3rd MEETING ON T-CELL AND NK-CELL BASED IMMUNOTHERAPIES FOR LYMPHOID MALIGNANCIES

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The Evolving Role of Checkpoint Inhibitors in Front-Line Hodgkin Lymphoma

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BOLOGNA, ROYAL HOTEL CARLTON

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Disclosures of Name Surname

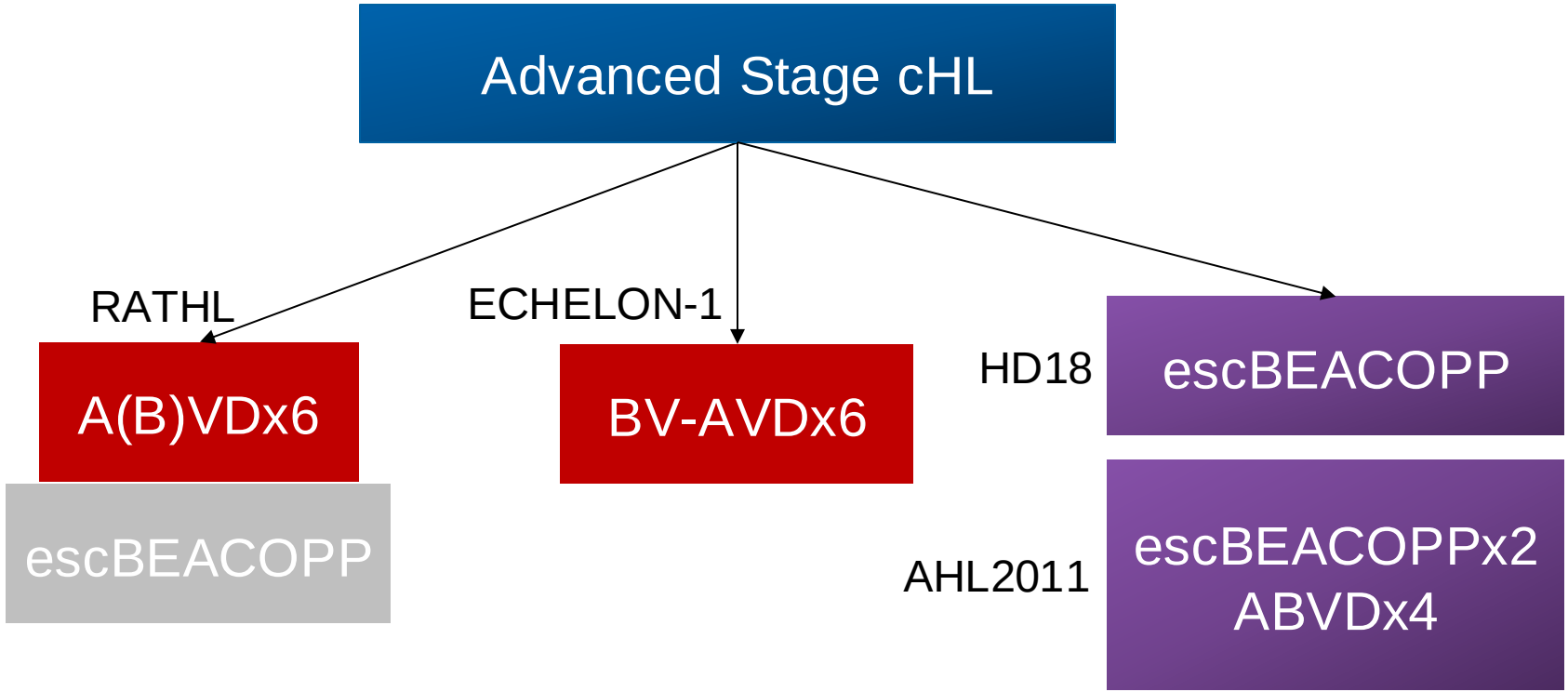
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Bristol Myers Squibb Genentech Merck Seattle Genetics AstraZeneca ADC Therapeutics	x		x				
KiTE Pharma Gilead Sciences	x						
Takeda Karyopharm Tubulis Regeneron Genmab Pfizer Caribou Biosciences Adicet Bio Abbvie Allogene Therapeutics			x				

Presentation Outline

- Checkpoint inhibitors in advanced stage classic Hodgkin lymphoma (cHL)
- Checkpoint inhibitors in early stage cHL
- Next Questions

Advanced Stage Disease

Standard Management of Advanced Stage cHL

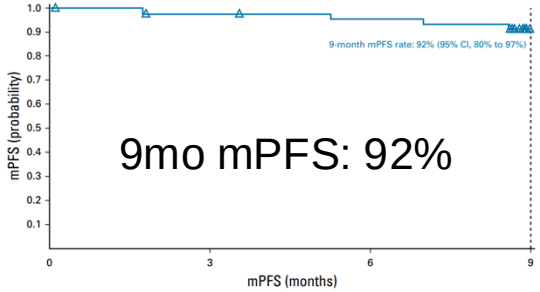


Ansell SM, et al. NEJM 2022, Borchmann P et al. Lancet 2018, Casasnovas O et al. *Lancet Oncol* 2019, Johnson P et al. NEJM 2016

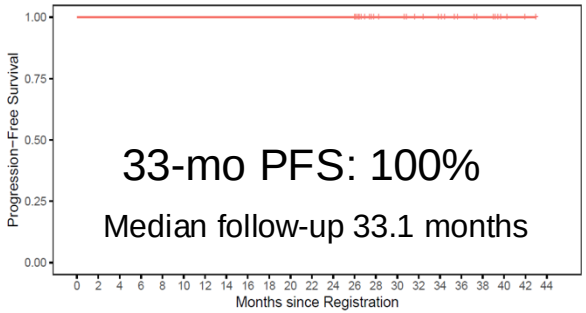
PD-1 blockade in advanced stage cHL safe and effective

- Studies of frontline PD-1 blockade in cHL have been promising[10,11,12,13]
  - N-AVD well-tolerated
  - Excellent PFS

