On the Horizon: Emerging Systemic Therapies for T-Cell Lymphomas

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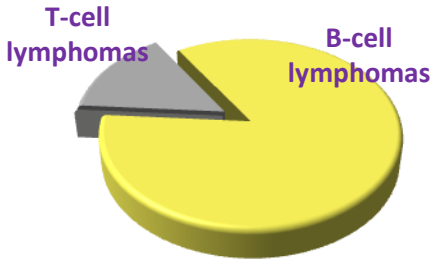
PTCL
Few (…of many) Facts

- PTCL accounts for ~10-15 % of all NHL

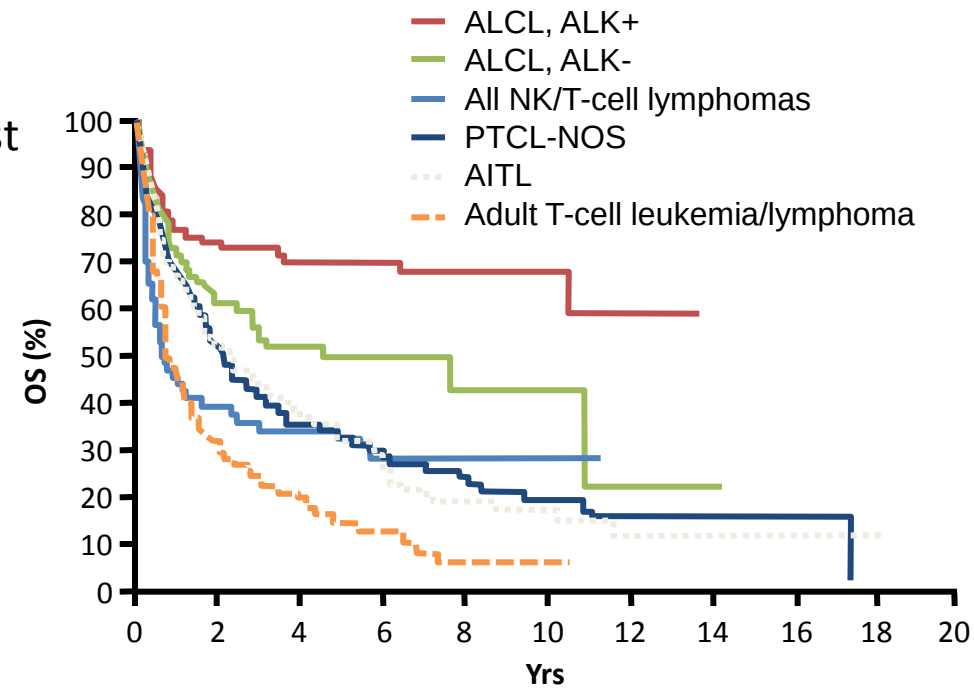


- PTCL subtypes: many entities with diverse biological features and clinical presentation

- Aggressive disease with an often poor prognosis with conventional treatment

The International PTCL and NK/TCL Study: OS in PTCL

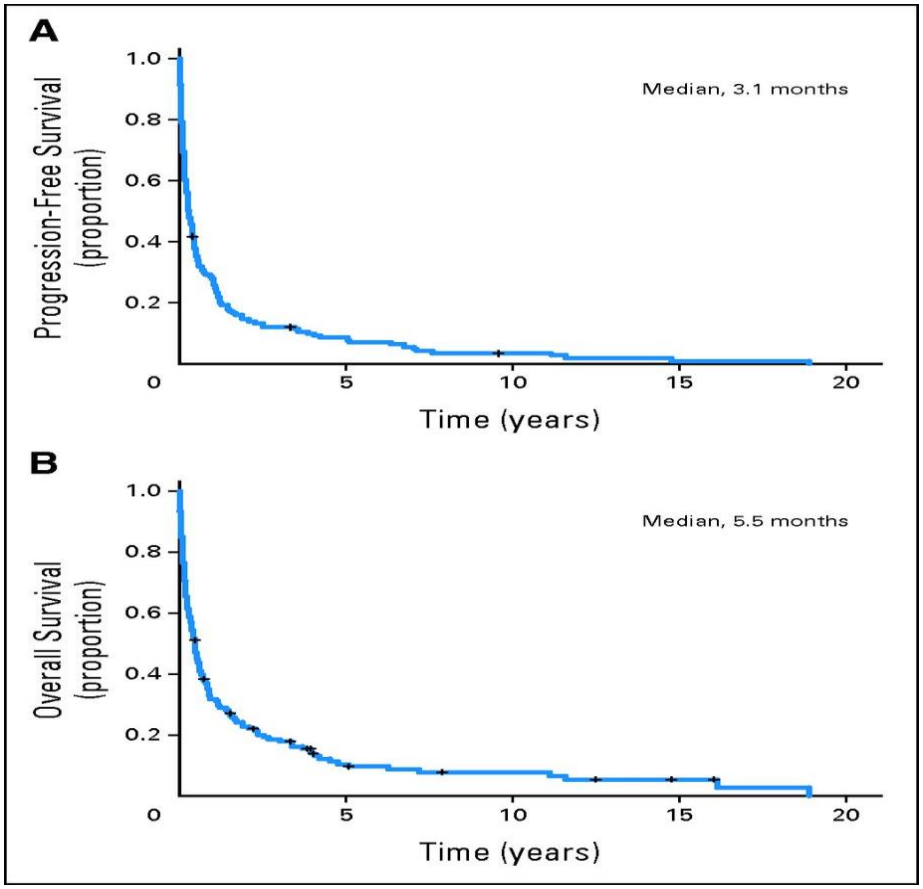
- Majority of patients (> 85%) with most common disease subtypes received anthracycline-containing regimen

