22nd INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

APRIL 4 - 5, 2025

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#IUCLS2025

Andrew M. Evens, DO, MBA, MSc
Rutgers Cancer Institute and RWJBarnabas Health

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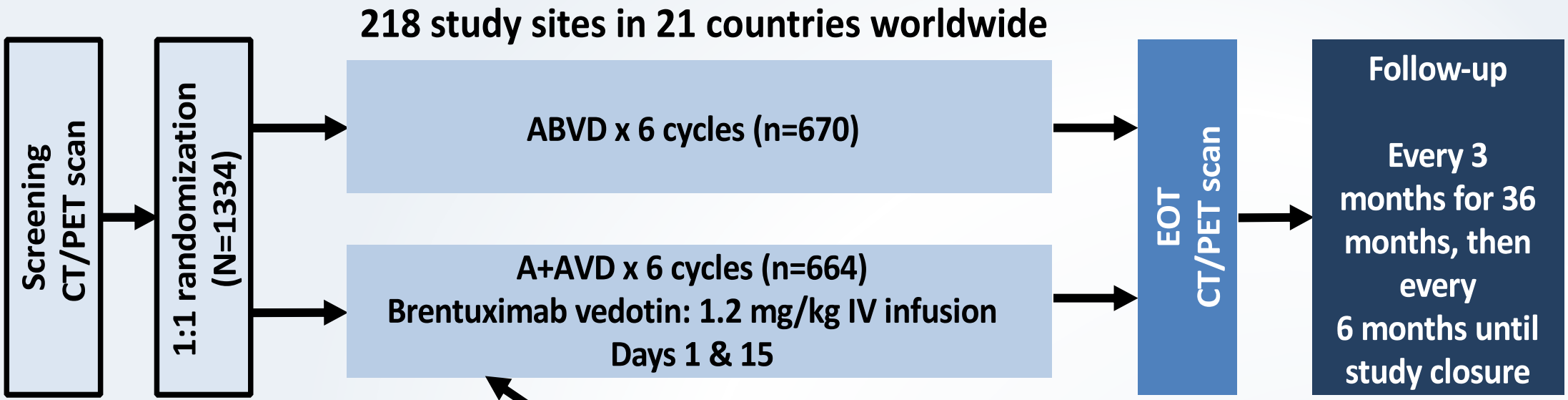
Disclosures

Andrew Evens, DO, MBA, MSc serves on the research advisory board for Pfizer, Genentech, CRISPR Therapeutics, Novartis, Pharmacyclics, and Incyte

ECHELON-1: A+AVD vs ABVD in Advanced cHL



- **Inclusion criteria**
  - cHL stage III or IV
  - ECOG PS 0, 1 or 2
  - Age ≥18 years
  - Measurable disease
  - Adequate liver and renal function

End-of-Cycle-2 PET scan

- Deauville 5; could receive alternate therapy per physician's choice (not a modified PFS event)

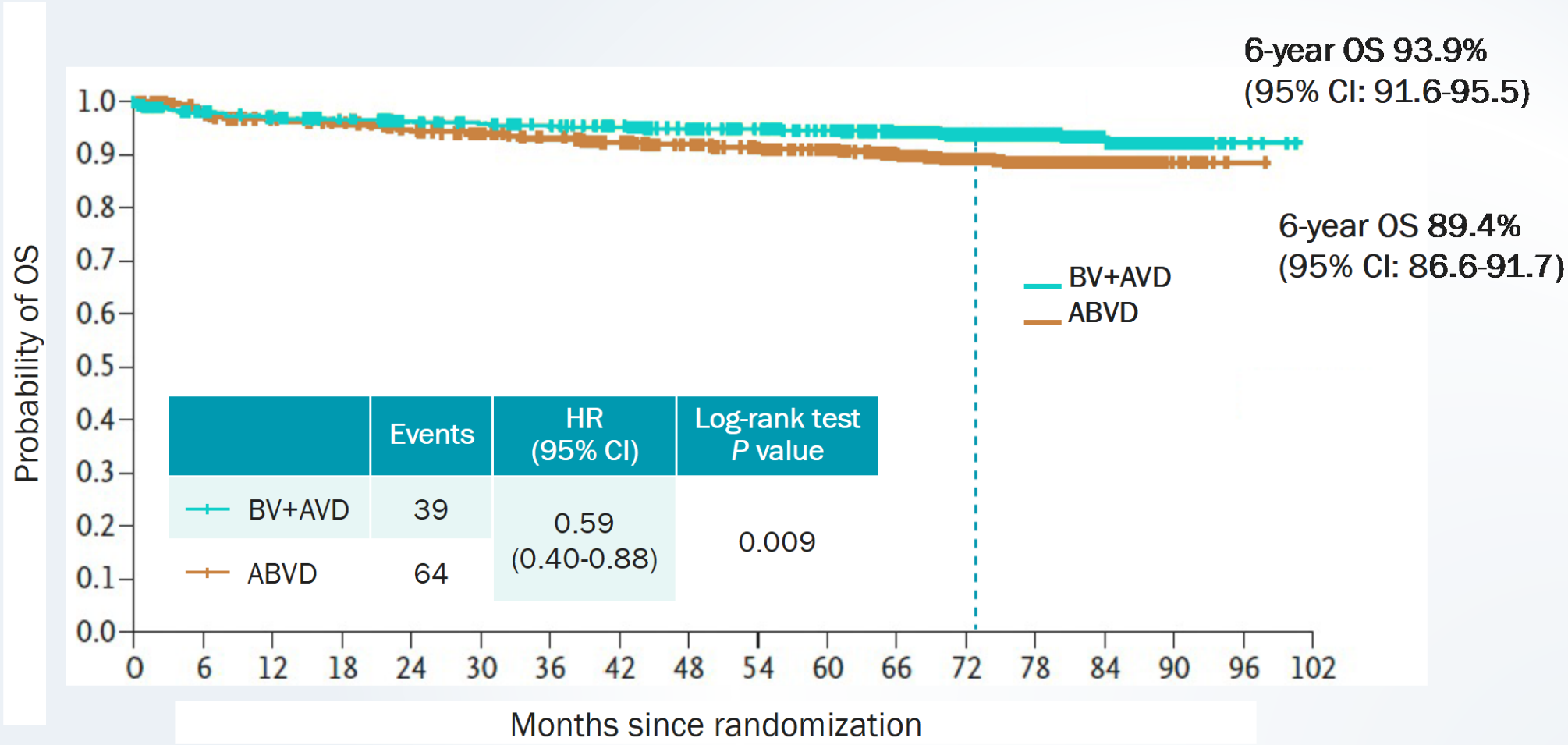
Primary endpoint: Modified PFS per IRF
Key secondary endpoint: Overall Survival

