22nd

INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

APRIL 4 - 5, 2025

WESTIN CHICAGO RIVER NORTH

#IUCLS2025

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22nd INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

"European Regimens"

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THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

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Disclosures

- **Ono Pharmaceuticals: Consultant**
- **BMS: Advisory Board**
- **Umoja: DSMB**

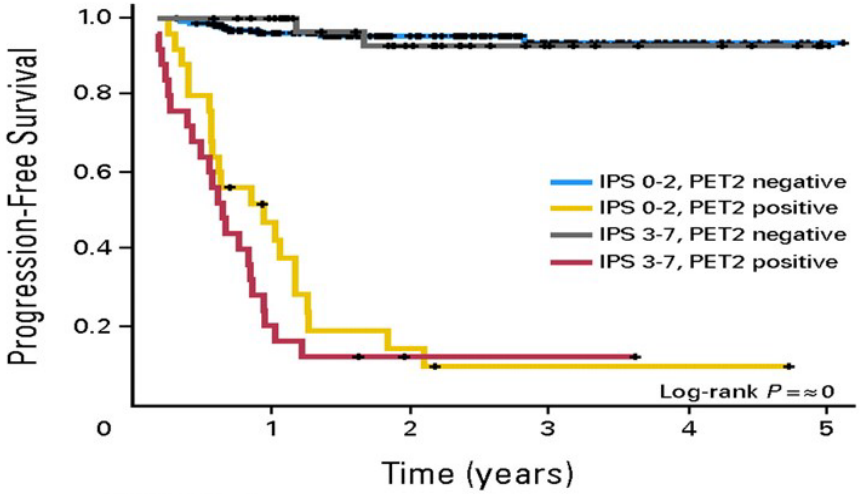
Contributions of the “European Regimens” to the management of cHL

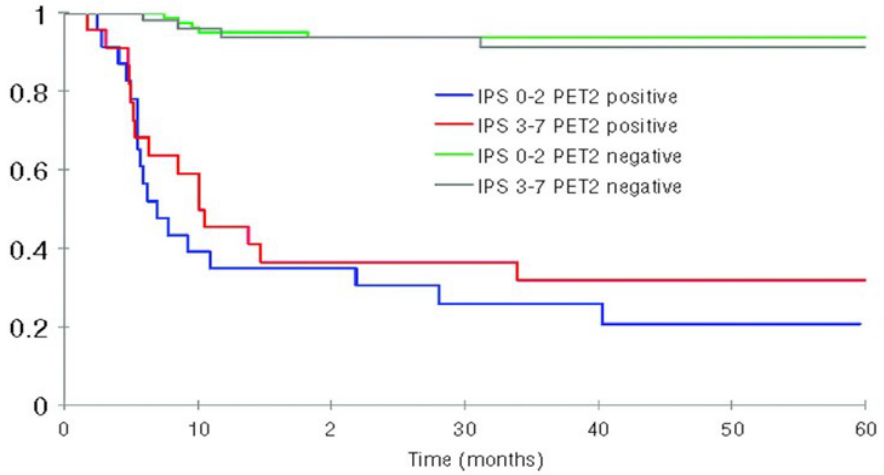
- Birth of PET derived algorithms
- Large clinical trials of early stage favorable and unfavorable cHL (HD10)
- “Rapid” trial in early-stage disease
- “RathI” in advanced stage disease
- The 40-year contributions of the GHSG, including early and advanced stage disease (HD1-21)
- Recent studies on BrECADD and importance of limited cycles

