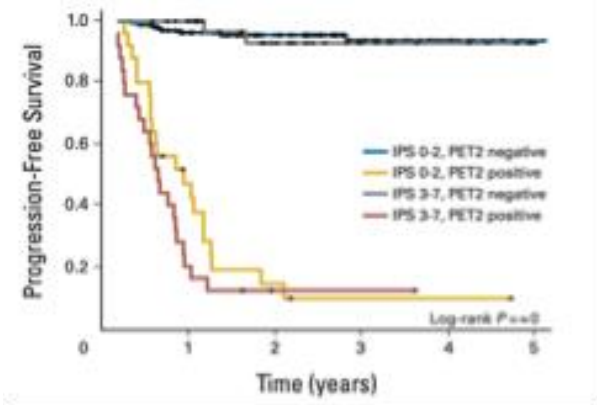
# Advanced stage cHL: Nivo-AVD/S1826 and beyond

*Sonali M. Smith, MD FASCO*
*Elwood V. Jensen Professor of Medicine*
*Chief, Section of Hematology/Oncology*
*Co-Leader, Cancer Service Line*
*The University of Chicago*
*smsmith@bsd.uchicago.edu*
*@SoniSmithMD*

AT THE FOREFRONT
UChicagoMedicine
Comprehensive Cancer Center

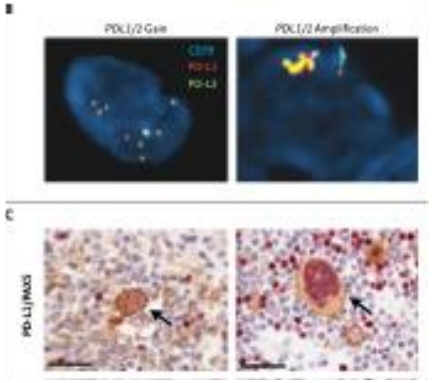
# Key paradigms in management of advanced stage cHL

## Interim PET is predictive of outcome



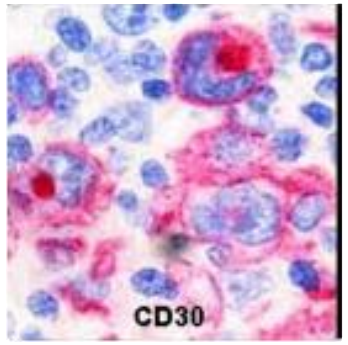

Gallamini JCO 2007

## Two "new" targets



Ansell N Engl J Med. 2015 Jan 22;372(4):311-9.

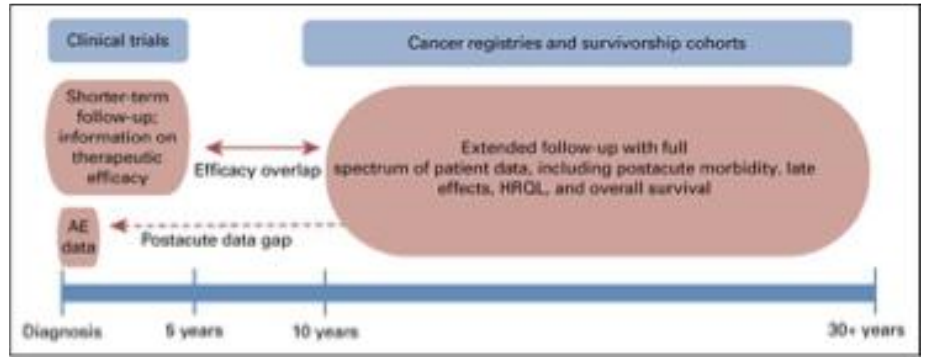
**Near-universal 9p24 amplification leads to PDL-1 and PDL-2 expression**




