18th Annual Indy Hematology Review

T. HOWARD LEE KEYNOTE LECTURE

State of the Art: Current and Emerging Treatment of Hodgkin Lymphoma

Ranjana Advani M.D.

Saul Rosenberg Professor of Lymphoma

Stanford MEDICINE

DISCLOSURES

- *Advisory Board*: Roche, Celgene, Takeda, Seattle Genetics, Epizyme, Sanofi, Kura, ADCT, Karyopharm, Merck, BMS, Daichi Sanyo, Incyte

- *Institutional research funding*: Seattle Genetics, Regeneron, Pharmacyclics, Merck, Forty-Seven, Cyteir, Millennium, ADCT, Kura

- Speaker's Bureau: none
- Stockholder: none
- Employee: none

T. Howard Lee

- Founder and President Emeritus of Hematology Oncology of Indiana
- Dedicated his career to the care of his patients
- Known for his work ethic.
  - He frequently would start hospital rounds at 4am and was always the last to leave the clinic.
  - A practice he kept until he retired at 65.
- His kindness and mentorship of young physicians and nurses was legendary.
- He is the only physician in Indianapolis whose likeness is honored in the hallways of two hospital systems
- A legendary educator who continues to support educational causes

Best words to describe Dr. T. Howard Lee:
"A friend, teacher, mentor and humanitarian", roles that he continues to fulfill even now

Courtesy Dr Ruemu Birhiray

Learning Objectives

- Optimize outcomes in front line therapy for classic Hodgkin lymphoma (CHL) beyond ABVD
- Harness the immune system in management of relapsed disease

Background

- Classic Hodgkin lymphoma represents ~ 10% of all lymphomas
- ~ 9000 new cases annually in the United States
- Highly curable with frontline therapy even in advanced stage disease
- At any given time, more cured survivors than patients with active disease

Classic Hodgkin Lymphoma

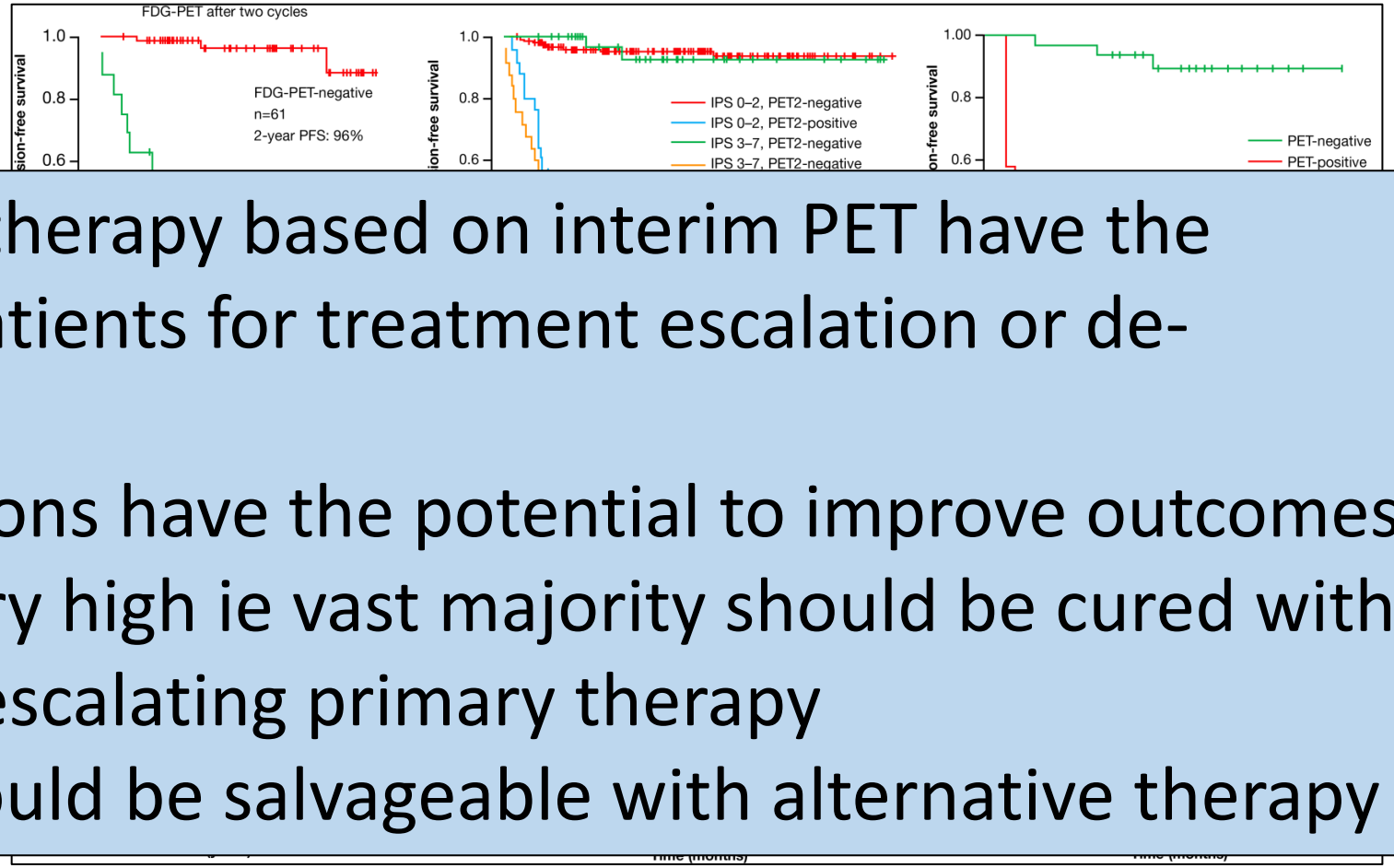
Expected Outcomes and Goals of therapy in 2021

	% Cure Rate	Therapeutic Priority
Early Favorable (Stage I-II)	≥ 90	Reduce Toxicity
Early unfavorable (stage I, II with risk factors)	80-85	Increase efficacy *and* decrease toxicity
Advanced stage (bulky IIB, III, IV)	75-85%	Increase efficacy *and* decrease toxicity

Risk factors: Bulk, B symptoms, Elevated ESR, extra-nodal sites, # nodal sites

Can very bad disease be distinguished from less bad disease?

Interim PET Response to therapy



- Can modification of therapy based on interim PET have the potential to select patients for treatment escalation or de-escalation?
- Can these modifications have the potential to improve outcomes?
  - NPV should be very high ie vast majority should be cured with continuing or de-escalating primary therapy
  - PET + patients should be salvageable with alternative therapy

Hutchings et al Blood 2006, Gallamini et al JCO 2007, Kostakoglu et al Cancer 2006, Hutchings et al Ann Oncol 2005
Gallamini et al. Haematologica 2006, Cerci JJ et al J Nucl Med 2010

Courtesy Dr Johnson

Current Treatment
Interim PET Response Adapted Strategies

Can we determine which subset of patients may benefit from therapy de-escalation or intensification?

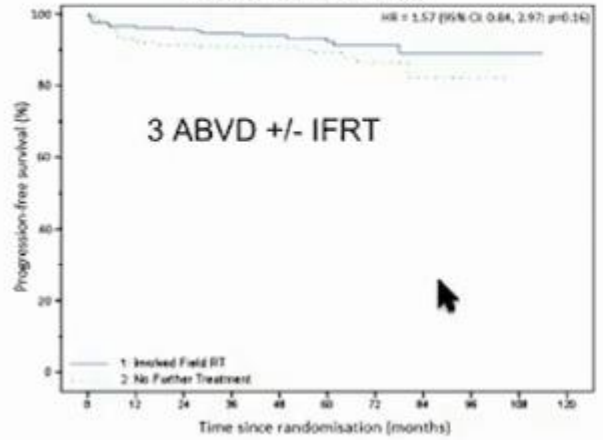
- **Two strategies for initial therapy**
  - ***Start with ABVD x 2: escalate or de-escalate therapy based on PET 2***
  - ***Start with BEACOPP esc x 2: escalate or de-escalate therapy based on PET 2***

Early stage: Deauville score > 2 considered positive for most studies

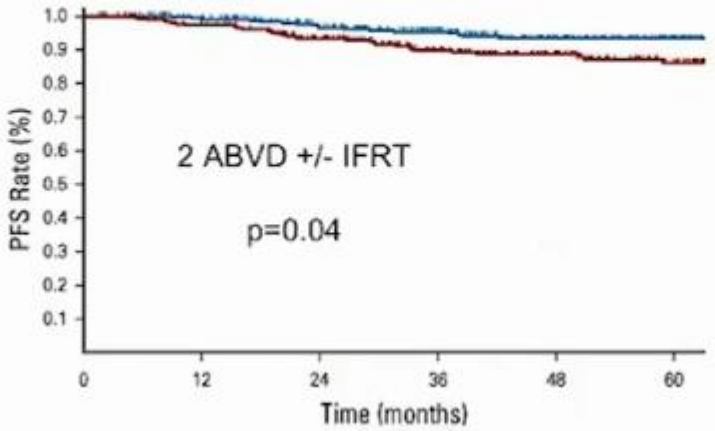
Advanced stage: Deauville score > 3 considered positive for most studies

