6th POSTGRADUATE LYMPHOMA CONFERENCE - Rome 2022

T cell Lymphoma: New Agents

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Stanford MEDICINE

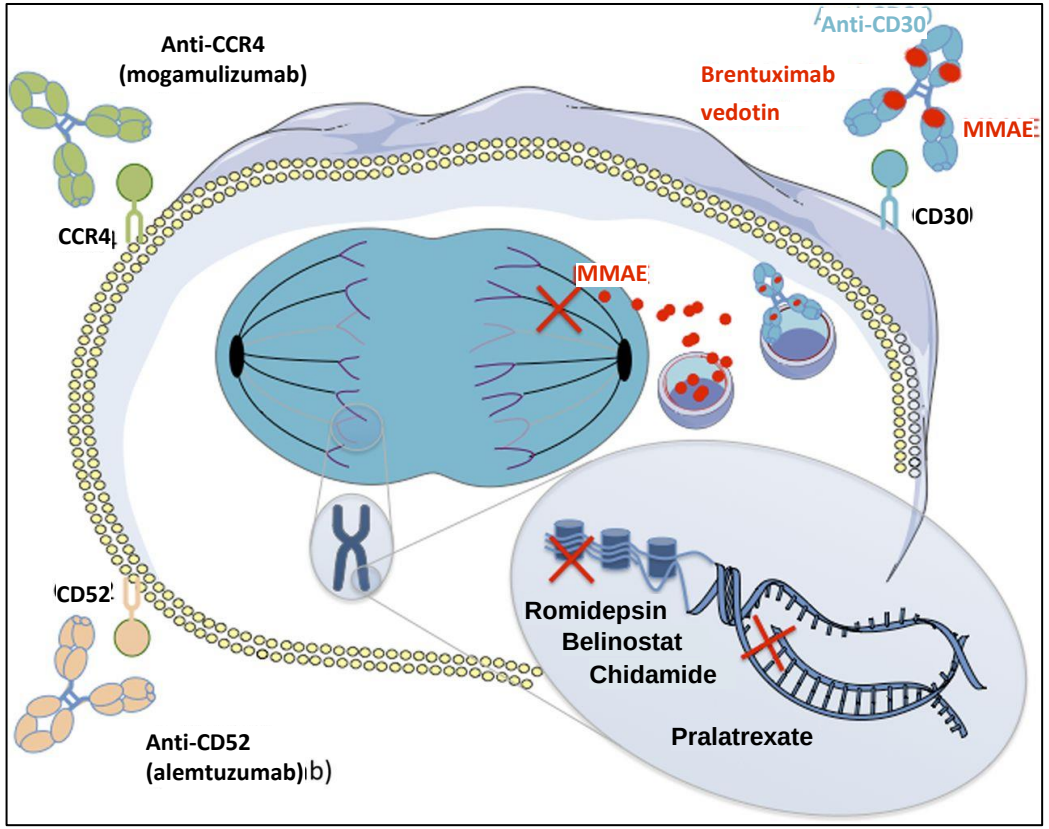
Disclosures

- 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

Approved drugs in relapsed/refractory PTCL



Mechanisms of action of new drugs in PTCL[1]

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)

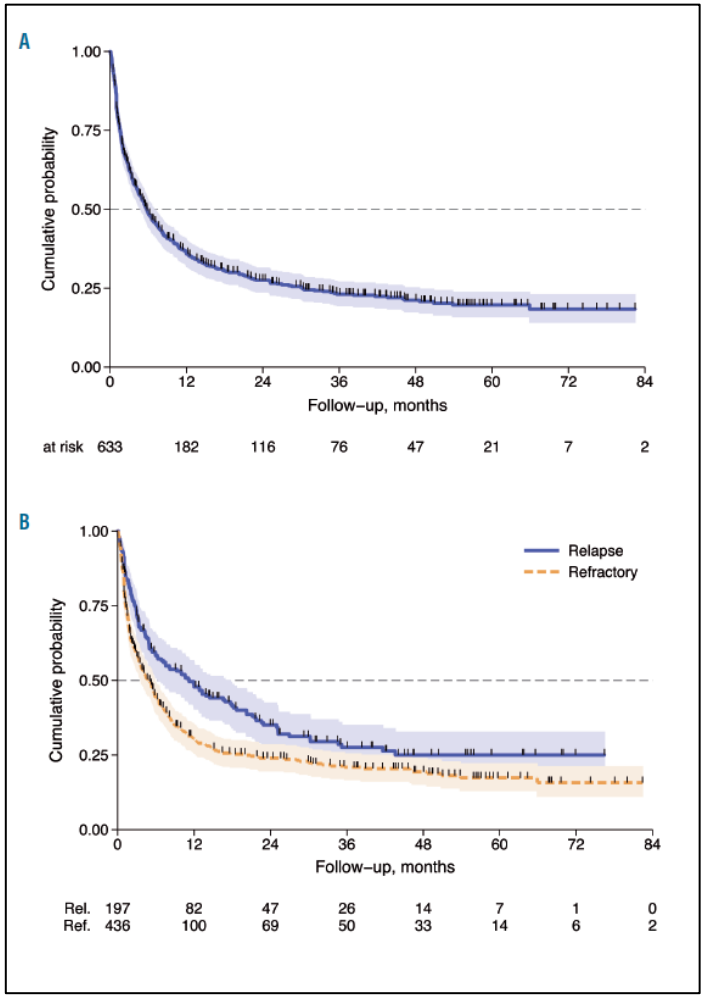
Bachy E, Coiffier B. Blood 2014;

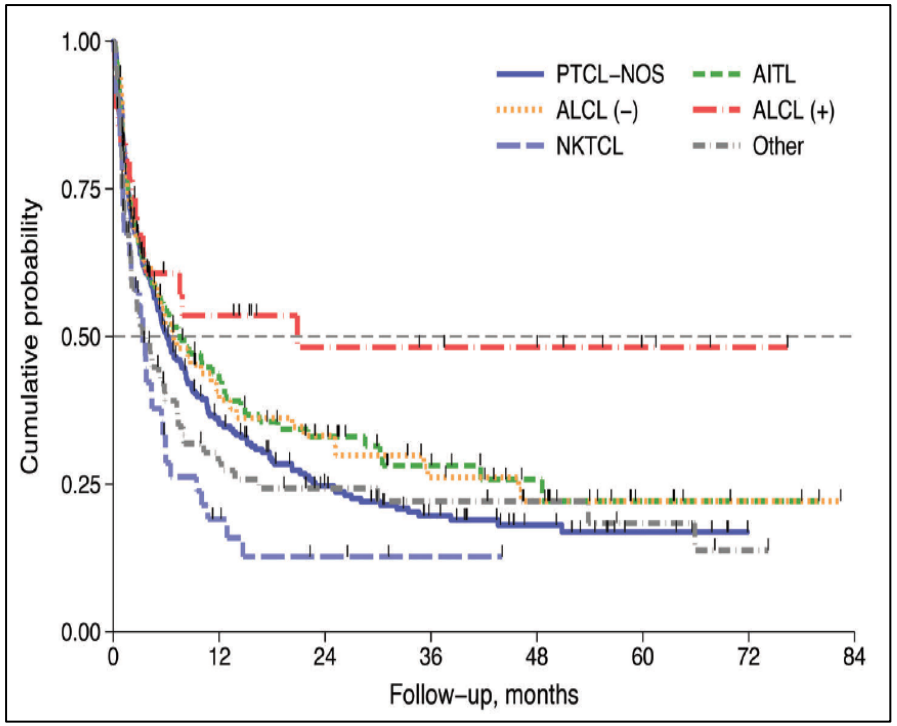
Clinical Activity of FDA *Approved* Therapeutics in Peripheral T-cell Lymphoma

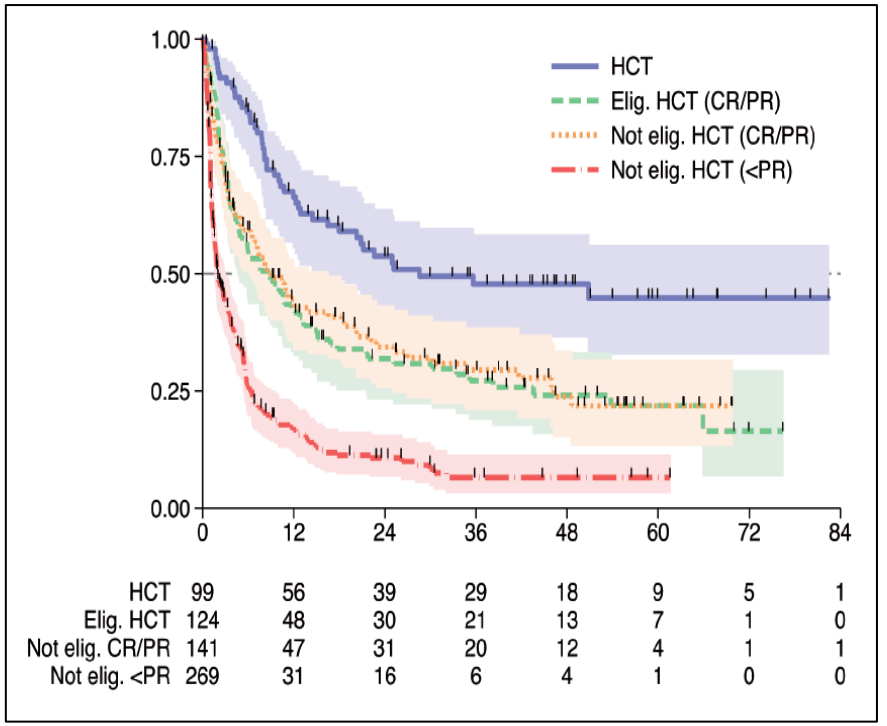
		Overall Response Rate	Complete Remission Rate	ORR PTCL-NOS	ORR AITL	ORR ALCL
FDA Approved	**Histone Deacetylase Inhibitors**					
	Romidepsin	25%	15%	29%	30%	24%
	Belinostat[15]	26%	11%	23%	54%	15%
	Anti-Folate					
	Pralatrexate[14]	29%	15%	32%	8%	29%
	CD30 Targeted Approaches					
	Brentuximab vedotin[26,44]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