http://pleiad.umdnj.edu/~dweiss/hd_types/hdlimmuno_img.html

**Strong CD30 expression**

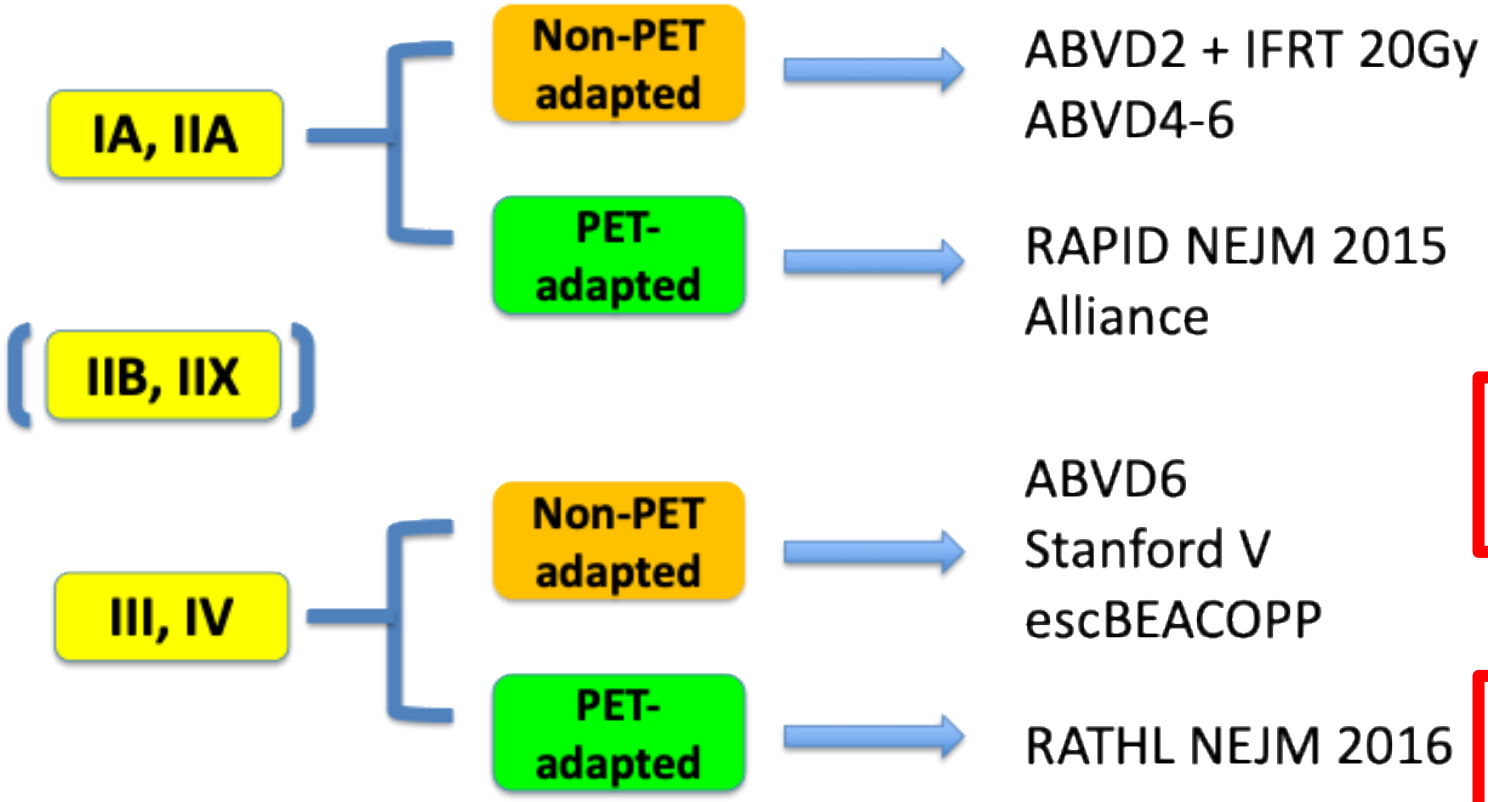
## Need for long-term follow up




Evens and Parsons, *JCO* 38:4131-33 2020

AT THE FOREFRONT
UChicagoMedicine
Comprehensive Cancer Center

# Snapshot of frontline standard treatment approach: PET-adapted and non-PET-adapted




**NEW!**

**ECHELON-1: BV-AVD > ABVD**

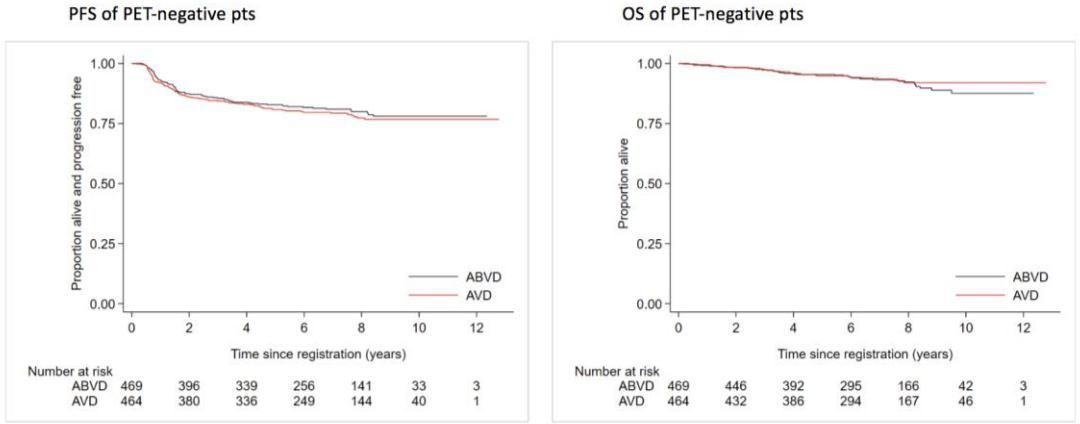
**S1826: NIVO-AVD > BV-AVD**

**BrECADD > escBEACOPP (with less toxicity)**

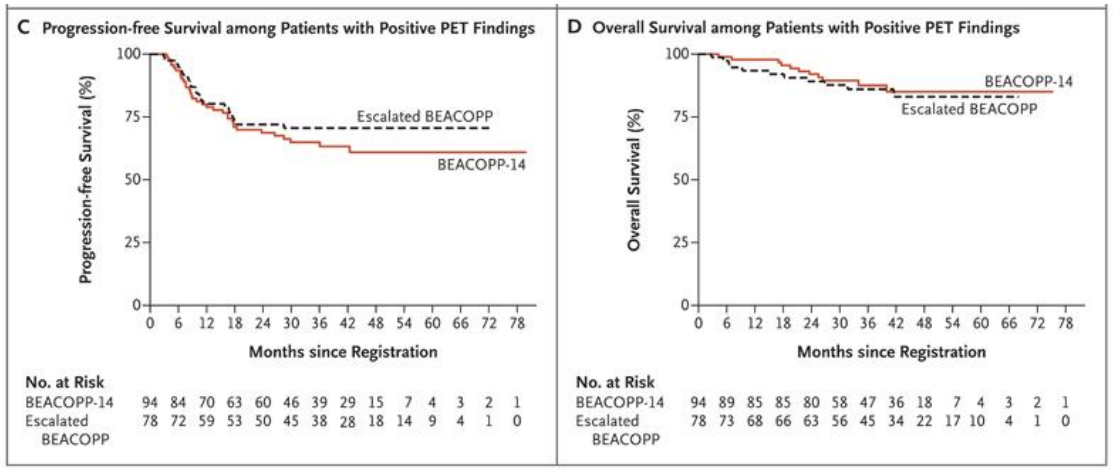
AT THE FOREFRONT
UChicagoMedicine
Comprehensive Cancer Center

# Treatment Guided by PET in *Advanced* Hodgkin Lymphoma: RATHL Trial

## PET-2 negative




## PET-2 positive



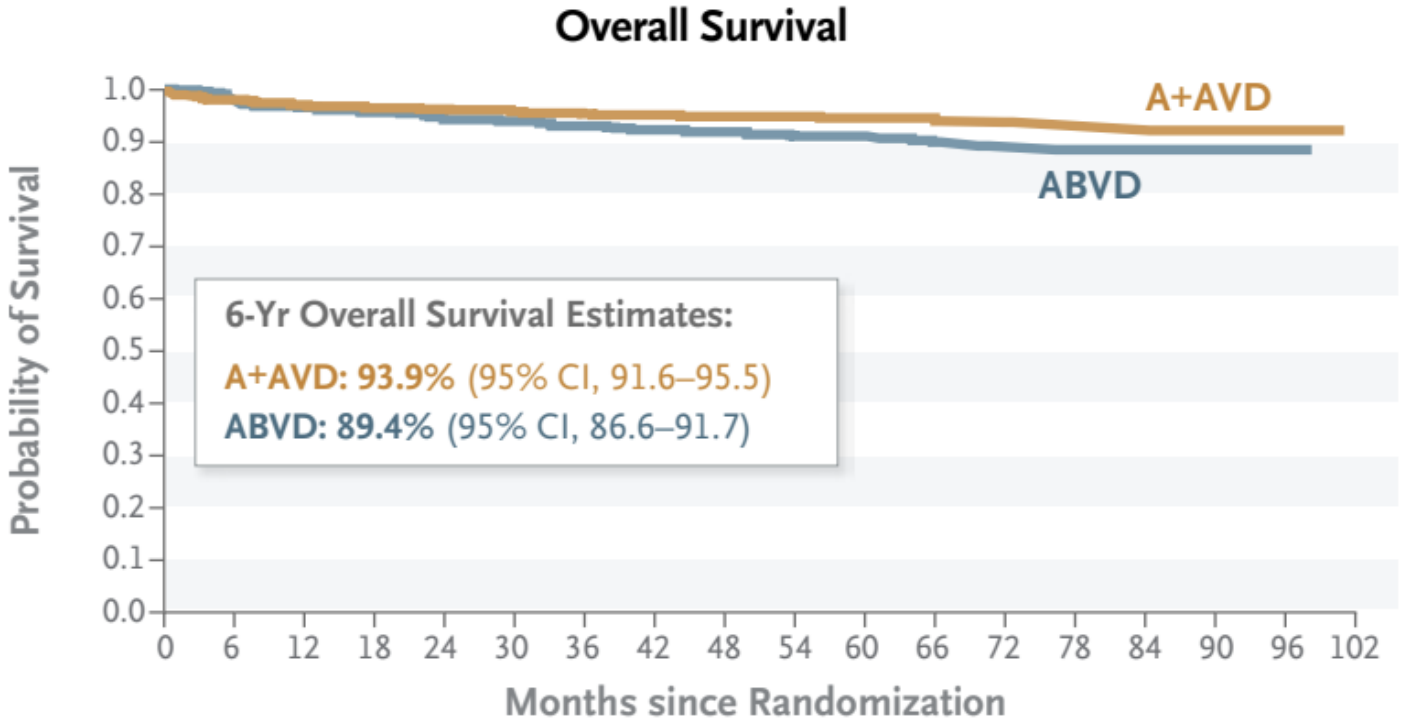

If you start with ABVD, you can drop the bleomycin if PET-2 negative

Not clear that escalating therapy in PET-2 patients improves outcome

Slide courtesy of Steve Ansell


Johnson et al. N Engl J Med. 2016 Jun 23;374(25):2419-29.
Luminari et al. ASH 2022; #315

# ECHELON-1: BV-AVD vs ABVD (non-PET-adapted) long-term follow up



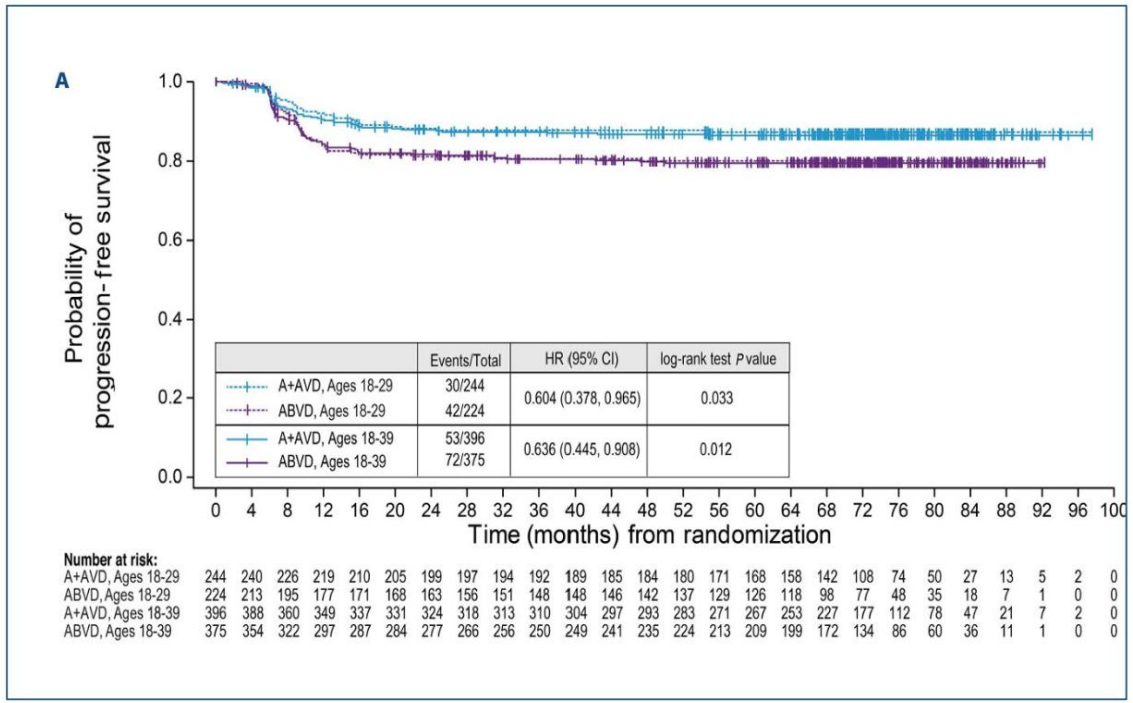

**4.5% improvement in overall survival at 6y**

AT THE FOREFRONT
UChicagoMedicine
Comprehensive Cancer Center

Ansell ASCO 2024; Ansell SM et al. DOI: 10.1056/NEJMoa2206125

# ECHELON-1: BV-AVD vs ABVD (non-PET-adapted) outcome by age groups and PET2

**PFS in AYA (age 18-39 years)**




7-year OS rates by subgroup (ITT).

