T-CELL LYMPHOMAS
NEW THERAPEUTIC APPROACHES

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DISCLOSURE

- Consultancy- Seagen, Verastem, Kiyowa Kirin, Mundi Pharma, Curio, Legend Biotech, Ono Pharmaceuticals

- Speakers Bureau- Seagen, Kiyowa Kirin

WHO CLASSIFICATION OF MATURE T-CELL AND NK/T CELL LYMPHOMAS 2016

T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
EBV-positive T-cell lymphoproliferative diseases of childhood
- Chronic active EBV infection, cutaneous
- Chronic active EBV infection, systemic
- Hydroa vacciniforme-like lymphoma
- Severe mosquito bite hypersensitivity
- Systemic EBV-positive T-cell lymphoma of childhood

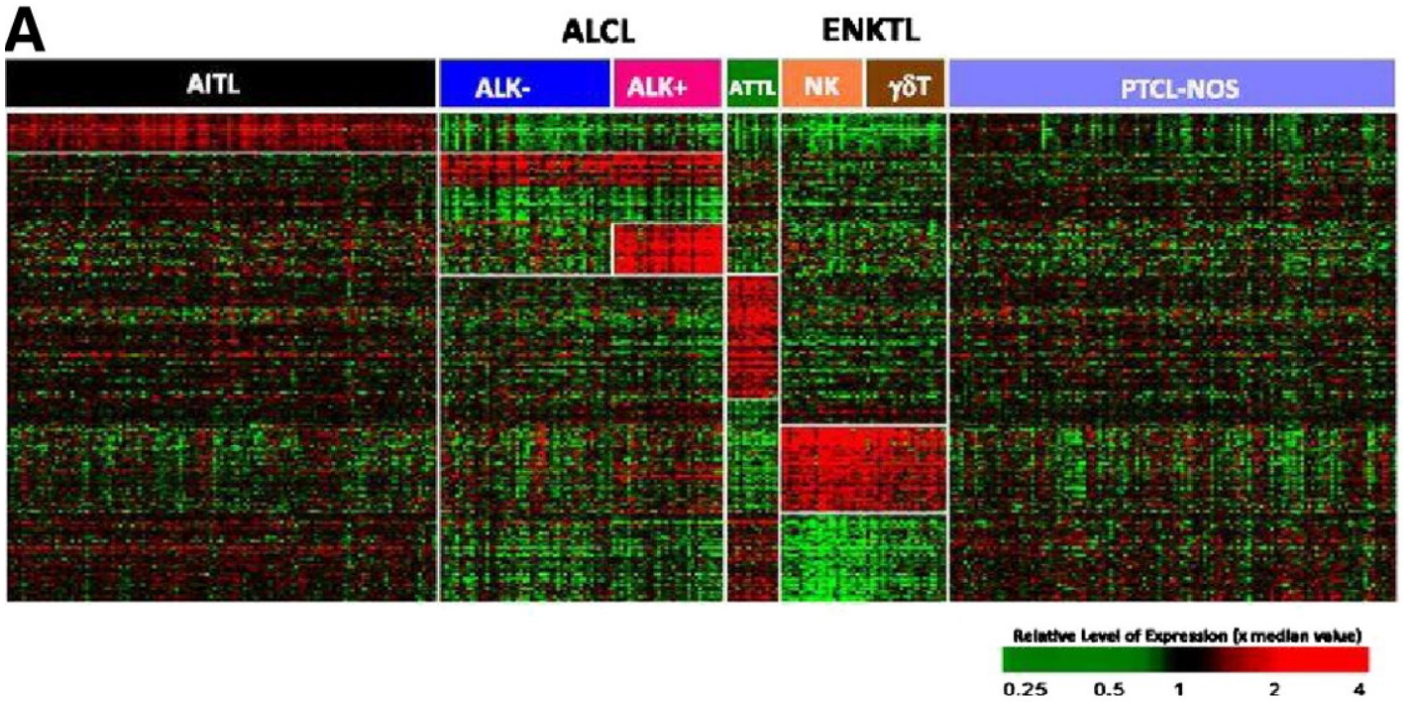
Adult T-cell leukemia/lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma*
Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract*
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30-positive T-cell lymphoproliferative disorders
- Lymphomatoid papulosis
- Primary cutaneous anaplastic large cell lymphoma

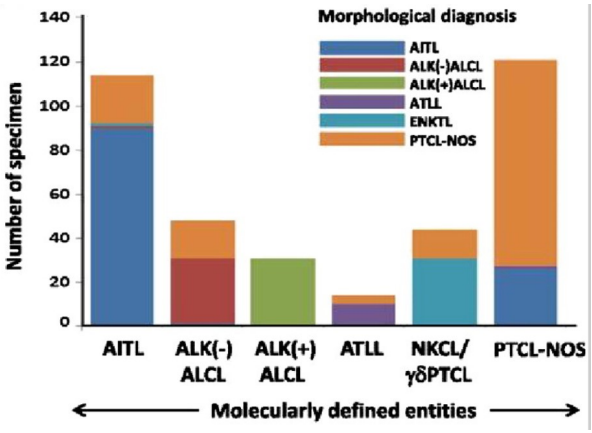
Primary cutaneous gamma-delta T-cell lymphoma
Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma
Primary cutaneous acral CD8-positive T-cell lymphoma*
Primary cutaneous CD4-positive small/medium T-cell lymphoproliferative disorder*
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
Follicular T-cell lymphoma*
Anaplastic large cell lymphoma, ALK-positive
Anaplastic large cell lymphoma, ALK-negative
Breast implant-associated anaplastic large cell lymphoma*

- GEP- led to molecularly defined groups of PTCL
- CNV
- NGS
- Integration of data

Pathogenesis
Prognostic markers
Therapeutic targets

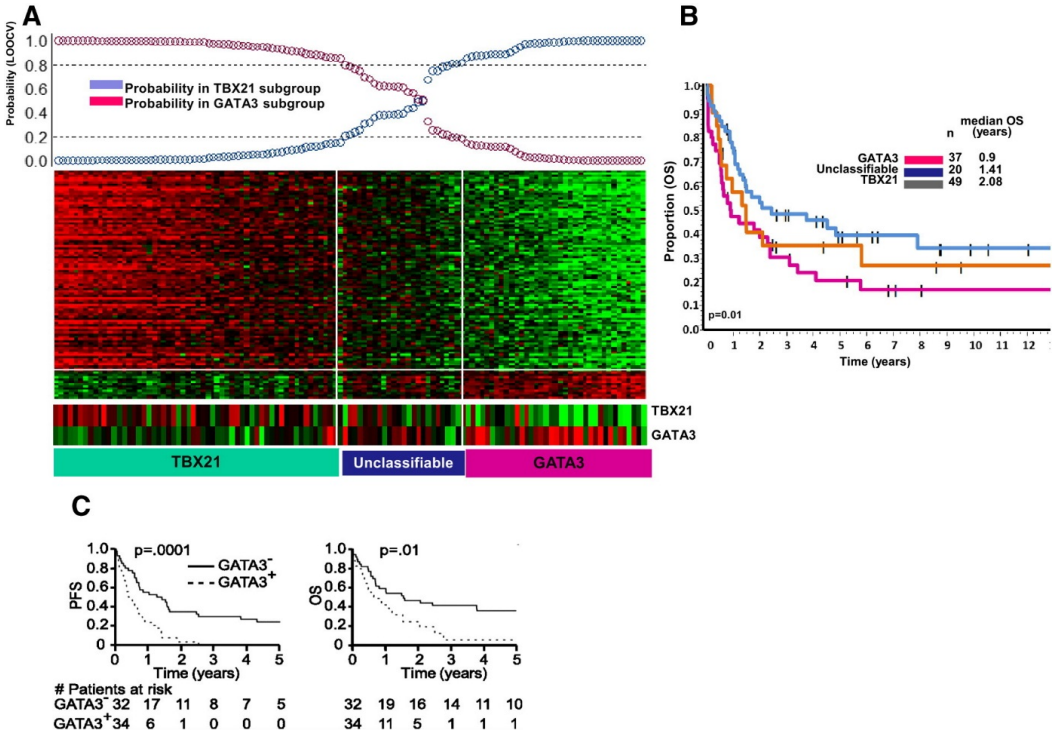
MOLECULARLY DEFINED ENTITIES IN PTCL





Iqbal et al 2016

MOLECULARLY DEFINED SUBGROUPS OF PTCL-NOS



Iqbal et al – 2014

CLINICAL EVALUATION OF MOLECULARLY DEFINED SUBSETS OF PTCL-NOS

PTCL-GATA 3

High expression of GATA 3 and its target genes

33% of PTCL-nos

GATA 3 is the master regulator of TH2 cell differentiation, regulates IL4, IL5 and IL13

Associated with PI3K-mTOR activation

PTCL-TBX21

High expression of TBX21 and its target genes

49% of PTCL

Master regulator of TH1 and cytotoxic T cell differentiation

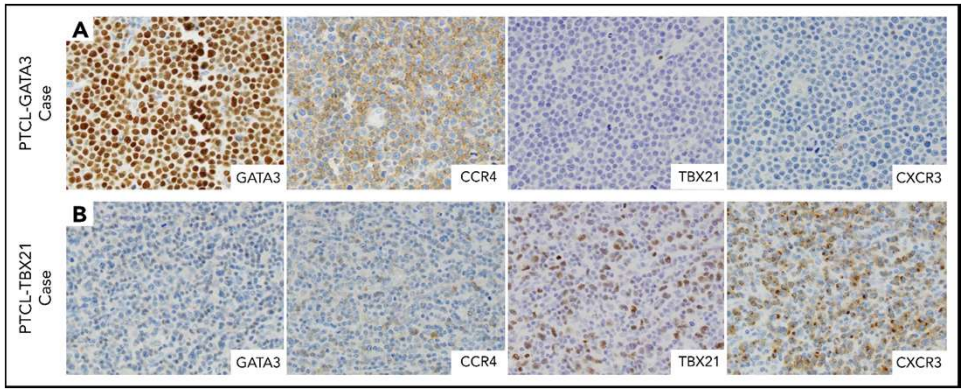
Regulates expression of Interferon gamma and granzyme B

