6th POSTGRADUATE LYMPHOMA CONFERENCE - Rome 2022

T cell Lymphoma
Time for targeted therapy?

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Stanford MEDICINE

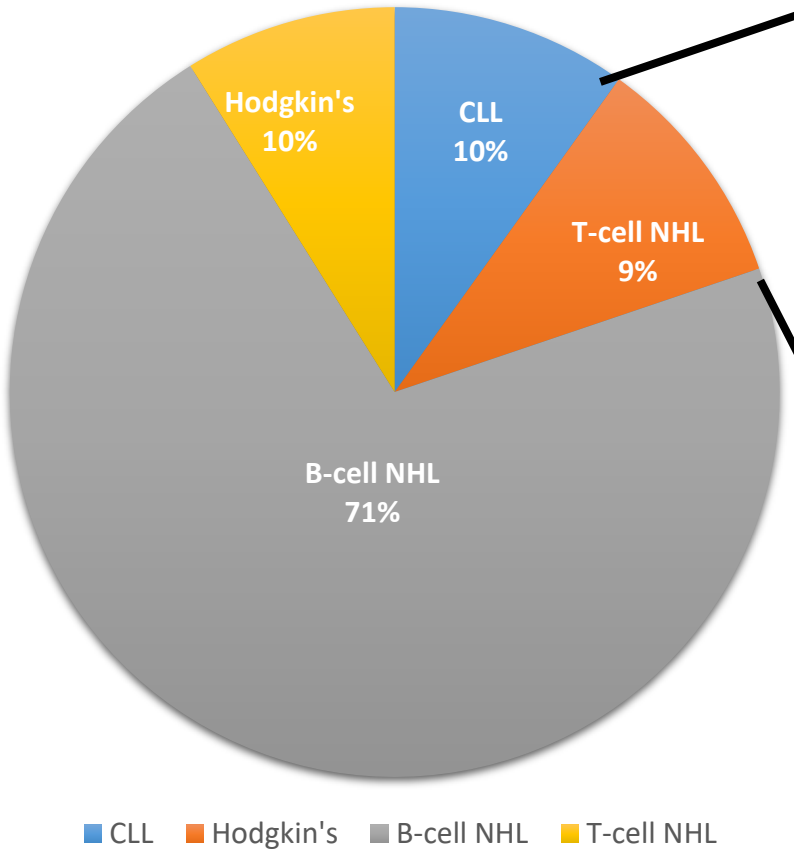
Disclosures

- Research Funding: Merck, Seattle Genetics, ADC therapeutics, Gilead, Merck, Cyteir, Regeneron, Daiichi

- SAB: Merck, BMS, Incyte, ADC therapeutics, Genentech/Roche, Epizyme, Incyte, BMS, Gilead, Beigene

- DSMC: Genentech/Roche, Sanofi

T-cell Lymphomas
complex heterogeneous group of lymphomas

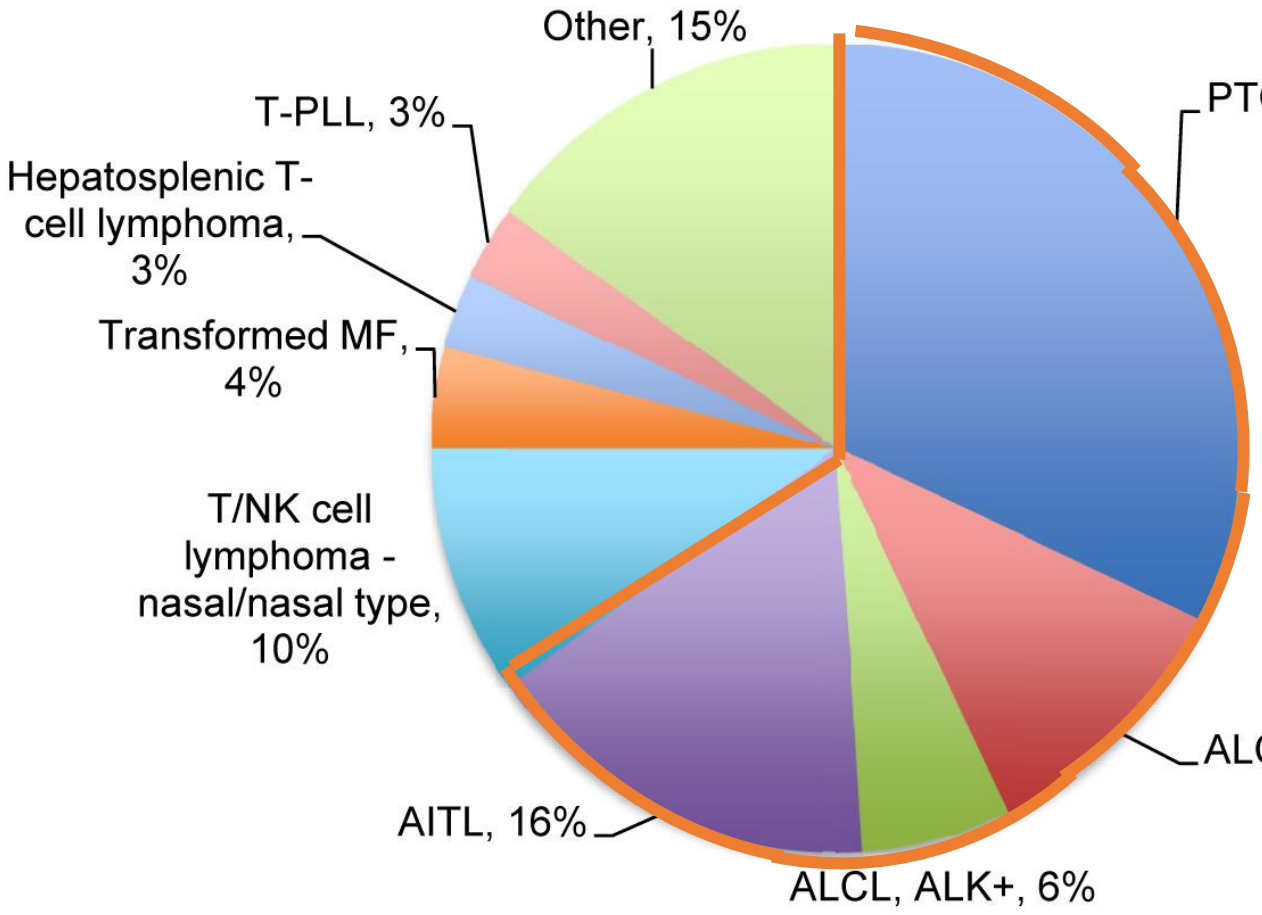


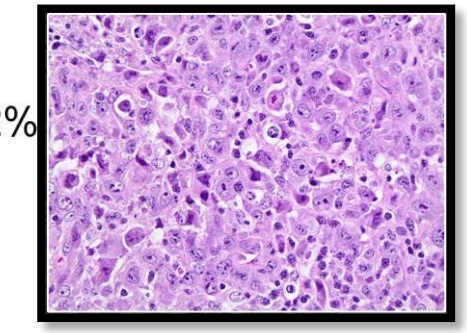
Adapted from Harrison's Internal Medicine 2017

T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV-positive T-cell lymphoma of childhood
Chronic active EBV infection of T- and NK-cell type, systemic form
Hydroa vacciniforme-like lymphoproliferative disorder
Severe mosquito bite allergy
Adult T-cell leukemia/lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma
Intestinal T-cell lymphoma, NOS
Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
Primary cutaneous acral CD8+ T-cell lymphoma
Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder
Peripheral T-cell lymphoma, not otherwise specified
Angioimmunoblastic T-cell lymphoma
Follicular T-cell lymphoma
Nodal peripheral T-cell lymphoma with T_{FH} phenotype
Anaplastic large cell lymphoma, ALK-positive
Anaplastic large cell lymphoma, ALK-negative
Breast-implant associated anaplastic large cell lymphoma.

Courtesy Dr Neha Shah

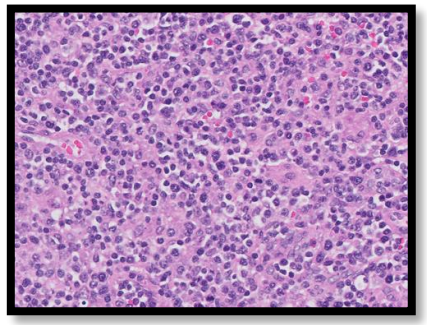
Different Histologies Immunophenotypically Different





