HDC SCT in Hodgkin Lymphoma
Changing paradigm

Saad Akhtar, M.D.

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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 3\textsuperscript{rd} or 4\textsuperscript{th} 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 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:


<table>
<thead>
<tr>
<th>Prognostic Score</th>
<th>No. of Patients (%)</th>
<th>Rate of Freedom from Progression (percent)</th>
<th>Rate of Overall Survival (percent)</th>
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<tr>
<td>Individual</td>
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<tr>
<td>0</td>
<td>115 (7)</td>
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<td>2</td>
<td>464 (29)</td>
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<tr>
<td>4</td>
<td>190 (12)</td>
<td>51 ± 2</td>
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<tr>
<td>≥5</td>
<td>111 (7)</td>
<td>42 ± 5</td>
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<td>0–2</td>
<td>939 (58)</td>
<td>74 ± 2</td>
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<td>301 (19)</td>
<td>47 ± 2</td>
<td>59 ± 2</td>
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Freedom from progression
Overall survival

We compare our results with this _______ before

<table>
<thead>
<tr>
<th>IPS</th>
<th>Patients (N = 740)</th>
<th>OS Age ≤ 65 Years (n = 686)</th>
<th>Original Report</th>
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<tr>
<td>0</td>
<td>57</td>
<td>98 ± 2</td>
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<td>94 ± 1</td>
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<tr>
<td>≥ 4</td>
<td>138</td>
<td>78 ± 4</td>
<td>83 ± 4</td>
</tr>
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NOTE. Plus-minus values are rate estimates plus or minus standard error. Abbreviations: FFP, freedom from progression; IPS, International Prognostic Score; OS, overall survival.
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
- Induction Failure: PR, NR / PD

**UPFRONT CONSOLIDATION**
- All Patients
- IPI Stratified

**RELAPSE**
- Sensitive, Resistant
Timing of HDC auto-SCT

UPFRONT
ABBREVIATED
INDUCTION
Risk factor STRATIFIED

INDUCTION FAILURE
PR
NR / PD

UPFRONT
CONSOLIDATION
ALL PATIENTS
Risk factor STRATIFIED

RELAPSE
SENSITIVE
RESISTENT
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

Overall Survival, %

Time (Months)

ASCT
+ 4 CHT
88% at 5 yrs
88% at 5 yrs
LogRank 0.00  P=.99

FFS, %

Time (Months)

ASCT
+ 4 CHT
75% at 5 yrs
82% at 5 yrs
LogRank 0.71  P=.4
Upfront Abbreviated Induction

Risk factor STRATIFIED

Induction Failure

PR
NR / PD

Upfront Consolidation

All Patients
Risk factor STRATIFIED

Relapse

Sensitive
Resistant

Timing of HDC auto-SCT

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

**Check response**

**RT to bulk/residual**

**Randomization**

**PVACE-BOP (x3)**

**HDC auto-SCT 34**

**PVACE-BOP x2 31**

Prednisolone vinblastine doxorubicine chlorambucil etoposide bleomycin vinristine procarbazine
Treatment like this → even in high risk group
Long term toxicity → concern for HDC auto-SCT in this setting
Timing of HDC auto-SCT

UPFRONT ABBREVIATED INDUCTION

INDUCTION FAILURE
PR
NR / PD

UPFRONT CONSOLIDATION
ALL PATIENTS
IPI STRATIFIED

RELAPSE
SENSITIVE
RESISTENT
EARLY / LATE / OTHER

- 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.
Timing of HDC auto-SCT

- **UPFRONT ABBREVIATED INDUCTION**
  - PR
  - NR / PD

- **UPFRONT CONSOLIDATION**
  - ALL PATIENTS
  - IPI STRATIFIED

- **RELAPSE**
  - SENSITIVE
  - RESISTENT
  - EARLY / LATE / OTHER
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 %

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 refractory HL patients
Intended accrual 66 patients

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

DFS is better

OS not significantly different
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

**INDUCTION FAILURE**
- PR
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**UPFRONT CONSOLIDATION**
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**RELAPSE**
- SENSITIVE
- RESISTENT
- EARLY / LATE / OTHER
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 outcome at relapse.
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)
Difficult to compare salvage chemotherapy alone vs HDC auto-SCT

Patient with disease chemosensitive to salvage chemotherapy $\rightarrow$ HDC auto-SCT

