Updates for Hodgkins lymphoma therapy

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Disclosures

Speaker's bureau: Beigene, Genentech

Advisory Boards: Bristol Myers Squibb, Abbvie, Incyte, Astra Zeneca

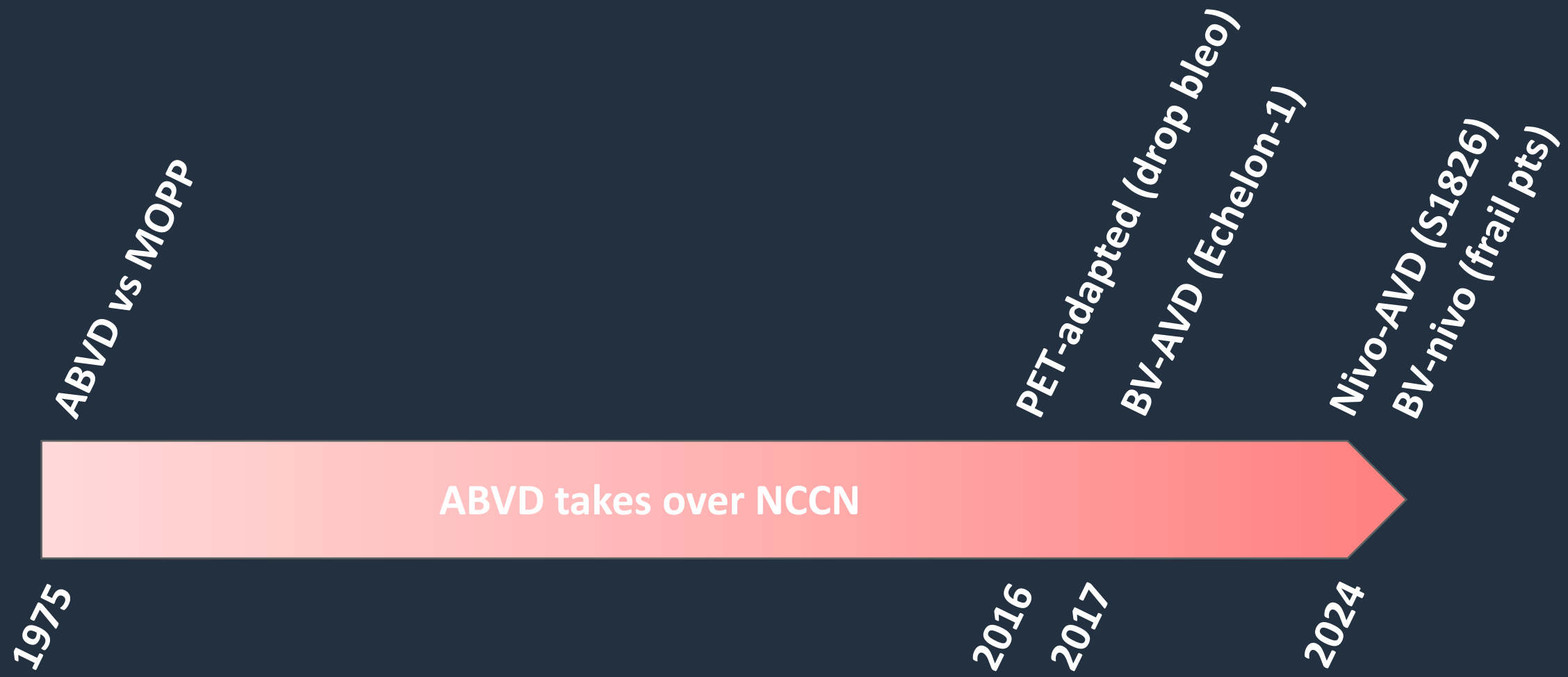
Research Funding: Abbvie

i3 Health and FLASCO have mitigated all relevant financial relationships

Outline

- Evolution of front-line therapy for classical Hodgkins lymphoma (cHL)
- Recent NCCN updates for advanced cHL
  - Nivolumab + AVD > Brentuximab vedotin (BV) + AVD per SWOG 1826
- NCCN updates for early stage, unfavorable risk cHL
  - Nivo-AVD (NivahI trial) & BV-AVD (Breach trial)
- Options for frail patients

Evolution of First-line Therapy in Advanced cHL



NCCN Guidelines Version 2.2025
Hodgkin Lymphoma (Age 18–60 years)

CLINICAL PRESENTATION:
Classic Hodgkin Lymphoma: Stage III–IV
PRIMARY TREATMENT[q]

