

Changing the landscape of treatment in Peripheral T-cell Lymphoma

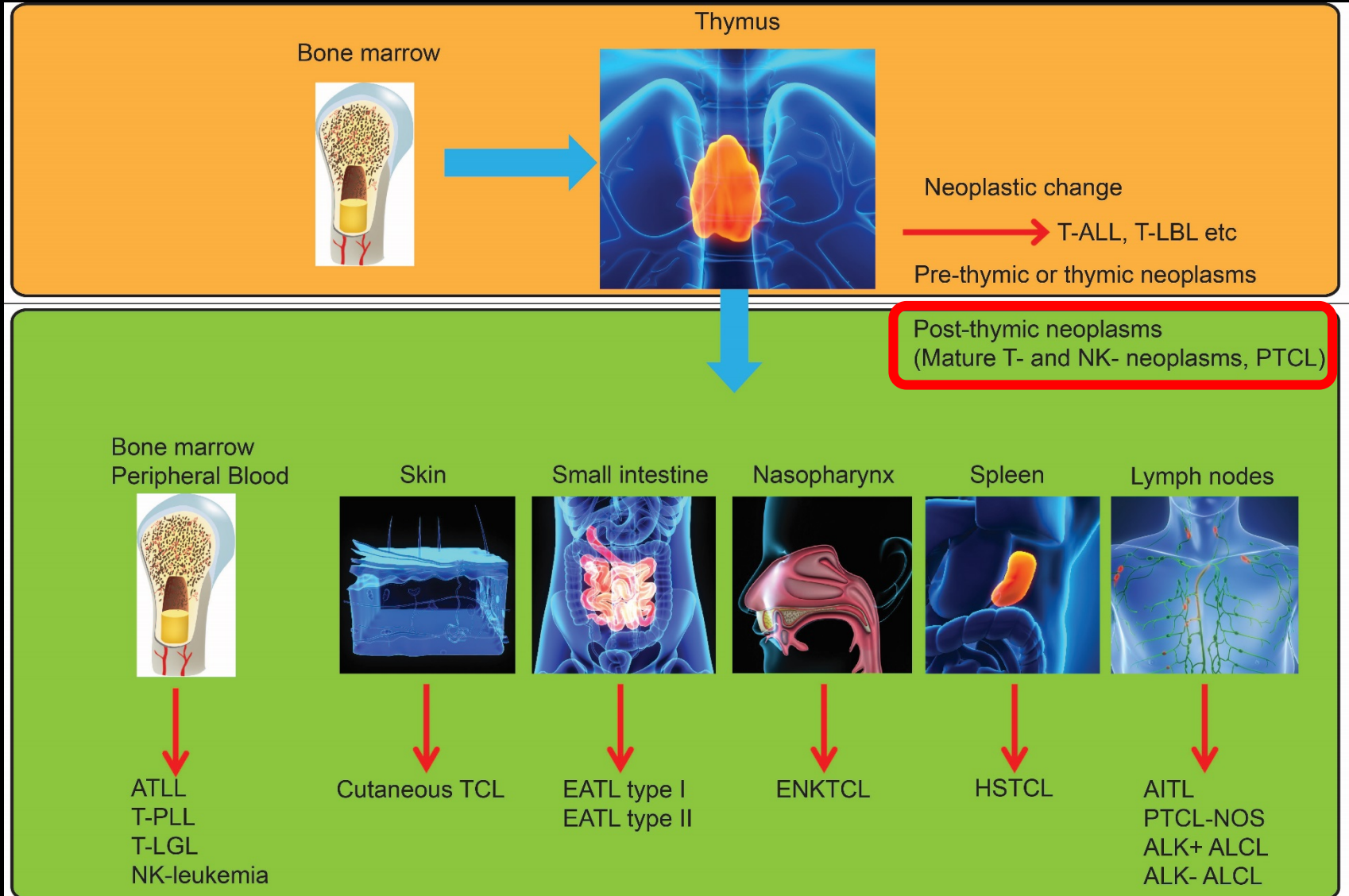
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What is “peripheral”



