Fred Hutch
Cancer Center

Management of Classical Hodgkin Lymphoma

Ryan Lynch, MD

University of Washington CME Board Review

Associate Professor, University of Washington

Associate Professor, Fred Hutch Cancer Center

October 8, 2025

UW Medicine

Disclosures

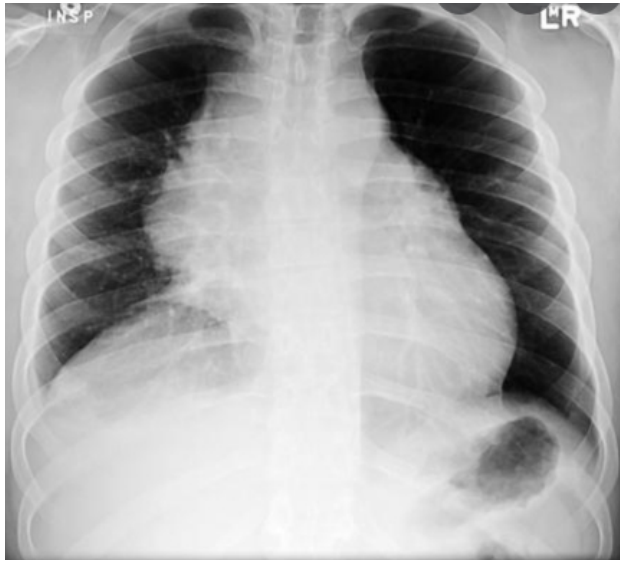
- Research Funding: TG Therapeutics, Incyte, Bayer, Cyteir, Genentech, Pfizer, Rapt, Merck, Janssen,Allogene;
- Consultancy/Honoraria: SeaGen, Abbvie, Janssen, Merck, ADC Therapeutics, Foresight Diagnostics, Genentech

Background

- Classical Hodgkin lymphoma (CHL) represents ~ 10% of all lymphomas
- 8500 new cases annually in the United States
- Highly curable with frontline therapy (chemotherapy +/- RT)
  - Early stage > 90%
  - Advanced stage ~ 75%

Presentation

- Painless lymphadenopathy
- B symptoms (20% stage I-II, 50% stage III-IV)
  - Fevers
  - Chills
  - Night sweats (DRENCHING!)
  - Unexplained weight loss (10%)
- Itching without rash
- Alcohol induced pain in involved sites (10%)
- Cough, light-headedness, compression of major blood vessels related to large (bulky) mass



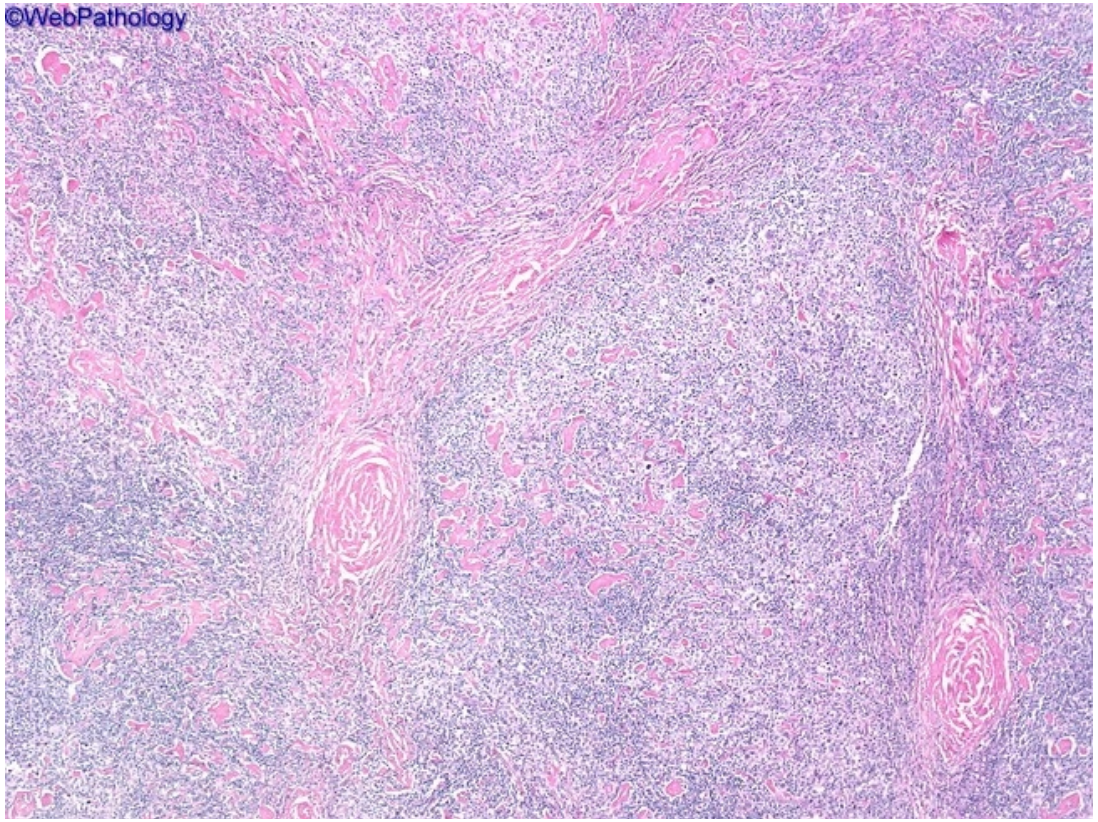
What causes Hodgkin lymphoma?

- Immune cell origin (thymus), so likely derives from a defective immune response
  - Environmental factors? Familial clustering?
  - Link to infectious mono (Epstein-Barr virus)
    - But most people who get mono don't get lymphoma!

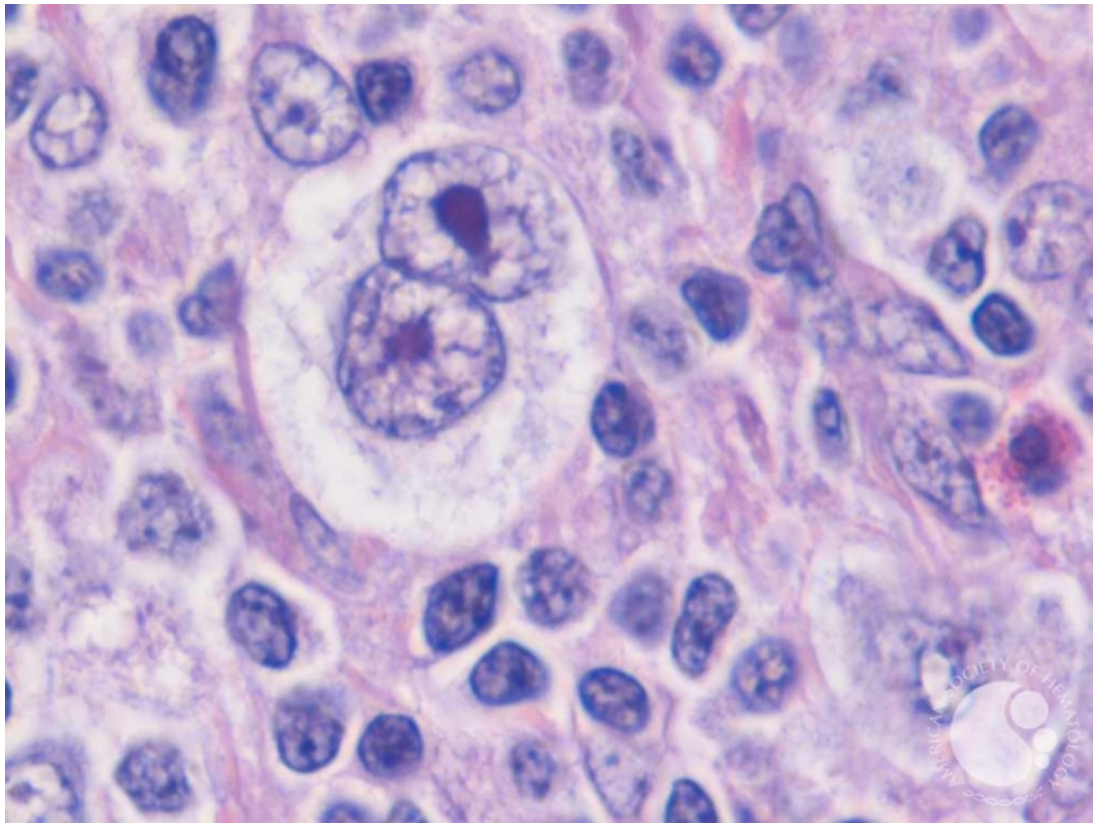
- NOT contagious!
- Can't pass to children!
  - Though first-degree family relative are more likely to develop this (not by much thought). Perhaps related to similar environment/genetics

Rare Hodgkin lymphoma cells

The malignant cell makes up < 1% of the tumor!

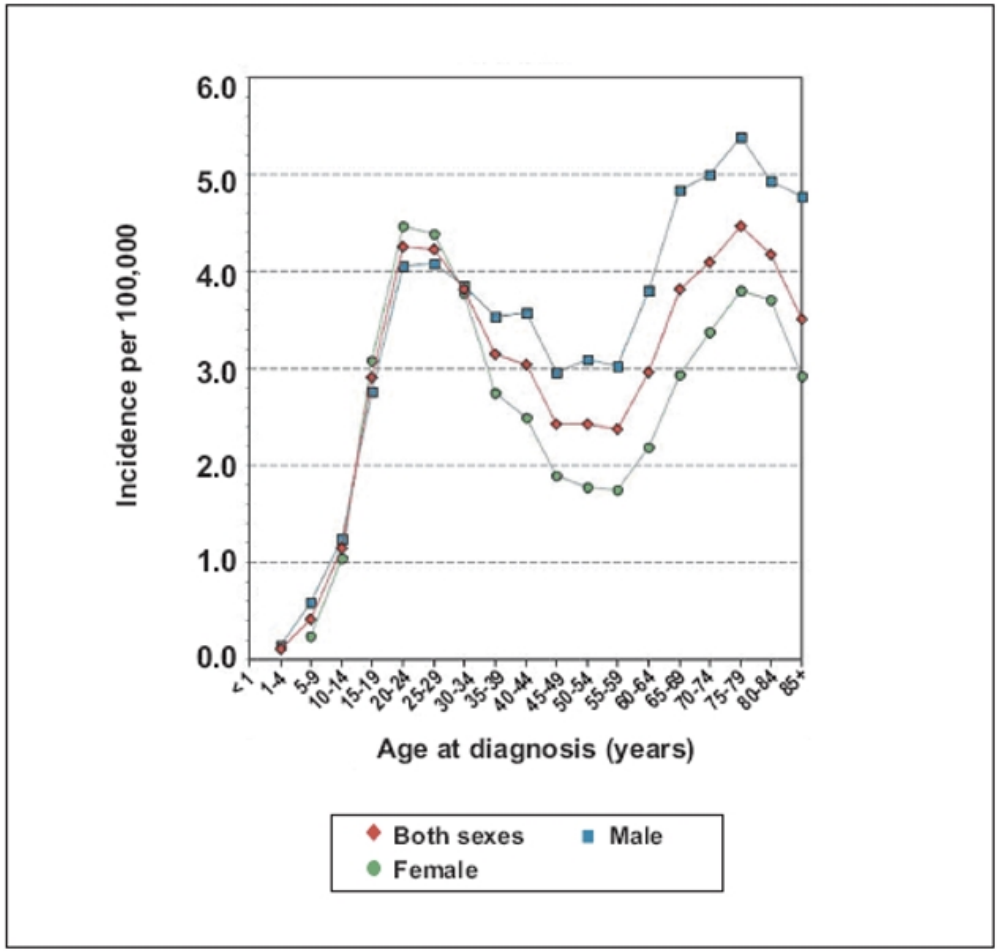


WebPathology.com



Hematology.org

Hodgkin lymphoma by age



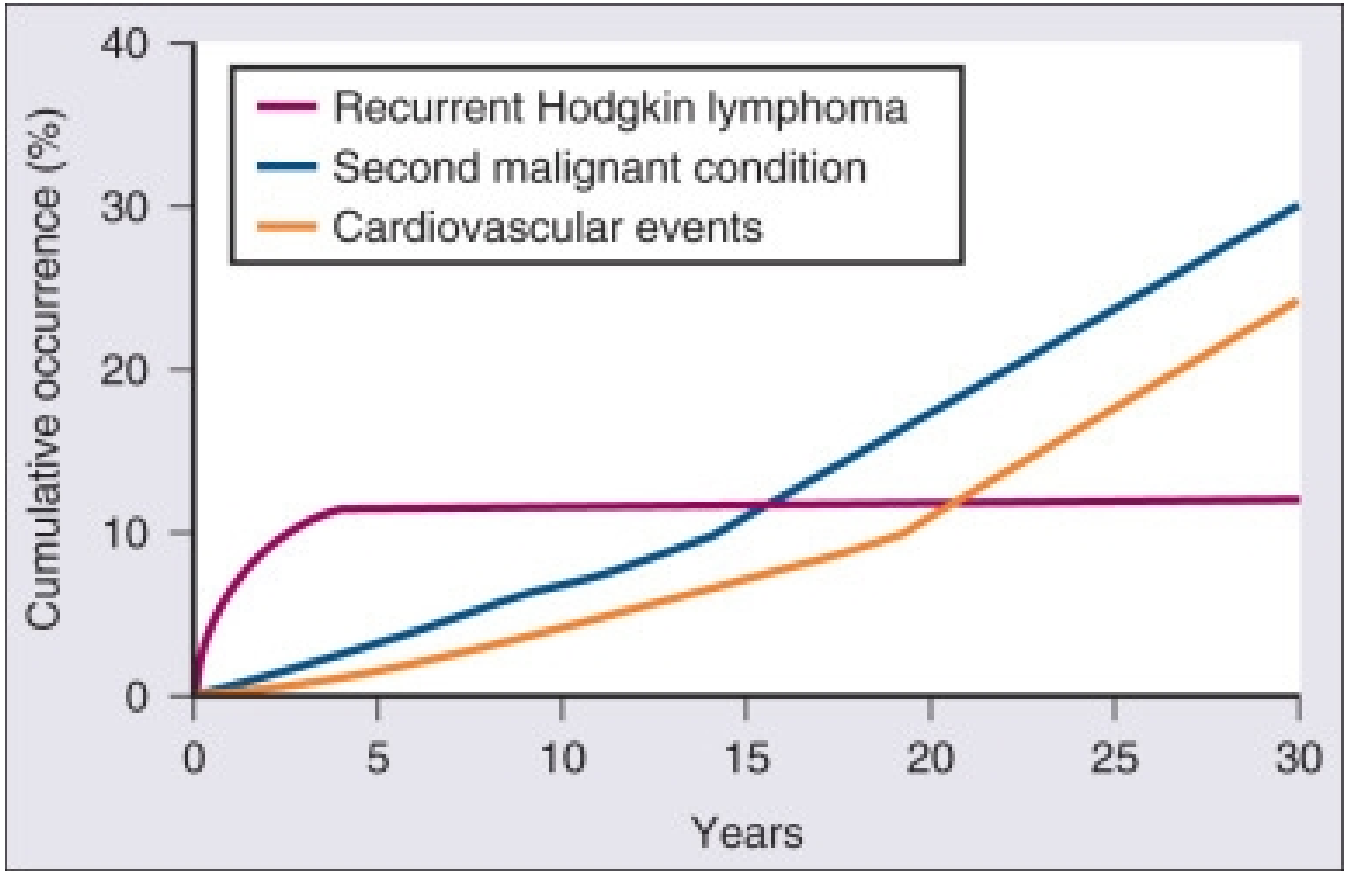
- One of the most common cancers to affect adolescents/young adults
- Incidence rises again in older adults
  - But so do most other kinds of cancer unfortunately

Evens et al. Cancer Network 2008

What have we learned over the years about Hodgkin lymphoma?

