New Agents in PTCL

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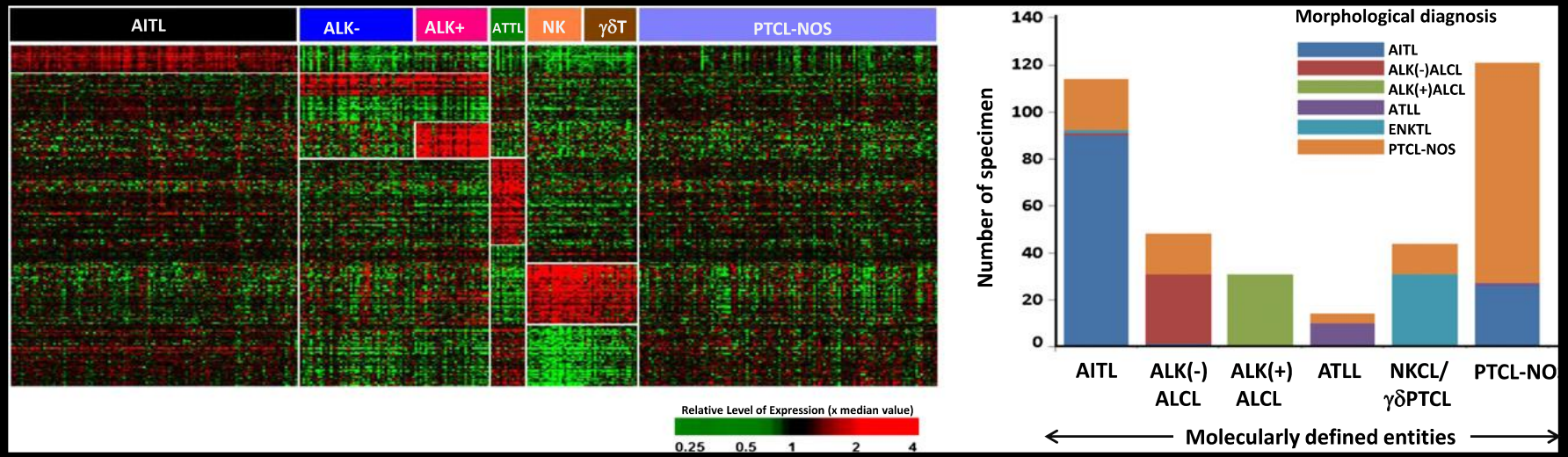
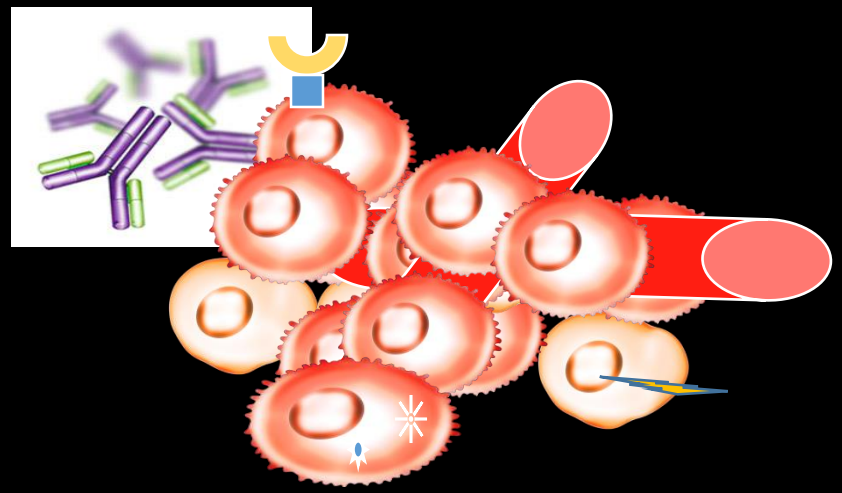
Molecular subtypes in T-NHL



Recurrent (and maybe targetable) mutations
RHOA, TET2, IDH2, DNMT3A, DUSP22, ALK.....
Some subtypes have stronger epigenetic signatures

Selected Therapeutics in PTCL

- Chemotherapy/DNA damage
  - Gemcitabine
  - Folate antagonists
  - Bendamustine
- Proteasome Inhibition
- Targeting epigenome
- Monoclonal antibodies
- Antibody-drug conjugates
- Protein kinase inhibitors



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%	15%	28
Belinostat	HDACi	II	129	Hematologic	26%	10%	13.6
Brentuximab	ADC	II	35	Neutropenia, neuropathy	41%	24%	7.6
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					
Nivolumab	Anti-PD1 mAB	I	5	Pneumonitis,rash	40%	0%	NR