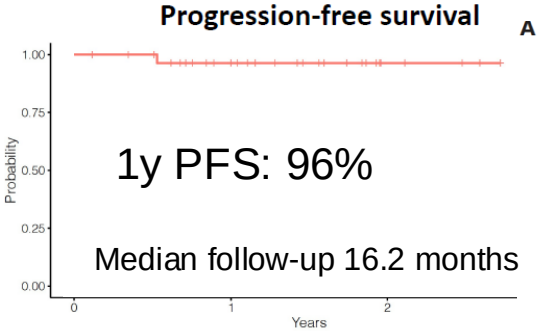
1L Nivolumab-AVD in advanced stage cHL



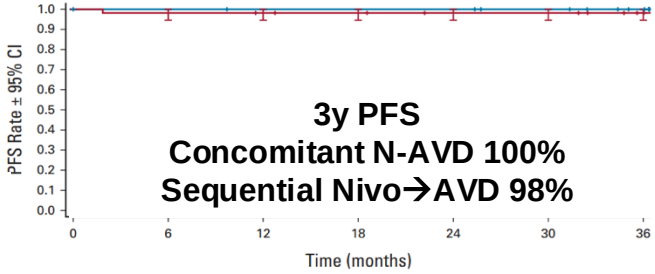
Sequential Pembro-AVD in cHL



Concurrent Pembro-AVD in cHL

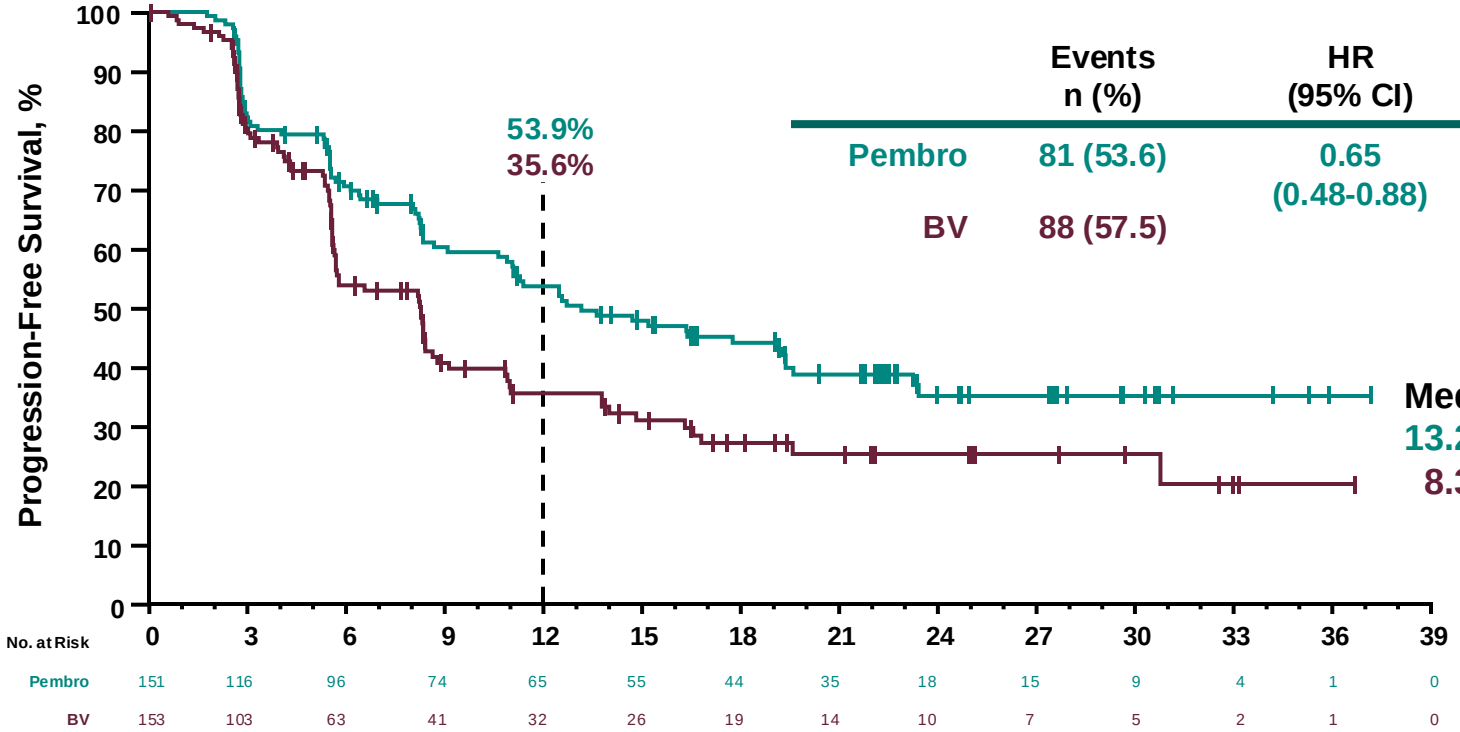


1L Nivolumab-AVD in early stage cHL



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

PD-1 superior to BV in R/R HL…

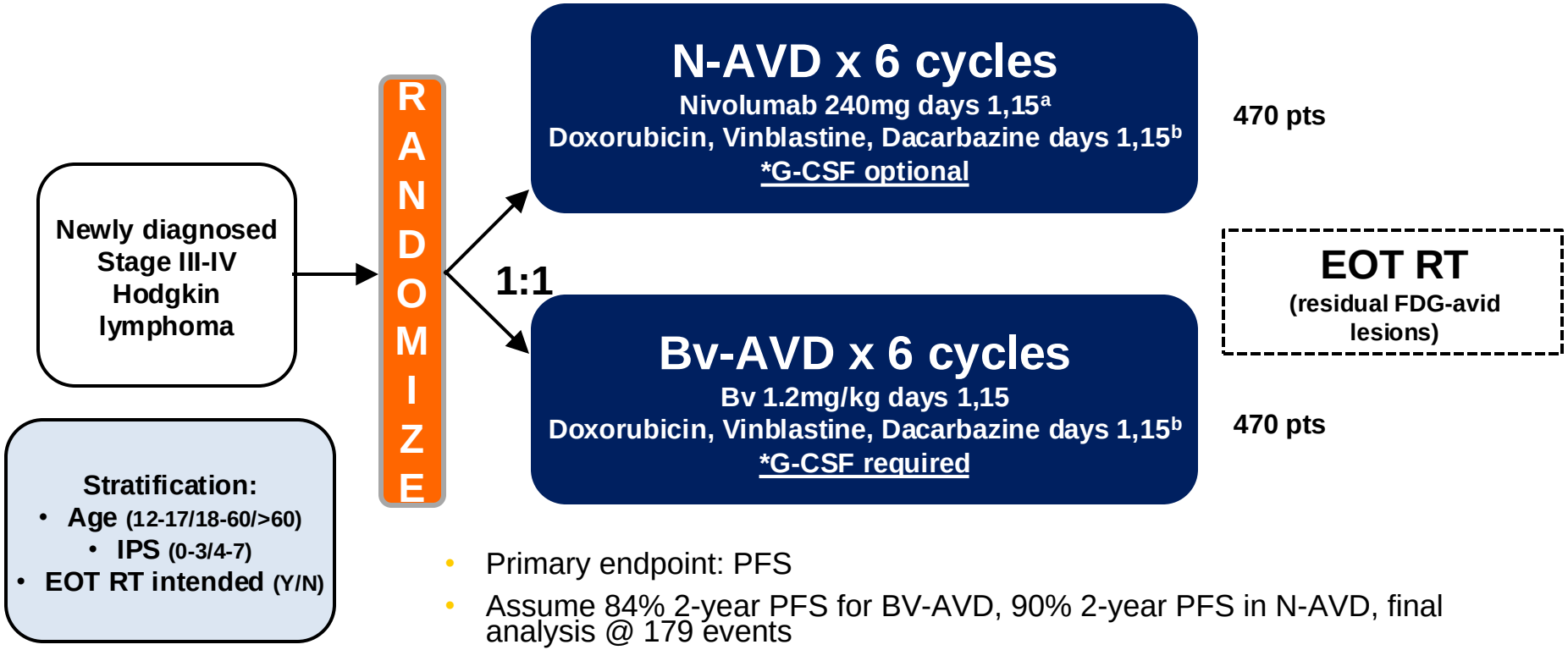


	Events n (%)	HR (95% CI)	*P* value
Pembro	81 (53.6)	0.65 (0.48-0.88)	0.00271
BV	88 (57.5)		

Median (95% CI)
13.2 mo (10.9-19.4)
8.3 mo (5.7-8.8)

Kuruvilla J et al ASCO 2020, Lancet Oncol 2021

S1826 Study Design



- Primary endpoint: PFS
- Assume 84% 2-year PFS for BV-AVD, 90% 2-year PFS in N-AVD, final analysis @ 179 events

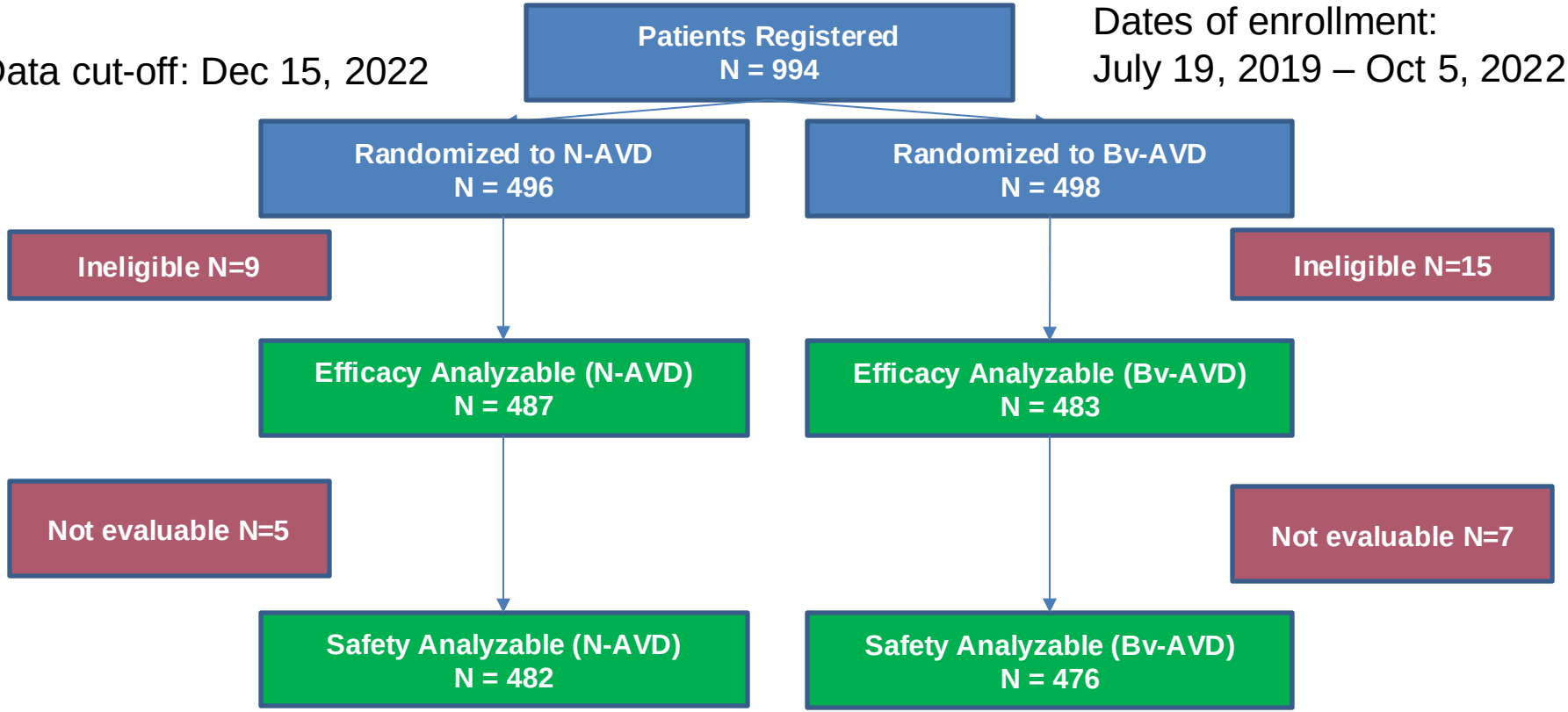
Herrera, AF et al. ASCO 2023.

[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

S1826 CONSORT Diagram

Data cut-off: Dec 15, 2022

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



Herrera, AF et al. NEJM in press.

S1826 Baseline Characteristics

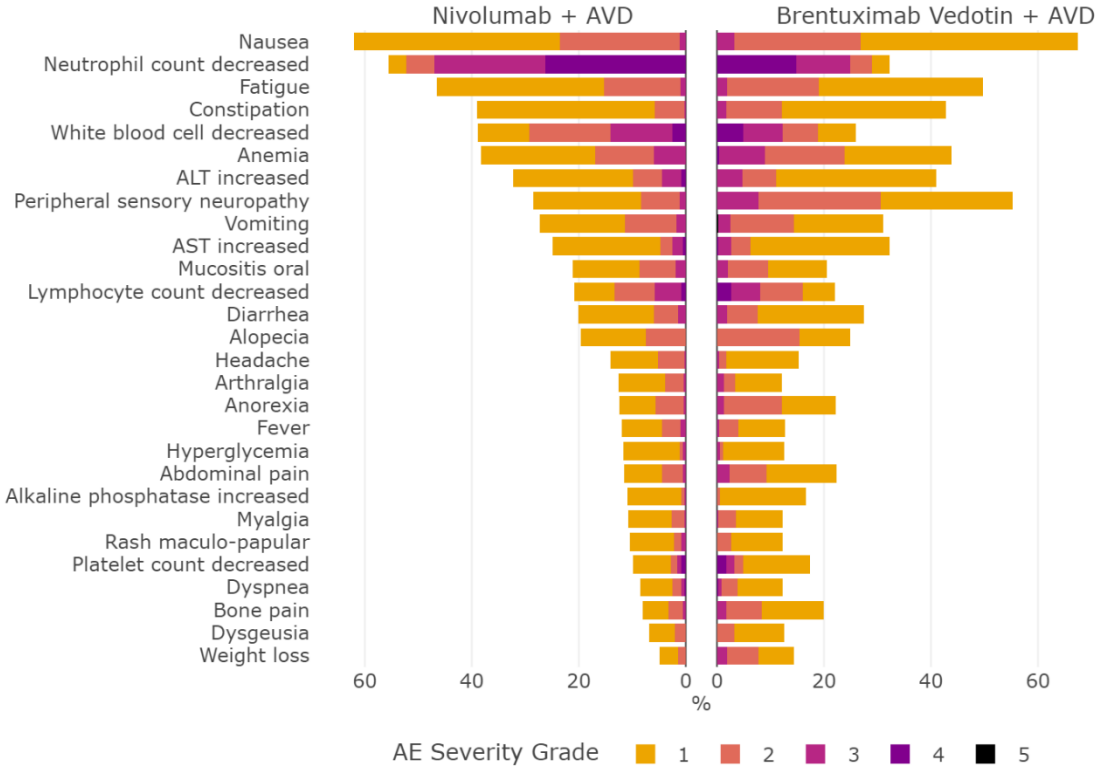
Baseline characteristics	N-AVD n=487 N (%)	Bv-AVD n=483 N (%)
Age, median (range)	27 (12-83)	26 (12-81)
12-17 years	118 (24%)	118 (24%)
18-60 years	321 (66%)	318 (66%)
≥ 61 years	48 (10%)	47 (10%)
Female Sex	216 (44%)	210 (43%)
Race		
White	372 (76%)	361 (75%)
Black	58 (12%)	56 (12%)
Asian	11 (2%)	17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

Herrera, AF et al. NEJM in press.

Adverse Events in ≥ 10% patients by Arm



Herrera, AF et al. NEJM in press.

AEs of interest: Hematologic

Toxicity	N-AVD n = 482		Bv-AVD n = 476	
	Any Gr N (%)	Gr ≥ 3 N (%)	Any Gr N (%)	Gr ≥ 3 N (%)
Neutropenia	272 (56%)	232 (48%)	160 (34%)	126 (26%)
Anemia	190 (39%)	29 (6%)	217 (46%)	43 (9%)
Thrombocytopenia	52 (11%)	9 (2%)	86 (18%)	16 (3%)
Received G-CSF	274 (56%)		467 (97%)	
Bone pain	40 (8%)		96 (20%)	

More neutropenia after N-AVD

More growth factor use, bone pain in Bv-AVD arm

Herrera, AF et al. NEJM in press.

