How I treat high-risk Hodgkin lymphoma in first line

Stephen M. Ansell, MD, PhD
Dorotha W. and Grant L. Sundquist Professor in Hematologic Malignancies Research
Chair, Division of Hematology
Mayo Clinic

Disclosures for Stephen Ansell, MD, PhD

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N/A = Not Applicable (no conflicts listed)

What is the goal of frontline therapy in Hodgkin lymphoma?

- To cure more patients
  - Treatment *needs to increase survival*
- To limit long term toxicity
  - Treatment *must not decrease survival*

Historically we had 2 approaches -

- Low-intensity first-line therapy (like ABVD)

  requires intensifying treatment for poor metabolic responders to improve lymphoma control
  - To possibly cure more patients.

- High-intensity first-line therapy (like escBEACOPP)

  requires a reduction in treatment in good responders, with the aim of improving safety.
  - To limit long term toxicity

- Need a PET-driven strategy to achieve this

Limited stage Hodgkin lymphoma – RT or not?

Risk Factors for Early-Stage Hodgkin lymphoma

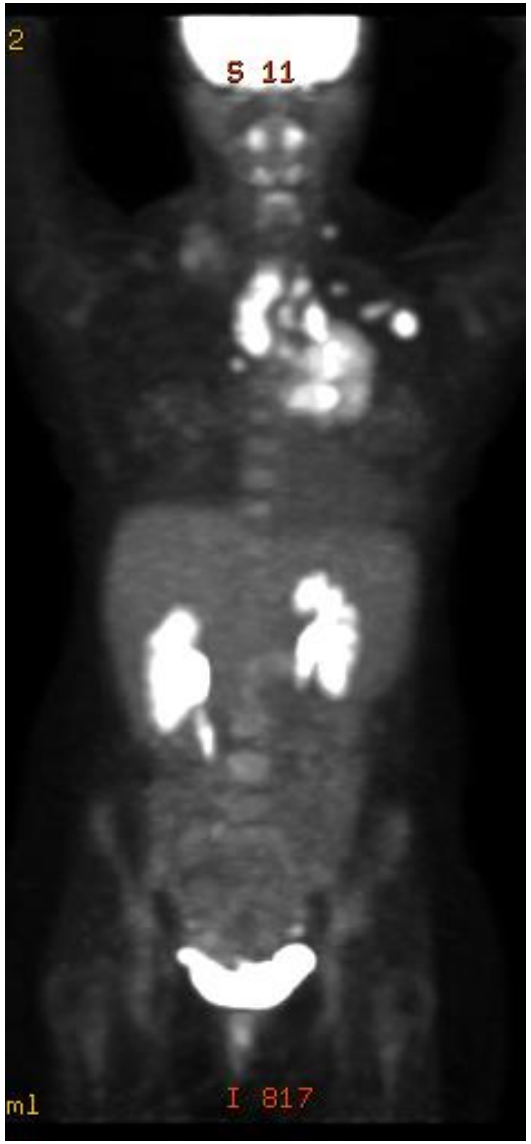


Table 1 | Definition of early stage unfavourable HL depending on the study groups*

Risk factors	EORTC	GHSG	NCIC/ECOG	NCCN 2010
Large mediastinal mass (>1/3)	Yes	Yes	No	Yes or >10 cm
Histology other than LP/NS	No	No	Yes	No
Age	≥50 years	No	≥40 years	No
Extranodal disease	No	Yes	No	>1 lesion
ESR ≥50 mm/h without B-symptoms or ≥30 mm/h with B-symptoms	Yes	Yes	Yes, if ≥50	Yes, if ≥50 or any B-symptoms
Number of nodal areas involved	≥4 nodal areas	≥3 nodal areas	≥4 nodal areas	≥3 nodal areas

*All patients must have stage I or II disease according to the Ann–Arbor classification (that is, involved lymph node regions only on one side of the diaphragm). Abbreviations: ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; ESR, erythrocyte sedimentation rate; GHSG, German Hodgkin Study Group; HL, Hodgkin Lymphoma; LP, lymphocyte predominance; NCCN, National Comprehensive Cancer Network; NCIC, National Cancer Institute of Canada; NS, nodular sclerosis.

Nat Rev Clin Oncol 2012 Aug; 9(8): 450-459

The role of the interim PET in limited stage cHL to direct therapy

RAPID Trial (n=571; 2/3 favorable) –

- PET negative – ABVD x3 versus ABVD x3 + IFRT
- PET Positive – ABVD x4 + IFRT

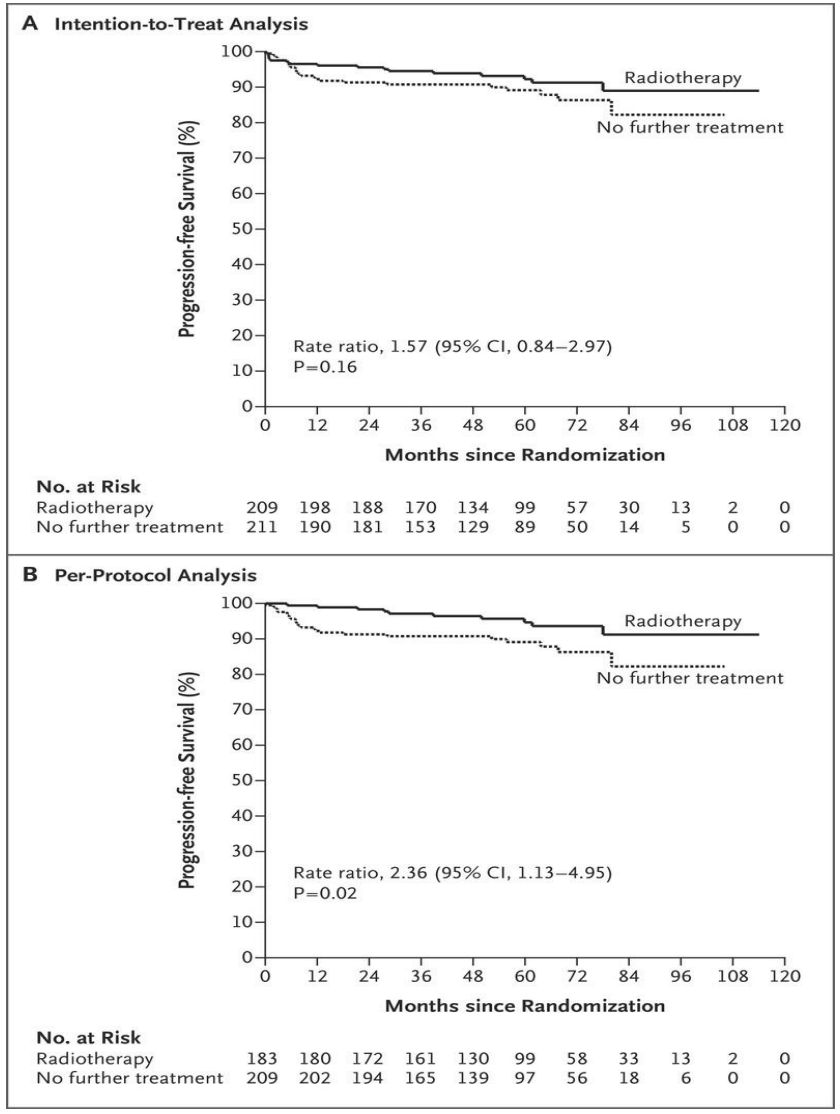
EORTC/LYSA/FIL H10 Trial (n=754; EORTC favorable) –

- Standard Arm – ABVD x3 + INRT
- Experimental Arm – PET directed
  - PET negative – ABVD x 4
  - PET positive – ABVD x 2, escBEACOPP x 2, INRT

GHSG HD16 (n=1150; GHSG favorable) –

- Standard Arm – ABVD x 2 + 20Gy IFRT
- Experimental arm – PET directed
  - IFRT only if PET positive

RAPID trial of PET-directed therapy for early-stage Hodgkin's lymphoma



PET negative –
ABVD x3 versus ABVD x3 + IFRT

Radford et al. N Engl J Med. 2015 Apr 23;372(17):1598-607.