Progressing $\rightarrow$ 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 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
<table>
<thead>
<tr>
<th>Author, year, Institution</th>
<th>Patients</th>
<th>f/u</th>
<th>EFS / PFS</th>
<th>OS</th>
<th>Prognostic factors for PFS or OS</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chopra 1993 Univ. College London</td>
<td>46 (of 155)</td>
<td>5 years</td>
<td>33 %</td>
<td>-</td>
<td>Tumor mass, relapse status females, 3 or more lines of chemo(PFS)</td>
<td>Factors for all patients</td>
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<tr>
<td>Bierman 1994 Nebraska</td>
<td>44</td>
<td>36 m</td>
<td>22 %</td>
<td>-</td>
<td>No comments</td>
<td>No comments</td>
</tr>
<tr>
<td>Reece 1995 Vancouver</td>
<td>30</td>
<td>3.6 years</td>
<td>42 %</td>
<td>30%</td>
<td>Bleomycin lung toxicity (OS)</td>
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<tr>
<td>Horning 1997 Stanford</td>
<td>29 (of 119)</td>
<td>40 m</td>
<td>60 %</td>
<td>32 %</td>
<td>B symptoms, response to salvage chemo, lung or marrow involvement at transplant (OS)</td>
<td>Factors for all patients % estimated from graph</td>
</tr>
<tr>
<td>Lazarus 1999 ABMTR (1989-95)</td>
<td>122</td>
<td>28 m After BMT</td>
<td>38 %</td>
<td>50 %</td>
<td>B symptoms at dx, performance status at HDC (OS)</td>
<td>Factor for PR-HL 12% treatment related mortality</td>
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<tr>
<td>André 1999 Paris</td>
<td>86</td>
<td>22 m from dx</td>
<td>25 %</td>
<td>35 %</td>
<td>Response to salvage chemo (OS)</td>
<td>78 of 86 patients with progressive disease</td>
</tr>
<tr>
<td>Sweetenham 1999 EBMT (1979-1995)</td>
<td>175</td>
<td>73 m</td>
<td>32 %</td>
<td>36 %</td>
<td>late transplant (after 18 months) (OS)</td>
<td>Factor for PR-HL No salvage chemo 75 patients(43%) 34/100 PD on salvage 66/100 SD or minimal response</td>
</tr>
<tr>
<td>Josting 8, 2000 German HLSG</td>
<td>70 (of 206)</td>
<td>52 m</td>
<td>31 %</td>
<td>43 %</td>
<td>Performance status, no CR1, age &gt; 50</td>
<td>Factor for PR-HL</td>
</tr>
<tr>
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<td>Patients</td>
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<td>70 (of 206)</td>
<td>52 ms</td>
<td>31 %</td>
<td>43 %</td>
<td>Performance status, no CR1, age &gt; 50</td>
<td>Factor for PR-HL</td>
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<td>Sureda 2001 GEL / TAMO Spain</td>
<td>75 (of 494)</td>
<td>26 ms</td>
<td>17 %</td>
<td>-</td>
<td>&gt; 1 prior chemo, response to salvage chemo (OS)</td>
<td>Factors for all patients PR-HL 49 and resistant relapse 26</td>
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<td>Fermé 2002 GELA</td>
<td>67 (of 157)</td>
<td>50 m</td>
<td>23 %</td>
<td>30 %</td>
<td>B symptoms, response to salvage chemo (OS)</td>
<td>Factors for all patients</td>
</tr>
<tr>
<td>Czyz 2004 Polish Centers</td>
<td>76</td>
<td>3 years</td>
<td>-</td>
<td>34 %</td>
<td>Bulky disease (OS)</td>
<td>Factor for PR-HL</td>
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<tr>
<td>Moskowitz 2004 Memorial SKCC</td>
<td>75</td>
<td>10 years For surviving</td>
<td>45 %</td>
<td>48 %</td>
<td>Response to salvage (OS)</td>
<td></td>
</tr>
<tr>
<td>Lavoie 2005 Vancouver</td>
<td>23 (of 100)</td>
<td>11.4 years</td>
<td>39 %</td>
<td>39 %</td>
<td>&gt; 1 prior chemo (PFS)</td>
<td></td>
</tr>
<tr>
<td>Mortabito 2006 Italian centers (1988-2002)</td>
<td>27 (of 72)</td>
<td>4 year</td>
<td>38 %</td>
<td>64 %</td>
<td>Achieving CR</td>
<td>Factors for all patients</td>
</tr>
<tr>
<td>Akhtar 2007 Saudi Arabia</td>
<td>66</td>
<td>38 m from dx 23 m after BMT</td>
<td>38 %</td>
<td>64 %</td>
<td>&gt; LDH for EFS Mediastinal invol for OS</td>
<td>Short f/u Uniform salvage and HDC</td>
</tr>
</tbody>
</table>

