Frontline approaches for previously untreated Hodgkin lymphoma

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Conflicts of Interest

- I have no conflicts of interest

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Management challenges in HL

- Most patients will be cured.

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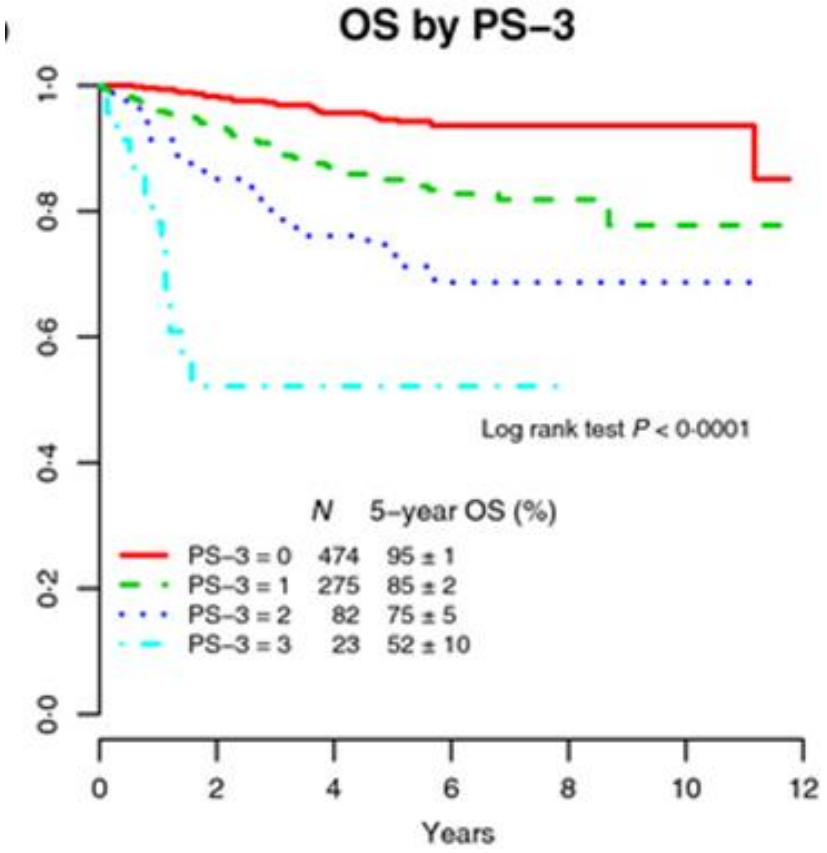
Management challenges in HL

- Most patients will be cured.
- Therapy is toxic.
- Ideal: precision approach
  - Limit therapy in patients with favorable disease
  - Escalate therapy only when necessary

Challenges to defining risk in advanced stage HL

- IPS 3, prognostic for FFP and OS:
  - Age
  - Stage
  - Hemoglobin

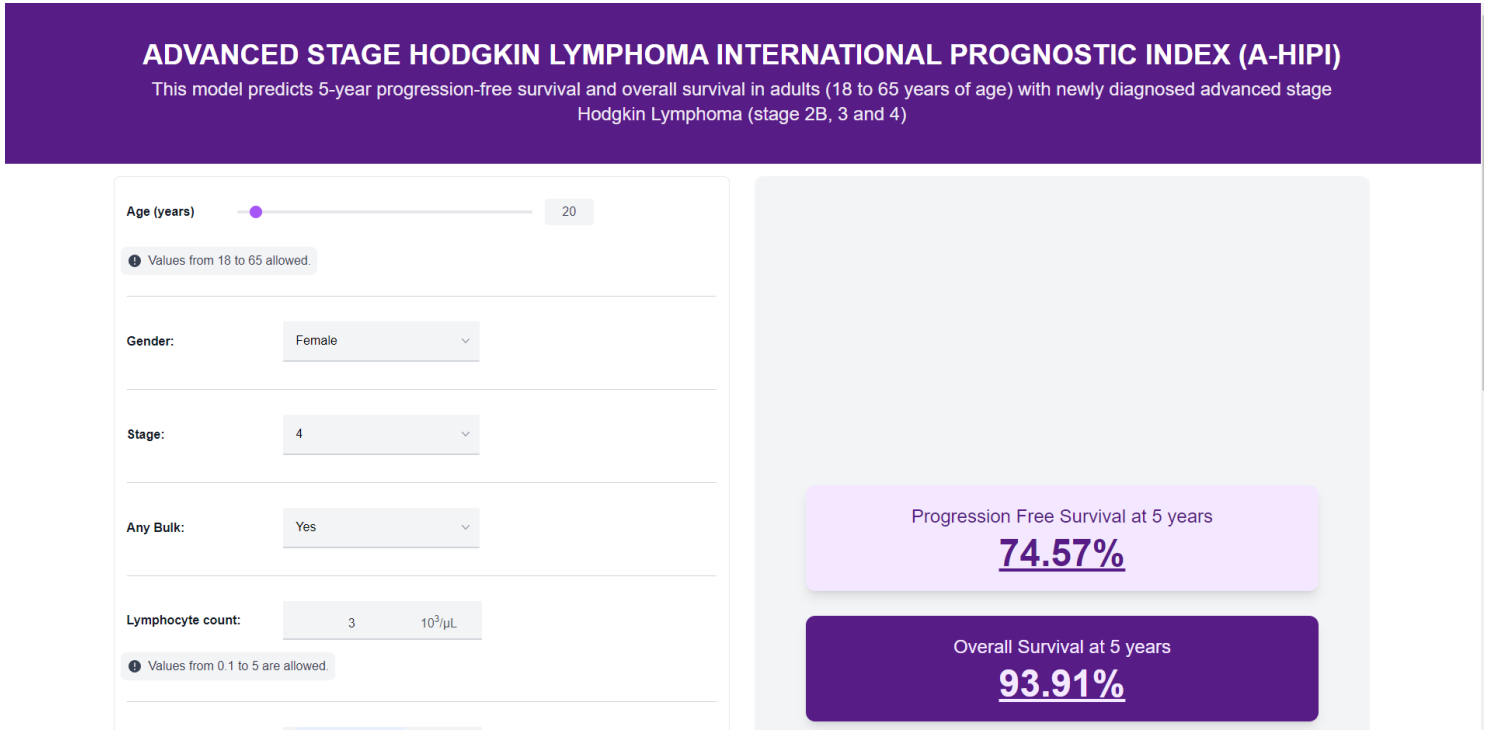
Only 3% of patients are in the high risk group for OS.



Diefenbach et al, BJH 171:530

A-HIPI prediction model: https://holistic-calculator.web.app/

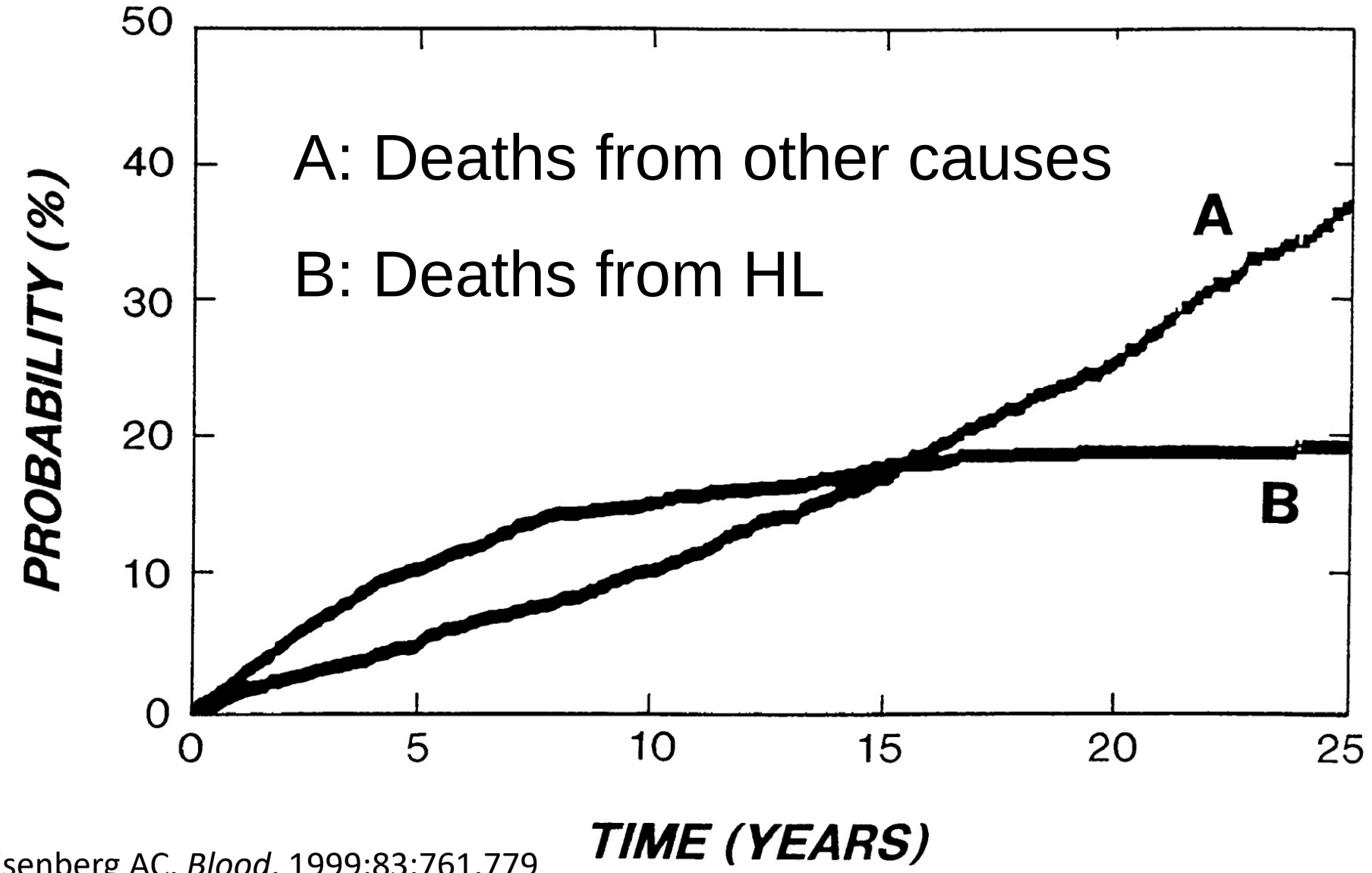
- Multivariable clinical prediction model to predict progression-free survival (PFS) and overall survival (OS) in advanced stage HL.
- Includes novel nonlinear relationships between age and absolute lymphocyte count (as continuous variables) with patient outcomes.
- A-HIPI had superior discrimination for OS and enhanced calibration for PFS and OS compared with the historic International Prognostic Score.



