Treatment of Relapsed and Refractory T-cell lymphoma

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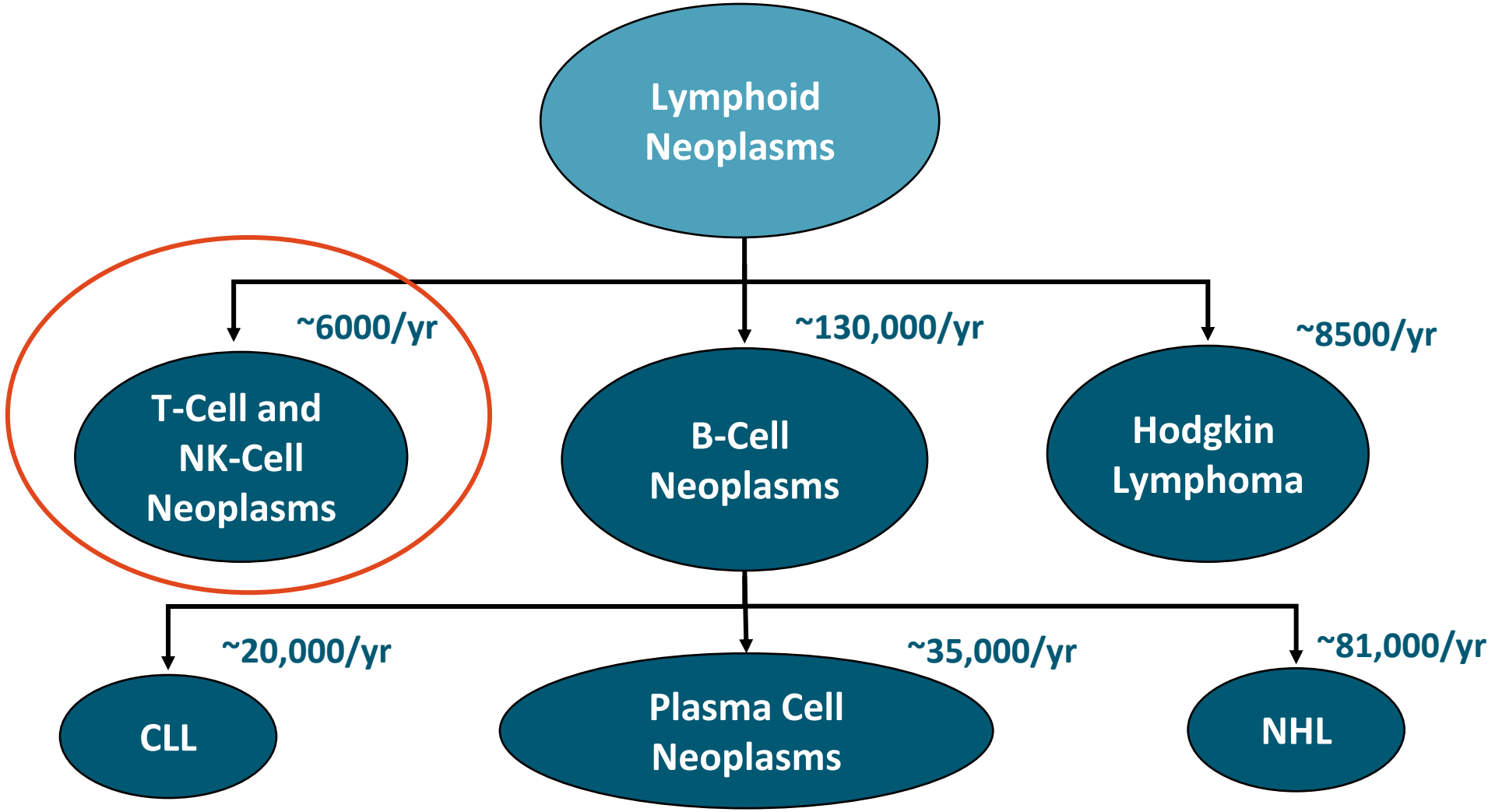
T-Cell Lymphoma Is a Rare Non-Hodgkin Lymphoma



ACS. Cancer Facts and Figures 2022. Harris. JCO. 1999;17:3835.

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T cell lymphoma

Heterogenous group of uncommon non-Hodgkin lymphoma

10-15 % of all NHLs

High incidence in Asia due to susceptibility to HTLV1 and EBV

PTCLs: subtypes that arise from mature T cell

Outcome of treatment are not as successful as B cell lymphoma

Best outcome: ALK positive ALCL (70% 5y OS)

Outcomes

Worse outcome for other subtypes

5y OS : 32% for PTCL-NOS

AITL

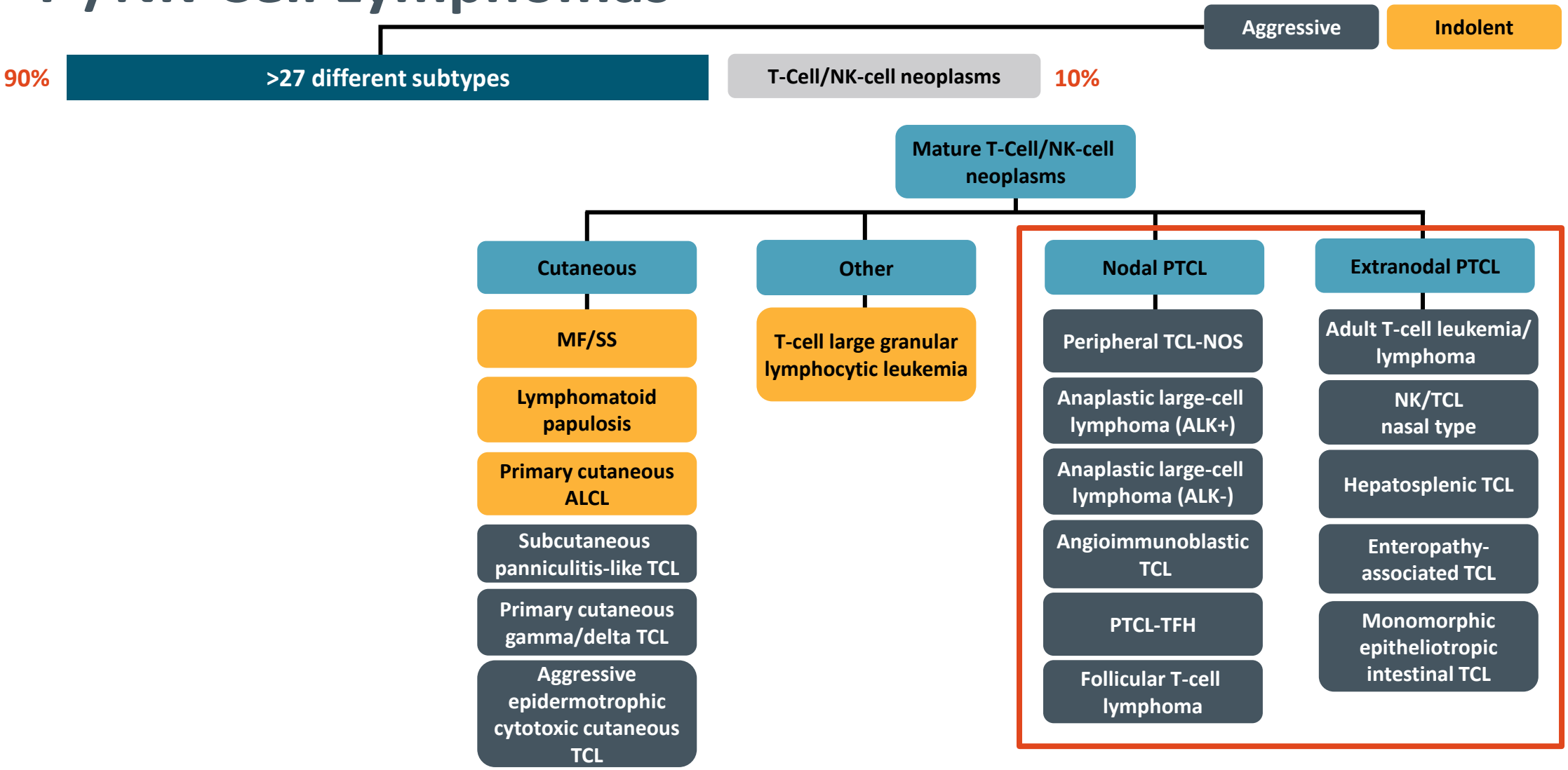
NKTCL

14% for ATLL

Five year OS for ALK negative ALCL : 49%

Entropathy assosciated T-cell lymphoma (EATL): Rare and Dismal outcome

PTCL Is a Heterogeneous Group of Aggressive Mature T-/NK-Cell Lymphomas



Sandell. Curr Oncol Rep. 2017;19:28. Swerdlow. Blood. 2016;127:2375.

