# STATO DELL'ARTE E NUOVI ORIZZONTI TERAPEUTICI NEL TRATTAMENTO DEI LINFOMI

## Il ruolo del brentuximab vedotin nel linfoma di Hodgkin in prima linea e nel paziente ricaduto/refrattario

Milano, 21 gennaio 2020

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Milano

# DISCLOSURES

Chiara Rusconi

| Company name | Research support | Advisory board | Other |
|---|---|---|---|
| CELGENE | X | X | |
| TAKEDA | | X | X (congress' partecipation) |
| ROCHE | | X | X (congress' partecipation) |
| ITALFARMACO | | X | |

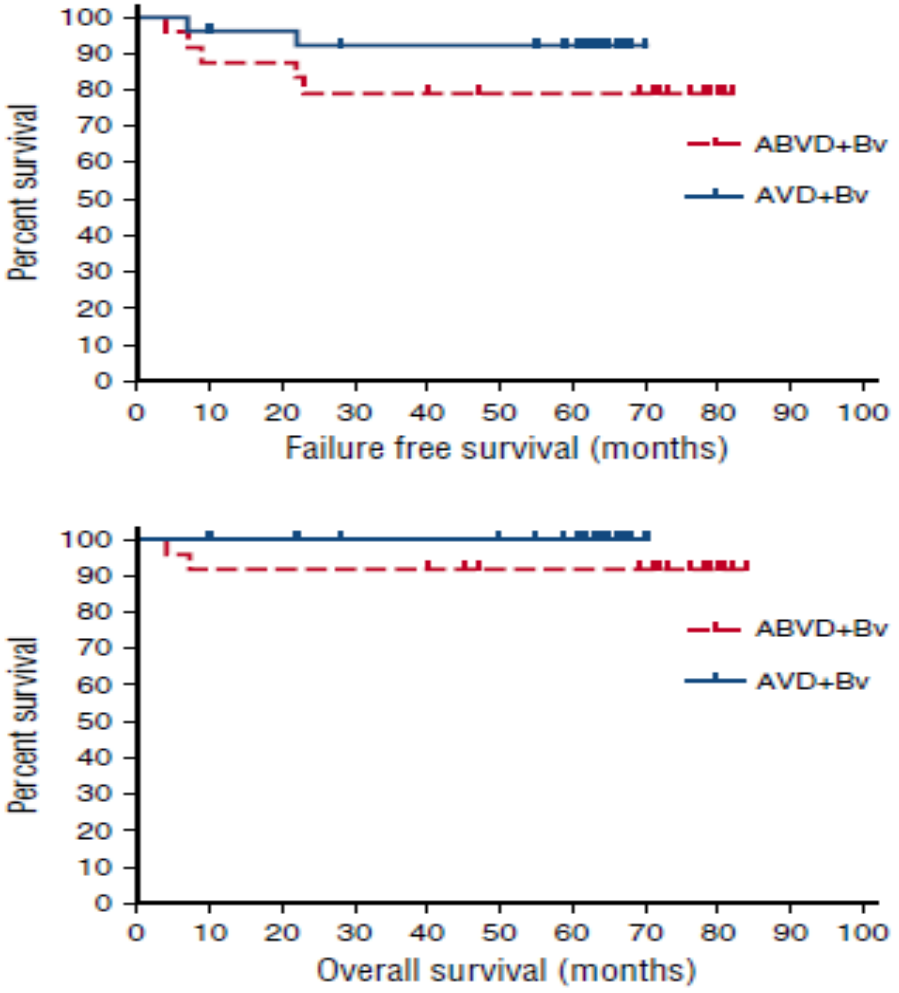
# Brentuximab Vedotin in cHL: first line

- Younger pts:
  - BV+concurrent chemo
- Elderly pts:
  - BV single agent
  - BV+concurrent chemo
  - BV+sequential chemo

# BV+ABVD/AVD

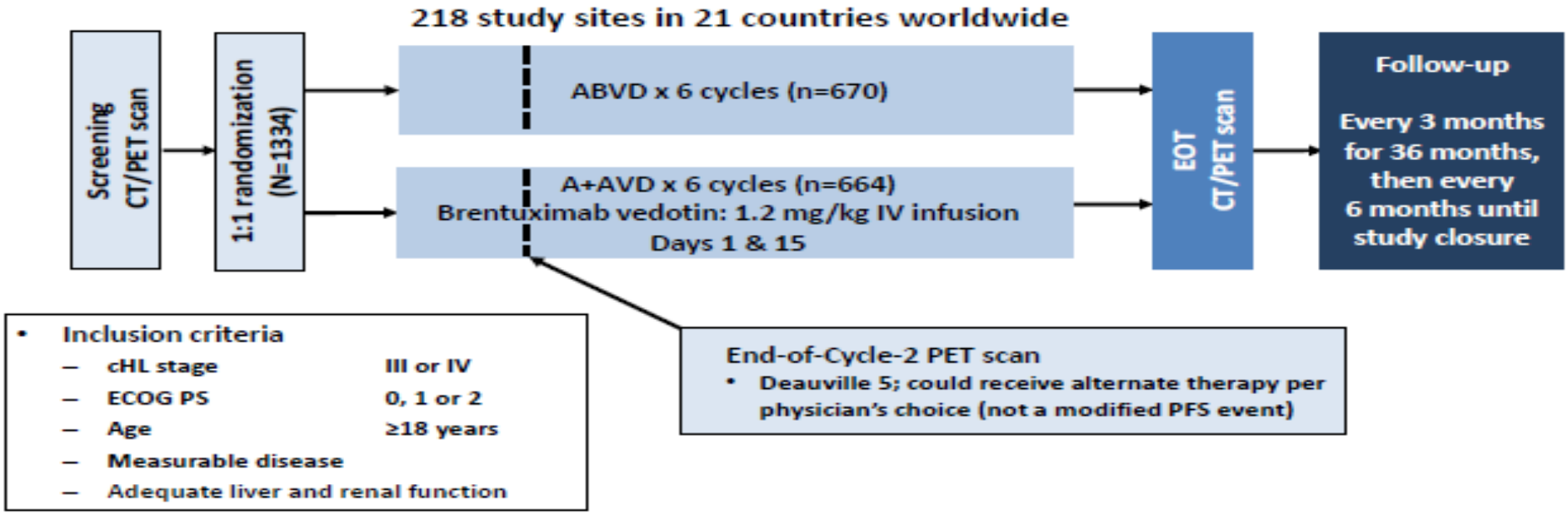
- Phase 1 trial: 25 young cHL pts AS
- **BV 1.2 mg/kg** every two weeks combined
- Excessive pulmonary toxicity (any even
  Bleomycine cannot be safely combined
- 26 pts treated with BV+AVD
- Update after a median follow-up of 5 year

**CR rate: 96%**
**5-years PFS: 92%**
**No unexpected late toxicity**




*Connors JM et al, Blood 2017*

# ABVD vs Bv-AVD in AS cHL: ECHELON-1 trial




**Primary endpoint: modified PFS (mPFS) = time to progression, death or non complete response (EOT PET: DS 3-4-5) and use of subsequent cancer therapy**

*Connors JM et al, NEJM 2017*

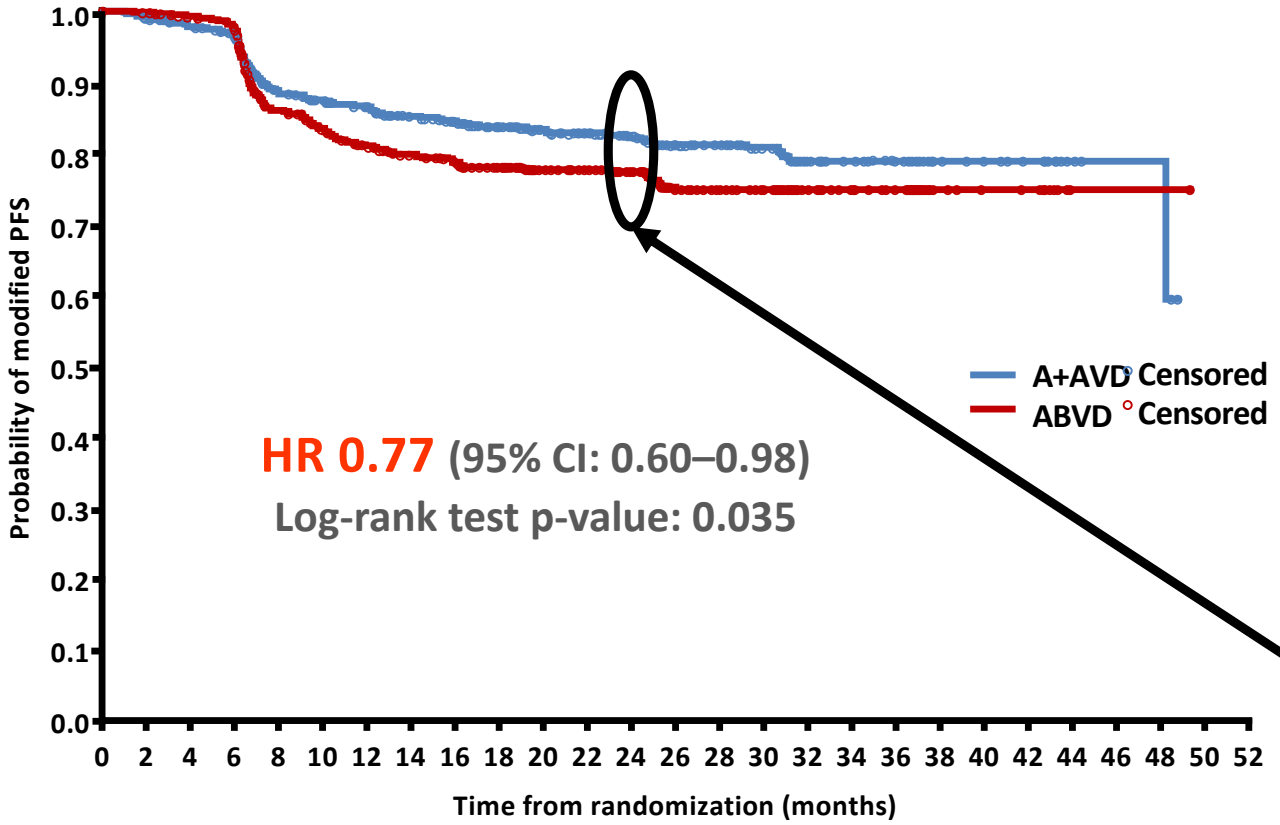
# ECHELON-1: patients characteristics

| Baseline patient characteristics | A+AVD N=664 | ABVD N=670 |
|---|---|---|
| Male, % | 57 | 59 |
| Not Hispanic or Latino, % | 86 | 86 |
| White, % | 84 | 83 |
| Median age, years (range) | 35 (18–82) | 37 (18–83) |
| Age, years, % | | |
| <45 | 68 | 63 |
| 45–59 | 19 | 22 |
| 60–64 | 4 | 6 |
| ≥65 | 9 | 9 |
| Median time since initial diagnosis, months | 0.92 | 0.89 |
| Region, % | | |
| Americas | 39 | 39 |
| Europe | 50 | 50 |
| Asia | 11 | 11 |

| Baseline disease characteristics | A+AVD N=664 | ABVD N=670 |
|---|---|---|
| Ann Arbor stage, % | | |
| III | 36 | 37 |
| IV | 64 | 63 |
| IPS risk factors, %* | | |
| 0–1 | 21 | 21 |
| 2–3 | 53 | 52 |
| 4–7 | 25 | 27 |
| ECOG PS, % | | |
| 0 | 57 | 57 |
| 1 | 39 | 39 |
| 2 | 4 | 4 |
| B symptoms, % | 60 | 57 |
| Bone marrow involvement, % | 22 | 23 |
| Sites of extranodal involvement, %† | | |
| None | 33 | 34 |
| 1 | 33 | 33 |
| >1 | 29 | 29 |