HoLISTIC

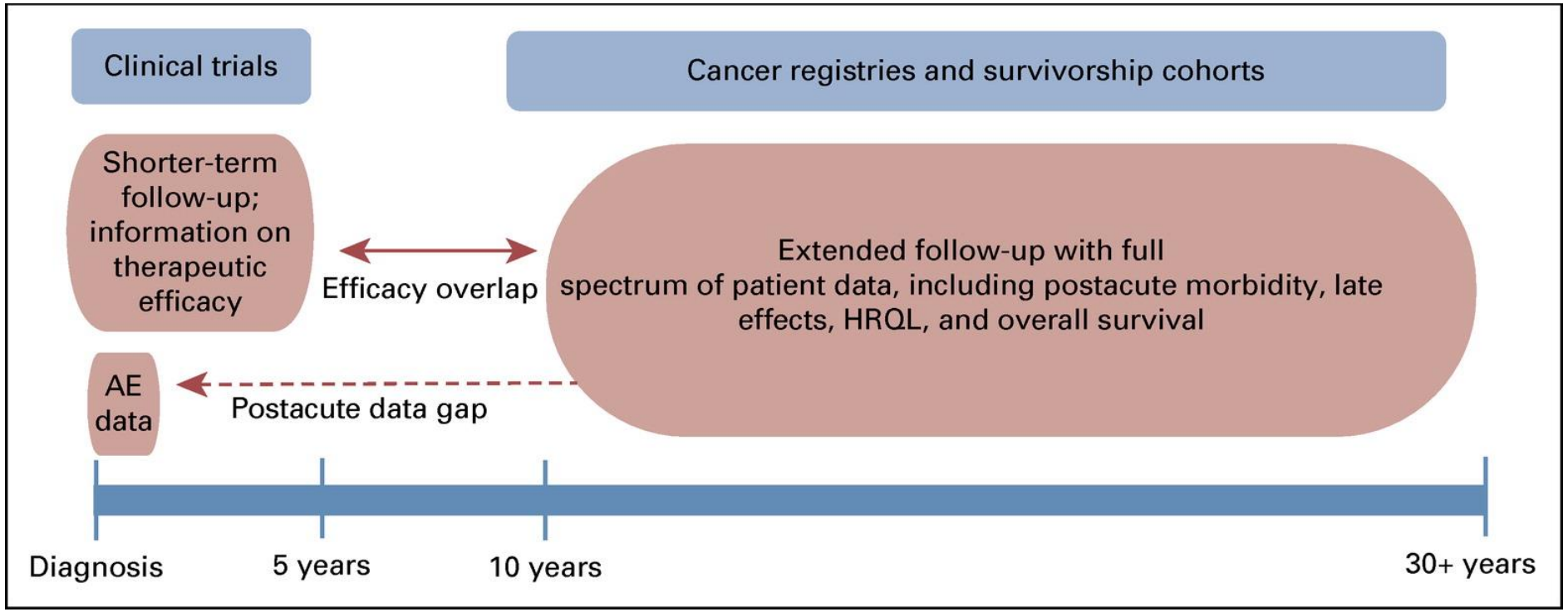
Rodday et al., *J Clin Oncol* 41:2076-86 2023

Late mortality after radiation therapy for HL



Aisenberg AC. *Blood*. 1999;83:761.779

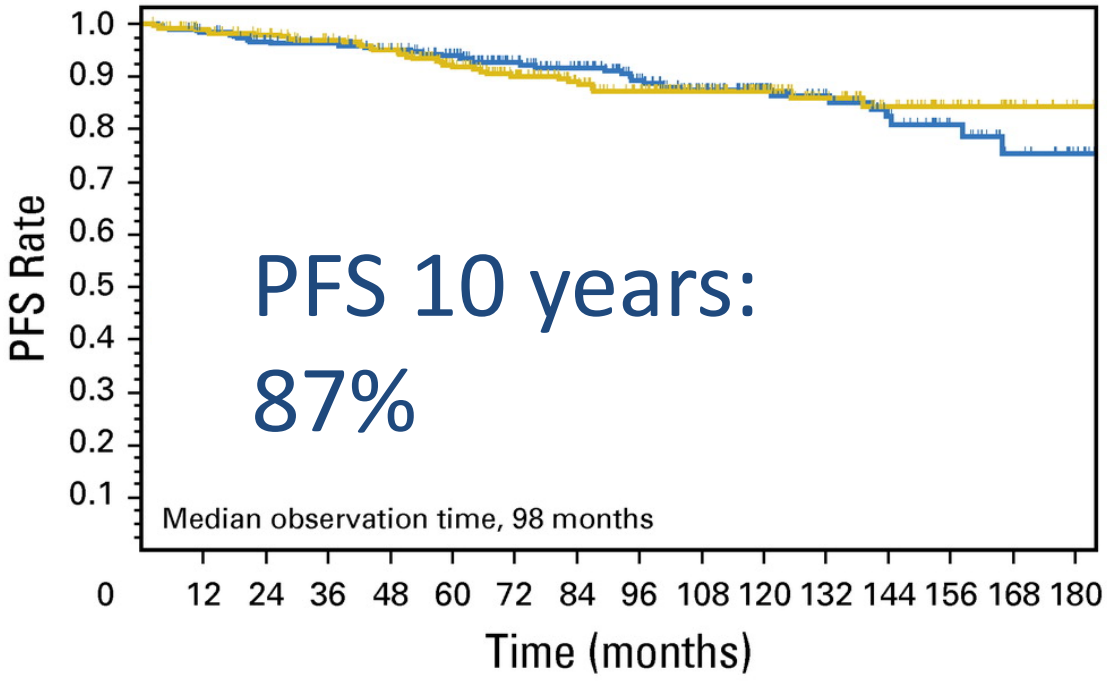
Challenges of studying HL: Need for long follow-up



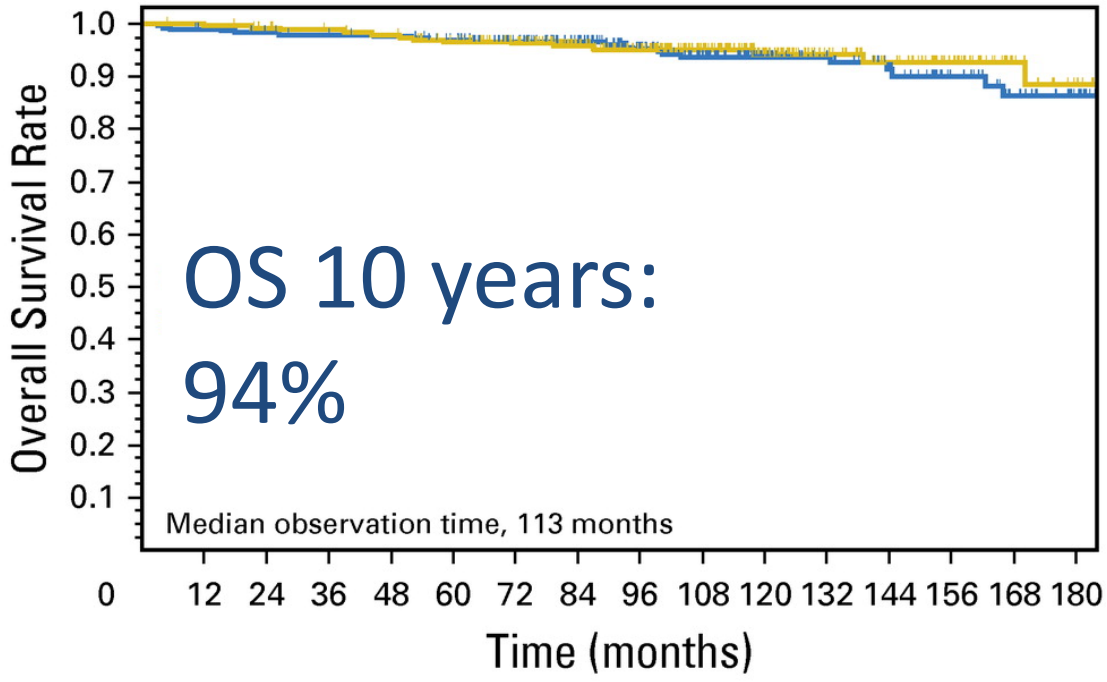
Evens and Parsons, *JCO* 38:4131-33 2020

Baseline outcomes for patients with HL

Mature outcomes for early stage favorable HL
HD10: ABVD x 4 + 30 Gy vs. ABVD x 2 + 20 Gy



PFS 10 years:
87%



OS 10 years:
94%

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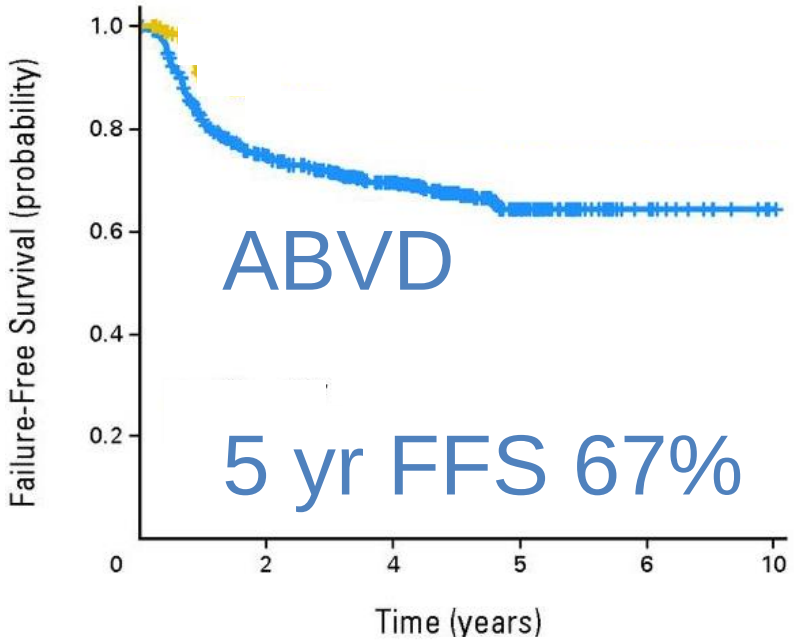
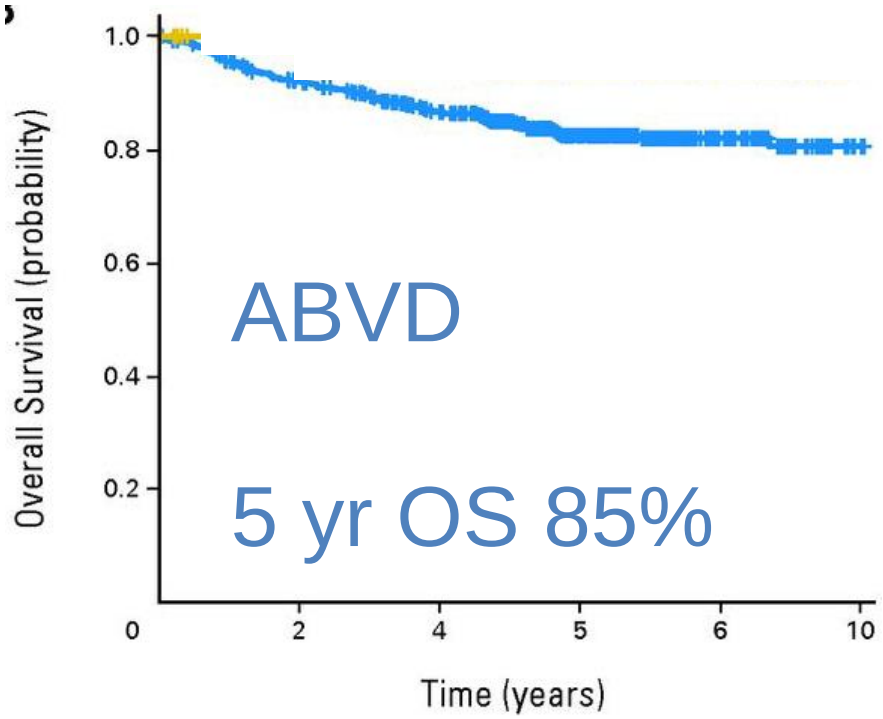
Sasse et al, *JCO* 35: 1999-2007 2017