Slide credit: clinicaloptions.com

Relapsed T-cell lymphoma

Most PTCL patients not achieve remission or relapse after treatment

International T-cell project: 937 patients received first line treatment

436(47%) patients were refractory

197(21%) patients had relapse

BC cancer agency: median OS and PFS after relapse are 5.5 and 3 months

Poor PS and refractory disease: independent predictor of inferior survival

Treatment options for relapse

Encourage to participate in clinical trials

Poorer OS and PFS without HCT (6 and 3 months)

Candidate for HCT: chemotherapy as a bridge then perform transplant

based on GEMCITABINE IFOSFOMIDE and CISPLATIN

Skamene and colleagues: similar ORR and OS with DHAP and GDP

A systematic review published in 2015 : 14 studies use 12 different protocols

similar responses

Not candidate for HCT: single novel agent(brentuximab,romidepsin,pralatraxate)

Indications for novel agents

In primary refractory disease

Early relapse (within six months of initial therapy)

Subsequent relapse

Non curative intent

In 2019

Received: 17 January 2019 | Revised: 18 February 2019 | Accepted: 12 March 2019

DOI: 10.1002/ajh.25463

RESEARCH ARTICLE

AJH WILEY

Single agents vs combination chemotherapy in relapsed and refractory peripheral T-cell lymphoma: Results from the comprehensive oncology measures for peripheral T-cell lymphoma treatment (COMPLETE) registry

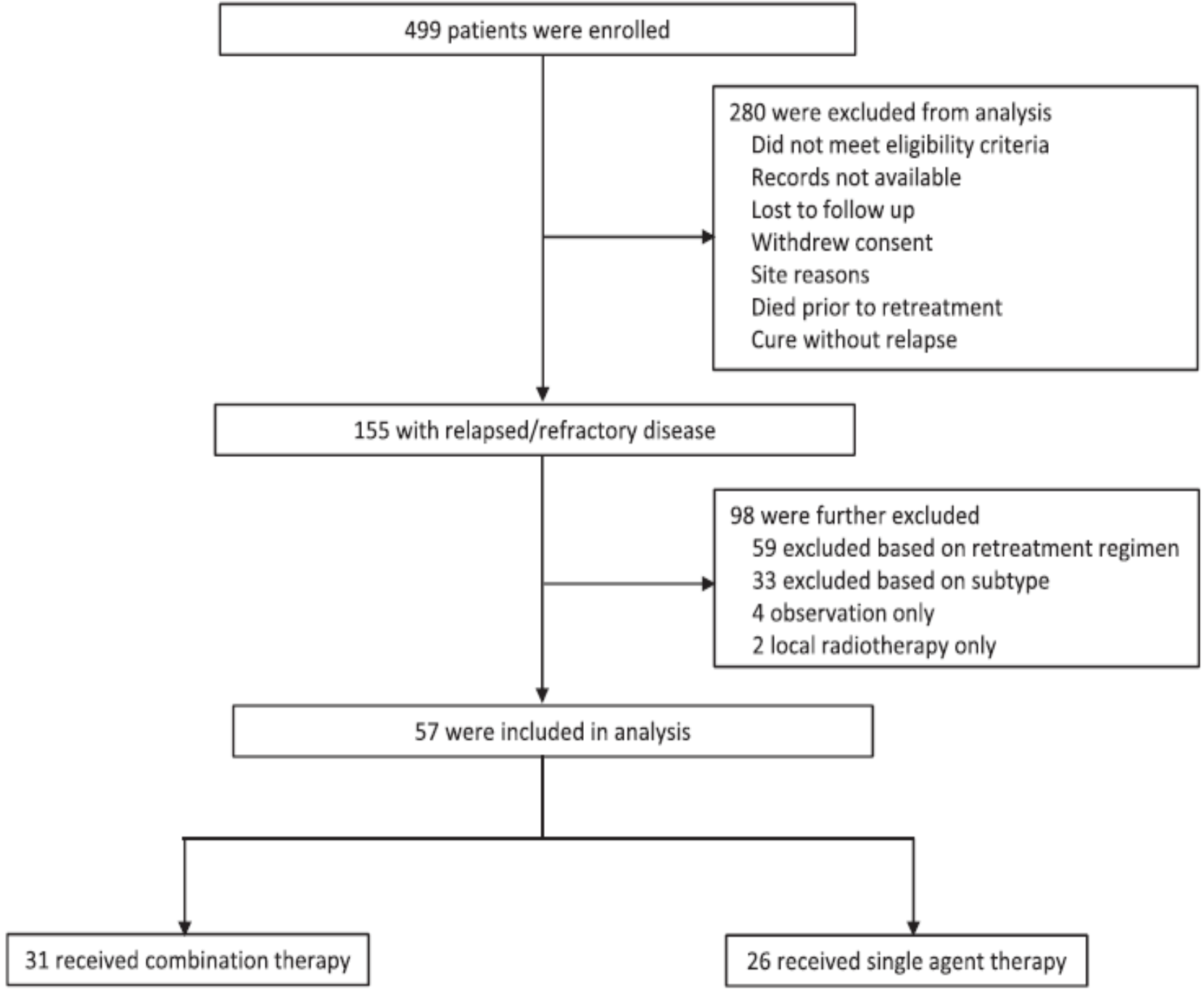
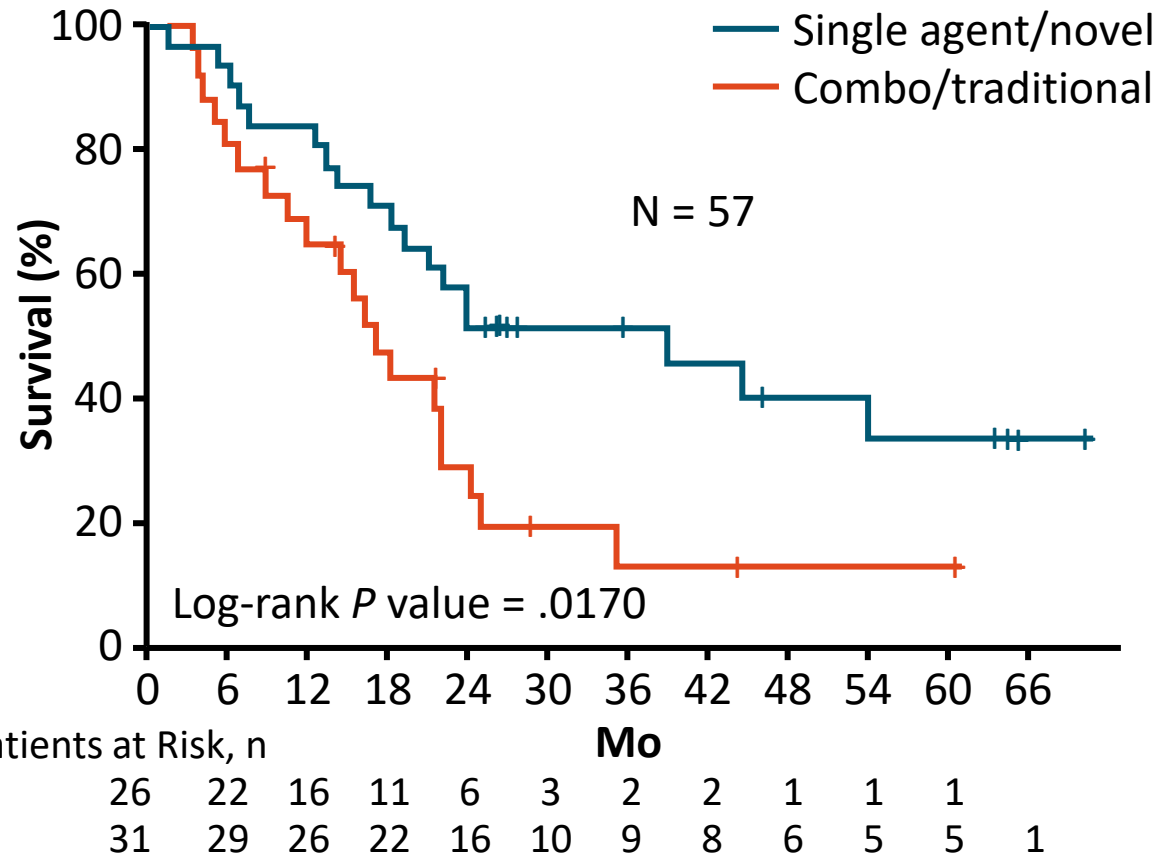