Classes of HDACi are based on chemical structure

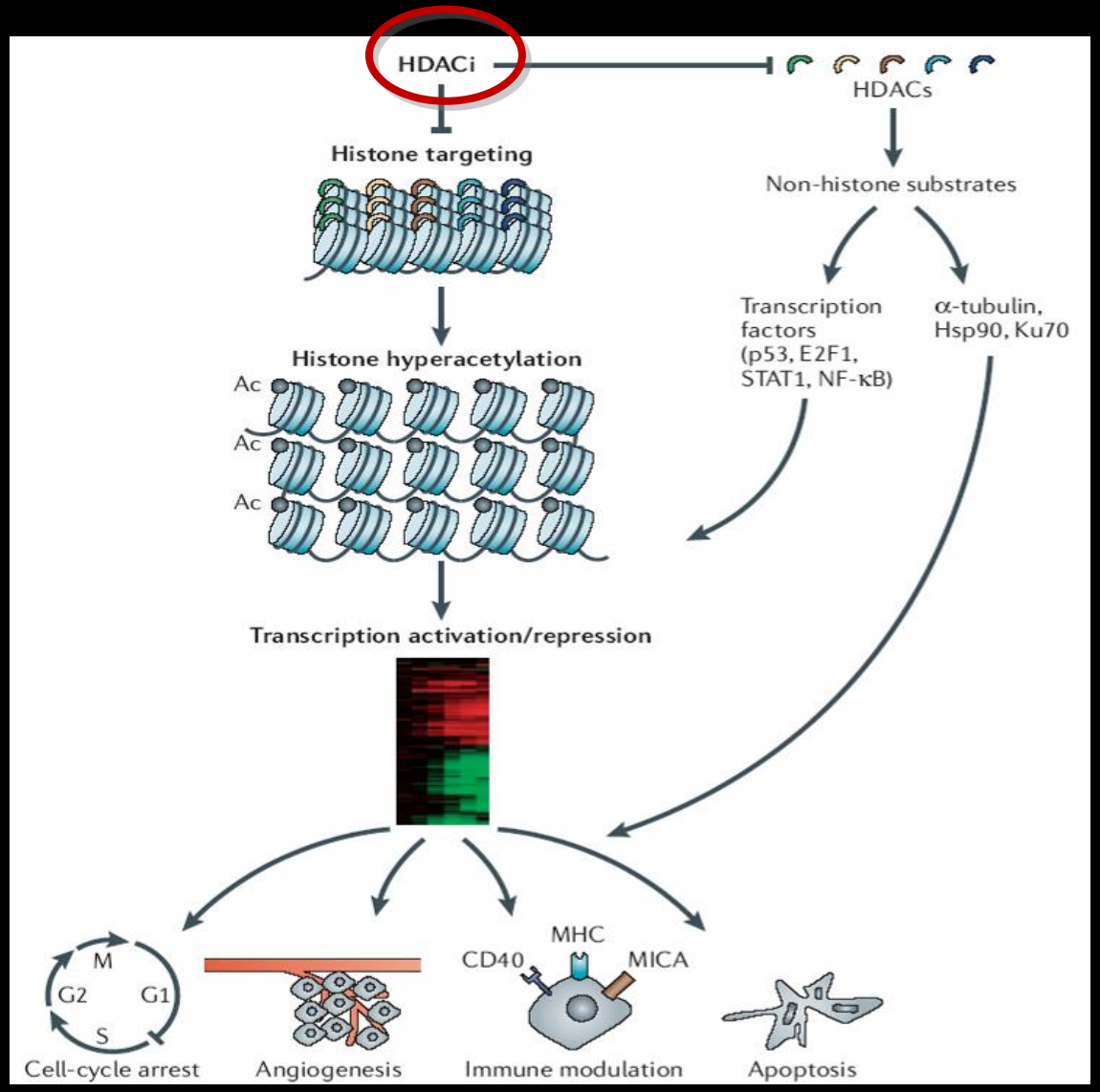
Cyclic tetrapeptides
- **Romidepsin**

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**

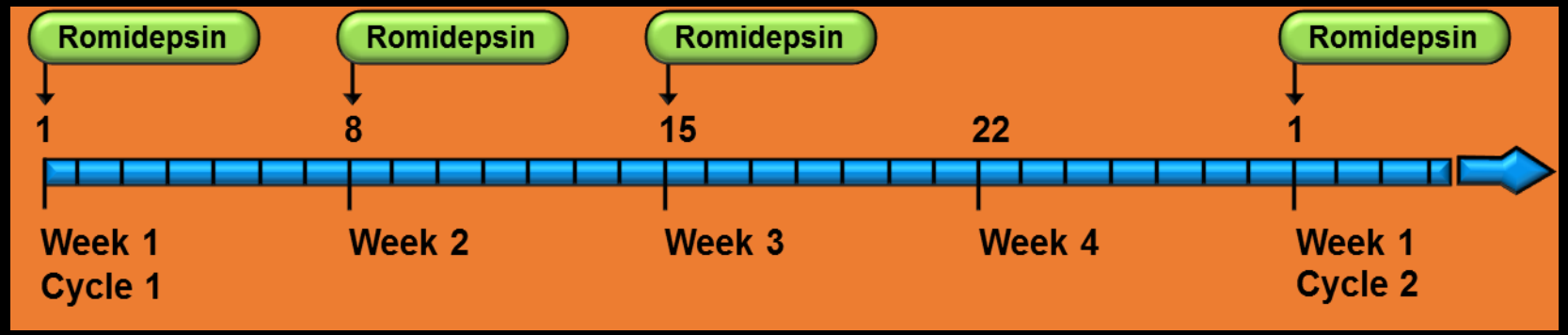
Impact on **multiple tumor pathways** by targeting both histone *and* non-histone substrates



