HOW I EVALUATE AND TREAT PATIENTS WITH HODGKIN LYMPHOMA

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DISCLOSURES

Honoraria: Seattle Genetics

Discussion of off-label drug use: pembrolizumab and nivolumab

CLINICAL CASE

- A 25 year old with no medical conditions presents with fevers, chills, and a 10-lbs weight loss.
- Imaging shows diffuse adenopathy above and below the diaphragm.
- An excisional lymph node biopsy shows classic Hodgkin lymphoma, nodular sclerosis subtype.
- Labs demonstrate an elevated erythrocyte sedimentation rate and lactate dehydrogenase, but otherwise no cytopenias.
- PET scan shows no avidity in the bone marrow.

Which of the following treatments is associated with the best outcomes?

QUESTION

Which of the following treatments would you recommend that is associated with the best progression-free survival at 2 years?

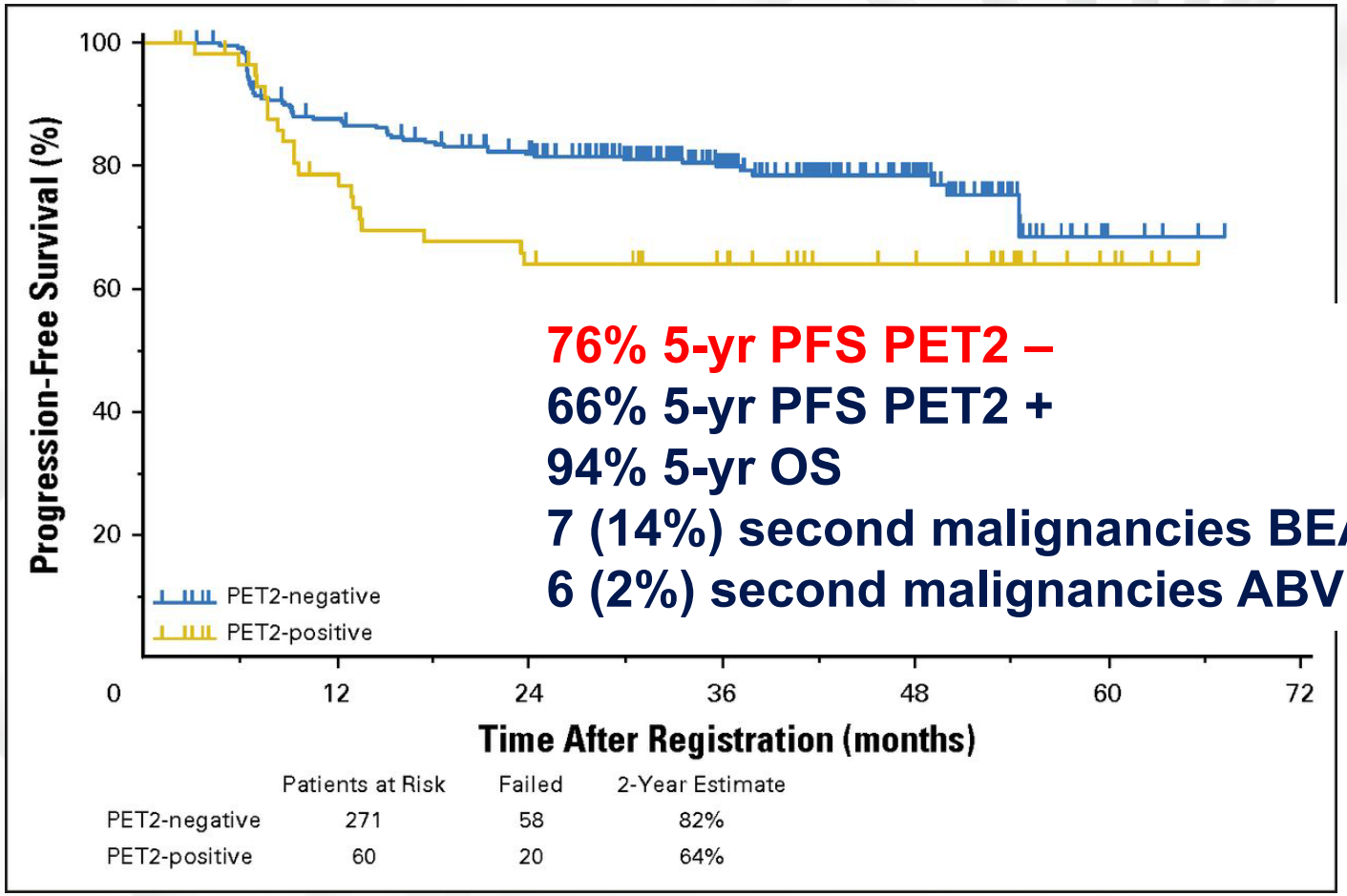
A. escBEACOPP x6
B. ABVD x 6
C. Brentuximab and AVD
D. Nivolumab and AVD

OBJECTIVES

- Discuss incorporation of novel agents into frontline therapy with AVD for advanced stage classic Hodgkin lymphoma
- Discuss updates for the Echelon-1 trial of Brentuximab and AVD.
- Discuss the emerging role of checkpoint blockade in the frontline setting.
- Discuss up and coming research for frontline Hodgkin lymphoma

LONG-TERM OUTCOMES OF PET-DIRECTED CHEMOTHERAPY IN STAGE 3-4 CL

SWOG 0816: A phase 2 study of escalation to BEACOPP following interim PET after ABVD



76% 5-yr PFS PET2 –
66% 5-yr PFS PET2 +
94% 5-yr OS
7 (14%) second malignancies BEACOPP
6 (2%) second malignancies ABVD

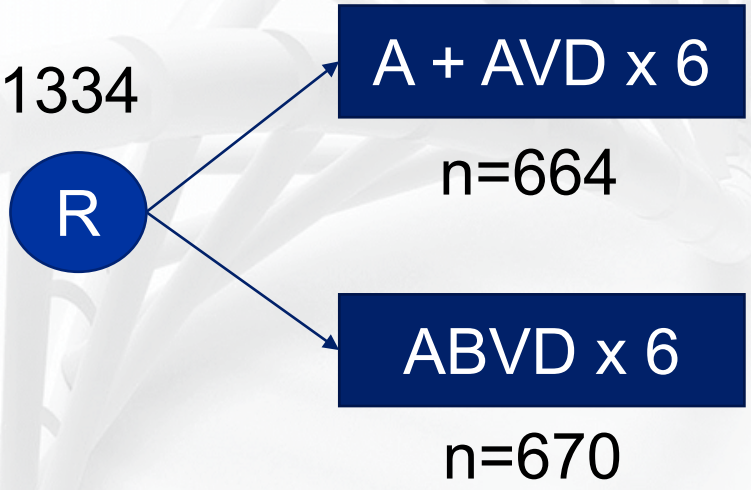
Stevens, et al. Blood, 2019 134 (15): 1238-1246

FRONTLINE BRENTUXIMAB TRIALS

ADVANCED STAGE: BRENTUXIMAB AND AVD

ECHELON-1 Randomized Phase 3 Clinical Trial

Inclusion Criteria:
Histologically confirmed classical Hodgkin lymphoma
Stage III-IV