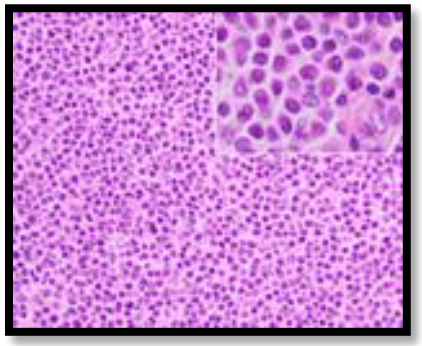
ALCL

- CD30 positive
- ALK+ or ALK-
- Large anaplastic cells



AITL/Nodal PTCL with TFH features/Follicular T-cell lymphoma

- 2 of the following:
  - BCL6
  - CD10
  - PD1
  - CXCL13
  - ICOS



PTCL NOS

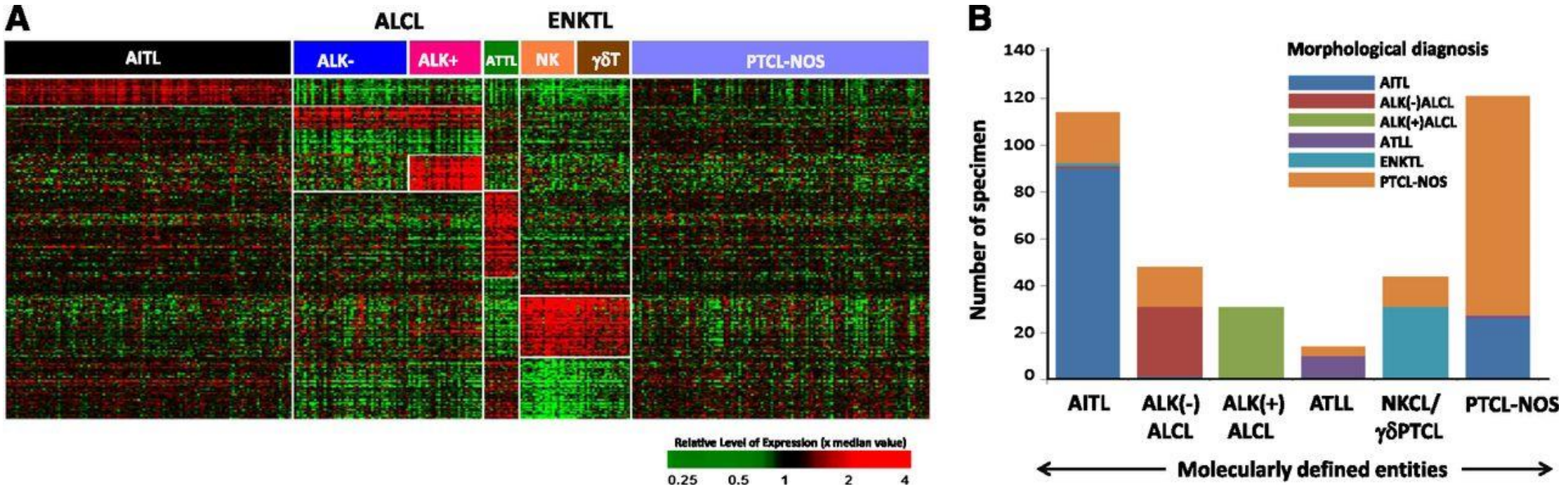
- Grab bag term

Hsi et al. Clin Lymph Myel Leukemia 2017; Amandor et al Blood 2019

Courtesy Dr Neha Shah

Gene Expression Signatures Characterize Disease Biology

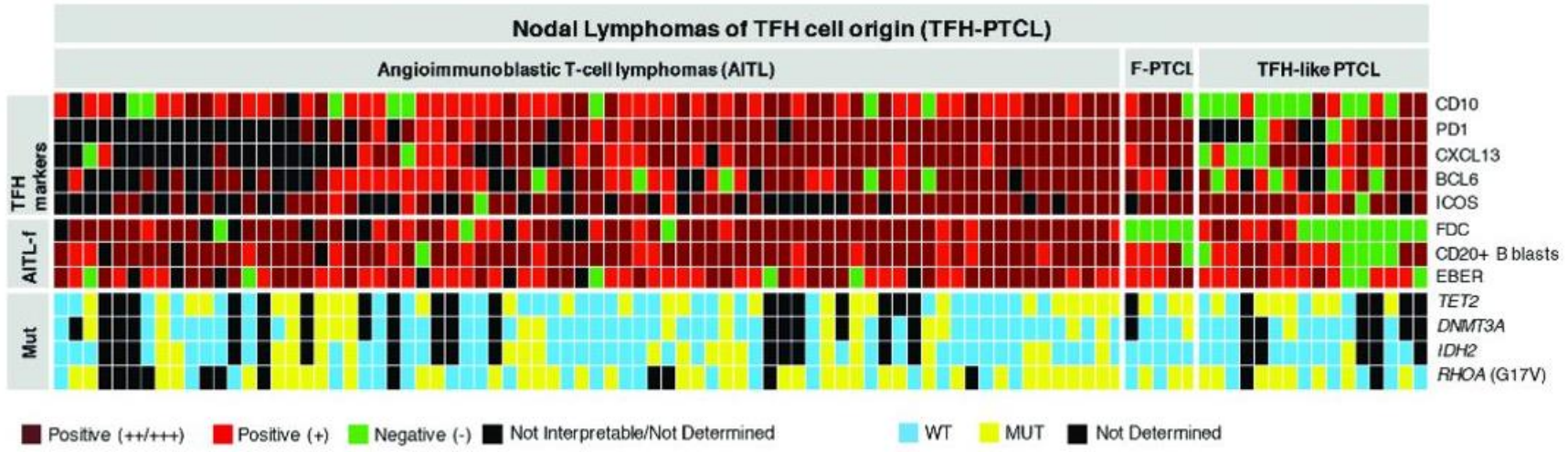
- Gene expression profiles of 372 patients show subtypes have distinct profiles



Heavican TB et al. Blood. 2019

Mutational Profile in Angioimmunoblastic TCL

- AITL contains recurrent mutations
  - TET2: ~55-75%
  - RHOA: ~67%
  - IDH2: ~33%
  - DNMT~3A: 20%
- PTCL-NOS with TFH phenotype has similar immunohistochemical and genetic profiles

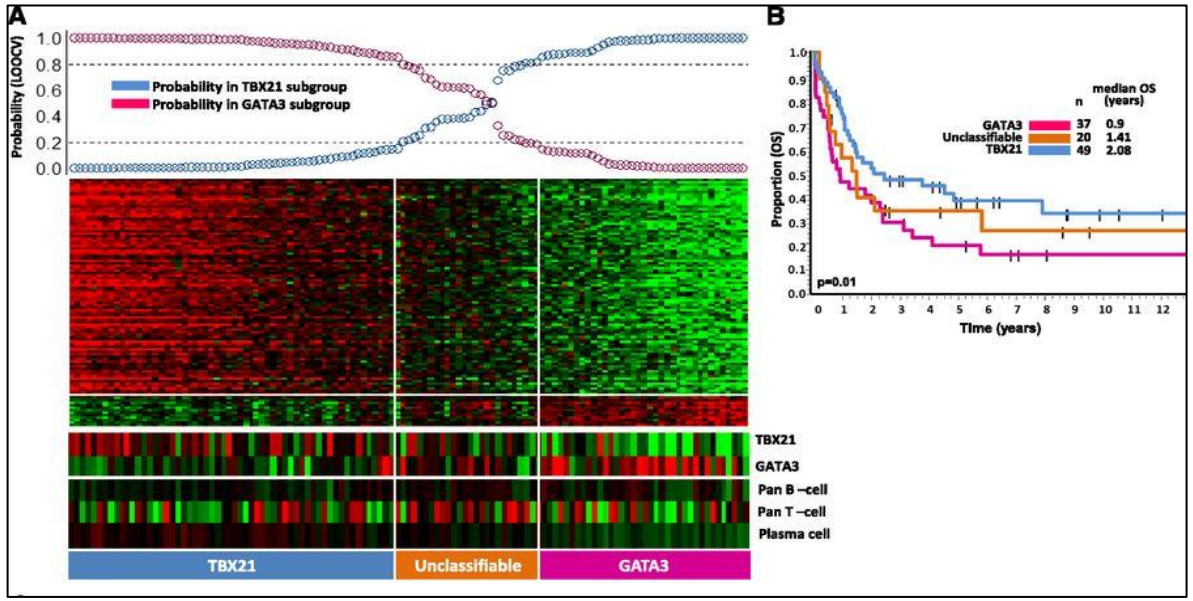


Dobay PM et al Haematologica. 2017

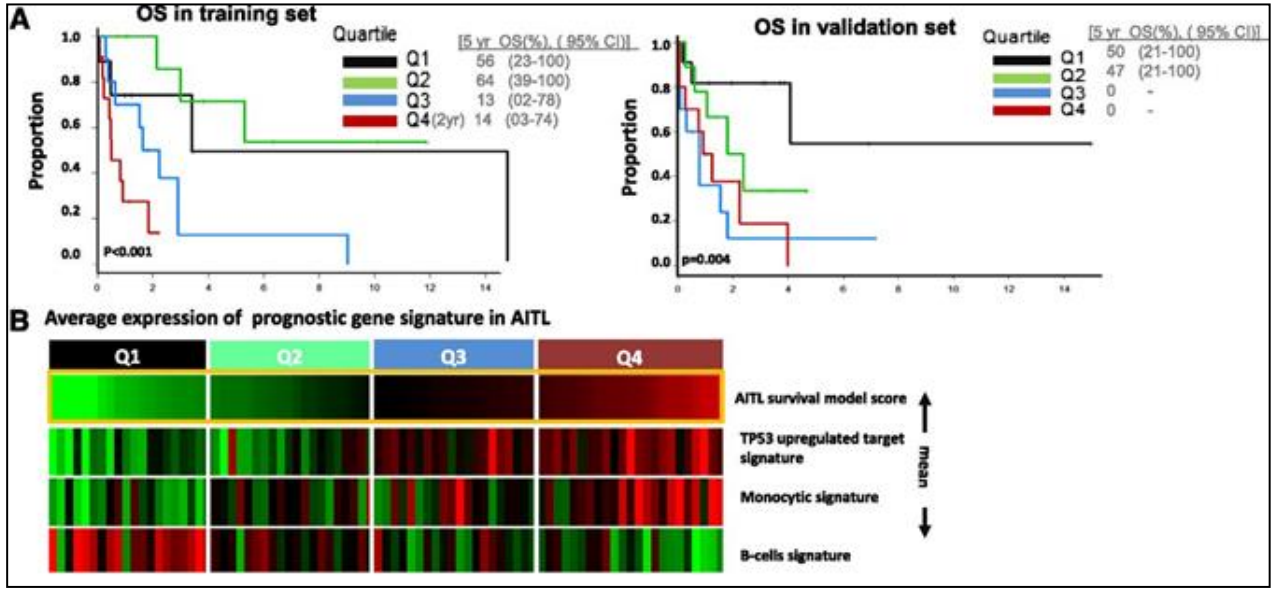
Gene Expression Signatures Can Risk Stratify Patients with PTCL and AITL

- GATA3 and TBX21 delineate distinct subgroups of PTCL-NOS
- A 34 gene expression signature can risk stratify AITL

