Management of Advanced Stage and Relapsed Hodgkin Lymphoma

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Disclosures: M Crump

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I work in a Radiation hospital which influences my views of radiation for cHL

CASE 3

You are asked to see a 31 year old male with a 2 month history of weight loss, convincing-sounding night sweats and bilateral neck and R axillary adenopathy. PET CT scan demonstrates, in addition, non-bulky mediastinal and epigastric/portal adenopathy; there is diffuse uniform bone marrow FDG uptake. Hb 107, WBC 19.4, lymphocytes 0.5, albumin 33.

Your first choice of treatment for this man is:

1. ABVD, with escalation to BEACOPP if post-cycle 2 PET is positive
2. Brentuximab vedotin + AVD x 6 cycles
3. escBEACOPP, with switch to ABVD x 4 if PET2 is negative
4. BrECADD (BV, etoposide, cyclo, doxorubicin, dacarbazine, dex), with reduction in number of cycles (from 6 to 4) if PET2 is negative
5. Nivolumab + AVD x 6 cycles

Objectives for this part

- Understand the data supporting current regimens for advanced stage Hodgkin lymphoma
- Review current salvage approaches in adults with relapsed/refractory HL
- Identify opportunities for (investigation of) transplant-free approaches in adults with relapsed cHL

Management of Advanced Stage Hodgkin Lymphoma: 2 ways

1 Chemotherapy → **PET2**

ABVD (RATHL)
escBEACOPP (HD18, AHL2011)
BrECADD (HD21)

neg → reduce therapy

Provide similar or better disease control, while doing less (or at least not more) harm

pos → escalate/augment therapy

2 **Brentuximab-AVD** (E-1)
Nivolumab-AVD (S1826)
→ 6 cycles → EOT PET scan

Lessons from PET-adapted trials in advanced stage HL

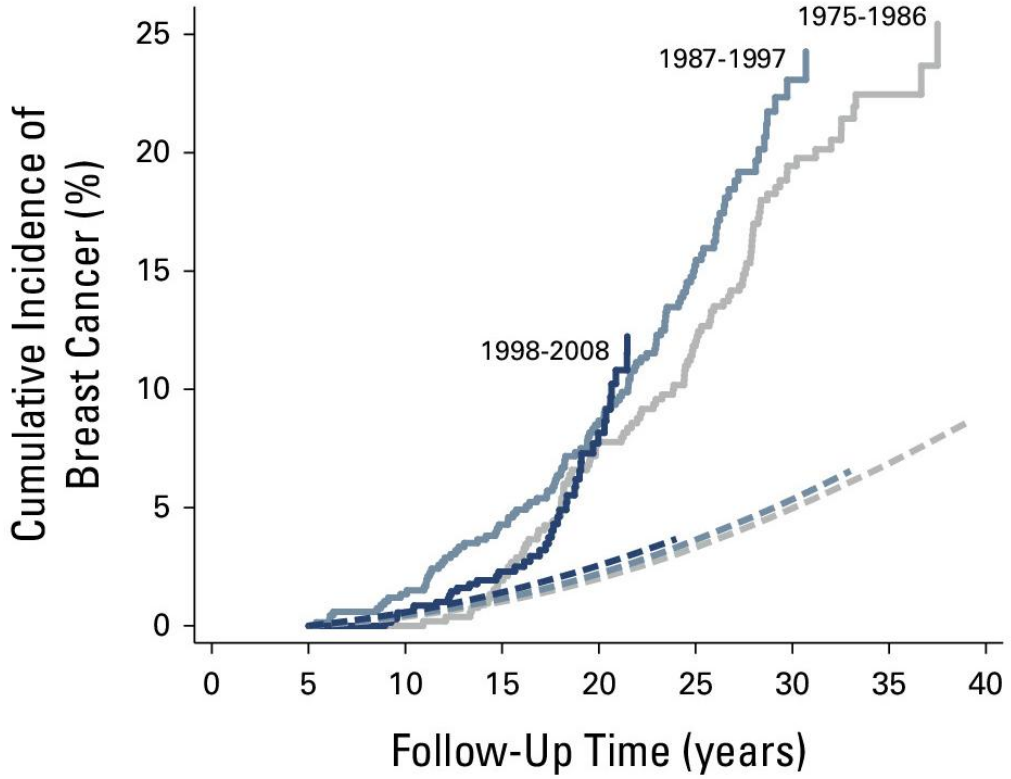
- Treatment de-escalation in patients with negative PET2 reduces toxicity without loss of benefit: similar PFS and OS
  - Toxicities avoided depend on starting regimen (ABVD vs escBEACOPP)

HD17 Kreissl Lancet Hematol 2021; AHL 2011 Casasnovas, J Clin Oncol 2022
RATHL Luminari, J Clin Oncol 2024

- Escalation of treatment for those with positive PET2 is <u>not</u> able to "make up the difference" when starting with ABVD
  - with the possible exception of local radiation for residual FDG-avid lesions (HD15)

SWOG 0816 Press, J Clin Oncol 2016; RATHL Luminari J Clin Oncol 2024
Engert, Hemasphere, 2017

Incidence of breast cancer in female HL survivors is not decreasing –despite less use of radiation



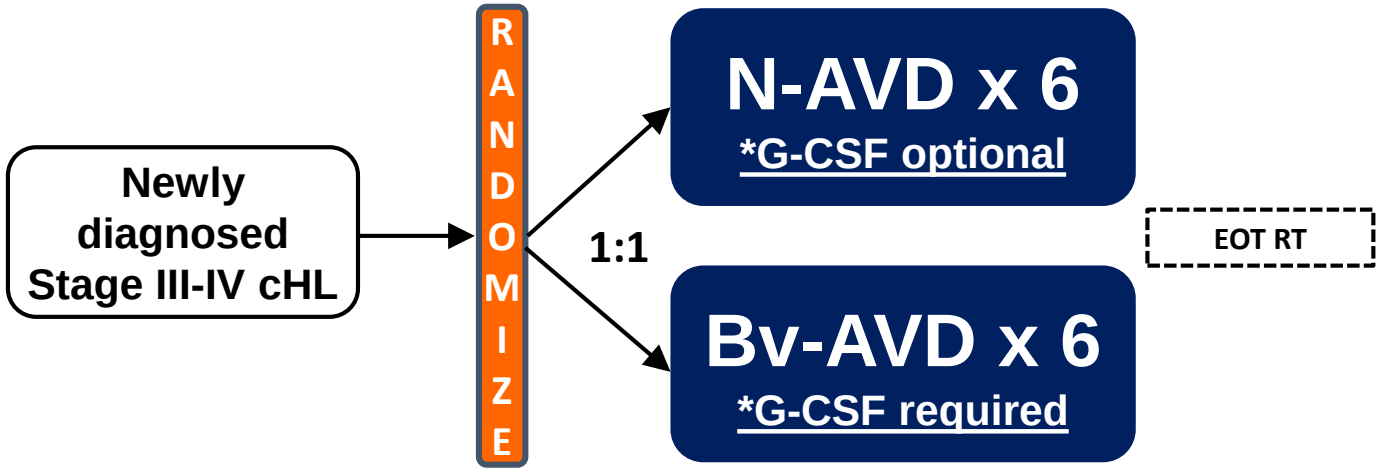
1964 women age 15-50 at diagnosis
Chest RT: 76%, doxorubicin: 57%

Treatment for HL	Standardized breast Ca incidence ratio
Mantle/axilla field; no doxorubicin	7.0 (5.2-9.2)
Doxorubicin, no radiation	2.5 (1.1-4.8)
Doxorubicin + mediastinum	2.8 (1.7-4.3)
Doxorubicin + mantle/axilla	3.8 (2.2-6.1)

