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APRIL 21-22, 2023



"Dual" Keynote Symposium: Experts Debate the Role of Transplant in PTCL



Con: Ranjana Advani M.D. Stanford University



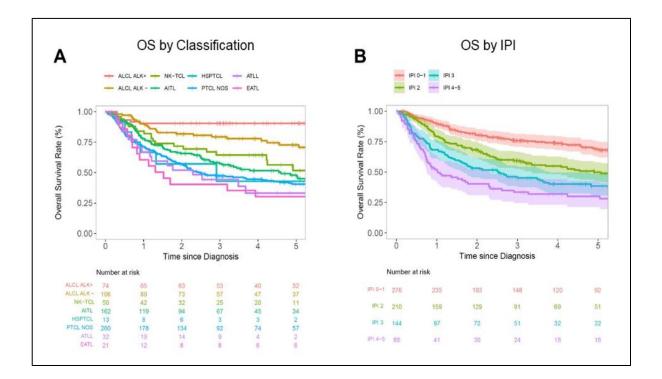
Disclosures

Entity	Nature of Relevant Financial Relationship
 Merck, Seattle Genetics, ADC therapeutics, Gilead, Merck, Cyteir, Regeneron, Daiichi 	 Institute research funding
 Merck, BMS, Incyte, ADC Therapeutics, Genentech/Roche, Epizyme, Incyte, BMS, Gilead, Beigene 	 Advisory Board
Genentech/Roche, Sanofi	Data Safety Monitoring Board

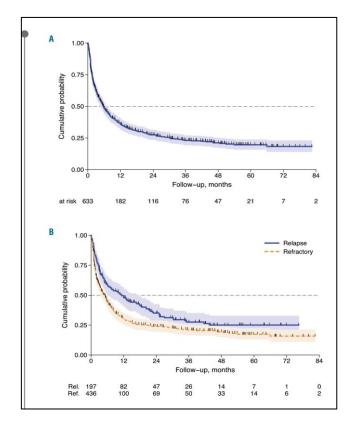
Challenges in defining standards of care in PTCL

- Rare: 10-15 % of NHL with geographic variation
 - clinical studies difficult
- Multiple subtypes
 - Morphologically and clinically heterogeneous
- Variable risk stratification tools
 - IPI, PIT, mPIT, PI-AITL, T-Cell score etc
- Paucity of prospective randomized controlled trials to guide treatment
- Therapies largely extrapolated from B cell paradigms

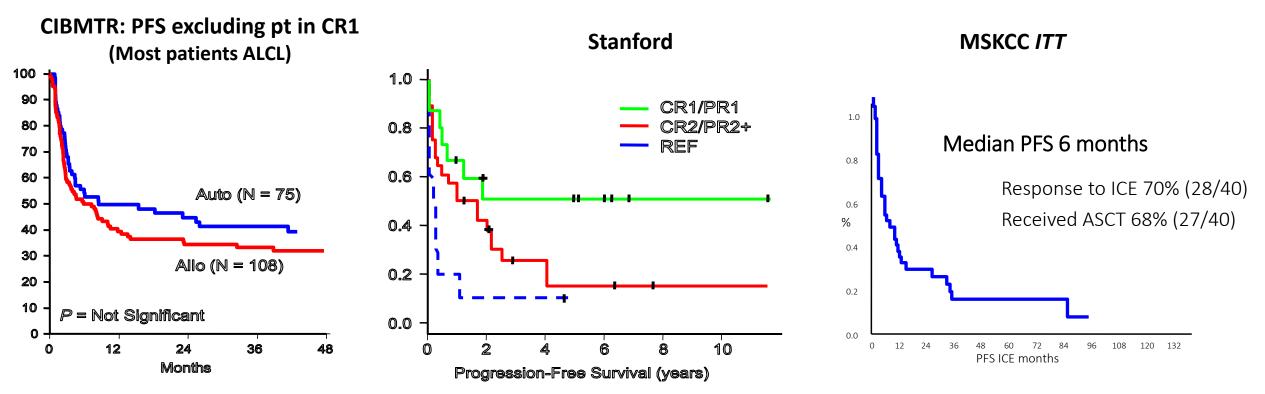
Patterns of Care and Clinical Outcomes PTCLs: The Lymphoma Epidemiology of Outcomes (LEO) and Molecular Epidemiology Resource (LEO-MER) Prospective Cohort Study



The outcome of PTCL patients relapsing after first-line therapy: a report from the prospective, International T-Cell Project



Autologous Transplantation in <u>Relapsed</u> PTCL: Retrospective Studies Provided a Rationale for ASCT in CR1



- Benefits are unclear
- Most single institution studies show low PFS rates while registry data suggests better outcomes

Smith S, et al. JCO 2013; Chen AI, et al. Biol Blood Marrow Transplant. 2008; Horwitz et al, ASH Annual Meeting Abstracts 2005;106:2679. Slide: Courtesy Dr Horwitz

What defines a 'standard' of care?

Unfortunately paucity of such data in PTCL

Therefore we rely on comparing outcomes form

- Retrospective studies/real world data etc
- Single arm prospective phase 2 studies
- Ability to select patients who might benefit from therapy A
- Cost-benefit ratio is justified

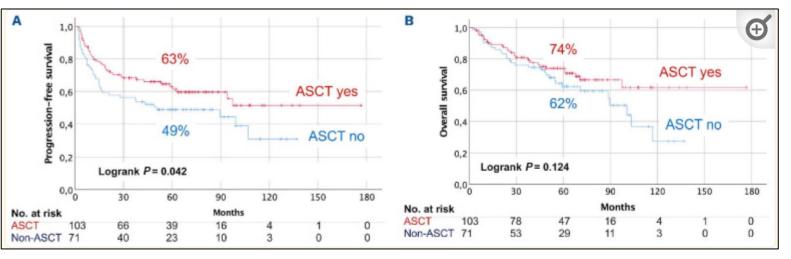
Selected studies comparing consolidation with ASCT vs other strategies in PTCL

