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T-cell lymphomas: Impact of classification on treatment

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  - BMS
  - Celgene
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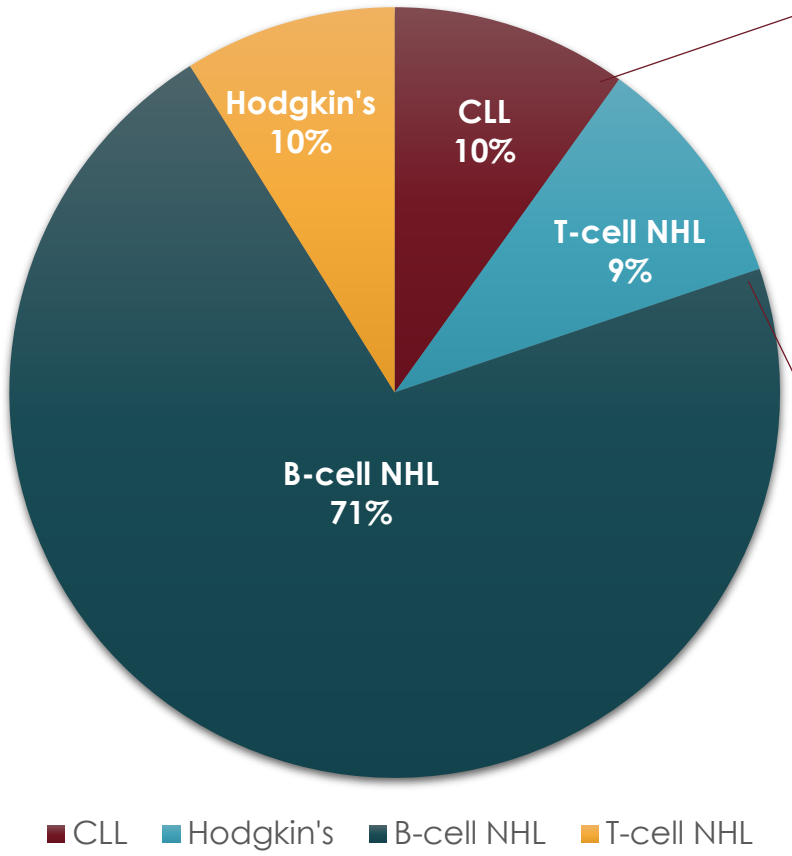
  - C4 Therapeutics
  - Daiichi Sankyo
  - Secura Bio

Audience Response Question

A 56 yo woman with a history of angioimmunoblastic T-cell lymphoma present to clinic with left axillary adenopathy and rash. She previously completed therapy with CHOEP for 6 cycles followed by a consolidative transplant 12 months ago. Left axillary biopsy shows recurrent angioimmunoblastic T-cell lymphoma with CD30 expression in 5% of cells. PET/CT shows left axillary, retroperitoneal, bilateral inguinal adenopathy as well as hypermetabolic splenomegaly. What therapy would you consider for this patient next?

1. ICE chemotherapy
2. Duvelisib
3. Brentuximab vedotin
4. Clinical trial of valemetostat
5. Gemcitabine oxaliplatin
6. Romidepsin

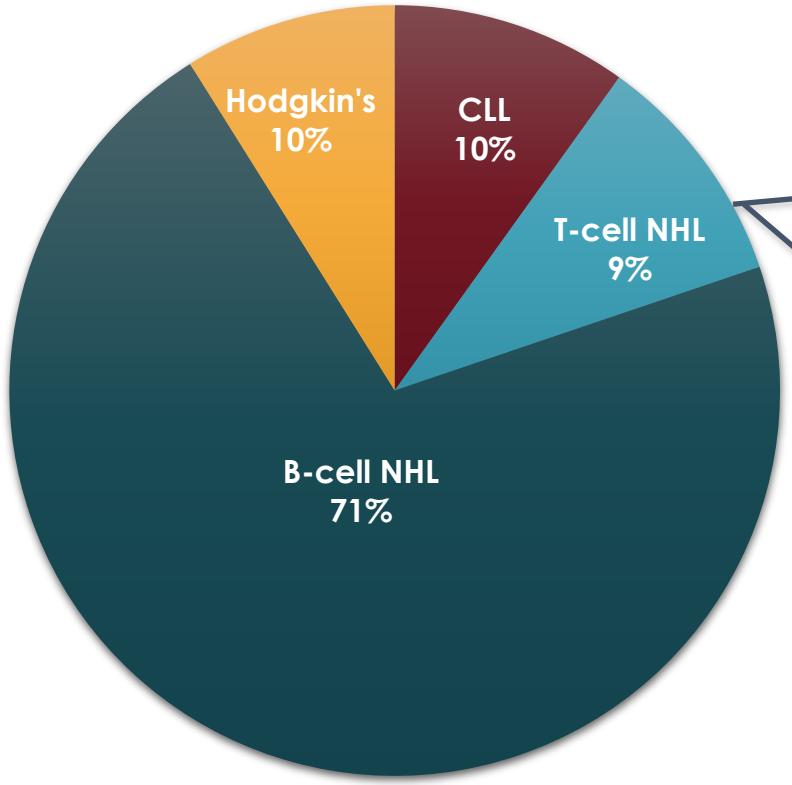
T-cell Lymphomas are a complex heterogeneous group of lymphomas



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.

T-cell Lymphomas are a complex heterogeneous group of lymphomas…that have been overly simplified



Systemic

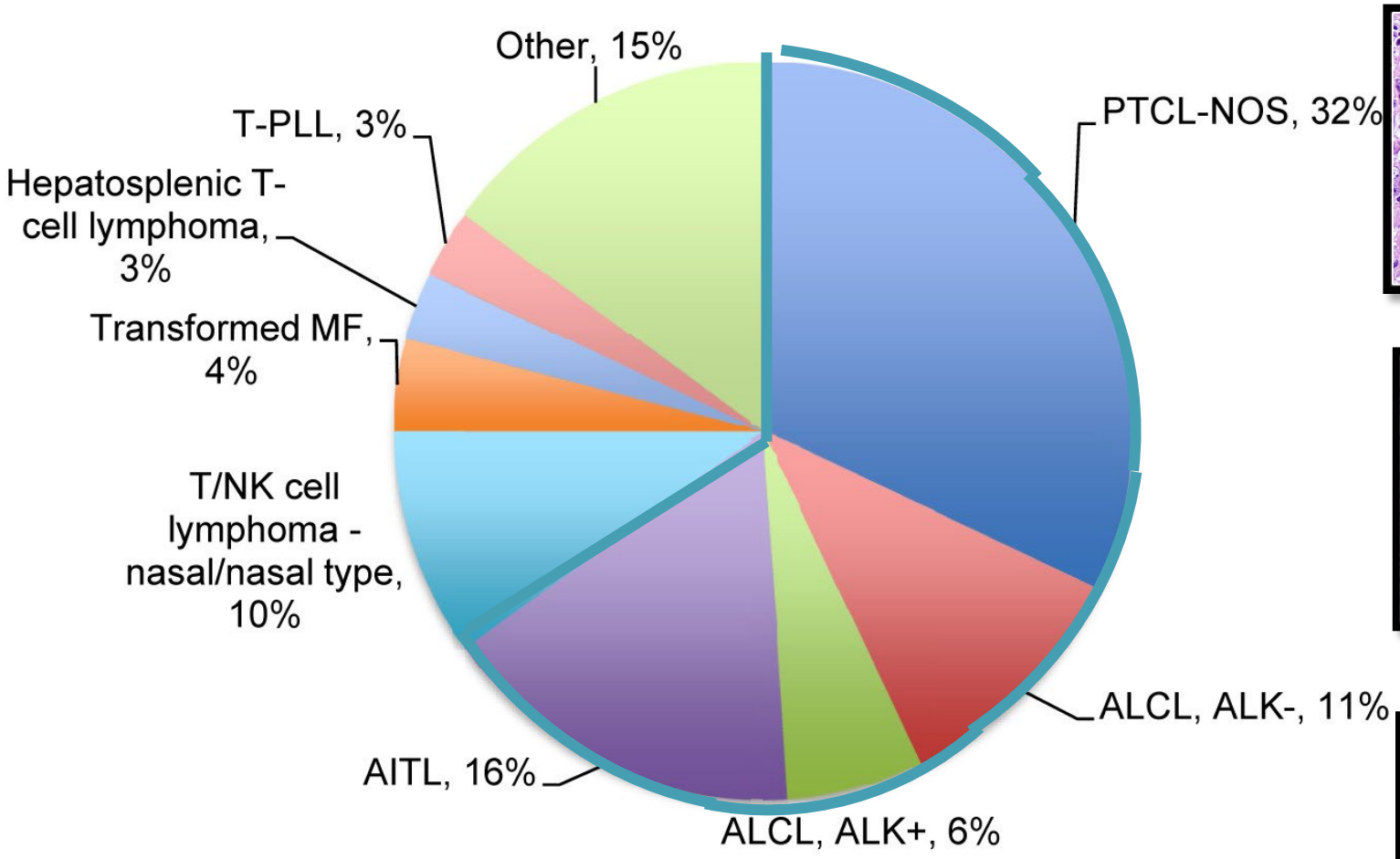
Treatment strategies derived from aggressive B-cell lymphomas

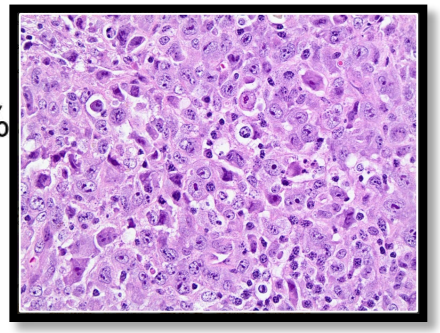
Cutaneous

Treatment strategies developed mostly in small studies

Adapted from Harrison's Internal Medicine 2017

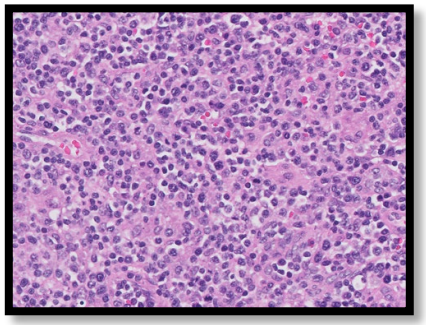
Different Histologies Immunophenotypically Different





