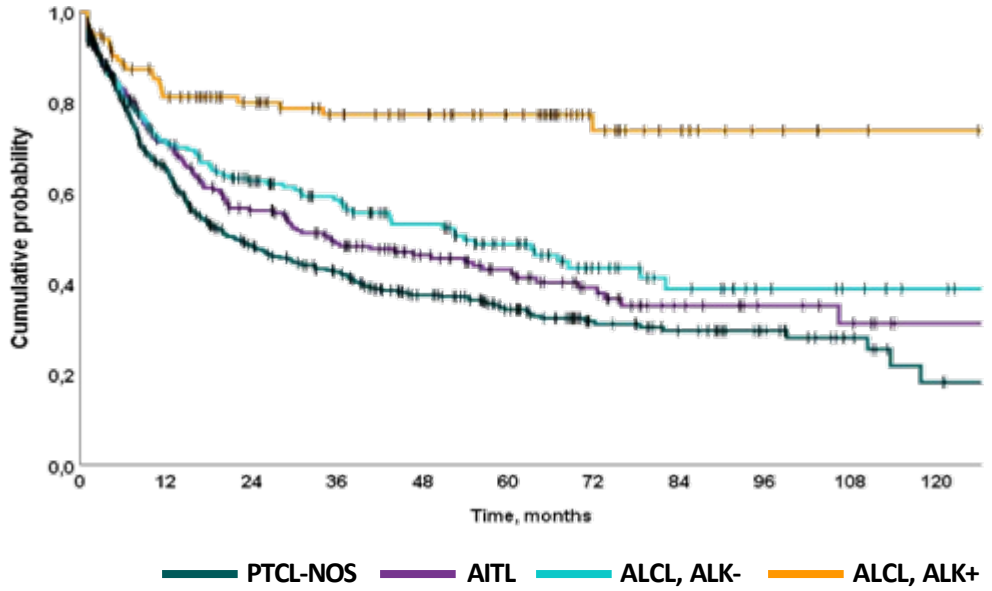
International T cell Lymphoma Project



Diagnosis	5-year OS (%)
PTCL-NOS	32
AITL	32
ALCL, ALK+	70
ALCL, AKL–	49

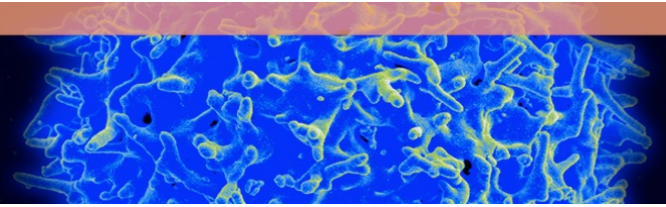
Vose JM, et al. *J Clin Oncol*. 2008

T Cell Project(T1)



Diagnosis	5-yr PFS	5-yr OS
PTCL-NOS	**24%**	**34%**
ALCL ALK -	**43%**	**49%**
ALCL ALK +	63%	77%
AITL	**30%**	**42%**

Bellei et al, Hematologica 2019

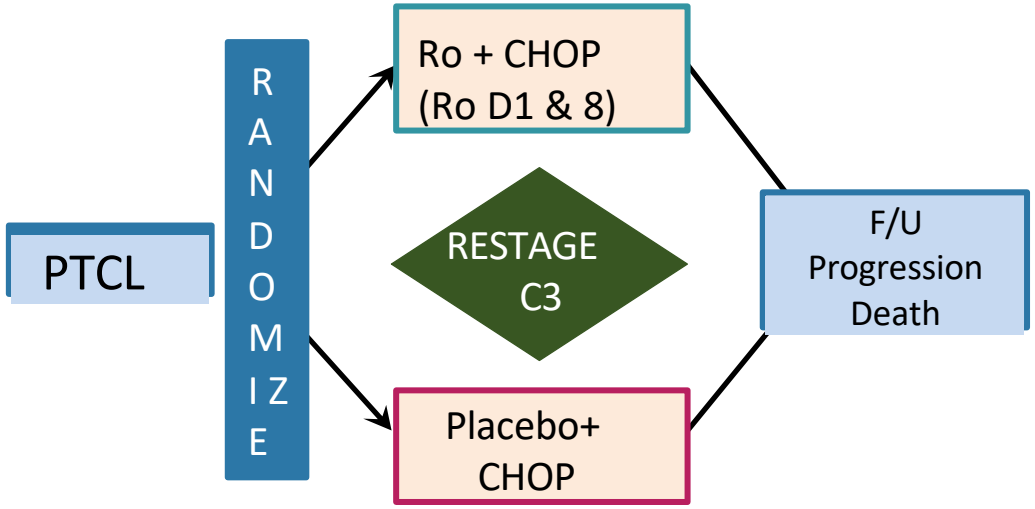


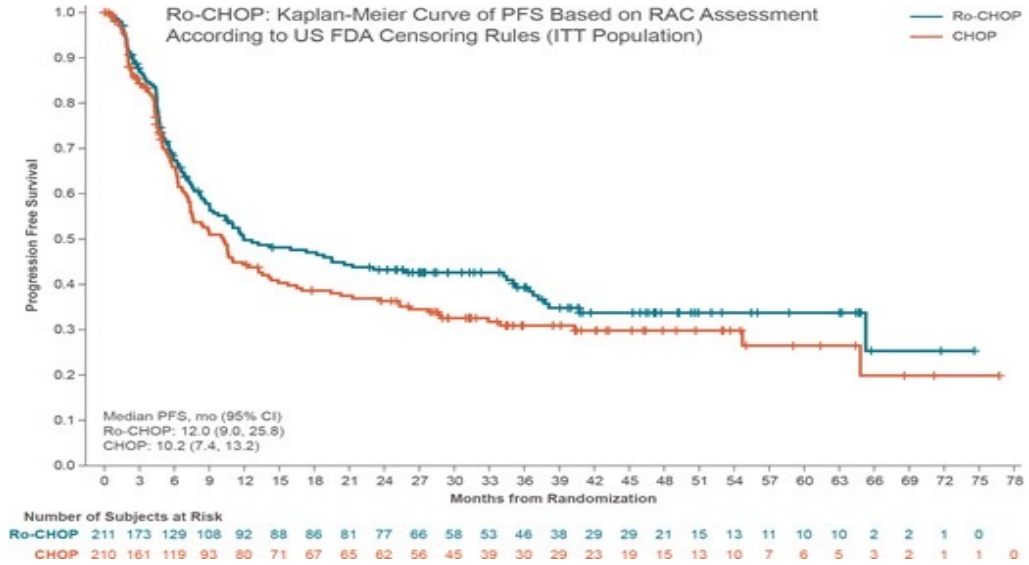
NCCN Guidelines for PTCL

	First-line Therapy*	ALCL†
Preferred regimens	**PTCL-NOS, AITL; EATL; MEITL; Nodal PTCL, TFH; FTCL** ▪ Brentuximab-CHP can be considered for CD30+ histologies ▪ Anthracycline-based combination chemotherapy	▪ CD30-directed ADC in combination with anthracycline-based combination chemotherapy (Category 1)
Other recommended regimens	▪ Newcastle regimen‡ (CHOP followed by IVE/MTX and ASCT for EATL) ▪ Asparaginase regimen for NK/T cell- R-GemOX, SMILE,etc	
First-line consolidation	▪ In patients with ALK-positive ALCL, HDT/ASCR should be considered only for high-risk IPI patients ▪ For other histologies (i.e., PTCL-NOS, ALCL, ALK–, and AITL, including nodal PTCL, TFH, and FTCL), consider HDT with ASCR ▪ Role of alloBMT upfront not defined	

*Although anthracycline-based regimens confer a favorable prognosis in ALK+ ALCL, these regimens have not provided the same favorable results for other PTCL histologies; clinical trial is therefore preferred for the management of these other histologies; †ALK– ALCL with a *DUSP22* rearrangement has been variably associated with a prognosis more similar to ALK+ ALCL disease, and treatment according to the ALK+ ALCL algorithm may be considered. ‡Studied only in patients with EATL.

Front line randomized trials in PTCL



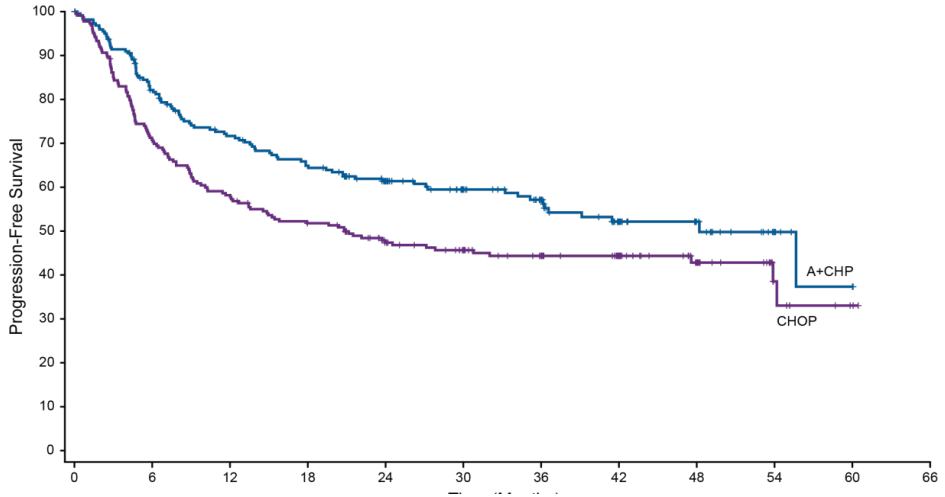


PFS 12.0 mo Ro-CHOP vs 10.2 mo CHOP, hazard ratio 0.81 (95% CI, 0.63-1.04; *P* = 0.096)

Bachy et al, JCO 2022

BV+CHP
Brentuximab Vedotin† + CHP‡
Q3W for 6-8 cycles +
Placebo for Vincristine
(n = 226)

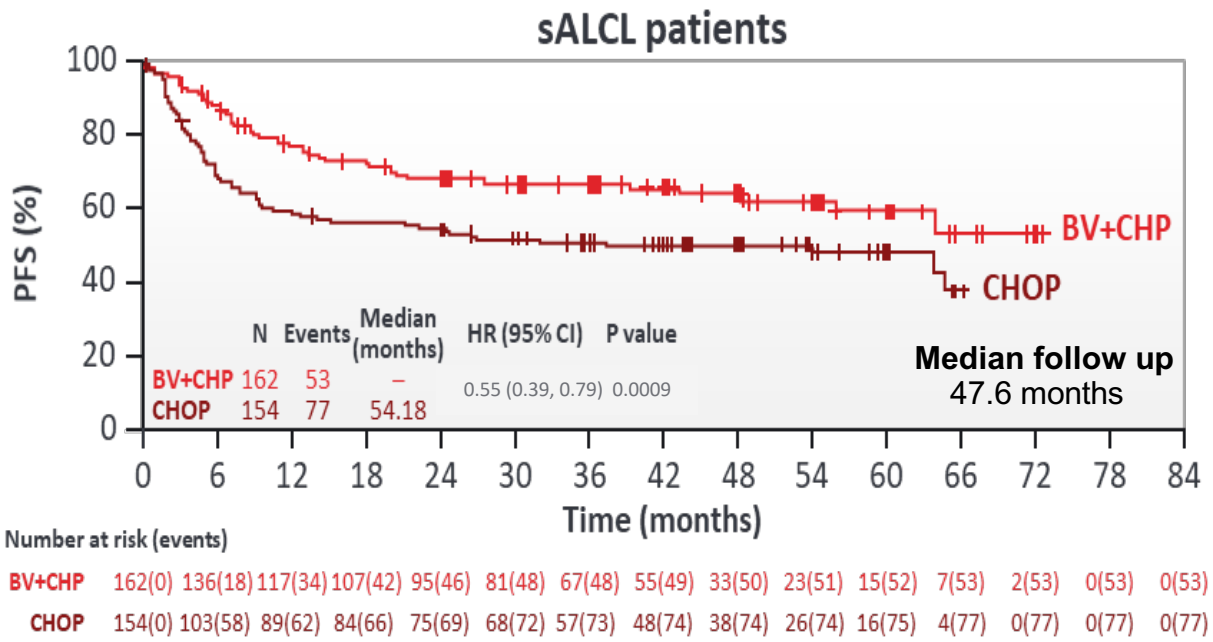
CHOP‡
Q3W for 6-8 cycles +
Placebo for Brentuximab Vedotin (n = 226)

