Peripheral T-cell Lymphomas

Including Primary Cutaneous Subtypes

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COI Disclosure

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PTCL/CTCL Landscape in 2019

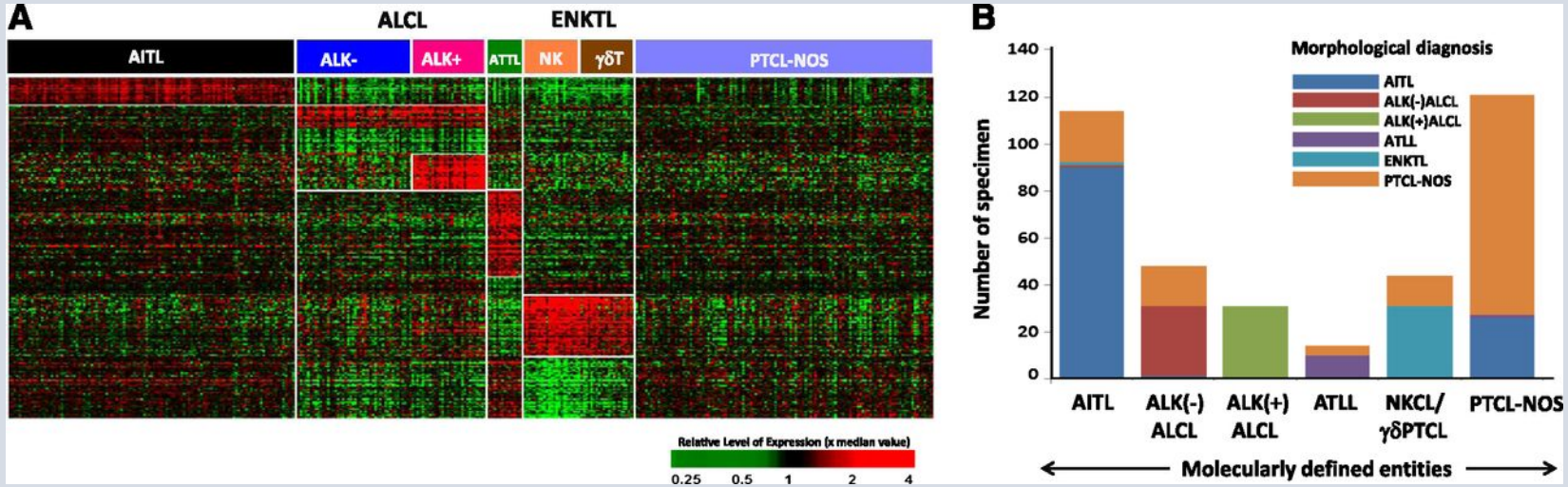
- WHO – 2016 Classification
- Clinical Outcomes in PTCL
- Front Line PTCL Therapy
    - Management of Selected Unique T-cell Malignancies
- New FDA-Approved Agents for Relapsed and Refractory PTCL
- CTCL Overview Including Management
- Recent Advances in CTCL Therapy

2016 - WHO Classification of PTCL

CTCL	Extranodal	Nodal	Leukemic
Mycosis Fungoides	NK/TCL Nasal Type	Peripheral TCL-NOS	Adult T-cell Leukemia/ Lymphoma
Sézary Syndrome	Enteropathy- Associated TCL	Anaplastic Large Cell Lymphoma, ALK +	Aggressive NK-Cell Leukemia
Primary Cutaneous CD30+ T-cell Disorders	Hepatosplenic TCL	Angioimmunoblastic TCL	T-cell Prolymphocytic Leukemia
Primary Cutaneous Gamma/Delta TCL	Subcutaneous Panniculitis-like TCL	Anaplastic Large Cell Lymphoma, ALK -	T-cell Large Granular Lymphocytic Leukemia
Hydroa vacciniforme-like Lymphoproliferative Disorder	Monomorphic Epitheliotropic Intestinal T-cell Lymphoma	Follicular TCL	Chronic Lymphoproliferative Disorder of NK-cells
Primary Cutaneous CD8+ Aggressive Epidermotropic TCL	Systemic EBV+ T-cell Lymphoma of Childhood	Nodal Peripheral TCL with TFH phenotype	
Primary Cutaneous Acral CD8+ TCL	Indolent T-cell Lymphoproliferative Disorder of the GI Tract		
Primary Cutaneous CD4+ Small/Medium T-cell Lymphoma			

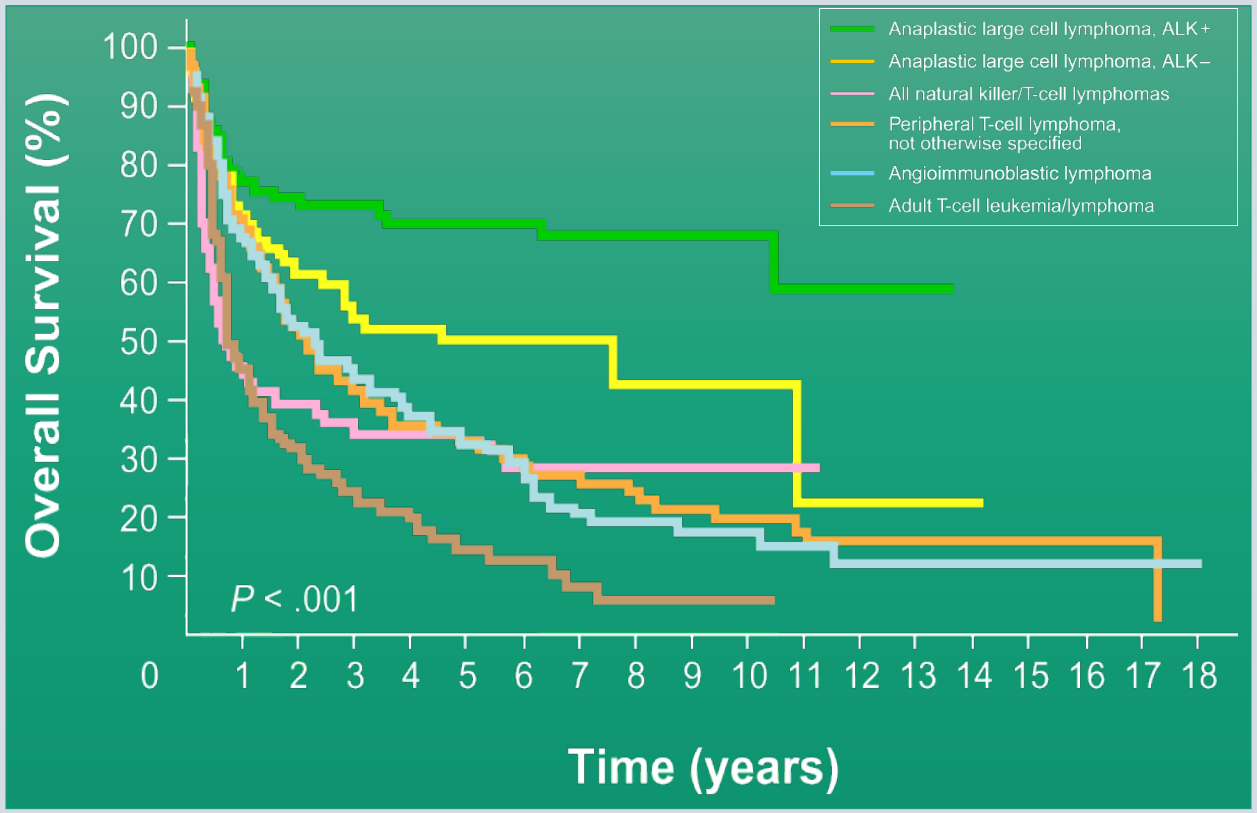
Molecular Diagnosis of PTCL Subgroups.

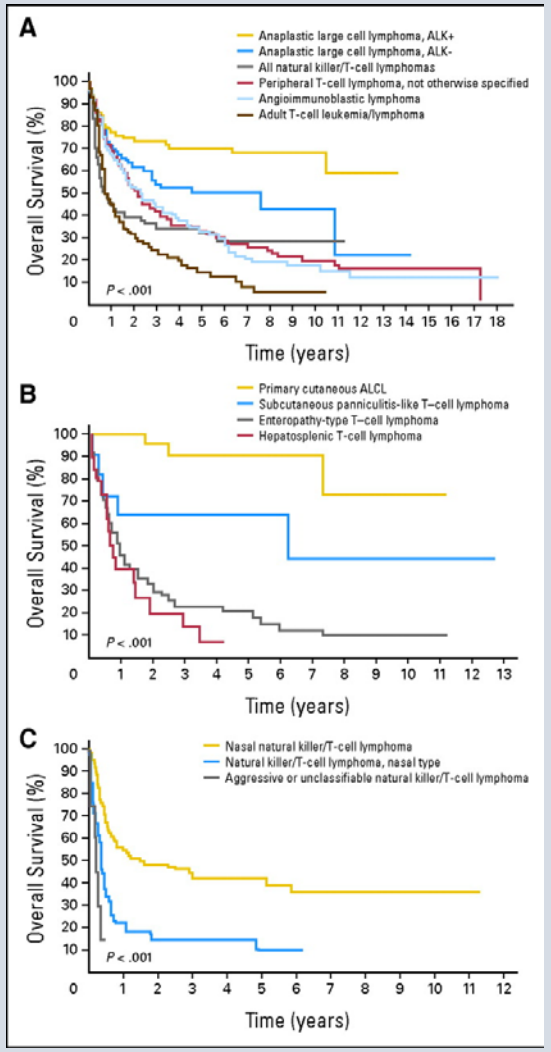
PTCL is not a single disease
Diverse genomic landscape => diverse biology/behavior



Iqbal J et al. *Blood* 2014;123:2915-2923

PTCL Prognosis is Indicative of Diverse Biology



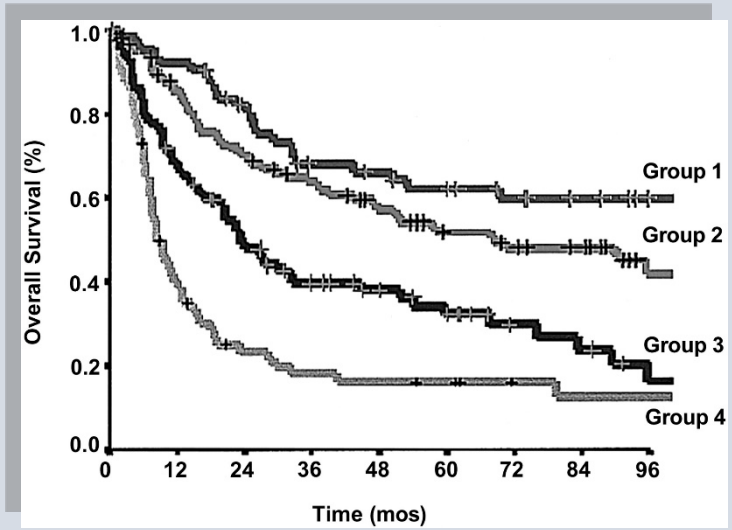


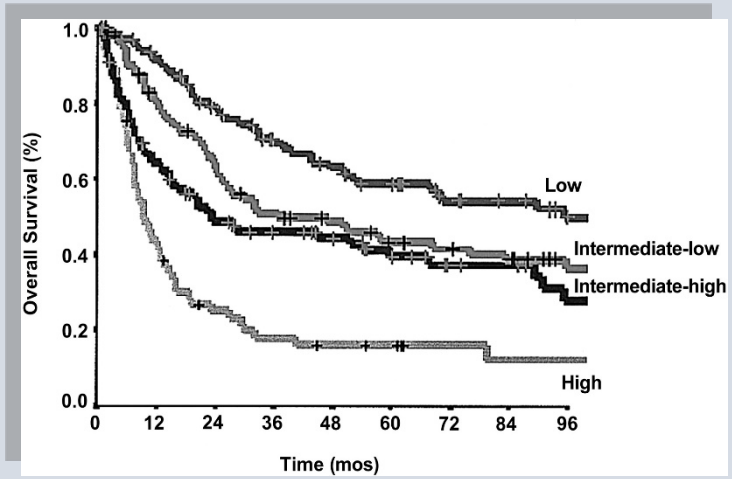
Armitage J, et al. *J Clin Oncol.* 2008;26:4124–4130.

Clinical Prognostic Models in PTCL

Clinical Variables	IPI	PIT	PIAI	KPI
Age	X	X	X	
Stage	X			X
LDH	X	X		X
ECOG PS	X	X	X	
X-nodal sites	X		X	
BM involvement		X		
Platelet count			X	
B-symptoms			X	X
Regional LN+				X

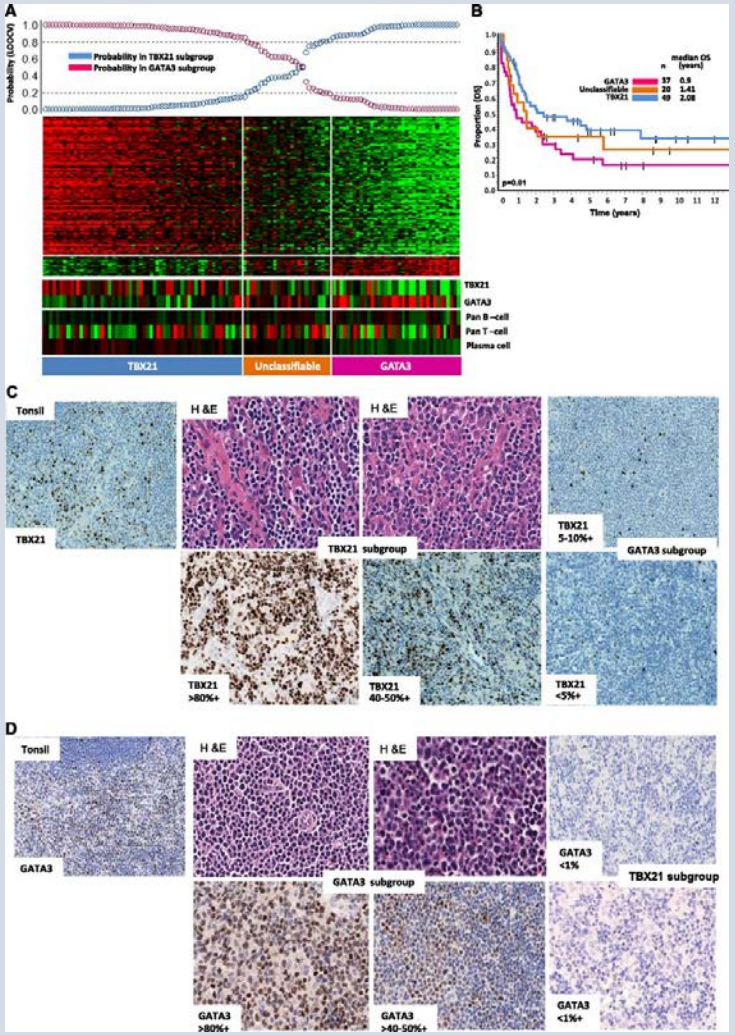
Prognosis of PTCL-NOS by Clinical Features: IPI and PIT





Gallamini A et al. *Blood* 2004;103:2474-2479

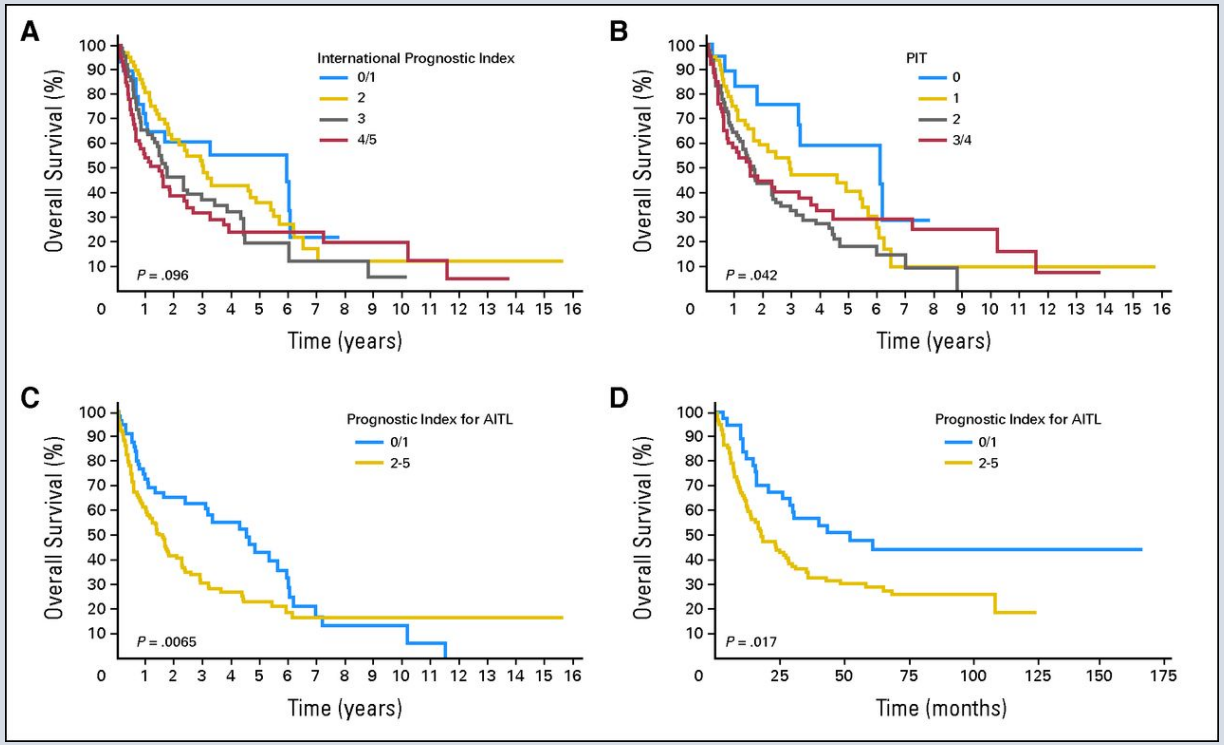
Prognosis of PTCL-NOS by Molecular Subgroups



