dvances in Malignant lymphomas: The case of extranodal and T-cell lymphomas

Santiago de Chile

April 5-6, 2016

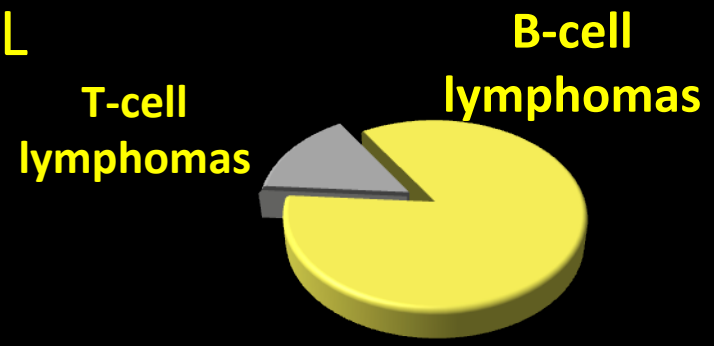
Auditorio Dr. Lucas Sierra
Hospital del Salvador
Av. Providencia 364

New Agents in PTCL

Barbara Pro, MD
Professor of Medicine
Robert H. Lurie Cancer Center-Northwestern University

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

First Challenge….

Classification

T-cell prolymphocytic leukemia

T-cell large granular lymphocytic leukemia

Chronic lymphoproliferative NK cells

Aggressive NK-cell leukemia

Adult T-cell lymphoma/leukemia

Systemic EBV-positive T-cell lymphoma

Extranodal NK/T-cell lymphoma, nasal type

Enteropathy-type intestinal T-cell lymphoma

Hepatosplenic T-cell lymphoma

Angioimmunoblastic T-cell lymphoma

Anaplastic large-cell lymphoma, ALK positive

Anaplastic large-cell lymphoma, ALK negative

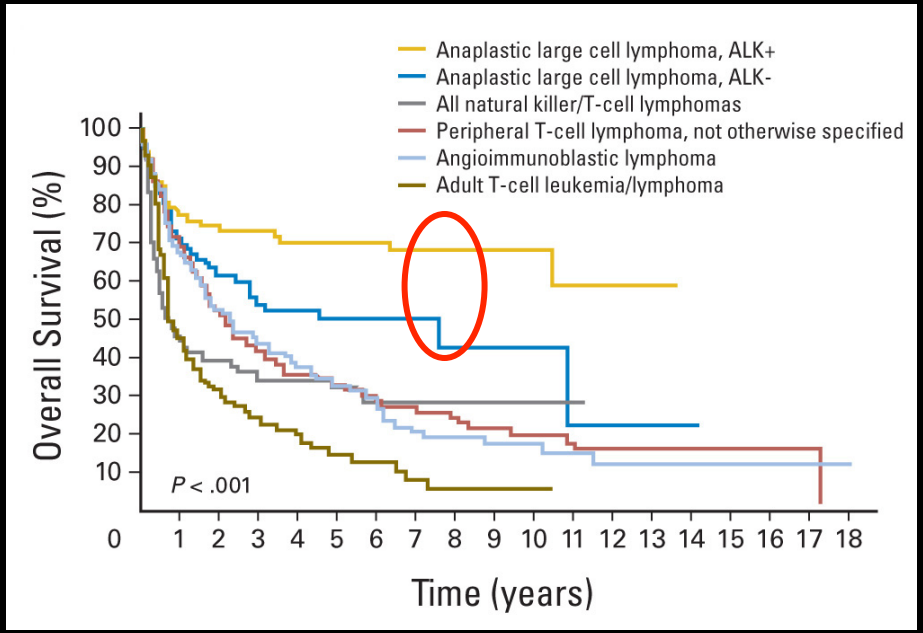
Peripheral T-cell lymphoma, NOS

- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30+ lymphoproliferative
- Primary cutaneous anaplastic large cell
- Lymphomatoid papulosis
- Borderline lesions
- Subcutaneous panniculitis-like T cell
- Primary cutaneous gamma-delta T cell
- Hydroa vacciniforme lymphoma
- Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T cell
- Primary cutaneous small/medium CD4+ T-cell lymphoma (provisional)

ow SH, et al. WHO classification of tumours of the haematopoletic and lymphoid tissues. 2008.

ond Challenge……
rall Survival in PTCL

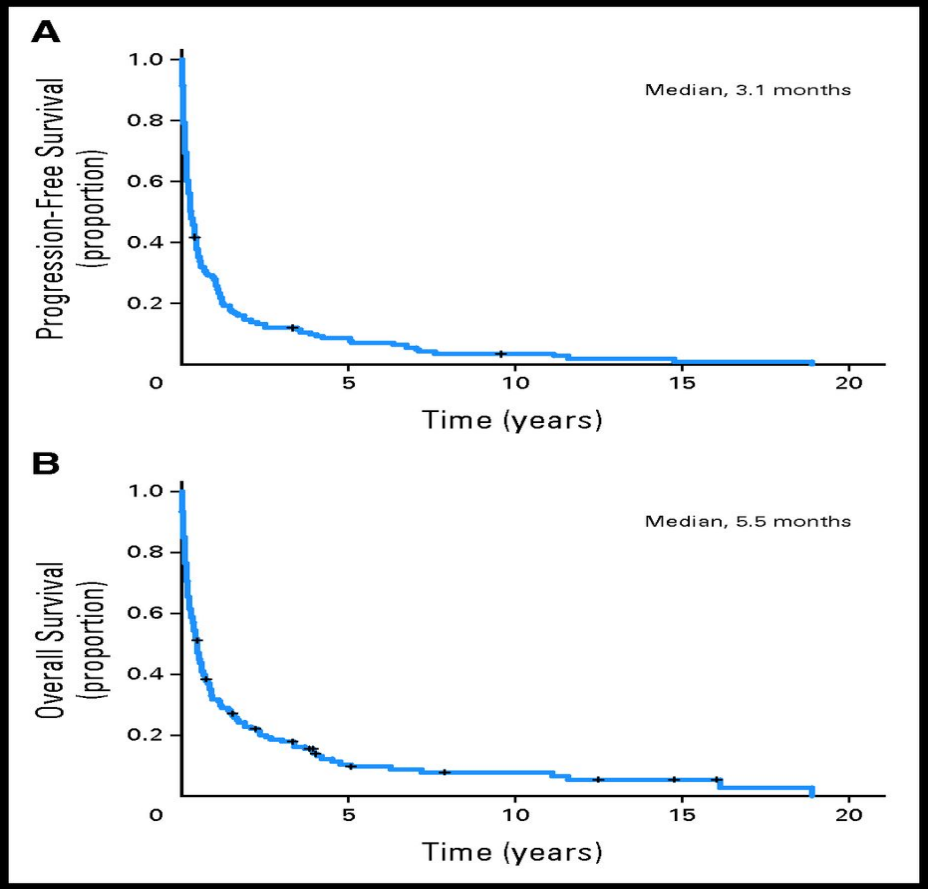
Majority of patients (> 85%) received an anthracycline-containing regimen