Primary Endpoint: Modified PFS

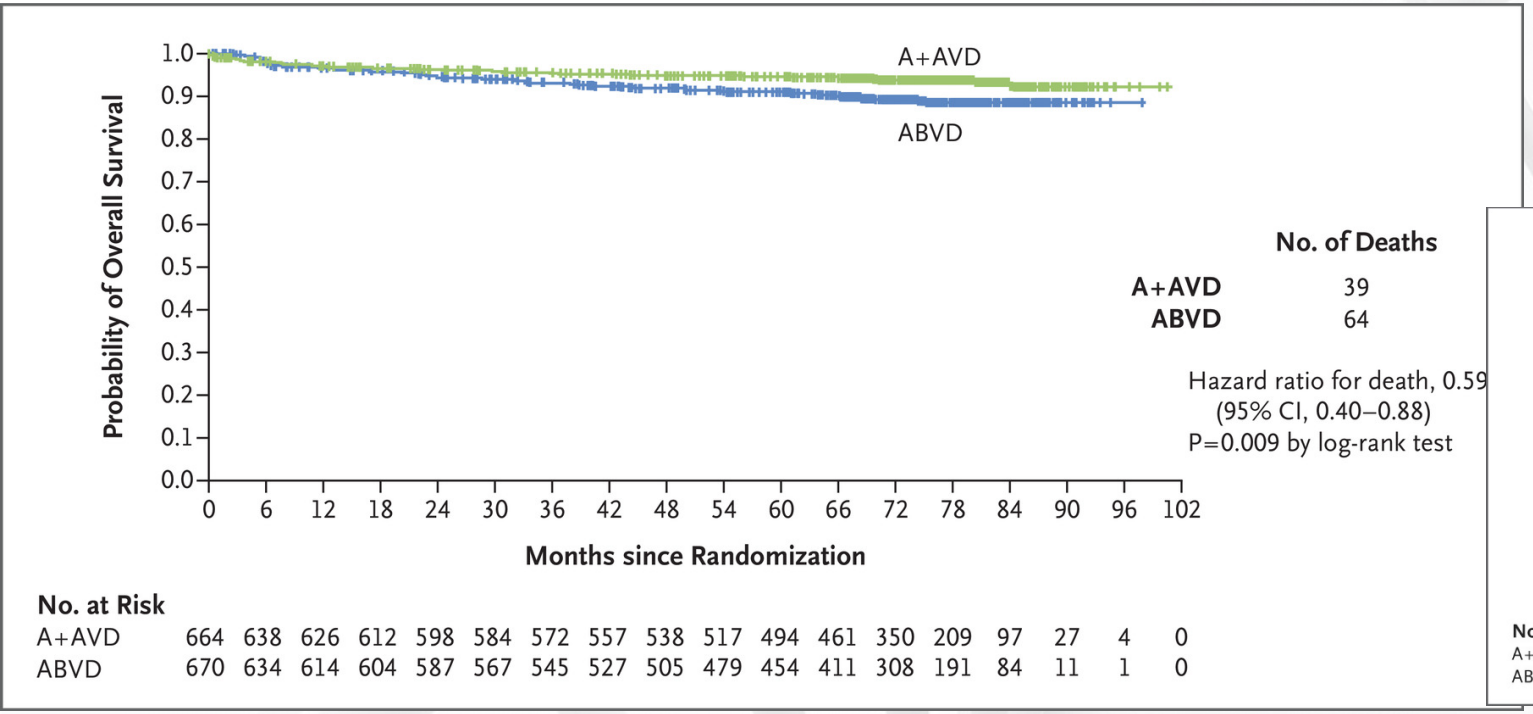
1. Progression
2. Death
3. Modified progression
   DV 3-5 followed by anti-cancer therapy

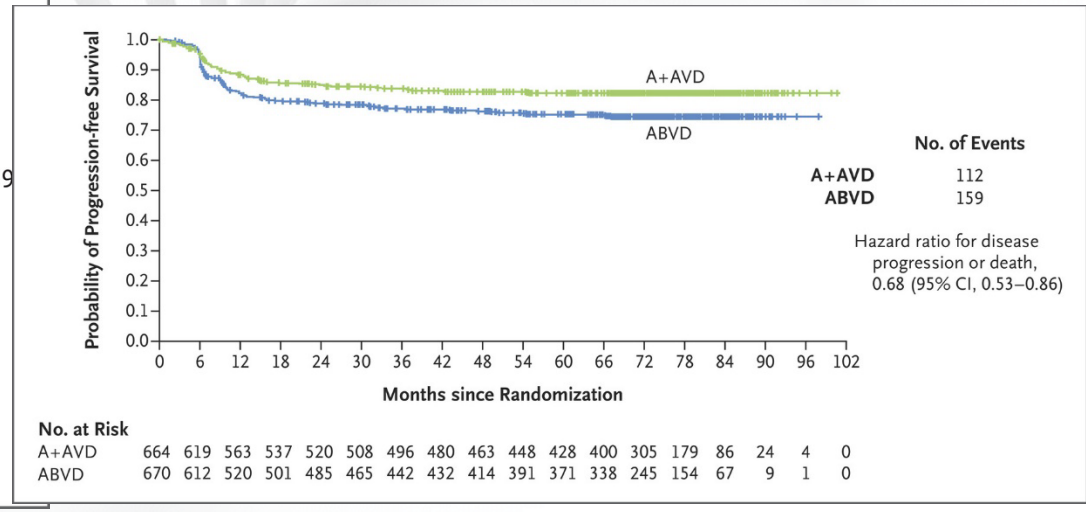
Key Secondary Endpoints: Overall survival

- PET2-negative (Deauville score, 1 to 3) or
- PET2-positive (Deauville score, 4 or 5)

Connors, et al. *N Engl J Med*. 2018;378:331-344

BRENTUXIMAB VEDOTIN- BASED THERAPY HAS AN OVERALL SURVIVAL BENEFIT





	A + AVD	ABVD
Overall Survival (6-yr)	**93.9%**	**89.4%**
PET2 negative	94.9%	90.6%
PET2 positive	95%	77%
Progression-free Survival (6-yr)	**82.3%**	**74.5%**

Ansell SM et al. NEJM, 2022; 387:310-320

TOXICITIES FROM A + AVD VERSUS ABVD

Key adverse events

Adverse Events (AE)	A + AVD	ABVD
> Gr 2 AE	83%	66%
Serious AE	43%	27%
Febrile neutropenia	21 (11*)%	8%
Peripheral Neuropathy	67 (26)%	43 (14)%
Pulmonary	2 (<1)%	7 (3)%
On-study Deaths	N=9	N=13

*G-CSF use

- More frequent, longer lasting, and more severe peripheral neuropathy
- Higher rates of febrile neutropenia