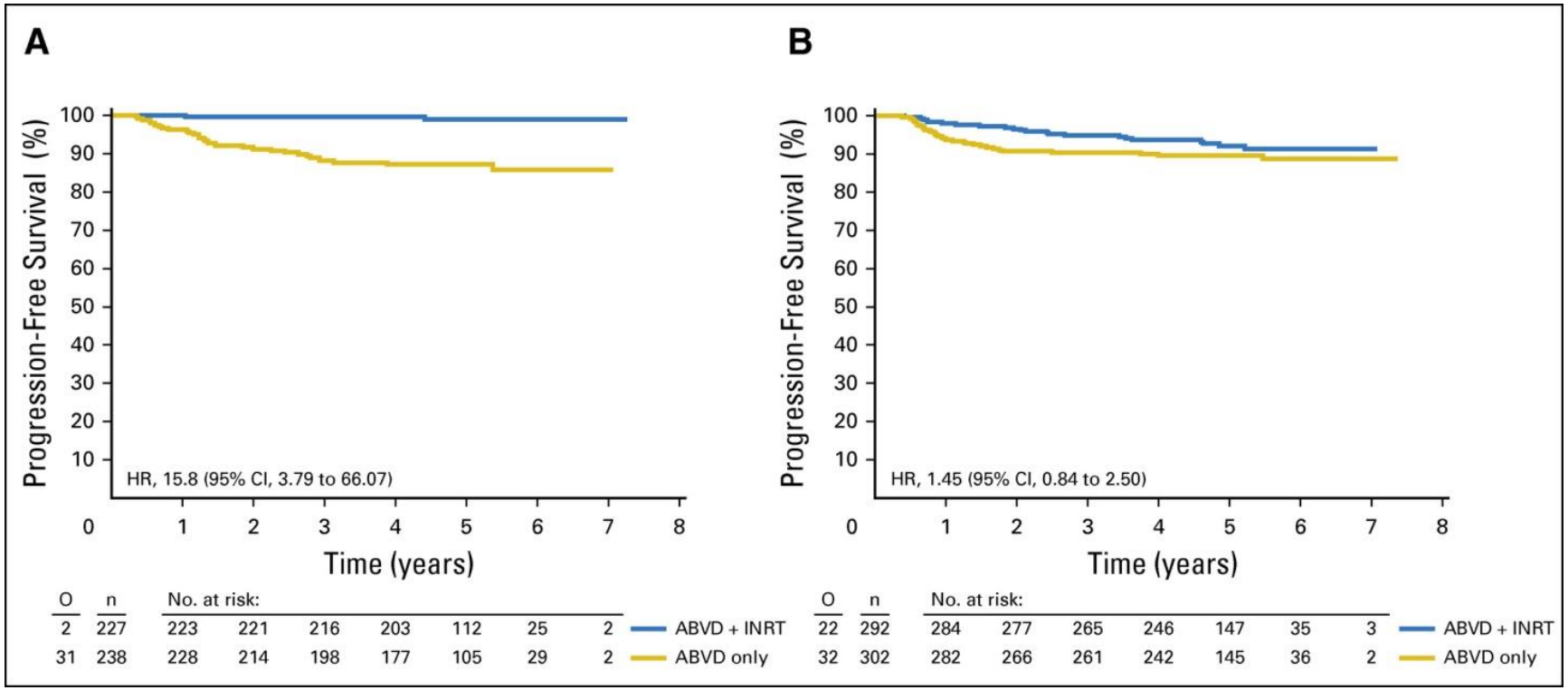
H10 Trial: Progression-free survival of 1,059 early positron emission tomography–**negative** patients

Standard Arm – ABVD x3 + INRT

Experimental Arm – PET directed

PET negative – ABVD x 4

PET positive – ABVD x 2, escBEACOPP x 2, INRT

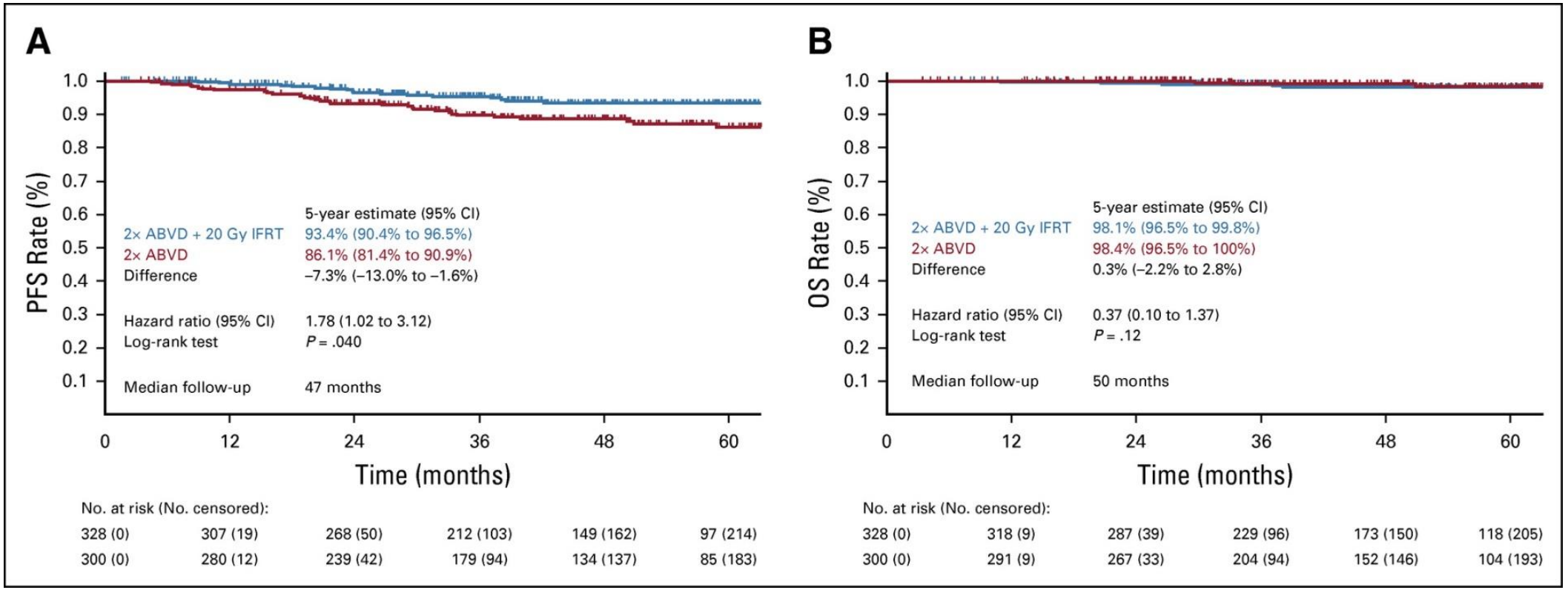


André et al. J Clin Oncol. 2017 Jun 1;35(16):1786-1794.