Preferred regimens:

- Nivolumab-AVD[r,y,z] (category 1) → HODG-7
  or
- BrECADD + G-CSF[r] (category 1) (for ages 18-61 y) → HODG-7

Stage III–IV

Useful in Certain Circumstances

- BV-AVD + G-CSF[r] (category 1) (if not a candidate for CPI; contraindicated in those with neuropathy) → HODG-8

or

- ABVD[h,y] x 2 cycles[r] (category 1) (if BV and CPI not available or contraindicated) → Restage with FDG-PET/CT[c,aa]
  - Deauville 1–3[s] → AVD x 4 cycles[bb] (adapted from RATHL)[5]
  - Deauville 4–5[s,v] → BrECADD + G-CSF[r,x] x 3 cycles → Restage with FDG-PET/CT[c]
    - Deau 1–3[s]
    - Deau 4–5[s]

[v] Special considerati
- The degree of abr influence further t be appropriate to Scans that remain post-chemotherap be considered if a (HODG-C 2 of 13)
- A Deauville 5 scor biopsy is not feasi

[c] Principles of FDG-PET/CT (HODG-A)

The NEW ENGLAND JOURNAL of MEDICINE

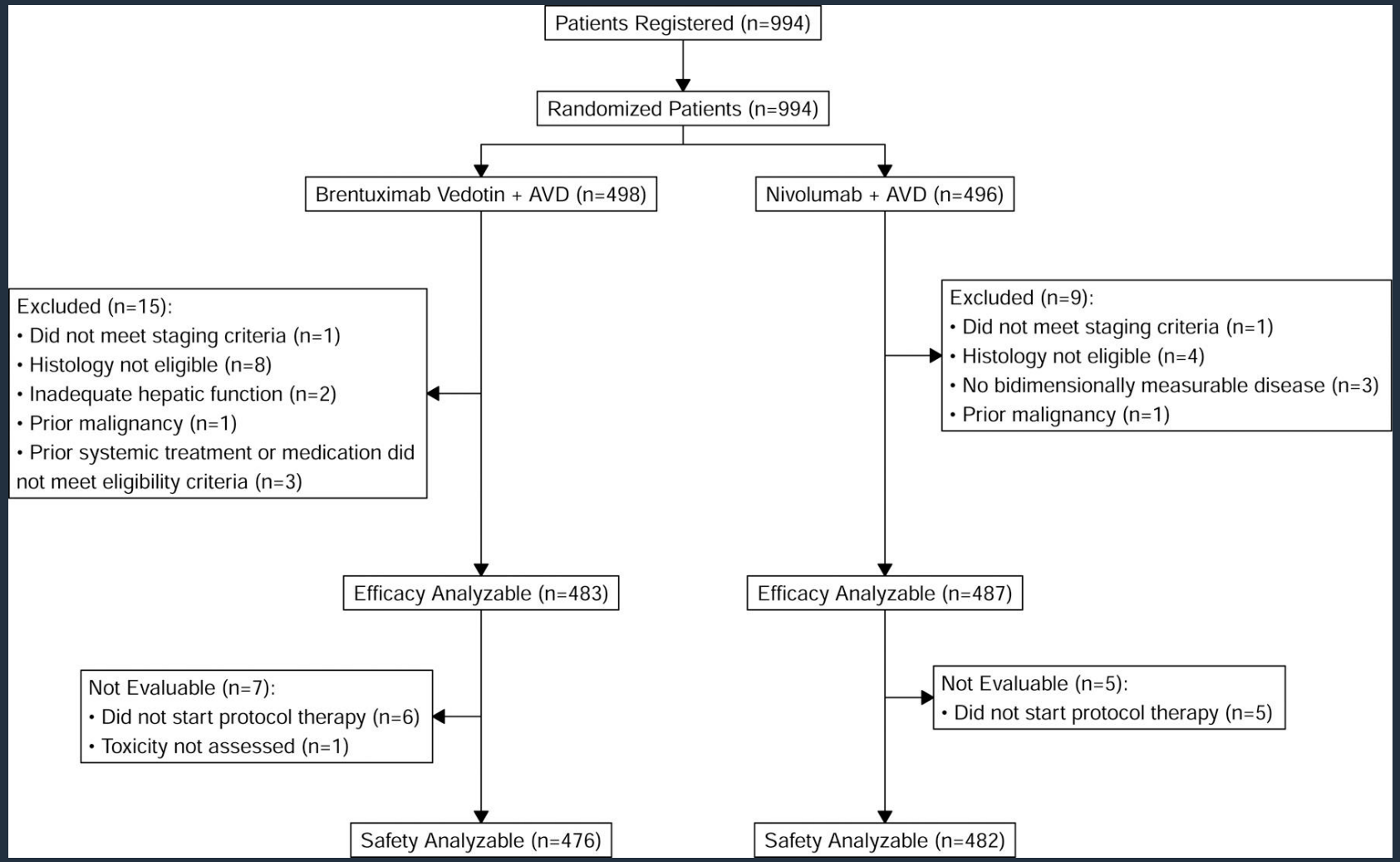
ESTABLISHED IN 1812 OCTOBER 17, 2024 VOL. 391 NO. 15

