Fred Hutch Cancer Center

# Management of Classical Hodgkin Lymphoma

**Christina Poh, MD**

University of Washington CME Board Review

Assistant Professor, University of Washington

Assistant Professor, Fred Hutch Cancer Center

September 25, 2024

UW Medicine

# Disclosures

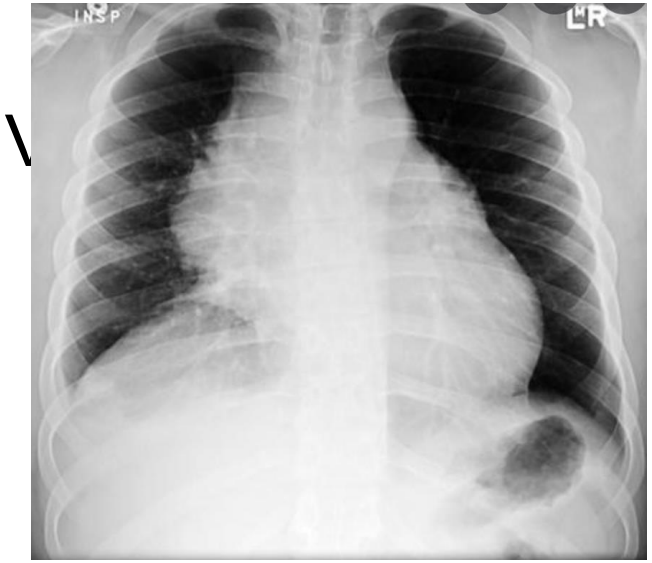
- Research Funding: Incyte, Dren Bio, Astex, Pfizer
- Consultancy: Acrotech, Beigene, Seagen, Ipsen

# Background

- Classical Hodgkin lymphoma (CHL) represents ~ 10% of all lymphomas
- 8500 new cases annually in the United States
- Highly curable with frontline therapy (chemotherapy +/- RT)
  - Early stage > 90%
  - Advanced stage ~ 75%

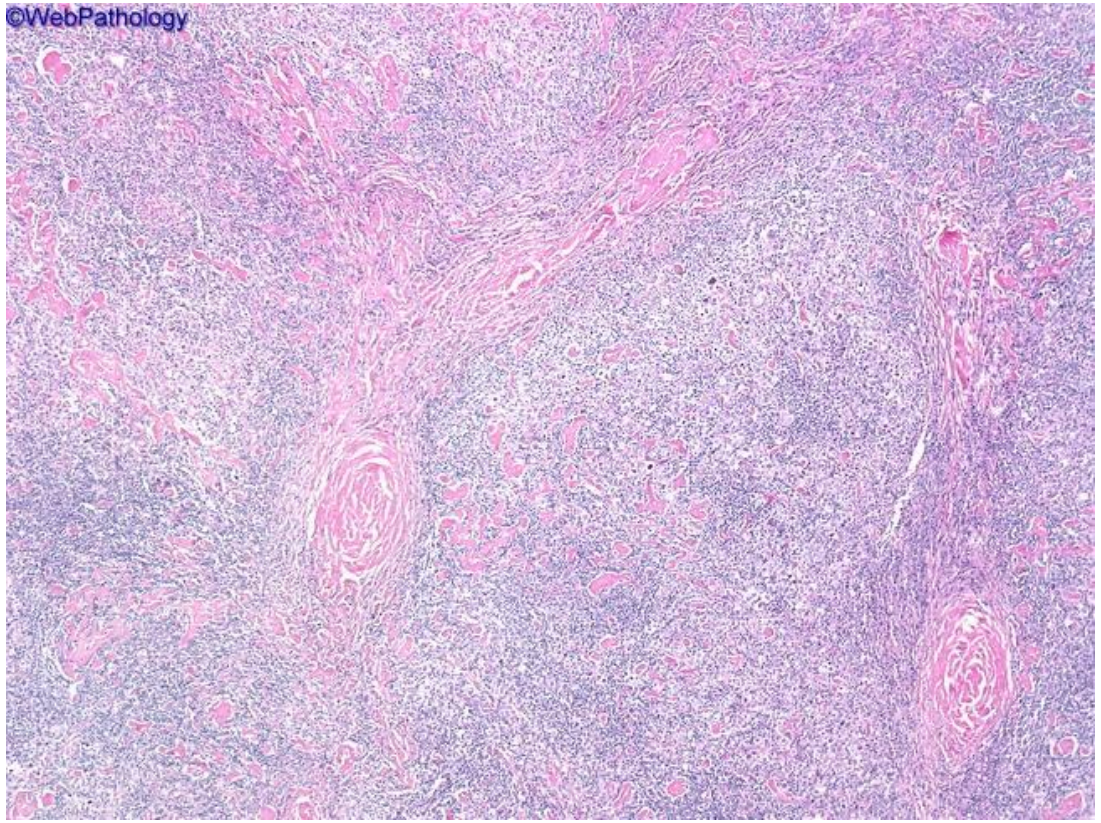
# Presentation

- Painless lymphadenopathy
- B symptoms (20% stage I-II, 50% stage III-IV
  - Fevers
  - Chills
  - Night sweats (DRENCHING!)
  - Unexplained weight loss (10%)
- Itching without rash
- Alcohol-induced pain in involved sites (10%)
- Cough, light-headedness, compression of major blood vessels related to large (bulky) mass