TABLE 2 Retreatment intent, best response, and duration of therapy

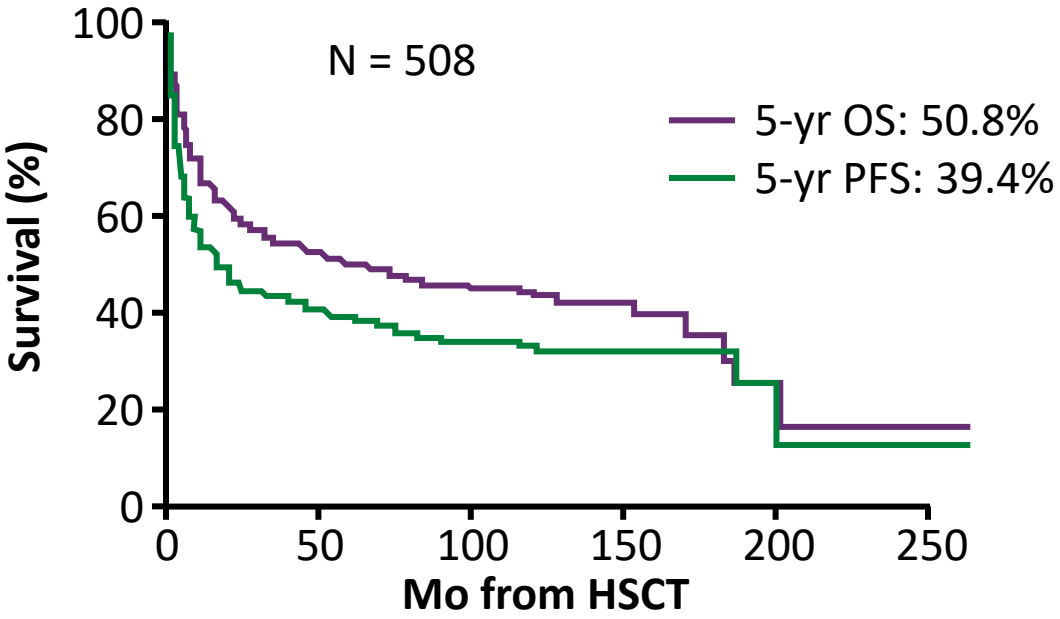
	Total (%)	Combination	Single	*P* value
Primary intent				
Cure	40/57 (70.2)	22/26 (84.6)	18/31 (58.1)	.0291
Palliative	17/57 (29.8)	4/26 (15.4)	13/31 (41.9)	
Mean number of cycles ± SD	3.8 ± 3.7	2.7 ± 1.7	4.8 ± 4.6	.0206
Best response				
Complete	17/55 (30.9)	5/26 (19.2)	12/29 (41.4)	.0195
Partial	12/55 (21.8)	7/26 (26.9)	5/29 (17.2)	
None	9/55 (16.4)	8/26 (30.8)	1/29 (3.4)	
Progressive	12/55 (21.8)	3/26 (11.5)	9/29 (31.0)	
Not evaluable	5/55 (9.1)	3/26 (11.5)	2/29 (6.9)	
Mean duration of treatment (months) ± SD	2.5 ± 3.1	1.5 ± 1.2	3.3 ± 3.9	.0648

Approaches and Outcomes in R/R PTCL

Complete Registry: OS[1]



Outcomes Postallogenic SCT for TCL[2]



Response	N	Median PFS in Mo (95% CI)	Median OS in Mo (95% CI)
CR	239	**44.6** (17.9-201.5)	**154.2** (72.8-201.5)
PR	164	**8.5** (6.1-16.6)	**31.3** (16.8-64.2)

1. Stuver. Am J Hematol. 2019;94:641. 2. Mehta-Sha. ASH 2020. Abstr 41.

Slide credit: clinicaloptions.com

Single agents VS combination

Greater complete and objective response rates with the use of single agents

Statistically significant greater overall and progression-free survival

More patients were bridged to curative transplantation

More toxicity occurred with the use of combination

Stem cell transplant

Lack of prospective randomized trial for SCT

Experts: strongly recommend ASCT for relapsed chemosensitive disease

Systematic review for ASCT outcomes: PFS 36% OS 47%

Progression 51% NRM 10%

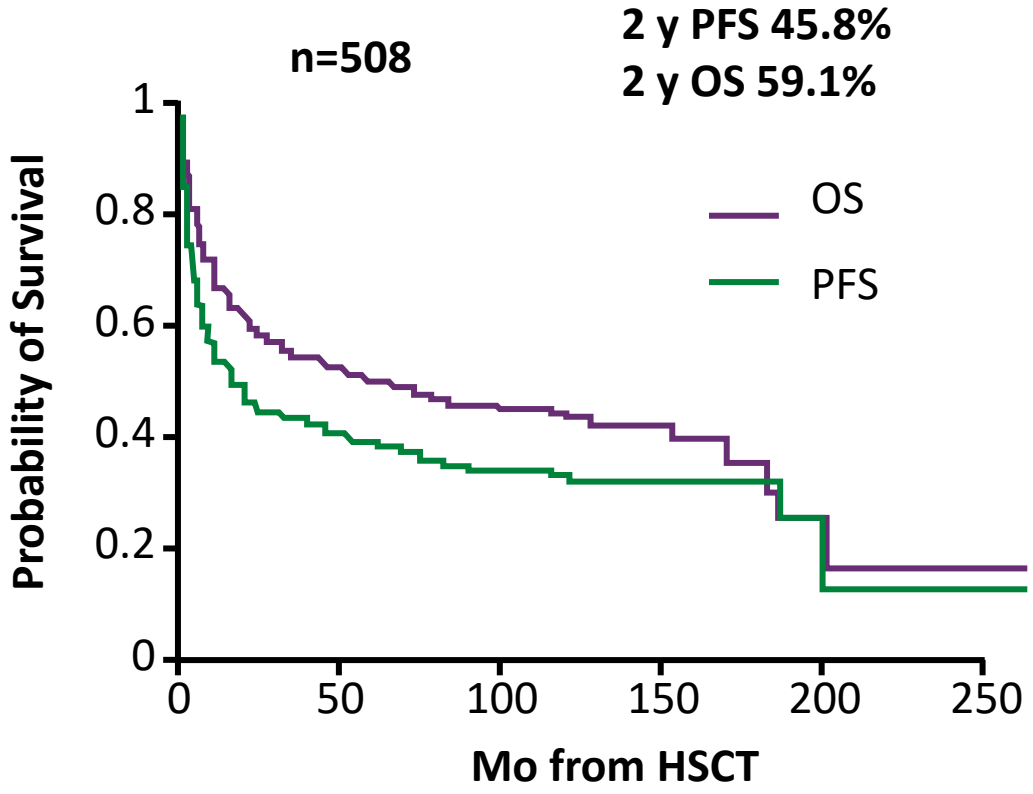
Schmits reviewed results of allo-SCT: 50% long term survival PFS 40%

both matched related and unrelated

less frequent haploidentical transplant

both myeloablative and RIC conditioning

Allogeneic SCT in PTCL/CTCL: Retrospective Multicenter Series 2000-2019



PTCL subtype	2 y PFS, %
AITL (n = 82)	56.4
PTCL-NOS (n = 133)	49.6
ALK – ALCL (n = 26)	34.9
ALK + ALCL (n = 18)	35.3
GvHD	**n/N, %**
Acute Chronic	245/489 (46) 192/473 (41)

- Rate of transplant-related mortality at 1 yr = 11.2%
- Prior studies demonstrate response to DLI → support GVL in PTCL

Mehta-Shah. ASH. 2020.

Slide credit: clinicaloptions.com

Table 1. Summary of select trials with targeted single agents in relapsed/refractory PTCL.

Agent	Class	Subtype	Trial phase	n	Median follow-up	ORR	CR	Median PFS	Median OS	Reference
Pralatrexate	Antifolate	PTCL	II	111	18 months	29%	11%	3.5 months	14.5 months	36
Romidepsin	HDAC inhibitor	PTCL	II	130	22.3 months	25%	15%	4 months	11.3 months	40
Romidepsin	HDAC inhibitor	PTCL	II	45	—	38%	18%	—	—	41
Belinostat	HDAC inhibitor	PTCL	II	129	—	25.8%	10.8%	1.6 months	7.9 months	42
Chidamide	HDAC inhibitor	PTCL	II	83	29 months	28%	14%	2.1 months	21.4 months	43
Brentuximab vedotin	Anti-CD30 antibody drug conjugate	ALCL	II	58	71.4 months	86%	57%	20 months	Not reached	44,54
Crizotinib	Tyrosine kinase inhibitor	ALK-positive ALCL	II	9	—	90.9%	100%	—	—	47
Duvelisib	PI3K-δ and PI3K-γ inhibitor	PTCL	I	16	—	50%	19%	8.3 months	8.4 months	48
Mogamulizumab	Anti-CCR4 antibody	CCR4-positive PTCL	II	29	—	34%	17%	2.0 months	14.2 months	51
Nivolumab	Anti-PD-1 antibody	PTCL	I	5	44 weeks	40%	0	14 weeks	—	55

Approved Drugs in Relapsed and Refractory PTCL

Agent	Drug Type	US (FDA) Indication	ORR, %	CR, %
Pralatrexate	Chemotherapy	Approved 2009 all R/R PTCL	29	11
Brentuximab vedotin	Anti-CD30 antibody–drug conjugate	Approved 2011 R/R ALCL (relapsed ALCL only)	86	57
Romidepsin	HDAC inhibitor	Approved 2012 R/R PTCL*	25	15
Belinostat	HDAC inhibitor	Approved July 2014 All R/R PTCL	25.8	10.8
Crizotinib	ALK inhibitor	Approved Jan 2021 R/R ALK+ ALCL for ages 1 y to young adult (21y)	88	81

*2021 withdrawn in US for R/R PTCL indication due to negative phase 3 study Ro-CHOP vs CHOP

O'Connor. JCO. 2011;29:1182. Pro. JCO. 2012;30: 2190. Coiffier. JCO. 2012;30:631.
O'Connor. JCO. 2015; 33:2492. Crizotinib PI.

