# HDC SCT in Hodgkin Lymphoma Changing paradigm

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# Outline of the talk ……. 20 min

- Introduction
- Historic trials
- Changes in the primary treatment and response adopted therapy
- Prognostic factors validation / evaluation at failure
- Salvage chemotherapy selection
- Conditioning regimens
- Post HDC auto-SCT consolidation
- Post HDC auto-SCT failure and management + allo SCT
- Available finances and resources - health systems

# In 20 minutes ??

No way

# Introduction

- Primary treatment for adult and pediatrics patients with HL, using current multi-agent anthracycline based chemotherapy ± XRT, **long term cure in**
  - 70% of patients
  - >95% for early favorable
  - 70-75% with advanced stage / high risk

# Introduction

- Unlike 80's and 90's, HDC auto-SCT was used as 3rd or 4th line treatment , now
  - most patients with first relapse or primary refractory disease are planned for HDC auto-SCT.
  - Most of the mature data is being reported on patients that underwent transplant 10-20 years ago.

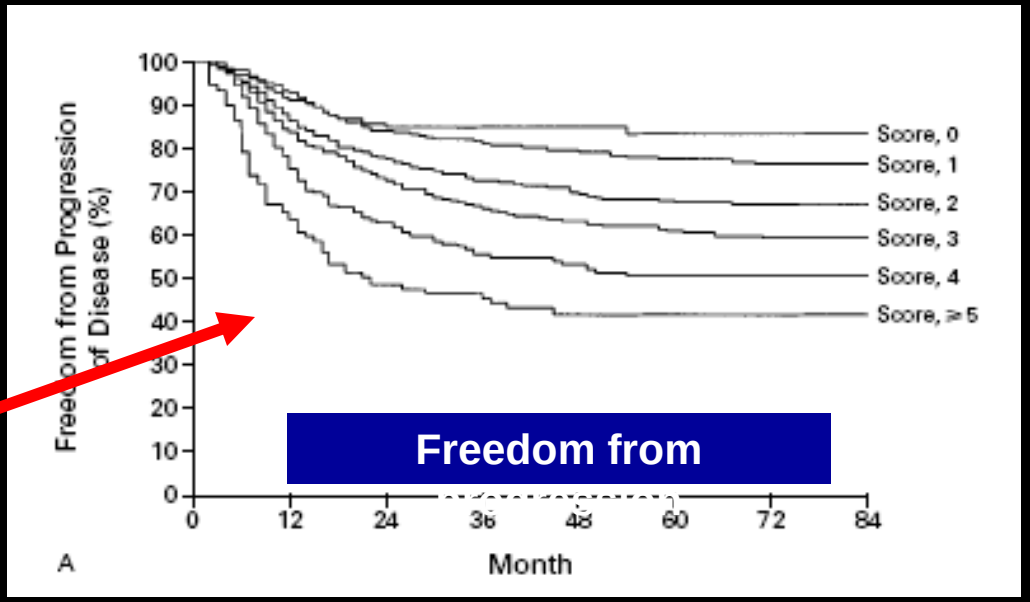
# Introduction

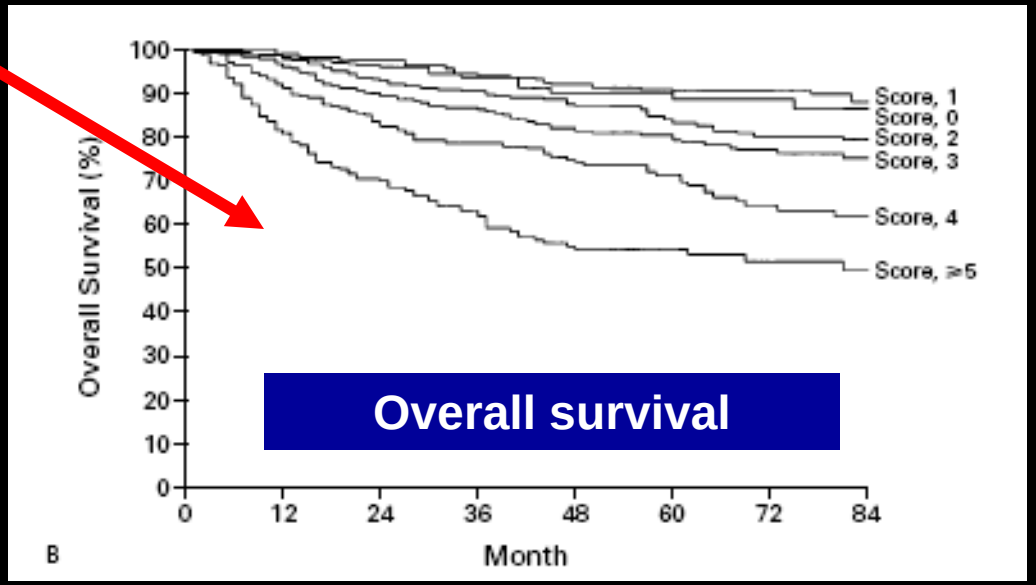
- I will be addressing some historic trials and the salient **differences and changes in the management** that have evolved over the last decade and
- either affected or likely to affect the outcome of HDC auto-SCT.
- These important issues impacting HDC auto-SCT outcomes were shown in in the outline

# Historic data and trials

**The International Prognostic Factors Project on Advanced Hodgkin's Disease has developed a prognostic score based on 7 adverse factors: Hasenclever D, Diehl V: N Engl J Med 1998; 339:1506-1514**

| Prognostic Score | No. of Patients (%) | Rate of Freedom from Progression | Rate of Overall Survival |
|---|---|---|---|
| | | percent | |
| Individual | | | |
| 0 | 115 (7) | 84±4 | 89±2 |
| 1 | 360 (22) | 77±3 | 90±2 |
| 2 | 464 (29) | 67±2 | 81±2 |
| 3 | 378 (23) | 60±3 | 78±3 |
| 4 | 190 (12) | 51±4 | 61±4 |
| ≥5 | 111 (7) | 42±5 | 56±5 |
| Grouped | | | |
| 0 or 1 | 475 (29) | 79±2 | 90±2 |
| ≥2 | 1143 (71) | 60±2 | 74±2 |
| 0–2 | 939 (58) | 74±2 | 86±2 |
| ≥3 | 679 (42) | 55±2 | 70±2 |
| 0–3 | 1317 (81) | 70±2 | 83±1 |
| ≥4 | 301 (19) | 47±2 | 59±2 |




We compare our results with this ------ before

Moccia AA, Donaldson J, Chhanabhai M et al. International Prognostic Score in Advanced-Stage Hodgkin's Lymphoma: Altered Utility in the Modern Era. *J Clin Oncol 2012; 30:3383-3388*

VOLUME 30 · NUMBER 27 · SEPTEMBER 20 2012
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

International Prognostic Score in Advanced-Stage Hodgkin's Lymphoma: Altered Utility in the Modern Era

*Alden A. Moccia, Jane Donaldson, Mukesh Chhanabhai, Paul J. Hoskins, Richard J. Klasa, Kerry J. Savage, Tamara N. Shenkier, Graham W. Slack, Brian Skinnider, Randy D. Gascoyne, Joseph M. Connors, and Laurie H. Sehn*

Rates of 5-Year OS According to International Prognostic Score

| IPS | Patients No. | Patients % | OS All Patients (N = 740) | OS Age ≤ 65 Years (n = 686) | | OS Original Report |
|---|---|---|---|---|---|---|
| 0 | 57 | 8 | 98 ± 2 | 98 ± 2 | 9 | 89 ± 2 |
| 1 | 195 | 26 | 97 ± 1 | 97 ± 1 | 7 | 90 ± 2 |
| 2 | 195 | 26 | 91 ± 2 | 92 ± 2 | 11 | 81 ± 2 |
| 3 | 155 | 21 | 88 ± 3 | 91 ± 3 | 13 | 78 ± 3 |
| 4 | 88 | 12 | 85 ± 4 | 88 ± 4 | 29 | 61 ± 4 |
| ≥ 5 | 50 | 7 | 67 ± 7 | 73 ± 7 | 17 | 56 ± 5 |
| 0-3 | 602 | 81 | 93 ± 1 | 94 ± 1 | 11 | 83 ± 1 |
| ≥ 4 | 138 | 19 | 78 ± 4 | 83 ± 4 | 26 | 59 ± 2 |

NOTE. Plus-minus values are rate estimates plus or minus standard error.
Abbreviations: FFP, freedom from progression; IPS, International Prognostic Score; OS, overall survival.

Improvement in outcome

# Historic trials

**Who** / **How** to transplant

Will not be addressed as most eligibility criteria, salvage chemo and HDC are likely equal

**When** to transplant

# Timing of HDC auto-SCT

**UPFRONT**

ABBREVIATED

INDUCTION

**UPFRONT**

CONSOLIDATION

ALL PATIENTS

IPI STRATIFIED

**INDUCTION FAILURE**

PR

NR / PD

**RELAPSE**

SENSITIVE

RESISTENT

# Timing of HDC auto-SCT

**UPFRONT**

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Risk factor STRATIFIED

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RESISTENT

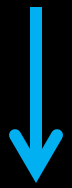
**High-dose therapy and autologous stem-cell transplantation versus conventional therapy for patients with advanced Hodgkin's lymphoma responding to front-line therapy. Federico M et al. JCO. 2003 15;21:2320-5**

**Stage IV HL and → at least 2 other risk factors**

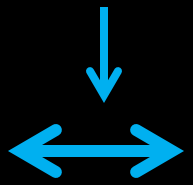
- elevated LDH
- Bulky mediastinal mass
- >1 extranodal area +
- Low hematocrit
- Inguinal involvement

