Peripheral T-cell Lymphomas
Clinical Presentation and New Drugs

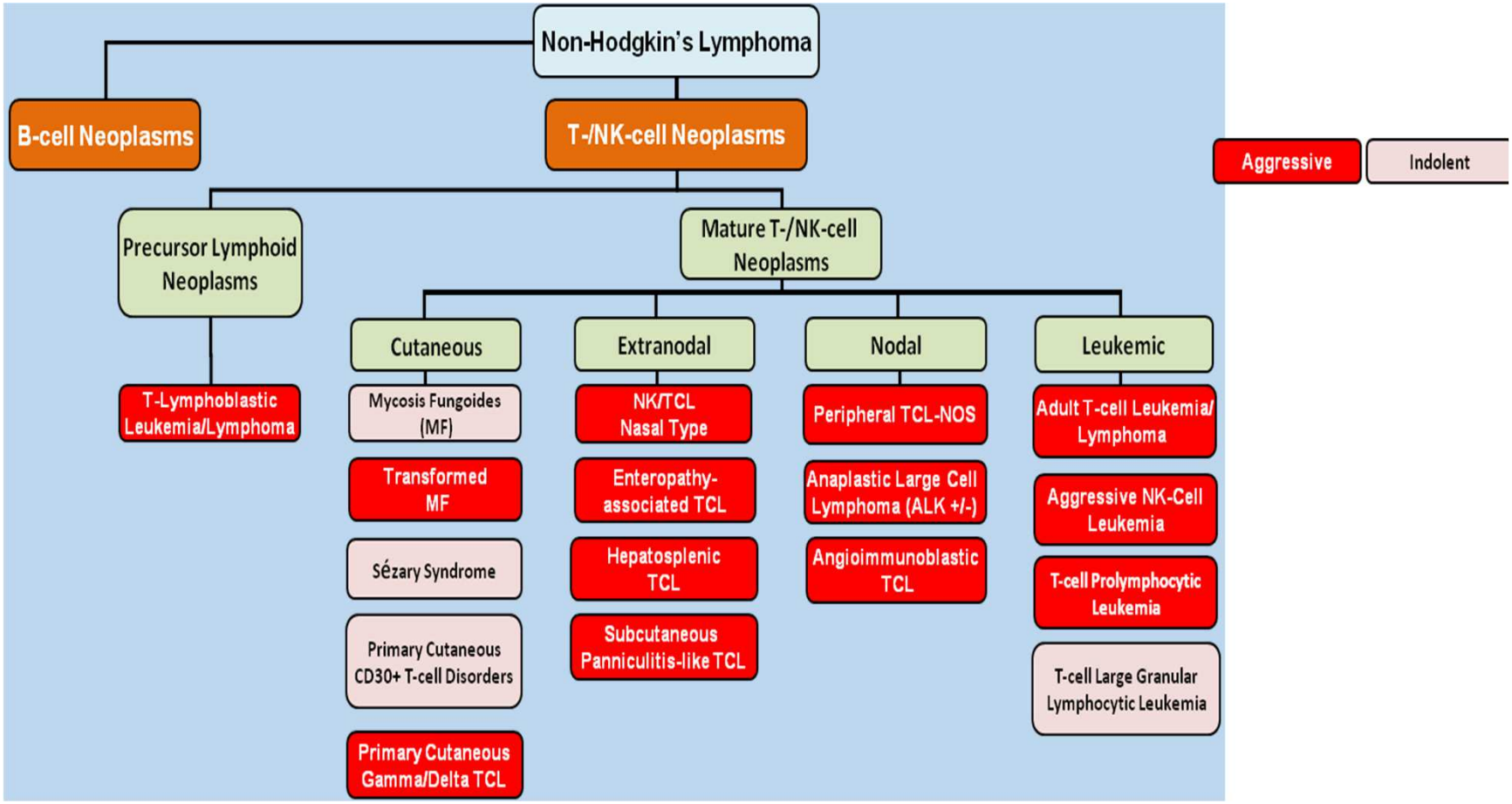
Barbara Pro, MD

6th International Workshop on PET in Lymphoma Menton, September 20-21, 2016

T-Cell Lymphomas…Few Facts

- Accounts for ~10%-15% of all NHL
- Increasing number of subtypes
- Classification relies on
  - Morphology
  - Immunophenotype
  - **Clinical/anatomical presentation**
- Few recurrent genetic or molecular lesions
- Expert hematopathology review essential
- Outcomes are often poor

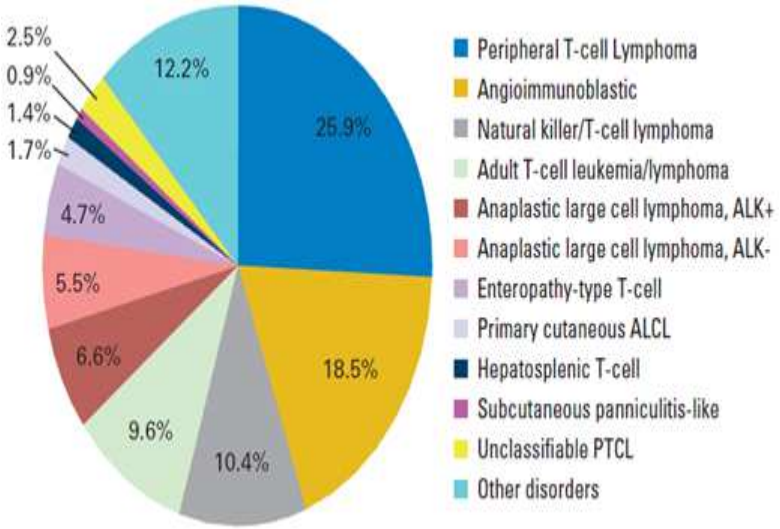
WHO 2008 Classification of PTCLs



Adapted from Swerdlow SH, et al. *WHO Classification of Tumours of Haematopoietic and*

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study: Pathology Findings and Clinical Outcomes



56% NODAL SUBTYPES

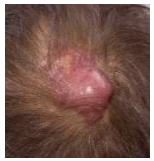
Table 1. Major Lymphoma Subtypes by Geographic Region

Subtype	% North America	% Europe	% Asia
PTCL-NOS	34.4	34.3	22.4
Angioimmunoblastic	16.0	28.7	17.9
ALCL, ALK positive	16.0	6.4	3.2
ALCL, ALK negative	7.8	9.4	2.6
NKTCL	5.1	4.3	22.4
ATLL	2.0	1.0	25.0
Enteropathy-type	5.8	9.1	1.9
Hepatosplenic	3.0	2.3	0.2
Primary cutaneous ALCL	5.4	0.8	0.7
Subcutaneous panniculitis-like	1.3	0.5	1.3
Unclassifiable T-cell	2.3	3.3	2.4

Abbreviations: PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; ALCL, anaplastic large-cell lymphoma; NKTCL, natural killer/T-cell lymphoma.

Vose J, et al. 2008;26:4124-4130

PTCL → Multiple diseases

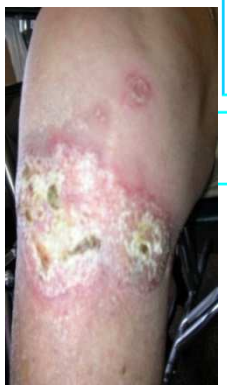


Alk positive good prognosis
Alk negative as bad as PTCL
but…

Systemic

ALCL

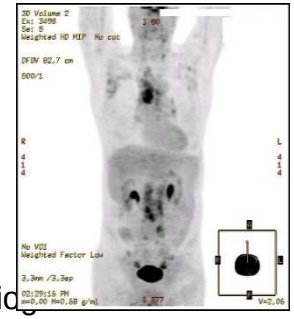
Cutaneous



Alk-
Spont regression
in up to 25%!