**Note:** EFS = Event-Free Survival, PFS = Progression-Free Survival, OS = Overall Survival, CR1 = Complete Remission 1, PR-HL = Poor Risk Hodgkin's Lymphoma, F/U = Follow-up, HDC = High-Dose Chemotherapy, BMT = Bone Marrow Transplant.
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
Timing of HDC auto-SCT

**UPFRONT**
- ABBREVIATED INDUCTION
- INDUCTION FAILURE
  - PR
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**UPFRONT CONSOLIDATION**
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**RELAPSE**
- SENSITIVE
- RESISTENT
- EARLY / LATE / OTHER
Changes in the primary treatment and response adopted therapy
Over the last 20 years ……………

- North American $\rightarrow$ ABVD

- European $\rightarrow$ 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 $\rightarrow$ positive
  - De-escalation if FDG-PET scan $\rightarrow$ Negative

- All these studies with short f/u for long term OS
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
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.

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 is 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 show FDG-PET scan alone or in combination with other factors as an important prognostic factor.
Improvement in outcome


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<th>Author</th>
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<th>Low albumin</th>
<th>PS</th>
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<td>X</td>
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</tr>
</tbody>
</table>
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
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

Eligibility (n = 329)
- Refractory to front-line Tx
- Relapse <12 months after front-line Tx
- Relapse ≥12 months after front-line Tx with extranodal disease

CR, PR or SD to salvage therapy

ASCT → R

BV
day 1 q21 days x 16

Placebo
day 1 q21 days x 16

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

- 329 randomly assigned
  - 165 assigned to brentuximab vedotin
    - 165 received allocated intervention
      - 6 excluded from follow-up
        - 4 withdrew consent
        - 2 died
        - 159 entered long-term follow-up
          - 165 included in intention-to-treat analysis set
          - 167 included in safety analysis set
  - 164 assigned to placebo
    - 160 received allocated intervention
      - 2 did not receive any allocated intervention
      - 2 received unallocated intervention
      - 5 excluded from follow-up
        - 5 withdrew consent
        - 159 entered long-term follow-up
          - 164 included in intention-to-treat analysis set
          - 160 included in safety analysis set

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
Median PFS 42.9 months
p=0.0013

24.1 months

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.
<table>
<thead>
<tr>
<th>N</th>
<th>Progression-free survival by independent review</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1</td>
<td>329 0.57 (0.40–0.81)</td>
<td>1.15 (0.67–1.97)</td>
</tr>
<tr>
<td>≥2</td>
<td>280 0.49 (0.34–0.71)</td>
<td>0.94 (0.53–1.67)</td>
</tr>
<tr>
<td>≥3</td>
<td>166 0.43 (0.27–0.68)</td>
<td>0.92 (0.45–1.88)</td>
</tr>
</tbody>
</table>

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
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.
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
### 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number</th>
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<tr>
<td>Objective response</td>
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<tr>
<td>Complete remission</td>
<td>35</td>
<td>34</td>
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<tr>
<td>Partial remission</td>
<td>41</td>
<td>40</td>
</tr>
<tr>
<td>Stable disease</td>
<td>22</td>
<td>22</td>
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<tr>
<td>Progressive disease</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Not evaluable</td>
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<tr>
<td>Median response duration, months</td>
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<tr>
<td>Median response duration–CR pts, months (n = 35)</td>
<td>20.5</td>
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<tr>
<td>Median PFS, months</td>
<td>5.6</td>
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<td>Median OS, months</td>
<td>22.4</td>
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</tbody>
</table>
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 Younes10

1City of Hope National Medical Center, Duarte, CA; 2Division of Medical Oncology, Department of Medicine, University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA; 3Division of Hematology and Medical Oncology, Department of Medicine, Loyola University Medical Center, Maywood, IL; 4Mayo Clinic, Rochester, MN; 5Division of Hematology and Oncology, Department of Medicine, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; 6British Columbia Cancer Agency Centre for Lymphoid Cancer, Vancouver, BC, Canada; 7German Hodgkin Study Group, Department of Internal Medicine I, University Hospital of Cologne, Cologne, Germany; 8Seattle Genetics, Inc., Bothell, WA; 9Millennium Pharmaceuticals, Inc., Cambridge, MA; and 10Memorial 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.
PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin’s Lymphoma

