Allogenic Bone Marrow Transplantation in Relapse/Refractory Hodgkin's Lymphoma

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Hodgkin's lymphoma (HL) is a rare lymphoma of B-cell origin

- classical Hodgkin's lymphoma (90%)
- nodular lymphocyte-predominant Hodgkin lymphoma (10%)
- up to 10% of HL cases are refractory to initial therapy, and up to 30% relapse after initial response
- approximately half of these patients can still be cured using high-dose chemotherapy and autologous hematopoietic stem cell transplant (AHSCT)
- . Despite the success of the antibody– drug conjugate brentuximab vedotin and immune checkpoint inhibitors in the treatment of relapsed and refractory disease, their curative potential is debatable and the majority of patients eventually progress

6 Facts About Hodgkin's Lymphoma Remissions and Relapse:

- **1. Remission doesn't mean "cured"**
- **2. Side effects from treatment are possible in remission**
  - fertility problems
  - increased susceptibility to infection
  - thyroid issues
  - lung damage
  - additional forms of cancer
- **3. Hodgkin's lymphoma increases the risk of a second cancer**
  - leukemia
  - breast cancer
  - lung cancer
  - thyroid cancer
  - bone cancer

- **4. Induction failure is different from relapse**
- **5. There are treatment options for relapse**
  - age
  - medical history
  - scope of disease
- **6. Lifestyle changes can help to manage a relapse**

- the standard-of-care-therapy for R/R HL approach remains centered around using high-dose chemotherapy and Allo-HSCT in patients that is responsive to chemotherapy
- cure close to 50% of these patients

- The relapsed/refractory Hodgkin lymphoma (R/R HL) after autologous stem cell transplant (autoSCT) has few therapeutic options apart from the allogenic stem cell transplant (alloSCT)
- who achieve a complete response (CR) it seems to be durable only after doing alloSCT

The Place of Transplantation in Hodgkin's Lymphoma in the Context of Targeted Immunotherapy

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Indications for HCT in cHL

Disease Risk	MSD	MUD	Alternative Sources	Auto-HCT
CR1	GNR/III	GNR/III	GNR/III	GNR/I
CR1>1, prev auto NO	D/III	D/III	GNR/III	S/I
CR>1, prev auto YES	S/II	S/II	CO/III	CO/III
Refractory	D/II	D/II	D/III	CO/III

Duarte R et al, BMT 2019

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CR1	GNR/III	GNR/III	GNR/III	GNR/I
CR1>1, prev auto NO	D/III	D/III	GNR/III	S/I
CR>1, prev auto YES	S/II	S/II	CO/III	CO/III
Refractory	D/II	D/II	D/III	CO/III

Duarte R et al, BMT 2019

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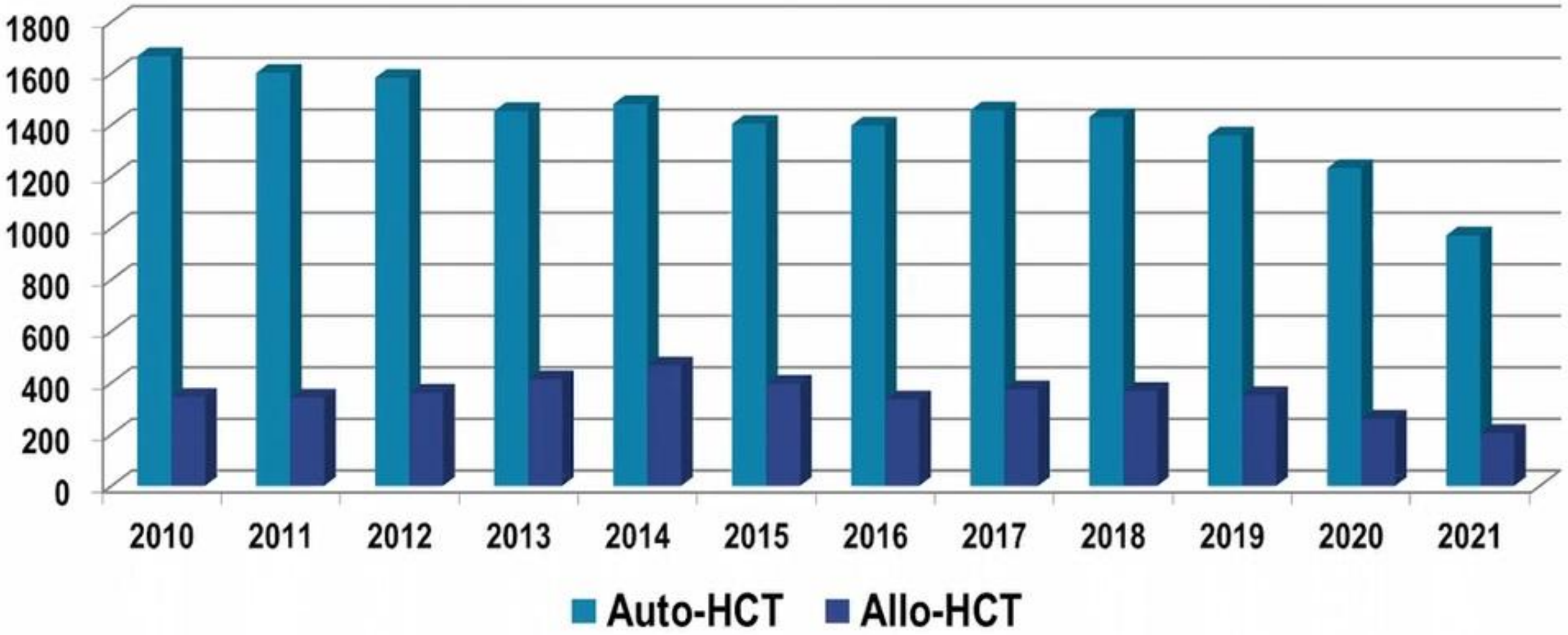
CR1	GNR/III	GNR/III	GNR/III	GNR/I
CR1>1, prev auto NO	D/III	D/III	GNR/III	S/I
CR>1, prev auto YES	S/II	S/II	CO/III	CO/III
Refractory	D/II	D/II	D/III	CO/III

Snowden J et al, submitted


1800
1600
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2010
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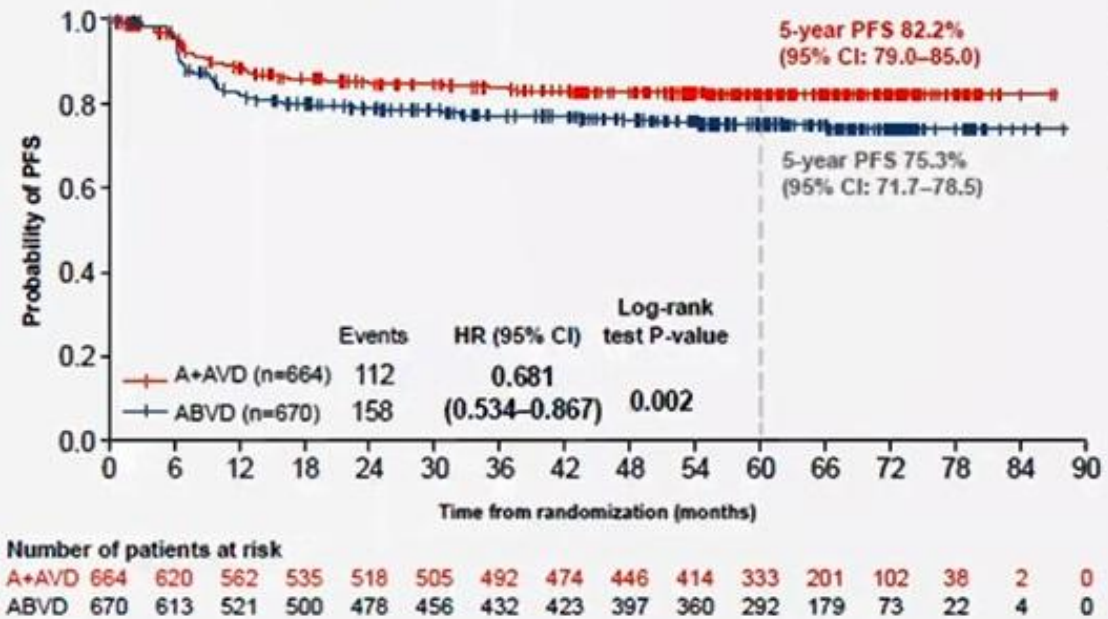
2018
2019
2020
2021
Auto-HCT
Allo-HCT

What Changes in cHL Therapy are Impacting Auto-HCT?