*Connors JM et al, NEJM 2017*

# ECHELON-1: modified PFS




## Number of events

| Category | A+AVD N=117 | ABVD N=146 |
|---|---|---|
| Progression | 90 | 102 |
| Death | 18 | 22 |
| Modified progression | 9 | 22 |
| Chemotherapy | 7 | 15 |
| Radiotherapy | 2 | 7 |

## Modified PFS estimates

| Time | A+AVD (95% CI) | ABVD (95% CI) |
|---|---|---|
| 2-year | 82.1 (78.7–85.0) | 77.2 (73.7–80.4) |

**No statistically significant differences in OS, ORR, CR**

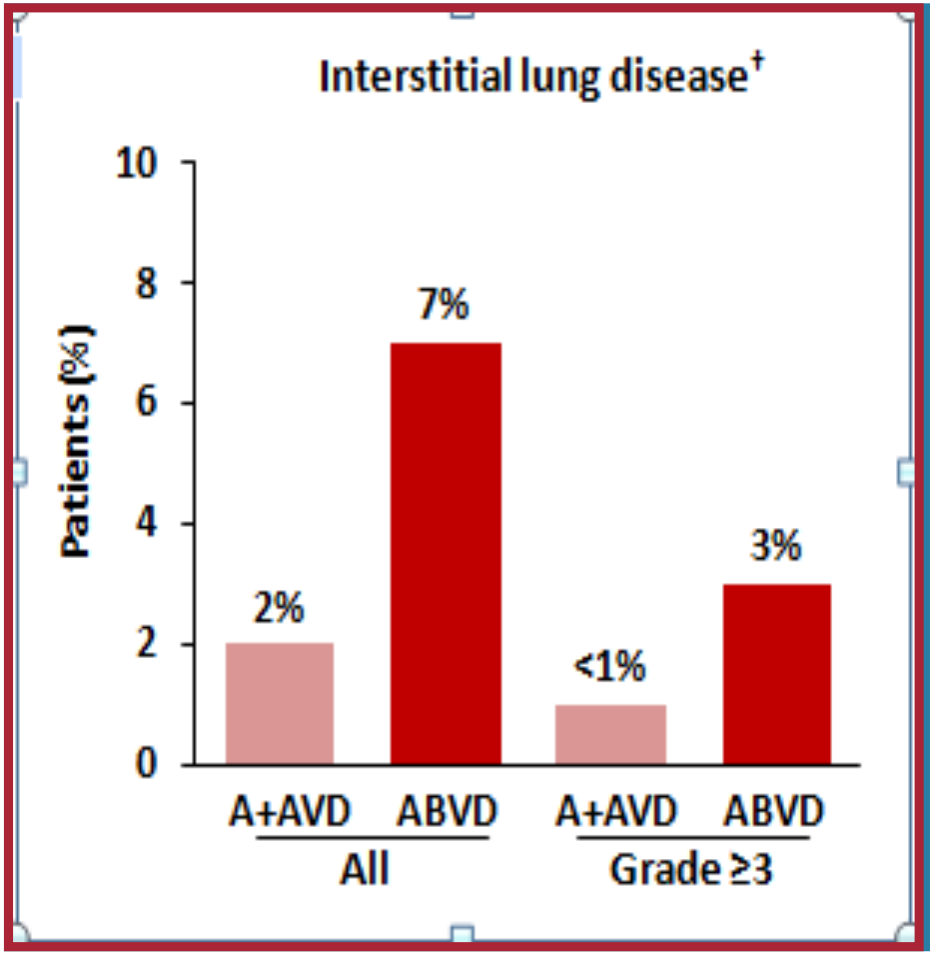
*Connors JM et al, NEJM 2017*

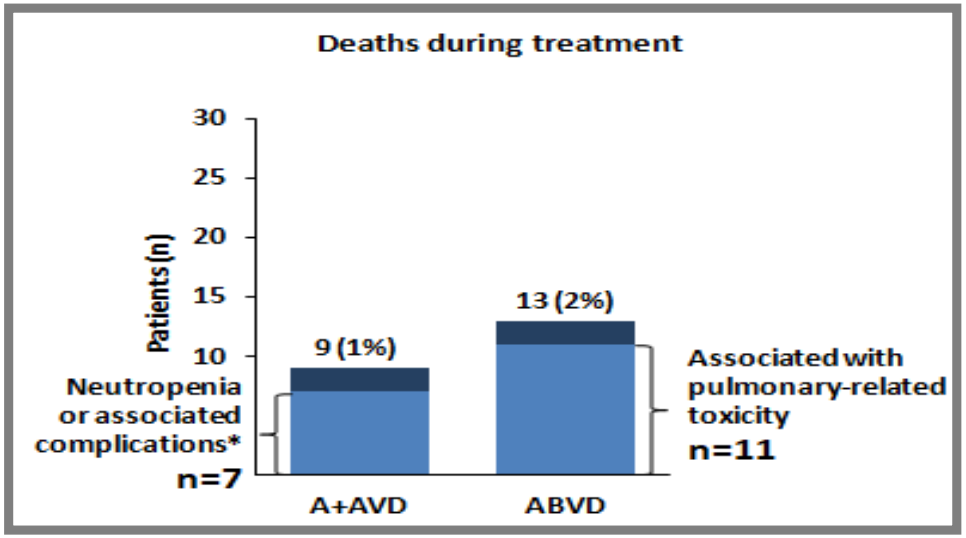
# ECHELON-1: safety

| Common adverse events, %* | A+AVD (N=662) | | ABVD (N=659) | |
|---|---|---|---|---|
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Neutropenia | 58 | 54 | 45 | 39 |
| Constipation | 42 | 2 | 37 | <1 |
| Vomiting | 33 | 3 | 28 | 1 |
| Fatigue | 32 | 3 | 32 | 1 |
| Peripheral sensory neuropathy | 29 | 5 | 17 | <1 |
| Diarrhea | 27 | 3 | 18 | <1 |
| Pyrexia | 27 | 3 | 22 | 2 |
| Peripheral neuropathy | 26 | 4 | 13 | <1 |
| Abdominal pain | 21 | 3 | 10 | <1 |
| Stomatitis | 21 | 2 | 16 | <1 |
| Febrile neutropenia | 19 | 19 | 8 | 8 |

