Yale SCHOOL OF MEDICINE

T-cell lymphoma: Clinical approaches and novel agents

Francine M. Foss, M.D.

Professor of Medicine

Hematology and Bone Marrow Transplantation Yale University School of Medicine

New Haven, Connecticut

PTCL entities
(WHO 2017 Classification)

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

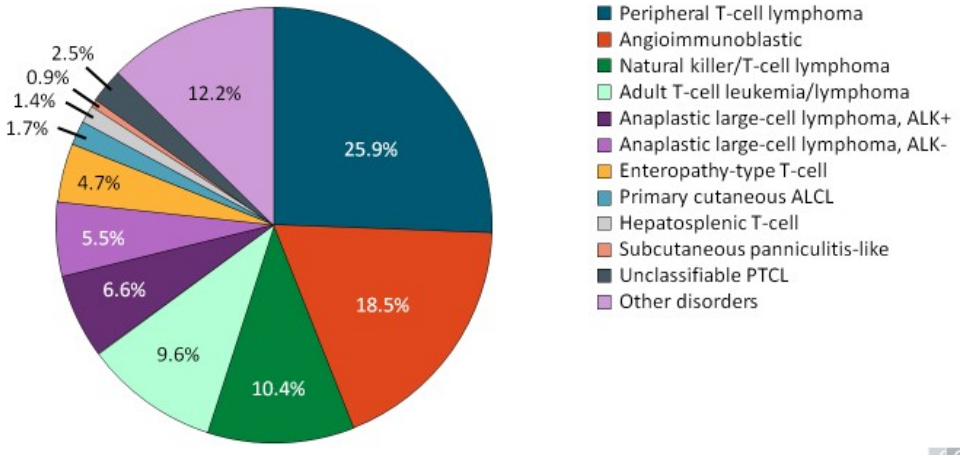
Extranodal

- 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

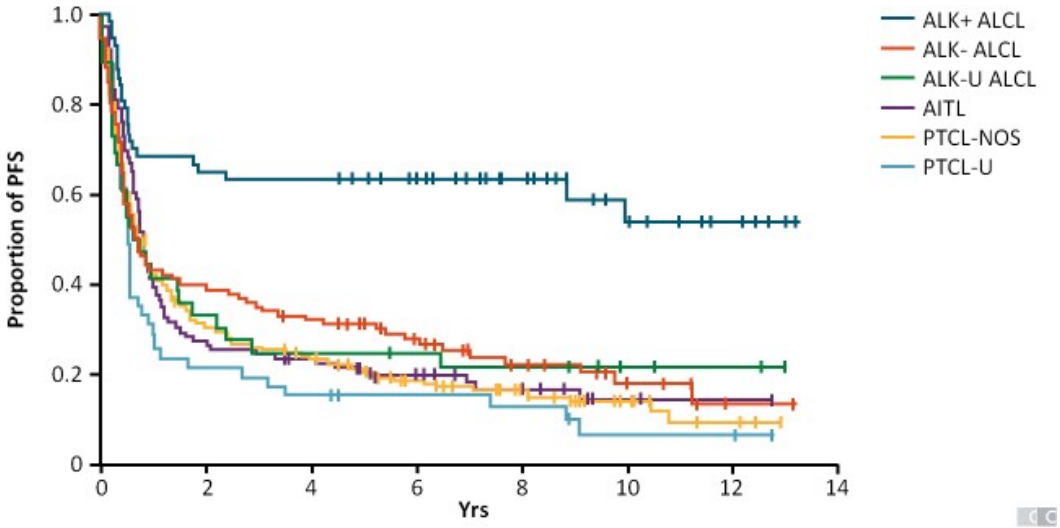
Courtesy of L. de Level Swerdlow. WHO Classification of Tumours, revised 4th edition, Vol. 2 (2017)

PTCL: Subtypes and PFS by subtype

Distribution of PTCL Subtypes, per International T-cell Project[1]



PFS by Subtype in Swedish Registry (N = 755)[2]

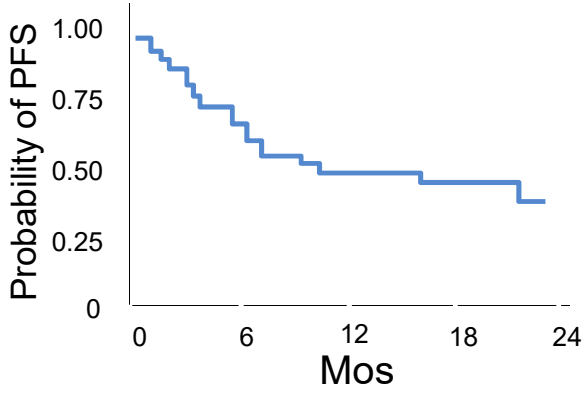


1. Vose. J Clin Oncol. 2008;26:4124. 2. Ellin. Blood. 2014;124:1570.

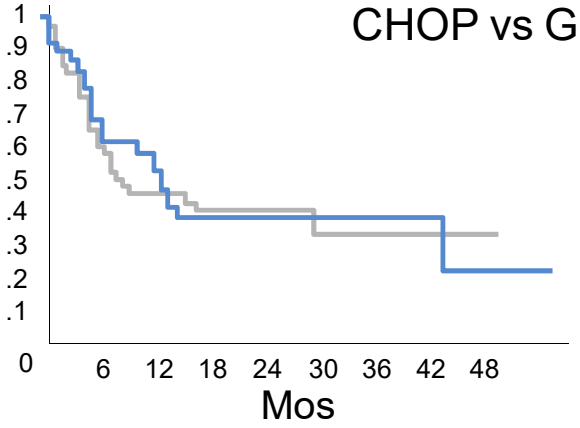
Selected attempts to improve upon CHOP for PTCL

N = 33
CR 52%
Est 2-yr PFS/OS: 39%
(95% CI 21-57)

CEOP –Pral[3]

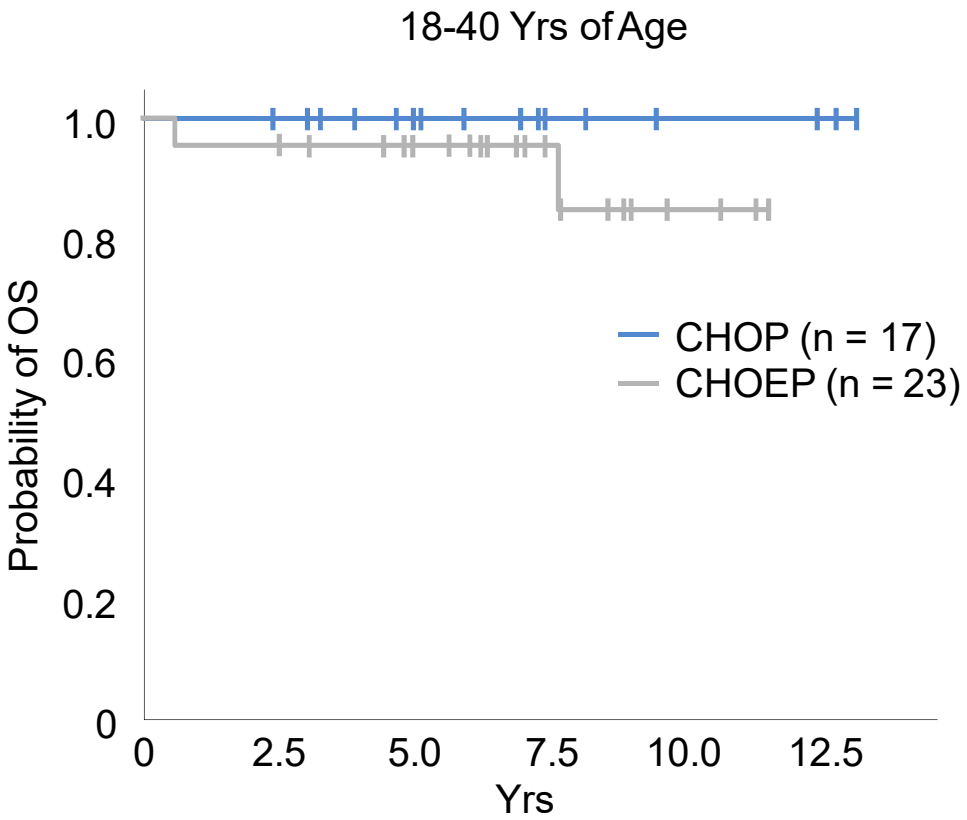


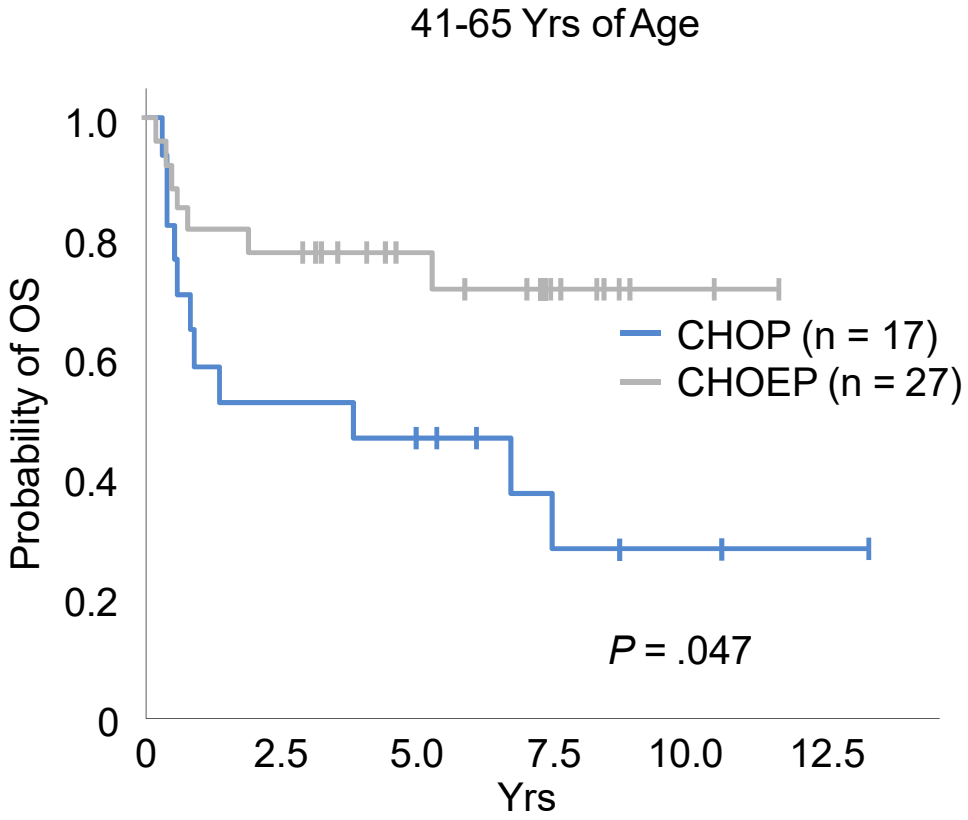
CHOP vs GEM-P[4]