Patients with a Deauville score of 5 following a Cycle 2 PET scan could receive alternative therapy at physician's discretion.

Modified PFS: Progression, death from any cause, or receipt of additional anticancer therapy for patients not in CR after completion of frontline therapy.

Connors et al. *N Engl J Med*. 2018;378:331-344.; slide courtesy of Alex Herrera.

ECHELON-1: OS per Investigator at 6-Year Follow-Up



No. of patients at risk

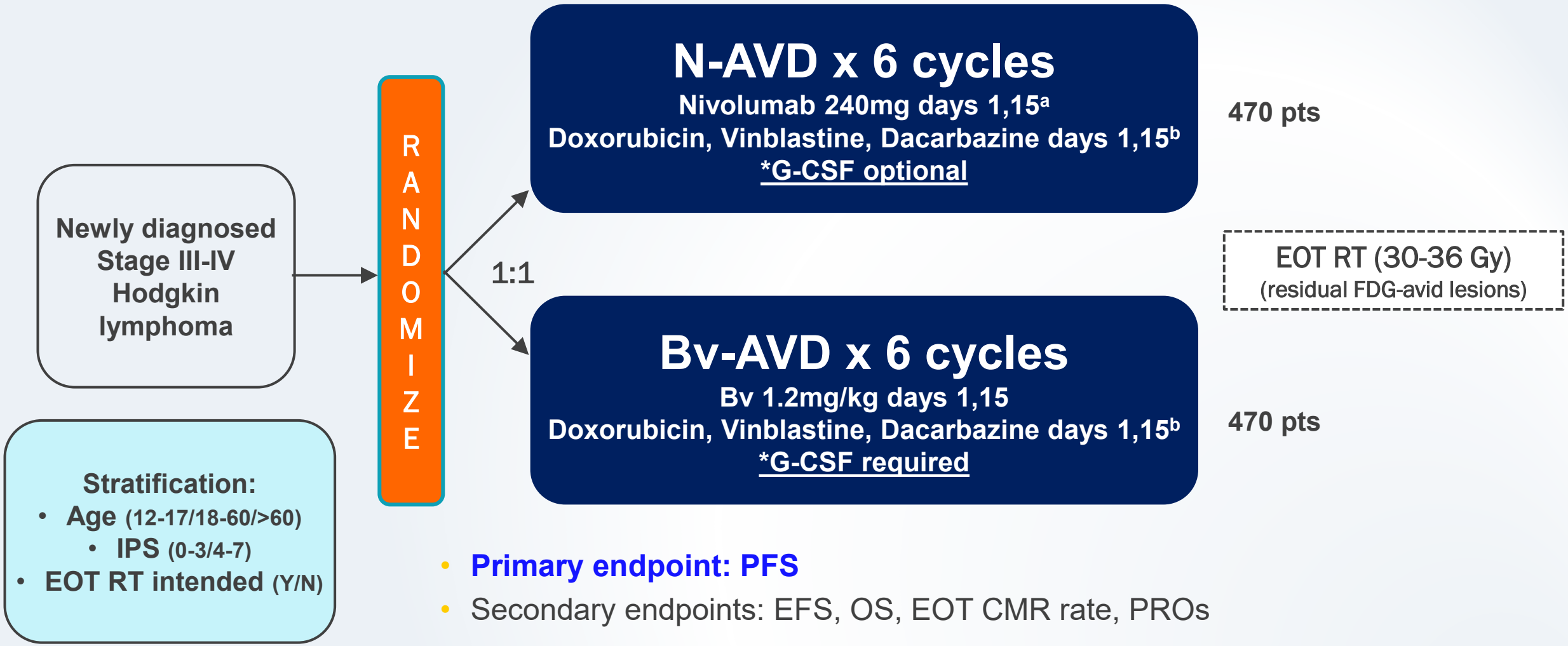
BV+AVD	664	638	626	612	598	584	572	557	538	517	494	461	350	209	97	27	4	0
ABVD	670	634	614	604	587	567	545	527	505	479	454	411	308	191	84	11	1	0

Ansell SM, et al. *N Engl J Med*. 2022;387(4):310-320.

