NOVEL THERAPIES FOR RELAPSED T-CELL LYMPHOMA

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DISCLOSURES

- Advisory boards for Kyowa Kirin, Daichii Sankyo, Secura Bio, and Seattle Genetics.

CLINICAL CASE

- A 75 year old with a history of PTCL, T-follicular helper subtype with CD30 positivity was initially treated with brentuximab vedotin and CHP chemotherapy x 6 cycles. He achieved a CR and now 3 months later is presenting with fevers, chills, and a 10-lbs weight loss.
- Imaging shows diffuse adenopathy above and below the diaphragm.
- He has anemia, with markers for hemolysis, thrombocytopenia.
- PET scan shows lymphadenopathy along with increased avidity in the bone marrow. Echocardiogram shows a normal ejection fraction with no valvular dysfunction. He has no other co-morbidities.

Which of the following are potential treatment options?

QUESTION

Which of the following are potential treatment options?

A. Brentuximab vedotin
B. Romidepsin
C. Multiagent chemotherapy and autologous transplant
D. Duvelisib

OBJECTIVES

- Discuss Treatment of relapsed nodal PTCL
- Discuss novel therapies including duvelisib, valemetostat, and CD70 as a target
- Discuss the evolving role of cellular therapy

LANDSCAPE OF THERAPIES FOR RELAPSED PTCL

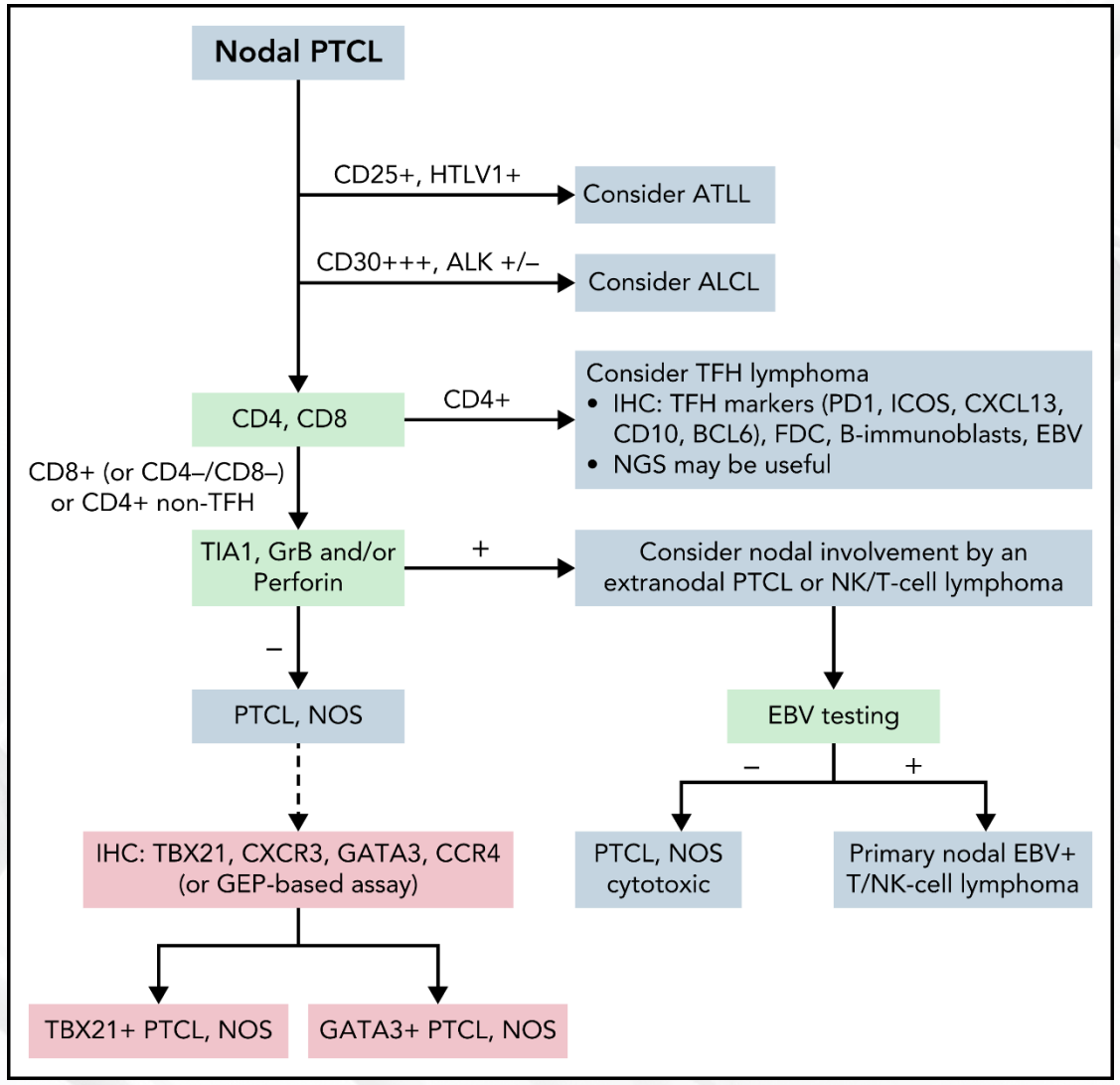
Table 3. Clinical trial efficacy data of licensed and available drug monotherapy

Drugs/ reference	Targeting site	Type of patients	Evaluable patients	ORR, %	CR/CRu, %	Median DoR, months	Median PFS, months	Median OS, months	Ref.
Pralatrexate	Antifolate	PTCL	109	29	11	10.5	3.5	14.5	[34]
Romidepsin	HDAC inhibitor	PTCL	130	25	15	28	4	—	[41, 42]
Belinostat	HDAC inhibitor	PTCL	120	25.8	10.8	13.6	1.6	7.9	[44]
Brentuximab vedotin	MoAb anti-CD30	ALCL	58	86	57	12.6	20	NR	[47]
Brentuximab vedotin	MoAb anti-CD30	PTCL	35	41	—	7.6	2.6	—	[48]
Lenalidomide	Immunomodulator	TCL	29[a]	24	—	5	4	12	[60]
Bendamustine	Alkylating agent	TCL	60	50	28	6.6	3.6	6.2	[59]
Bortezomib	Proteazome inhibitor	TCL	12	67	17				[62]
Alemtuzumab	Mo Ab anti-CD52	PTCL	14	35.7	21.4				[64]

[a]Only the data of patients who had relapsed/refractory PTCL were reported.

Abbreviations: —, not available; ALCL, anaplastic large-cell lymphoma; CR, complete remission; CRu, unconfirmed complete remission; DoR, duration of response; HDAC, histone deacetylase; MoAb, monoclonal antibodies; NR, not reached; OS, overall survival; PFS, progression-free survival; PTCL, peripheral T-cell lymphoma; Ref., reference; TCL, T-cell lymphoma.