1. Simon. Br J Haem. 2010. 2. d'Amore. ASH 2018. 3. Advani. Br J Haem. 2016;172:636. Gleeson. Lancet Haem. 2018;5:E190.

Nordic Lymphoma Group: OS with addition of etoposide to CHOP in ALK+ ALCL





Cederleuf. Br J Haematol. 2017;178:739.

ECHELON-2: Brentuximab Vedotin + CHP vs CHOP in previously untreated CD30+ PTCL

- Multicenter, randomized, double-blind, double dummy, active-controlled phase III trial

Stratification for IPI score (0-1 vs 2-3 vs 4-5), histologic subtype (ALK+ sALCL vs other subtypes)

Adult patients with previously untreated CD30+ (≥ 10% expression) PTCL*
(N = 452)

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

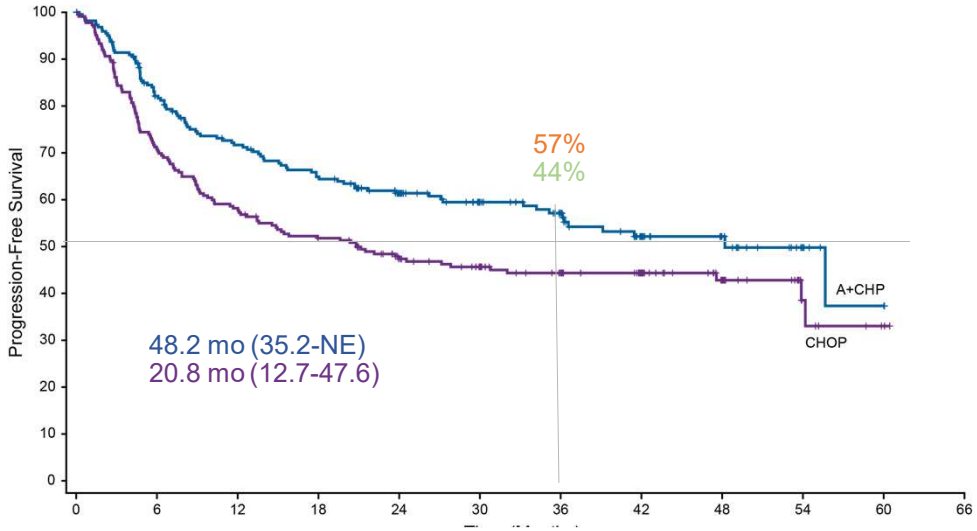
CHOP‡
Q3W for 6-8 cycles +
Placebo for Brentuximab Vedotin
(n = 226)

End-of-treatment PET

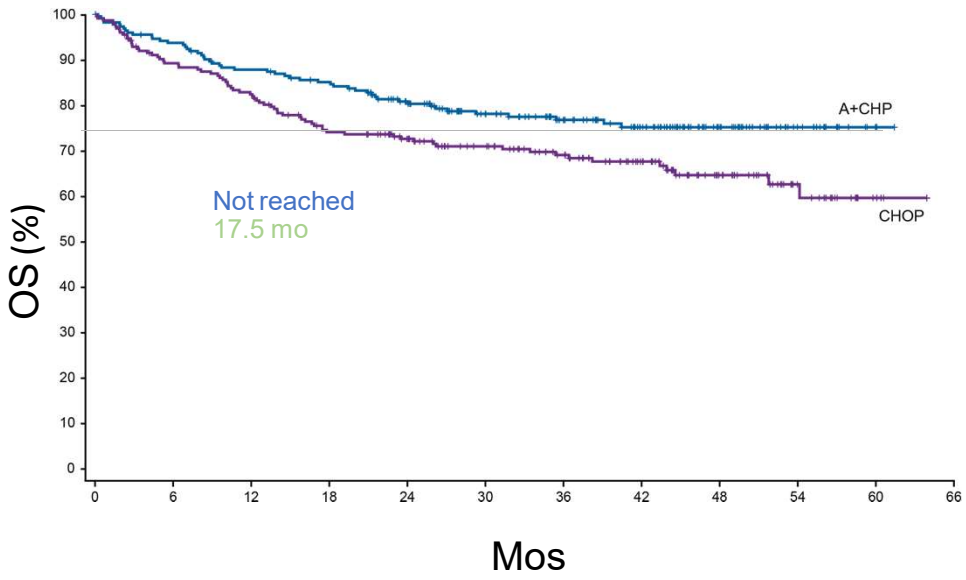
- Primary endpoint: PFS per BICR (SCT or RT consolidation not considered events)
- Secondary endpoints: OS, PFS per BICR in sALCL patients, CR, ORR, safety

Horwitz. Lancet. 2019;393:229.

ECHELON-2: PFS and OS with BV + CHOP vs CHOP alone in ALCL



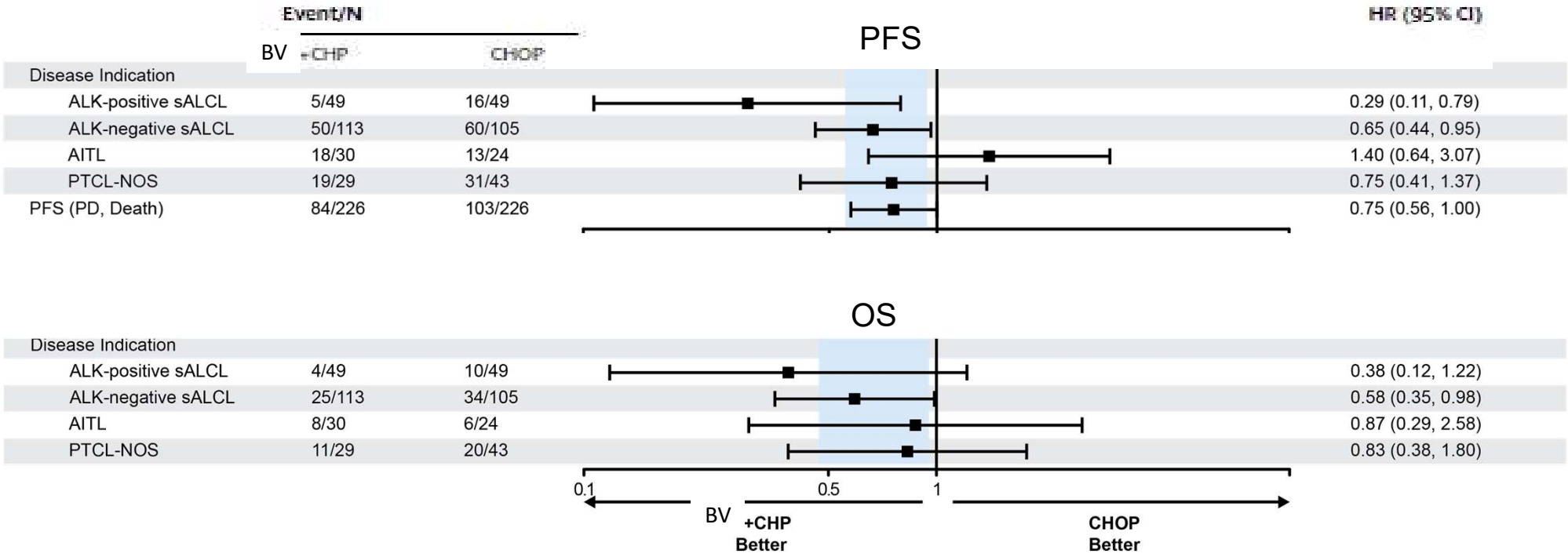
Treatment	Events, n (%)	HR (95% CI)	*P* Value
BV+CHP	95 (42)	0.71 (0.54-0.93)	.011
CHOP	124 (55)		



Treatment	Deaths, n (%)	HR (95% CI)	*P* Value
BV+CHP	51 (23)	0.66 (0.46-0.95)	.0244
CHOP	73 (32)		

Horwitz. Lancet. 2019;393:229.