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

Romidepsin-Pivotal Study-Design

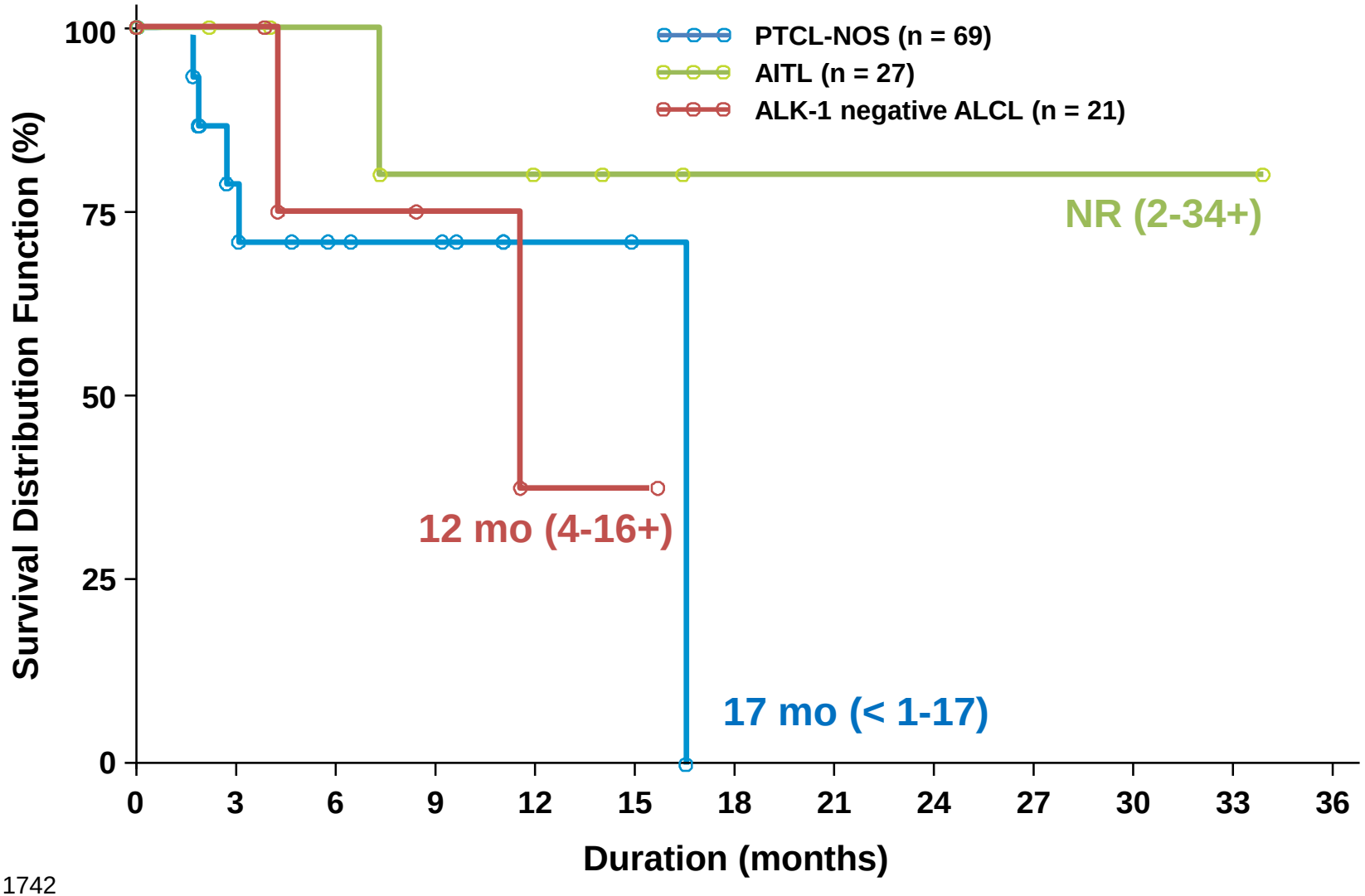
- Phase 2, open-label, single-arm, international study
- N = 131 patients enrolled; 130 with histopathologically confirmed PTCL
- Dosing: romidepsin 14 mg/m^2 (4-hour intravenous infusion) on days 1, 8, and 15 of a 28-day cycle × 6 cycles
  - Patients with SD or response could continue to receive treatment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

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

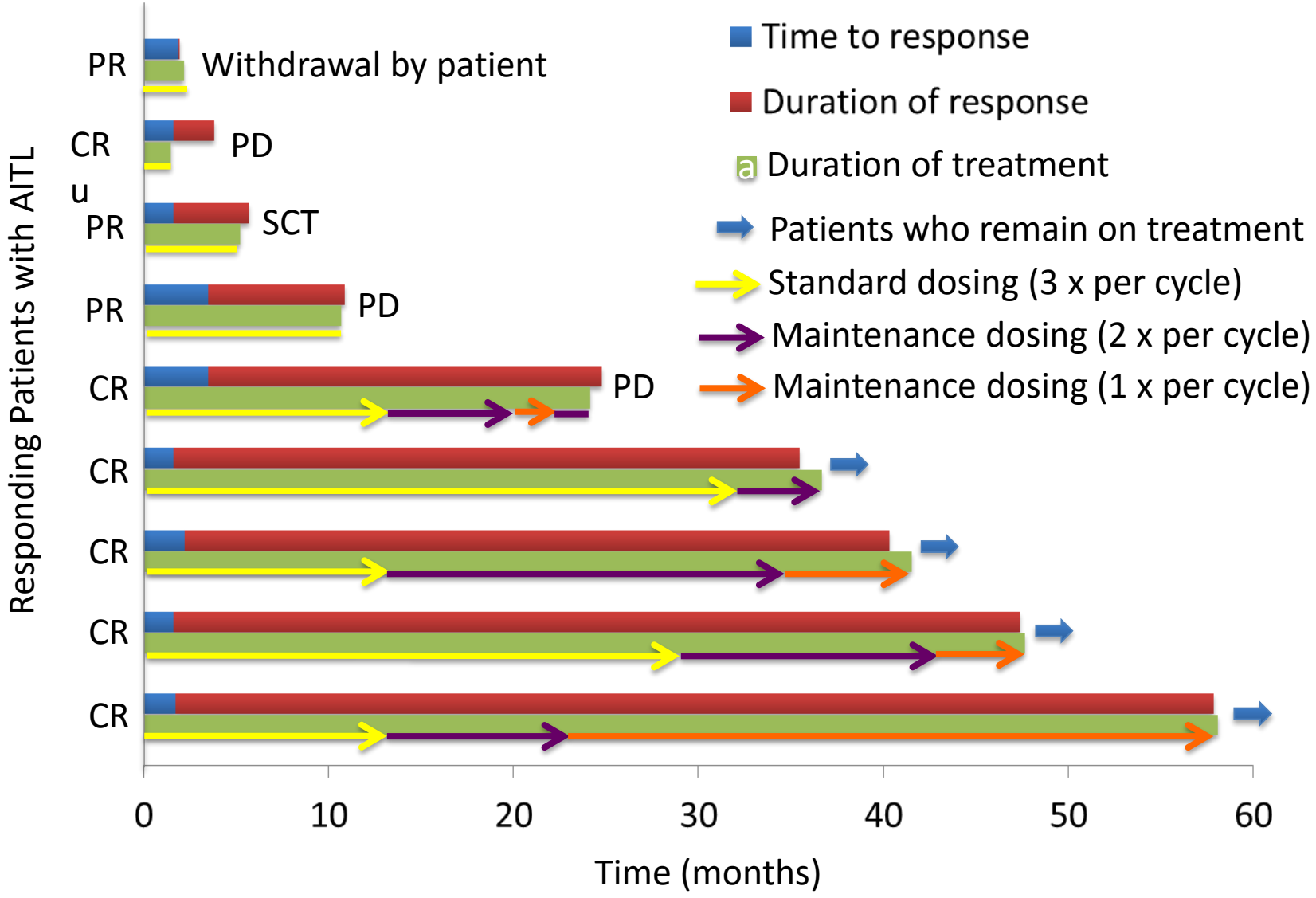
Duration of Response (IRC)