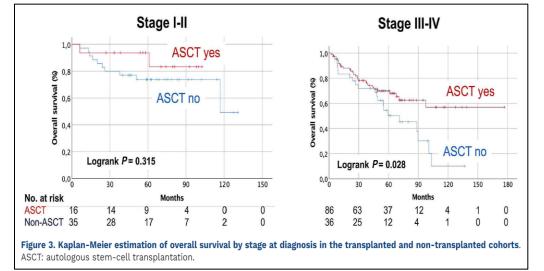
Author	Reference	Lymphoma Subtypes	Number of Patients	Induction Regimen	Consolidation Strategies	Survival in Patients in Complete Remission After Induction
Savage et al., 2022	36	ALCL, AITL, PTCL, NOS (mostly ALK – ALCL) in CR after induction	211	BV-CHP (<i>n</i> = 114) CHOP (<i>n</i> = 97)	Autologous SCT vs. no consolidation	BV-CHP + Auto SCT: 3-yr PFS 80.4% BV-CHP + no SCT: 3-yr PFS 54.9% CHOP + Auto SCT: 3-yr PFS 67.2% CHOP + no SCT: 3-yr PFS 54.1%
Advani et al., 2021	38	AITL	282	Anthracycline-based w/o etoposide 65%, anthracycline-based with etoposide 16% Other 19%	Autologous SCT vs. no consolidation	Auto SCT: 5-yr PFS 79% No auto SCT: 5-yr PFS 31% Auto SCT: 5-yr OS 89% No auto SCT: 5-yr OS 52%
Park et al., 2018	39	All PTCL	499	Anthracycline-based w/o etoposide 42%, anthracycline-based with etoposide 21% Other 37%	Autologous SCT vs. no consolidation	Auto SCT: 5-yr OS 87.8% No auto SCT: 5-yr OS 70.2%
Brink et al., 2022	3	ALK – ALCL, AITL, PTCL, NOS	213	CHOP or CHOEP	Autologous SCT vs. no consolidation	Auto SCT: 5-yr OS 82% No auto SCT: 5-yr OS 47%
Martin et al., 2022	37	ALK – ALCL, AITL, PTCL, NOS	174	CHOP $(n = 126)$ CHOEP $(n = 16)$ Other $(n = 32)$	Autologous SCT vs. no consolidation	Auto SCT: 5-yr PFS 63% No auto SCT: 5-yr PFS 49% Auto SCT: 5-yr OS 74% No auto SCT: 5-yr OS 62%
Janikova et al., 2019	20	All PTCL	906	Heterogeneous protocols	Autologous SCT vs. no consolidation	Auto SCT: 5-yr PFS 41% * No auto SCT: 5-yr PFS 46% * Auto SCT: 5-yr OS 49% * No auto SCT: 5-yr OS 59.5% *
Ellin et al., 2014	22	All PTCL	755	CHOP or CHOEP $(n = 499)$	Autologous SCT vs. no consolidation	Better for the auto SCT group (estimates not given) *
Schmitz et al., 2021	55	All PTCL other than ALK ALCL	104	$CHOEP \times 4 + DHAP \times 1$	Autologous SCT vs. allogeneic SCT (if donor available)	Auto SCT: 3-yr PFS 39% * Allo SCT: 3-yr PFS 43% * Auto SCT: 3-yr OS 70% * Allo SCT: 3-yr OS 57% *
			tion-to-transplant (or intent to t hmitz et al., 2022, which is a rar		than based on the achievement	of remission after induction. NB: All studies

The Numbers Game Truth (deception) in reporting

	Author	Reference	Lymphoma Subtypes	Number of Patients	Induction Regimen	Consolidation Strategies	Survival in Patients in Complete Remission After Induction		
	Savage et al., 2022	36	ALCL, AITL, PTCL, NOS (mostly ALK – ALCL) in CR after induction	N=452 211 N=67(CR)	BV-CHP (<i>n</i> = 114) CHOP (<i>n</i> = 97)	Autologous SCT vs. no consolidation	BV-CHP + Auto SCT: 3-yr PFS 80.4% BV-CHP + no SCT: 3-yr PFS 54.9% CHOP + Auto SCT: 3-yr PFS 67.2% CHOP + no SCT: 3-yr PFS 54.1%		
· · ·	Advani et al., 2021 resentation o		AITL	²⁸² N=27 (CR)	Anthracycline-based w/o etoposide 65%, anthracycline-based with etoposide 16% Other 19%	Autologous SCT vs. no consolidation	Auto SCT: 5-yr PFS 79% No auto SCT: 5-yr PFS 31% Auto SCT: 5-yr OS 89% No auto SCT: 5-yr OS 52%		
	on number of pts ie not TT in most studies		•		ALPTCL	⁴⁹⁹ N=36 (CR)	Anthracycline-based w/o etoposide 42%, anthracycline-based with etoposide 21% Other 37%	Autologous SCT vs. no consolidation	Auto SCT: 5-yr OS 87.8% No auto SCT: 5-yr OS 70.2%
Actual re	sults for ASCT	- based	Y.	N=117/86 (CR)	CHOP or CHOEP	Autologous SCT vs. no consolidation	Auto SCT: 5-yr OS 82% No auto SCT: 5-yr OS 47%		
	on a fraction of total pts in most studies who are highly selected		PT/ NOS		CHOP ($n = 126$) CHOEP ($n = 16$) Other ($n = 32$)	Autologous SCT vs. no consolidation	Auto SCT: 5-yr PFS 63% No auto SCT: 5-yr PFS 49% Auto SCT: 5-yr OS 74% No auto SCT: 5-yr OS 62%		
			selected		All PTCL	N=103 (CR) 906 N=181	Heterogeneous protocols	Autologous SCT vs. no consolidation	Auto SCT: 5-yr PFS 41% * No auto SCT: 5-yr PFS 46% * Auto SCT: 5-yr OS 49% * No auto SCT: 5-yr OS 59.5% *
	Ellin et al., 2014	22	All PTCL	N=104	CHOP or CHOEP $(n = 499)$	Autologous SCT vs. no consolidation	Better for the auto SCT group (estimates not given) *		
	Schmitz et al., 2021	55	All PTCL other than ALK ALCL	N=67/45 (CR)	$CHOEP \times 4 + DHAP \times 1$	Autologous SCT vs. allogeneic SCT (if donor available)	Auto SCT: 3-yr PFS 39% * Allo SCT: 3-yr PFS 43% * Auto SCT: 3-yr OS 70% * Allo SCT: 3-yr OS 57% *		
				ion-to-transplant (or intent to tr umitz et al., 2022, which is a ran		than based on the achievement	of remission after induction. NB: All studies		