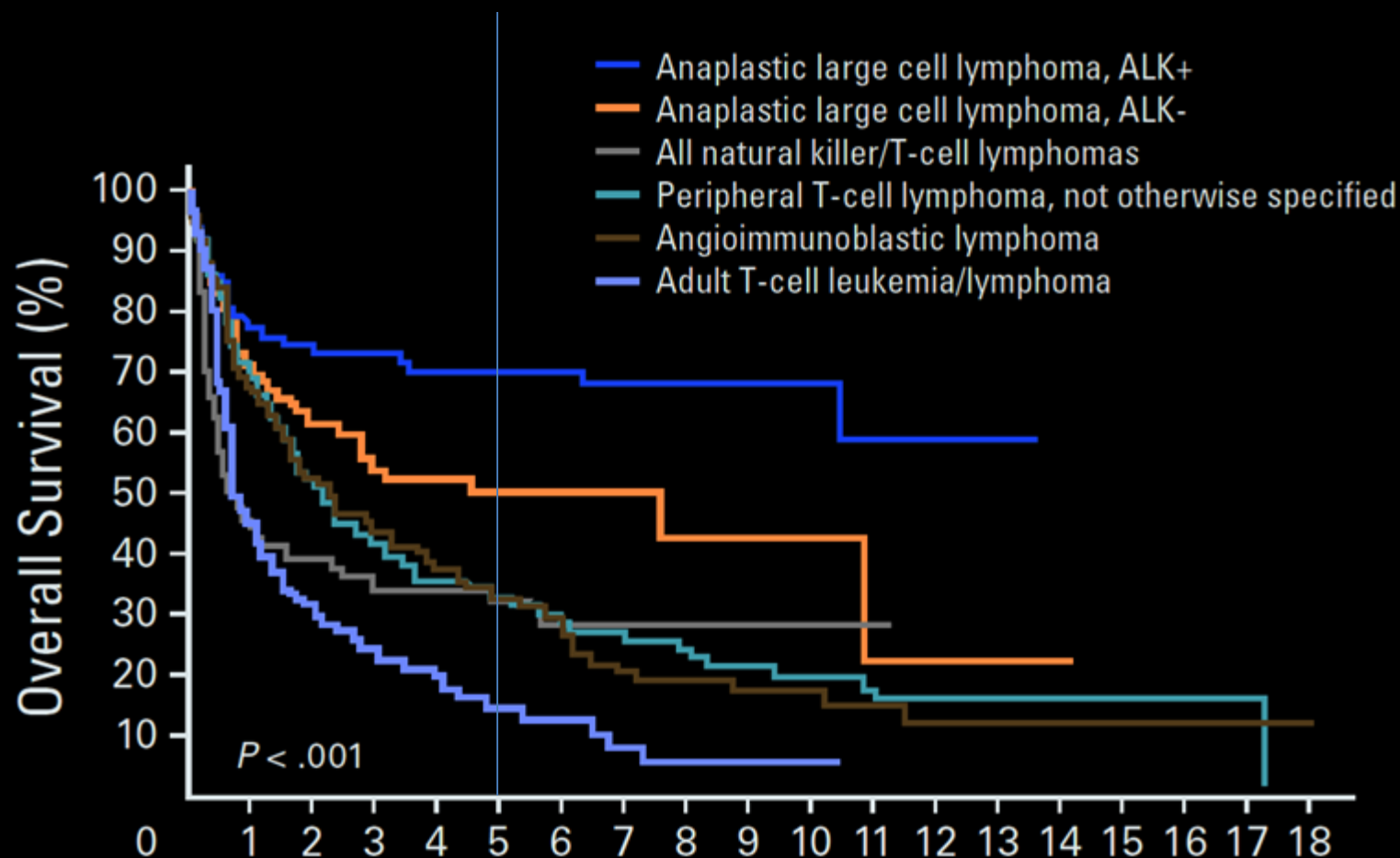
2008 WHO CLASSIFICATION OF MATURE T/NK

NEOPLASM – 22 DISTINCTIVE SUBTYPES -

Cutaneous	Extranodal	Nodal	Leukemic
Mycosis Fungoides (MF)	NK/TCL Nasal Type	Peripheral TCL-NOS	Adult T-Cell Leukemia/ Lymphoma
Sézary Syndrome	Enteropathy- Associated TCL	Anaplastic Large Cell Lymphoma (ALK +)	T-cell Prolymphocytic Leukemia
Primary Cutaneous $\gamma\delta$ TCL	Hepatosplenic TCL	Anaplastic Large Cell Lymphoma (ALK -)	T-Cell Large Granular Lymphocytic Leukemia
Primary Cutaneous CD8+ aggressive epidermotropic	Subcutaneous Panniculitis-Like TCL	Angioimmunoblastic TCL	Aggressive NK cell leukemia
Primary Cutaneous CD4+ small/medium	Systemic EBV+ T-cell childhood lymphoprolif		
Primary Cutaneous CD30+ T-Cell Disorders	Hydroa Vacciniforme- Like lymphoma		
<ul style="list-style-type: none">Lymphomatoid papulosisPrimary cutaneous anaplastic large cell lymphoma	Chronic lymphoproliferative disorder of NK cells		

- Incidence <1 per 100,000
- About 10-15% of lymphoma
- Geographic variation
- Morphology and IHC based classification

Poor outcome of T-cell lymphoma



Better classification?

Molecular analysis

For better treatment strategy?

Current therapeutic approach

Frontline therapy

- CHOP
 - Overall response ~ 60-65%
 - CR rate ~ 50-55%

Recent frontline clinical trials

- CHOP + X
 - Romidepsin (Coiffier et al, ASH 2014, n=35, CR 51%)
 - Belinostat (Johnston et al. ASH 2015, n=23, CR 72%)
 - Vorinostat (Oki et al, BJH2013, n=14, CR 93%)
 - Alemtuzumab (Gallamini. Blood 2007, N=24, CR 71%)
 - Brentuximab (Fanale et al, JCO 2014, n=26, CR 88%)
 - ONTAK (Foss et al. Leuk Lymph 2013, n=49, CR 55%)
 - Bortezomib (Kim et al. Eur J Cancer, n=46, CR 65%)
 - Pralatrexate (Advani et al. and Phase I ongoing)

Current approach

- CHOP (age > 60)
- CHOEP (age ≤ 60 yo) and if CR, auto-SCT.

For recurrence

- Lack of “Effective salvage treatment...”
 - Except for ALCL

NCCN

Treatment Guidelines for Relapsed PTCL

Candidate for transplant

Clinical trial (preferred)

Bendamustine

Belinostat

Brentuximab vedotin

DHAP

ESHAP

EPOCH

GDP

GemOx

ICE

Pralatrexate

Romidepsin

Non-Candidate for Transplant

Clinical trial (preferred)

