Paper del trasplantament de progenitors hematopoètics en el tractament del limfoma de Hodgkin l'era dels nous fàrmacs

Diada Internacional de la Societat Catalana de Hematologia i Hemotèrapia

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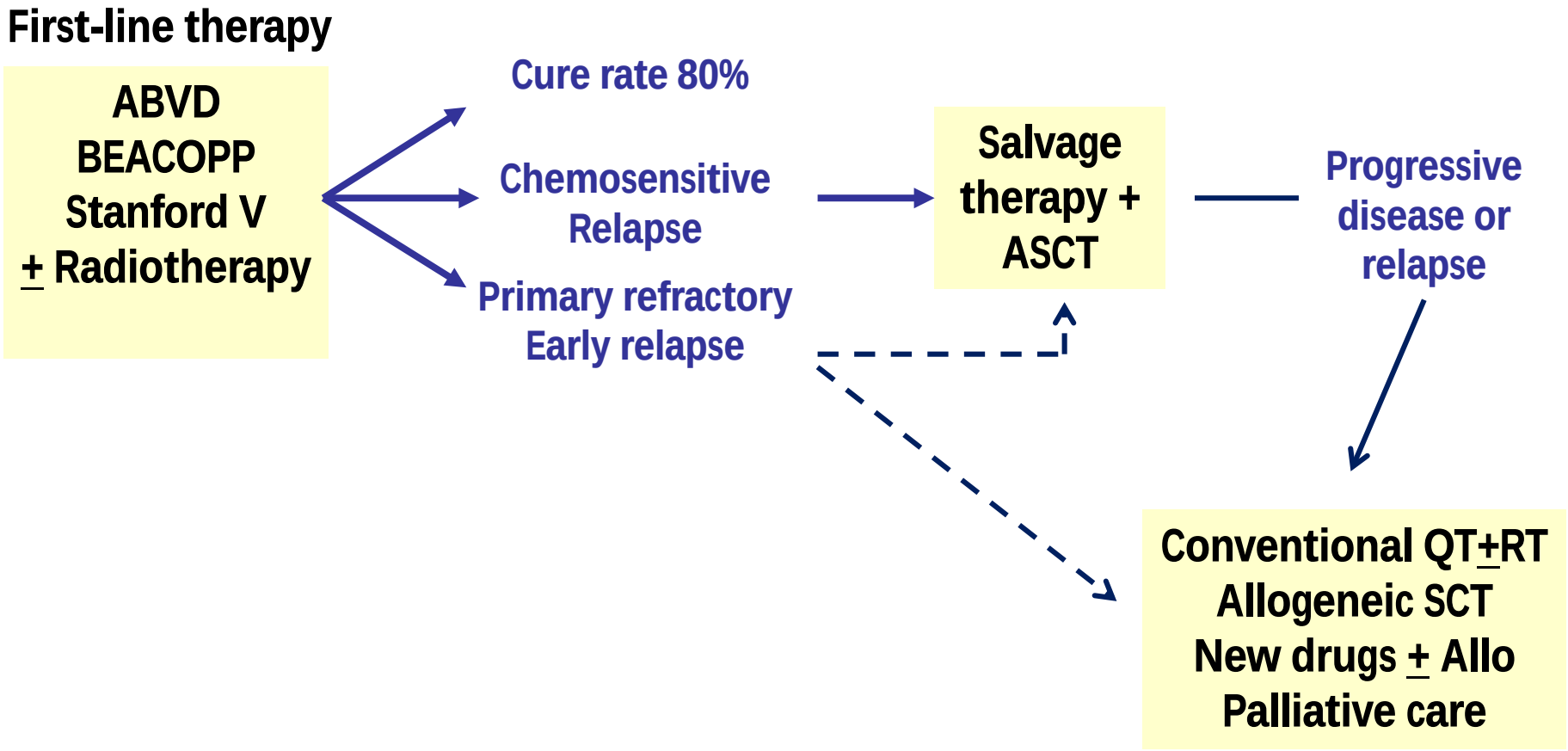
Current paradigm of HL treatment



EBMT classification of transplant procedures for adults with HL—2015

Disease risk	*Allogeneic*			*Autologous*
	Sibling donor	*Well-matched URD*	*Alternative donor*	
First remission	GNR/III	GNR/III	GNR/III	GNR/I
Chemosensitive relapse, prev auto no	D/III	D/III	GNR/III	S/I
Chemosensitive, prev auto yes	S/II	S/II	CO/III	CO/III
Refractory	D/II	D/II	D/III	CO/III

GNR =generally not recommended; D= developmental, further trials are needed; *S= standard of care generally indicated in suitable patients;* CO = clinical option, can be carried after careful assessment of risks and benefits.

Sureda et al, BMT 2015

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Sureda et al, BMT 2015

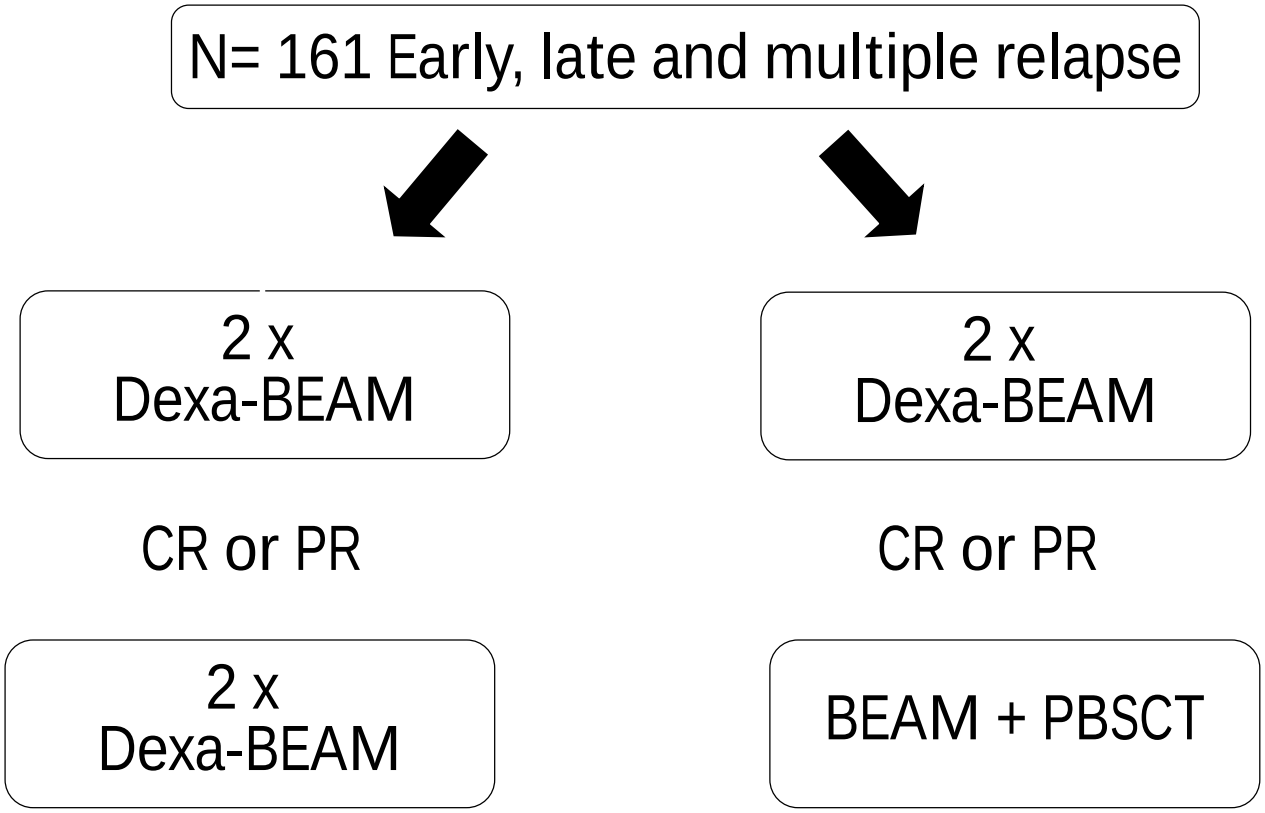
ASCT is the standard therapy for chemosensitive HL relapsing after 1st Line Chemotherapy

BNLI Trial
Mini-BEAM + ABMT *vs* Mini-BEAM

	N. of patients	TRM	EFS (3 yrs)	*p* value
Mini-BEAM	20	9	10	
Mini-BEAM + ABMT	20	5	53	0.025

Linch et al, Lancet 1992

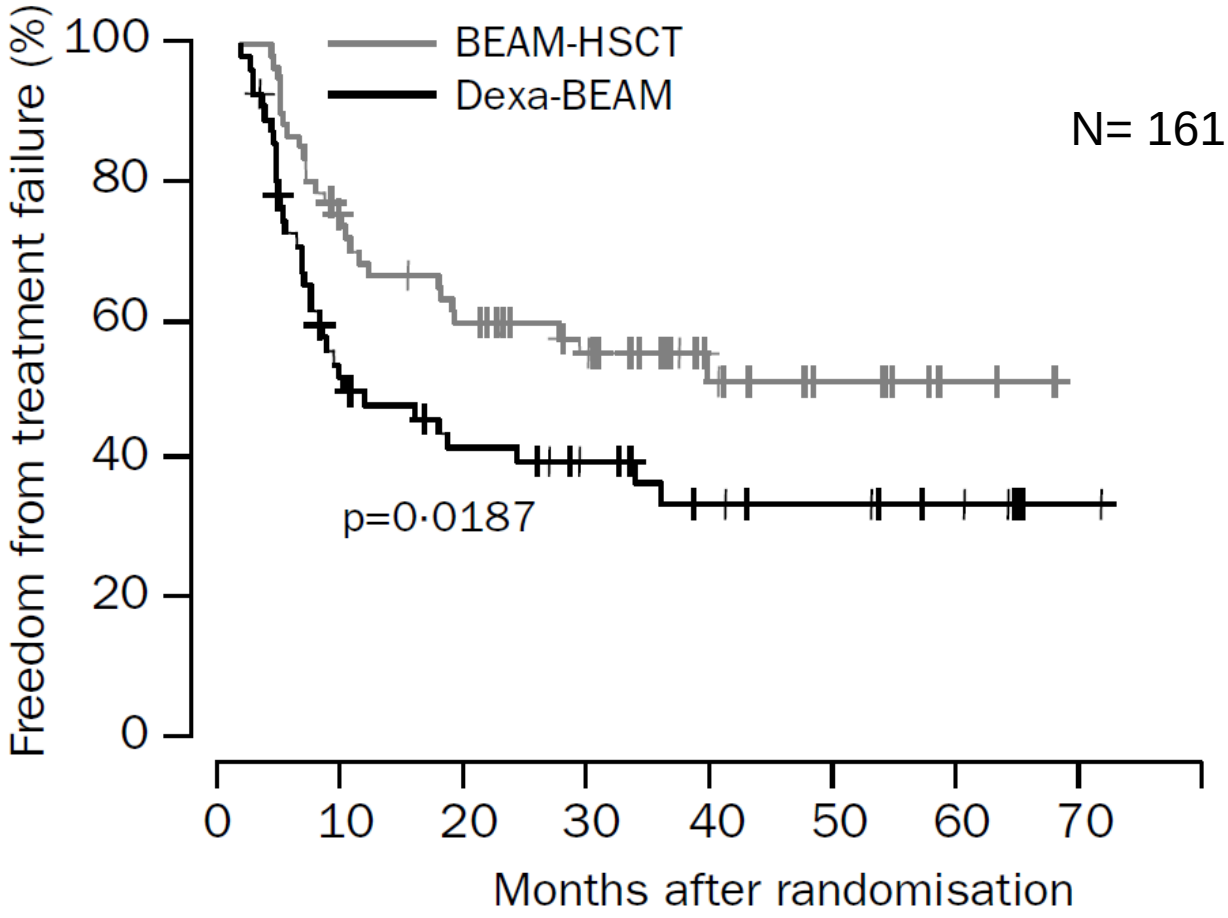
ASCT is the standard therapy for HL Relapsing after 1st Line CT
HDR1 Trial (GHSG/EBMT)
Dexa-BEAM + ASCT *vs* Dexa-BEAM



