Integrazione dei nuovi farmaci nel programma trapiantologico dei linfomi: un caso clinico

Massimo Martino (Reggio Calabria)

STORIA CLINICA (1)

- Paziente di 42 anni, maschio; normopeso; forte fumatore (circa 30 sigarette al giorno); non bevitore di alcolici
- ***Professione*** : Assicuratore; Ciclista amatoriale
- ***Anamnesi Familiare***: Padre deceduto per neoplasia polmonare, madre in abs, due germani in abs, un figlio di 5 anni in abs
- ***Anamnesi Pat. Remota***: Nessuna rilevante comorbiditia, ad eccezione di una rinocongiuntivite allergica
- ***Anamnesi Patologica Prossima***: Dicembre 2011, dopo un intenso allenamento in bicicletta, comparsa di prurito diffuso. Assume antistaminico ed il prurito nei primi giorni si attenua in maniera significativa per poi ricomparire. Successivamente la sviluppa una tosse secca, febbricola (37.5°C), sudorazione notturna.

STORIA CLINICA

Gennaio 2012: si reca al P.S. del nosocomio cittadino per una crisi recidivante di dispnea ed il riscontro fortuito di una tumefazione in regione sovraclaveare sinistra

Esame obiettivo: presenza di edema sottocutaneo del volto con turgore delle vene giugulari; modesto pallore cutaneo; linfoadenomegalie laterocervicali a sinistra di circa 2 cm; ipofonesi plessica e assenza del fremito vocale tattile e del murmure vescicolare in regione interscapolo-vertebrale e sottoscapolare sinistra

Radiografia del torace: presenza di versamento pleurico basale sinistro e slargamento del mediastino superiore soprattutto a destra.

Il paziente è ricoverato in reparto di Chirurgia Toracica

ITER DIAGNOSTICO

Ematochimica: Emocromo: Globuli Bianchi 15.000 mmc (N.76%, E.15%, L6%, M3%), Hb 11.5 gr/dl normocromica, normocitica, Piastrine 445.000 mmc; LDH 1032 U/L, Ferritinemia alta, transferrina bassa, sidermia bassa; Beta 2 microglobulinemia 3 mg/L, HIV, HCV, HBV, TOXO, CMV ed EBV negativi per infezioni attive, VES 60 mm/h

TAC del torace e dell'addome: conferma del versamento pleurico e della presenza di linfoadenomegalie nel mediastino antero-superiore (no bulky), escludendo linfoadenomegalie addominali e/o l'interessamento viscerale epato-splenico

Esame citologico del liquido pleurico: presenza di linfociti, granulociti eosinofili, istiociti e cellule mesoteliali iperplastiche, ma non cellule con caratteri di malignità.

Chiesta consulenza ematologica

ITER DIAGNOSTICO

Si decise di sottoporre il paziente alle seguenti indagini diagnostiche:

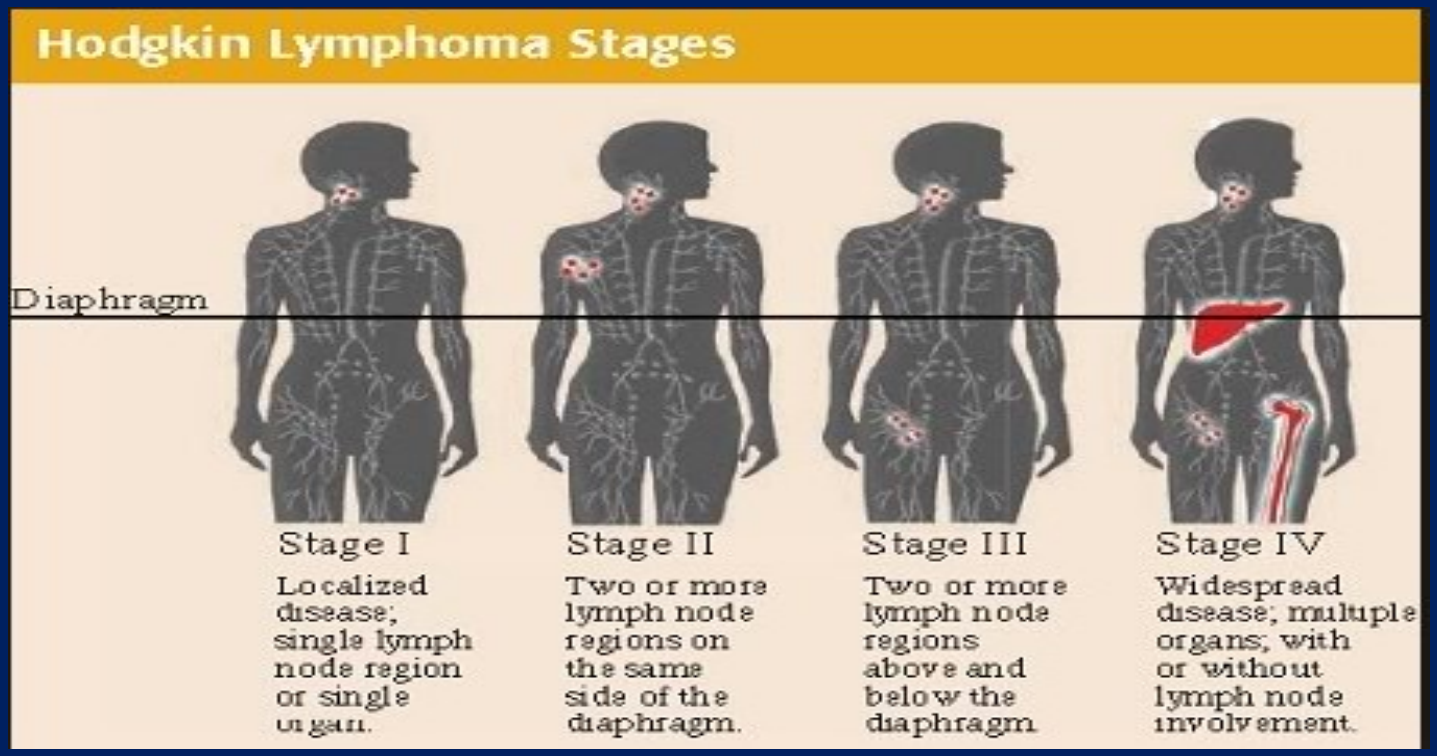
a) ***Biopsia linfonodale laterocervicale sinistra:*** diagnosi istologica di Linfoma di Hodgkin classico-varietà scleronodulare

b) ***Biopsia osteo-midollare:*** quadro complessivo di ipocellularità, con infiltrato linfo-plasmacellulare reattivo

c) ***Esame citofluorimetrico su sangue midollare***: presenza di linfociti T (CD3+, CD5+, con rapporto CD4/CD8 0.6) e linfociti B (CD19+, CD20+), con normale rapporto di distribuzione fra le varie popolazioni

d) ***18-FGT PET-TC*:** conferma di linfoadenomegalie sovraclaveari e nel mediastino antero-superiore

DIAGNOSI



Linfoma di Hodgkin classico-varietà scleronodulare

Stadio clinico di Ann Arbor: II B

Unfavorable (VES e sintomi B)- No-bulky disease

TRATTAMENTO DI PRIMA LINEA

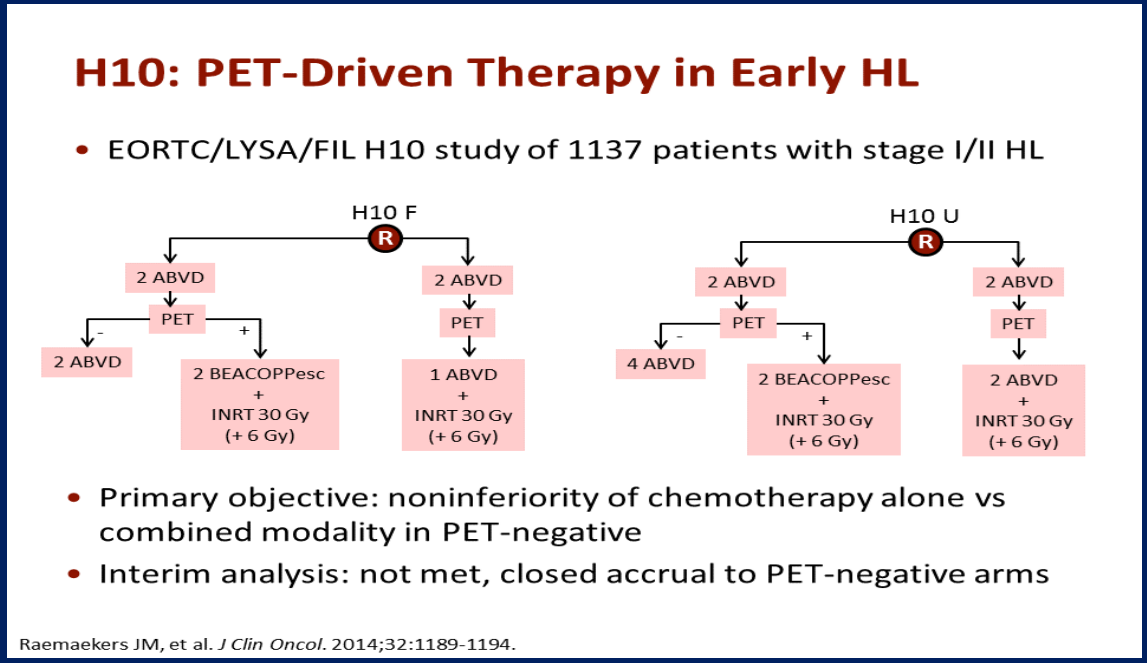
Marzo 2012

ABVD 2 cicli

(interim PET)