| Group, % (95% CI) | A+AVD OS Rate, % (95% CI) n=664 | ABVD OS Rate, % (95% CI) n=670 | HR (95% CI) p-value |
|---|---|---|---|
| All pts | 93.5 (91.1–95.2) n=664 | 88.8 (85.8–91.1) n=670 | 0.62 (0.42–0.90) 0.01 |
| PET2 negative | 95.0 (92.8–96.6) | 90.2 (87.2–92.5) | 0.57 (0.37–0.87) |
| PET2 positive | 90.7 (72.3–97.1) n=47 | 74.0 (59.9–83.8) n=58 | 0.34 (0.11–1.03) 0.05 |
| Aged <40 years | 98.2 (96.2–99.1) n=396 | 95.0 (91.9–96.9) n=375 | 0.39 (0.16–0.95) 0.032 |
| Aged <60 years | 96.4 (94.4–97.7) | 92.9 (90.3–94.9) | 0.49 (0.29–0.83) |
| Aged ≥60 years | 72.6 (60.6–81.5) | 66.7 (55.9–75.5) | 1.01 (0.59–1.71) 0.98 |
| Stage III | 92.1 (87.6–95.1) n=237 | 90.3 (85.3–93.7) n=246 | 1.01 (0.54–1.87) 0.98 |
| Stage IV | 94.2 (91.3–96.2) n=425 | 88.1 (84.3–91.0) n=421 | 0.49 (0.30–0.79) 0.003 |

**Improvement across all subgroups except older patients**

**Prognostic significance of PET2 positivity diminishes**

AT THE FOREFRONT
UChicagoMedicine
Comprehensive Cancer Center

Crosswell Haematologica 2024; Ansell ASCO 2024; Ansell SM et al. DOI: 10.1056/NEJMoa2206125

2023 ASCO® ANNUAL MEETING

# SWOG S1826, a Randomized Study of Nivolumab(N)-AVD Versus Brentuximab Vedotin(BV)-AVD in Advanced Stage (AS) Classic Hodgkin Lymphoma (cHL)

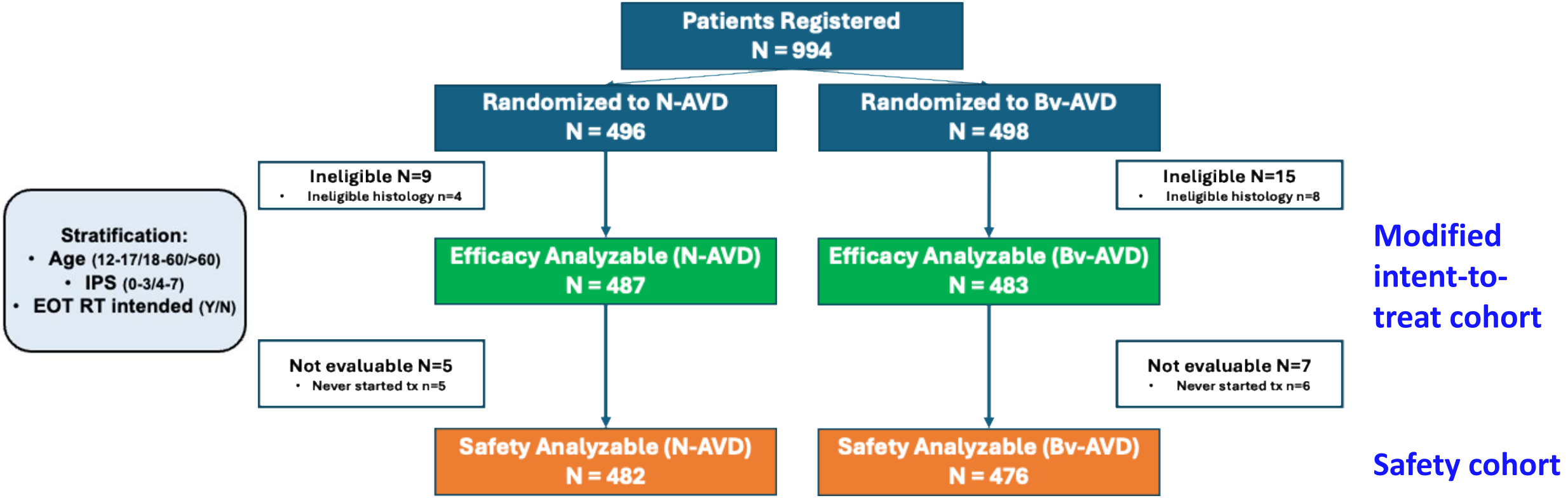
***Alex F. Herrera, MD***[1], *Michael L. LeBlanc, PhD*[2], *Sharon M. Castellino, MD, MSc*[3], *Hongli Li, MS*[2], *Sarah C. Rutherford, MD*[4], *Andrew M Evens, DO, MSc*[5], *Kelly Davison, MD*[6], *Angela Punnett, MD*[7], *David C. Hodgson, MD, MPH, FRCPC*[8], *Susan K Parsons, MD, MRP*[9], *Sairah Ahmed, MD*[10], *Carla Casulo, MD*[11], *Nancy L. Bartlett, MD*[12], *Joo Y. Song, MD*[13], *Richard F. Little*[14], *Brad S. Kahl, MD*[12], *John P. Leonard, MD*[4], *Sonali M. Smith, MD*[15], *Kara M. Kelly, MD*[16], *and Jonathan W. Friedberg, MD, MSSc*[11]

*[1]City of Hope, Duarte, CA, [2]SWOG Statistical Center, Fred Hutchinson Cancer Research Center, Seattle, WA, [3]Emory University, Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Atlanta, GA, [4]Weill Cornell Medicine-New York Presbyterian Hospital, New York, NY, [5]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, [6]McGill University, Montreal, QC, Canada, [7]Hospital for Sick Children, Toronto, ON, Canada, [8]Department of Radiation Oncology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada, [9]Tufts Medical Center, Tufts University School of Medicine, Boston, MA, [10] University of Texas M.D. Anderson Cancer Center, Houston, TX, [11]Division of Hematology/Oncology, University of Rochester, Rochester, NY [11]Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada, [12]Washington University School of Medicine in St. Louis, St. Louis, MO, [13]Department of Pathology, City of Hope, CA [14]Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD [15] Department of Oncology, University of Chicago, Chicago, IL, [16]Department of Pediatric Oncology, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