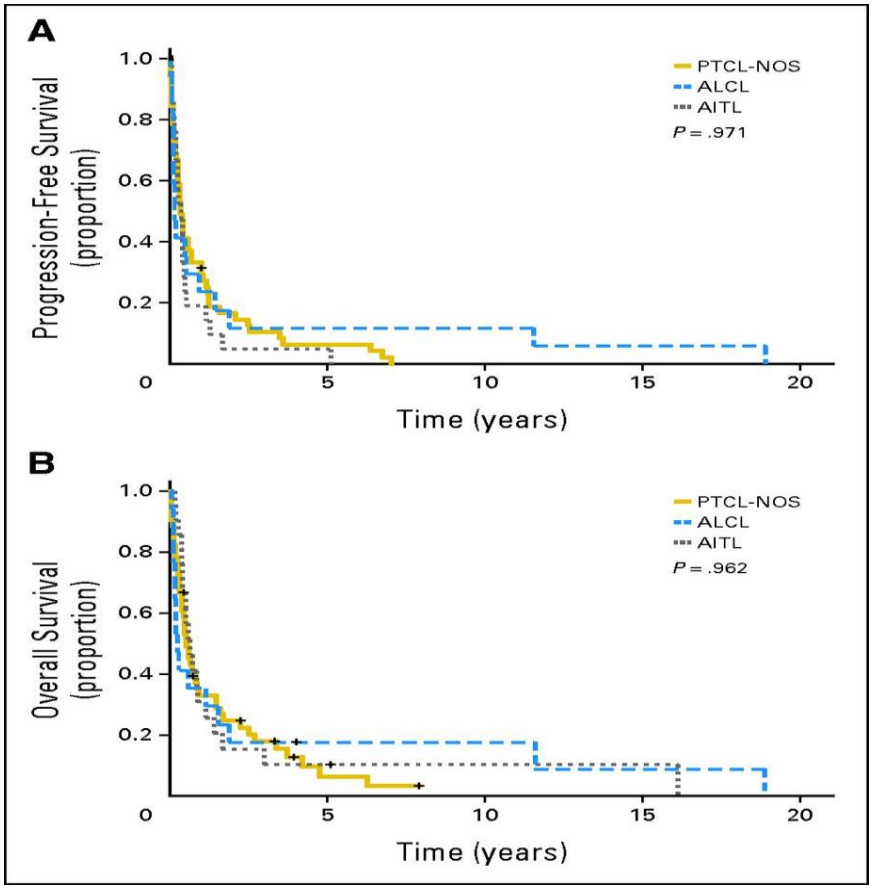


	PTCL Subtypes					
	ALK+ ALCL	**ALK– ALCL**	**PTCL-NOS**	**AITL**	**NK/TCL**	**ATLL**
5-yr OS rate, %	70	49	32	32	32	14

International T-Cell Lymphoma Project. J Clin Oncol. 2008;26:4124-4130.

First Relapse or Progression of PTCL





Mak V et al. JCO 2013;31:1970-1976

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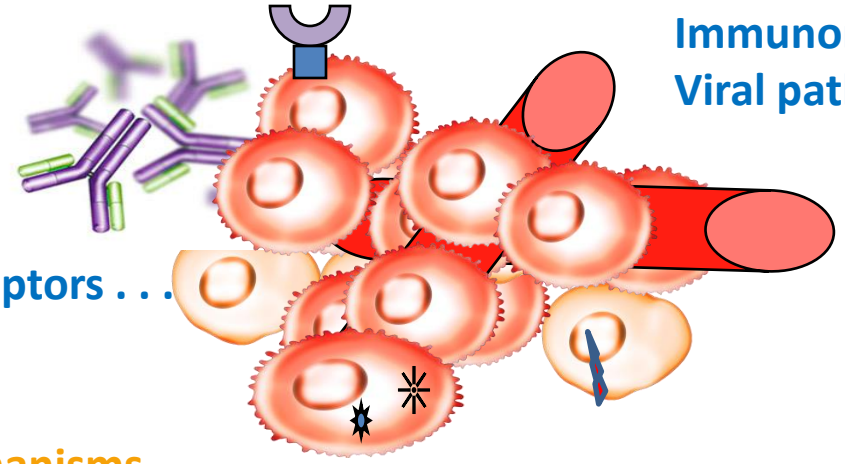
Targeting Peripheral T-Cell Lymphoma

Targeting the Cancer Cell

Surface Antigens/Receptors

- CD2
- CD4
- CD25
- CD30
- Chemokine receptors . . .



Cellular Survival Mechanisms

- Proteasome inhibition
- HDAC inhibition
- Death receptors and ligands
- Cell-cycle arrest
- Signal transduction inhibition

Targeting the Microenvironment

- Angiogenesis
- Immunomodulation
- Viral pathogens

Genetic alterations

AITL: *RHOA, TET2, IDH2, DNMT3A, CD28*

ALCL, ALK+: t(2;5)(*NPM/ALK*)

Agents With Activity in T-Cell Lymphomas

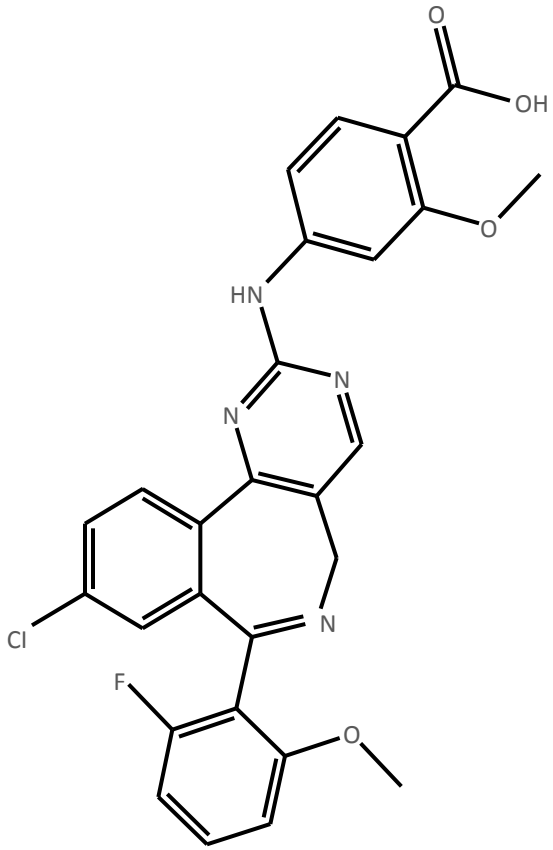
Agent	MOA
Romidepsin	HDAC inhibitor
Pralatrexate	Folate analog
Alisertib (MLN8237)	Aurora kinase A inhibitor
Belinostat (PXD101)	HDAC inhibitor
Bendamustine	Alkylating agent
Brentuximab vedotin	Anti-CD30 monoclonal antibody-toxin conjugate
Bortezomib	Proteasome inhibitor
Lenalidomide	Immunomodulator
IPI-145	PI3Kδ inhibitor
Mogamulizumab (KW-0761)	Defucosylated anti-CCR4 monoclonal antibody
Tipifarnib	Farnesyltransferase inhibitor

