

# Where are we in first line therapy for Hodgkin Lymphoma?

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# Where are we in first line therapy for Hodgkin Lymphoma?

Peter Johnson

Professor of Medical Oncology

University of Southampton, UK



## Case presentation

20 year old female

Felt a swelling in her neck

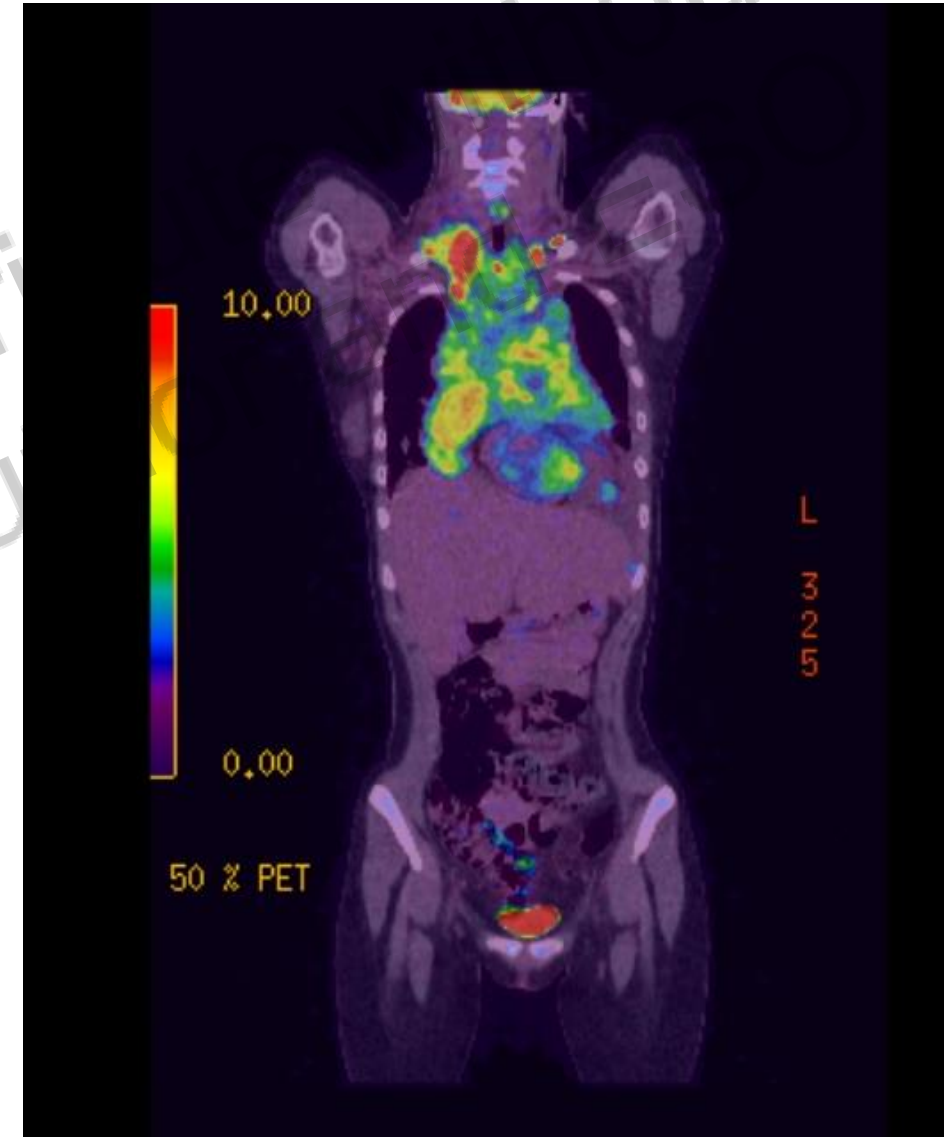
Breathless on exertion

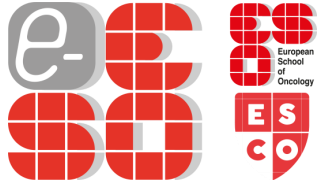
Otherwise well

Normal blood count, ESR 10mm/hr

Histology: Nodular sclerosing Hodgkin lymphoma

Stage II<sub>AX</sub> (unfavourable)





## A range of possible treatments...

4 ABVD + 30Gy IFRT

(GHSO HD11: J Clin Oncol 2010; 28:4199-4206)

2 ABVD and if PET-2 negative 4 AVD, avoid RT

(RATHL: NEJM 2016; 374:2419-29)

2 ABVD and if PET-2 negative 4 ABVD, avoid RT

(EORTC/FIL/LYSA H10u: J Clin Oncol 2017; 35:1786-1794)

2 escBEACOPP + 2 ABVD, avoid RT if PET-4 negative

(GHSO HD17: Lancet Oncol 2021; 22:223-234)

4 BV-AVD and if PET-2 negative, avoid RT

(MSKCC: J Clin Oncol. 2021;39(20):2257-2265.)

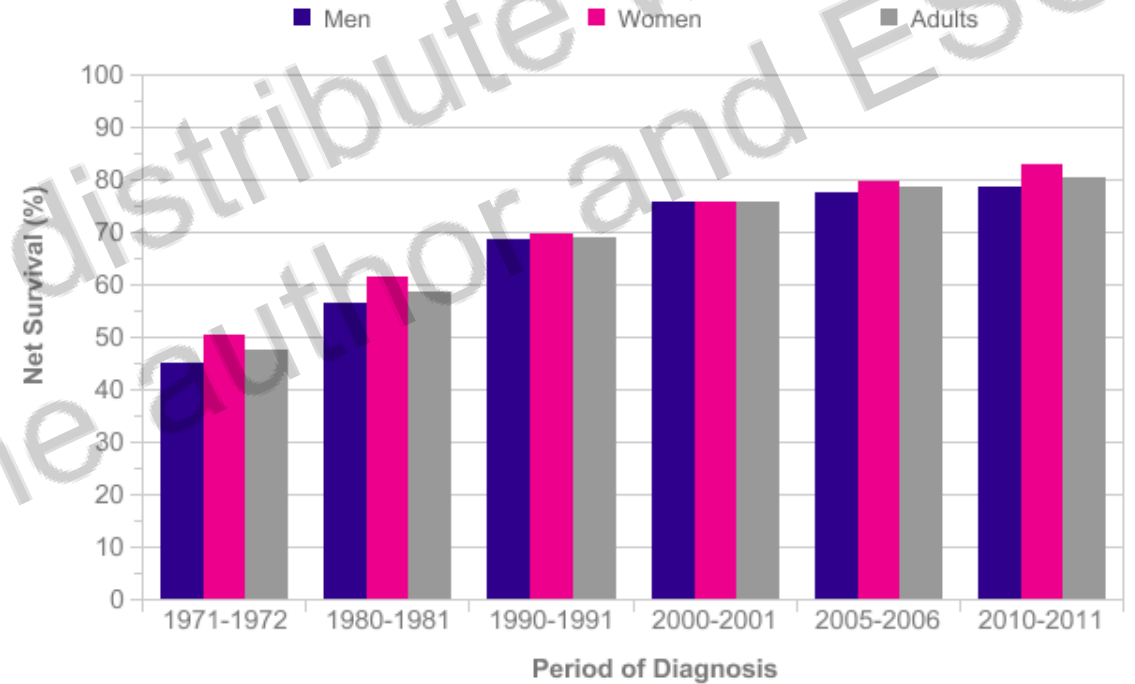
3 Pembrolizumab + 4 AVD and if PET-2 negative, avoid RT

(NU16H08. Blood. 2021;137(10):1318-1326; Blood Adv 2022; Sep 9)

## Overall results of therapy

- $\geq 90\%$  cures with first line therapy
- 90-95% in early stages
- 85-90% in advanced disease
- 80% live 10 years or more

### Age-Standardised Ten-Year Net Survival, England and Wales



Prepared by Cancer Research UK

**Original data sources:**

Survival estimates were provided on request by the Cancer Research UK Cancer Survival Group at the London School of Hygiene and Tropical Medicine.

<http://www.lshtm.ac.uk/eph/ncde/cancersurvival/>



# Comparison of mortality compared to the general population

Excess mortality at all ages, but lower in young and early stage cases

Competing risks are notable

Recent trials show more deaths from other causes than Hodgkin lymphoma: disease control and survival are not the same thing

