New
Drugs
In Hematology
October 1, 2018

# Hodgkin Lymphoma

## Status of the art of treatment

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# Early Stage

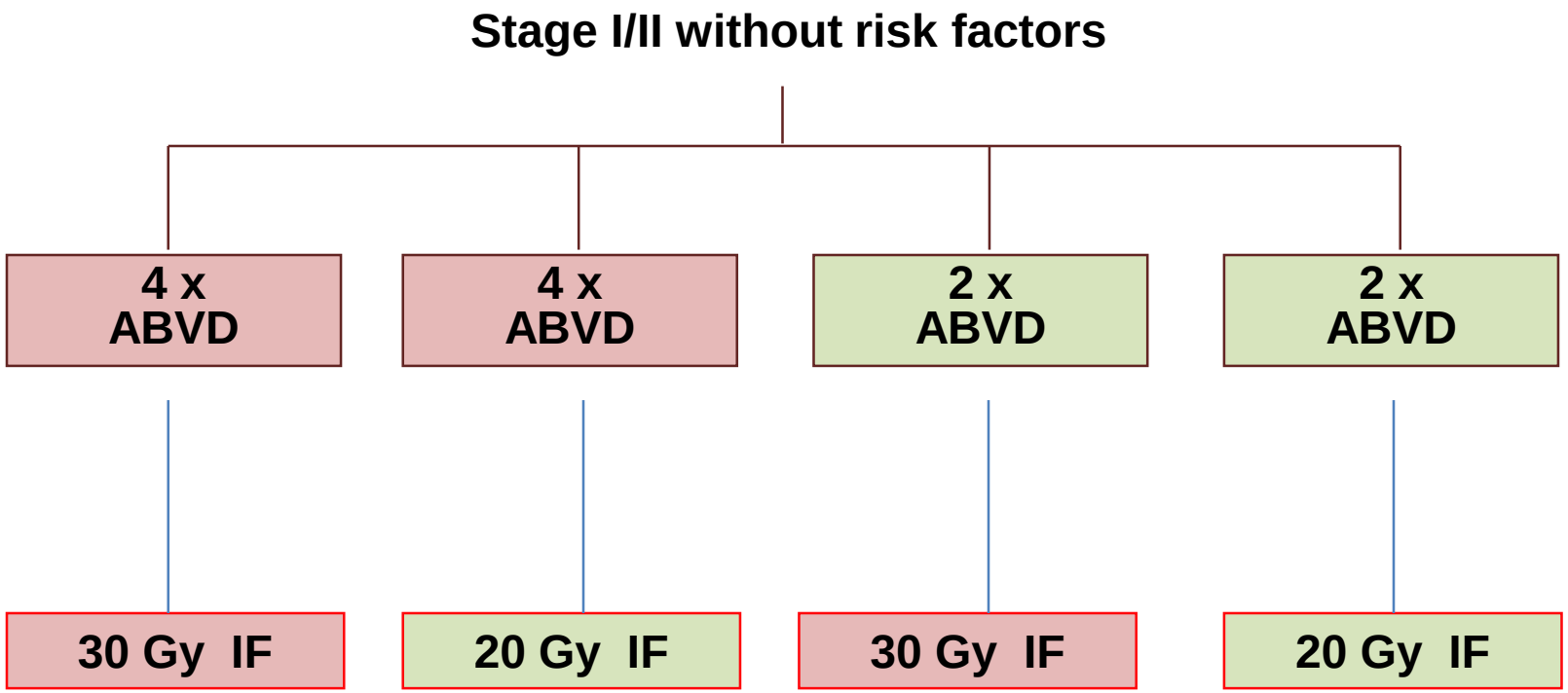
# HL Staging

| Stage I | Stage II | Stage III | Stage IV |
|---|---|---|---|
| Early Stage : Favorable | | Advanced Stage | |
| Early Stage : Unfavorable | | | |

# Regional Variations in Defining Early Stage HL and Treatment Options

| Early (limited) stage I/II HL | | | | |
|---|---|---|---|---|
| EORTC | | GHSG | | North America |
| Favorable | Unfavorable | Favorable | Unfavorable | |
| | 1. Bulky mediastinal mass | | 1. Bulky mediastinal mass | No bulk<br>No B symptoms |
| | 2. Elevated ESR | | 2. Elevated ESR | |
| | 3. Nodal regions ≥ 4 | | 3. Nodal regions ≥ 3 | |
| | 4. Age ≥ 50 years | | 4. Extra-nodal disease | |

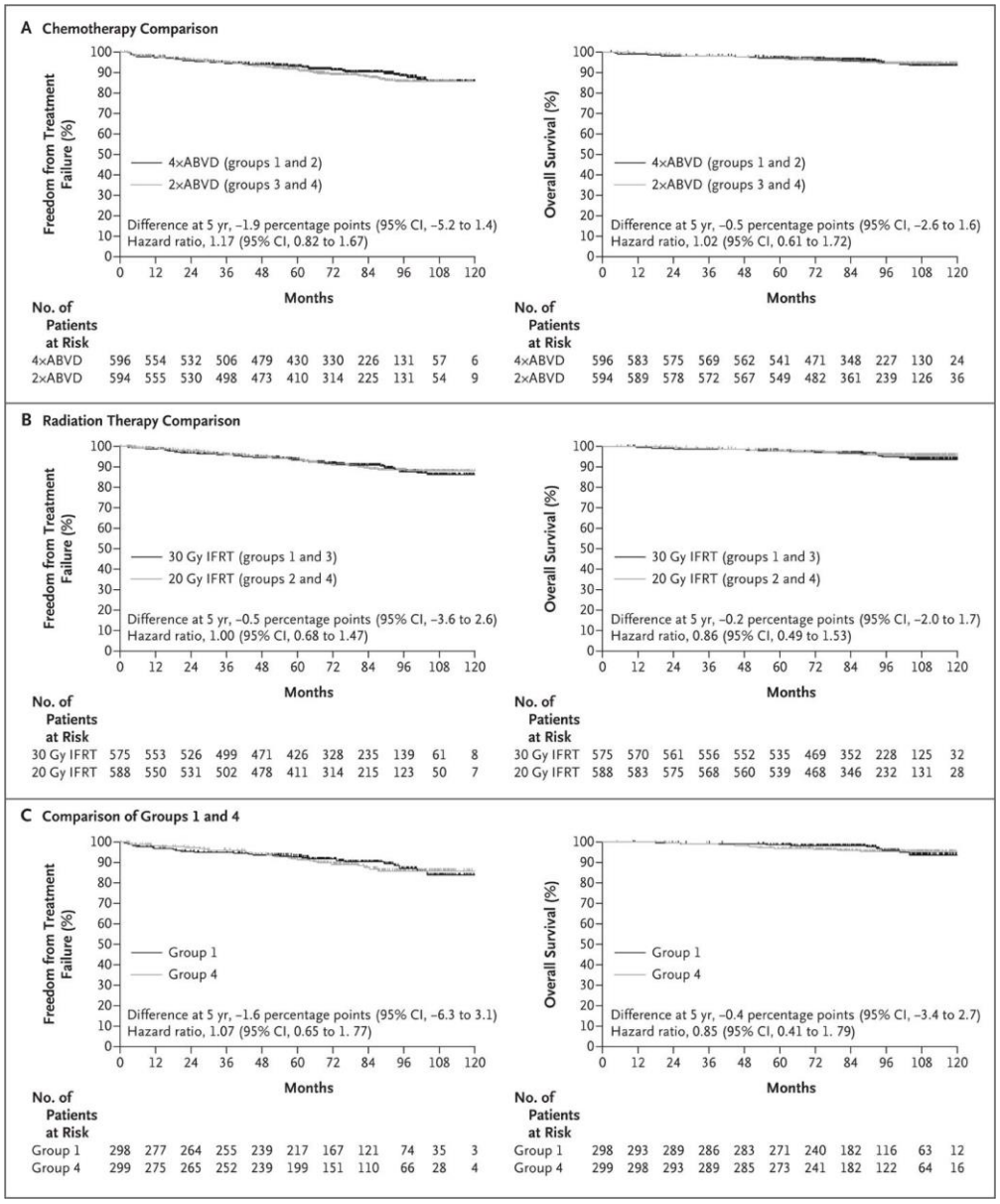
# Early stage favorable HL
## HD10 Study
## (n=1190)




Engert A et al. N Engl J Med 2010;363:640-652

# Early stage favorable HL: HD10 Study

**Freedom from Treatment Failure** **Overall Survival**

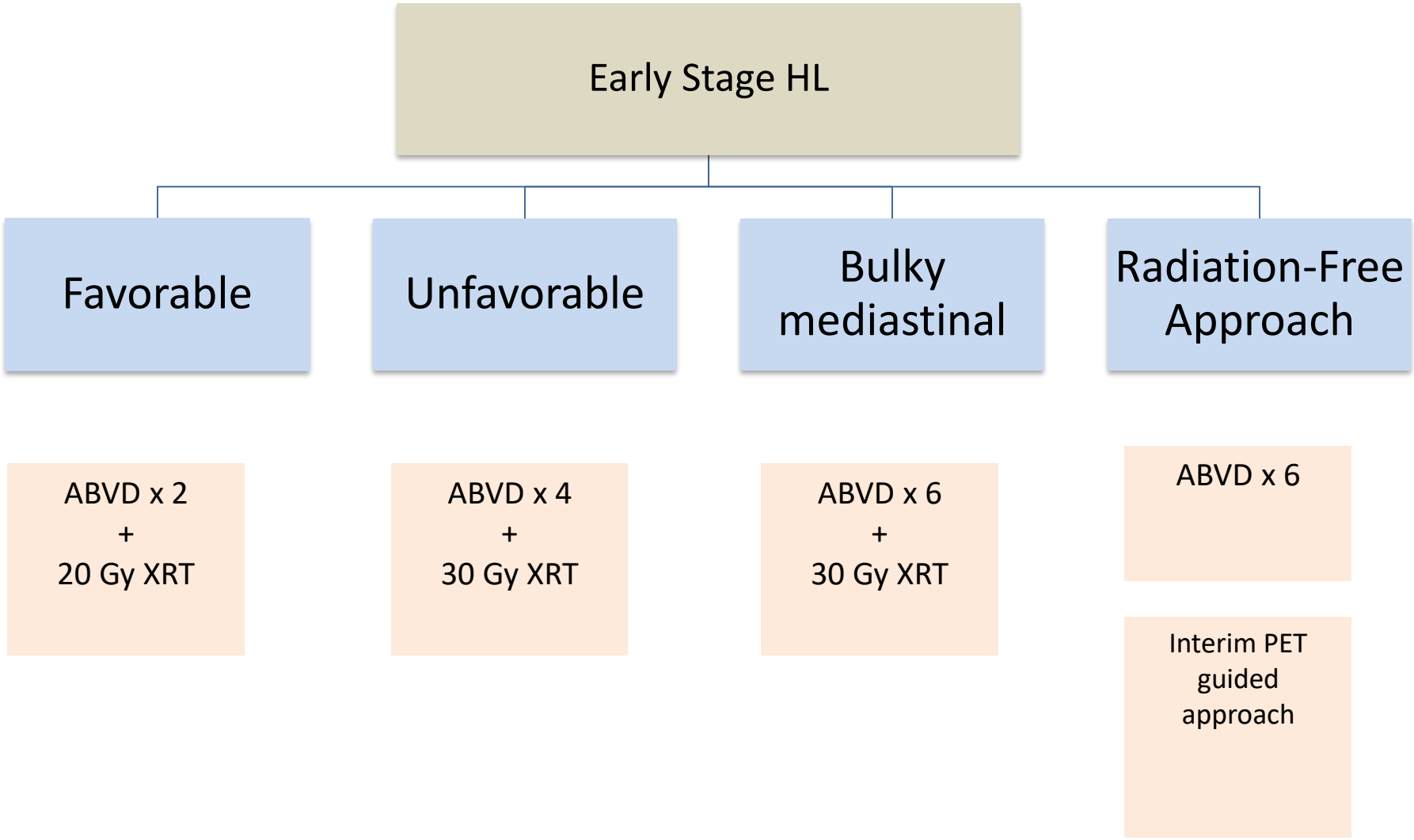



Chemo comparison
4 vs 2 ABVD

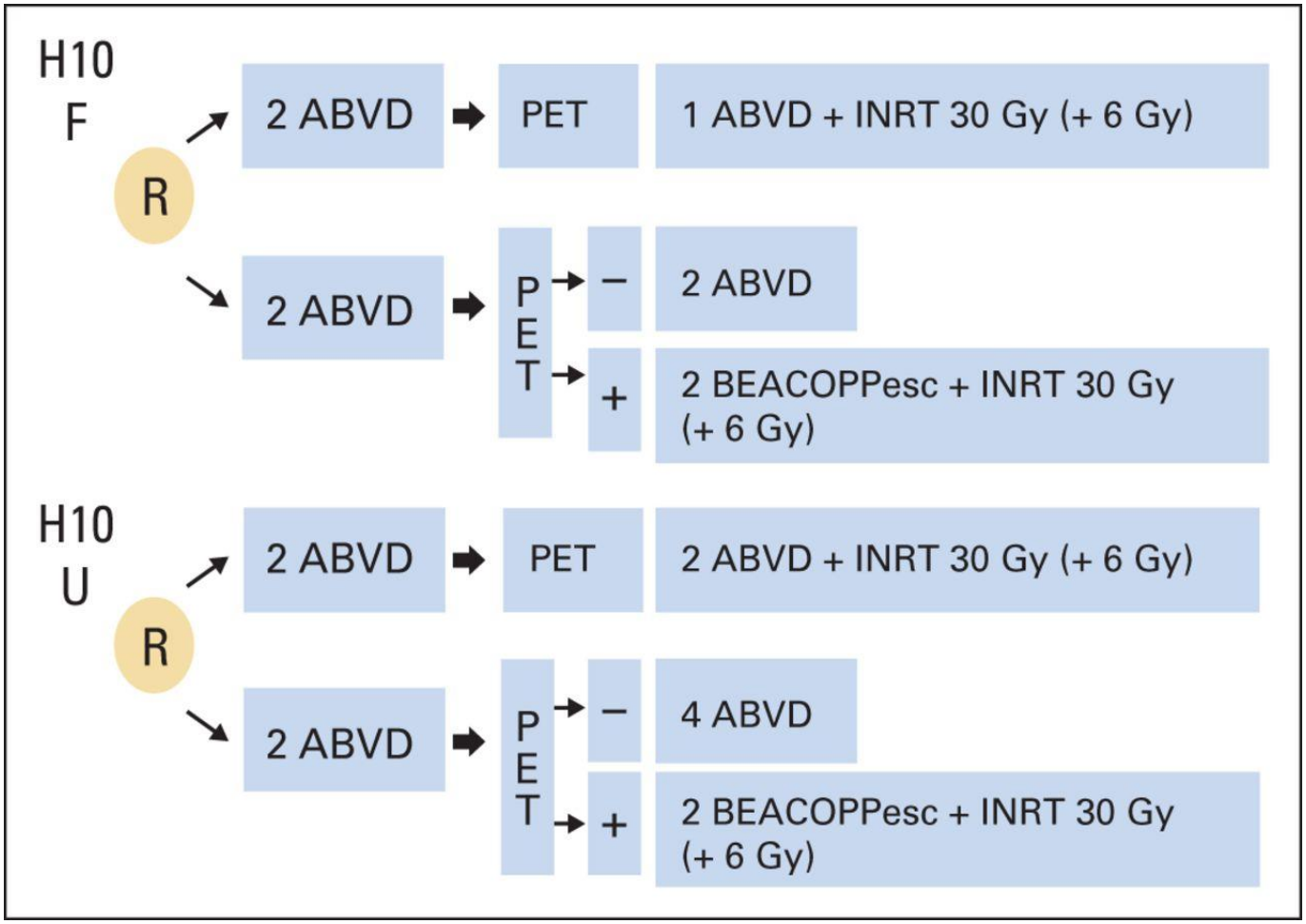
XRT comparison
30 vs 20 Gy

Group 1 and 4 comparison
ABVD x 4 + 30 Gy
vs
ABVD x 2 + 20 Gy

**Engert A et al. N Engl J Med 2010;363:640-652**


Early Stage HL
Favorable
Unfavorable
Bulky mediastinal
Radiation-Free Approach
ABVD x 2
+
20 Gy XRT
ABVD x 4
+
30 Gy XRT
ABVD x 6
+
30 Gy XRT
ABVD x 6
Interim PET guided approach