Iqbal J et al. *Blood* 2014;123:2915-2923

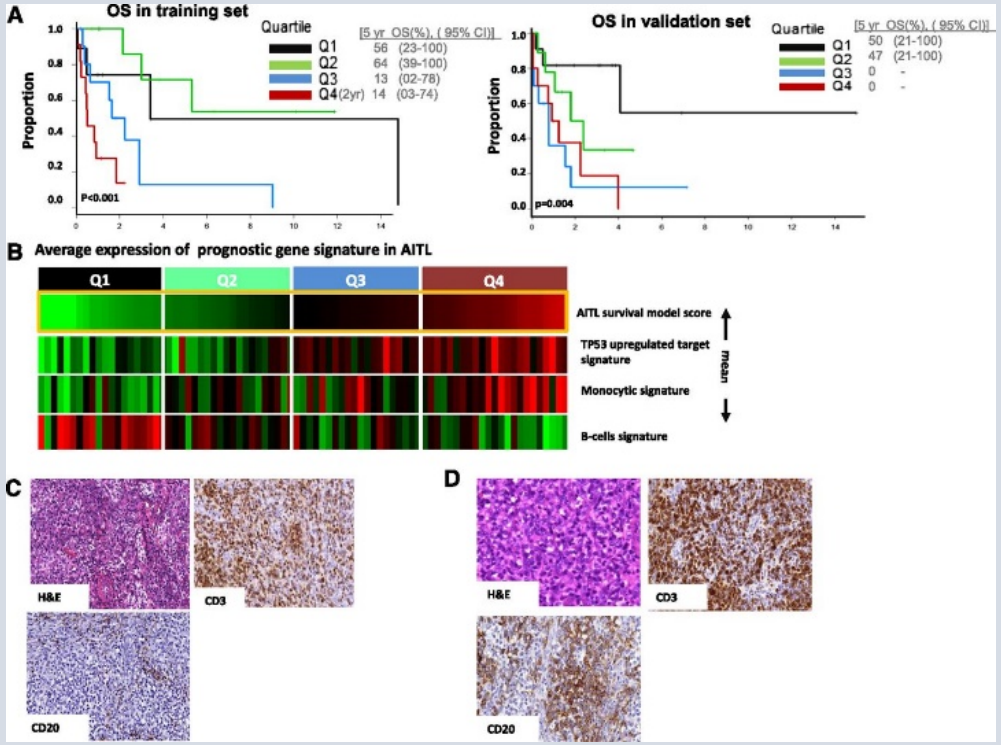
blood

Prognosis of AITL by Clinical Features: PIAI



Federico M. et al. *J Clin Oncol*. 2013 31:240-246

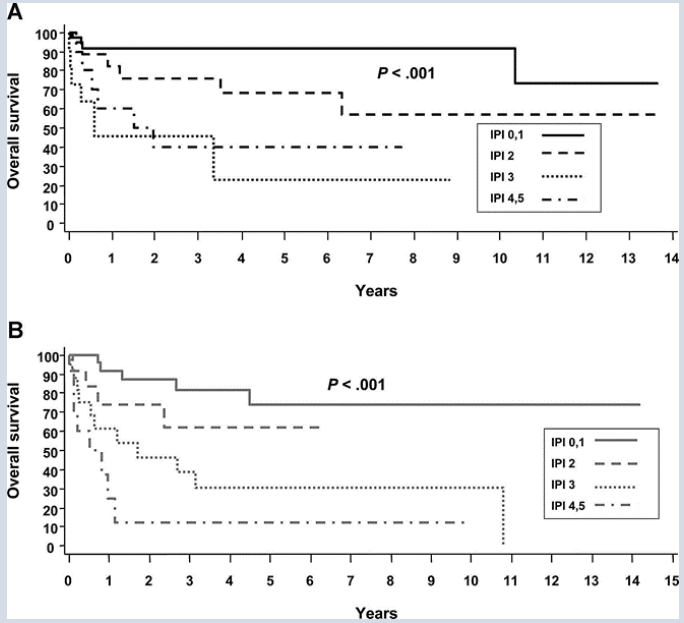
Prognosis of AITL by Molecular Subgroups



Iqbal J et al. *Blood* 2014;123:2915-2923

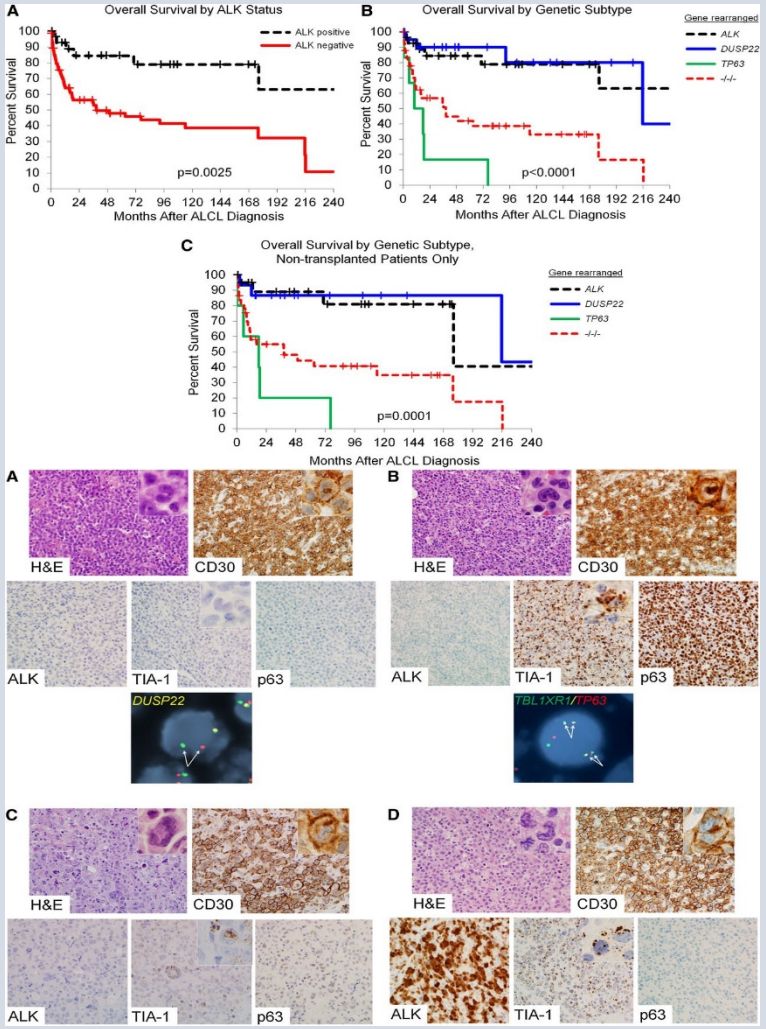
blood

Prognosis of ALCL by Clinical Features: IPI



Savage K J et al. *Blood* 2008;111:5496-5504

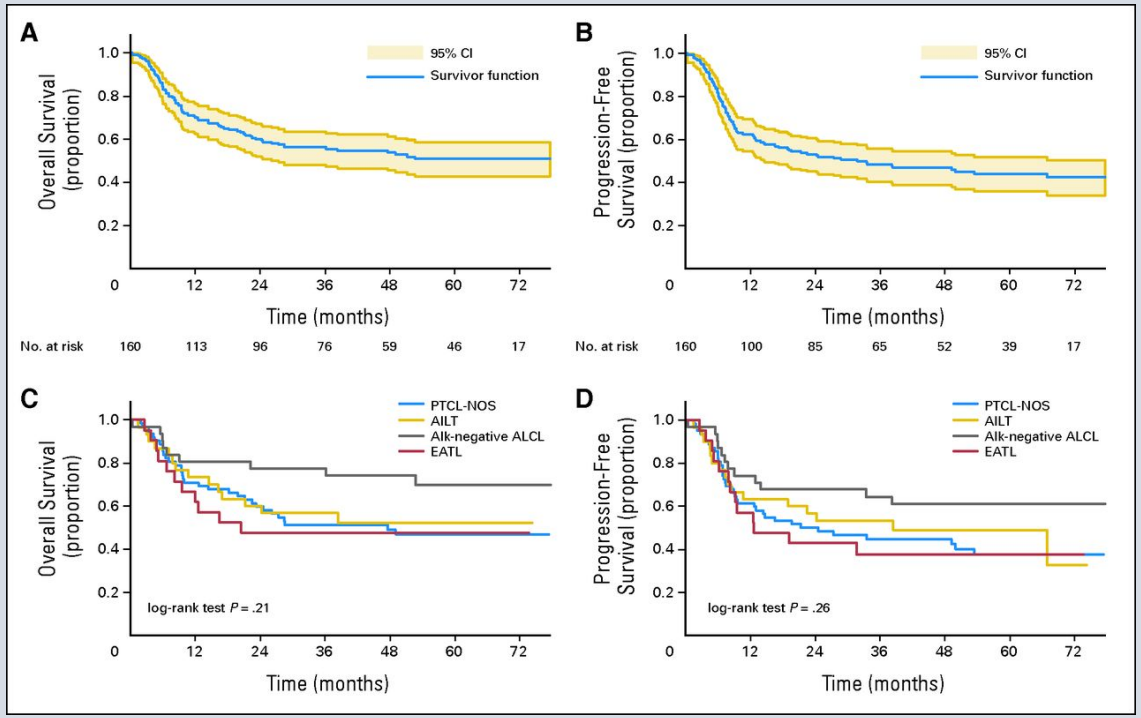
Prognosis of ALCL by Molecular Subgroups



Iqbal J et al. *Blood* 2014;123:2915-2923

blood

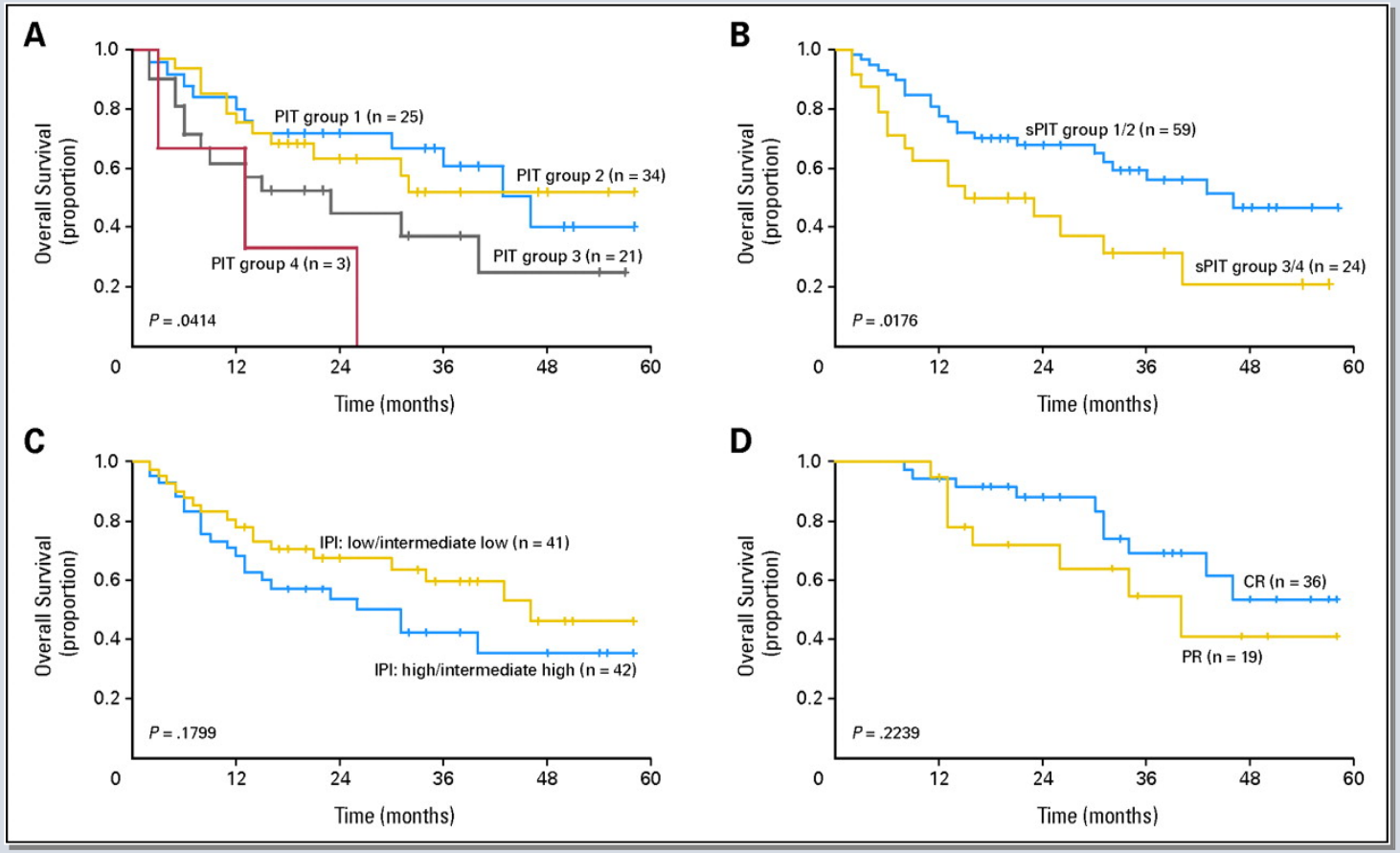
PTCL Prognosis: High-Dose Therapy



	OS		PFS	
Subtype	3-yr	5-yr	3-yr	5-yr
PTCLu (n=62)	51%	45%	43%	34%
AIL (n=30)	57%	50%	54%	47%
ALCL alk-neg (n=31)	77%	73%	64%	64%
Enteropathy (n=21)	52%	44%	47%	40%

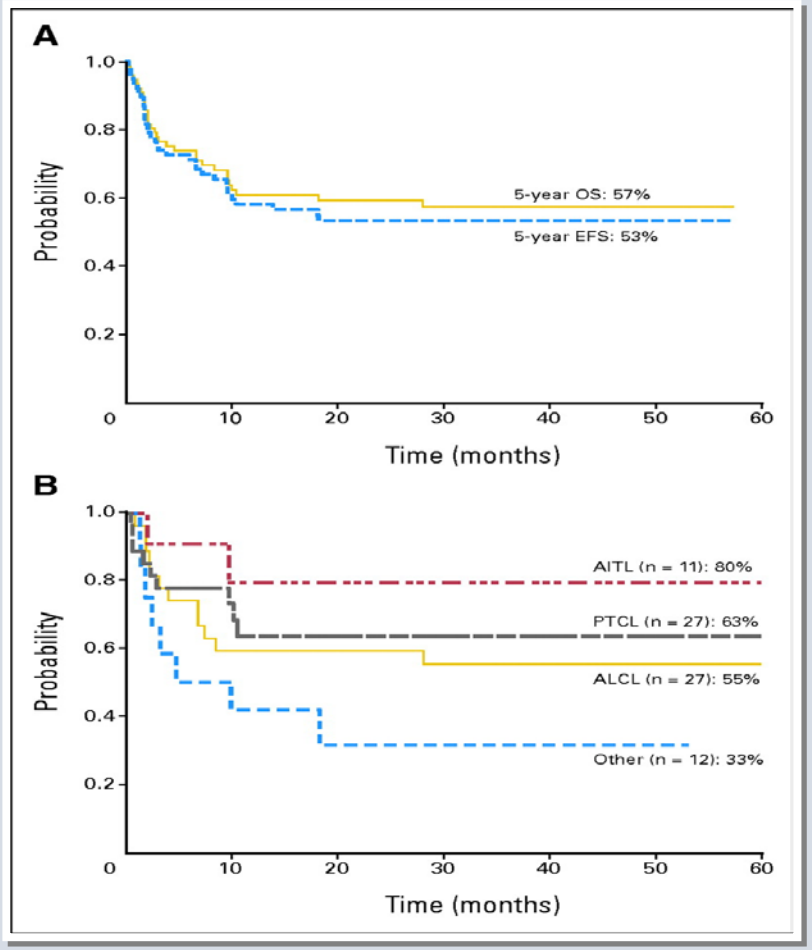
D'Amore F. et al. *J Clin Oncol*. 2012 30:3093-3099

PTCL Prognosis: High-Dose Therapy

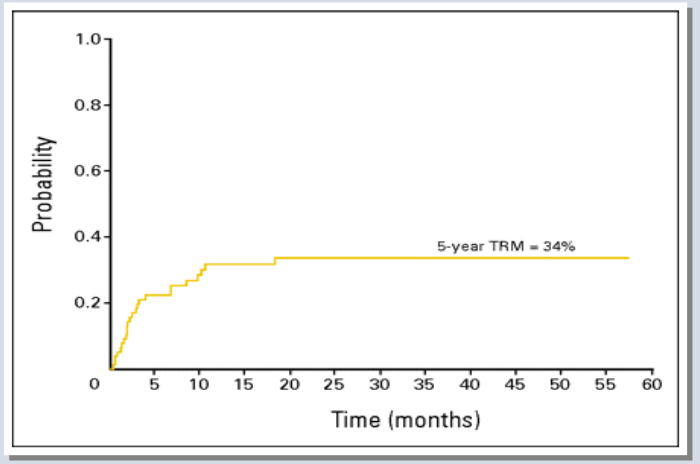


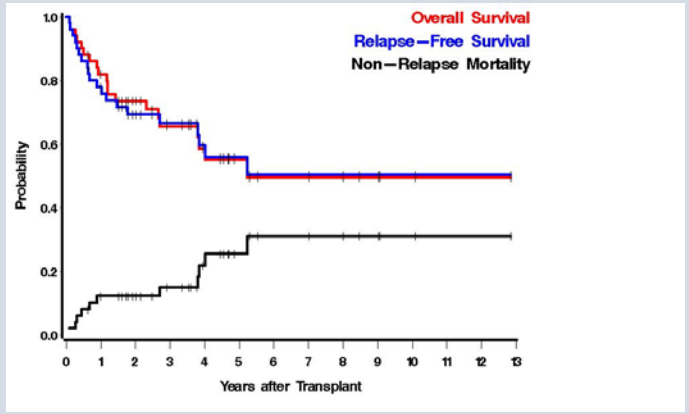
Reimer P. et al. *J Clin Oncol*. 2009 27:106-113