Nivolumab+AVD in Advanced-Stage Classic Hodgkin's Lymphoma

A.F. Herrera, M. LeBlanc, S.M. Castellino, H. Li, S.C. Rutherford, A.M. Evens, K. Davison, A. Punnett, S.K. Parsons, S. Ahmed, C. Casulo, N.L. Bartlett, J.M. Tuscano, M.G. Mei, B.T. Hess, R. Jacobs, H. Saeed, P. Torka, B. Hu, C. Moskowitz, S. Kaur, G. Goyal, C. Forlenza, A. Doan, A. Lamble, P. Kumar, S. Chowdury, B. Brinker, N. Sharma, A. Singh, K.A. Blum, A.M. Perry, A. Kovach, D. Hodgson, L.S. Constine, L.K. Shields, A. Prica, H. Dillon, R.F. Little, M.A. Shipp, M. Crump, B. Kahl, J.P. Leonard, S.M. Smith, J.Y. Song, K.M. Kelly, and J.W. Friedberg

SWOG 1826

Trial Design

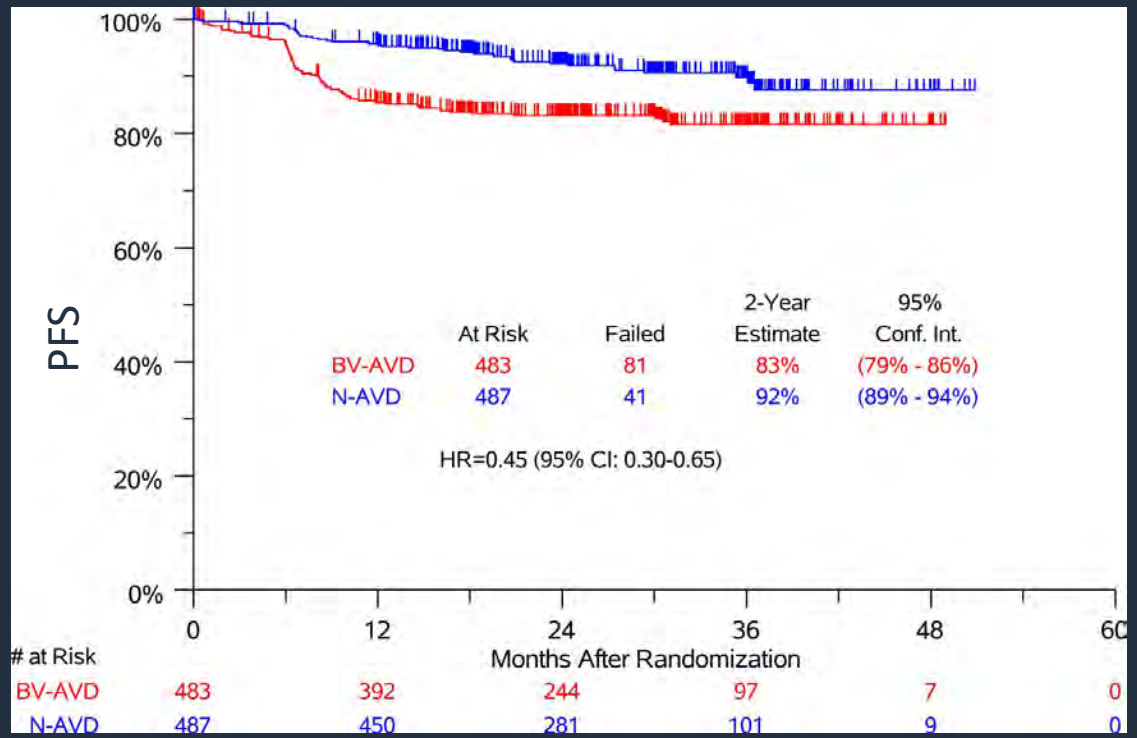