Neppelenbroek, J Clin Oncol 2024

New frontline approaches for advanced stage cHL

S1826 Eligibility Criteria



Key Inclusion

- Age ≥ 12 years old
- HIV+ eligible, if controlled
- Zubrod PS 0-2 (Peds: Lansky)
- LVEF ≥ 50% (or SF ≥ 27%)
- CrCl ≥ 30 mL/min (Peds: CrCl/GFR ≥ 70, SCr ≤ 1.5 ULN)
- Tbili ≤ 2 x ULN and AST/ ALT ≤ 3 x ULN

Key Exclusion

- Interstitial lung disease or pneumonitis
- Peripheral neuropathy ≥ Gr2
- Active autoimmune disease

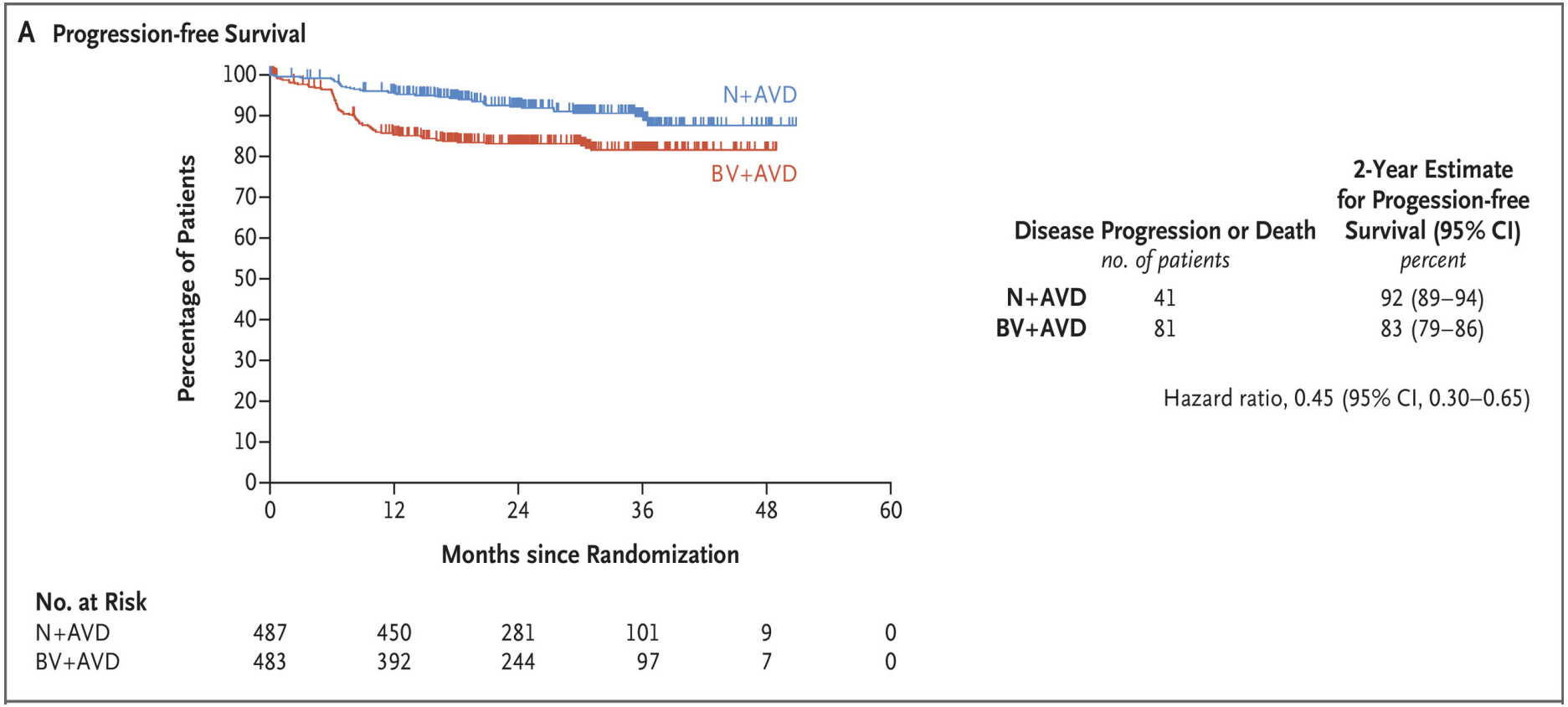
End of Treatment Response Data

- Responses assessed by investigators by PET-CT using 2014 Lugano Classification

Deauville Score	N-AVD (Assessed) n=339 N (%)		Bv-AVD (Assessed) n=318 N (%)	
1	93	(27.4%)	67	(21.0%)
2	131	(38.6%)	103	(32.4%)
3	65	(19.2%)	58	(18.2%)
CMR (DS 1-3)	**289**	**(85.2%)**	**228**	**(71.7%)**
4	27	(8.0%)	35	(11.0%)
5	12	(3.5%)	33	(10.4%)
DS 4-5	**39**	**(11.5%)**	**68**	**(21.4%)**
DS X	**11**	**(3.2%)**	**22**	**(6.9%)**