2007: Birth of PET-adapted therapy

A Gallamani
Pier Luigi ZInzani

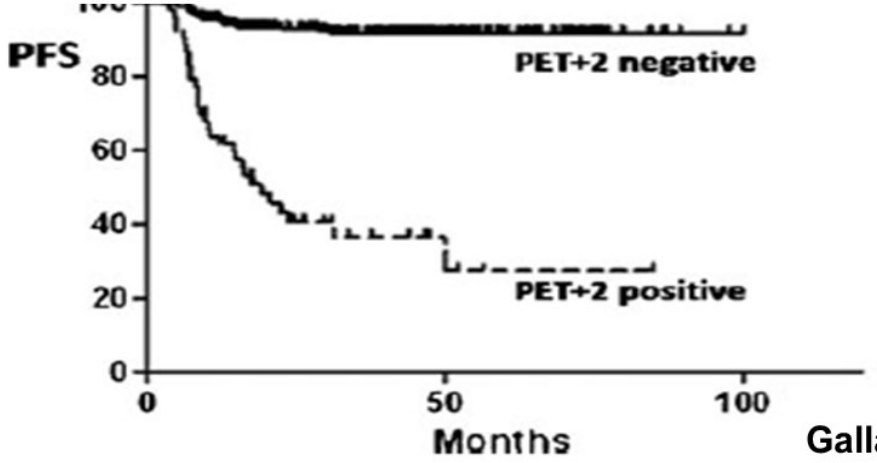
PET-2
IHP





PET-2
Deauville criteria
Neg 1-3
Pos 4-5

PET-2
IHP

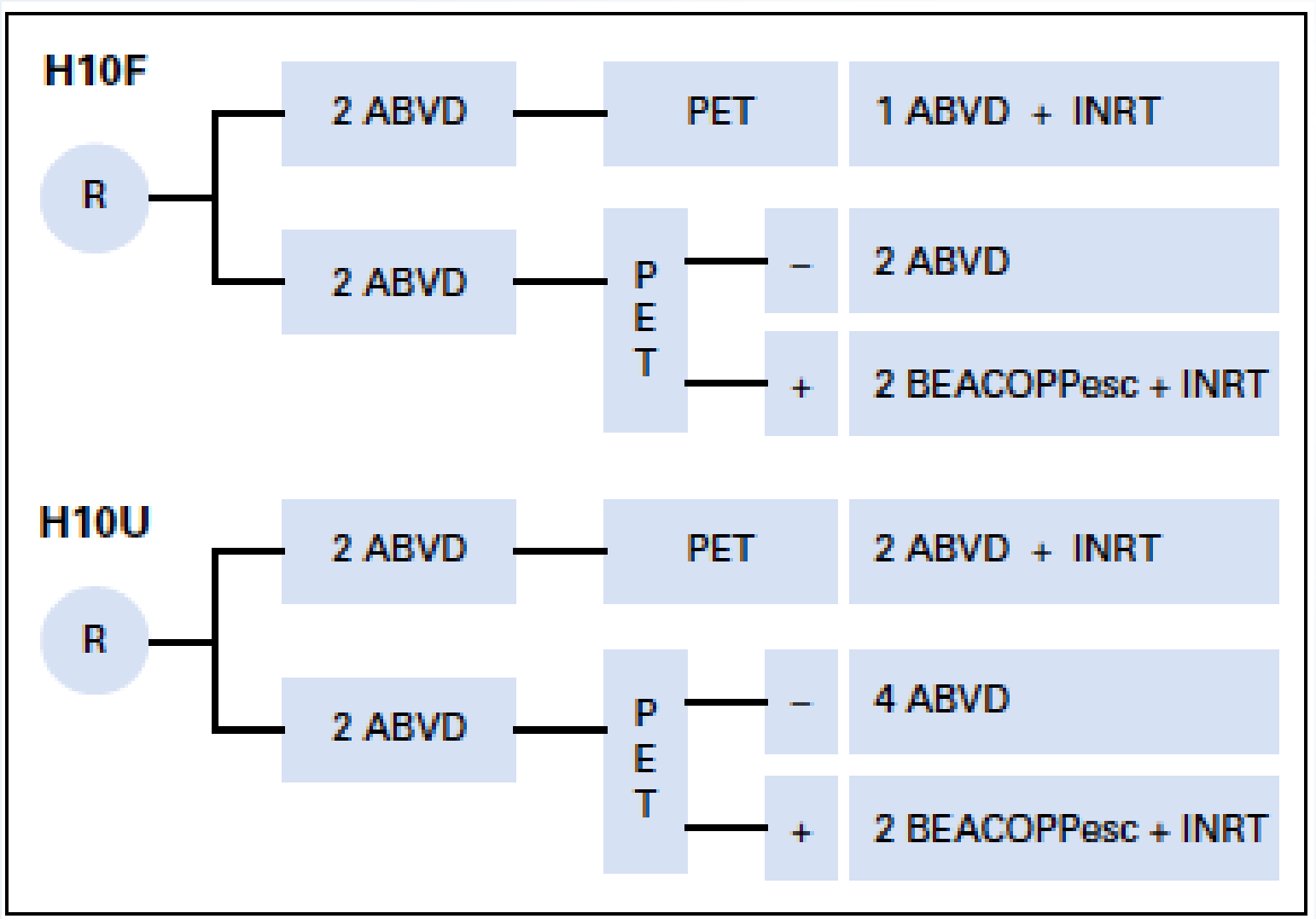


PET-2 predicts for long-term PFS of
90-95% if negative
30-35% if positive

Gallamini A et al. JCO 2007;25:3746-3752, Gallamini A Haematologica 2014 99: 1107-1113; Zinzani PL et al. Eur J Nucl Med Imaging (2012) 39:4-12

EORTC/LYSA HD 10 Study Schema

Marc Andre

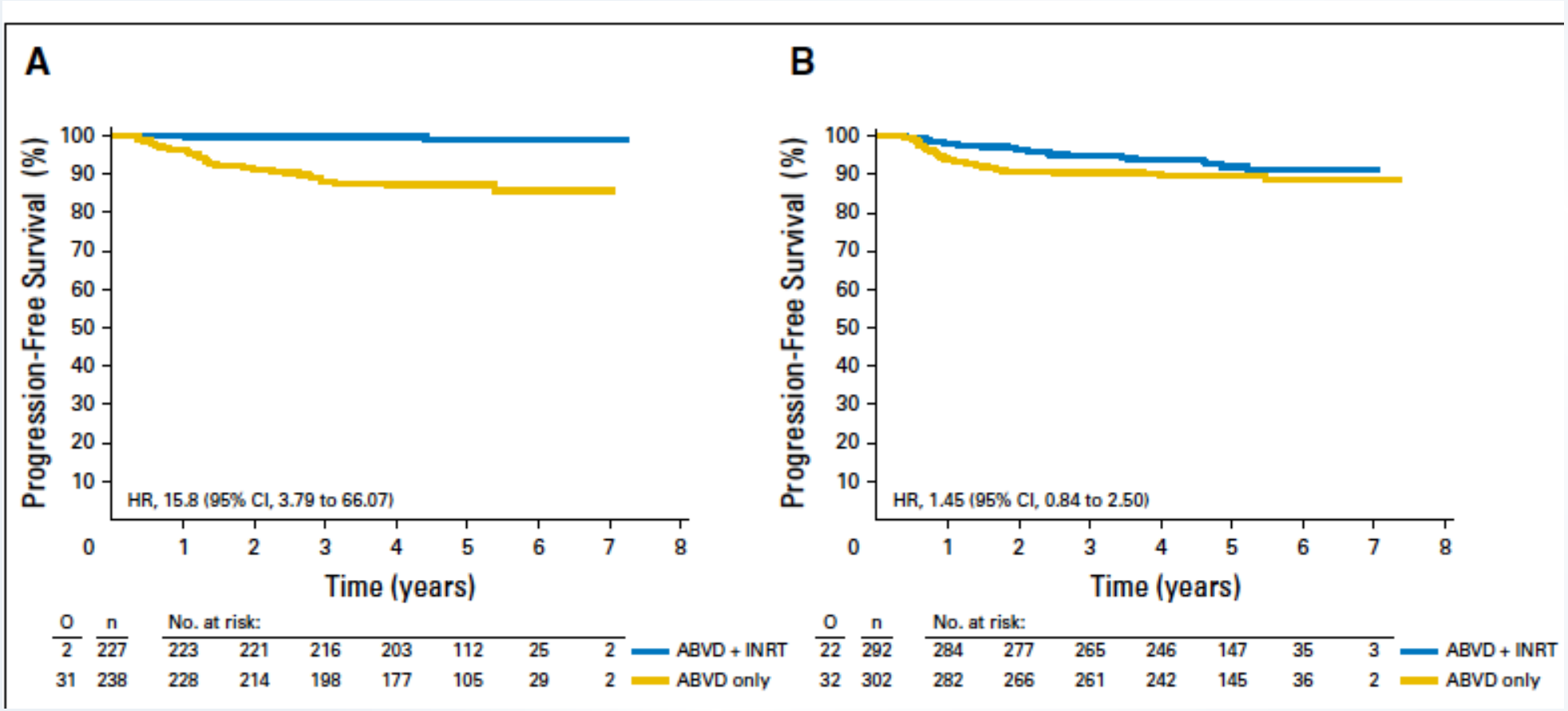


Andre et al JCO (2017) 35:1786

HD 10 PET negative patients (n=1059)