PTCL-NOS

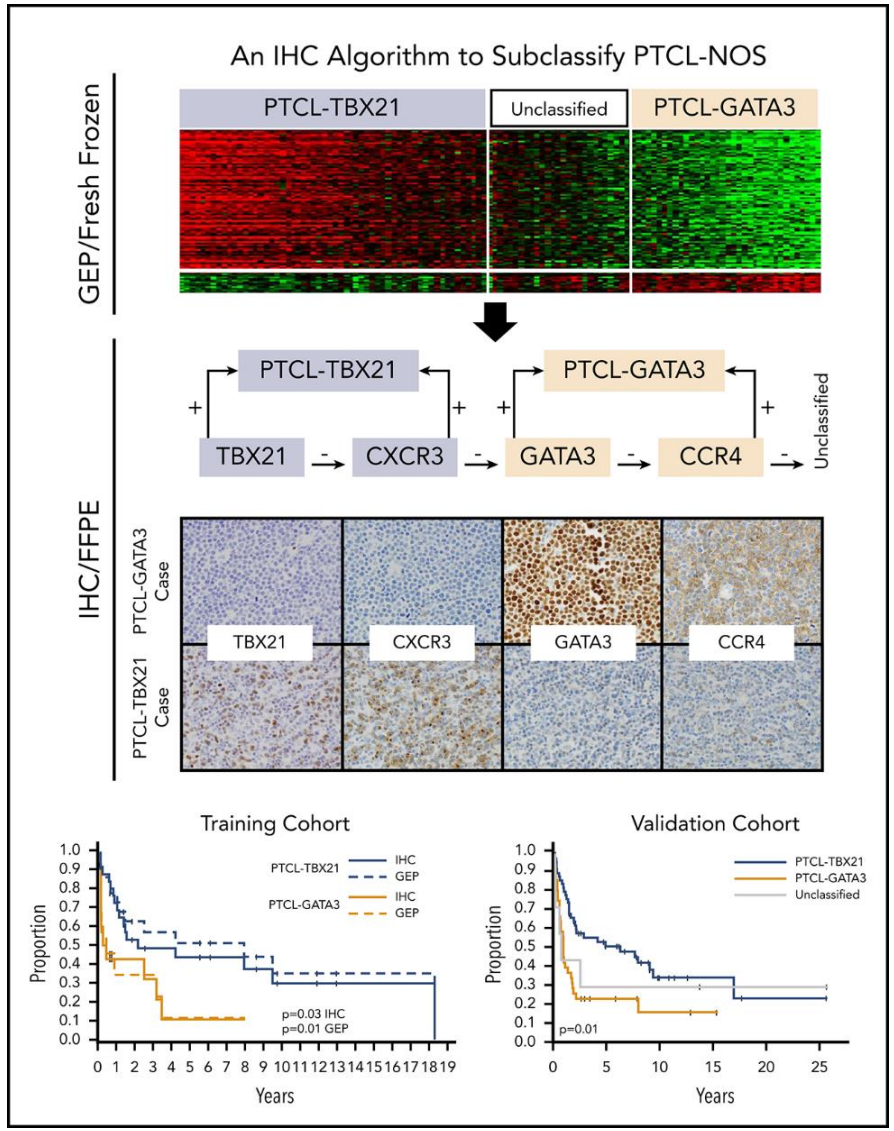


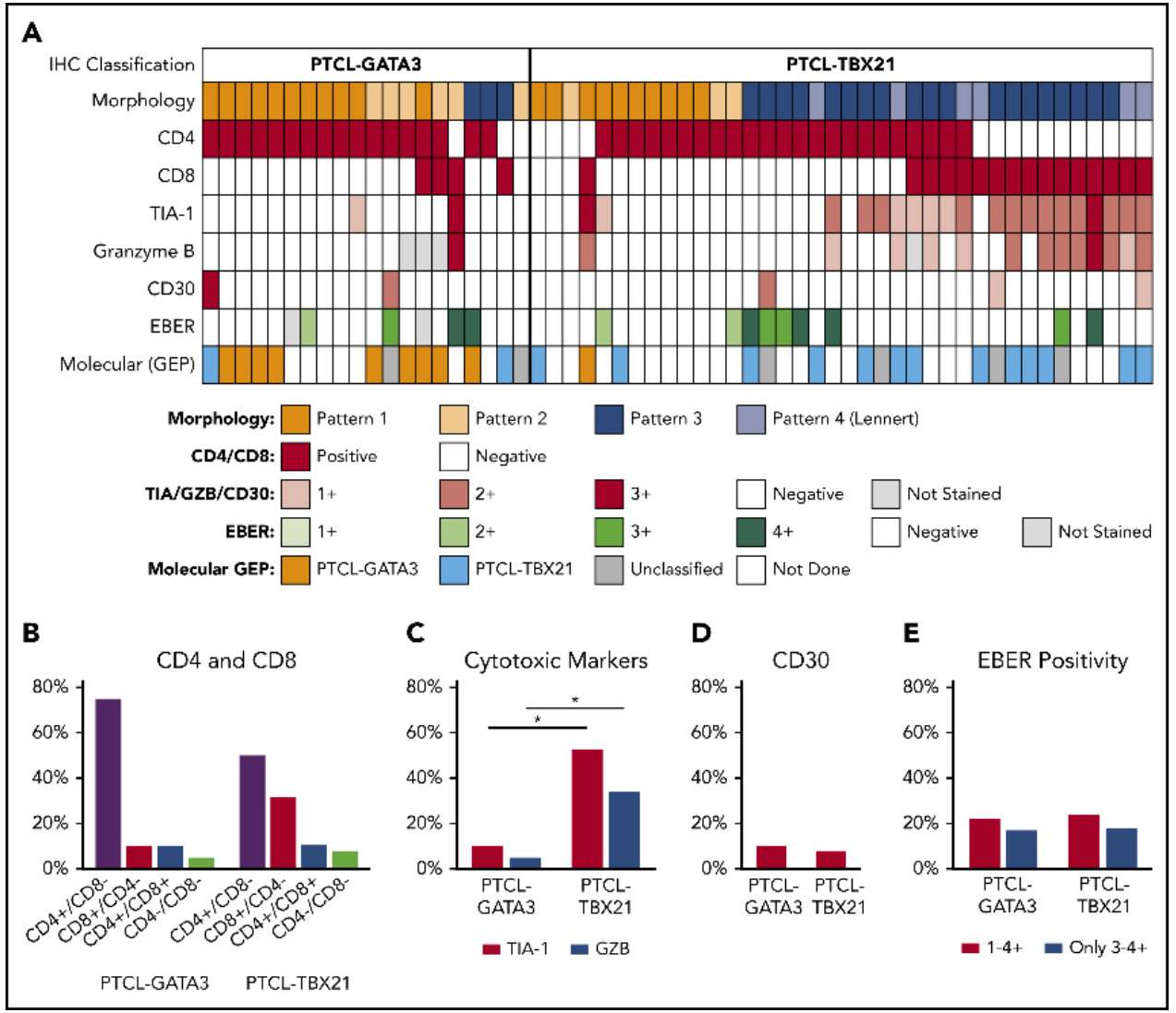
AITL



Heavican TB et al. Blood. 2019

Reproducing the molecular subclassification of PTCL–NOS by IHC

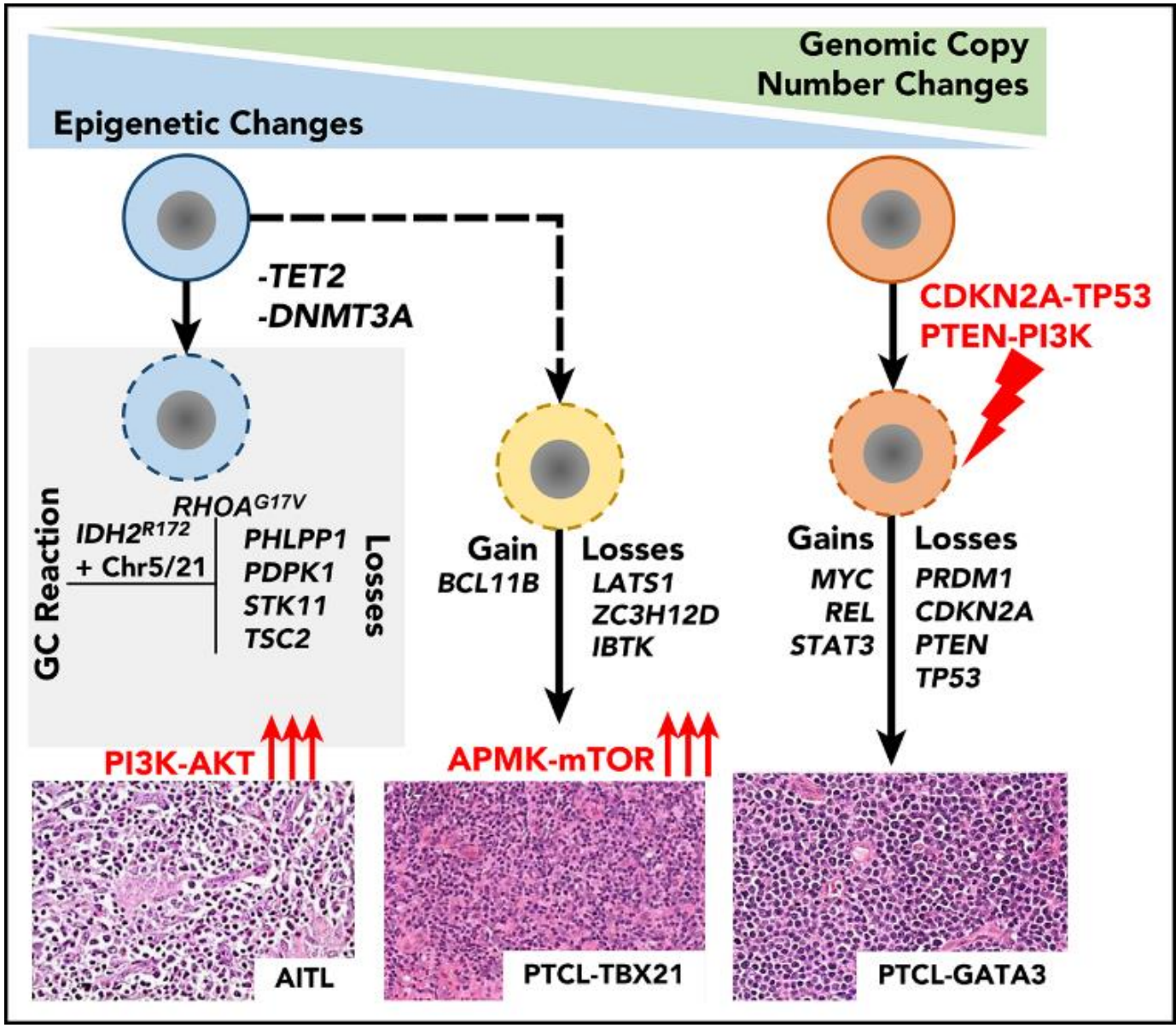




Amador et al Blood 2019

Genetic Drivers in Subtypes and Subgroups of PTCL

- Chr5 and chr21 gains co-occurred with *IDH2*^{R172} mutation in AITL,
- *IDH2* wild-type cases had deletions targeting PI3K–AKT–mTOR.
- PTCL-NOS molecular subgroups (PTCL-GATA3 and PTCL-TBX21) had distinct genetic aberrations
- *CDKN2A* loss showed prognostic significance

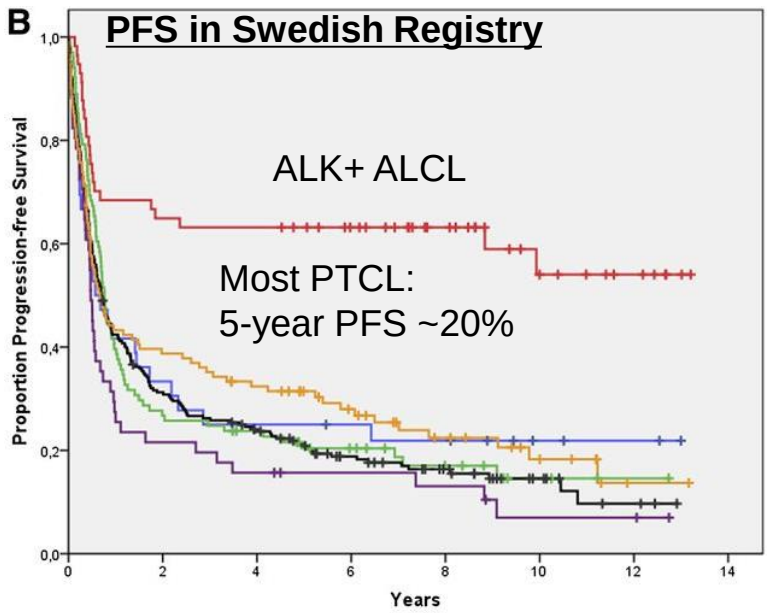


Heavican TB, et al. *Blood.* 2019

PTCL: Outcomes with CHOP/CHOEP therapy

Untreated PTCL
- PTCL, not otherwise specified
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell Lymphoma, ALK-

→ 4 cycles CHOP based chemotherapy → PET/CT with CR or PR → 2 more cycles CHOP based chemotherapy → Consolidate with autologous transplant



Outcomes By Intent to Consolidated with Auto-HSCT in Swedish Registry		
	Auto-SCT (n = 128)	No Auto-SCT (n = 124)
5 yr OS	48%	26%
5 yr PFS	41%	20%

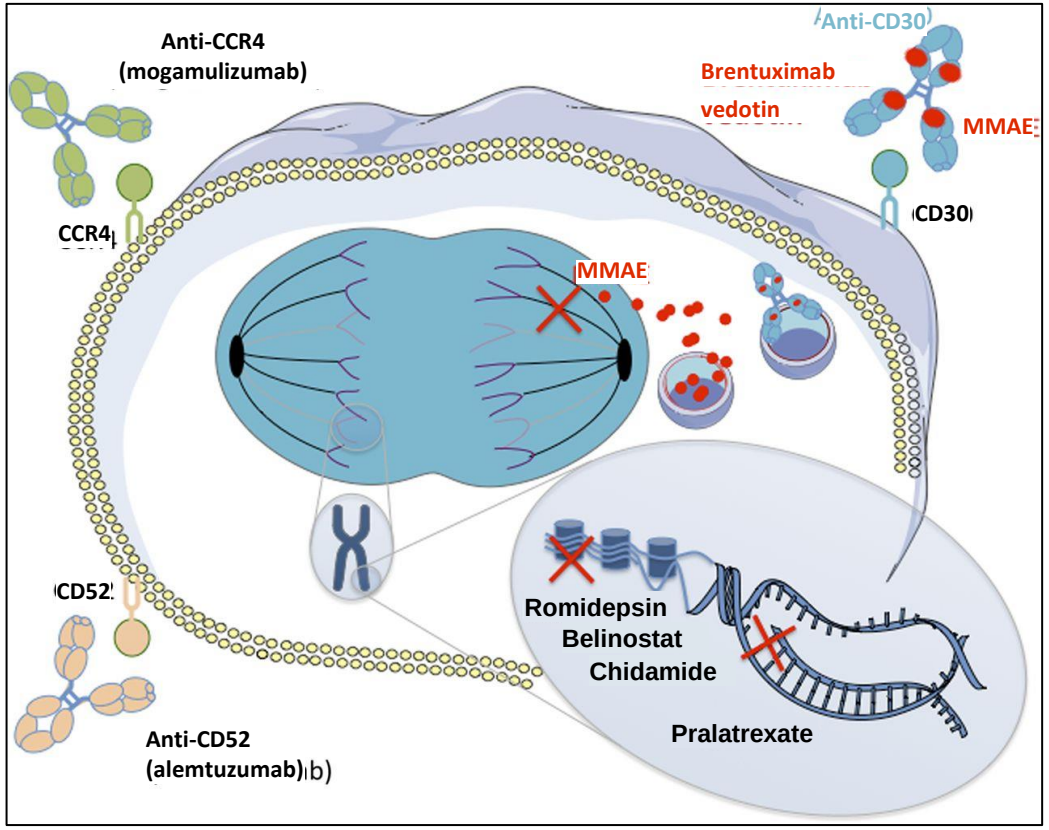
d'Amore et al. JCO 2012; Ellin et al Blood 2014, Mehta-Shah Clin Leuk Lymph Myel 2014

Courtesy Dr Neha Shah

Front Line therapy of PTCL

Time for targeted therapy?

