How much « less to get more »

Hodgkin Lymphoma management
18 March 2023

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Lysa
THE LYMPHOMA STUDY ASSOCIATION

CHU UCL NAMUR

BHS initiatives for young hematologist

- Cantera: lymphoma seminar in Barcelona 25-28 april 2023 (Dr Hanne MASSA)
- ESH
- Partners supported initiatives

Absolute excess of risk of second cancer

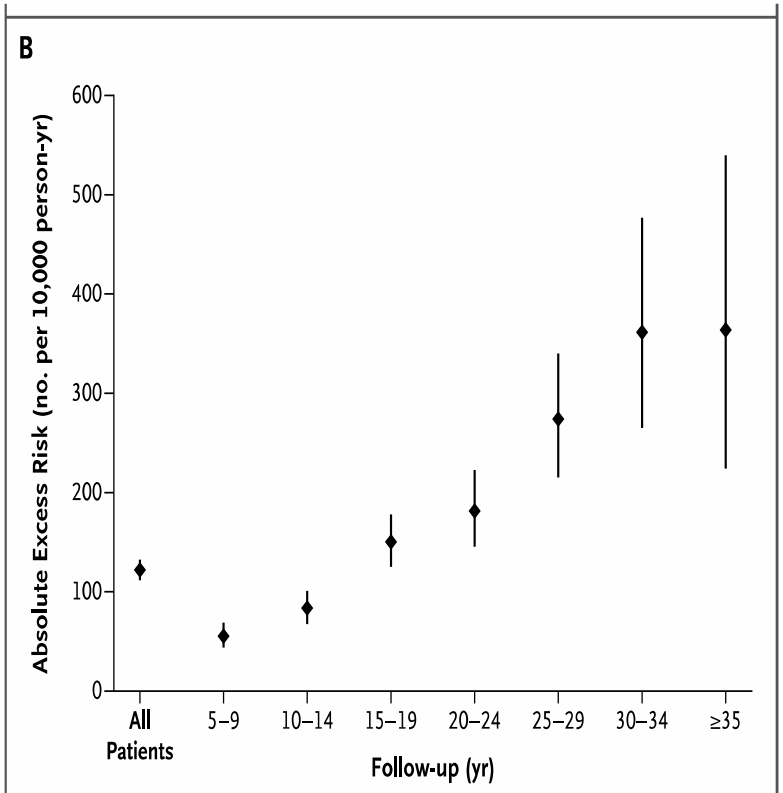


Figure 1. Standardized Incidence Ratios and Absolute Excess Risks of Any Subsequent Malignant Neoplasm after Treatment for Hodgkin's Lymphoma, According to Follow-up Interval.

The standardized incidence ratio is a comparison of the incidence of second cancer observed in the study cohort with the expected incidence in the general population. Vertical lines indicate 95% confidence intervals.

Schaapveld M, NEJM, 2015

Treatment of HL

1L: Cure…

15%

2L: Cure!

50%

3L: Cure?

Our need

The Hodgkin lymphoma clinicians are very active

Early stage : Rapid, H10 and HD16-17, BREACH

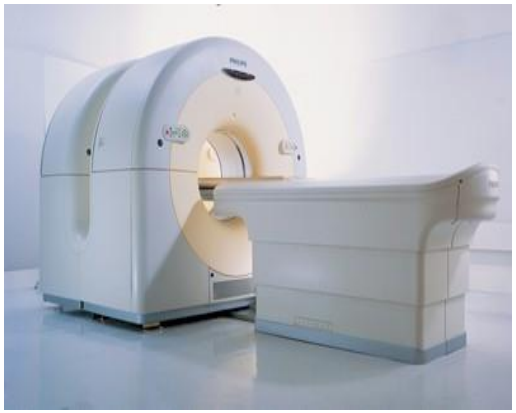
Advanced stage: Rathl, AHL2011, HD18 and Echelon 1

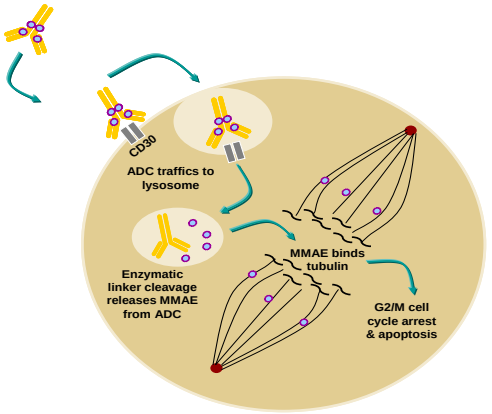
Relapse: Aethera

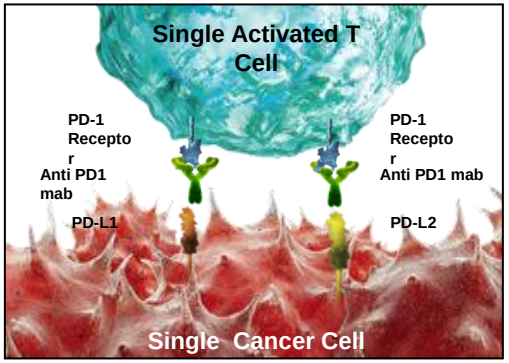
Brentuximab Vedotin and check point inhibitors

My task

How do we try to adapt our guidelines to the emergence of PET adapted therapy, BV and CPI?







Main messages

- Localized
  - CMT remains a SOC in PET2 neg but…
  - PET2+ (DS 4 or 5) : BEACOPPesc
  - Intermediate: 2 BEACOPPesc + 2 ABVD

- Advanced:
  - ABVD or BEACOPPesc (PET2 adapted)
  - BV-AVD for stage IV only (01/05/2023)

- Relapses: ASCT and BV maintenance

- CPI after BV (and ASCT)

Preview

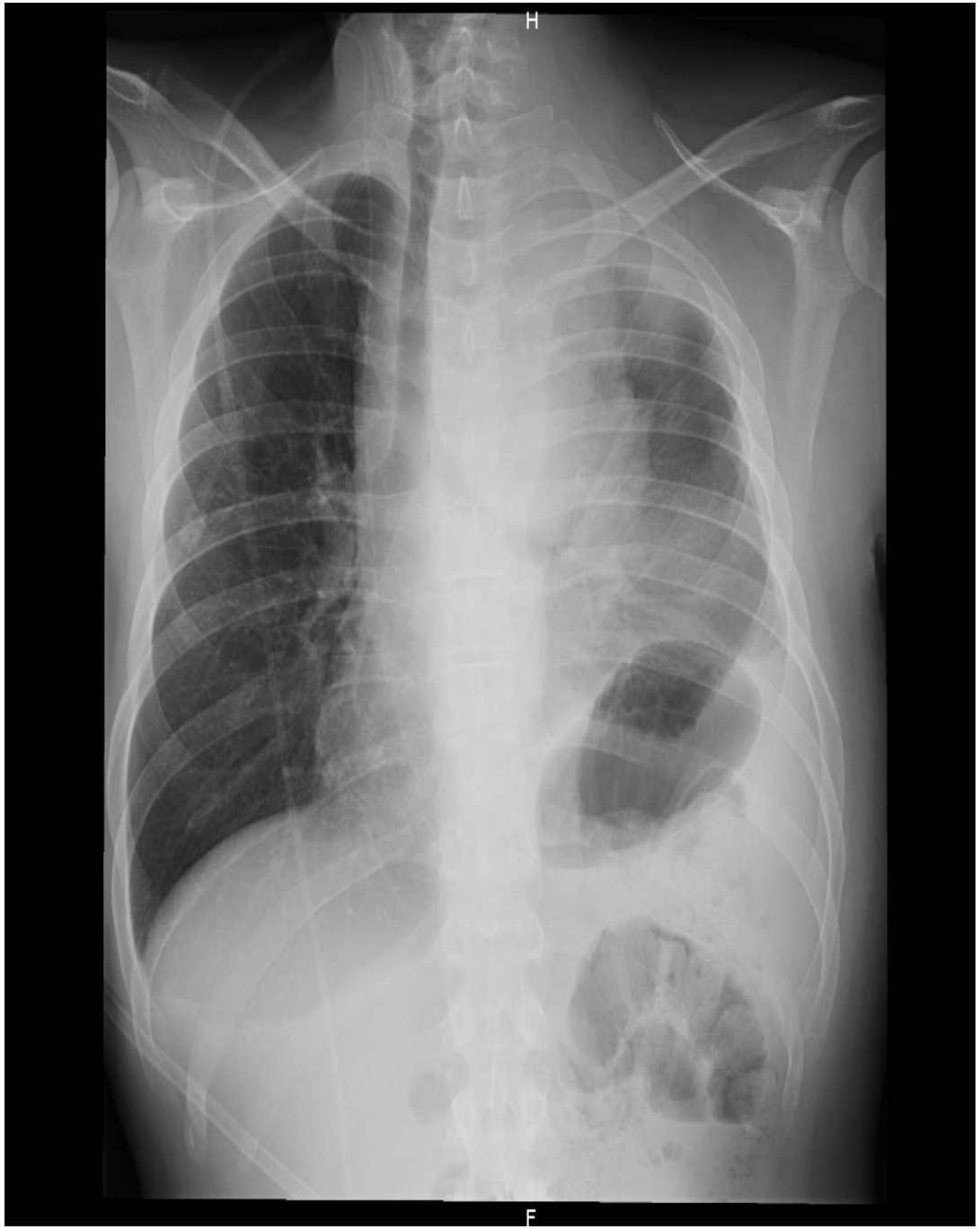
- Initial work-up and Fup
- First-line treatment
  - Localised
  - Advanced
- Relapses

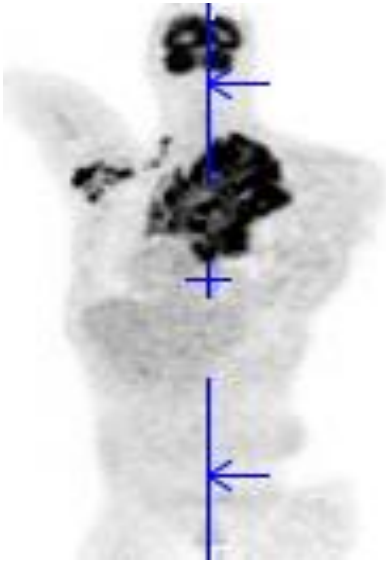
HL work-up

- Biopsy
- Blood count, serologies, βHCG, PET CT
- Echocardiography, pulmonary function test
- Reproductive counselling
- Early PET and EOT PET
- **NO fup PET in asymptomatic patients**

RISK FACTORS ACCORDING TO COOPERATIVE TREATMENT GROUPS

	EORTC-LYSA	GHSG
Risk factors (RF)	**A - mediastinal mass**	**A - mediastinal mass**
	B - Age ≥ 50yr	**B - Extra nodal site E**
	C - ESR ≥ 50	**C - ESR ≥ 50**
	D - ≥ 4 nod.areas	**D - ≥ 3 nod.areas**
	E - B + ESR > 30	
Stage:		
Favorable (F)	**I – II without RF**	**I – II without RF**
Unfavorable (UF)	**I – II with 1 or + RF**	**I – IIA with 1 or + RF**
Or intermediate		**II B with C/D without A/B**





In GHSG, IIB with bulky mediastinum is considered and treated as advanced disease.