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

Prospective International T cell Project
PTCL outcome after failing front line therapy



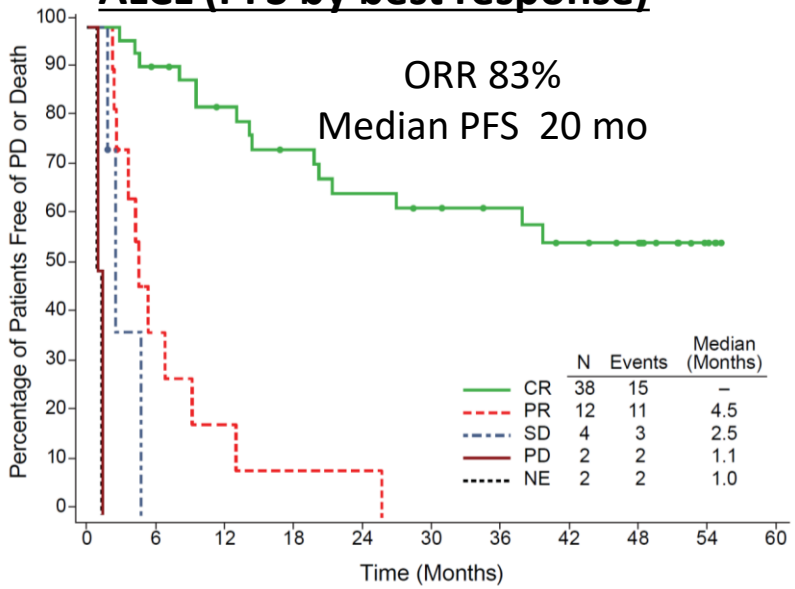




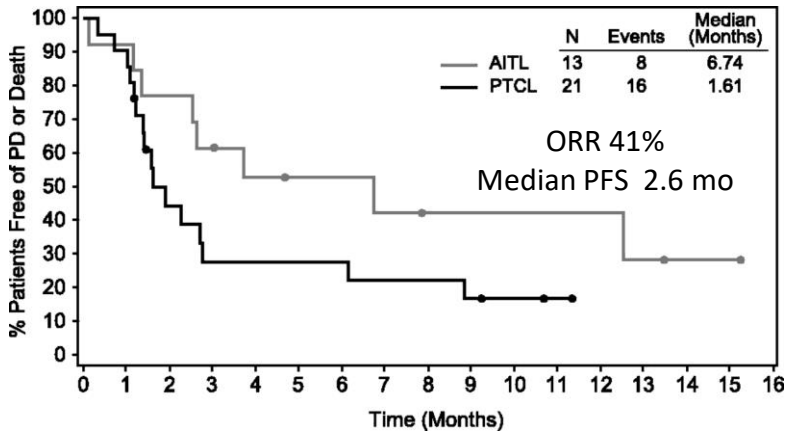
Bellei et al Hematologica 2018

Single Agent Brentuximab vedotin

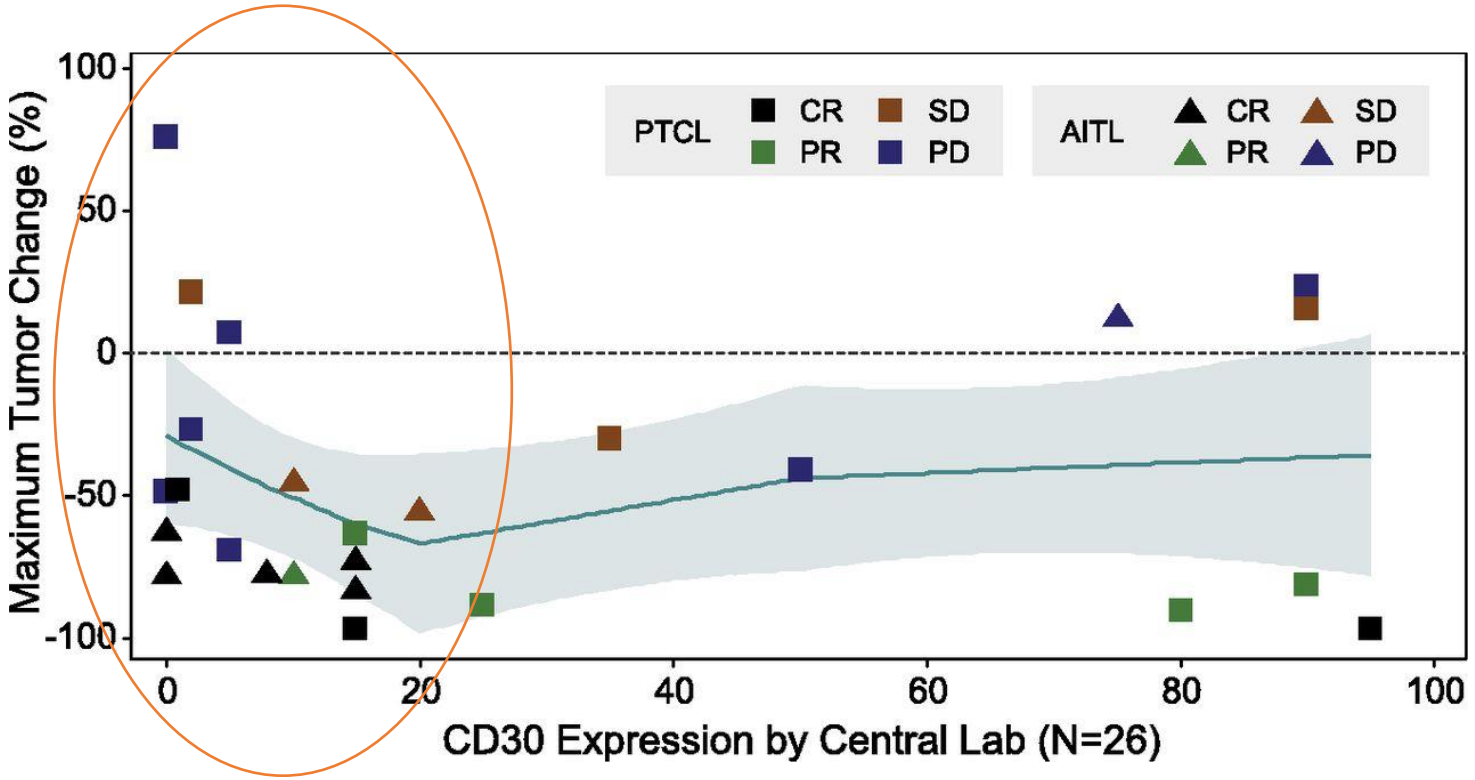
ALCL (PFS by best response)



PTCL and AITL PFS



Maximum tumor size decrease by quantitative CD30 expression.