PET adapted approaches for early stage disease: PFS

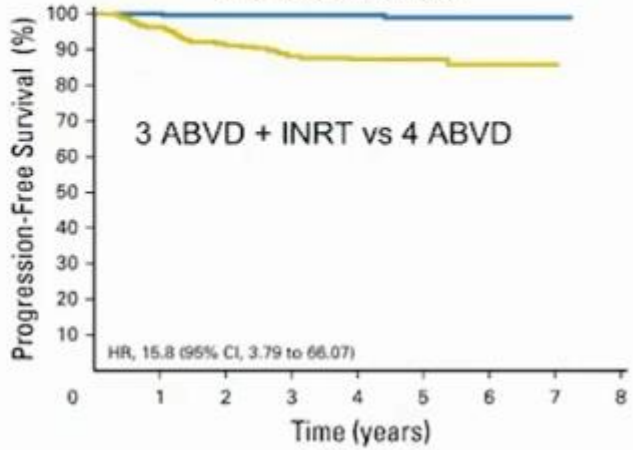
RAPID 5 yr EFS 96.0 vs 90.1%



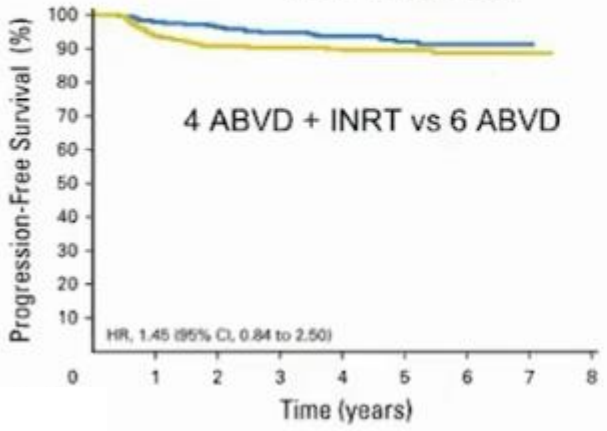
HD 16 5 yr PFS 93.4 vs 86.1%



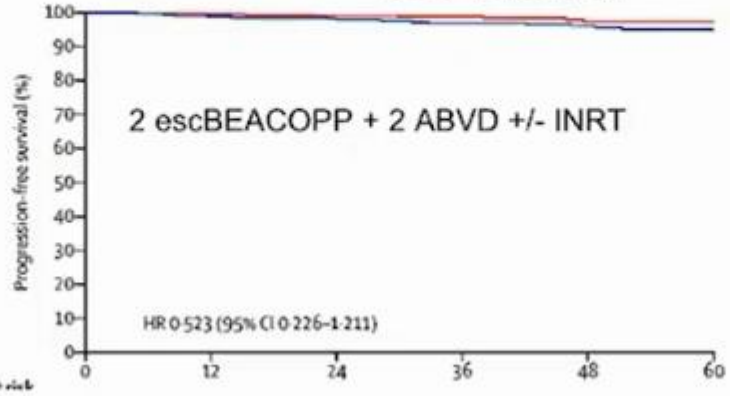
H10 F 5 yr PFS 99. 0 vs 87.1%



H10 U 5 yr PFS 92.1 vs 89.6%



HD 17 5 yr PFS 97.3 vs 95.1%



N Engl J Med 2015; 372:1598-1607

J Clin Oncol 2017: 35:1786-1794

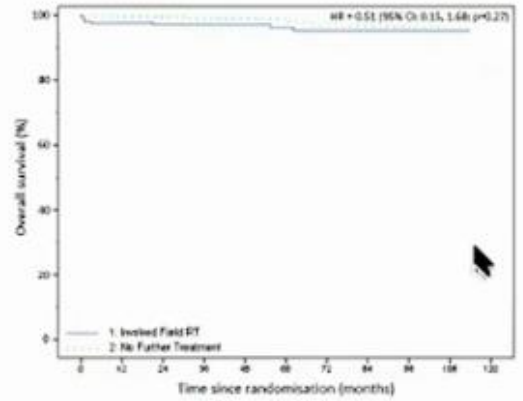
J Clin Oncol 2019;37:2835-2845

Lancet Oncol 2021: 22:223-234

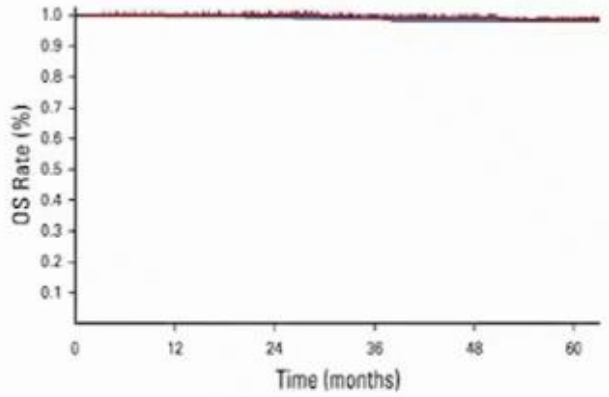
Johnson ICML 2021

PET adapted approaches for early stage disease
OS after therapy de-escalation

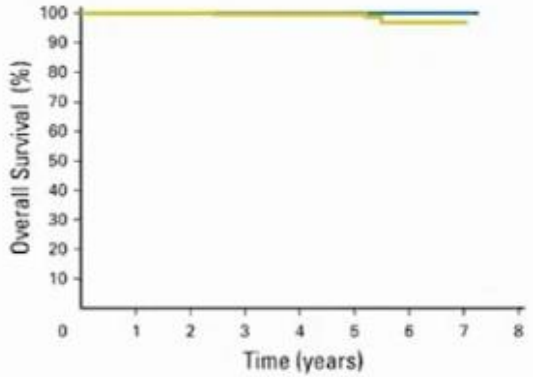
RAPID 3 yr OS 97.1 vs 99.5%



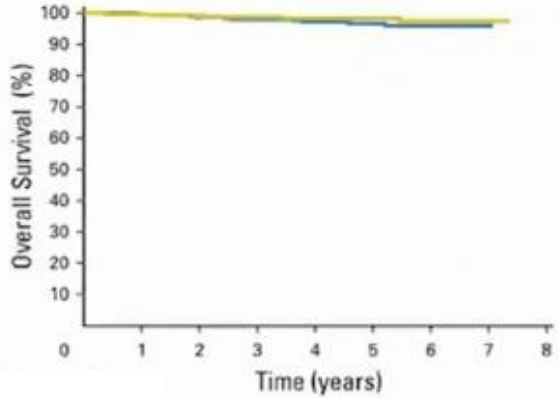
HD 16 5 yr OS 98.1 vs 98.4%



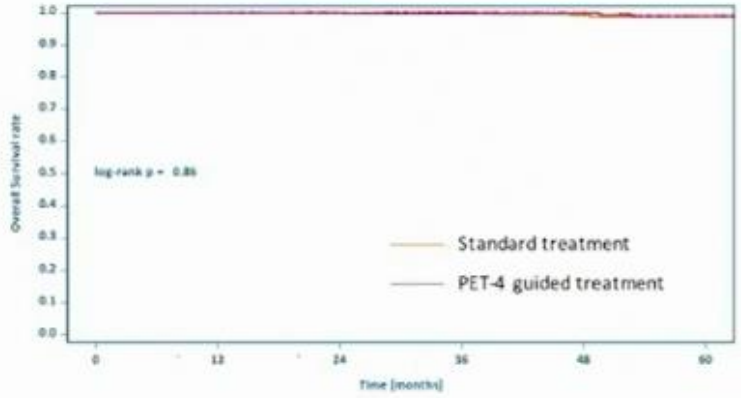
H10 F 5 yr OS 100 vs 99.6%



H10 U 5 yr OS 96.7 vs 98.3%



HD17 5 yr OS 98.8 vs 98.4%



N Engl J Med 2015; 372:1598-1607

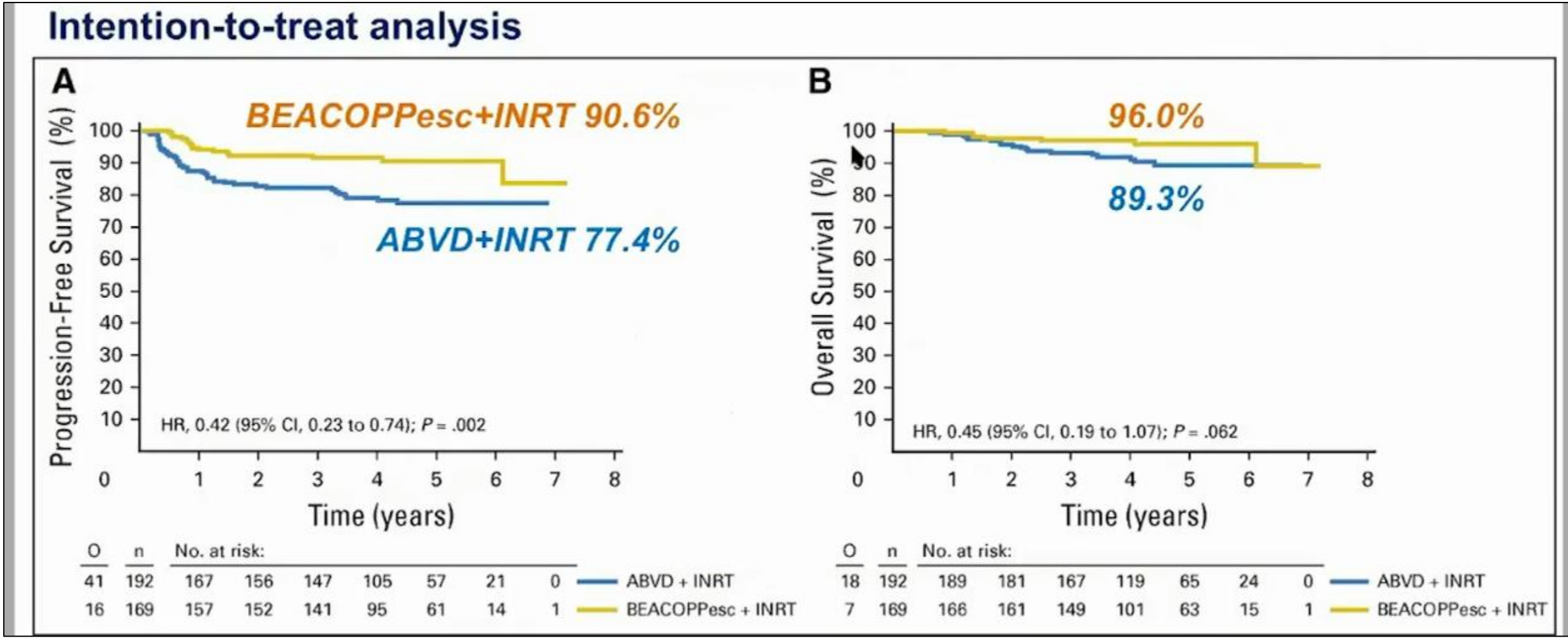
J Clin Oncol 2017: 35:1786-1794

J Clin Oncol 2019;37:2835-2845

Lancet Oncol 2021: 22:223-234

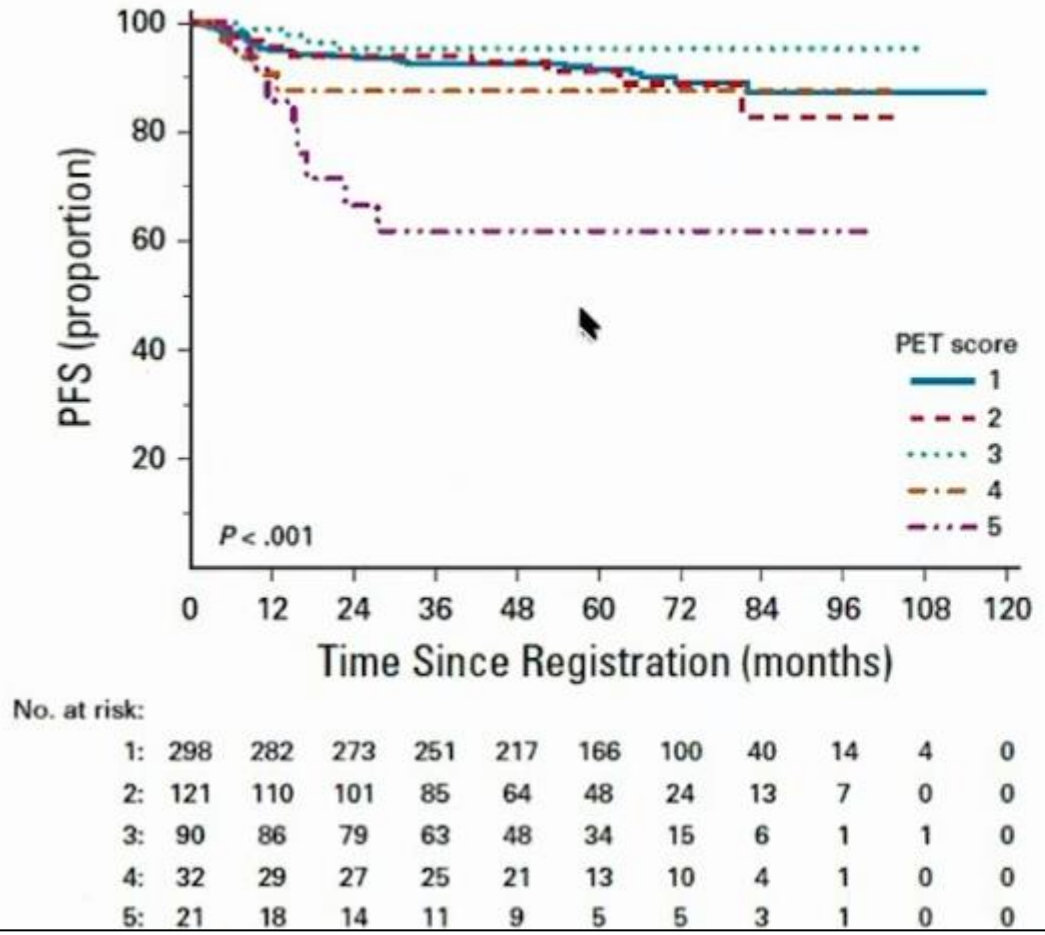
Johnson ICML 2021

H10: PFS and OS
Randomized trial of therapy escalation after positive interim PET



Andre et al J Clin Oncol 2017

RAPID Trial
Interim PET score outweighs baseline risk variables



Comparison		5 year PFS (95% CI)
PET	1	91.5 (88.2 – 94.8)
	2	91.1 (85.2 – 97.0)
	3	95.3 (90.8 – 99.8)
	4	87.5 (76.1 – 98.9)
	5	61.9 (41.1 – 82.7)
EORTC	F	91.4 (88.1 – 94.7)
	U	87.3 (82.0 – 92.6)