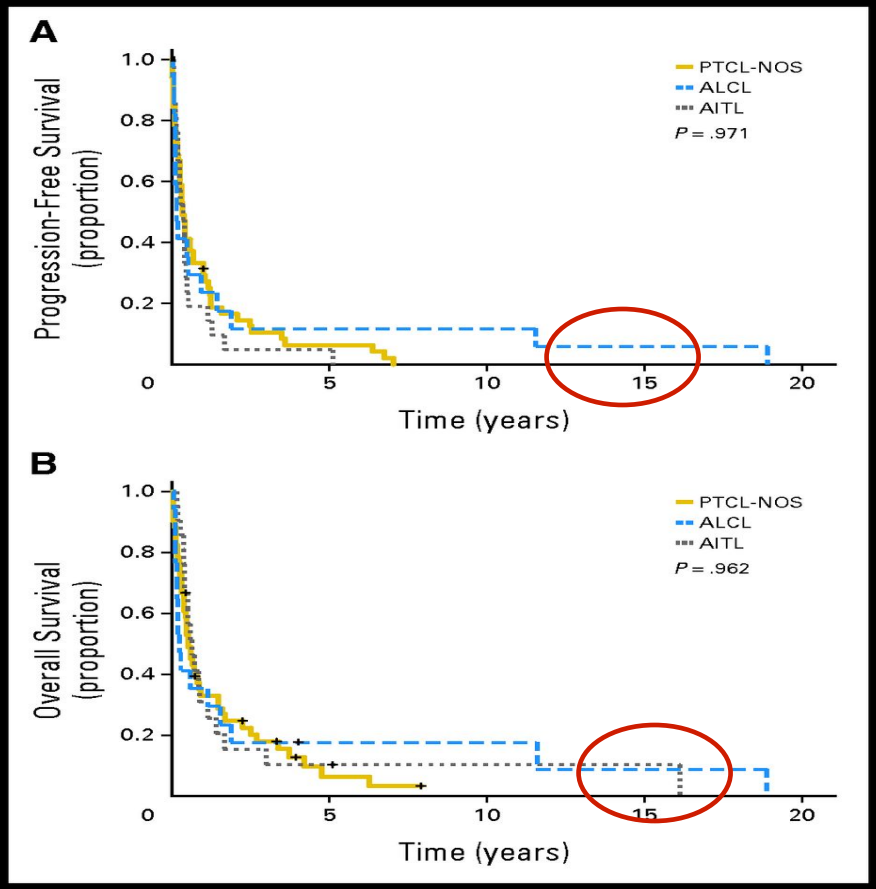


PTCL Subtypes						
	ALK+ ALCL	ALK– ALCL	PTCL-NOS	AITL	NK/TCL	ATLL
5-yr OS rate	70%	49%	32%	32%	42%	14%

et al. J Clin Oncol. 2008;26:4124-4130.

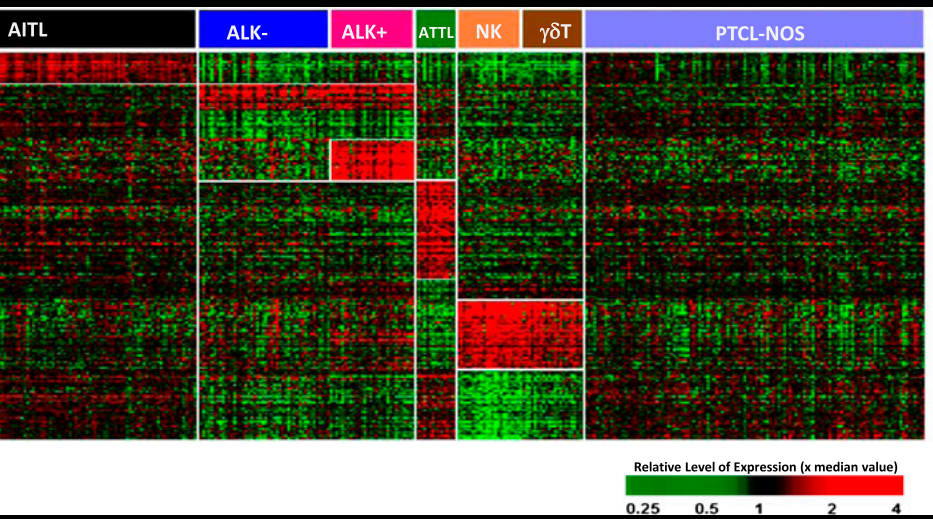
First Relapse or Progression of PTCL

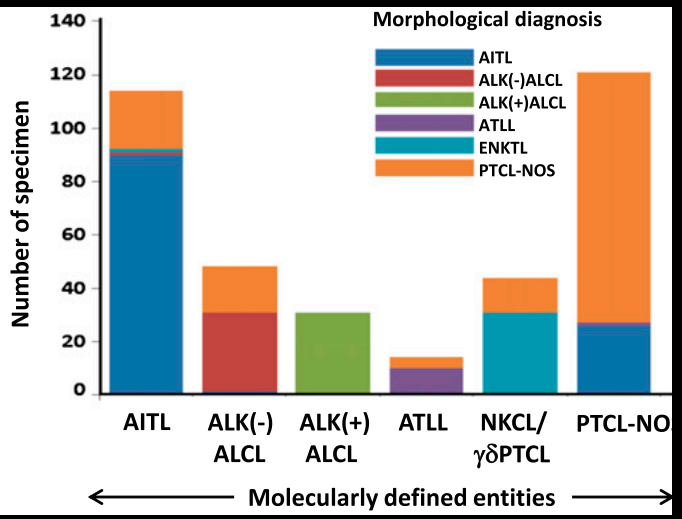




al. JCO 2013;31:1970-1976

cular subtypes in T-NHL

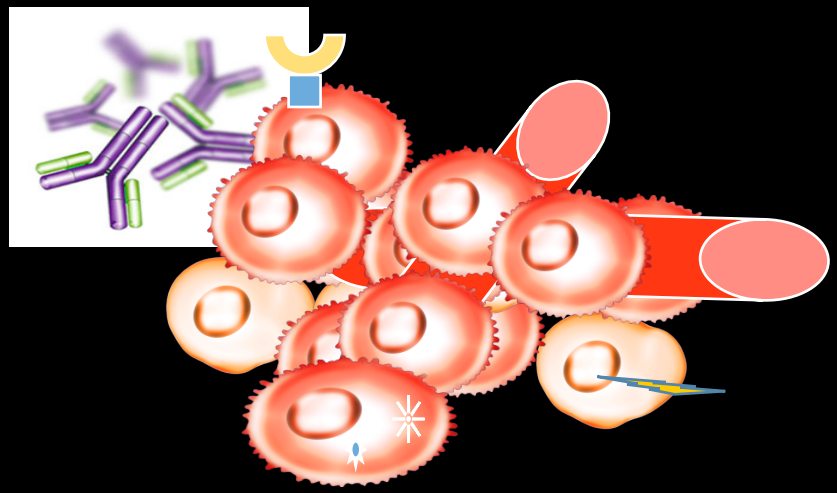




urrent (and maybe targetable) mutations
A, TET2, IDH2, DNMT3A, DUSP22, ALK.....
e subtypes have stronger epigenetic signatures

Selected Therapeutics in PTCL

notherapy/DNA damage
emcitabine
olate antagonists
endamustine
asome Inhibition
eting epigenome
oclonal antibodies
ody-drug conjugates
in kinase inhibitors



nmary of Selected Novel agents

	MOA	Phase	Patients (n)	Toxicity (grade 3 or>)	ORR	CRR	DOR (r
ved							
te	Folate antagonist	II	111	Mucositis	29%	11%	
n	HDACi	II	130	Thrombocytopenia Neutropenia Infections	25%	15%	
	HDACi	II	129	Hematologic	26%	10%	
ab	ADC	II	35	Neutropenia, neuropathy	41%	24%	
der Investigations							
zumab	Anti-CCR4 mAb	II	37	Neutropenia,rash	34%	17%	
	Aurora A KI	II	37	Hematologic, FN	24%	5%	
	PI3KI	I	33	Transaminitis,rash Neutropenia	47%	12%	
	ALKi	II	9		100%	100%	2-yr
	Anti-PD1 mAB	I	5	Pneumonitis,rash	40%	0%	