PET-Guided Treatment in Early-Stage Favorable Hodgkin Lymphoma: HD16 Trial

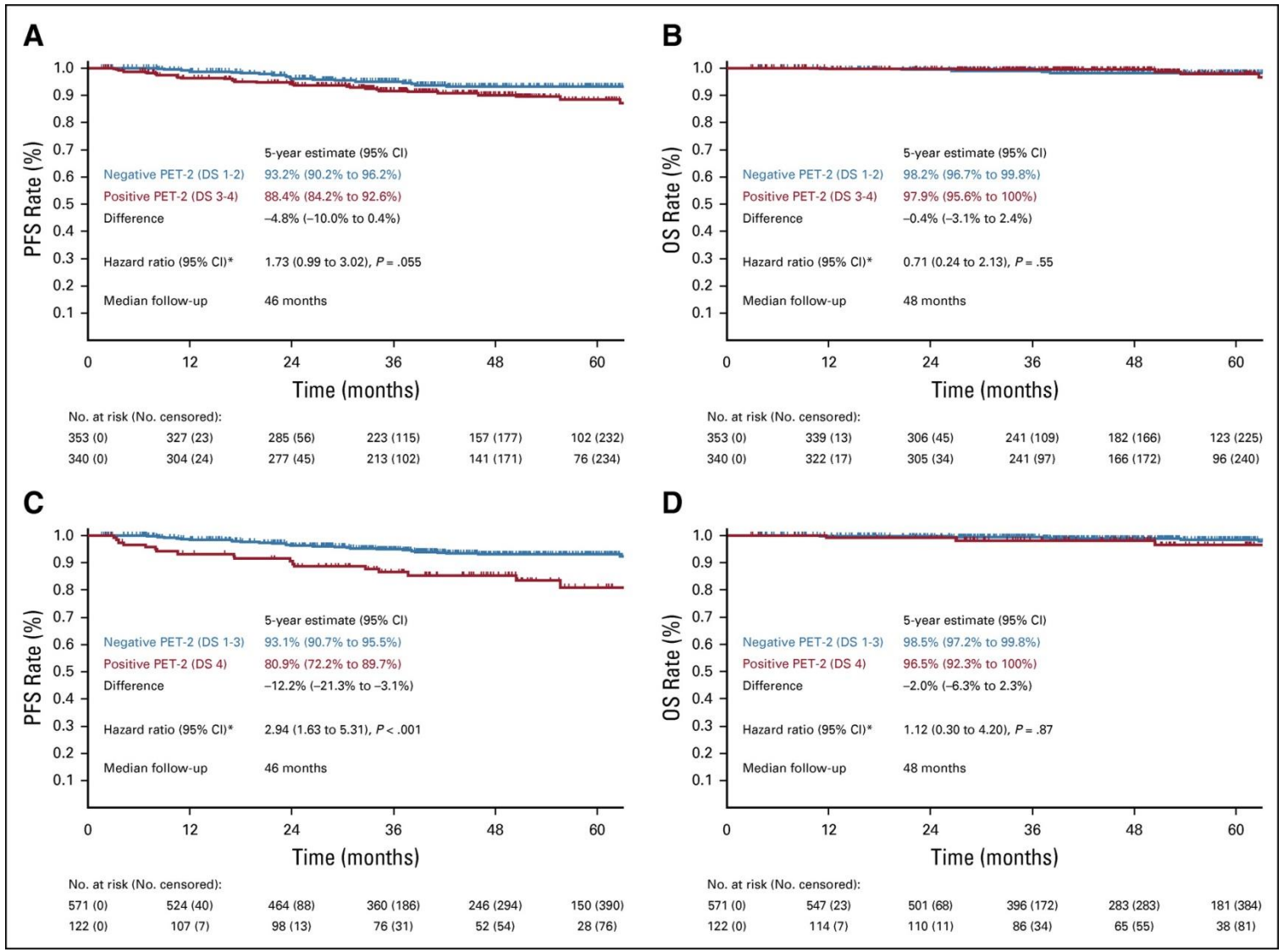
Standard Arm – ABVD x 2 + 20Gy IFRT

Experimental arm – PET directed
IFRT only if PET positive



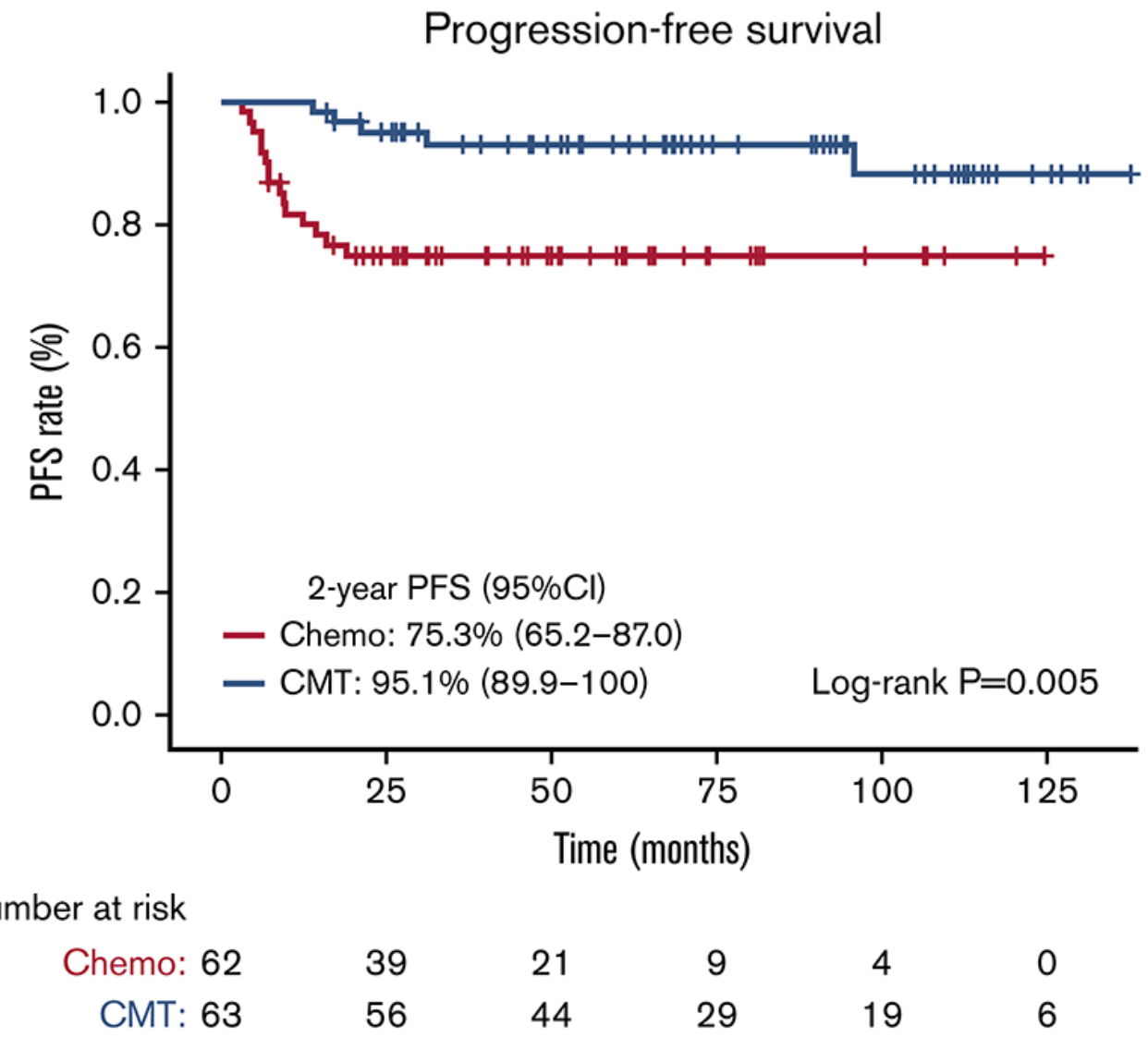
Fuchs et al. J Clin Oncol. 2019 Nov 1;37(31):2835-2845.

HD16: PET-2–neg and PET-2–pos patients assigned to receive RT: Does the DS cut point matter?



Fuchs et al. J Clin Oncol. 2019 Nov 1;37(31):2835-2845.

A real-world study of combined modality therapy for early-stage Hodgkin lymphoma: too little treatment impacts outcome



- In the real-world setting, CMT improved outcomes for patients with PET2-positive and unfavorable disease.
- Similar to clinical trials, favorable, non-bulky, and PET2-negative subgroups had comparable survival outcomes with chemotherapy alone.

Chohan KL, et al. Blood Adv. 2022 Jul 26;6(14):4241-4250.

Limited stage Hodgkin lymphoma – RT or not?

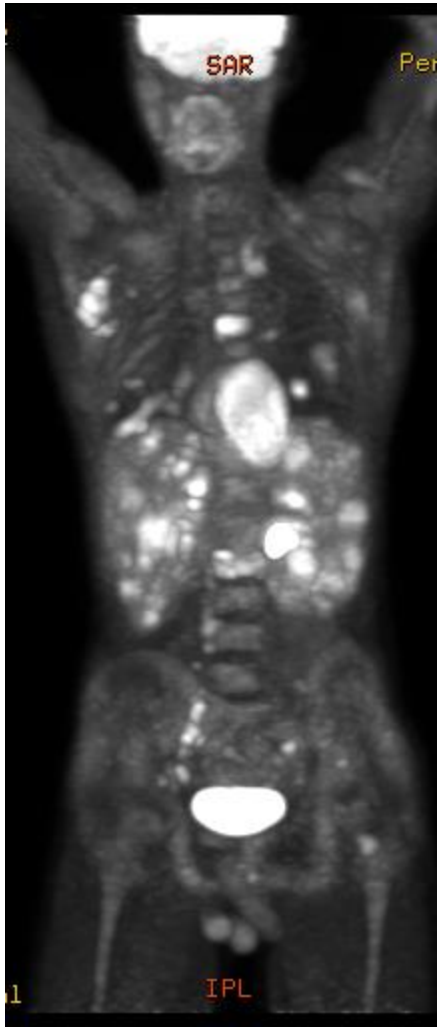
- PET-directed therapy is feasible and may impact therapy, but not as one may think –
  - If PET2 is negative, omitting RT negatively impacts PFS
  - If PET2 is positive, escalating therapy may improve outcome

My view –

- Simply omitting RT should be done with caution particularly in patients with bulky disease, poor prognostic features
- Consider proton beam, clinical trial adding novel agents

Advanced stage Hodgkin lymphoma – BV(N)-AVD vs A(B)VD?

