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Different front-line treatments related to the histologic subtypes in PTCL: Is it possible today?

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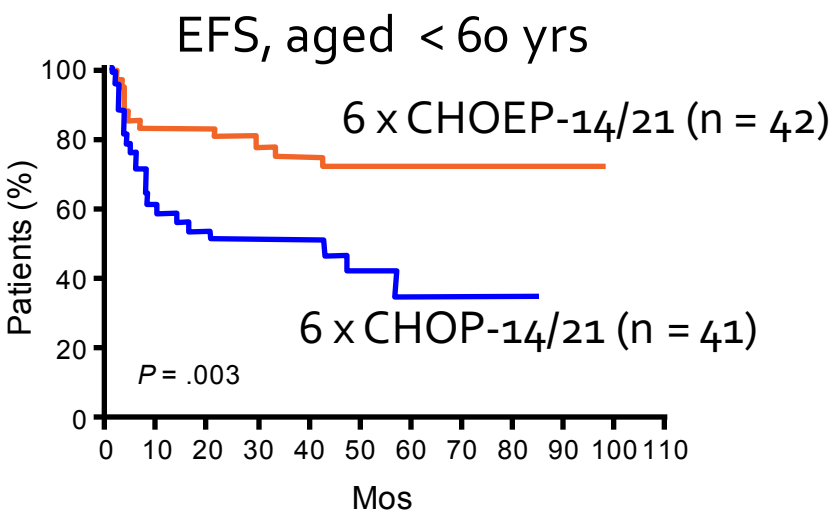
Many things are possible…

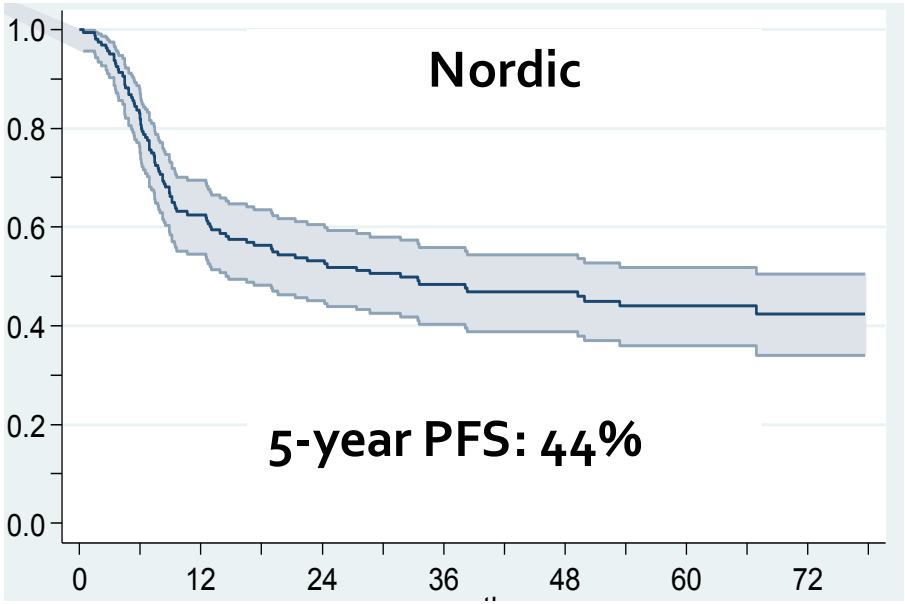
But that doesn't necessarily make them a good idea

"Standard" Approaches to the Initial Treatment of PTCL

"Standard" Approaches: CHOP or CHOEP +/-ASCT



CHOEP q2 weeks x 6-ASCT



Schmitz N, et al. Blood. 2010;116:3418-3425. D'Amore, et al. *J Clin Oncol.* 2012;30(25):3093-3099

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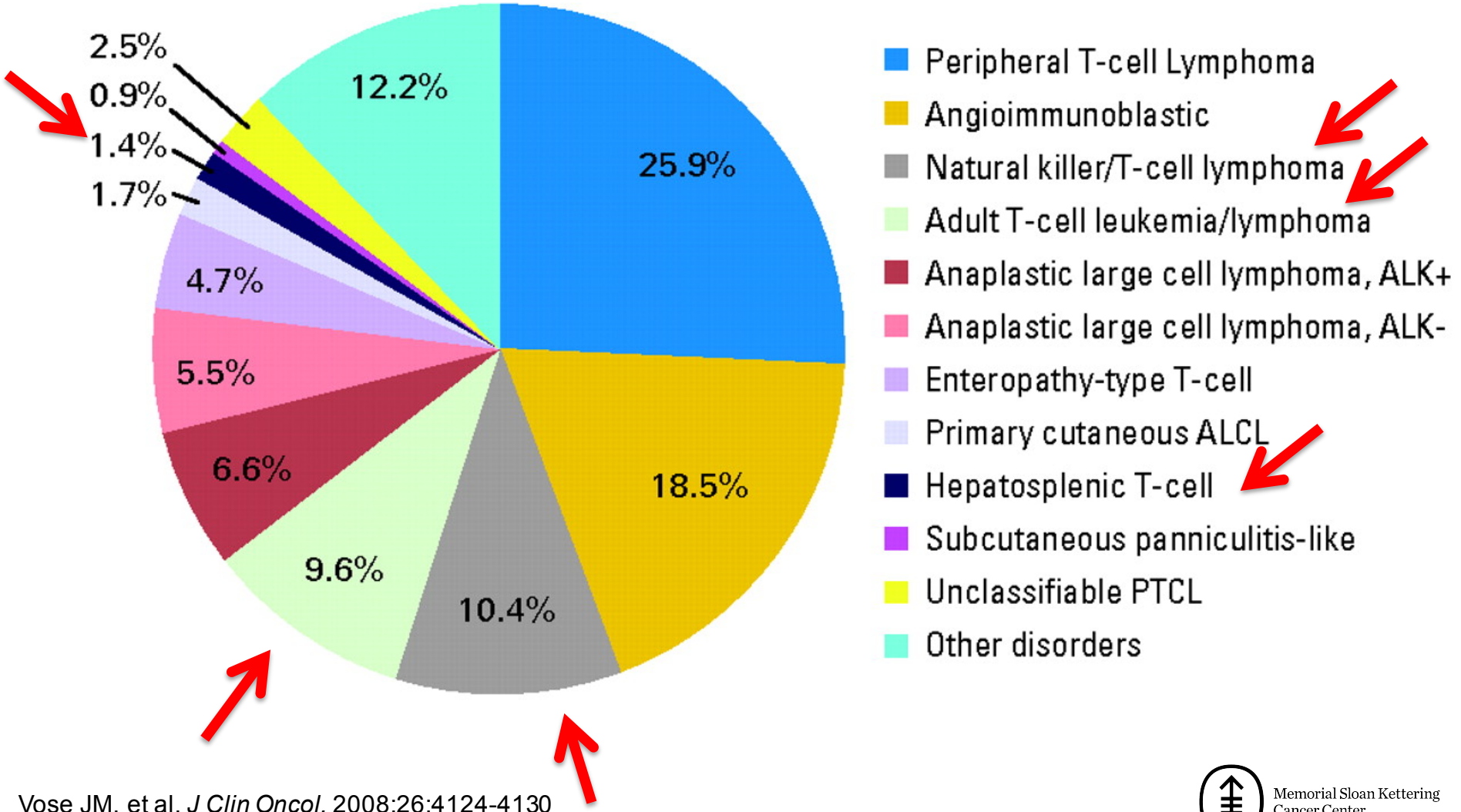
Proportion of Major T-cell Subtypes: North America



Vose JM, et al. *J Clin Oncol.* 2008;26:4124-4130

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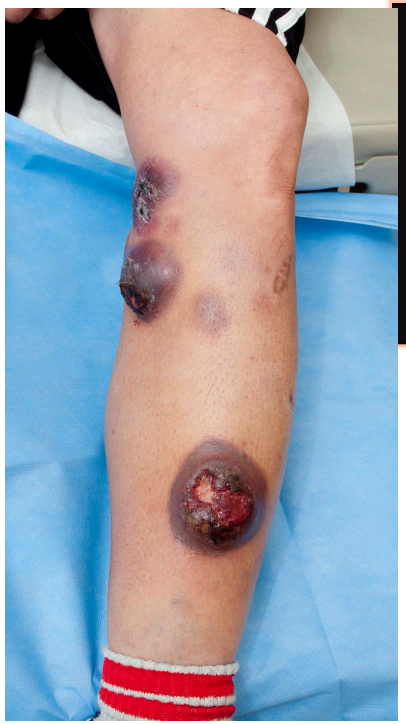
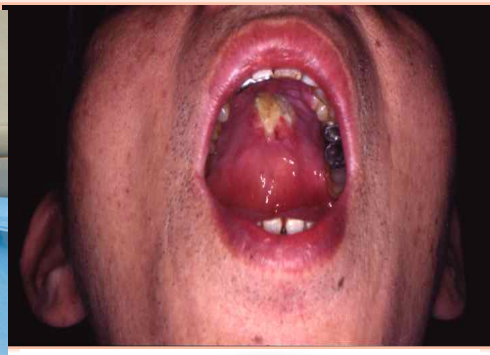
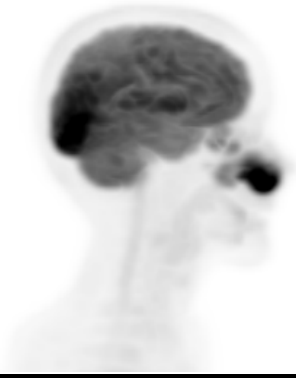
NK/T-cell Lymphoma

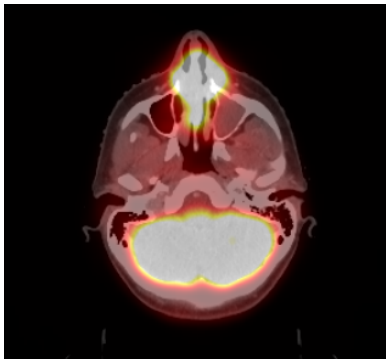
NK/T-cell Lymphoma

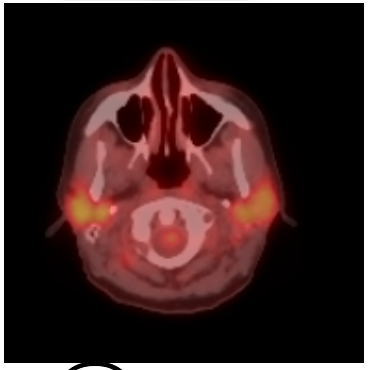
- EBV driven lymphoma
- More common in Asia and Central/South America
  - NA-4-5% of TCL
  - Asia >20% of TCL
- Almost always presents in the nose or nasopharynx
- Less often: paranasal sinuses, tonsil, Waldeyer's ring, and oropharynx.
- Other sites: skin, salivary glands, testis, and gastrointestinal tract
- Quantitative of plasma EBV prognostic and predictive