More Effective Drugs in the First Line Treatment → Less Primary Refractoriness and Relapsed Disease

AFTER 5-YEAR FOLLOW-UP

PFS per investigator in the ITT population at 5-year follow-up*
(ITT; N=1334)

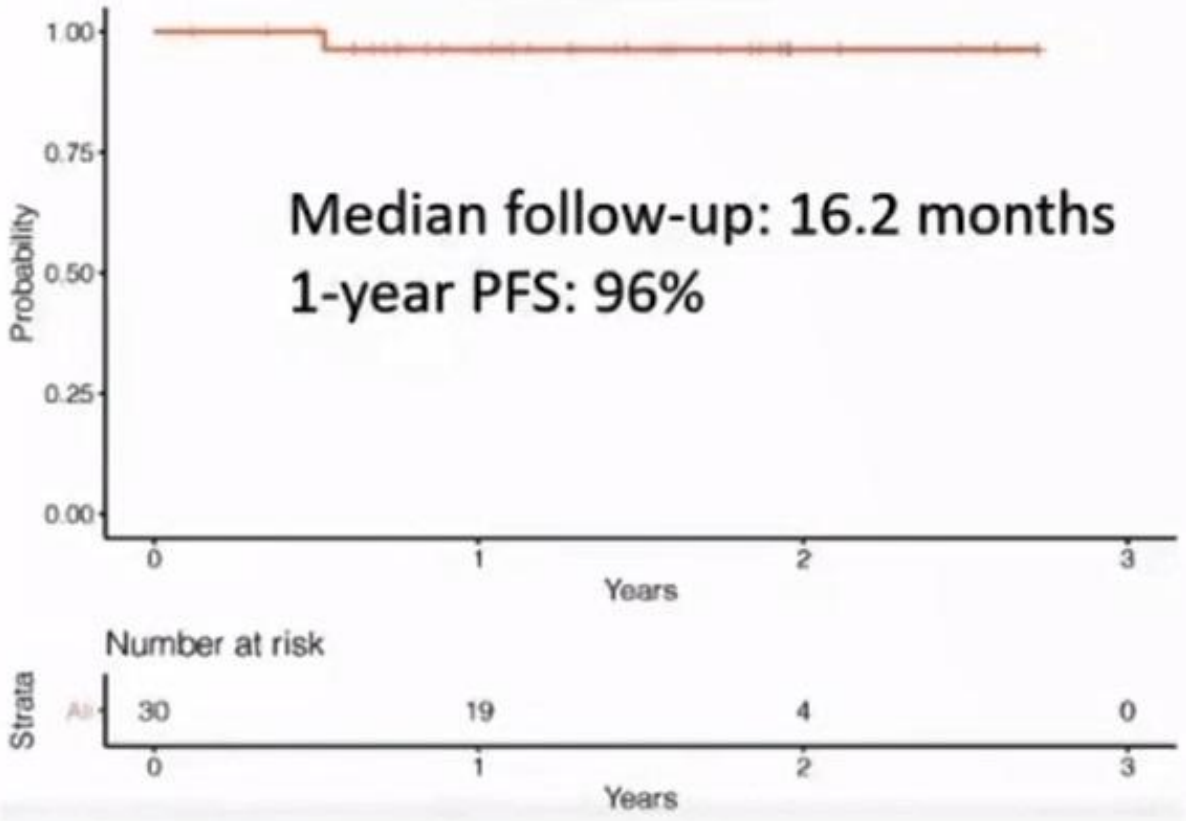


Characteristics	A+AVD n=664	ABVD n=670	Total N=1.334
IPI score, n (%)			
0 or 1	142 (21)	141 (21)	283 (21)
2 or 3	355 (53)	355 (53)	712 (53)
4 to 7	167 (25)	167 (25)	339 (25)
PET2 status, n (%)			
Positive	47 (7)	58 (9)	105 (8)
Negative	588 (89)	578 (86)	1,166 (87)
Unknown/unavailable	29 (4)	34 (5)	63 (5)

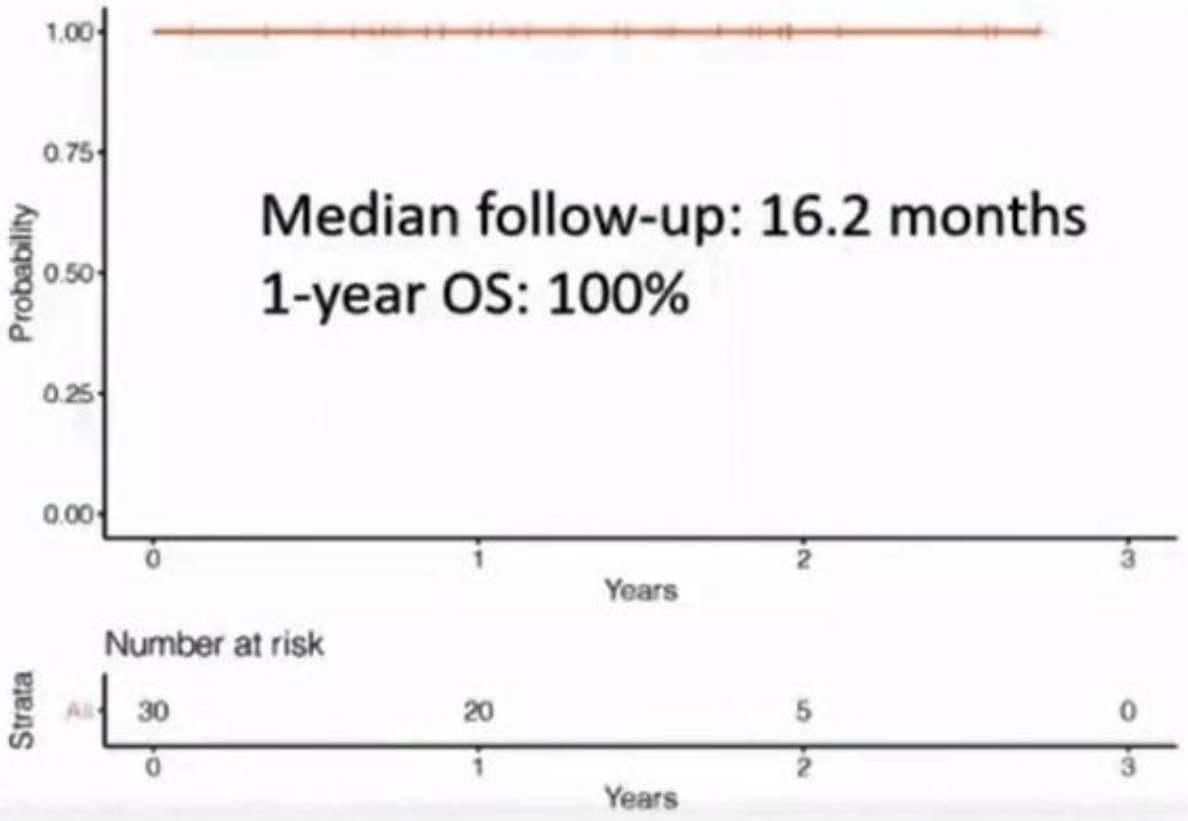
- Median follow-up time was 60.9 months (95% CI: 60.8–61.0)
- At 5-year follow-up, the prespecified number of events required to trigger an OS analysis has not been reached
- OS was a prespecified key secondary endpoint