No Prior Overall Survival Advantage of Intensified Therapy Compared With ABVD in Advanced-stage HL

2003	ABVD vs. MOPP/ABV	Duggan (Intergroup)
2003	ABVD vs. ABVD/ASCT	Federico
2004	ABVD vs. COPP/ABV/IEMP vs. COPP/ABVD	GHSG
2005	ABVD vs. Stanford V vs. MOPPEBCAD	Gobbi
2005	ABVD vs. ChlVPP/EVA vs. alternating EVA, ChlVPP	Johnson
2006	ABVD vs. MOPP/ABV vs. ABVPP	GELA
2009	ABVD vs. Stanford V	UK
2010	ABVD vs. BEACOPP std x 4 + RT	Milan
2011	ABVD vs. Stanford V vs. MOPPEBCAD	Chiesesi
2011	ABVD vs. BEACOPP esc x 4 vs. BEACOPP std x 4	Milan
2012	ABVD vs. BEACOPP esc 6 vs 8	GHSG
2013	ABVD vs. Stanford V vs. BEACOPP-14	US Intergroup
2014	ABVD vs. BEACOPP 4/4	Mounier (LYSA)
2016	ABVD vs. BEACOPP 4/2 vs. COPP/EBV/CAD	Merli
2016	ABVD vs. BEACOPP 4 esc/4 std	Carde (EORTC)
2016	ABVD vs. AVD (PET2 negative)	Johnson

S1826 Study Design



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

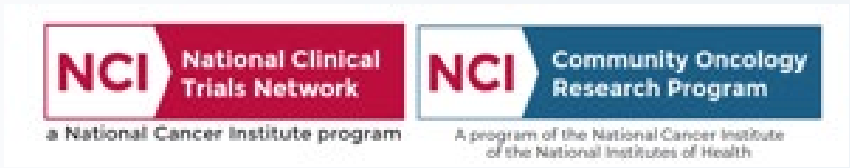
Presented by: Alex F. Herrera, MD

[a] Nivolumab 3mg/kg for ages ≤ 17, max 240mg
[b] Conventional doses of AVD: Stephens DM et al Blood 2019, Ansell SM et al NEJM 2022

Acknowledgments

Patients, families, caregivers, research teams

Funding provided by: National Cancer Institute of the National Institutes of Health U10CA180888,U10CA180819, U10CA180820, U10CA180821, U10CA180863, U10CA180886 and Bristol-Myers Squibb, Bv provided by Seagen (Canada only)



S1826 Baseline Characteristics

Baseline characteristics	N-AVD n=487 N (%)	Bv-AVD n=483 N (%)
Age, median (range)	27 (12-83)	26 (12-81)
12-17 years	118 (24%)	118 (24%)
18-60 years	321 (66%)	318 (66%)
≥ 61 years	48 (10%)	47 (10%)
Female Sex	216 (44%)	210 (43%)
Race		
White	372 (76%)	361 (75%)
Black	58 (12%)	56 (12%)
Asian	11 (2%)	17 (4%)
Other/Unknown	46 (9%)	49 (10%)
Hispanic	66 (14%)	58 (12%)

Baseline characteristics	N-AVD n=487 N (%)	Bv-AVD n=483 N (%)
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+	11 (2%)	5 (1%)