ABVD 4 cicli

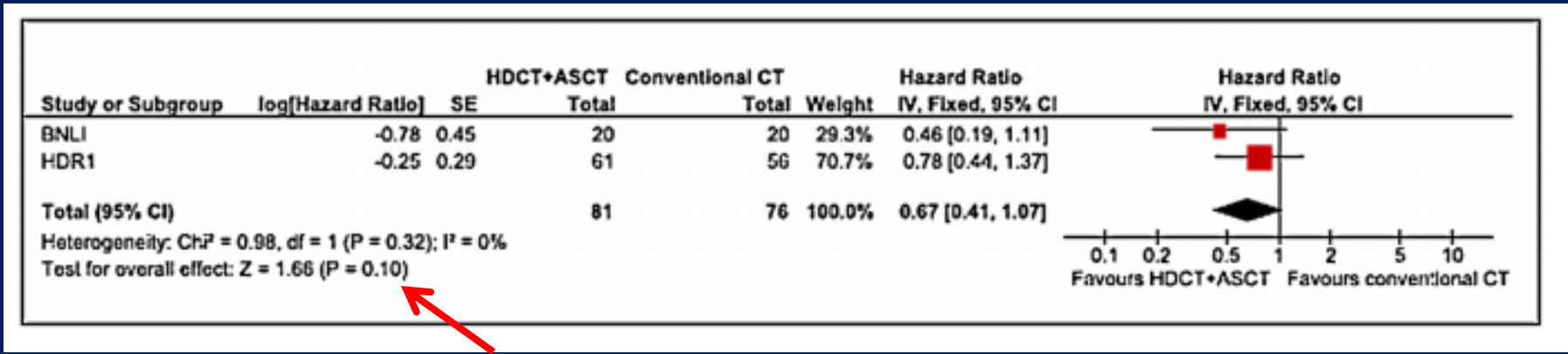
Agosto 2012



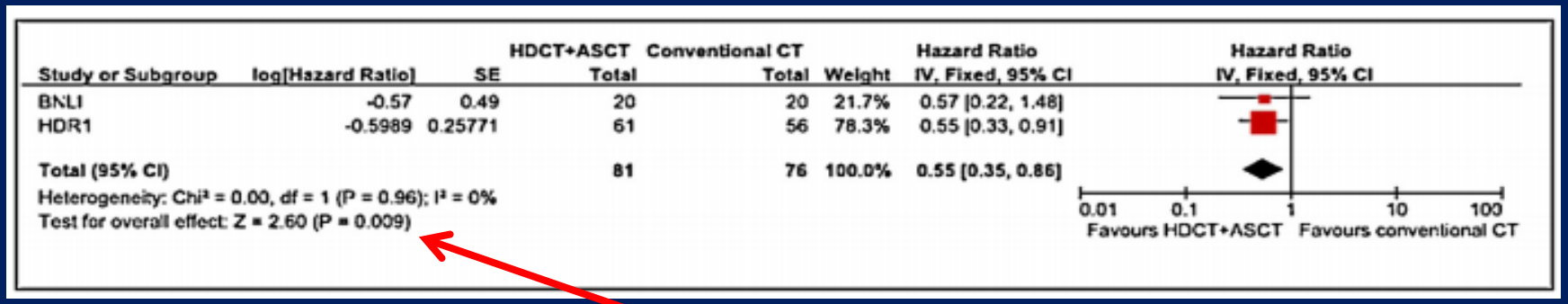
- La sintomatologia riferita, l'edema del volto, il turgore delle vene giugulari e le linfoadenomegalie laterocervicali regredirono dopo 2 cicli.
- Interim PET, dopo 2 cicli : negativa
- PET-CT dopo 6 cicli: adenopatie iperfissanti in regione sovra-retroclaveare e base collo sx, ilo polmonare

Treatment for relapsed/refractory HL patients

Currently, the standard of care is salvage chemotherapy followed by high-dose chemotherapy and consolidation with ASCT



. **Forest-plot for overall survival.**



Forest plot: progression-free survival

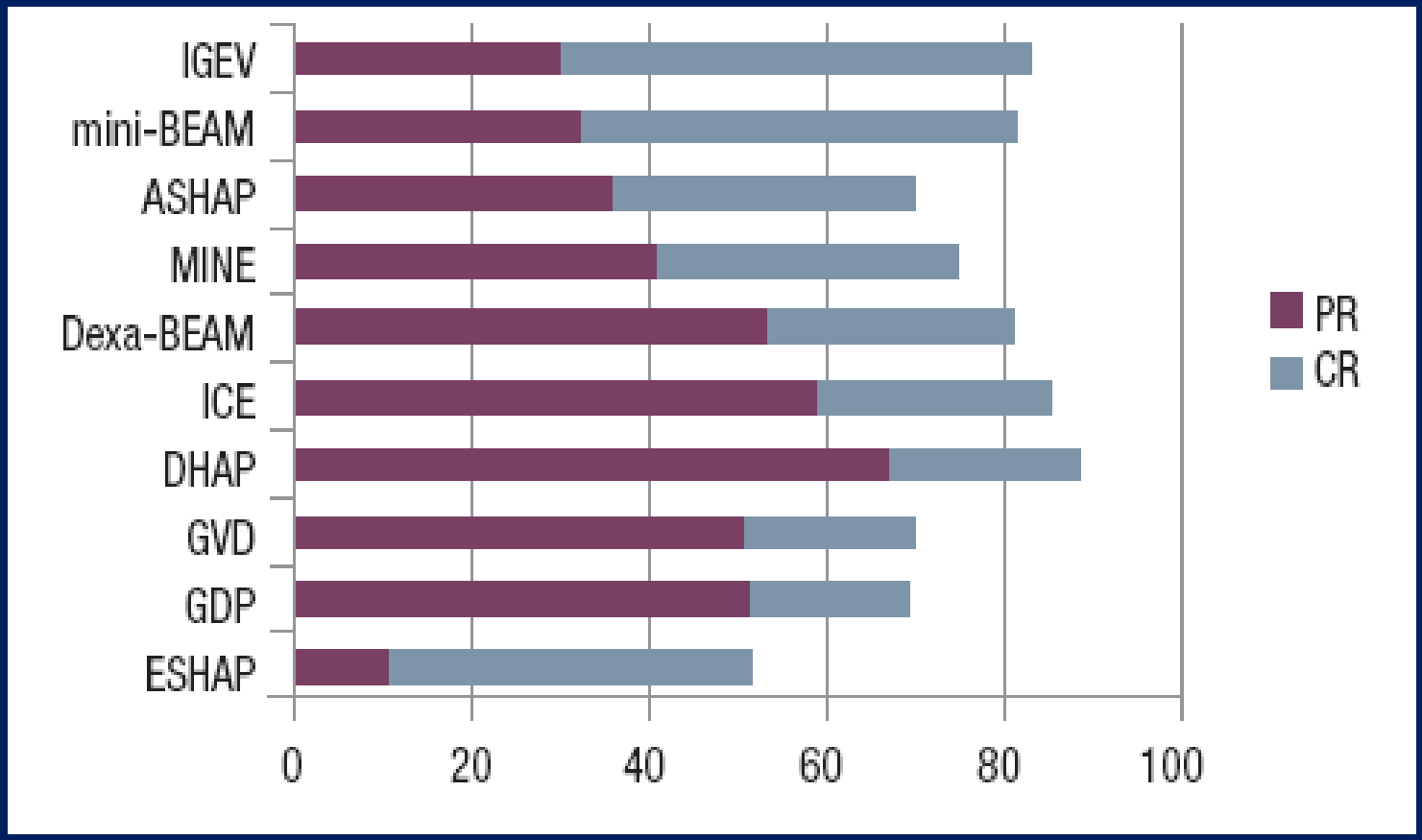
High-dose chemotherapy followed by autologous stem cell transplantation for patients with relapsed or refractory Hodgkin lymphoma: A systematic review with meta-analysis

M. Rancea et al. / Critical Reviews in Oncology/Hematology 92 (2014) 1–10

Treatment for relapsed/refractory HL patients

Several questions remain:

First, which salvage chemotherapy do we use?



CHEMIOTERAPIA DI SALVATAGGIO

Settembre-Dicembre 2012:

IGEV (Ifosfamide, gemcitabina, vinorelbina e prednisolone) 4 cicli.

Collezione cellule stamminali al 2° ciclo (10**x10^6 CD34+ cells/kg)**.

Several questions remain: Which salvage chemotherapy?

BV + ESHAP as Second-Line Salvage Chemotherapy Before ASCT (BRESHAP)