Barrington et al J Clin Oncol 2019

GHSG HD17 Trial: Final Analyses

Patients with early-stage unfavorable HL (N = 1100):

- Randomized to standard chemotherapy + RT vs PET-adapted experimental approach
- All patients treated with 2 × $BEACOPP_{esc}$ + 2 × ABVD

66% of patients were PET4 negative (Deauville 1-2) → no RT in the experimental arm

5-year PFS:

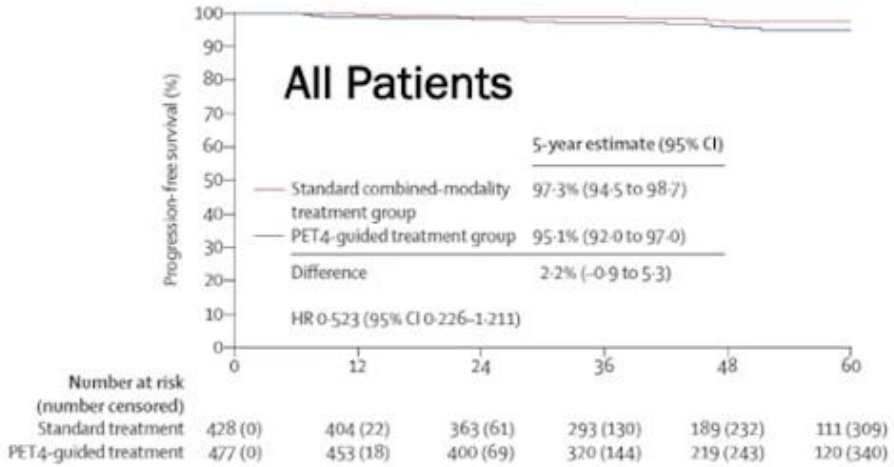
- 97.3% in the standard arm vs 95.1% in the experimental arm
- Difference between the 2 groups was -2.2% (95% CI: -5.3%, 0.9%), excluding the lower margin of -8%

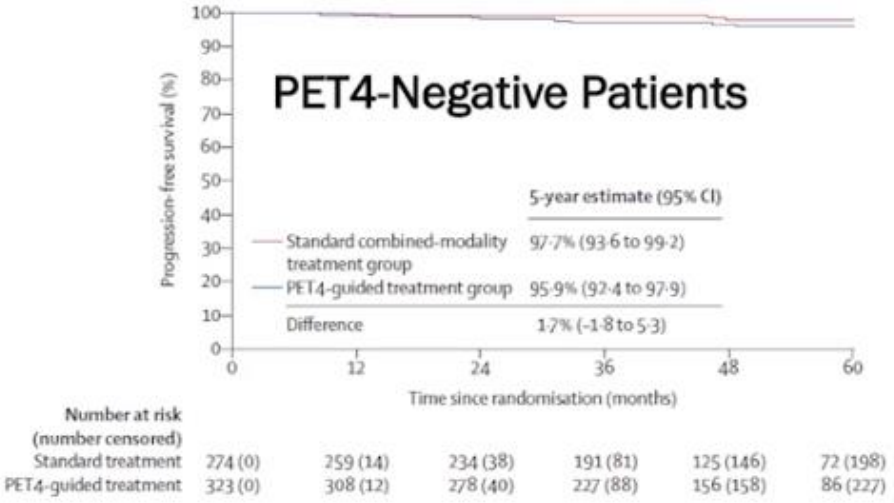
5-year OS:

- Identical in the 2 arms (98.8% vs 98.4%)

PET response-adapted approach now SOC in GHSG, with RT only to PET4-positive patients

Borchmann P, et al. *Lancet Oncol*. 2021;22:223-234.





Summary of Current Strategies In ESHL

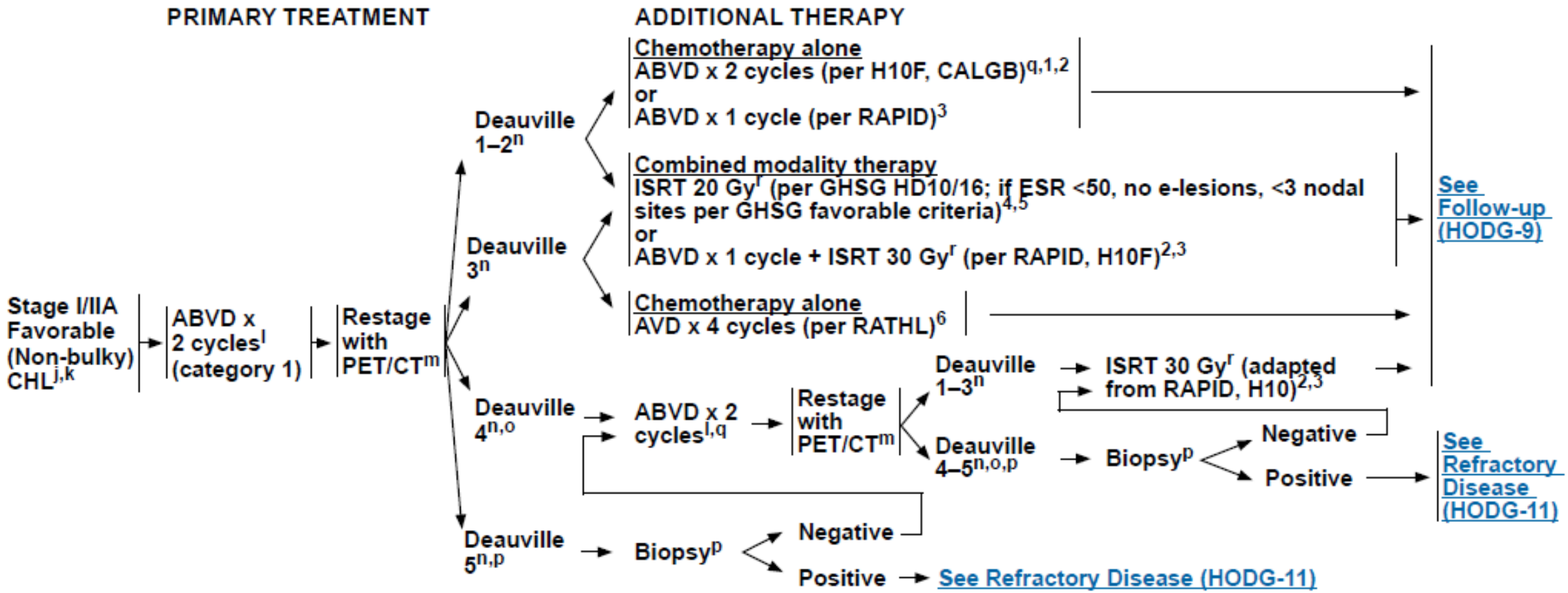
- Patient selection important
  - differences in GHSG vs EORTC vs NCCN criteria
- Patients with negative PET (DS 1-2) scan after 2-3 cycles of ABVD:
  - Good outcome (PFS > 90%), BUT experience more treatment failure (~ 3-12%) than those receiving RT.
  - No impact on OS
  - ***Outcomes for DS 3 suboptimal with ABVD x 4 alone (PFS 77%)***
- Patients with negative PET (DS 1-2) scan after “2 + 2”
  - Excellent outcomes with NO RT
- RT is appropriate for patients with a positive interim or end-of-therapy PET scan
- INRT/ISRT appears adequate to prevent relapse
- Will likely have fewer long term /late effects than previously seen with EFRT
- Long-term follow up important

