Relapse after Autologous Stem Cell Transplantation: Anti-PD1 Consolidation vs Allogeneic stem cell transplant

Safa Najafi M.D.
Motamed cancer institute

Definite answer

- This study was not sufficient to elucidate on this matter, due to the small number of patients exposed to alternative strategies (as Nivolumab/Brentuximab) and short term follow up.
- Only a few patients were exposed to anti-PD-L1 and Brentuximab previously to the alloSCT.

The alloSCT is used for R/R HL since the early 1980s

- A meta-analysis about alloSCT in HL patients showed that relapse free survival rates at 3-years was31%(95%CI: 25–37), the overall survival(OS) was 50% (95% CI: 41–58),
- The role of the alloSCT in HL is well established nowadays,with a follow-up longer than 15 years.(adventage)

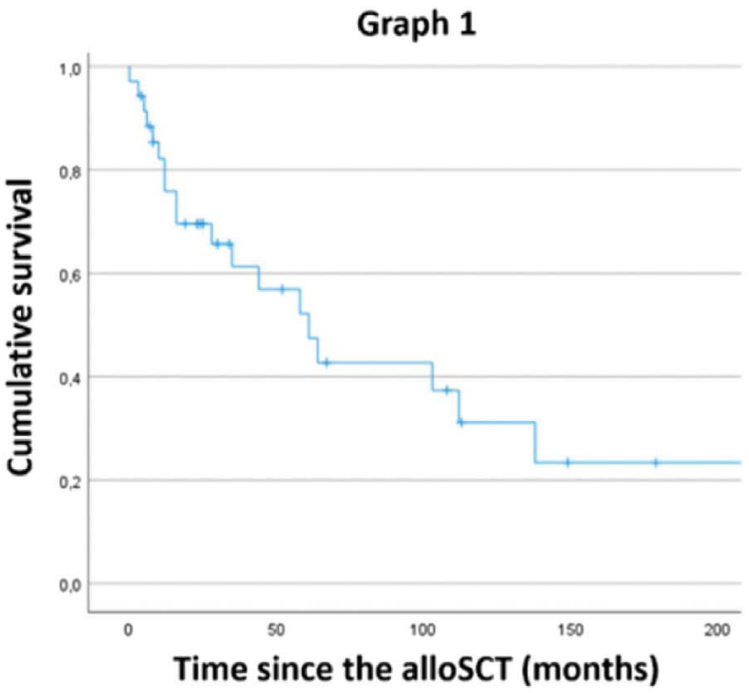
non-relapse mortality (NRM)

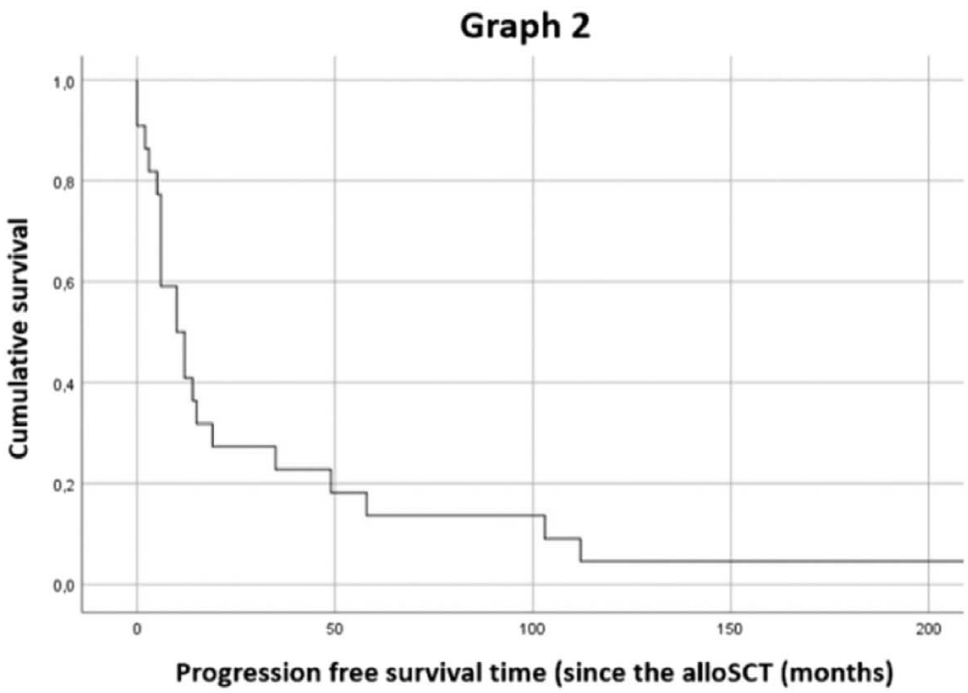
- Day-200 NRM was defined as **death before day-200 after transplant that was not preceded by recurrent or progressive malignancy**.
- Relapse-related mortality (RRM) was defined as death that was preceded by a relapse or progression of malignancy.
- non-relapse mortality (NRM)was 28% to 42%(95%CI: 1–19). Other studies showed similar results.