- 1820s - “Hodgkin’s disease” – Thomas Hodgkin
- 1960s- First limited-stage patients cured with radiation therapy
- 1960s-1970s- NCI devised regimen called “MOPP” that cured many advanced patients
  - M = mustard (the same as mustard gas!)
- Over the years, long term toxicities of high dose radiation and intensive chemo were recognized

Early cure, late effects



Bartlett et al. Abeloff's Clinical Oncology 2020

Historical advances in CHL management

- Limited stage
  - Definitive “Mantle” RT evolved to combined modality therapy
- Advanced stage
  - Evolution from MOPP to safer regimens (ABVD)

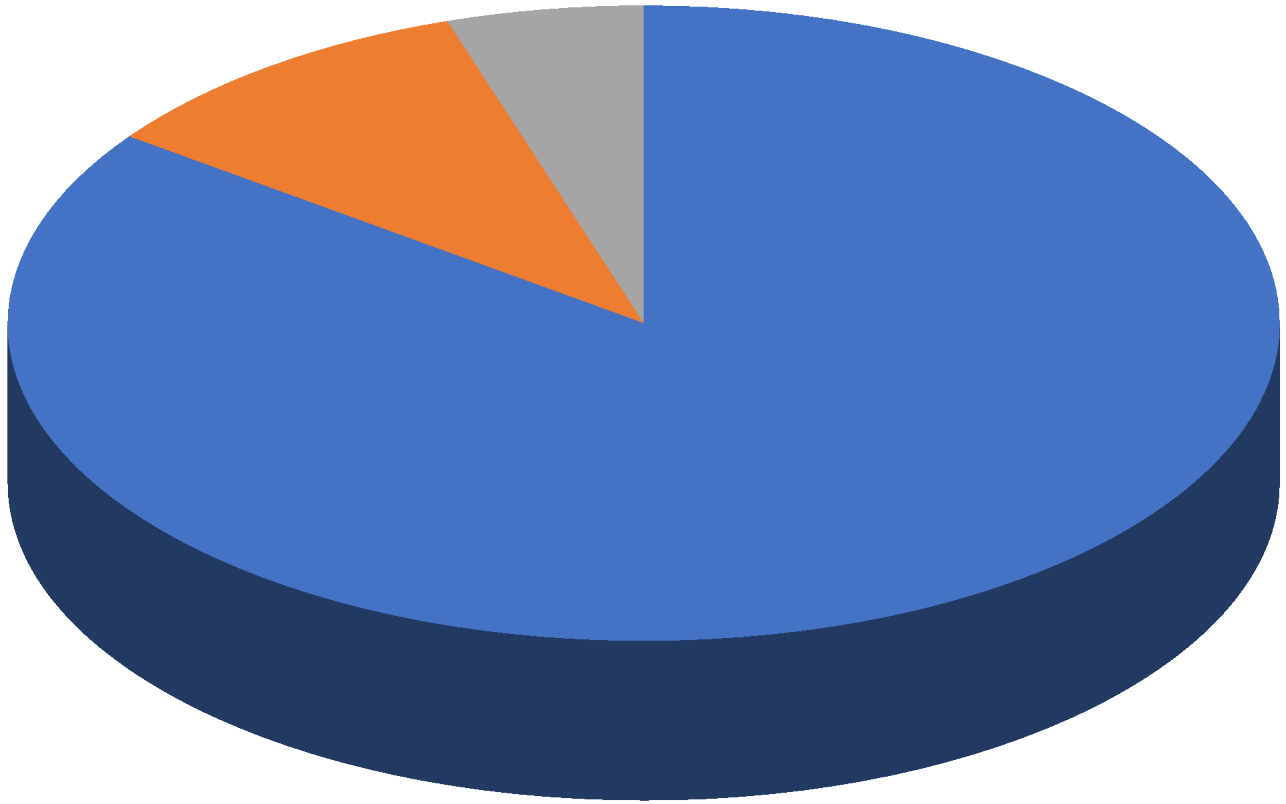
- Widespread adoption of PET/CT in the 2000s allowed for more accurate staging, response assessment, as well as allowing for more limited radiation fields.

New drugs for Hodgkin lymphoma

- The FDA approval of 3 drugs for CHL since 2011 has sparked a wave of new advances
  - Brentuximab vedotin: 2011
  - Nivolumab: 2016
  - Pembrolizumab: 2017
- While the initial approvals were as monotherapy in the relapsed setting, we have since learned more about how these agents can improve outcomes in CHL in various combinations and even in untreated patients.

- What have we learned so far, and how may this change long-standing principles in CHL management?

Hodgkin Lymphoma in 2025



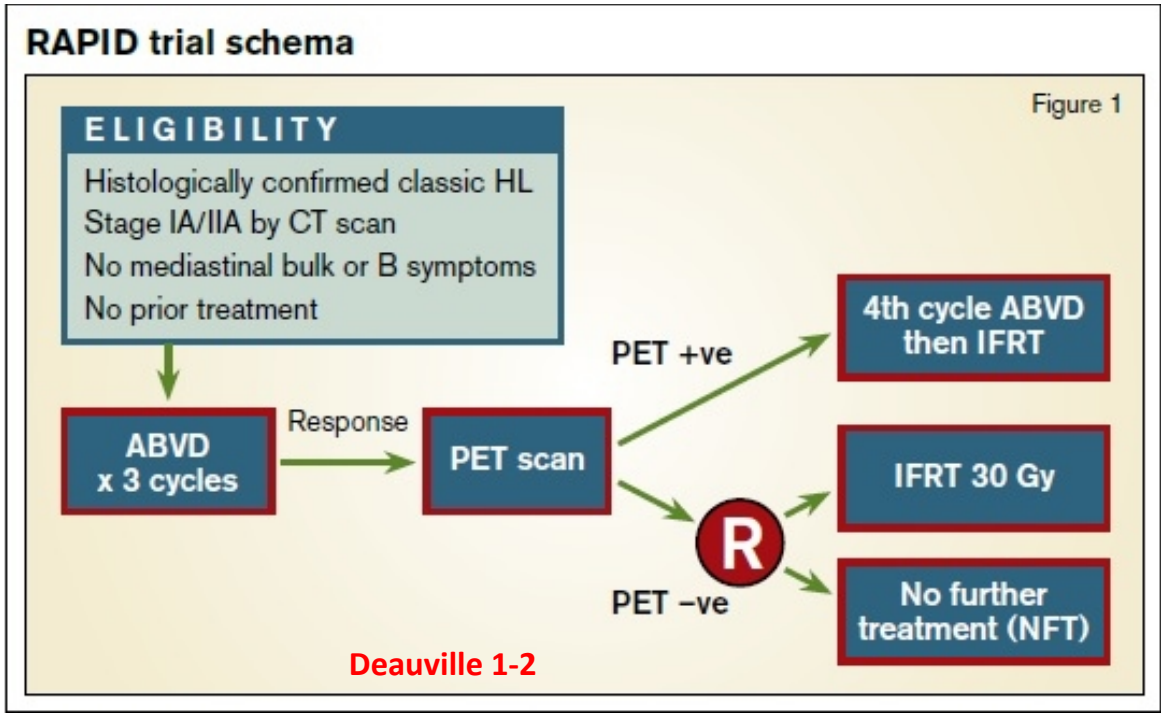
Cured with primary therapy
Cured with auto transplant
Transplant ineligible or relapse post transplant

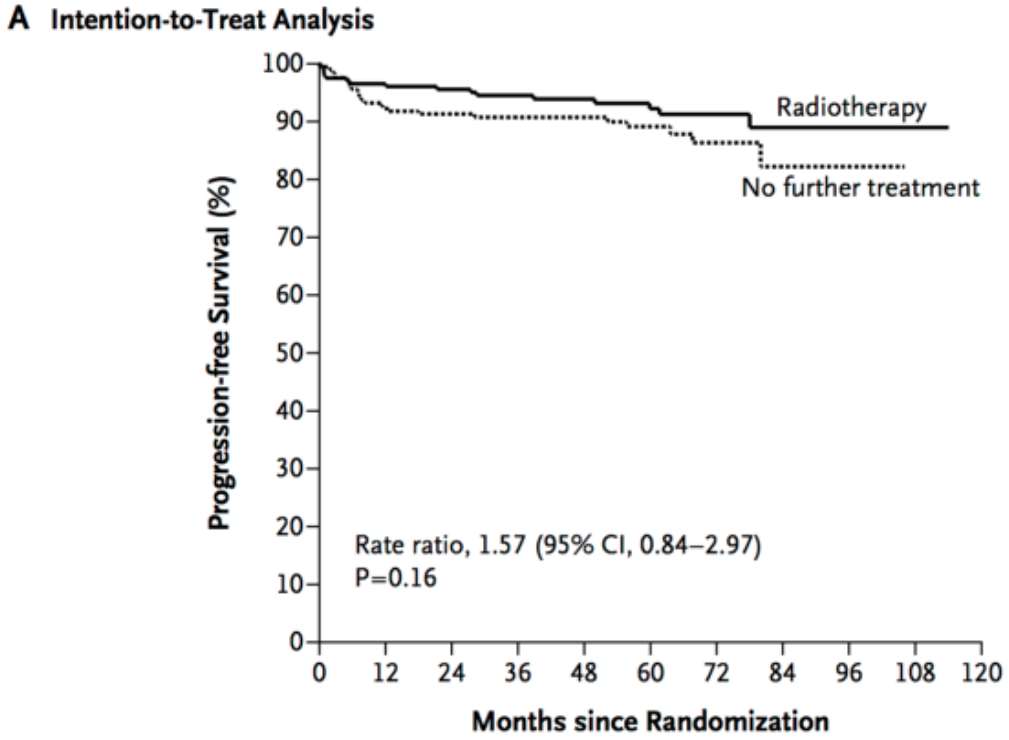
Limited Stage Hodgkin Lymphoma

- Favorable (Stage I or II, one or two nodal sites)
  - Abbreviated combined modality therapy

- Unfavorable (3 or more nodal sites, bulky, B symptoms)
  - Combined modality therapy
  - Chemotherapy alone
  - Role of novel agents???

RAPID – PET-adapted therapy in limited stage CHL





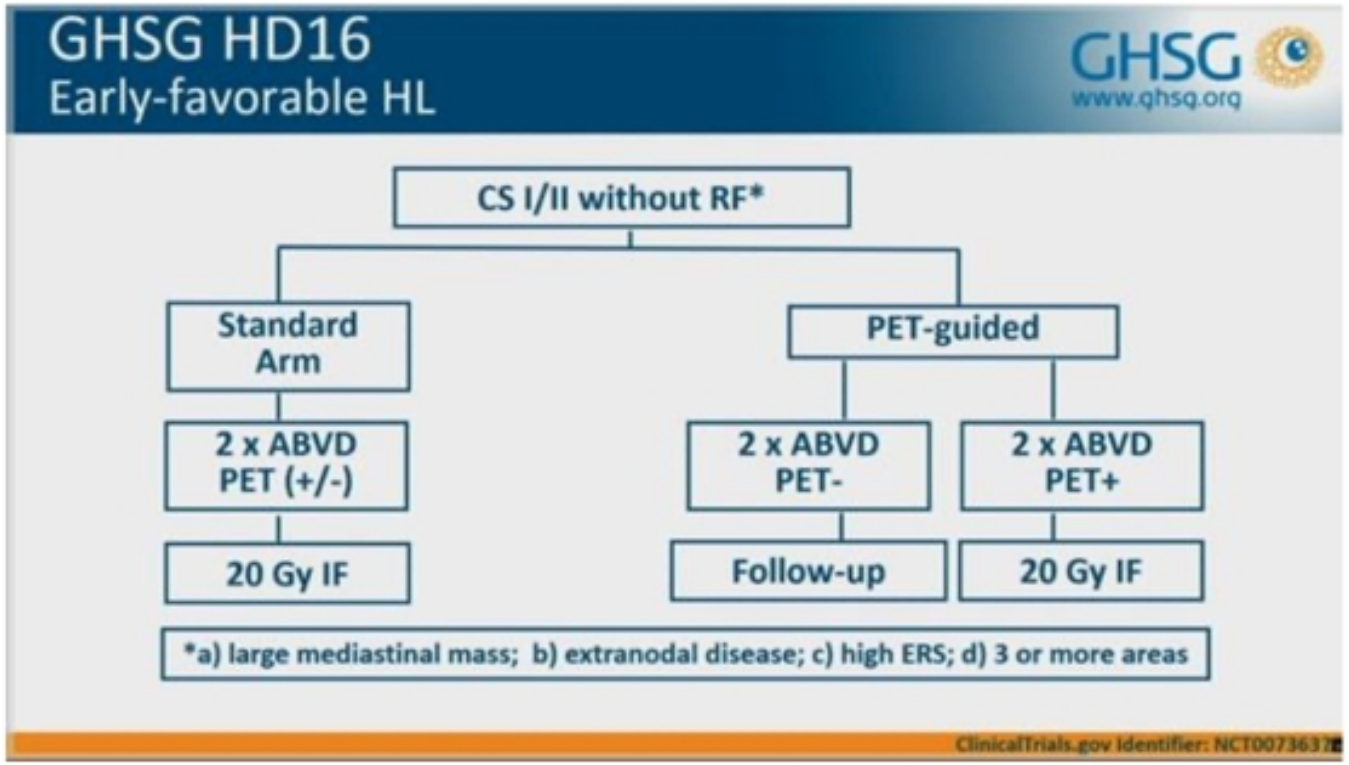
Missed non-inferiority target, but has been adopted into NCCN guidelines

Radford J et al: N Engl J Med 372:1598-607, 2015

HD16 – Early stage HL without risk factors

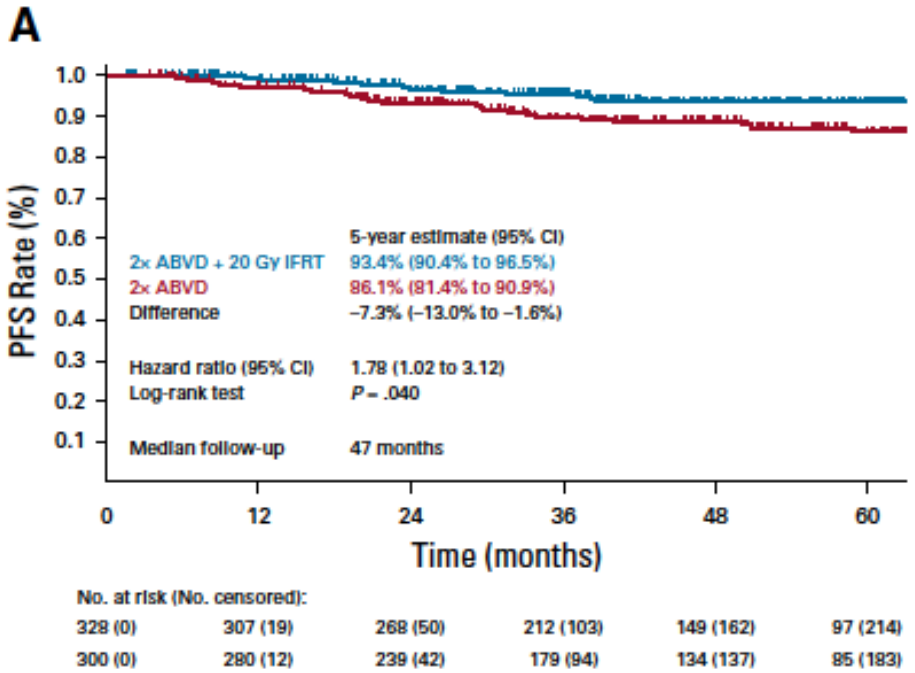
- Risk factors
  - Age ≥ 50
  - Large Mediastinal mass
  - ESR > 30 mm/h with B symptoms
  - ESR > 50 mm/h w/o B symptoms
  - **> 2 nodal sites**