NCCN Guidelines Version 4.2021
Hodgkin Lymphoma (Age ≥18 years)

NCCN Guidelines Index
Table of Contents
Discussion

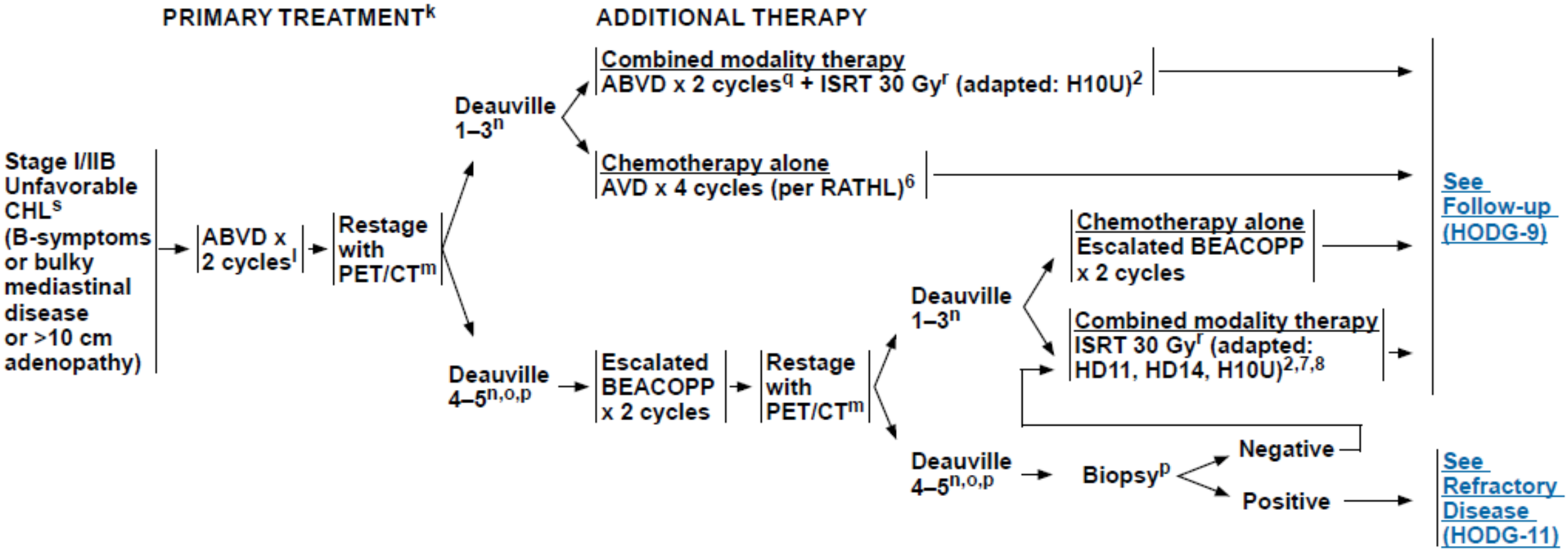
CLINICAL PRESENTATION:
Stage I/IIA Favorable (Non-Bulky) CHL[h,k]

Important Considerations:
- Selection of treatment (combined modality therapy or chemotherapy alone) should be based upon patient age, sex, family history of cancer or cardiac disease, comorbid conditions, and sites of involvement (especially within mediastinum or axilla).
- In general, treatment with combined modality therapy provides for a better PFS/FFP, but no difference in overall survival.
- Most patients will benefit from multidisciplinary input prior to final treatment decisions.



CLINICAL PRESENTATION:
Stage I/IIB Unfavorable CHL[h,k] (B-symptoms or bulky mediastinal disease or >10 cm adenopathy)

Important Considerations:
- Selection of treatment (combined modality therapy or chemotherapy alone) should be based upon patient age, sex, family history of cancer or cardiac disease, comorbid conditions, and sites of involvement (especially within mediastinum or axilla).
- In general, treatment with combined modality therapy provides for a better PFS/FFP, but no difference in overall survival.
- Most patients will benefit from multidisciplinary input prior to final treatment decisions.



How does one apply these various results in day-to-day practice?

- To help individualize therapy, a thoughtful discussion is required where other factors also need to be considered to assess risk from primary therapy
  - Age and sex of patient
  - Anatomic extent of disease and resultant normal tissue exposure to RT
  - Cumulative toxicity of additional cycles of chemotherapy if RT is avoided
  - Added toxicity from salvage therapy

<u>Defining disease distribution for therapy selection</u>

Optimizing/ Individualization of Therapy

Balance between immediate cure and prevention of late toxicity

Considerations for chemotherapy

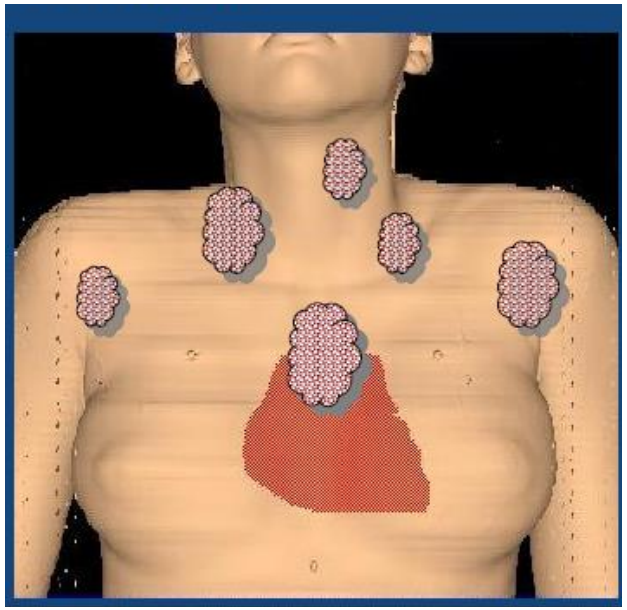
- Females < age 35 yr
  - Axillary and/or mediastinal involvement
- Inability to limit RT dose to important cardiac subunits

Considerations for CMT

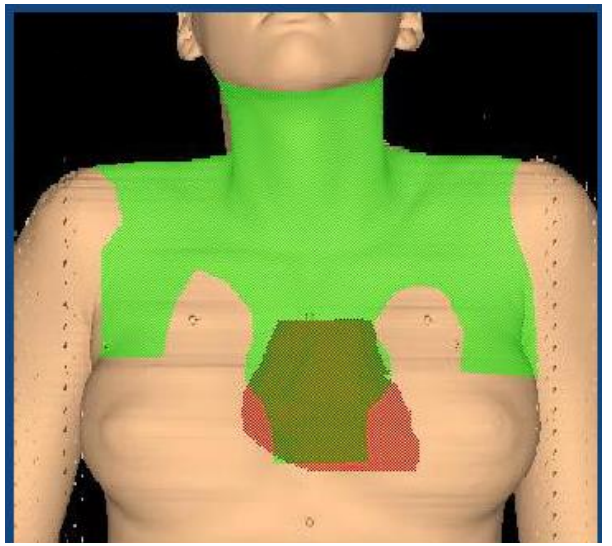
- Patients with favorable disease, especially when it is possible to limit the duration of chemotherapy
- Patients with a positive interim PET scan (~ 25%)
- Patients with bulky adenopathy
- Geographic areas where ASCT, PET imaging not easily available or cost-prohibitive

Individualization of Treatment

- 23 year old female
- IIA, 5 sites, no other risk factors
- PET CR to ABVD x 2



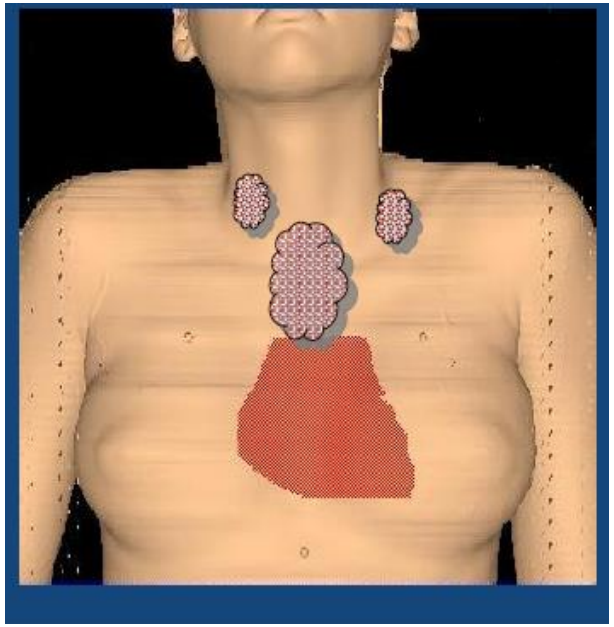
- Disease distribution requires substantial normal tissue to be treated with IFRT
- Chemotherapy alone chosen



