21ST INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM™

Are Checkpoint Inhibitors the Standard of Care for Frontline Hodgkin Lymphoma?

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THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

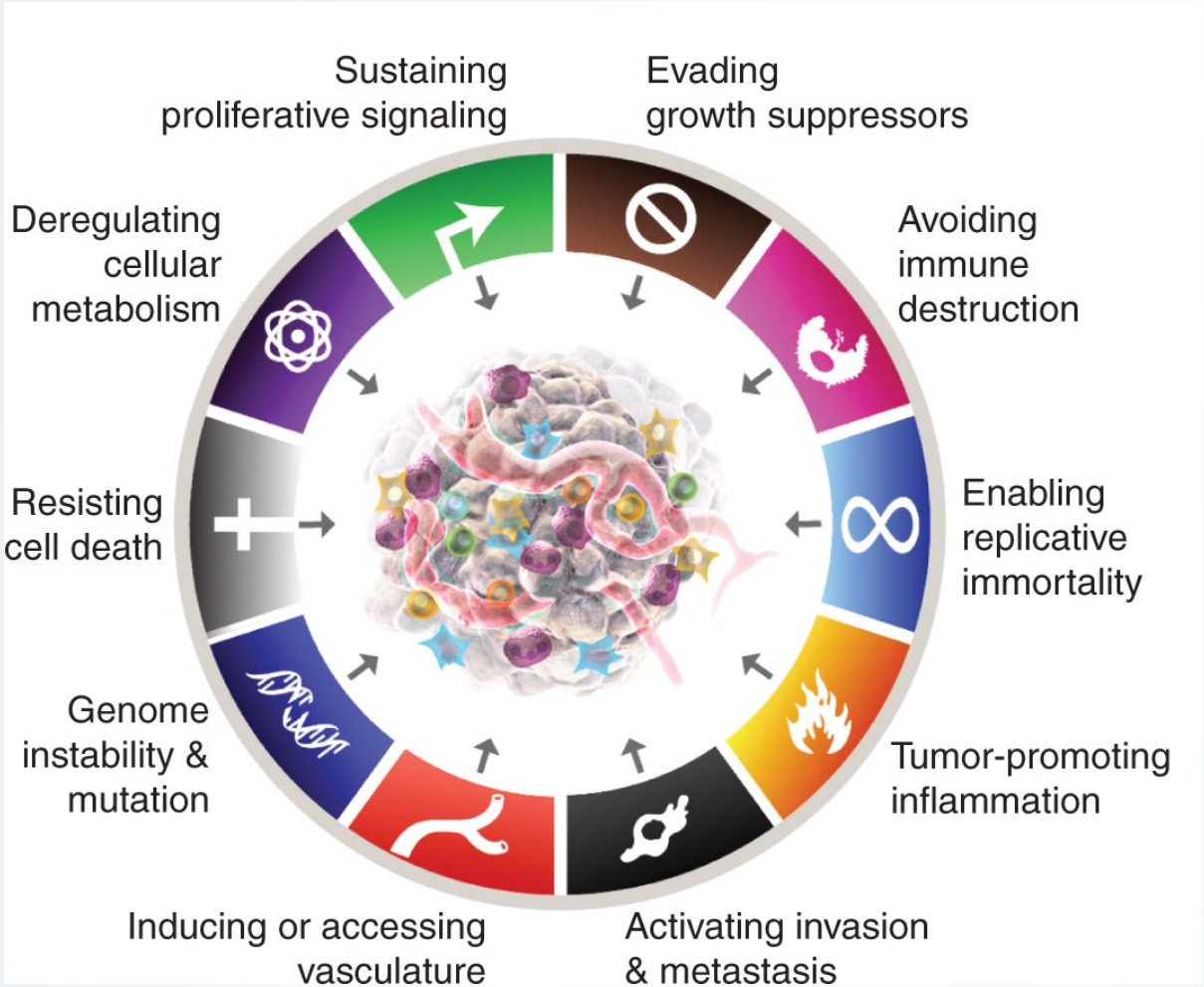
Disclosures

Consulting: Novartis, Bristol Meyers Squibb, Eli Lilly, GenMab, ADCT, ImmPACT Bio, Seattle Genetics, Regeneron, Caribou Biosciences, Abbvie

Research Funding: Genentech, Celgene, CRISPR Therapeutics, Morphosys AG, Caribou Biosciences, Repare Therapeutics, Artiva Biotherapeutics, Newave, AstraZeneca, ImmPACT Bio

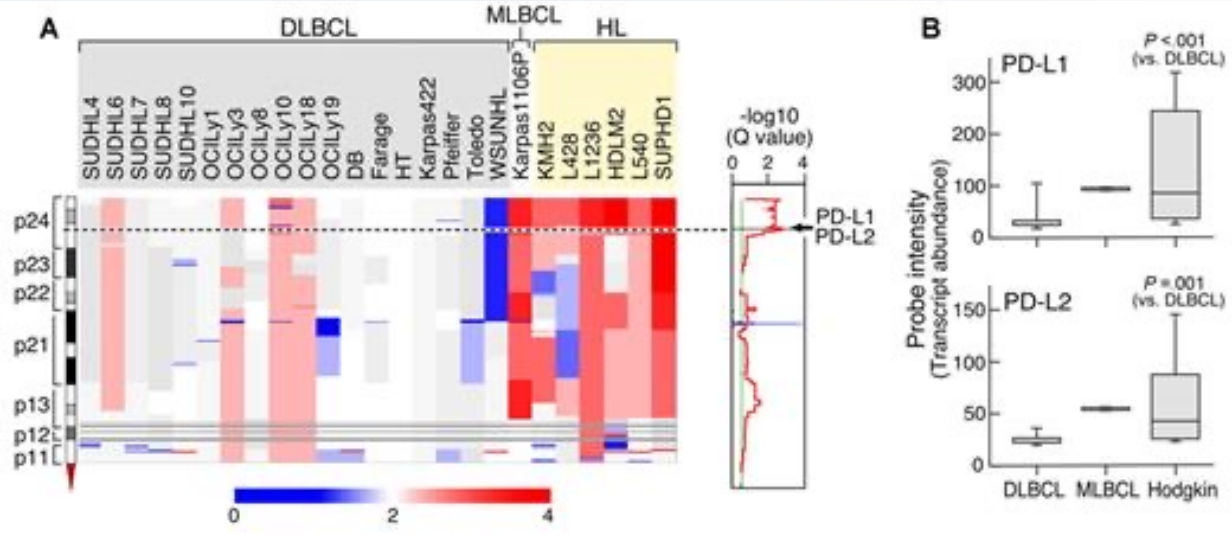
Immune Evasion and Hodgkin Lymphoma

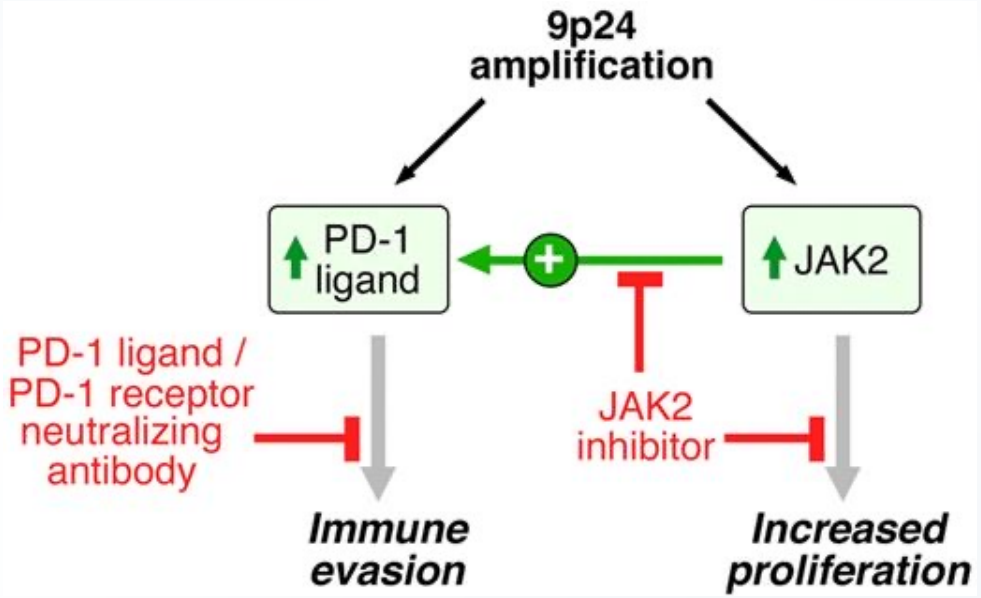
Immune Evasion is a Hallmark of Cancer



Hanahan D. Cancer Discovery (2022) 12 (1): 31-46.