PET neg = Deauville 1-2



Fuchs et al JCO 2019

HD16 - Inferior PFS in PET2-neg patients without RT

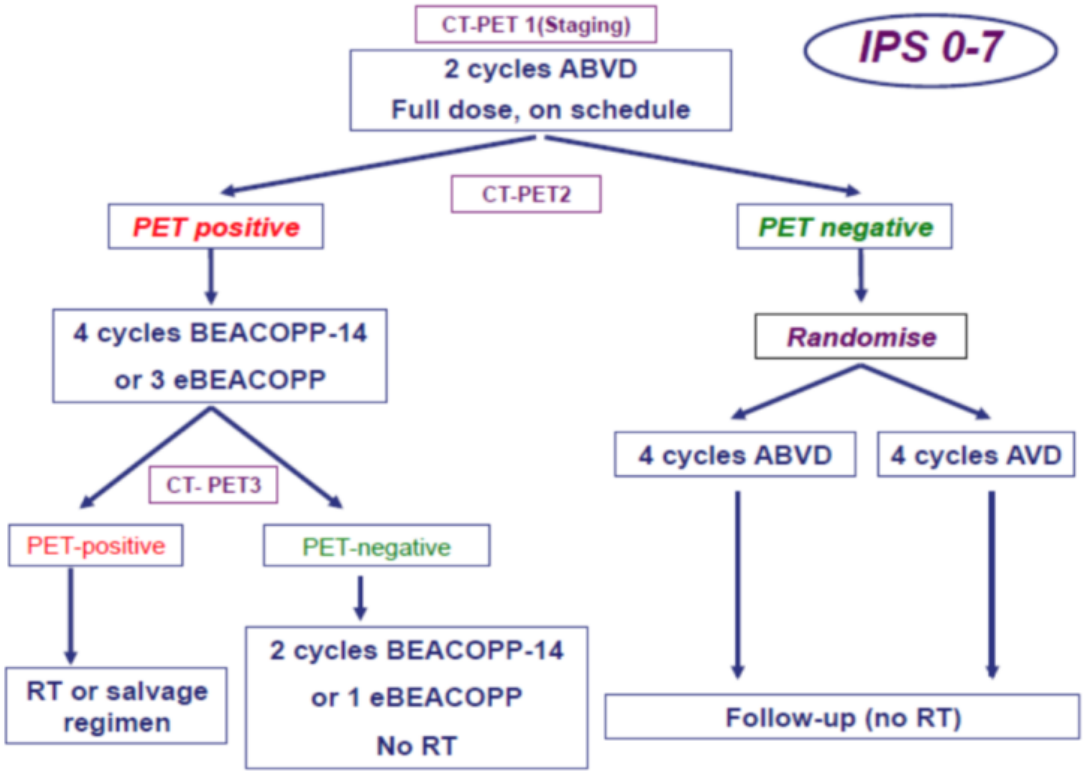


Radiation CANNOT be omitted in PET negative early stage favorable patients after 2 cycles ABVD without reduction in PFS

Fuchs et al JCO 2019

RATHL – PET-adapted therapy in early stage unfavorable and advanced stage CHL

Stage IIA with bulk and/or ≥ 3 sites
Stage IIB-IV

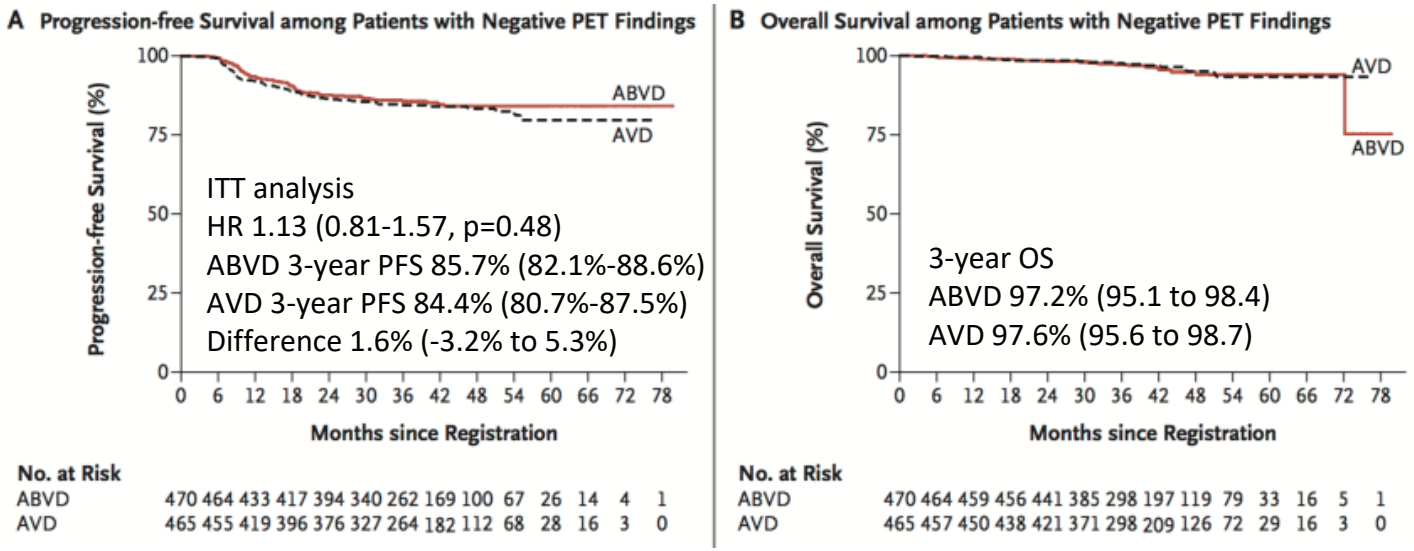


Characteristic	Number or %
Median age	33 (18-79)
Male	55%
Stage II	41%
III	31%
IV	28%
B symptoms	61%
Bulky disease	31%
PS 0-1	96%
IPS 0-1	34%
2-3	49%
≥ 4	18%

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

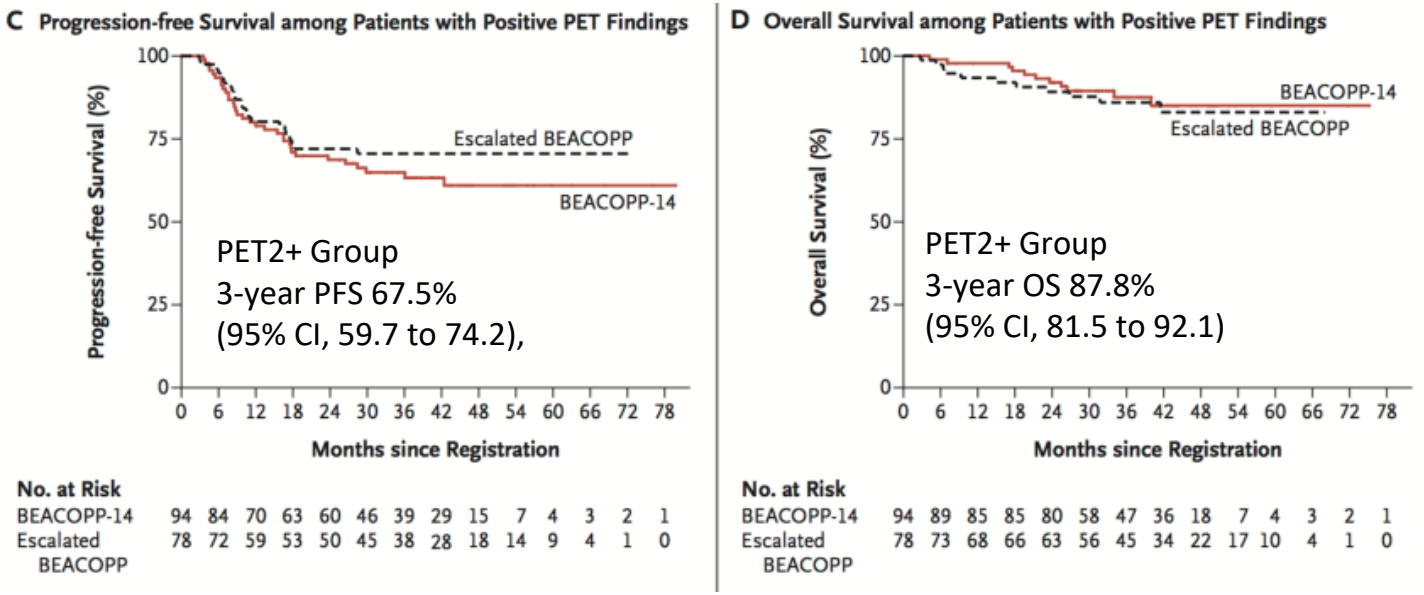
RATHL – Results in PET2-negative patients

- No statistical difference in 3-year PFS and OS
- Just outside pre-determined non-inferiority margin of 5%



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

RATHL – Results in PET2-positive patients



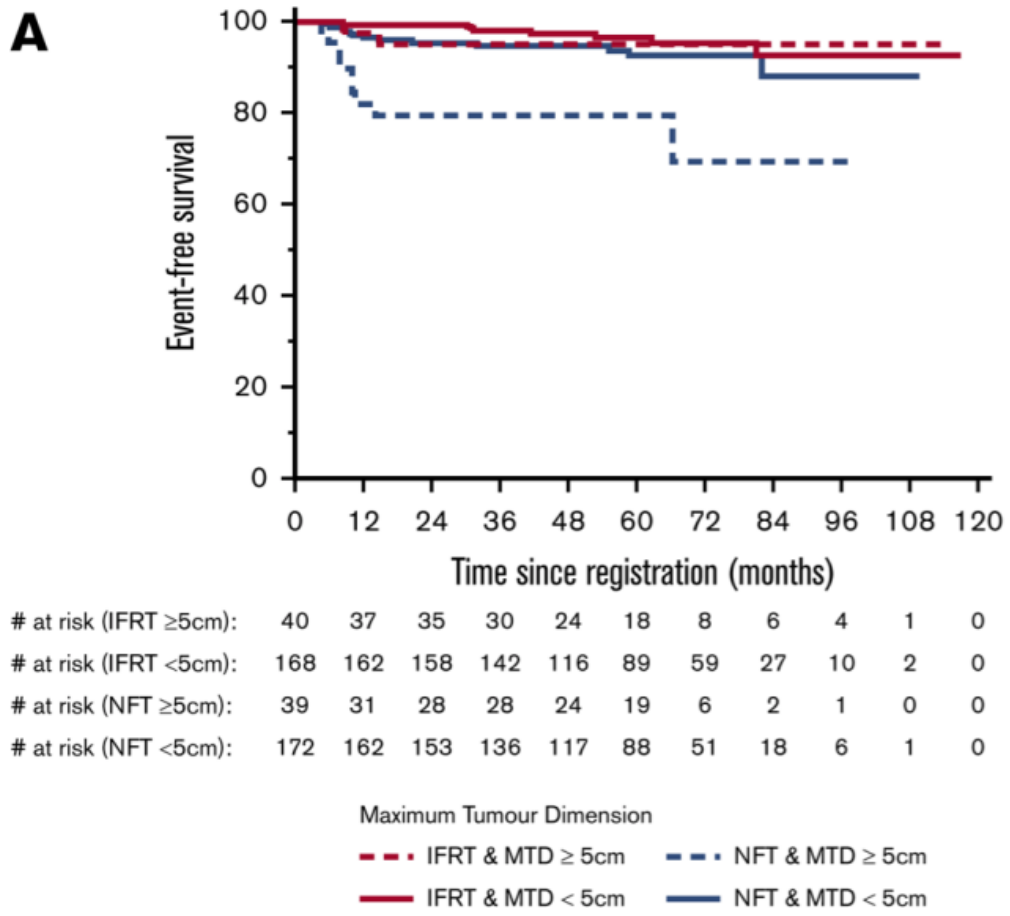
- **Improved PFS in PET2 positive patients compared to historical controls**

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

Are there limitations to PET-adapted therapy in CHL?

RAPID trial – impact of maximum tumor dimension

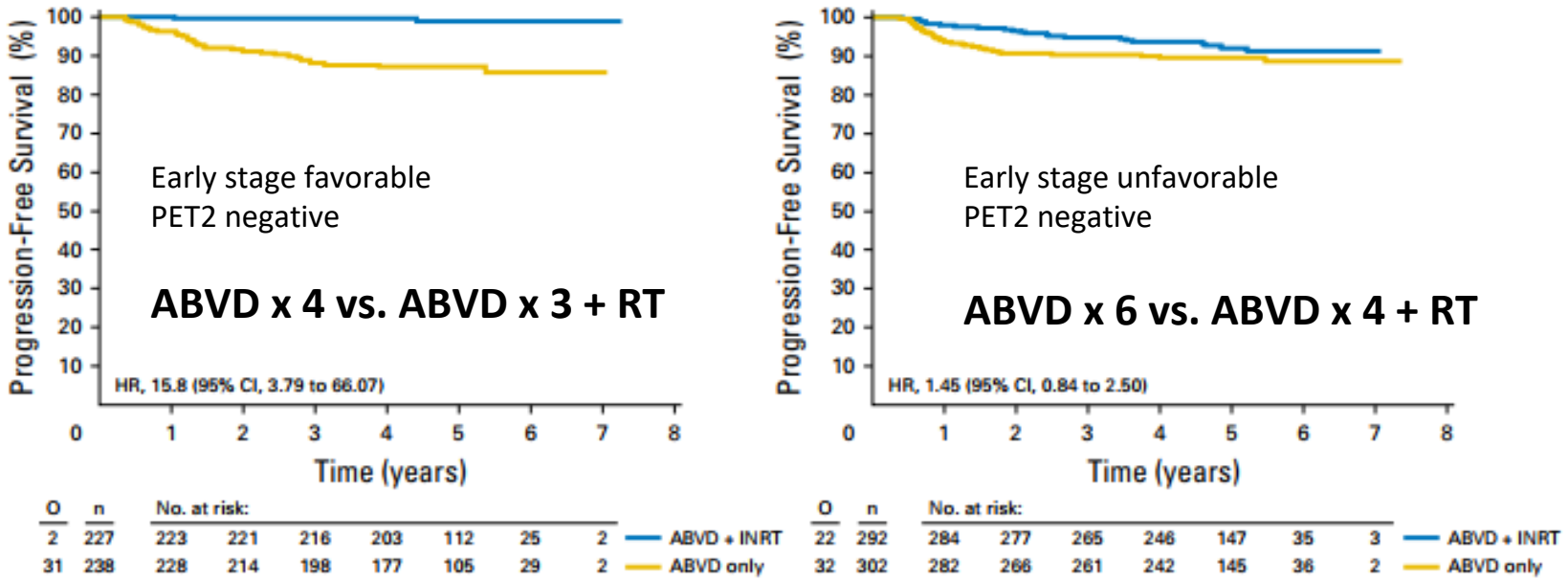
- MTD ≥ 5 cm correlates with worse outcomes when RT omitted