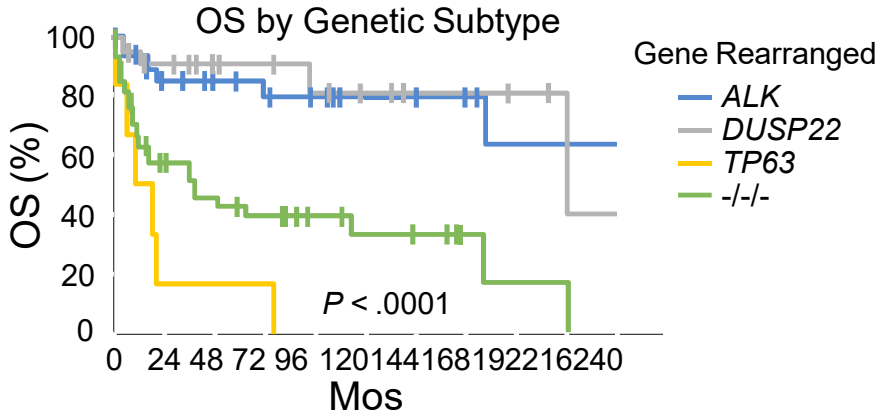
ECHELON-2: PFS and OS by PTCL subtypes

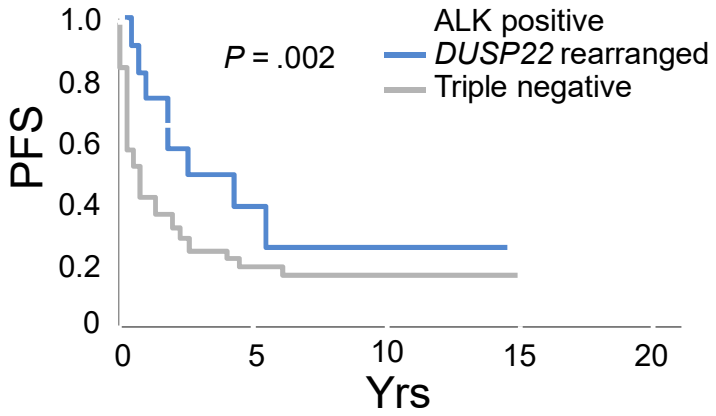


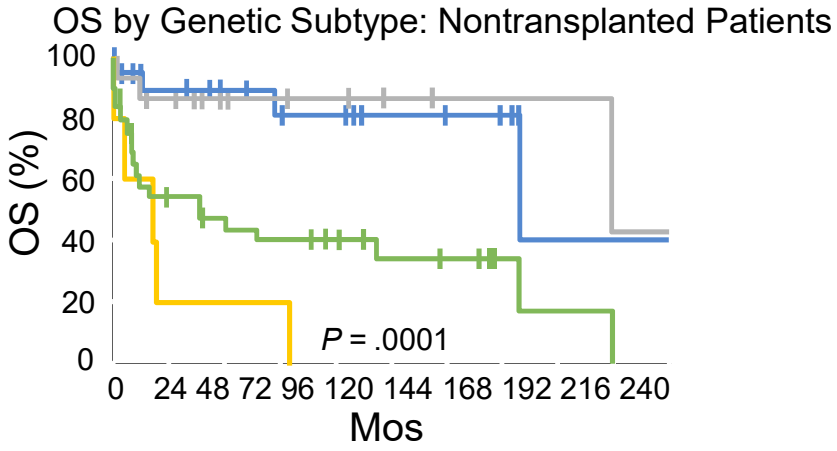
- Frontline treatment with BV+CHP superior to CHOP for patients with CD30-positive PTCL
- PFS and OS benefits greatest in patients with sALCL

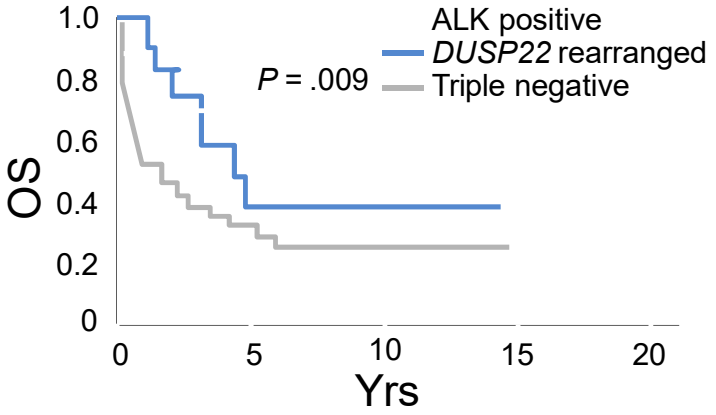
Horwitz. Lancet. 2019;393:229.

ALK-neg ALCL-recurrent chromosomal rearrangements with DUSP22









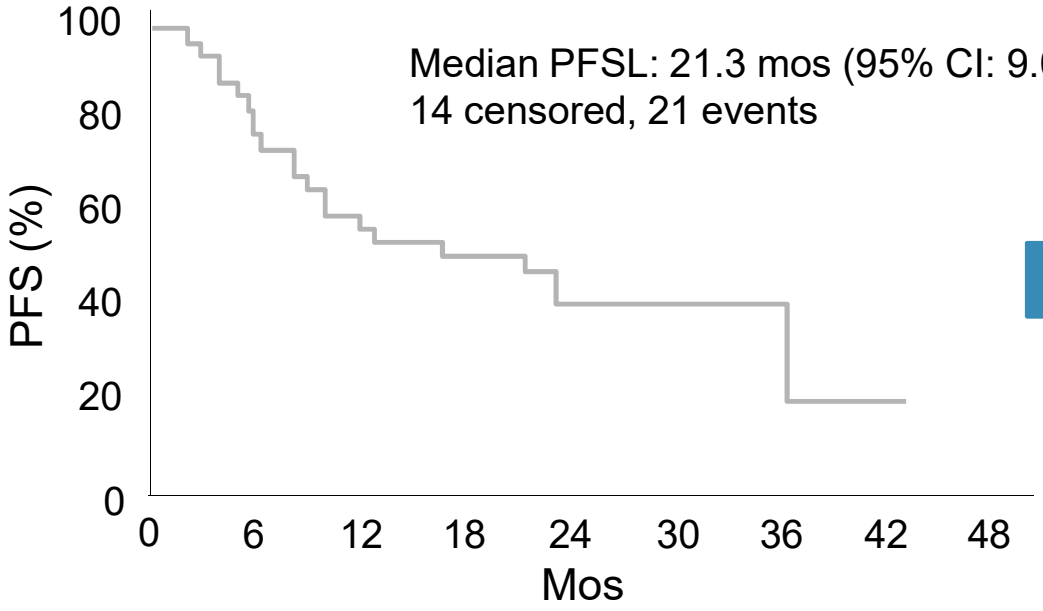
Castellar. Blood. 2014;124:1473. Hapgood. Br J Haematol. 2019;186:e28.

ECHELON-2: What conclusions can be drawn from the data?

- OS benefit with BV + CHP
  - Most of the patients were ALCL
    - Consolidation? ECHELON-2 doesn't really address this (Savage et al)
      - ALK+ BV-CHP (ASCT? Probably not)
      - ALK- BV-CHP (ASCT? Maybe with DUSP-22 status can avoid transplant
        - DUSP-22
        - Early Stage
  - Other subtypes of PTCL (AITL, PTCLnos, etc)
    - Study not powered to evaluate response in subtypes
    - But this may be an option for CD30+ patients
    - No data yet on CHOPE with BV, better than CHOPE alone, is etoposide necessary in the BV era?
    - Additional data needed to determine true benefit of BV-CHP (ongoing trials)

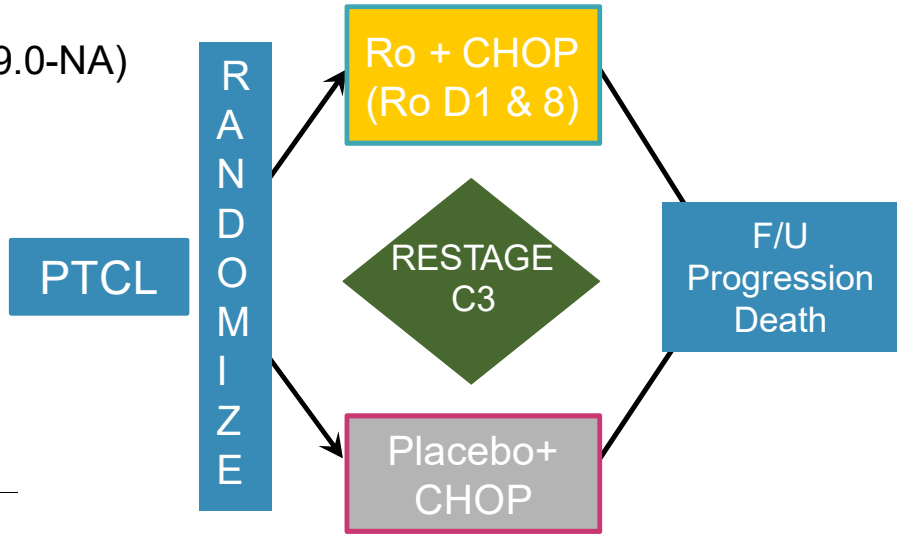
Front line therapy with CHOP ± Romidepsin

Phase I/II



Median PFSL: 21.3 mos (95% CI: 9.0-NA); median follow-up
PFS at 30 mos: 41.0% (95% CI: 24.7-57.3)

Phase III



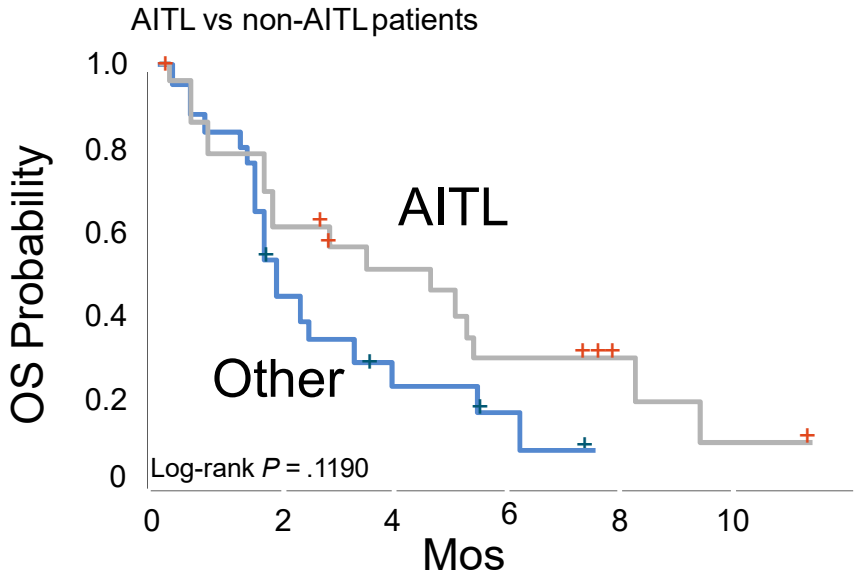
400+ patients accrued

Primary endpoint: PFS

Depuis. Lancet Haematol. 2015. NCT01796002.

