Hodgkin Lymphoma

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Goals

- Provide an overview of the evidence supporting current clinical practice
- Since this also serves as a board review, I will refrain from addressing “early” data, unless it may immediately affect clinical practice
- I will try to summarize the points that are most likely to be addressed or not addressed on the exam

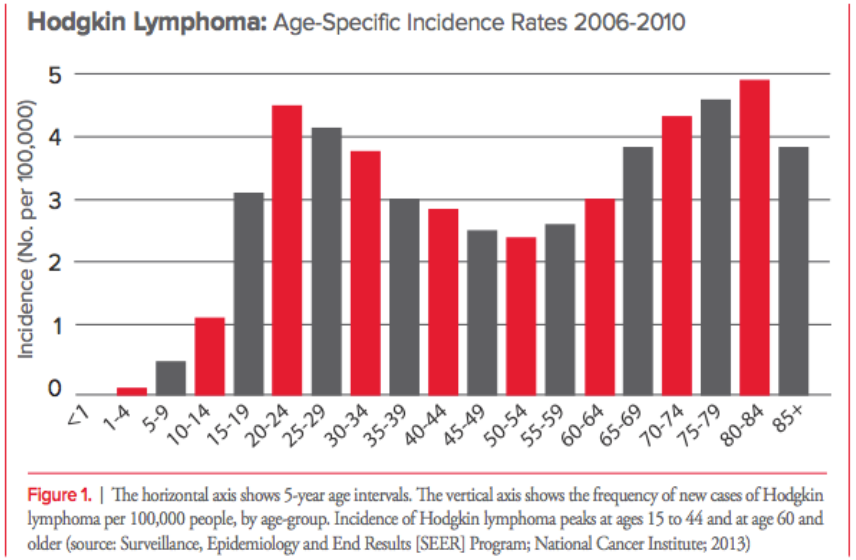
Outline

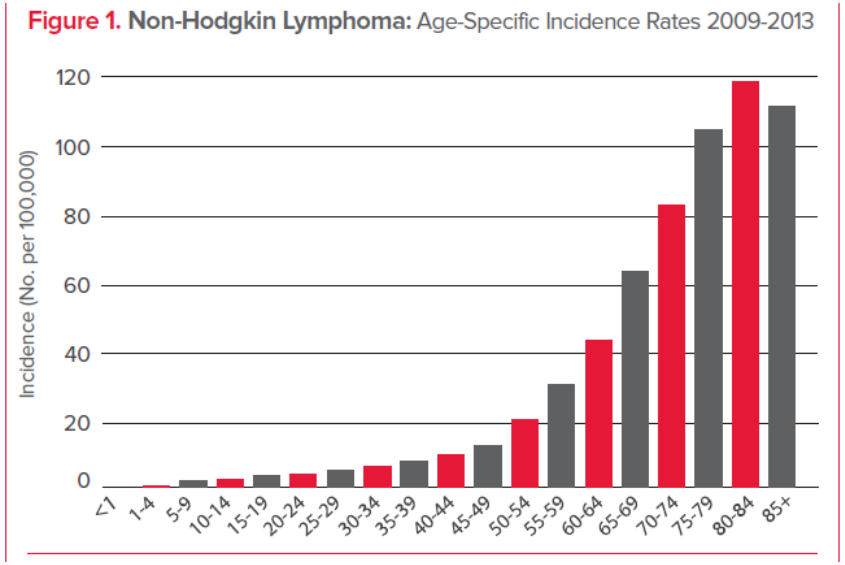
- Background
- Early Stage (Stage I-II)
- Advanced Stage (Stage III-IV)
- Relapsed/refractory patients
- Survivorship
- Nodular lymphocyte predominant HL

Background

- Classical Hodgkin lymphoma (CHL) represents ~ 10% of all lymphomas
- 8000 new cases annually in the United States
- Highly curable with frontline therapy (chemotherapy +/- RT)
  - Early stage > 90%
  - Advanced stage ~ 75%

Hodgkin vs. non-Hodgkin lymphoma incidence by age





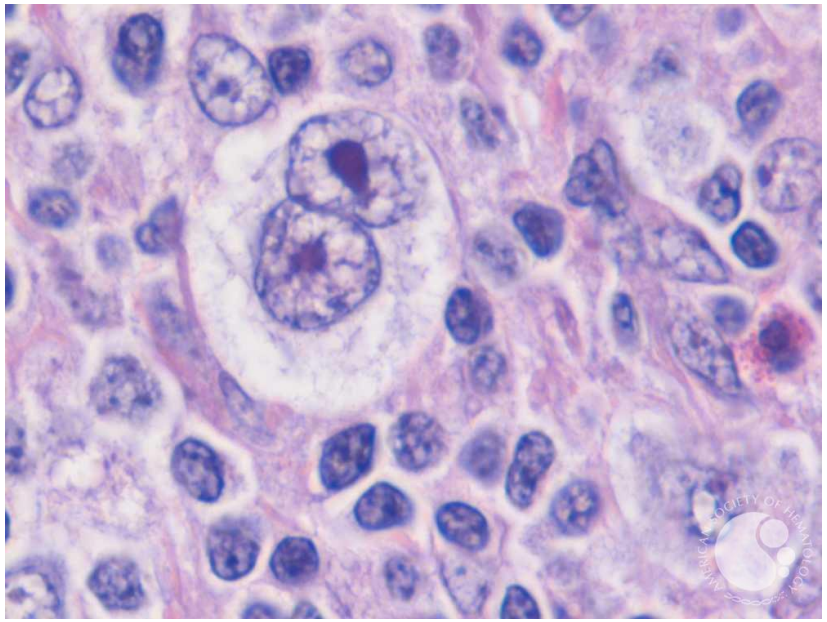
SEER Data, chart from Leukemia & Lymphoma Society

Hodgkin lymphoma can be challenging to diagnose

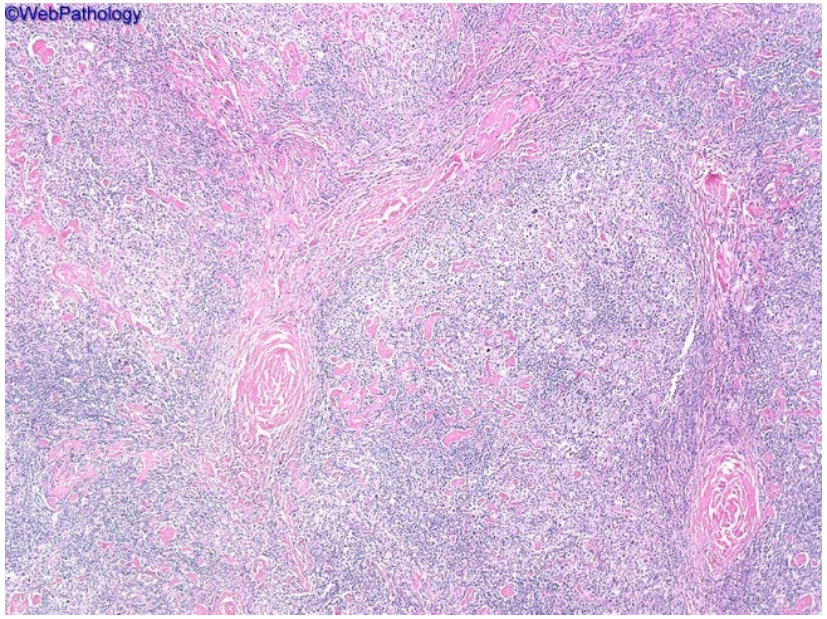
- Mostly comprised of an inflammatory infiltrate with bands of sclerosis
- FNA and flow cytometry often negative
- CORE biopsies are often sufficient, but if there are insufficient RS cells in the specimen, it may be non-diagnostic
- Excisional biopsies when possible offer the highest chance of diagnosis and excluding similar entities
  - Diffuse large B-cell lymphoma
  - Primary mediastinal B-cell lymphoma
  - Nodular lymphocyte predominant Hodgkin lymphoma
  - Anaplastic large cell lymphoma (peripheral T-cell lymphoma)
- **It is common to see patients with symptoms for 6-12 months before diagnosis!**

Hodgkin Reed-Sternberg cell

The malignant cell is rare



Hematology.org



WebPathology.com

Hodgkin lymphoma staging

Stage	Definition
I	single lymph node or extranodal site
II	two or more involved lymph node regions on the same side of the diaphragm
III	lymph node involvement on both sides of the diaphragm
IV	presence of diffuse or disseminated involvement of one or more extralymphatic organs

- A – absence of B symptoms
- B – Presence of B symptoms

- Stage I-II – Early stage
  - Favorable
  - Unfavorable
- Stage III-IV - Advanced stage
  - Risk stratified by International Prognostic Score (IPS)

Unfavorable Criteria – early stage

Risk Factor	GHSG	EORTC	NCCN
Age		≥50	
Histology			
ESR and B symptoms	>50 if A; >30 if B	>50 if A; >30 if B	>50 or any B symptoms
Mediastinal mass	MMR > .33	MTR > .35	MMR > .33
# Nodal sites	>2*	>3*	>3
E lesion	any		
Bulky			>10 cm

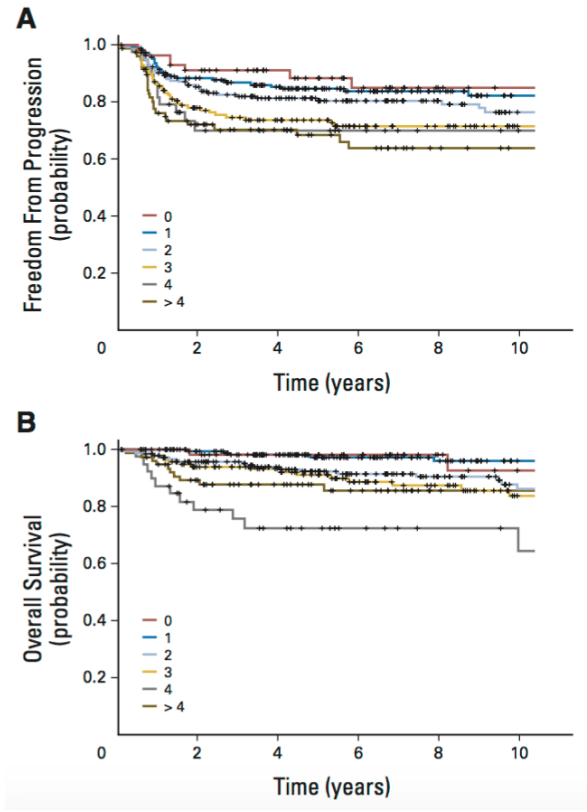
GHSG = German Hodgkin Study Group
EORTC = European Organization for the Research and Treatment of Cancer

MMR = Mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter
MTR = Mediastinal thoracic ratio, maximum width of mediastinal mass/intrathoracic diameter at T5-6

NCCN Guidelines, Hodgkin Lymphoma, Version 3.2016

IPS – risk stratification for advanced HL

- Serum albumin < 4 g/dL
- Hemoglobin < 10.5 g/dL
- Male
- Age >45 y
- Stage IV
- WBC: ≥15,000/microL
- Absolute lymphocyte count <600/uL and/or <8 % of the total WBC