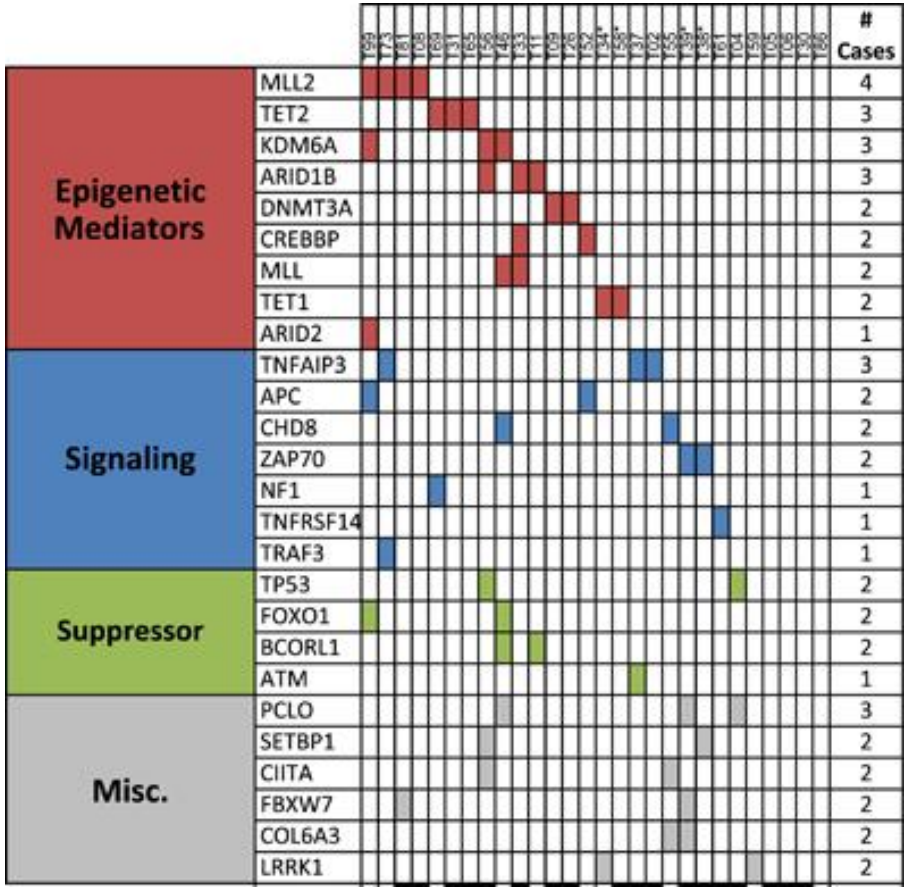


Consider Brentuximab vedotin for CD30 Expression >1%

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

Mutational Landscape in T-cell Lymphomas

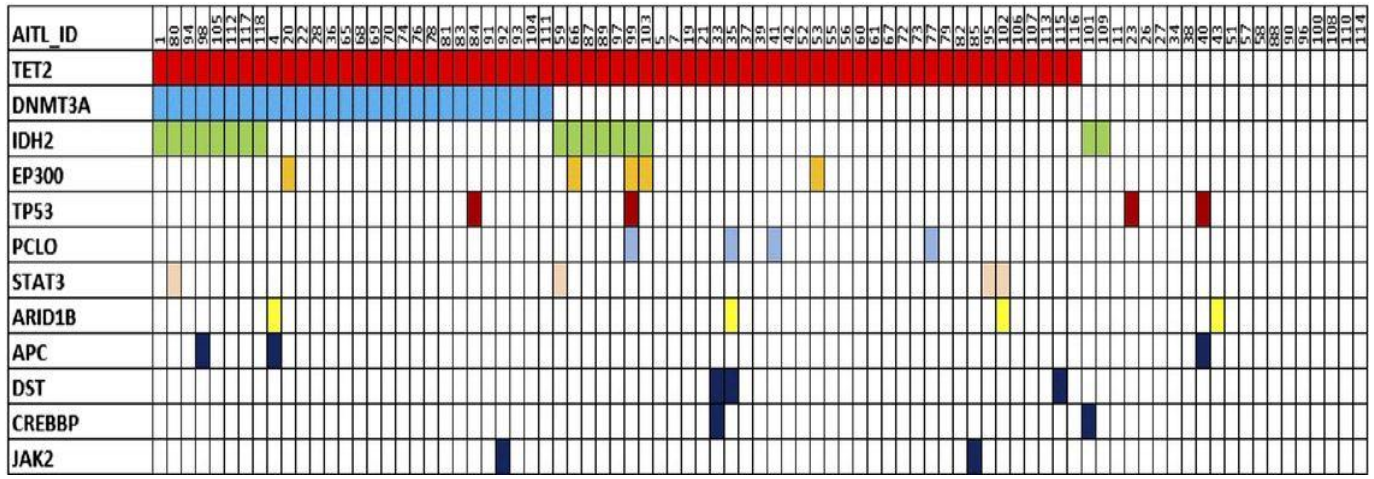
Mutations in chromatin modifiers are common in T-cell lymphomas (75% cases)

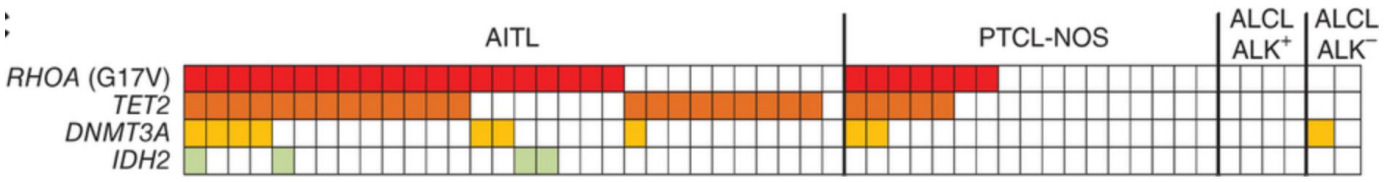


Schatz Leukemia 2014

Recurrent mutations in AITL

TET2: ~55-75%, RHOA: ~67% , IDH2: ~33%, DNMT3A: 20%

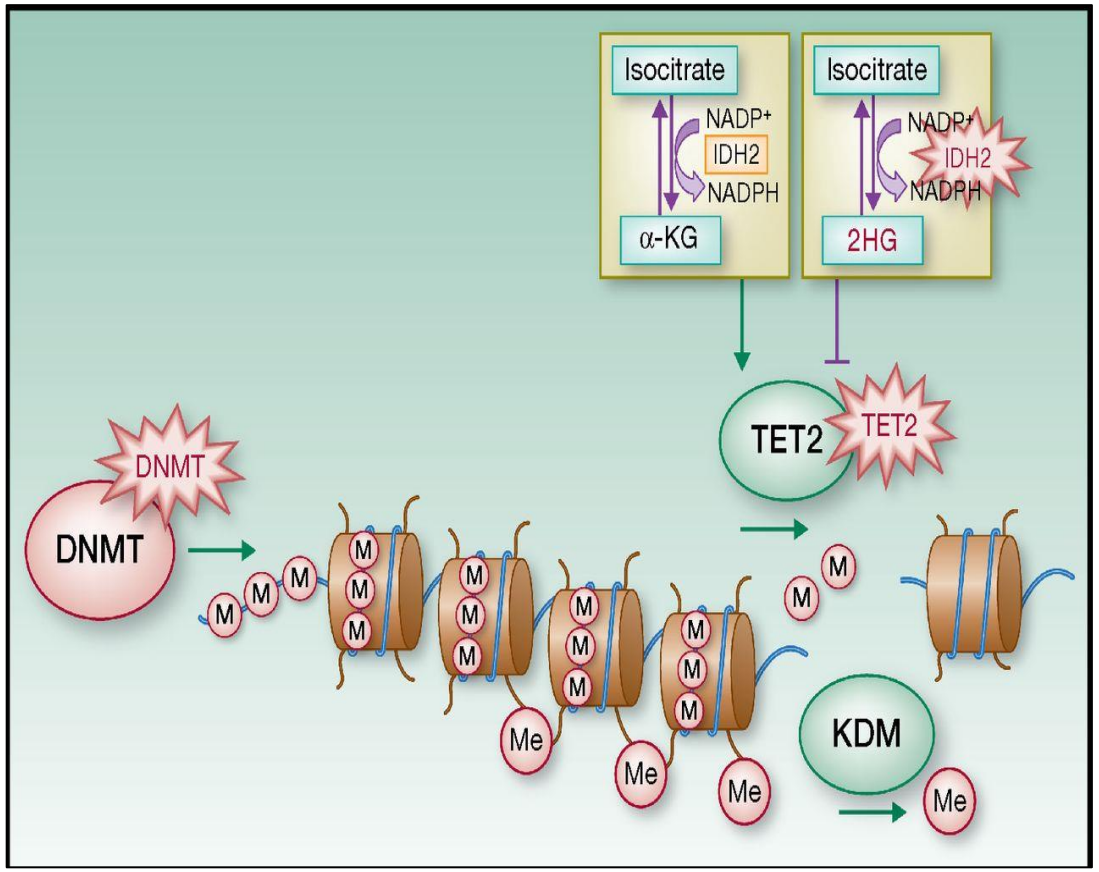




Odejide O et al. Blood 2014; Palomero et al Nature Genetics 2014 Chao Wang et al. Blood 2015

Mutations in epigenetic genes in AILT and PTCL-NOS affect DNA methylation

- **TET proteins**: involved in epigenetic control of transcription
- **DNMT3A gene** involved in cytosine methylation
- **Mutations in IDH2**: catalyzes the conversion of alpha-ketoglutarate to beta-hydroxyglutarate (2-HG)
- **Supra-normal levels of 2-HG** lead to hypermethylation of epigenetic targets and block cellular differentiation



O'Connor et al Clin Cancer Res 2014

Mutated Gene	AITL	PTCL-NOS	EATL
TET2	47-83%	38-49%	20%
IDH2R172	30-45%	0-6%	
DNMT3A	26%	27%	
RHOA	67-68%	0-18%	

Sakata-Yanagimoto et al Nat Genetics 2013, Palomero et al Nat Genetics 2013, Cairns et al Blood 2012, Lemonnier et al Blood 2012, Odejide et al Blood 2014

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

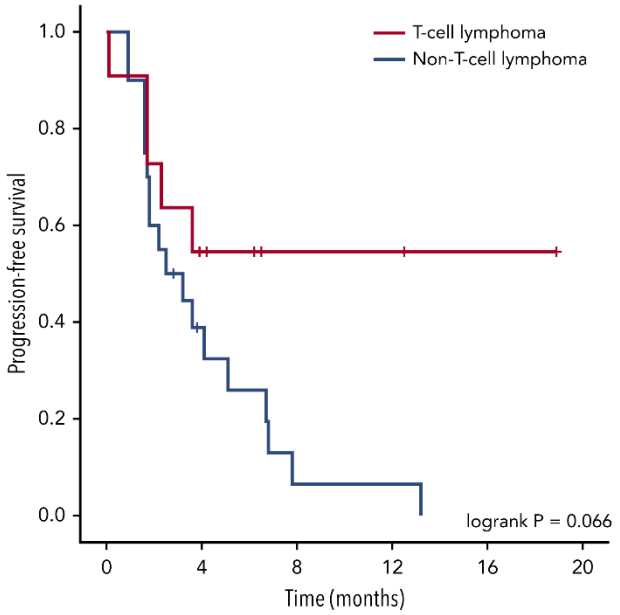
Romidepsin and 5-Azacitadine

T-cell lymphoma cell lines show synergy between HDACi and hypomethylating agents

Background

- Epigenetic dysregulation and aberrant DNA methylation in PTCL provides rationale for testing hypomethylating agents
- Azacytidine an epigenetic modifier inhibits DNA methyl transferase
- 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