Alemtuzumab

Bendamustine

Belinostat

Bortezomib

Brentuximab

Cyclosporine for AITL

EPOCH

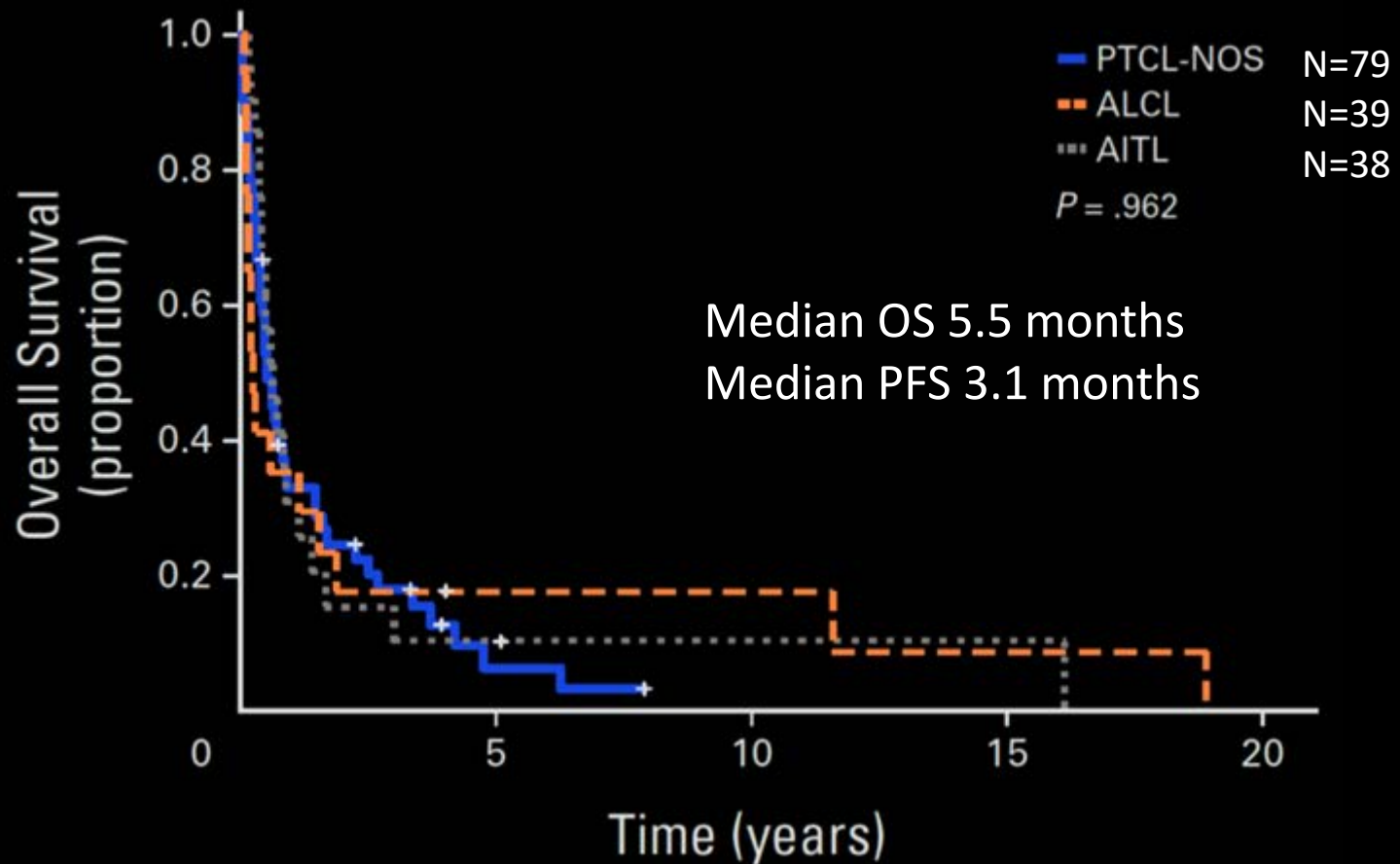
Gemcitabine

Pralatrexate

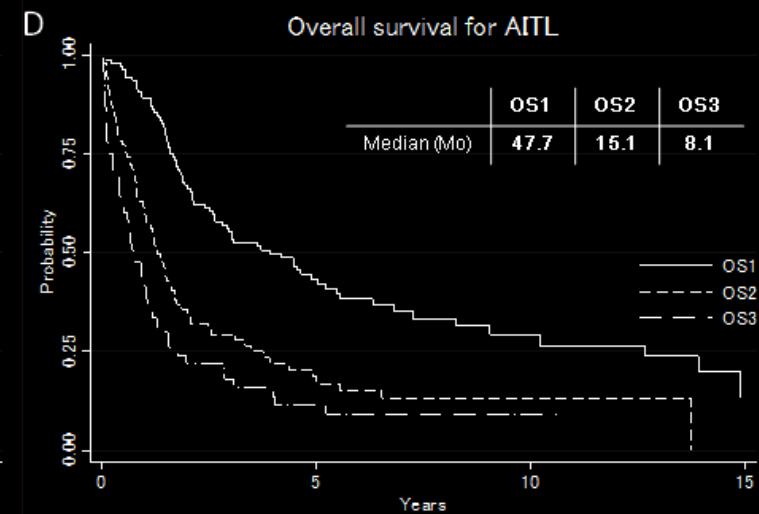
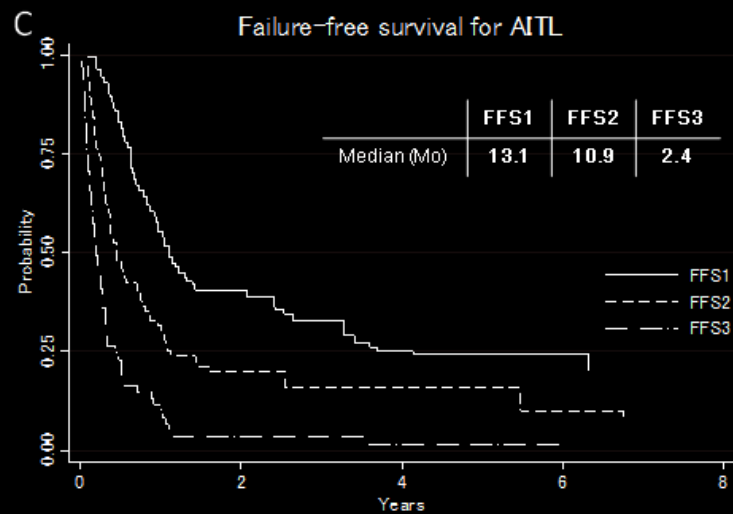
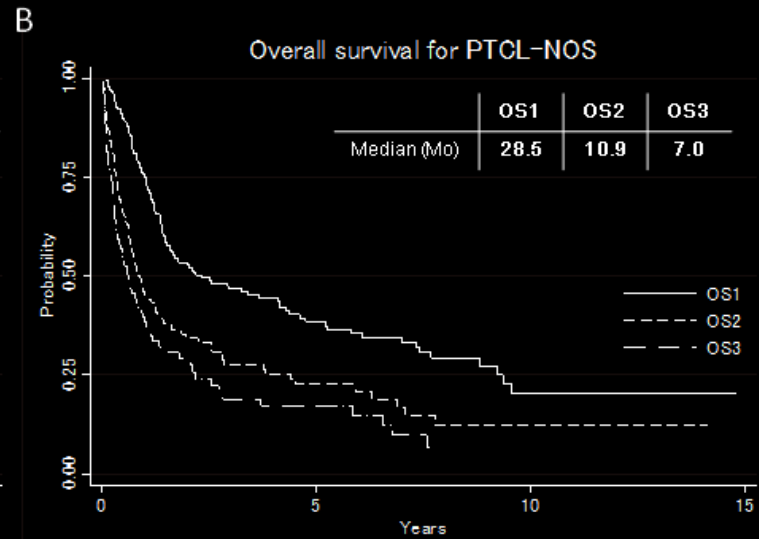
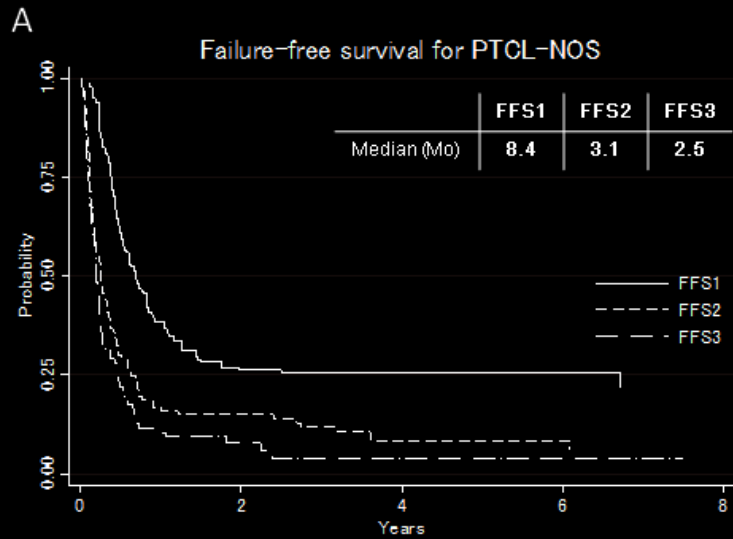
Radiation therapy