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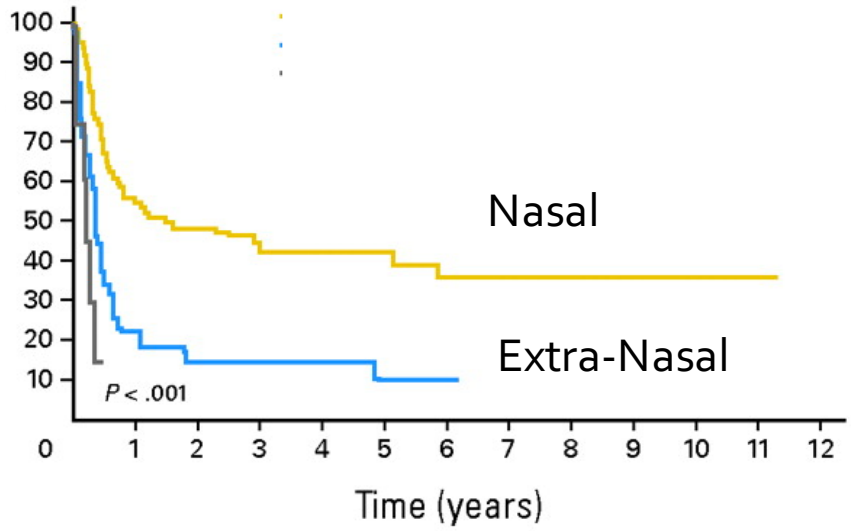
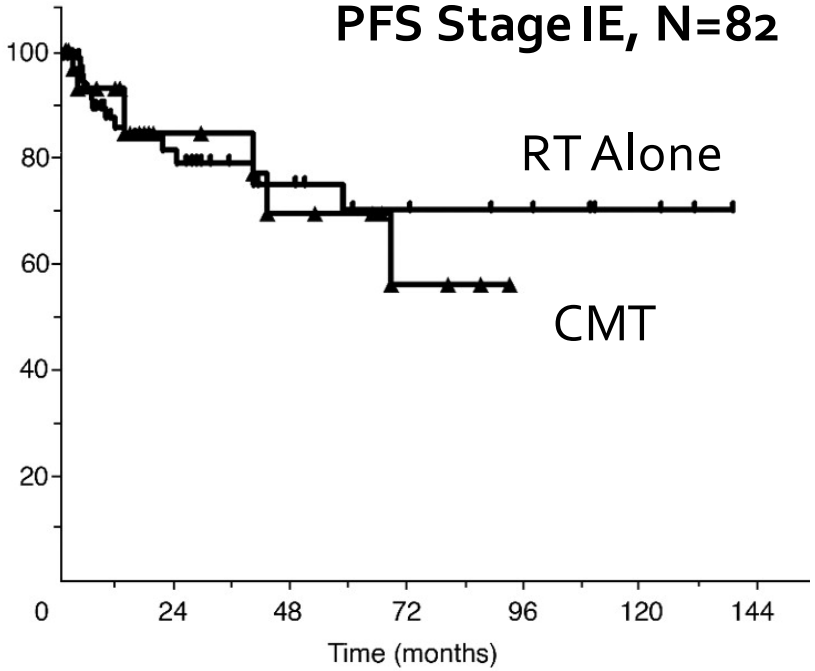
NK/T cell Lymphoma- Early stage

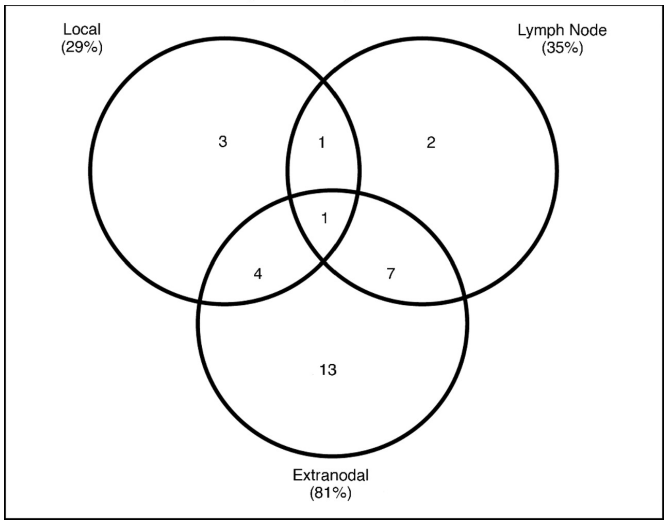
Overall Survival



PFS Stage IE, N=82

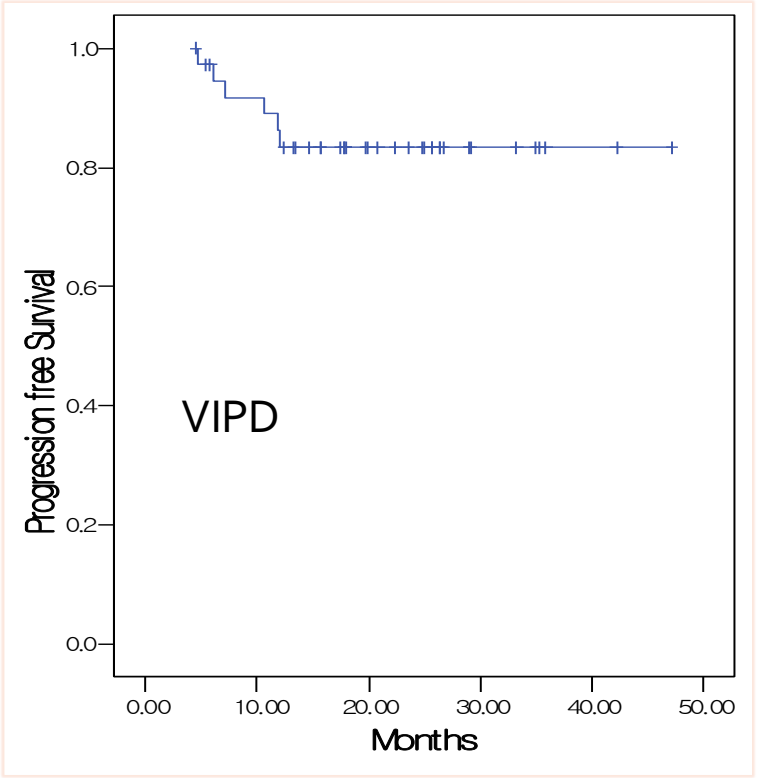


- Prognosis favors early stage/localized to nasopharynx
- Historically no benefit to CMT over RT alone
- RT alone doses >50Gy
- Patterns of failure



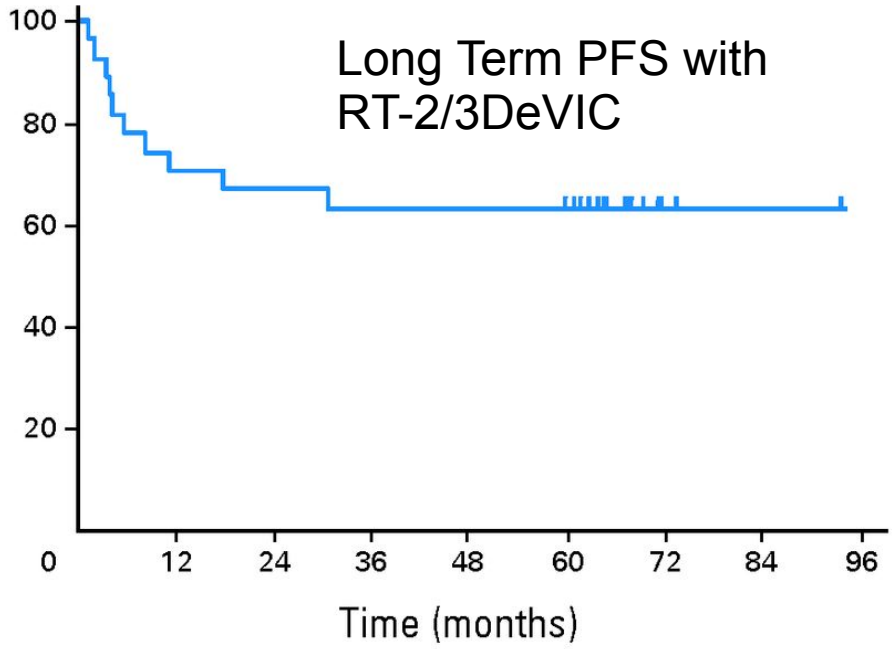
International T-Cell Lymphoma Project JCO 2008;26:4124-4130
Li Y et al. JCO 2006;24:181-189

Outcomes for Chemotherapy With Radiotherapy in Stage I/II Nasal NK/T



RT + Cisplatin followed by
Etoposide: 100 mg/m2 IV, days 1-3
Ifosfamide: 1200 mg/m2 IV, days 1-3
Cisplatin: 33 mg/m2 IV, days 1-3
Dexamethasone: 40 mg IV or orally, days 1-4

Kim et al. JCO December 10, 2009 vol. 27 no. 35

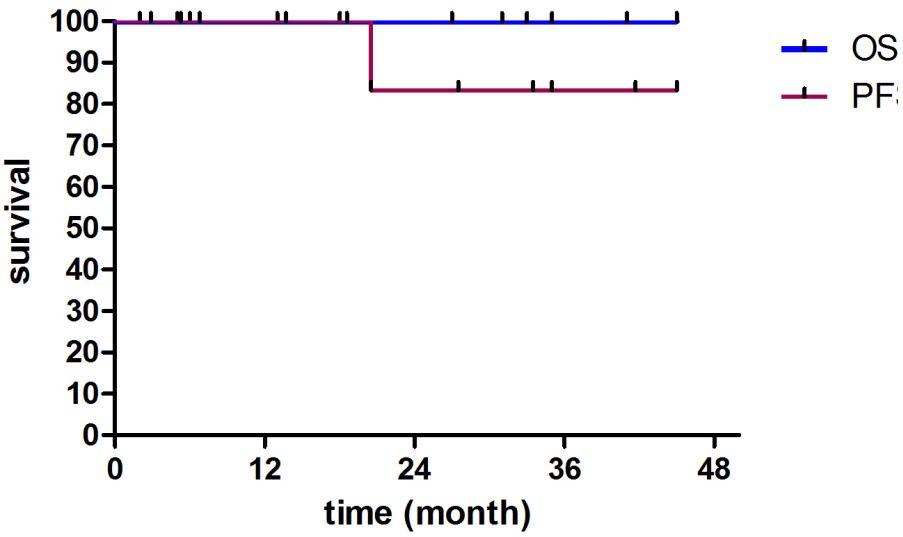


Concurrent radiation with
Dexamethasone: 40 mg IV, days 1-3
Etoposide: 67 mg/m2 IV, days 1-3
Ifosfamide: 1000 mg/m2 IV, days 1-3
Carboplatin: 200 mg/m2 IV, day 1