Table 1. Summary of the key studies evaluating the role of AlloHSCT in cHL.

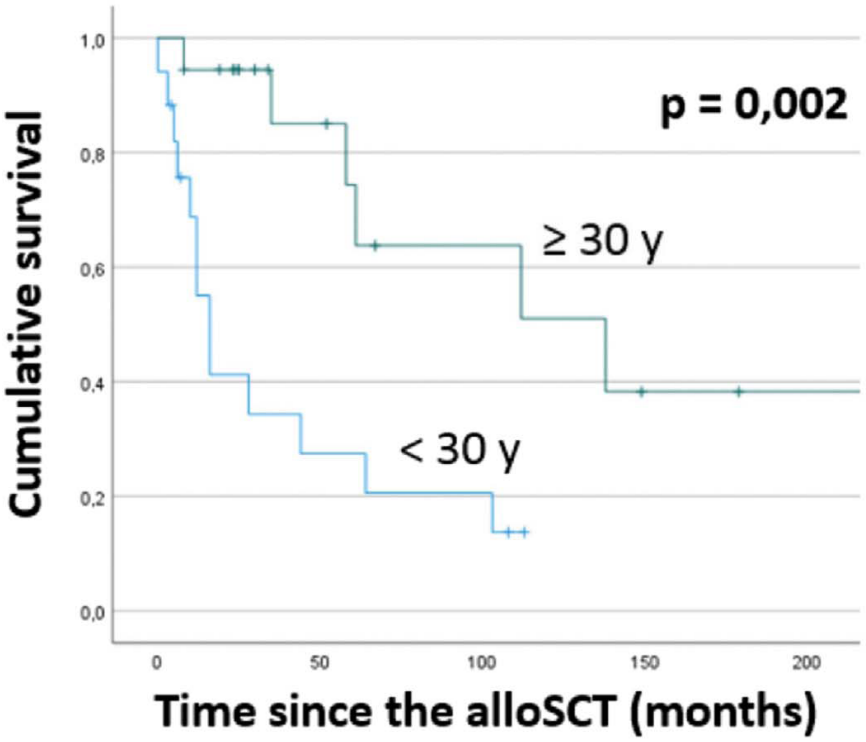
Study	Type	Number of Patients	Prior AHSCT	Donor Type	Conditioning	PFS	OS
Sureda et al. [34]	Retrospective registry (EBMT)	168	52%	MSD for more than 70%, rest are MUD	MAC 47%, RIC 53%	20% MAC and 18% RIC at 5 years	22% MAC and 28% RIC at 5 years
Anderlini et al. [35]	Single center prospective	58	83%	MSD 43%, 57% MUD	RIC 100% (fludarabine and Melphalan)	32% at 2 years	64% at 2 years
Robinson et al. [36]	Retrospective registry (EBMT)	285	80%	MSD 60%, MUD 33%	RIC 100% Fludarabine based (79.5%), low dose TBI (16%)	25% at 3 years	29% at 3 years
Devetten et al. [37]	Retrospective registry (CIBMTR)	143	89%	Unrelated 100% (matched in 77%)	RIC/NMA 100% Melphalan based 34%	20% at 2 years	37% at 2 years
Marcais et al. [38]	Multicenter retrospective in France	191	92%	MSD 60%, MUD 40%	RIC 100% Fludarabine and busulfan in 36%	39% at 3 years	63% at 3 years
Kako et al. [39]	Retrospective registry (Japanese society for HSCT)	122	67%	MSD 39% MUD 17%	MAC 30% RIC 62%	31%	66% at 3 years
Sarina et al. [40]	Retrospective multicenter in Italy	104	100%	MSD 55% MUD 32%	RIC 100% (Fludarabine based in 100%)	31% at 2 years	57% at 2 years

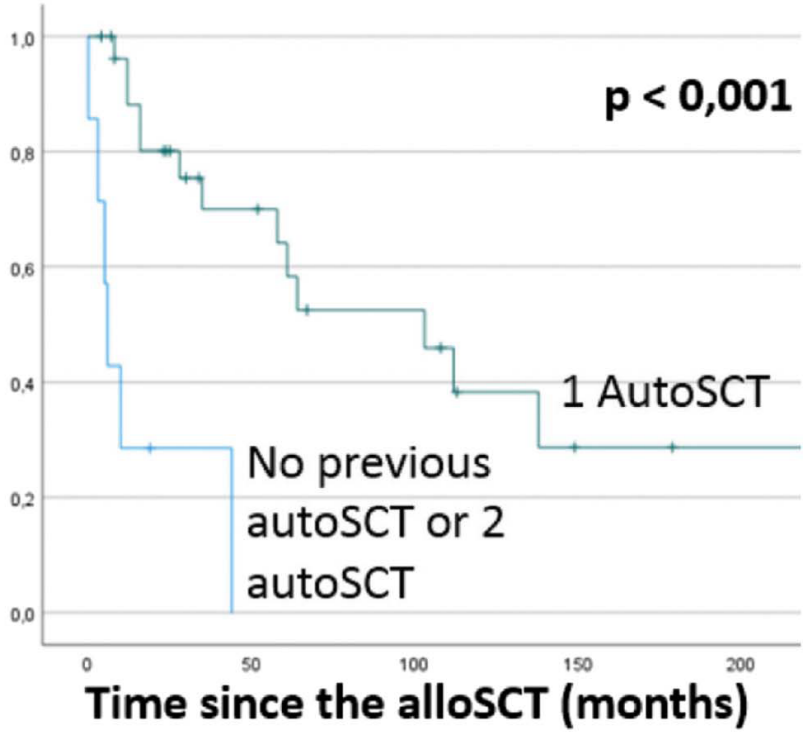
More than 11 cohort each of them 30 patients with almost same result (what dose slop say???)