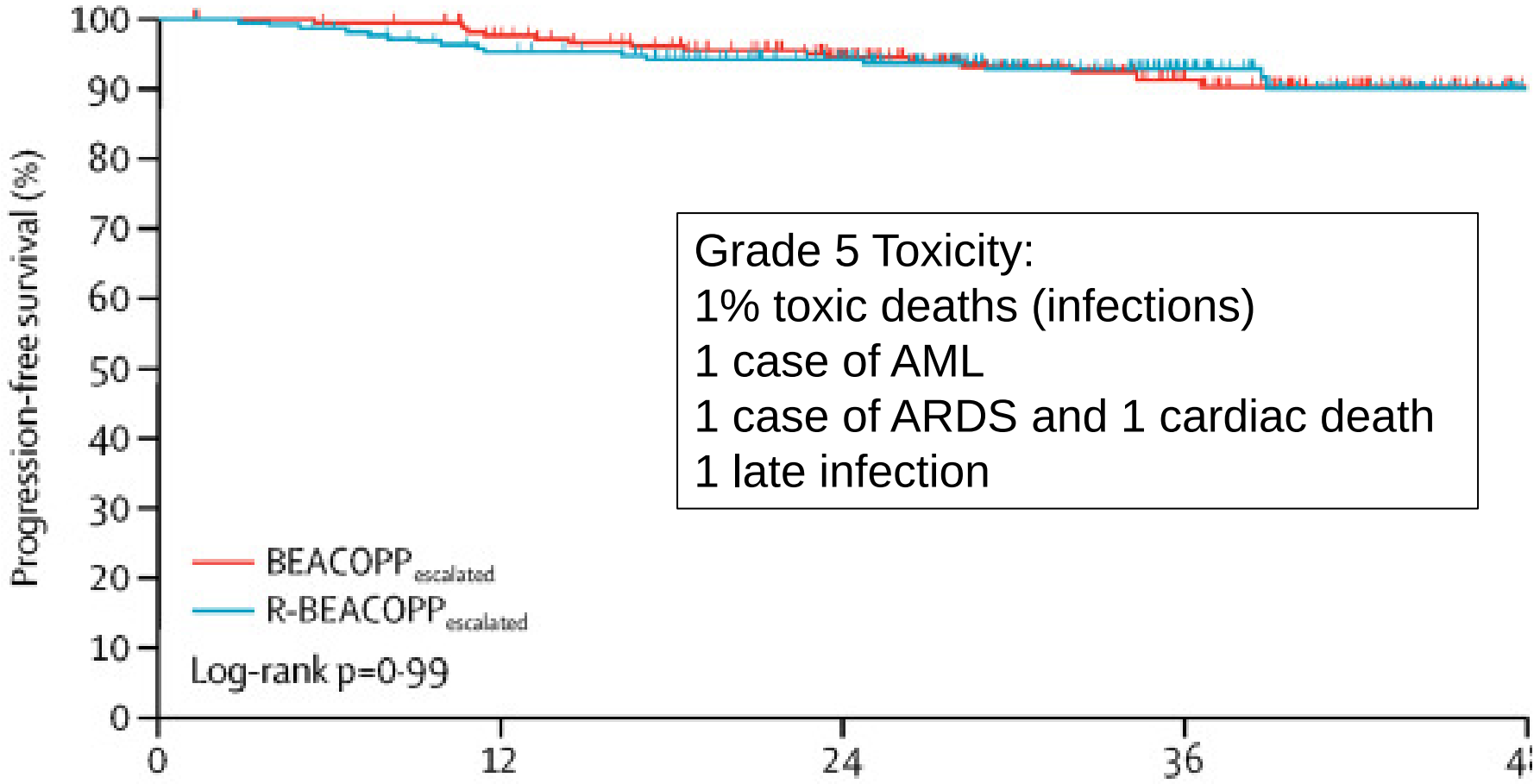
Mature outcomes for advanced HL





Gordon et al, *JCO* 31: 684 2013

BEACOPP HD18 PFS



Grade 5 Toxicity:
1% toxic deaths (infections)
1 case of AML
1 case of ARDS and 1 cardiac death
1 late infection

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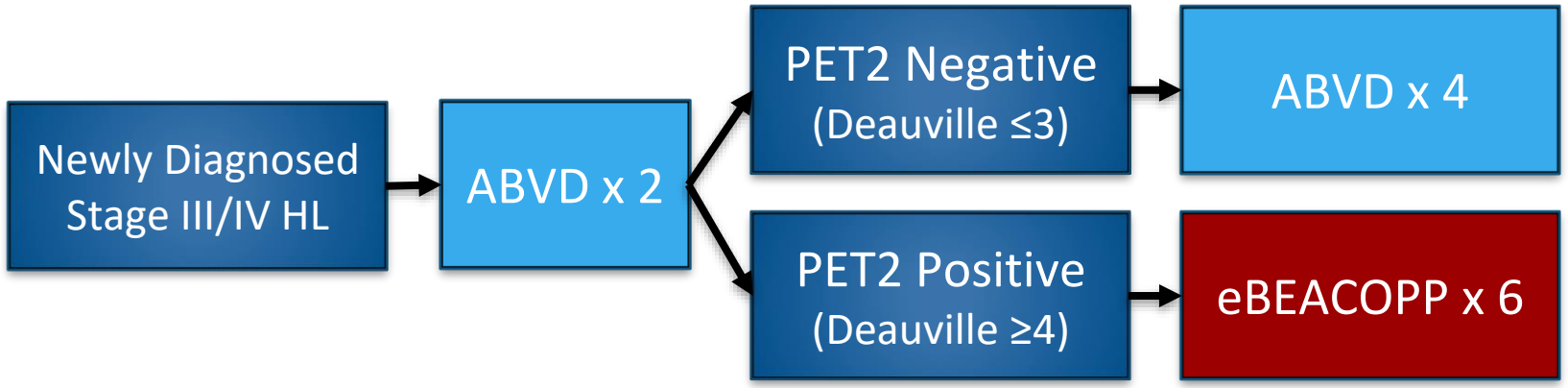
Borchmann et al. *Lancet* 390:2790 2017

Improving outcomes with response adaptation

S0816 HL Treatment Schema



Primary endpoint: 2-year Progression-Free Survival (PFS)

- Overall Goal: Improve from 70% to 78%
- Goal for PET2 +: Improve from 30% to 48%

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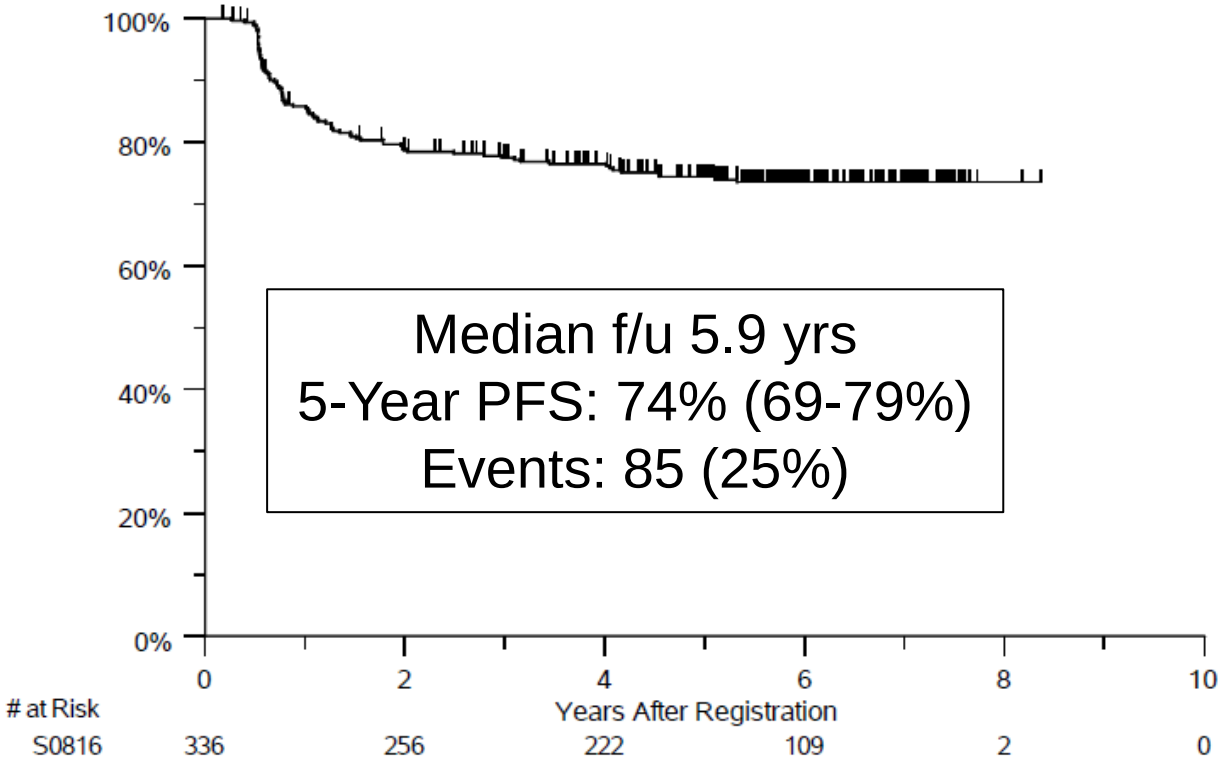
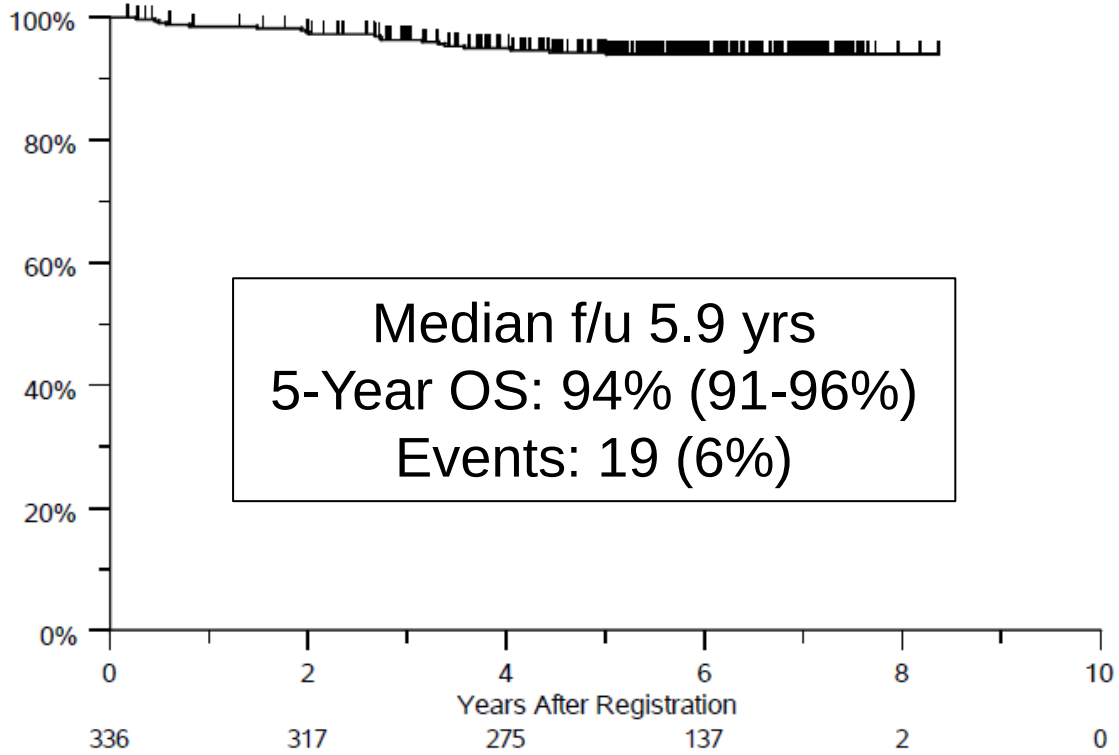
Press et al., *JCO* 34:2020-7, 2016

