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Where are we in first line therapy for Hodgkin Lymphoma?

Expert: **Prof Peter W.M. Johnson**, Cancer Research UK Centre, Southampton General Hospital, Southampton, United Kingdom

Discussant: **Dr Astrid Pavlovsky**, Clinical Research Center - FUNDALEU, Buenos Aires, Argentina

Where are we in first line therapy for Hodgkin Lymphoma?

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Case presentation

20 year old female

Felt a swelling in her neck

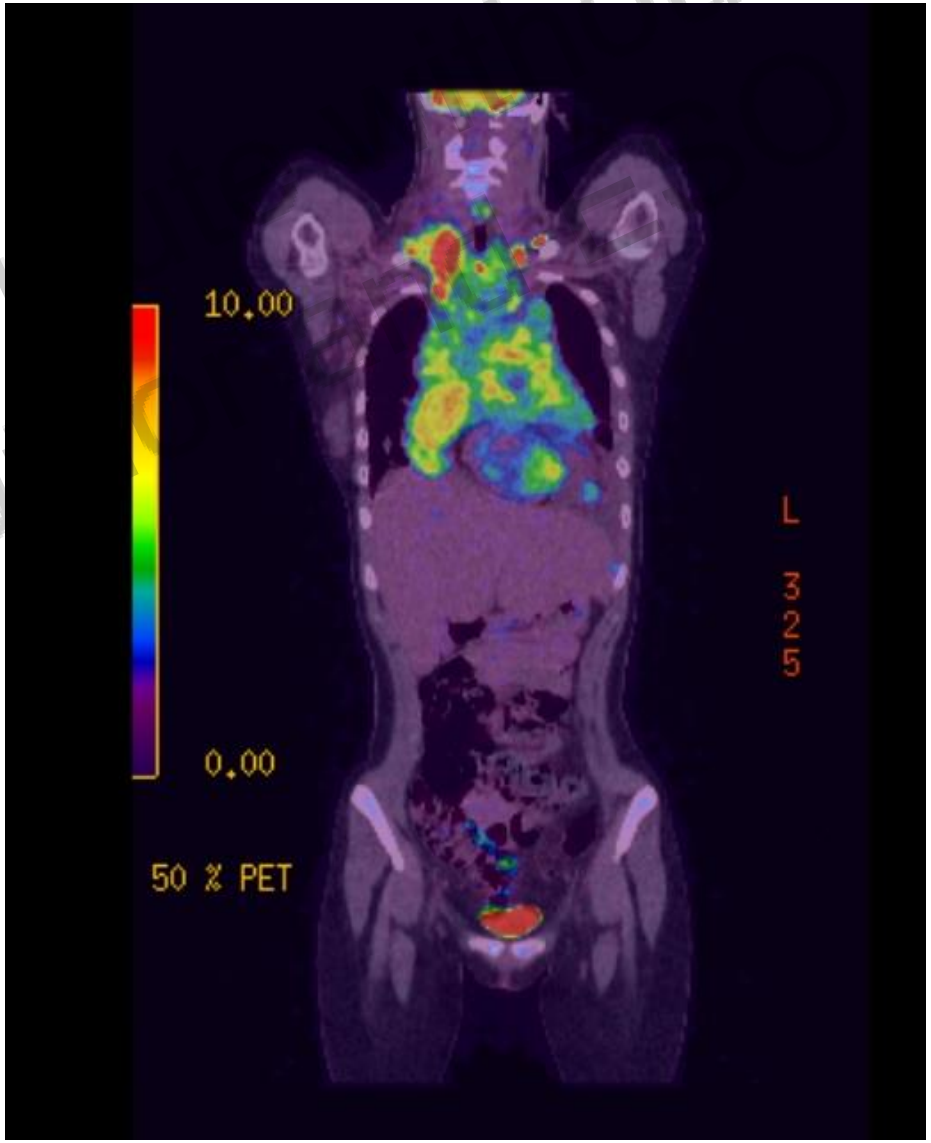
Breathless on exertion

Otherwise well

Normal blood count, ESR 10mm/hr

Histology: Nodular sclerosing Hodgkin lymphoma

Stage II_{AX} (unfavourable)



A range of possible treatments...

4 ABVD + 30Gy IFRT

(GHSG 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

(GHSG 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.)

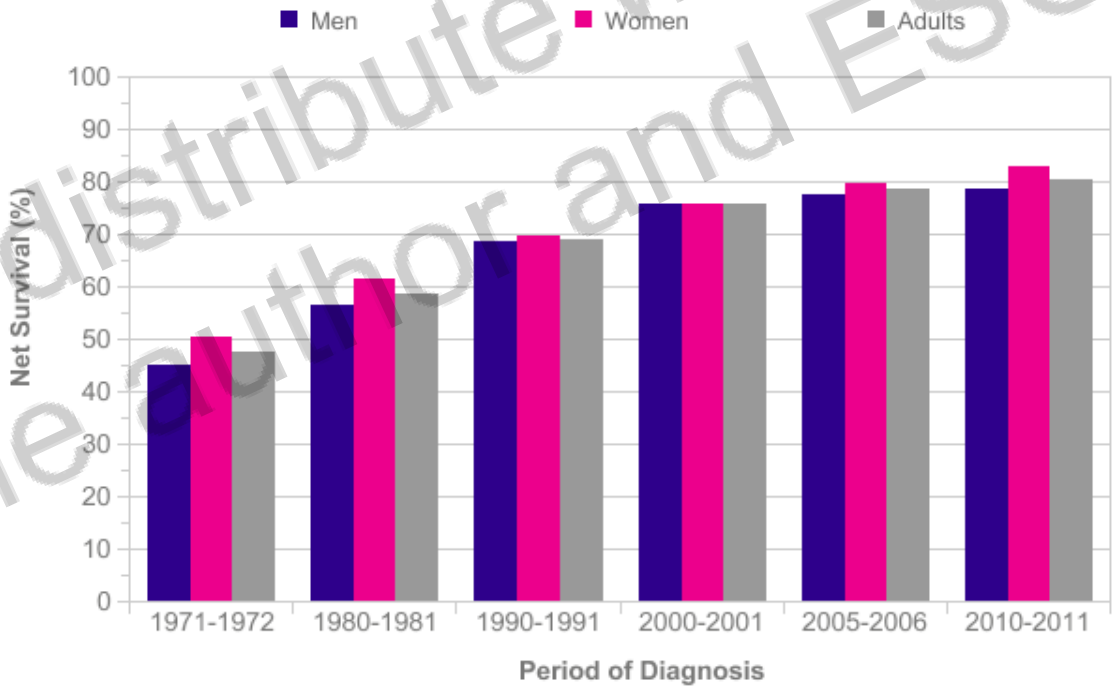
3 Pembrolizumab + 4 AVD and if PET-2 negative, avoid RT