Pralatrexate: First FDA-Approved Drug in R/R PTCL

- "Cousin" of methotrexate with ↑ uptake and retention in malignant cell
- Specificity for PTCL
- PROPEL: Phase II study patients with PTCL with progression following ≥1 line of therapy
- Overall ORR 29% (N=111)

Figure not available

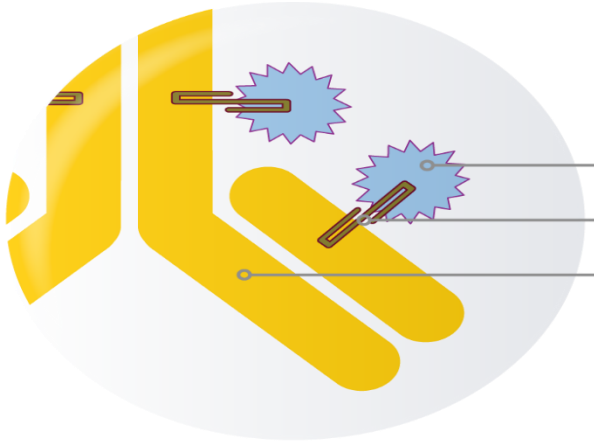
Toxicity	Grade 3, %	Grade 4, %
Mucositis*	18	4
Thrombocytopenia	14	19
Neutropenia	14	8

*Mucositis can be abrogated with leucovorin and alternate schedule 'Columbia Regimen' with ramp up

O'Connor. JCO. 2011;29:1182.

Slide credit: clinicaloptions.com

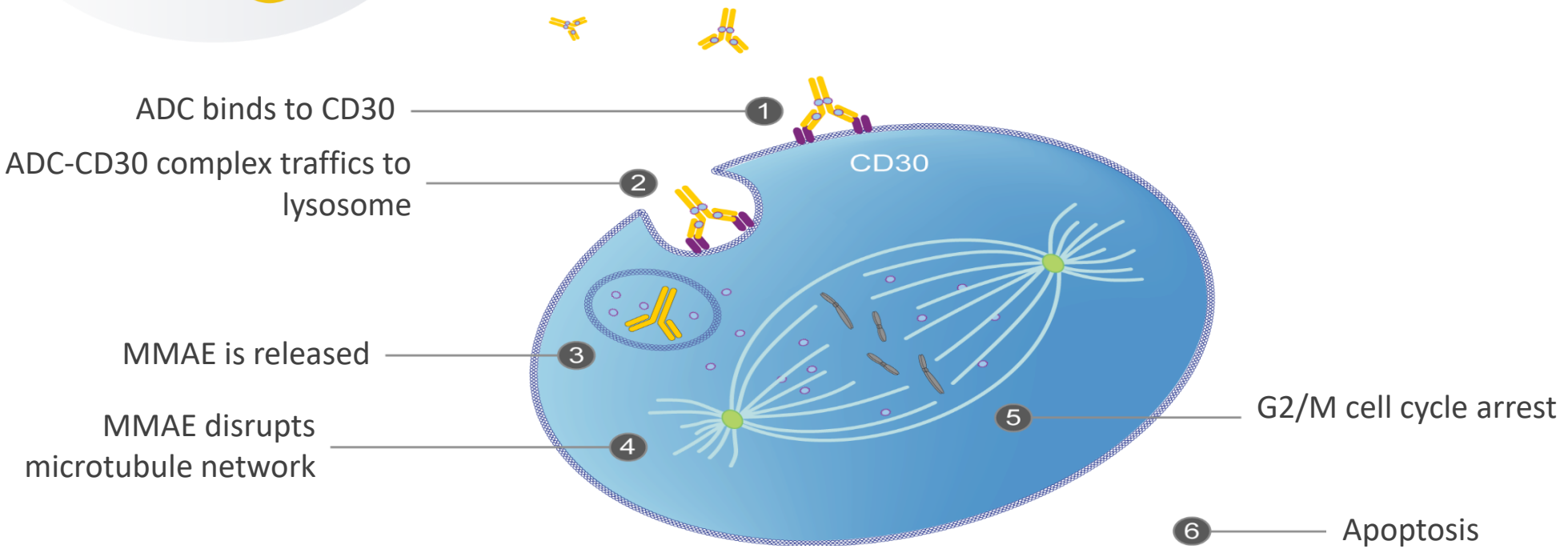
Brentuximab Vedotin Mechanism of Action



Monomethyl auristatin E (MMAE), potent antitubulin agent

Protease-cleavable linker

Anti-CD30 monoclonal antibody

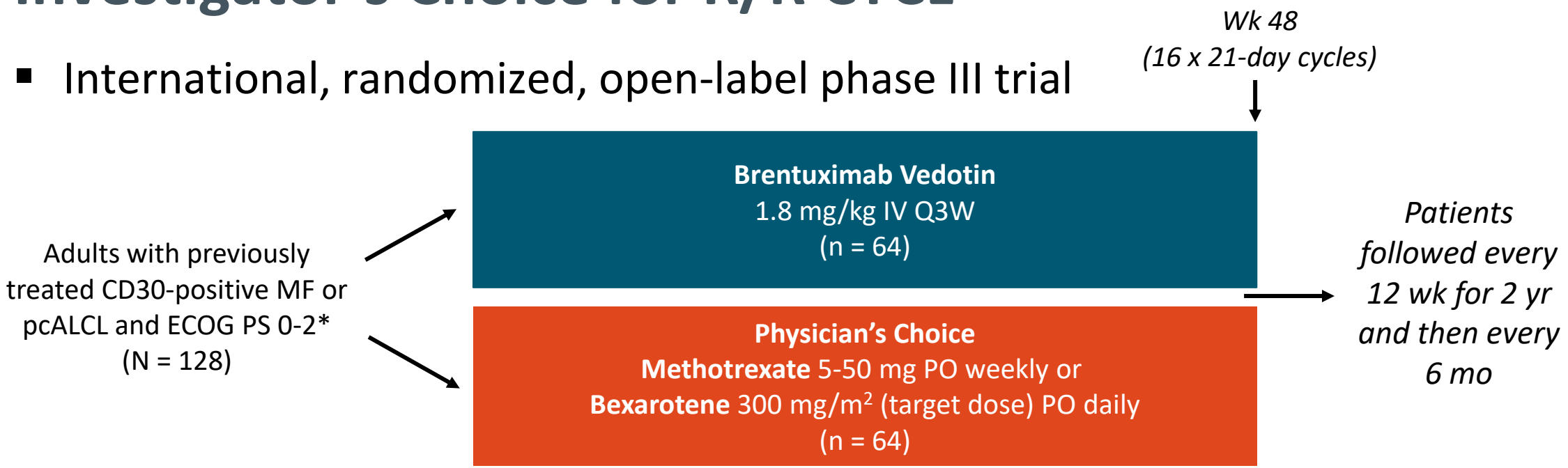


Brentuximab vedotin PI. 2018. Younes. NEJM. 2010;363:1812.