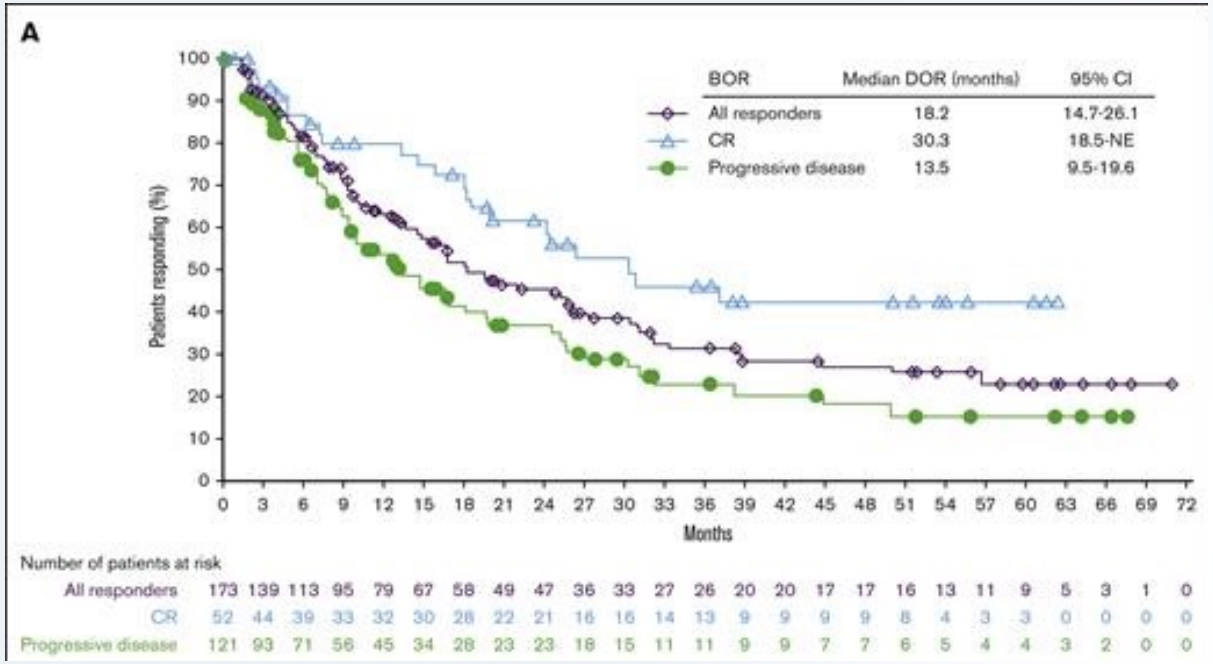
Amplification of 9q24 in Hodgkin Lymphoma Leads to Immune Evasion due to Overexpression of PD-L1 and PD-L2

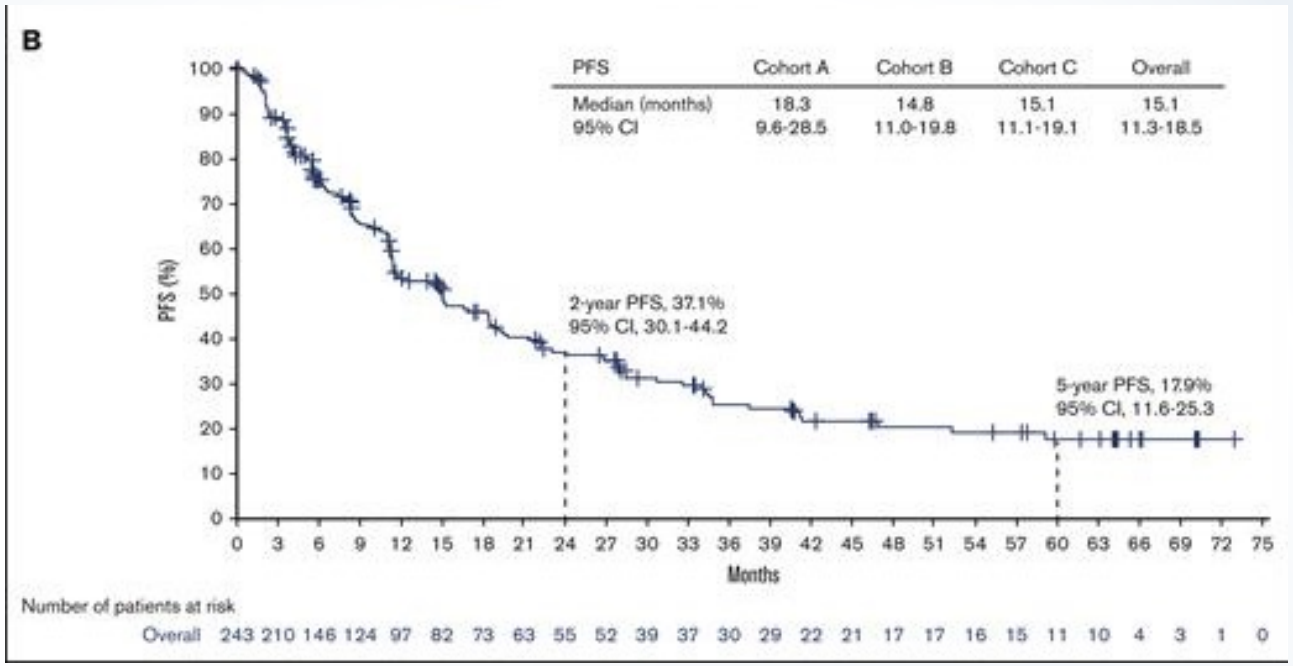




Green MR et al. Blood (2010) 116 (17): 3268-3277.

