Newly Diagnosed *PTCL*

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Disclosures

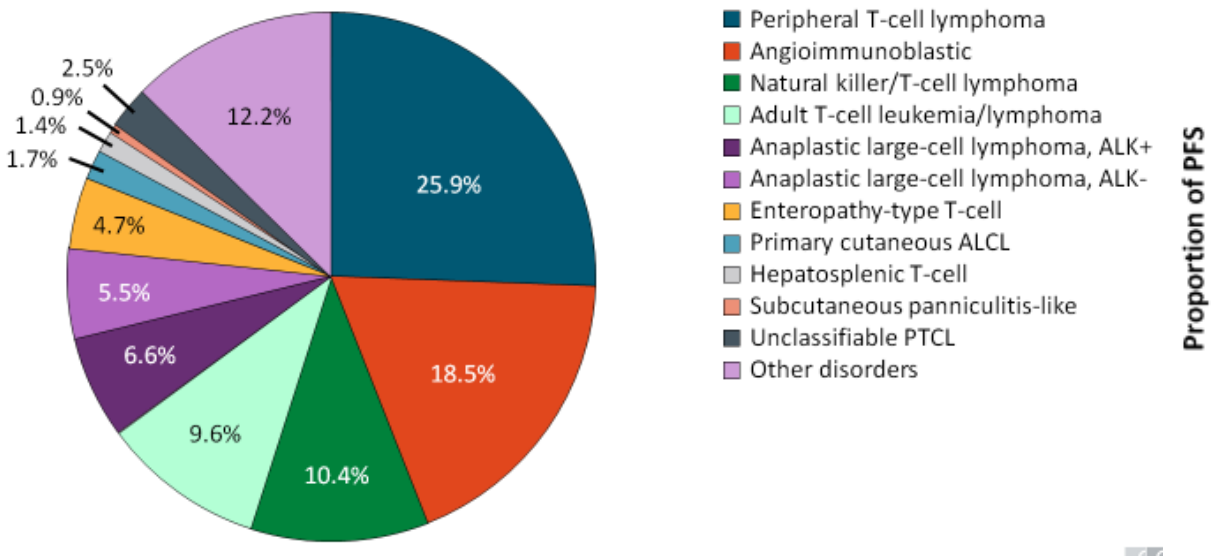
Honoraria, Research Grants: **Seattle Genetics**

Honoraria, Research Grants: **Takeda**

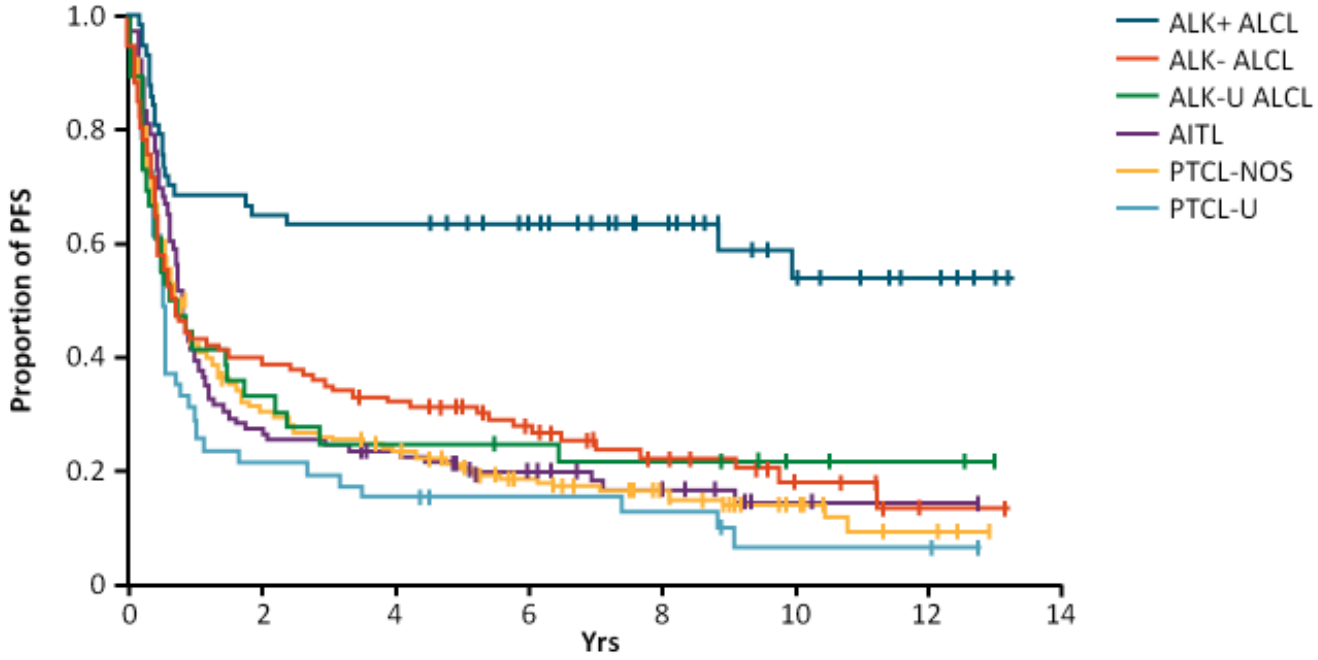
Research Grant: **Verastem**

PTCL: Diversity and Outcome

Distribution of PTCL Subtypes, per International T-cell Project[1]



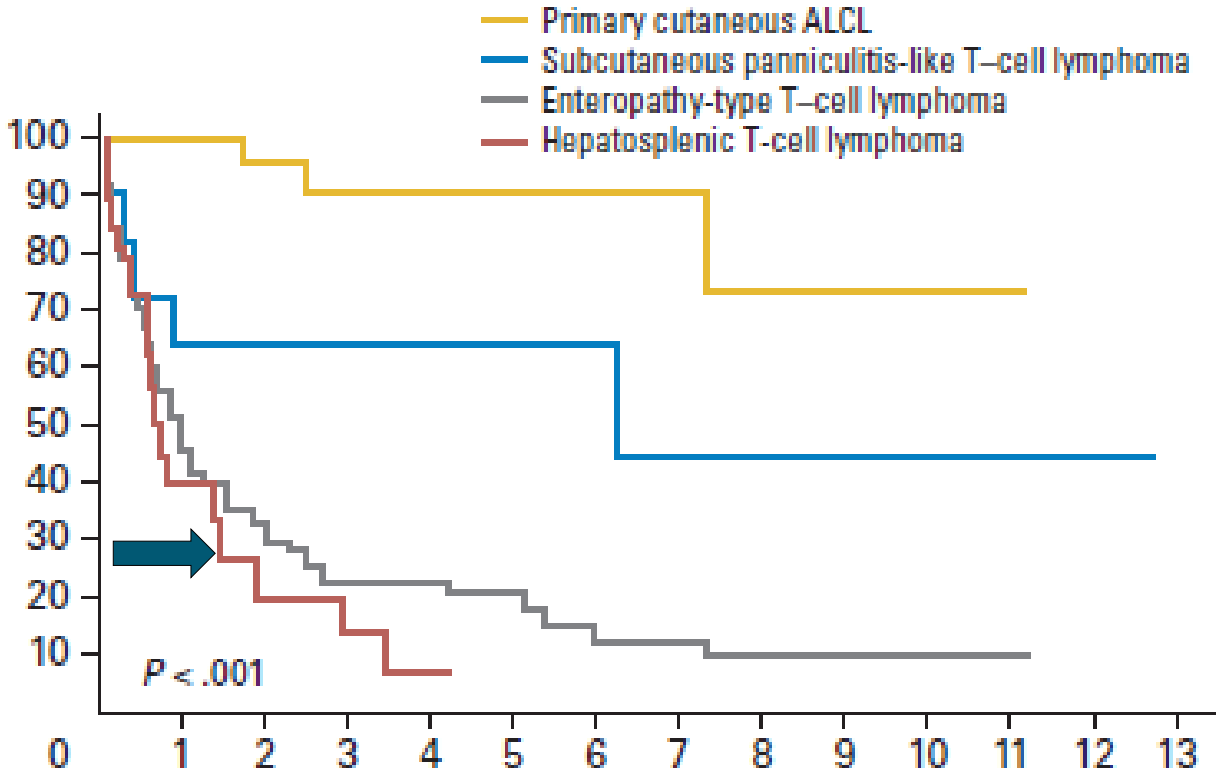
PFS by Subtype in Swedish Registry (N = 755)[2]