Primary focus of research is to

- improve this result
- minimise toxicity

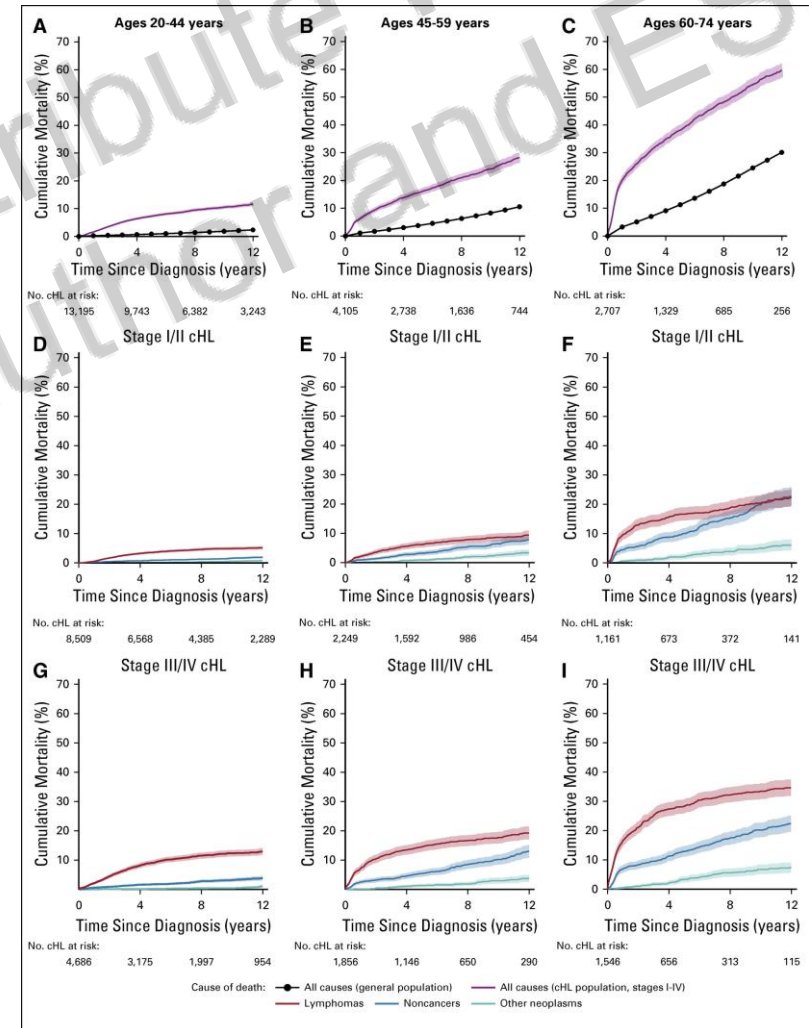
All stages

Early stage

Advanced stage

Young

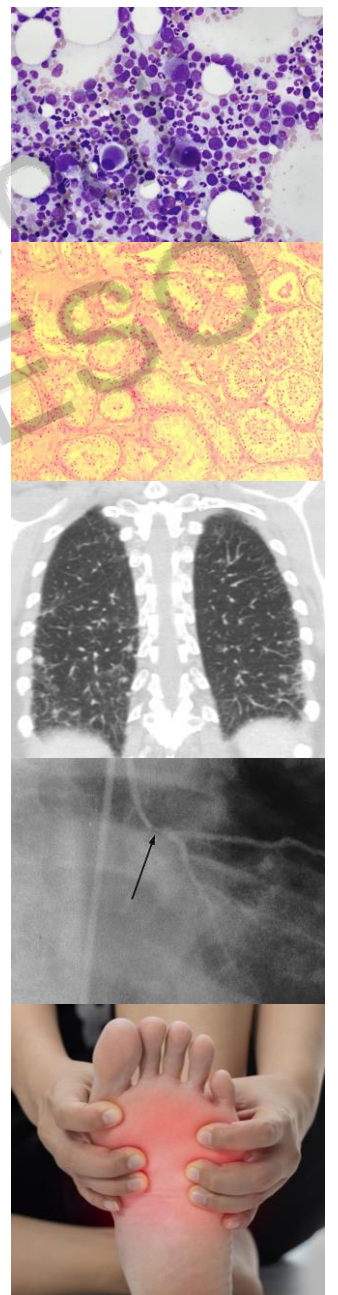
Old



Graça M. et al.; *J Clin Oncol* 2020; 38:4149-4162

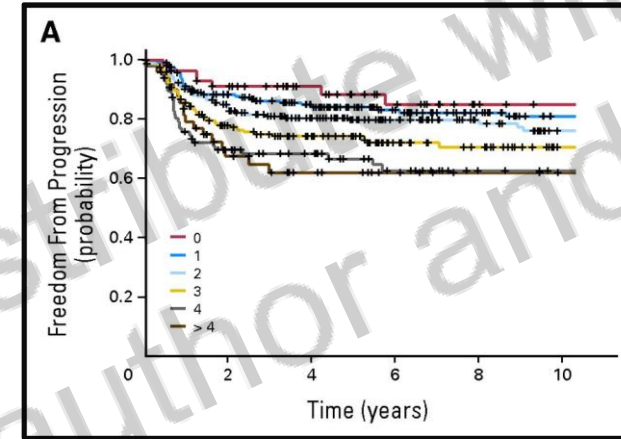
## Considerations in the choice: competing risks

- Short-term toxicity of myelosuppression
- Second cancers, cardiac disease from radiotherapy field
- Future fertility
- Pulmonary fibrosis
- Cardiac muscle damage
- Neuropathy
- Initial treatment failure: need for second line therapy

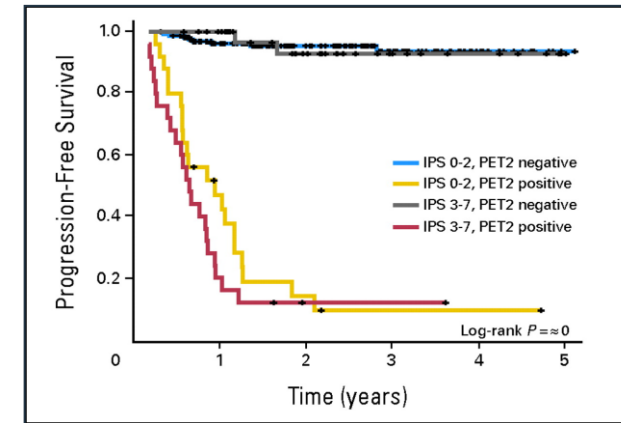
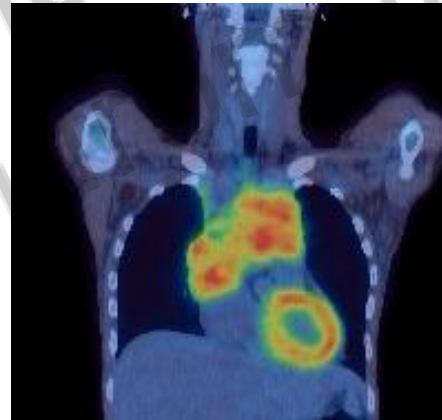
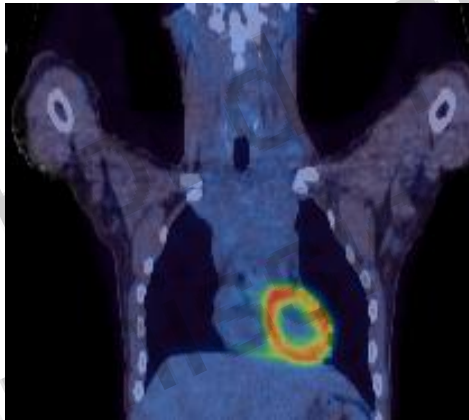


# Can we distinguish worse from less bad disease?

- Baseline clinical features: partly
- Baseline biological assessments: not yet
- The response to therapy: yes