Moccia et al. J Clin Oncol 30:3383-8, 2012

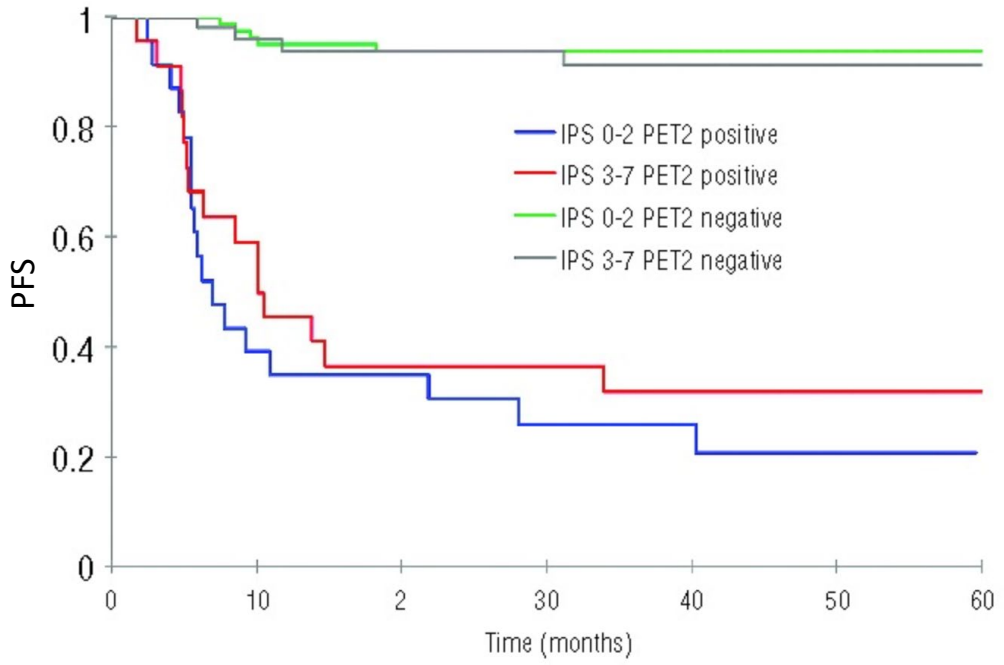
Deauville 5-point score

- Standardizes PET/CT response assessment
- Based on mediastinal and liver max SUV
- Reduces inter-user variability

Score	PET/CT scan result
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

Barrington SF, et al. J Clin Oncol 32:3048-58, 2014

Prognostic value of interim-PET using Deauville 5-point criteria



Gallamini A et al. Haematologica 99:1107-13, 2014

Hodgkin Lymphoma

Expected outcomes and goals of therapy in 2020

Stage	% Cured with primary therapy	Therapeutic Priority
Early stage favorable (Stage I-II)	90	Reduce Toxicity
Early stage unfavorable (stage I, II with risk factors*)	80-85	Increase Efficacy
Advanced stage (bulky IIB, III, IV)	75-80	Increase Efficacy

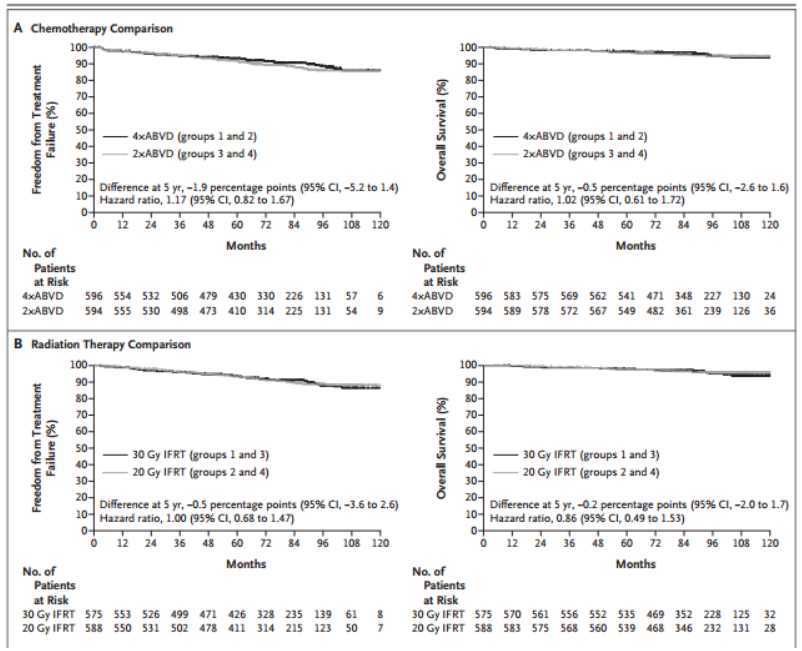
* Large mediastinal mass, extranodal extension, ≥ 3 nodal sites, elevated ESR; age ≥ 50, MC histology

Take home - background

- Fair game
  - Ann arbor staging
  - Deauville score (would be in the context of a clinical question, but should know what it means if a question says “PET scan was Deauville 2”
- Should understand, but likely don’t need to memorize
  - Components of IPS score
  - Favorable/unfavorable criteria
    - EXCEPT for GHSG > 2 sites = unfavorable

Early Stage

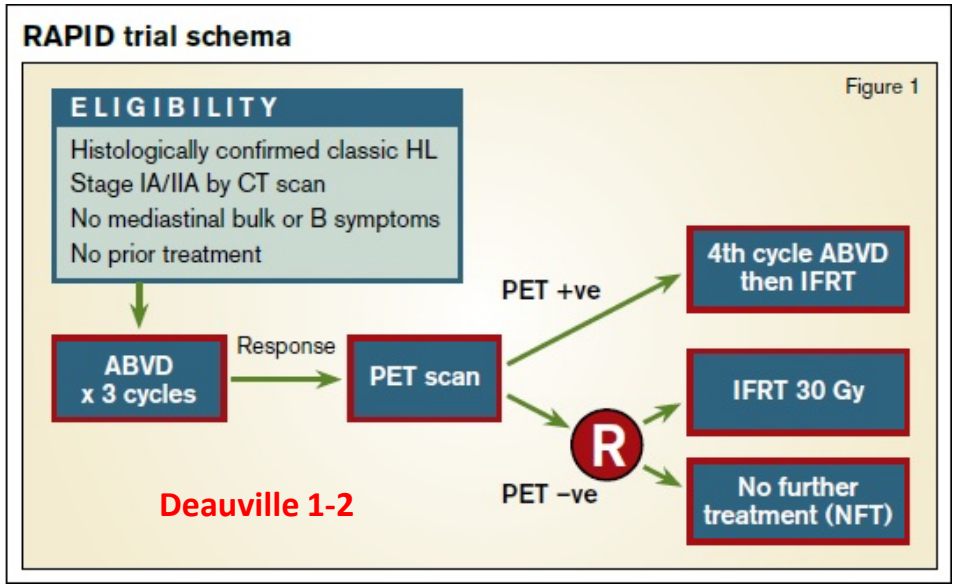
Early stage favorable HL- abbreviated chemo plus radiation

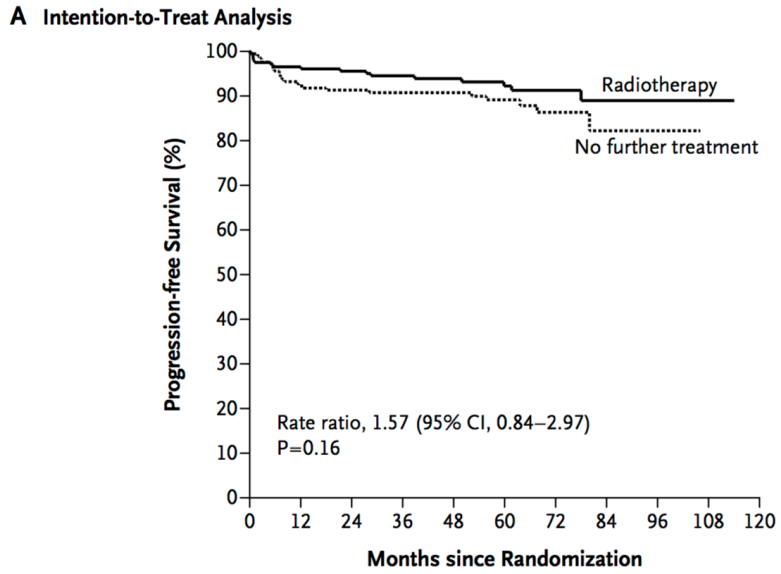


Engert A, et al: N Engl J Med 363:640-52, 2010

- GHSG HD10 trial
- 4 Arm study
  - Chemo ABVD x2 vs. x4
  - RT 30 Gy vs. 20 Gy
- ABVD X 2 + 20 Gy IFRT = ABVD X 4 + 30 Gy IFRT
- GHSG unfavorable criteria
  - ESR > 50, > 30 if B symptoms
  - MMR > 0.33
  - More than 2 nodal sites
  - Any E lesion