Relapsed/Refractory PTCL
FDA-Approved agents

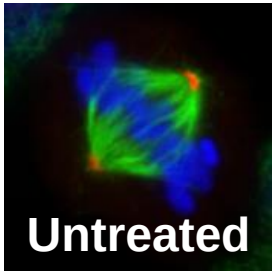
Agent	Dose/schedule	N	ORR (%)	CR (%)	DOR, Mos
Pralatrexate	30 mg/m2 weekly X 6	111	29	11	10.1
Romidepsin	14 mg/m2 Weekly X 3 Q 28 days	131	25	14	17
Belinostat	1000 mg/m2 Daily x5 Q21 days	24 120	25 26	8 11	3 8
Brentuximab Vedotin (ALCL)	1.8 mg/kg Q 21 days	58	86	57	12.6

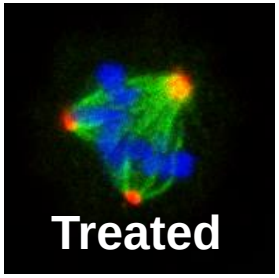
O'Connor OA, et al. J Clin Oncol. 2011;29:1182-1189; Coiffier B, et al. J Clin Oncol. 2012;30:631-636; O'Connor et al. ASCO 2014. Pro B, et al. J Clin Oncol. 2012;30:2190-2196

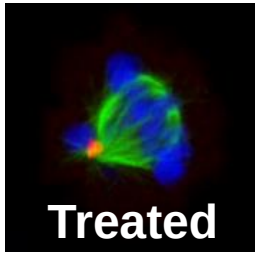
Alisertib: Aurora A Kinase Inhibitor



- Leads to mitotic arrest
  - Abnormal spindles, unseparated centrosomes
  - Cells undergo apoptosis
- Phase II trial in B-cell and T-cell NHL (N = 48)
  - ORR: 27% (50% [4/8] in T-cell lymphoma)
  - Common grade 3/4 AEs: neutropenia, leukopenia, anemia, thrombocytopenia, stomatitis

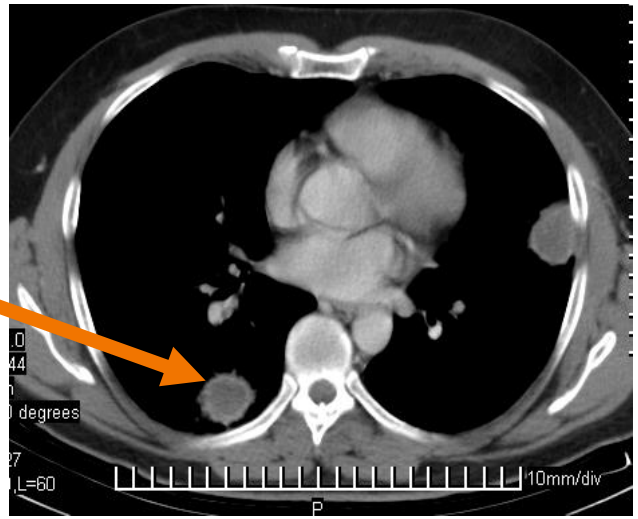


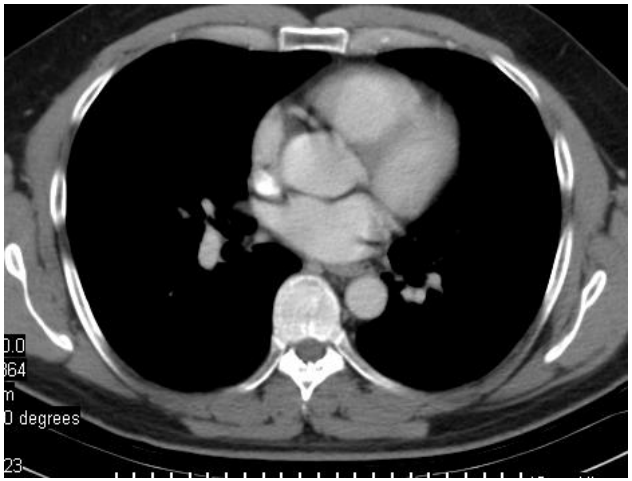


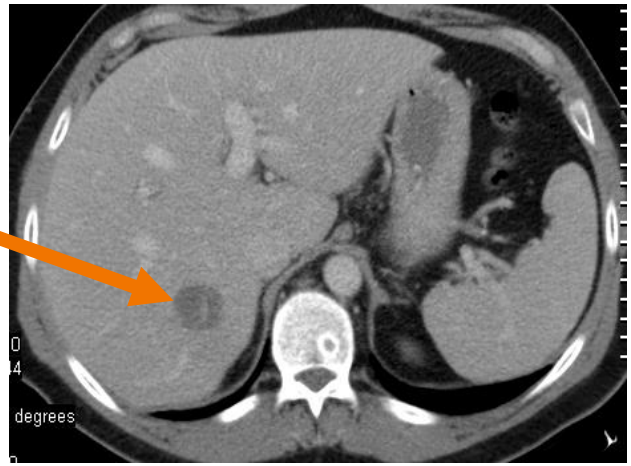


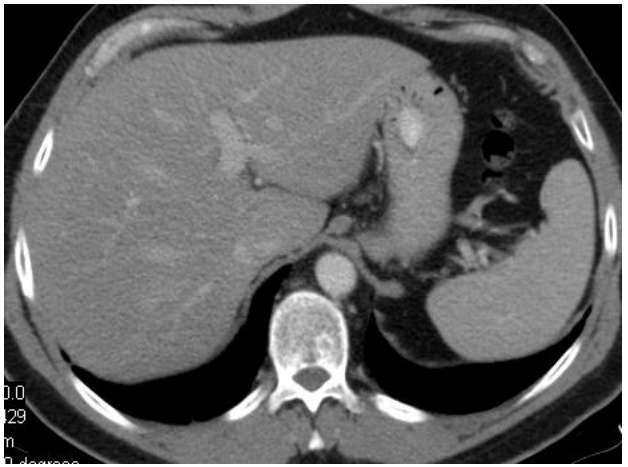
Friedberg J, et al. J Clin Oncol. 2013;