NF-kB activation

IHC algorithm

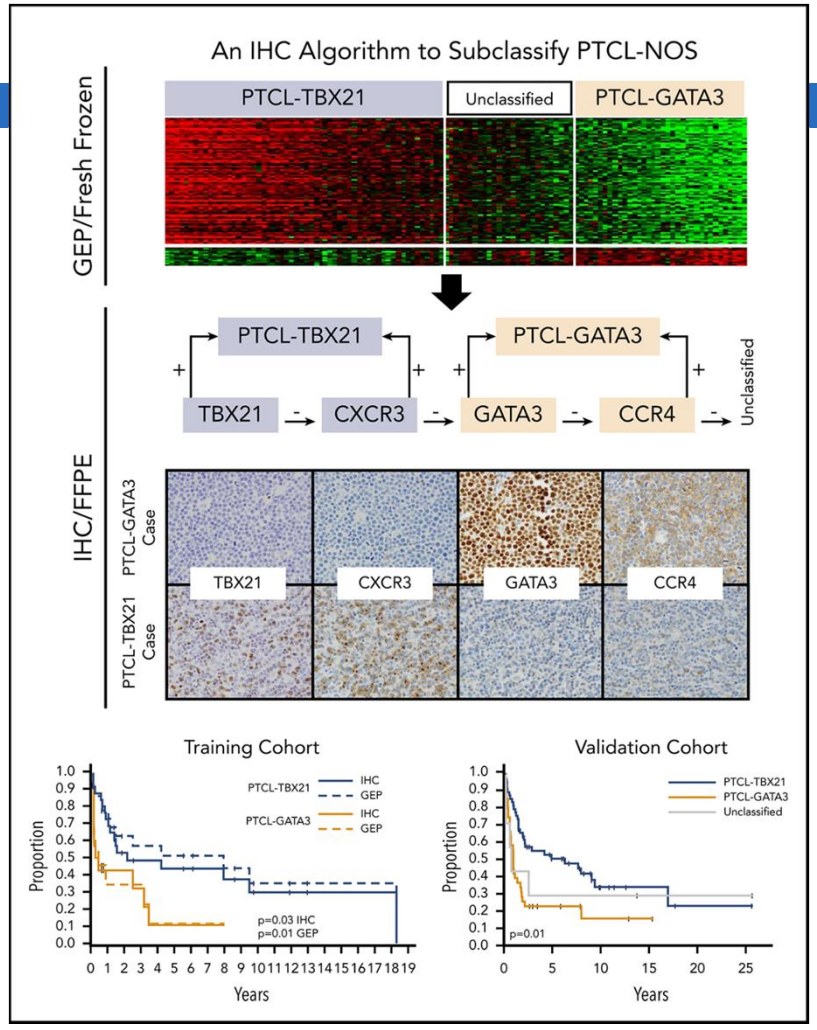
PTCL-GATA 3--- GATA3, CCR4

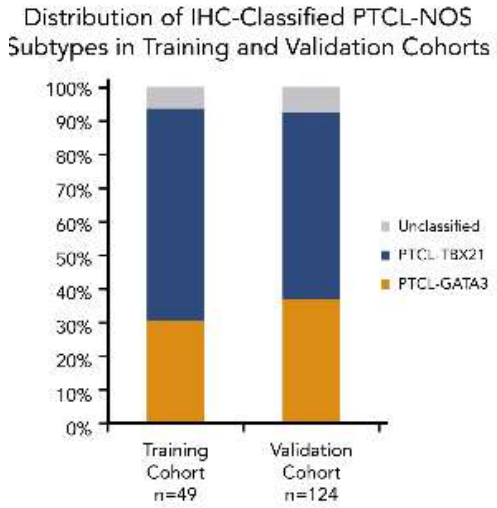
PTCL-TBX21 ---- TBX21 ad nCXCR3



Chan et al 2019

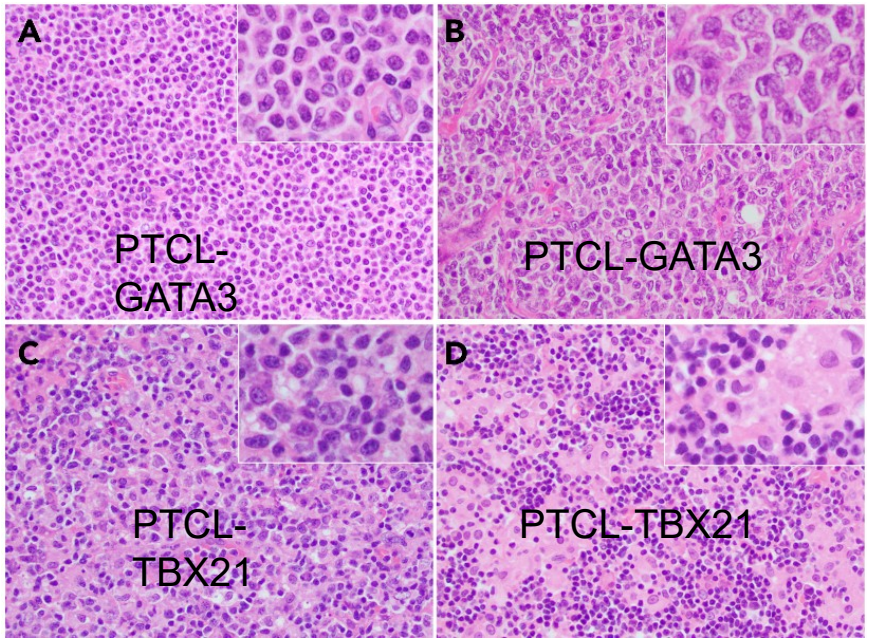
REPRODUCING THE MOLECULAR SUBCLASSIFICATION OF PERIPHERAL T-CELL LYMPHOMA–NOS BY IMMUNOHISTOCHEMISTRY