Registries/Retrospective Study ASCT as consolidation of first-line chemotherapy in patients with PTCL a multicenter GELTAMO/FIL study





2001-2011 N=286

- 174 with CR
- ASCT n= 103, No ASCT n=71 No progression for 3 months post initial therapy for eligibility

More pts >60y in non ASCT arm

• 27% vs 11%

No data on how CR defined (CT vs PET) Med f/u 65.5 months Included mostly low risk pts

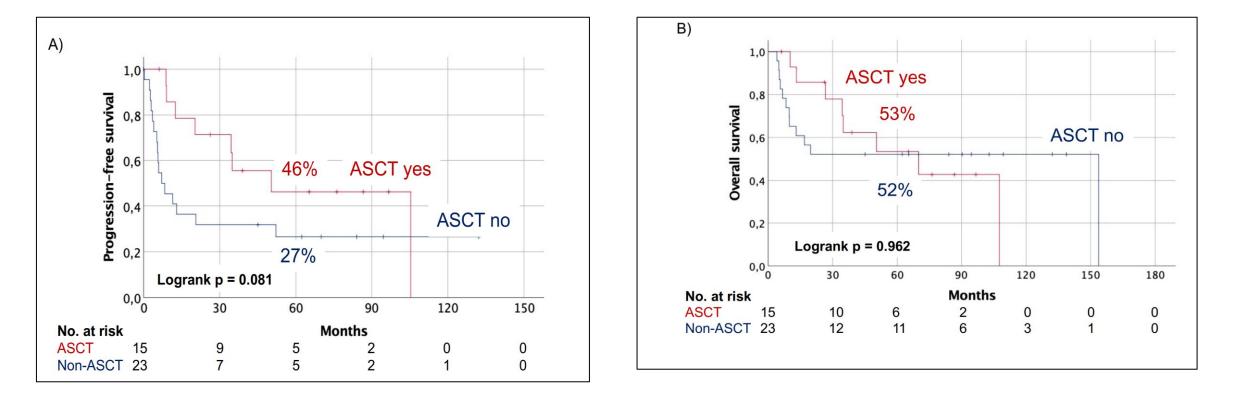
- IPI 0-1: 45% , PIT 0-1: 71.9%
- IPI 2-3: 41%, PIT 2: 17.5%
- IPI 4-5: 9.6%, PIT 3-4: 10.6%

No results of outcome within IPI groups

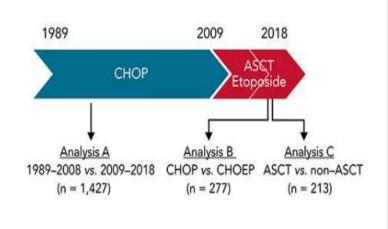
Garcia-Sancho et al, Haematologica 2022

ASCT as consolidation of first-line chemotherapy in patients with PTCL: a multicenter GELTAMO/FIL study: Outcomes in PR pts

No statistically significant differences in pts with a PR



Registries/Retrospective studies Impact of Etoposide and ASCT on survival among patients aged <65 years with stage II to IV PTCL (Dutch Series)



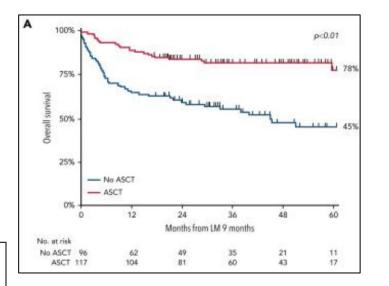
2014-2018 (cohort C) N=213

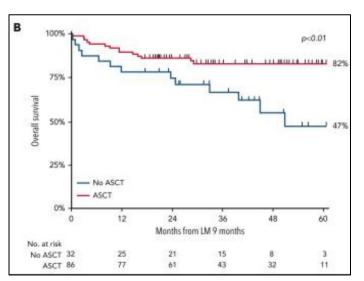
- ASCT: N=117 (CR: n=86): 40%
- No ASCT N=96 (CR: n=32): 15%
 IPI 0-2: 77% (vs 67%)

Median f/u 28.9 mths

No data on how CR defined (CT vs PET) Benefit largely in CR pts and ALK-ALCL and AITL

No results of outcome within IPI groups



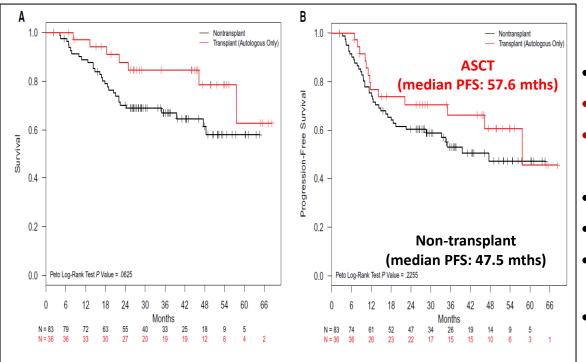


	Panel A ASCT	no ASCT	Panel B ASCT	no ASCT	CR pts
	A001			TIU ASCT	
ALK- ALCL					
Number of patients	28	16	22	6	
5-year OS (95% CI)	96% (77%-99%)	47% (20%-70%)	100%	44% (7%-78%)
AITL					
Number of patients	48	46	31	18	
5-year OS (95% CI)	76% (55%-88%)	39% (19%-58%)	87% (69%-95%)	27% (2%-66%)
PTCL NOS					
Number of patients	41	34	33	8	
5-year OS (95% CI)	<mark>68% (50%-81%</mark>)	49% (30%-66%)	67% (46%-81%)	60% (20%-859	%)

Abbreviations: OS; overall survival, CI; confidence interval, ASCT; autologo te etem cell transplantation, ALCL; Anaplastic large T-cell lymphoma, PTCL NOS; Peripheral T-cell lymphoma, not otherwise specified, AITL; Angioimmunoblastic T-cell lymphoma.