Slide credit: clinicaloptions.com

ALCANZA: Brentuximab Vedotin vs Investigator's Choice for R/R CTCL

- International, randomized, open-label phase III trial



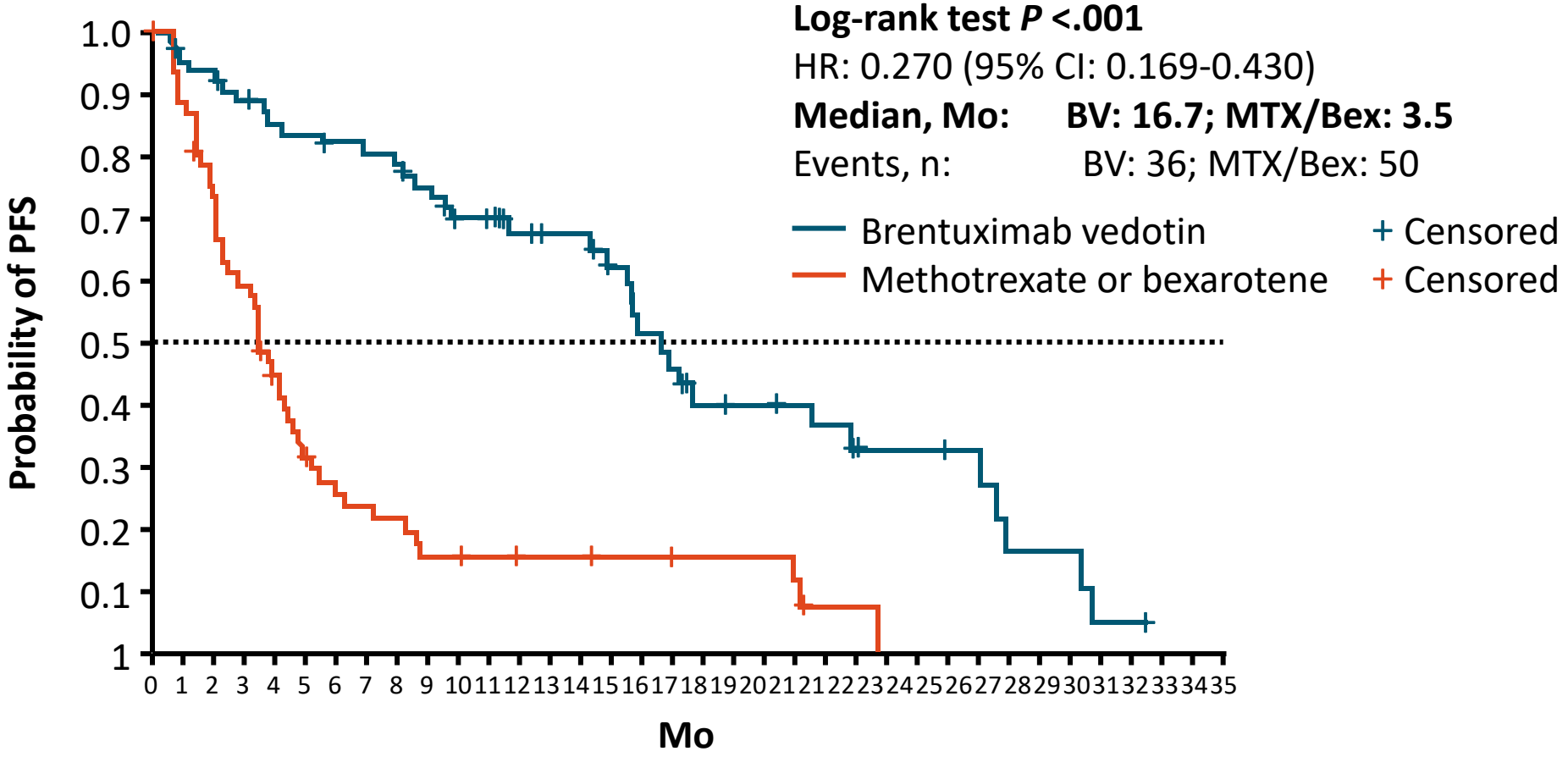
*≥1 previous systemic therapy required for patients with MF; previous radiotherapy or ≥1 previous systemic therapy for patients with pcALCL.

- **Primary endpoint:** ORR4 (objective global response lasting ≥4 mo)
- **Secondary endpoints:** CR, PFS, QoL, PN
- **Not prespecified endpoints:** TTNT, ORR

Prince. Lancet. 2017;390:555.

Slide credit: clinicaloptions.com

ALCANZA: PFS



Patients at Risk, n

Brentuximab vedotin	64	59	58	54	51	50	48	47	46	43	38	38	29	27	27	23	19	17	13	12	12	11	10	8	7	7	7	6	3	3	3	1	1
Methotrexate or bexarotene	64	54	42	34	24	17	13	12	11	8	8	7	7	6	6	5	5	5	3	4	4	3	1	1									

Prince. Lancet. 2017;390:555.

Slide credit: clinicaloptions.com

Brentuximab Vedotin Phase II Study: Outcomes in R/R Systemic ALCL

Measure	N = 58	95% CI
ORR, %	86	74.6-93.9
▪ CR	57	43.2-69.8
▪ PR	29	
SD, %	3	
PD, %	5	
Histologically ineligible, %*	3	
Not evaluable, %	2	
Median DoR, mos	12.6	5.7-NE
Median DoR with CR, mos	13.2	10.8-NE
Median PFS, mos	13.3	6.9-NE
Median OS, mos	Not reached	14.6-NE

*2 patients scored as nonresponders

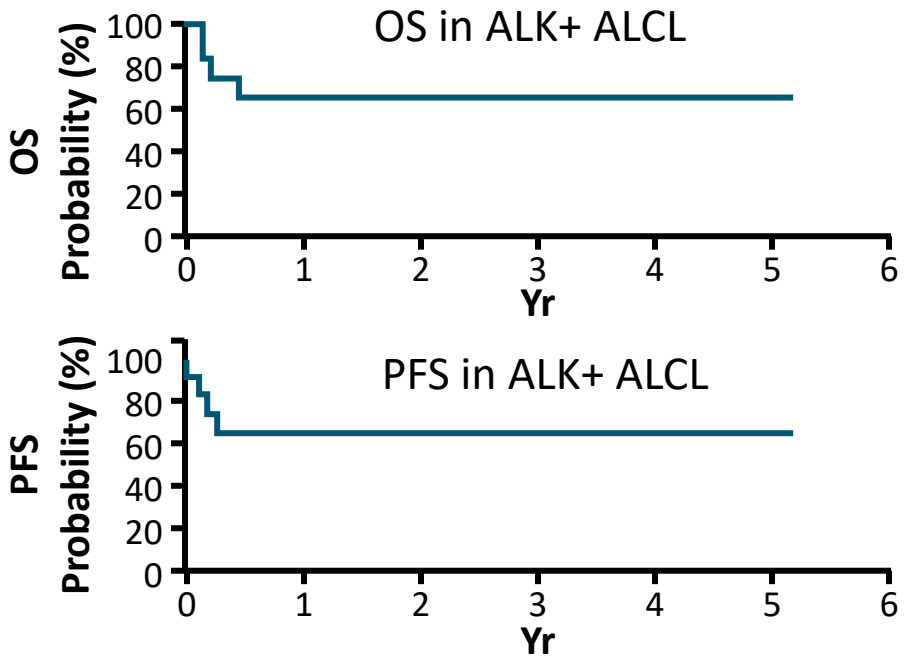
Pro. J Clin Oncol. 2012;30:2190.

Slide credit: clinicaloptions.com

Studies in Relapsed/Refractory Lymphoma or Leukemia

Crizotinib in R/R ALK-ALCL in Children and Adolescents

- ORR: 83.3% (10/12) with CR 58.3% (7/12)[1,2]

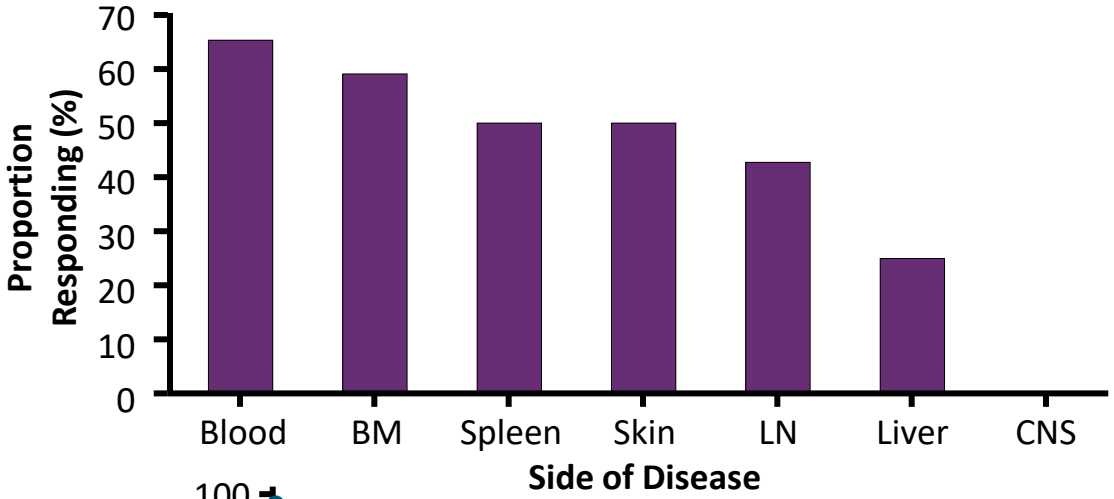


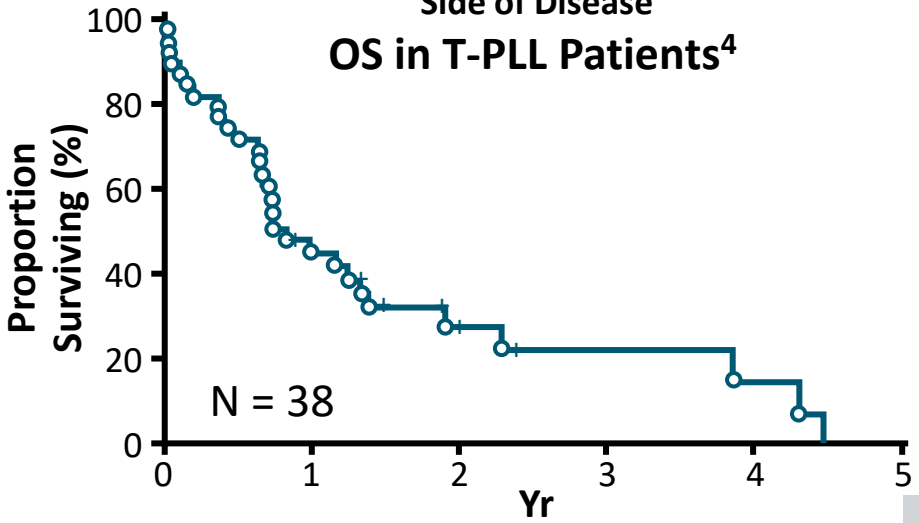
FDA Approval January 2021[3]