Ilidge et al. Blood Advances 2020

EORTC H10 trial

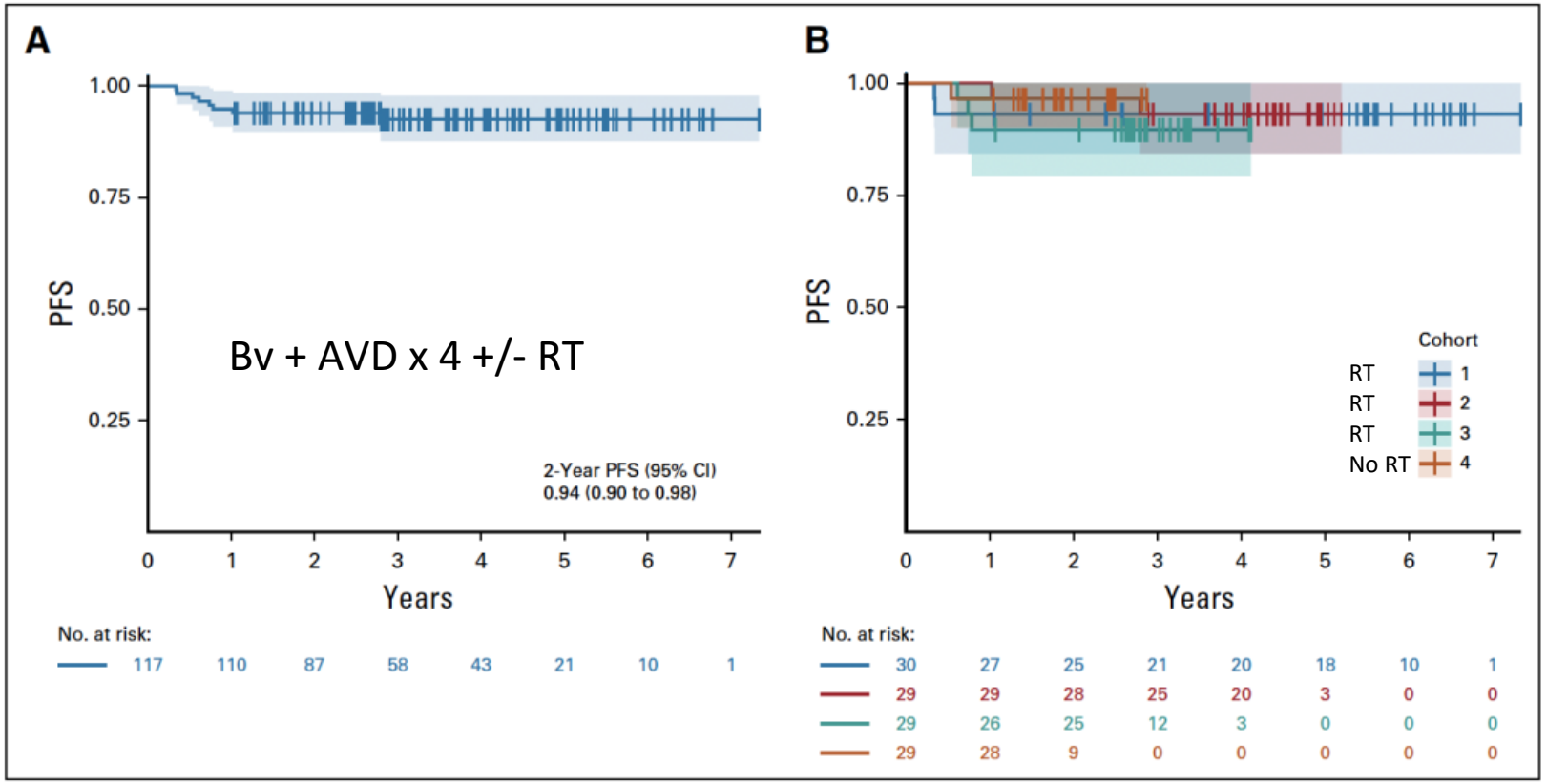
Inferior outcomes in PET2- patients with abbreviated chemo and no RT



Andre MPE, et al. J Clin Oncol 35:1786-1794, 2017

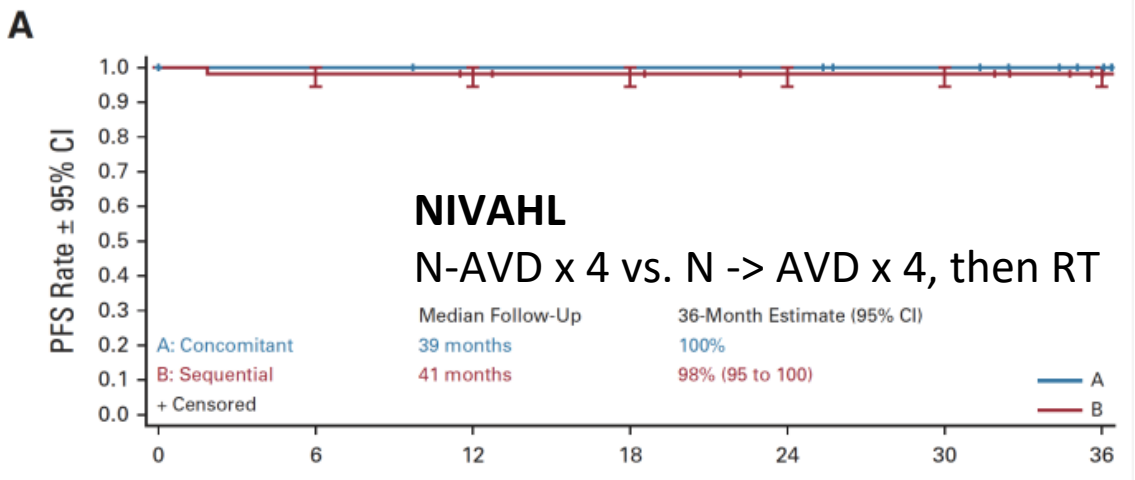
Moving novel agents into earlier combinations

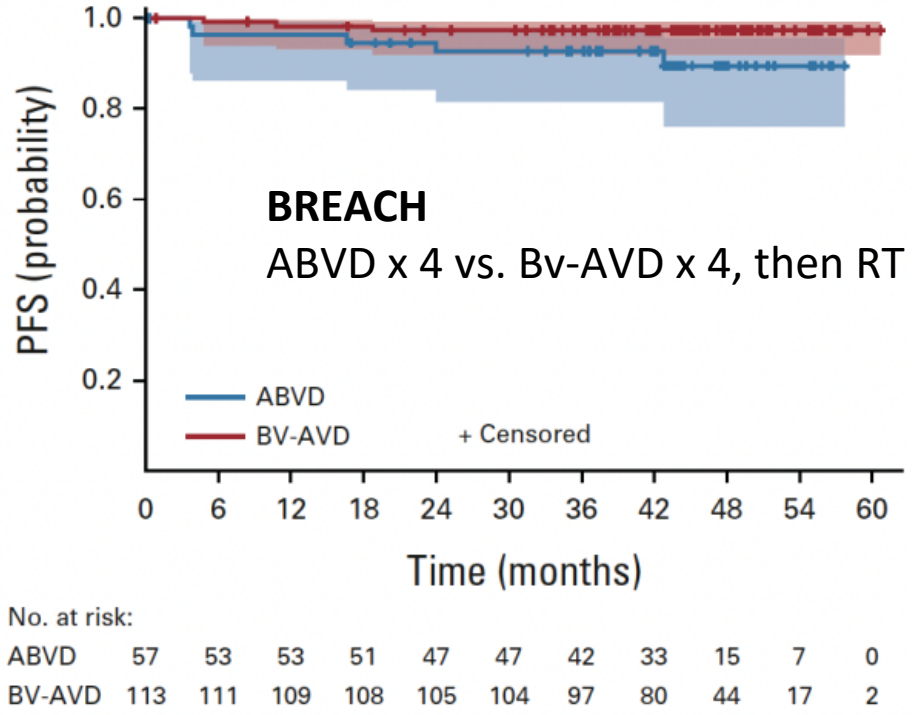
Limited Stage CHL - Bv + AVD x 4 +/- RT



Kumar et al. JCO 2021

PD1-inhibitors or Bv with chemo in Limited Stage CHL + RT





Brockelman et al. JCO 2023,
Fornecker et al. JCO 2023

Limited Stage Hodgkin Lymphoma

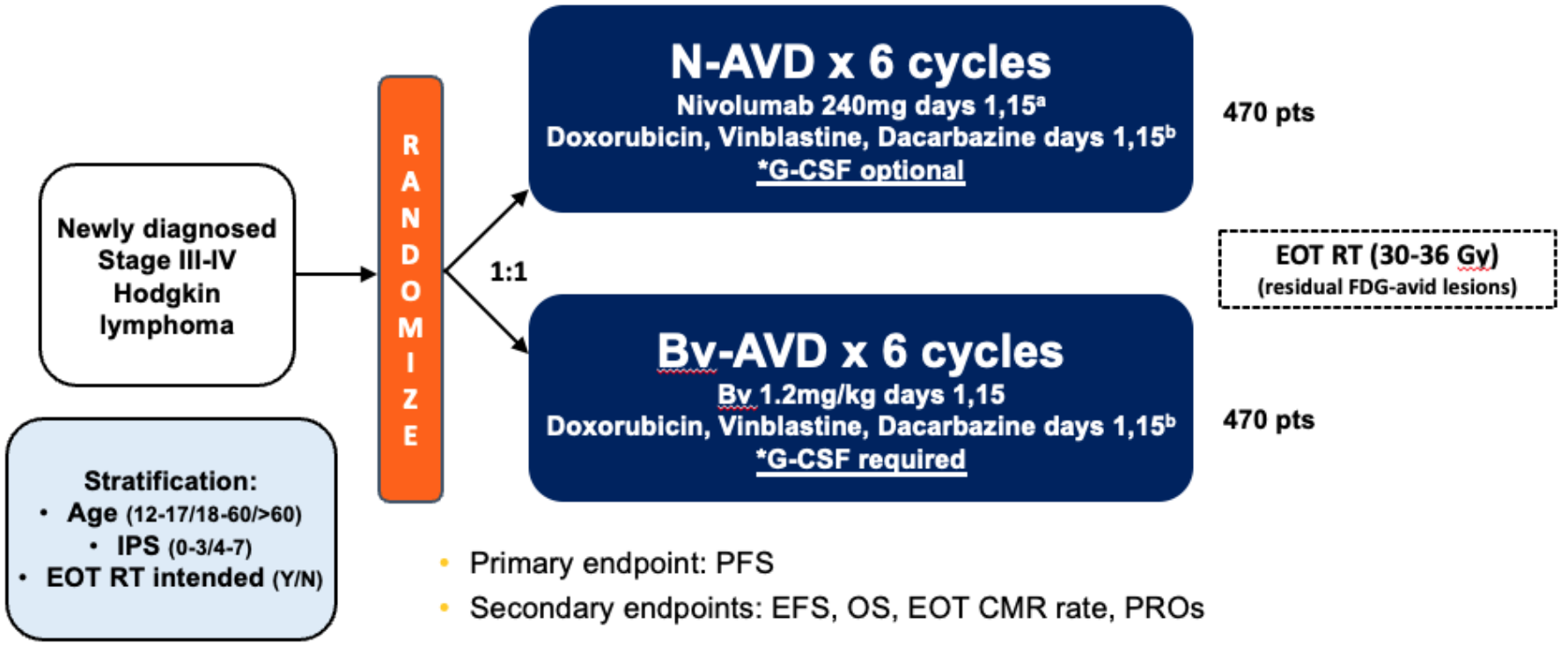
- Favorable (Stage I or II, one or two nodal sites)
  - ABVD x 2 + 20 Gy
  - ABVD x 4 in select PET2 negative patients

- Unfavorable (3 or more nodal sites, bulky, B symptoms)
  - Combined modality therapy
    - ABVD x 4 + RT if PET2 negative (Consider ABVD x 6 + RT If PET2+)
  - Chemotherapy alone
    - Would not recommend if PET2+ after ABVD
    - ABVD x 4-6: Careful counseling in select patients if PET2 neg
      - RATHL
  - Role of novel agents
    - ???
    - BV-AVD x 4 + RT and Nivo-AVD x 4 + RT in NCCN guidelines based on phase 2 data

Advanced Stage Hodgkin Lymphoma

S1826 Study design

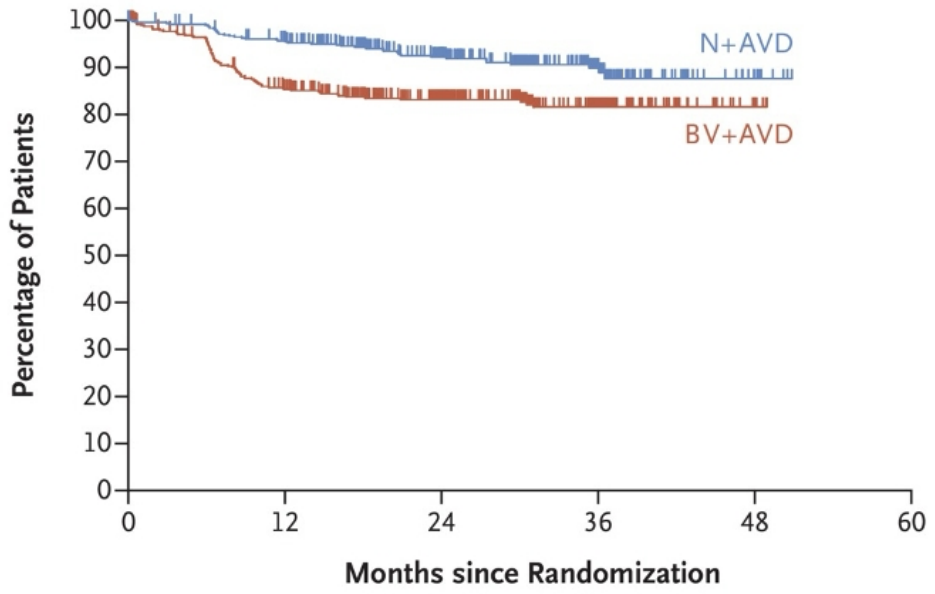
Is Brentuximab vedotin or nivolumab superior in combination with AVD?



Herrera et al. ICML 2023

S1826 – Primary Endpoint – ANVD superior to Bv-AVD

A Progression-free Survival



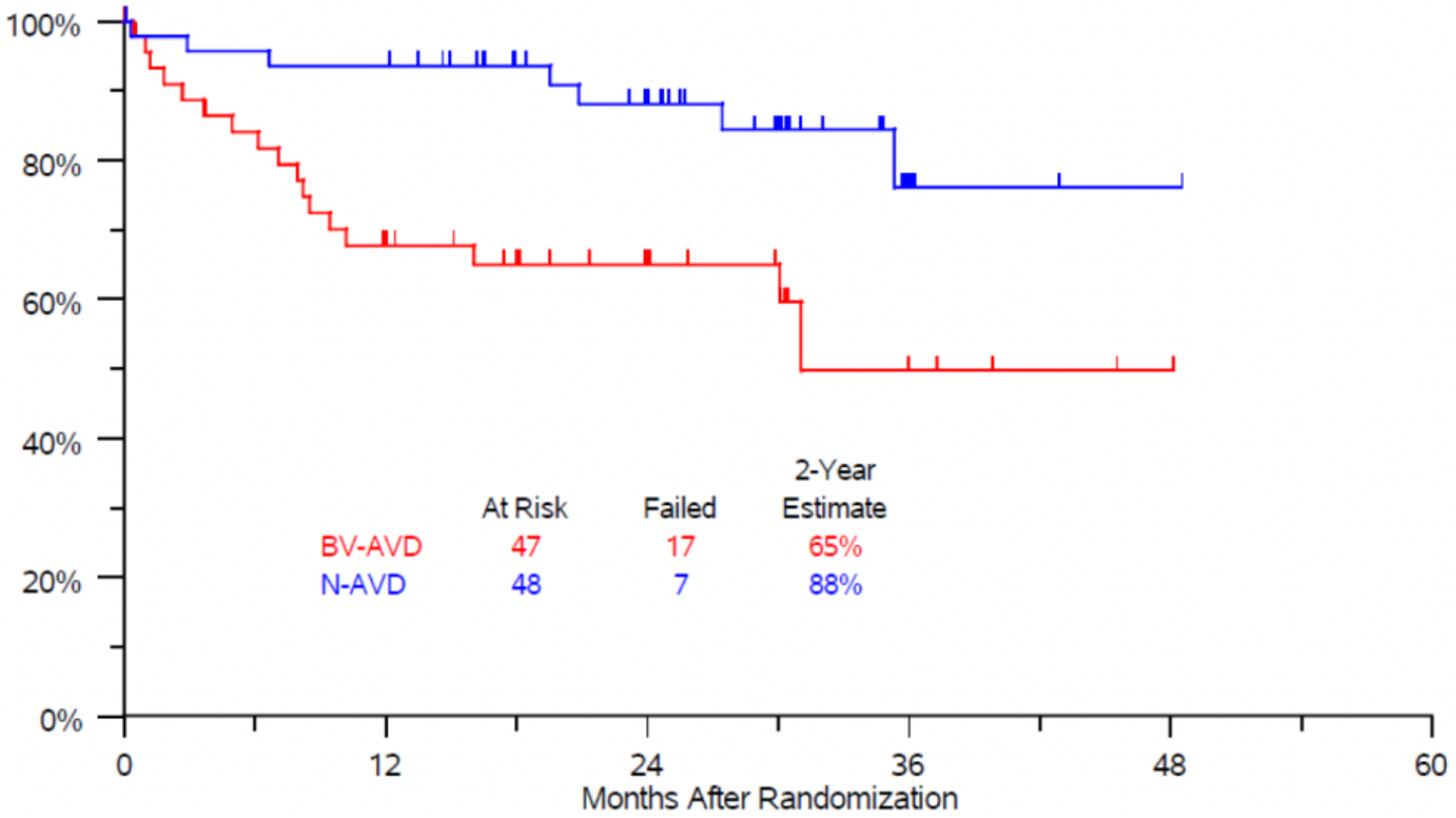
No. at Risk						
N+AVD	487	450	281	101	9	0
BV+AVD	483	392	244	97	7	0