ABVD / anthracycline chemo x 4

CR or PR 208

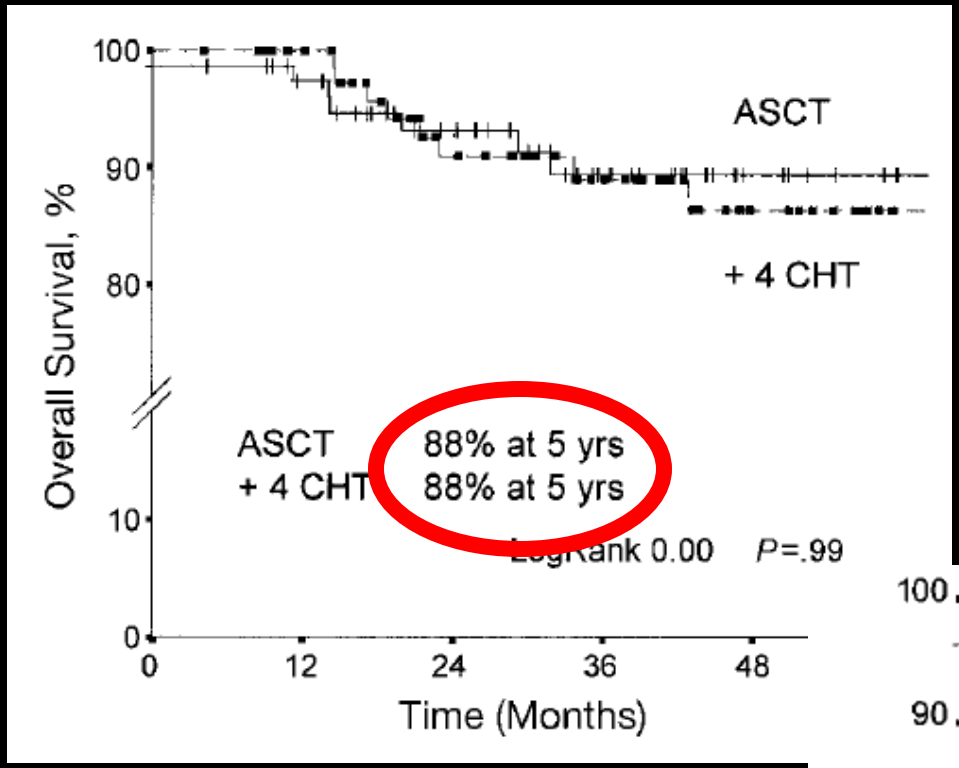


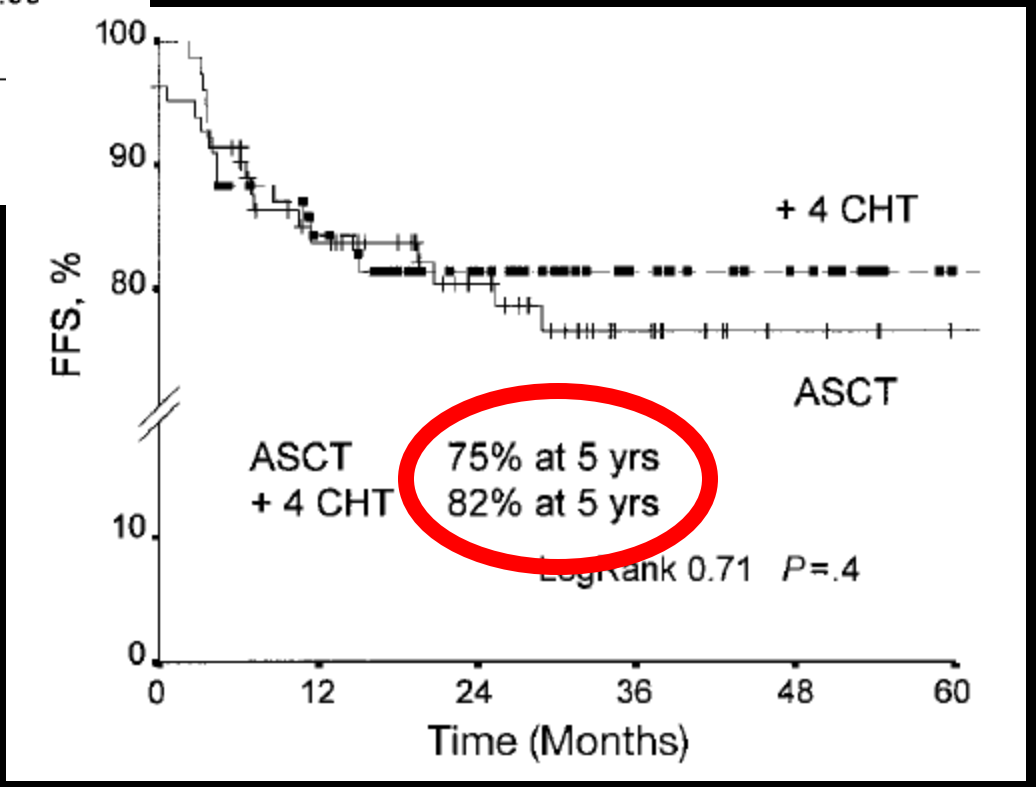
**Randomization 163**



HDC auto-SCT 83

Same chemo x4 80


100
90
80
10
0
Overall Survival, %
ASCT
+ 4 CHT
ASCT 88% at 5 yrs
+ 4 CHT 88% at 5 yrs
LogRank 0.00 P=.99
0
12
24
36
48
Time (Months)


100
90
80
10
0
FFS, %
+ 4 CHT
ASCT
ASCT 75% at 5 yrs
+ 4 CHT 82% at 5 yrs
LogRank 0.71 P=.4
0
12
24
36
48
60
Time (Months)

# Timing of HDC auto-SCT

**UPFRONT**

ABBREVIATED

INDUCTION

Risk factor STRATIFIED

**UPFRONT**

CONSOLIDATION

ALL PATIENTS

Risk factor STRATIFIED

**INDUCTION FAILURE**

PR

NR / PD

**RELAPSE**

SENSITIVE

RESISTENT

**A population-based study of intensive multi-agent chemotherapy with or without autotransplant for the highest risk Hodgkin's disease patients identified by the Scotland and Newcastle Lymphoma Group (SNLG) prognostic index. A Scotland and Newcastle Lymphoma Group study (SNLG HD III).** Eur J Cancer. 2002 Apr;38(6):795-806.

- High risk HL (numerical prognostic index – Proctor index) → 178
- 120 /178 eligible
- 93% CR after chemo x 3
- 65/ 107 in CR randomized

PVACE-BOP (x3)

prednisolone
vinblastine
doxorubicine
chlorambucil
etoposide
bleomycin
vinistine
procarbazine

Check response

↓

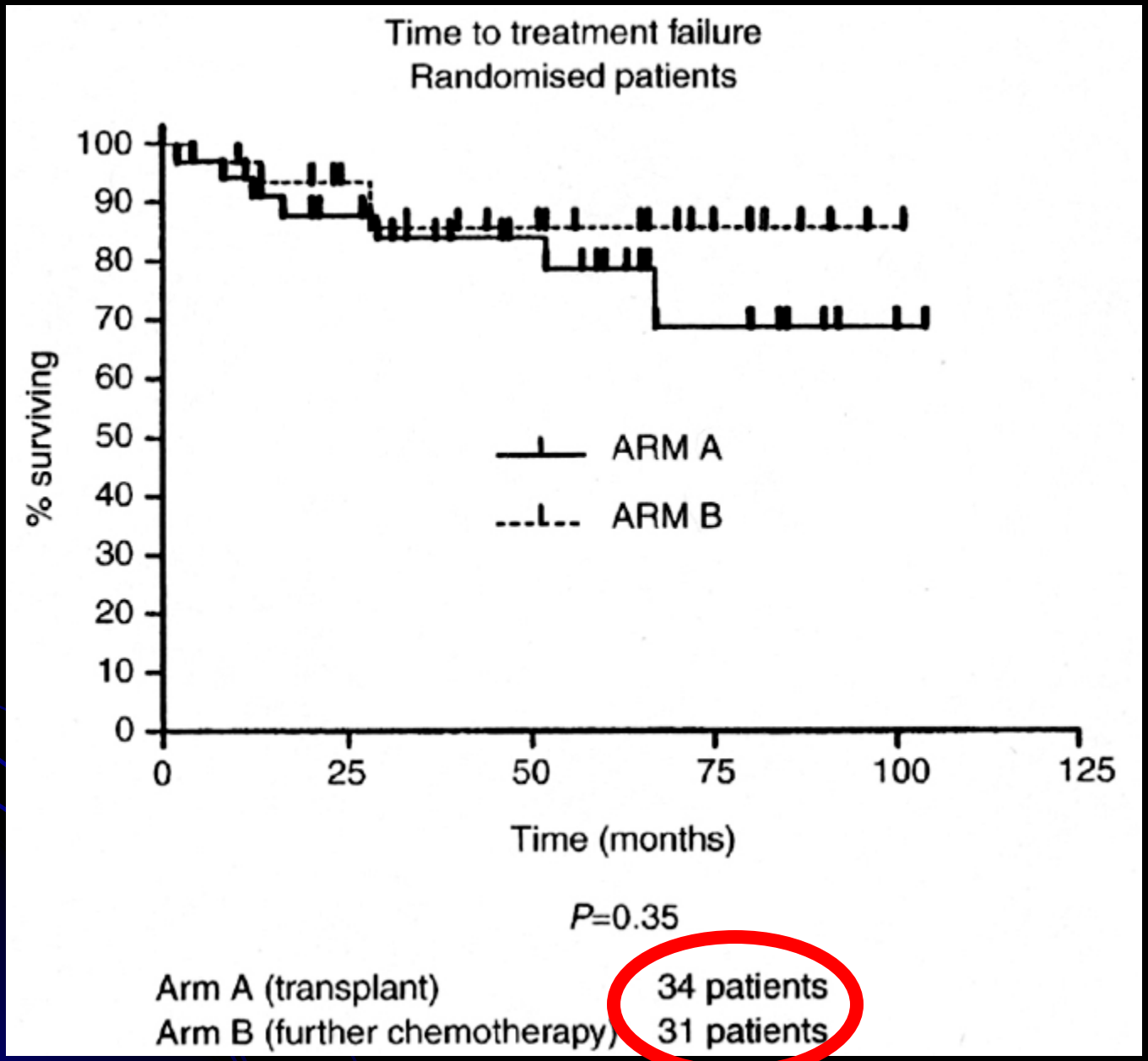
RT to bulk/residual

↓ CR patients only

**Randomization 65**

↓

HDC auto-SCT 34 ↔ PVACE-BOP x2 31


Time to treatment failure
Randomised patients
100
90
80
70
60
50
40
30
20
10
0
% surviving
ARM A
ARM B
0
25
50
75
100
125
Time (months)
P=0.35
Arm A (transplant) 34 patients
Arm B (further chemotherapy) 31 patients