Brink et al, Blood 2022

The role of transplant at first remission: Registries/Retrospective studies COMPLETE (pts in CR)



	cancers
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MDPI

Review

Controversies in the Front-Line Treatment of Systemic Peripheral T Cell Lymphomas

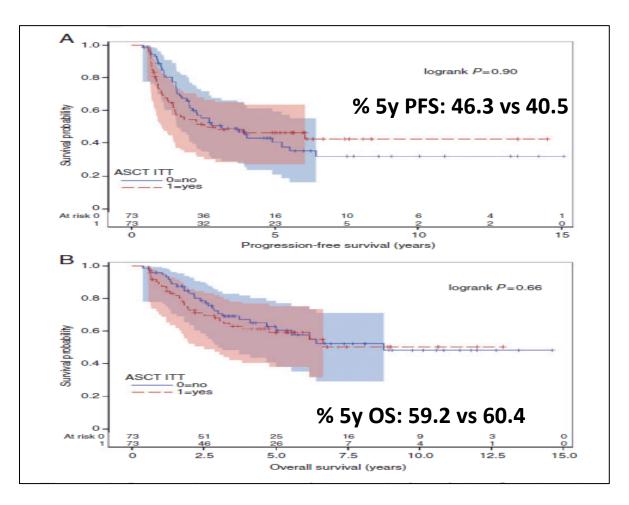
Marc Sorigue ^{1,*} and Outi Kuittinen ^{2,3,4}

Park et al Cancer. 2019

- 2010-2014, N=499 Med f/u 2.8 y
- 213 with CR (119 included, 36 had ASCT vs 83 no ASCT)
- ASCT n=36 represents 17% of pts in CR
 - IPI 0-2: 64%
- PFS and OS: P=NS
- No data on how CR defined (CT vs PET)
- ASCT was associated with superior OS for AITL (n=17), ST III-IV (n=33) and intermediate-to-high IPI (n=13). Low IPI NO diff
- Multivariable analysis, ASCT was independently associated with improved survival (hazard ratio, 0.37; 95% CI, 0.15-0.89).

Indeed, in the COMPLETE registry, despite the overall lack of significance in the multiple comparisons carried out, the difference in OS curves seemed greater than that of the PFS curves, perhaps suggesting that factors impacting OS beyond the disease itself were at play

Registries/Retrospective studies The role of transplant at first remission: LYSA (pts in CR) Propensity score matching in an ITT population (determined pre therapy)

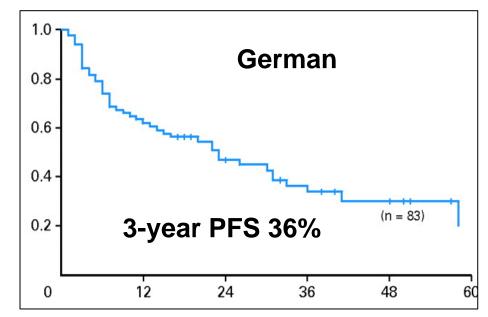


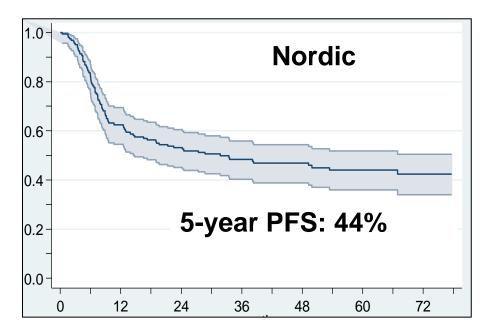
- 2000-2015, med f/u 4.8y
- N=269 (CR: 217, PR: 52)
- ASCT N=134 , No ASCT N=135
- No progression for 3 months post initial therapy for eligibility
- ASCT PTS: aa IPI 0-1: 30% (vs 49%), 2-3: 70% (vs 30%)
- No data on how CR defined (CT vs PET)
- No significant difference in PFS or OS in patients with PTCL who received ASCT consolidation or no ASCT following CR on first-line therapy
 - **PFS:** HR 1.02; 95% CI 0.69, 1.50
 - **OS:** HR 1.08; 95% CI 0.68, 1.69
- No diff in outcomes for pts in PR or advanced stage/high IPI
- Causes of death similar in both arms (mainly PD)

Prospective Phase 2 Multicenter Studies in PTCL

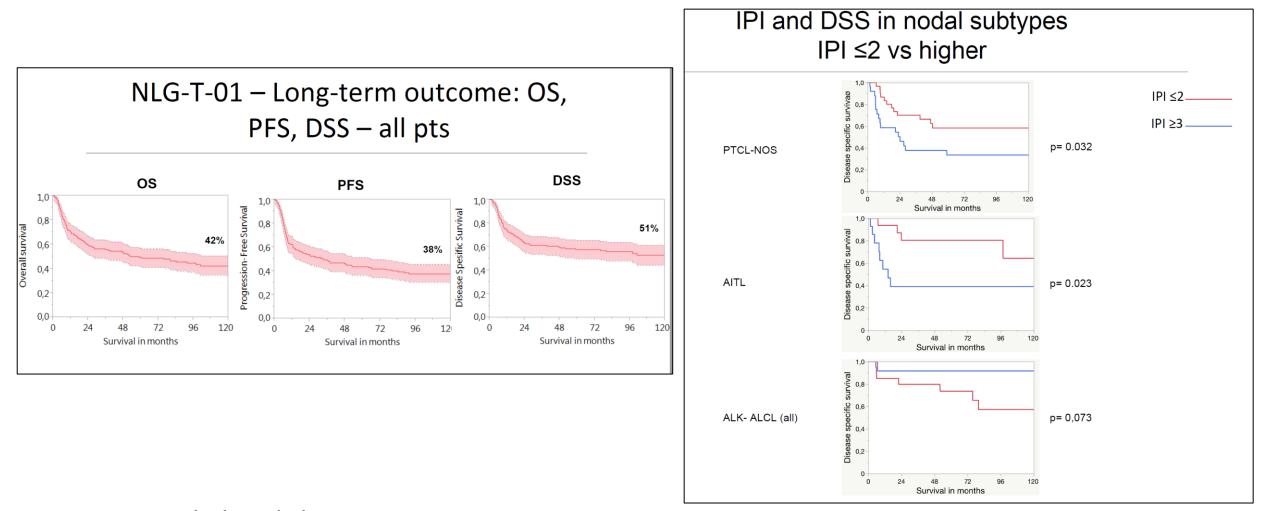
	СНОР	СНОЕР
N	83	118
PTCL	39%	39%
AITL	33%	19%
ALCL	16%	19%
IPI		
1	14%	28%
2	35%	32%
3	45%	19%
4-5	6%	21%
Med Age	47	57
ORR	79%	82%
CR	39%	51%