S1826/CCTG HDC.1: Nivo-AVD compared to Bv-AVD

2-year PFS N-AVD 92% Bv-AVD 83%



ASH2025 update

3y PFS N-AVD 91%

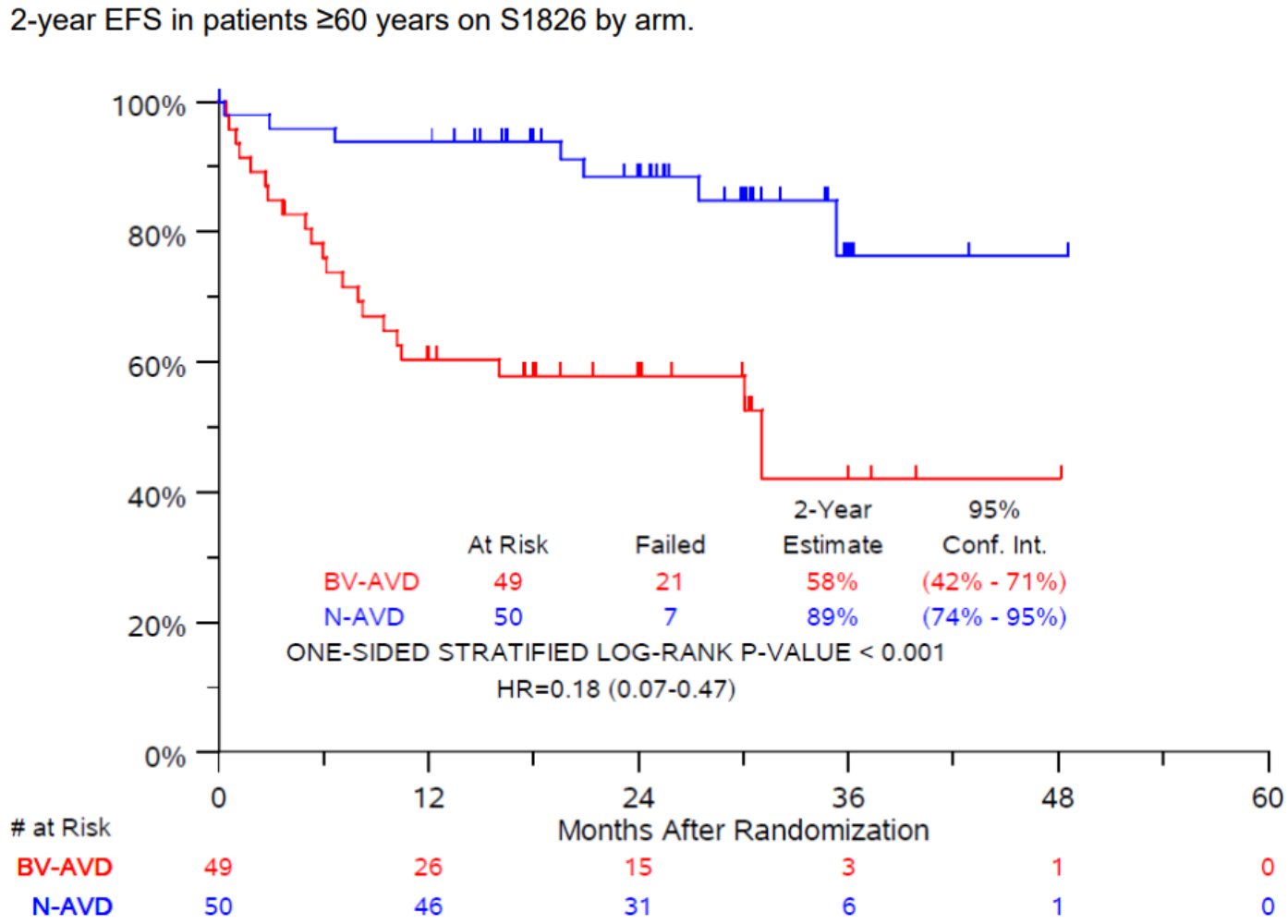
vs BV-AVD 82%

Herrera, N Engl J Med 2024

S1826/HDC.1 toxicity highlights

- Similar rates of febrile neutropenia, infection
  - GCSF prescribed in BV arm (98%); received in ~ 50% of patients in nivo arm
- More peripheral neuropathy in patients receiving BV
  - All grades 55% vs 29%; grade $\geq$3 8% vs 1 %
- Low rates of immunologic and non-hematologic toxicity
- Discontinuation of study drug: nivolumab 11%, brentuximab 22%

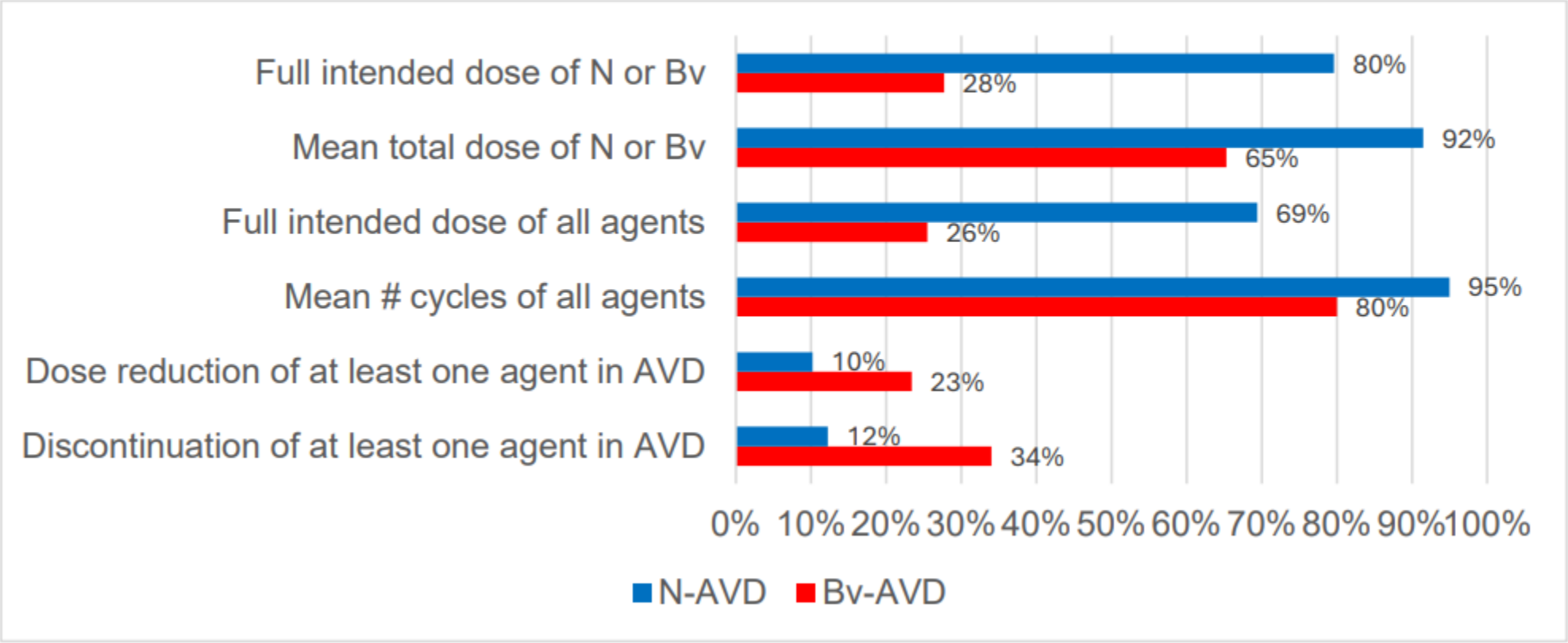
N-AVD results improved EFS compared to BV-AVD



Rutherford, J Clin Oncol 2025

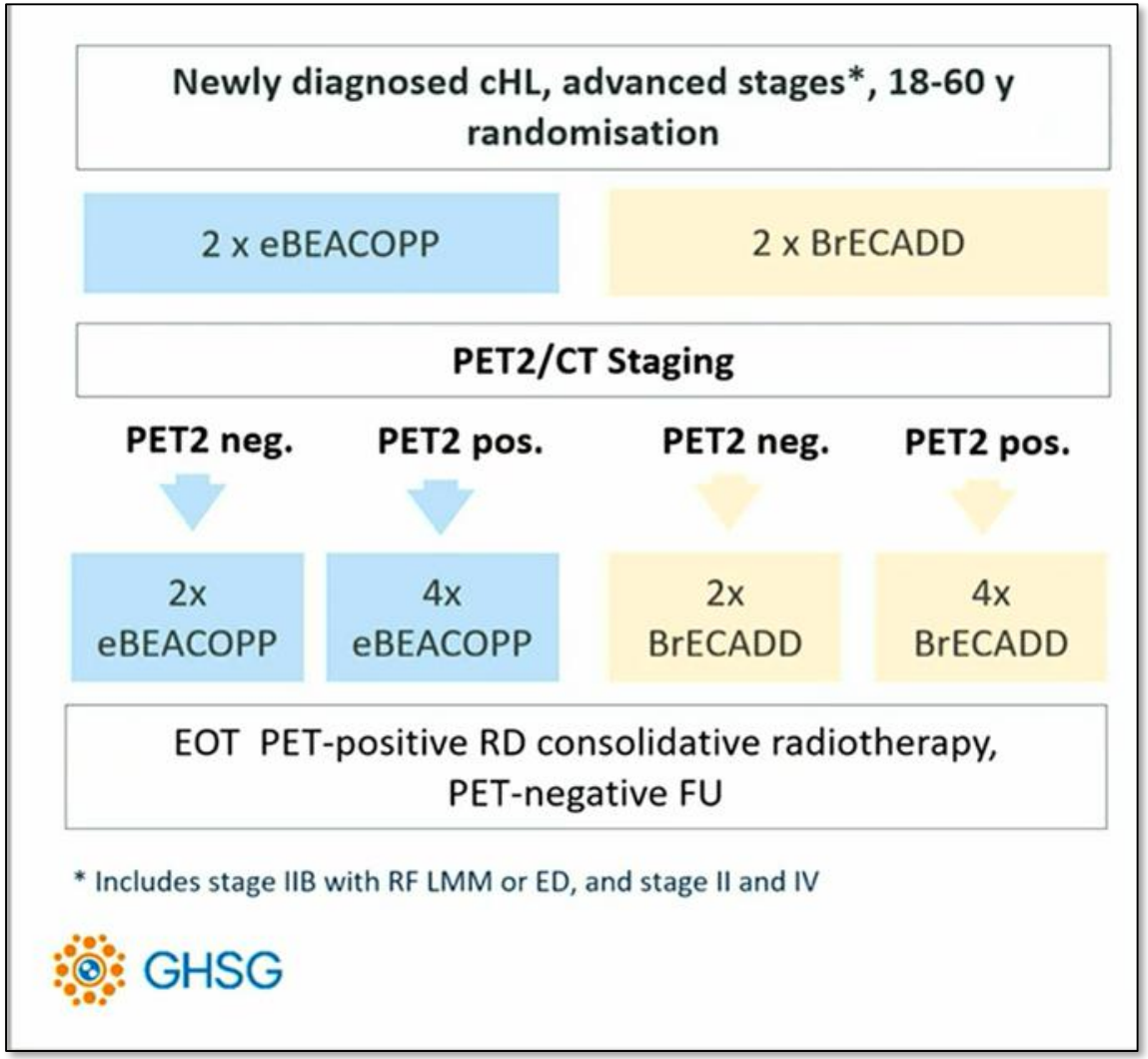
N-AVD was better tolerated that BV-AVD in patient age >60 yrs in S1826

Percentage of treatment received including dose reductions and discontinuations of agents in AVD for older patients randomized to N-AVD (blue) and BV-AVD (red).