*Connors JM et al, NEJM 2017*

# ECHELON-1: treatment-emergent toxicity

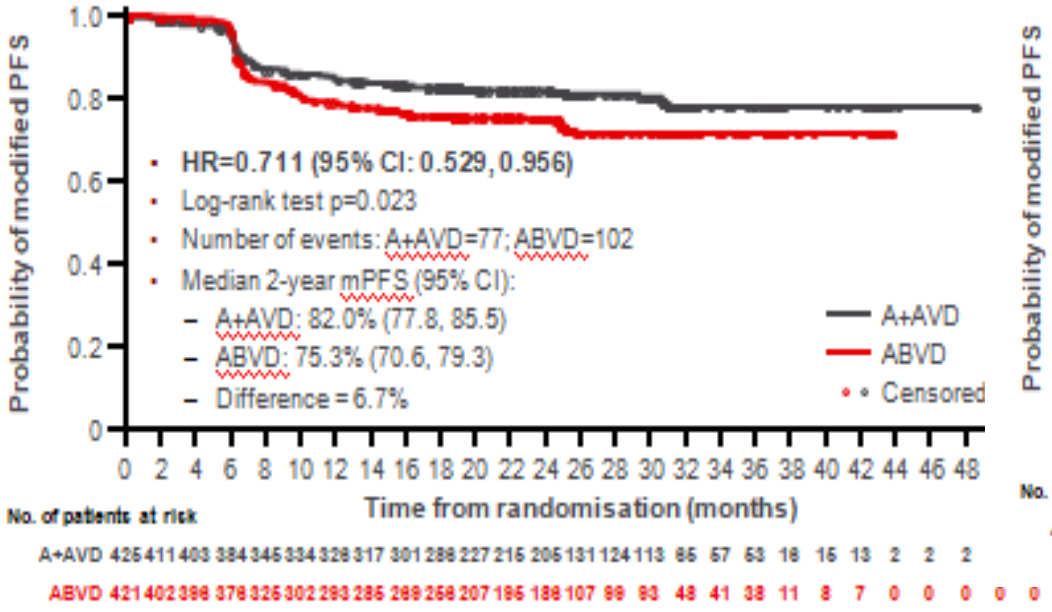


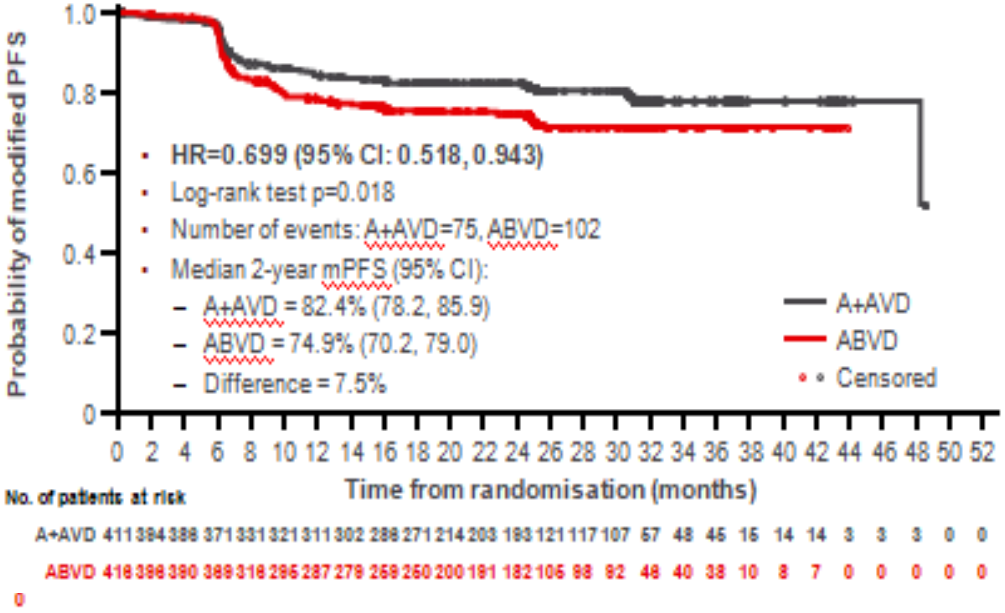

*Connors JM et al, NEJM 2017*

# ECHELON-1: subgroups analysis

## Stage IV




## Baseline extranodal sites ≥1*




*Hutchings M et al, EHA 2018 Oral Presentation*

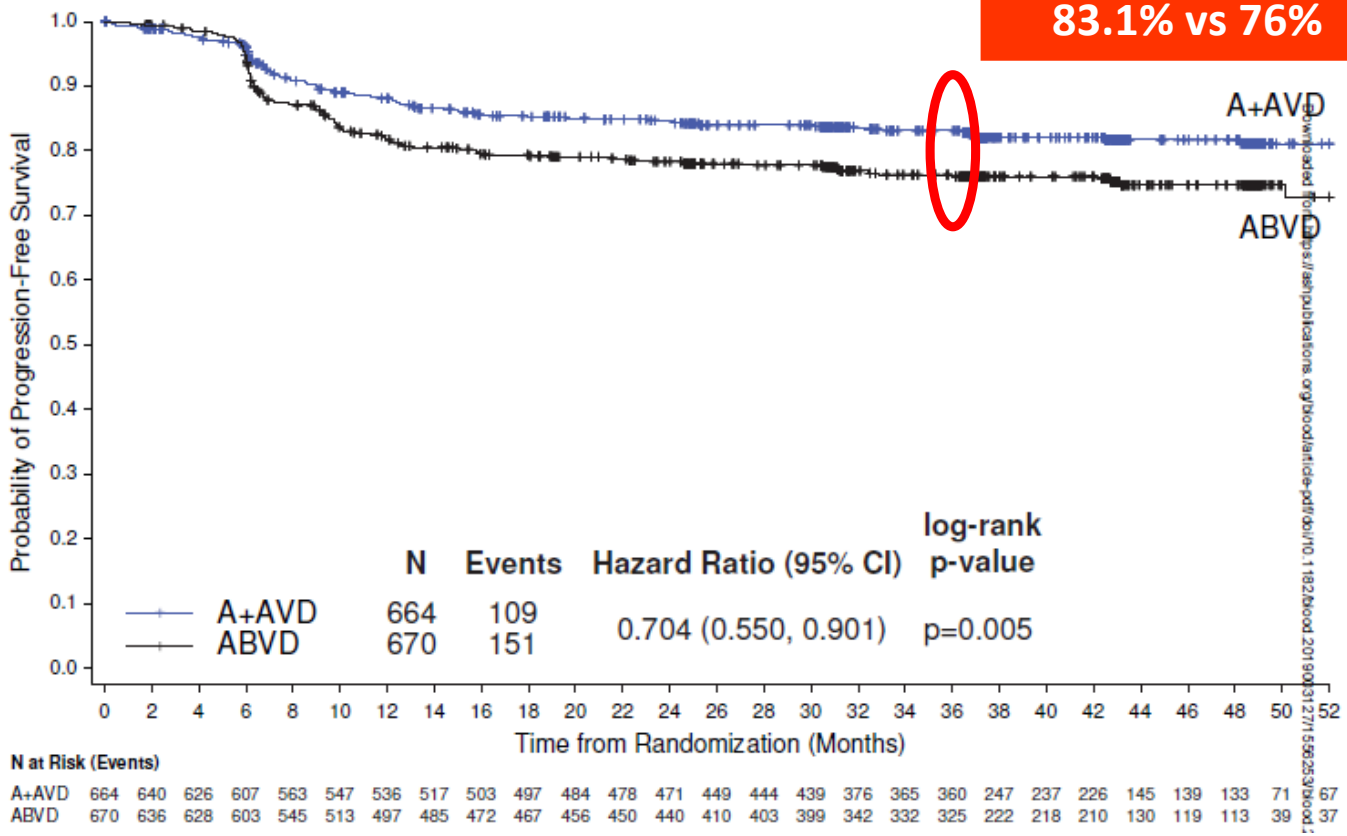
# ECHELON-1 2020

| Characteristic | A+AVD (n = 664) | ABVD (n = 670) | Total (N = 1334) |
|---|---|---|---|
| Male sex, n (%) | 378 (57) | 398 (59) | 776 (58) |
| Age, median (range), years | 35 (18-82) | 37 (18-83) | 36 (18-83) |
| <60 years, n (%) | 580 (87) | 568 (85) | 1148 (86) |
| ≥60 years, n (%) | 84 (13) | 102 (15) | 186 (4) |
| Regions, n (%) | | | |
| Americas | 261 (39) | 262 (39) | 523 (39) |
| Europe | 333 (50) | 336 (50) | 669 (50) |
| Asia | 70 (11) | 72 (11) | 142 (11) |
| International Prognostic Score, n (%) | | | |
| 0 or 1 | 141 (21) | 141 (21) | 282 (21) |
| 2 or 3 | 354 (53) | 351 (52) | 705 (53) |
| 4 to 7 | 169 (25) | 178 (27) | 347 (26) |
| ECOG performance status, n (%) | | | |
| 0 | 376 (57) | 378 (57) | 754 (57) |
| 1 | 260 (39) | 263 (39) | 523 (39) |
| 2 | 28 (4) | 27 (4) | 55 (4) |
| PET2 status | | | |
| Positive | 47 (7) | 58 (9) | 105(8) |
| Negative | 588 (89) | 577 (86) | 1165(87) |
| Unknown/unavailable | 29 (4) | 35 (5) | 64 (5) |

*Straus D al, Blood 2020*

# ECHELON-1 2020

**PFS@3 years:**
**83.1% vs 76%**




*Straus D al, Blood 2020*

# ECHELON-1 2020

| % (95% CI) | A+AVD n = 664 | ABVD n = 670 | Difference (%) | HR (95% CI)[a] | *P* Value[b] |
|---|---|---|---|---|---|
| All patients | 83.1 (79.9-85.9) | 76.0 (72.4-79.2) | 7.1 | 0.70 (0.55-0.90) | 0.005 |
| PET2(−) | 85.8 (82.6-88.5) n = 577 | 79.5 (75.8-82.7) n = 573 | 6.3 | 0.69 (0.52-0.91) | 0.009 |
| PET2(+) | 67.7 (53.8-78.3) n = 58 | 51.5 (38.2-63.4) n = 63 | 16.2 | 0.59 (0.33-1.07) | 0.077 |

**Ready to get rid of PET-oriented strategies? If A-AVD you can:**

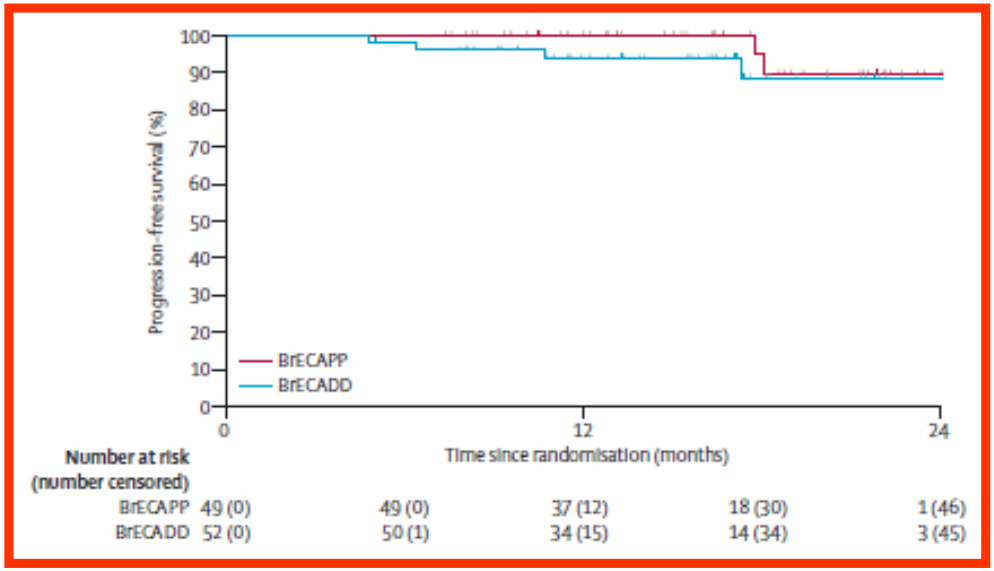
- avoid real-time disease assessment @ cycle 2, which may be challenging in some settings
- spare bleomycin-exposure to the totality of pts
- avoid additional early and late toxicity of intensified strategies in PET2+ pts

***Straus D al, Blood 2020***

# Not only ABVD…

**BrECADD:**

**brentuximab vedotin 1·8 mg/kg on day 1**
etoposide 150 mg/m² on days 2–4
doxorubicin 40 mg/m² on day 2
cyclophosphamide 1250 mg/m² on day 2
dacarbazine 250 mg/m² on days 3–4
dexamethasone 40 mg on days 2–5

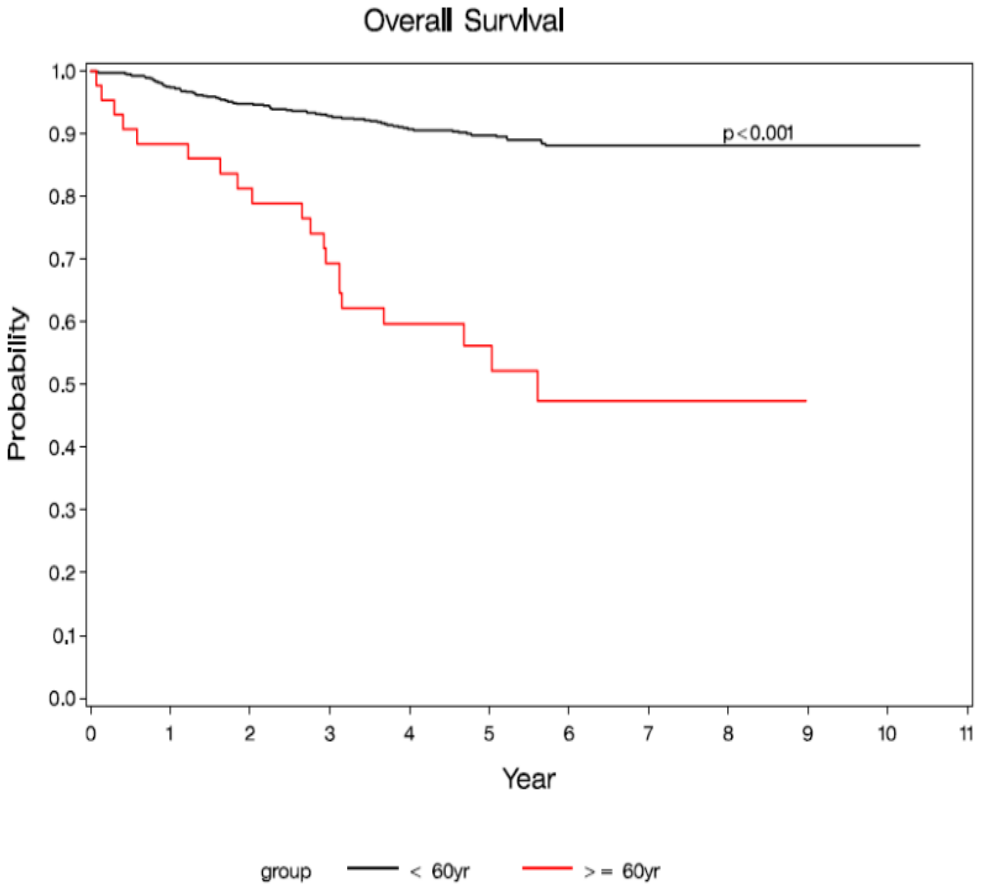



Both eBEACOPP variants met primary efficacy endpoint.
BrECADD regimen associated with more favorable toxicity profile.
**Phase 3 HD21 trial: BrECADD vs eBEACOPP**

***Eichenauer DA et al, Lancet Oncology 2017***

# cHL: the elderly issue

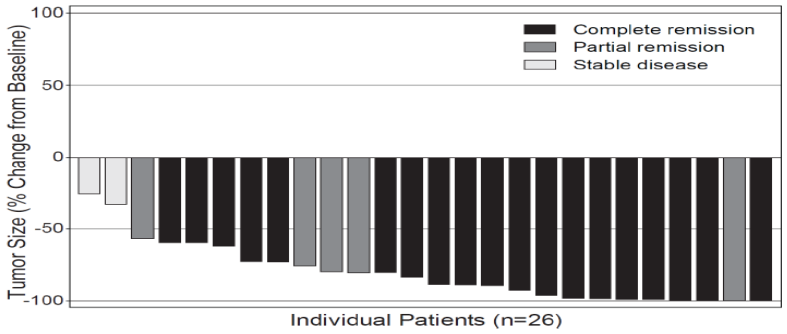
- Defined: age ≥60 years
- Under-represented in clinical trials: <5-10% (vs 15-25% population)
- Outcomes disproportionately inferior to younger patients (and other cancers)