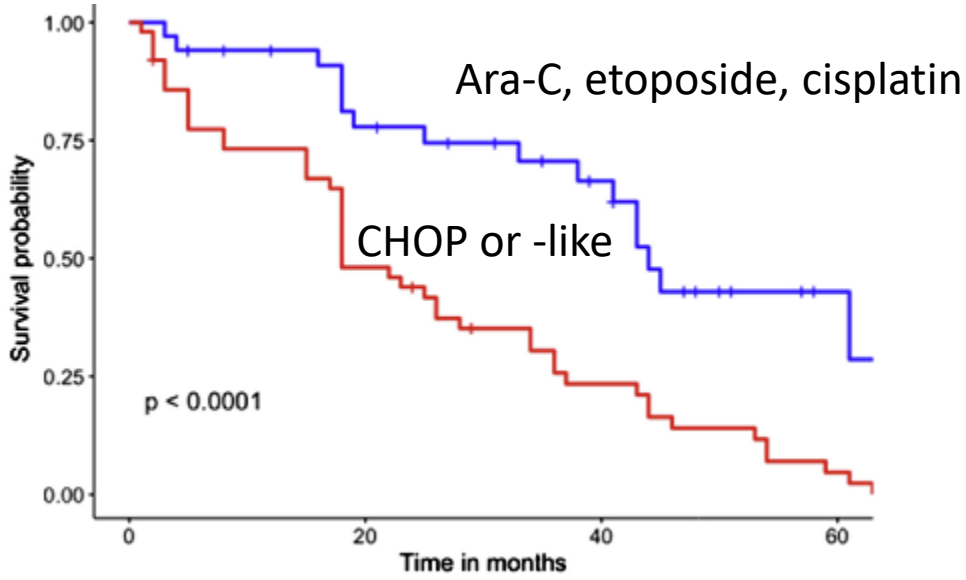


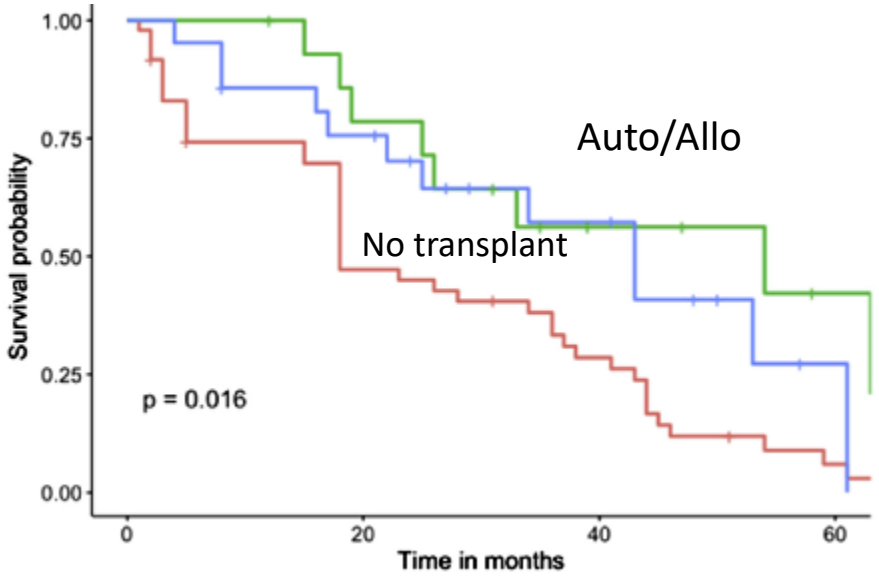
The nodal subtypes account for 66% of North American cases

1. Vose. J Clin Oncol. 2008;26:4124. 2. Ellin. Blood. 2014;124:1570.

Hepatosplenic T-Cell Lymphoma





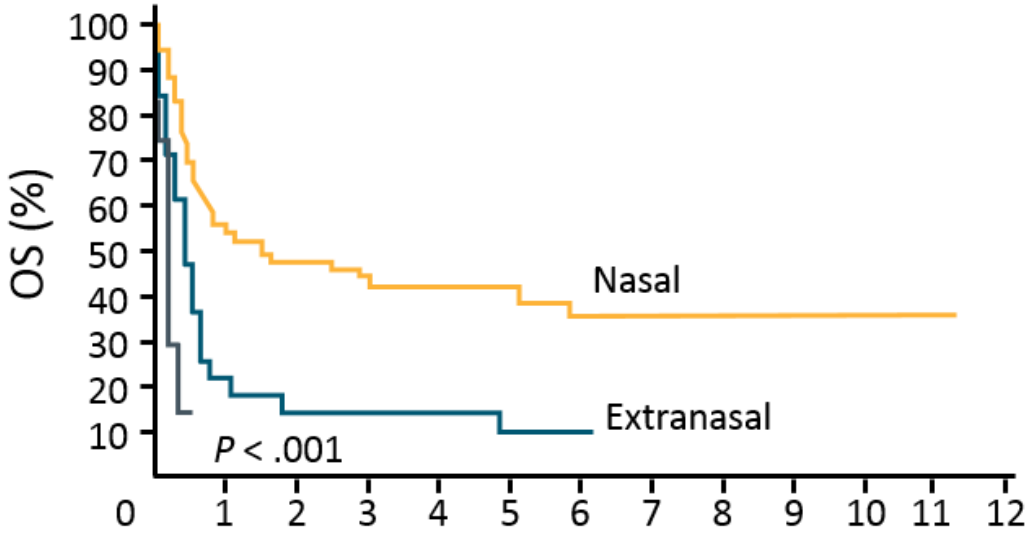


Vose. J Clin Oncol. 2008;26:4124 Klebaner. Clin Lymphoma Myeloma Leuk. 2019

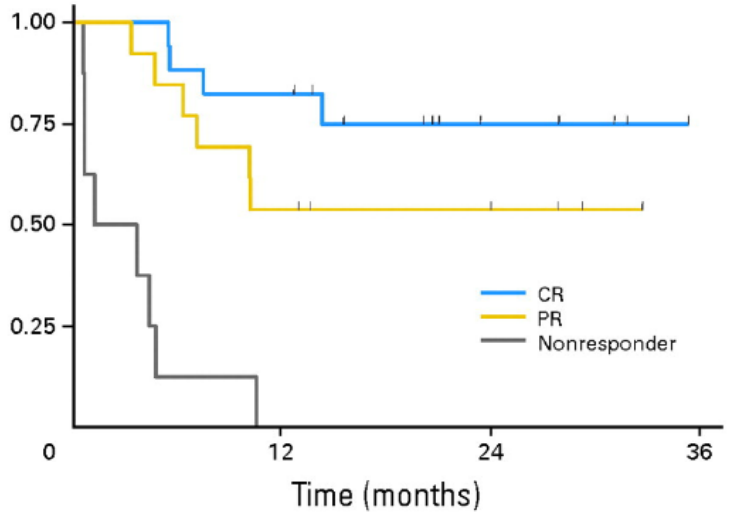
NK/T-Cells, Nasal Type

Suggested treatment regimens

- Sequential combined modality
  - Dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide (SMILE, mSMILE)
  - L-asparaginase, methotrexate, dexamethasone (AspaMetDex)
  - Gemcitabine-based combination
  - Consolidation with XRT
- Concurrent chemoradiotherapy (CCRT)
  - 50 Gy RT + 3 courses dexamethasone, etoposide, ifosfamide, carboplatin (DeVIC)
  - 40 to 52.8 Gy RT + cisplatin followed by 3 cycles etoposide, ifosfamide, cisplatin, dexamethasone (VIPD)