# Timing of HDC auto-SCT

**UPFRONT**

ABBREVIATED

INDUCTION

**UPFRONT**

CONSOLIDATION

ALL PATIENTS

IPI STRATIFIED

Treatment like this→ even in high risk group

Long term toxicity → concern for HDC auto-SCT in this setting

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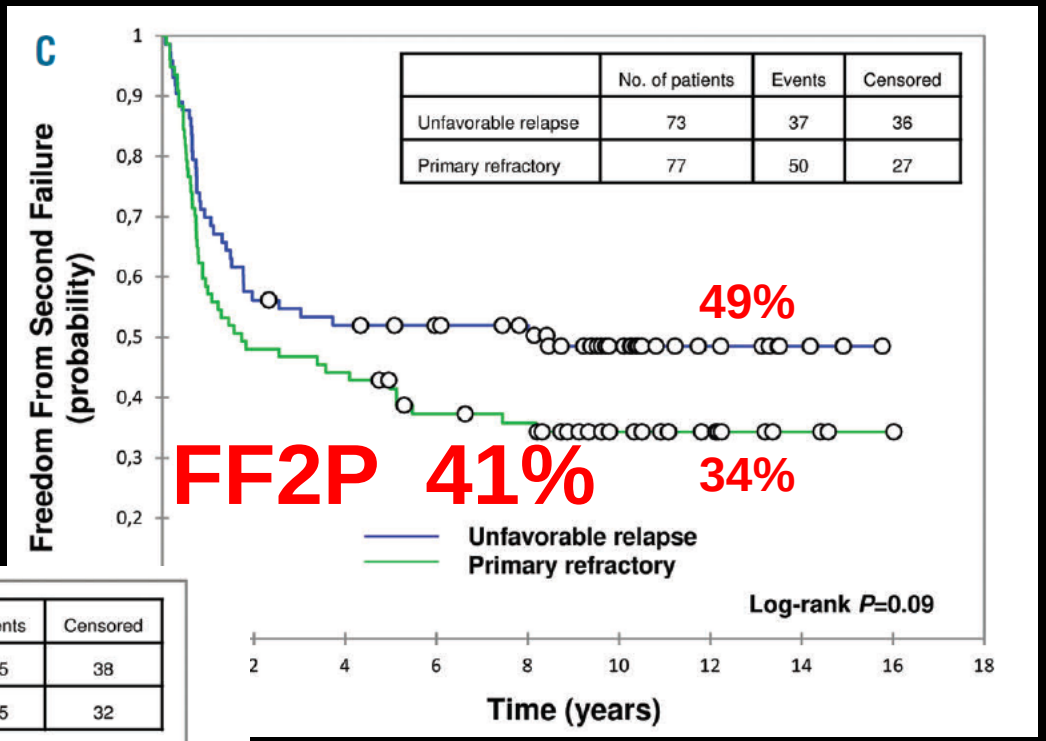
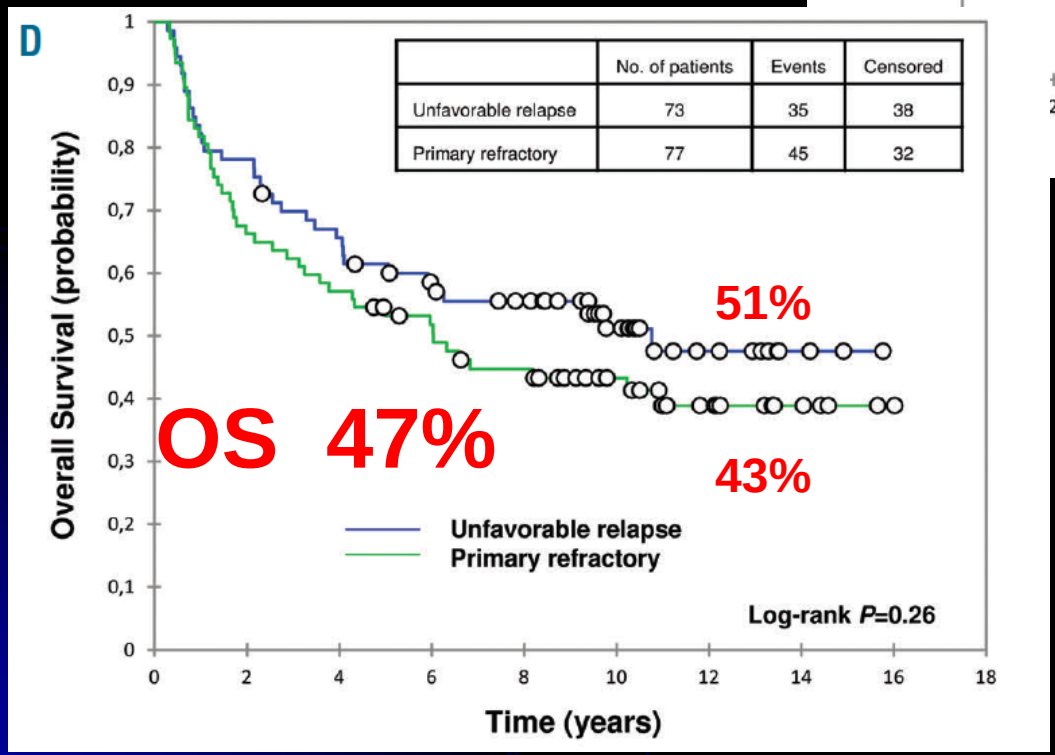
RESISTENT

EARLY / LATE / OTHER

**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 D et al. Haematologica. 2016 101:474-81.**

- Phase II trial
- Risk-adapted strategy
- Single vs tandem HDC auto-SCT for relapsed/refractory disease
- Risk factors
  - primary refractory disease OR
  - 2/3 risk factors:
    - relapse <12 months
    - stage III-IV or
    - relapse in a previously XRT area post chemo+XRT




**Tandem** HDC auto-SCT results are not different from historic control and patients with primary refractory and high risk with **single** HDC auto-SCT.

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# Relapsed disease

Relapsed disease is the most common indication for HDC auto-SCT in HL

# Relapsed disease

Likely hood of cure for patients relapsing after anthracycline based chemo who received salvage chemotherapy +/- XRT

Historic perspective 1990s

**At best → 20 – 40 %**


- Bonadonna G et al. Ann Oncol. 1991;2(Suppl 1):9–16.
- Longo DL et al. J Clin Oncol. 1992;10(2):210–218.
- Lohri A et al. Blood. 1991;77(10):2292–2298.
- Yuen AR et al.. Blood. 1997;89(3):814–822.

# Relapsed disease

HDC auto-SCT

Vs

Salvage

Phase III trials

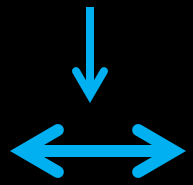
**Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. Linch D. Lancet 1993; 341: 1051**

Relapsed and refectory HL patients

Intended accrual 66 patients

Relapsed / refractory

**Randomization 40**

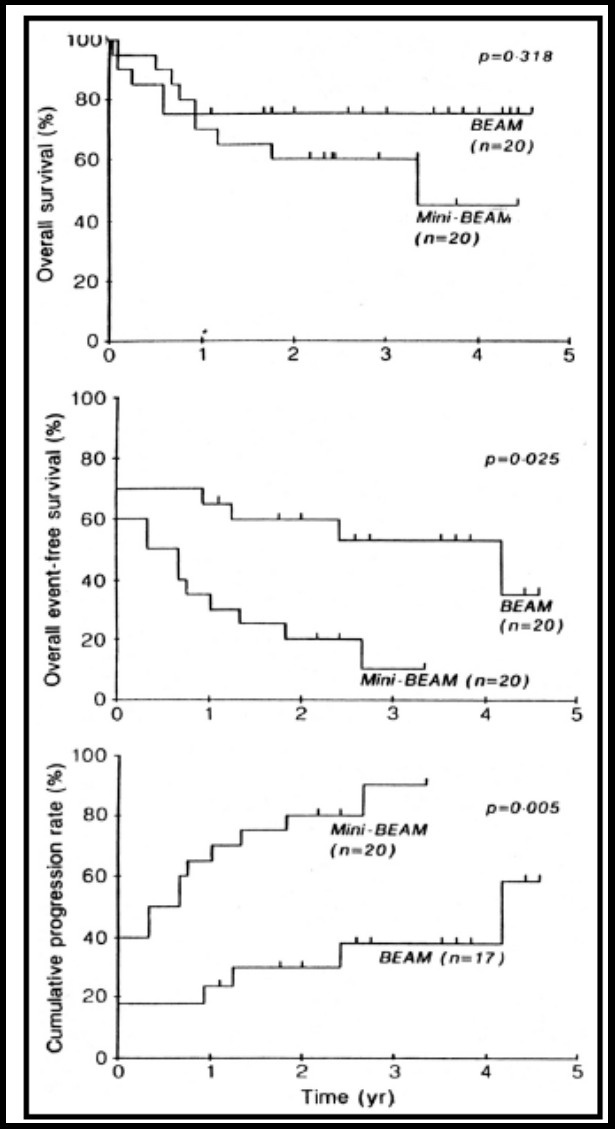


HDC auto-SCT 20

Mini-BEAM 20

# BNLI trial

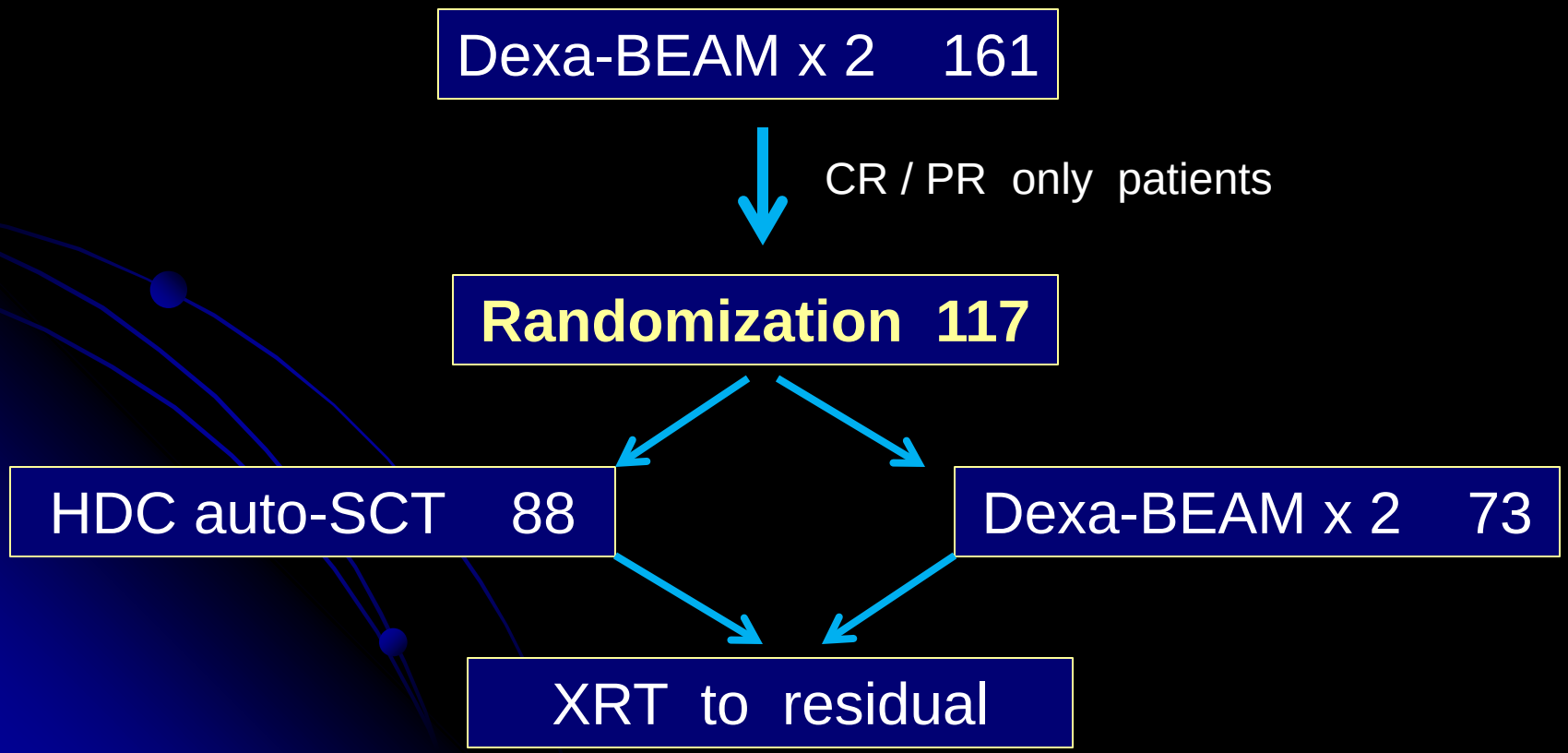
- 40 patients → ONLY
- 3 yr EFS 53% vs 10% (*P*=0.025)
- PFS → *P*= 0.005
- Closed early →patients refused non HDC auto-SCT arm
- No difference in OS → *P*=0.318 patients who failed mini BEAM were offered HDC auto-SCT

