



After 45 years of ABVD, how is first-line therapy rapidly changing in Hodgkin's Lymphoma?

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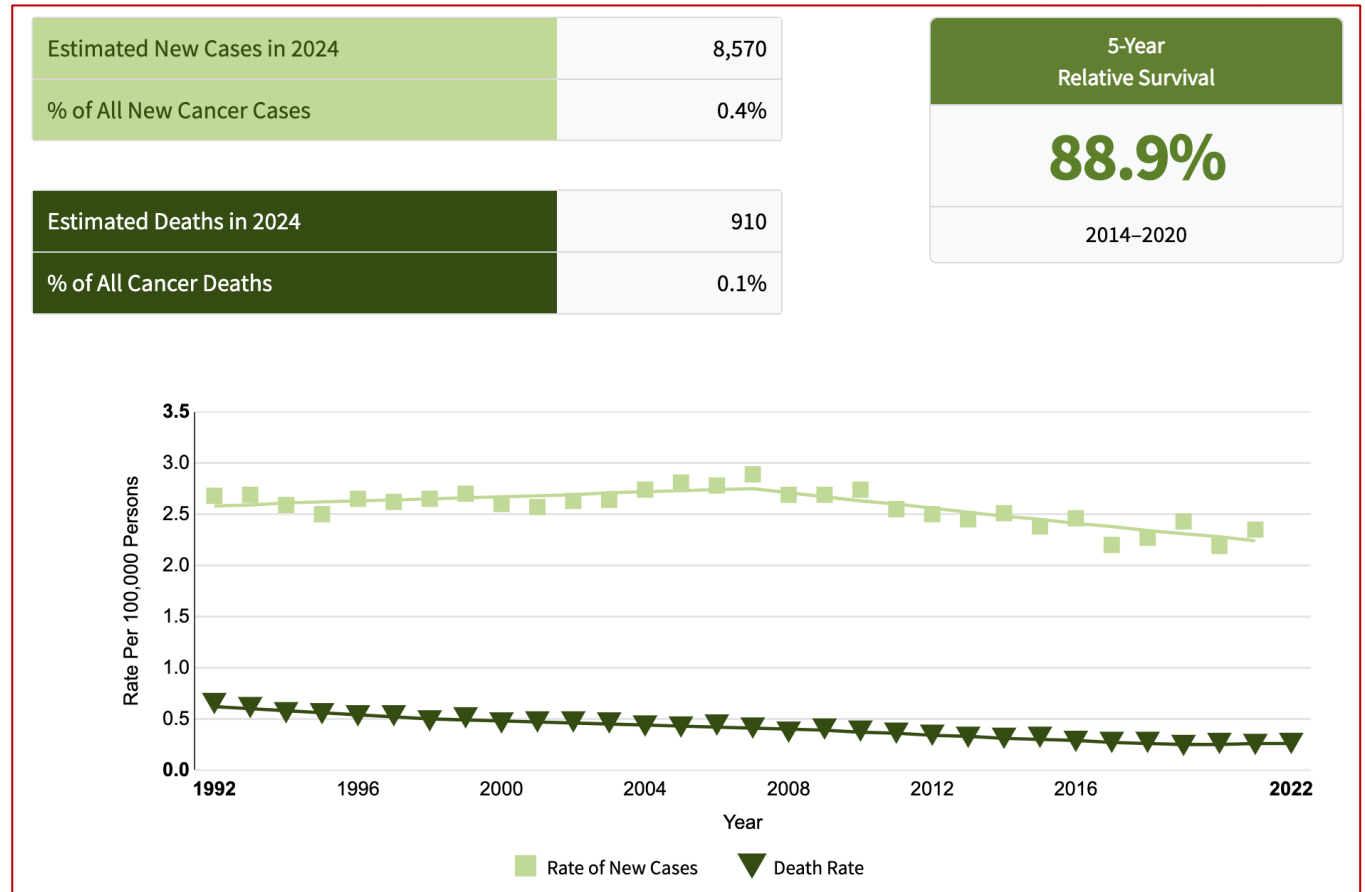
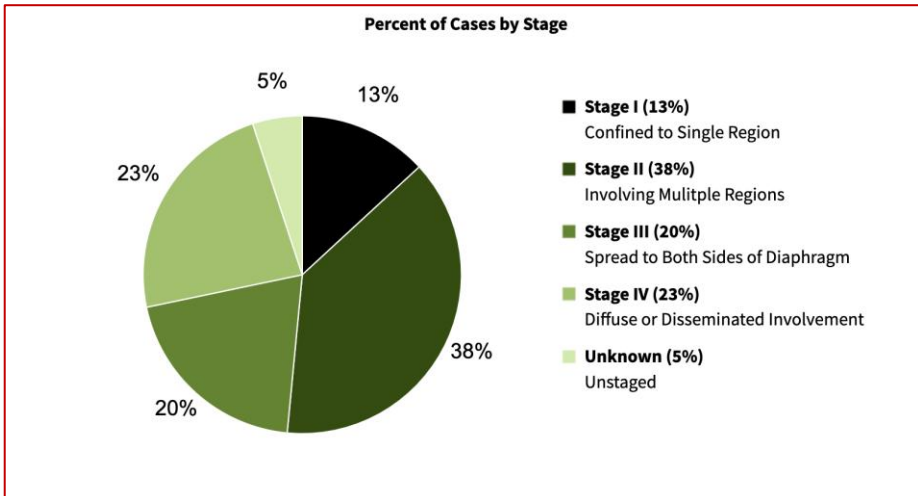
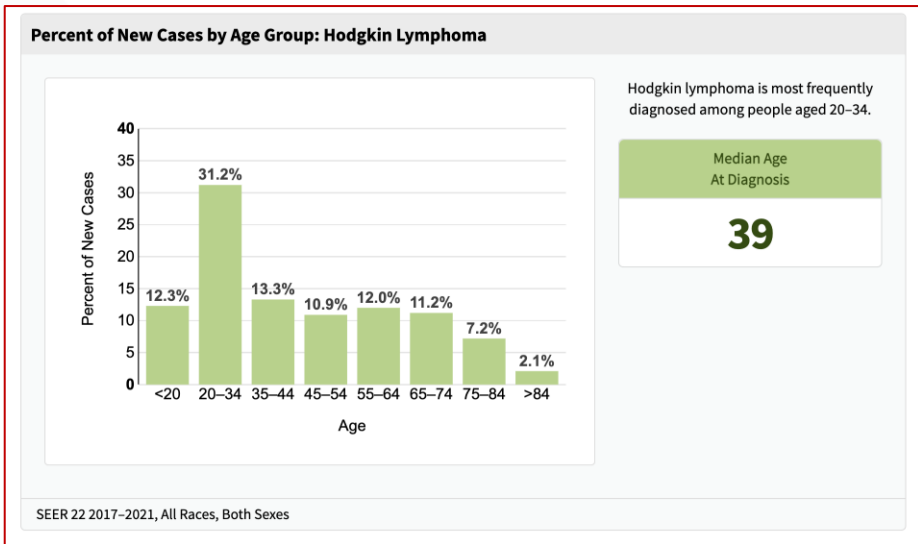
Dana Farber Cancer Institute

Harvard Medical School

Disclosures

Name of Company	Research support	Employee	Consultant	Stockholder	Speaker's Bureau	Scientific Advisory Board	Other
Genmab						X	
Pierre Fabre			X				
Research to Practice					X		
Kite Pharma			X				