Preview

- Initial work-up and Fup
- First-line treatment
  - Localised
  - Advanced
- Relapses

Five-point scale (Deauville scale)

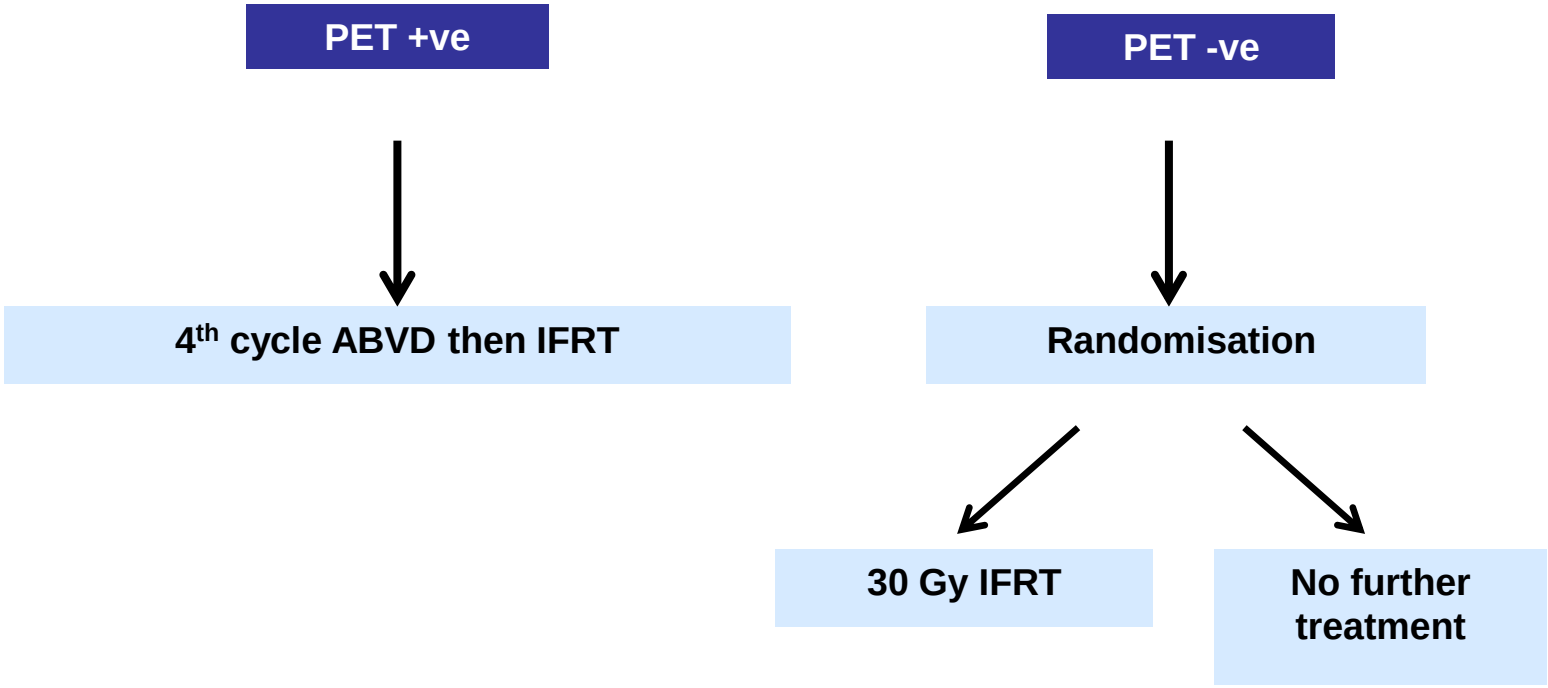
1) no uptake
2) uptake ≤ mediastinum — Negative
3) uptake > mediastinum but ≤ liver
4) uptake > liver at any site — Positive
5) uptake > liver ± new sites of disease

Meignan, et al., Leuk Lymphoma 2009
Barrington, et al., Eur J Nucl Med Mol Imaging 2010
Meignan, Eur J Nucl Med Mol Imaging 2010

UK NCRI RAPID trial in early favorable HL

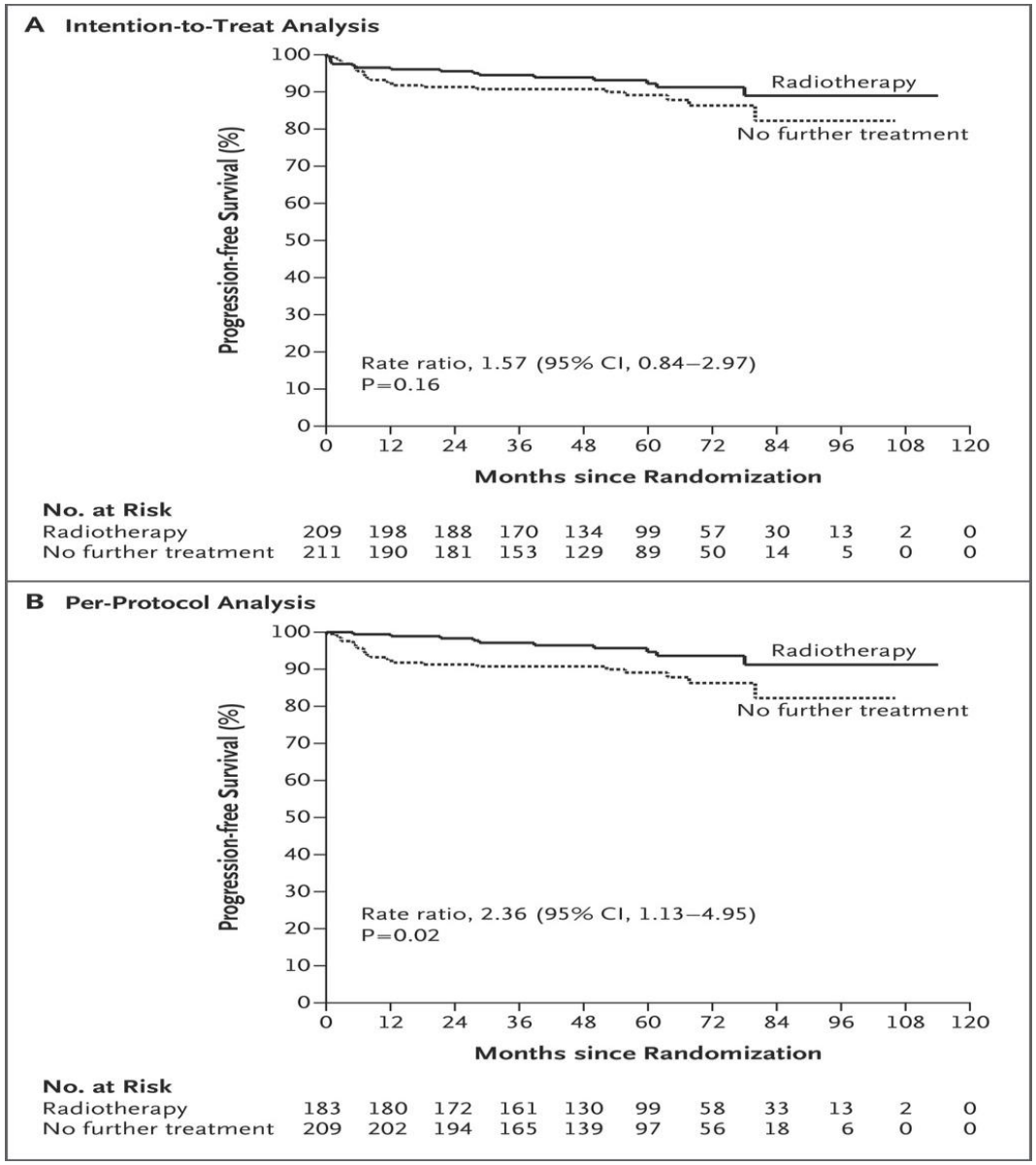
Initial treatment: **ABVD x 3**

Re-assessment: **if response, PET scan performed**



NEVER use G-CSF after ABVD !

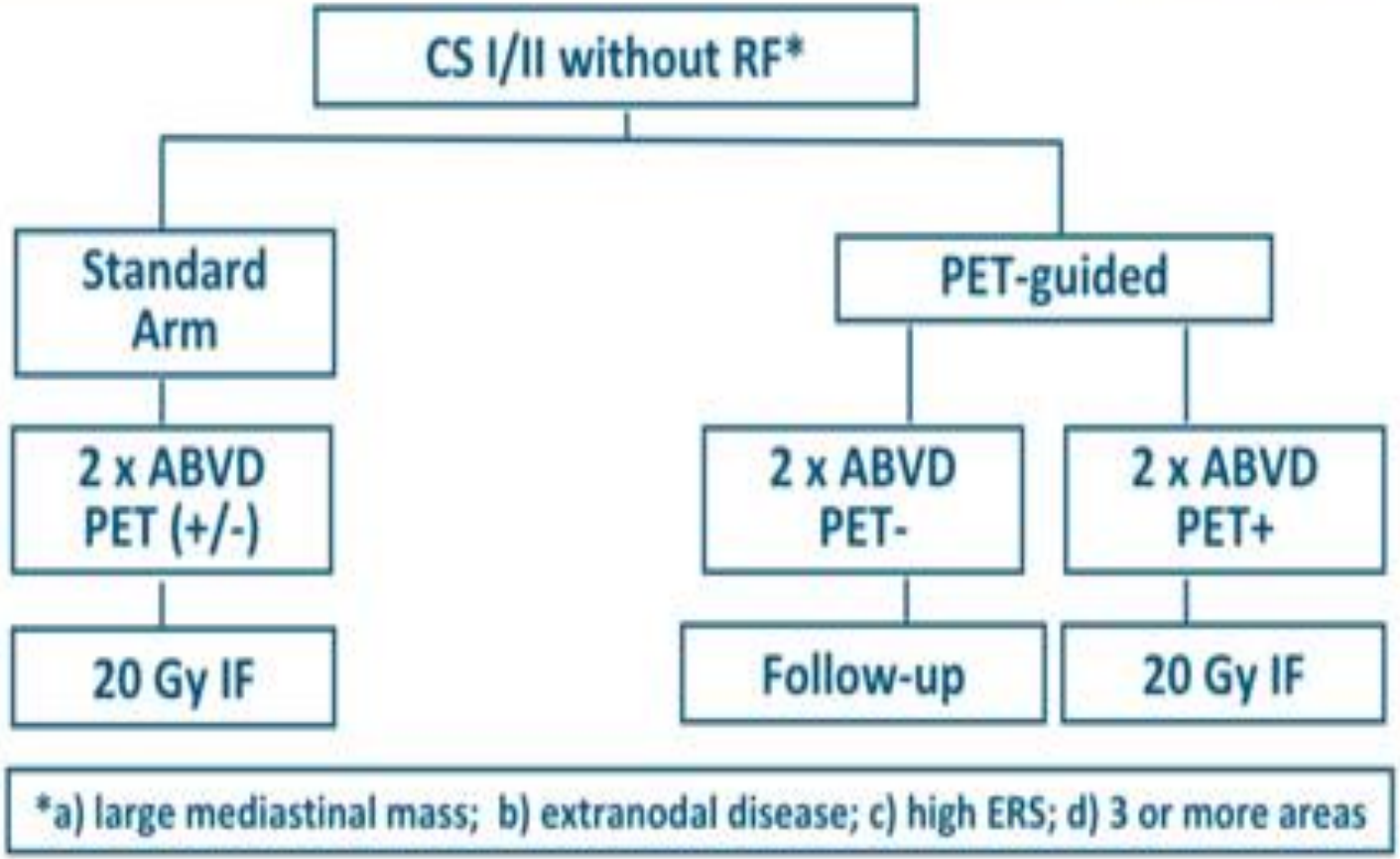
Progression-free Survival.