AEs of interest: Infectious

Toxicity	N-AVD n = 482	Bv-AVD n = 476
Febrile Neutropenia	28 (6%)	33 (7%)
Sepsis	8 (2%)	16 (3%)
Infections/Infestations (Gr ≥ 3)	22 (5%)	35 (7%)

No increased infectious toxicity in N-AVD arm

Herrera, AF et al. NEJM in press.

AEs of Interest: Peripheral Neuropathy

Toxicity	N-AVD n = 482		Bv-AVD n = 476	
	Any Gr N (%)	Gr ≥ 3 N (%)	Any Gr N (%)	Gr ≥ 3 N (%)
Peripheral sensory neuropathy	139 (29%)	5 (1%)	266 (56%)	39 (8%)
Peripheral motor neuropathy	20 (4%)	1 (0%)	35 (7%)	6 (1%)

More neuropathy in Bv-AVD arm

Herrera, AF et al. NEJM in press.

AEs of Interest: Peripheral Neuropathy

Toxicity	N-AVD n = 482			Bv-AVD n = 476		
	Gr 1 (%)	Gr 2 (%)	Gr ≥ 3 N (%)	Gr 1 (%)	Gr 2 (%)	Gr ≥ 3 N (%)
Peripheral sensory neuropathy	98 (20%)	36 (7%)	5 (1%)	115 (24%)	112 (24%)	39 (8%)
Peripheral motor neuropathy	13 (3%)	7 (1%)	1 (0%)	12 (3%)	17 (4%)	6 (1%)

Higher grade neuropathy in Bv-AVD arm

Herrera, AF et al. NEJM in press.

AEs of Interest: Immune/Other

Toxicity	N-AVD n = 482		Bv-AVD n = 476	
	Any Grade No (%)	Grade ≥ 3 No (%)	Any Grade No (%)	Grade ≥ 3 No (%)
ALT increased	**160 (33%)**	**22 (5%)**	**201 (42%)**	**23 (5%)**
AST increased	**125 (26%)**	**12 (2%)**	**160 (34%)**	**14 (3%)**
Rash maculo-papular	54 (11%)	4 (1%)	58 (12%)	0 (0)
Hypothyroidism	**35 (7%)**	**1 (0%)**	**3 (1%)**	**0 (0)**
Rash acneiform	17 (4%)	0 (0)	12 (3%)	0 (0)
Pneumonitis	11 (2%)	3 (1%)	15 (3%)	10 (2%)
Gastritis	9 (2%)	3 (1%)	8 (2%)	0 (0)
Hyperthyroidism	**13 (3%)**	**0 (0)**	**0 (0)**	**0 (0)**
Colitis	6 (1%)	1 (0%)	6 (1%)	4 (1%)

Low rates of immune-related adverse events

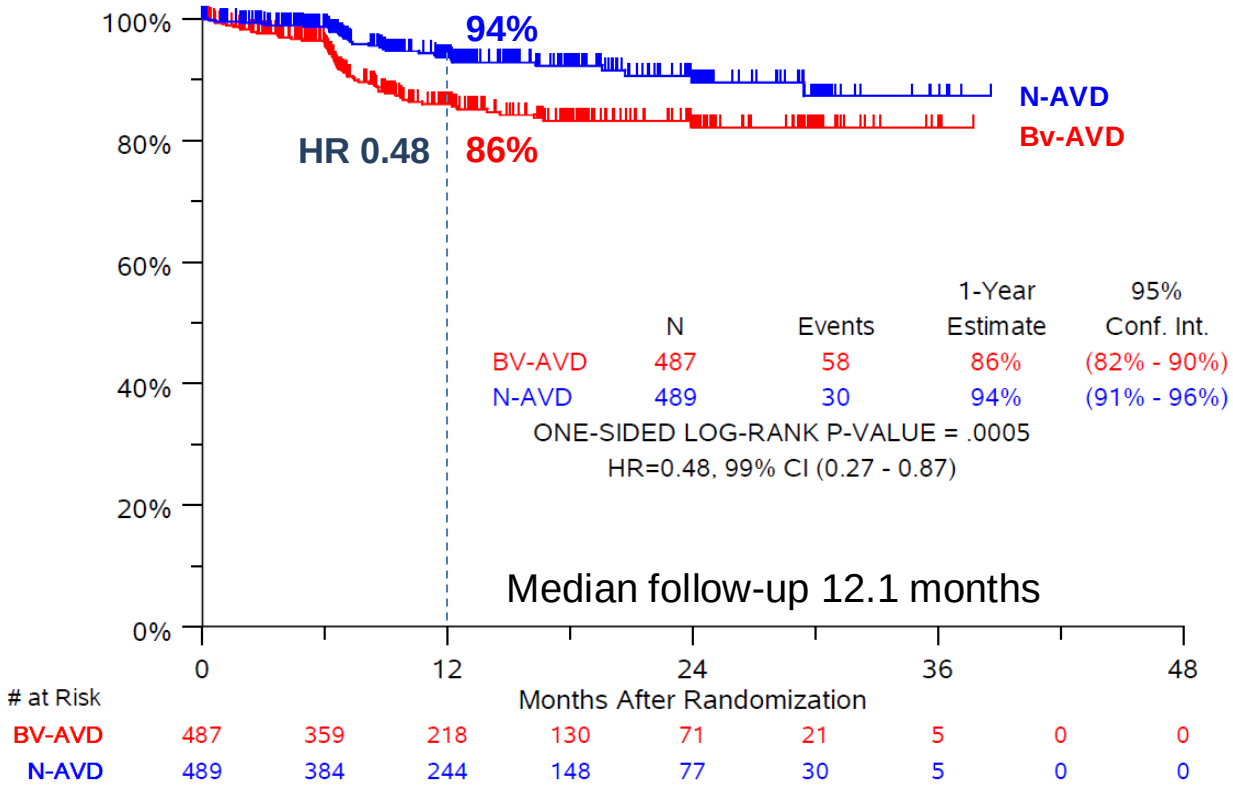
Herrera, AF et al. NEJM in press.

Treatment Discontinuation and Deaths

Disposition	N-AVD (n=487) N (%)	Bv-AVD (n=483) N (%)
Completed treatment	450 (92.4%)	425 (88%)
Discontinued all treatment early	**37 (7.6%)**	**58 (12%)**
Adverse event	20 (4.1%)	20 (4.1%)
Refusal unrelated to AE	9	13
Progression/relapse	**0 (0%)**	**9 (1.9%)**
Death on treatment	**3 (0.6%)**	**8 (1.7%)**
Other – not protocol specified	5	8
Any discontinuation Bv or Nivolumab	**46 (9.4%)**	**107 (22.2%)**
Received radiotherapy	**3 (0.6%)**	**4 (0.8%)**

Herrera, AF et al. NEJM in press.

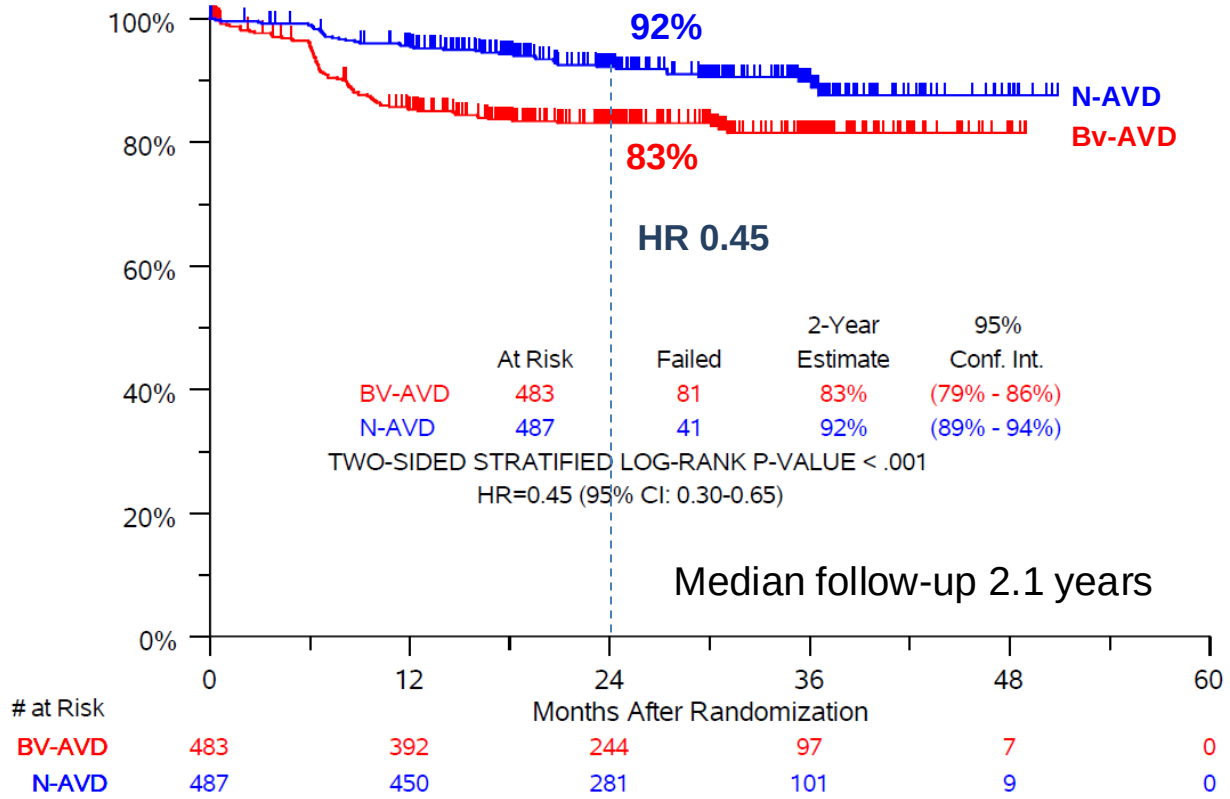
N-AVD improves PFS compared to Bv-AVD



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

Herrera, AF et al. ASCO 2023.

Benefit of N-AVD sustained with 2y FU

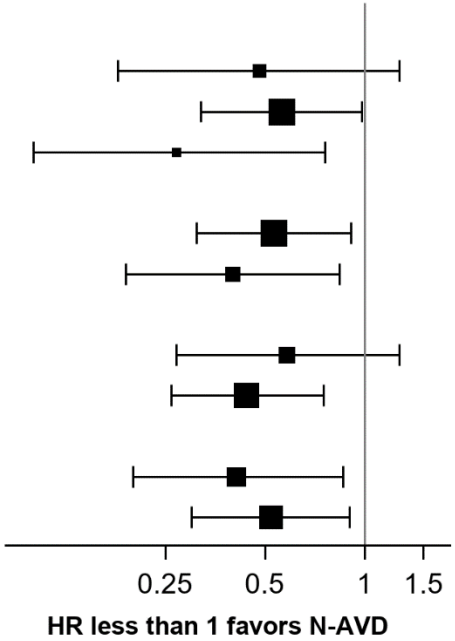


2-year PFS
N-AVD 92%
Bv-AVD 83%

Herrera, AF et al. NEJM in press.