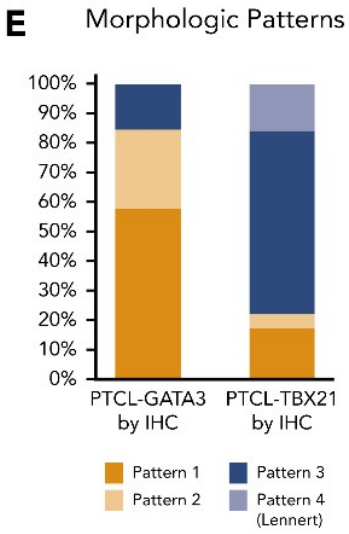


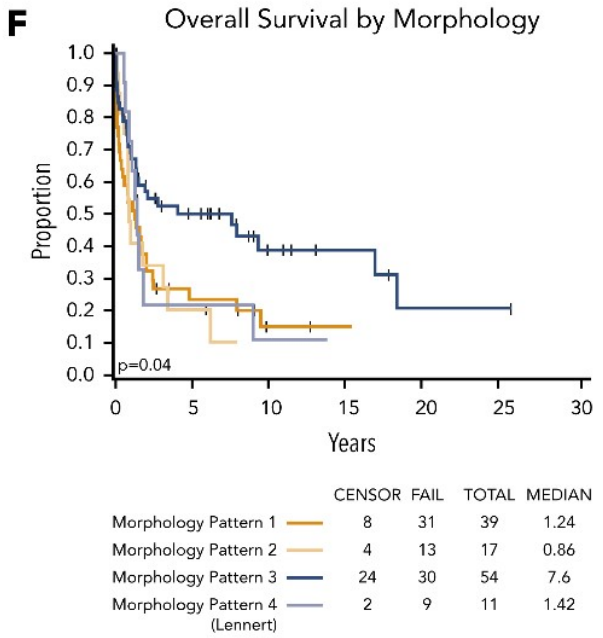


Amador et al: Blood 2019

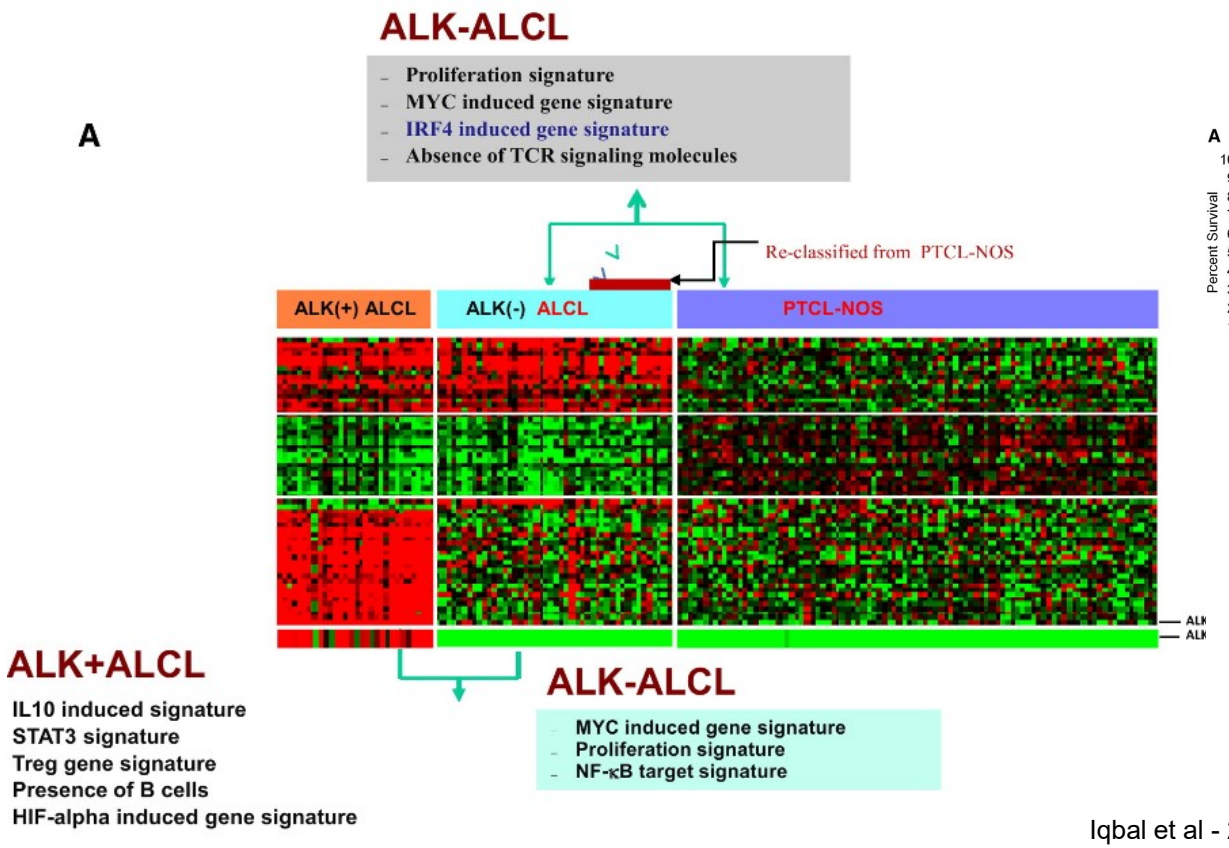
DISTINCT MORPHOLOGICAL FEATURES IN PTCL-NOS CLASSIFIED BY IHC ALGORITHIM

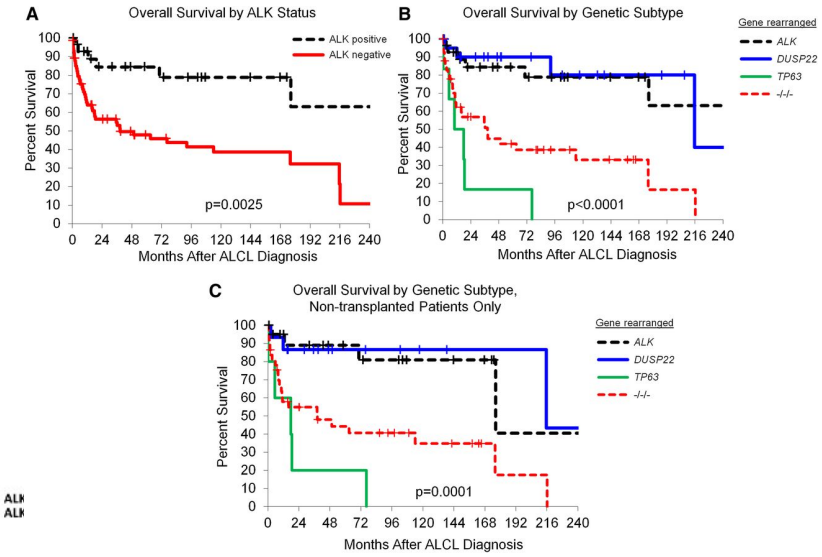






SPECIFIC GENE EXPRESSION SIGNATURES OF ALCL SUBTYPES



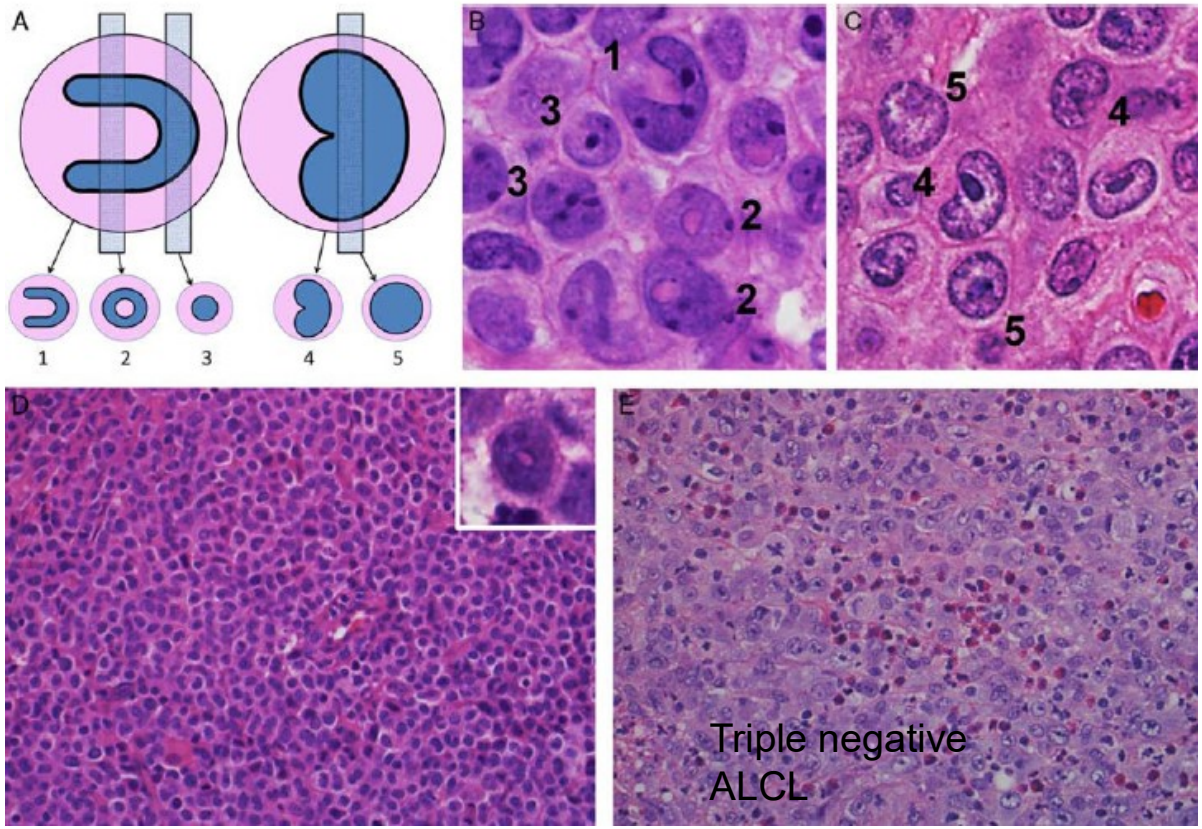


Iqbal et al - 2016

Edgardo R. Parrilla Castellar et al. Blood 2017

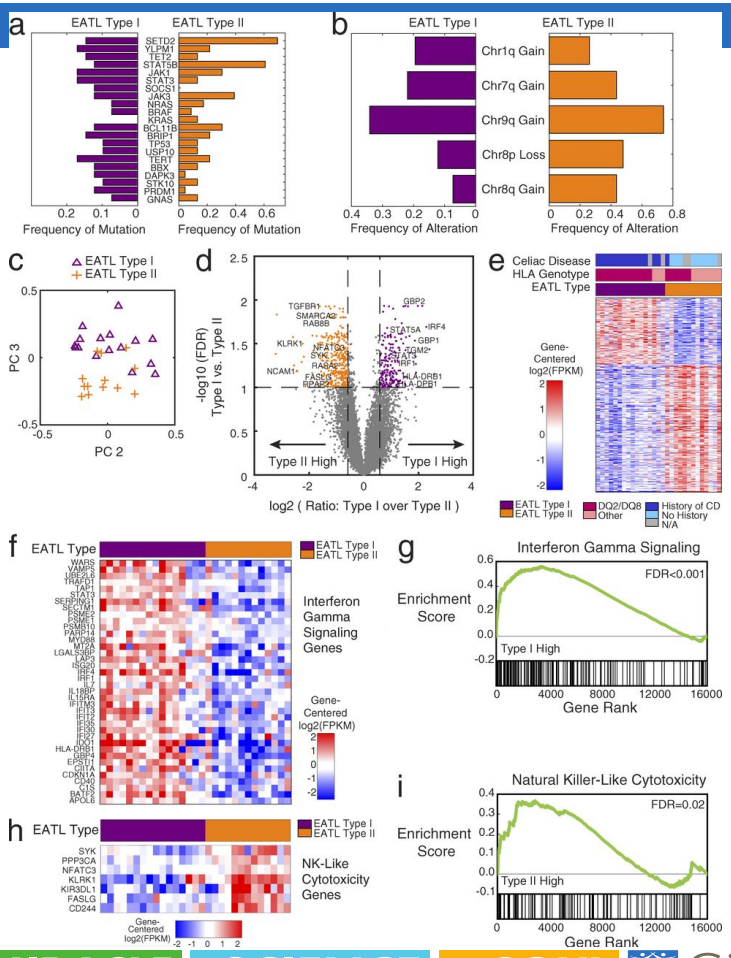
MORPHOLOGIC FEATURES OF DUSP-22 REARRANGED ALK-VE ALCL

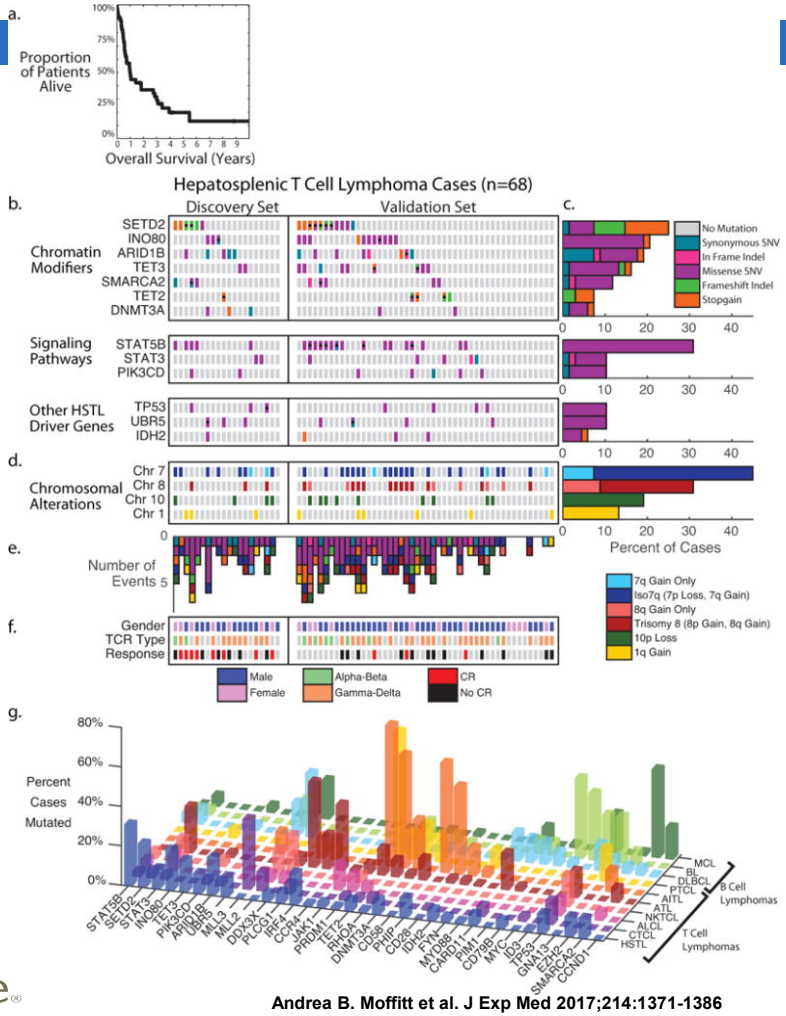
- 30% of alk-ve ALCL are DUSP22 rearranged
- DUSP22 rearranged cases were more likely to have doughnut cells, less likely to be pleomorphic and had sheet like growth of cells