NR, not reached.

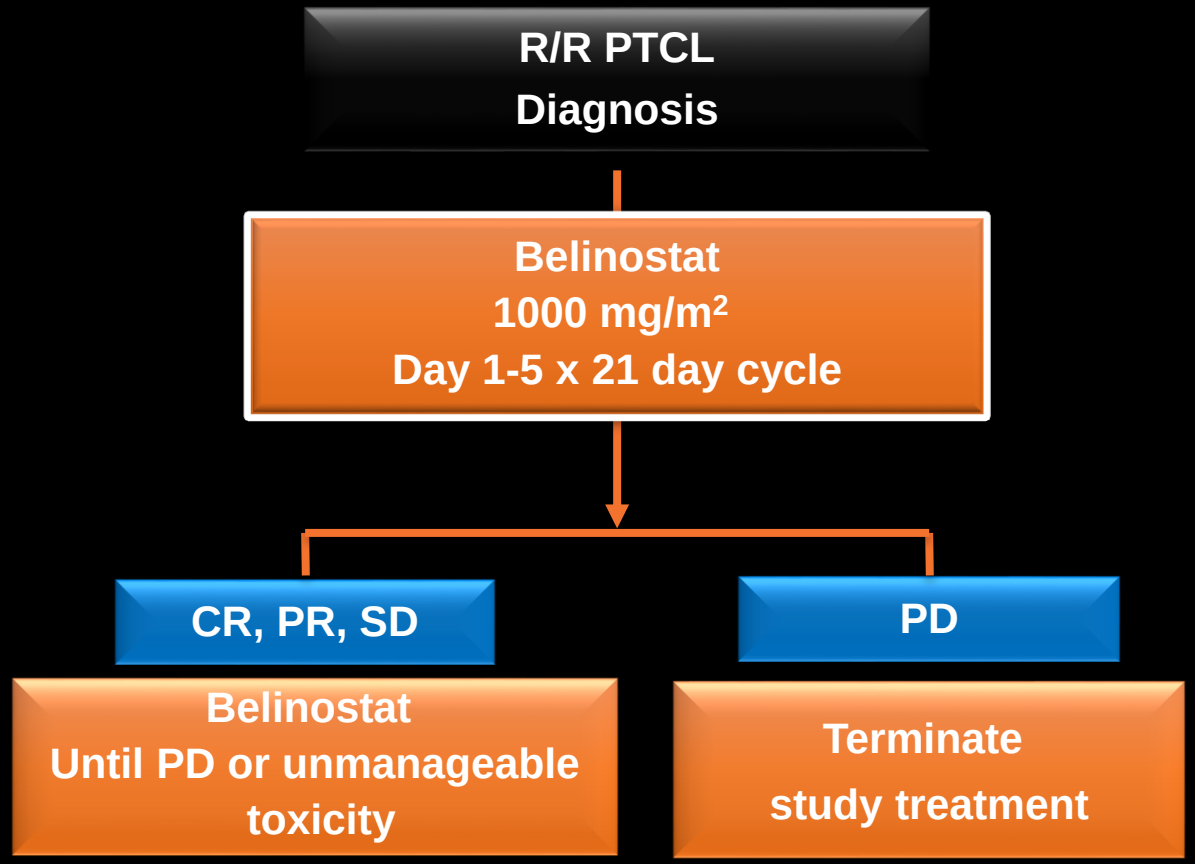
Pro et al. ASH 2014 abstract # 1742

Efficacy of Romidepsin in AITL



Pro et al. ASH 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

O'Connor O. 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%)

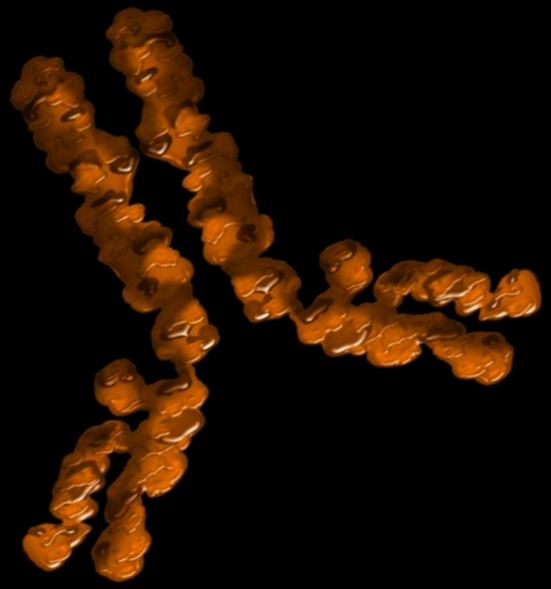
1.Cairns et al, *Blood* 2012
2. Lemonnier et al, *Blood* 2012
3. O'Connor et al, JCO 2011
4. Pro et al ASH 2014
5. Horwitz et al ICML 2013