On the basis of a maximum allowable difference of 7 percentage points, this study **did not show noninferiority** of the strategy of no further treatment

GHSG HD16
Early-favorable HL

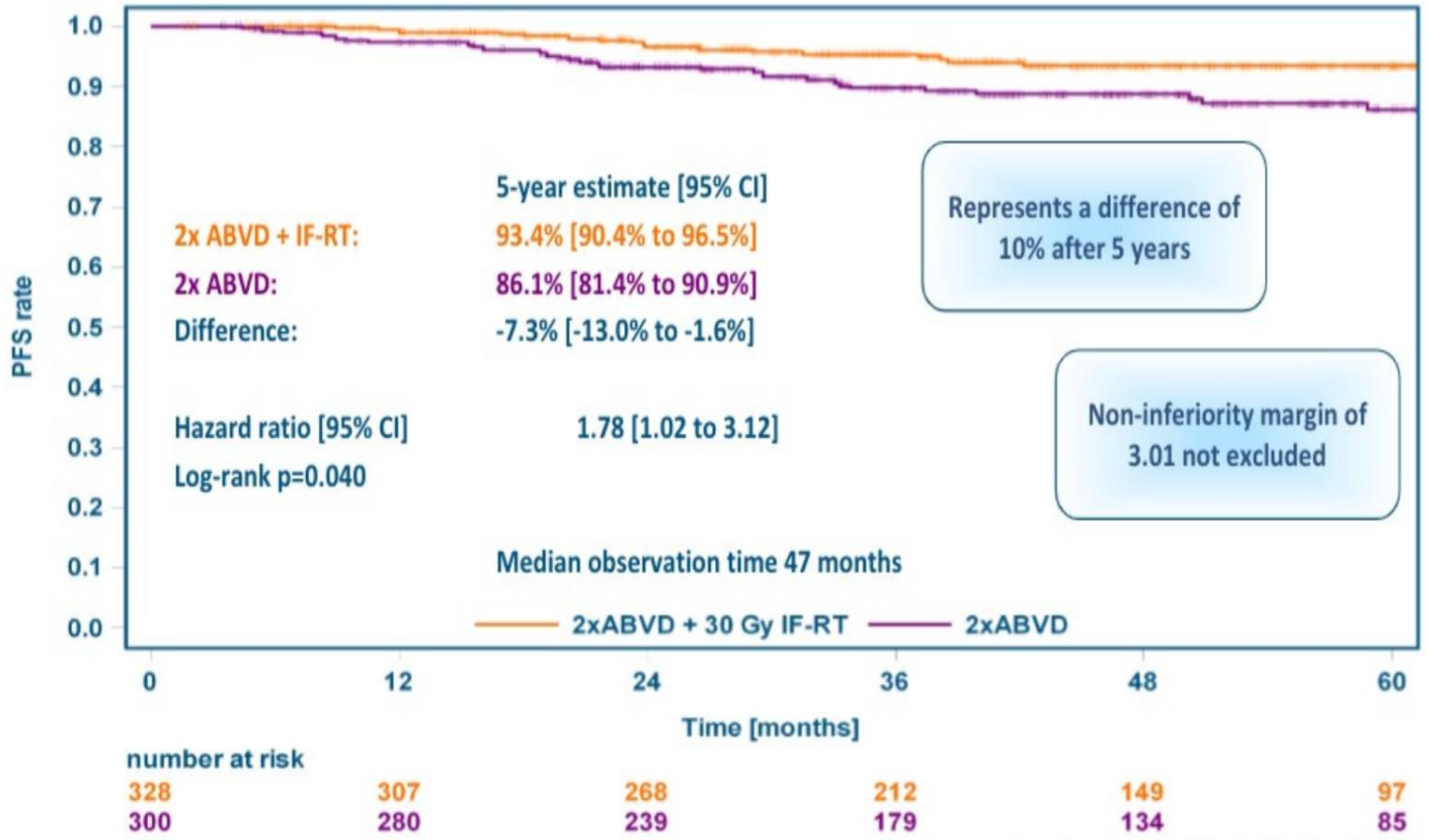
GHSG
www.ghsg.org



ClinicalTrials.gov Identifier: NCT00736320

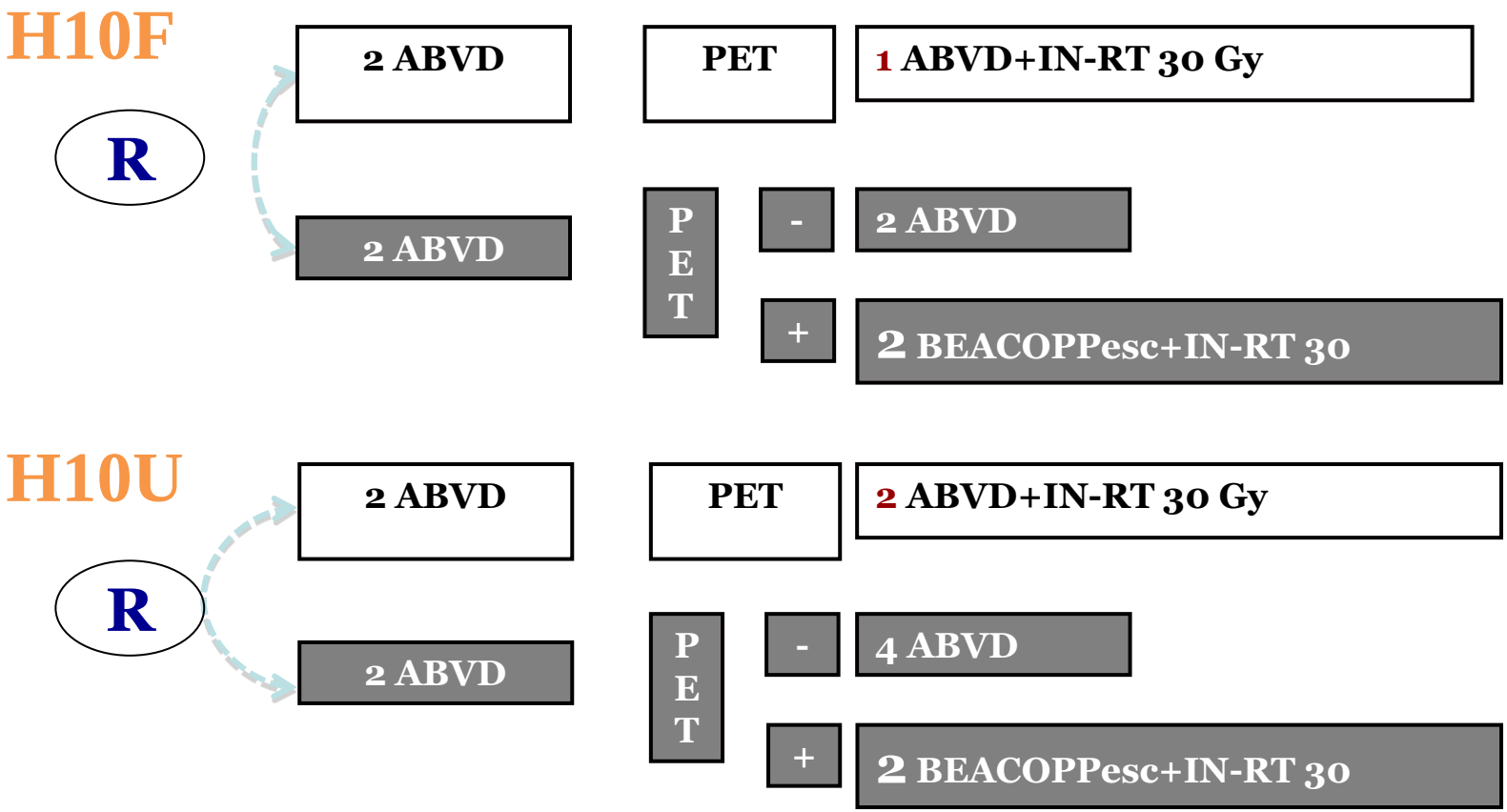
HD16: Progression-free survival
PET-negative patients

GHSG
www.ghsg.org



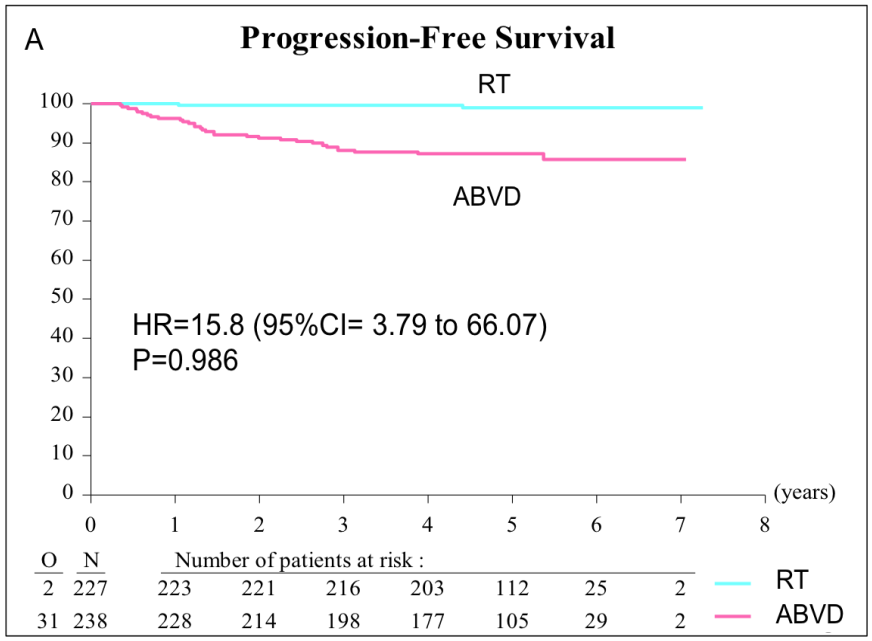
Final analysis of the HD16 trial, October 2018