Connors, et al. *N Engl J Med*. 2018;378:331-344

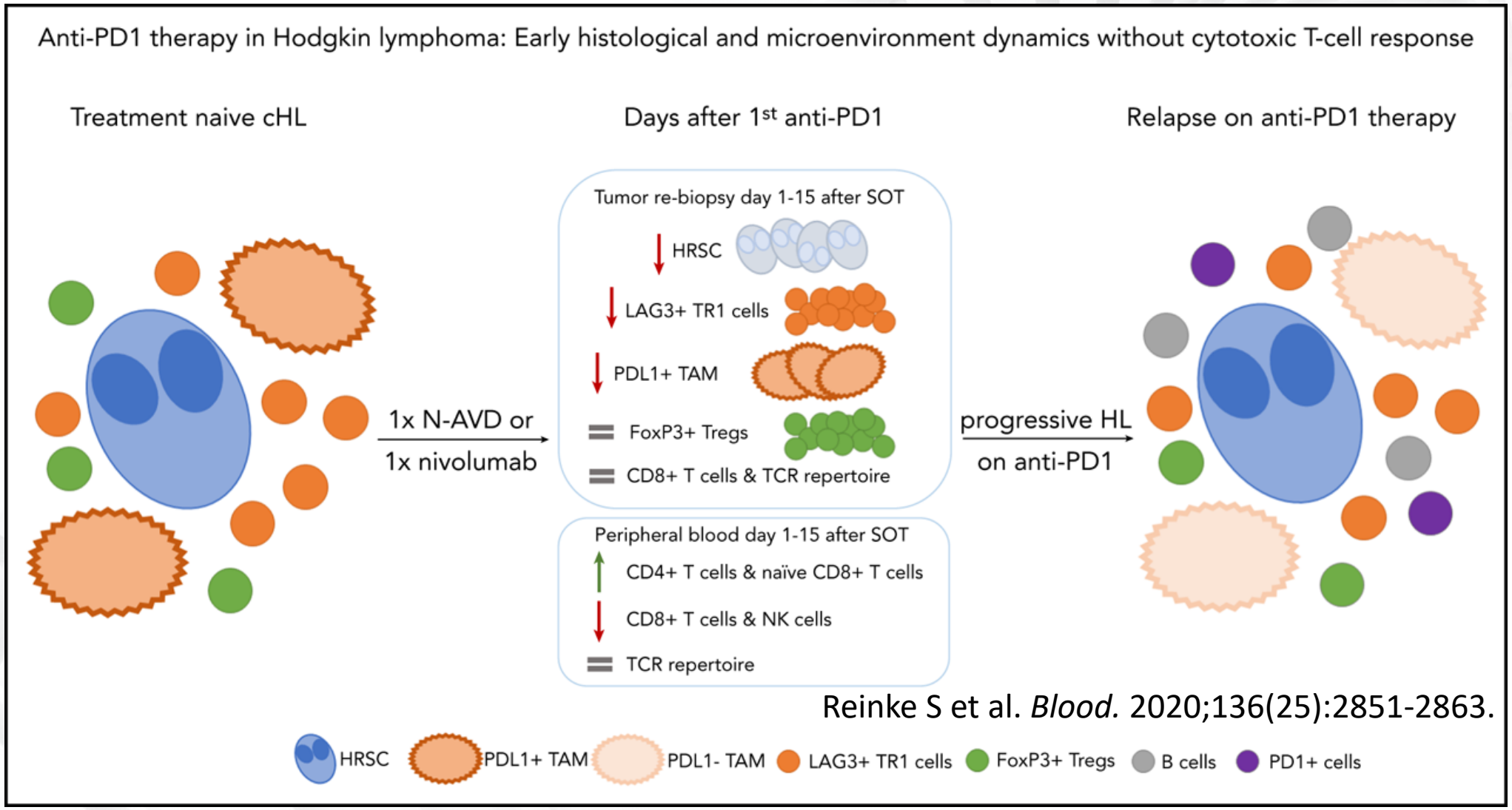
FRONTLINE PD-1 TRIALS

WHAT IS UNIQUE ABOUT CHECKPOINT BLOCKADE IN HODGKIN LYMPHOMA (HL)?

- Highest response rates among all malignancies
- Unique mechanism of action
  - Genetic predisposition (9p24.1 alterations)
  - Less likely immunologic

Chen et al, J Clin Oncol, 2017; Younes et al. The Lancet 2016; Armand JCO 2018;

ANTI-PD-1 DISRUPTS THE HODGKIN TME, BUT DOES NOT ACTIVATE AN IMMUNE CYTOTOXIC T-CELL RESPONSE.



Reinke S et al. *Blood.* 2020;136(25):2851-2863.

WHAT ARE THE DATA FOR PD-1 BLOCKADE FOR FRONTLINE HODGKIN LYMPHOMA?

Nivolumab

- Checkmate-205: Nivolumab + AVD (advanced stage)
- NIVAHL: Sequential vs. concurrent Nivolumab and AVD (early unfavorable)
- Concurrent N AVD vs. A AVD (S1826: Results presented at ASCO and Lugano as a plenary)

Pembrolizumab

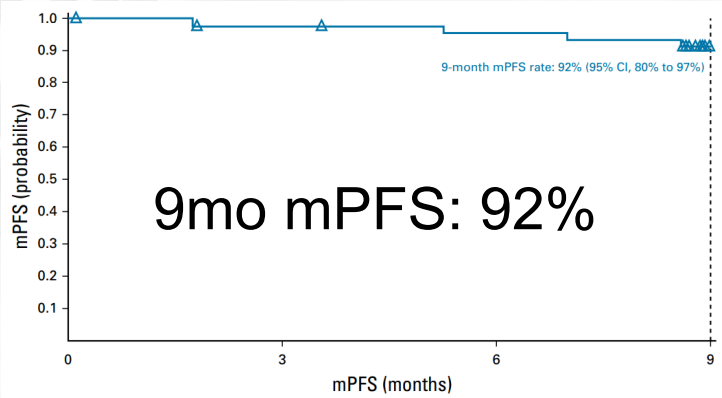
- Sequential pembrolizumab and AVD (early unfavorable or advanced)
- Concurrent pembrolizumab and AVD (early unfavorable or advanced)
- **KEYNOTE-C11:** Sequential pembrolizumab and AVD (early unfavorable or advanced)

INCORPORATING PD-1 BLOCKADE INTO INITIAL CHL THERAPY IS WELL-TOLERATED AND HIGHLY EFFECTIVE

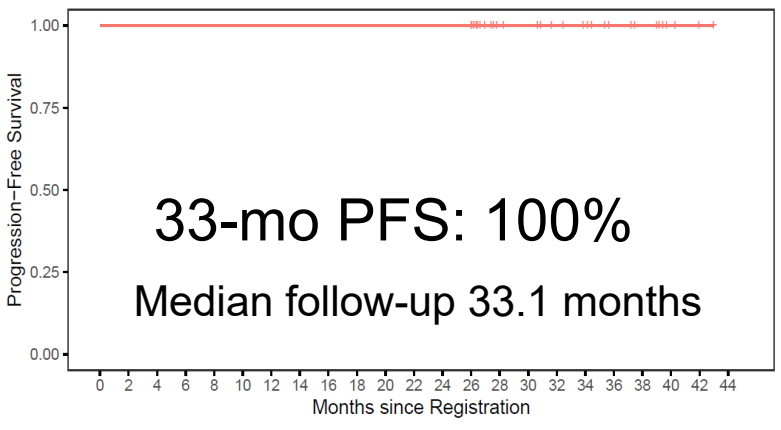
Studies of frontline PD-1 blockade in cHL have been promising[10,11,12,13]