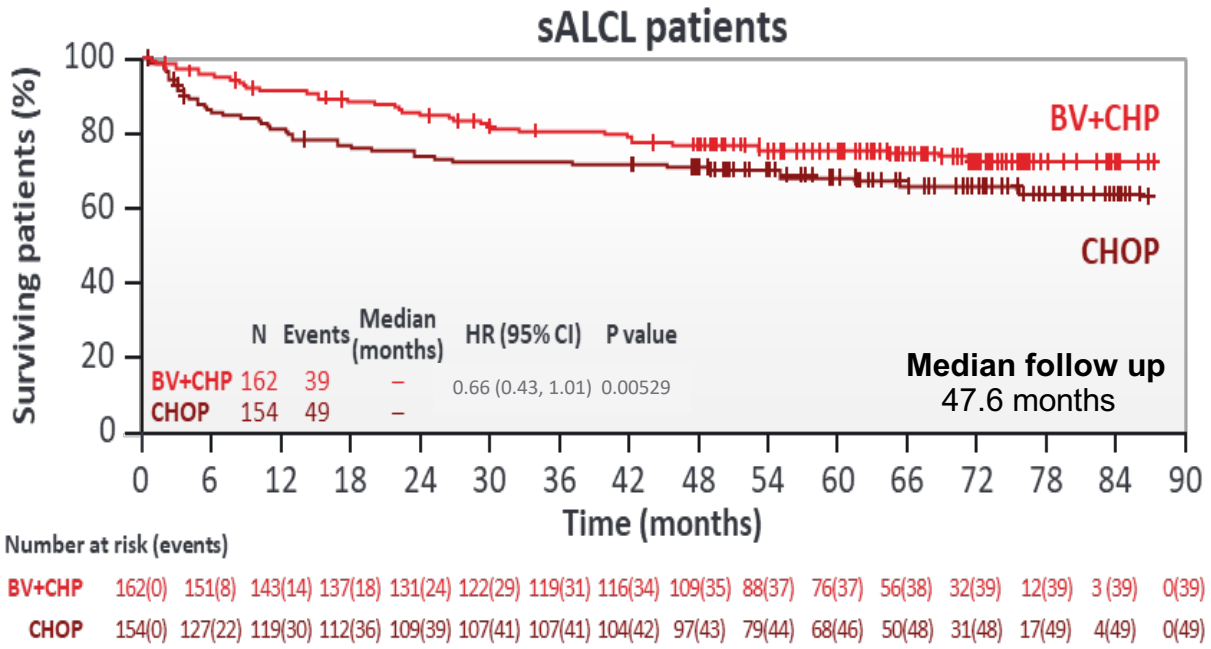


Treatment	Events, n (%)	HR (95% CI)	*P* Value
BV+CHP	95 (42)	0.71 (0.54-0.93)	.011
CHOP	124 (55)		

Horwitz et al, Lancet 2019

Echelon-2: outcomes in ALCL- 5 year update



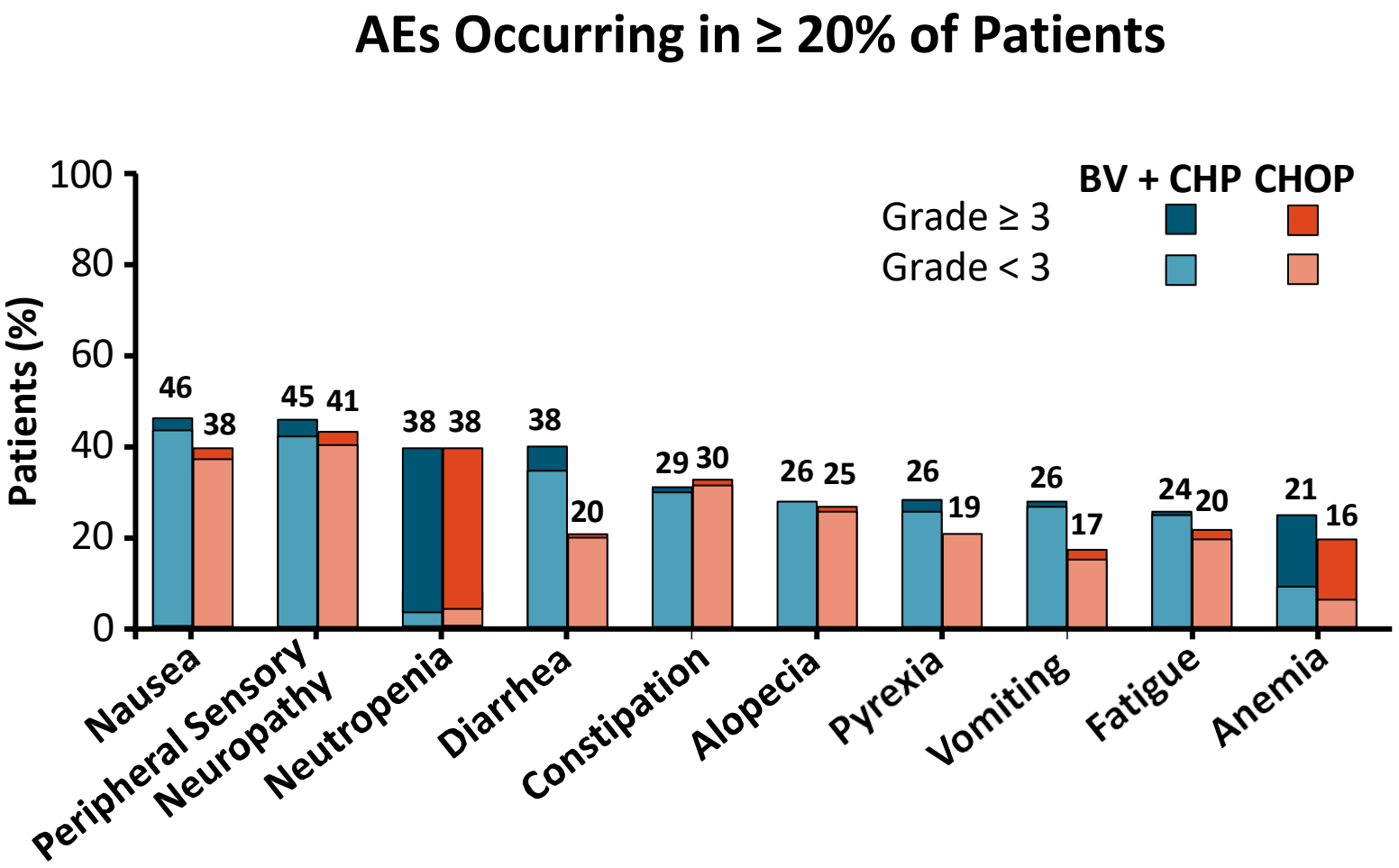


Horwitz SM, et al. Ann Oncol 2022;33:288–98.

Echelon-2: adverse events

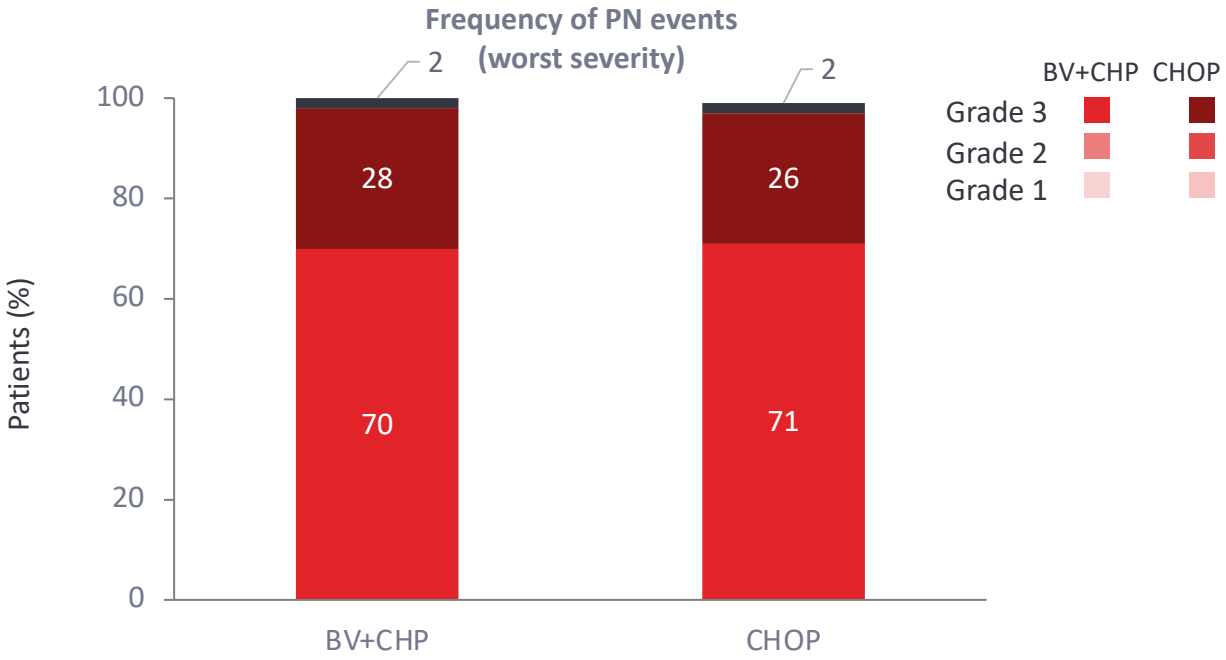
AE, n (%)	BV+CHP (n = 223)	CHOP (n = 226)
Any AE	221 (99)	221 (98)
Grade ≥ 3 AEs	147 (66)	146 (65)
Serious AEs	87 (39)	87 (38)
Death due to AEs	7 (3)	9 (4)

Subjects, n (%)	BV+CHP (n=223)	CHOP (n=226)
Treatment-emergent PN	117 (52)	124 (55)
Resolution of all PN events	58 (50)	79 (64)
Ongoing PN at last follow up	61 (52)	45 (36)
Grade 1	44 (72)	32 (71)
Grade 2	15 (25)	12 (27)
Grade 3	2 (1)	1 (1)



Horwitz S, et al. Lancet 2019. Horwitz S, et al. ASH 2018. Abstract 997.

Echelon-2: incidence and severity of neuropathy



	BV+CHP (n=223)	CHOP (n=226)
Any PN event, n (%)	117 (52)	124 (55)
Resolution of all PN events, n (%)*	71 (85)	82 (85)
Improvement of PN events, n (%)†	13 (15)	15 (15)

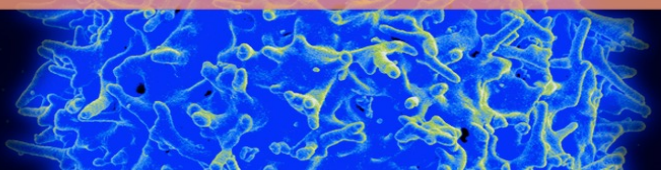
At 5-year follow-up, BV+CHP continues to have a manageable safety profile:
Similar resolution or improvement of PN events was seen for BV+CHP (n (%), 84 [72]) vs CHOP (97 [78]).
For ongoing PN events, BV+CHP 98% vs CHOP 98% were Grade 1 or 2

*Resolution was defined as resolved/recovered with or without sequelae; or return to baseline or lower severity as of the latest assessment for pre-existing events. †Improvement was defined as decrease by at least 1 grade from the worst grade with no higher grade thereafter. Patients with improvement in any event at last follow up were those with at least one improved event and the date of improvement was before last follow up date. Patients with all events resolved were excluded.

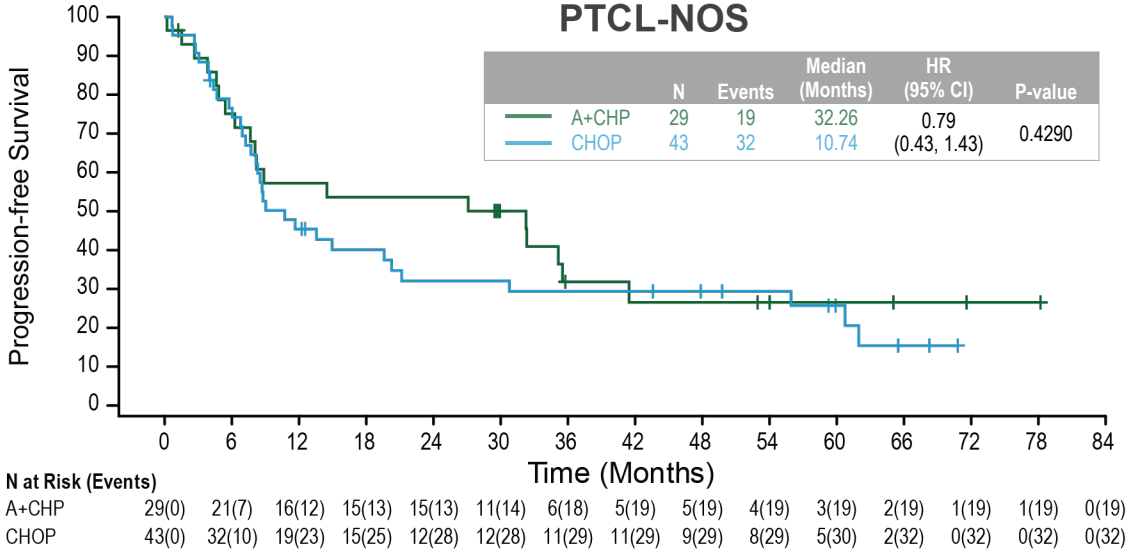
BV+CHP, brentuximab vedotin plus cyclophosphamide, doxorubicin, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; PN, peripheral neuropathy.