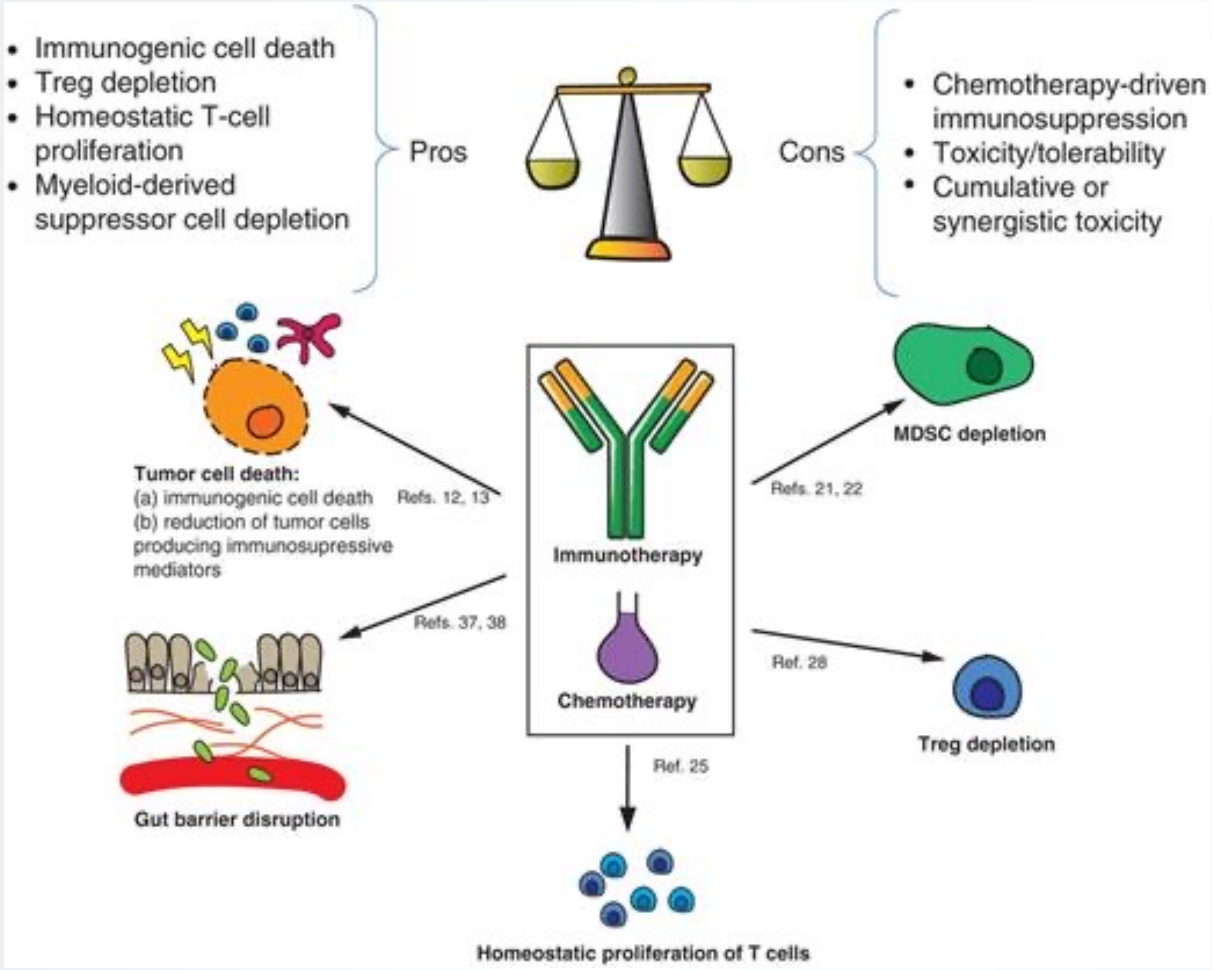
Nivolumab monotherapy is effective and durable, but not for every patient





Ansell et al. Blood Adv (2023) 7 (20): 6266-6274.

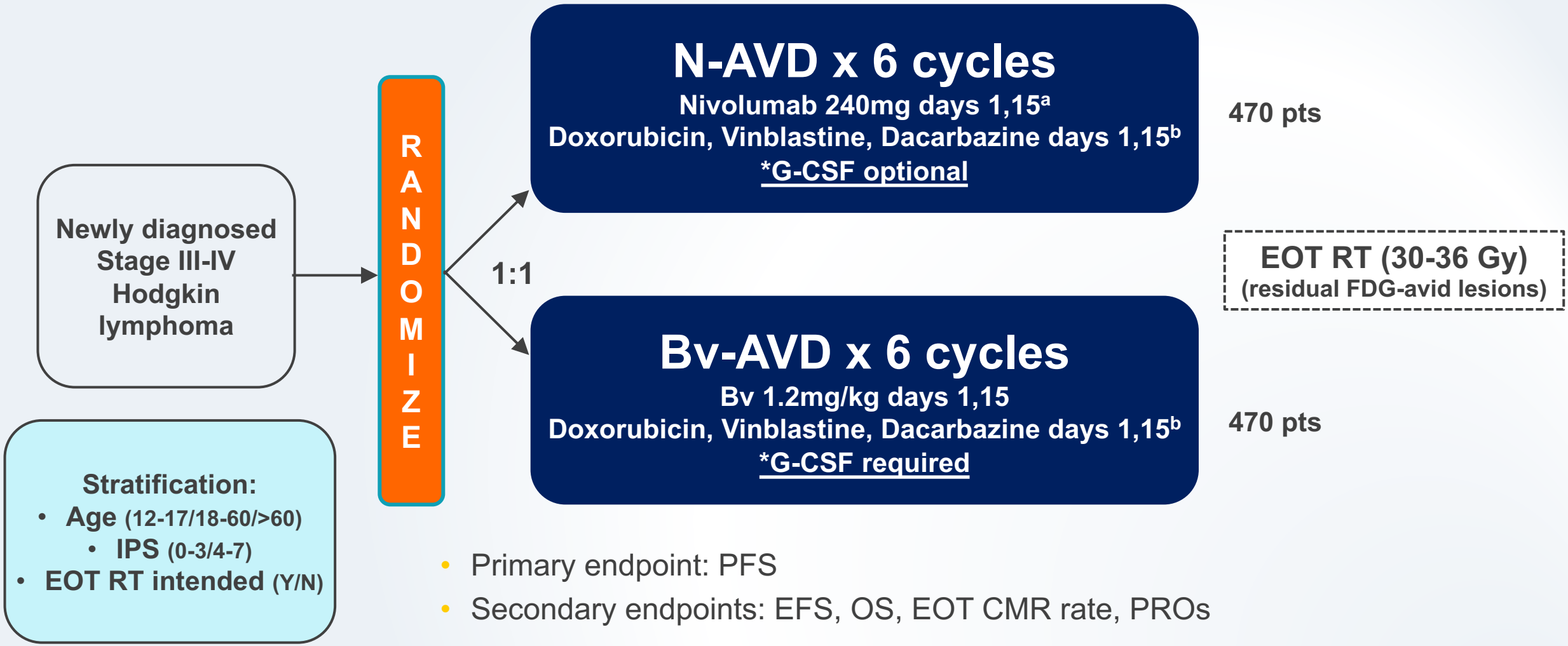
Synergism Between Chemotherapy and immunotherapy



Salas-Benito D et al. Cancer Discovery (2021) 11 (6): 1353-1367.

Discussion of S1826

S1826 Study Design



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

Slide Courtesy of Dr. Alex F. Herrera, MD
Presented at 2023 ICML Plenary Session (Lugano, Switzerland).

[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 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

AEs of interest: Hematologic

Toxicity	N-AVD n = 483		Bv-AVD n = 473	
	Any Gr N (%)	Gr ≥ 3 N (%)	Any Gr N (%)	Gr ≥ 3 N (%)
Neutropenia	268 (55%)	227 (47%)	152 (32%)	118 (25%)
Anemia	185 (38%)	29 (6%)	207 (44%)	42 (9%)
Thrombocytopenia	48 (10%)	8 (2%)	82 (17%)	15 (3%)
Received G-CSF	265 (54%)		463 (98%)	
Bone pain	39 (8%)		94 (20%)	

More neutropenia after N-AVD

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

AEs of interest: Infectious

Toxicity	N-AVD n = 483	Bv-AVD n = 473
Febrile Neutropenia	26 (5%)	32 (7%)
Sepsis	9 (2%)	16 (3%)
Infections/Infestations	22 (5%)	36 (8%)

No increased infectious toxicity in N-AVD arm

AEs of Interest: Peripheral Neuropathy

Toxicity	N-AVD n = 483		Bv-AVD n = 473	
	Any Gr N (%)	Gr ≥ 3 N (%)	Any Gr N (%)	Gr ≥ 3 N (%)
Peripheral sensory neuropathy	138 (29%)	6 (1%)	262 (55%)	37 (8%)
Peripheral motor neuropathy	20 (4%)	1 (0%)	35 (7%)	6 (1%)