Outcomes for patients with cHL continue to improve over time

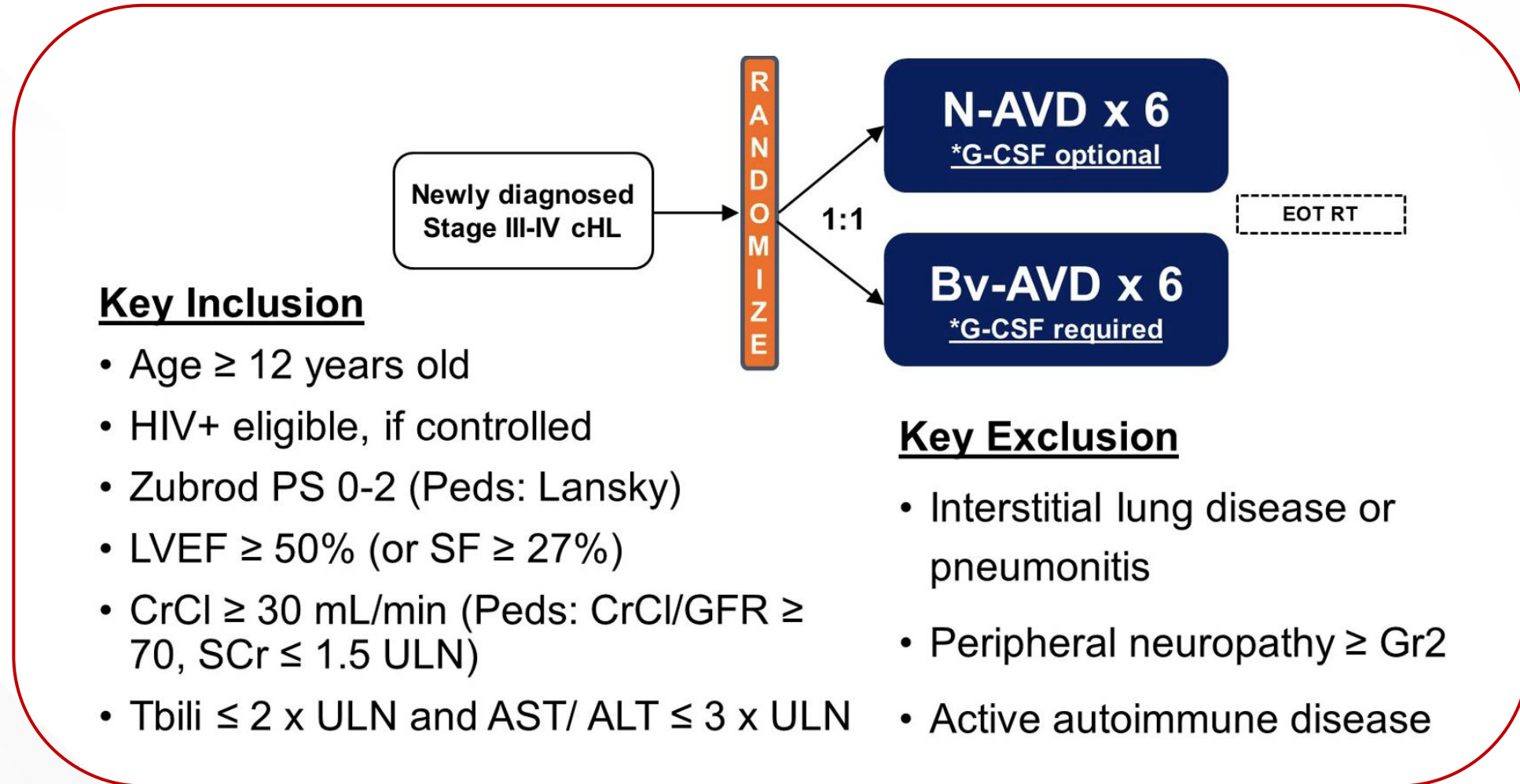


<https://seer.cancer.gov/statfacts/html/hodg.html>



**Advanced-stage HL: N-AVD
versus BrECADD**

Schema S1826: N-AVD vs BV-AVD

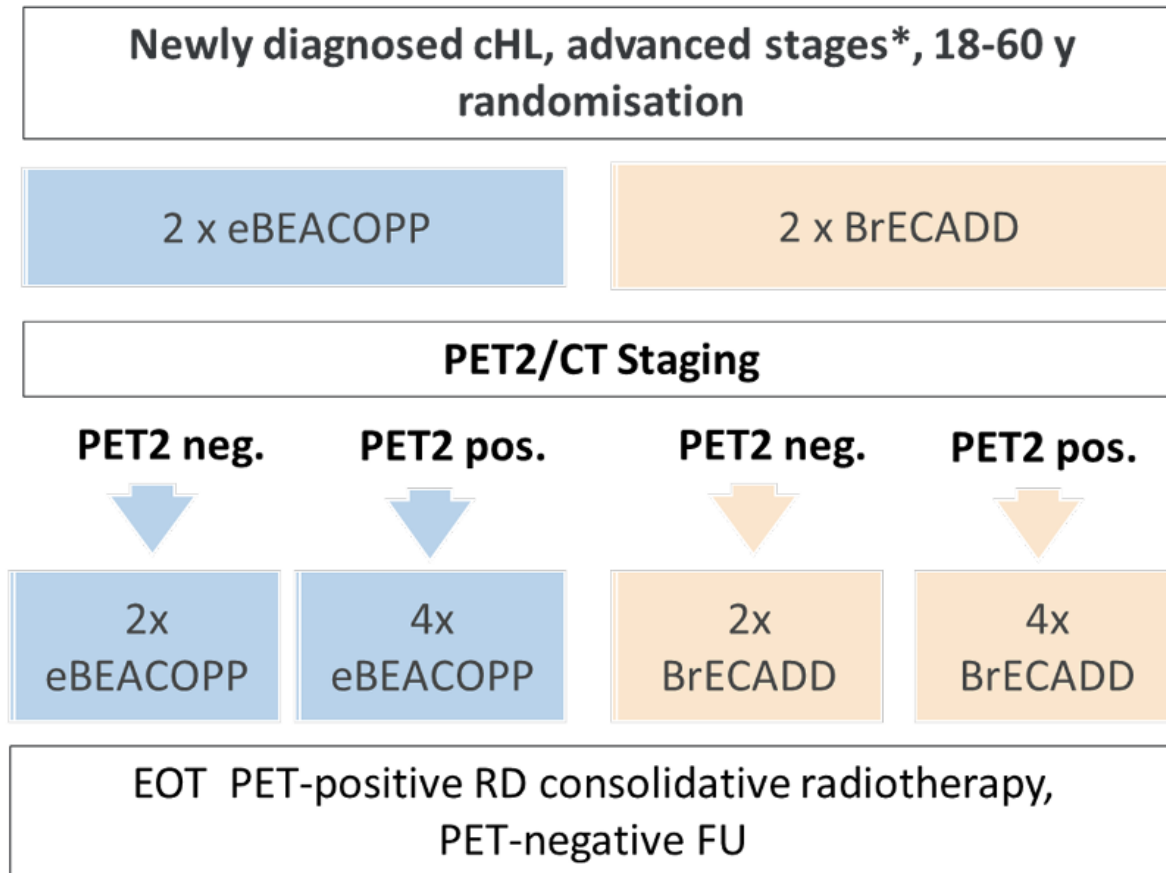


Nivolumab dosing/schedule

Nivolumab:	240 mg day 1,15
Doxorubicin:	25 mg/m² day 1,15
Vinblastine	6 mg/m² day 1,15
Dacarbazine:	375 mg/m² day 1,15

Cycle length = 28 days

HD21: BEACOPP vs BrECADD



* Includes stage IIB with RF LMM or ED, and stage II and IV

Co-primary endpoints:
**Superiority for treatment
related morbidity**
Non-inferiority for efficacy

BrECADD dosing/schedule

Brentuximab vedotin:	1.8 mg/kg day 0
Etoposide:	150 mg/m² days 1-3
Cyclophosphamide:	1250 mg/m² days 1
Doxorubicin:	40 mg/m² day 1
Dacarbazine:	250 mg/m² day 2-3
Dexamethasone:	40 mg days 1-4
Cycle length = 21 days	

36% of patients required 6 cycles of BrECADD

	eBEACOPP (n=740)	BrECADD (n=742)	Total (n=1482)
Response after two chemotherapy cycles			
Central PET review after two cycles (post-amendment)	669 (90%)	677 (91%)	1346 (91%)
Complete metabolic response (DS1-3) after two cycles	430/669 (64%)	430/677 (64%)	860/1346 (64%)
Therapy adherence			
Cycles received that were recommended	707 (95%)	708 (96%)	1415 (95%)

N-AVD

Patient populations

BrECADD

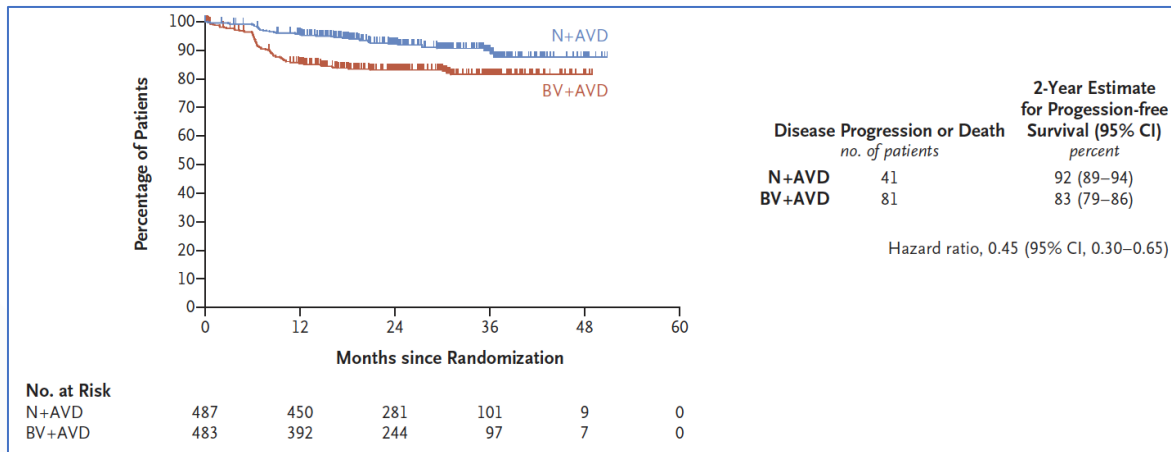
Characteristic	N+AVD (N = 487)	BV+AVD (N = 483)
Age		
Median (range) — yr	27.6 (12.0–83.7)	26.8 (12.0–81.7)
Distribution — no. (%)		
12–17 yr	118 (24)	118 (24)
18–60 yr	321 (66)	318 (66)
>60 yr	48 (10)	47 (10)

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)

	eBEACOPP (n=740)	BrECADD (n=742)
Median age, years	31 (24–42)	31 (24–42)
Ann Arbor stage		
IIa	0	2 (<1%)
IIb	117/739 (16%)	115 (16%)
IIIa	132/739 (18%)	129 (17%)
IIIb	156/739 (21%)	164 (22%)
IVa	112/739 (15%)	104 (14%)
IVb	222/739 (30%)	228 (31%)
Risk factors		
Large mediastinal mass	235/735 (32%)	253/739 (35%)
Extranodal involvement	175/735 (24%)	202/739 (27%)
Involvement of 3 or more nodal areas	655/735 (89%)	667/739 (90%)
High erythrocyte sedimentation rate	470/709 (66%)	481/708 (68%)
International Prognostic Score		
0–1	175 (24%)	195 (26%)
2–3	395 (53%)	390 (53%)
4–7	170 (23%)	157 (21%)