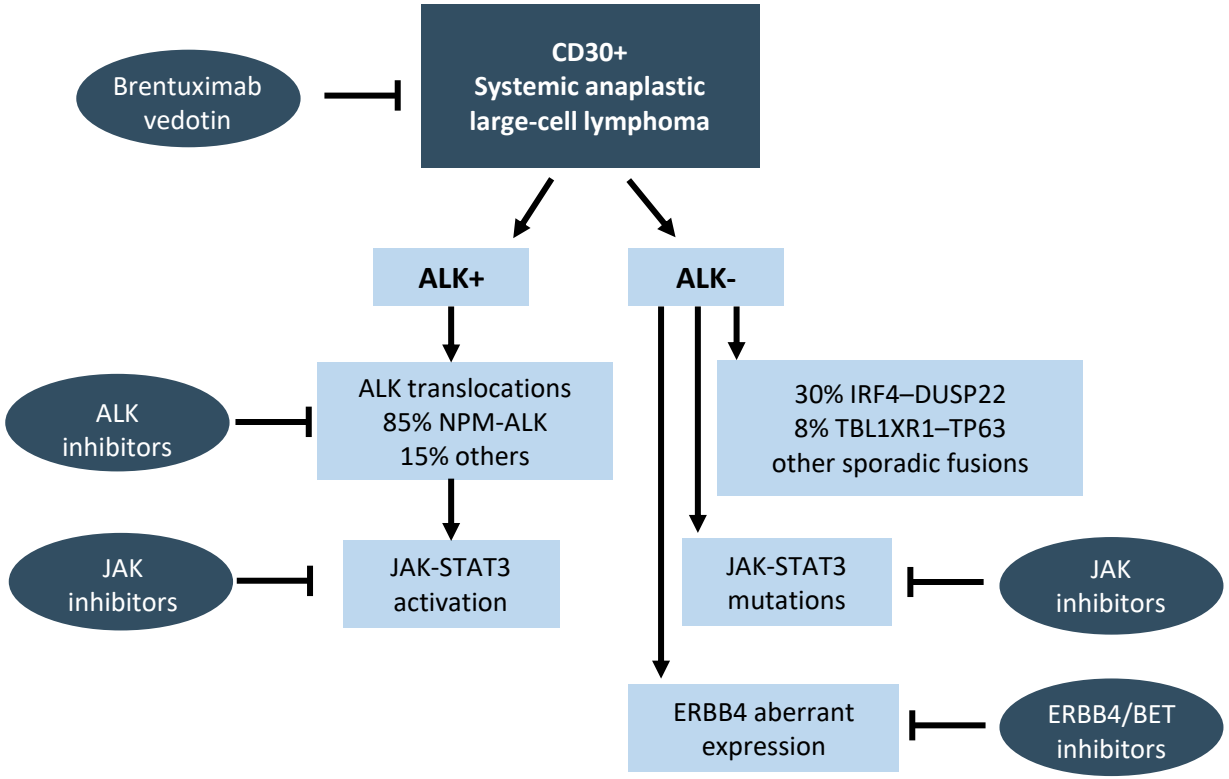
Adding novel agents to frontline setting
Approved drugs in relapsed/refractory PTCL



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)

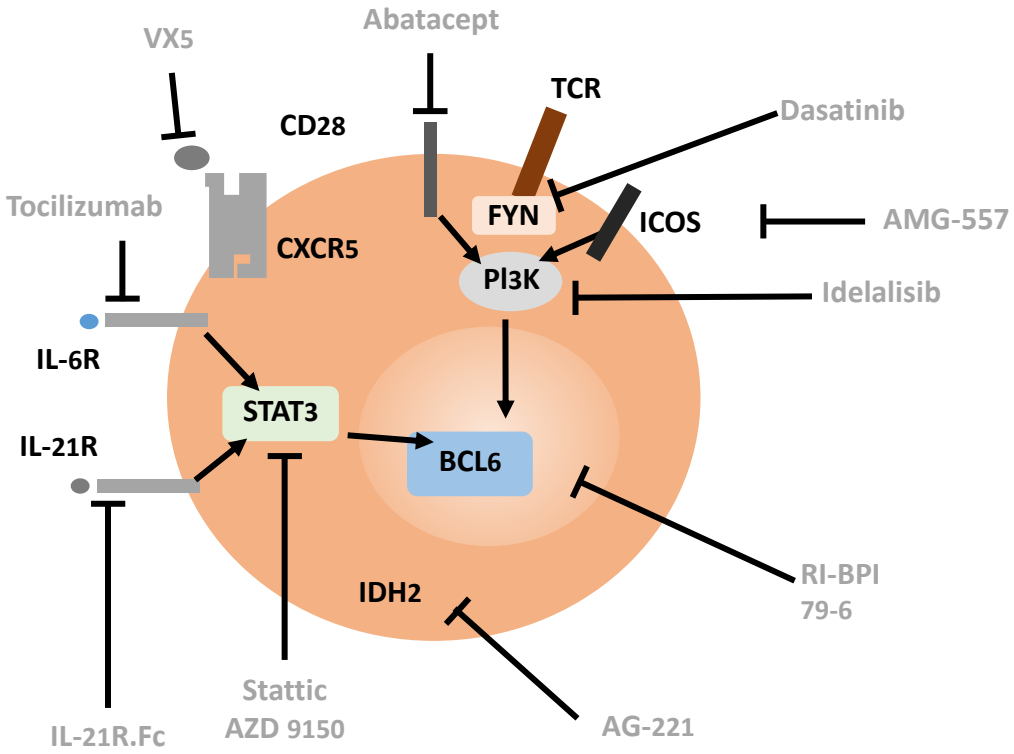
Potential targeted therapies

ALCL



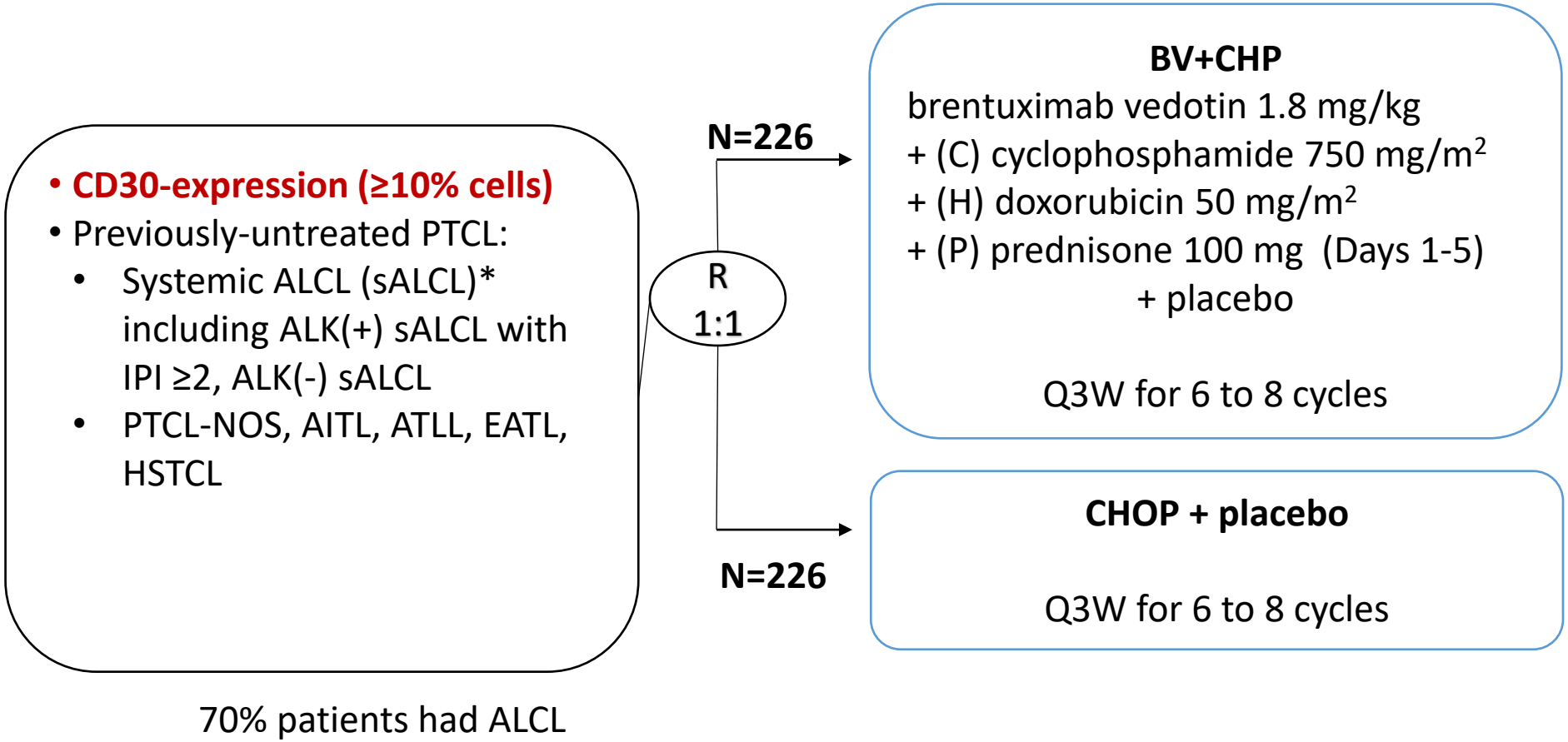
Mereu E, et al. Oncotarget 2017

AITL



Cortés JR etal Curr Opin Hematol 2016

ECHELON-2: BV-CHP vs CHOP



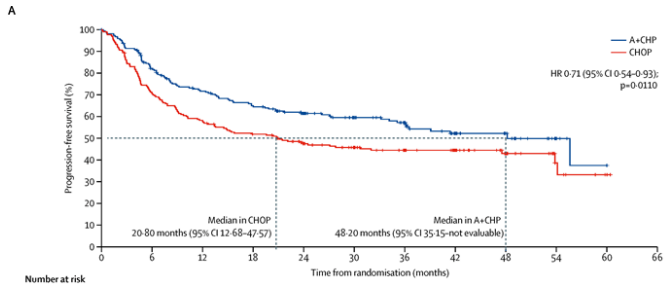
70% patients had ALCL

Horwitz Lancet 2019

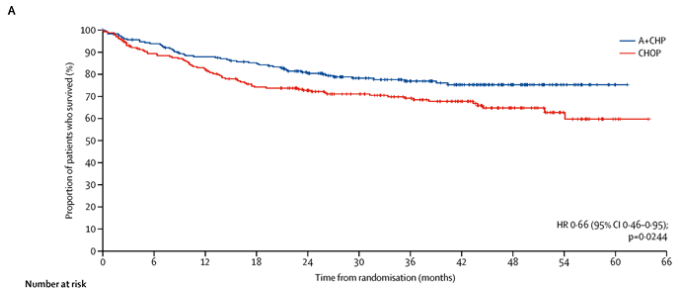
ECHELON-2: BV-CHP vs CHOP

- BV-CHP improves PFS (HR 0.71)
  - 3 year PFS: BV-CHP: 57% vs. CHOP: 44%
  - 34% reduction in risk of death
- Difference was most pronounced in ALCL
  - Less pronounced with AITL (HR 0.87) or PTCL (HR 0.83)
- BV approved in combination with chemotherapy for frontline use in CD30+ PTCL