Rutherford, J Clin Oncol 2025

BrECADD for advanced HL GHSG HD21:



Phase III RCT

- Co-primary endpoints: treatment related morbidity (TRMB) and PFS
- TRMB: any CTCAE grade 3-4 organ toxicity or grade 4 hematologic toxicity (anemia, platelets, infection)

- 1500 pts enrolled July 2016- August 2020, 9 countries, 233 trial sites

P Borchmann, ISHL 2022, ICML 2023

BrECADD regimen

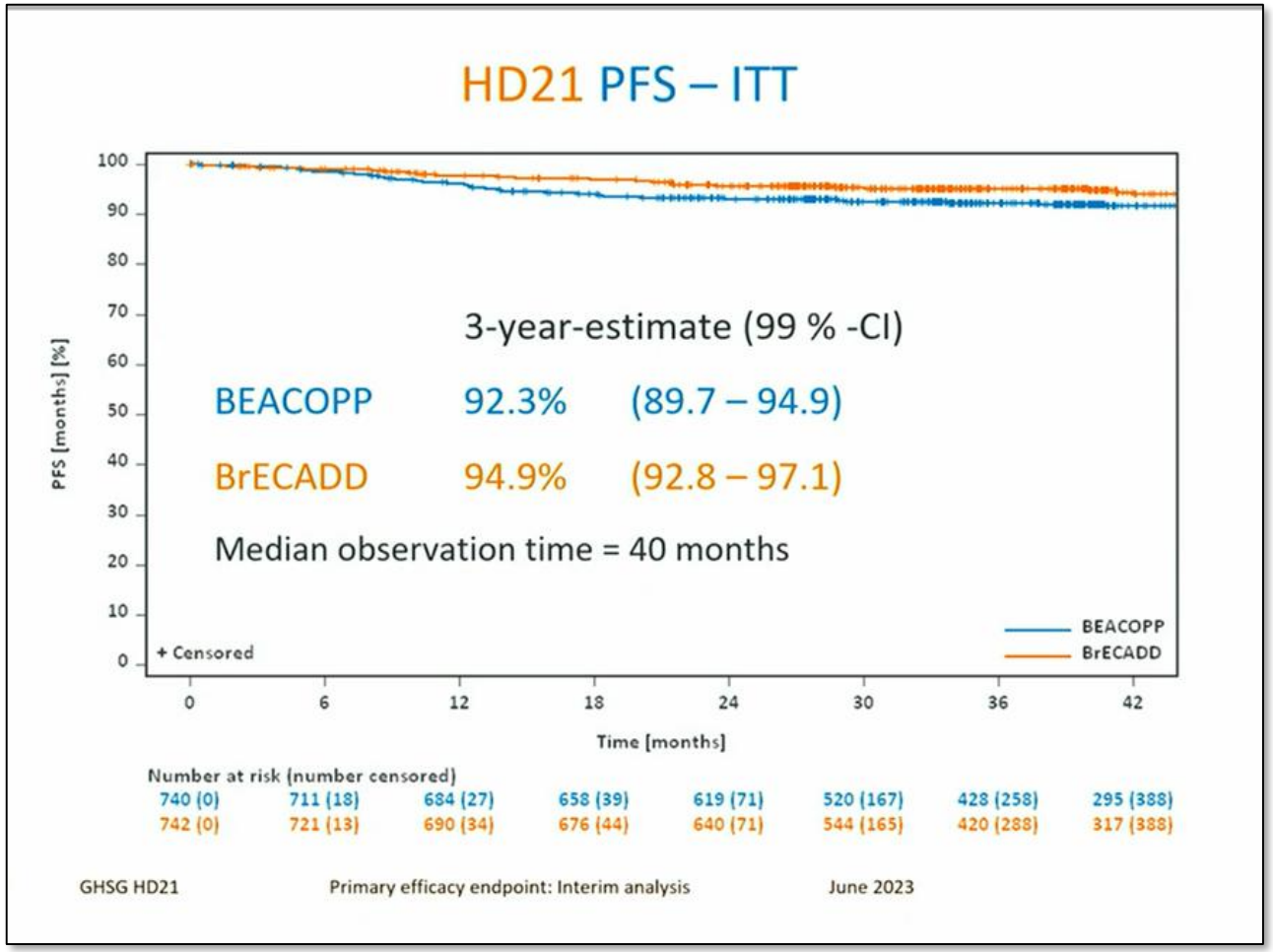
Selected based on toxicity profile from rPh2 trial vs BrECAPP

Drug	Day	BEACOPP[1] Dose (mg/m²)	*BrECADD* Dose (mg/m²)	Potential improvement
Bleomycin	8	10	-	lung tox
Etoposide	1–3	200	*150*	hem tox, transfusion frequency
Doxorubicin	1	35	*40*	
Cyclophosphamide	1	1250	*1250*	
Vincristine	8	1.4	-	neuropathy
Brentuximab vedotin	1	-	*1.8 mg/kg*	
Procarbazine	1–7	100	-	gonadal tox, sAML/MDS
Prednisone	1–14	40	-	weight, bone, infections
Dacarbazine	2–3	-	*250*	
Dexamethasone	1–4	-	*40*	

Eichenauer, Lancet Oncol 2017

BrECADD for advanced HL: less toxic, better PFS

Acute treatment related toxicity		
CTCAE Gr. 3-4	BEACOPP (N=732)	BRECADD (N=738)
Anemia	59%	30%
Thrombo'penia	72%	55%
Leukopenia	94%	87%
Infection	19%	20%
<u>Transfusions</u>		
RBCs	22%	8%
platelets	13%	6%
Organ toxicity	17%	19%