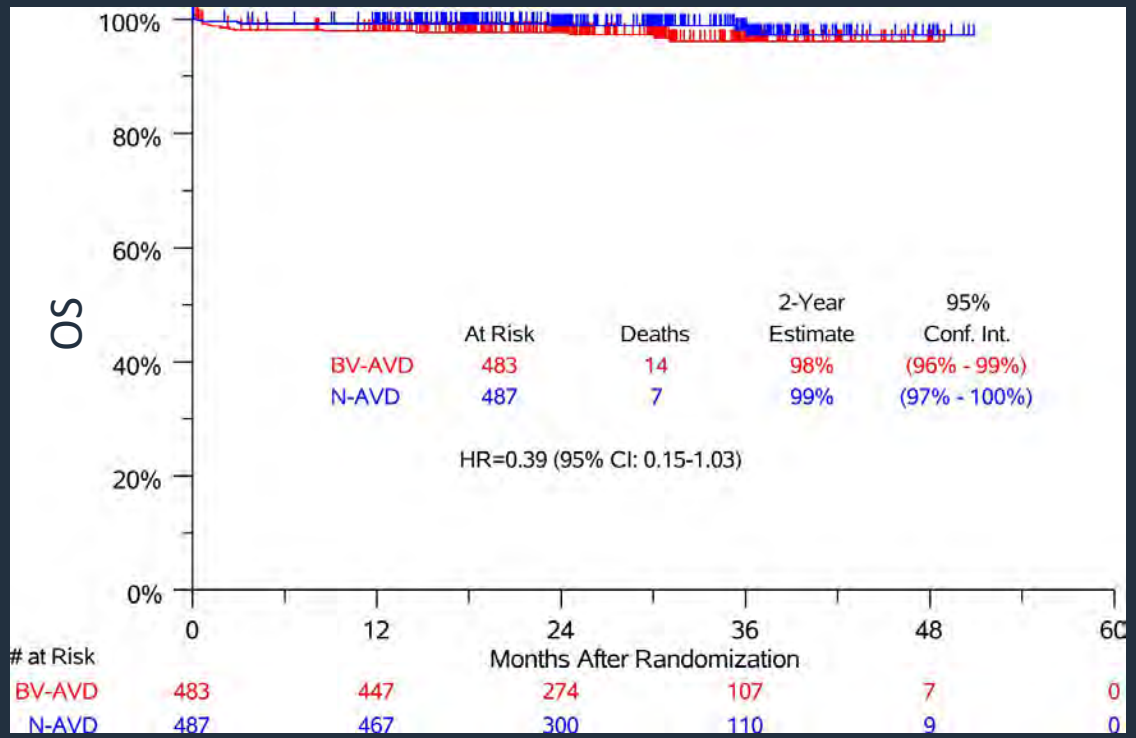
Herrera et al., NEJM 2024

Baseline characteristics	N-AVD n=487 N (%)	Bv-AVD n=483 N (%)
Age, median (range)	27.6 (12.0–83.7)	26.8 (12.0–81.7)
12–17 years	118 (24%)	118 (24%)
18–60 years	321 (66%)	318 (66%)
> 60 years	48 (10%)	47 (10%)
Female Sex	216 (44%)	210 (43%)
Race		
White	372 (76%)	361 (75%)
Black	58 (12%)	56 (11%)
Asian	11 (2%)	17 (4%)
Other/Unknown	46 (9%)	49 (10%)
Hispanic ethnicity	66 (14%)	58 (12%)
Stage		
III	185 (38%)	168 (35%)
IV	302 (62%)	315 (65%)
B symptoms present	288 (59%)	273 (57%)
IPS Score		
0–3	332 (68%)	328 (68%)
4–7	155 (32%)	155 (32%)
Bulky disease > 10cm	156 (32%)	127 (26%)
HIV positive	11 (2%)	5 (1%)