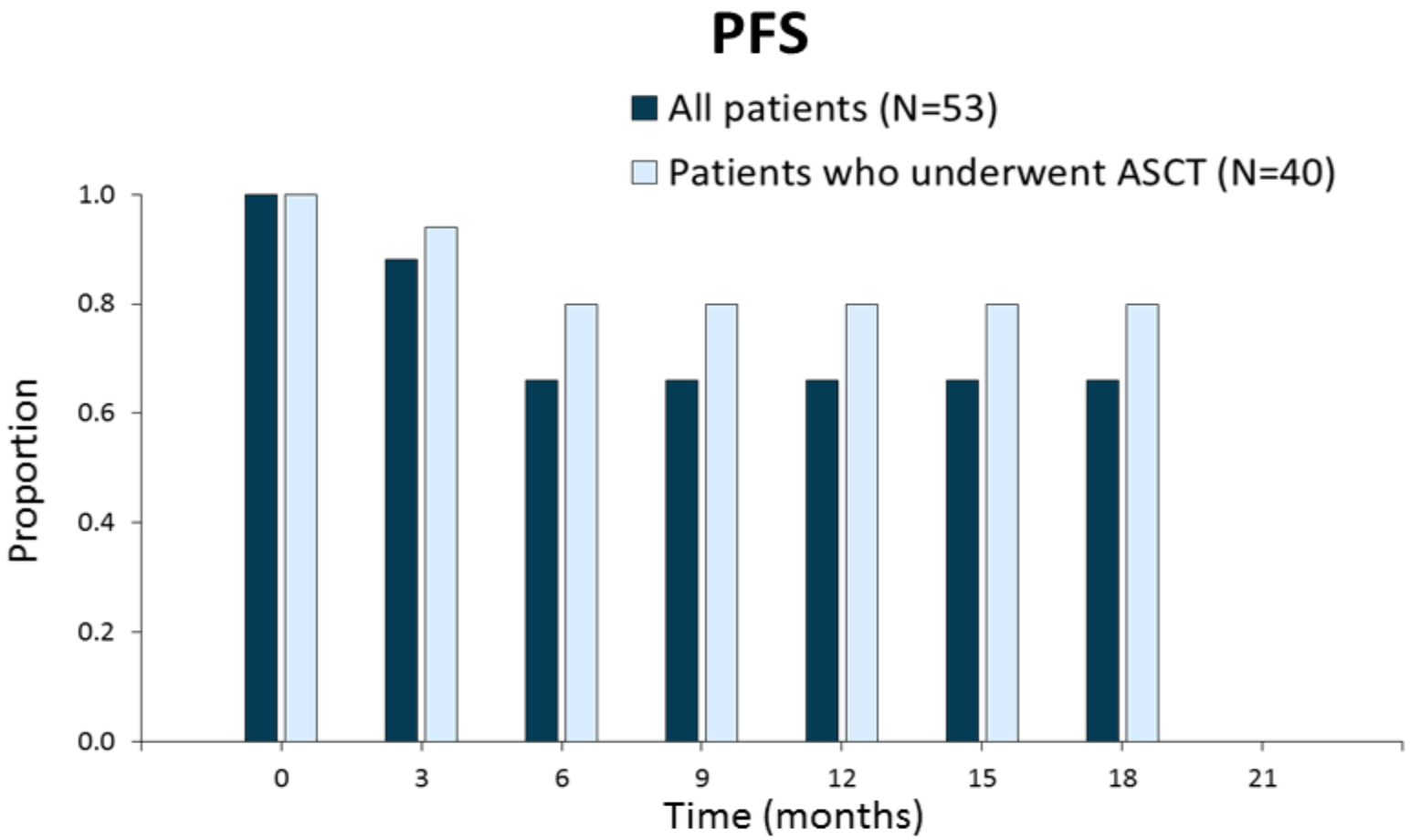
- Phase 1/2 (n=70) GELTAMO study of 3 doses of BV (09-1.8 mg/kg) + ESHAP as salvage chemotherapy after 1 prior therapy
- Initial results of phase 1

Patients	• 9 evaluable for response after 3 cycles
Grade ≥3 AEs	• 2 neutropenia, 1 thrombocytopenia
Stem cell mobilization	• 9/9 after first or second cycle, with no Grade ≥3 AEs
PET-CT before ASCT	• 8/9 no evidence of disease • 1 PET-positive with no lesions on CT
ASCT	• 6/9 transplanted; median 9 days neutrophil recovery, 10 days platelet recovery • All 9 patients reached CR after ASCT

Garcia-Sanz R, et al. ASH 2015. Abstract 582.

Several questions remain: Which salvage chemotherapy?

BV + Bendamustine as Salvage Chemotherapy Before ASCT



LaCasce AS, et al. ASH 2015. Abstract 3982.

Several questions remain: Which salvage chemotherapy?

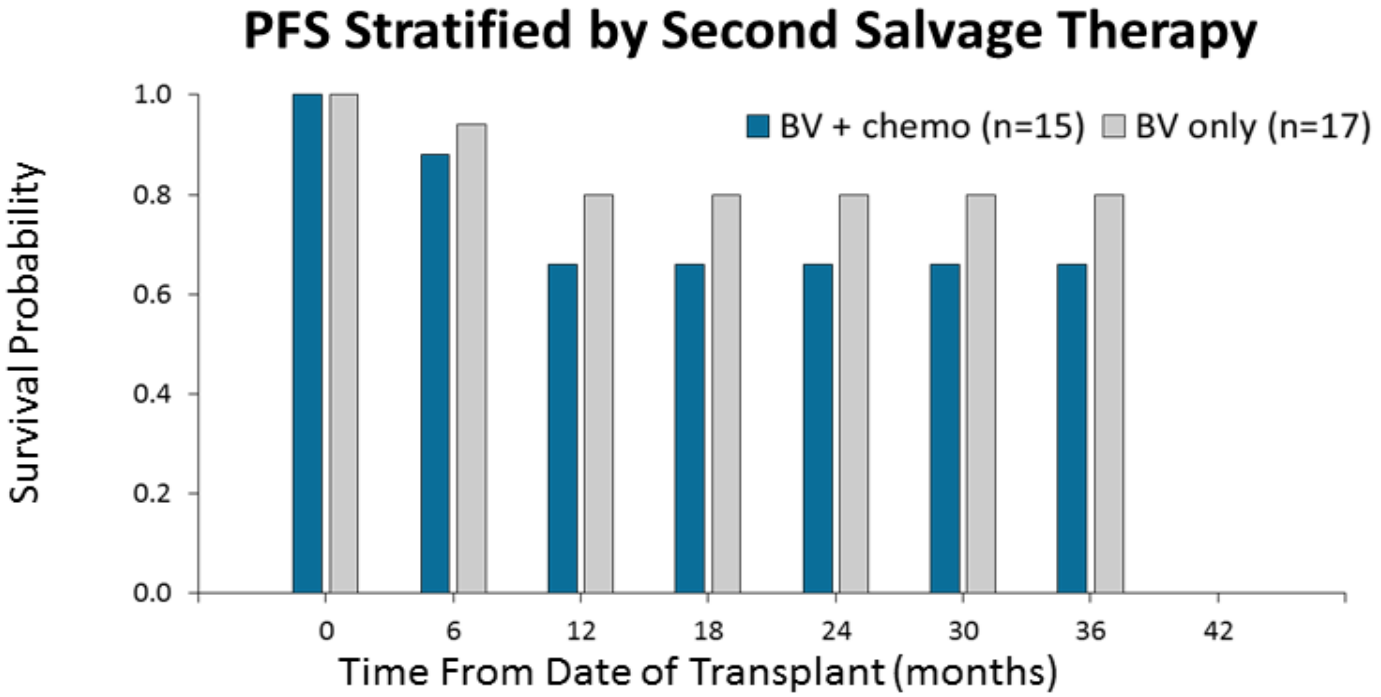
BeGEV as Salvage Chemotherapy Before ASCT (Bendamustine, Gemcitabine And Vinorelbine)

Responses	• ORR 83%, CR 73%
2-year survival	• Overall: PFS 51%, OS 69% • In responders: OS 86% • OS was higher for BeGEV-responding (CR+PR) patients compared with those in whom the induction regimen failed (2-year OS: 86% vs 0%, *P*<.001)
ASCT	• 43 (88%) patients transplanted • Median 11 days neutrophil recovery • 12 days platelet recovery
Grade ≥3 AEs	• 7 febrile neutropenia • 4 infection • 8 thrombocytopenia and neutropenia

Santoro A, et al. ASH 2015. Abstract 581.

Several questions remain: Which salvage chemotherapy?

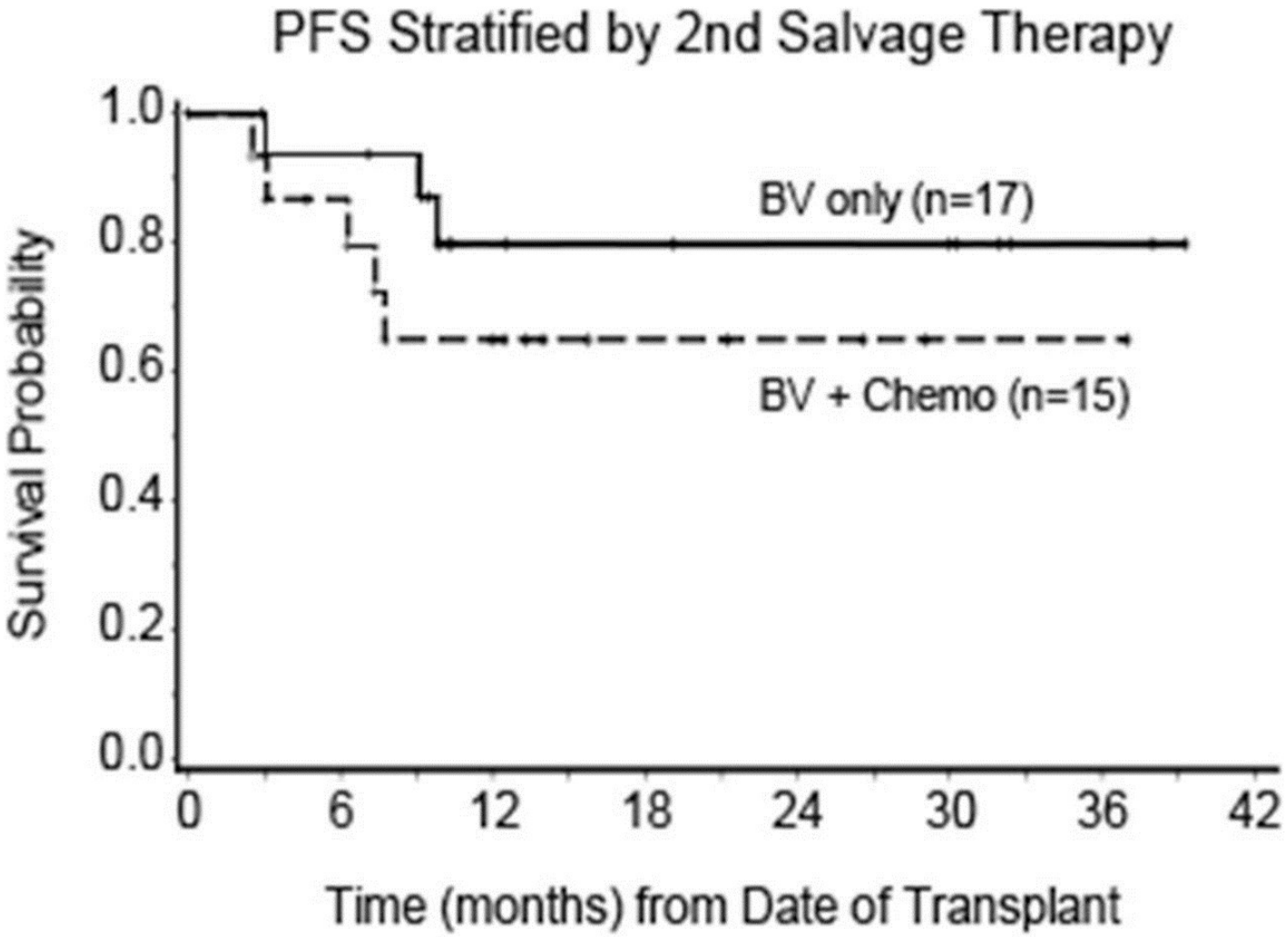
BV (+ Chemotherapy) as First-Line Salvage Before ASCT



18-month results by CR status	• PFS=78% CR, 50% non-CR • OS=89% CR, 88% non-CR
18-month PFS by additional chemotherapy	• PFS=80% BV only • 65% BV + chemotherapy

Chen R, et al. ASH 2015. Abstract 519.