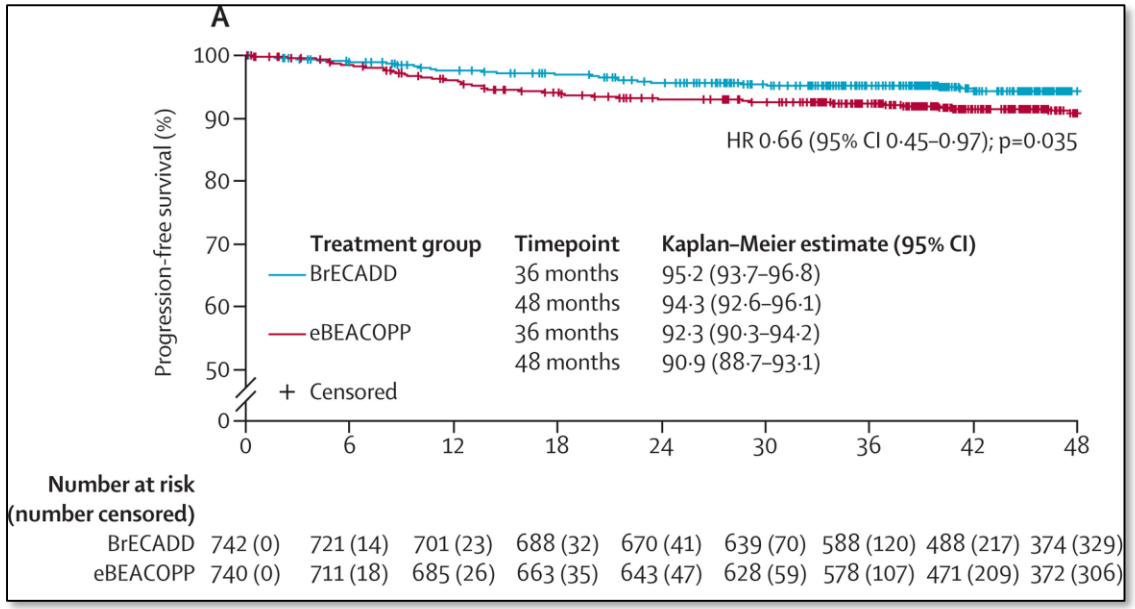


RR 1.41, p <0.001

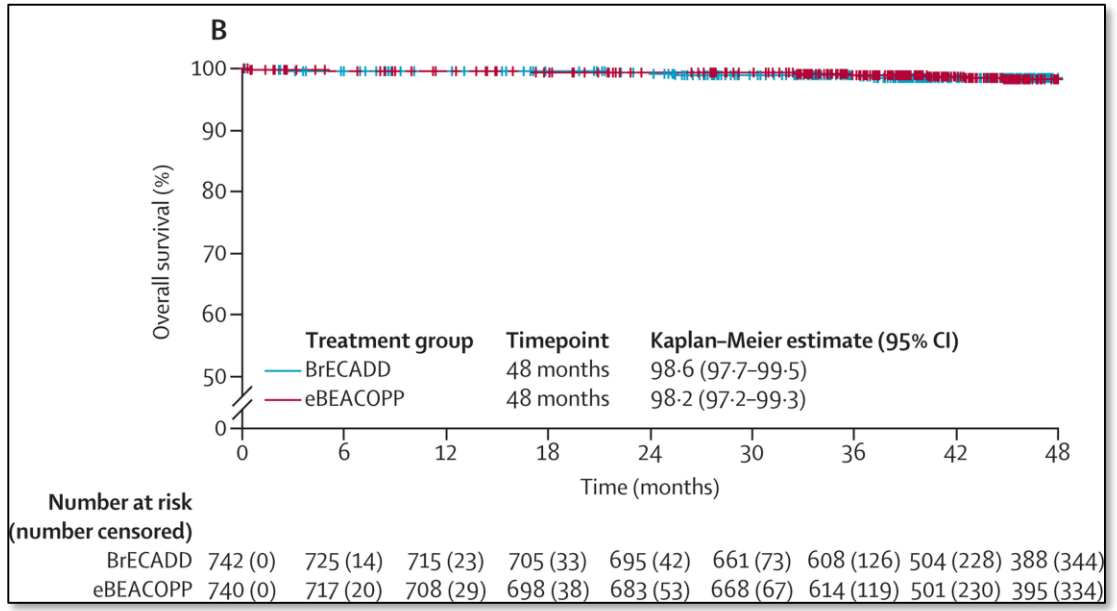
P Borchmann, ISHL 2022, ICML 2023

BrECADD vs escBEACOPP in stage IIBE-IV classical HL

Progression-free survival



Overall survival

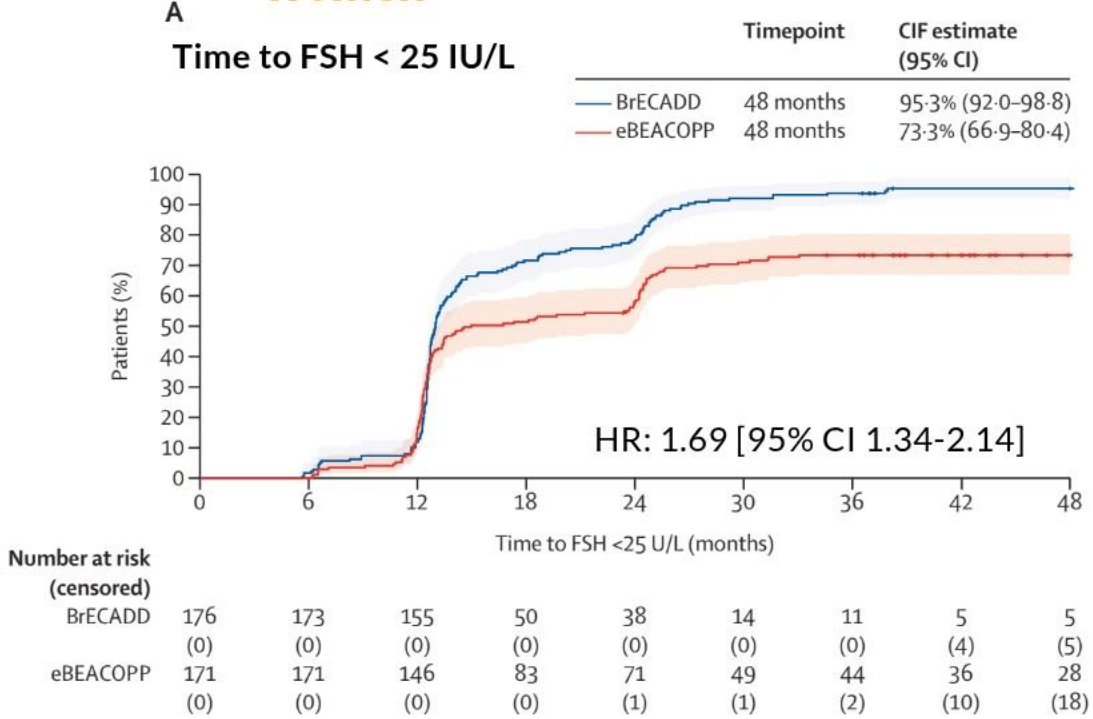


Borchmann, Lancet 2024

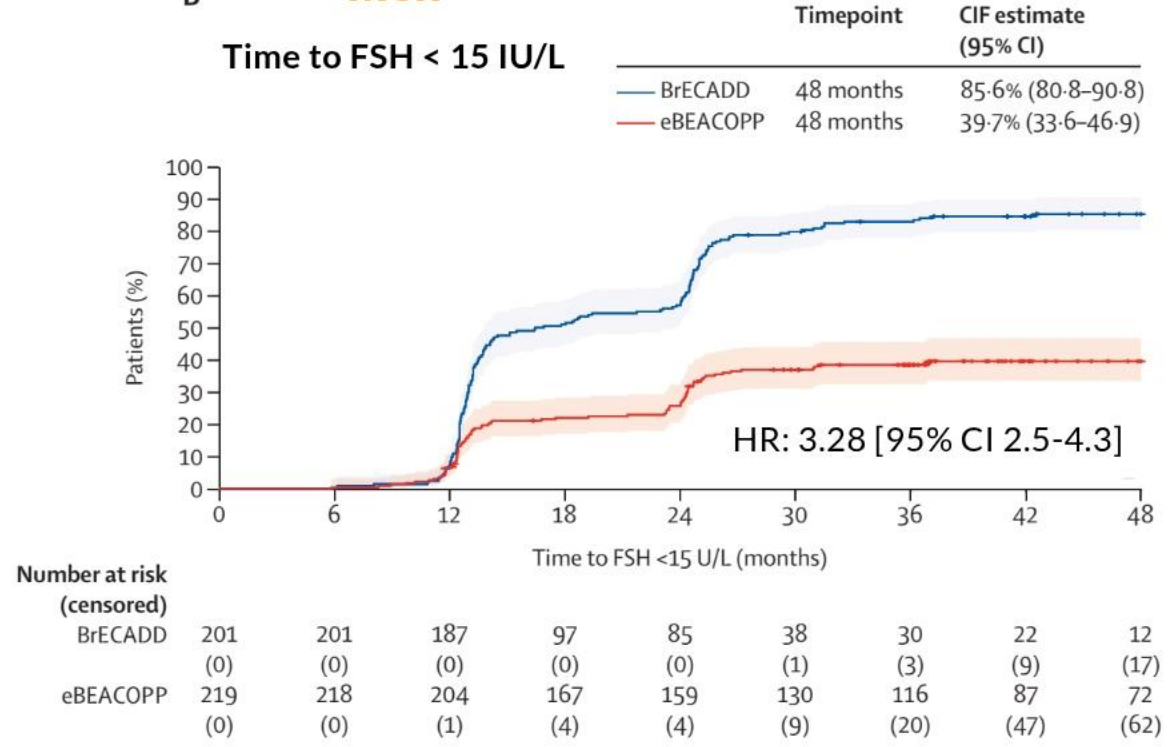
4-year gonadal recovery

Women & men assigned to BrECADD had significantly higher 4-year gonadal function recovery (measured by FSH)