- N-AVD well-tolerated
- Excellent PFS

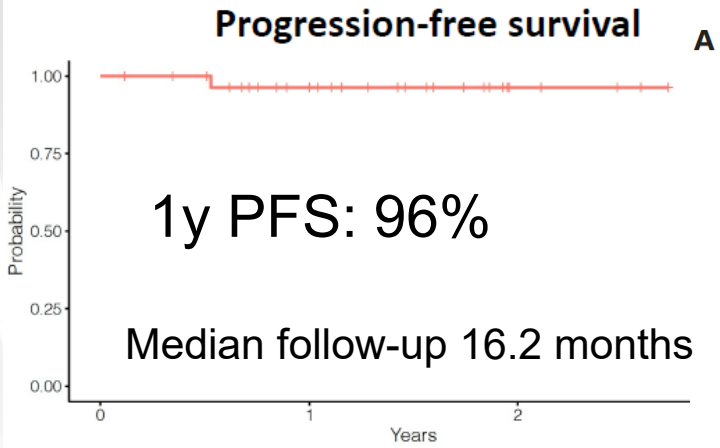
1L Nivolumab-AVD in advanced stage cHL



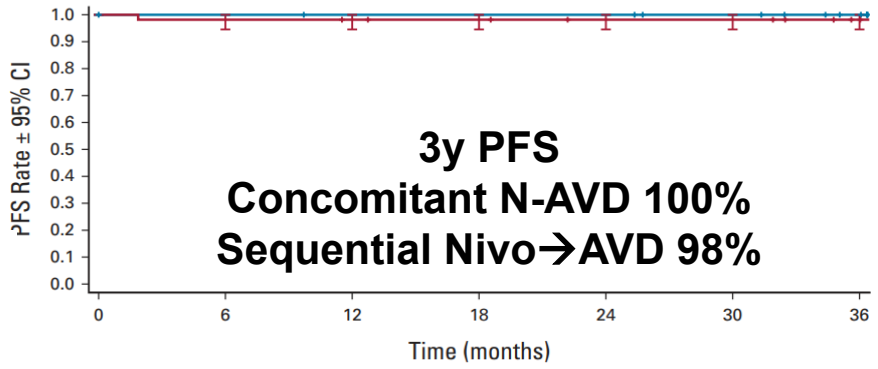
Sequential Pembro-AVD in cHL



Concurrent Pembro-AVD in cHL



1L Nivolumab-AVD in early stage cHL

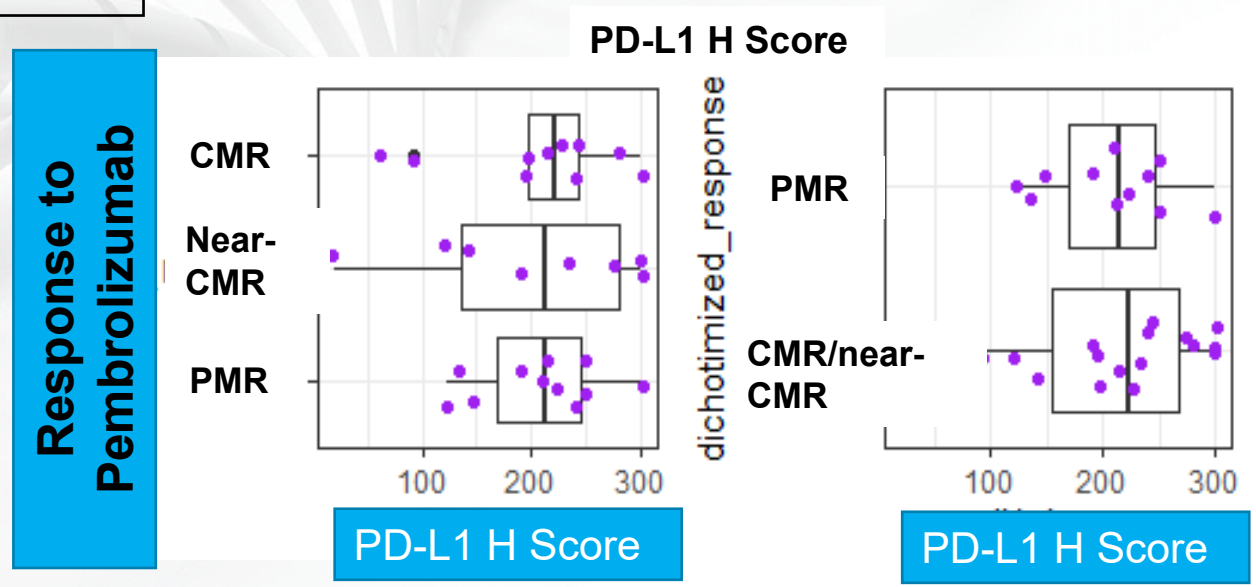


10. Bröckelmann PJ et al JCO. 2023 11. Ramchandren R et al JCO 2019 12. Allen PB, et al Blood. 2021 13. Lynch RC et al Blood 2023

NO CORRELATION BETWEEN PD-1 MARKERS AND RESPONSE

	CMR/near CMR (n=19)	PMR (n=11)	p-value
PD-L1 H score	221.5 (20.0-300)	213.0 (122.0-300)	>0.9
PD-L1 H score tercile			>0.9
PD-L2 H score	15.0 (0.0-180)	20.0 (0.0-135)	0.4
PD-L2 H score tercile			0.3
STAT 3 H score	300.0 (60.0-300)	300.0 (140.0-300)	>0.9
9p24.1 alteration			0.4
Polysomy or Copy gain	10 (59%)	4 (36%)	0.2
Amplification by ratio	7 (41%)	7 (64%)	

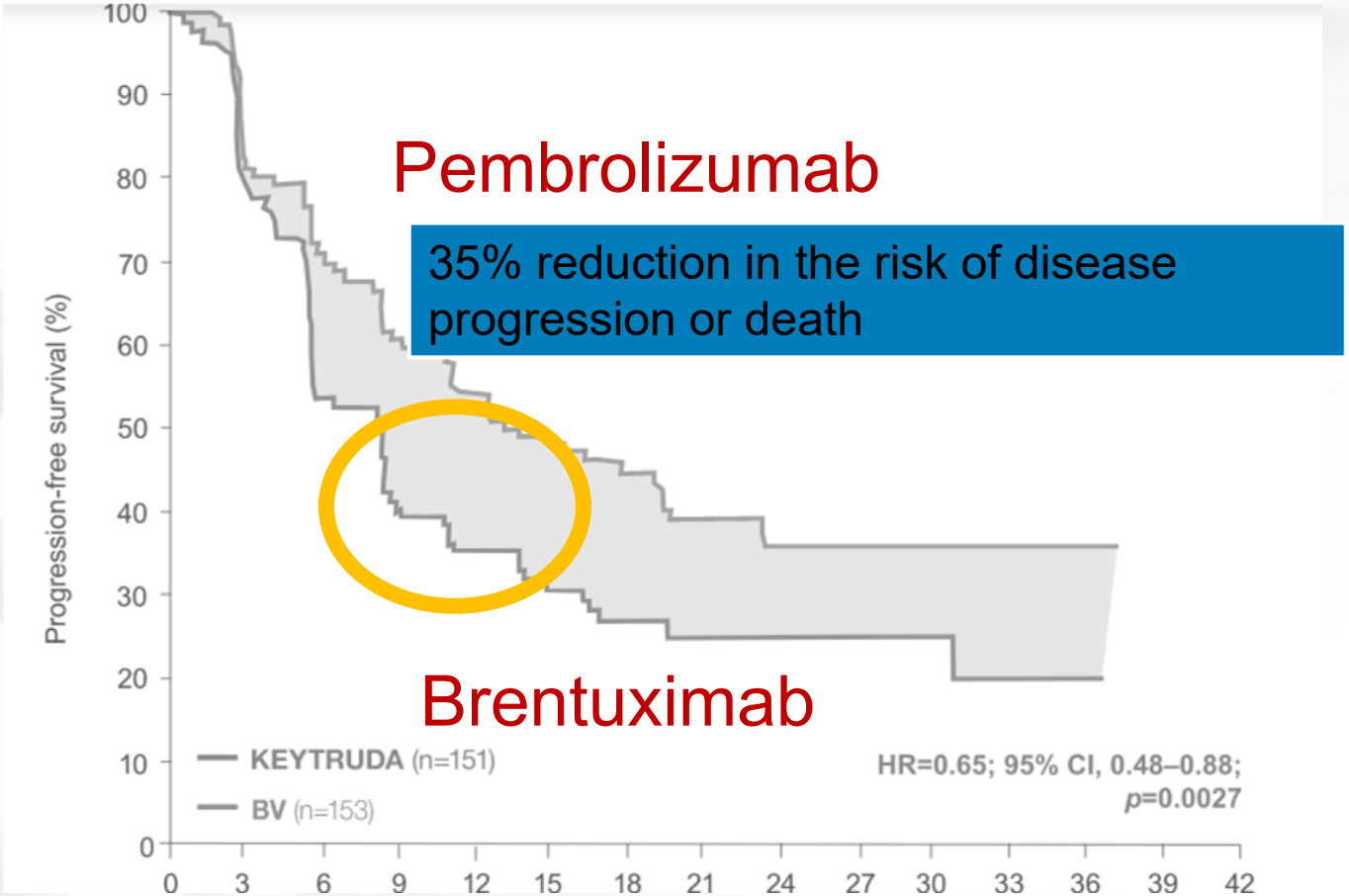
PD-L1 expression



Allen, PB… Winter LN et al. Blood Adv. 2022 Sep 9

PD-1 BLOCKADE IS SUPERIOR TO BRENTUXIMAB VEDOTIN

Kaplan-Meier Estimates of PFS in Pembrolizumab vs. Brentuximab (BV)



Kuruvilla Jet al. Lancet Oncol. 2021 Apr;22(4):512-524.