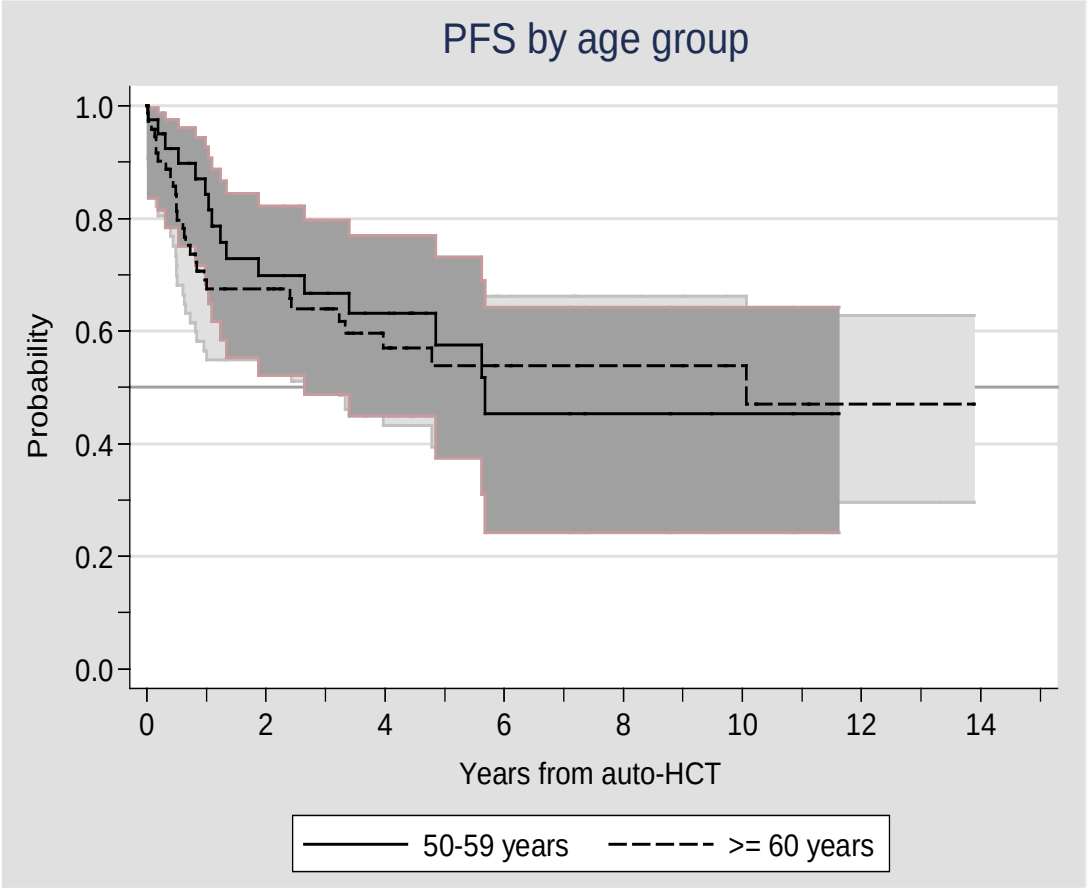
Schmitz et al, Lancet 2002

Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial

Schmitz et al, Lancet 2002



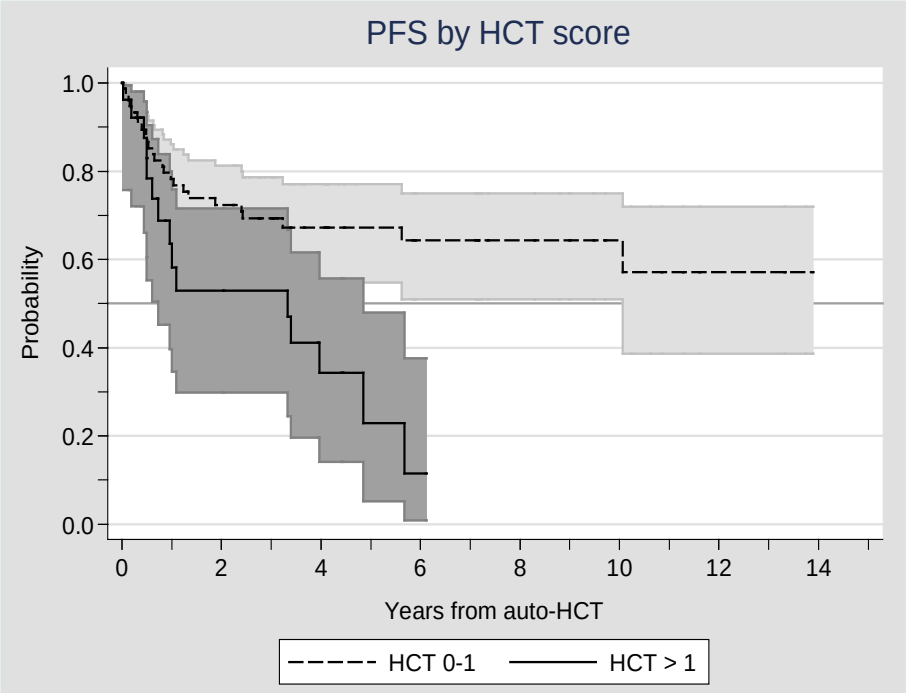
Age is not a limitation for autologous SCT



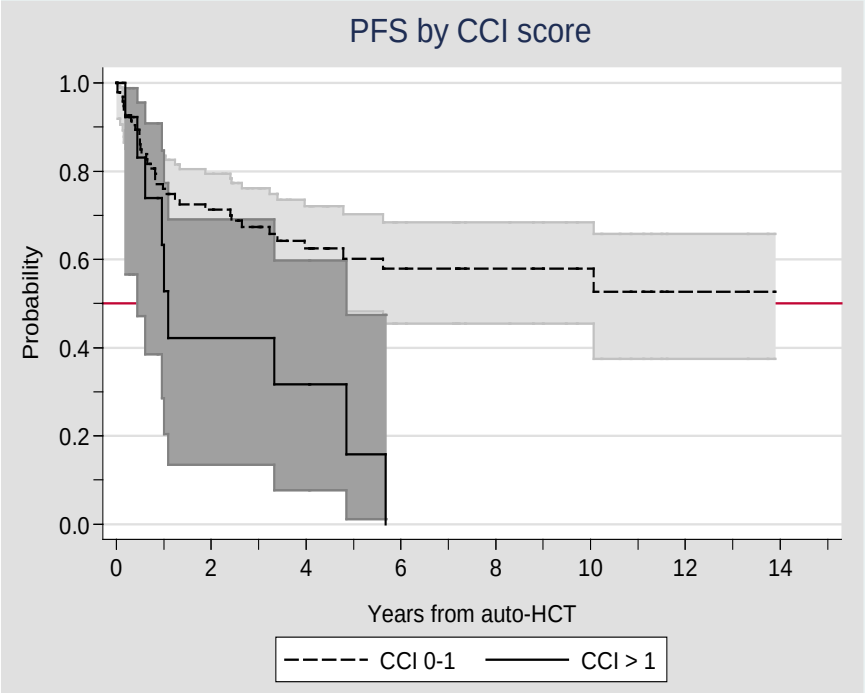
Carmen Martínez et al, GELTAMO, Submitted 2016

...but commorbidities should be taken into account!

Hematopoietic Cell Transplant Comorbidity Index (HCT-CI)

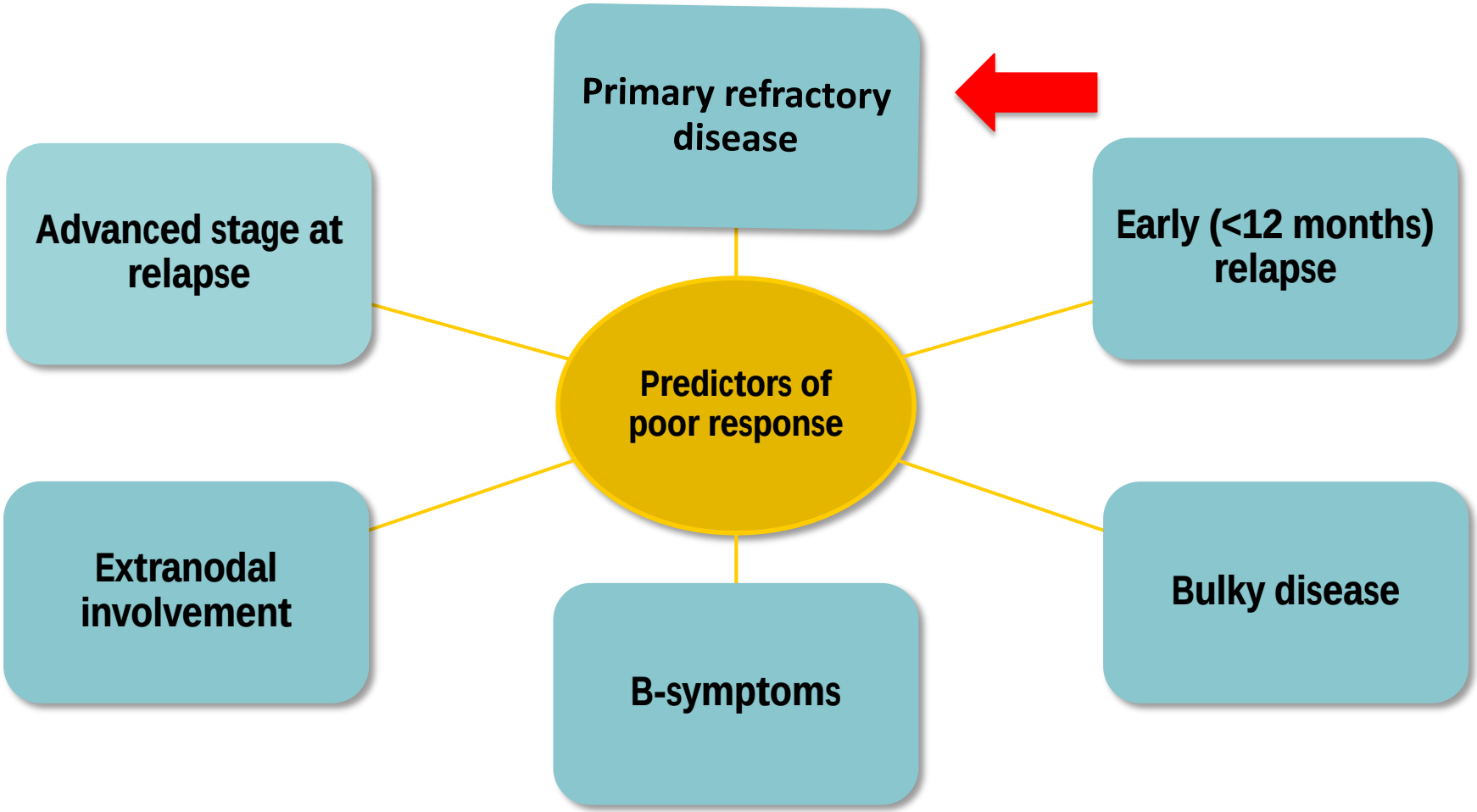


Charlson Comorbidity Index (CCI)



Carmen Martínez et al, GELTAMO, Submitted 2016

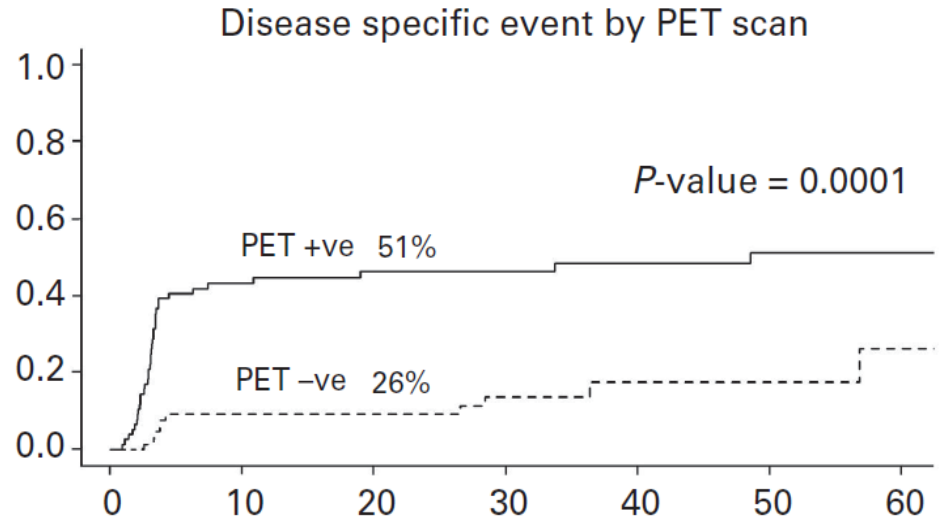
Not all Relapsing Patients do so Well after an Autologous Stem Cell Transplantation

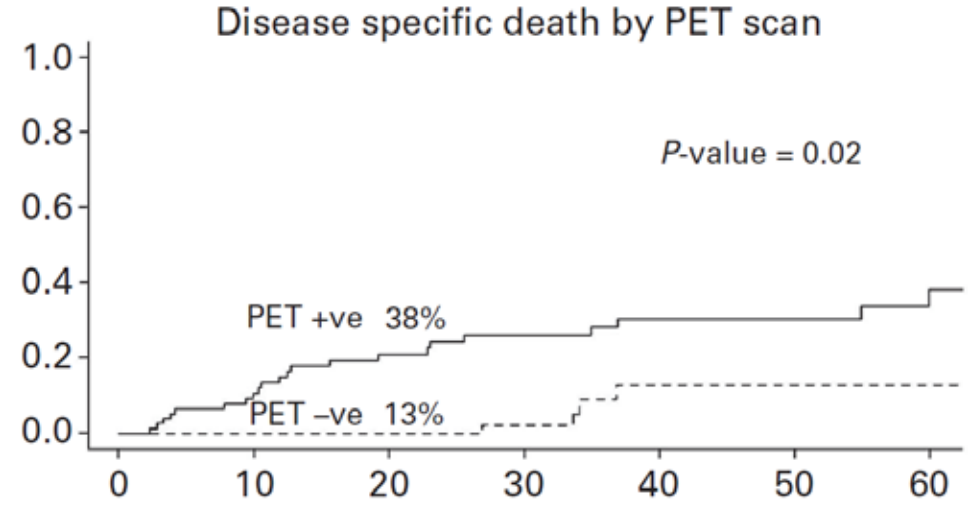


Is further improvement in the ASCT setting possible?