Moccia AA et al., J Clin Oncol. 2012;30:3383-8

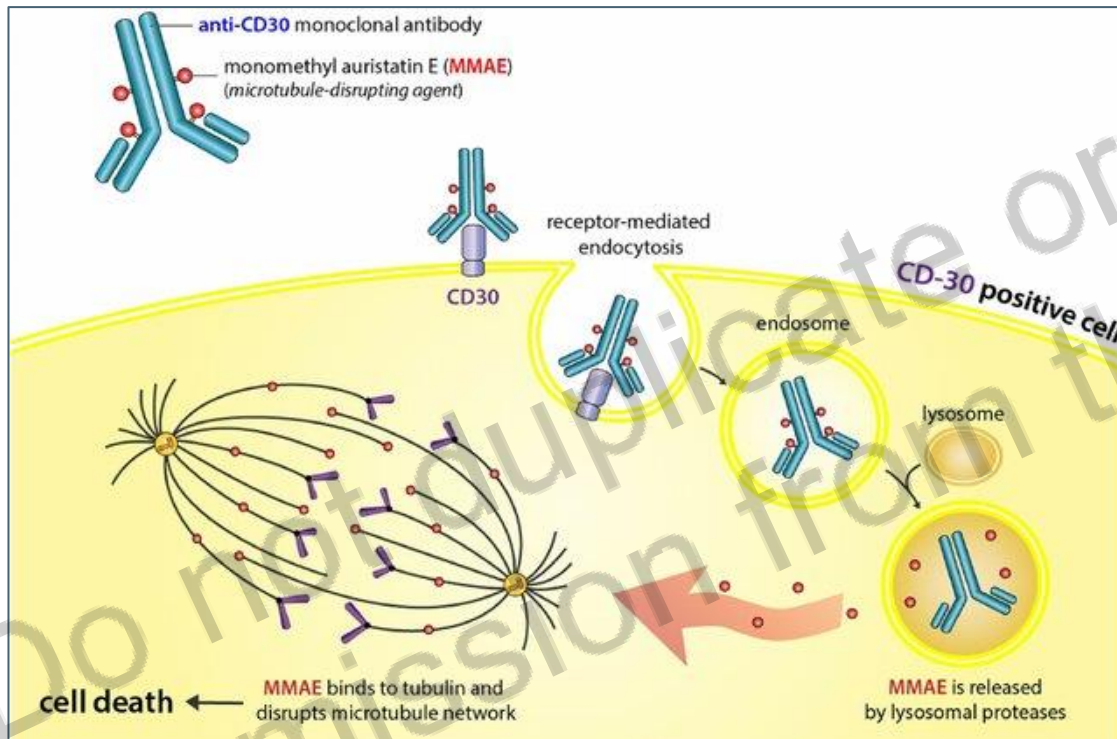


Gallamini A et al. J Clin Oncol. 2007;25:3746-3752

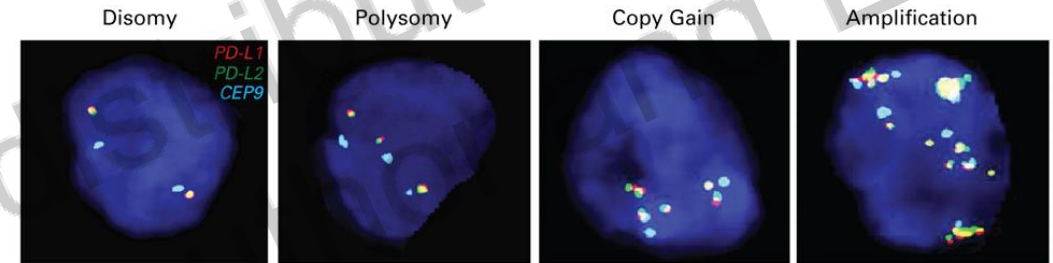


# Newer options for systemic therapy

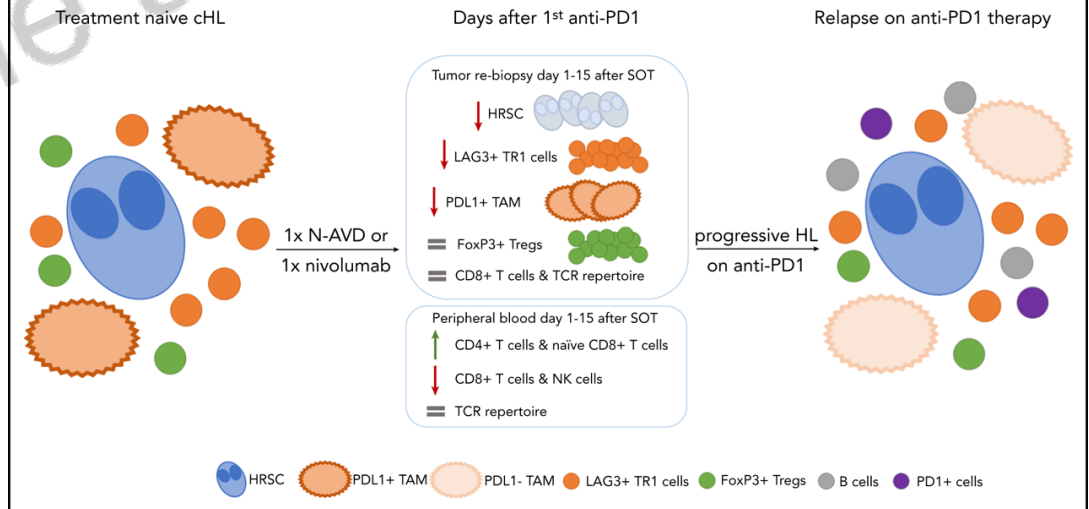
## Anti-CD30 antibody-drug conjugate



## Anti-PD1 antibodies



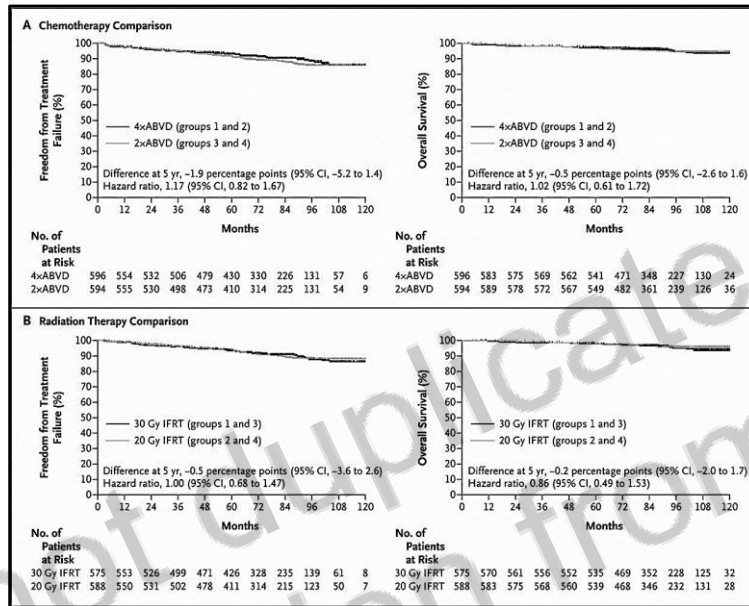
Anti-PD1 therapy in Hodgkin lymphoma: Early histological and microenvironment dynamics without cytotoxic T-cell response



Reinke et al., Blood, 2020, 136: 2851–2863

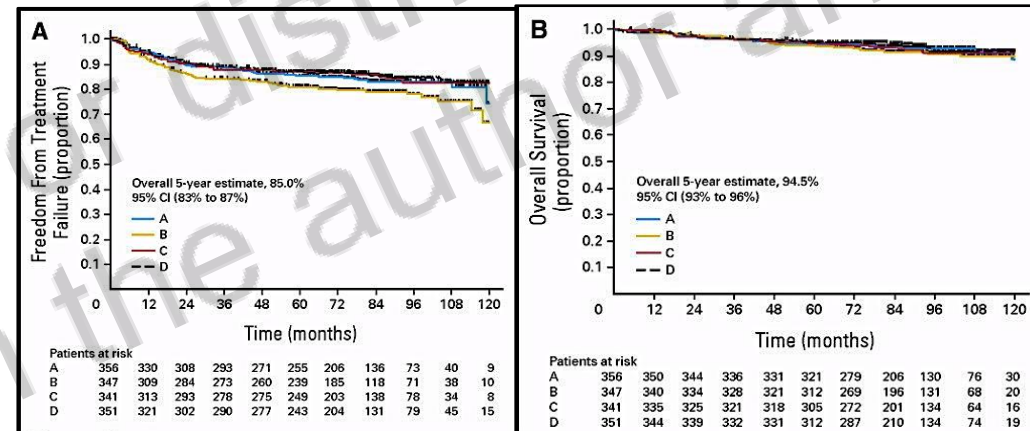
# Early stage: standard of care

Early Favourable disease  
2 vs 4 ABVD + 20Gy vs 30Gy IFRT



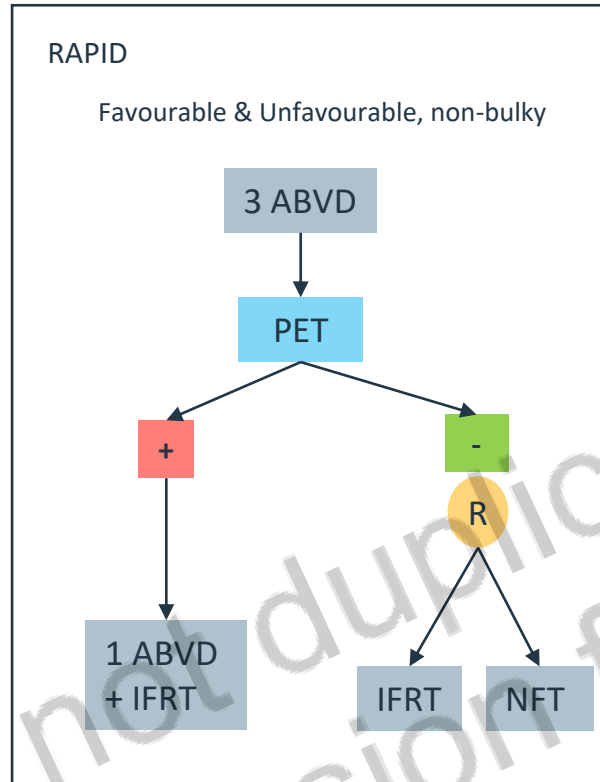
Results equivalent for all 4 arms: 5yr  
FFTF 92% OS 97%

Early Unfavourable disease  
4 ABVD vs 4 BEACOPP + 20Gy vs 30Gy



ABVD + 20Gy inferior on FFTF

# Randomised trials to test the role of interim PET

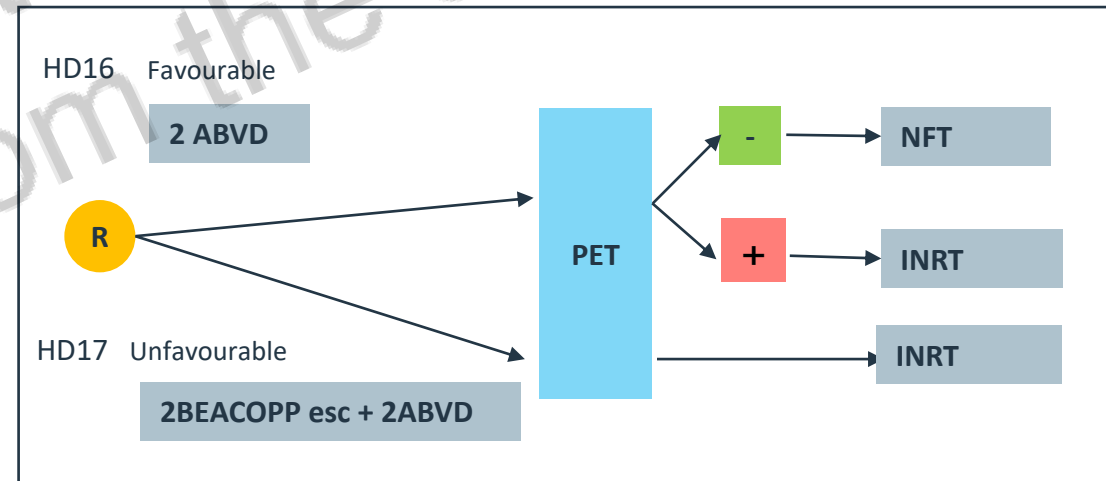
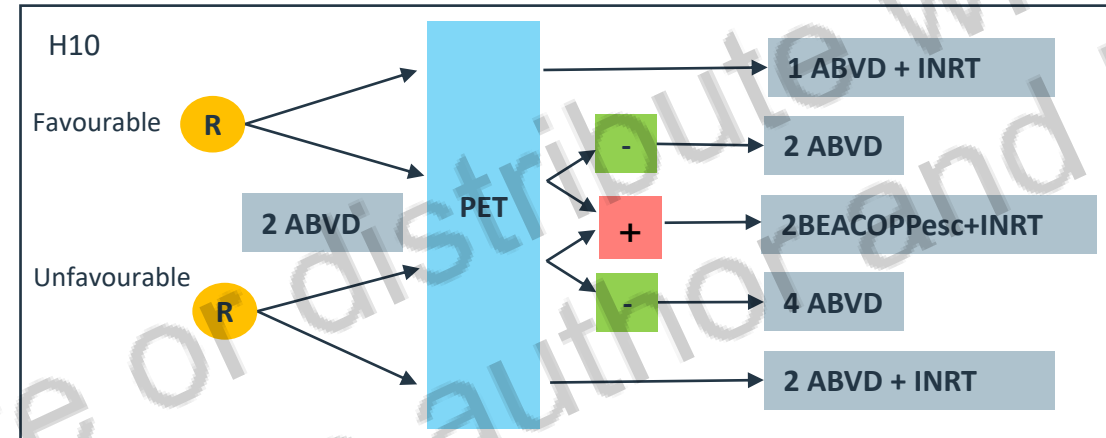