Favorable

Unfavorable

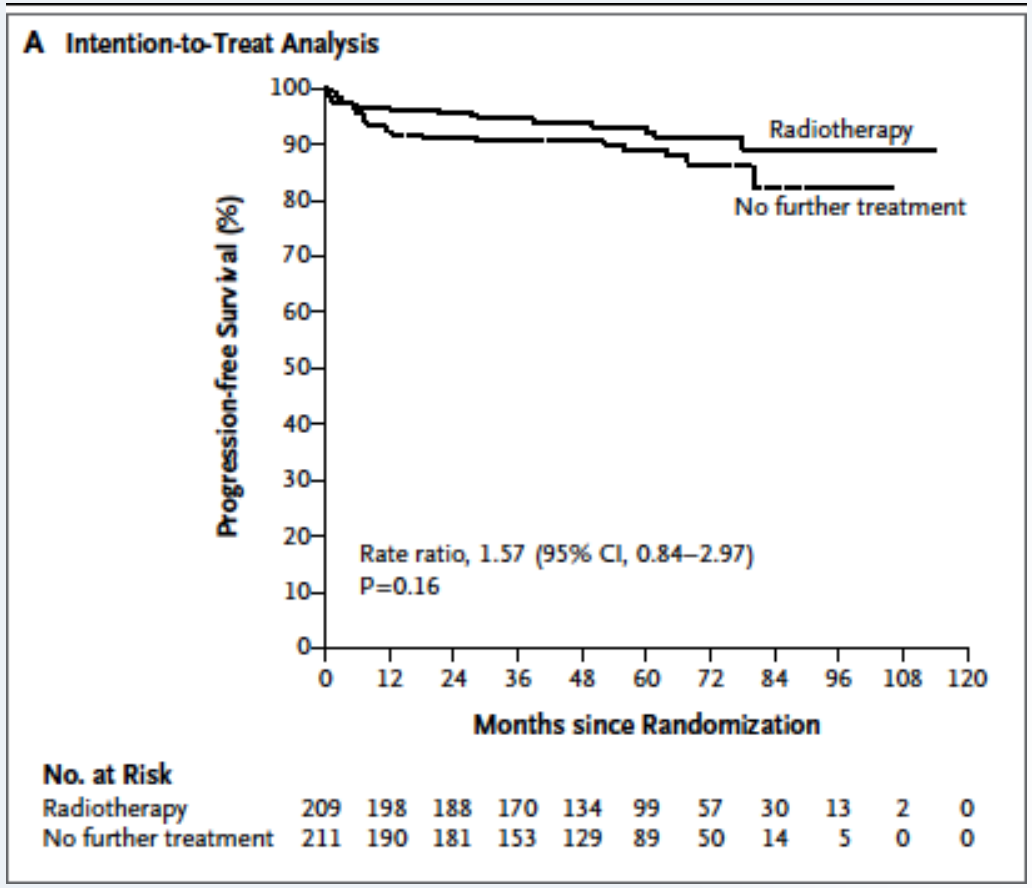


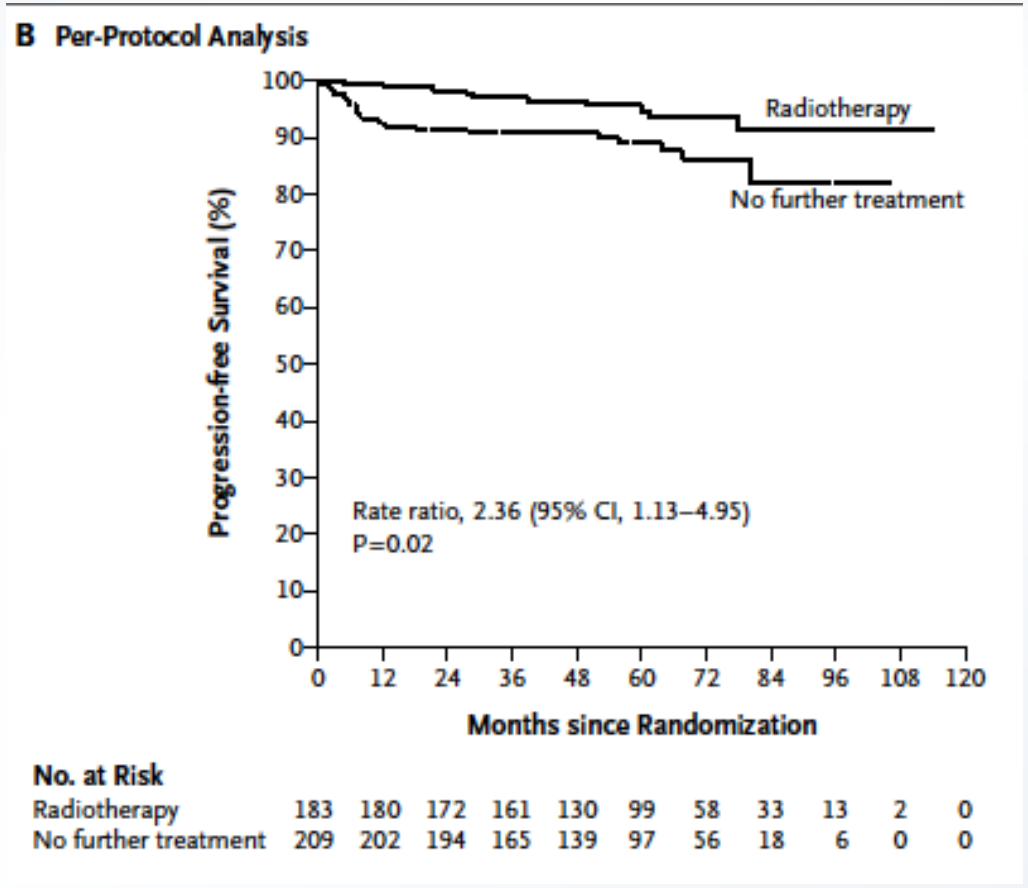
After ABVD x 2 and negative PET, pts had 2 (favorable) or 4 (unfavorable) more cycles of ABVD and +/- INRT
In chemotherapy alone group favorable had ABVD x 4 and unfavorable had ABVD X 6