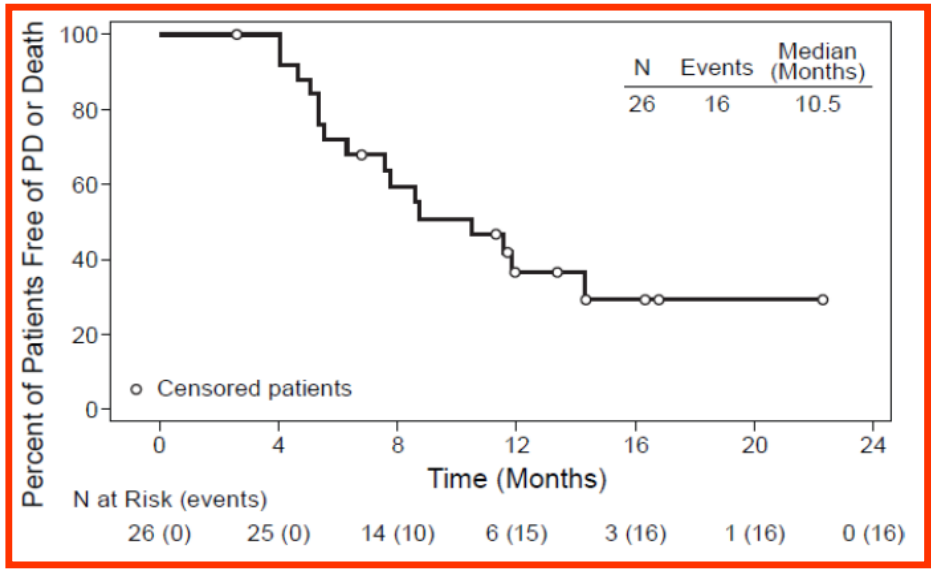



*Evens AM et al, BJH 2013*

# Elderly: BV first line

- 27 pts > 60 y.o. not eligible fo stardard chemo (investigator judgment!)
- Median age 78, range 64-92
- **CR 19 (73%), PFS 10.5 months**
- Median N cycles: 8 (range 1-23)
- 14 (52%) pts dose delays, 11(41%) permanent dose reduction
- **PN 21 pts (78%) , G3 PN 8 (30%)**




*Forero-Torres A et al, Blood 2015*

# Elderly: BV first line combo

- Phase 2 non-randomized trial
- 42 elderly (≥60 years) treatment-naive cHL pts
- Ineligible for (85%) **or declined** frontline standard chemotherapy
- 22 pts received **BV 1.8 mg/kg+Dacarbazine 375 mg/mq** up to 12 cycles; 20 pts received **BV 1.8 mg/kg+Bendamustine 90/70 mg/mq** up to 6 cycles
- Subsequent BV monotherapy was allowed in both arms
- Primary objective: **ORR**

- **ORR: 100%** in both arms; CRR: 62% BV-DTIC, 88% BV-Benda
- **Median PFS:** 17.9 ms BV-DTIC (not reached for CR pts), not reached BV-Benda

***Friedberg JW et al, Blood 2017***

# BV - combo: toxicity

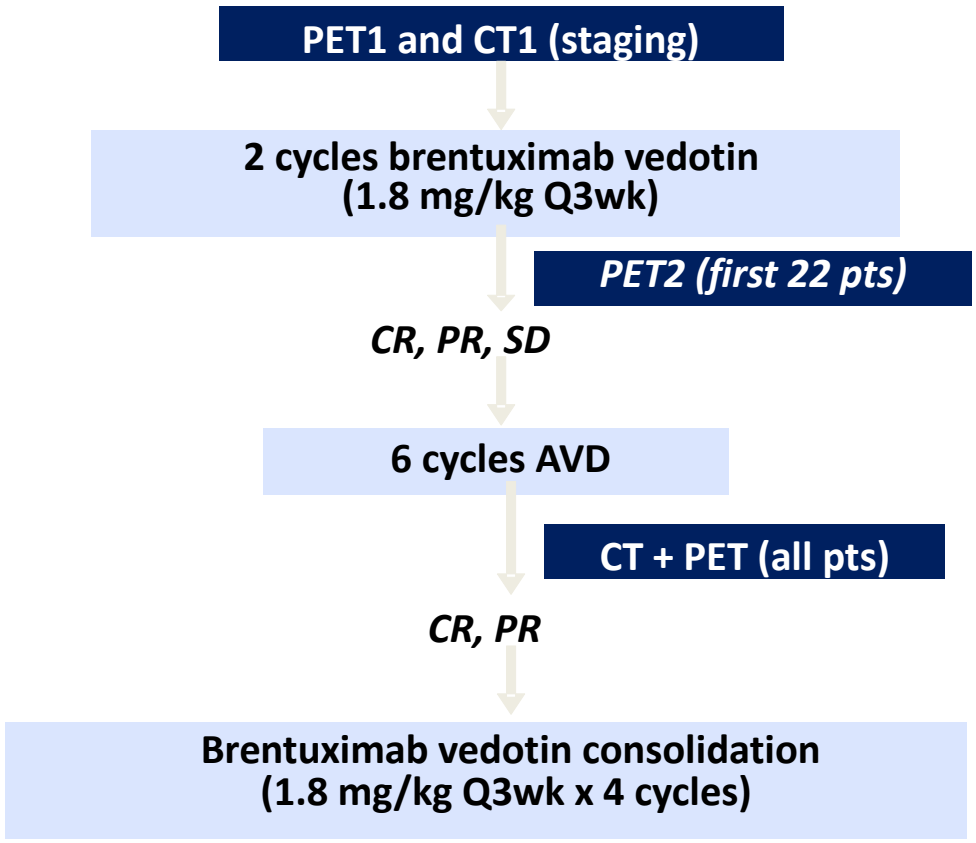
| | BV+DTIC (N=22) n (%) | BV+Bendamustine (N=20) n (%) |
|---|---|---|
| Any treatment-emergent adverse event* | 22 (100) | 20 (100) |
| Treatment-related adverse events | 22 (100) | 19 (95) |
| ≥ Grade 3 adverse events | 10 (45) | 18 (90) |
| Serious adverse events | 4 (18) | 13 (65) |
| Adverse events leading to treatment discontinuation | 12 (55) | 12 (60) |
| Deaths within 30 days of last dose | 0 | 2 (10)† * |

* 1 PD, 1 unknown

- **High activity** was demonstrated with BV in combination with DTIC or Bendamustine in cHL elderly frail patients
- **BV plus Bendamustine poorly tolerated**

*Friedberg JW et al, Blood 2017*

# Sequential Bv-AVD




**Primary endpoint: CR rate after AVD**

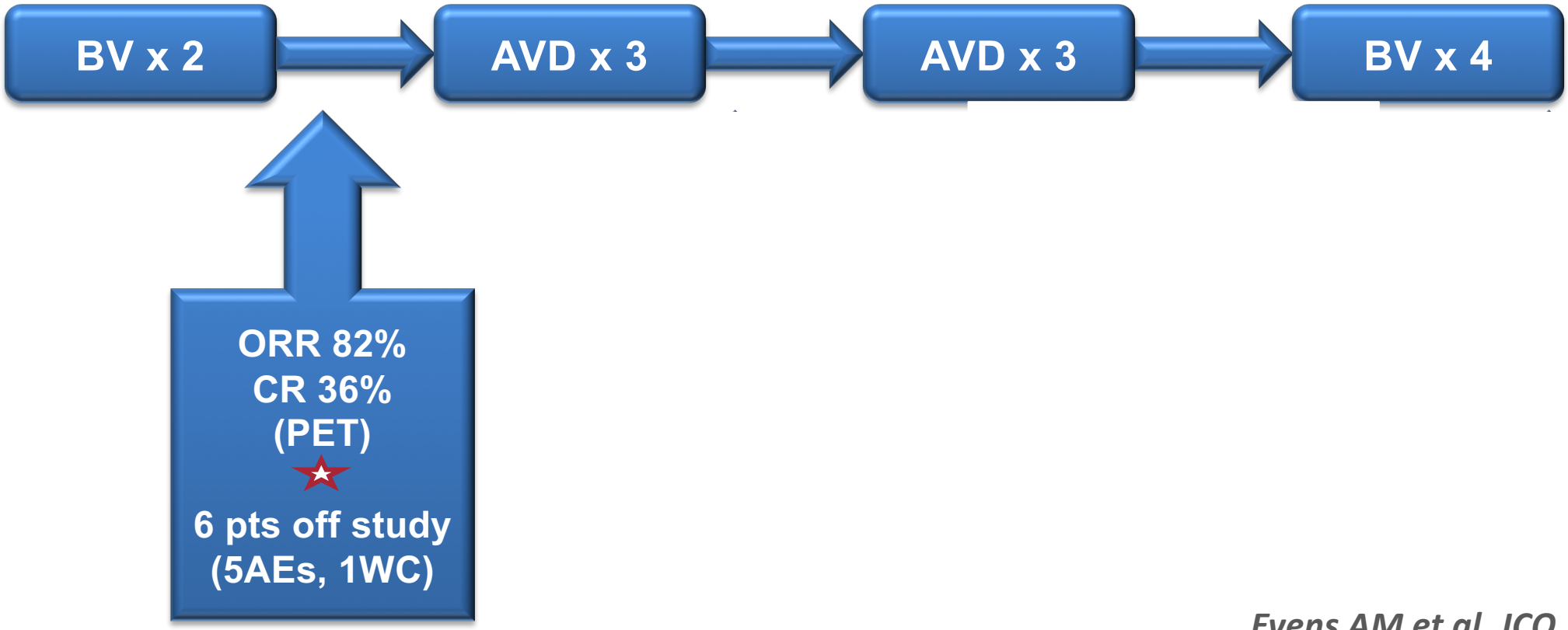
| Characteristic | Data (N=48) |
|---|---|
| Age | Median 69 years (60-88) |
| Gender | M 62%, F 38% |
| Histology | NS 46%, MC 25%, NOS 25% LR 4% |
| ECOG PS | 0: 40%; 1: 41%; 2: 19% |
| Stage | III/IV in 81% (others IIX) |
| B symptoms | 37% |
| IPS≥3 | 58% |
| BM + | 23% |
| Functional status | Median CIRS 7 (0-20)<br>12% loss IADLs |

*Evens AM et al, JCO 2018*

# Sequential Bv-AVD: response and feasibility

**5 AEs**: nausea, fatigue, diarrhea, pneumonia, ☆ fatal pacreatitis

Discontinuation due to: toxicity 35%, refusal 7%, progressive disease/death 6%




*Evens AM et al, JCO 2018*

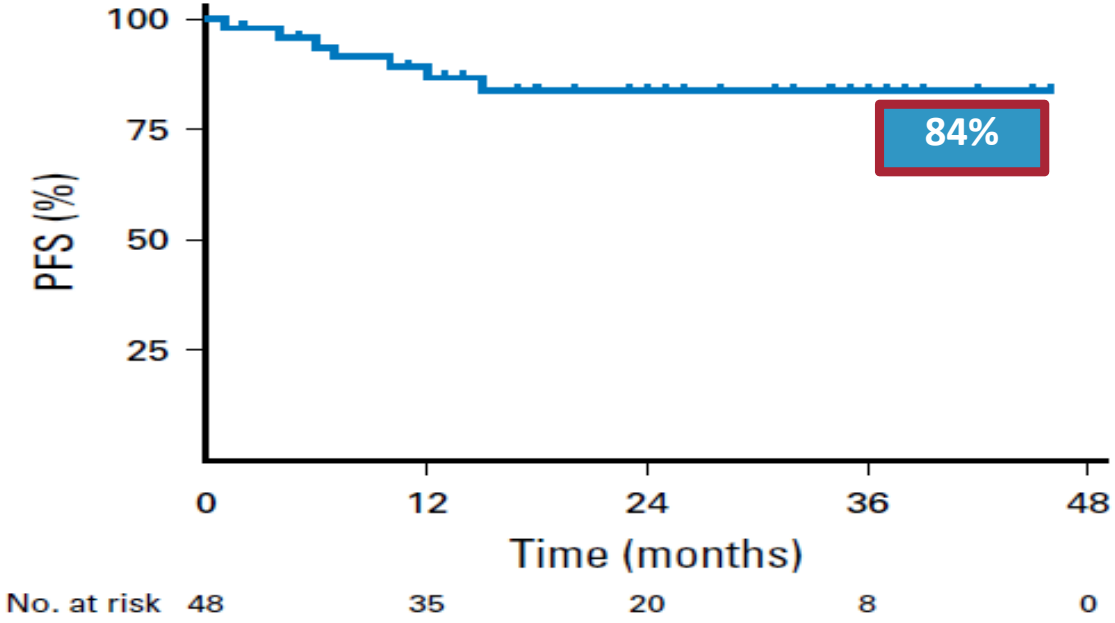
# Sequential Bv-AVD: toxicity

| Adverse Event | Grade 3 | | Grade 4 | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Neutropenia | 8 | 17 | 13 | 27 |
| Lymphopenia | 4 | 8 | 0 | |
| Leucopenia | 3 | 6 | 1 | 2 |
| Febrile neutropenia | 3 | 6 | 1 | 2 |
| Pneumonia | 3 | 6 | 0 | |
| Diarrhea | 2 | 4 | 1 | 2 |
| Increased transaminases | 2 | 4 | 0 | |
| Muscle weakness | 2 | 4 | 0 | |
| Peripheral neuropathy (sensory) | 2 | 4 | 0 | |
| Fatigue | 2 | 4 | 0 | |
| Pancreatitis | 1 | 2 | 1 | 2* |

