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Allogeneic Stem cell transplant in PTCL – not a great choice

Paris, March 31st, 2023

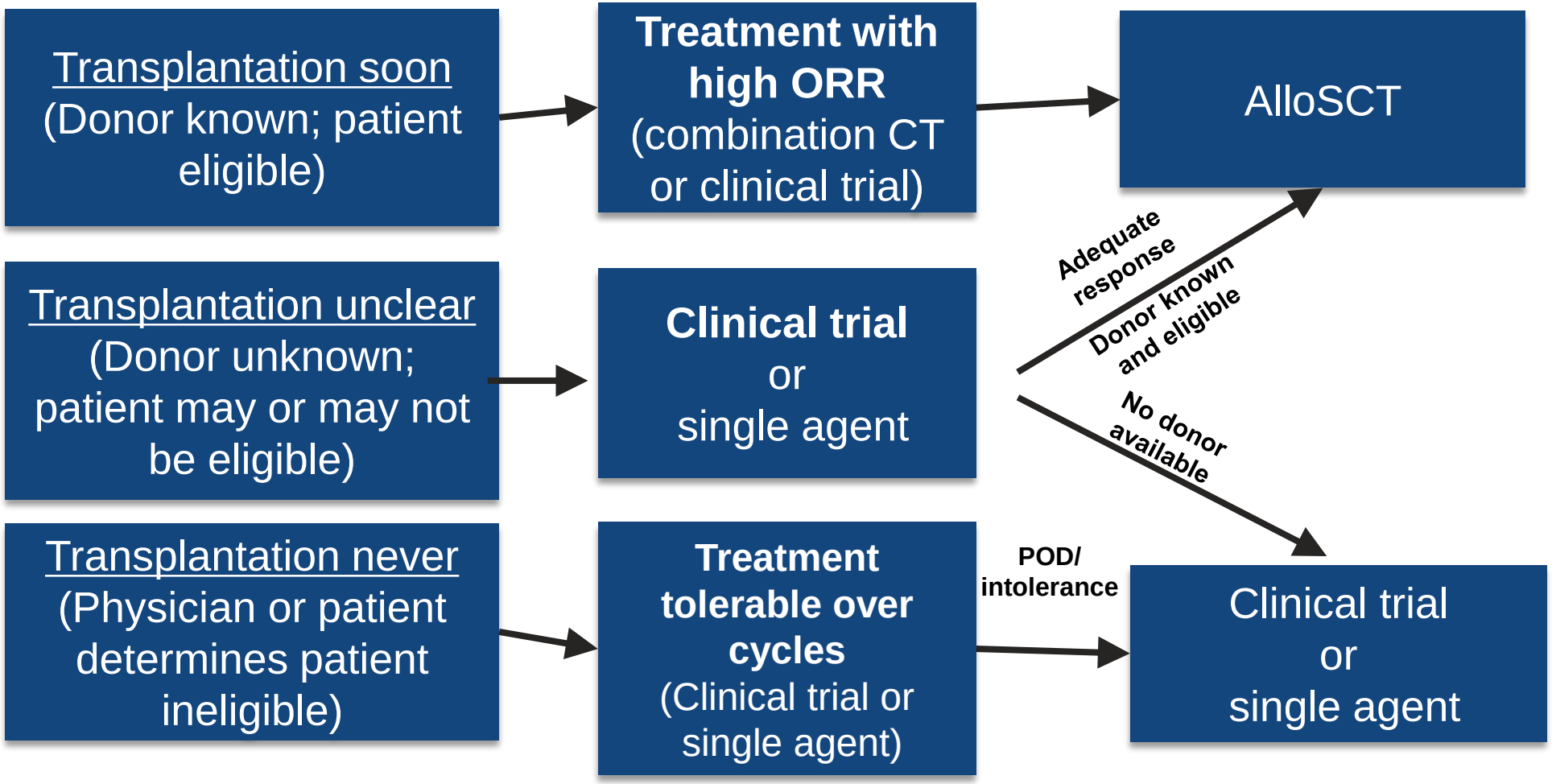
Memorial Sloan Kettering Cancer Center

Disclosures:

Consulting and research funds - ADCT therapeutics, Kite, Secura Bio, Genmab, Kyowa Kirin, Astra Zeneca.

…I propose AlloSCT to my eligible r/r PTCL patients…

Algorithmic Approach to Patients with Relapsed PTCL (NOS, AITL, ALCL)



Adapted from Lunning MA et al. *J Clin Oncol*, 2013;31:1922-1927.

Satisfying pre-conditions to propose AlloSCT as a good option:

1. Graft vs lymphoma effect

2. Depth of remission before AlloSCT
   - AlloSCT in first line PTCL

3. Donor type

4. Treatment-related mortality

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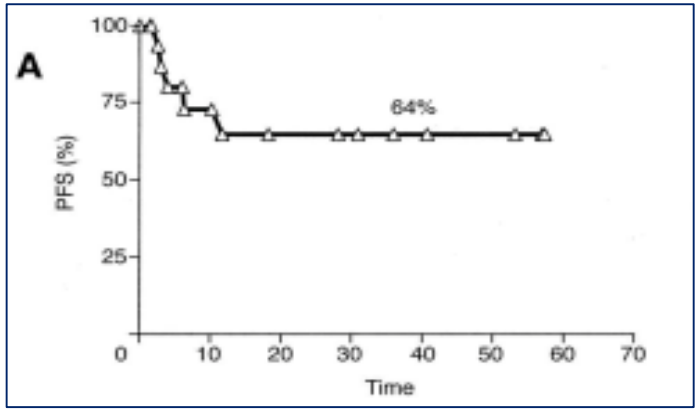
1. Graft vs lymphoma effect

Corradini and colleagues 2004

17 patients with PTCL-NOS, AITL and ALCL transplanted from HLA identical family donors (1 MUD)

RIC with thiotepa, cyclophosphamide and fludarabine
14/17 alive at 28 months, 12 in CR



HOWEVER,… relatively high RELAPSE RATE NOTED in larger series:

Hamadani 2022 EBMT+ CIBMTR	1942 patients
PFS 3y: Haplo 50%; MSD 50%; MUD TCD+ 48% MUD TCD- 52%	

Mehta Shah 2020	508 patients
PFS 5y: 39.5%;	

Mamez 2020	147 patients
GRFS 2y: CR/PR2 45%; PD 30%;	

Wulf 2019	126 patients
PFS 3y: 37%	

Smith 2013	126 patients
relapse 3y: MAC 37%; RIC 42%;	

Corradini et Al, JCO 2004
Hamadani Blood Advances 2022
Mehta Shah, ASH 2020
Mamez Journal of Hematology and Oncology 2020
Wulf, Bone Marrow transplant 2019
Smith, JCO 2013