PFS benefit consistent across subgroups (1y)

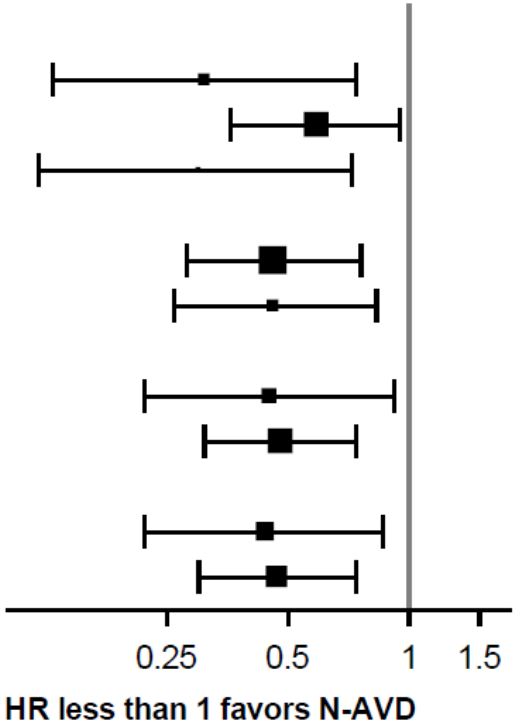
Subgroup	N + AVD Events/N (%)	BV + AVD Events/N (%)	HR (95% CI)	P Value
Age				
12 - 17 y	6/120 (5.0)	12/117 (10.3)	0.48 (0.18, 1.27)	0.140
18 - 60 y	19/323 (5.9)	32/323 (9.9)	0.56 (0.32, 0.98)	0.042
> 60 y	5/46 (10.9)	14/47 (29.8)	0.27 (0.10, 0.76)	0.013
IPS				
0 - 3	20/331 (6.0)	36/330 (10.9)	0.53 (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



Herrera, AF et al. ASCO 2023.

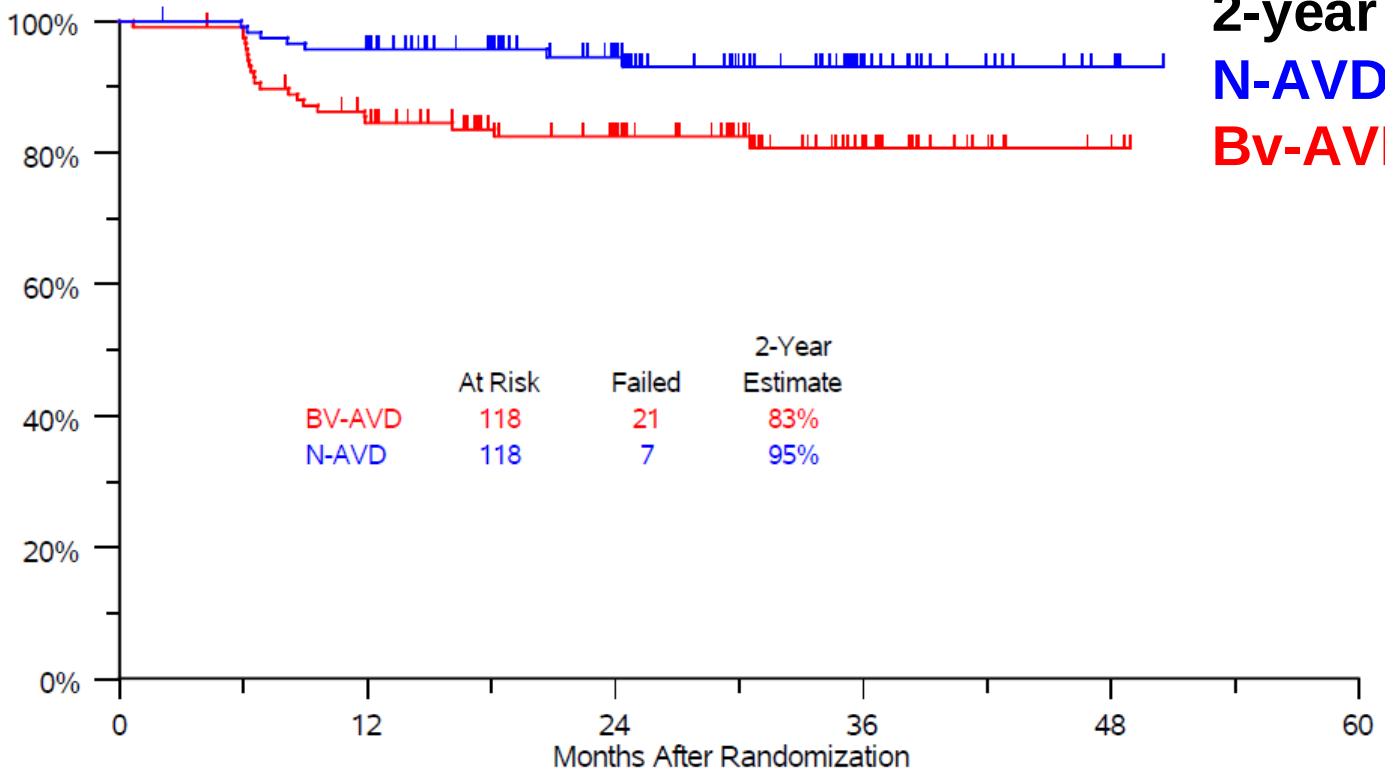
PFS benefit consistent across subgroups (2y)

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. NEJM in press.

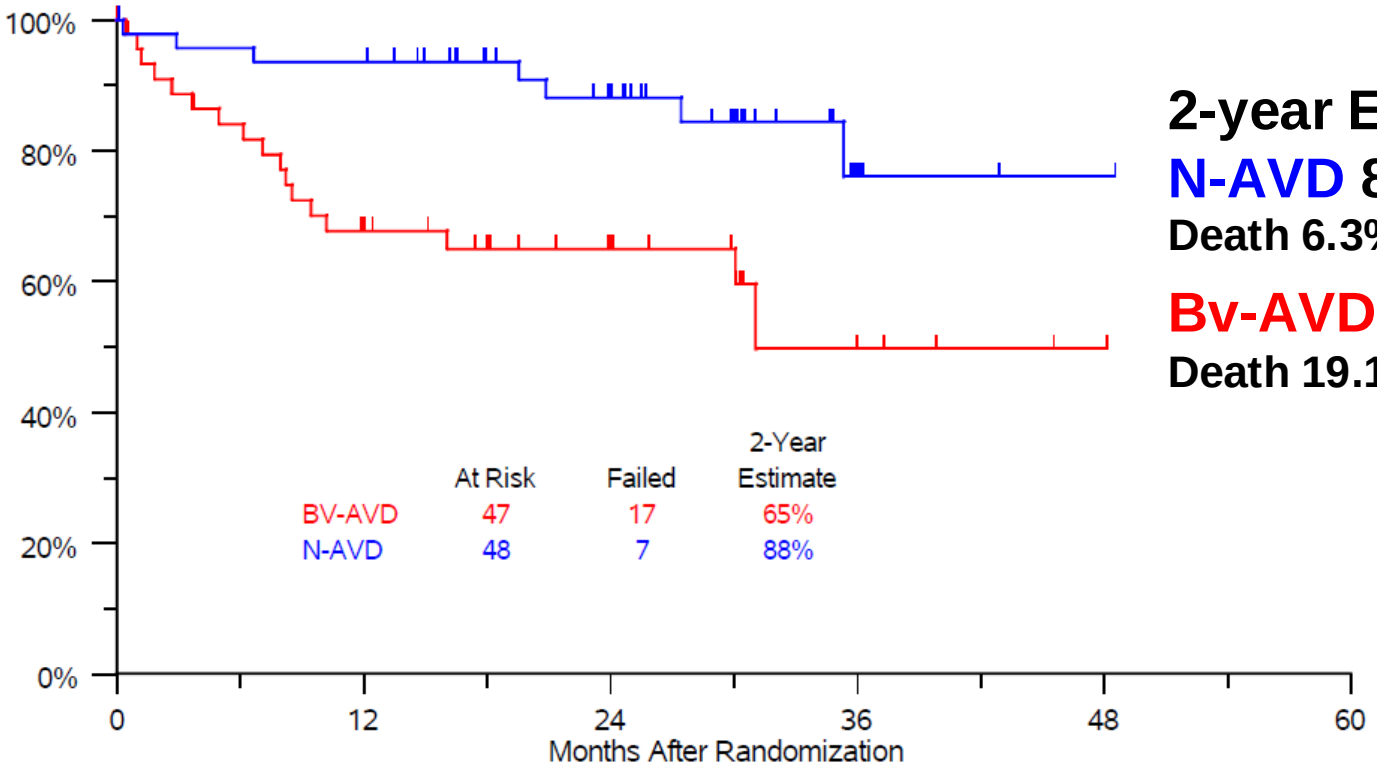
N-AVD > BV-AVD in pediatric patients



2-year EFS
N-AVD 95%
Bv-AVD 83%

Herrera, AF et al. NEJM in press.

N-AVD >> BV-AVD in older patients (61+yo)



2-year EFS

N-AVD 88%

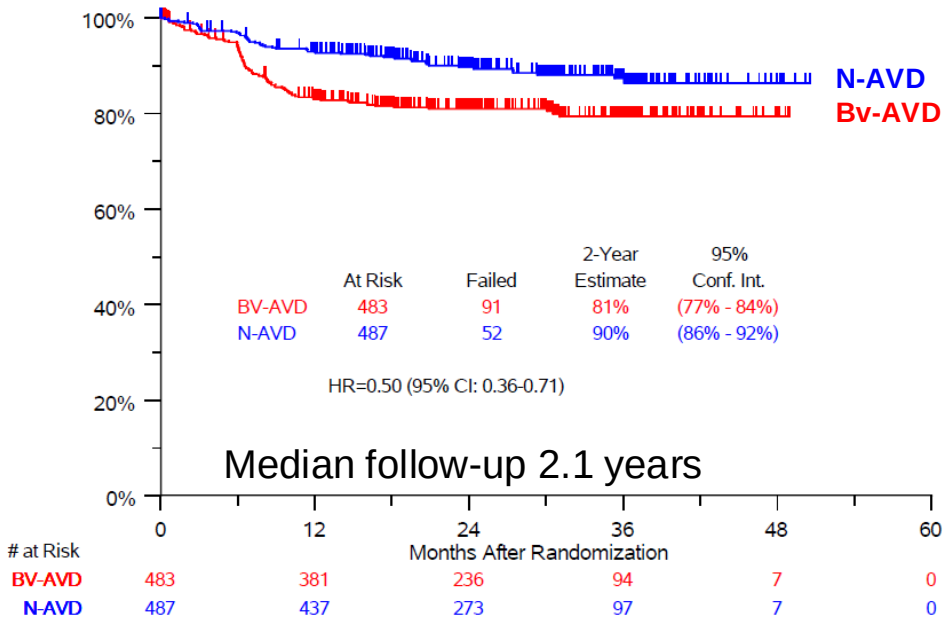
Death 6.3%

Bv-AVD 65%

Death 19.1%

Herrera, AF et al. NEJM in press.

