



Multidisciplinary Approaches to Cancer Symposium

Advanced-Stage Hodgkin Lymphoma: What's Changed for Frontline Therapy

Azra Borogovac, MD, MS
Assistant Clinical Professor
Division of Lymphoma
City of Hope

Disclosures

- Kite Advisory Board, Prior Speakers Bureau for Janssen

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.



Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

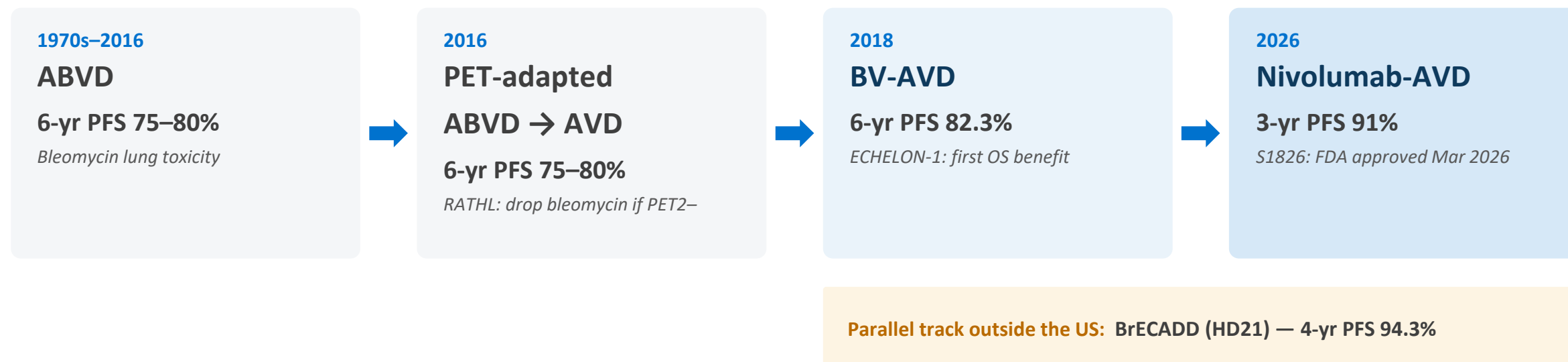
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Will provide demographics of hodgkin lymphoma including any challenges to treatment or access based on race or ethnicity.*
- *Implicit bias for older patients to receive chemotherapy for lymphoma.*

