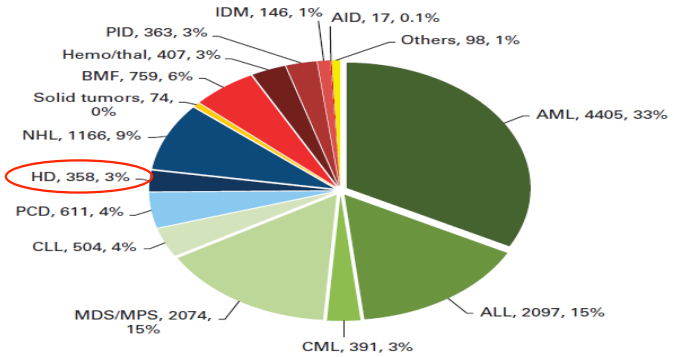
Timing dell'allotrapianto nel linfoma di Hodgkin nell'era dei nuovi farmaci

Bari, 6-7/6/2017

Luca Castagna

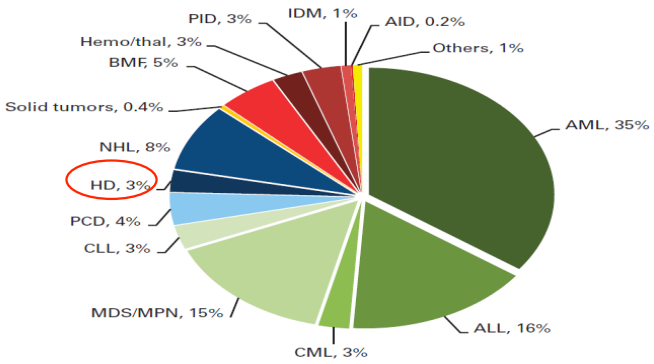
Background

EBMT activity 2011

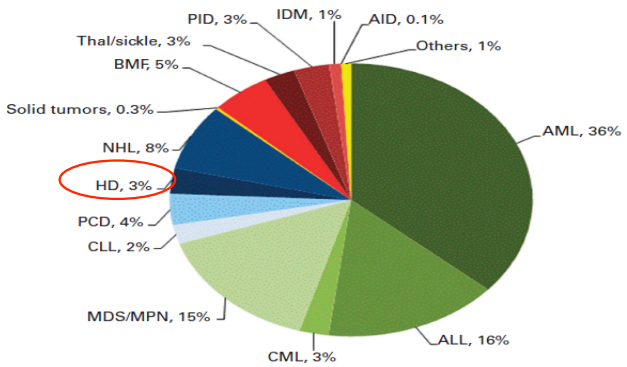


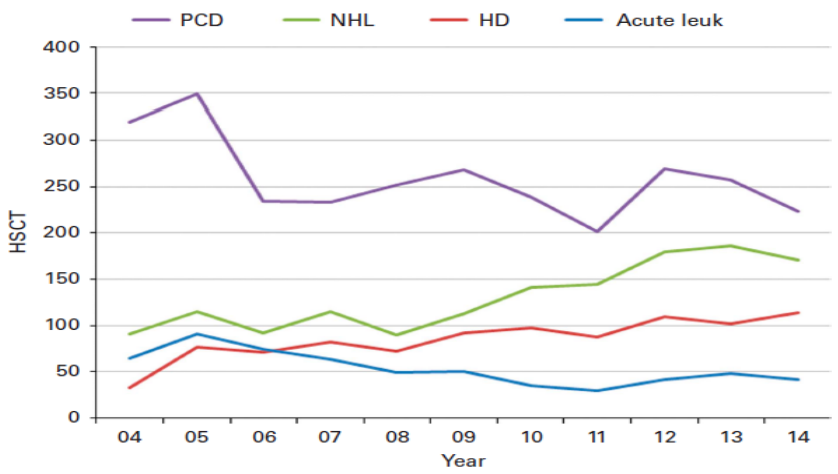
EBMT activity 2013

Allogeneic



EBMT activity 2014





Background

Disease status	HLAid sib	WM UD	Alternative donor	ASCT
CR1	GNR	GNR	GNR	GNR
CT S relapse, no previous HDC	D	D	GNR	S
CT S relapse, previous HDC	**S**	**S**	**CO**	**CO**
Refractory	D	D	D	**CO**

Sureda, BMT 2015

HL and allo-SCT

- Does Graft versus HL exists?
  - **Probably yes => DLI effect**

- Are HL cells suitable of immunological control?
  - **Definitively yes => CPI effect**

Competitors

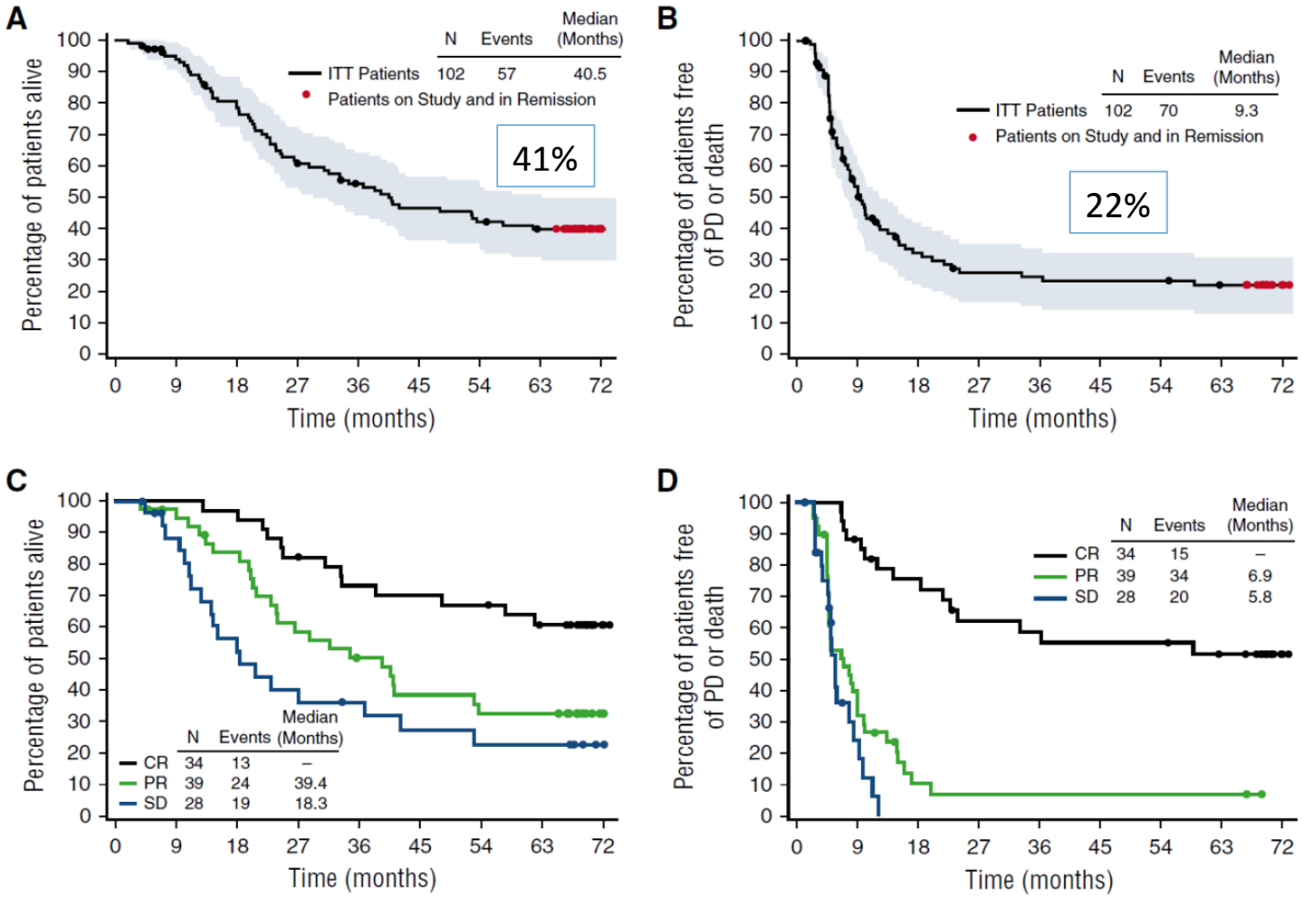
- Brentuximab vedotin (BV)
- Check point inhibitors (CPI)
  - Nivolumab
  - Pembrolizumab
- Association BV + CPI
- PI3Kinase inhibitors