Andre et al JCO (2017) 35:1786

“Rapid” Study

John Radford



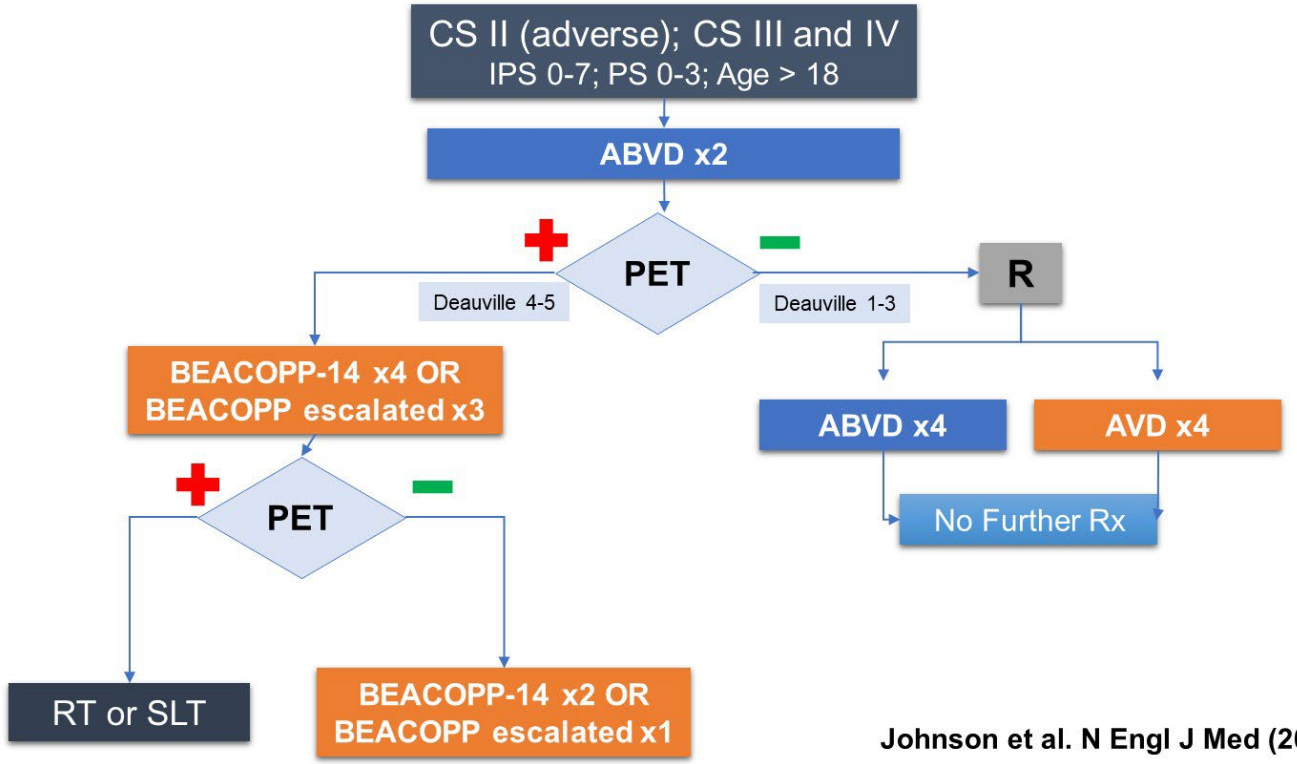


n= 420 ITT (A)
n=392 per protocol (B)
Data for PET negative patients

Radford, J et al NEJM (2015) 373:17

2016: PET-adapted RATHL – balance of efficacy and toxicity

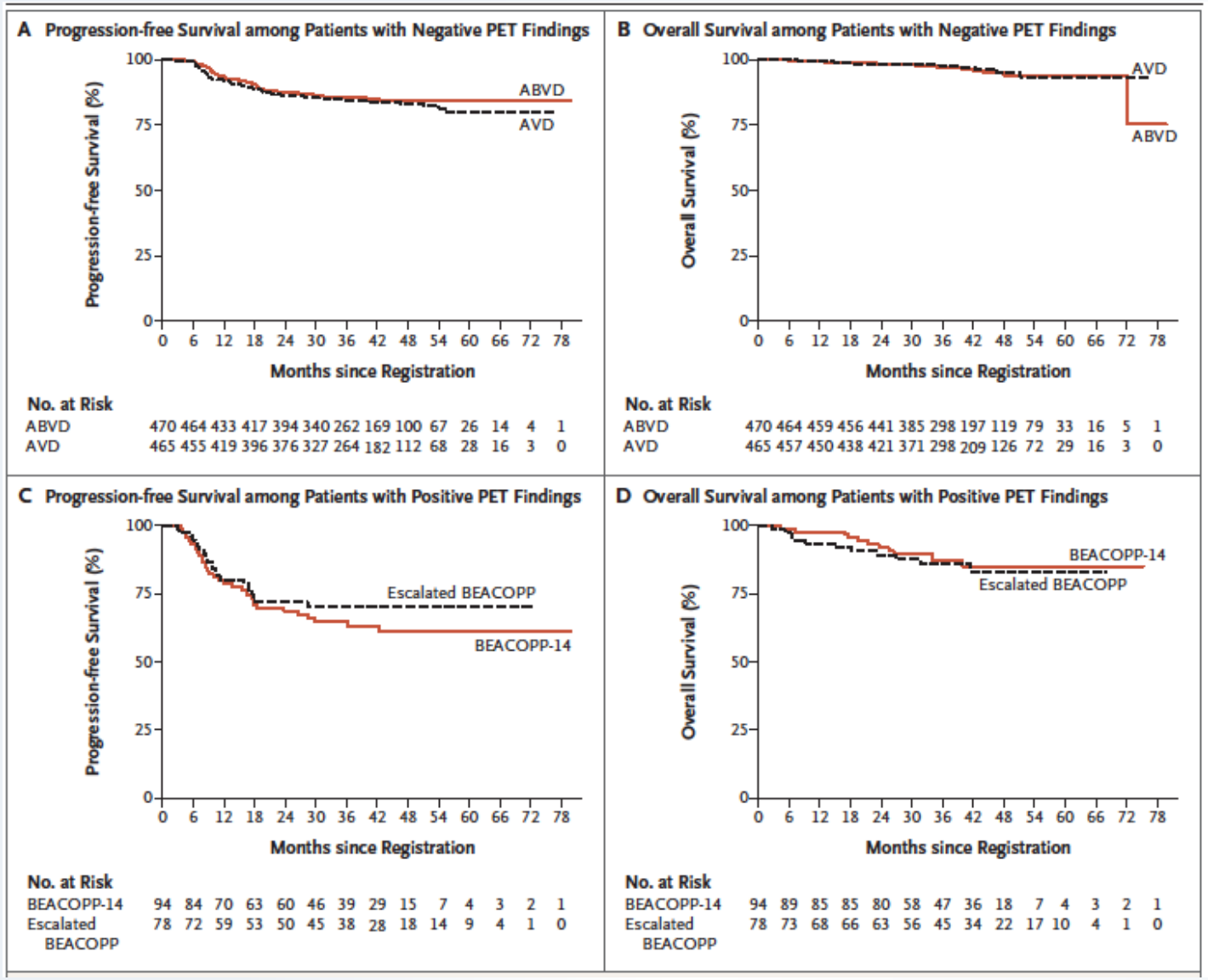
2016: PET-adapted RATHL – balance of efficacy and toxicity



Johnson et al. N Engl J Med (2016) 374: 2419-2429

Peter Johnson

"Rathl" Study



Johnson et al NEJM (2016) 374:25

Studies of the GHSG (1987-2024)

Early Stage 2001-2019

HD 4, 7, 10, 13, 16

Volker Diehl

HD4: 40Gy EF, 40EF + 10 IF
HD7: 30Gy EF + 10 Gy IF
2 x ABVD + 30 +10
HD 10: 4 x ABVD + 30 IF vs 20 IF
2 x ABVD + 30 IF vs 20 IF
HD13 30 Gy IF + 2 x ABVD vs 2 x ABV vs 2 x AVD vs 2 x AV
HD16: 2 x ABVD PET +/– 20 Gy IF vs 2 x ABVD PET + 20Gy IF and PET – No RT

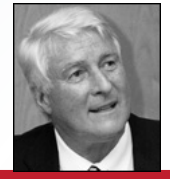
M Fuchs

Advanced Stage 2003-2011

HD 3, 6, 9, 12,15,18, 21

HD3: 3 x COPP + various RT doses and CEVD chemotherapy
HD6: 4 x COPP/ABVD vs COPP/ABVD/IMAEP + 30Gy bulk, 40Gy residual
HD9: 4 x COPP/ABVD + 30 Gy bulk and 40Gy residual; 8 x BEACOPP + 30 Gy bulk and 40Gy residual; 8 x escBEACOPP + 30Gy bulk 40Gy residual
HD12: 8 x escBEACOPP +/- RT; 4 x escBEACOPP+ 4 BEACOPP + 30Gy; 4 x escBEACOPP+ 4 x BEACOPP and no RT

Volker Diehl



P Borchman

Intermediate Stage 1987- 2010

HD 1,2,5,8,11,14

A Engert

P Borchman

P. Brockelmann

M Fuchs

B. VonTreskow

HD1: 2 x COPP/ABVD + 40Gy
vs 20 Gy EF + 20Gy bulk
HD2: 40Gy TNI, 3 x COPP/ABVD + 20Gy IF and 40 on bulk
HD5: 2 x COPP/ABVD + 30 Gy EF and 40 bulk; 2 x COPP/ ABV /IMEP + 30 Gy IF and 40 bulk
HD8: 2 x COPP/ABVD + 30 Gy EF + 10 Gy bulk; 2 x COPP/ABVD + 30 Gy IF + 10 on bulk
HD 11: 4 x ABVD + 30 vs 20 Gy IF; 4 x BEACOPP _ 300 vs 20 IF
HD 14: 4 x ABVD + 30 Gy IF; 2 x escBEACOPP + 2 x ABVD + PET + 30Gy IF; 2 x esc BEACOPP+ 2 x ABVD + PET+ 30Gy, PET neg no RT