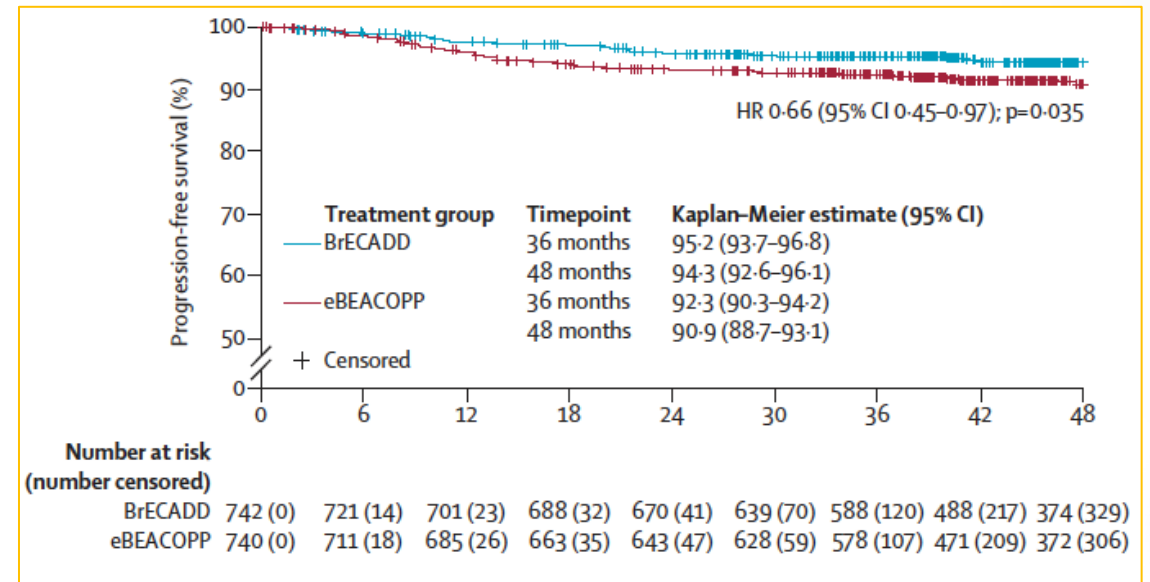
Efficacy

N-AVD



2 yr PFS 92%

BrECADD

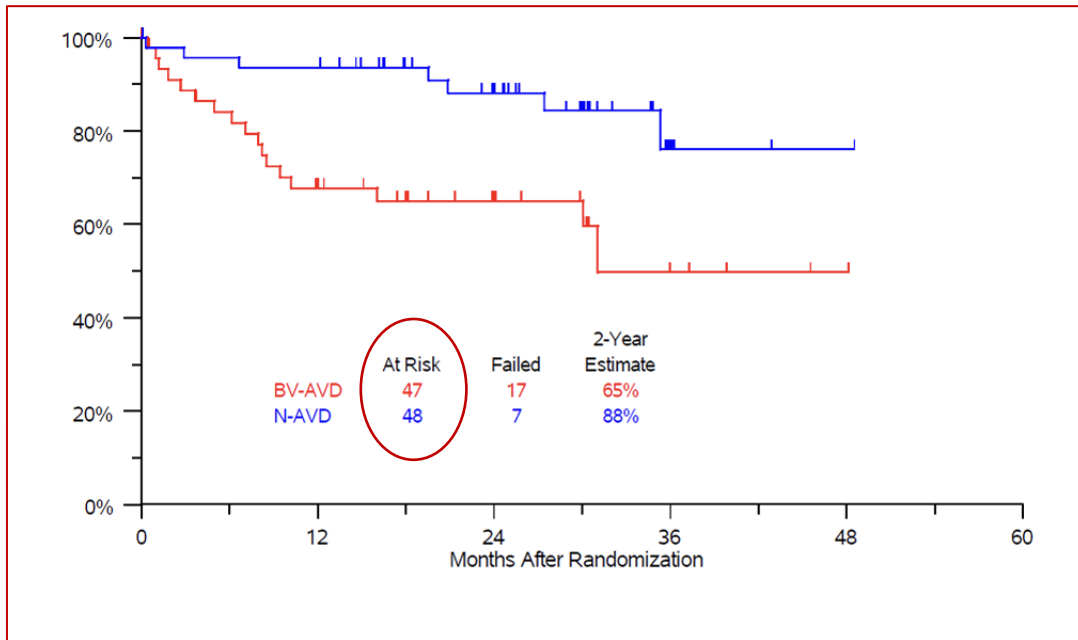


4 yr PFS 94%

Patients > age 60

N-AVD

BrECADD



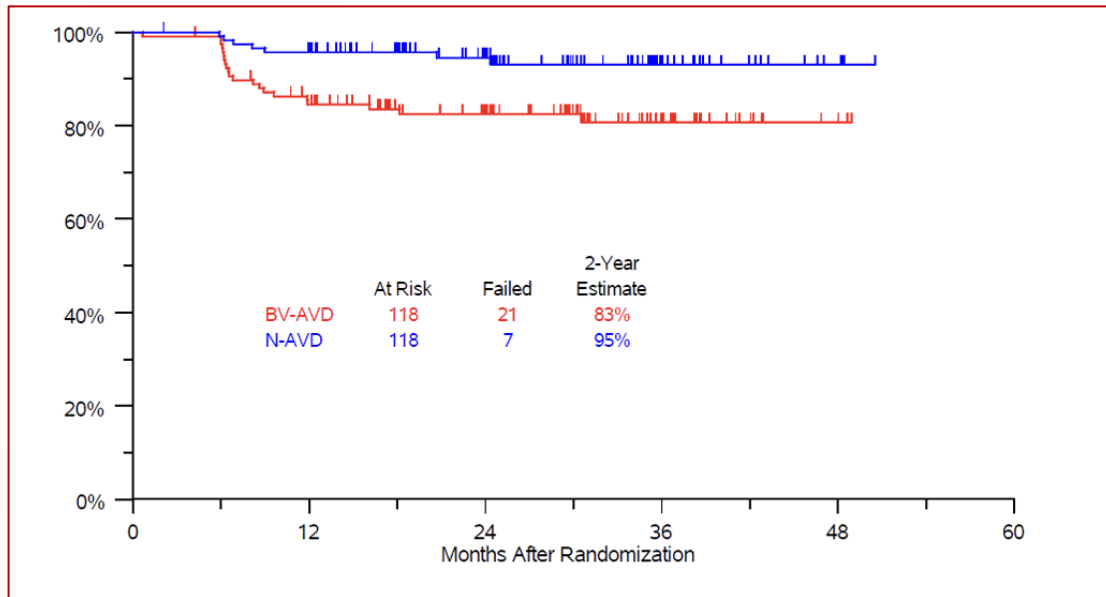
2 year PFS 88%



Patients age 12-17

N-AVD

BrECADD



2-year PFS 95%

Radiotherapy

N-AVD

RADIATION THERAPY



Only seven patients received radiation therapy — three in the N+AVD group and four in the BV+AVD group.

<1%

BrECADD

	eBEACOPP (n=740)	BrECADD (n=742)	Total (n=1482)
Status at end of chemotherapy			
Radiotherapy recommended	127 (17%)	125 (17%)	252 (17%)
Radiotherapy documented	112 (15%)	104 (14%)	216 (15%)

15%

acute toxicity

N-AVD

BrECADD

PRBC
transfusion



Gr 3:6%

24%

platelet
transfusion



Gr 4:1%

17%

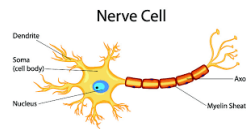
febrile
neutropenia



6%

28%

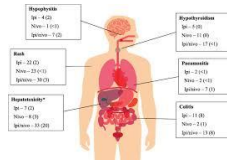
sensory PN



29%

39%

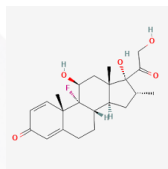
immune
toxicity



11% d/c nivo

0%

steroid
toxicity



+

Late effects

N-AVD

BrECADD



cardiac

Higher dose of doxorubicin

? impact of dexrazoxane

More RT, possibly mediastinal



fertility

Low risk

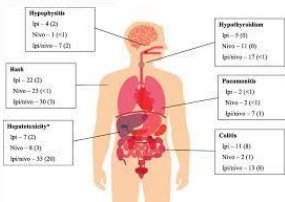
Higher risk, especially if 6 cycles of therapy



myelotoxicity

Low risk

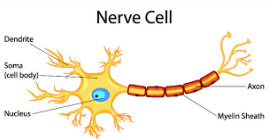
Higher risk, especially if 6 cycles of therapy



Immune toxicity

Low risk
Except thyroiditis

No risk

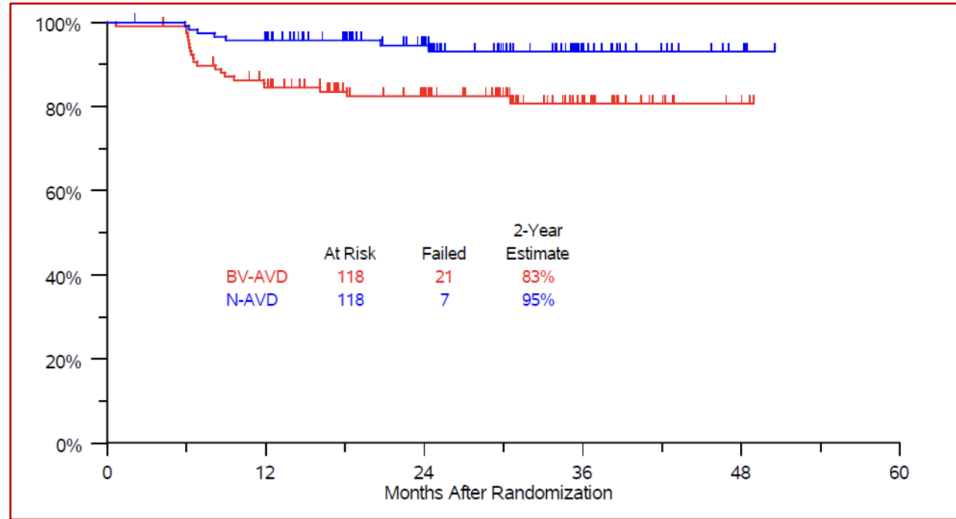


neuropathy

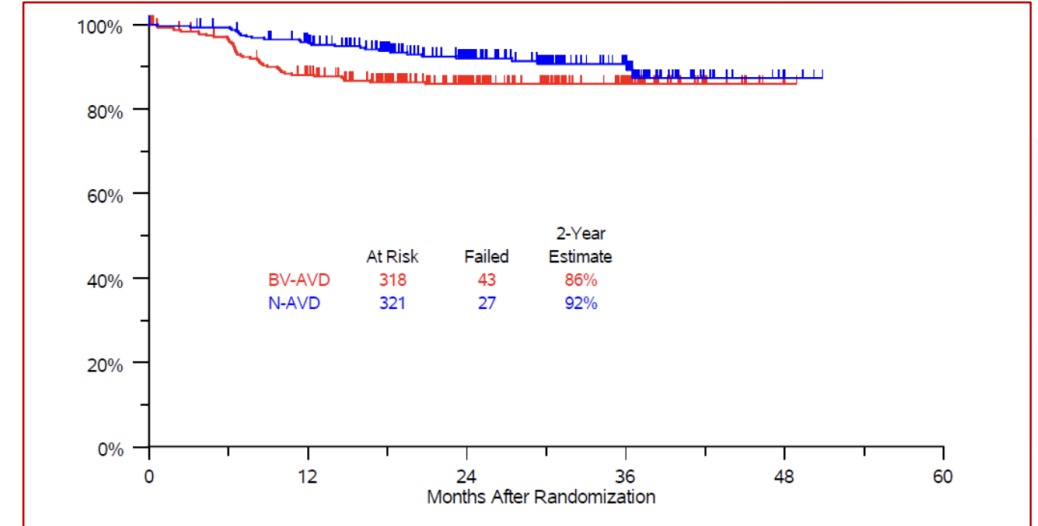
Similar risk

Similar risk

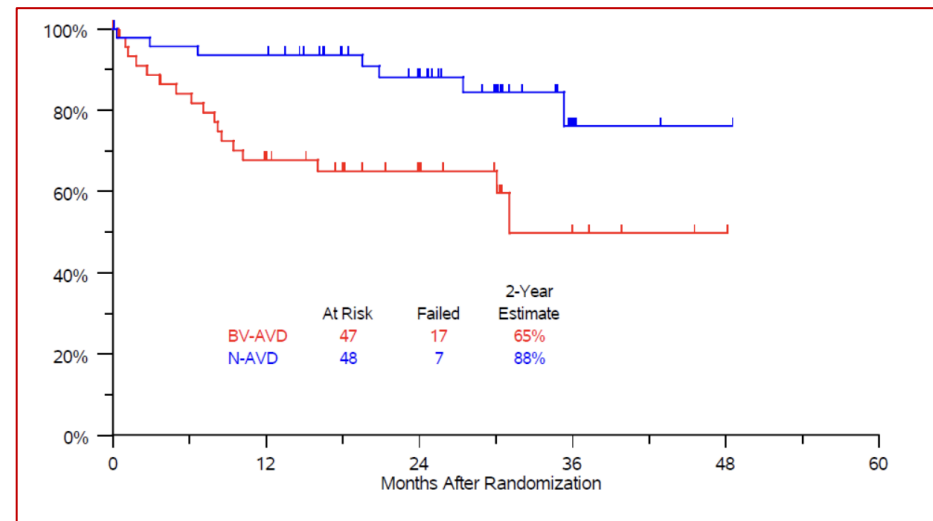
Nivo-AVD has rapidly become the standard of care for advanced stage HL in the US