King et al : Am J Surg Pathology 2017

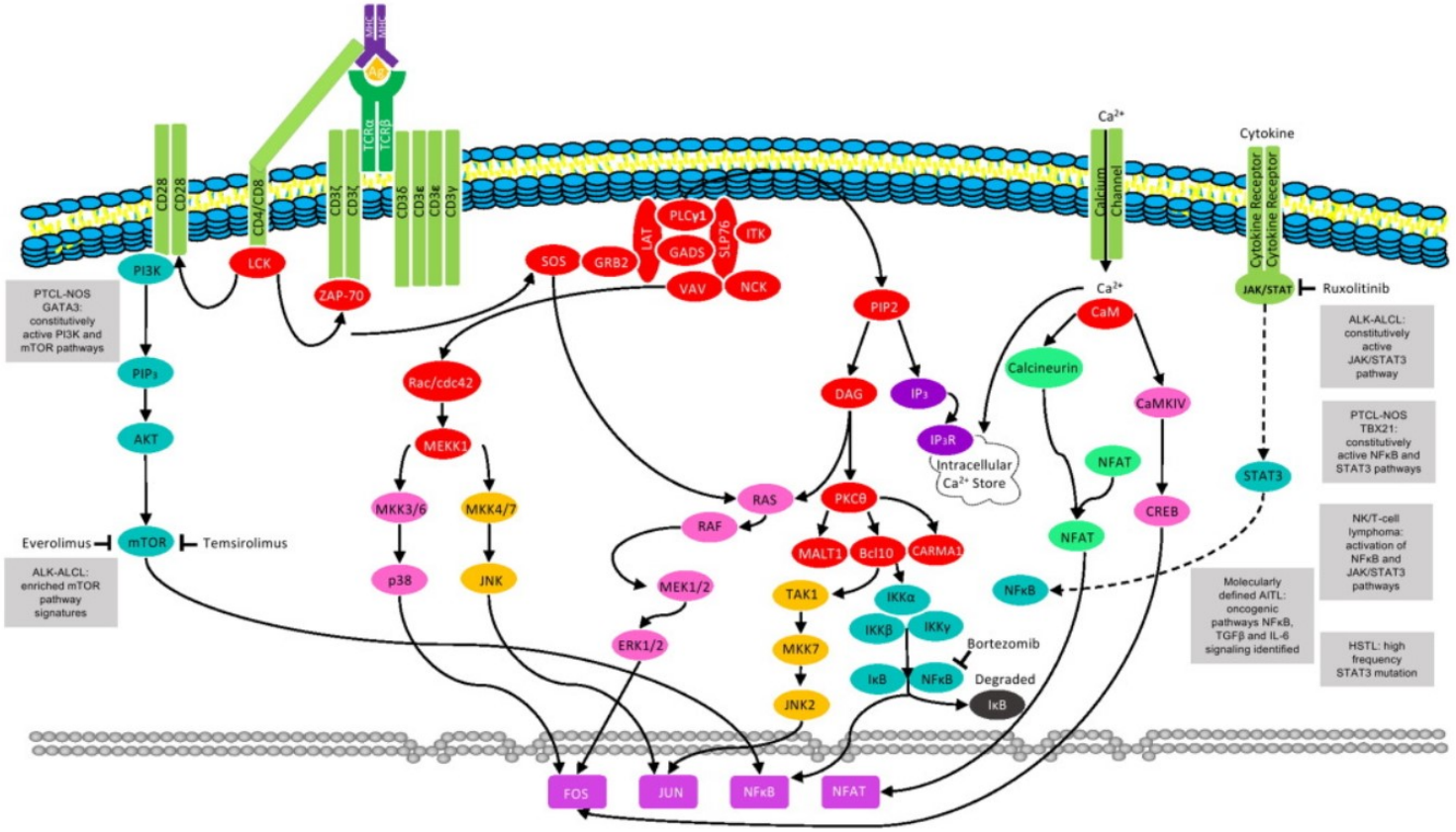
GENETIC LANDSCAPE OF DIFFERENT SUBTYPES OF PTCL





Andrea B. Moffitt et al. J Exp Med 2017;214:1371-1386

POTENTIAL THERAPEUTIC TARGETS FOR PTCL



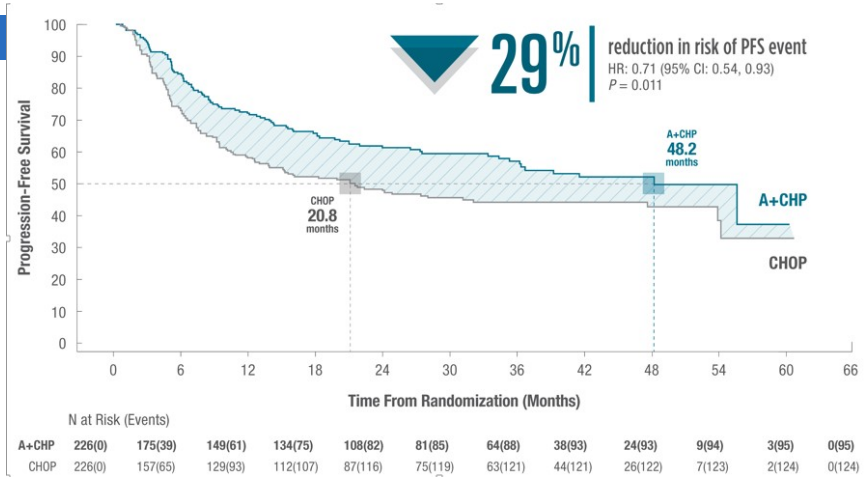
BRENTUXIMAB + CHP FOR CD30 + PTCL

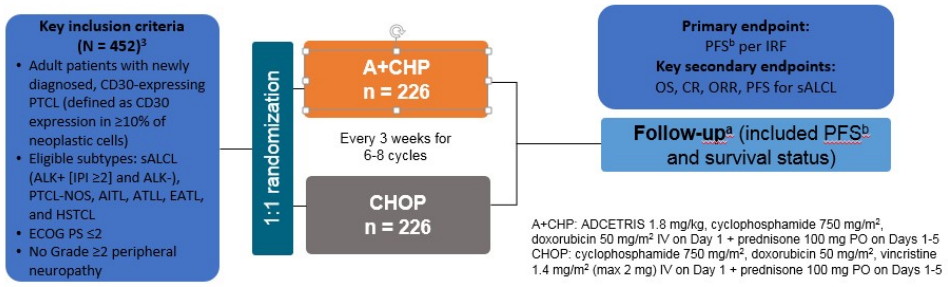
Echelon -2 Frontline treatment with A+CHP vs CHOP for newly diagnosed, CD30-expressing PTCLs demonstrated a 29% reduction in risk of PFS event (HR: 0.71; 95% CI: 0.54-0.93; *P* = 0.011)

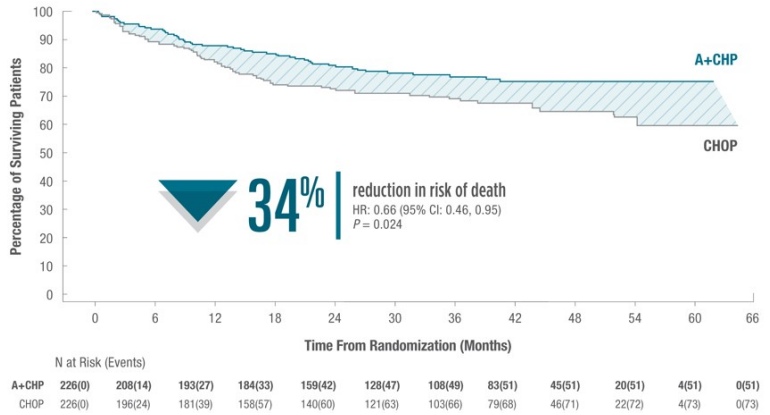
A+CHP more than doubled median PFS vs CHOP (48.2 vs 20.8 months, respectively)

34% reduction in risk of death with A+CHP (HR: 0.66; 95% CI: 0.46-0.95; *P* = 0.024)[1]. Median OS was not reached in either arm

A+CHP has a comparable safety to CHOP







Horwitz et al : Lancet 2019

EXPLORATORY ANALYSIS – IMPACT OF STEM CELL TRANSPLANT IN ECHELON-2

- ECHELON 2- role of consolidative transplant was not studied explicitly
- In patients treated with A+CHP only 50/226 (22%) underwent transplant
- alk-ALCL - 76/113 were in CR on the A+CHP arm and 27/76 (36%) received transplant
- Median PFS for patients with SCT was not reached vs 55.6 months without transplant
- Non- ALCL patients – 38/64 (59%) on the A=CHP arm were in CR and 11/38 (29%) had SCT
- Median PFS in SCT was not reached and was 33.2 months in non SCT patients
- Standard PFS and multivariate proportional hazards regression analysis favored transplant
- Transplant was done less frequently in Asian countries

	ALK– sALCL N=76		Non-sALCL N=38		Combined N=114	
	SCT (n=27)	No SCT (n=49)	SCT (n=11)	No SCT (n=27)	SCT[a] (n=38)	No SCT (n=76)
Estimated PFS at 3 years, % (95% CI)	80.4 (59.1, 91.4)	56.9 (40.6, 70.3)	70.1 (32.3, 89.5)	46.7 (26.7, 64.4)	76.1 (56.9, 87.6)	53.3 (40.7, 64.3)
Univariate, HR (95% CI)	0.49 (0.19, 1.27)		0.36 (0.10, 1.26)		0.38 (0.18, 0.82)	
Multivariate, HR (95% CI) adjusting for:						
Age[b]	0.54 (0.20, 1.45)		0.32 (0.09, 1.15)		0.39 (0.18, 0.86)	
Region[c]	0.47 (0.18,1.22)		0.37 (0.10, 1.33)		0.38 (0.18, 0.82)	
Age[b] + Region[c]	0.52 (0.19, 1.41)		0.32 (0.09, 1.19)		0.39 (0.18, 0.86)	
Median follow-up[d], mos (95% CI)	29.9 (24.2, 36.1)	41.6 (29.8, 42.0)	49.8 (21.2, 54.0)	42.6 (29.5, 53.9)	35.9 (24.5, 41.9)	41.6 (33.2, 42.1)

Table presents HR of PFS for pts who achieved CR on A+CHP, SCT vs no SCT; HR<1 favors SCT; all HRs were stratified for baseline IPI score (0–1; 2–3; 4–5).

PFS was measured from randomization to progressive disease, death, or receipt of subsequent systemic chemotherapy to treat residual or progressive PTCL as determined by the investigator, whichever came first. Consolidative SCT was not considered an event.

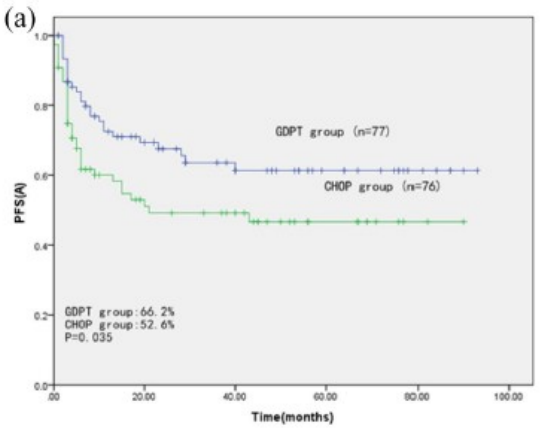
a. Includes 2 allogeneic SCTs
b. <65; ≥65 yr
c. Non-Asia (rest of world); Asia (Taiwan, Japan, and South Korea)
d. Median follow-up is calculated for PFS using the Kaplan-Meier method of switching the PFS event and censored status.