Herrera et al., NEJM 2024

Survival Advantage with Nivo-AVD Compared to BV-AVD

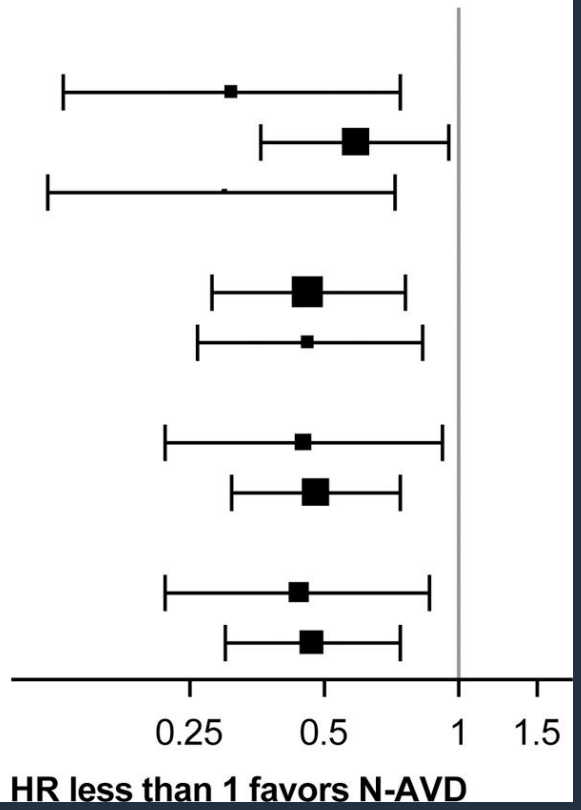




Herrera et al., NEJM 2024

Subgroup Analysis

Subgroup	N + AVD Events/N	(%)	BV + AVD Events/N	(%)	HR (95% CI)
Age					
12 - 17 y	7/118	(5.9)	21/118	(17.8)	0.31 (0.13, 0.74)
18 - 60 y	27/321	(8.4)	43/318	(13.5)	0.59 (0.36, 0.95)
> 60 y	7/48	(14.6)	17/47	(36.2)	0.30 (0.12, 0.72)
IPS					
0 - 3	24/332	(7.2)	48/328	(14.6)	0.46 (0.28, 0.76)
4 - 7	17/155	(11.0)	33/155	(21.3)	0.46 (0.26, 0.83)
Stage					
III	12/185	(6.5)	22/168	(13.1)	0.45 (0.22, 0.92)
IV	29/302	(9.6)	59/315	(18.7)	0.48 (0.31, 0.74)
Symptoms					
A	12/199	(6.0)	27/210	(12.9)	0.44 (0.22, 0.86)
B	29/288	(10.1)	54/273	(19.8)	0.47 (0.30, 0.74)



Herrera et al., NEJM 2024

Nivo-AVD favored in all subgruops

Adverse Events

- Immune-related events infrequent with Nivo-AVD
- Significantly lower PN with nivo-AVD
- Higher rate of treatment discontinuation in BV-AVD arm
- Higher rate of neutropenia in nivo-AVD arm, gcsf was not mandatory

Adverse Events	N-AVD	BV-AVD
	n = 482	n = 476
	Any Grade	Any Grade
	No (%)	No (%)
Nausea	312 (65%)	331 (70%)
Fatigue	228 (47%)	242 (51%)
Neutrophil count decreased	272 (56%)	160 (34%)
Anemia	190 (39%)	217 (46%)
Peripheral sensory neuropathy	139 (29%)	266 (56%)
Constipation	193 (40%)	204 (43%)
ALT increased	160 (33%)	201 (42%)
White blood cell decreased	197 (41%)	128 (27%)
Vomiting	134 (28%)	157 (33%)
AST increased	125 (26%)	160 (34%)
Diarrhea	100 (21%)	129 (27%)
Alopecia	103 (21%)	124 (26%)
Lymphocyte count decreased	103 (21%)	109 (23%)
Mucositis oral	107 (22%)	100 (21%)
Anorexia	61 (13%)	106 (22%)
Abdominal pain	58 (12%)	107 (22%)
Headache	69 (14%)	75 (16%)
Platelet count decreased	52 (11%)	86 (18%)
Bone pain	40 (8%)	96 (20%)
Alkaline phosphatase increased	54 (11%)	81 (17%)
Fever	62 (13%)	61 (13%)
Arthralgia	64 (13%)	58 (12%)
Hyperglycemia	57 (12%)	63 (13%)
Rash maculo-papular	54 (11%)	58 (12%)
Myalgia	52 (11%)	57 (12%)
Dyspnea	42 (9%)	58 (12%)
Weight loss	25 (5%)	71 (15%)
Dysgeusia	35 (7%)	59 (12%)

Herrera et al., NEJM 2024

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NCCN Guidelines Version 2.2025
Hodgkin Lymphoma (Age 18–60 years)