RAPID trial – PET adapted elimination of XRT in early stage HL

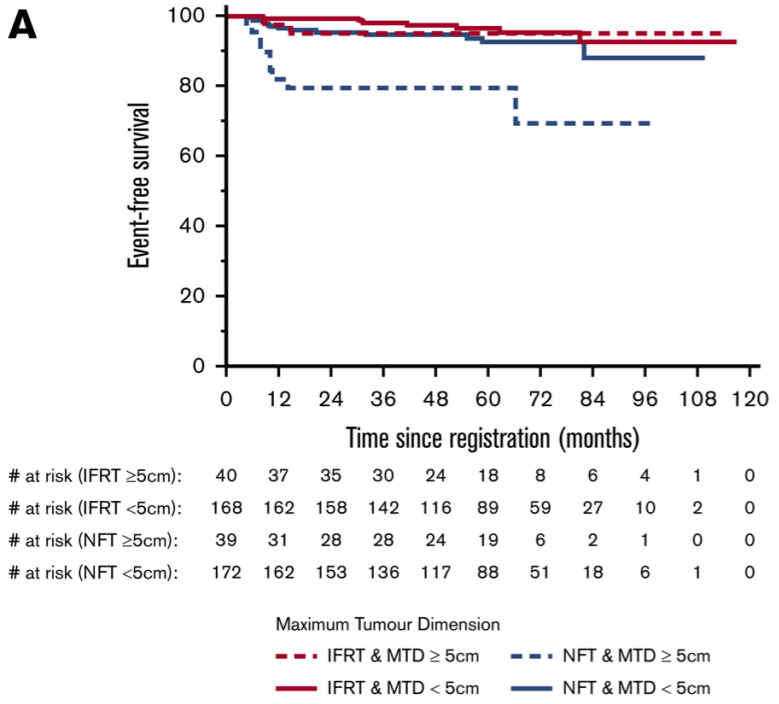




* No difference in OS

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

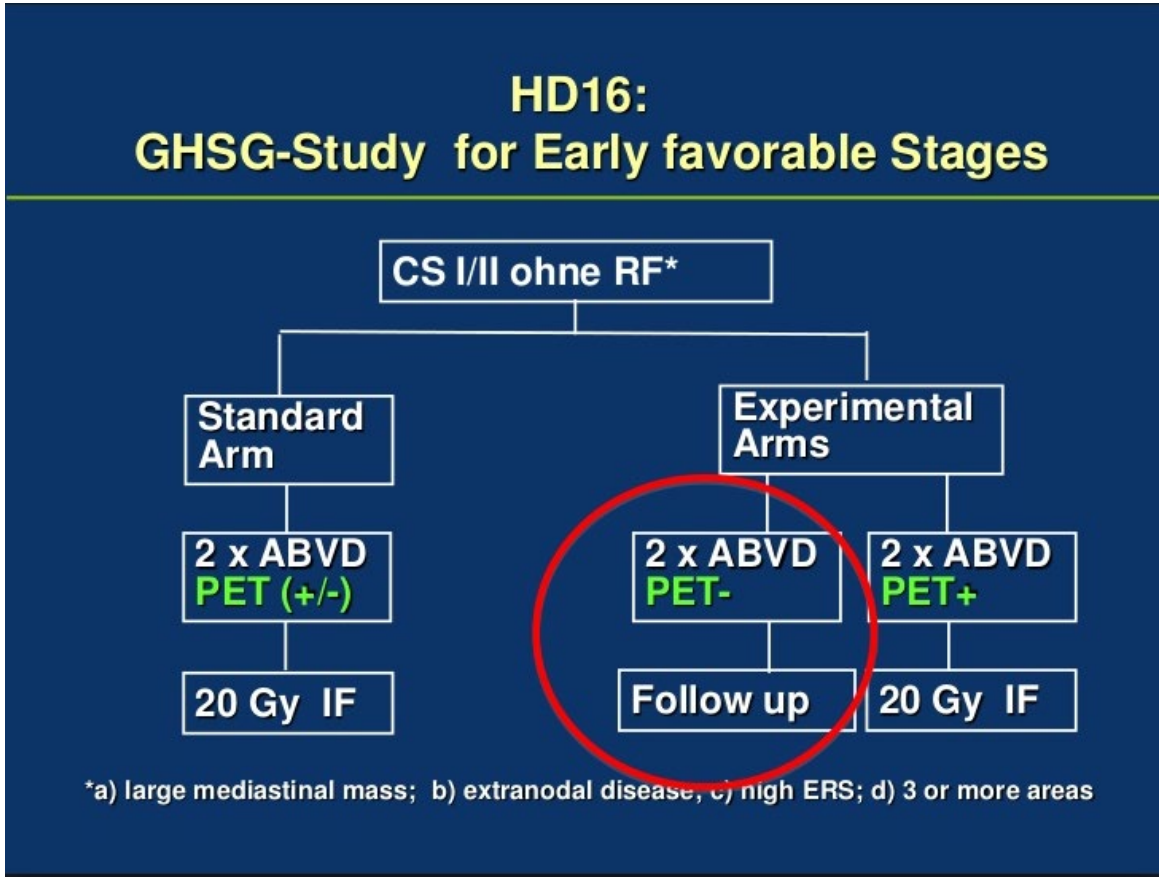
Maximum tumor dimension impacts outcomes when RT omitted



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

Adapted from Ilidge et al. Blood Advances 20

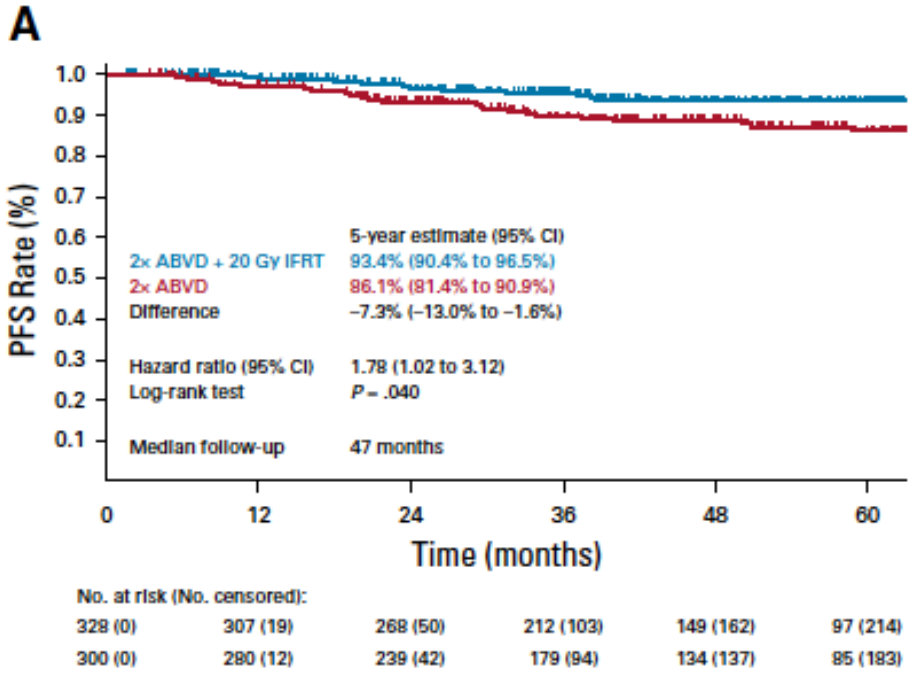
HD16 study



Deauville 1-2

Adapted from slide from Volker Diehl 2011

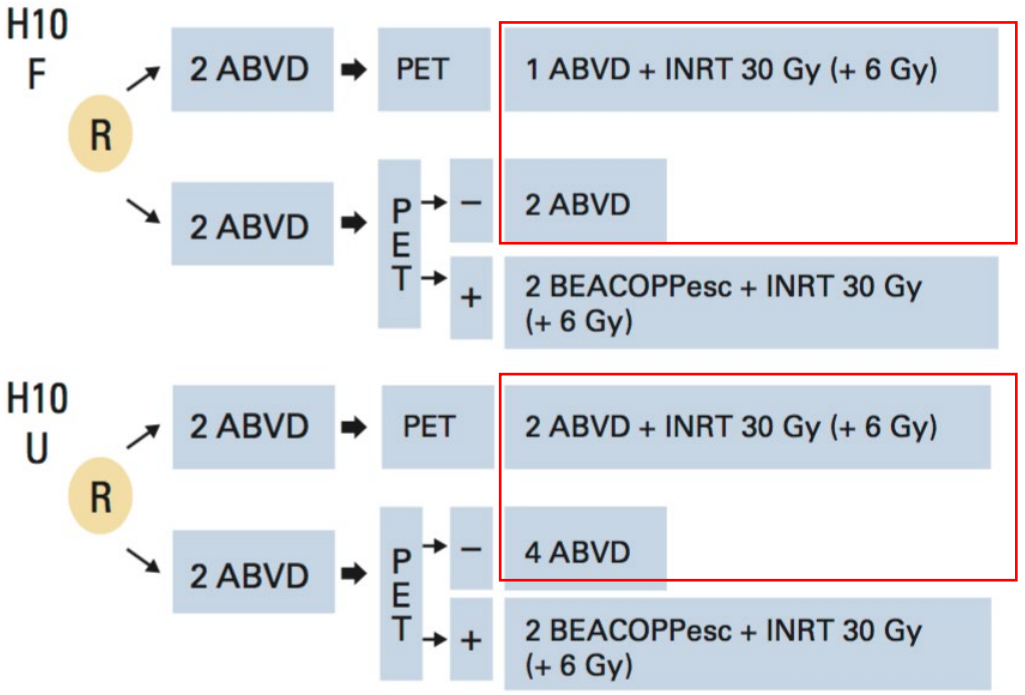
Inferior outcomes seen in early stage PET2neg patients with omission of RT



- **Radiation CANNOT be safely omitted in PET negative early stage favorable patients after 2 cycles ABVD**

Fuchs et al. JCO 2018

EORTC H10 - PET-adapted therapy in early stage HL

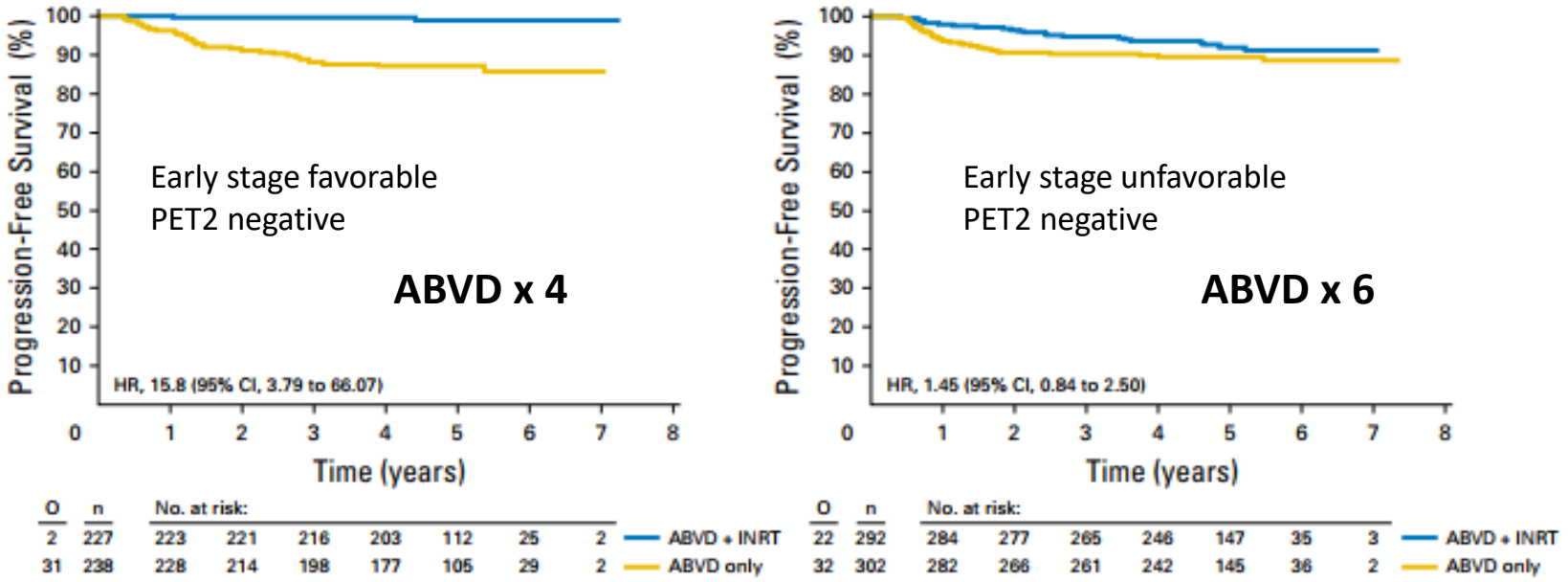


Deauville criteria not used (IHP criteria)

1950 patients enrolled

- **PET-negative experimental arm closed by independent data monitoring committee due to excess events**

Higher risk of progression in ES-favorable patients without RT



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

Early Stage Boards Take Home Points

- **GHSG early stage favorable patients can be treated with ABVD x 2 + 20 Gy**
- ABVD x 4-6 + RT is reasonable in other cases of early stage HL
  - If not meeting RAPID criteria and considering omitting RT, then ABVD x 6 should be given
- **Patients who are interim PET positive represent higher risk group and should receive consolidative RT**
- Radiotherapy offers small PFS benefit even in interim PET negative patients
  - RAPID – PET3 neg represents low risk group that can have RT eliminated in select patients
- **Unlikely to have a question that asks you if should or should not give RT in interim PET neg patients**

Advanced Stage

How do we treat advanced stage HL?

- ABVD
  - **Doxorubicin, bleomycin**, vinblastine, dacarbazine
- Escalated BEACOPP
  - **Bleomycin**, etoposide, **doxorubicin**, cyclophosphamide, vincristine, procarbazine, prednisone
- ~~Stanford V (for IPS 0-2, never seen it used for advanced stage HL, even at Stanford)~~

- Brentuximab vedotin + AVD (FDA approval March 2018)

How do we treat advanced stage HL?