CLASSIFICATION OF NODAL PERIPHERAL T-CELL LYMPHOMAS



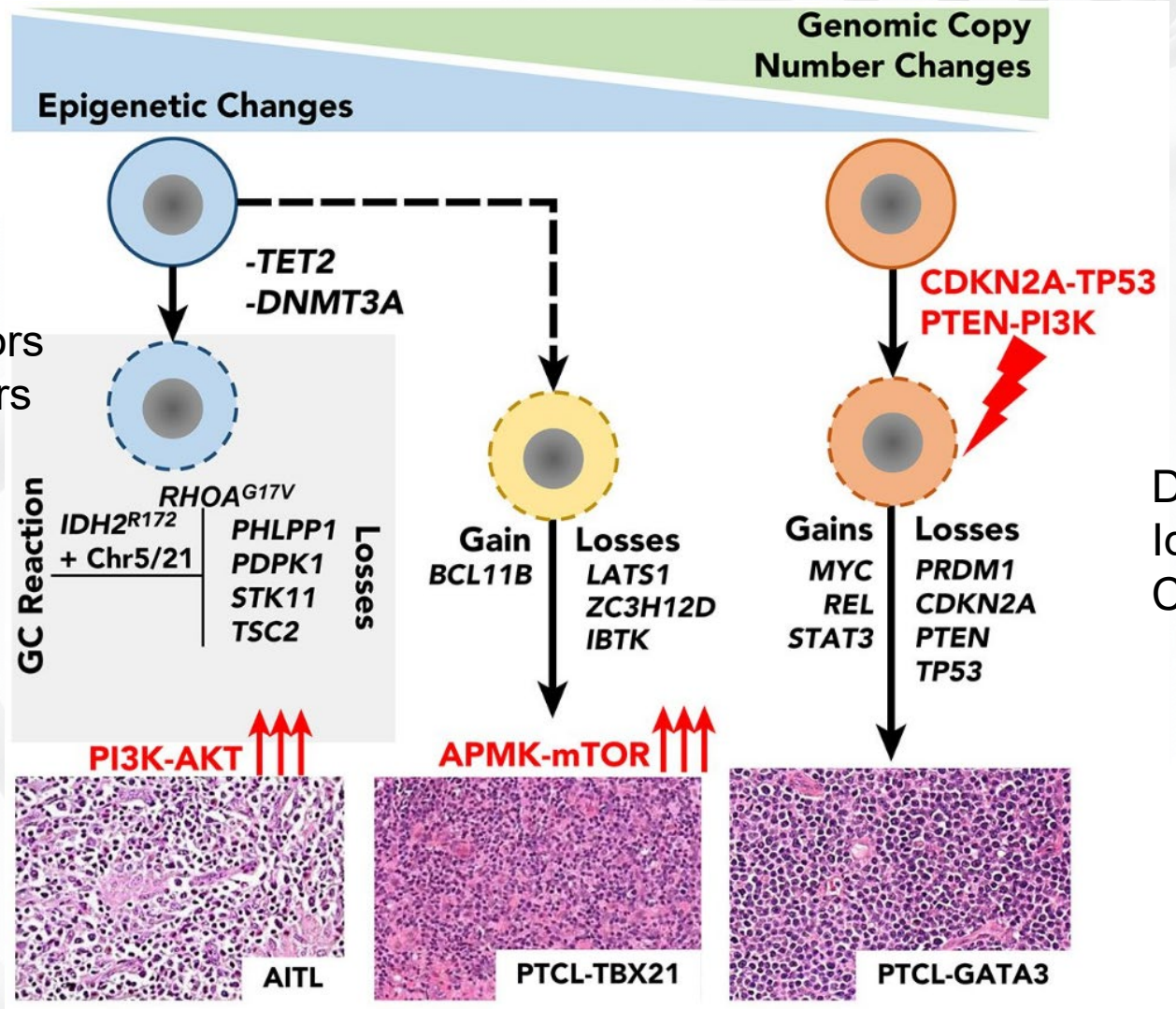
The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Elias Campo et al, Blood, 2022, Figure 5.

TARGETING GENETIC SUBTYPES IN PTCL,NOS AND AITL

Romidepsin
Belinostat
EZH2 inhibitors
IDH2 inhibitors
Azacitadine
Decitabine



Duvelisib
Idelalisib
Copanlisib

Tayla B. Heavican, Genetic drivers of oncogenic pathways in molecular subgroups of peripheral T-cell lymphoma, Blood, 2019

MOLECULAR TARGETS

- **Duvelisib** (IPI-145) is an oral inhibitor of phosphatidylinositol 3-kinase (PI3K)-δ/γ isoforms

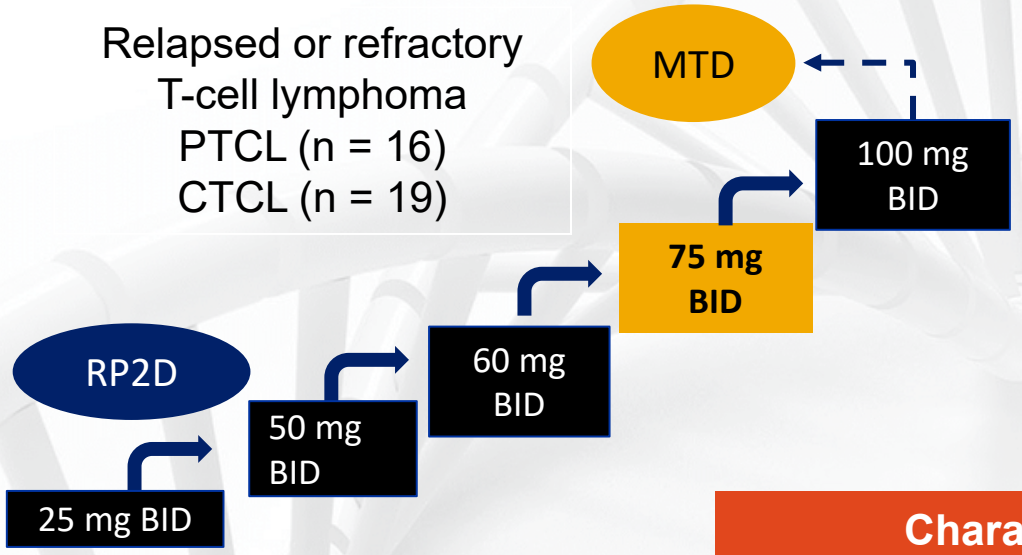
- Copy number alterations deletions in TFH lymphomas are common in the following pathways:
  - *PTEN*, *STK11*, and *TSC2* and/or *MYC* amplification
  - These pathways likely converge to constitutively activate PI3K–AKT–mTOR signaling.

- PI3K-δ/γ inhibition kills malignant T-cells directly and indirectly
  - Direct inhibition of malignant T-cell growth by blocking PI3K-δ and/or PI3K-γ signals for survival, proliferation, and differentiation of malignant cells
  - Augmenting immune responses in the TME

Tayla B. Heavican, Genetic drivers of oncogenic pathways in molecular subgroups of peripheral T-cell lymphoma, Blood, 2019

PHASE I TRIAL OF DUVELISIB MONOTHERAPY: EFFICACY IN PTCL AND CTCL

Relapsed or refractory
T-cell lymphoma
PTCL (n = 16)
CTCL (n = 19)



Characteristic	CTCL Cohort
MF/MF with LCT/SS/pcALCL, n	9/4/5/1
Stage IB/II-IIB/III-IIIA/IV-IVA, %	26/21/16/37
Prior lines of systemic therapy, median (range)*	6 (2-10)

*most commonly bexarotene and HDAC inhibitors

Slide credit: clinicaloptions.com

MOLECULAR TARGETING PI3K: EFFICACY

R/R PTCL (n = 16) and CTCL (n = 19)