Age 12-17



Age 18-60

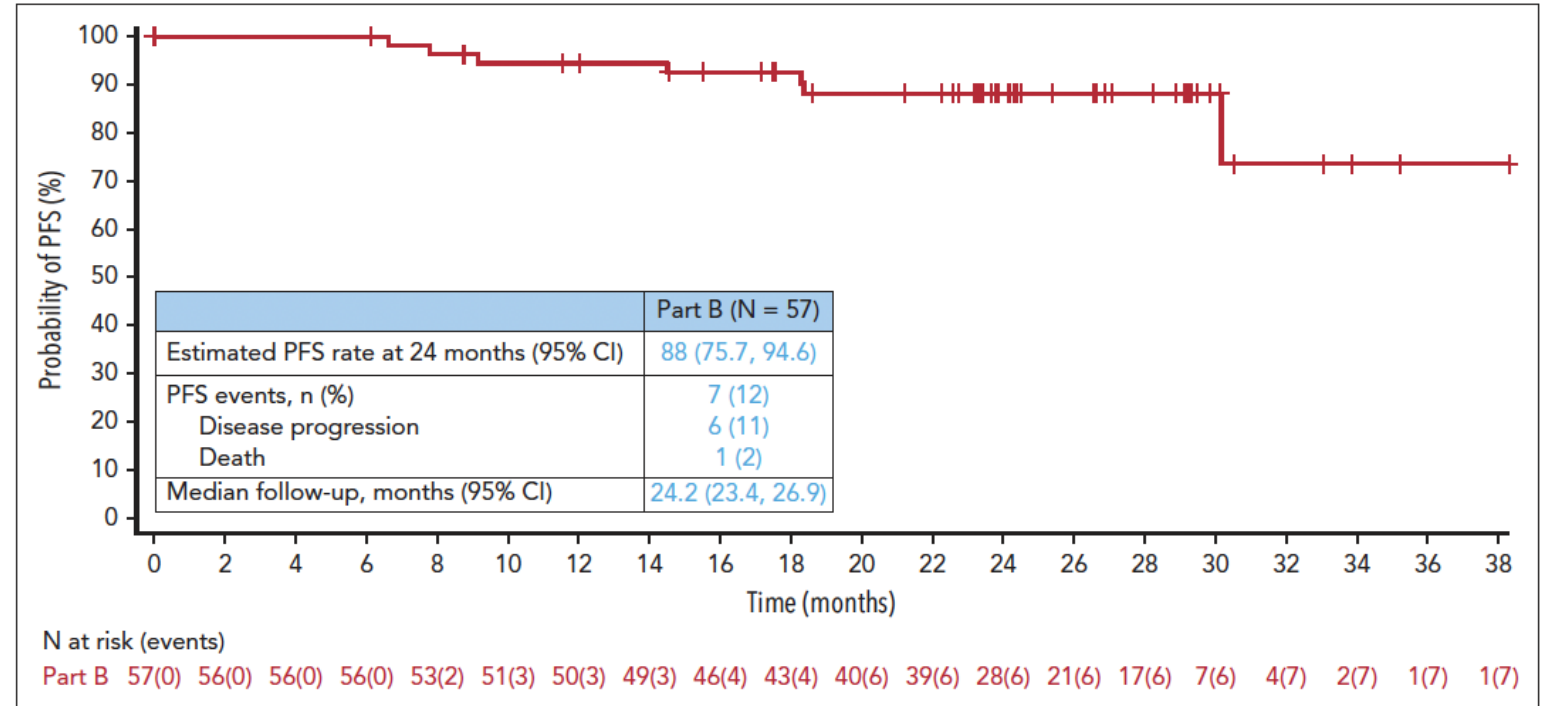


Age > 60

Herrera et al. NEJM 2024.

BV-nivo-doxorubicin-dacarbazine: small study but with some recurrences after 12 months

Demographics	Total (N = 57)
Age (y), median (range)	35.0 (19-78)
Age (y), range, n (%)	
<60	51 (89)
≥60	6 (11)
Sex, n (%)	
Female	27 (47)
Male	30 (53)
Ethnicity, n (%)	
Hispanic	9 (16)
Not Hispanic	46 (81)
Unknown	2 (4)
Race, n (%)	
White	50 (88)
Black or African American	2 (4)
Asian	1 (2)
Multiple	1 (2)
Unknown	3 (5)
Disease stage at diagnosis, n (%)	
II	18 (32)
Bulky*	17 (30)
III	10 (18)
IV	29 (51)
Extranodal disease present at initial diagnosis, n (%)	28 (49)
B symptoms present at initial diagnosis, n (%)	33 (58)
International Prognostic Score, n (%)	
0-1	13 (23)
2-3	32 (56)
4-7	12 (21)



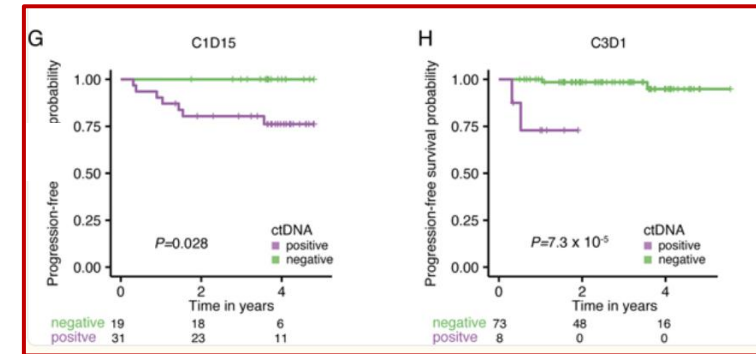
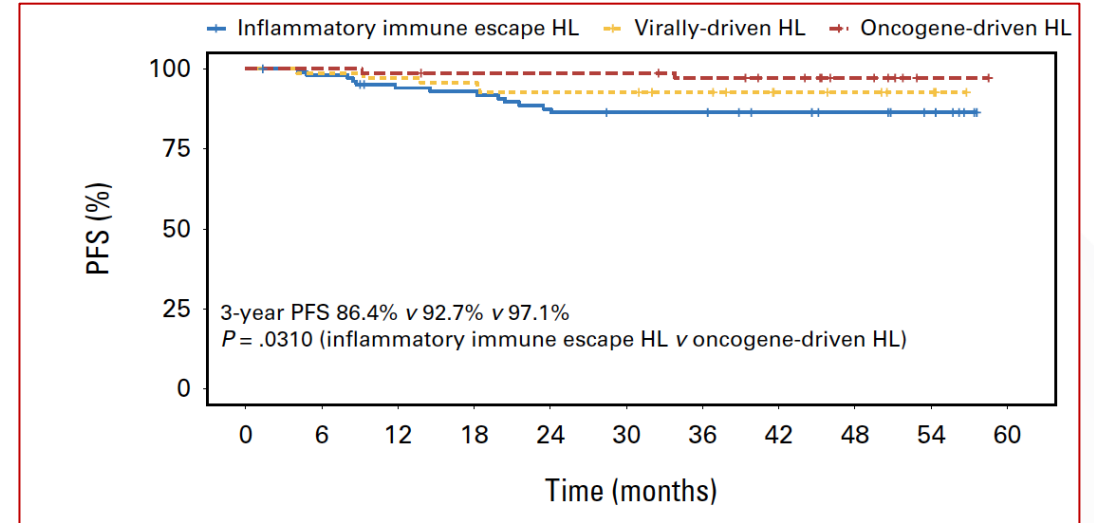
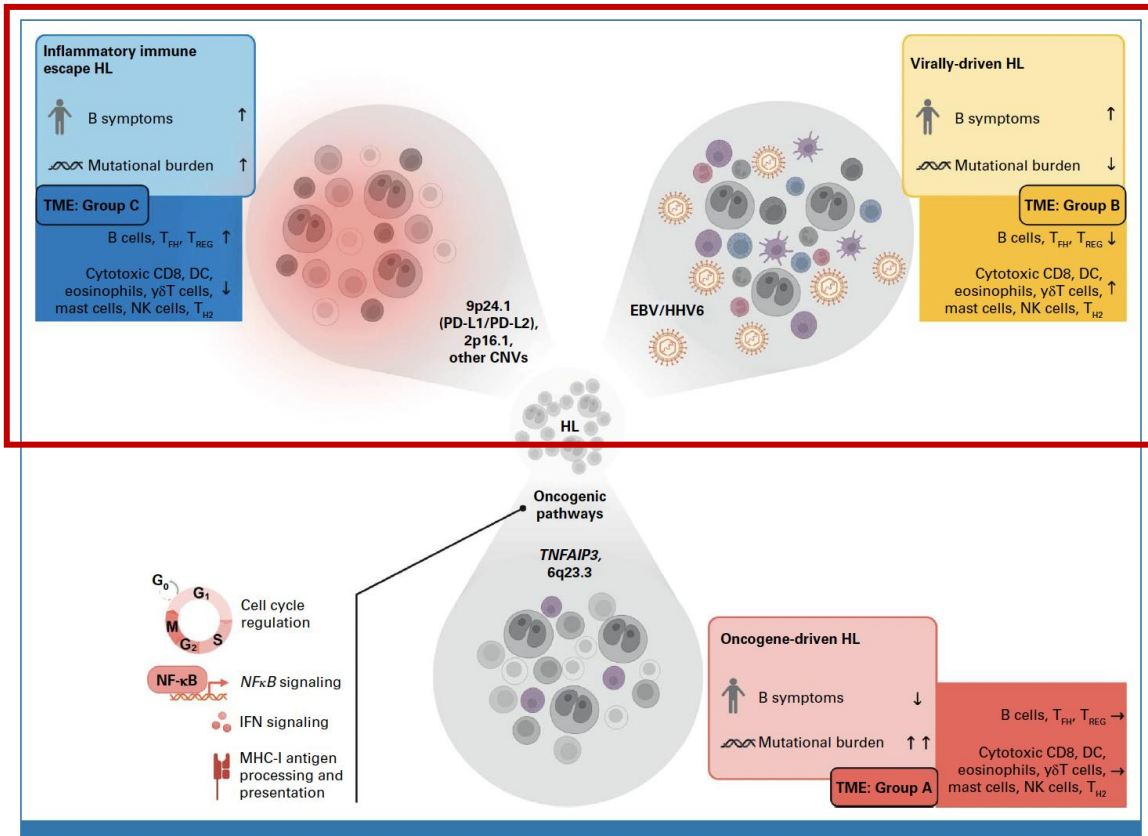
Summary of N-AVD vs BrECADD: personalize to the patient

N-AVD with excellent PFS and less toxicity than BrECADD.