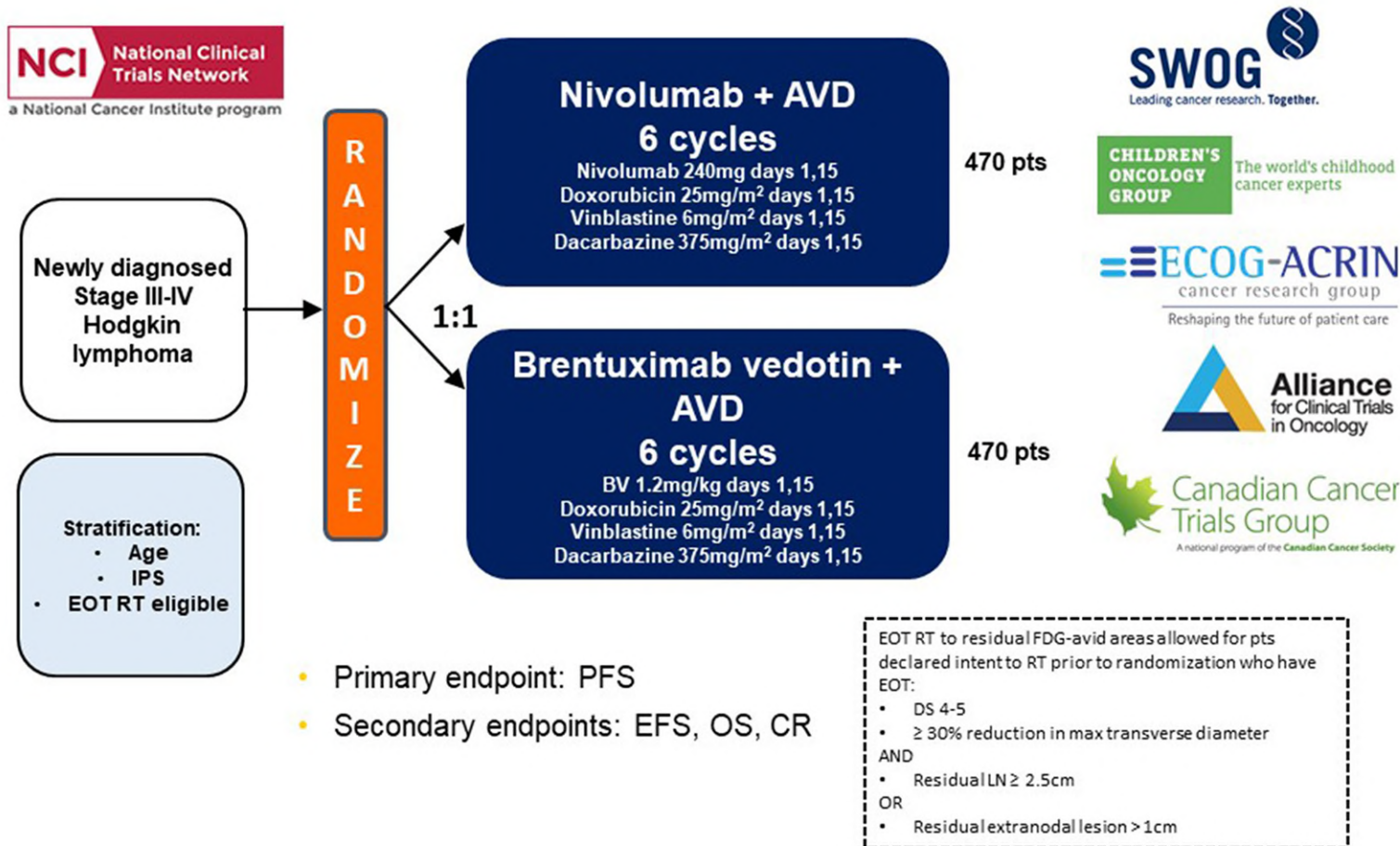


Evolution of frontline therapy in advanced-stage cHL



Each step has traded toxicity, not just efficacy. Nivolumab-AVD is the first step that improved both.

S1826: A Phase III Randomized Trial of Nivolumab (Opdivo) or Brentuximab Vedotin (Adcetris) Plus AVD in Patients (Age ≥ 12 Years) With Newly Diagnosed Advanced Stage Classical Hodgkin Lymphoma



SWOG S1826 — study design

Open to age ≥ 12

first NCTN trial to enroll adolescents and adults together

Six cycles, both arms

no PET-adapted change in therapy

Nivolumab 240 mg d1, d15

3 mg/kg if < 40 kg

G-CSF optional with N-AVD

mandated with BV-AVD

End-of-treatment RT

only for residual FDG-avid disease, pre-declared

A pragmatic design: fixed duration, no PET-driven escalation, and the populations usually excluded were let in.



Who was actually enrolled

- 994 patients randomized 1:1
- 24% adolescents age 12–17
- 10% age ≥ 60
- 60–65% stage IV disease
- 32% IPS 4–7
- 26–32% bulky disease
- Included patients with HIV on ART, CD4 ≥ 200

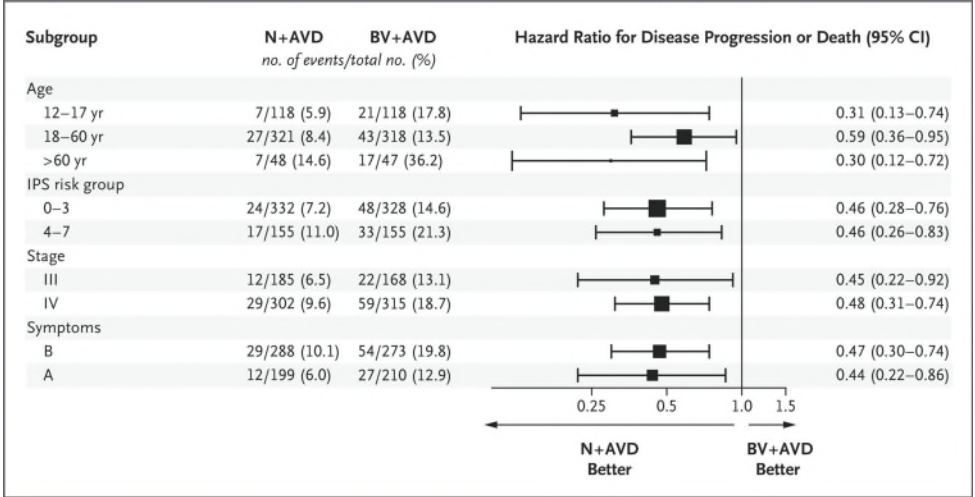
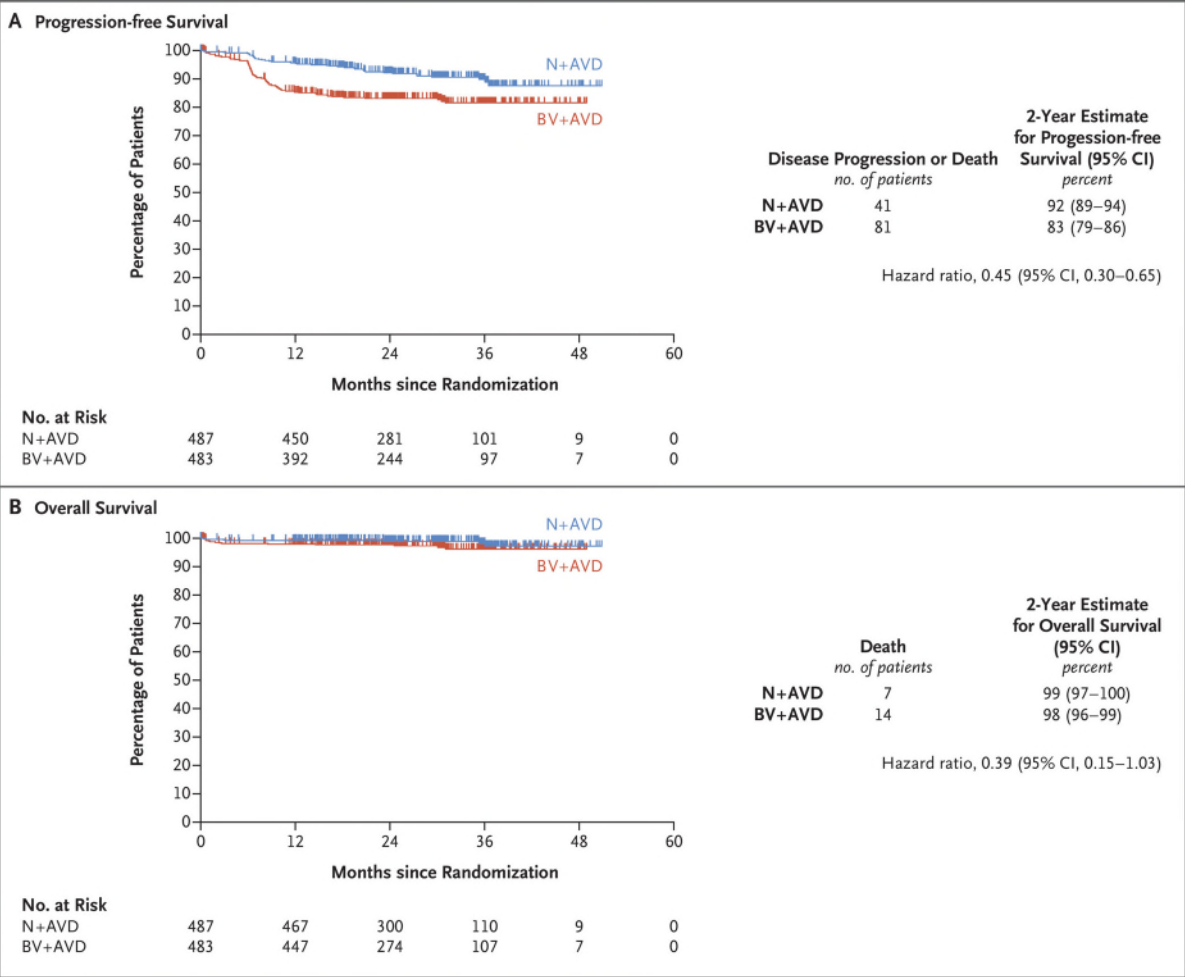
This is a high-risk, all-comers population that looks like the clinic patients we see