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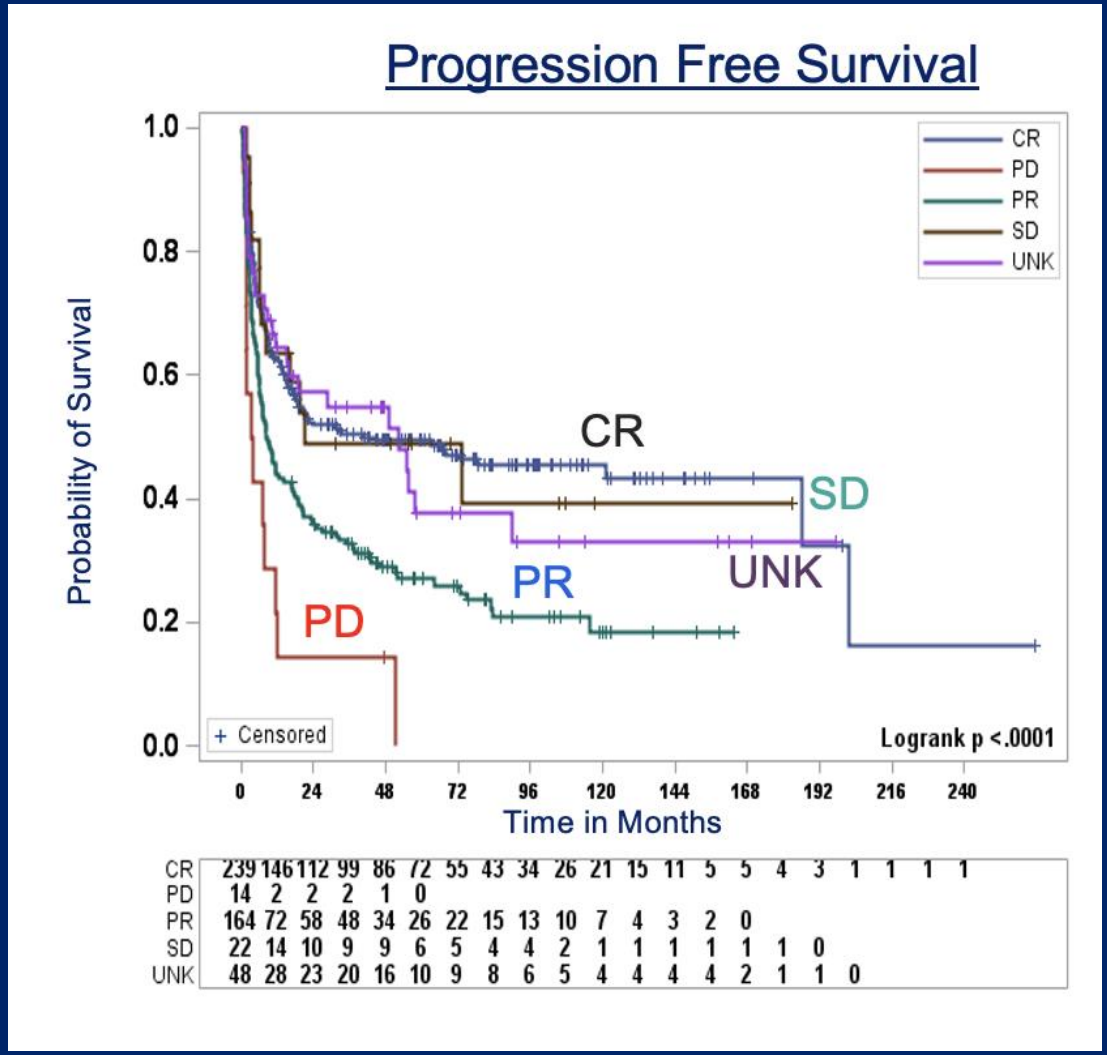
2. Depth of remission at time of transplant



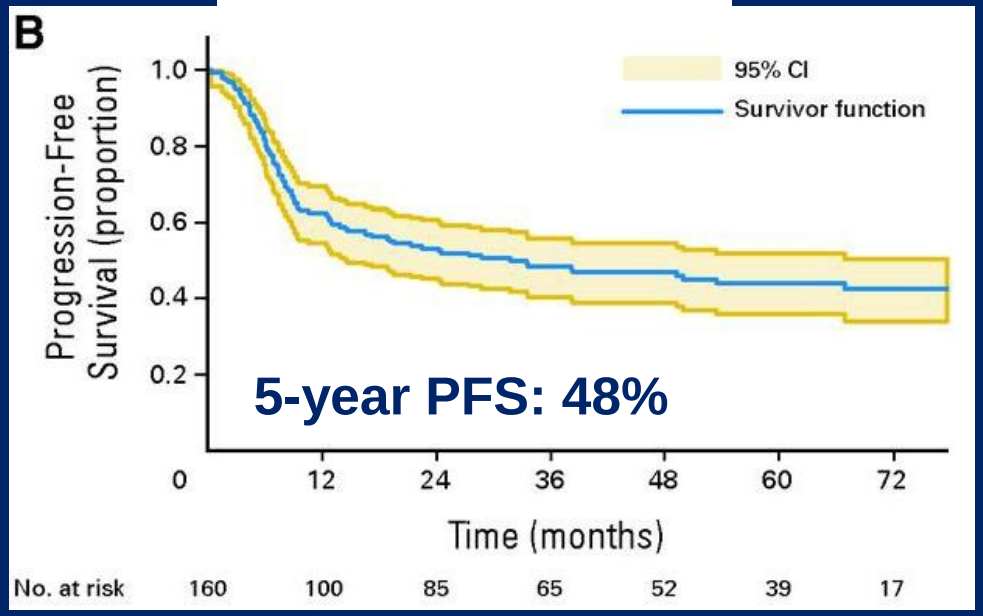
Response	N	Median PFS in months (95% CI)	Median OS in months (95% CI)
CR	**239**	**44.6** (17.9-201.5)	**154.2** (72.8-201.5)
PR	**164**	**8.5** (6.1-16.6)	**31.3** (16.8-64.2)
SD	**22**	**21.0** (6.0- NR)	**12.4** (12.5-NR)
PD	**14**	**3.5** (1.5-11.2)	**8.9** (2.3-51.4)

Responses were based on the treating physician determination (CT or PET/CT)