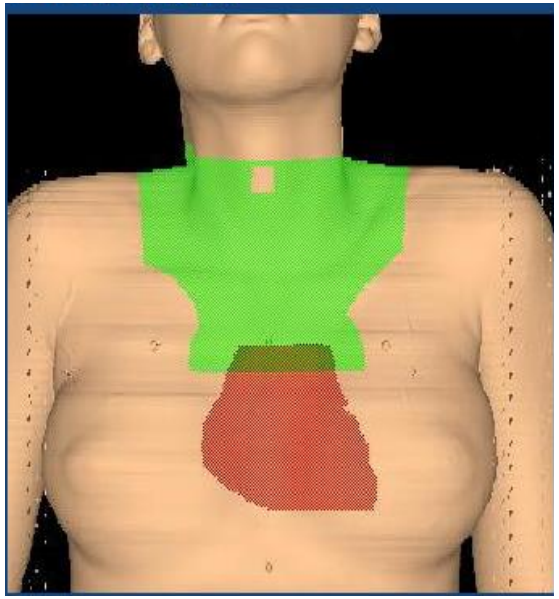
Courtesy: Dr Hodgson

Individualization of Treatment

- 39 year old female
- IIA, 3 sites, elevated ESR
- CR after ABVD x 2



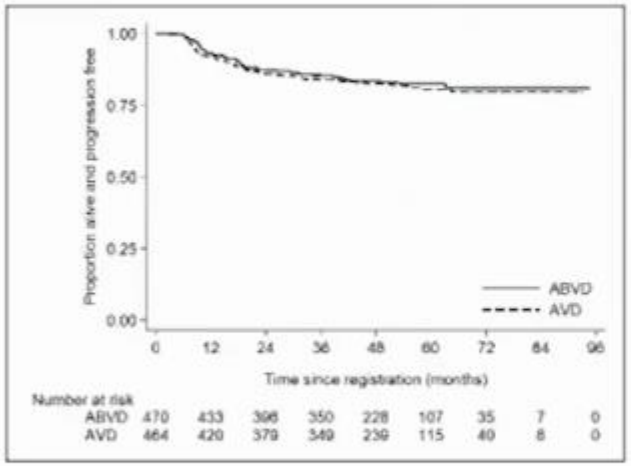
• Age >35 and absence of axillary disease means lower breast cancer risk with ISRT
• CMT chosen
• If 2 sites of disease: ABVDx2 + 20Gy



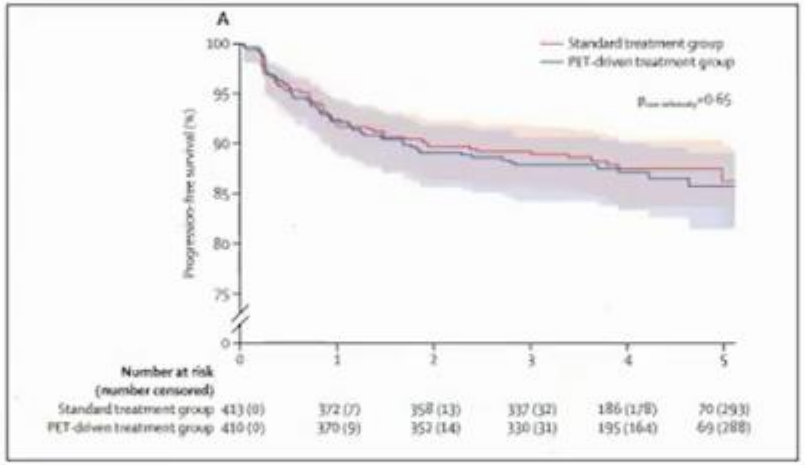
Courtesy: Dr Hodgson

PET adapted approaches for advanced stage disease
PFS after de-escalation in interim PET negative patients

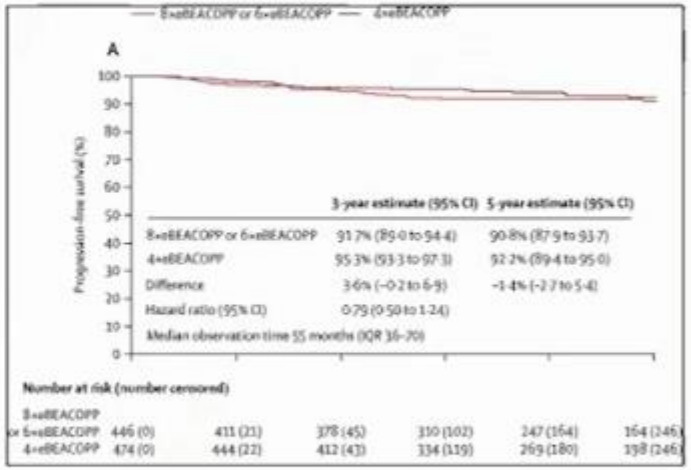
RATHL 5 Year PFS 81.6%



LYSA 5 Year PFS 89.4% vs 88.4%



HD18 5 Year PFS 91.7 vs 90.8%

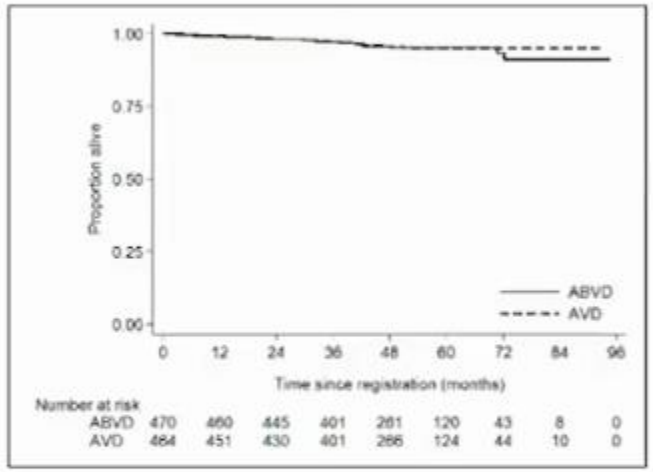


N Engl J Med, 2016. 374:2419-29
Lancet Oncol 2019. 20:202-215
Lancet 2017; 6736(17)32134-7

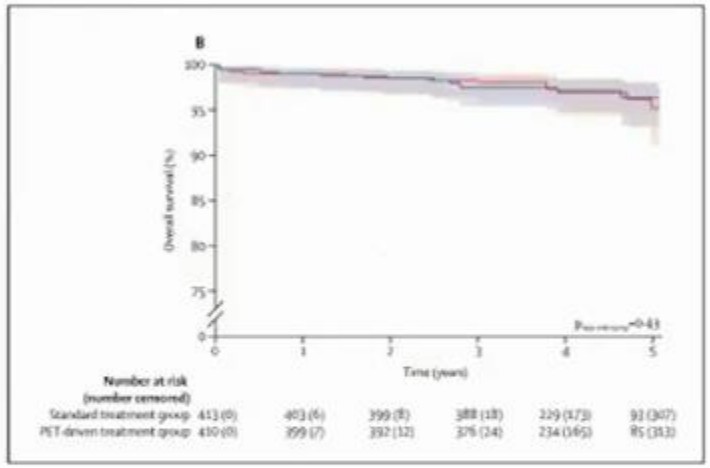
Johnson ICML 2021

PET adapted approaches for advanced stage disease
OS after therapy de-escalation in interim PET negative patients

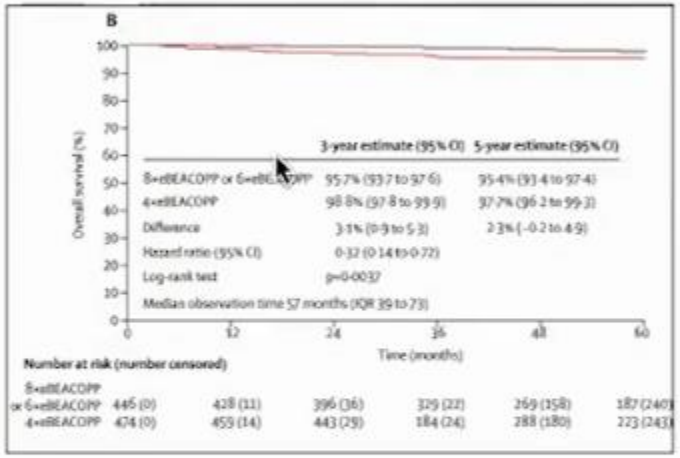
RATHL 5 Year OS 95.1%



LYSA 5 yr OS 96.4% vs 95.2%



HD18 5 Year OS 95.4 vs 97.7%



N Engl J Med, 2016. 374:2419-29
Lancet Oncol 2019. 20:202-215
Lancet 2017; 6736(17)32134-7

Johnson ICML 2021

IGITL/FIL HD 0607 Trial: PET negative pts (interim and EOT)
No role for RT even in bulky disease

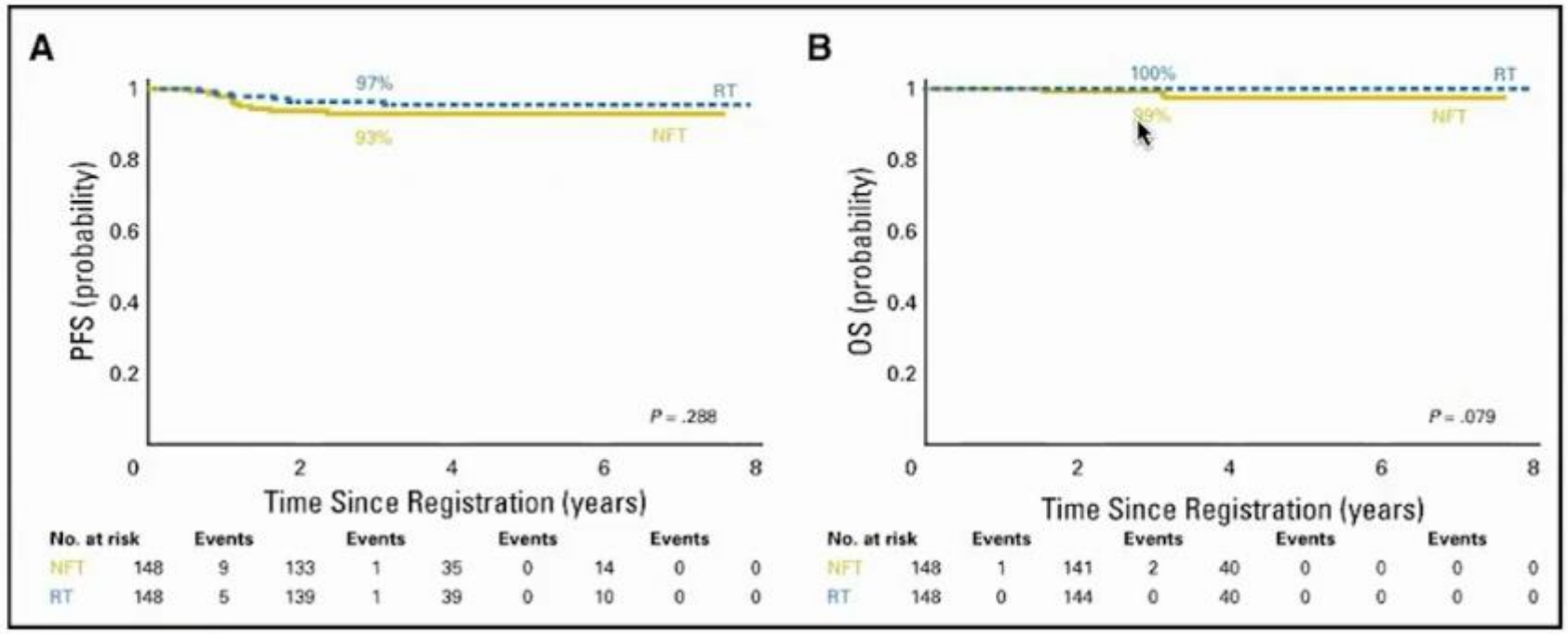
Stage IIB-IV

2 ABVD

PET - complete 6 ABVD (+/- IFRT if >5cm mass)