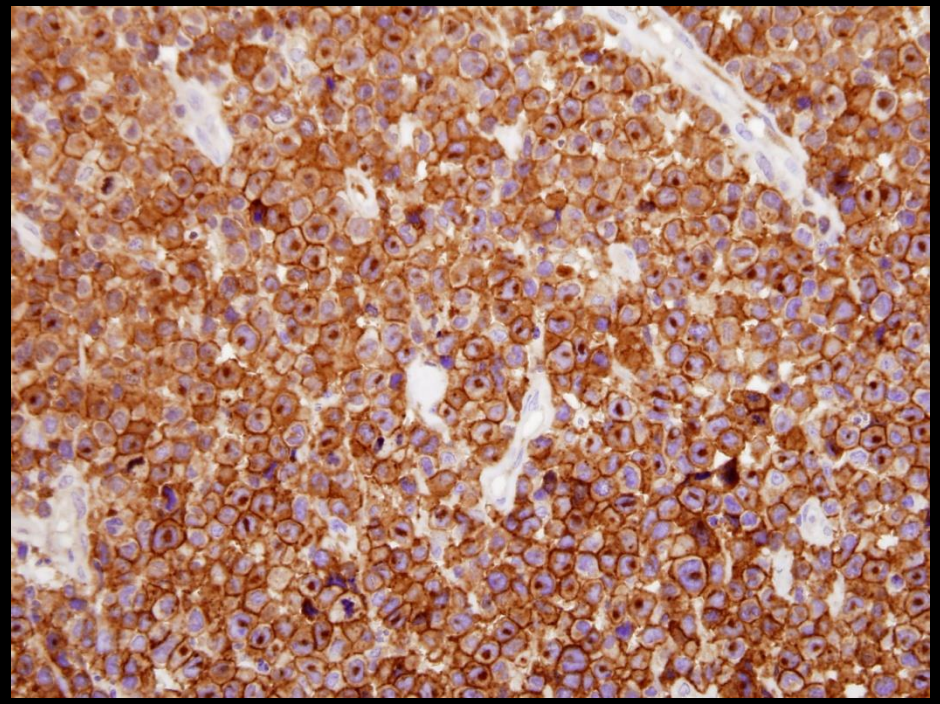
HDACi in T-cell Lymphomas

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

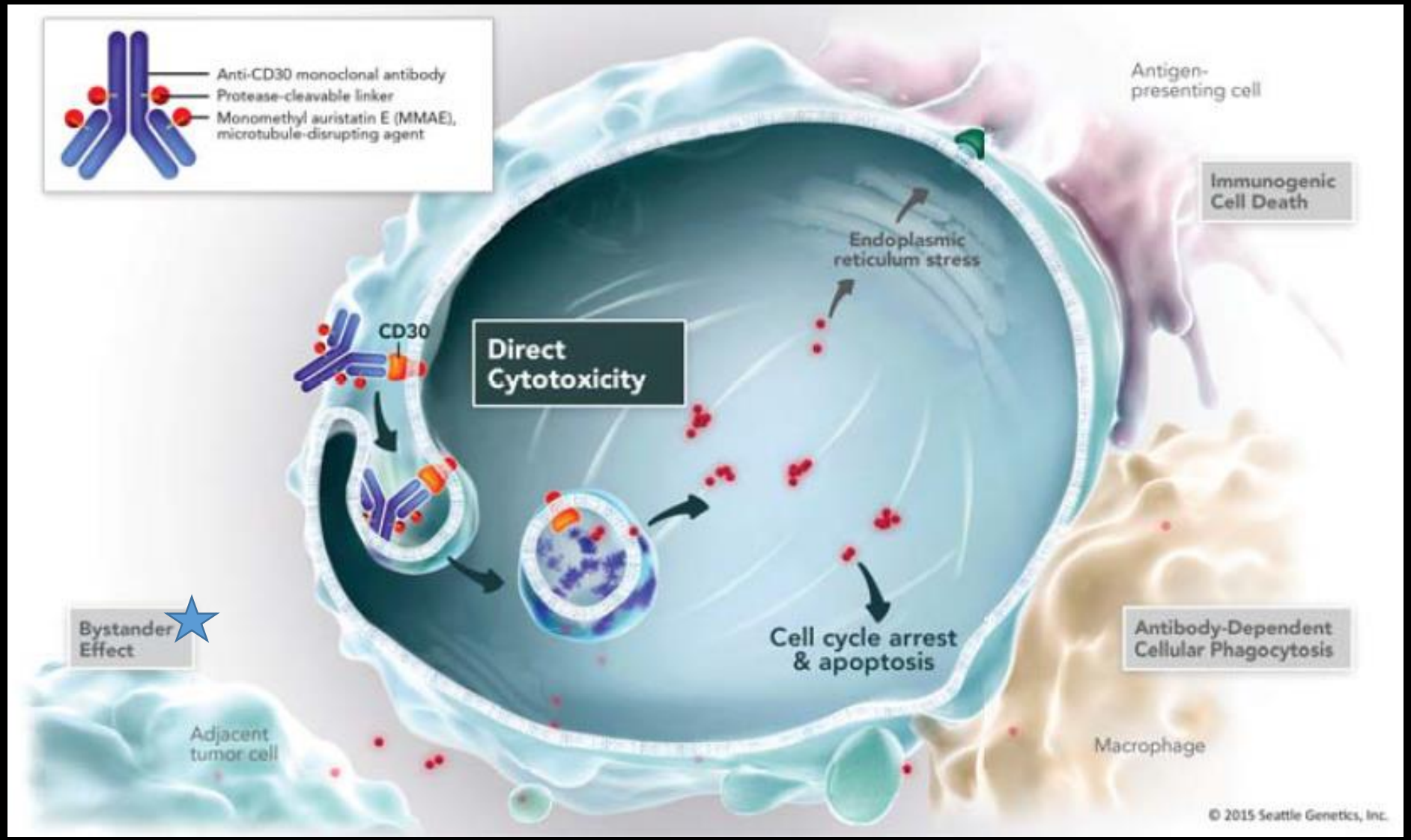
- Maintenance strategy effective in responders