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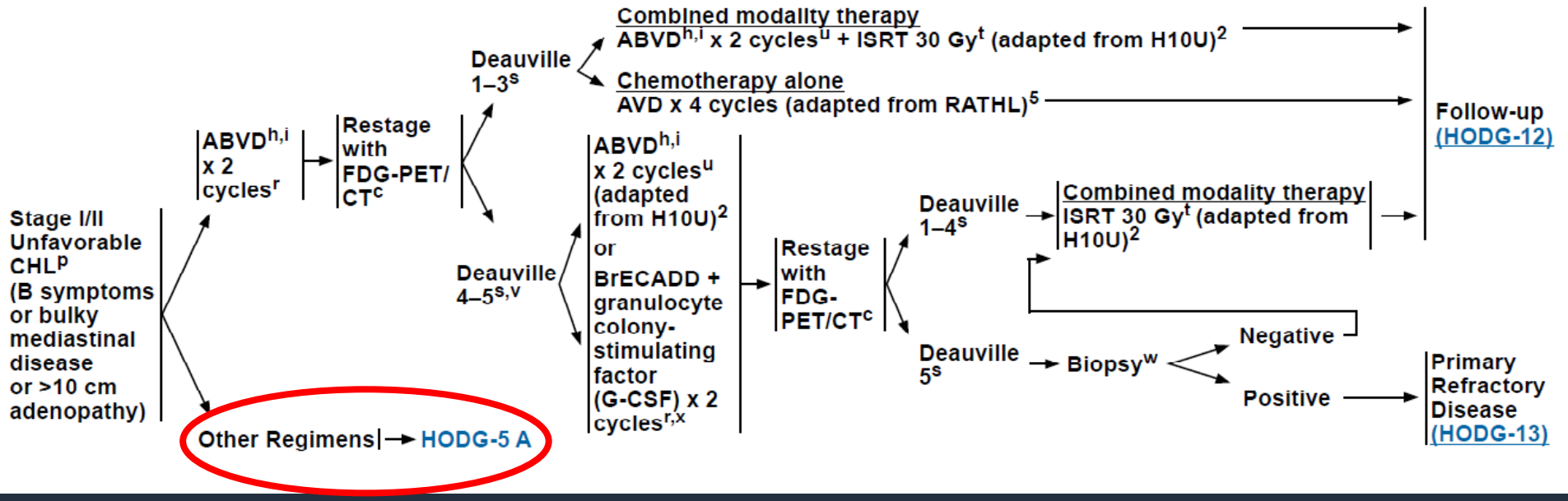
Discussion

CLINICAL PRESENTATION:
Classic Hodgkin Lymphoma: Stage I/II Unfavorable (B symptoms or bulky mediastinal disease or >10 cm adenopathy)[p]

Important Considerations:
- All patients will benefit from multidisciplinary team (including radiation oncology) input prior to final treatment decisions.
- Treatment with CMT provides for a better PFS/FFP, but no difference in overall survival.
- Selection of treatment (CMT or chemotherapy alone) should be based on patient age, sex, family history of cancer or cardiac disease, comorbid conditions, and sites of involvement (especially within mediastinum or axilla).
- For patients assigned female at birth with intact breast tissue:
  - Chemotherapy alone may be preferred for those <30 years where recommended breast DVH constraints are exceeded, if cardiac constraints cannot be met, or in the presence of high-risk comorbidities.
  - CMT may be preferred if the doxorubicin dose would exceed 200 mg/m^2 provided that breast and cardiac constraints can be met.

PRIMARY TREATMENT[q]

ADDITIONAL THERAPY



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PRIMARY TREATMENT[q] | **ADDITIONAL THERAPY**

Stage I/II Unfavorable CHL[p] (B symptoms or bulky mediastinal disease

→ Nivolumab-AVD x4 cycles[r] + ISRT 30 Gy[t] (B symptoms and/or bulky disease, adapted from NIVAHL)[6]

or

Brentuximab vedotin (BV)-AVD + G-CSF x4 cycles[r] + ISRT 30 Gy[t] (adapted from BREACH)[7]

→ Restage with FDG-PET/CT[c]

→ Deauville 1–3[s] → Follow-up (HODG-12)

→ Deauville 4–5[s] → Biopsy[w]

→ Negative → Follow-up (HODG-12)

→ Positive → Primary Refractory Disease (HODG-13)

Reduced-chemo Regimens for Early Stage, Unfavorable Risk cHL

NIVAHL (Brockelmann et al., JCO 2023)

- Nivo-AVD x 4 cycles -> 30 Gy ISRT
  - Sequential (nivo x 4, nivo-AVD x 2, AVD x 2)
  - Concomitant (nivo-AVD x 4)
- Median f/u 41 mo
- PFS 98% & 100%, respectively
- OS 100% both groups
- Low rates of grade 3-4 AEs
  - 15% on thyroid supplementation
  - Preserved FEV1 & DLCO