Representative study, inclusive of high-risk pts

Presented by: Alex F. Herrera, MD

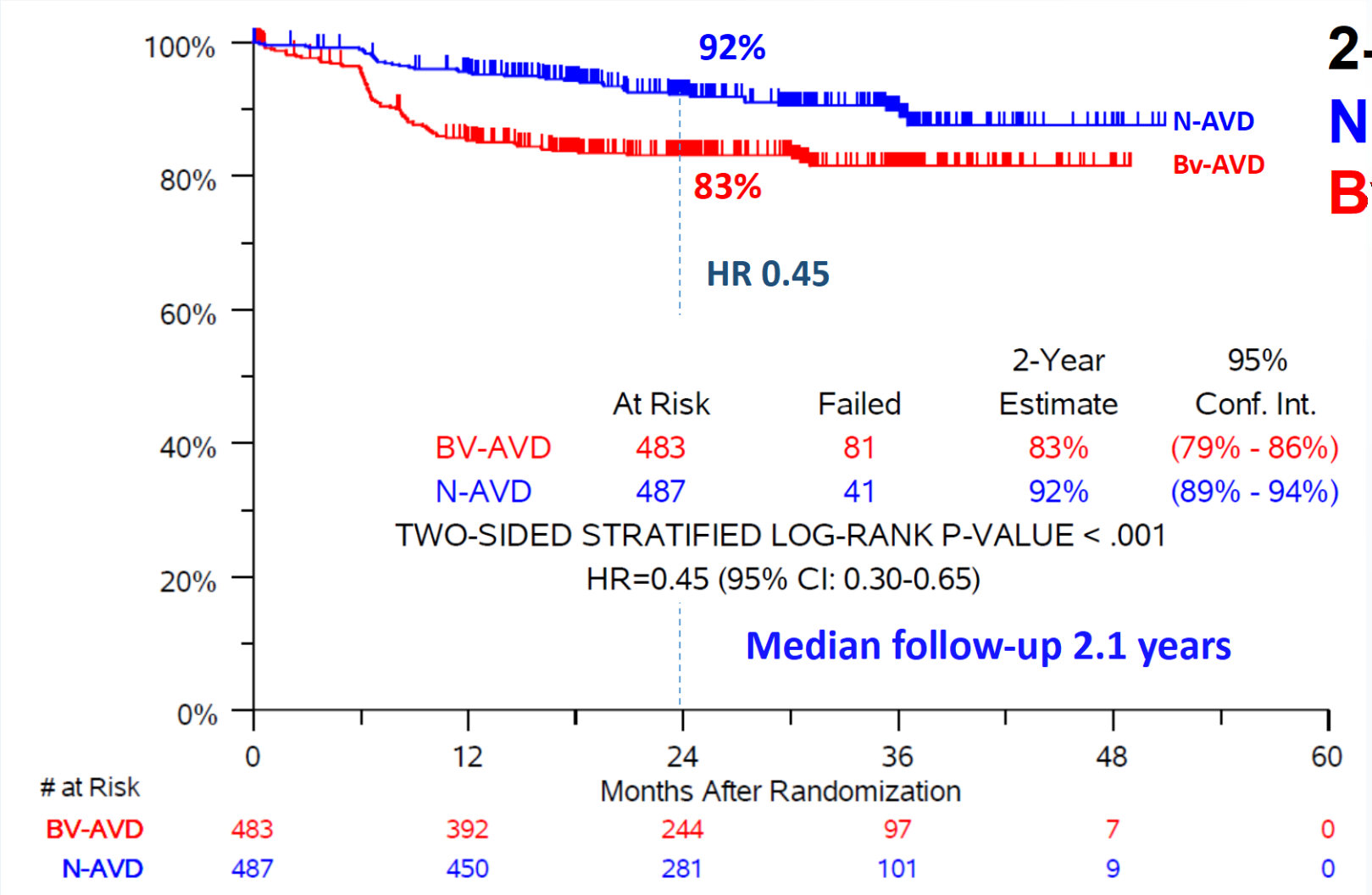
Herrera, AF et al. N Eng J Med. 2024 Oct 17;391(15):1379-138.

N-AVD largely better tolerated than BV-AVD

	Received G-CSF	Gr ≥ 3 neutropenia	Febrile neutropenia	Gr ≥ 3 infections, infestations	Sepsis	Bone pain
N-AVD (n = 482)	56%	48%	6%	5%	2%	8%
BV-AVD (n = 476)	97%	26%	7%	7%	3%	20%

	Peripheral sensory Neuropathy All Gr/Gr 2+	Peripheral motor neuropathy All Gr/Gr 2+	Thyroid dysfunction	ALT increased	Pneumonitis	Colitis
N-AVD (n = 482)	29%/8%	4%/1%	10%	33%	2%	1%
BV-AVD (n = 476)	56%/32%	7%/5%	1%	42%	3%	1%

PFS benefit of N-AVD sustained with 2y follow-up

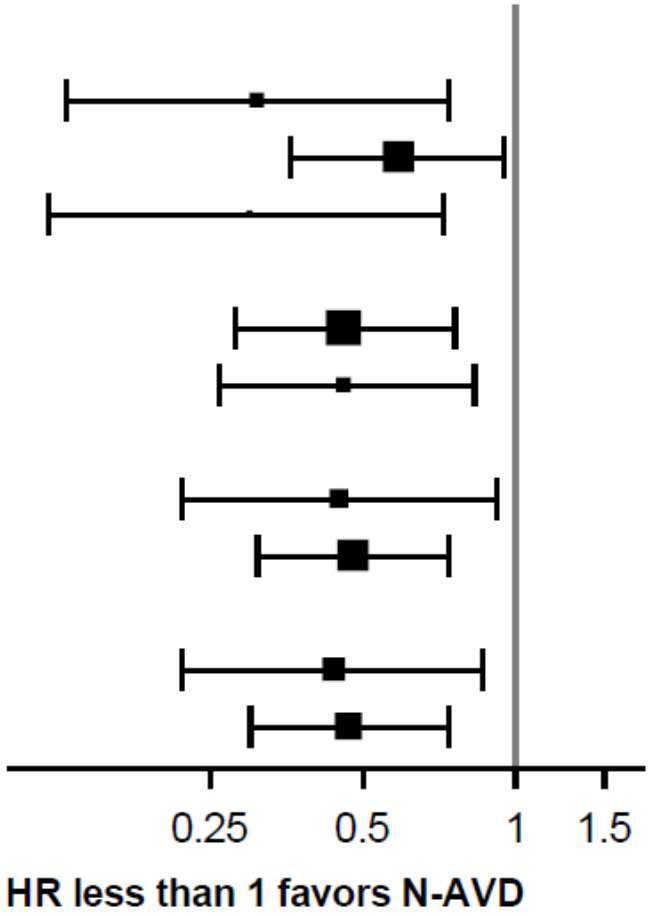


2-year PFS
N-AVD 92%
Bv-AVD 83%

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

PFS benefit consistent across all subgroups at 2 years

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

S1826 Update Conclusions

PFS benefit with N-AVD over Bv-AVD in advanced stage cHL sustained at 2 years of FU