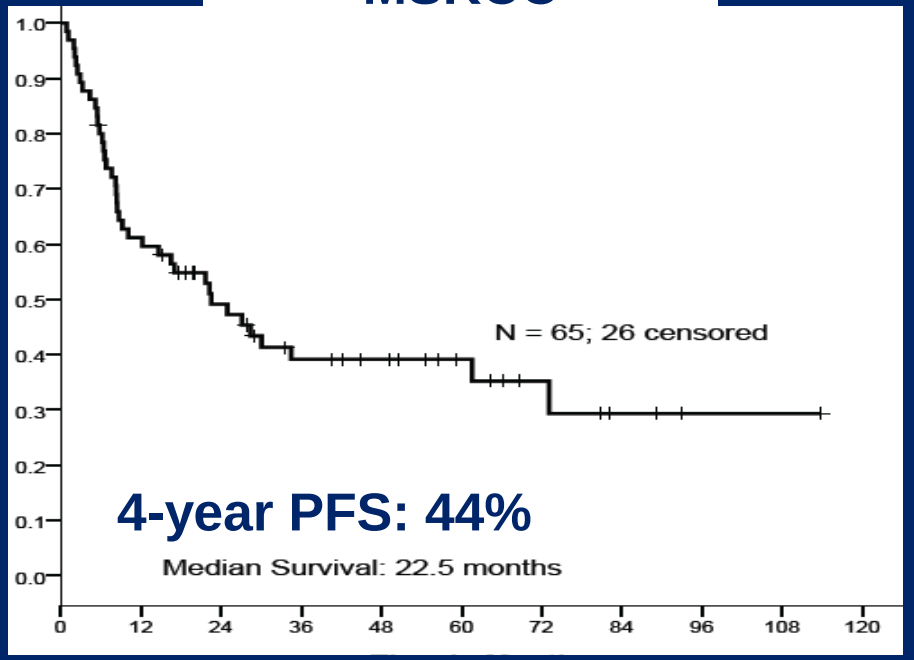
Mehta-Shah N ASH 2020

~ 45% of PTCL patients in CR1 achieve prolonged remission after CT + AutoSCT

Nordic



MSKCC



Swedish Registry

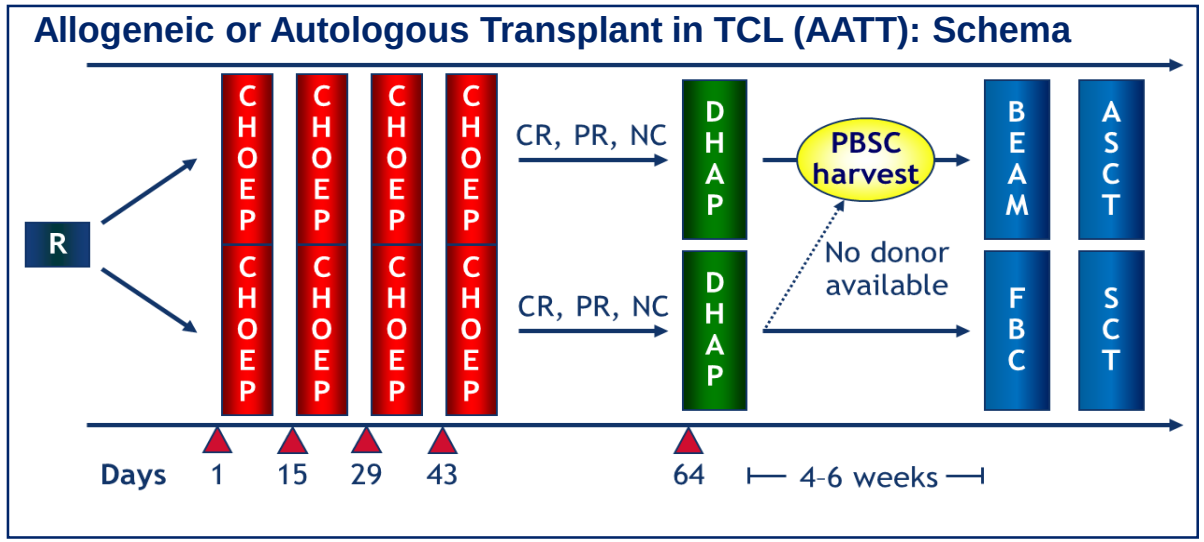
	Auto-SCT ITT (n = 128)	Non–auto-SCT (n = 124)
5 yr OS	48%	26%
5 yr PFS	41%	20%

D'Amore et Al, JCO 2012
Ellin et Al, Blood 2014
Mehta-Shah Clin Leuk Lymph Myel 2014

AlloSCT in first remission in PTCL?

Randomized phase III trial from LYSA and GLA comparing Auto to Allo for consolidation in first remission

- Halted 2/2 futility at interim analysis
- Underlines the limitations of transplant in CR1 and need for improved upfront therapy



1/3 patients never underwent consolidation

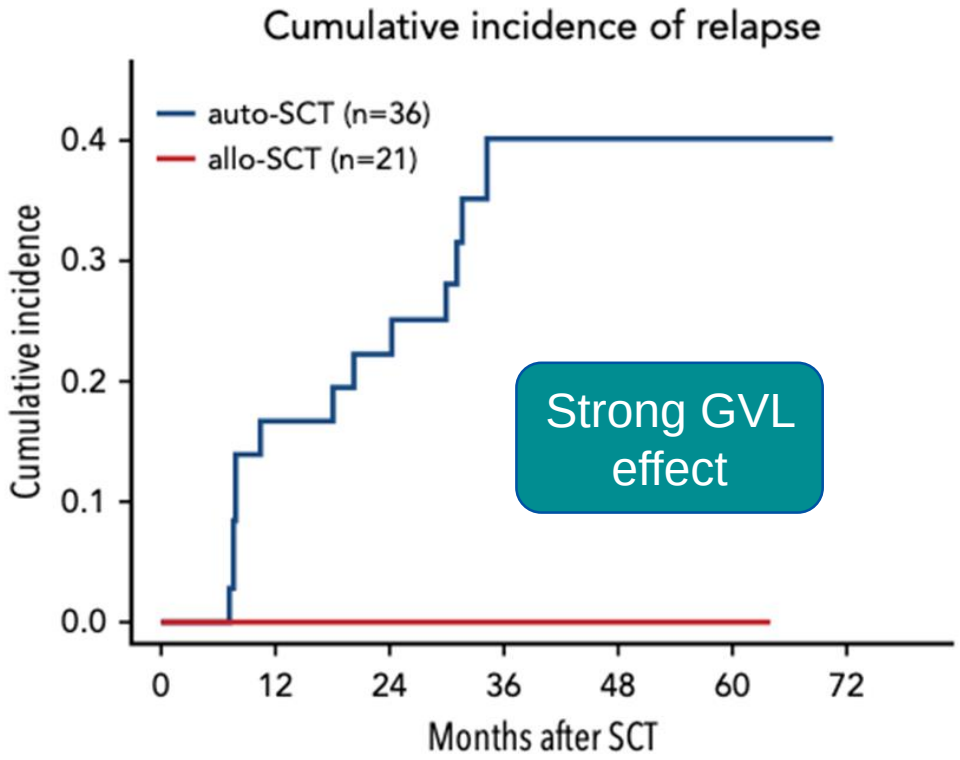
- 32% had disease progression prior to consolidation
- 6/33 (18%) without suitable donor