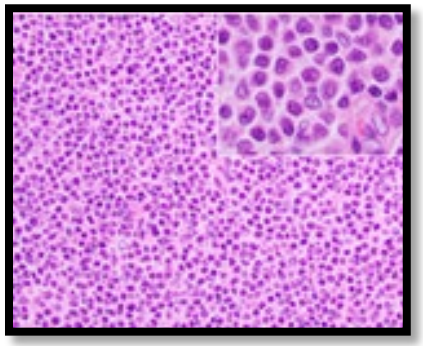
ALCL

- 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



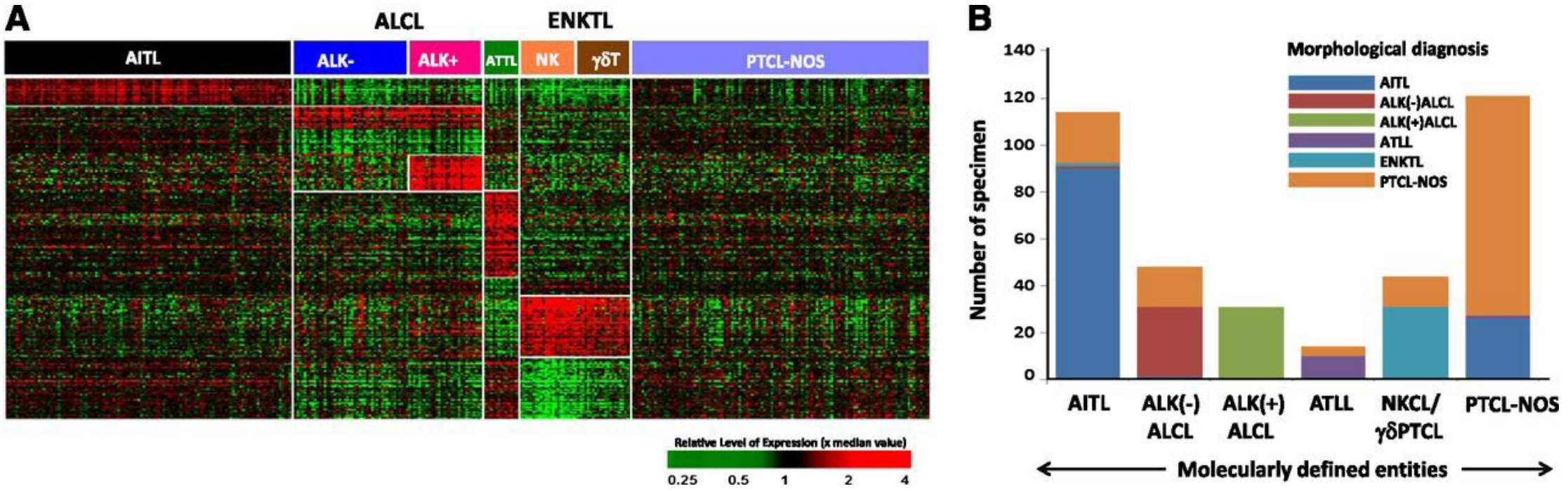
PTCL NOS

- Grab bag term

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

Gene Expression Signatures Characterize Disease Biology

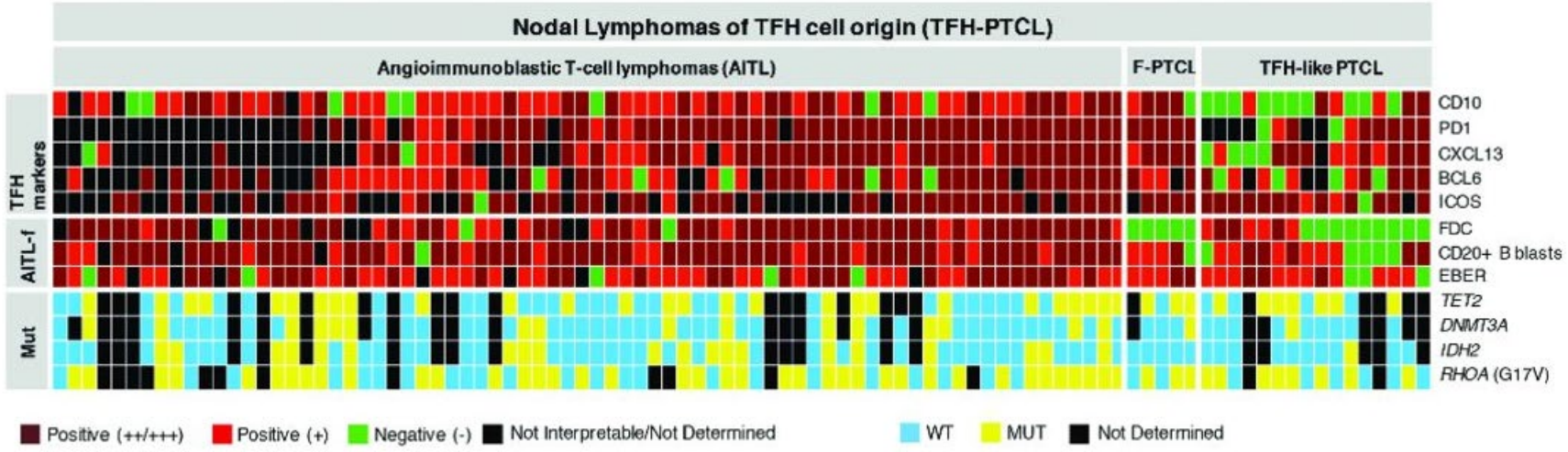
- Gene expression profiles of 372 patients show subtypes have distinct gene expression profiles



Heavican TB et al. Blood. 2019;133:1664-1676.

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

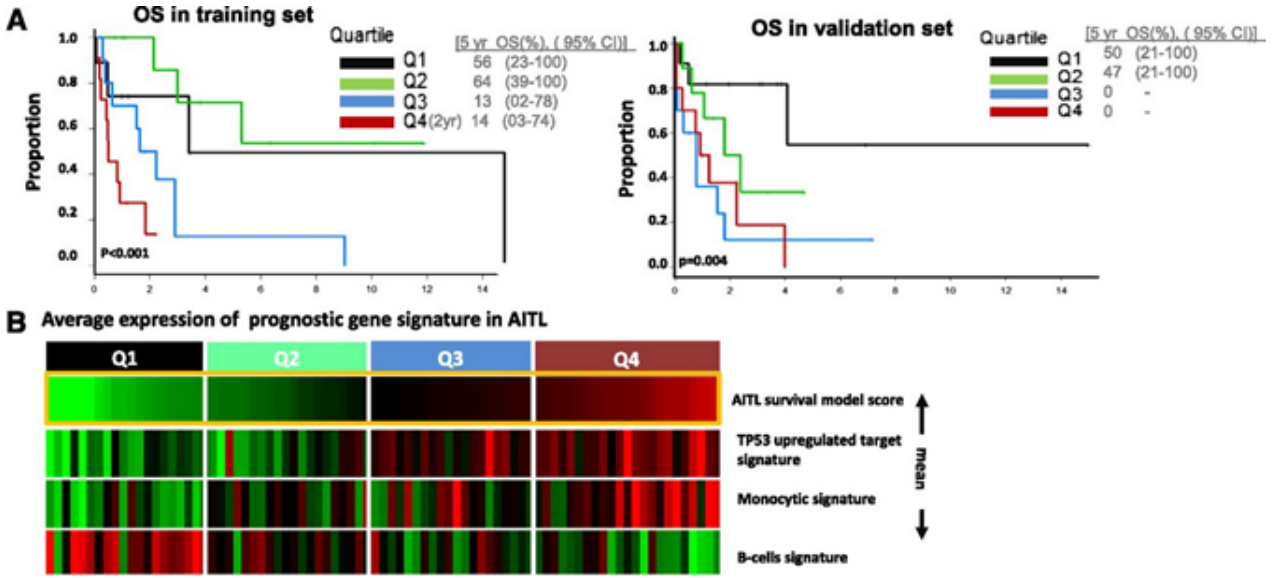


Dobay PM et al Haematologica. 2017

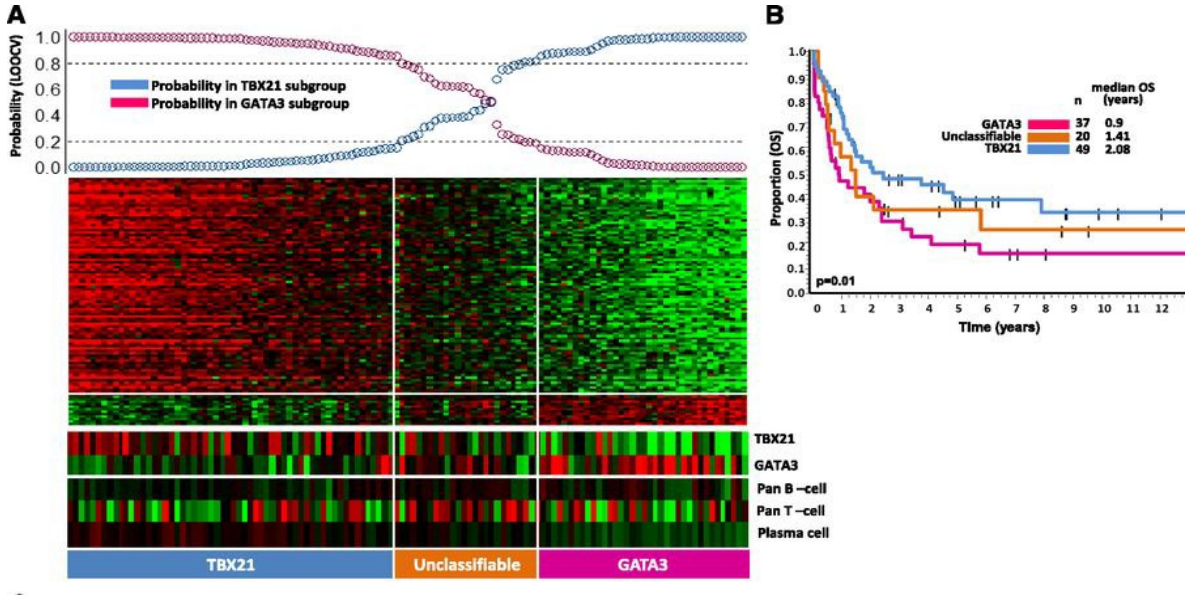
Gene Expression Signatures Can Risk Stratify Patients with PTCL and AITL