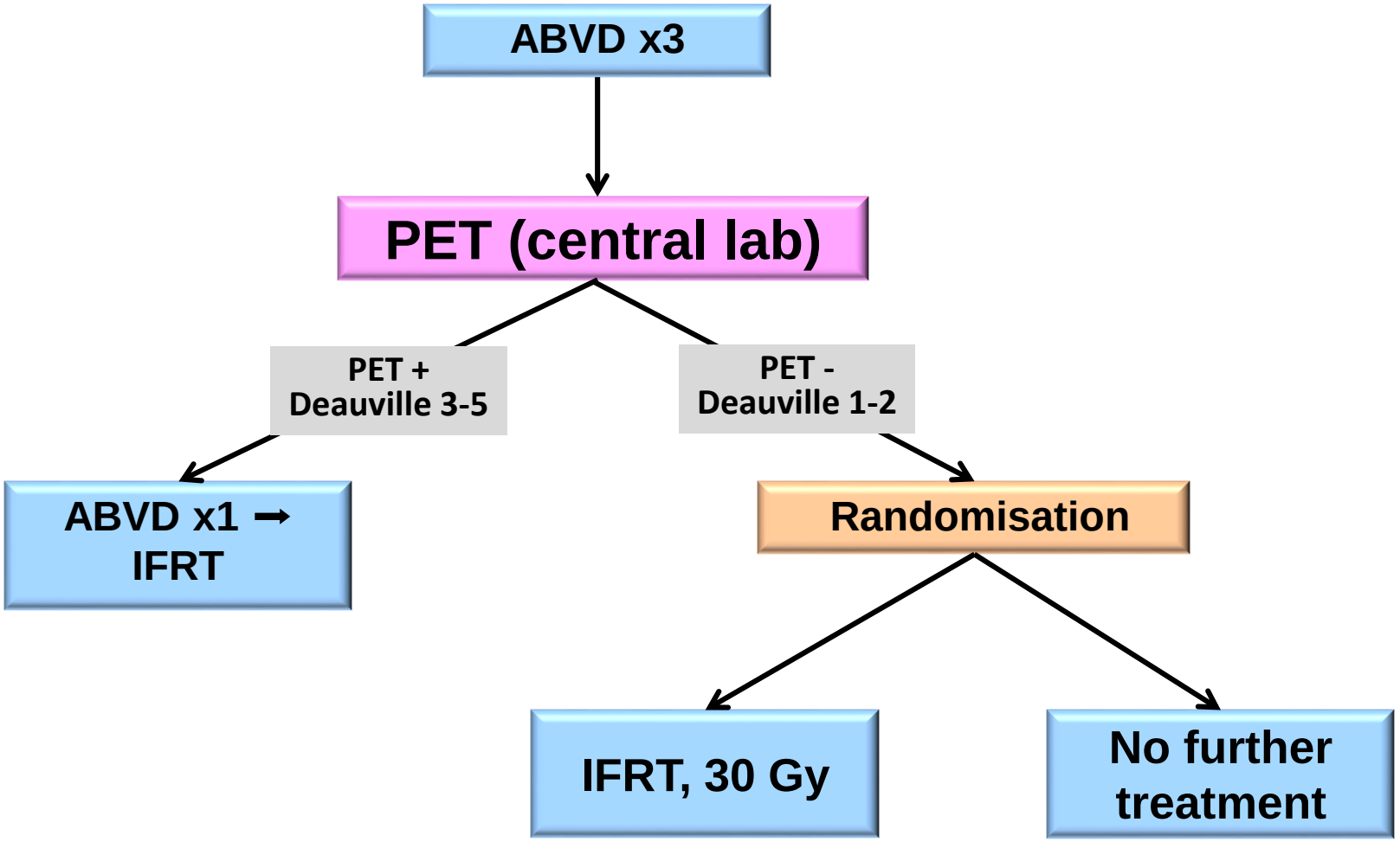
# EORTC H10 Study




**John M.M. Raemaekers et al. JCO 2014;32:1188-1194**

# RAPID Study

Stage I/II, no bulk, no B symptoms




Radford J et al. N Engl J Med 2015;372:1598-1607

# FDG-PET assessment
# Deauville criteria  or 5 point score

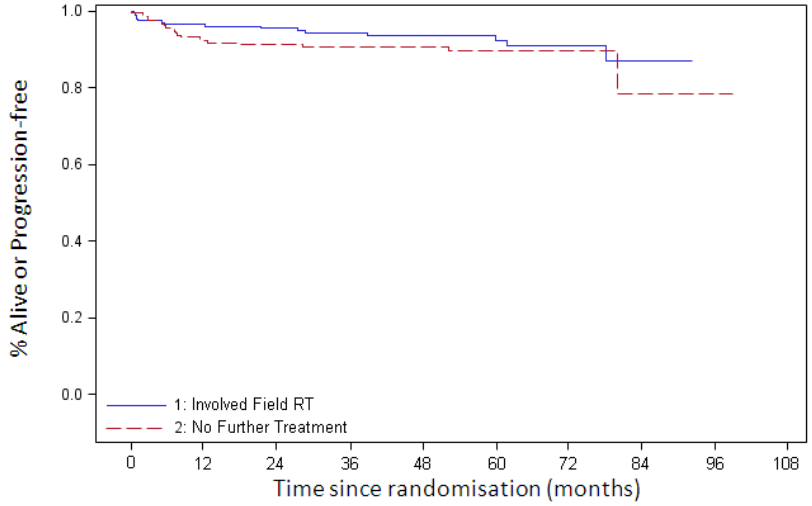
| Score | FDG-PET / CT scan result |
|---|---|
| 1 | No uptake above background |
| 2 | Uptake ≤ mediastinum |
| 3 | Uptake > mediastinum but ≤ liver |
| 4 | Uptake moderately more than liver uptake, at any site |
| 5 | Markedly increased uptake at any site or new sites of disease |

Score of 1 or 2 = PET negative

# PFS in the randomised PET –ve population (intention to treat, n=420)

**3 year PFS** 94.5% vs 90.8%

HR 1.51 in favour of IFRT, p=0.23

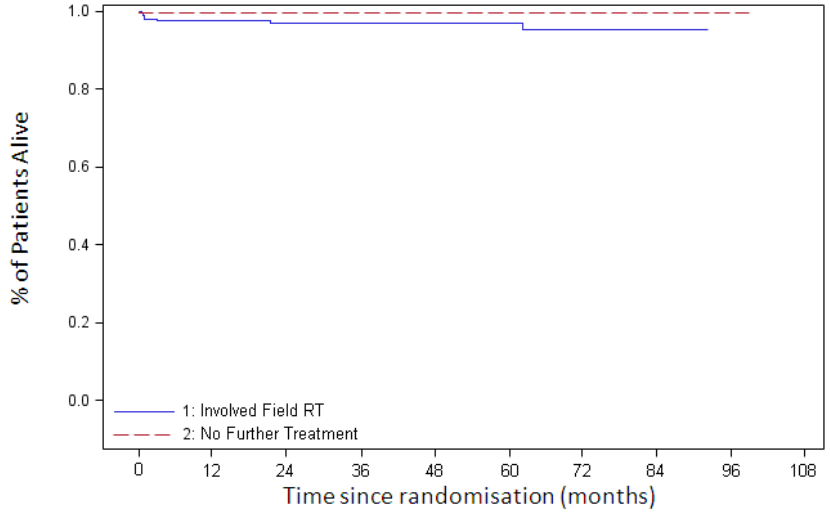



Number at risk:

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| IFRT | 209 | 198 | 176 | 138 | 105 | 68 | 39 | 17 | 0 | 0 |
| NFT | 211 | 190 | 165 | 134 | 101 | 60 | 18 | 4 | 2 | 0 |

**3 yr OS** 97.1% vs 99.5%

HR 0.15 in favour of NFT, p= 0.07

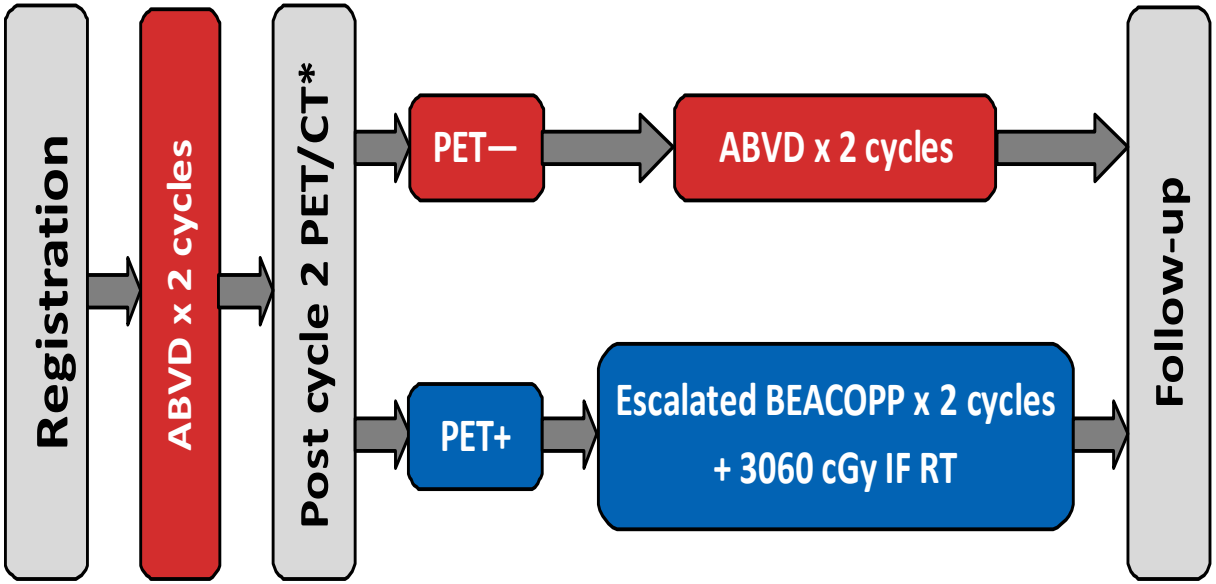



Number at risk:

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| IFRT | 209 | 200 | 179 | 143 | 109 | 71 | 40 | 17 | 0 | 0 |
| NFT | 211 | 204 | 178 | 145 | 109 | 65 | 20 | 6 | 2 | 0 |

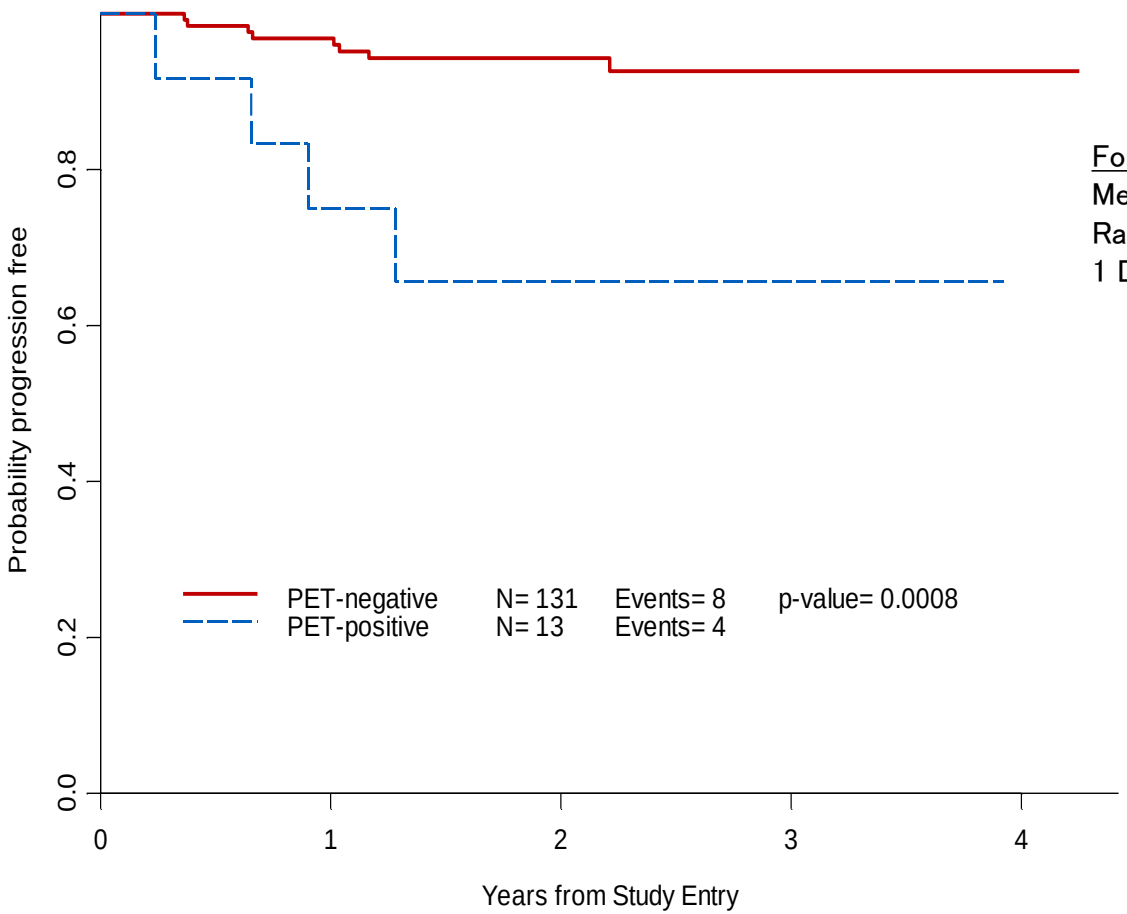
Radford J et al. N Engl J Med 2015;372:1598-1607

# CALGB 50604 Design




- Phase II trial in newly-diagnosed stages I/II non-bulky HL conducted in Intergroup (CALGB/Alliance, SWOG, ECOG)
  - Favorable (17%)
  - Unfavorable (75%)
  - Unknown (7%)

# Progression-Free Survival



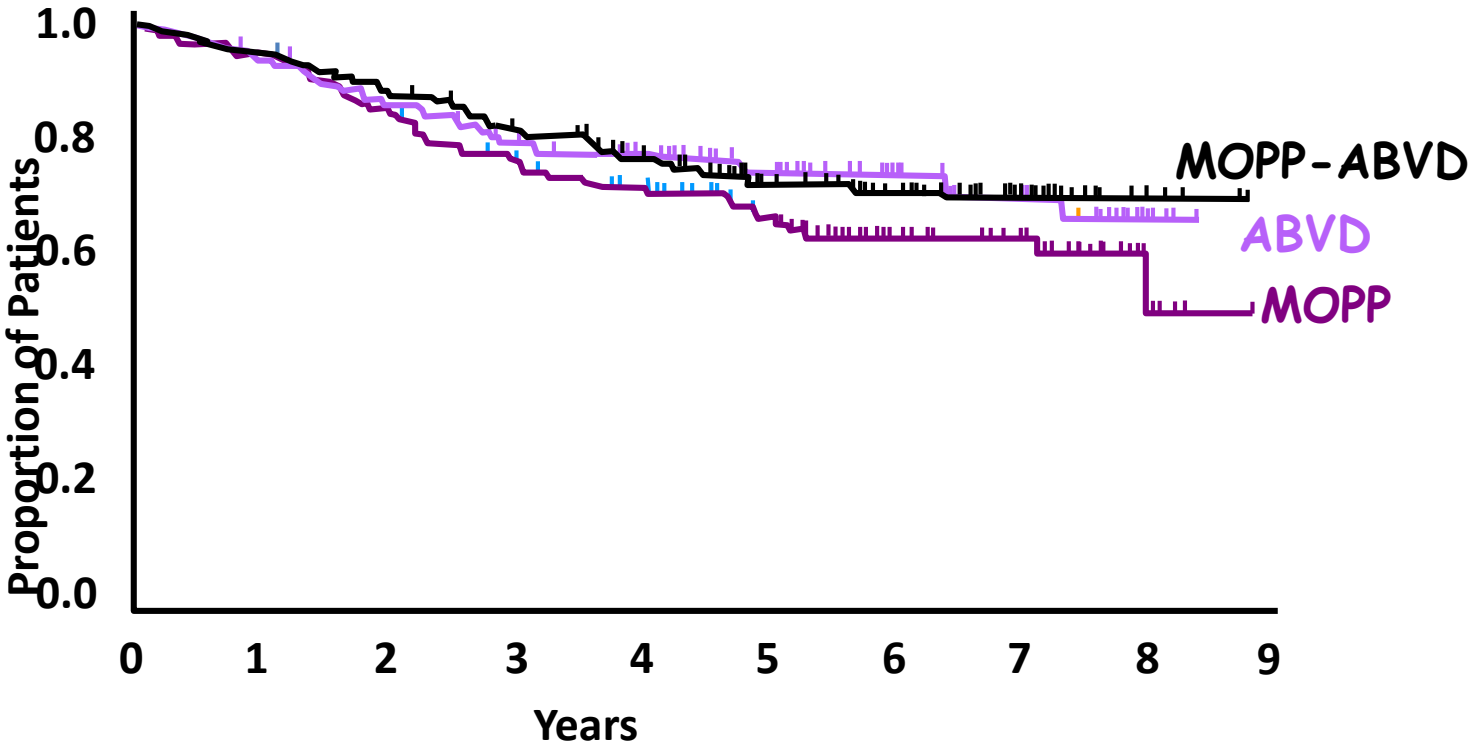

Follow-up time
Median: 2.1 years
Range: <1 month – 4.3 years
1 Death (suicide, PET-positive)

| | Est. 3-yr PFS | Hazard Ratio |
|---|---|---|
| PET - | 92% (84%-96%) | 6.04 (1.82-20.08) |
| PET + | 66% (32%-86%) | |

Straus DJ, et al. *Blood.* 2015;126. Abstract 578.