Horwitz SM, et al. ASH 2020, Poster #1150

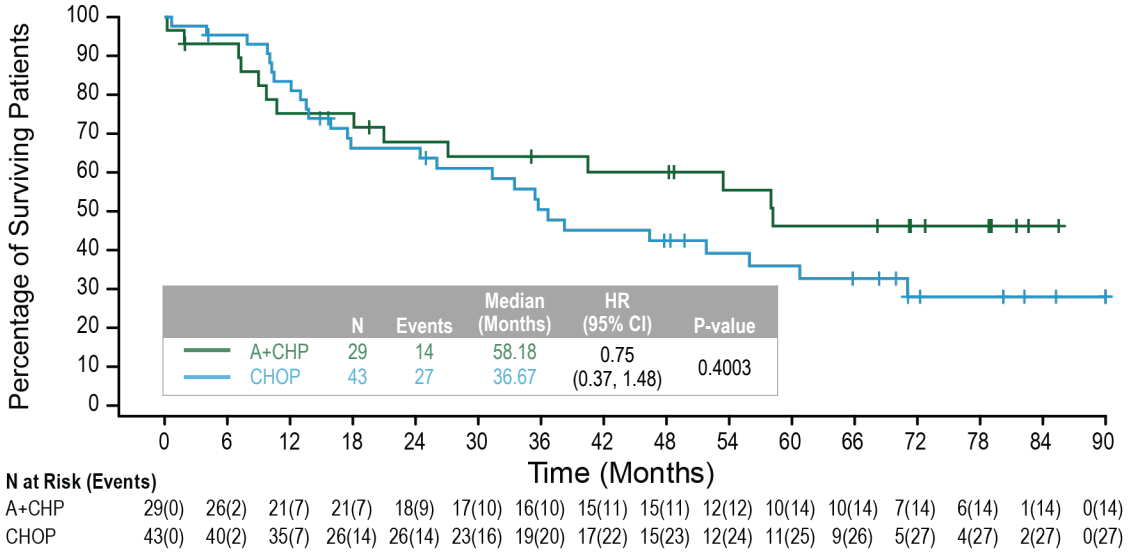
Echelon-2: 5 year outcomes for PFS and OS



PTCL-NOS

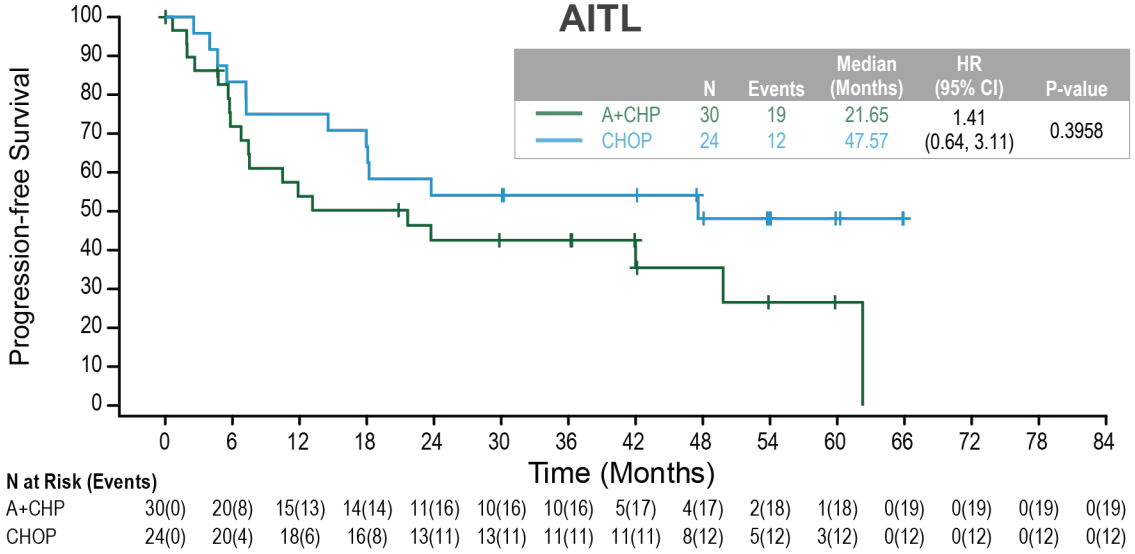


N at Risk (Events)															
A+CHP	29(0)	21(7)	16(12)	15(13)	15(13)	11(14)	6(18)	5(19)	5(19)	4(19)	3(19)	2(19)	1(19)	1(19)	0(19)
CHOP	43(0)	32(10)	19(23)	15(25)	12(28)	12(28)	11(29)	11(29)	9(29)	8(29)	5(30)	2(32)	0(32)	0(32)	0(32)

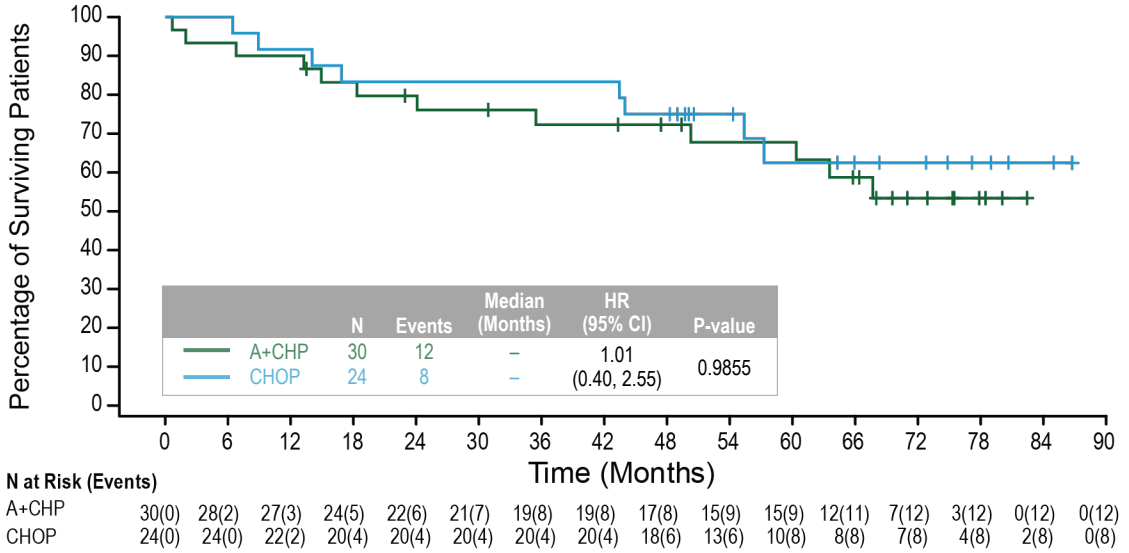


N at Risk (Events)															
A+CHP	29(0)	26(2)	21(7)	21(7)	18(9)	17(10)	16(10)	15(11)	15(11)	12(12)	10(14)	10(14)	7(14)	6(14)	1(14)	0(14)
CHOP	43(0)	40(2)	35(7)	26(14)	26(14)	23(16)	19(20)	17(22)	15(23)	12(24)	11(25)	9(26)	5(27)	4(27)	2(27)	0(27)

AITL



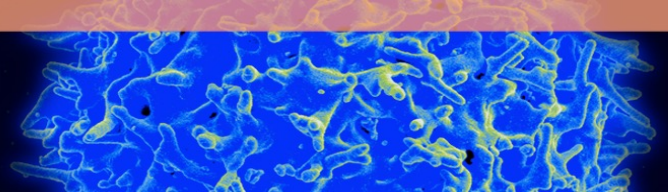
N at Risk (Events)															
A+CHP	30(0)	20(8)	15(13)	14(14)	11(16)	10(16)	10(16)	5(17)	4(17)	2(18)	1(18)	0(19)	0(19)	0(19)	0(19)
CHOP	24(0)	20(4)	18(6)	16(8)	13(11)	13(11)	11(11)	11(11)	8(12)	5(12)	3(12)	0(12)	0(12)	0(12)	0(12)



N at Risk (Events)															
A+CHP	30(0)	28(2)	27(3)	24(5)	22(6)	21(7)	19(8)	19(8)	17(8)	15(9)	15(9)	12(11)	7(12)	3(12)	0(12)	0(12)
CHOP	24(0)	24(0)	22(2)	20(4)	20(4)	20(4)	20(4)	20(4)	18(6)	13(6)	10(8)	8(8)	7(8)	4(8)	2(8)	0(8)

Horwitz et al ASH 2021 a1150

Other front line trials in PTCL



CHOP ± alemtuzumab
CHOP+/- romidepsin
CHOP vs BV-CHP
CHOP vs GEM-P

CHOP followed by ± pralatrexate

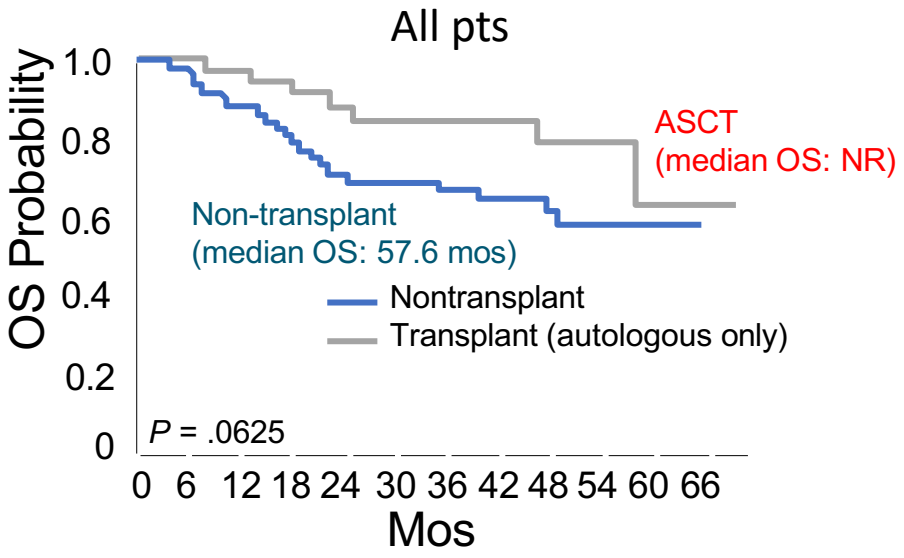
CEOP/pralatrexate
CHOP + everolimus
CHOP + lenalidomide
CHOP + denileukin diftitox

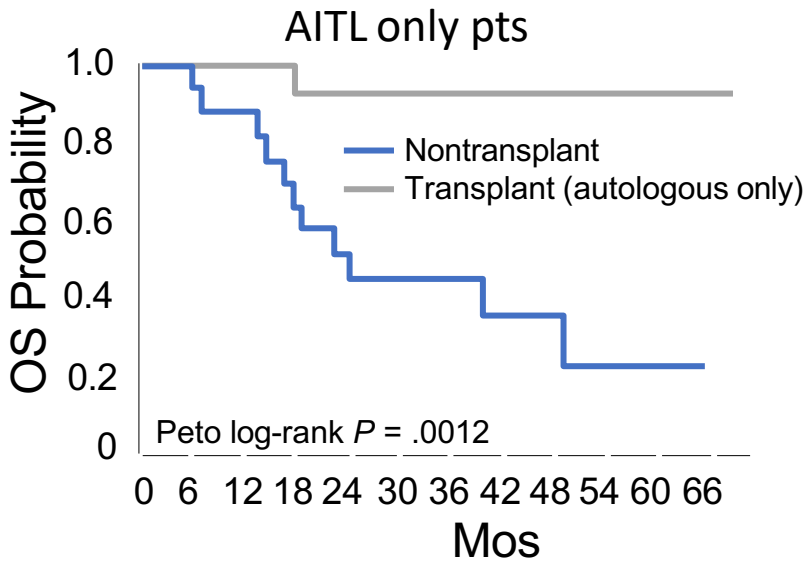
ClinicalTrials.gov. NCT00725231. NCT01420679. NCT01336933. NCT01198665. NCT01719835. NCT01280526 NCT00453427.

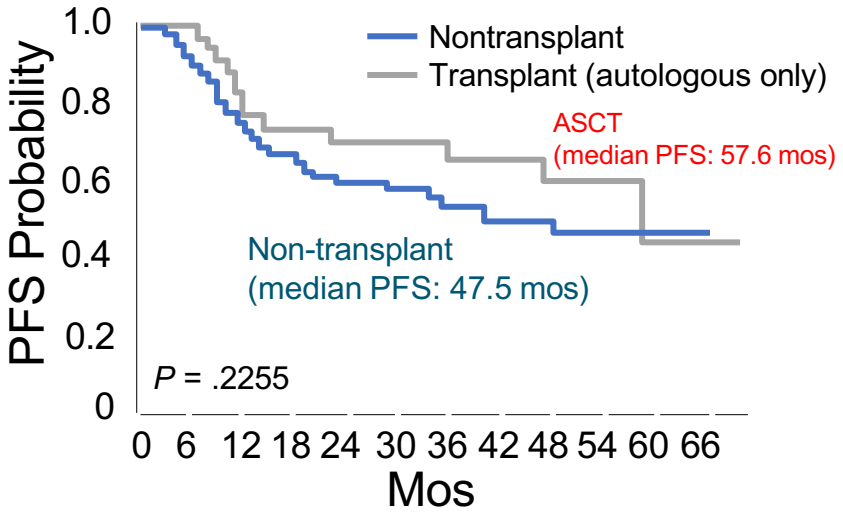
Transplant in first remission: COMPLETE STUDY

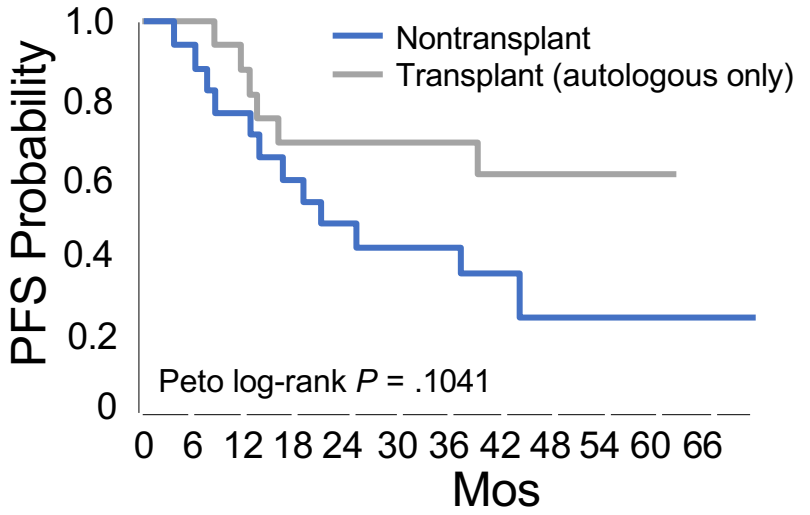
COMPLETE is a prospective registry of 500 patients in the US enrolled at diagnosis