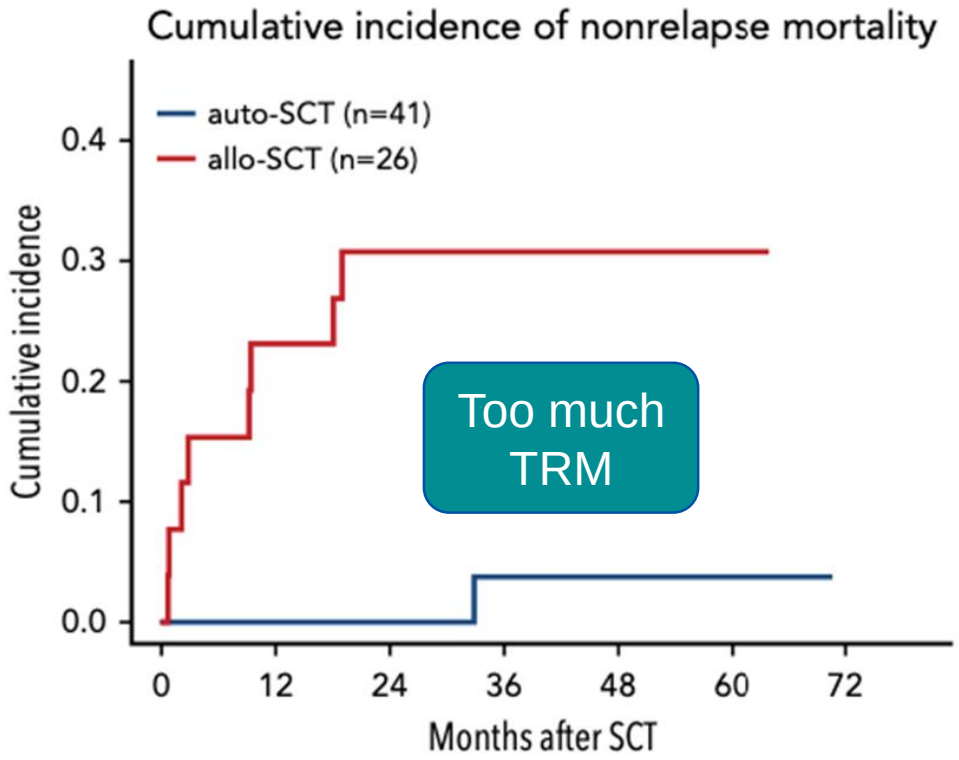
	Randomized		Transplanted	
	Auto	Allo	Auto	Allo
PTCL NOS	16 (30%)	15 (33%)	11 (27%)	8 (32%)
AITL	17 (33%)	20 (43%)	16 (40%)	12 (48%)
ALCL ALK-	9 (17%)	5 (11%)	8 (20%)	3 (12%)
Other	7 (13%)	3 (6%)	5 (12%)	2 (7%)

Schmits N et Al, Blood 2021

AlloSCT in first remission

Primary endpoint EFS at 3 y. No differences in EFS, PFS, OS but:





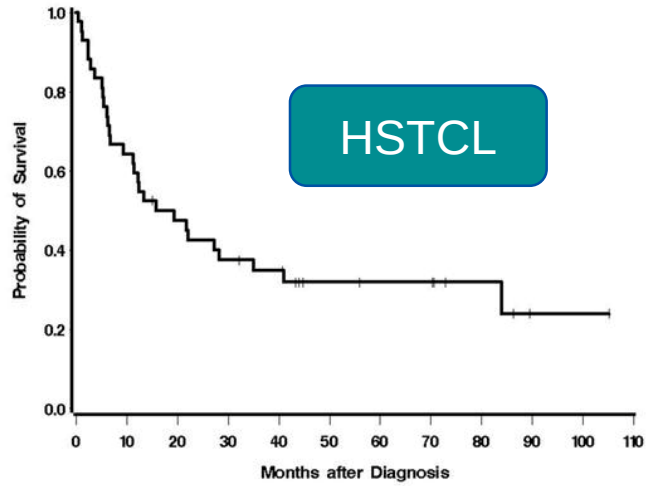
In the ITTP, 3y OS was 70% for Auto vs 57% for Allo; **PFS was 39% for Auto vs 43%** for AlloSCT

Schmits N et Al, Blood 2021

AlloSCT in first remission

- **Hepatosplenic T-cell lymphoma (HSTCL)**

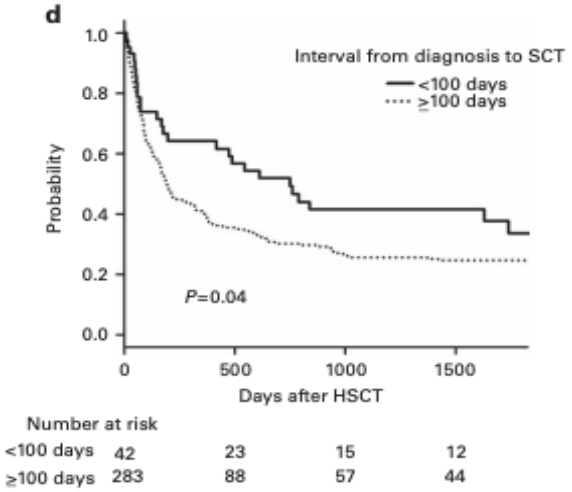
North American PTCL consortium data: 12 of 13 HSTCL who achieved long-term survival received AlloSCT



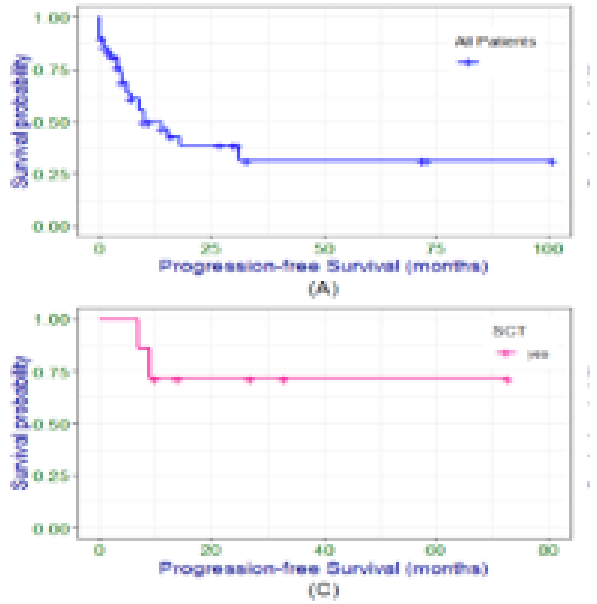
- **Adult T-cell leukemia/lymphoma (ATLL)**

Largest registry from Japan suggested that early transplant <100 days from diagnosis is associated with better outcomes.