Prognostic Factors in Hodgkin Lymphoma

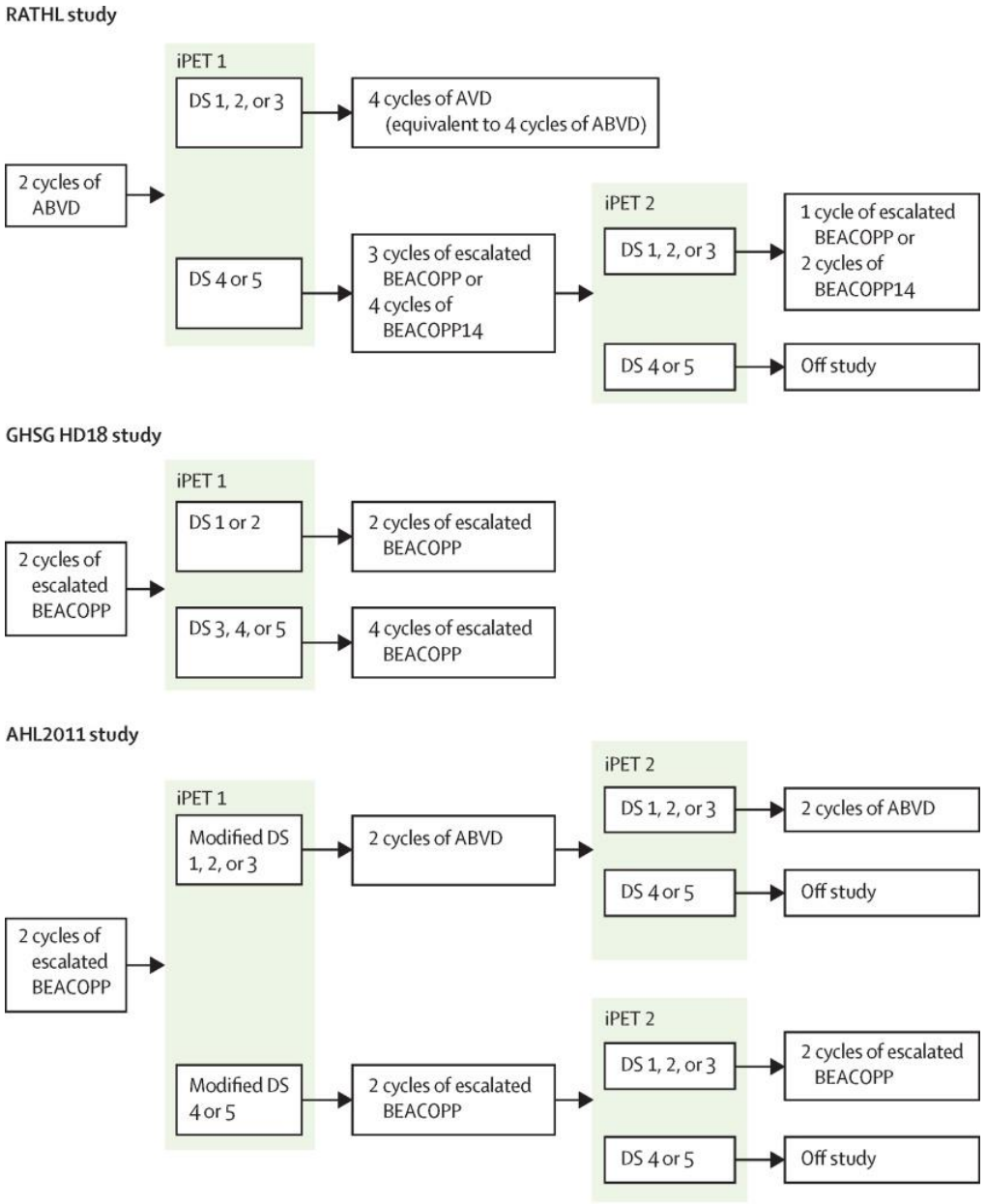


Advanced Disease

Age ≥ 45 years
Stage IV
Male sex
White blood count ≥ 15,000 cells/μl
Lymphocyte count < 600 cells /μl or <8%
Albumin < 4.0 g/dL
Hemoglobin < 10.5 g/dL

Hasenclever et al. NEJM 1998; 339: 1506-1514

The role of PET scans in advanced stage cHL to direct therapy



Start low – switch to intense therapy if needed
Drop toxic drug if doing well

Start high – decrease number of cycles of intense therapy if doing well

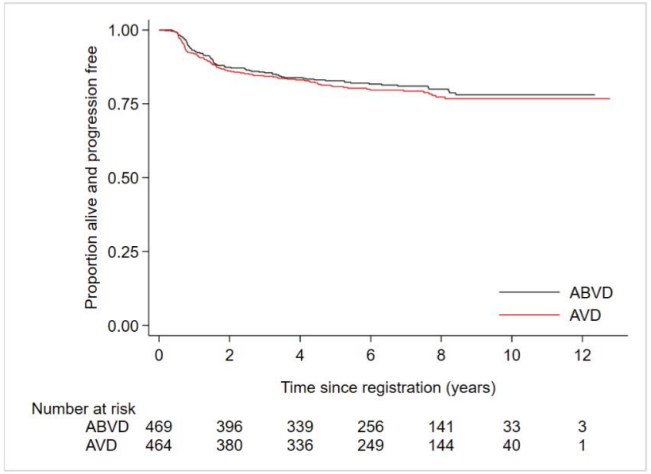
Start high – switch to less intense therapy if doing well
Test whether PET approach impacts outcome

Trotman et al. Lancet Haematol. 2021 Jan;8(1):e67-e79.

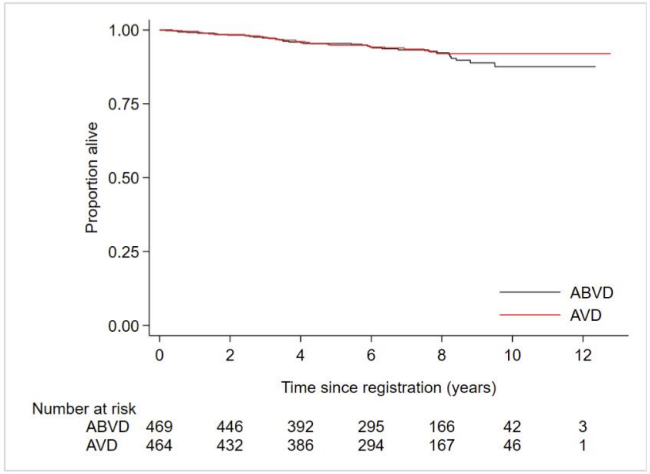
Treatment Guided by PET in Advanced Hodgkin Lymphoma: RATHL Trial

PET-2 negative

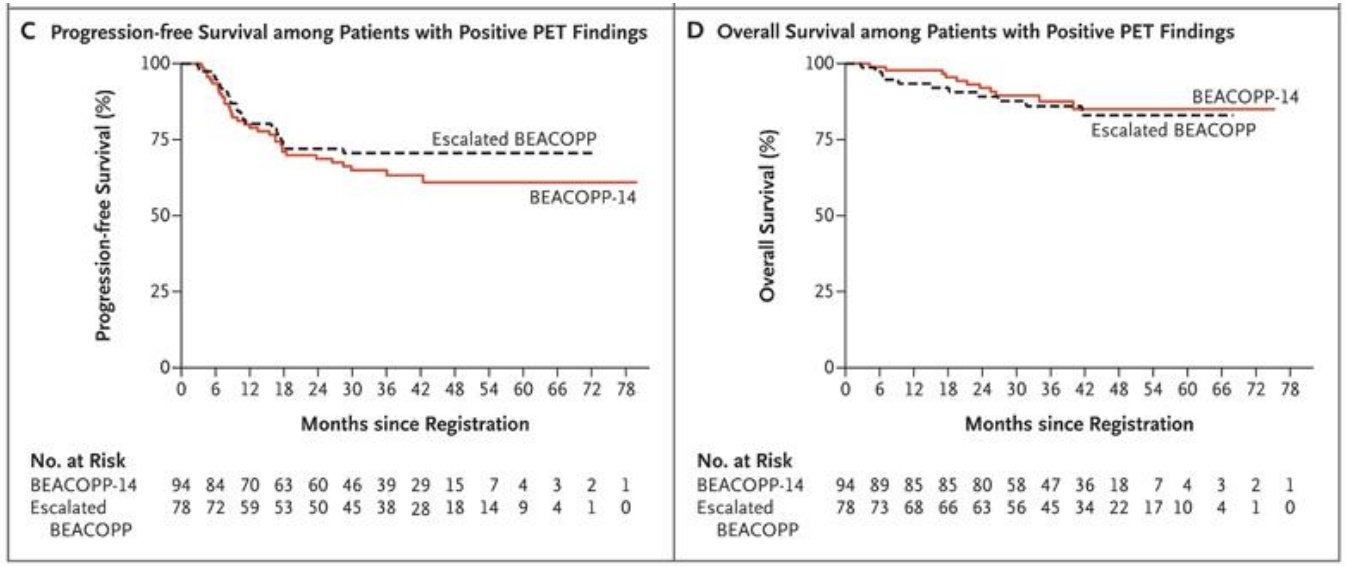
PFS of PET-negative pts



OS of PET-negative pts



PET-2 positive



My conclusions –

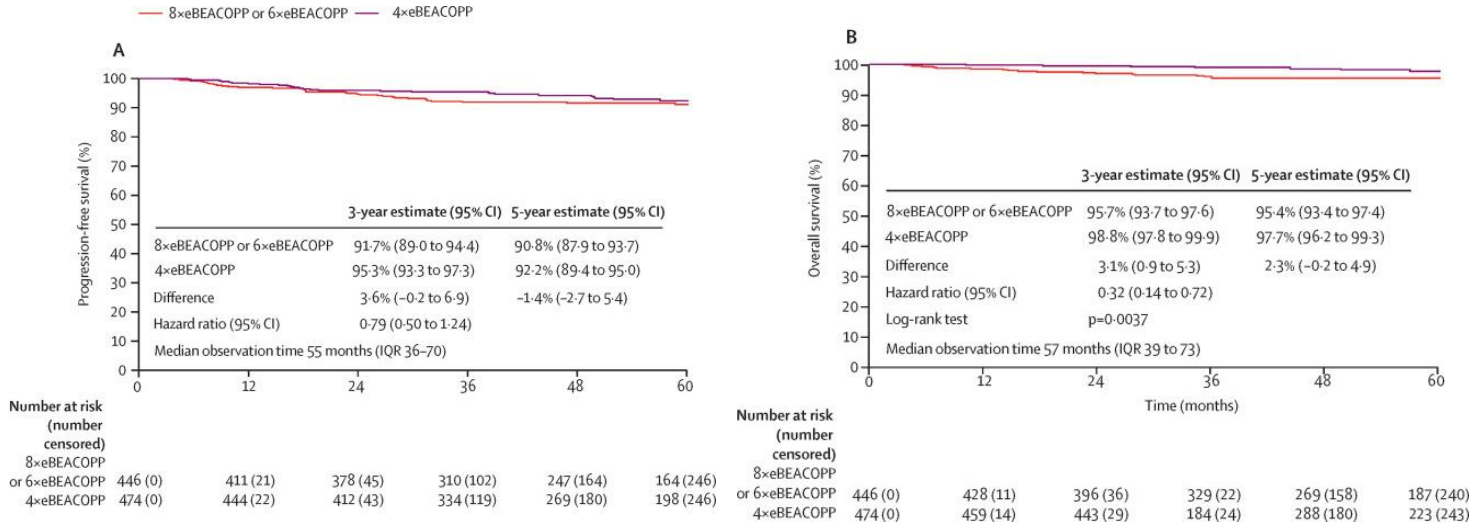
If you start with ABVD, you can drop the bleomycin if PET-2 negative