H10

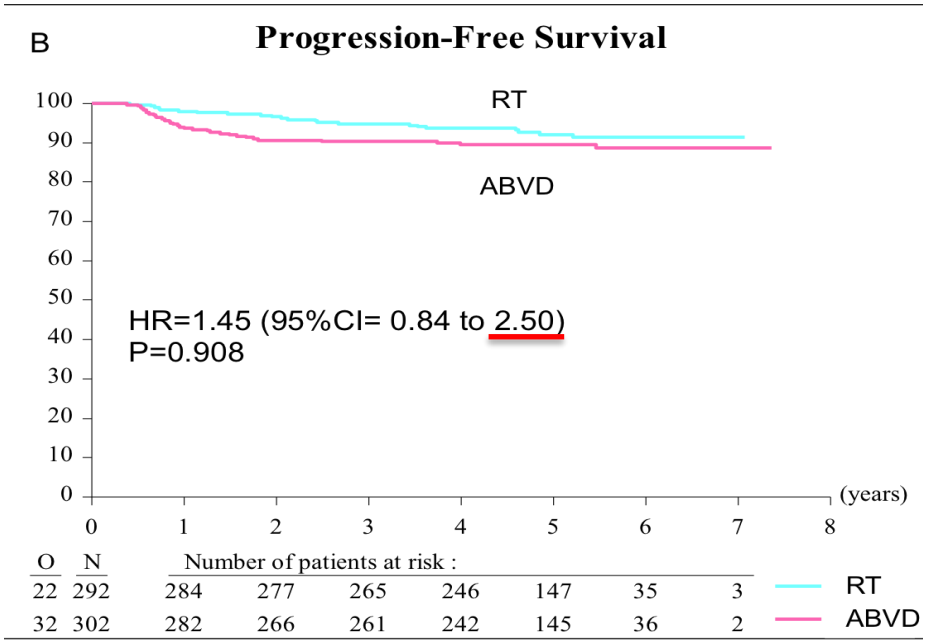


M. André, JCO, 2017

favorable group



unfavorable group

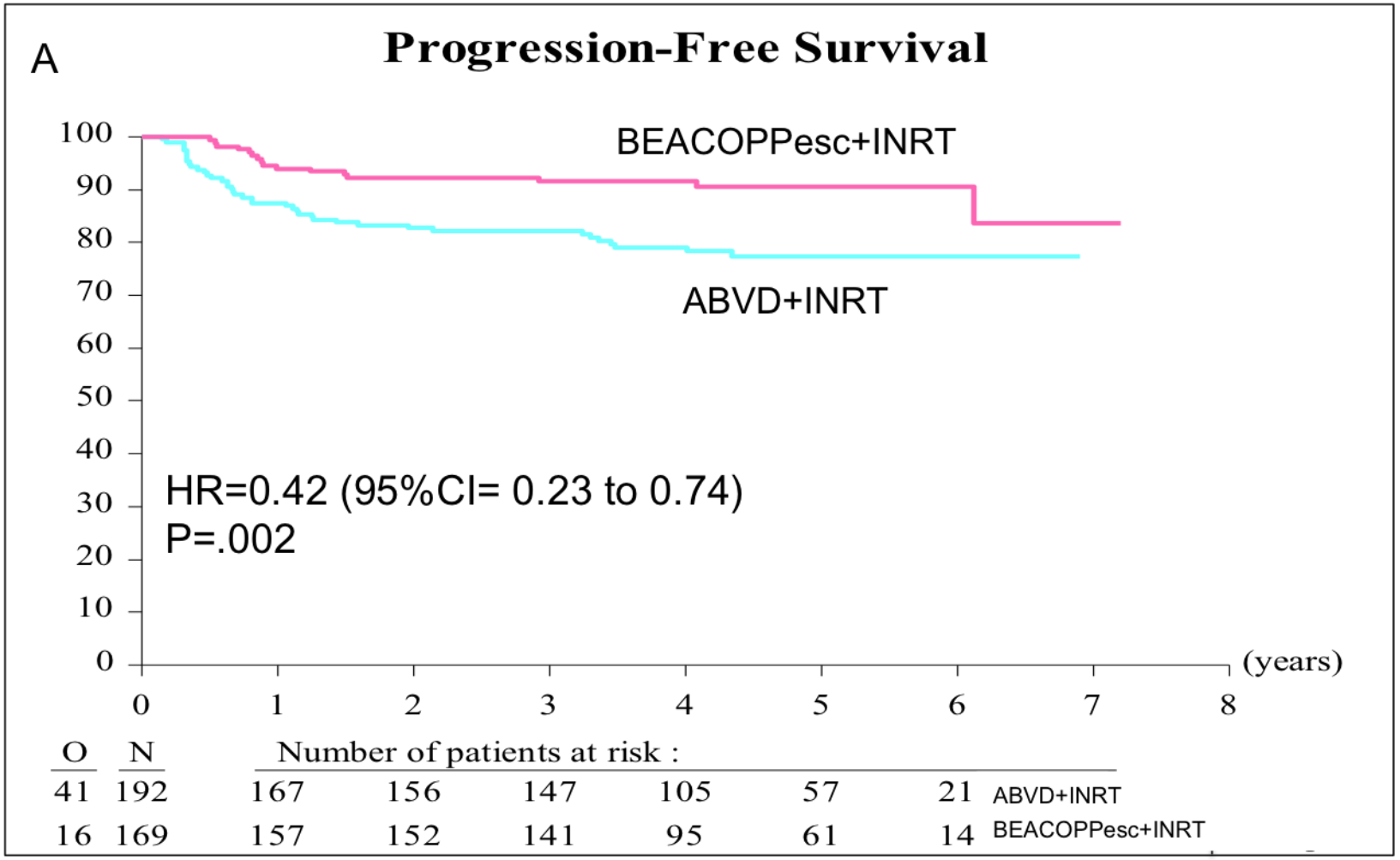


Non-inferiority is concluded if the upper bound of the 95% confidence interval for the estimated hazard ratio does not exceed the non-inferiority margin.

F group: HR < 3.20
U group: HR < 2.10 (upper bound is 2.50)

M. André, JCO, 2017

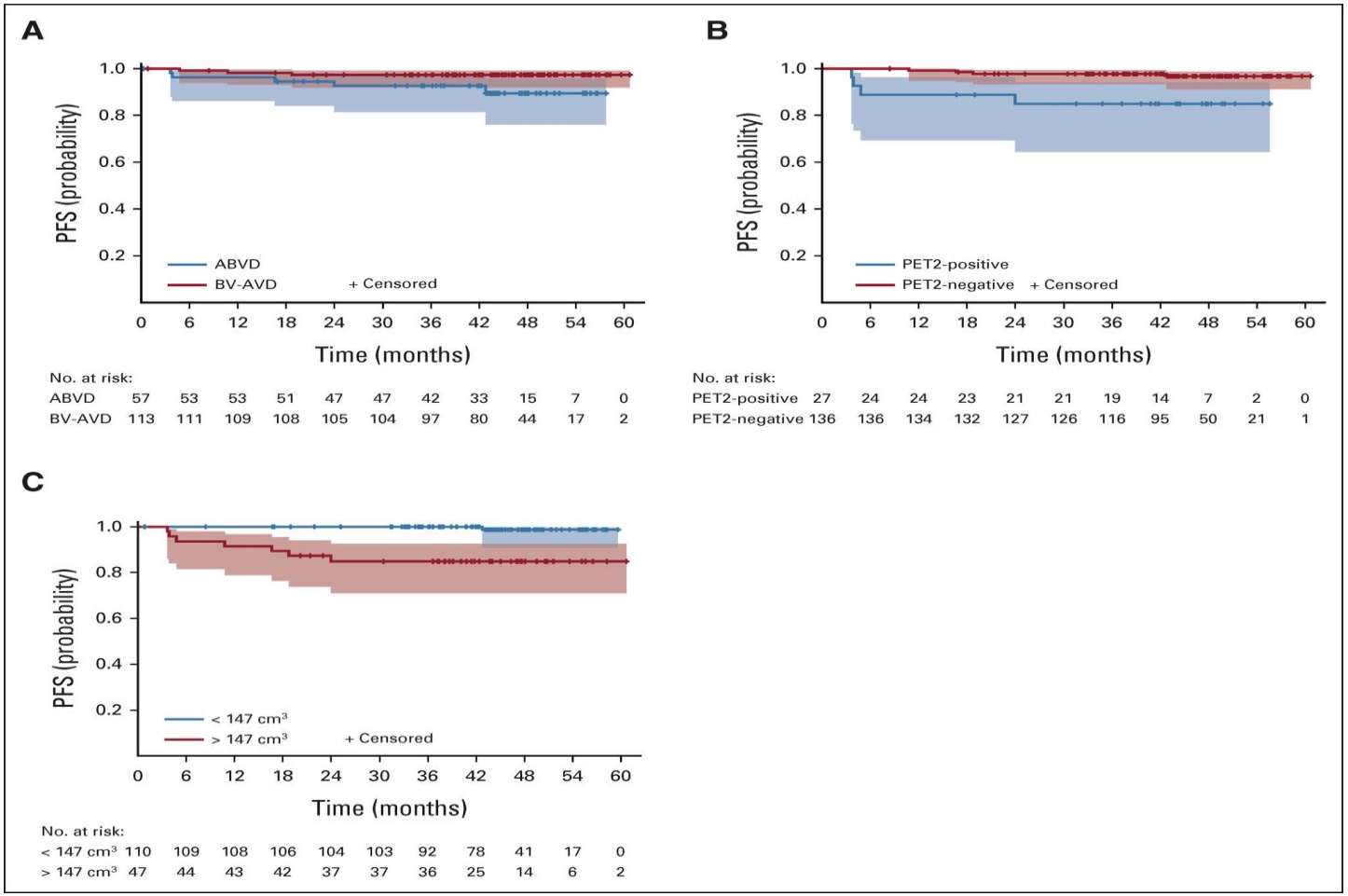
H10: PET positive



HR: Hazard Ratio BEACOPPesc *vs.* ABVD

M. André, JCO, 2017

BREACH: BV-AVD first line



L. Fornecker, JCO, 2023

Preview

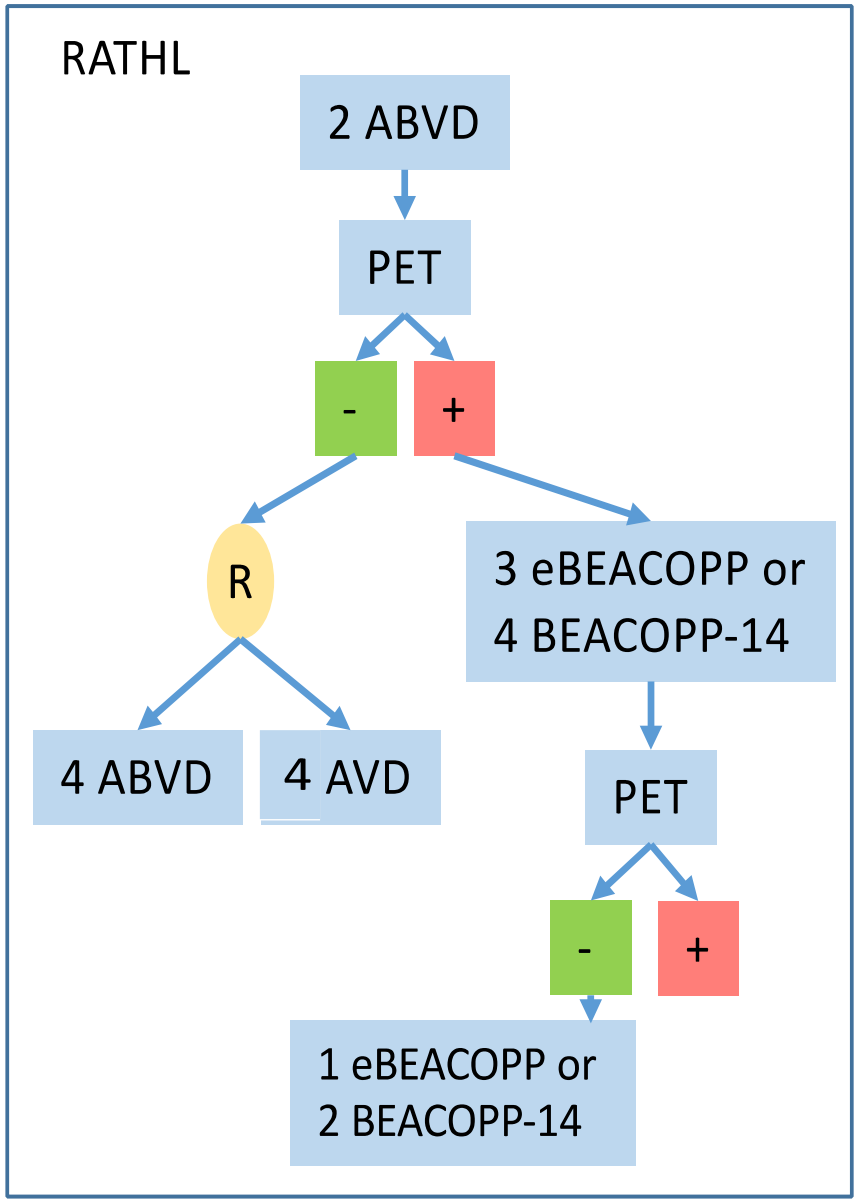
- First-line treatment
  - Localised
  - Advanced
- Relapses