ATLL



pcGDTCL



- **Primary cutaneous gamma-delta T-cell lymphoma (pcGDTCL)**

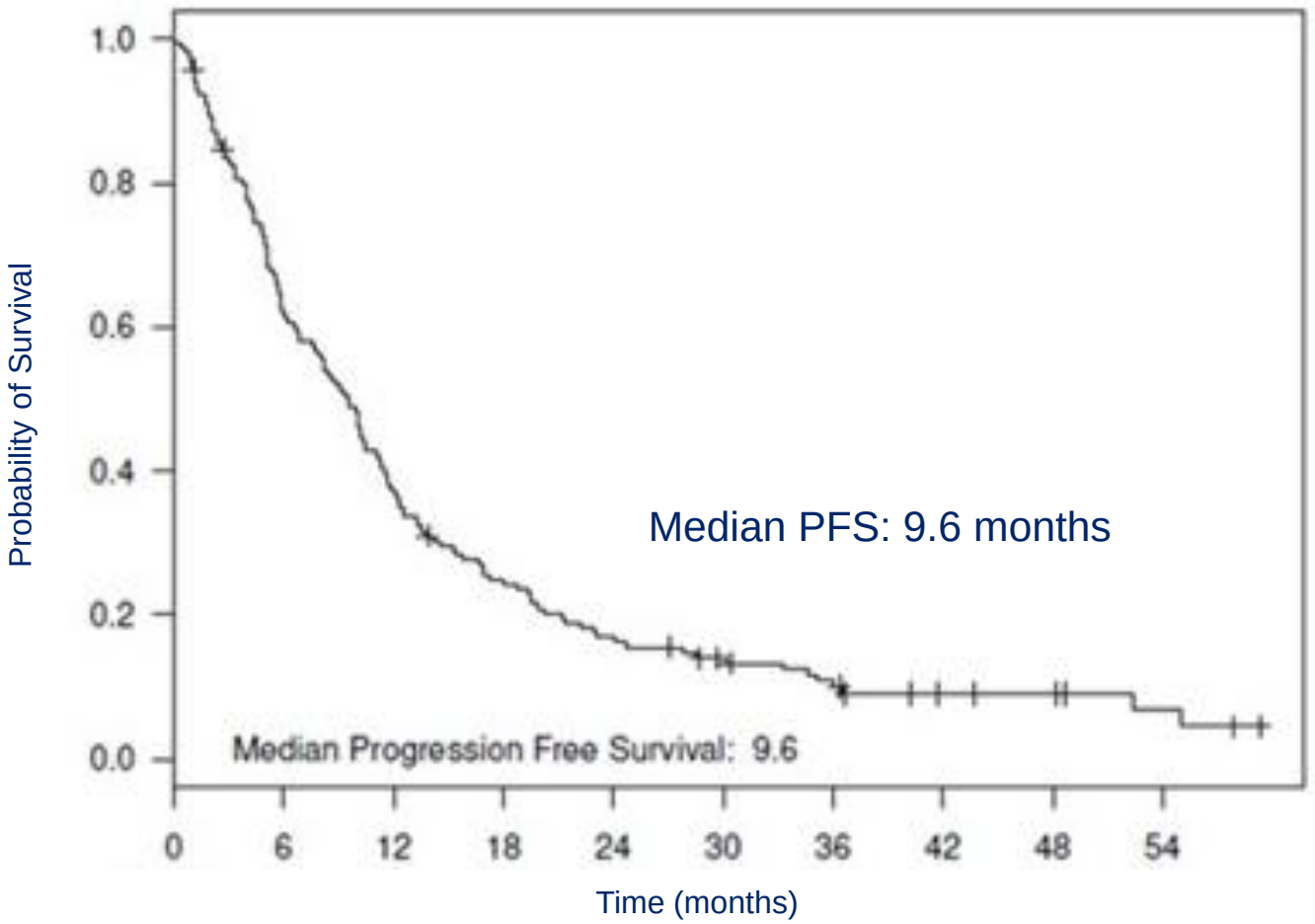
improved long-term survival of patients consolidated with AlloSCT in first remission

Shustov AR et Al, Blood 2013
Fuji S et Al. Bone Marrow Transplant 2016
David KA et Al, ASH 2019

Outcomes in relapsed/refractory PTCL

At least 60% of our patients with non-ALCL PTCL will relapse
Outcomes are poor

PFS in Relapsed/Refractory PTCL (n=499)



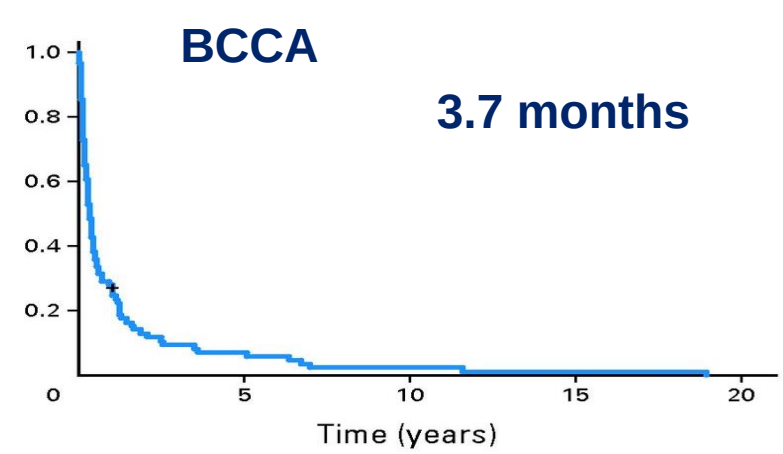
Lansogan ACTA Hematol 2019

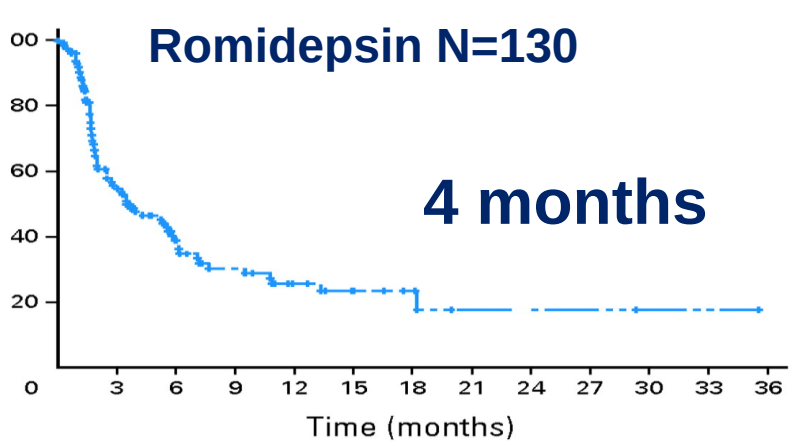
More than 55% of the PTCL will relapse, what are the chances of a CR2?

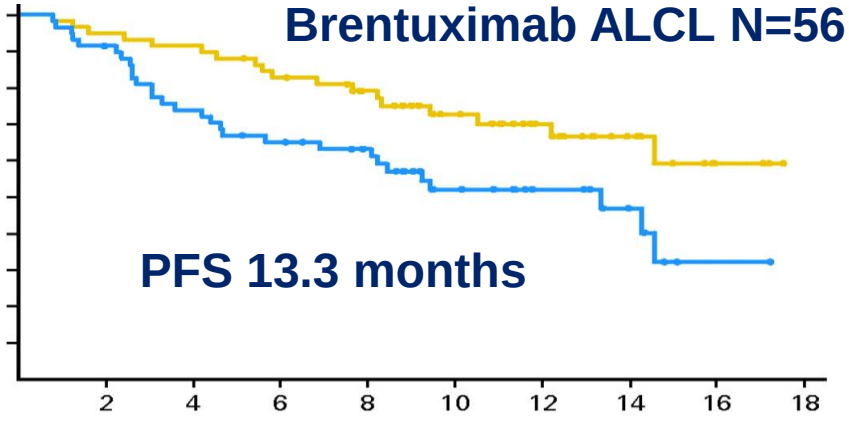
FDA-approved drugs for r/r PTCL	Overall Response Rate	Complete Remission Rate	ORR PTCL-NOS	ORR AITL	ORR ALCL
Hystone Deacetylase Inhibitors					
Romidepsin	25%	**15%**	29%	30%	24%
Belinostat	26%	**11%**	23%	54%	15%
Anti-folate					
Pralatrexate	29%	**15%**	32%	8%	29%
CD30 targeted approaches					
Brentuximab vedotin	69%	**44%**	33%	54%	86%