Classes of HDACi are based on chemical structure

c tetrapeptides
midepsin

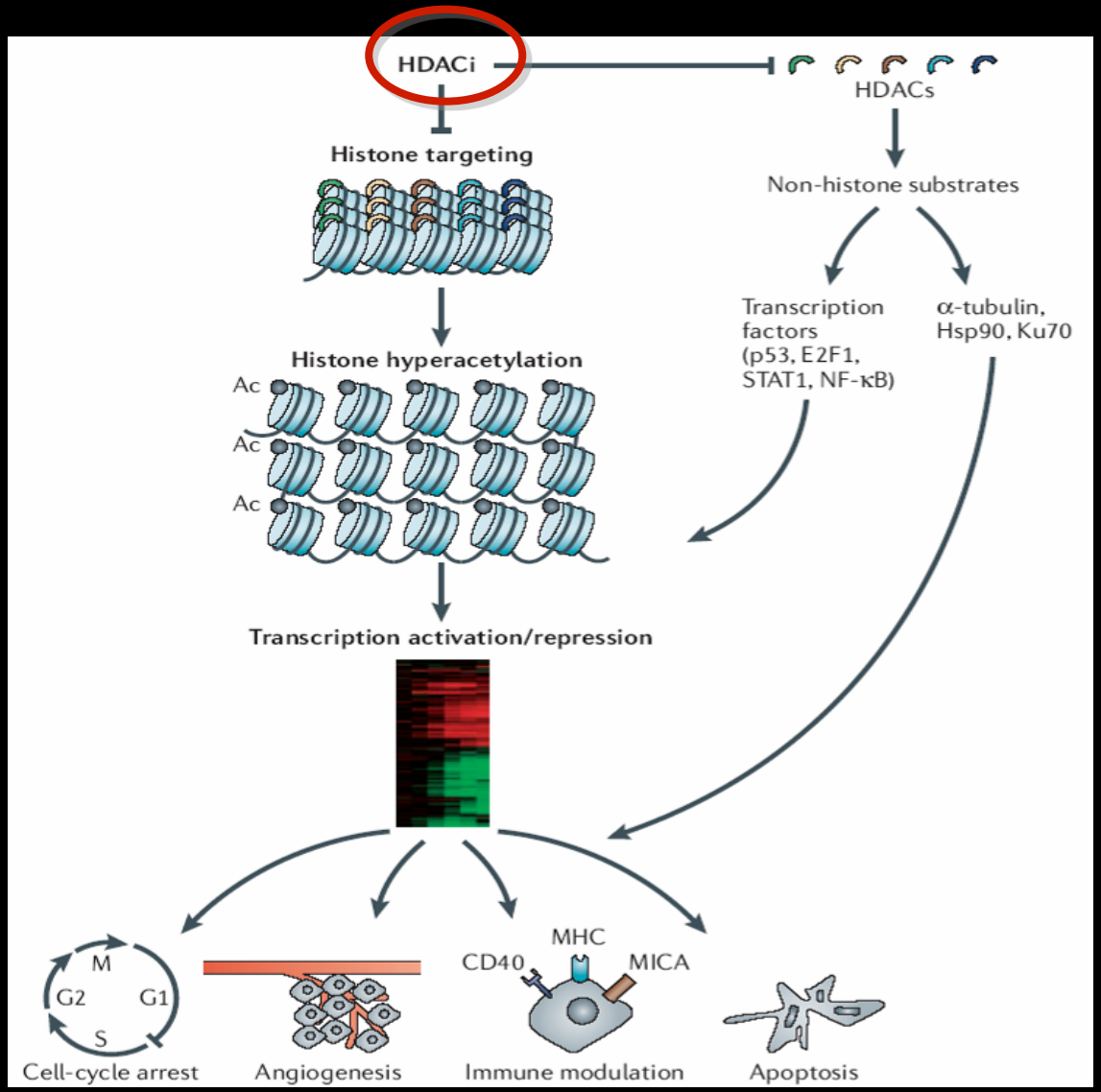
oxamates
rinostat (SAHA)
nobinostat (LBH589)
linostat (PXD101)

amides
tinostat (SNDX-275)
GCD-0103

HDACi have the same specificity or
for the 11 different target HDACs

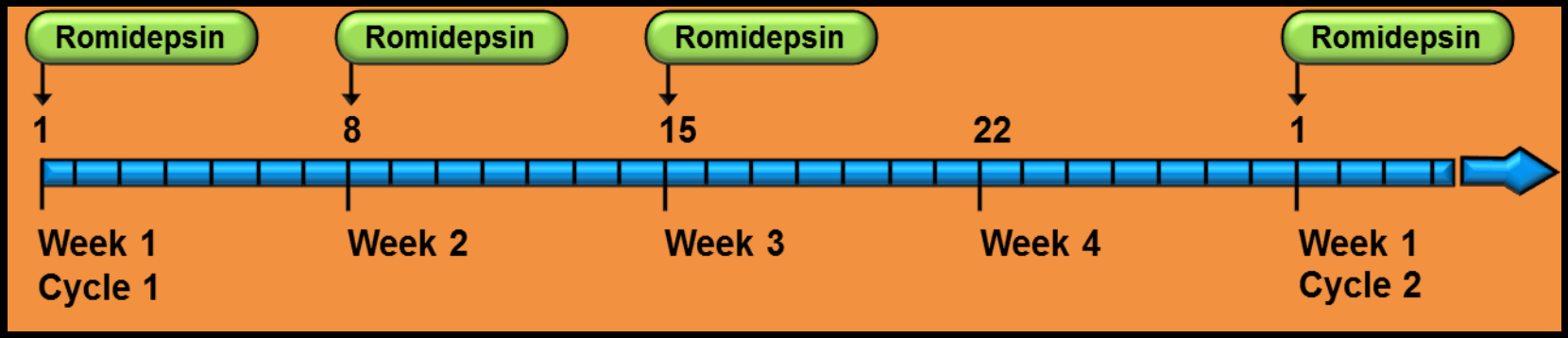
on **multiple tumor pathways** by
ng both histone *and* non-histone
tes

l., Nat Rev Drug Discovery. 2006; **5**, 769.