	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'Conor et al. 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

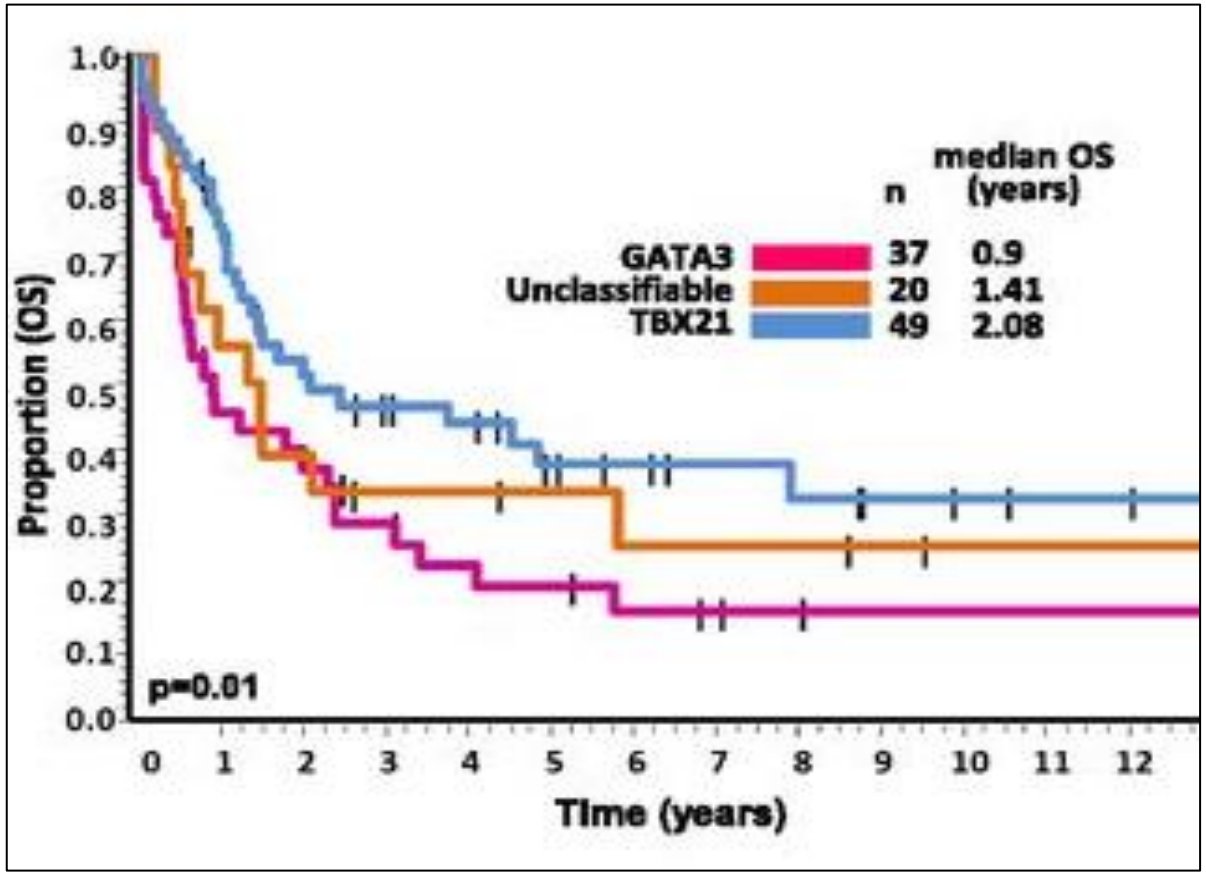
Histology	N	CR	PR	ORR
PTCL	7	1	1	2/7 (29%)
AITL*	5	4	1	5/5 (100%)
CTCL	3	-	1	1/3 (33%)
NK/T	1	-	-	0/1 (0%)
Total	16	5	3	8/16 (50%)

- Response rate in AITL 100%

Mehta-Shah AJH 2021

Other Targets in T Cell Lymphoma

PTCL: Gata3 high tumors show a worse OS enriched for PI3K-induced signatures



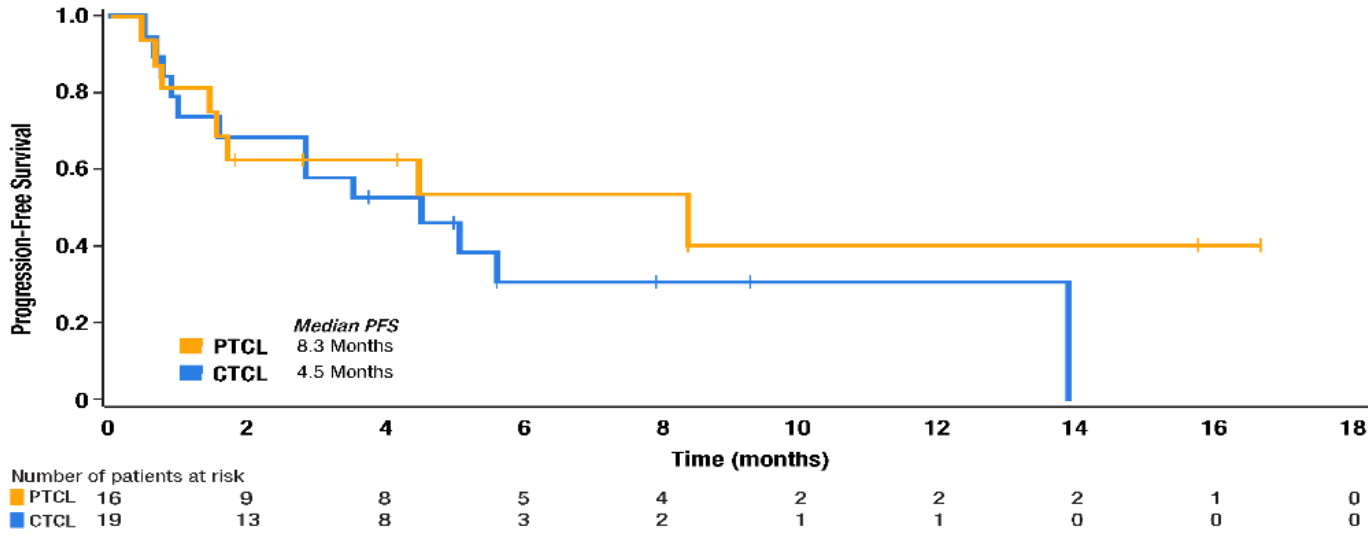
Iqbal J et al. Blood 2014

Duvelisib (P13K gamma-delta inhibitor) in TCL

- Duvelisib is an oral PI3 kinase δγ inhibitor
- Was approved for CLL and follicular lymphoma (25mg BID) (recently withdrawn)

- 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

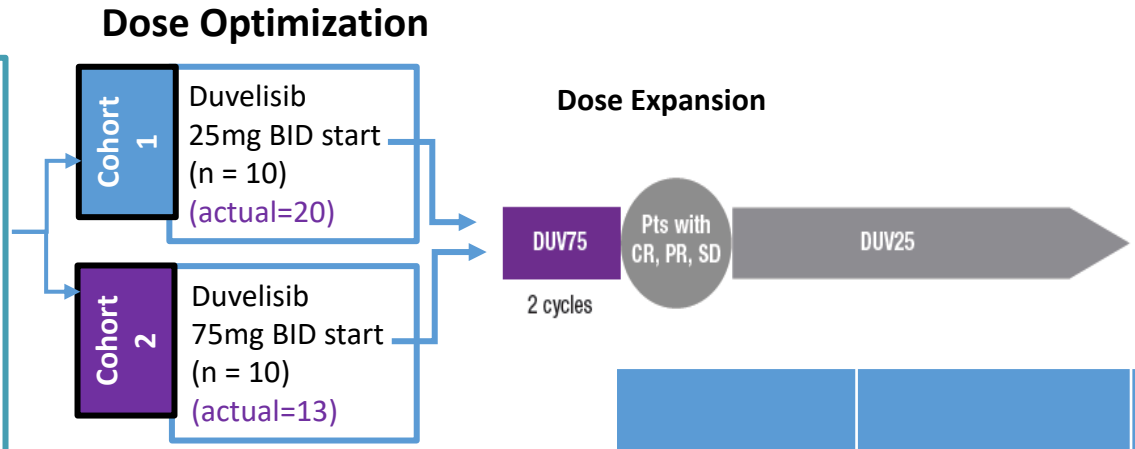
- Response to duvelisib associated with intrapatient changes in serum cytokine profile