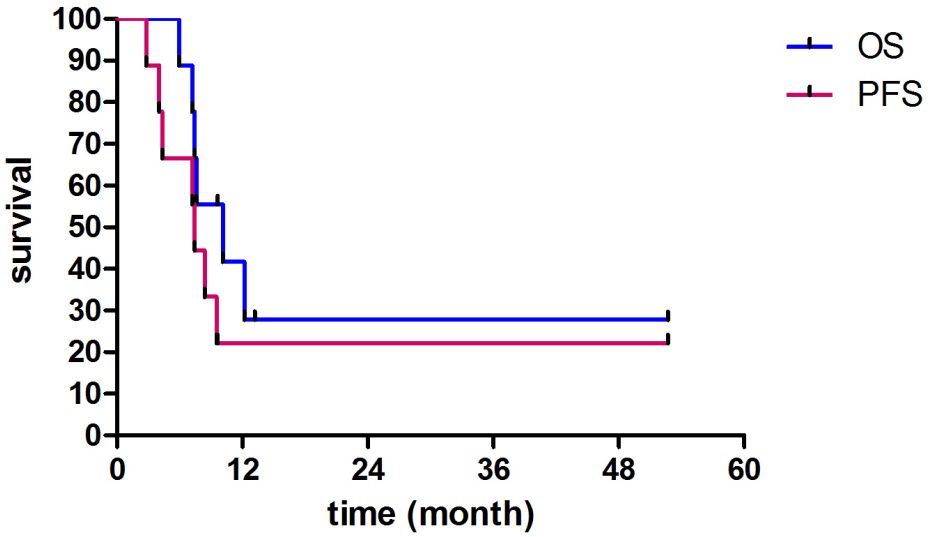
Yamaguchi et al JCO November 10, 2012 vol. 30 no. 32

NK/T cell Lymphoma: MSKCC Results with mSMILE* according to Stage

OS and PFS for early stage with m-SMILE



OS and PFS for advanced stage with m-SMILE



Drug	Dose	Route	Day
Methotrexate	2000 mg/m²	IV	1
Dexamethasone	40 mg	IV	2,3,4
Ifosfamide	1500 mg/m²	IV	2,3,4
Etoposide	100 mg/m²	IV	2,3,4
Peg-L-asparaginase	1500-2500 IU/m²	IM/IV	~ 5
XRT	4500 cGy		

CR 80%

Shunan Qi
A.Yahalom
M.Lunning

*Modified from Yamaguchi et al Cancer Sci. 2008 May;99(5):1016-20

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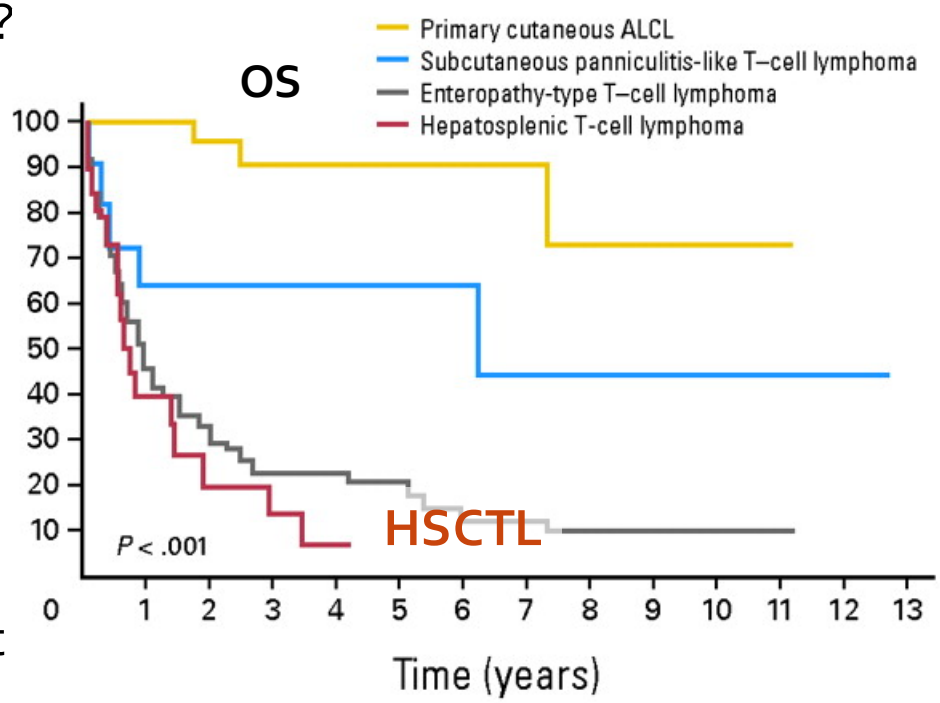
Hepatosplenic T-cell lymphoma

Hepatosplenic T-cell lymphoma

- Young age, usually male
- Associated with immunosuppression-IBD
- Anti-TNF > other immunosuppressive?
- Often very aggressive course
- Clinical Features
  - Splenomegaly, BM+ ~100%,
  - Hepatomegaly 80-90%
  - Elevated LFTs 50%,
  - LDH markedly elevated
  - Peripheral blood in 50–80%
  - Lymphadenopathy usually absent
  - Cytopenia
    - Hypersplenism and/or HLH



Ferreri, Govi, Pileri; Critical Reviews in Oncology/Hematology 83 (2012) 283–292
Voss et al, Clin Lymphoma Myeloma Leuk. Feb 2013; 13(1): 8–14.
Vose JM, et al. *J Clin Oncol.* 2008;26:4124-4130

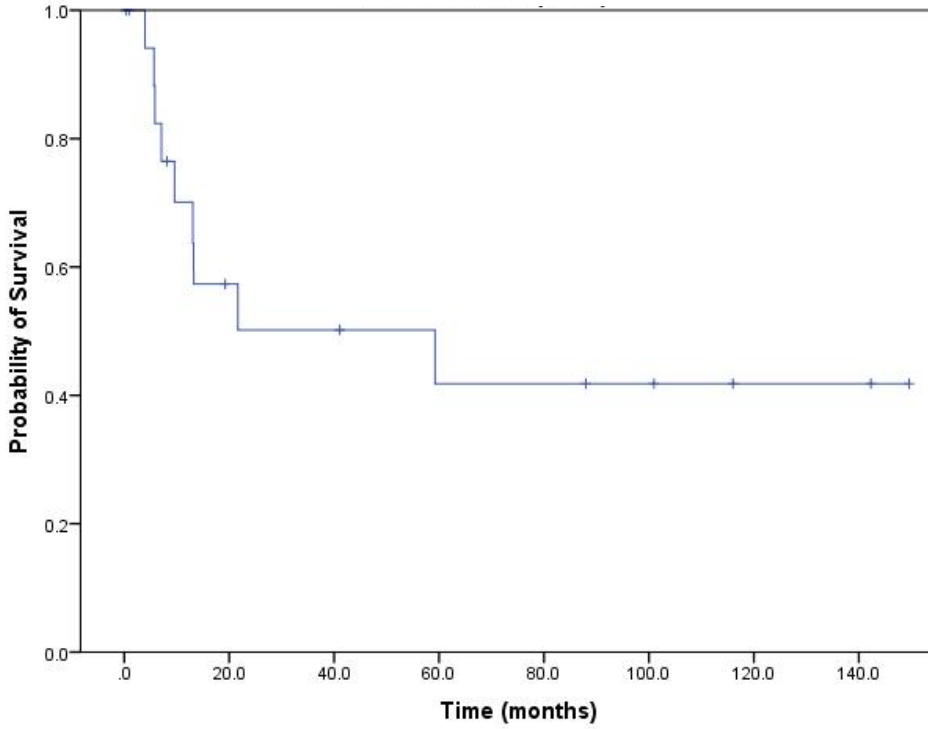
HSTCL

Induction phase		Consolidation phase		
Regimen	Response	Regimen	Response	Status
CHOP	CR	Chemotherapy	CR	DOD
CHOP-like	CR	Chemotherapy	CR	DOD
CHOP-like	CR	Auto BMT	CR	DOD
CHOP-like	CR	Auto BMT	CR	DOD
CHOP-like	CR	Chemotherapy	CR	DOD
CHOP-like	CR	Allo BMT	CR	DOD
CHOP-like	PR	Auto PBSC	CR	DOD
CHOP-like	PR	Auto PBSC	Failure	DOD
CHOP-like	CR	Chemotherapy	CR	DOD
CHOP-like	Failure	—	—	DOD
CHOP	Failure	—	—	DOD
CHOP-like	Failure*	—	—	DOD
CHOP-like	CR	Allo BMT	NE	TRD
CHOP	Failure	—	—	DOD
CHOP-like	CR	Chemotherapy	CR	DOD
CHOP-like	PR	Allo BMT	NE	TRD
Platinum-Ara-C based	PR	Auto PBSC	CR	Alive
CHOP	Failure	—	—	DOD
Platinum-Ara-C based	PR	Auto PBSC	CR	Alive
CHOP-like	Failure	—	—	DOD
CHOP-like	Failure	—	—	DOD