Patient example:
Relapsed enteropathy-associated NHL









Pre Alisertib

Post Alisertib

Alisertib: Clinical Trial in PTCL

- S1108: Phase II multicenter intergroup single arm study
- Patient population: relapsed refractory peripheral T-cell NHL
  - PTCL NOS, angioimmunoblastic, anaplastic large cell, extranodal NK/T-cell, adult T-cell
  - Transformed MF
- Normal organ function
- ANC ≥1500/mm^3, platelets ≥ 75,000/mm^3

- Schema: 21 day cycle
  - Alisertib 50 mg po BID x 7 days
  - Dose reduction to 40 mg BID, 30 mg BID allowed for toxicity

Barr et al. ASCO 2014, abstract 8523

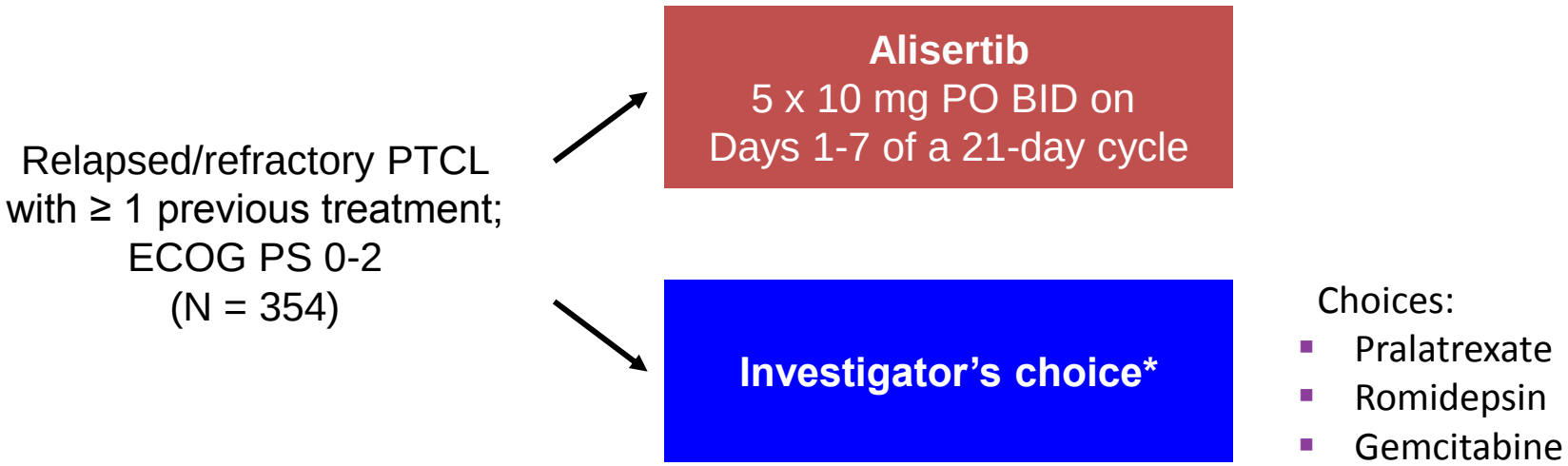
Clinical Activity

Category	N = 37 (%)
PTCL response rate	**30%**
Transformed MF response rate	**0%**
Complete response	**2 (5)**
Partial response	**7 (19)**
Stable disease	**7 (19)**

Barr et al. ASCO 2014, abstract 8523

Alisertib or Single-Agent Chemotherapy in Patients With Relapsed/Refractory PTCL

- Multicenter, randomized, open-label phase III trial



- Primary endpoint: ORR, PFS
- Secondary endpoints: CR, OS, DoR, time to response, TTP, safety

ClinicalTrials.gov. NCT01482962.

Alisertib in T-cell Lymphoma: Future Directions

- International randomized phase III trial comparing alisertib to investigator's choice
- Phase I: combination with romidepsin
- Phase I: combination with vorinostat
- Preclinial: combination with PI3K inhibition

Brentuximab Vedotin in Relapsed or Refractory Mature T-/NK-Cell Lymphomas

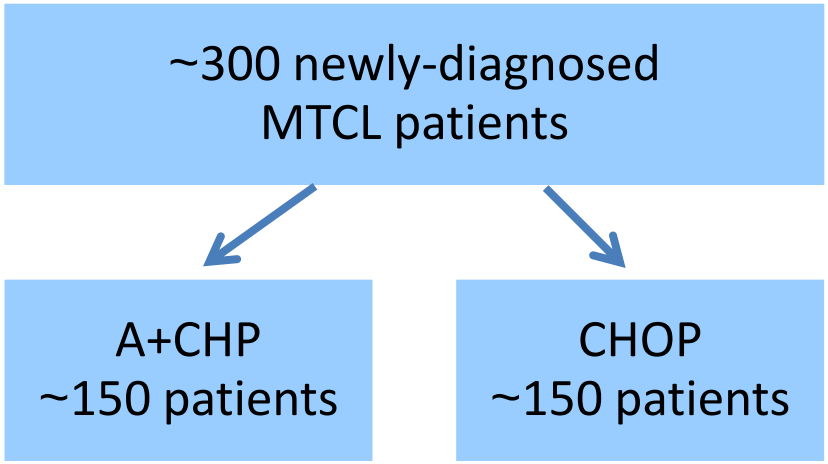
Response, n (%)	Best Clinical Response per Investigator				
	CR	PR	SD	PD	ORR (CR + PR)
Mature T-/NK-cell lymphomas (n = 22)	6 (27)	2 (9)	6 (27)	8 (36)	8 (36)
AITL (n = 10)	4 (40)	1 (10)	2 (20)	3 (30)	5 (50)
PTCL-NOS (n = 12)	2 (17)	1 (8)	4 (33)	5 (42)	3 (25)

- Median duration of objective response has not been reached (range to date: 0.1+ to 18+ wks)

Oki Y, et al. International Conference on Malignant Lymphoma 2013. Abstract 152.