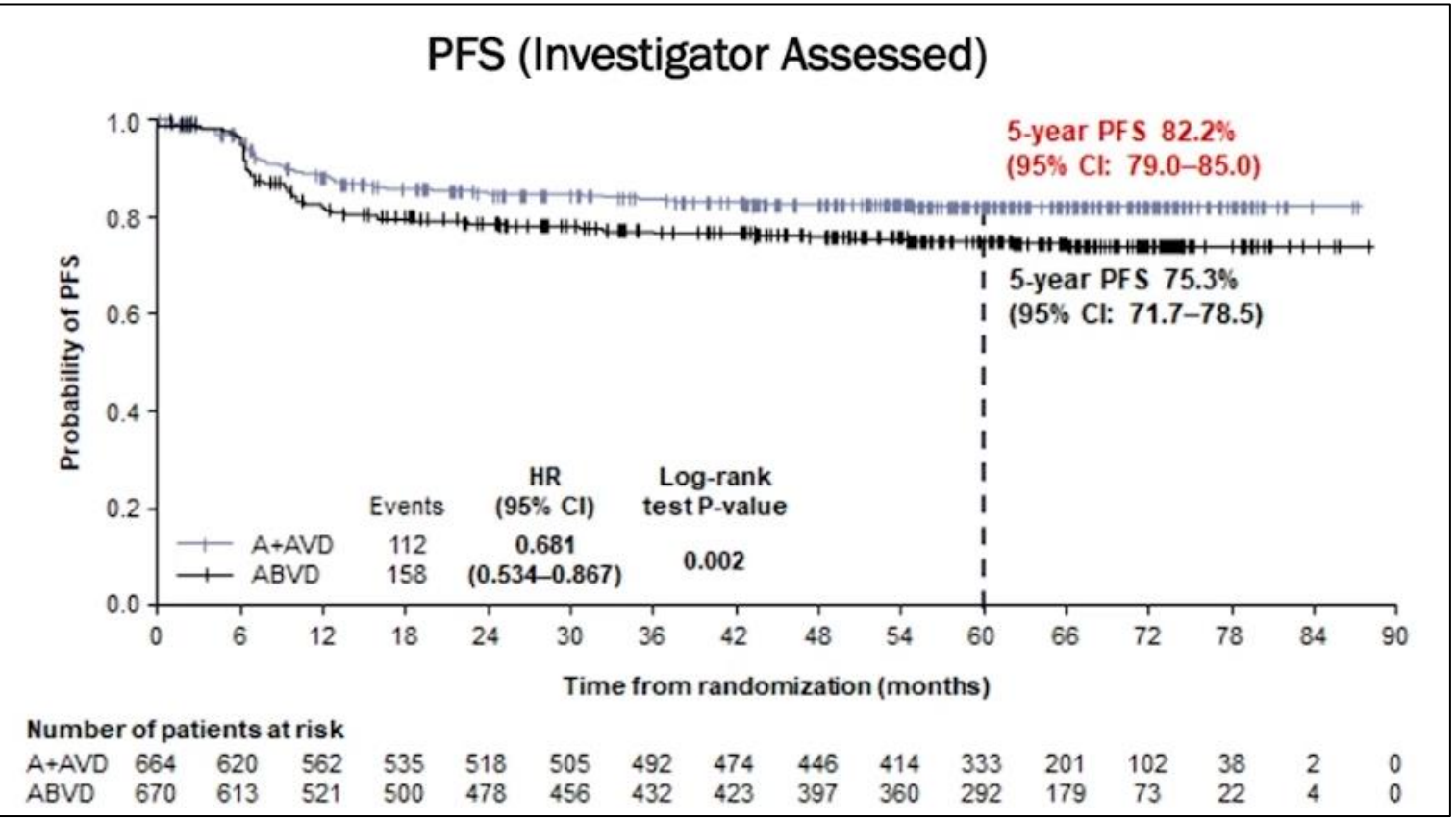
IFRT -/+

PFS **OS**



Gallamini et al J Clin Oncol 2020

ECHELON-1: 5year Update
BV-AVD vs ABVD in Stage II/IV CHL



PET-2 negative pts

- **5y PFS**: BV-AVD 84.9% vs ABVD 78.9% (p=0.0035)

PET-2 positive pts

- **5y PFS**: BV-AVD 60.6% vs ABVD 45.9% (p=0.23)

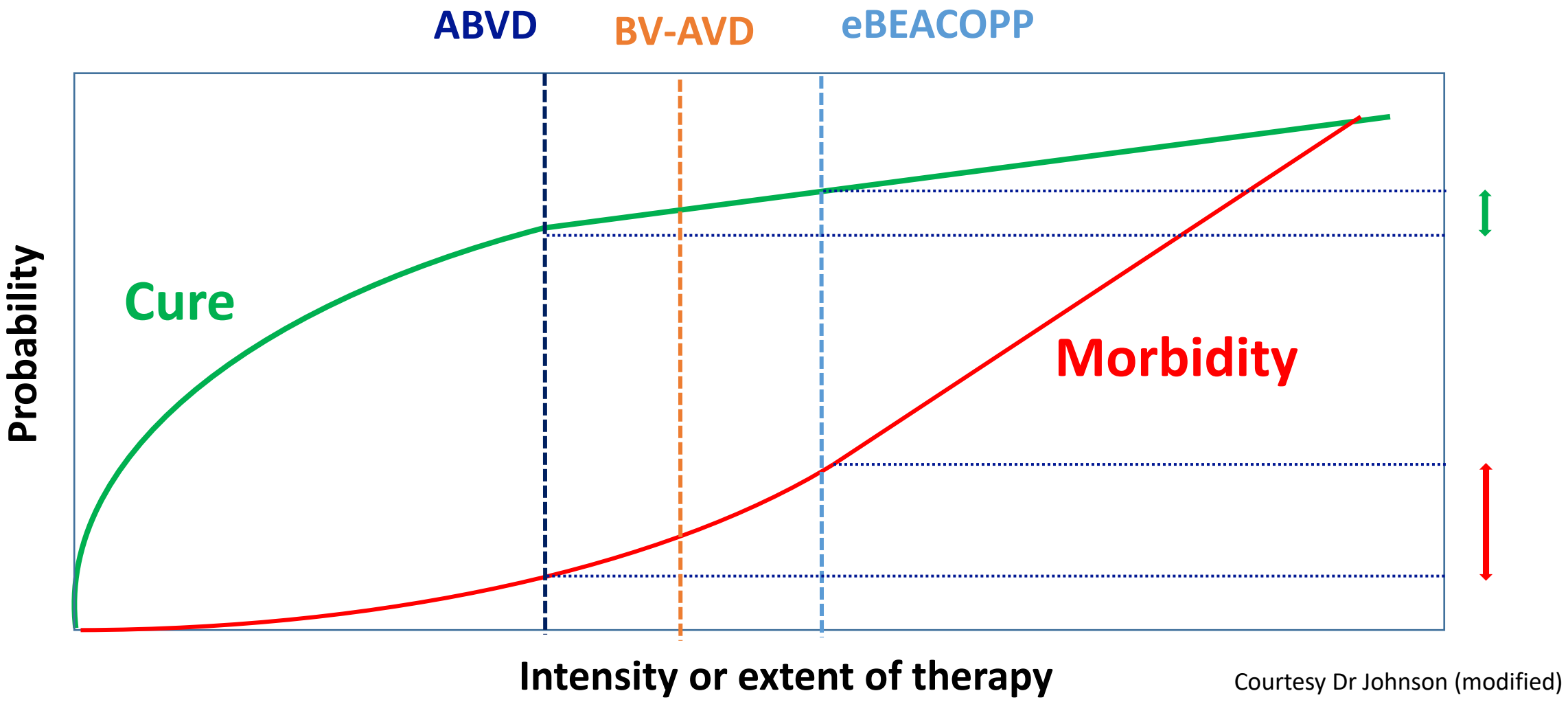
- **Ongoing neuropathy: BV-AVD 19% vs ABVD 9%**
- **Fertility similar both arms**

Strauss et al Lancet Hemat 2021

Summary of Current Strategies In Advance HL

- Interim PET is predictive
  - NPV higher with more intense/effective therapy, less extensive, lower risk disease
- De-escalation of therapy does not impact OS
- Escalation of therapy if interim PET positive after ABVD x 2 promising
- Bleomycin can be omitted after ABVD x 2 if PET negative (DS 1-3)
- Using BV instead of Bleomycin (BV-AVD): 6.9% improvement in PFS@5y, but no OS difference
  - No increase in infertility or secondary malignancy
- In interim PET neg pts 4 esc BEACOPP=6 esc BEACOPP
- Choice of therapy is a balance of efficacy versus toxicity