Belhadj et al BLOOD, 15 DECEMBER 2003, VOLUME 102, NUMBER 13

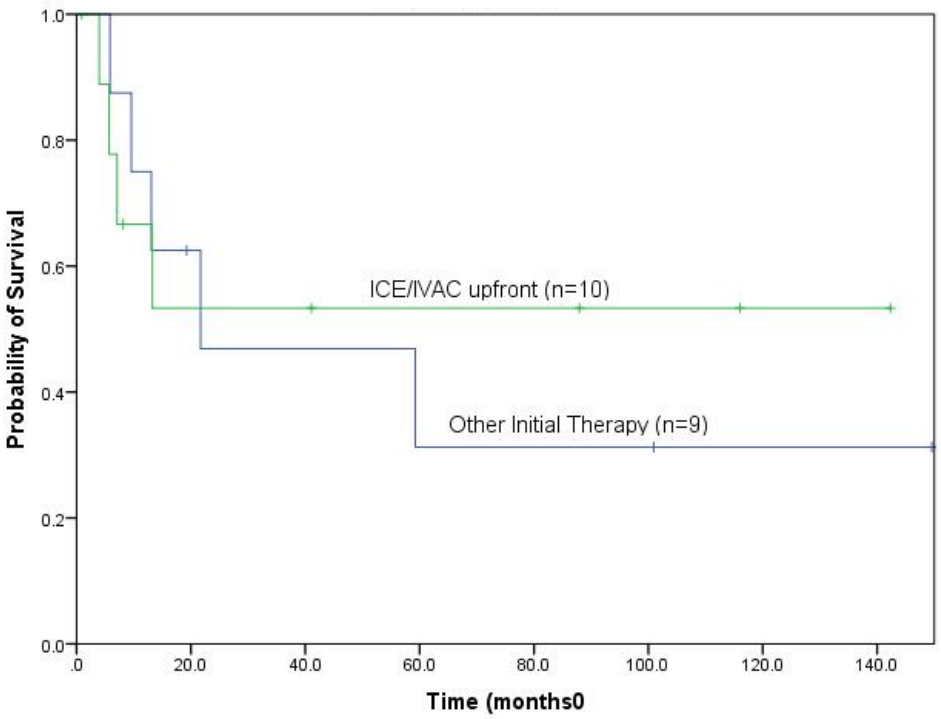
MSKCC Experience with Hepatosplenic TCL Non-CHOP induction-HSCT

Overall Survival N=19



Median OS: 59.2 mo

Overall Survival by Induction



Median OS
- ICE/IVAC upfront: Not Reached
- Other: 21.7 months
- Allo N=8
- Auto N=4

Updated data from: Voss, Lunning et al, Clin Lymphoma Myeloma Leuk. Feb 2013; 13(1): 8–14.

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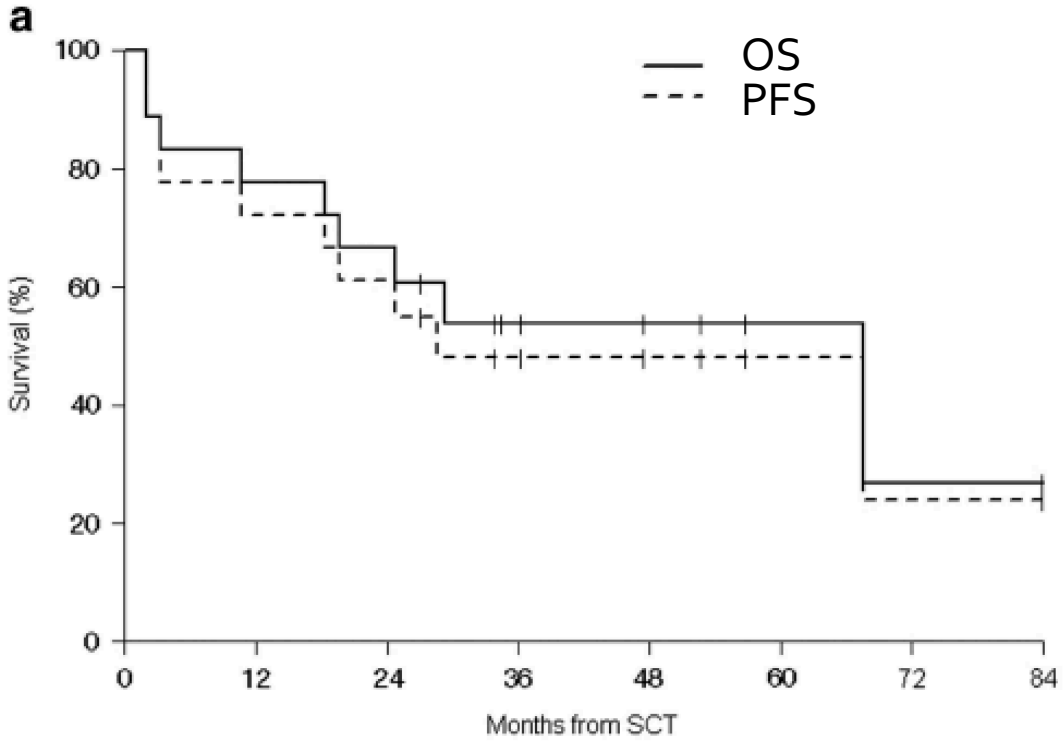
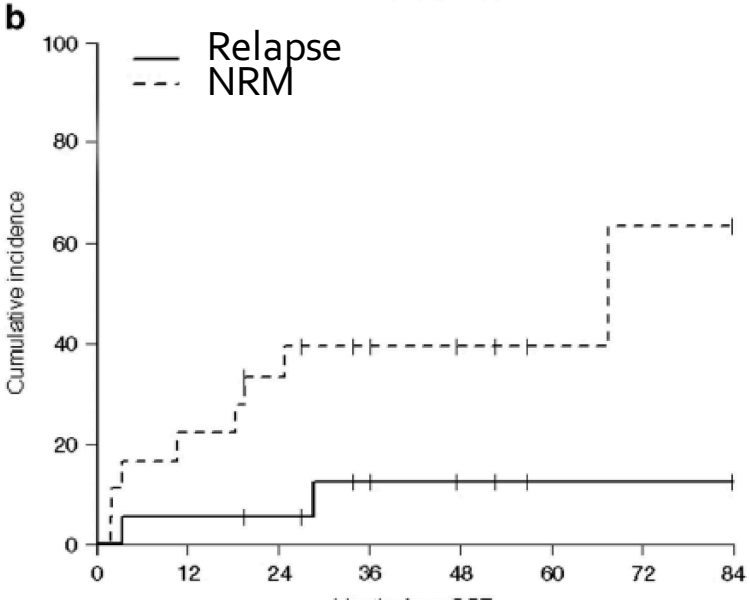
HSCTL
Allo-HSCT: EBMT



N= 25
Allo HSCT 18: 3 yr PFS 48%
Auto HSCT 7: 5 Relapsed



Tanase et al, Leukemia (2015) 29, 686–688

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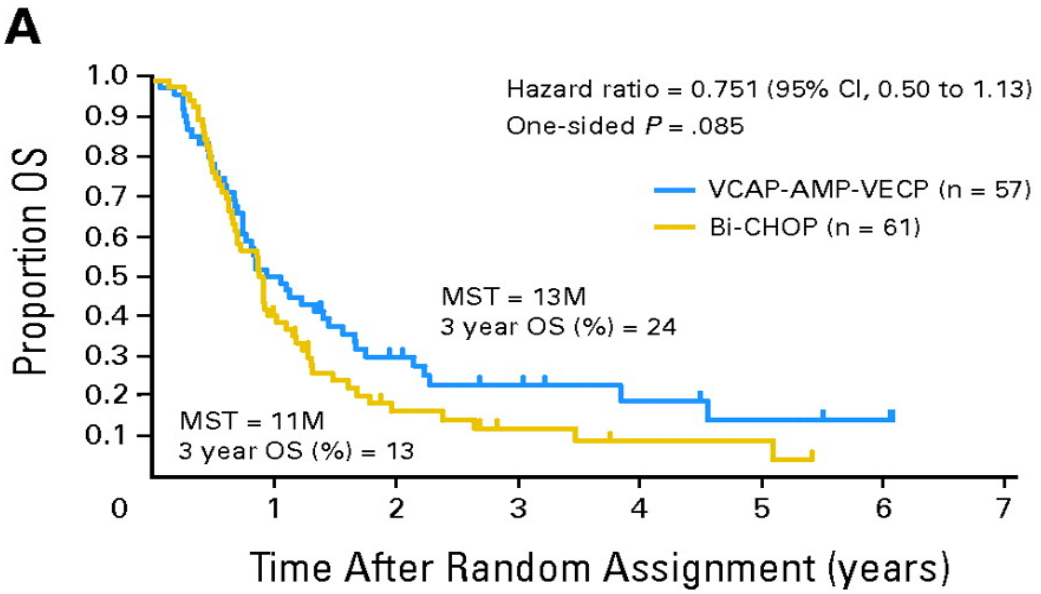
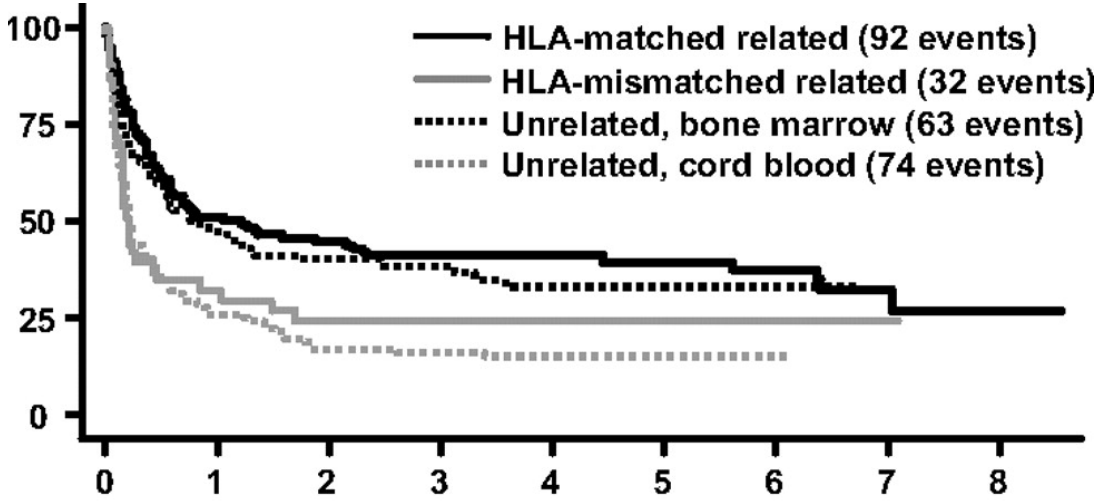
Adult T-cell Leukemia/Lymphoma
HTLV-1 Associated Lymphomas

ATLL



OS w/Allo



Tsukasaki K et al. JCO 2007;25:5458-5464; Hishizawa M et al. Blood 2010

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Different front-line treatments related to the histologic subtypes in PTCL: Is it possible today?