- **ABVD**
- **Escalated BEACOPP**

- Brentuximab vedotin + AVD

ABVD vs. escBEACOPP

- 75% success rate (FFS)
- Extremely low infertility
- Low rates of
  - heme toxicity
  - febrile neutropenia
  - treatment-related mortality
- 1% secondary malignancies at 10 years

- 90% success rate (FFTF)
- High rates of infertility that increases with age (~60% at age 30)
- Higher rates of
  - heme toxicity
  - febrile neutropenia
  - treatment-related mortality
- 10% secondary malignancies at 10 years

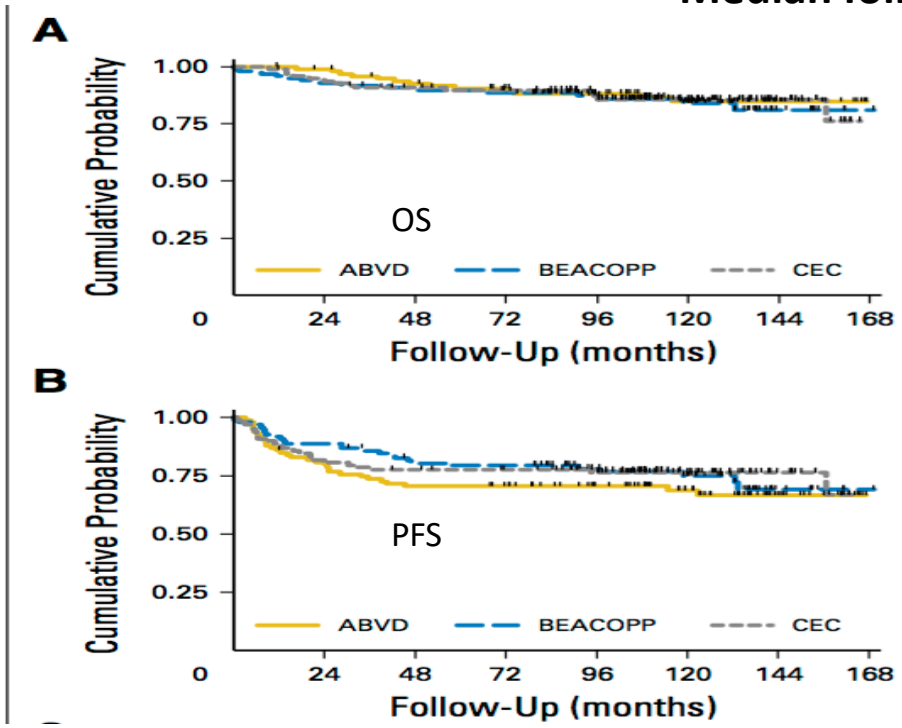
With long term follow-up (10 years), no statistical difference in overall survival

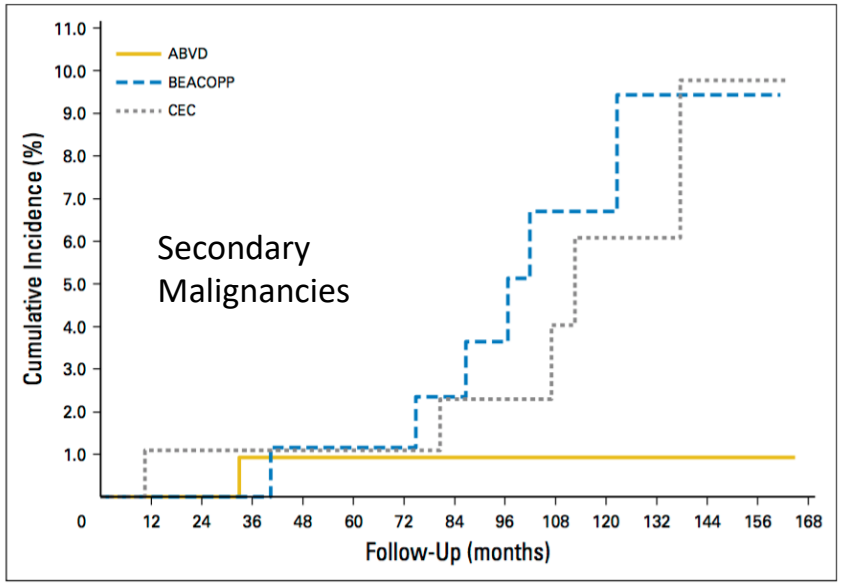
Why is escBEACOPP x 6 not standard of care in North America?