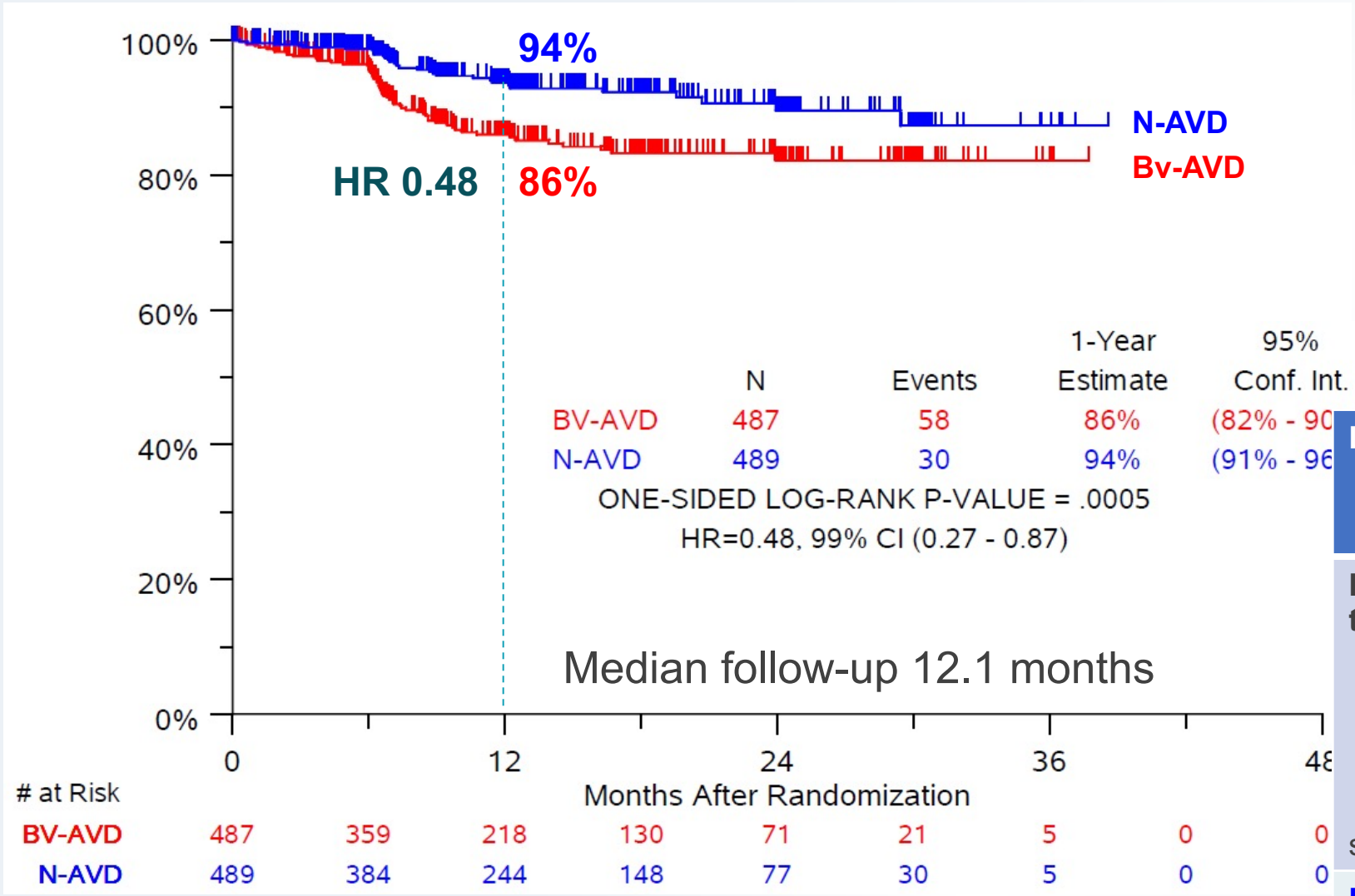
More neuropathy in Bv-AVD arm

AEs of Interest: Immune/Other

Toxicity	N-AVD n = 483		Bv-AVD n = 473	
	Any Grade No (%)	Grade ≥ 3 No (%)	Any Grade No (%)	Grade ≥ 3 No (%)
ALT increased	**156 (32%)**	**22 (5%)**	**194 (41%)**	**22 (5%)**
AST increased	**120 (25%)**	**12 (2%)**	**153 (32%)**	**13 (3%)**
Rash maculo-papular	51 (11%)	4 (1%)	58 (12%)	0 (0)
Hypothyroidism	**33 (7%)**	**1 (0%)**	**3 (1%)**	**0 (0)**
Rash acneiform	18 (4%)	0 (0)	12 (3%)	0 (0)
Pneumonitis	10 (2%)	2 (0%)	15 (3%)	10 (2%)
Gastritis	10 (2%)	3 (1%)	8 (2%)	0 (0)
Hyperthyroidism	**14 (3%)**	**0 (0)**	**0 (0)**	**0 (0)**
Colitis	5 (1%)	1 (0%)	6 (1%)	4 (1%)

Low rates of immune-related adverse events

N-AVD improves PFS compared to Bv-AVD



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

Disposition	N-AVD (n=489) N (%)	Bv-AVD (n=487) N (%)
Discontinued all treatment early	**39 (8%)**	**57 (12%)**
Adverse event	22 (4%)	18 (4%)
Refusal unrelated to AE	10	14
Progression/relapse	**0 (0%)**	**7 (1.4%)**
Death on treatment	**2 (0.4%)**	**8 (1.6%)**
Other – not protocol specified	5	10
Discontinued Bv or Nivolumab	**53 (11%)**	**109 (22%)**
Received radiotherapy	**2 (0.4%)**	**4 (0.8%)**

Nivolumab-AVD is better tolerated and improves PFS vs Bv-AVD in older patients (aged ≥60 years) with advanced stage Hodgkin lymphoma (cHL) on S1826

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Progression-Free Survival (PFS) and Toxicity with Nivolumab-AVD Compared to Brentuximab Vedotin–AVD in Pediatric Advanced Stage Classic Hodgkin Lymphoma (cHL)- S1826

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S1826 Older Pts Baseline Characteristics

Baseline characteristics	N-AVD N = 48 N (%)	Bv-AVD N = 49 N (%)
Age, median (range)	66.4 (60-84 y)	67.1(60-87 y)
Age 60-69	31 (65%)	36 (74%)
Age 70-79	14 (29%)	12 (24%)
Age ≥80	3 (6%)	1 (2%)
Female Sex	19 (40%)	18 (37%)
Race		
White	43 (90%)	40 (82%)
Black	1 (2%)	2 (4%)
Asian	1 (2%)	1 (2%)
Other/Unknown	3 (6%)	6 (12%)
Hispanic	5 (10%)	5 (10%)