N Engl J Med 2015; 372:1598-1607

J Clin Oncol 2017; 35:1786-1794

J Clin Oncol 2019;37:2835-2845

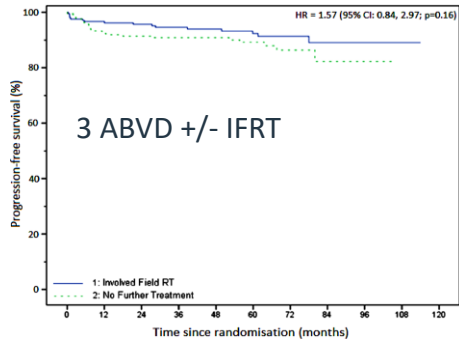
Lancet Oncol 2021; 22:223-234



# Control of lymphoma after de-escalation in PET-negative groups

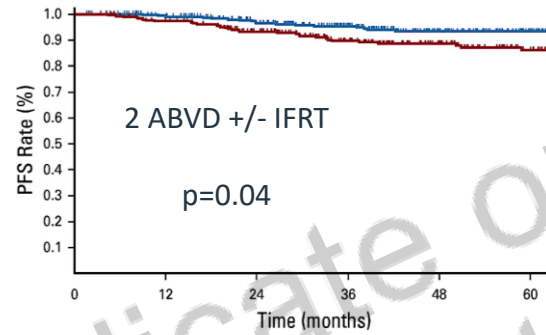
## RAPID

5 yr EFS  
96.0 vs 90.1%



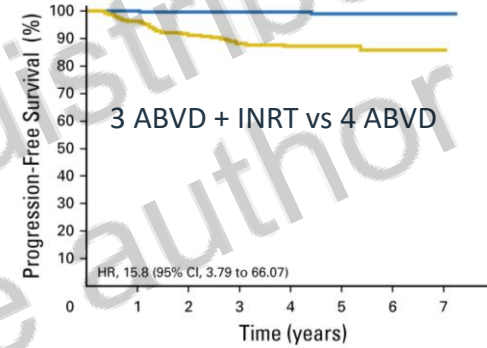
## HD 16

5 yr PFS  
93.4 vs 86.1%



## H10 F

5 yr PFS  
99.0 vs 87.1%



N Engl J Med 2015; 372:1598-1607

J Clin Oncol 2017; 35:1786-1794

J Clin Oncol 2019;37:2835-2845

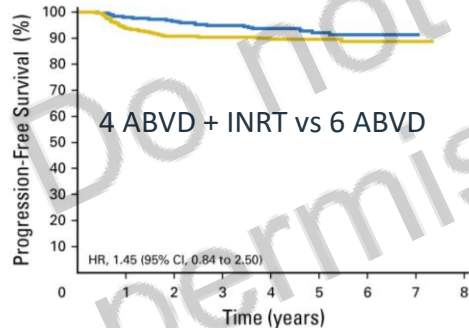
Lancet Oncol 2021; 22:223-234

J Clin Oncol 2021; 39:2257-2265

Blood Adv 2022; Sep 9

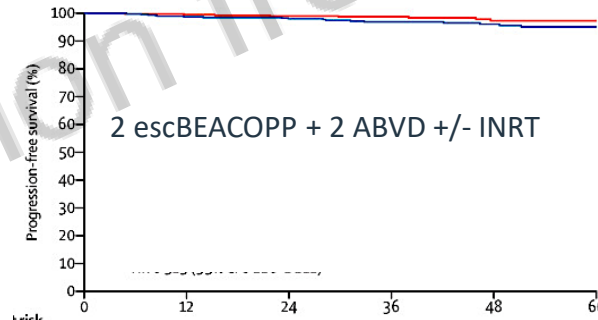
## H10 U

5 yr PFS  
92.1 vs 89.6%



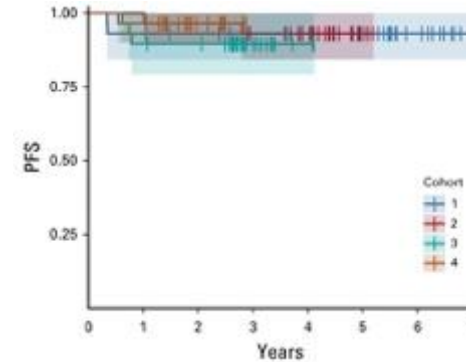
## HD 17

5 yr PFS  
97.7 vs 95.9%



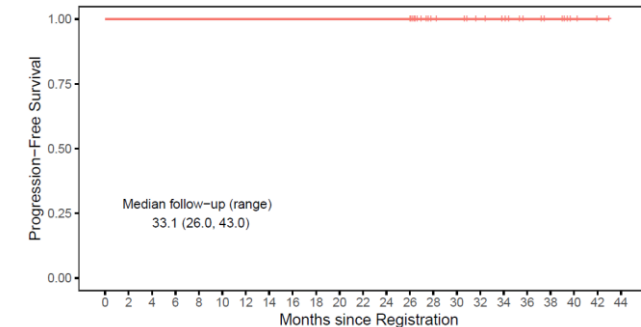
## MSKCC BV+AVD

2 yr PFS  
94%



## Pembro+AVD

33mo PFS  
100%

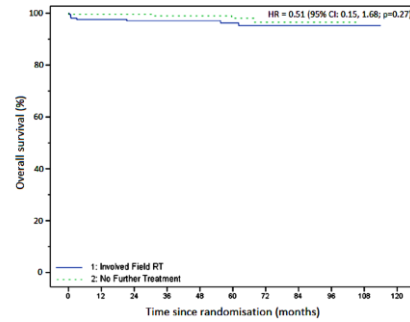




# Overall Survival after de-escalation in PET-negative groups

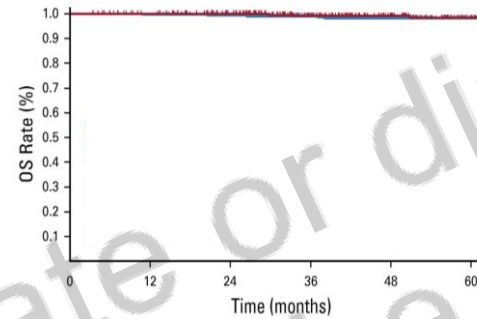
**RAPID**

3 yr OS  
97.1 vs 99.5%



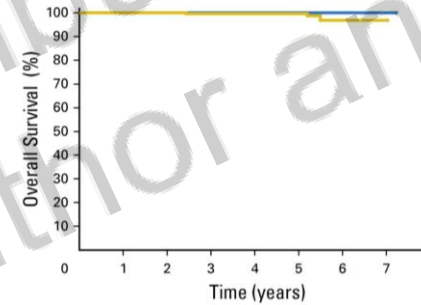
**HD 16**

5 yr OS  
98.1 vs 98.4%