Women



Men



Slide courtesy Dr Reut Harel

Ferdinandus, Lancet Oncol 2025

SECOND LINE THERAPY

Approaches to intensive therapy for R/R Hodgkin Lymphoma

Salvage therapy

Chemotherapy comparisons

- DHAP vs DHAP → HDS cyclo, etoposide, MTX

- CCTG HD.11: pembrolizumab + BV vs GDP

High-dose chemotherapy

High-dose therapy comparisons

- none

Post-remission strategies

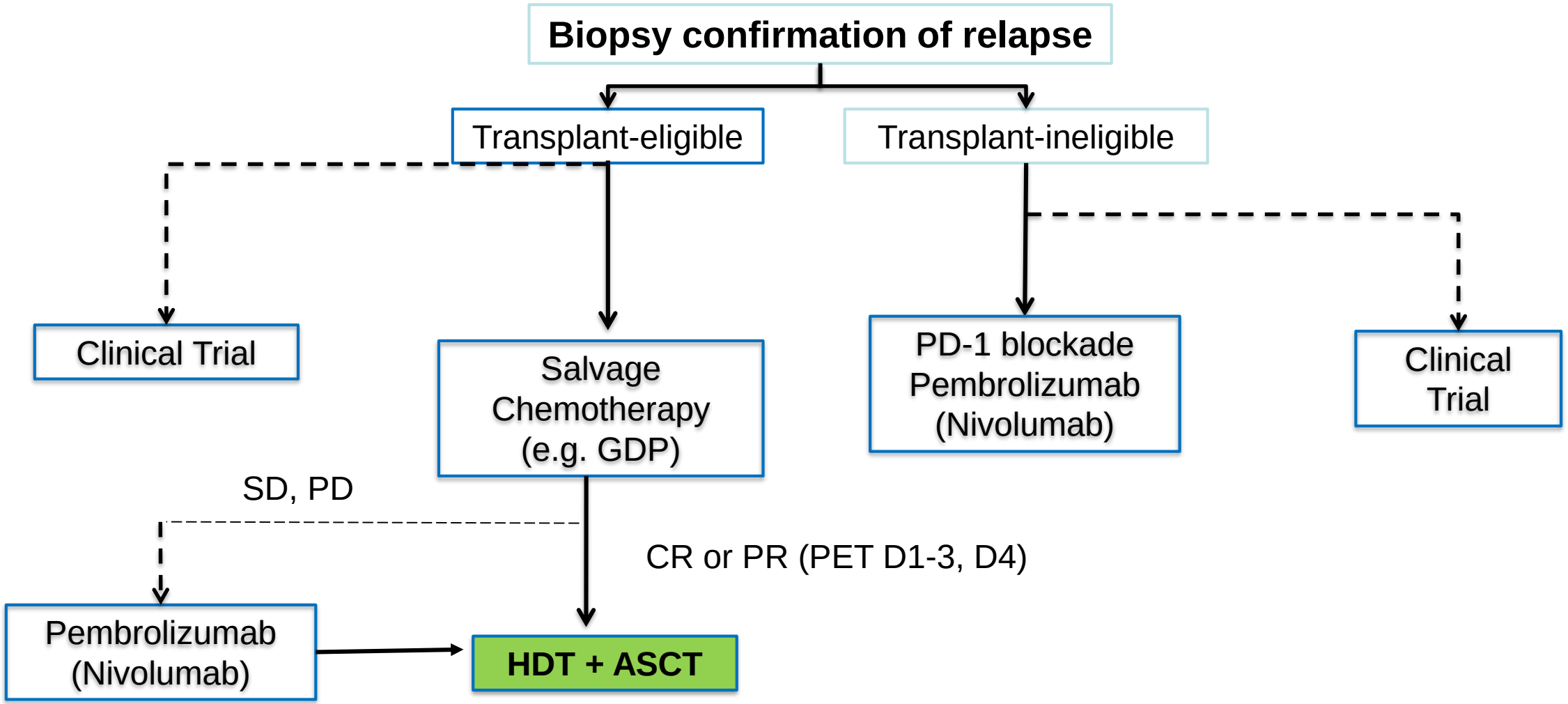
Maintenance

- brentuximab vedotin vs placebo

Post-transplant involved-field radiation

- D4 after salvage, bulky disease

Relapsed and Refractory Hodgkin Lymphoma



Courtesy of Dr T Aoki

Combining brentuximab, PD1 antibodies with salvage chemotherapy

BV + conventional salvage:

ICE, DHAP, ESHAP

- ~1/3-1/2 refractory
- Complete response by PET ~70-80%
- PFS at 2 years 70-80%

Garcia-Sanz R, Ann Oncol 2019

Stamatoullas A, ASH 2019

Kersten MJ, Hematologica 2021

PD1 antibodies + conventional salvage: ICE, GVD

- Smaller studies, ~1/2 refractory
- Complete response by PET 85-95%
- Follow-up for PFS short but encouraging, higher at 2 yrs than with BV?