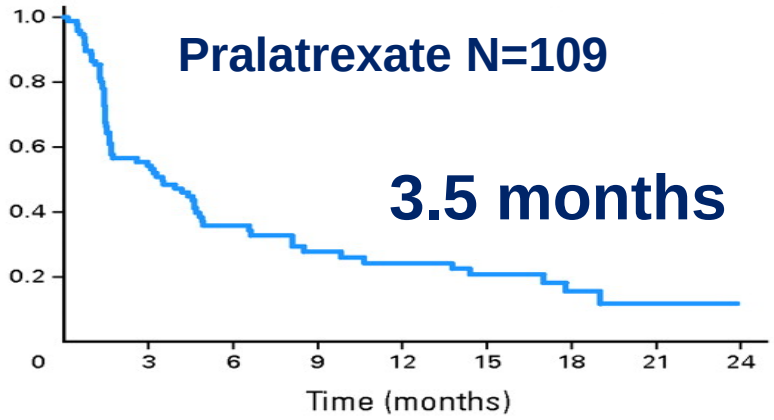
O' Connor OA, et al. *J Clin Oncol*. 2011;29:1182-1189,
Coiffier B, et al. *J Clin Oncol*. 2012;30:631-636,
O'Connor OA et al ASCO 2013;
Horwitz, S et al ICML 2013,
Pro B, et al. J Clin Oncol. 2012;30:2190-2196,
Horwitz S M et al. Blood 2014;123:3095-3100

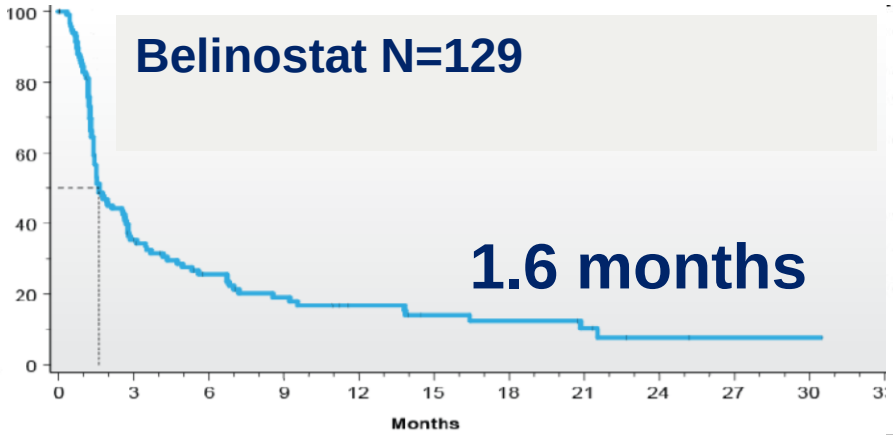
FDA approved treatments for R/R PTCL – Progression-free survival

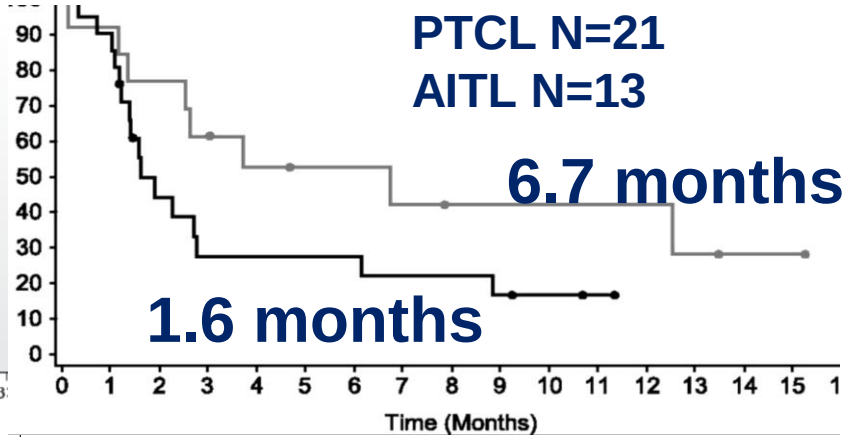












Mak V et al. JCO 2013;31:1970-1976, O'Connor OA, et al. *J Clin Oncol*. 2011;29:1182-1189,Coiffier B, et al. *J Clin Oncol*. 2012;30 :631-636, O'Connor OA et al ASCO 2013, Pro B, et al. J Clin Oncol. 2012;30:2190-2196, Horwitz S M et al. Blood 2014;123:3095-3100

Other Therapies in Development in TCL/other targets

Clinical Trials are available for relapsed patients

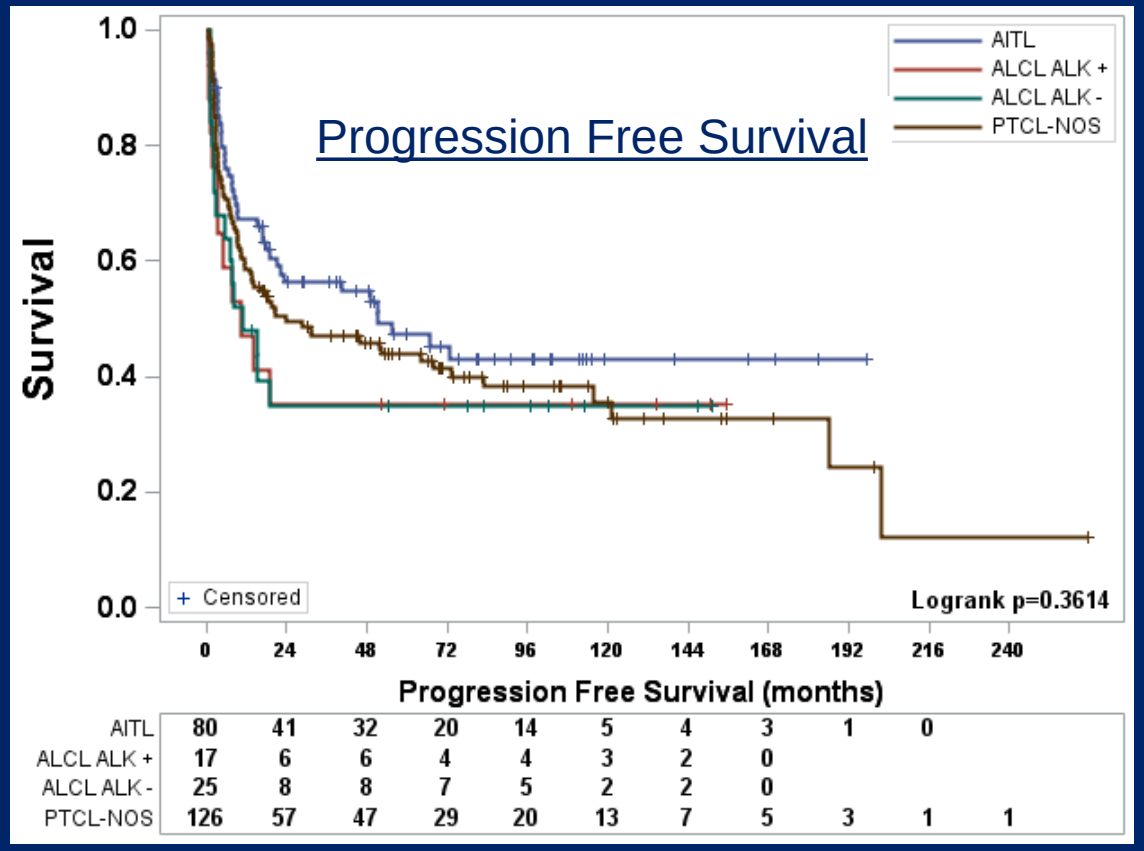
- Duvelisib
- EZH1/2 inhibitors
- Targeting the JAK/STAT
- Anti CD47 strategies
- Cell Therapies
- ADCs
- Bispecifics