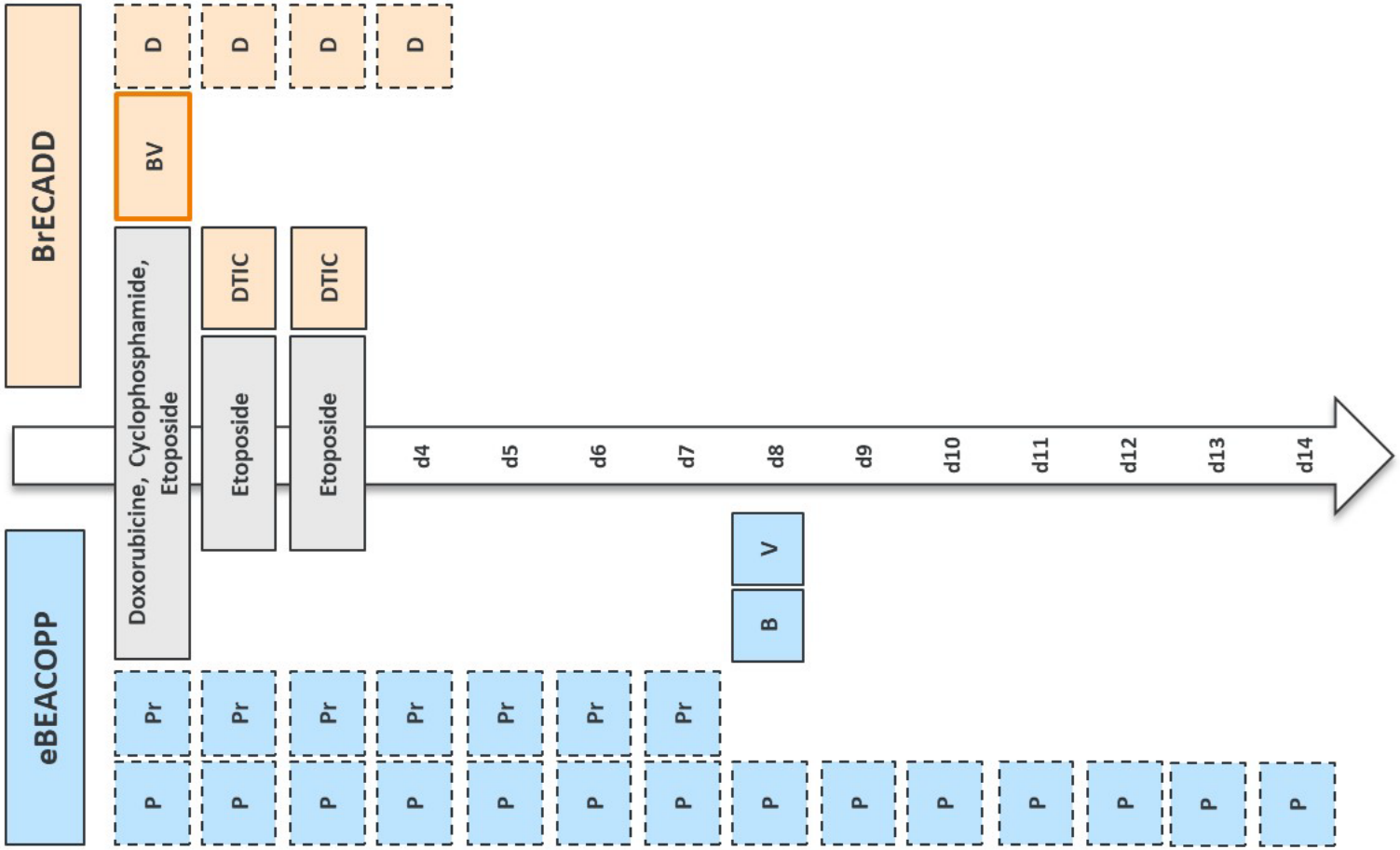
Advanced Stage 2011-2024 (Introducing PET based Rx)

HD15: 8 x escBEACOPP + RT to residual 2.5cm,vs 6 x escBEACOPP + 30Gy 2.5 residual vs 8 x BEACOPP14 + 30Gy to 2.5 residual
HD18: 3 x escBEACOPP + 3 x escBEACOPP + Rituxan + 30Gy + PET guided to 2.5 residual; 6 x escBEACOPP vs 4 x escBEACOPP + 30Gy to 2.5 residual
HD21: BrECADD vs escBEACOPP

A Engert

P Borchman

GHSG HD21 remodeling “eBEACOPP” to “BrECADD”



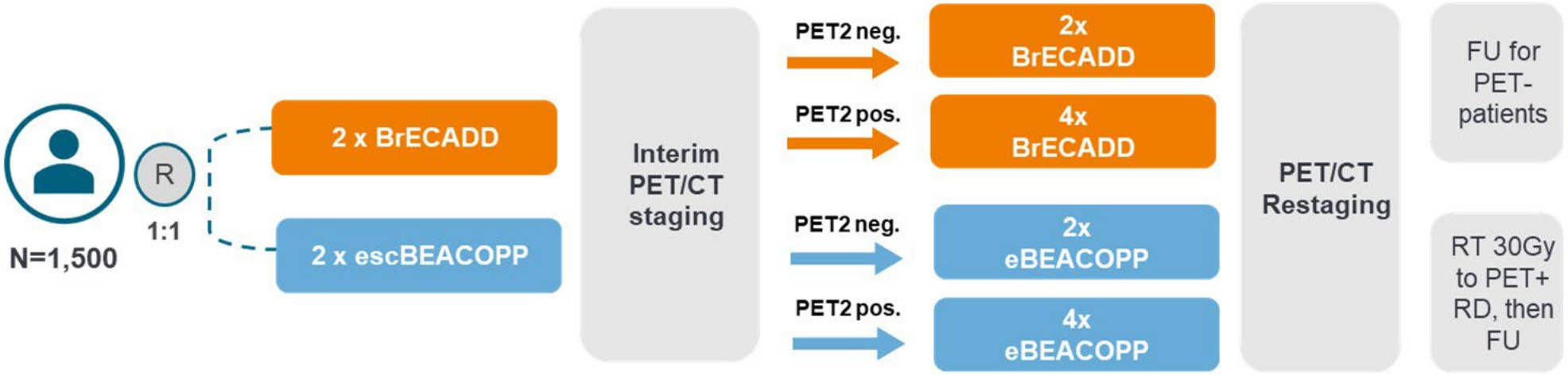
- The Kairos backbone **doxorubicin, cyclophosphamide, etoposide** was retained
- Introducing **Brentuximab Vedotin** (BV), **therefore omitting Bleomycin** (B, **pulmonary toxicity**) **and Vincristin** (V, **neuropathy**)
- Replacing **Procarbazine** (Pr) with the **less geno- and gonadotoxic Dacarbazine** (DTIC)
- Replacing 14 days of **Prednisone** (P) to 4 days of **Dexamethasone** (D)