- For some rare subtypes it is not only possible but probably should be done
- NK/T-cell
  - Localized
    - Short course chemotherapy- VIPD or SMILE or gem/oxaliplatin, asparaginase + XRT
  - Advanced
    - SMILE or other L-asparaginase containing regimen-consider consolidation but unclear best option
- HSTCL-non-CHOP (ICE or IVAC) induction followed by SCT
- ATLL--non-CHOP (VCAP-AMP-VECP or EPOCH) induction followed by Allo SCT

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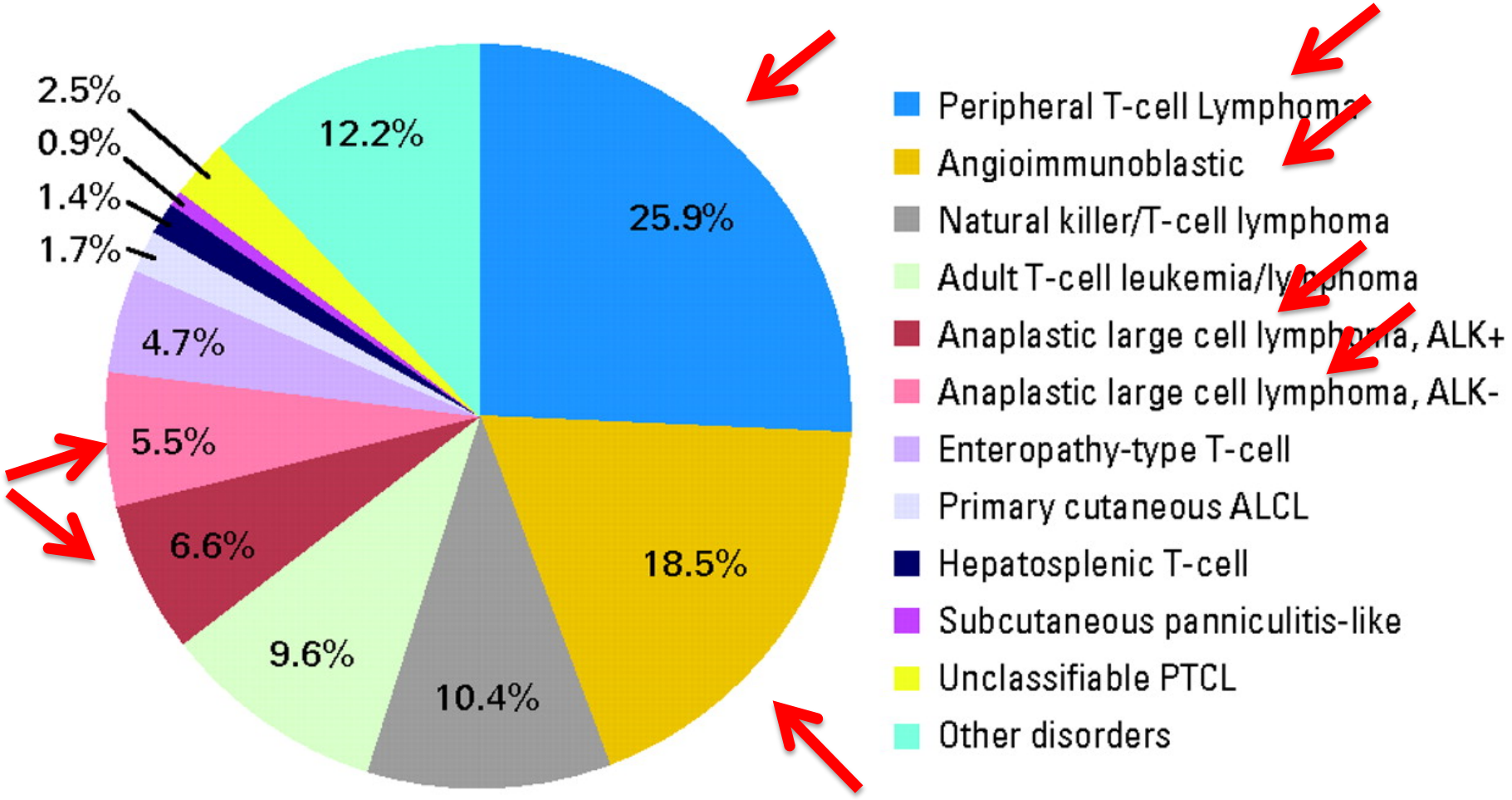
What about "more common" subtypes?

Proportion of Major T-cell Subtypes: North America



Vose JM, et al. *J Clin Oncol.* 2008;26:4124-4130

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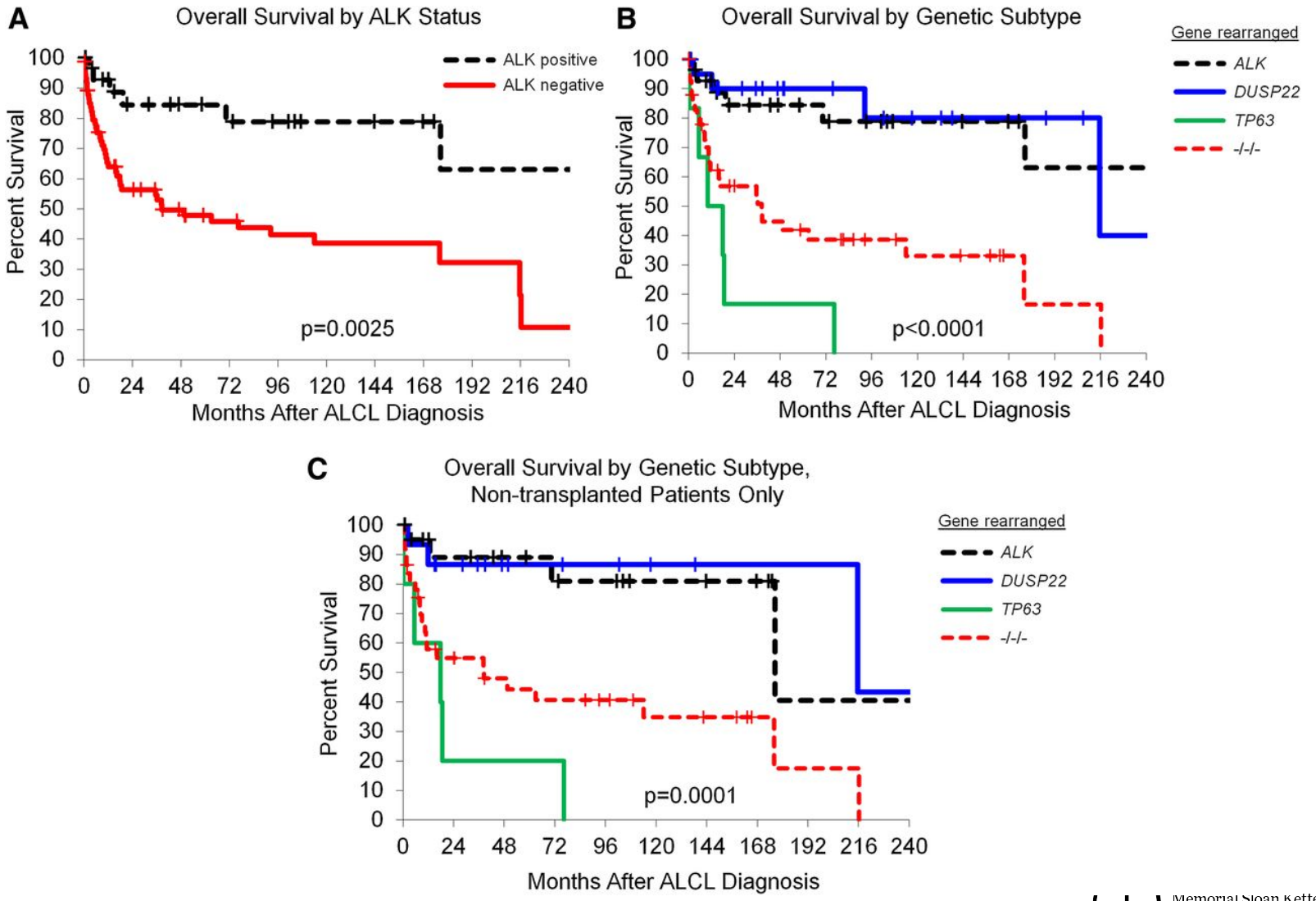
What about "more common" subtypes?

For ALCL (Maybe other CD30 +)

Its plausible

Prognostic impact of ALK, DUSP22 and TP63 rearrangements in a ALCL



Edgardo R. Parrilla Castellar et al. Blood 2014;124:1473-1480

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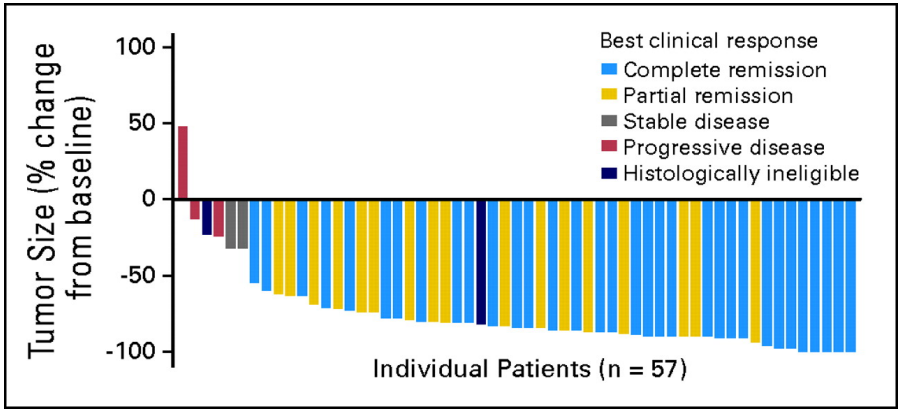
Brentuximab Vedotin in PTCL

PTCL	Best Clinical Response				Overall Response
	CR n (%)	PR n (%)	SD n(%)	PD n (%)	CR + PR n (%)
Mature T-/NK-cell (n=34)	8 (24)	6 (18)	6 (18)	14 (41)	**14 (41)**
AITL (n=13)	5 (38)	2 (15)	3 (14)	3 (23)	**7 (54)**
PTCL-NOS (n=21)	3 (14)	4 (19)	3 (14)	11 (52)	**7 (33)**