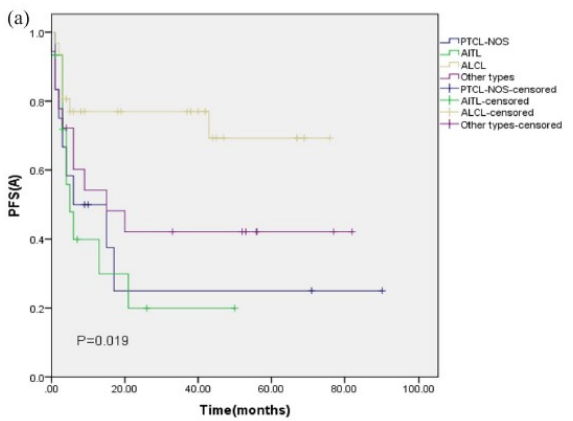
Savage et al ;ASH 2019

GDPT vs CHOP in the upfront treatment of PTCL

Subgroups	Responses (%)					
	GDPT		CHOP		*p* value	
CR	ORR	CR	ORR	CR	ORR	
PTCL-NOS	9 (47.4)	15 (78.9)	0 (0.0)	3 (25.0)	0.015	0.003
AITL	4 (18.2)	12 (54.5)	3 (20)	5 (33.3)	0.003	0.204
ALCL	10 (55.6)	12 (66.7)	16 (51.6)	23 (74.2)	0.790	0.574
Other types	10 (55.6)	12 (66.7)	2 (11.1)	7 (38.9)	0.005	0.095
p value	0.046	0.437	<0.001	0.005		

Group and gene	Response	Number of patients		*p* value
		Low expression	High expression	
GDPT group (*n*=42)				
ERCC1	CR+PR	7	11	0.856
	SD+PD	10	14	
RRM1	CR+PR	8	10	0.650
	SD+PD	9	15	
CHOP group (*n*=39)				
TOP2A	CR+PR	8	11	0.648
	SD+PD	7	13	
TUBB3	CR+PR	13	5	0.708
	SD+PD	14	7	





WHAT WE KNOW SO FAR

- CHOP based therapies remain the back bone of upfront therapy (CR 31-67%)
- **For CD30+ lymphomas and ALCL- ----- BV+CHP – based on randomized data and shown to impact survival**
- Role of Etoposide if the upfront regimen continues to be debated. Best data is by Schimdt, et al. <60, normal LDH, improved OS. CHOEP followed by high dose ASCT has been used by several groups. Metanalysis by Deng et al did not show a difference between CHOP and CHOPE (Onco targets 2019)
- CHOP+Romdepsin (Ro-CHOP) – Initial results ORR 78% including 66% CR. Randomized phase 3 ongoing.
- CHOP+Pralatrexate - ORR 89%, CR 67%
- CHOP+Belinostat – ORR 86%, CR 67%, PR 19%
- CHOEP+Revlimid – ORR 88% and CR 38%. Len maintenance arm
- CHEP+BV – Ongoing. Possible EPCH+BV?
- Chidamide + CHOP, Chidmaide + CHOEP (ORR 68%, CR 43%)
- GDPT vs CHOP,- 42% vs 27% longer PFS and OS
- Mogamulizumab combinations – EPOCH, mLSG15

APPROVED AGENTS FOR THE TREATMENT OF RR PTCL

AGENT	HISTOLOGY	ORR/CR	ORR/CR	DURATION
PRALATREXATE 2009	PTCL- all subtypes	29%/11%	PTCL- nos 32% sALCL- 35% AITL- 8% other – 38%	DOR = 10.1 months (,1-22.1)
ROMIDEPSIN 2009	PTCL- all subtypes	25%/15%	PTCL- nos—29/14 AITL- 30/19 Alk-ve ALCL -24/19	DOR 28 months (1-48) Median OS= 11.3 months Time to CR =3.7months
BELINOSTAT 2014	PTCL- all subtypes	26%/11%	PTCL-nos-23% AITL-46%/18% ALCL- 15% ENKTCL-50%	DOR= 13.6 months (4.5-29.4)
BRENTUXIMAB VEDOTIN 2011	sALCL	86%/59%	Highest responses in ALCL- other subtypes much less	DOR = 13.2 (5.7-26.3) OS- 70% at 1 yr. 64% at 4 yrs
MOGAMULIZUMAB 2012	ATLL	50/31	Approved for CTCL in the US, ATLL and CCR4 expressing PTCL in Japan	Median PFS 5.2 months
CHIDAMIDE 2014	PTCL	28/14	Approved in China	Median PFS 2.1 month, OS 21.4 months

RECENT UPDATES REGARDING SINGLE AGENT PRALATREXATE FOR R/R PTCL

	PROPEL[1]	Maruyama 2017[2]	Admojo 2018[3]	Hong 2019[4]
Patients (n)	109	20	31	71
Median lines of prior therapy	3	3	3	2
CR	10%	10%	6.5%	20%
ORR	29%	44%	32%	52%
ORR (2nd line use)	35%	-	75%	76%
ORR (by subtypes)				
• PTCL-NOS	32%	50%	50%	50%
• AITL	8%	44%	38%	55%
• ALCL	35%	50%	0%	83%

1. O'Connor O., …. Shustov A., et al. *J Clin Onc* 2011; 29:1182-89
2. Maruyama et al.Cancer Science.2017,108(10):2061-2068.
3. Admojo. Presentation at Blood 2018.
4. Hong et al. Targeted Oncology 2019.

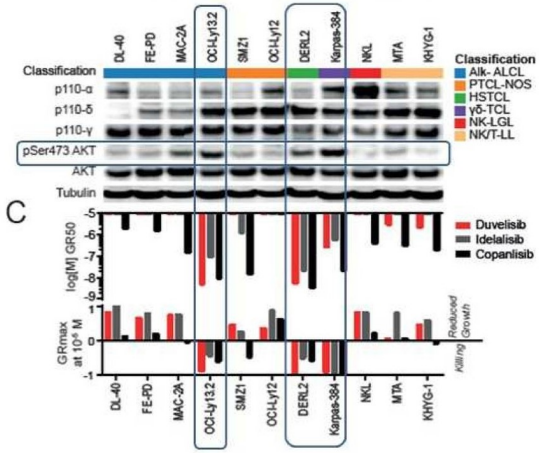
USE OF LEUCOVORIN

- In PROPEL – mucositis was most common side effect – grade 2 and above 52% of patients
- PDX followed by Leucovorin 50mg IV – 24 hrs later Geskin et al 2014
- Leucovorin reduced incidence of mucositis – retrospective study Foss et al 2016
- **Prospective study** – Pralatrexate (SD + Vit supplements) followed by Leucovorin 25mg tid for 2 days (24 hrs later) - Shustov et al ASH 2018
  - **Mucositis was reported in 4 patients – no grade 3 or higher**

The preemptive use of Leucovorin alongwith Vit B12 and Folate supplements to prevent mucositis is now in the NCCN guidelines

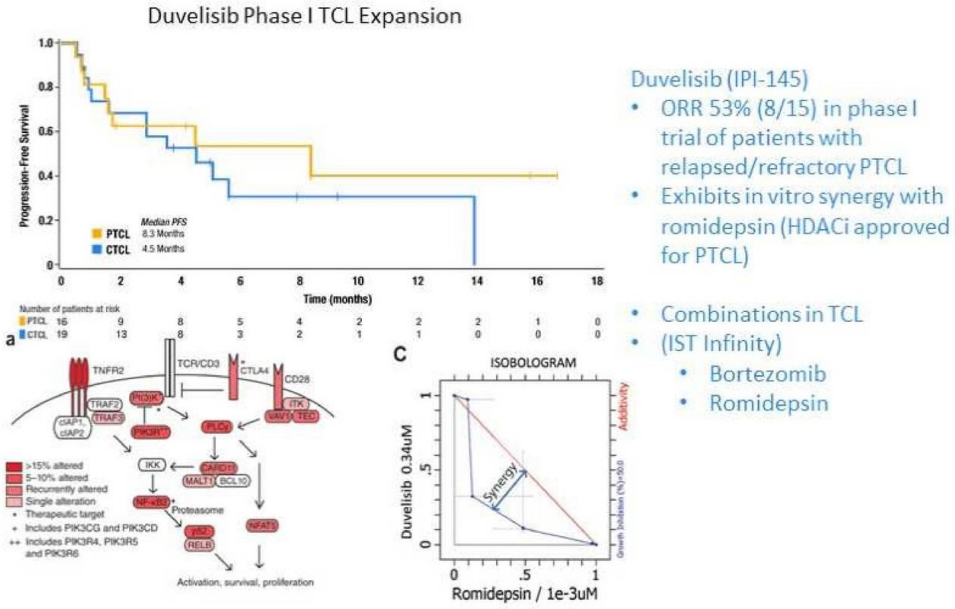
TARGETING PI3 KINASE

Constitutive activity of pAKT TCL cell lines predicts sensitivity to duvelisib



Using cell line data to predict response to PI3 kinase inhibitors

Targeting PI3K in PTCL



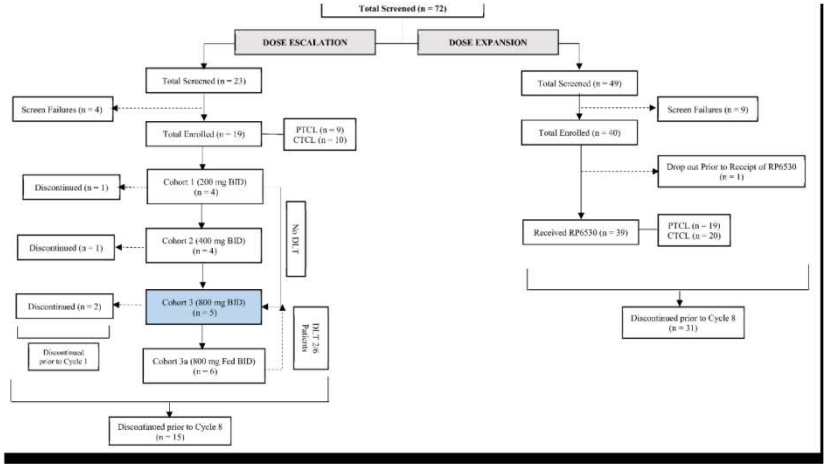
Duvelisib (IPI-145)

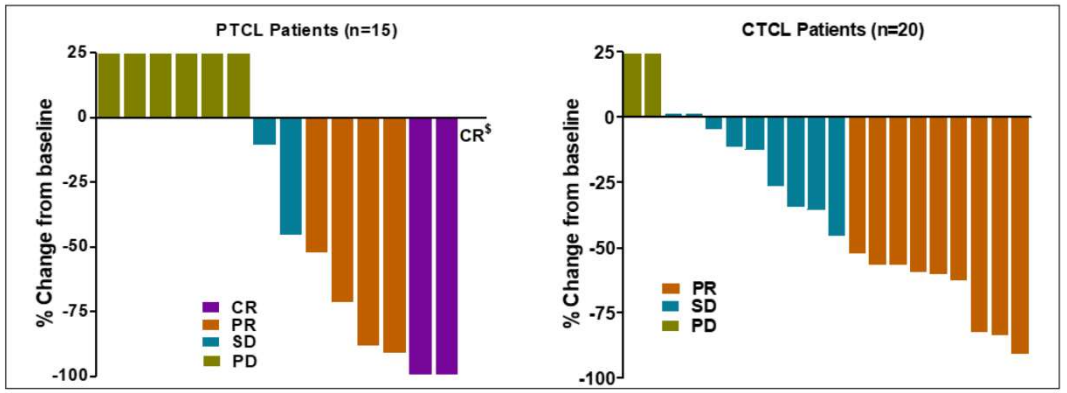
- ORR 53% (8/15) in phase I trial of patients with relapsed/refractory PTCL
- Exhibits in vitro synergy with romidepsin (HDACi approved for PTCL)

- Combinations in TCL
- (IST Infinity)
  - Bortezomib
  - Romidepsin

Horwitz et al, ASH 2014; Ungewickell et al. ,*Nature Genetics* 47, 1056–1060 (2015)

TENALISIB





$Non-measurable disease; positive bone marrow became negative (CR)

Significant TEAEs	Dose Expansion (*N* = 19) *n* (%), E	Dose Escalation (*N* = 39) *n* (%), E	Total (*N* = 58) *n* (%), E
Alanine aminotransferase increased	5 (26.3%), 5	6 (15.4%), 7	11 (19.0%), 12
Aspartate aminotransferase increased	4 (21.1%), 4	7 (17.9%), 8	11 (19.0%), 12
Anemia	2 (10.5%), 2	3 (7.7%), 6	5 (8.6%), 8
Neutropenia	2 (10.5%), 2	2 (5.1%), 2	4 (6.9%), 4
Hyponatremia	2 (10.5%), 2	2 (5.1%), 2	4 (6.9%), 4
Thrombocytopenia	1 (5.3%), 1	2 (5.1%), 2	3 (5.2%), 3
Fatigue	1 (5.3%), 1	2 (5.1%), 3	3 (5.2%), 4

n = Number of patients with at least one event; E = Count of events. TEAEs = Treatment emergent adverse events.