Romidepsin-Pivotal Study-Design

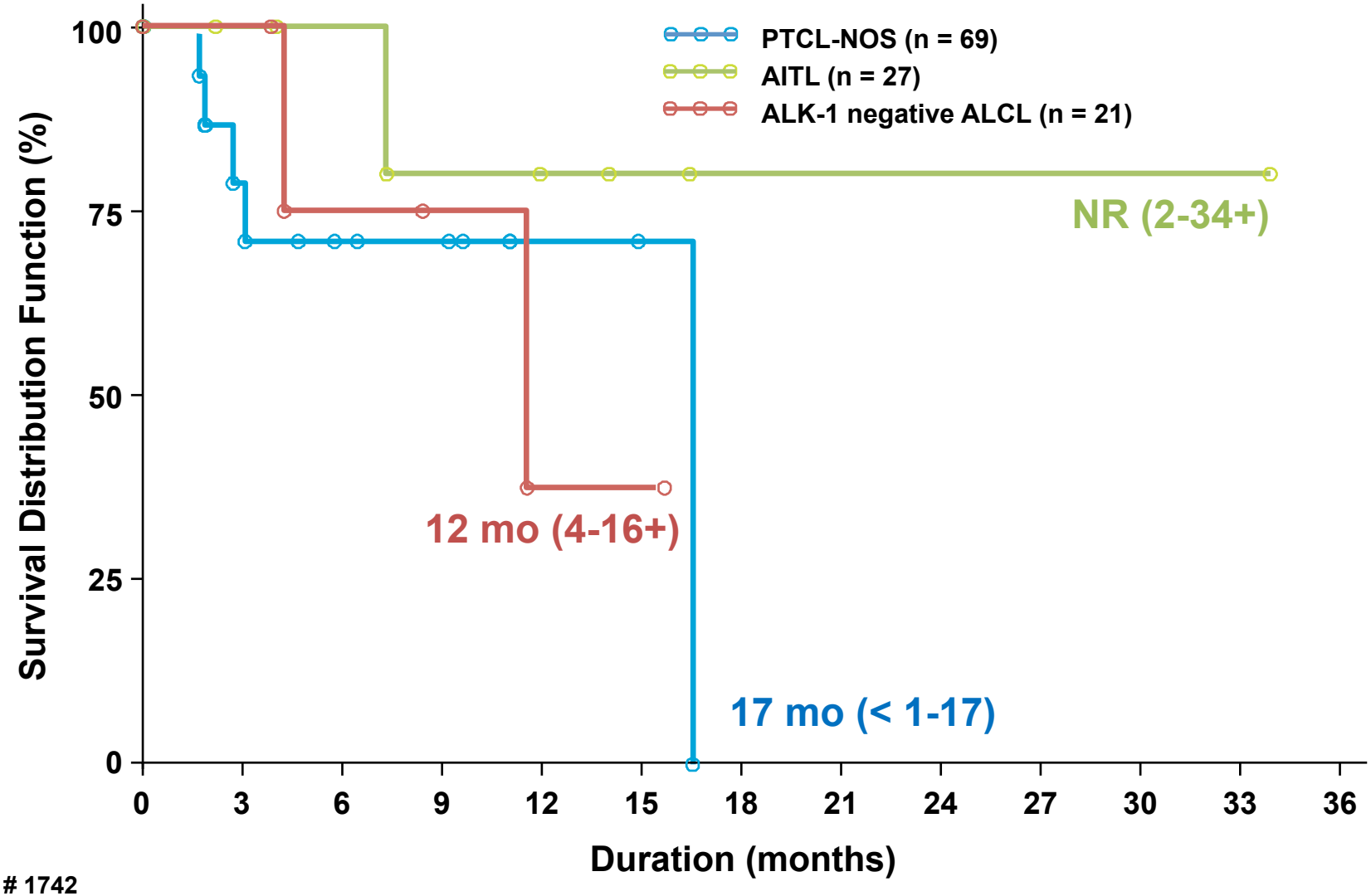
- Phase 2, open-label, single-arm, international study
- N = 131 patients enrolled; 130 with histopathologically confirmed PTCL
- Dosing: romidepsin 14 mg/m^2 (4-hour intravenous infusion) on days 1, 8, and 15 of a 28-day cycle × 6 cycles
  - Patients with SD or response could continue to receive treatment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



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)

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

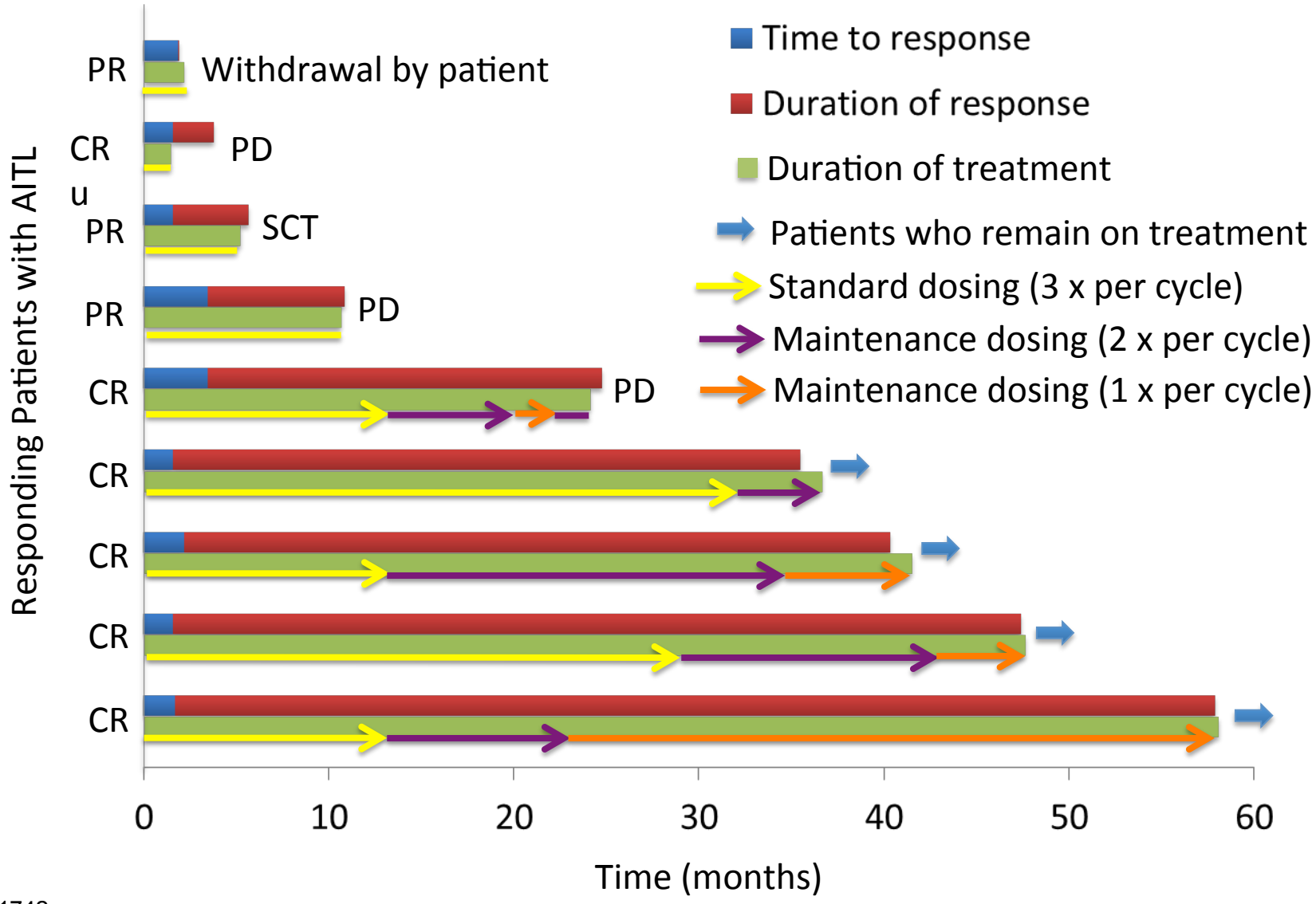
Duration of Response (IRC)



ached.