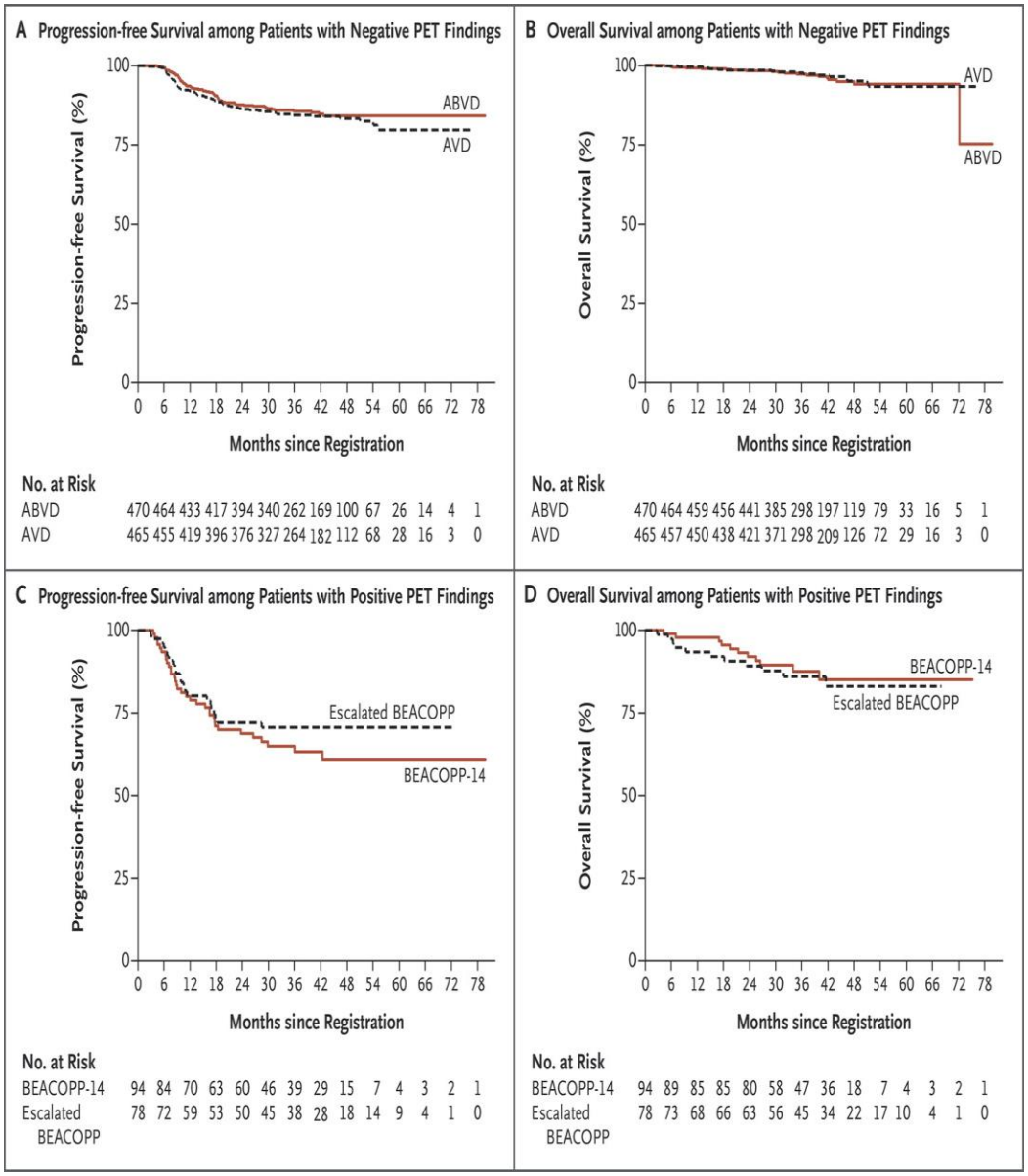
Advanced HL

- Advanced stage HL is usually treated with chemotherapy alone. Additional RT is confined to patients with residual disease after chemotherapy.

- Patients up to 60 years are treated with either 2ABVD + 4 AVD or 2 BEACOPPes + 4 ABVD, or 4 BEACOPPesc.

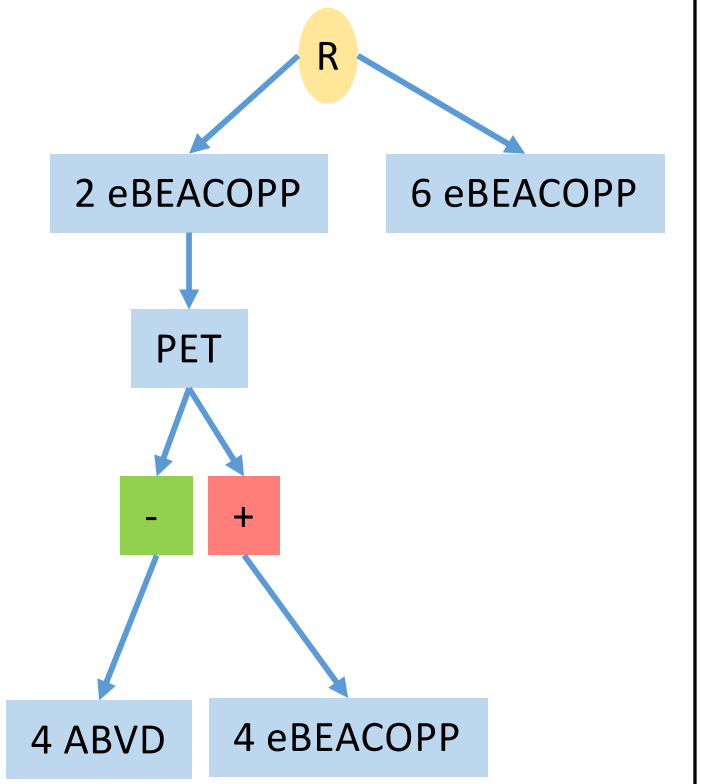
- BV-AVD will be available in Belgium for stage IV only on 01/05/2023