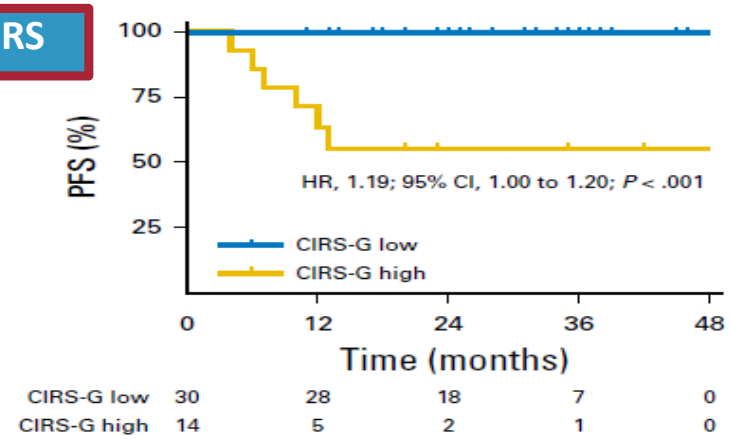
**27%** of patients experienced **grade 2 PN** (6% motor, 21% sensitive); 9/13 PN reverse to grade 1 or lower at 90 days after EOT

***Evens AM et al, JCO 2018***

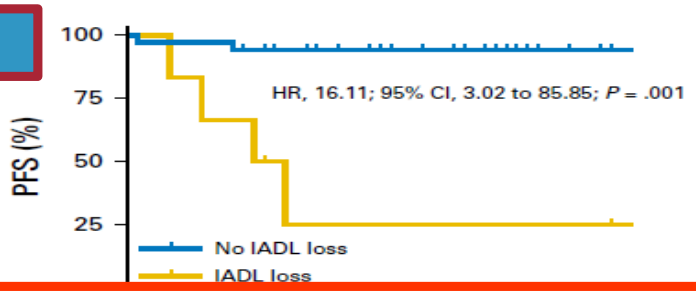
# Sequential Bv-AVD: survival




CIRS




IADL




**Sequential Bv-AVD:** well tolerated and effective; geriatric based measures are strongly associated with survival

*Evens AM et al, JCO 2018*

# Brentuximab Vedotin in cHL: salvage therapy

- Post-ASCT salvage:
  - BV single agent
- Pre-ASCT debulking:
  - BV single agent
  - BV plus chemo
  - BV plus CPI

# BV post HSCT failure: 5-years update

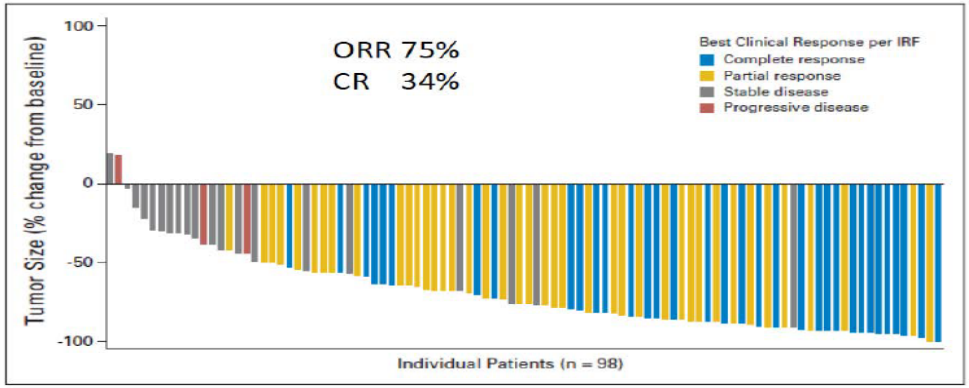
**102 cHL pts R/R after ASCT** (2 ASCT: 11%)

Median age: 31 (15-77)

N° of previous therapy lines: 3.5 (1-13)

Primary refractory disease: 72%

ORR: 76%, **CRR 34%;** Median DOR: 6.7 ms (10.5 CR pts); **Median PFS: 5.6 ms**, Median OS: 22.4 ms

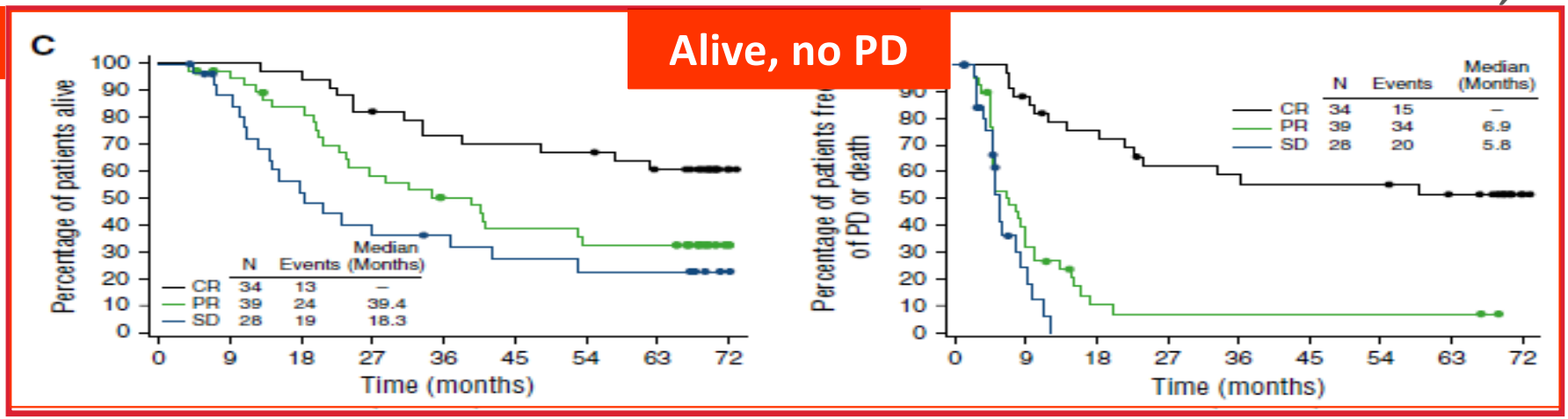



94% patients achieved tumour reduction

*Younes A et al, JCO 2012*

**OS**

**Alive, no PD**




**Median follow-up: 35 ms (1.8-73 ms)**

*Chen R et al, Blood 2016*

# BV as bridge to transplant

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Results of a mu
evaluating the
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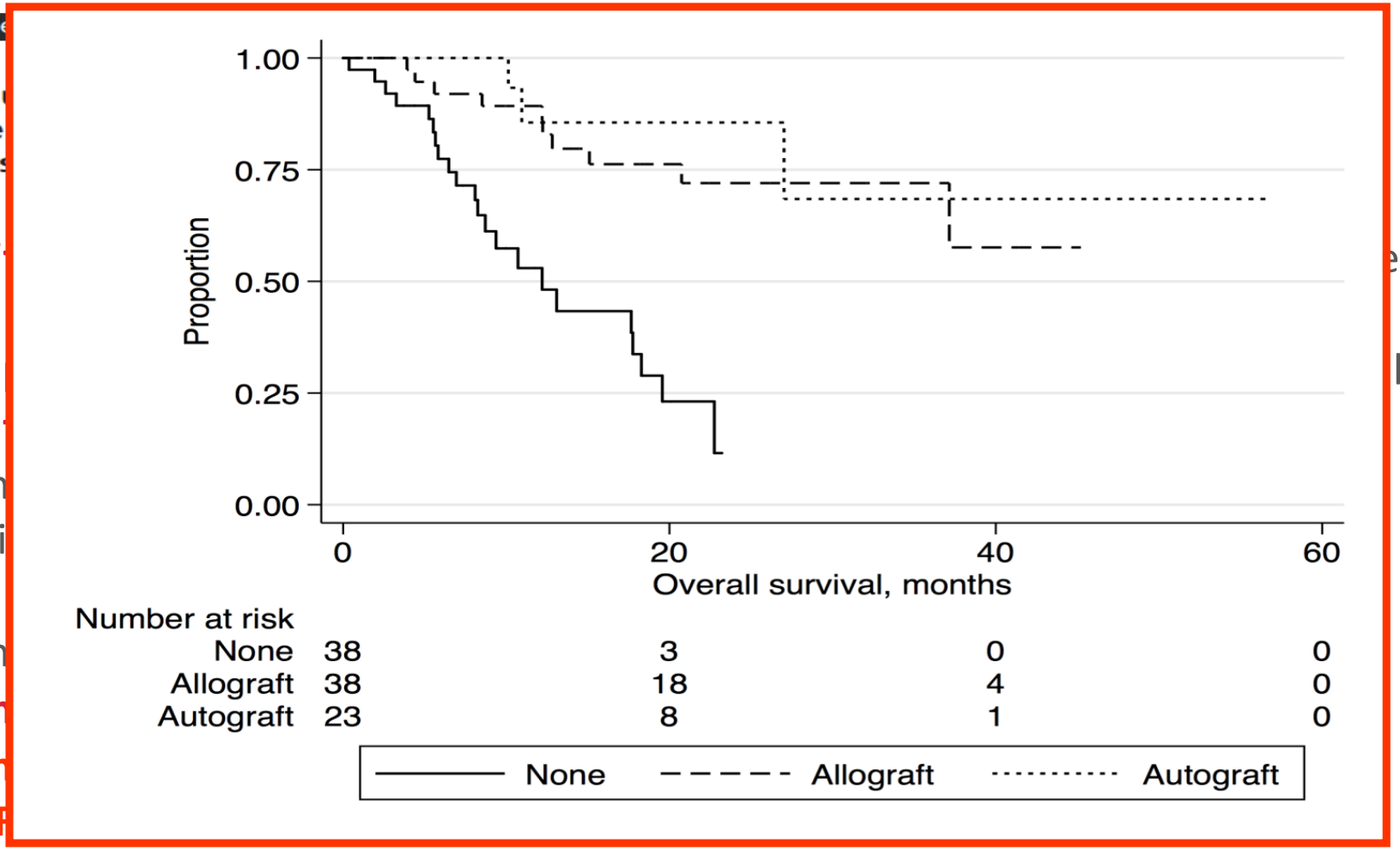
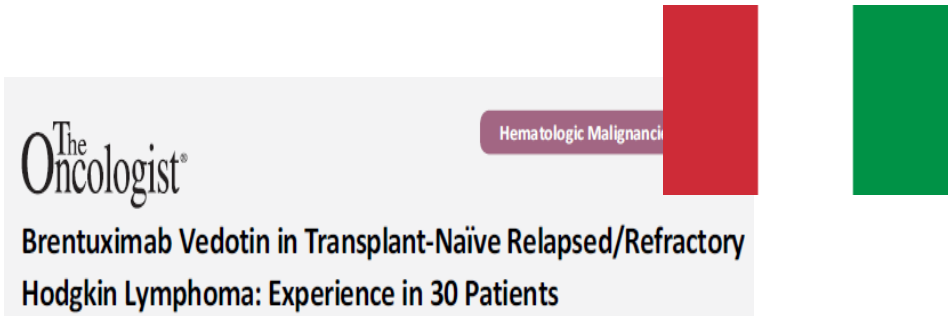
**ORR/CR**