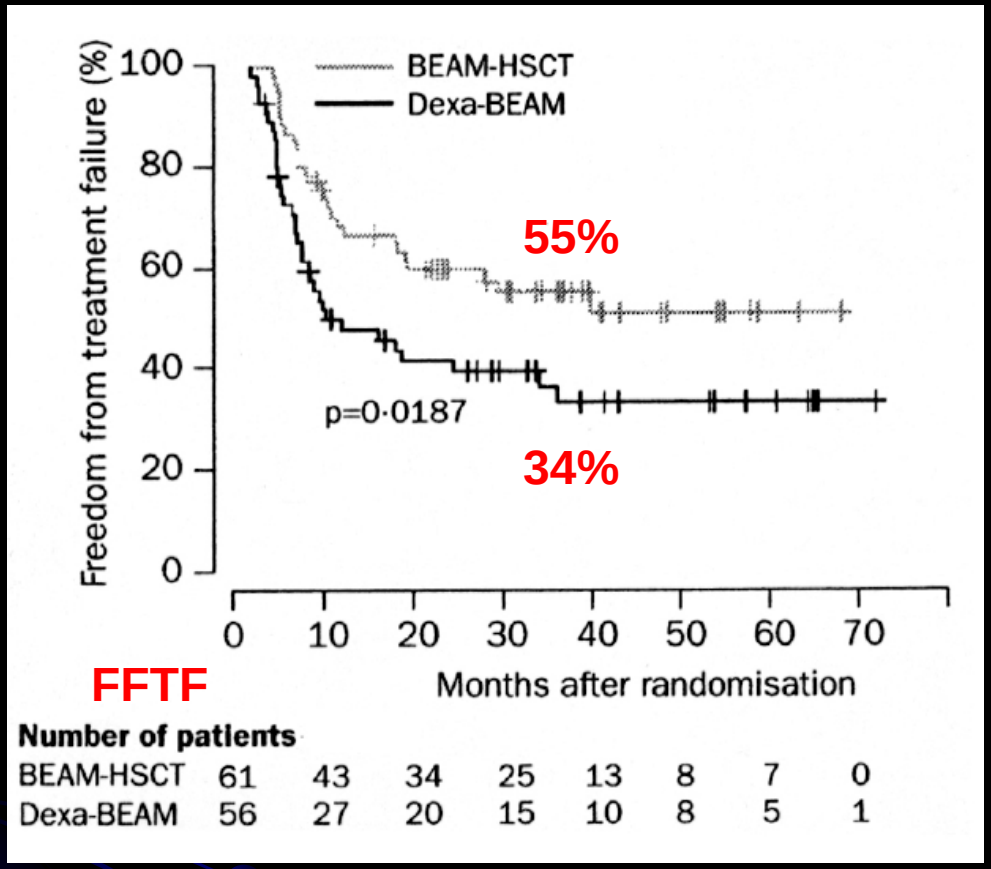


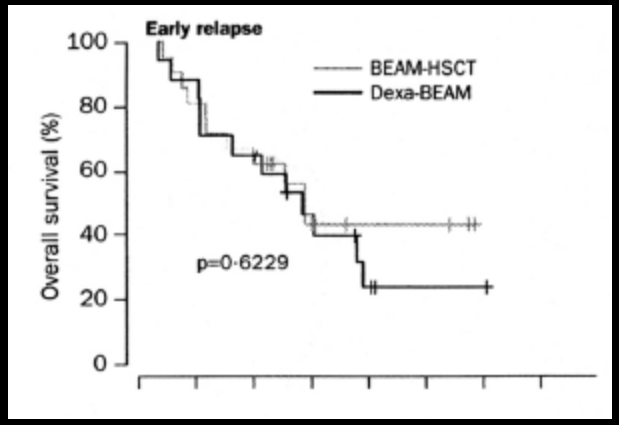
**Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial.**

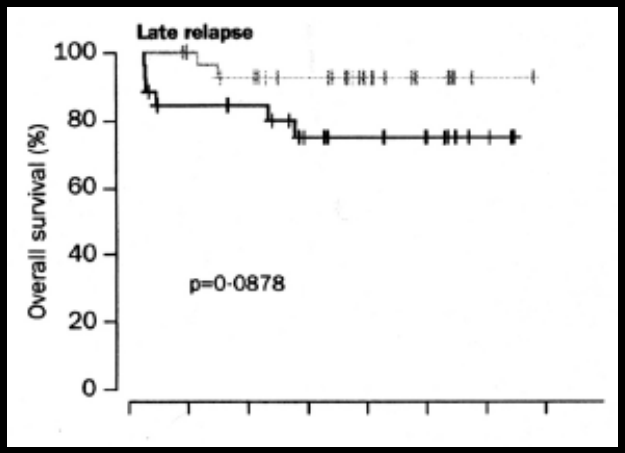
Schmitz N et al. Lancet **2002**;359: 2065

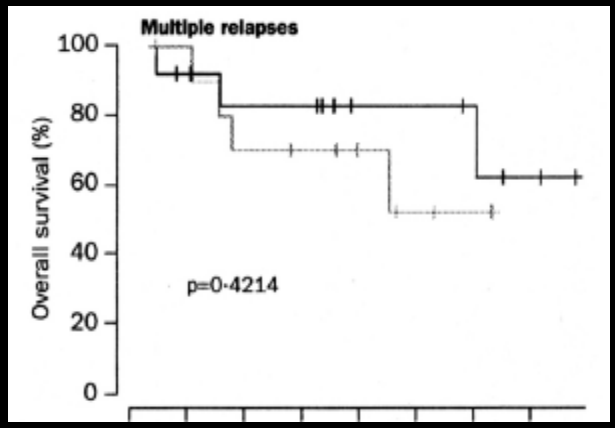
**GHSG/EBMT trial** → Relapsed ( early, late, multiple) HL patients






**GHSG / EBMT trial**

**DFS is better**

**OS not significantly different**

**OVERALL SURVIVAL**

# BNLI and GHSG/EBMT trials

The lack of a survival benefit in these randomized trials has been attributed to patients in the non-transplant arm

**undergoing transplant at the time of second /next relapse**

# Timing of HDC auto-SCT

## UPFRONT

ABBREVIATED

INDUCTION

## UPFRONT

CONSOLIDATION

ALL PATIENTS

IPI STRATIFIED

## INDUCTION FAILURE

PR

NR / PD

## RELAPSE

SENSITIVE

RESISTENT

EARLY / LATE / OTHER

# PR-HL, Salvage vs HDC auto-SCT

- The outcome of HDC auto-SCT in primary refractory Hodgkin's lymphoma (PR-HL) is not as encouraging as in relapsed HL.

- Many studies have shown that duration of CR is one of the most important determinant of out come at relapse

# PR-HL, Salvage vs HDC auto-SCT

## What is refractory Definition ?

- partial response after *planned treatment* (PR)
- no response (NR)
- stable disease (SD)
- progressive disease (PD)
- relapsing within 3 months of finishing the planned treatment ( short CR / CRu)
- ? <12 CR (not included in most reports/early relapse)

# PR-HL, Salvage vs HDC auto-SCT

- Difficult to compare salvage chemotherapy alone vs HDC auto-SCT
- Patient with disease chemosensitive to salvage chemotherapy → HDC auto-SCT
- Progressing → not offered HDC auto-SCT

# PR-HL, Salvage vs HDC auto-SCT

- 1078 pts>> 82 refractory
- Chemotherapy (24) or HDC (27)
- 21 PD>>died (29%) patients were not candidate for curative intent therapy.
- HDC ASCT clearly showed survival benefit over conventional dose salvage
- 4 year OS **81% vs 38%** (P = 0.019)
- Morabito F, Stelitano C, Luminari S, et al: The role of high-dose therapy and autologous stem cell transplantation in patients with primary refractory Hodgkin's lymphoma: a report from the Gruppo Italiano per lo Studio dei Linfomi (GISL). Bone Marrow Transplant 37:283-8, 2006

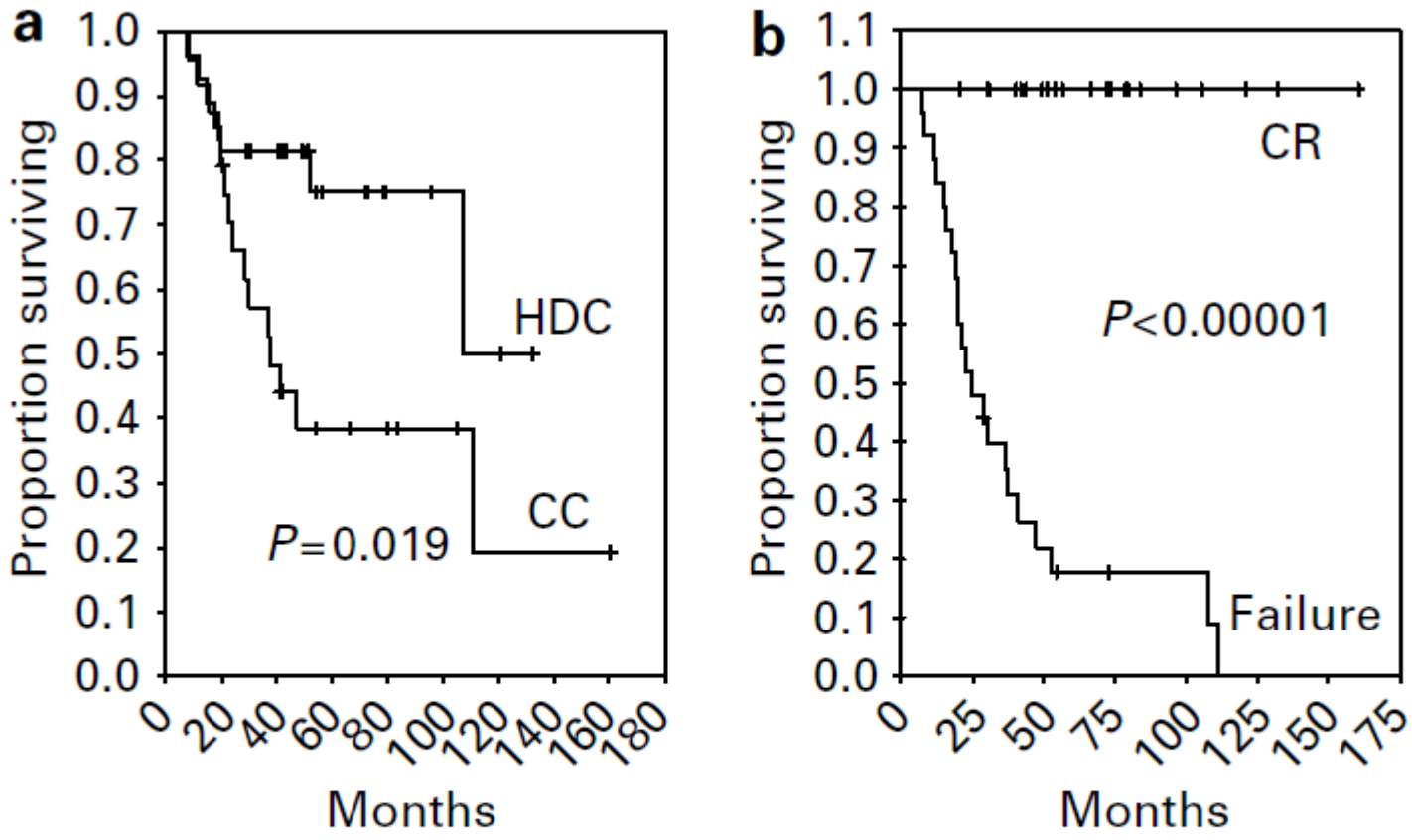



**Figure 2** Kaplan–Meier estimates of OS for patients according to therapy (**a**) and to the achievement of CR regardless of the therapeutic approach (**b**).