Not clear that escalating therapy in PET-2 patients improves outcome

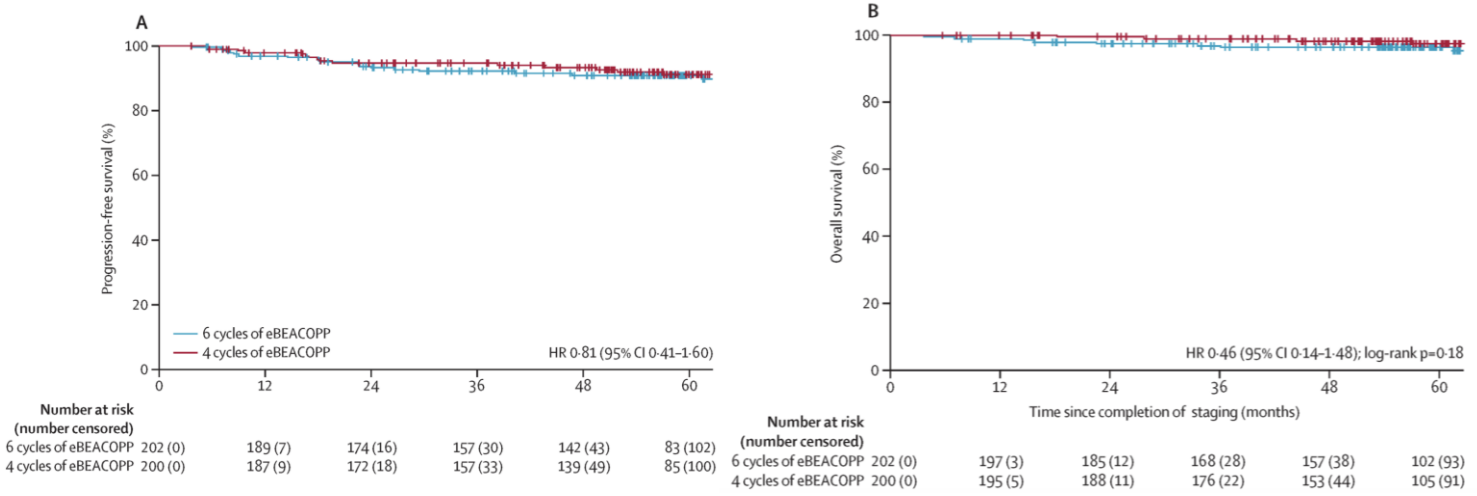
Johnson et al. N Engl J Med. 2016 Jun 23;374(25):2419-29.
Luminari et al. ASH 2022; #315

HD18: PFS and overall survival for patients with negative PET-2

4 cycles vs 6/8 cycles



4 cycles vs 6 cycles



My conclusions –

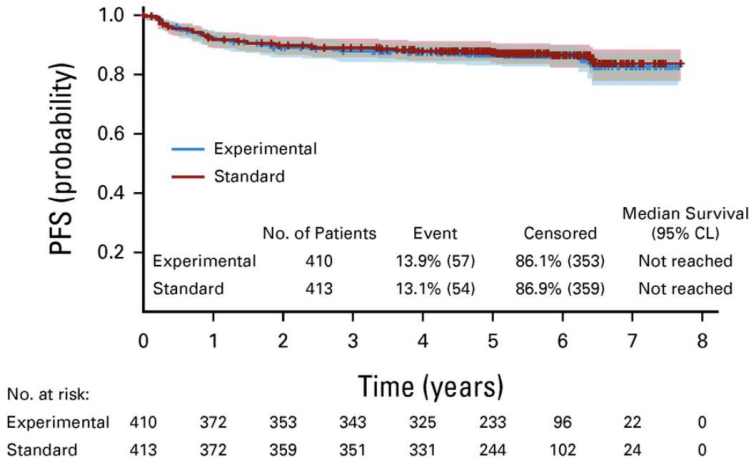
If you start with eBEACOPP, you can decrease to 4 cycles if PET-2 negative

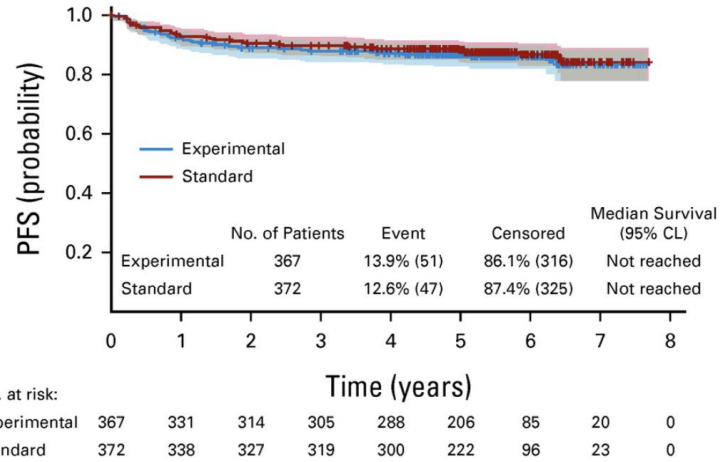
8 cycles of escBEACOPP decreases survival compared to 4 cycles

Borchmann et al. Lancet. 2018 Dec 23;390(10114):2790-2802.
Kreissl et al. Lancet Haematol. 2021 Jun;8(6):e398-e409.

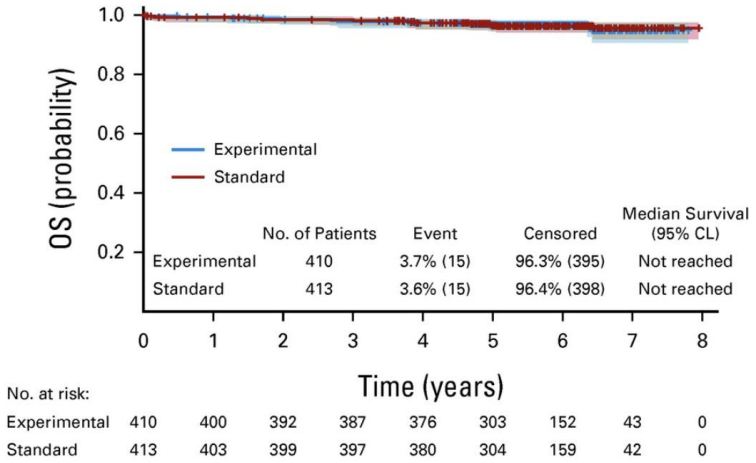
AHL2011: PFS and survival outcomes by treatment group

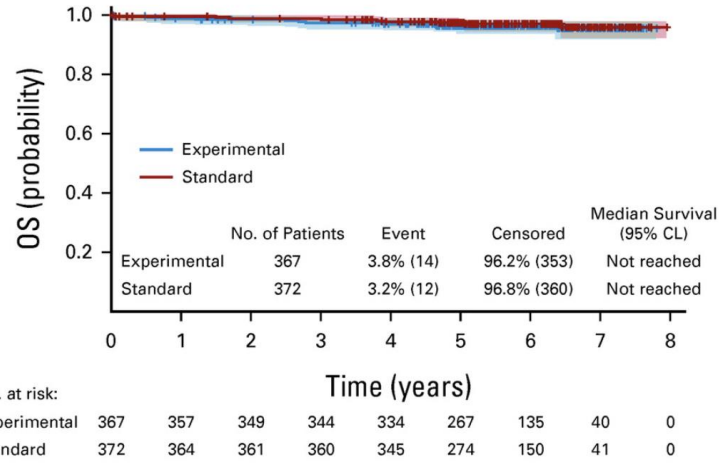
Intent to Treat





Per Protocol





My conclusions –

If you start with escBEACOPP, you can switch to ABVD if PET-2 negative

Whether based on ITT or per protocol, a PET-directed treatment approach doesn't actually impact survival.

Casasnovas et al. Lancet Oncol. 2019 Feb;20(2):202-215.