S0816 advanced stage HL Long-term follow-up: Limitations of a PET-adapted approach





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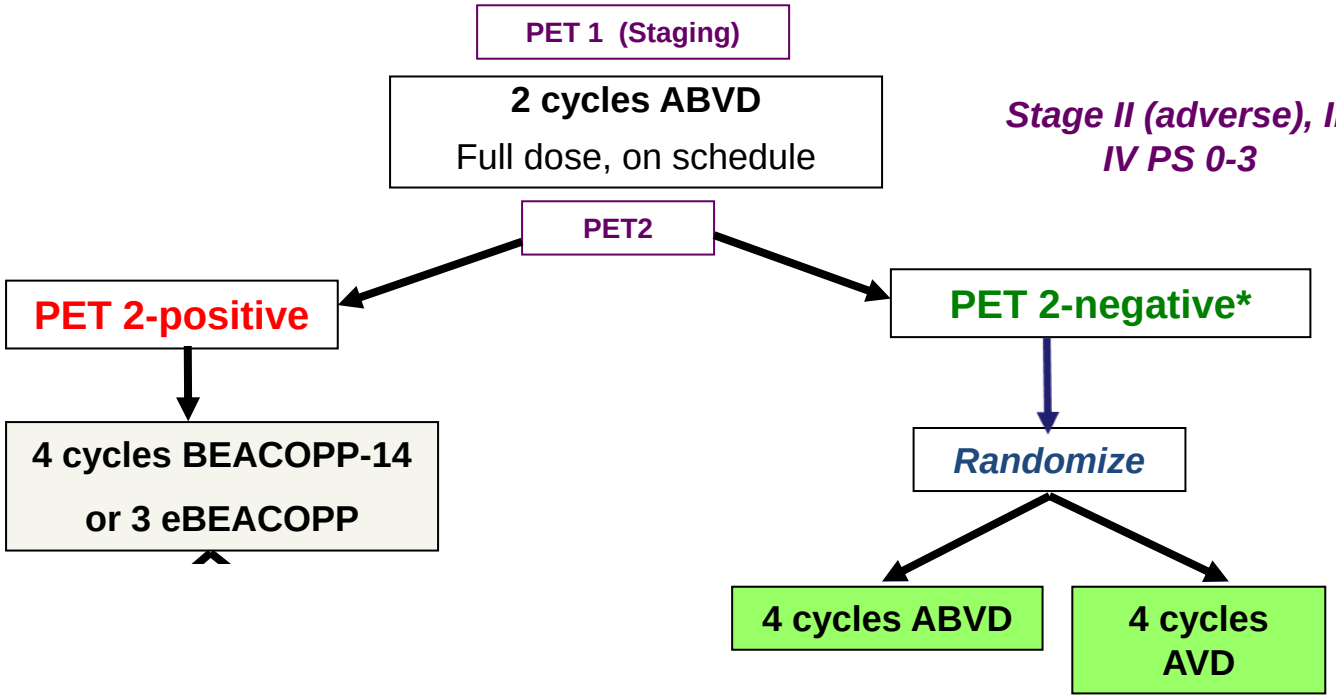
Stephens et al., *Blood* 134:1238-1246 2019

RATHL study: PET adaptation for advanced stage HL



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Johnson et al., *NEJM* 374:2419 2016

Summary: recent response-adapted trials in advanced stage HL

- RATHL: Eliminating bleomycin for PET-2 negative patients after ABVD is safe and does not impact efficacy.

- PET adaptation is not final answer for ABVD-treated patients, as 20% of patients treated with a PET-adapted approach still relapse; majority of whom are PET-2 negative.

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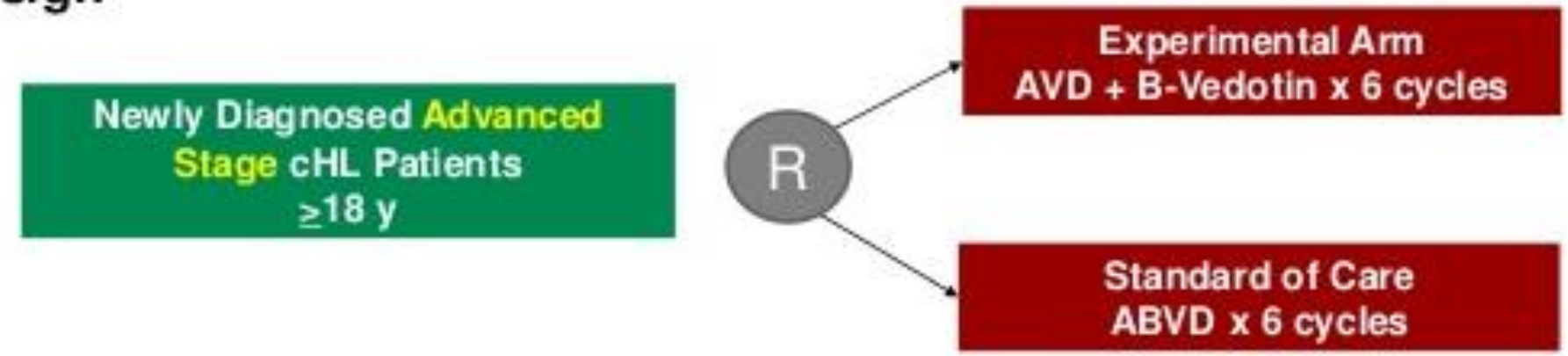
Improving outcomes with incorporation of novel agents

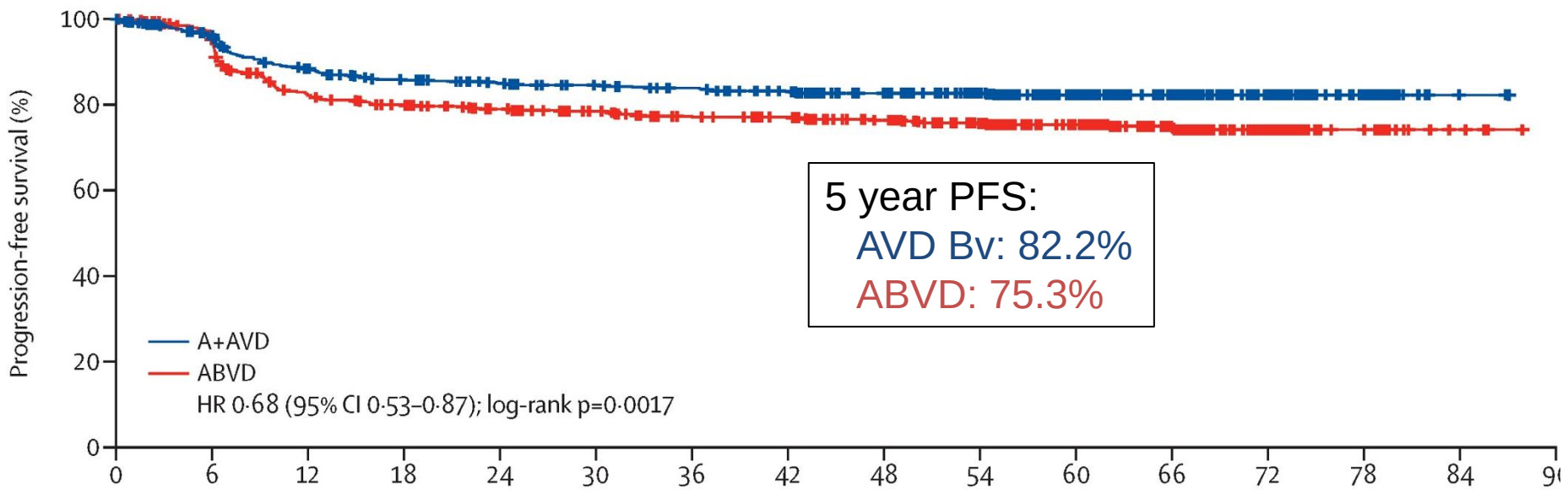
ECHELON-1 advanced HL: AVD-brentuximab versus ABVD