Herrera AF, et al. N Engl J Med 2024;391:1379-1389

Table 1. Characteristics of the Patients at Baseline (Modified Intention-to-Treat Population).*		
Characteristic	N+AVD (N = 487)	BV+AVD (N = 483)
Age		
Median (range) — yr	27.6 (12.0–83.7)	26.8 (12.0–81.7)
Distribution — no. (%)		
12–17 yr	118 (24)	118 (24)
18–60 yr	321 (66)	318 (66)
>60 yr	48 (10)	47 (10)
Female sex — no. (%)	216 (44)	210 (43)
Race or ethnic group — no. (%)†		
White	372 (76)	361 (75)
Black	58 (12)	56 (12)
Asian	11 (2)	17 (4)
Other or unknown	46 (9)	49 (10)
Hispanic	66 (14)	58 (12)
Disease stage — no. (%)		
III	185 (38)	168 (35)
IV	302 (62)	315 (65)
B symptoms present — no. (%)‡	288 (59)	273 (57)
IPS — no. (%)§		
0–3	332 (68)	328 (68)
4–7	155 (32)	155 (32)
Bulky disease — no. (%)¶	156 (32)	127 (26)
HIV-positive status — no. (%)	11 (2)	5 (1)



Primary results: PFS and OS



Consistent across every subgroup

- Age 12–17, 18–60 and > 60
- IPS 0–3 and IPS 4–7
- Stage III and stage IV
- A and B symptoms



Three-year follow-up: the separation holds

Subgroup	N-AVD	BV-AVD	Hazard ratio
Overall	91%	82%	—
Stage III	93%	86%	0.42
Stage IV	89%	80%	0.55
IPS 0–3	92%	84%	0.45
IPS 4–7	87%	77%	0.57

3-year progression-free survival by subgroup

Also at three years

- **Overall survival** 98% vs 97% (HR 0.48, p = 0.09)
- **Event-free survival** improved, HR 0.56
- **Deaths** 8 with N-AVD vs 15 with BV-AVD
- **Second cancers** 6 patients (1.2%) after N-AVD, mostly non-Hodgkin lymphoma vs 11 (2.3%) after BV-AVD
- **Safety** no new signals emerged



Safety: fewer toxicities to manage

N-AVD vs BV-AVD

Peripheral neuropathy

29% vs 56% *grade ≥3: 9% vs 32%*

Any-cause early discontinuation

7.6% vs 12%

Discontinued nivolumab or BV

9.4% vs 22.2%

Received G-CSF

56% vs 97% *optional with N-AVD*

Neutropenia

higher with N-AVD *without more febrile neutropenia*

Less neuropathy, fewer discontinuations, and far less growth-factor use.

Table 2. Adverse Events of Any Grade (Modified Intention-to-Treat Population).*		
Event	N+AVD (N = 482)	BV+AVD (N = 476)
	number (percent)	
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-cells 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)
Maculopapular rash	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)

* Shown are adverse events occurring in more than 10% of the patients in either group. Data reflect an information fraction of 70%. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

Adverse Event Type	N-AVD	BV-AVD
	n = 482	n = 476
	Grade ≥ 3	Grade ≥ 3
	No (%)	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%)



The new toxicity conversation: immune-related events

9%

Any immune-mediated event

2.7% grade 3–4

Baseline and on-treatment

- TSH every cycle or two
- LFTs, glucose each cycle
- HIV, HBV, HCV before cycle 1
- Baseline echo

What you will actually see

- **Thyroid** commonest; hypo more than hyper;
- **Hepatitis** transaminitis
- **Colitis** any new persistent diarrhea
- **Rash, arthralgia** usually low grade
- **Rare but lethal** myocarditis, pneumonitis, adrenal crisis, new diabetes with DKA

How to act on it

- Grade 1: continue, monitor closely
- Grade 2: hold, prednisone 0.5–1 mg/kg, taper over 4–6 weeks
- Grade $\geq$ 3: hold or stop, prednisone 1–2 mg/kg, involve the relevant specialist
- Events can begin weeks to months after the last dose

Remember patients are being treated for cure. Treat AEs early and minimize dose delays and discontinuations.