Reimer, P. et al et al. JCO 2009 (German) D'Amore, et al. JCO 2012 (Nordic)





Long-Term Follow-up of Clinical Outcome Determinants and Correlative Biological Features from the Nordic NLG-T-01 Trial

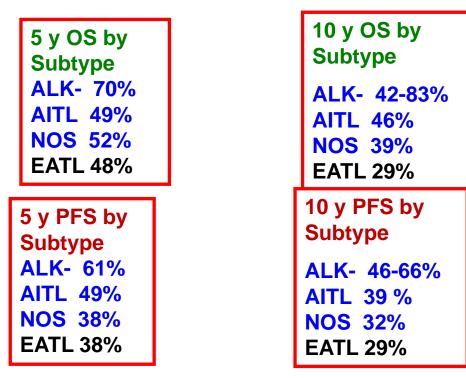


Relander et al, Abstract #614 ASH 2022

NORDIC LYMPHOMA GROUP

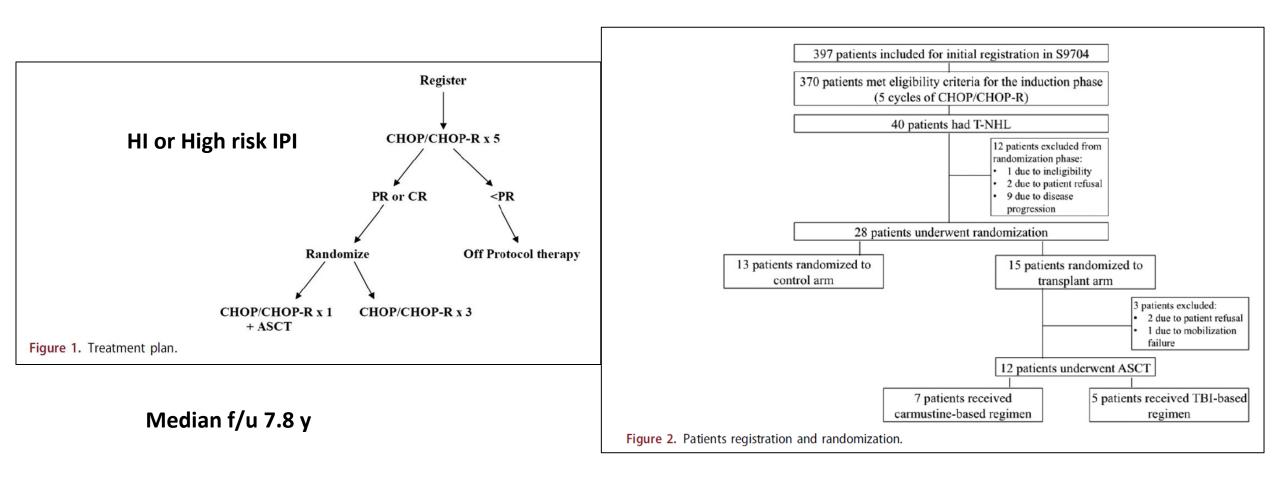
10-year overall, progression-free and disease-specific survival

10-yr OS	10-yr PFS	10-yr DSS
83%*	66%**	100%
42%	46%	66%
46%	39%	53%
39%	32%	47%
29%	29%	33%
	83%* 42% 46% 39%	83%* 66%** 42% 46% 46% 39% 39% 32%



NLG-T-01: Long-term follow-up Causes of death					
	Time	e from diagr	osis		
Causes of death	<24 mo	24 - 59 mo	≥ 60 mo	Total	
Lymphoma	56 (86,2%)	8 (50,0%)	4 (50 <i>,</i> 0%)	68 (76,4%)	
Toxicity	8 (12,3%)	1 (6,3%)	0 (0,0%)	9 (7,9%)	
2nd malignancy	0 (0,0%)	4 (25,0%)	1 (12,5%)	5 (2,3%)	
Other causes	1 (1,5%)	3 (18,8%)	2 (25,0%)	6 (6,7%)	
Unknown	0 (0,0%)	0 (0,0%)	1 (12,5%)	1 (1,1%)	
N of deaths	65	16	8	89	

Autologous transplantation as consolidation for high-risk aggressive PTCL: a SWOG 9704 intergroup trial subgroup analysis



Autologous transplantation as consolidation for high-risk aggressive PTCL: a SWOG 9704 intergroup trial subgroup analysis

	Randomized ($n = 28$)	Non-randomized ($n = 12$)	al %	-11	L Control	At Risk [13 15	Deaths 5-	year Esti- 45%
ge			š š	80% -	Transplant	15	9	40%
Median	50 years	43 years	2	1				
Range	26-65	34–61	Sr.	000/				
iender – no. (%)			e e	60% –				
Males	19 (68%)	6 (50%)	fre	-				
Females	9 (32%)	6 (50%)	ż /	40% -			J	
listologic subtype – no. (%)			0	40 /0 7				
PTCL-NOS	11 (39%)	9 (75%)	SS	-				
ALCL	10 (36%) N=3 ALK -	+ 3 (25%)	Le	20% -				
Angioimmunoblastic T-cell lymphoma	7 (25%)	0 (0%)	60					
ge-adjusted IPI risk group			ď	1				
High-intermediate risk	18 (64%)	-	_	0% +			1 1 1	
High risk	10 (36%)	-		0	5	10		15
-symptoms at diagnosis – no. (%)	21 (75%)	8 (67%)		v	V	Dendendertier		
tage IV disease at diagnosis – no. (%)	14 (50%)	9 (75%)			Years After	Randomization		