BV in relapsed/refractory patients

	Younes 2012	Rothe 2012	Zinzani 2013	Gibb 2013
N	102	45	65	18
Relapse after HDC	100%	87%	92%	33%
ORR	75%	60%	29/70%	72%
CR	34%	22%	21%	17%
PR	41%	38%	8%	55%
DOR all responding	6.7M	8M	6.8M	5M
DOR CR	20 M	13M (CR+PR)	/	/
ALLO (elegible/done)	102/6	39/0	62/9	18/4
OS	73%@3y	83%@1y	74%@20M	/
PFS	58%@3y	43%@1y	23%@20M	20%@1y
Response max	3 cycles	/	3 cycles	4 cycles

Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma

Robert Chen,[1,*] Ajay K. Gopal,[2,*] Scott E. Smith,[3] Stephen M. Ansell,[4] Joseph D. Rosenblatt,[5] Kerry J. Savage,[6] Joseph M. Connors,[6] Andreas Engert,[7] Emily K. Larsen,[8] Dirk Huebner,[9] Abraham Fong,[8] and Anas Younes[10]



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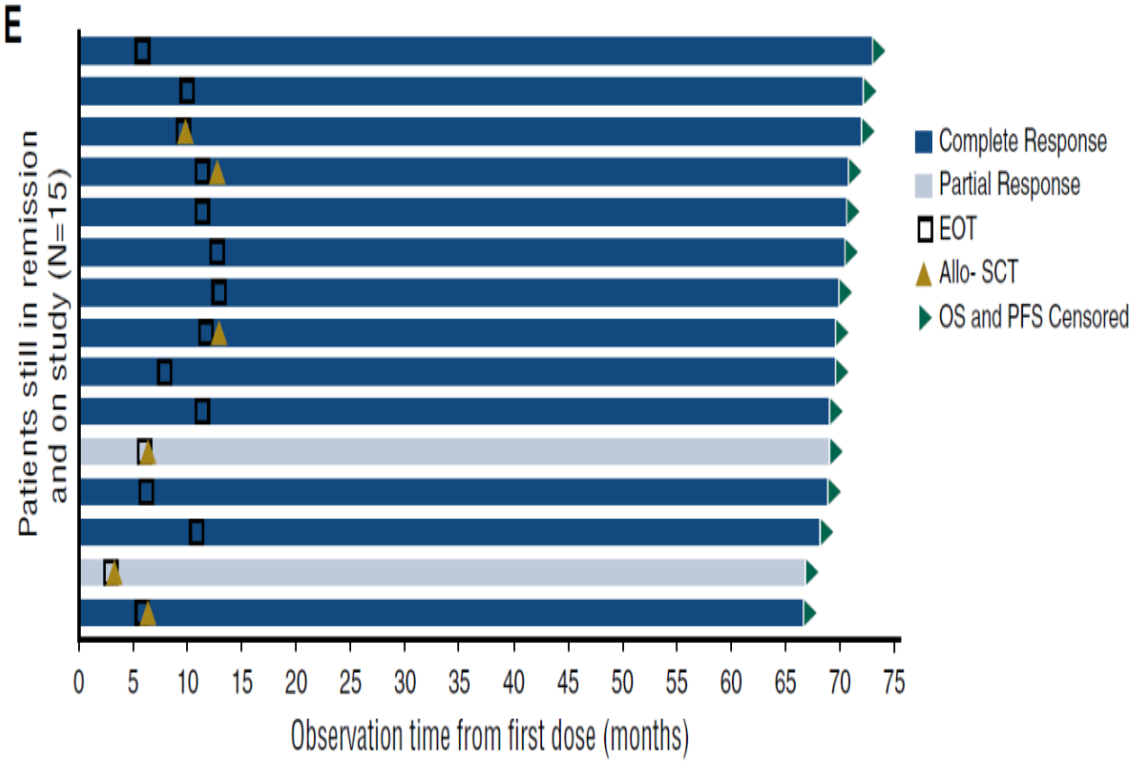