AITL

Syndrome more than disease
Autoimmune phenomena
Not rare > 20% cases
Some patients indolent course
Response to steroids alone
EBV role? Rituxan?
Role of microenvironment/angio



T-cell lymphomas

PTCL-U
"**Wastebasket**"

Nodal disease is common
Low-bulk
More advanced stage

HSL

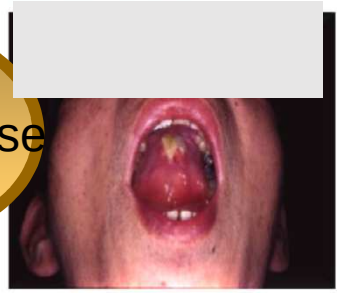
Transplant

Young patients
Homing: Spleen BM
Pancytopenia
Median survival< 1 year

NK-T

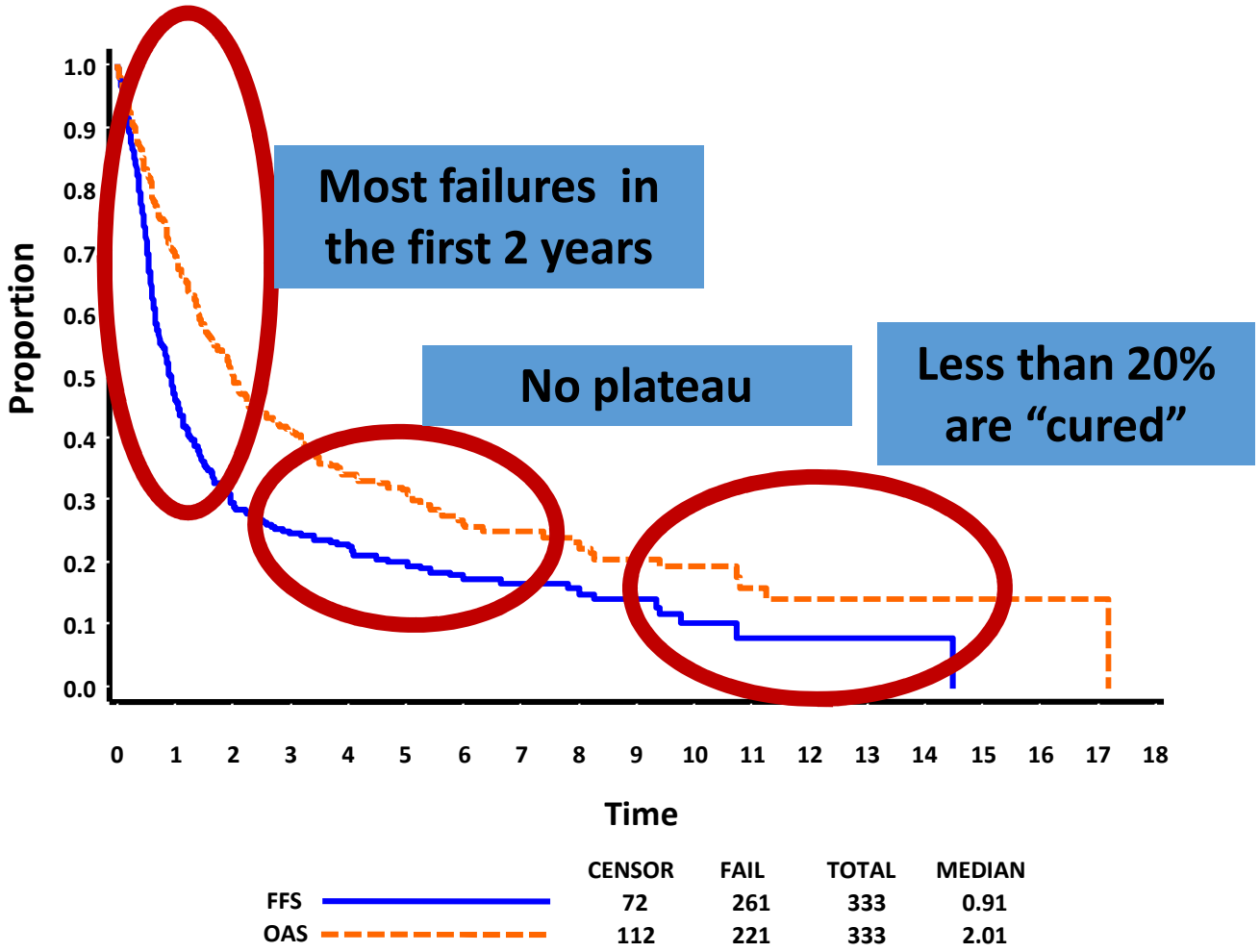
Asparaginase

EBV associated
Midline destructive lesions
XRT more effective than CHT
Fatal when disseminated



Peripheral T-cell Lymphoma-NOS

OS and FFS



Armitage J, et al. *J Clin Oncol.* 2008;26:4124–4130**, International T-cell Classification Project**

PTCLs: Guidelines for Initial treatment

Suggested regimens:

- CHOP (cyclophosphamide,doxorubicin,vincristine,prednisone)
- CHOEP(cyclophosphamide,doxorubicin,vincristine,etoposide, prednisone)
- HyperCVAD (cyclophosphamide,doxorubicin,vincristine,dexamethasone) alternating with methotrexate and cytarabine
- CHOP followed by ICE (ifosfamide, carboplatin, etoposide) or
- IVE (ifosfamide,etoposide,and epirubicin) alternating with intermediate dose methotrexate (New Castle Regimen)
- Dose adjusted EPOCH

NCCN guidelines:
Clinical trials preferred with the exception of ALK + ALCL

Historical data with CHOP?

Selected Studies

Reference	Treatment	Histology	N	ORR	CR	PFS / EFS
Savage KJ, et al.	Almost all CHOP-like	PTCL, US	11	84%	64%	29% (5 yr)
Reimer P, et al.	CHOP-like CT, Prospective	PTCL (32) / AITL / ALCL	33	73%	39%	ASCT
Simon KJ, et al.	CHOP vs VIP-rABVD, Prospective	PTCL (30) / AITL / ALCL	43	62%	39% (PTCL 29%)	41% (2 yr) Lower for PTCL

- ◆ORR 60-80%
- ◆CR 39-60%
- ◆Lack of durable remissions

VIP-rABVD, etoposide, ifosfamide, cisplatin alternating with doxorubicin, bleomycin, vinblastine, dacarbazine (VIP-reinforced-ABVD).

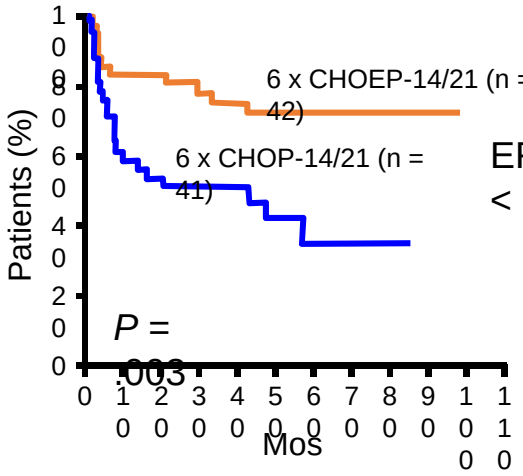
Savage KJ, et al. *Ann Oncol*. 2004;15(10):1467-1475; Reimer P, et al. *J Clin Oncol.* 2009;27(1):106-113;
Simon A, et al. *Br J Haematol*. 2013;151(2):159-166.

Novel Approaches

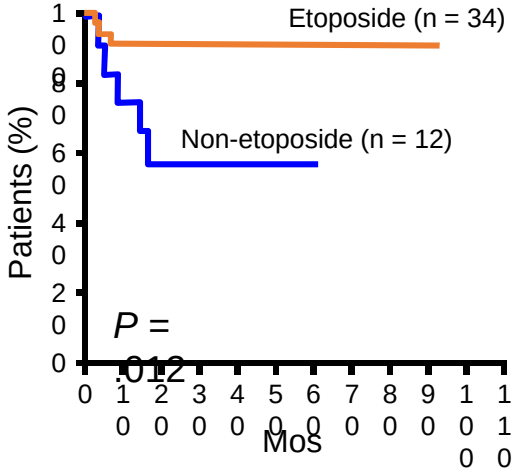
Adding to CHOP……

ABMT for Consolidation

Adding Etoposide to CHOP: German Prospective High-Grade NHL Studies

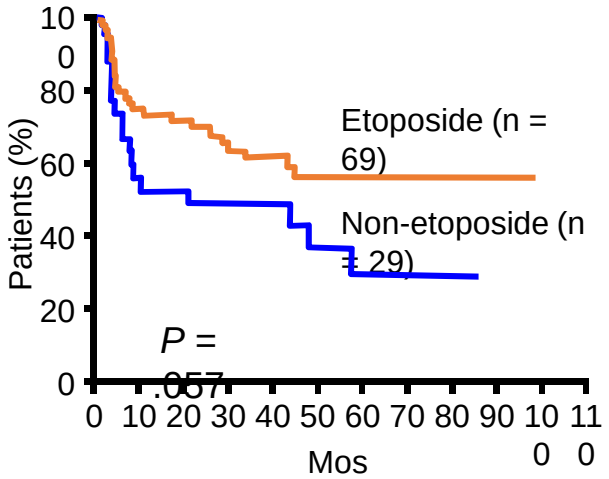


EFS, aged < 60 yrs



EFS, ALCL, ALK+

PTCL Subtype	n
ALCL, ALK+	78
ALCL, ALK-	113
PTCL-NOS	70
AITL	28
Other	31
Total	320