Progression Free Survival



Overall Survival

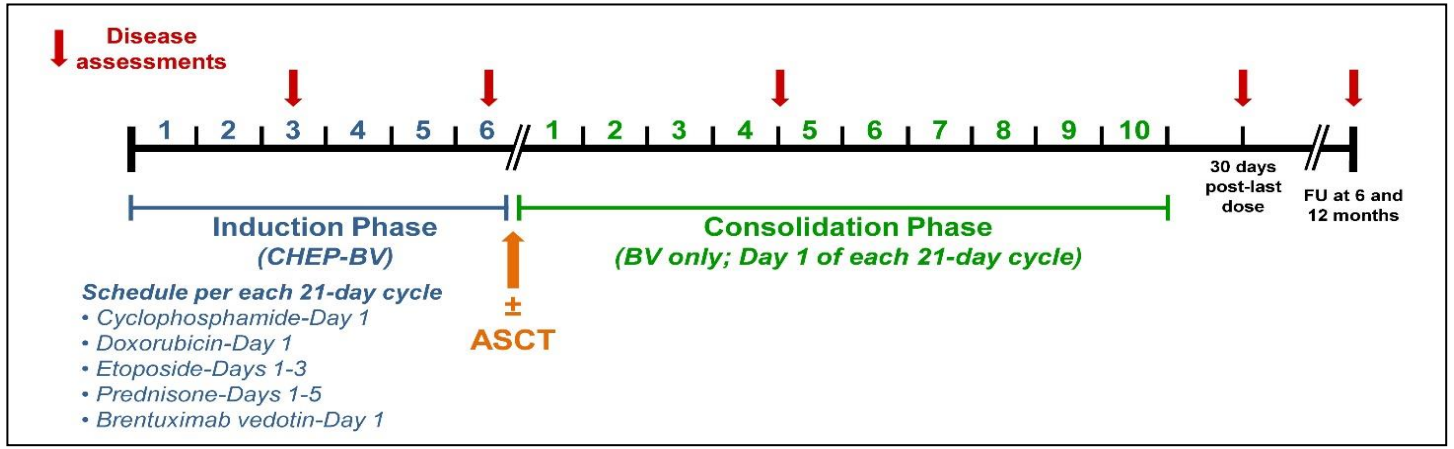


5-Year OS by Histology

	BV-CHP	CHOP
ALCL (n=316)	75.8%	68.7%
AITL (n=54)	62.5%	67.8%
PTCL-NOS (n=72)	46.2%	35.9%

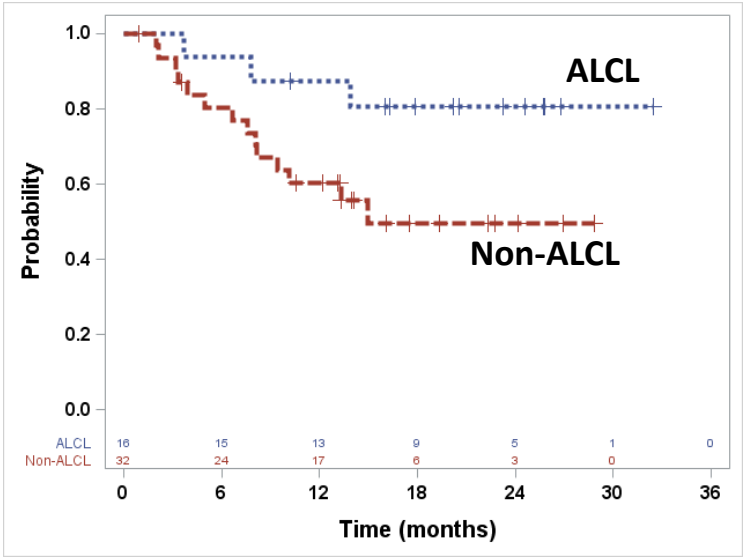
Horwitz Lancet 2019

Frontline Therapy with BV-CHEP + BV Maintenance (n=46)



Response assessment by investigators: 2014 Lugano classification

Response	ALCL (n=16)	Non-ALCL (n=30)	AITL (n=17)	PTCL NOS (n=11)	PTCL TFH (n=2)
ORR	15 (94%)	27 (90%)	16 (94%)	9 (82%)	2 (100%)
CR	15 (94%)	22 (73%)	14 (82%)	6 (55%)	2 (100%)
PR	0	5	2	3	0
SD	0	0	0	0	0
PD	1	3	1	2	0



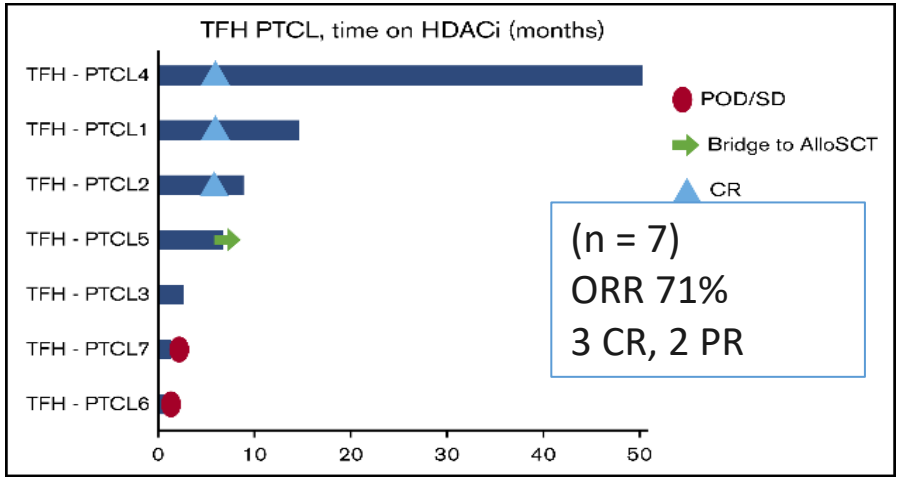
18mo PFS

- **ALCL 81%**
- **non-ALCL 49%**
  - **ALCL (n=16): ASCT 7 vs no 9**
  - **Non-ALCL (n=32): ASCT 17 vs no 15**

Herrera ASH 2021

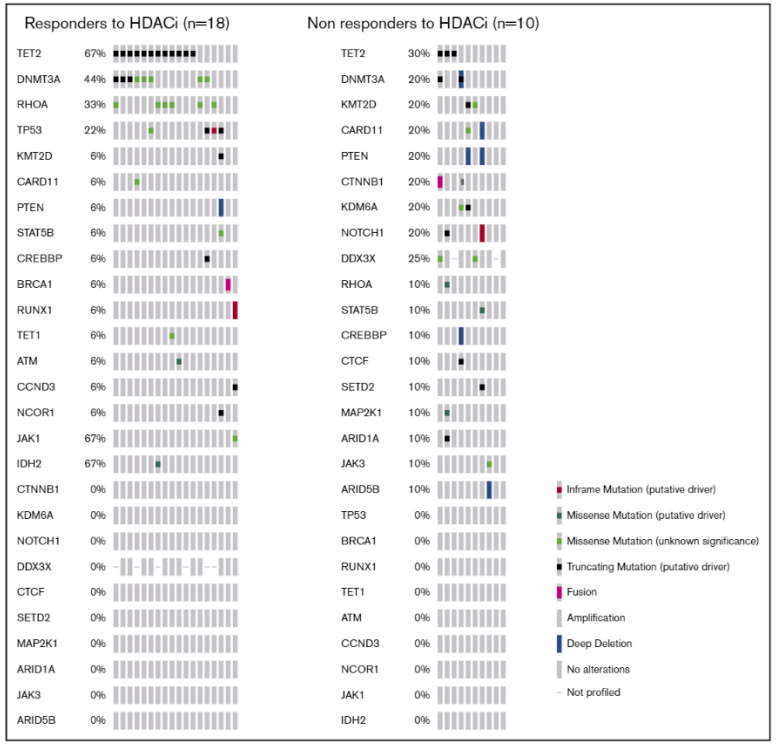
TFH Phenotype Predicts Response to HDAC Inhibitors in Relapsed/Refractory PTCL

Response	TFH (n = 76)		Non-TFH (n = 51)		
	ORR, n/total (%)	CR, n/total (%)	ORR, n/total (%)	CR, n/total (%)	*P**
Overall (n = 127)	43/76 (56.5)	22/76 (28.9)	15/51 (29.4)	10/51 (19.6)	.0035
Single agent (n = 97)	32/59 (54.2)	15/59 (25.4)	12/38 (31.5)	8/38 (21.0)	.0371
Combinations (n = 30)	11/18 (61.1)	7/18 (38.8)	3/12 (25.0)	2/12 (16.6)	.0717



Typical AITL/TFH mutations in *TET2*, and/or *DNMT3A*, and/or *RHOA* present in

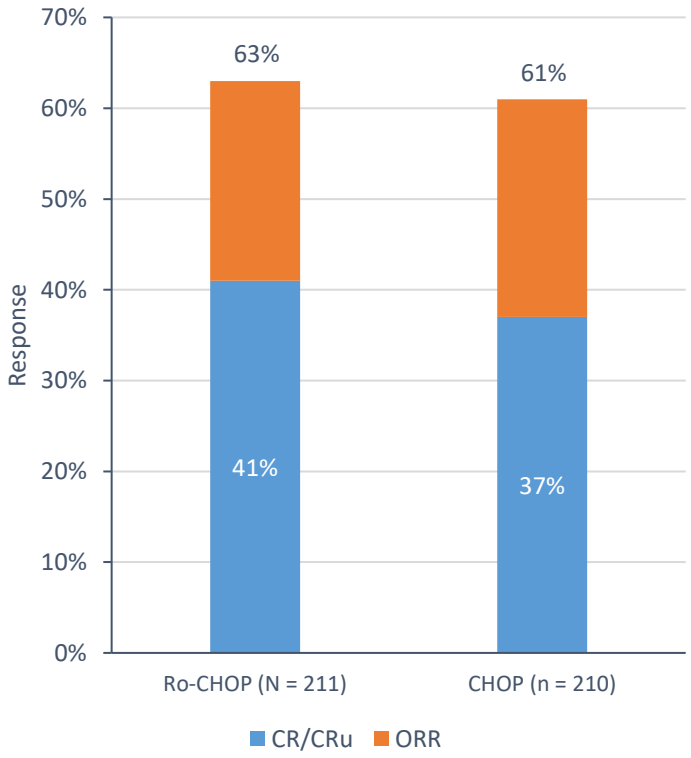
- Responders 15/18 (83%)
- Non-responders 4/10 (40% (*P* = .034)