**N-AVD with relatively short follow-up and more time necessary
to ensure remissions are durable.**

**BrECADD with the best efficacy of any regimen in advanced
stage cHL.**

Moving forward



Inflammatory/immune escape and viral driven HL may be particularly well suited to PD-1 based combinations

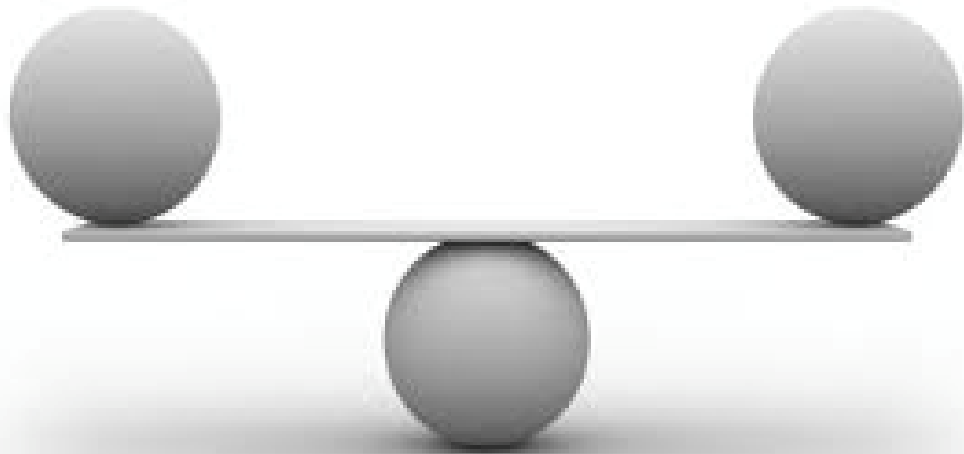
Heger et al. JCO 2024.

CT DNA may allow for the administration of less chemotherapy

Alig et al. Nature 2024.

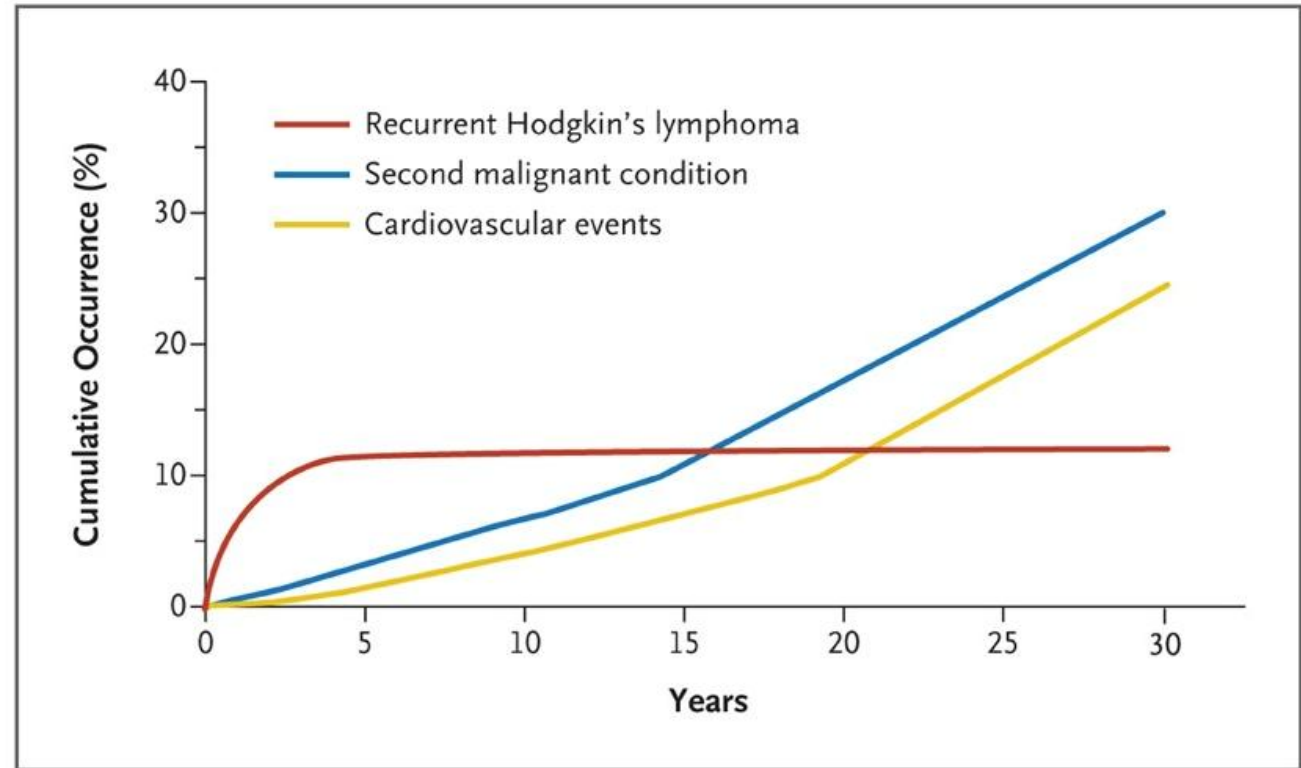
**Early-stage HL: improving
outcomes/limiting late toxicity**

Competing risks in early stage Hodgkin lymphoma



Risk of relapse

Late Toxicity




Armitage. NEJM 2010.

RT related late effects

Secondary cancer:
Long latency
Increasing risk over
time
Relates to dose and
field