# S1826 CONSORT Diagram

Data cut-off: Dec 15, 2022

Dates of enrollment:
July 19, 2019 – Oct 5, 2022




**Modified intent-to-treat cohort**

**Safety cohort**

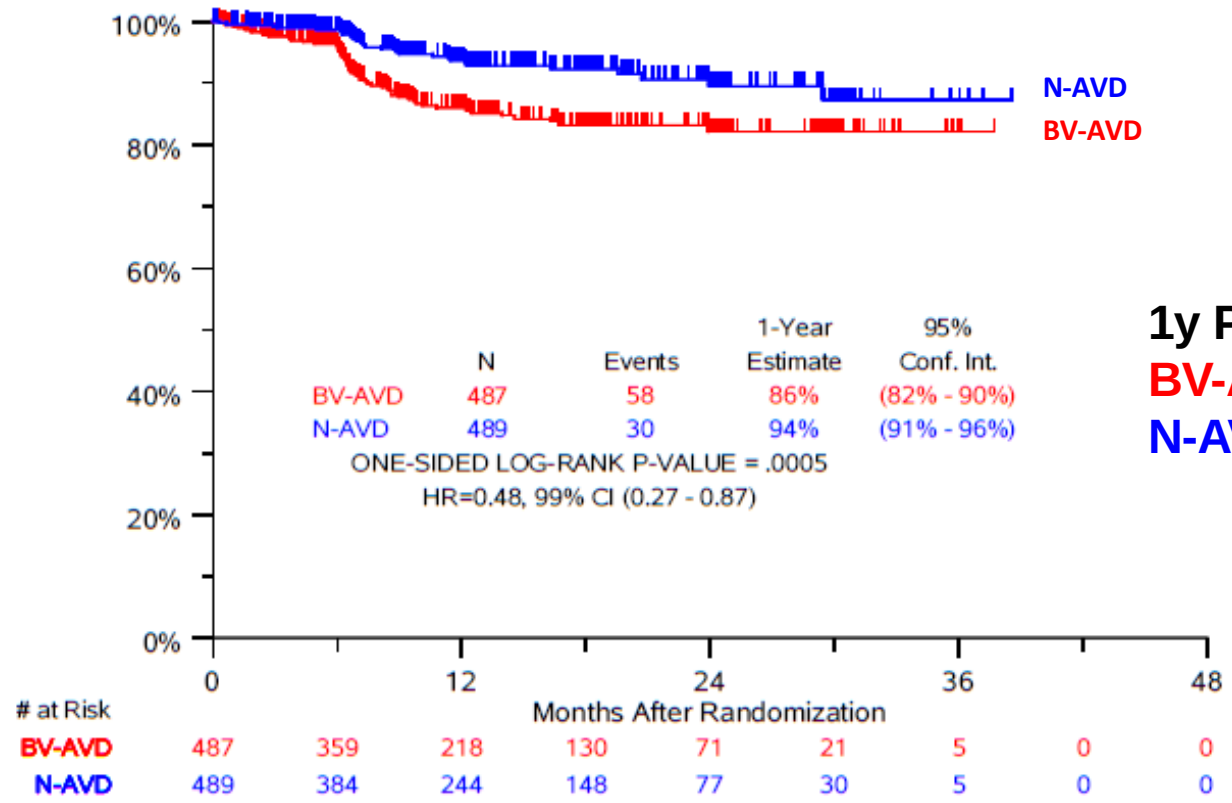
- **Primary endpoint: PFS**
- Secondary endpoints: EFS, OS, EOT CMR rate, PROs

AT THE FOREFRONT
UChicagoMedicine
Comprehensive Cancer Center

Presented by: Alex F. Herrera, MD

**Herrera, AF et al. N Eng J Med. 2024 Oct 17;391(15):1379-138.**

# ASCO Plenary 2023: N-AVD improves PFS compared to BV-AVD



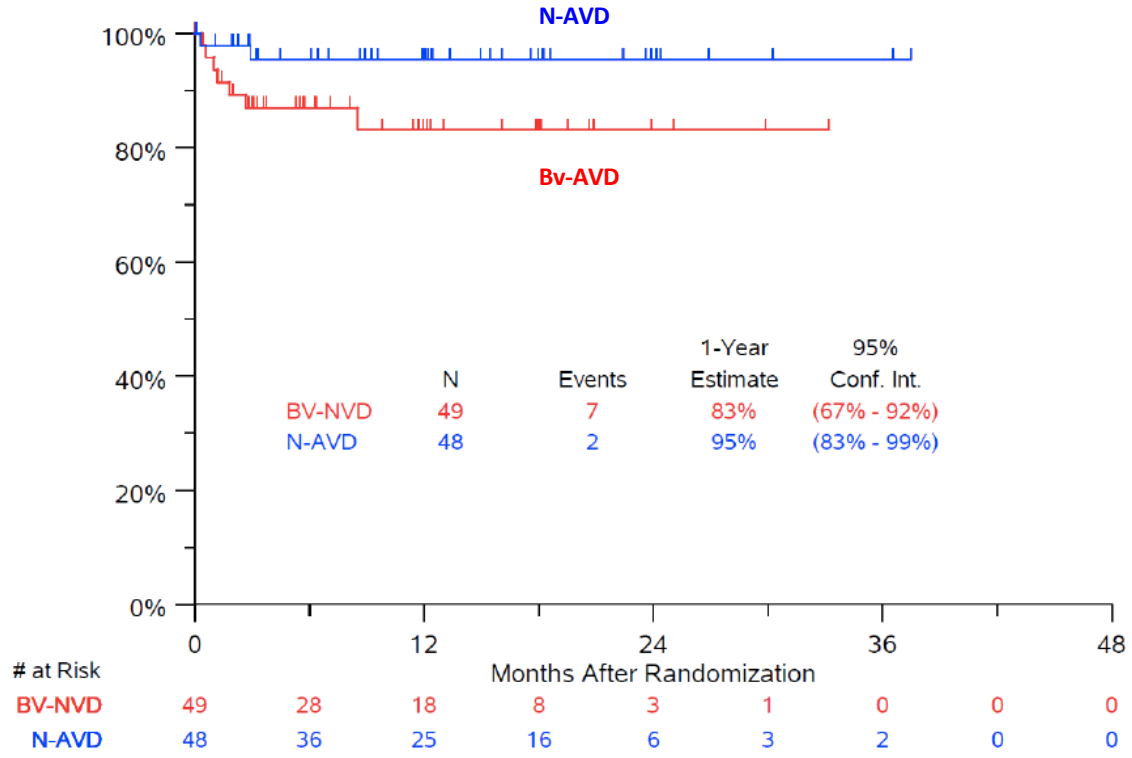

**1y PFS**
**BV-AVD 86%**
**N-AVD 94%**

**Median follow-up 12.1 months**

AT THE FOREFRONT
UChicagoMedicine
Comprehensive Cancer Center

SWOG CANCER RESEARCH NETWORK
NCI National Clinical Trials Network
NCI Community Oncology Research Program

# Fewer deaths occurred on N-AVD vs Bv-AVD




**1-year OS**
**N-AVD 95%**
**Bv-AVD 83%**

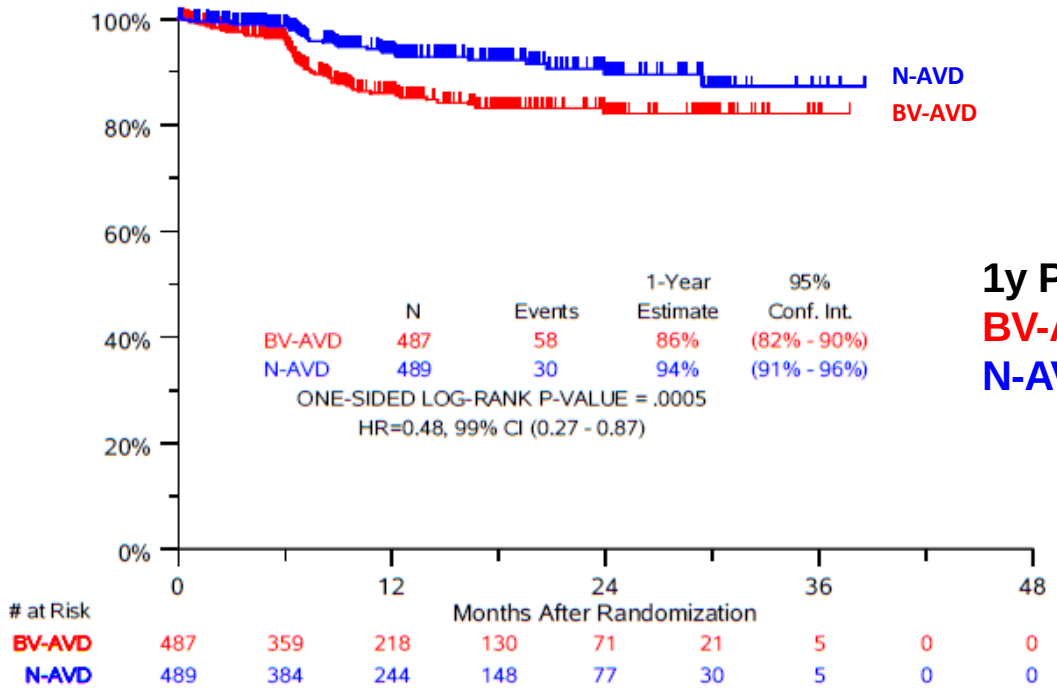
Median follow-up
12.1 months

p-value = 0.091
HR=0.35,
95% CI (0.07-1.75)