Concurrent Pembrolizumab with AVD for Untreated cHL

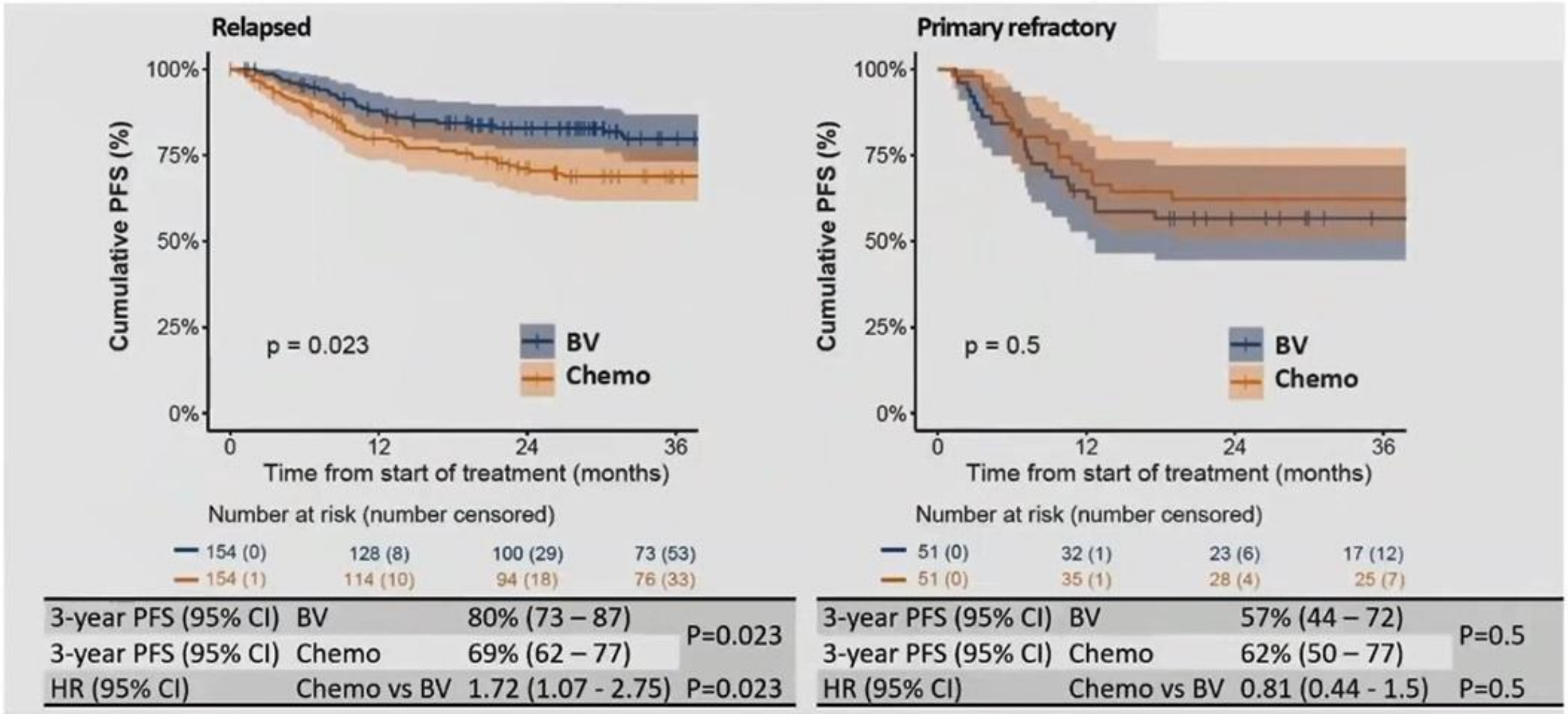
Progression-free survival



Overall survival



Is BV + Chemo Better Than Chemo Alone to Rescue cHL Patients Before Auto-HCT?



3-year PFS (95% CI)	BV	80% (73 – 87)	P=0.023
3-year PFS (95% CI)	Chemo	69% (62 – 77)	
HR (95% CI)	Chemo vs BV	1.72 (1.07 - 2.75)	P=0.023

3-year PFS (95% CI)	BV	57% (44 – 72)	P=0.5
3-year PFS (95% CI)	Chemo	62% (50 – 77)	
HR (95% CI)	Chemo vs BV	0.81 (0.44 - 1.5)	P=0.5

Driessen J et al, ASH2021 [11]

Phase II Study of Pembrolizumab + GVD as Second Line Therapy for Relapsed / Refractory cHL

- **Eligibility**: relapsed or refractory cHL following 1-line of therapy
- **Primary endpoint**: CR (by Deauville 3) rate after 2-4 cycles