Lenalidomide as a novel agent: Data in relapsed or refractory PTCL (EXPECT Trial)

Response, % (n)	ITT (N = 54)	AITL (n = 26)
Tumor control	52 (28)	58 (15)
ORR	22 (12)	31 (8)
▪ CR/CRu	11 (6)	15 (4)
▪ PR	11 (6)	15 (4)
Stable disease	30 (16)	27 (7)
POD	33 (18)	23 (6)
D/c without response assessment	15 (8)	19 (5)



Morschhauser. Eur J Cancer. 2013;49:2869

Phase II REVAIL study: Lenalidomide + CHOP21 in elderly patients with AITL

Elderly patients with AITL (N = 78)

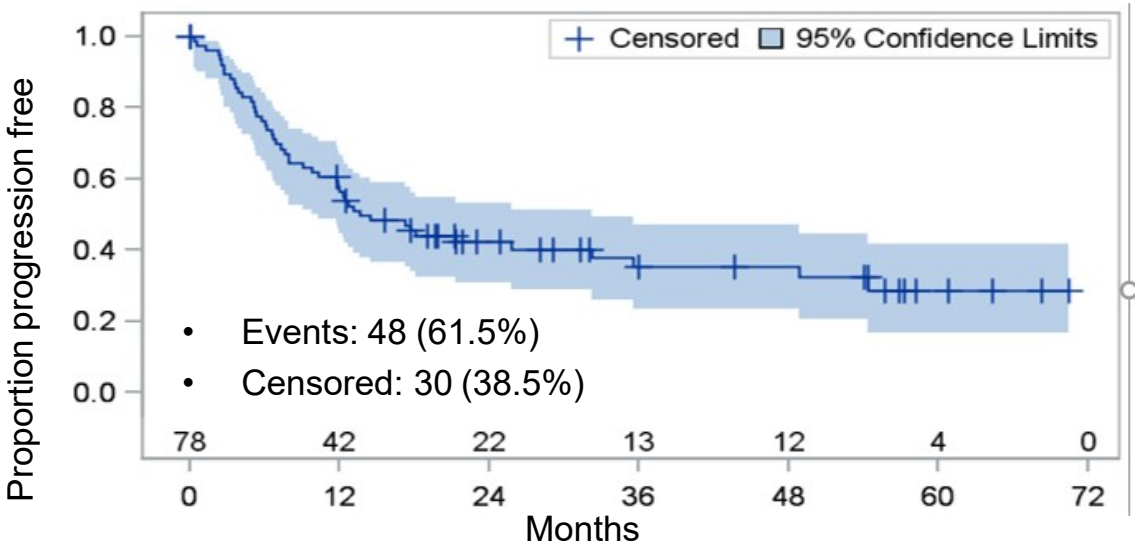
Induction Phase (12 weeks)

Lenalidomide 25 mg D1-14 + CHOP21 + MTX IT Q3W

Consolidation Phase (13 weeks)

Lenalidomide + CHOP21

Response assessment



- Median PFS: 13.7 mo (95% CI: 9.8-32.3)
- 2-yr PFS: 42% (95% CI: 30.9-53.2)

Lemonnier. ASH 2018. Abstract 999.

Consolidation in front line treatment: Autologous stem cell transplantation

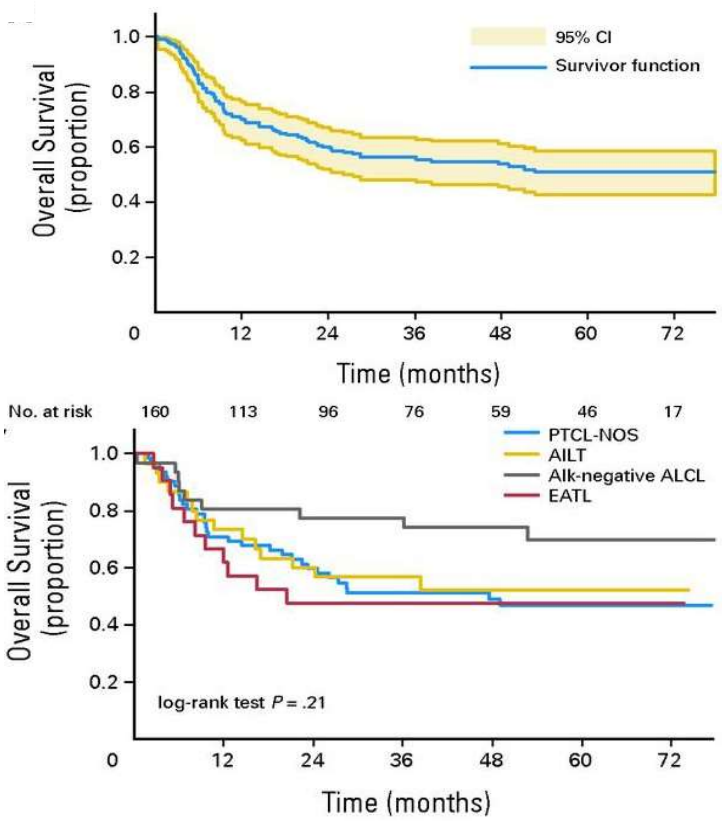
CHO(E)P-14 x 3-6 cycles
(n = 160)

ORR: 82%
CR: 51%

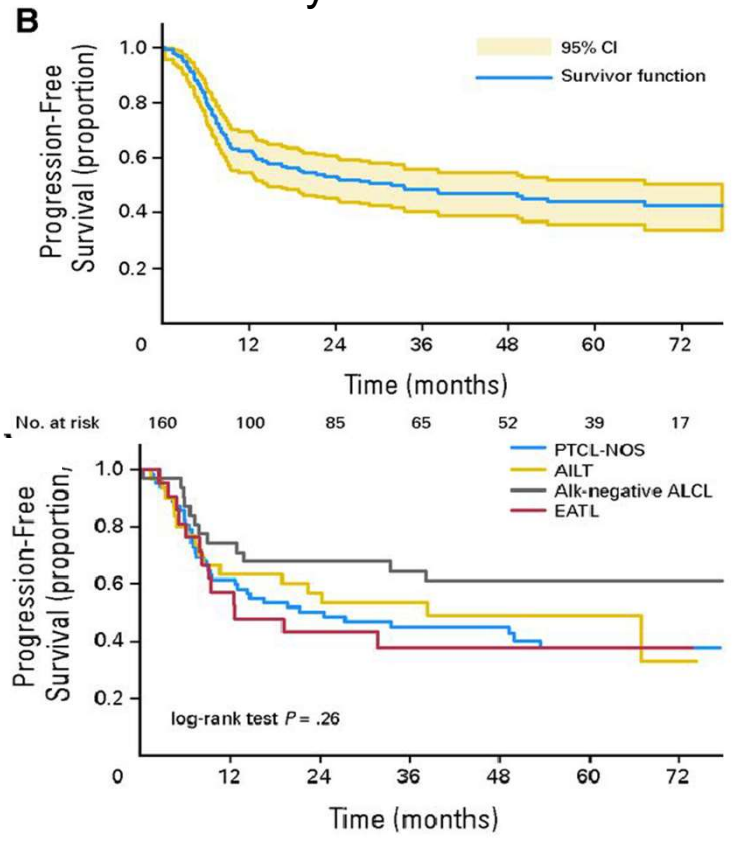
PR or CR

BEAM or BEAC + Autologous SCT
(n = 115 [72%])