Design



Connors et al. *NEJM* 378:331 2018

Echelon-1: Long-term follow-up



5 year PFS:
AVD Bv: 82.2%
ABVD: 75.3%

Second cancers (n):
AVD Bv: 19
ABVD: 29

Pregnancies/partner pregnancies:
AVD BV: 44/31
ABVD: 26/30

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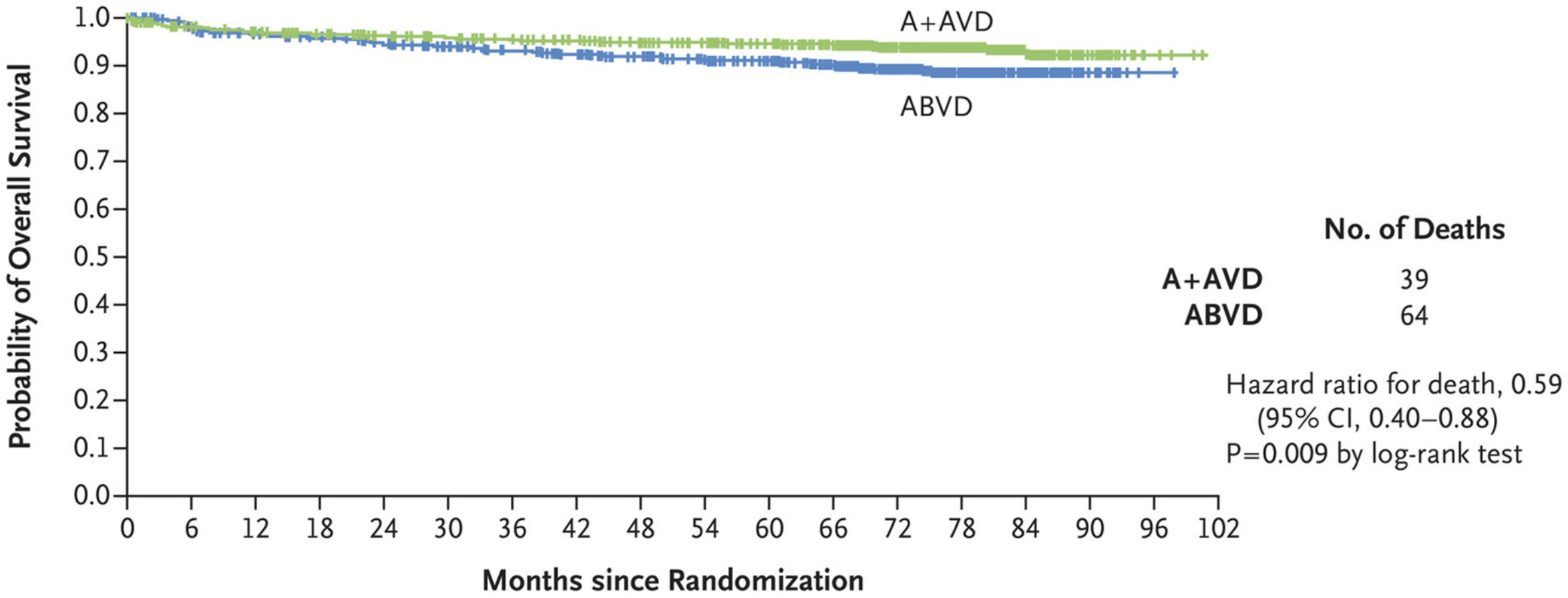
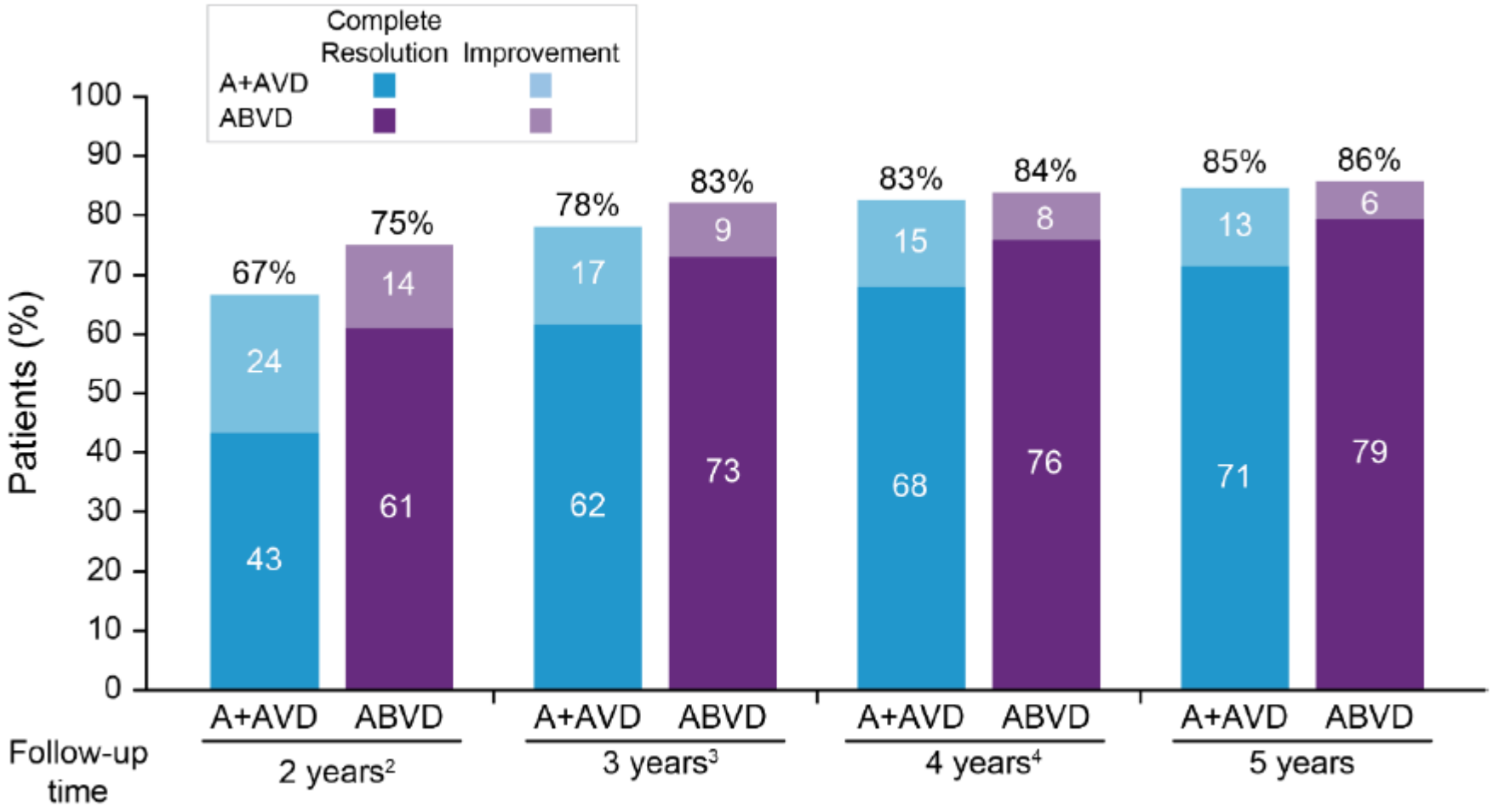
Straus et al, *Lancet Haem* 85:e410-21 2021

Echelon-1: Overall survival



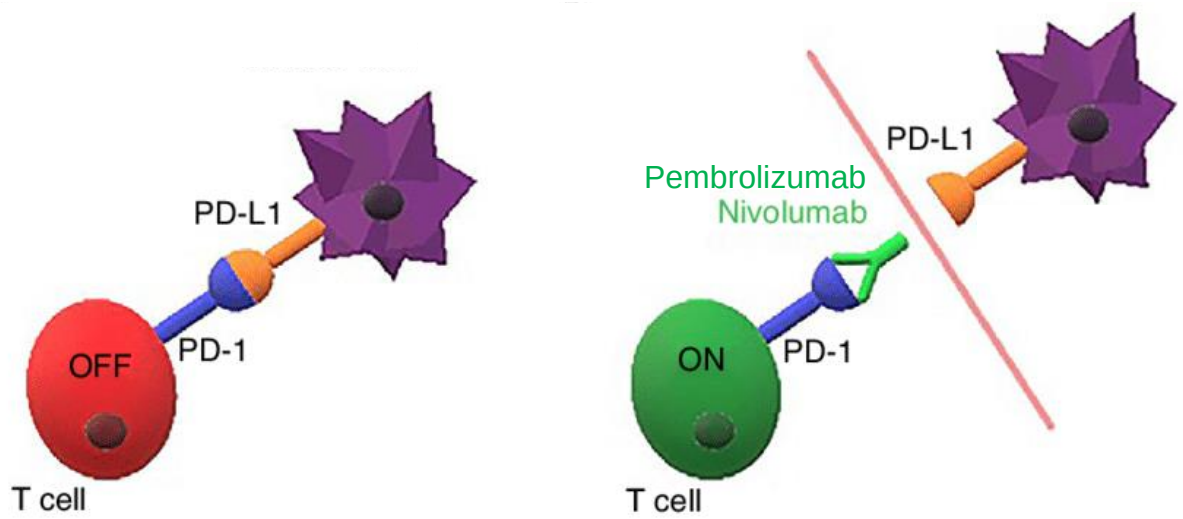
Ansell et al, *NEJM 387*:310-20 2022

Echelon-1: Neuropathy

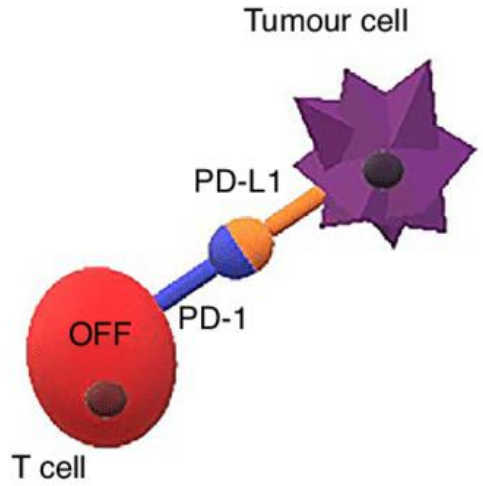


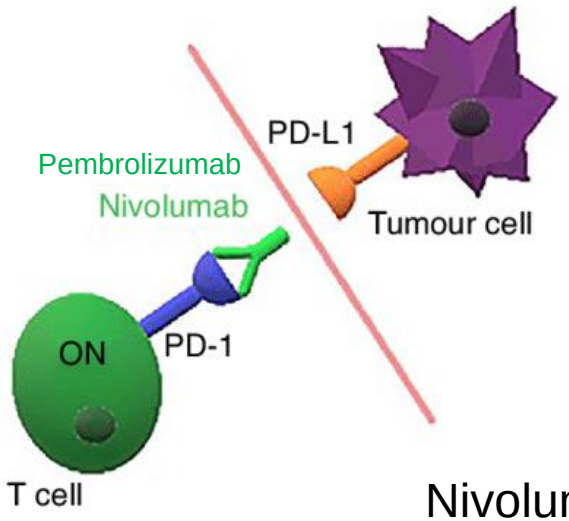
Straus et al, *Lancet Haem* 85:e410-21 2021