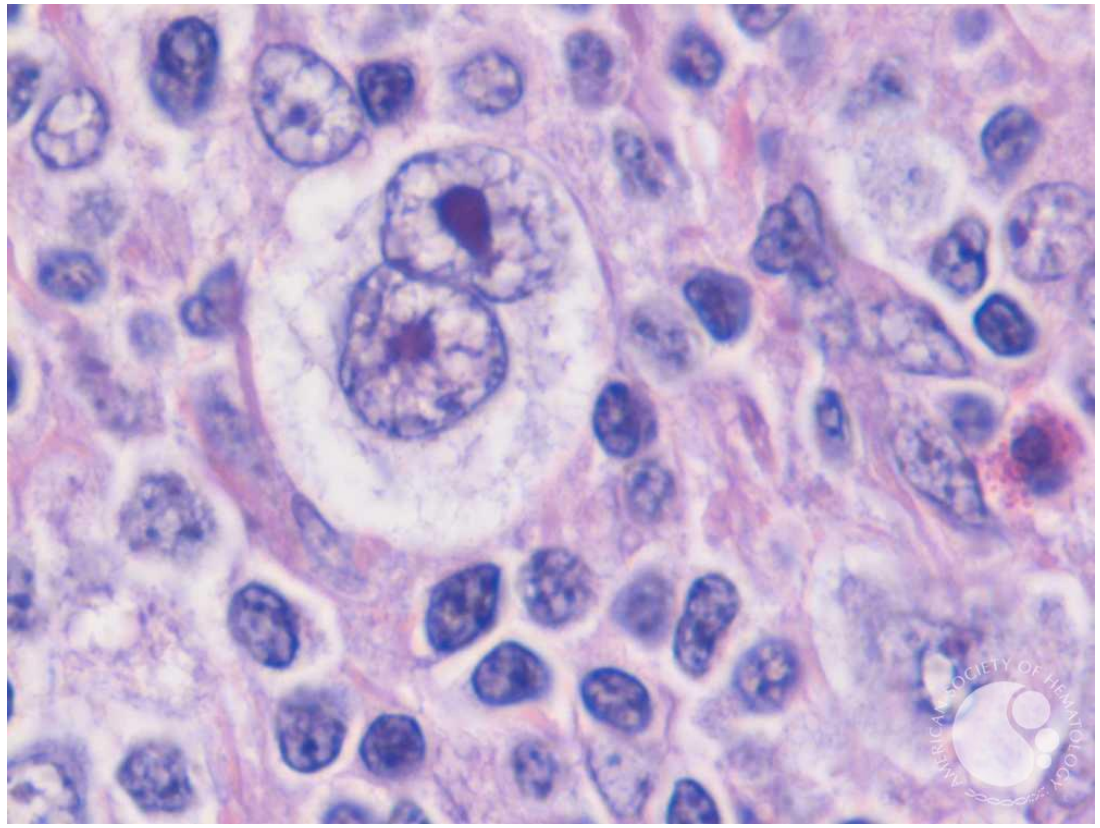


# Rare Hodgkin lymphoma cells

**The malignant cell makes up < 1% of the tumor!**

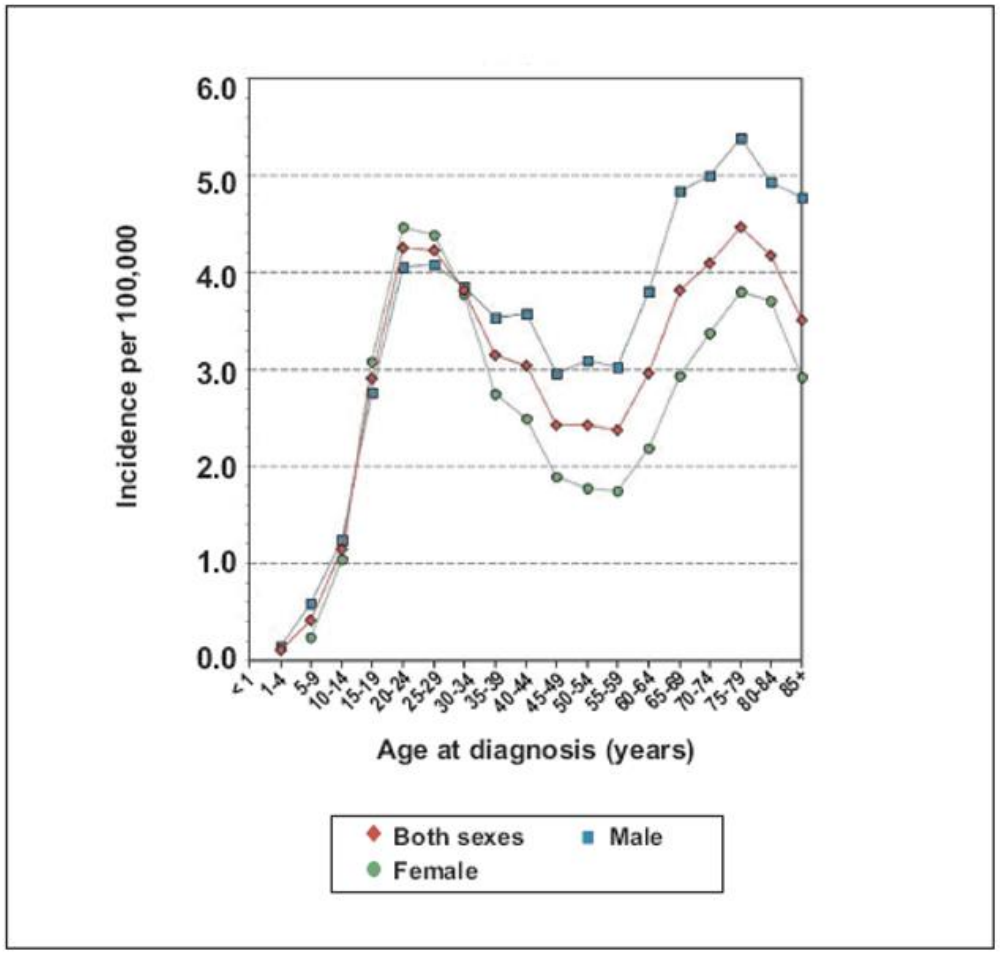



WebPathology.com



Hematology.org

# Hodgkin lymphoma by age



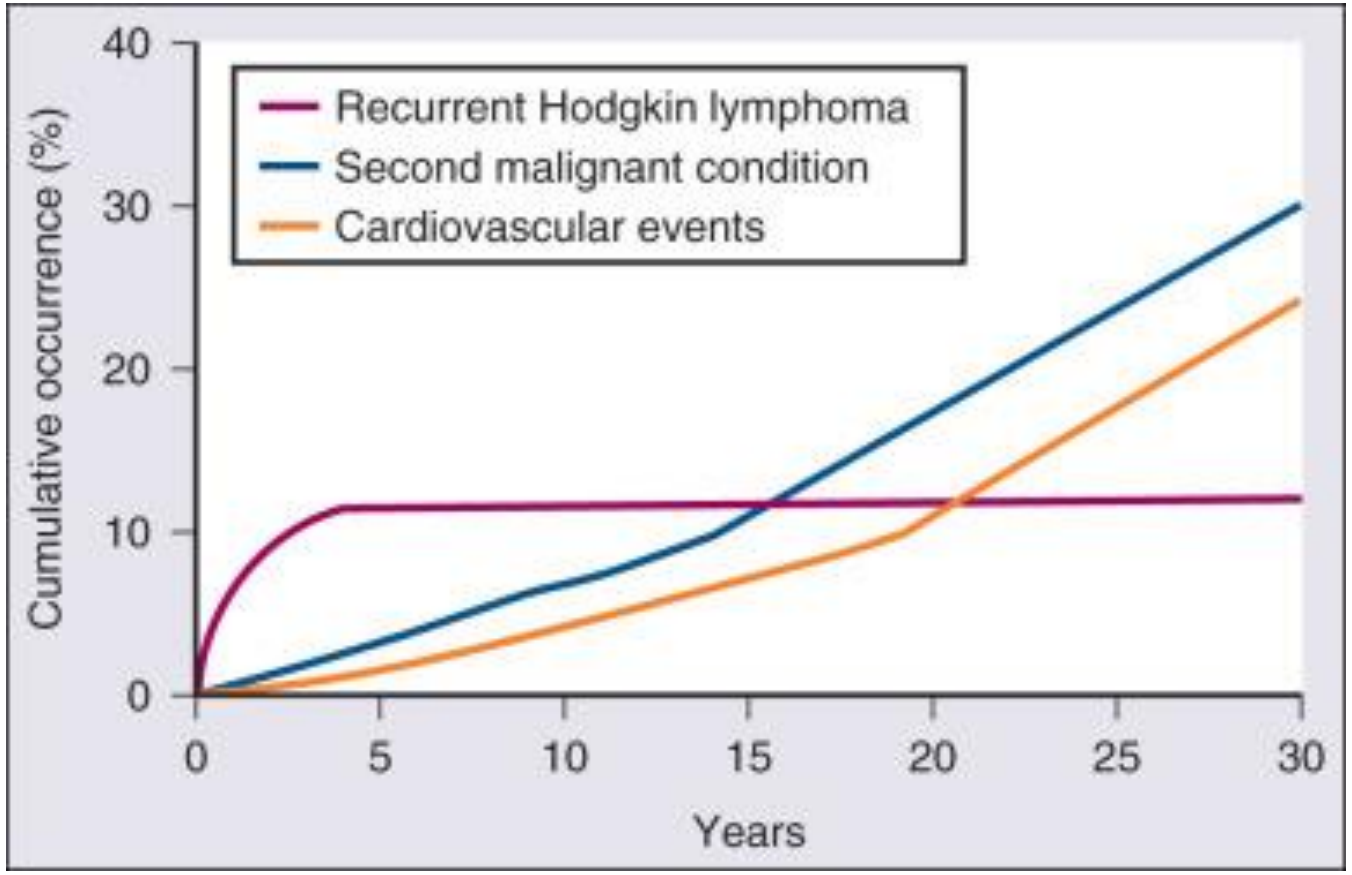

- One of the most common cancers to affect adolescents/young adults
- Incidence rises again in older adults
  - But so do most other kinds of cancer unfortunately

Evens et al. Cancer Network 2008

# What have we learned over the years about Hodgkin lymphoma?

- 1820s - “Hodgkin’s disease” – Thomas Hodgkin
- 1960s- First limited-stage patients cured with radiation therapy
- 1960s-1970s- NCI devised regimen called “MOPP” that cured many advanced patients
  - M = mustard (the same as mustard gas!)
- Over the years, long-term toxicities of high dose radiation and intensive chemo were recognized

# Early cure, late effects




Bartlett et al. Abeloff's Clinical Oncology 2020

# Historical advances in CHL management

- Limited stage
  - Definitive “Mantle” RT evolved to combined modality therapy
- Advanced stage
  - Evolution from MOPP to safer regimens (ABVD)

- Widespread adoption of PET/CT in the 2000s allowed for more accurate staging, response assessment, as well as allowing for more limited radiation fields.

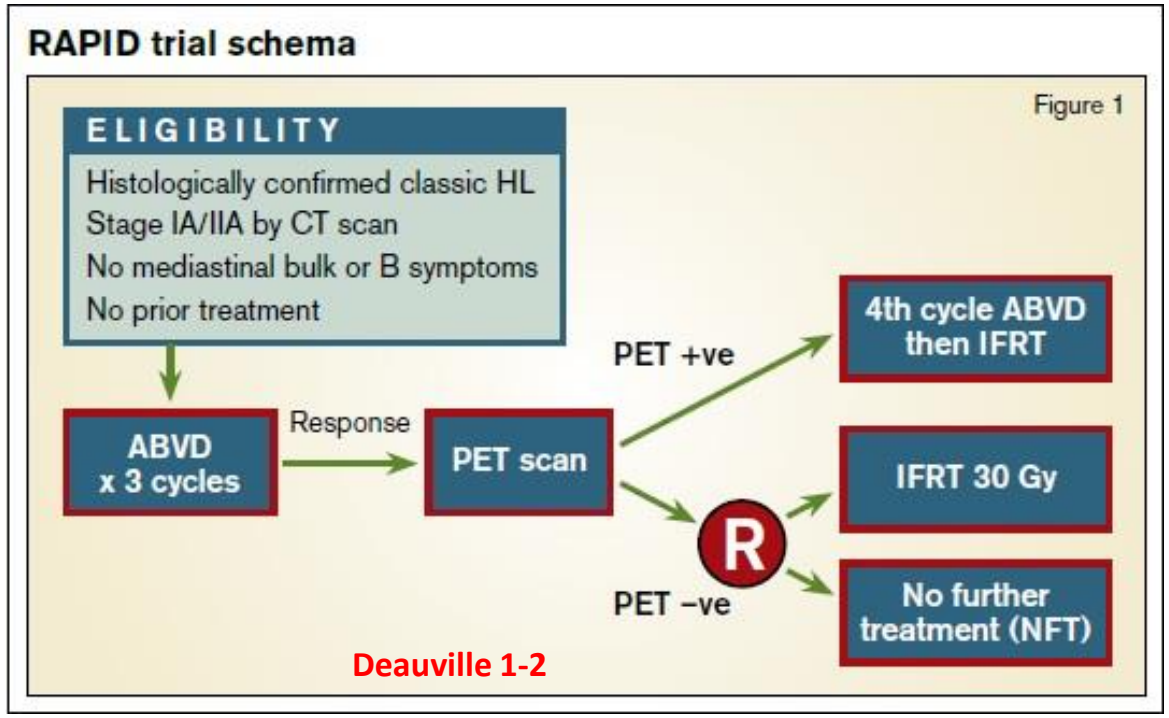
# New drugs for Hodgkin lymphoma

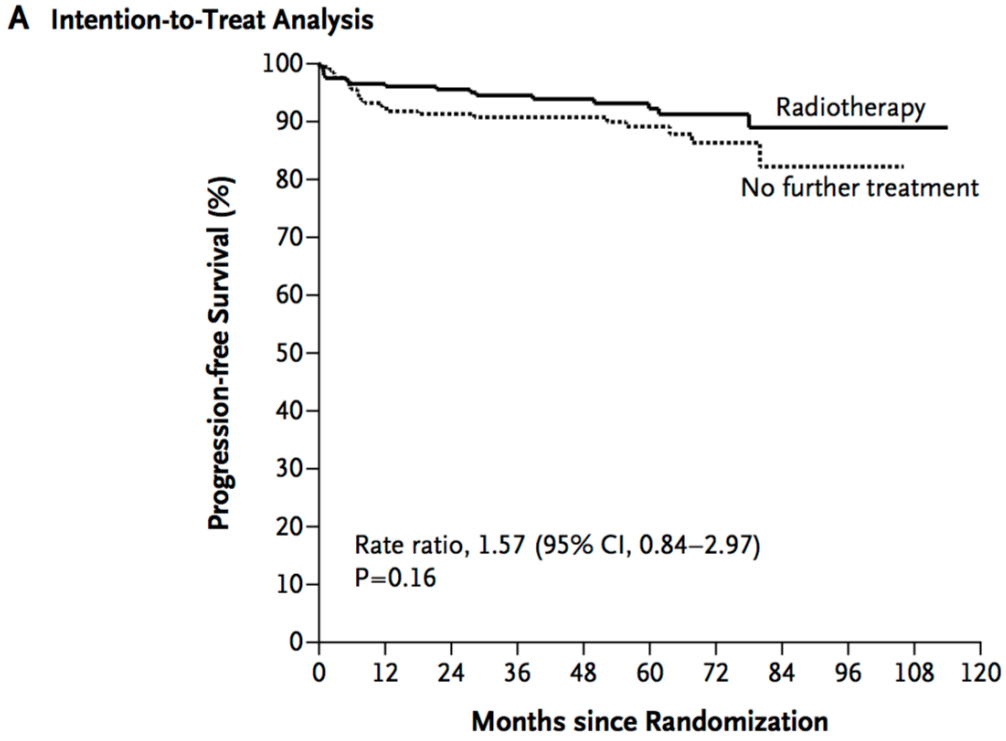
- The FDA approval of 3 drugs for CHL since 2011 has sparked a wave of new advances
  - Brentuximab vedotin: 2011
  - Nivolumab: 2016
  - Pembrolizumab: 2017

- While the initial approvals were as monotherapy in the relapsed setting, we have since learned more about how these agents can improve outcomes in CHL in various combinations and even in untreated patients.