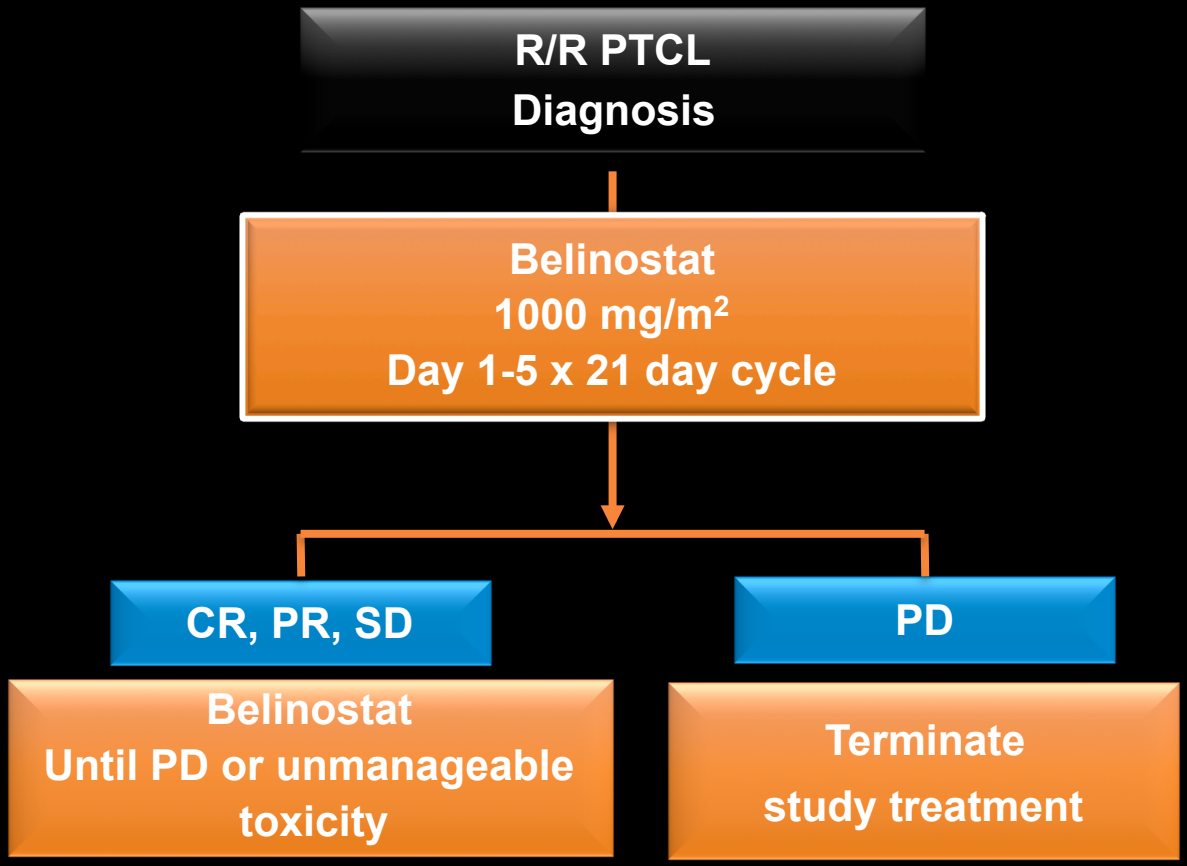
SH 2014 abstract # 1742

Efficacy of Romidepsin in AITL



H 2014 abstract # 1742

BELIEF TRIAL DESIGN
International, open label, single-arm study



- **Primary objective**:
  - ORR (CR or PR) in patients with R/R PTCL treated with belinostat monotherapy
- Exploratory analyses were conducted to determine response by PTCL subtype

. et al. J Clin Oncol 2015

PTCL Response Assessed by Central Review

Response	CPRG confirmed Efficacy Analysis Set (N=120)	
	n (%)	(95% CI)
CR+PR	31 (26)	(18-35)
CR	13 (11)	(6-18)
PR	18 (15)	
SD	18 (15)	
PD	48 (40)	
NE	23 (19)	

NE = not evaluable due to death (n=7), clinical progression (n=10), patient withdrawal (n=5) or lost to follow-up (n=1) prior to first radiologic assessment

O'Connor O. et al. J Clin Oncol 2015

Mutations in Epigenetic Regulators in T cell Lymphoma

	Pralatrexate	Romidepsin	Belinostat
ORR, Overall	27-29%[3]	25%[4]	26%[5]
Complete response rate	11%	15%	11%
AITL N	13	27	22
ORR, AITL	8%	**30%**	**46%**

Subtype	IDH2R172 [1]	IDH2R140[1]	TET2 [2]
PTCL-NOS	0/43	0/43	22/58 (40%) T_{FH} 58% vs other 24%
ALCL	0/50	0/50	0/18
AITL	25/101	1/101	40/86 (47%)

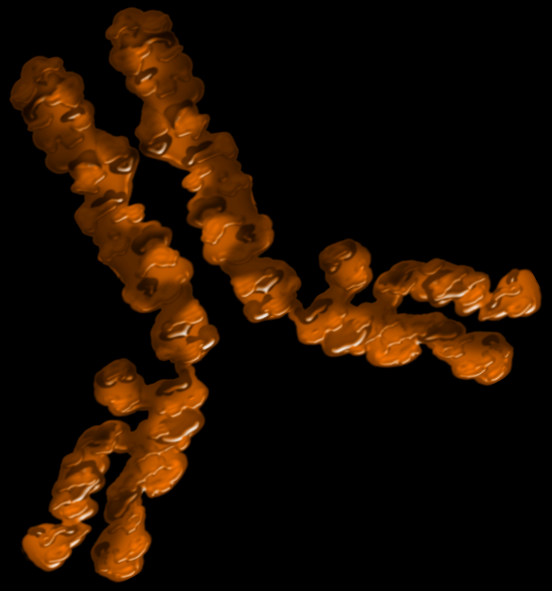
1.Cairns et al, *Blood* 2012
2. Lemonnier et al, *Blood* 2012
3. O'Connor et al, JCO 2011
4. Pro et al ASH 2014
5. Horwitz et al ICML 2013

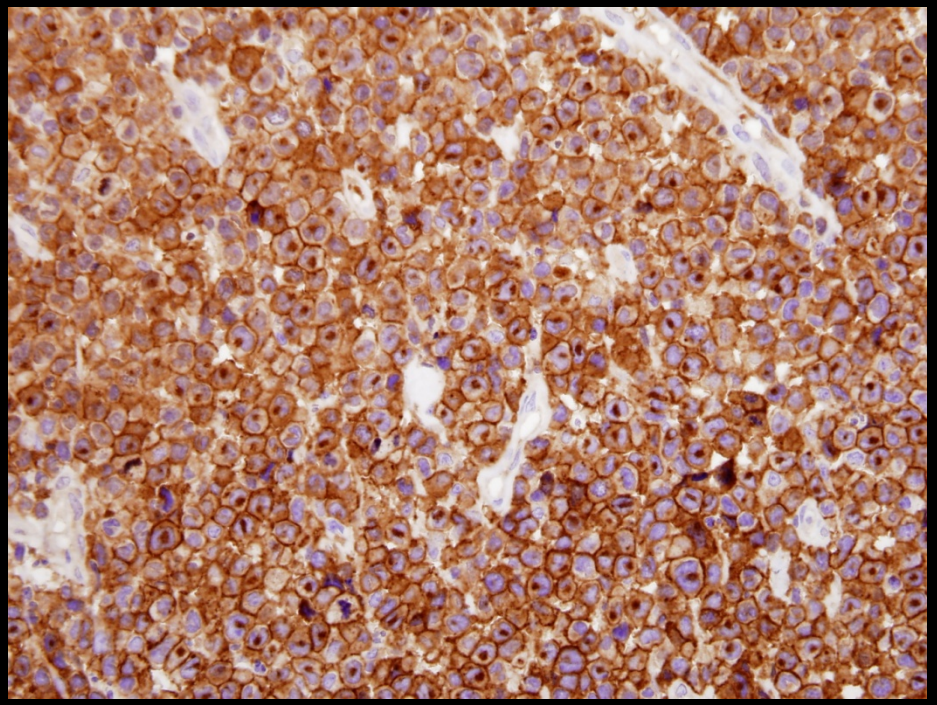
HDACi in T-cell Lymphomas

- Approval in the relapsed/refractory setting
- Selection should (?) be based on
  - **PTCL subtype**
  - **Schedule**
  - **Toxicity profile**
- Studies ongoing in the frontline and relapsed setting