Checkpoint inhibition in HL

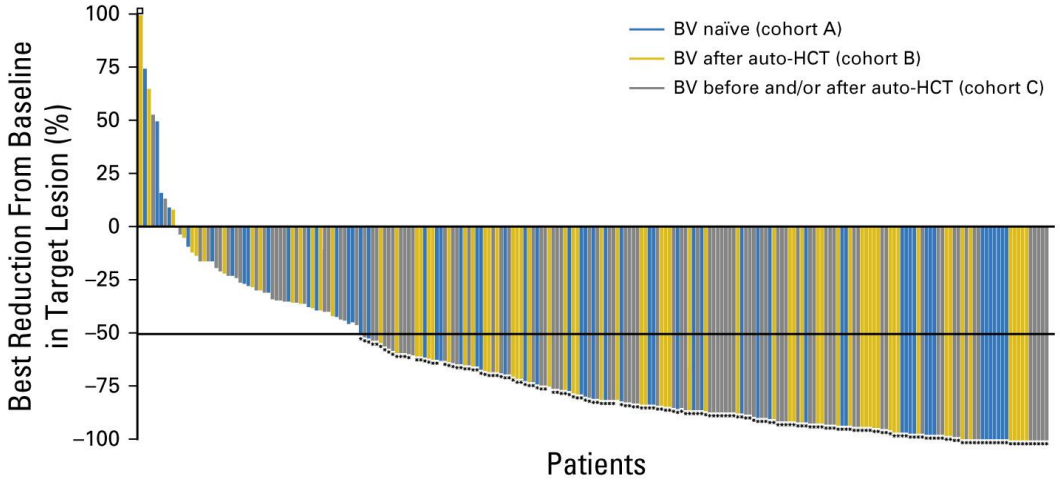


Checkpoint inhibition in HL





Nivolumab: response rate 69%



Armand et al., *JCO* 36:1428-39 2018

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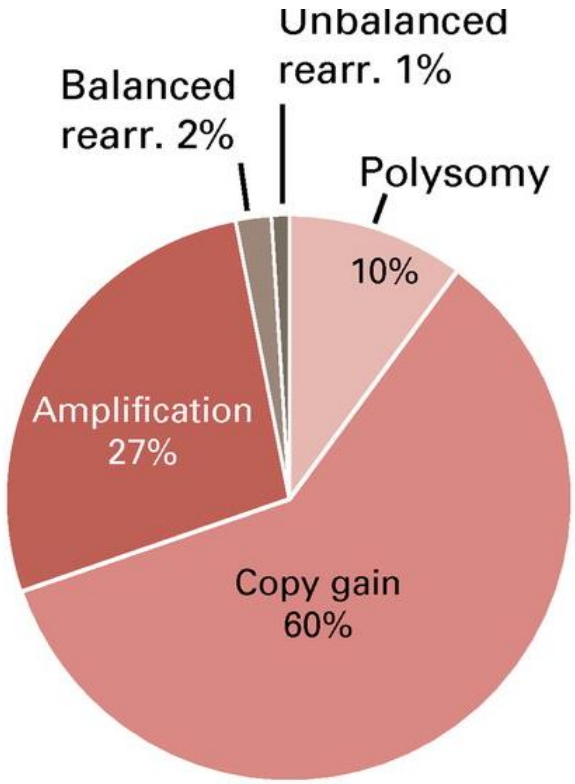
Why is HL so sensitive to PD1 inhibition?

Reed Sternberg cells exhibit frequent copy number alterations of 9p24.1 and the genes encoding the programmed death 1 (PD-1) receptor ligands, *PD-L1* and *PD-L2.*

Highest single-agent response rates in any tumor type.

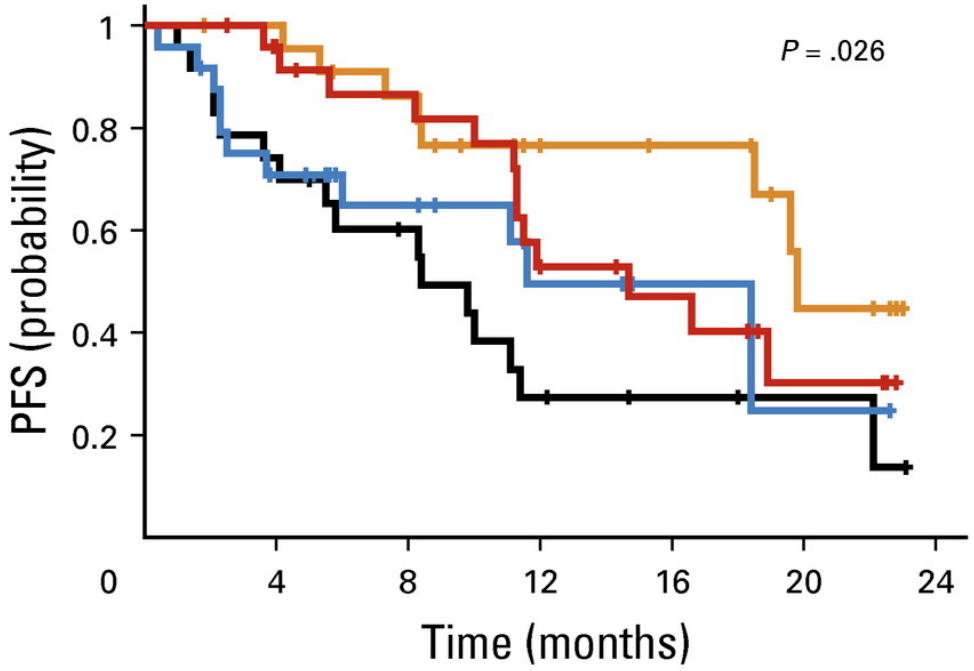


Roemer et al., *JCO* 36:942-50 2018

Why is HL so sensitive to PD1 inhibition?

9p24.1/*PD-L1*/*PD-L2* genetic alterations and PD-L1 expression may predict clinical outcome to checkpoint blockade therapy.

PFS according to PD-L1 H-score for malignant cells, quartiles



Roemer et al., *JCO* 36:942-50 2018

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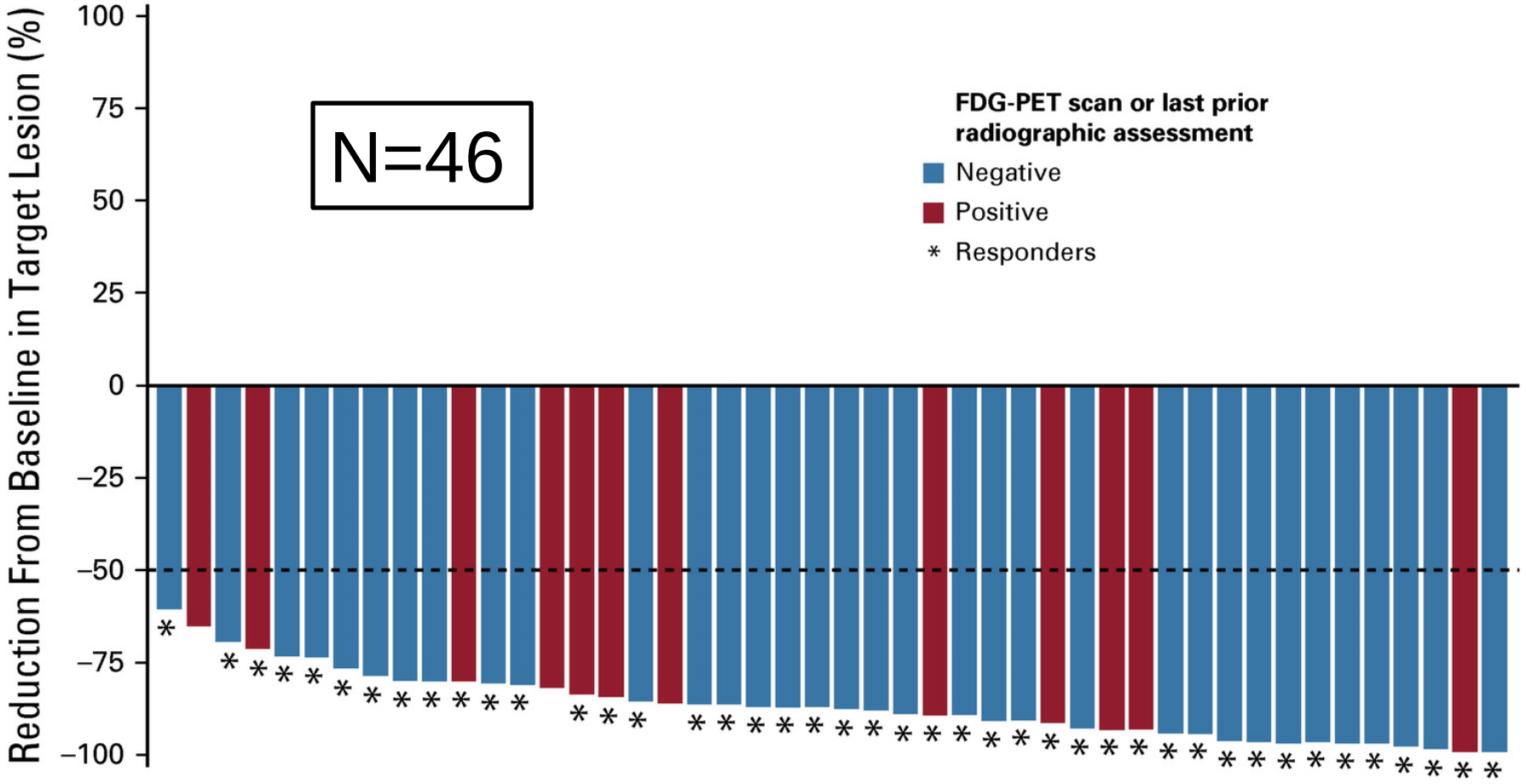
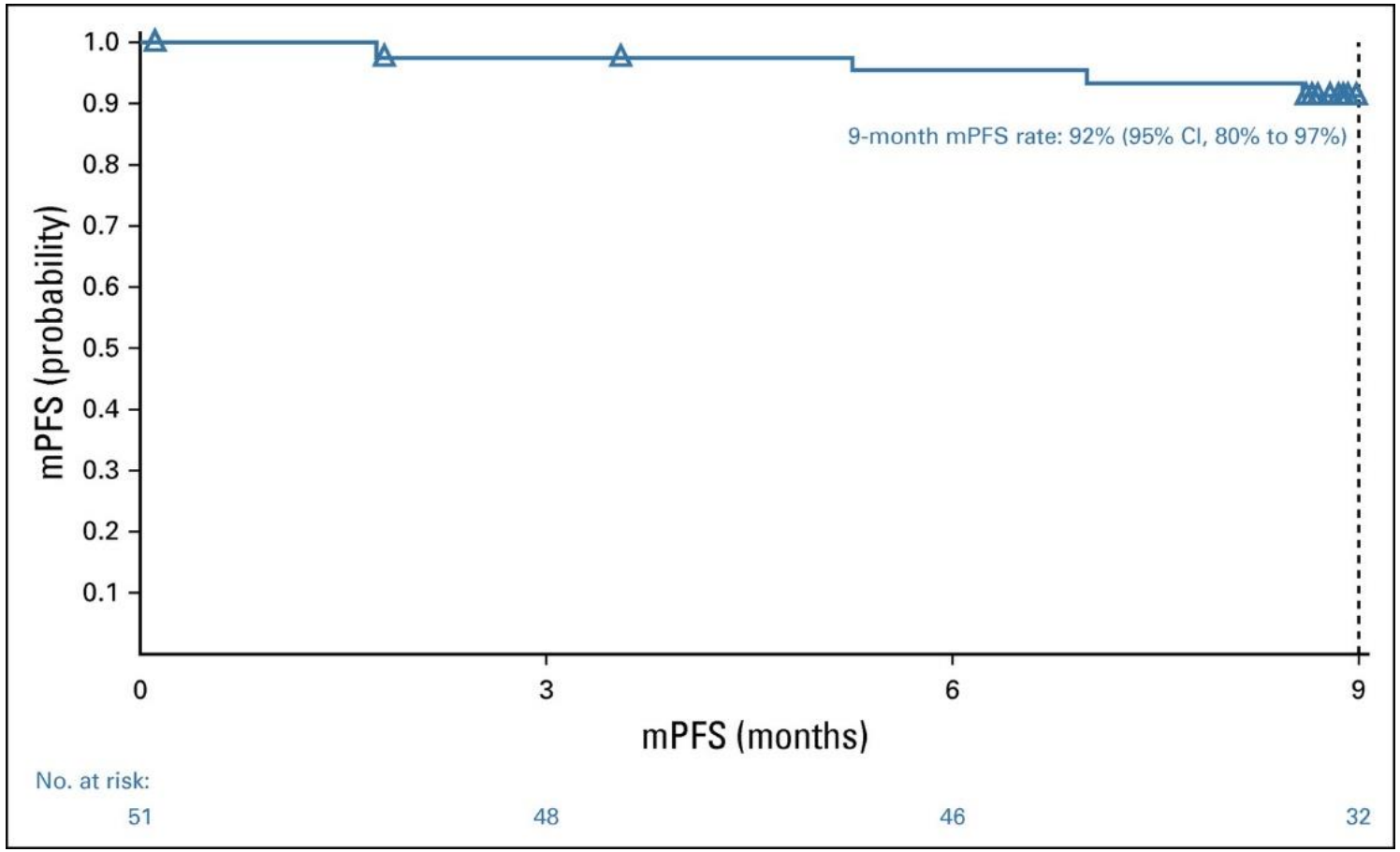
Checkmate 205:
AVD + Nivolumab for advanced stage HL