Slide courtesy of Dr. Sarah C. Rutherford, MD

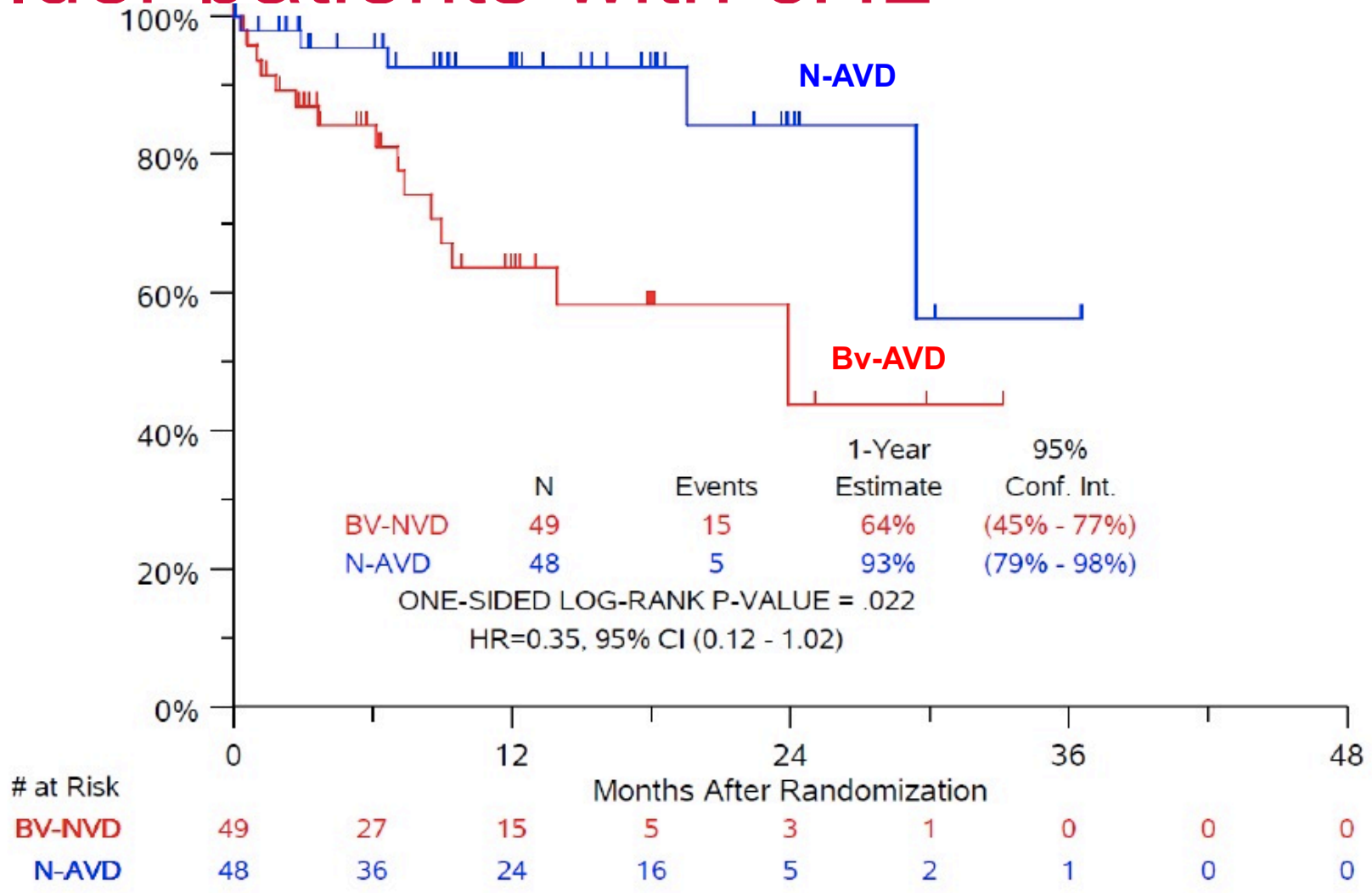
One-third of pts on Bv-AVD discontinued treatment early including 10% who died

Disposition	N-AVD N = 48, N (%)	Bv-AVD N = 49, N (%)
Treatment ongoing	1 (2%)	2 (4%)
Completed treatment	42 (88%)	31 (63%)
Discontinued all treatment early	**5 (10%)**	**16 (33%)**
Adverse event	2 (4%)	7 (14%)
Refusal unrelated to AE	1 (2%)	2 (4%)
Progression/relapse	0 (0%)	1 (2%)
Death on treatment	**1 (2%)**	**5 (10%)**
Other – not protocol specified	1 (2%)	1 (2%)
Received protocol radiotherapy	0 (0%)	0 (0%)

15% discontinued nivolumab and 39% discontinued Bv early, primarily due to AEs

Slide courtesy of Dr. Sarah C. Rutherford, MD

N-AVD markedly improves PFS over Bv-AVD in older patients with cHL



1-year PFS
N-AVD 93%
Bv-AVD 64%

Median follow-up
12.1 months

p-value = 0.022
HR=0.35,
95% CI (0.12-1.02)

Slide courtesy of Dr. Sarah C. Rutherford, MD

Majority of deaths on Bv-AVD due to infection/sepsis

Cause of death	N-AVD	Bv-AVD
Infection	1	3
Sepsis	1	2*
Pneumonitis	0	1
Unknown	0	1
Total OS events	**2**	**7**

Non-relapse mortality
N-AVD 4% vs Bv-AVD 14%

Slide courtesy of Dr. Sarah C. Rutherford, MD

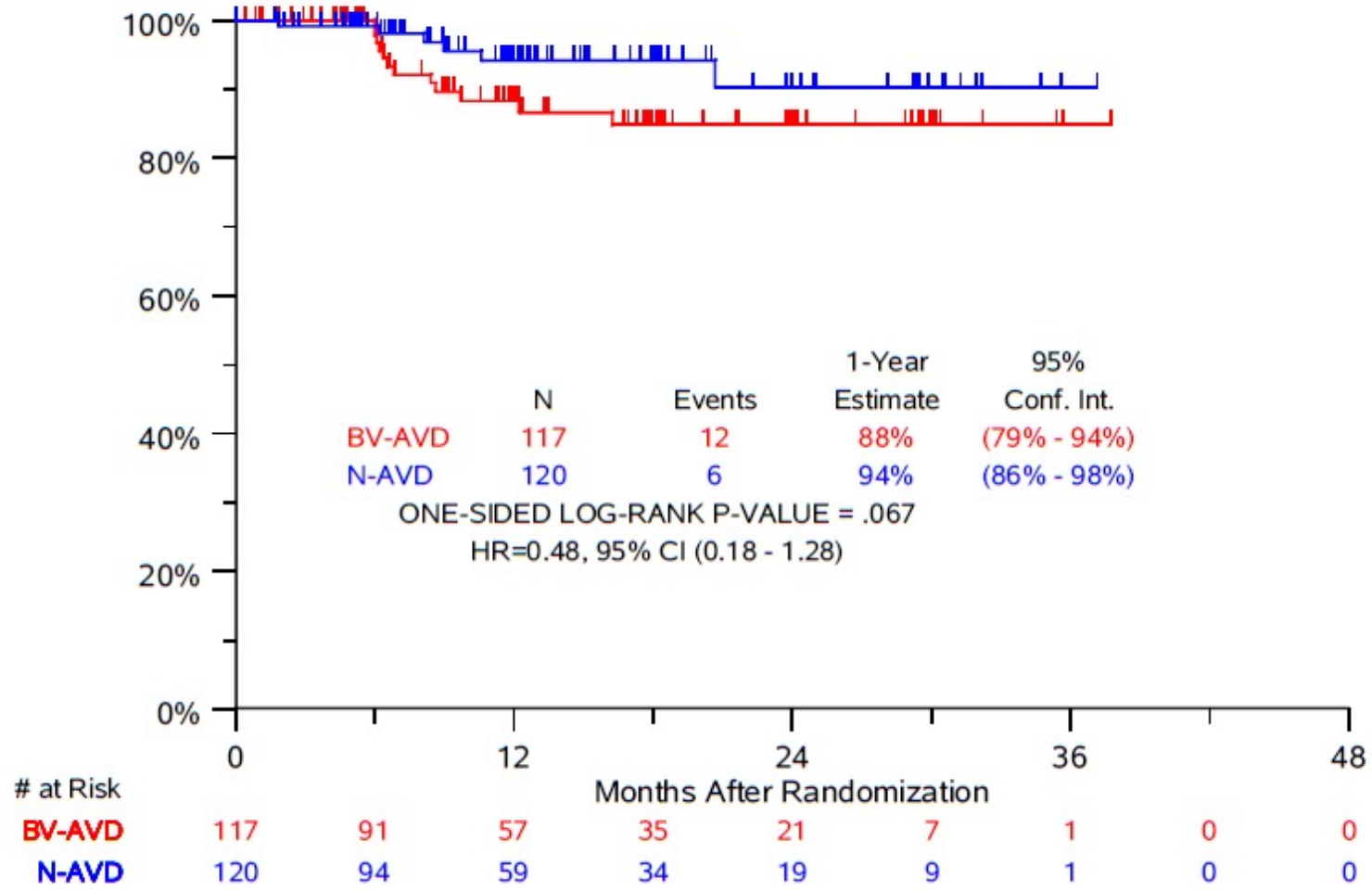
*1 death from COVID-19/sepsis

S1826 Pediatric Cohort (<18 years old)

Patient characteristics	N-AVD n=120 N (%)	Bv-AVD n=117 N (%)
Age, median (range)	15.4 (12-17.9)	15.6 (12-17.9)
Female Sex	52 (43.3%)	66 (56.4%)
Race		
White	84 (70%)	79 (67.5%)
Black	18 (15%)	17 (14.5%)
Asian	0 (0%)	4 (3.4%)
Other/Unknown	18 (15%)	17 (14.5%)
Hispanic	25 (20.8%)	17 (14.5%)