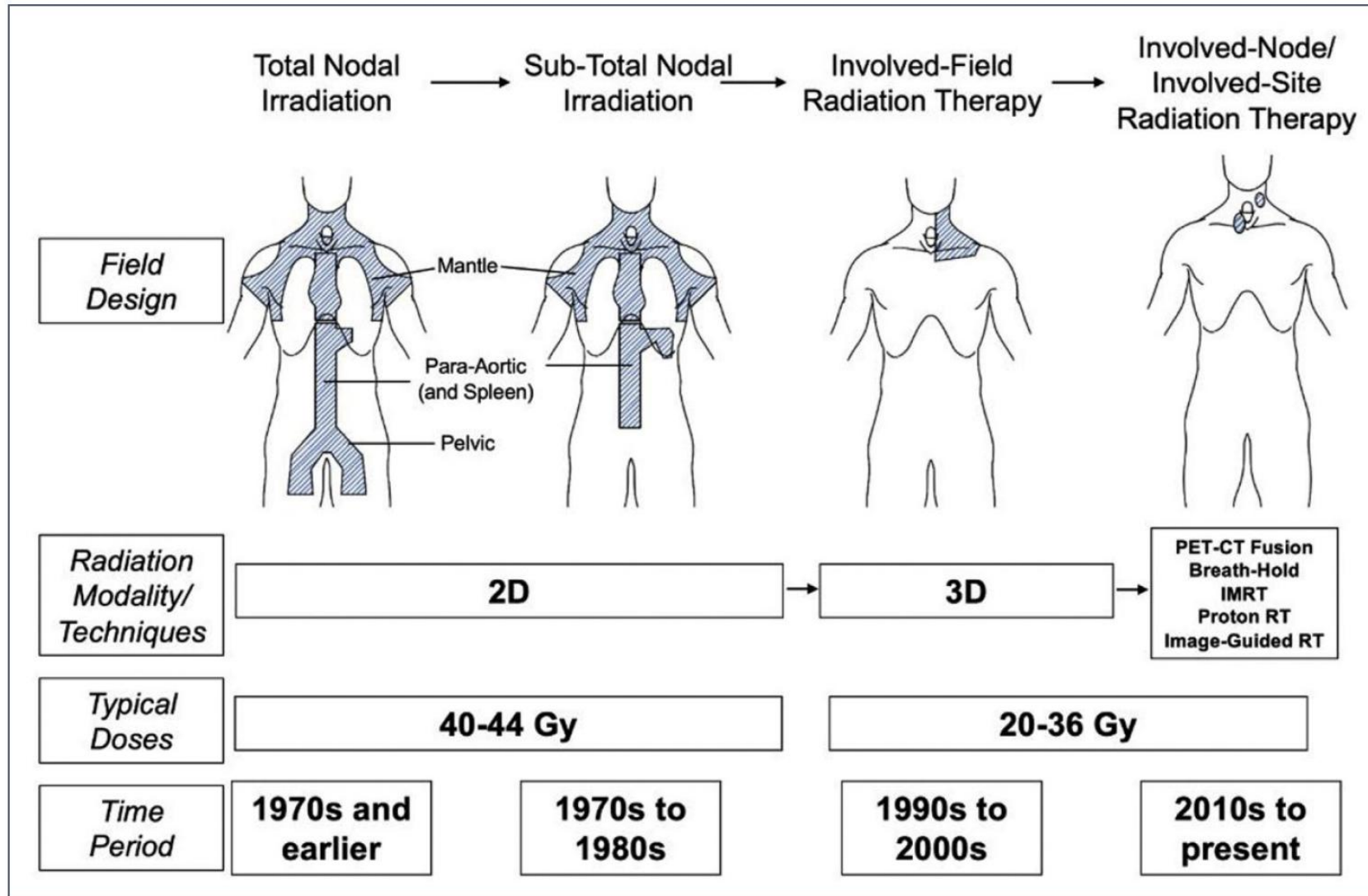


Secondary cancer:
Breast cancer ↑ <30
Lung 
GI
Sarcoma
Thyroid

Cardiovascular
disease:
CAD
Valvular
Pericardial
Conduction



Evolution of radiotherapy techniques over time

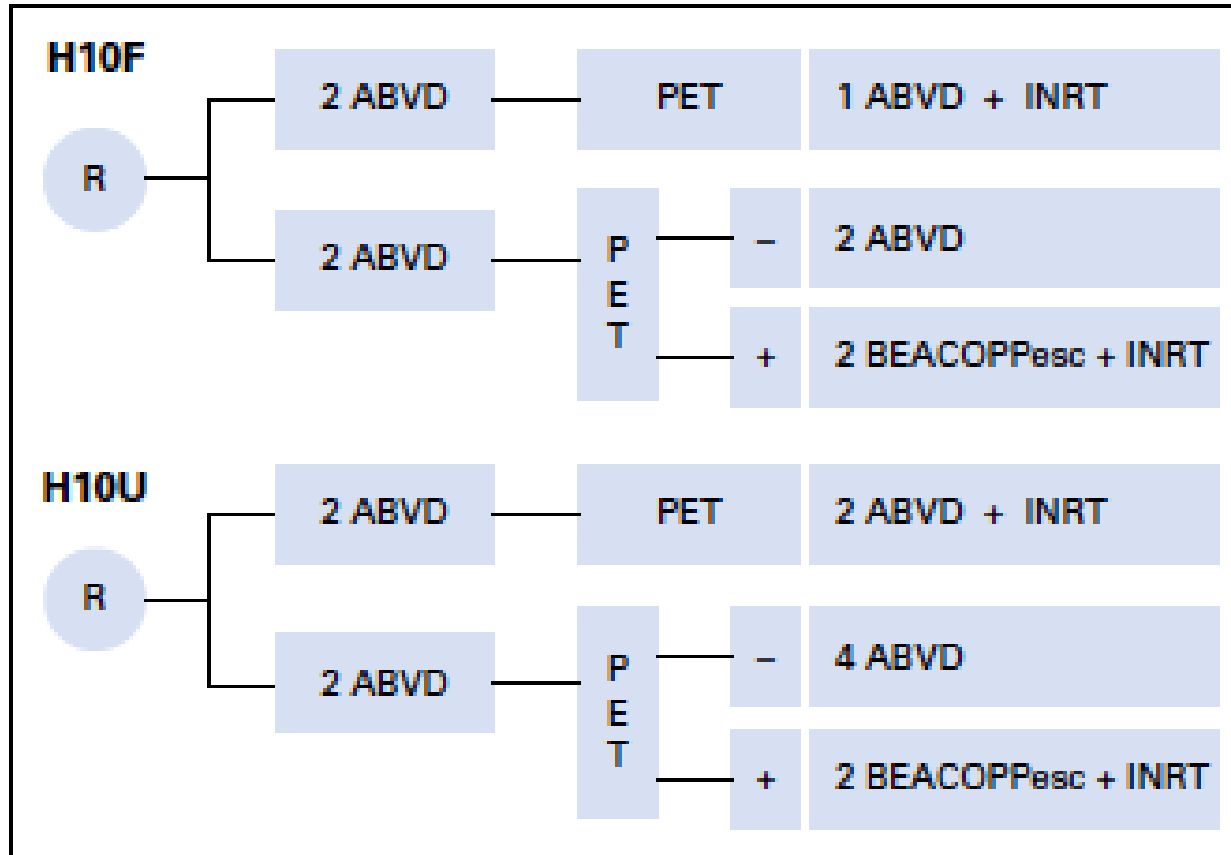


Bergom et al. JACC: Cardiooncology 2021.

Early-stage HL therapy

Current standard of care	Recent advances	On-going
ABVD chemotherapy PET adapted/ individualized use of RT	Many phase 2 studies with encouraging PFS with less RT	Randomized study to assess impact of BV and PD-1 inhibitors

EORTC H10: Testing PET adapted therapy in early-stage Hodgkin lymphoma



Risk factors:

LMA (> 1/3 max intrathoracic diameter)

Age \geq 50

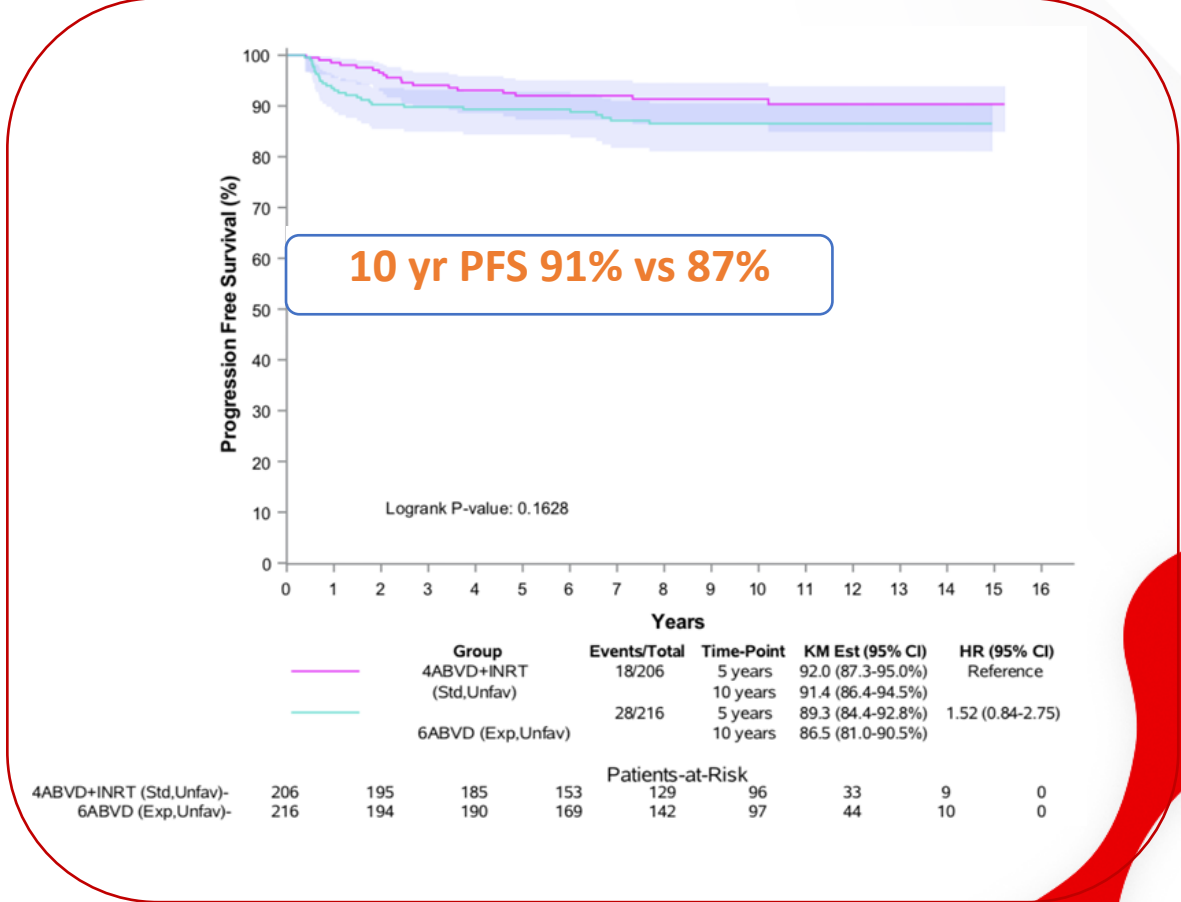
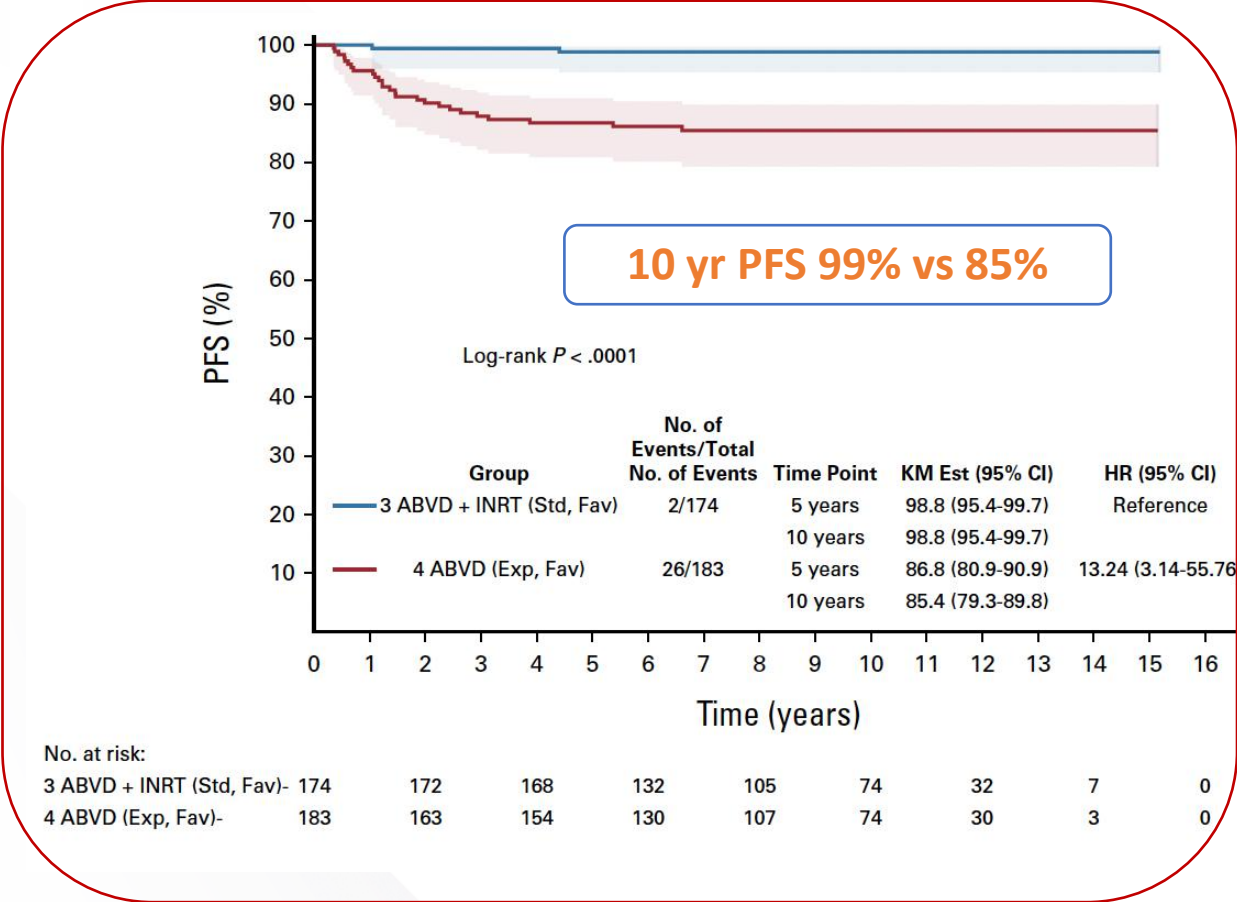
ESR \geq 50 without B sx

ESR \geq 30 with B sx

> 3 lymph node groups

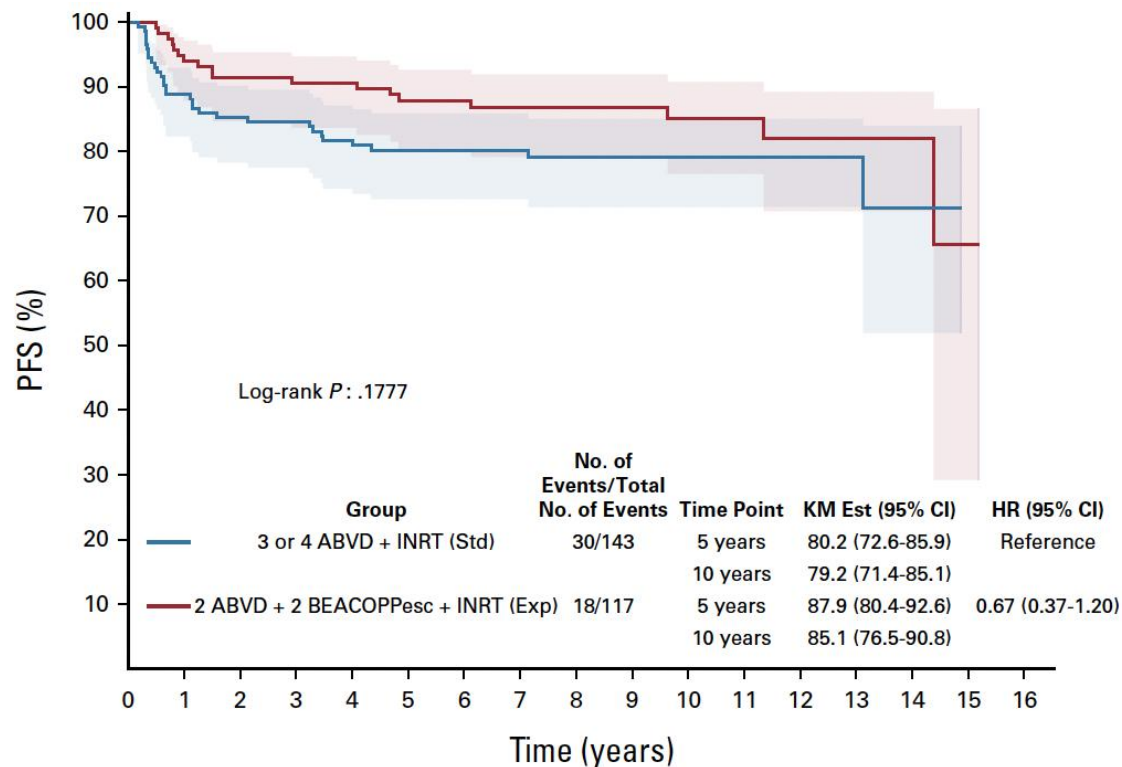
Long term follow-up of PET 2 negative patients