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

Overall results of therapy

- ≥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

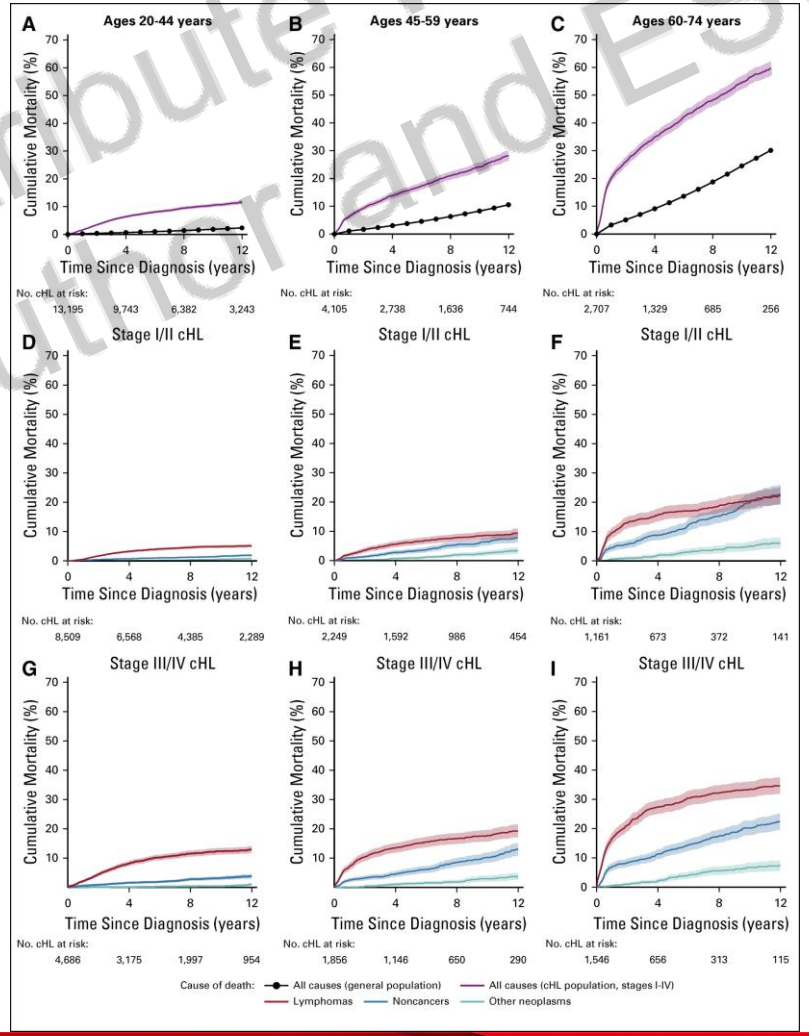
Young

Old

All stages

Early stage

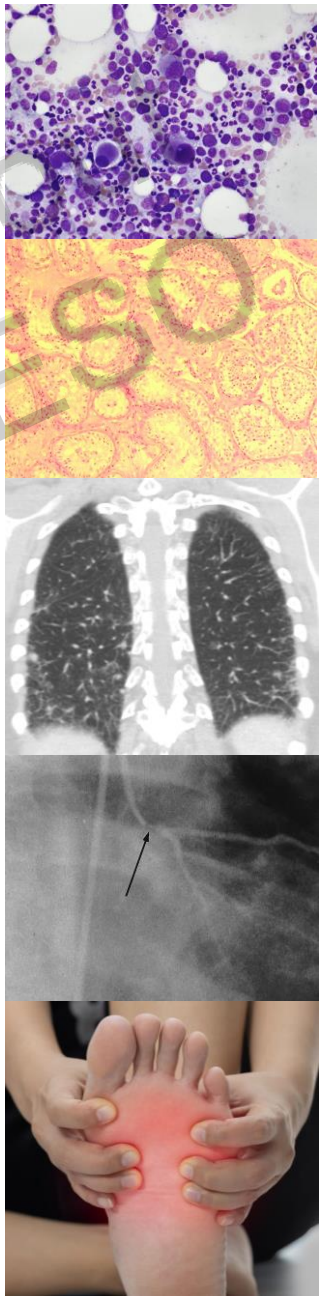
Advanced stage



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

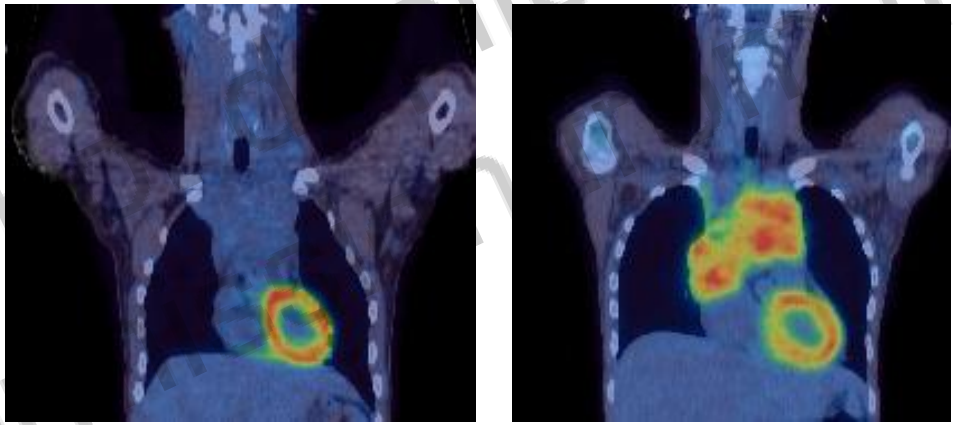
Considerations in the choice: competing risks

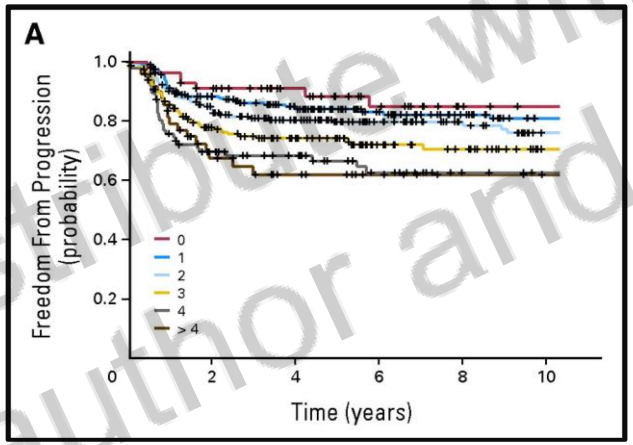
- Short-term toxicity of myelosuppression
- Second cancers, cardiac disease from radiotherapy field
- Future fertility
- Pulmonary fibrosis
- Cardiac muscle damage
- Neuropathy
- Initial treatment failure: need for second line therapy



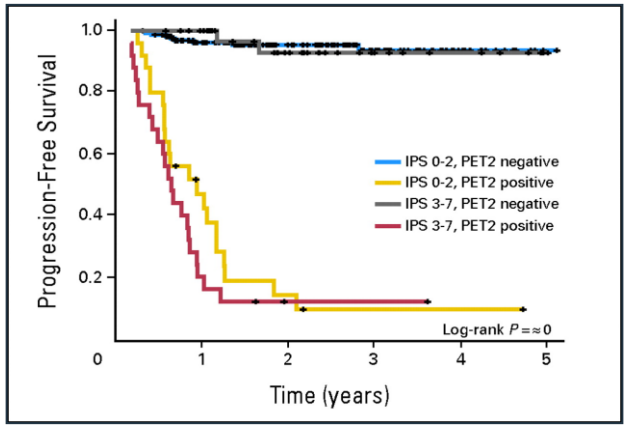
Can we distinguish worse from less bad disease?

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





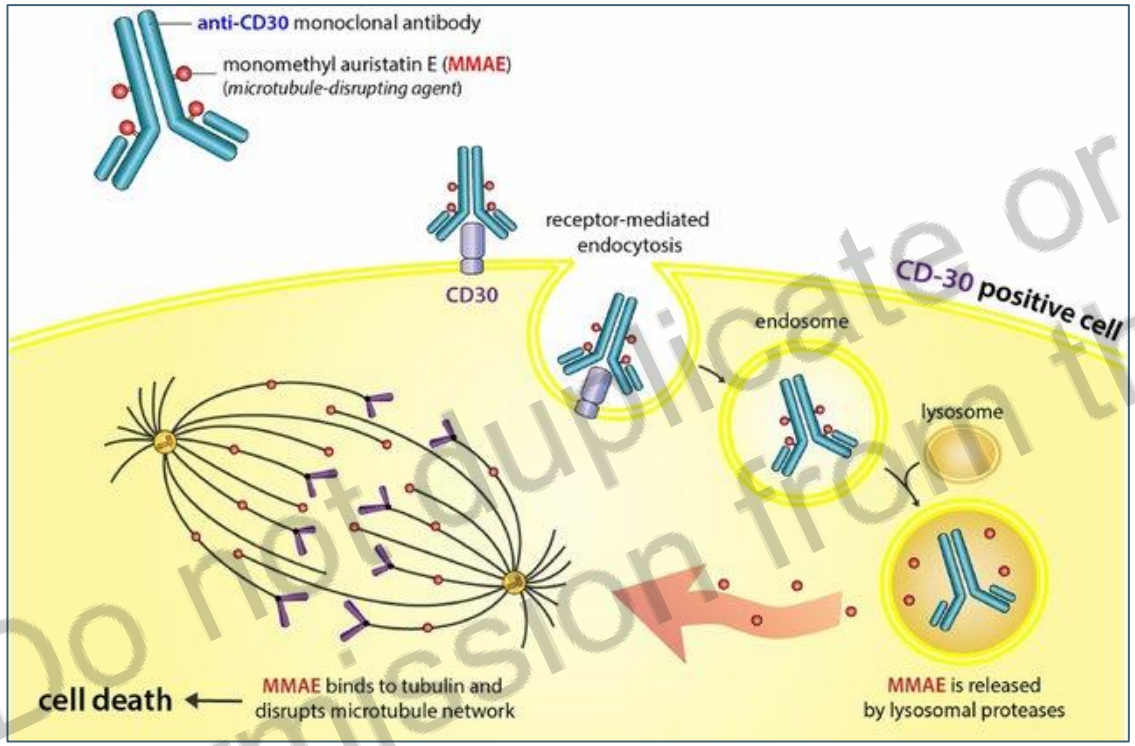
Moccia AA et al., J Clin Oncol. 2012;30:3383-8