- 119 pts with nodal PTCL had CR
- 36 of those underwent ASCT
- ASCT was associated with superior survival for stage III–IV and intermediate-to-high IPI
- ASCT improved OS and PFS with AITL but not other PTCL subtypes
- Multivariate analysis, ASCT was independently associated with improved survival (HR: 0.37; 95% CI 0.15, 0.89)





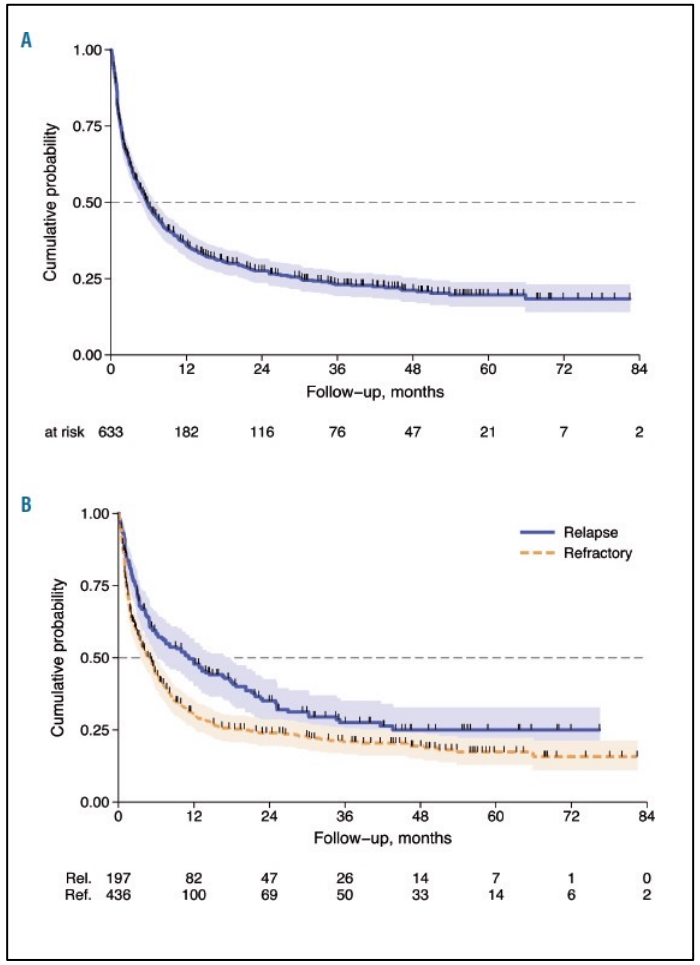




Park. Cancer 2019; 125:1507.

Relapsed/refractory PTCL

Outcomes for relapsed/refractory patients from the T Cell Project



Bellei et al Hematologica 2018, Bachy E, Coiffier B. Blood 2014;

Approved drugs for relapsed/refractory PTCL

Drugs	Class	Indications
Pralatrexate	Antifolate	US FDA: PTCL (2009)
Romidepsin	HDAC inhibitor	US FDA: CTCL (2009) and PTCL (2011)
Brentuximab vedotin	Anti-CD30 ADC	US FDA: ALCL (2011)
Belinostat	HDAC inhibitor	US FDA: PTCL (2014)
Mogamulizumab	Anti-CCR4 mAb	Japan: ATLL (2012), PTCL and CTCL (both 2014)
Chidamide	HDAC inhibitor	China: PTCL (2014)
Forodesine	PNP inhibitor	Japan: PTCL (2017)
E7777 (Ontak)	IL2 Fusion Toxin	Japan: PTCL, CTCL (2021)

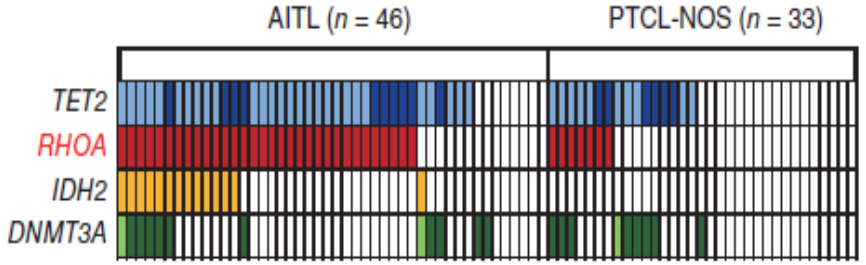
Picking a drug for a specific subtype

		Overall Response Rate	Complete Remission Rate	ORR PTCL-NOS	ORR AITL	ORR ALCL
FDA Approved	**Histone Deacetylase Inhibitors**					
	Romidepsin	25%	15%	29%	30%	24%
	Belinostat[15]	26%	11%	23%	54%	15%
	Anti-Folate					
	Pralatrexate[14]	29%	15%	32%	8%	29%
	CD30 Targeted Approaches					
	Brentuximab vedotin[26,44]			33%	54%	86%

O'Connor OA, et al. J Clin Oncol. 2011,Coiffier B, et al. J Clin Oncol. 2012, Pro B, et al. J Clin Oncol. 2012, Horwitz S M et al. Blood 2014

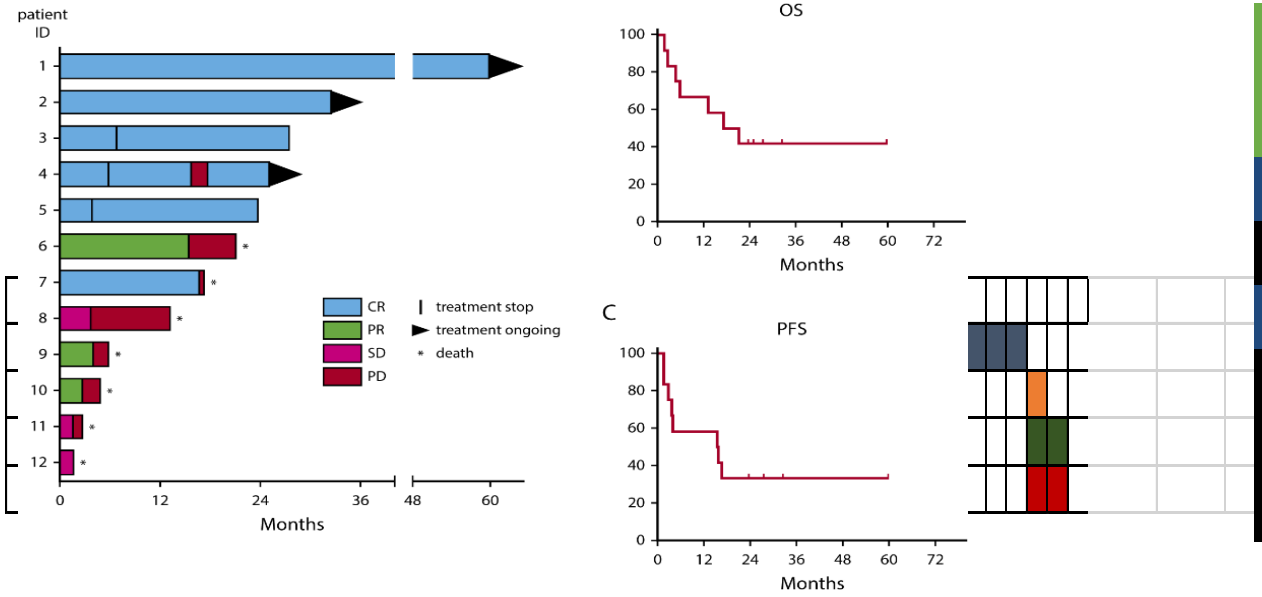
Mutations of DNA methylation genes in PTCL

Recurrent mutations of genes involved in DNA methylation regulation have been described in PTCL and in angioimmunoblastic T cell lymphoma



Phase II study of 5-azacitidine in AITL

- N = 12 patients with stage III/IV AITL
- **5-azacytidine** (median of 5.5 cycles), plus rituximab in 6/12 patients
- ORR 75%: CR 6/12 ; PR 3/12; SD 3/12



Phase I study of oral 5-azacitidine and romidepsin

5-azacitidine: 100 mg/day d1-14, to 300 mg/day, d1-21

Romidepsin 10 mg/m², d8,15,to 14 mg/m²,d8,15,22,21-35 day cycles

Response, n (%)	All Patients (N = 31)	T-cell Lymphoma (n = 11)
ORR	10 (32)	8 (73)
CR	7 (23)	6 (55)
PR	3 (10)	2 (18)
SD	7 (23)	0
PD	11 (35)	2 (18)
Not evaluable	3 (10)	1 (9)

Sakata-Yanagimoto et al. *Nat Gen* 2014; Courtesy of Dr. F. Lemonnier & Pr. Ph. Gaulard

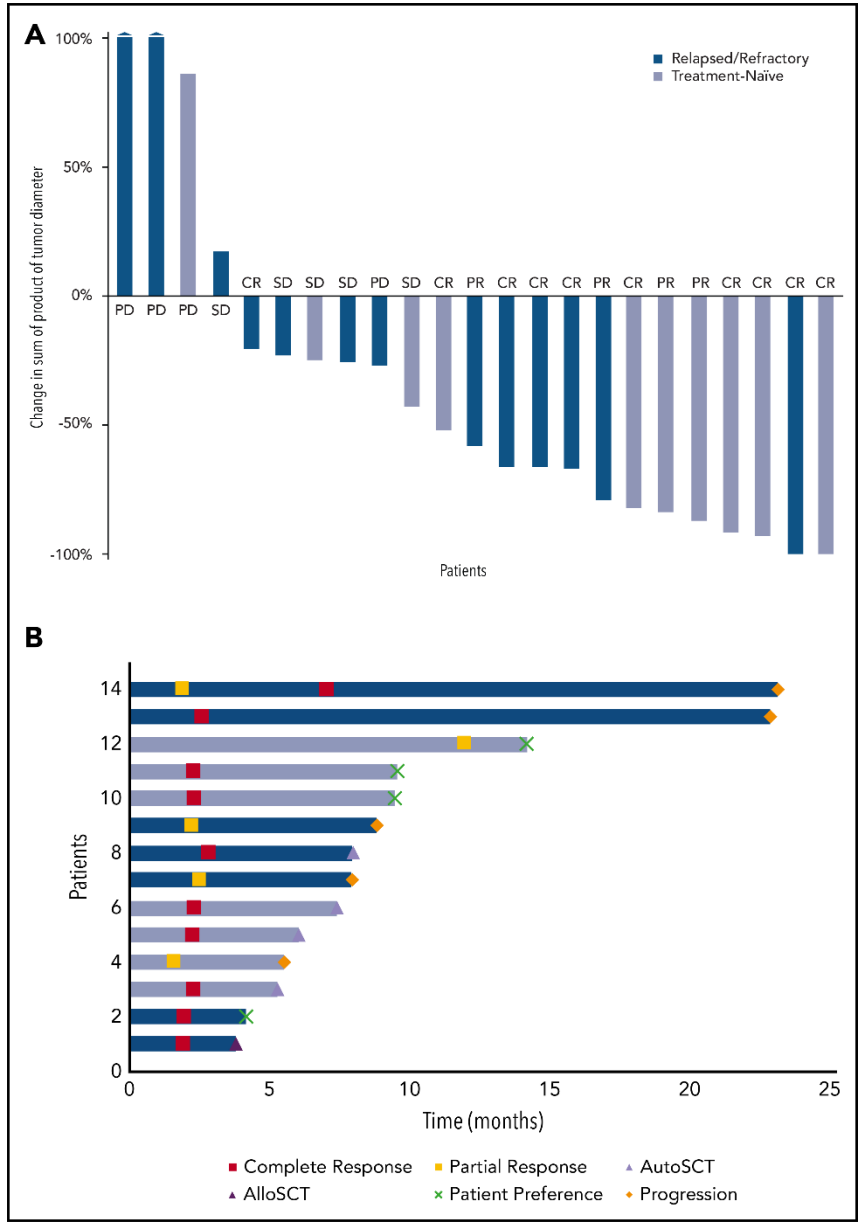
Falchi et al, Blood 2021

Multicenter phase II study of romdepsin and 5-azacytidine

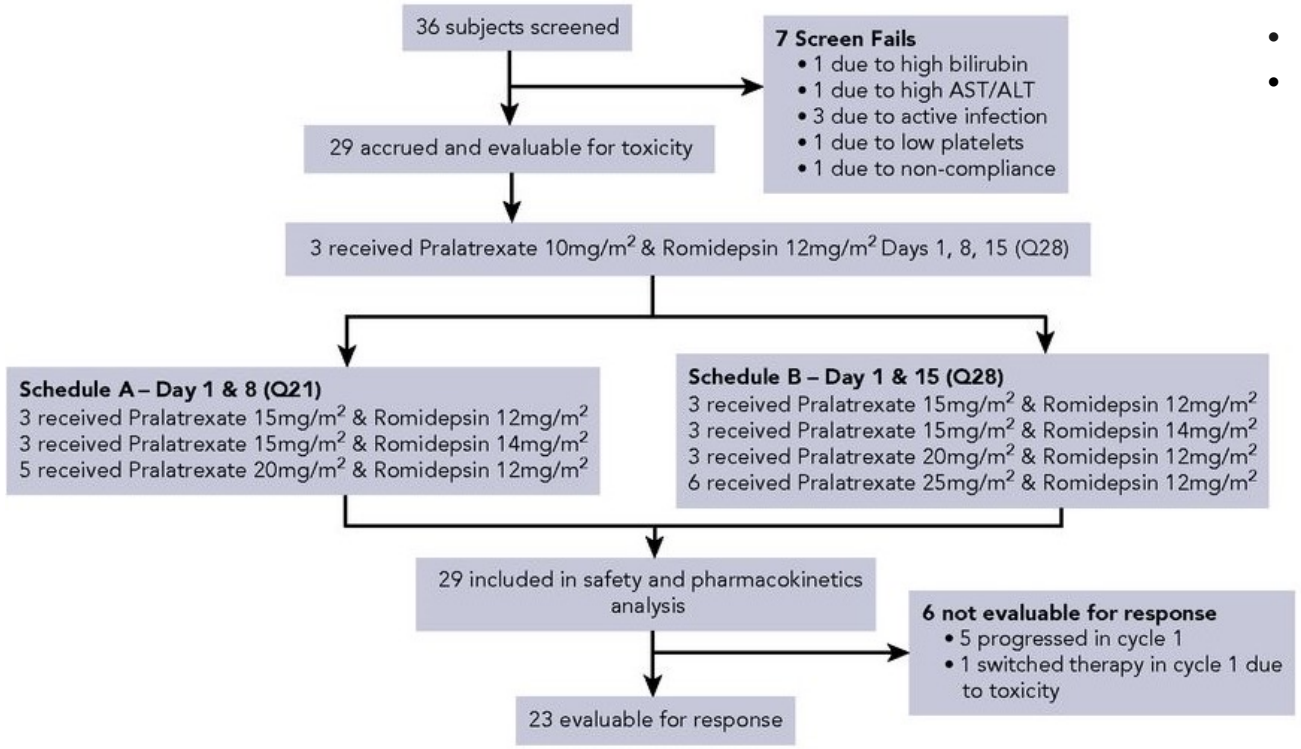
- Front line or R/R PTCL pts eligible
- Azacytidine 300 mg days 1 to 14, Romidepsin 14 mg/m^2 on days 8, 15, and 22 every 35 days.
- ORR 61% , CR 48%
- T-follicular helper cell (tTFH) higher ORR
- Gr 3 to 4 AEs were thrombocytopenia (48%), neutropenia (40%), lymphopenia (32%), and anemia (16%)
- Median PFS 8 mo, median OS not reached , median DOS 20.3 months
- Responders had higher average number of mutations in genes involved in DNA methylation and histone deacetylation