Patients age ≥ 60: the largest benefit in the trial

Prespecified subset: 103 patients age ≥ 60

89%

2-yr PFS with N-AVD
vs 64% with BV-AVD

96%

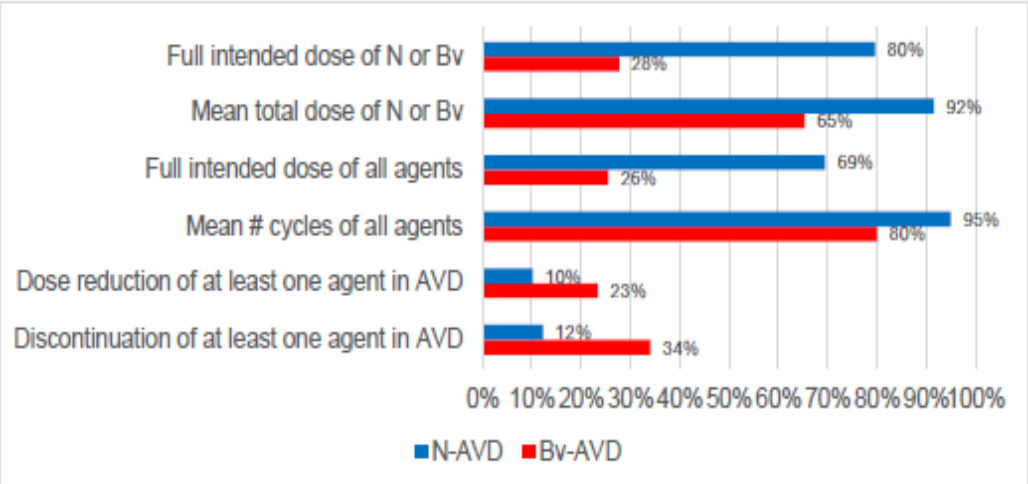
2-yr OS with N-AVD
vs 85% with BV-AVD

Why this matters in the community

- HR for PFS 0.24 -> the largest effect size in any subgroup
- Any-grade neuropathy 33% vs 68%; sepsis 6% vs 21%
- Fewer dose reductions and fewer discontinuations

Age alone is no longer a reason to de-escalate -> assess fitness, then treat with curative intent.

Can start with dose reduced AVD in borderline patients.



Fewer dose reductions/discontinuations

Table S4: Adverse events of interest

Toxicity	N-AVD N=49	Bv-AVD N=47	p-value ¹	N-AVD N=49	Bv-AVD N=47	p-value ¹
	Any grade N (%)	Any grade N (%)		Gr ≥ 3 N (%)	Gr ≥ 3 N (%)	
Febrile Neutropenia	6 (12%)	9 (19%)	0.41	6 (12%)	9 (19%)	0.41
Sepsis	3 (6%)	10 (21%)	0.038	3 (6%)	10 (21%)	0.038
Infections/Infestations ²	9 (18%)	16 (34%)	0.10	3 (6%)	10 (21%)	0.038

Toxicity	N-AVD N=49	Bv-AVD N=47	p-value ¹	N-AVD N=49	Bv-AVD N=47	p-value ¹
	Any grade N (%)	Any grade N (%)		Gr ≥ 2 N (%)	Gr ≥ 2 N (%)	
Peripheral sensory neuropathy	16 (33%)	32 (68%)	0.001	5 (10%)	24 (51%)	<0.0001
Peripheral motor neuropathy	4 (8%)	7 (15%)	0.35	0 (0)	4 (9%)	0.0537