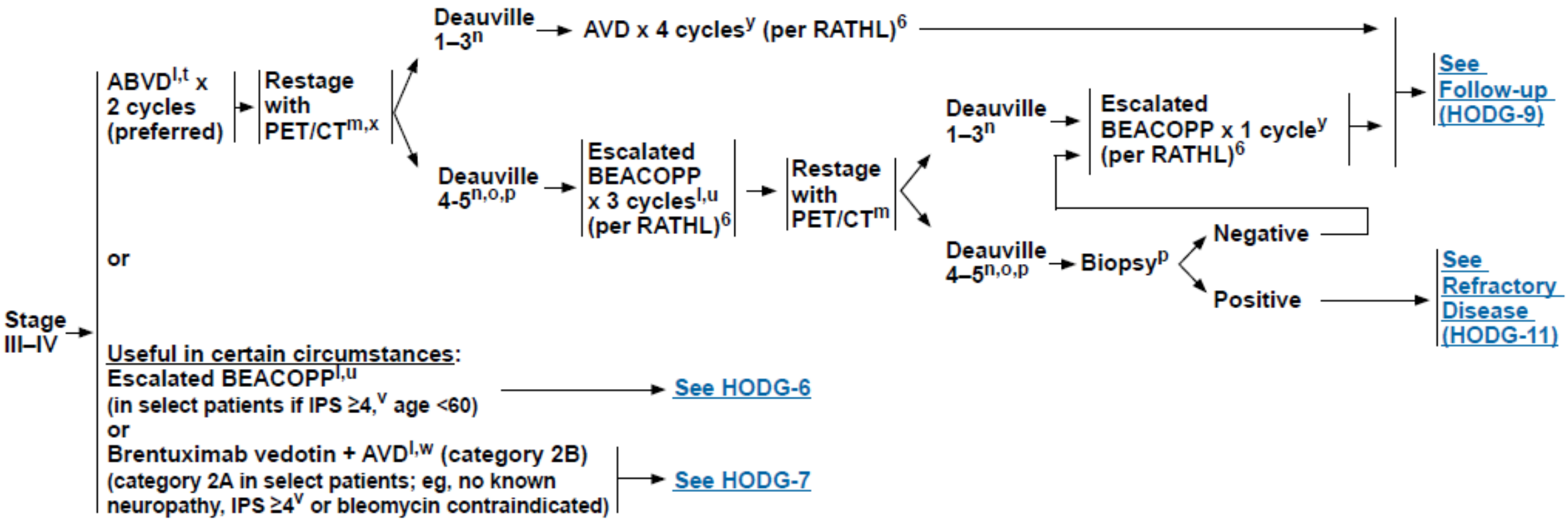
The Dilemma Of Therapy



Courtesy Dr Johnson (modified)

CLINICAL PRESENTATION:
Stage III–IV CHL[h,k]

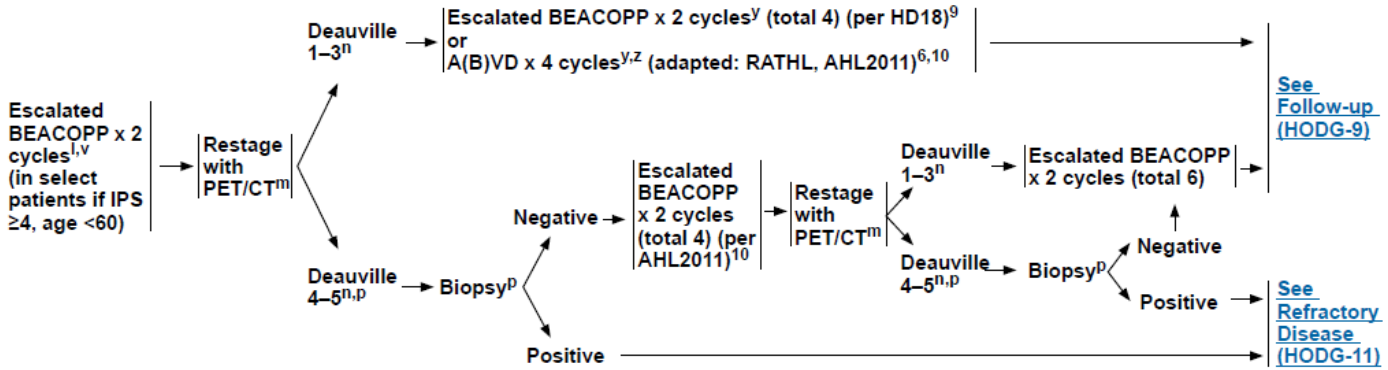
PRIMARY TREATMENT[k]



NCCN Guidelines Version 4.2021
Hodgkin Lymphoma (Age ≥18 years)

CLINICAL PRESENTATION:
Stage III–IV CHL[h]

PRIMARY TREATMENT[k]
(continued from HODG-5)



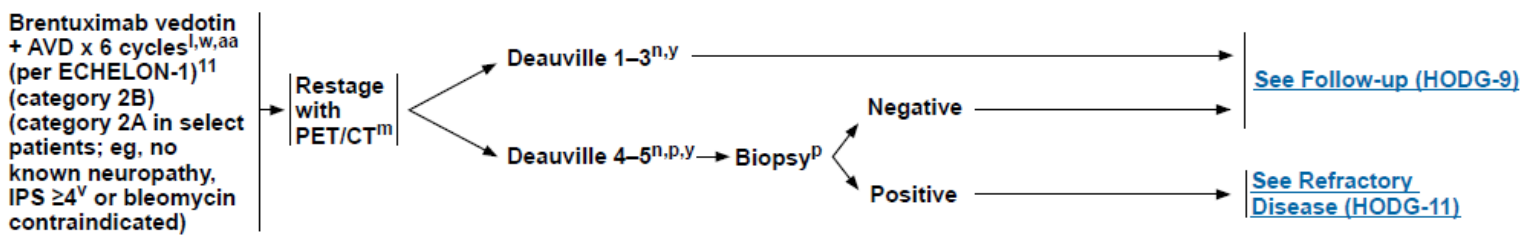
National Comprehensive Cancer Network®

NCCN Guidelines Index
Table of Contents
Discussion

NCCN Guidelines Version 4.2021
Hodgkin Lymphoma (Age ≥18 years)

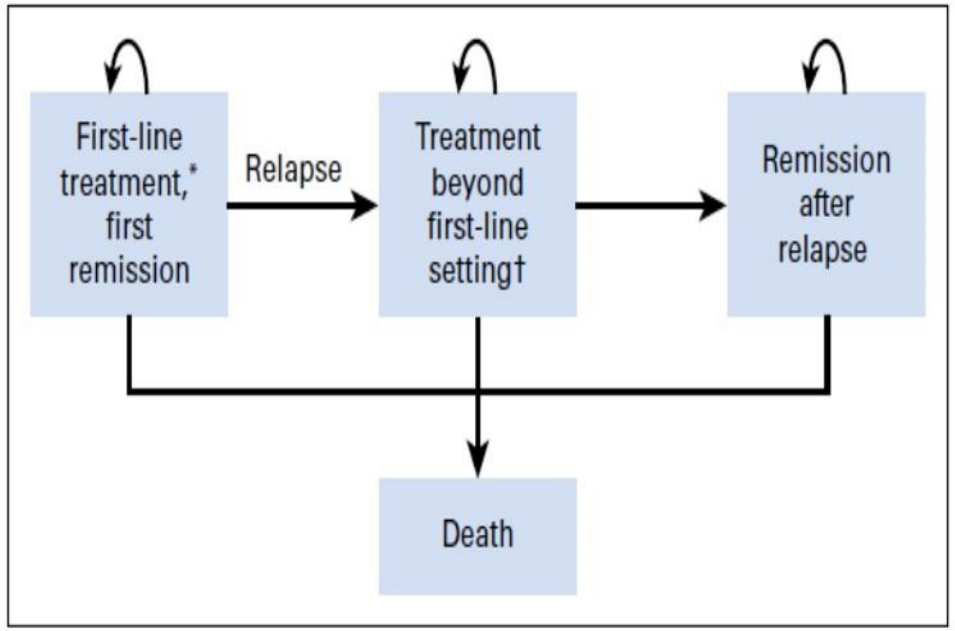
CLINICAL PRESENTATION:
Stage III–IV CHL[h]

PRIMARY TREATMENT[k]
(continued from HODG-5)



Cost-Effectiveness Analysis of BV With Chemotherapy in Newly Diagnosed Stage III and IV Hodgkin Lymphoma

Markov Model

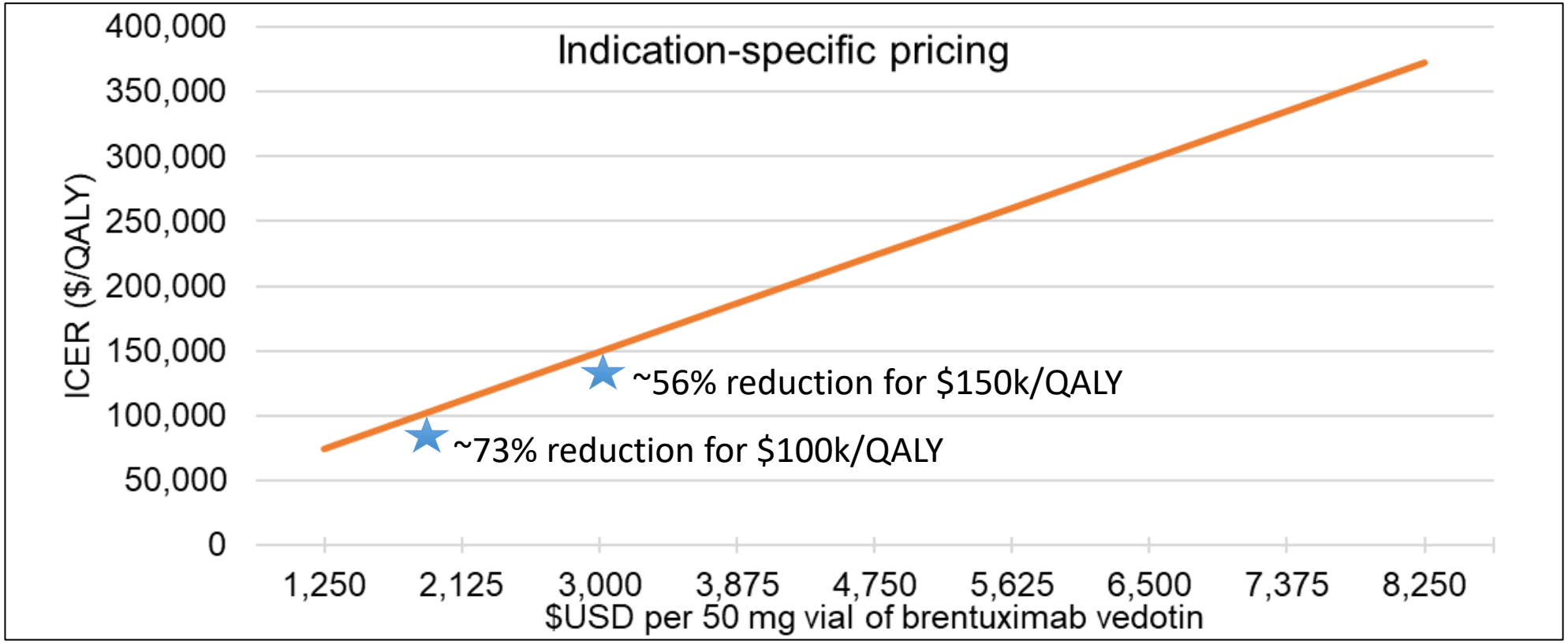


	Average Wholesale Prices accessed on LexiComp	
	ABVD	**AAVD (with pegfilgrastim prophylaxis)**
4-week cycle	**$608**	**$47436**
6-month treatment course	**$3648**	**$284616**

Huntington et al JCO 2018

When might BV + AVD be cost-effective?