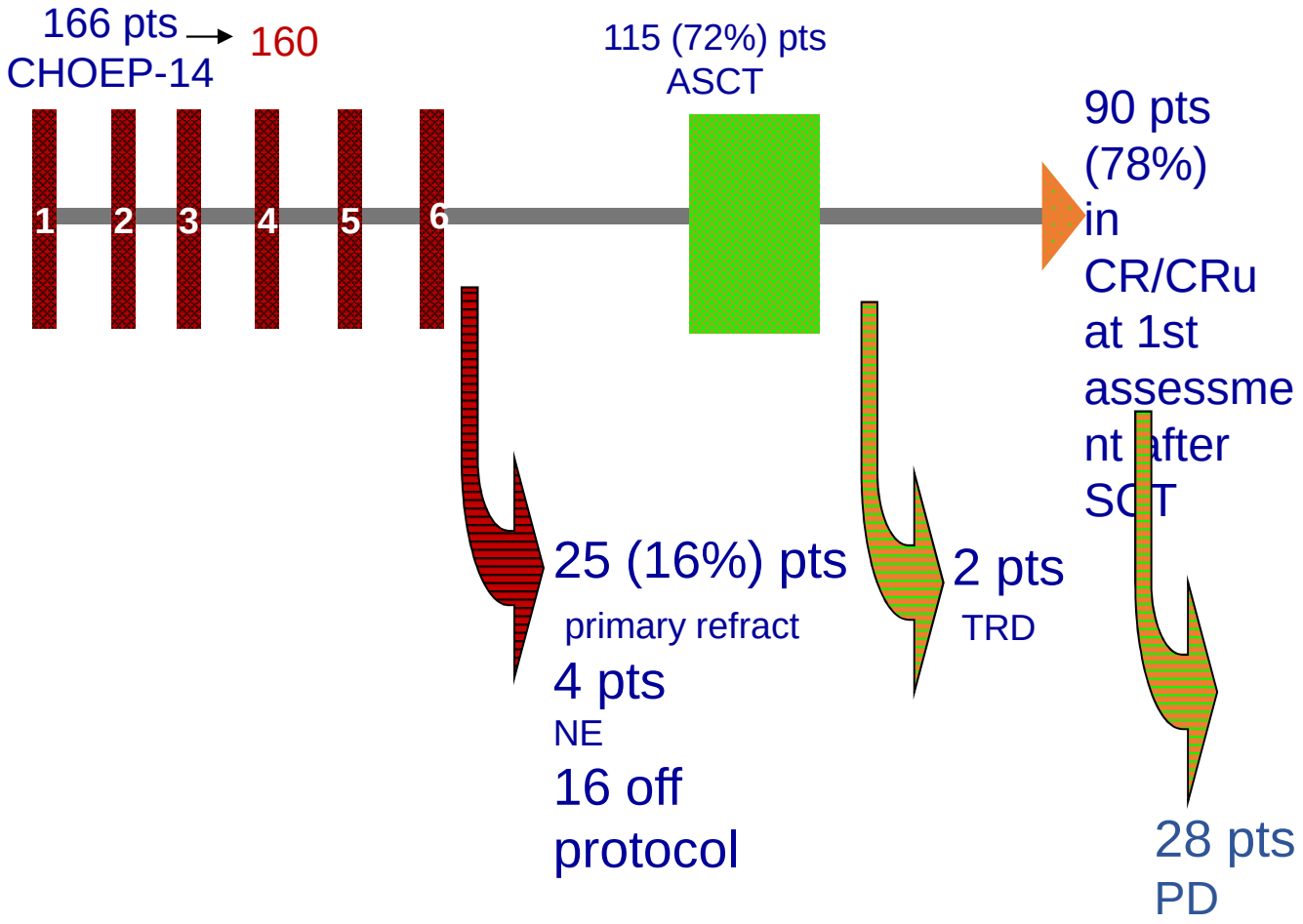
EFS, other subtypes

Schmitz N, et al. Blood. 2010;116:3418-

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

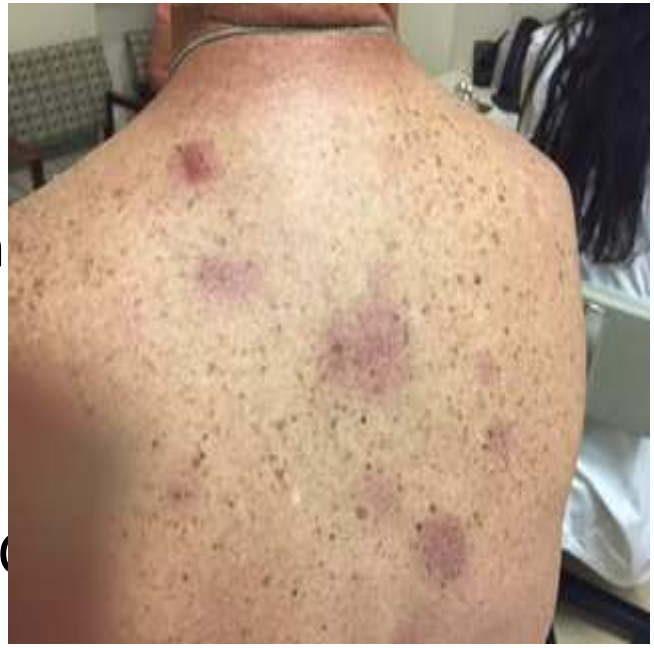
Up-Front Autologous Stem-Cell Transplantation in Peripheral T-Cell Lymphoma: NLG-T-01

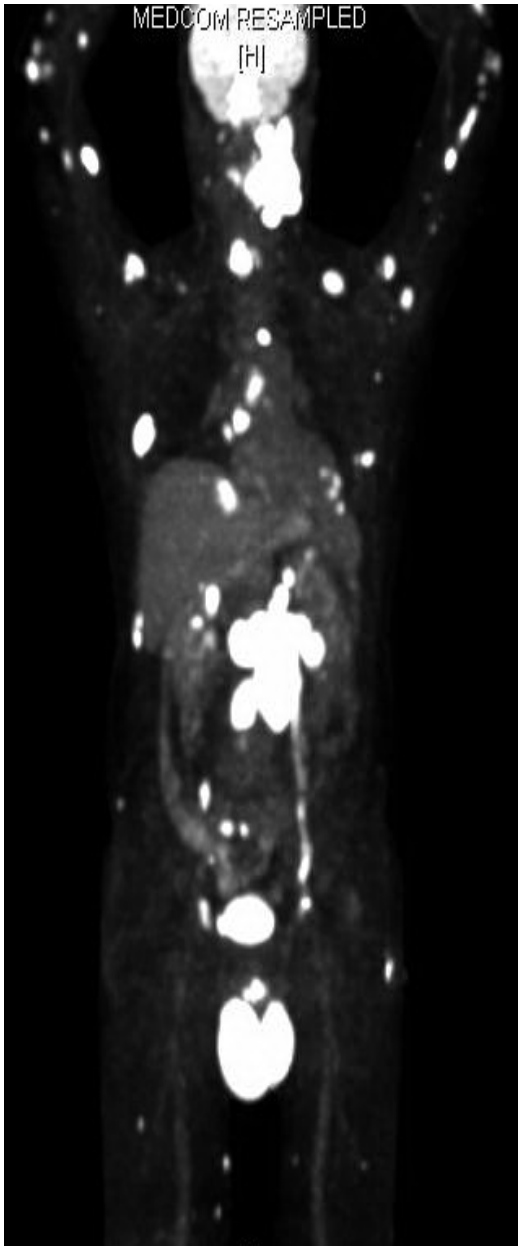
Francesco d'Amore, Thomas Relander, Grete F. Lauritzsen, Esa Jantunen, Hans Hagberg, Harald Anderson, Harald Holte, Anders Österborg, Mats Merup, Peter Brown, Outi Kuittinen, Martin Erlanson, Bjørn Østenstad, Unn-Merete Fagerli, Ole V. Gadeberg, Christer Sundström, Jan Delabie, Elisabeth Ralfkiaer, Martine Vornanen, and Helle E. Toldbod