	Disease Progression or Death *no. of patients*	2-Year Estimate for Progession-free Survival (95% CI) *percent*
N+AVD	41	92 (89–94)
BV+AVD	81	83 (79–86)

Hazard ratio, 0.45 (95% CI, 0.30–0.65)

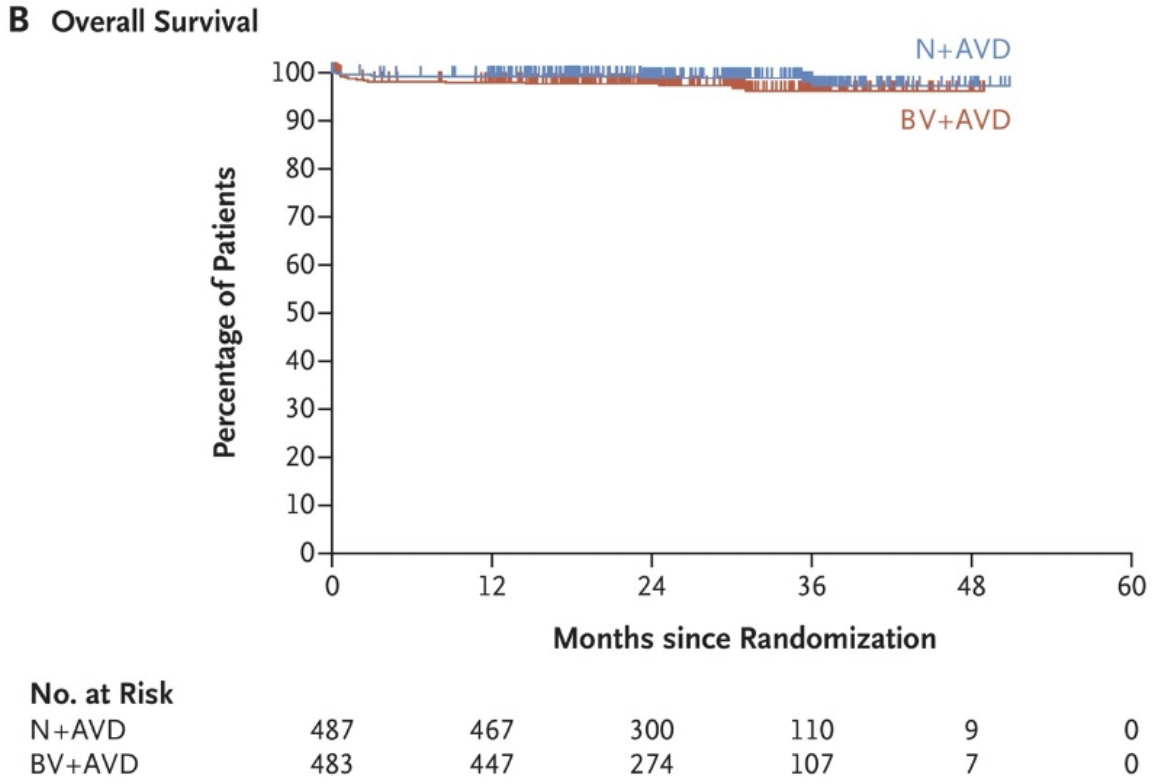
Herrera et al NEJM 2024

S1826 – Age 60+: ANVD far superior to Bv-AVD



Herrera et al NEJM 2024

S1826 – Overall Survival Comparison



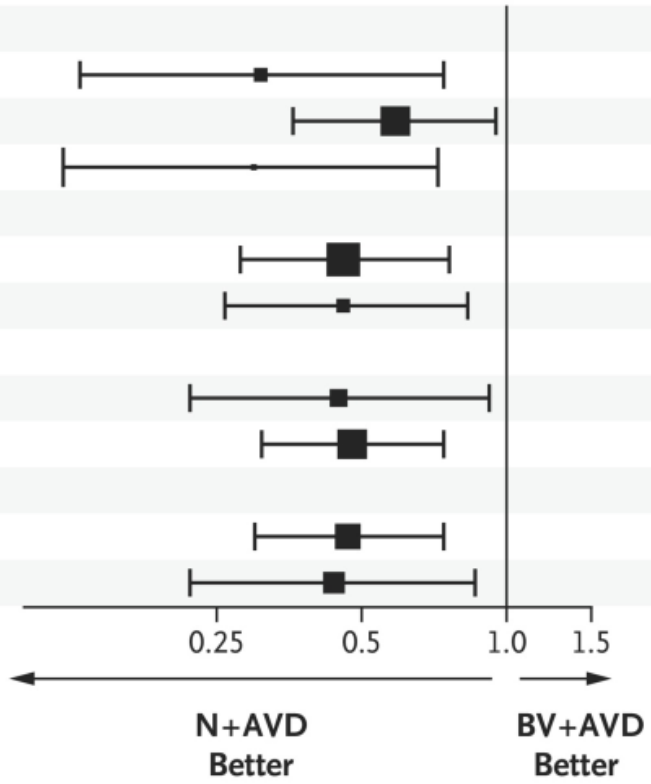
	Death *no. of patients*	2-Year Estimate for Overall Survival (95% CI) *percent*
N+AVD	7	99 (97–100)
BV+AVD	14	98 (96–99)

Hazard ratio, 0.39 (95% CI, 0.15–1.03)

Herrera et al NEJM 2024

S1826 – Sub-group analysis

Subgroup	N+AVD	BV+AVD	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of events/total no. (%)		
Age			
12–17 yr	7/118 (5.9)	21/118 (17.8)	0.31 (0.13–0.74)
18–60 yr	27/321 (8.4)	43/318 (13.5)	0.59 (0.36–0.95)
>60 yr	7/48 (14.6)	17/47 (36.2)	0.30 (0.12–0.72)
IPS risk group			
0–3	24/332 (7.2)	48/328 (14.6)	0.46 (0.28–0.76)
4–7	17/155 (11.0)	33/155 (21.3)	0.46 (0.26–0.83)
Stage			
III	12/185 (6.5)	22/168 (13.1)	0.45 (0.22–0.92)
IV	29/302 (9.6)	59/315 (18.7)	0.48 (0.31–0.74)
Symptoms			
B	29/288 (10.1)	54/273 (19.8)	0.47 (0.30–0.74)
A	12/199 (6.0)	27/210 (12.9)	0.44 (0.22–0.86)



PFS benefit seen across all ages, IPS score, and stage

Herrera et al NEJM 2024

S1826 – Treatment analysis

	Total		Nivolumab + AVD		Brentuximab Vedotin + AVD	
	n	%	*n*	%	*n*	%
Eligible Patients	970	100.0%	487	100.0%	483	100.0%
Completed treatment	875	90.2%	450	92.4%	425	88.0%
Discontinued all treatment early	95	9.8%	37	7.6%	58	12.0%
Adverse event	40	4.1%	20	4.1%	20	4.1%
Refusal unrelated to AE	22	2.3%	9	1.8%	13	2.7%
Progression/relapse	9	0.9%	0	0	9	1.9%
Death	11	1.1%	3	0.6%	8	1.7%
Other – not protocol specified	13	1.3%	5	1.0%	8	1.7%
Any discontinuation of Bv or Nivolumab*	153	15.8%	46	9.4%	107	22.2%
Discontinued Bv or Nivo, but continued other agents**	78	8.0%	19	3.9%	59	12.2%
Received any G-CSF	741	76.4%	274	56.3%	467	96.7%

Numerically higher rates of on-treatment study drug discontinuation and death in Bv arm

Herrera et al NEJM 2024

S1826 – Grade 3+ Adverse Events

Adverse Event Type	N-AVD n = 482 Grade ≥ 3 No (%)	BV-AVD n = 476 Grade ≥ 3 No (%)
Neutrophil count decreased	232 (48%)	126 (26%)
White blood cell decreased	73 (15%)	61 (13%)
Anemia	29 (6%)	43 (9%)
Lymphocyte count decreased	30 (6%)	41 (9%)
Febrile neutropenia	28 (6%)	33 (7%)
ALT increased	22 (5%)	23 (5%)
Peripheral sensory neuropathy	5 (1%)	39 (8%)
AST increased	12 (2%)	14 (3%)
Platelet count decreased	9 (2%)	16 (3%)
Sepsis	8 (2%)	16 (3%)

- Higher rate of G3+ neutropenia in ANVD arm did not translate to increased febrile neutropenia
  - GCSF not mandatory with ANVD

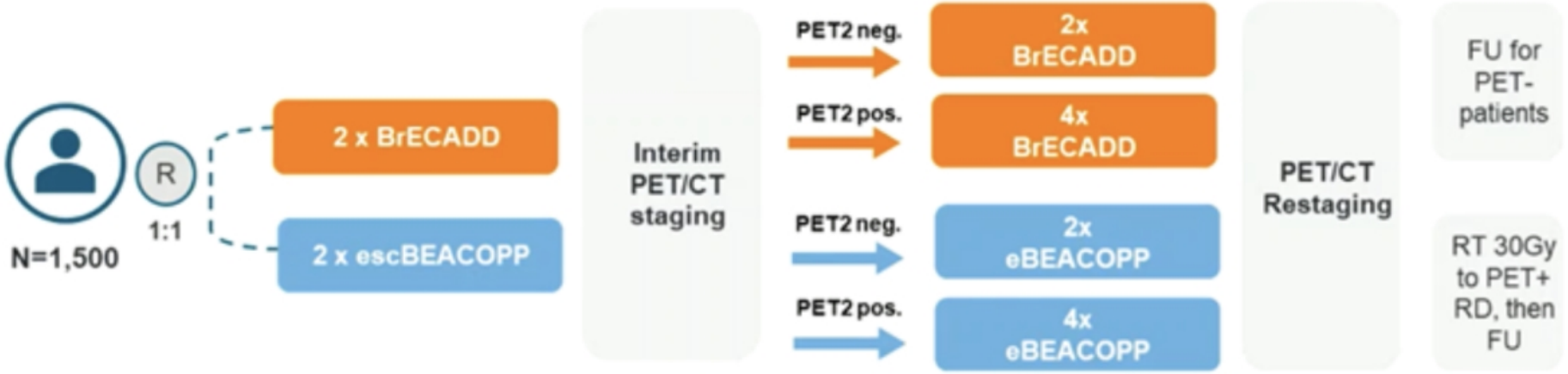
Herrera et al NEJM 2024

Clinical Questions

- Should all untreated advanced stage patients receive a regimen containing a checkpoint inhibitor?
  - **Virtually all patients should receive ANVD, including those age 60+**
    - Limited exceptions (eg. not a candidate for chemo, autoimmune disease, prior solid organ transplant
  - Superior PFS and safety profile of ANVD vs. Bv-AVD
    - No GCSF required
    - Less peripheral sensory neuropathy
    - Less early treatment discontinuation

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)

- Borchmann et al. EHA 2024, Lancet 2024

HD21: Toxicity

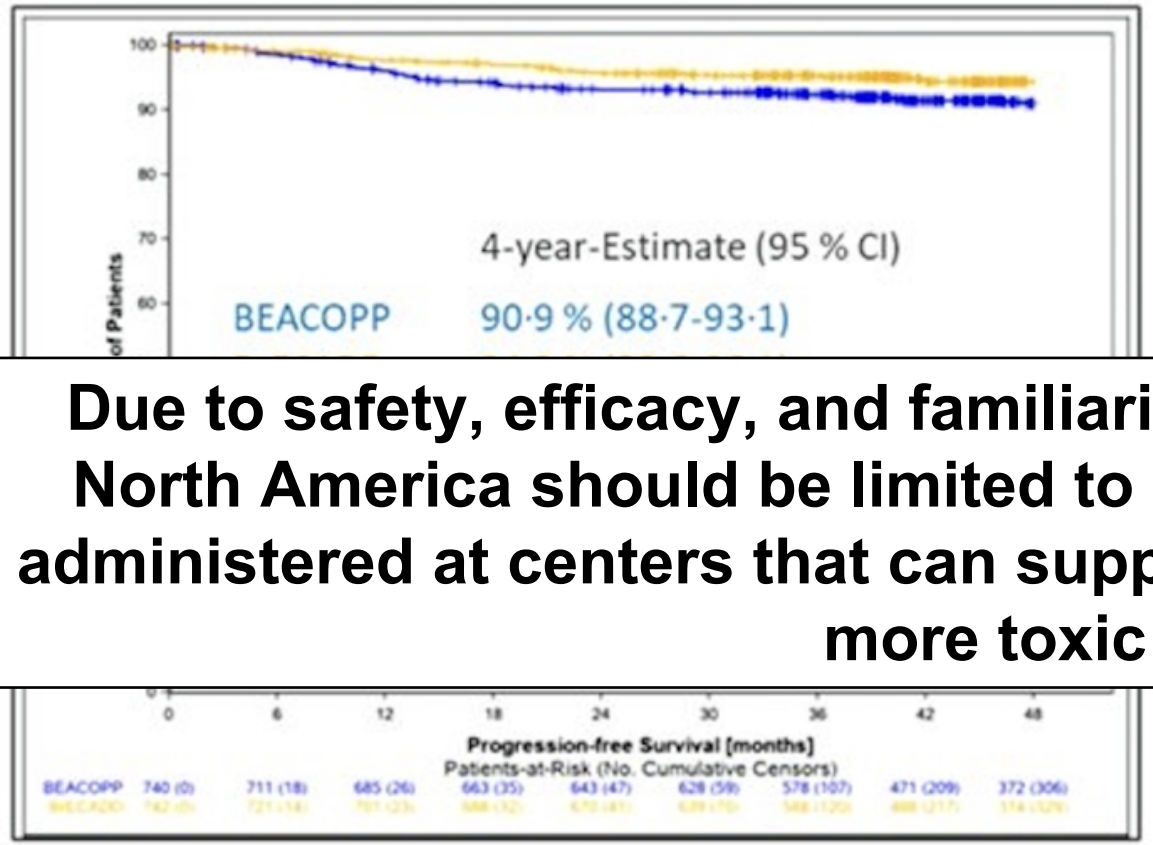
Anemia	59%	30%
Thrombocytopenia	72%	55%
Leukopenia	94%	87%
Neutropenic fever	21%	28%
Infection	19%	20%
Any non-heme	17%	19%