5-year OS 51%



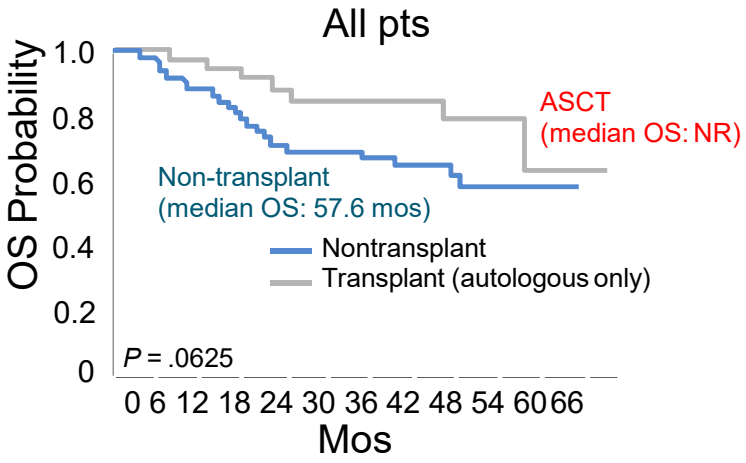
5-year PFS 44%

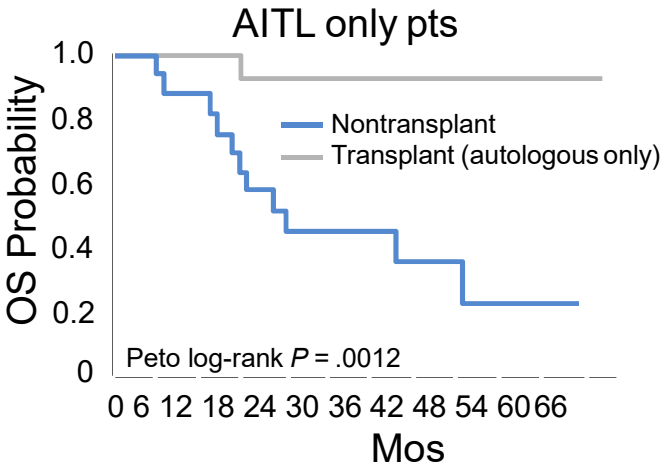


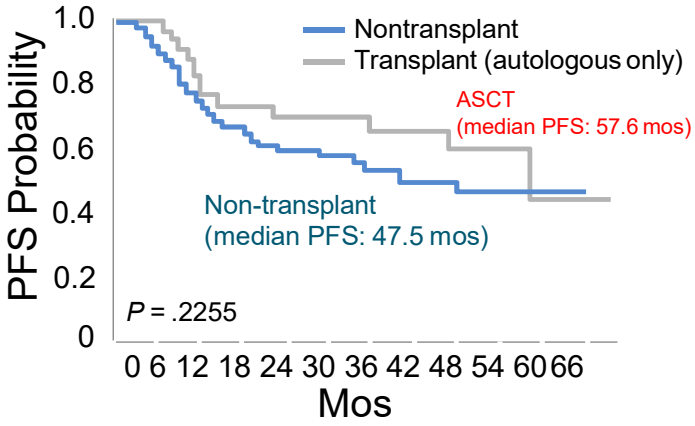
D'Amore. J Clin Oncol. 2012;30:3093.

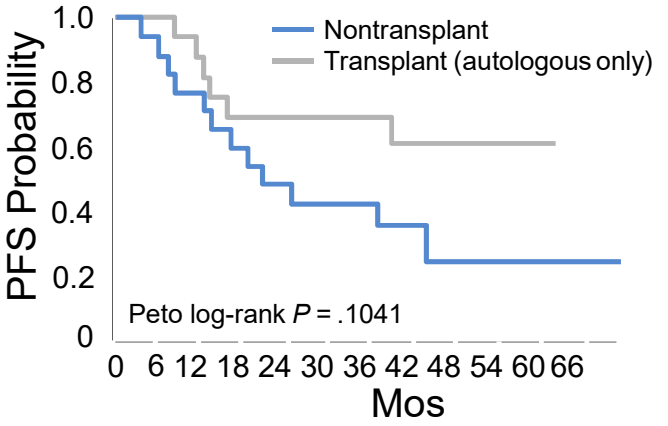
Transplant in first remission: Real world experience from the COMPLETE Registry

- Patients in CR1
- 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.

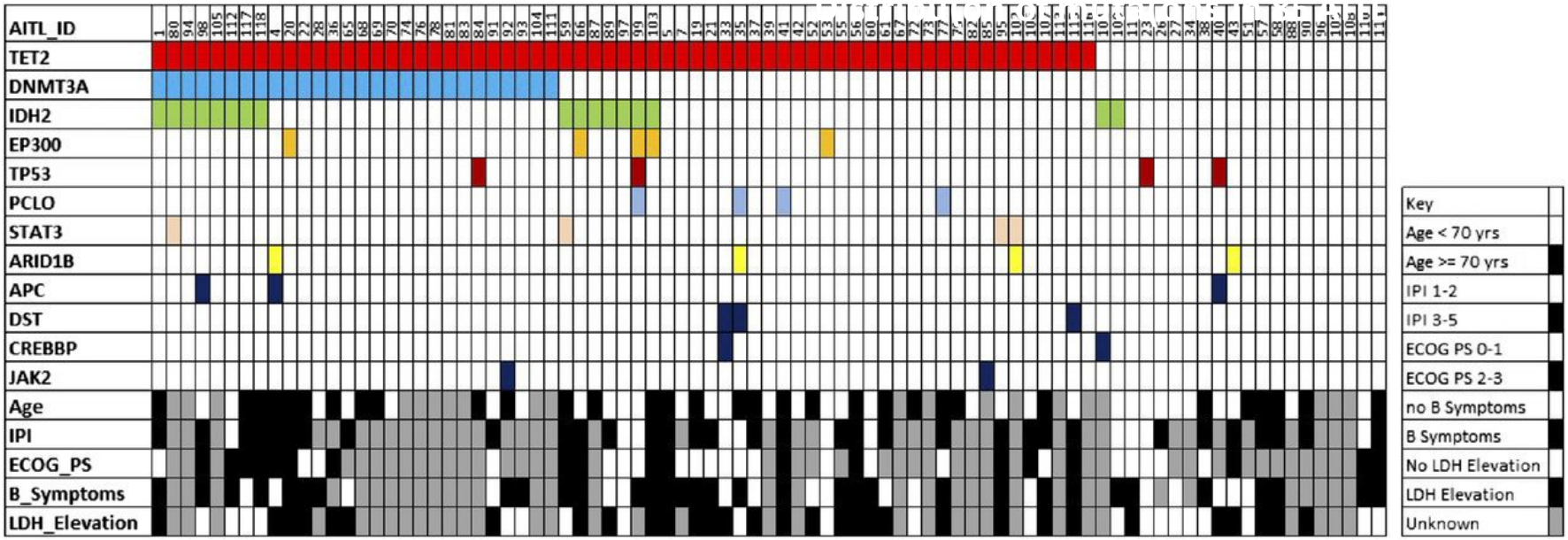
FDA-approved agents* for relapsed/refractory T-cell lymphoma

Study	Agent	N	ORR, %	CR, n (%)	Median PFS, mo	Median OS, mo	Median DOR, mo
PROPEL[1]	Pralatrexate	109	29 (AITL: 8)	12 (11)	3.5	14.5	10.1
Phase II trial[2,3]	Romidepsin	130	25 (ITL: 30)	19 (15)	20 (w/response)	30 (w/response)	28
BELIEF[4]	Belinostat	120	25.8 (ITL: 45)	10.8	1.6	7.9	13.6
Phase II trial[5]	Brentuximab (ALCL only)	58	86	66	20	NR	25.6
Phase II trial[6]	Chidamide*	256	39	10.5	129 days	--	148 days

1. O'Connor. J Clin Oncol. 2011;29:1182. 2. Coiffier. J Clin Oncol. 2012;30:631. 3. Coffier. J Hematol Oncol. 2014;7:11. 4. O'Connor. J Clin Oncol. 2015.
5. Pro. Blood. 2017;130:2709. 6. Shi. J Hematol Oncol. 2017;10:69.

Relevance of epigenetic therapy in PTCL-addressing mutational status

- Recurrent epigenetic mutations occur in angioimmunoblastic T-cell lymphoma (AITL) and PTCL not otherwise specified (PTCL-NOS) with features of T-follicular helper cells (TFH-like, WHO 2016))[1,2]
  - *TET2* mutations (80%), *DNMT3A* mutations (20%), *IDH2* mutations (25% to 30%)

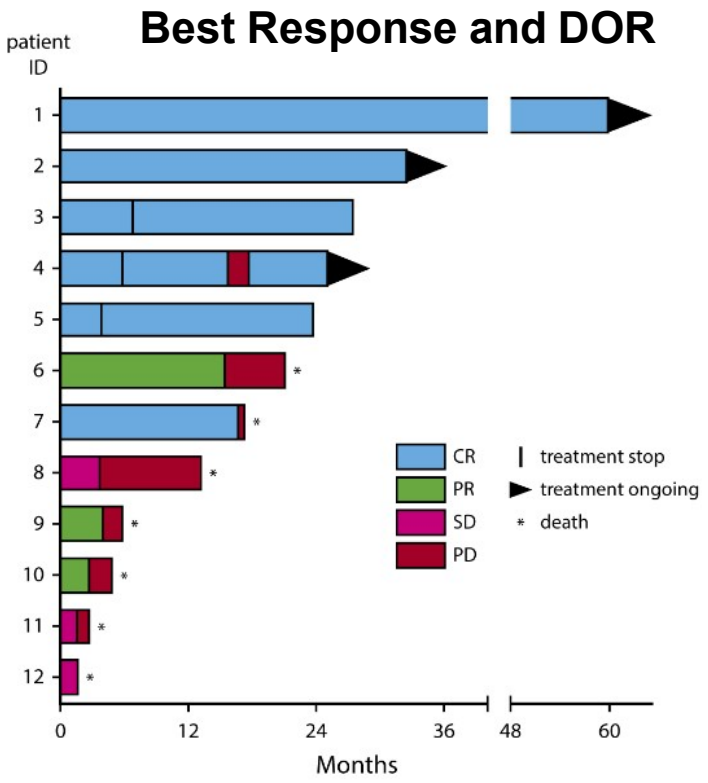


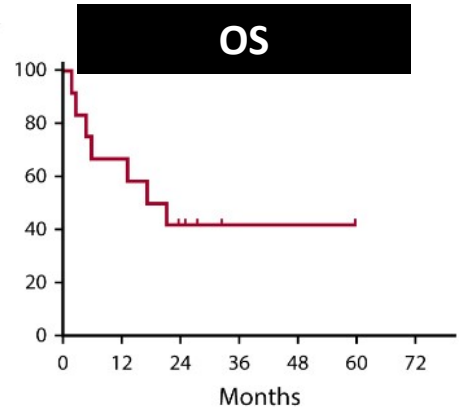
1. Odejide. Blood. 2014;123:1293. 2. Swerdlow. Blood. 2016;127:2375.