Romidepsin

Poor outcome after 1st relapse/progression



MDACC experience of RR PTCL



Relapsed/Refractory PTCL

Combination chemotherapy regimens

Agents	Dose/schedule	N	ORR (%)	CR (%)	DOR, Mos
Ifosfamide Carboplatin Etoposide	5g/m ² d1 AUC5 d1 100mg/m ² d1-3	40	70	35	PFS 6 months
Gemcitabine Oxaliplatin Dexamethasone	1000 mg/m ² d 1 100mg/m ² d 1 20 mg/d d1-4	24	38	8	NR
Ifosfamide Methotrexate Etoposide	1000mg/m ² d1-5 30mg/m ² d1,3 100mg/m ² d1-3	32	28	15	NR 3-yr PFS 12%
Gemcitabine Cisplatin Methylprednisolone	1000mg/m ² d 1,8,15 100 mg/m ² d 15 1000mg d1-5	16	69	19	NR PFS 123 days

Horwitz S et al, ASH 2005

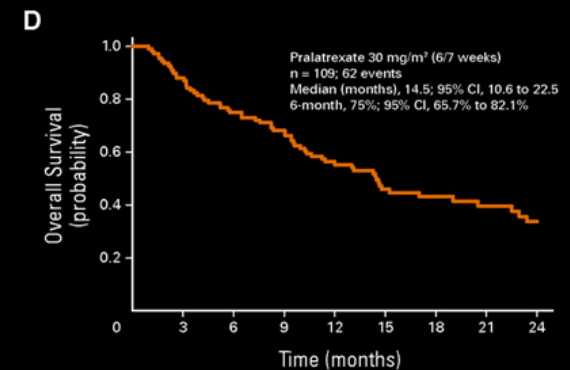
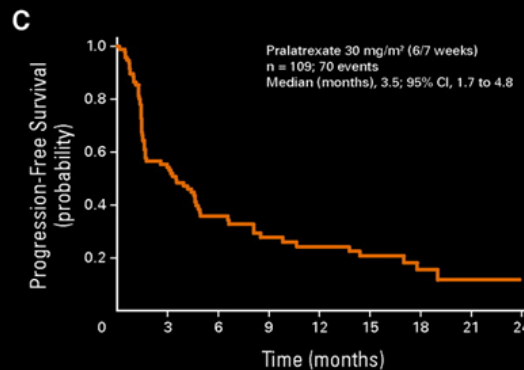
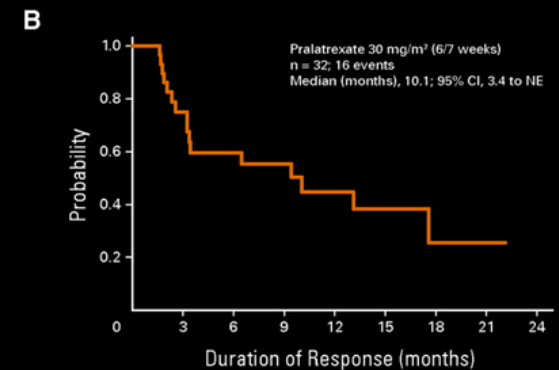
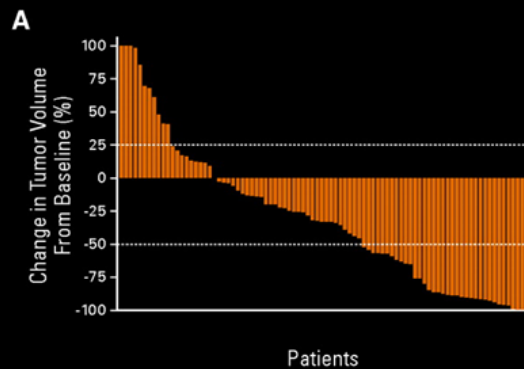
Yao Y et al, Leuk Lymphoma 2012