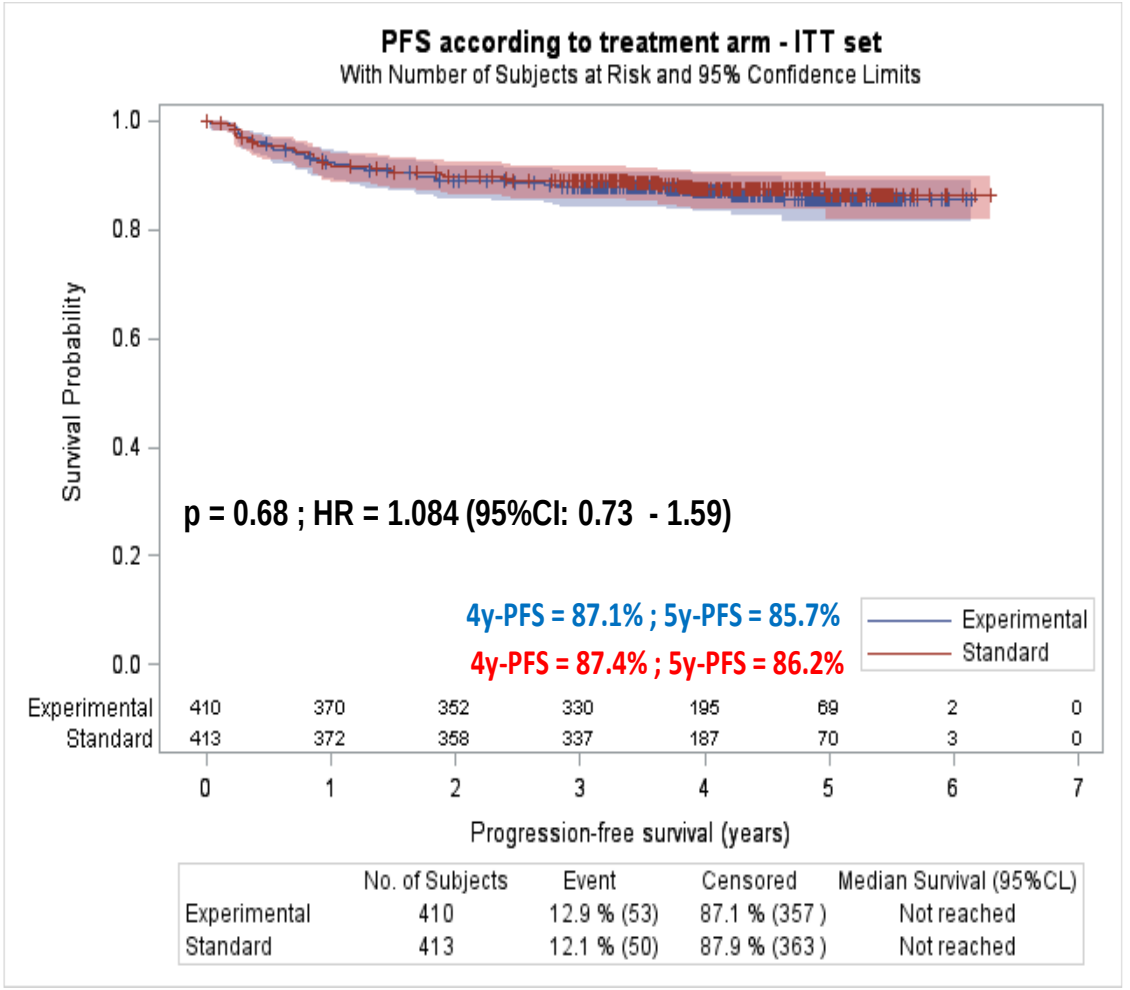




P. Johnson, NEJM, 2016

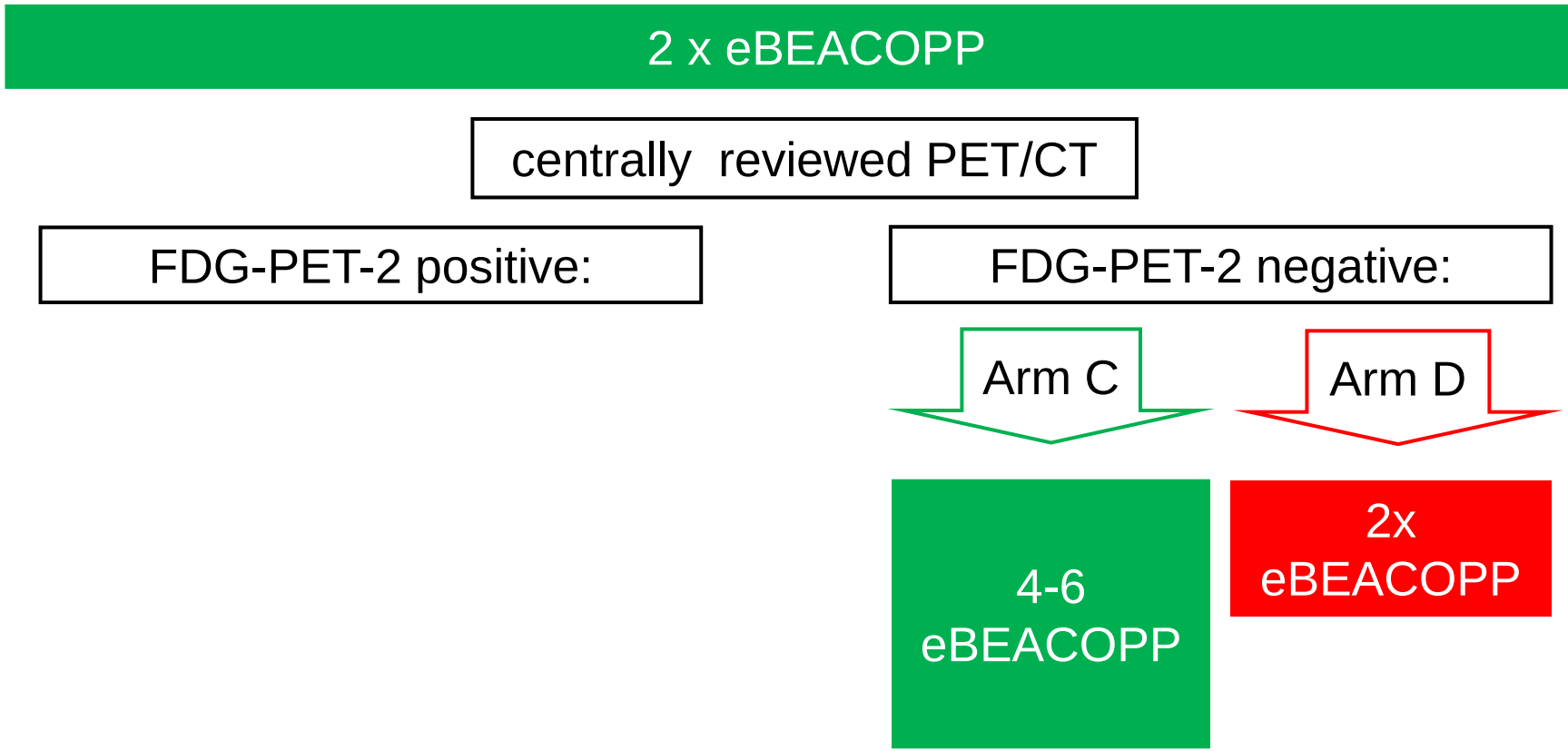
LYSA AHL2011





O. Casasnovas, Lancet Oncol, 2018

The GHSG HD18 study
PET-guided therapy of advanced-stage HL

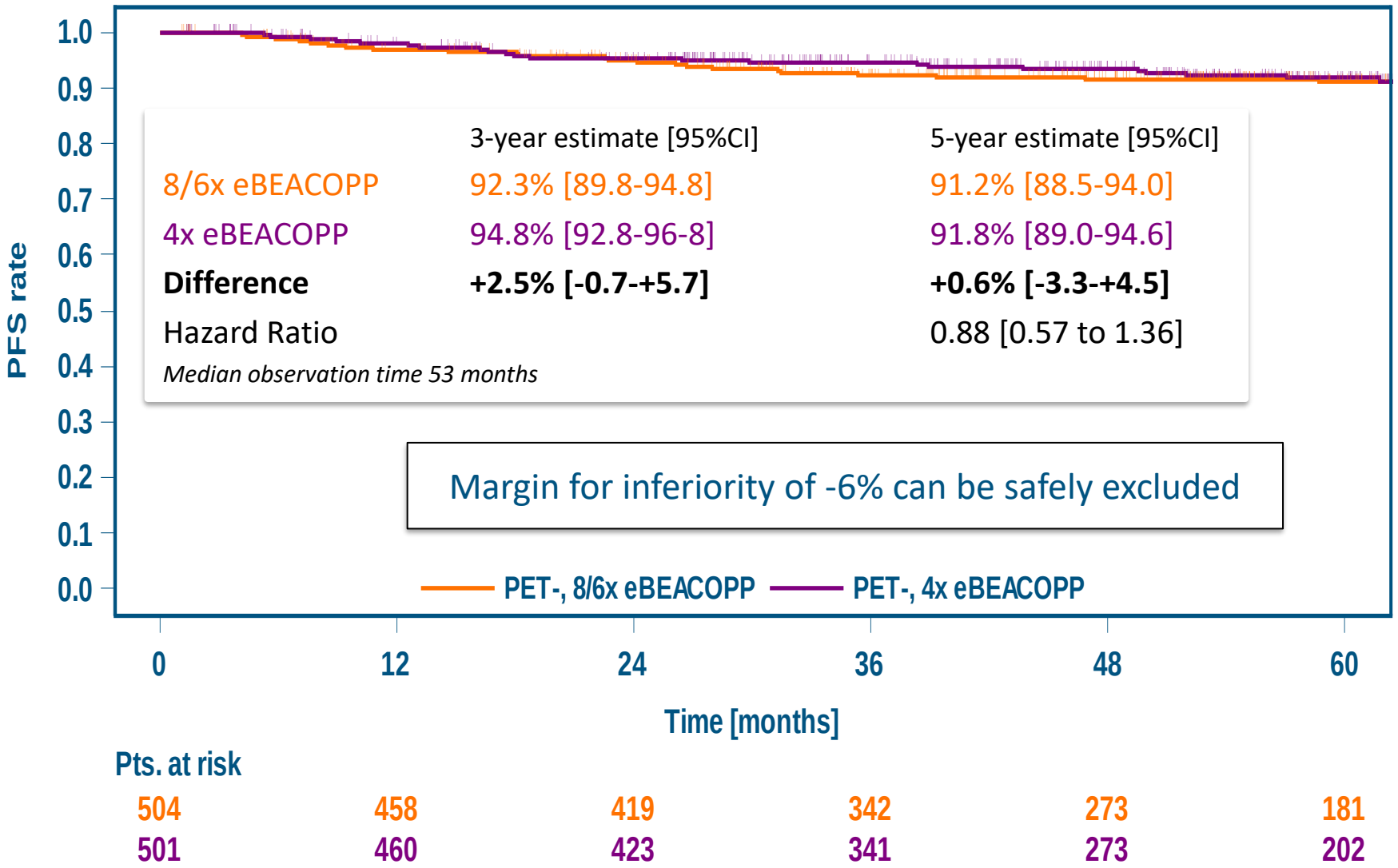


Does metabolic response determined by PET after two cycles (PET-2) allow adaption of treatment intensity?