# Advanced Stage

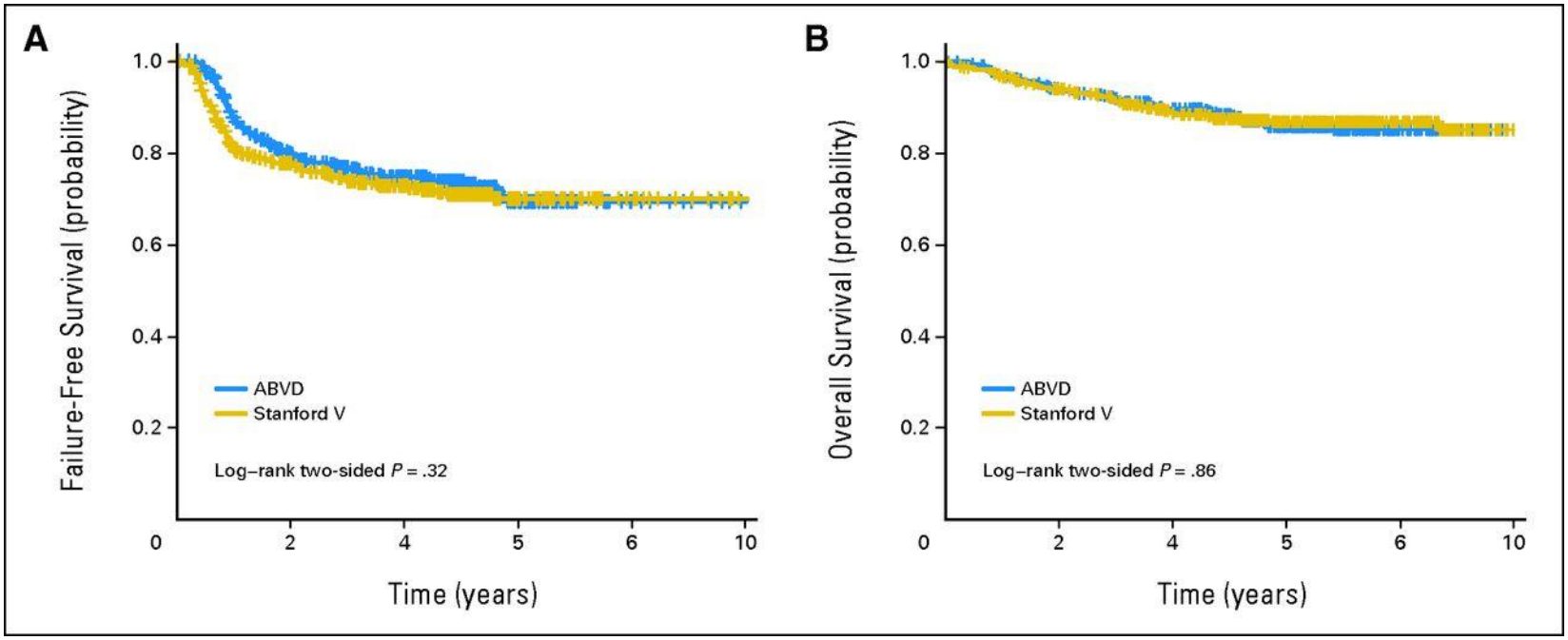
# Advanced Stage HL




| Regimen | No. of Patients | No. (%) of Treatment Failures | Median Survival |
|---|---|---|---|
| MOPP | 123 | 44 (36) | None |
| ABVD | 115 | 32 (28) | None |
| MOPP-ABVD | 123 | 31 (25) | None |
| All | 361 | 107 (30) | |

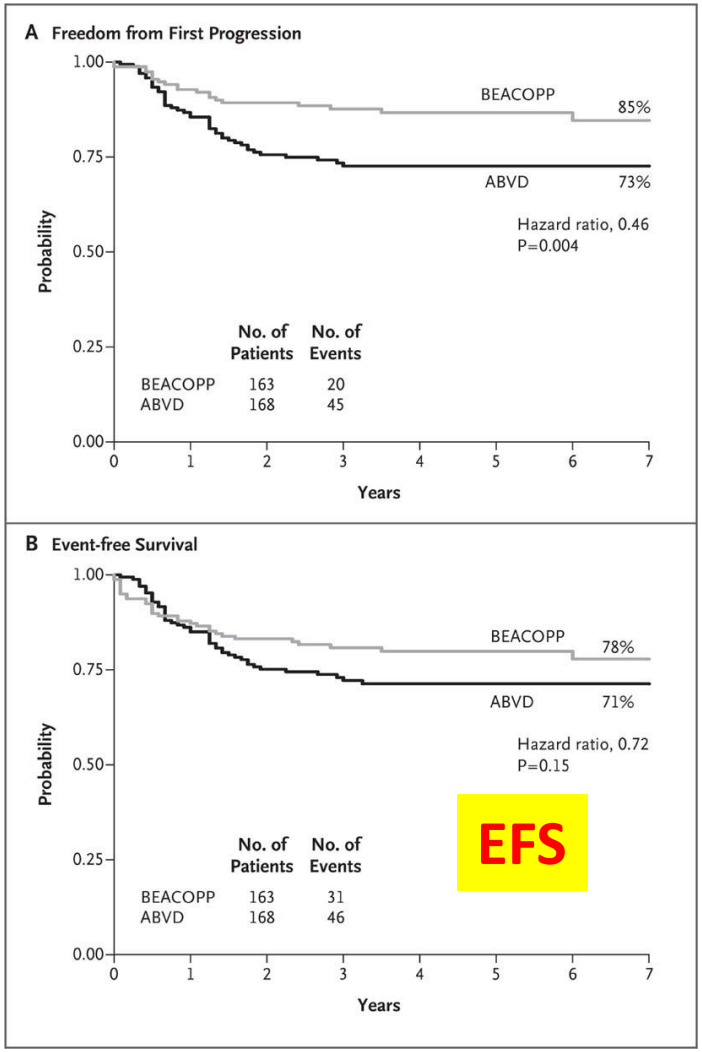
Canellos et al, NEJM 1992

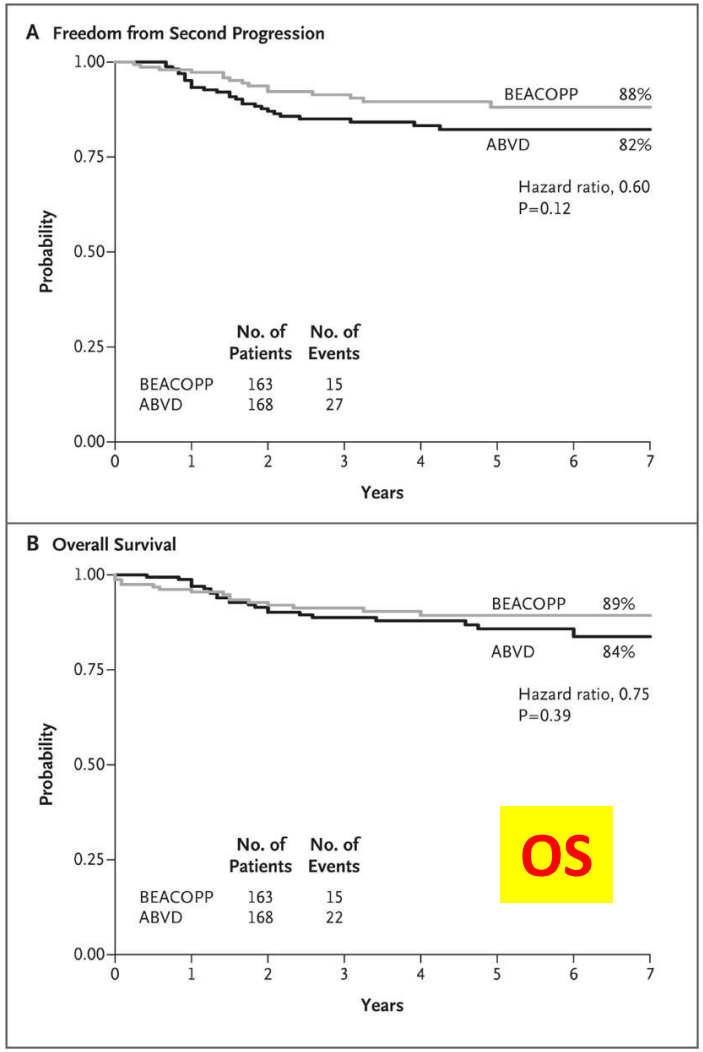
# ABVD vs Stanford V




**Gordon L I et al. JCO 2013;31:684-691**

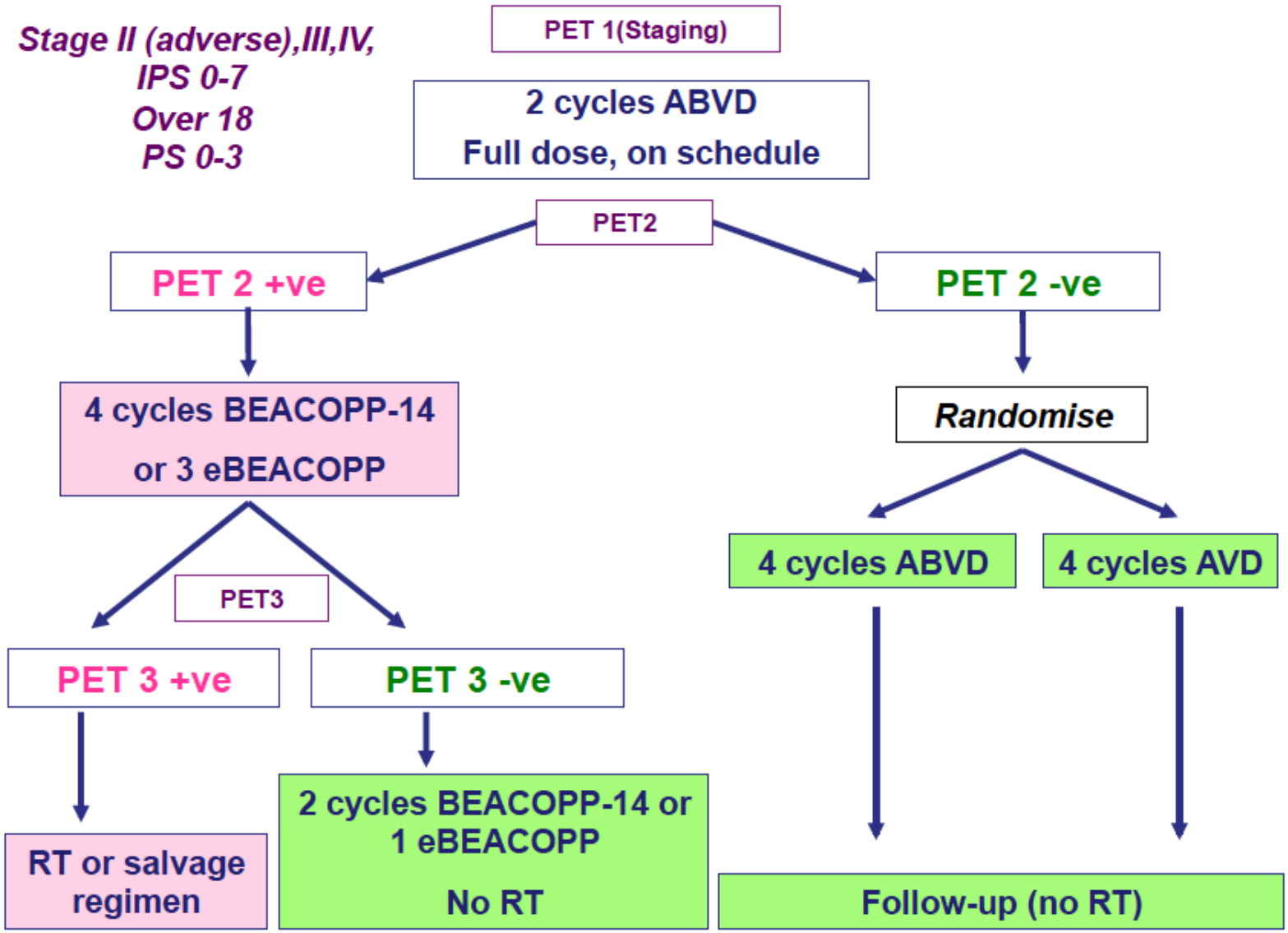
# ABVD vs BEACOPP



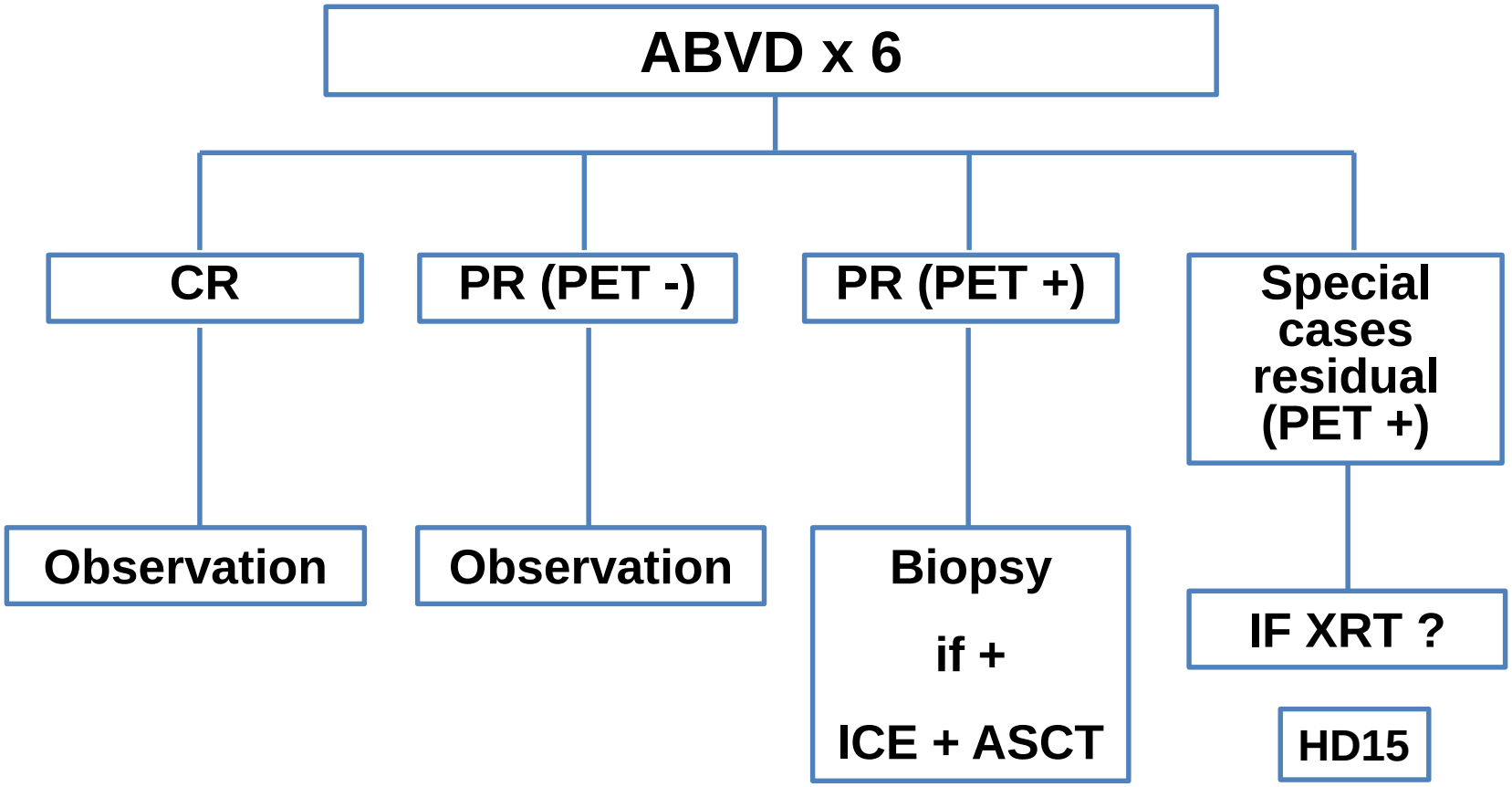

Viviani S et al. N Engl J Med 2011;365:203-212

# RATHL Trial



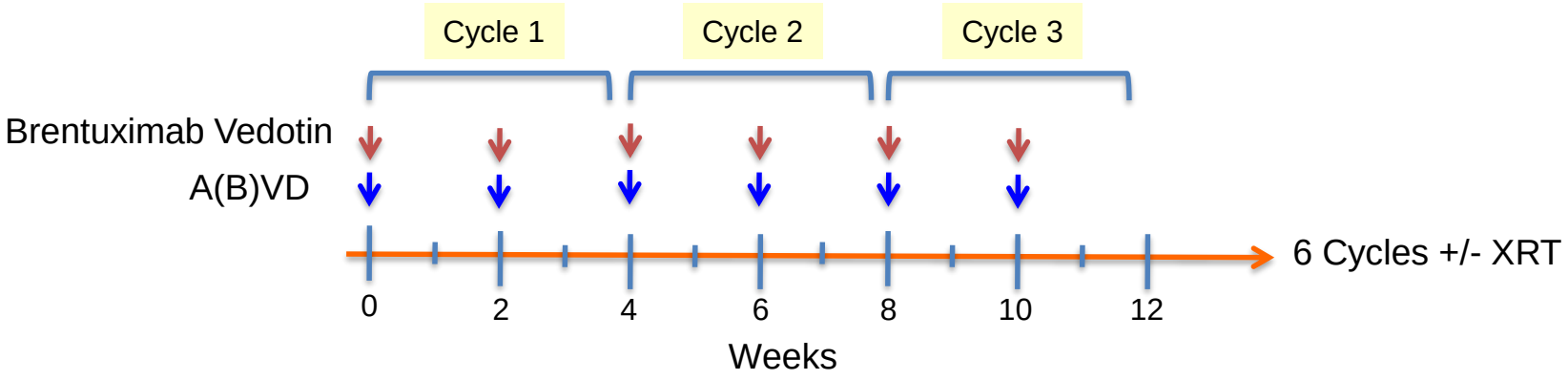

Johnson, P ICML 2015

# Treatment of advanced stage HL



# Phase 1 ABVD/AVD + brentuximab vedotin

## Stage IIa bulky, IIB, III-IV




Younes A, Ansell S, et al, Lancet Oncology 2013

# Dose-Escalation Cohorts

Patients were enrolled into 1 of 5 cohorts:

Brentuximab vedotin + ABVD
N=25 total

- Cohort 1 (0.6 mg/kg) N=6
- Cohort 2 (0.9 mg/kg) N=13
- Cohort 3 (1.2 mg/kg) N=6