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

AITL



PTCL-NOS

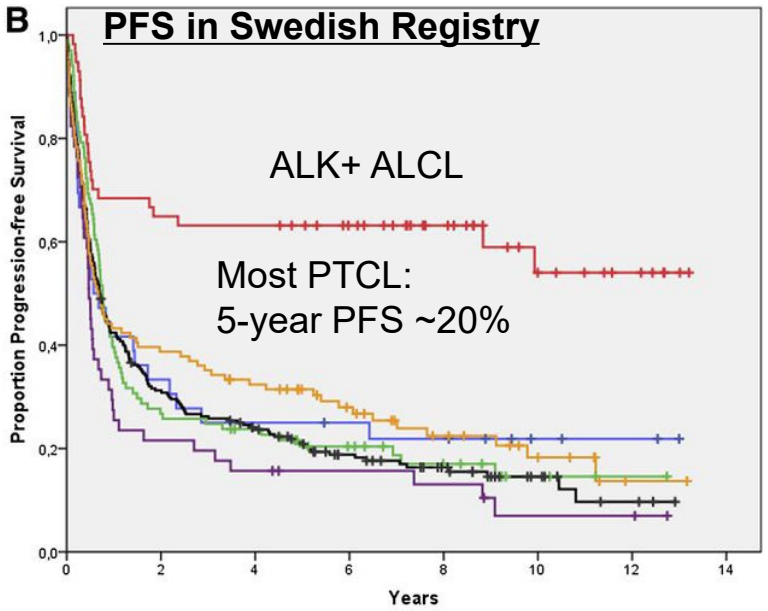


Heavican TB et al. Blood. 2019

Background: Peripheral T-cell Lymphomas (PTCL)

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

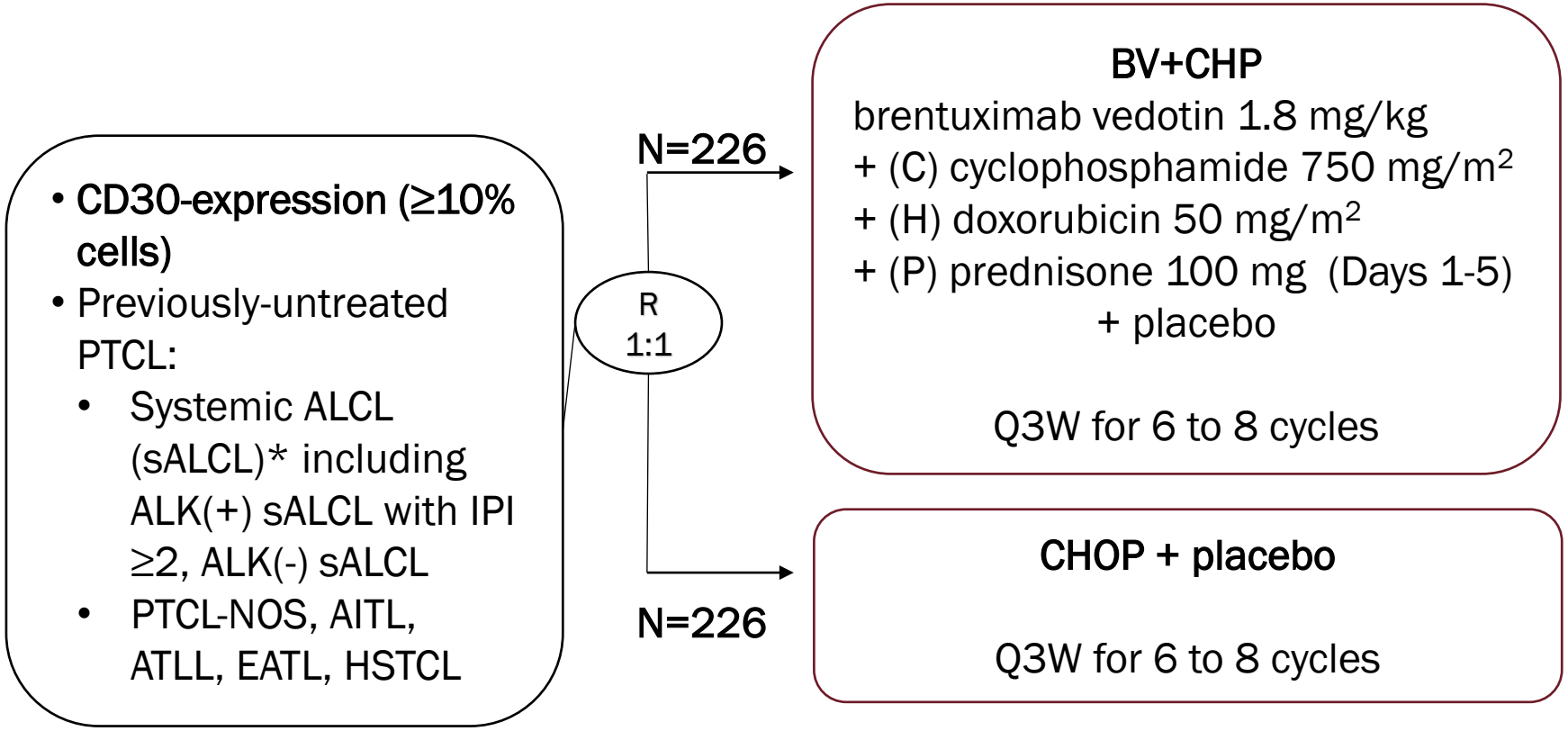


Outcomes By Intent to Consolidated with Auto-HSCT in Swedish Registry		
	Auto-SCT (n = 128)	No Auto-SCT (n = 124)
5 yr OS	48%	26%
5 yr PFS	41%	20%

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

Personalizing Therapy in the Frontline Setting

ECHELON-2: BV-CHP vs CHOP



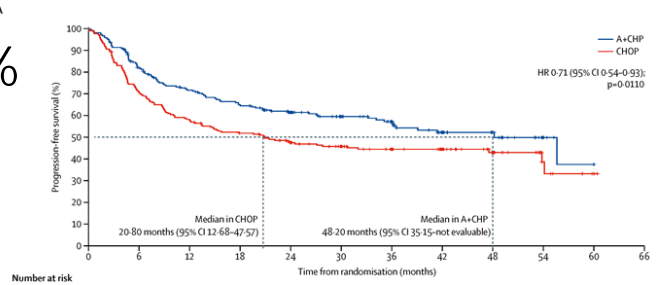
70% patients had ALCL

Horwitz Lancet 2019

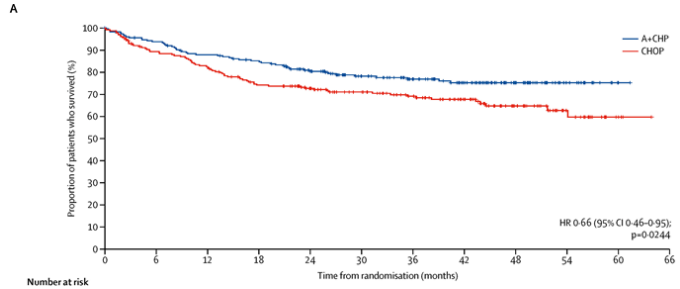
ECHELON-2: BV-CHP vs CHOP

- 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



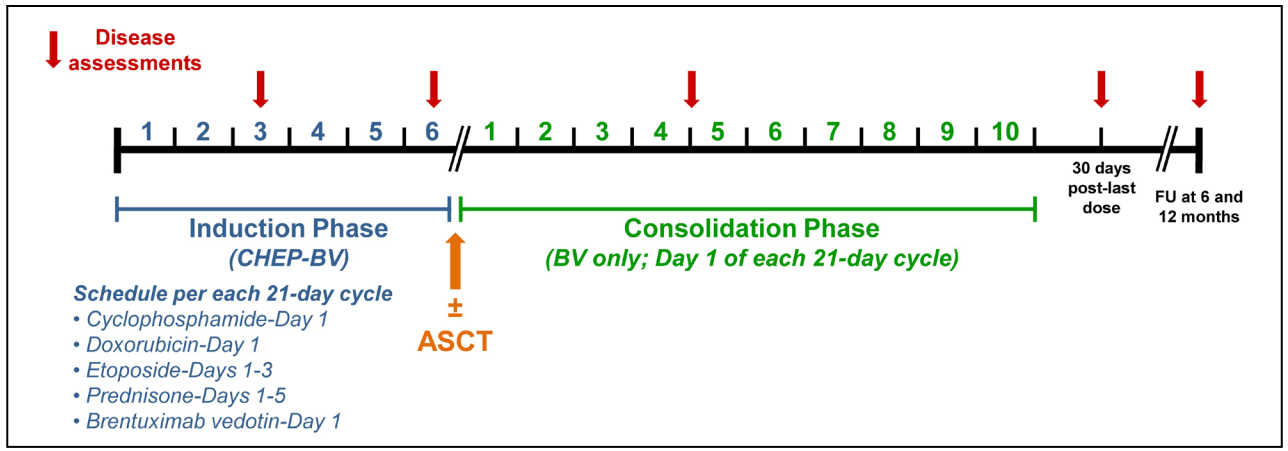
Overall Survival



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%

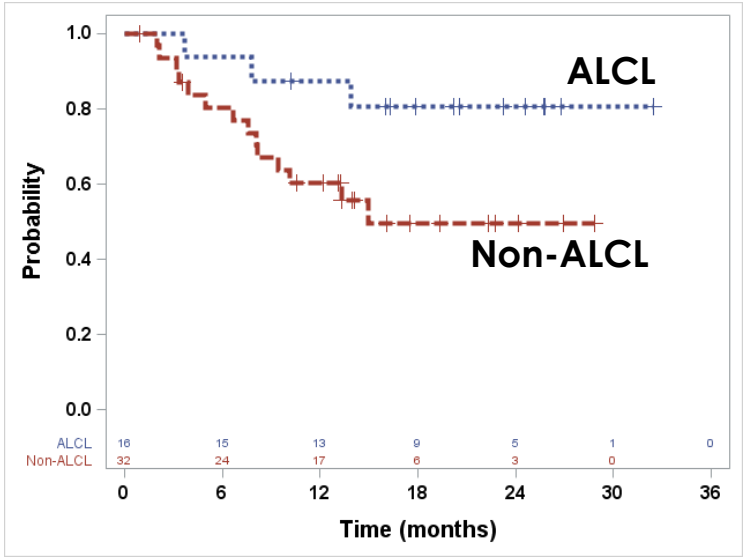
Frontline Therapy with BV-CHEP + BV Maintenance (n=46)