Targeting CD30





Brentuximab Vedotin
Mechanism of Action and Proposed Secondary Effects



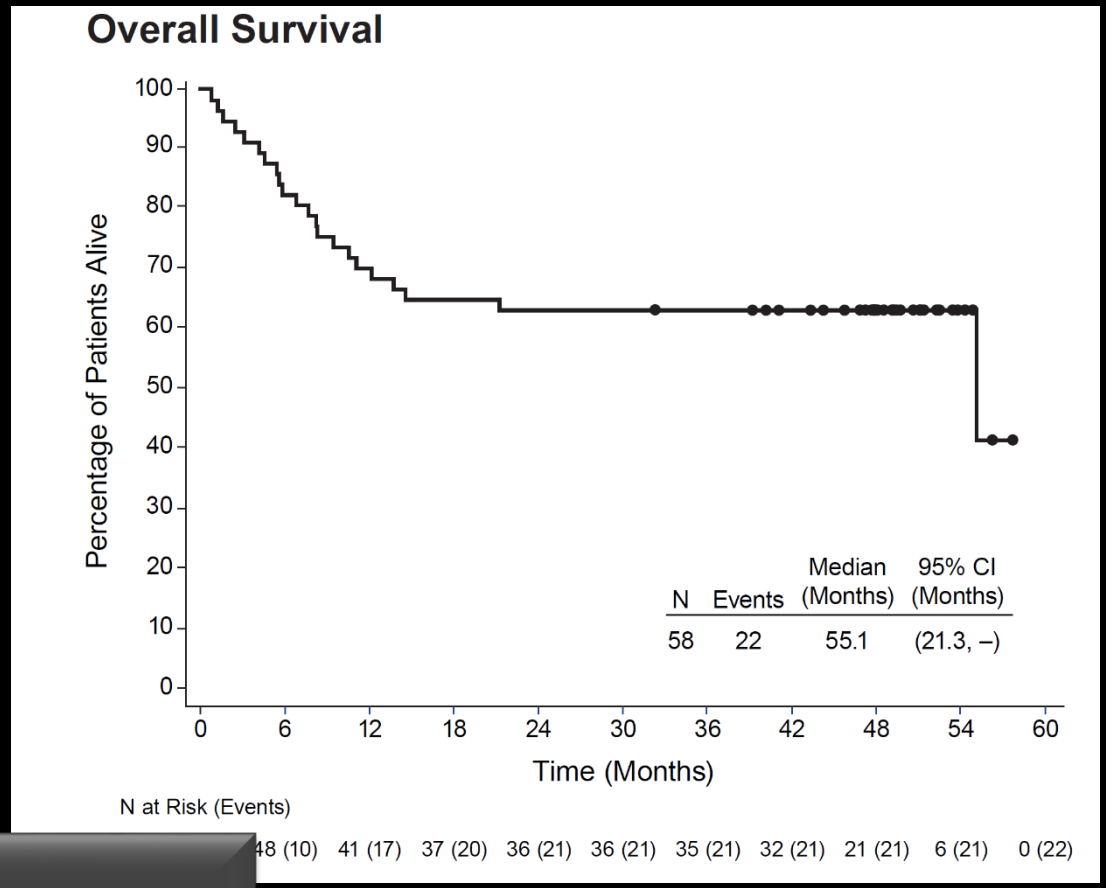
Pivotal Phase II Study ALCL

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

Long-Term Follow-up



Future directions:

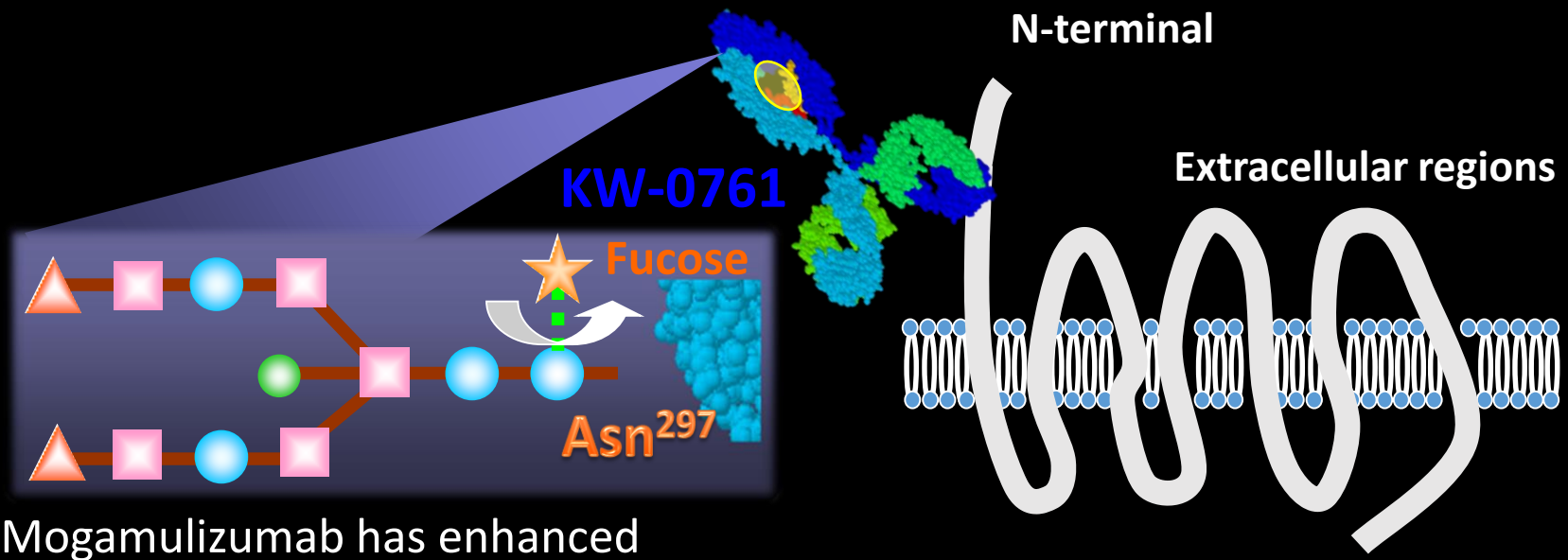
Role in CD30 + PTCL

Combination therapy in front=line and R/R setting

Maintenance vs retreatment

Frontline 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 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

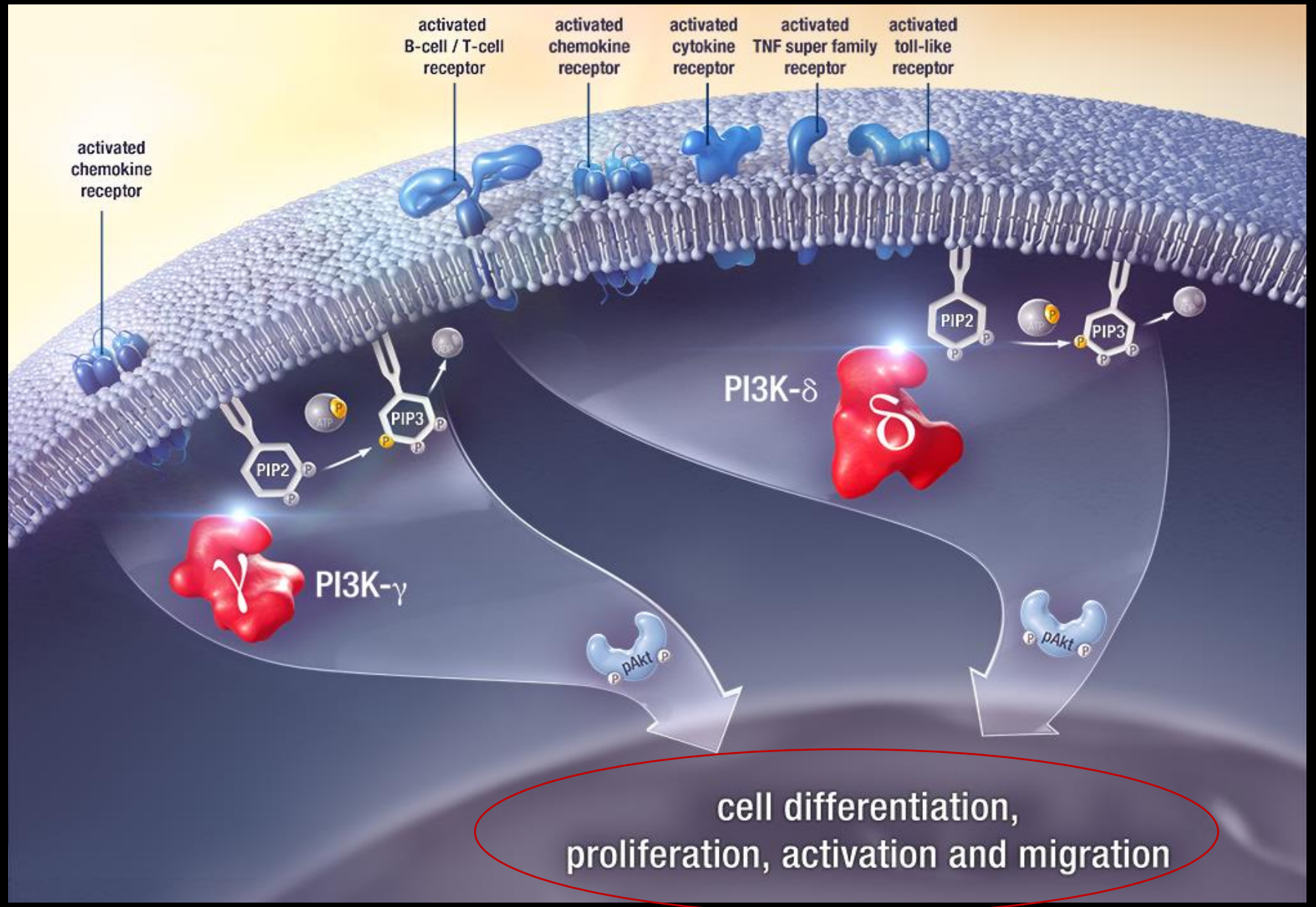
Mogamulizumab (KW-0761): Studies in Patients With T-Cell Lymphoma

- 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%)