Event-Free Survival



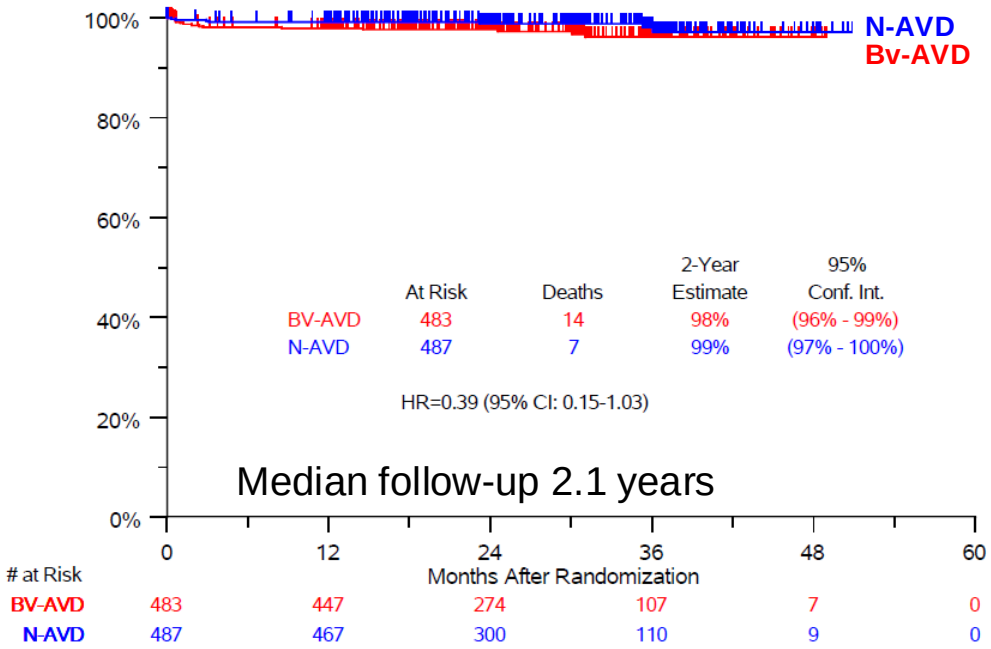
2-year EFS
N-AVD 90%
Bv-AVD 81%

EFS events: death, progression, non-protocol treatment before progression

Type of EFS Event	N-AVD N=487	BV-AVD N=483
Non-protocol chemo prior to PD	10 (2.1%)	7 (1.4%)
Non-protocol RT prior to PD	3 (0.6%)	5 (1.0%)
Progression/Relapse	32 (6.6%)	67 (13.9%)
Death without progression	7 (1.4%)	12 (2.5%)
Total EFS events	52 (10.7%)	91 (18.8%)

Herrera, AF et al. NEJM in press.

Overall Survival



Cause of Death	N-AVD N=487	BV-AVD N=483
Infection/Sepsis	4	6
Lymphoma	1	2
Medical issues other than cancer	2	4
New primary malignancy	0	1
Unknown	0	1
Total	**7**	**14**

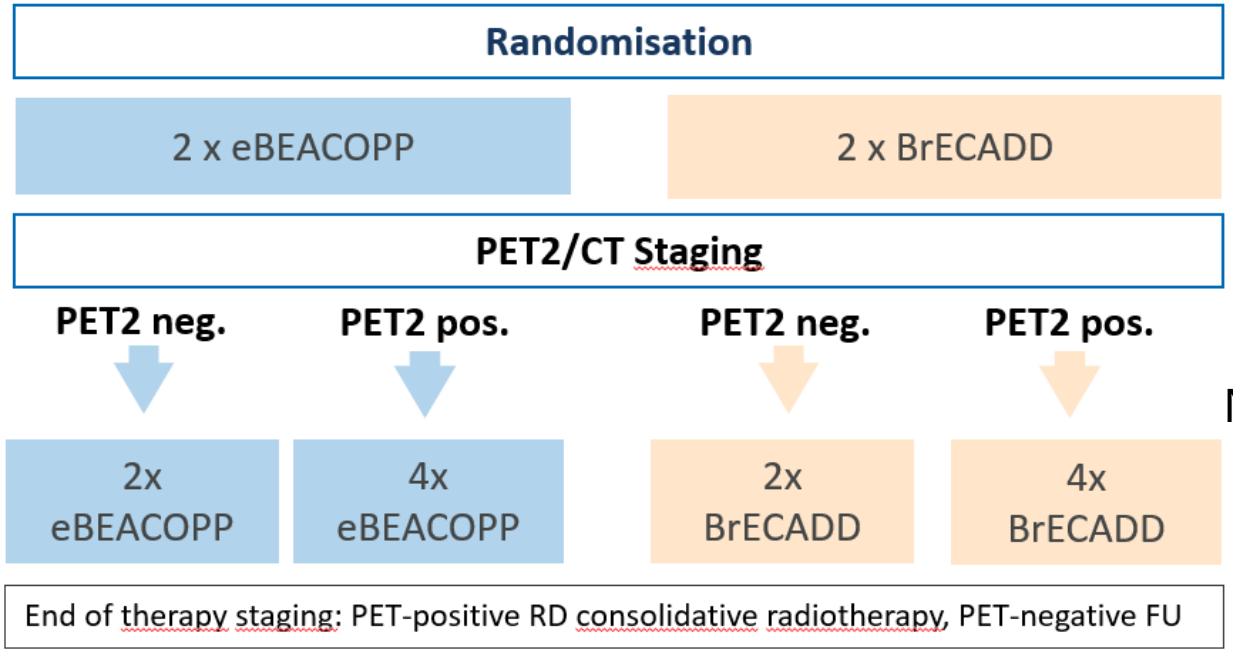
Herrera, AF et al. NEJM in press.

S1826 Conclusions

- **N-AVD improved PFS compared to Bv-AVD in advanced stage cHL**
  - N-AVD improved EFS versus Bv-AVD
- N-AVD was well-tolerated
  - Few immune-related adverse events
- < 1% of patients received consolidative RT
  - May reduce late effects
- 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**

HD21: Reducing toxicity of escBEACOPP

- Advanced stage cHL < 60y



Non-inferiority design

Borchmann P et al, ICML 2023

HD21: Reducing toxicity of escBEACOPP

Drug	Day	BEACOPP[1] Dose (mg/m²)	*BrECADD* Dose (mg/m²)	Potential improvement
Bleomycin	8	10	-	lung tox
Etoposide	1–3	200	*150*	hem tox, transfusion frequency
Doxorubicin	1	35	*40*	
Cyclophosphamide	1	1250	*1250*	
Vincristine	8	1.4	-	neuropathy
Brentuximab vedotin	1	-	*1.8 mg/kg*	
Procarbazine	1–7	100	-	gonadal tox, sAML/MDS
Prednisone	1–14	40	-	weight, bone, infections
Dacarbazine	2–3	-	*250*	
Dexamethasone	1–4	-	*40*	

Borchmann et al, Abstract #T002 ISHL 2022

GHSG HD21 clinical implications of observed differences

Toxicity	eBEACOPP (%)	BrECADD (%)
Anemia (at least 1 red cell transfusion)	22	8
Thrombocytopenia (at least 1 platelet transfusion)	13	6

	eBEACOPP (%)	BrECADD (%)
Sensory PNP		
All grades	49	38
Grade 2	14	6

Grade 3	eBEACOPP (%)	BrECADD (%)
Treatment related mortality	< 1%	0%

Gonadal dysfunction? FSH (U/l) in HD21

female patients (18-39) per arm

	BEACOPP (N=326)		BrECADD (N=331)	
	N	Mean	N	Mean
N (min FU12 m)	145	**27,2** U/l	149	**13,4** U/l

- FSH normal values (cycle dependent): 1,7 – 21,5 U/l
- FSH documented in:

  58 % in BEACOPP and 57 % in BrECADD

male patients (18-49) per arm

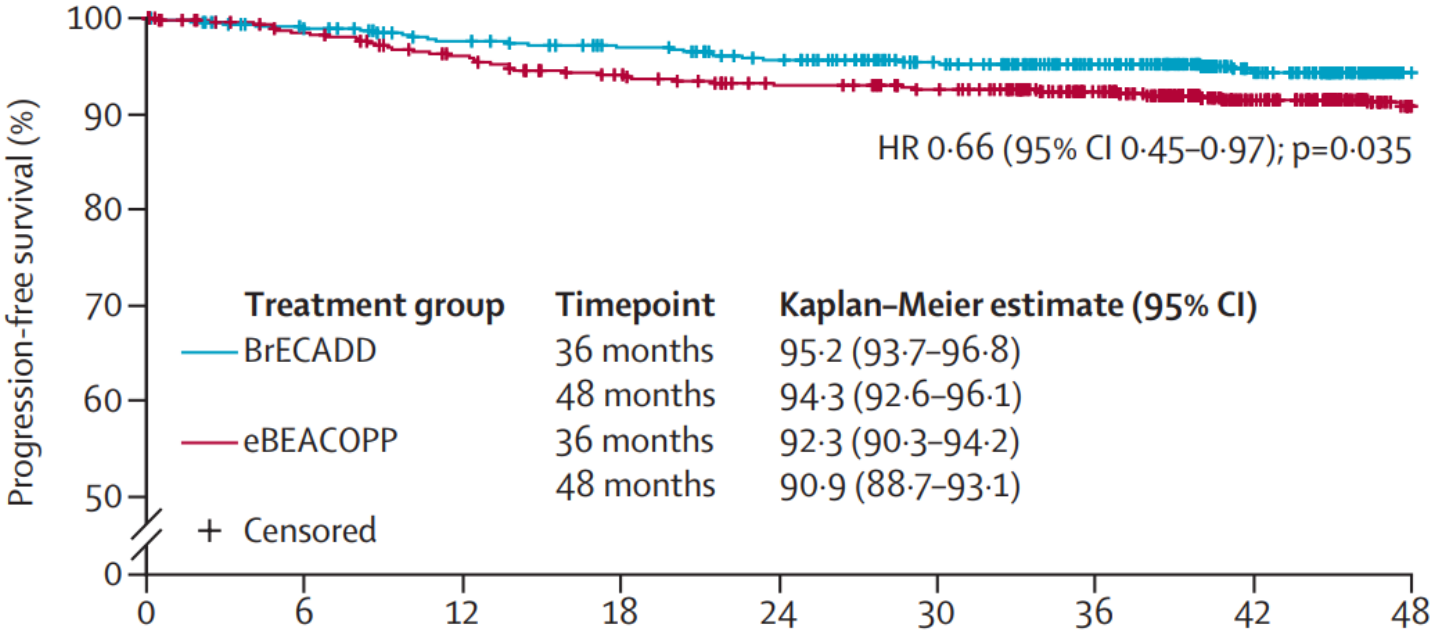
	BEACOPP (N=418)		BrECADD (N=417)	
	N	Mean	N	Mean
N (min FU12 m)	189	**20,5** U/l	178	**11,9** U/l

- FSH normal values:

  FSH: 1.5 – 12.4 U/l
- FSH was documented in:
  45 % in BEACOPP and 45 % in BrECADD