For pediatric patients 1 yr of age or older and young adults with R/R, systemic ALCL that is ALK positive

Study ADVL0912: 26 patients; ORR: 88% (95% CI: 71%-96%; CR: 81%)[1,2]

Remission Rate in T-PLL With CAMPATH-1H[4]



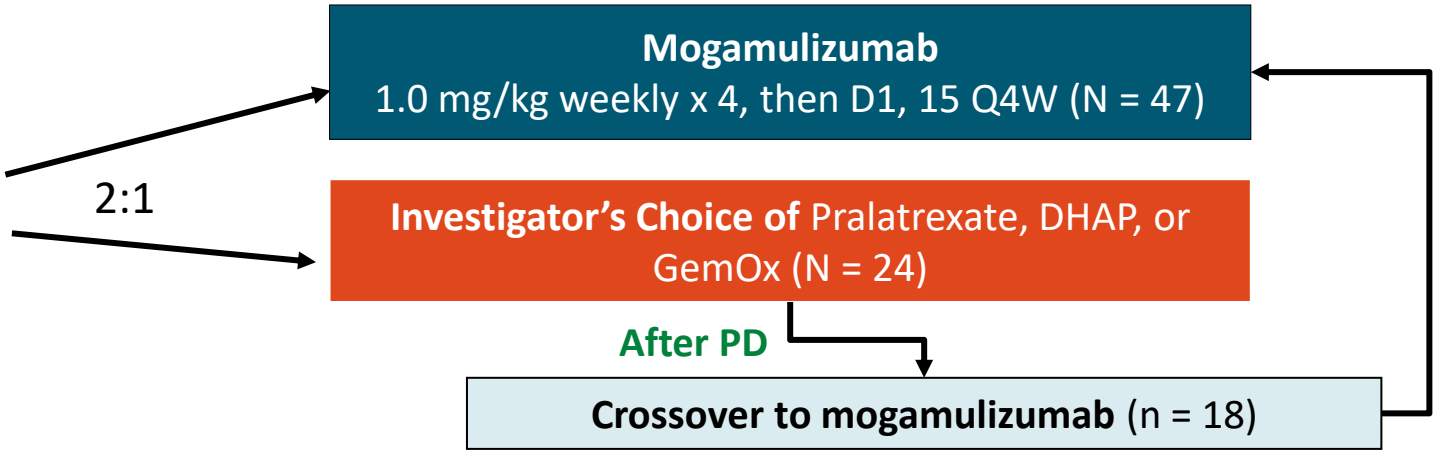


1. Bossi. Am J Hematol. 2020;95:E319. 2. NCT00939770. 3. Crizotinib PI. 4. Dearden. Blood. 2001;98:1721.

Slide credit: clinicaloptions.com

Phase II of Mogamulizumab vs Investigator's Choice in R/R ATL

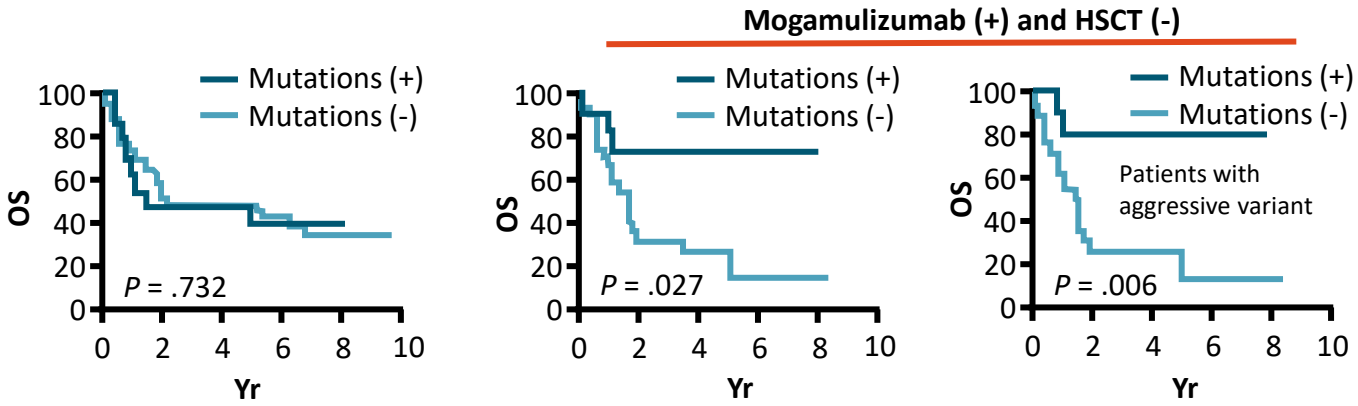
Patients 18 yr of age or older with HTLV-1–positive ATL, excluding smoldering disease; relapsed/refractory; ECOG PS 0-2



- Primary objective: ORR

Response, n (%)	Mogamulizumab (N = 47)	Investigator's Choice (N = 24)
Investigator assessment		
Best response	16 (34)	0
Confirmed	7 (15)	0
Independent review		
Best response	13 (28)	2 (8)
Confirmed	5 (11)	0

Survival According to CCR4 Mutations[2]



- CCR4 mutations associated with superior outcome in ATL w/mogamulizumab treatment

1. Phillips. Haematologica. 2019;104:993. 2. Sakamoto. Blood. 2018; 132:758.

Slide credit: clinicaloptions.com

First-In-Human Study of EZH1 AND EZH2 Dual Inhibitor Valemetostat in R/R PTCL: Efficacy Summary

Parameter	All PTCL (N = 44)	PTCL Subtype				ATL (N = 14)
		AITL (n = 17)	PTCL-NOS (n = 20)	ALCL (n = 2)	Other TCL (n = 5)	
Best response, n (%)						
▪ CR	12 (27.3)	**8 (47.1)**	4 (20.0)	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)
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)
DoR, median, wk (95% CI)	56.0 (44.43, –)	– (5.86, –)	56.0 (8.14-56.0)	–	– (8.14, –)	– (6.14, –)
PFS, median, wk (95% CI)	52 (16.14, –)	52 (16.1, –)	64 (8.1-64.0)	– (8.1, –)	15.9 (8.0, –)	– (8.14, –)

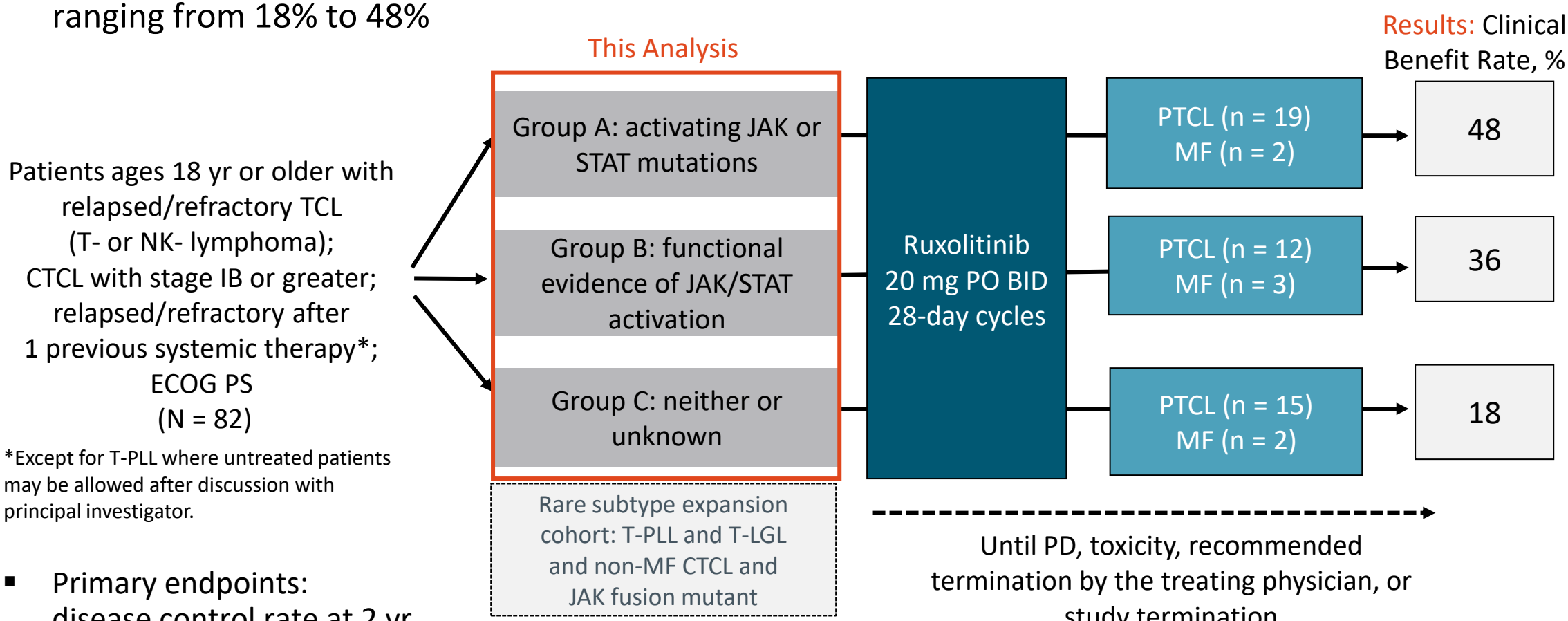
- Median follow-up times: PTCL, 19.93 wk (range: 3.1-68.1); ATL, 23.07 wk (range: 3.3-125)

Kusumoto. EHA 2021. Abstr S218.