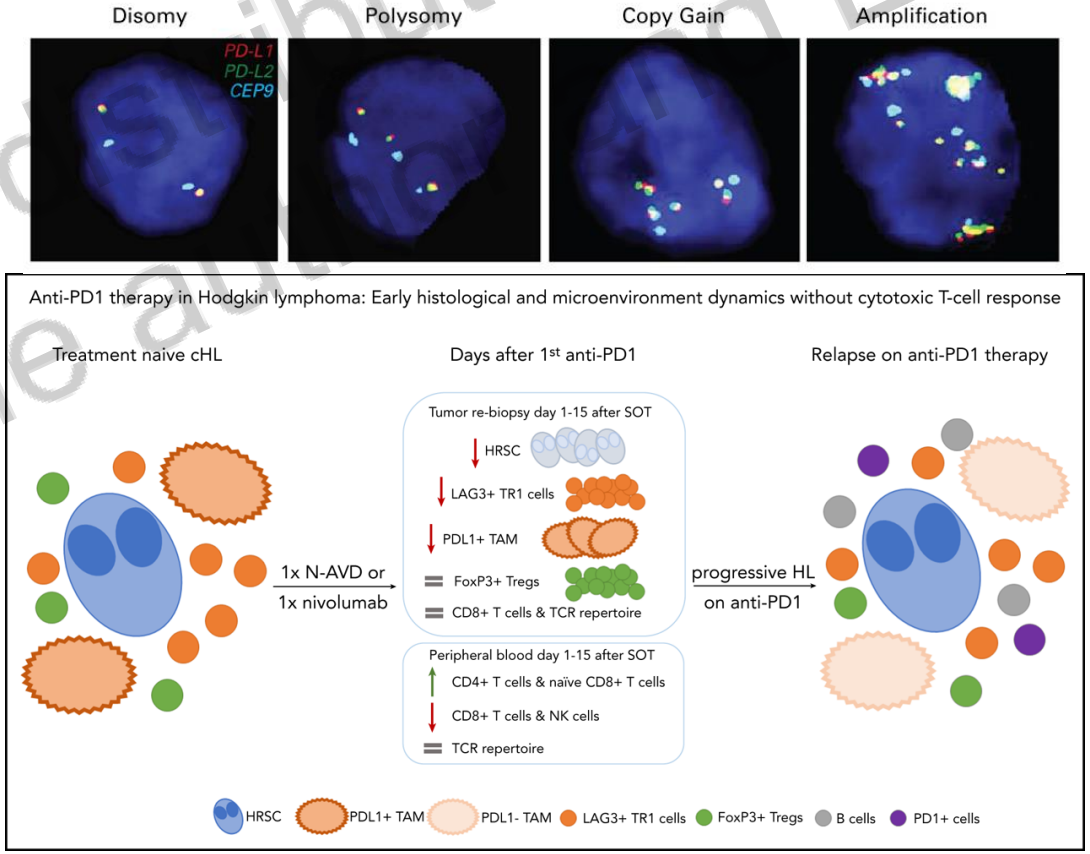
Gallamini A et al. J Clin Oncol. 2007;25:3746-3752

Newer options for systemic therapy

Anti-CD30 antibody-drug conjugate



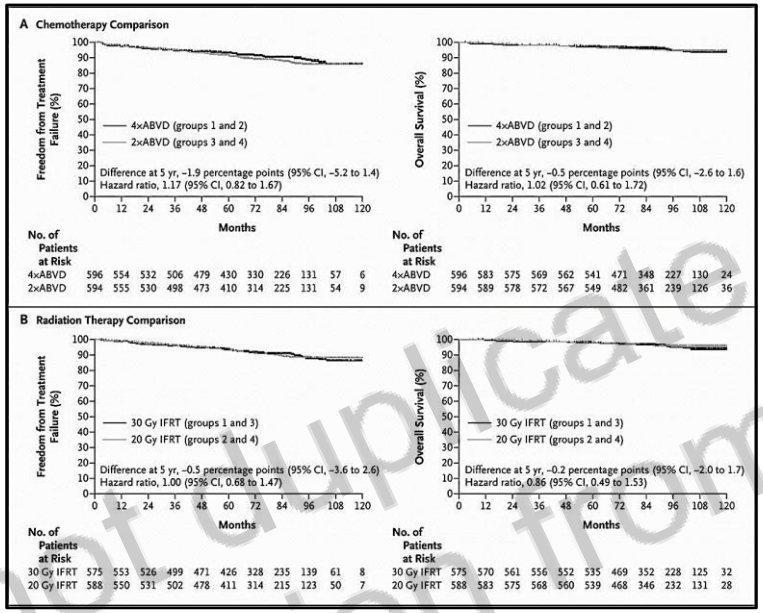
Anti-PD1 antibodies



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

Early stage: standard of care

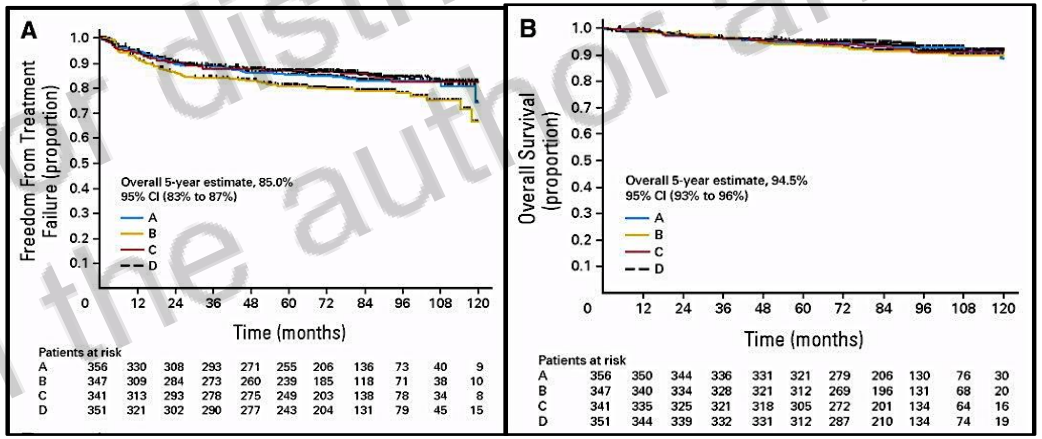
Early Favourable disease
2 vs 4 ABVD + 20Gy vs 30Gy IFRT



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

Engert A et al. N Engl J Med 2010;363:640-652.

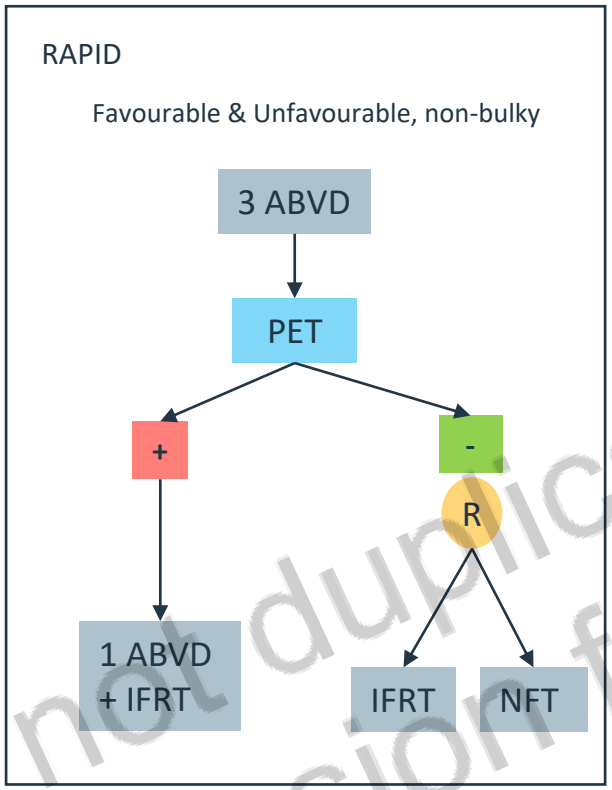
Early Unfavourable disease
4 ABVD vs 4 BEACOPP + 20Gy vs 30Gy