Park B et al, Leuk Lymphoma 2005

Arkenau HT et al, Haematologica 2007

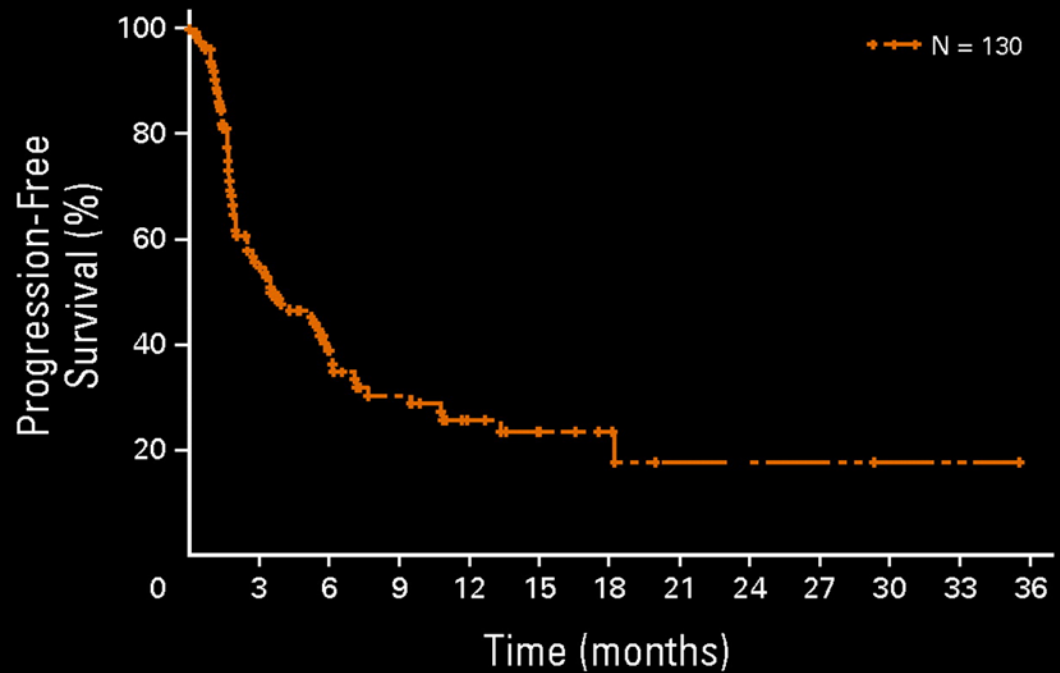
Pralatrexate

- NOS (n=59)
 - RR 32%
- AITL (n=13)
 - RR 8%
- ALCL (n=16)
 - RR 35%
- Transformed MF
 - RR 25%



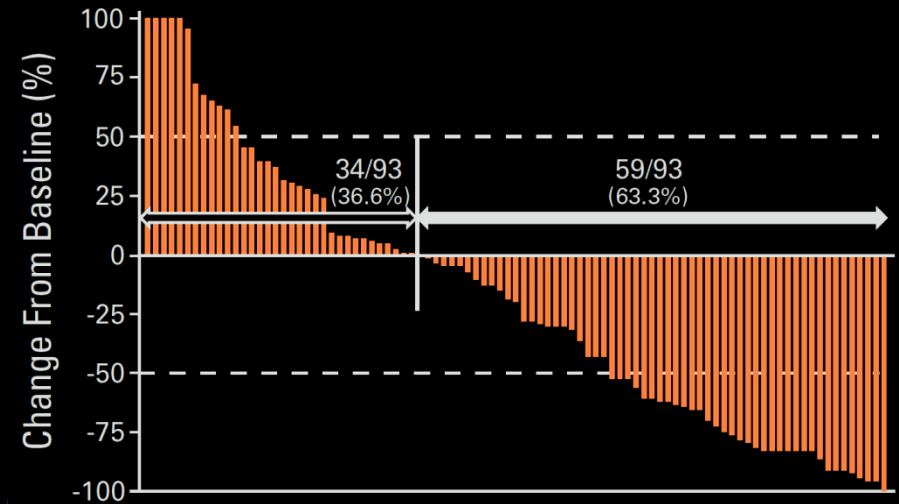
Romidepsin

- NOS (n=69)
 - RR 29% CR 14%
- AITL (n=27)
 - RR 30% CR 19%
- ALCL (n=21)
 - RR 24% CR 19%

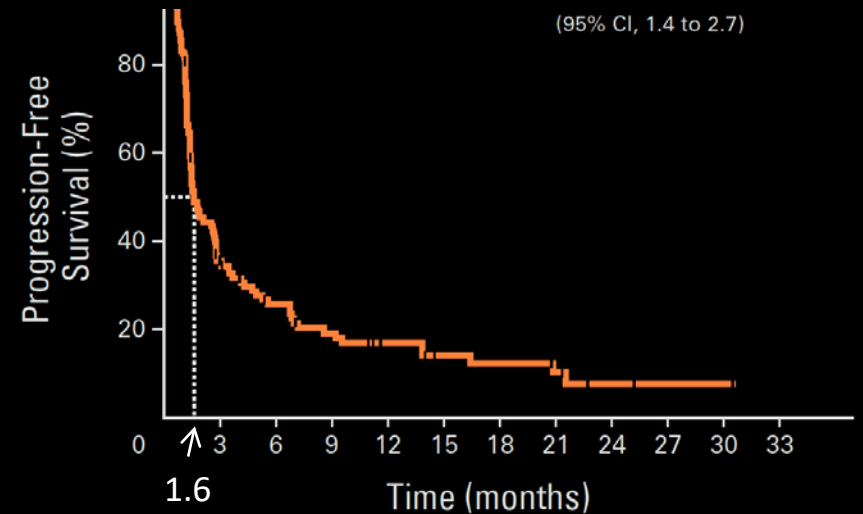


Belinostat

- Overall (n=120)
 - RR 26% CR 11%
- NOS (n=77)
 - RR 23%
- AITL (n=22)
 - RR 46%
- ALCL (n=15)
 - RR 15%