Data cutoff: November 2, 2020.

Phase II Biomarker-Driven Study of Ruxolitinib: Study Design

- Ruxolitinib demonstrates effectiveness of JAK/STAT targeting in TCL with clinical benefit rate ranging from 18% to 48%



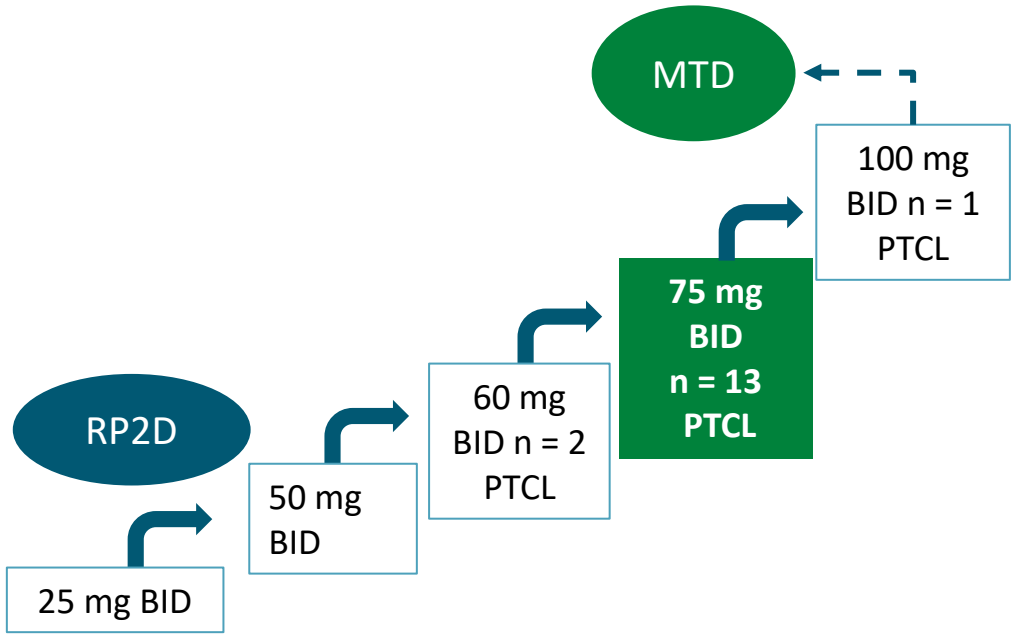
- Primary endpoints: disease control rate at 2 yr

Moskowitz. Blood. 2021;[Epub]. NCT02974647.

Slide credit: clinicaloptions.com

Phase I Trial of Duvelisib Monotherapy: Efficacy in PTCL

Patients with R/R PTCL: N = 16



Parameter	Duvelisib 75 mg BID (n = 13)	All PTCL (N = 16)
ORR, n (%)	**7 (54)**	**8 (50)**
[95% CI]	**[25.1-80.8]**	**[24.7-75.3]**
Best overall response, n (%)		
▪ CR	2 (15)	3 (19)
▪ PR	5 (38)	5 (31)
▪ SD	1 (8)	1 (6)
▪ PD	5 (38)	6 (37)
▪ Unknown	0	1 (6)
Median time to response, mo (range)	1.9	1.9 (1.6-3.5)
Median PFS, mo (95% CI)	8.3	8.3 (1.4-NR)
Median OS, mo (95% CI)	16.2	8.4 (4.3-NR)

- Response to duvelisib was observed across a spectrum of PTCL subtypes
  - 3 CRs in EATL, AITCL, and PTCL-NOS
  - 5 PRs in AITCL, ALCL, PTCL-NOS, and SPTCL (n = 2)

Horwitz. Blood. 2018;131:888. Flinn. Blood. 2018;131:877.

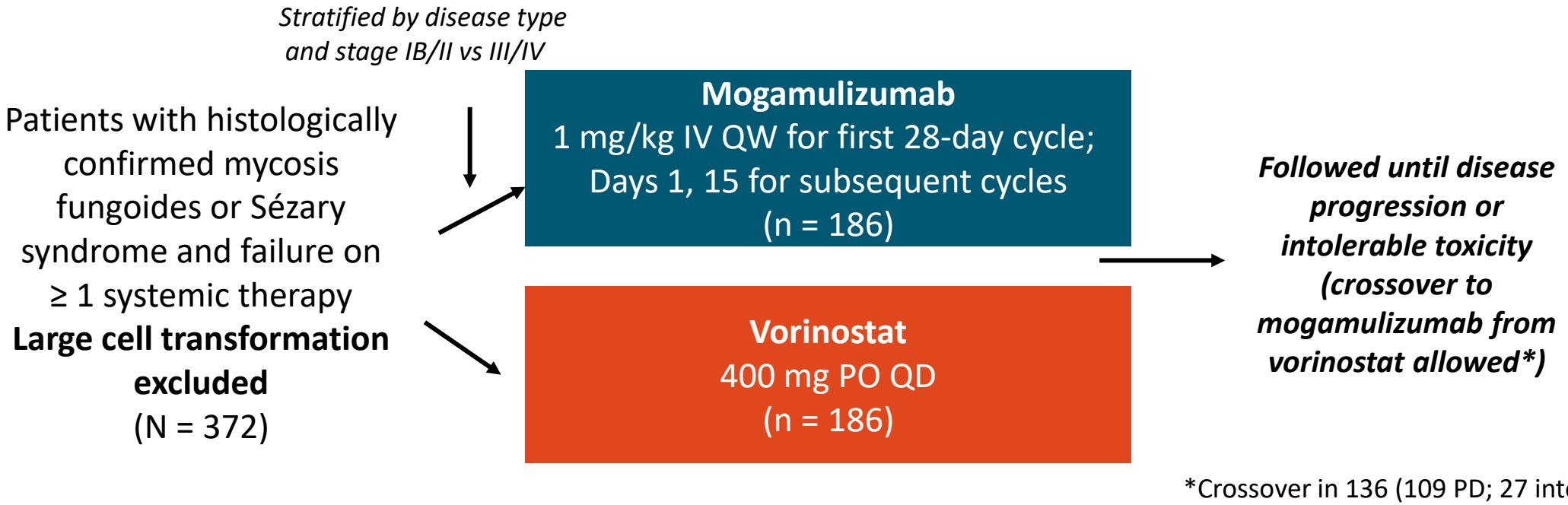
Slide credit: clinicaloptions.com

Current Therapy Considerations in Relapsed/Refractory PTCL

- Is the patient a transplant candidate? Allogeneic SCT vs autologous SCT?
- What are the approved drugs in R/R PTCL? What else may be available?
- Are there subtype-specific considerations? Can disease biology inform drug choices?