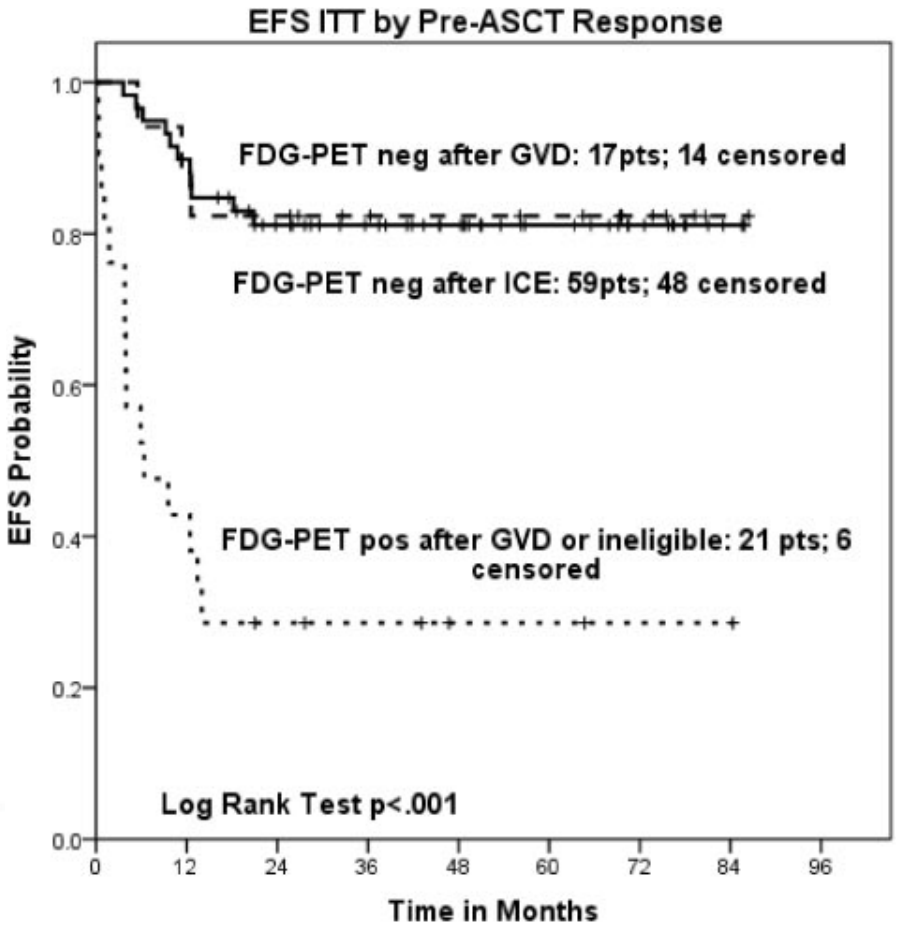
- PET-CT: standard imaging test in lymphoma management
  - Inclusion of PET/CT evaluation in the ASCT
  - Risk adapted-therapeutic programs
- Use new drugs
  - Increase response rate prior to ASCT
  - Maintenance therapy after ASCT

Impact of PET-negativity before transplant on ASCT outcome





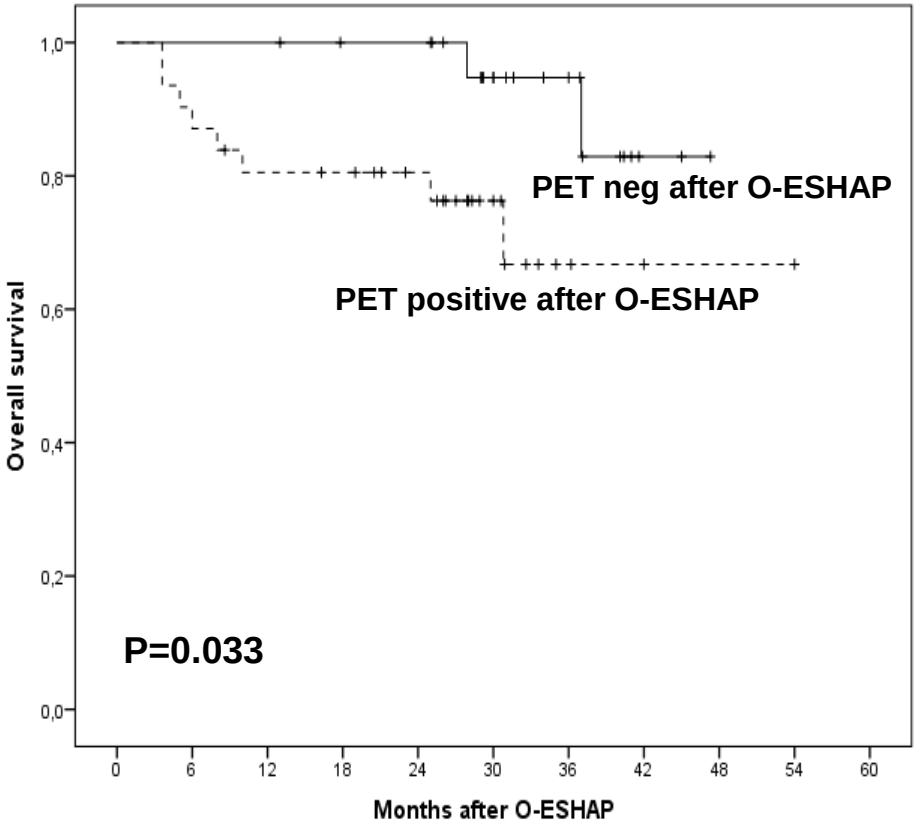
Akhtars et al, BMT 2013

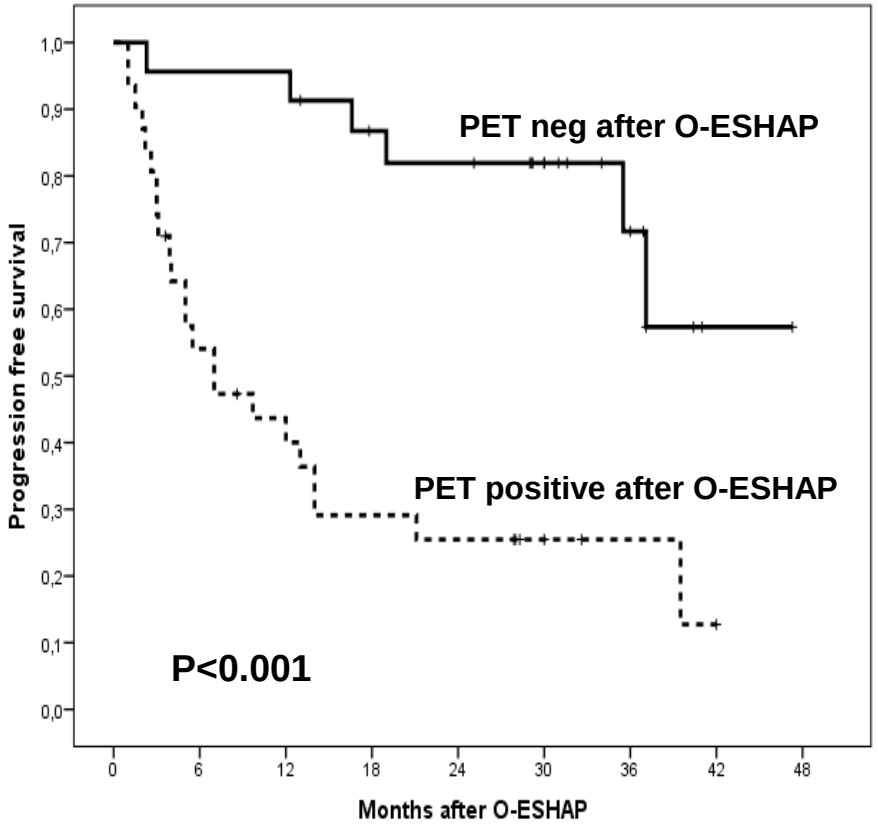


Gentzler et al, BJH 2014

Corporació Sanitària CLÍNIC

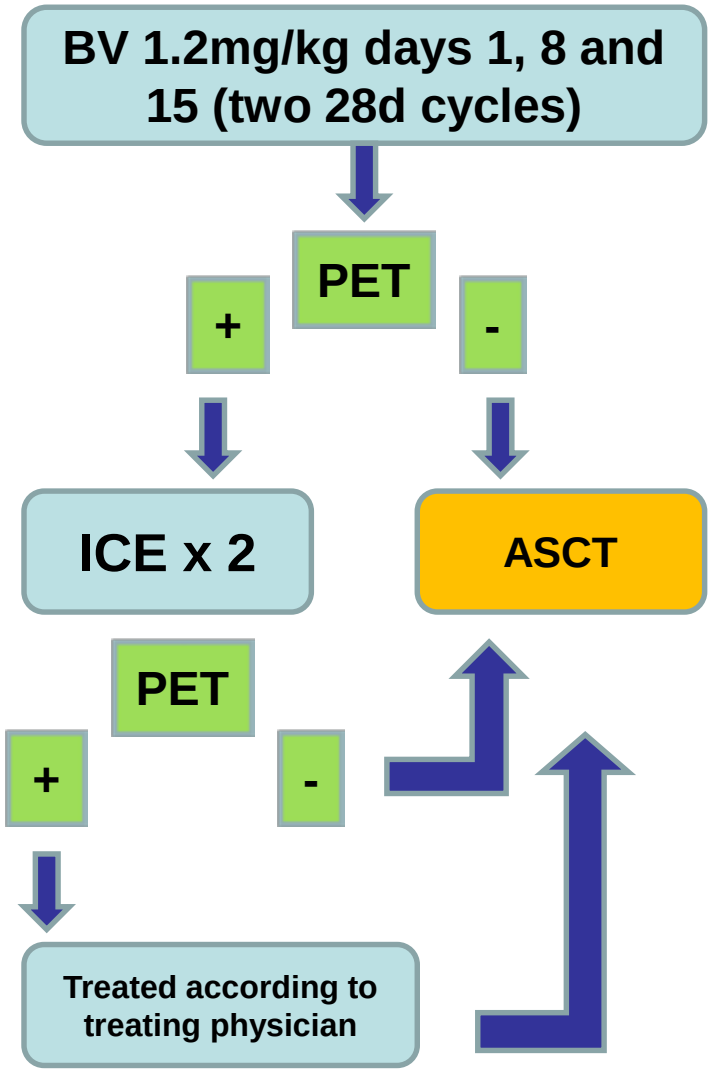
Ofatumumab-ESHAP GELTAMO trial
Impact of PET on ASCT outcome



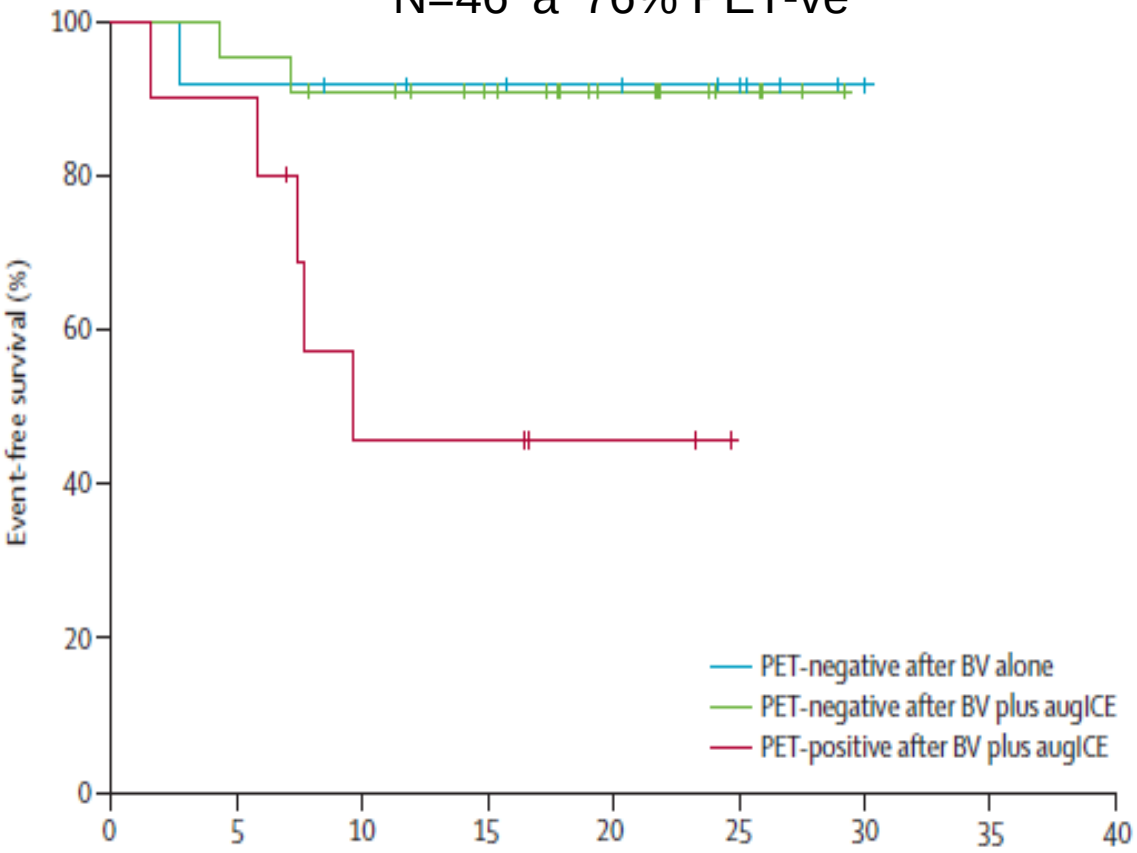


C. Martínez et al, GELTAMO, Br J Haematol 2016

PET-adapted sequential salvage therapy with brentuximab vedotin followed by augmented ifosamide, carboplatin, and etoposide for patients with relapsed and refractory Hodgkin's lymphoma: a non-randomised, open-label, single-centre, phase 2 study