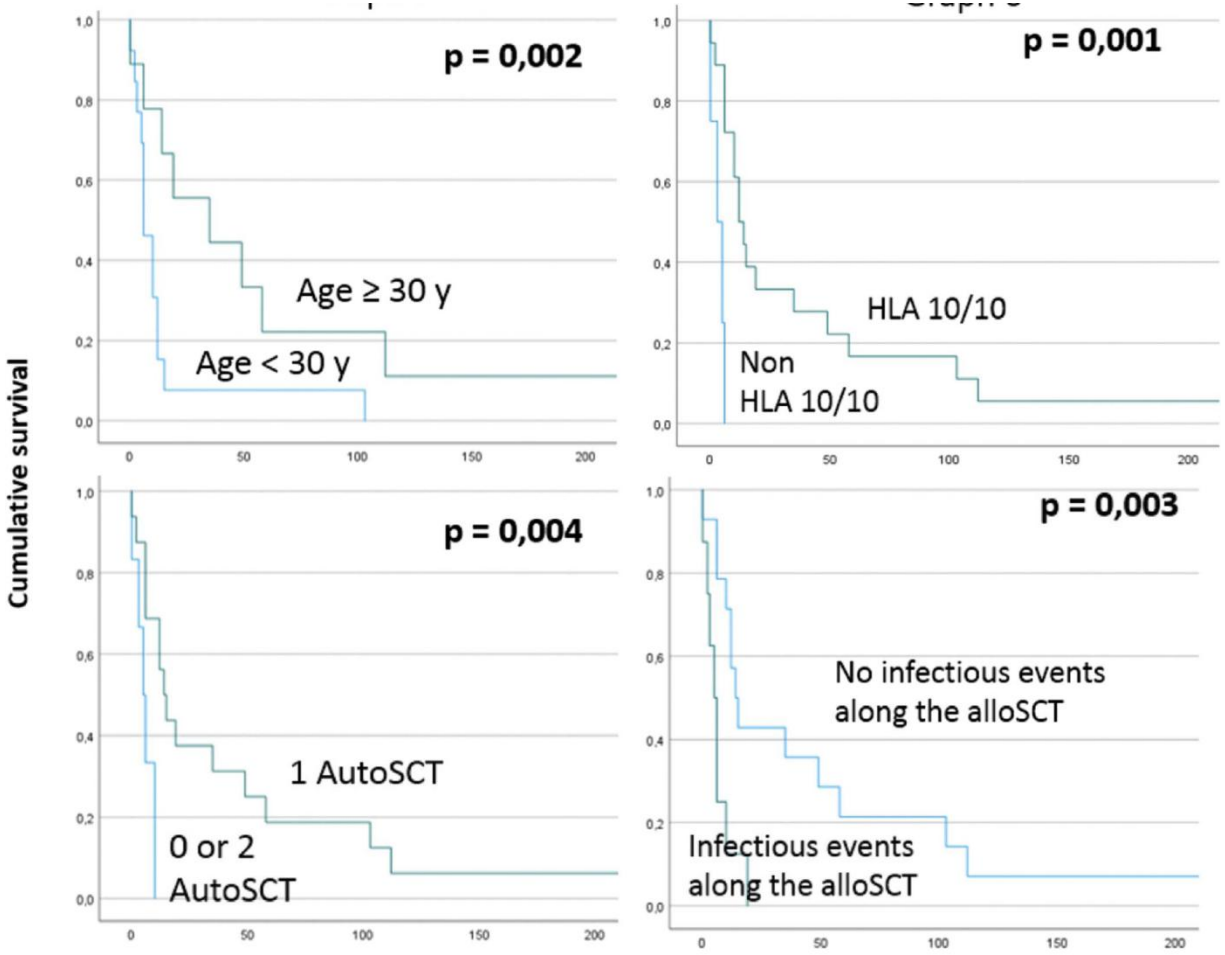


In refractory cases it dismal but in relapse it futile





In non HLA match nothing to say in full match a little



Regimen intensity effect (Allo-HCT)

- MAC: myeloablative conditioning with NRM up to 40% and lower rate of relapse 30% improve in event free survival 48%.
- RIC: reduced intensity conditioning with NRM of 23% and relapse rate 52% and EFS of 36%.
- So this suggests improved outcome using MAC regimens in current area largely due to decrease NRM

GVHD is treatment or headach

- The literature reports nearly 48% of aGvHD (grade II or more in 15%) and 47% of cGvHD (extensive in 46%). This population had aGvHD in a similar rate, but cGvHD was more frequent and severe.
- This higher frequency cGvHD was the most probable cause for the higher NRM.