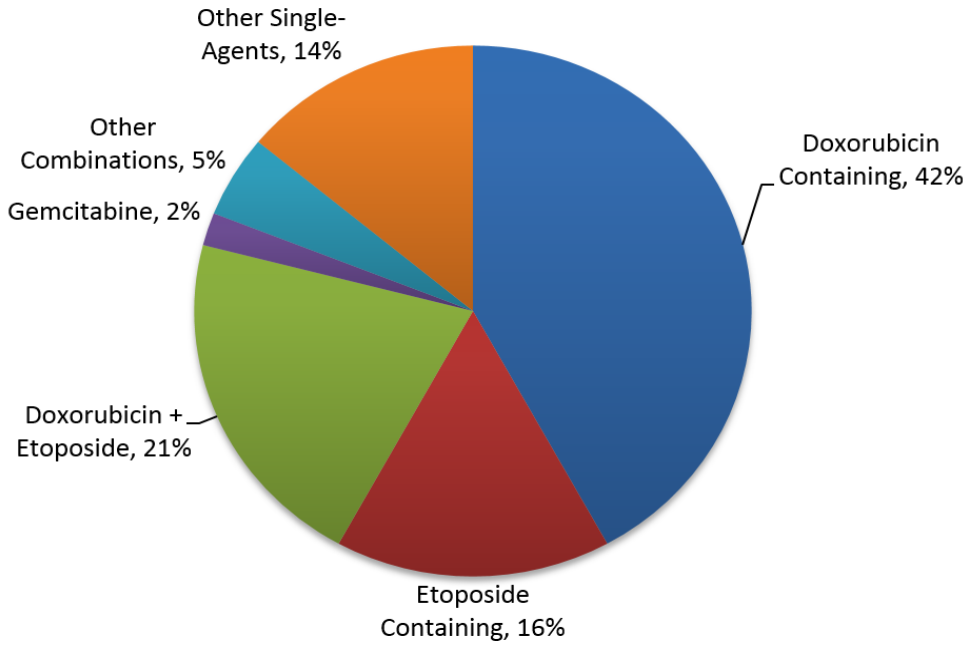
OS with SMILE



Yamaguchi M, et al. J Clin Oncol. 2011;29:4410-4416

Common Nodal Subtypes Complete Registry

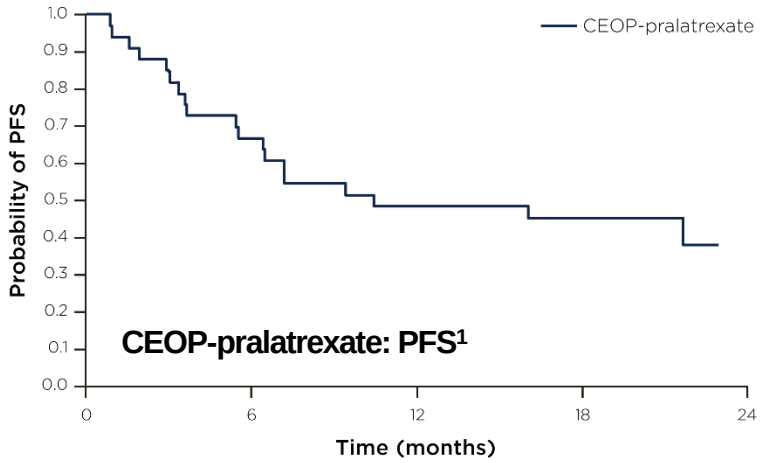
Histopathology	N 234
PTCL-NOS	140 (51.3)
AITL	71 (26.0)
ALCL	62 (22.7)
ALK-	49 (79.0)
ALK + (IPI 2-5)	13 (21.0)

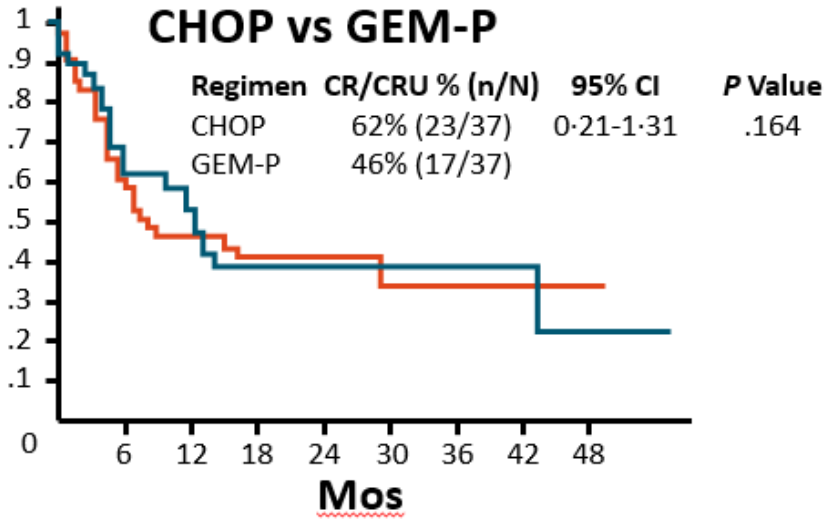


Carson K et al. Cancer 2017

Attempts to improve upon CHOP

- Addition of novel agent(s) to existing SoC induction therapy
  - CHO(E)P + drug(s) X
  - Novel drug combinations and auto/allogeneic transplant in first remission





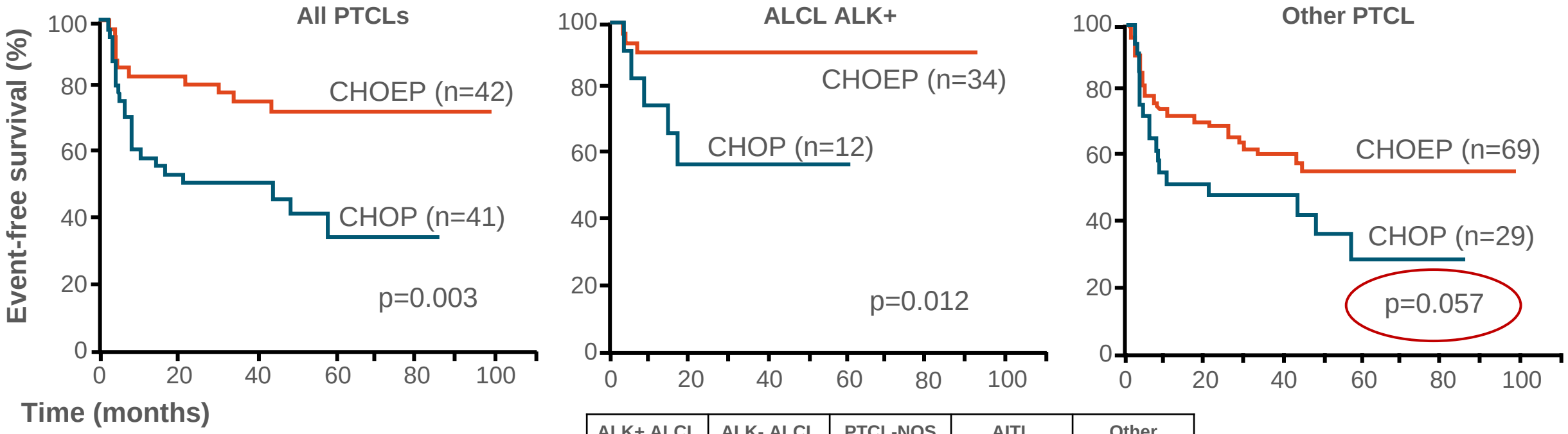
Response/ survival N=33	CEOP- pralatrexate
CR rate, % (n/N)	52 (17/33)
2-year PFS, % (95% CI)	39 (21–57)
2-year OS, % (95% CI)	60 (39–76)

Response/ survival N=87	GEM-P	CHOP	p-value
CR rate, % (n/N)	62 (23/37)	46 (17/37)	0.164[2]
2-year PFS, % (95% CI)	38 (23–53)	37 (21–52)	0.82[2]
2-year OS, % (95% CI)	64 (46–77)	51 (33–67)	0.30[2]

1. Advani RH. *Br J Haem* 2016;172:535–544; 2. Gleeson M. *Lancet Haem* 2018;5:e190–e200; 3. Gleeson M. *Lancet Haem* 2018;5:e190–e200

Addition of etoposide to CHOP improves event-free survival outcomes in young patients (<60 years) with PTCL

- Results from seven trials of the German high-grade NHL study group: T-cell lymphoma subset analysis
- A positive effect of etoposide on event-free survival was confirmed in a subset analysis of ALK-positive ALCL
- This trend continued when the remaining PTCL subentities were analysed together



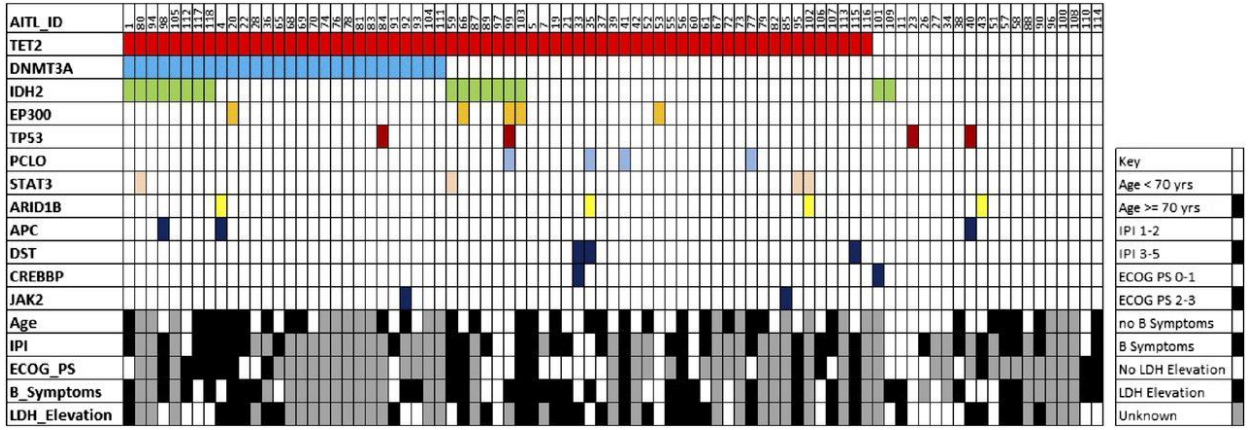
	ALK+ ALCL	ALK- ALCL	PTCL-NOS	AITL	Other
Patients, % (N=320)	24.4	35.3	21.9	8.8	9.7

Schmitz N. *Blood* 2010;116:3418–3425.