ECHELON-2 Phase 3 Study

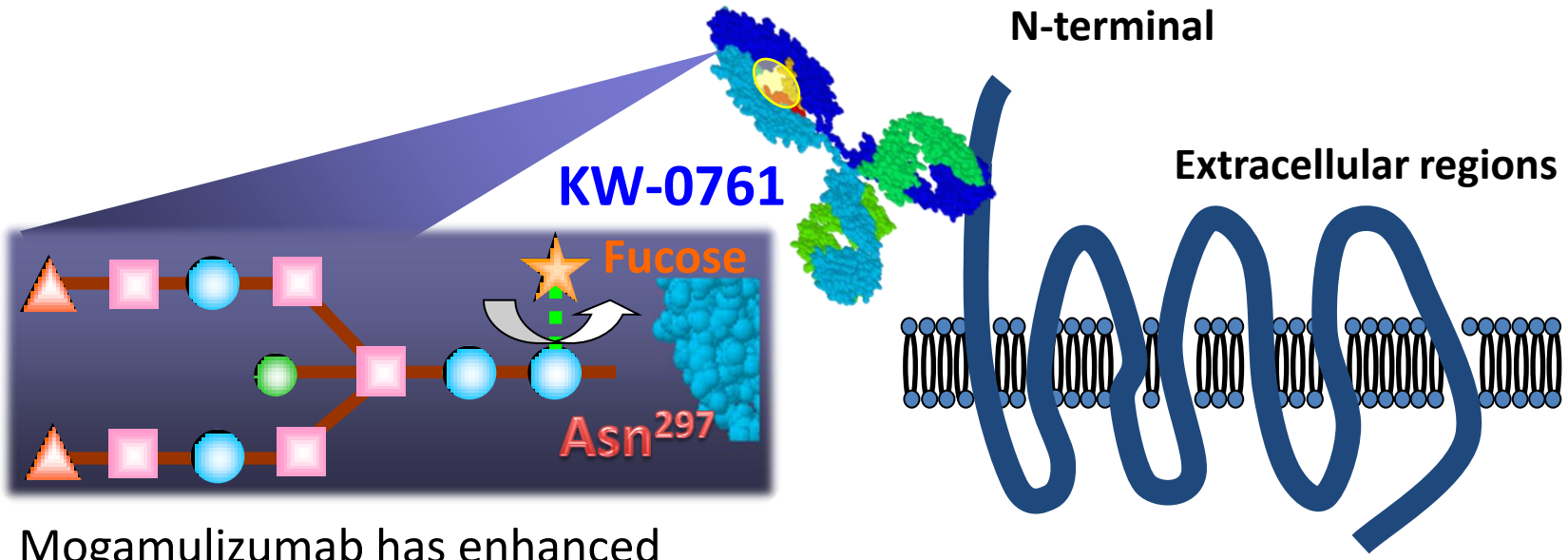
- Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of brentuximab vedotin and CHP (A+CHP) vs CHOP for the frontline treatment of CD30+ MTCL*
- Enrolling approximately 300 patients at 130 sites in 14 countries (ClinicalTrials.gov #NCT01777152)



Stratified by:

- MTCL histology: ALK-positive sALCL, all others
- IPI score: 0–1, 2–3, 4–5

Mogamulizumab: A Defucosylated Humanized Anti-CCR4 Antibody



- Mogamulizumab has enhanced ADCC due to defucosylated Fc region[1,2]

- CCR4 is highly expressed (~ 90%) in ATLL[3]
- Significantly associated with skin involvement ($P < .05$) and unfavorable outcomes[3]

1. Shinkawa T, et al. J Biol Chem. 2003;278:3466-3473. 2. Ishii T, et al. Clin Cancer Res. 2010;16:1520-1531. 3. Ishida T, et al. Clin Cancer Res. 2003;9:3625-3634.