**Median PFS/OS: 5.6 ms/37.8 ms**

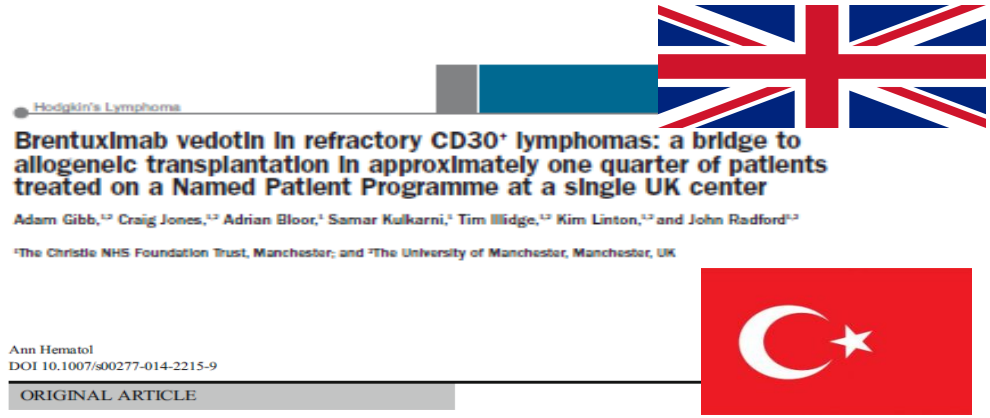



*Eyre TA et al, BJH 2017*

# BV: real-life experiences

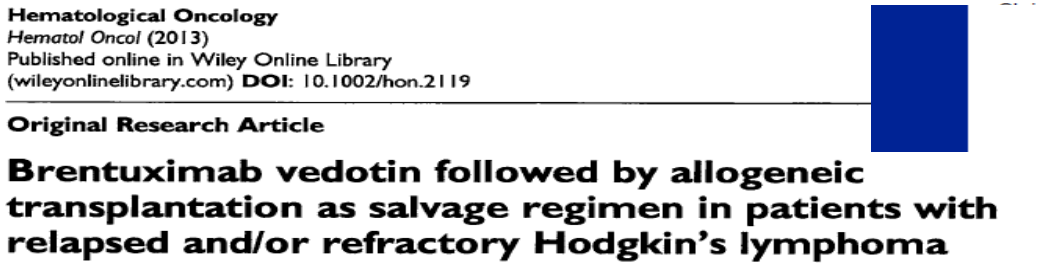










# BV

- DHAP
- ICE
- ESHAP
- BENDA

haematologica 2019; 104:e151

**Phase I dose-escalation study of brentuximab-vedotin combined with dexamethasone, high-dose cytarabine and cisplatin, as salvage treatment in relapsed/refractory classical Hodgkin lymphoma: The HOVON/LLPC Transplant BRaVE study**

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

Alison J Moskowitz, Heiko Schöder, Joachim Yahalom, Susan J McCall, Stephanie Y Fox, John Gerecitano, Ravinder Grewal, Paul A Hamlin, Steven Horwitz, Rachel Kobos, Anita Kumar, Matthew Matasar, Ariela Noy, M Lia Palomba, Miguel-Angel Perales, Carol S Portlock, Craig Sauter, Neerav Shukla, Peter Steinherz, David Straus, Tanya Trippett, Anas Younes, Andrew Zelenetz, Craig H Moskowitz

Brentuximab vedotin and ESHAP is highly effective as second-line therapy for Hodgkin lymphoma patients (long-term results of a trial by the Spanish GELTAMO Group)

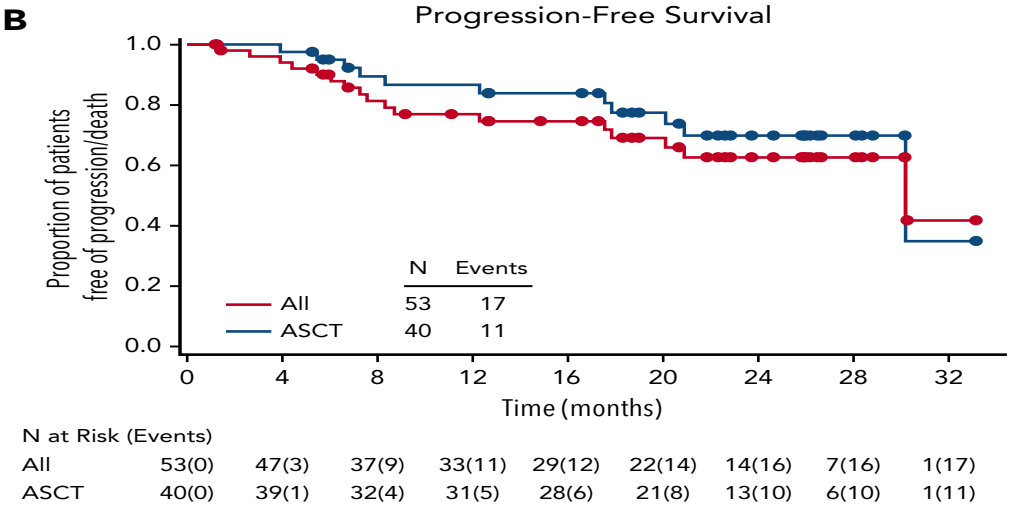
R. Garcia-Sanz[1,2*], A. Sureda[3], F. de la Cruz[4], M. Canales[5], A. P. Gonzalez[6], J. L. Pinana[7], A. Rodriguez[8], A. Gutierrez[9], E. Domingo-Domenech[3], B. Sanchez-Gonzalez[10], G. Rodriguez[11], J. Lopez[12], M. Moreno[13], M. J. Rodriguez-Salazar[14], S. Jimenez-Cabrera[15], M. D. Caballero[1,2] & C. Martinez[16]

CLINICAL TRIALS AND OBSERVATIONS | JULY 5, 2018

**Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma**

| | N=55 |
|---|---|
| Median age, (range) | 36 years (19–79) |
| Gender (% female/male) | 56/44 |
| ECOG status, n (%) | |
| 0 | 36 (65) |
| 1 | 18 (33) |
| 2 | 1 (2) |
| Median time since HL diagnosis, (range) | 13.8 months (3–98 |
| Stage III/IV at diagnosis, n (%) | 29 (53) |
| Baseline disease status, n (%) | |
| Primary refractory | 28 (51) |
| Relapsed | 27 (49) |
| No. of pts with remission duration ≤ 1 yr | 10 (18) |
| B symptoms, n (%) | 12 (22) |
| Bulky disease, n (%) | 5 (9) |
| Extranodal disease, n (%) | 17 (31) |
| Bone marrow involvement, n (%) | 9 (16) |
| PET | 8 (15) |
| Bone marrow biopsy | 3 (15)[a] |
| Median International Prognostic Score (IPS[b]), (range) | 2 (0-5) |

**BBV**



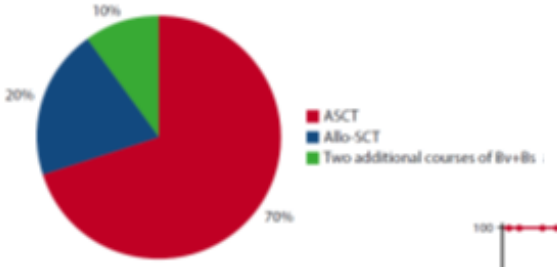

| Best clinical response In 53 pts | % |
|---|---|
| ORR | 92.5 |
| CR | 73.6 |
| PR | 18.9 |
| Refractory | 64 |
| Relapsed | 84 |

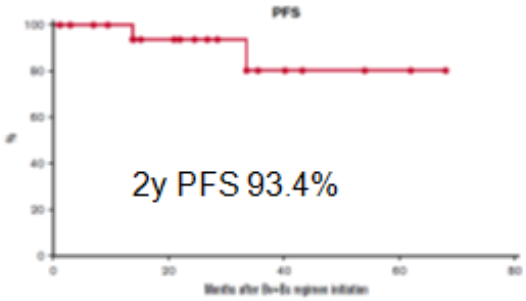
*LaCasce A et al, Blood 2018*

# Benda-BV…

## …as second salvage

**Brentuximab vedotin followed by bendamustine supercharge for refractory or relapsed Hodgkin lymphoma**



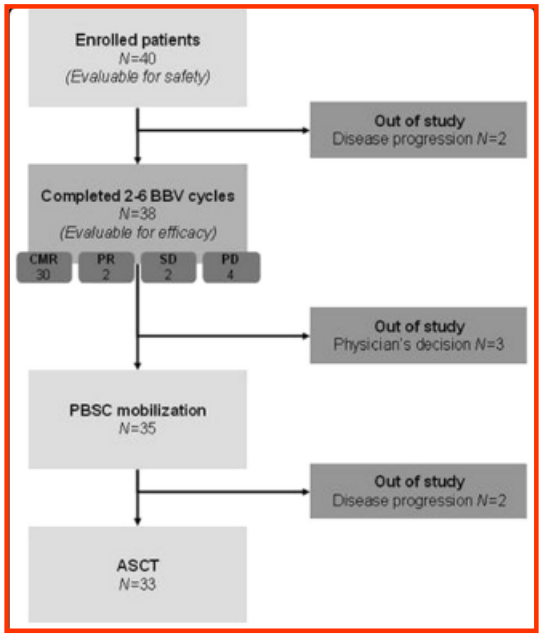




At post-Bv+Bs reevaluation, 80% of patients had deep metabolic responses with Deauville 5-point scale scores≤2.

*Picardi et al, Blood Advances 2019*

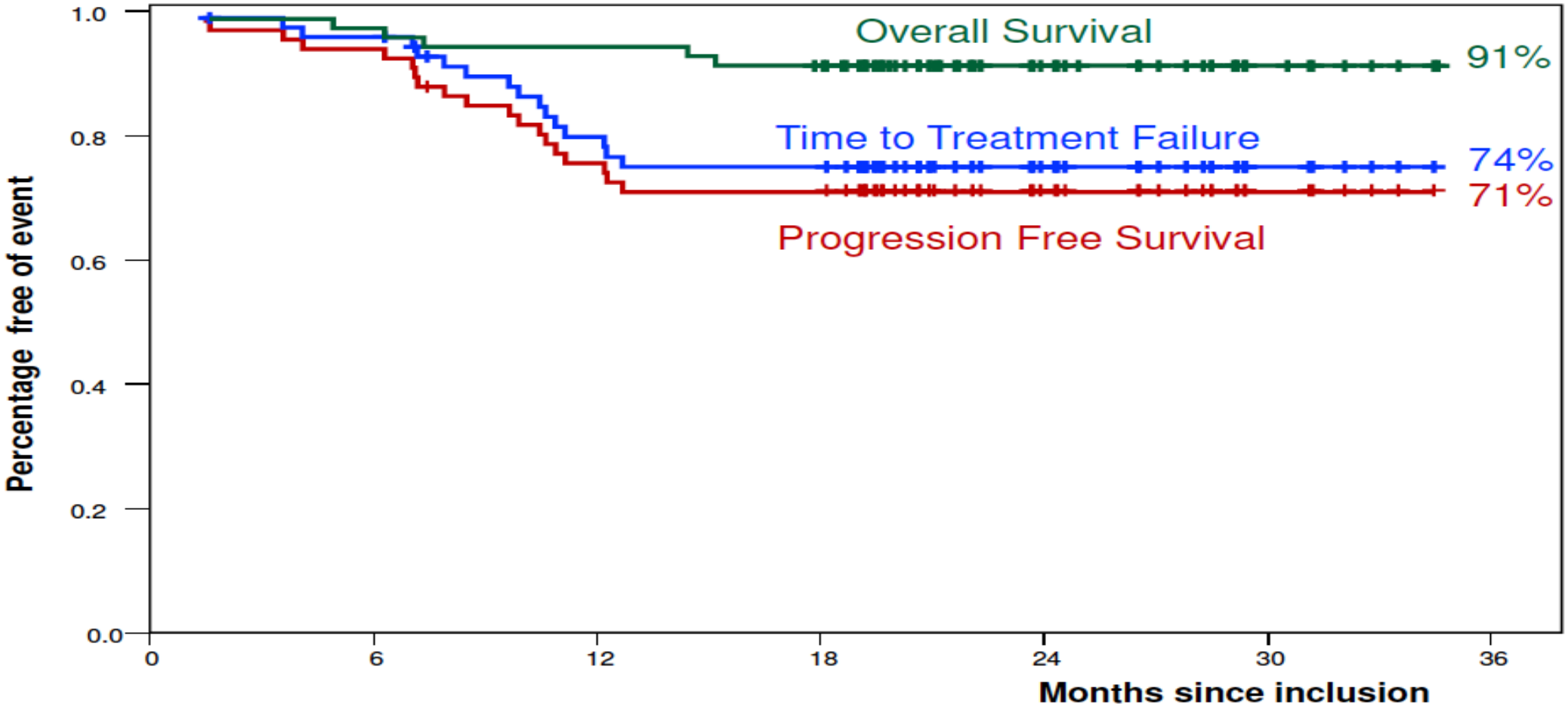
## …as first salvage

First salvage treatment with bendamustine and brentuximab vedotin in Hodgkin lymphoma: a phase 2 study of the Fondazione Italiana Linfomi