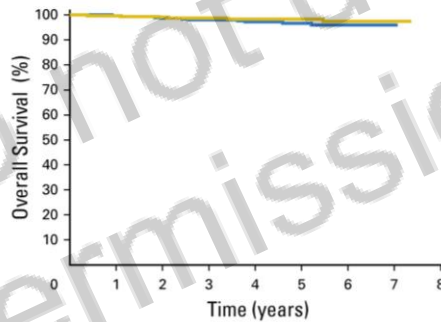
**H10 F**

5 yr OS  
100 vs 99.6%



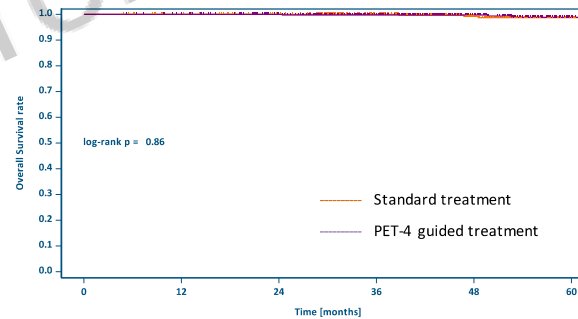
**H10 U**

5 yr OS  
96.7 vs 98.3%



**HD17**

5 yr OS  
98.8 vs 98.4%



N Engl J Med 2015; 372:1598-1607

J Clin Oncol 2017; 35:1786-1794

J Clin Oncol 2019;37:2835-2845

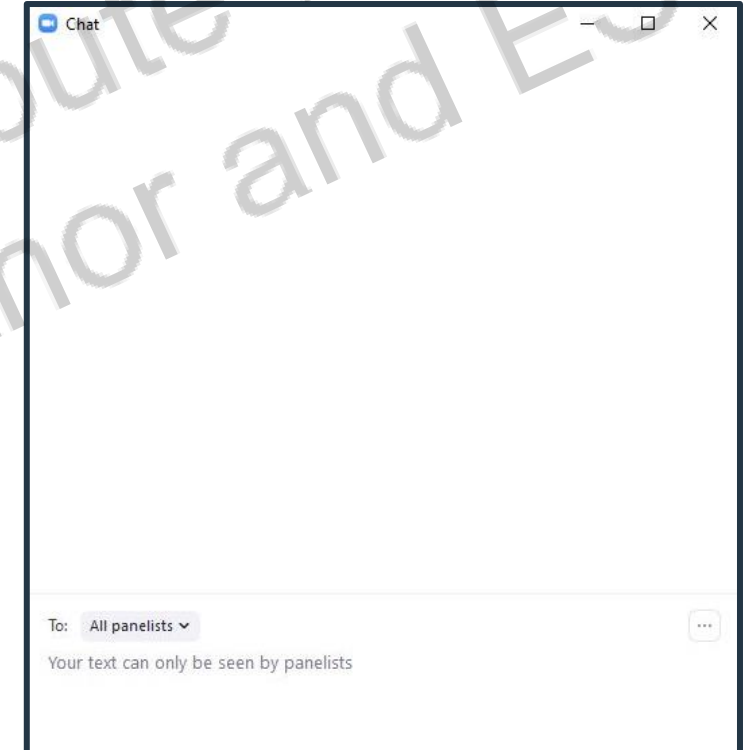
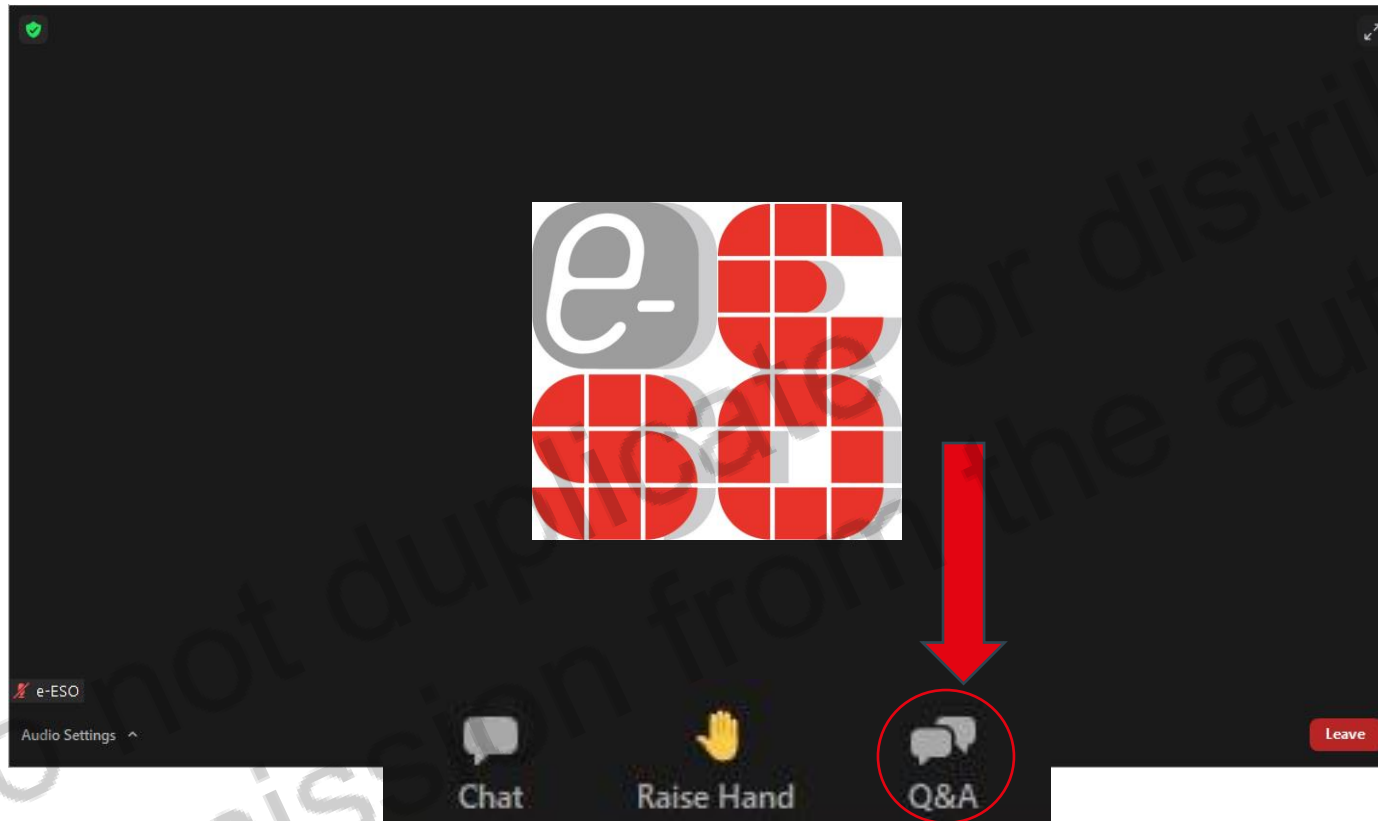
Lancet Oncol 2021; 22:223-234

# Putting the evidence together: early stage disease

- Combined modality therapy is currently standard, *but...*
- Therapy adapted by iPET is reasonable and safe
- **Chemotherapy-only approaches should be considered:**
  - For people with low MTV at presentation if the iPET after 2 ABVD is negative (DFPS 1-3)
  - For people with unfavourable disease given 2 eBEACOPP + ABVD with negative PET
  - For people at high risk of second cancer/cardiac damage from IFRT
- Might this soon be an academic question?

**Yes, if the results of anti-PD1 with chemotherapy hold up**

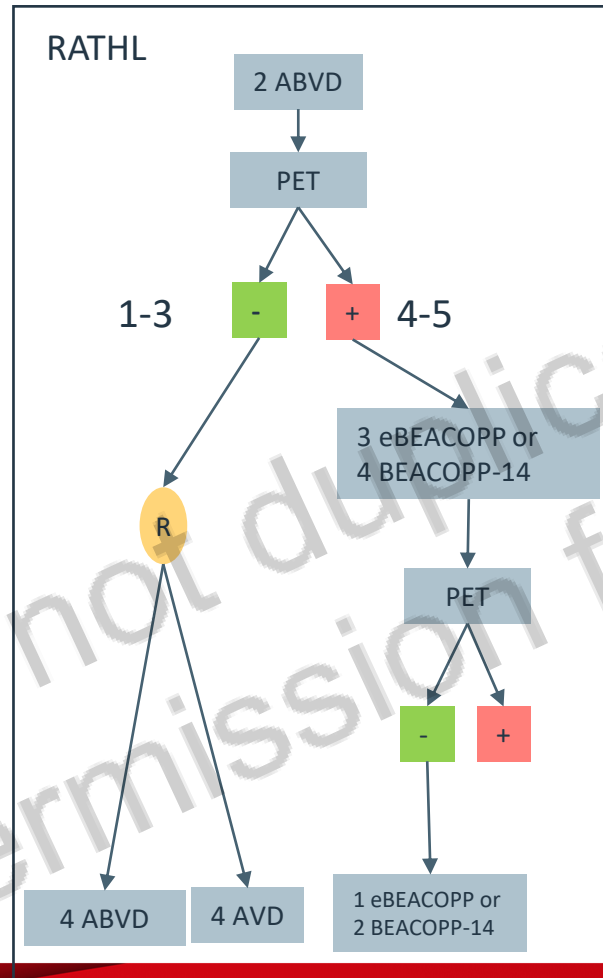
**Your views are important!**  
**Remember that you can ask questions and send comments at any time.**



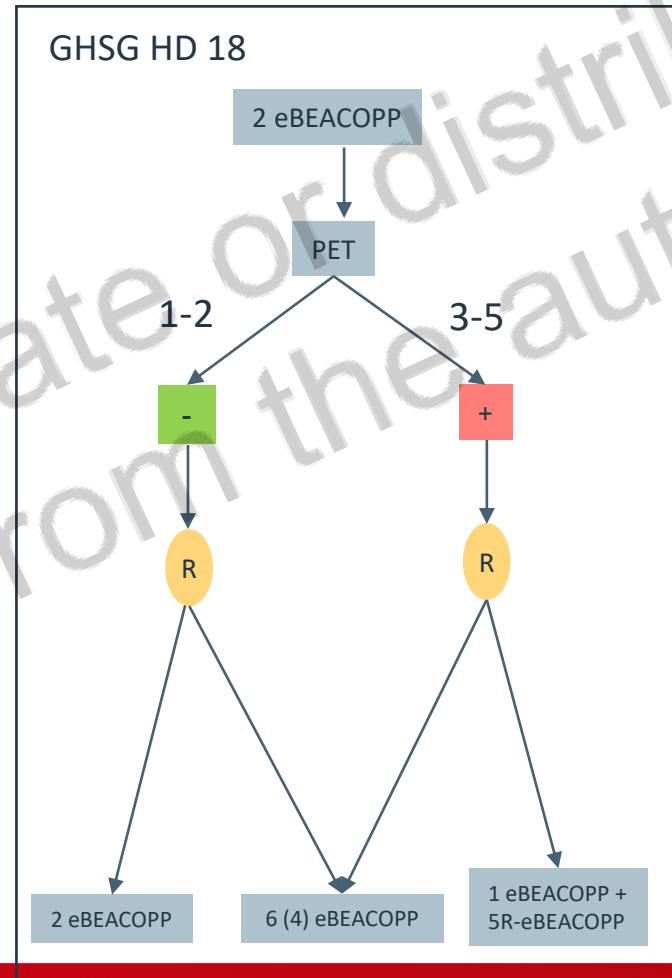
Click on the Q&A button  
to send your questions and comments