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

Herrera ASH 2021

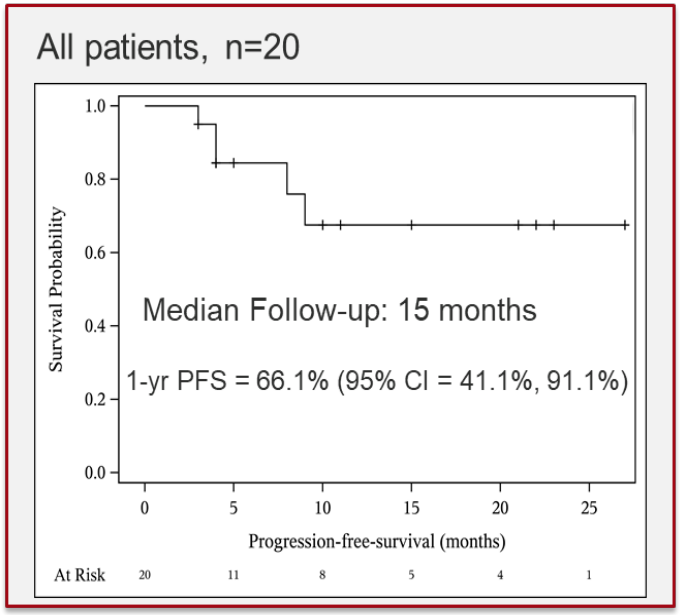


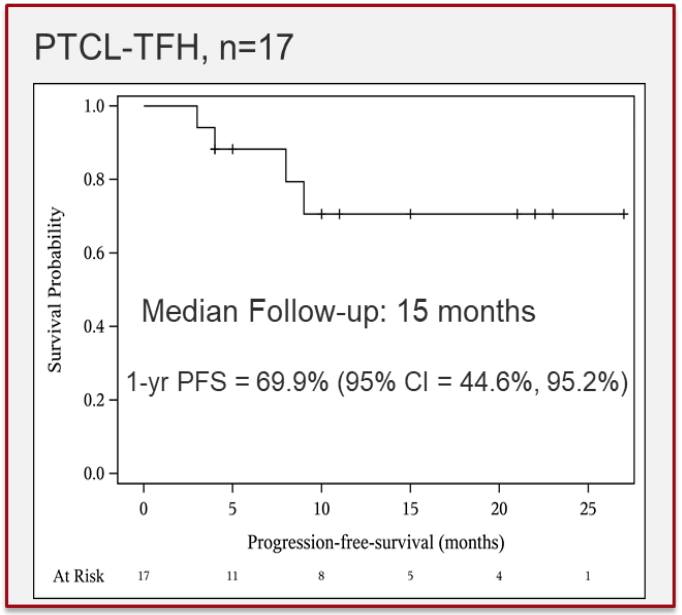
18mo PFS

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

Azacitidine-CHOP: Phase II study

- 5-azacitidine shown to be active it AITL (ORR 9/12)
  - AITL has high rate of mutations in TET2, RHOA, IDH2, DNMT3A
- CC-486 (oral azacitidine) has been safely combined with RCHOP
- Phase II multicenter study (n=20)
  - 17/20 patients had AITL or PTCL-NOS, TFH phenotype
  - 16/20 were CD30 <5%
- ORR (n=20): 85% (55% CR)
- At EOT, ORR: 75% (75% CR)





Lemmonier Blood 2018; Ruan ASH 2020

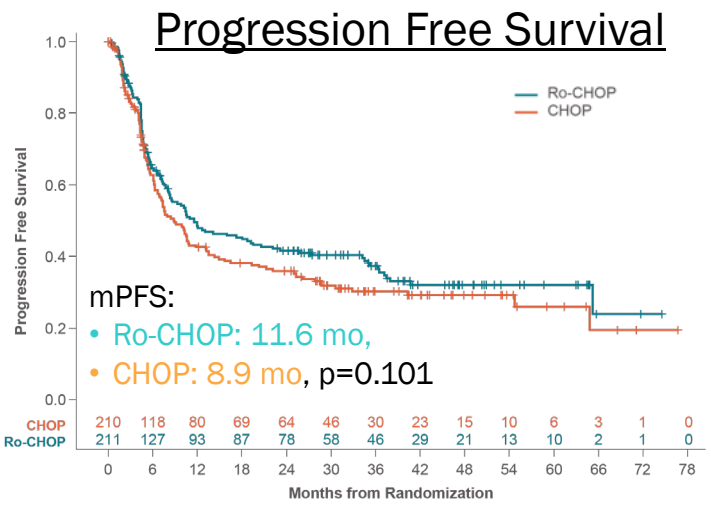
Romidepsin-CHOP vs CHOP

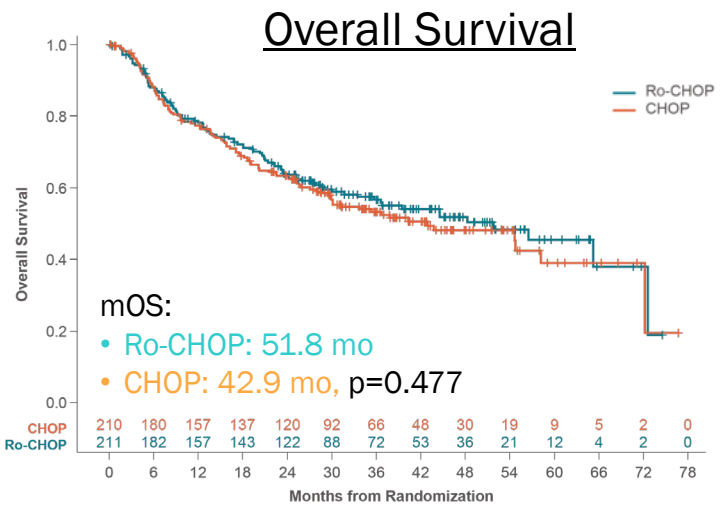
- Romidepsin: Histone deacetylase inhibitor approved for CTCL and NCCN listed for PTCL
  - ORR 25%, CR 15%
  - Shown to be more effective in TFH phenotype PTCL
- Randomized phase III study by LYSA (n=421)

- **Key Inclusion Criteria**
- Aged 18-80 y
- Histologically proven PTCL : PTCL-NOS, AITL, ALK-neg ALCL, EATCL, HSTCL, SPTCL
- ECOG PS 0-2
- Key Exclusion Criteria
- Other subtypes of PTCL
- Autologous or allogeneic transplant planned as consolidation
- CNS or meningeal involvement
- Abnormal renal, hepatic, and marrow function unless related to lymphoma