MAVORIC: Mogamulizumab vs Vorinostat in Previously Treated CTCL

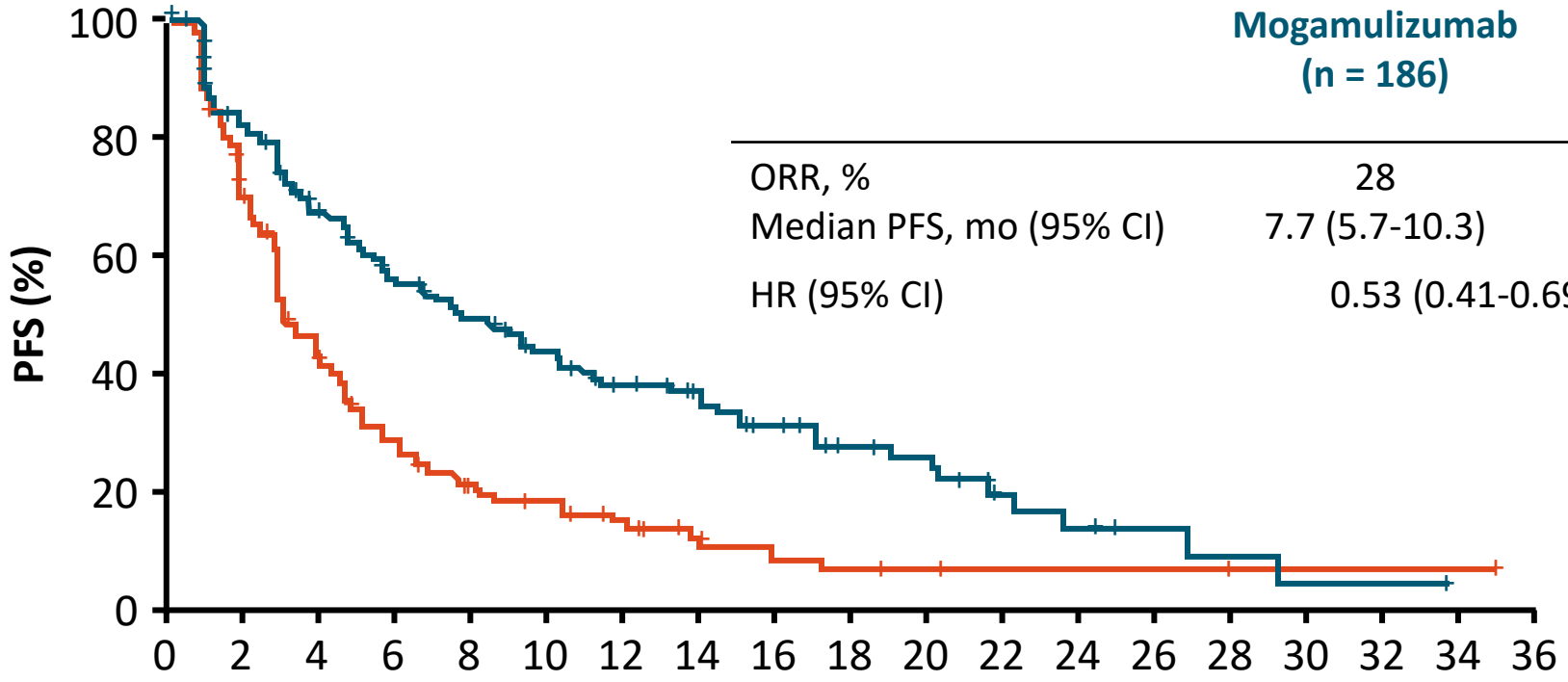
- Multicenter, international, open-label, randomized phase III trial



*Crossover in 136 (109 PD; 27 intolerance)

- Primary endpoint: PFS, using global composite response score based on skin, blood, lymph nodes, and viscera

MAVORIC: PFS of Mogamulizumab vs Vorinostat in Previously Treated CTCL



	Mogamulizumab (n = 186)	Vorinostat (n = 186)
ORR, %	28	5
Median PFS, mo (95% CI)	7.7 (5.7-10.3)	3.1 (2.9-4.1)
HR (95% CI)	0.53 (0.41-0.69); *P* <.0001	

Patients at Risk, n																			
Mogamulizumab	186	138	100	77	65	50	39	32	22	16	14	7	5	3	2	1	1	0	0
Vorinostat	186	111	61	36	23	18	13	8	5	4	3	2	2	2	1	1	1	1	0

Kim. Lancet Oncol. 2018;19:1192.

Slide credit: clinicaloptions.com

Brentuximab Vedotin at Variable CD30 Levels in CTCL

- CD30 expression is variable in MF/SS[1]
  - Median of 13% expression (n = 30)
  - By more sensitive techniques, >90% of samples were CD30+
- Response rate by CD30 level[1]
  - ORR 70% (total population)
  - CD30 <5% less likely to respond
    - 17% ORR <5% expression
    - 83% ORR >5% expression

Figure not available

1. Kim. JCO. 2015;33: 3750. 2. Kim. Eur J Cancer. 2021; 148:411.

Slide credit: clinicaloptions.com

CELL THERAPY

Anti-CD30 CAR-T cell treatments are in development

A phase Ib/II anti-CD30 CAR-T trial of 24 patients

A phase I dose escalation study of a CD5-directed CAR-T cell therapy in RR T-cell leukemia and lymphoma patients as a bridge to allo-SCT

Treatment is safe and does not appear to induce T-cell aplasia

Slide credit: clinicaloptions.com

Anti-T cell receptor β-chain

Two genes associated : *TRBC1* and *TRBC2*

Normal T cells will therefore have a mixture of cells

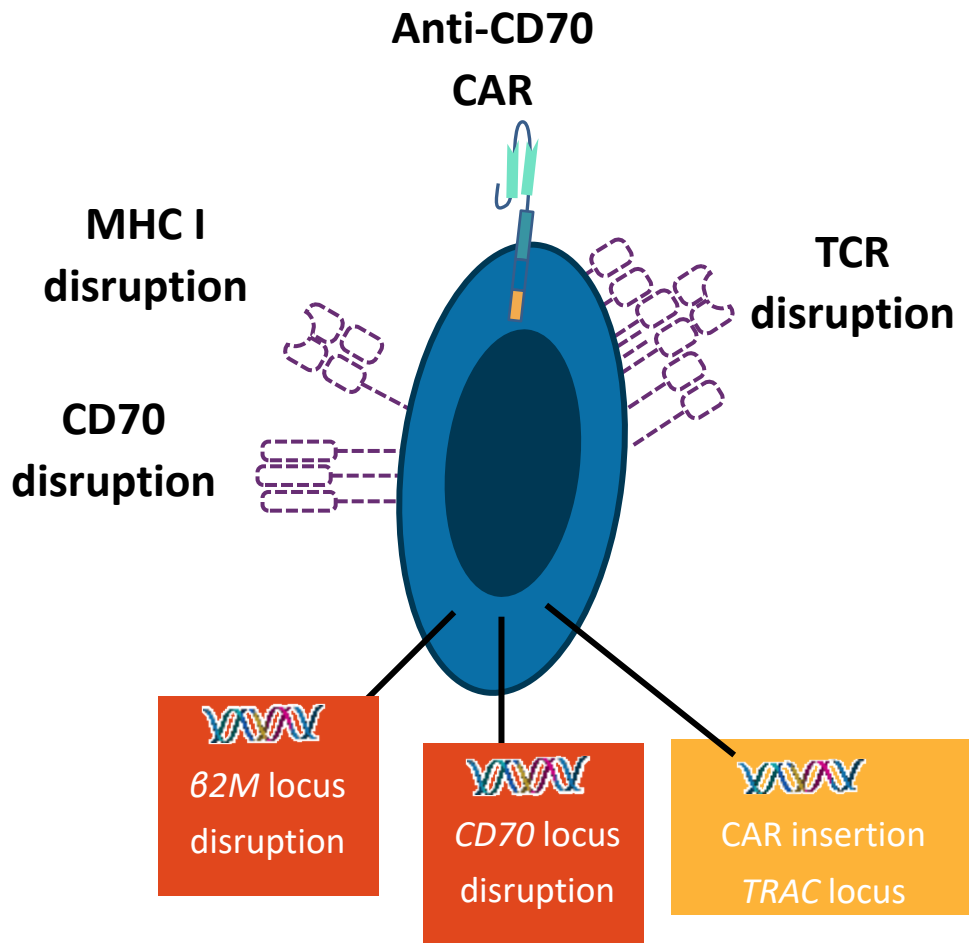
Malignant T cells result in exclusive expressionof one constant domain

Make it an attractive target for cell therapy

phase I/II : assessing an constant domain 1 (TRBC1) CAR-T cell therapy in RR TRBC1-expressing PTCL-NOS, AITL, and ALCL

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

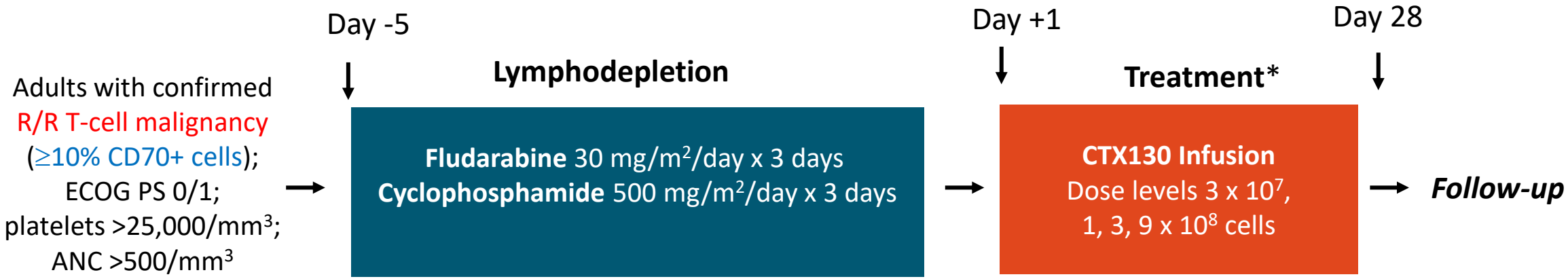


Dequeant. Cancer Res. 2021;81:1537. Iyer. EHA 2022. Abstr S262.Marques-Piubelli. Histopathology. 2022;81:272.

Slide credit: clinicaloptions.com

COBALT-LYM: CD70-Directed Allogenic CAR T-Cell Therapy Study in R/R T-Cell Malignancies

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



*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)

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Other Agents of Interest in the Lymphoma Pipeline

- SGN-CD70A monoclonal antibody (NCT04227847)
- Duvelisib + nivolumab (NCT04652960)
- Anti-ICOS monoclonal antibodies

THANK YOU

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