At least one PRBC transfusion	52%	24%
At least one platelet transfusion	34%	17%

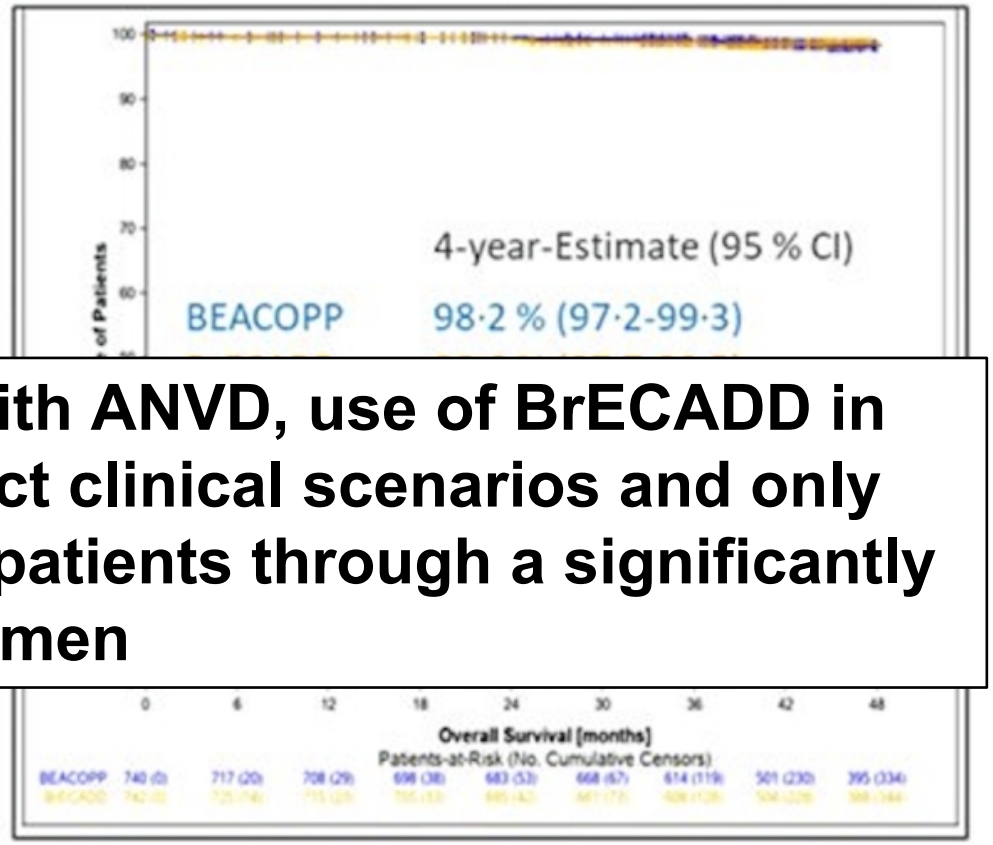
- Borchmann et al. EHA 2024, Lancet 2024

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

Progression-free survival



Overall survival

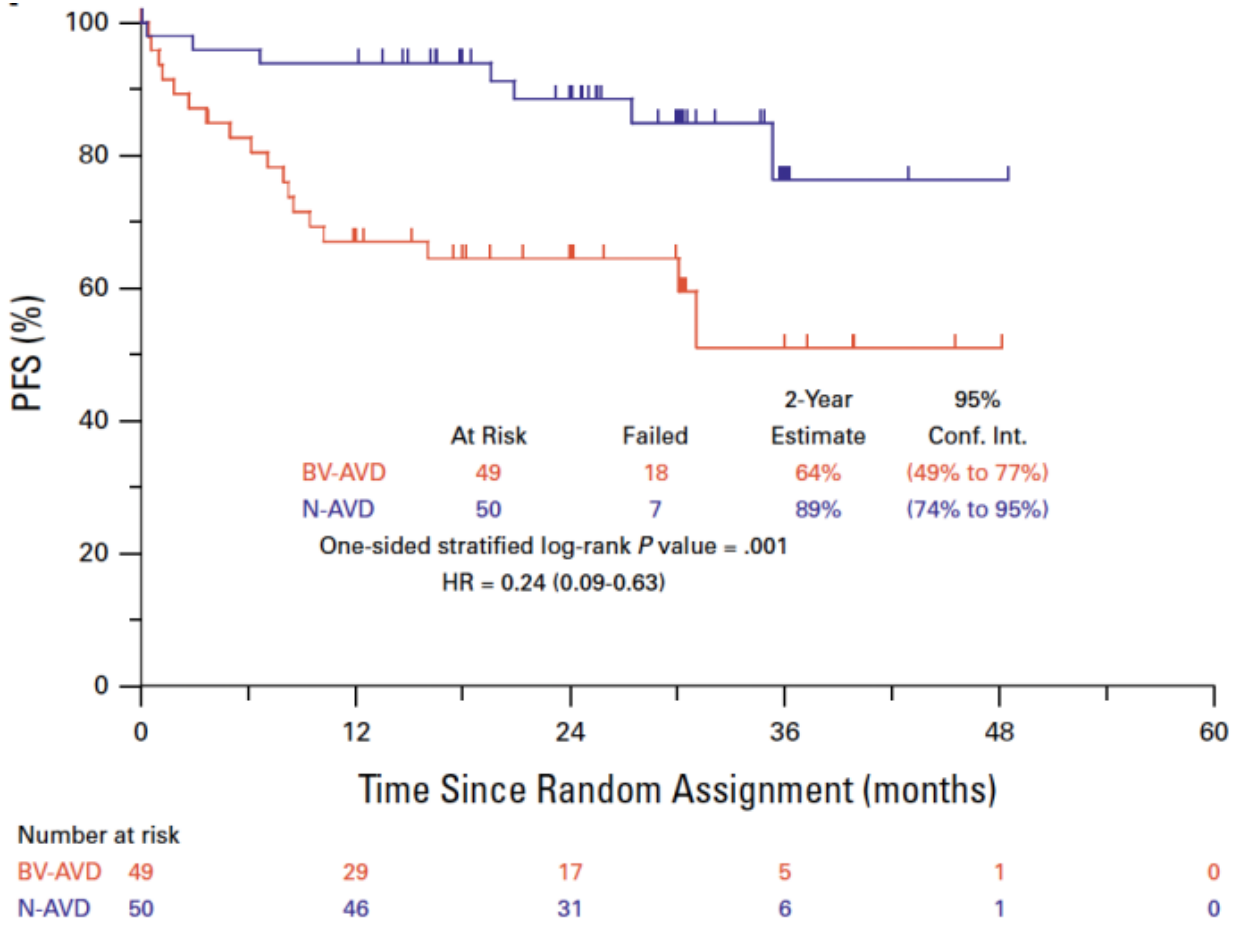


Due to safety, efficacy, and familiarity with ANVD, use of BrECADD in North America should be limited to select clinical scenarios and only administered at centers that can support patients through a significantly more toxic regimen

- Borchmann et al. EHA 2024, Lancet 2024

S1826 in older patients (Age 60+)

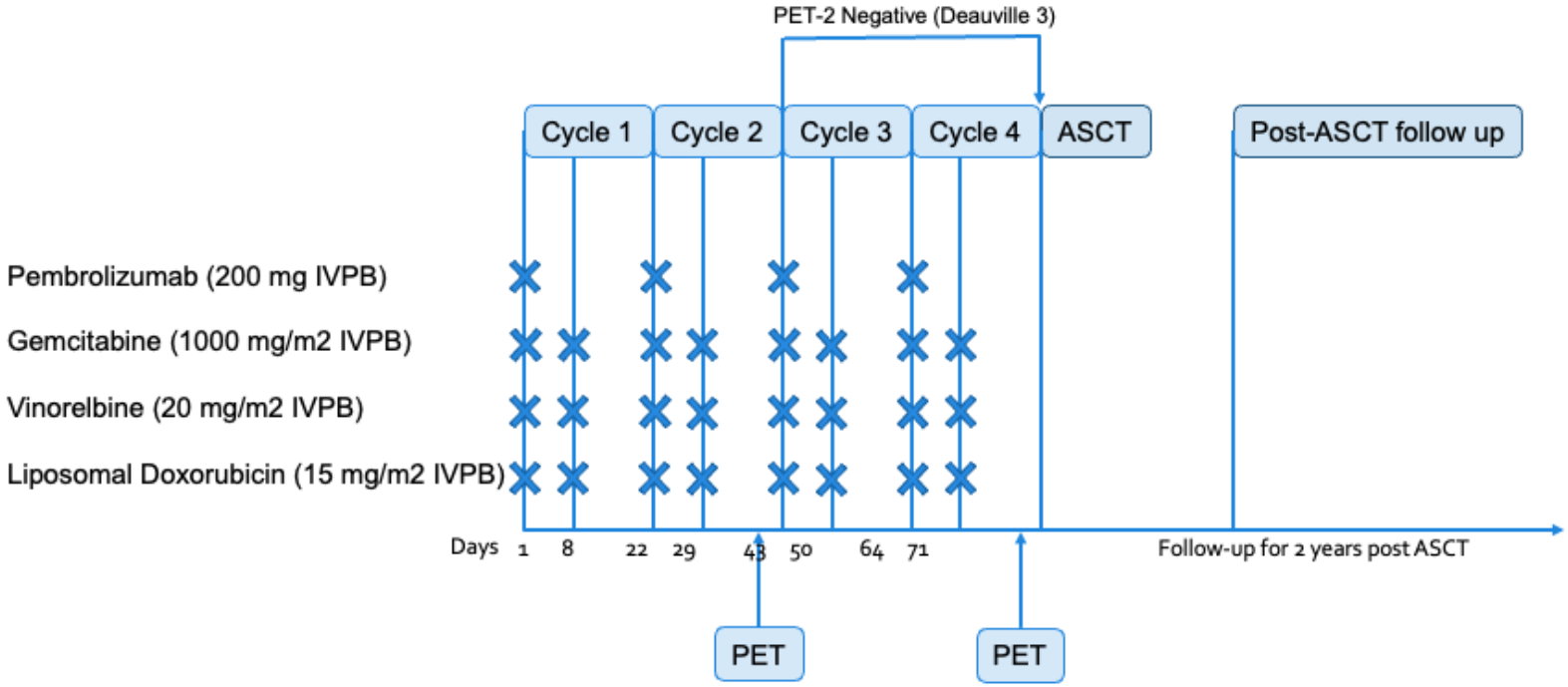
- Brentuximab vedotin vs. nivolumab plus AVD chemotherapy for untreated Advanced Stage Classic Hodgkin lymphoma
  - 99 patients
- More Serious Adverse events seen in BV-containing regimen
  - G3+ Febrile neutropenia (19% vs. 12%)
  - G3+ Sepsis (21% vs. 6%)



Rutherford et al. JCO 2025

Relapsed Hodgkin Lymphoma

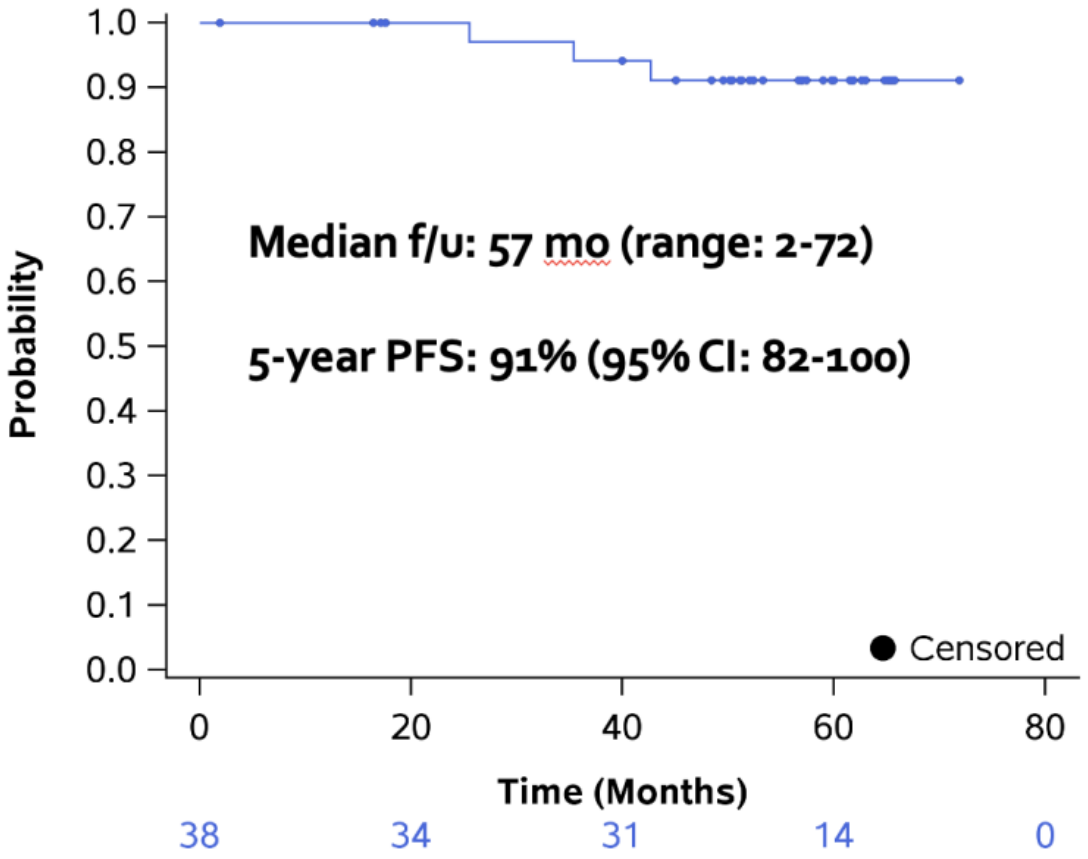
Pembrolizumab + GVD with intention to ASCT



- 39 pts (38 evaluable; 1 with composite lymphoma)
- ORR: 100%
- CR: 95% (92% after 2 cycles)
- 36 transplanted (2 opted out)
- 1 relapse, 2 deaths (unrelated)

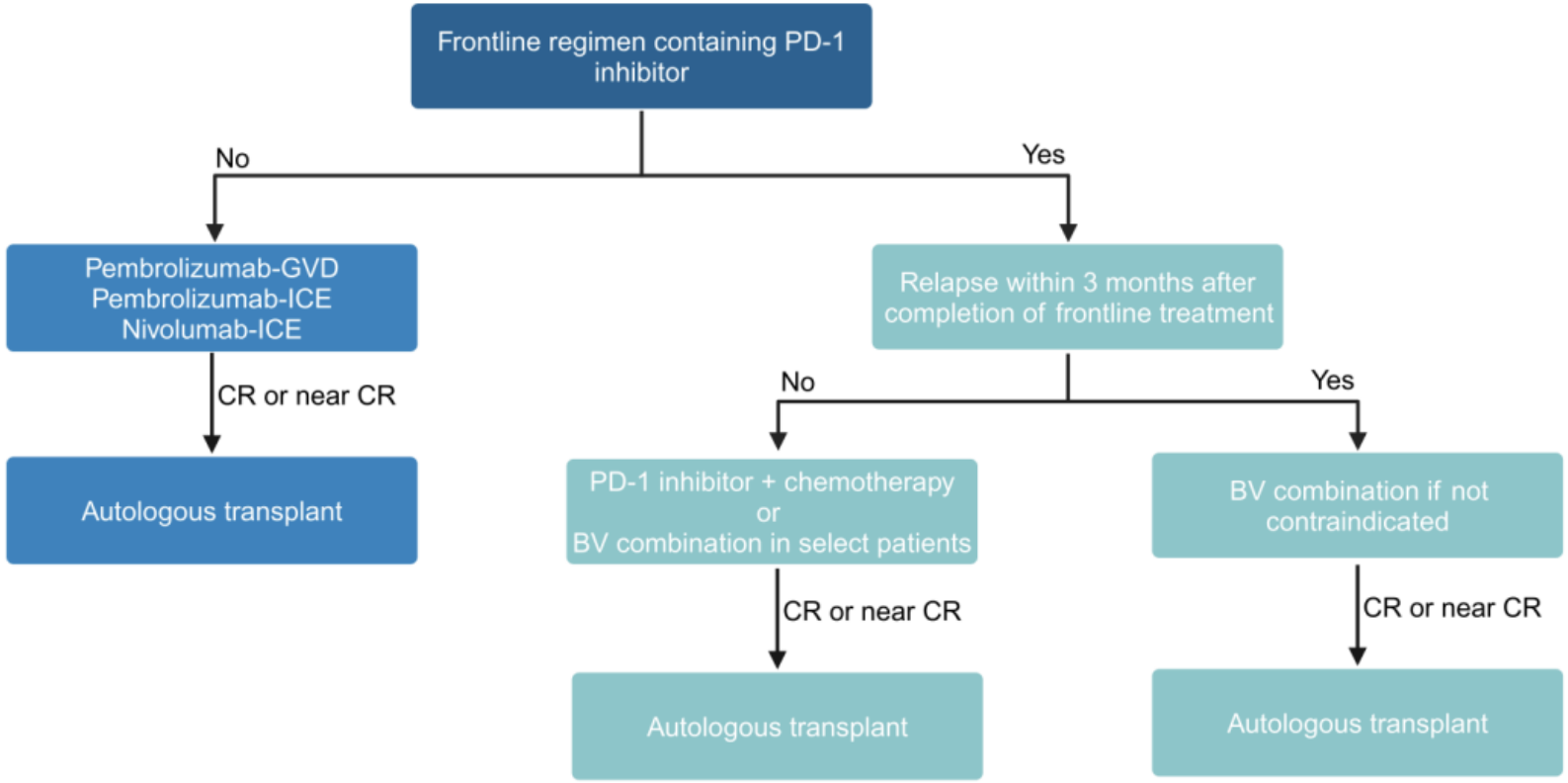
Moskowitz et al. JCO 2021, ISHL 2024

Pembrolizumab + GVD with intention to ASCT



Moskowitz et al. JCO 2021, ISHL 2024

Approach to ASCT eligible R/R CHL patients who received frontline checkpoint inhibitor