CHOP
6 cycles

CHOP+ Romi (12mg/m2) D1, 8
6 cycles



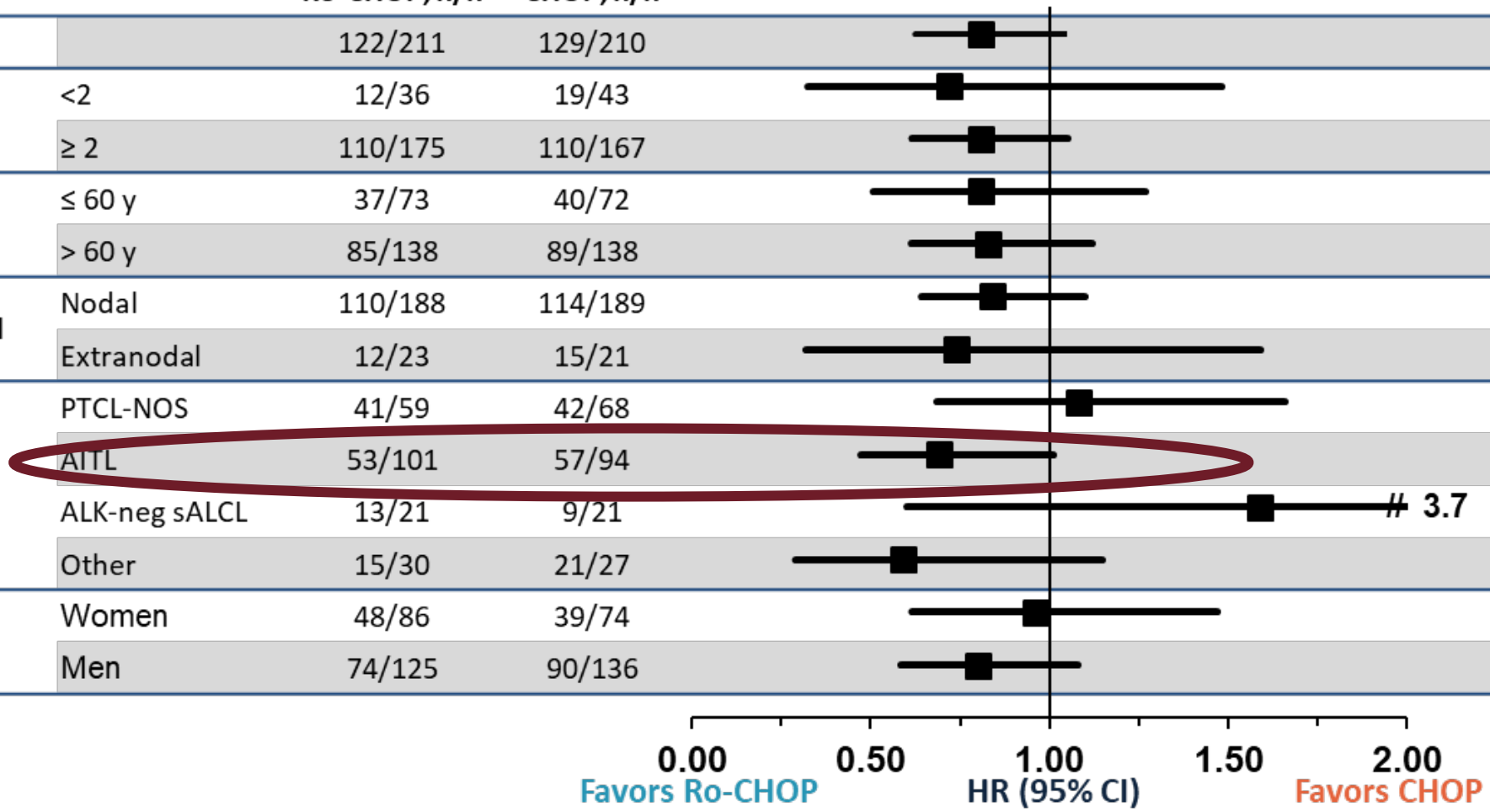


No difference in OS or PFS

Bachy ASH 2020; Coiffer JCO 2012; Ghione Blood Advances 2020

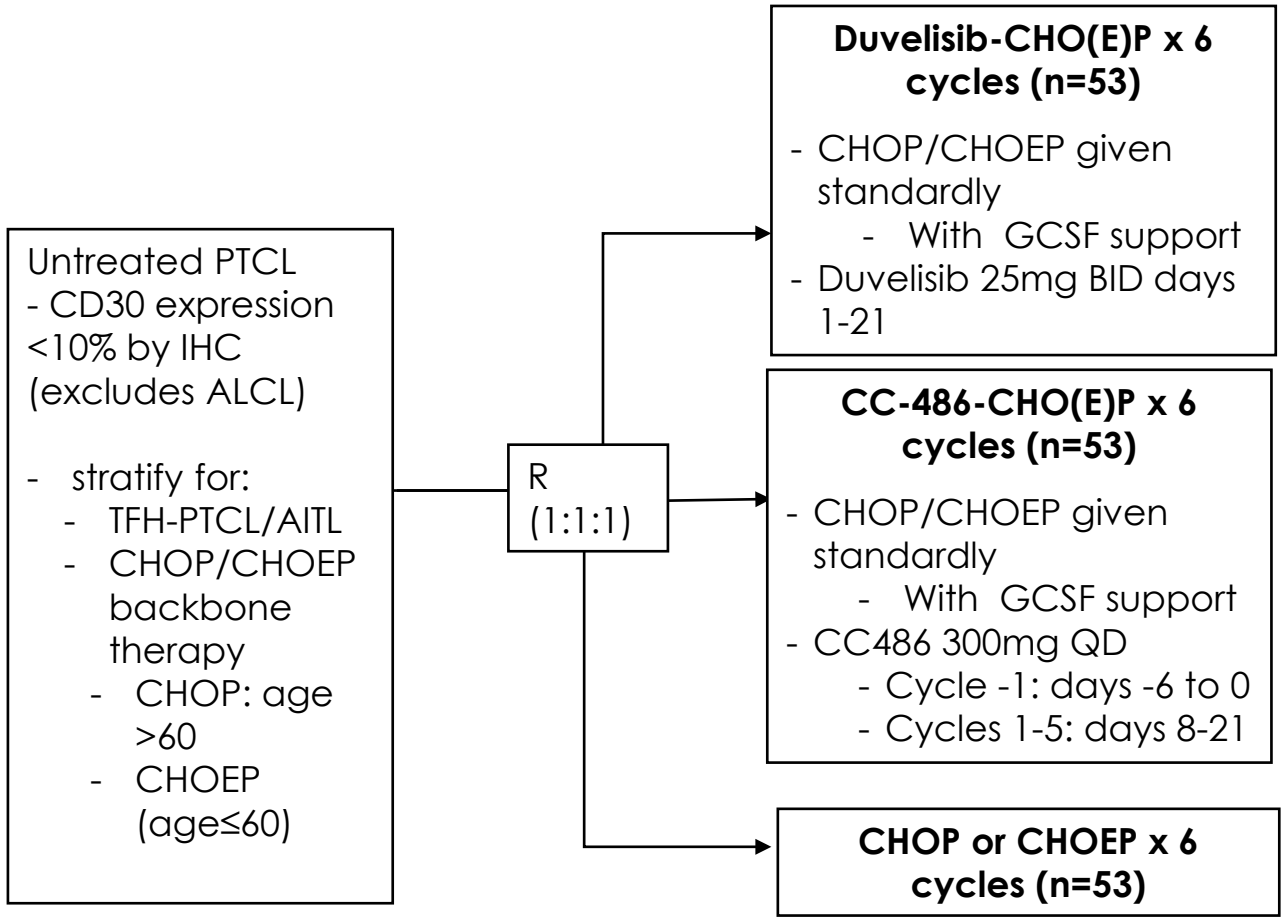
Ro-CHOP: Subgroup Analysis of PFS (ITT Population)

		Ro-CHOP, n/n	CHOP, n/n
Overall		122/211	129/210
Baseline IPI	<2	12/36	19/43
	≥ 2	110/175	110/167
Age	≤ 60 y	37/73	40/72
	> 60 y	85/138	89/138
Nodal vs Extranodal	Nodal	110/188	114/189
	Extranodal	12/23	15/21
Histology	PTCL-NOS	41/59	42/68
	AITL	53/101	57/94
	ALK-neg sALCL	13/21	9/21
	Other	15/30	21/27
Sex	Women	48/86	39/74
	Men	74/125	90/136



Bachy ASH 2020

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

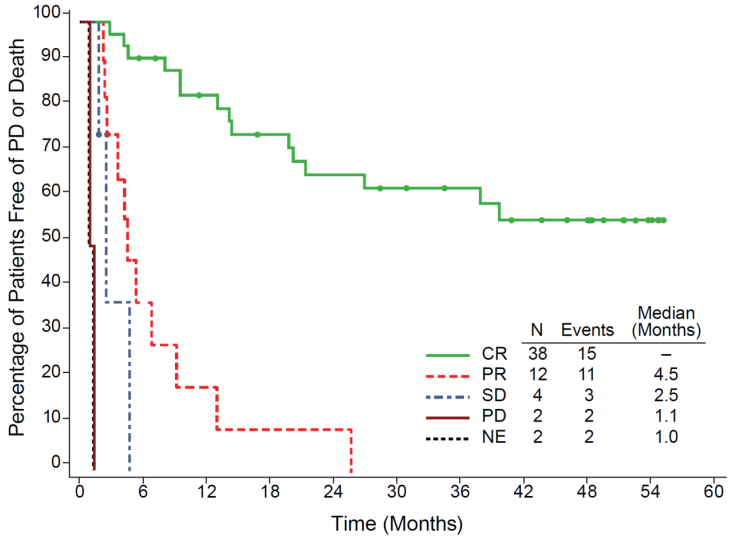
Personalizing Therapy in the Relapsed/Refractory Setting

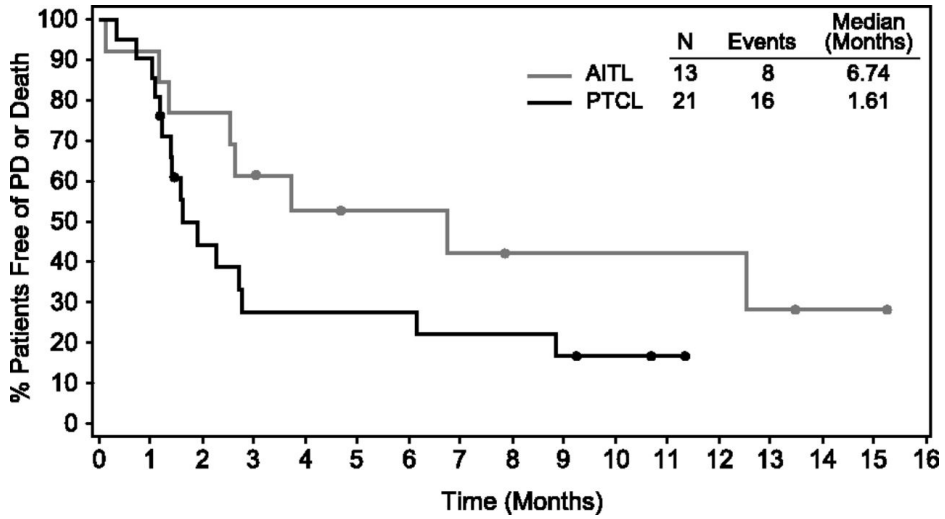
Clinical Activity of Standard Chemotherapy in R/R PTCL

Regimen	N	ORR/CR%	DOR
ICE	40	70% / 35%	mPFS: 6 months
GemDexCis	51	80% / 47%	mPFS: 4 months
ESHAP	22	32% / 18%	mPFS: 2.5mo
Gemcitabine	20	55% / 30%	mDOR: 34 mo
Bendamustine	60	50% / 28%	mDOR: 3.5 mo
Romidepsin	45	25% /15%	mDOR: 8.9 mo
Bellinostat	57	26% / 11%	mDOR: 8.3 mo
Pralatrexate	111	29%/ 15%	mDOR: 7.6 mo
Brentuximab vedotin	34	69% / 44%	mPFS: 6.7 mo

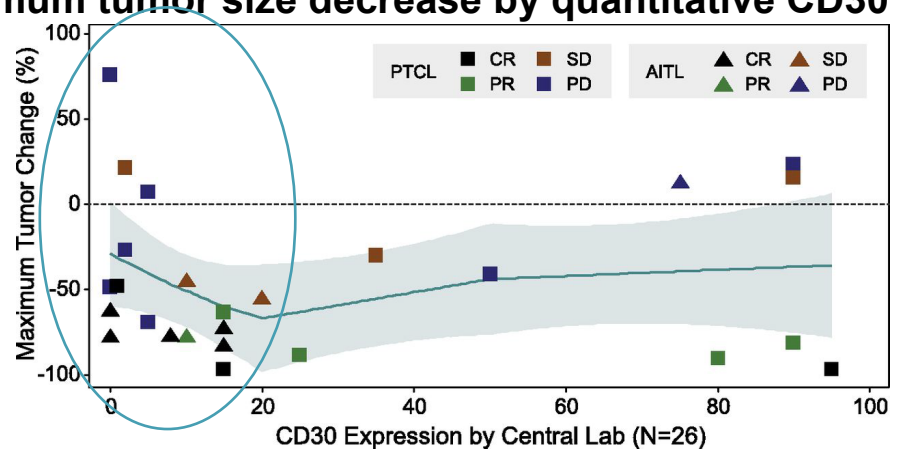
Damaj et al JCO 2013
Zinzani et al Ann Oncol 2012
Kogure et al Ann Hematol 2014
Arkenau et al Heamtologica 2007
Parkin et al Blood 2013
Horwitz et al Blood 2005
Mehta-Shah, ASH Education Book 2019

Who benefits most from brentuximab based strategies?





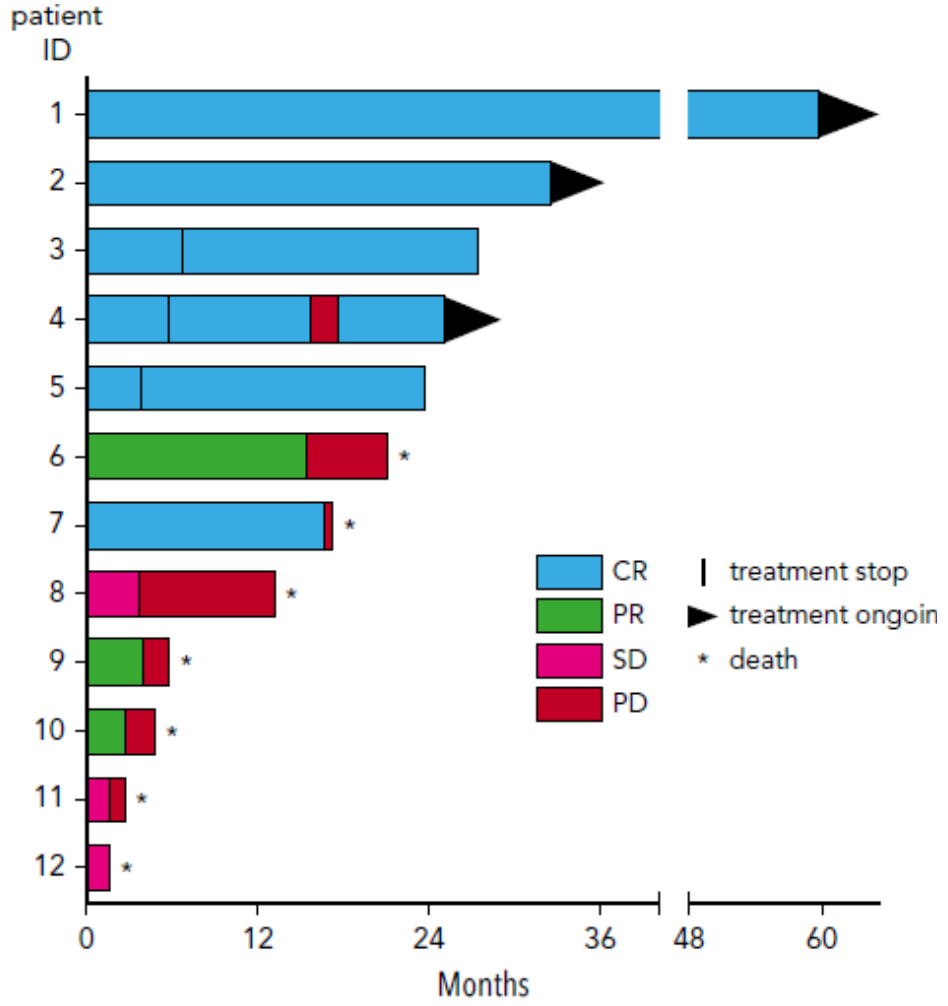
Maximum tumor size decrease by quantitative CD30 expression.