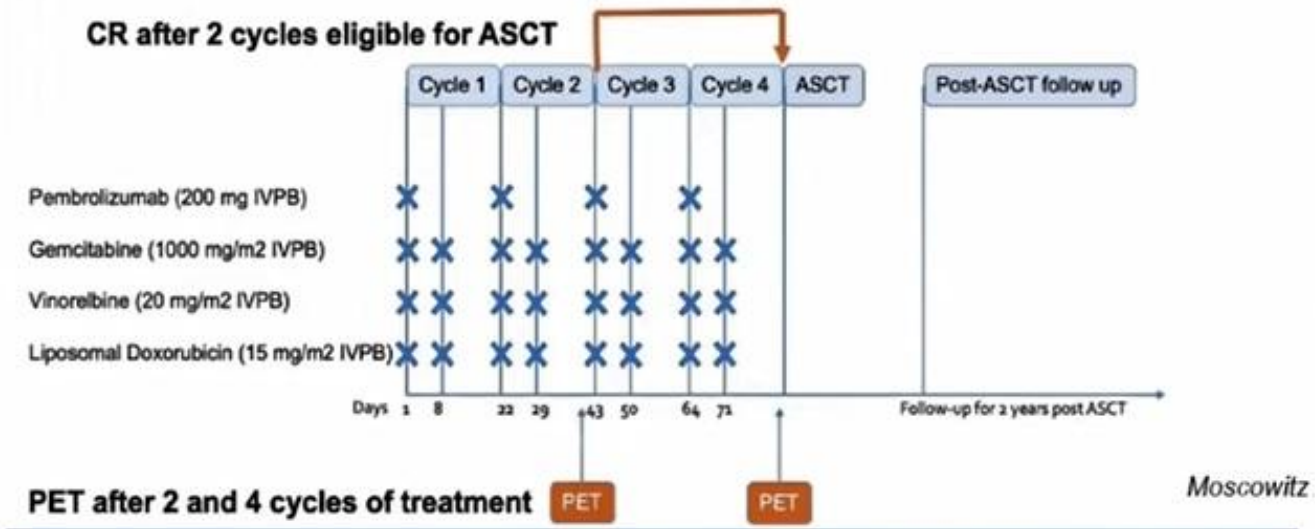
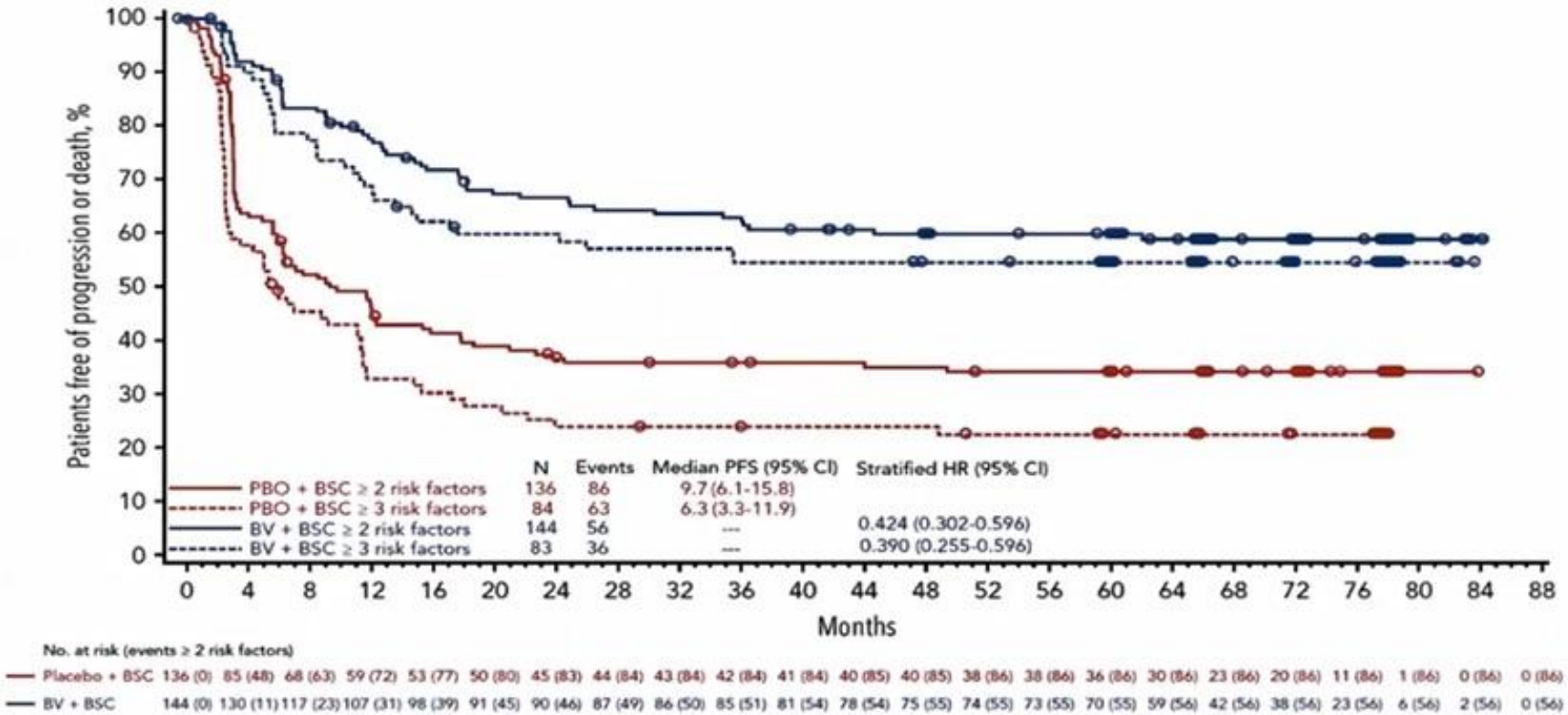


TABLE 3. Efficacy

Characteristic	Pembro-GVD × 2 (n = 38)[a]	Pembro-GVD × 4 (n = 7)	Pembro-GVD Overall (n = 38)
ORR, % (95% CI)	100 (91 to 100)	100 (59 to 100)	100 (91 to 100)
CR, % (95% CI)	92 (79 to 98)	71 (29 to 96)	95 (82 to 99)
PR, % (95% CI)	8 (2 to 21)	29 (4 to 71)	5 (1 to 18)
Best response, No. (%)			
CR	35 (92)	5 (71)	36 (95)
PR	3 (7.9)	2 (29)	2 (5.3)

Moscowitz A et al, J Clin Oncol 2021 [12]

Consolidation with Brentuximab Vedotin after Auto-HCT. Higher Benefit in Higher Risk Patients



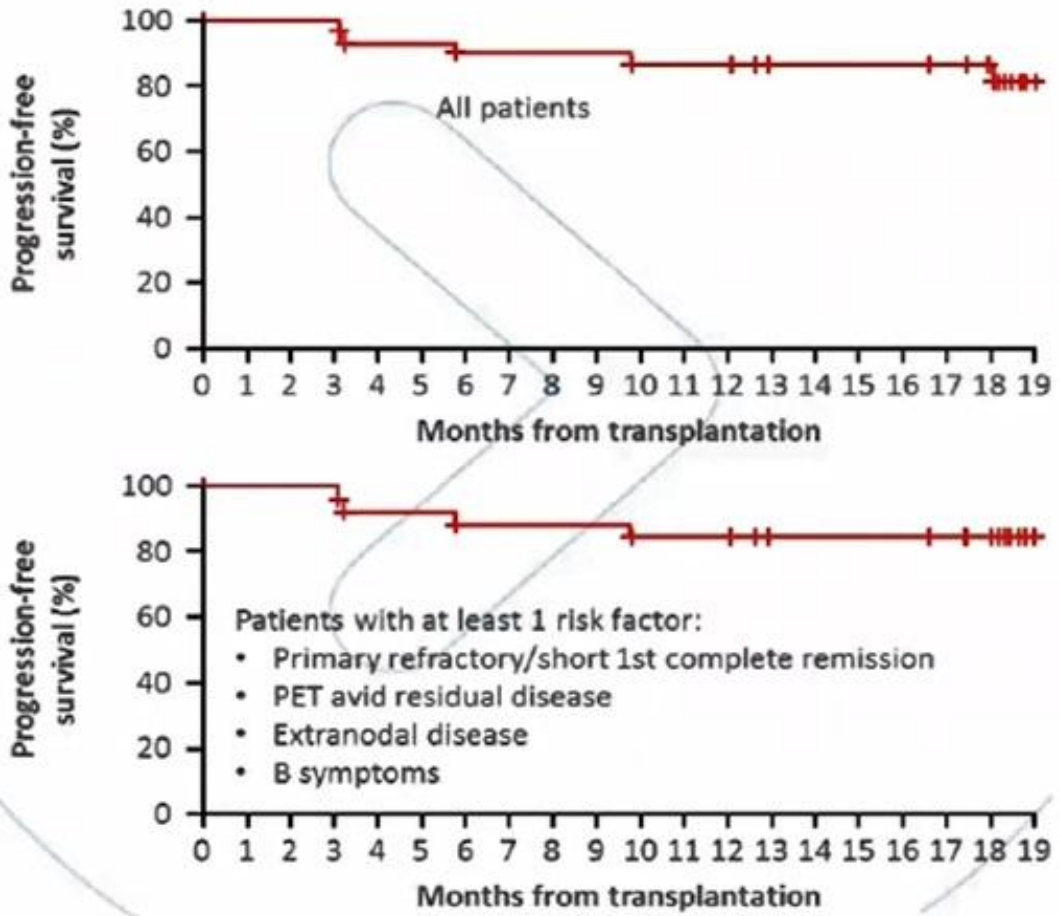
Risk factors:

- Relapse or < 12 m/ primary refractory
- Extranodal disease
- <CR to salvage therapy
- B sx at relapse
- ≥2 salvage regimens

Moscowitz C et al, Blood 2018

Consolidation with Pembrolizumab After Auto-HCT Resulted in Promising PFS

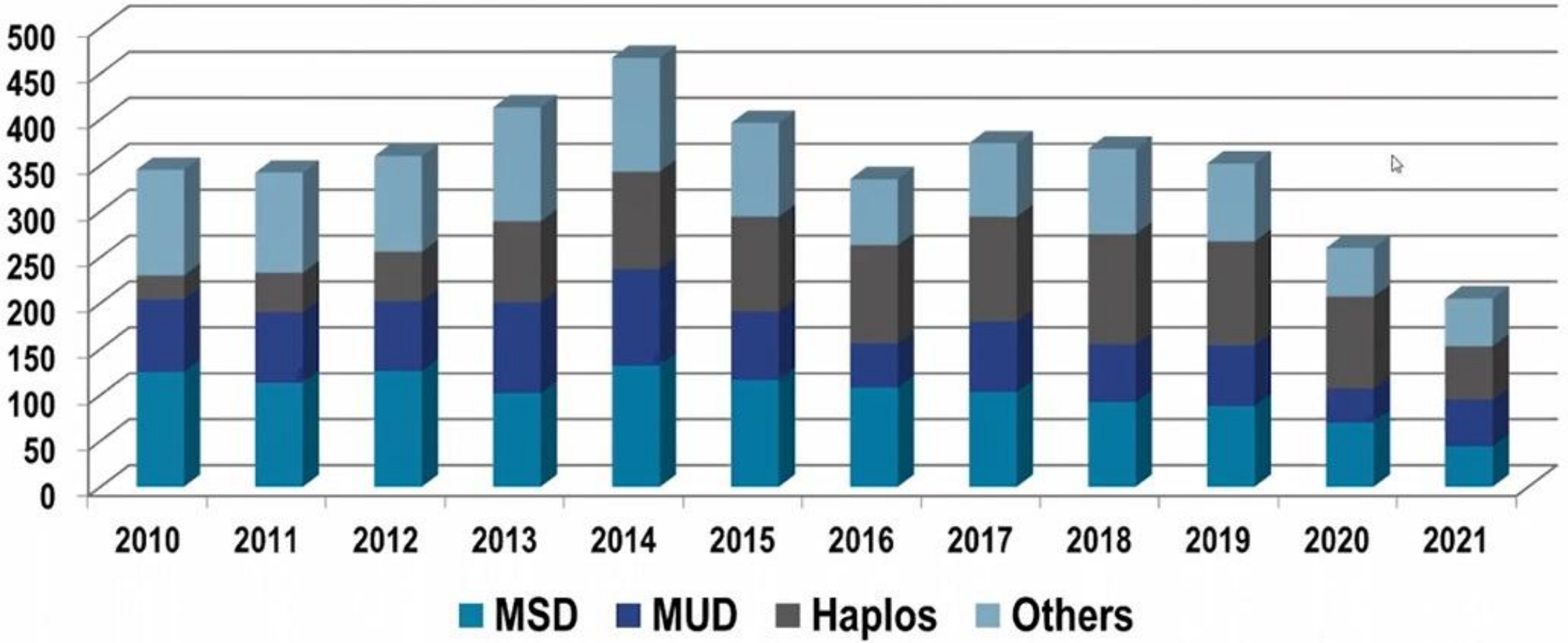
Baseline patient characteristics		n (%) or median (range)
Total		30 (100)
Age, years		33 (20–69)
Sex	Male	16 (53)
	Female	14 (47)
Frontline therapy	A(B)VD†	24 (77)
	Brentuximab vedotin-A(B)VD	1 (3)
	ABVE-PC	1 (3)
	BEACOPP‡	2 (7)
	RCHOP/REPOCH	2 (7)
Prior exposure to brentuximab vedotin / nivolumab or pembrolizumab / radiotherapy		6 (20) / 6 (20) / 7 (23)
Conditioning regimen - BEAM		30 (100)
Risk factors	Primary refractory disease	17 (57)
	Relapse within 12 months	5 (17)
	Extranodal disease at relapse	8 (27)
	At least 1 of above 3 factors	26 (87)
	Residual disease after salvage	3 (10)
	B symptoms at relapse	2 (7)
	>1 salvage therapy	5 (17)
	At least 1 of above 6 factors	27 (90)
	At least 2 of above 6 factors	12 (40)
Disease status at study entry (post-ASCT)	Partial remission	2 (7)
	Complete remission	28 (93)



Armand P et al, Blood 2019

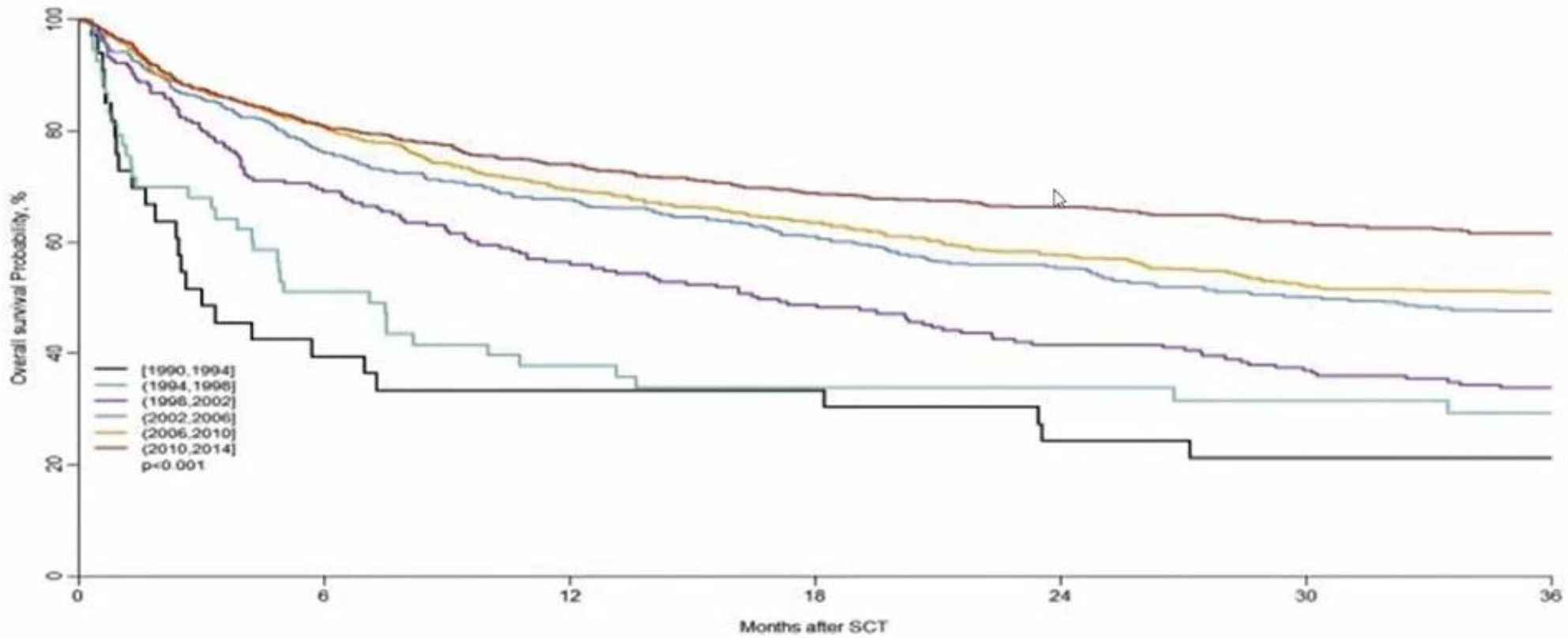
Allo-HCT is the Only Curative Strategy For Patients Who Relapse After Auto-HCT But …. Why Numbers Are Decreasing?