Second neoplasia

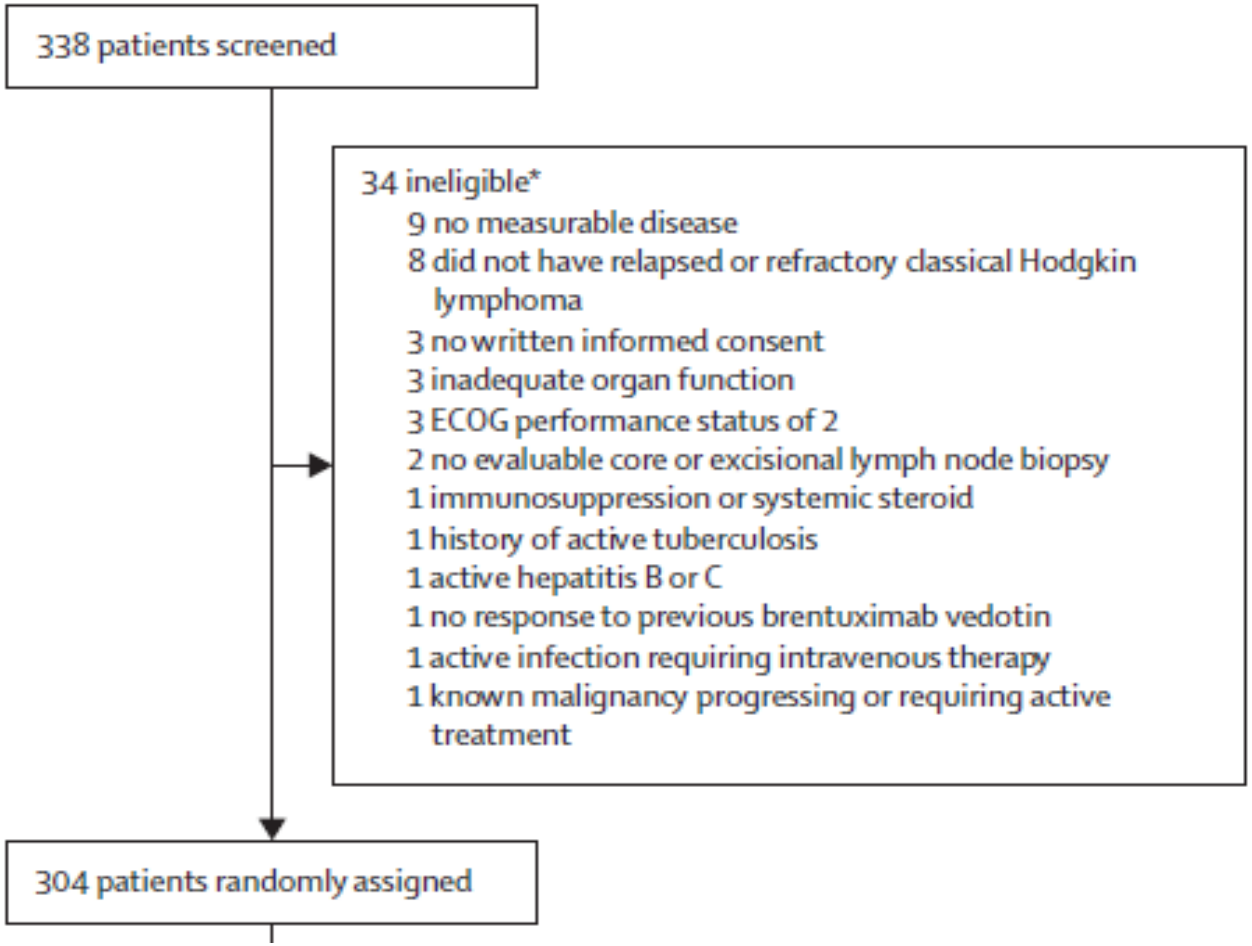
- the incidence of a second neoplasia was 14%