Pro B et al. JCO 2012, ASH 2014; Horwitz et al. Blood 2015

5-Azacitidine in T-cell Lymphomas

- 5-azacitidine has shown 75% response rate in AITL (9/12 responses)
- T-cell lymphoma cell lines show synergy between HDACi and hypomethylating agents
- More pronounced with romidepsin and apoptosis is highly dependent on HDACi concentration
- Evaluated the synergy regarding changes in pattern of methylation and DNA fragmentation
- 5-Azacitidine + CHOP shows high CR rate in AITL

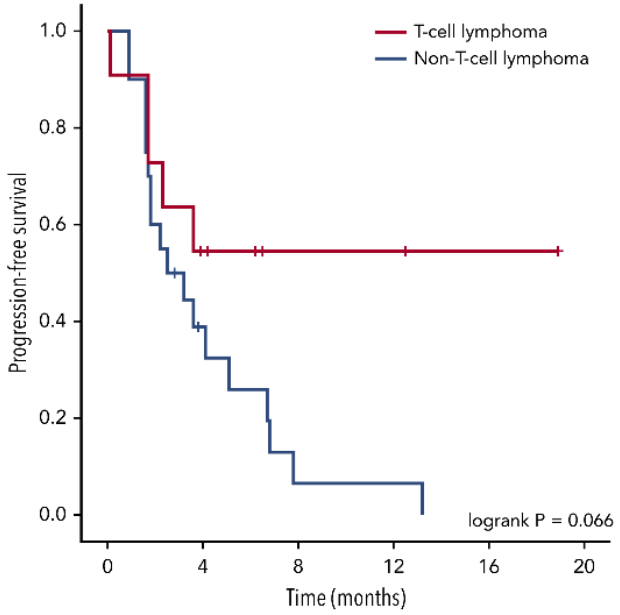


Lemmonier F et al. Blood. 2018; Ruan ASH 2020

Romidepsin and 5-Azacitadine

- MTD: Oral 5-aza 300mg (days 1-14), romidepsin 14mg/m^2 (days 8, 15, 22)
- Toxicities were expected (predominantly hematologic)
- ORR in 8/11 patients (73%)
  - 5 patients consolidated with allogenic transplant
- Saw similar pattern of demethylation at specific CPG islands
- Patients with TET2 mutations responded

	ORR % (N)	CR % (N)	PR % (N)
All Patients (n=28)	32% (10)	23% (7)	10% (3)
T-cell Lymphoma (n=11)	73% (8)	55% (6)	18% (2)



O'Connor OA Blood. 2019

Romidepsin+ Lenalidomide Combinations in Relapsed/Refractory T-cell Lymphoma

Romidepsin-Lenalidomide

Histology	N	CR	PR	ORR
CTCL	9	1	3	4/9 (44%)
PTCL (incl ATLL)	15	2	6	8/15 (53%)
Total	24	3	9	12/24 (50%)

Romidepsin-Lenalidomide-Carfilzomib

Histology	N	CR	PR	ORR
PTCL	7	1	1	2/7 (29%)
AITL*	5	4	1	5/5 (100%)
CTCL	3	-	1	1/3 (33%)
NK/T	1	-	-	0/1 (0%)
Total	16	5	3	8/16 (50%)

- Response rate in AITL 100%

Mehta-Shah AJH 2021

TFH-Phenotype May Be More Sensitive to Histone Deacetylase Inhibitor Based Therapy

	TFH (n=24)		Non TFH (n=17)		p
Response	ORR	CR	ORR	CR	
Overall	14 (58%)	7 (29%)	5 (30%)	2 (12%)	0.11
Single agent (n=21)	4 (36%)	1 (9%)	1 (10%)	1 (10%)	0.31
Combinations (n=20)	10 (77%)	6 (46%)	4 (57%)	1 (14%)	0.61

- Median time to progression:
  - 6 mo for TFH vs. 2 mo for non-TFH (p=0.0046, HR 0.31)

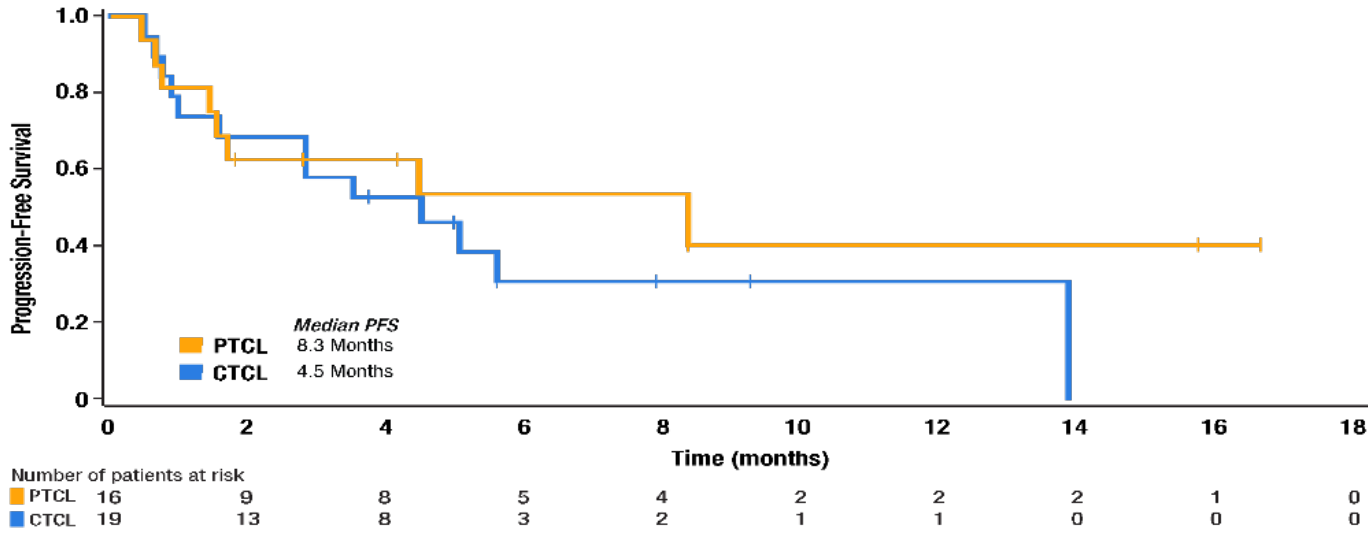
Ghione Blood Adv 2020

Duvelisib (P13K gamma-delta inhibitor) in TCL

- Duvelisib is an oral PI3 kinase δγ inhibitor
- Approved for CLL and follicular lymphoma (25mg BID)

- Duvelisib found to be potent in T-cell Lymphoma cell lines

- Phase I study
  - PTCL (n=16) : ORR 50% in PTCL
  - CTCL (n=19): ORR 31.6%
  - Some responses were durable



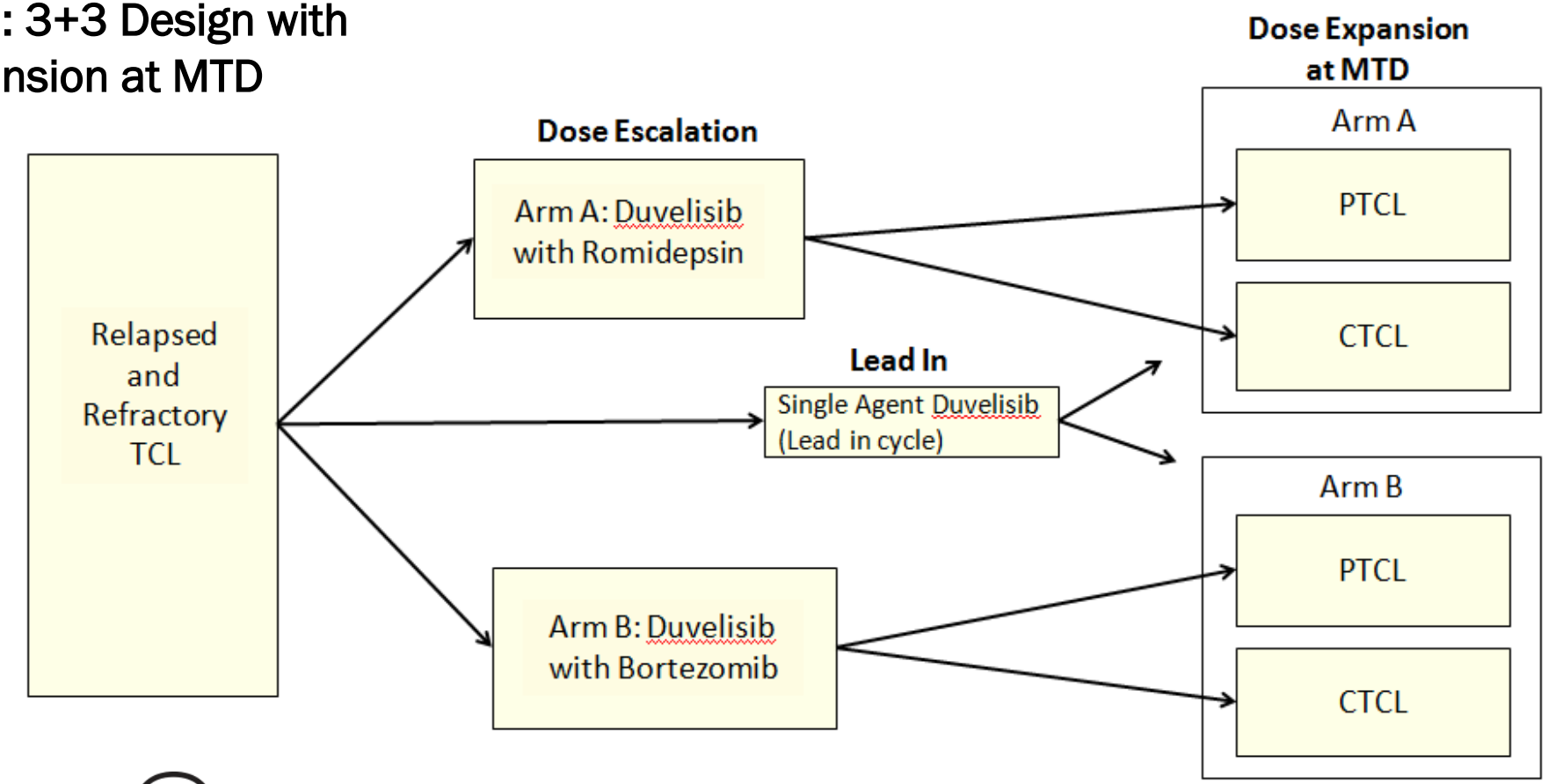
- In patient derived xenograft models of PTCL, duvelisib resulted in change in distribution of macrophages from immunosuppressive (M2) to immunostimulatory (M1) phenotype