Borchmann et al, Abstract #T002 ISHL 2022

HD21: BrECADD >> escBEACOPP



Borchmann P et al, Lancet 2024

BrECADD vs S1826 Baseline Characteristics

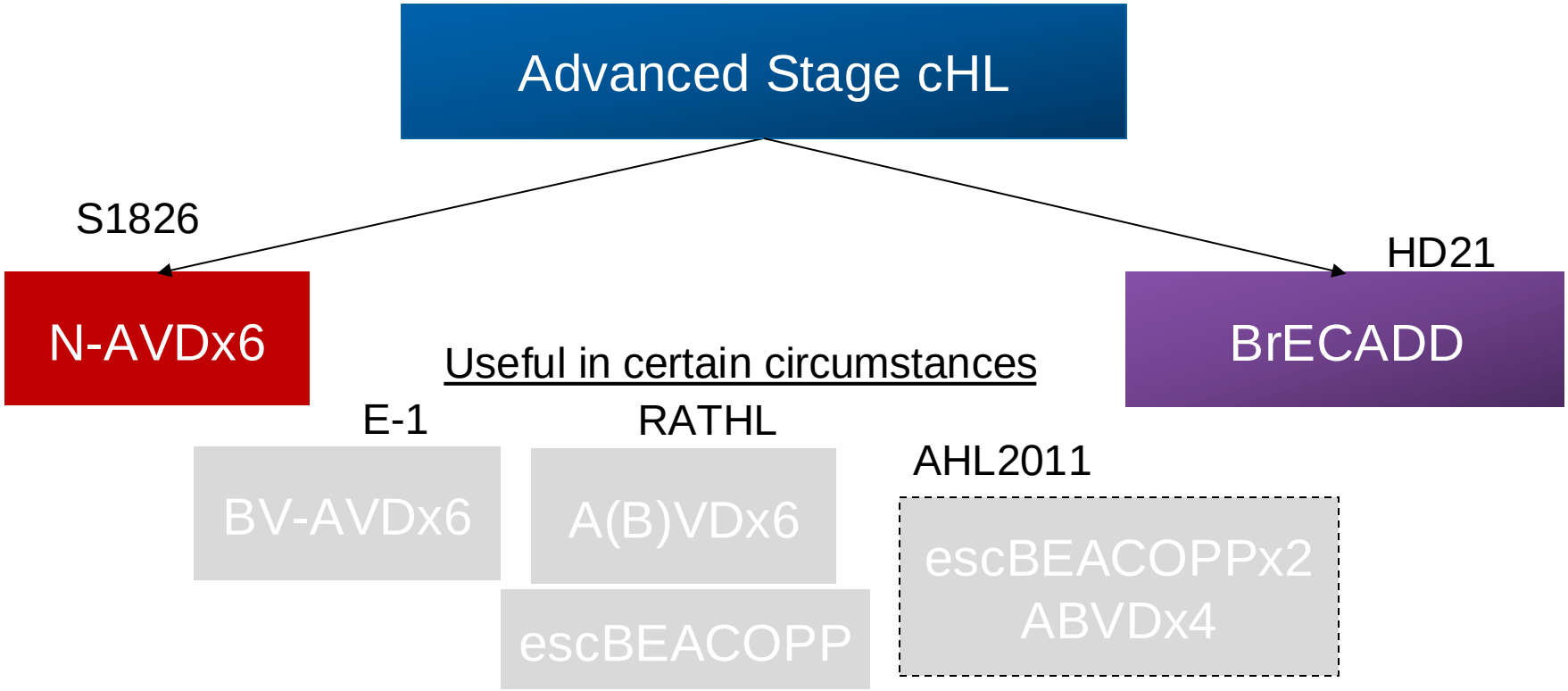
- 91% White
- Ages 18-60 only
- HIV+ excluded
- Stage IIB (+ extranodal and/or bulky), III, IV
  - Stage IV = 45% (vs 63% in S1826)
- IPS 4-7 = 21% (vs 32% in S1826)

Tolerability of BrECADD

Toxicity	Frequency (%)
Gr ≥ 3 anemia	30% (vs 6%)
PRBC transfusion	24%
Gr ≥ 3 thrombocytopenia	55% (vs 2%)
Platelet transfusion	17%
Gr ≥ 3 leukopenia	87% (vs 47%)
Febrile neutropenia	28% (vs 5%)
Gr ≥ 3 infection	20% (vs 5%)

- Use of consolidative radiation: BrECADD 14% vs S1826 < 1%

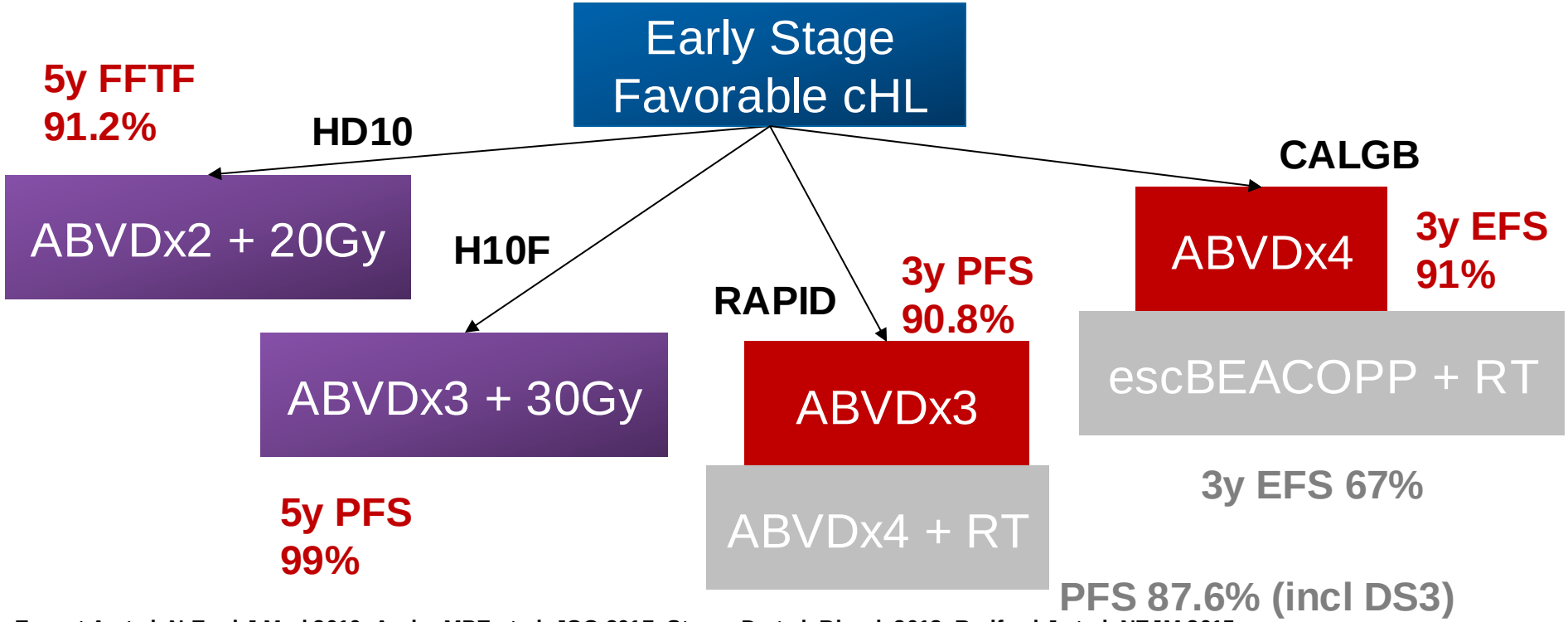
Current Management of Advanced Stage cHL



Herrera AF, et al. ASCO 2022. Borchmann P, et al. ICML 2022. Ansell SM, et al. NEJM 2022, Borchmann P et al. Lancet 2018, Casasnovas O et al. *Lancet Oncol* 2019, Johnson P et al. NEJM 2016

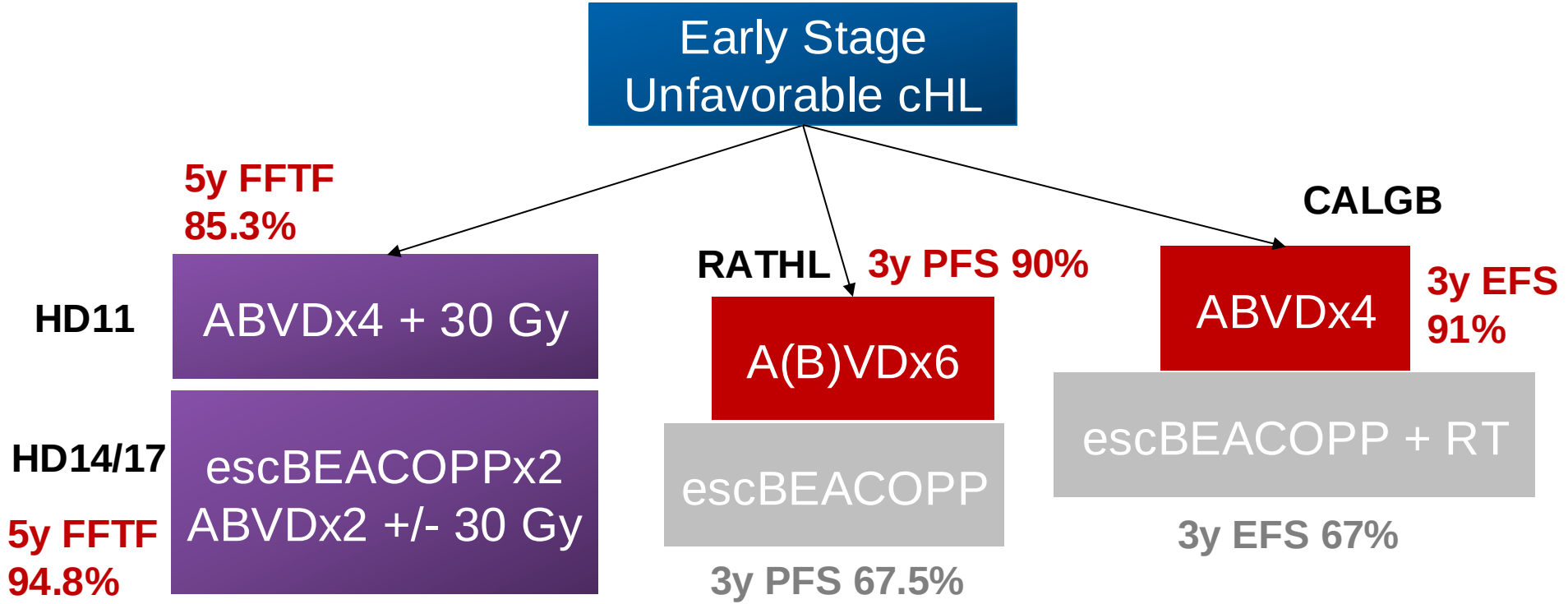
Early Stage Disease

Standard Management of Early Stage cHL



Engert A et al. N Engl J Med 2010, Andre MPE et al. JCO 2017, Straus D et al. Blood. 2018, Radford J et al. NEJM 2015

Standard Management of Early Stage cHL

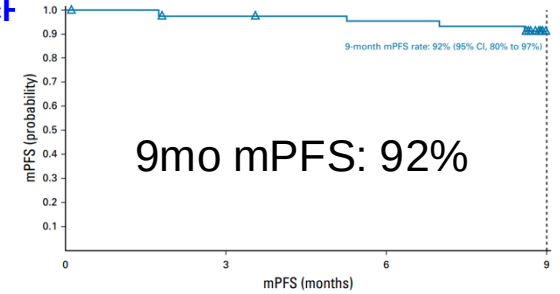


Eich HT et al. JCO 2011, von Tresckow B et al. JCO 2012, Straus D et al. Blood. 2018, Johnson P et al. NEJM 2016