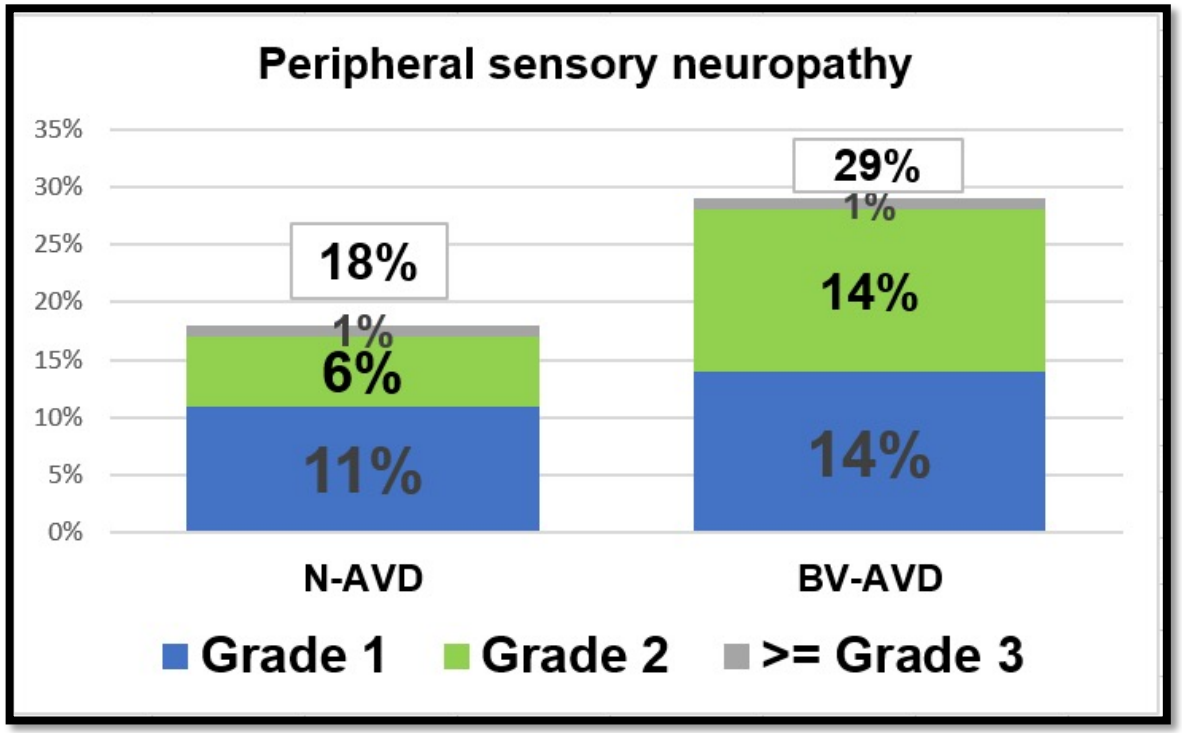
Disease characteristics	N-AVD n=120 N (%)	Bv-AVD n=117 N (%)
Stage		
III	56 (46.7%)	47 (40.2%)
IV	63 (52.5%)	67 (57.3%)
Not reported	1 (0.8%)	3 (2.6%)
B symptoms present	68 (56.6%)	64 (54.7%)
IPS Score		
0-3	89 (74.2%)	83 (70.9%)
4-7	31 (25.8%)	34 (29.1%)
Bulky disease > 10 cm	56 (46.7%)	48 (41%)

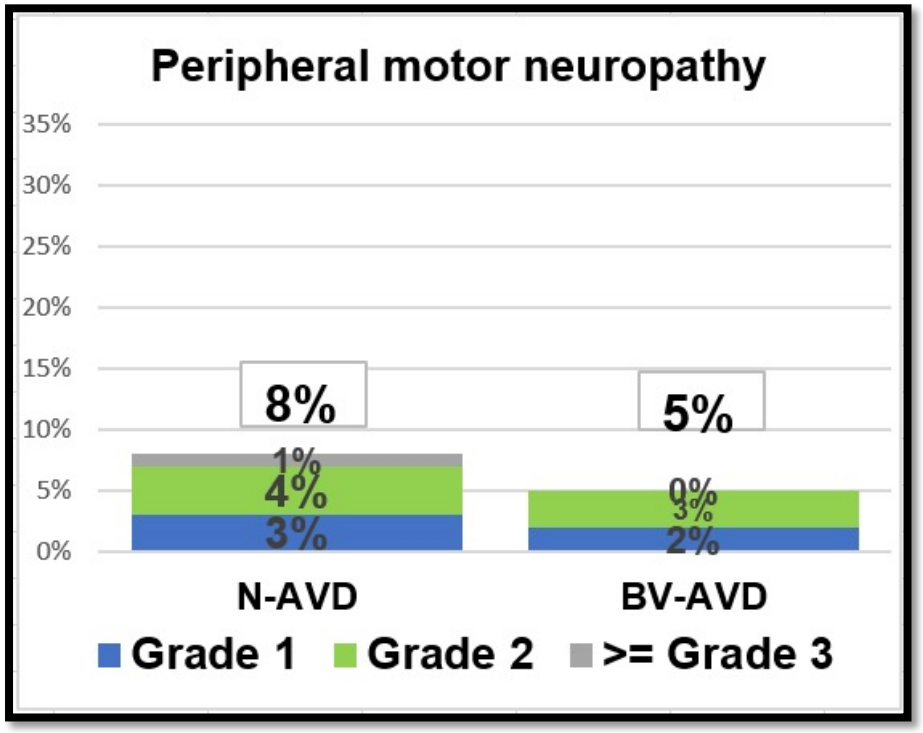
12 Month Progression Free Survival



Data as of December 15, 2022

Peripheral Neuropathy





Slide courtesy of COG and Dr. Sharon Castellino, MD

Pediatric Cohort: Treatment Discontinuation

Disposition	N-AVD (n=120)	Bv-AVD (n=117)
Treatment ongoing	8	16
Completed treatment	102	98
Discontinued all treatment early Adverse event Refusal unrelated to AE Death on treatment	10 7 3 0	3 3 0 0
Discontinued Bv or Nivolumab due to AE	9/10 **	3/3 ##
Received radiotherapy	0	2

**hyperglycemia; panic attack; ## neuropathy; pneumonitis

AEs of Interest: Immune/Other

Toxicity	N-AVD n =119		Bv-AVD n = 111	
	Any Grade No (%)	Grade ≥ 3 No (%)	Any Grade No (%)	Grade ≥ 3 No (%)
ALT increased	50 (42%)	8 (7%)	60 (54%)	7 (6%)
AST increased	44 (37%)	3 (3%)	49 (44 %)	6 (5%)
Rash maculo-papular	2 (2%)	0 (0%)	16 (14%)	0 (0%)
Rash acneiform	3 (3%)	0 (0%)	6 (5%)	0 (0%)
Pneumonitis	3 (3%)	1 (1%)	1 (3%)	1 (1%)
Gastritis	6 (5%)	1 (1%)	2 (2%)	0 (0%)
Hypothyroidism	6 (5%)	0 (0%)	1 (0%)	0 (0%)
Hyperthyroidism	2 (2%)	0 (0%)	0 (0%)	0 (0%)
Colitis	0 (0%)	0 (0%)	1 (1%)	1 (1%)

Overall, Low Rates of Immune-Related Adverse Events

Conclusions about S1826

- **N-AVD** improved **PFS and EFS** compared to Bv-AVD

- N-AVD was **well tolerated** with fewer patients discontinuing therapy
  - Concerning *10%* of elderly patients (>60 years old) died while receiving Bv-AVD with *33%* of these patients discontinuing Bv-AVD early.
  - Bv-AVD better tolerated in pediatric patients, but still *concerning rates of neuropathy* in Bv-AVD treated patients.