GHSG

Borchman et al Lancet 2024; 404: 341

GHSG HD21 study design and primary endpoints

HD21 is an international randomized, open-label, phase 3 study of BrECADD versus eBEACOPP in adult patients < 60 yo with previously untreated, AS-cHL



Co-primary objectives:

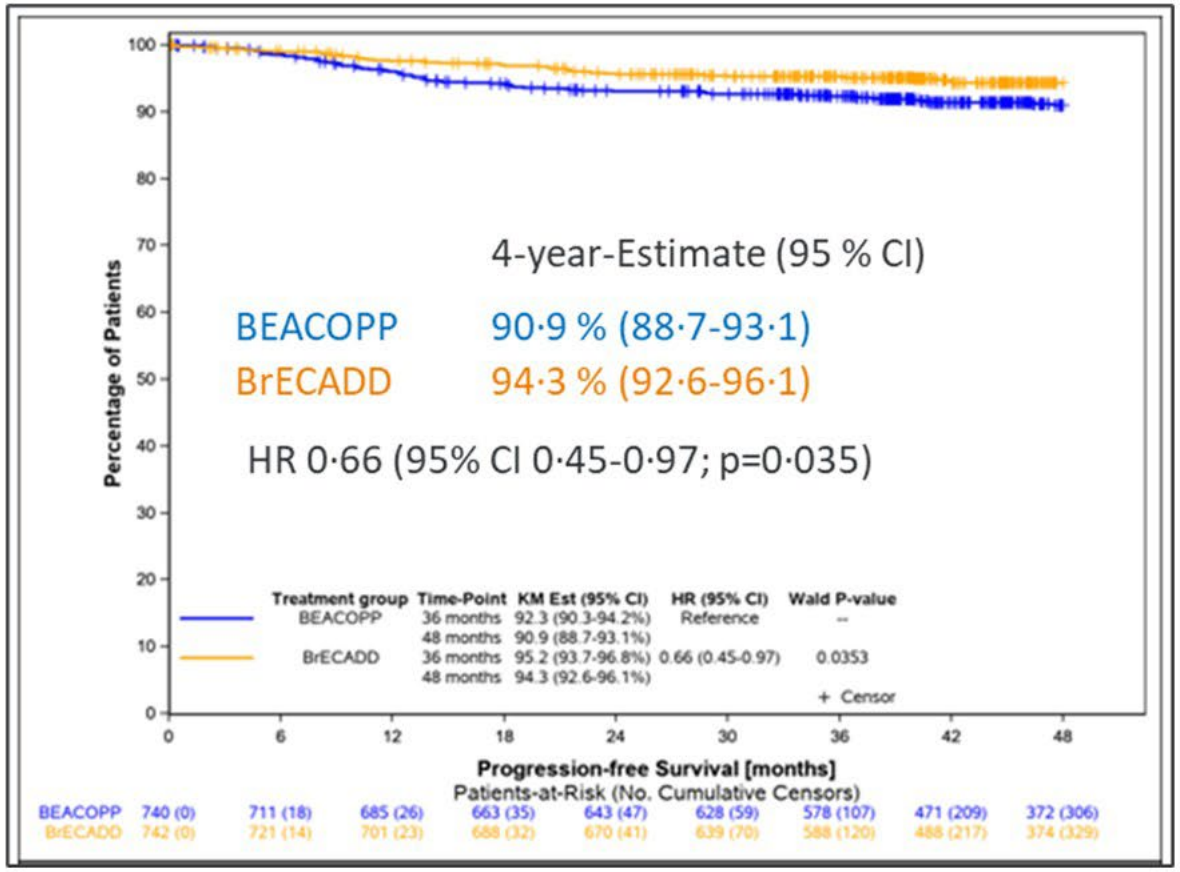
- Demonstrate **superior tolerability** defined by treatment-related morbidity (TRMB) with BrECADD.
- Demonstrate **non-inferior efficacy** of 4-6 x BrECADD compared with 4-6 x BEACOPP determined by PFS (NI margin 6%, HR to be excluded 1.69)

GHSG

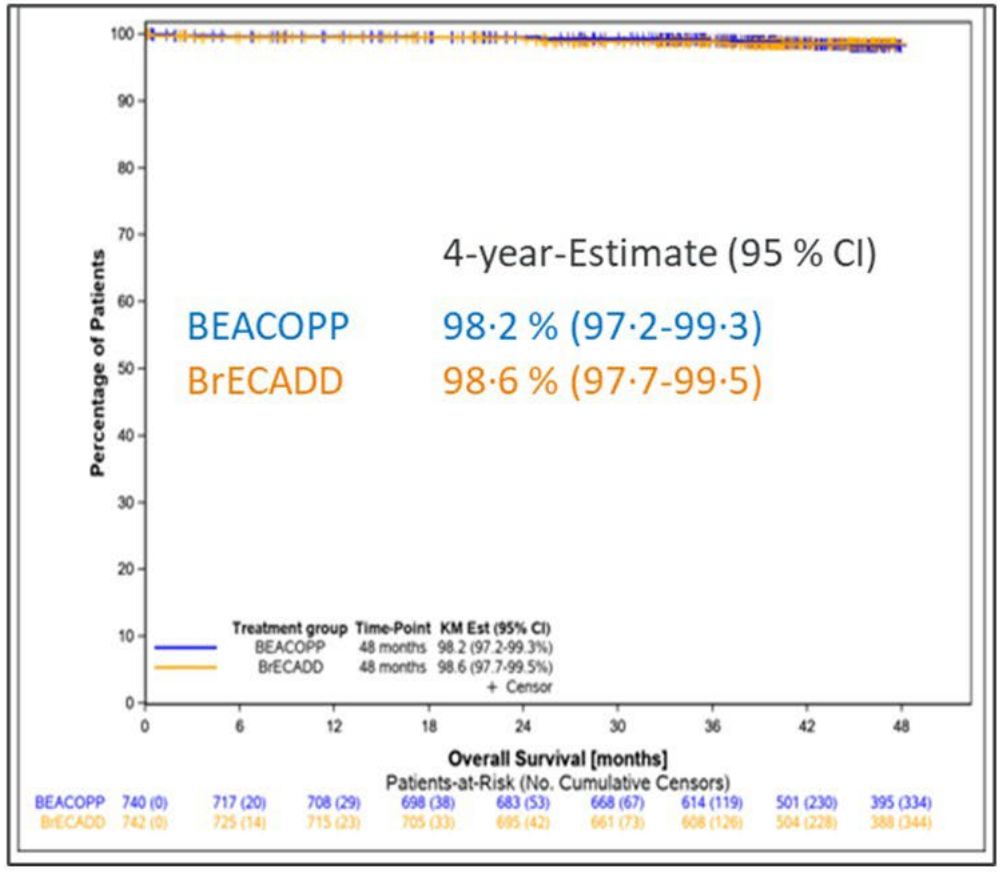
Borchman et al Lancet 2024; 404: 341

HD21 final analysis: BrECADD is superior to eBEACOPP (mFU 48 m)