Several questions remain: Which salvage chemotherapy?



Robert Chen et al. Blood 2015;126:519

CHEMIOTERAPIA DI SALVATAGGIO

Settembre-Dicembre 2012:

IGEV (Ifosfamide, gemcitabina, vinorelbina e prednisolone) 4 cicli.

Collezione cellule staminali al 2° ciclo (10**x10^6 CD34+ cells/kg)**.

18F-FDG PET scan pre-trapianto : riduzione globale della captazione a livello delle precedenti sedi linfonodali → risposta parziale

ALTE DOSI DI CHEMIOTERAPIA

Non donatore disponibile (1 sorella HLA compatibile al terzo mese di gravidanza; 1 fratello aploidentico; attivazione registro MUD)

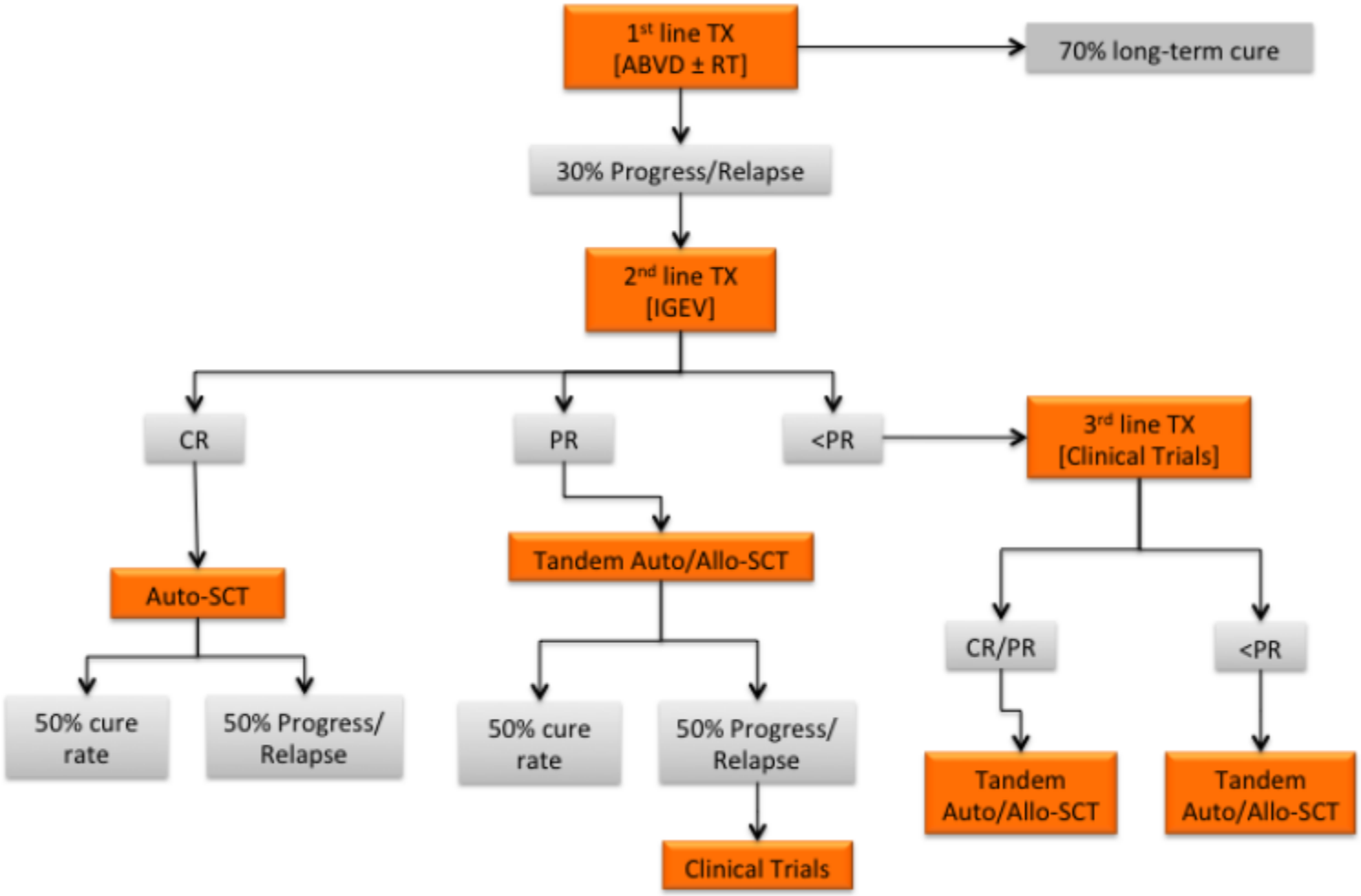
Febbraio 2013:

Alte dosi di chemioterapia (Condizionamento FEAM– Fotemustine, Etoposide, Citarabina e melphalan) + ASCT (reinfusione di 5 x10^6 CD34+/kg). Mucosite WHO 3, Nausea/Vomito WHO 2, Diarrea WHO 1

Maggio 2013: (3 mesi post-ASCT)

18F-FDG PET: Remissione Completa

Treatment algorithm for relapsed/refractory cHL



Castagna *et al*. Mediterr J Hematol Infect Dis 2015

FOLLOW-UP

Novembre 2013: (8 mesi post-ASCT)

18F-FDG PET scan: captazione del segnale a livello sovraclavicolare dx laterocervicale sx (SUV 4.6). Esame Obiettivo: linfoadenopatie palpabili. Biopsia linfonodale: Conferma della recidva

Treatment for relapsed/refractory HL patients

- **Several questions remain:**

  which patients do we treat with standard of care?

  which patients do we consider to be high-risk?

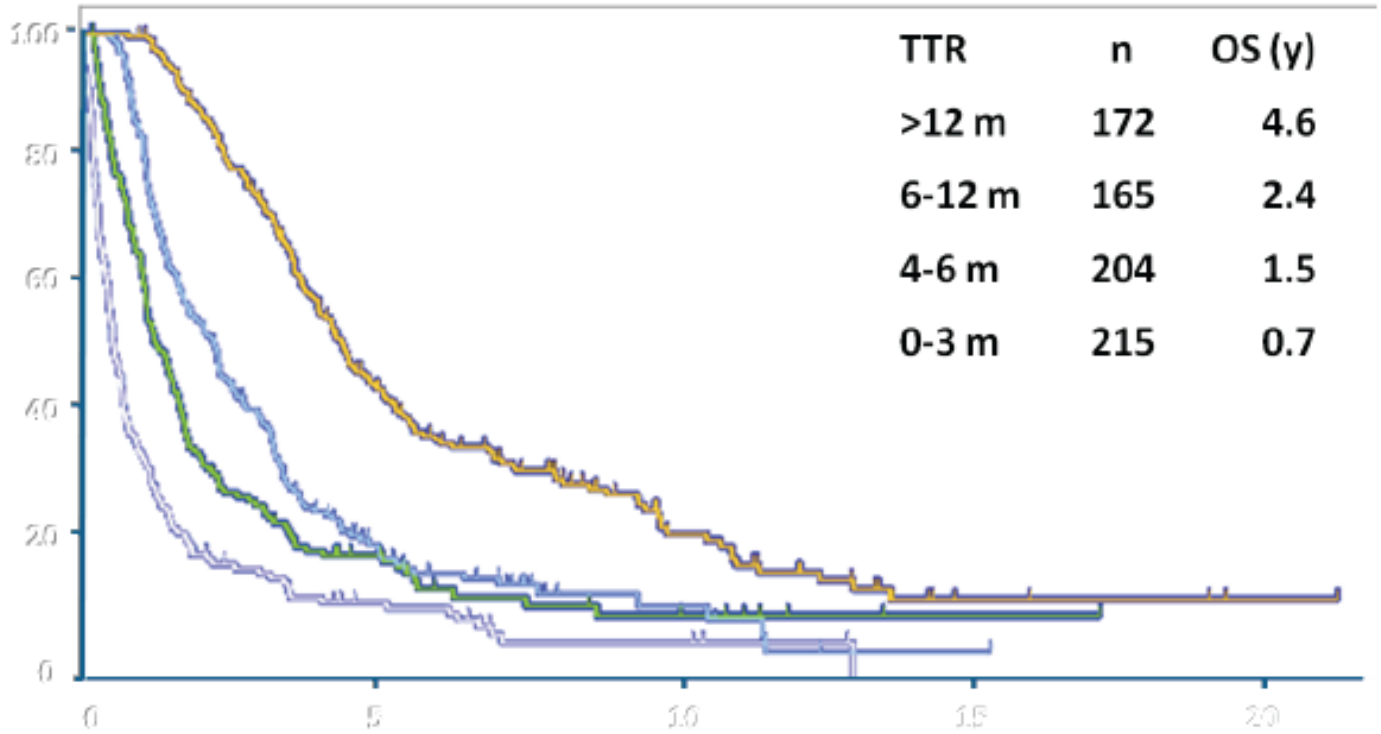
Which patients do we consider to be high-risk?