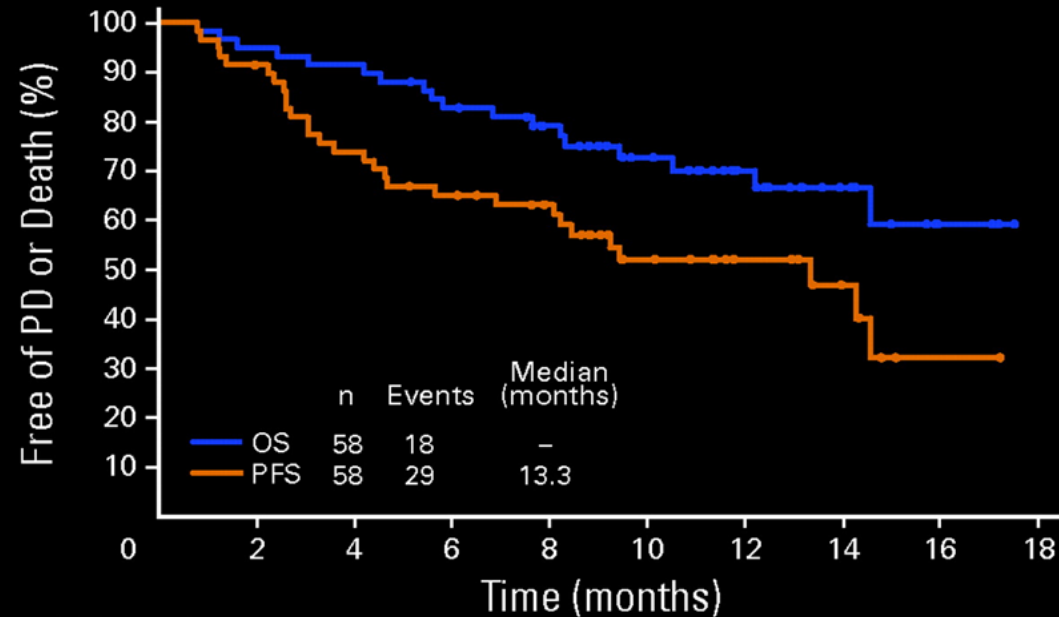
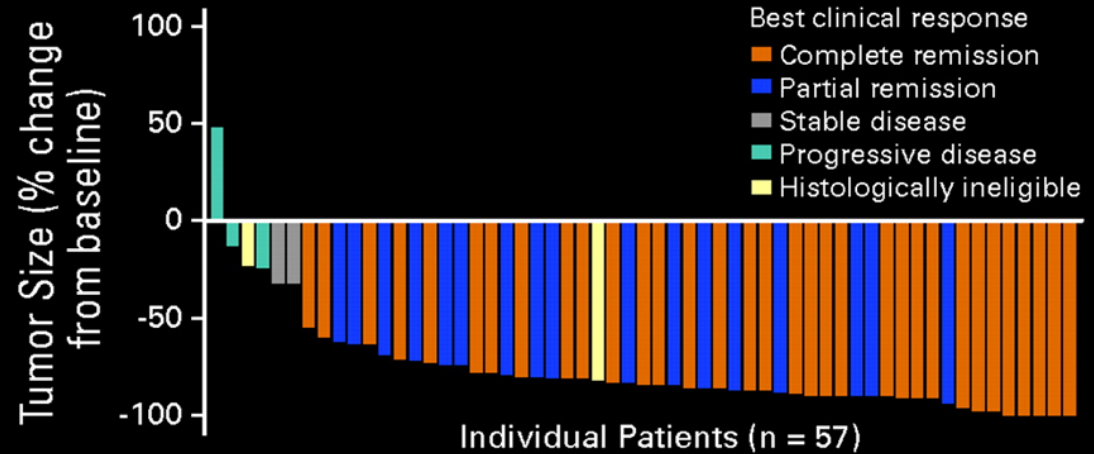
Patients With Response Assessment