***Non-relapse mortality***
***N-AVD 4% vs Bv-AVD 14%***

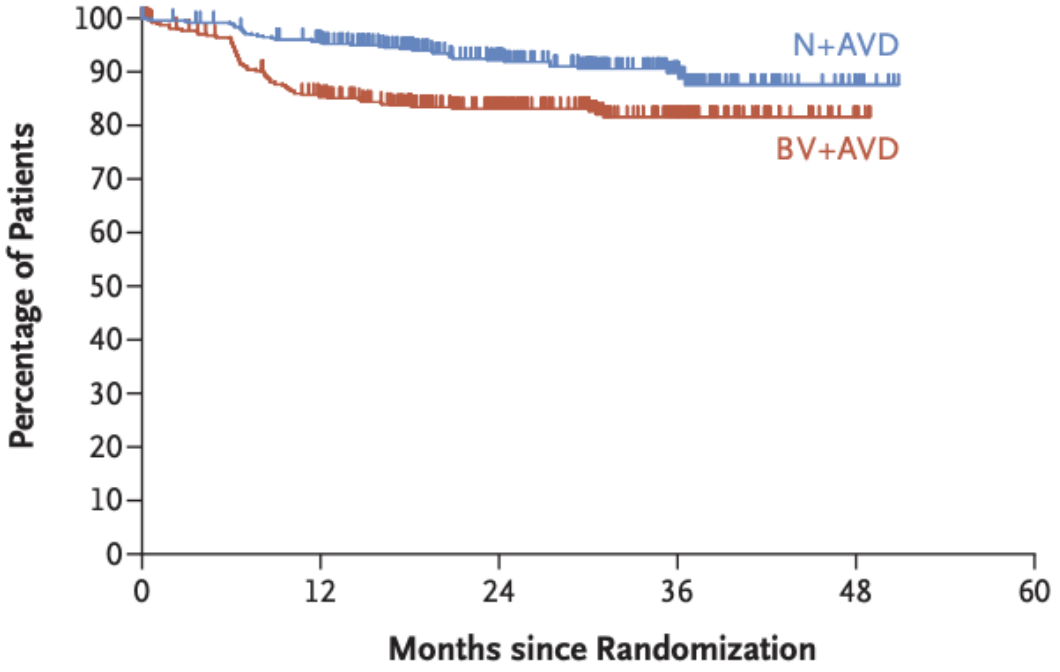
Rutherford ASH 2023, abstr 181

# SWOG S1826: N-AVD improves PFS compared to BV-AVD




**1y PFS**
**BV-AVD 86%**
**N-AVD 94%**

**Median follow-up 12.1 months**




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| N+AVD | 487 | 450 | 281 | 101 | 9 | 0 |
| BV+AVD | 483 | 392 | 244 | 97 | 7 | 0 |

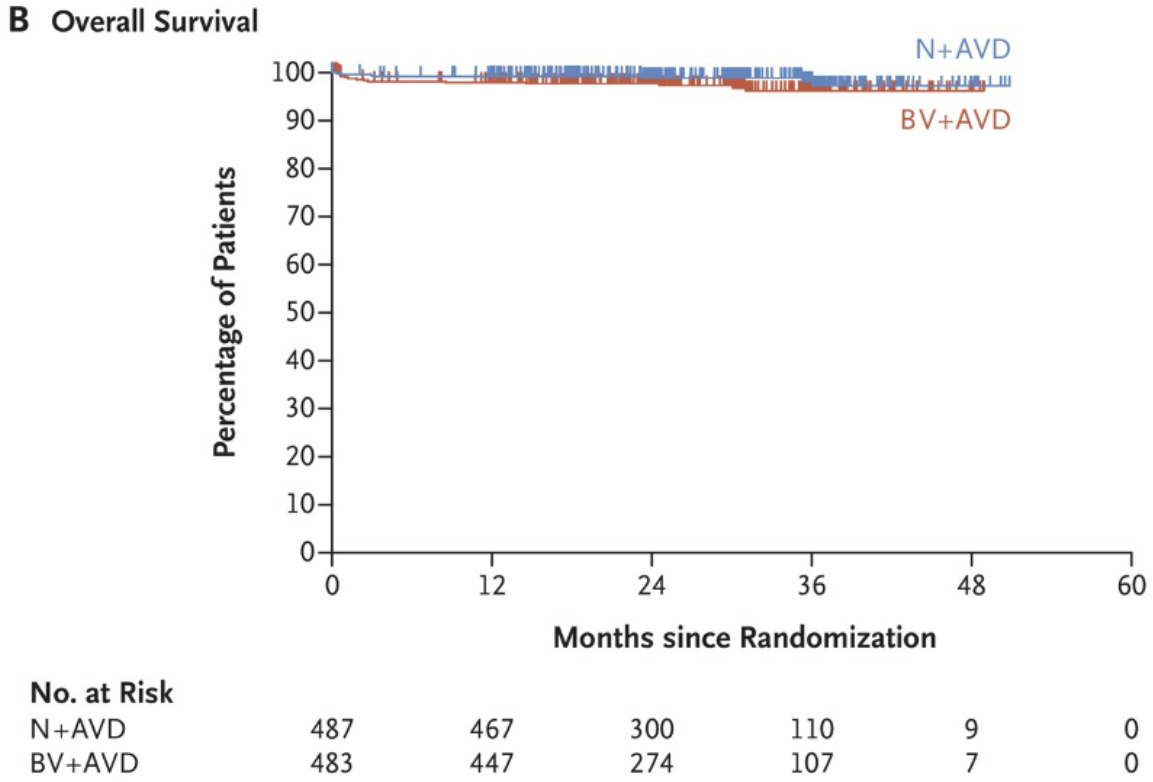
**Median follow-up 2.1y**

AT THE FOREFRONT UChicagoMedicine Comprehensive Cancer Center

SWOG CANCER RESEARCH NETWORK
NCI National Clinical Trials Network a National Cancer Institute program
NCI Community Oncology Research Program

Herrera ASCO Plenary 2023; Herrera N Engl J Med 2024;391:1379-1389

# S1826 – Overall Survival Comparison




| | Death *no. of patients* | 2-Year Estimate for Overall Survival (95% CI) *percent* |
|---|---|---|
| **N+AVD** | 7 | 99 (97–100) |
| **BV+AVD** | 14 | 98 (96–99) |

Hazard ratio, 0.39 (95% CI, 0.15–1.03)

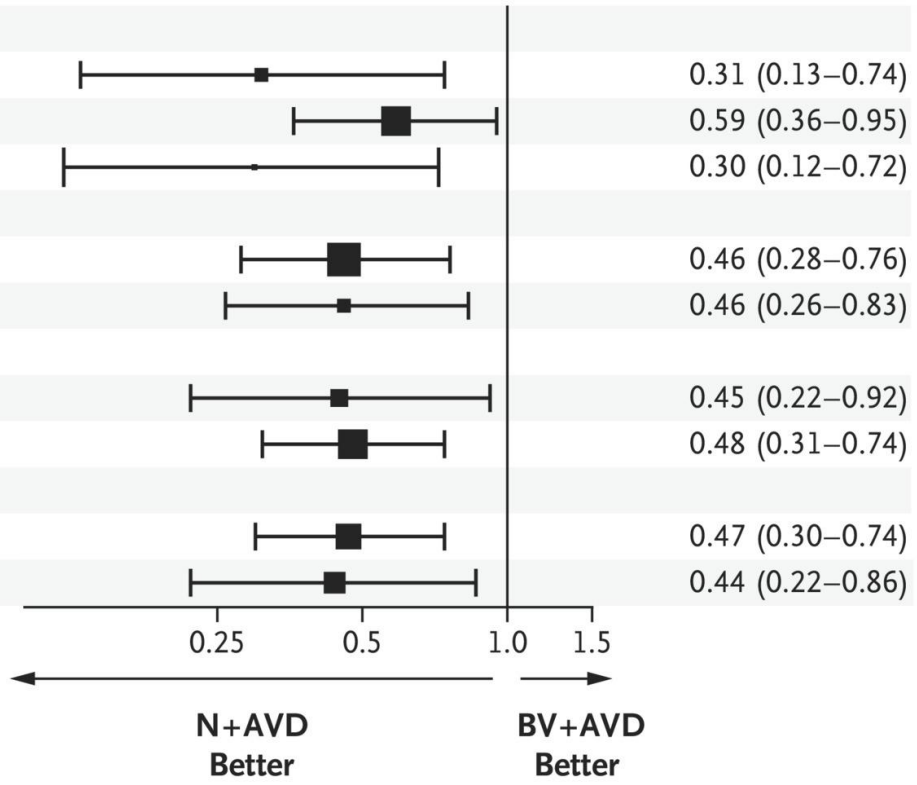
Herrera et al NEJM 2024



Slide courtesy of Ryan Lynch

# S1826 – Sub-group analysis

| Subgroup | N+AVD | BV+AVD |
|---|---|---|
| | *no. of events/total no. (%)* | |
| Age | | |
| 12–17 yr | 7/118 (5.9) | 21/118 (17.8) |
| 18–60 yr | 27/321 (8.4) | 43/318 (13.5) |
| >60 yr | 7/48 (14.6) | 17/47 (36.2) |
| IPS risk group | | |
| 0–3 | 24/332 (7.2) | 48/328 (14.6) |
| 4–7 | 17/155 (11.0) | 33/155 (21.3) |
| Stage | | |
| III | 12/185 (6.5) | 22/168 (13.1) |
| IV | 29/302 (9.6) | 59/315 (18.7) |
| Symptoms | | |
| B | 29/288 (10.1) | 54/273 (19.8) |
| A | 12/199 (6.0) | 27/210 (12.9) |