P. Borchmann, Lancet, 2017

HD18 for PET-2-negative patients

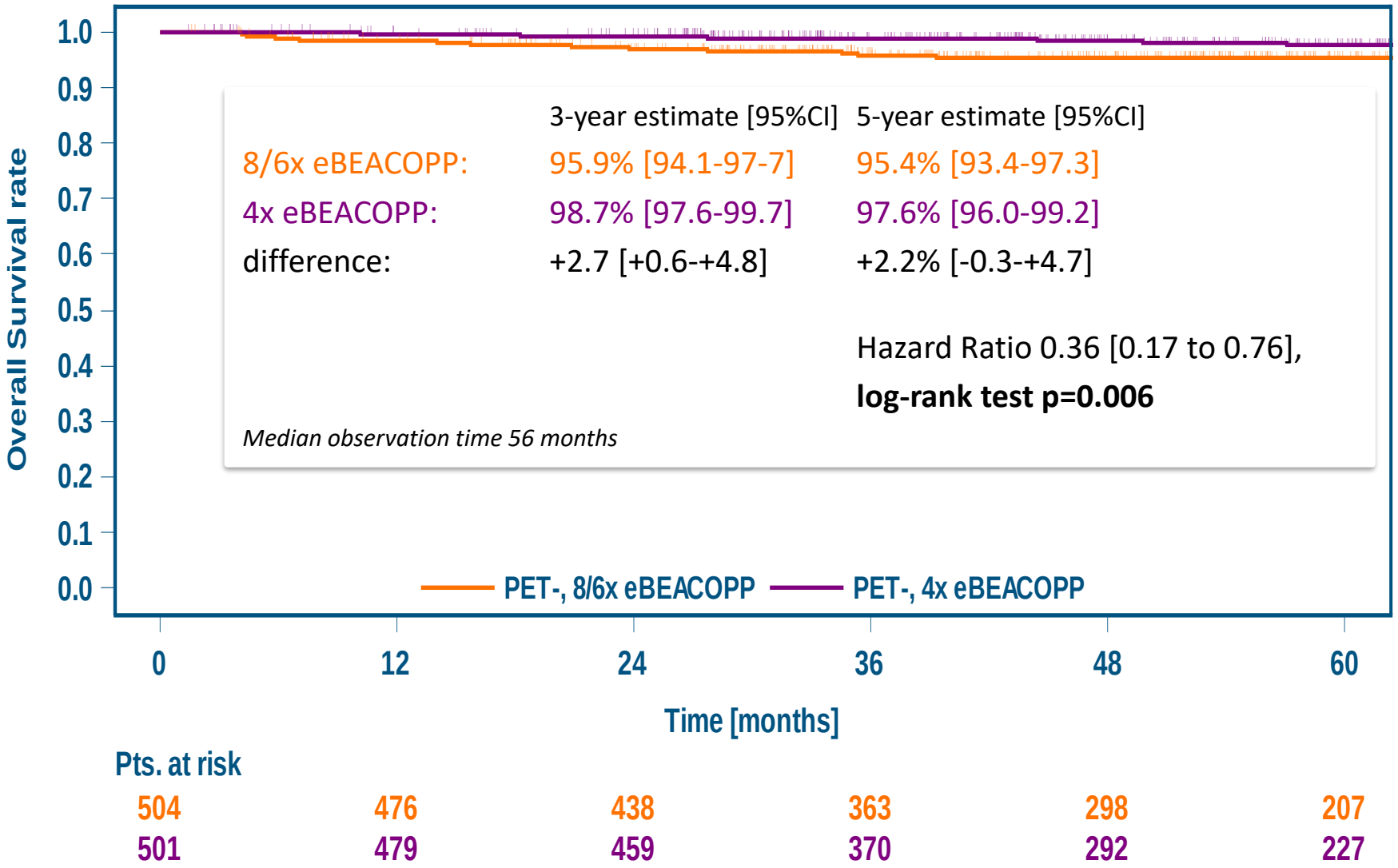
Progression-free survival



P. Borchmann, Lancet, 2017

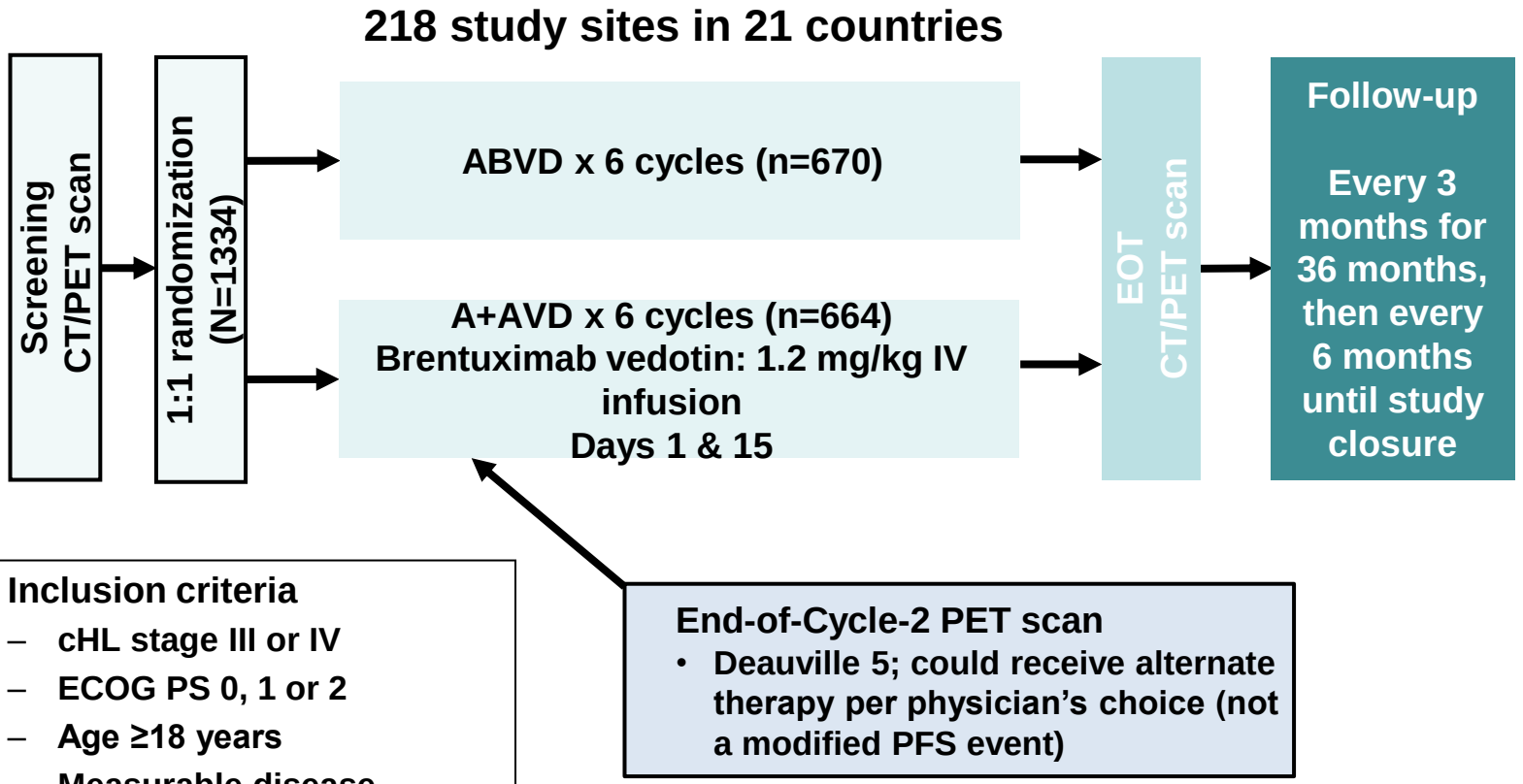
HD18 for PET-2-negative patients

Overall survival



P. Borchmann, Lancet, 2017

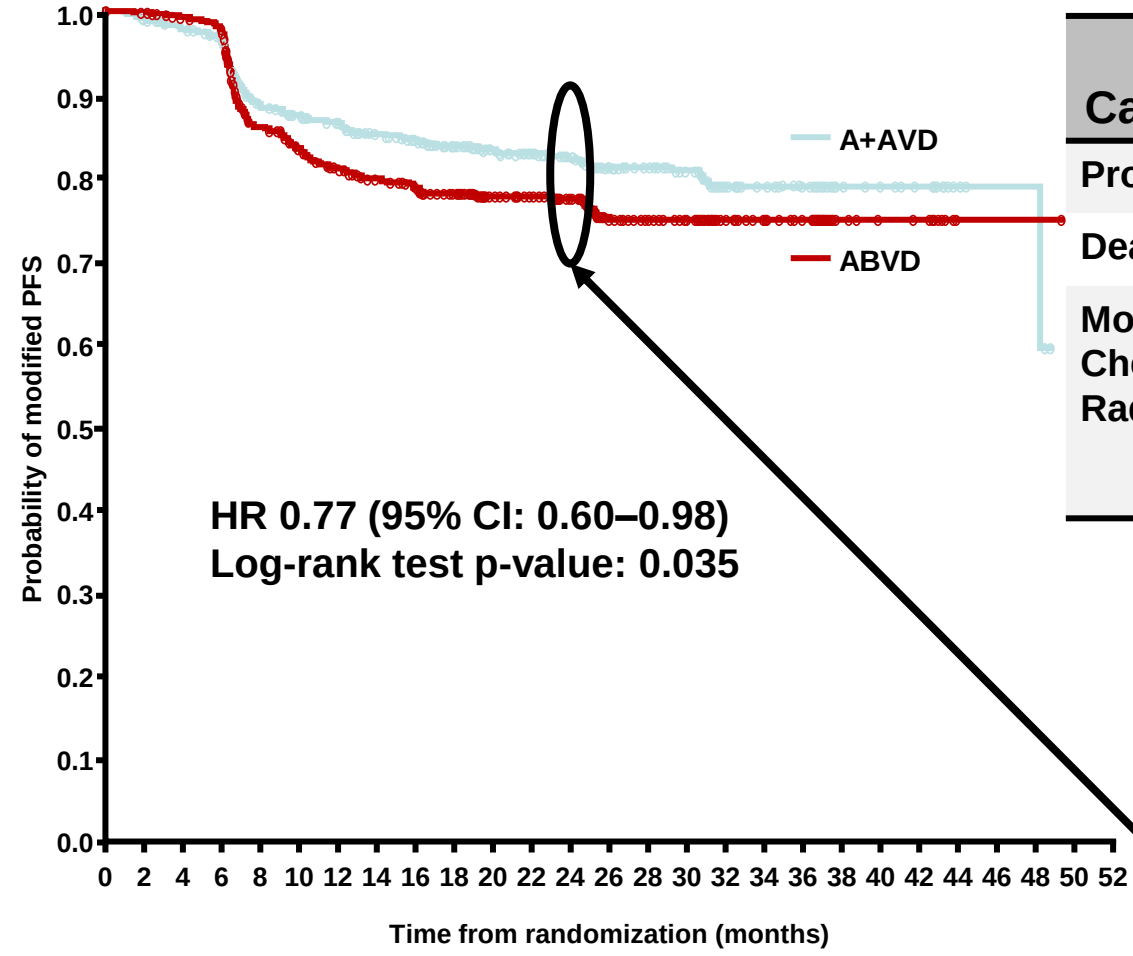
ECHELON-1: Open-label, randomized, phase 3 study of A+AVD versus ABVD in patients with newly diagnosed advanced cHL



- **Inclusion criteria**
  - cHL stage III or IV
  - ECOG PS 0, 1 or 2
  - Age ≥18 years
  - Measurable disease
  - Adequate liver and renal function

Connors JM, NEJM, 2017

Modified PFS per independent review



No. of patients at risk:

A+AVD	664	640	623	606	544	530	516	496	474	447	350	334	311	200	187	174	99	85	77	27	24	21	6	4	4	0	0
ABVD	670	644	626	613	522	496	476	459	439	415	328	308	294	179	168	153	78	68	62	16	13	12	1	1	1	0	0

Number of events

Category	A+AVD N=117	ABVD N=146
Progression	90	102
Death	18	22
Modified progression	9	22
Chemotherapy	7	15
Radiotherapy	2	7

Modified PFS estimates

Time	A+AVD (95% CI)	ABVD (95% CI)
2-year	82.1 (78.7–85.0)	77.2 (73.7–80.4)

Median follow-up (range): 24.9 months (0.0–49.3)

Connors JM, NEJM, 2017

RESEARCH SUMMARY

Overall Survival with Brentuximab Vedotin in Stage III or IV Hodgkin's Lymphoma

Ansell SM et al. DOI: 10.1056/NEJMoa2206125

CLINICAL PROBLEM

In the ECHELON-1 trial involving patients with newly diagnosed stage III or IV Hodgkin's lymphoma, first-line treatment with the antibody–drug conjugate brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (A+AVD) offered a benefit in modified progression-free survival over standard treatment with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). Data on overall survival are needed.

CLINICAL TRIAL

Design: The phase 3, multicenter, open-label, randomized ECHELON-1 trial examined the efficacy and safety of A+AVD, as compared with ABVD, in adult patients with previously untreated stage III or IV Hodgkin's lymphoma.

Intervention: 1334 patients were randomly assigned to receive A+AVD or ABVD on days 1 and 15 of each 28-day cycle for up to six cycles. The key secondary end point was overall survival. (The primary end point, modified progression-free survival, was reported previously.)

RESULTS

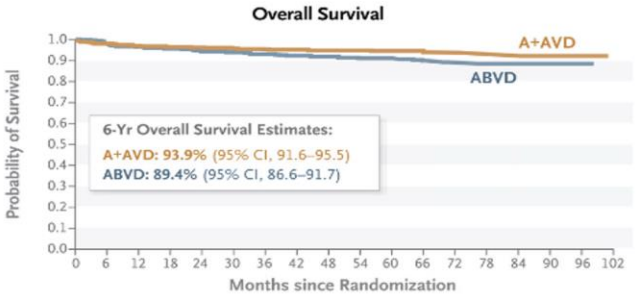
Efficacy: During a median follow-up of 73 months, overall survival significantly favored A+AVD over ABVD.

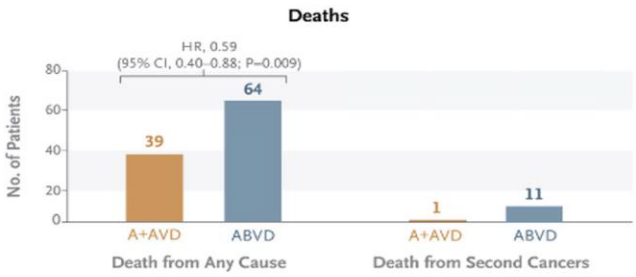
Safety: Deaths associated with second cancers and pulmonary toxicity were more common with ABVD than with A+AVD. However, the incidence of myelotoxic effects was greater with A+AVD. In addition, peripheral neuropathy occurred more frequently with A+AVD; most cases resolved or ameliorated by the end of follow-up.

LIMITATIONS AND REMAINING QUESTIONS

- The large disparity in deaths from second cancers is unexplained.
- Cause of death was investigator-assessed, and contextual information was not always provided.

Links: Full Article | NEJM Quick Take | Editorial





CONCLUSIONS

Patients with previously untreated stage III or IV Hodgkin's lymphoma who received A+AVD (brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine) had significantly longer overall survival than those who received standard treatment with ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine).