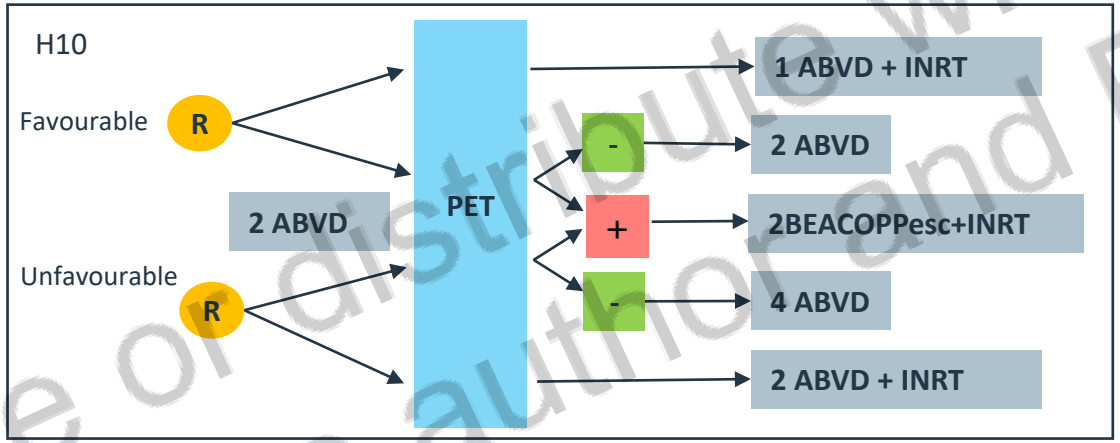


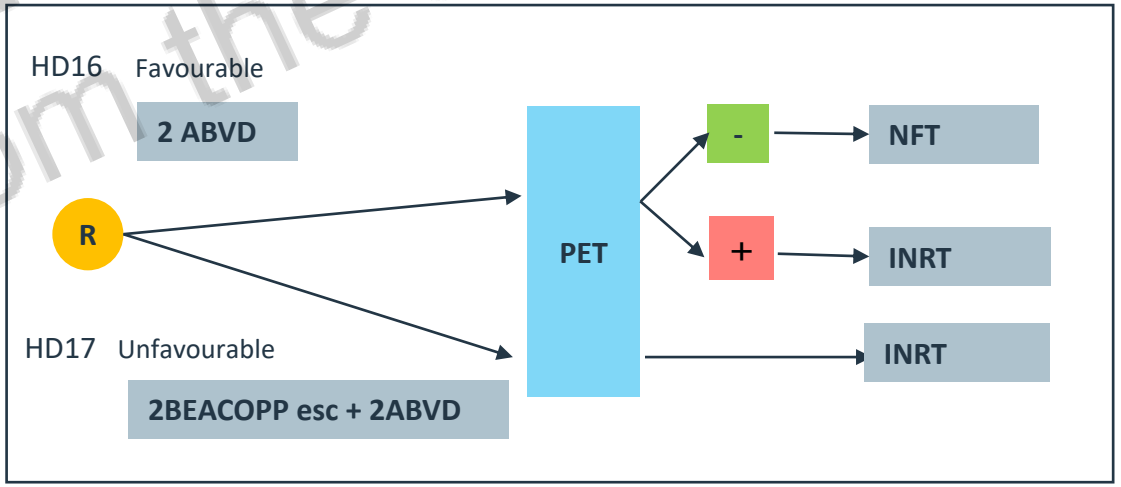
ABVD + 20Gy inferior on FFTF

Eich H T et al. J Clin Oncol 2010; 28:4199-4206

Randomised trials to test the role of interim PET







N Engl J Med 2015; 372:1598-1607

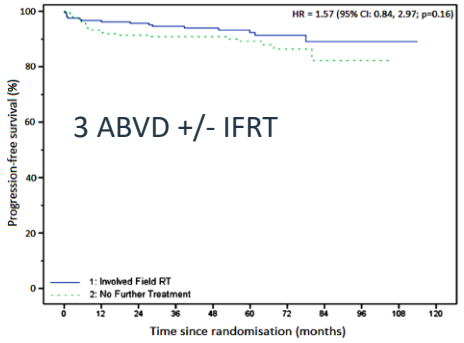
J Clin Oncol 2017: 35:1786-1794

J Clin Oncol 2019;37:2835-2845

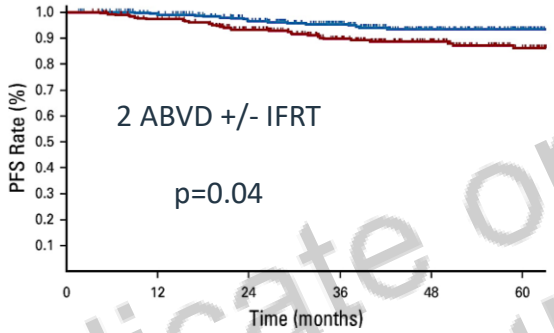
Lancet Oncol 2021: 22:223-234

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

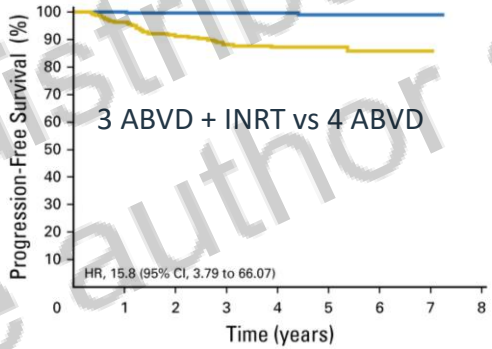
RAPID 5 yr EFS 96.0 vs 90.1%



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

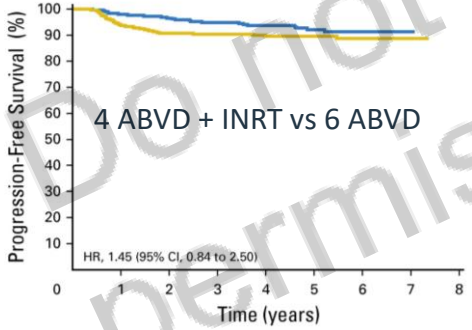
J Clin Oncol 2019;37:2835-2845

Lancet Oncol 2021: 22:223-234

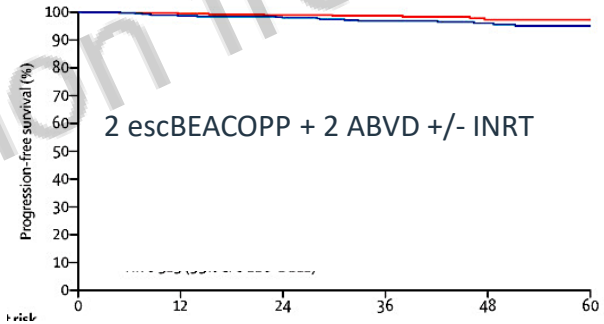
J Clin Oncol 2021: 39:2257-2265

Blood Adv 2022: Sep 9

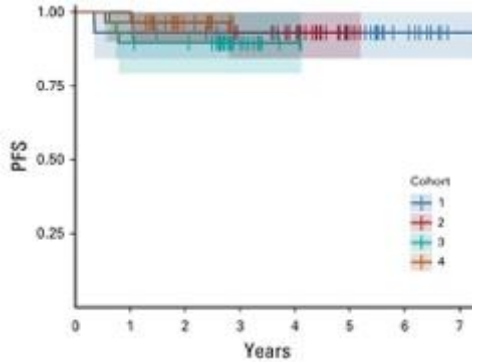
H10 U 5 yr PFS 92.1 vs 89.6%