Brentuximab vedotin + AVD
N=26 total

- Cohort 4 (1.2 mg/kg) N=6
- Expansion cohort (1.2 mg/kg) N=20

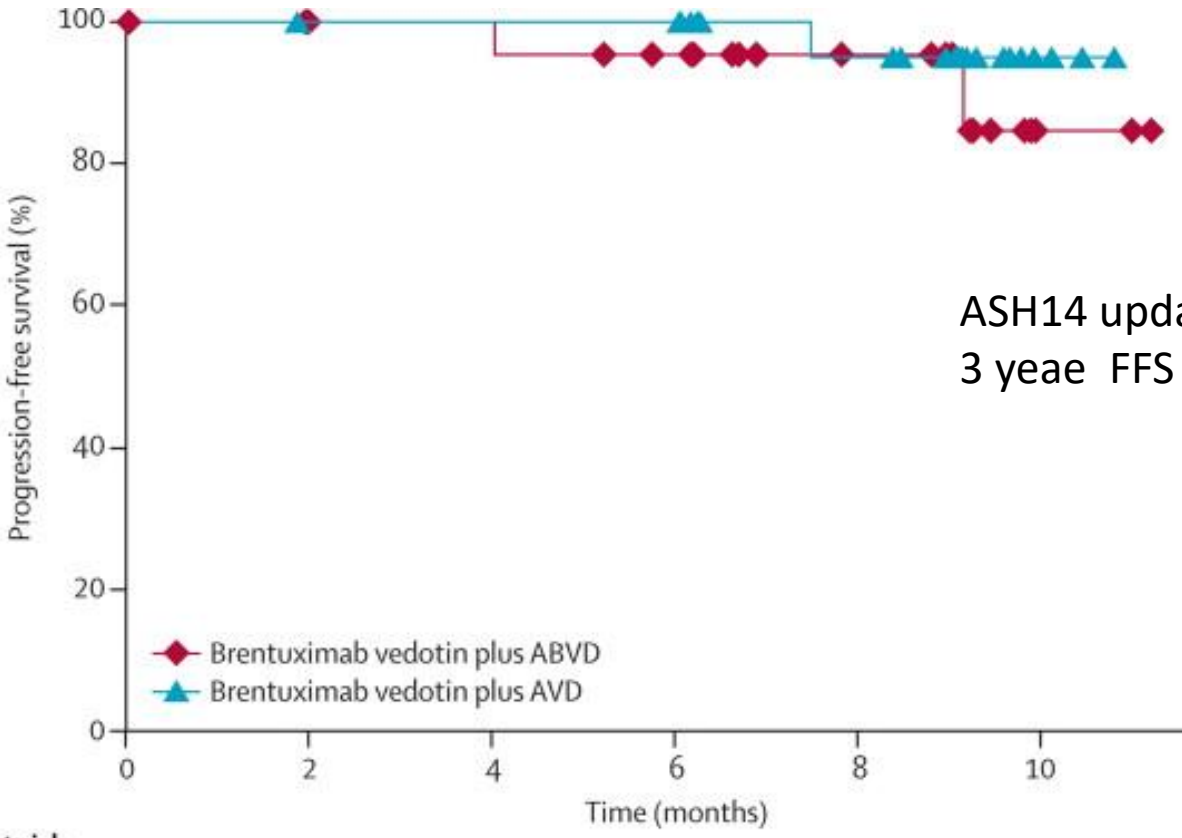
- Dose-limiting toxicities were defined as any Cycle 1 toxicity requiring ≥7-day delay in ABVD or AVD
- Study has completed enrollment
- All patients in the AVD expansion cohort are currently receiving treatment

# ABVD or AVD + brentuximab vedotin

| | ABVD with brentuximab vedotin N=25 | AVD with brentuximab vedotin N=26 |
|---|---|---|
| Any event | 11 (44) | 0 |
| Pulmonary toxicity | 9 (36) | 0 |
| Interstitial lung disease | 1 (4) | 0 |
| Pneumonitis | 1 (4) | 0 |
| | | |
| PET negative results | 100% | 92% |
| % CR at end of therapy | 95% | 96% |

Younes A, Ansell S, et al, Lancet Oncology 2013

# Phase-I Study of Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin lymphoma: PFS



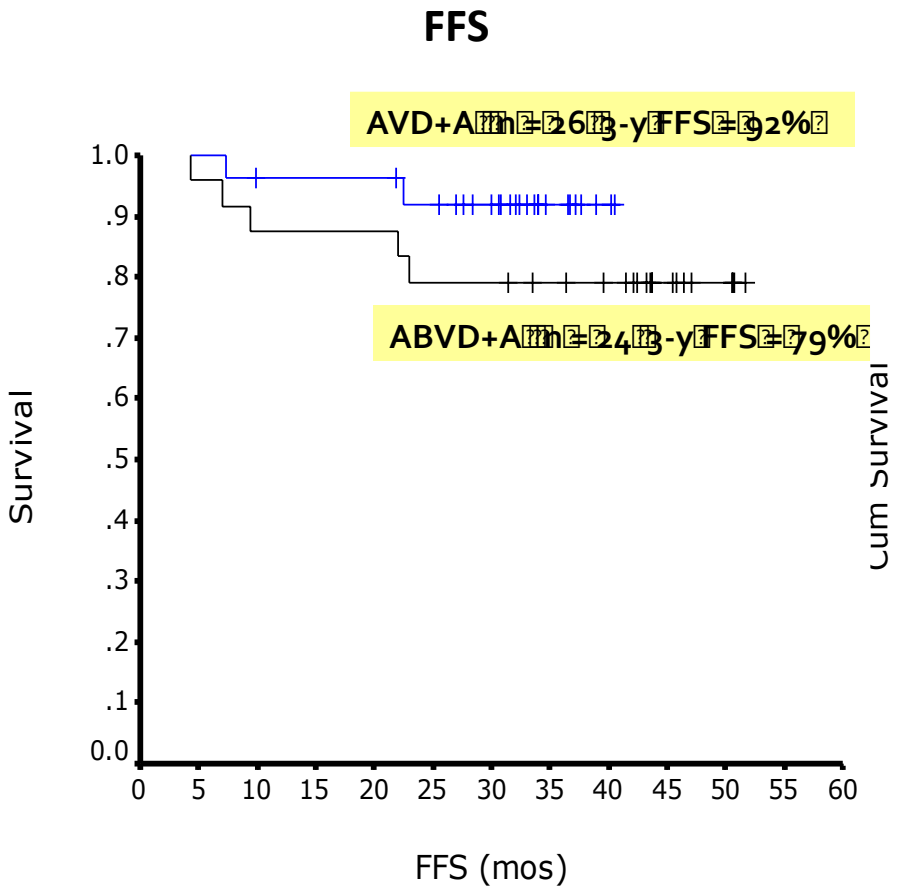

| Number at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Brentuximab vedotin plus ABVD | 25 (0) | 23 (0) | 22 (0) | 19 (1) | 13 (1) | 2 (2) | 0 (2) |
| Brentuximab vedotin plus AVD | 26 (0) | 25 (0) | 25 (0) | 25 (0) | 19 (1) | 3 (1) | 0 (1) |

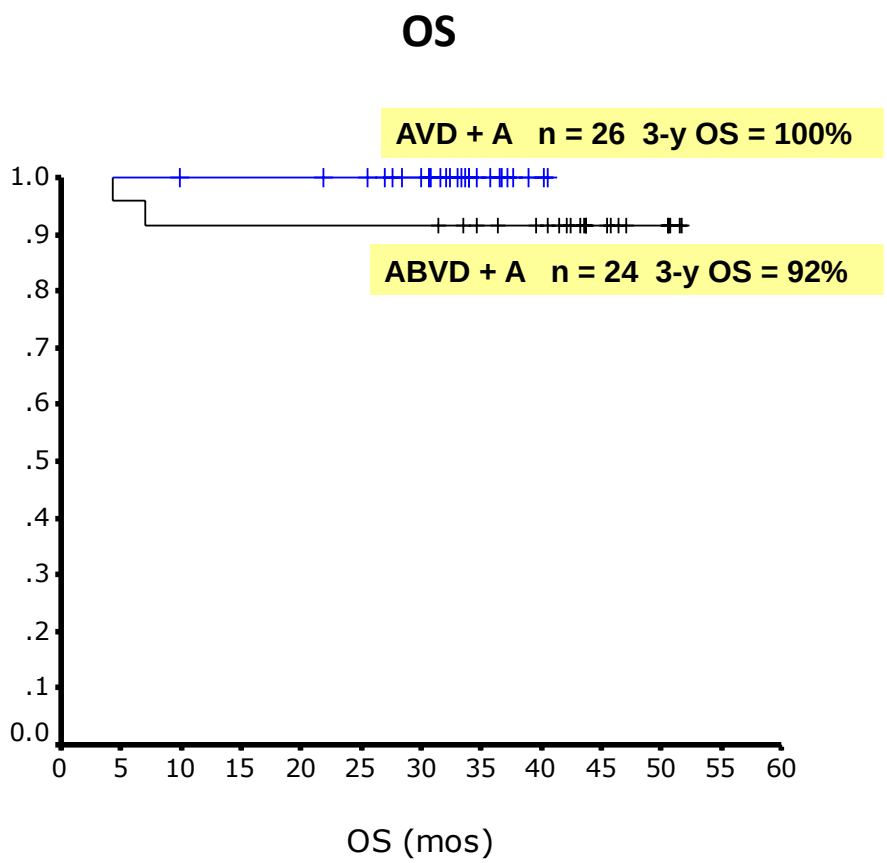
ASH14 update: of A= AVD
3 yeae FFS 96%, OS 100%

Younes, A et al: The Lancet Oncology, Volume 14, Issue 13, 2013, 1348 - 1356

# Phase-I Brentuximab vedotin + AVD Advanced stage HL

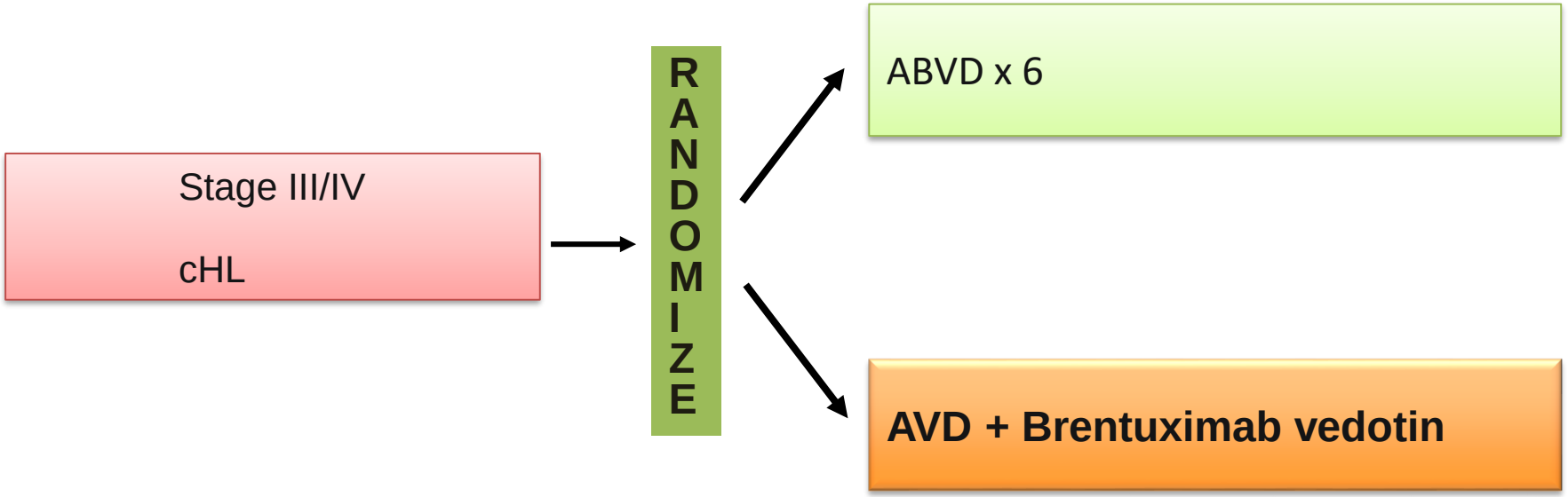
## 3-Year follow up



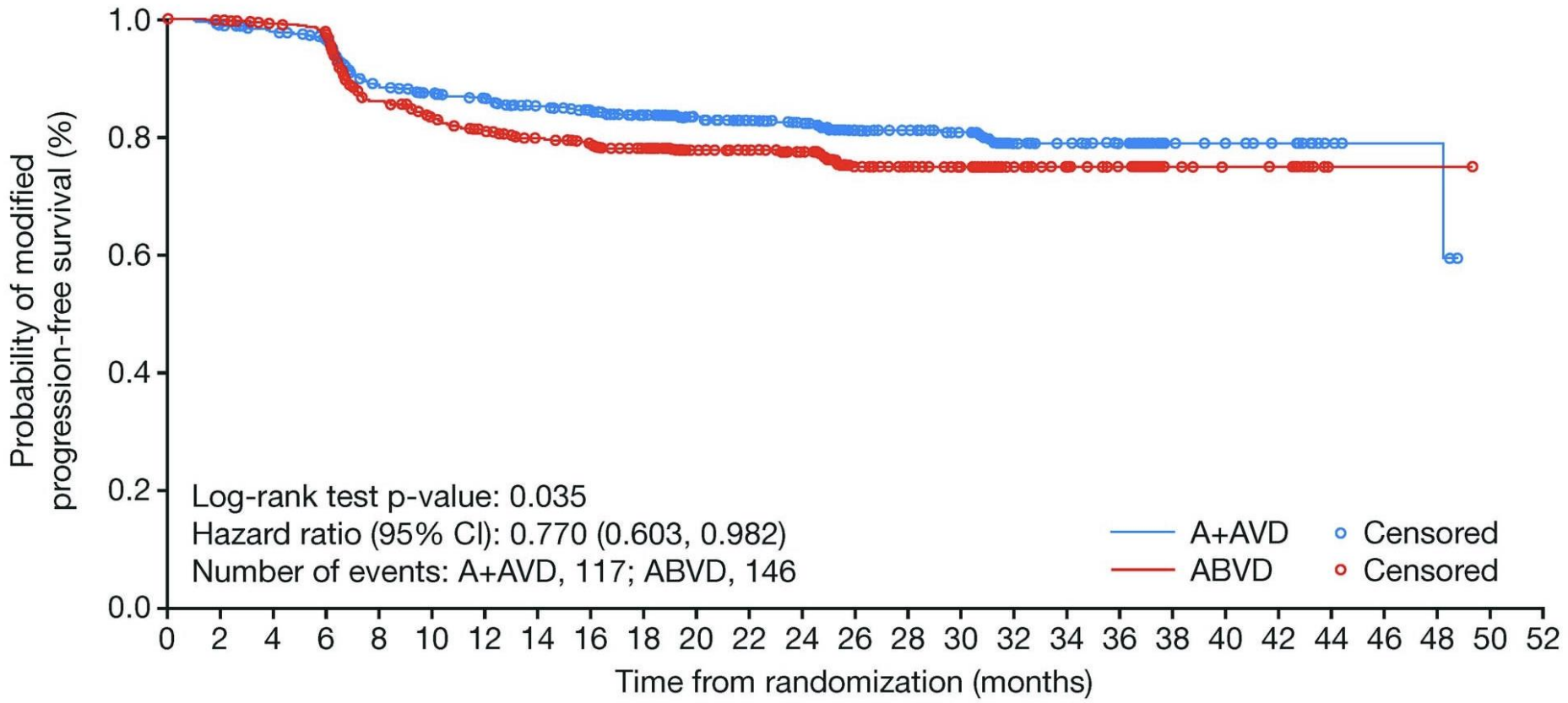




Connors J et al , ASH 2014

# Randomized Study in Newly Diagnosed Advanced Stage HL



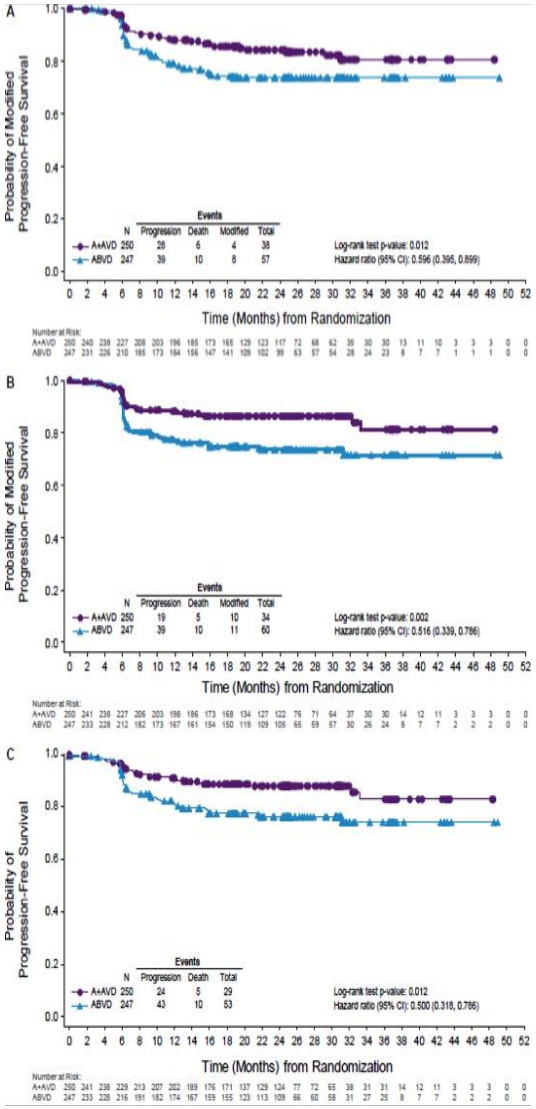
# Randomized Study in Newly Diagnosed Advanced Stage HL (Echelon-1)




Number of patients at risk:

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A+AVD | 664 | 640 | 623 | 606 | 544 | 530 | 516 | 496 | 474 | 447 | 350 | 334 | 311 | 200 | 187 | 174 | 99 | 85 | 77 | 27 | 24 | 21 | 6 | 4 | 4 | 0 | 0 |
| ABVD | 670 | 644 | 626 | 613 | 522 | 496 | 476 | 459 | 439 | 415 | 328 | 308 | 294 | 179 | 168 | 153 | 78 | 68 | 62 | 16 | 13 | 12 | 1 | 1 | 1 | 0 | 0 |