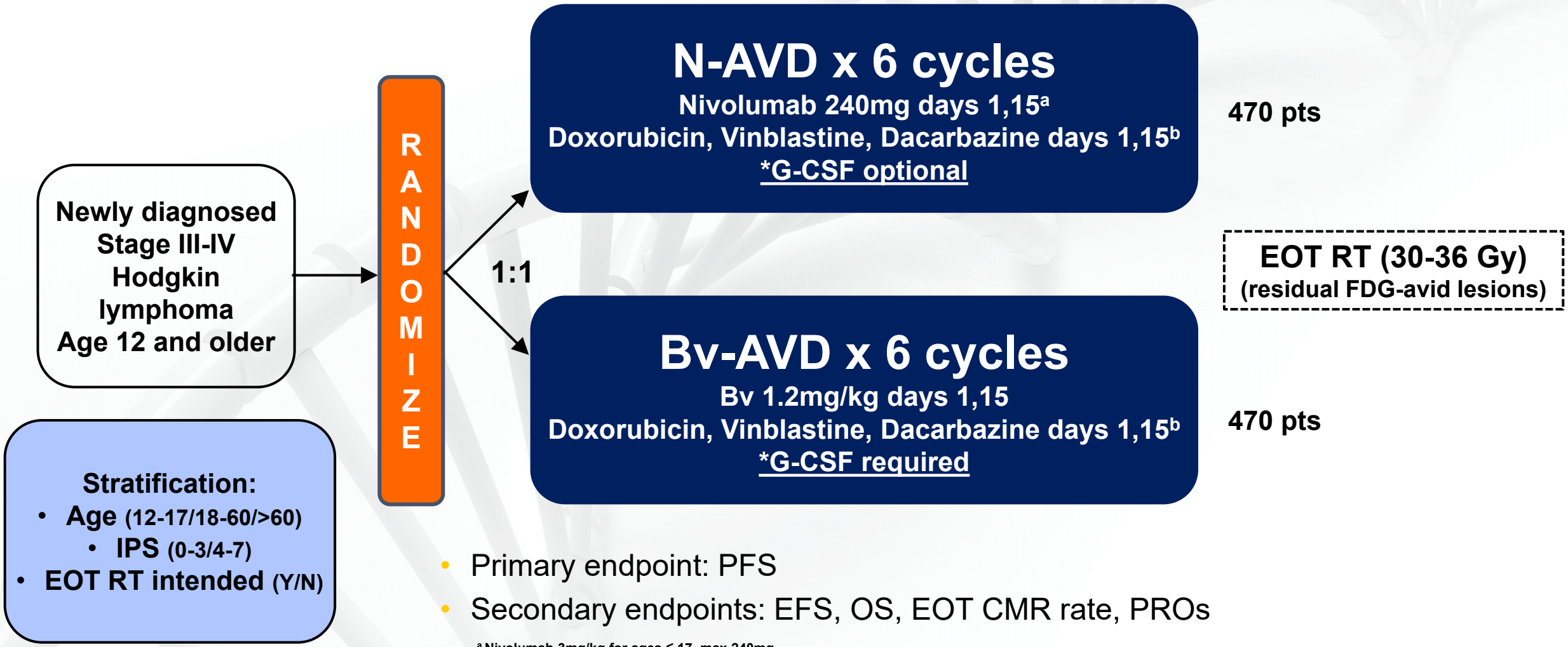
PEMBROLIZUMAB IS BETTER TOLERATED THAN BRENTUXIMAB

KENOTE 204 vs. Brentuximab

Adverse Events	Pembrolizumab (n=148)	Brentuximab vedotin (n=152)
Any TRAE	74.3%	77.0%
Gr 3-4	19.6%	**25.0%**
Hypothyroidism	15.5%	1.3%
Pneumonitis	10.8%	2.6%
Peripheral neuropathy	2%	**18.4%**
Nausea	4.1%	**13.2%**

Kuruvilla Jet al. Lancet Oncol. 2021 Apr;22(4):512-524.

S1826 STUDY DESIGN



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

[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

Slide Courtesy of Alex Herrera, MD

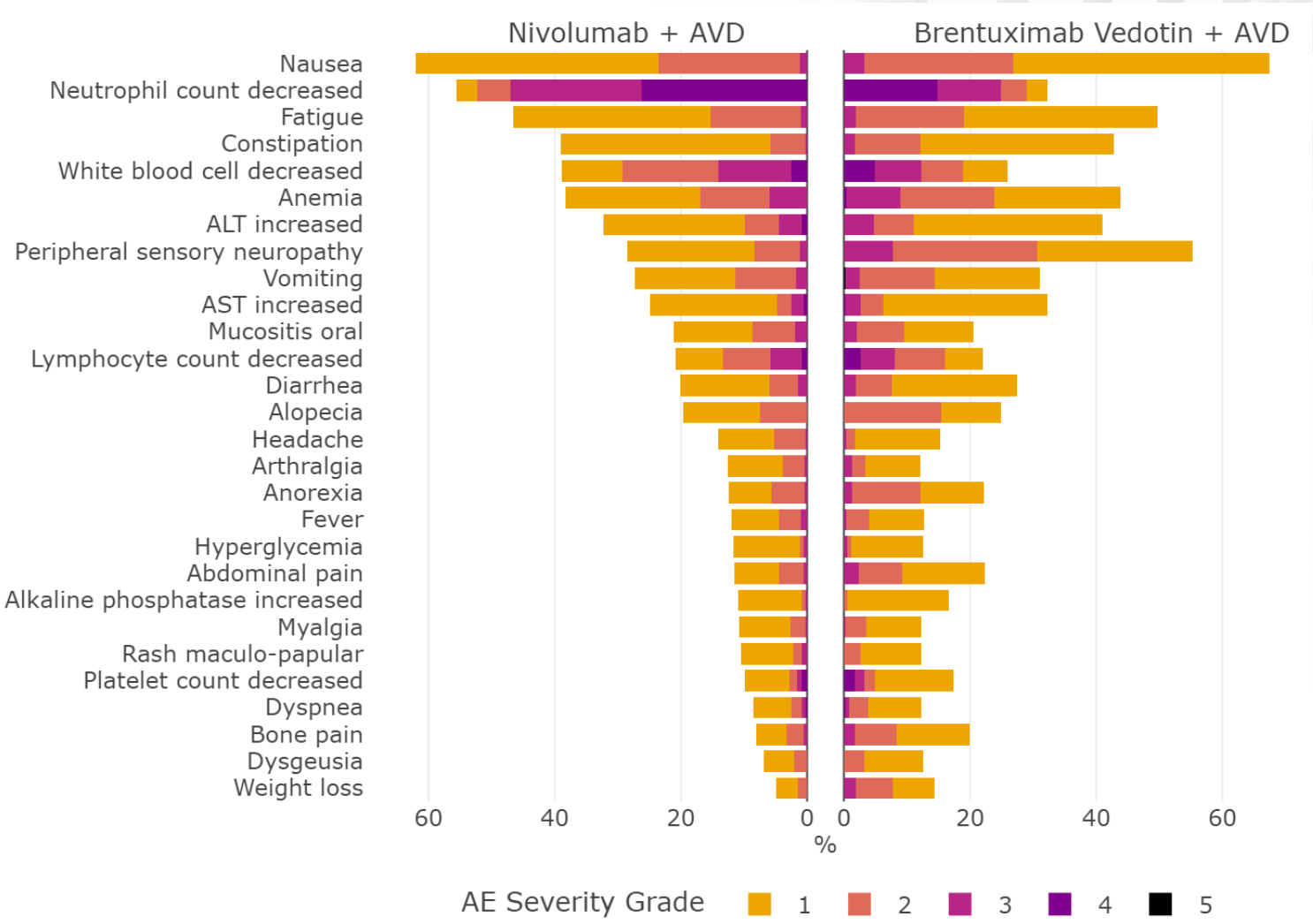
S1826 BASELINE CHARACTERISTICS

Baseline characteristics	N-AVD n=489 N (%)	Bv-AVD n=487 N (%)
Age, median (range)	27 (12-83)	26 (12-81)
12-17 years	120 (25%)	117 (24%)
18-60 years	323 (66%)	323 (66%)
≥ 61 years	46 (9%)	47 (10%)
Female Sex	218 (45%)	213 (44%)
Race		
White	375 (77%)	364 (75%)
Black	57 (12%)	56 (11%)
Asian	11 (2%)	17 (3%)
Other/Unknown	46 (9%)	50 (10%)
Hispanic	68 (14%)	59 (12%)