	Overall response	Complete response	Partial response
All pts (23)	61%	43%	17%
Front line (10)	70%	50%	20%
R/R disease (13)	54%	38%	15%
tFH (15)	80%	60%	20%

Falchi et al, Blood 2022

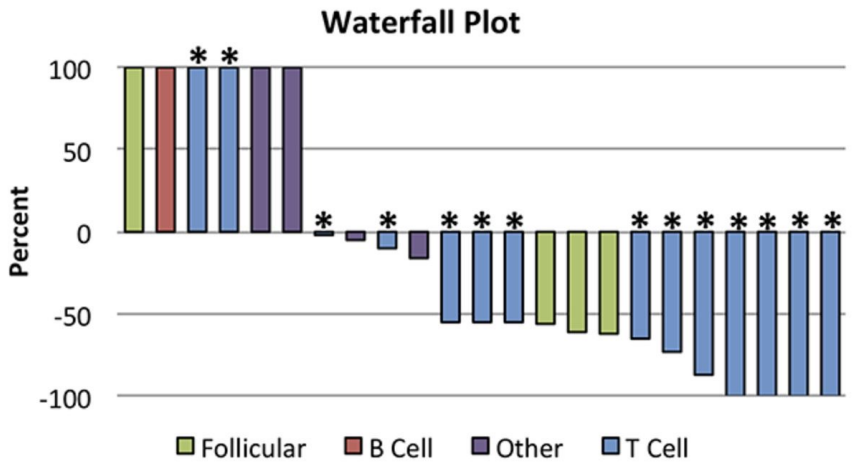


Phase I study of romdepsin and pralatrexate



- Twenty-three patients were evaluable for response.
- In 23 pts, ORR 57% , 71% (10/14) in PTCL
- Gr ¾ adverse events included anemia (29%), oral mucositis (14%), thrombocytopenia (28%), and neutropenia (20%),sepsis (7%), fever (3%), and pneumonia (3%)

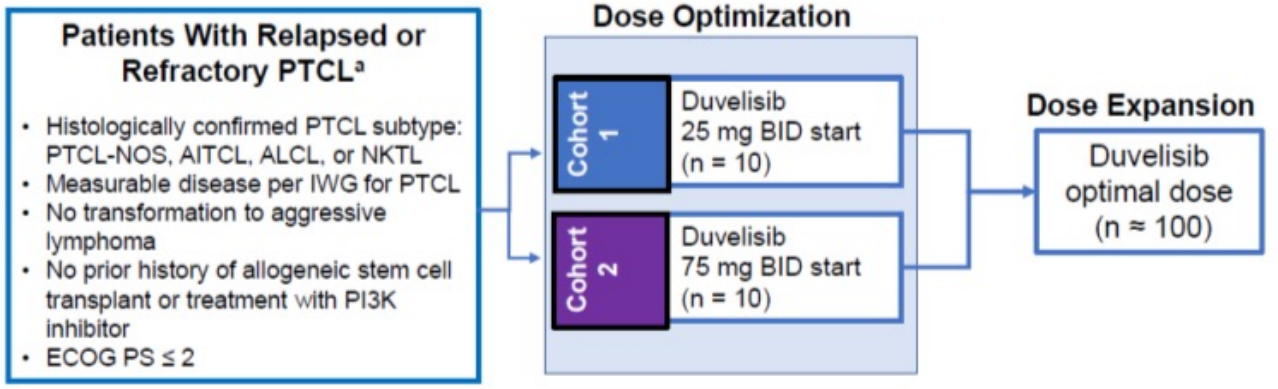
Pralatrexate and Romidepsin are Highly Effective in T-Cell Lymphoma



12/14 T-Cell Lymphoma Derived Benefit:
2 SD, 6 PR, 4 CR (ORR=71%)

Amengual et al, Blood 2018

PI3Kinase as a target: Duvelisib



- Studied in single agent phase II study (PRIMO) n=78
  - 75mg BID x 2 cycles→ 25mg BID unless progression/intolerance
  - ORR 50%, CR 32%
  - Grade ≥3 transaminitis 24%
- In combination study of duvelisib 75mg BID and romidepsin (n=66):
  - ORR 55%, CR 34%
  - Grade ≥3 transaminitis 14%

Safety:
Treatment interruptions and/or dose reductions most commonly required for AST/ALT elevation, rash, diarrhea, and pyrexia.
Neutropenia in 20%. Grade ≥ 3 infections in 29%.

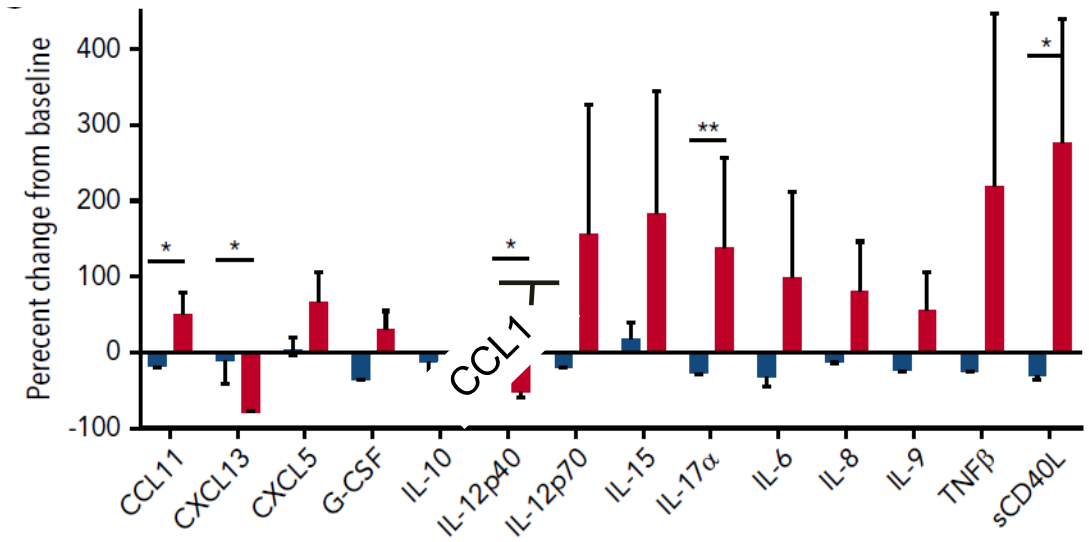
- Duvelisib NCCN Compendium listed for PTCL 2021

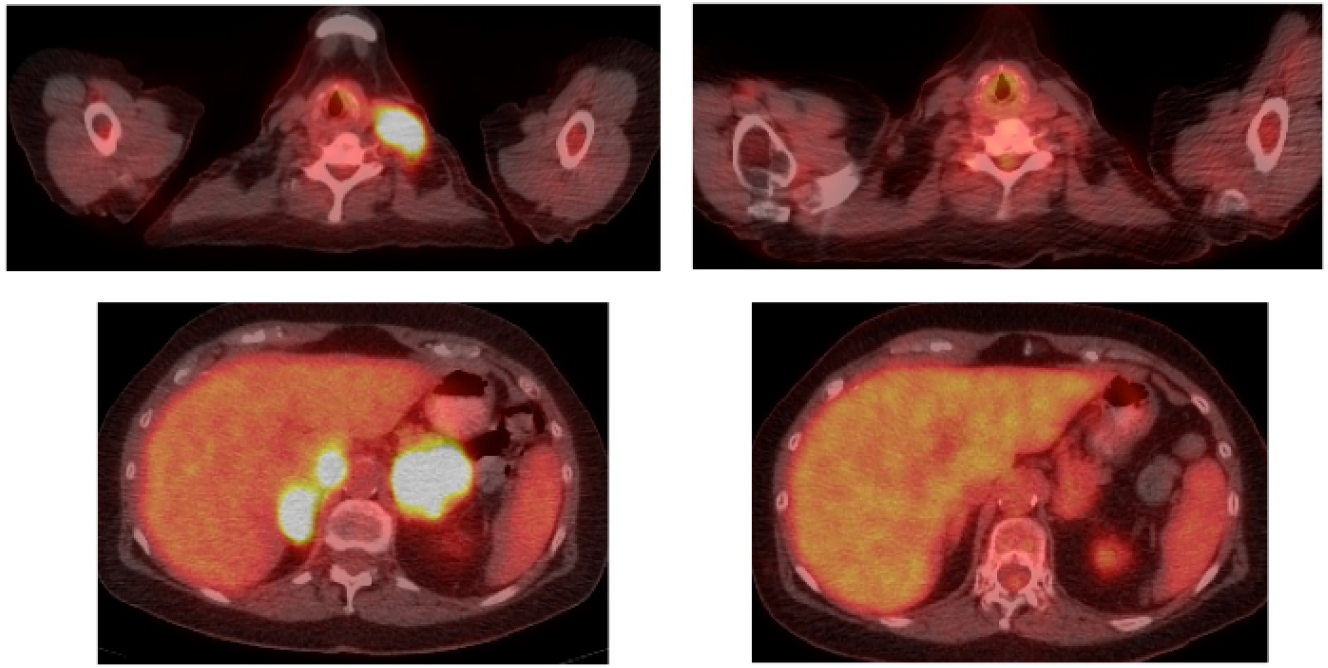
	Cohort 1 25 mg BID (N=20)	Cohort 2 75 mg BID (N=13)	Dose Expansion 75mg BID x 2 cycles→ 25mg BID (n=78)	
ORR (%)	35%	54%	50%	
CR (%)	25%	31%	32%	

Horwitz et al Blood 2018, Brammer ASH 2021; Cheun et al Cancers 2020

Duvelisib biomarkers predictive of response

- Serum cytokines measured at baseline and at cycle 1 day 8.
- Changes observed in responding patients:
  - Increases in CCL1, IL-17α, and sCD40L
  - Decreases in CXCL13 and IL-12p40.





Predose **Cycle 1 Post**

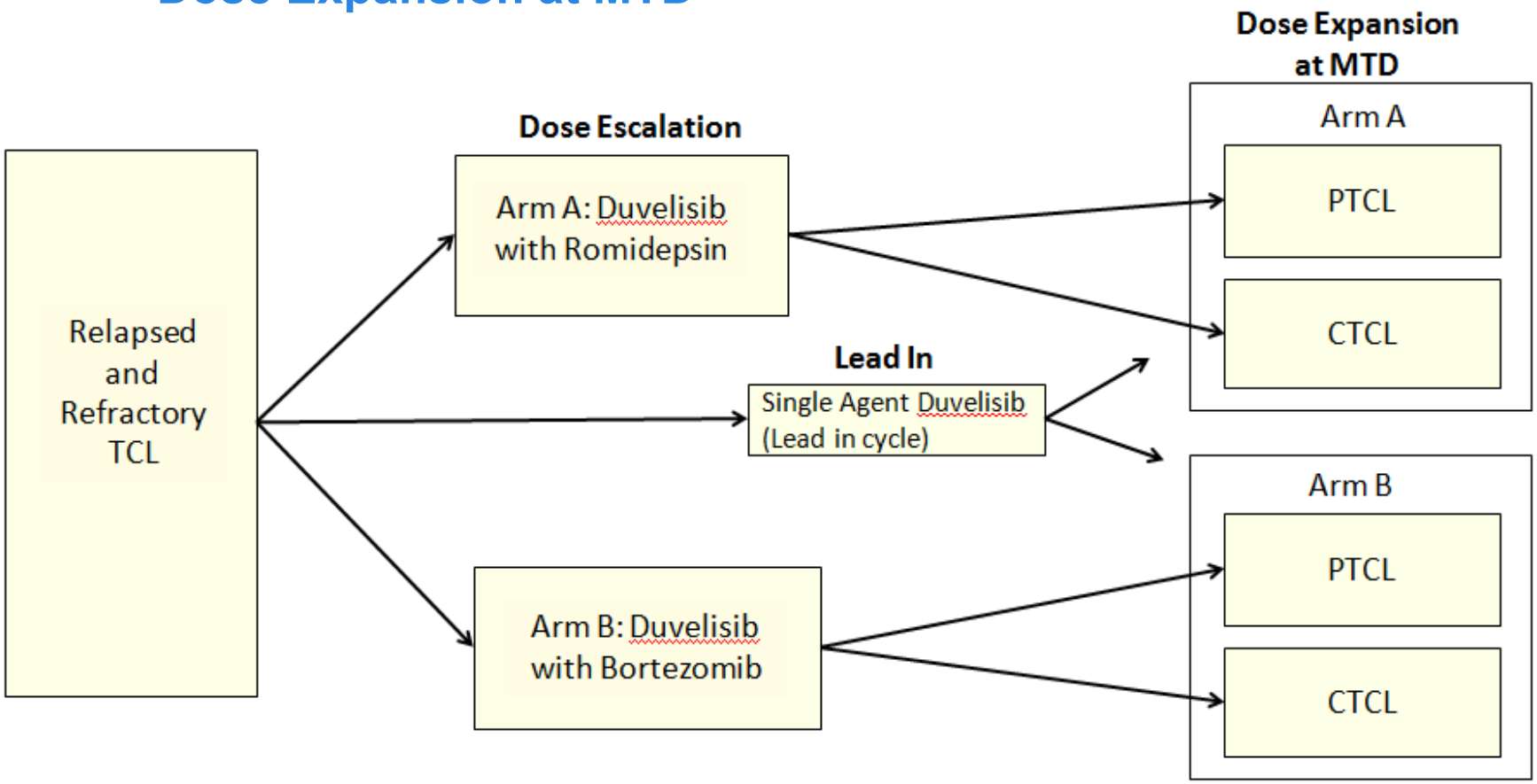
CT scans from a 71-year-old woman with relapsed AITL. Prior therapies- CHOP, pralatrexate, vorinostat, brentuximab vedotin

Horwitz et al. 2018. Blood 131(8).