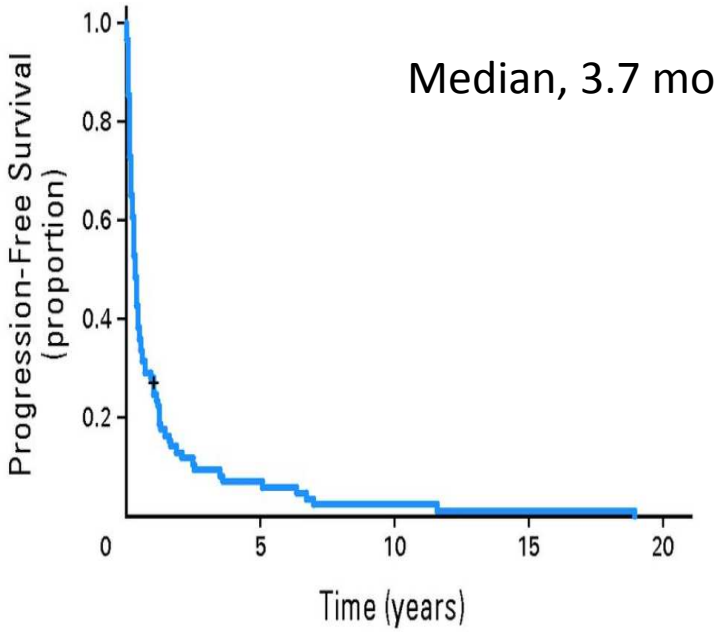
Clinical case

64 y/o male
Stage IIIA T cell lymph
Favor “PTCL-NOS”
CHOEP X 3 cycles
PET/CT : CR
2 additional cycles of C

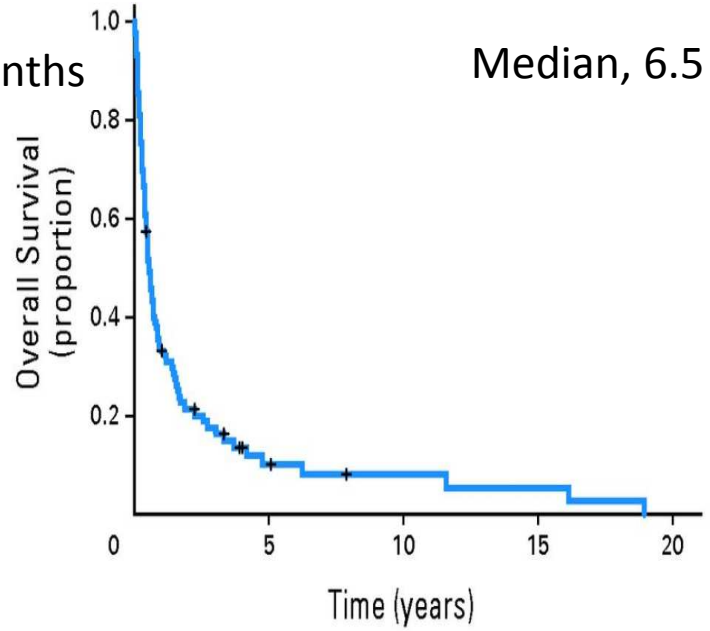




PFS and OS after 1st relapse in PTCL



Median, 3.7 months



Median, 6.5 months

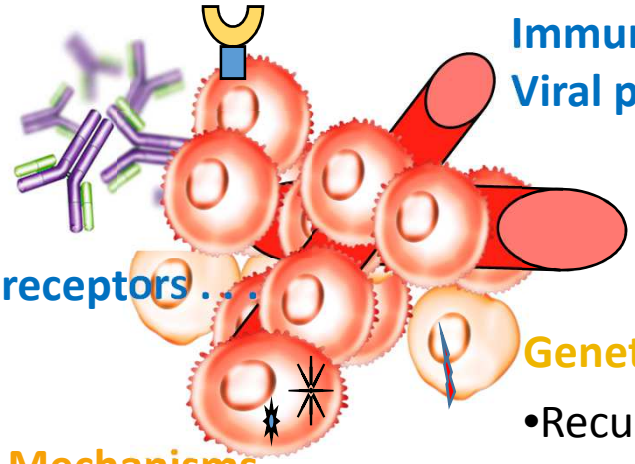
Mak V et al. JCO 2013;31:1970-197(

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

- Recurrent (and maybe targetable) mutations
- Rhoa,TET2,IDH2,DNMT3A,DUSP22
- Some subtypes have stronger epigenetic signatures

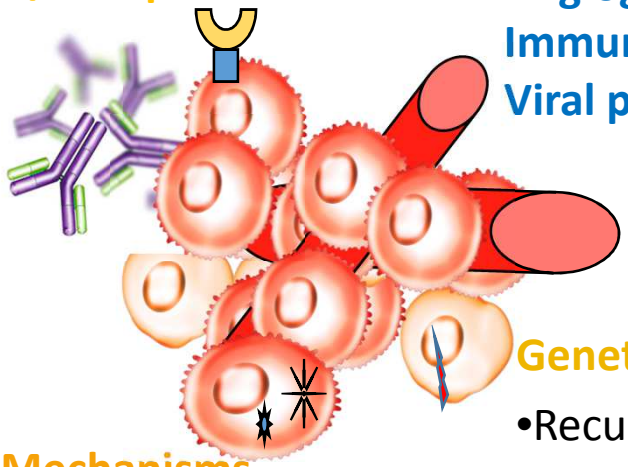
AITL: *RHOA, TET2, IDH2, DNMT3A, CD28*

Targeting Peripheral T-Cell Lymphoma

Targeting the Cancer Cell

Surface Antigens/Receptors

CD2
CD4
CD25
CD30
CCR4



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

- Recurrent (and maybe targetable) mutations
- Rhoa,TET2,IDH2,DNMT3A,DUSP2 2,ALK
- Some subtypes have stronger epigenetic signatures

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

Summary of Selected Novel agents

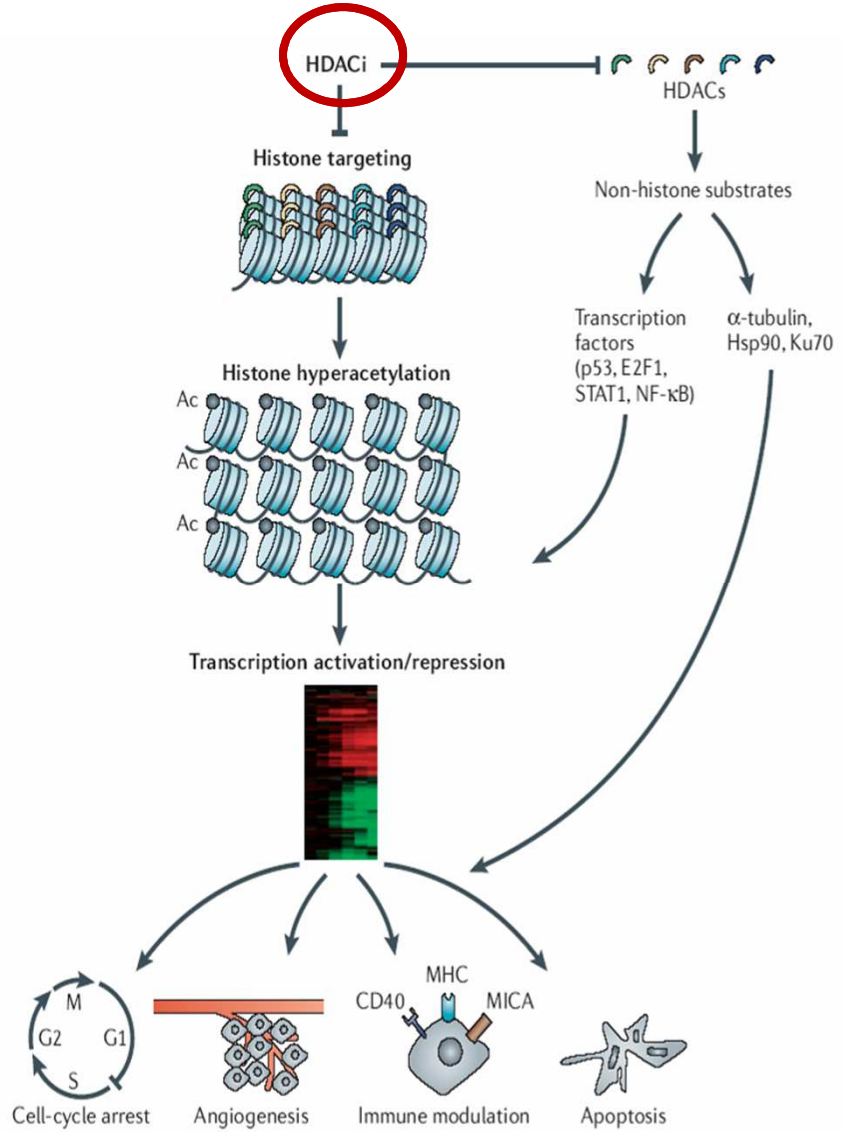
Agent	MOA	Phase	Patients (n)	Toxicity (grade 3 or>)	ORR	CRR	DOR (months)
FDA approved							
Pralatrexate	Folate antagonist	II	111	Mucositis	29%	11%	10.3
Romidepsin	HDACi	II	130	Thrombocytopenia Neutropenia Infections	25%	14%	17
Belinostat	HDACi	II	129	Hematologic	26%	11%	8
Brentuximab	ADC	II	58	Neuropathy	86%	57%	12.6
Agents Under Investigations							
Mogamulizumab	Anti-CCR4 mAb	II	37	Neutropenia,rash	34%	17%	8.2
Alisertib	Aurora A KI	II	37	Hematologic, FN	24%	5%	NR
Duvelisib	PI3KI	I	33	Transaminitis,rash Neutropenia	47%	12%	NR
Crizotinib	ALKi	II	9		100%	100%	2-yr PFS 64%