# Randomised trials to test the role of interim FDG-PET in Advanced stage disease

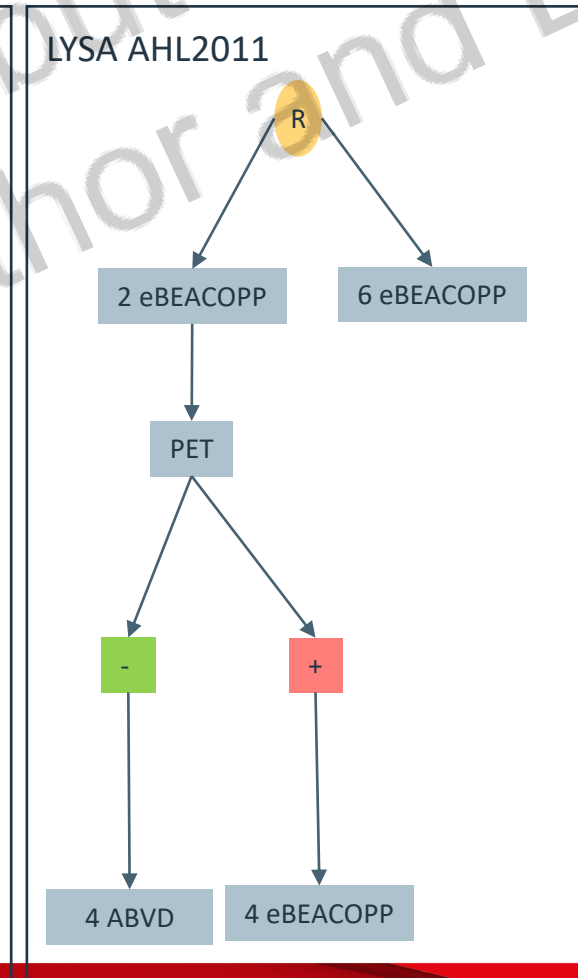
Johnson P. et al., 2016  
New Engl J Med, 374:2419-29



Borchmann P et al., 2017  
Lancet (17): 32134-73



Casasnovas RO et al., 2019. Lancet Oncology,20:202-215





# Control of lymphoma after de-escalation in PET-negative groups

**RATHL**

**5 Year PFS  
81.6%**

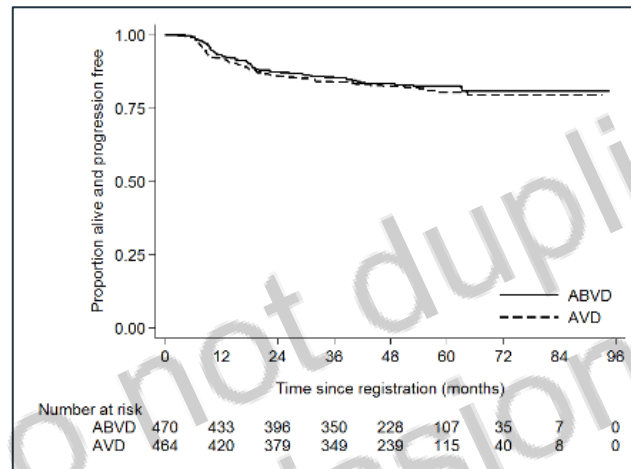
**LYSA**

**5 Year PFS  
89.4% vs 88.4%**

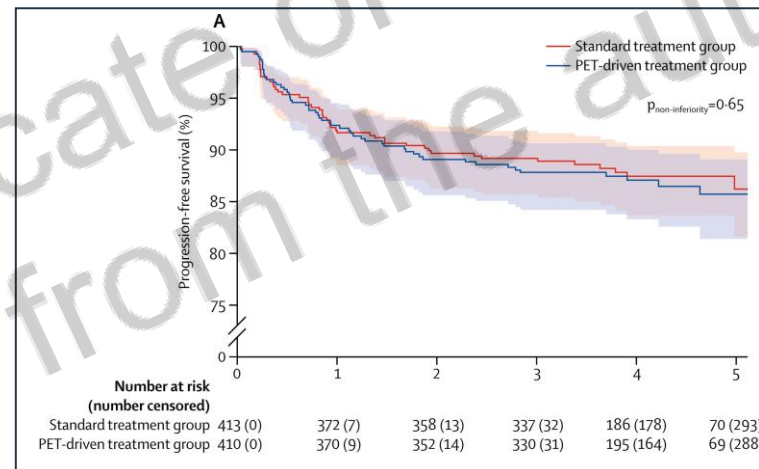
**HD18**

**5 Year PFS  
91.7 vs 90.8%**

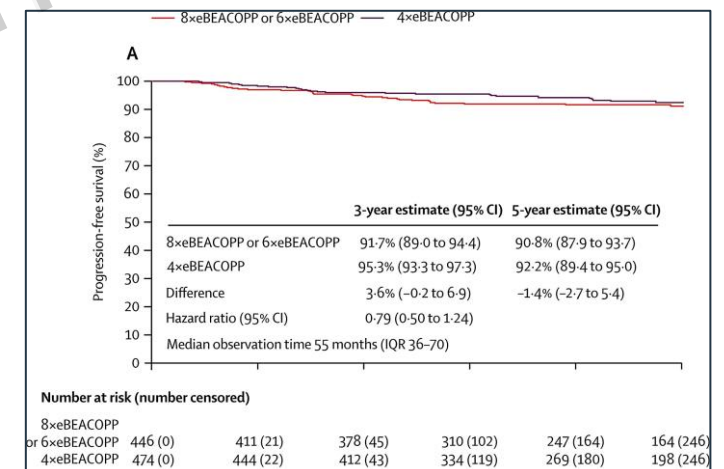
ABVD vs AVD



ABVD vs BEACOPP



4 eBEACOPP vs 2 eBEACOPP



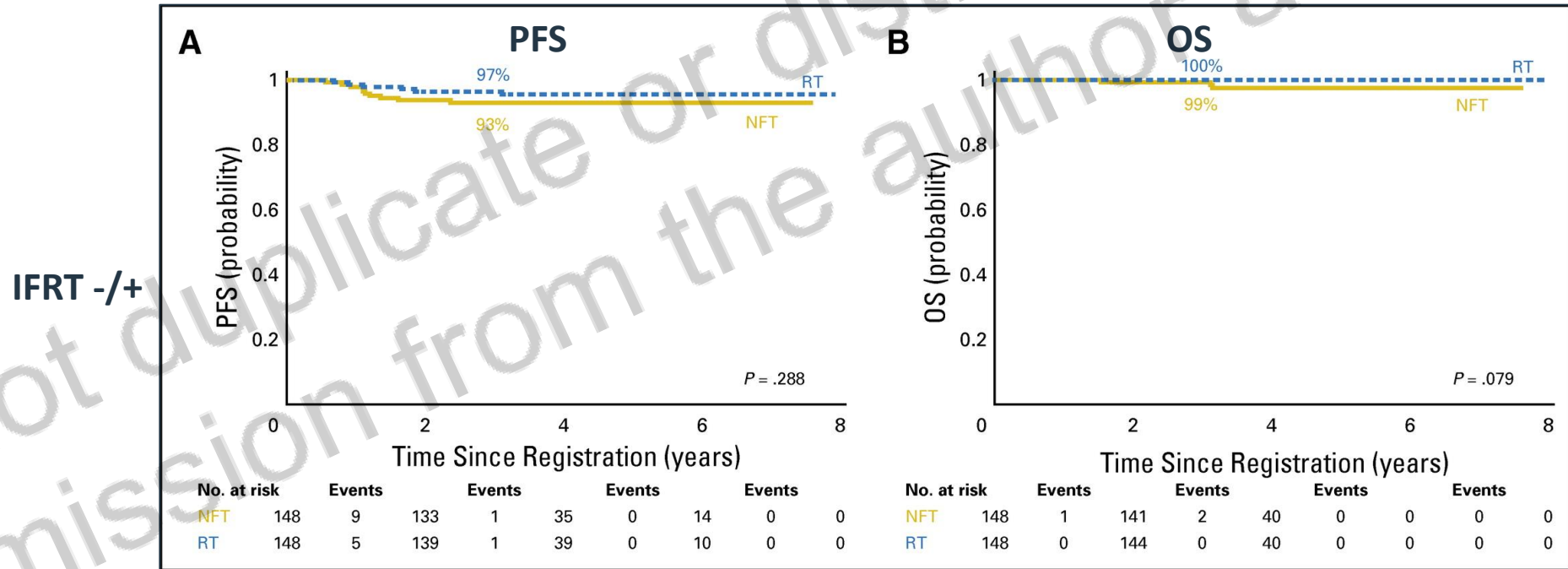
**N Engl J Med, 2016. 374:2419-29**  
**Lancet Oncol 2019. 20:202-215**  
**Lancet 2017; 6736(17)32134-7**