No. at risk 120 39 24 17 12 8 7 5 2 1 1

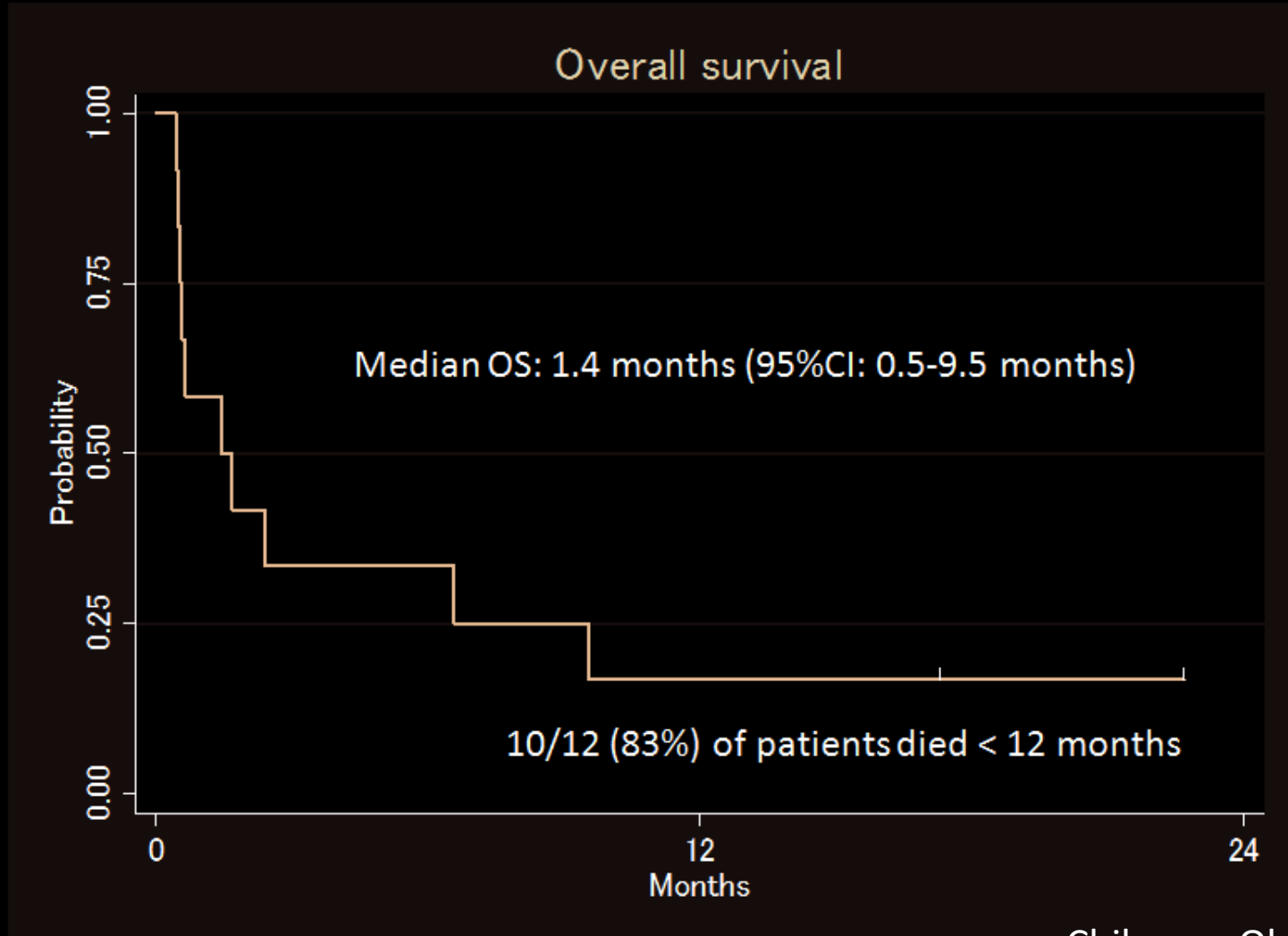
Brentuximab vedotin in ALCL

- ALCL N=58
- ORR 86%
- CR 29%
- DOR 12.6 mo



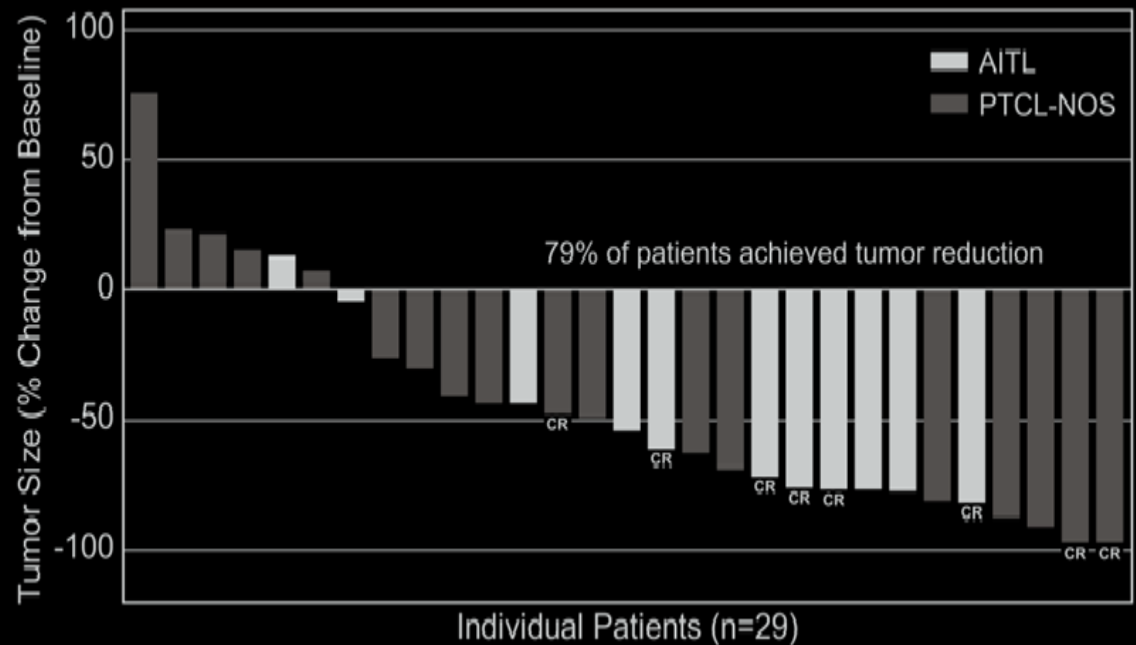
	No. at risk/events									
OS	58/0	55/3	53/5	47/10	39/12	29/15	20/16	11/17	4/18	0/18
PFS	58/0	52/5	42/15	36/20	31/21	19/26	12/26	7/27	2/29	0/29

Poor OS after BV failure



Brentuximab vedotin in other PTCL

- NOS N=21
 - ORR 33%
 - CR 14%
 - PFS 1.6 mo
- AITL N=13
 - ORR 54%
 - CR 38%
 - PFS 6.7mo



Recently FDA-approved drugs

Agent	N	ORR (%)	CR (%)	DOR, Mos	PFS
Pralatrexate	111	29	19	10.1	3.5 mo
Romidepsin	131	25	15	17	4 mo
Belinostat	129	25	10	8.3	
Brentuximab Vedotin (ALCL)	58	86	57	12.6	13.3 mo
Brentuximab vedotin (NOS)	21	33	14		1.6 mo
Brentuximab vedotin (AITL)	13	54	38		6.7 mo

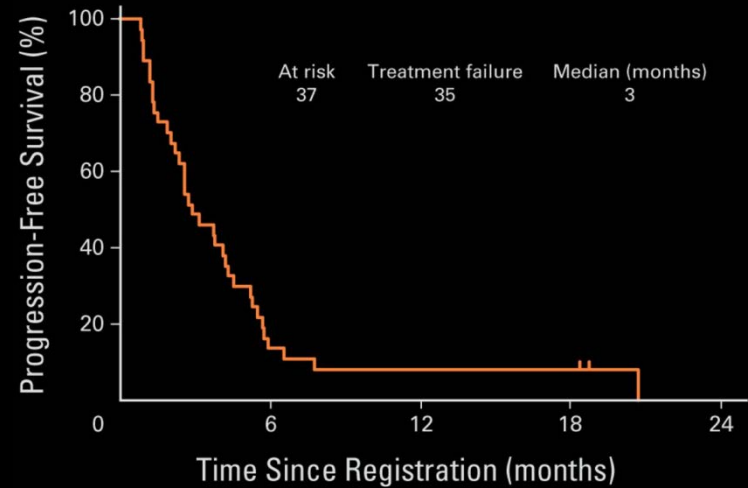
Relapsed/Refractory PTCL (Other Agents)

Agent	N	ORR(%)	CR(%)	DOR/Note	Ref
Alemtuzumab	14	36	21	<12 months	Enblad Blood 2004
Denileukin diftitox	27	48	22	PFS 6 mo	Dang BJH 2006
Mogamulizumab	29	34	17	NR	Ogura JCO 2014
Nivolumab	5	40	0	NR	Lesokhin ASH 2014
Lenalidomide	39	26	8	5 mo	Toumishey Cancer 2014
Cyclosporine (AILT)	12	67	25	2-120 mo	Advani Leuk Lymph 2007
Crizotinib (ALK+ALCL)	14	60	36	8.3 mo	Gambacorti-Passerini ASH 2013
Bortezomib	15	67	17	7-14 mo	Zinzani JCO 2007 (PTCL only 2)
Alisertib	8	50	13	NR	Friedberg JCO 2014
Duvelisib (IPI145)	16	47	12	OS 36 wks	Horwitz ASH 2014
Bendamustine	60	50	28	3.5 mo	Damaj JCO 2013
Gemcitabine	20	55	30	28 mo	Zinzani Ann Oncol 2010