9/102

Female,
Younger
Relapsed
ECOG
Limited disease

Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma

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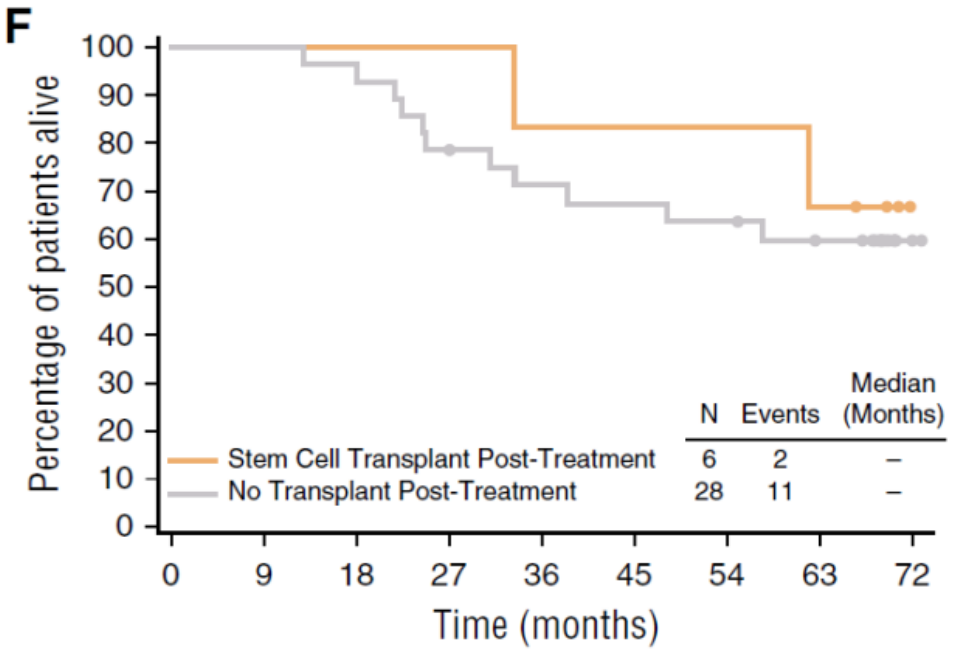
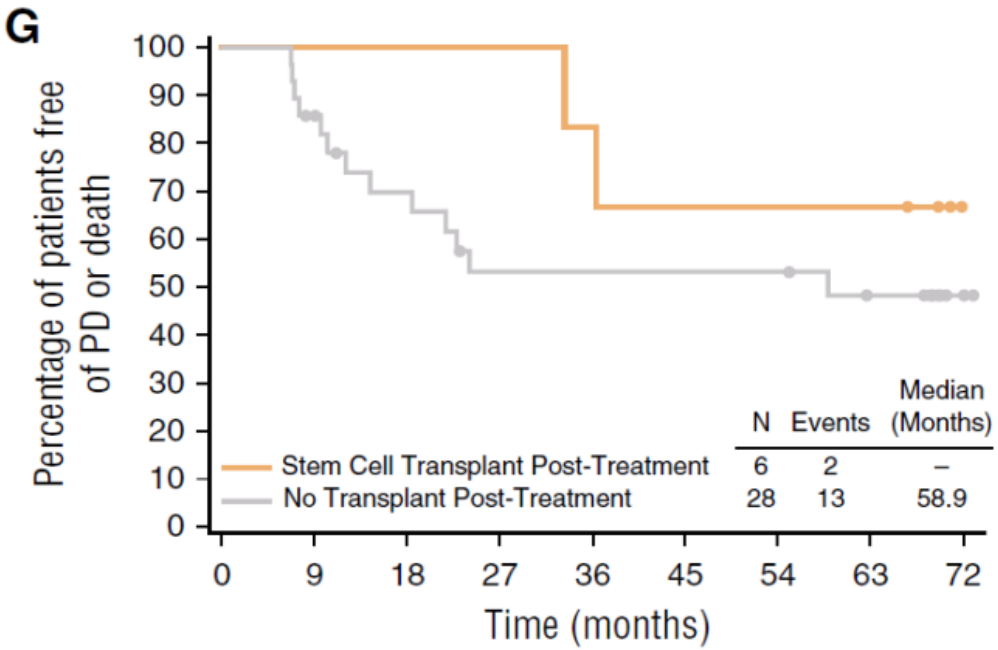
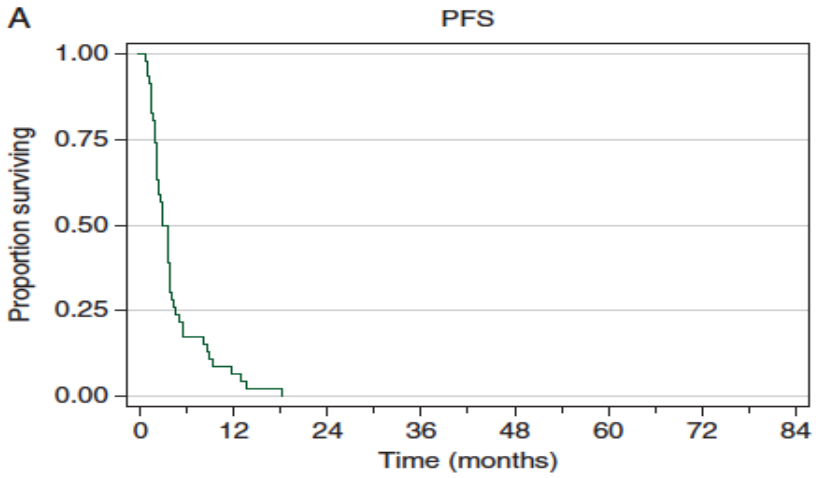


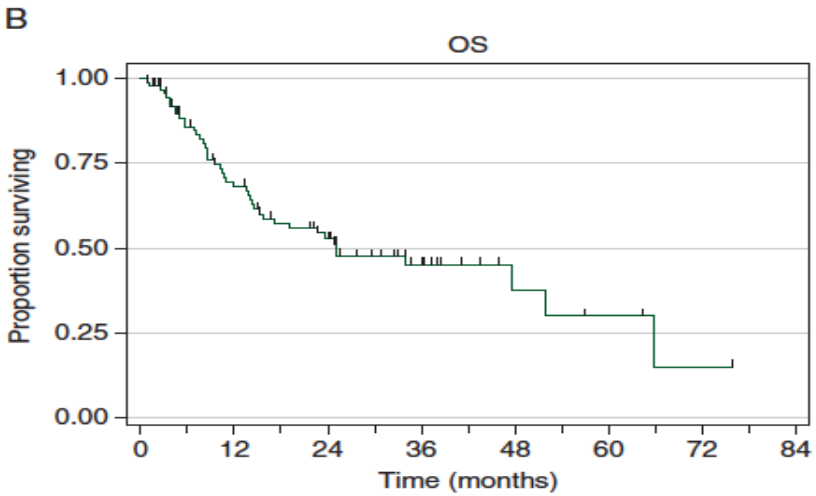


BV in relapsed/refractory patients

n = 100, 71% HDC



PFS 3.5 M

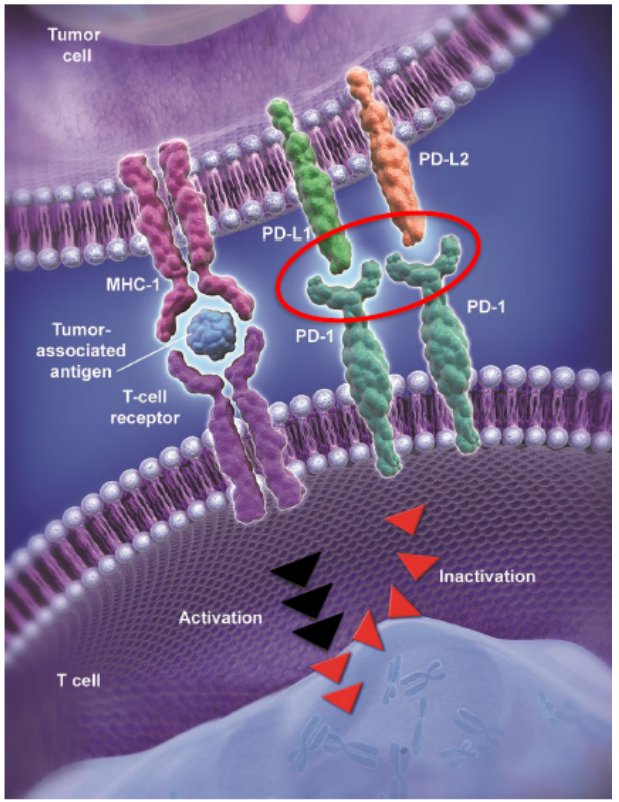


OS 24M

Cheah, Ann Oncol 2016

The PD-1 and PD-L1/L2 Pathway

- PD-1 is an immune checkpoint receptor
- **Binding of PD-1 by its ligands PD-L1 or PD-L2 leads to downregulation of T-cell function**
- **This mechanism is usurped by many tumors**