- Response to duvelisib associated with intrapatient changes in serum cytokine profile

Horwitz SM Blood. 2018

Duvelisib with either Romidepsin or Bortezomib in Rel/Refractory T-cell Lymphomas

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



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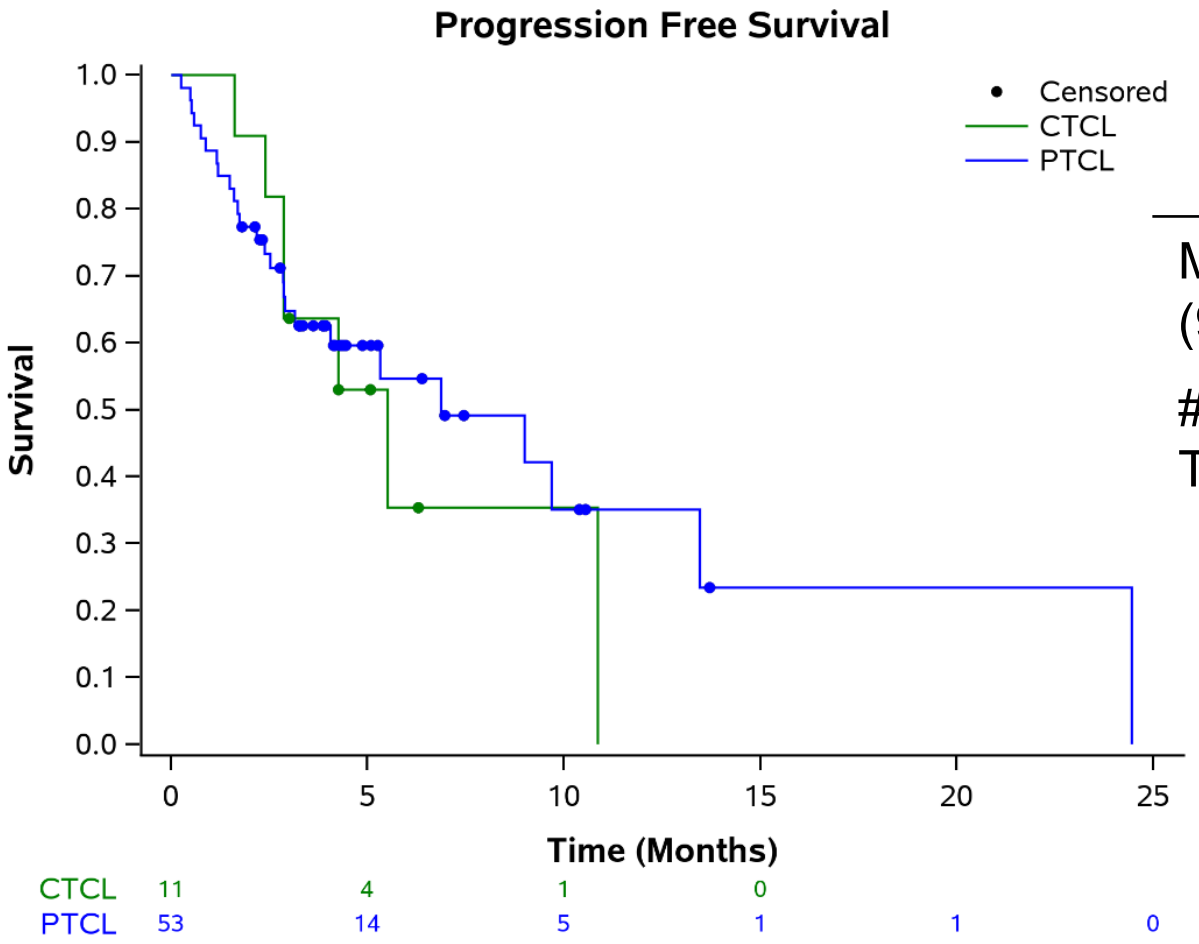
Efficacy of Romidepsin + Duvelisib

Histology	Treated (n)	Evaluable (n)	ORR, n (%)	CR, n (%)
Peripheral T-Cell Lymphoma	**55**	**53**	**31 (58)**	**22 (40)**
PTCL, NOS	20	19	10 (53)	6 (32)
AITL/TFH	19	19	13 (68)	11 (58)
ALCL	3	3	3 (100)	2 (67)
Primary cutaneous γδ TCL	3	3	1 (33)	1 (33)
Aggressive epidermotropic CD8+ TCL	2	2	1 (50)	1 (50)
HSTCL	2	2	1 (50)	0
MEITL	2	1	0	0
Other (pcPTCL, T PLL, ATLL, PTLD)	4	4	2 (50)	1 (25)
Cutaneous T-Cell Lymphoma	**11**	**11**	**4 (36)**	**0**
Mycosis Fungoides	7	7	2 (29)	0
Large Cell Transformation*	3	3	0	0
Sezary Syndrome	4	4	2 (50)	0
Large Cell Transformation*	1	1	0	0
Overall	66	64	35 (55)	22 (34)

Horwitz SM ASH 2021

Romidepsin + Duvelisib



	PTCL	CTCL
Median PFS (95% CI)	6.9 Mo (4.1 – 24.5)	5.5 Mo (2.9 – 10.9)
# of patients → Transplant	15 (28%)	0

Well Tolerated:

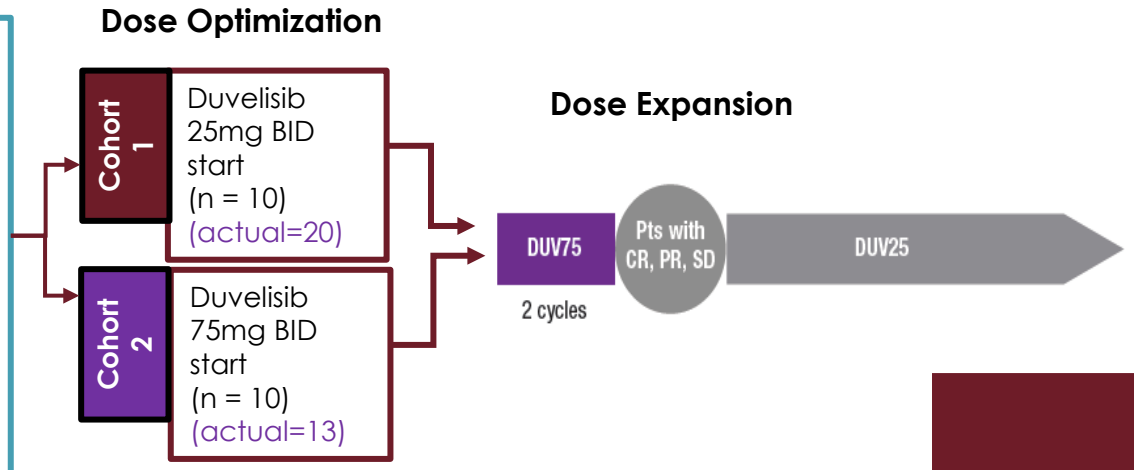
- Grade ≥3 toxicities at MTD:
- Transaminitis 14%
- Diarrhea: 15%
- Neutropenia: 36%
- Thrombocytopenia: 10%
- Infections: 10%

Horwitz et al ICML 2021

PRIMO: Duvelisib Single Agent in PTCL

Relapsed or Refractory PTCL[a]

- Histologically confirmed PTCL subtypes: PTCL-NOS, AITCL, ALCL, and NKTL
- Measurable disease per IWG for PTCL
- No transformation to aggressive lymphoma
- No prior history of allogeneic stem cell transplant or treatment with PI3K inhibitor
- ECOG PS ≤2



Grade ≥3 toxicities :