Mutations of DNA Methylation Genes in PTCL: New Targets for Therapy

- Recurrent mutations of genes involved in DNA methylation regulation have been described in PTCL
- Higher incidence in angioimmunoblastic T-cell lymphoma (AITL) and PTCL not otherwise specified (PTCL-NOS), with features of T-follicular helper cells (TFH-like)
- HDAC inhibitors like romidepsin and belinostat act on this pathway

Distribution of mutations in 85 AITL cases



Odejide. Blood. 2014;123:1293.

Ro-CHOP: Clinical Response and Survival Outcomes

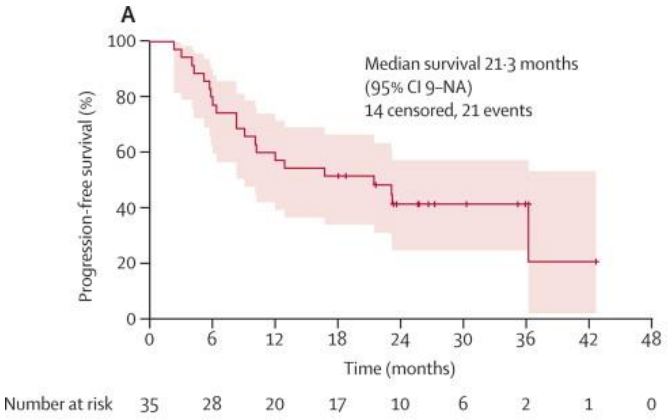
	Total (N=35)
Objective Response, n (%)	**24 (68)**
Complete Remission	18 (51)
Partial Remission	6 (17)

DLT reached at the dose of Romidepsin of 12 mg/m^2 on days 1 and 8

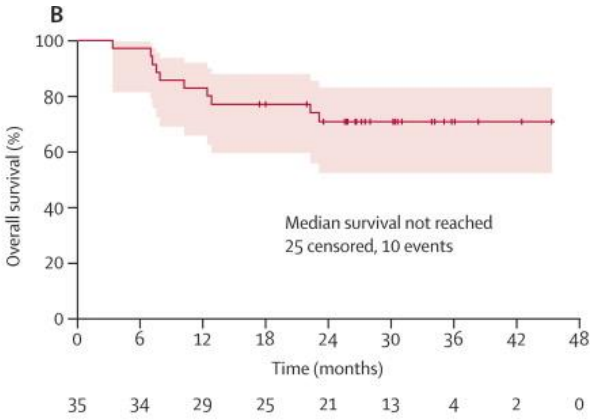
Phase III trial of Ro-CHOP vs CHOP nears completion of accrual

Entire efficacy population

PFS

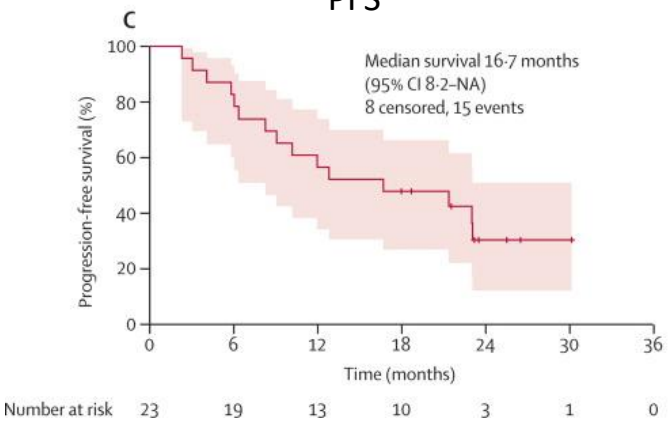


OS

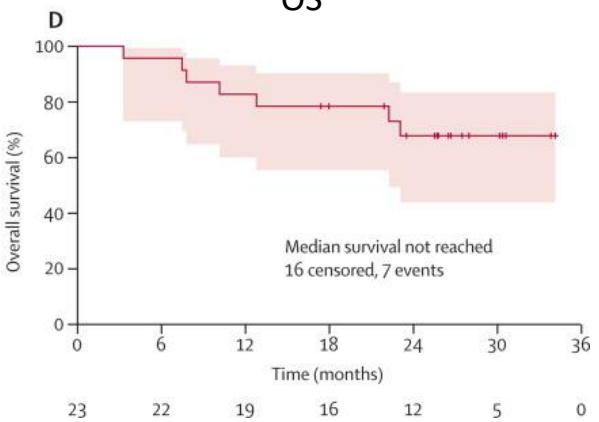


Population of patients treated at the recommended romidepsin dose of 12 mg/m^2

PFS



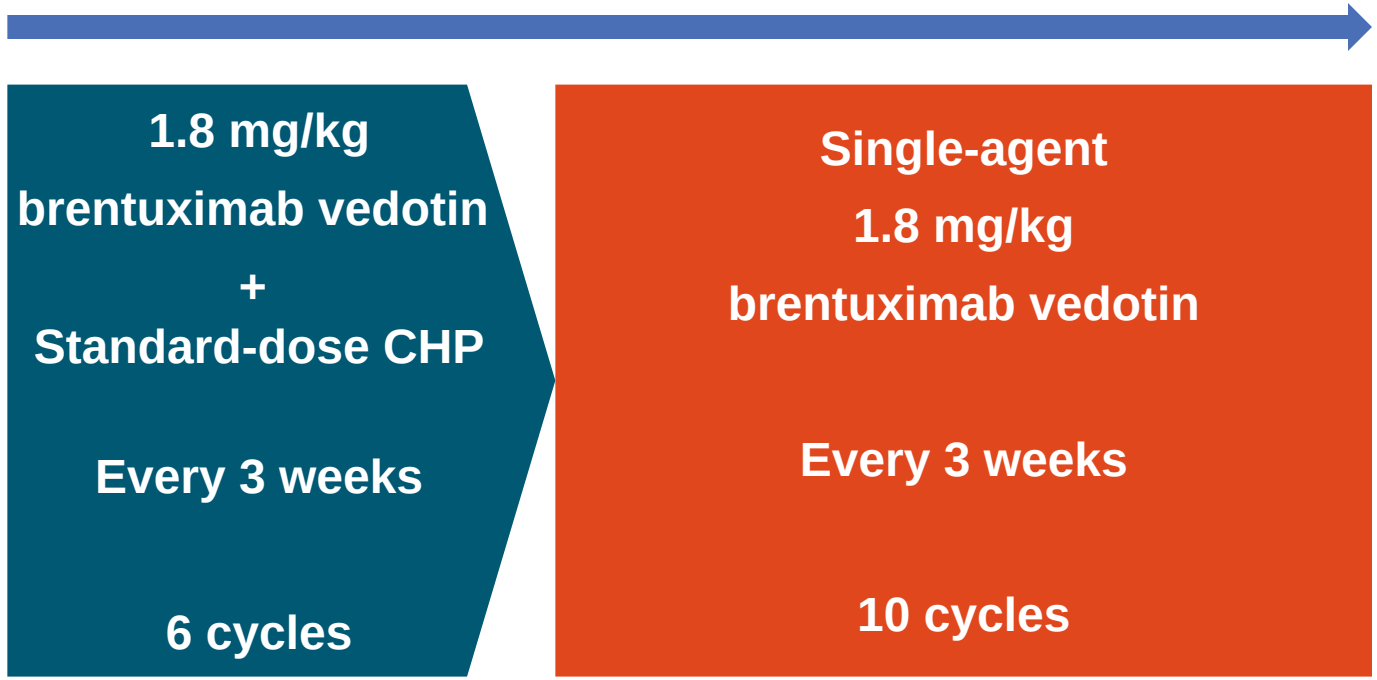
OS



Dupuis, J. et al. *Lancet Haematol*. 2015; 2:e160-65.