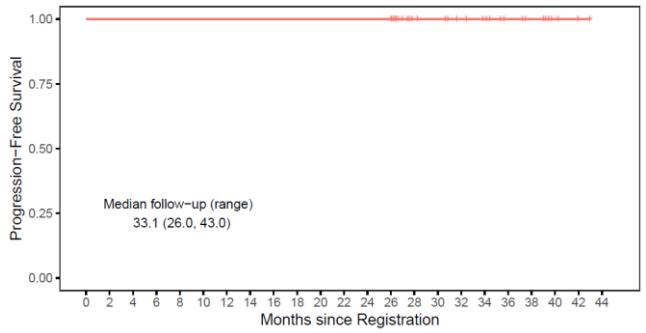
HD 17 5 yr PFS 97.7 vs 95.9%



MSKCC BV+AVD 2 yr PFS 94%

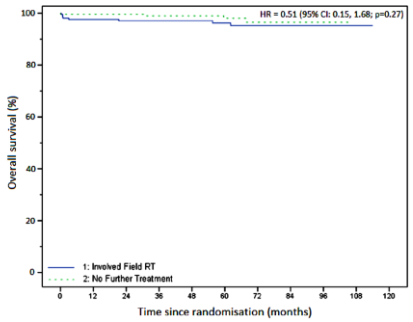


Pembro+AVD 33mo PFS 100%

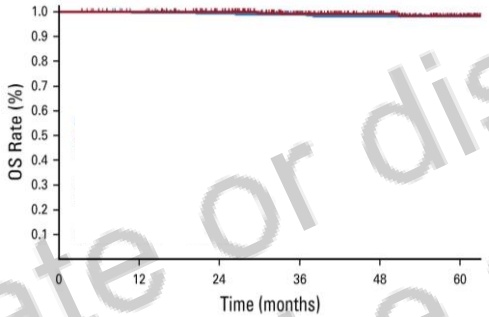


Overall Survival after de-escalation in PET-negative groups

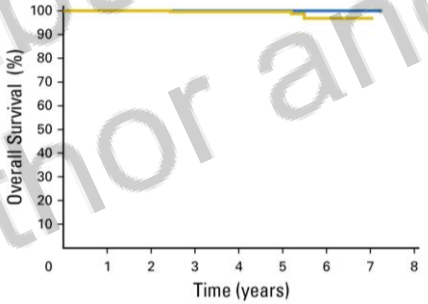
RAPID — 3 yr OS 97.1 vs 99.5%



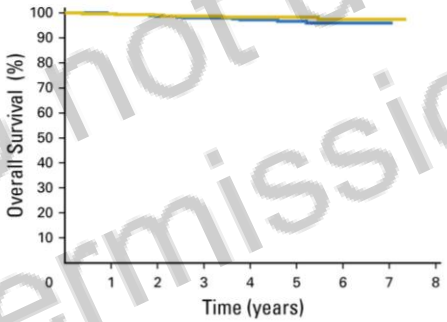
HD 16 — 5 yr OS 98.1 vs 98.4%



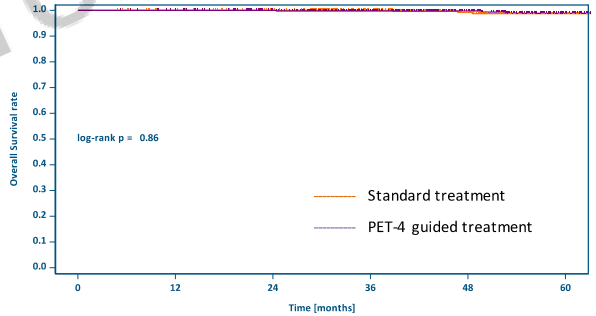
H10 F — 5 yr OS 100 vs 99.6%



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

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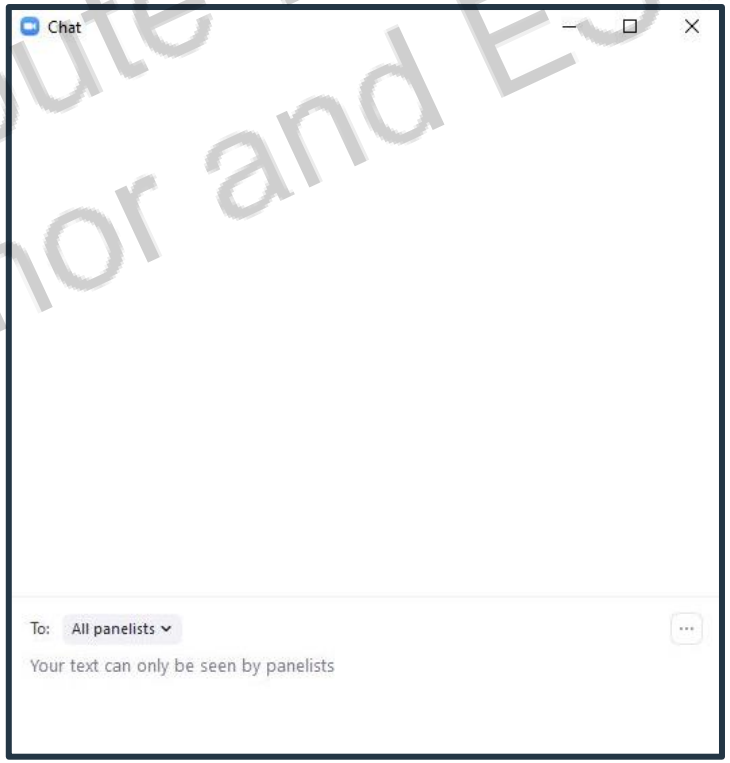
Your views are important!

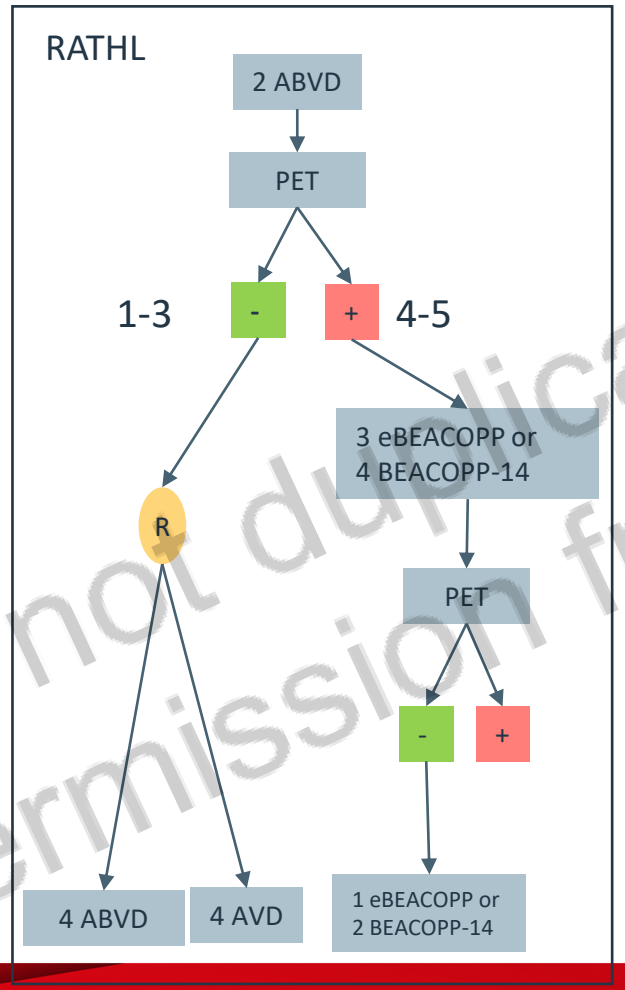
Remember that you can ask questions and send comments at any time.



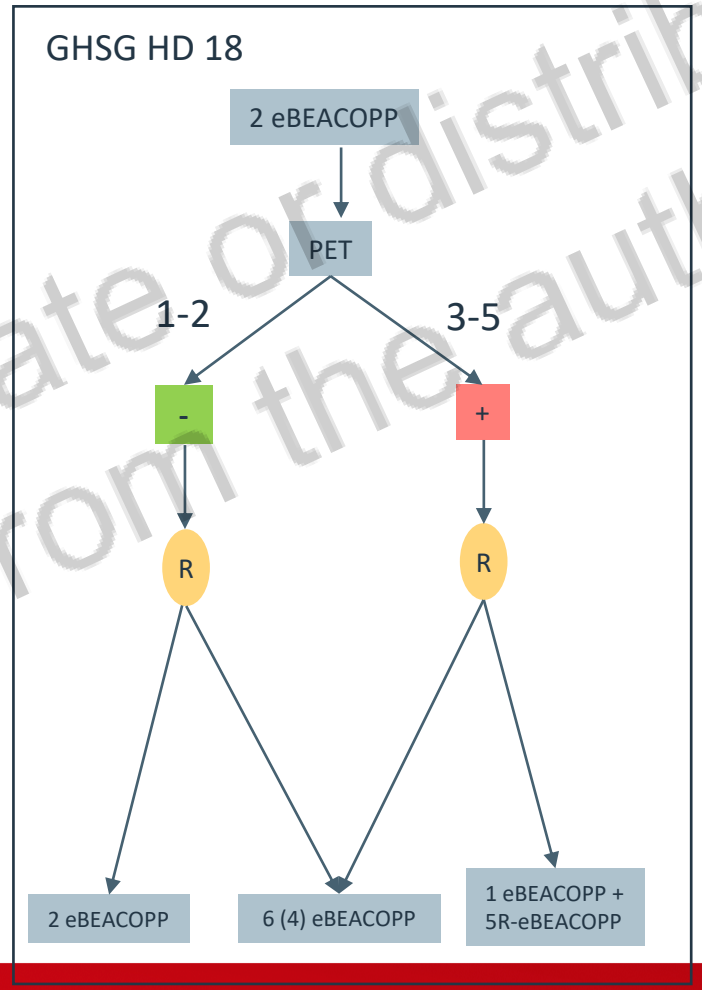
Click on the Q&A button
to send your questions and comments