# Brentuximab Vedotin plus Chemotherapy in North American Subjects with Newly Diagnosed Stage III or IV cHL




**modified PFS per IRF (A)**

**modified PFS per investigator assessment (B)**

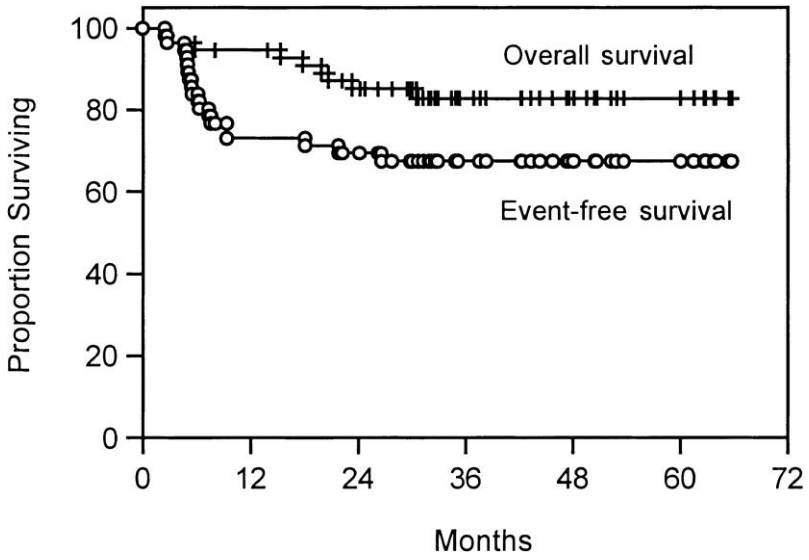
The 2-year : 86.4% A+AVD arm and 73.6% in the ABVD arm (an absolute difference of 12.8%)

**PFS per investigator assessment (C)**

- **Primary Refractory/Relapsed cHL**

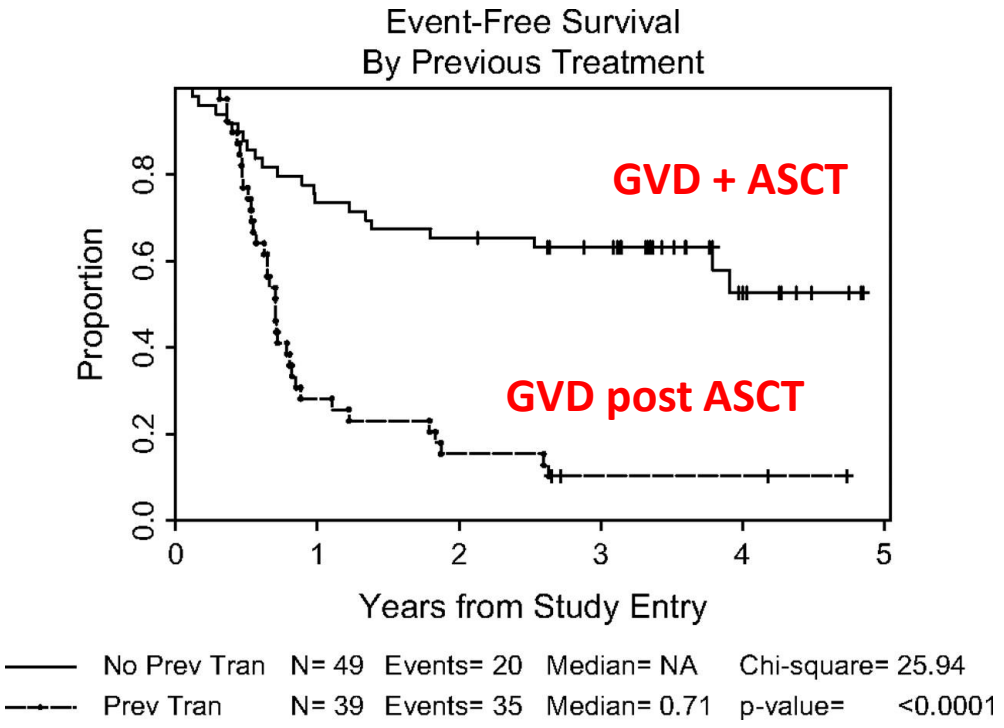
# ASCT for Relapsed/Refractory HL

## ICE + ASCT




Moskowitz C H et al. Blood 2001;97:616-623

## GVD + ASCT




Bartlett N et al. Ann Oncol 2007;18:1071-1079

# Results of salvage pre-transplant regimens in cHL

| Regimen | ORR (%) | CRR (%) | References |
|---|---|---|---|
| ICE (ifosfamide, carboplatin, etoposide) | 88 | 26 | Moskowitz et al (2001) |
| IVE (ifosfamide, epirubicin, etoposide) | 85 | 37 | Proctor et al (2001) |
| MINE (mitoxantrone, ifosfamide, vinorelbine, etoposide) | 75 | 34 | Ferme et al (1995) |
| IVOx (ifosfamide, etoposide, oxaliplatin) | 76 | 32 | Sibon et al (2011) |
| IGEV (ifosfamide, gemcitabine, vinorelbine) | 81 | 54 | Santoro et al (2007) |
| GEM-P (gemcitabine, cisplatin, methylprednisolone) | 80 | 24 | Chau et al (2003) |
| GDP (gemcitabine, dexamethasone, cisplatin) | 70 | 52 | Baetz et al (2003) |
| GVD (gemcitabine, vinorelbine, liposomal doxorubicin) | 70 | 19 | Bartlett et al (2007) |
| Mini-BEAM (carmustine, etoposide, cytarabine, melphalan) | 84 | 32 | Colwill et al (1995) |
| DexaBEAM (dexamethasone, carmustine, etoposide, cytarabine, melphalan) | 81 | 27 | Schmitz et al (2002) |
| ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) | 73 | 41 | Aparicio et al (1999) |
| ASHAP (doxorubicin, methylprednisolone, cytarabine, cisplatin) | 70 | 34 | Rodriguez et al (1999) |
| DHAP (dexamethasone, cytarabine, cisplatin) | 89 | 21 | Josting et al (2002) |
| DHAOx (dexamethasone, cytarabine, oxaliplatin) | 74 | 43 | Rigacci et al (2010) |
| Bendamustine (NB. more heavily pre-treated cohort) | 53 | 33 | Moskowitz et al (2013) |

# Brentuximab vedotin in pre-ASCT therapy

| | N | % CR | % CR with BV | Reference |
|---|---|---|---|---|
| ICE | 97 | 60% | N/A | Mockowitz C, BLOOD 2012 |
| BV->ICE | 46 | 73% | 27% | Moskowitz A, Lancet Oncol 2015 |
| BV -> chemo | 36 | | 33% | Chen R, ASH 2014 |
| BV+Benda | 34 | 82% | N/A | LaCasce A, ASH 2014 |

# BV combination regimens

| | BV + bendamustine | BV + ESHAP | BV + ICE |
|---|---|---|---|
| N | 55 | 66 | 16 |
| Dose | -1.8 mg/kg BV on D1<br>-Bendamustine D1 and D2 | -1.8 mg/kg BV on D1<br>-ESHAP days 1-4 | -1.5 mg/kg BV on D1 and 8<br>-ICE days 2-4 |
| Response Rates | 93% ORR<br>74% CR | 94% ORR<br>70% CR | 94% ORR<br>88% CR<br>69% CR (IR) |
| Toxicity | 56% infusion reaction | Myelosuppression, infections | Myelosuppression, Peripheral neuropathy |
| PFS/OS | 12 months PFS 80% | 18 months TTF 74% | N/A |

LaCase A et al, ASH 2015
Garcia-Sanz R et al. ASH 2016
Cassaday R et al, ASH 2016

# 1105 Preliminary Results from a Phase 1/2 Study of Brentuximab Vedotin in Combination with Nivolumab in Patients with Relapsed or Refractory Hodgkin Lymphoma

**Alex F Herrera, MD**[1], Nancy L Bartlett, MD[2], Radhakrishnan Ramchandren, MD[3*], Julie M Vose, MD[4], Alison J Moskowitz, MD[5], Tatyana A Feldman, MD[6], Ann S LaCasce, MD[7], Stephen M Ansell, MD, PhD[8*], Craig H. Moskowitz, MD[5], Keenan Fenton[9*], Kazunobu Kato, MD[10], Abraham Fong, MD, PhD[9] and Ranjana H Advani, MD[11]

# Nivolumab + Brentuximab Salavage Therapy for HL

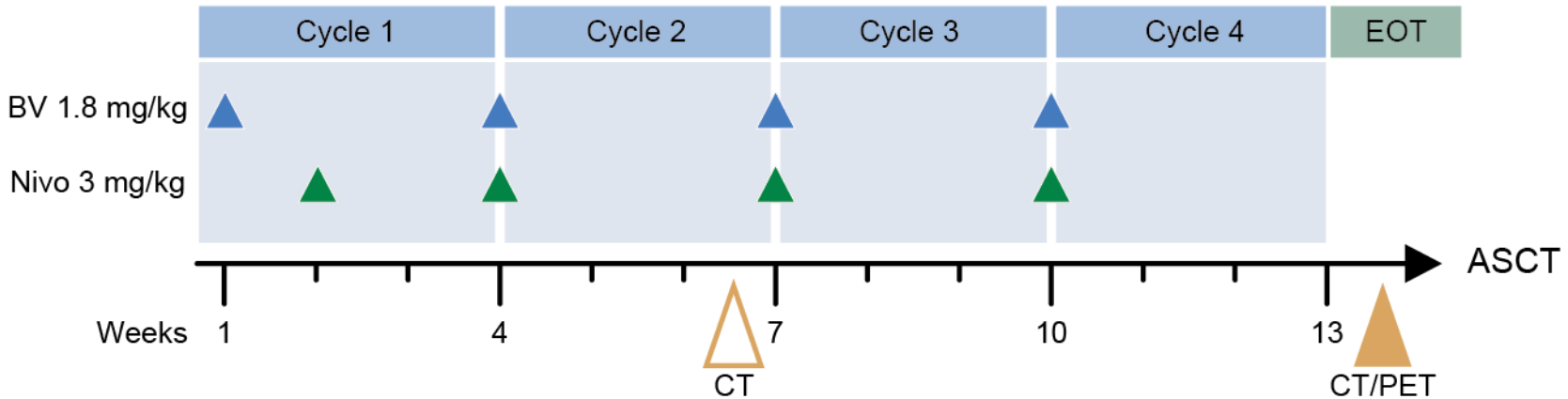
Brentuximab Vedotin 1.8mg/kg

Nivolumab 240 mg

Q 3wks x 4

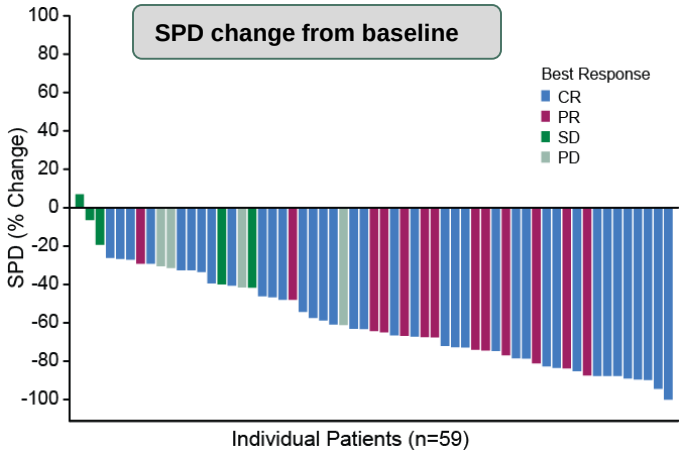
→ Restage

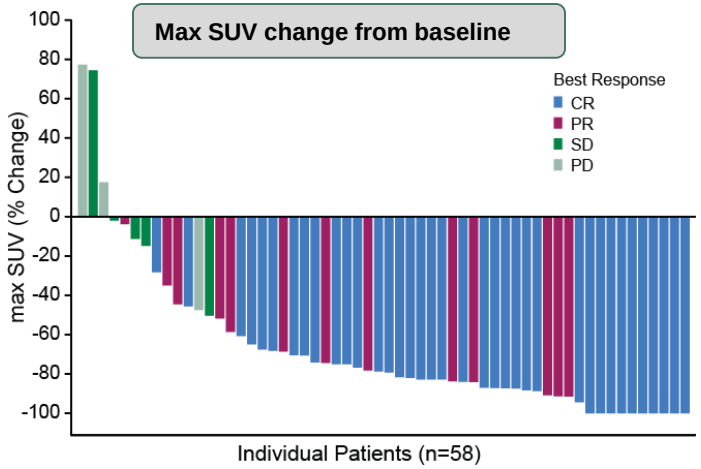
- PR/CR → Stem cell collection => BEAM ASCT
- < PR → Chemo salvage → Stem cell collection => BEAM ASCT



# Tumor Response (N=59)

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



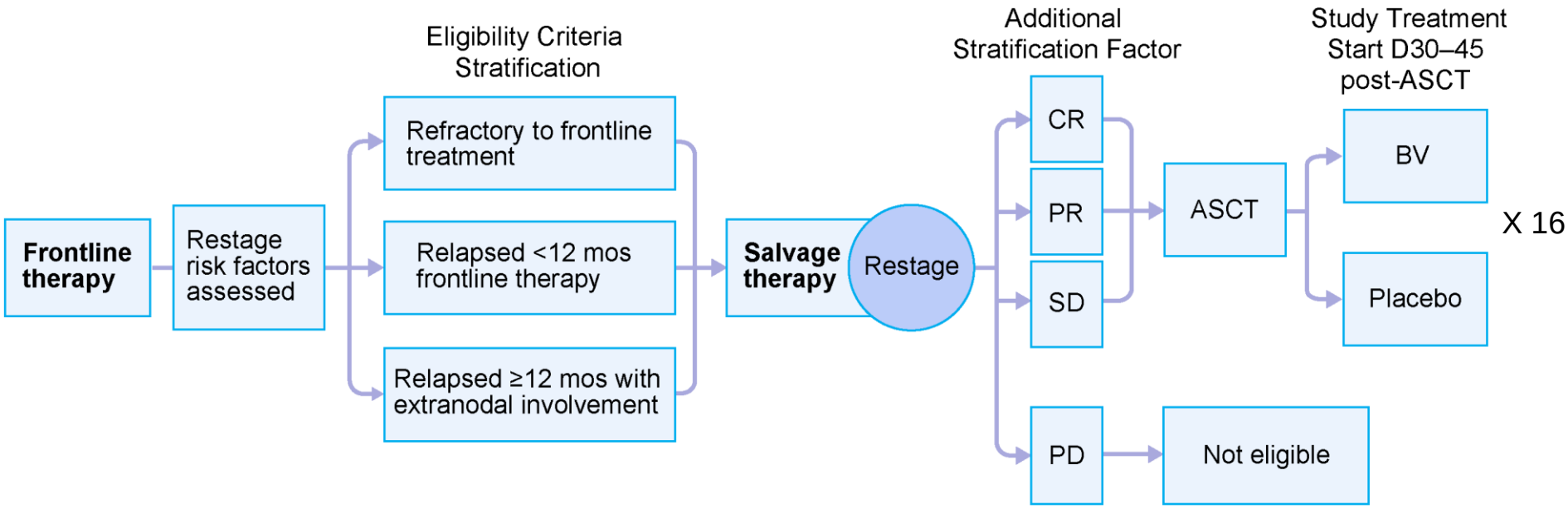

| | **N = 59**<br>n (%) |
|---|---|
| **Complete response (CR)** | **37 (63)** |
| Deauville ≤ 2 | 29 (49) |
| Deauville 3 | 7 (12) |
| Deauville 5[a] | 1 (2) |
| **Partial response (PR)** | **13 (22)** |
| Deauville 4 | 7 (12) |
| Deauville 5 | 6 (10) |
| **No metabolic response (SD)** | **5 (8)** |
| Deauville 5 | 5 (8) |
| **Progressive disease (PD)** | **3 (5)** |
| Deauville 5 | 2 (3) |
| Missing | 1 (2) |
| **Clinical Progression (CP)** | **1 (2)** |

a. 1 pt had uptake in lymph node, but no evidence of disease was found on biopsy

SPD, sum of the product of the diameters; SUV, standard uptake value

# The AETHERA study

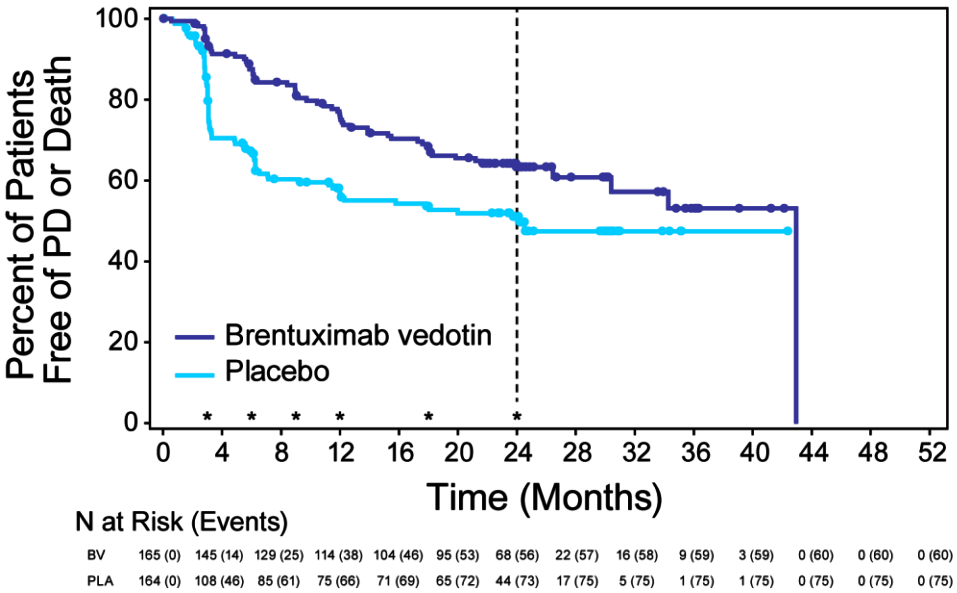
**329 patients were randomised at 78 sites in North America and Europe**