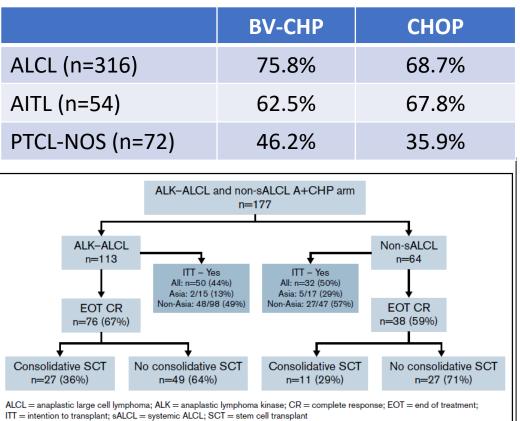
Autologous Transplantation for PTCL

- Overall results- 3-5 yr PFS 36-44% in prospective phase 2 studies
- Is it really better than historical controls without ASCT (no RCT, only~ 30% make it to ASCT)??
 - Best results in:
 - Younger pts, lower IPI
 - ALK- ALCL, ?AITL, Chemosensitive -CR1, Genetic Subtypes-DUSP22?
 - Poorer results in:
 - Older pts, higher IPI
 - Less chemosensitive disease , PTCL-NOS, Genetic Subtypes-P53, CDKN2A?

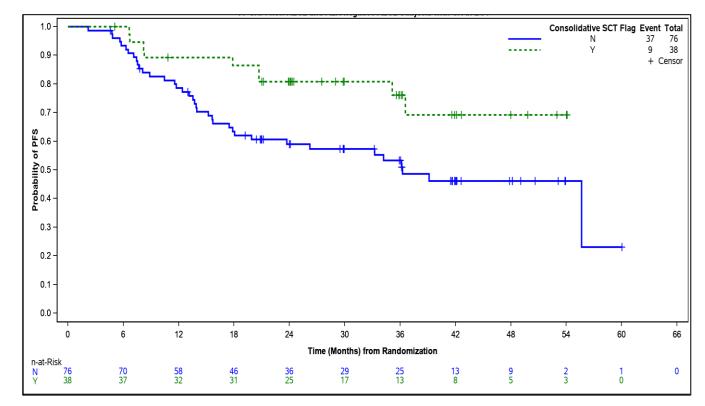
Does getting an ASCT in CR1 really confer a better prognosis ?? Likely a a surrogate for more favorable characteristics?

Role of stem cell transplant in CD30+ PTCL following frontline brentuximab vedotin plus CHP or CHOP in ECHELON-2

5y Update



19% patients underwent a consolidative autologous transplant in CR



Numerical PFS estimates favor the use of consolidative SCT in patients with PCTL in a CR at EOT after frontline BV+CHP.

Horwitz Lancet 2019 Savage et al, Blood Advances 2022

ECHELON-2 : Autologous Transplantation <u>after BV+CHP</u> in CD30+ PTCL in CR1 Are there differences in the ASCT vs Non-ASCT groups?

	ALK– sALC N=76	L	Non–sALCL N=38	
	SCT (n=27)	No SCT (n=49)	SCT (n=11)	No SCT (n=27)
Male, n (%)	16 (59)	24 (49)	6 (55)	15 (56)
Age in years, median (range)	50 (18-68)	59 (20-85)	57 (35-73)	66 (49,77)
IPI score, n (%)				
0–1	11 (41)	21 (43)	2 (18)	4 (15)
2–3	12 (44)	25 (51)	7 (64)	21 (78)
4–5	4 (15)	3 (6)	2 (18)	2 (7)
Stage III/IV, n (%)	22 (82)	31 (63)	11 (100)	23 (85)

- Rates of ASCT were 36% of ALK-ALCL and 29% in non-ALCL
- Patients receiving ASCT were younger and more likely to have advanced stage
- No clear difference in IPI?

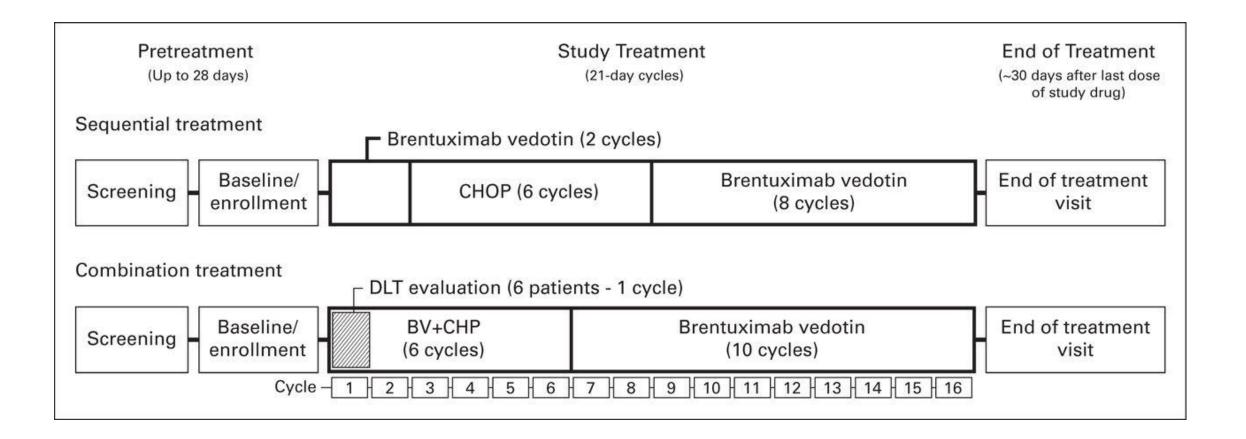
ECHELON-2 Autologous Transplantation <u>after CHOP</u> in CD30+ PTCL in CR1 Are there differences in the ASCT vs Non-ASCT groups

	ALK– sALCL N=53		Non-sALCL N=44	Non-sALCL N=44		Combined N=97	
	SCT (n=13)	No SCT (n=40)	SCT (n=16)	No SCT (n=28)	SCT (n=29)	No SCT (n=68)	
Estimated PFS at 3 years, % (95% CI)	58.6 (26.7-80.6)	62.7 (45.2-76.0)	73.7 (44.1-89.2)	42.9 (24.6-60.0)	67.2 (46.3-81.5)	54.1 (41.2-65.3)	
Estimated PFS at 5 years, % (95% CI)	58.6 (26.7-80.6)	55.7 (35.2-72.1)	43.0 (8.8-74.6)	42.9 (24.6-60.0)	48.9 (21.6-71.6)	50.9 (37.4-62.9)	
Univariate, HR (95% CI)	0.67 (0.24-1.3	89)	0.57 (0.22-1.4	47)	0.63 (0.32-1.2	24)	