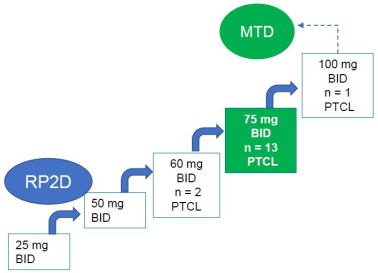
Huen et al – Cancers 2020

DUVELISIB

Duvelisib Monotherapy: Clinical Activity in PTCL

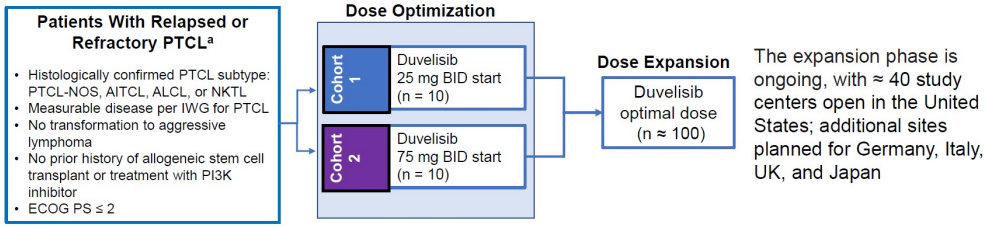
Phase 1 Trial[1,2]

Patients with RR PTCL: N = 16



	Duvelisib 75 mg BID (n = 13)	All PTCL (N = 16)
ORR, n (%) [95% CI]	**7 (54) [25.1-80.8]**	**8 (50) [24.7-75.3]**
Best overall response, n (%)		
Complete response	2 (15)	3 (19)
Partial response	5 (38)	5 (31)
Stable disease	1 (8)	1 (6)
Progressive disease	5 (38)	6 (37)
Unknown	0	1 (6)
Median time to response (range), mo	1.9	1.9 (1.6-3.5)
Median PFS (95% CI), mo	8.3	8.3 (1.4-NR)
Median OS (95% CI), mo	16.2	8.4 (4.3-NR)

- Response to duvelisib was observed across a spectrum of PTCL subtypes
  - 3 CRs in EATL, AITCL, and PTCL-NOS
  - 5 PRs in AITCL, ALCL, PTCL-NOS, and SPTCL (n = 2)



The expansion phase is ongoing, with ≈ 40 study centers open in the United States; additional sites planned for Germany, Italy, UK, and Japan

Primary objectives: identify the optimal dose of duvelisib and examine its efficacy, safety, and tolerability at the optimal dose

- Primary endpoint
  - IRC-assessed ORR
- Secondary endpoints
  - Safety, DOR, PFS, DCR (ie, CR + PR + SD ≥ 8 weeks), and OS
- Exploratory endpoints
  - PK and PD biomarkers

	Patients With Hematologic Malignancies[1]		Patients With TCL[2]
	Duvelisib 25 mg BID (n = 66)	Duvelisib 75 mg BID (n = 124)	Duvelisib[a] (n = 35)
All grades, n (%)			
ALT or AST increased	23 (35)	59 (48)	20 (57)
Diarrhea	33 (50)	49 (39)	11 (31)
Neutropenia	21 (32)	23 (18)	7 (20)
Colitis	6 (9)	7 (6)	4 (11)
Grade ≥ 3, n (%)			
ALT or AST increased	12 (18)	29 (23)	14 (40)
Diarrhea	10 (15)	12 (10)	0
Neutropenia	17 (26)	18 (14)	6 (17)
Colitis	5 (8)	4 (3)	2 (6)

[a]27 patients (77%) with TCL were treated at the MTD of oral duvelisib (75 mg) twice daily on a 28-day cycle. The other 8 patients received 25 mg (n = 1), 50 mg (n = 1), 60 mg (n = 4),or 100 mg (n = 2) twice daily.

Duvelisib in Patients with Relapsed/Refractory Peripheral T-Cell Lymphoma from the Phase 2 Primo Trial: Dose Optimization Efficacy Update and Expansion Phase Initial Results

25 patients dosed in the dose expansion phase
ORR 49%, CR 30% and median DOR 12.2 months

Hope®

Pro et al : ASH 2020

TARGETING THE JAK/STAT PATHWAY

Final Results of a Phase II Biomarker-Driven Study of Ruxolitinib in Relapsed and Refractory T-Cell Lymphoma

- JAK/STAT pathway genes were evaluated by NGS
- IHC was used to assess STAT3
- Enrollment based on mutational status and STAT 3 expression
- Tissue samples collected at baseline, on treatment and end of treatment

- ORR was 23%
- Responders had low pS6 expression in pretreatment biopsies

Moskowitz et al –ASH 2019

Table 1. Patient characteristics

Characteristics	Total (n=53)	Cohort 1 (n=18)	Cohort 2 (n=14)	Cohort 3 (n=21)
Median age	**62(19-88)**	**69 (44-78)**	**69 (44-78)**	**57 (19-76)**
Male, n (%)	**27 (51%)**	**9 (50%)**	**7 (50%)**	**11 (52%)**
Histology, n (%)				
Peripheral T-cell Lymphoma	**46 (87)**	**18 (100)**	**12 (86)**	**16 (76)**
PTCL, NOS	12 (23)	2 (11)	5 (36)	5 (24)
AITL/PTCL-TFH	9 (17)	2 (11)	5 (36)	2 (9.5)
T-PLL	8 (15)	7 (39)	1 (6)	
T-LGL	5 (9)	2 (11)		3 (14)
ALCL	4 (8)	2 (11)		2 (9.5)
ATLL	3 (6)			3 (14)
HSTCL	2 (4)	2 (11)		
G/D-TCL	1 (2)			1 (5)
SPTCL	1 (2)		1 (6)	
MEITL	1 (2)	1 (6)		
Cutaneous T-cell Lymphoma	**7 (13)**		**2 (14)**	**5 (24)**

Table 2. Response by cohort

Response by cohort	n=48 (evaluable)	Cohort 1 (n=18)	Cohort 2 (n=13)	Cohort 3 (n=17)
Complete response	3 (6%)	1 (6%)	2 (15%)	0
Partial Response	8 (17%)	4 (22%)	2 (15%)	2 (12%)
Stable disease > 6 months	6 (13%)	3 (17%)	2 (15%)	1 (6%)
Overall response rate (95% CI)	23% (12 to 37)	28% (10 to 55)	31% (9 to 61)	12% (1 to 36)
Clinical benefit rate (95% CI)	35% (22 to 51)	44% (22 to 69)	46% (19 to 75)	18% (4 to 43)

Table 3. Response by histology

Response by histology	n=48 (evaluable)	Overall response rate	Clinical benefit rate
PTCL, NOS	11	18%	18%
AITL/PTCL-TFH	9	33%	44%
T-PLL	8	25%	50%
CTCL	5	20%	20%
T-LGL	4	25%	75%
ALCL	3	33%	33%
ATLL	3	0%	0%
HSTCL	2	50%	50%
G/D-TCL	1	0%	0%
SPTCL	1	0%	100%
MEITL	1	0%	0%

Abbreviations: AITL (angioimmunoblastic T cell lymphoma);ALCL (anaplastic large cell lymphoma); ATLL (adult T cell lymphoma lymphoma/leukemia); CTCL (cutaneous T cell lymphoma); G/D TCL (primary cutaneous gamma/delta T-cell lymphoma); HSTCL (hepatosplenic T cell lymphoma); LGL (large granular lymphocyte leukemia); MEITL (monomorphic epitheoliotropic intestinal T cell lymphoma); MF (mycosis fungoides); PTCL-NOS (peripheral T cell lymphoma, not otherwise specified); PTCL-TFH (peripheral T cell lymphoma with T-follicular helper phenotype); SPTCL (subcutaneous panniculitis-like T cell lymphoma); T-PLL (T-cell prolymphocytic leukemia)

CD38 directed therapies for NK/T cell LYMPHOMA

- CD38 expression can be seen in NK/T cell lymphomas and may have prognostic significance- Wang et al 2015

- Daratumumab targets CD38 and induces ADCC
- 32 pts
- Median fu of 16.7 months- ORR 25%
- Median DOR 55 days
- Median PFS 53 days
- Response was no associated with CD38 expression
- EBV DNA reduction was seen more commonly in responders

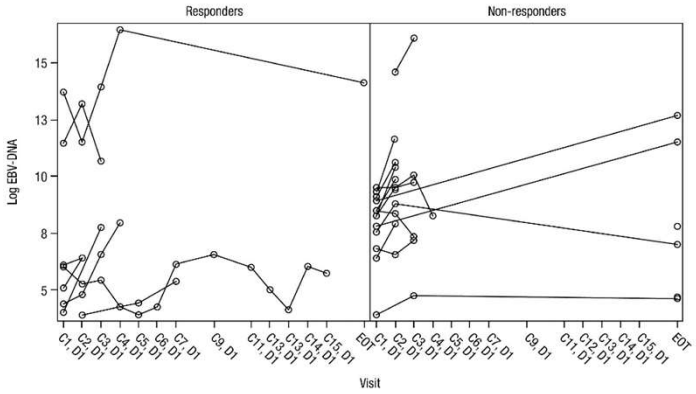
Table 1. Overall Best Response Based on Central Review

	DARA (n = 32)
ORR, n (%; 95% CI)	8 (25.0; 95% CI, 11.5-43.4)
Clinical benefit rate (CR + PR + SD), n (%; 95% CI)	13 (40.6; 95% CI, 23.7-59.4)
CR, n (%)	0
PR, n (%)	8 (25.0)
SD, n (%)	5 (15.6)
PD, n (%)	14 (43.8)
NE, n (%)	5 (15.6)

Table 2. Most Common (>20%) All-grade TEAEs

n (%)	DARA (n = 32)
Pyrexia	22 (69)
Headache	8 (25)
Chills	8 (25)
Increased alanine aminotransferase	8 (25)
Increased aspartate aminotransferase	8 (25)
Anemia	8 (25)
Thrombocytopenia	8 (25)
Fatigue	7 (22)
Leukopenia	7 (22)
Neutropenia	7 (22)

Figure: EBV-DNA levels.