- Updated **2-year follow up** data coming soon
  - N-AVD poised to be the **new standard-of-care** for frontline treatment of AS-HL

Frontline Treatment of Early-Stage Hodgkin Lymphoma Patients with Immunotherapy

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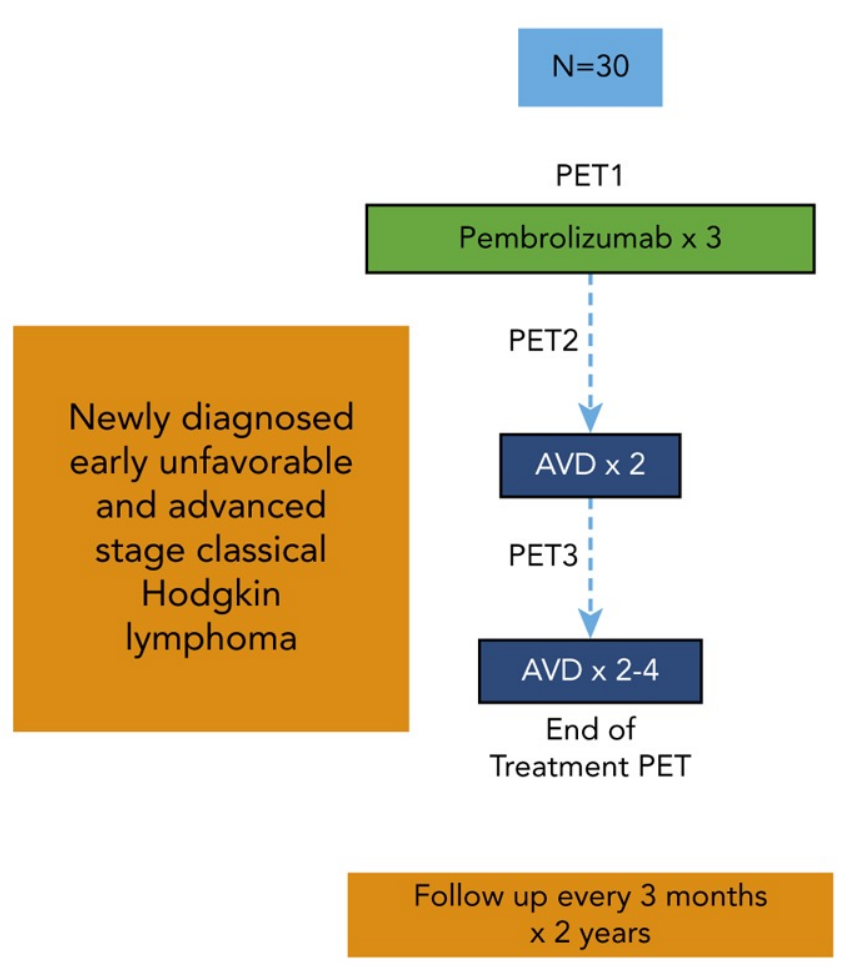
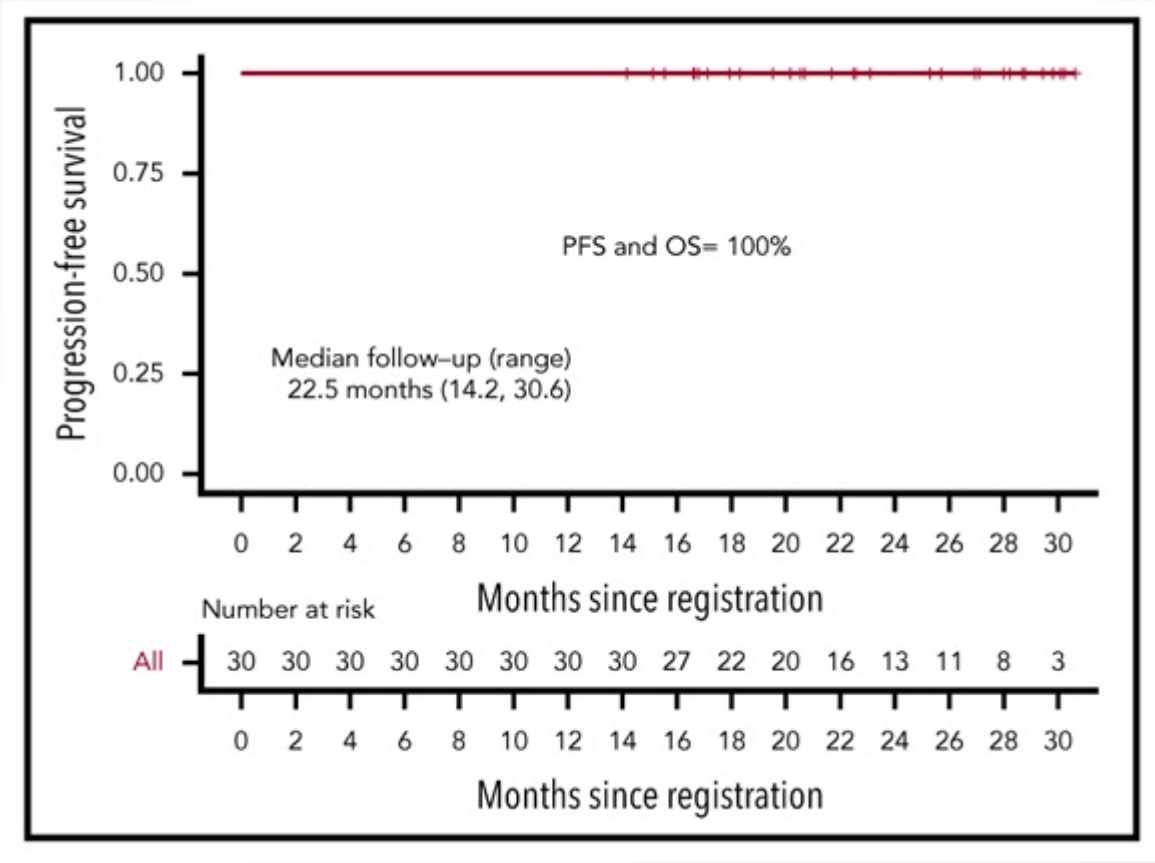
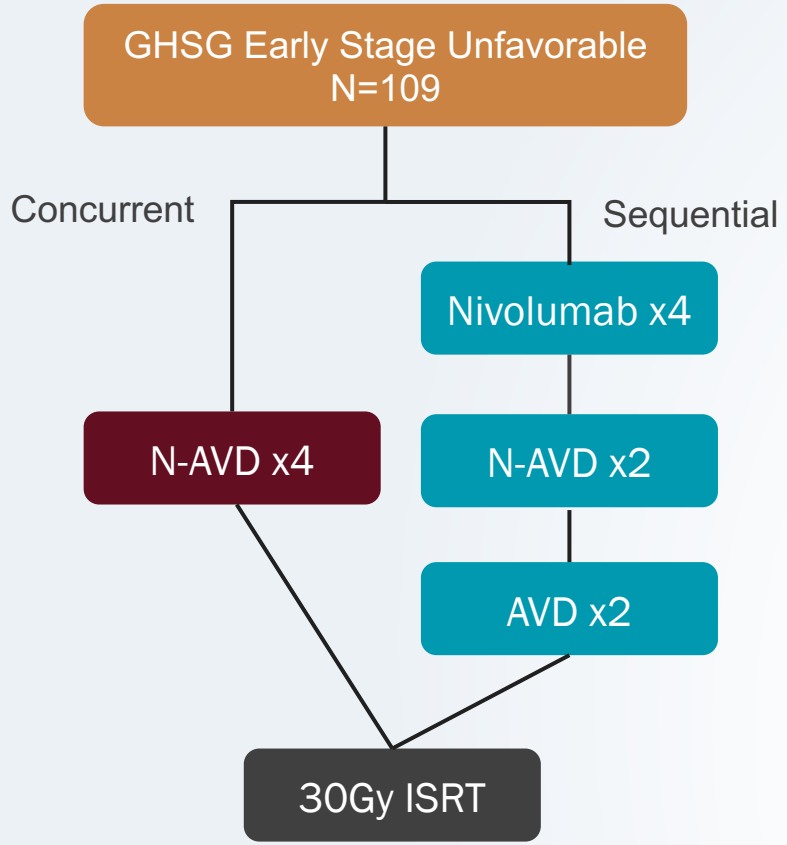
Sequential Pembrolizumab and Chemotherapy