Horwitz SM Blood. 2018

PRIMO: Duvelisib Single Agent in PTCL

Relapsed or Refractory PTCL

- 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%

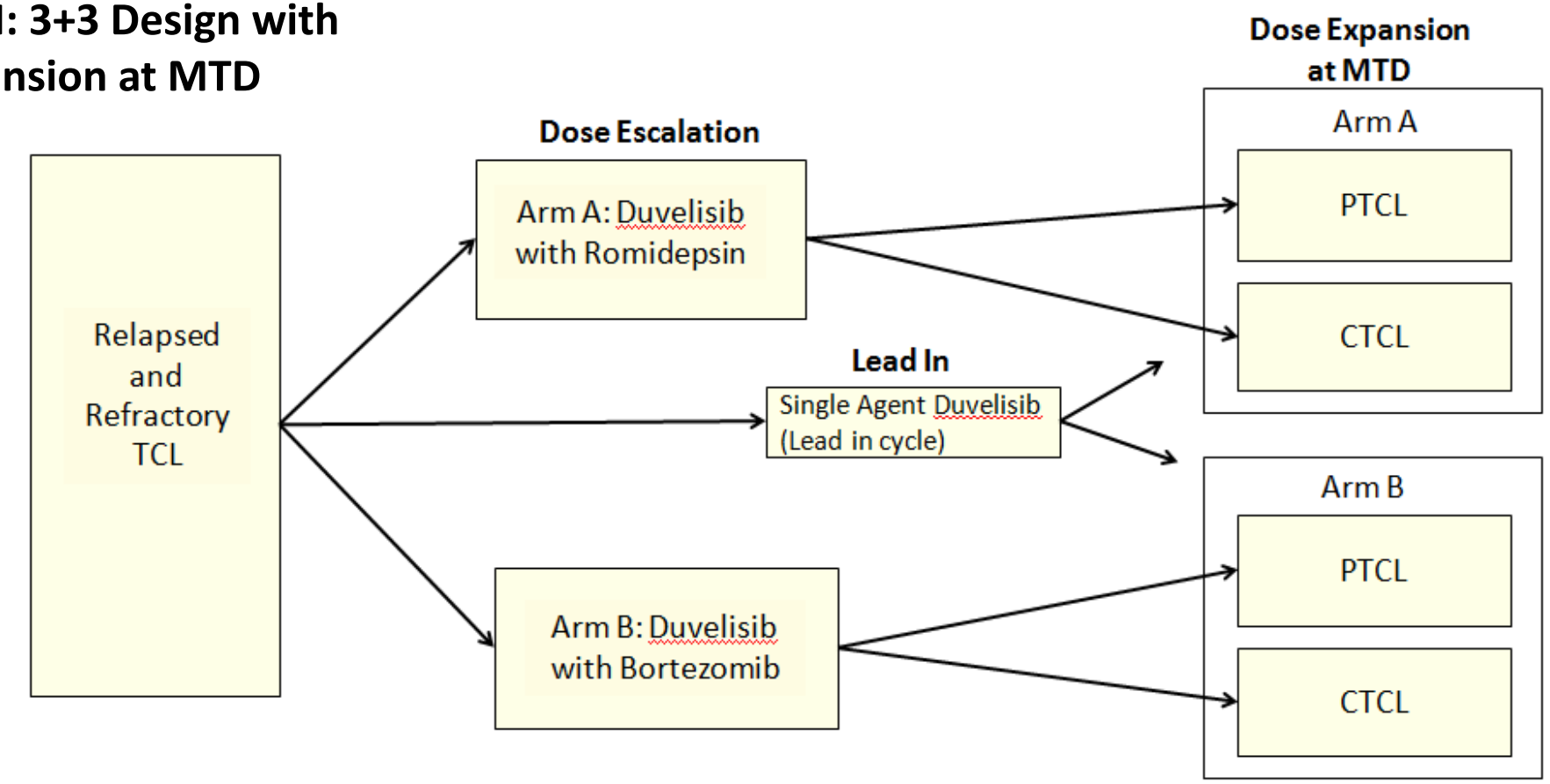
	Cohort 1 25 mg BID (N=20)	Cohort 2 75 mg BID (N=13)	Dose Expansion 75mg BID x 2 cycles→ 25mg BID (n=78)
ORR (%)	35%	54%	50%
CR (%)	25%	31%	32%

Brammer ASH 2021

NCT 03372057

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

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



Memorial Sloan Kettering Cancer Center 1884 · DANA-FARBER CANCER INSTITUTE · Stanford MEDICINE · Washington University in St. Louis SCHOOL OF MEDICINE · LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers

Duvelisib + Romidepsin Efficacy

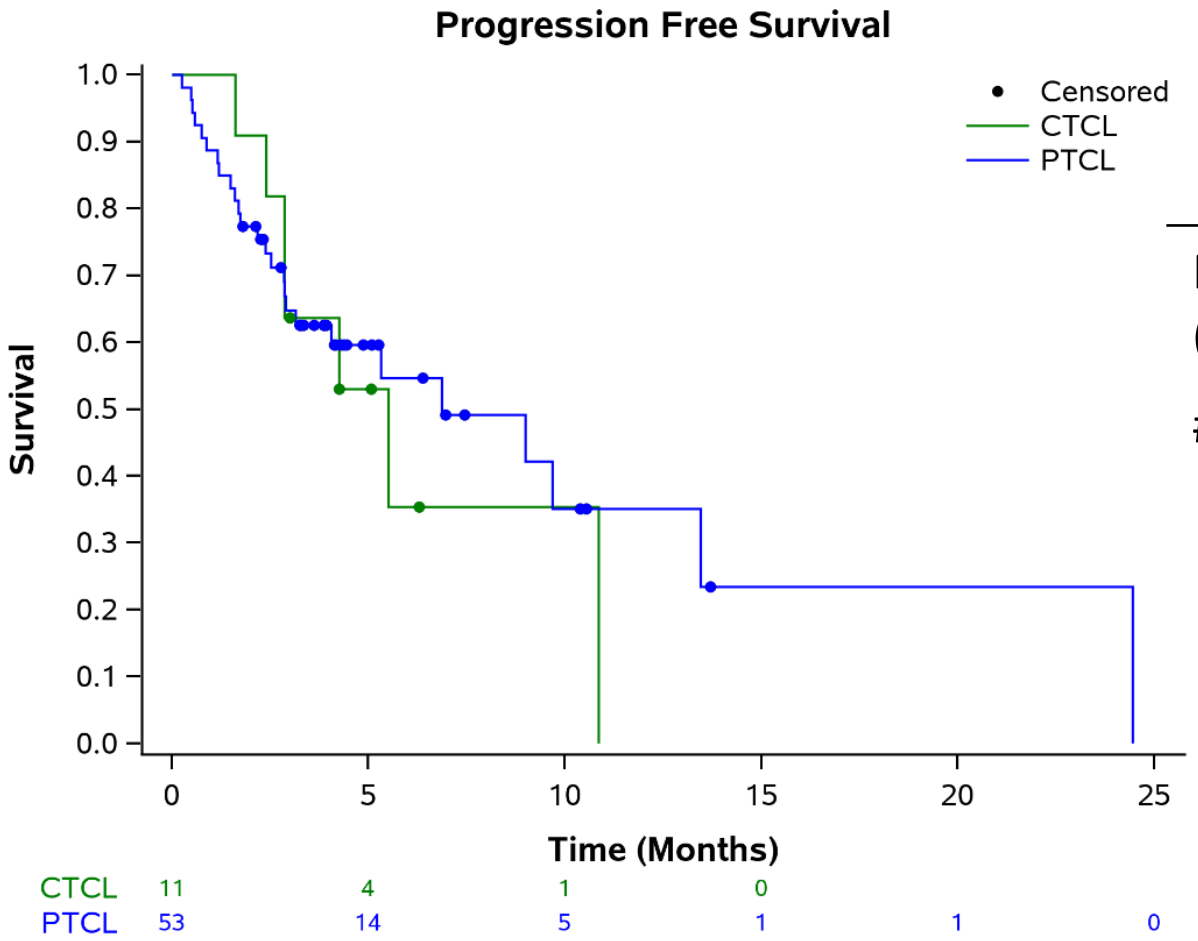
	#pts Evaluable for Response	Overall Response Rate	Complete Response	Partial Response
CTCL	4	2 (50%)	0	2 (50%)
PTCL	11	7 (64%)	4 (36%)	3 (27%)
(AITL/Tfh)	5	3 (60%)	2 (40%)	1 (20%)
(PTCL-NOS)	4	3 (75%)	2 (50%)	1 (25%)
TOTAL	**15/16**	**9 (60%)**	**4 (27%)**	**5 (33%)**

MTD: Romidepsin (10mg/m2 IV) + Duvelisib (75mg PO, BID)

Grade 3/4 Adverse Events: Neutropenia (27%), fatigue (8%), LFT abnormalities (8%)