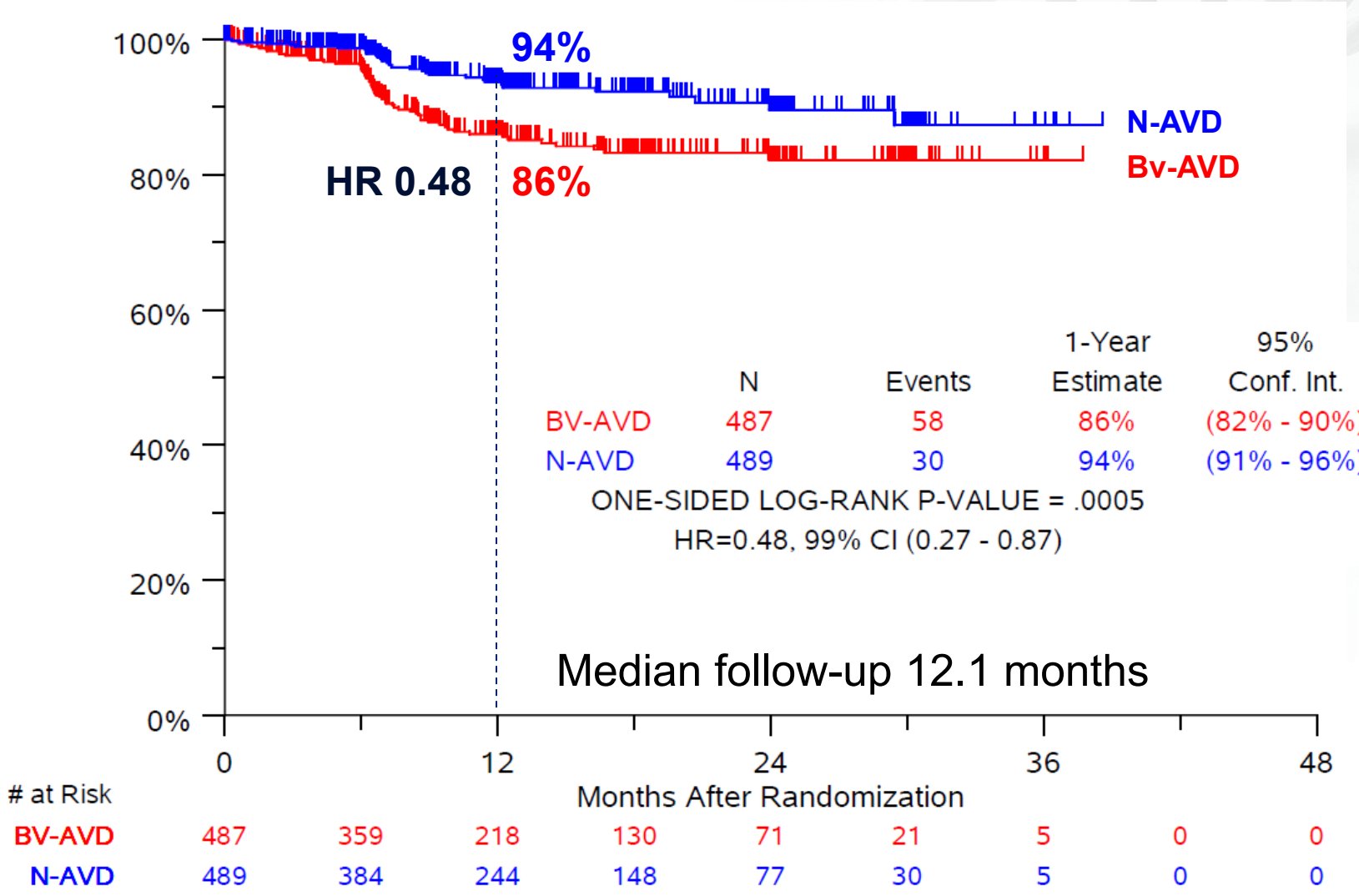
Baseline characteristics	N-AVD n=489 N (%)	Bv-AVD n=487 N (%)
Stage		
III	187 (38%)	167 (34%)
IV	301 (62%)	317 (65%)
Not reported	1 (0.2%)	3 (1%)
B symptoms present	286 (58%)	274 (56%)
IPS Score		
0-3	331 (68%)	330 (68%)
4-7	158 (32%)	157 (32%)
Bulky disease > 10cm	155 (32%)	131 (27%)
HIV+	10 (2%)	5 (1%)