¹Two-sided Fisher's exact test

²Toxicity category

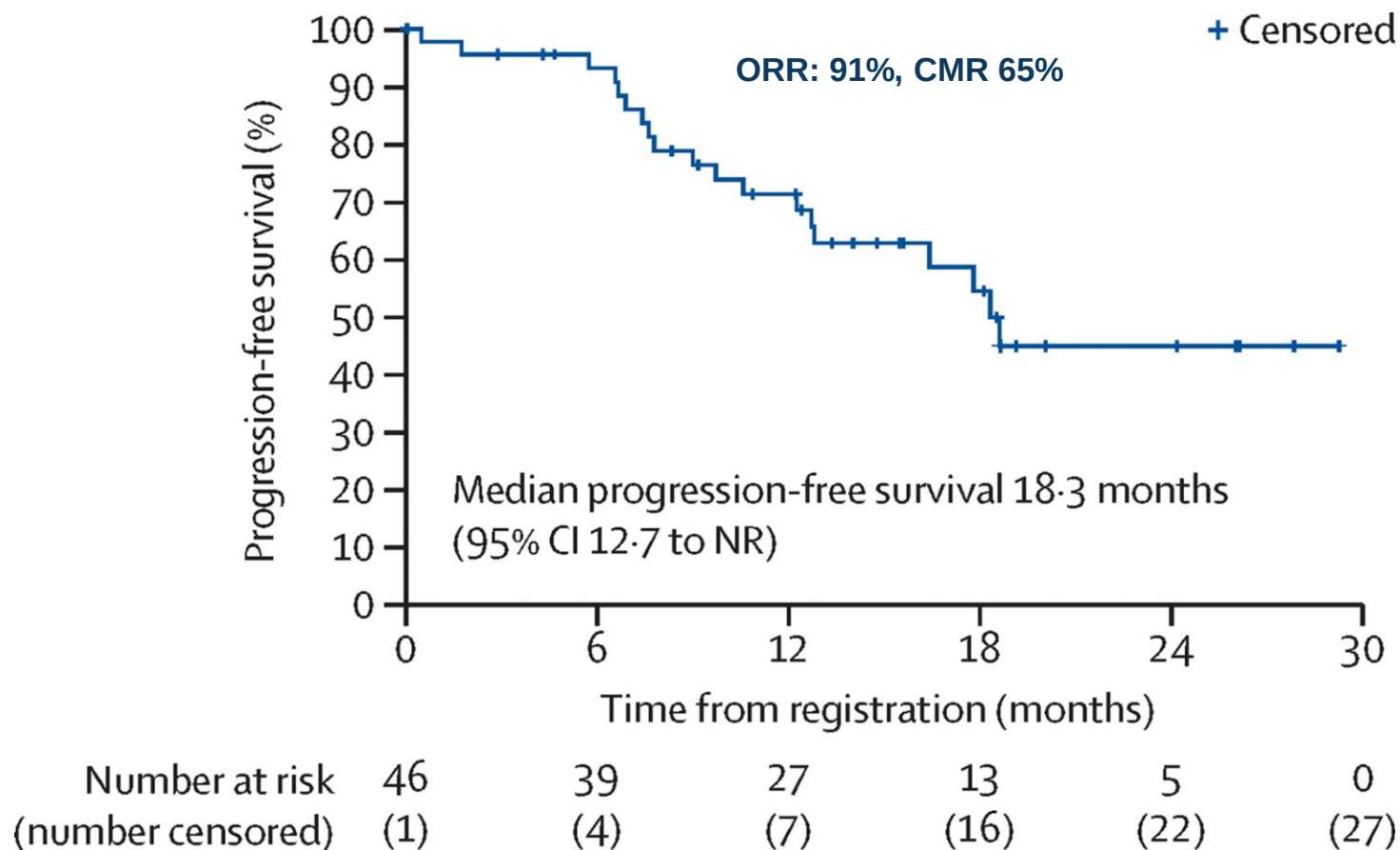
Fewer adverse events



Frail or chemotherapy-ineligible patients

- Phase 2 study evaluated BV-Nivo (q3 weeks) for 8 cycles in elderly/frail or chemo-ineligible patients.
- Included patients with stage I-IV disease
- Median age 71.5 (64-77), 33% with Stage II
- 30% had dose adj, primarily for NT

A reasonable chemotherapy-free option, but responses are not as durable, so treat fit older patients with N-AVD instead.



Response assessment: PET no longer drives the decision

What the S1826 imaging analysis showed

- Interim and end-of-treatment FDG-PET predicted 3-year PFS poorly in patients treated with N-AVD
- The trial was not PET-adapted: every patient received six cycles regardless of interim response
- Radiation was given to 0.6% of patients — residual FDG avidity was usually not acted on

What to do instead

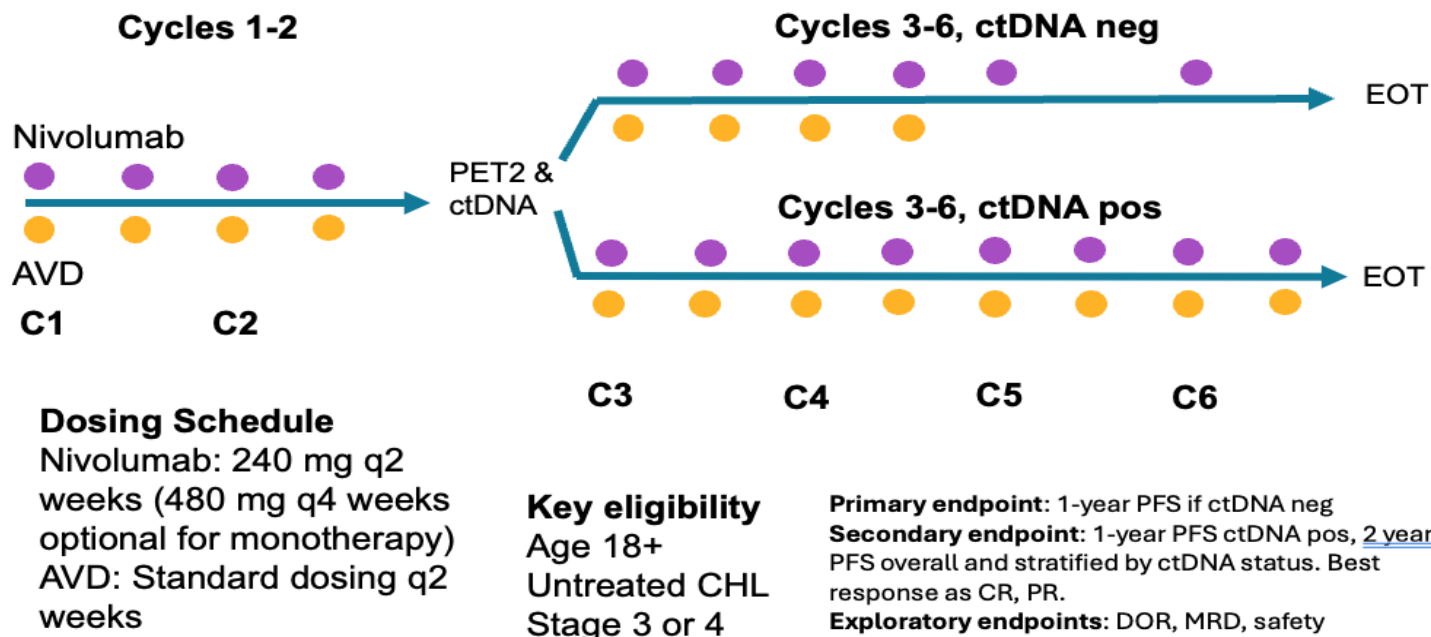
- Complete six cycles; Consider **NOT** doing an interim PET
- Deauville 4–5 at end of treatment: re-image in 6–8 weeks or biopsy before declaring refractory
- Consider immune-related flare, thymic rebound and reactive nodes as alternative explanations
- No routine surveillance PET after complete response