Importance of long term follow-up: HD2000

ABVD x 6 vs escBEACOPP x 4 + $BEACOPP_{baseline}$ x 2

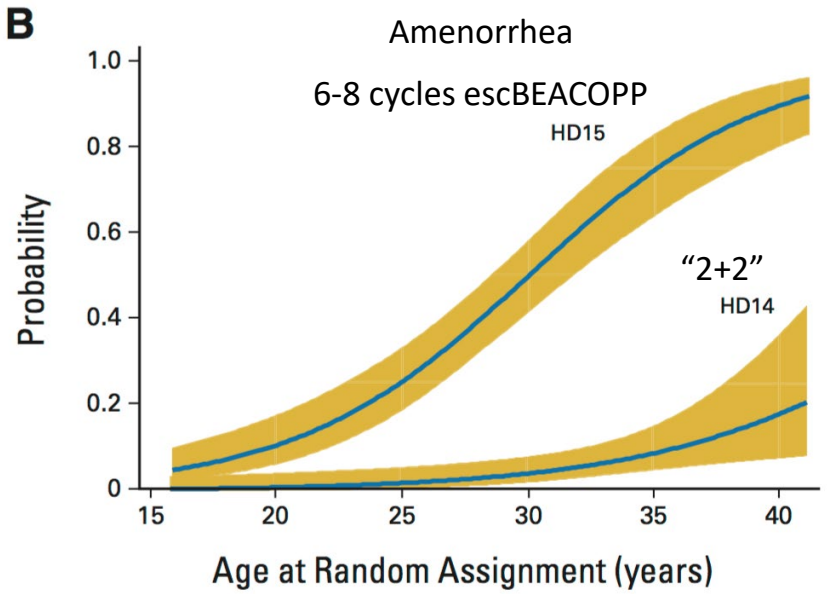
Median follow up 10 years

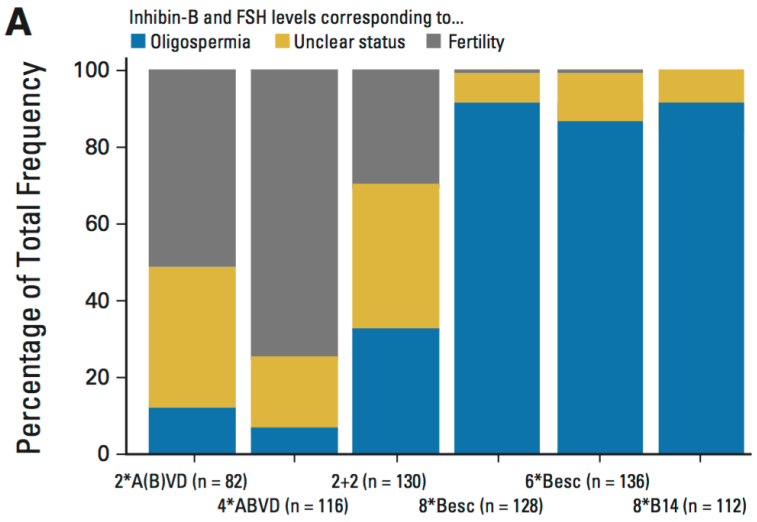




Merli F, Luminari S, Gobbi PG, et al:. J Clin Oncol, 2015

Sterility with BEACOPP

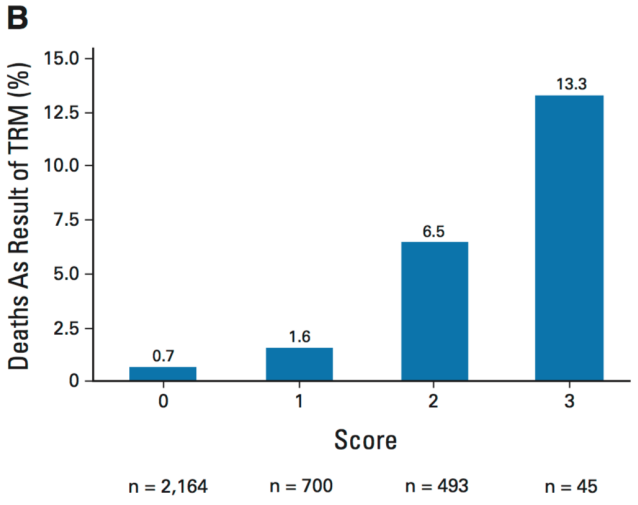


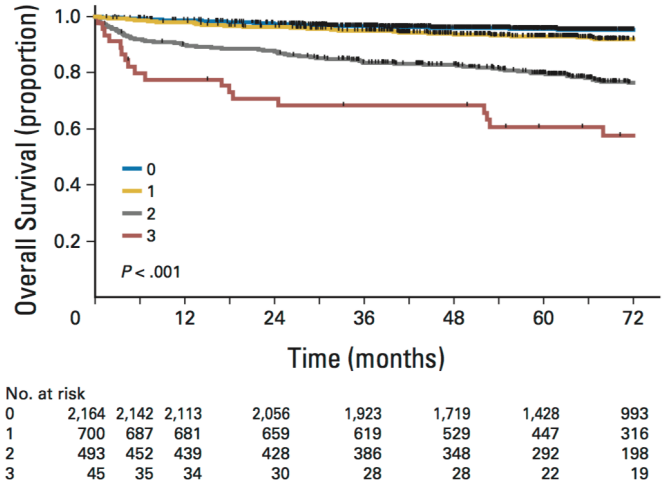


Behringer K, et al. J Clin Oncol 31:231-9, 2013

escBEACOPP is not for everyone

Treatment-related mortality risk score



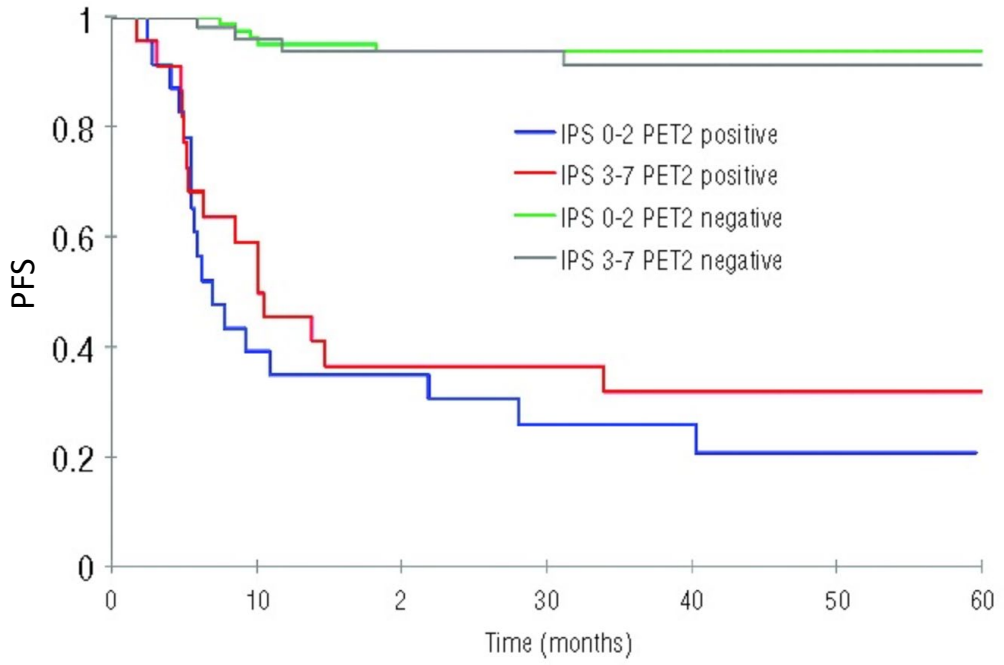


Points	Age	PS
0	< 40	0-1
1	40 - 49	2
2	≥ 50	

Wongso D, et al. J Clin Oncol 31:2819-24, 2013

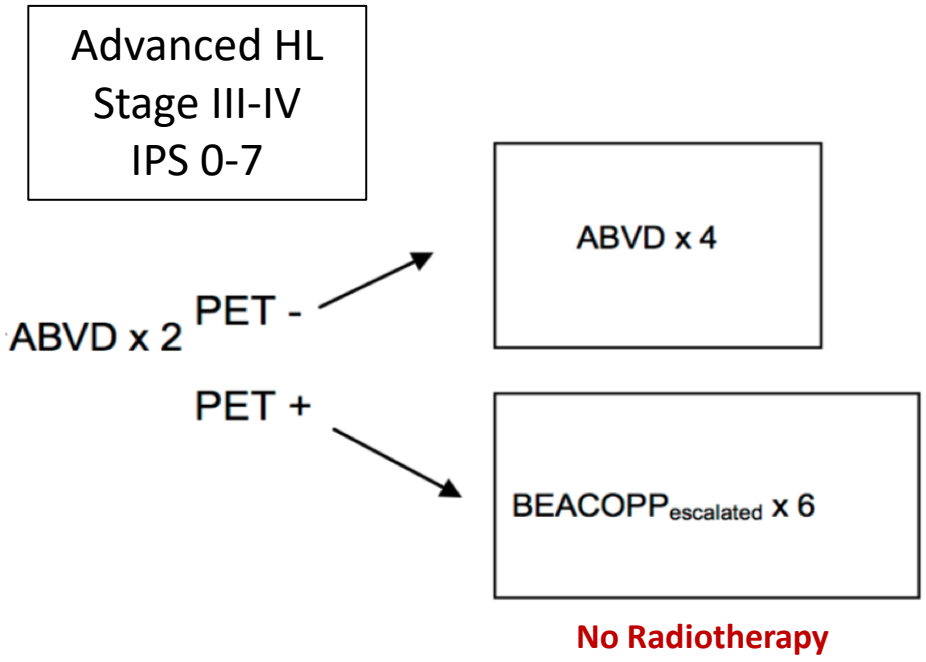
Can we determine which subset of patients may benefit from intensification of treatment to escBEACOPP?

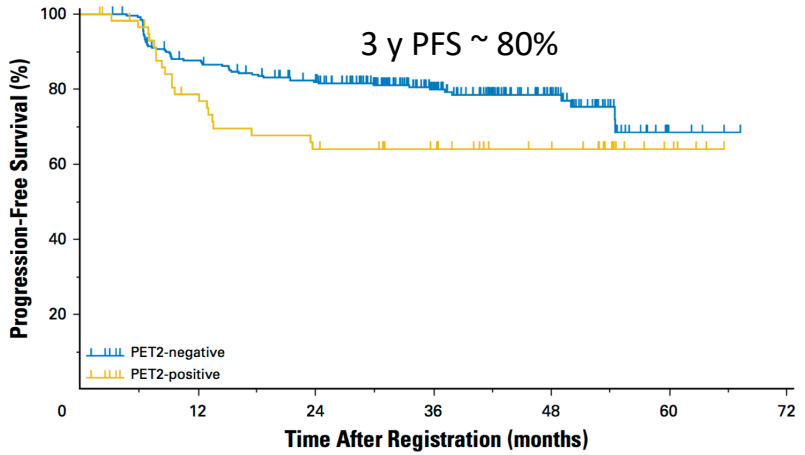
Prognostic value of interim-PET using Deauville 5-point criteria



Gallamini A et al. Haematologica 99:1107-13, 2014

US Intergroup S0816 trial: Study design

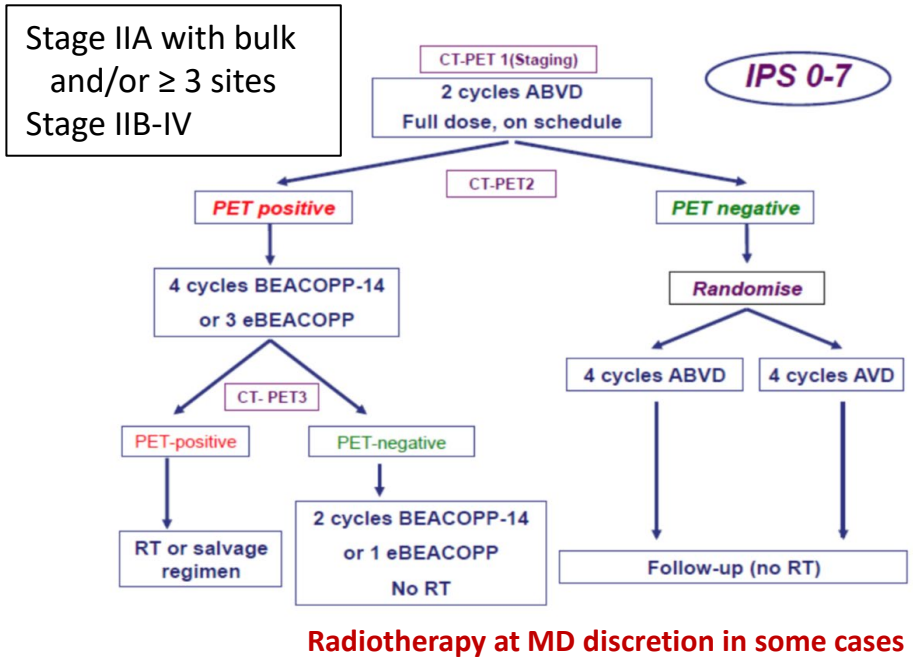




- **Median follow up 39.7 months**
- **escBEACOPP x6 after positive PET-2 improves PFS compared to historical controls**

Press OW, et al: J Clin Oncol, 2016

RATHL Trial: Study design



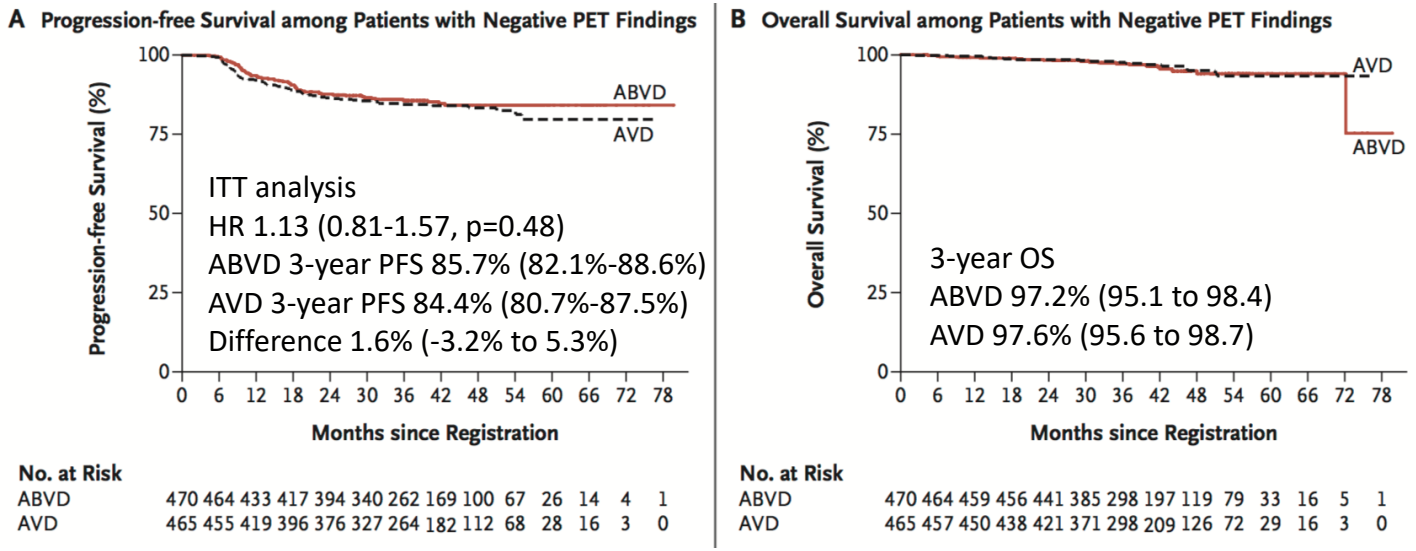
Radiotherapy at MD discretion in some cases

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

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

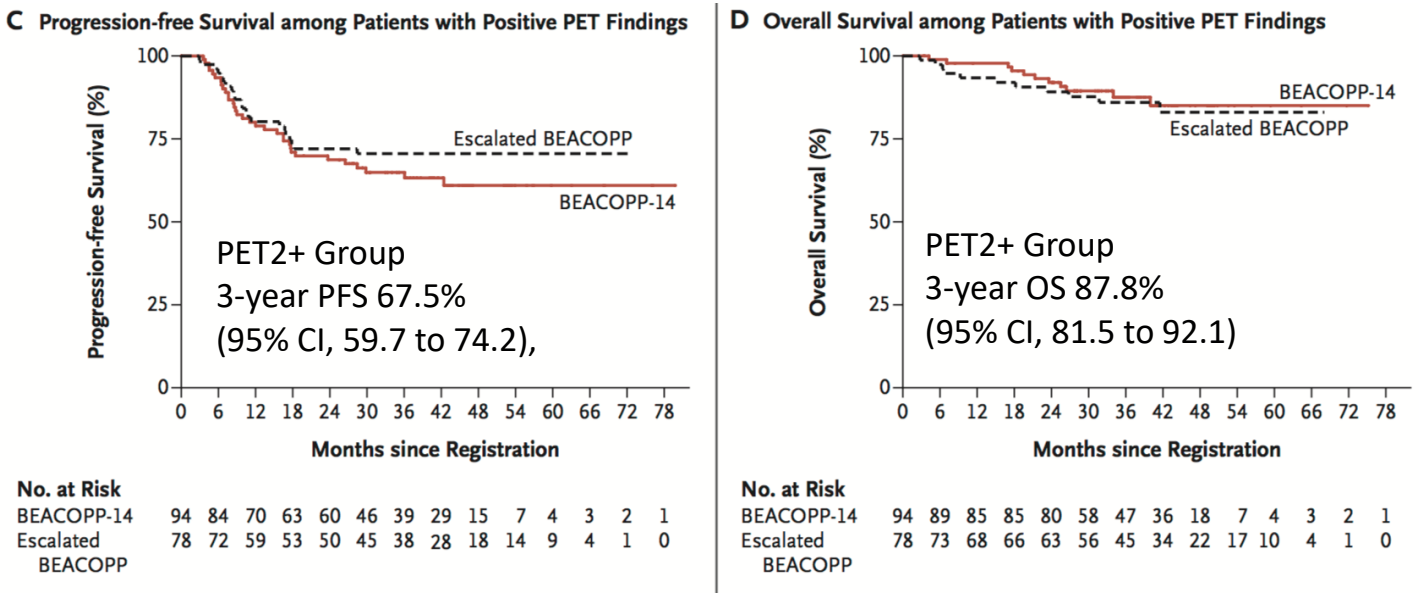
RATHL Trial: Results in PET2 negative patients