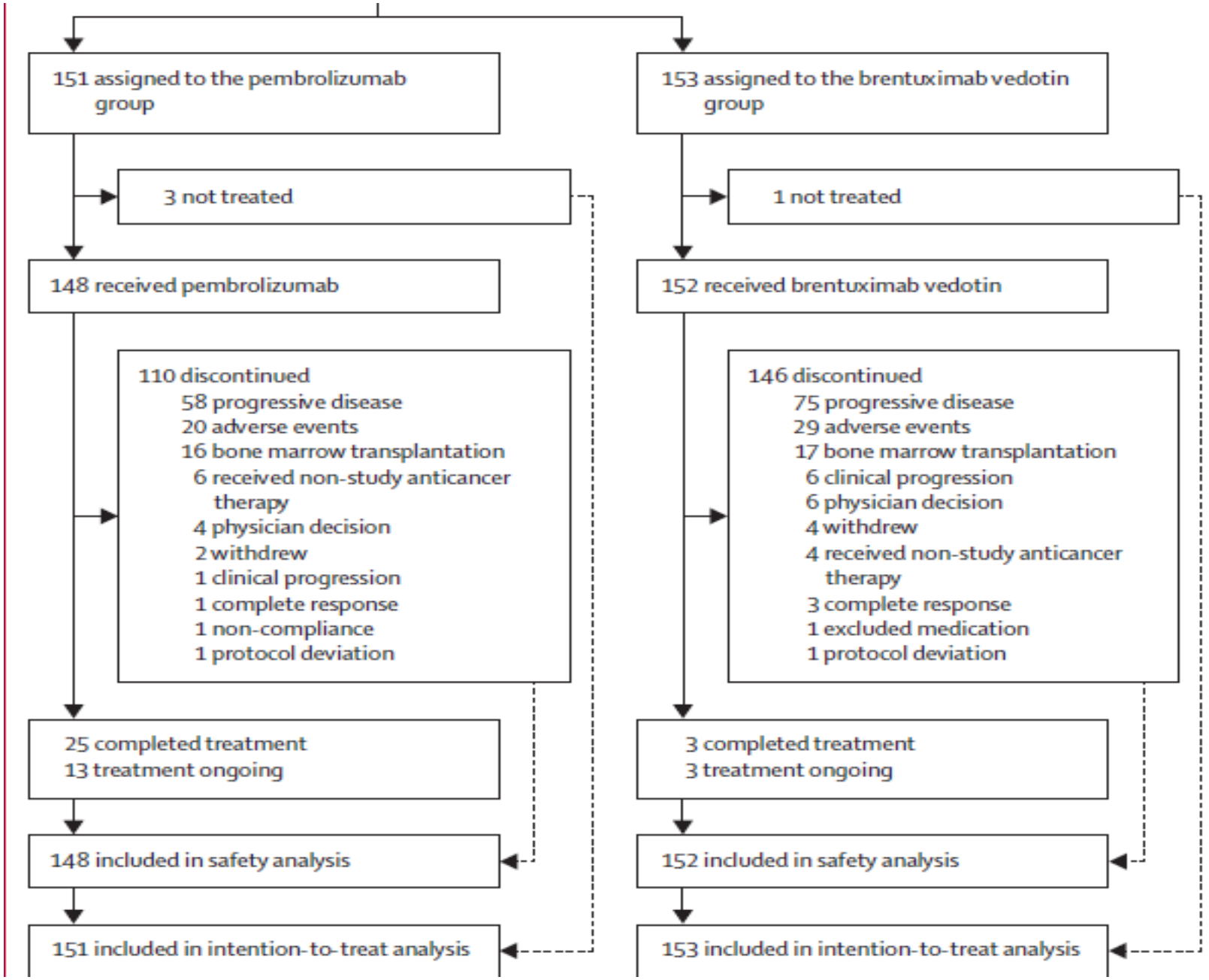
usually described in the literature. Possible factors contributing to this rate are the radiation and chemotherapy previously used, the conditioning regimen for the alloSCT, immunodeficiency from incomplete recovery after alloSCT, immune stimulation and suppression from GvHD and its treatment.

Pembrolizumab versus brentuximab vedotin in relapsed or refractory classical Hodgkin lymphoma (KEYNOTE-204):