Preview

- First-line treatment
  - Localised
  - Advanced
- Relapses

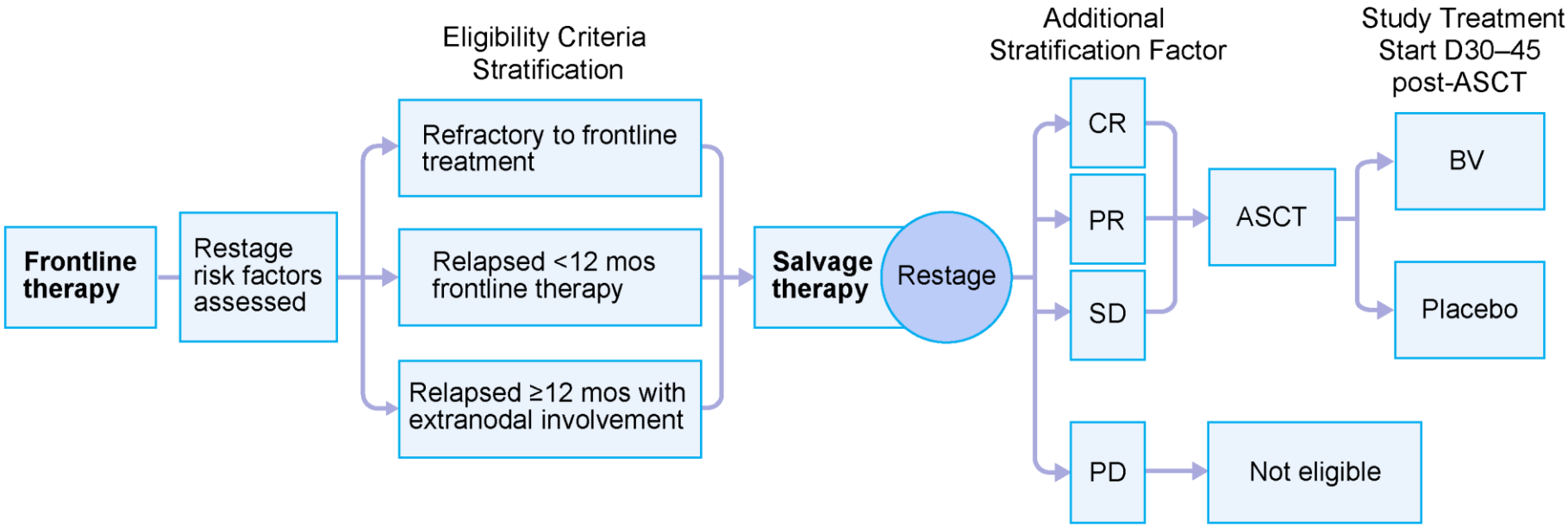
Relapsing HL

- For most patients with refractory or relapsed HL, the treatment of choice consists of high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) [II, A].

- Consolidating treatment with the antibody-drug conjugate brentuximab vedotin was shown to improve the tumor control in high-risk patients receiving high-dose chemotherapy and ASCT [II, B].

AETHERA: phase 3 trial of brentuximab vedotin vs placebo in relapsed or refractory HL pts at risk of relapse post ASCT

Objectives: *Primary:* PFS per IRF; *Secondary:* OS, safety/tolerability



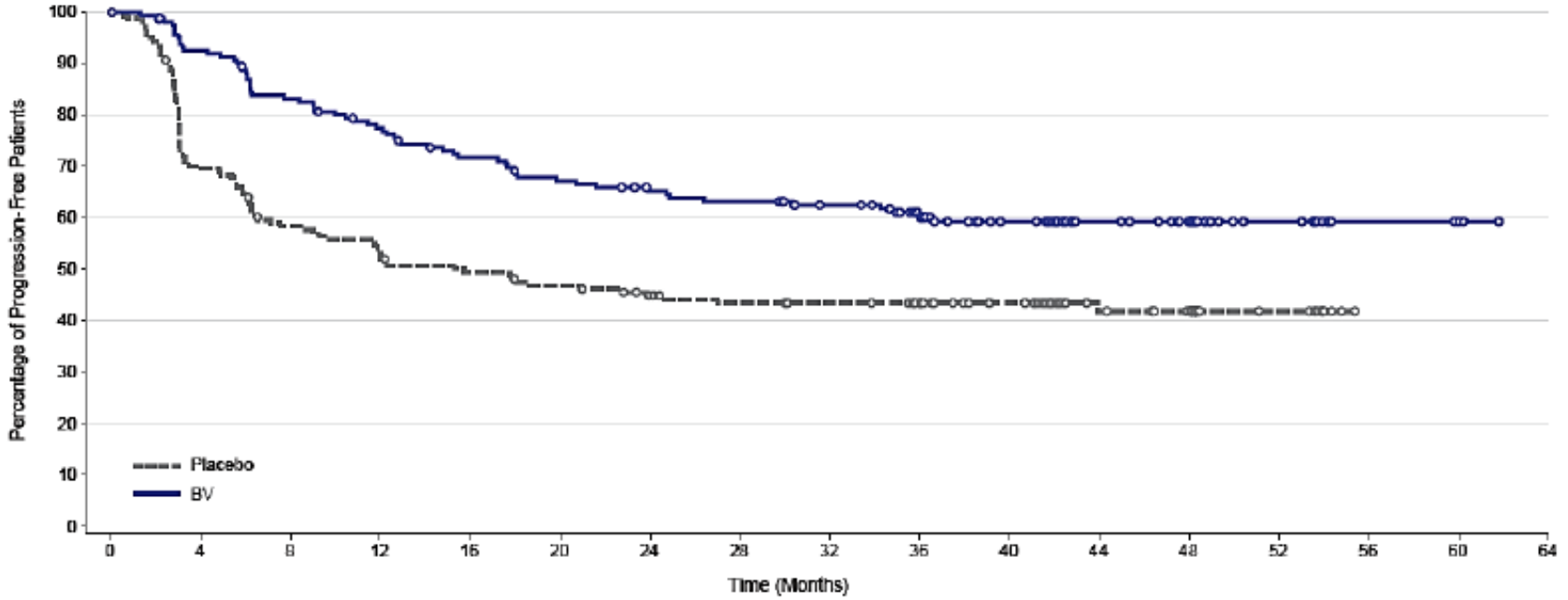
Dose and schedule: Pts were randomized 1:1 to receive 16 21-day cycles of brentuximab vedotin 1.8 mg/kg IV day 1 or placebo

- Pts who progressed on placebo could receive brentuximab vedotin in another trial

Moskowitz CH. Lancet 2015

AETHERA: Updated PFS

PFS* per Investigator – 3 Years Since Last Patient Randomized



N at Risk (Events)

BV	165 (0)	149 (12)	133 (27)	122 (36)	111 (45)	103 (52)	97 (55)	94 (58)	87 (59)	74 (61)	56 (63)	39 (63)	32 (63)	13 (63)	4 (63)	3 (63)	0 (63)
Placebo	164 (0)	113 (48)	92 (67)	83 (76)	77 (81)	72 (85)	65 (88)	61 (90)	59 (90)	54 (90)	44 (90)	26 (91)	22 (91)	9 (91)	0 (91)	0 (91)	0 (91)

			PFS Rate, % (95% CI)			
	Treatment cycles (median)	Events	24 months	36 months	Median PFS (mos)	Hazard ratio
BV (N=165)	15	63	65 (57, 72)	61 (53, 68)	–	0.52
Placebo (N=164)	15	91	45 (37, 52)	43 (36, 51)	15.8	

*Includes clinical assessments of lymphoma

Sweetenham J, et al. *Blood.*2015;126: Abstract 3172S

Anti PD1

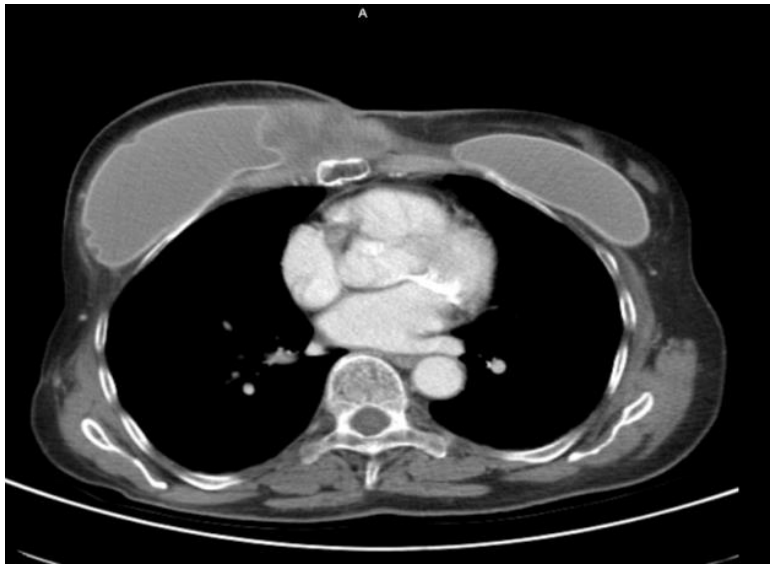
- Nivolumab:
  - After BV and ASCT
- Pembrolizumab
  - After BV and ASCT
  - After 2 lines (ASCT not mandatory)

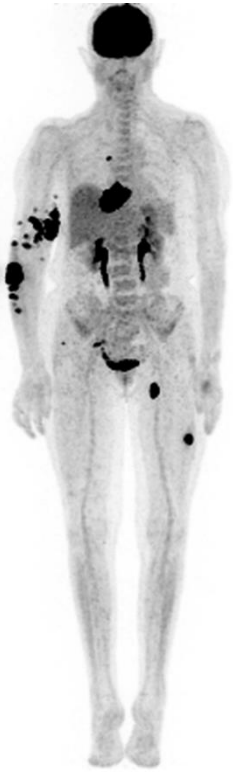
Conclusions

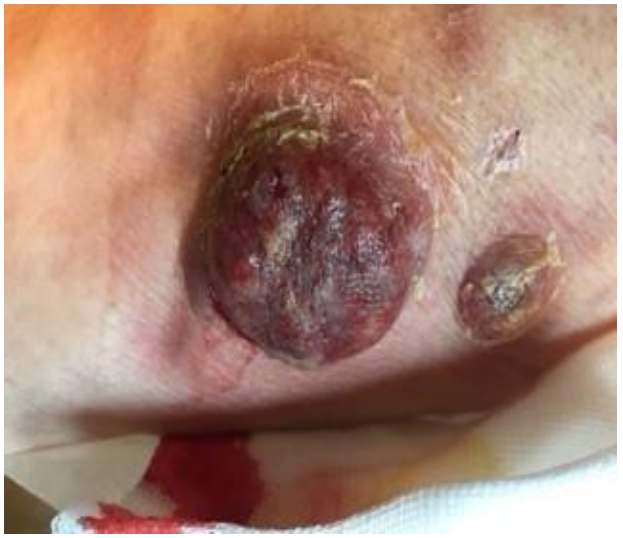
- The treatment of HL has become PET adapted:
  - Localised: PET2 neg: ABVD +RT but….
  - Localised: PET2 +: go to BEACOPPesc
  - Intermediate: 2 BEACOPPesc + 2 ABVD
  - Advanced:
    - 4 BEACOPPesc, 2 BEACOPPesc +4 ABVD, 6 A(B)VD, 6 BV-AVD

- New drugs (BV and CPI) are available for relapses…that are becoming very unfrequent.

Breast implant associated anaplastic large cell lymphoma







Belgian registry: marc.andre@chuuclnamur.uclouvain.be