Duvelisib combination studies

Parallel Phase I: 3+3 Design with Dose Expansion at MTD

MTD was determined to be Dose Level 3 (Romidepsin-10mg/m2 IV and Duvelisib-75mg PO, BID)

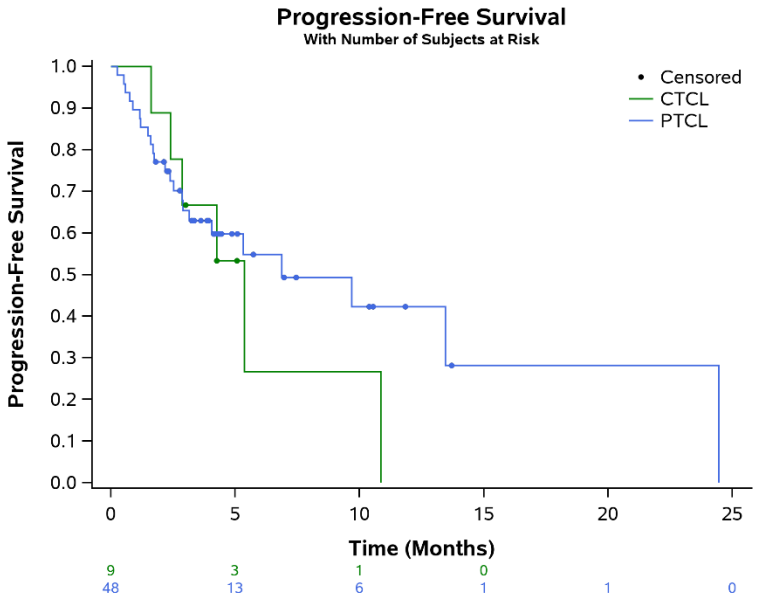


Participating Institutions
Memorial Sloan Kettering*
Dana Farber Cancer Institute
Stanford University
Washington University in St. Louis
Funding from Verastem -> Secura Bio
Support from the LLS

Horwitz ASH 2021

Duvelisib and romidepsin- a novel combination

	PTCL	CTCL
n	48	9
events	23	6
Censored	25	3
Median PFS (95% CI)	6.8 Mo (4.0 – NR)	5.3 Mo (2.8 – NR)
# of patients → Transplant	14 (29%)	0



Fewer immune mediated side effects of duvelisib when given with romidepsin

Event	initiated with single agent lead in cycle n=10	initiated with combination at MTD n=49
Transaminase	**4 (40%)**	**4 (8%)**
ALT	3 (30%)	4 (8%)
AST	1 (10%)	2 (4%)
Diarrhea	**3 (30%)**	**6 (12%)**
Neutrophil count decreased	**2 (20%)**	**19 (39%)**
Platelet count decreased	**1 (10%)**	**5 (10%)**
Infections	**0**	**6 (12%)**
Rash	**2 (20%)**	**4 (8%)**

Horwitz et al, Hematologic Oncology 2021

ASTX660- a novel XIAP inhibitor

(ASTX660) in Relapsed/Refractory PTCL and CTCL

ASTX660

Novel Mechanism of Action[1]

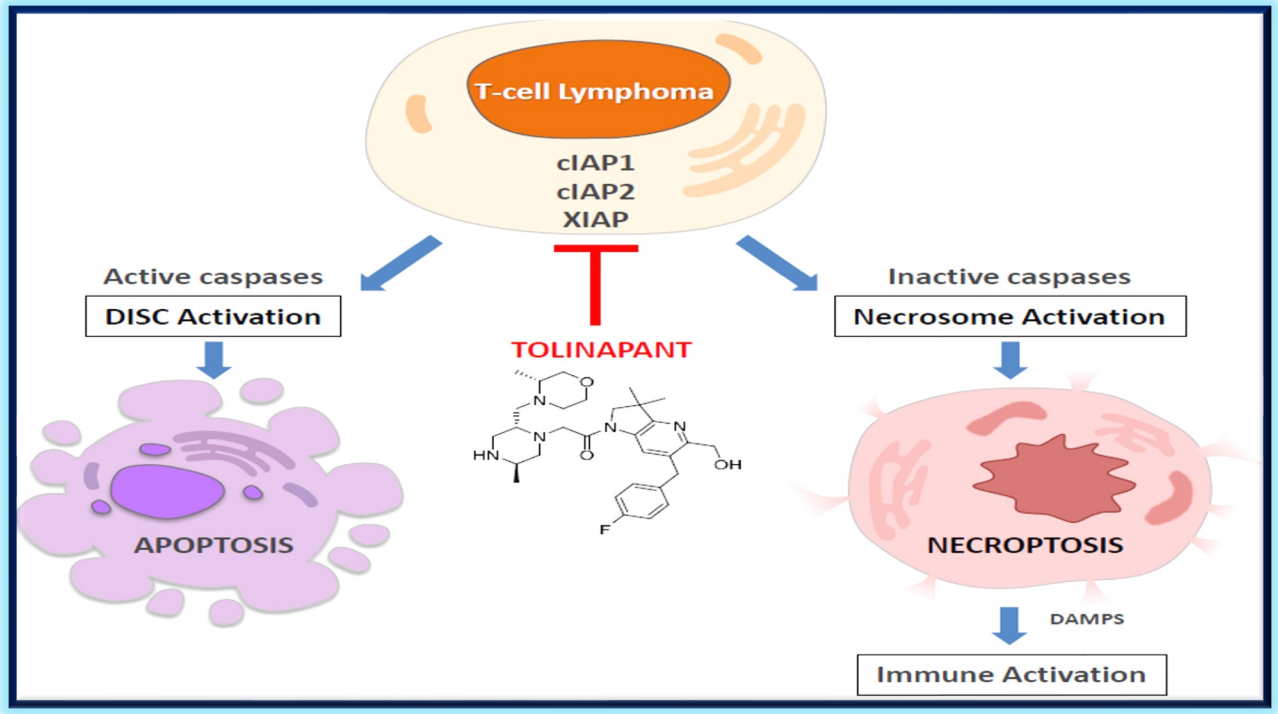
- Oral non-peptidomimetic antagonist of inhibitor of apoptosis proteins (IAPs), cIAP1, cIAP2 and XIAP
- Recent data demonstrates both apoptosis and immunomodulation

Phase 1: low efficacy in other tumour types, recommended phase 2 dosing (RP2D) achieved

>250 subjects dosed with tolinapant to date

Manageable safety profile

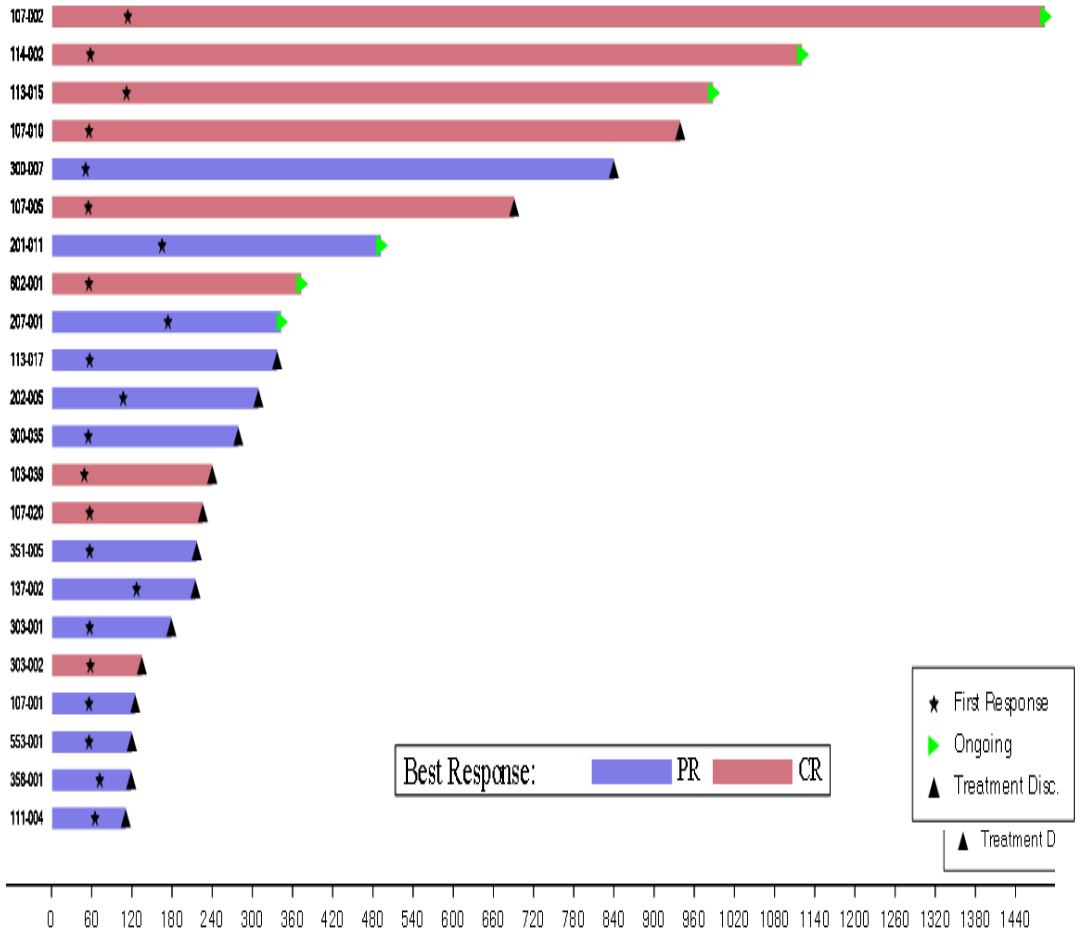
- Minimal myelosuppression



1: Ferrari N *et al*, *Blood Advances, 2021;* Johnson C *et al,* J Med Chem 2018; Ward G *et al*, Mol Cancer Ther 2018

ASTX660 in Relapsed/Refractory PTCL and CTCL

Phase 2: Open Label Non-Randomized Basket Trial , PTCL and CTCL cohorts



Michot et al, EHA 2022

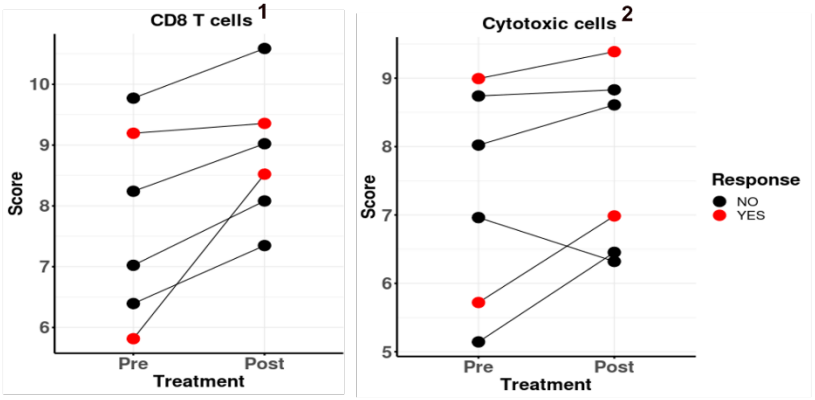
	PTCL(n=99)	CTCL (n=51)
ORR	22% (22 pt)	28% (14 pt)
PFS median	1.8 mo	5.5 mo
DOR median	6.5 mo	8.8 mo

Best overall response PTCL	N = 96
CR	9 (9.4%)
PR	13 (13.5%)
SD	16 (16.7%)
PD	58 (60.4%)