DARA, daratumumab; ORR, objective response rate; CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; TEAE, treatment-emergent adverse event;C, cycle; D; day; EOT, end of treatment.

Huang et al: ASH 2019

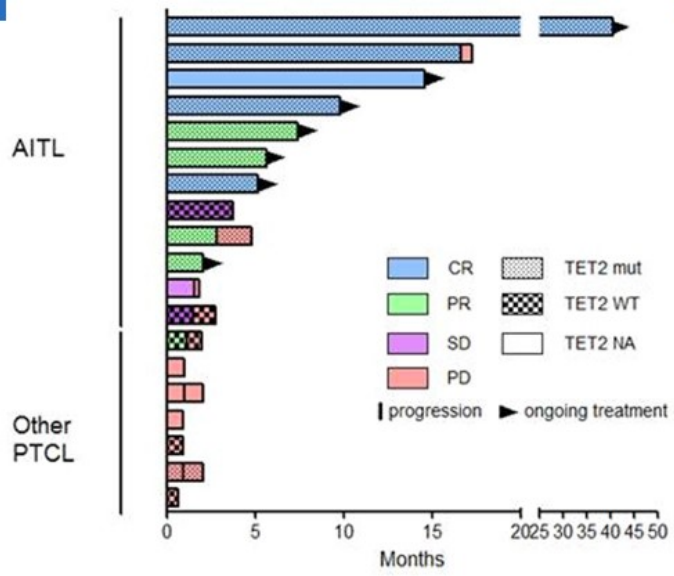
UPDATES IN EPIGENETIC THERAPY

Common epigenetic mutations in PTCL

	AITL	PTCL with TFH	PTCL-nos	Alk+ALCL	ALK-ve ALCL	ATLL
RHOAG17V	70%		25%			Present
TET2	33-82%		20-49%		50%	
IDH2 – R172	13-32%		7%			
DNMT3	23-38%		36		16	

	AITL	Other PTCL*	p
	12	7	
Median age, y	71 [39 – 85]	59 [32 – 83]	0,09
Male/Female	7/5	5/2	0,65
IPI at diagnosis			
- 1-2	3	1	1
- 3	3	2	
- 4-5	6	4	
PIT at diagnosis			
- <3	3	3	0,62
- 3-4	9	4	
Ann Arbor stage III-IV	12	7	1
LDH level > ULN	9	7	0,26
PS≥2	6	6	0,17
Previous ASCT	2	1	1
Median number of previous therapy	2	3	0,12
TET2 mutation	8/10 (80%)	1/4 (25%)	0,09
ORR	9 (75%)	1 (15%)	0,0198
CR	5 (41%)	0 (0%)	0,106

* ATLL: 3 patients, EATL: 1 patient, PTCL-NOS: 2 patients, transformed MF: 1 patient

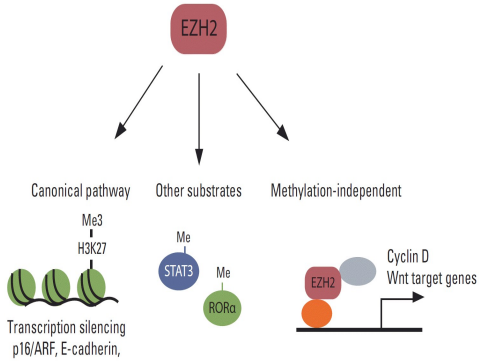


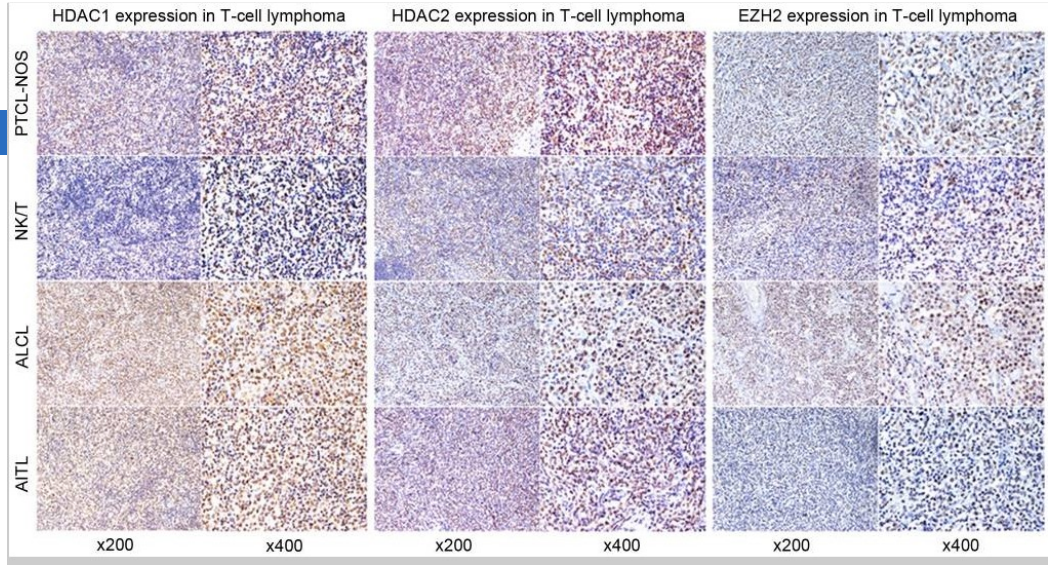
Results of 5-Azacytidine (5-AZA) treatment in 19 R/R PTCL patients-
Median number of cycles was 3
Sustained responses seen in AITL with TET2 mutations

Richard Delarue et al. Blood 2016;128:4164

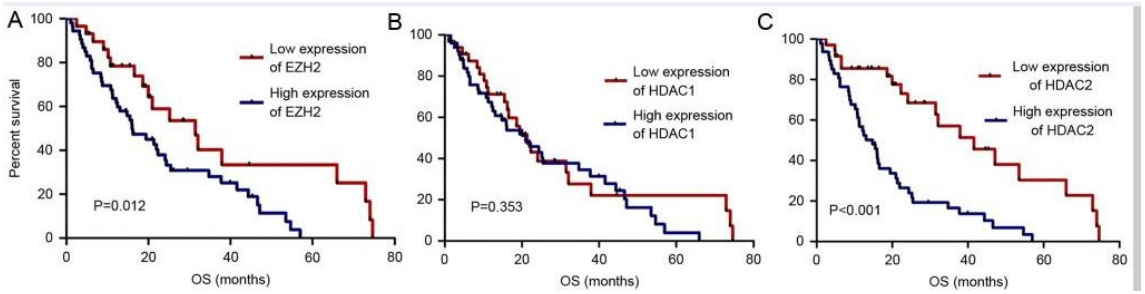
EZH2 TARGETING

EZH2 participates in histone methylation and transcriptional repression
Part of the PRC2 complex





Neoplasm	EZH2	HDAC1	HDAC2
PTCL	53/82	50/82	47/82
PTCL-NOS	29/43	24/43	25/43
AICL	6/10	5/10	6/10
NK/TCL	7/14	8/14	8/14
ALCL	11/15	13/15	8/15



High expression of EZH2 and HDAC2 associated with poor survival

Zhang et al: Oncol letter 2019

DOUBLETS AND TRIPLETS –TARGETED AGENTS

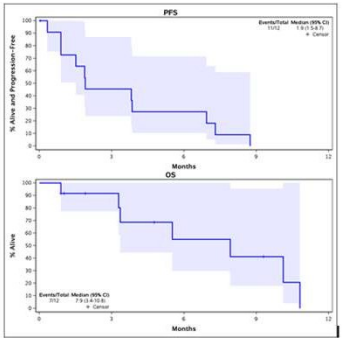
COMBINATION	N	RESULTS	MAIN TOXICITY/DLT
PRALATREXATE + ROMIDEPSIN-2018	14	ORR 71%, PFS 4.4 months	Mucositis, thrombocytopenia
DUVELISIB+ROMI-2017	29	ORR 50%- median TTR 51 days	
DUVELISIB + BORETEZOMIB- 2017		ORR 53%- median TTR 52 days	
ALISERTIB + ROMIDEPSIN-2017	3	ORR 25%	Hematologic, fatigue, infection
CHIDAMIDE+THALIDOMIDE+CYCLOPHOSPHAMIE- 2017	12	ORR 83%,CR41%, PR33%	Neutorpenia, thrombocytopenia
ROMIDEPSIN+ AZACITIDINE- 2019	31	ORR73%, CR55 %	Neutropenia, thrombocytopenia
LENALIDOMIDE+VORINOSTAT- 2014	8	ORR 25%, PFS 2.2 months , OS 6.7 months	hematologic
ROMIDEPSIN PLUS LENALIDOMIDE- 2017	21	ORR in PTCL 50%. Median EFS 15.5 weeks, Median OS not reached	Neutropenia, thrombocytopenia
ROMIDEPSIN+LENALIDOMIDE+CARFLIZOMAB- 2017	16	ORR 45%, CR 36%, PR 9%- median EFS 13.6 months	Hematologic, DVT, infection
PANOBINOSTAT + BORETEZOMIB-2015	23	ORR 43% median DOR 5.6 months	Thrombocytopenia, diarrhea, neuropathy
DURVALUMAB + ROMIDEPSIN+ 5 AZA	Ongoing		
DURVALUMAB + PRALATREXATE	Ongoing		

IMMUNE CHECK POINT INHIBITORS- NOT A BIG HIT AS SINGLE AGENTS

NIVOLUMAB

Table 1: Patient Characteristics	Total N=12
Age	
Median (Range), years	65 (35- 75)
Male Gender, n (%)	6 (50.0%)
Performance Score, n (%)	
0	7 (58.3%)
1	4 (33.3%)
2	1 (8.3%)
T-cell Lymphoma Subtype, n (%)	
Anaplastic Large Cell Lymphoma, ALK negative	1 (8.3%)
Angioimmunoblastic T-Cell Lymphoma	6 (50.0%)
Enteropathy-associated T-Cell Lymphoma	1 (8.3%)
Hepatosplenic Gamma Delta T-Cell Lymphoma	1 (8.3%)
Peripheral T-cell Lymphoma, not otherwise specified	3 (25.0%)
Ann Arbor Stage, n (%)	
3	1 (8.3%)
4	11 (91.7%)
Extranodal Involvement, n (%)	11 (91.7%)
Prior Autologous Stem Cell Transplant, n (%)	6 (50.0%)
Off Treatment Reason, n (%)	
Adverse Event: off treatment for pancreatitis	1 (8.3%)
Disease Progression during Active Treatment	10 (83.3%)
Other: patient's health deteriorated quickly due to the lymphoma	1 (8.3%)