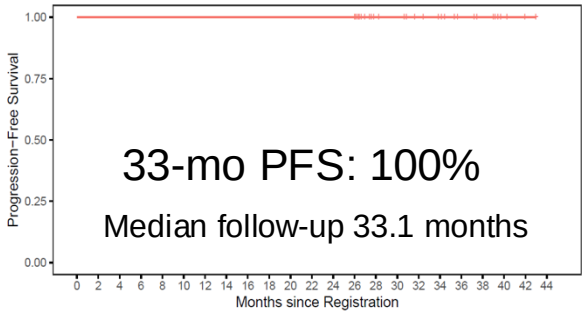
PD-1 blockade in early stage cHL safe and effective

- Studies of frontline PD-1 blockade in cHL have been promising[10,11,12,13]
  - N-AVD well-tolerated
  - Excellent PFS

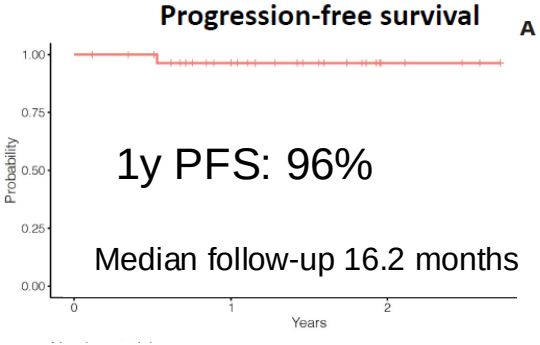
1L Nivolumab-AVD in advanced stage cH



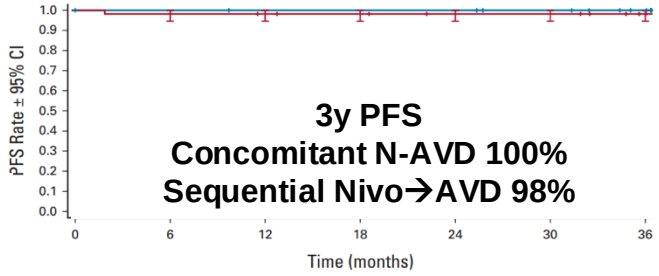
Sequential Pembro-AVD in cHL



Concurrent Pembro-AVD in cHL



1L Nivolumab-AVD in early stage cHL

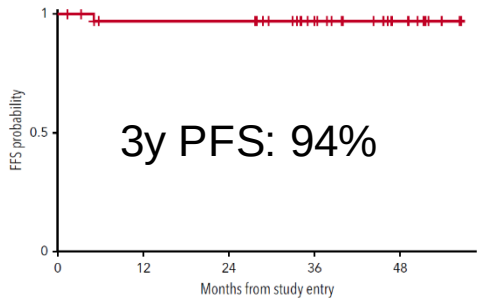


10. Bröckelmann PJ et al JCO. 2023 11. Ramchandren R et al JCO 2019 12. Allen PB, et al Blood. 2021 13. Lynch RC et al Blood 2023

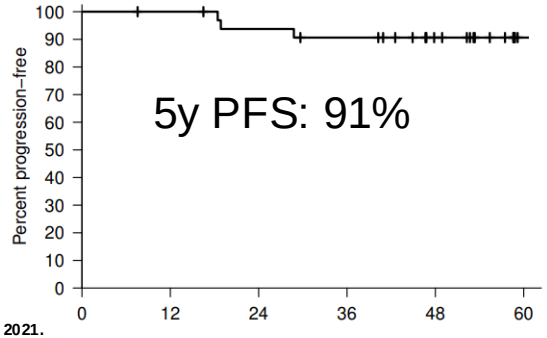
BV in early stage is safe and effective

- Studies of frontline BV in cHL have been promising
  - Well-tolerated
  - Excellent PFS

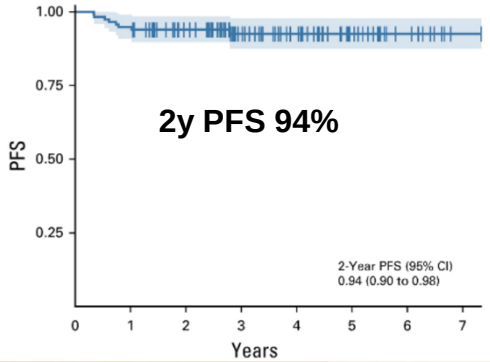
BV-AVD in early stage non-bulky cHL



BV-AD in early stage non-bulky cHL

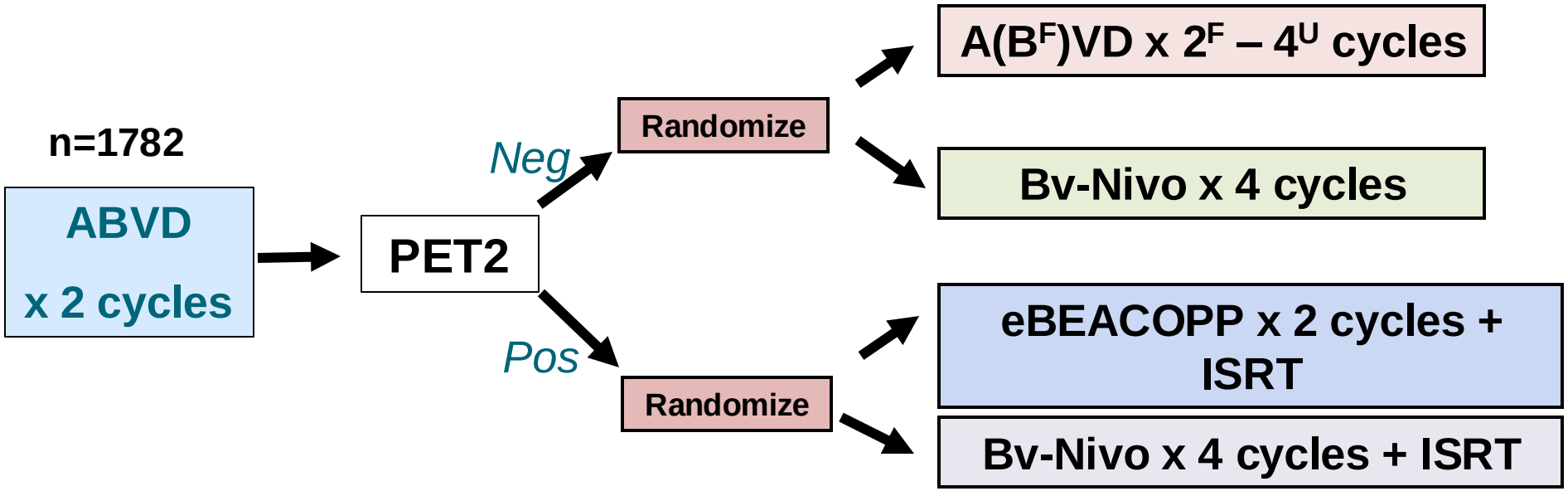


BV-AVD+/-RT in early unfavorable cHL



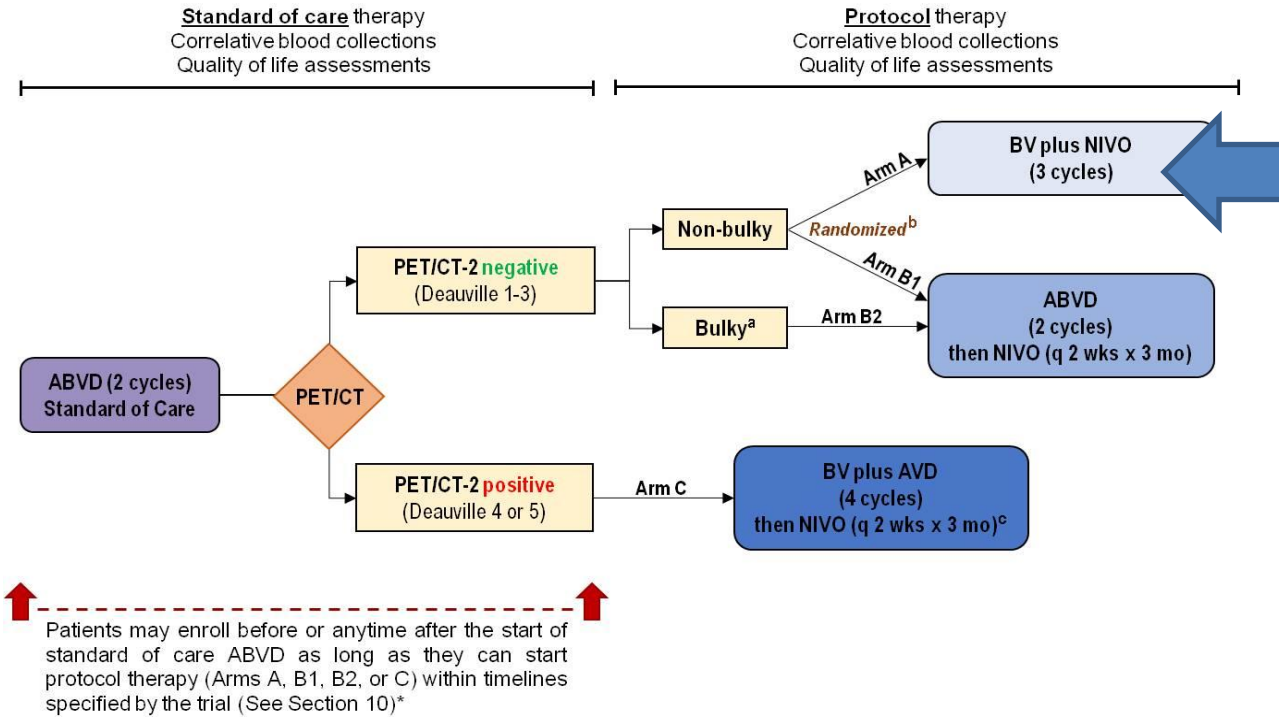
Abramson J, et al Blood 2019; Abramson J, et al. Blood Adv 2022; Kumar A, et al JCO 2021.