Relapsed ALCL-86% ORR



BV + CH-P

	ALCL N (%)	Other N (%)	Total N (%)
ORR	19 (100)	7 (100)	26 (100)
CR	16 (84)	7 (100)	23 (88)
PR	3 (16)	--	3 (12)

Horwitz S et al. Blood 2014;123:3095-3100
Pro et al. JCO 2012;30:2190-2196
Fanale et al JCO Oct 1, 2014:3137-3143;

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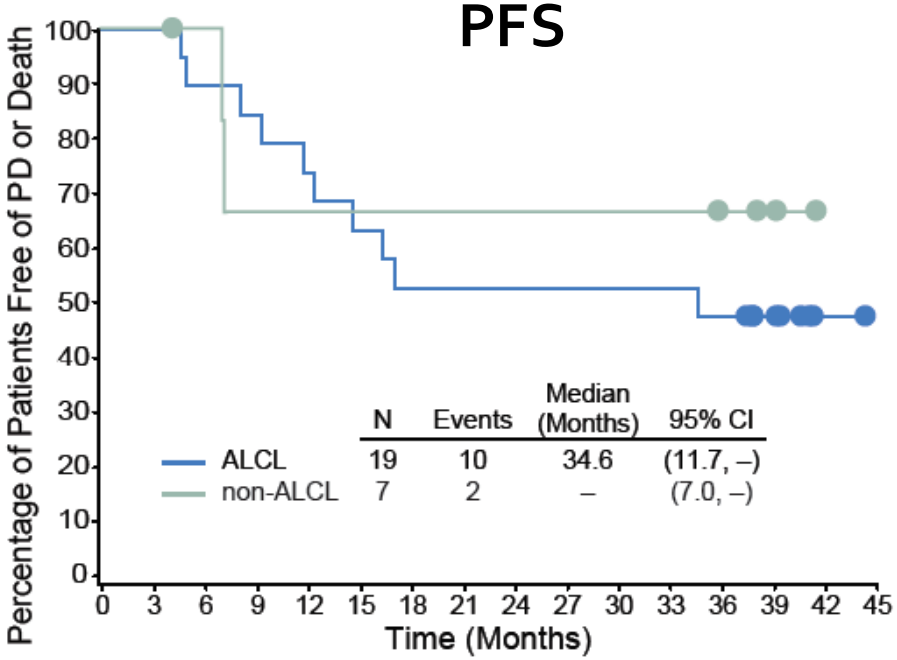
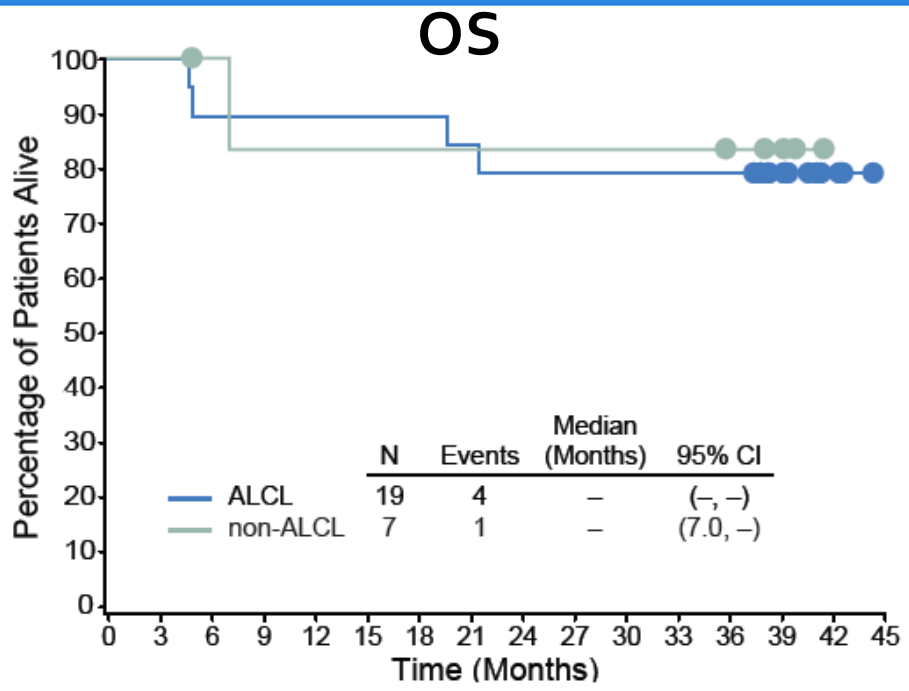
BV + CH-P in TCL





- Median follow-up 38.7 mos (range, 4.6 to 44.3),
- Estimated 3-yr PFS rate was 52% (95% CI: 31, 69)
  - ALCL (47%)
  - non-ALCL pts (71%)
- Estimated 3-yr OS rate was 80% (95% CI: 59, 91)
  - 79% for ALCL pts
  - 86% non-ALCL pts

Horwitz et al, ASH 2015, Abstract No. 1537

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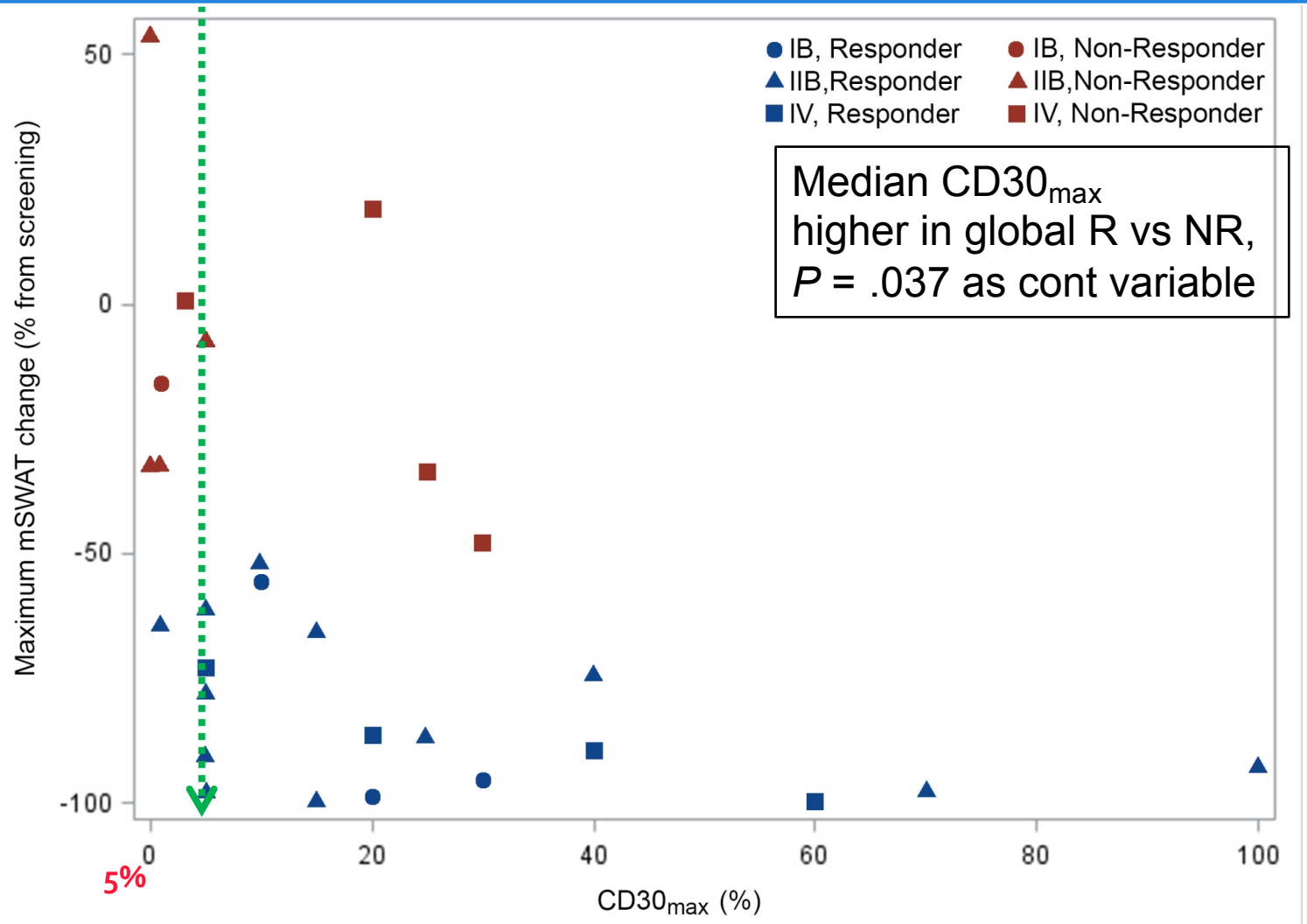
Mycosis Fungoides/Sezary Syndrome
Correlation of skin/global response with tissue $CD30_{max}$ by IHC