PFS benefit consistent across subgroups

N-AVD improved EFS versus Bv-AVD

N-AVD was better tolerated than Bv-AVD

Fewer treatment discontinuations

Less neuropathy, no increased infections, few immune-related adverse events

No new toxicity signals observed

< 1% of patients received consolidative RT

Follow-up ongoing to assess long-term safety, OS, and PROs

Key step towards harmonizing pediatric and adult therapy of cHL

N-AVD is a new standard therapy for advanced stage cHL

S1826 vs BrECADD: Differences in study population and design

	S1826: Nivo-AVD	HD21: BrECADD
Patient Characteristics	Ages 12-83 years (median 31 years; 10% ≥60 years)	Ages 18-60 years (median 27 years)
Patient Characteristics	Black race 12%; HIV+ 2%	Black race 0%; HIV+ 0%
Stage	III-IV (62% stage IV)	IIB-IV (16% stage II; 45% stage IV)
PET-based	No	Yes
Treatment duration	24 weeks	12 weeks PET-2 negative (two-thirds); 18 weeks PET-2 positive (one-third)
Use of radiotherapy	<1%	14%

Tolerability Much Better with Nivo-AVD (and Survival Similar)

	S1826: Nivo-AVD	HD21: BrECADD
HRQL studies done	Yes	Yes
Key heme toxicities (grade 3+)	anemia 6%; thrombocytopenia 2%	anemia 30%; thrombocytopenia 55%
Febrile neutropenia (FN), Infection/sepsis (grade 3+)	FN 2% (GCSF not mandatory); infection/sepsis 2%	FN 28% (mandatory GCSF); infection/sepsis 20%
Sensory neuropathy (grade 2+)	9%	16%
Survival	2-year PFS and OS: 92% and 99%, respectively	4-year PFS and OS: 94% and 99%, respectively

SOC for Advanced-Stage HL in 2025

- Most adult advanced-stage HL patients ages 12-60 years
  - –Nivo-AVD
  - –?? exceptions
    - Active auto-immune disease
    - Previous anthracycline (BrECADD: 160 mg/m2 for PET-2-negative (240 mg/m2 for PET-2-positive disease) vs 300 mg/m2 for N-AVD)
- What about older patients (or significant co-morbidities)
  - –S1826 (vs sequential Bv-AVD-Bv)!
- Will we be able to individualize treatment at the patient level in future (at least: pros/cons across varied choices)?

The HoLISTIC Consortium

- In 2018, Drs. Parsons and Evens formed an international consortium, *HoLISTIC* (Hodgkin Lymphoma International STudy for Individual Care)
- 80+ members pediatric & adult hematology, radiation, epidemiology, imaging, biology, statistics/modeling, and patient advocates & societies
- Comprehensive individual patient data (IPD) on >30,000 HL patients from 25 recent, international phase III clinical trials (untreated early and advanced stage HL) and 6 major cancer registries
- Goal: enhance clinical decision making given unique individual patient and disease factors, and alternative treatment options
  - unify and harness worldwide, multi-source data to define early HL outcomes and non-cancer post-acute & late effects for individual pts

www.hodgkinconsortium.com

Journal of Clinical Oncology®

original reports abstract

The Advanced-Stage Hodgkin Lymphoma International Prognostic Index: Development and Validation of a Clinical Prediction Model From the HoLISTIC Consortium

Angie Mae Rodday, PhD, MS[1]; Susan K. Parsons, MD, MRP[1]; Jenica N. Upshaw, MD, MSc[1,2]; Jonathan W. Friedberg, MD[3]; Andrea Gallamini, MD[4]; Eliza Hawkes, MBBS, DMedSc[5]; David Hodgson, MD[6]; Peter Johnson, MD[7]; Brian K. Link, MD[8]; Eric Mou, MD[9]; Kerry J. Savage, MD, MSc[6]; Pier Luigi Zinzani, MD, PhD[10]; Matthew Maurer, DMSc, MS[11]; and Andrew M. Evens, DO, MBA, MSc[12]

PURPOSE The International Prognostic Score (IPS) has been used in classic Hodgkin lymphoma (cHL) for 25 years. However, analyses have documented suboptimal performance of the IPS among contemporarily treated patients. Harnessing multisource individual patient data from the Hodgkin Lymphoma International Study for Individual Care consortium, we developed and validated a modern clinical prediction model.

METHODS Model development via Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis guidelines was performed on 4,022 patients with newly diagnosed advanced-stage adult cHL from eight international phase III clinical trials, conducted from 1996 to 2014. External validation was performed on 1,431 contemporaneously treated patients from four real-world cHL registries. To consider association over a full range of continuous variables, we evaluated piecewise linear splines for potential nonlinear relationships. Five-year progression-free survival (PFS) and overall survival (OS) were estimated using Cox proportional hazard models.