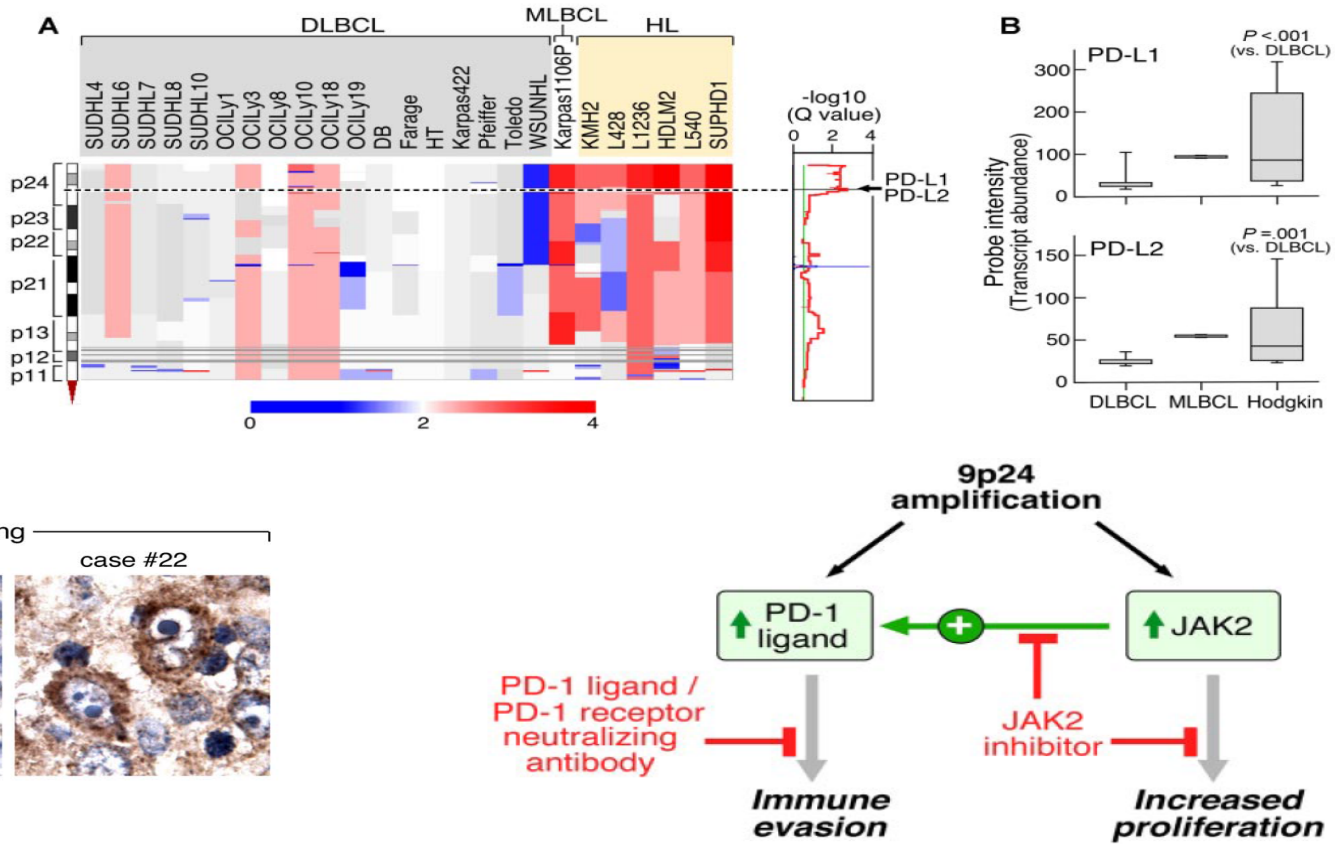


Keir ME et al. *Annu Rev Immunol*. 2008.
Pardoll DM. *Nat Rev Cancer*. 2012.

Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma

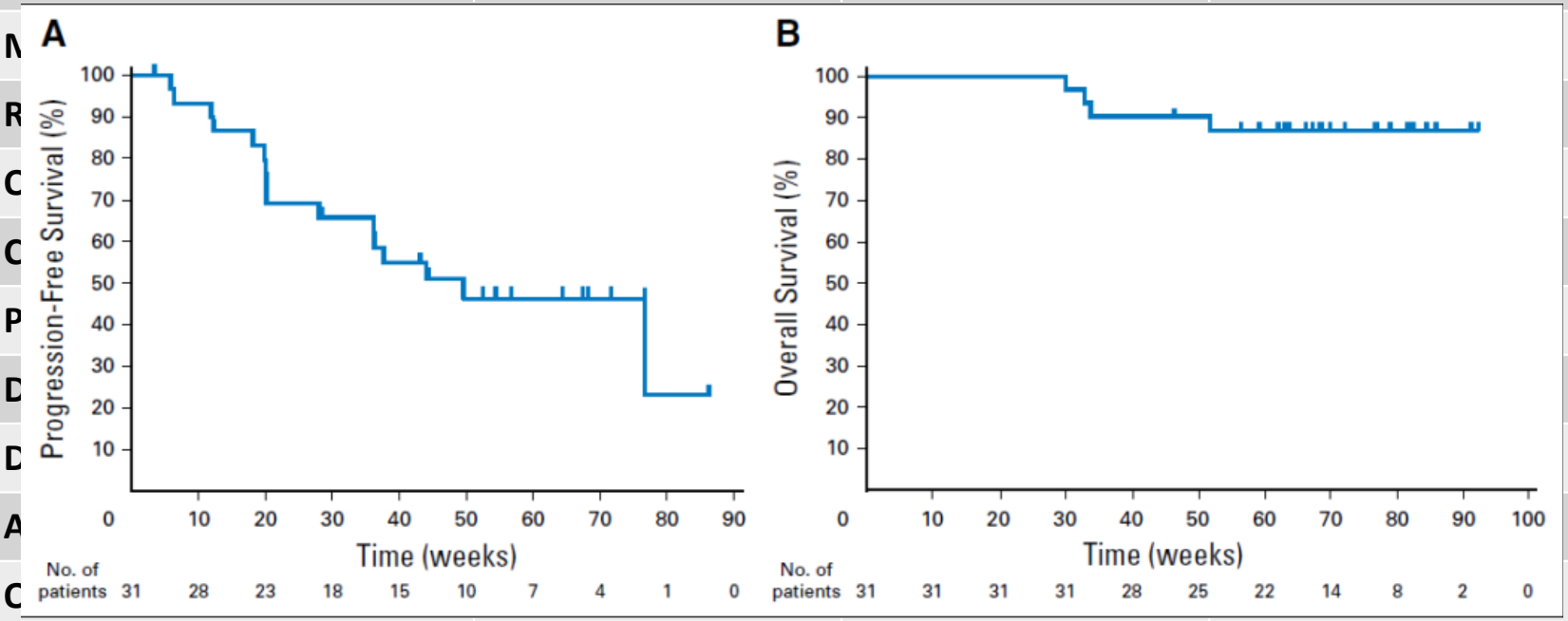
M Green, Blood, 2010

- Chromosome 9p24.1 amplification and increased expression of PD-L1 in HL and MLBCL cell lines



Clinical results with CPI

	Ansell 2014	Younes 2016	Armand 2016
N	23	80	31
PFS	86% 24w	77% 6M	46% 1y
Response max	/	2.1M	/