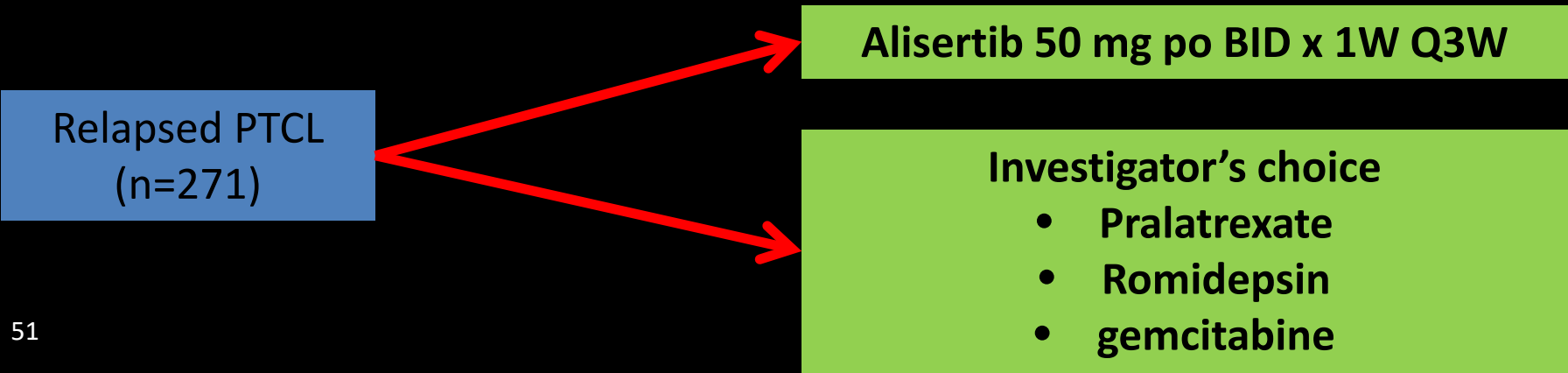
Alisertib

- Phase II study for PTCL
- n=37
- ORR 30%, CR 3%
- No response in tMF

- Phase III study terminated



Barr et al. JCO 2015



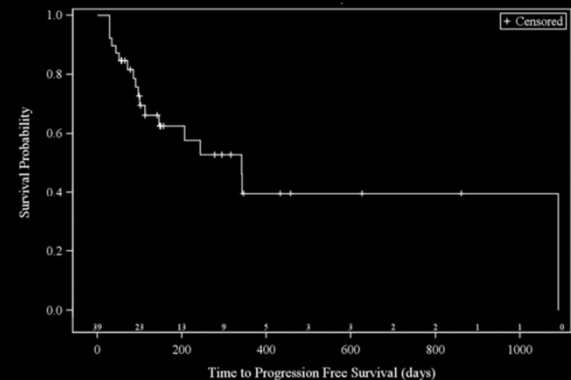
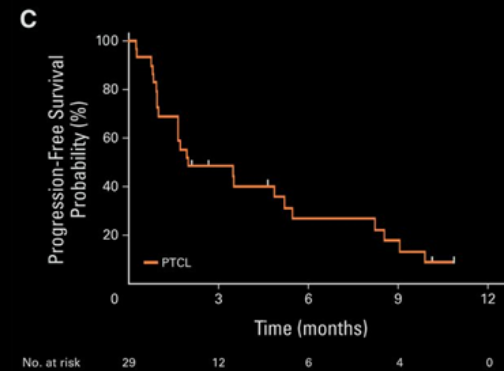
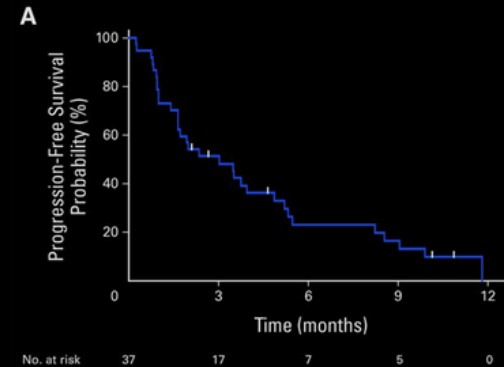
Mogamulizumab

- Phase II (n=38, 30 PTCL and 8 CTCL)
- ORR 35%, CR 14%

Ogura et al. JCO 2014

- US Phase I/II for CTCL (n=38)
- ORR 37%

Duvic et al. Blood 2015



Bortezomib

- Italian phase II study (n=15)
- ORR 67%
- CR 17%
- Responders were mostly CTCL

Zinzani et al. JCO 2007

Duvelisib (IPI145) in TCL

- 17 CTCL and 16 PTCL
- 31 evaluable
- ORR in PTCL 47% including CR 13%
- AST/ALT G3/4 in 36%
- Rash 21%
- 30% discontinued therapy due to AE.

Active agents / Candidates

1. Epigenetic therapy
 1. HDAC inhibitor
 2. DNMT inhibitor
2. PI3K/AKT/mTOR pathway
 1. PI3K inhibitor
 2. AKT inhibitor
 3. mTOR inhibitor
3. JAK/STAT pathway
 1. JAK inhibitor
 2. STAT3 inhibitor
4. Aurora A Kinase inhibitor
5. IDH2 inhibitor
6. Proteasome inhibitor/NFkB
7. Antibodies
 1. Brentuximab vedotin (CD30)
 2. Alemtuzumab (CD52)
 3. Denileukin diftitox (CD25)
 4. Mogamulizumab (CCR4)
 5. MEDI570 (ICOS)
8. Immunomodulator
 1. Revlimid
 2. PD1 inhibitor
 3. PDL1 inhibitor
9. Chemotherapies
 1. Gemcitabine
 2. Pralatrexate
 3. Bendamustine
 4. L-asparaginase
10. Other kinase inhibitors
11. CAR T cells!

Future directions

- Frontline
 - Chemotherapy + Targeted
 - Stuck with X-CHOP trials?
 - Targeted + Targeted
 - Effective doublet / triplet to be pushed to frontline
 - **Apply effective therapy from salvage settings**
 - Association with molecular profile
 - Maintenance therapy vs autologous SCT for CR
- Salvage
 - Combination of target therapy
 - Effective transplant regimen (better than BEAM)
 - Immune therapy (PD1/PDL1/CART cells antiCD30, anti CD5)

Thanks!