AHOD2131: PET-adapted BV-Nivo in early stage cHL



[a] 1 cycle = 28 days
[b] PET2 positive defined as Deauville 4 or 5

COH IIT 18157: A Phase 2 Study of PET-Adapted Incorporation of BV and Nivolumab into Radiation-Free Frontline Management of Early Stage HL



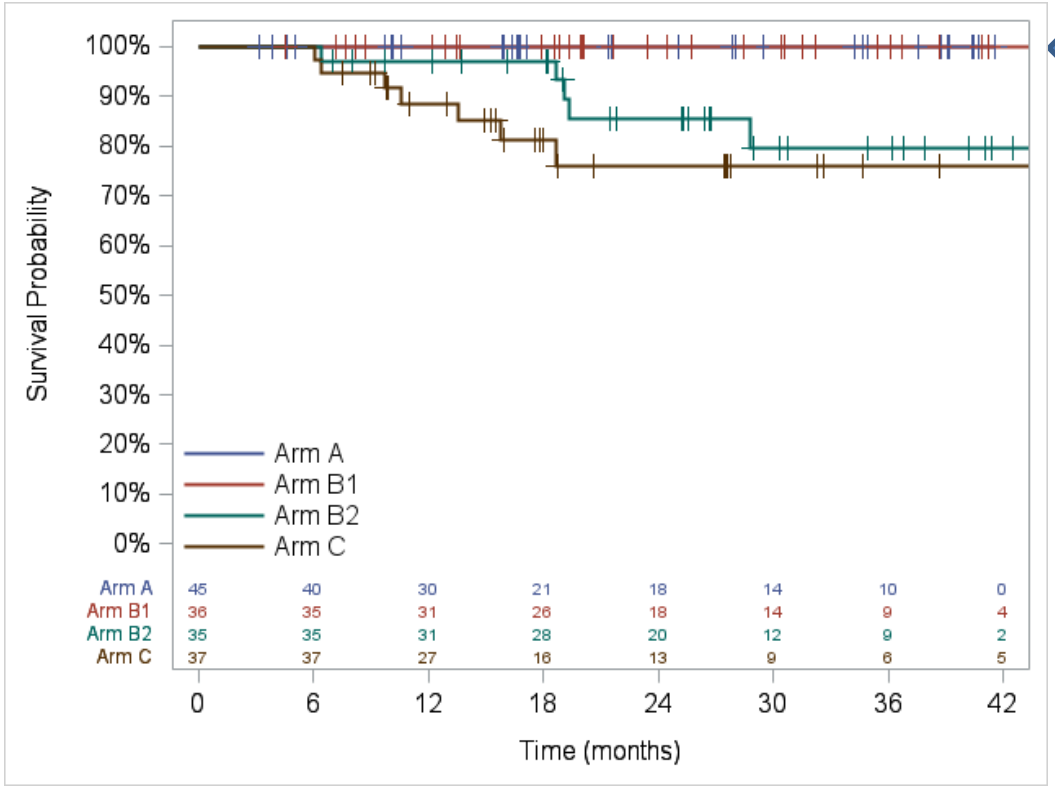
Experimental arm of upcoming Phase 3 COG early stage HL trial

Baseline Characteristics

Baseline Characteristics	N=153
Age (median/range)	31 (18-73)
Male	78 (51%)
Hispanic	
Yes	19 (12%)
No	126 (82%)
Not disclosed/Unknown	8 (5%)
Race	
White	117 (77%)
Asian	10 (7%)
Black	8 (5%)
Pacific Islander	2 (1%)
More than 1 race	2 (1%)
Undisclosed/Unknown	14 (9%)
Histology	
HL, NOS	59 (39%)
Lymphocyte rich or lymphocytic predominant	3 (2%)
Mixed cellularity	8 (5%)
Modular Sclerosis	83 (54%)
EBV	
Negative	63 (41%)
Positive	22 (14%)
Unknown	68 (44%)

Baseline Characteristics	N=153
Extra-nodal disease	
Yes	22 (14%)
No	125 (82%)
Unknown	6 (4%)
B symptoms	
Yes	48 (31%)
No	97 (63%)
Unknown	8 (5%)
Stage	
Stage I	17 (11%)
Stage II	134 (88%)
Missing	2 (1%)
GHSG criteria	
Favorable	54 (35%)
Unfavorable	91 (59%)
Missing	8 (5%)
Largest tumor size	
<5cm	72 (47%)
5 cm+	79 (52%)
< 10 cm	127 (83%)
10 cm+	24 (16%)
Missing	2 (1%)

Incorporating Nivo +/- BV in PET2-negative early stage cHL highly effective



PET2 negative arms

PET2 Negative Arms
Arm A: ABVDx2 → BV-Nivo x 3
Arm B1: ABVDx2 → ABVD x 2, Nivo x 6

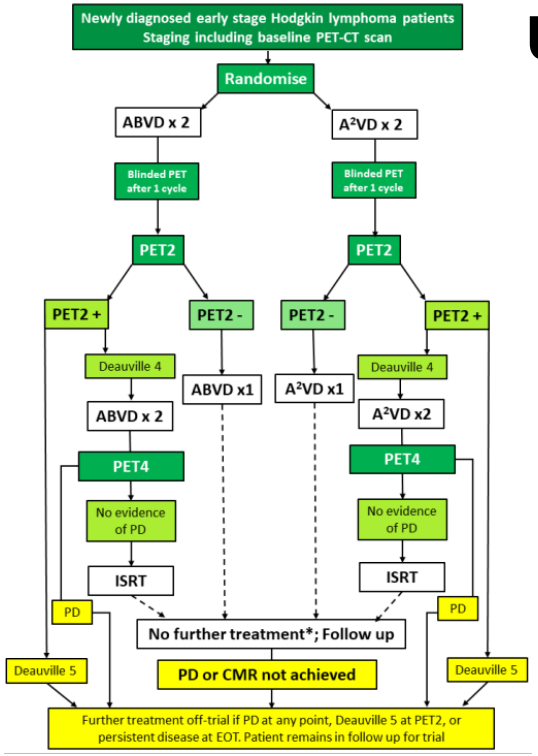
Arm B2 (bulky) ABVDx2 → ABVD x 2, Nivo x 6

PET2 Positive
Arm C: ABVDx2 → BV-AVD x 4, Nivo x 6

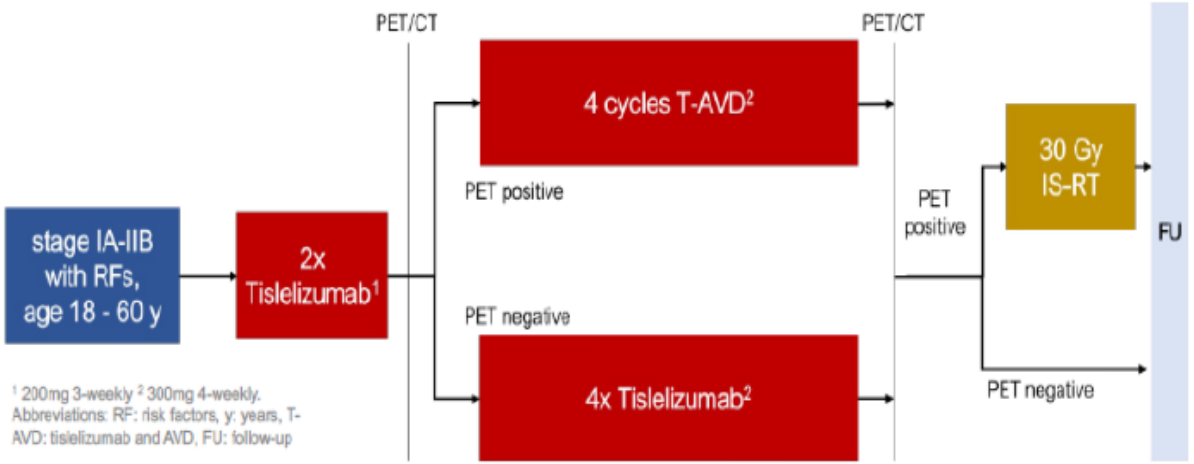
Unpublished, ASH 2024

Ongoing studies in early cHL

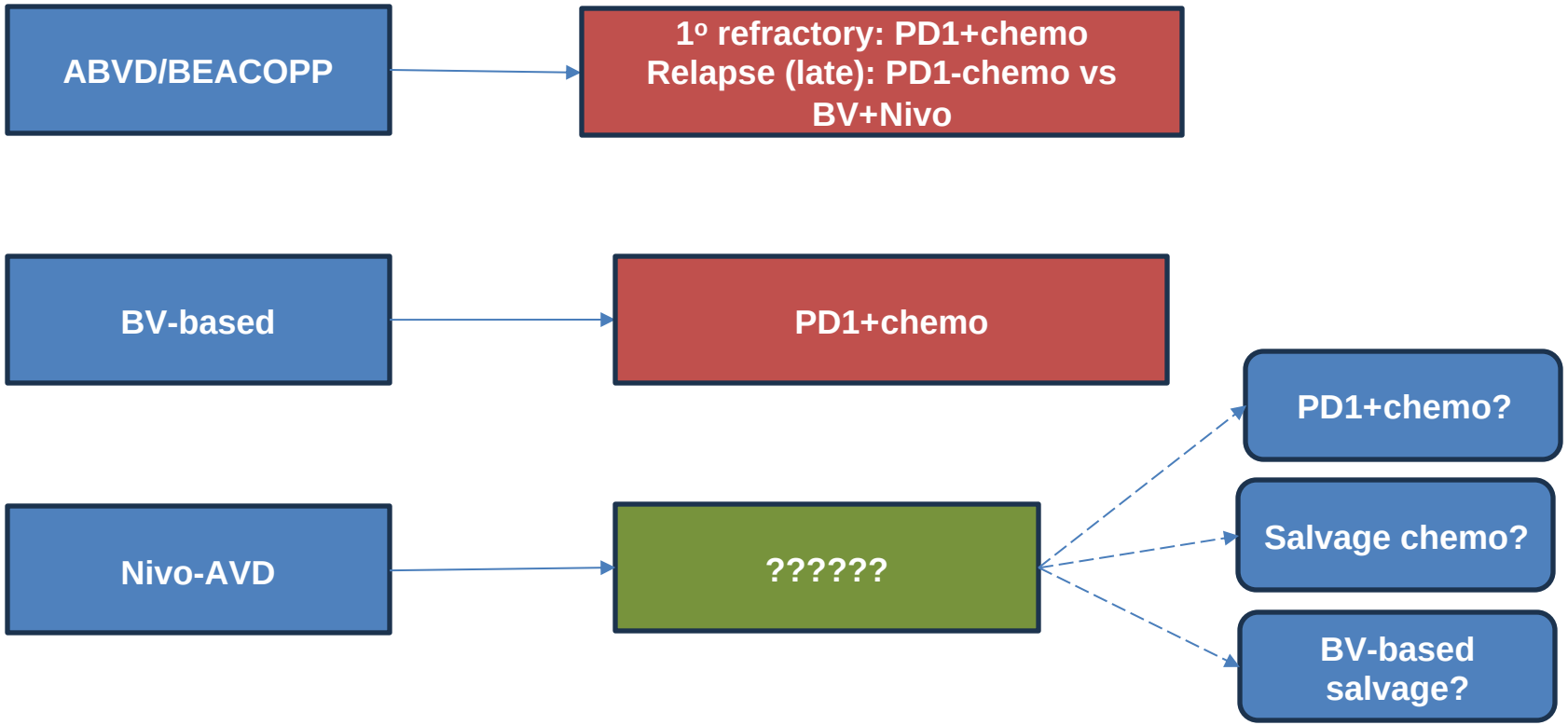
UK RADAR



INDIE (GHSG)



Next Questions: What's Next After Frontline Therapy



Conclusions

- Moving PD-1 blockade into earlier lines of cHL treatment has been promising and established a new paradigm of immunotherapy-based treatment of cHL
- Nivo-AVD improved PFS over BV-AVD
- Nivo-AVD better tolerated than BV-AVD
- Future questions
    - Nivo-AVD vs BrECADD?
    - How to salvage frontline anti-PD-1 relapses?