Phase I Frontline Combination Study of Brentuximab Vedotin + CHP

Arms 2 & 3: Combination Therapy



- Phase 1, open-label, multicenter study
- Arm 2 designed to determine recommended dose of brentuximab vedotin in combination with CHP (CHOP without vincristine) to be further evaluated in Arm 3
  - **The maximum-tolerated dose was not exceeded at 1.8 mg/kg q3wk**

*Arm 1 investigated sequential brentuximab vedotin and CHOP

Fanale, M et al, *JCO*, 2014;32:3137-3143

First-line brentuximab vedotin + CHP in patients with CD30+ PTCL: best response by diagnosis

Efficacy: combination treatment[1], n (%)	sALCL (n=19)	Other diagnoses (n=7)	Total (N=26)
Objective response rate	19 (100)	7 (100)	26 (100)
CR	16 (84)	7 (100)	23 (88)
PR	3 (16)	–	3 (12)
Median PFS	–	–	Not reached
Median OS	–	–	Not reached

PTCL-NOS: n=2
AITL: n=2
ATLL: n=2
EATL: n=1

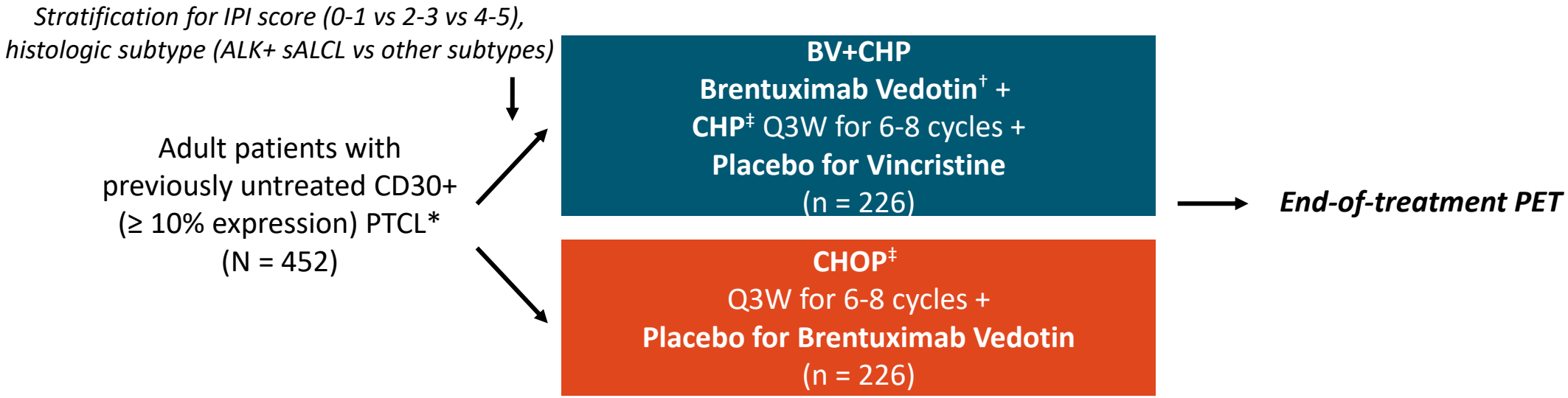
5-year follow up[2]

- Median follow up: 59.6 months (range, 4.6–66.0 months) from first dose
- Median OS and PFS were not reached
  - Estimated 5-year PFS and OS rates were 52% and 80%, respectively
- In total, 95% of patients (n=18) with treatment-emergent peripheral neuropathy reported resolution or improvement of symptoms
- At the end of the study, 50% of patients (n=13) remained in remission; PFS ranged from 37.8+ to 66.0+ months

Fanale MA et al. *J Clin Oncol* 2014;32:3137–3143; 2. Fanale MA et al. *Blood* 2018;131:2120–2124.

ECHELON-2: Brentuximab Vedotin + CHP vs CHOP in Previously Untreated CD30+ PTCL

- Multicenter, randomized, double-blind, double dummy, active-controlled phase III trial



*PTCL includes sALCL (including ALK+ sALCL with IPI ≥ 2 and ALK- sALCL), PTCL-NOS, AITL, ATLL, EATL, HSTCL. Study targeted 75% (± 5%) ALCL in line with European regulatory commitment. †Brentuximab vedotin: 1.8 mg/kg. ‡Cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 (CHOP only), prednisone 100 mg on Days 1-5. G-CSF primary prophylaxis, consolidative RT, SCT per investigator discretion.

- Primary endpoint: PFS per BICR (SCT or RT consolidation not considered events)
- Secondary endpoints: OS, PFS per BICR in sALCL patients, CR, ORR, safety

Horwitz. Lancet. 2019;393:229.

Baseline characteristics in ECHELON-2

Characteristic	A+CHP (N=226)	CHOP (N=226)
Male, n (%)	133 (59)	151 (67)
Age, years, median (range)	58 (18–85)	58 (18–83)
IPI score, n (%)		
0–1	53 (23)	48 (21)
2–3	140 (62)	144 (64)
4–5	33 (15)	34 (15)
Stage III/IV, n (%)	184 (81)	180 (80)

Characteristic	A+CHP (N=226)	CHOP (N=226)
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)

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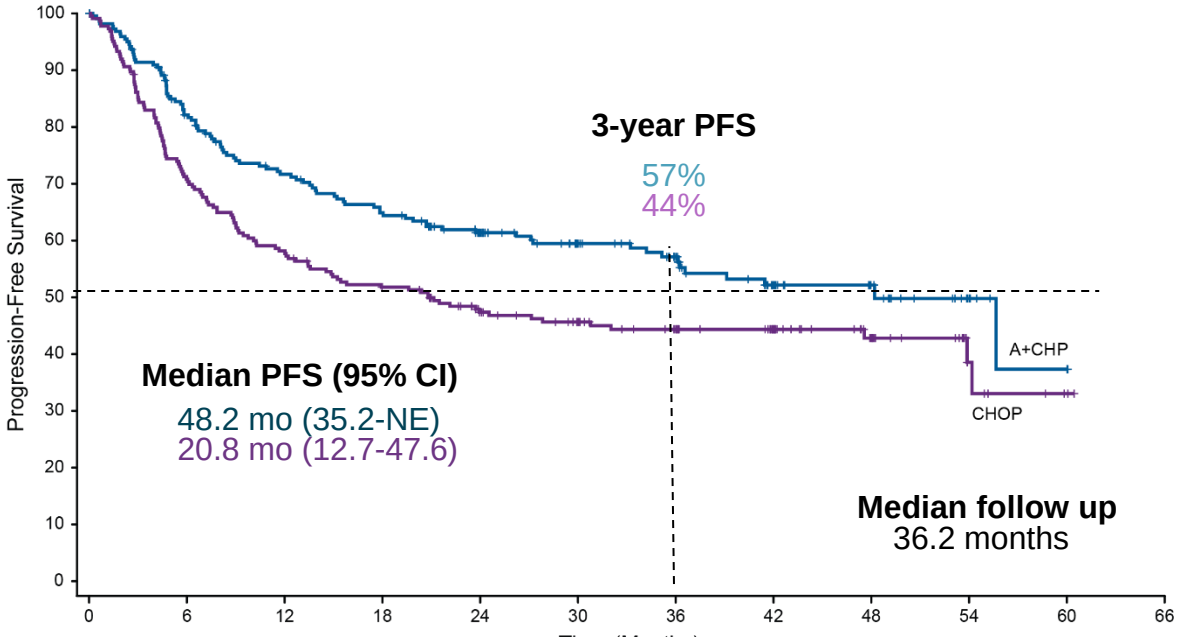
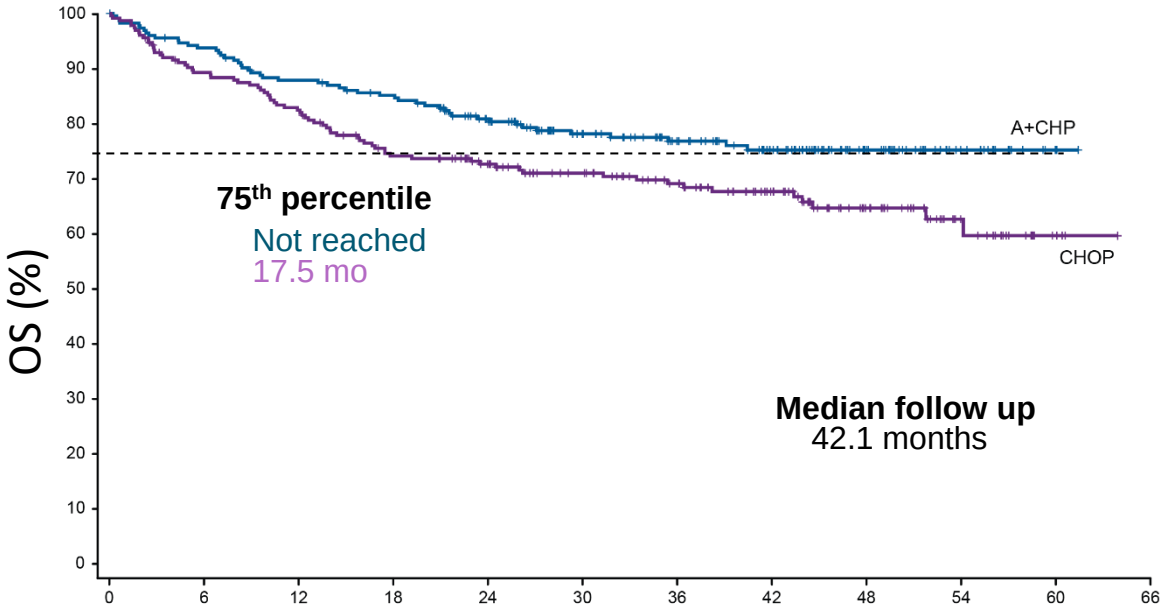
Horwitz SM et al. *Lancet* 2019;393(10168):229–240.