- Transaminitis: 24%
- Diarrhea: 15%
- Neutropenia: 8%
- Rash: 16%

	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%

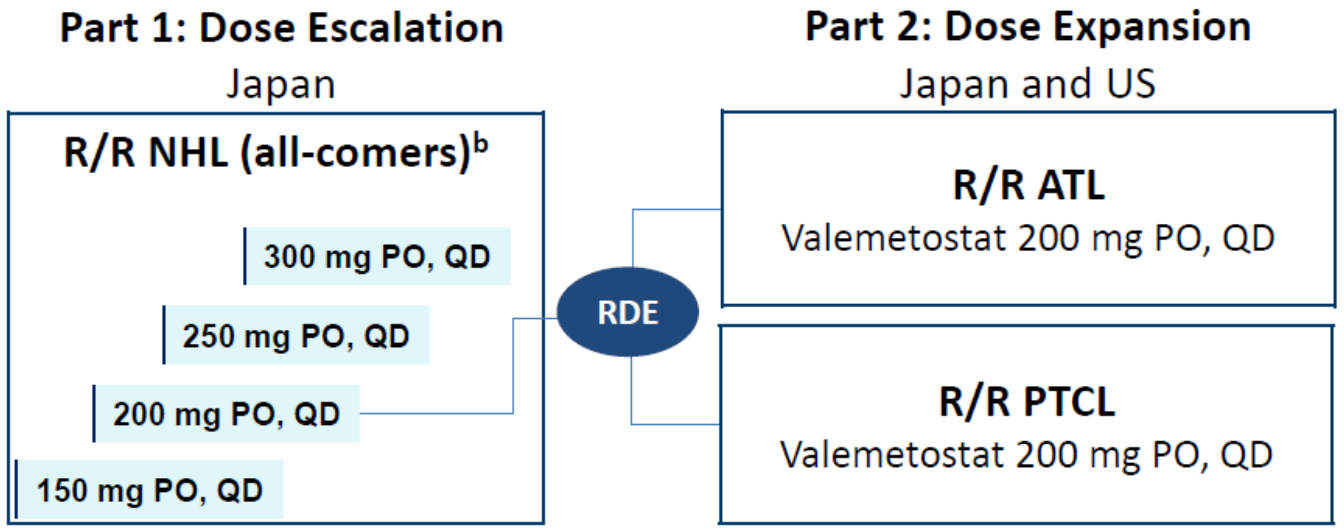
Brammer ASH 2021

NCT 03372057

Valmetostat (EZH2 inhibitor) Phase 1/2 study

Patients with R/R NHL

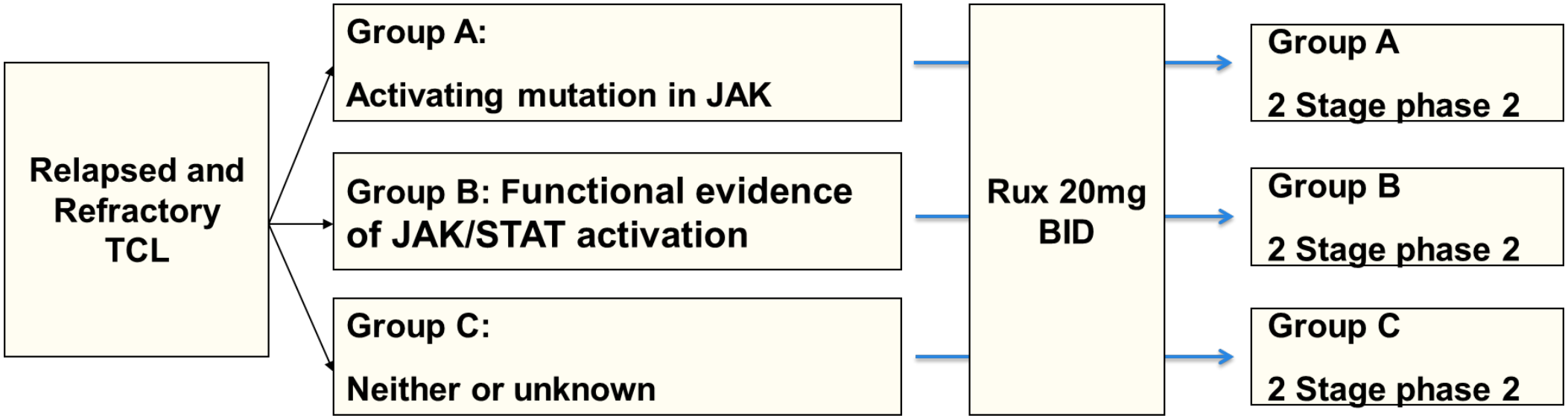
- Age ≥20 (Japan) or ≥18 (US) years
- ECOG PS 0 or 1
- Patients with ATL: positive test result for HTLV-1



	All PTCL (n=44)	AITL (n=17)	PTCL-NOS (n=20)	ALCL (n=2)	Other TCL (n=5)
ORR (%)	54.5%	65%	50%	50%	40%
CR (%)	27.3%	47%	20%	50%	0%

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

Ruxolitinib in T-cell Lymphoma



	Cohort 1 (n=20)	Cohort 2 (n=14)	Cohort 3 (n=18)
ORR	6 (30%)	4 (29%)	2 (11%)

Moskowitz AJ et al. *Blood.* 2019;134(Supplement_1):4019.

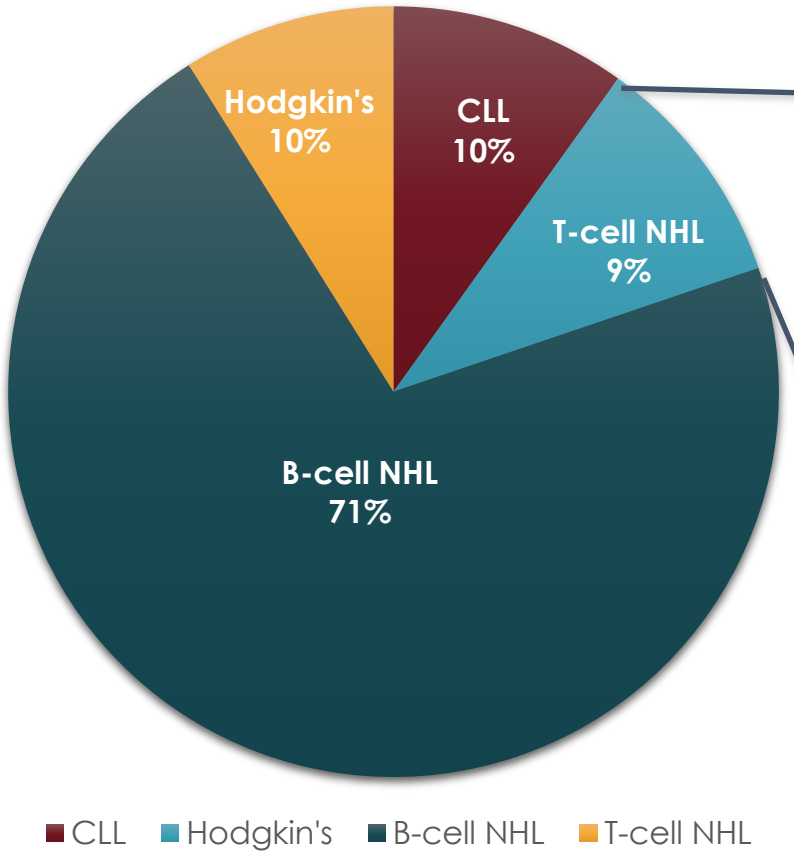
ALK inhibition in ALK expressing ALCL

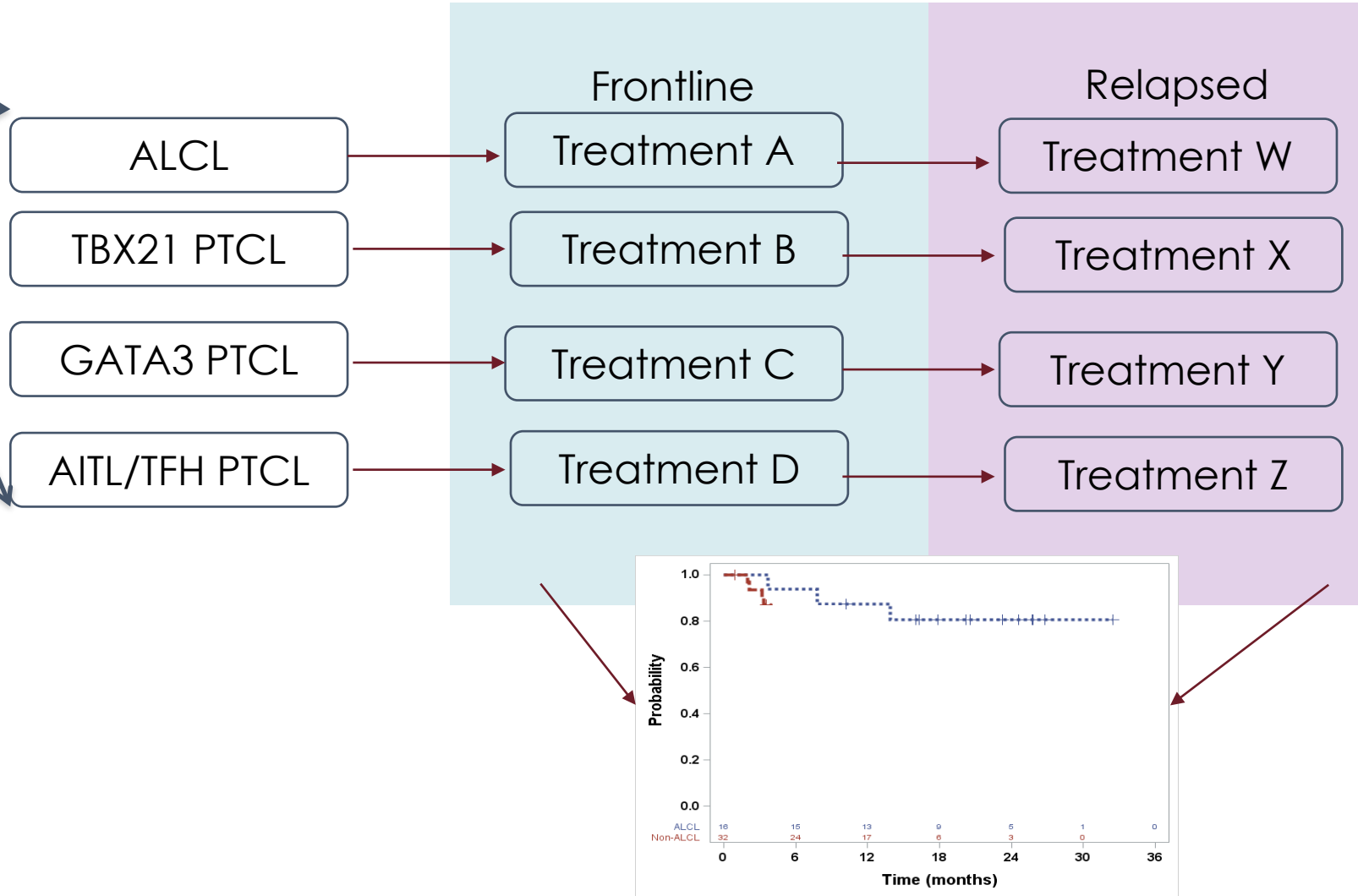
- ALK inhibitors are approved for ALK expressing lung cancer
- ALK rearrangements seen in ALK+ ALCL
  - t(2,5) leading to fusion of ALK to NPM1 or ALK to other partner genes
- Crizotinib studied in ALK+ ALCL by the Children's Oncology Group

Outcome	ALCL165 (n=6)	ALCL280 (n=20)	Overall (n=26)
ORR	6 (83%)	18 (90%)	24 (92%)
CR	5 (83%)	16 (80%)	21 (81%)
PR	0	2 (10%)	2 (8%)
SD	1 (17%)	2 (10%)	3 (12%)
PD	0	0	0 (0%)

Mosse et al JCO 2018

Hopefully, in the future…





Adapted from Harrison's Internal Medicine 2017

Audience Response Question

A 56 yo woman with a history of angioimmunoblastic T-cell lymphoma present to clinic with left axillary adenopathy and rash. She previously completed therapy with CHOEP for 6 cycles followed by a consolidative transplant 12 months ago. Left axillary biopsy shows recurrent angioimmunoblastic T-cell lymphoma with CD30 expression in 5% of cells. PET/CT shows left axillary, retroperitoneal, bilateral inguinal adenopathy as well as hypermetabolic splenomegaly. What therapy would you consider for this patient next?

1. ICE chemotherapy
2. Duvelisib
3. Brentuximab vedotin
4. Clinical trial of valemetostat
5. Gemcitabine oxaliplatin
6. Romidepsin

Thank you!

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MEDICINE & BIOLOGICAL SCIENCES