# Limited stage CHL

# RAPID trial

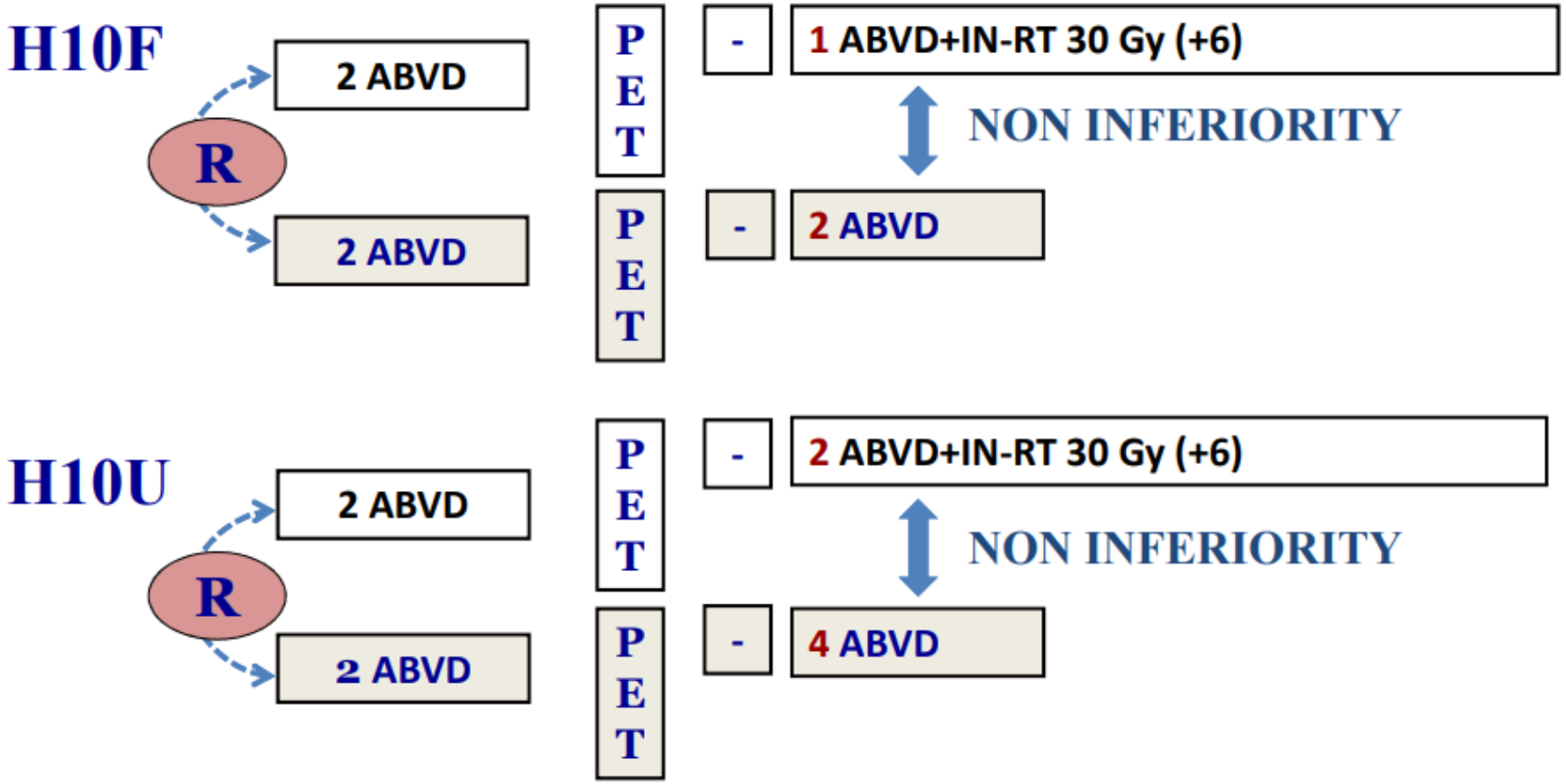



**Missed non-inferiority target, but has been adopted into NCCN guidelines**

Radford J et al: N Engl J Med 372:1598-607, 2015

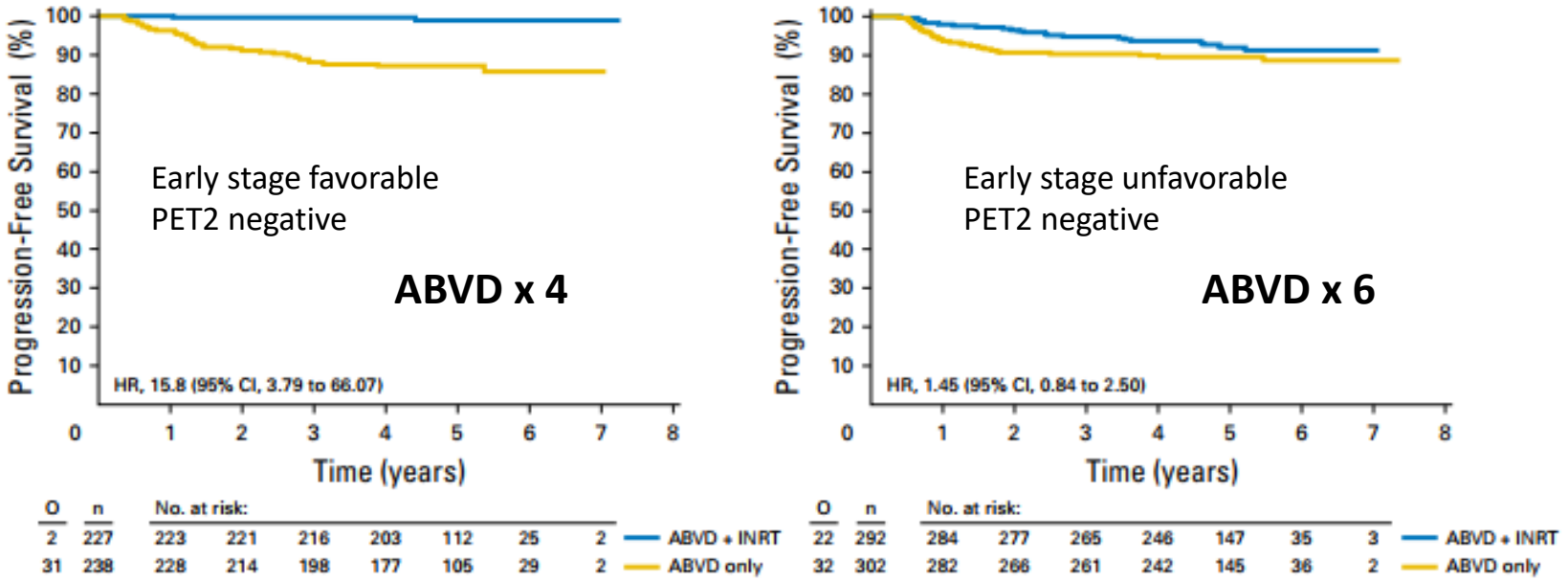
# EORTC/LYSA/FIL H10 trial




Andre MPE, et al. J Clin Oncol 35:1786-1794, 2017

# EORTC/LYSA/FIL H10 trial

## Inferior outcomes in PET2- patients with abbreviated chemo and no RT




Andre MPE, et al. J Clin Oncol 35:1786-1794, 2017

# Summary – Upfront limited stage

- Early PET defines 2 risk populations in stage I-II (favorable vs unfavorable)
  - PET adapted strategy is warranted
- Early PET-positive patients:
  - Escalation of therapy (BEACOPP) improves PFS
- Early PET negative patients:
  - H10 failed to demonstrate non-inferiority of PFS in no radiotherapy arm
  - Less benefit for combined modality in unfavorable group
  - Overall survival is excellent regardless of radiotherapy
- No novel therapy approved in limited stage

# Risk factors to consider

**UNFAVORABLE RISK FACTORS**

**Unfavorable Risk Factors for Stage I–II Hodgkin Lymphoma**

| Risk Factor | GHSG | EORTC | NCCN |
|---|---|---|---|
| Age | | ≥50 | |
| Histology | | | |
| ESR and B symptoms | >50 if A; >30 if B | >50 if A; >30 if B | ≥50 or any B symptoms |
| Mediastinal mass | MMR >0.33 | MTR >0.35 | MMR >0.33 |
| # Nodal sites | >2* | >3* | >3 |
| E lesion | any | | |
| Bulky | | | >10 cm |

GHSG = German Hodgkin Study Group
EORTC = European Organization for Research and Treatment of Cancer

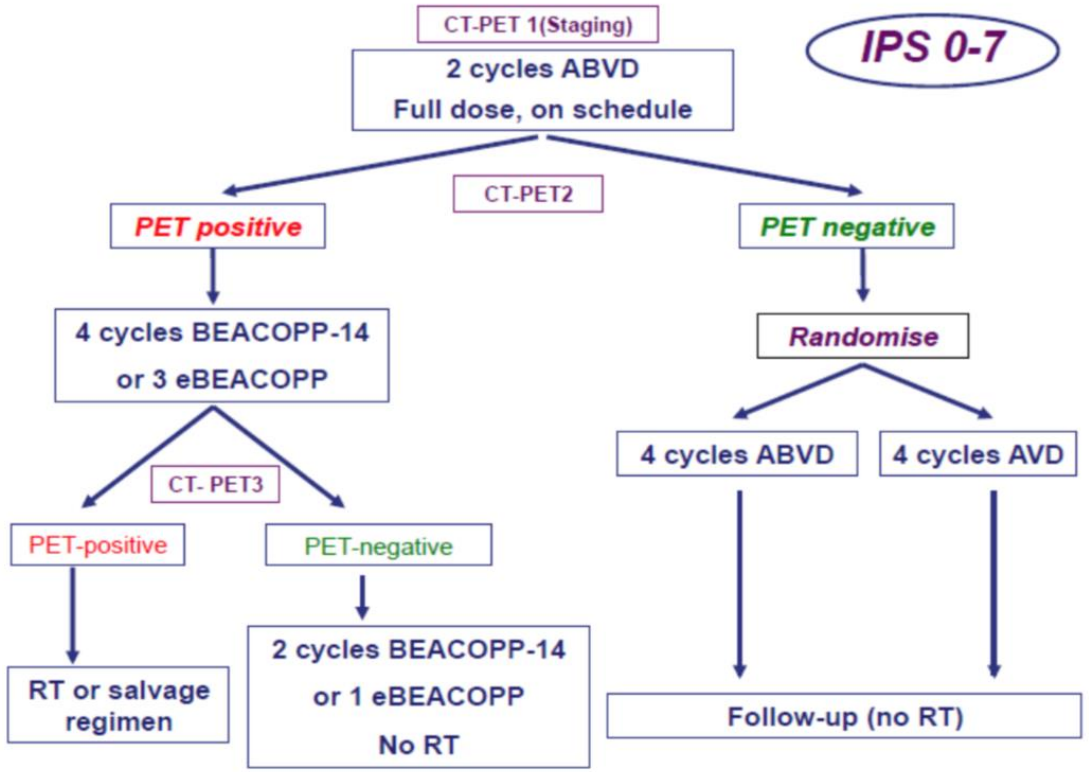
MMR = Mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter
MTR = Mediastinal thoracic ratio, maximum width of mediastinal mass/intrathoracic diameter at T5–6

NCCN Guidelines v3.2024

# Advanced stage CHL

# RATHL – PET-adapted therapy in advanced stage CHL

Stage IIA with bulk and/or ≥ 3 sites
Stage IIB-IV

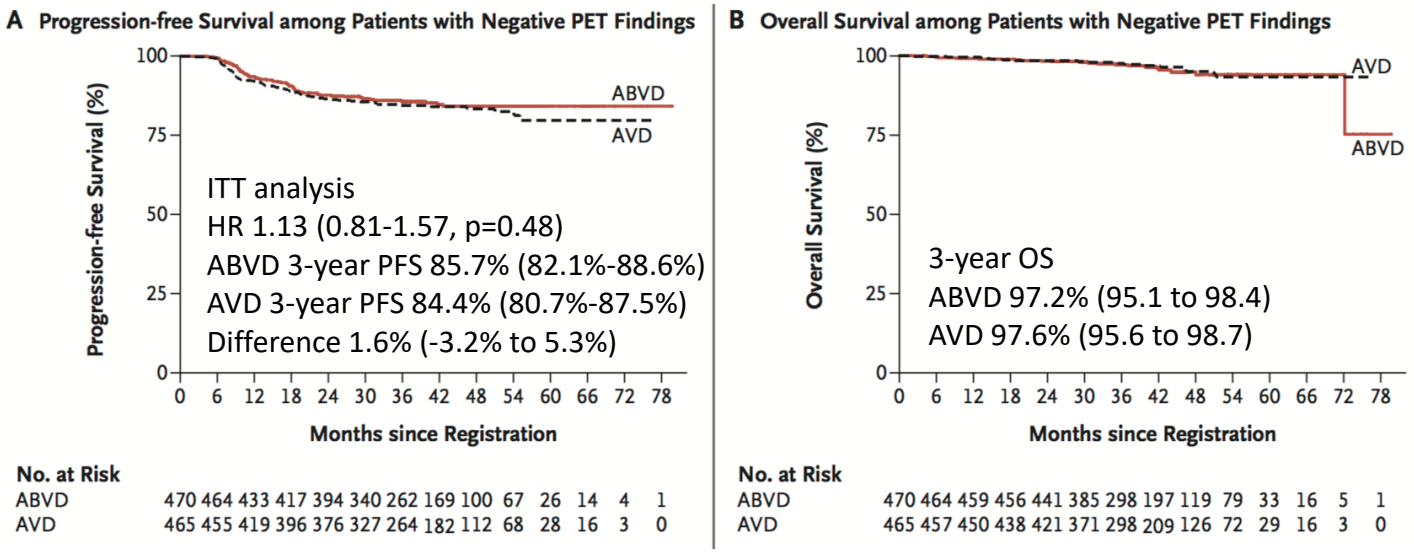



| Characteristic | Number or % |
|---|---|
| Median age | 33 (18-79) |
| Male | 55% |
| Stage II<br>III<br>IV | 41%<br>31%<br>28% |
| B symptoms | 61% |
| Bulky disease | 31% |
| PS 0-1 | 96% |
| IPS 0-1<br>2-3<br>≥ 4 | 34%<br>49%<br>18% |

Johnson P, et al. N Engl J Med 374:2419-29, 2016

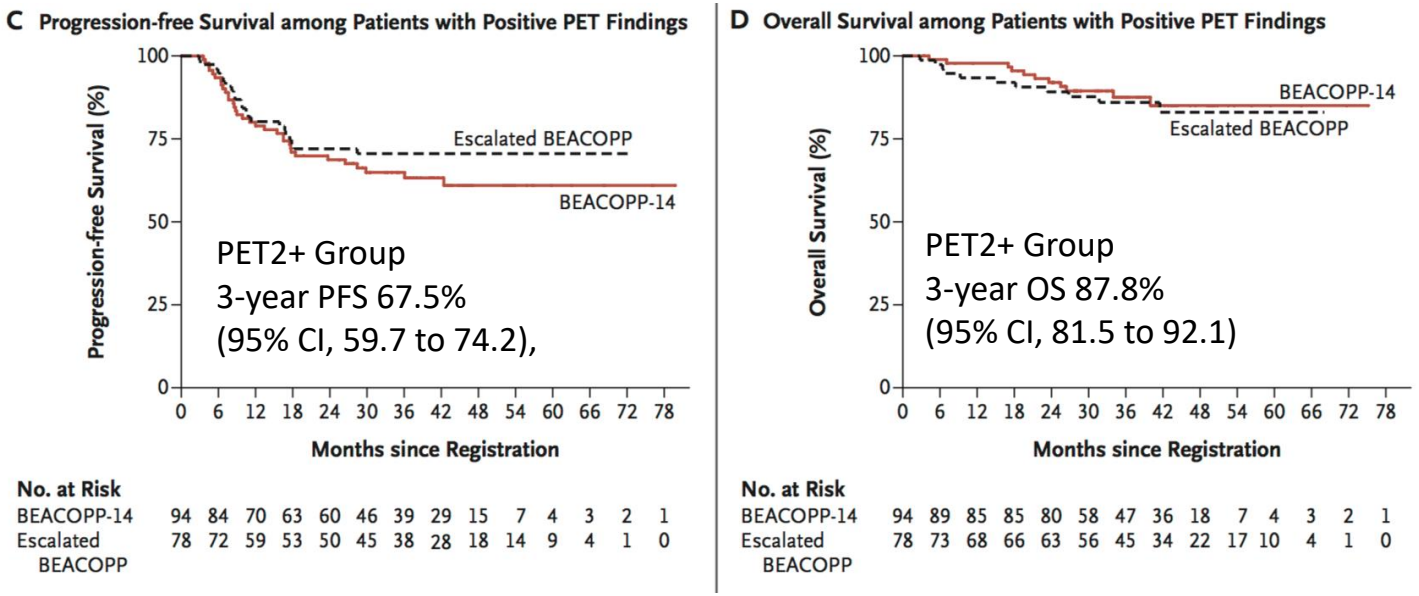
# RATHL – Results in PET2-negative patients

- No statistical difference in 3-year PFS and OS
- Just outside pre-determined non-inferiority margin of 5%