PTCL Prognosis: Allo-HCT



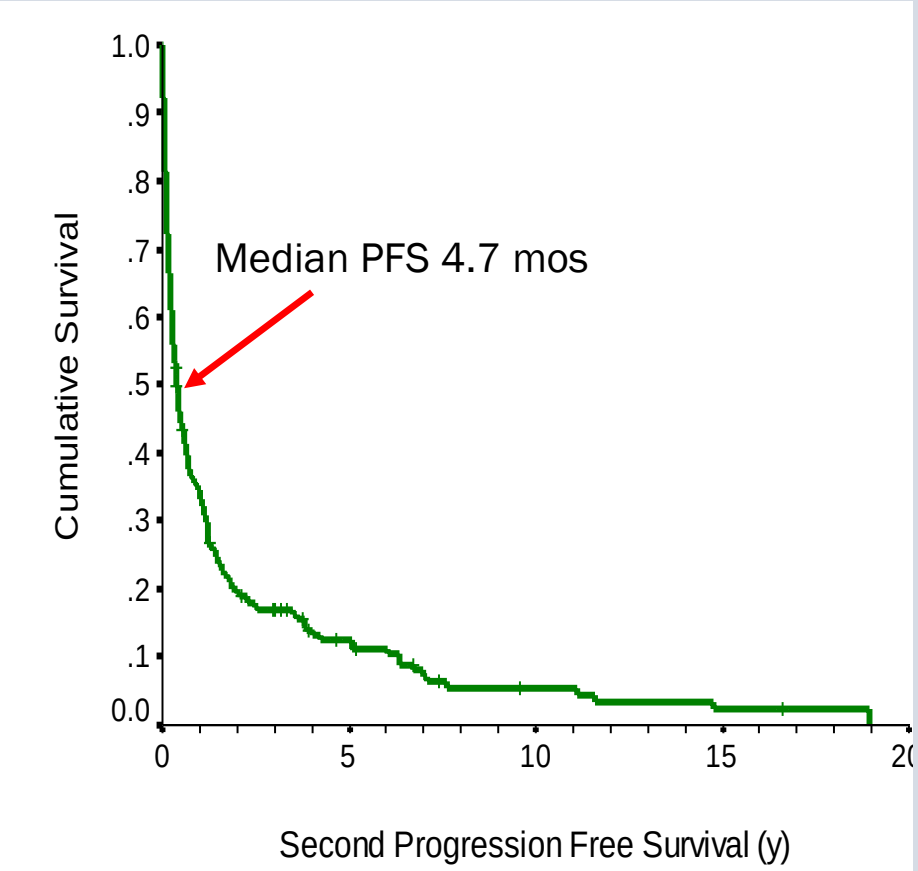
Le Gouill S. et al. *J Clin Oncol*. 2008 26:2264-2271

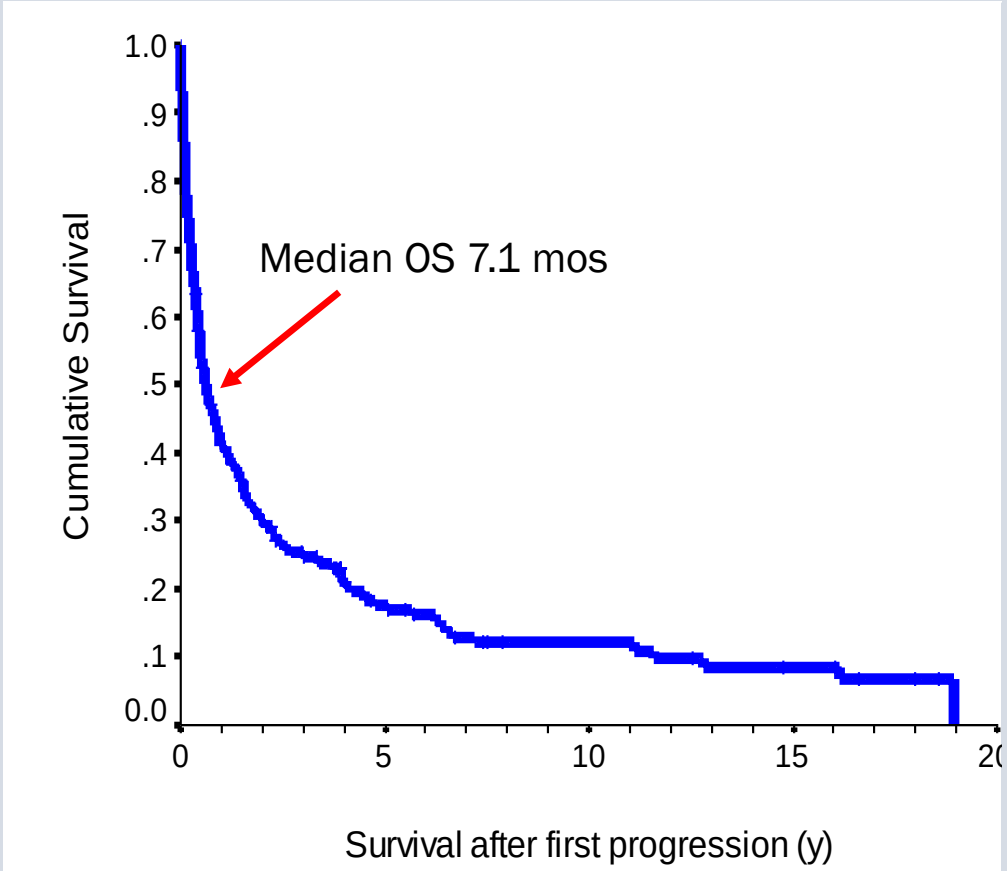




Shustov A. et al. *Br J Haem*. 2010 150:170-178

Survival in PTCL Post 1st Relapse or Progression



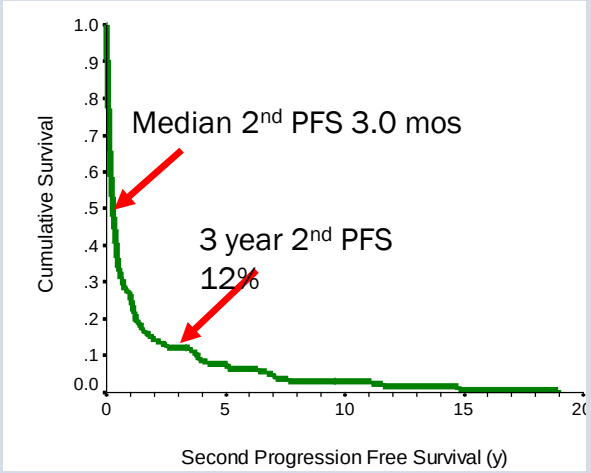


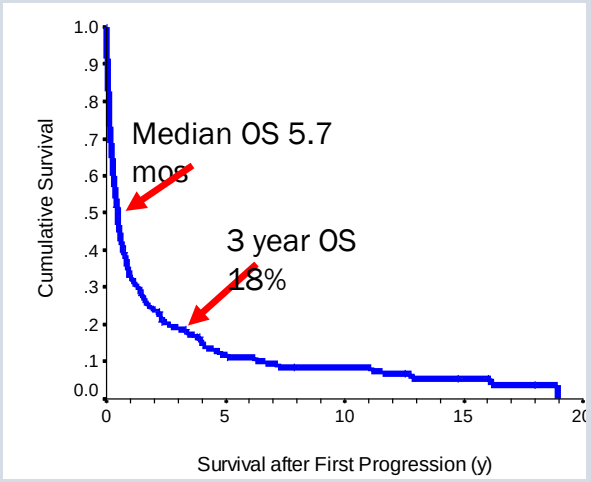
Savage K. et al. *J Clin Oncol*. 2013; 31:1970-1976

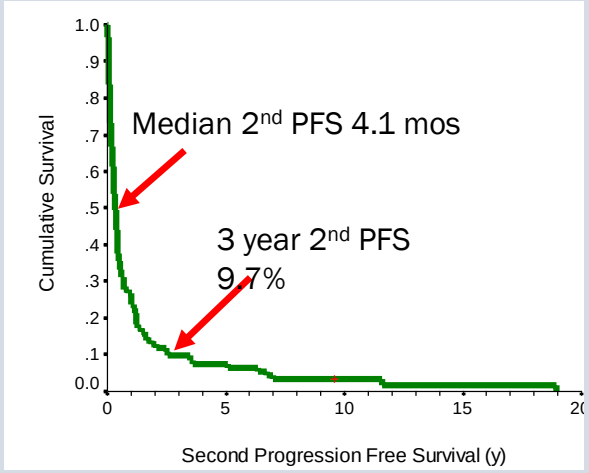
Survival in PTCL Post 1st Relapse or Progression

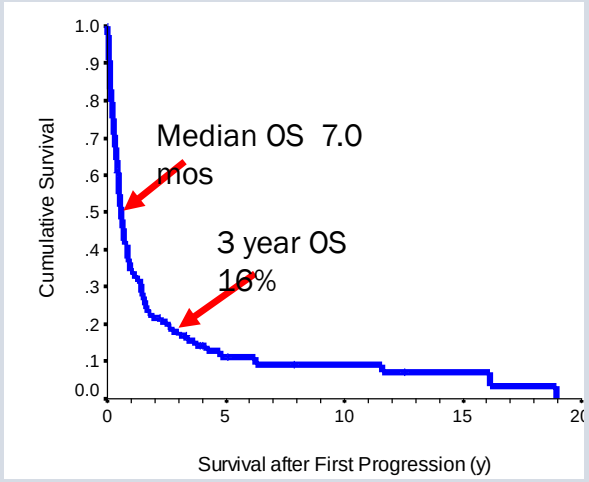
Historical Chemotherapy does not improve outcomes in relapsed or refractory PTCL

Patients not treated with chemotherapy









Patients treated with chemotherapy

Savage K. et al. *J Clin Oncol*. 2013; 31:1970-1976

PTCL Therapy: NCCN Guidelines

First-Line Therapy:

- Clinical trial
- ALCL, ALK+ histology
  - CHOP-21 (cyclophosphamide, doxorubicin, vincristine, prednisone)
  - CHOEP-21 (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone)
- Other histologies (ALCL, ALK–; PTCL, NOS; AITL; EATL), regimens that can be used include:
- Preferred regimens (in alphabetical order)
  - CHOEP
  - CHOP-14
  - CHOP-21
  - Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
- Alternative regimens (in alphabetical order)
  - CHOP followed by IVE (ifosfamide, etoposide, epirubicin) alternating with intermediate-dose methotrexate [Newcastle Regimen] [studied only in patients with EATL]
  - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with high-dose methotrexate and cytarabine

First-Line Consolidation:

- Consider consolidation with high-dose therapy and stem cell rescue
  - Patients with low IPI ALCL, ALK+ disease in remission do not need consolidative transplant

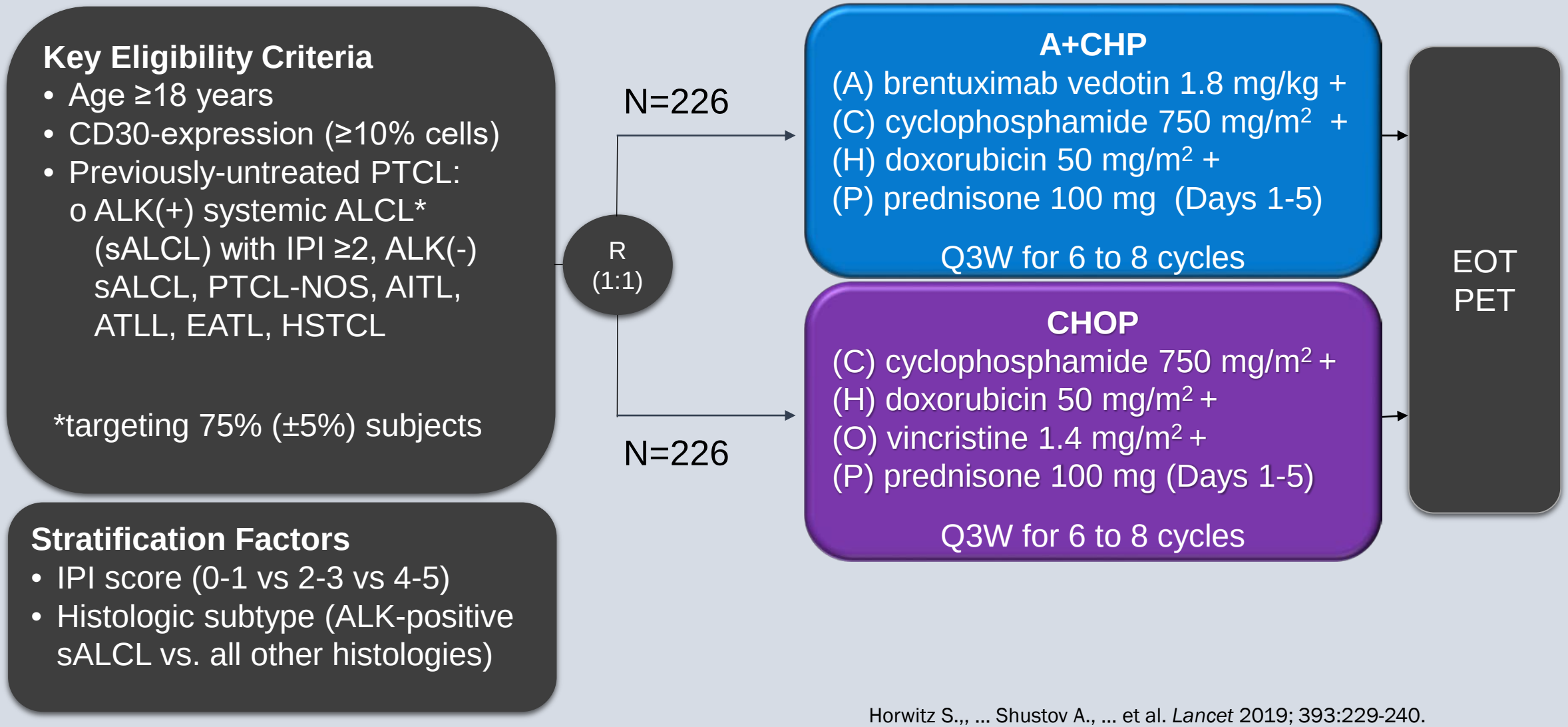
Horwitz S., ... Shustov A., et al. 2018 *J Natl Compr Canc Netw* 16(2):123-135

The Phase 3 ECHELON-2 Trial: Results of a Randomized, Double-Blind, Active-Controlled Study of Brentuximab Vedotin and CHP (A+CHP) Versus CHOP in Previously Untreated Subjects with CD30-Expressing Peripheral T-Cell Lymphomas (PTCL)

Steven Horwitz, Owen A O'Connor, Barbara Pro, Tim Illidge, Michelle Fanale, Ranjana Advani, Nancy L Bartlett, Jacob Haaber Christensen, Franck Morschhauser, Eva Domingo-Domenech, Giuseppe Rossi, Won Seog Kim, Tatyana Feldman, Anne Lennard, David Belada, Árpád Illés, Kensei Tobinai, Kunihiro Tsukasaki, Su-Peng Yeh, Andrei Shustov, Andreas Hüttmann, Kerry J Savage, Sam Yuen, Swaminathan Iyer, Pier Luigi Zinzani, Zhaowei Hua, Meredith Little, Shangbang Rao, Joseph Woolery, Thomas Manley, Lorenz Trümper

American Society of Hematology Annual Meeting; San Diego, California, December 1-4, 2018, Abstract #997

ECHELON-2 Study Design



Horwitz S.,, ... Shustov A., ... et al. *Lancet* 2019; 393:229-240.