RESULTS The median age in the development cohort was 33 (18-65) years; nodular sclerosis was the most common histology. Kaplan-Meier estimators were 0.77 for 5-year PFS and 0.92 for 5-year OS. Significant predictor variables included age, sex, stage, bulk, absolute lymphocyte count, hemoglobin, and albumin, with slight variation for PFS versus OS. Moreover, age and absolute lymphocyte count yielded nonlinear relationships with outcomes. Optimism-corrected c-statistics in the development model for 5-year PFS and OS were 0.590 and 0.720, respectively. There was good discrimination and calibration in external validation and consistent performance in internal-external validation. Compared with the IPS, there was superior discrimination for OS and enhanced calibration for PFS and OS.

CONCLUSION We rigorously developed and externally validated a clinical prediction model in > 5,000 patients with advanced-stage cHL. Furthermore, we identified several novel nonlinear relationships and improved the prediction of patient outcomes. An online calculator was created for individualized point-of-care use.

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ASSOCIATED CONTENT
Data Supplement
Author affiliations and support information (if applicable) appear at the end of this article.
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INTRODUCTION

Classic Hodgkin lymphoma (cHL) is a B-cell malignancy that occurs predominantly in younger adults and is generally associated with favorable disease outcomes.[1] However, there is no single consensus-based or individualized treatment approach globally beyond use of multiagent chemotherapy with curative intent.

The most widely used prognostication tool in cHL has been the International Prognostic Score (IPS), published in 1998 by the German Hodgkin Study Group.[2] The IPS identified seven clinical factors (IPS7) prognostic for survival at 5 years in newly diagnosed advanced-stage disease. While used over the past 25 years, this score requires updating for several reasons. First, management strategies and outcomes for cHL have improved over the past 10-20 years.[1,3] Recent studies suggested poor calibration of the IPS7 among contemporarily treated patients.[4,5] Second, clinical prediction modeling techniques have grown in sophistication since the IPS7 was developed. For example, the IPS7 relied on dichotomous categorization of patient and disease factors with limited information about model performance (discrimination and calibration). Furthermore, the IPS7 was developed based on complete case analyses, but missing data were frequent, requiring the use of imputation strategies that were not externally validated.

The Advanced-Stage Hodgkin Lymphoma International Prognostic Index (A-HIPI): Development and Validation of a Clinical Prediction Model from the HoLISTIC Consortium

ascopubs.org/doi/full/10.1200/JCO.22.02473

SCAN ME

Rodday AM, et al. *J Clin Oncol*. 2023;41(11):2076-2086.

Online Calculator for Point-of-care Use (QxMD)

Calculate by QxMD

All Calculators Become a Contributor

Calculator | About | References

A-HIPI

Questions

1.	Age?	18 years
2.	Albumin?	3.8 g/dL
3.	Bulk?	no bulk
4.	Gender?	Female
5.	Hemoglobin?	10.5 g/dL
6.	Lymphocyte count?	1 10^3/uL
7.	Stage?	Stage III