N=46 à 76% PET-ve



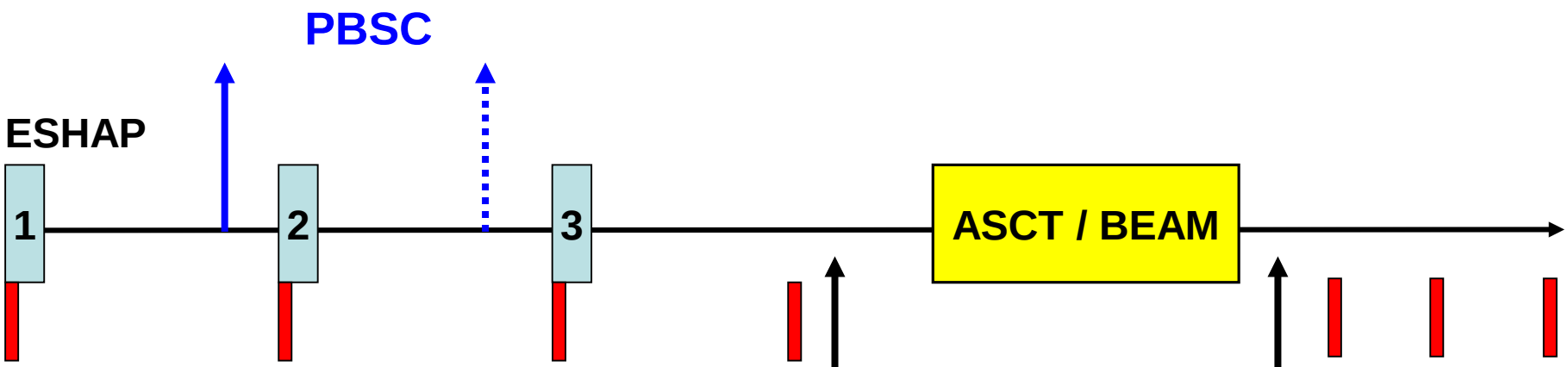
Moskowitz, Lancet Oncol 2015

Brentuximab Vedotin + Bendamustine: An Effective First Salvage Therapy in R/R HL prior to ASCT

Design	• Phase I/II treatment combination study • 55 patients • 1.8 mg/kg brentuximab vedotin D1; 90 mg/m^2 bendamustine D1–2, every 3 weeks, at least 2 cycles, up to 6 cycles in an outpatient setting
Efficacy	• **ORR: 93%** • **CR: 74%** • Peripheral blood stem cells collection adequate
Safety	• Premedication was required for combination therapy • The most common AEs were infusion-related reactions (56%): pyrexia (26%), chills (20%), dyspnoea and nausea (15% each), flushing (13%)

La Casce et al. ASH 2014

Phase I-II trial of Brentuximab Vedotin in Pre-transplant Induction and Consolidation for Relapsed or Refractory HL. GELTAMO



Brentuximav Vedotin*: 1,8 mg/Kg, 1st day ESHAP and day +21 after 3rd ESHAP (c/21 – 28d)

± Radiotherapy (if Bulky)

BV post-ASCT (3 doses)

Phase I + Phase II

- N=36
  - Primary refractory 21 (58%)
  - Relapse 15 (5 early)
- Stem cell collection: 24 patients (no failures)
- Evaluable for response n=24
  - ORR 96%
  - CR 83%

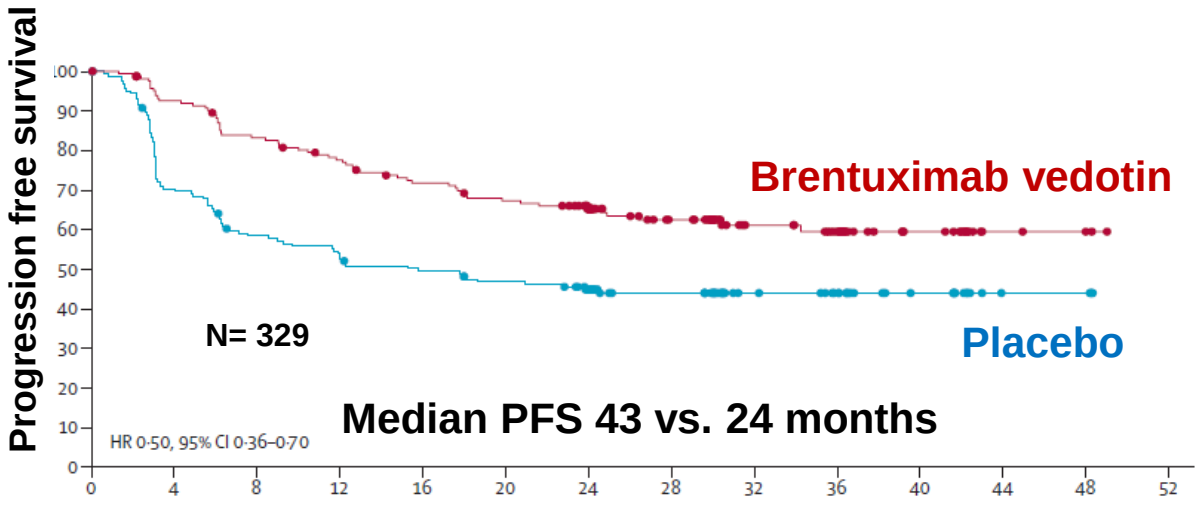
García-Sanz,….Martínez C. ASH 2015

A Randomized, Double-Blind Placebo-Controlled Phase 3 Trial of SGN-35 vs Placebo in High-Risk HL Patients Ungergoing and ASCT (AETHERA Trial)

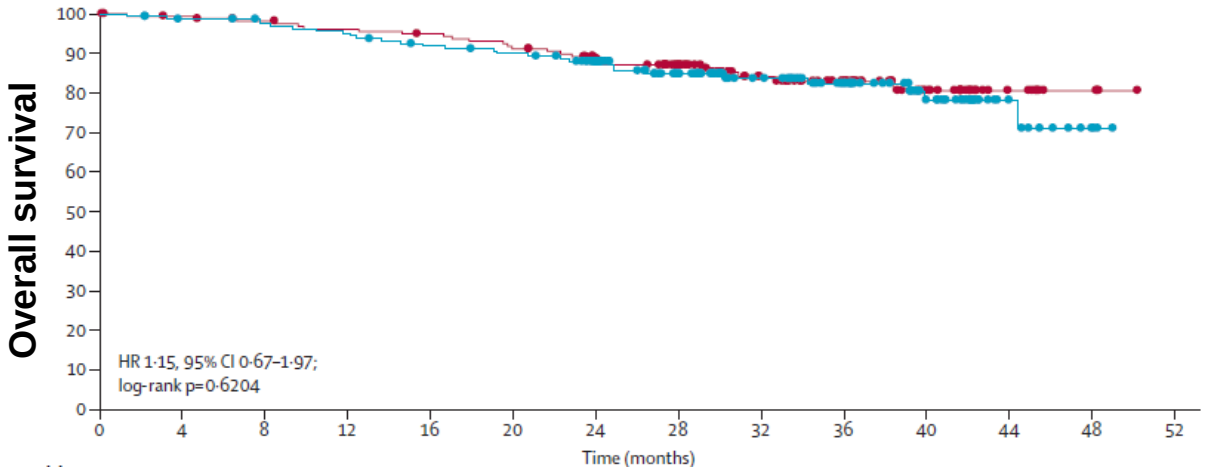
SeattleGenetics

Inclusion criteria:

- ≥18 years
- Primary refractory HL
- HL relapse:
  - CR < 12 months
  - Extranodal



SGN-35 (brentuximab vedotin)1,8mg/kg/3w, 16 cycles post-trasplant **vs. placebo**

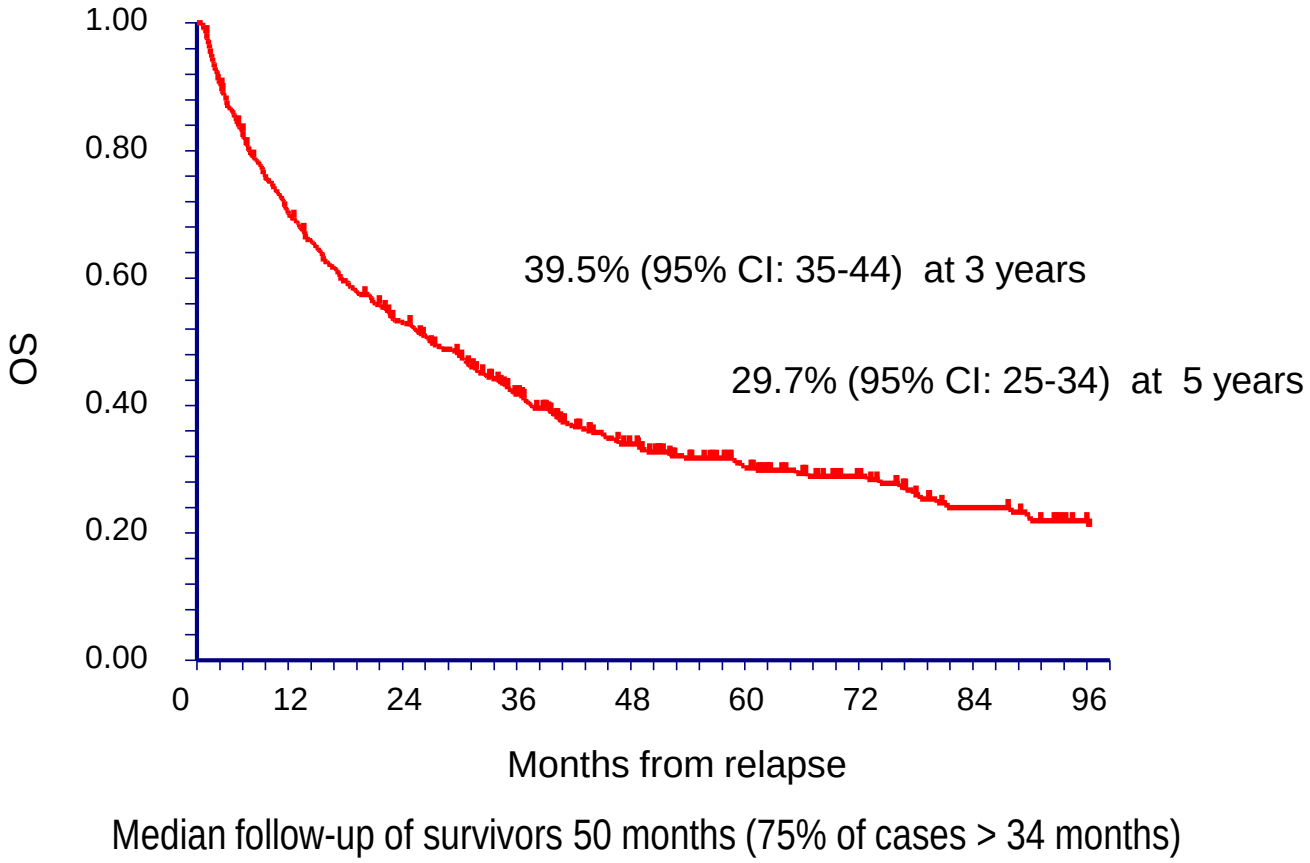


Moskowitz C, Lancet, March 2015

Overall survival from relapse after an ASCT. The experience of the LWP EBMT/GITMO

- N=462

- Salvage therapy after ASCT failure
  - 64% CT/RT
  - 29% AlloSCT
  - 8% 2nd ASCT



Median follow-up of survivors 50 months (75% of cases > 34 months)