Representative study, inclusive of high-risk pts

ADVERSE EVENTS IN ≥ 10% PATIENTS BY ARM



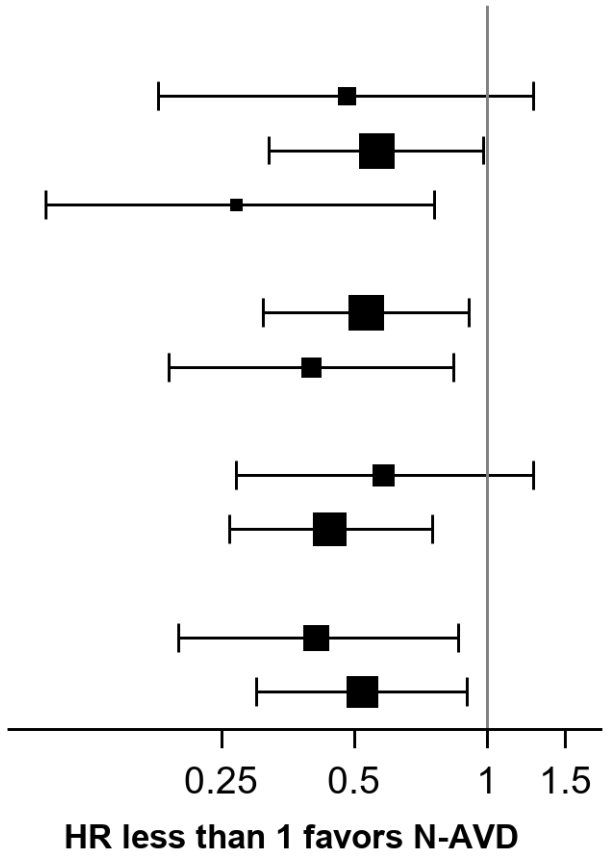
N-AVD IMPROVES PFS COMPARED TO BV-AVD



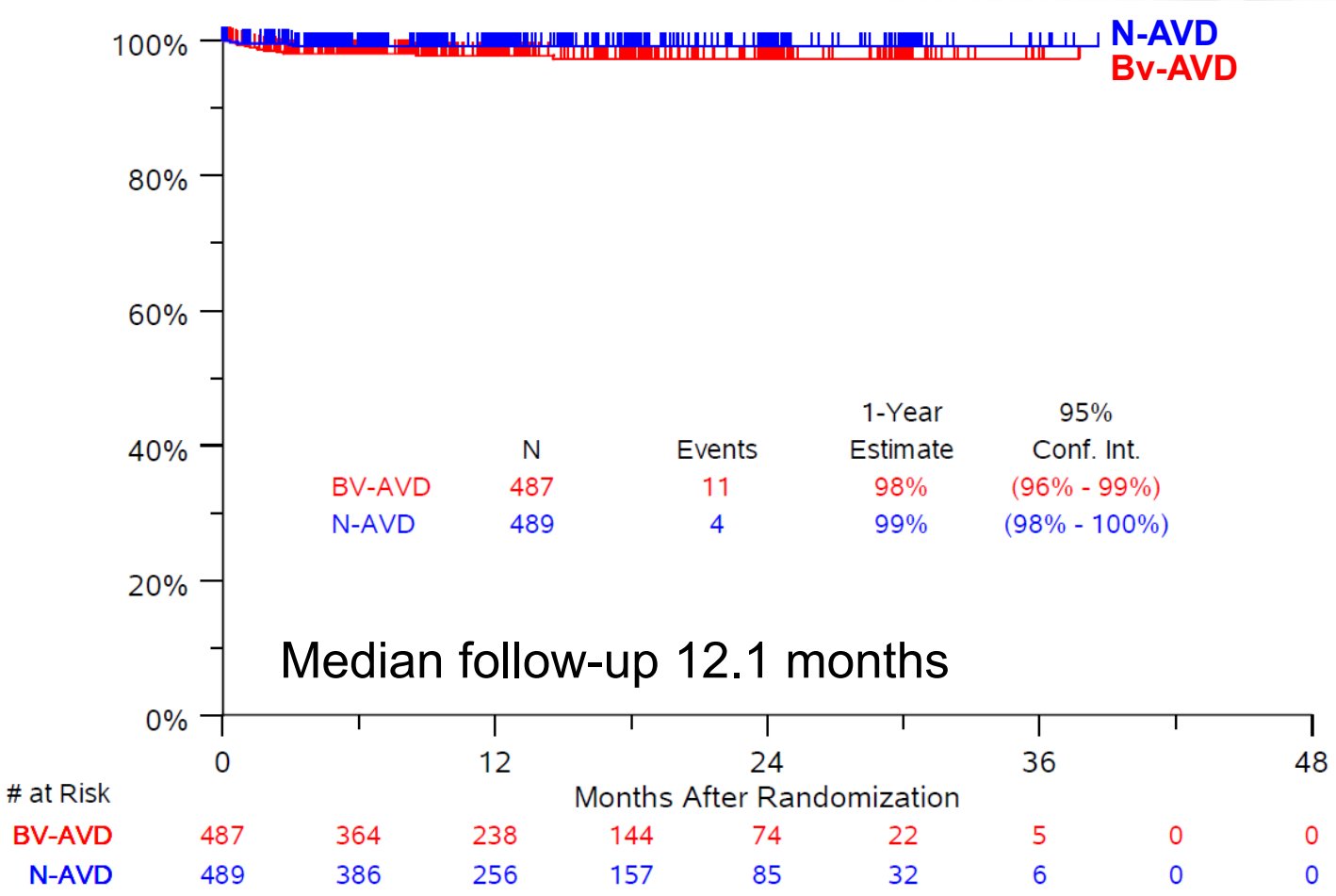
1-year PFS
N-AVD 94%
Bv-AVD 86%

PFS BENEFIT CONSISTENT ACROSS SUBGROUPS

Subgroup	N + AVD Events/N (%)	BV + AVD Events/N (%)	HR (95% CI)	P Value
Age				
12 - 17 y	6/120 (5.0)	12/117 (10.3)	0.48 (0.18, 1.27)	0.140
18 - 60 y	19/323 (5.9)	32/323 (9.9)	0.56 (0.32, 0.98)	0.042
> 60 y	5/46 (10.9)	14/47 (29.8)	0.27 (0.10, 0.76)	0.013
IPS				
0 - 3	20/331 (6.0)	36/330 (10.9)	0.53 (0.31, 0.91)	0.023
4 - 7	10/158 (6.3)	22/157 (14.0)	0.40 (0.19, 0.84)	0.015
Stage				
III	11/187 (5.9)	15/167 (9.0)	0.58 (0.27, 1.27)	0.176
IV	19/301 (6.3)	43/317 (13.6)	0.44 (0.26, 0.75)	0.003
Symptoms				
A	10/202 (5.0)	24/210 (11.4)	0.41 (0.20, 0.86)	0.017
B	20/286 (7.0)	34/274 (12.4)	0.52 (0.30, 0.90)	0.020



OVERALL SURVIVAL



Cause of death	N-AVD	Bv-AVD
Infection	2	4
Sepsis	1	2*
Cardiac arrest	0	1
Pneumonitis	0	1
Dehydration, vomiting, cHL	0	1
cHL	1**	0
Unknown	0	2
Total OS events	**4**	**11**

* 1 death from COVID-19/sepsis
** never received treatment, unevaluable for toxicity

S1826 CONCLUSIONS

- **N-AVD was superior to Bv-AVD in advanced stage cHL in this head to head randomized trial of stage 3-4 cHL in children and adults**
- N-AVD was better tolerated – fewer patients discontinued therapy
- Key step towards harmonizing pediatric and adult therapy of cHL
- **N-AVD is poised to be a new standard therapy for advanced stage cHL**

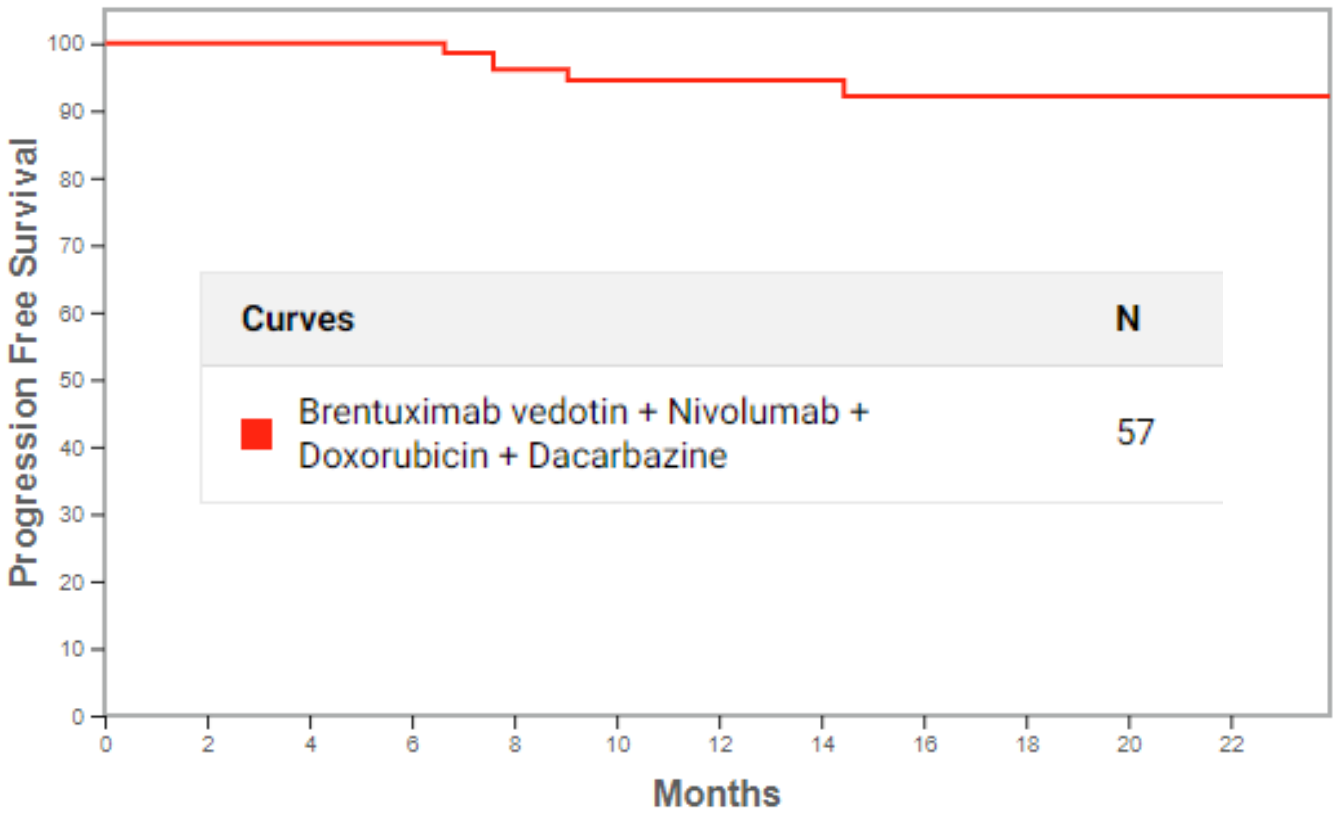
AN + AD (SGN35=027 PART B)

Treatment: AN+AD x 4 (BV 1.2 mg/kg, nivolumab 240 mg, doxorubicin 25 mg/m2, and dacarbazine 375 mg/m2). Day 1, 15

Patients: N=129 pts were enrolled
- Stage I =11%
- Stage II =89%, without bulky disease

Response: 76 evaluable
ORR=93%; 69/76 CR, 2/76 PR

Toxicity:
- No early discontinuation for treatment-emergent Aes, no deaths, or febrile neutropenia.
- Immune-mediated AEs: 21(17%), hyperthyroidism (6%), hypothyroidism (6%), maculo-papular rash (3%), and pneumonitis (2%).



HJ. Lee et al. Blood 2022; 140 (Supplement 1): 9399–9401.