Moskowitz, et al. ASH 2018

Romidepsin + Duvelisib



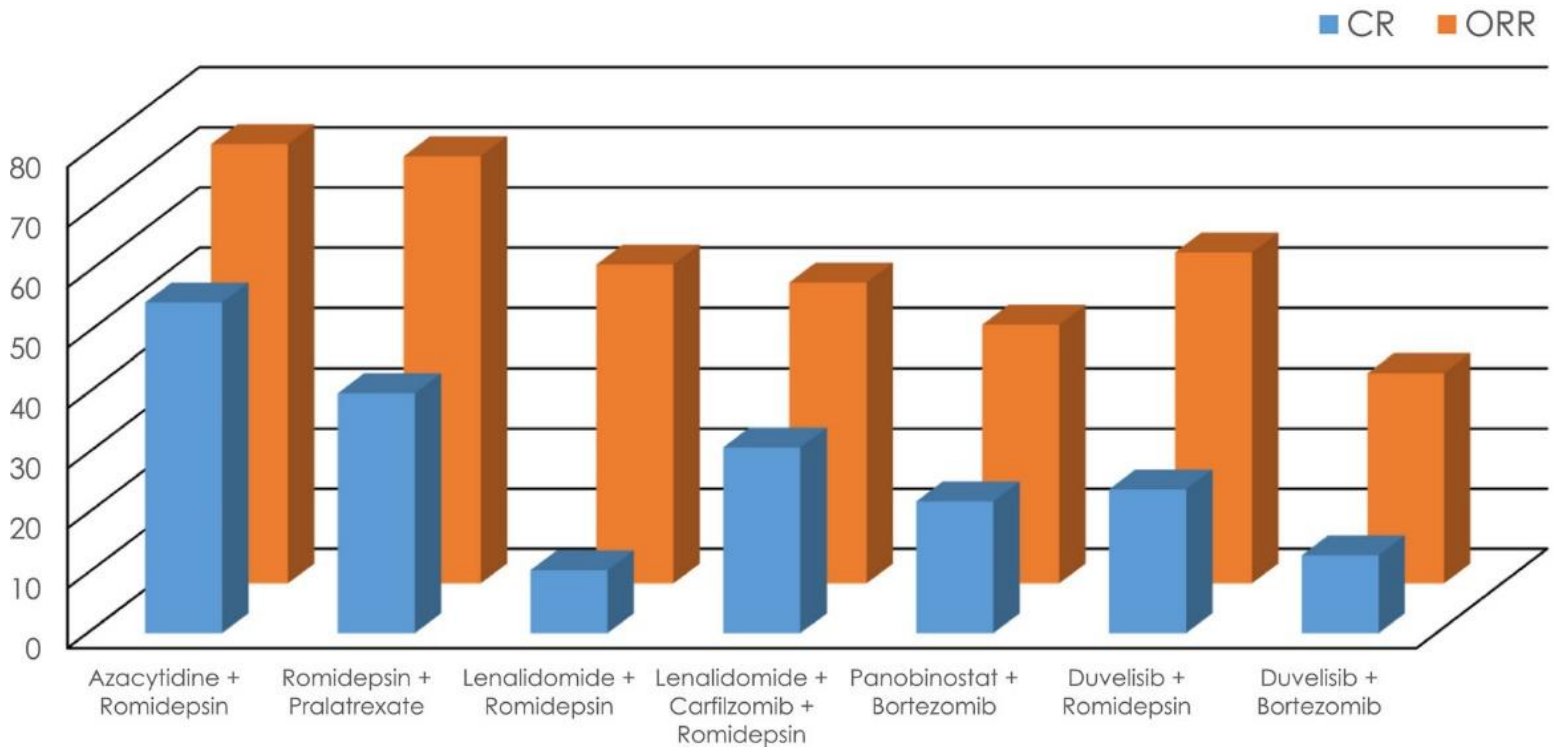
	PTCL	CTCL
Median PFS (95% CI)	6.9 Mo (4.1 – 24.5)	5.5 Mo (2.9 – 10.9)
# of patients → Transplant	15 (28%)	0

Well Tolerated:

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

Horwitz et al ICML 2021

Activity of Novel : Novel Combinations in Patients with Mature T-Cell Lymphomas



	ORR (%)	CR (%)
Azacytidine + Romidepsin	73	55
Pralatrexate + Romidepsin	71	40
Lenalidomide + Romidepsin	53	10.5
Lenalidomide + Carfilzomib + Romidepsin	50	31
Panobinostat + Bortezomib	43	22
Duvelisib + Romidepsin	55	24
Duvelisb + Bortezomib	35	13

Marici et al CA: A Cancer Journal for Clinicians 2019

T-cell entities and JAK-STAT activation

PTCL subtype	n	% with JAK/STAT activating mutations
Alk-negative anaplastic large cell lymphoma[1]	88	18%
Extranodal NK/T cell lymphoma[2]	51	5.9%
T-cell prolymphocytic leukemia[3]	50	76%
γδ-T cell lymphomas[2]	24	33%
Monomorphic epitheliotropic intestinal T-cell lymphoma[2]	19	36.8%
Large granular lymphocytic leukemia[4,5]	77	40%
Sezary Syndrome[6]	66	11%

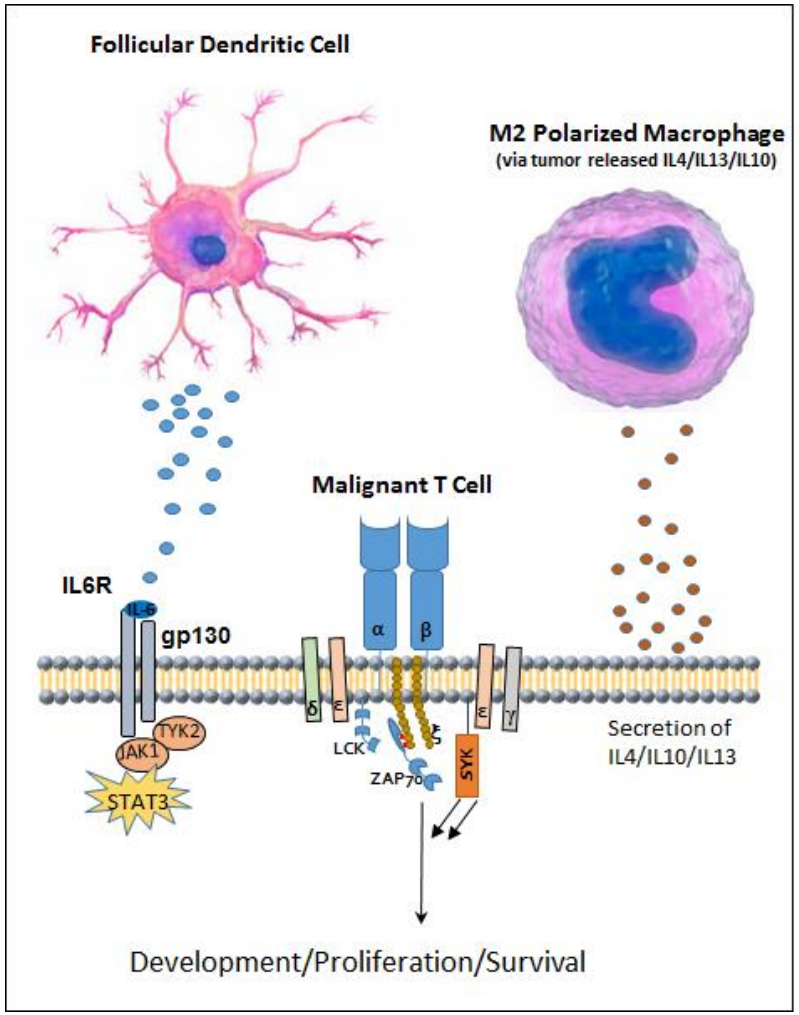
Subset	n	% positive pSTAT3
PTCL-NOS	59	27%
AITL	38	29%
ALK+ ALCL	15	93%
ALK- ALCL	28	57%
ENKTCL	12	50%

[1]Crescenzo R et al. Cancer cell 2015. [2]Kucuk C et al. Nature communications 2015;. [3]Kiel MJ et al. Blood 2014;124. [4]Koskela H et al. N Engl J Med 2012, [5]Jerez A et al. Blood 2012;. [6]Kiel M et al. Nature communications 2015; Gupta et al ASH 2013.

Courtesy of A. Moskowitz

Cerdulatinib (JAK/SYK inhibitor) Rationale

- PTCL frequently expresses SYK/ITK fusion protein
- Expression of SYK/ITK fusion protein in mice generates lymphoproliferative disease
- JAK inhibition may lead to disruption of the tumor microenvironment



Courtesy of A. Moskowitz

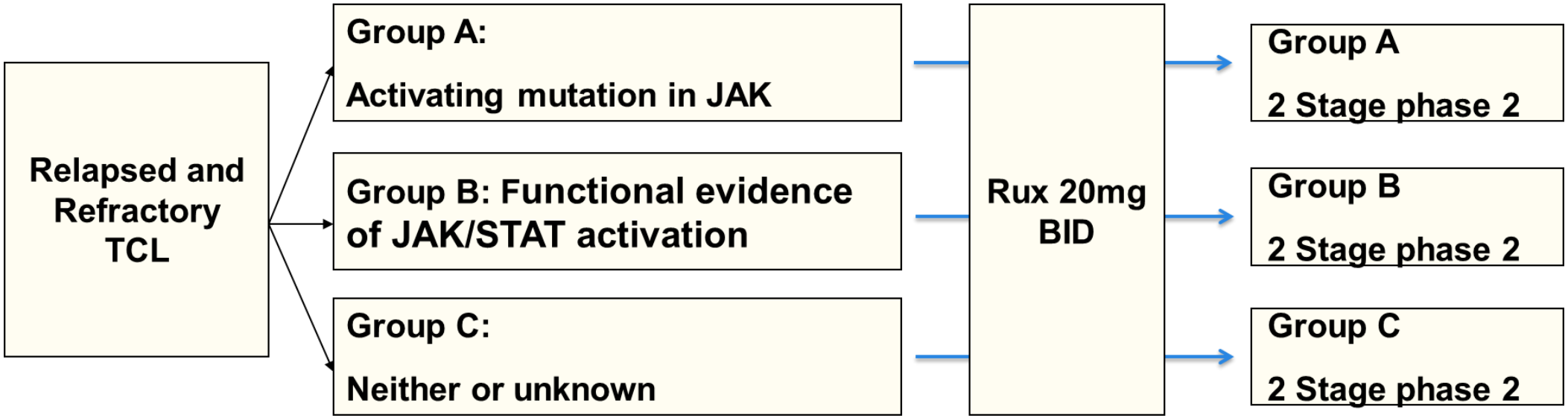
Cerdulatinib Efficacy

Response	AITL	PTCL-NOS	PTCL-Other	CTCL
n	27	11	26	40
Objective response rate Complete response %)	**52%** 37%	**0%** 0%	**31%** 15%	**43%** 8%