BREACH (BV-AVD, Fornecker et al., JCO 2023)

- BV-AVD or ABVD x 4 cycles -> 30 Gy ISRT
- PET negativity after 2 cycles:
  - 82% vs 75%, respectively
- 2-yr PFS in whole treatment arms:
  - 97% vs 92%
- Patients with high tumor volume (TMTV):
  - 2-yr PFS 90% vs 70%
- Grade 3-4 AEs, 86% vs 69%
  - Grade 3-4 PN 3% vs 2%
  - Grade 3-4 neutropenia 75% vs 62%

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Hodgkin Lymphoma (Age >60 Years or Unfit for Intensive Therapy)

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PRINCIPLES OF SYSTEMIC THERAPY[a]
Primary Systemic Therapy Regimens

Classic Hodgkin Lymphoma in Adults Age >60 Years or Adults Unfit for Intensive Therapy

Primary Systemic Therapy Regimens (Listed In Alphabetical Order)	
	Age >60 Years and Candidate for Anthracycline
Stage I–II Favorable Disease	• A(B)VD[c,d,e,k] (2 cycles) + ISRT[f,1,11,12] • A(B)VD[c,d,e,k] (3 cycles) ± ISRT[f] (if CR)[1,11,12]
Stage I–II Unfavorable	• A(B)VD[c,d,e,k] (2 cycles) followed by AVD (4 cycles), if FDG-PET scan is negative after 2 cycles of ABVD.[13] ▸ Patients with a positive FDG-PET scan after 2 cycles of ABVD need individualized treatment. • A(B)VD[c,d,e,k] x 4 cycles + ISRT[f,14] • BV x2 cycles followed by AVD x6 cycles, conditionally followed by BV x2 cycles in patients with CR or PR and no neuropathy[i,15] • Nivolumab-AVD x4 cycles + ISRT[d,f,j,10]
Stage III–IV Disease	• BV x2 cycles followed by AVD x6 cycles, conditionally followed by BV x2 cycles in patients with CR or PR and no neuropathy[i,15] (if contraindications to CPI) • Nivolumab-AVD x6 cycles[d,f,j,16,17] (preferred)

Primary Systemic Therapy Regimens (Listed In Alphabetical Order)	
	Any Age and Not a Candidate for Anthracycline
Stage I–IV	• BV-DTIC (dacarbazine) ± ISRT[f,18,19] • BV-nivolumab ± ISRT[f,20] • Nivolumab or pembrolizumab ± ISRT[f] (if contraindications to BV)

CLINICAL TRIALS AND OBSERVATIONS

CME Article

Brentuximab vedotin, nivolumab, doxorubicin, and dacarbazine for advanced-stage classical Hodgkin lymphoma

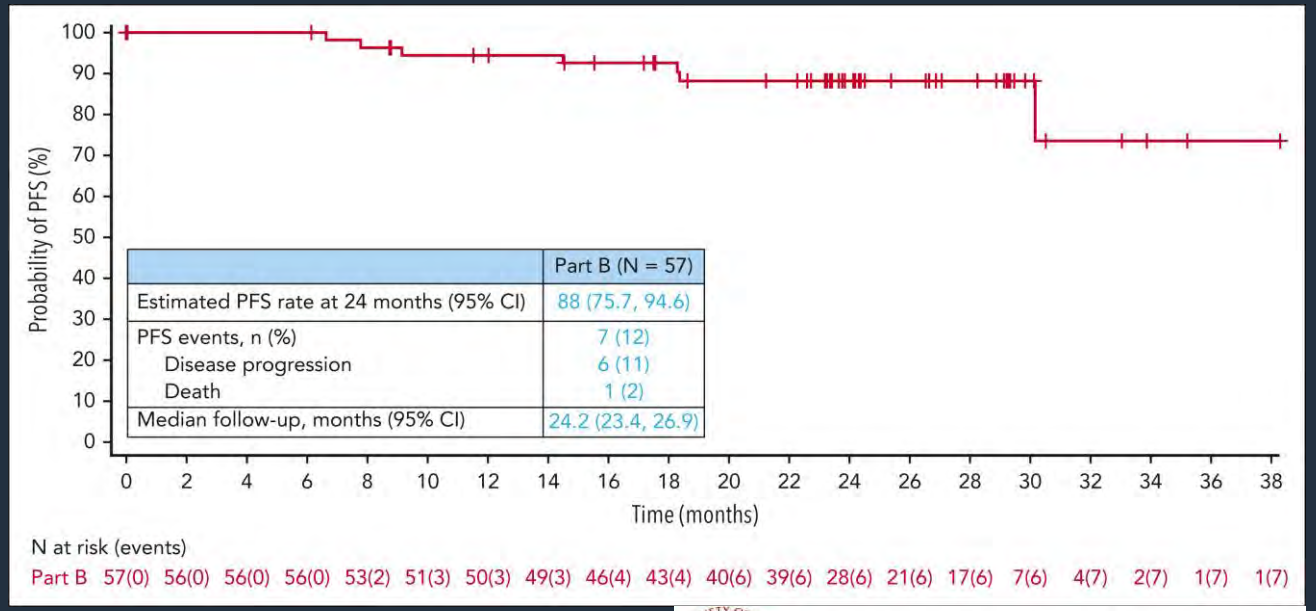
Hun Ju Lee,[1] Rod Ramchandren,[2] Judah Friedman,[3] Jason Melear,[4] Ian W. Flinn,[5] John M. Burke,[4] Yuliya Linhares,[6] Paul Gonzales,[7] Matthew Peterson,[8] Mihir Raval,[4] Rangaswamy Chintapatla,[9] Tatyana A. Feldman,[10] Habte Yimer,[4] Miguel Islas-Ohlmayer,[4,11] Ameet Patel,[11] Leland Metheny,[12] Asad Dean,[4] Vishal Rana,[13] Mitul D. Gandhi,[4] John Renshaw,[4] Linda Ho,[14] Michelle A. Fanale,[14] Wenchuan Guo,[14] and Christopher A. Yasenchak[15]