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

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

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

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>Total (N = 31)</th>
<th>% (90% CI)</th>
<th>Progressed After Transplantation (n = 22)</th>
<th>% (90% CI)</th>
<th>Transplantation Ineligible (n = 9*)</th>
<th>% (90% CI)</th>
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<tbody>
<tr>
<td>Overall response rate</td>
<td>20</td>
<td>65 (48 to 79)</td>
<td>16</td>
<td>73 (53 to 87)</td>
<td>4</td>
<td>44 (17 to 75)</td>
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<tr>
<td>Complete remission</td>
<td>5</td>
<td>16 (7 to 31)</td>
<td>3</td>
<td>14 (4 to 32)</td>
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<td>22 (4 to 55)</td>
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<tr>
<td>Partial remission</td>
<td>15</td>
<td>48 (33 to 64)</td>
<td>13</td>
<td>59 (40 to 77)</td>
<td>2</td>
<td>22 (4 to 55)</td>
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<tr>
<td>Stable disease</td>
<td>7</td>
<td>23 (11 to 38)</td>
<td>4</td>
<td>18 (7 to 37)</td>
<td>3</td>
<td>33 (10 to 66)</td>
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<tr>
<td>Progressive disease</td>
<td>4</td>
<td>13 (5 to 27)</td>
<td>2</td>
<td>9 (2 to 26)</td>
<td>2</td>
<td>22 (4 to 55)</td>
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</table>

*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

<table>
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<tr>
<th>Response</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Combined</th>
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<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
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<tr>
<td>PR</td>
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<td>ORR</td>
<td>21</td>
<td>70</td>
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<tr>
<td>Stable Disease</td>
<td>6</td>
<td>20</td>
<td>4</td>
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<tr>
<td>Previous lines</td>
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<tr>
<td>Median age</td>
<td>36</td>
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<td>33</td>
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</table>
Allogeneic ???  RIC vs MAC


- > 3 lines 57%
- HLA – sib 87%
- MUD 13%
- Previous HDC auto-SCT 55%
- At allo → refractory 49%
NRM has significantly decreased

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MAC</th>
<th>RIC</th>
<th>p-value</th>
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<tr>
<td>Non relapse mortality</td>
<td>13%</td>
<td>12%</td>
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<tr>
<td>Relapse</td>
<td>41%</td>
<td>52%</td>
<td>0.16</td>
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<tr>
<td>Event free survival</td>
<td>48%</td>
<td>36%</td>
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<td>Overall survival</td>
<td>73</td>
<td>62</td>
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<tr>
<td>DONOR SOURCE</td>
<td>CONDITIONING</td>
<td>Timing of allo-SCT</td>
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<td>--------------------------------------------------------</td>
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<tr>
<td>Match related donor → MRD</td>
<td>Myeloablative</td>
<td>post HDC auto-SCT relapse</td>
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<tr>
<td>Match unrelated donor → MUD</td>
<td>Reduced intensity</td>
<td>refractory to 1&lt;sup&gt;st&lt;/sup&gt; salvage but sensitive to 2&lt;sup&gt;nd&lt;/sup&gt; salvage. NO previous HDC auto-SCT</td>
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</tr>
<tr>
<td>Partially mismatched related donor → HAPLO</td>
<td>Non myeloablative</td>
<td>Refractory to salvage</td>
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<tr>
<td>Umbilical cord → Cord blood</td>
<td>With or without DLI</td>
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</tr>
<tr>
<td></td>
<td>With or without CTX post SCT</td>
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</table>
Availability of financial resources in various health care systems

BV x16 vs allo
SPECIAL REPORT

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

A Sureda1, P Bader2, S Cesaro3, P Dreger4, RF Duarte1, C Dufour5, JHF Falkenburg6, D Farge-Bancel7, A Gennery8, N Kröger9, F Lanza10, JC Marsh11, A Nagler12, C Peters13, A Velardi14, M Mohty15,17 and A Madrigal16,17 for the European Society for Blood and Marrow Transplantation

<table>
<thead>
<tr>
<th>Disease</th>
<th>Disease status</th>
<th>Sibling donor allo-HSCT</th>
<th>Well-matched URD allo-HSCT</th>
<th>Alternative donor allo-HSCT</th>
<th>ASCT</th>
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<td>GNR/III</td>
<td>GNR/III</td>
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<td>Chemosensitive relapse, no prior auto-HSCT</td>
<td>D/III</td>
<td>D/III</td>
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<td>Chemosensitive relapse, prior auto-HSCT</td>
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<td>S/II</td>
<td>CO/III</td>
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<tr>
<td></td>
<td>Refractory</td>
<td>D/II</td>
<td>D/II</td>
<td>D/III</td>
<td>CO/III</td>
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</table>
Thanks to all those who helped manage these patients

BMT clinic staff
All oncology staff
All the nurses involved
Apheresis and Immunology lab