Ramchandren et al, *JCO* 37:1997-2007, 2019

mPFS: AVD + Nivolumab



Ramchandren et al, *JCO* 37:1997-2007, 2019

Checkmate 205: AVD + Nivolumab for advanced stage HL: Immune-related adverse events

Nonendocrine IMAEs		
Rash	3 (6)	0
Hepatitis*	2 (4)	2 (4)
ALT increased	2 (4)	2 (4)
AST increased	1 (2)	1 (2)
Infusion-related reaction	1 (2)	0
Endocrine IMAEs		
Hypothyroidism/thyroiditis	9 (18)	0
Hyperthyroidism	4 (8)	0

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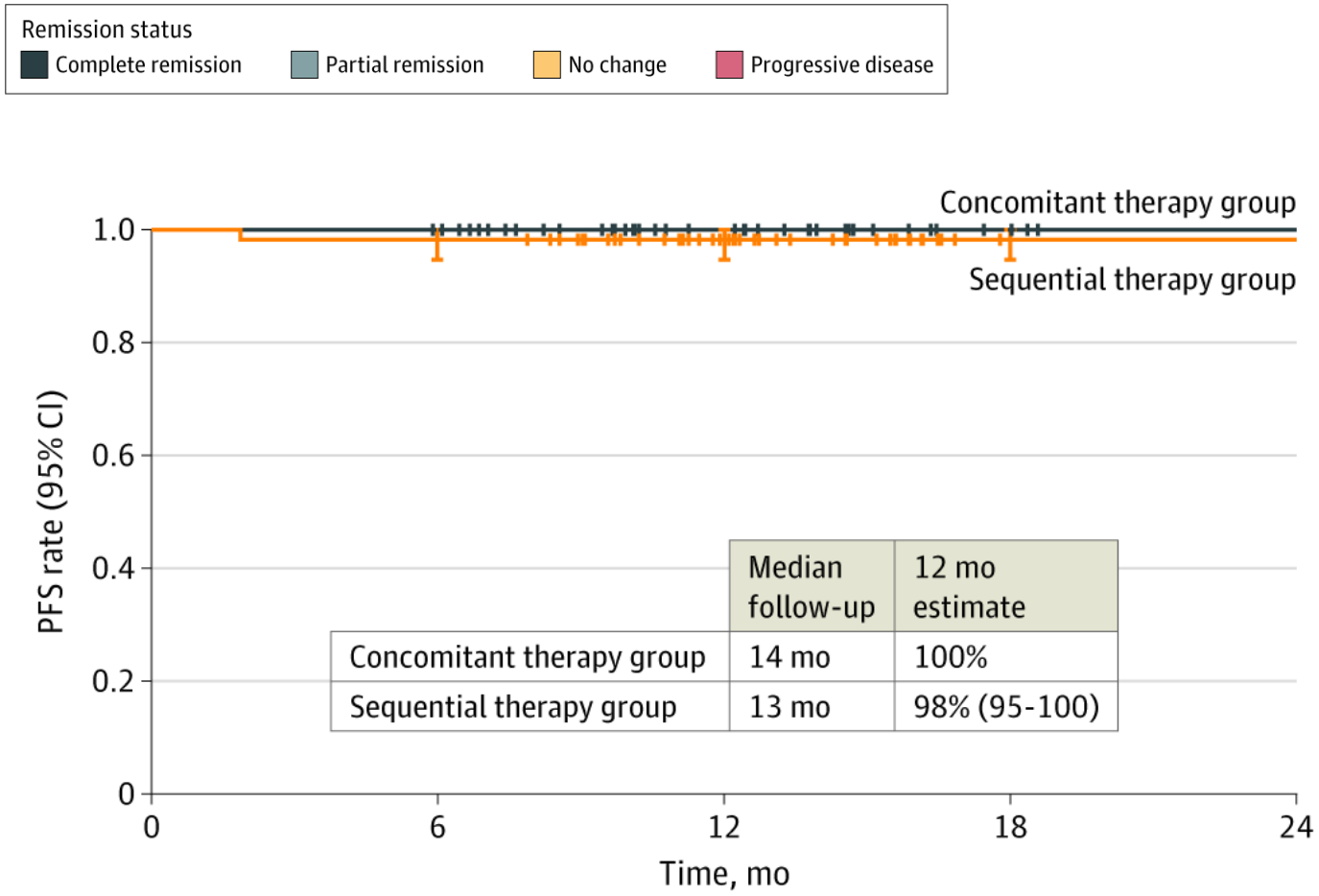
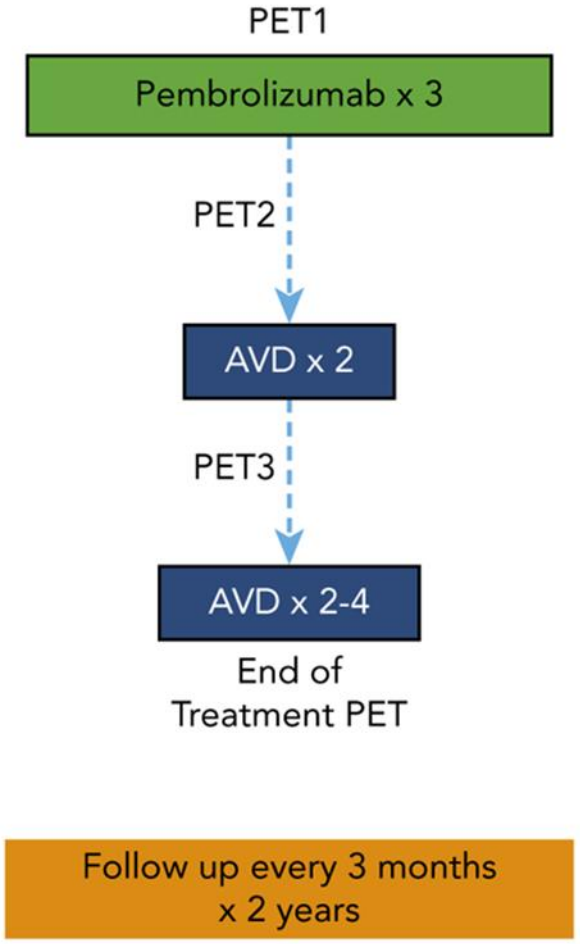
Ramchandren et al, *JCO* 37:1997-2007, 2019

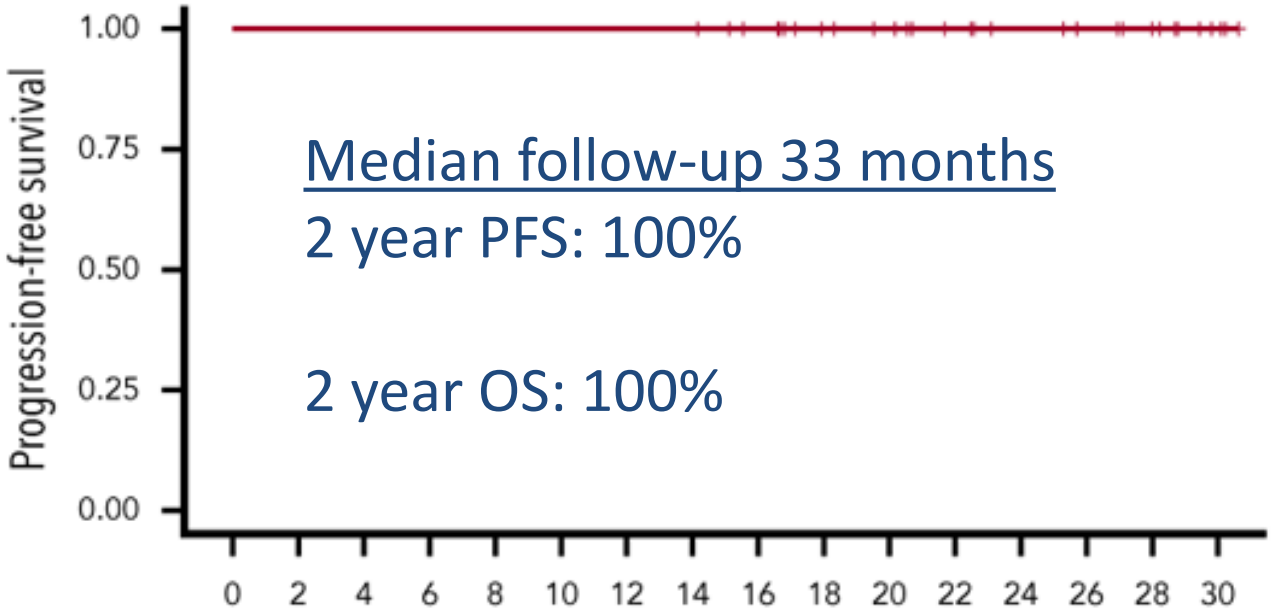
AVD-Nivolumab in Early Stage Unfavorable HL