ASTX660 in Relapsed/Refractory PTCL and CTCL

Biopsies

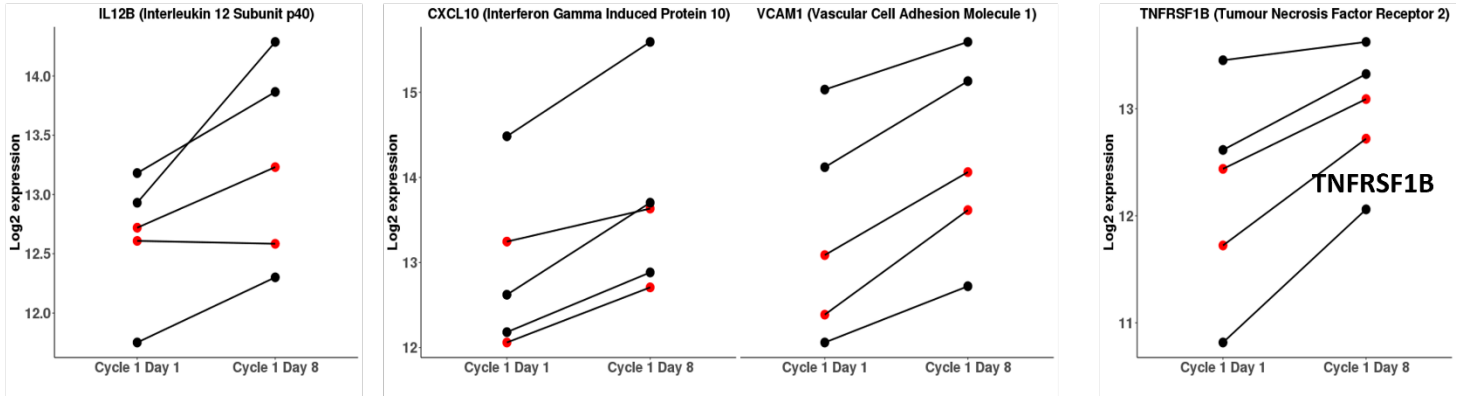
CD8 and cytotoxic cell recruitment



- Consistent with preclinical models, post-treatment PTCL samples show evidence of increased immune cell recruitment and soluble immune mediators

Plasma

T cell differentiation | Mediators of leukocyte recruitment | TNF pathway modulation

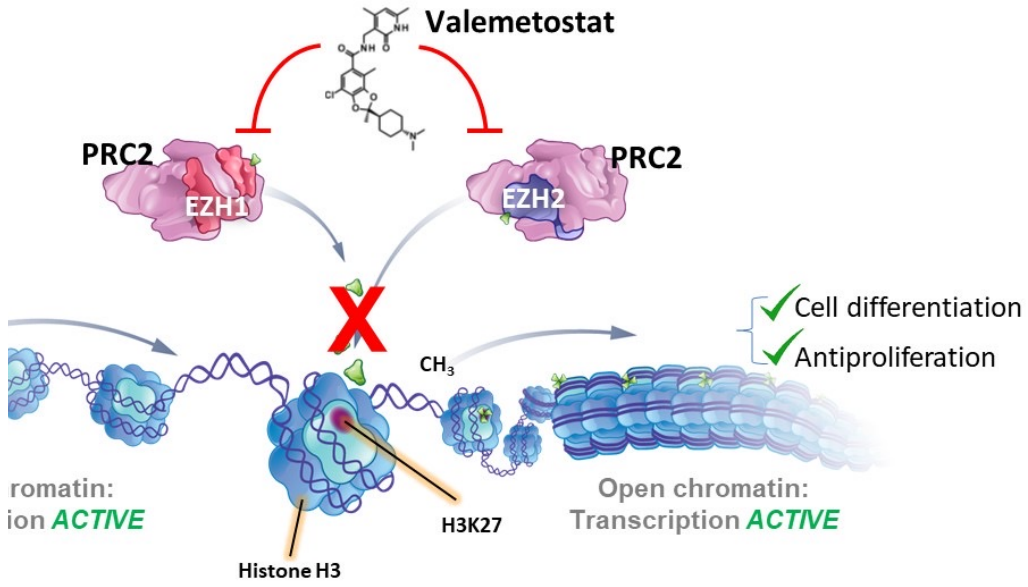


Adverse Event	Phase 2 Total (N=150) N (%)
Total Number of TEAEs	142
Subjects with >1 TEAE	68 (45.3)
Lipase increased	23 (15.3)
Rash (combined terms)	16 (10.7)
Amylase increased	10 (6.7)
Anaemia	7 (4.7)
Thrombocytopenia	7 (4.7)
Neutropenia	6 (4.0)
Febrile neutropenia	3 (2.0)
Pancreatitis	2 (1.3)
Tumor Flare	2 (1.3)
Acute kidney injury	2 (1.3)
Ejection fraction decrease	2 (1.3)
Hypercalcemia	2 (1.3)
Pruritis	2 (1.3)

Ferrari N *et al.*, *Blood Advances, 2021*

Valemetostat Tosylate: inibiitor of EZH1/EZH2

- Prevents trimethylation of H3K27
- Increases expression of genes silenced by H3K27me3, including those associated with the regulation of cell proliferation and differentiation[1-4]
- EZH2 is overexpressed in PTCLs and significantly overexpressed in ATL cells[1,2]



Phase I/II study of valemetostat in PTCL

Patients with R/R NHL

- Age ≥20 (Japan) or ≥18 (US) years
- ECOG PS 0 or 1
- Patients with ATL: positive test result for HTLV-1

Part 1: Dose Escalation
Japan

R/R NHL (all-comers)[b]

- 300 mg PO, QD
- 250 mg PO, QD
- 200 mg PO, QD
- 150 mg PO, QD

RDE

Part 2: Dose Expansion
Japan and US

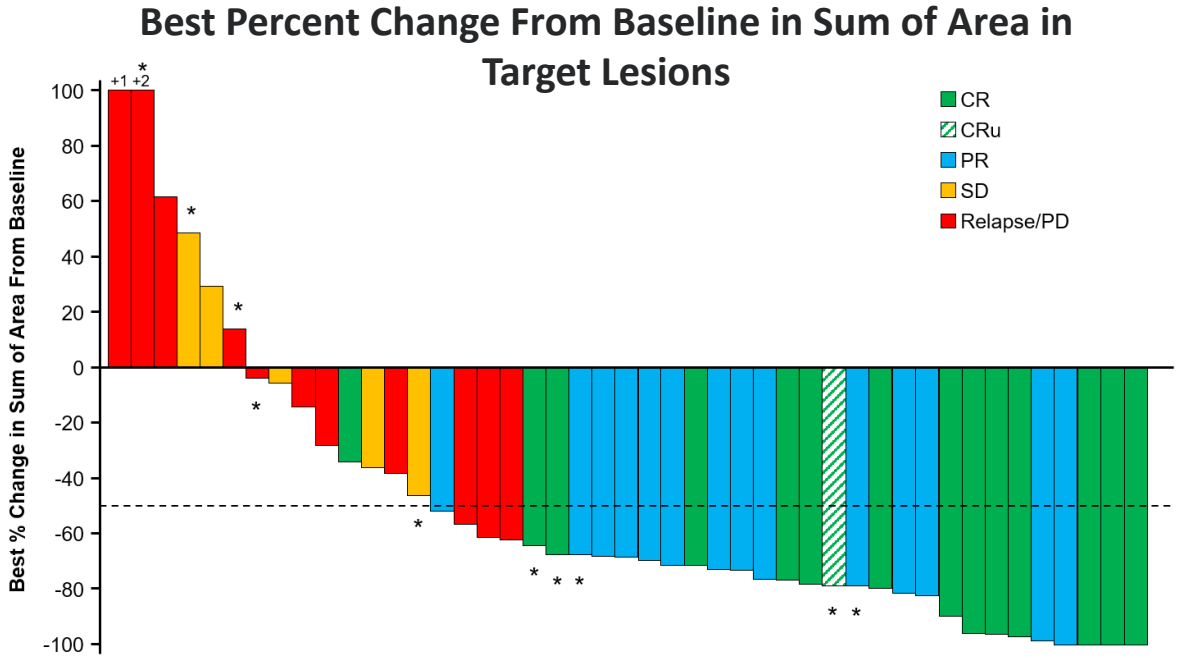
R/R ATL
Valemetostat 200 mg PO, QD

R/R PTCL
Valemetostat 200 mg PO, QD

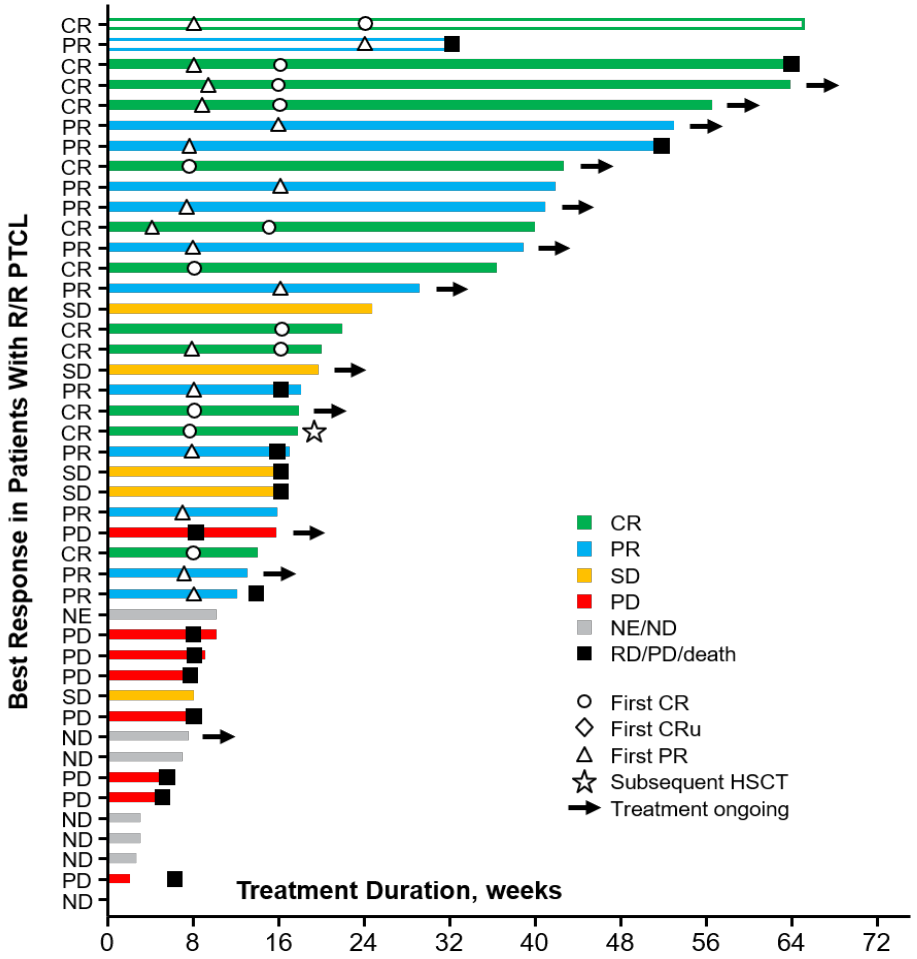
1. Honma D, et al. *Cancer Sci*. 2017;108(10):2069-2078. **2.** Yamagishi M, et al. *Cell Rep*. 2019;29(2017. Abstract 4670. **4.** Nakagawa M, et al. ASH 2017. Abstract 590. **5.** Juan AH, et al. *Cell Rep*. 2016;17(5):1369-1382. **6.** Peirs S. *Immunol Rev.* 2015;263:50-67.

Phase I/II study of Valemetostat: results

	All PTCL (n=44)	AITL (n=17)	PTCL-NOS (n=20)	ALCL (n=2)	ATLL (N=14)
ORR (%)	54.5%	65%	50%	50%	57%
CR (%)	27.3%	47%	20%	50%	28%



Foss et al, Blood 2021



- Ongoing international single arm phase II study (VALENTINE (NCT 04703192)

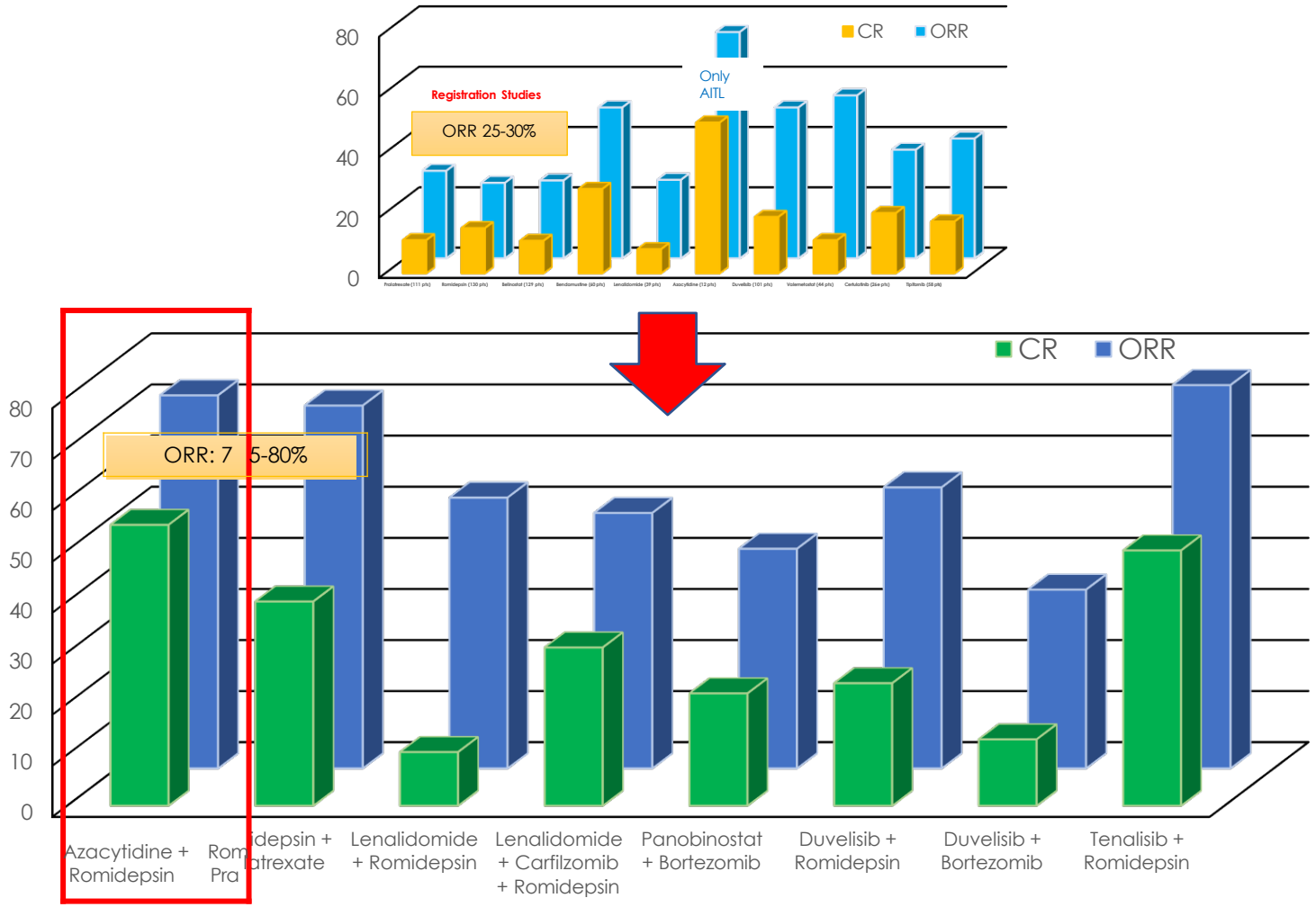
Phase I/II study of valemetostat: adverse events