Results

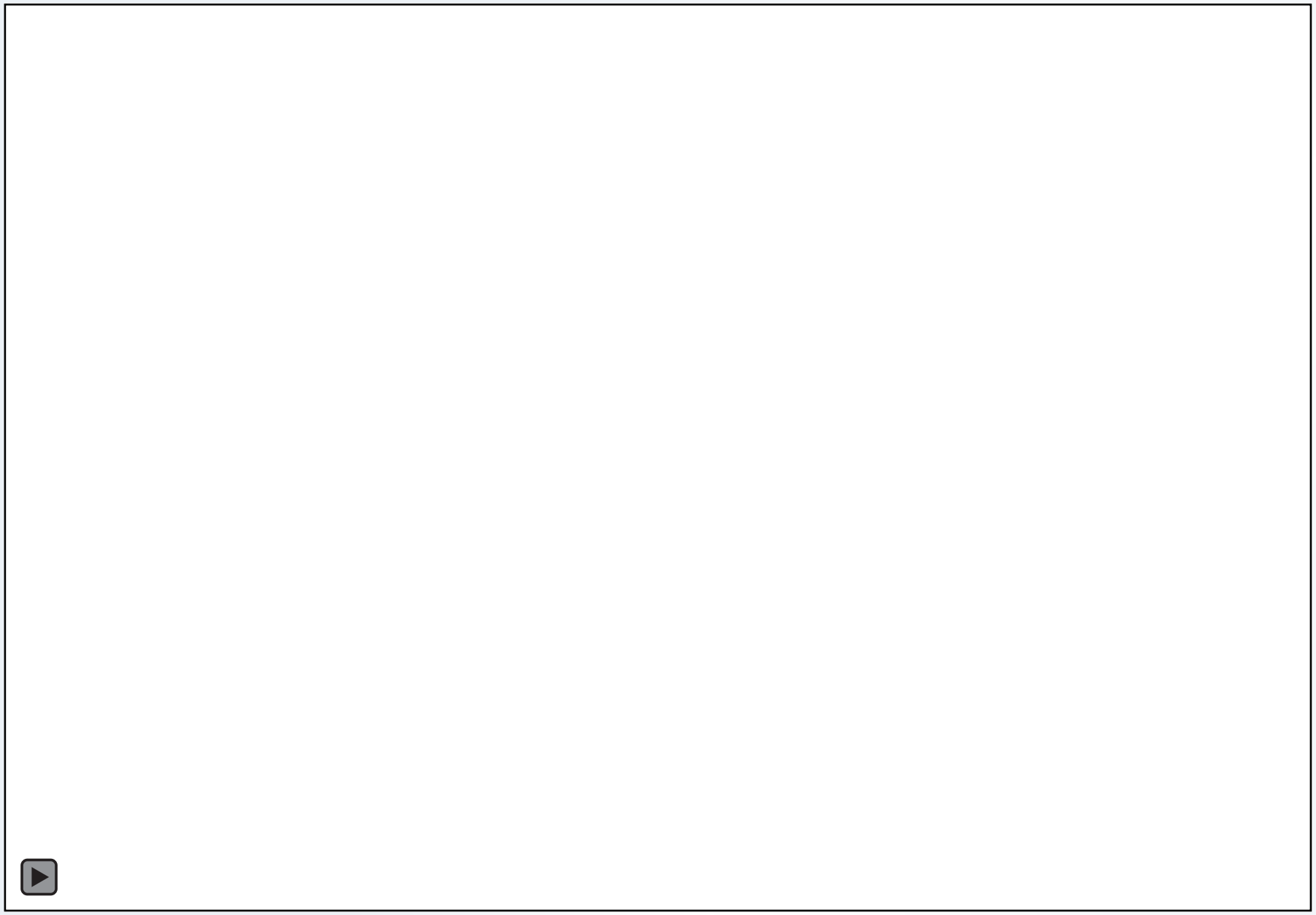
Progression Free Survival at 5 years

74.62%

Overall Survival at 5 years

94.85%

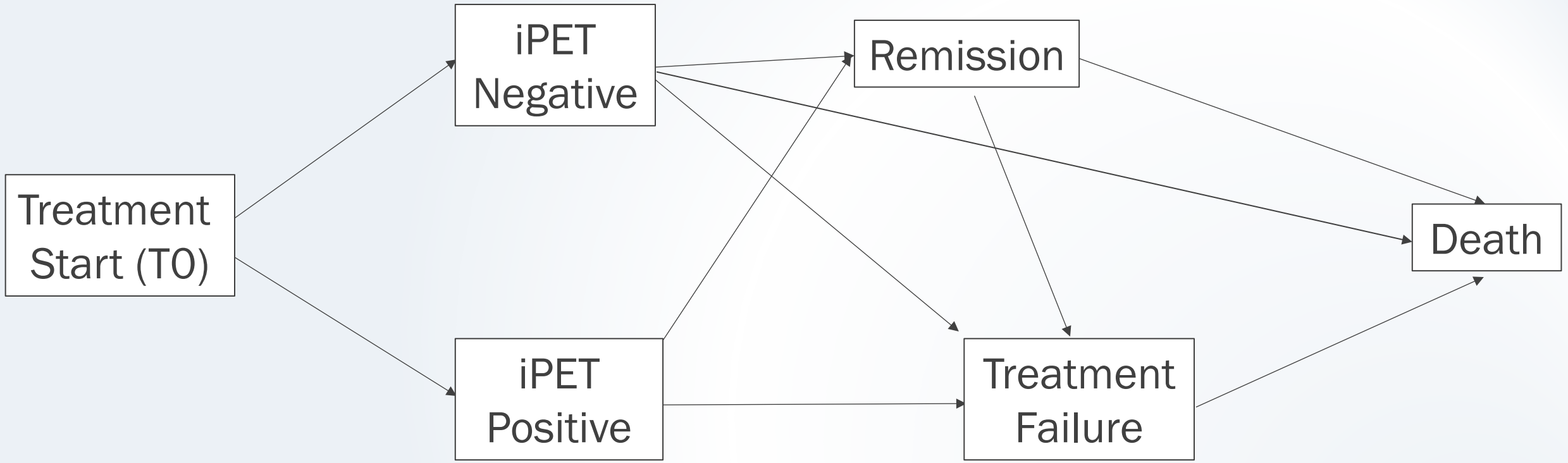
A-HIPI: identification of risk groups and creation of an online tool



Maurer M et al. *Blood Advances,* 2025

Chen R and Gordon LI. Blood Advances (commentary)

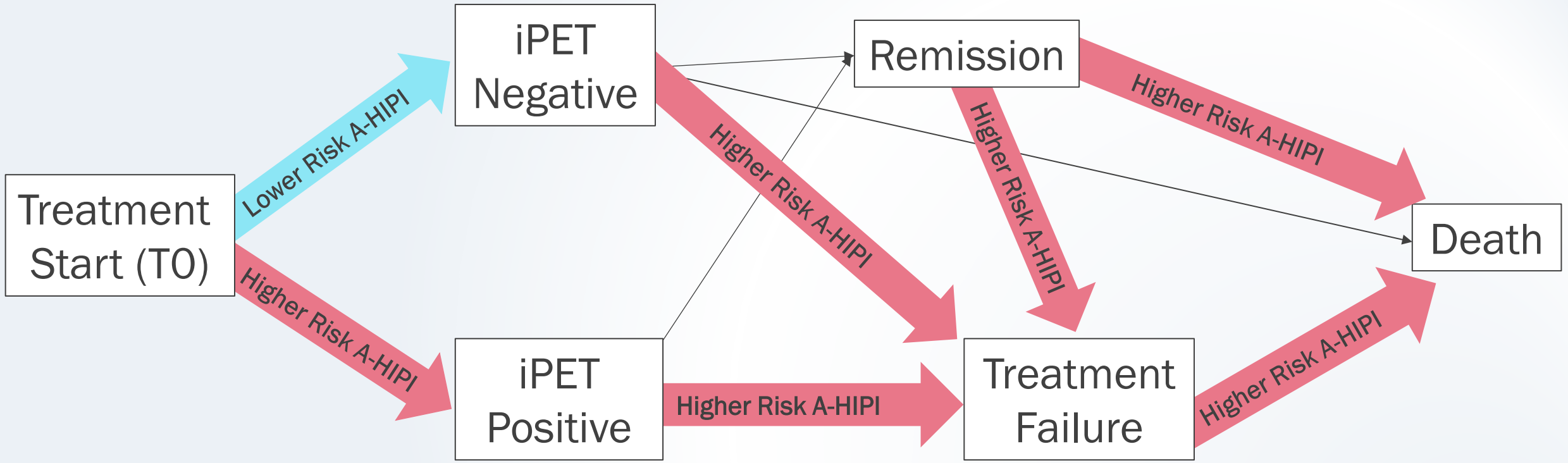
What is impact of baseline A-HIPI across disease course?