- Grade 3/4 Toxicities: Infections (29%), Elevated Lipase (21%), Elevated amylase (18%), neutropenia (8%), anemia (7%), fatigue (6%)

Horwitz ASH 2019

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

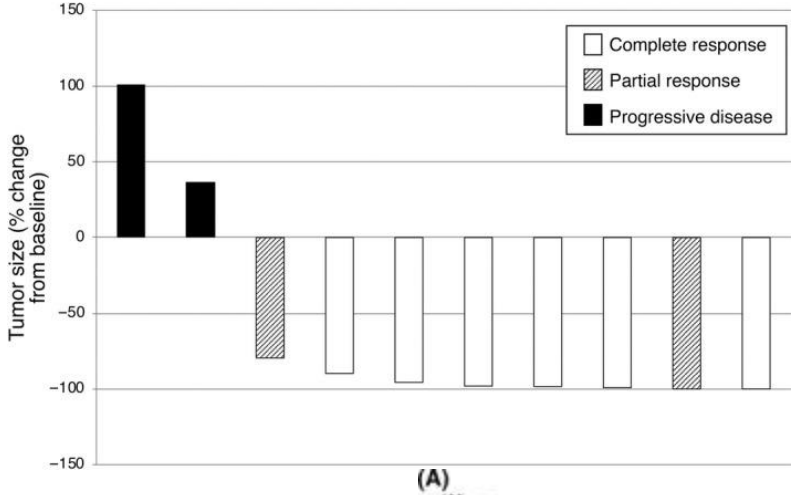
- ALK inhibitors are approved for ALK expressing lung cancer
- ALK rearrangements seen in ALK+ ALCL
  - t(2,5) leading to fusion of ALK to NPM1 or ALK to other partner genes
- Crizotinib studied in ALK+ ALCL by the Children's Oncology Group

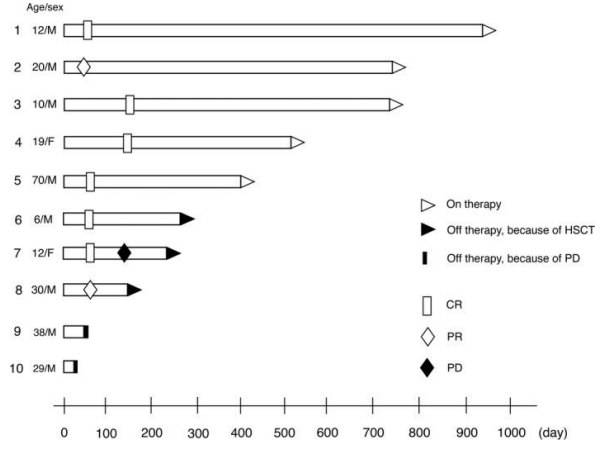
Outcome	ALCL 165 (n=6)	ALCL 280 (n=20)	Overall (n=26)
ORR	6 (83%)	18 (90%)	24 (92%)
CR	5 (83%)	16 (80%)	21 (81%)
PR	0	2 (10%)	2 (8%)
SD	1 (17%)	2 (10%)	3 (12%)
PD	0	0	0 (0%)

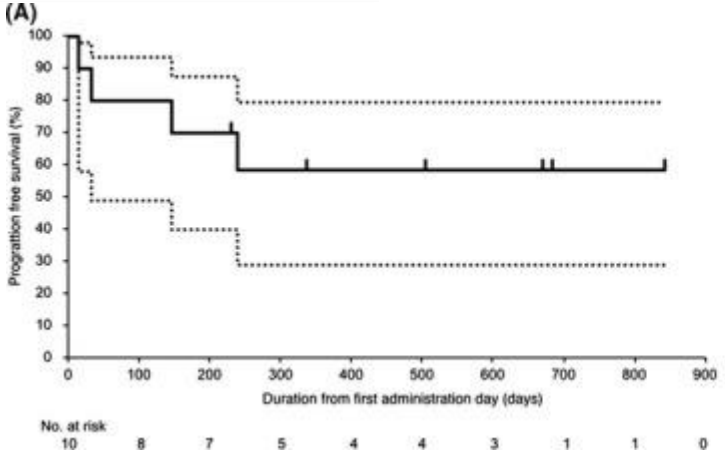
Mosse et al JCO 2018

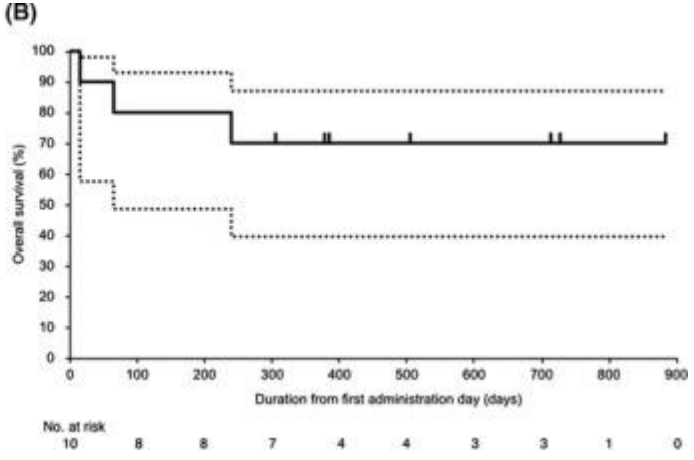
Alectinib: 2nd generation oral ALK inhibitor in R/R ALK + ALCL: Approved 2/2020 in Japan

ORR 80%, Well tolerated (gr 3 ANC 20%)
1y PFS 60%, OS 70%







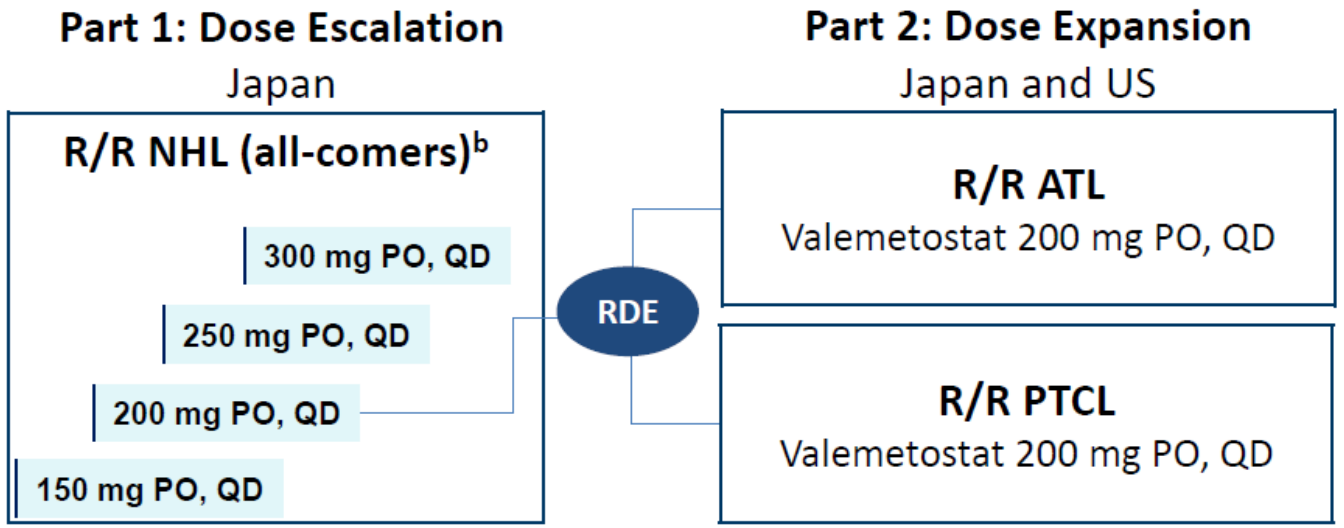


Fukano et al Ca Sci 2020

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



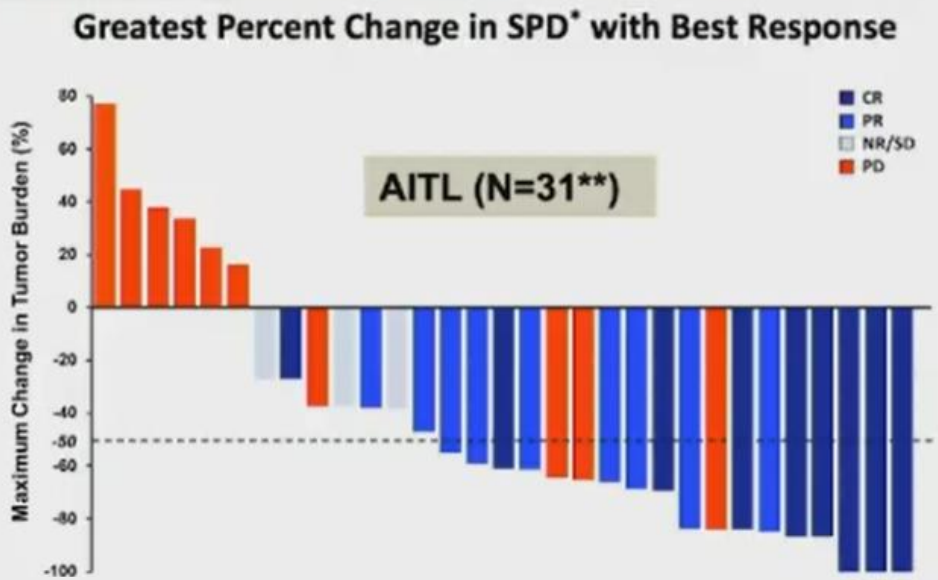
	All PTCL (n=44)	AITL (n=17)	PTCL-NOS (n=20)	ALCL (n=2)	Other TCL (n=5)
ORR (%)	54.5%	65%	50%	50%	40%
CR (%)	27.3%	47%	20%	50%	0%