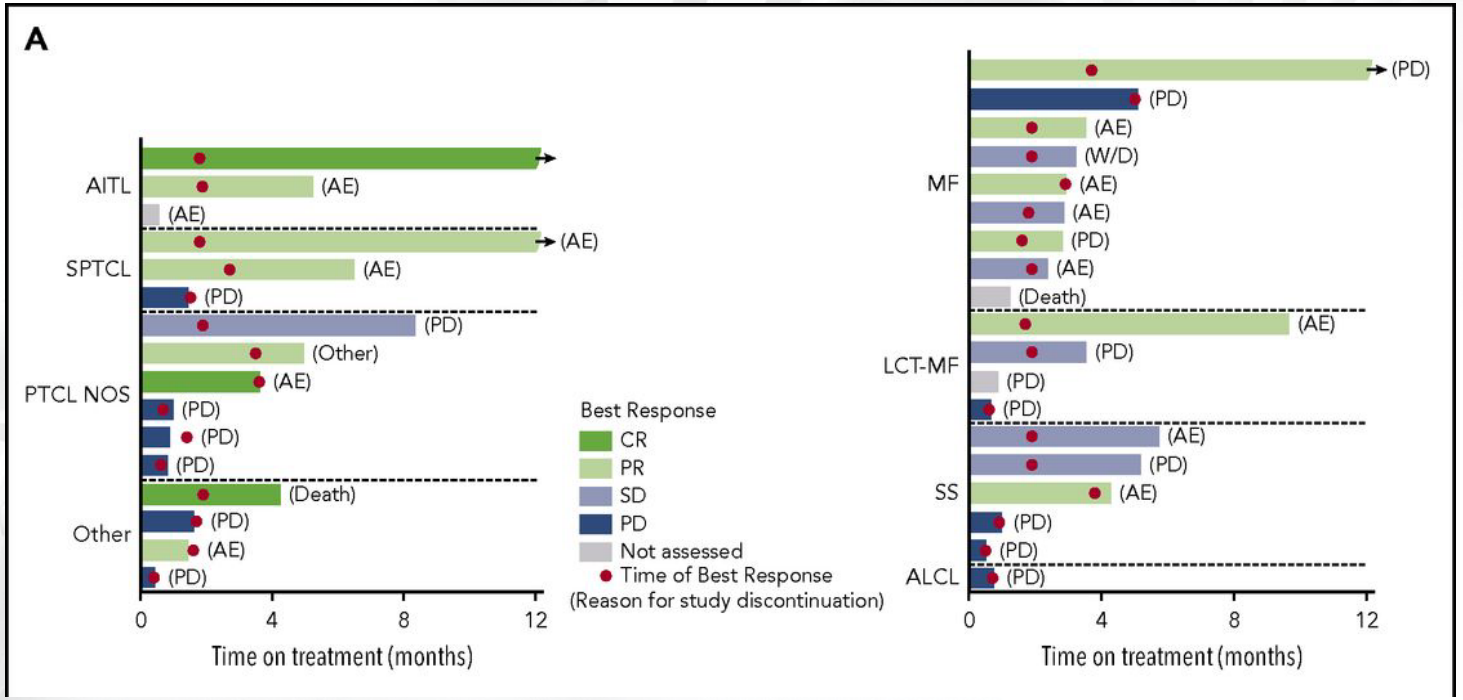
ORR

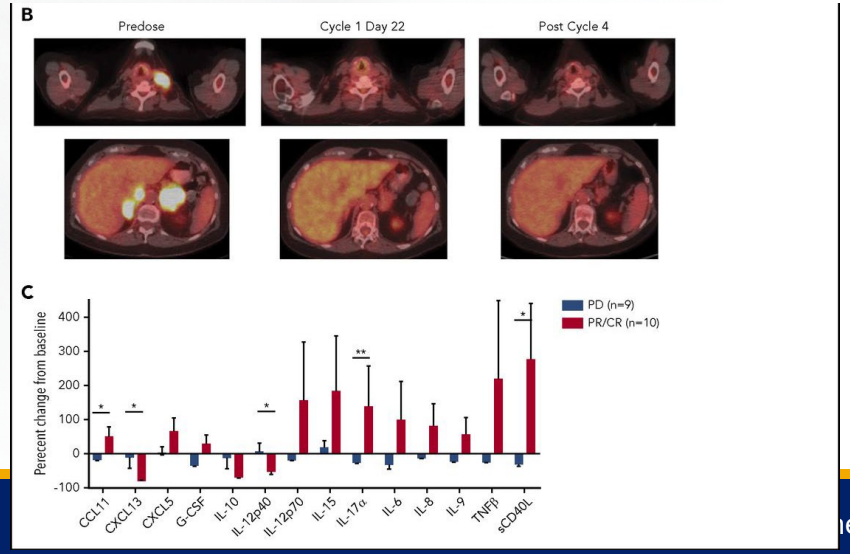
- PTCL = 50%
- CTCL= 31.6%

Correlation to p-AKT

- In vitro, duvelisib potently killed
  - **3/4** TCL lines constitutive phospho-AKT

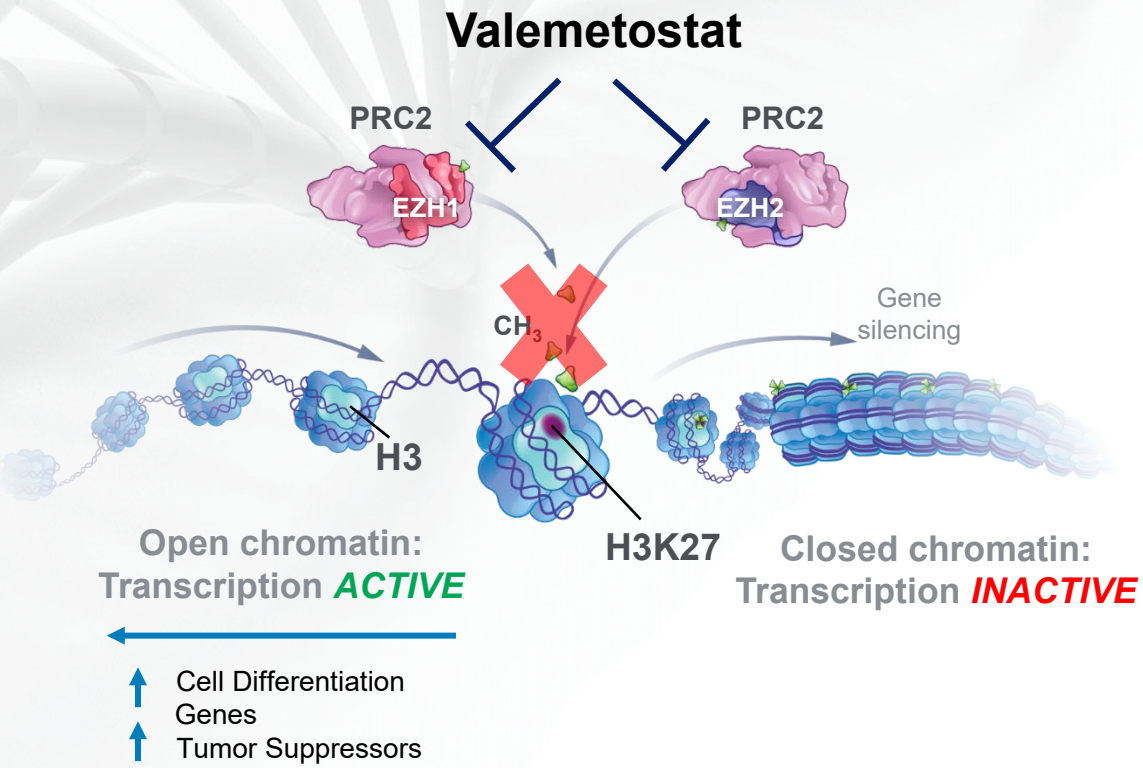
    versus
  - **0/7** lines lacking pAKT





VALEMETOSTAT IS A POTENT AND SELECTIVE DUAL INHIBITOR OF EZH1 AND EZH2

- Inhibits EZH1 and EZH2 through competitive inhibition of SAM[1,2]
  - SAM is a methyl-providing co-factor[3]
- Reduces trimethylation of H3K27[1,2]
- Alters gene expression patterns[1]
- Attenuates the proliferation of EZH1- and EZH2-dependent cancer cells[1]



SAM, S-adenosyl-L-methionine.
References in notes.