Positive PET = Deauville 3-5
81% of patients PET2 negative



Long term follow-up of PET 2 positive patients

Positive PET = Deauville 3-5
19% of patients PET2 positive



10 yr PFS 80% vs 85%

No. at risk:

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
3 or 4 ABVD + INRT (Std)-	143	121	112	93	73	51	22	6	0							
2 ABVD + 2 BEACOPPesc + INRT (Exp)-	117	107	101	87	74	45	21	6	0							

Nivolumab + AVD (concurrent and sequential) in early unfavorable HL very promising though all patients received RT

Randomized phase 2

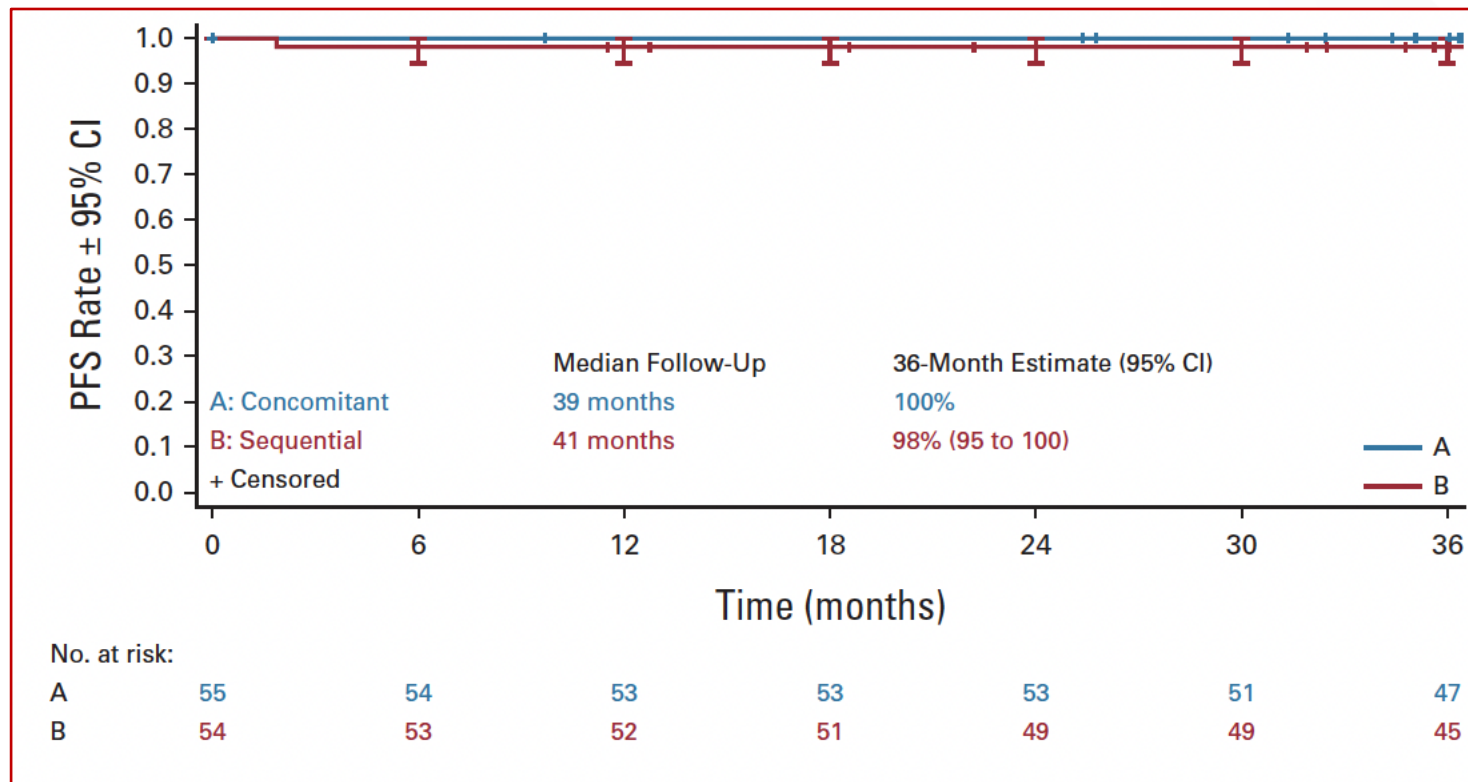
A: 4 x N-AVD

B: 4 x N

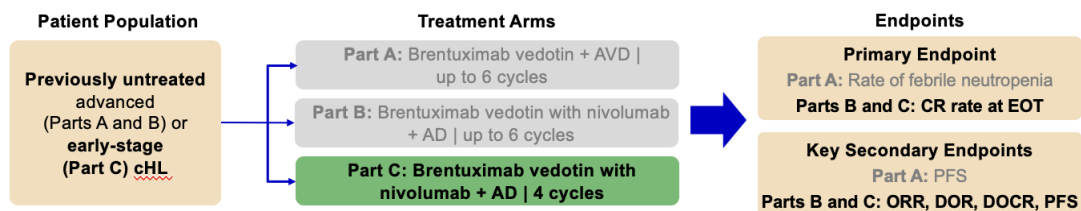
2 x N-AVD

2 x AVD

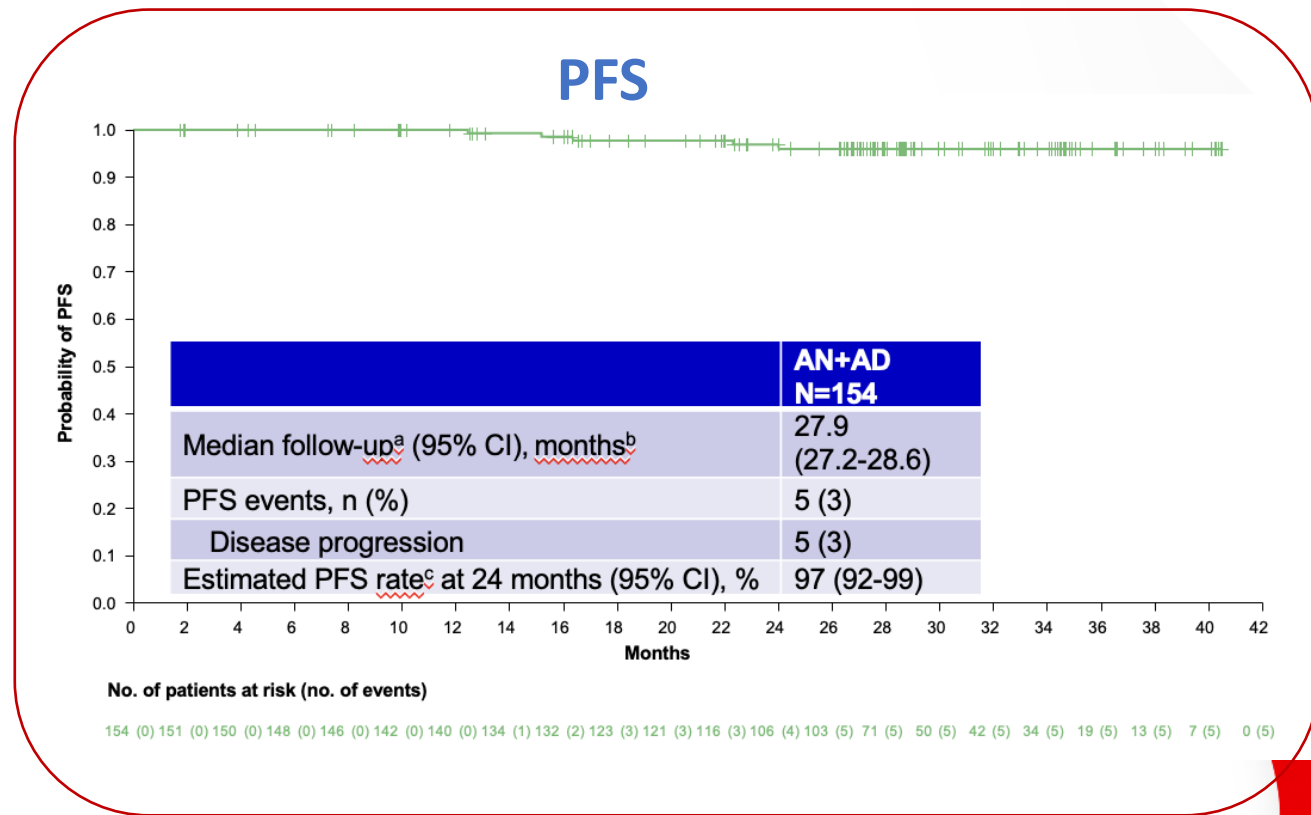
30 Gy
ISRT



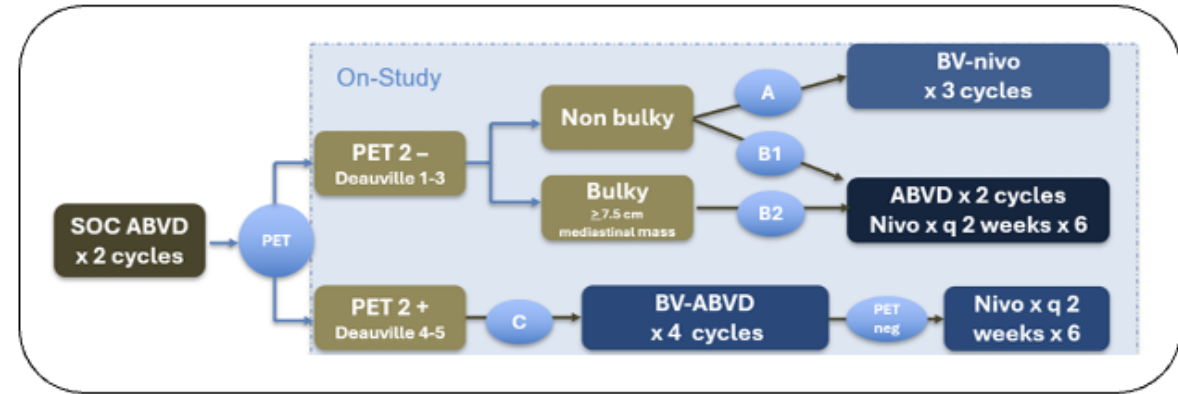
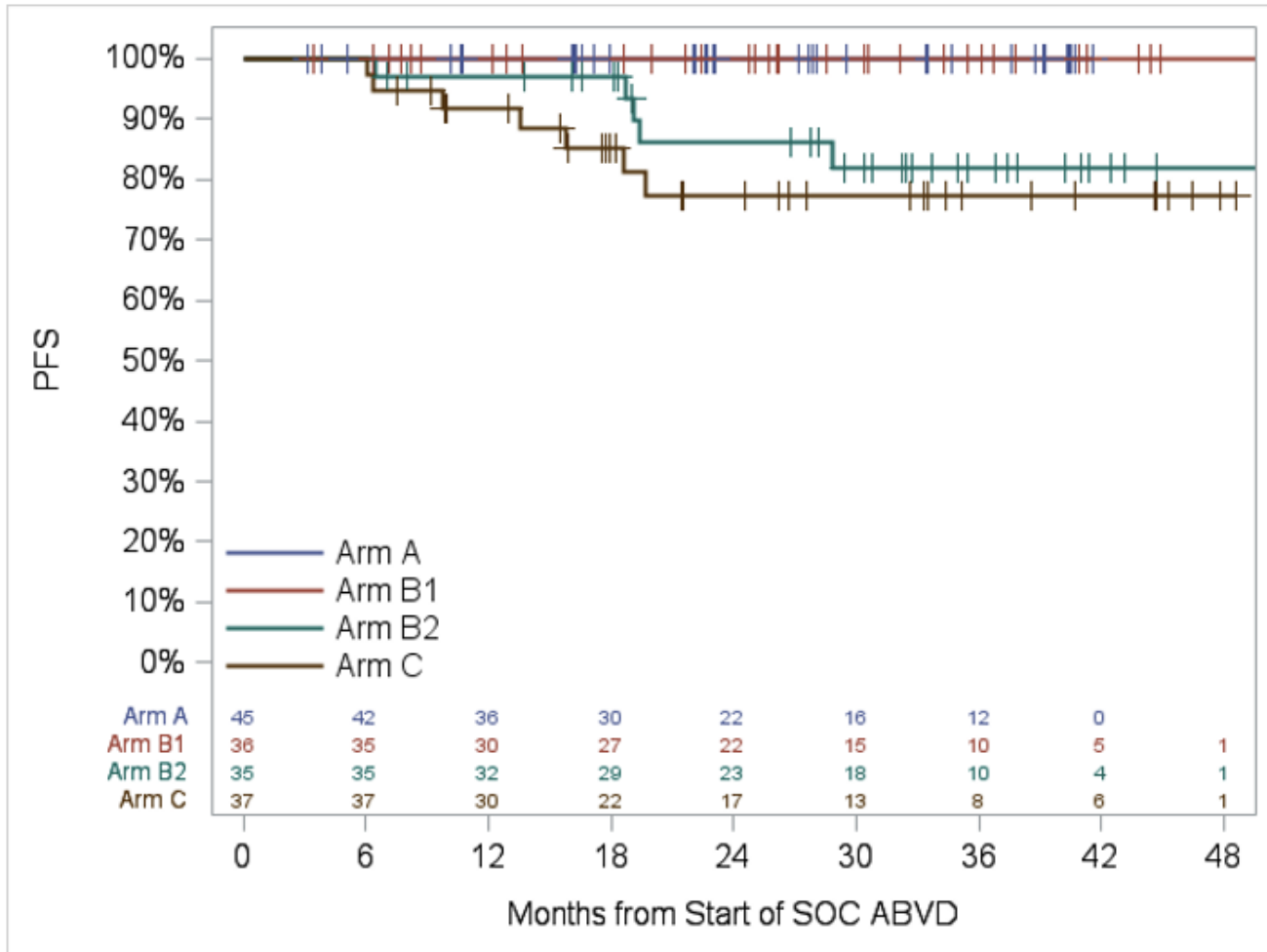
Updated Analysis of Brentuximab Vedotin, Nivolumab, Doxorubicin, and Dacarbazine for Nonbulky, Early-Stage CHL



- 98% of patients received 4 cycles of treatment
- Six patients (4%) received subsequent treatment, 2 of whom received consolidative radiotherapy



A Randomized Phase 2 Study Incorporating Nivolumab and Brentuximab Vedotin into Radiation-Free Treatment of Early Stage CHL



PFS (95% CI)	# of PD/Rel	18-month	24-month
Arm A (n=45)	0	100%	100%
Arm B1 (n=36)	0	100%	100%
Arm B2 (n=35)	5	97% (81-100%)	86% (67-95%)
Arm C (n=37)	7	85% (68-94%)	77% (57-89%)

No deaths reported thus far.
Median follow-up is 27.7 months (range 3.2-51.0).