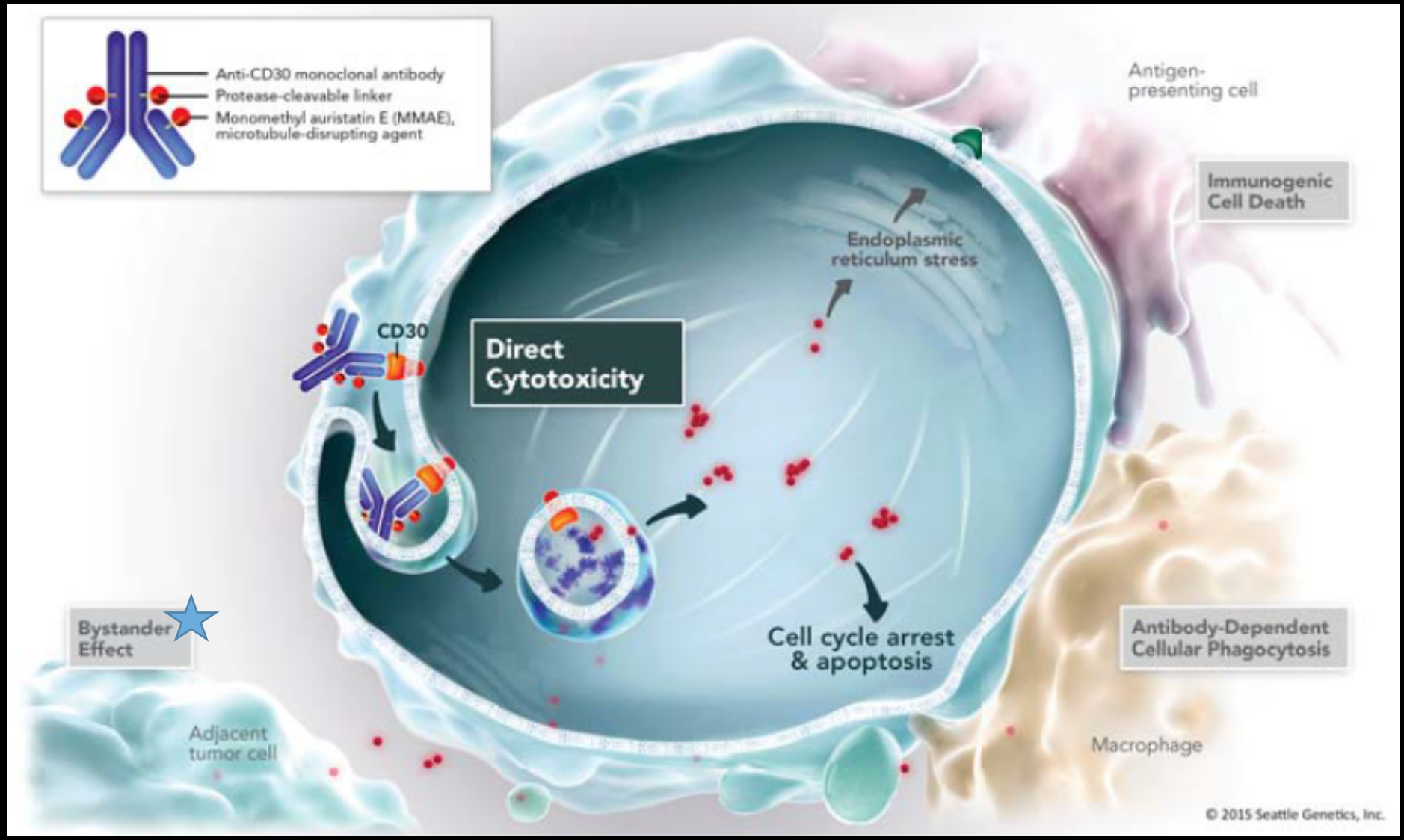
- Maintenance strategy effective in responders

rgeting CD30





tuximab Vedotin
hanism of Action and Proposed Secondary Effects

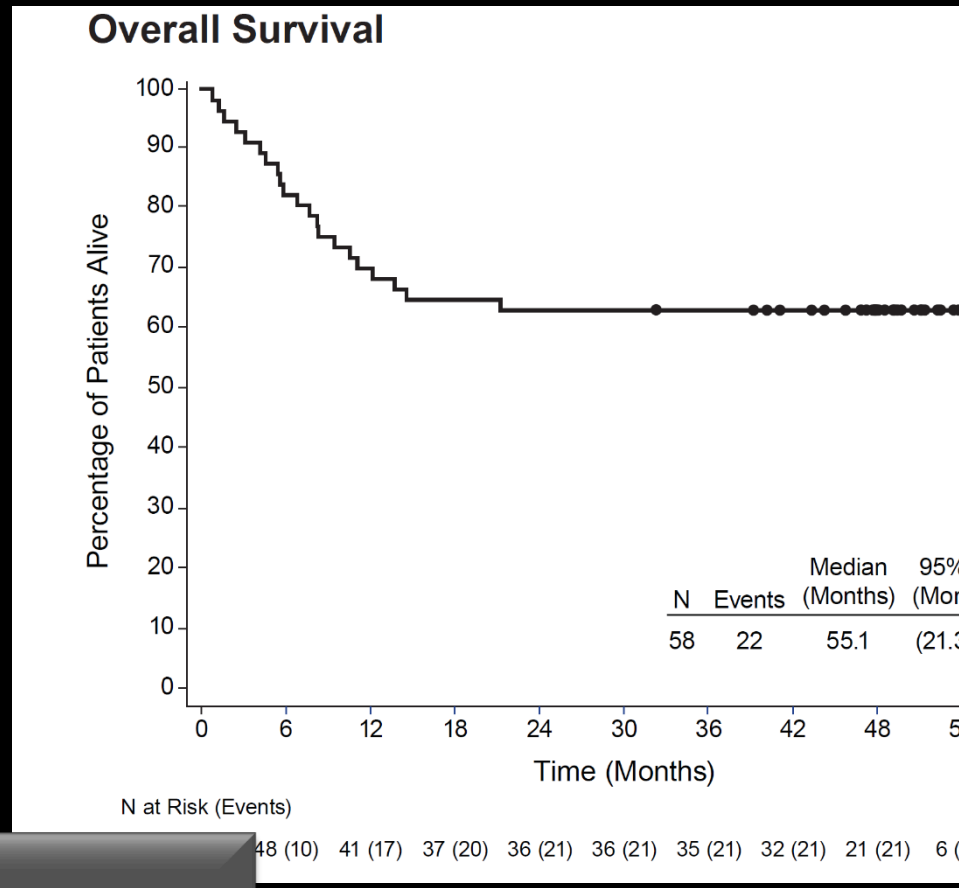


tal Phase II Study ALCL Long-Term Follow-u

t Response (N=58)

	IRF*	Investigator
e response rate	50 (86)*	50 (86)
ponse		
ete remission (CR)	34 (59)	38 (66)
emission (PR)	16 (28)	12 (21)
disease (SD)	2 (3)	4 (7)
ssive disease (PD)	3 (5)	2 (3)
gy ineligible (HI)	2 (3)	0 (0)
luable (NE)	1 (2)	2 (3)