Classes of HDACi are based on chemical structure

Cyclic te
- **Romidepsin**

Hydroxamates
- **Vorinostat (SAHA)**
- **Panobinostat (LBH589)**
- **Belinostat (PXD101)**

Benzamides
- **Entinostat (SNDX-275)**
- **MGCD-0103**



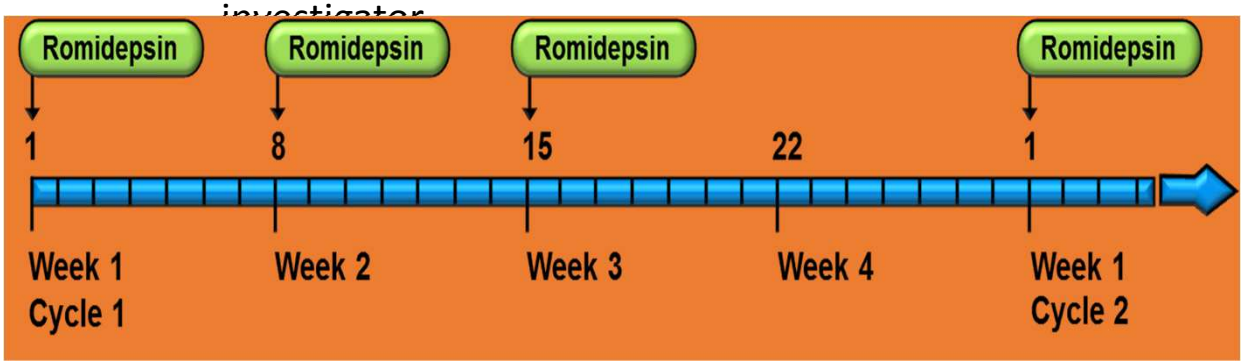
-Not all HDACi have the same specificity or affinity for the 11 different target HDACs

Impact on **multiple tumor pathways** by targeting both histone *and* non-histone substrates

Bolden et al., Nat Rev Drug Discovery. 2006; **5**, 769.

Romidepsin-Pivotal Study-Design

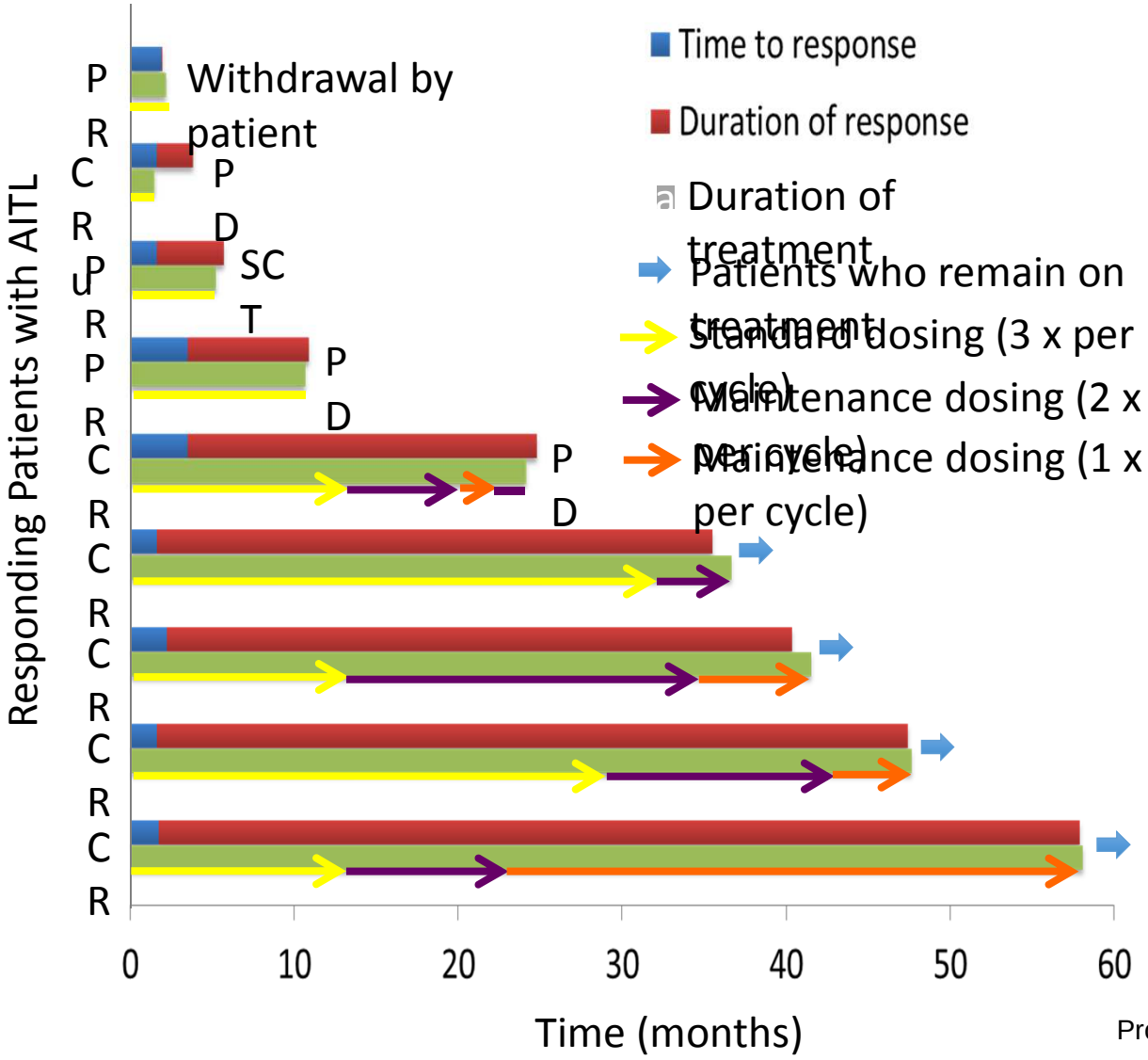
- Phase 2, open-label, single-arm, international study
- N = 131 patients enrolled; 130 with histopathologically confirmed PTCL
- Dosing: romidepsin 14 mg/m^2 (4-hour intravenous infusion) on days 1, 8, and 15 of a 28-day cycle × 6 cycles
  - Patients with SD or response could continue to receive treatment beyond 6 cycles at discretion of patient and investigator



Best response	PTCL-NOS (n=69)	AITL (n=27)	Alk- ALCL (n=21)
ORR	20 (29)	8 (30)	5 (24)
CR/CRu	10 (14)	5 (19)	4 (19)
PR	10 (14)	3 (11)	1 (5)
SD	16 (23)	9 (33)	5 (24)