ORR and CR rates look generally better than the FDA-approved compounds in phase 1-2 trials, but duration of response is still an issue

Outcomes of AlloSCT by PTCL subtype

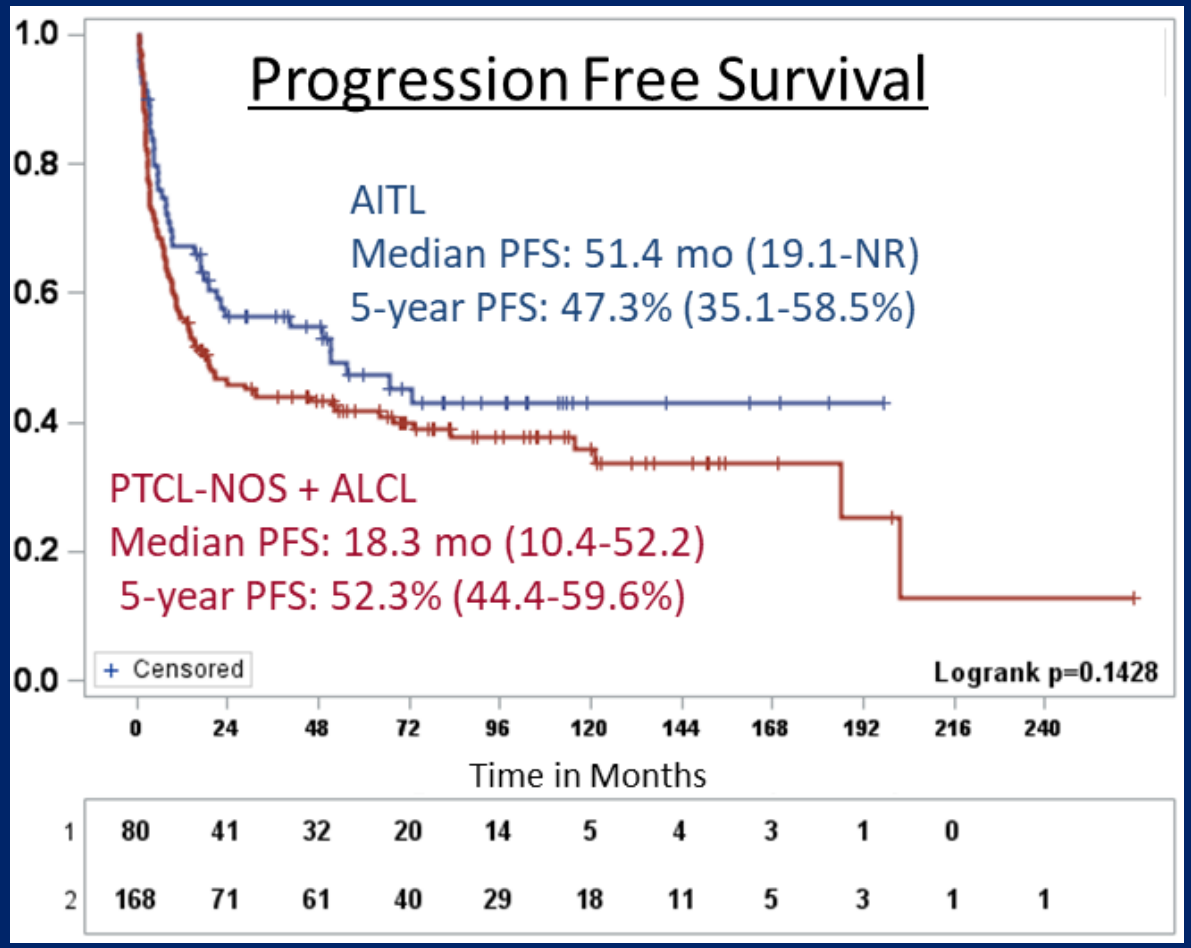
5 year PFS

AITL:	**47.3%**
PTCL-NOS:	**43.9%**
ALCL, ALK + :	**35.3%**
ALCL, ALK- :	**34.9%**



CIBMTR analysis showed in AITL (n=249):

- **4 year OS: 56%**
- **4 year PFS: 49%**



Mehta-Shah ASH 2020; Epperla et al J Hematol Oncol 2019

PFS by subtype

	PTCL-NOS	AITL	NK/T	Hepatosplenic	CTCL	ALCL, ALK+	ALCL ALK-	ALCL, ALK UNK	Subcutanous Panniculitis like TCL	Enteropathy Associated TCL	Primary Cutaneous Gamma Delta	Other
N	133	82	20	34	67	18	26	7	11	7	6	97
2–yr PFS (95% CI)	49.6%	56.4%	30.0%	54.7%	33.9%	35.3%	34.9%	14.3%	55.6%	33.3%	33.3%	48.1%
5- yr PFS (95% CI)	43.9%	47.3%	30.0%	48.6%	18.6%	35.3%	34.9%	14.3%	55.6%	33.3%	33.3%	42.2%

For R/R TCL often PFS = OS post AlloSCT

Overall Survival (OS)