Morabito F et al: The role of high-dose therapy and autologous stem cell transplantation in patients with primary refractory Hodgkin's lymphoma: a report from the Gruppo Italiano per lo Studio dei Linfomi (GISL). **Bone Marrow Transplant 37:283-8, 2006**

| Author, year, Institution | Patients | f/u | EFS / PFS | OS | Prognostic factors for PFS or OS | Comments |
|---|---|---|---|---|---|---|
| Chopra 1993 Univ. College London | 46 (of 155) | 5 years | 33 % | - | Tumor mass, relapse status females, 3 or more lines of chemo(PFS) | Factors for all patients |
| Bierman 1994 Nebraska | 44 | 36 m | 22 % | - | No comments | No comments |
| Reece 1995 Vancouver | 30 | 3.6 years | 42 % | 30% | Bleomycin lung toxicity (OS) | Factor for PR-HL OS 30% estimated from graph |
| Horning 1997 Stanford | 29 (of 119) | 40 m | 60 % | 32 % | B symptoms, response to salvage chemo, lung or marrow involvement at transplant (OS) | Factors for all patients % estimated from graph |
| Lazarus 1999 ABMTR (1989-95) | 122 | 28 m After BMT | 38 % | 50 % | B symptoms at dx, performance status at HDC (OS) | Factor for PR-HL 12% treatment related mortality |
| André 1999 Paris | 86 | 22 m from dx | 25 % | 35 % | Response to salvage chemo (OS) | 78 of 86 patients with progressive disease |
| Sweetenham 1999 EBMT (1979-1995) | 175 | 73 m | 32 % | 36 % | late transplant ( after 18 months) (OS) | Factor for PR-HL No salvage chemo 75 patients(43%) 34/100 PD on salvage 66/100 SD or minimal response |
| Josting [8], 2000 German HLSG | 70 (of 206) | 52 m | 31 % | 43 % | Performance status, no CR1, age > 50 | Factor for PR-HL |

| Author, year, Institution | Patients | f/u | EFS / PFS | OS | Prognostic factors for PFS or OS | Comments |
|---|---|---|---|---|---|---|
| Josting 2000 German HLSG | 70 (of 206) | 52 ms | 31 % | 43 % | Performance status, no CR1, age > 50 | Factor for PR-HL |
| Sureda 2001 GEL / TAMO Spain | 75 (of 494) | 26 ms | 17 % | - | > 1 prior chemo, response to salvage chemo (OS) | Factors for all patients PR-HL 49 and resistant relapse 26 |
| Fermé 2002 GELA | 67 (of 157) | 50 m | 23 % | 30 % | B symptoms, response to salvage chemo (OS) | Factors for all patients |
| Czyz 2004 Polish Centers | 76 | 3 years | - | 34 % | Bulky disease (OS) | Factor for PR-HL |
| Moskowitz 2004 Memorial SKCC | 75 | 10 years For surviving | 45 % | 48 % | Response to salvage (OS) | Factor for PR-HL All biopsy proven, very long F/U |
| Lavoie 2005 Vancouver | 23 (of 100) | 11.4 years | 39 % | 39 % | > 1 prior chemo (PFS) | Factors for all patients Very long F/U 9% second malignancy at 15 y |
| Mortabito 2006 Italian centers (1988-2002) | 27 ( of 72) | 4 year | | 81 % | Achieving CR | Factors for all patients HDC vs curative chemo vs palliative chemo |
| Akhtar 2007 Saudi Arabia | 66 | 38 m from dx 23 m after BMT | 38 % | 64 % | > LDH for EFS Mediastinal invol for OS | Short f/u Uniform salvage and HDC |

# Relapsed disease

**Definite indicated**

- Relapse < 2 year after completion of primary chemotherapy
- Relapse with B symptoms
- Relapse in extranodal sites
- Relapse in previously irradiated sites
- Relapse as stage III-IV
- Relapse with Bulky disease

**Controversial but probably indicated**

- Relapse only in previously unirradiated lymph nodes, in the absence of B-symptoms, occurring > 1 year after completion of primary chemotherapy

# Timing of HDC auto-SCT

**INDUCTION FAILURE**

PR

NR / PD

Superior EFS and in some studies, better OS

Better OS when compare with historic control

Large selection bias

Considered standard option

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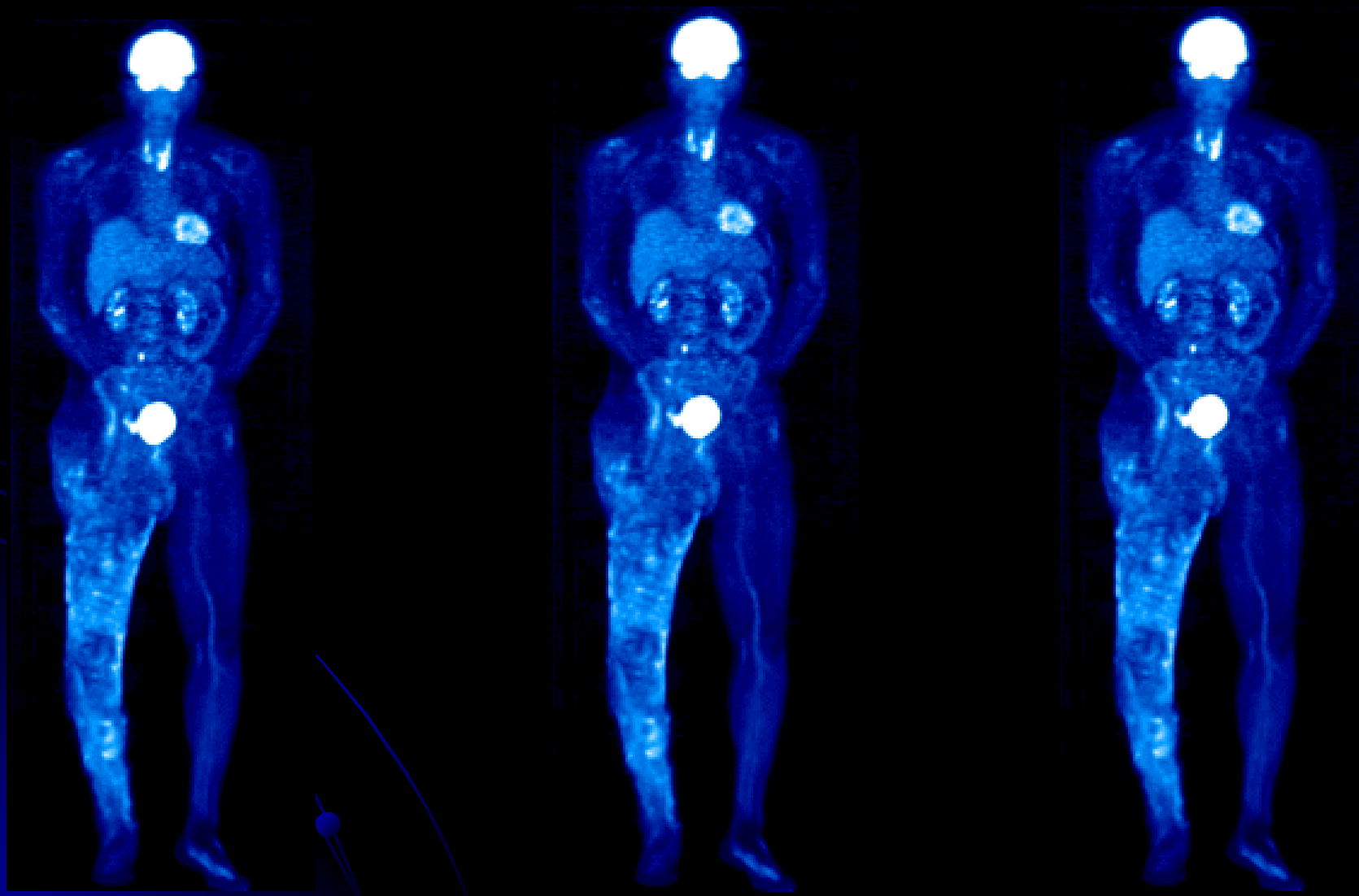
# Changes in the primary treatment and response adopted therapy



# Over the last 20 years ……

- North American → ABVD
- European → ABVD and BEACOPP / BEACOPP-escalated
- Main change is FDG-PET scan based decision making in clinical trials focused on two main themes
  - Escalation if FDG-PET scan → positive
  - De-escalation if FDG-PET scan → Negative
- All these studies with short f/u for long term OS

# Over the last 20 years ……

- An ongoing phase III ECHELON-1 trial has integrated CD-30 antibody brentuximab vedotin (BV) in upfront setting and comparing ABVD as a control arm to AVD-BV.

- What will be the long term outcome of patients failing in these FDG-PET scan response based treatment paradigms ?
- Will they be behaving differently compared to those who failed ABVD and BEACOPP
- AVD-BV → the outcomes of salvage therapy and HDC auto-SCT remains to be seen
- ? These issues are likely to emerge in next few years.

# Prognostic factors validation and evaluation at the time of first failure

# Prognostic factors

- A prognostic factor is a measurement or classification of an individual patient, performed at or soon after diagnosis that gives information on the likely outcome of the disease.

- It is generally the probability of cure for various values of a prognostic factor.

# Prognostic factors

It may be used for informing the patient, or defining or describing the study population or adjusting the data analysis

the most important role of the prognostic factor is in helping choose an appropriate treatment strategy.

Andreas Josting. Expert Rev. Hematol;2010:3, 583-592


www.foodiechat.com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Fruit and
Mint
Salad

# Prognostic factors

- Factors tested for primary disease can be tested again for their predictive values in relapsed / refractory setting

- They may or may not be valid in this setting

- As long as there is no **paradigm shift** in **staging** / **chemotherapy** / **response evaluation** / **supportive care** / **post HDC auto-SCT failure management,** they are likely to reflect their prognostic significance

# Prognostic factors

- Hodgkin Lymphoma International Prognostic Score →most widely used→in patients with newly diagnosed advanced HL

- Its utility has already been challenged due to improvement in OS over the last 20 years

- FDG-PET scan response after salvage is an important prognostic factor. Many reports → FDG-PET scan alone or in combination with other factors as an important prognostic factor.