Progression-free survival



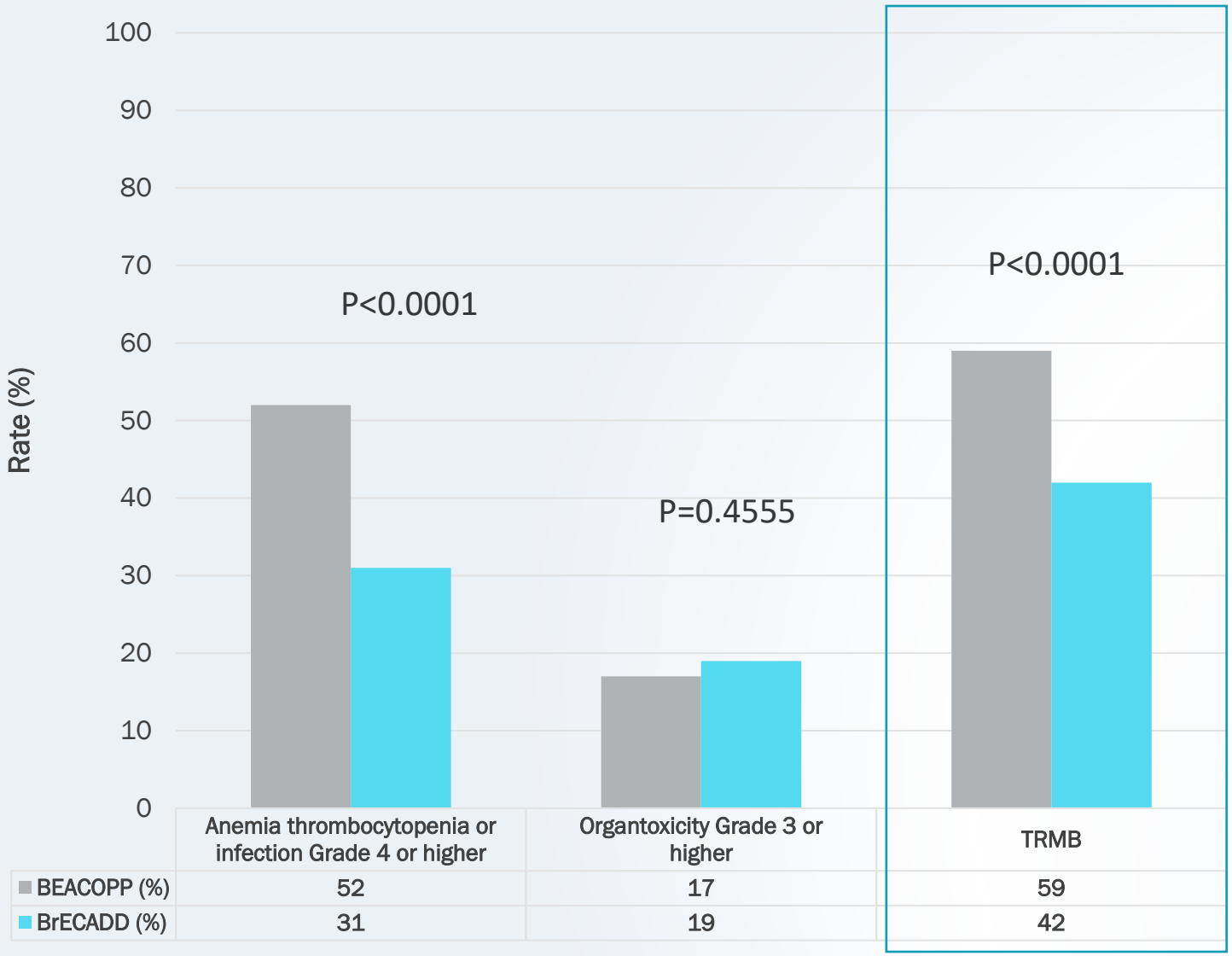
Overall survival



GHSG

Borchman et al Lancet 2024; 404: 341

HD21: Reduced TRMB with BrECADD



Additionally: BrECADD vs eBEACOPP

- ↓ Ery transfusions (24% vs 53%)
- ↓ Thromb transfusions (17% vs 34%)

- ↓ PNP (38% vs 49%, ≥°2 7% vs 16%)

- ↓ TR mortality: 0% vs <1%

- ↓ FSH values (= ↑ gonadal function):
  - ♀ 13.4 U/l vs 27.2 U/l (REF <21.6)
  - ♂ 11.9 U/l vs 20.5 U/l (REF <12.5)

Borchman et al Lancet 2024; 404: 341

GHSG HD21 key findings

- The HD21 study has challenged the SOC eBEACOPP with the novel BrECADD regimen for advanced stage classic Hodgkin lymphoma. We report the final analysis of this international randomized phase III trial with 1.500 patients and a mature median follow-up of 48 months. We found that

1. **BrECADD is more active than eBEACOPP** reaching
   - an unprecedentedly high 4-year PFS of 94.3%
   - with most patients (64%) receiving only 4 cycles (i.e. 12 weeks) of treatment.

2. **BrECADD is better tolerated than eBEACOPP:** TRMB relative risk 0·72 (p<0·0001) with
   - resolution of TRMB events in > 99% of patients at 12 months follow-up
   - a clinically highly relevant reduction of neuropathy and gonadal dysfunction

➢ PET2-guided individualized BrECADD has a very favourable risk-benefit ratio. We thus recommend it as **standard treatment option for AS-cHL.**

GHSG

Borchman et al Lancet 2024; 404: 341

My Take on BreCADD vs BEACOPP

- Logical, sequential approach
- Keep the Adriamycin, cyclophosphamide, etoposide backbone
- Add Brentuximab and drop Bleomycin and Vincristine
- Substitute DTIC x 2 days for Procarbazine x 7 days to reduce 2nd malignancy and fertility concerns
- Dexamethasone x 4 days instead of Prednisone x 14
- An excellent option for advanced stage cHL
- 64% had only 4 cycles based on PET 2 data
- Who are the ideal candidates for this approach?

Second Cancers after cHL treatment[6]

- Breast cancer most common[1]
- Absolute excess risk was 22.9 (range 1.1-174) cases/10K person years[2]
- Risk by age 50 was 35%, while in BRCA1 and BRCA2 mutation carriers was 31% and 10% respectively[3]
- Age at cHL treatment was most important risk factor (puberty highest)[2, 3]
- Combined modality highest risk; Interval 17.7 years (range 12.2-21.6)[4]
- Chemotherapy alone peak 5-9 years after treatment[5]