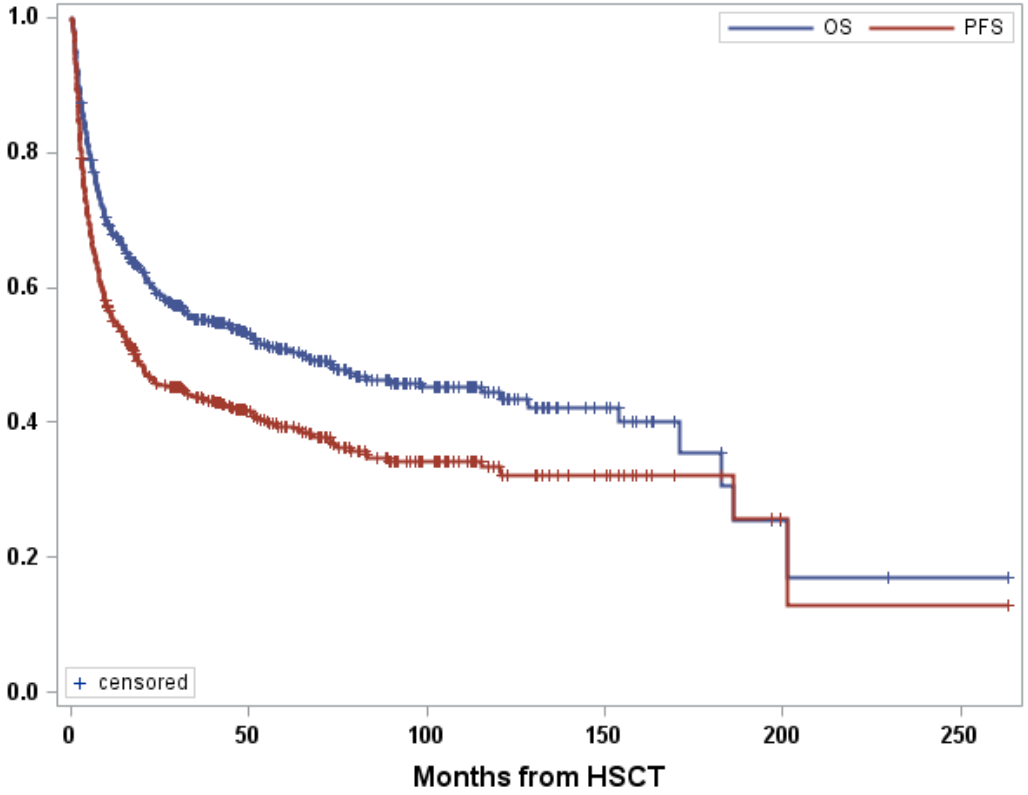
- **2 years: 59.1%** (95%CI: 54.6-63.3%)
- **5 years: 50.8%** (95%CI: 46.1-55.3%)

Progression Free Survival (PFS)

- **2 years: 45.8%** (95%CI: 41.3-50.2%)
- **5 years: 39.4%** (95%CI: 34.9-43.9%)

Median time from relapse to death post-Allo:

10.2 mo (0-158.4 mo)



Mehta-Shah ASH 2020

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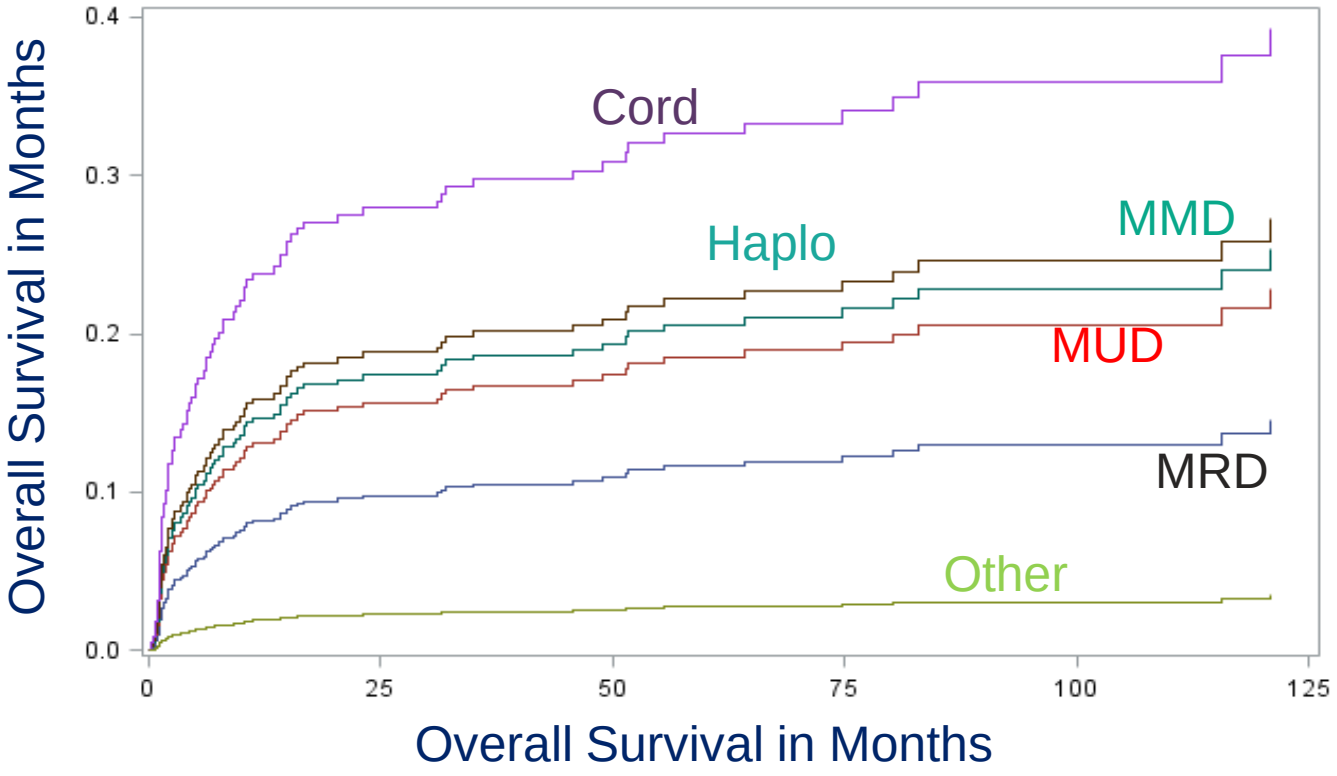
Treatment-related mortality (TRM) by donor type

1 yr TRM was 11.2% (95%CI:8.5%-14.0%)



Donor	TRM at 12 mo	95% CI
MRD (n=192)	8.2%	(5.5-12%)
MUD (n=183)	13.1%	(9.7-17.8%)
MMD (n=53)	14.7%	(8.7-24.6%)
Haplo (n=18)	15.9%	(6.0-42.2%)
Cord (n=25)	23.8%	(13.3-42.6%)
Other (n=36)	19.0%	(2.8-12.7%)

- **Acute GvHD**: 245/489 (46%)
- **Chronic GvHD** 192/473 (40.6%)
- Increased HCT-CI score was associated with increased TRM (p=0.012)

CTCL - Allogeneic Stem Cell Transplant

Metanalysis of 266 patients with AS CTCL from 5 studies.

- Commonly used RIC or non-myeloablative therapies and TSEB as part of conditioning
- **Non-relapse mortality rate was 19%**
- Pooled OS rates of 59% (at 1-4 years) were observed in spite of advanced disease in most cases.
- Pooled **PFS rate of 36%** highlights the risk of the disease relapse after allo-HCT.

Iqbal M et al. *Biol Blood Marrow Transplant*. 2020;26:76-82.

Conclusions

1. **Graft vs lymphoma effect** → probably true for some patients, but very low PFS compared to risks, and only curve that reaches a plateau is AITL

2. **Depth of remission before AlloSCT** → extremely unlikely to obtain CR and maintain
   - AlloSCT in first line PTCL → not recommended except rare cases

3. **Donor type** → Cord, Haplo MMD unfortunately have very high TRM

4. **Treatment-related mortality** → Particularly high in CTCL (19%), with PFS of only 36%

Thank you!