STUDY OF VALEMETOSTAT MONOTHERAPY IN PATIENTS WITH R/R NHL

A phase 1, multicenter study of valemetostat monotherapy in patients with R/R NHL

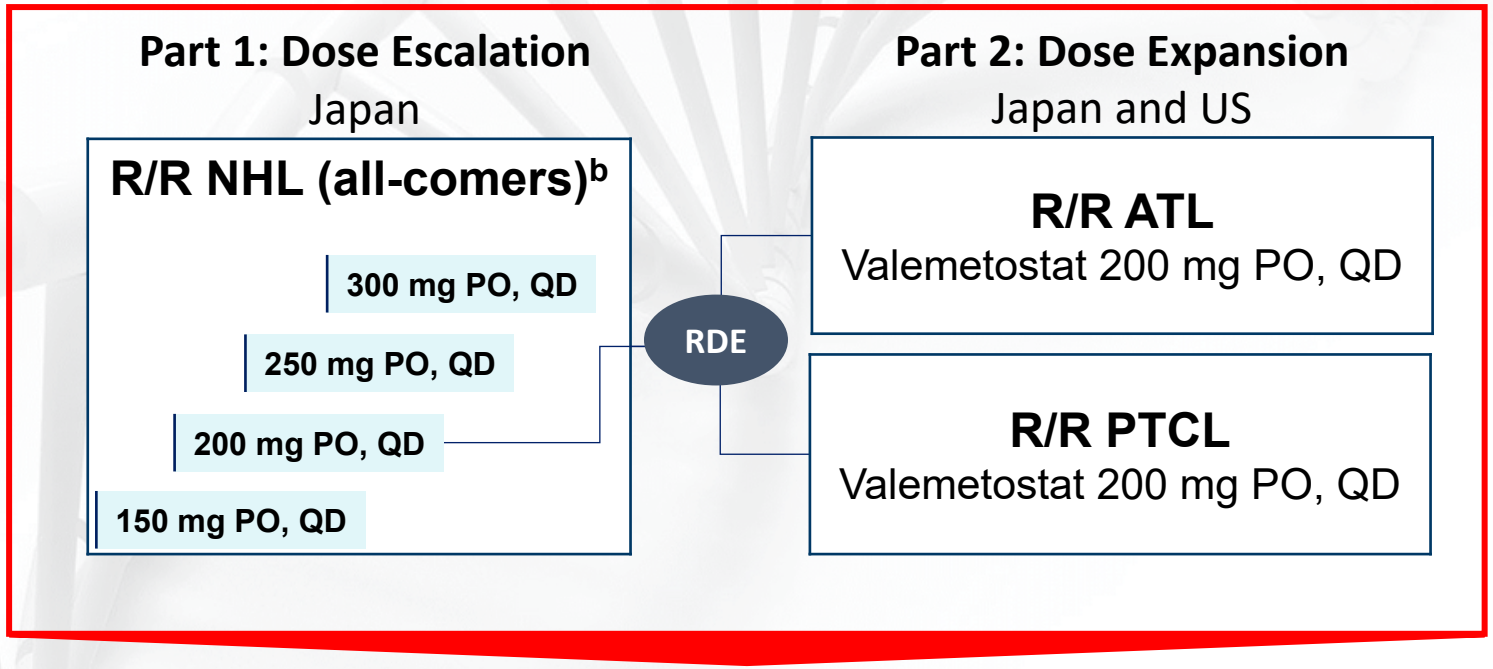
DS3201-A-J101; NCT02732275

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

Primary endpoints
- Safety (including DLTs, TEAEs)
- Recommended phase 2 dose
- Pharmacokinetics

Secondary endpoints
- Safety
- Antitumor effect[a]



- Safety analysis: all NHL (N=77)
  - B-cell NHL (n=19)
  - T-cell NHL (n=58)
- Safety and efficacy analyses: T-cell NHL (n=58)
  - PTCL (n=44)
  - ATL (n=14)

[a]According to the 2007 revised International Working Group Criteria for Malignant Lymphoma or "Definition, prognostic factors, treatment, and response criteria of adult T-cell leukemia-lymphoma: a proposal from an international consensus meeting." [b]Each dosage was tested with 3 patients.

References in notes.

BASELINE DEMOGRAPHICS OF T-CELL LYMPHOMA COHORT

	PTCL (n=44)	ATL (n = 14)
Female, n (%)	17 (38.6)	6 (42.9)
Age, median (range), years	68.5 (40-82)	66.5 (37-78)
≥ 65 years, n (%)	28 (63.6)	7 (50.0)
ECOG PS, n (%)[e]		
0	17 (38.6)	8 (57.1)
1	27 (61.4)	5 (35.7)
WHO classification, n (%)		
ATL	–	14 (100.0)
AITL	17 (38.6)	–
ALCL	2 (4.5)	–
PTCL-NOS	20 (45.5)	–
Others	5 (11.4)	–
Prior line of Tx, median (range)	2 (0-9)	2.5 (1-8)
Prior HSCT (n, %)	9 (20.5)	2 (14.3)
Autologous, n	8	0
Allogeneic, n	1	2

- PTCL: 42 patients were treated with 200 mg, and 2 were treated with 150 mg
- ATL: 12 patients were treated with 200 mg, and 2 were treated with 150 mg

Kusumoto S. EHA 2021. Abstract S218.

VALEMETOSTAT SAFETY ACROSS ALL HISTOLOGIES

Most Common TEAEs (Occurring in ≥20% of patients with TCL)	Patients, %	
	All Histologies (N=77)	
	All Grades	Grade ≥3
Platelet count decreased	47 (61.0)	13 (16.9)
Dysgeusia	40 (51.9)	0
Anemia	31 (40.3)	9 (11.7)
Neutrophil count decreased	27 (35.1)	18 (23.4)
Alopecia	26 (33.8)	0
WBC count decreased	23 (29.9)	12 (15.6)

- Grade ≥3 platelet count decreased and thrombocytopenia[a] occurred in 13 (16.9%) and 2 (2.6%) patients with all histologies, respectively

[a]Study sites could choose to enter thrombocytopenia or platelet count decreased as a term. [b]In order of frequency reported for patients with TCL (n=58). [c]Including 19 patients with BCLs. [d]Grade 3 platelet count decreased, CTCAE 5.0 definition: <50,000-25,000/mm^3; <50.0-25.0 × 10^9/L.

Kusumoto S. EHA 2021. Abstract S218.

VALEMETOSTAT EFFICACY IN J101 STUDY

Parameter	All PTCL (n=44)	T-cell Lymphoma Subtype				
		AITL (n=17)	PTCL-NOS (n=20)	ALCL (n=2)	Other TCL (n=5)	ATL (n=14)
ORR, n (%)	24 (54.5)	11 (64.7)	10 (50.0)	1 (50.0)	2 (40.0)	8 (57.1)
95% CI	38.8-69.6	38.3-85.8	27.2-72.8	1.3-98.7	5.3-85.3	28.9-82.3
Best response, n (%)						
CR	12 (27.3)	8 (47.1)	4 (20.0)	0 (0.0)	0 (0.0)	4 (28.6)
PR	12 (27.3)	3 (17.6)	6 (30.0)	1 (50.0)	2 (40)	4 (28.6)
PD	8 (18.2)	2 (11.8)	4 (20.0)	1 (50.0)	1 (20.0)	3 (21.4)
Median PFS, weeks	52	52	64	-	15.9	-
(95% CI)	(16.14, -)	(16.1, -)	(8.1-64.0)	(8.1, -)	(8.0, -)	(8.14, -)

- Median DOR: 56.0 weeks (95% CI: 44.43, –)

Median follow-up times: PTCL , 19.93 (range, 3.1-68.1) weeks; ATL, 23.07 (range, 3.3-125) weeks.
[a] For PTCL, 42 patients were treated with 200 mg, and 2 were treated with 150 mg. For ATL, 12 patients were treated with 200 mg, and 2 were treated with 150 mg.
[b] Patients with ALCL include those with ALK-positive and -negative ALCL. [c] Consists of 7 patients with acute and 7 patients with lymphomatous subtypes.
References in notes.

Kusumoto S. EHA 2021. Abstract S218.

Data cutoff: 2 November 2020.