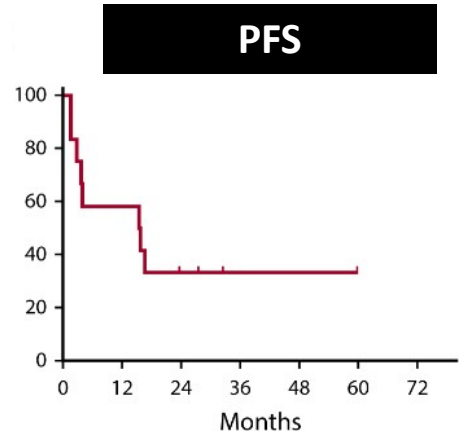
5-Azacitidine in AITL

- N = 12 patients with stage III/IV AITL
  - Median age: 70.5 yrs; IPI 3-5 75%, median of 2 prior lines of therapy (range: 0-6)
- Treatment: 5-azacytidine (median of 5.5 cycles), plus rituximab in 6/12 patients
- ORR 75%: CR 6/12 ; PR 3/12; SD 3/12
- Progressive disease: n = 7
  - After 2, 2, 3, 4, 4, et 20 cycles
- 3 pts stopped treatment after 5,7, and 6 cycles.
  - 2 remained in CR > 18 mo after discontinuation of 5-azacytidine.
  - 1 pt relapsed, but achieved a CR upon treatment reinitiation
- Median PFS: 15 months
- Median OS: 21 months

Lemonnier. Blood. 2018;132:2305.







Oral 5-Azacitidine and Romidepsin in PTCL: Phase I Study

- International, open-label, single-arm phase I study with 3+3 design

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)

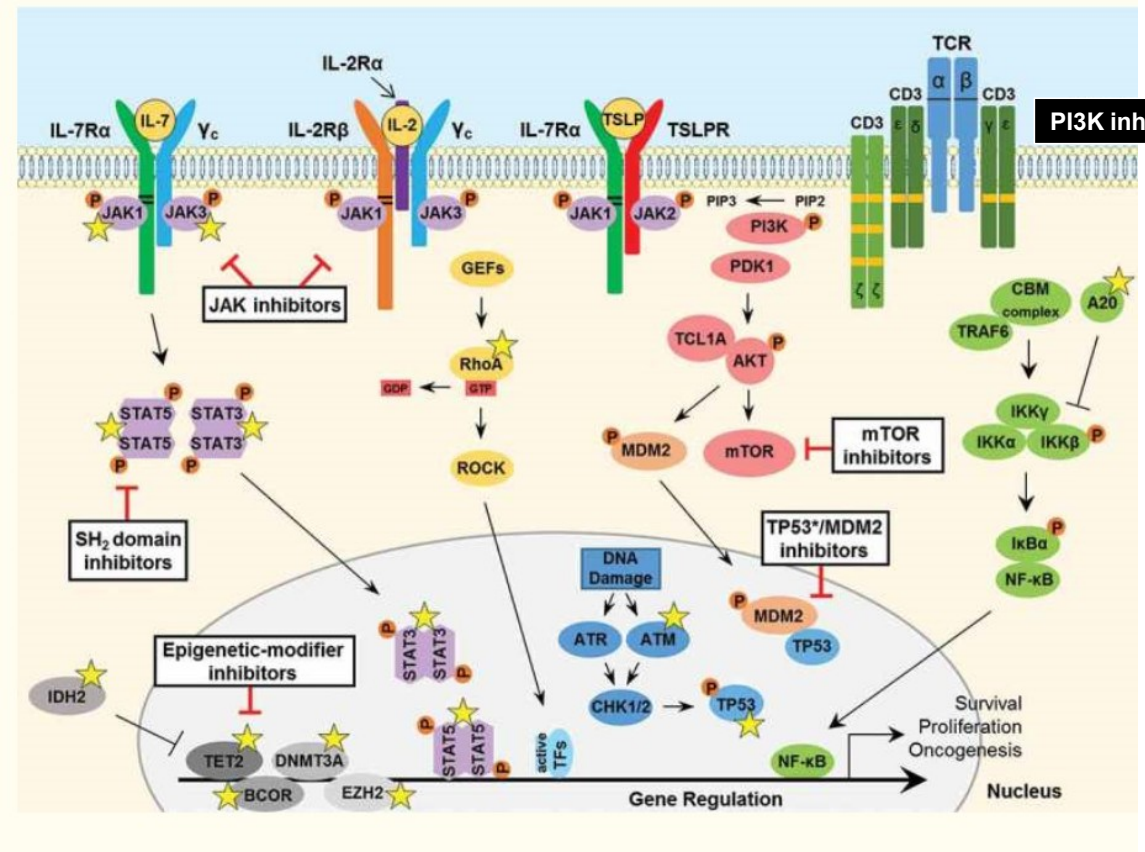
7 Cohorts

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

Romidepsin 10 mg/m^2, d8,15, to 14 mg/m^2, d8,15,22, on 21- to 35-day cycles

O'Connor. Blood. 2019;134:1395.

Developing new agents for PTCL



Orlova. Expert Opin Ther Targets. 2018;22:45-57.

Relevant pathways to explore

Duvelisib: oral PI3K γδ inhibitor

Population		Best Response, n (%)			Median Time to Response, months (Range)
	n	CR	PR	ORR	
All TCL	35	3 (8.5)	9 (26)	**14 (40)**	1.9 (1.6-3.5)
PTCL	16	3 (19)	5 (31)	**8 (50)**	1.9 (1.5-3.5)
CTCL	19	0	6 (32)	**6 (32)**	2.4 (1.6-3.8)

CRs: 1 EATCL, 1 PTCL-NOS

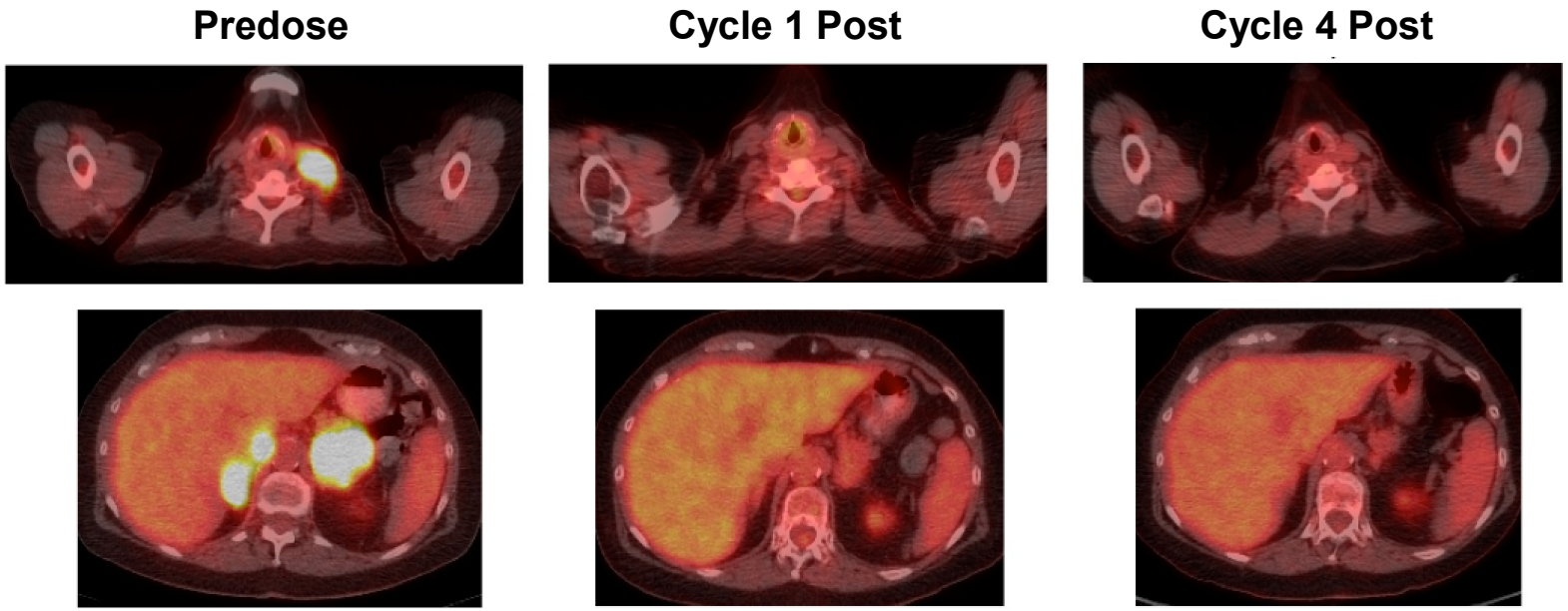
PRs: 2 AITCL, 2 SPTCL, 1 PTCL-NOS, 1 ALCL (ALK negative)

NCT03372057: Study of Duvelisib in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma (PTCL) – ongoing

1. Horwitz. Blood. 2018;131:888. 2. Horwitz. ICML 2019. Abstract33

Duvelisib: Early pharmacodynamic response as predictive biomarker for clinical response