A patient with a Deauville 4 end-of-treatment PET after N-AVD is far more likely to be cured than refractory. Biopsy or get a short interval follow-up scan before starting to salvage.

PRECISE-HL study- ctDNA based de-escalation

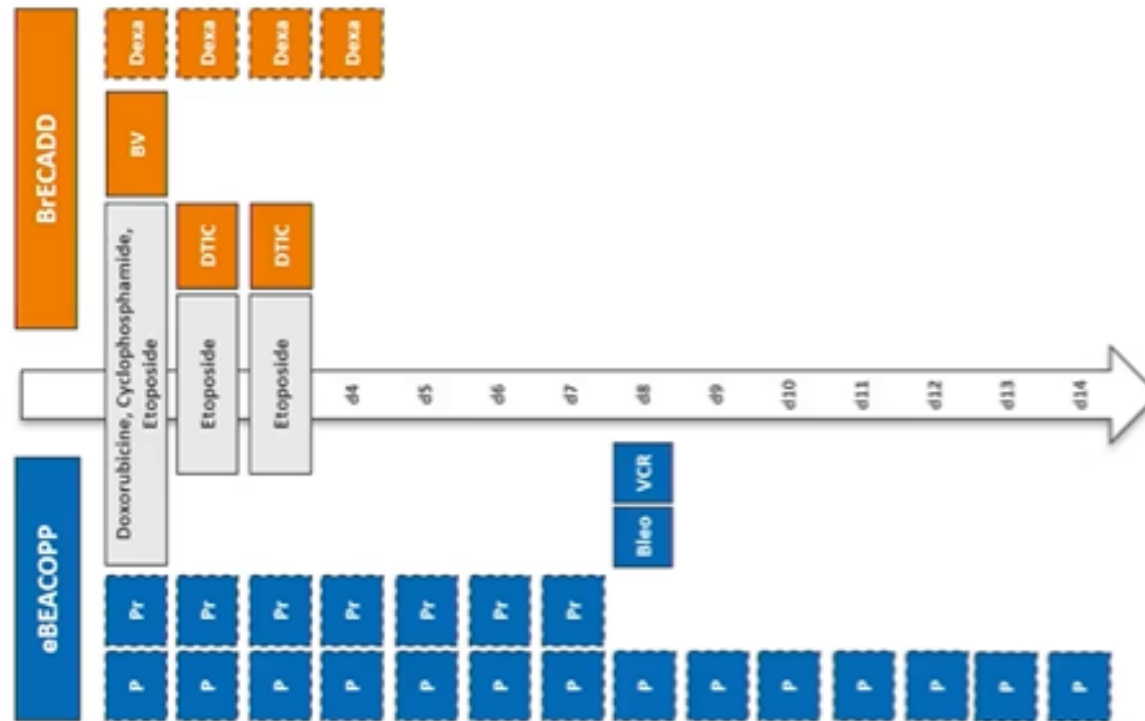
ctDNA is a better predictor than PET

- Multiple studies using ctDNA with the PhasedSeq platform have demonstrated that MRD is a better predictor of PFS than PET in Hodgkin lymphoma.
- PRECISE-HL is a ctDNA adaptive study that will determine if we can de-escalate chemotherapy based on MRD negativity after C2.
- Plans to include early stage II unfavorable are also underway.



Currently open and enrolling in multiple US sites including City of Hope, but must refer prior to C1D1.

GHSB HD21 The BrECADD regimen



The Kairos backbone with **doxorubicin, cyclophosphamide, etoposide** was retained and **brentuximab vedotin** added.

Problematic drugs were removed with the aim to improve acute and long-term tolerability:

- **Bleomycin** (pulmonary toxicity)
- **Vincristin** (neurotoxicity)
- **Procarbazine** (gonadal and genotoxicity)
- **14 days of Prednisone** (infection risk)

Resulting in a less complex protocol suitable for outpatient treatment.