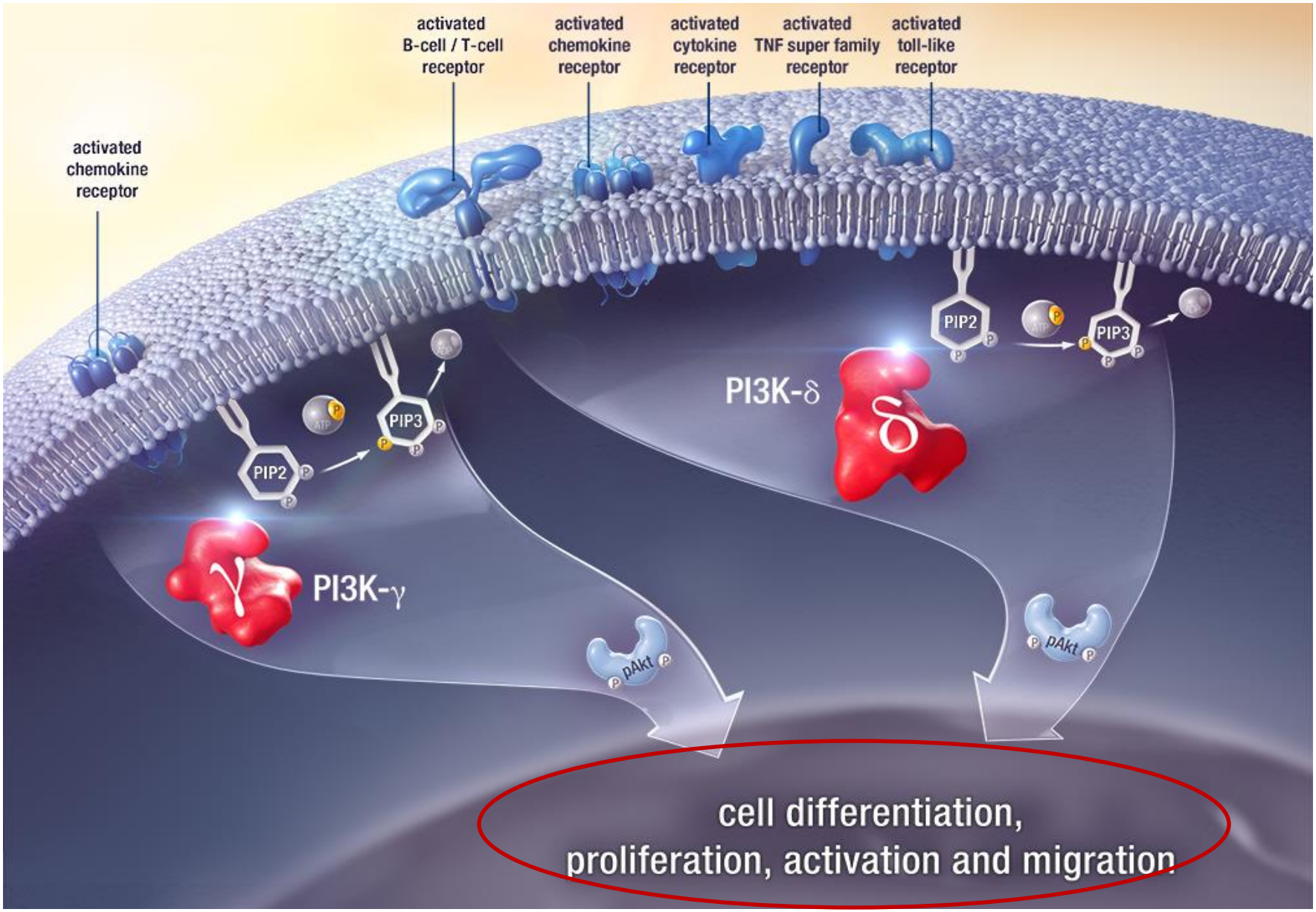
Courtesy of T. Ishida

Mogamulizumab (KW-0761): Studies in Patients With T-Cell Lymphoma

- Active in phase II study in patients with ATLL (N = 28)[1]
  - ORR: 50% (13/26); 8 CR
  - Median PFS: 5.2 mos
  - Median OS: 13.7 mos
  - AEs: infusion reactions (89%), skin rash (63%)
- Mycosis fungoides/Sezary syndrome (N = 38)[2]
  - ORR: 37% (MF: 29%; SS: 47%)
- Approved in Japan for the treatment of ATLL
- Ongoing multicenter, randomized phase III clinical trial of mogamulizumab vs vorinostat in patients with MF/SS[3]

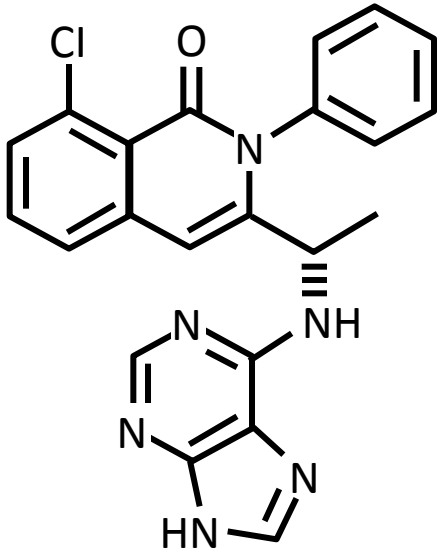
1. Ishida T, et al. J Clin Oncol. 2012;30:837-842. 2. Duvic M, et al. 2012 ASH. Abstract 3697.
3. ClinicalTrials.gov. NCT01728805.

PI3K-δ and PI3K-γ Support the Growth and Survival of B-cell and T-cell Malignancies



IPI-145: A PI3K-δ,γ Inhibitor

PI3K Isoform	PI3K-δ	PI3K-γ
Expression	Primarily Leukocytes	Primarily Leukocytes
Biochemical Activity (K_D)	23 pM	243 pM
Whole Blood Assay (IC_{50})	96 nM Anti-FcεR1	1028 nM fMLP



IPI-145

- Potent oral inhibitor of PI3K-δ and PI3K-γ isoforms
  - Selective for PI3K over other protein and lipid kinases
- Inhibits malignant B-cell and T-cell survival
  - Direct effects on tumor cells
  - Disrupting tumor cell interactions within the microenvironment

DiNitto J, et al. Keystone Symposia: PI3-Kinase and Interplay with Other Signaling Pathways 2013. Abstract 1032. Palombella V, et al. Keystone Symposia: PI3-Kinase and Interplay with Other Signaling Pathways 2013. Horwitz S, et al. ASCO 2013. Abstract 8518.

IPI-145-02: Phase 1 Study of Duvelisib in Advanced Hematologic Malignancies

- T-cell Lymphoma (TCL) patients completed enrollment in August 2013
  - Duvelisib administered orally BID in 28-day cycles to 35 TCL patients
  - 25 mg (n=1), 50 mg (n=1), 60 mg (n=4), 75 mg (MTD; n=27), 100 mg (n=2)
- Key Study Endpoints
  - Pharmacodynamics: changes in cytokines, chemokines, and matrix metalloproteinases (MMPs) in patient serum, and early PET (Cycle 1 Day 22)
  - Tumor response based on standard disease-specific criteria
    - Systemic/Peripheral TCL (PTCL) = IWG criteria (Cheson et al, 2007)
    - Cutaneous TCL (CTCL) = mSWAT assessment (Olsen et al, 2011)
  - Safety: adverse events (AEs) per CTCAE version 4.03

Horwitz S. et al, ASH 2014 Abstract 803

Patient Characteristics

Characteristics	PTCL N=16	CTCL N=19
Disease subtype	AITCL=3, SPTCL=3, ALCL=2, EATCL=1, NKTCL=1, PTCL NOS=6	MF=9, MF-LCT=4, Sézary=5, pcALCL=1
Age (years), median (range)	70 (34, 86)	64 (48, 81)
Female, n (%)	8 (50)	11 (58)
Prior Systemic Therapies, median (range)	2.5 (1, 7)	6 (2, 11)
Months from Last Therapy to First Dose, median (range)	1.6 (0.4, 24.8)	0.7 (0.2, 2.8)
ECOG Score 0 / 1 / 2 / missing, n	1 / 10 / 4 / 1	4 / 13 / 2 / 0
IPI Score at Screening, n (%)		
0	1 (6)	2/18 (11)
1-2	5 (31)	9/18 (50)
3-5	10 (63)	7/18 (39)

MF = mycosis fungoides; LCT = large-cell transformed; AITCL= angioimmunoblastic TCL; SPTCL= subcutaneous panniculitic TCL; pcALCL= primary cutaneous anaplastic large cell lymphoma; EATCL= enteropathy-associated TCL; NKTCL= natural killer TCL; NOS= not otherwise specified.