ECHELON-2: PFS and OS with BV + CHOP vs CHOP Alone in ALCL



Mos

Treatment	Events, n (%)	HR (95% CI)	*P* Value
BV+CHP	95 (42)	0.71 (0.54-0.93)	.011
CHOP	124 (55)		



Mos

Treatment	Deaths, n (%)	HR (95% CI)	*P Value*
BV+CHP	51 (23)	0.66 (0.46-0.95)	.0244
CHOP	73 (32)		

Horwitz. Lancet. 2019;393:229.

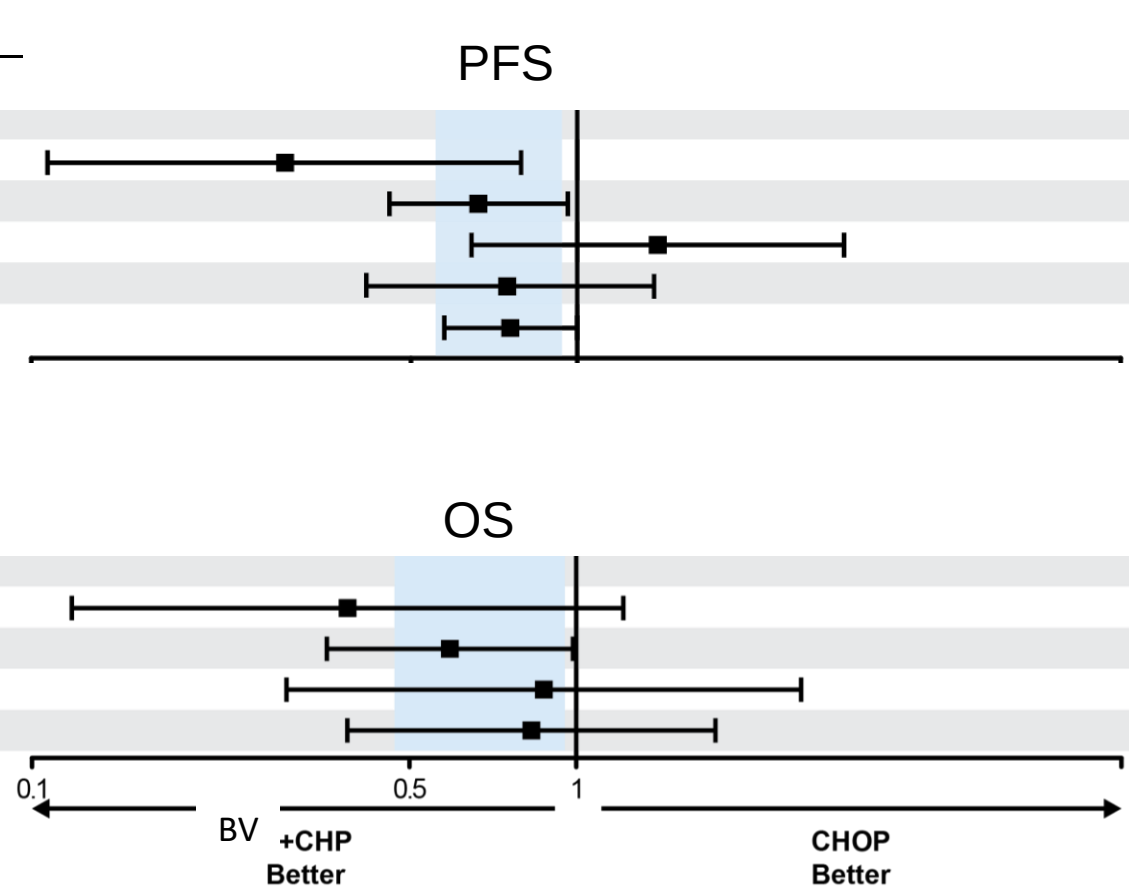
ECHELON-2: PFS and OS by PTCL Subtypes

PFS

	Event/N		HR (95% CI)
	BV +CHP	CHOP	
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)
PFS (PD, Death)	84/226	103/226	0.75 (0.56, 1.00)

OS

Disease Indication			
ALK-positive sALCL	4/49	10/49	0.38 (0.12, 1.22)
ALK-negative sALCL	25/113	34/105	0.58 (0.35, 0.98)
AITL	8/30	6/24	0.87 (0.29, 2.58)
PTCL-NOS	11/29	20/43	0.83 (0.38, 1.80)



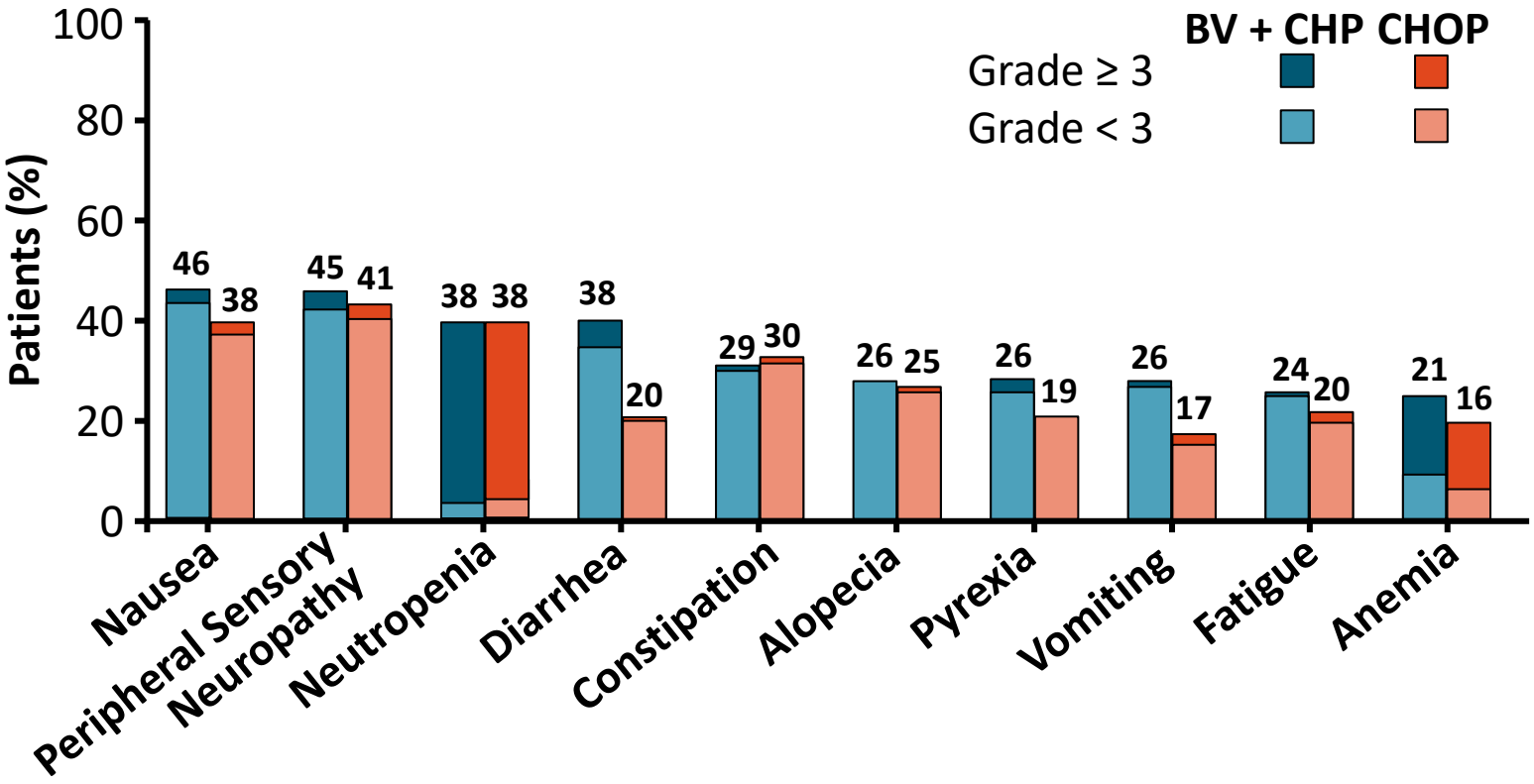
- Frontline treatment with BV+CHP superior to CHOP for patients with CD30-positive PTCL
- PFS and OS benefits greatest in patients with sALCL