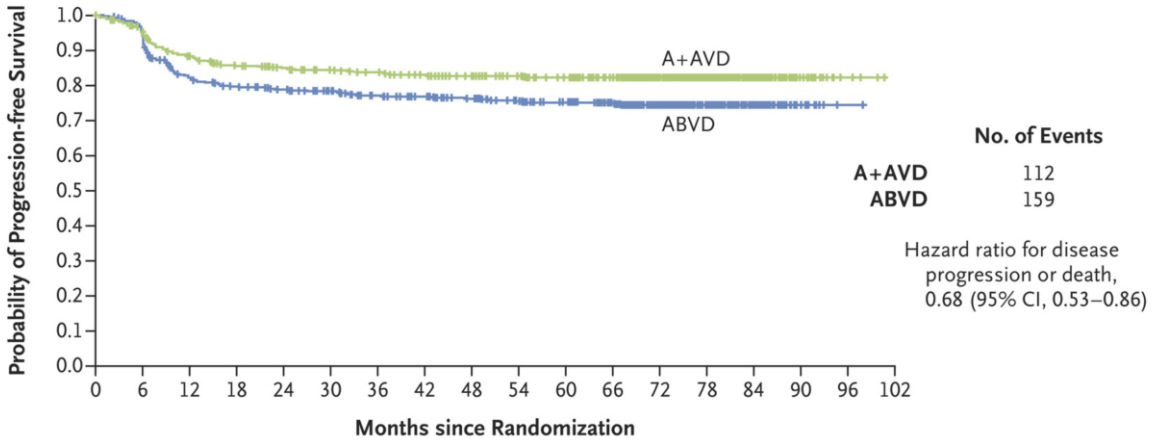
Casasnovas R, et al. J Clin Oncol. 2022 Apr 1;40(10):1091-1101.

A PET-driven strategy definitely decreases toxicity – but it doesn't really improve survival

Adding **novel targeted agents** to well-tolerated treatment combinations (like AVD) may achieve both low toxicity and improved outcome

Outcomes with Brentuximab Vedotin + AVD vs. ABVD in Stage III or IV Hodgkin's Lymphoma

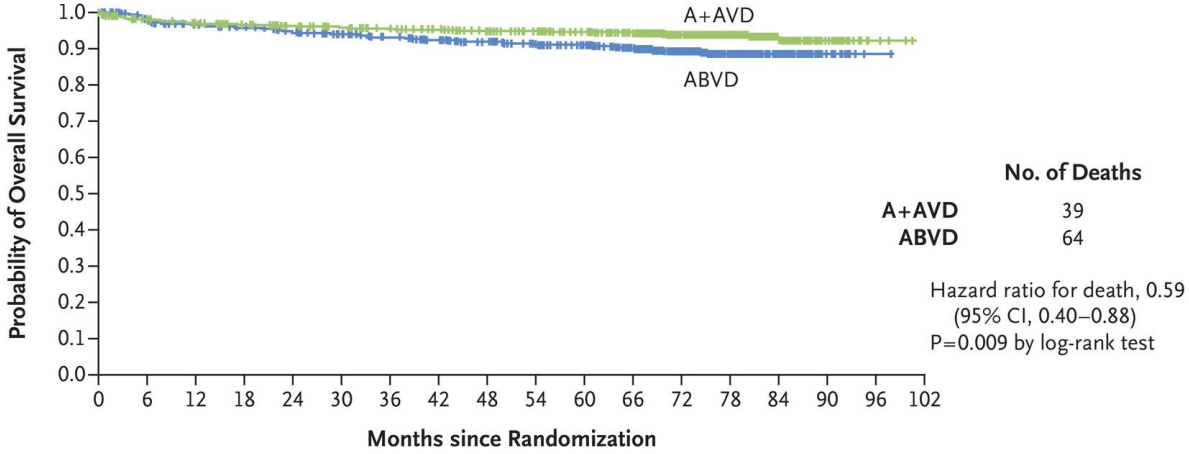
PFS



No. at Risk

A+AVD	664	619	563	537	520	508	496	480	463	448	428	400	305	179	86	24	4	0
ABVD	670	612	520	501	485	465	442	432	414	391	371	338	245	154	67	9	1	0

Overall Survival

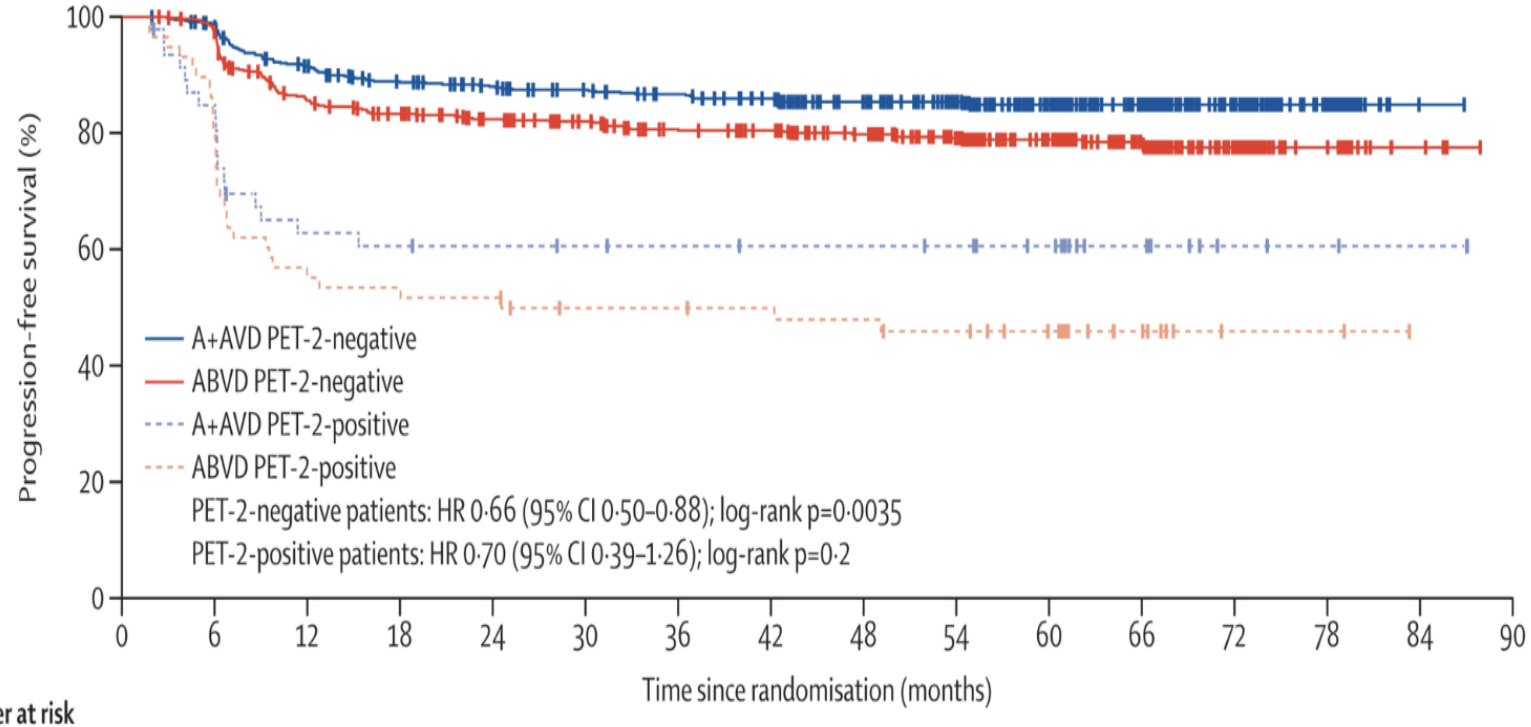


No. at Risk

A+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 Jul 28;387(4):310-320.

Outcome with Brentuximab Vedotin + AVD is improved vs. ABVD in both PET positive and PET-negative patients



Number at risk (number censored)																
A+AVD PET-2-negative	588 (0)	572 (6)	526 (13)	500 (23)	484(35)	472 (44)	460 (52)	444 (64)	417 (88)	386 (119)	312 (191)	189 (314)	98 (405)	36 (467)	1 (502)	0 (503)
ABVD PET-2-negative	578 (0)	558 (4)	483 (13)	463 (20)	442(36)	424 (52)	400 (68)	392 (76)	368 (97)	334 (128)	271 (190)	170 (290)	70 (388)	20 (438)	4 (454)	0 (458)
A+AVD PET-2-positive	47 (0)	39 (1)	28 (2)	27 (2)	26(3)	25 (4)	24 (5)	23 (6)	23 (6)	22 (7)	18 (11)	10 (19)	3 (26)	2 (27)	1 (28)	0 (29)
ABVD PET-2-positive	58 (0)	46 (0)	32 (0)	31 (0)	30(0)	26 (3)	26 (3)	25 (4)	24 (4)	22 (5)	18 (9)	8 (19)	2 (25)	2 (25)	0 (27)	0 (27)

6-year **OS favored A+AVD** for **both PET2-negative** patients (94.9% vs. 90.6) **and PET2-positive** patients (95% vs. 77%).

Straus DJ, et al. Lancet Haematol. 2022 Feb;9(2):e91.