Median follow up 41 months



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

RATHL trial: Results in PET2 positive patients



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

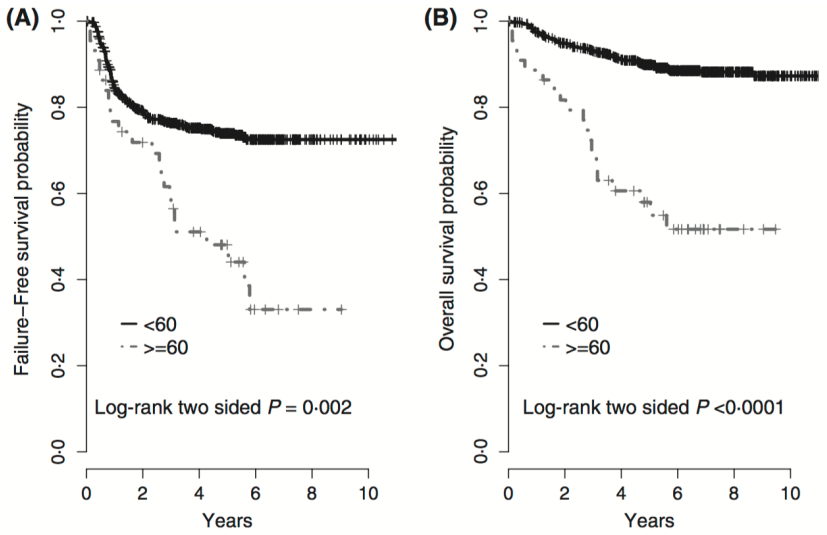
Johnson P, et al. N Engl J Med 374:2419-29, 2016

ABVD in patients age ≥ 60

- GHSG analysis of 117 patients receiving ABVD on HD10 and HD11 studies
  - Lower proportion of patients with RDI ≥ 80% (59% vs. 85%)
  - Higher TRM (5% vs. <1%)

Böll B, et al. J Clin Oncol 31:1522-9, 2013

Inferior outcomes in advanced HL patients age ≥ 60



- 45 patients treated with ABVD or Stanford V in E2496 trial

Evens AM, et al. Br J Haematol 161:76-86, 2013

Increased toxicity and TRM in patients age ≥ 60

	Age ≥ 60 years (n = 45)			Age < 60 years (n = 789)		
	Grade†			Grade†		
	3	4	5	3	4	5
Toxicity type	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Haematological	11 (24)	31 (69)	–	372 (47)	308 (39)	–
Non-haematological	14 (31)	6 (13)	4 (9)	322 (41)	53 (7)	2 (<1)

- 11/45 (24%) patients developed bleomycin lung toxicity
  - 2/11 (18%) died

Evens AM, et al. Br J Haematol 161:76-86, 2013

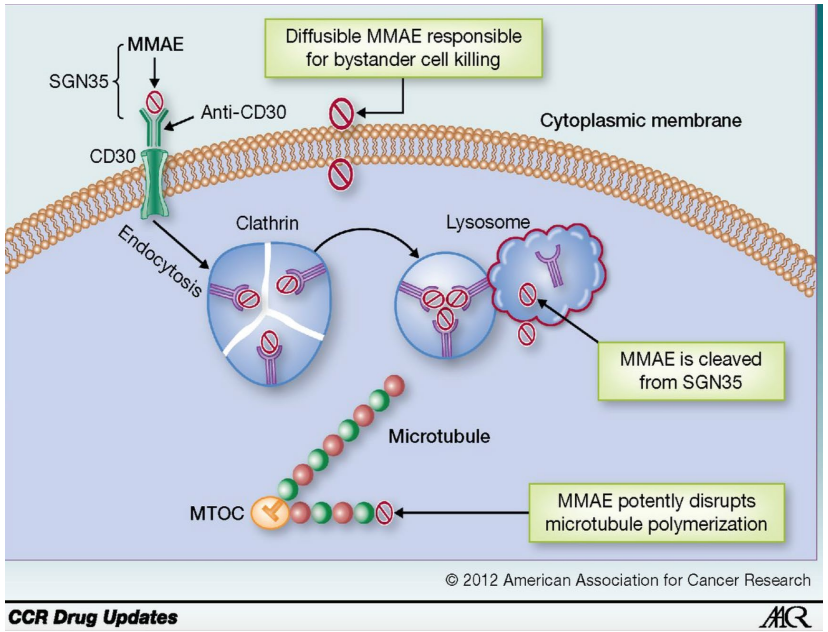
- De-escalation based on negative interim PET has been widely adopted and integrated into NCCN guidelines
- Escalation to escBEACOPP remains controversial due to lack of control arm, though is an option for select patients

- Do novel agents have the opportunity to improve efficacy while minimizing long term side effects?

Brentuximab vedotin

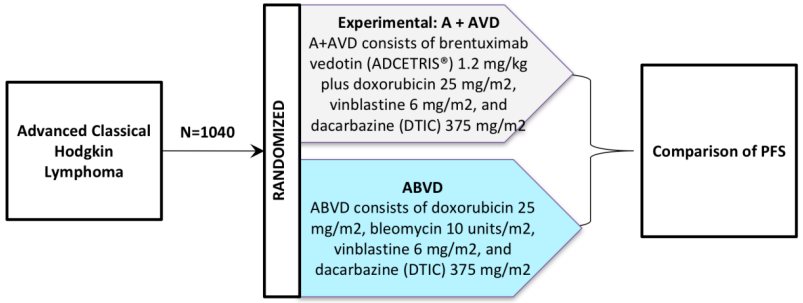
- Anti-CD30 antibody-drug conjugate
- FDA approved
  - Relapsed HL after auto HSCT
  - Failure of 2 regimens in patients not eligible for transplant
  - Consolidation for high risk HL patients after auto HSCT
  - CD30+ mycosis fungoides/cutaneous ALCL
  - Relapsed ALCL

  - *Untreated Advanced HL with chemotherapy*



Deng C, et al. Clin Cancer Res 19:22-7, 2013

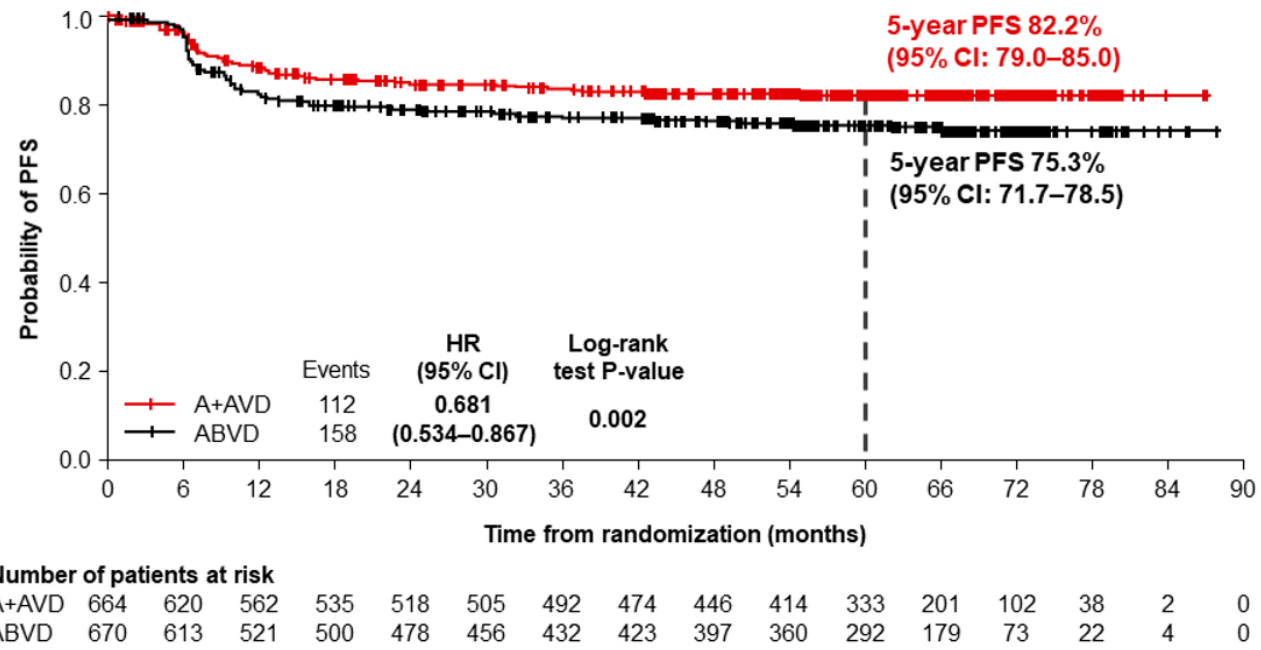
Can brentuximab improve outcomes in patients with advanced stage HL?



- International phase III randomized clinical trial
  - Brentuximab + AVD (A-AVD)
  - ABVD

Characteristic	Number or %
Median age Age ≥ 45 Age ≥ 60	36 (18-83) 34% 14%
Male	58%
Stage III IV	36% 64%

A-AVD associate with modest mPFS improvement over ABVD



- Median follow up 60 months
- Primary endpoint - 5 year modified PFS
  - A-AVD: 82.2% (95% CI 79.0-85.0)
  - ABVD: 75.3% (95% CI 71.7–78.5)

Benefit not as strong as predicted but was statistically significant

Not enough events for OS analysis

Connors et al. NEJM 2018
Straus et al. Blood 2020, ASH 2020

A-AVD associated with higher rates of toxicity

- A-AVD: 7/9 on study deaths due to neutropenia (no primary GCSF)in the A+AVD arm were associated with neutropenia
- ABVD: 11/13 on study deaths due to pulmonary toxicity
- Protocol later amended to give A-AVD patients primary GCSF (n=83)
  - Febrile neutropenia reduced from 19% to 11%
  - Grade ≥3 infections reduced from 18% to 11%.

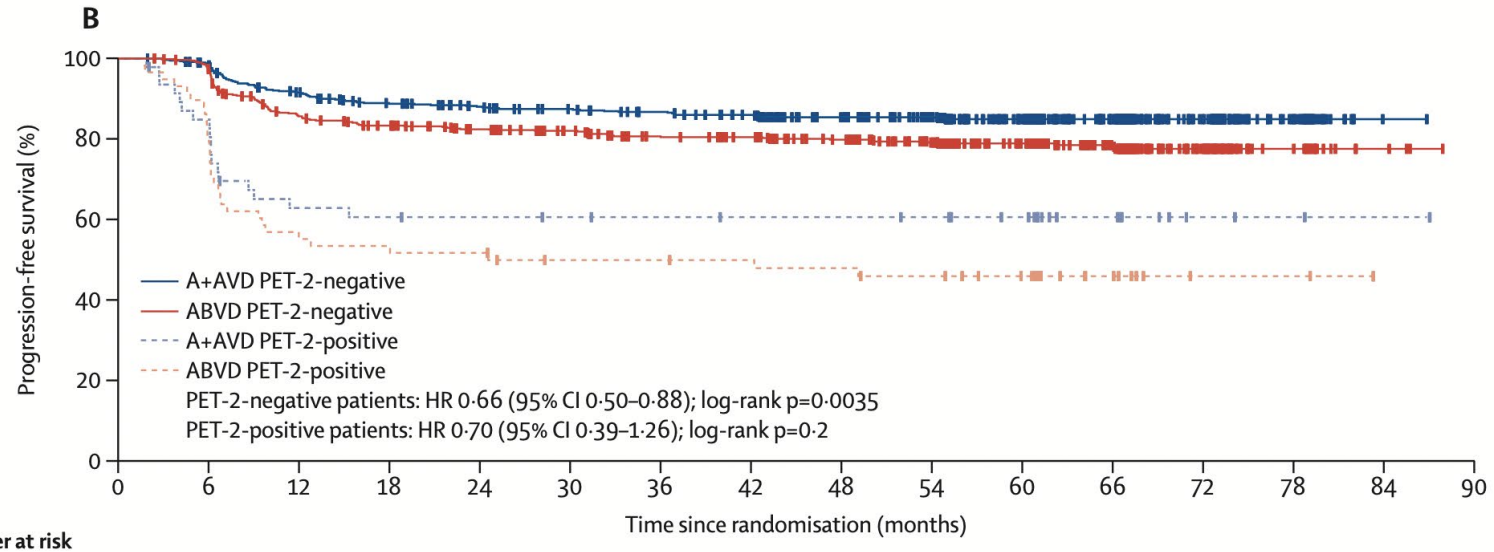
Toxicity	A-AVD	ABVD
Neutropenia	58%	45%
Febrile neutropenia	19%	8%
Grade ≥ 3 infection	18%	10%
Peripheral neuropathy	67%	43%
Peripheral neuropathy grade ≥ 3	11%	2%
Pulmonary toxicity grade ≥ 3	≤ 1%	3%

Should A-AVD be the new standard of care for advanced stage HL?