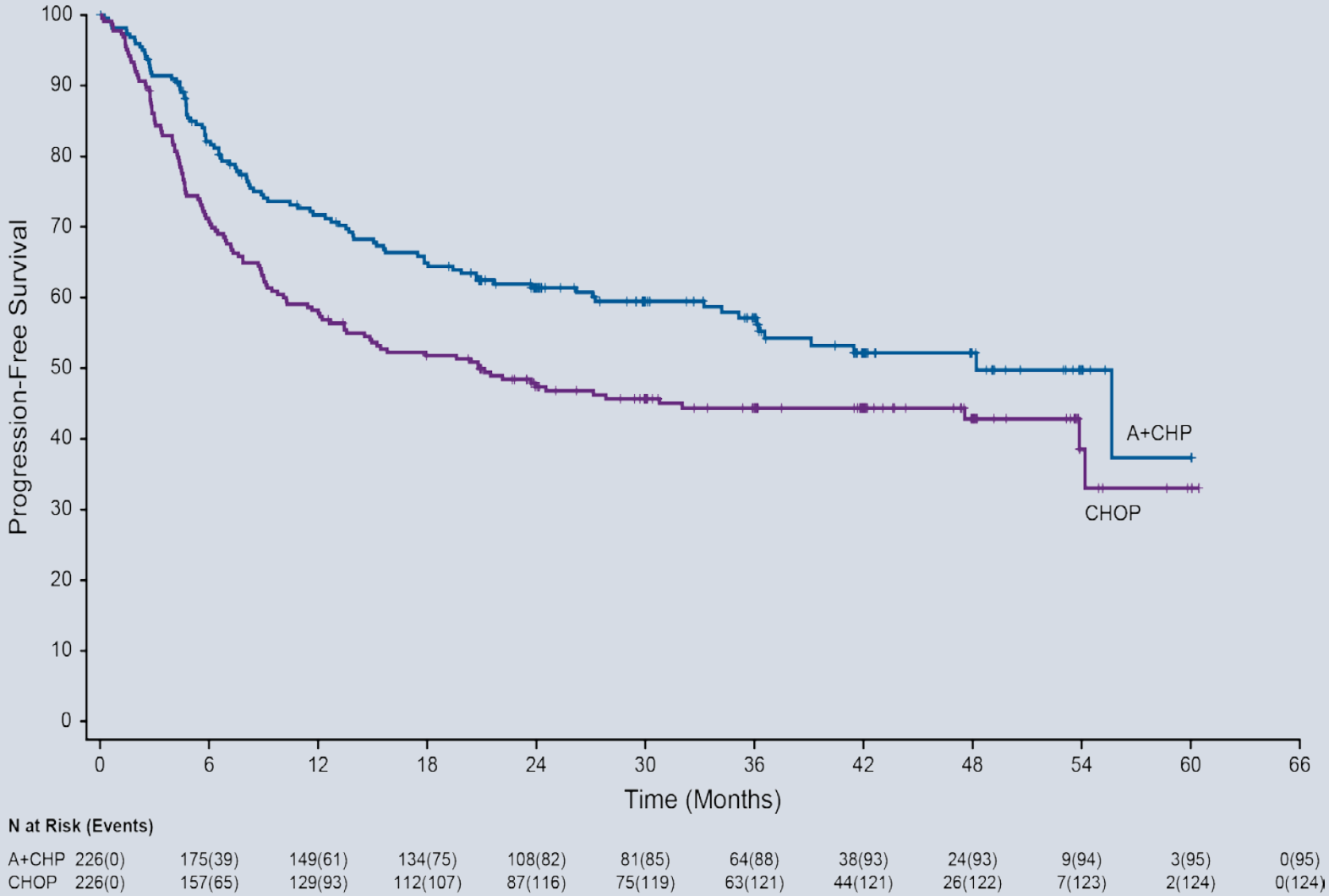
ECHELON-2: Baseline Characteristics

	A+CHP (N=226)	CHOP (N=226)
Male, n (%)	133 (59)	151 (67)
Age in years, median (range)	58 (18-85)	58 (18-83)
IPI score, n (%)		
0-1	52 (23)	48 (21)
2-3	141 (62)	145 (64)
4-5	33 (15)	33 (15)

	A+CHP (N=226)	CHOP (N=226)
Stage III/IV disease, n (%)	184 (81)	180 (80)
Disease Diagnosis, n (%)		
sALCL	162 (72)	154 (68)
ALK+	49 (22)	49 (22)
ALK-	113 (50)	105 (46)
PTCL-NOS	29 (13)	43 (19)
AITL	30 (13)	24 (11)
ATLL	4 (2)	3 (1)
EATL	1 (0)	2 (1)

Horwitz S.,, ... Shustov A., ... et al. *Lancet* 2019; 393:229-240.

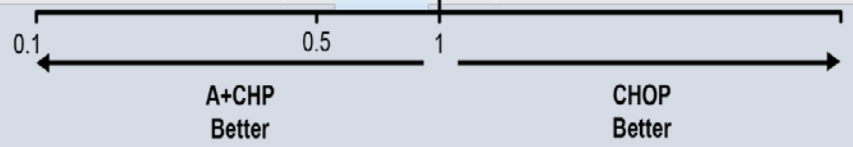
ECHELON-2: PFS



Horwitz S.,, ... Shustov A., ... et al. *Lancet* 2019; 393:229-240.

ECHELON-2: Prespecified Subset Analyses

ITT Subgroups	Event/N A+CHP	Event/N CHOP	Hazard Ratio (95% CI)
Overall	95/226	124/226	0.71 (0.54, 0.93)
IPI Score			
0–1	18/52	27/48	0.53 (0.29, 0.97)
2–3	56/141	77/145	0.71 (0.50, 1.00)
4–5	21/33	20/33	1.03 (0.55, 1.92)
Age			
<65 years	54/157	75/156	0.67 (0.47, 0.95)
≥65 years	41/69	49/70	0.70 (0.46, 1.08)
Gender			
Male	59/133	80/151	0.80 (0.57, 1.13)
Female	36/93	44/75	0.49 (0.31, 0.78)
Baseline ECOG Status			
0/1	76/174	105/179	0.66 (0.49, 0.89)
2	19/51	19/47	0.98 (0.51, 1.87)
Disease Stage			
I/II	15/42	19/46	0.95 (0.48, 1.88)
III	29/57	35/67	0.69 (0.42, 1.14)
IV	51/127	70/113	0.64 (0.45, 0.93)
Disease Indication			
ALK-positive sALCL	5/49	16/49	0.29 (0.11, 0.79)
ALK-negative sALCL	50/113	60/105	0.65 (0.44, 0.95)
AITL	18/30	13/24	1.40 (0.64, 3.07)
PTCL-NOS	19/29	31/43	0.75 (0.41, 1.37)



Horwitz S.,, ... Shustov A., ... et al. *Lancet* 2019; 393:229-240.

Special Management Scenarios

- Subcutaneous Panniculitis-Like T-cell Lymphoma
  - Never CHOP
  - Bexarotin, Pralatrexate, Combination ±Prednisone
  - Cyclosporin A, Hydroxychloroquine
- T-cell Prolymphocytic Leukemia
  - Never CHOP
  - Alemtuzumab ±Pentostatin; Allogeneic SC Transplant
  - Bendamustin

Special Management Scenarios

- Hepatosplenic T-cell Lymphoma; Other Gamma-Delta T-cell Lymphomas
  - Never CHOP
  - DHAP, ESHAP followed by Allogeneic SC Transplant
  - Hyper-CVAD followed by Allogeneic SC Transplant
- Large Granular Lymphocyte Disorder with Autoimmune Cytopenias
  - Never CHOP
  - Low-dose oral Methotrexate, Cyclosporine A, Prednisone, Growth Factors
  - Alemtuzumab in low doses

Special Management Scenarios

- Indolent Lymphoproliferative Disorder of the GI tract
  - Never CHOP
  - DO NOT TREAT asymptomatic patients
- Management of older patients with newly Dx PTCL
  - Strongly consider palliative intent from the time of Dx (Ex. ALCL)
  - AITL is a paradigm of the epigenetic malignancy

Special Management Scenarios

- Early stage extranodal NK-cell lymphoma, nasal-nasal type
  - Concurrent DEVIC + XRT
  - Concurrent VIPD + XRT
  - XRT ± Cisplatin in older patients.
- Advanced stage extranodal NK-cell lymphoma, nasal type
  - SMILE in younger fit patients, L-Aspa-Dex in older patients
  - Autologous or allogeneic HCT could be considered.

Special Management Scenarios

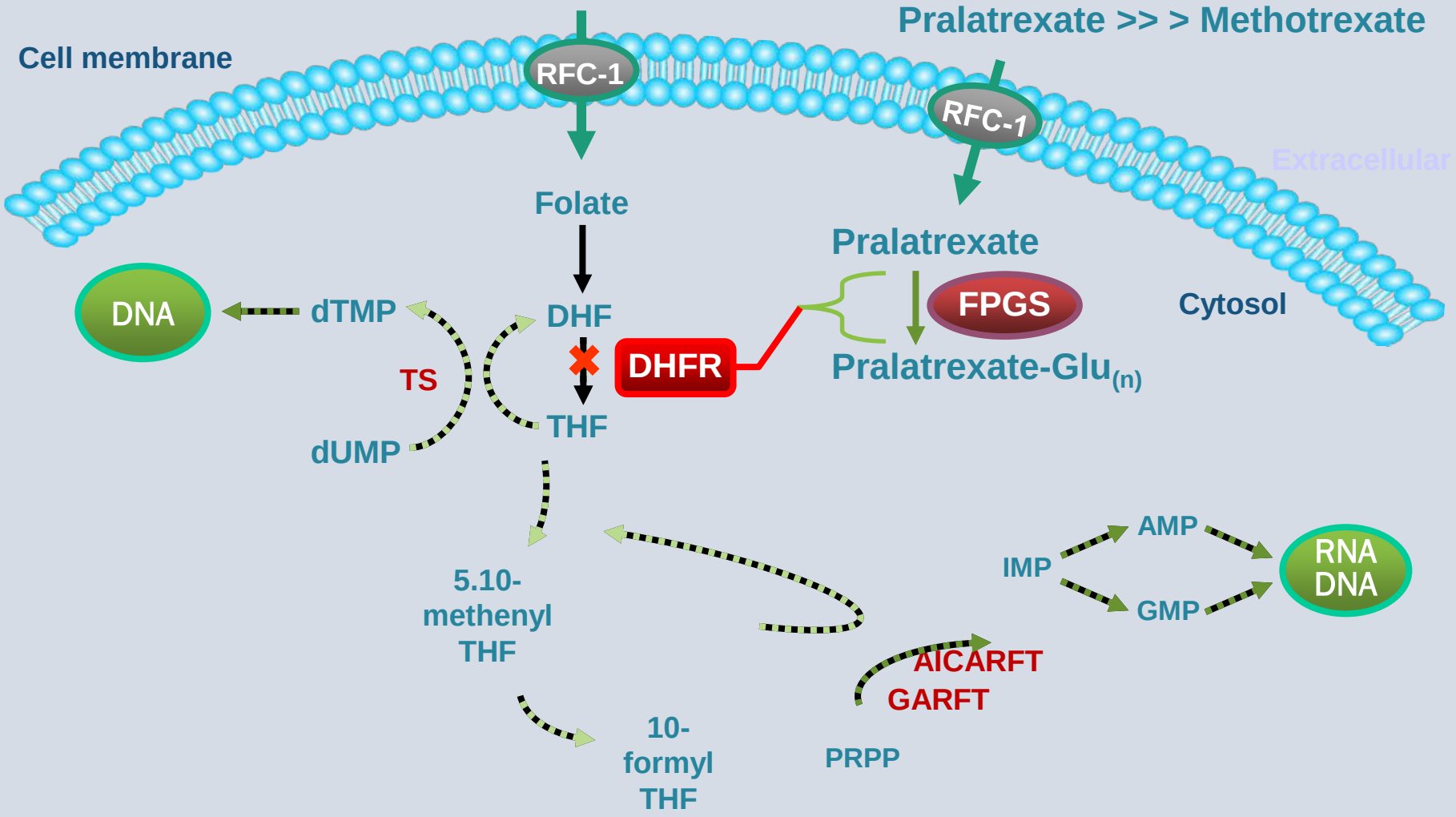
- Genomic or Targeted Genomic Testing
  - AITL: TET2, IDH1/2, RHOA
  - ALK- ALCL: DUSP22, TP63
  - LGL: STAT3, STAT5
  - PTCL-NOS: Full panel (?)
  - Other PTCLs: Full panel (?)

FDA-Approved Agents in PTCL

- PTCL
  - Pralatrexate
  - Romidepsin
  - Brentuximab Vedotin (ALCL)
  - Belinostat

- CTCL
  - Vorinostat
  - Bexarotin
  - Romidepsin
  - Brentuximab Vedotin (CD30+ CTCL)
  - Mogamulizumab (CTCL)

Pralatrexate: Mechanism of Action



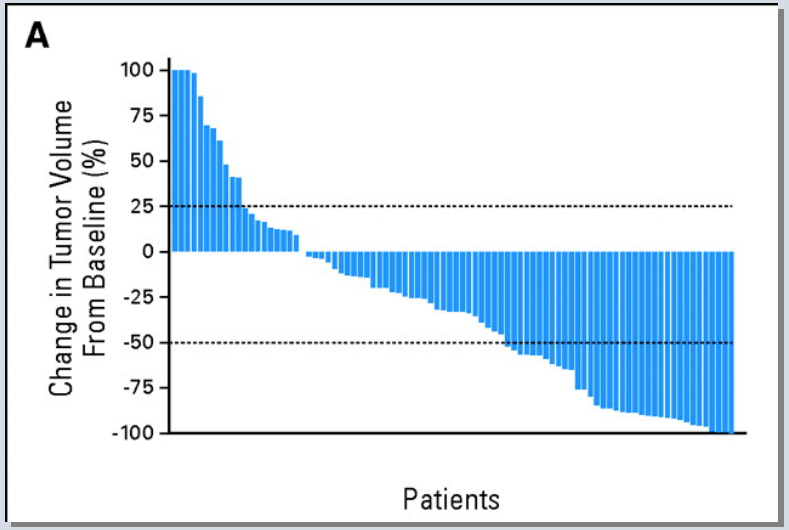
Phase II Trial of Pralatrexate in Relapsed or Progressive Peripheral T-Cell Lymphoma Following Prior Systemic Therapy

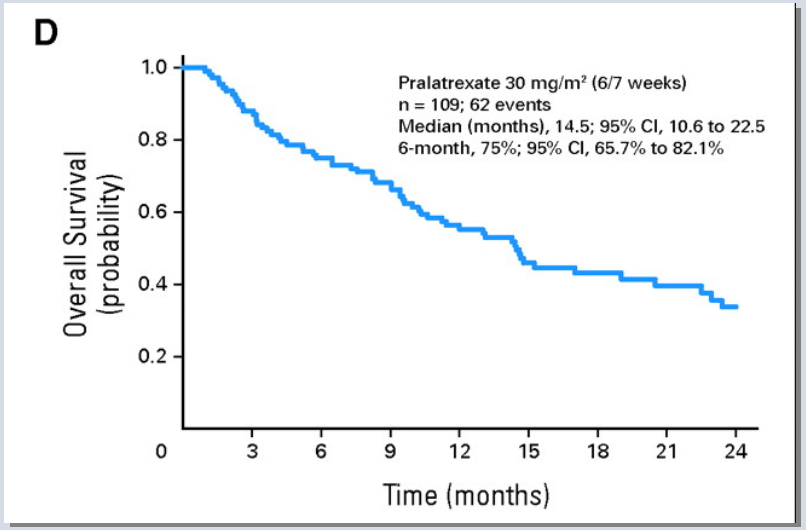
- Patient population:
  - 113 enrolled
  - 109 with confirmed PTCL
  - Failed ≥1 prior systemic therapy
- Treatment regimen: Pralatrexate 30 mg/m^2, weekly X 6 / 7 weeks
- Primary endpoint: CR/CRu by independent review
- Secondary endpoints including: ORR, duration of response, TTP, tolerability, and safety

O'Connor O., ... Shustov A., et al. *J Clin Onc* 2011; 29:1182-89

Pralatrexate in Relapsed/Refractory PTCL

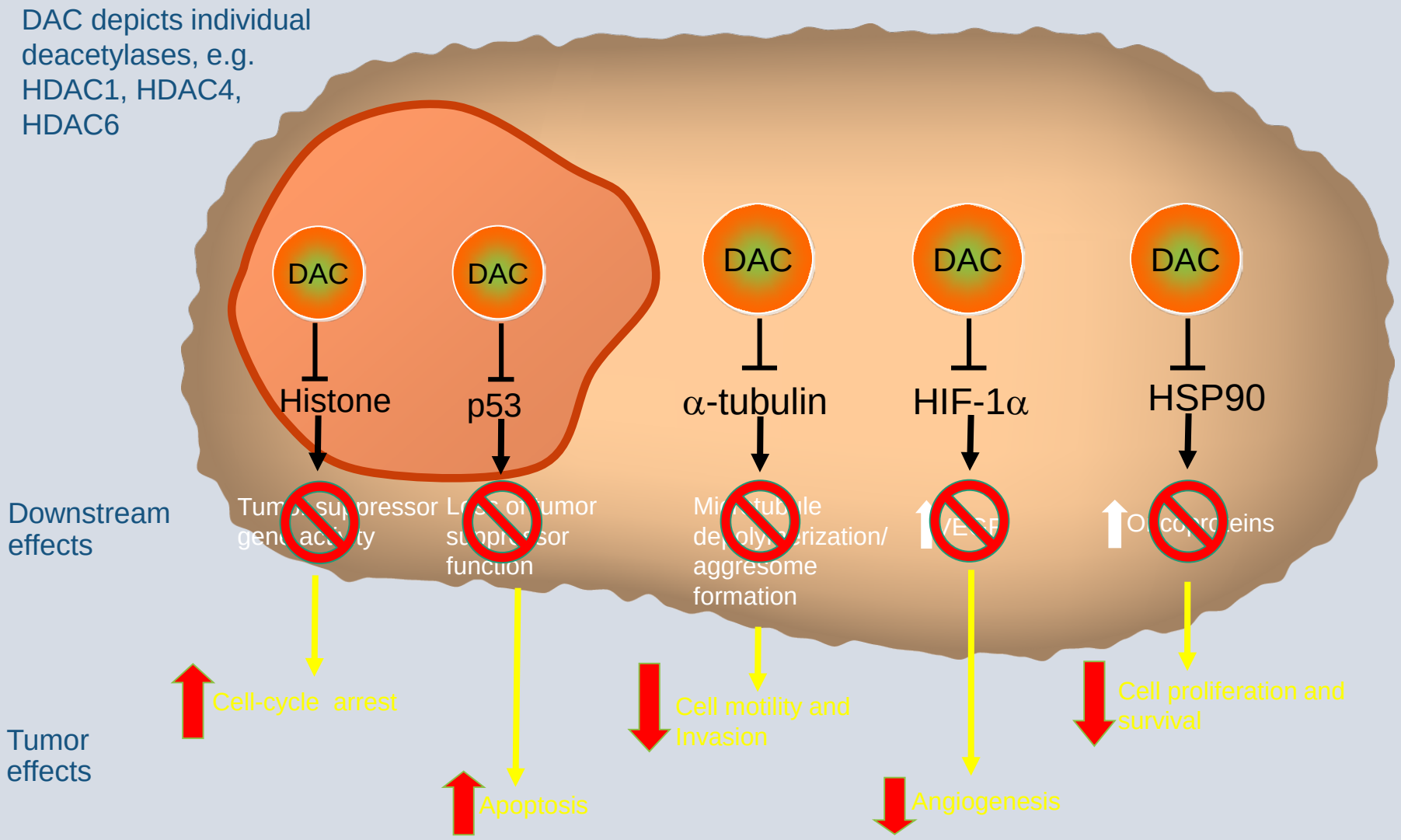
Response	Independent Review Committee Analysis (n = 109)
Overall Response Rate	32 (29%)
Complete response	12 (11%)
Partial response	20 (18%)
Median DOR, mo (95% CI)	10.1 (3.4-NE)
Median PFS, mo (95% CI)	3.5 (1.7-4.8)





O'Connor O., ... Shustov A., et al. *J Clin Onc* 2011; 29:1182-89

HDAC Inhibition



Phase II Trial of Romidepsin in Relapsed or Progressive Peripheral T-Cell Lymphoma Following Prior Systemic Therapy

- Patient population:
  - 131 enrolled
  - 130 with confirmed PTCL
  - Failed ≥1 prior systemic therapy
- Treatment regimen: romidepsin 14 mg/m^2, days 1, 8, and 15 q 28 days × 6 cycles; continued beyond 6 cycles in responding patients at investigator and patient discretion
- Primary endpoint: CR/CRu by independent review
- Secondary endpoints including: ORR, duration of response, TTP, tolerability, and safety

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

Romidepsin in Relapsed Peripheral T-Cell Lymphoma

Response	Independent Review Committee Analysis (n = 130)
Overall Response Rate	34 (26%)
Complete response	10 (8%)
Unconfirmed complete response	7 (5%)
Duration of Response	**Median (Range)**
Overall	12 (<1.0-26.0+) months
Complete response/unconfirmed complete response	Not reached (<1.0-26.3+) months)

- Responses reported in PTCL (not otherwise specified) (29%), angioimmunoblastic TCL (33%), and ALK1$^-$ ALCL (24%)
- Similar response rates in patient subgroups according to number of prior therapies (<3 vs ≥3), prior SCT (yes vs no), and refractory to most recent therapy (yes vs no)

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

BELIEF: Belinostat Phase 2 Trial in Relapsed and Refractory PTCL

- Patient population:
  - 129 enrolled
  - 120 evaluable PTCL
  - Failed ≥1 prior systemic therapy
- Treatment regimen: belinostat 1,000 mg/m^2, IV days 1-5, q 21 days
- Primary endpoint: ORR by independent review
- Secondary endpoints including: CR, DOR, TTP, tolerability, and safety

O'Connor O., ..., and Shustov, A. *J Clin Oncol.* 2015;33(23):2492-2499.