Post CHOP

- No real difference in ALK- ALCL with ASCT or no ASCT
- Numerical difference at 3 years but not 5 years in non-ALCL with ASCT or no ASCT

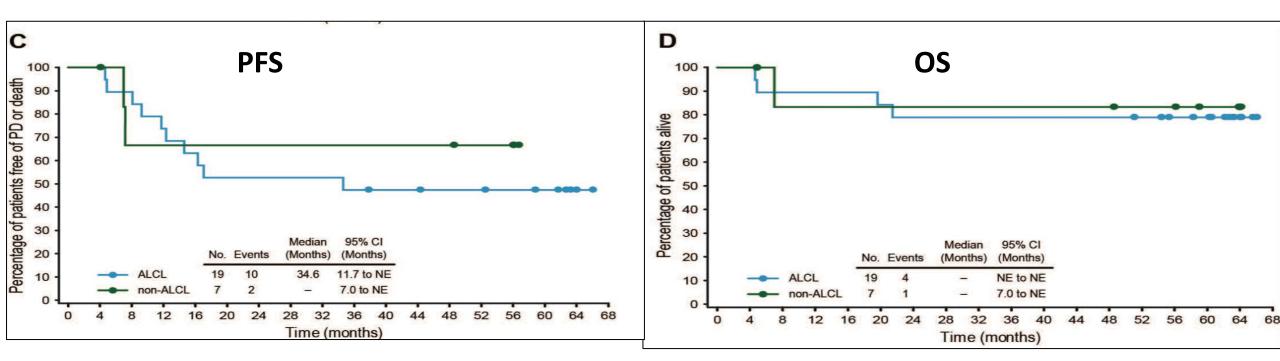
Phase I: BV + CHP-BV, BV- CHOP-BV : Schema



Fanale et al JCO 2014

BV + CHP-BV; 5 Year PFS, OS (no transplant)

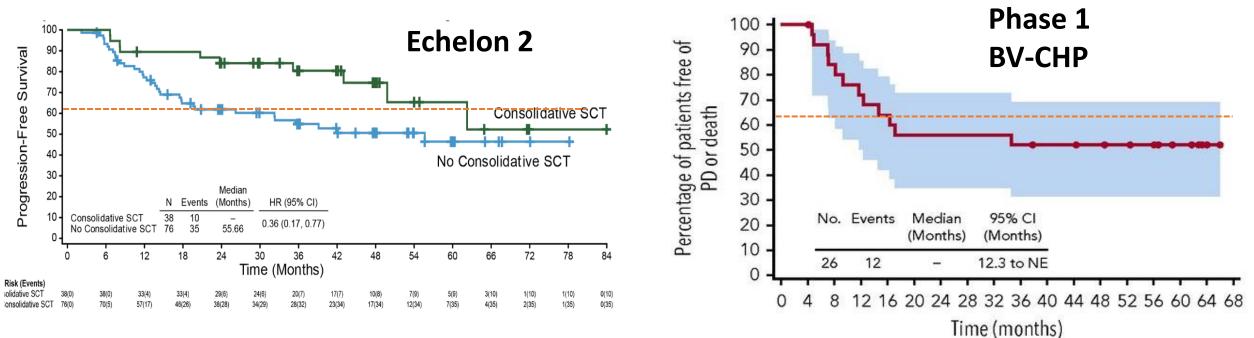
	ALCL; N (%)	Other; N (%)	Total; N (%)
ORR	19 (100)	7 (100)	26 (100)
CR	16 (84)	7 (100)	23 (88)
PR	3 (16)		3 (12)



Fanale et al Blood 2018

Slide Courtesy Dr Horwitz

Autologous Transplantation after BV+CHP in CD30+ PTCL



- Median PFS at 5 years with BV-CHP
 - Echelon 2-CR1
 - BV-CHP-ASCT is just above BV-CHP without ASCT
- BV-CHP phase 1 without ASCT-just above 50%
- Is there a real difference?

Slide Courtesy Dr Horwitz

Savage et al Blood Adv 2022; Fanale et al; Blood 2018

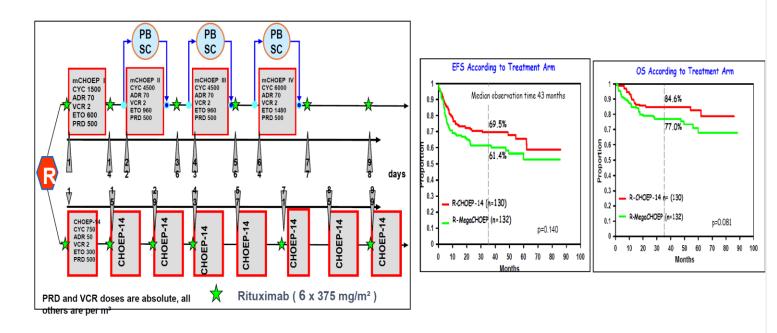
Autologous Transplantation after BV+CHP in CD30+ PTCL

- ECHELON2 was not designed to statistically evaluate the question of consolidative transplant
- Lack or randomization with regard to ASCT in ECHELON-2 (as with other studies) leaves open the question as to whether ASCT in CR1
- Data is imperfect and is best hypothesis generating

History a great teacher Aggressive B cell NHL: Consolidation with ASCT

- Was considered a "standard" of care in DLBCL for patients with high-risk disease
 - Widely adopted based on prospective phase 2 data and retrospective data

R-CHOEP vs R-MegaCHOEP: (DSHNHL) Final Results



UNTIL

• RCT showed no benefit!!

Schmitz N et al. Blood 2010

What defines a 'standard' of care?

Based on current data it is premature to adopt ASCT in remission as standard of care



Dr Pro and I actually agree!!