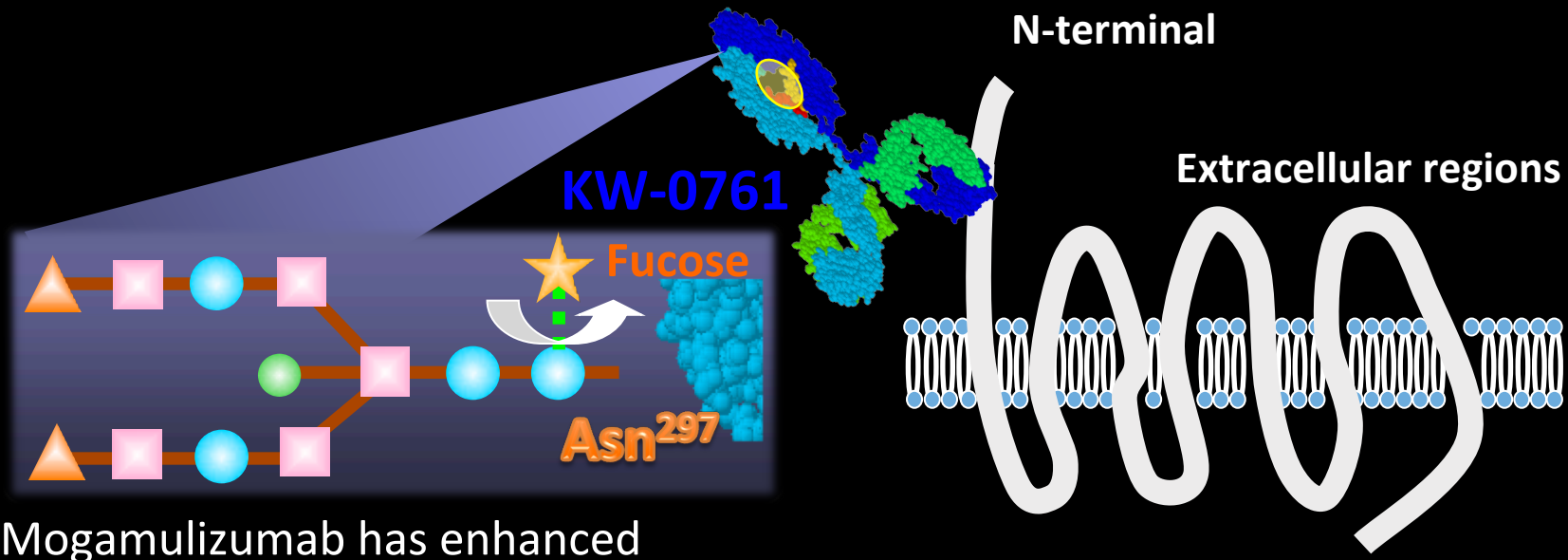
ary endpoint



e directions:

- n CD30 + PTCL
- nation therapy in front=line and R/R setting
- enance vs retreatment
- ine Therapy ⇨ ECHELON 2

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 involvemen
- ($P < .05$) 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

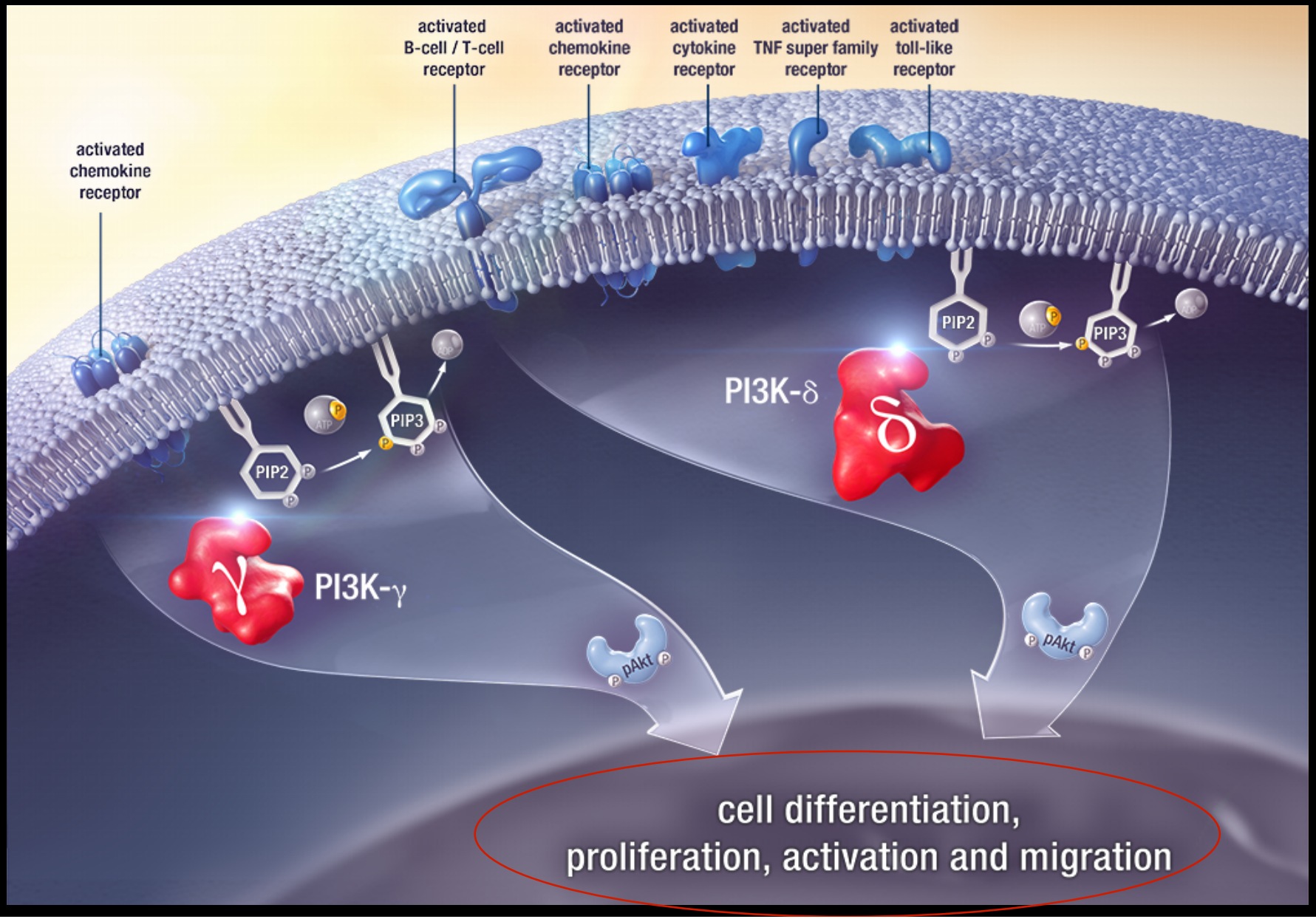
Mogamulizumab (KW-0761): Studies in Patients With T-Cell Lymphoma

- 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%)