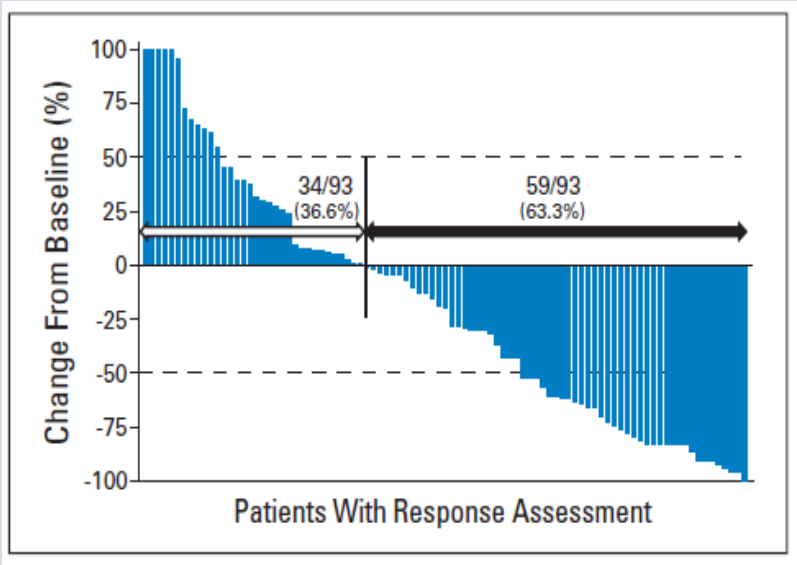
BELIEF: Belinostat Phase 2 Trial

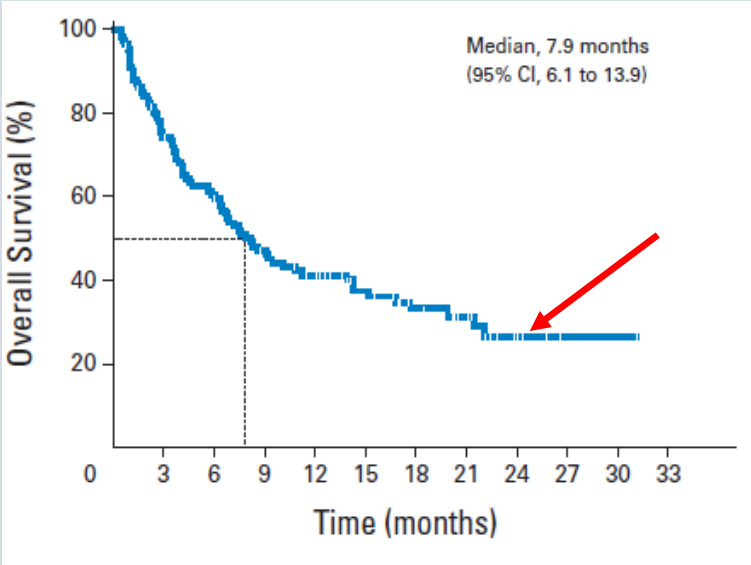
	Efficacy Analysis Set (N=120)	
Response	n (%)	(95% CI)
ORR	31 (26)	(18-35)
CR	13 (11)	(6-18)
PR	18 (15)	
SD	18 (15)	
PD	48 (40)	
NE	23 (19)	

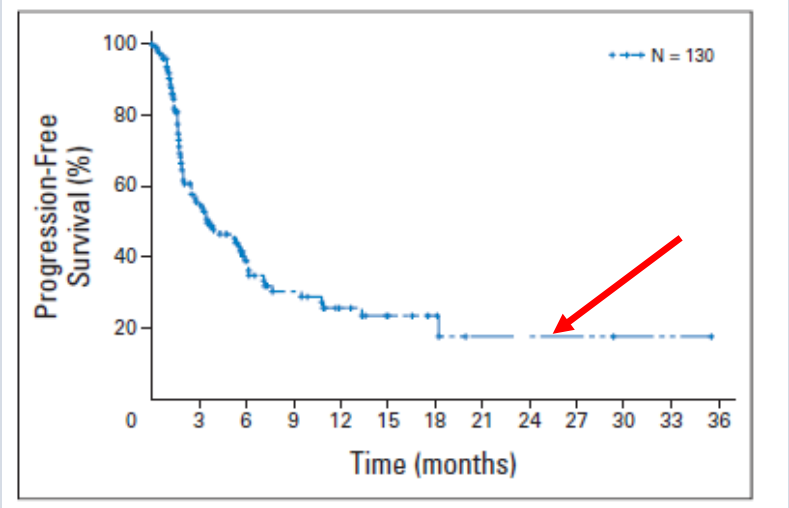
NE= not evaluable due to death (n=7), clinical progression (n=10), patient withdrawal (n=5), or lost to follow-up (n=1) prior to first radiologic assessment.

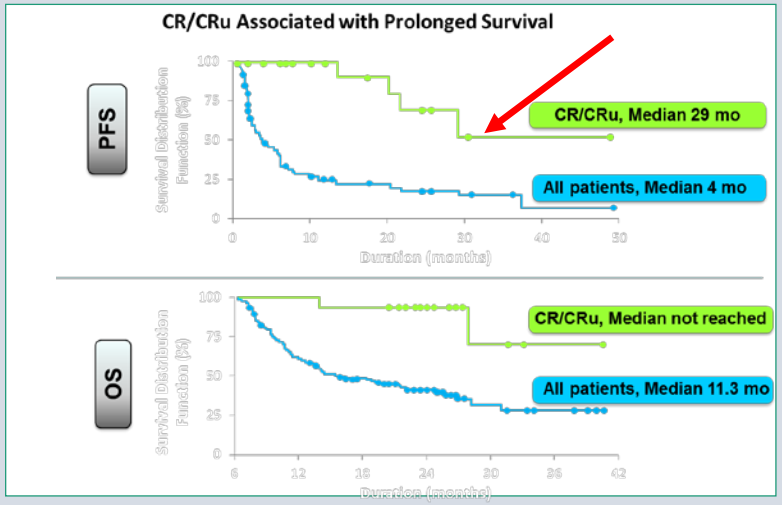
O'Connor O., ..., and Shustov, A. *J Clin Oncol.* 2015;33(23):2492-2499.

HDACi Are Not Fully Understood

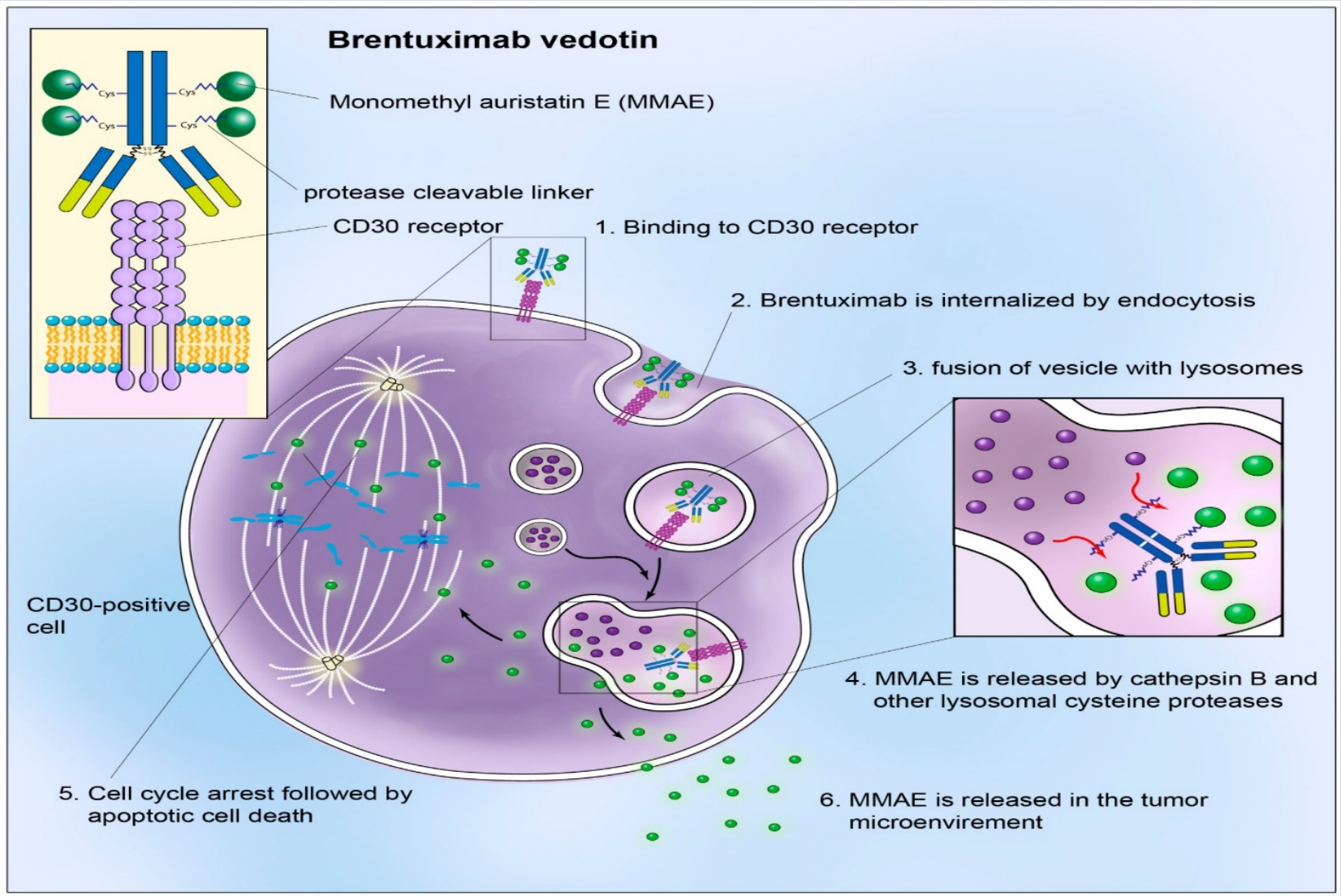








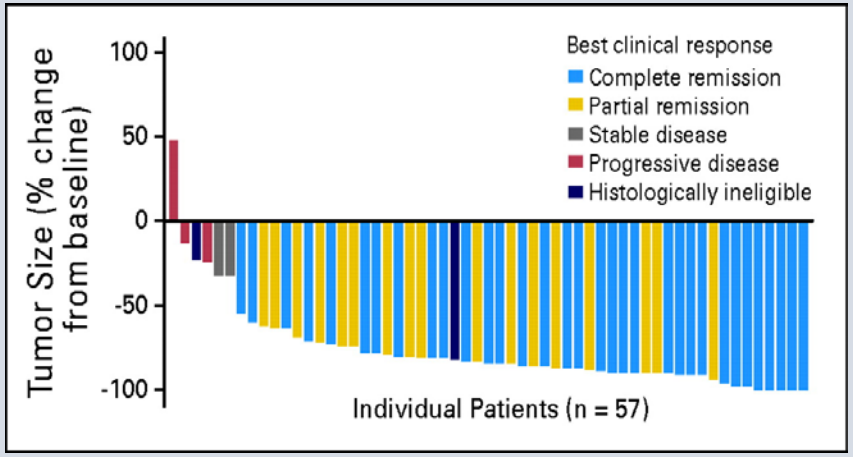
Brentuximab Vedotin: Mechanism of Action

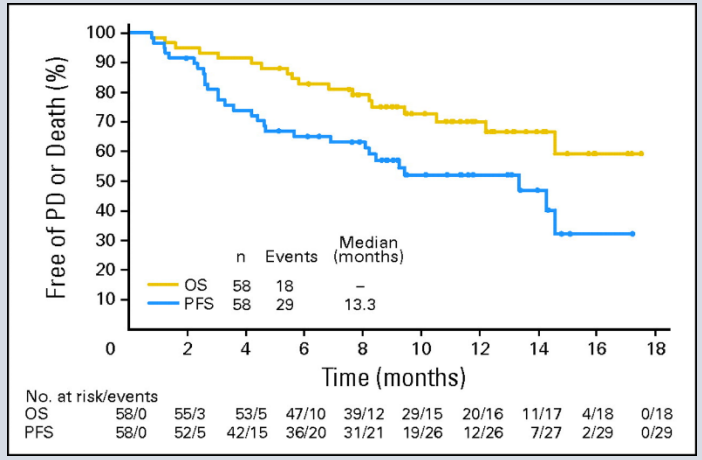


Repr. from Shustov A. *Ther Adv Hematol*. 2013

B-VEDOTIN IN RELAPSED/REFRACTORY ALCL

Measure	Central Review (IWC)	
	N (58)	% (95% CI)
Overall response (CR + PR)	50	86 (75-94)
Complete response (CR+CRu)	33	57 (43-70)
Partial response (PR)	17	29 (NE)
Median DOR, mo (95% CI)	12.6	5.7 - NE
Median PFS, mo (95% CI)	13.3	6.9 - NE





Pro B., …., and Shustov, A. *J Clin Onc* 2012;30(18):2190-96

CD30 Across Most PTCL Subtypes vs ALCL: International PTCL Study

Subtype (n)	CD30 Expression (%)			
	0-5%	6-49%	50-80%	>80%
PTCL-NOS (168)	54	32	7	7
AITL (167)	55	42	2	1
EATL (27)	74	11	4	11
ATLL (120)	50	37	8	5
Nasal NK/T (73)	53	34	6	7
Extranasal NK/T (30)	27	27	23	23

Courtesy of Dennis Weisberger, University of Nebraska.

Brentuximab Vedotin in Relapsed Non-ALCL PTCL

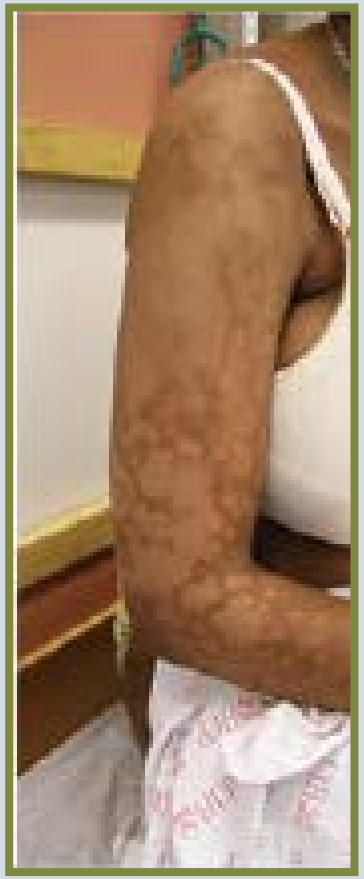
	AITL (n=13)	PTCL-NOS (n=21)	Total (N=34)
ORR	7 (54%)	7 (33%)	14 (41%)
Complete remission	5 (38%)	3 (14%)	8 (24%)
Partial remission	2 (15%)	4 (19%)	6 (18%)
Stable disease	3 (23%)	3 (14%)	6 (16%)
Progressive disease	3 (23%)	11 (52%)	14 (41%)
Progression-free survival	6.74 mo	1.61 mo	2.6 mo

- Comparatively restricted patient population (PTCL-NOS and AILT **ONLY**)
- Short duration of DOR/PFS compared to other agents (DOR ~2 months)
- Not a heavily treated patient population (median prior therapies=2)

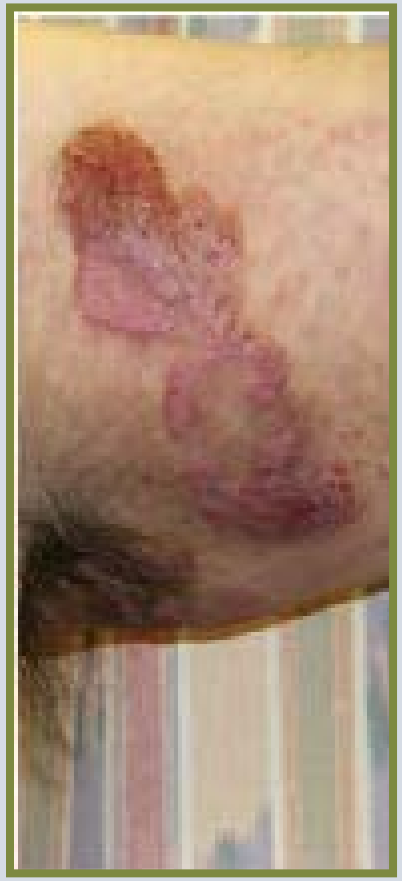
Horwitz S, et al. *Blood*, 2014; 123(20):3095-3100.