Moskowitz C, et al The Lancet 2015

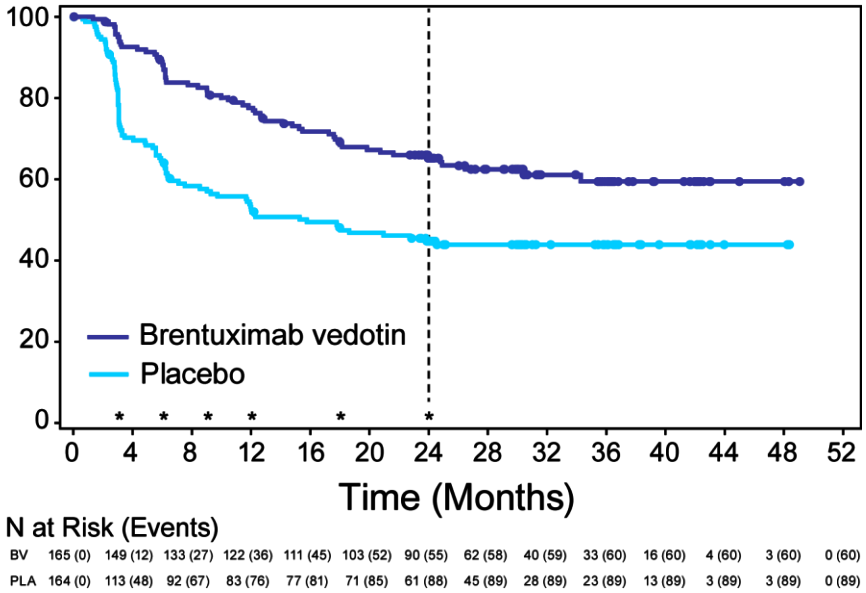
# Progression-free survival

## PFS per IRF




| | BV (N=165) | Placebo (N=164) |
|---|---|---|
| **Hazard Ratio (95% CI)** | **0.57 (0.40–0.81, P=0.001)** | |
| Events | 60 | 75 |
| Median PFS (months) | 43 | 24 |
| 2-year PFS rate | 63% | 51% |

## PFS per Investigator†




| | BV (N=165) | Placebo (N=164) |
|---|---|---|
| **Hazard Ratio (95% CI)** | **0.50 (0.36–0.70)** | |
| Events | 60 | 89 |
| Median PFS (months) | -- | 16 |
| 2-year PFS rate | 65% | 45% |

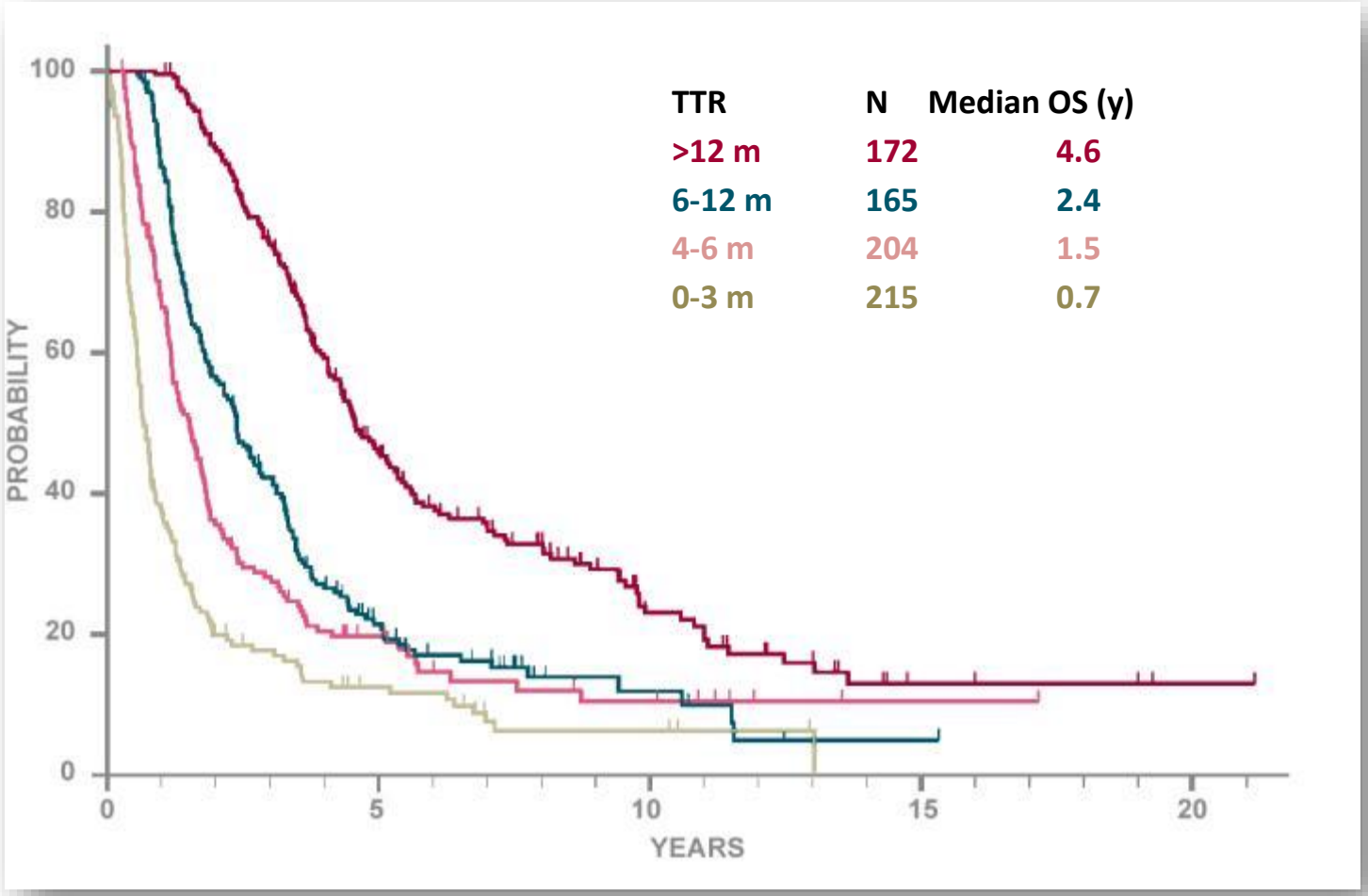
* Regularly scheduled CT scans

† Includes information from both radiographic assessments and clinical lymphoma assessments



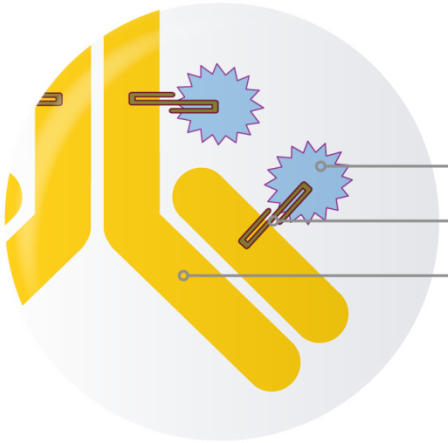
Moskowitz C, et al The Lancet 2015

# OVERALL SURVIVAL BY TIME TO RELAPSE AFTER TRANSPLANT




Horning S et al, Ann Oncol 2008:19 (suppl 4):Abstract 118
Arai S et al. Leukaemia and Lymphoma. 2013. In print

# BRENTUXIMAB VEDOTIN (SGN-35) : MECHANISM OF ACTION

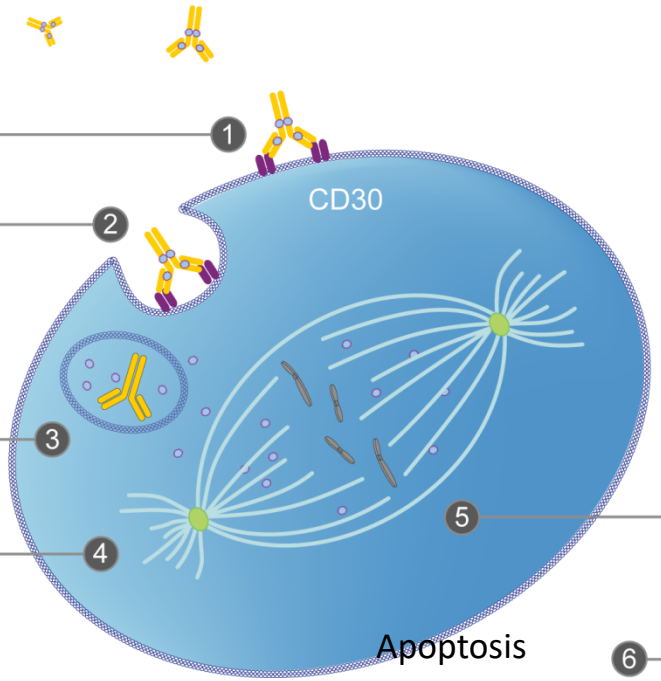


Brentuximab vedotin (SGN-35) ADC

monomethyl auristatin E (MMAE), potent antitubulin agent

protease-cleavable linker

anti-CD30 monoclonal antibody




ADC binds to CD30

ADC-CD30 complex traffics to lysosome

MMAE is released

MMAE disrupts Microtubule network

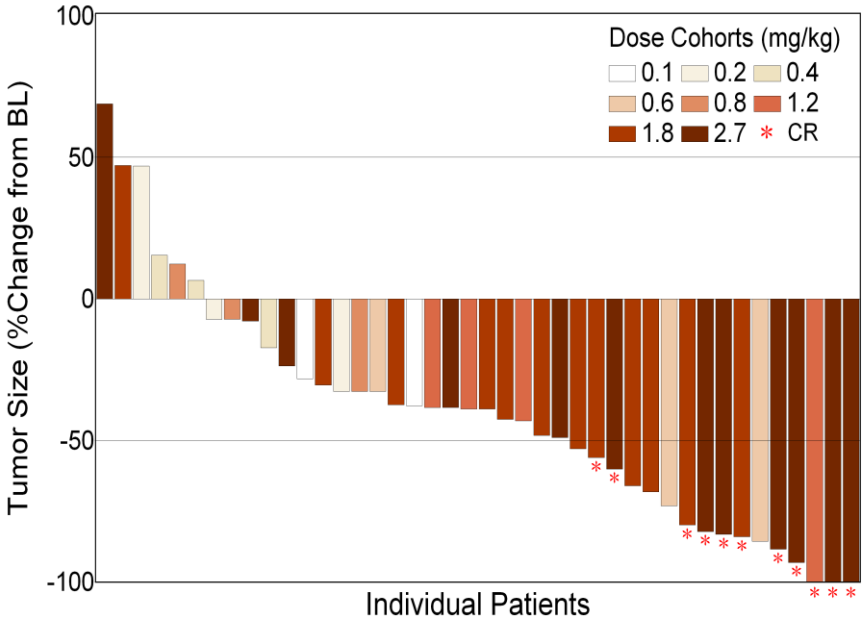
G2/M cell cycle arrest

Apoptosis

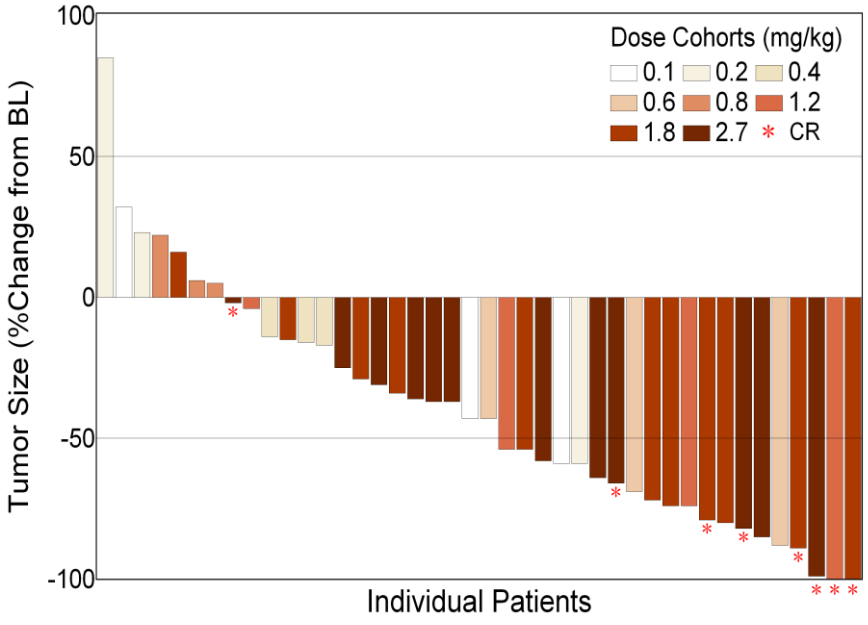
Younes A et al. N Engl J Med 2010; 363:1812-21 (appendix)