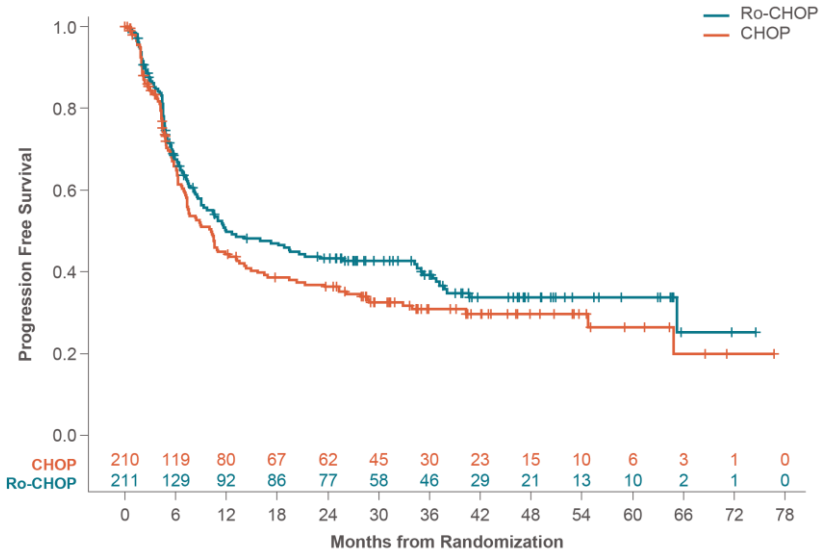
Ghione P, et al. Blood Adv. 2020

Romidepsin Plus CHOP vs CHOP in Previously Untreated PTCL
LYSA Randomized Phase III study

Ro-CHOP: Response at End of Treatment

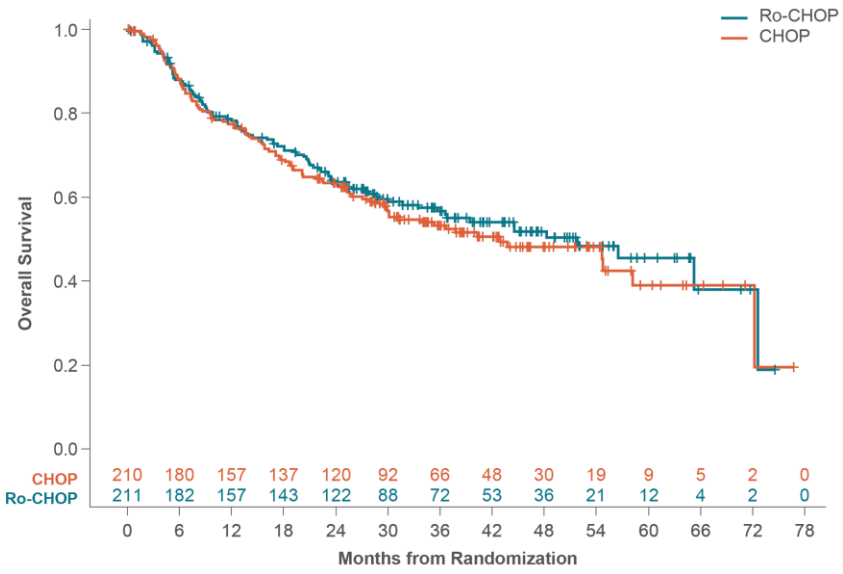


Ro-CHOP: PFS by independent RAC (ITT Population)*



	Ro-CHOP (n = 211)	CHOP (n = 210)
PFS, median (95% CI), mo	12.0 (9.0-25.8)	10.2 (7.4-13.2)
HR (95% CI)	0.81 (0.63-1.04)	
P value	0.096	

Ro-CHOP: OS (ITT Population)



	Ro-CHOP (n = 211)	CHOP (n = 210)
OS, median (95% CI), mo	51.8 (35.7-72.6)	42.9 (29.9-NR)
HR (95% CI)	0.90 (0.68-1.20)	
P value	0.477	

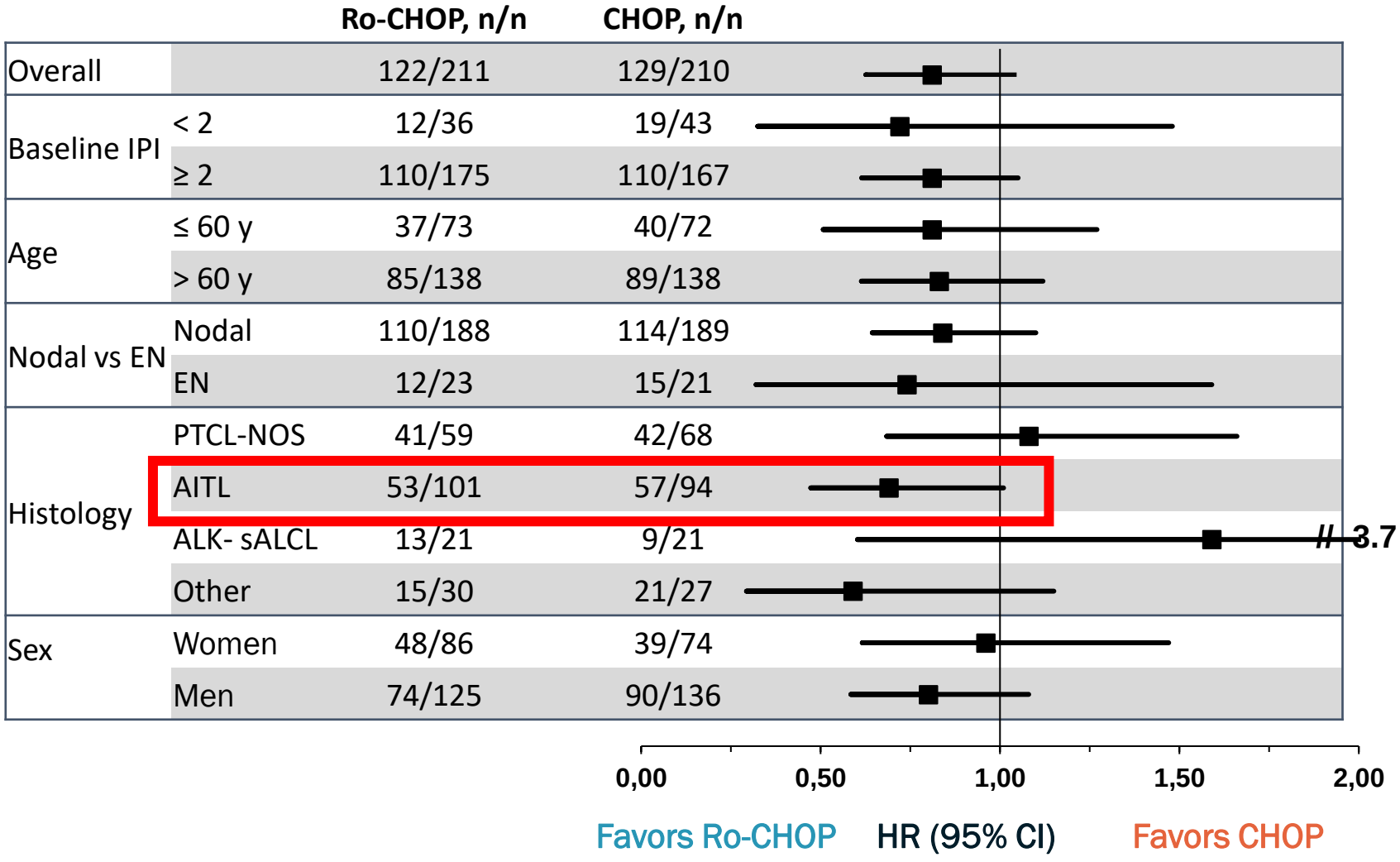
Bachy E, et al. ASH 2020. Abstract 39.

Ro-CHOP
Additional toxicity, Unselected patients

Dose Reductions and Interruptions

≥ 1 TEAE Dose Modification, n (%)	Ro-CHOP (n = 210)	CHOP (n = 208)
Romi red	77 (37)	NA
Romi interrupt	132 (63)	NA
Romi DC	17 (8)	NA
CHOP red	54 (26)	31 (15)
CHOP interrupt	75 (36)	42 (20)
Completed All 6 Cycles w/o Red or Inter, n (%)	**Ro-CHOP (n = 210)**	**CHOP (n = 208)**
Romi	62 (30)	NA
CHOP	112 (53)	125 (60)

Subgroup Analysis of PFS (ITT Population)



Bachy E, et al. ASH 2020. Abstract 39.

Phase 1b/2 Study of Chidamide + CHOP in PTCL

Table 1. Patient demographics and disease characteristics

Baseline characteristic, n (%)	30 (100)
Pathologic subtypes	
PTCL- NOS	12 (40)
AITL	8 (26.7)
ALK+ ALCL	4 (13.3)
ALK- ALCL	3 (10)
Other[1]	3 (10)
Age, median (range)	52.5 (42, 58)
Male	19 (63.3)
ECOG PS >0	12 (40)
Ann Arbor Stage III/IV	19 (63.3)
LDH elevated	8 (26.7)
B symptoms present	10 (33.3)
PIT risk group	
0- 1	29 (96.7)
2- 4	1 (3.3)

Table 2.Dose- limiting toxicities and patient allocation

Group	Total (n= 30)	Dose- escalation cohort (n= 15)	Expansion cohort (n= 15)	DLTs (n= 2)
20mg	9	6	3	1 pt, Gr 3 febrile neutropenia
25mg	9	3	6	
30mg	9	3	6	
35mg	3	3	0	1 pt, Gr 3 vascular access complication

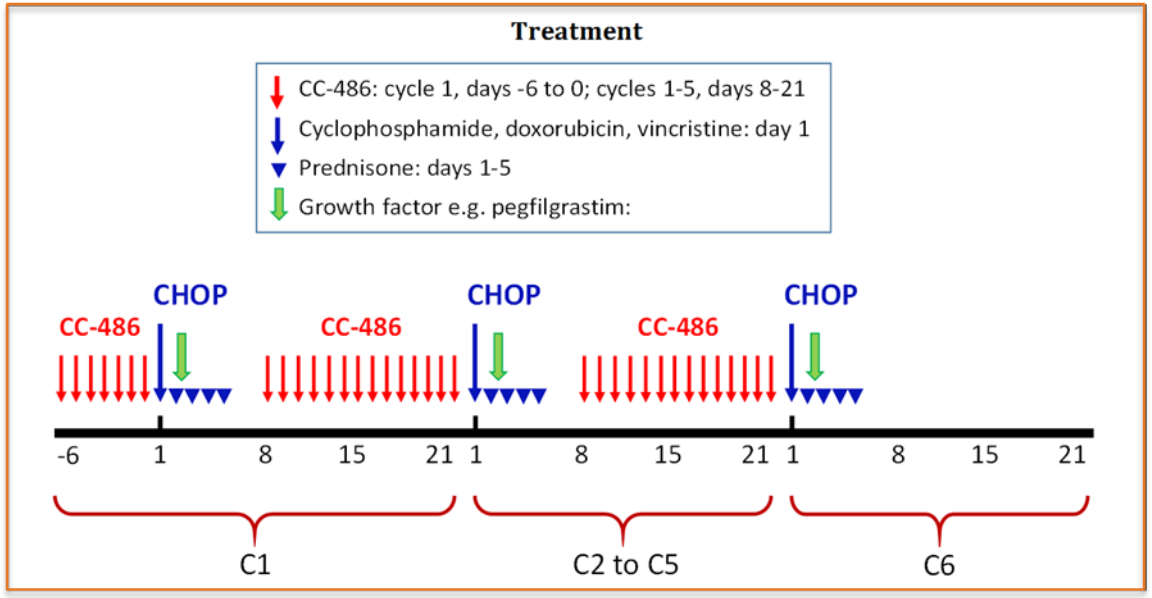
Table 3. Response evaluated at the end of combination treatment

	20mg (n= 9)	25mg (n= 9)	30mg (n= 9)	35mg (n= 3)	Total (n= 30)
Overall response	8 (100)	7 (77.8)	7 (77.8)	1 (50)	23 (82.1)
CR or CRu	4 (50)	4 (44.4)	5 (55.6)	0	13 (46.4)
PR	4 (50)	3 (33.3)	2 (22.2)	1 (50)	10 (35.7)
SD	0	1 (11.1)	0	0	1 (3.6)
PD	0	1 (11.1)	2 (22.2)	1 (50)	4 (14.3)
NA	1*	0	0	1**	2

Shi et al ASH 2020 # 2840

Epigenetic Targets
Oral Azacitidine (CC-486) Plus CHOP as Initial Treatment for PTCL

Phase 2 Study Design



- CC486 at 300 mg daily from day -6 to day 0 for cycle 1 priming, and on days 8-21 following cycles 1-5.
- Patients in CR/PR following 6 cycles of treatment have the option to proceed to consolidative HSCT.