Johnson P, et al. N Engl J Med 374:2419-29, 2016

# RATHL – Results in PET2-positive patients

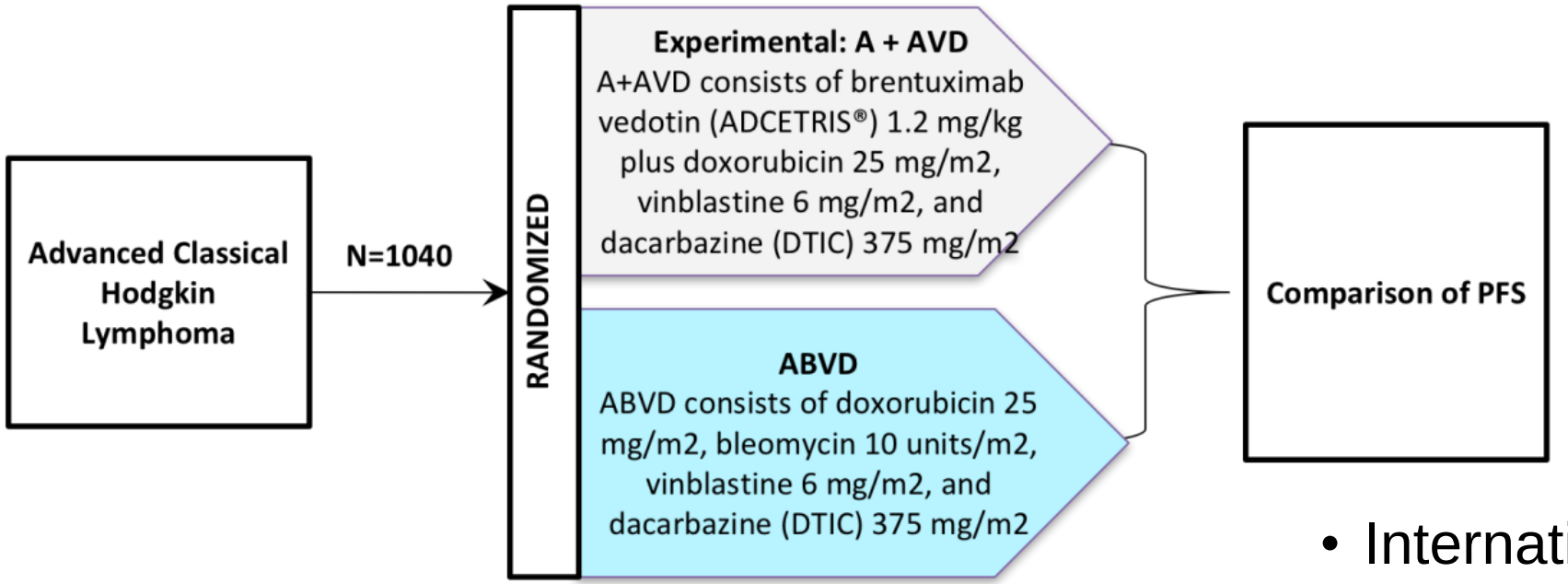



**Improved PFS in PET2 positive patients compared to historical controls**

Johnson P, et al. N Engl J Med 374:2419-29, 2016

# Is BV superior to bleomycin in untreated CHL?

## ECHELON-1 Study




| Characteristic | Number or % |
|---|---|
| Median age<br>Age ≥ 45<br>Age ≥ 60 | 36 (18-83)<br>34%<br>14% |
| Male | 58% |
| Stage III<br>IV | 36%<br>64% |

- International phase III randomized clinical trial
  - Brentuximab + AVD (A-AVD)
  - ABVD

# A-AVD associated with higher rates of toxicity

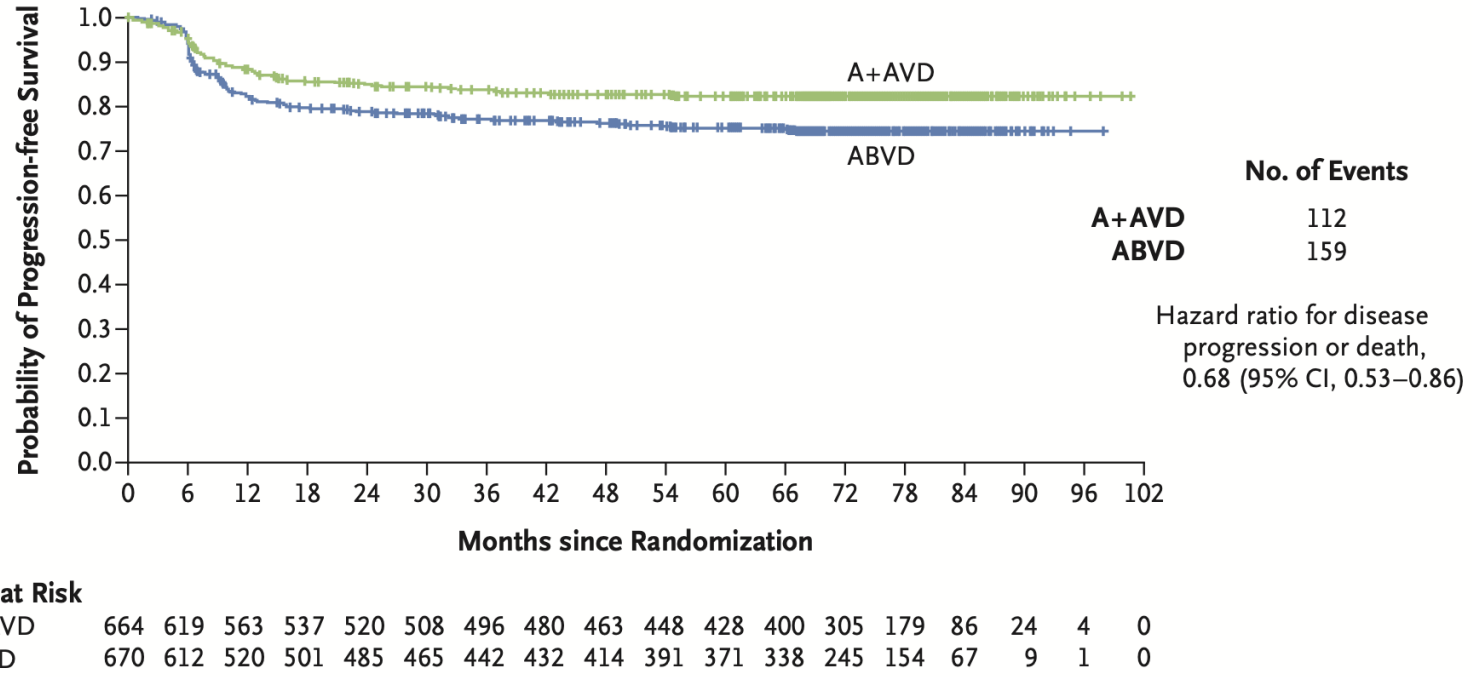
- A-AVD: 7/9 on study deaths due to febrile neutropenia
- ABVD: 11/13 on study deaths due to pulmonary toxicity
- Protocol later amended to give A-AVD patients primary GCSF (n=83)

| Toxicity | A-AVD | ABVD |
|---|---|---|
| Neutropenia | 58% | 45% |
| Febrile neutropenia | 19% | 8% |
| Grade ≥ 3 infection | 18% | 10% |
| Peripheral neuropathy | 67% | 43% |
| Peripheral neuropathy grade ≥ 3 | 11% | 2% |
| Pulmonary toxicity grade ≥ 3 | ≤ 1% | 3% |

Connors et al. NEJM 2018

# A-AVD associated with superior PFS in advanced CHL

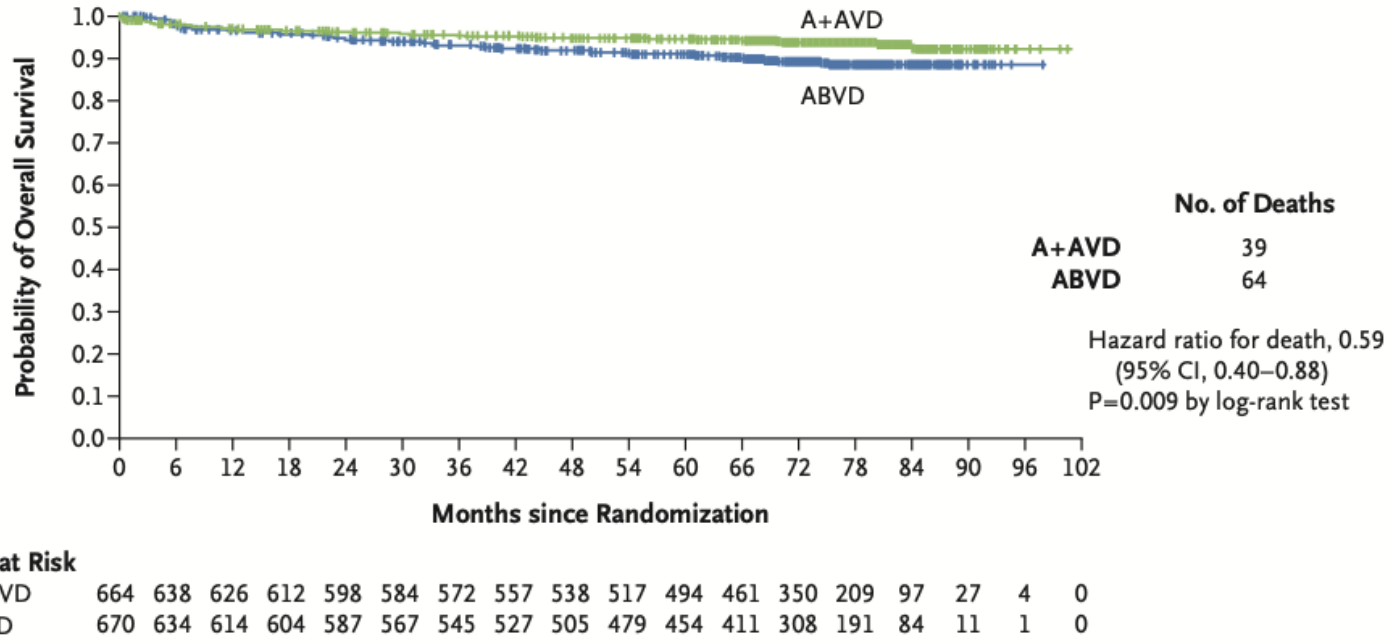
- Median follow up 72.6 months
- Primary endpoint - 6 year mPFS
  - A-AVD: 82.3%
  - ABVD: 74.5%




Connors et al. NEJM 2018
Straus et al. Lancet Haematology 2021
Ansell et al. NEJM 2022

# A-AVD demonstrated superior overall survival

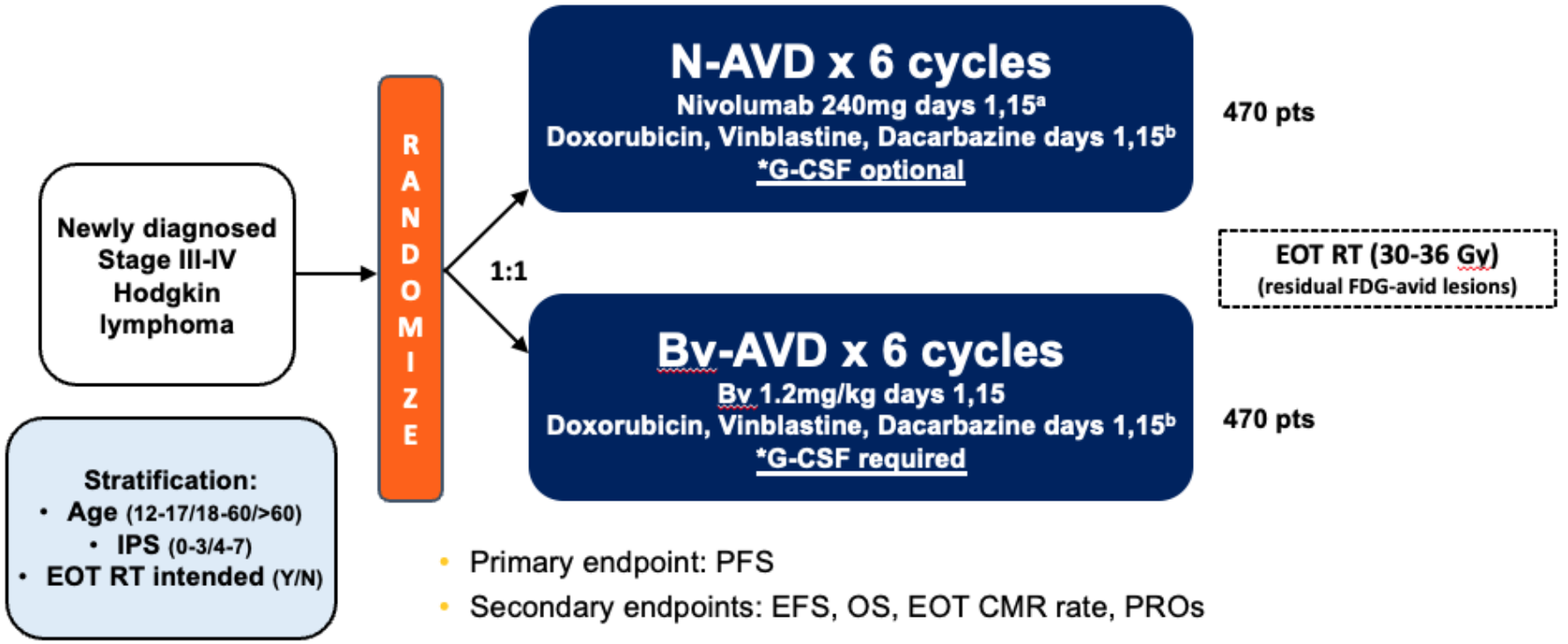
- Most deaths in both arms due to HL or complications of HL therapy
- **Less than half of patients who relapsed after ABVD subsequently received BV**
- < 20% relapsed patients in both arms received a PD1 inhibitor
- Rate of 2nd cancers/deaths in ABVD arm much higher than seen in prior studies
  - Increased older patients?
  - Undiagnosed CD30+ composite lymphomas