Horwitz. Lancet. 2019;393:229.

ECHELON-2: AEs

AE, n (%)	BV+CHP (n = 223)	CHOP (n = 226)
Any AE	221 (99)	221 (98)
Grade ≥ 3 AEs	147 (66)	146 (65)
Serious AEs	87 (39)	87 (38)
Death due to AEs	7 (3)	9 (4)

Subjects, n (%)	BV+CHP (n=223)	CHOP (n=226)
Treatment-emergent PN	117 (52)	124 (55)
Resolution of all PN events	58 (50)	79 (64)
Ongoing PN at last follow up	61 (52)	45 (36)
Grade 1	44 (72)	32 (71)
Grade 2	15 (25)	12 (27)
Grade 3	2 (1)	1 (1)

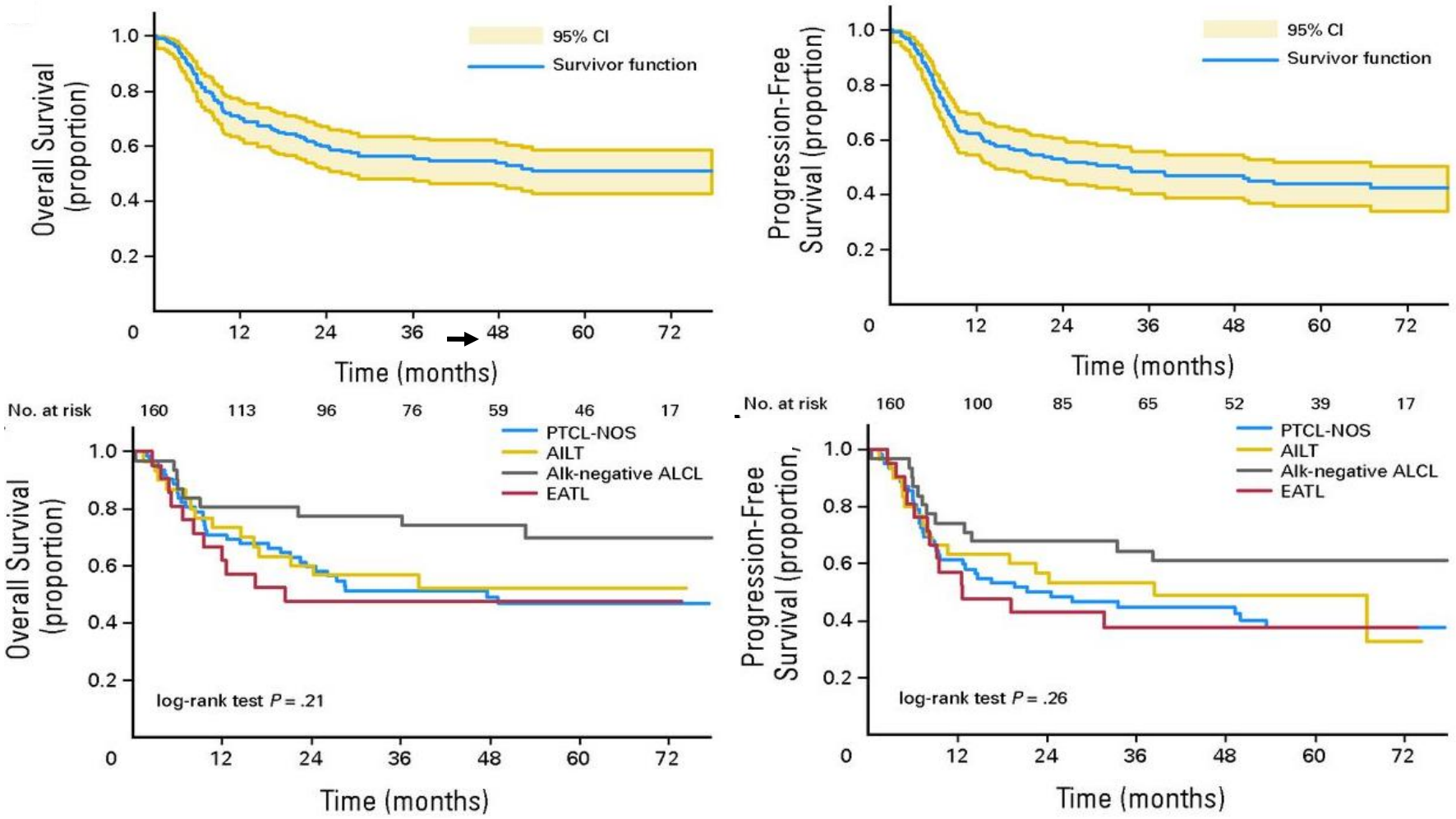


Horwitz. Lancet. 2019;393:229. Horwitz. ASH 2018. Abstract 997.

ECHELON-2: Summary and Conclusions

- ECHELON-2 first prospective trial in PTCL to show OS and PFS benefit over CHOP
  - 29% reduction in the risk of a progression event
    - 3-yr PFS: BV+CHP 57% vs CHOP 44%
  - 34% reduction in the risk of death
- BV+CHP has a comparable safety profile to CHOP
- Brentuximab vedotin FDA approved in combination with CHP for adults with previously untreated sALCL or other CD30-expressing PTCL

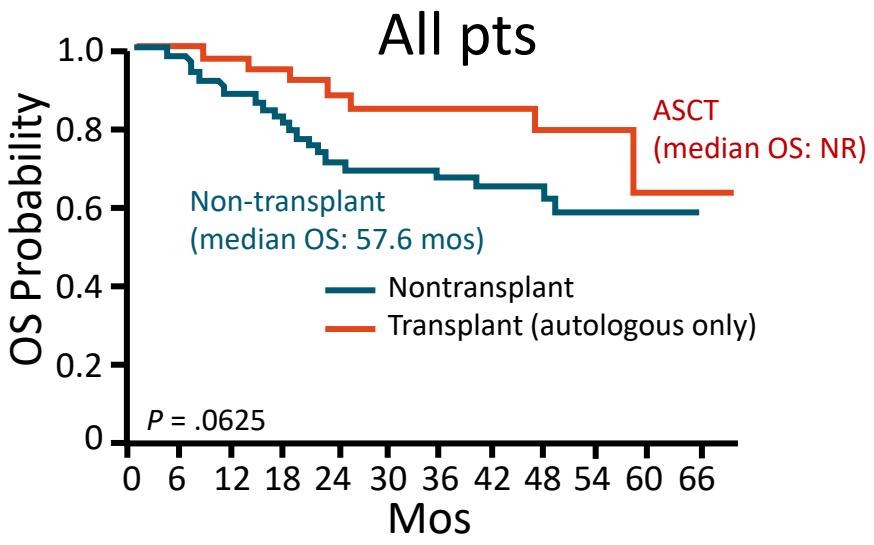
NORDIC: OS and PFS with CHO(E)P Followed by HDT and ASCT in Untreated PTCL