Horwitz S. et al, ASH 2014 Abstr. 803

Clinical Activity in TCL

Population		Best Response, n (%)					Median Time to Response, months (Range)
	n	CR	PR	SD	PD	ORR	
All TCL	33	2 (6)	12 (36)	7 (21)	12 (36)	**14 (42)**	1.9 (1.5, 3.8)
PTCL	15	2 (13)	6 (40)	1 (7)	6 (40)	**8 (53)**	1.9 (1.5, 3.5)
CTCL	18	0	6 (33)	6 (33)	6 (33)	**6 (33)**	2.4 (1.6, 3.8)

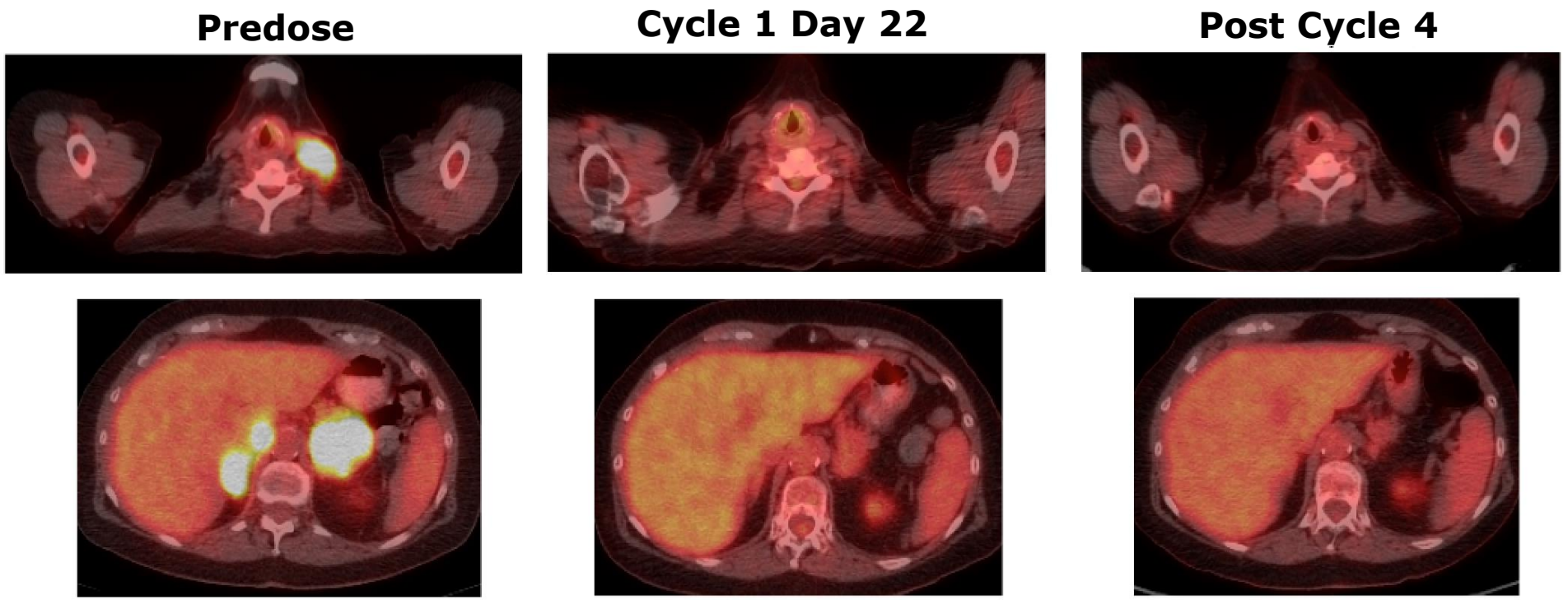
Includes evaluable patients = at least 1 on-treatment response assessment or PD without assessment
CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease
ORR = CR + PR

- Clinical activity observed across PTCL and CTCL subtypes
  - PTCL: CRs in 1 EATCL and 1 PTCL NOS
    PRs in 2 AITCL, 2 SPTCL, 1 PTCL NOS, 1 ALCL (ALK-negative)
  - CTCL: PRs in 4 MF, 1 Sézary syndrome, and 1 MF-LCT

Horwitz S. et al, ASH 2014 Abstr. 803

Early Pharmacodynamic Response in PET Avid Disease May Predict Best Clinical Response

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



- 10 patients evaluated with PET (PET-CT) at Cycle 1 Day 22, 6 with a reduction in SUV, 4 with an increase in SUV
- 83% (5/6) with PET response had a subsequent clinical response (CR or PR)
- 100% (4/4) without PET response had disease progression

Horwitz S. et al, ASH 2014 Abstract 803

High Activity of Tipifarnib in T-Cell Lymphoma

- Single arm, single agent Phase II trial in relapsed/refractory lymphoma . N=93
- Primary endpoint of Response Rate
- Tipifarnib given 300 mg bid 21 days of 28-day cycles
- Three cohorts:
  - Cohort 1: Aggressive B-NHL (N=42)
  - Cohort 2: Indolent B-NHL (N=15)
  - Cohort 3: T-NHL and HL (N=36)
- Safety findings (grade3-4): 37% neutropenia, 31% thrombocytopenia, 11% anemia