Ansell et al NEJM 2022

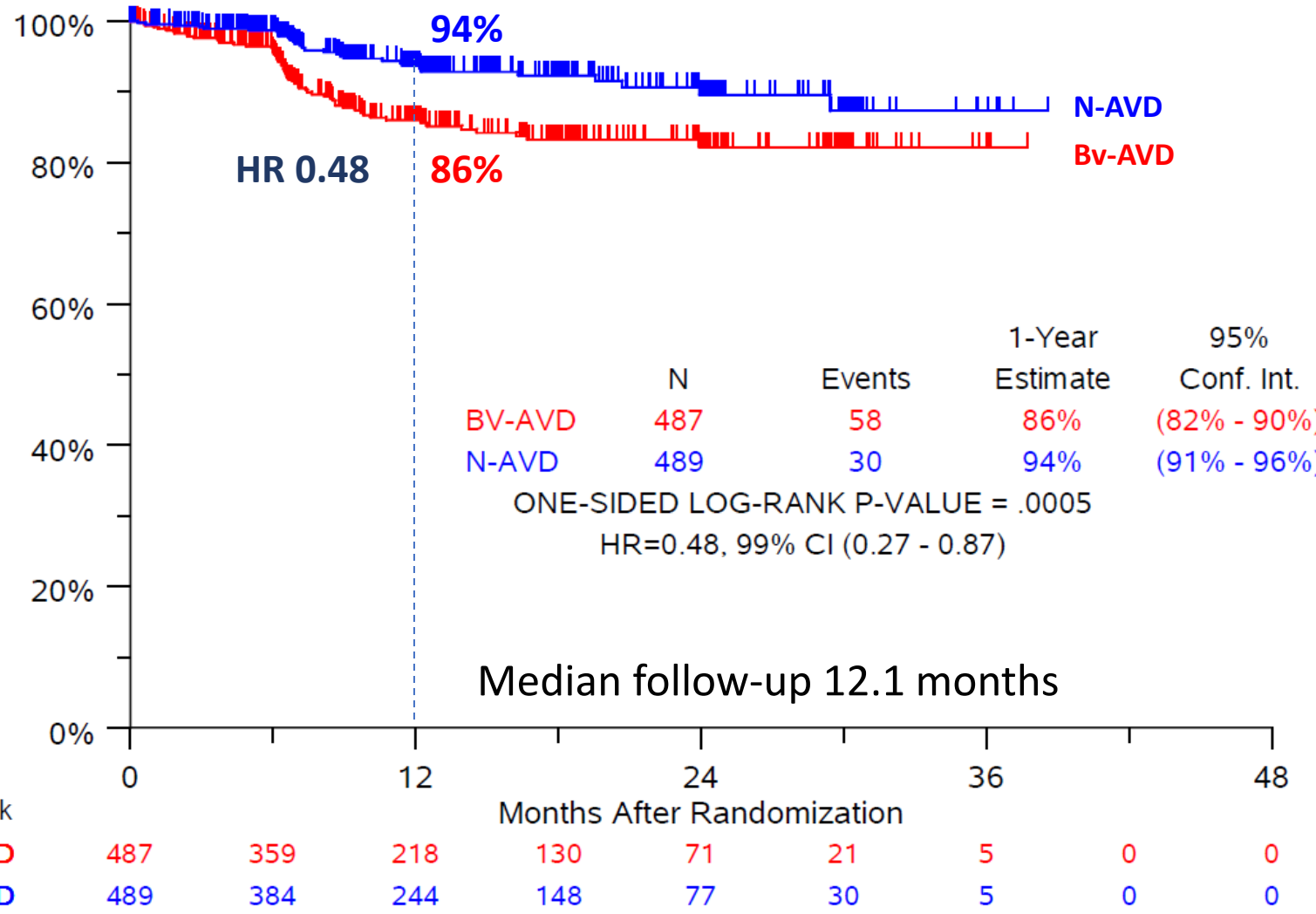
# S1826 Study design

## Is Brentuximab vedotin or nivolumab superior in combination with AVD?




Herrera et al. Hematological Oncology 2023

# S1826 - N-AVD improves PFS compared to Bv-AVD




**1-year PFS**
**N-AVD 94%**
**Bv-AVD 86%**

Adapted from Herrera et al Hematological Oncology 2023

# AEs of interest: Hematologic

| Toxicity | N-AVD n = 483 | | Bv-AVD n = 473 | |
|---|---|---|---|---|
| | Any Gr N (%) | Gr ≥ 3 N (%) | Any Gr N (%) | Gr ≥ 3 N (%) |
| Neutropenia | 268 (55%) | 227 (47%) | 152 (32%) | 118 (25%) |
| Anemia | 185 (38%) | 29 (6%) | 207 (44%) | 42 (9%) |
| Thrombocytopenia | 48 (10%) | 8 (2%) | 82 (17%) | 15 (3%) |
| Received G-CSF | 265 (54%) | | 463 (98%) | |
| Bone pain | 39 (8%) | | 94 (20%) | |

**More neutropenia after N-AVD**

**More growth factor use, bone pain in Bv-AVD arm**

Adapted from Herrera AF et al. Hematological Oncology 2023

# AEs of interest: Infectious

| Toxicity | N-AVD n = 483 | Bv-AVD n = 473 |
|---|---|---|
| Febrile Neutropenia | 26 (5%) | 32 (7%) |
| Sepsis | 9 (2%) | 16 (3%) |
| Infections/Infestations | 22 (5%) | 36 (8%) |

**No increased infectious toxicity in N-AVD arm**

Adapted from Herrera AF et al. Hematological Oncology 2023

# S1826 Treatment discontinuation and deaths

| Disposition | N-AVD (n=489) N (%) | Bv-AVD (n=487) N (%) |
|---|---|---|
| Treatment ongoing | 22 | 30 |
| Completed treatment | 428 | 400 |
| **Discontinued all treatment early** | **39 (8%)** | **57 (12%)** |
| Adverse event (AE) | 22 (4%) | 18 (4%) |
| Refusal unrelated to AE | 10 | 14 |
| **Progression/relapse** | **0 (0%)** | **7 (1.4%)** |
| **Death on treatment** | **2 (0.4%)** | **8 (1.6%)** |
| Other – not protocol specified | 5 | 10 |
| **Discontinued Bv or Nivolumab** | **53 (11%)** | **109 (22%)** |
| **Received radiotherapy** | **2 (0.4%)** | **4 (0.8%)** |

Adapted from Herrera AF et al. Hematological Oncology 2023

# S1826 – Older Patients

**Figure: Progression-Free Survival for Patients Aged ≥60 years Enrolled on S1826.**

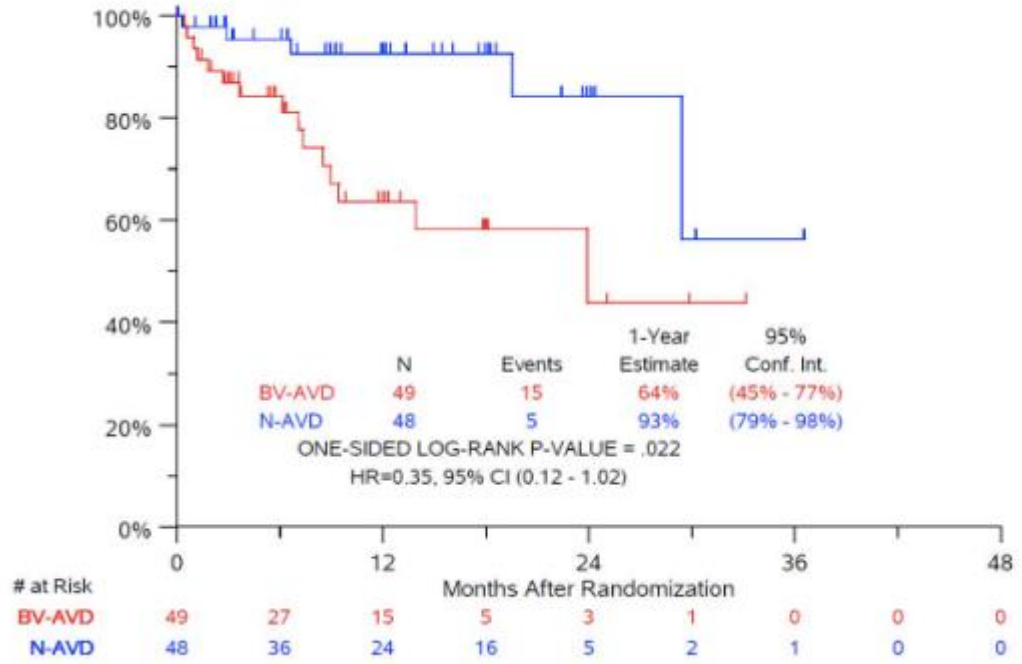



**Table: Key Adverse Events by Treatment Arm (Any Grade and Grade ≥3).**

| | N-AVD (N=48) | Bv-AVD (N=47) | | N-AVD (N=48) | Bv-AVD (N=47) | |
|---|---|---|---|---|---|---|
| **Adverse Event** | **Any Grade** | **Any Grade** | **p-value[3]** | **Grade ≥3** | **Grade ≥3** | **p-value[3]** |
| Febrile neutropenia | 6 (13%) | 9 (19%) | 0.42 | 6 (13%) | 9 (19%) | 0.42 |
| Sepsis | 3 (6%) | 10 (21%) | 0.04 | 3 (6%) | 10 (21%) | 0.04 |
| Infections and infestations | 9 (19%) | 16 (34%) | 0.11 | 3 (6%) | 10 (21%) | 0.04 |
| Peripheral sensory neuropathy[1] | 15 (31%) | 31 (66%) | 0.001 | 1 (2%) | 5 (11%) | 0.11 |
| Peripheral motor neuropathy[2] | 4 (8%) | 7 (15%) | 0.36 | 0 (0%) | 1 (2%) | 0.49 |

[1]Peripheral sensory neuropathy by grade (gr): for N-AVD, gr 1: 21%, gr 2: 8%, and gr 3: 2%; for Bv-AVD, gr 1: 17%, gr 2: 38%, and gr 3: 11%.

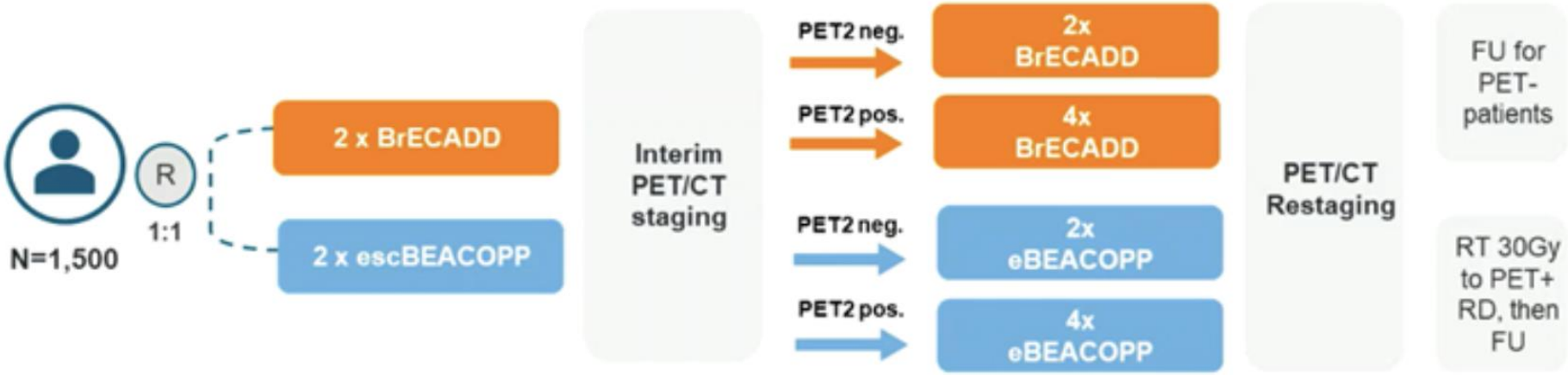
[2]Peripheral motor neuropathy by gr: for N-AVD, gr 1: 8%; for Bv-AVD gr 1: 6%, gr 2: 6%, and gr 3: 2%.