Brockelmann et al., *JAMA Oncology* 6:872-80 2020

AVD-Pembrolizumab in early and advanced HL





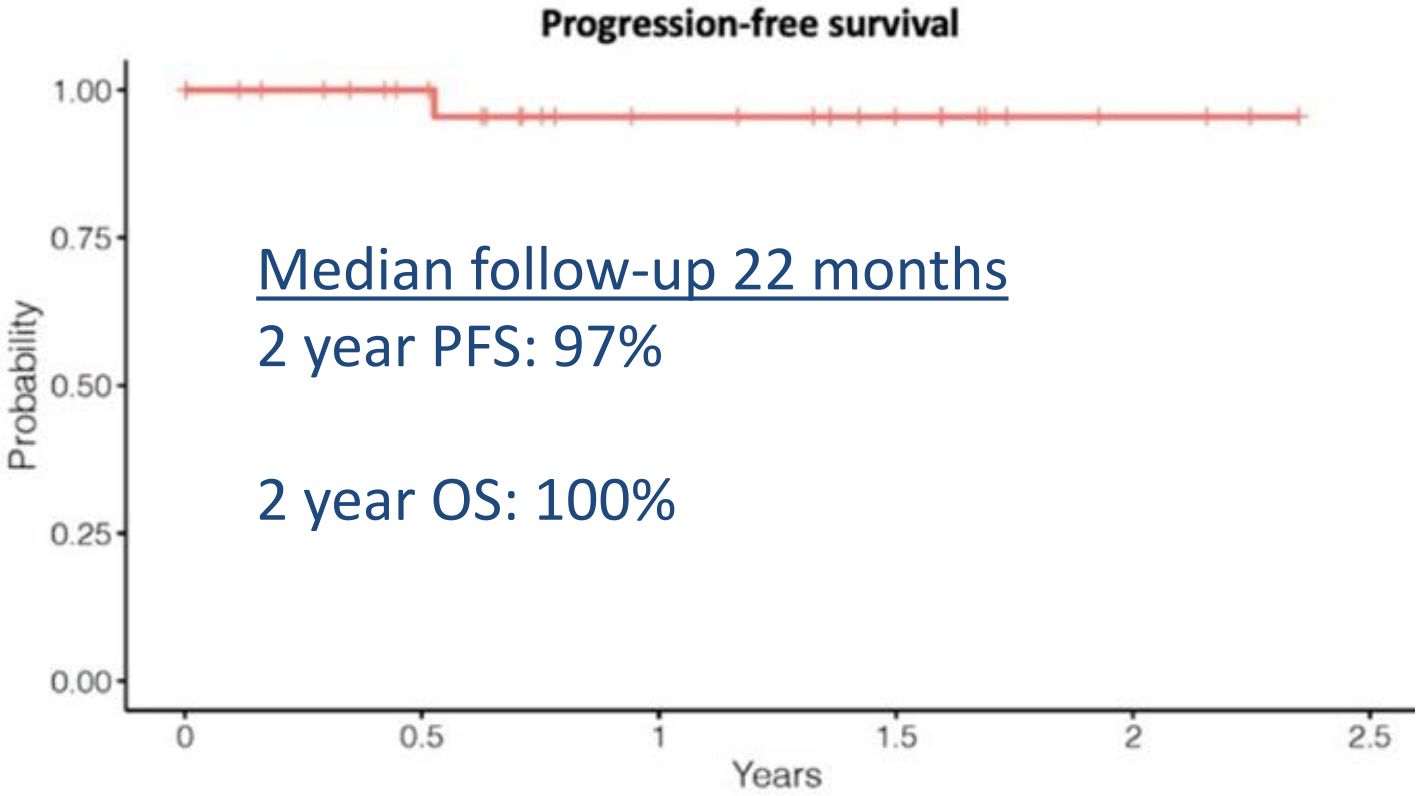
Median follow-up 33 months

2 year PFS: 100%

2 year OS: 100%

Allen et al., *Blood Advances*: in press 2022

AVD-Pembrolizumab for early and advanced HL (N=30)



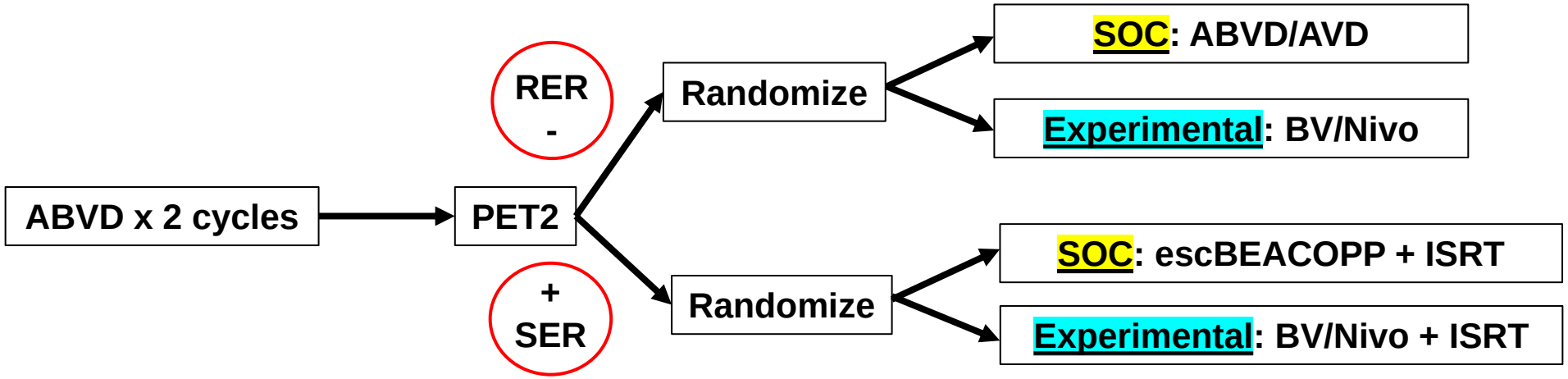
Median follow-up 22 months

2 year PFS: 97%

2 year OS: 100%

Lynch et al., *Blood* in press 2023

AHOD2131: Response-adapted therapy for early stage HL



RER: Rapid Early Responders
SER: Slow Early Responders

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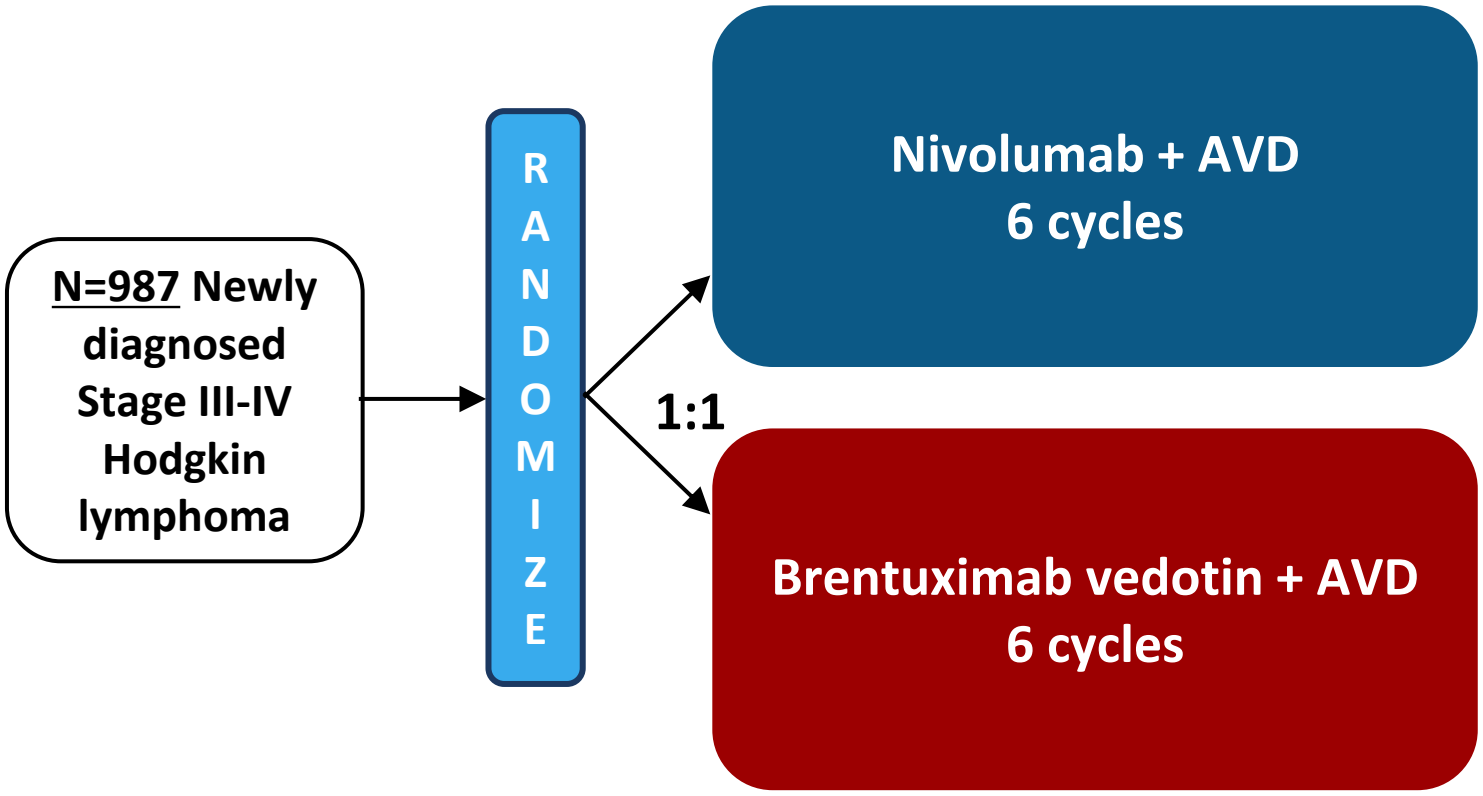
SWOG CANCER RESEARCH NETWORK
Alliance for Clinical Trials in Oncology
ECOG-ACRIN cancer research group
CHILDREN'S ONCOLOGY GROUP
NCI National Clinical Trials Network

North American Study: S1826



S1826 Leadership

Alex Herrera
SWOG

Andrew Evens
ECOG-Acrin

Sarah Rutherford
Alliance

Sharon Castellino
COG

Kelly Davidson
CCTG

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S1826: Progress

March 2023:

- Second interim analysis by DMSC
- **Recommendation: primary endpoint met; immediate reporting of results**
- ASCO and Lugano presentations

Conclusions: Hodgkin lymphoma

- Most patients are cured; burden of late effects mandates precision approach which has remained elusive.
- Early incorporation of checkpoint blockade exciting direction:
  - Underlying genetic rationale
  - Impact on microenvironment
  - Predictive biomarkers
- Early stage studies: continued refinement to safely eliminate radiation therapy
- Current S1826 trial may define a new standard of care for most adolescent and adult patients with advanced stage disease.

HERE RESTS THE BODY
OF
THOMAS HODGKIN M. D.
OF BEDFORD SQUARE,
LONDON
A MAN DISTINGUISHED
ALIKE
FOR SCIENTIFIC
ATTAINMENTS
MEDICAL SKILL
AND SELF SACRIFICING
PHILANTHROPY
HE DIED AT JAFFA
THE 4TH OF APRIL 1866
IN THE 68th YEAR OF HIS
AGE

Thomas Hodgkin grave
Jaffa, Israel 2011