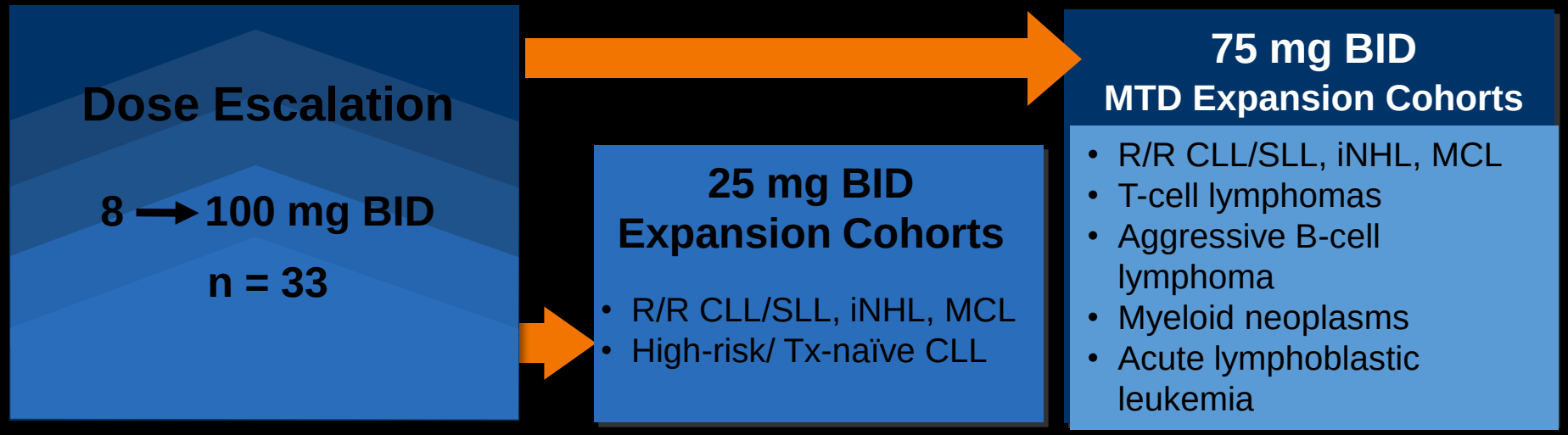
- Active in phase II study in patients with TCL (N=37))[2]
  - ORR: 35 %, CR 13%
  - Median PFS 3 months
- Approved in Japan for the treatment of ATLL
- Ongoing multicenter, randomized phase III clinical trial of mogamulizumab vs vorinostat in patients with MF/SS[3]

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.

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
- 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)

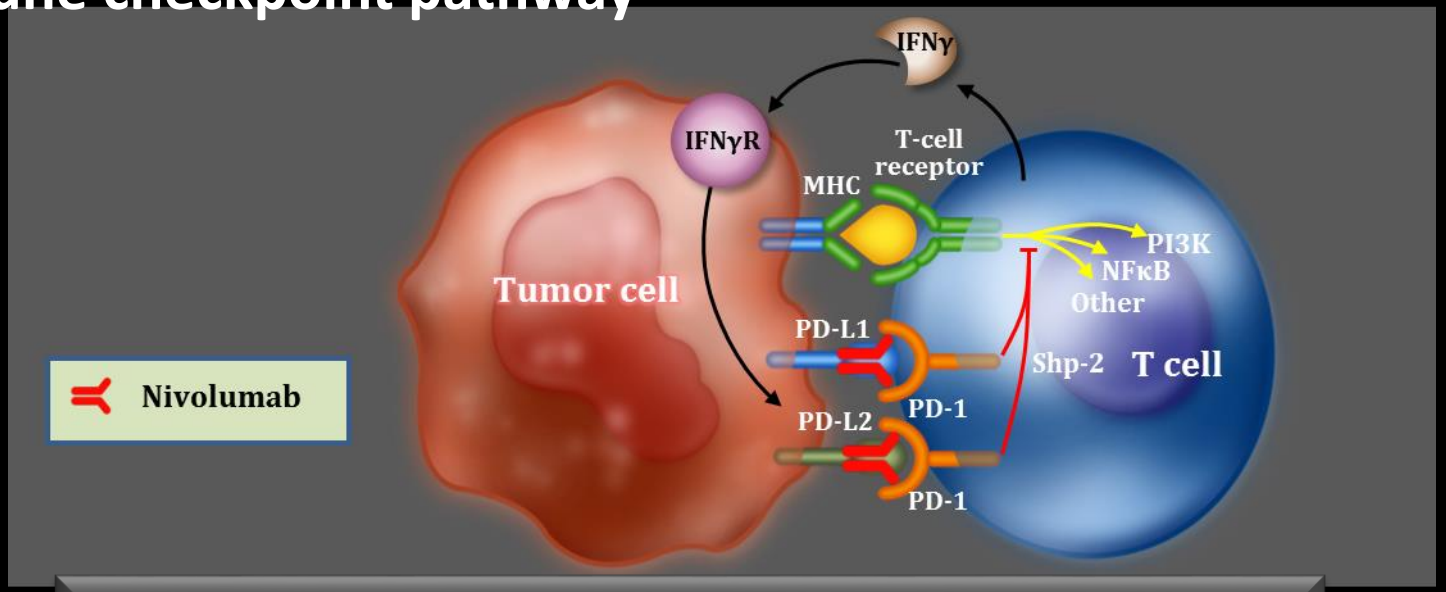
Includes evaluable patients = at least 1 on-treatment response assessment or PD without assessment
CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease
ORR = CR + PR

- 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

Horwitz S. et al, ASH 2014 Abstr. 803

Immune Checkpoint Inhibitors

Nivolumab is a fully human immunoglobulin G4 monoclonal antibody targeting the programmed death-1 (PD-1) immune checkpoint pathway



Phase I Study
23 patients with NHL
ORR 17%
PTCL
ORR 40% (2/5)

Lesokhin AM, 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

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

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

•Newly diagnosed patients with histologically proven ALCL Disease must be (CD)30 positive

•Disease must be anaplastic lymphoma kinase (ALK) positive)

•Patients must have stage II, III, or IV disease

•Up to 21 years of age

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

Agents under investigation

Agent	MOA	Phase
RP-6530	PI3Ki	I
CUDC-907	HDAC + PI3K	I
Carfilzomib	PI	I
AG-221	IDH2i	I/II
Selinexor	NEi	I

Finally….
Molecular targeted approaches in T-cell Lymphomas

Grazie!

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