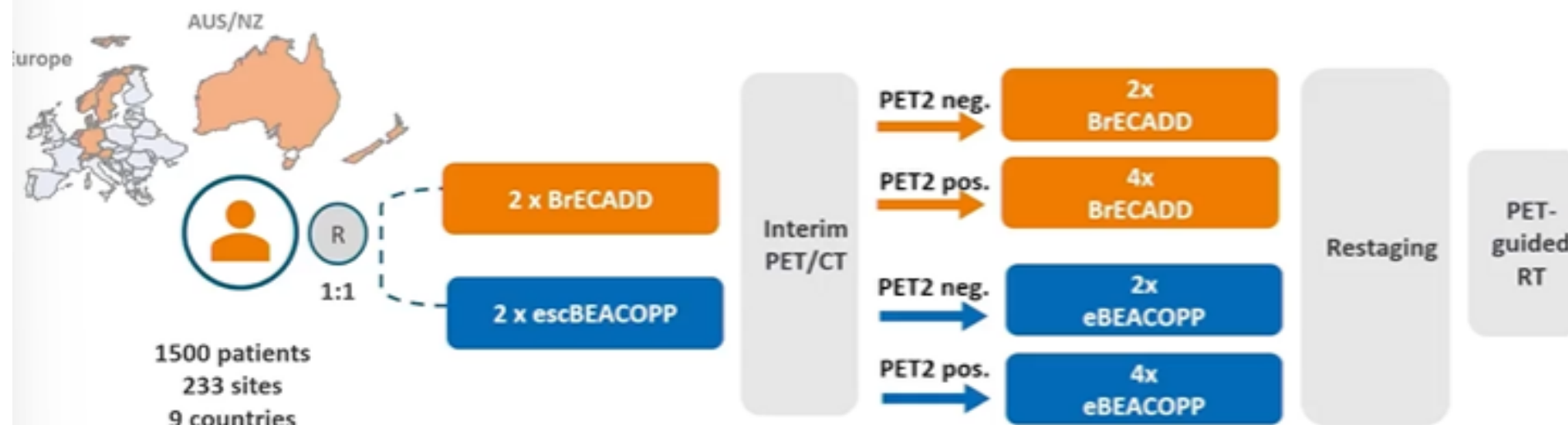
Borchmann et al, Lancet, 2024

BV administration on d0 as recommend by GHSB

The BrECADD regimen was built to reduce long-term toxicity: bleomycin, vincristine, procarbazine and 14 days of prednisone all removed.

GHSB HD21 study design and primary endpoints

Randomized, open-label, Phase 3 trial of BrECADD versus eBEACOPP in patients with newly diagnosed AS-cHL



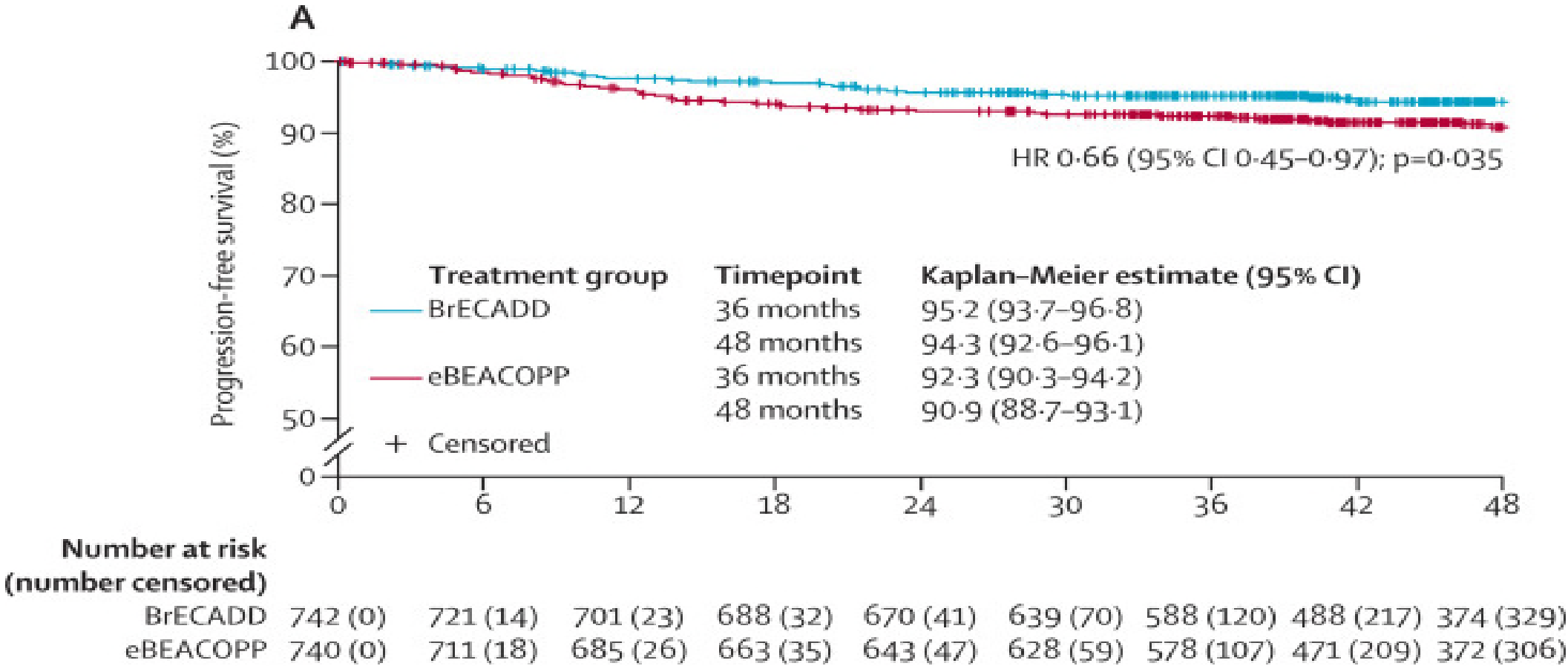
Co-primary objectives:

- Demonstrate better acute tolerability, i.e. reduced treatment-related morbidity (TRMB) with BrECADD .
- Demonstrate non-inferior efficacy of BrECADD in terms of PFS



PET-guided: most patients finish after 4 cycles, and radiation is reserved for residual FDG-avid disease.