# Phase-I Brentuximab Vedotin in Relapsed HL Treatment Response

**Investigator Assessment**



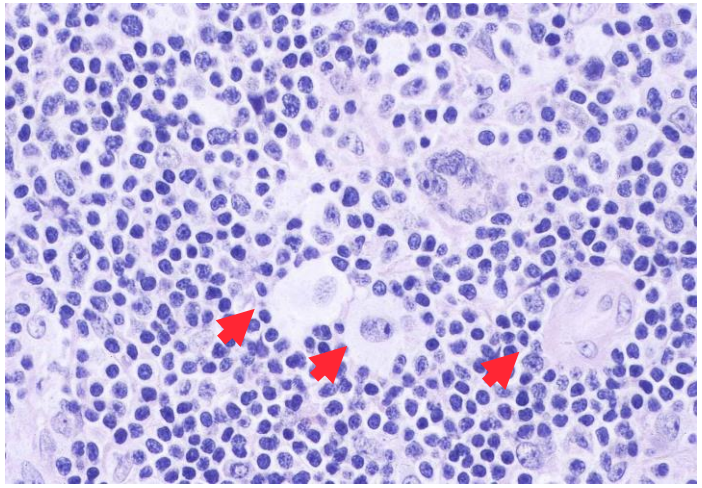

**IRF Assessment**

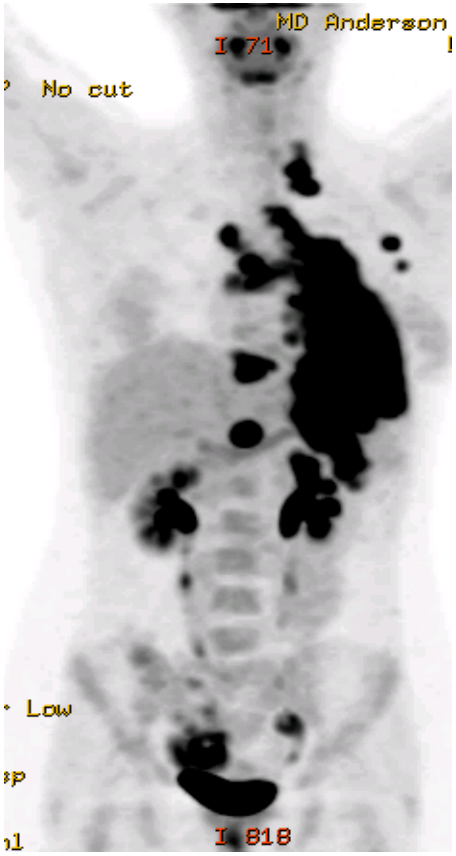


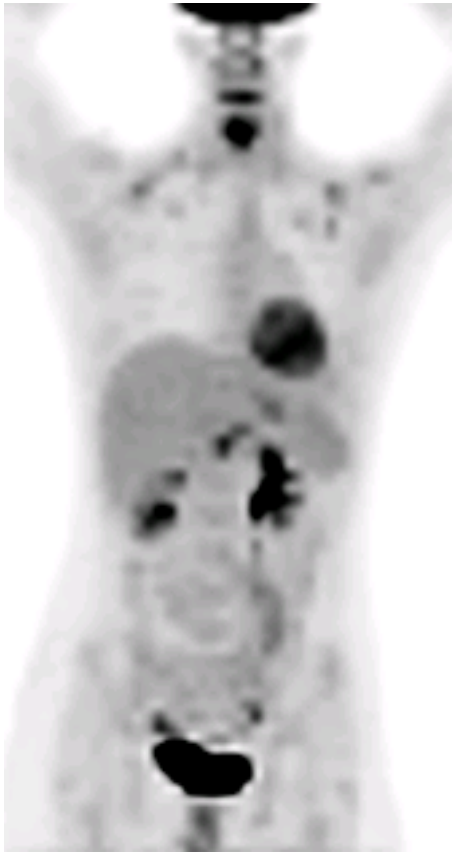

**Younes A, et al.** N Engl J Med 2010; 363:1812-1821

# Phase I Brentuximab Vedotin in Relapsed HL

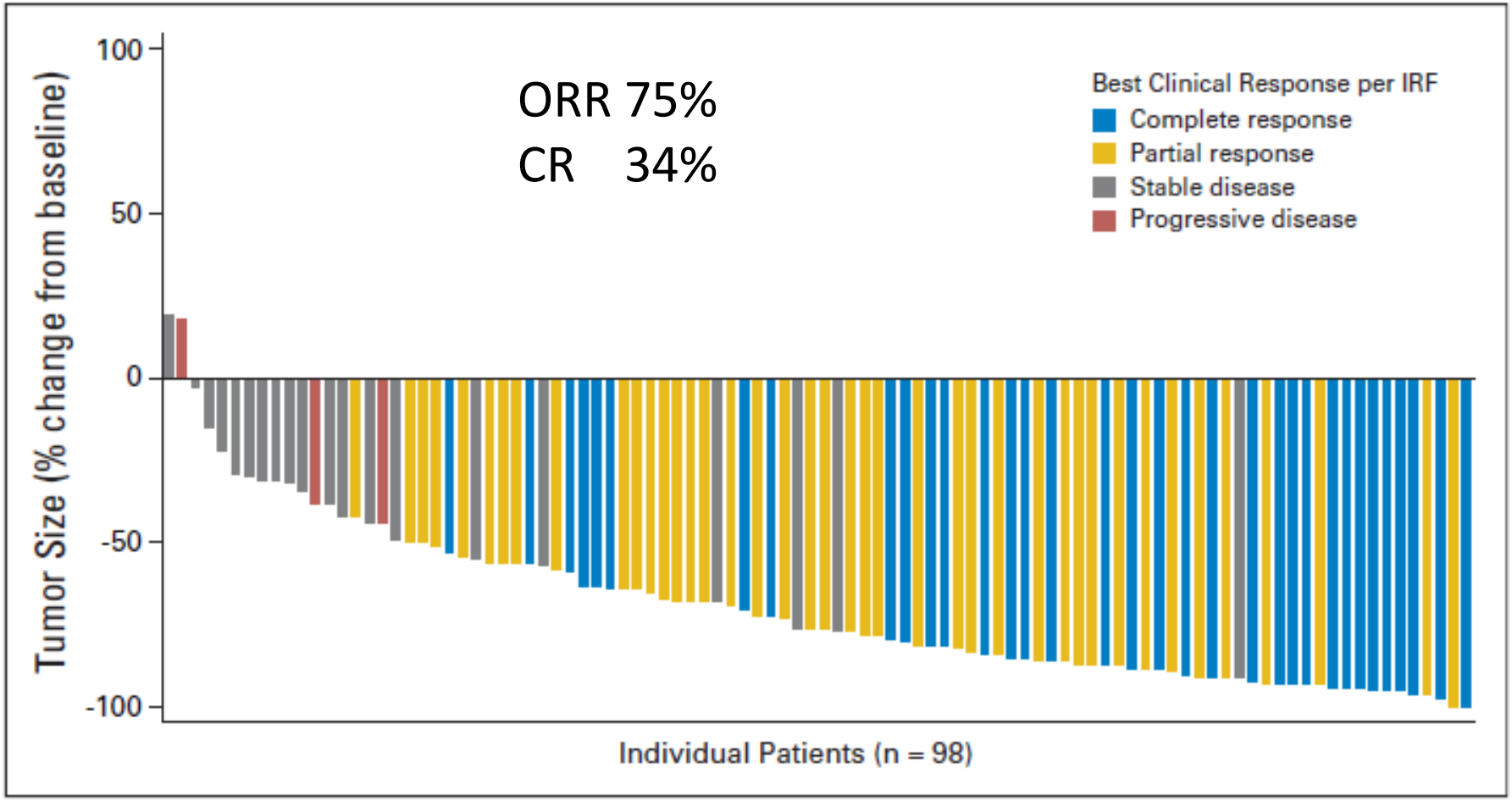
- 21-year-old female
- HL diagnosed 2003
  - ABVD + XRT to mediastinum
  - ICE
  - BEAM→ASCT
  - HDAC-inhibitor
- SGN-35 2.7 mg/kg x 8 cycles
  - Best clinical response: CR
  - CT 93% reduction, PET-
  - PET negative





# Phase II pivotal study of brentuximab vedotin in relapsed HL post ASCT



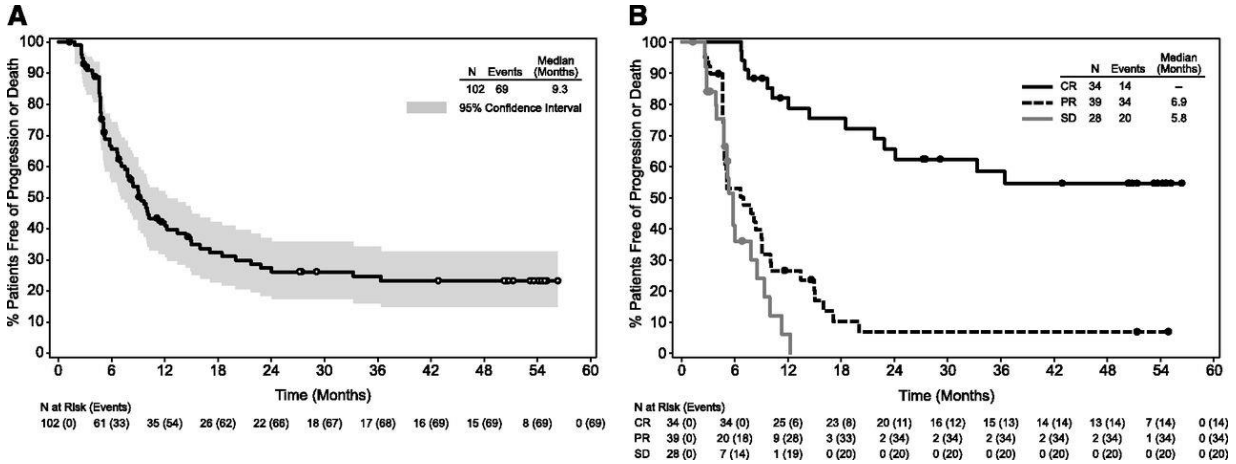

94% patients achieved tumour reduction

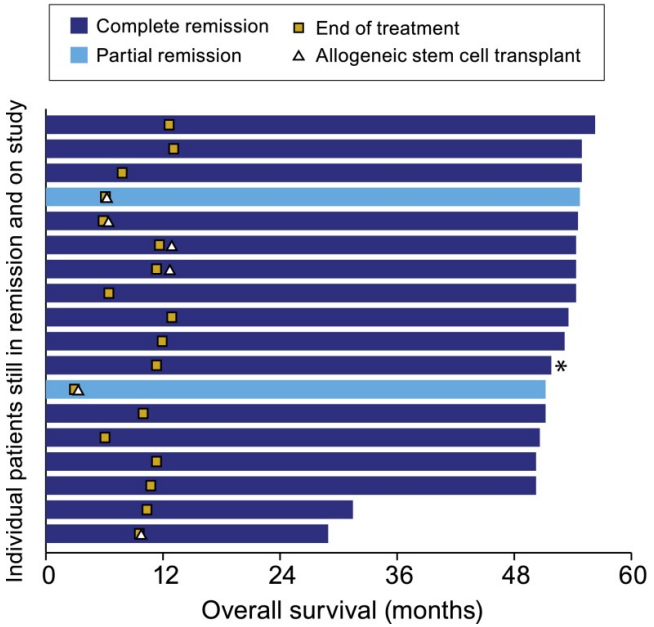
IRF – independent review facility

Younes A et al. J Clin Oncol 2012;30: 2183-9.

# Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma

**PFS following treatment with brentuximab vedotin.**



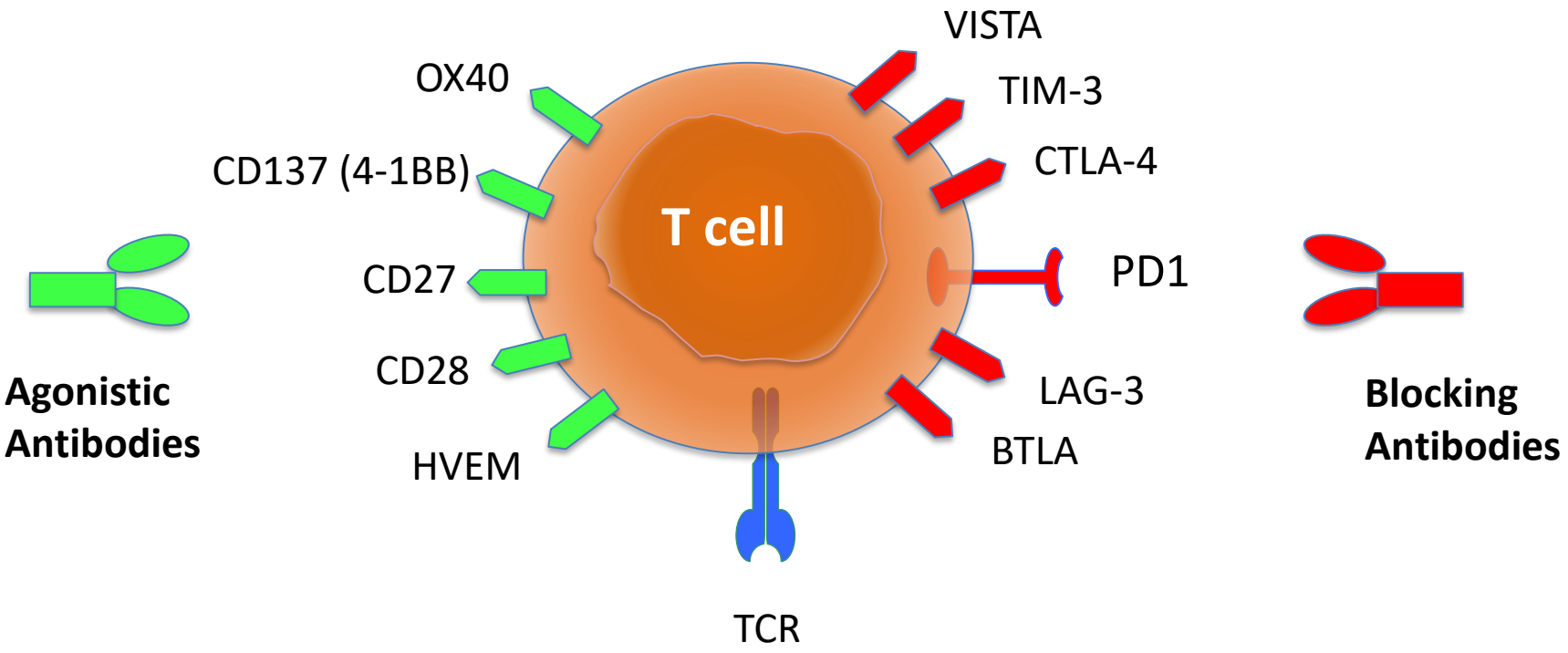




4/16 in CR had all0-SCT

Ajay K. Gopal et al. Blood 2015;125:1236-1243

# Therapeutic Activation of Autologous T Cells

## Immune checkpoint inhibitors



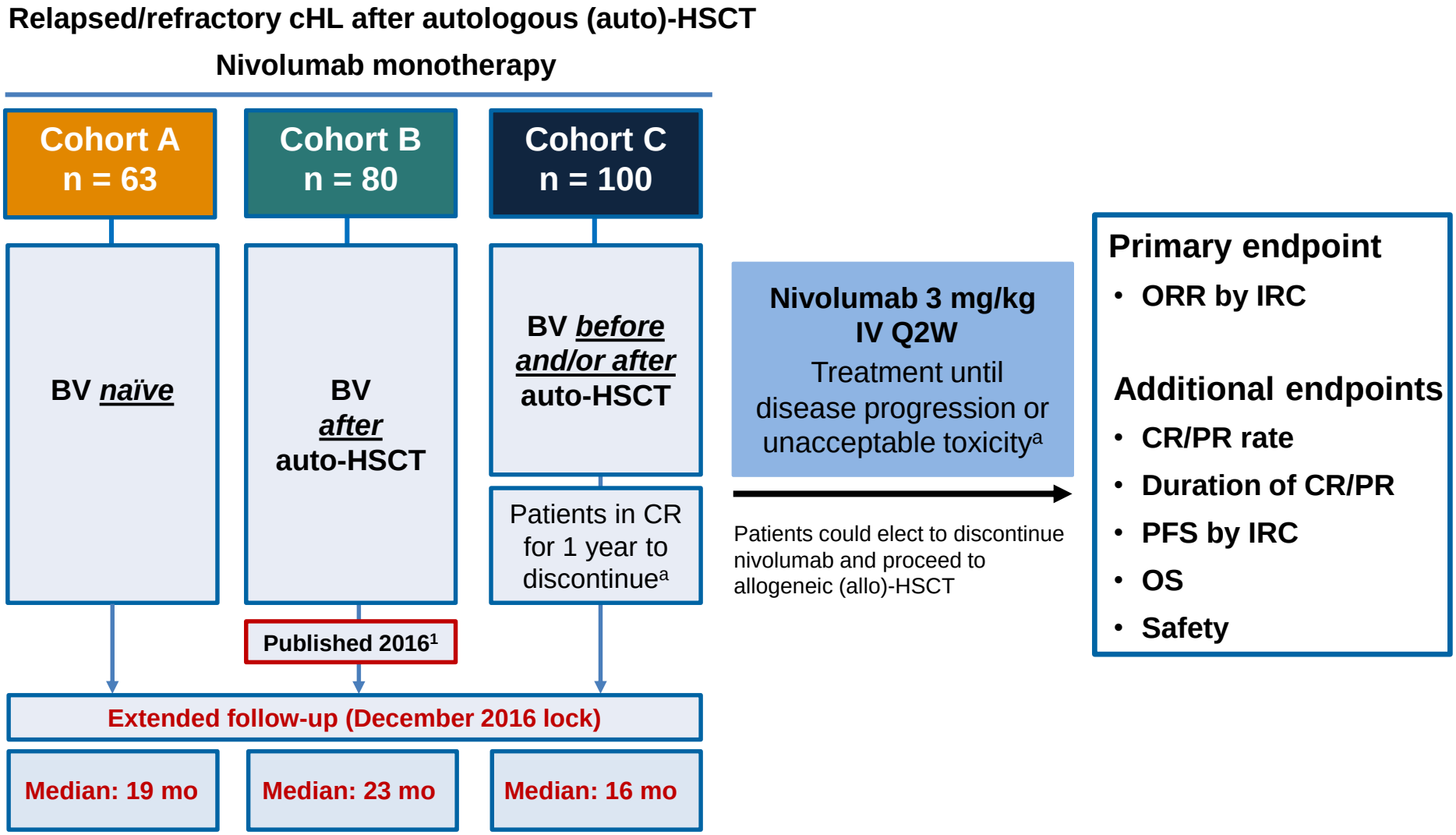

Adapted from Batlevi et al, Nature Rev Clin Oncol 2015

# Results of PD1 Blocking Antibodies in Relapsed HL

## Phase-I Studies

| Drug | Dose/Schedule | N | % ORR | % CR | ORR in BV treated HL | 1st Author |
|---|---|---|---|---|---|---|
| Pembrolizumab (humanized IgG4) | 10 mg/kg IV Q 2wks | 29 | 66% | 21% | 66% (n=19) | Armand P, JCO 2016 |
| Nivolumab (Fully human IgG4) | 3 mg/kg IV Q 2wks | 23 | 87% | 17% | 70% (n=16) | Ansell S NEJM 2015 |

# Phase 2 CheckMate 205 Study Design



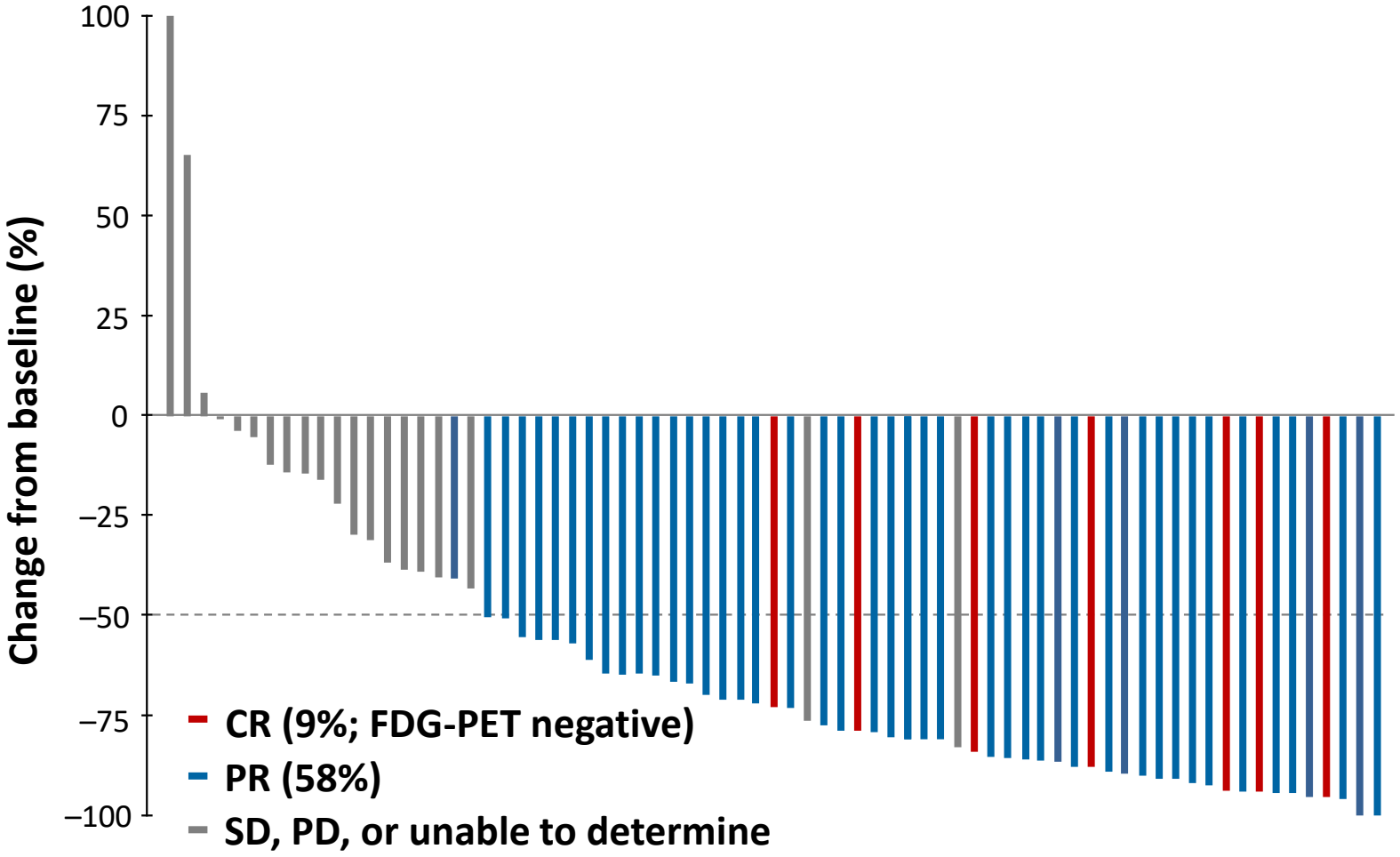

BV = brentuximab vedotin; CR = complete remission; HSCT = hematopoietic stem cell transplant; IRC = Independent Radiology Review Committee; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial remission; Q2W = every two weeks.