Ansell SM et al. N Engl J Med. 2022 Jul 28;387(4):310-320.

BrECADD Proves Non-inferior to eBEACOPP in Advanced Classical Hodgkin Lymphoma (HD21 trial)

BrECADD - brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone

1500 patients, 749 were randomly assigned to eBEACOPP and 751 were assigned to BrECADD.

At a median follow-up of 40 months, the estimated 3-year PFS rate with BrECADD (n = 740) was 94.9% (99% CI, 92.8%-97.1%) vs 92.3% (99% CI, 89.7%-94.9%) with eBEACOPP (n = 742) in the intention-to-treat (ITT) population (HR, 0.63; 99% CI, 0.37-1.07).

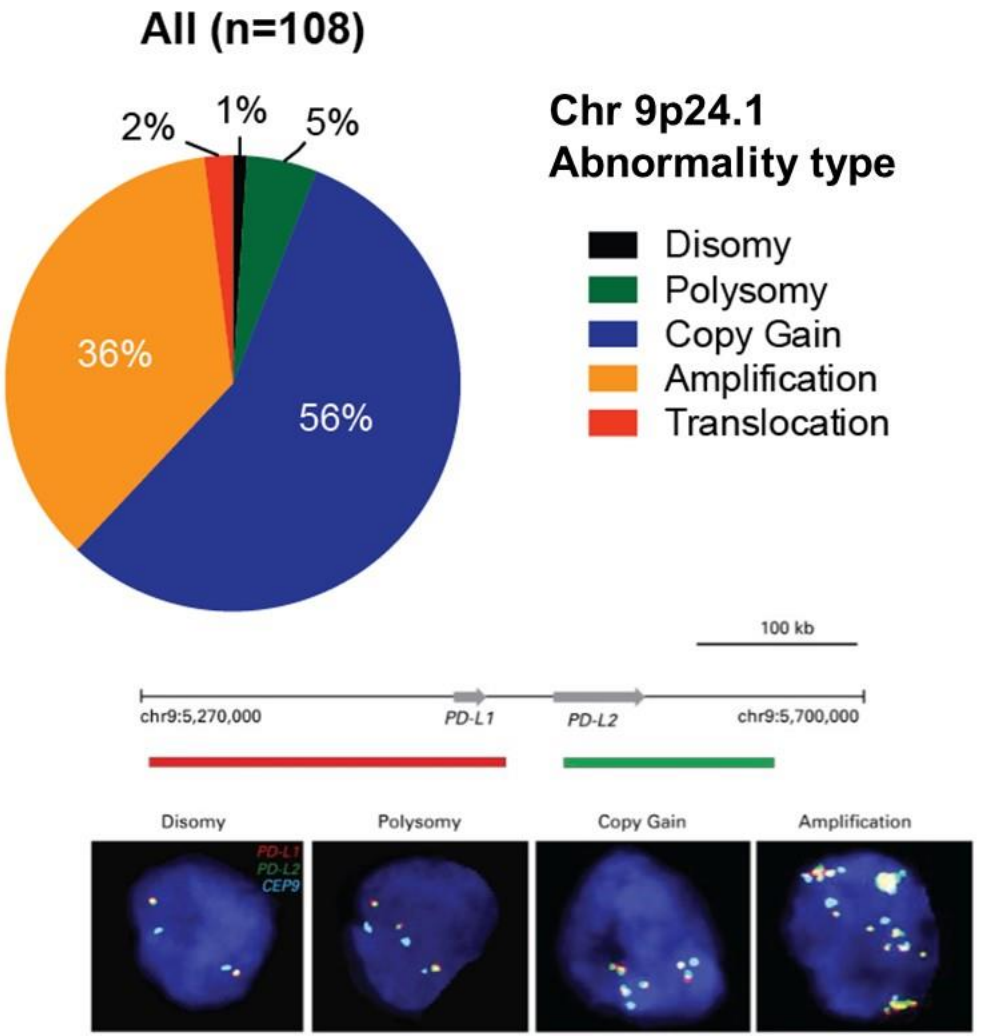
The 1-year PFS rate with BrECADD was 97.5% (99% CI, 96%-99%).

The estimated 3-year OS rate was 98.5% in both the BrECADD and eBEACOPP arms

Borchmann P, et al. *Hematol Oncol*. 2023;41(suppl 2):881-882. doi:10.1002/hon.3196_LBA5

Rationale for PD-1 blockade in cHL

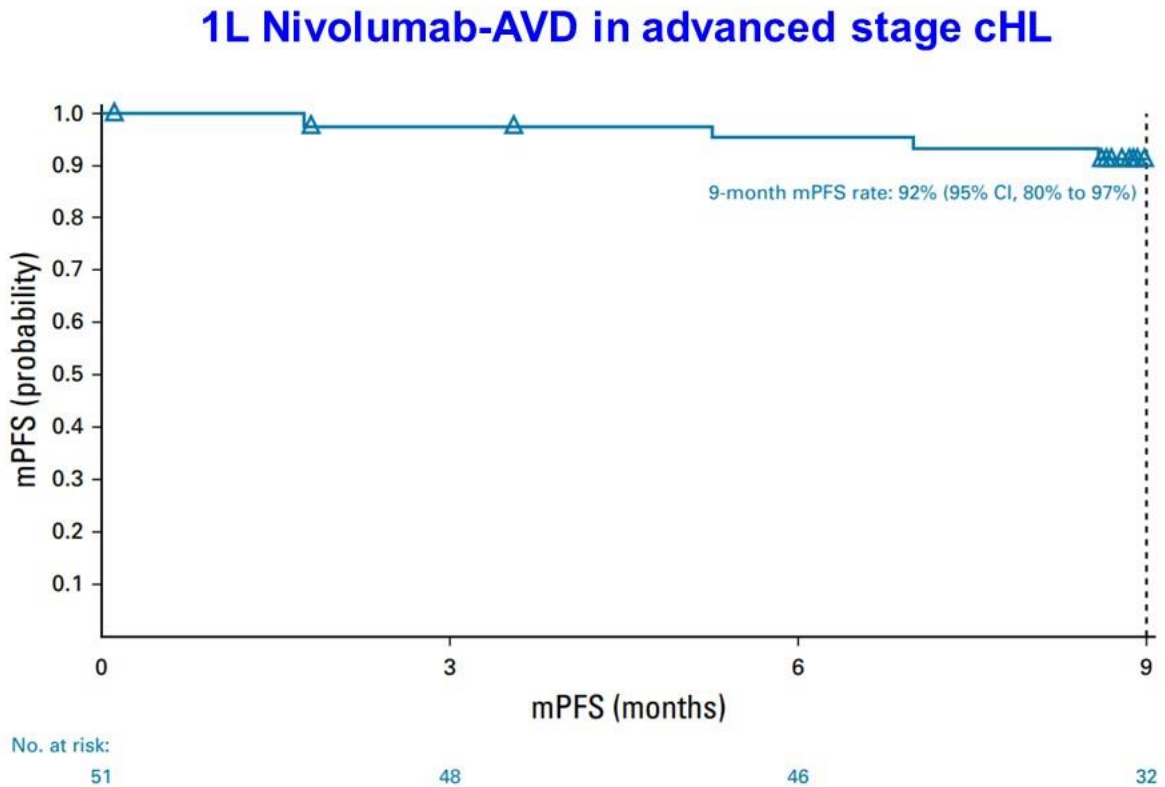
- PD-1 ligand genetic alterations (chr 9p24.1) central to cHL pathogenesis[7]
  - More 9p24.1 genetic alteration in advanced stage cHL[7]
  - ↑ 9p24.1 alteration → poorer outcome with standard frontline therapy[7]
- Nivolumab highly effective in relapsed or refractory cHL (ORR ~70%) [8,9]