GHSB HD21 Progression Free Survival



4-year PFS 94%, the highest reported in advanced cHL! Less gonadal toxicity than eBEACOPP, but it is not the US standard and demands more upfront support.



Choosing frontline therapy in 2026

Nivolumab-AVD

Almost everyone, age ≥ 12

- 3-yr PFS 91%
- Best data in age ≥ 60 and IPS 4–7
- Least neuropathy
- Needs immune toxicity monitoring

BrECADD

Young, fit, wants the shortest course

- 5-yr PFS 94%
- Usually 4 cycles, PET-guided
- Less gonadal toxicity than eBEACOPP
- Not the US standard; more upfront support

BV-AVD

When PD-1 blockade is contraindicated

- 6-yr PFS 82%, OS benefit shown
- Mandatory G-CSF and PJP prophylaxis
- Neuropathy is the limiting toxicity

ABVD

Access or cost dominates the decision

- 6-yr PFS 75–80%
- No longer a standard option for advanced stage HL

Nivolumab+AVD is now the standard → the other three can be considered if there are specific reason not to use Nivolumab.

Relapse after frontline PD-1: a new problem

No standard current standard exists for relapsed disease

- Relapse should always be proven with biopsy; then refer early for transplant
 - PD1 blockade prior to transplant helps “prime” the cells and improves transplant outcomes.
- A PD1 salvage regimen may be considered ([Pembro-GVD](#), [BV-Nivo](#))
- If patients relapse <3 months, can consider BV based regimen (ie. [BV-ICE](#))

What we still do not know

- How well PD-1 retreatment works specifically after frontline nivolumab
- Real World Evidence will be highly informative
- Whether autologous transplant is still required for every patient who achieves a complete metabolic response on immunotherapy-based salvage
- Currently different transplant-free approaches are being investigated under trial

Only about 1 in 10 patients will relapse → consult a lymphoma subspecialist to help make decisions on next line of therapy

Where disparities show up in Hodgkin lymphoma

1 · DIAGNOSIS

Later stage, later care

- Hispanic and black patients more often diagnosed at advanced stage
- **Insurance:** uninsured and Medicaid patients present with more stage IV and B symptoms, and have about twice the risk of death vs private insurance
- Gaps in Medicaid coverage before diagnosis are linked to later stage

2 · TREATMENT

Insurance is not enough

- **NY Medicaid, age ≤ 39 :** Black patients had a 58% higher risk of death than White patients with the same coverage
- **Where care happens:** treatment outside an NCI-affiliated center, HR 2.71 for HL death
- Uneven access to novel agents, radiation

3 · CLINICAL TRIALS

Who gets studied

- **Black patients:** 2.8% of lymphoma trial enrollees vs 10.7% of cases
- **Hispanic patients:** 5.4% vs 17.1%
- **Older adults:** excluded by age from 25% of phase 2–3 trials, and by other criteria from another 54%

4 · SURVIVORSHIP

Cure is not the finish line

- **AYAs (15–39) and adults > 55** have inferior outcomes compared with other ages
- Unequal access to long-term follow-up for cardiac, thyroid and second-cancer risk
- Financial toxicity and psychosocial burden fall hardest on AYAs and uninsured patients

In Hodgkin lymphoma, the most prominent barrier to cure is access to the standard therapies.



Closing the gaps: what a community practice can do

1 · DIAGNOSIS

Shorten the path

- Fast-track biopsy for a young adult with persistent adenopathy or B symptoms
- Financial counselor at the first visit: screen insurance, protect Medicaid continuity
- Professional interpreter from the first visit, not family members

2 · TREATMENT

Same regimen for everyone

- Co-manage with a lymphoma center by e-consult or tumor board, so no one has to move for care
- Prior-authorization and co-pay assistance
- Geriatric assessment (G8 or CARG), not age, to decide intensity
- Plan transport

3 · CLINICAL TRIALS

Ask everyone

- Check for an open trial at every new diagnosis, and at every relapse
- Offer trials to every eligible patient, not only the 'easy' ones

4 · SURVIVORSHIP

Hand off the whole plan

- Treatment summary with cumulative anthracycline dose and any radiation fields
- Follow COG long-term follow-up guidelines for AYAs; transition to adult care deliberately
- Fertility referral before cycle 1: California law (SB 600) requires coverage for all state regulated insurance plans (Medi-Cal is excluded)

Measure internal data: The practices that close these gaps, are the ones that track their own data by race, insurance and age.



Five take-away points

1

Nivolumab-AVD is the frontline standard for stage III–IV cHL, age $\geq$ 12

3-year PFS 91% vs 82%; FDA approved 20 March 2026; NCCN lists it among preferred regimens

2

The PFS benefit holds across all populations

Stage IV, IPS 4–7, age $\geq$ 60 (2-yr PFS 89% vs 64%), adolescents, and patients with HIV

3

Interim PET no longer needed

Six cycles regardless; residual FDG avidity needs re-imaging or biopsy before you call it refractory

4

No standard salvage regimens for relapsed disease

Pembro-GVD, BV-ICE, and BV-Nivo are reasonable salvage options. Refer to transplant early.

5

The biggest barrier to curing patients now is access

Age should not preclude use of curative therapy with Nivo-AVD. Offer all patients clinical trials when available. Connect all patients to survivorship resources.

Thank You

Aborogovac@coh.org

Cell: 949-844-1738

cityofhope.org