NOVEL AGENTS IN CTCL

- Duvelisib
- PD-1 inhibitors
- Anti-CD70

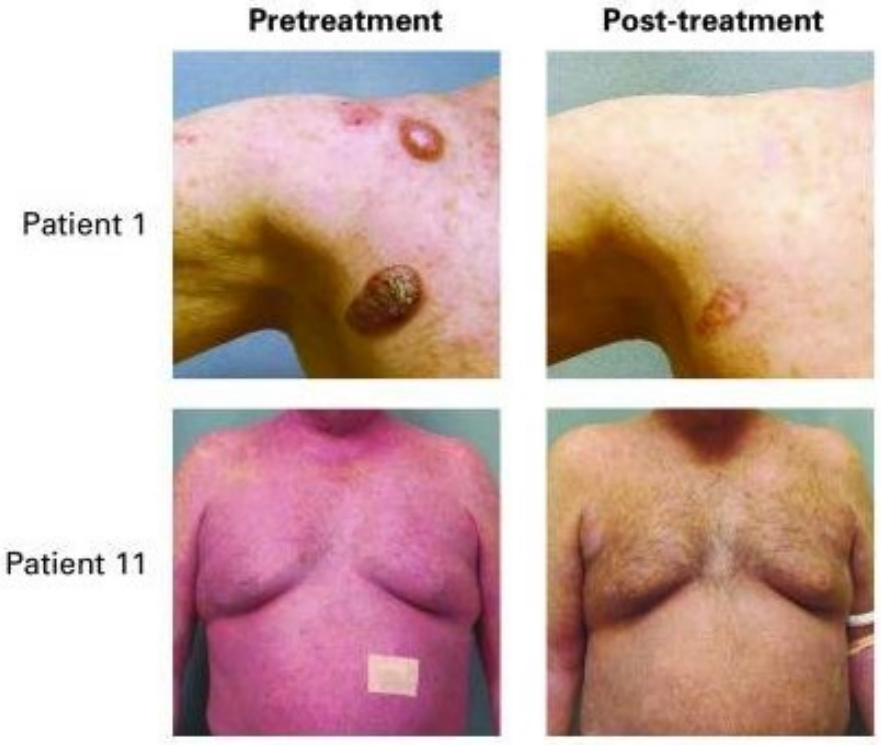
CITN-10: PHASE II STUDY OF PEMBROLIZUMAB IN R/R MF/SS

Adults with advanced stage (IIB-IV) relapsed /refractory MF/SS (N=24)

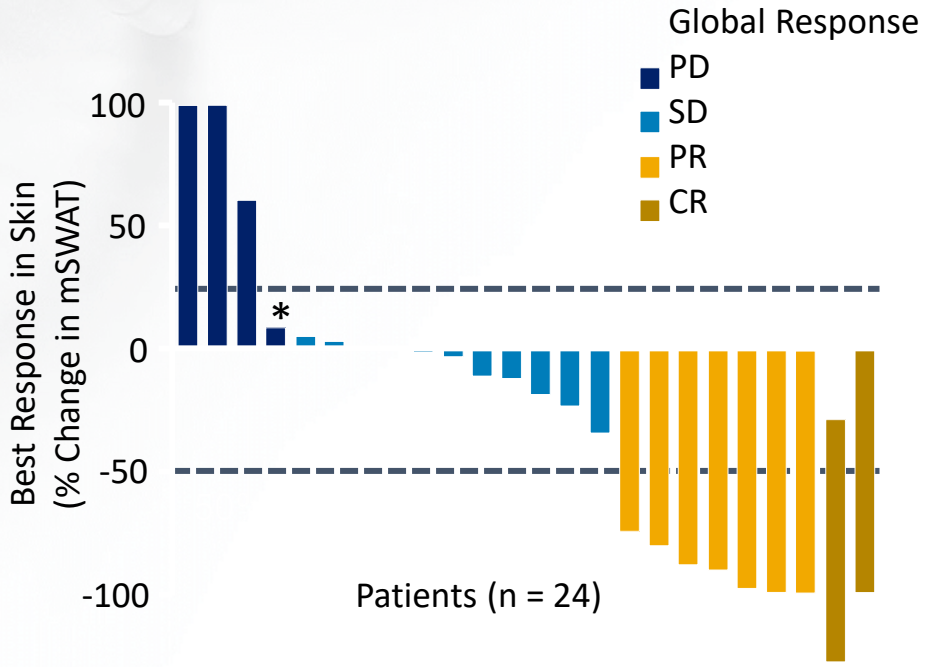
Pembrolizumab
2 mg/kg IV Q3W up to 24 mo

- 8/15 patients with SS had transient skin toxicity
  - -3/8 with toxicity had a response
  - -1/7 without skin toxicity achieved response

Parameter	MF/SS (N = 24)
ORR, n (%)	**9 (38)**
CR, n (%)	2 (8.3)
PR, n (%)	7 (29.1)



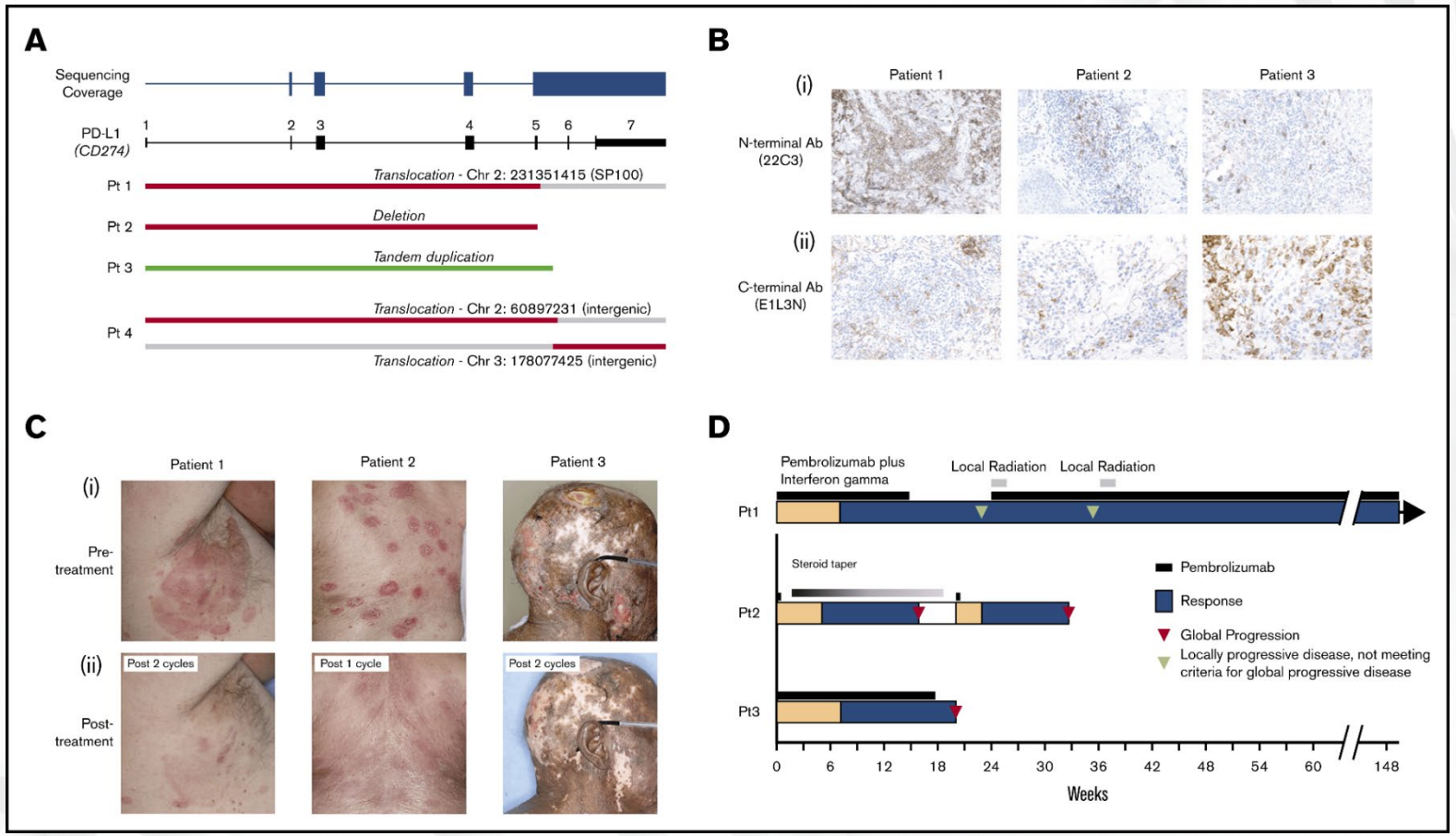
65% PFS at 1 year



Khodadoust. JCO. 2020;38:20.