Standard therapy vs. immuno-oncology for children and adults with newly diagnosed stage I and II classic HL: AHOD 2131



Favorable Risk

ABVD x 2 cycles

PET-2

RER

SER

Randomize

Randomize

Arm A
ABVD x
2 cycles

Arm B
Bv-Nivo x
4 cycles

End of
Protocol
Therapy

End of
Protocol
Therapy

Arm C
eBEACOPP
x 2 cycles

ISRT

End of
Protocol
Therapy

Arm D
Bv-Nivo x
4 cycles

ISRT

End of
Protocol
Therapy

Planned enrollment
1875 patients
(ages 5-60 years)

Unfavorable Risk

ABVD x 2 cycles

PET-2

RER

SER

Randomize

Randomize

Arm E
AVD x 4
cycles

End of
Protocol
Therapy

Arm F
Bv-Nivo x
4 cycles

End of
Protocol
Therapy

Arm G
eBEACOPP
x 2 cycles

ISRT

End of
Protocol
Therapy

Arm H
Bv-Nivo x
4 cycles

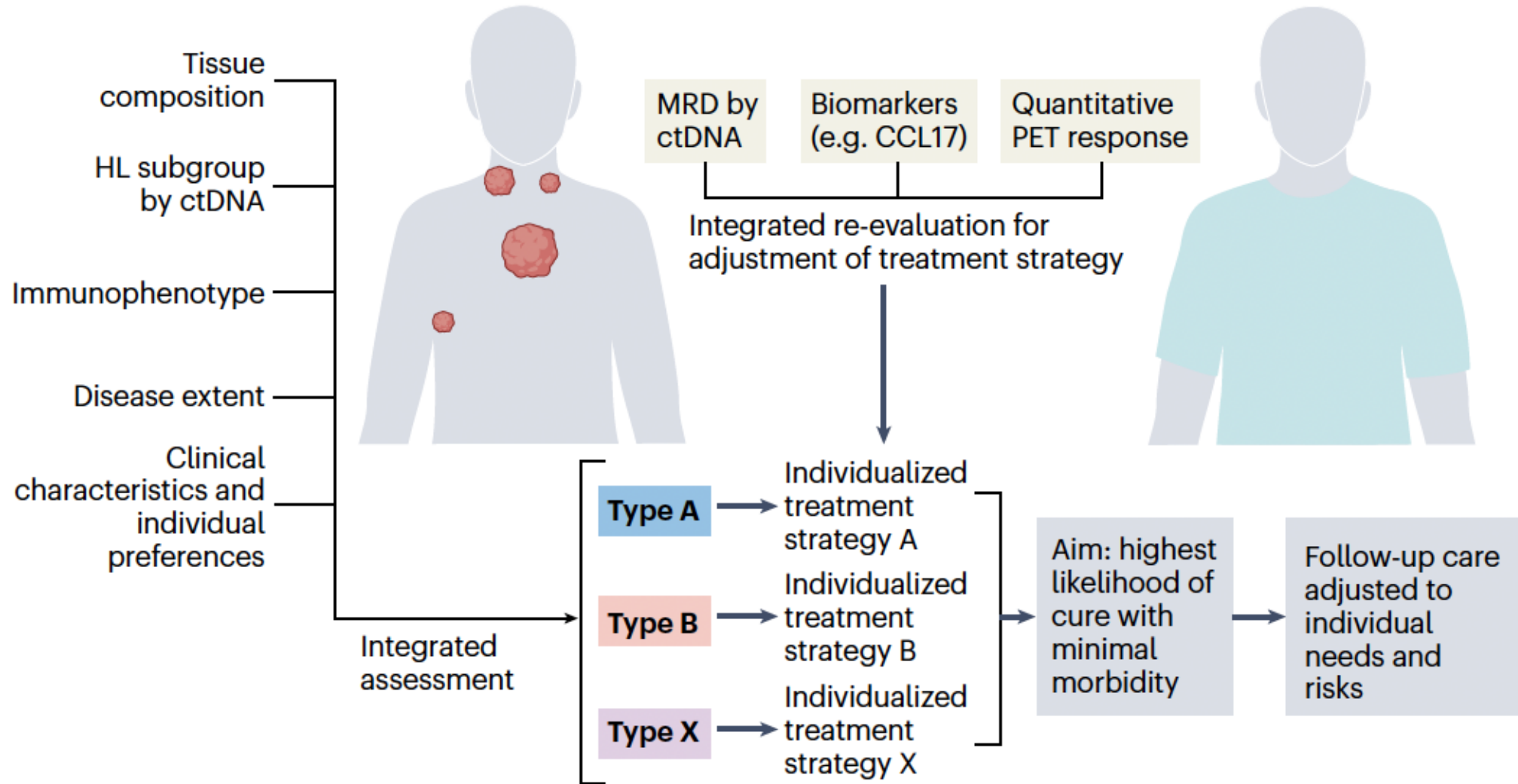
ISRT

End of
Protocol
Therapy



NCT05675410

Future directions in cHL



Summary



The vast majority of will experience long term disease control after front-line therapy



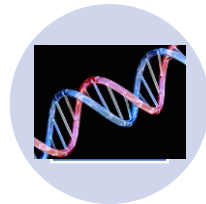
Balancing efficacy vs late toxicity key for individual patients



Incorporating novel agents (where approved/available) standard in advanced stage disease



Novel agents remain experimental in early-stage cHL



ctDNA may allow for improved risk adapted approaches



Ben Lampson
(Blueprint Bio)

Cathy Wu (Lab)
Mark Murakami (Lab)
Andy Lane (Lab)
Margaret Shipp (Lab)
Andrea Ng (Rad Onc)
Lakshmi Nayak (Neuroonc)



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