Patient and Disease Characteristics

Clinical Characteristics	Number	Percentage
Number of patients	21	100%
Median age in year (range)	66 (22-77)	
Gender Male	13	62%
Female	8	38%
ECOG > 1	8	38%
Stage III-IV	19	90%
LDH Elevated	10	48%
Bone marrow involvement	7	33%
CD30 ≥ 5%	5	24%
PTCL subtypes		
PTCL-TFH	17	81%
PTCL-NOS	3	14%
ATLL	1	5%
IPI 0-2	12	57%
3-5	9	43%

Ruan J, et al. ASH 2021.

Oral Azacitidine (CC486) Plus CHOP
Efficacy and Safety

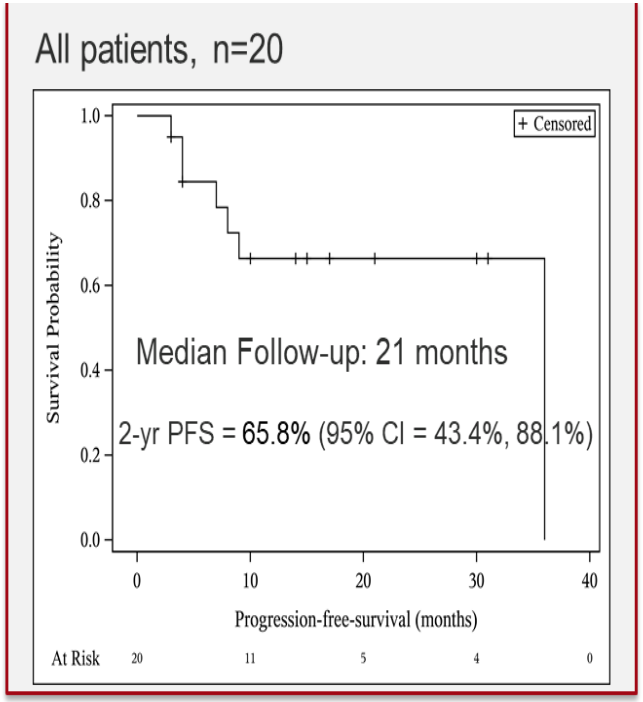
Objective Responses

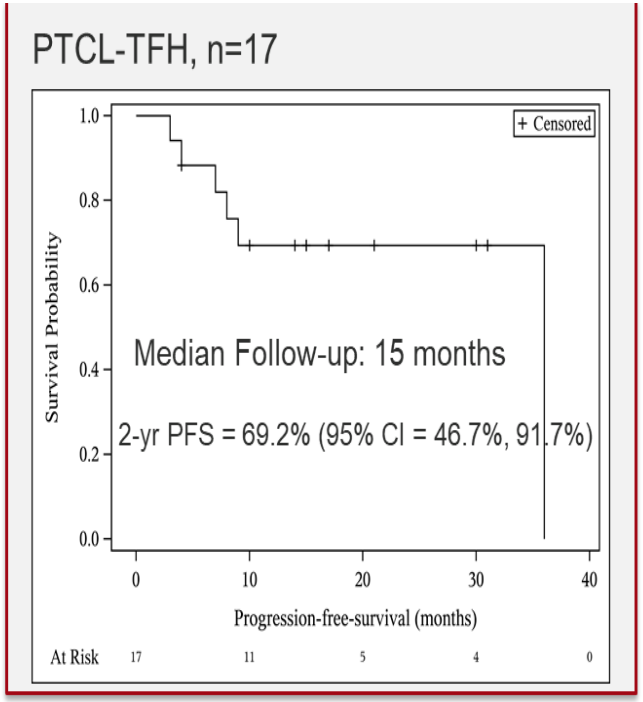
Response	Interim*			EOT*		
	No. Pt	Evaluable (n=20)	PTCL-TFH (n=17)	No. Pt	Evaluable (n=20)	PTCL-TFH (n=17)
ORR	17	85%	94%	15	75%	88%
CR	11	55%	59%	15	**75%**	**88%**
PR	6	30%	35%	0	0	0
SD	2	10%	0	1	5%	0
PD	1	5%	6%	2	10%	6%
Discontinuation	0	0	0	2	10%	6%
Median follow-up		15 months (range 9-23)				

"*": Interim – following 3 cycles of treatment; EOT following 6 cycles of treatment.
"#": Dicontinuation due to 1) disease progression; 2) strongyloides infection.

- **Grade 3-4 toxicities in > 10% :**
  - Neutropenia 71% (N =15)
  - Febrile Neutropenia 14% (N = 3)
  - Anemia 14% (N = 3)
  - Thrombocytopenia 10% (N = 2)
  - Fatigue 14% (N = 3)
  - Hyponatremia 14% (N = 3)

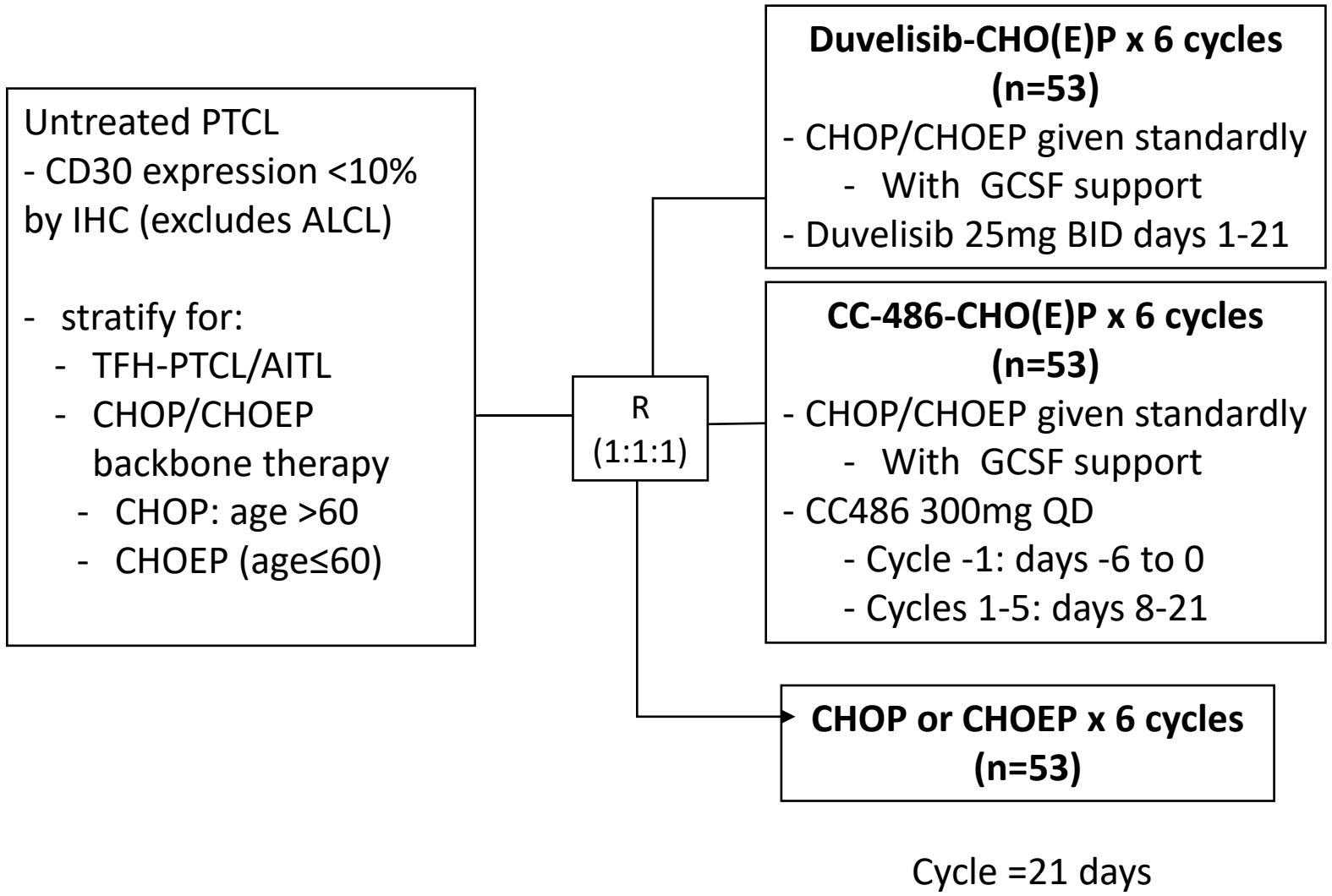
Progression-Free Survival





Ruan J, et al. ASH 2021.