GENETIC ALTERATIONS IN THE PD-1 PATHWAY IN CTCL

Malignant T-cells with increased PD-L1 may be susceptible to PD-1 blockade



Genetic disruptions of the PD1/PD-L1 pathway are recurrent in MF with large cell transformation

Structural variants (SVs) involving *CD274*, the gene encoding PD-L1 leading to increased PD-L1 protein expression

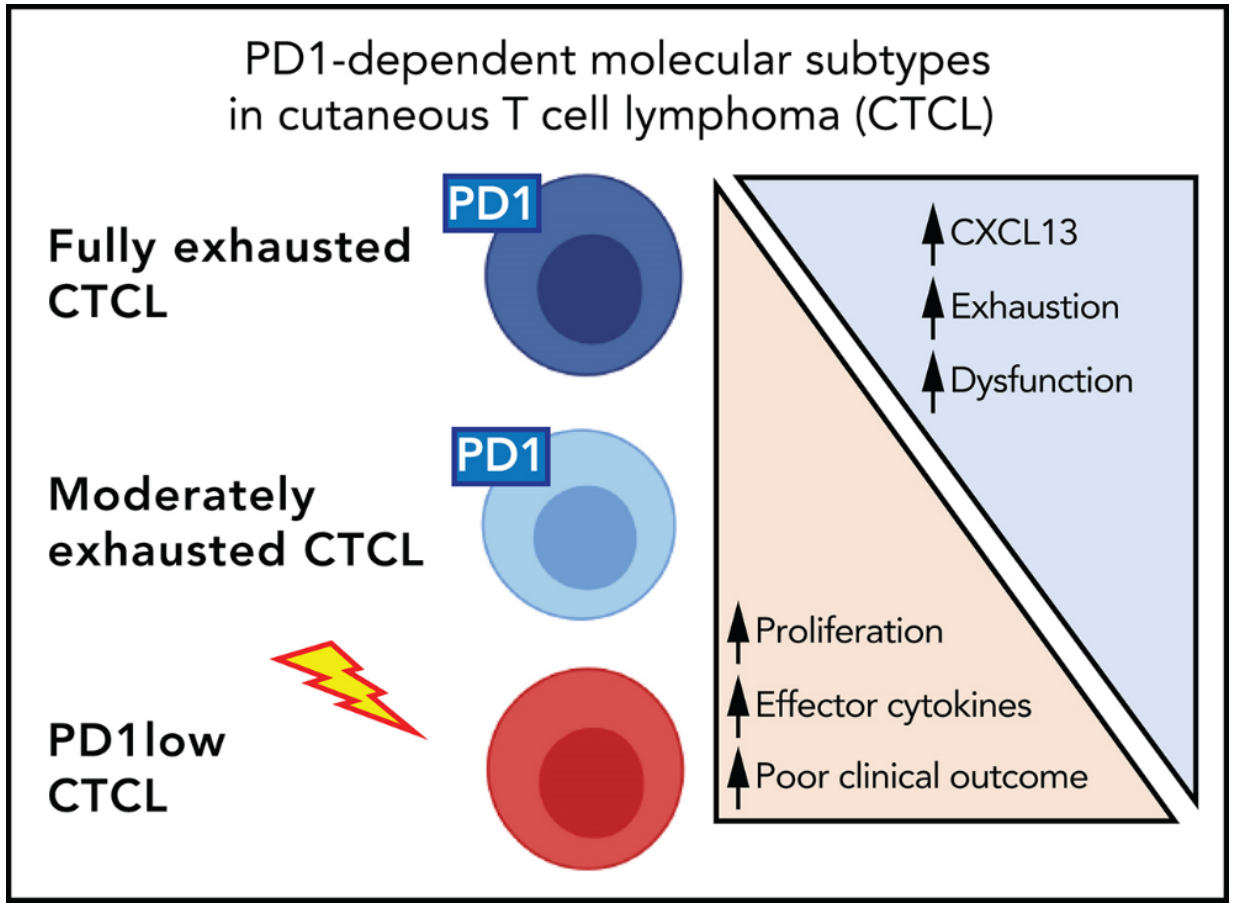
3 patients with tMF and SVs of *CD274* were treated with pembrolizumab and had a response.

69 MF patients, 11 SVs of PDL1 identified, all in patients with LCT.

Beygi. Blood Adv. 2021;5:771.

PD-1 DELETIONS ARE SEEN IN LEUKEMIC MF/SS AND ARE ASSOCIATED WITH POOR OUTCOMES

PD1 mutations drive aggressive behavior.



PD1 was highly expressed in ***non-*** proliferating samples but was not expressed in highly proliferative samples

PD1 deletions lead to **reversal of T-cell exhaustion in malignant T-cells** and are associated with a worse prognosis

Like terminally exhausted T cells, fully exhausted CTCLs have limited proliferative capacity

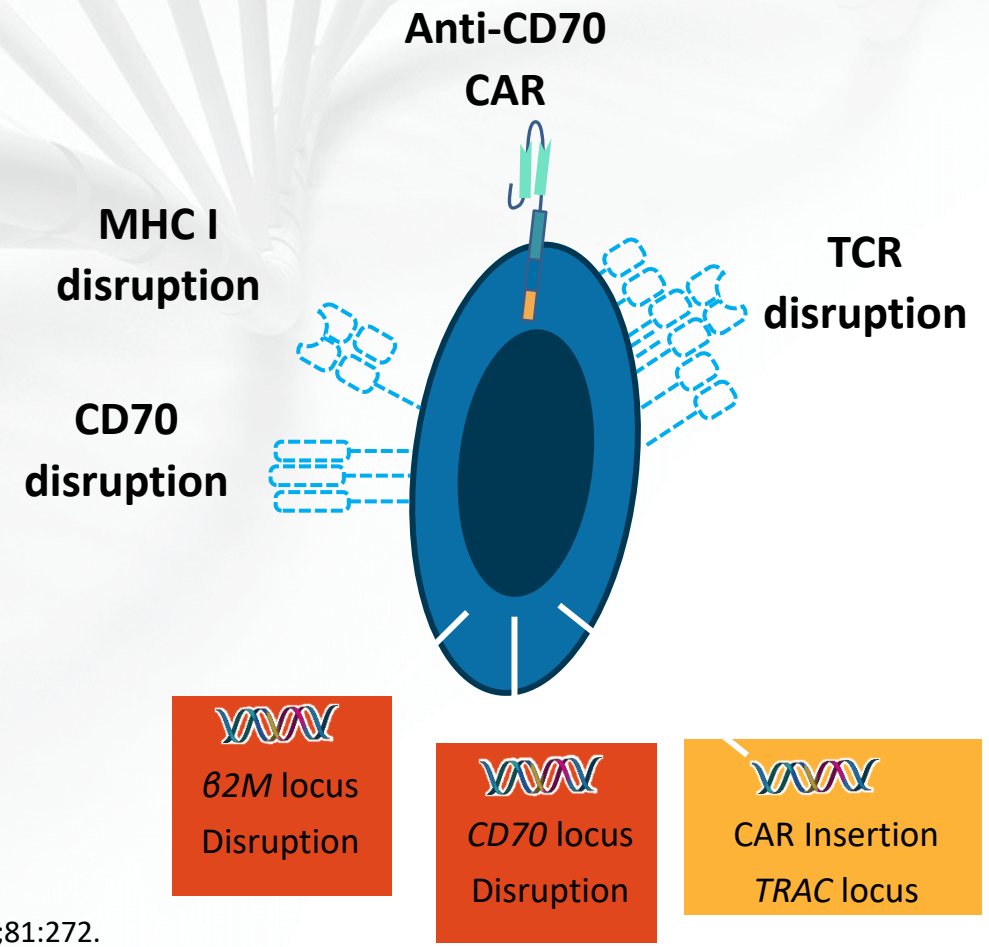
PD1 deletions are sufficient to reverse the exhaustion phenotype and predict significantly worse survival

Park. Blood.2021;138:1225.