Kuczmarski, Lynch RC. Hemasphere 2024

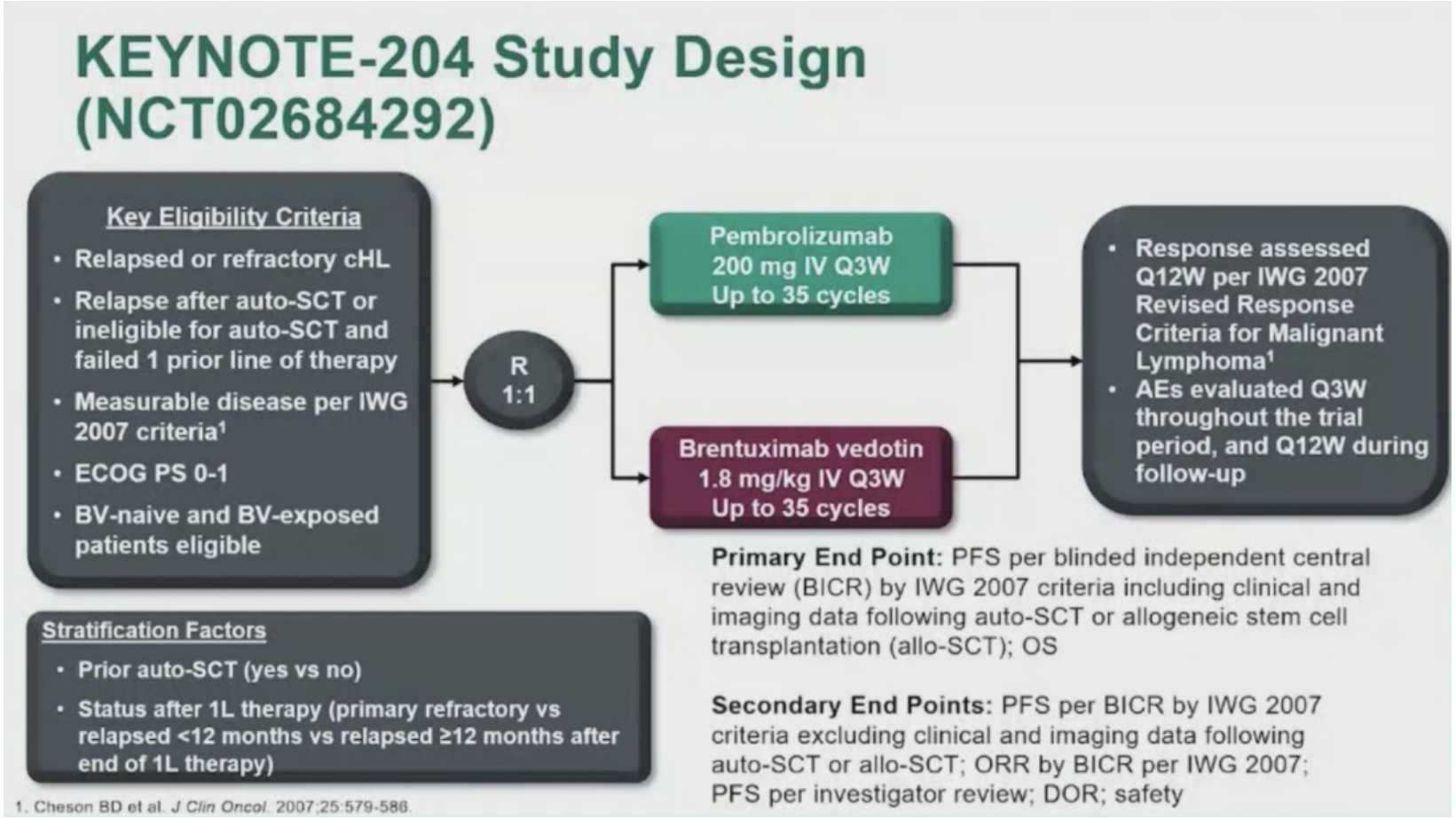
Second line salvage regimens prior to ASCT

- Historical chemo combinations cured approximately half of patients
  - ICE, DHAP, GVD
- Numerous brentuximab vedotin (Bv)-based combinations have been reported in phase 2 studies
  - ~ 70-80% with long term remission
  - Bv-ICE, Bv-benda
  - Use if refractory to frontline PD1-inhibitor
- Early data from PD1-based combinations suggest perhaps 90-100% may achieve long term remission after ASCT
  - Pembro-GVD, Pembro-ICE, Nivo-ICE
  - Use if PD1 inhibitor naïve or relapse > 3 months after frontline therapy

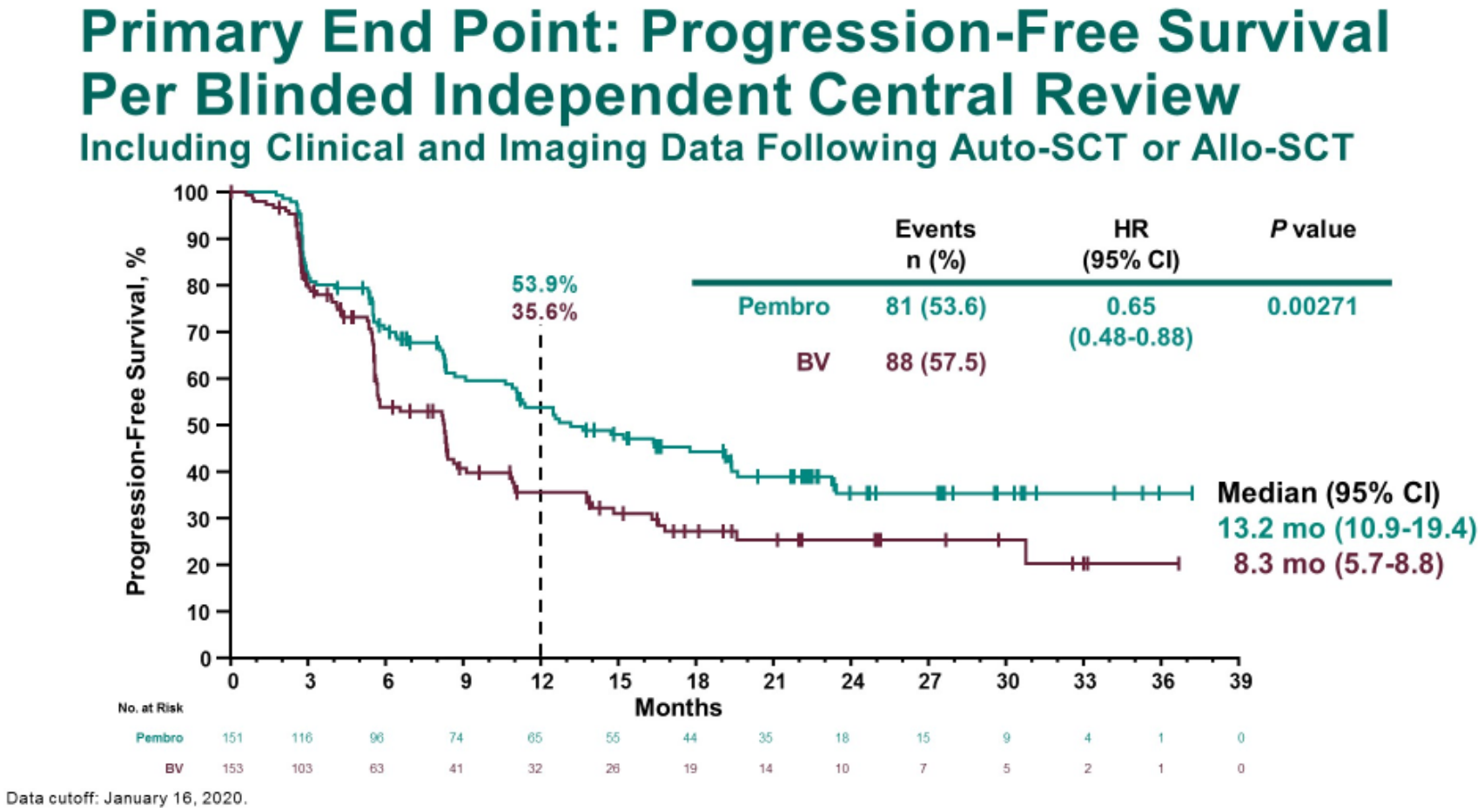
Moskowitz CH et al. Blood 2001, Josting et al. Ann Oncol 2002, Bartlett et al. Ann Oncol 2007, Lynch et al. Lancet Heme 2021, LaCasce et al. Blood 2018, Advani et al. Blood 2021, Mei et al. Blood 2022, Bryan, LJ et al. JAMA Oncology 2023

Relapsed Hodgkin Lymphoma – not eligible for ASCT

Pembrolizumab vs. Bv in R/R Hodgkin lymphoma



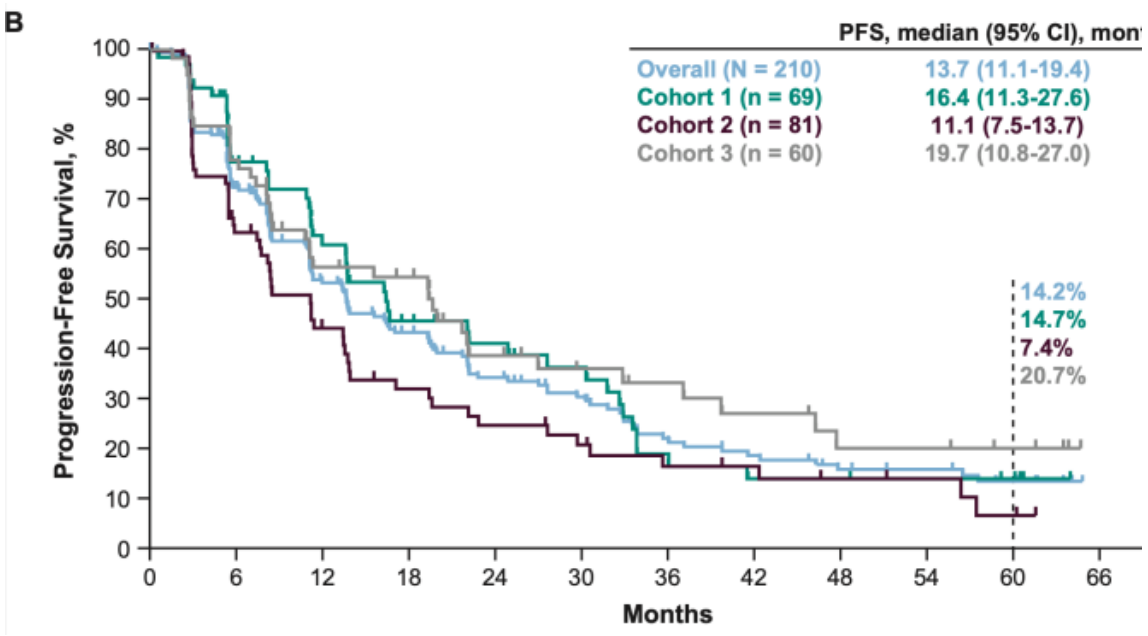
Pembrolizumab superior to Bv in transplant ineligible R/R HL