[3]Two-sided Fisher's Exact Test

Adapted from Rutherford et al ASH 2023

# GHSG HD21 study design and primary endpoints

**HD21 is an international randomized, open-label, phase 3 study of BrECADD versus eBEACOPP in adult patients < 60 yo with previously untreated, AS-cHL**




**Co-primary objectives:**

- Demonstrate **superior tolerability** defined by treatment-related morbidity (TRMB) with BrECADD.
- Demonstrate **non-inferior efficacy** of 4-6 x BrECADD compared with 4-6 x BEACOPP determined by PFS (NI margin 6%, HR to be excluded 1.69)

Borchmann et al. EHA 2024, Lancet 2024

# Comparison of escBEACOPP vs. BrECADD

## escBEACOPP

| Drugs (21 day cycle) | Dose | Route | Date |
|---|---|---|---|
| Bleomycin | 10 mg/m2 | IV | D8 |
| Etoposide | 200 mg/m2 | IV | D1-3 |
| Cyclophosphamide | 1250 mg/m2 | IV | D1 |
| Doxorubicin | 35 mg/m2 | IV | D1 |
| Vincristine | 1.4 mg/m2 | IV | D8 |
| Procarbazine | 100 mg/m2 | PO | D1-7 |
| Prednisolone | 40 mg/m2 | PO | D1-14 |
| GCSF | Mandatory | | |

## BrECADD

| Drugs (21 day cycle) | Dose | Route | Date |
|---|---|---|---|
| Brentuximab vedotin | 1.8 mg/kg | IV | D0 |
| Etoposide | 150 mg/m2 | IV | D1-3 |
| Cyclophosphamide | 1250 mg/m2 | IV | D1 |
| Doxorubicin | 40 mg/m2 | IV | D1 |
| Dacarbazine | 250 mg/m2 | IV | D2-3 |
| Dexamethasone | 40 mg/m2 | PO | D1-4 |
| GCSF | Mandatory | | |

Borchmann et al. EHA 2024, Lancet 2024

# HD21: Toxicity

| Causes of Death | eBEACOPP | BrECADD |
|---|---|---|
| Hodgkin Lymphoma | 1 (0.1%) | 3 (0.4%) |
| Not disease-related | 11 (1.5%) | 9 (1.2%) |

| | eBEACOPP | BrECADD |
|---|---|---|
| Any second malignancies | 13 (1.8%) | 19 (2.6%) |

Borchmann et al. EHA 2024, Lancet 2024

# HD21: Toxicity

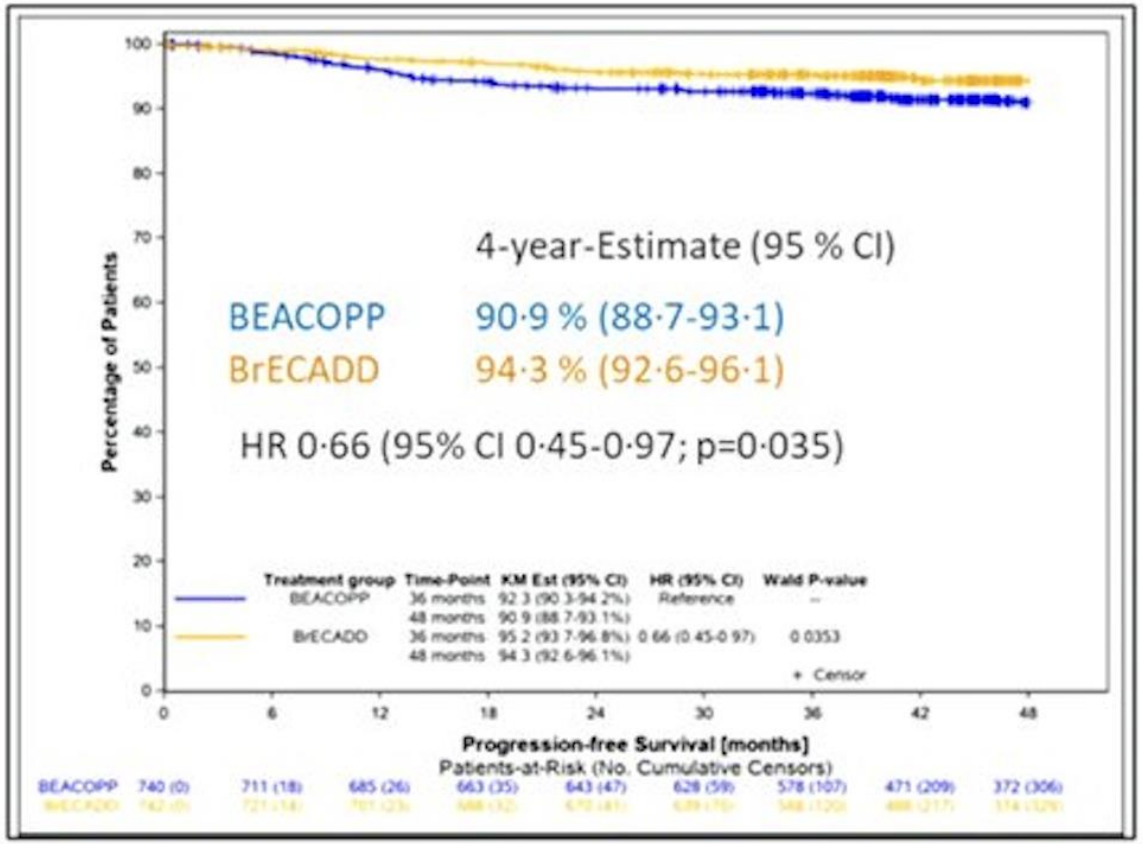
| Grade 3+ Toxicities | eBEACOPP N=740 | BrECADD N=742 |
|---|---|---|
| Anemia | 59% | 30% |
| Thrombocytopenia | 72% | 55% |
| Leukopenia | 94% | 87% |
| Neutropenic fever | 21% | 28% |
| Infection | 19% | 20% |
| Any non-heme | 17% | 19% |

| | eBEACOPP N=740 | BrECADD N=742 |
|---|---|---|
| At least one PRBC transfusion | 52% | 24% |
| At least one platelet transfusion | 34% | 17% |

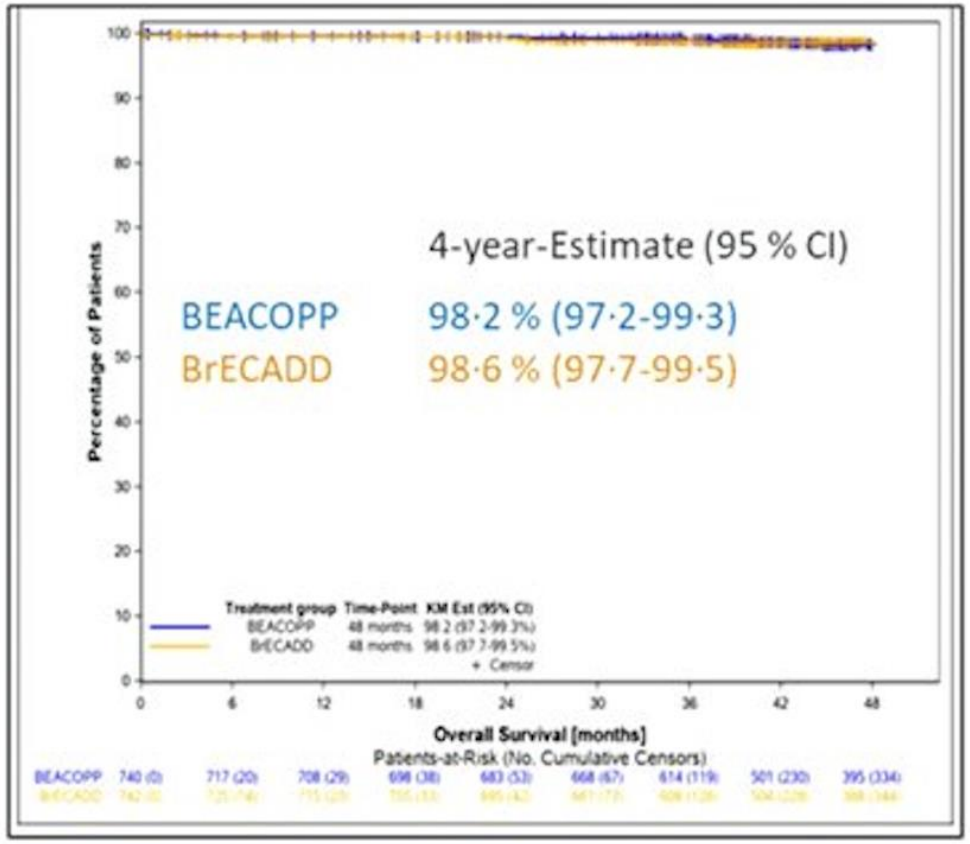
Borchmann et al. EHA 2024, Lancet 2024

# HD21 final analysis: BrECADD is superior to eBEACOPP (mFU 48 m)

## Progression-free survival




## Overall survival




Borchmann et al. EHA 2024, Lancet 2024

# BrECADD vs. ANVD: What to choose?

## BrECADD

- “Shorter time to completion
  - (12 weeks if PET2 neg, 18 weeks if PET2 pos vs. 24 weeks ANVD)
- Less cumulative anthracycline
  - 160 or 240 mg/m2 vs. 300 mg/m2
- Numerically higher PFS
  - 4-year PFS 94% vs. 1 year PFS 94%
- Avoid autoimmune side effects

## ANVD

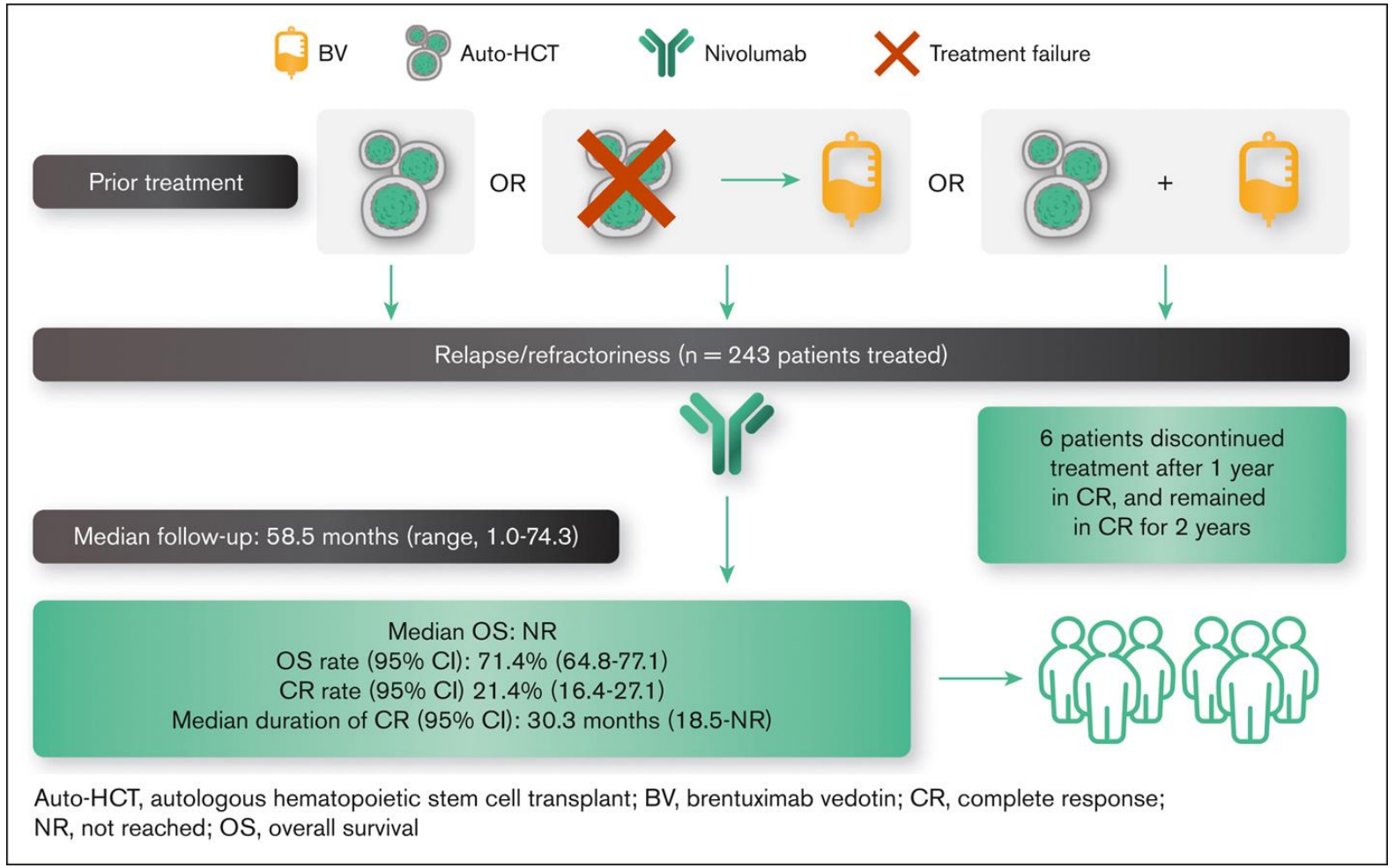
- Less heme toxicity/infection
  - G3 infection 5% vs. 20%
  - Febrile neutropenia 5% vs. 28%
- Fewer treatment visits
  - Only 12 total infusion days
  - Does not account for lab visits
- No GCSF required
- Can be given safely to patients Age 60+
  - Rutherford et al. ASH 2023
- Chemo backbone not associated with infertility or high rates of 2$^{nd}$ cancers
- Less Anemia/Transfusion
  - Grade 3+ 5% vs. 30%

# Summary – Upfront advanced stage

- High-quality evidence on long-term follow-up to use Bv-AVD for advanced stage
  - More toxic however
- Nivolumab + AVD: No FDA approval but in NCCN (category 2B)
  - Can also be administered safely to those age 60+
  - Await published manuscript
- BrECADD: highly effective and shorter duration (less anthracycline) – but very toxic (category 2B in NCCN)
- Short term – High rate of G3+ infections, FN, Heme tox
  - Long term - Infertility? Second Cancers?