CT scans from a 71-year-old woman with relapsed AITCL. Prior therapies: rituximab (ITP), CHOP, pralatrexate, vorinostat, brentuximab vedotin



Horwitz. Blood. 2018;131:888

Checkpoint inhibitors in PTCL

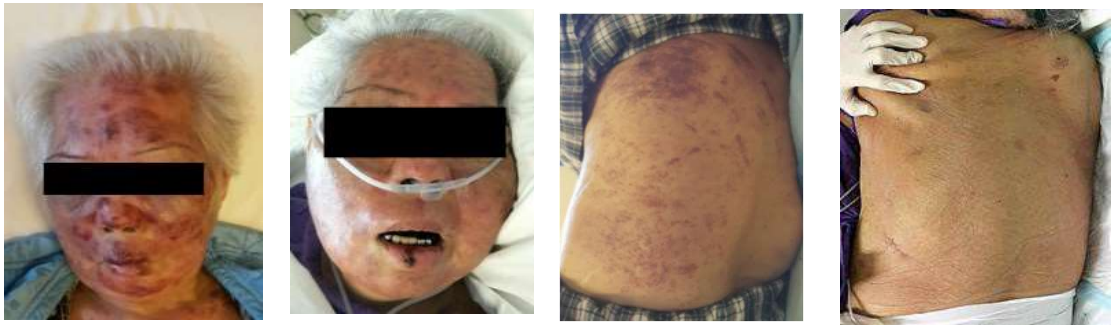
Pembrolizumab in R/R PTCL

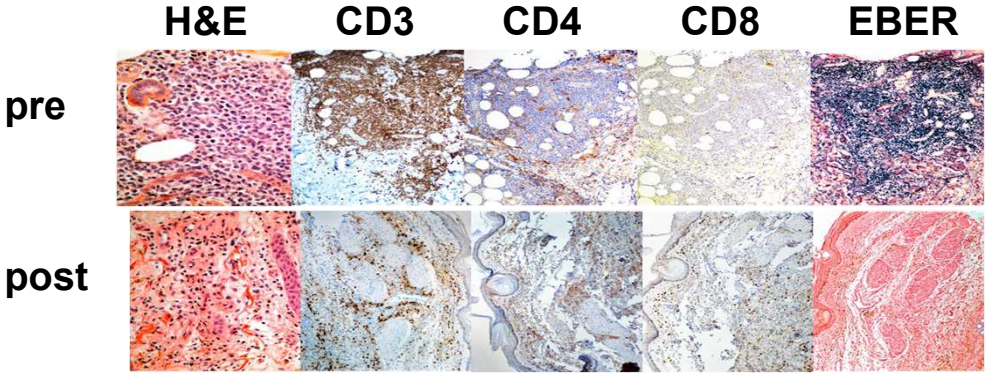
- 13 patents
- ORR: 33 %
- Median PFS: 3.2 months

Nivolumab in R/R PTCL

- 23 patients with NHL
- ORR 17%
- ORR : 40% (2/5)

Nivolumab in NKT cell lymphoma, nasal type





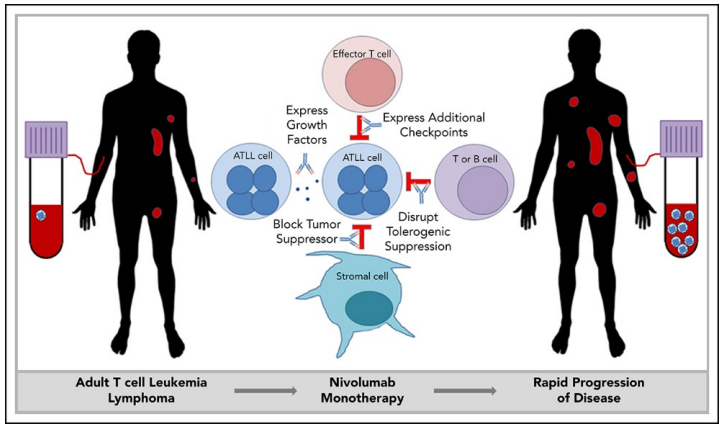
Barta. Clin Lymphoma Myeloma Leuk. 2019:19:356.
Kwong. Blood 2017

Checkpoint inhibitors in PTCL

IMMUNOBIOLOGY AND IMMUNOTHERAPY

Rapid progression of adult T-cell leukemia/lymphoma as tumor-infiltrating Tregs after PD-1 blockade

Daniel A. Rauch,[1] Kevin C. Conlon,[2] Murali Janakiram,[3] Jonathan E. Brammer,[4] John C. Harding,[1] B. Hilda Ye,[5] Xingxing Zang,[3,6] Xiaoxin Ren,[6] Sydney Olson,[1] Xiaogang Cheng,[1] Milos D. Miljkovic,[2] Hemalatha Sundaramoorthi,[1] Ancy Joseph,[1] Zachary L. Skidmore,[1] Obi Griffith,[1] Malachi Griffith,[1] Thomas A. Waldmann,[2] and Lee Ratner[1]

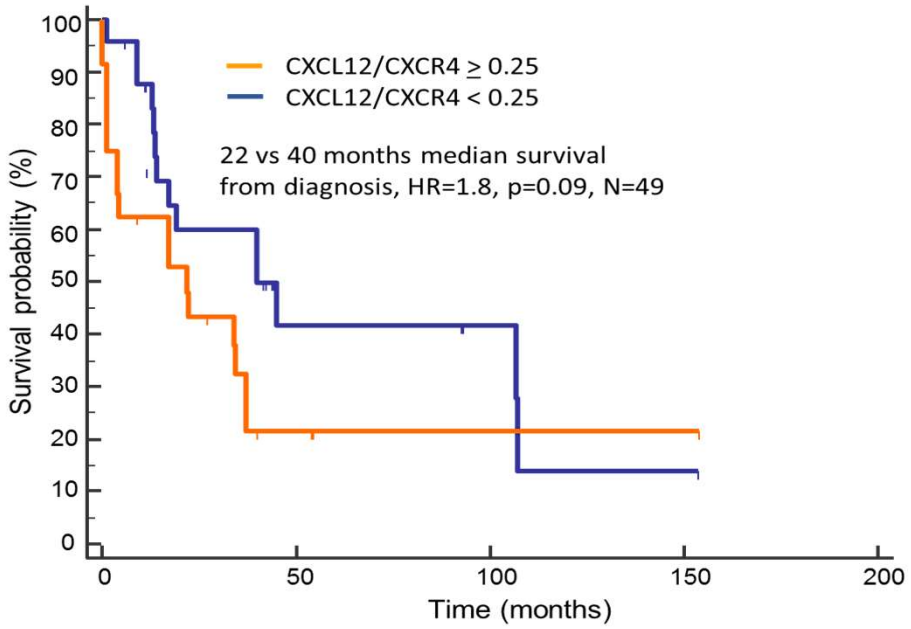


Other single agents for relapsed/refractory PTCL

Agent	Disease	Main Target	N	Phase	ORR, CR %	Median PFS/DOR mos	Median OS mos	Reference
Bendamustine	PTCL	Alkylating agent, purine ring	60	II	50, 28	3.6/3.5	6.2	Damaj et al, 2013
Mogamulizumab	CCR4+ PTCL + CTCL	Anti-CCR4 antibody	29	I	34, 17	2/--	14.2	Ogura et al, 2014
Lenalidomide	PTCL	Cereblon	39	II	26, 8	4/5	12	Tournishey et al, 2015
Copanlisib	NHL	PI3K αδ	17	II	21, 14	--	--	Dreyling et al, 2017
Tenalisib	PTCL, CTCL	PI3K δ/γ	32 eval	I/Ib	47,--	--	--	Huen et al, 2018
Tipifarnib	AITL, CXCL12+ TCL	CXCL-12	43	Interim analysis	45,--	--	--	Witzig et al, 2019

Tipifarnib is a CXCL12/CXCR4 pathway inhibitor

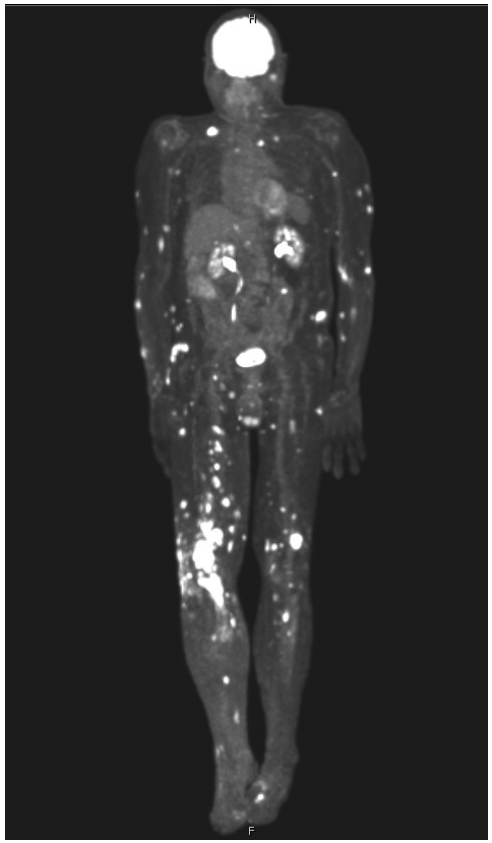
- **Key characteristics of CXCL12**
  - Expressed primarily by immune cells, endothelial cells and stromal fibroblasts that constitute the tumor microenvironment
- **High CXCL12 expression defines poor prognosis in PTCL**
  - 50% of AITL and 35% of PTCL-NOS have high CXCL12 expression
  - Trend for worse prognosis in AITL and PTCL-NOS patients with tumors with high CXCL12 expression[1]
- **Tipifarnib is a CXCL12/CXCR4 pathway inhibitor**
  - Tipifarnib downregulates CXCL12 secretion ex-vivo in stroma cultures