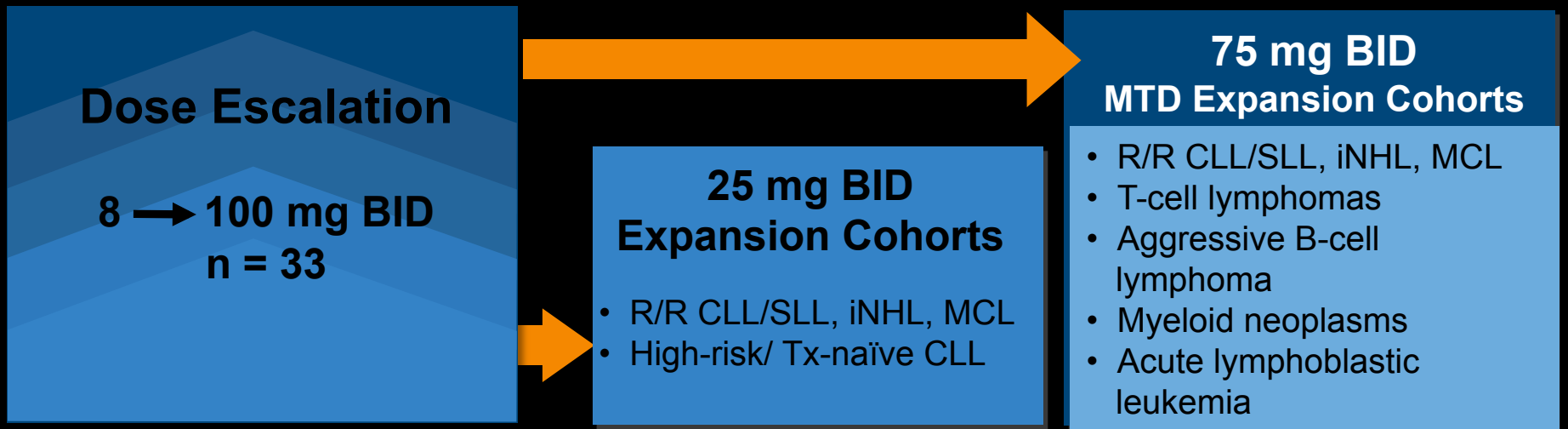
- Active in phase II study in patients with TCL (N=37))[2]
  - ORR: 35 %, CR 13%
  - Median PFS 3 months
- Approved in Japan for the treatment of ATLL
- Ongoing multicenter, randomized phase III clinical trial of mogamulizumab vs vorinostat in patients with MF/SS[3]

1. Ishida T, et al. J Clin Oncol. 2012;30:837-842. 2. Ogura M, et al. J Clin Oncol. 2014;32:1157-63
3. ClinicalTrials.gov. NCT01728805.

PI3K
d PI3K-γ Support the Growth and Survival of B-cell and T-cell
cies



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
- Expansion cohorts enrolling

Safety Population (N=117)

- 34 CLL (includes 2 SLL)
- 51 B-cell lymphoma / 17 T-cell lymphoma / 15 Other

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)

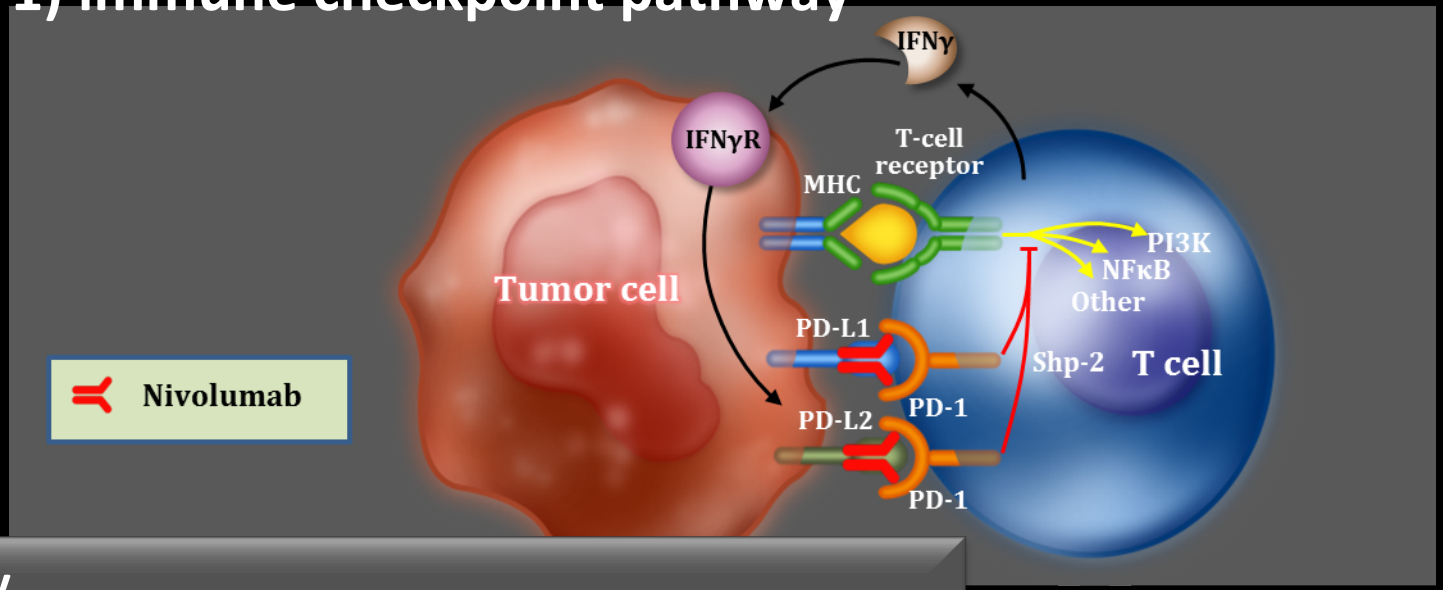
Includes evaluable patients = at least 1 on-treatment response assessment or PD without assessment
CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease
ORR = CR + PR

- 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

z S. et al, ASH 2014 Abstr. 803

une Checkpoint Inhibitors

nab is a fully human immunoglobulin G4 monoclonal
y targeting the programmed
(PD-1) immune checkpoint pathway



Study
ents with NHL
%

% (2/5)

, et al. *Blood*. 2014;124 abstract 291.

Genetic Alterations in PTCLs

PTCL, NOS: t(5:9)(*ITK/SYK*), *RHOA*, *FYN*

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

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

ALCL, ALK-: t(6;7)(*DUSP22/FRA7H*), *TP63, PRDM1*, del *TP53*

HSTCL: isochromosome 7q, +8, *STAT3, STAT5B*

ENKTCL: *JAK3, ADAM3A*, del *PRDM1* and *HACE1*

EATL type 1: gains of 9q34, 3q27, 1q, 5q, del 16q

EATL type 2: gains of 9q34, 8q (*MYC*), del 16q

zotinib

LK+ 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

SE I-II study in combination with chemotherapy in untreated patients

y diagnosed patients with histologically proven

isease must be (CD)30 positive

se must be anaplastic lymphoma kinase (ALK)

e)

nts must have stage II, III, or IV disease

21 years of age

rti Passerini et al. J. Natl. Cancer Inst. 2014;106:2; NCT01979536

ly....

ecular targeted approaches in T-cell Lymphomas

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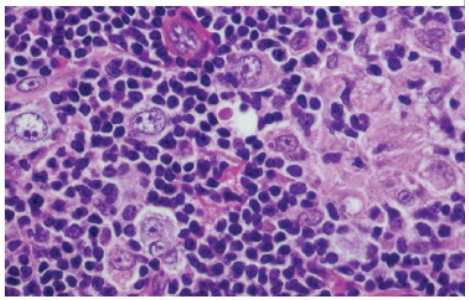
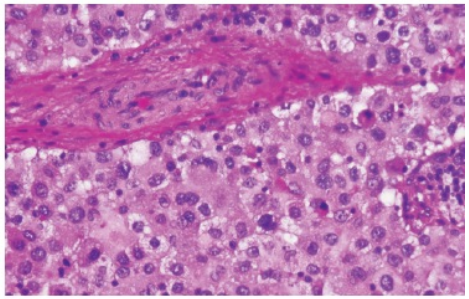
Chicago Lymphoma Symposium

May 6–7, 2016





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The goal of this educational activity is to facilitate a forum for physicians, researchers, and other allied healthcare professionals to discuss biologic, diagnostic, and therapeutic aspects of Hodgkin and non-Hodgkin lymphomas.

Grazie!

barbara.pro@nm.org