Coiffier B, et al. *J Clin Oncol*. 2012;30(6):631-636

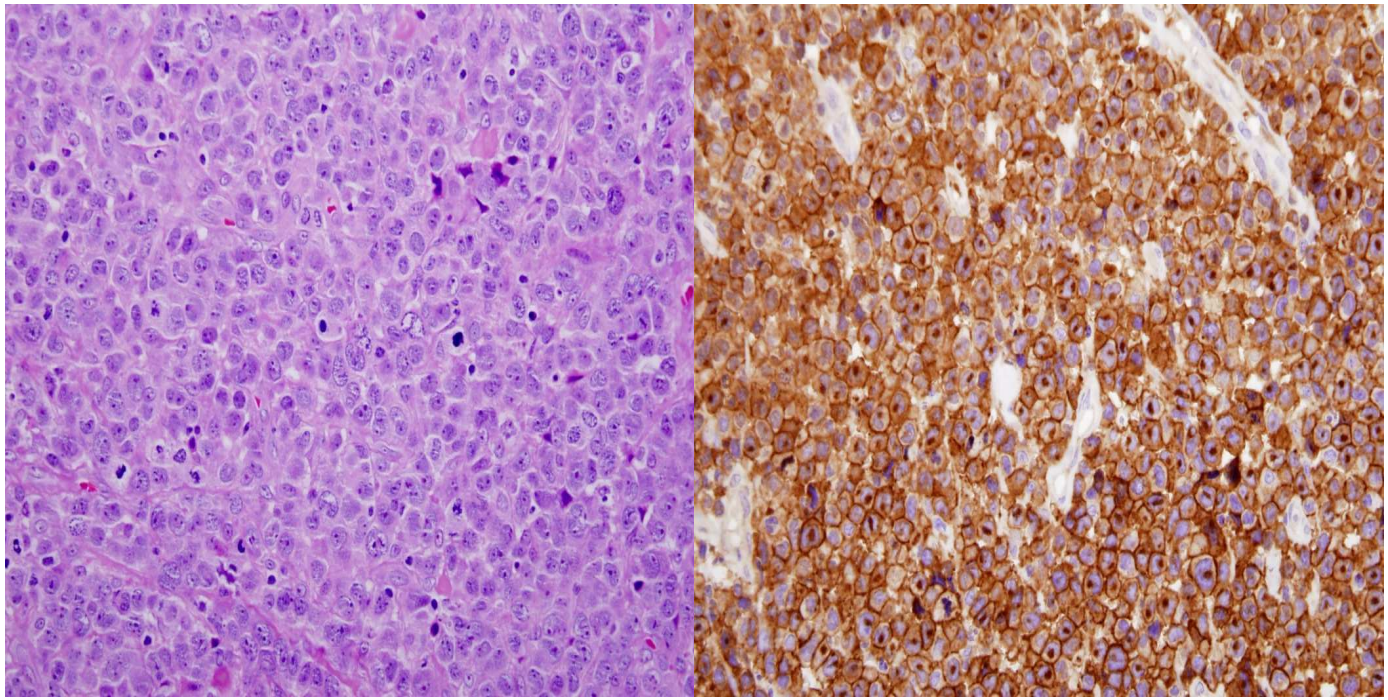
Efficacy of Romidepsin in AITL



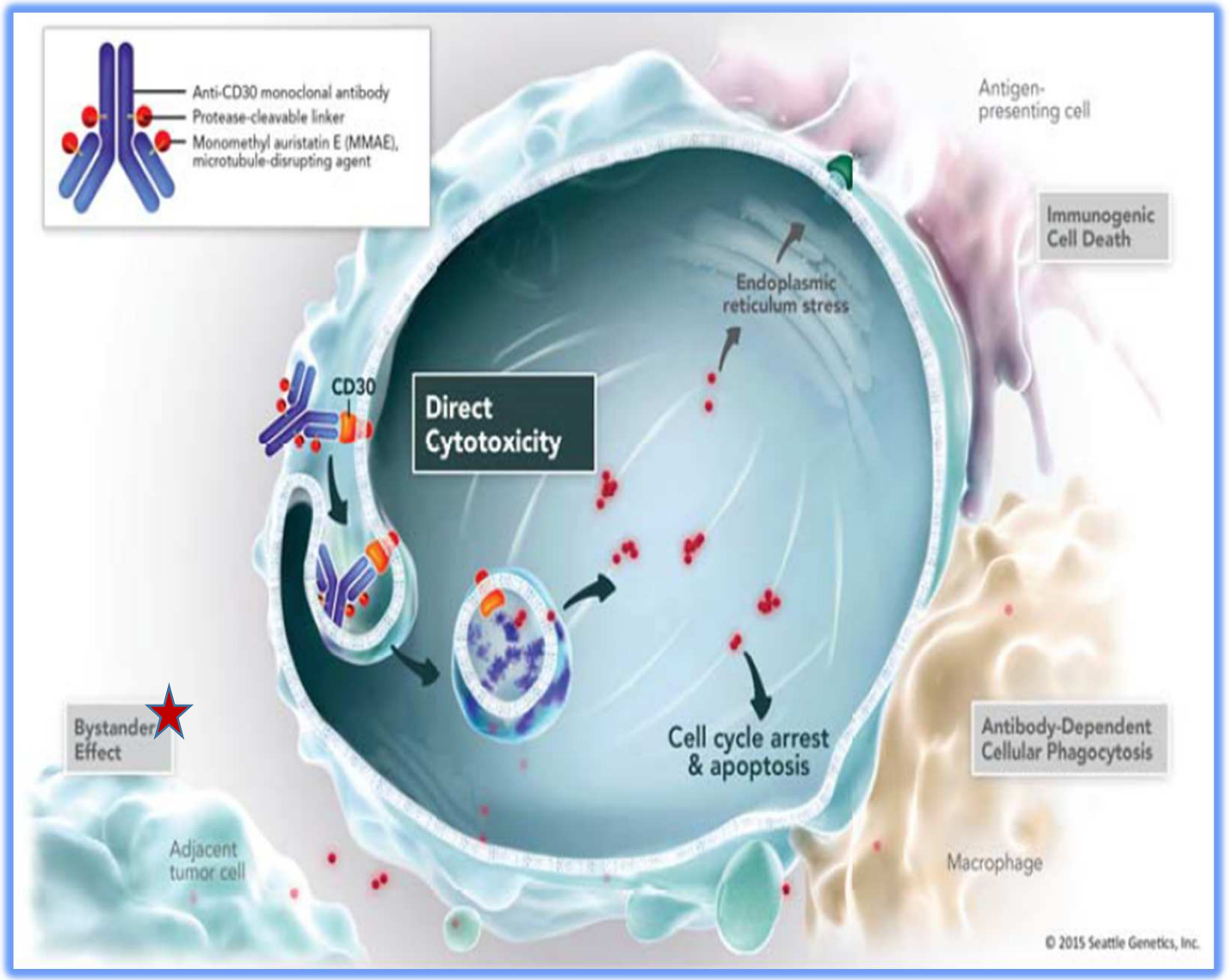
Pro et al. ASH 2014 abstract # 1

Targeted Therapy in ALCL

Targeting CD30



Targeting CD30
Brentuximab Vedotin

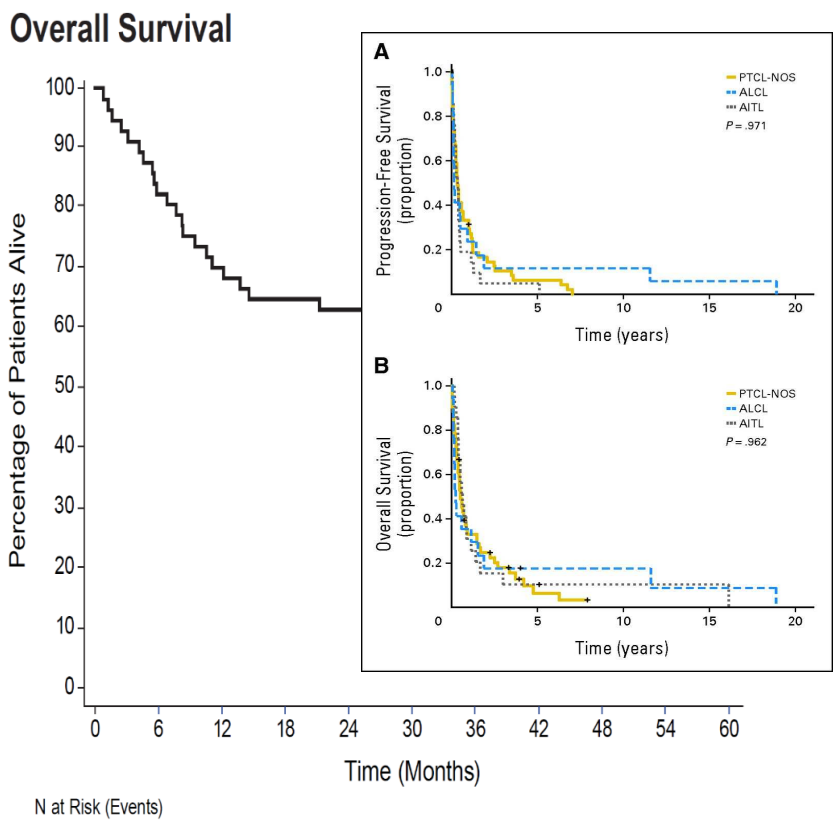


Pivotal Phase II Study ALCL – Long-Term Follow-

Best Response (N=58)