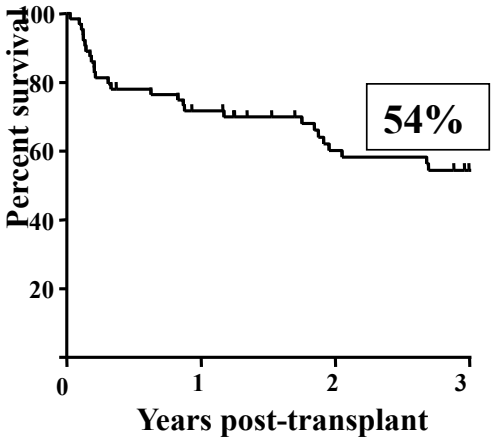


Haplo vs HLAid for HL relapsed post-HDC

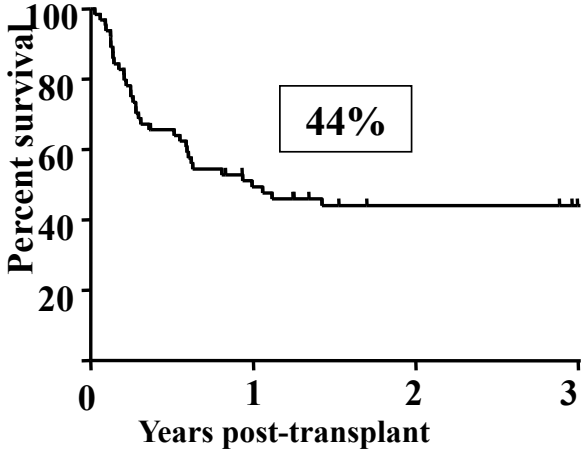
	N 64	HLAid n 34	Haplo n 30	p
Median age	31 (18-66)	31 (18-62)	31 (19-66)	0,8
Sex M/F	30/20	24/10	20/10	0,7
N lines CT (median)	4 (3-13)	4 (3-13)	4 (3-8)	0,8
Median time after Auto-Tx (ms)	19,1 (1,7-130)	17,6 (1,9-117)	20,5 (1,7-130)	0,1
Disease status at ALLO **CR** **PR** **SD/PD**	 25 (39%) 23 (37%) 16 (24%)	 11 (32%) 13 (38%) 10 (30%)	 14 (46%) 10 (33%) 6 (21%)	0,4
Stem cell source **BM** **PBSC**	 25 (40%) 39 (60%)	 2 (6%) 32 (94%)	 23(76%) 7 (24%)	**<0.0001**
HCT-CI (n= 45) **0-1** **2** **>3**	N=49 16 (25%) 13 (20%) 20 (31%)	N= 20 3 (8%) 6 (16%) 11 (32%)	N= 29 13 (43%) 7 (23%) 9 (30%)	0,08
Conditioning **NMA** **RIC** **MAC**	 35 (54%) 25 (39%) 4 (7%)	 15(44%) 16 (47%) 3 (9%)	 20 (66%) 9 (30%) 1 (4%)	0,1