C. Martínez et al. Ann Oncol 2013

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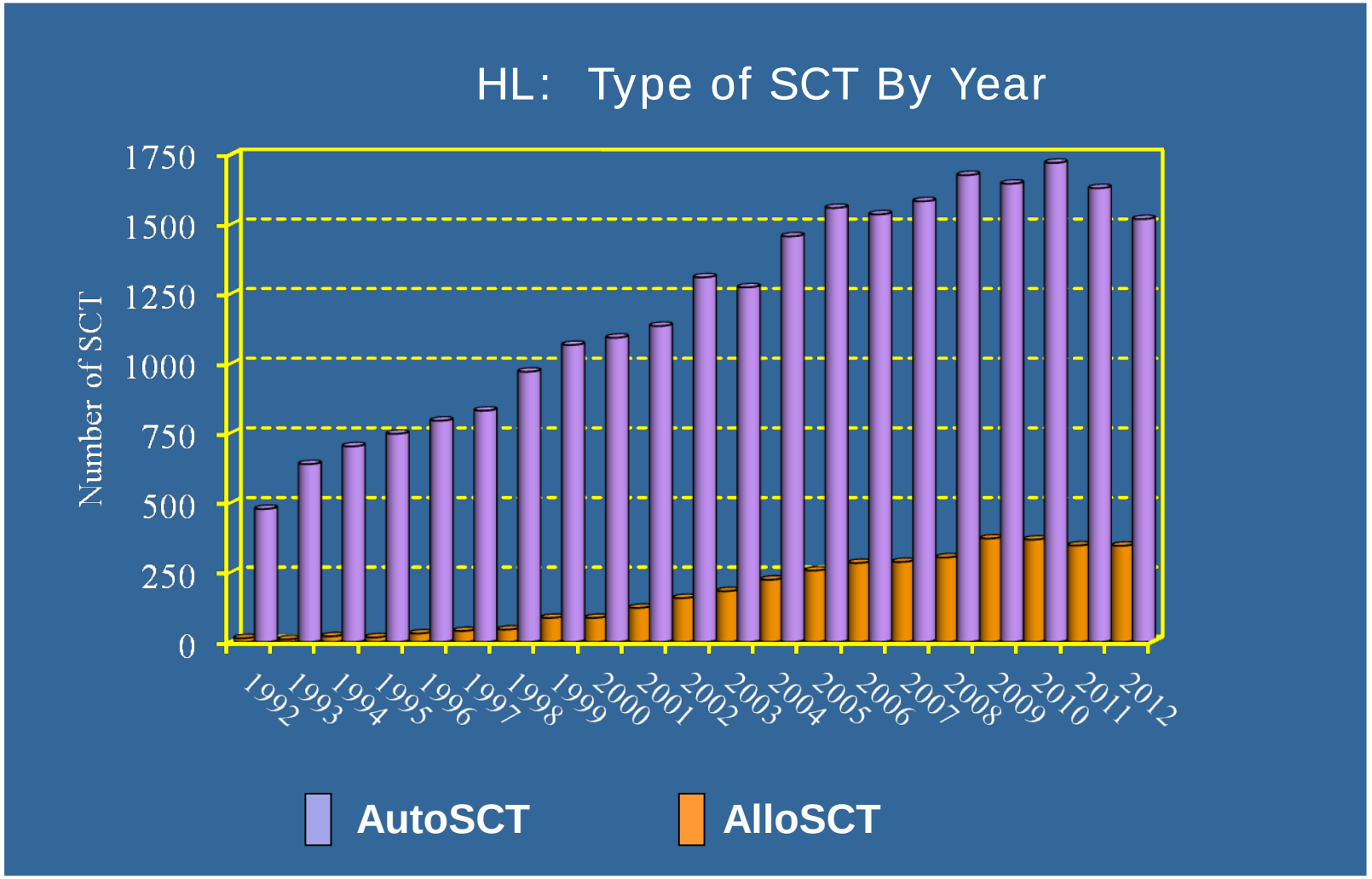
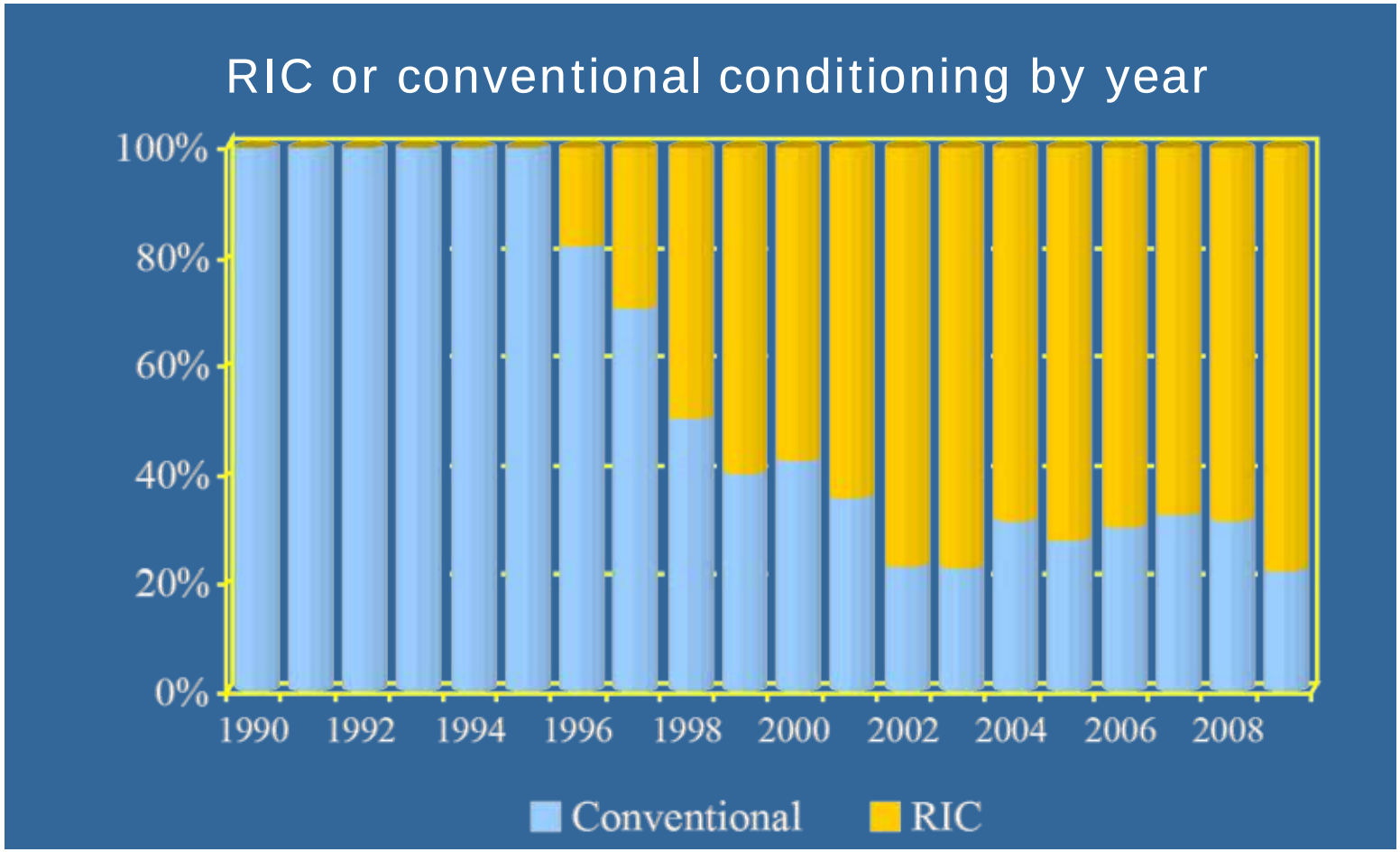
Sureda et al, BMT 2015