	IRF*	Investigator
Objective response rate	50 (86)*	50 (86)
Best response		
Complete remission (CR)	34 (59)	38 (66)
Partial remission (PR)	16 (28)	12 (21)
Stable disease (SD)	2 (3)	4 (7)
Progressive disease (PD)	3 (5)	2 (3)
Histology ineligible (HI)	2 (3)	0 (0)
Not evaluable (NE)	1 (2)	2 (3)

* Primary endpoint



Future directions:

Role in CD30 + PTCL

Combination therapy in R/R setting

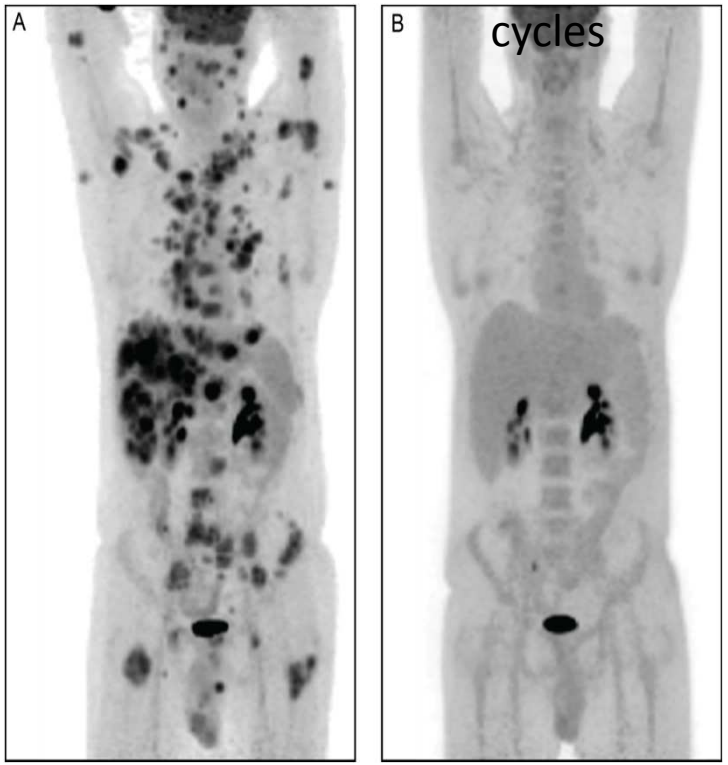
Maintenance vs retreatment

Frontline Thera[illegible] ECHELON 2

Pro et al. ASH Dec 2014, Abstract 3095

Case study

- 48-year-old male, ALK+ sALCL
- Prior treatment:
  - CHOP
  - VAPEC B
  - ASCT
- Cycle 4 restaging: CR
- Patient experienced tumor lysis syndrome after first dose, recovered
- Patient received 8 cycles in total



Pro B et al. J Clin Oncol 2012;30:2190–6.

PFS and OS by cycle 4 PET status and ALK status

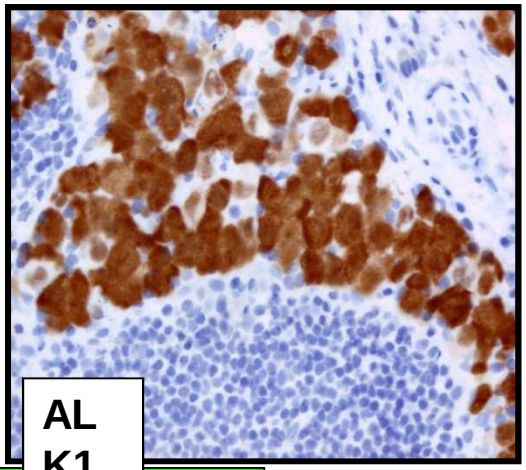
Status	4-yr PFS (95% CI)	4-yr OS (95% CI)
PET4 status		
PET+ (n=20)	16% (0%, 32%)	50% (28%, 72%)
PET- (n=28)	63% (44%, 83%)	86% (72%, 99%)
ALK status		
ALK+ (n=16)	37% (11%, 62%)	56% (32%, 81%)
ALK- (n=42)	38% (22%, 54%)	67% (52%, 81%)

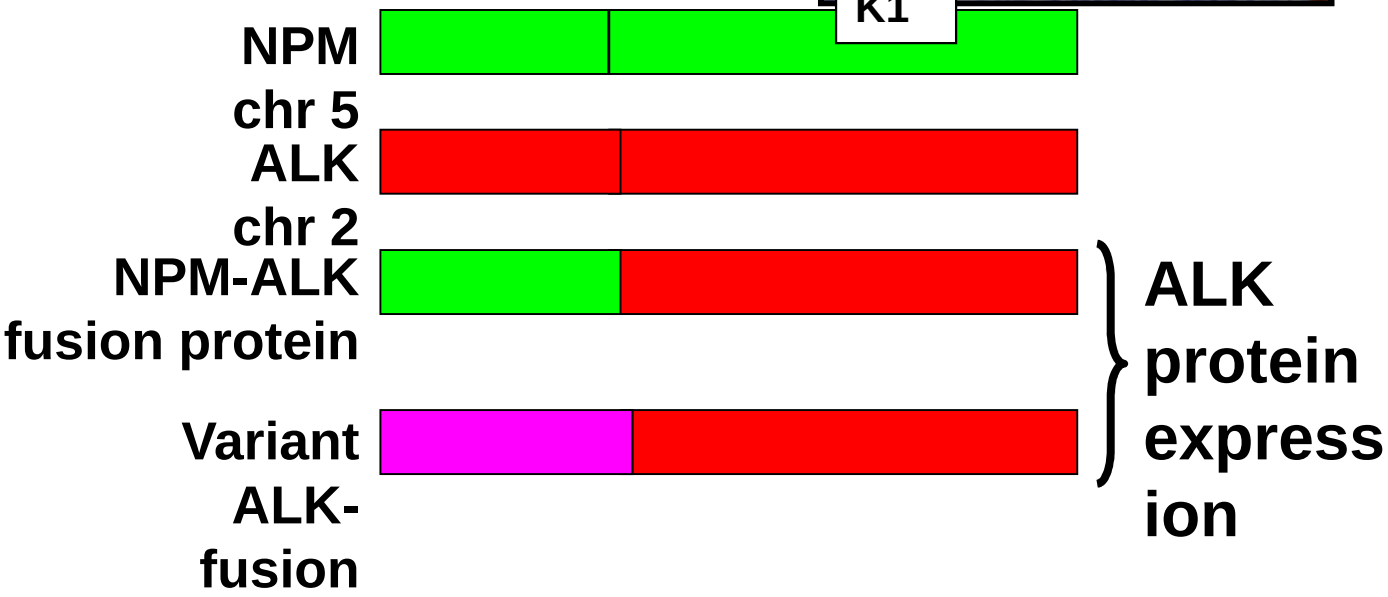
tract 3095

Targeted Therapy in ALCL
Targeting ALK

- 60% of ALCL associated with overexpression of the ALK protein = ALK^+

typical t(2;5) (p23;35)