- Grade ≥3 platelet count decreased and thrombocytopenia[a] occurred in 13 (16.9%) and 2 (2.6%) patients with all histologies, respectively

Most Common TEAEs (occurring in ≥20% of patients with TCL)[b]	All Histologies[c] (N=77)		PTCL (N=44)		ATL (N=14)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Platelet count decreased[d]	47 (61.0)	13 (16.9)	21 (47.7)	5 (11.4)	9 (64.3)	3 (21.4)
Dysgeusia	40 (51.9)	0	20 (45.5)	0	8 (57.1)	0
Anemia	31 (40.3)	9 (11.7)	15 (34.1)	6 (13.6)	5 (35.7)	1 (7.1)
Neutrophil count decreased	27 (35.1)	18 (23.4)	13 (29.5)	8 (18.2)	6 (42.9)	5 (35.7)
Alopecia	26 (33.8)	0	12 (27.3)	0	6 (42.9)	0
WBC count decreased	23 (29.9)	12 (15.6)	10 (22.7)	6 (13.6)	4 (28.6)	3 (21.4)
Diarrhea	22 (28.6)	1 (1.3)	13 (29.5)	0	3 (21.4)	0
Lymphocyte count decreased	22 (28.6)	17 (22.1)	7 (15.9)	6 (13.6)	2 (14.3)	2 (14.3)
ALT increased	16 (20.8)	1 (1.3)	7 (15.9)	0	3 (21.4)	1 (7.1)
Nausea	16 (20.8)	0	11 (25.0)	0	3 (21.4)	0

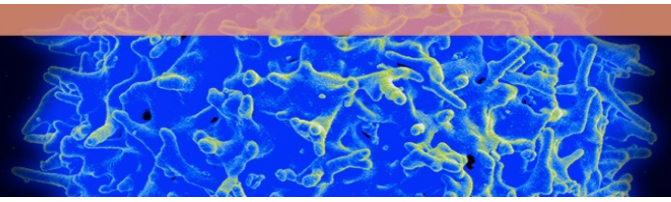
Foss et al, Blood 2021

Novel/Novel drug development in PTCL



Drug Combination	ORR (%)	CR (%)
Azacytidine + Romidepsin *O'Connor et al; Blood 2019* *Falchi & Ma et al; Blood 2021*	73	55
Pralatrexate + Romidepsin *Amengual et al; Blood 2017*	71	40
Lenalidomide + Romidepsin *Mehta-Shah et al; JCO 2015*	53	10.5
Lenalidomide + Carfilzomib + Romidepsin *Mehta-Shah et al; Blood 2016*	50	31
Panobinostat + Bortezomib *Tan et al; Lancet Hem 2015*	43	22
Duvelisib + Romidepsin *Horwitz et al; Blood 2018*	55	24
Duvelisb + Bortezomib *Horwitz et al; Blood 2018*	35	13
Tenalisib + Romidepsin Iyer et al; ASH 2021	75	50

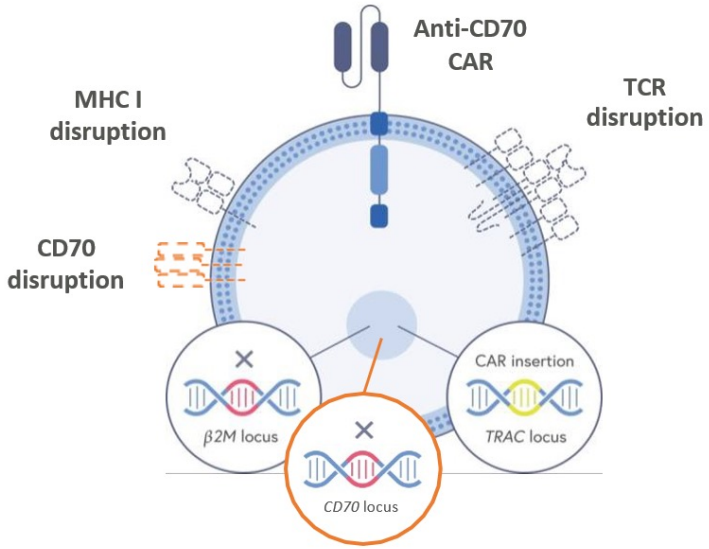
Immunotherapy in PTCL



- Allogeneic SCT is potentially curative in relapsed setting
- T-cell Checkpoint inhibitors
  - Subtype specific responses
  - NK, MF/SS
  - Risk of hyper-progression and lack of predictors precludes wider use
- CD47 Strategies
  - Combination Studies ongoing (Magrolimab + Mogamulizumab in CTCL)
- CAR
  - CART-Early studies CD5, 7, 30, 37, 4, CCR4, TCRB1, others
  - ? Need for allo backup
  - Other cell types/sources
  - Allo-T, NK, Myeloid
- Bi-specifics
  - CD30, PD-1

CD70 Allogeneic CAR T

- CTX130 is an investigational allogeneic, CRISPR/Cas9 gene-edited, anti-CD70 CAR-T cell therapy with TRAC, β2M, and CD70 disruptions
- CTX130 is manufactured starting with T cells collected from a healthy donor, which are then selected and edited before expansion and cryopreservation for off-the-shelf treatment of patients



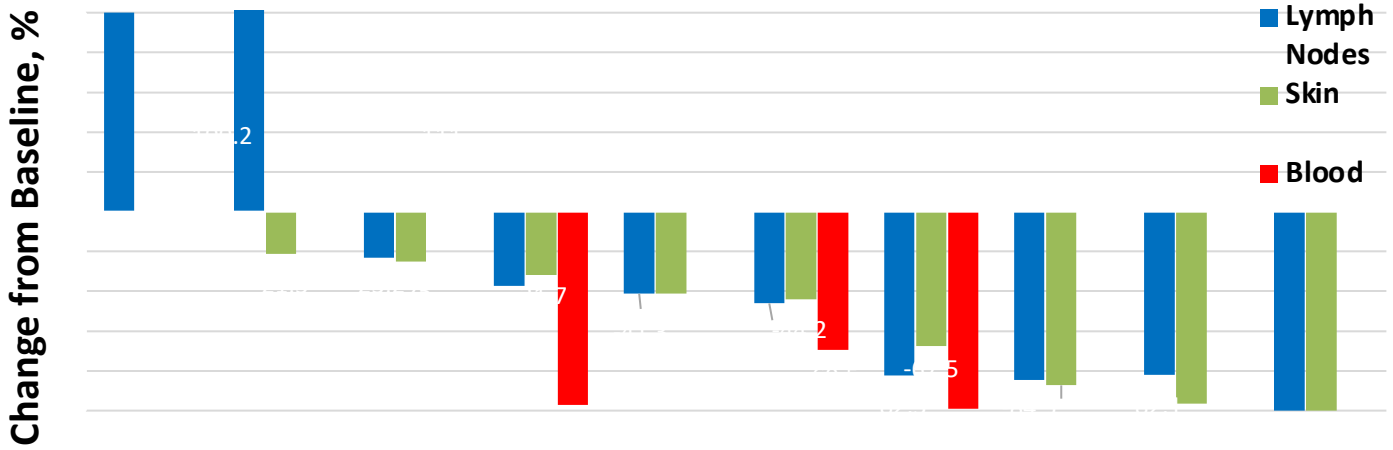
Cell dose (CAR+ T cells)	D L1 $3x10^7$ N=4	DL2 $1x10^8$ N=4	DL3 $3x10^8$ N=5	DL4 $9x10^8$ N=5	DL≥3 N=10
ORR	2 (50)	0	3 (60)	3 (60)	6 (60)
CRR	1 (25)	0	3 (60)*	1 (20)	4 (40)
CR + PR + SD	3 (75)	1 (25)	5 (100)	4 (80)	9 (90)

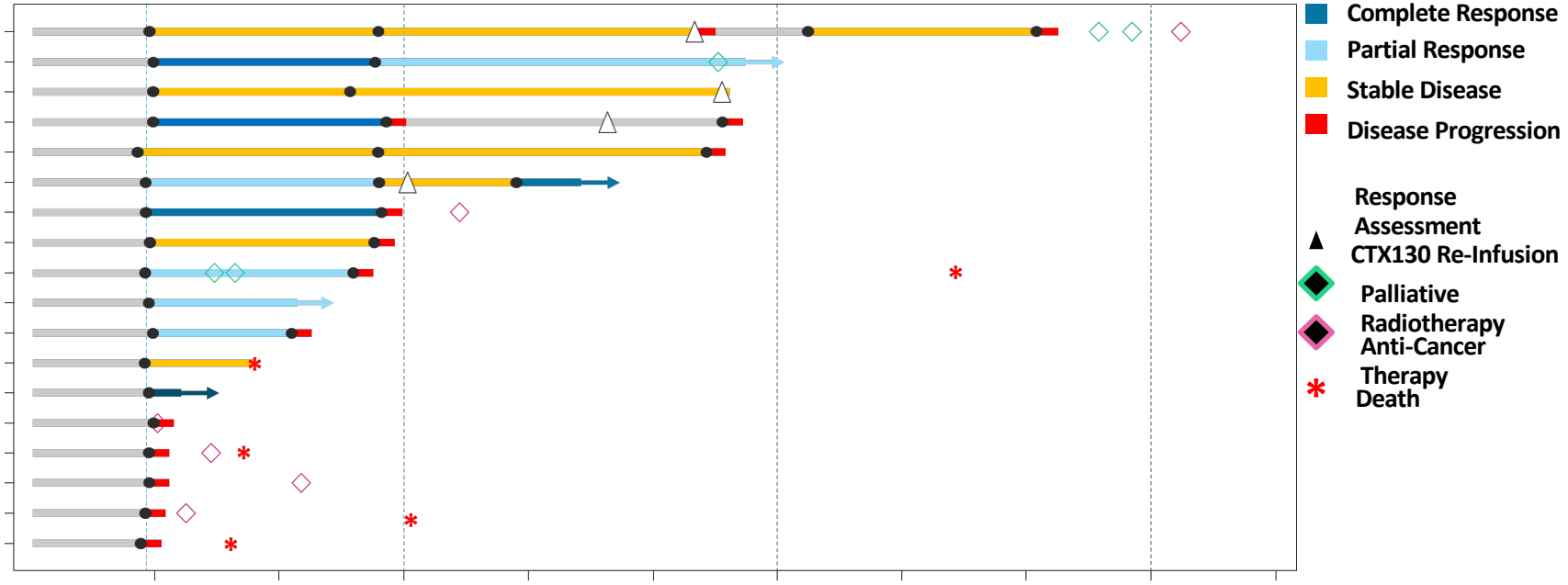
β2M, β2-microglobulin; CAR, chimeric antigen receptor; MHC, major histocompatibility complex; TCR, T-cell receptor; TRAC, T-cell receptor alpha constant.

Reference: Dequeant M-L, et al. CD70 knockout: A novel approach to augment CAR-T cell function. Poster presented at American Association for Cancer Research 2021. April 10-15 and May 17-21, 2021.

COBALT-LYM (NCT04502446) STUDY

Responses were observed across compartments (lymph nodes, skin, blood) in patients with CTCL





- Median CD70+ expression amongst patients with relapsed / refractory T cell lymphoma was 90%
- CTX130 has demonstrated an acceptable safety profile in heavily pretreated patients with relapsed / refractory T cell lymphomas
- We have observed clinically meaningful responses with CTX130, including a 40% CR rate at DL ≥3

Case Study | Single-Dose Complete Response With CTX130

Subject Overview

Patient profile

- 47-year-old male with stage IVA2 transformed mycosis fungoides (tMF)
- 5 prior lines of therapy
- Refractory after last treatment with brentuximab vedotin
- CD70+ expression was 100% at baseline

Efficacy

- CR at D28 after a single infusion of 9 x 10^8 CAR+ T cells
- Remains in CR at M3

Safety

- Gr 3 anemia (D3) & Gr 3 neutropenia (D4)
- All other AEs were Gr 1

Responses