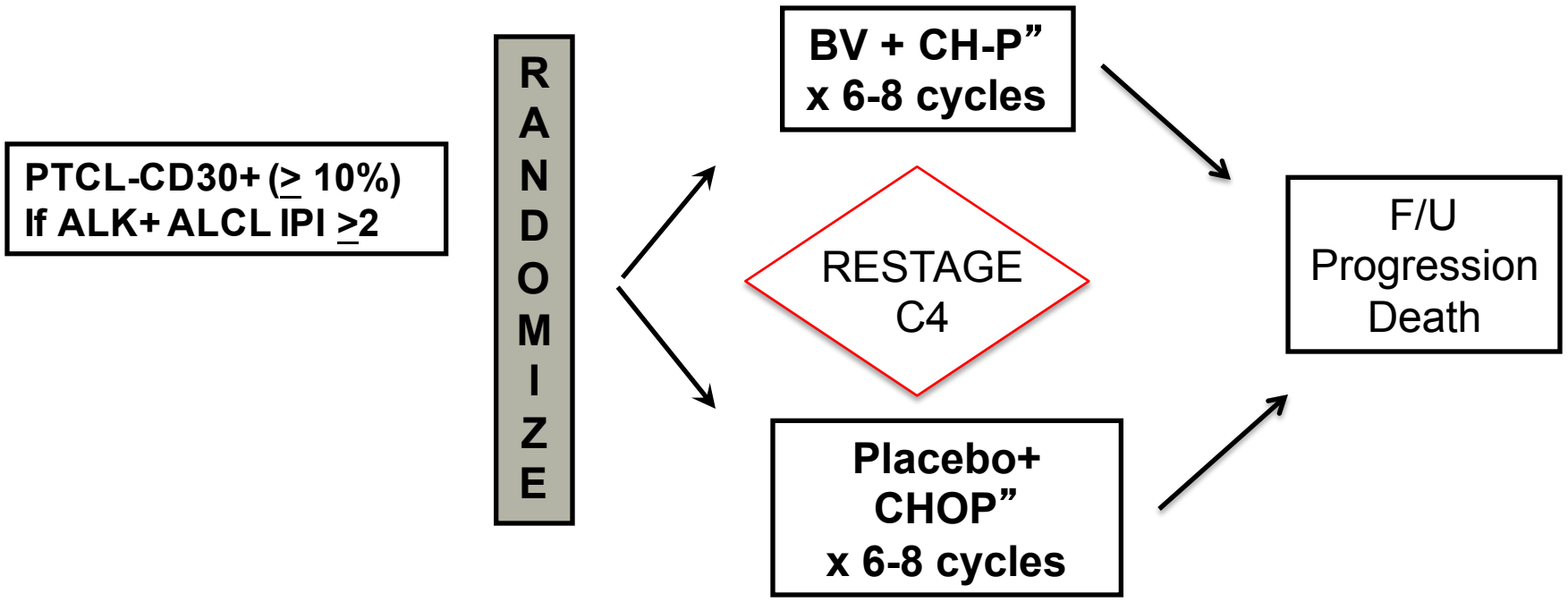


Median $CD30_{max}$ higher in global R vs NR, *P* = .037 as cont variable

Global ORR by $CD30_{max}$ <5% vs ≥5%, 17% vs. 83%, *P* = .0046

Kim et al JCO 2015

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Brentuximab Vedotin and CHP (A+CHP) Versus CHOP in the Frontline Treatment of Patients with CD30-positive Mature T-cell Lymphomas



N=300
Primary endpoint
PFS approx. 45% improvement

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What about the "most common" subtypes?
AITL or PTCL NOS

not there yet

FDA Approved Agents for PTCL: ORR (%)

	Pralatrexate	Romidepsin	Belinostat	Brentuximab vedotin
ALL	29	25	26	
PTCL, NOS	31	29	23	33
AITL	**8**	30	**46**	54
ALCL	29	24	15	**86**

O' Connor OA, et al. *J Clin Oncol*. 2011;29:1182-1189
Coiffier B, et al. *J Clin Oncol*. 2012;30:631-636
O'Connor OA et al, ASCO 2013;
Horwitz, S et al ICML 2013
Pro B, et al. J Clin Oncol. 2012;30:2190-2196
Horwitz S M et al. Blood 2014;123:3095-3100

Lumiere Study: Response

Response n (%)	Alisertib (n=96)	Comparator			
		All (n=85)	Pralatrexate (n=45)	Gemcitabine (n=22)	Romidepsin (n=18)
ORR (CR + PR)	35%	46%	44%	36%	61%
CR	19	28	29	23	33
PR	17	18	16	14	28
SD	30	20	24	14	17
PD	34	34	31	50	22

O'Connor et al ASH 2015 abstract 341

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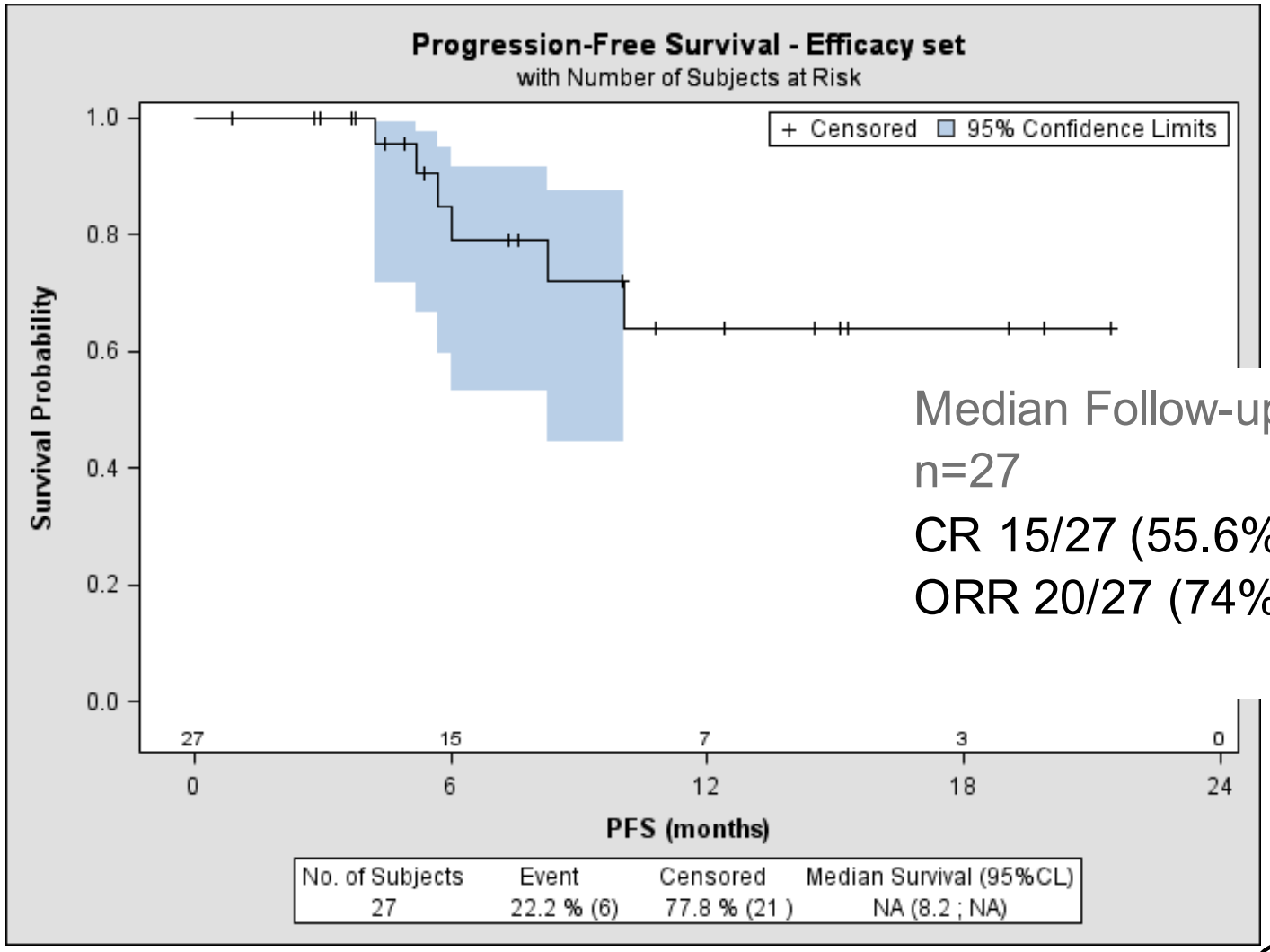
Romidepsin-CHOP Phase I-II PFS



Median Follow-up 10 months

n=27

CR 15/27 (55.6%)

ORR 20/27 (74%)

1 year estimated PFS 63.9% (95%CI 35.4 – 82.5)

Delarue et al ASH 2014

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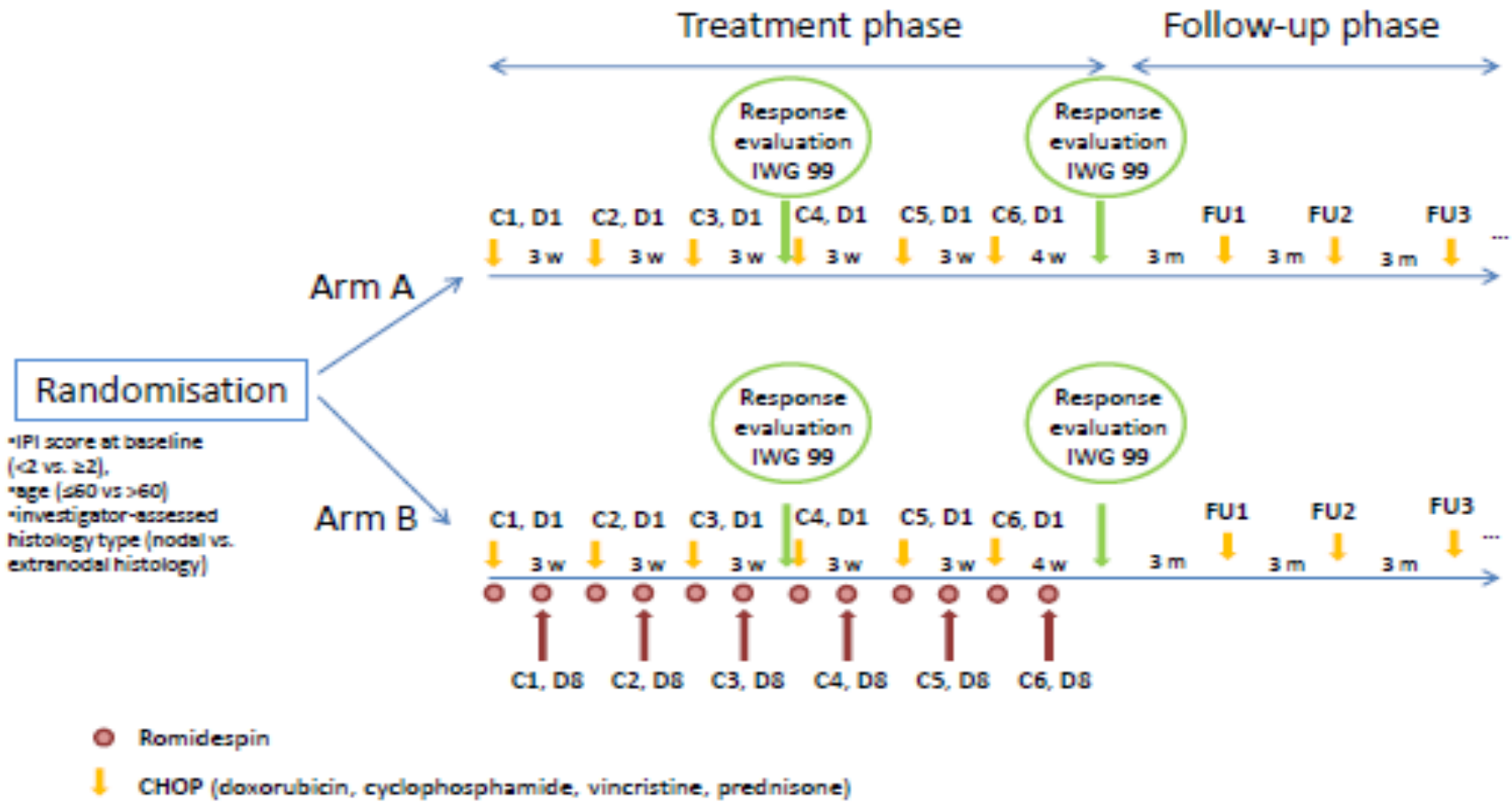
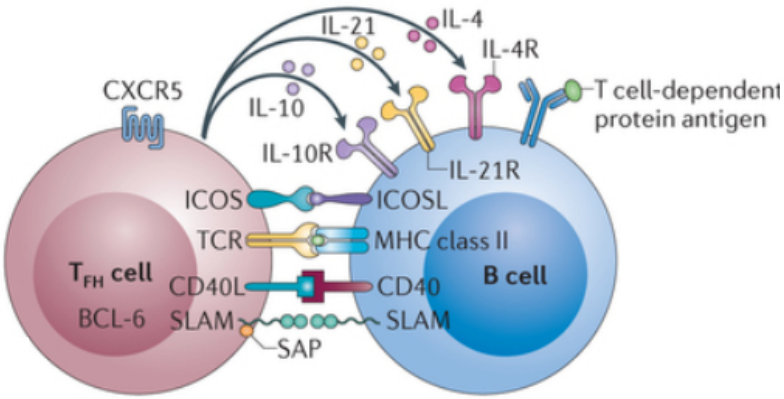
Phase III Ro-CHOP Study