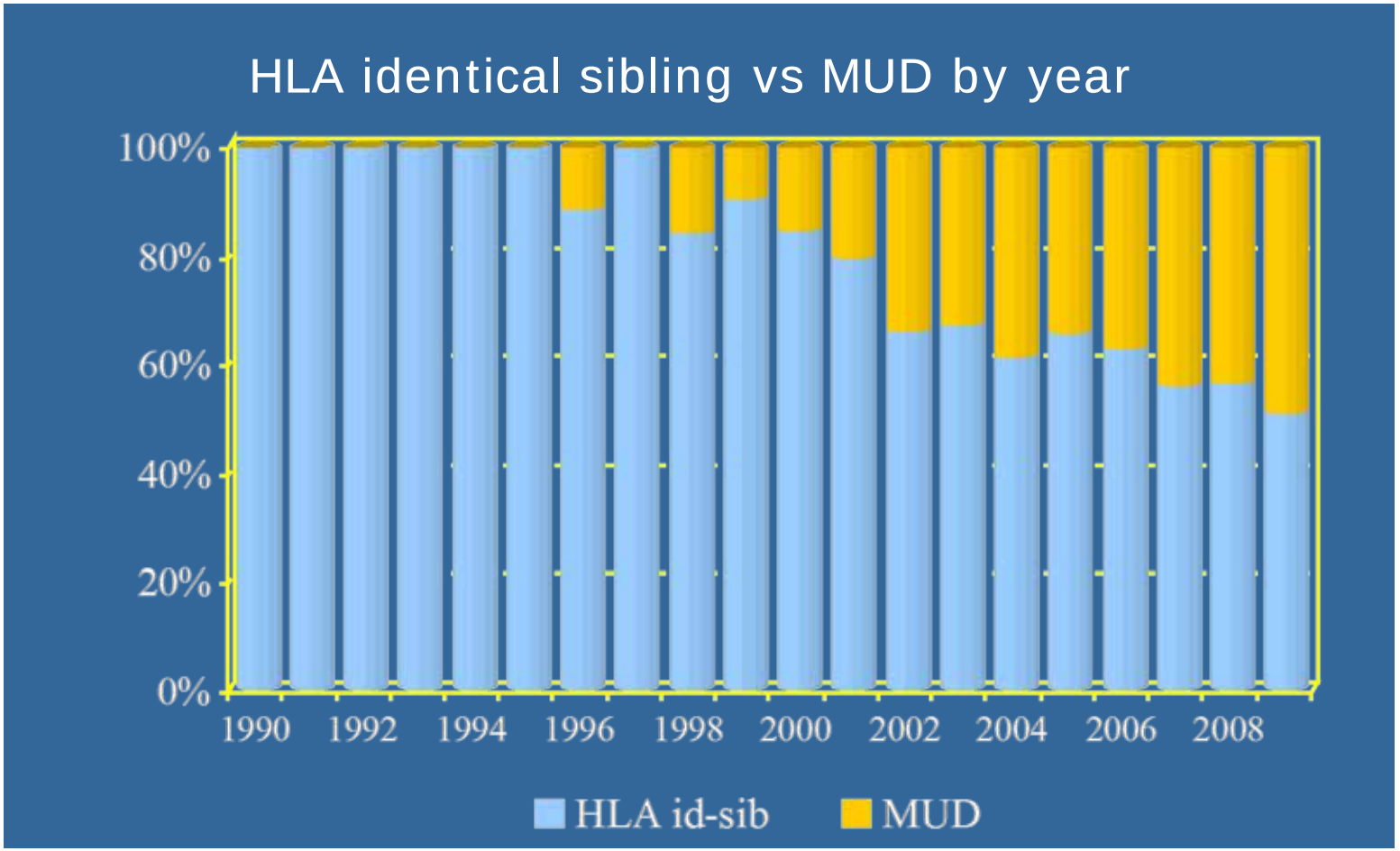
EBMT Registry: SCT for HL 1992-2012



RIC vs MAC in allo-SCT: 1990-2009



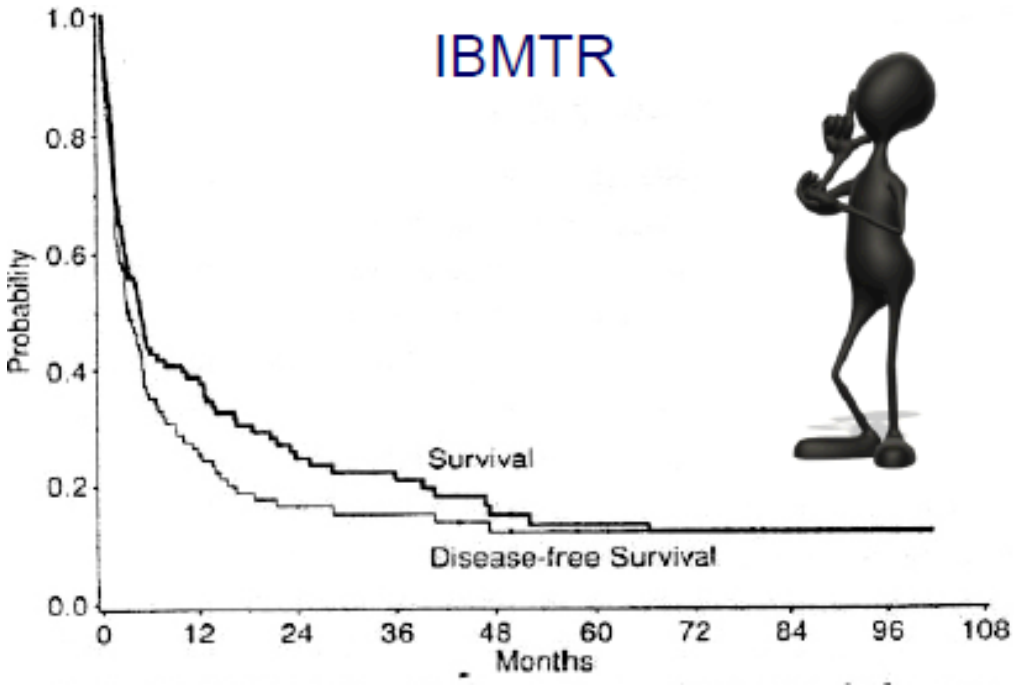
HLA identical sibling vs MUD: 1990-2009



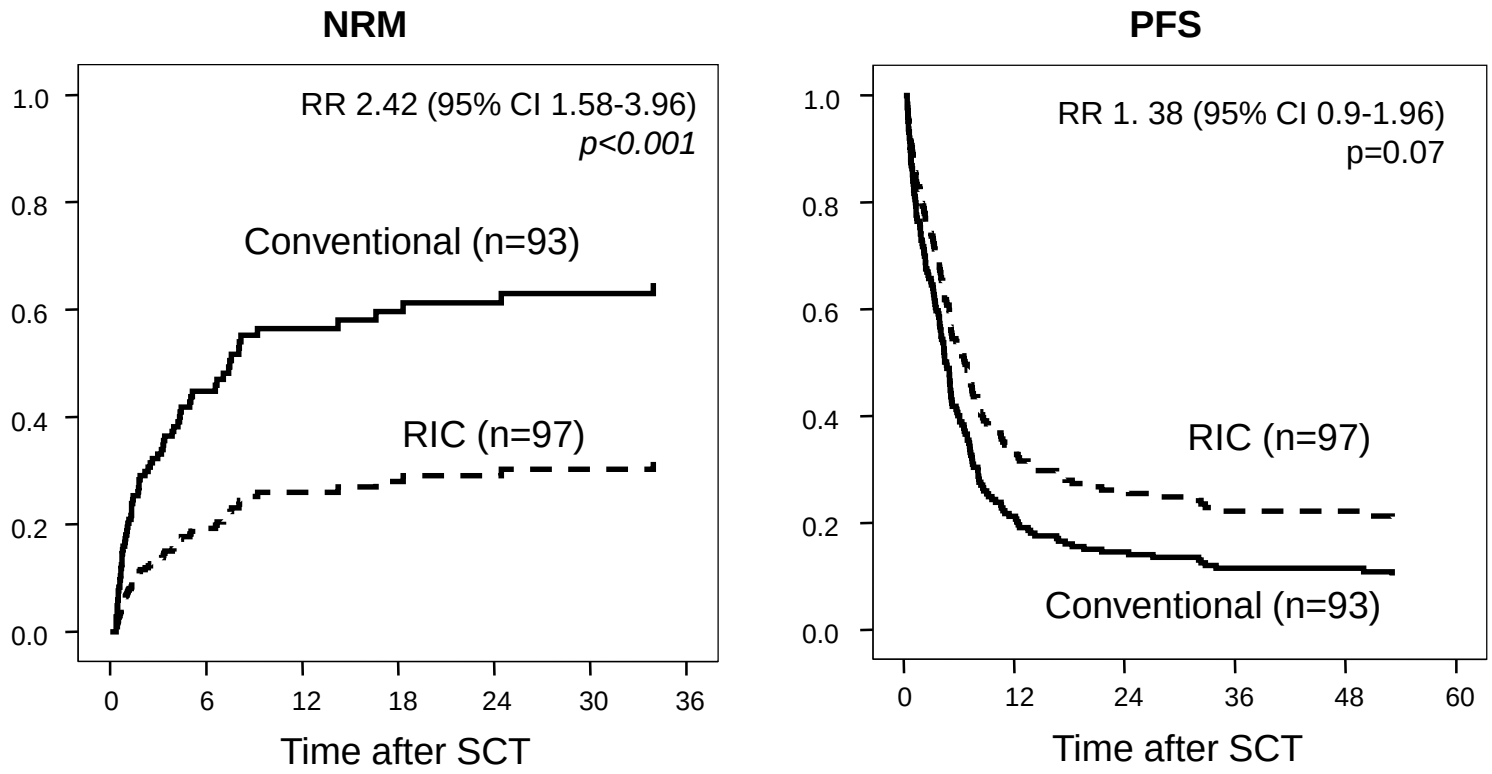
AlloSCT using conventional conditioning regimens is associated a high NRM

Restrospective study form IBMTR, *Gajewski JL, JCO 1996*

- n= 100
- Sibling donor
- Prior to alloSCT
  - 89 pts with active HL
  - 50 pts KS < 90%
  - 27 active infection
- Results:
  - SG 21% 3 y
  - SLE 15% 3 y
  - Relapse 65%



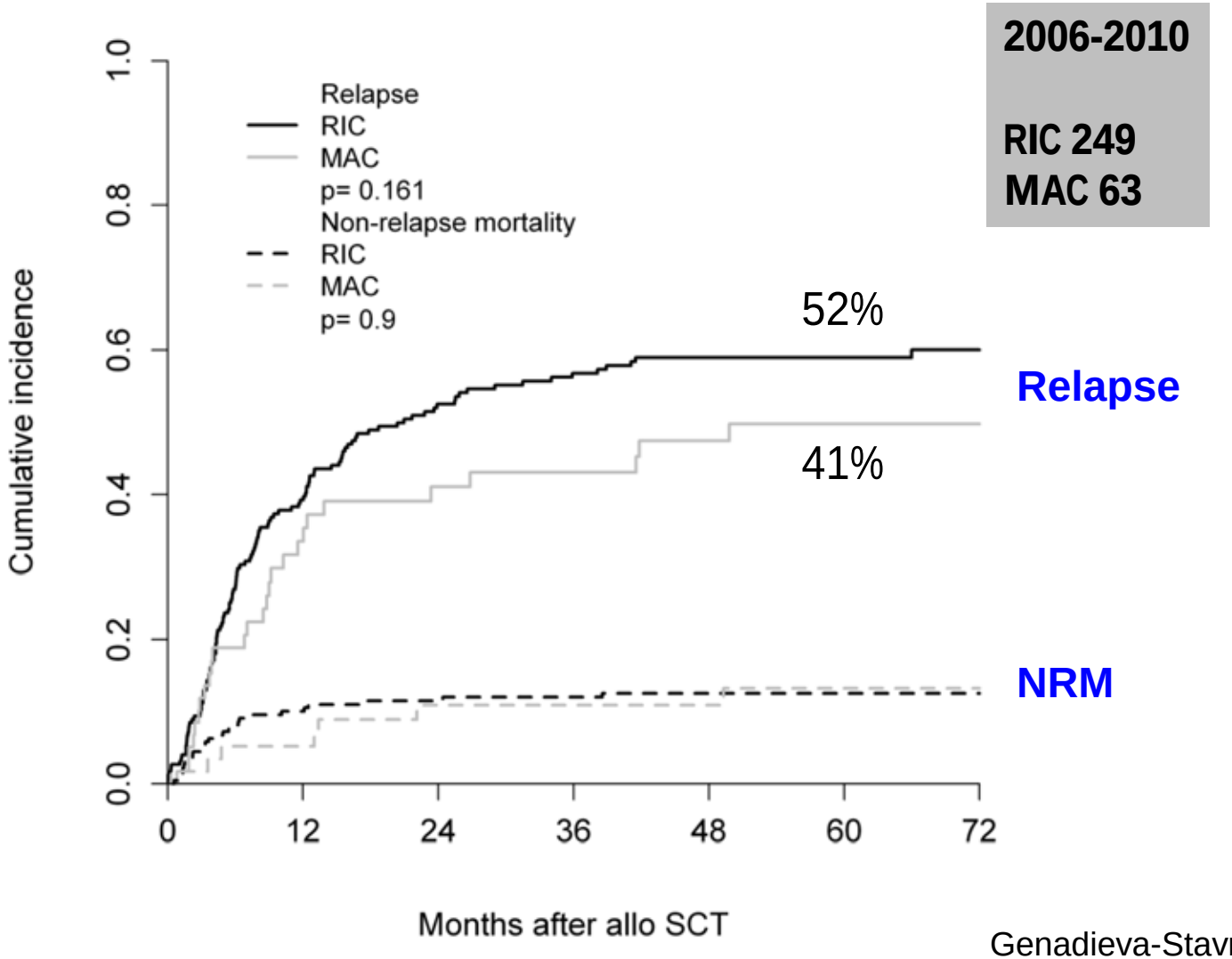
We Have Been Able to Reduce NRM with RIC Protocols



Estimate of the NRM and PFS based on a COX model, adjusted by all covariates with impact on the outcomes. RR and p values from multivariate Cox model.

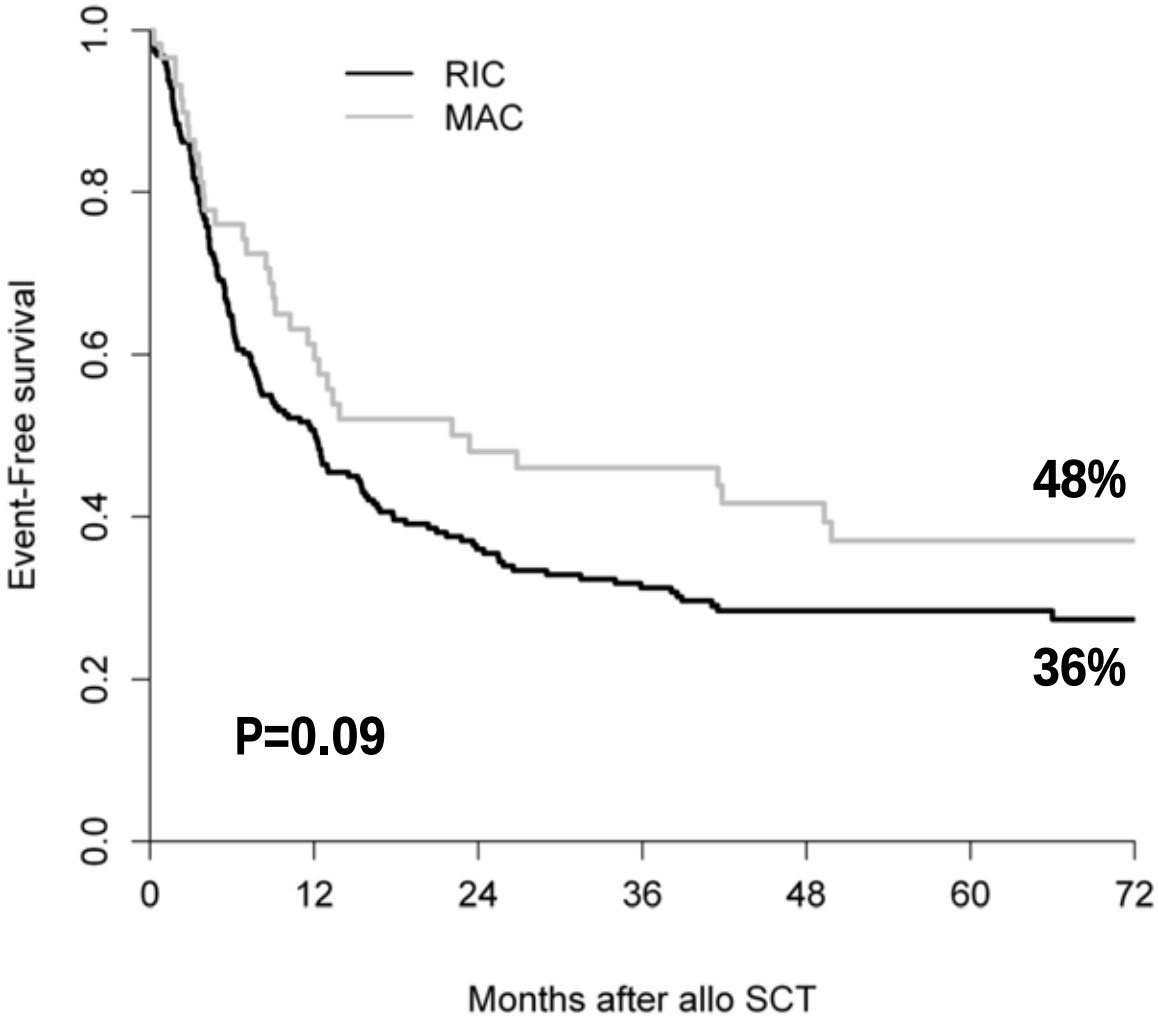
Sureda et al, JCO 2008

Myeloablative Versus Reduced Intensity AlloSCT in recent years
A Retrospective Analysis of LWP-EBMT