Herrera A, Blood 2022

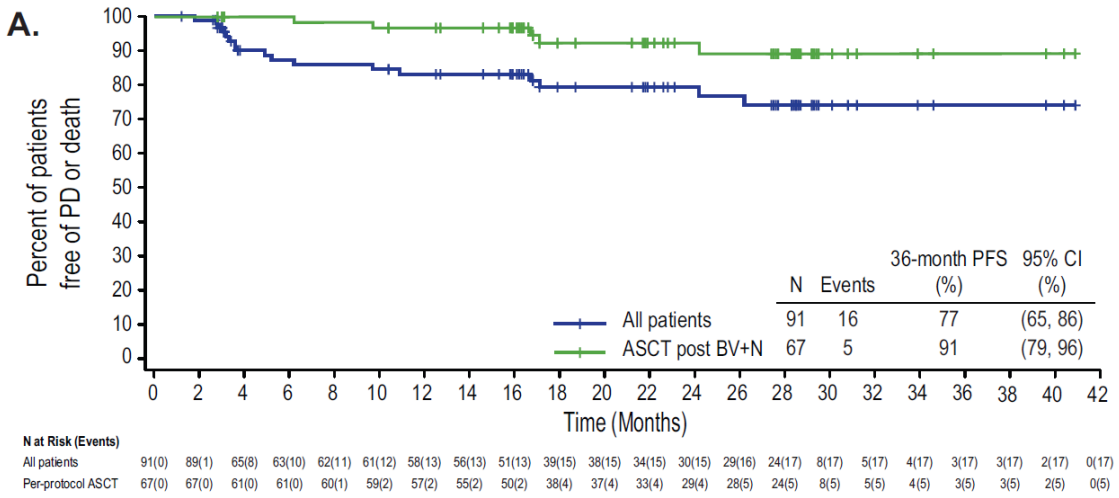
Bryan LJ, JAMA Oncol 2023

Moskowitz A, J Clin Oncol 2021

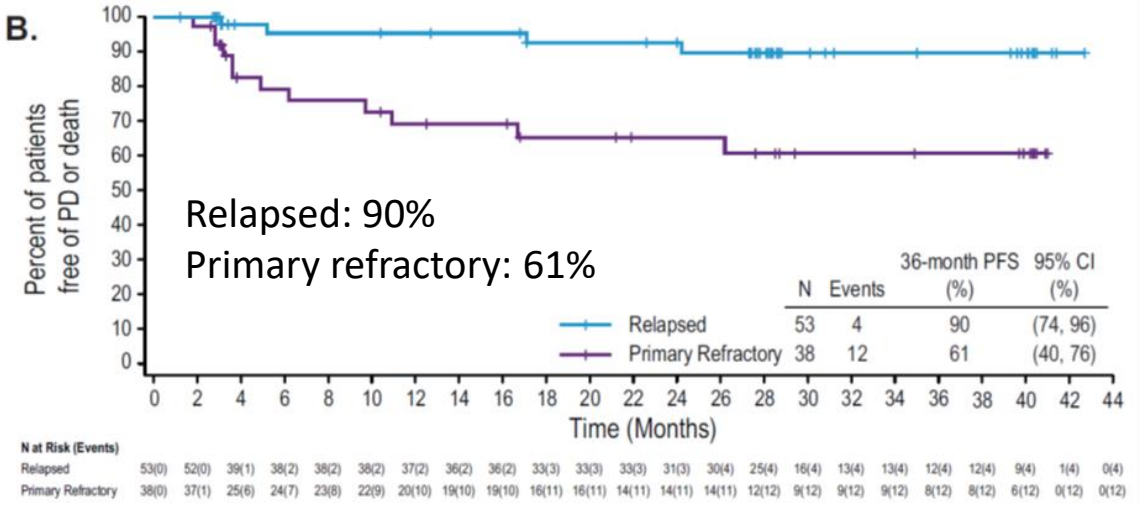
Brentuximab vedotin + nivolumab in RR cHL

Brentuximab (1.8 mg/kg)
Nivolumab (3.0 mg/kg IV)
} 3-week cycles for up to 4 cycles

- 93 patients enrolled from 11 sites Oct 2015-Sept 2017
- Med age 34 (18-69), 42% refractory, 32% rel < 1yr, most: 1 prior line of therapy



ASCT per protocol: 91%
All patients: 77%



Herrera A, Blood 2018
Advani R, Blood 2021

The Impact of PD-1-Based Combinations Before Autologous Stem Cell Transplant (ASCT) on Outcomes in Classical Hodgkin Lymphoma

Introduction and Methods

Optimal salvage prior to ASCT in r/r cHL remains undefined

There is increasing use of PD-1 based combinations in r/r cHL based on multiple single-arm phase 2 trials

A retrospective analysis of r/r cHL patients who underwent ASCT was performed focusing on the impact of salvage therapy.

Years 2010-2022

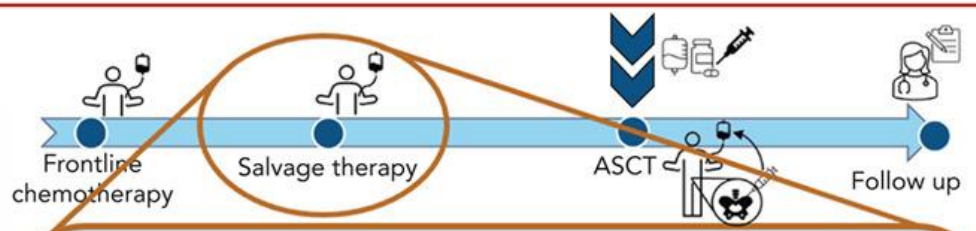
1280 Patients

6 US centers

Primary End Point
Progression-Free Survival

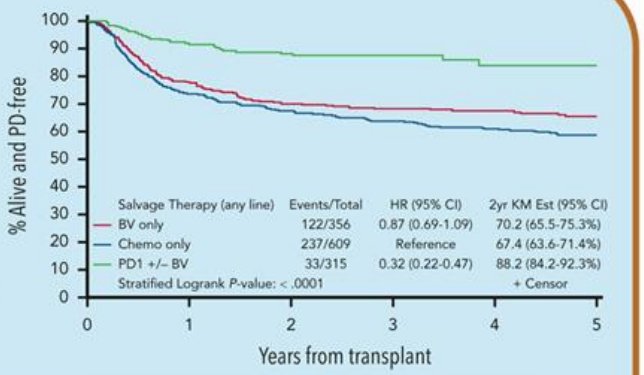
PD-1 | BV* | Chemo

*Brentuximab vedotin (BV)-based salvage without PD-1 blockade



Main Findings

- Patients who received PD-1 blockade pre-ASCT had a significantly higher 2-year PFS compared to patients who received BV without PD-1 inhibitors or chemotherapy only (Figure 1). This remains significant even in patients transplanted in complete metabolic response.



- PD-1 blockade remained a significant variable on multivariate analysis including when controlled for disease status pre-ASCT

Variable	Hazard Ratio (95% CI)	P-value
Salvage (any)		< .0001
BV only	0.77 (0.58-1.03)	.0770
Chemo only	Reference	
PD1 +/– BV	0.33 (0.21-0.51)	< .0001
B-symptoms at relapse	1.4 (1.07-1.63)	.0143
Primary Refractory	1.44 (1.11-1.87)	.0059
Relapse <12m	1.48 (1.09-2.00)	.0110
Transplant Year Prior to 2015	1.20 (0.93-1.55)	.1549
Extranodal at relapse	1.47 (1.16-1.85)	.0012
2+ Prior Lines	1.69 (1.29-2.21)	.0001
Pre-ASCT Response		
CR	0.20 (0.13-0.32)	< .0001
PR	0.30 (0.19-0.47)	< .0001
SD/PD	Reference	< .0001

Desai, Blood 2026

CCTG HD.11: Randomized Phase 2 Trial of Pembrolizumab + Brentuximab Vedotin or GDP Salvage Therapy in patients pre-ASCT

Key Eligibility Criteria

- **Relapsed or Refractory cHL**
- **Eligible for ASCT after one prior line of therapy**
- **Measurable disease by Lugano 2014 criteria**
- **ECOG PS 0-1**
- **BV-naive and BV-exposed patients eligible**

R 1:1

Pembrolizumab 200 mg IV Q3W + Brentuximab Vedotin 1.8 mg/kg IV Q3W for 4 cycles

GDP (gemcitabine, dexamethasone, cisplatin) Q3W for 3 cycles

Response assessment with PET-CT[1]

PET Deauville 1-3 ASCT with consolidative RT and/or BV maintenance at investigator discretion

PET Deauville 4-5 ASCT or Alternate salvage/ASCT

Stratification Factors

- Prior Brentuximab vedotin and/or PD-1 inhibitor with primary therapy (Y/N)
- Duration of response to prior therapy (Refractory vs. Relapsed < 1 year vs Relapsed > 1 year

Primary End Point: PET-CR by Lugano 2014 (Deauville 1-3)

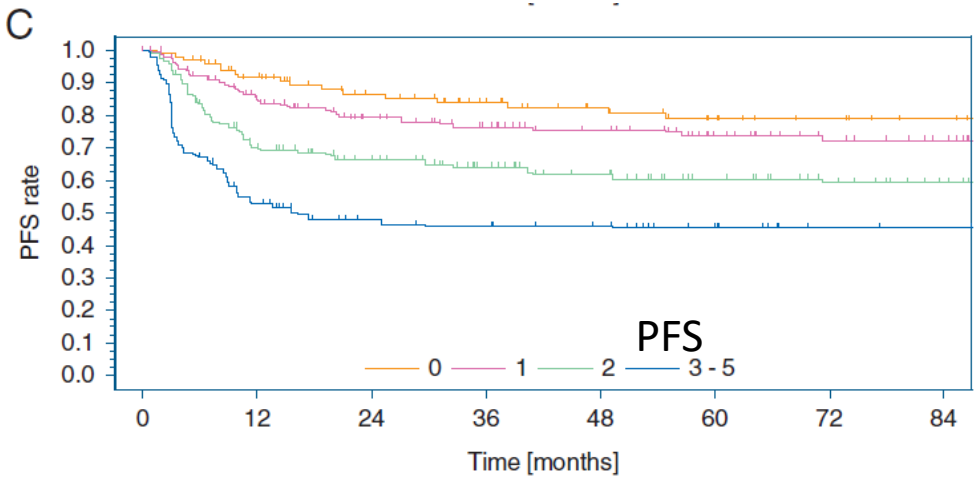
Secondary End Points: PFS, EFS, OS, transplantation rate, toxicity and safety, HRQOL,health economics
Exploratory: translational correlatives, PET radiomics, RECIL criteria response