- an interim analysis of a multicentre, randomised, open-label, phase 3 study

R/R 40% relapse after AUTO-BMT

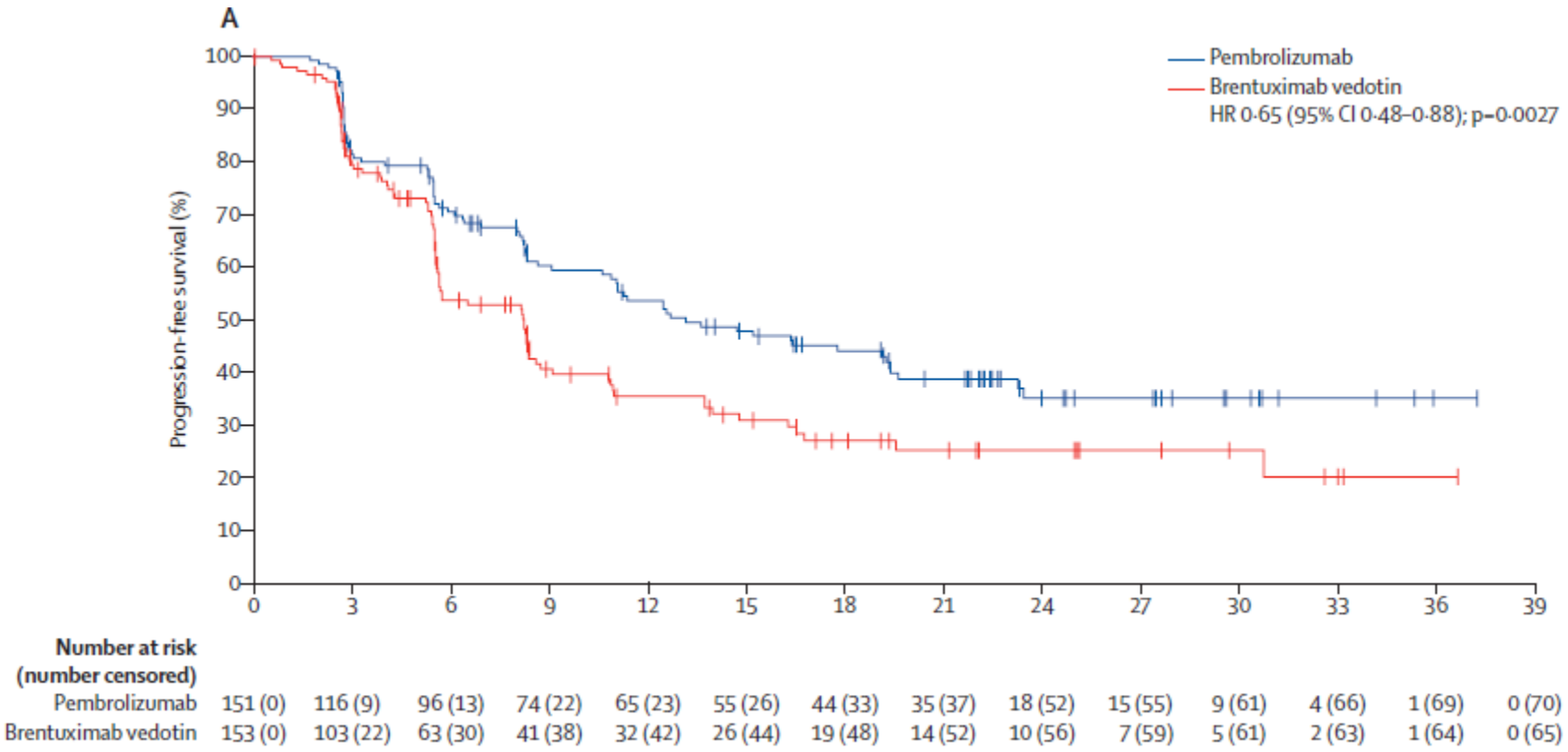



151 assigned to the pembrolizumab group
153 assigned to the brentuximab vedotin group
3 not treated
1 not treated
148 received pembrolizumab
152 received brentuximab vedotin
110 discontinued
58 progressive disease
20 adverse events
16 bone marrow transplantation
6 received non-study anticancer therapy
4 physician decision
2 withdrew
1 clinical progression
1 complete response
1 non-compliance
1 protocol deviation
146 discontinued
75 progressive disease
29 adverse events
17 bone marrow transplantation
6 clinical progression
6 physician decision
4 withdrew
4 received non-study anticancer therapy
3 complete response
1 excluded medication
1 protocol deviation
25 completed treatment
13 treatment ongoing
3 completed treatment
3 treatment ongoing
148 included in safety analysis
152 included in safety analysis
151 included in intention-to-treat analysis
153 included in intention-to-treat analysis