**PFS benefit seen across all ages, IPS score, and stage**

Herrera et al NEJM 2024



Slide courtesy of Ryan Lynch

# S1826 – Treatment analysis

| | Total | | Nivolumab + AVD | | Brentuximab Vedotin + AVD | |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % |
| **Eligible Patients** | 970 | 100.0% | 487 | 100.0% | 483 | 100.0% |
| **Completed treatment** | 875 | 90.2% | 450 | 92.4% | 425 | 88.0% |
| **Discontinued all treatment early** | 95 | 9.8% | 37 | 7.6% | 58 | 12.0% |
| Adverse event | 40 | 4.1% | 20 | 4.1% | 20 | 4.1% |
| Refusal unrelated to AE | 22 | 2.3% | 9 | 1.8% | 13 | 2.7% |
| Progression/relapse | 9 | 0.9% | 0 | 0 | 9 | 1.9% |
| Death | 11 | 1.1% | 3 | 0.6% | 8 | 1.7% |
| Other – not protocol specified | 13 | 1.3% | 5 | 1.0% | 8 | 1.7% |
| **Any discontinuation of Bv or Nivolumab*** | 153 | 15.8% | 46 | 9.4% | 107 | 22.2% |
| **Discontinued Bv or Nivo, but continued other agents**** | 78 | 8.0% | 19 | 3.9% | 59 | 12.2% |
| **Received any G-CSF** | 741 | 76.4% | 274 | 56.3% | 467 | 96.7% |

**Numerically higher rates of on-treatment study drug discontinuation and death in Bv arm**

Herrera et al NEJM 2024



Slide courtesy of Ryan Lynch

# S1826 – Grade 3+ Adverse Events

| Adverse Event Type | N-AVD n = 482 Grade ≥ 3 No (%) | BV-AVD n = 476 Grade ≥ 3 No (%) |
|---|---|---|
| Neutrophil count decreased | 232 (48%) | 126 (26%) |
| White blood cell decreased | 73 (15%) | 61 (13%) |
| Anemia | 29 (6%) | 43 (9%) |
| Lymphocyte count decreased | 30 (6%) | 41 (9%) |
| Febrile neutropenia | 28 (6%) | 33 (7%) |
| ALT increased | 22 (5%) | 23 (5%) |
| Peripheral sensory neuropathy | 5 (1%) | 39 (8%) |
| AST increased | 12 (2%) | 14 (3%) |
| Platelet count decreased | 9 (2%) | 16 (3%) |
| Sepsis | 8 (2%) | 16 (3%) |

- Higher rate of G3+ neutropenia in ANVD arm did not translate to increased febrile neutropenia
  - GCSF not mandatory with ANVD

Herrera et al NEJM 2024



Slide courtesy of Ryan Lynch

# S1826 Older Pts Baseline Characteristics

| Baseline characteristics | N-AVD N = 48 N (%) | Bv-AVD N = 49 N (%) |
|---|---|---|
| Age, median (range) | 66.4 (60-84 y) | 67.1(60-87 y) |
| Age 60-69 | 31 (65%) | 36 (74%) |
| Age 70-79 | 14 (29%) | 12 (24%) |
| Age ≥80 | 3 (6%) | 1 (2%) |
| Female Sex | 19 (40%) | 18 (37%) |
| Race | | |
| White | 43 (90%) | 40 (82%) |
| Black | 1 (2%) | 2 (4%) |
| Asian | 1 (2%) | 1 (2%) |
| Other/Unknown | 3 (6%) | 6 (12%) |
| Hispanic | 5 (10%) | 5 (10%) |

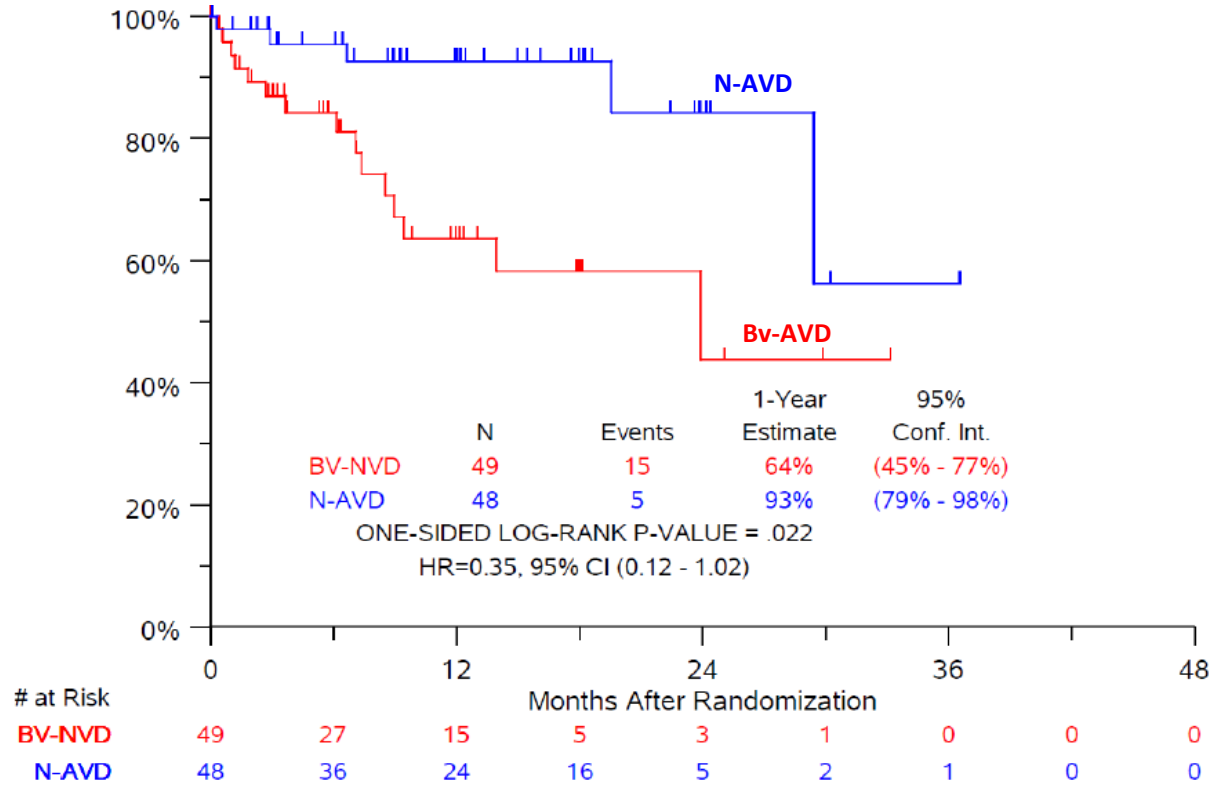
| Baseline characteristics | N-AVD N = 48 N (%) | Bv-AVD N = 49 N (%) |
|---|---|---|
| Stage | | |
| III | 16 (33%) | 22 (45%) |
| IV | 32 (67%) | 27 (55%) |
| B symptoms present | 25 (52%) | 27 (55%) |
| IPS Score | | |
| 0-3 | 24 (50%) | 27 (55%) |
| 4-7 | 24 (50%) | 22 (45%) |
| Bulky disease > 10cm | 7 (15%) | 5 (10%) |
| HIV+ | 0 (0%) | 1 (2%) |
| Elevated bilirubin | 4 (8%) | 4 (8%) |

*slight imbalance

AT THE FOREFRONT
UChicagoMedicine
Comprehensive Cancer Center

Rutherford ASH 2023, abstr 181

# S1826: N-AVD markedly improves PFS over Bv-AVD in older patients with cHL



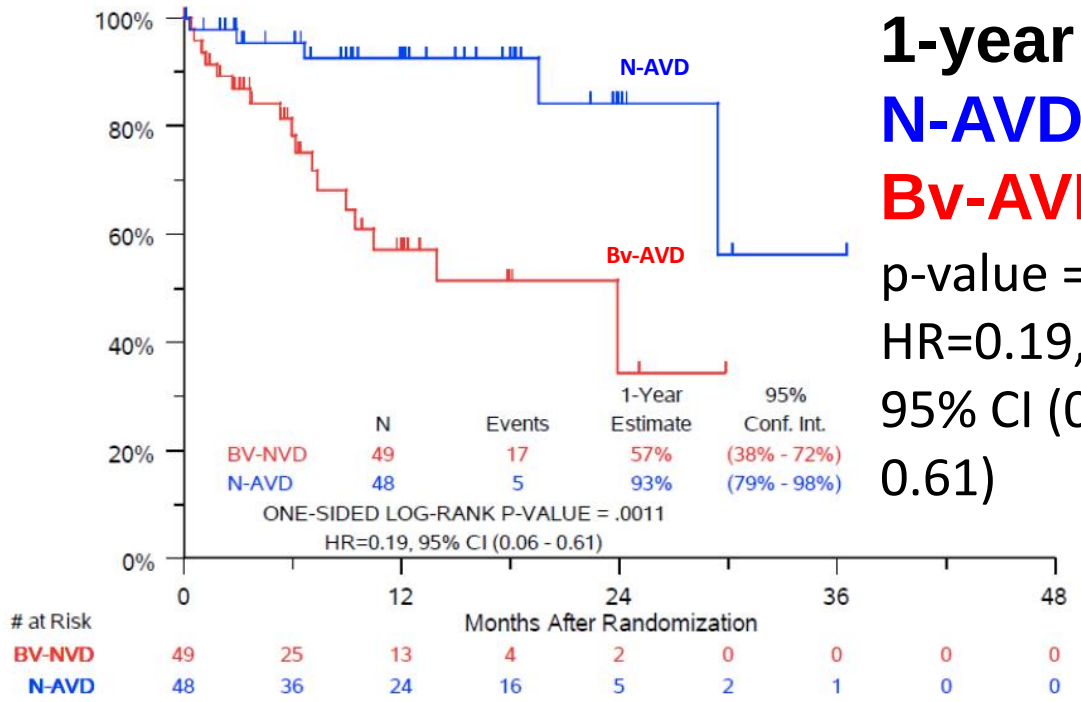

**1-year PFS**
**N-AVD 93%**
**Bv-AVD 64%**

Median follow-up
12.1 months

p-value = 0.022
HR=0.35,
95% CI (0.12-1.02)