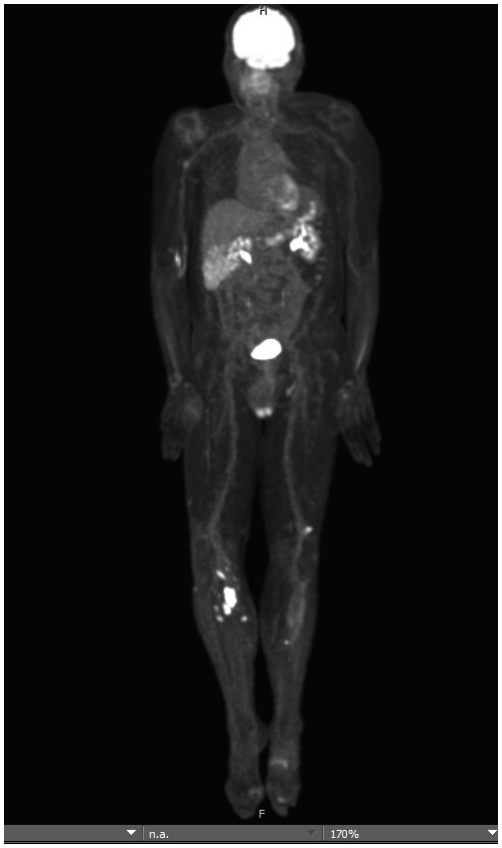
Trend for poor prognosis with high CXCL12 expression (adjusted to CXCR4) in AITL and PTCL NOS pts

[1] Witzig 2018 *Blood* 132:2937 | [2] Gualberto EHA 2019 #PS1002 | [3] Gualberto *Blood* 2017 130:3957

Tumor reduction in PTCL-NOS patient with tipifarnib



Baseline



End of Cycle 2

- 77 yo male with PTCL-NOS Stage IV
- CHOP x 5 with initial response then progression in skin
- At baseline visit had multiple skin nodules biopsy proven relapsed PTCL
- After two cycles of tipifarnib patient had near CR

High activity of tipifarnib in AITL with KIR3DL2 mutations

- AITL expresses high levels of CXCL12 and is sensitive to tipifarnib.
- ~50% of AITL carry mutations of KIR3DL2 and are highly sensitive to tipifarnib (50% CR rate).
- High Allele Frequency of KIR3DL2 mutation predicted complete response to tipifarnib treatment (ROC AUC=0.94, p<0.0001)..

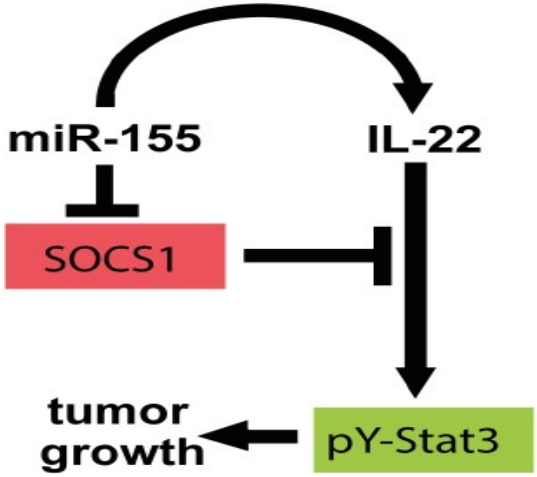
Best Response to Tipifarnib (N=16 AITL with sequenced tumors)

	KIR3DL2 Mutant	KIR3DL2 Wild Type
N	8	8
Overall Best Response		
Complete Response (CR)	4	-
Partial Response (PR)	2	2
Stable Disease (SD)	2	-
Progressive Disease (PD)	-	6
Not evaluable (NE)	-	-
Overall Response Rate (CR + PR)	**75%**	**25%**
95% CI	35.9 - 95.4	4.6 - 64.1
Clinical Benefit Rate (CR + PR + SD)	**100%**	**25%**
95% CI	64.1 - 100.0	4.6 - 64.1

Presented at 15-ICML: Gualberto et. al. Abstract 156-P

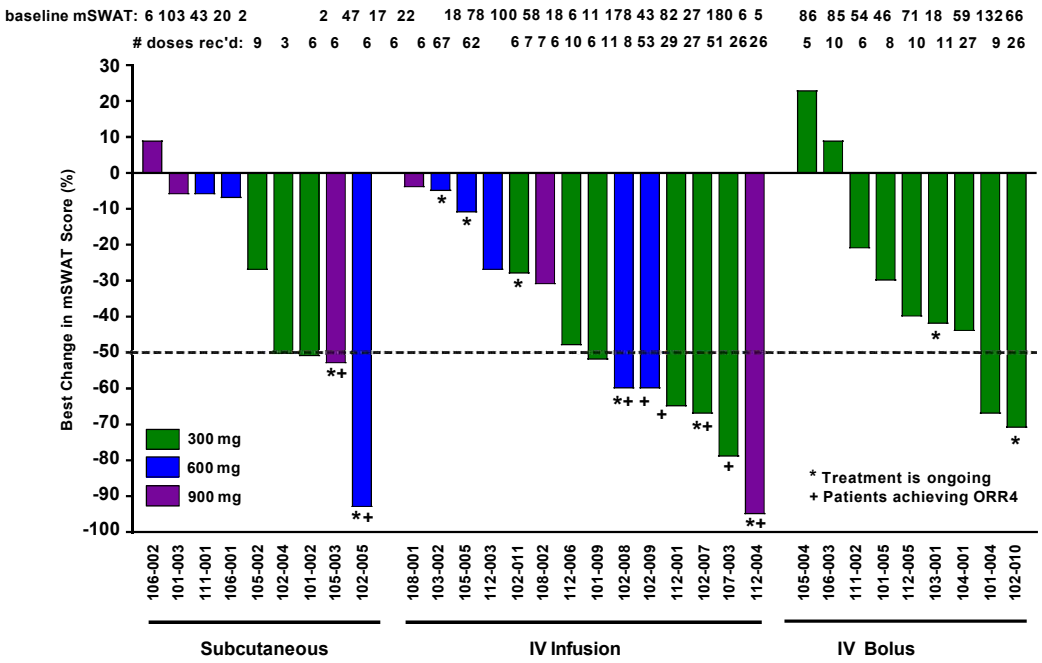
Inhibitors of micro RNA: miR-155

- Highly expressed in ALK- ALCL and in MF/SS
- Drives growth of ALCL xenografts
- Directly targets SOCS1 and C/EBPb
- HTLV-1 Tax activates miR-155 transcription and ATL has high miR-155 levels
- JAK/STAT, NFκB and PI3K signaling pathways are regulated by miR-155
- Phase I trial in MF/SS
  - Intralesion, subcut, IV
  - DLBCL, PTCL cohorts
  - HTLV-1 ATLL

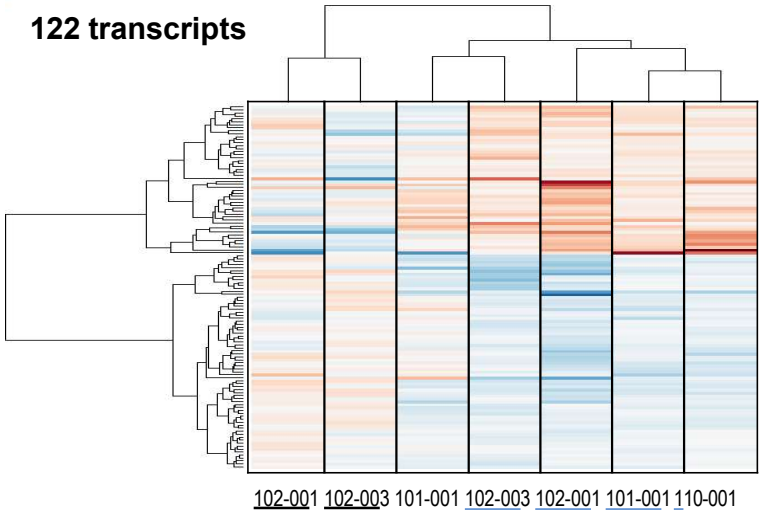


Response to cobomarsen in patients with CTCL

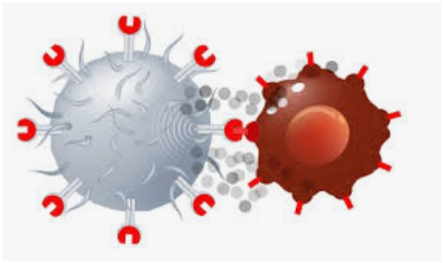
IV Infusion – best activity



Gene expression vs placebo



Complexities of developing CAR-T cells for T-cell lymphomas



T Cells Expressing a Fully-Human Anti-CD30 Chimeric Antigen Receptor for Treating CD30-Expressing Lymphomas	Lymphoma, Large-Cell, Anaplasitc; Hodgkin Disease; Lymphoma, Hodgkins; Enteropathy-Associated T-Cell Lymphoma; Lymphoma, Extranodal NK-T-Cell
CD30 CAR T Cells, Relapsed CD30 Expressing Lymphoma (RELY-30)	Hodgkin's Lymphoma; Non-Hodgkin Lymphoma

CD3, CD4, CD5, CD7: : Fratricide, T cell aplasia (AIDS-like)
CCR4: Wide expression with safety concerns
TRBC1/2: Ongoing phase I/II trial

Alternative approaches

CRISPR editing of TCR locus or viral delivery of DNA-? Aplasia
Myeloid transduced cells
RNA CAR