[a]Could restart treatment if relapse within 2 years

1. Younes A, et al. *Lancet Oncol* 2016;17:1283–1294

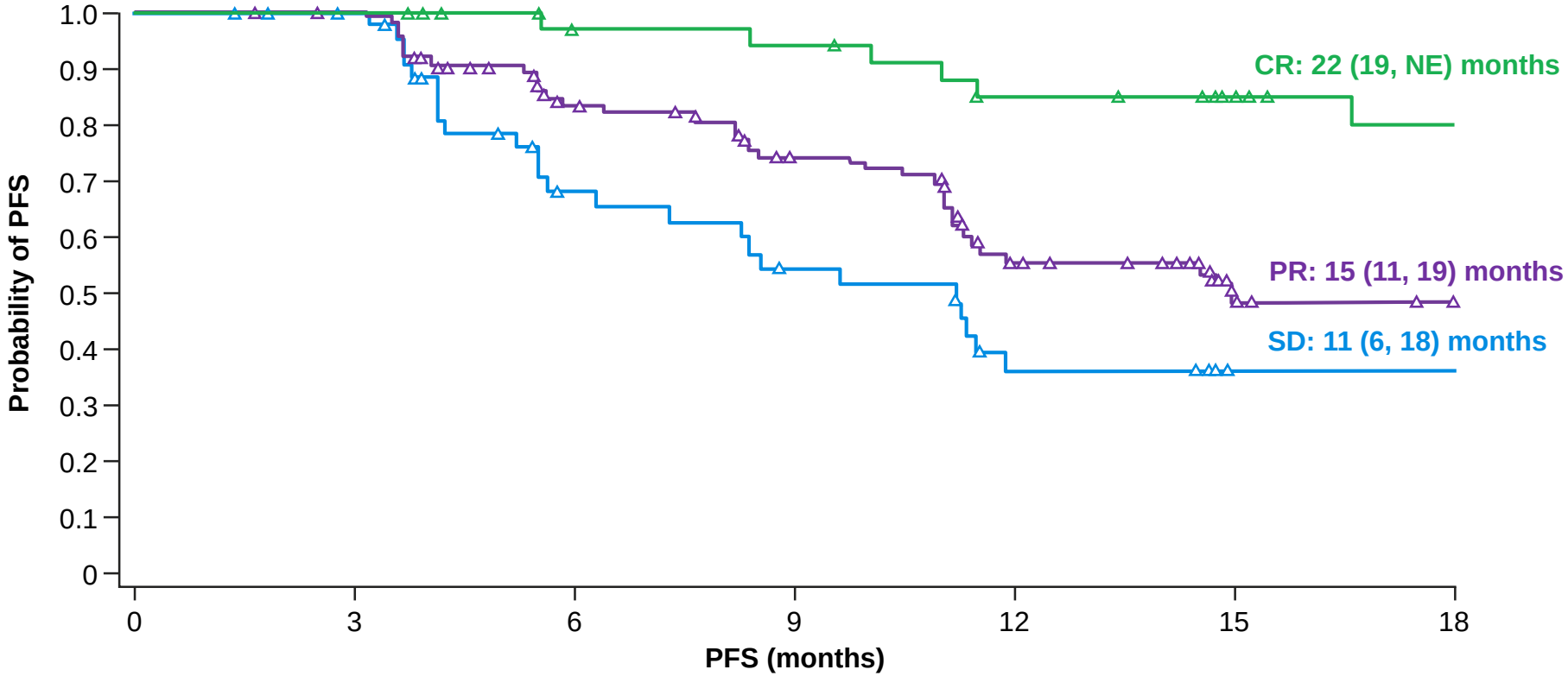
# Tumor Burden Change From Baseline (all response-evaluable patients)

- All but 1 responder had a reduction of ≥50% from baseline in tumor burden




Younes A, et al: Lancet Oncology 2016

# Progression-Free Survival by Best Overall Response



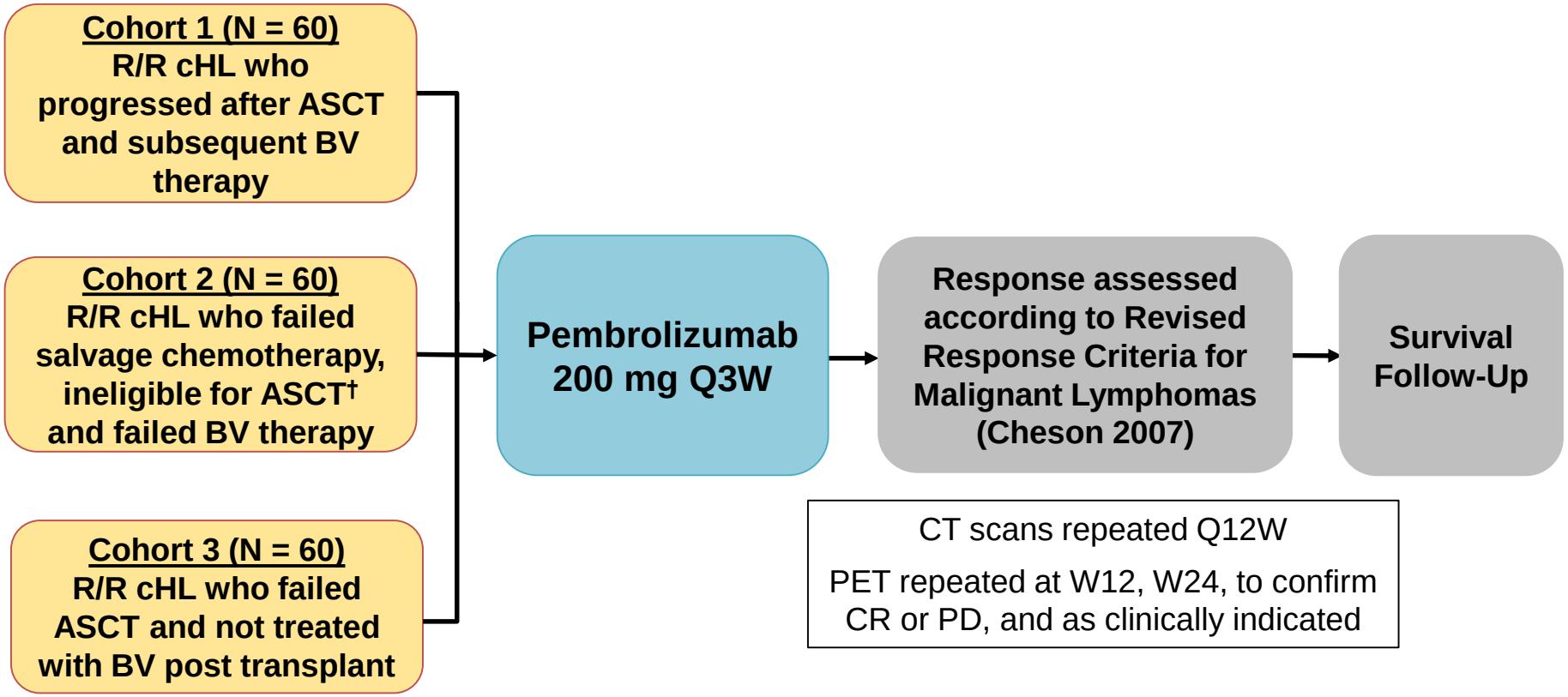

**Number of patients at risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| CR | 40 | 40 | 33 | 32 | 27 | 20 | 16 |
| PR | 128 | 126 | 89 | 71 | 46 | 25 | 21 |
| SD | 47 | 44 | 25 | 19 | 11 | 8 | 8 |

- Median PFS for all 243 patients was 15 (11–19) months

All values are medians (95% CI). SD = stable disease

# KEYNOTE-087: Study Design




- **Primary end point:** ORR (central review)
- **Secondary end points:** ORR (investigator review), PFS, OS
- Prespecified interim analysis, based on investigator-assessed response, performed after 30 patients in all 3 cohorts reached first response assessment

†Unable to achieve a CR or PR to salvage chemotherapy

# Results of PD1 Blocking Antibodies in Relapsed HL

## Results of Phase-II Studies

### Post ASCT and Brentuximab Vedotin

| Drug | Dose/Schedule | N | % ORR | % CR | 1st Author/Ref |
|---|---|---|---|---|---|
| Pembrolizumab (humanized IgG4) | 200 mg IV Q 3wks | 69 | 72% | 21% | Chen, R/ JCO 2017 |
| Nivolumab (Fully human IgG4) | 3 mg/kg IV Q 2 wks | 80 | 66% | 9% | Younes, A/Lancet Oncology 2016 |

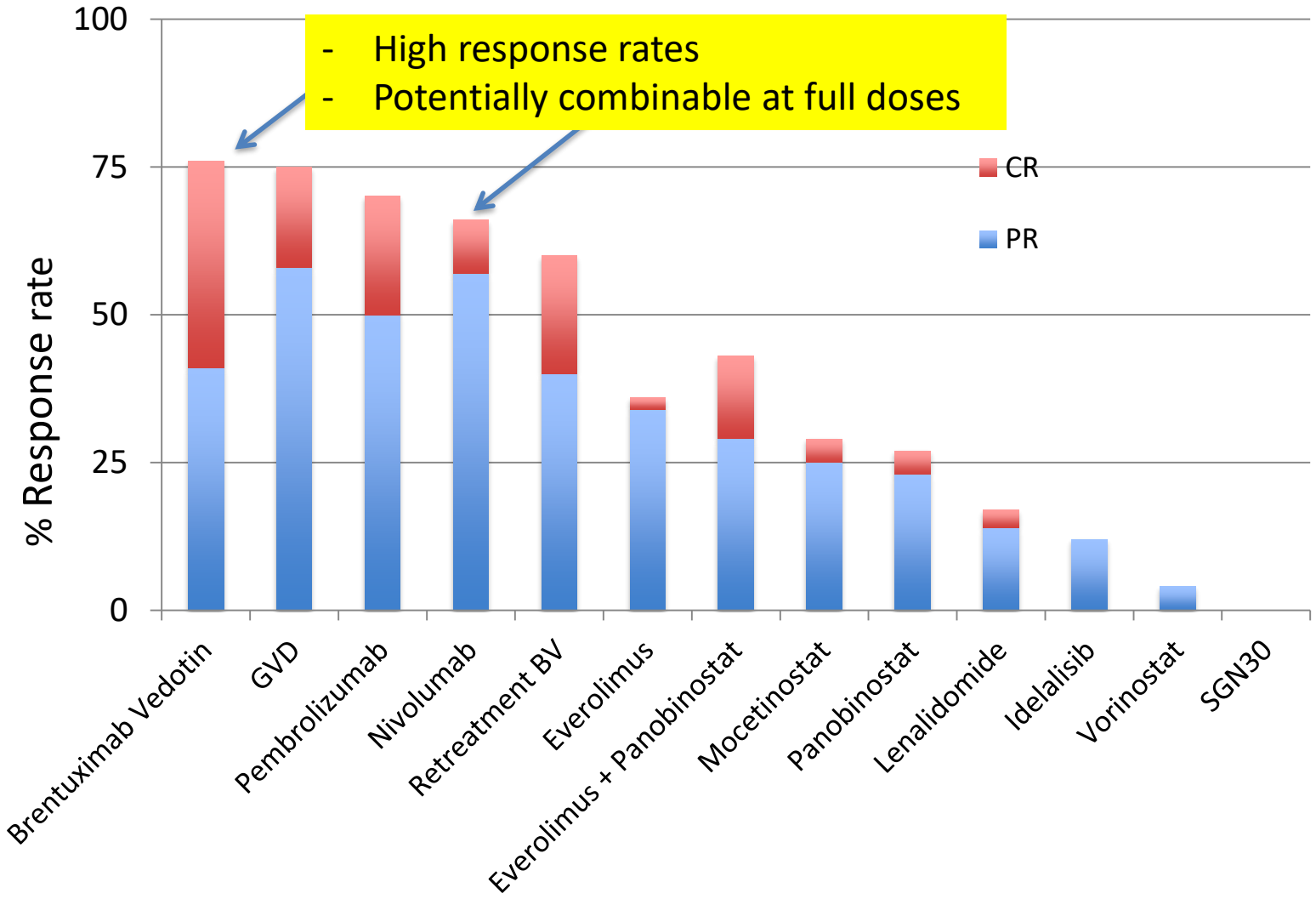
# Results of PD1 Blocking Antibodies in Relapsed HL

## Results of Phase-II Studies

### Post ASCT but No PRIOR Brentuximab Vedotin

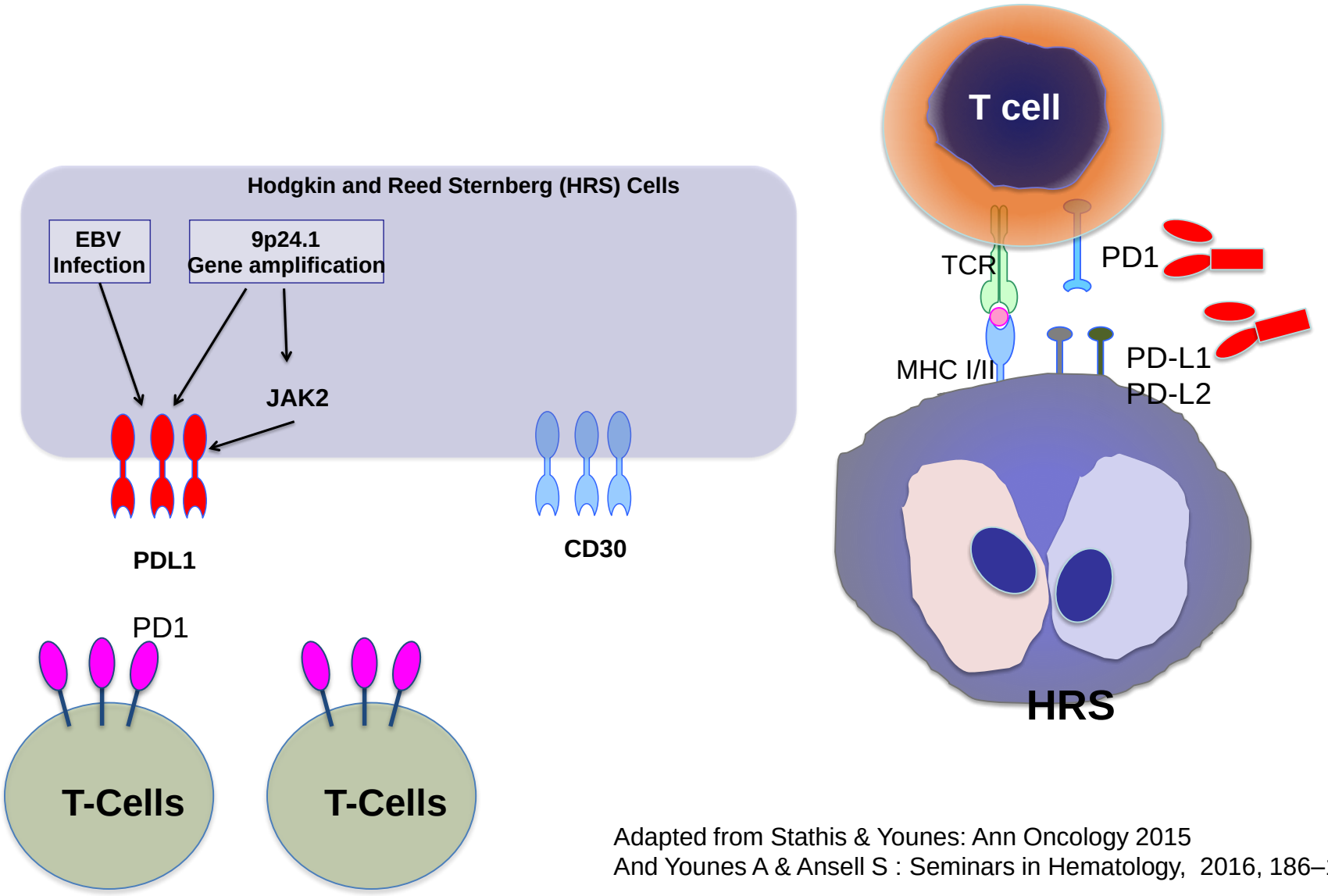
| Drug | Dose/Schedule | N | % ORR | % CR | 1st Author/Ref |
|---|---|---|---|---|---|
| Pembrolizumab (humanized IgG4) | 200 mg IV Q 3wks | 60 | 67% | 21% | Chen, R/ JCO 2017 |
| Nivolumab (Fully human IgG4) | 3 mg/kg IV Q 2 wks | 63 | 68% | 22% | Fanale, M/ ICML2017 |

# Single agent activity of novel agents in relapsed cHL




Updated from Betlevi and Younes, Hematology Am Soc Hematol Educ Program. 2013
Smith, K et al : Hodgkin Lymphoma, Hoffan Textbook of Hematology 2015 (In Press)

# HRS Cells Express High Levels of PDL-1




Adapted from Stathis & Younes: Ann Oncology 2015
And Younes A & Ansell S : Seminars in Hematology, 2016, 186–189

# Conclusions

- Brentuximab Vedotin is a highly active single agent in relapsed HL
- Combination strategies are ongoing in front-line, second line, and post transplant setting
- In the era of highly active new agents, the role of ASCT in second line treatments needs to be re-examined
- Immune checkpoint inhibitors are active agents in BV failures
- BV + PD-1 antibodies seems to be safe and effective, and may provide a new backbone for future drug development in HL
- Standard of care therapy is likely to change in the next few years