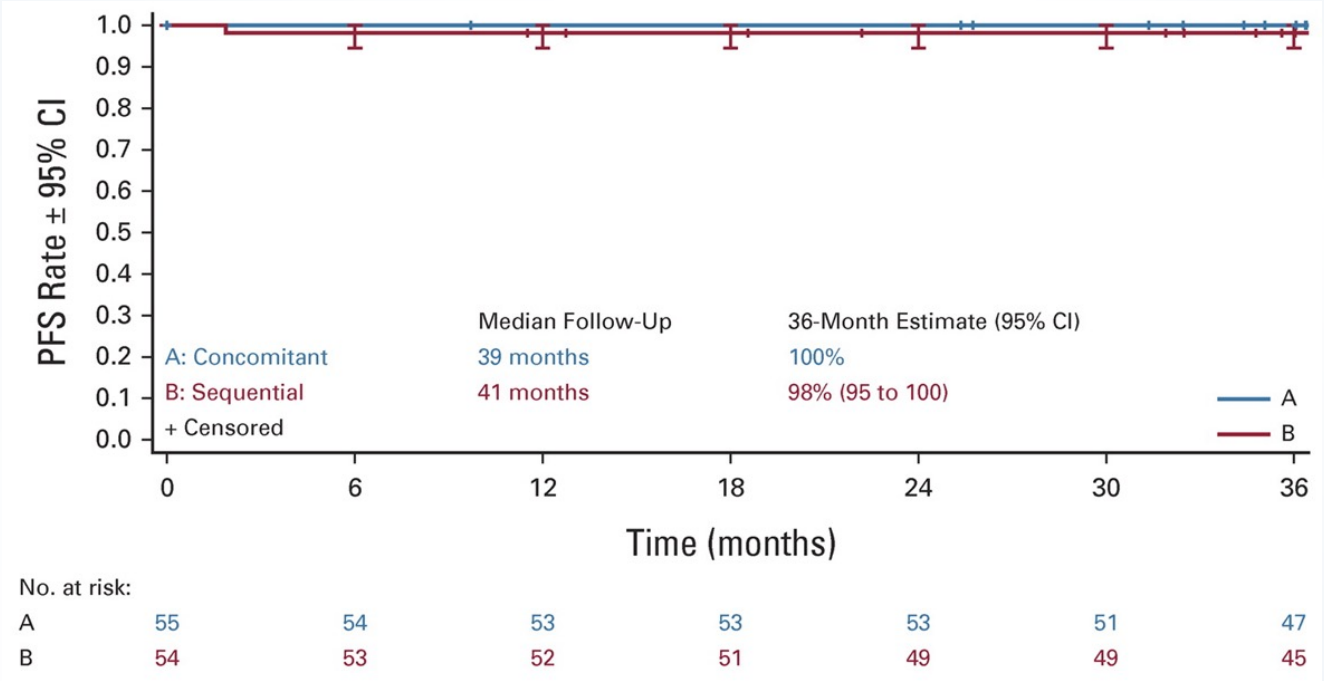




Allen PB et al. Blood (2021) 137 (10): 1318-1326.

NIVAHL



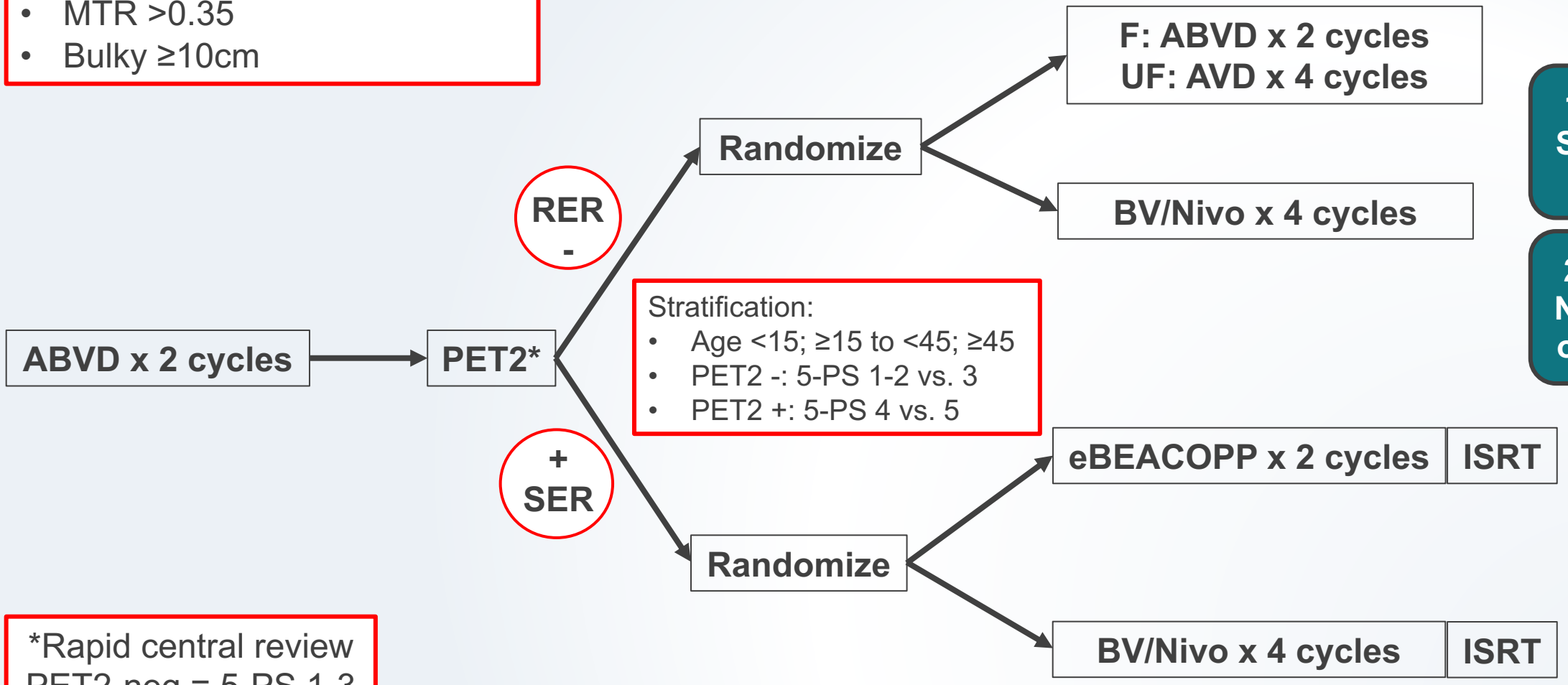


Brockelmann PJ et al. JCO (2023) 41 (6): 1193-1199.

AHOD2131 TRIAL DESIGN

EORTC Favorable/Unfavorable:
- Age ≥50
- >3 nodal sites
- ESR >50 if A; >30 if B
- MTR >0.35
- Bulky ≥10cm

Abbreviated Inclusion:
- Newly diagnosed, previously untreated stage I or II cHL
- Ages 5-60



Stratification:
- Age <15; ≥15 to <45; ≥45
- PET2 -: 5-PS 1-2 vs. 3
- PET2 +: 5-PS 4 vs. 5

1º endpoint: Superiority of 3-year PFS

2º endpoint: Noninferiority of 12 year OS

*Rapid central review
PET2-neg = 5-PS 1-3

RER: Rapid Early Responders
SER: Slow Early Responders

Conclusions of frontline treatment of ES-HL with immunotherapy

- Encouraging data of both concurrent and sequential therapies with essentially **100% PFS** in all trials so far.

- Large confirmatory phase III study, **AHOD2131**, currently accruing patients.
  - Immunotherapy options not currently approved for frontline ES-HL treatment.

Thank you!