Genadieva-Stavrik et al, accepted

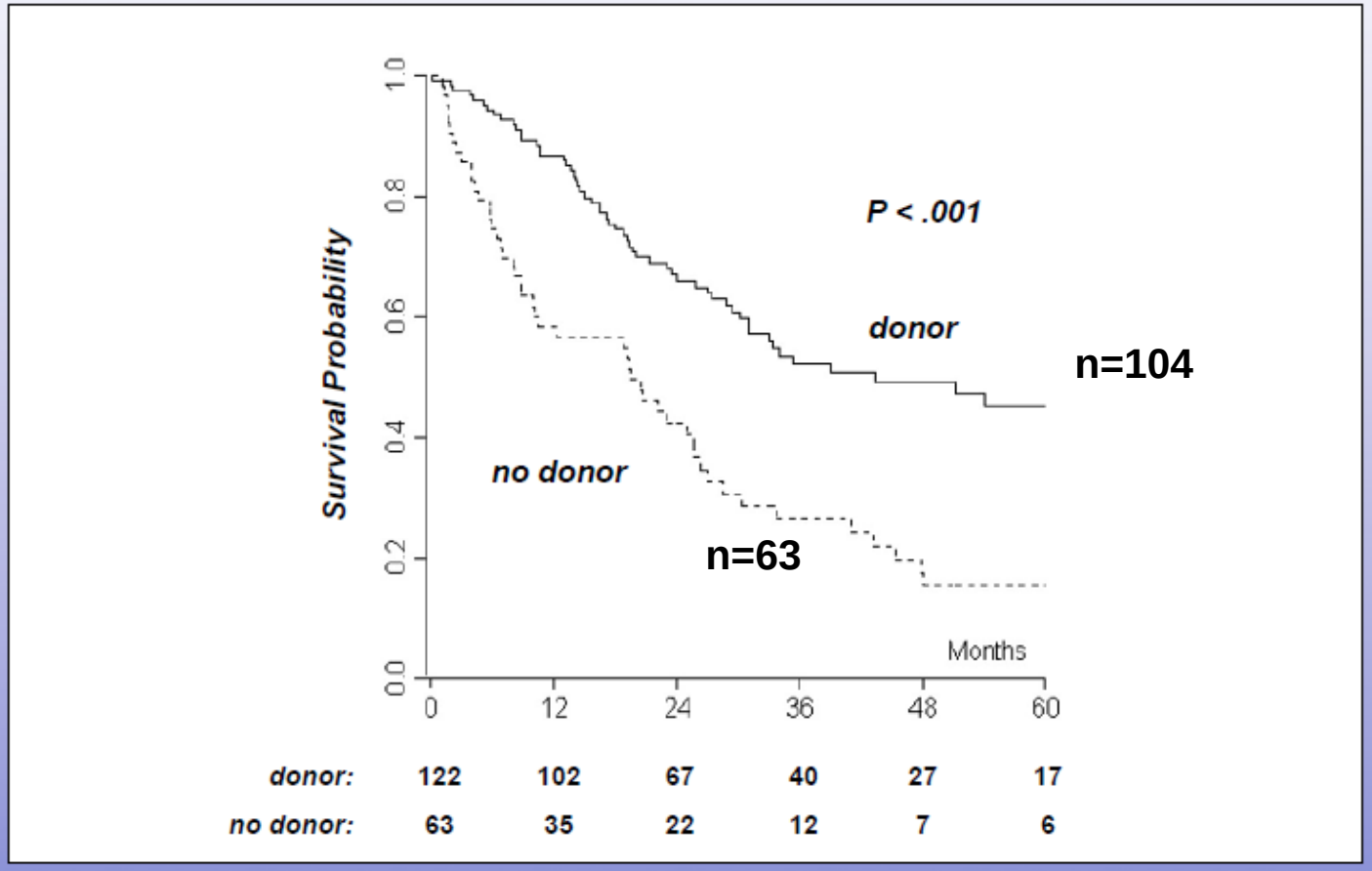
RIC vs. MAC: Event Free Survival



Genadieva-Stavrik et al, accepted

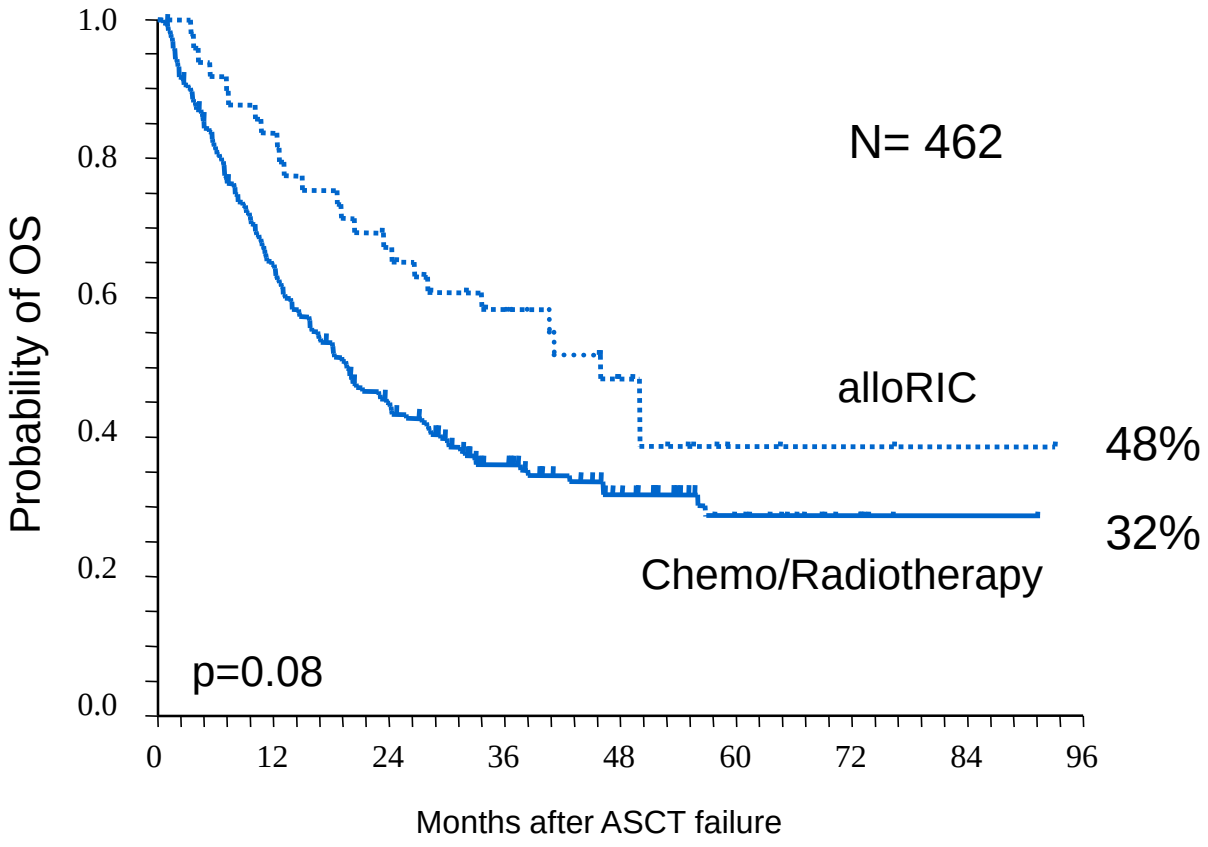
AlloRIC offers better results than non-transplant strategies. The GITMO experience

Overall survival from autograft



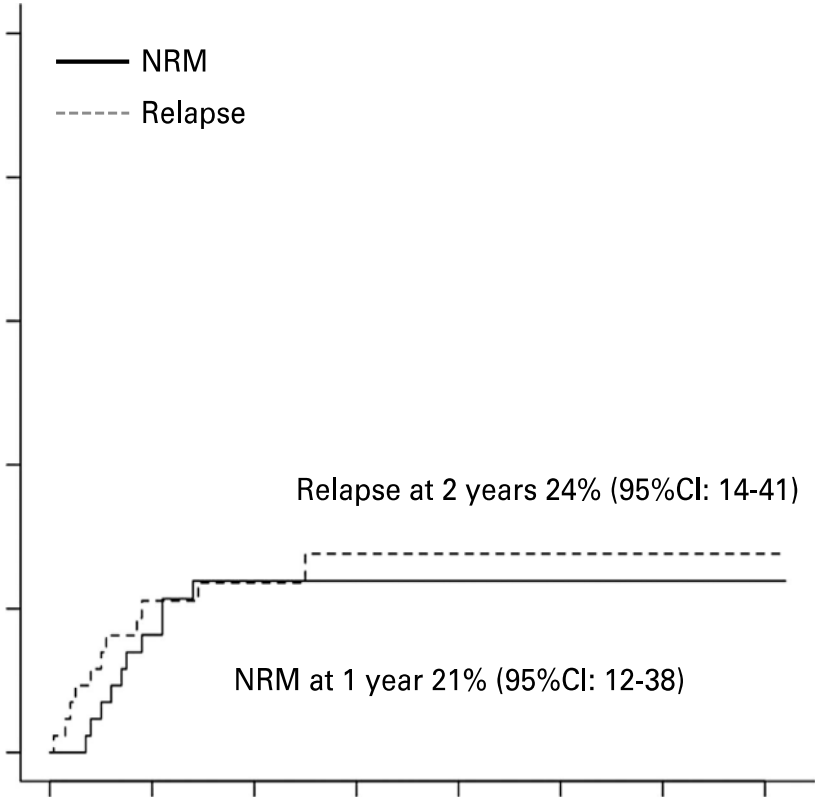
Sarina et al. *Blood* 2010;115:3671-7

Comparison of alloRIC vs. chemo/radiotherapy strategies after autoSCT failure: the experience of the LWP-EBMT



C. Martínez et al.; Ann Oncol 2013; 24:2430

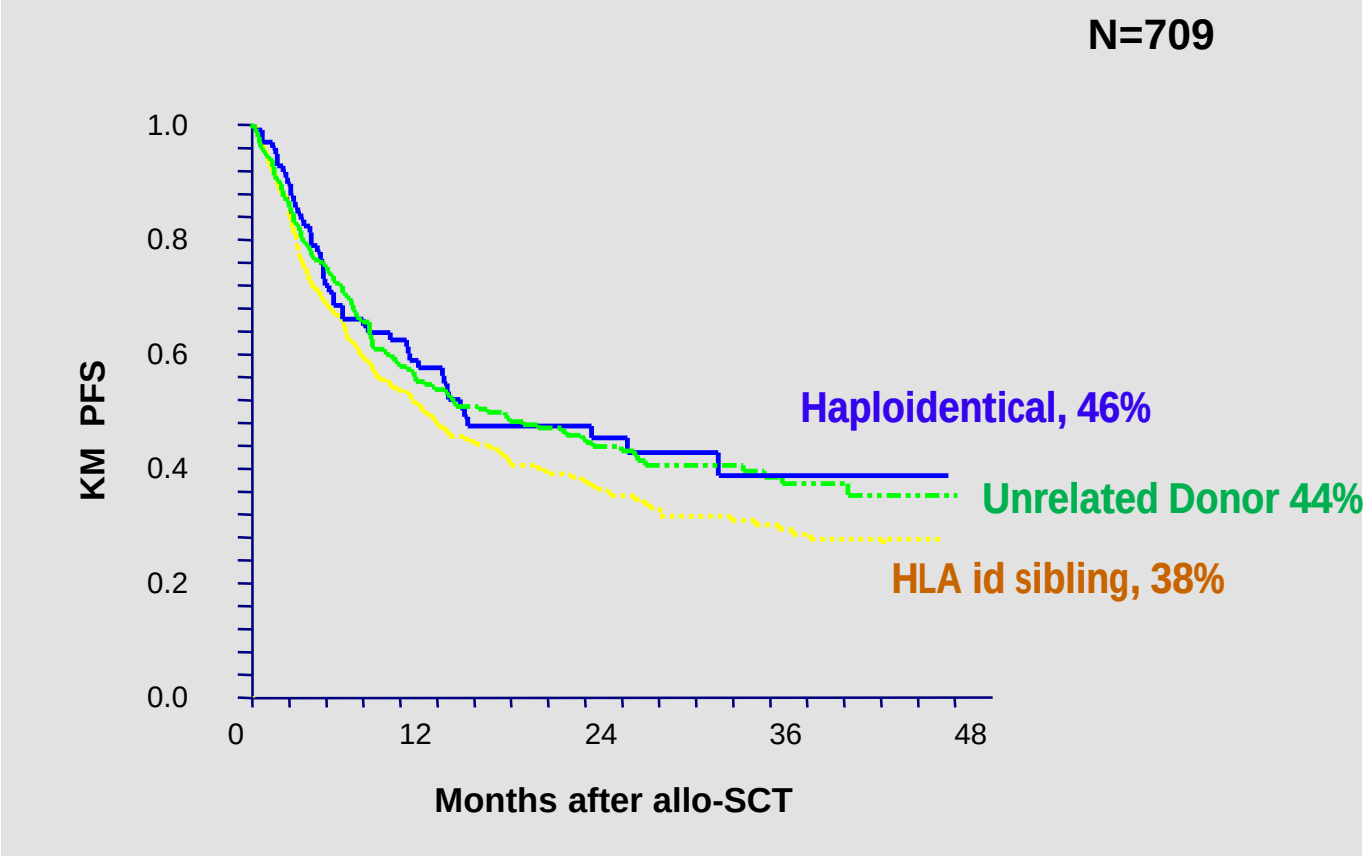
Haploidentical SCT with busulfan-based RIC and post-transplant cyclophosphamide as GVHD prophylaxis in relapsed/refractory HL: Spanish experience