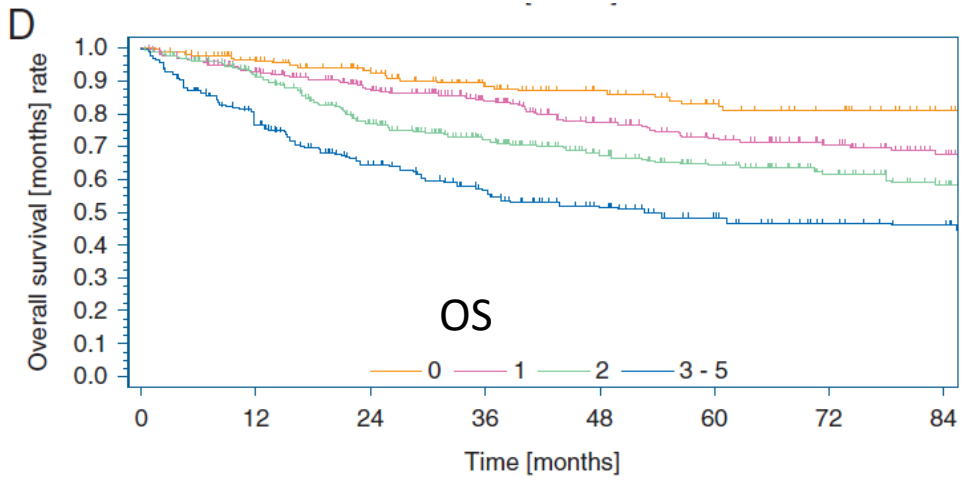
Canadian Cancer Trials Group

PIs: K Savage, J Kuruvilla

Clinical prognostic factors identify patients with excellent outcome post-ASCT: do they need it?

- Evaluation of 1045 patients undergoing ASCT from Germany, Denmark and US (MSKCC); more that 20 potential clinical risk factors
- Multivariable analysis: *5 significant non-redundant RFs:*
- Time to rel <3mos, stage IV, PS ≥1, bulk >5cm, non-response to therapy (< PR by CT or PET)



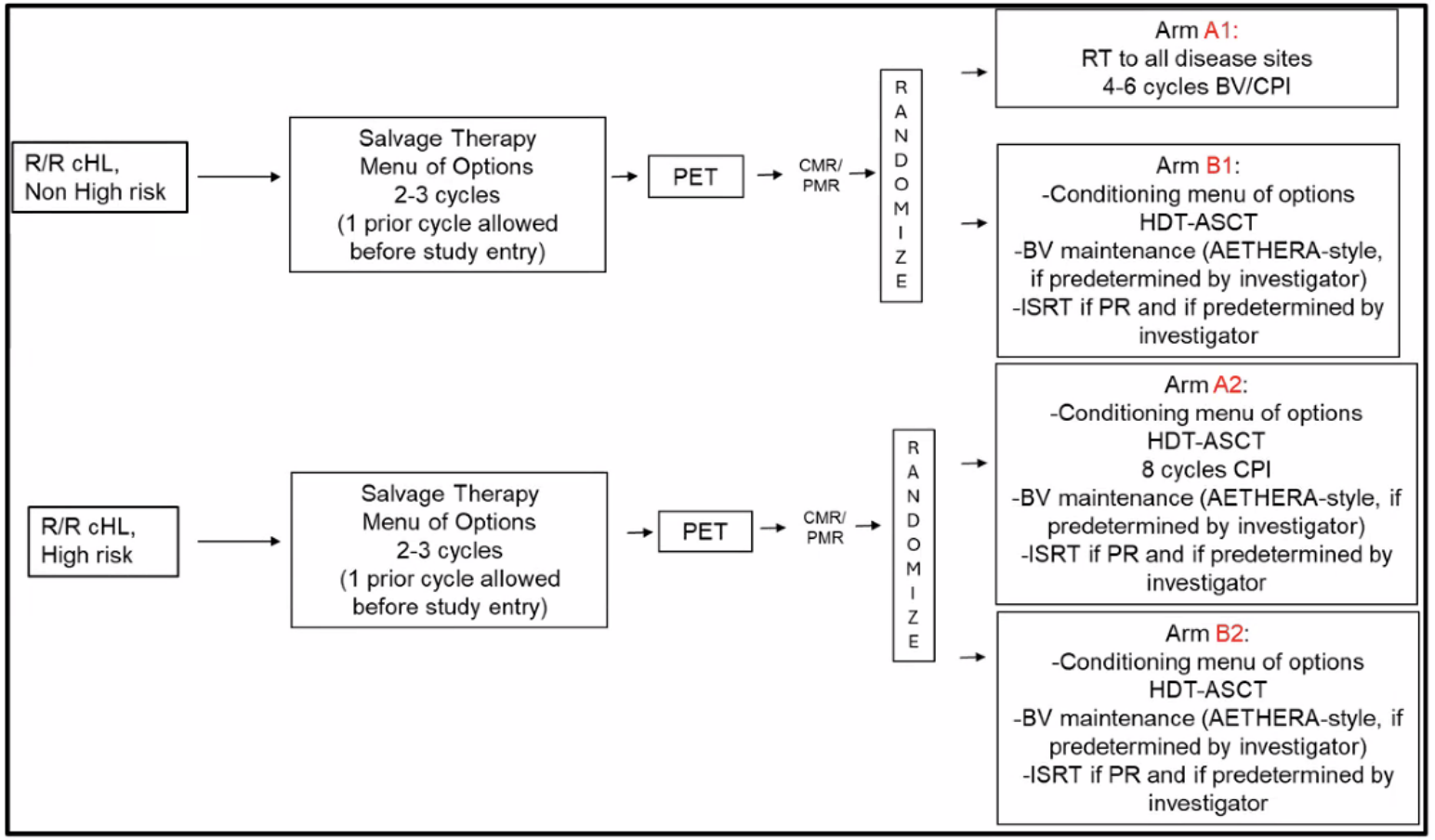


HRs equally weighted
~ 1.67 for PFS
~1.70 for OS

Brockelmann P, Ann Oncol 2017

Future Direction for ASCT?

- NCTN trial of R/R HL in development, led by ECOG



Goal in non-high-risk cohort: demonstrate non-inferiority of ISRT + CPI/Bv maintenance compared to HDC/ASCT

Goal in high-risk cohort: demonstrate efficacy of CPI in addition to HDC/ASCT

Treatment options for advanced cHL 2026

- BrECADD will replace escBEACOPP
  - PET guided approaches still (cost) effective (shorter duration of therapy, less toxicity)
  - Early data on fertility prospects are helpful in guiding patient discussions
  - Localized residual FDG uptake on EOT PET scan: INRT recommended option (based on HD15 etc)
- Nivolumab + AVD will replace BV-AVD for patients with stage III-IV cHL
  - Advantages particularly important in patients older that age 60: first RCT data to demonstrate improvement in older patients
  - 6 months of therapy, significant anthracycline dose (vs 4 BrECADD)
  - Longer follow-up on immune-mediated toxicities, fertility and durability of response will be important

Salvage treatment options for cHL in 2026

How do we sequence BV and PD1 antibody therapy?

- Should patients progressing after BV-containing first-line therapy receive PD1 antibody with salvage chemotherapy?
  - Probably, based on phase II data
- Is it better to re-treat with PD1 antibody, with chemo, for patients progressing after Nivo-AVD?
  - Possibly? Retrospective data
- Can patients with low risk of recurrence be treated without ASCT at first relapse?
  - What is the best chemo-immunotherapy strategy? Include IFRT?
  - How do we define the patient population (long CR1, localized/amenable to CMT, other features?)