 Need trials comparing front-line therapy to transplant Current Oncology Reports (2020) 22: 44 https://doi.org/10.1007/s11912-020-00902-1

LYMPHOMAS (MR SMITH, SECTION EDITOR)

Therapy of Peripheral T Cell Lymphoma: Focus on Nodal Subtypes

Pamela B. Allen¹ · Barbara Pro²

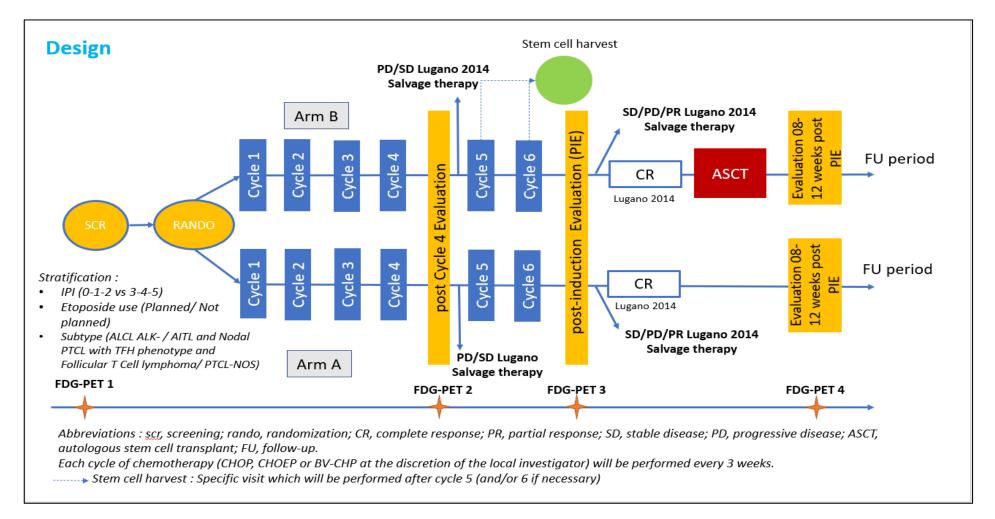
Published online: 16 April 2020 $\hfill {\Bbb C}$ Springer Science+Business Media, LLC, part of Springer Nature 2020

The role of transplant as part of the frontline strategy in PTCL continues to be a topic of debate due to lack of randomized data and conflicting results from retrospective and prospective analyses.

Its role following brentuximab-based therapy is less clear given the limited data from the ECHELON-2 trial

At this time, there is insufficient evidence to broadly support allogeneic transplant as part of the frontline strategy, however, reduced toxicity of allogeneic SCT with recent advances, may alter the risk to benefit ratio

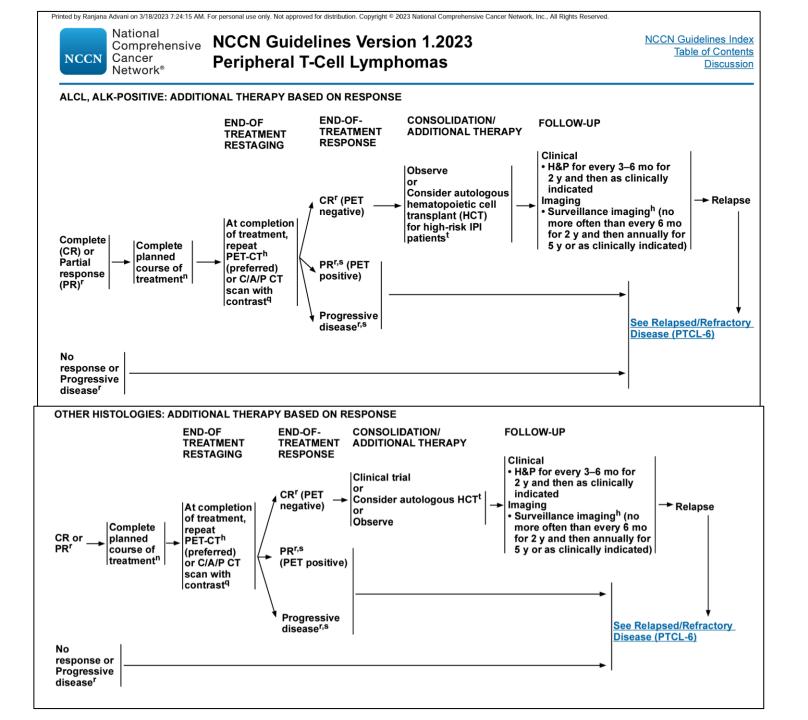
TRANSCRIPT – LYSA Design

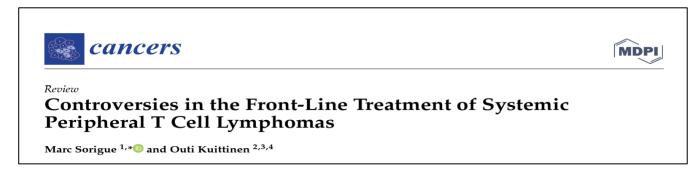


Principal objective: Demonstrate significant PFS improvement in PTCL patients who achieve CR after 6 cycles

Secondary objectives: OS, ORR, CRR, and DoR at the end of ASCT, QoL, Cost-Effectiveness Analysis (CEA), Budget Impact Analysis (BIA)

Sample size: 204 (102 in each arm) with assumptions: 2-sided α risk of 5%; power: 80%





- Even if the evidence was mostly favorable, substantial caution would be warranted
- This is because not all data that physicians use—sometimes subconsciously—in clinical practice are captured by standard variables and uncaptured data cannot be adjusted for
- This is liable to be particularly relevant when analyzing SCT
 - high intensity of the procedure, only the fittest patients will be recommended
 - numerous considerations (medical, social, socioeconomic) are also included in the evaluation of whether to recommend the procedure or not
- The lack of randomized data proving the benefit of autologous SCT in CR1 is particularly concerning because a growing number of experts and guidelines recommend this strategy without a solid evidence basis, and such evidence will not be obtained if it becomes the standard of care on the basis of a (questionable) lack of equipoise

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APRIL 21-22, 2023



"Dual" Keynote Symposium: Experts Debate the Role of Transplant in PTCL



Con: Ranjana Advani M.D. Stanford University



Backup

Prognostic significance of FDG-PET/CT in determining upfront autologous stem cell transplantation for the treatment of PTCL