[1]MD Anderson Cancer Center, Houston, TX; [2]University of Tennessee Medical Center, Knoxville, TN; [3]Florida Cancer Specialists and Research Institute, Palm Springs, FL; [4]US Oncology Research, The Woodlands, TX; [5]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN; [6]Miami Cancer Institute, Baptist Health South Florida, Miami, FL; [7]Brooke Army Medical Center, Fort Sam Houston, TX; [8]Uvalde Memorial Hospital, Uvalde, TX; [9]Kadlec Clinic, Kennewick, WA; [10]John Theurer Cancer Center at Hackensack Meridian Health, Hackensack, NJ; [11]Oncology Hematology Care, Cincinnati, OH; [12]University Hospitals Cleveland Medical Center, Cleveland, OH; [13]University of Colorado Health Hematology and Oncology, Colorado Springs, CO; [14]Pfizer Inc, Bothell, WA; and [15]Willamette Valley Cancer Institute and Research Center, Eugene, OR

Lee *et al.*, Blood 2025

BV+Nivo+AD (Lee et al., *Blood* 2025)

- 57 pts with cHL treated (age ≥ 12)
  - Bulky stage II & stage III/IV
- Up to 6 cycles of therapy
  - Days 1,15 q28days
  - BV 1.2 mg/kg, nivo 240 mg
- 88% CR, 88% 2yr PFS
  - 94% 2-yr PFS for bulky stage II pts (n=17)
- 9% Gr 3-4 neutropenia
  - No febrile neutropenia
  - 49% rec'd gcsf
- 44% neuropathy, 4% Gr 3
- 5% pneumonitis, 4% colitis
- No XRT given



	Part B (N = 57)
Estimated PFS rate at 24 months (95% CI)	88 (75.7, 94.6)
PFS events, n (%)	7 (12)
Disease progression	6 (11)
Death	1 (2)
Median follow-up, months (95% CI)	24.2 (23.4, 26.9)

Summary

- Newer agents allow for reduced chemotherapy in advanced classical Hodgkins lymphoma
  - Improved outcomes by replacing bleomycin
- Nivolumab + AVD has superior outcomes in advanced cHL compared to BV-AVD
  - consider BV-AVD for patients with contraindications to CPI
- Both nivo-AVD & BV-AVD are showing significant responses in early-stage, unfavorable risk cHL
- Multiple reduced-intensity options for elderly and/or frail patients

Selected References

1. Bonadonna et al., *Cancer* 1975 PMID 54209
2. Johnson et al., NEJM 2016 PMID 27332902
3. Straus et al., *Lancet Haematol* 2021 PMID 34048680
4. Herrera et al., *NEJM* 2024 PMID 39413375
5. Friedberg et al., *Blood* 2024 PMID 39388158
6. Fornecker et al., *J Clin Oncol* 2023 PMID 35867960
7. Brockelmann et al., *JAMA Oncol* 2023 PMID 36508302

Thank you

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