Haplo vs HLAid for HL relapsed post-HDC

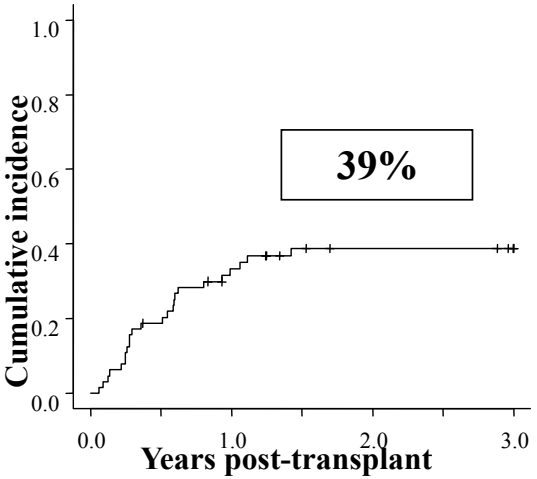
3y-OS



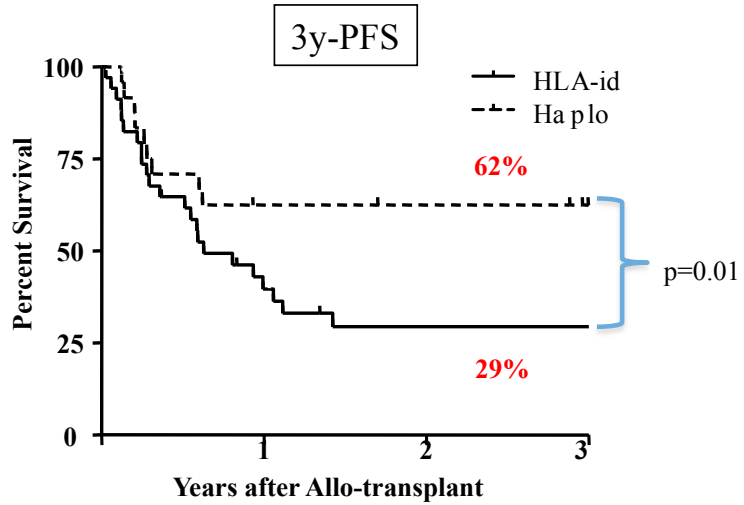
3y-PFS

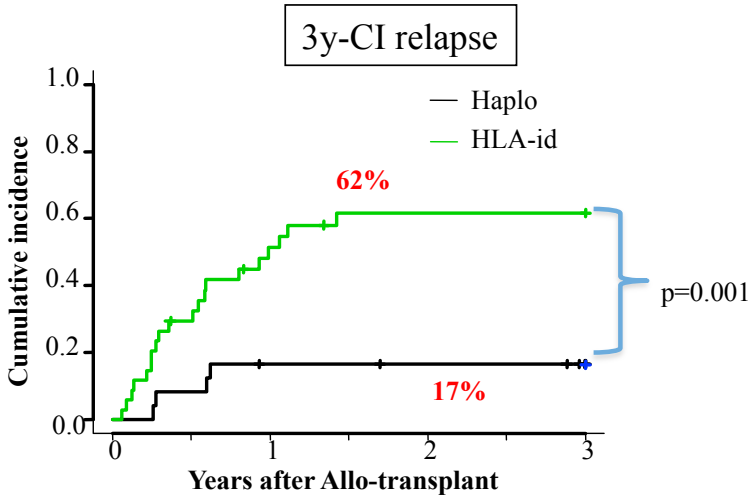


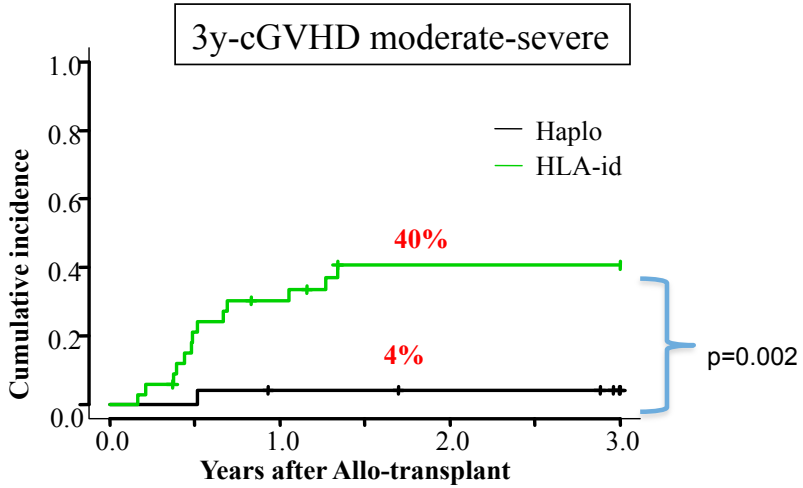
3y-CI relapse

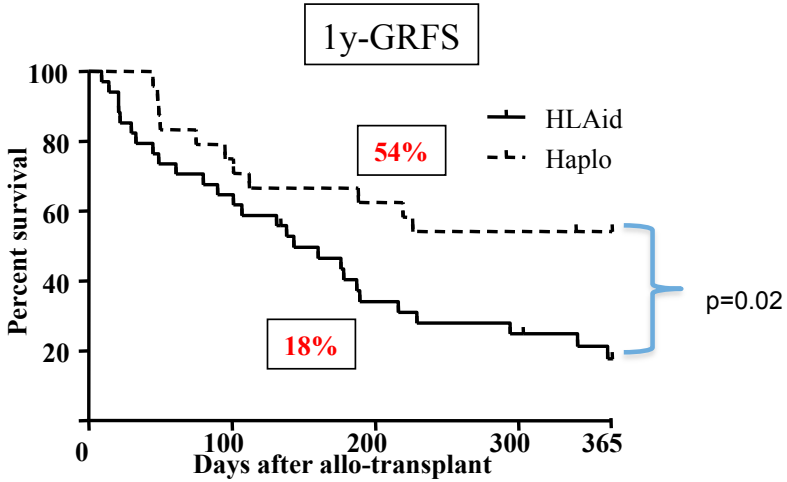


Haplo vs HLAid for HL relapsed post-HDC

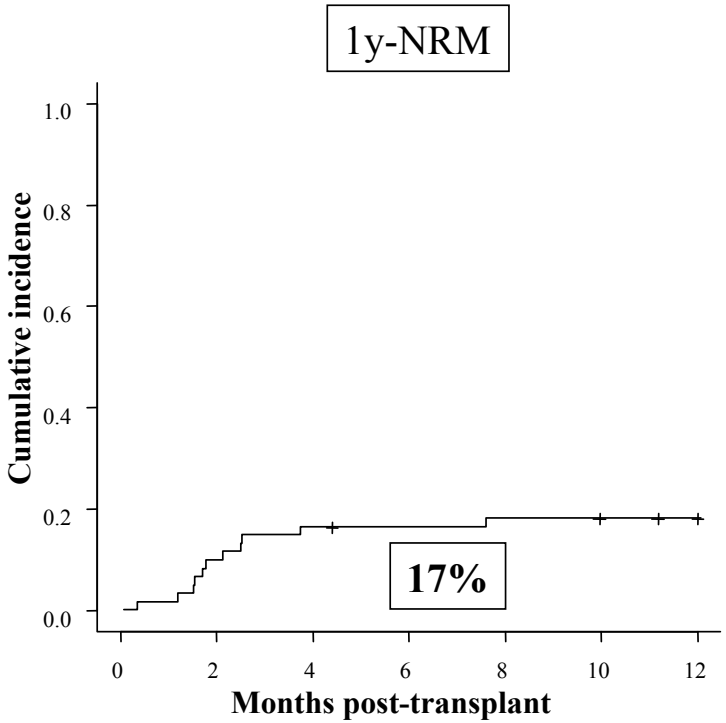


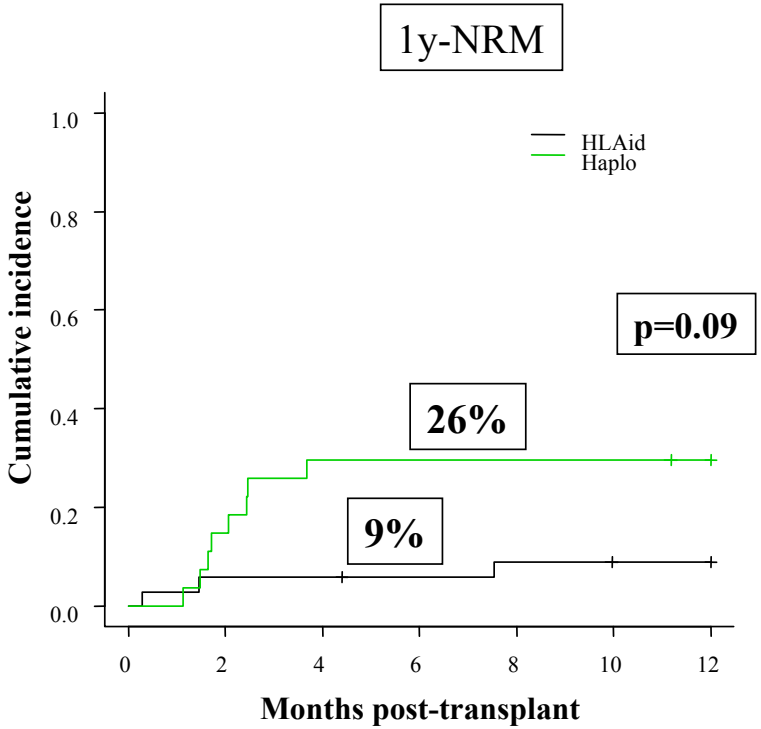






Haplo vs HLAid for HL relapsed post-HDC





Haplo vs HLAid for HL relapsed post-HDC

Characteristics	3y-OS HR	p	3y-PFS HR	p	1y-NRM HR	p
Not CR vs CR	**12 (3.5-41.2)**	**<0.0001**	**4.6 (1.9-11)**	**0.001**	**8 (1.4-43)**	**0.01**
Haplo vs HLAid	1 (0.1-10.1)	0.9	0.4 (0.05-3.8)	0.4	9.4 (0.4-200)	0.1
PBSC vs BM	0.4 (0.05-4)	0.4	0.4 (0.05-4.1)	0.4	2.6 (0.1-54)	0.5
RIC/MAC vs NMA	2.3 (0.8-6.2)	0.1	3.2 (1.1-8.6)	**0.02**	9.1 (0.9-87)	**0.05**
HCT-CI $\geq$3 vs <3	2.7 (0.9-8.3)	0.06	1.8 (0.6-4.7)	0.2	2.8 (0.6-11.7)	0.1

Haplo vs HLAid CR and PR

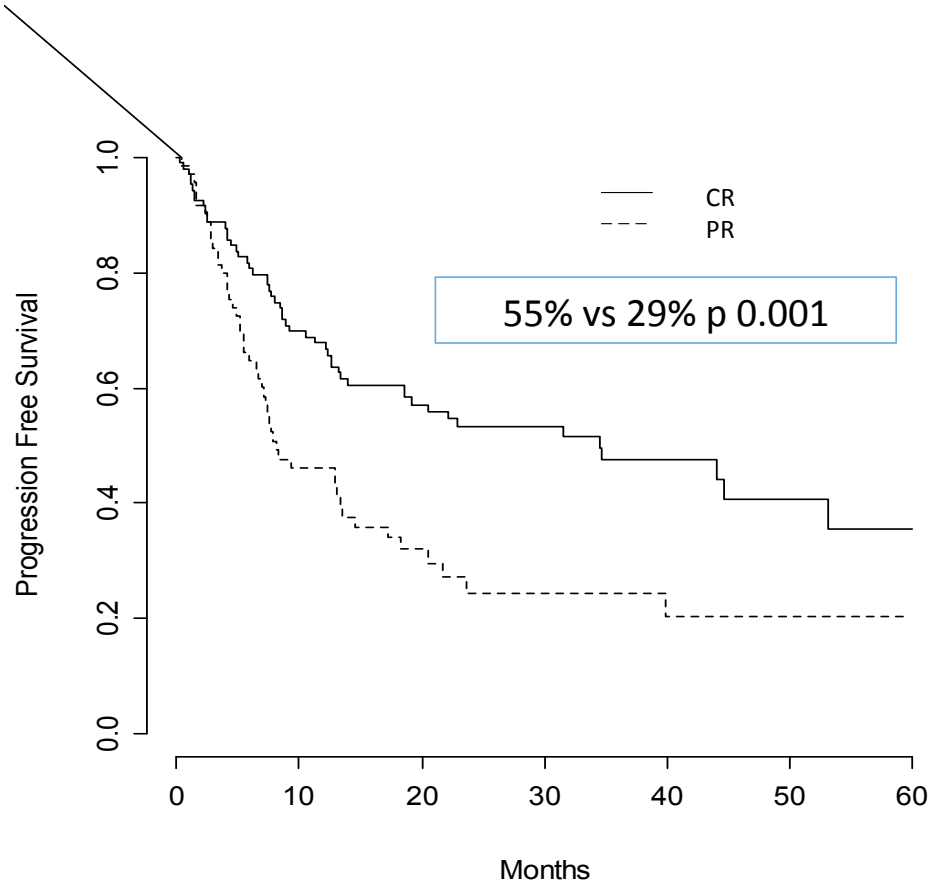
	All pts N= 198	HLA-id N= 133	Haplo N= 65	p
Age, years (median, range)	32 (18-66)	32 (18-65)	31 (18-65)	0.8
Sex M/F	113/85	77/56	36/29	0.7
Number of CT lines (median, range)	2 (1-12)	2 (1-2)	4 (2-12)	**<0.001**
Relapse after HDC	170/198 (86%)	110/133 (83%)	60/65 (92%)	
Disease status at transplantation				
CR	119 (60%)	82 (62%)	37 (60%)	
PR	79 (40%)	51 (38%)	28 (40%)	
Donors				/
HLA sibling	/	57 (43%)	/	
MUD	/	76 (57%)	/	
Haplo		/	48	
Stem cell source				**<0.001**
PBSC	119 (60%)	114 (86%)	5 8(%)	
BM	61 (31%)	18 (13%)	43 (92%)	
miss	10 (9%)	1 (1%)	/	
ATG prophylaxis GVHD				/
No	/	57	/	
Yes	76	76	/	
Conditioning regimens				**<0.001**
NMAC	58 (29%)	/	58 (89%)	
RIC	101 (51%)	94 (71%)	7 (11%)	
MAC	39 (20%)	39 (29%)	/	