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

Tipifarnib

- Tipifarnib is a potent, oral farnesyltransferase inhibitor
- In-licensed to Kura Oncology from Janssen
- Well characterized and manageable safety profile
  - (> 5,000 patients treated by Janssen program)
- Two different schedules have emerged:
  - 300 mg po bid days 1-21 q28 days
  - 600 - 900 mg po bid days 1-7 and days 15-21 q28 days

Significant Reduction in Tumor Burden with Tipifarnib Treatment – AITL Patients



Efficacy in relapsed/refractory disease

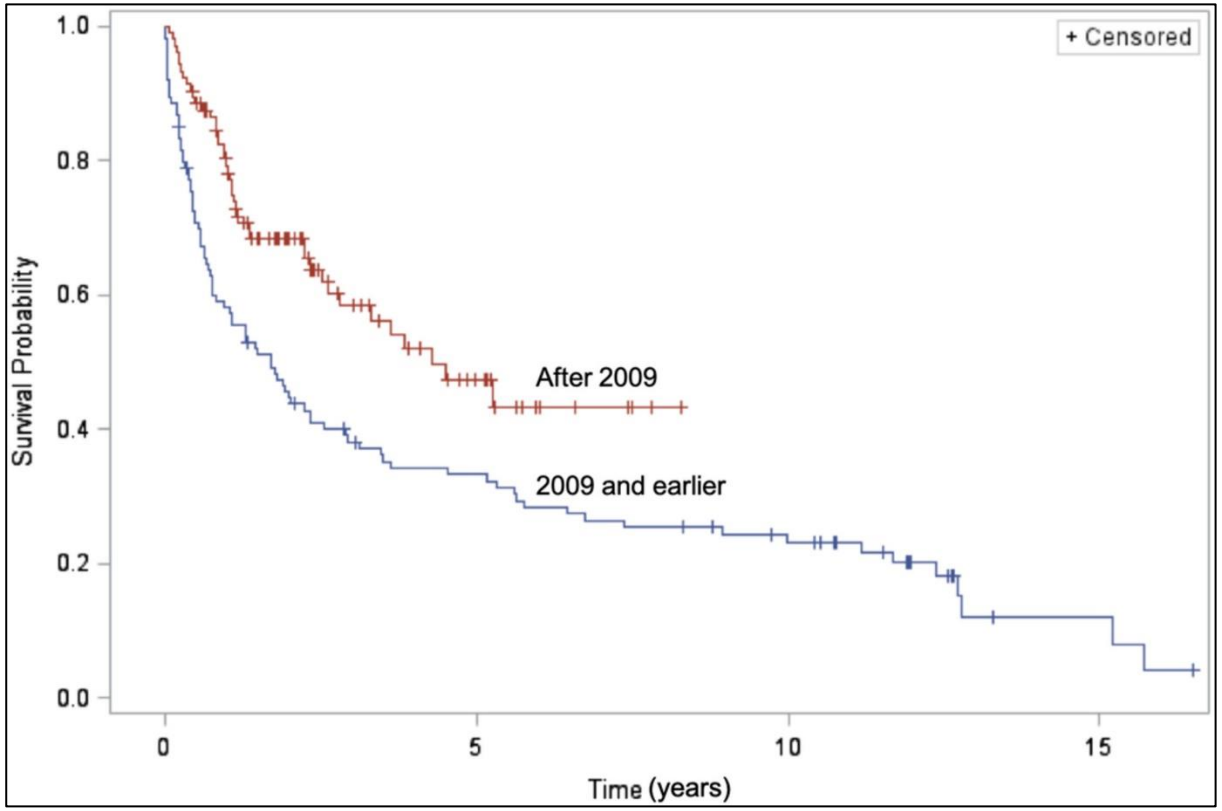
- **PTCL (PTCL-NOS + AITL)**: An ORR of 40%, including 17% complete responses, was achieved in patients with R/R PTCL.
  - Further biomarker analysis ongoing in PTCL-NOS group
- **AITL:** Tipifarnib achieved an ORR of 56%, including 28% complete responses, in unselected patients
  - 75% ORR if the tumor had a responder mutation (DNMT3A, IDH1/2 and RhoA genes)

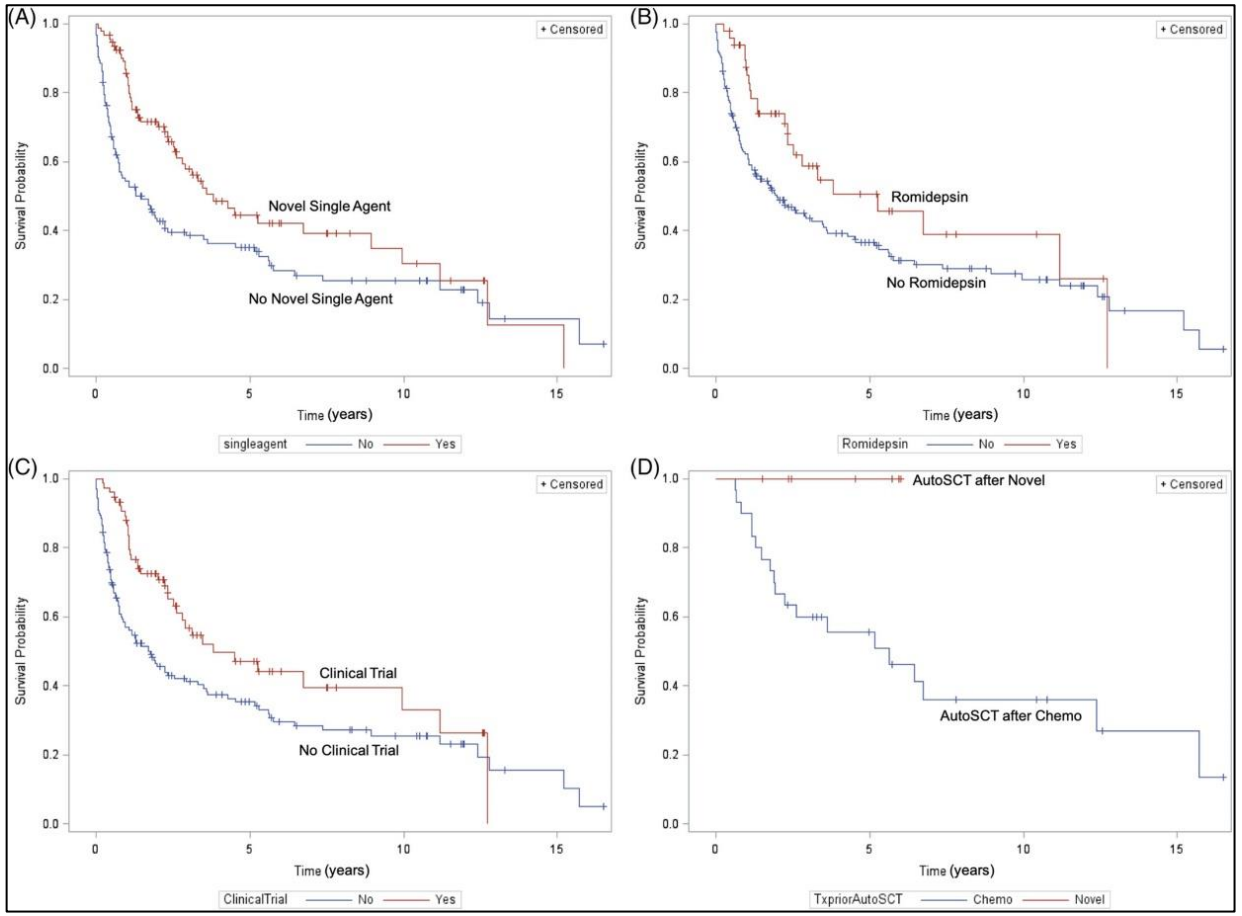
Wtzig et al ASH 2021

Immune Therapies in PTCL

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

Survival benefit in patients with peripheral T-cell lymphomas after treatments with novel therapies and clinical trials





Ma et al Hematological Oncology, 2019

T cell Lymphoma: New Agents

- Relapsed PTCL remains heterogeneous and poor prognosis
- Allogenic transplant only potentially curative option at relapse
- Newer Approaches promising BUT----
  - Epigenetic therapies, signaling targets, immune therapy
  - Likely also need subtype specific approaches
- Development impacted by pharma discontinuations (Romidepsin/Duvelisib)
- No home run
- Efforts need to be biology based/individualized in well designed trials
- Clinical trial enrollment and international cooperation critical