Moccia AA, Donaldson J, Chhanabhai M et al. International Prognostic Score in Advanced-Stage Hodgkin's Lymphoma: Altered Utility in the Modern Era. *J Clin Oncol 2012; 30:3383-3388*

VOLUME 30 · NUMBER 27 · SEPTEMBER 20 2012
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

International Prognostic Score in Advanced-Stage Hodgkin's Lymphoma: Altered Utility in the Modern Era

*Alden A. Moccia, Jane Donaldson, Mukesh Chhanabhai, Paul J. Hoskins, Richard J. Klasa, Kerry J. Savage, Tamara N. Shenkier, Graham W. Slack, Brian Skinnider, Randy D. Gascoyne, Joseph M. Connors, and Laurie H. Sehn*

Rates of 5-Year OS According to International Prognostic Score

| IPS | Patients No. | Patients % | OS All Patients (N = 740) | OS Age ≤ 65 Years (n = 686) | | OS Original Report |
|---|---|---|---|---|---|---|
| 0 | 57 | 8 | 98 ± 2 | 98 ± 2 | 9 | 89 ± 2 |
| 1 | 195 | 26 | 97 ± 1 | 97 ± 1 | 7 | 90 ± 2 |
| 2 | 195 | 26 | 91 ± 2 | 92 ± 2 | 11 | 81 ± 2 |
| 3 | 155 | 21 | 88 ± 3 | 91 ± 3 | 13 | 78 ± 3 |
| 4 | 88 | 12 | 85 ± 4 | 88 ± 4 | 29 | 61 ± 4 |
| ≥ 5 | 50 | 7 | 67 ± 7 | 73 ± 7 | 17 | 56 ± 5 |
| 0-3 | 602 | 81 | 93 ± 1 | 94 ± 1 | 11 | 83 ± 1 |
| ≥ 4 | 138 | 19 | 78 ± 4 | 83 ± 4 | 26 | 59 ± 2 |

NOTE. Plus-minus values are rate estimates plus or minus standard error.
Abbreviations: FFP, freedom from progression; IPS, International Prognostic Score; OS, overall survival.

Improvement in outcome

| Author | Total # | B s/s | extranodal | < 12 m | III -IV | anemia | Age >45 | Lymphopenia | Low albumin | PS | bulky | PR after sal | HL-IPS | others |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Moskowitz** | **65** | X | X | **X** | | | | | | | | | | |
| **Josting** | **422** | | | **X** | X | X | | | | | | | | |
| **Josting** | **206** | | | | | | X 50 | | | X | | | | No CR-1 |
| **Bierman** | **379** | | | | | X | X | X | X | | | | | |
| **Sureda** | **357** | | X 2 | **X** | | | | | | | X | **X** | | <1995 |
| **Sureda** | **494** | | | | | | | | | | | **X** | | <1991 ≥2 lines |
| **Akhtar** | **141** | | | | | | | | | | | **X** | **X** | |

- Are these prognostic factors still able to discriminate outcome?
- What would be the best combination of prognostic factors at the time of relapse and progression?
- Failure after more aggressive treatment / after BV may be an indication of resistant disease / poor outcome post HDC auto-SCT
- Should a positive FDG-PET scan after salvage chemotherapy warrant another line of salvage to achieve a CR prior to HDC
- Do we have a therapy that can overcome any of the above mentioned poor prognostic factors?

# Salvage chemotherapy selection

# Salvage chemotherapy selection

- There is no superiority of a specific salvage chemotherapy regimen over the others
- ESHAP ICE DHAP mini/Dexa BEAM
  IMVP-16 GDP IGEV GemOx

- Many new **non**-platinum based regimens

# Salvage chemotherapy selection

- Use of BV as single agent or in combination with other salvage chemotherapy regimens and with nivolumab (ASH) 2016.

- Limited phase II trials have shown superior response rate of these combinations, but with a higher toxicity

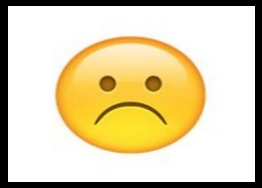
- It may take few years before an effective / safe dosing schedule and combination of BV + chemotherapy or other agents will be available in this setting.

- What will be the best salvage combination for this group in the presence of BV?
- What will be the outcomes of HDC auto-SCT in those who had received BV during primary treatment?
- How BV use before HDC auto-SCT will impact post HDC failure?

# Conditioning regimens

# Conditioning regimens

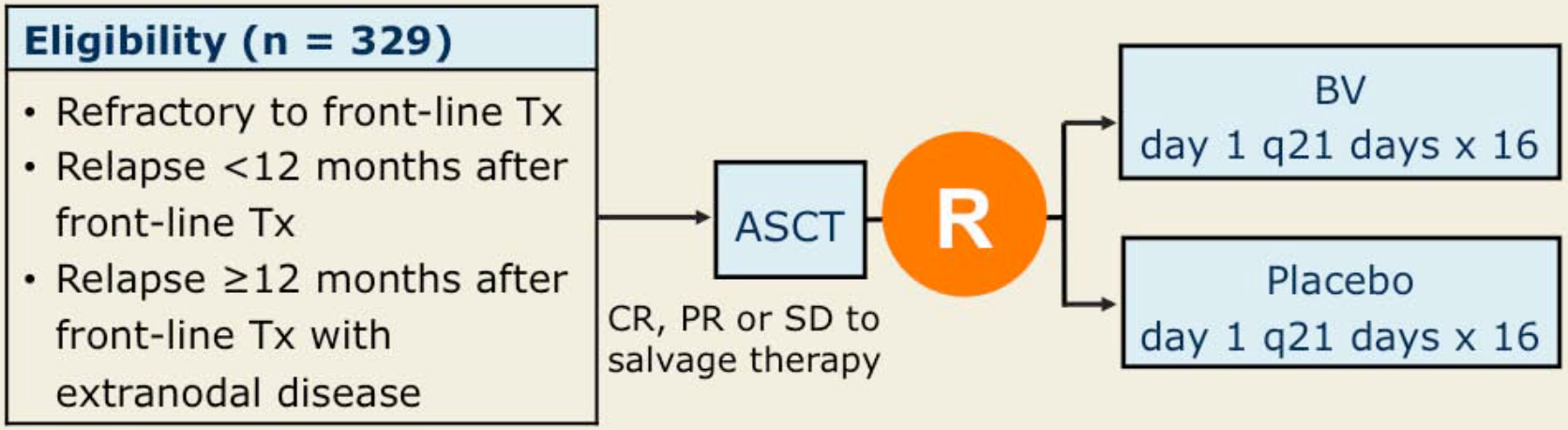
- There is no new large scale data exploring newer autologous conditioning regimens
- BEAM or with cyclophosphamide (BEAC), or etoposide (CBV) and cyclophosphamide -TBI are still the most common regimens.
- LEAM 300 vs 200 lomustine



- Gemcitabine and bendamustine are also reported in limited number of patients

# Post HDC auto-SCT consolidation

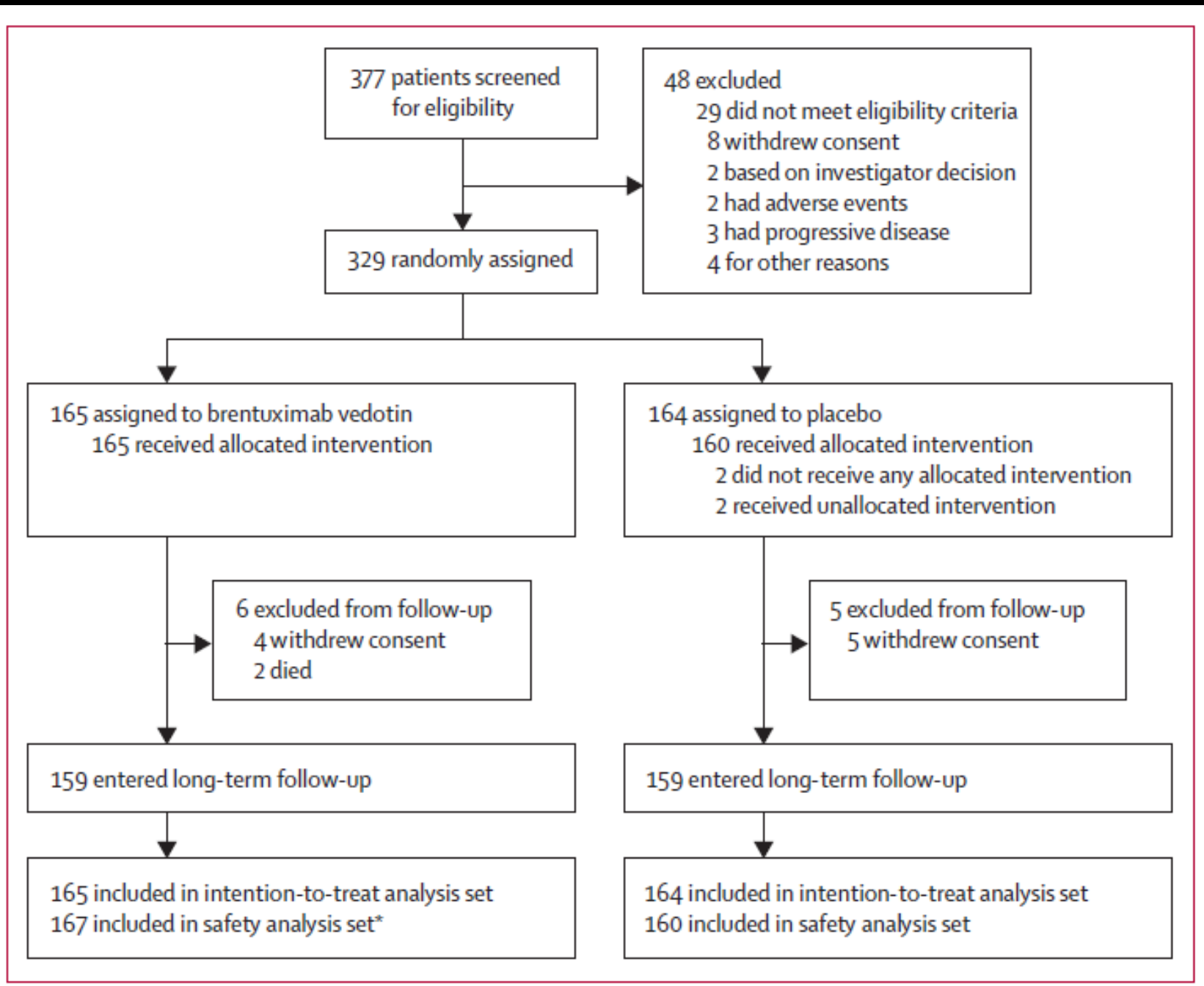
# Phase III AETHERA Study Design




Patients who experienced disease progression on the placebo arm could subsequently receive BV on another trial.

- **Primary endpoints:** Progression-free survival per independent review
- **Secondary endpoints:** Overall survival, safety, tolerability

Moskowitz CH et al. *Proc ASH* 2014;Abstract 673.