- **FOR**
- Improved 5 year mPFS
- Fewer relapses mean fewer patients subjected to cost/toxicity/infertility due to auto transplant
- Febrile neutropenia/infection likely overstated since only 83 patients had later mandated GCSF
- Not up to individual providers to decide a regimen based on cost if patients insurance will cover a more efficacious treatment

- **AGAINST**
- **NNT: 14 patients to prevent one treatment failure (based on 5 year data)**
- **Most patients who relapse can likely be salvaged with brentuximab-based salvage regimen**
- A-AVD is more toxic
- A-AVD + GCSF costs $$$
  - > $100,000 for Brentuximab alone

Interim PET in the A-AVD era

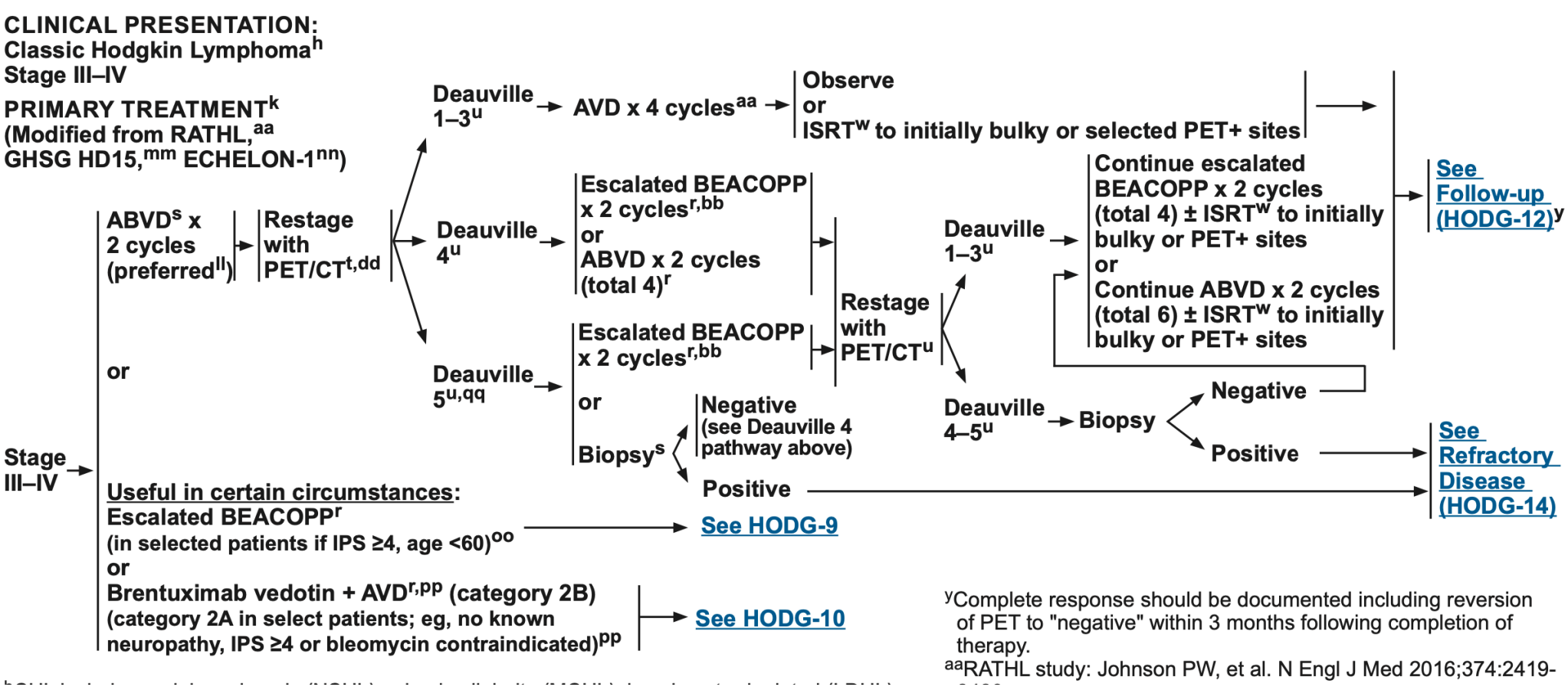


Number at risk (number censored)																
A+AVD PET-2-negative	588 (0)	572 (6)	526 (13)	500 (23)	484(35)	472 (44)	460 (52)	444 (64)	417 (88)	386 (119)	312 (191)	189 (314)	98 (405)	36 (467)	1 (502)	0 (503)
ABVD PET-2-negative	578 (0)	558 (4)	483 (13)	463 (20)	442(36)	424 (52)	400 (68)	392 (76)	368 (97)	334 (128)	271 (190)	170 (290)	70 (388)	20 (438)	4 (454)	0 (458)
A+AVD PET-2-positive	47 (0)	39 (1)	28 (2)	27 (2)	26(3)	25 (4)	24 (5)	23 (6)	23 (6)	22 (7)	18 (11)	10 (19)	3 (26)	2 (27)	1 (28)	0 (29)
ABVD PET-2-positive	58 (0)	46 (0)	32 (0)	31 (0)	30(0)	26 (3)	26 (3)	25 (4)	24 (4)	22 (5)	18 (9)	8 (19)	2 (25)	2 (25)	0 (27)	0 (27)

- PET+ better than anticipated with A-AVD, PET- not as good as expected (seen in all studies)
- A-AVD 5-year PFS in PET+ similar to that seen in patients who received escBEACOPP in prior studies
- **Better surrogate outcomes are needed!**

Straus et al. Lancet Haematology 2021

NCCN Hodgkin Guidelines



[y]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.

[aa]RATHL study: Johnson PW, et al. N Engl J Med 2016;374:2419-

Take home points for boards– Advanced stage

- **It is reasonable to omit bleomycin after cycle 2 if interim PET negative (Deauville 1-3)**
- escBEACOPP should NOT be given to patients age 60+
- For younger patients, you will not have to decide between AAVD, ABVD, escBEACOPP, but should get at least 6 cycles
  - AAVD has not been widely adopted by experts outside of high risk patients (stage IV, IPS 4+) due to toxicity concerns (cat 2B except for IPS 4-7)
- Unlikely to have questions on escalation after positive interim PET due to lack of control arm (not in NCCN guidelines, but can be done for select patients

Relapsed/refractory HL

- Clinical trials strongly recommended in this setting!

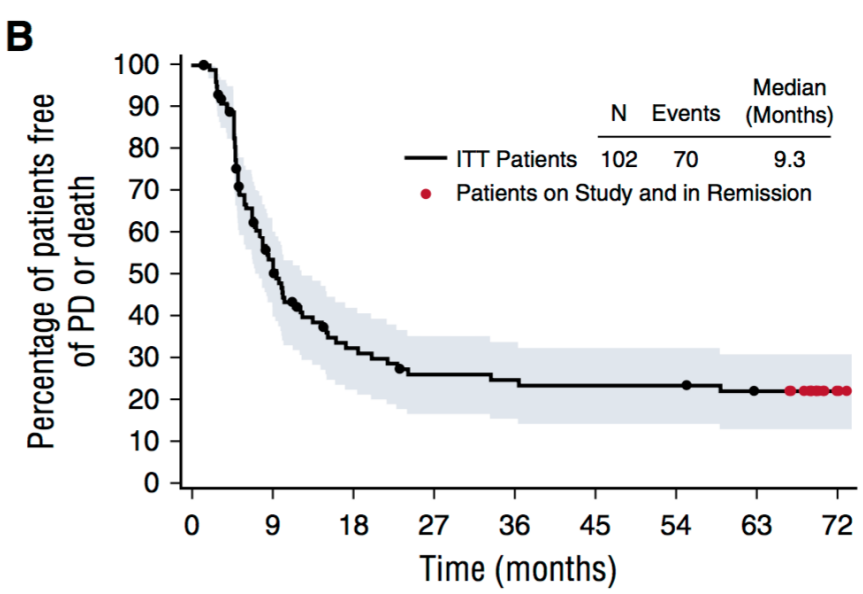
- 1st relapse in autologous transplant eligible patient
  - Salvage chemotherapy followed by autologous transplant
    - ICE, DHAP, GND, Brentuximab + bendamustine, Brentuximab + nivolumab (older patients)
      - Increasing evidence that brentuximab-based salvage may have higher CR rates
    - Brentuximab maintenance x 1 year for those with relapse within 1 year or extranodal sites at relapse (unclear impact in those with prior brentuximab)
  - Patients who do not achieve complete metabolic response are unlikely to be cured with transplant and should be considered for alternate salvage or treatment with novel agents