Rutherford ASH 2023, abstr 181

# S1826: EFS benefit with N-AVD over Bv-AVD is also significant in older pts




**1-year EFS**

**N-AVD 93%**

**Bv-AVD 57%**

p-value = 0.0011

HR=0.19,

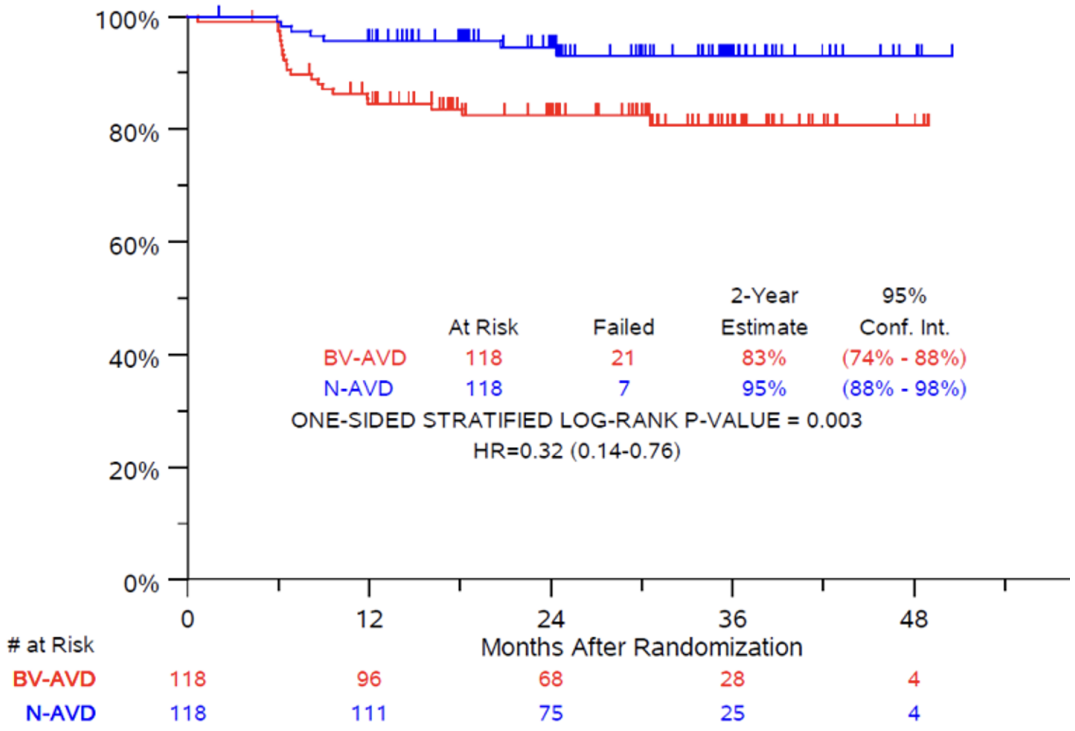
95% CI (0.06-0.61)

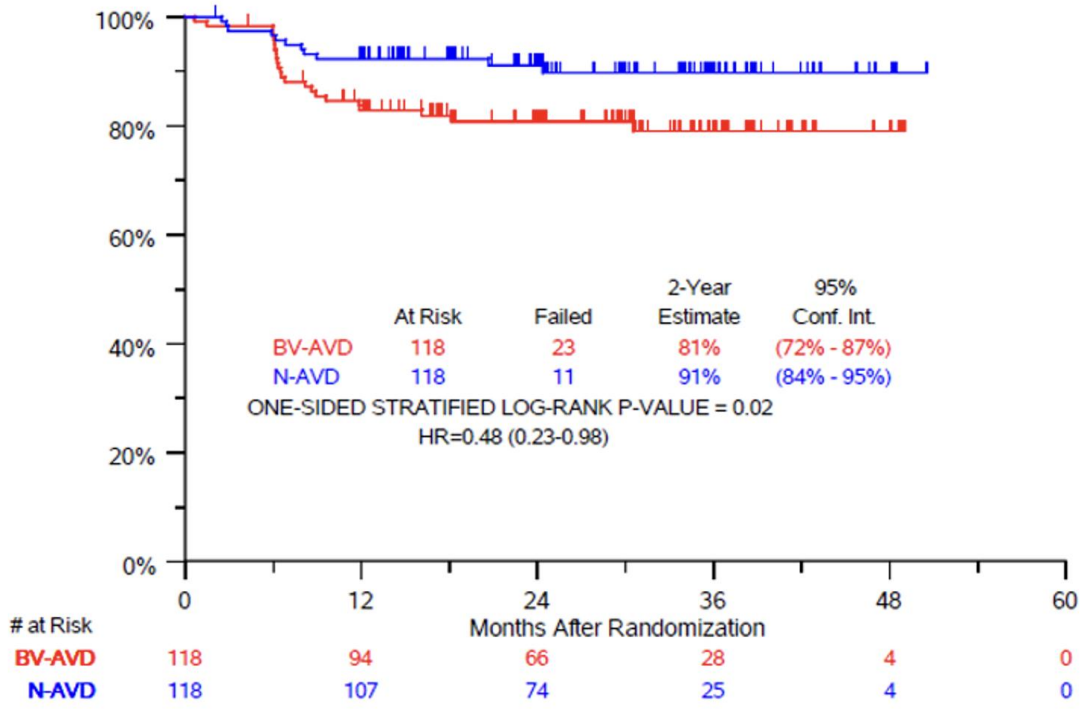
**Majority of events on Bv-AVD were progression/ relapse (16%) and death (12%)**

| EFS event | N-AVD | Bv-AVD |
|---|---|---|
| **Progression/Relapse** | **3** | **8** |
| **Death without progression** | **2** | **6** |
| Non-protocol chemotherapy before PD | 0 | 1 |
| Non-protocol immunotherapy before PD | 0 | 0 |
| Non-protocol RT prior to PD | 0 | 2 |
| **Total EFS Event** | **5** | **17** |

Rutherford ASH 2023, abstr 181

# S1826: PFS and EFS Outcomes in pediatric patients (< 18yo)




**Events:** non-protocol chemo or RT, progression, death

**Only 3 patients total received protocol-specified RT**

Castellino ASH 2024 (manuscript submitted)

# S1826: Toxicities of interest (infusion reactions and IRAEs) in pediatric patients

| Toxicity | N-AVD (N = 118) | | BV-AVD (N = 118) | |
|---|---|---|---|---|
| | Any Grade No. (%) | Grade ≥ 3 No. (%) | Any Grade No. (%) | Grade ≥ 3 No. (%) |
| Infusion-related reactions | 15 (13%) | 4 (3%) | 6 (5%) | 0 (0) |
| **Potential irAEs** | | | | |
| ALT Increased[##] | 54 (46%) | 8 (7%) | 67 (57%) | 9 (8%) |
| AST increased [##] | 48 (41%) | 3 (3%) | 56 (47%) | 7 (6%) |
| Gastritis | 5 (4%) | 1 (1%) | 2 (2%) | 0 (0) |
| Colitis | 0 (0) | 0 (0) | 1 (1%) | 1 (1%) |
| Pneumonitis[##] | 3 (3%) | 1 (1%) | 1 (1%) | 1 (1%) |
| Hypothyroidism | 6 (5%) | 0 (0) | 1 (1%) | 0 (0) |
| Hyperthyroidism | 2 (2%) | 0 (0) | 0 (0) | 0 (0) |
| Rash maculo-papular | 3 (3%) | 0 (0) | 17 (14%) | 0 (0) |
| Rash acneiform | 3 (3%) | 0 (0) | 5 (4%) | 0 (0) |
| Arthralgia | 13 (11%) | 1 (1%) | 6 (5%) | 0 (0) |