Slide credit: clinicaloptions.com

CTX130: ANTI-CD70 ALLOGENEIC CAR T-CELL THERAPY FOR T-CELL LYMPHOMA

- Autologous CAR T-Cell Therapy approaches in T-cell lymphoma difficult due to potential for fratricide, and malignant T cell contamination
- CD70 is a member of the TNF receptor subfamily highly expressed in up to 85% of TCL tumor samples
- CTX130 is an investigational CD70-targeted allogeneic CAR T-cell therapy with TRAC, β2M, and CD70 disruptions
- Manufactured from healthy donor T cells and offers off-the-shelf availability



Dequeant. Cancer Res. 2021;81:1537. Iyer. EHA 2022. Abstr S262.Marques-Piubelli. Histopathology. 2022;81:272.

COBALT-LYM: CD70-DIRECTED ALLOGENIC CAR-T CELL THERAPY STUDY IN R/R T-CELL MALIGNANCIES

Multicenter, open-label, dose-escalation phase I study

Adults with confirmed R/R T-cell malignancy (≥10% CD70+ cells); ECOG PS 0-1; platelets >25,000/mm^3; ANC > 500/mm^3 (N = 18)

*A second course of CTX130 could be given if loss of CR but had experienced clinical benefit

Primary endpoint: safety and ORR

Secondary endpoints: PFS, OS

Patient Characteristics	All Dose Levels (N=18)
PTCL/CTCL, n	8/10
Prior lines of therapy, median (range)	4 (1-8)
Second CTX130 infusion received, n (%)	5 (28)

Iyer. EHA 2022. Abstr S262.

COBALT-LYM: ADVERSE EVENTS OF INTEREST

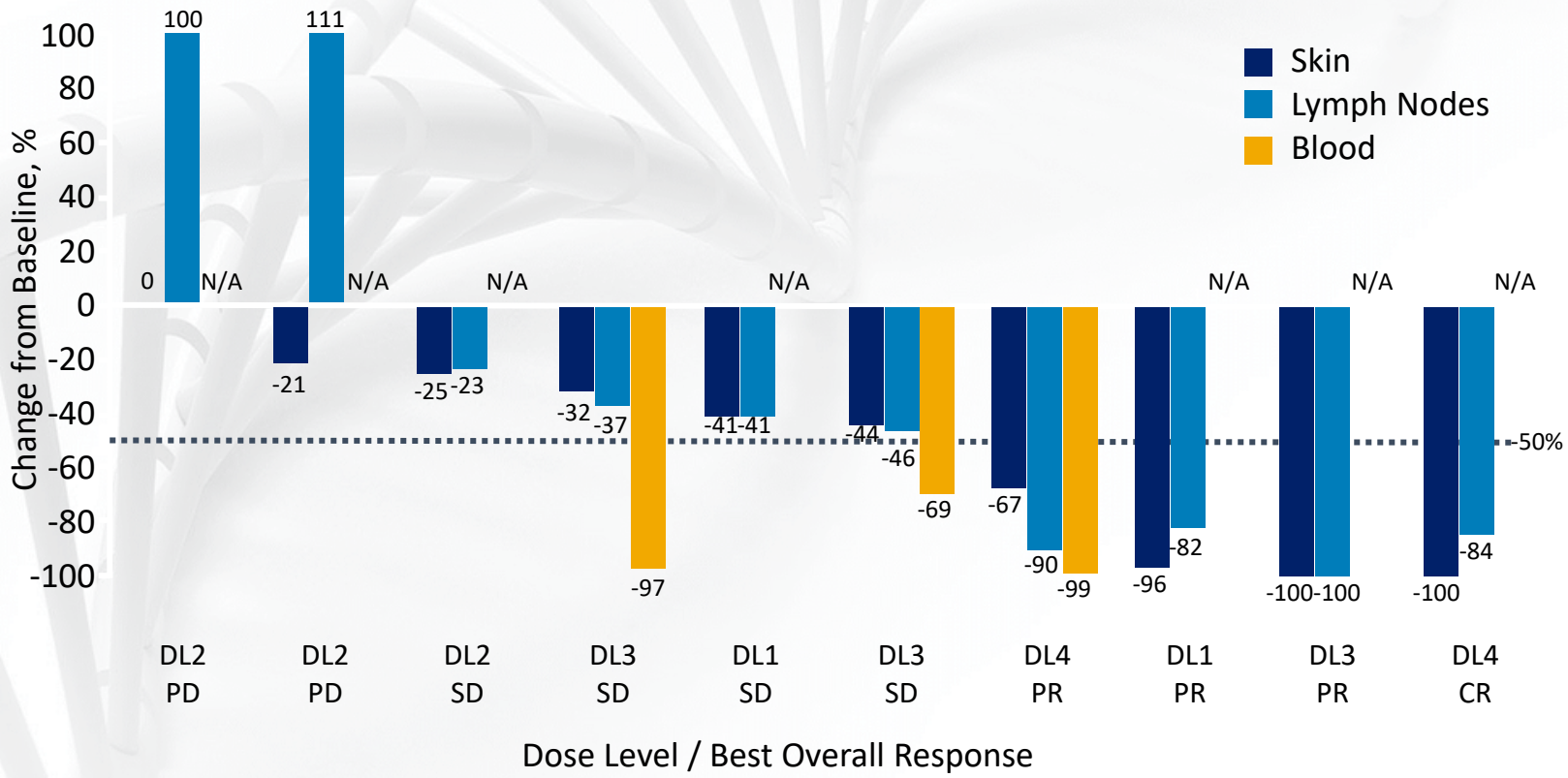
	Dose Level 1 3×10^7 n = 4		Dose Level 2 1×10^8 n = 4		Dose Level 3 3×10^8 n = 5		Dose Level 4 9×10^8 n = 5		Dose Level ≥ 3 n = 10	
	Gr 1-2	**Gr ≥3**	**Gr 1-2**	**Gr ≥3**	**Gr 1-2**	**Gr ≥3**	**Gr 1-2**	**Gr ≥3**	**Gr 1-2**	**Gr ≥3**
Cytokine Release Syndrome, n (%)	1 (25)	-	1 (25)	-	4 (80)	-	4 (80)	-	**8 (80)**	-
ICANS, n (%)	-	-	-	-	3 (60)	-	-	-	**3 (30)**	-
Infections, n (%)	2 (50)	1 (25)	-	1 (25)	2 (40)	1 (20)	1 (20)	1 (20)	**3 (30)**	**2 (20)**

No instances of graft versus host disease, dose-limiting toxicities, or tumor lysis syndrome

Iyer. EHA 2022. Abstr S262.