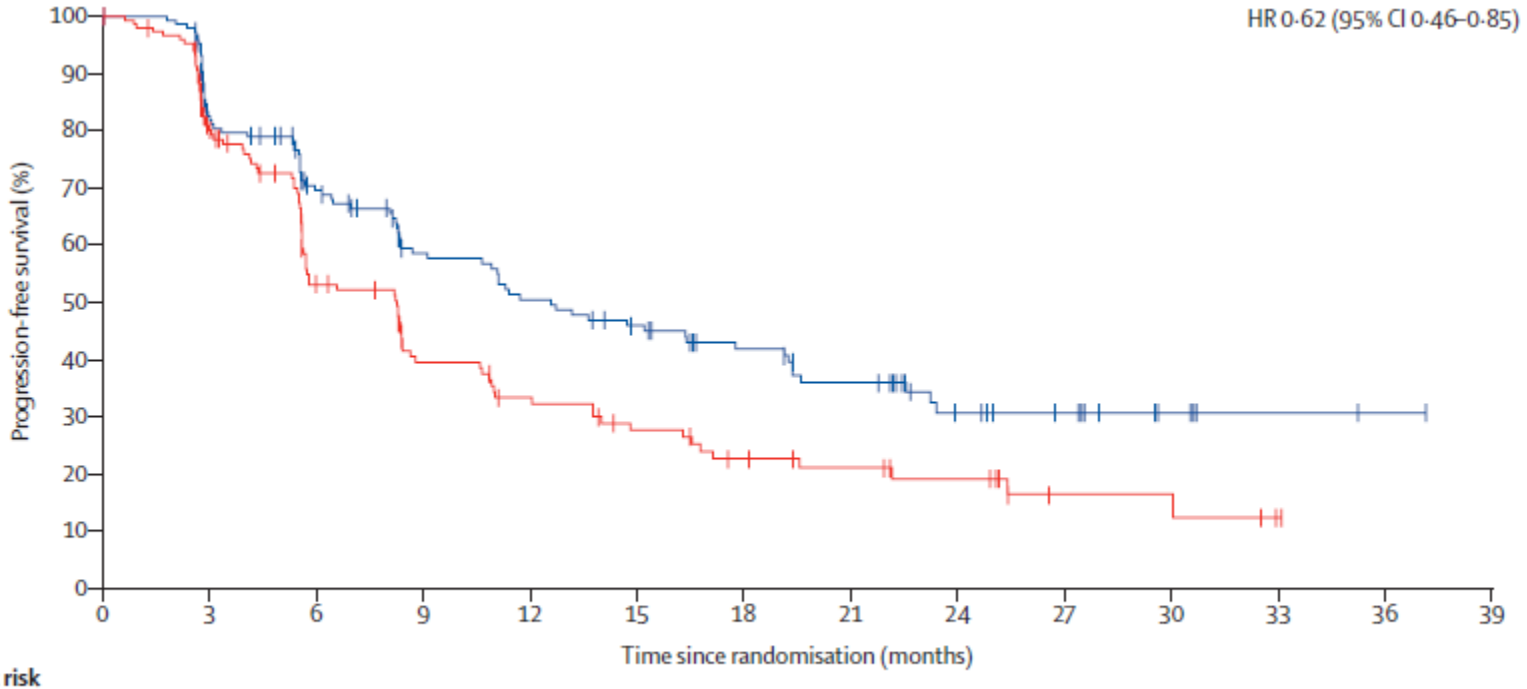
40% relapse after AUTO

Previous autologous HSCT		
Yes	56 (37%)	56 (37%)
No (ie, ineligible for autologous HSCT)	95 (63%)	97 (63%)
Disease status after front-line therapy		
Primary refractory	61 (40%)	62 (41%)
Relapsed <12 months	42 (28%)	42 (27%)
Relapsed ≥12 months	48 (32%)	49 (32%)
Number of previous lines of therapies	2 (2–3)	3 (2–3)
1	27 (18%)	28 (18%)
≥2	124 (82%)	125 (82%)
Previous brentuximab vedotin	5 (3%)	10 (7%)
Previous radiotherapy	58 (38%)	61 (40%)