Defining the High-risk Relapsed/Refractory HL Patient

Author	n	Factor	Outcome
Brice, et al. 1997	214	– Time to relapse (≤12 m vs > 12 m) – Stage III or IV at relapse – Relapse within previously irradiated sites	0 RF: 4-yr OS 93% 1 RF: 4-yr OS 59% 2 RF: 4-yr OS 43%
Josting, et al. 2002	422	– Time to relapse (≤12 m vs > 12 m) – Stage III or IV at relapse – Anemia at relapse	0/1 RF: FF2F 45% 2 RF: 32% 3 RF: 18%
Moskowitz, et al. 2001	65	– B symptoms – Extranodal disease – CR < 12 mo	0/1 RF: EFS 83% 2 RF: 27% 3 RF: 10%
		– Chemosensitivity	Very adverse factor in many analyses

The different scores are based on the most important factors: early relapse, (relapsing within the first year after first-line therapy), refractory disease, and tumor burden (higher risk with higher disease tumor burden)

Overall Survival After Relapse After Autologous Stem Cell Transplantation

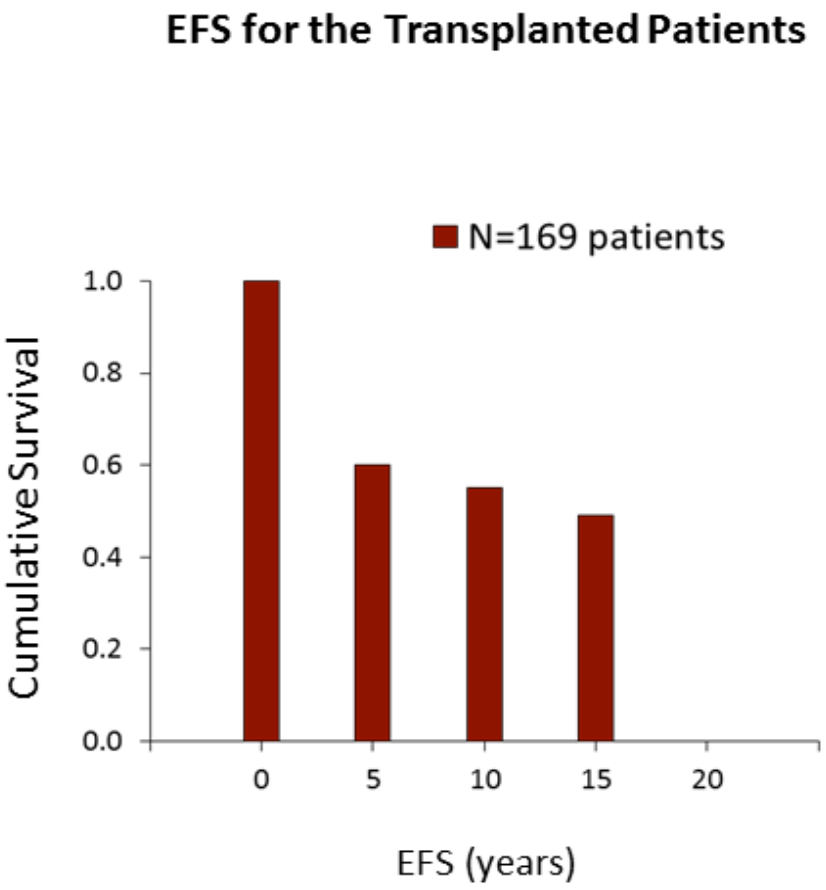


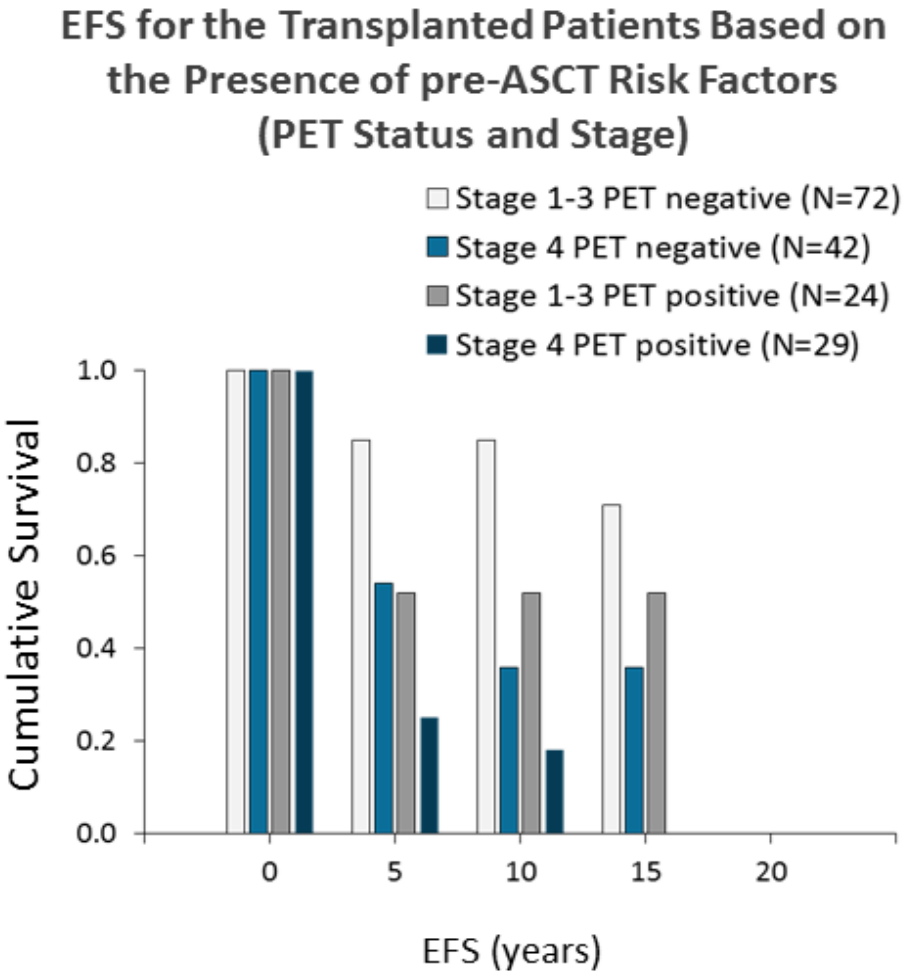
An analysis of 800 patients from Europe and the United States showed that three-quarters of patients relapsed within the first year after high-dose chemotherapy,

Arai S, et al. *Leuk Lymphoma. 2013;54(11):2531-2533*

Which patients do we consider to be high-risk?

Predictors of Response in Primary Refractory HL





Shah GL, et al. ASH 2015. Abstract 520.

Which patients do we consider to be high-risk?

RisPACT: Risk Factors Post-ASCT

- **Goal:** identify and validate risk factors for survival post-ASCT
- **Patient population:** 656 patients treated with single ASCT, plus separate validation cohort of 390 patients
- **Risk factors represent different dimensions:**
  - Spread of disease = stage IV disease
  - Proliferation rate = time to relapse ≤ 3 months
  - Patient constitution = ECOG PS ≥ 1
  - Tumor mass = bulk ≥ 5 cm
  - Chemosensitivity = nonresponse to salvage therapy (< PR or PET-positive residues)

Bröckelmann PJ, et al. ASH 2015. Abstract 1978.

Which patients do we consider to be high-risk?

Prognostic Score for PFS After ASCT in HL

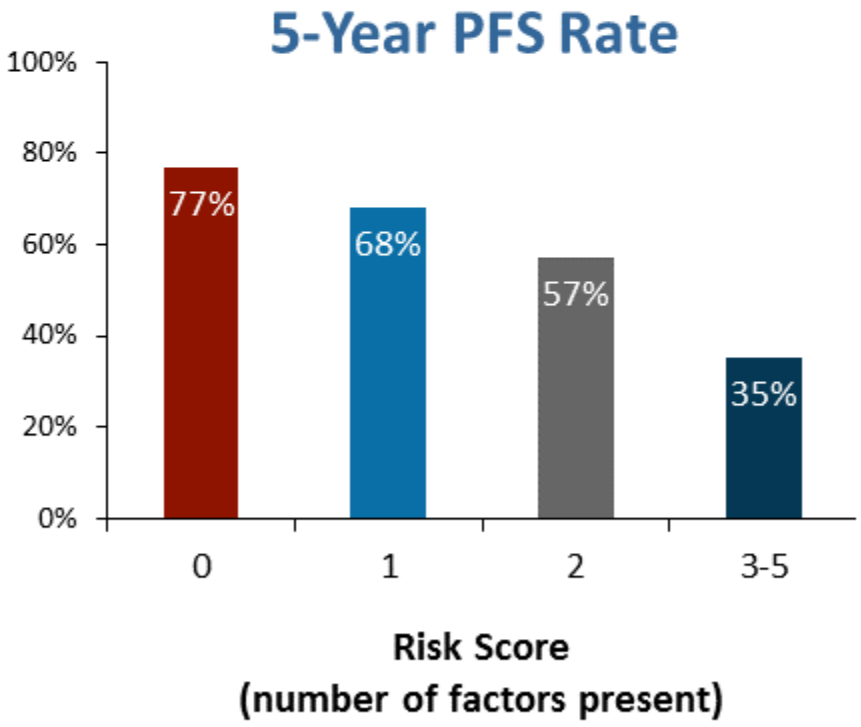
	5-Year PFS	5-Year OS	Multivariate Analysis
Stage IV disease			
Yes	66.9%	76.6%	
No	48.1%	58.1%	HR 1.85, *P*=.0009
TTR ≤3 months			
Yes	63.7%	75.4%	
No	45.6%	47.9%	HR 1.96, *P*=.0261
ECOG PS ≥1			
Yes	65.8%	76.0%	
No	55.4%	68.2%	HR 1.51, *P*=.0392
Bulk ≥5 cm			
Yes	66.9%	76.0%	
No	50.2%	64.2%	HR 1.60, *P*=.0114
<PR to salvage chemotherapy			
Yes	65.9%	77.3%	
No	46.8%	58.0%	HR 1.59, *P*=.0416
Prognostic score			
0	76.8%	87.7%	
1	67.9%	79.1%	HR 1.58, *P*=.0764
2	56.7%	70.0%	HR 2.33, *P*=.0012
3-5	34.8%	46.5%	HR 5.04, *P*<.0001