HCT in cHL. The EBMT Experience



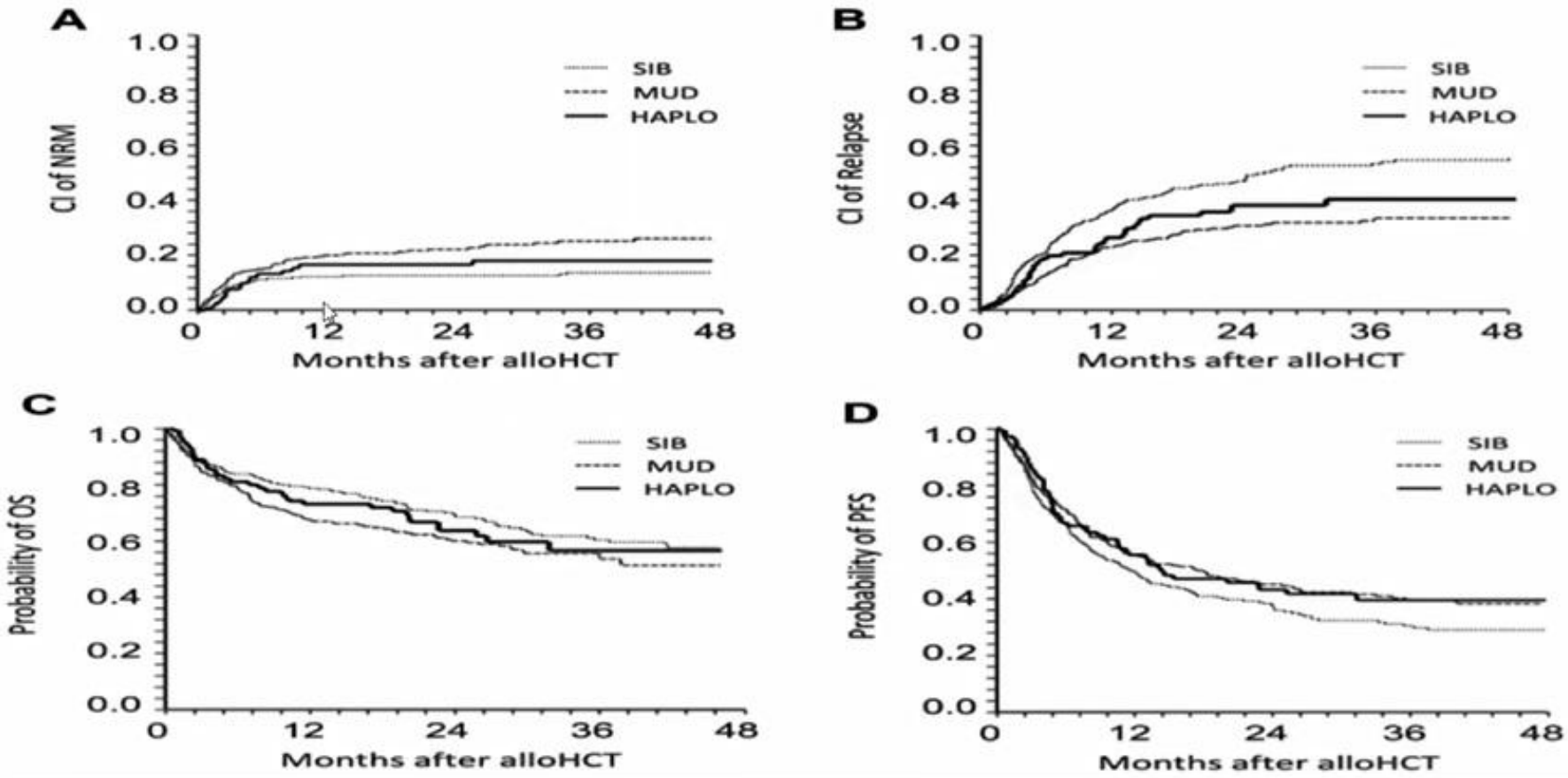
EBMT Database, with permission

Results of Allo-HCT Have Improved Over Time. The EBMT Experience



Sureda A et al, Bone Marrow Transplant 2020

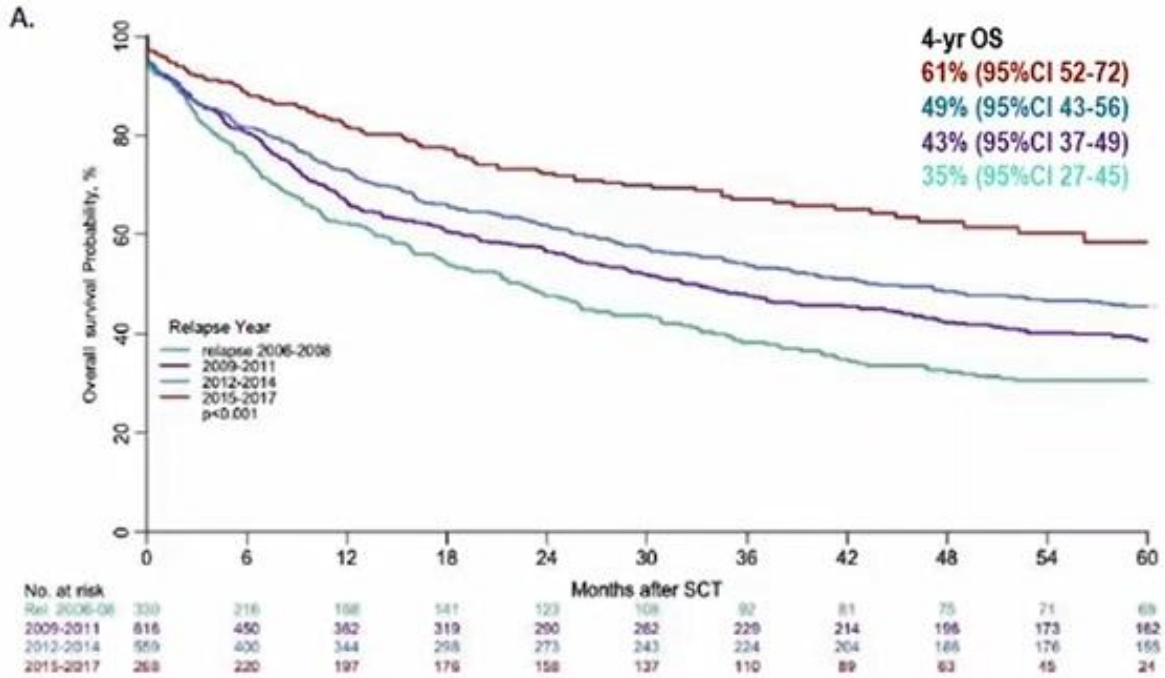
Haplo-HCT with Cy-Post Compare Favourably with MSD and MUDs