CTCL

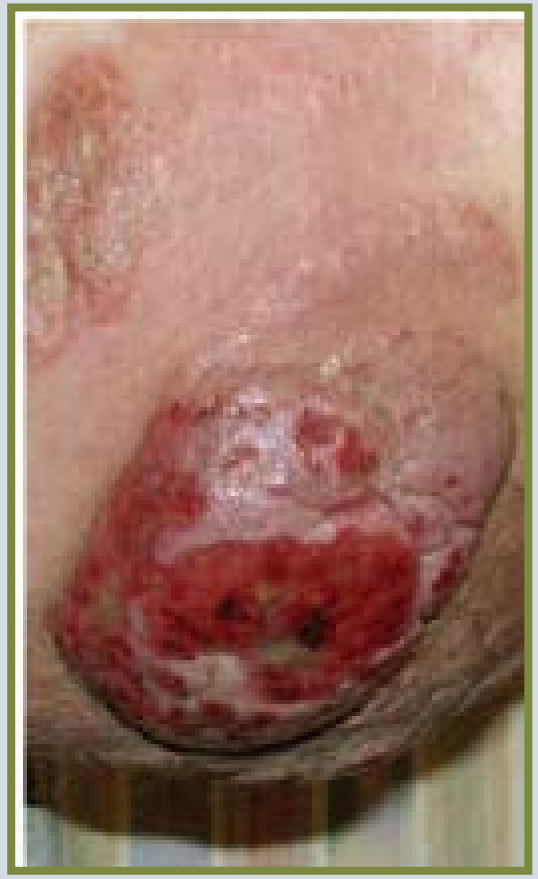
Cutaneous T-Cell Lymphoma
Cutaneous Manifestations



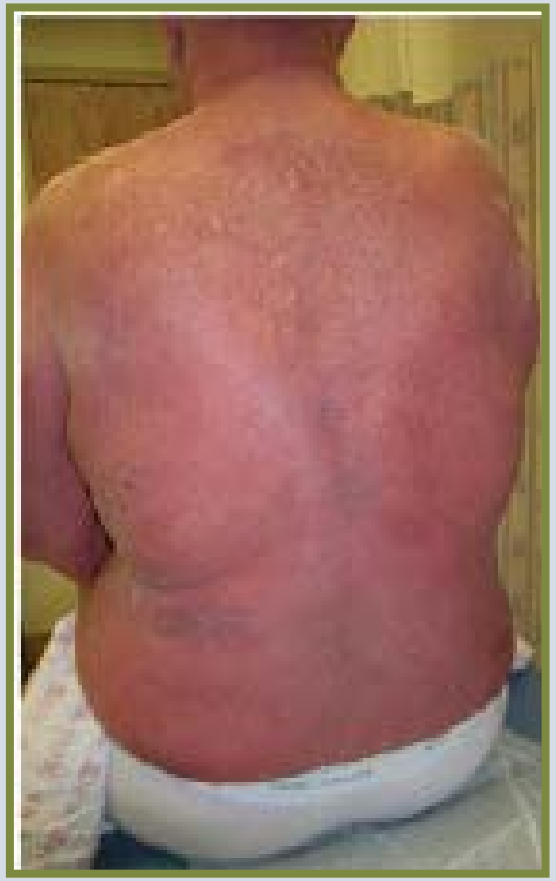
Patch



Plaque



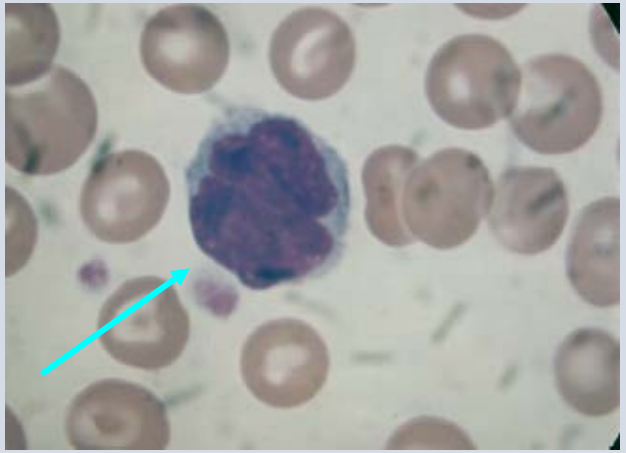
Tumor



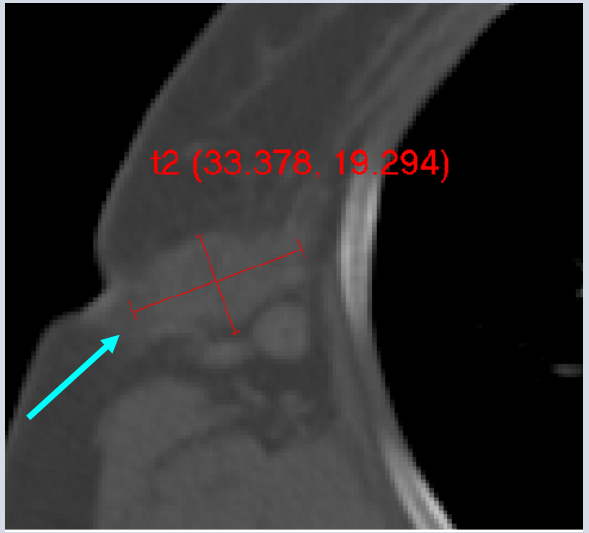
Erythroderma

Kim EJ, et al. *J Clin Invest*. 2005;115:798-812.

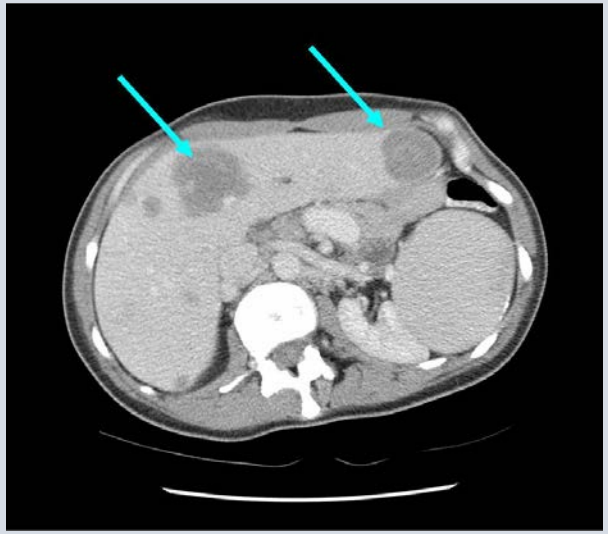
Cutaneous T-Cell Lymphoma
Extracutaneous Manifestations



Blood (Sézary cell)



Lymph node



Viscera

Cutaneous T-cell Lymphoma
ISCL/EORTC Updated Staging System

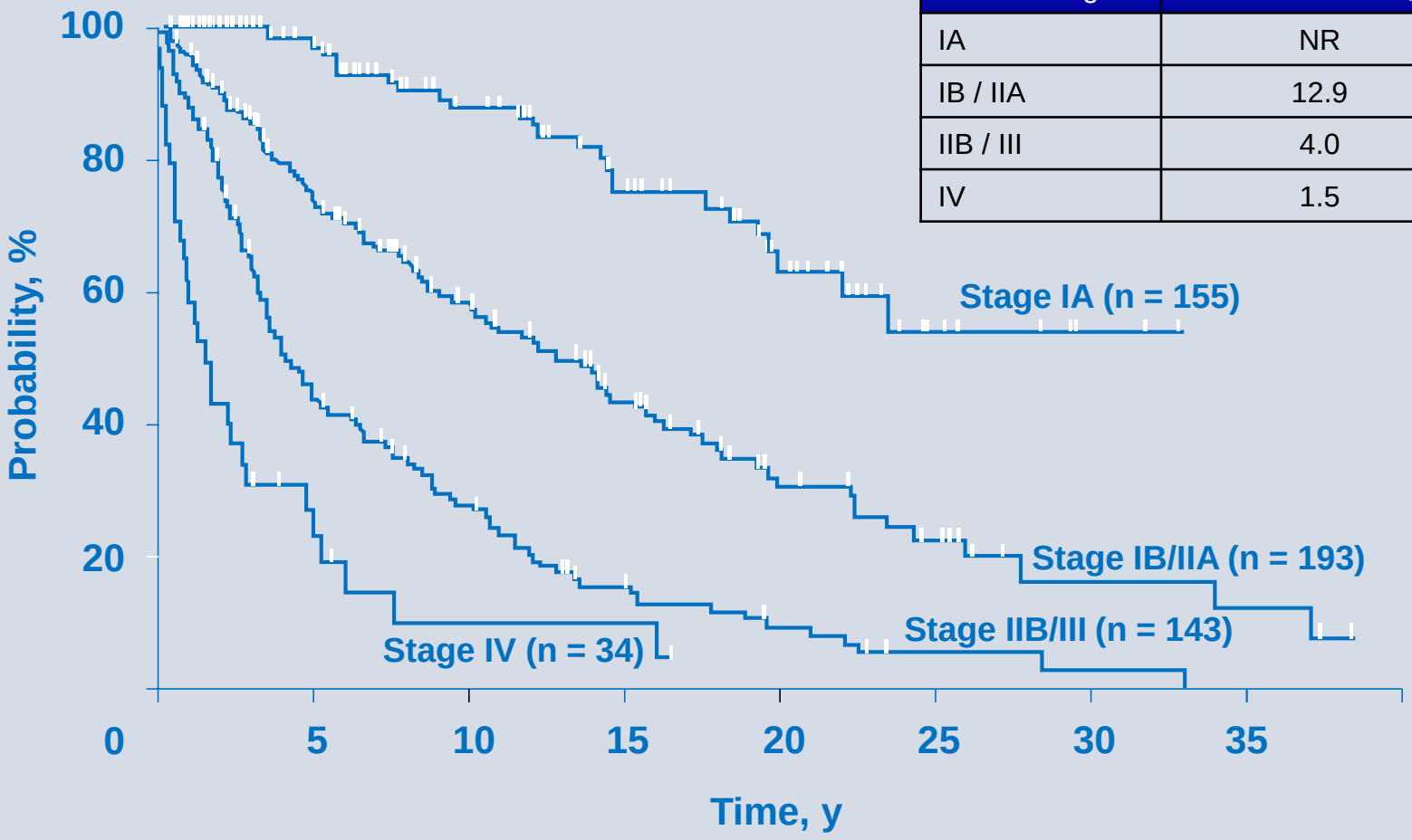
Clinical Stage	T	N	M	B
IA	1	0	0	0,1
IB	2	0	0	0,1
II	1,2	1,2	0	0,1
IIB	3	0-2	0	0,1
III	4	0-2	0	0,1
IIIA	4	0-2	0	0
IIIB	4	0-2	0	1
IVA_1	1-4	0-2	0	2
IVA_2	1-4	3	0	0-2
IVB	1-4	0-3	1	0-2

Olsen E, et al. *Blood*. 2007;110:1713-1722.

CTCL, cutaneous T-cell lymphoma; EORTC, European Organization of Research and Treatment of Cancer; ISCL, International Society for Cutaneous Lymphomas.

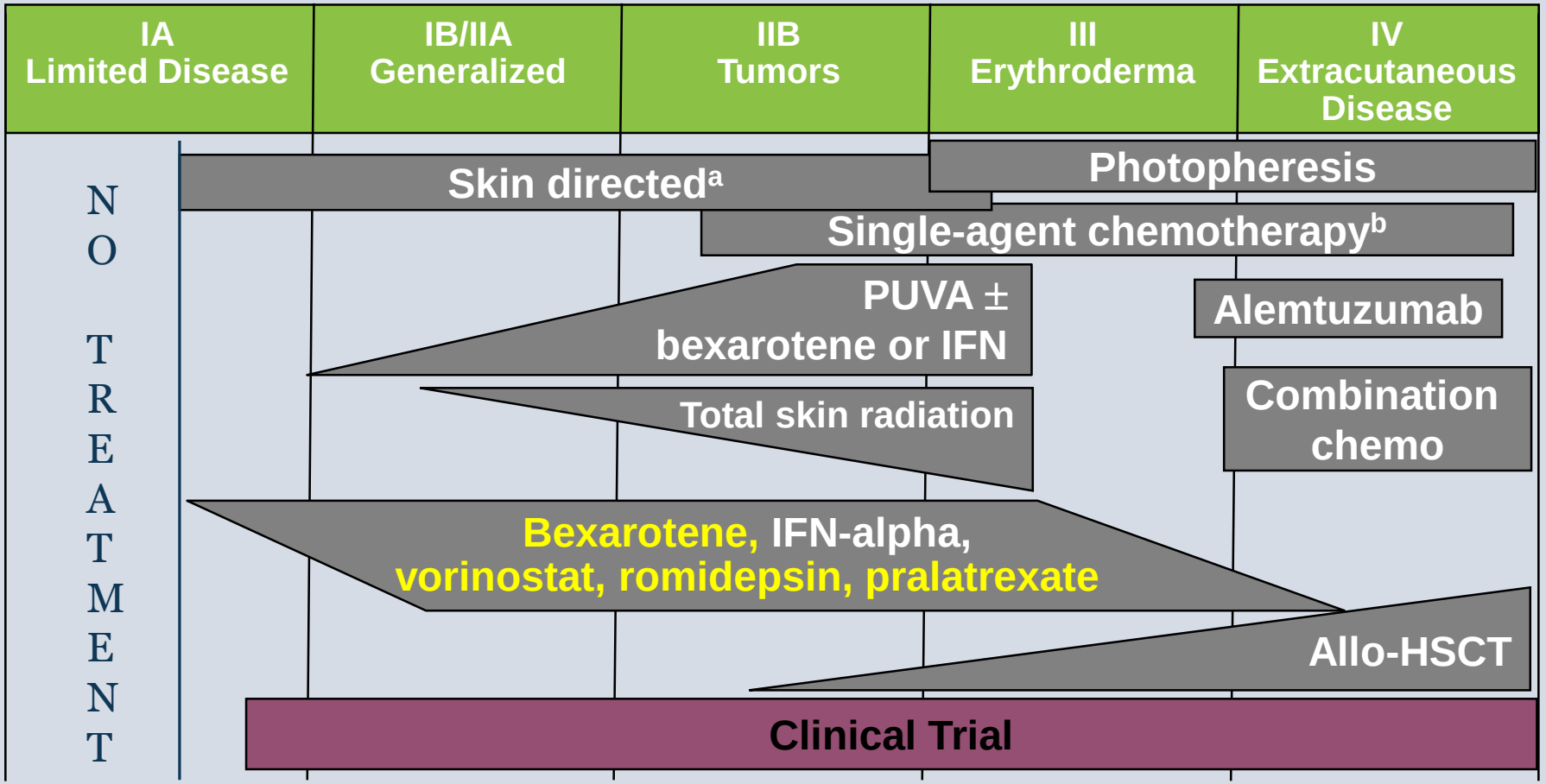
Overall Survival by Clinical Stage

Clinical Stage	Median Survival, y	5-yr OS,%
IA	NR	96
IB / IIA	12.9	73
IIB / III	4.0	44
IV	1.5	27



Kim YH, et al. *Arch Dermatol*. 2003;139:857-866.

CTCL: NCCN Practice Guidelines 2018



NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas. V.1.2018.