Progressive free survival in all patients

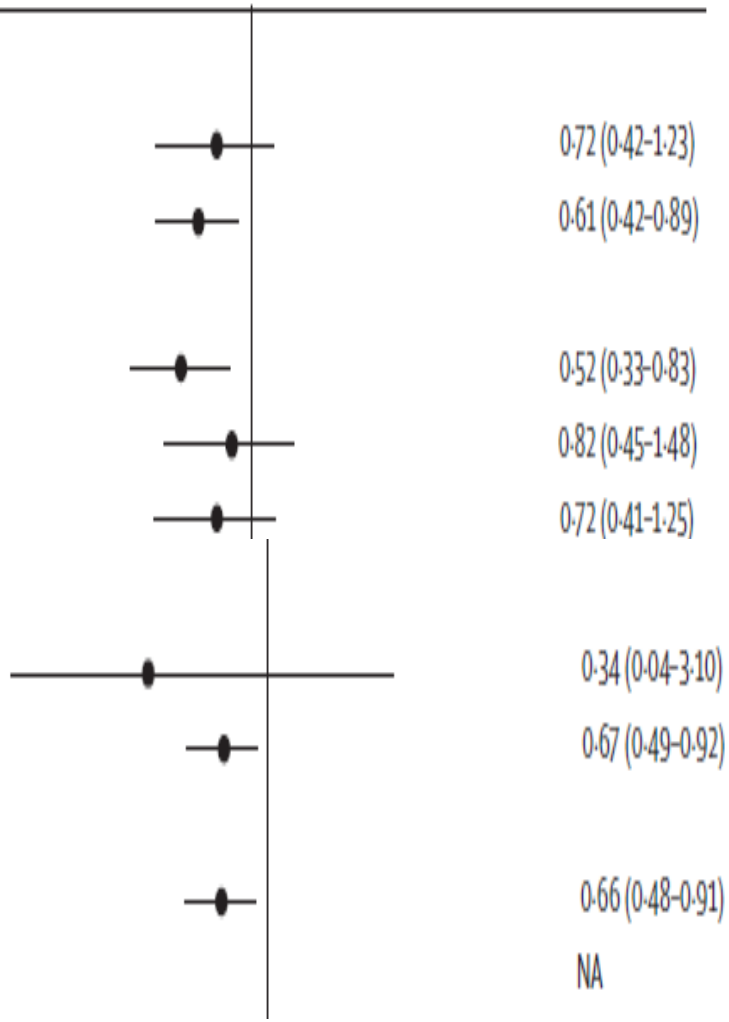


PFS in relapse after AUTO



Number at risk (number censored)														
Pembrolizumab	151 (0)	112 (13)	87 (22)	65 (31)	56 (31)	48 (34)	37 (41)	30 (43)	16 (54)	11 (59)	5 (65)	2 (68)	1 (69)	0 (70)
Brentuximab vedotin	153 (0)	98 (27)	58 (36)	39 (41)	30 (44)	23 (46)	17 (48)	13 (51)	10 (53)	4 (58)	4 (58)	1 (60)	0 (61)	0 (61)

	Pembrolizumab group		Brentuximab vedotin group		HR (95% CI)
	n/N	Median progression-free survival (95% CI)	n/N	Median progression-free survival (95% CI)	
Previous autologous stem-cell transplantation					
Yes	30/56	14·7 (8·3–NR)	27/56	10·8 (5·8–19·6)	0·72 (0·42–1·23)
No	51/95	12·5 (8·3–19·4)	61/97	5·7 (5·5–8·3)	0·61 (0·42–0·89)
Disease status after front-line therapy					
Primary refractory	34/61	12·5 (8·2–23·4)	38/62	5·5 (3·1–8·2)	0·52 (0·33–0·83)
Relapsed <12 months	22/42	16·4 (8·3–NR)	24/42	11·0 (8·2–16·6)	0·82 (0·45–1·48)
Relapsed ≥12 months	25/48	13·6 (7·0–NR)	26/49	8·3 (5·6–14·0)	0·72 (0·41–1·25)
Previous use of brentuximab vedotin					
Yes	1/5	NR (2·9–NR)	6/10	5·6 (2·6–8·4)	0·34 (0·04–3·10)
No	80/146	12·7 (9·1–19·3)	82/143	8·3 (5·7–10·8)	0·67 (0·49–0·92)
PD-L1 status					
≥1%	78/142	12·7 (9·1–19·3)	77/133	8·3 (5·7–9·1)	0·66 (0·48–0·91)
<1%	NA	NA	1/3	NR (5·8–NR)	NA



Comparable CR

	Pembrolizumab group (n=151)	Brentuximab group (n=153)
Proportion of patients with objective response	99 (65·6% [57·4–73·1])	83 (54·2% [46·0–62·3])
Best overall response		
Complete response	37 (25%)	37 (24%)
Partial response	62 (41%)	46 (30%)
Stable disease	21 (14%)	36 (24%)
Progressive disease	26 (17%)	28 (18%)
Not evaluable	1 (1%)	1 (1%)
No assessment	4 (3%)	5 (3%)

Data are n (% [95% CI]) or n (%).

Table 2: **Objective response as assessed by blinded independent central review by International Working Group 2007 criteria**

Side effects

	Pembrolizumab group (n=148)				Brentuximab vedotin group (n=152)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any	81 (55%)	23 (16%)	5 (3%)	1 (1%)	79 (52%)	32 (21%)	6 (4%)	0
Hypothyroidism	23 (16%)	0	0	0	2 (1%)	0	0	0
Pyrexia	18 (12%)	1 (1%)	0	0	9 (6%)	0	0	0
Pruritus	16 (11%)	0	0	0	8 (5%)	0	0	0
Diarrhoea	12 (8%)	2 (1%)	0	0	7 (5%)	0	0	0
Fatigue	13 (9%)	0	0	0	16 (11%)	0	0	0
Pneumonitis	6 (4%)	3 (2%)	3 (2%)	0	0	1 (1%)	0	0
Hyperthyroidism	8 (5%)	0	0	0	0	0	0	0
Rash	8 (5%)	0	0	0	7 (5%)	0	0	0

Side effects

	Pembrolizumab group (n=148)				Brentuximab vedotin group (n=152)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Tubulointerstitial nephritis	0	0	0	0	0	0	1 (1%)	0
Interstitial lung disease	1 (1%)	2 (1%)	0	0	0	1 (1%)	0	0
Pleurisy	0	1 (1%)	0	0	0	0	0	0
Pulmonary embolism	0	0	0	0	0	1 (1%)	0	0
Eczema	3 (2%)	0	0	0	0	1 (1%)	0	0
Urticaria	1 (1%)	1 (1%)	0	0	0	0	0	0
Capillary leak syndrome	0	1 (1%)	0	0	0	0	0	0
Hypotension	0	0	0	0	0	1 (1%)	0	0
Hypovolaemic shock	0	0	0	0	0	0	1 (1%)	0