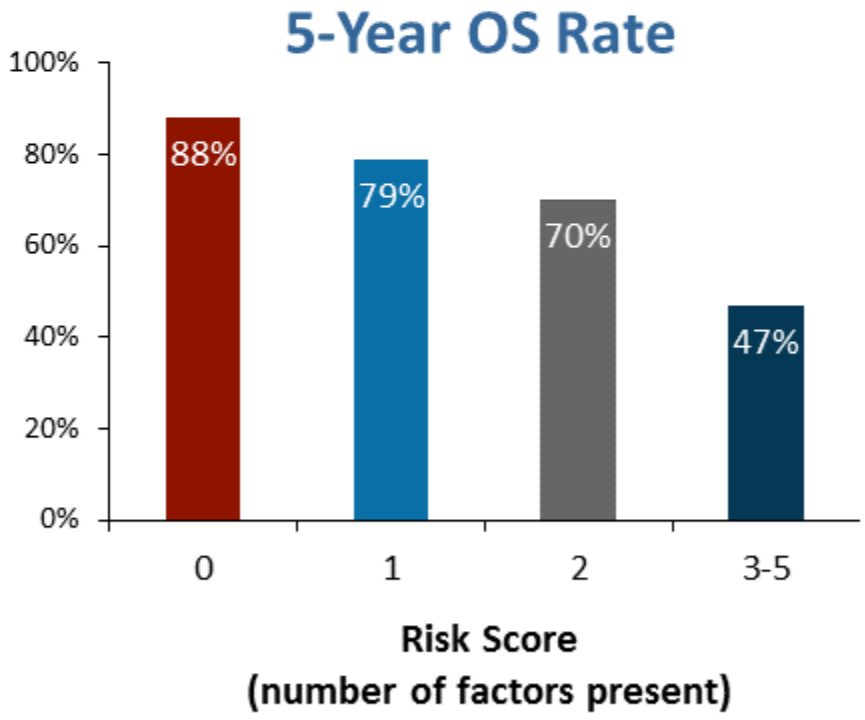
Bröckelmann PJ, et al. ASH 2015. Abstract 1978.

Which patients do we consider to be high-risk?

RisPACT: Risk Factors Post-ASCT (cont)

- **Prognostic score:** increasing number of equally weighted factors predicts poorer prognosis





Bröckelmann PJ, et al. ASH 2015. Abstract 1978.

Improving the Outcome of High-risk Patients

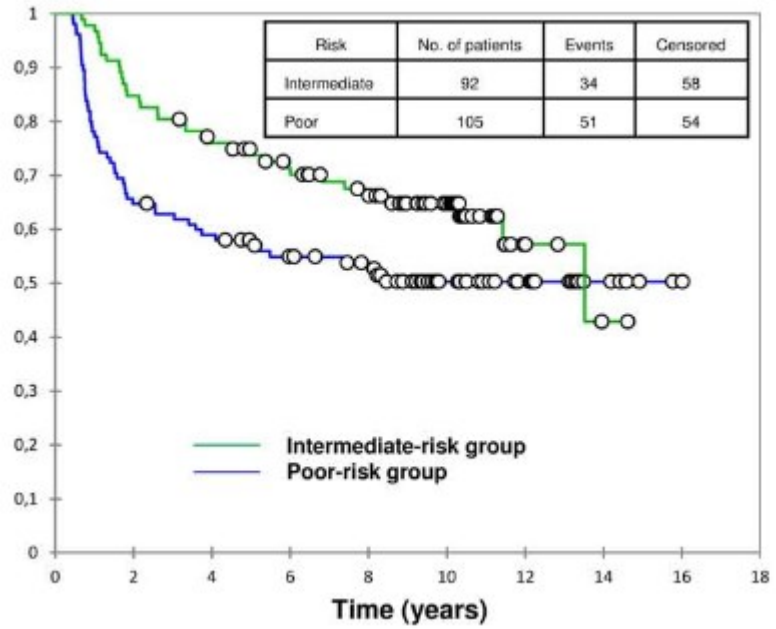
Treatment strategies that focus on intensification:

1. *Tandem transplantation*: phase 2 data only

2. *PET response adapted*: phase 2 data only

3. *Brentuximab vedotin*: phase 3 data

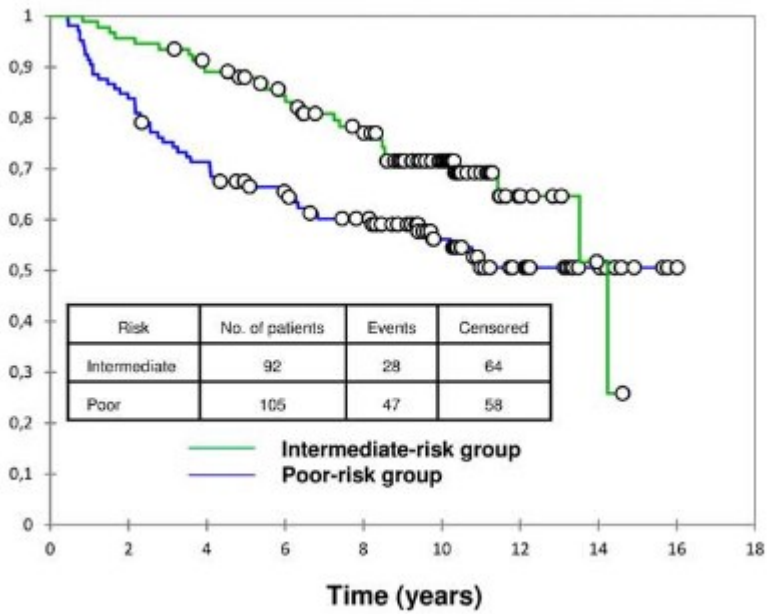
Outcomes of patients completing autologous stem-cell transplantation.



Freedom from second failure (FF2F)

Risk assessed at the onset of salvage treatment based on:

- ✓ primary refractory status
- ✓ number of risk factors at first relapse
  - relapse <12 months after the end of first-line treatment,
  - stage III or IV at relapse,
  - and/or relapse in previously irradiated site (>30 Gy)



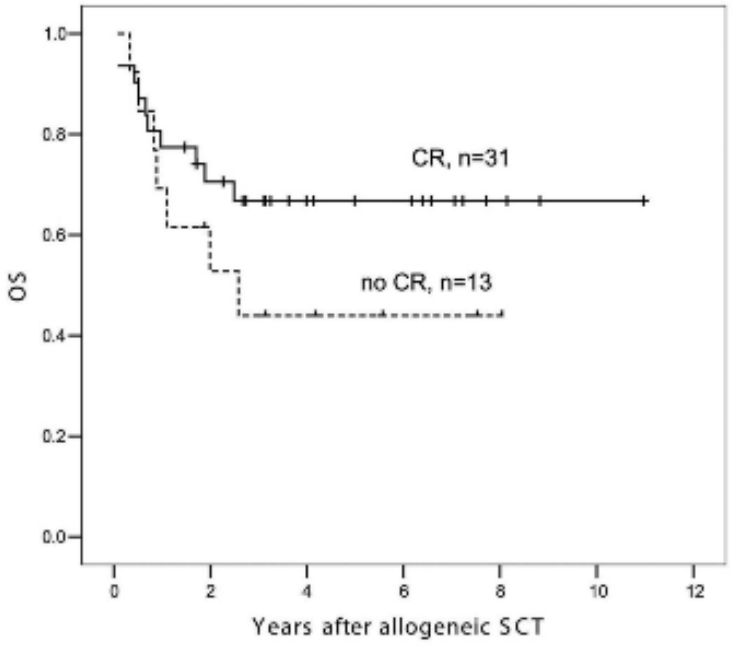
overall survival

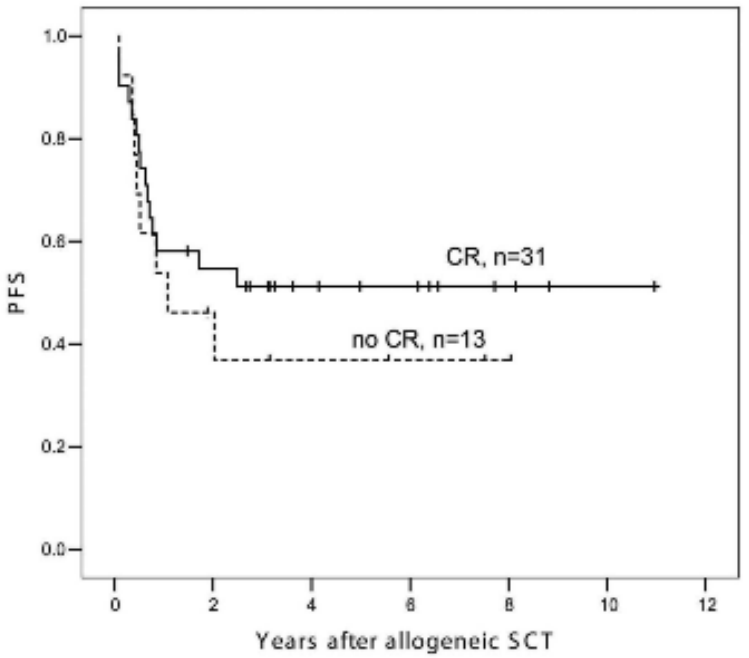
Poor-risk group: primary refractory HL or two or more risk factors at relapse;
Intermediate-risk group: only one risk factor at relapse.