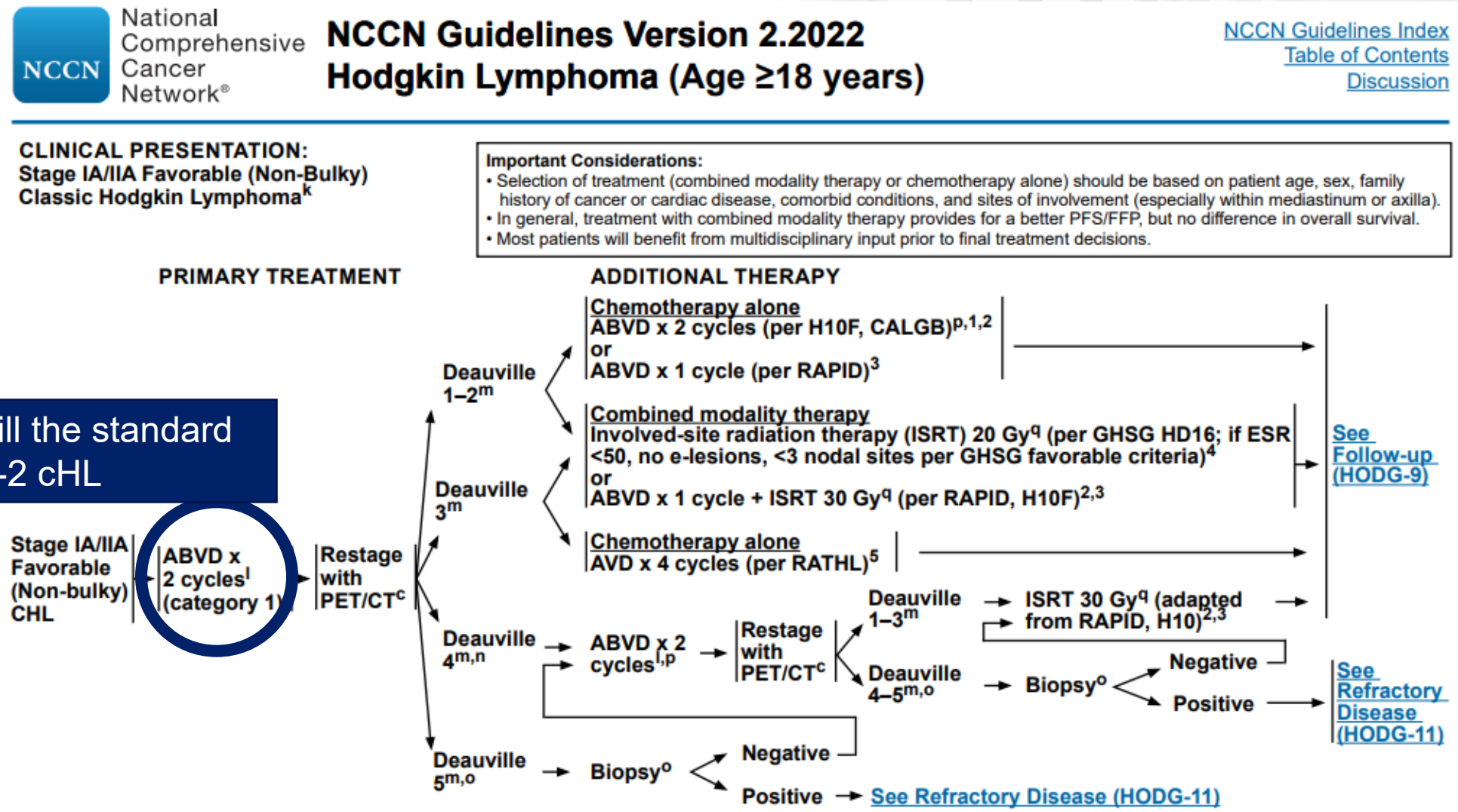
TRADITIONAL CHEMOTHERAPY APPROACHES- IS THERE STILL A ROLE?

Where would we still consider traditional chemotherapy alone?

- Early stage
- Older patients or those with significant co-morbidities for whom checkpoint blockade and brentuximab are contraindicated
- Outside of North America**
  - Difficulty with access/payment for brentuximab
  - European countries with experience using escalated BEACOPP

EARLY STAGE: ALL PATHWAYS START WITH CHEMOTHERAPY ALONE

ABVD is still the standard for stage 1-2 cHL

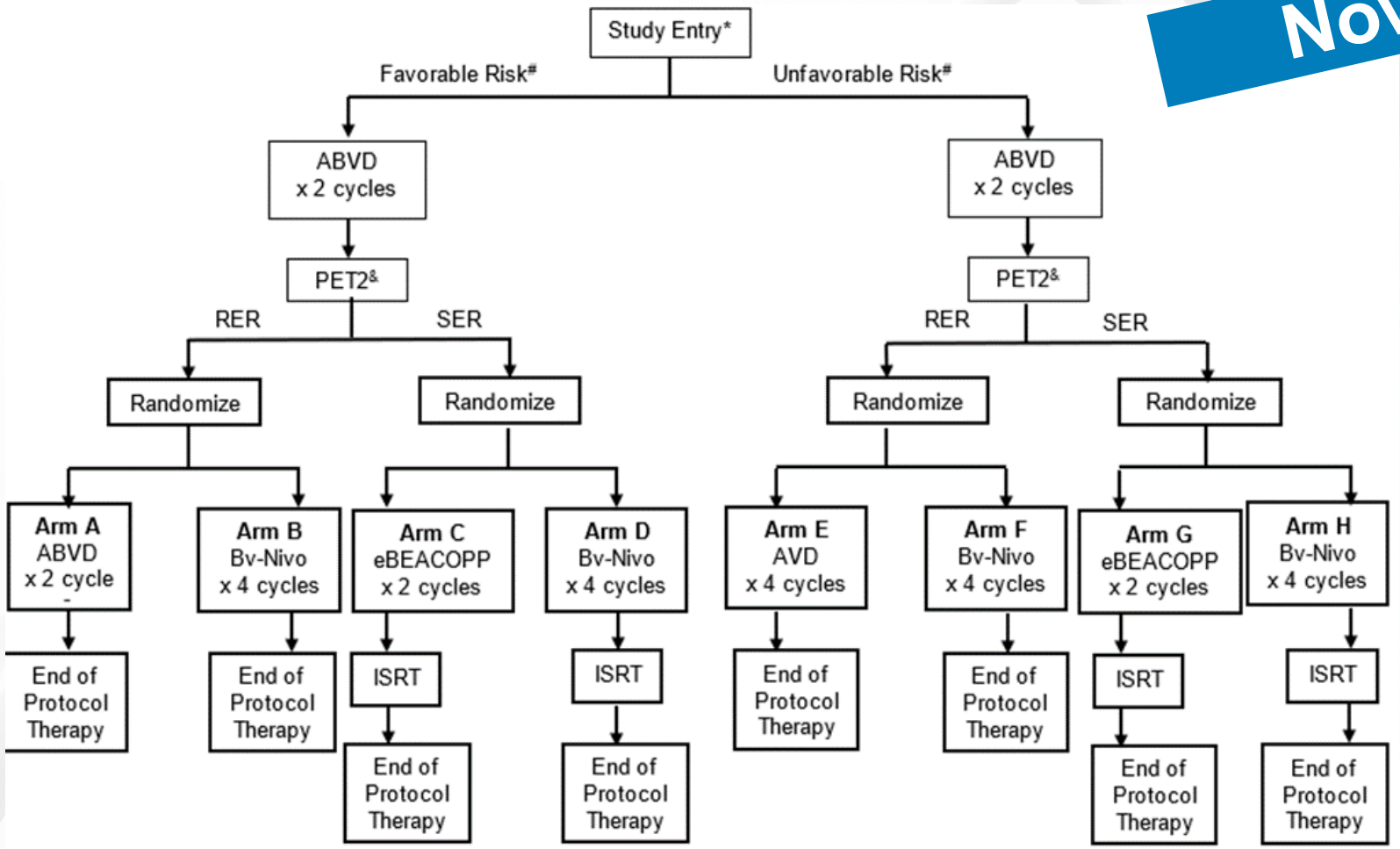


NOVEL APPROACHES COMBINING PD-1 BLOCKADE AND BRENTUXIMAB

- Response adapted therapy with brentuximab and nivolumab (phase 2)
- Response adapted therapy with brentuximab and nivolumab versus chemotherapy alone (phase 3)
- Combination of nivolumab and brentuximab with chemotherapy

AHOD 2131: A RANDOMIZED PHASE 3 STUDY OF NIVOLUMAB AND BRENTUXIMAB FOR RAPID EARLY RESPONDERS WITH STAGE I AND II CLASSIC HODGKIN LYMPHOMA

Now enrolling!



Eligibility:

- Age 5-60
- Stage 1-2 favorable or unfavorable
- Treatment naive

Sample Size Projections
N=1782 over 5 years
PET negative = 1514
PET positive = 268

SUMMARY

- Brentuximab vedotin and AVD is associated with an overall survival benefit for frontline advanced stage Hodgkin lymphoma, but new data demonstrating superiority of nivolumab + AVD has relegated this regimen to those who are not candidates for immunotherapy.

- Nivolumab + AVD demonstrated superior efficacy and tolerability compared to brentuximab AVD in the phase 3 SWOG 1826 trial, making it the new standard of care for advanced stage cHL

- ABVD-based traditional chemotherapy remains the standard of care for early stage Hodgkin lymphoma *at this time*.

THANK YOU!

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