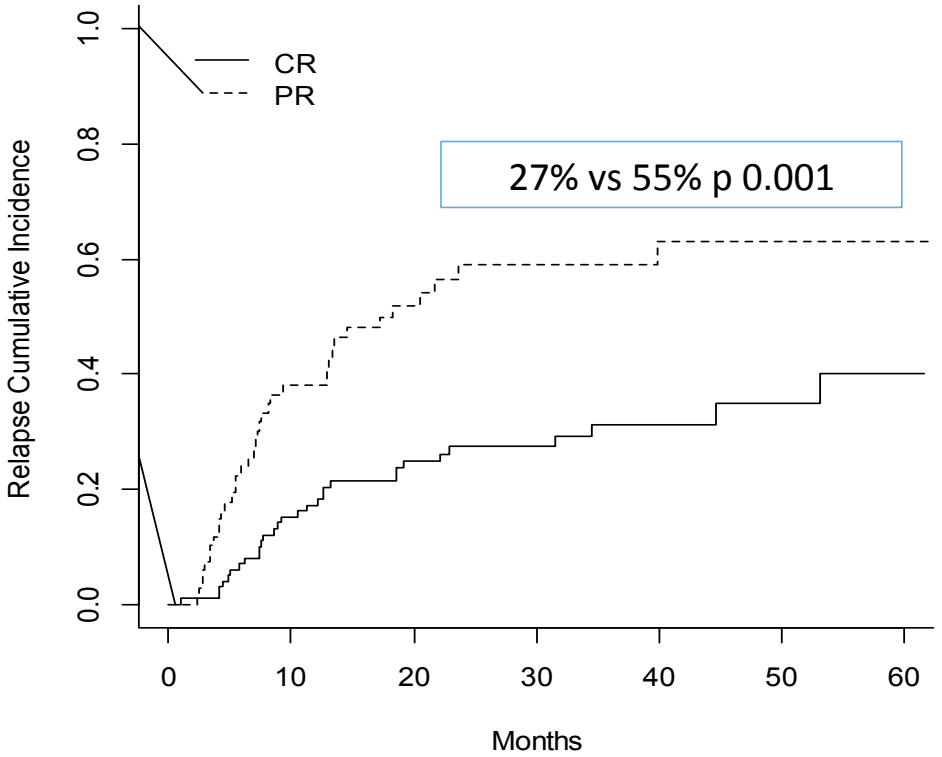
Median follow up:
31M (range 0.2-74.1)

HAPLO vs HLAid CR and PR

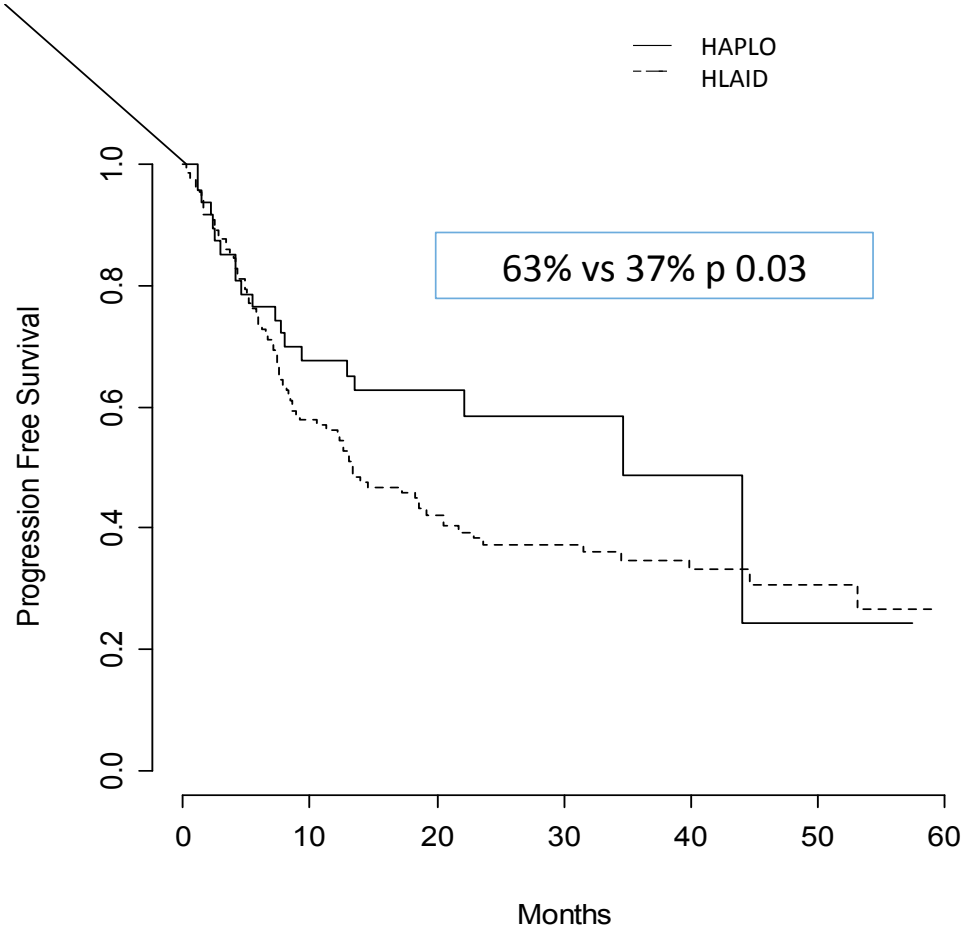
	N	2y PFS	p	2y OS	p	2y RI	p	1y NRM	p
All	198	45%		66%		38%		14%	
CR vs PR	119 vs 79	55% vs 29%	**0.001**	74% vs 55%	**0.03**	27% vs 55%	**< 0.001**	13% vs 16%	0.8
Haplo vs HLAid	65 vs 133	63% vs 37%	**0.03**	67% vs 63%	0.6	24% vs 44%	**0.008**	13% vs 15%	0.9
CR Haplo vs	37	75%	**< 0.001***	83%	0.1	11%	**< 0.001**	14%	0.8
CR HLAid vs	82	47%		67%		34%		13%	
PR Haplo vs	28	44%		58%		44%		11%	
PR HLAid	51	22%		54%		60%		18%	