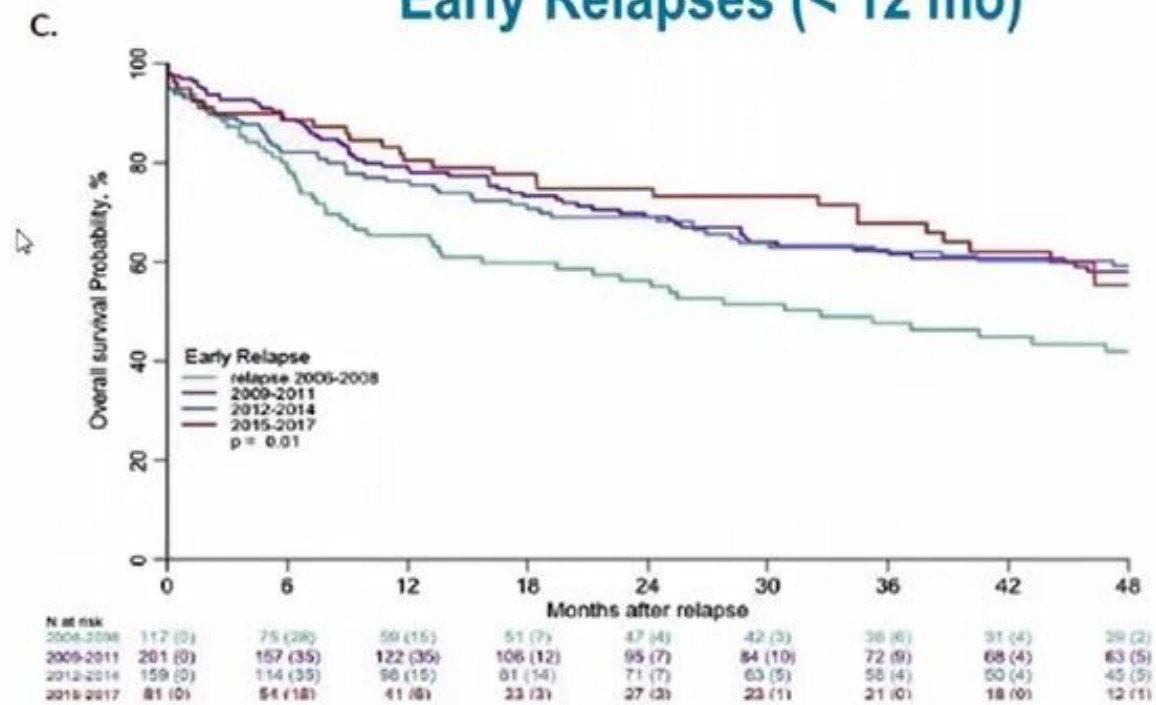
Martinez C et al, J Clin Oncol 2017

New Treatment Strategies Have Been Able to Improve OS After Auto-HCT

Global Population of Patients



Early Relapses (< 12 mo)



Bazarbachi Al et a, Leuk (in press)

Allotransplants after CPIs

N = 209
- 87 Haplo/PtCy
- 25 non-Haplo/PtCy
- 91 non-Haplo/non-PtCy
- 6 PtCy + ATG

Median age: 31.5 yrs

Male patients - 60%

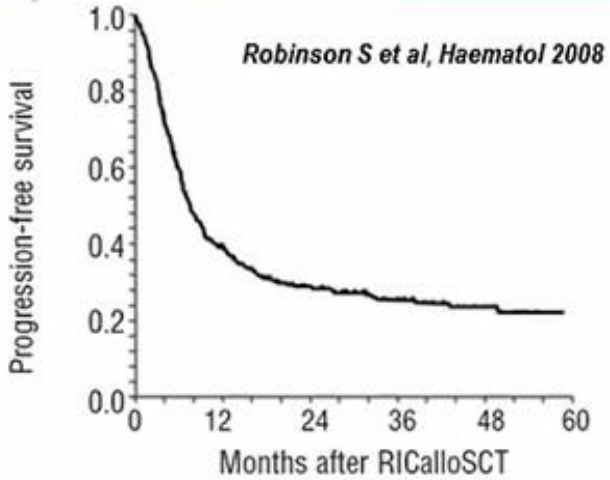
HCT-CI
- 0-2 - 129
- ≥ 3 – 66

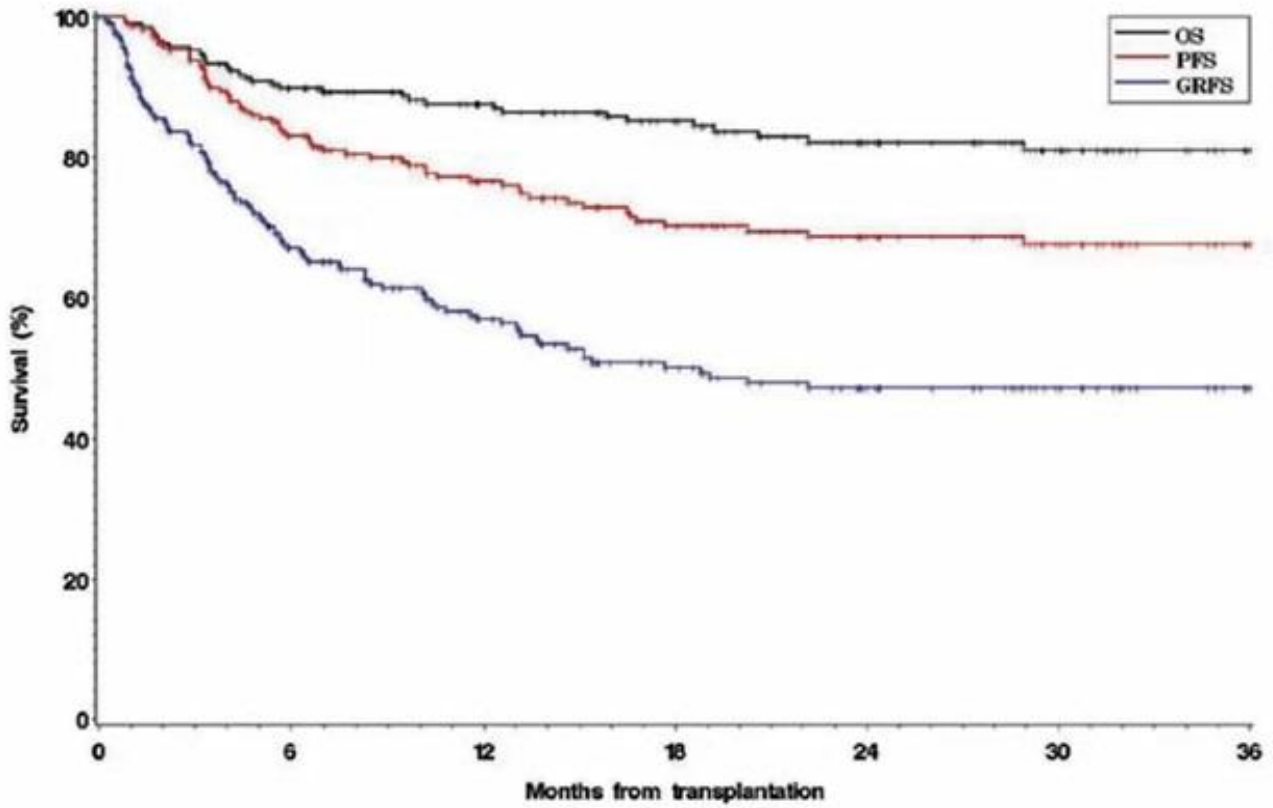
Median number of tx: 4 (2-11)