Witzig T. et al. Blood 118(18);4882-9,2011

Phase II of Tipifarnib in T-cell lymphoma

- Cohort 3 (T-cell and HL)
- ORR=31% (11/36); 6 CR; 5 PR

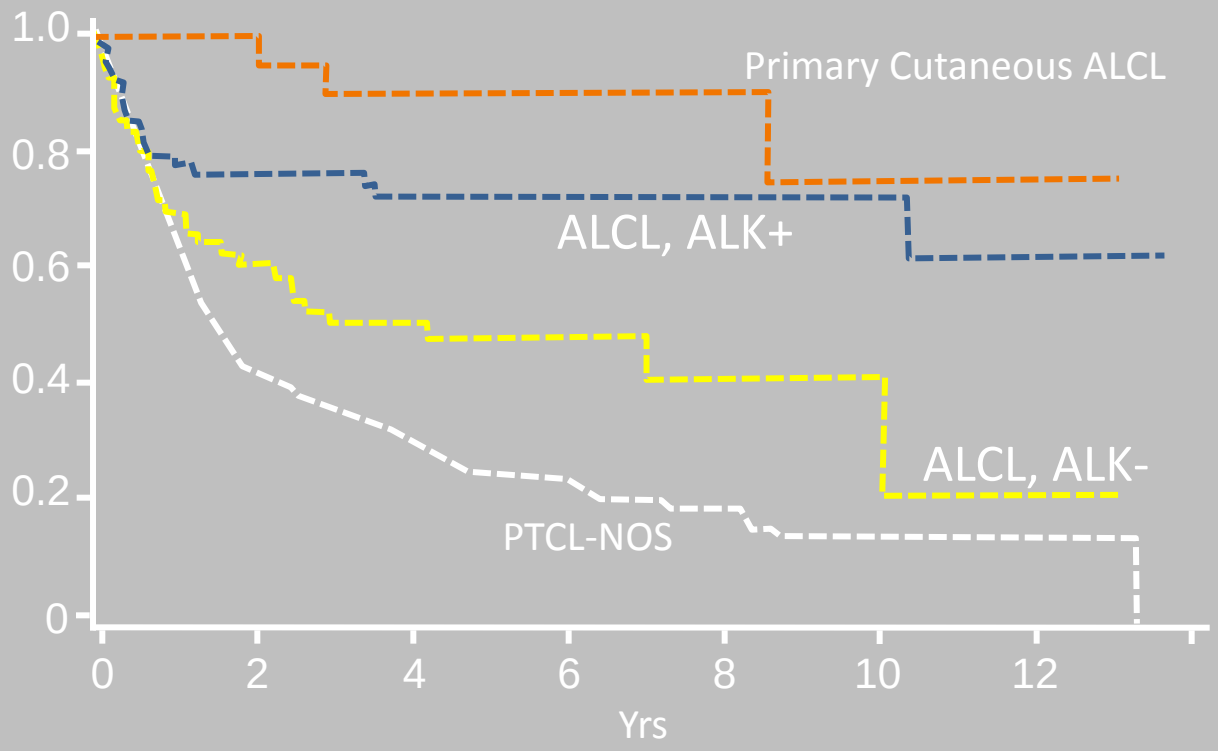
- T-cell NHL 41% (7/17)
  - MF-50% (2/4)
  - PTCL-50% (4/8), 3 CRs, 1 PR
  - ALCL-20% (1/5)

- DOR: median 11.3 months
- OS: median 19.7 months

Witzig T. et al. Blood 118(18);4882-9,2011

Anaplastic Large Cell Lymphoma

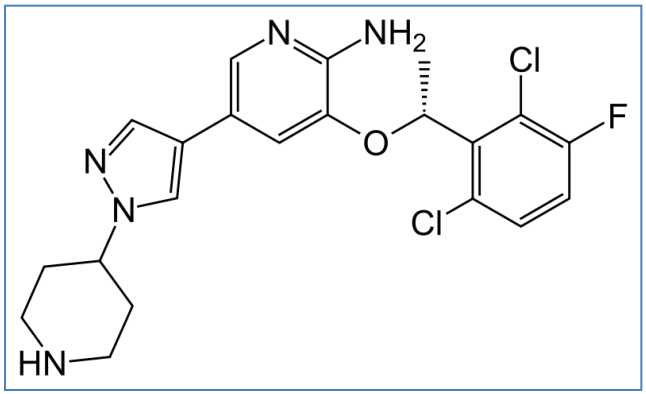
	ALK+ ALCL	ALK- ALCL
5-yr OS	**%**	**%**
All	70	49
IPI 0/1	90	74
IPI 4/5	33	13
5-yr FFS	**%**	**%**
All	60	36
IPI 0/1	80	62
IPI 4/5	25	13



Vose J, et al. J Clin Oncol. 2008;28:4124-4130.
Savage KJ, et al. Blood. 2008;111:5496-5504.

Crizotinib

- Tyrosine kinase inhibitor of anaplastic lymphoma kinase (ALK)
  - Competitive binding to ATP binding pocket
  - Inhibits *c-Met* / Hepatocyte growth factor receptor tyrosine kinase
  - Approved for late-stage ALK expressing NSCLC
    - EML-ALK fusion
  - *ROS1* rearrangements



Phase I Study: Crizotinib for R/R ALK+ Pediatric Tumors

- 9 ALCL patients enrolled, ALK+ by FISH or IHC
- All received previous multiagent chemotherapy
- 7 CRs
  - Rx with doses 165-280 mg/m^2 BID
  - CR onset: C1 (n = 2), C2 (n = 3), C3 (n = 1), C5 (n = 1)
- 5 patients remain on Rx: 7+ to 30+ cycles
- 3 patients removed from Rx to receive SCT: 4-9 cycles

Mossé YP, et al. Lancet Oncol. 2013;14:472-480.

Crizotinib

- 11 ALK+ relapsed NHL patients (9 ALCL)
  - Median of 3 prior therapies
  - Clinical responses in 10 of 11
    - All 9 ALCL pts achieved complete remissions lasting 2-40+ months
    - Negative for *NPM/ALK* by PCR
    - 2 -yr PFS 64%
  - Non-cross resistant with brentuximab

Gambacorti Passerini et al. J. Natl. Cancer Inst. 2014;106:2

ALK small molecule inhibitors

Crizotinib	Pfizer	MET/ALK	Approved for ALK+ late stage NSCLC
CH5424802	Chugai Pharm	ALK	I/II
LDK378	Novartis	ALK	I
AP26113	Ariad Pharm	ALK/EGFR	I/II
ASP3026	Astellas Pharma	ALK	I
X-396	Xcovery	ALK	Preclinical
GSK-1838705	GlaxoSmithKline	ALK/IGF-1R	Preclinical
NMS-E628	Nerviano Med. Sci.	ALK/TRK	Preclinical

Going Forward…..New Strategies

- Add a novel agent to an existing regimen
  - CHOP +….
- Use maintenance approach
- Create a different chemotherapy platform for first line treatment using novel drugs
- ***Investigate treatments which are effective for specific subtypes***
- Brentuximab → **ALCL**
- Mogamulizumab → **ATLL**
- L-asparaginase → **NK-T**

- To continue to make progress, we should continue to encourage participation in clinical trials