Highlighting relationships with $p<0.1$

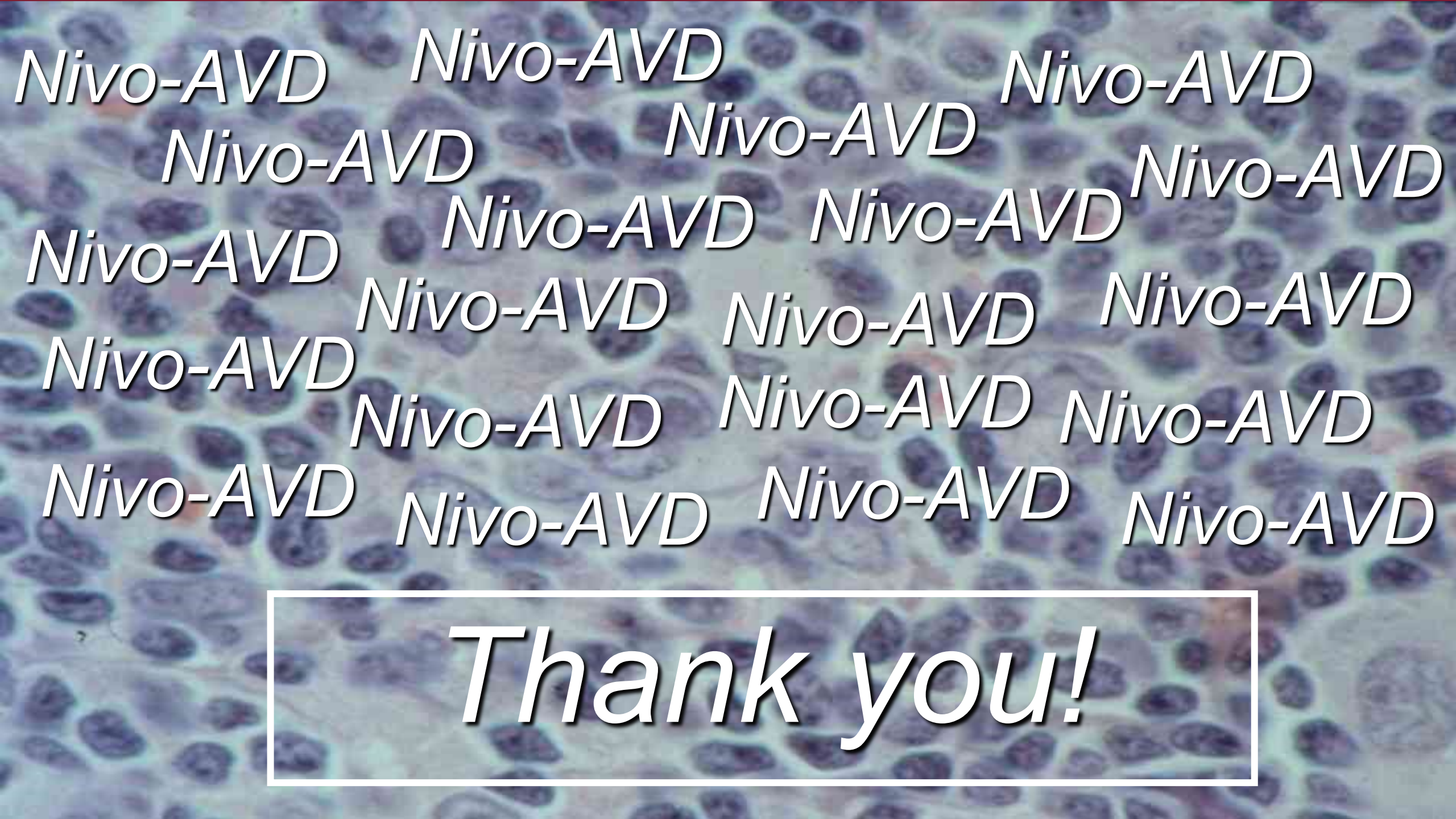
(Rodday et al ASH 2024)

Baseline A-HIPI is prognostic across disease course



Highlighting relationships with $p<0.1$

(Rodday et al ASH 2024)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Thank you!