# Radiotherapy is not needed if interim PET is negative, even in those with bulk disease

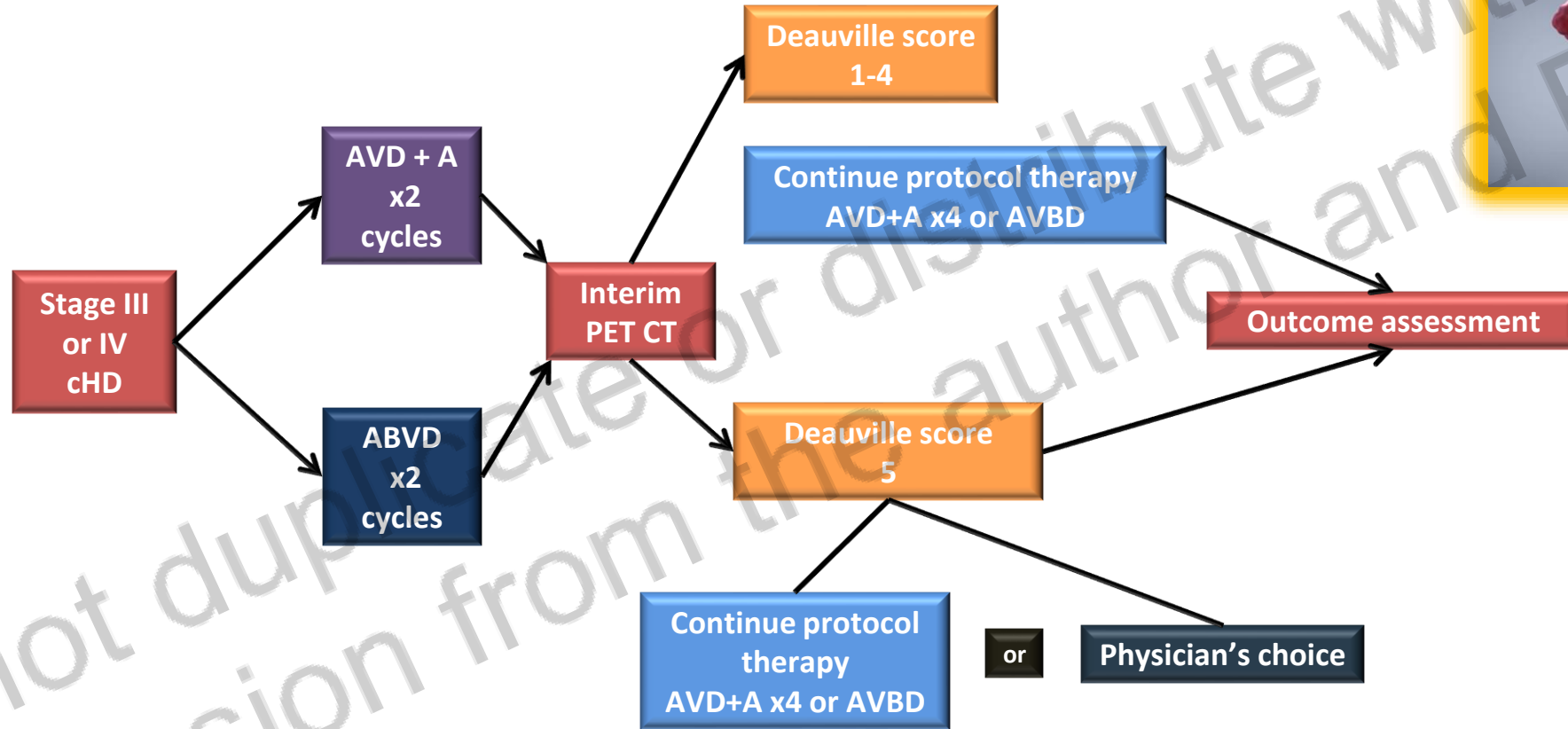
Stage IIB-IV

2 ABVD

PET - complete 6 ABVD (+/- IFRT if >5cm mass)



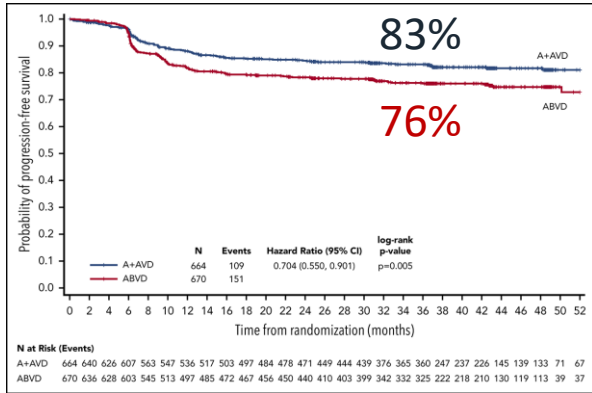
# ECHELON-1 phase III study



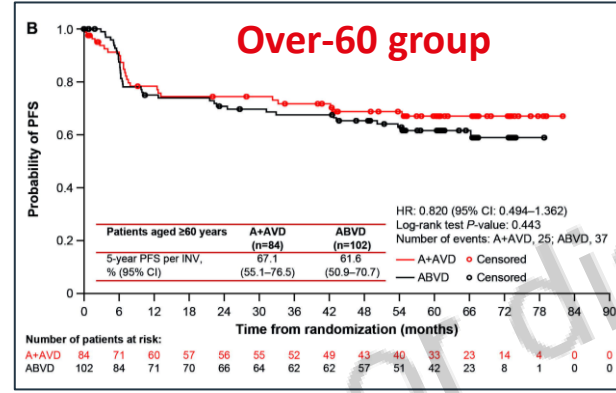
Primary endpoint: *modified* PFS per IRC, defined as first of:

- progression,
- death from any cause,
- PET with Deauville score 3-5 after frontline tx and subsequent anticancer tx

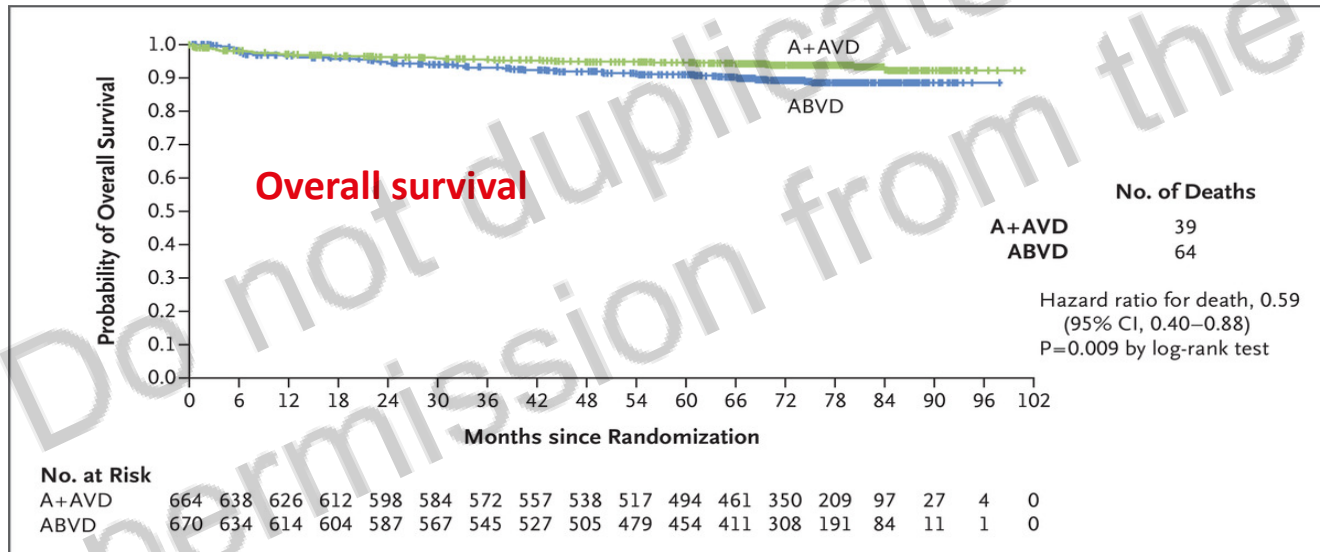
# Echelon-1 published outcomes



Straus D et al, Blood 2020;135:735-742



Evens A et al, Haematologica 2022;107:1086-1094



Subgroup	A+AVD no. of deaths/total no. of patients (%)	ABVD no. of deaths/total no. of patients (%)	Hazard Ratio for Death (95% CI)
Overall	39/664 (5.9)	64/670 (9.6)	0.59 (0.40-0.88)
Age			
<60 yr	19/580 (3.3)	35/568 (6.2)	0.51 (0.29-0.89)
≥60 yr	20/84 (24)	29/102 (28.4)	0.83 (0.47-1.47)
<45 yr	9/451 (2.0)	18/423 (4.3)	0.44 (0.20-0.99)
≥45 yr	30/213 (14.1)	46/247 (18.6)	0.75 (0.47-1.18)
Geographic region			
Americas	11/261 (4.2)	27/262 (10.3)	0.40 (0.20-0.80)
North America	9/250 (3.6)	26/247 (10.5)	0.33 (0.15-0.70)
Europe	26/333 (7.8)	32/336 (9.5)	0.78 (0.47-1.32)
Asia	2/70 (3)	5/72 (7)	0.37 (0.07-1.91)
No. of IPS risk factors			
0 or 1	7/142 (4.9)	7/141 (5.0)	0.97 (0.34-2.77)
2 or 3	17/355 (4.8)	26/357 (7.3)	0.62 (0.33-1.14)
4-7	15/167 (9.0)	31/172 (18.0)	0.48 (0.26-0.88)
Cancer stage at baseline			
III	17/237 (7.2)	20/246 (8.1)	0.86 (0.45-1.65)
IV	22/425 (5.2)	43/421 (10.2)	0.48 (0.29-0.80)
B symptoms at baseline			
Present	30/400 (7.5)	39/381 (10.2)	0.71 (0.44-1.14)
Absent	9/264 (3.4)	25/289 (8.7)	0.37 (0.17-0.80)
Extranodal site at baseline			
0	22/217 (10.1)	19/228 (8.3)	1.18 (0.64-2.19)
1	9/217 (4.1)	17/223 (7.6)	0.51 (0.23-1.14)
>1	8/194 (4.1)	25/193 (13.0)	0.30 (0.14-0.67)
ECOG performance-status score at baseline			
0	15/376 (4.0)	21/378 (5.6)	0.70 (0.36-1.37)
1	19/260 (7.3)	34/263 (12.9)	0.54 (0.31-0.94)
2	5/28 (18)	9/27 (33)	0.41 (0.14-1.23)
Sex			
Male	19/378 (5.0)	45/398 (11.3)	0.43 (0.25-0.73)
Female	20/286 (7.0)	19/272 (7.0)	0.96 (0.51-1.80)

SM Ansell et al. N Engl J Med 2022;387:310-320.