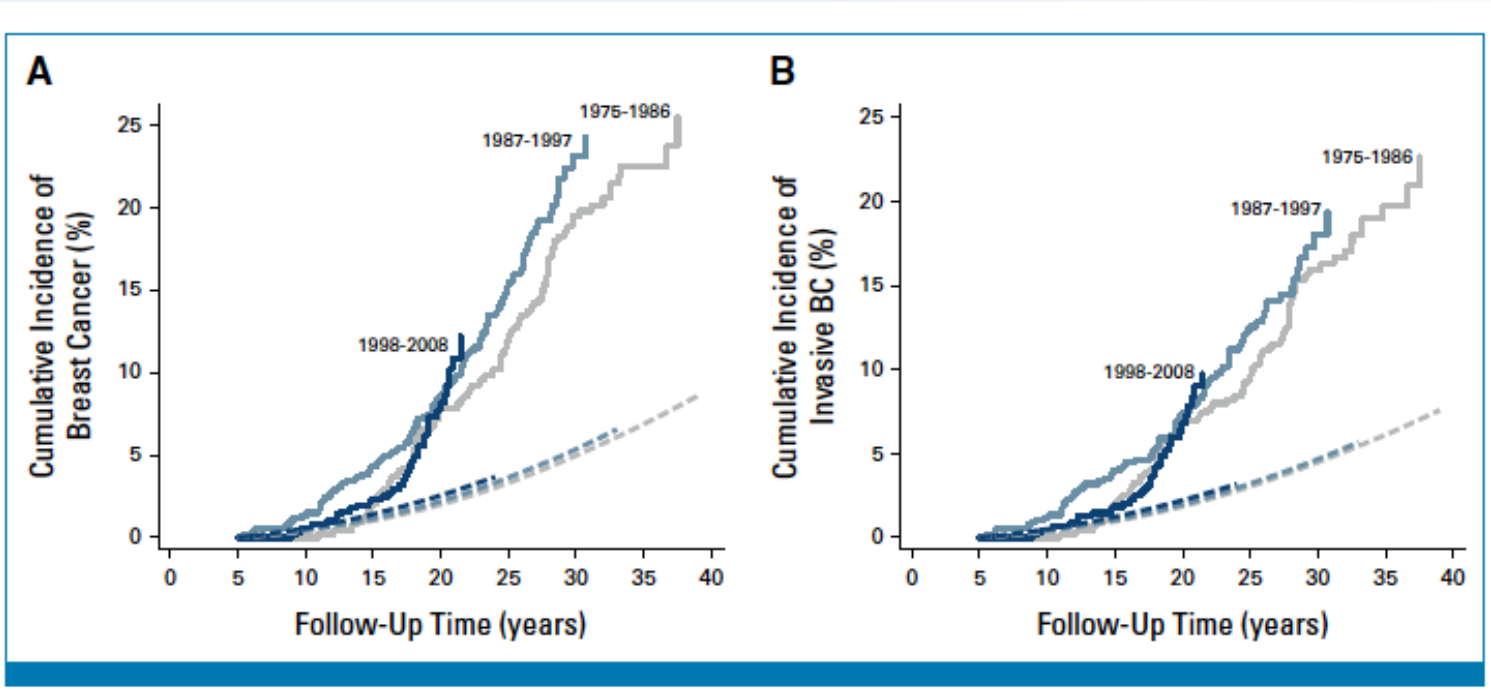
[1] Schaapveld et al NEJM (2015) 373:2499
[2] Ibrahim et al 2012 BMC Cancer (2012) 12: 197
[3] Moskowitz, CS et al 2017 JCO(2017) 37:2120
[4] Swerdlow et al JCO (2012) 30:2745
[5] Swerdlow et al JCO (2011) 20:4096
[6] Bakkach et al Crit Rev in Oncology/Hematology (2021)157:103175

Adriamycin Dose and Breast Cancer Risk in cHL

- n=1,964 female 5-year cHL survivors
- Treated between age 15-50
- 20 Dutch hospitals between 1975-2008
- Adriamycin exposure analysed using multivariable Cox regression analyses
- Median follow up 21.6 years (IQR 15.8-27.1 years)
- n=252 women developed invasive or ductal breast cancer
- 30-year cumulative incidence was 20.8% (95% CI 18.2-23.4)

Neppelenbroek et al JCO 2024; 42:1903-1913

Cumulative Incidence of Breast Cancer in female cHL survivor by treatment period



A) Solid lines = cumulative incidence of BC or DCIS Stratified by treatment period.

Dashed lines = expected incidence

B) Invasive BC excluding DCIS

Neppelenbroek et al JCO 2024; 42:1903-1913

Adriamycin Dose and Breast Cancer Risk in cHL

- BC risk increased 1.18-fold (95% CI, 10.5-1.32) per additional 100 mg/m^2 (P_{trend} =.005)

- Risk associated with Adriamycin was not modified by age at first treatment (HR < 21 years vs > 21 years was 1.5 vs 1.3 or chest RT (HR 1.9 vs 1.2 without or with mantle field

- > 1.5x risk of BC in those with>200 mg/m^2 Adriamycin vs none

Neppelenbroek et al JCO 2024; 42:1903-1913

Adriamycin, RT and Breast Cancer Risk in cHL

	Breast Cancer HR
Chest RT vs no Chest RT	2.99, 95% CI 1.28-6.99, p=0.0117
Adriamycin < 250/m^2 vs > 250/m^2	0.45, 95% CI 0.18-1.12, p=0.085

n=1089
1/1991 to 12/2018
Age: 12-60
Primary endpoint: overall cumulative incidence of breast cancer from anthracycline exposure to 12/2023

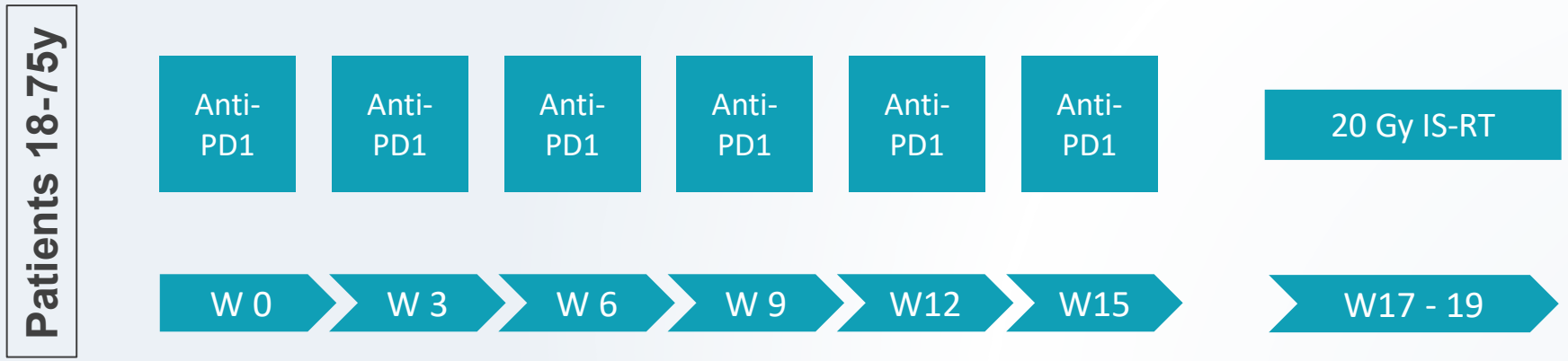
Machlab et al Abstract 4432 ASH 2024

When might BrECADD be an alternative to the “non-European” regimens for cHL?

- Strong family history of breast cancer or BRCA1 or BRCA2 mutations
- Autoimmune diseases when CPI might pose a problem
- Patients started on CPI who have significant autoimmune issues (rare so far in the US experience)

If local lymphoma control with RT using low intensity chemotherapy remains relevant, can we then maybe replace chemotherapy by PD-1 inhibition?

PREFER



Can we cure patients without chemotherapy?

Michael Fuchs

Contributions of the “European Regimens” to the management of cHL

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- Recent studies on BrECADD and importance of limited cycles