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

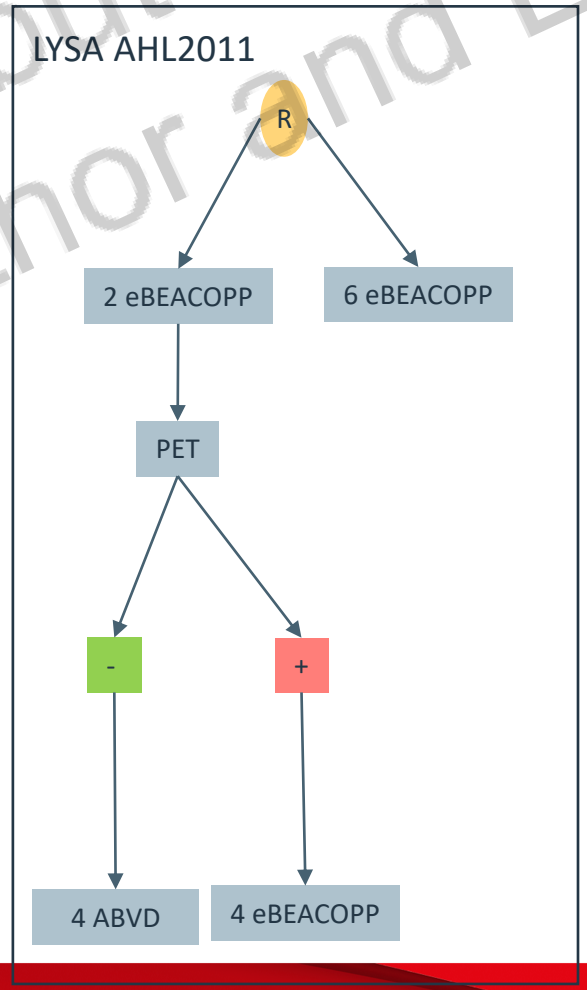
Johnson P. et al., 2016
New Engl J Med,. 374:2419-29



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



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



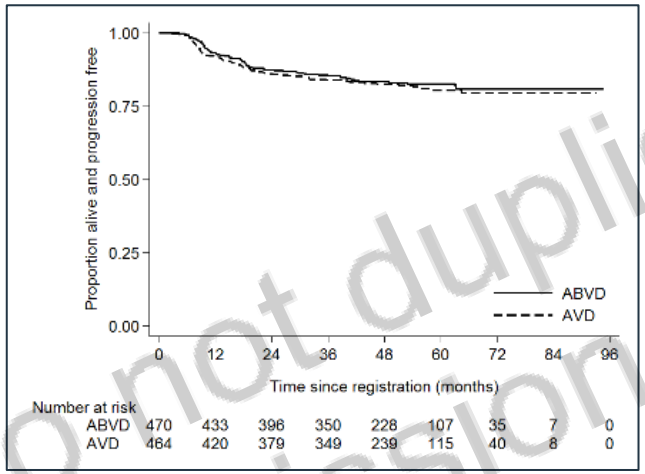
Control of lymphoma after de-escalation in PET-negative groups

RATHL **5 Year PFS 81.6%**

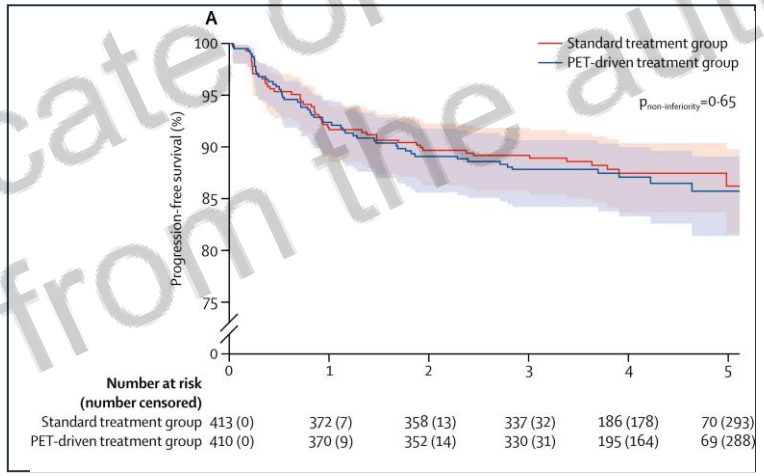
LYSA **5 Year PFS 89.4% vs 88.4%**

HD18 **5 Year PFS 91.7 vs 90.8%**

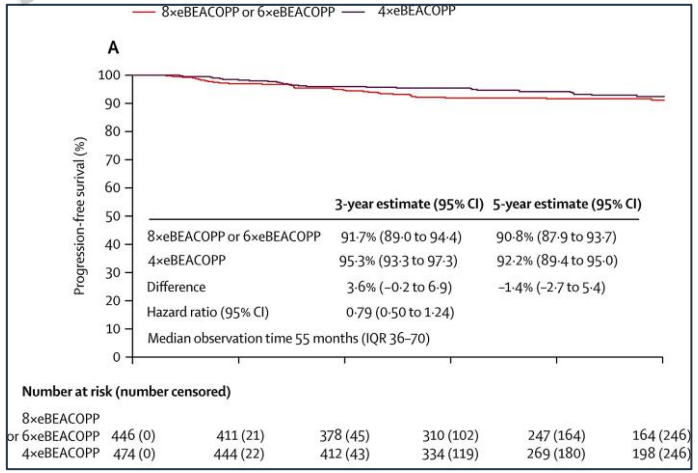
ABVD vs AVD



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

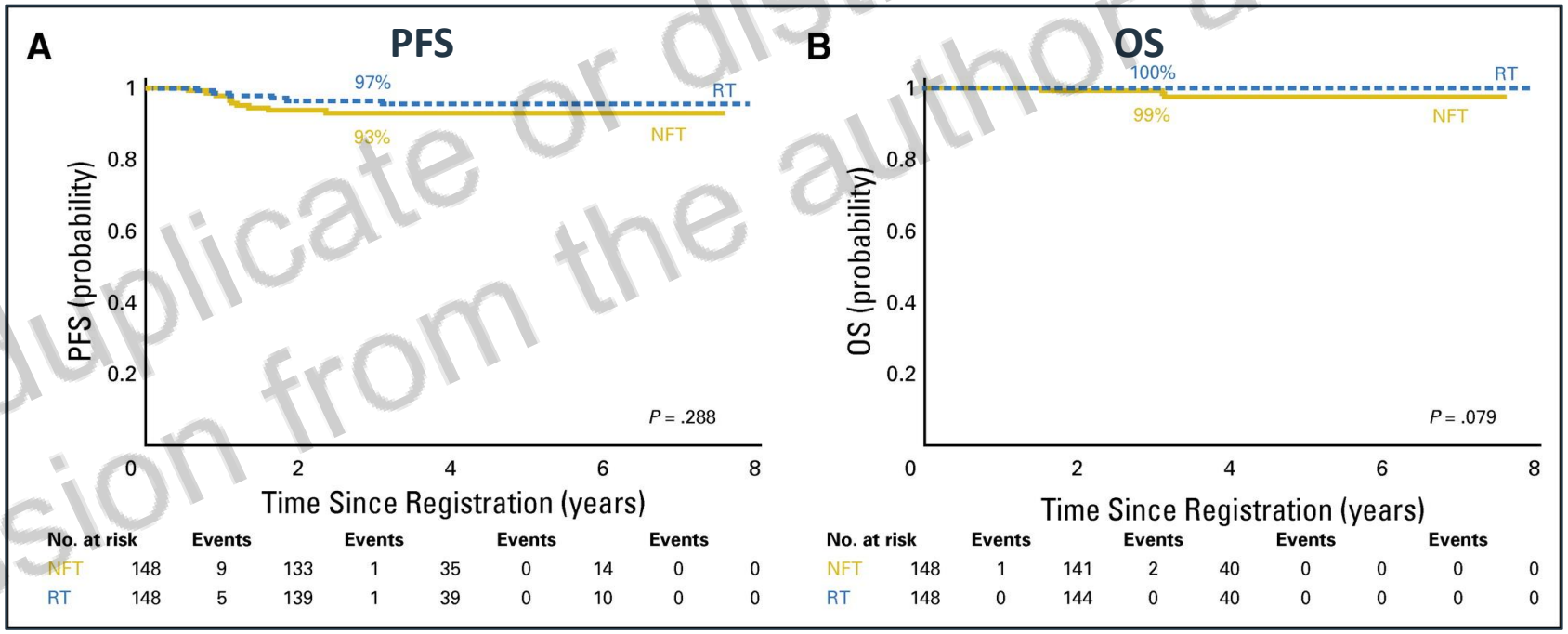
Radiotherapy is not needed if interim PET is negative, even in those with bulk disease