FDA Approved Systemic Agents in Cutaneous T-Cell Lymphoma

Agent (Class)	CTCL Indication	Study	N	Stage	ORR	DOR
Bexarotene (Retinoid x-receptor activator)[1]	Cutaneous manifestations	Pivotal	62	IIB-IVB	32%	5+ mo
Vorinostat (HDAC inhibitor)[2,3]	Cutaneous manifestations	Pivotal	74	IA-IVB	30%	6+ mo
		Supportive	33	IA-IVB	24%	4 mo
Romidepsin (HDAC inhibitor)[4]	Cutaneous TCL	Pivotal	96	IB-IVA	34%	15 mo
		Supportive	71	IA-IVB	35%	11 mo

[1]Miller V, et al. *J Clin.Onc.,* 1997; 15(2): 790-95

[2]Duvic M, et al., *Blood*, 2007; 109(1): 31-39

[3]Olsen E, et al. *J Clin.Onc.,* 2007; 25(21): 3109-15

[4]Piekarz R, et al. *J Clin.Onc.,* 2009; 27(32): 5410-16

Non-Approved Systemic Agents in Cutaneous T-Cell Lymphoma

Agent (Class)	Use in CTCL	Study	N	Stage	ORR	DOR
Pralatrexate (Anti-folate)[1]	Advanced CTCL	Phase I-II	54	IB-IVA	45%	NR mo
Liposomal Doxorubicin (Anthracycline)[2]	Advanced CTCL	Phase II	49	IIB-IVB	41%	6 mo
Gemcitabine (Anti-metabolite)[3]	Advanced CTCL	Phase II	44	IIB-IVB	70%	12 mo

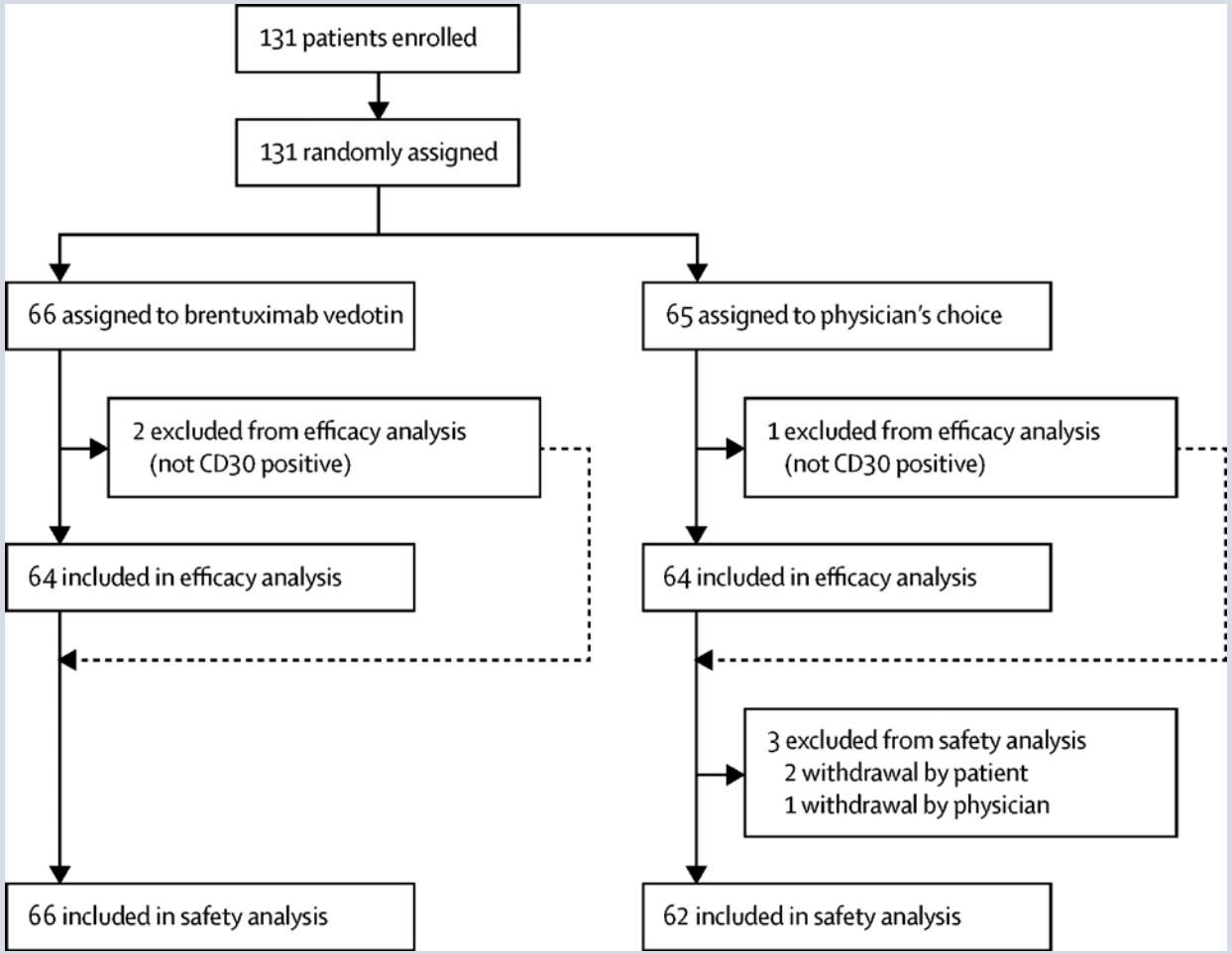
[1]Horwitz S.,... Shustov A, et al., *Blood*, 2012; 119(18): 4115-22

[2]Dummer R. et al., *J Clin. Onc.*, 2012; 30(33): 4091-97

[3]Zinzani PL, et al. *J Clin.Onc., 2000; 18(13): 2603-06*

CTCL: 2019 Update

Phase III Randomized Trial of Brentuximab Vedotin vs. Physician's Choice in Cutaneous CD30+ T-Cell Lymphoma (ALCANZA)



- Dx: CD30+ MF or pcALCL (>10% CD30+ cells)
- ≥ 1 prior systemic therapy failure
- Treatment regimen: B-vedotin 1.8 mg/kg q 21 days; MTX 5-50 mg PO QW; Bexarotene 300 mg/sqm PO QD
- Primary endpoint: OGR lasting ≥ 4 months per independent review
- Secondary endpoints including: CR, DOR, PFS, Symptom Improvement, and safety/tolerability

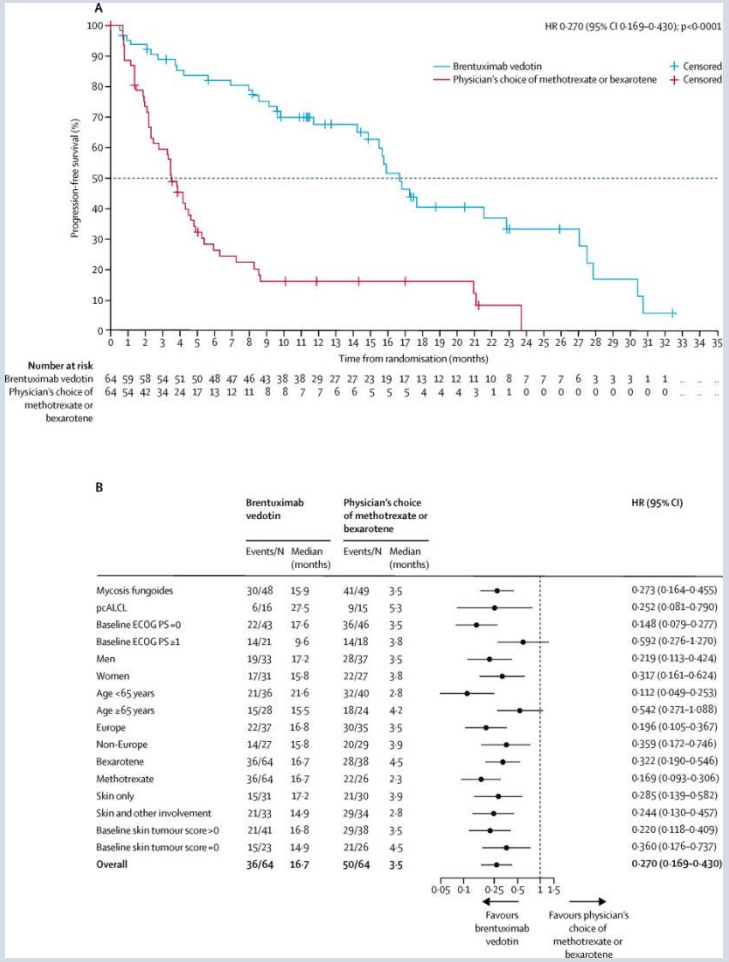
Miles P, et al. *Lancet* 2017;390: 555-566.

Phase III Randomized Trial of Brentuximab Vedotin vs. Physician's Choice in Cutaneous CD30+ T-Cell Lymphoma (ALCANZA)

	Brentuximab vedotin				Physician's choice of methotrexate or bexarotene			
	Total (n=64)	ORR4	ORR	CR	Total (n=64)	ORR4	ORR	CR
ITT population	64 (100%)	36 (56%)*	43 (67%)	10 (16%)	64 (100%)	8 (13%)†	13 (20%)	1 (2%)
Mycosis fungoides	48 (75%)	24 (50%)	31 (65%)	5 (10%)	49 (77%)	5 (10%)	8 (16%)	0
Stage‡§								
IA–IIA	15 (31%)	6 (40%)	8 (53%)	1 (7%)	18 (37%)	4 (22%)	5 (28%)	0
IIB	19 (40%)	12 (63%)	13 (68%)	3 (16%)	19 (39%)	1 (5%)	3 (16%)	0
IIIA–IIIB	4 (8%)	2 (50%)	3 (75%)	0	2 (4%)	0	0	0
IVA	2 (4%)	2 (100%)	2 (100%)	1 (50%)	9 (18%)	0	0	0
IVB	7 (15%)	2 (29%)	4 (57%)	0	0	NA	NA	NA
pcALCL	16 (25%)	12 (75%)	12 (75%)	5 (31%)	15 (23%)	3 (20%)	5 (33%)	1 (7%)
Disease involvement‡								
Skin only	9 (56%)	8 (89%)	8 (89%)	4 (44%)	11 (73%)	3 (27%)	5 (45%)	1 (9%)
Extracutaneous disease	7 (44%)	4 (57%)	4 (57%)	1 (14%)	4 (27%)	0	0	0

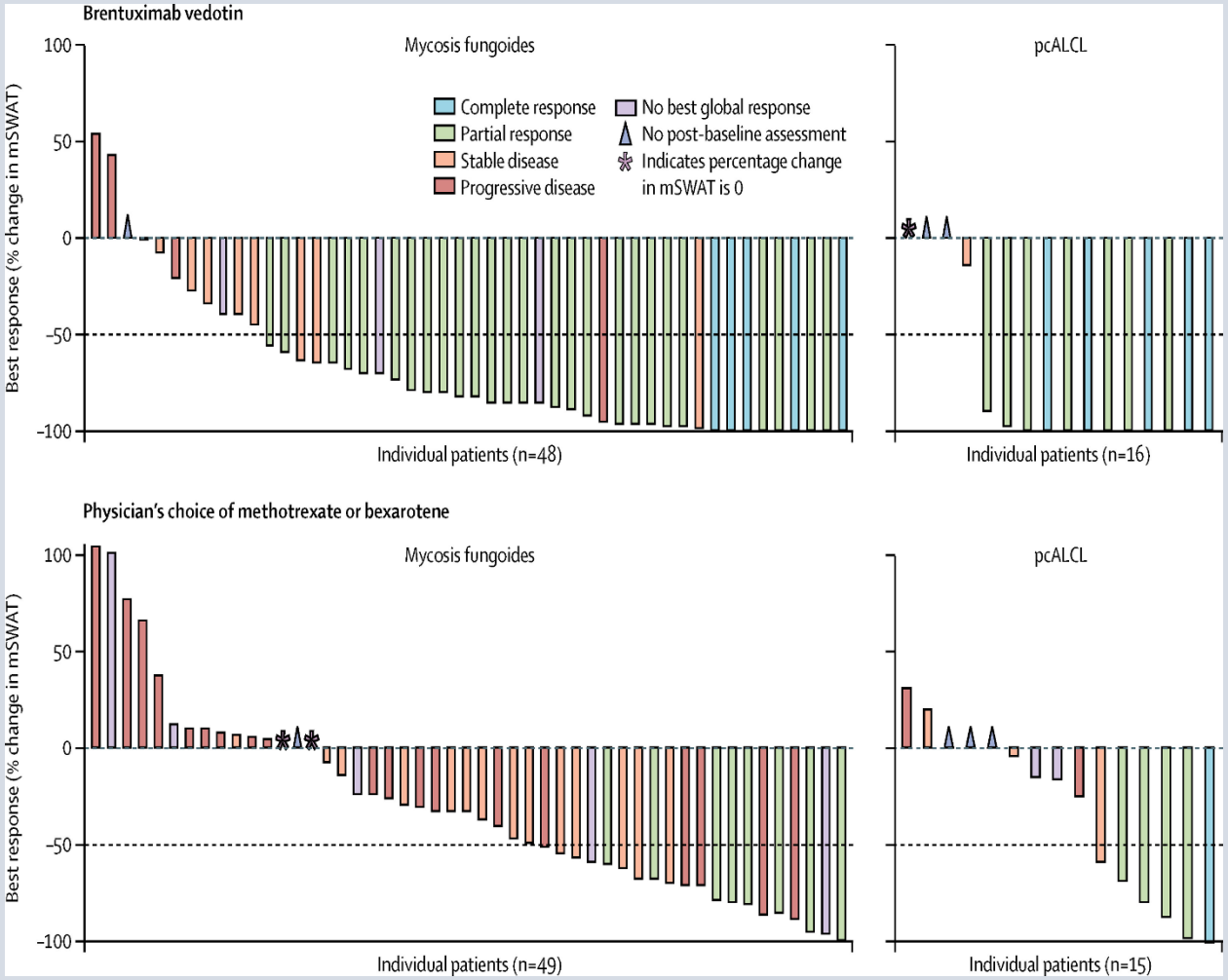
Data are n (%). ORR4, ORR, and CR percentages are based on the number of patients in the total column. ORR4=achieved an objective response lasting at least 4 months. ORR=achieved an objective response. CR=achieved a complete response. ITT=intent to treat. NA=not applicable. pcALCL=primary cutaneous anaplastic large-cell lymphoma. *One patient with mycosis fungoides in the brentuximab vedotin group achieved a partial response after C1, C2, and C3, and discontinued because of an adverse event. About 4·3 months later the patient received chemotherapy (gemcitabine) before end-of-treatment visit. Total duration of response, including after receipt of gemcitabine, was 4·8 months. †One patient with pcALCL in the bexarotene group who achieved partial response after C2 and sustained it at C5 chose to withdraw from treatment. The patient received subsequent therapy (methotrexate) about 3·5 months into the response to bexarotene but before end-of-treatment visit. Total duration of response, including after receipt of methotrexate, was 4·4 months. ‡Percentage in each subcategory in the total column is based on the number of patients in each disease subtype. §One patient in each group had incomplete staging data and are not included in the table: one patient in the brentuximab vedotin group had partial response and one patient in the physician's choice group had no response.

Table 2: **Patient responses by clinical stage at baseline**

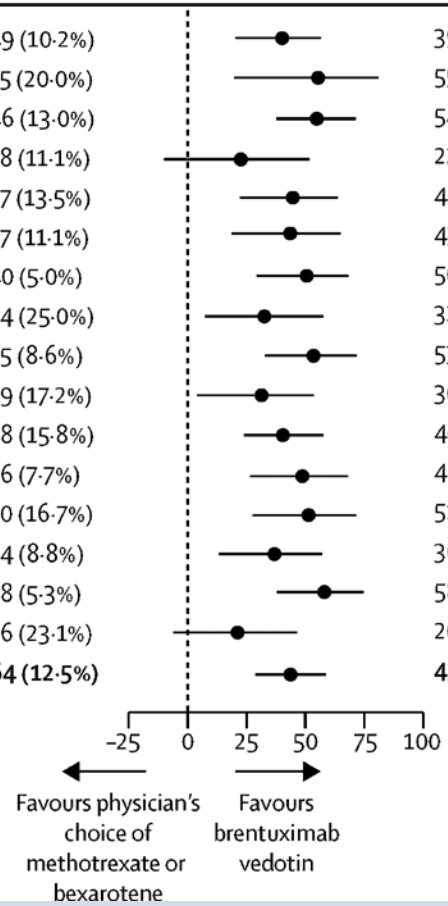


Miles P, et al. *Lancet* 2017;390: 555-566.

Phase III Randomized Trial of Brentuximab Vedotin vs. Physician's Choice in Cutaneous CD30+ T-Cell Lymphoma (ALCANZA)

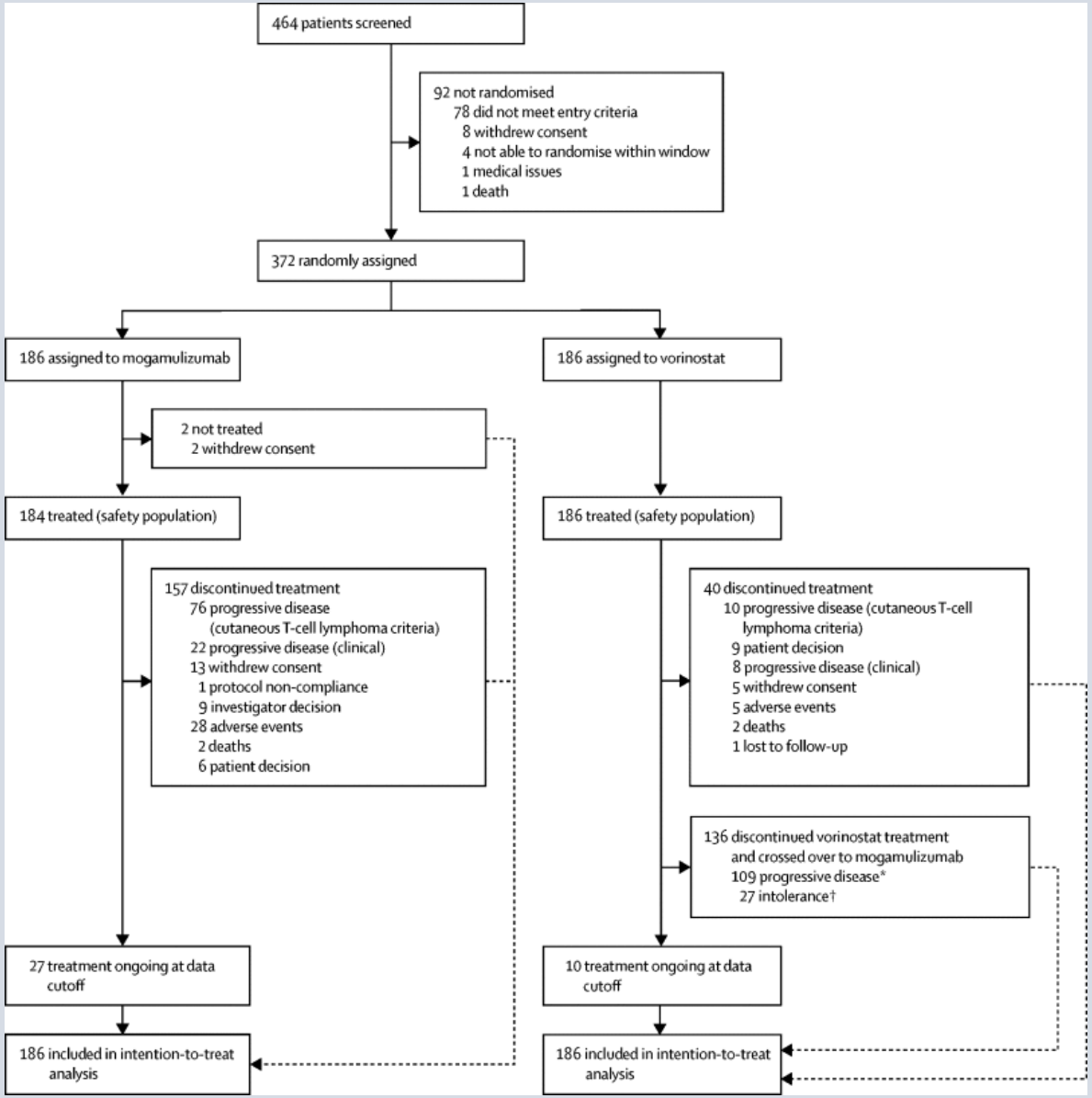


	Brentuximab vedotin, n/N (%)	Physician's choice of methotrexate or bexarotene, n/N (%)	Difference in percentages (95% CI)
Mycosis fungoides	24/48 (50·0%)	5/49 (10·2%)	39·8 (19·9 to 56·2)
pcALCL	12/16 (75·0%)	3/15 (20·0%)	55·0 (19·7 to 80·4)
Baseline ECOG PS=0	29/43 (67·4%)	6/46 (13·0%)	54·4 (37·3 to 71·5)
Baseline ECOG PS≥1	7/21 (33·3%)	2/18 (11·1%)	22·2 (–10·2 to 51·2)
Men	19/33 (57·6%)	5/37 (13·5%)	44·1 (21·3 to 63·3)
Women	17/31 (54·8%)	3/27 (11·1%)	43·7 (18·5 to 64·7)
Age <65 years	20/36 (55·6%)	2/40 (5·0%)	50·6 (29·3 to 68·3)
Age ≥65 years	16/28 (57·1%)	6/24 (25·0%)	32·1 (6·9 to 57·4)
Europe	23/37 (62·2%)	3/35 (8·6%)	53·6 (32·7 to 71·3)
Non-Europe	13/27 (48·1%)	5/29 (17·2%)	30·9 (4·2 to 53·5)
Bexarotene	36/64 (56·3%)	6/38 (15·8%)	40·5 (23·7 to 57·3)
Methotrexate	36/64 (56·3%)	2/26 (7·7%)	48·6 (26·7 to 67·7)
Skin only	21/31 (67·7%)	5/30 (16·7%)	51·1 (27·3 to 71·0)
Skin and other involvement	15/33 (45·5%)	3/34 (8·8%)	36·6 (12·3 to 56·3)
Baseline skin tumour score >0	26/41 (63·4%)	2/38 (5·3%)	58·2 (38·1 to 74·1)
Baseline skin tumour score =0	10/23 (43·5%)	6/26 (23·1%)	20·4 (–5·5 to 46·3)
Overall	**36/64 (56·3%)**	**8/64 (12·5%)**	**43·8 (29·1 to 58·4)**



Miles P, et al. *Lancet* 2017;390: 555-566.