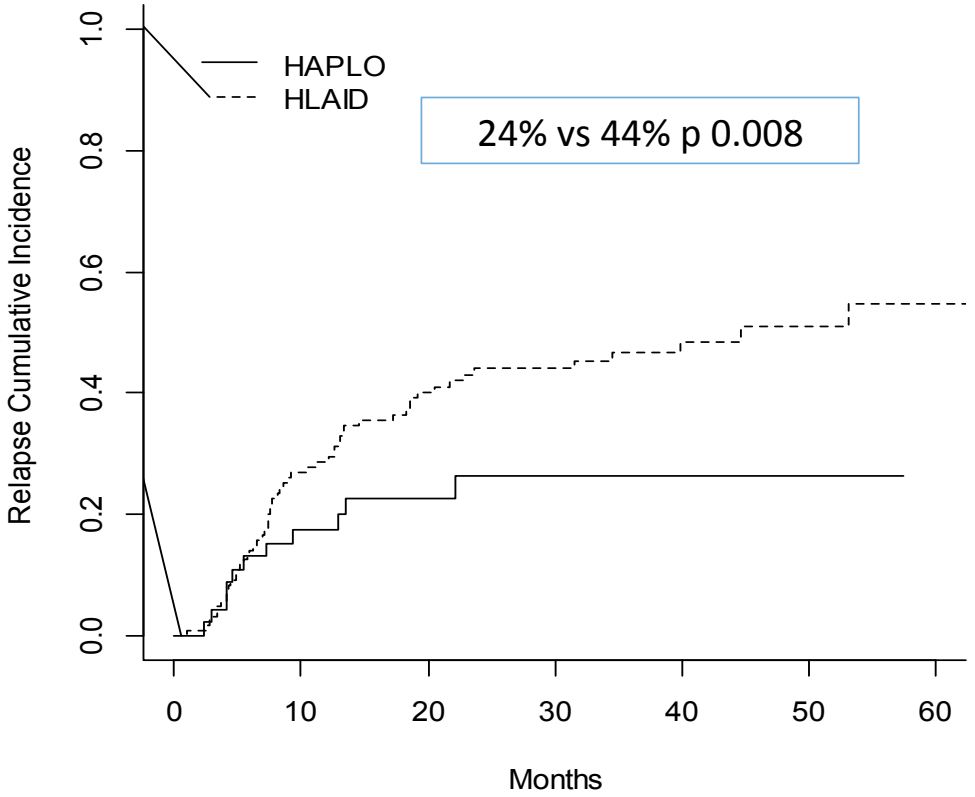
HAPLO vs HLAid CR and PR





HAPLO vs HLAid CR and PR

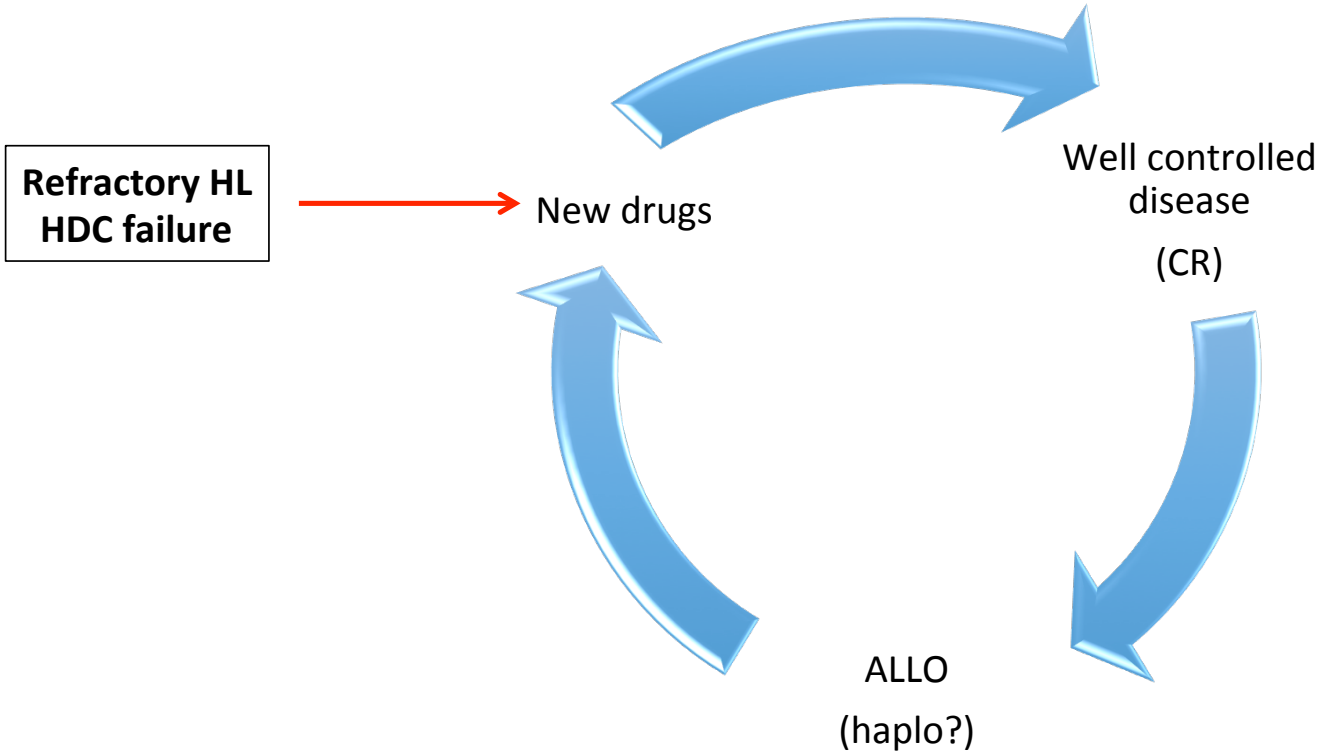




HAPLO vs HLAid CR and PR

MV	HR	CI95%	P value
PFS			
Disease Status at ALLO	0.51	0.34-0.75	<0.001
Haplo vs HLAid	0.56	0.35-0.89	0.014
OS			
Disease Status at ALLO	0.57	0.35-0.93	0.023
Age	0.04	1.00-1.05	0.043
Relapse			
Haplo vs HLAid	0.37	0.23-0.60	<0.001
Disease Status at ALLO	0.43	0.43-0.79	0.006

ALLO in HL


Refractory HL
HDC failure
New drugs
Well controlled disease
(CR)
ALLO
(haplo?)

Conclusions

- Allo-SCT must be considered for HL patients relapsed or progressed after HDC o refractory to salvage therapies
- New drugs should be integrated in the treatment strategy before allo-SCT and, if possible, after allo-SCT for those at higher risk of relapse
- Allo-SCT toxicity can be modified by immunomodulatory drugs, but this cannot be an exclusion criterion.
- Similarly, immunomodulatory drugs used after allo-SCT, can be induce important side effects.