Panel A: Progression Free Survival and Overall Survival



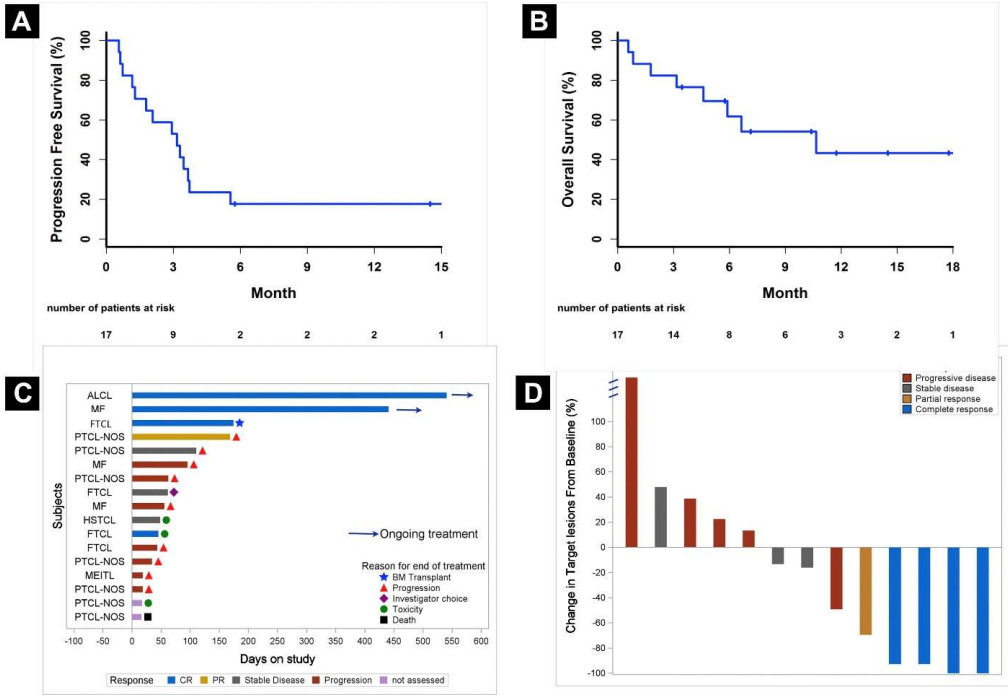
Hyper progression seen in 4 patients

ORR- - 33%

Median PFS 1.9 months

Bennani et al –ASH 2019

PEMBROLIZUMAB

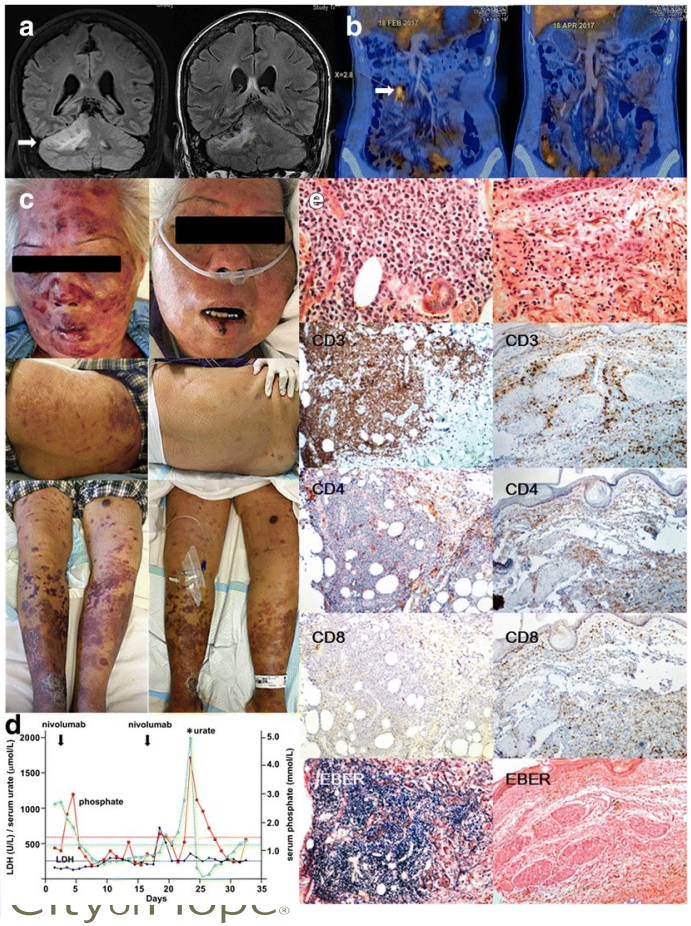


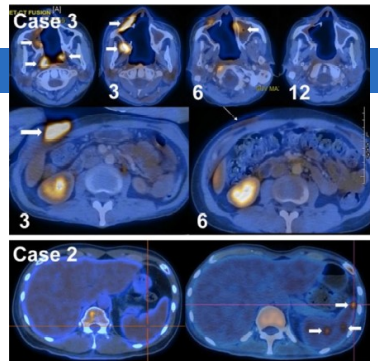
N=18, ORR 33%, 4/13- CR, median PFS 3.2 months, median OS 10.6 months

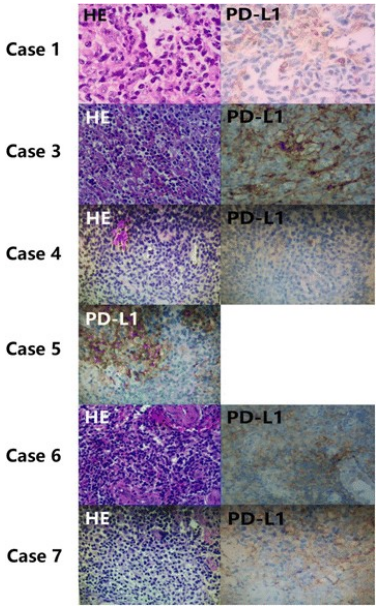
Barta et al- Clin lymphoma leukemia 2019

MAJOR TURNING POINT IN NK/T-CELL LYMPHOMAS

- High expression of PD1 seen in NK/T-cell lymphomas driven by EBV
- High response rates to PD1 blockade in RR disease- Disappearance of EBV from responding tumors
- Treatment was safe even in post allogenic transplant patients







Kwong, et al. 2017 Blood.

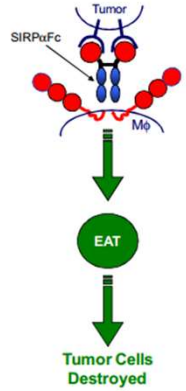
IMMUNE CHECKPOINT INHIBITORS COMBINATION WITH CHEMOTHERAPY OR OTHER AGENTS FOR PTCL

- Pembrolizumab + Romidepsin- ongoing – ORR 44% in 15 evaluable patients, 2 patients had hyperprogression – Iyer et al: ASH 2019
- Pembrolizumab + Pralatrexate- phase 1 started at COH. 3 patients enrolled – 1 CR, no POD
- Nivolumab+EPOCH- upfront therapy- just started
- Pembrolizumab Plus Copanlisib
- Ongoing trials for NK T cell lymphoma with single agent PD1 inhibitors

ENROLLING MACROPHAGES IN THE FIGHT AGAINST LYMPHOMA

Blocking the CD47 "Do Not Eat" Signal with SIRPαFc

CD47 on tumor cells delivers a stop signal to macrophages to suppress phagocytosis



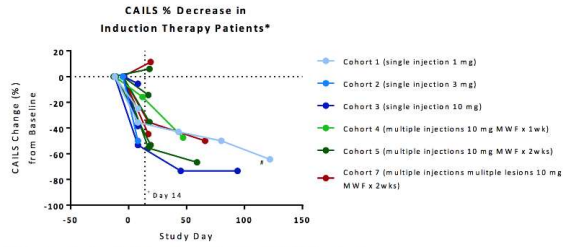
The CD47 stop signal is blocked by SIRPαFc, allowing macrophages to phagocytose tumor cells

SIRPαFc:

- Binds to CD47 with nanomolar affinity
- Disrupts the interaction of CD47 with cell surface SIRPα
- Enables macrophage-mediated killing of tumor cells *in vitro*
- Exhibits potent *in vivo* anti-leukemic activity in AML xenograft models
- Is in pre-clinical development as a therapy for AML

CD47 Blockade by Hu5F9-G4 and Rituximab in Non-Hodgkin's Lymphoma

Ranjana Advani, M.D., Ian Flinn, M.D., Ph.D., Leslie Popplewell, M.D., Andres Forero, M.D., Nancy L. Bartlett, M.D., Nilanjan Ghosh, M.D., Ph.D., Justin Kline, M.D., Mark Roschewski, M.D., Ann LaCasce, M.D., Graham P. Collins, M.D., Thu Tran, B.S., Judith Lynn, M.B.A., et al.



* Patients received maximally 2 weeks of study treatment (induction phase)
† Response assessments beyond day 14 are provided if patients have not progressed or continued onto another therapy
# The first patient treated obtained a CR of the injected lesion that is ongoing after 52+ weeks

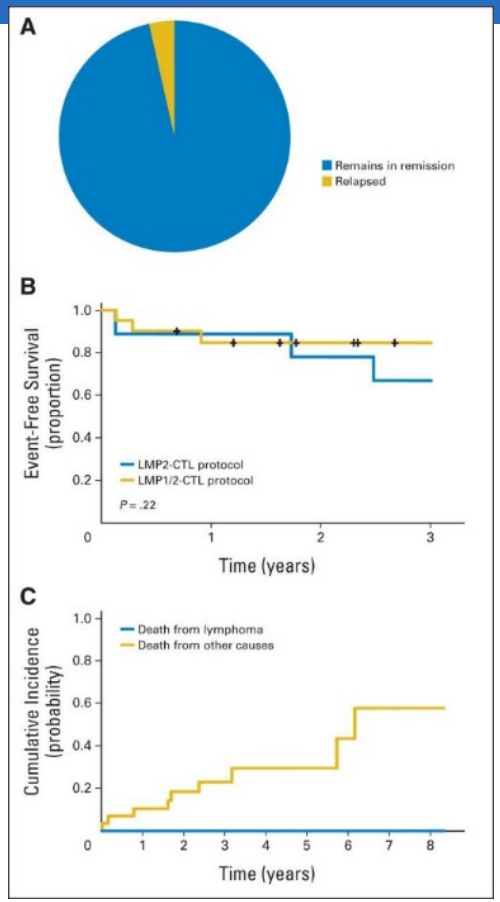
Intratumoral injection

Novel approaches

- Phase II Study to Assess AFM13 in Patients With R/R CD30-positive T-cell Lymphoma or Transformed Mycosis Fungoides (REDIRECT)- CD30/CD16A
- ADC-301- a Novel Pyrrolobenzodiazepine-Based CD25-Targeting Antibody Drug Conjugate, in a Phase 1 Study of Relapsed/Refractory Non-Hodgkin Lymphoma Shows Activity in T-Cell Lymphoma- ORR 50% in the phase 1 study
- CAR-T cell – allo CAR-T targeting CD 70 – first patient has been treated
- CAR-T targeting CD 30 – trials in progress

TARGETING EBV FOR THE TREATMENT OF NK/T CELL LYMPHOMAS

- Autologous Cytotoxic T cells targeting EBV viral latent proteins
- Expansion of LMP- cytotoxic TL using autologous dendritic cells
- 50 patients received these cells including 11 NK/T
- 39 (9/11) achieved and maintained remission
- Phase II study is ongoing



Bollard et al: J Clin Oncol 2013

Thank You