A051902: A randomized phase II study of duvelisib or 5-azacitidine in addition to CHOP or CHOEP in comparison to CHOP/CHOEP



- Primary Objective:
  - To compare the PET CR rate of duvelisib or 5-azacitidine in combination with CHOP/CHOEP compared to CHOP/CHOEP
- Primary Endpoint:
  - 25% difference PET CR rate
- Correlative Studies:
  - Monitoring MRD
    - Alizadeh
  - Gene Expression Profiling and Custom Capture Sequencing
    - Dave
  - Patient Reported Outcomes
    - Thanarajasingam
  - PET/CT Evaluation
    - Schoder and Wright

NCT04803201

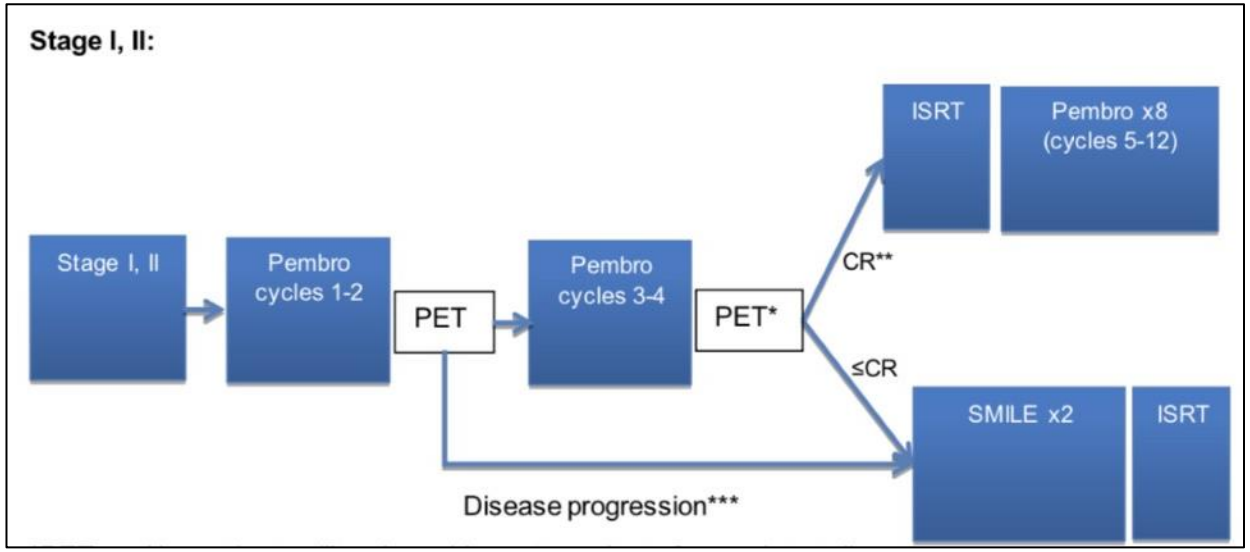
Checkpoint Inhibition in T-cell Lymphoma

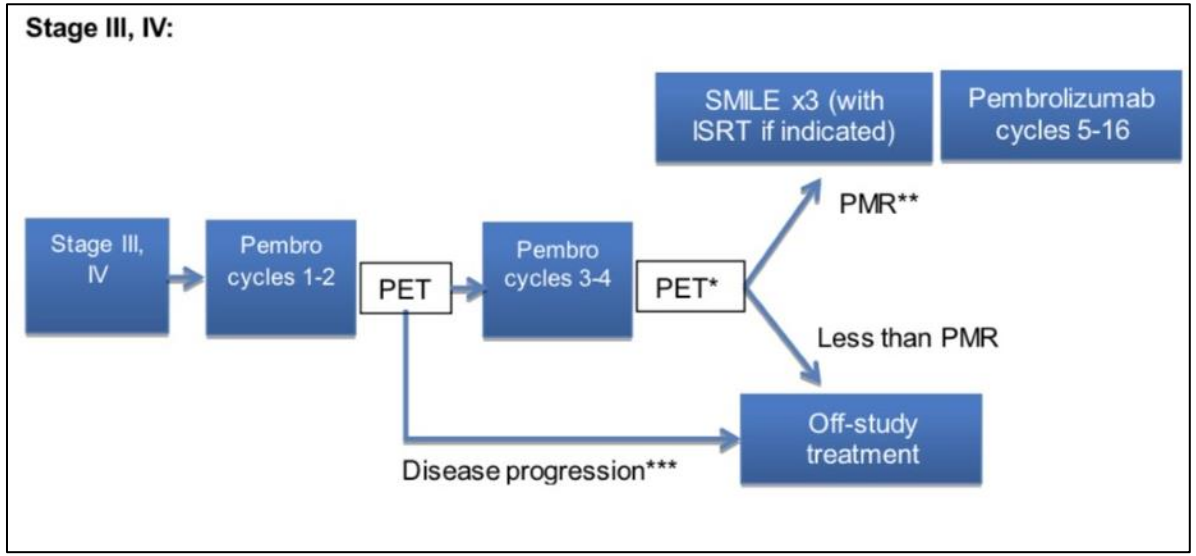
- PDL1 expression in TCL:
  - 15% of PTCL and 27% CTCL
  - Higher expression in cells of the microenvironment
- Multiple ongoing single agent and combination studies
- In extranodal NK/T-cell lymphoma, PD1 inhibition has been promising and durable
- In ATLL, 3 patients with rapid progression of disease with nivolumab

Histology	Agent	ORR
Cutaneous T-cell Lymphoma	Pembrolizumab	38% (N=24)
Cutaneous T-cell Lymphoma	Nivolumab	13% (N=15)
Peripheral T-cell Lymphoma	Nivolumab	40% (N=5)
Extranodal NK/T-cell Lymphoma	Pembrolizumab	100% (N=5)
Extranodal NK/T-cell Lymphoma	Pembrolizumab	57% (N=7)
Extranodal NK/T-cell Lymphoma	Sintilimab	60.7% (N=28)
Adult T-cell Leukemia/Lymphoma	Nivolumab	0%

Lesokhin JCO 2016; Ratner NEJM 2018; Li J Hematol Oncol 2018; Khodadoust ASH 2018; Tao ASCO 2019; Kwong Blood 2017

NCT 03728972: Pembro in ENKL



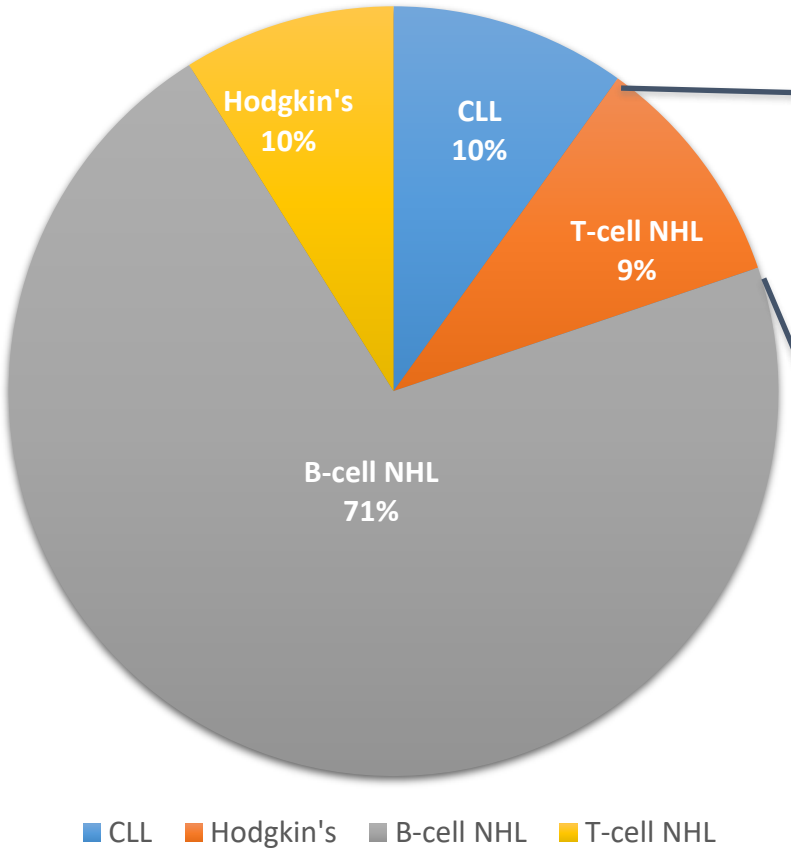


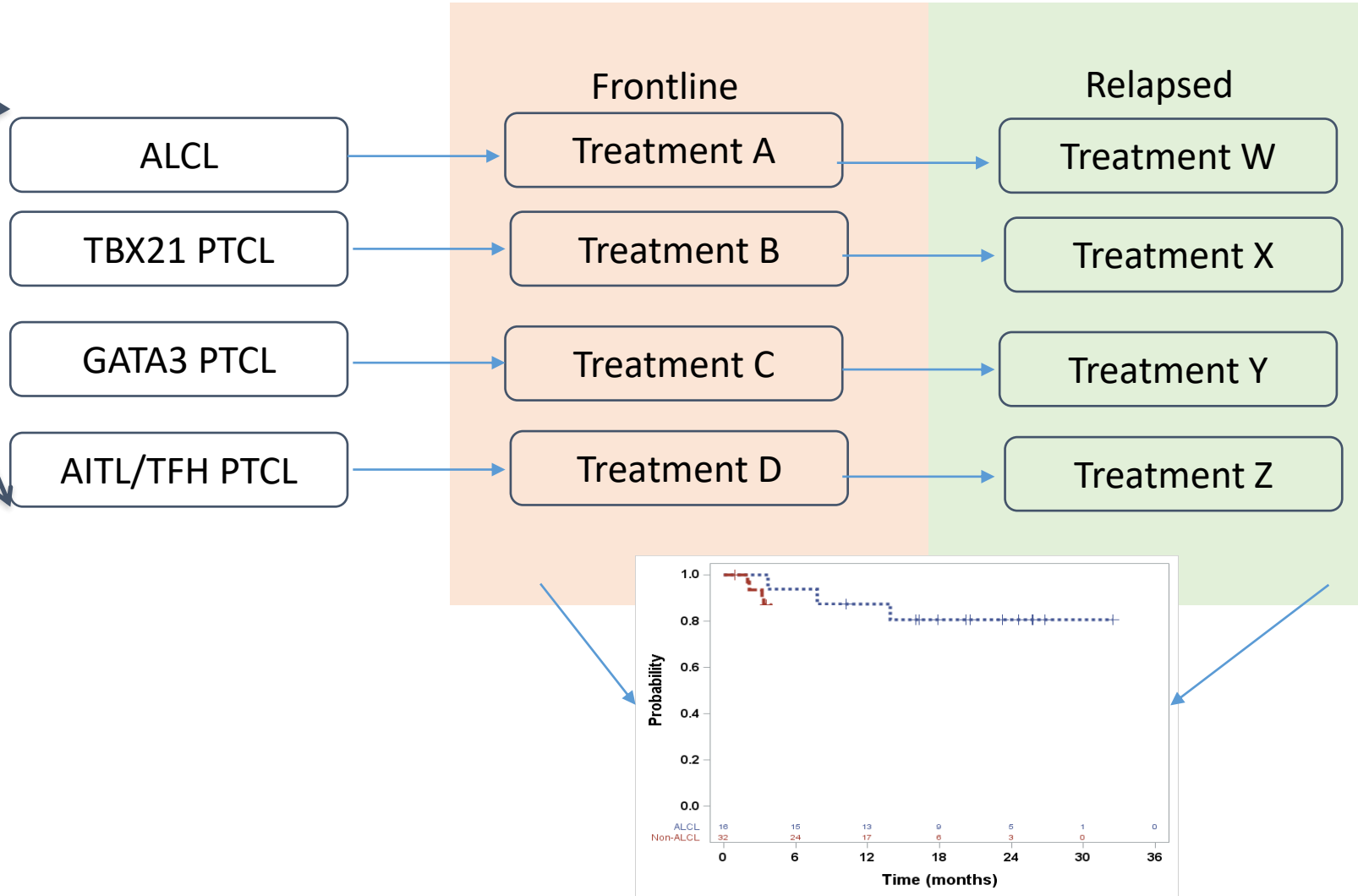
*PET-positive patients will undergo biopsy to evaluate for persistent disease
**Or biopsy showing no evidence of lymphoma
***Patients with an "indeterminant response" by the LYRIC criteria (evidence of disease progression on PET but with clinical improvement) can be considered for another 2 cycles of pembrolizumab after discussion with the MSK PI.[1] See section 9.1 for details.
Abbreviations: ISRT (involved site radiation therapy), SMILE (steroids, methotrexate, ifosfoamide, asparaginase, etoposide)

T cell Lymphoma
Time for targeted therapy?

- Significant strides in understanding biological heterogeneity and targets identified
- PTCL remains heterogeneous
- PTCL-NOS a shrinking entity
- For TFH subtype: epigenetic targeting
- ALCL: BV based regimen
- ENKL: Pembro containing regimen
- Rest ?

Hopefully, in the future…





Adapted from Harrison's Internal Medicine 2017

Courtesy Dr Neha Shah