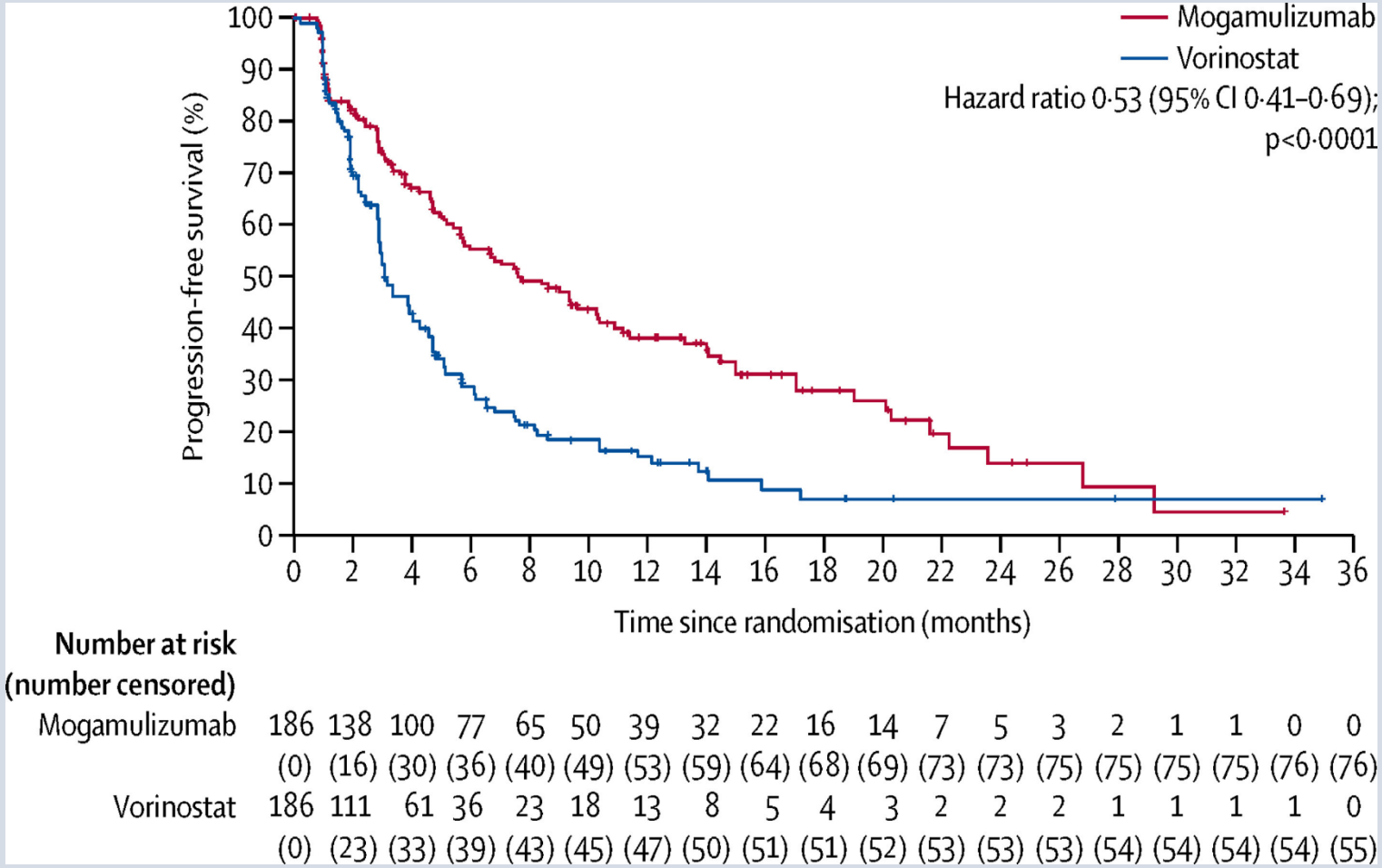
Phase III Randomized Trial of Mogamulizumab vs. Vorinostat in Previously Treated Cutaneous T-cell Lymphoma (MAVORIC)

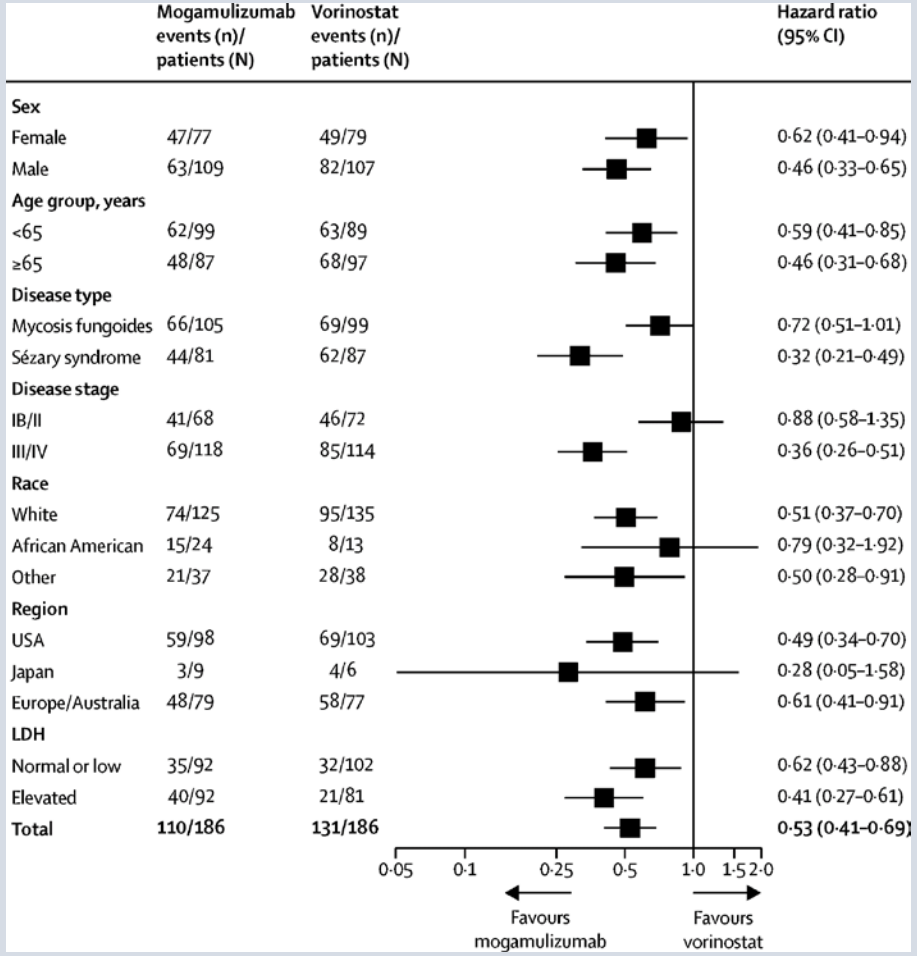


- Dx: stage IB-IVB MF or SS
- ≥ 1 prior systemic therapy failure
- Treatment regimen: Mogamulizumab 1 mg/kg IV QW -> Q2W; Vorinostat 400 mg PO QD; crossover allowed.
- Primary endpoint: PFS per investigator
- Secondary endpoints including: OGR, coOGR, DOR, Symptom Improvement, and safety/tolerability

Kim Y, … Shustov A., … et al. *Lancet Onc* 2018; 19(9):1192-1204.

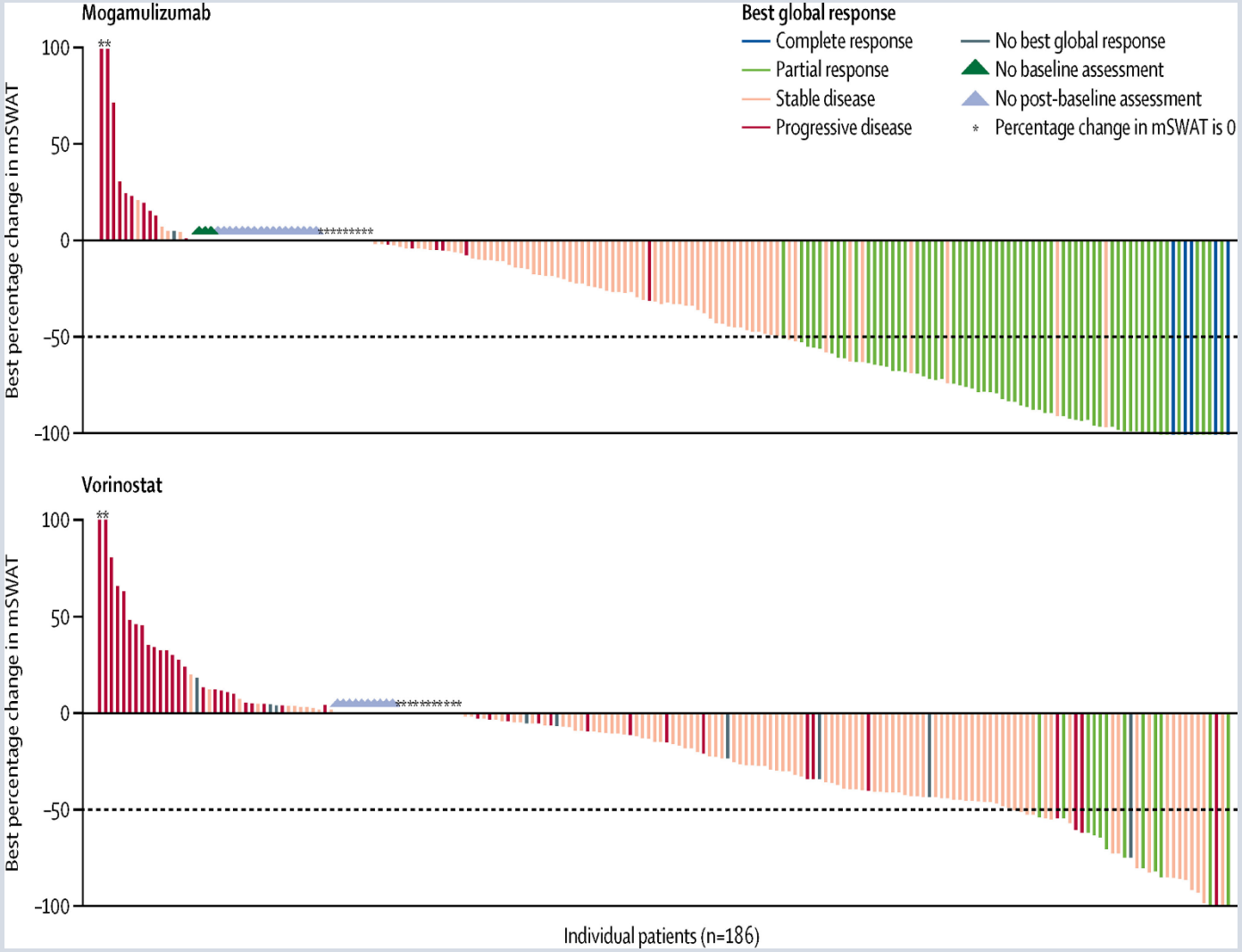
Phase III Randomized Trial of Mogamulizumab vs. Vorinostat in Previously Treated Cutaneous T-cell Lymphoma (MAVORIC)





Kim Y, … Shustov A., … et al. *Lancet Onc* 2018; 19(9):1192-1204.

Phase III Randomized Trial of Mogamulizumab vs. Vorinostat in Previously Treated Cutaneous T-cell Lymphoma (MAVORIC)



	Mogamulizumab (n=184)				Vorinostat (n=186)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Blood and lymphatic system disorders								
Thrombocytopenia [†]	25 (14%)	0	0	0	63 (34%)	11 (6%)	2 (1%)	0
Gastrointestinal disorders								
Abdominal pain	7 (4%)	0	0	0	21 (11%)	0	0	0
Constipation	20 (11%)	1 (1%)	0	0	32 (17%)	2 (1%)	0	0
Diarrhoea	42 (23%)	1 (1%)	0	0	106 (57%)	9 (5%)	0	0
Nausea	27 (15%)	1 (1%)	0	0	76 (41%)	3 (2%)	0	0
Vomiting	11 (6%)	0	0	0	23 (12%)	1 (1%)	0	0
General disorders and administration-site conditions								
Asthenia	10 (5%)	0	0	0	23 (12%)	4 (2%)	0	0
Fatigue	40 (22%)	3 (2%)	0	0	59 (32%)	11 (6%)	0	0
Peripheral oedema	27 (15%)	0	0	0	26 (14%)	1 (1%)	0	0
Pyrexia	30 (16%)	1 (1%)	0	0	11 (6%)	0	0	0
Infections and infestations								
Cellulitis	2 (1%)	3 (2%)	1 (1%)	0	6 (3%)	4 (2%)	0	0
Pneumonia [†]	2 (1%)	6 (3%)	1 (1%)	1 (1%)	0	1 (1%)	0	2 (1%)
Sepsis	1 (1%)	2 (1%)	0	1 (1%)	1 (1%)	0	4 (2%)	1 (1%)
Upper respiratory tract infection	19 (10%)	0	0	0	7 (4%)	2 (1%)	0	0
Injury, poisoning, and procedural complications								
Infusion-related reaction	58 (32%)	3 (2%)	0	0	1 (1%) [‡]	0	0	0
Investigations								
Aspartate aminotransferase increased	6 (3%)	2 (1%)	0	0	11 (6%)	1 (1%)	0	0
Blood creatinine increased	6 (3%)	0	0	0	52 (28%)	0	0	0
Weight decreased	10 (5%)	1 (1%)	0	0	31 (17%)	2 (1%)	0	0
Metabolism and nutrition disorders								
Decreased appetite	12 (7%)	2 (1%)	0	0	44 (24%)	2 (1%)	0	0
Musculoskeletal and connective tissue disorders								
Muscle spasms	9 (5%)	0	0	0	27 (15%)	2 (1%)	0	0
Nervous system disorders								
Dizziness	12 (7%)	0	0	0	19 (10%)	0	0	0
Dysgeusia	6 (3%)	0	0	0	53 (28%)	1 (1%)	0	0
Headache	23 (13%)	0	0	0	28 (15%)	1 (1%)	0	0
Respiratory, thoracic, and mediastinal disorders								
Pulmonary embolism	0	0	0	0	0	4 (2%)	1 (1%)	2 (1%)
Skin and subcutaneous tissue disorders								
Alopecia	13 (7%)	0	0	0	36 (19%)	0	0	0
Drug eruption [‡]	36 (20%)	8 (4%)	0	0	1 (1%)	0	0	0
Vascular disorders								
Hypertension	9 (5%)	8 (4%)	0	0	13 (7%)	12 (6%)		

Kim Y, … Shustov A., … et al. *Lancet Onc* 2018; 19(9):1192-1204.

FDA Approved Systemic Agents in Cutaneous T-Cell Lymphoma, 2019 Update

Agent (Class)	CTCL Indication	Study	N	Stage	ORR	DOR
Romidepsin (HDAC inhibitor)	Cutaneous TCL	Pivotal Supportive	96 71	IB-IVA IA-IVB	34% 35%	15 mo 11 mo
Bexarotene (Retinoid x-receptor activator)	Cutaneous manifestations	Pivotal	62	IIB-IVB	32%	5+ mo
Vorinostat (HDAC inhibitor)	Cutaneous manifestations	Pivotal Supportive	74 33	IA-IVB IA-IVB	30% 24%	6+ mo 4 mo
Brentuximab Vedotin	CD30+ MF, pcALCL	Randomized Ph3	131	IB-IVB	50% 75%	15+ mo
Mogamulizumab	Cutaneous TCL	Randomized Ph3	372	IB-IVB	24%	25 mo 20 mo

THANK YOU