# Cost-effectiveness of first-line treatment options for patients with advanced-stage Hodgkin lymphoma: a modelling study

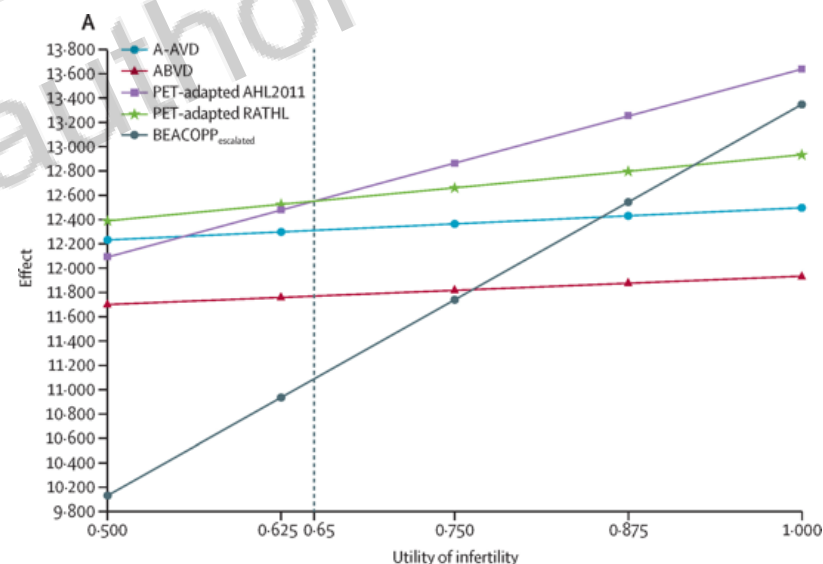
Abi Vijenthira, Kelvin Chan, Matthew C Cheung, Anca Prisca

Lancet Haematol 2020; 7:e146-156

**Interpretation** Our results suggest that, when considering cost, effectiveness, and short and long-term toxicities, the preferred treatment strategy for patients with newly diagnosed advanced-stage Hodgkin lymphoma is the PET-adapted de-escalation regimen starting with BEACOPP and de-escalating to ABVD as appropriate.

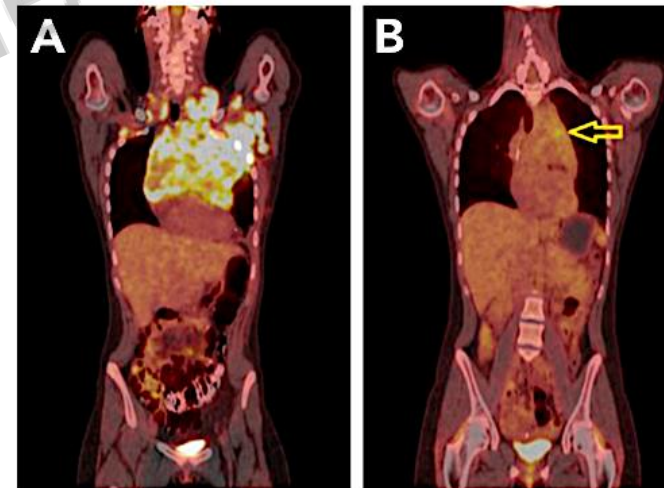
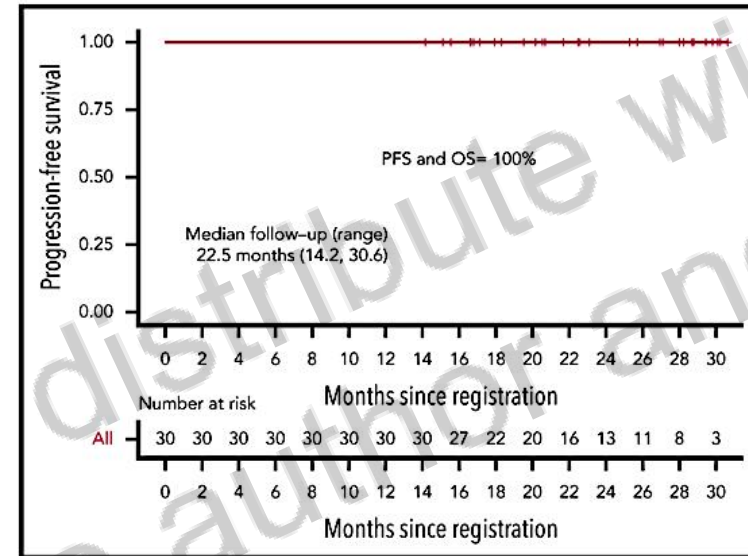
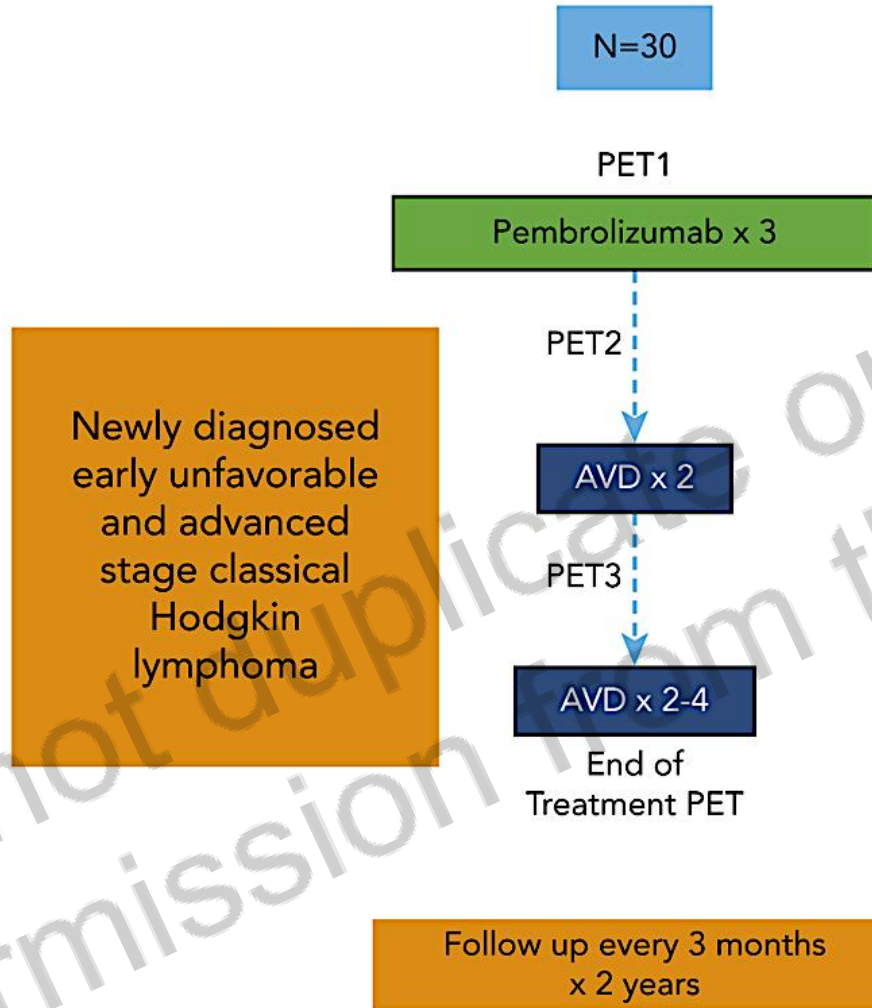
	QALYs (95% CI)	Change in QALYs	Life-years (95% CI)	Change in life-years	Direct costs, \$ (95% CI)	Change in costs, \$
AHL2011	13.2 (10.2–14.4)	0.5	14.6 (13.7–15.1)	0.5	\$53 129 (31 914–94 446)	–\$11 043
RATHL	12.7 (9.5–13.9)	0.3	14.1 (13.2–14.5)	0.4	\$64 172 (40 903–105 084)	–\$12 605
BEACOPP	12.4 (10.3–13.8)	0.1	13.7 (12.2–14.6)	0.3	\$76 777 (47 614–120 972)	–\$164 079
A-AVD	12.3 (9.2–13.7)	0.6	13.4 (12.6–14.1)	1.2	\$240 856 (194 122–296 271)	\$146 055
ABVD	11.7 (9.0–13.1)	..	12.2 (11.2–13.0)	..	\$94 801 (63 402–141 379)	..

Costs are in CAN\$. A-AVD=brentuximab vedotin, doxorubicin, vinblastine, dacarbazine. ABVD=doxorubicin, bleomycin, vinblastine, dacarbazine. BEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone.



One-way sensitivity analysis of utility of infertility. Only if the utility of infertility is less than 0.65 does RATHL become the dominant strategy

# Pembrolizumab + AVD



Response to single-agent pembrolizumab

## Choice of initial therapy: advanced disease

- Combining risk-adapted and response-adapted approaches
- Newer antibody-based therapies seem likely to replace chemotherapy-alone regimens
  - In worse-prognosis disease
  - If costs are manageable: PET-adapted approaches may help
- Initial therapy with A+AVD:
  - Results in higher PFS and small increment in OS compared to non-PET adapted ABVD
  - Appears less toxic but more costly than escBEACOPP
- De-escalation after negative iPET retains efficacy and should reduce morbidity
  - no RT
  - no bleomycin
  - reducing to ABVD
  - fewer cycles of BEACOPP

# Conclusions



- Although Hodgkin's lymphoma is usually curable, there is still scope to improve outcomes, especially for:
  - those with very high risk disease
  - those with positive interim PET scans
  - older patients
- A combination of risk-adapted and response-adapted treatment seems the best approach
- The antibody-targeted treatments are giving impressive results in early studies: the model of care continues to evolve and improve





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