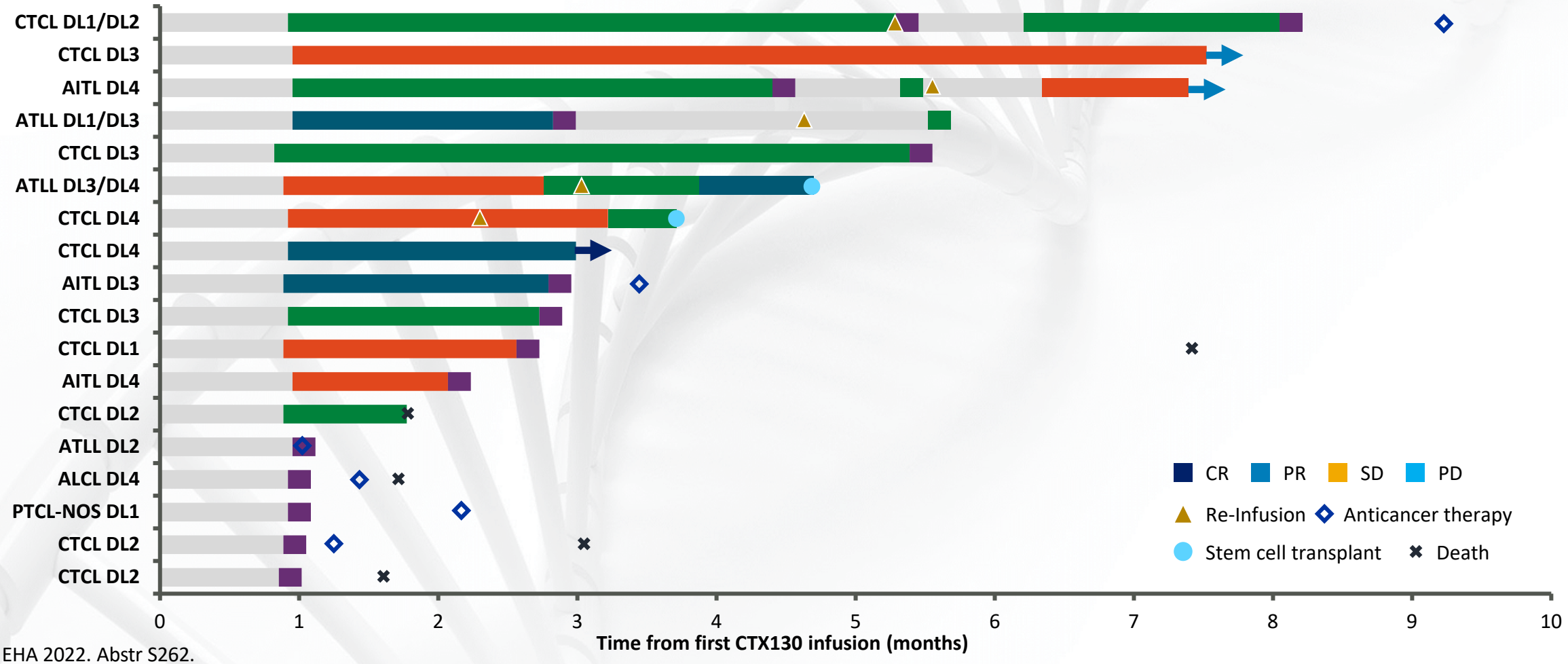
COBALT-LYM: CTCL RESPONSE RATES IN ALL DISEASE COMPARTMENTS

Response, n (%)	CTCL Cohort	
	DL≥ 3 (n=5)	Total (n=10)
ORR	3 (60)	4 (40)
CR	2 (40)	1 (10)
PR	2 (40)	3 (30)
DCR	4 (80)	8 (80)



Iyer. EHA 2022. Abstr S262.

COBALT-LYM: RESPONSES IN ALL PATIENTS



Iyer. EHA 2022. Abstr S262.

CASE STUDY: CR WITH SINGLE-INFUSION OF CTX130

Patient profile

- 47-year-old male with stage IVA2 transformed mycosis fungoides (tMF)
- 5 prior lines of therapy
- Refractory after last treatment with brentuximab vedotin
- CD70+ expression: 100% at baseline

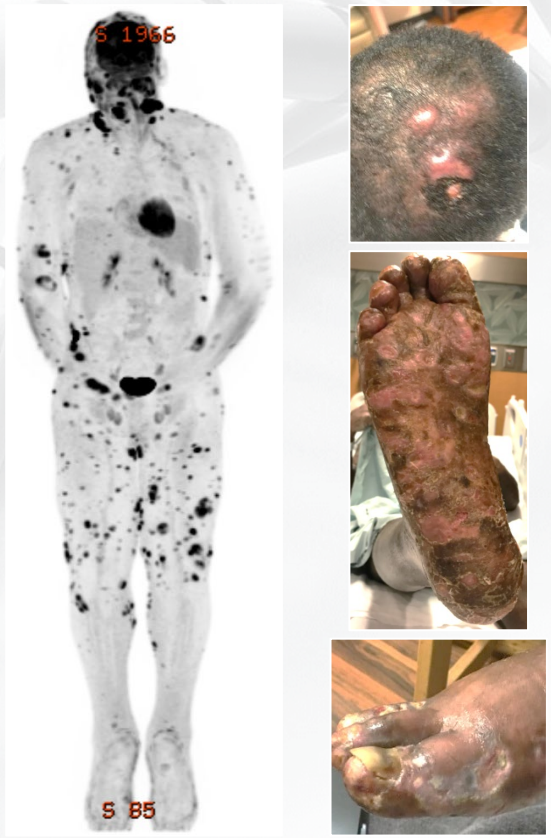
Efficacy

- CR at D28 after a single infusion of $9x10^8$ CAR+ T cells
- Remains in CR at Month 3

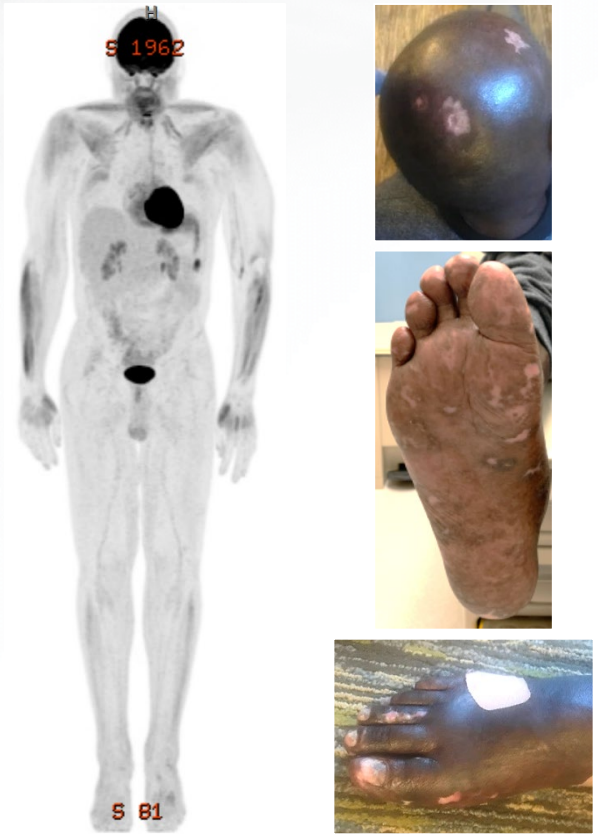
Safety

- Gr 3 anemia (D3) & Gr 3 neutropenia (D4)
- All other AEs were Gr 1

Pre-Treatment | mSWAT = 84.74



Post-CTX130 (D18 skin, D28 PET) | mSWAT = 0



Iyer. EHA 2022. Abstr S262. Courtesy of Swaminathan P. Iyer

OTHER AGENTS OF INTEREST IN THE LYMPHOMA PIPELINE

- SGN-CD70A monoclonal antibody (NCT04227847)
- Duvelisib + Nivolumab (NCT04652960)
- Anti-ICOS monoclonal antibodies
- Tolinapant and oral decitabine/cedazuridine in PTCL

THANK YOU!

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Clinical trials of interest in T-cell lymphoma

- Frontline trial of duvelisib vs. oral azacytadine in CD30 negative PTCL
- Pembrolizumab + brentuximab in CD30 + TCL
- Nivolumab + duvelisib in CTCL
- Tolinapant (ASTX6660) and oral decitabine/cedazuridine in PTCL
  - Novel oral nonpeptidomimetic, small-molecule antagonist of cellular/X-linked inhibitors of apoptosis proteins (cIAP1/2 and XIAP)