Best response to CPIs CR – 39%

Median time from last dose CPIs to Allo-HCT, 81 days

CR before allo-HCT – 58%





Merryman RW et al, Leuk 2021

Allotransplants after CPIs

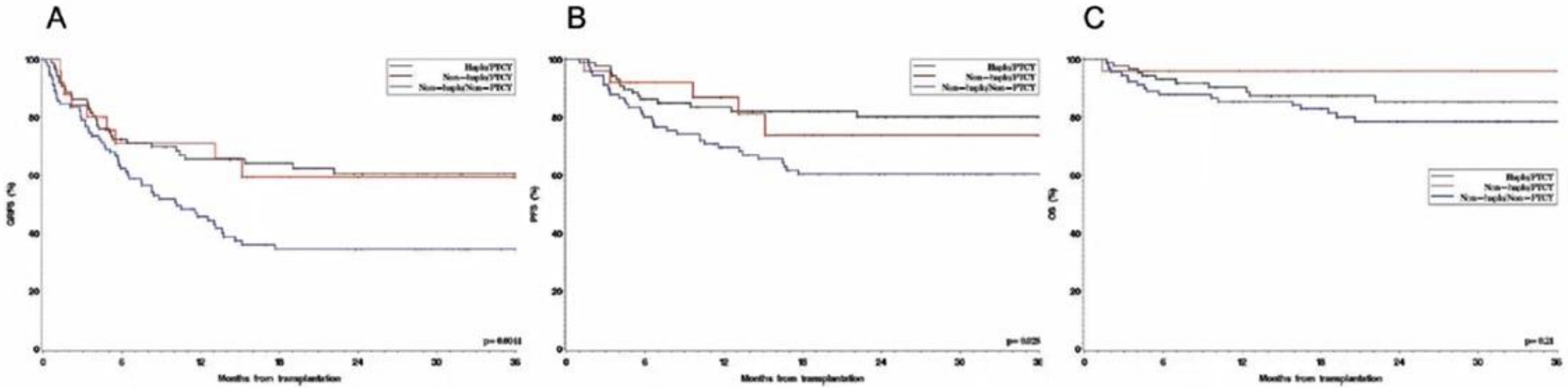
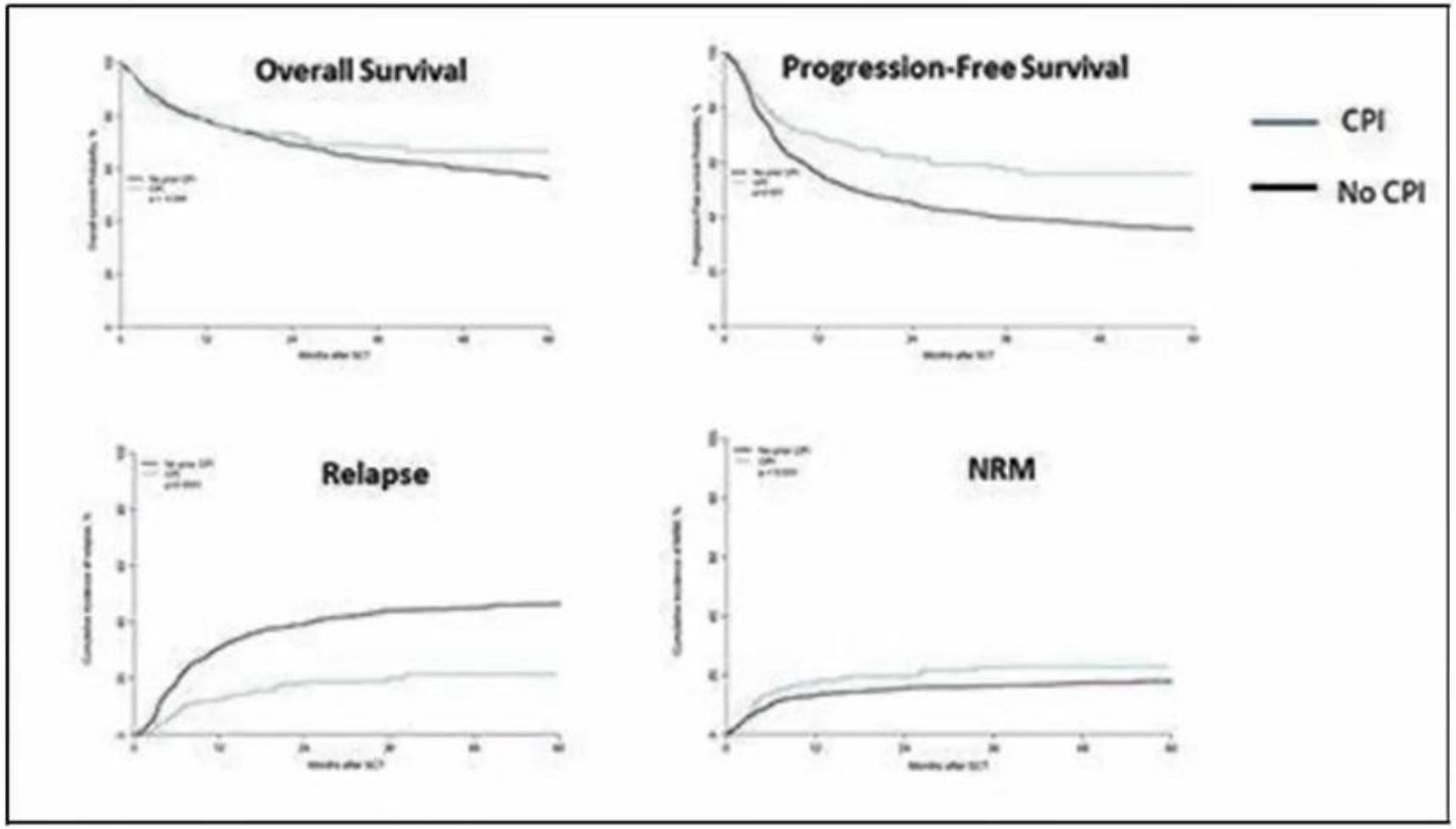


Fig. 2 Survival outcomes based on donor type and GVHD prophylaxis regimen. A GRFS, **B** PFS, **C** OS based on donor type and GVHD prophylaxis regimen. (Note: the six patients who received PTCy + ATG are not included in this figure).

Merryman RW et al, Leuk 2021

Better PFS and Lower RR after allo-HCT in Patients Pre-Treated with CPIs?



Perales MA et al, EBMT 2022 (Presidential Symposium)

Which Is the Best Sequence?

Brentuximab Vedotin → Check Point Inhibitor (NIVO, PEMBRO) → Allogeneic Stem Cell Transplantation

No Curative Potential

Better short-term toxicity profile

Results Less mature

Known Curative Potential

Significant morbi-mortality

Long-term Follow Up

Well identified risk-adapted patient's profile

Conclusions

- Times are changing for patients with relapsed/refractory Hodgkins' lymphoma
  - More effective first line therapies
- Results of auto-HCT have improved over time (better candidates, new drugs)
- Allo-HCT is still the only curative strategy for those patients that relapse after auto-HCT but allo-HCT "is competing" with very effective and less toxic strategies, and .... more to come

New Treatments and classical SCT
Summary Hodgkin's Lymphoma

Indications to autologous and allogeneic SCT in HL remain mostly unchanged

New treatments (ADC, CPI) are combined with both autlogous and allogeneic SCT and improve their results

Due to better results of second line treatment, the frequency of allogeneic SCT, mostly used as third line treatment is declining