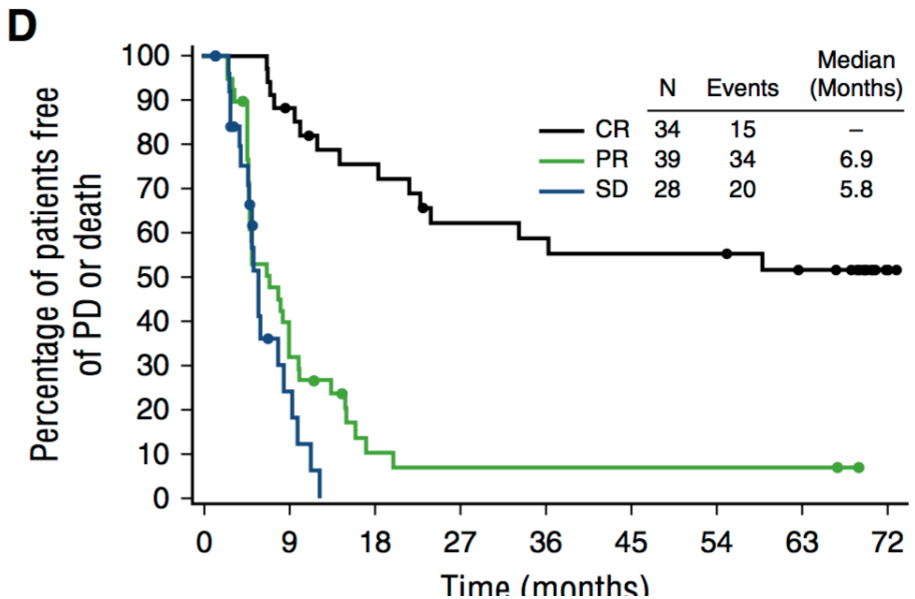
Novel drugs in treatment of relapsed HL

- Anti-CD30 antibody/drug conjugate
  - Brentuximab vedotin

- PD1 inhibitors
  - Nivolumab
  - Pembrolizumab

Brentuximab in patients who relapsed after autologous transplant

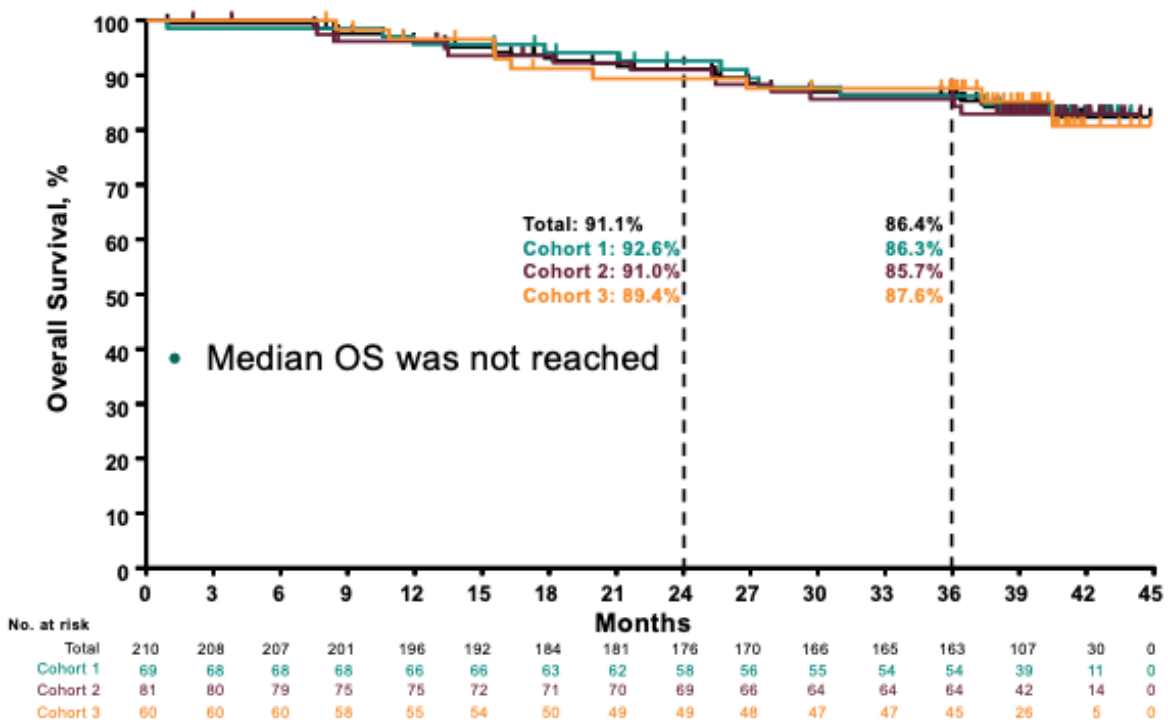


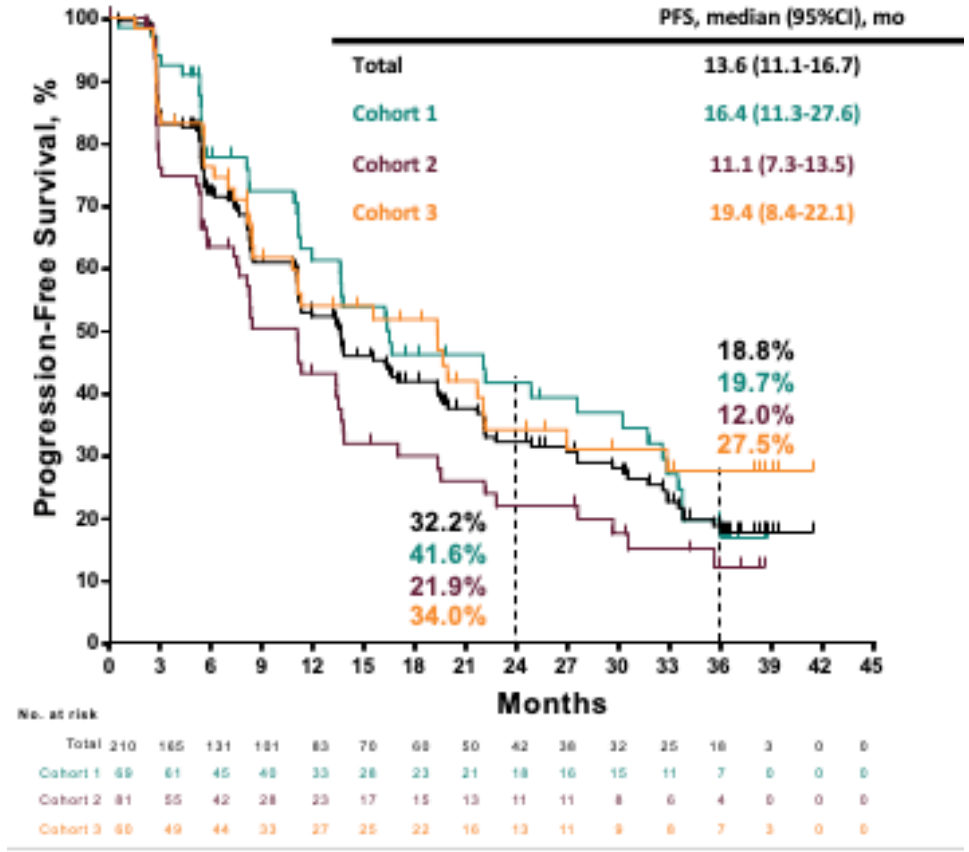


- **5 year end of study analysis**
- **9% (9/100) of patients achieved sustained CR without additional therapy**

Chen R, et al: Blood 128:1562-6, 2016

Long term follow up - pembrolizumab

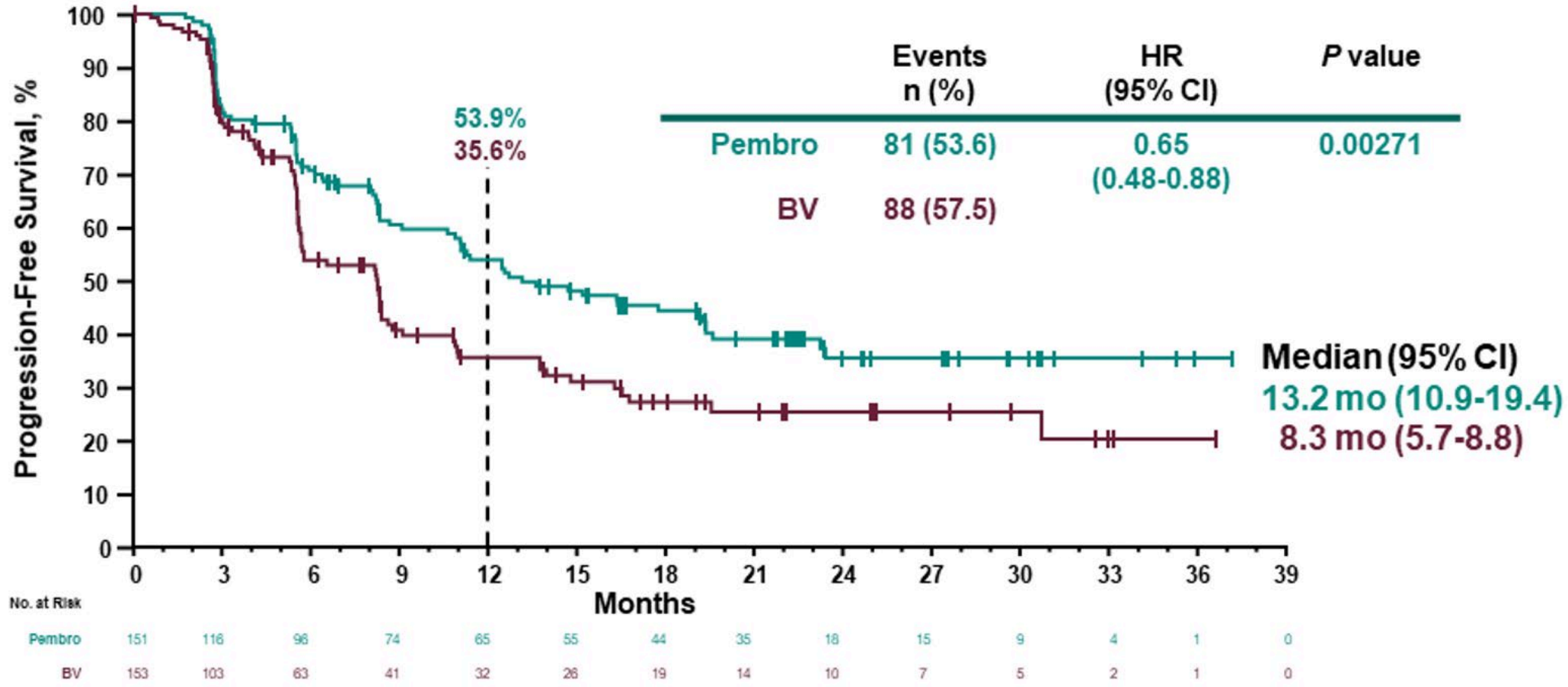




- Visually, PFS and OS appear better with pembro (3 year OS 86%!)

Zinzani et al. ASH 2019

Keynote-204 – Pembro vs. brentuximab in R/R CHL



Pembrolizumab now with FDA label for 2nd line therapy onwards

Kuruvilla et al ASCO 2020

Boards take home points – relapsed HL

- **Salvage chemo then auto HCT if in CR for 1st relapse/primary refractory disease and transplant eligible**
- **Brentuximab maintenance x 1 year for those with relapse within 1 year/extranodal sites at relapse**
- Know mechanisms of novel agents and toxicities
  - Brentuximab – NEUROPATHY and cytopenias (esp if with chemo) and
  - PD1 inhibitors – autoimmune effects
- Transplant ineligible/transplant failure
  - For boards – new data – but Pembrolizumab > Brentuximab with randomized data
  - In clinical practice – these patients should be STRONGLY considered for trials (combinations of novel agents)

Boards take home points – relapsed HL

- **Salvage chemo then auto HCT if in CR for 1st relapse/primary refractory disease and transplant eligible**
- **Brentuximab maintenance x 1 year for those with relapse within 1 year/extranodal sites at relapse**
- Know mechanisms of novel agents and toxicities
  - Brentuximab – NEUROPATHY and cytopenias (esp if with chemo) and
  - PD1 inhibitors – autoimmune effects
- Transplant ineligible/transplant failure
  - For boards – would give brentuximab then PD1 agents (may be changing due to recent keynote-204 data)
  - In clinical practice – these patients should be STRONGLY considered for trials (combinations of novel agents)

Survivorship

- THERE IS ALMOST ALWAYS A SURVIVORSHIP QUESTIONS – THEY LOVE THIS TOPIC!!!

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?

CHL vs. NLPHL pathology

	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-ABVD) 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
  - Consider biopsy for unexplained cytopenias
    - Anemia common, but other cytopenias are not
- Avoid routine growth factors with ABVD due to ? increased risk of pulmonary toxicity (no primary prophylaxis)
- NO dose delays with ABVD due to neutropenia – treat on time with standard doses. Inferior outcomes with decreased dose intensity. Consider prophylactic antibiotics
- Repeat biopsy with refractory disease or relapse prior to starting subsequent therapy.

Questions?