# Relapsed/Refractory CHL

# Checkmate-205

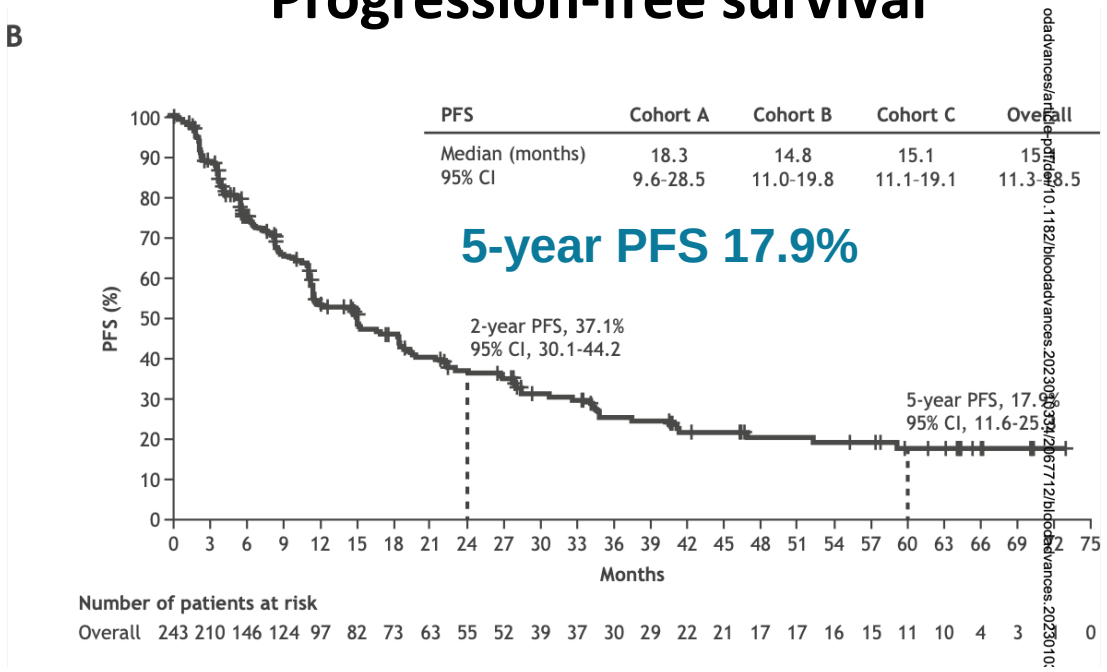



Auto-HCT, autologous hematopoietic stem cell transplant; BV, brentuximab vedotin; CR, complete response; NR, not reached; OS, overall survival

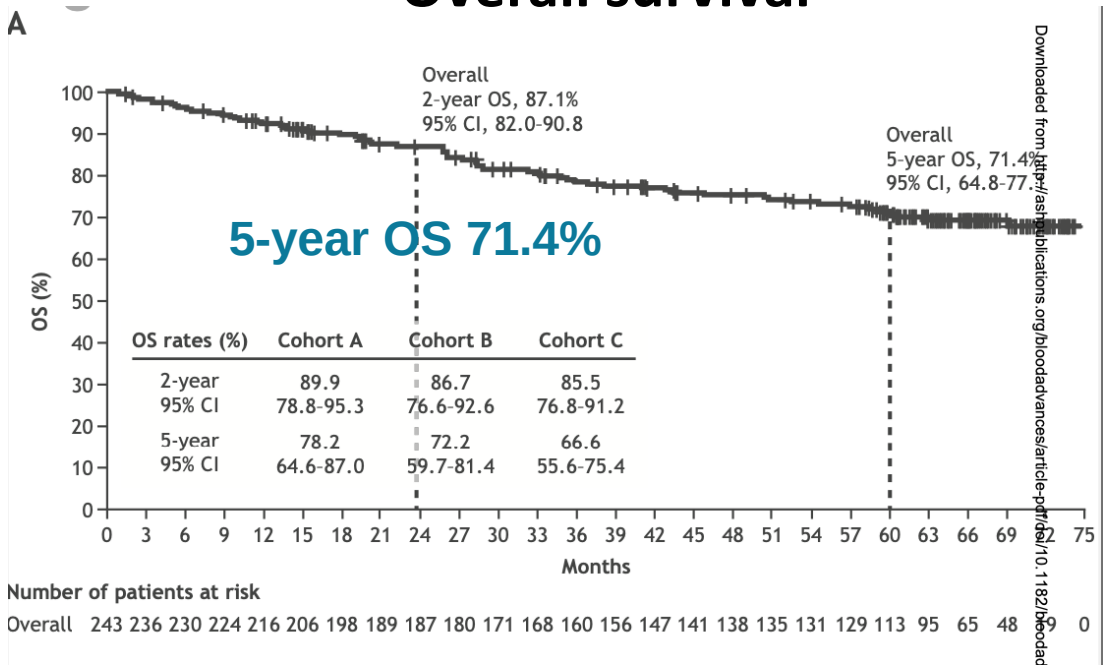
Ansell et al. Blood Advances 2023

# Checkmate-205

## Progression-free survival

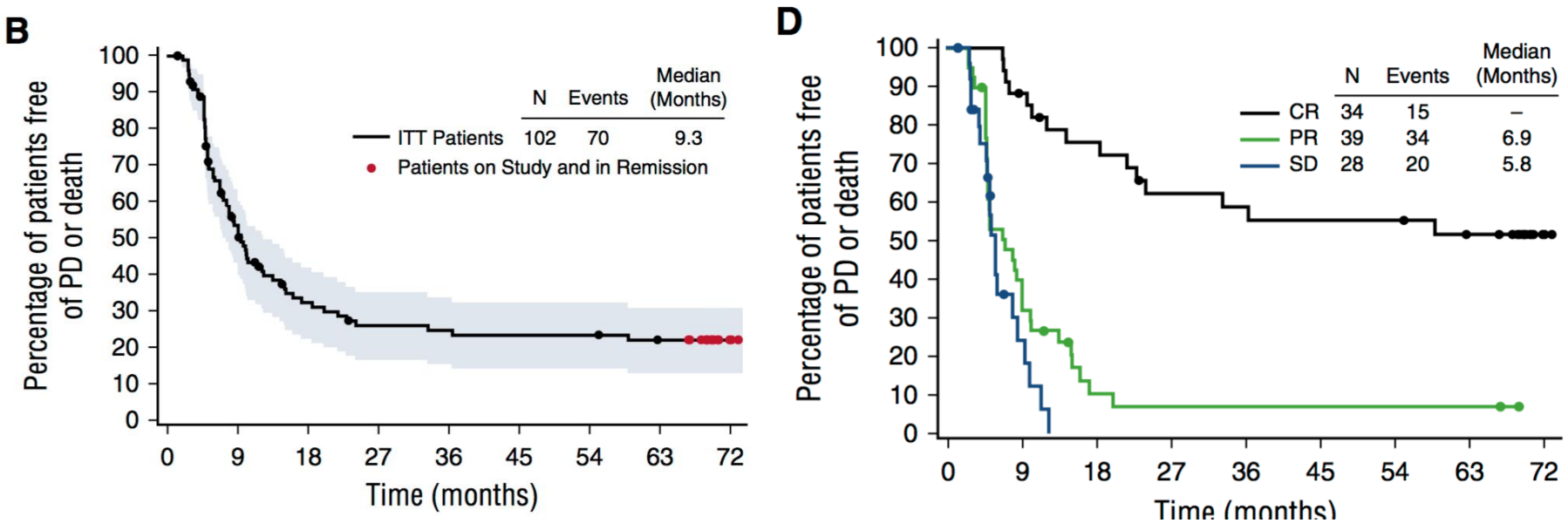



## Overall survival




Ansell et al. Blood Advances 2023

# Brentuximab in patients who relapsed after autologous transplant

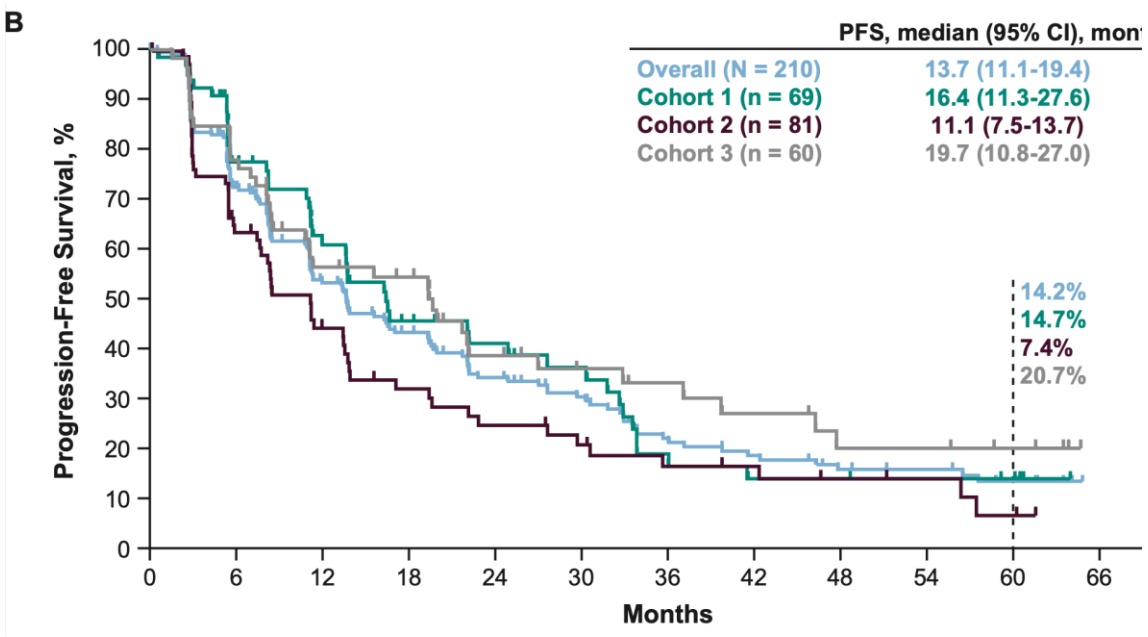


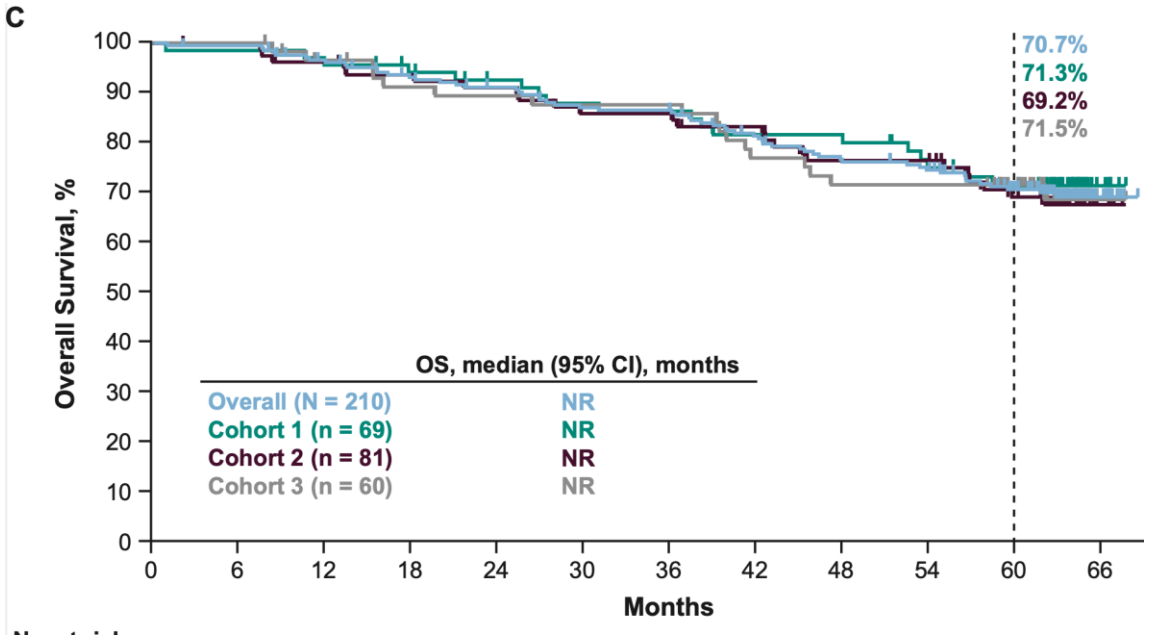

- **5 year end of study analysis**
- **9% (9/100) of patients achieved sustained CR without additional therapy**