Crizotinib

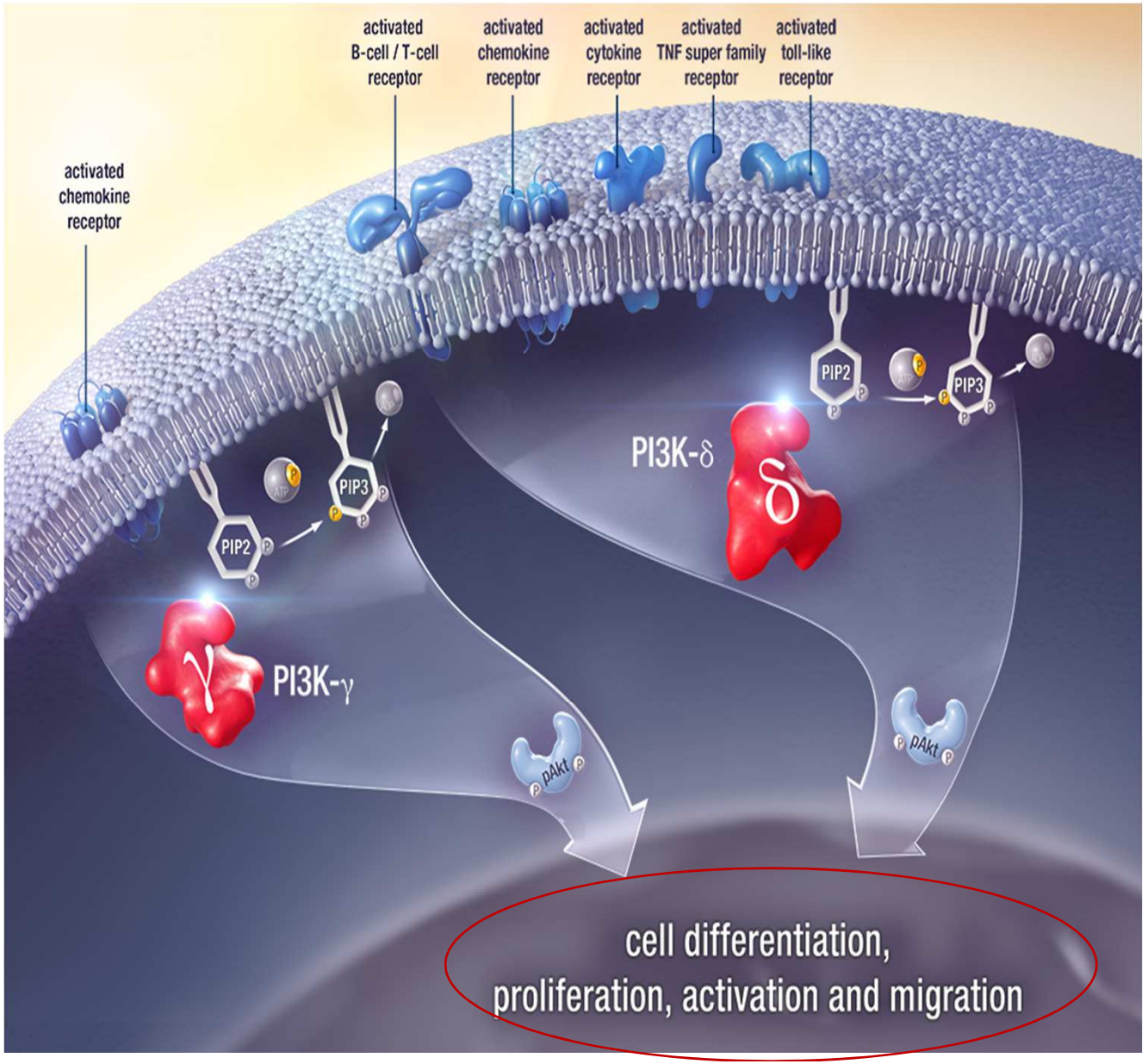
- 11 ALK+ relapsed NHL patients (9 ALCL)
  - Median of 3 prior therapies
  - Clinical responses in 10 of 11
    - All 9 ALCL pts achieved complete remissions lasting 2-40+ months
    - Negative for *NPM/ALK* by PCR
    - 2 -yr PFS 64%
  - Non-cross resistant with brentuximab

Ongoing PHASE I-II study in combination with chemotherapy in untreated patients

Gambacorti Passerini et al. J. Natl. Cancer Ins

Targeting PI3K

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



Duvelisib (IPI-145) Phase 1 Study

MTD reached at 75 mg BID

- 2 dose limiting toxicities (DLTs) at 100 mg BID:
  - Gr 3 rash; Gr 3 ALT/AST elevation
  - Limited myelosuppression, rare pneumonitis

Clinical Activity in TCL

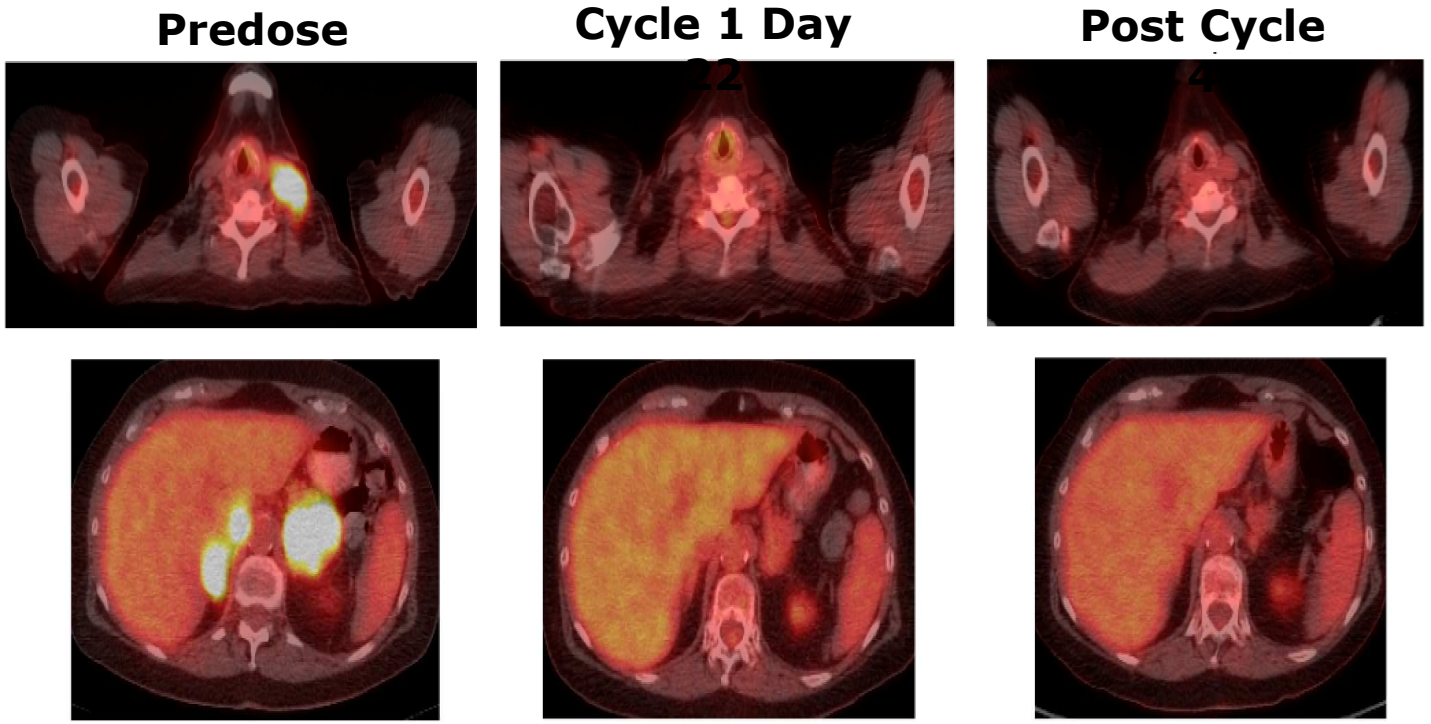
Population		Best Response, n (%)					Median Time to Response, months (Range)
	n	CR	PR	SD	PD	ORR	
All TCL	33	2 (6)	12 (36)	7 (21)	12 (36)	**14 (42)**	1.9 (1.5, 3.8)
PTCL	15	2 (13)	6 (40)	1 (7)	6 (40)	**8 (53)**	1.9 (1.5, 3.5)
CTCL	18	0	6 (33)	6 (33)	6 (33)	**6 (33)**	2.4 (1.6, 3.8)

- 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

Horwitz S. et al, ASH 2014 Abs

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 Abstrac

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

Ongoing PHASE I-II study in combination with chemotherapy in untreated patients

Gambacorti Passerini et al. J. Natl. Cancer Ins

Going Forward.....

Targeted Therapy in PTCL ?

- Subtype-specific treatments

CD30+ →	Brentuximab Vedotin
ALK+ ALCL →	Alk inhibitors
ATLL →	Mogamulizumab
NK-T →	Asparaginase- based treatments, EBV directed cell therapy
PTCL-NOS →	Pralatrexate , ? Others
AITL	HDACi, immunosuppressive therapy

- Combinations needed to improve CR rate for most

- Consolidation
  - If no transplant maintenance strategy?

Curr Hematol Malig Rep
DOI 10.1007/s11899-015-0291-0

The Value and Relevance of the T Cell Lymphoma Registries and International Collaborations: the Case of COMPLETE and the T-Cell Project

Monica Bellei[1] · Chadi Nabhan[2] · Emanuela Anna Pesce[1] · Luana Conte[3] · Julie M. Vose[4] · Francine Foss[5] · Massimo Federico[1]

Northwestern Medicine®

Grazie !

Northwestern Medicine

Robert H. Lurie Comprehensive Cancer Center of Northwestern University