Stage IIB-IV

2 ABVD

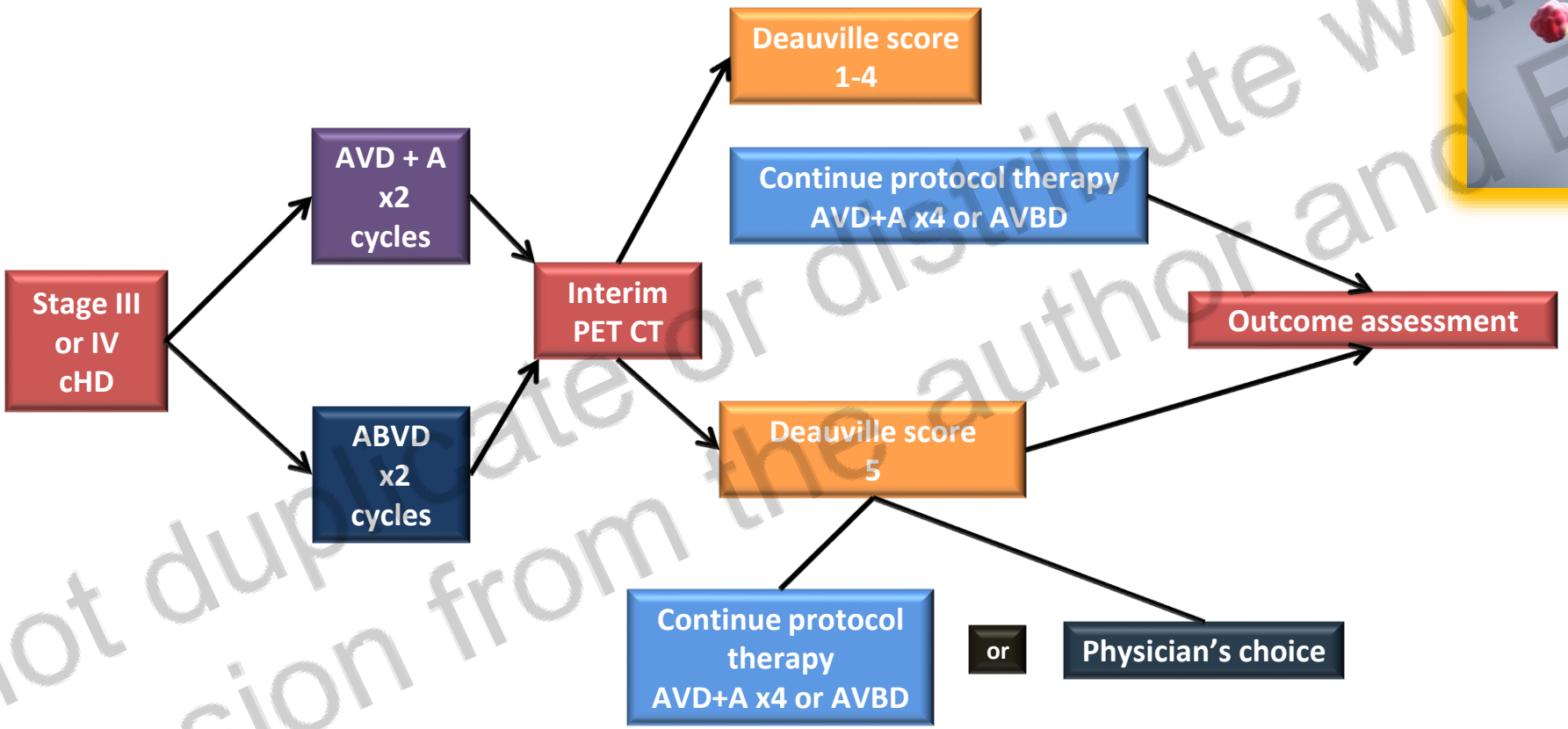
PET - complete 6 ABVD (+/- IFRT if >5cm mass)

IFRT -/+



Gallamini A et al, J Clin Oncol 2018; 36:454-462

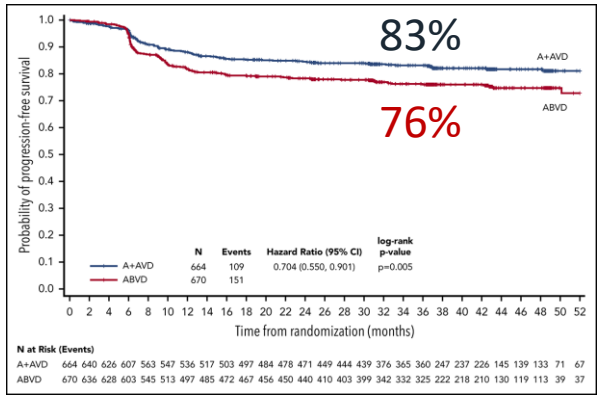
ECHELON-1 phase III study



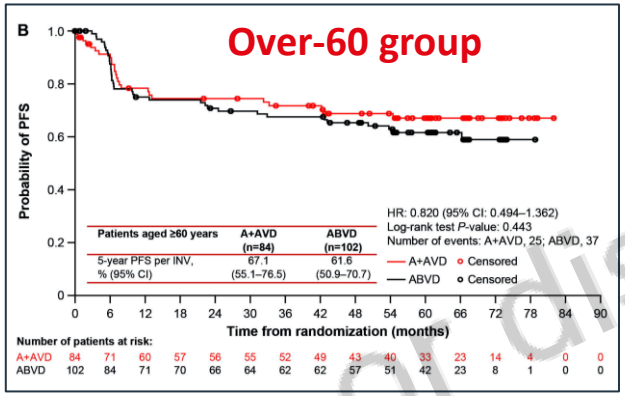
Primary endpoint: *modified* PFS per IRC, defined as first of:

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

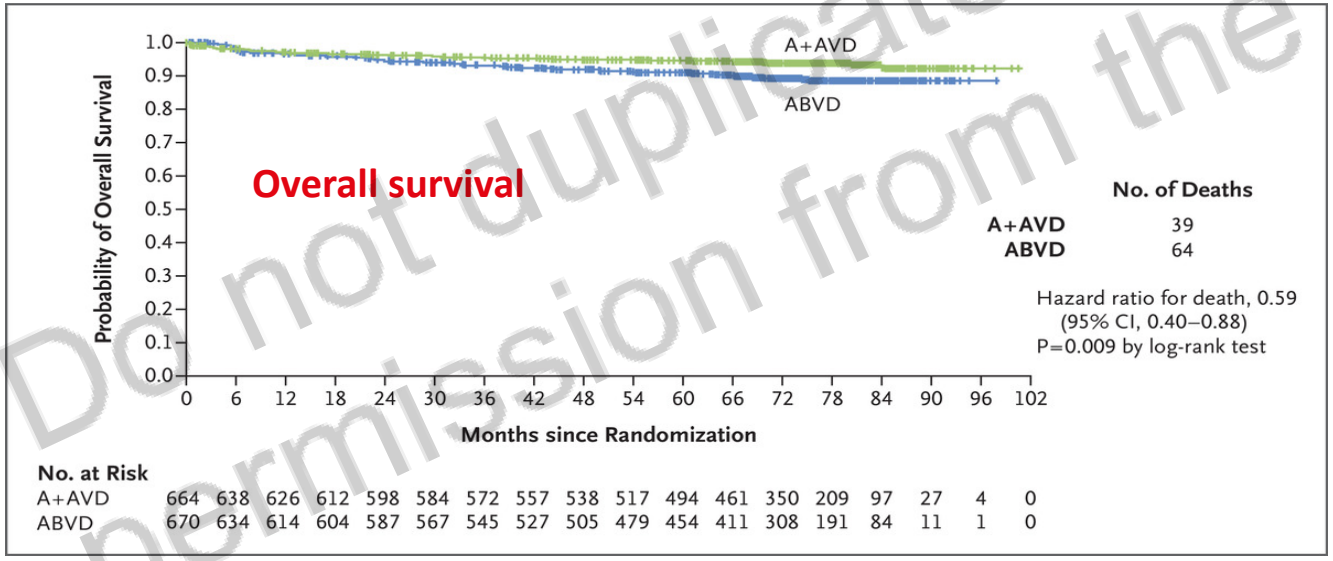
Echelon-1 published outcomes

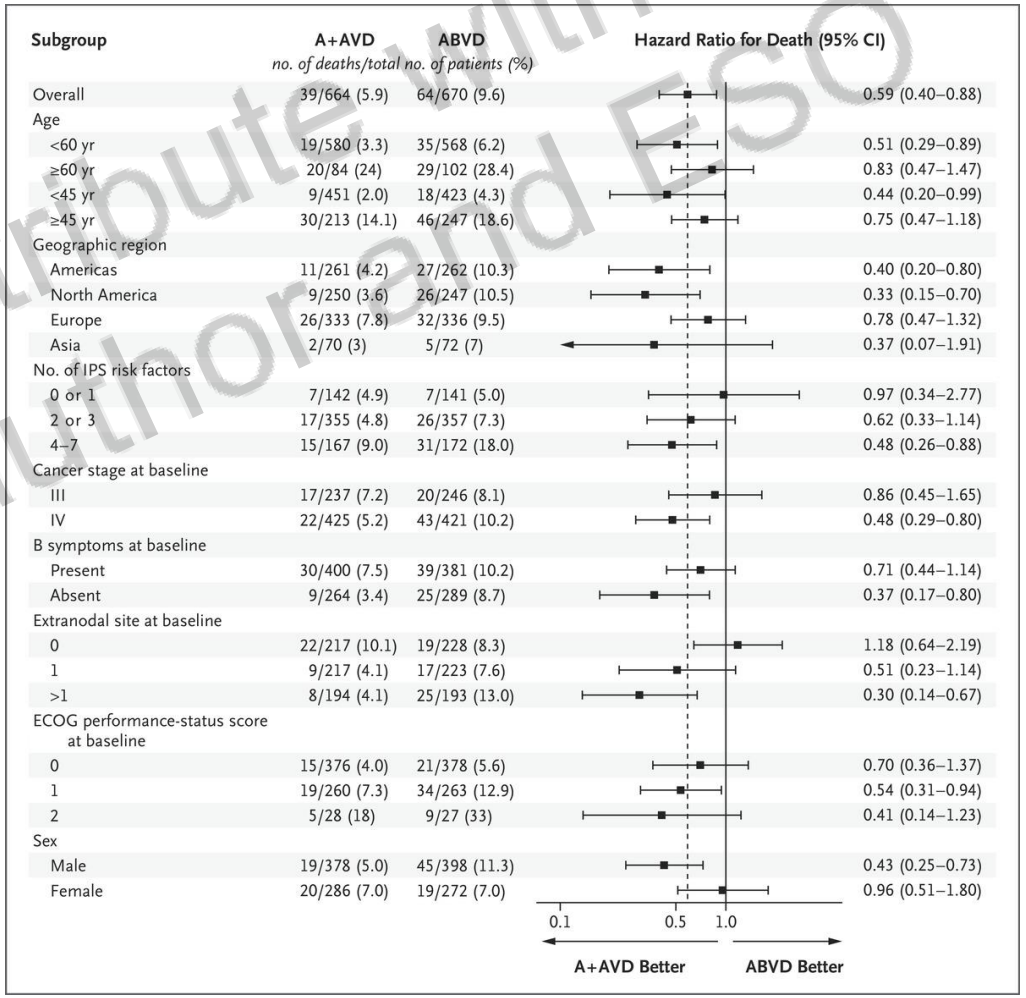


Straus D et al, Blood 2020;135:735-742



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





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

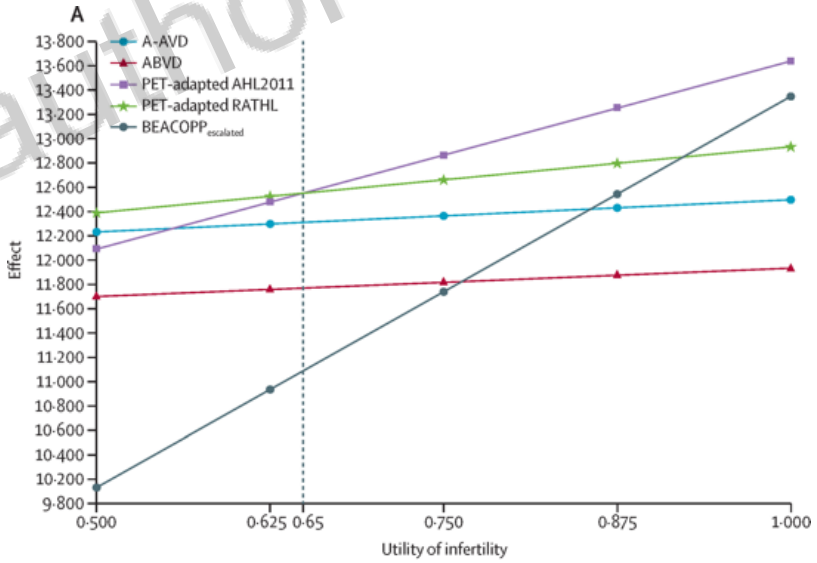
Abi Vijenthira, Kelvin Chan, Matthew C Cheung, Anca Prica

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

N=30

PET1

Pembrolizumab x 3

PET2

AVD x 2

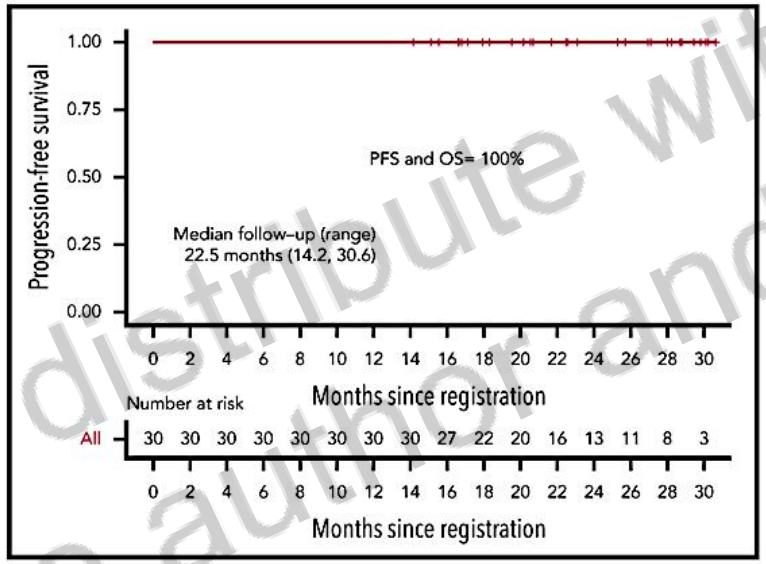
PET3

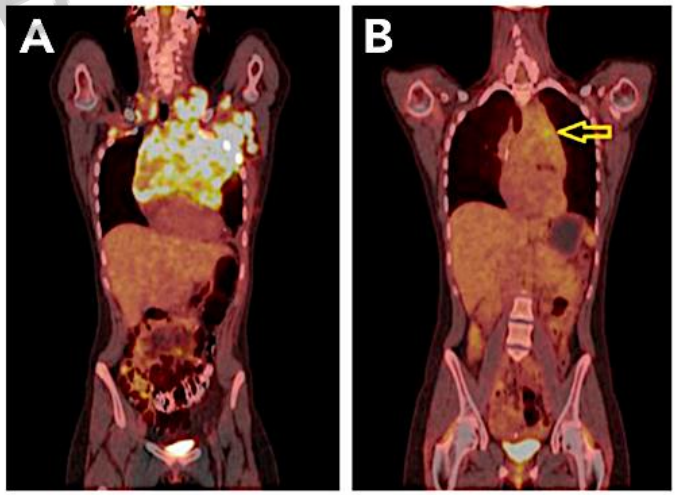
AVD x 2-4

End of Treatment PET

Newly diagnosed early unfavorable and advanced stage classical Hodgkin lymphoma

Follow up every 3 months x 2 years





Response to single-agent pembrolizumab

Allen PB et al., Blood. 2021;137:1318-1326

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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