377 patients screened for eligibility
48 excluded
29 did not meet eligibility criteria
8 withdrew consent
2 based on investigator decision
2 had adverse events
3 had progressive disease
4 for other reasons
329 randomly assigned
165 assigned to brentuximab vedotin
165 received allocated intervention
164 assigned to placebo
160 received allocated intervention
2 did not receive any allocated intervention
2 received unallocated intervention
6 excluded from follow-up
4 withdrew consent
2 died
5 excluded from follow-up
5 withdrew consent
159 entered long-term follow-up
159 entered long-term follow-up
165 included in intention-to-treat analysis set
167 included in safety analysis set*
164 included in intention-to-treat analysis set
160 included in safety analysis set

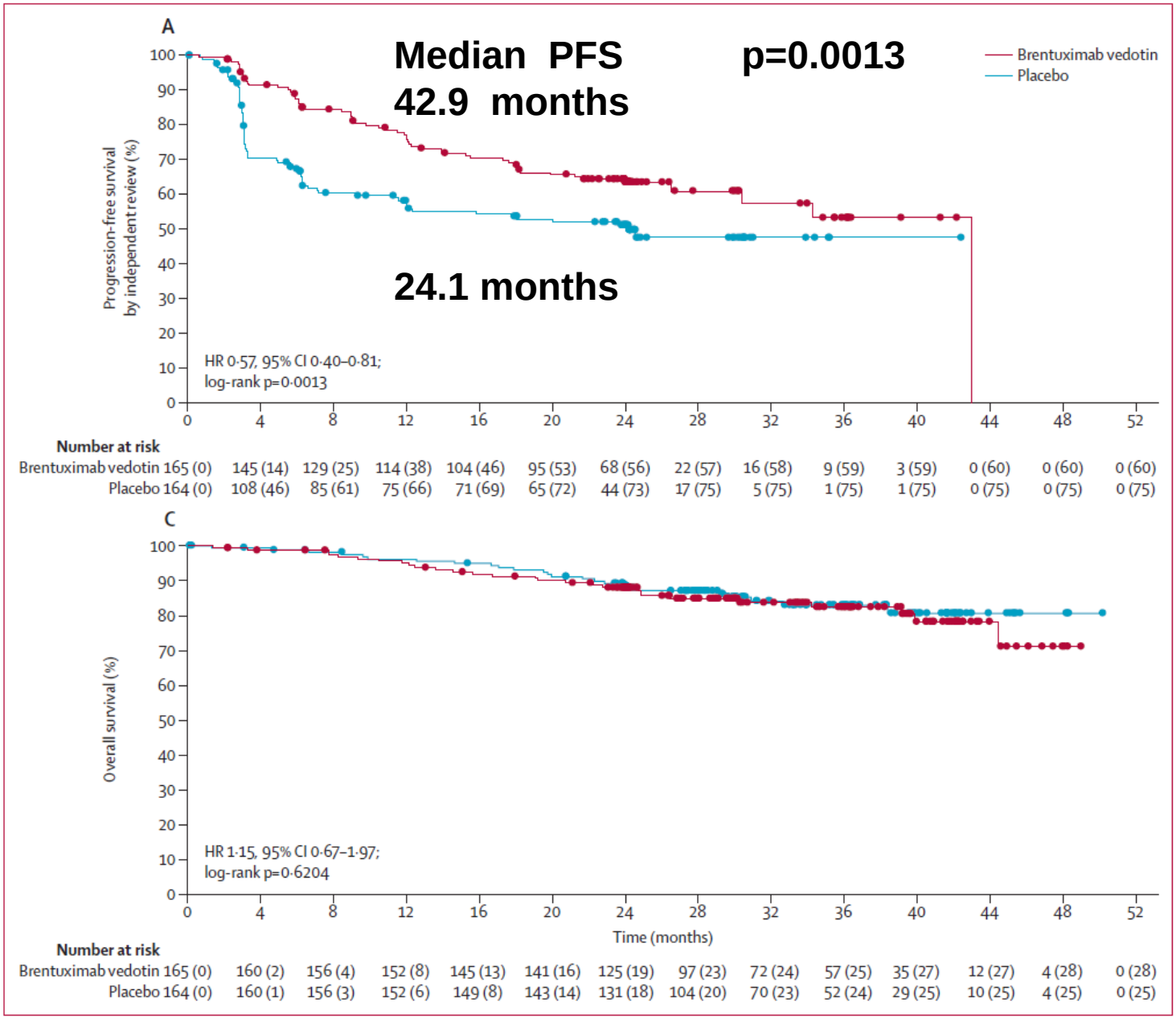



*Figure 2:* **Progression-free and overall survival analyses**
Kaplan-Meier plots showing the primary endpoint of progression-free survival by independent review (A), progression-free survival by investigator assessment (B), and interim analysis of overall survival (C). Filled circles show censored patients. No p value was calculated for the analysis in panel B.

| | N | Progression-free survival by independent review | Overall survival |
|---|---|---|---|
| ≥1 | 329 | 0·57 (0·40–0·81) | 1·15 (0·67–1·97) |
| ≥2 | 280 | 0·49 (0·34–0·71) | 0·94 (0·53–1·67) |
| ≥3 | 166 | 0·43 (0·27–0·68) | 0·92 (0·45–1·88) |

Data are hazard ratio (95% CI), unless otherwise indicated. Risk factors were primary refractory Hodgkin's lymphoma or relapse less than 12 months from completion of frontline therapy, partial response or stable disease as best response to most recent salvage therapy, extranodal disease at pre-autologous stem-cell transplantation relapse, B symptoms at pre-autologous stem-cell transplantation relapse, or two or more previous salvage therapies

*Table 2:* Hazard ratios for progression-free and overall survival by number of risk factors

**post-hoc analysis**

# AETHERA

- ASH 2016, Moskowitz C recommended use of BV post HDC auto-SCT in patients with at least 2/5 risk factors

  - (a) relapsed HL, initial CR <12 months or refractory 1st line
  - (b) <CR to most recent salvage chemotherapy
  - (c) extranodal involvement at the start of salvage
  - (d) B symptoms at the time of salvage
  - (e) >1 salvage chemotherapy required to achieve PR/CR

- This was apparently not a preplanned analysis in AETHERA trial nor so far endorsed by the other AETHERA investigators.
  - Education Program of the American Society of Hematology American Society of Hematology Education Program. 2016 Dec 02;2016(1):331-8.

# A E T H E R A

- So far, there is no OS benefit reported in AETHERA trial
- Could early vs. late use of BV post HDC auto-SCT will be of same benefit?
- Given the very high cost of this drug and while waiting for survival benefit at this time, careful selection to identify an agreed upon high risk group that may truly benefit from BV is warranted.
- What will be the role of BV after early vs late failure of patients enrolled in upfront BV use (ECHELON-1 trial comparing ABVD to AVD-BV)?

# Post HDC auto-SCT treatment failure and management

VOLUME 30 · NUMBER 18 · JUNE 20 2012

JOURNAL OF CLINICAL ONCOLOGY

# Results of a Pivotal Phase II Study of Brentuximab Vedotin for Patients With Relapsed or Refractory Hodgkin's Lymphoma

*Anas Younes, Ajay K. Gopal, Scott E. Smith, Stephen M. Ansell, Joseph D. Rosenblatt, Kerry J. Savage,*

| Parameter | Number 102 | % |
|---|---|---|
| Objective response | 76 | 75 |
| Complete remission | 35 | 34 |
| Partial remission | 41 | 40 |
| Stable disease | 22 | 22 |
| Progressive disease | 3 | 3 |
| Not evaluable | 1 | 1 |
| Median response duration, months | 6.7 | |
| Median response duration–CR pts, months (n = 35) | 20.5 | |
| Median PFS, months | 5.6 | |
| Median OS, months | 22.4 | |

Brief Report

blood

CLINICAL TRIALS AND OBSERVATIONS

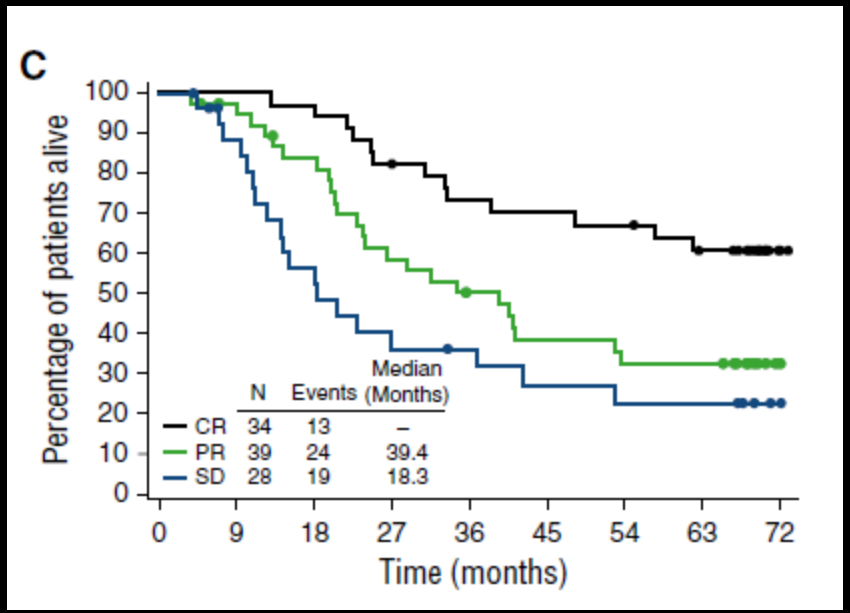
# Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma

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]

[1]City of Hope National Medical Center, Duarte, CA; [2]Division of Medical Oncology, Department of Medicine, University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA; [3]Division of Hematology and Medical Oncology, Department of Medicine, Loyola University Medical Center, Maywood, IL; [4]Mayo Clinic, Rochester, MN; [5]Division of Hematology and Oncology, Department of Medicine, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; [6]British Columbia Cancer Agency Centre for Lymphoid Cancer, Vancouver, BC, Canada; [7]German Hodgkin Study Group, Department of Internal Medicine I, University Hospital of Cologne, Cologne, Germany; [8]Seattle Genetics, Inc., Bothell, WA; [9]Millenium Pharmaceuticals, Inc., Cambridge, MA; and [10]Memorial Sloan Kettering Cancer Center, New York, NY

## Key Points

- A total of 38% of patients who achieved CR (13 of 34) on brentuximab vedotin have remained in remission for >5 years and may be cured.
- Nine of the 13 patients (9% of all enrolled patients) have remained in long-term remission without a consolidative allogeneic transplant.