Chen R, et al: Blood 128:1562-6, 2016

# Pembrolizumab in relapsed CHL

## Most patients will progress after 1 year, but prolonged overall survival



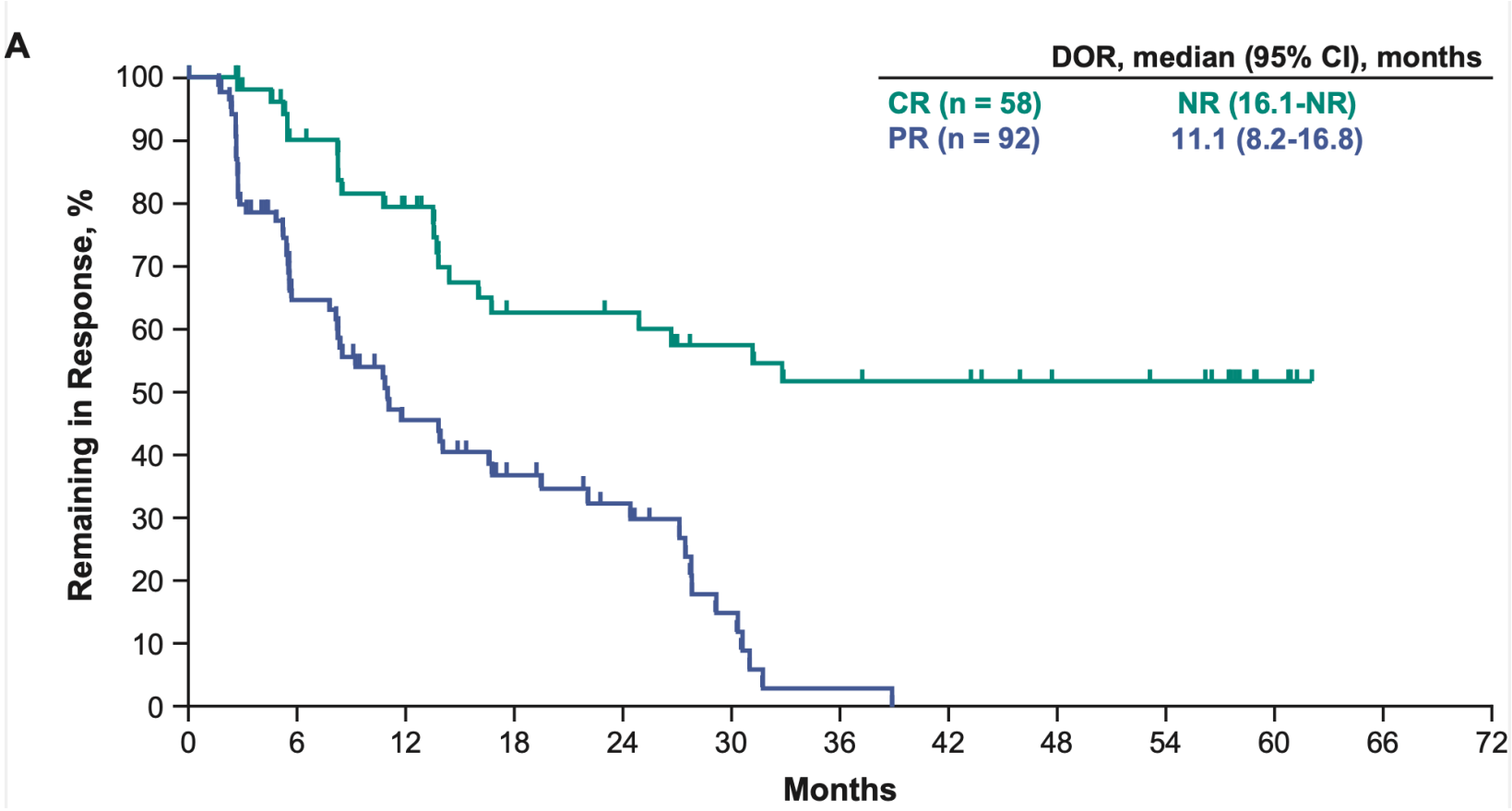




## PD1 inhibitors change the natural history of R/R CHL

Armand P et al. Blood 2023

# Pembrolizumab in relapsed CHL

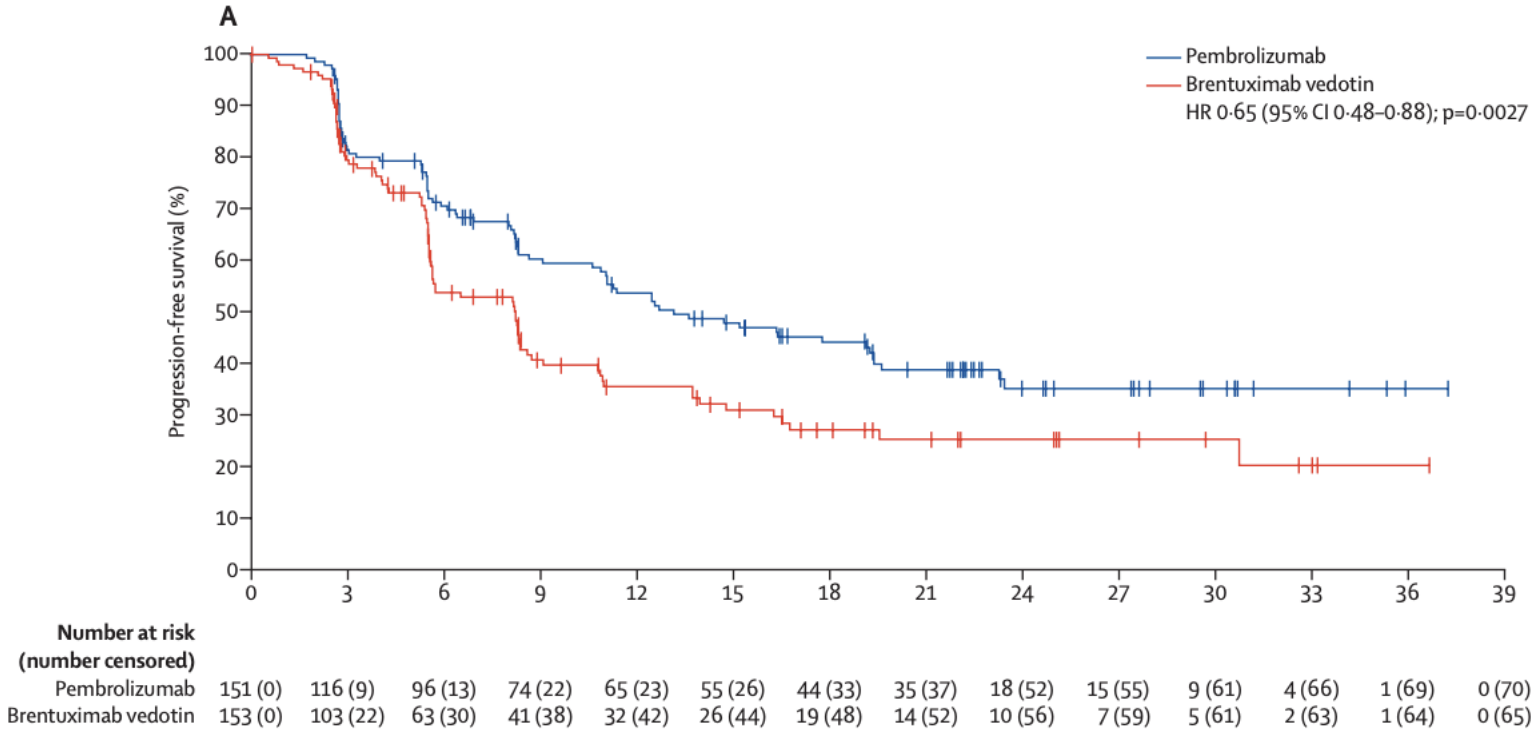
**Some patients in CR have durable responses off therapy with long term follow up!**




Armand P et al. Blood 2023

# Keynote-204 – Pembrolizumab vs. brentuximab in R/R CHL

## Pembrolizumab now with FDA label for 2nd line therapy onwards

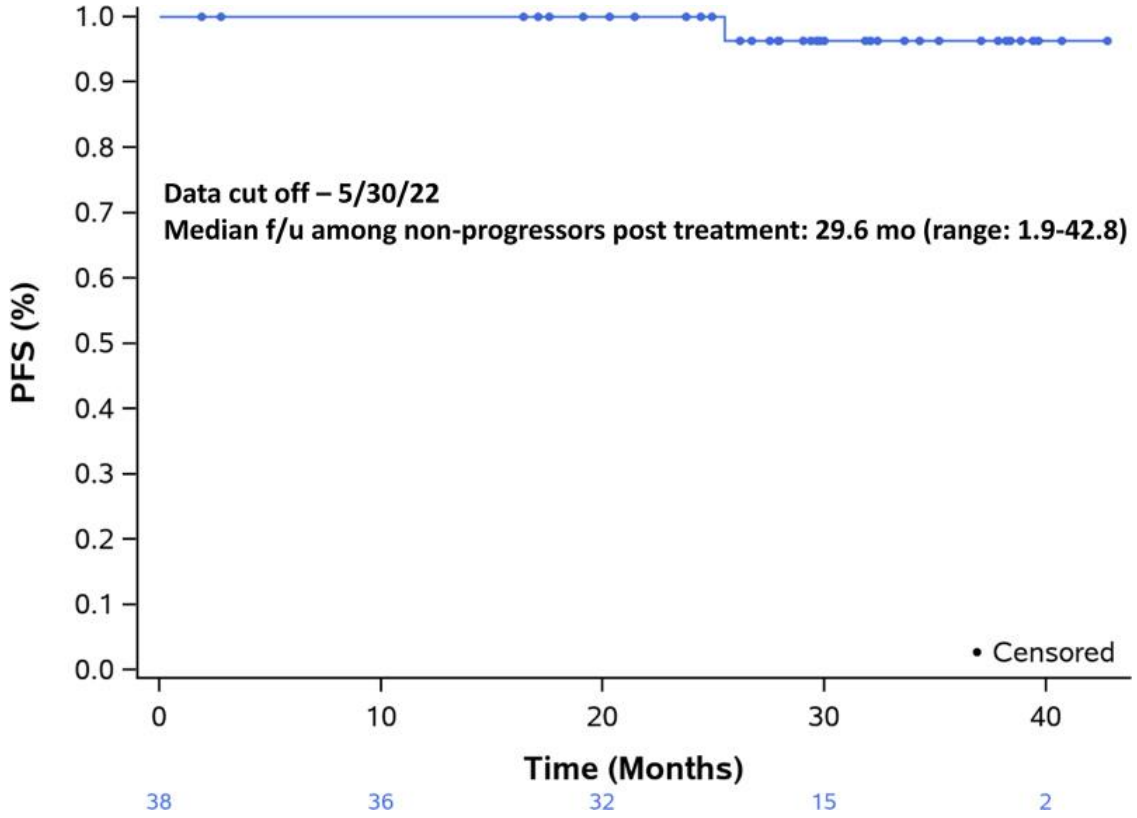



Kuruvilla et al. Lancet Oncology 2021

# Pembro + chemo highly active prior to autologous transplant

## Pembrolizumab, gemcitabine, vinorelbine, doxil

Study ongoing evaluating the role of pembro maintenance instead of auto transplant in responding patients




Moskowitz et al, JCO 2021, ISHL 2022

# Summary – Relapsed/refractory disease

- Historical chemo combinations cured approximately half of patients
  - ICE, DHAP, GVD
- Numerous Bv-based combinations have been reported in phase 2 studies
  - ~ 70-80% with long term remission
  - Bv-ICE, Bv-bendamustine, Bv-nivolumab
- Early data from PD1-based combinations suggest perhaps 90-100% may achieve long term remission after ASCT
  - Pembro-GVD, Pembro-ICE, Nivolumab-ICE
- Select treatment based on novel agents used in frontline treatment

Moskowitz CH et al. Blood 2001, Josting et al. Ann Oncol 2002, Bartlett et al. Ann Oncol 2007, Lynch et al. Lancet Heme 2021, LaCasce et al. Blood 2018, Advani et al. Blood 2021, Mei et al. Blood 2022, Bryan, LJ et al. JAMA Oncology 2023

# Survivorship

# NCCN Surveillance Guidelines

**Relapse detection**

- Clinic visits
  - Every 3 months for first 2 years
  - Every 6 months years 3-5
  - Every 12 months beyond year 5
- Imaging
  - **NO PET SCANS IN ABSENCE OF SUSPECTED RELAPSE/SYMPTOMS**
  - **CT at clinician discretion in first 2 years**
- **Lab studies**
  - CBC, ESR (if elevated at diagnosis), chemistry panel

**Late effect detection**

- Clinic visits
  - Every 3 months for first 2 years
  - Every 6 months years 3-5
  - Every 12 months beyond year 5
- **Imaging**
  - **Breast imaging 7 years post RT or at age 40**
  - Cardiac echo at 10 year intervals
  - Carotid US at 10 year intervals if neck RT
- Lab studies
  - CBC, ESR (if elevated at diagnosis), chemistry panel
  - **TSH if neck RT yearly** , Lipid panel every other year (can be done with PCP)

# NLPHL

# Nodular lymphocyte predominant Hodgkin lymphoma

- VERY rare subtype (about 400 new cases in US each year)
- Typically acts like an indolent lymphoma, so wide variety of treatment options (observation, chemotherapy, radiation) are accepted depending on clinical scenario

- So what can they test you on?

# Nodular lymphocyte predominant Hodgkin lymphoma

| | Classical HL | Nodular lymphocyte predominant HL |
|---|---|---|
| Tumor cells | Diagnostic RS cells. Mononuclear or lacunar cells | "L&H" or "**popcorn" cells** |
| Background | Lymphocytes, histiocytes, eosinophils, plasma cells | Lymphocytes, histiocytes |
| Fibrosis | Common | **Rare** |
| CD15 | + (15% can be negative) | - |
| CD30 | + | **-** |
| CD20 | - | **+** |
| PAX5 | Dim + | + |
| EBV | +/- | - |

# Other take home points - NLPHL

- Consider chemotherapy (rituximab containing regimen, R-CHOP, R-CVP) for advanced stage, symptomatic patients
- Observation reasonable in asymptomatic advanced stage patients
- Limited stage patients have high rates of disease control with radiotherapy
- Late relapse common, often > 10 years after initial treatment
- Patients can **transform to T-cell/histiocyte rich DLBCL**
  - Spleen involvement highly predictive of eventual transformation
  - Re-biopsy if suspicion of transformation
  - **DOES NOT TRANSFORM TO CLASSICAL HODGKIN LYMPHOMA!**

# Other special issues

- No bone marrow biopsy needed at diagnosis if PET used for staging and no marrow involvement
- NO dose delays with ABVD due to neutropenia – treat on time with standard doses. Inferior outcomes with decreased dose intensity.
- Repeat biopsy with refractory disease or relapse prior to starting subsequent therapy.

Fred Hutch
Cancer Center

# Thank you

- Clinical team, research staff, mentors/colleagues
- PATIENTS!
- We can’t research how to improve therapies without clinical trial participation!

UW Medicine