Single Or Tandem Autologous Stem-Cell Transplantation For First-Relapsed Or Refractory Hodgkin Lymphoma: 10-Year Follow-Up Of The Prospective H96 Trial By The LYSA / SFGM-TC Study Group

Sibon *et al*. Haematologica. 2015 Dec 31

Tandem autologous-allogeneic stem cell transplantation as a feasible and effective procedure in high-risk HL patients.





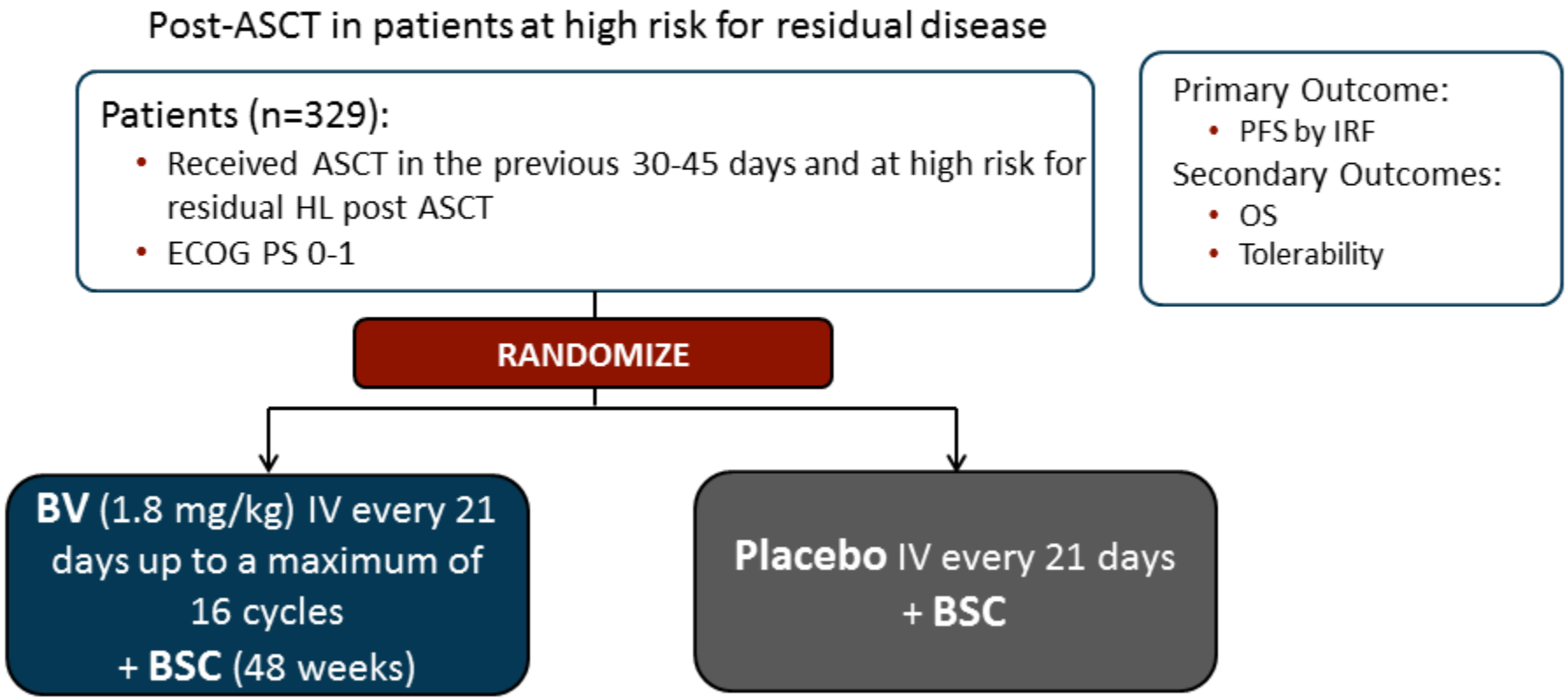
OS according to CR *vs. active disease* *before allogeneic SCT in HL patients(n=44): 67% (95%CI: 50-84) vs. 44% (95%CI: 16-72)*

PFS according to CR *vs. active disease* before allogeneic SCT in HL patients (n=44): 51% (95%CI: 33-69) vs. 37% (95%CI: 10-64)

Crocchiolo *et al*. Haematologica 2015; 100:e425

AETHERA Study Design

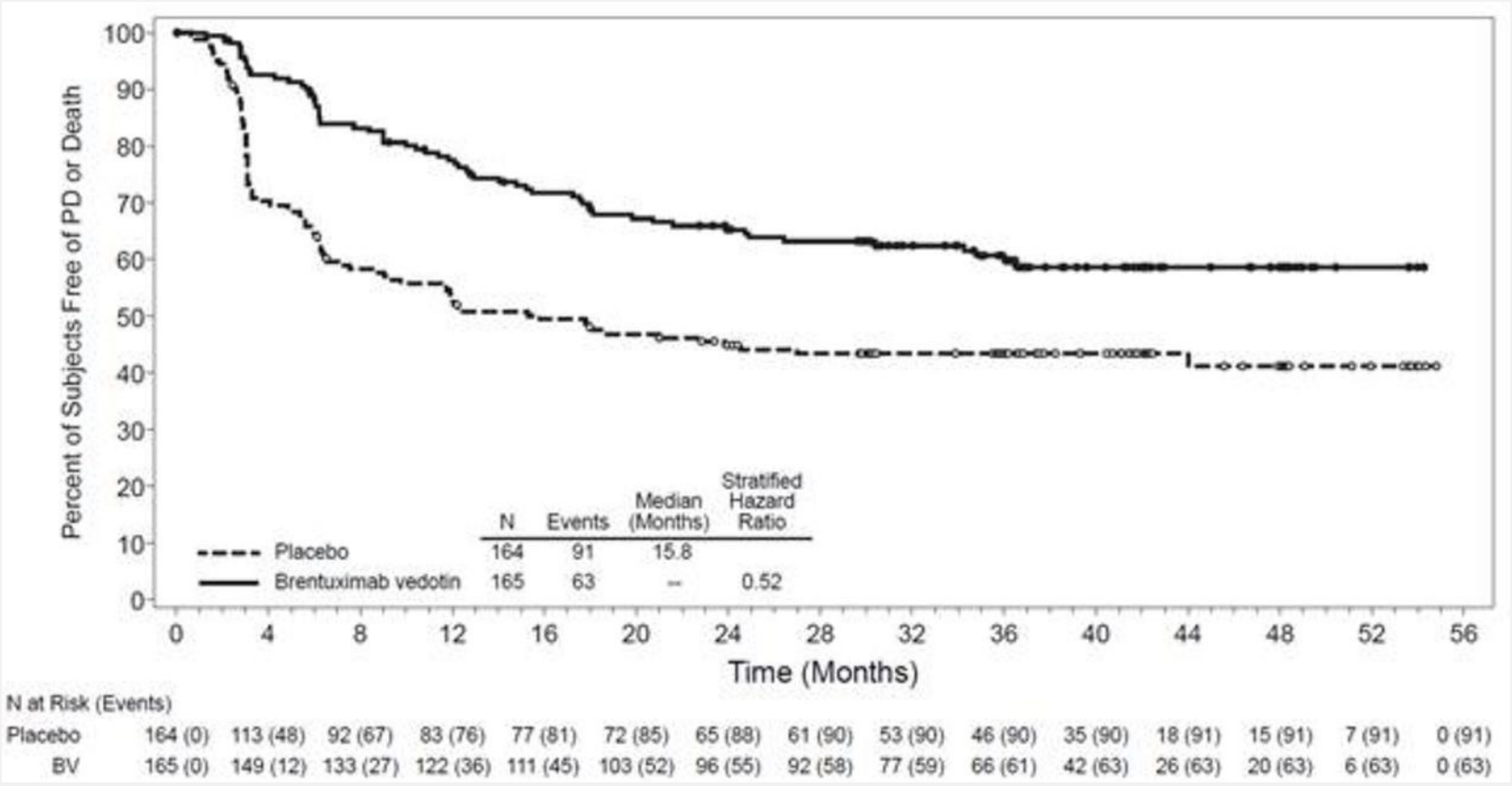
A randomized, double-blind, placebo-controlled, phase 3 study of BV and BSC vs placebo and BSC in the treatment of patients at high risk for residual HL following ASCT



Moskowitz CH, et al. *Lancet.* 2015;385:1853-1862.

Additional 1-Year Update on AETHERA

Progression-Free Survival per Investigator Assessment.



Sweetenham et al. Blood 2015;126:3172

TRATTAMENTO DI TERZA LINEA

Dicembre 2013: Brentuximab vedotin 1.8 mg/kg x 14 cicli ogni 21 giorni (Neuropatia sensoriale periferica di grado lieve; Fatigue).

18F-FDG PET scan (dopo il 3° ciclo): riduzione del metabolismo a livello delle documentate linfoadenopatie sovra-claveari; due aree di aumentato metabolismo a livello del polmone di destra (possibile espressione di infiammazione).

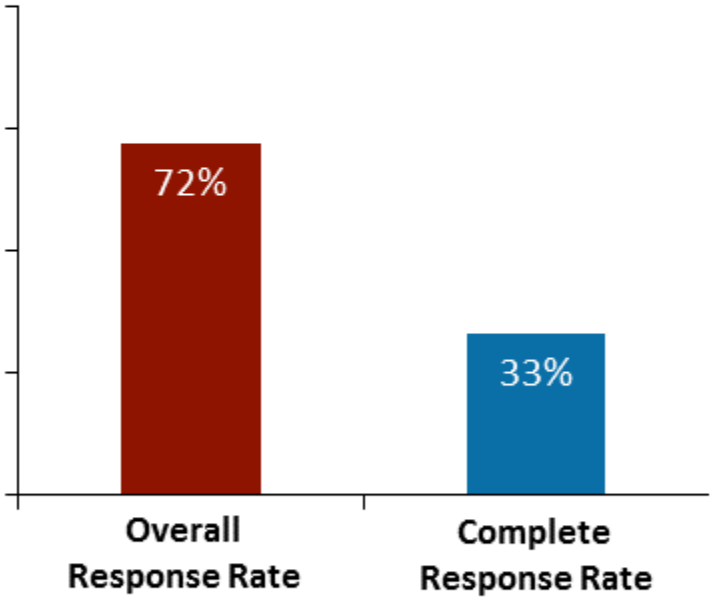
18F-FDG PET scan (dopo il 6° ciclo): due nuove aree di aumentato metabolismo a livello paratracheale destro. Esame negativo a livello sovraclaveare e laterocervicale.