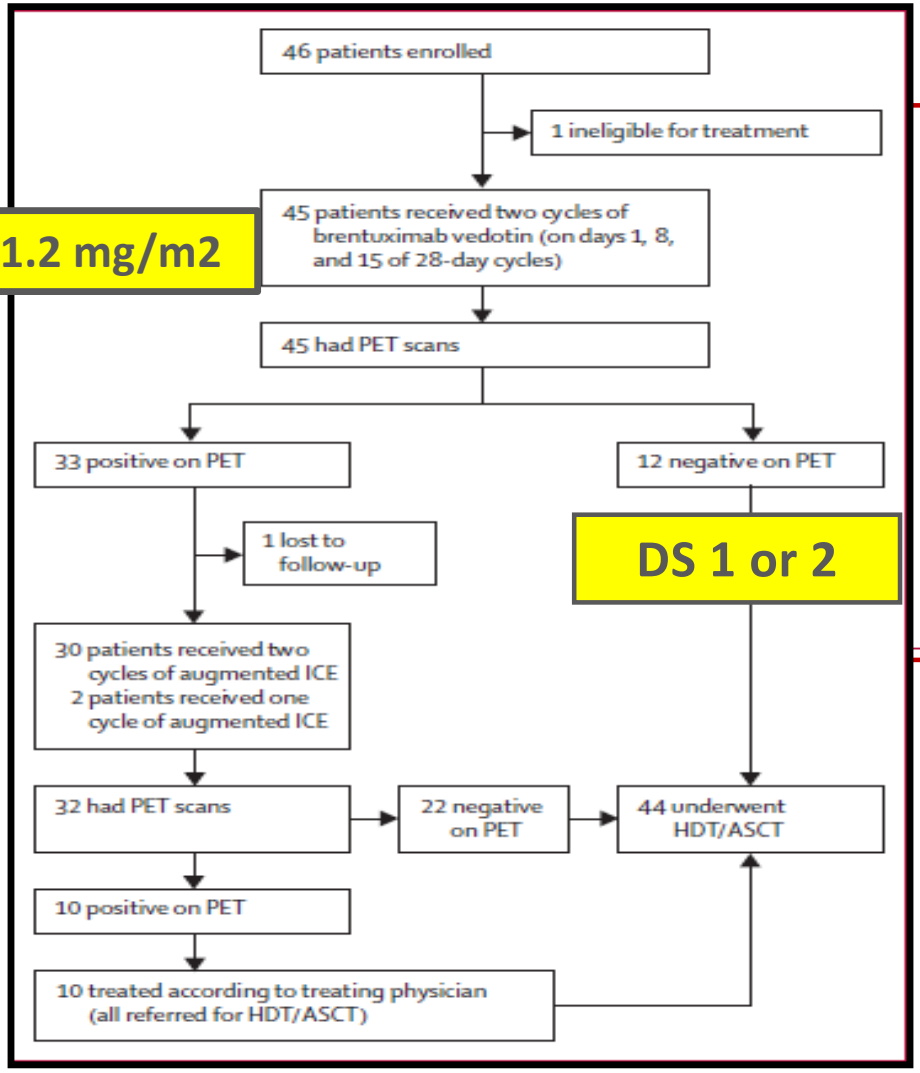

*Broccoli et al, Blood Cancer Journal 2019*

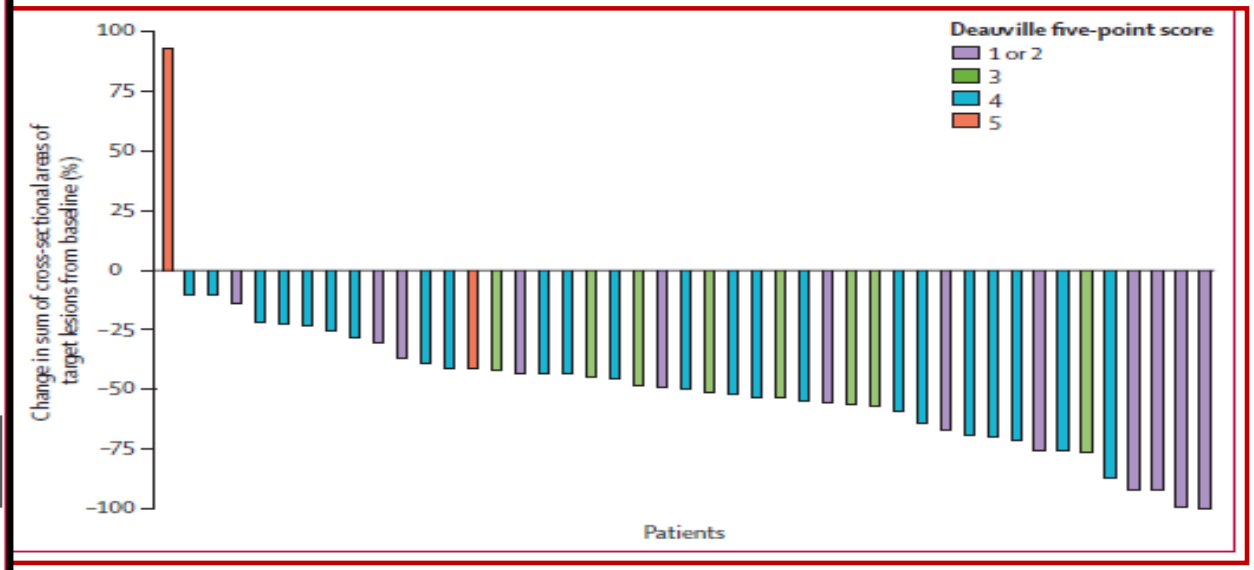
# BrESHAP




*Garcia-Sanz R et al, Ann Oncol 2019*

# Brentuximab-Vedotin +/- augICE pre-ASCT

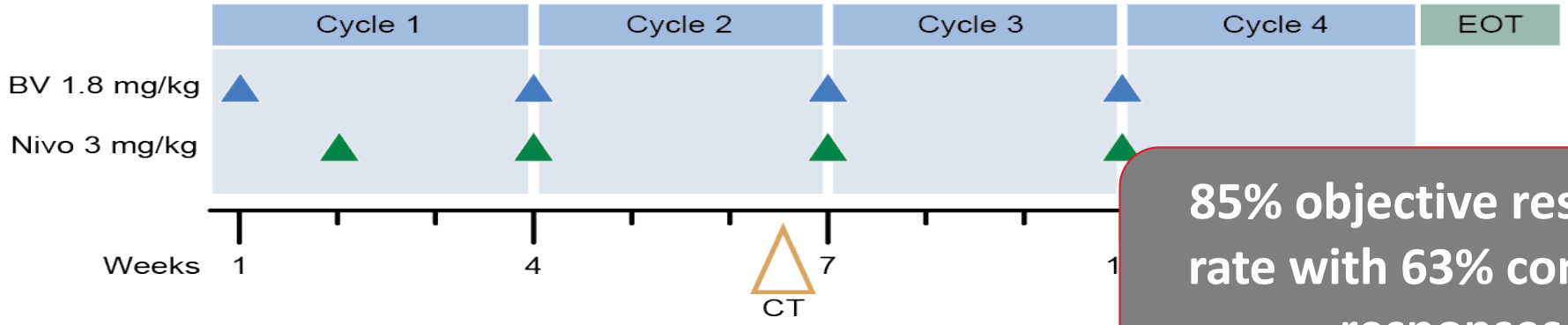



| | Post-BV PET (n=45) | Post-augICE PET (n=32) |
|---|---|---|
| **Deauville score** | | |
| 1* | 4 (9%) | 8 (25%) |
| 2* | 8 (18%) | 14 (44%) |
| 3 | 8 (18%) | 2 (6%) |
| 4 | 23 (51%) | 8 (25%) |
| 5 | 2 (4%) | 0 (0%) |

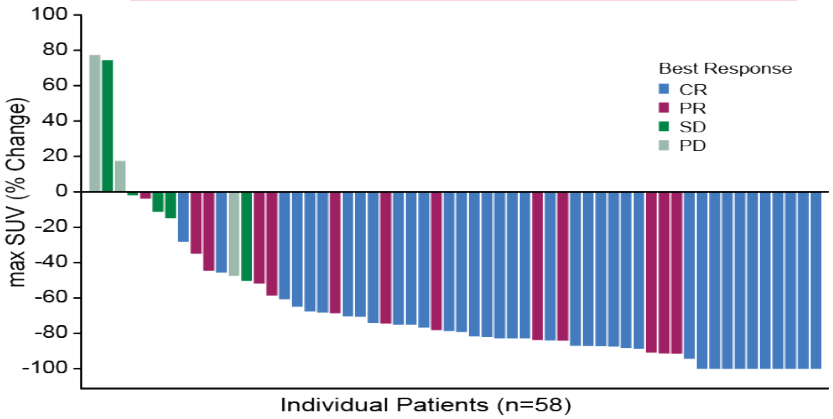
*Mosckowitz AJ et al, Lancet Oncol 2015*

# Nivolumab&Brentuximab-Vedotin as bridge to ASCT




**85% objective response rate with 63% complete responses**

| **Patient demographics and disease characteristics** | **N = 62** |
|---|---|
| Median age, years (range) | 36 (18-69) |
| Gender (M/F) | 30/32 |
| Disease status relative to frontline tx, n (%) | |
| Primary refractory | 28 (45) |
| Relapsed, remission duration ≤1 yr / >1 yr | 19 (31) / 15 (24) |
| Bulky disease at baseline, n (%) | 8 (13) |
| Extranodal disease at baseline, n (%) | 16 (26) |
| Disease stage at initial diagnosis, n (%) | |
| I/II | 37 (60) |
| III/IV | 24 (39) |
| Unknown | 1 (2) |
| Median prior therapies[a] (range) | 1 (1-3) |
| Prior chemotherapy regimens, n (%) | |
| ABVD | 56 (90) |
| BEACOPP | 2 (3) |
| Stanford V | 2 (3) |
| Other[b] | 6 (10) |
| Prior radiation | 9 (15) |