- International randomized, open-label study
- Principal objective: PFS improvement
- Planned accrual: 420 patients



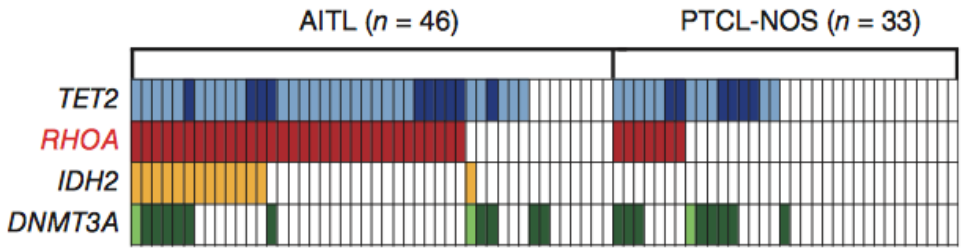
IDH2 Mutations in T Cell Lymphoma

T follicular helper CD4+ cells (TFH)



BCL6+
CXCR5+
PD1+

TFH-like lymphoma (AITL and some PTCL-NOS)



Sakata-Yanagimoto et al, *Nat Gen* 2014

IDH1/2 and Tet2 are mutually exclusive in AML but co-occur in TFH-like lymphoma

AG-221 (mIDH2 inhibitor)

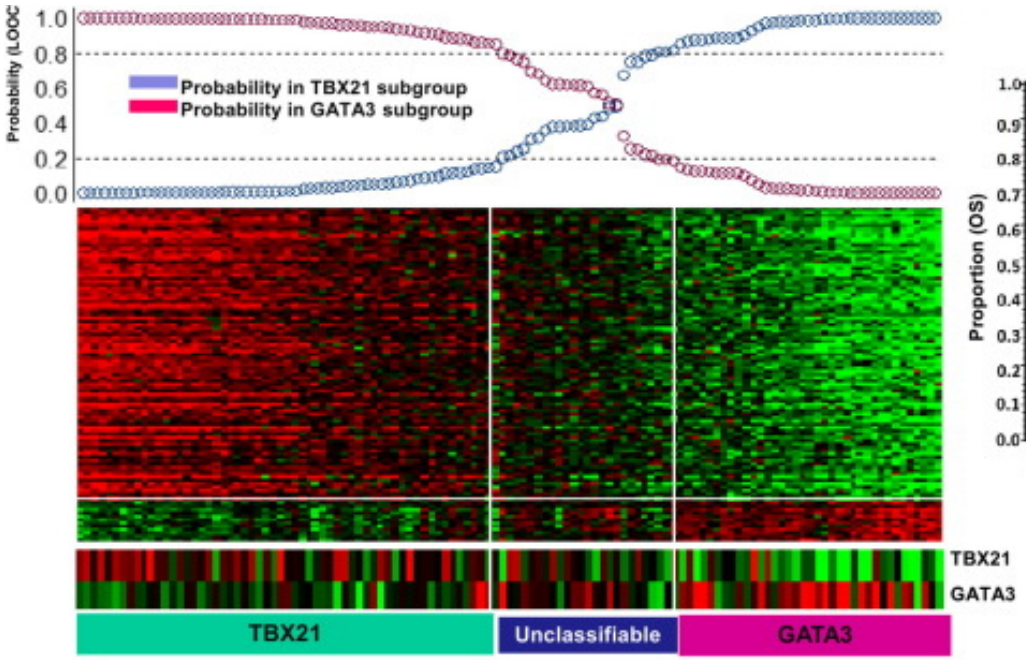
Phase I

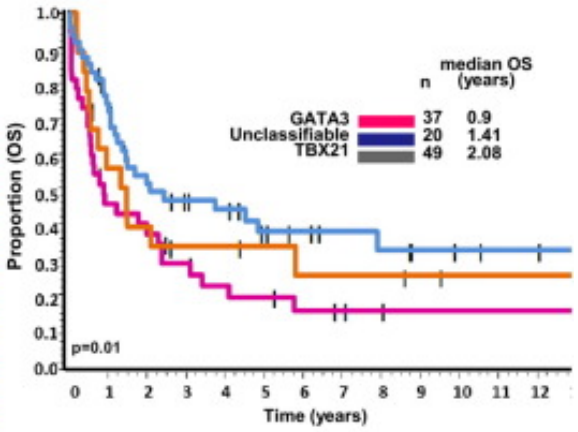
AITL, Glioma, Non-glioma solid

Expansion Cohorts

- AITL
- Glioma
- Non-glioma solid

Molecular subgroups within PTCL-NOS





- GATA3
  - 33% of cases
  - TH2 Transcription factor
  - Poor clinical outcome
  - PI3K and mTOR pathways
- TBX21
  - 49% of cases
  - TH1 Transcription factor Plasma cell-like gene signature (good outcome)
  - Cytotoxic cell-like gene signature (poor outcome)
  - NFkB and STAT3

Javeed Iqbal et al; Blood Reviews, 18 August 2015

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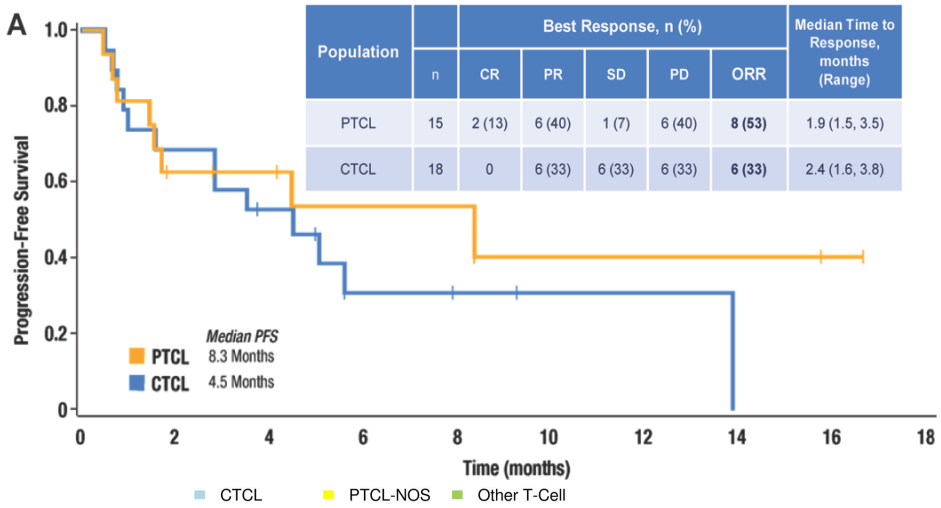
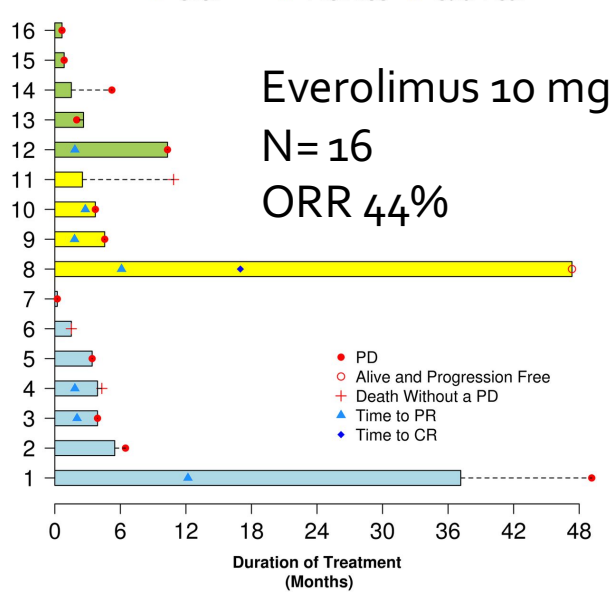
Targets for subsets of PTCL

Duvelisib (IPI-145): ORR 53%



Population	n	Best Response, n (%) CR	PR	SD	PD	ORR	Median Time to Response, months (Range)
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)



Everolimus 10 mg/D
N= 16
ORR 44%

Other Agents

- Jak Inhibitors
- MTOR Inhibitors
- Checkpoint Inhibitors
- Demethylating Agents
- Lenalidomide
- Syk inhibitors
- ITK inhibitors

- It is possible that subsets of PTCL may benefit from subtype specific approaches
- But understanding this will take sequential clinical trials
- With correlates to identify predictive biomarkers

Horwitz et al. ASH 2014;
Witzig et al. Blood 2015;126:328-335

Different front-line treatments related to the histologic subtypes in PTCL: Is it possible today?

- For some rare subtypes (NK/T, HSTCL, ATLL)
  - Yes
- For the more common subtypes
  - Not Really
- ALCL
  - Rare need for consolidation for ALK+ or perhaps DUSP22 rearranged
  - CD30 (ALCL and others), we should have data soon
- PTCL-NOS, AITL
  - No compelling data at present to support other than standard approach
  - Enough targets and targeted agents that this may be possible but defining who will benefit will be challenging…but not today

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