18F-FDG PET scan (dopo il 13 ciclo): negativa

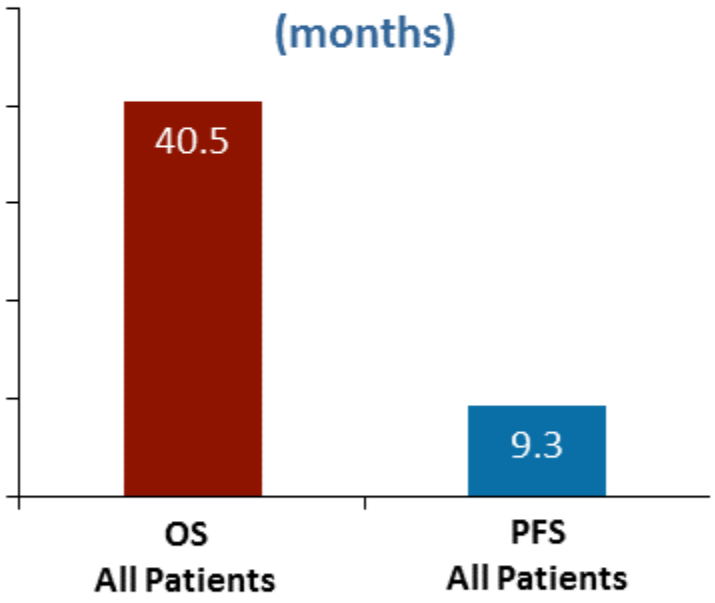
Long-term Outcomes With Brentuximab Vedotin Post-ASCT

Final 5-Year Results of Pivotal Trial

Response Rates



Median Survival (months)



- Median OS and median PFS not reached in patients achieving CR

Chen R, et al. ASH 2015. Abstract 2736.

ALLOGENEIC STEM CELLS TRANSPLANTATION

Effettuato in remissione completa nel Novembre 2014.

Donatore: 34 anni , femmina, germano, matched.

Condizionamento: Thiotepa, Fludarabina, Ciclofosfamide

Profilassi GVHD: ciclosporina A e metotrexate.

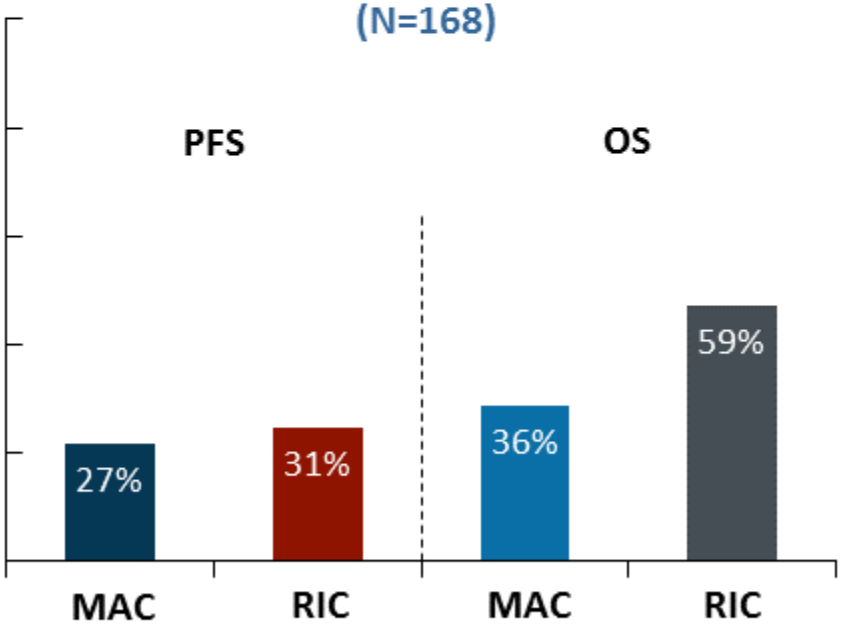
No GVDH acuta.

December 2015: Remissione Completa. GVHD Cronica limitata

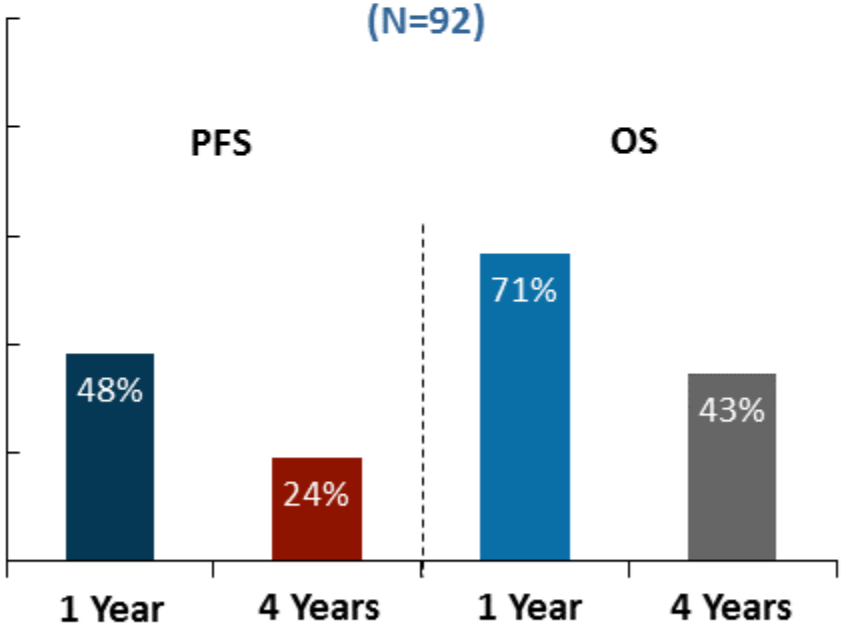
Allogeneic Transplantation in HL

- **Most common use:** Post-ASCT in young patients with chemosensitive disease[a]

EGBMT Trial: Myeloablative vs Reduced-Intensity Conditioning[b] (N=168)

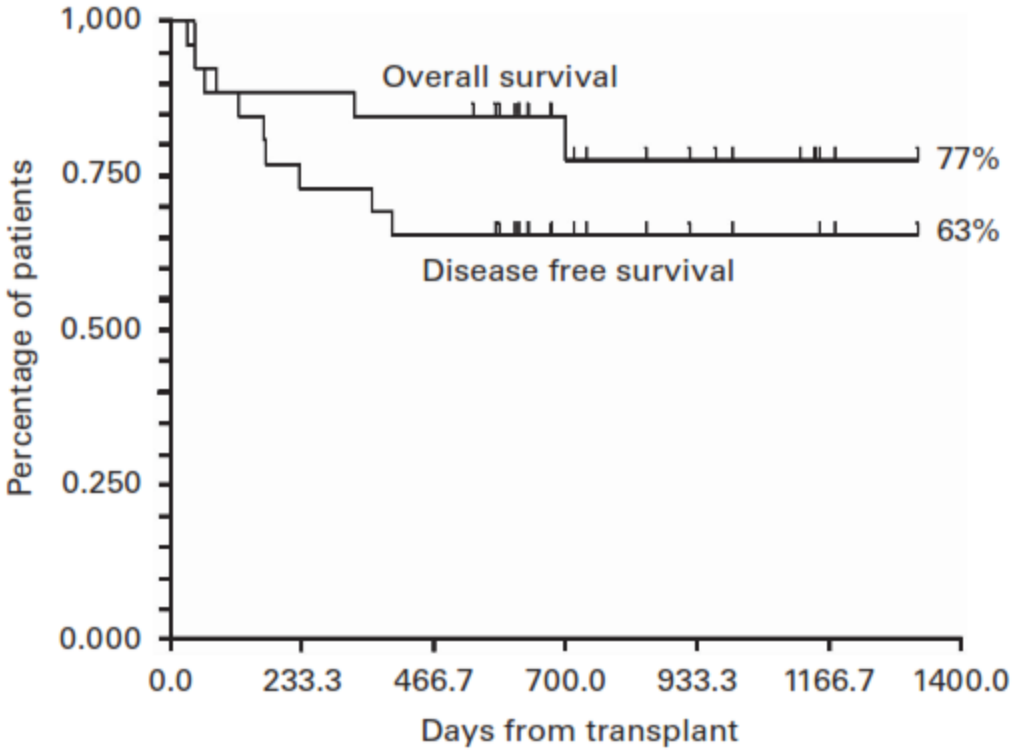


GELTAMO/EGBMT Trial: Reduced-Intensity Conditioning[c] (N=92)



a. Sureda A, et al. *Curr Treat Options Oncol*. 2014;15:238-247.
b. Sureda A, et al. *J Clin Oncol*. 2008;26:455-462.
c. Sureda A, et al. *Haematologica*. 2012;97:310-317.

Unmanipulated haploidentical BMT following non-myeloablative conditioning and post-transplantation CY for advanced Hodgkin's lymphoma



Actuarial overall survival (77%) and disease-free durvival (63%) in 26 patients with advanced Hodgkin's disease

Raiola *et al*. Bone Marrow Transplant. 2014 Feb;49(2):190-4.

Incorporating Novel Therapies in the Treatment Paradigm for Relapsed HL