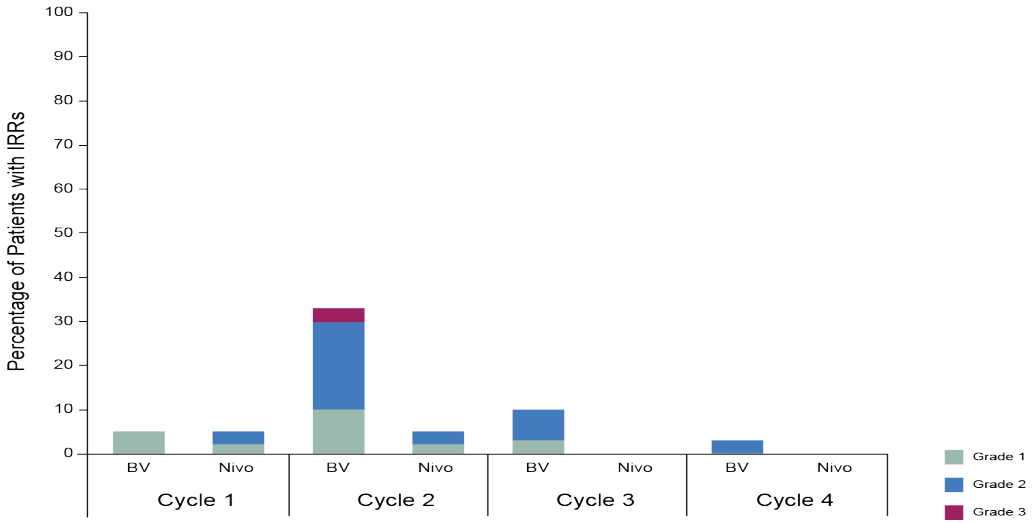



*Herrera AF et al, Blood 2018*

# Nivolumab&Brentuximab-Vedotin as bridge to ASCT

**IRRs occurred in 25 pts (41%), most frequently during the Cycle 2 BV infusion→mandatory premedication**

**No impact on cell stem harvest. No unusual post-ASCT toxicities.**




54 pts underwent ASCT

**6-month PFS 89% for all pts**

*Herrera AF et al, Blood 2018*

# BV in cHL: summary

**First line:**

- Promising data on BV-sequential AVD in elderly pts
- ECHELON-1: BV-concurrent AVD as an alternative to PET oriented strategy in AS pts

**Salvage:**

- BV monotherapy is an effective and well known strategy in post-ASCT salvage
- BV combined with chemotherapy as bridge to ASCT improves CR rate
- BV combined with CPI represents a chance for chemo-free salvage

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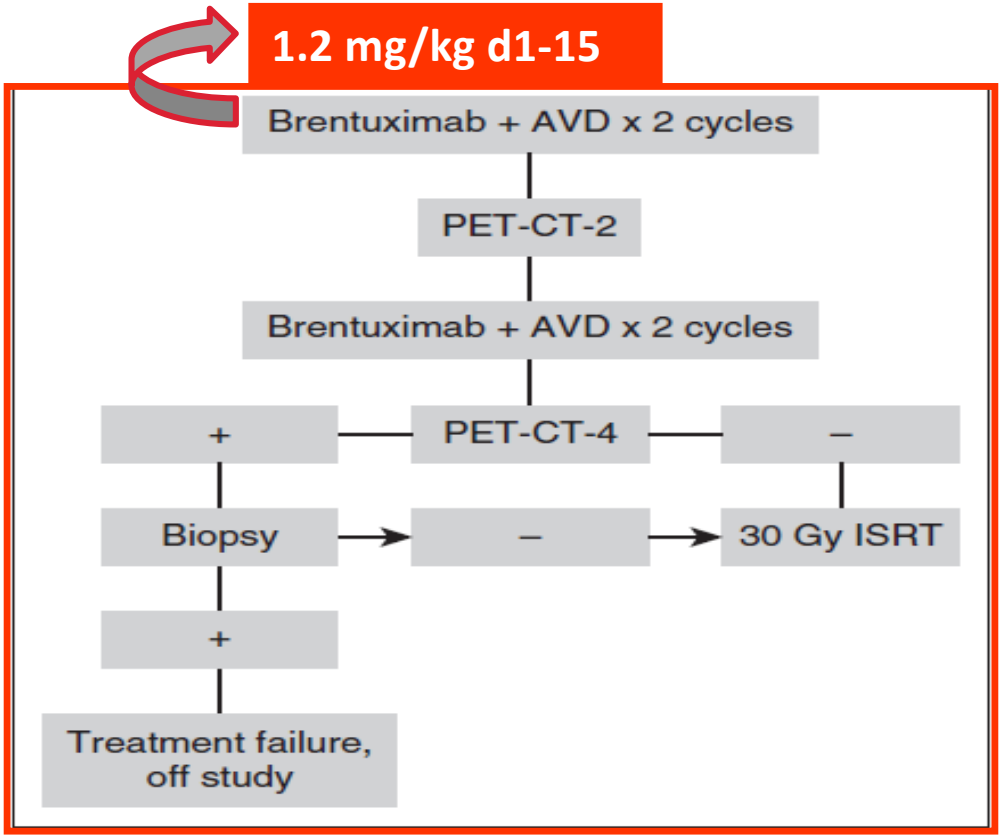
EMATOLOGICA
LOMBARDA


Grazie per l'attenzione!

# BV+chemo first line: Early Stage cHL




**PET negativity (DS 1-2-3):**

**89% after 2 cycles, 92% at end of therapy**

**PFS@1y: 93%**

30 pts , Early Unfavorable

| Unfavorable risk features | | |
|---|---|---|
| B symptoms | 14 | 47 |
| ESR >50 or ESR >30 with B symptoms | 20 | 67 |
| Nodal sites >2 | 20 | 67 |
| Extranodal involvement | 14 | 47 |
| Bulk ≥10 cm on CT | 14 | 47 |
| Bulk ≥1/3 MMR on CXR | 17 | 57 |

- Most frequent gr3 AE: **neutropenia**
- **PN 40%** (gr1: 10 pts, gr3: 2 pts)
- 3 pts FUO, 2 pts admitted for fever w/o neutropenia
- **No drug-related pneumonitis**
- Transient reversible impairment of PFTs

*Kumar A et al, Blood 2016*

# ECHELON-1: critical issues

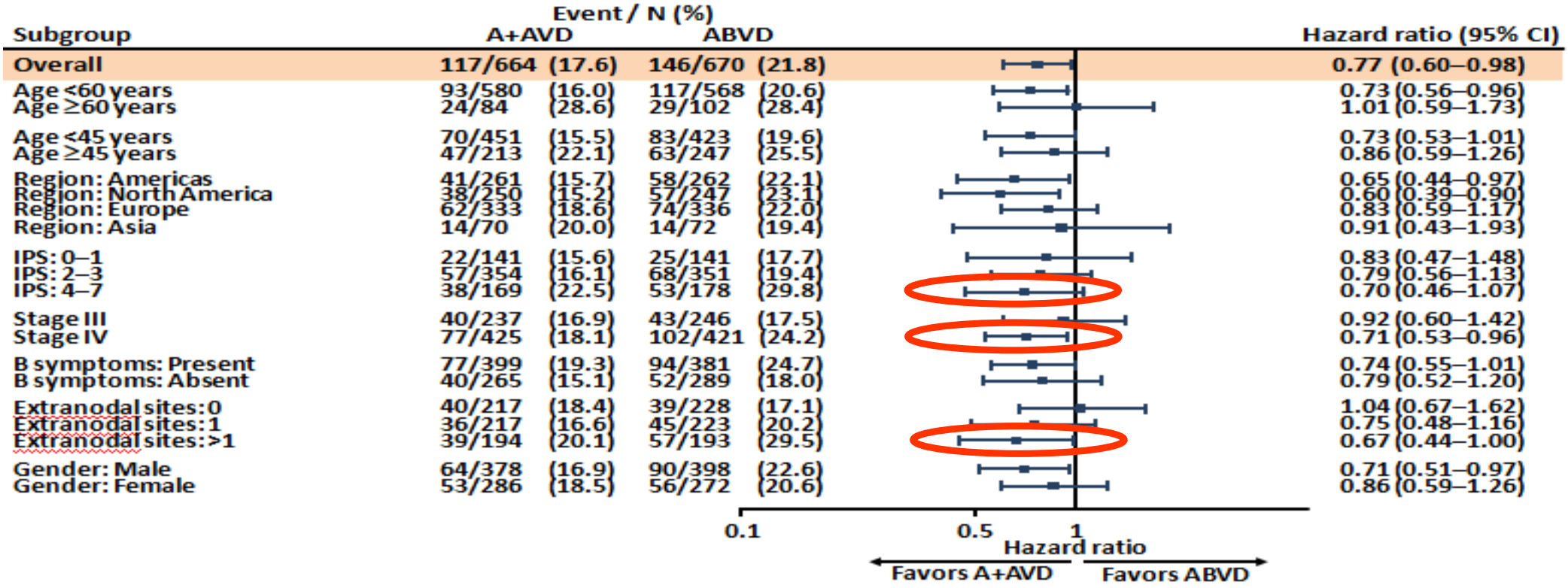
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Cost-Effectiveness Analysis of Brentuximab Vedotin With Chemotherapy in Newly Diagnosed Stage III and IV Hodgkin Lymphoma

*Scott F. Huntington, Gottfried von Keudell, Amy J. Davidoff, Cary P. Gross, and Sapna A. Prasad*

- Is modified PFS an adequate end point?
- Is a PFS advantage of 4.9% satisfactory?
- No advantage in OS
- Increased toxicity, G-CSF primary prophylaxis is required; incomplete data on fertility
- EOT DS:3 usually considered negative!
- EOT DS 4 and 5: a biopsy is required in routine pratice
- Cost-effectiveness?

# ECHELON-1 trial: subgroups analysis




*Connors JM et al, NEJM 2017*

# FIL_ELDHL protocol

## INCLUSION

Diagnosis of classical Hodgkin Lymphoma

Age ≥ 65 year-old

Evaluation of CGA at baseline

Signed informed consent

Previously untreated patients

All pts, regardless if addressed to curative-intent or palliative tx or not

## EXCLUSION

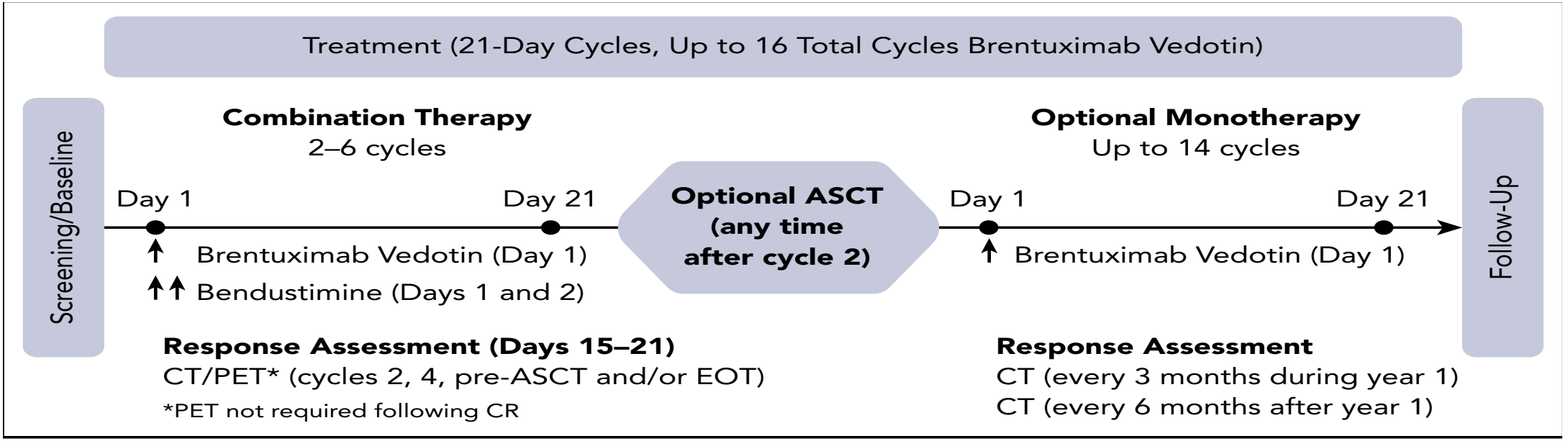
None

ClinicalTrials.gov Identifier: NCT03552003

# BBV

## BV: 1,8 mg/kg d 1 + Bendamustine 90 mg/mq d 1+2, q 3 weeks

## 2-6 cycles--- → ASCT-- →+/- BV (up to 16 total cycles)




*LaCasce A et al, Blood 2018*

# Towards a chemo-free salvage?

- **BV** activates the immune system and initiates an antitumor response through the induction of immunogenic cell death
- **Nivolumab** targets PD-1 and restores an effective antitumor response