7. Roemer MGM et al JCO 2016. 8. Armand P et al JCO 2018. 9. Younes A et al Lancet Oncol 2016.

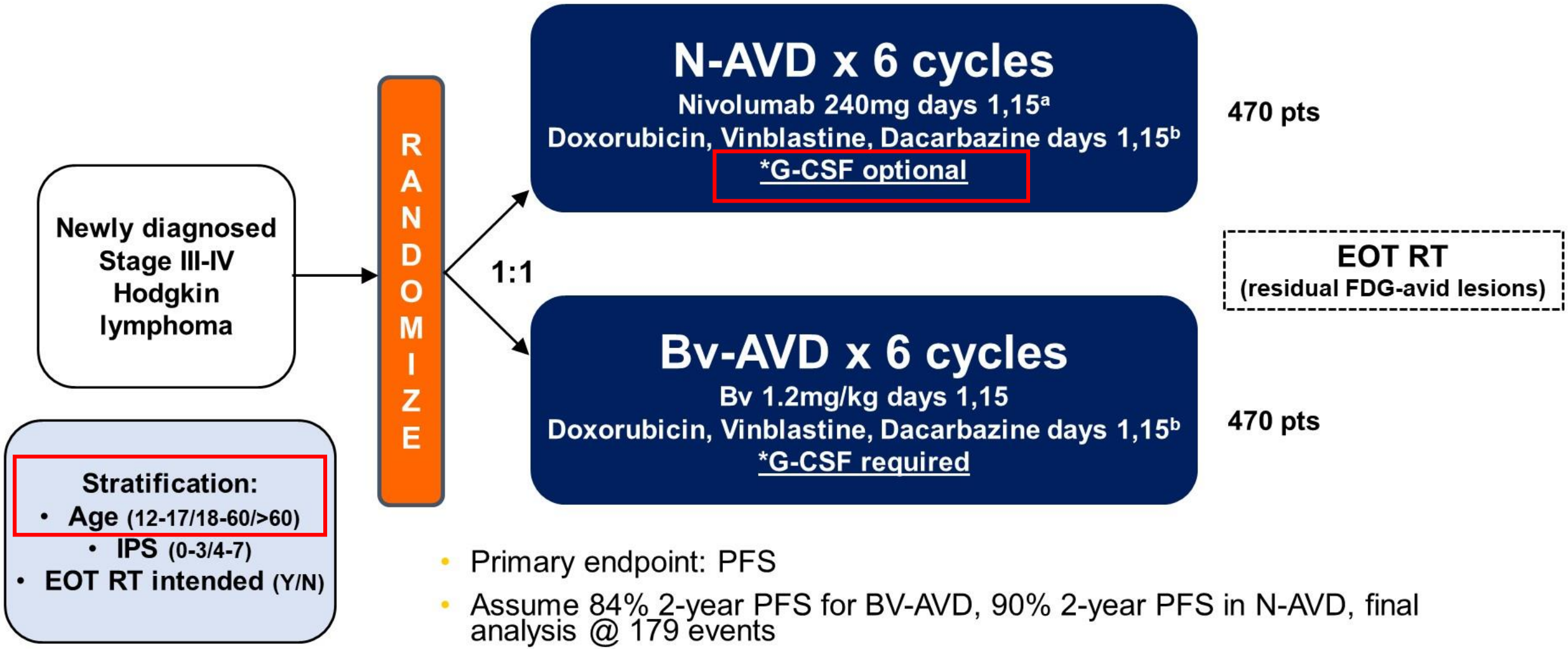
Incorporating PD-1 blockade into initial cHL therapy is well-tolerated and highly effective

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



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

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

[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

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 (95%)	
Bone pain	39 (8%)		94 (20%)	

More neutropenia after N-AVD

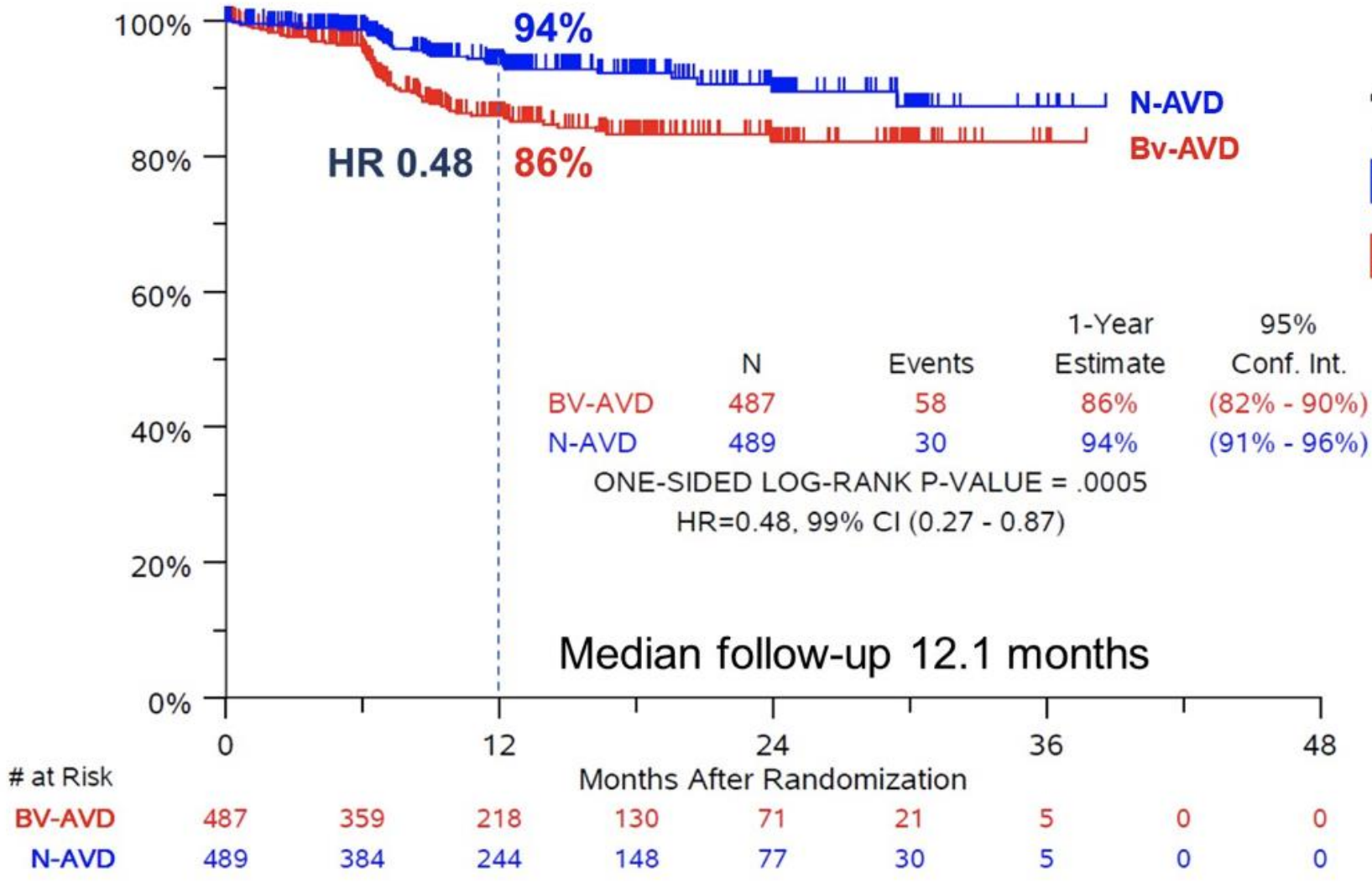
More growth factor use, bone pain in Bv-AVD arm

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

Nivolumab+AVD for Newly Diagnosed Advanced-Stage cHL

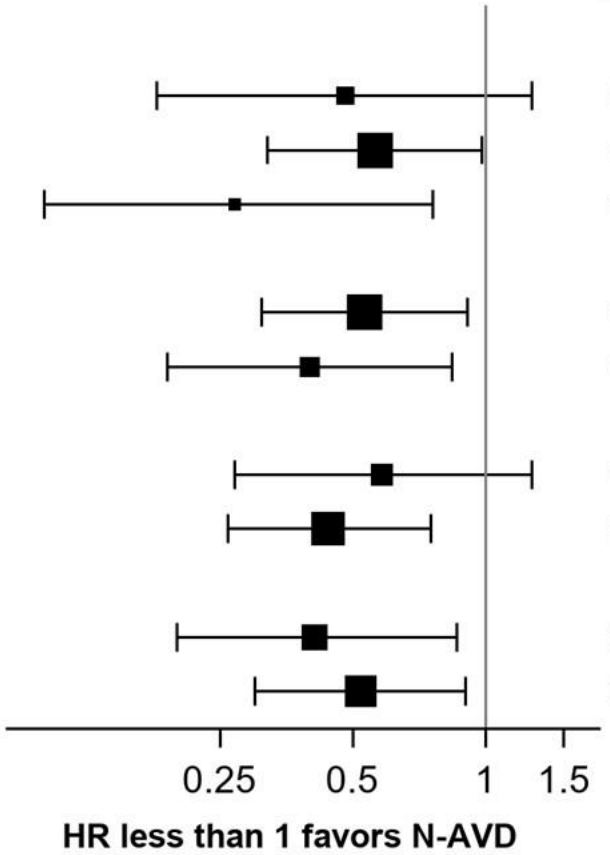


1-year PFS
N-AVD 94%
Bv-AVD 86%

Herrera et al. J Clin Oncol 41, 2023 (suppl 17; abstr LBA4).

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



Conclusions

- First-line N-AVD improved PFS compared to Bv-AVD in advanced stage Hodgkin lymphoma
- N-AVD was well-tolerated
  - Few immune-related adverse events
  - <1% received RT
- Study included adolescent patients, demonstrating that protocols could be harmonized across the pediatric-adult spectrum
- Issues to think about:
  - Short follow-up
  - How will those curves change over time?
  - What will we do in the relapse setting?
- **Likely practice-changing**

Advanced stage Hodgkin lymphoma – BV(N)-AVD vs A(B)VD?

- PET-directed therapy omitting bleomycin as per RATHL is feasible and impacts pulmonary toxicity of therapy
- BV + AVD is associated with more neutropenia (requires growth factor administration) and more neuropathy

My take –

- It is hard to argue with a survival advantage for BV-AVD
- BV-AVD allows for a “set it and leave it” approach
- N-AVD may be better than BV-AVD