Castellino ASH 2024 (manuscript submitted)

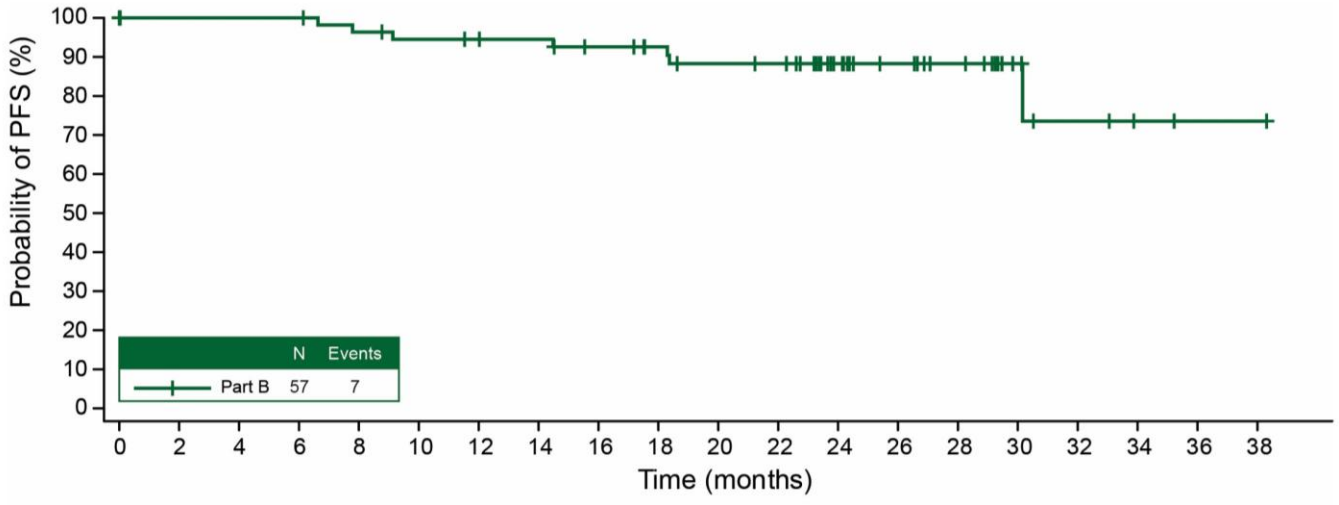
# Advanced stage classical Hodgkin lymphoma: treatment options and considerations in 2025

| RATHL | BV-AVD | Nivo-AVD | BrECADD |
|---|---|---|---|
| • Resource limited<br>• Very low-risk disease | • No checkpoint inhibitor available<br>• Severe autoimmune conditions | • Treatment of choice if available<br>• Older patients<br>• Pediatric patients | • Desire for shorter treatment duration<br>• Less cumulative chemotherapy doses |

AT THE FOREFRONT
UChicagoMedicine
Comprehensive Cancer Center

# Brentuximab Vedotin, Nivolumab, Doxorubicin, and Dacarbazine for *Advanced Stage* Classical Hodgkin Lymphoma

| Overall Response at EOT per Investigator, n (%) | Part B<br>N = 56, Efficacy Evaluable |
|---|---|
| **ORR at EOT (CR+PR)[a,b]** | 53 (95) |
| 95% CI for ORR | (85.1, 98.9)[c] |
| **CR** | 50 (89) |
| 95% CI for CR | (78.1, 96.0)[c] |
| **PR** | 3 (5) |
| 95% CI for PR | (1.1, 14.9)[c] |
| **SD** | 0 |
| **PD** | 2 (4) |
| **IR[d],** | 1 (2) |




Slide courtesy of Steve Ansell

Lee et al. ASH 2023, abstract 608

# “And beyond…”

- Major discussions related to the next generation of clinical trials in advanced stage cHL
- De-escalation of therapy
  - Decreased number of cycles
  - Replace chemotherapy with novel agents
- New technologies
  - Use of MRD to guide treatment cycles
  - Radiomics?

# 9th Post-graduate Lymphoma Conference: Frontline cHL Questions

AT THE FOREFRONT
UChicagoMedicine
Comprehensive Cancer Center

# 1. Which of the following clinical trials relies on PET-adapted therapy in classical Hodgkin lymphoma?

1. ECHELON-1
2. ECHELON-2
3. GHSG HD21
4. S1826

**RATIONALE**

The correct answer is choice 3. GHSG HD21 is a randomized phase 3 trial of eBEACOPP versus BreCADD. Patients undergo PET2/CT after 2 cycles of chemotherapy, and then assigned to either 2 versus 4 additional cycles of the respective arms based on PET-response. ECHELON-1 is a randomized phase 3 trial of BV-AVD versus ABVD without response-adapted treatment. S1826 is a randomized phase 3 trial of nivo-AVD versus BV-AVD without response-adapted treatment. ECHELON-2 is a randomized trial in CD30 positive T-cell lymphomas and is not relevant for cHL.

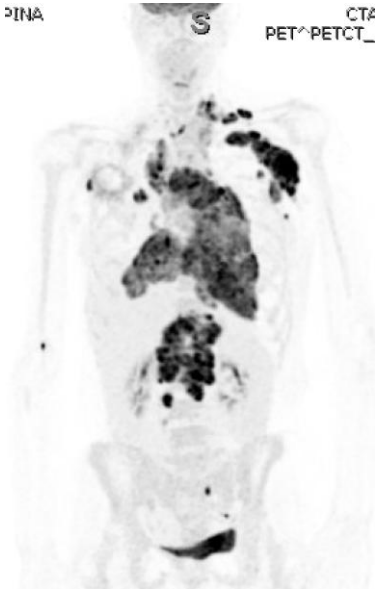
# 2. What was the frequency of immune-related adverse effects on nivo-AVD in the S1826 trial leading to treatment discontinuation?

1. <1%
2. 1-5%
3. 5-10%
4. 10-15%

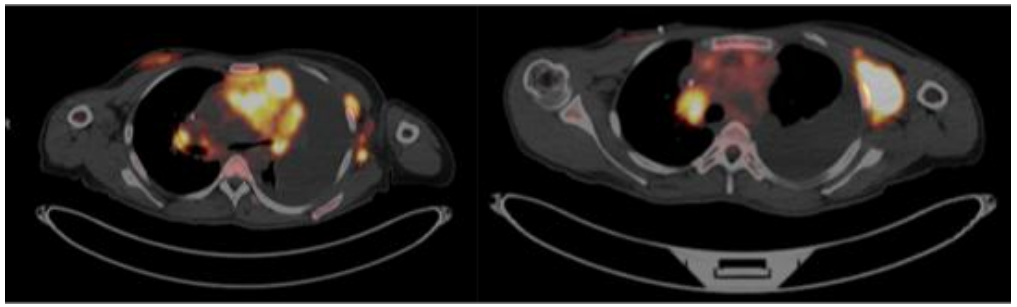
**RATIONALE**

The correct answer is choice 1. Essentially no patients stopped nivo-AVD related to IRRAE's. In Supplemental Table 9, there is a list of immune-related adverse events for both arms of the trial. Numerically increased immune-related adverse effects on the nivo-AVD arm include transaminase elevation and pneumonitis. However, the frequency of these effects is very small, and did not lead to treatment discontinuation in any patients.

# A 26 yo woman with presents with chest pain and SOB. PET scan is at the right. Biopsy shows cHL. Which of the following statements is correct regarding S1826 and GHSG HD21?



1. The cumulative dose of anthracyclines is higher in BV-AVD compared to nivo-AVD.
2. The cumulative dose of anthracyclines is higher in nivo-AVD compared to BreCADD.
3. The cumulative dose of anthracyclines is lower in BV-AVD compared to BreCADD.
4. The cumulative dose of anthracyclines is higher in BreCADD compared to nivo-AVD.



# A 26 yo woman with presents with chest pain and SOB. PET scan is at the right. Biopsy shows cHL. Which of the following statements is correct regarding S1826 and GHSG HD21?

1. The cumulative dose of anthracyclines is higher in BV-AVD compared to nivo-AVD.
2. The cumulative dose of anthracyclines is higher in nivo-AVD compared to BreCADD.
3. The cumulative dose of anthra
   lower in BV-AVD compare
4. The cumulative dose of ar
   higher in BreCADD compa

**RATIONALE**

The correct answer is choice 2. In S1826, the total dose of doxorubicin is 300mg/m2 and is the same in both the nivo-AVD and the BV-AVD arms. Therefore, choice 1 is not correct. The dose of doxorubicin is 40mg/m2 every 21d for BreCADD; given the PET-adapted strategy, a significant portion of patients completed treatment with only 4 cycles of therapy and less than 200mg/m2 of doxorubicin.