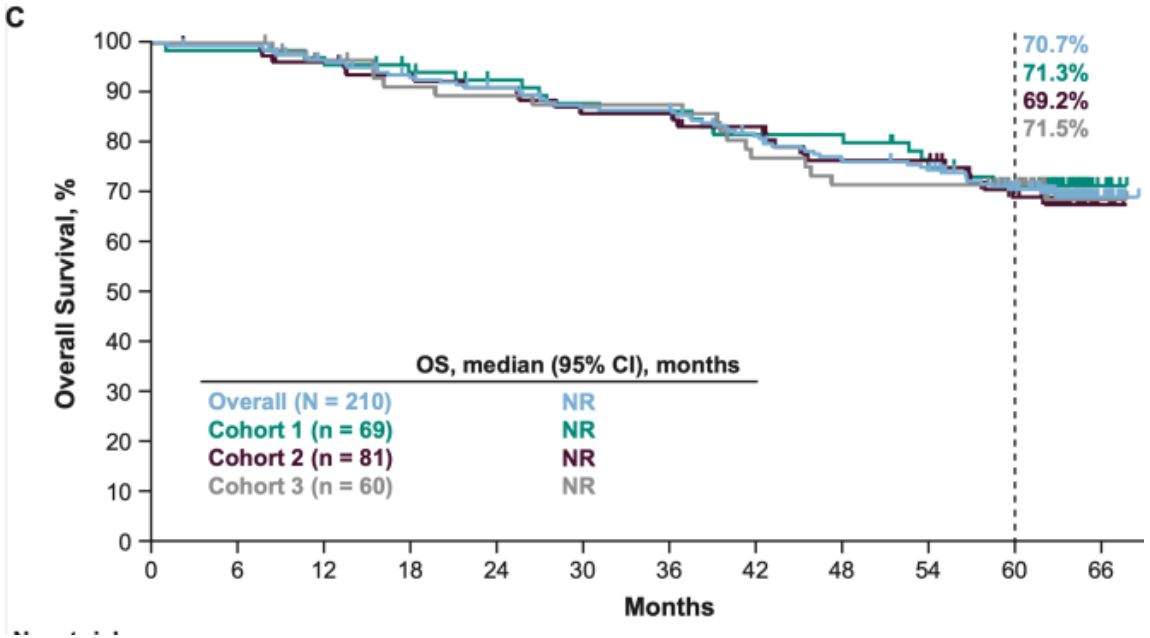


Kuruvilla et al. ASCO 2020

Pembrolizumab in relapsed CHL

Most patients will progress after 1 year, but prolonged overall survival



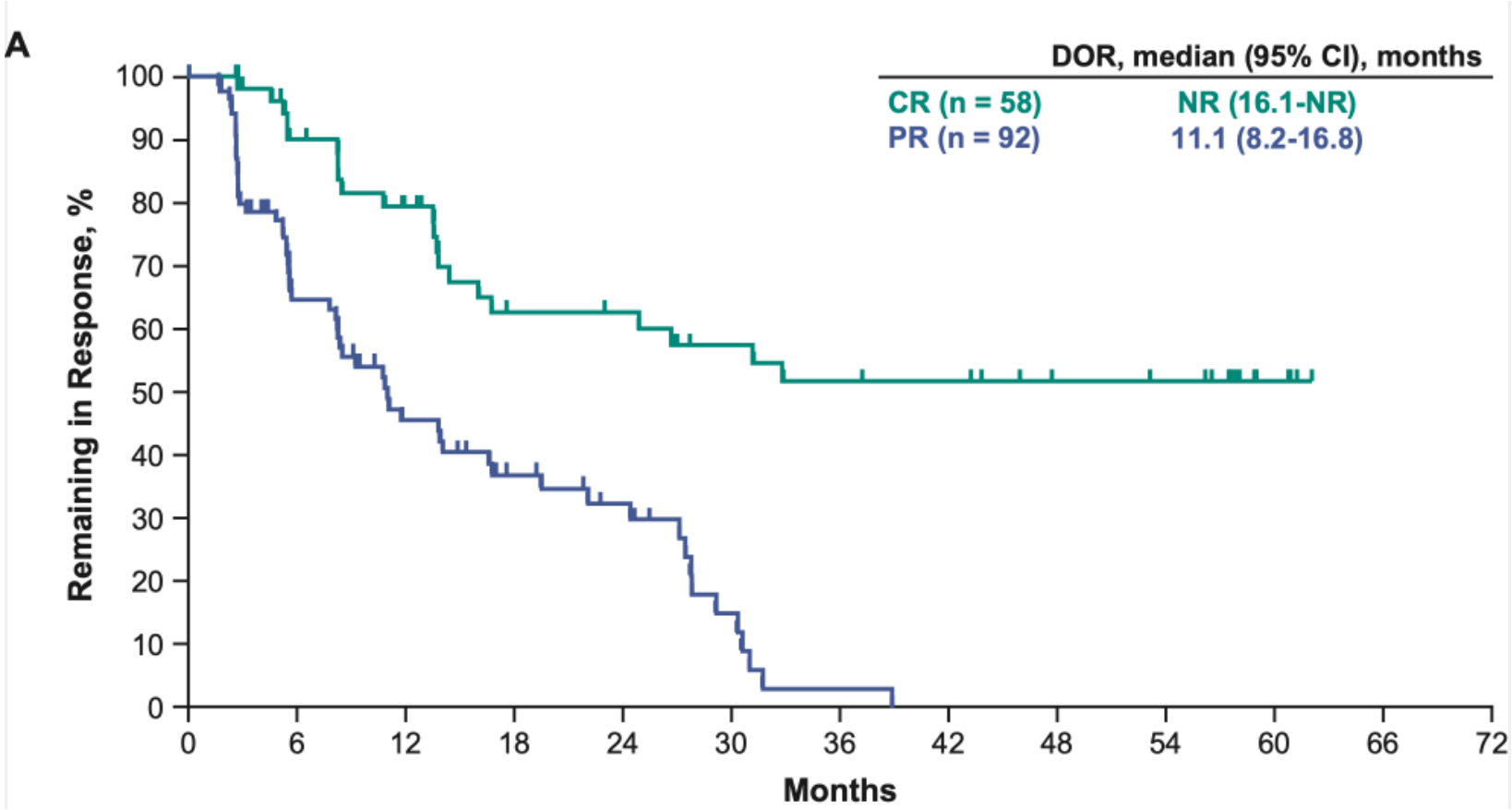


PD1 inhibitors change the natural history of R/R CHL

Armand P et al. Blood 2023

Pembrolizumab in relapsed CHL

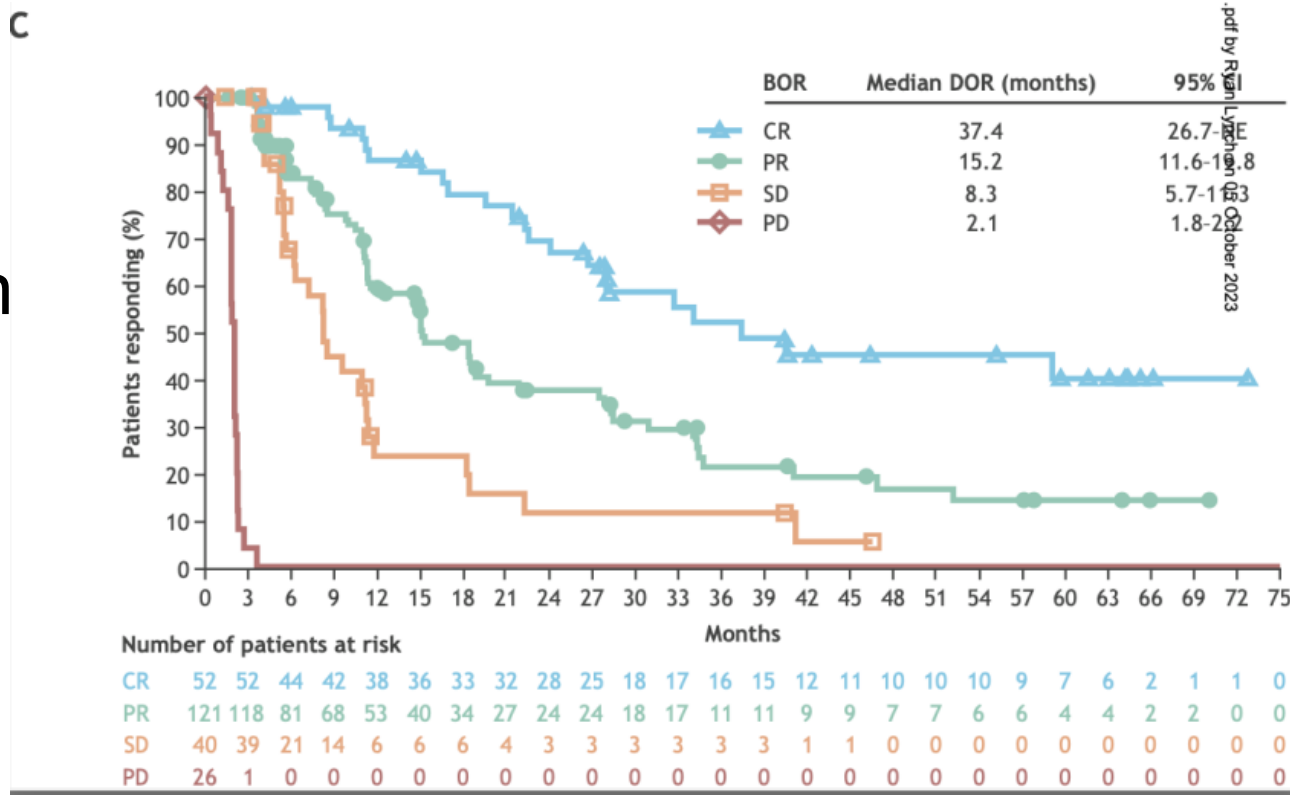
Some patients in CR have durable responses off therapy with long term follow up!



Armand P et al. Blood 2023

Checkmate-205

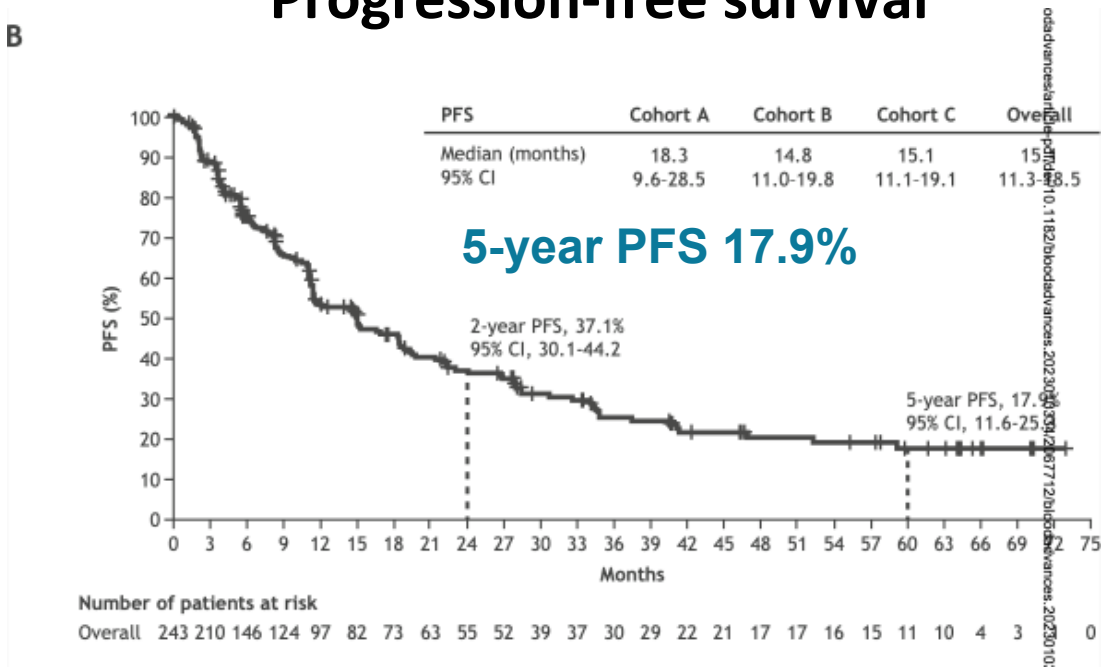
- Nivolumab every 2 weeks
- Relapsed/refractory post auto transplant
- Treatment beyond progression eventually allowed in protocol amendment
- If CR > 1 year, could discontinue and resume upon progression
- 5-year follow up



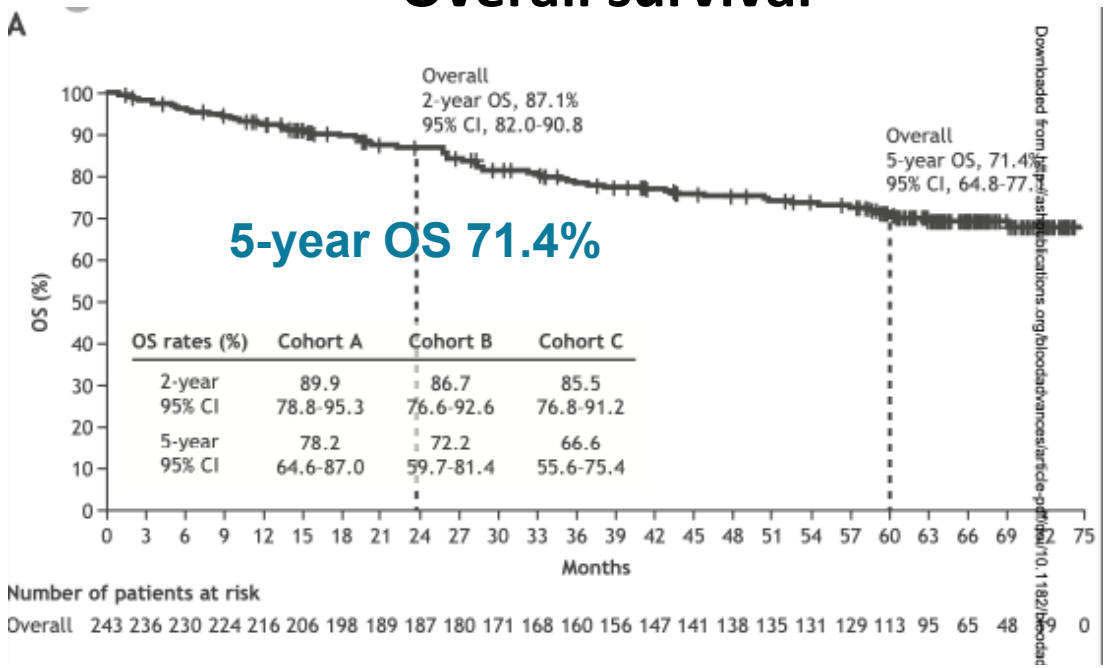
Ansell et al. Blood Advances 2023

Checkmate-205

Progression-free survival



Overall survival



Ansell et al. Blood Advances 2023

Second line salvage regimens – not ASCT eligible

- PD1-inhibitor preferred
  - Can treat beyond progression if benefitting
  - Can combine brentuximab + nivolumab
  - Single agent brentuximab limited by neuropathy
- No other agents on the horizon
  - Various combinations in NCCN based on small phase 2 studies
- Consider allogeneic transplant in select patients

Survivorship

THERE IS ALMOST ALWAYS A SURVIVORSHIP QUESTIONS – THEY LOVE THIS TOPIC ON THE BOARDS!!!

NCCN Surveillance Guidelines

Relapse detection

- Clinic visits
  - Every 3 months for first 2 years
  - Every 6 months years 3-5
  - Every 12 months beyond year 5
- Imaging
  - **NO PET SCANS IN ABSENCE OF SUSPECTED RELAPSE/SYMPTOMS**
  - **CT at clinician discretion in first 2 years**
- **Lab studies**
  - CBC, ESR (if elevated at diagnosis), chemistry panel

Late effect detection

- Clinic visits
  - Every 3 months for first 2 years
  - Every 6 months years 3-5
  - Every 12 months beyond year 5
- **Imaging**
  - **Breast imaging 7 years post RT**
  - Cardiac echo at 10 years
  - Carotid US at 10 years if neck RT
- Lab studies
  - CBC, ESR (if elevated at diagnosis), chemistry panel
  - **TSH if neck RT yearly** , Lipid panel every other year (can be done with PCP)

Nodular lymphocyte predominant Hodgkin lymphoma

- VERY rare subtype (about 400 new cases in US each year)
- Typically acts like an indolent lymphoma, so wide variety of treatment options (observation, chemotherapy, radiation) are accepted depending on clinical scenario

- So what can they test you on?

Nodular lymphocyte predominant Hodgkin lymphoma

	Classical HL	Nodular lymphocyte predominant HL
Tumor cells	Diagnostic RS cells. Mononuclear or lacunar cells	"L&H" or "popcorn" cells
Background	Lymphocytes, histiocytes, eosinophils, plasma cells	Lymphocytes, histiocytes
Fibrosis	Common	Rare
CD15	+ (15% can be negative)	-
CD30	+	-
CD20	-	+
PAX5	Dim +	+
EBV	+/-	-

Other take home points - NLPHL

- Consider chemotherapy (rituximab containing regimen, R-CHOP, R-CVP) for advanced stage, symptomatic patients
- Observation reasonable in asymptomatic advanced stage patients
- Limited stage patients have high rates of disease control with radiotherapy
- Late relapse common, often > 10 years after initial treatment
- Patients can **transform to T-cell/histiocyte rich DLBCL**
  - Spleen involvement highly predictive of eventual transformation
  - Re-biopsy if suspicion of transformation
  - **DOES NOT TRANSFORM TO CLASSICAL HODGKIN LYMPHOMA!**

Other special issues!!!

- No bone marrow biopsy needed at diagnosis if PET used for staging and no marrow involvement
- NO dose delays with ABVD/ANVD due to neutropenia – treat on time with standard doses. Inferior outcomes with decreased dose intensity. GCSF optional (2nd ppx or older patient)
- GCSF mandatory for concurrent Bv-chemo regimens
- Repeat biopsy with refractory disease or relapse prior to starting subsequent therapy.

Conclusions

- Novel agents (Bv, PD1-inhibitors) in combination with chemo have improved outcomes vs. ABVD in advanced stage CHL
  - Early results show N-AVD > Bv-AVD
    - Longer follow up may be needed to determine if late relapses are seen with ANVD
- Smaller studies in early stage HL suggest improved efficacy with Bv or PD1
  - Can this allow for abbreviated chemo without RT?
- PD1 inhibitors remain important in the relapsed setting even with prior PD1-inhibitor exposure

Fred Hutch
Cancer Center

Thank you

- Clinical team, research staff, mentors/colleagues
- PATIENTS!
- We can’t research how to improve therapies without clinical trial participation!

UW Medicine