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 22, 2015 VOL. 372 NO. 4

# PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma

**Table 3. Clinical Activity in Nivolumab-Treated Patients.***

| Variable | All Patients (N=23) | Failure of Both Stem-Cell Transplantation and Brentuximab (N=15) | No Stem-Cell Transplantation and Failure of Brentuximab (N=3) | No Brentuximab Treatment (N=5)† |
|---|---|---|---|---|
| Best overall response — no. (%) | | | | |
| Complete response | 4 (17) | 1 (7) | 0 | 3 (60) |
| Partial response | 16 (70) | 12 (80) | 3 (100) | 1 (20) |
| Stable disease | 3 (13) | 2 (13) | 0 | 1 (20) |
| Progressive disease | 0 | 0 | 0 | 0 |
| Objective response | | | | |
| No. of patients | 20 | 13 | 3 | 4 |
| Percent of patients (95% CI) | 87 (66–97) | 87 (60–98) | 100 (29–100) | 80 (28–99) |
| Progression-free survival at 24 wk — % (95% CI)‡ | 86 (62–95) | 85 (52–96) | NC§ | 80 (20–97) |
| Overall survival — wk | | | | |
| Median | NR | NR | NR | NR |
| Range at data cutoff¶ | 21–75 | 21–75 | 32–55 | 30–50 |

87% RR

* NC denotes not calculated, and NR not reached.
† In this group, two patients had undergone autologous stem-cell transplantation and three had not.
‡ Point estimates were derived from Kaplan–Meier analyses; 95% confidence intervals were derived from Greenwood's formula.
§ The estimate was not calculated when the percentage of data censoring was above 25%.
¶ Responses were ongoing in 11 patients.

VOLUME 34 · NUMBER 31 · NOVEMBER 1, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

**phase 1b KEYNOTE-013**

# Programmed Death-1 Blockade With Pembrolizumab in Patients With Classical Hodgkin Lymphoma After Brentuximab Vedotin Failure

*Philippe Armand, Margaret A. Shipp, Vincent Ribrag, Jean-Marie Michot, Pier Luigi Zinzani, John Kuruvilla, Ellen S. Snyder, Alejandro D. Ricart, Arun Balakumaran, Shelonitda Rose, and Craig H. Moskowitz*

**Table 3.** Antitumor Activity of Pembrolizumab (efficacy analysis set)

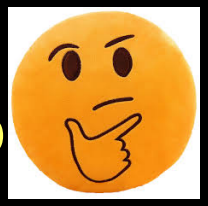
| | Total (N = 31) | | Progressed After Transplantation (n = 22) | | Transplantation Ineligible (n = 9*) | |
|---|---|---|---|---|---|---|
| Best Overall Response | No. | % (90% CI†) | No. | % (90% CI†) | No. | % (90% CI†) |
| Overall response rate | 20 | 65 (48 to 79) | 16 | 73 (53 to 87) | 4 | 44 (17 to 75) |
| Complete remission | 5 | 16 (7 to 31) | 3 | 14 (4 to 32) | 2 | 22 (4 to 55) |
| Partial remission | 15 | 48 (33 to 64) | 13 | 59 (40 to 77) | 2 | 22 (4 to 55) |
| Stable disease | 7 | 23 (11 to 38) | 4 | 18 (7 to 37) | 3 | 33 (10 to 66) |
| Progressive disease | 4 | 13 (5 to 27) | 2 | 9 (2 to 26) | 2 | 22 (4 to 55) |

*One patient refused transplantation and was included in the transplantation ineligible group. That patient achieved a complete remission as best response.
†Based on binomial exact confidence interval method.

# KEYNOTE-087 multi-cohort phase 2 study

| Cohort 1 | Cohort 2 | Cohort 3 |
|---|---|---|
| Failed BV post auto-SCT 30 pts | Failed BV NO auto-SCT (refractory) 30 pts | NO BV post auto-SCT 30 pts |

| Response | Cohort 1 | | Cohort 2 | | Combined | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| PR | 15 | 50 | 16 | 53 | 31 | 51.7 |
| CR | 6 | 20 | 8 | 27 | 14 | 23 |
| ORR | 21 | 70 | 24 | 80 | 45 | 75 |
| Stable Disease | 6 | 20 | 4 | 13 | 10 | 16.7 |
| Previous lines | | | | | ≥4 in 67% | |
| Median age | 36 | | 33 | | | |

# Allogeneic ???  RIC vs MAC

- Myeloablative versus reduced intensity allogeneic stem cell transplantation for relapsed/refractory Hodgkin's lymphoma in recent years: a retrospective analysis of the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation.
- Genadieva-Stavrik S et al. Ann Oncol. 2016 Dec;27(12):2251-2257

- **≥ 3 lines** **57%**
- **HLA – sib** **87%**
- **MUD** **13%**
- **Previous HDC auto-SCT** **55%**
- **At allo → refractory** **49%**

# NRM has significantly decreased

| Parameter | MAC 63 | RIC 249 | p-value |
|---|---|---|---|
| **Non relapse mortality** | 13% | 12% | 0.6 |
| **Relapse** | 41% | 52% | 0.16 |
| **Event free survival** | 48% | 36% | 0.09 |
| **Overall survival** | 73 | 62 | 0.13 |

| Author | Year | Study design | No. patients | Donor source | Regimen | PFS | OS | TRM |
|---|---|---|---|---|---|---|---|---|
| Alvarez | 2006 | Prospective | 40 | MRD | RIC | 32% @ 2 years | 48% @ 2 years | 25% @ 1 year |
| | | | | MUD | | | | |
| Anderlini | 2005 | Retrospective | 40 | MRD | RIC | 37% @ 1,5 years (FM) | 73% @ 1,5 years (FM) | 5% @ 1,5 years (FM) |
| | | | | MUD | | 21% @ 1,5 years (FC) | 39% @ 1,5 years (FC) | 22% @ 1,5 years (FC) |
| Anderlini | 2008 | Prospective | 58 | MRD | RIC | 32% @ 2 years | 64% @ 2 years | 15% @ 2 years |
| | | | | MUD | | | | |
| Burroughs | 2008 | Retrospective | 90 | MRD | NMAC | 23% @ 2 years (MRD) | 53% @ 2 years (MRD) | 21% @ 2 years (MRD) |
| | | | | MUD HAPLO | | 29% @ 2 years (MUD) | 58% @ 2 years (MUD) | 8% @ 2 years (MUD) |
| | | | | | | 51% @ 2 years (HAPLO) | 58% @ 2 years (HAPLO) | 9% @ 2 years (HAPLO) |
| Corradini | 2007 | Phase II | 32 | MRD | RIC | NR | 32% @ 3 years | 3% @ 3 years |
| Crocchiolo | 2015 | Retrospective | 111 | MRD | MAC/NMAC/RIC | 61% @ 3 years | 68% @ 3 years | 17% @ 3 years |
| | | | | MUD HAPLO UCB | | | | |
| Devetten | 2009 | Retrospective | 143 | MUD | NMAC/RIC | 30% @ 1 year | 56% @ 1 year | 33% @ 2 years |
| | | | | | | 20% @ 2 years | 37% @ 2 years | |
| Gajewski | 1996 | Retrospective | 100 | MRD | MA | 15% @ 3 years | 21% @ 3 years | NR |
| Majhail | 2006 | Prospective | 21 | UCB | RIC | UCB: 25% @ 2 years | UCB: 51% @ 2 years | UCB 11% at 100 days |
| | | | | MRD | | MRD: 20% @ 2 years | MRD: 50% @ 2 years | MRD 17% at 100 days |

| Author | Year | Study design | No. patients | Donor source | Regimen | PFS | OS | TRM |
|---|---|---|---|---|---|---|---|---|
| Marcais | 2013 | Retrospective | 191 | UCB<br>MRD<br>MUD | RIC | 39% @ 3 years | 63% @ 3 years | 16% @ 3 years |
| Milpied | 1996 | Retrospective | 45 | MRD | MAC | 15% @ 4 years | 25% @ 4 years | 48% @ 4 years |
| Peggs | 2005 | Prospective | 49 | MRD<br>MUD | RIC | 39% @ 4 years | 56% @ 4 years | 15% @ 2 years |
| Peggs | 2007 | Retrospective | 67 | MRD | RIC/DLI | 39% @ 4 years (MF-A)<br>25% @ 4 years (MF) | 62% @ 4 years (MF-A)<br>39% @ 4 years (MF) | 7% @ 2 years (MF-A)<br>29% @ 2 years (MF) |
| Peggs | 2011 | Retrospective | 76 | MRD<br>MUD | RIC | NR | 64% @ 4 years | 59% @ 4 years |
| Raiola | 2014 | Retrospective | 26 | HAPLO | NMAC | 63% @ 3 years | 77% @ 3 years | 4% @ 2 years |
| Robinson | 2002 | Retrospective | 188<br>(52 HL) | MRD<br>MUD | RIC | 46% @ 1 year | 62% @ 1 year<br>50% @ 3 years | 25.5% @ 1 year<br>34.3% @ 2 years |
| Robinson | 2009 | Retrospective | 285 | MRD<br>MUD | RIC | 29% @ 4 years | 25% @ 4 years | 19% @ 1 year |
| Sarina | 2010 | Retrospective | 185 | MRD | RIC | 31% @ 2 years | 57% @ 2 years | 12.7% @ 2 years |
| Sureda | 2012 | Phase II | 92 | MUD | RIC | 24% @ 4 years | 43% @ 4 years | 15% @ 1 year |
| Thomson | 2008 | Phase II | 38 | MRD | RIC | 42% @ 5 years | 65% @ 10 years | 13% @ 1 year |

| DONOR SOURCE | CONDITIONING | Timing of allo-SCT |
|---|---|---|
| Match related donor → MRD | Myeloablative | post HDC auto-SCT relapse |
| Match unrelated donor → MUD | Reduced intensity | refractory to 1st salvage but sensitive to 2nd salvage. NO previous HDC auto-SCT |
| Partially mismatched related donor → HAPLO | Non myeloablative | Refractory to salvage |
| Umbilical cord →Cord blood | With or without DLI | |
| | With or without CTX post SCT | |

# Availability of financial resources in various health care systems

## BV x16 vs allo

Bone Marrow Transplantation (2015) **50,** 1037–1056

**www.nature.com/bmt**

**SPECIAL REPORT**

# Indications for allo- and auto-SCT for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2015

A Sureda[1], P Bader[2], S Cesaro[3], P Dreger[4], RF Duarte[1], C Dufour[5], JHF Falkenburg[6], D Farge-Bancel[7], A Gennery[8], N Kröger[9], F Lanza[10], JC Marsh[11], A Nagler[12], C Peters[13], A Velardi[14], M Mohty[15,17] and A Madrigal[16,17] for the European Society for Blood and Marrow Transplantation

| *Disease* | *Disease status* | *Sibling donor allo-HSCT* | *Well-matched URD allo-HSCT* | *Alternative donor allo-HSCT* | *ASCT* |
|---|---|---|---|---|---|
| HL | CR1 | GNR/III | GNR/III | GNR/III | GNR/I |
| | Chemosensitive relapse, no prior auto-HSCT | D/III | D/III | GNR/III | S/I |
| | Chemosensitive relapse, prior auto-HSCT | S/II | S/II | CO/III | CO/III |
| | Refractory | D/II | D/II | D/III | CO/III |

# Thank You

مستشفى الملك فيصل التخصصي ومركز الأبحاث

King Faisal Specialist Hospital & Research Centre

Gen. Org. مؤسسة عامة

# Thanks to all those who helped manage these patients

BMT clinic staff

All oncology staff

All the nurses involved

Apheresis and Immunology lab