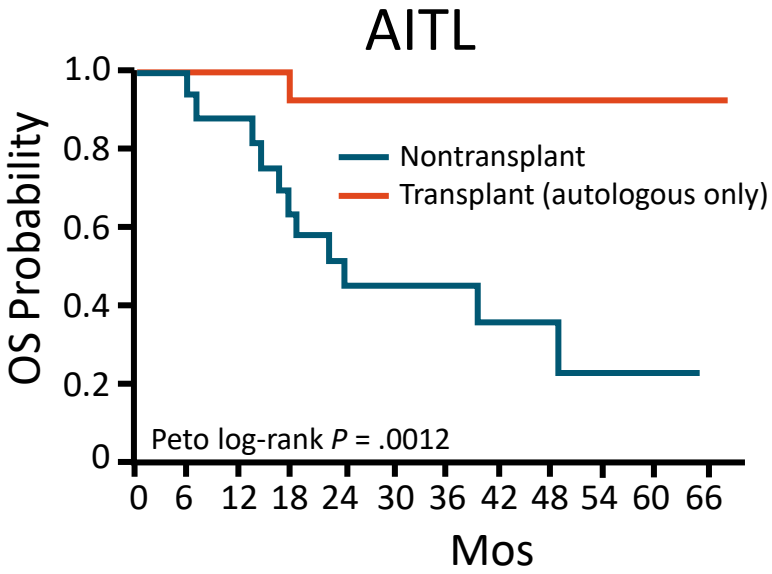


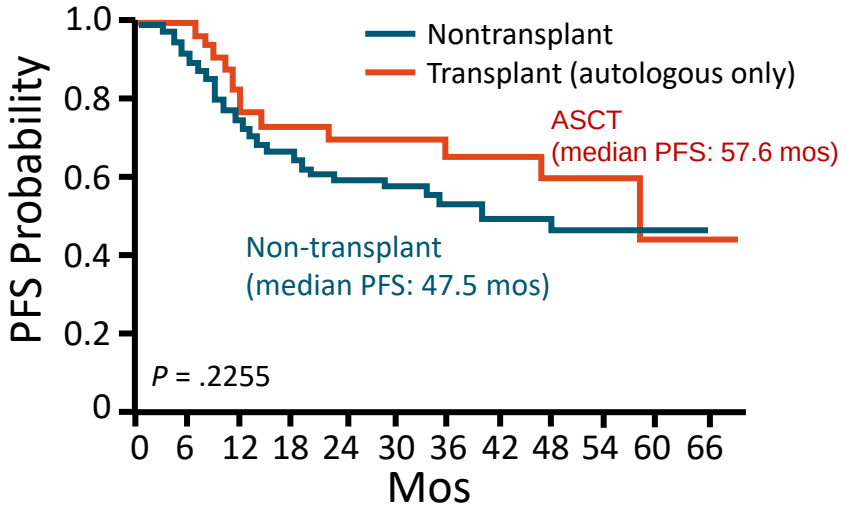
D'Amore. J Clin Oncol. 2012;30:3093.

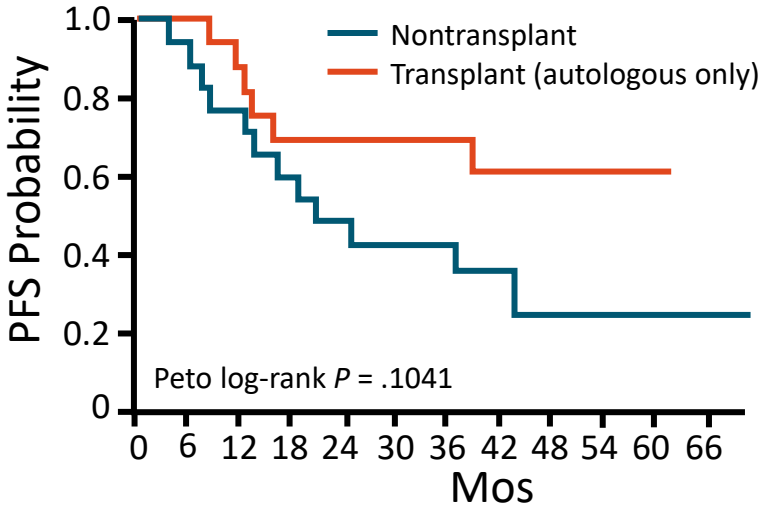
The Role of Transplant For Consolidation Complete Study

- Multivariate analysis, ASCT associated with improved survival





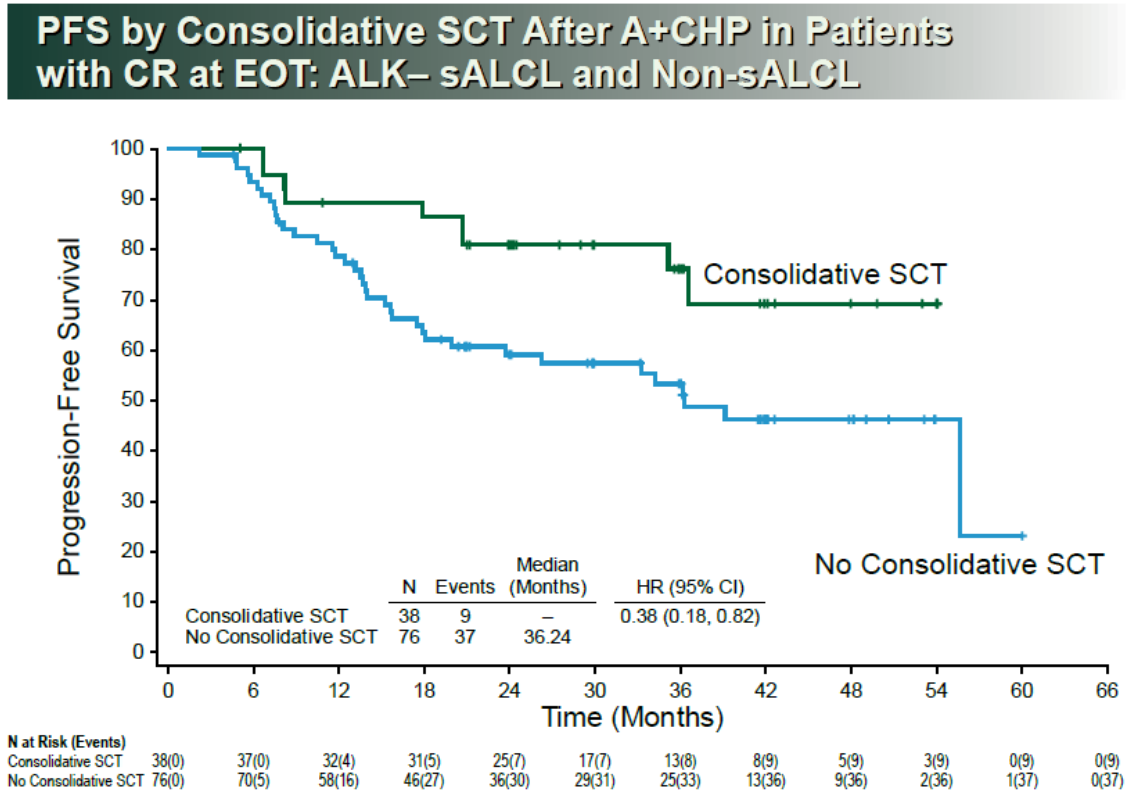




Park. *Cancer* 2019; 125:1507.

The Role of Transplant For Consolidation
ECHELON-2

- Numerical PFS estimates favor the use of consolidative SCT in pts in CR after A +CHP
- Consolidative SCT infrequent in Asian countries



Savage K, et al. TCLF 2020

Changing Treatment Paradigm of PTCL
Where We Are

- **sALCL**
  - BV-CHP has a PFS and OS benefit over CHOP
    - Addition of etoposide (?)
- **PTCL-NOS**
  - If CD30 pos. BV-CHP but not clear if there is benefit in FH subtype
- **AITL**
  - Benefit of BV+CHP not clear and numbers small
  - Awaiting data from ongoing studies with epigenetic modifiers
- Standard of care still ASCT in CR1 with the exception of ALK+ ALCL low IPI
- Aggressive extranodal subtypes should be treated with alternative strategies

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Thank You!

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