Gayoso et al, BMT 2016

Haplo vs. conventional donors in R/R HL

LWP-EBMT retrospective study



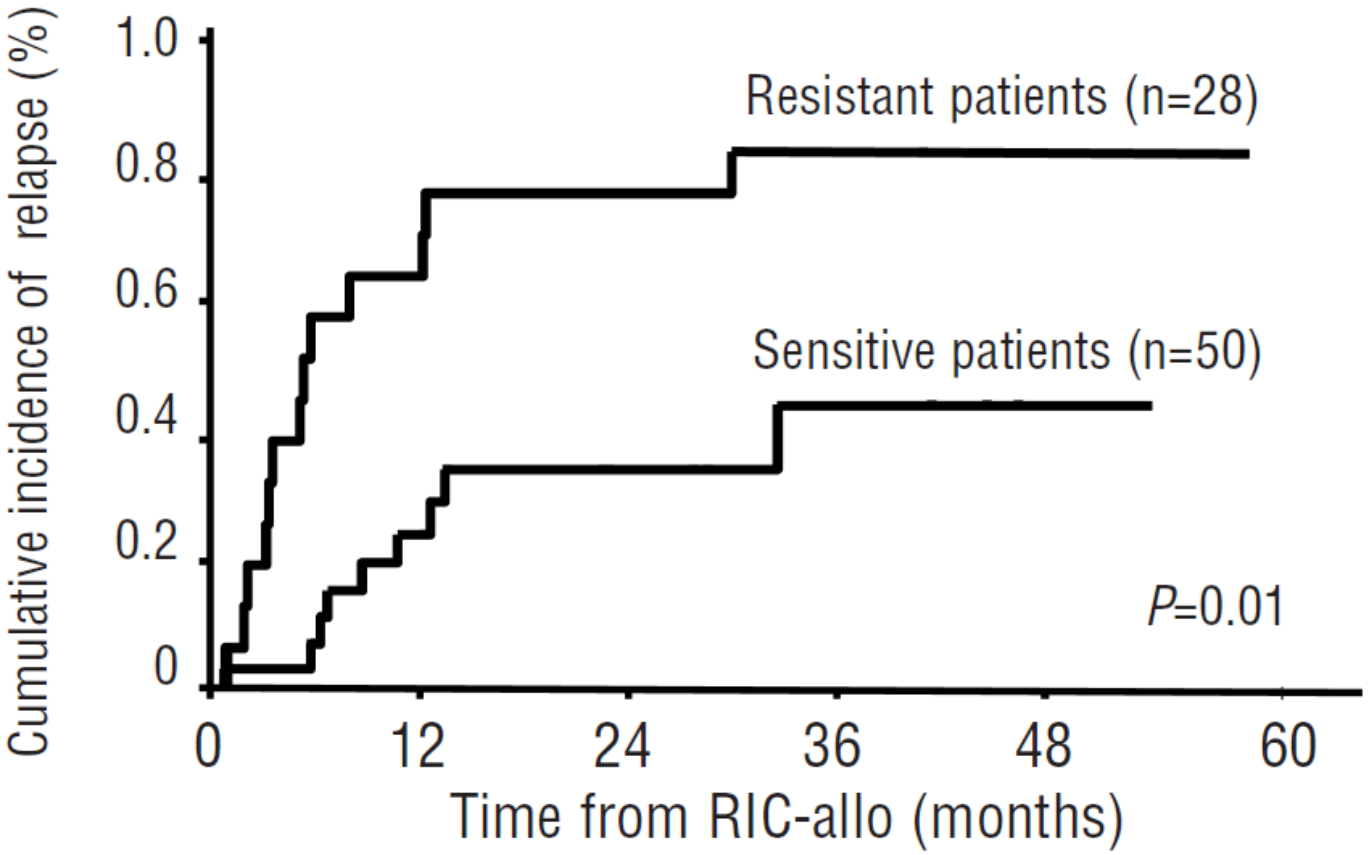
C. Martínez, EBMT 2016

Relapse rate remains a major issue after alloSCT

Author, year	Relapse Rate	Impact of disease status
Alvarez et al, 2006	47% (3 yrs)	2.5 (1.2 – 5.6), p = 0.01
Anderlini et al, 2008	55% (2 yrs)	2.9 (0.9 – 8.8), p = 0.05
Sureda et al, 2008	58% (5 yrs)	1.51 (0.95 – 2.39), p = 0.08
Robinson et al, 2009	59% (5 yrs)	2.1 (1.5 – 2.9), p < 0.001
Claviez et al, 2009	44% (5 yrs)	2.1 (1.0 – 4.4), p = 0.04
Devetten et al, 2009	47% (2 yrs)	----
Sureda et al, 2012	59% (3 yrs)	2 (1.6 – 3), p = 0.01

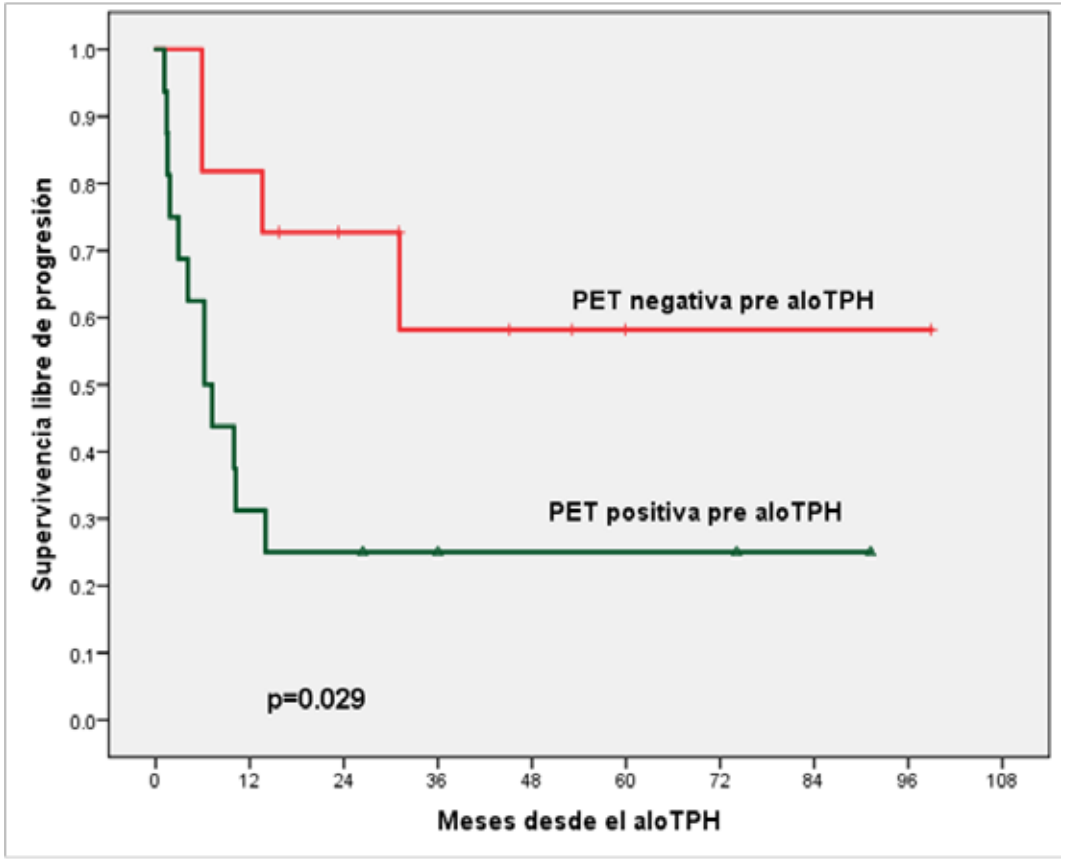
~ 40-60%

Disease status is the most important predictive factor for relapse



Sureda et al. Haematologica 2012

Impact of PET-negativity before transplant on AlloSCT outcome



N= 27

Ortíz V, Diada Internacional Societat Catalana Hematologia, 2016

Patients with R/R HL who received reduced intensity allo-SCT post brentuximab vedotin

Baseline characteristics

	N=19*
Median age, years (range)	31 (23–55)
Prior chemotherapy regimens, median (range)	5 (3–8)
Prior ASCT, n	18/19
Prior XRT, n	10/19
Best response to brentuximab vedotin, %	CR: 42%; PR: 42%; SD: 11%; PD: 5%
Number cycles of brentuximab vedotin, median (range)	8 (2-16)
Disease status at time of allo-SCT	CR : 37%; PR: 37%; SD: 11%; PD: 16%

* Treated at City of Hope or Seattle Cancer Care Alliance/Fred Hutchinson Cancer Center

Chen R et al. Oral presentation at ICML 2013, Lugano, Switzerland

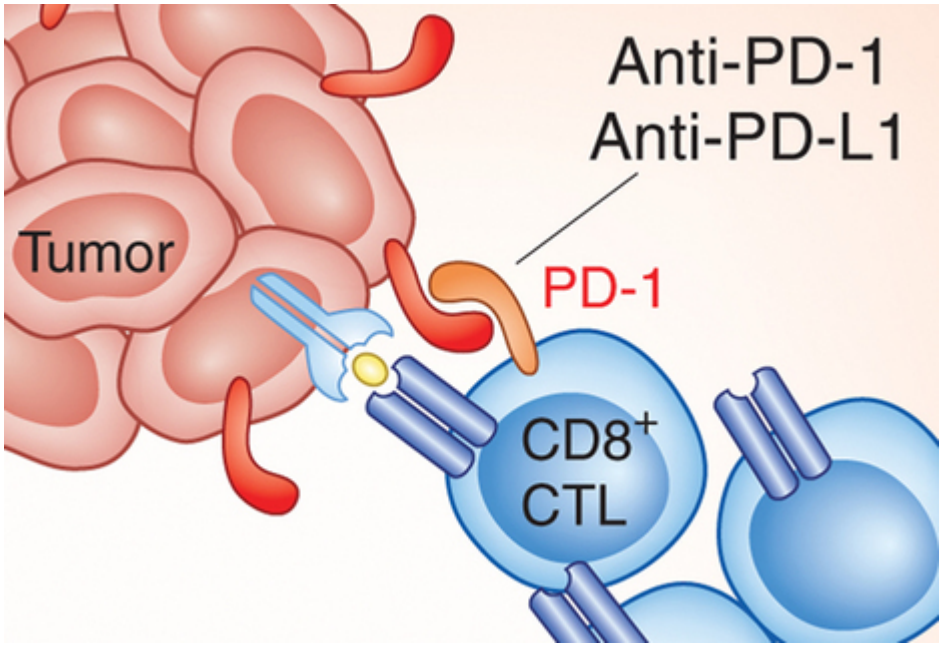
Brentuximab pre-allo: post-transplant clinical outcomes

- The addition of BV did not adversely affect engraftment, GVHD or OS

	N=19
Median follow-up, months	25.6
2 - year OS, %	79.3 (CI: 56.0, 91.1)
2 - year PFS, %	59.3 (CI: 43.9, 71.7)
2 – year PFS in CR patients, %	71.4 (CI: 40.3, 88.3)
2 - year PFS in non-CR patients, %	54.6 (CI: 37.5, 68.9)

Chen R et al. Oral presentation at ICML 2013, Lugano, Switzerland

PD-1 inhibitors



Nivolumab
Pembrolizumab

↓

ORR 53%-87%

Safety and Efficacy of Allogeneic HSCT after Treatment with Programmed Cell Death 1 (PD-1) Inhibitors

Merryman et al ASH 2015

- Retrospective analysis of alloSCT outcome after PD-1 inh (nivolumab or pembrolizumab)

Characteristics	N=19 (11 HL)
Number of treatment lines prior to antiPD-1	4 (2-8)
Prior ASCT	79%
Cycles of antiPD-1	8 (3-20)
Salvage therapy between antiPD-1 and alloSCT	74%
Time between last dose of antiPD-1 and alloSCT	130 days (7-260)
Disease status at transplant: CR / Refractory	63% / 16%
RIC regimen	100%

Safety and Efficacy of Allogeneic HSCT after Treatment with Programmed Cell Death 1 (PD-1) Inhibitors

Merryman et al ASH 2015

- **Toxicity**
  - 3 cases of VOD (16%) à one fatal
  - 180-day CI of acute GVHD I-II 32%, III-IV 11%
  - 1 year CI of chronic GVHD 30%
  - 4 treatment-related death: 1 VOD, 3 severe acute GVHD within 14 days of transplant
  - 6 patients: febrile syndrome with elevated transaminases (n=3), rash (n=4), and arthralgias (n=1) shortly after transplant

- **Eficacy**
  - Relapse 3 patients
  - Median follow-up 10 (3-23) months à 1y OS 78%, PFS 67%
  - 1year CI of relapse 11%
  - 1year CI of NRM 22%

Conclusions

- The introduction of **PET** in the evaluation of disease status before ASCT and of **new drugs** is “already changing” the landscape of relapsed / refractory HL

- Results of **ASCT** will improve with:
  - Better selection of ASCT candidates
  - Better disease response before ASCT
  - Maintenance tx after ASCT in high risk patients

- With respect to **allo-SCT**:
  - More information is needed
  - BV can improve the results of allo-SCT if used as a “bridge to”
  - Caution should be taken with the use of check point inhibitors
  - Outcome of haplo-SCT do not seem to differ from “standard sources”