Lowering the price of brentuximab in the first-line

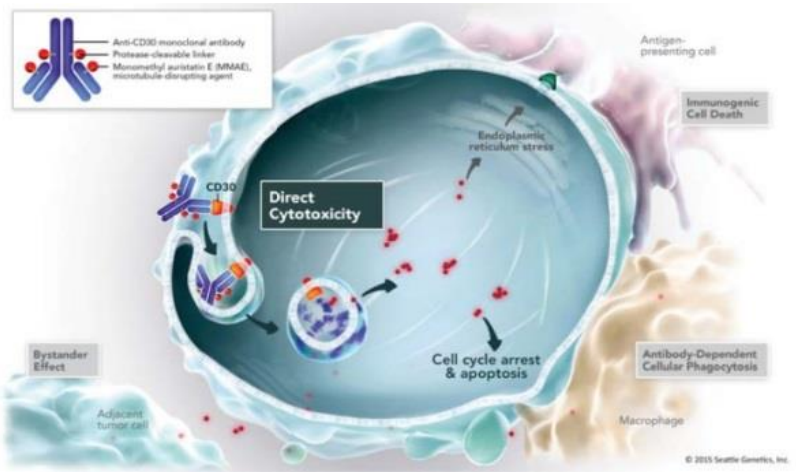


Acquisition costs for BV in the first-line setting would need to be reduced by 56% to 73% for ICERs of $150,000 to $100,000 per QALY, respectively

Huntington et al JCO 2018

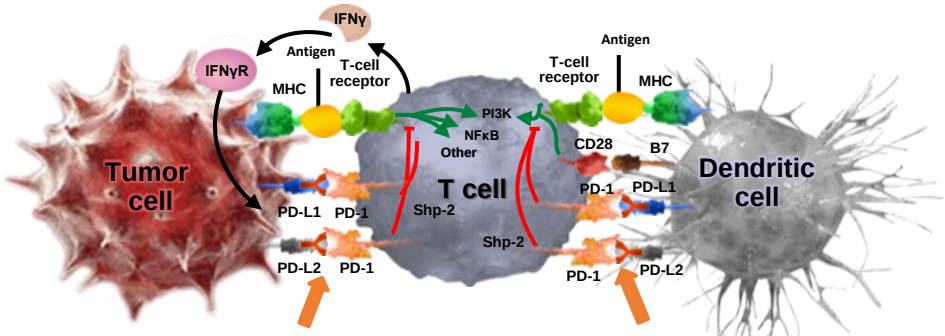
Harnessing the Immune System in management of CHL

Approved novel agents



- Hodgkin Reed Sternberg (HRS) cells express CD 30
- Brentuximab Vedotin (BV) is an anti CD30 antibody drug conjugate (MMAE) which disrupts the microtubule network and triggers an immune response through the induction of endoplasmic reticulum stress
- Approved for R/R disease, advanced stage front line with AVD and maintenance post transplant

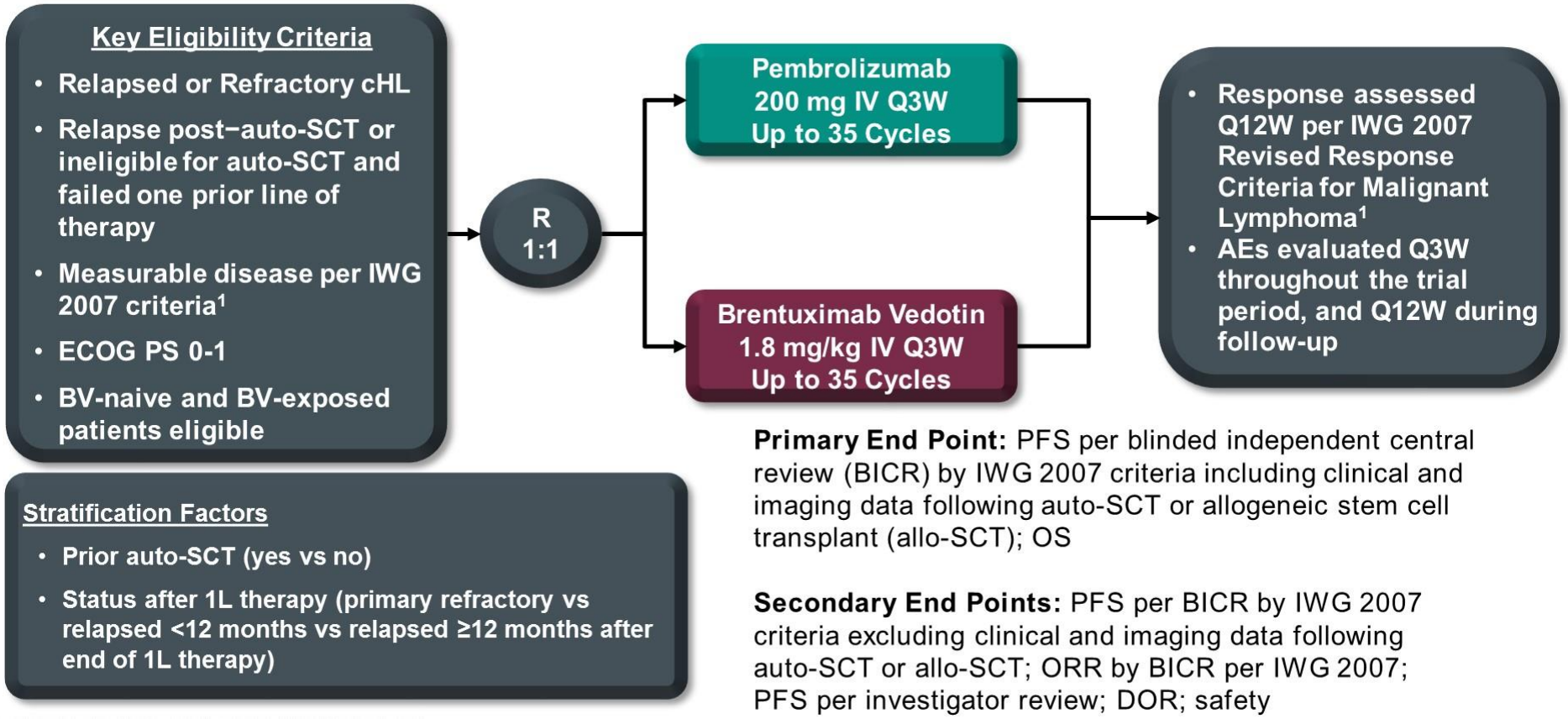
- HRS harbors genetic alterations of 9p24.1 containing PD ligands and express PD-L1
- Binding of PD-1 to its ligands inhibits T-cell activation, allowing tumors to evade the immune response
- Nivolumab/Pembrolizumab target the PD-1 immune checkpoint pathway and restores antitumor immune responses
- Approved for R/R disease



Nivolumab/Pembrolizumab blocks the PD-1 receptor

Comparison of BV vs Pembro in pts ineligible or have relapsed after ASCT

KEYNOTE-204 Study Design (NCT02684292)



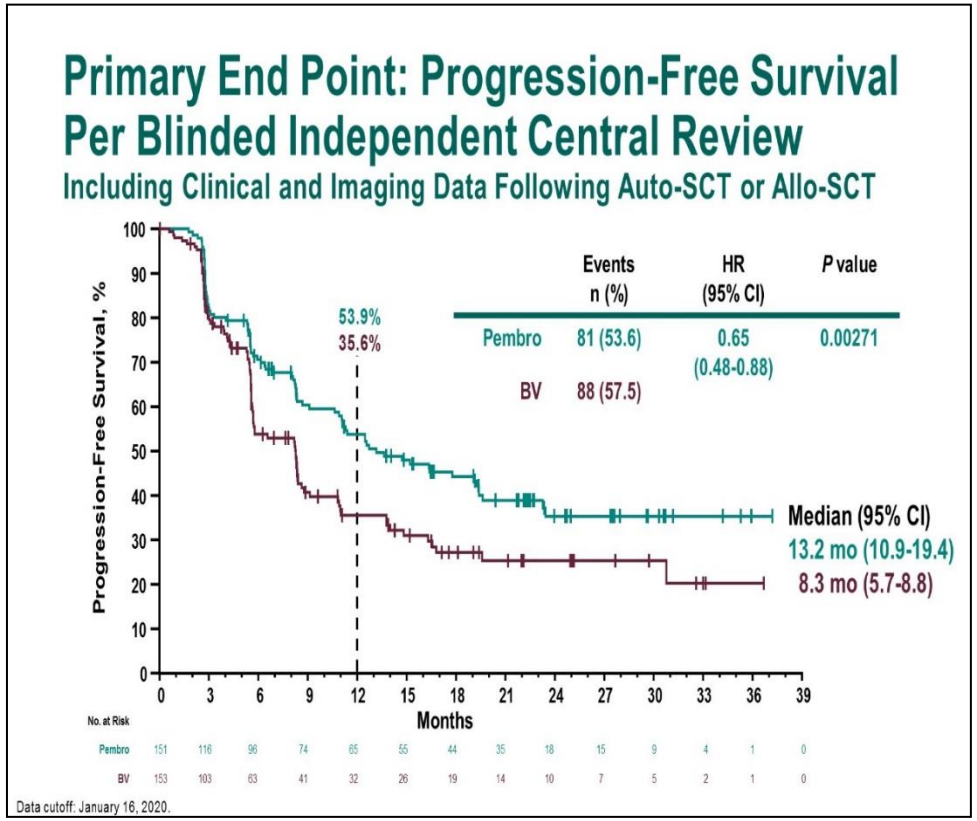
Primary End Point: PFS per blinded independent central review (BICR) by IWG 2007 criteria including clinical and imaging data following auto-SCT or allogeneic stem cell transplant (allo-SCT); OS

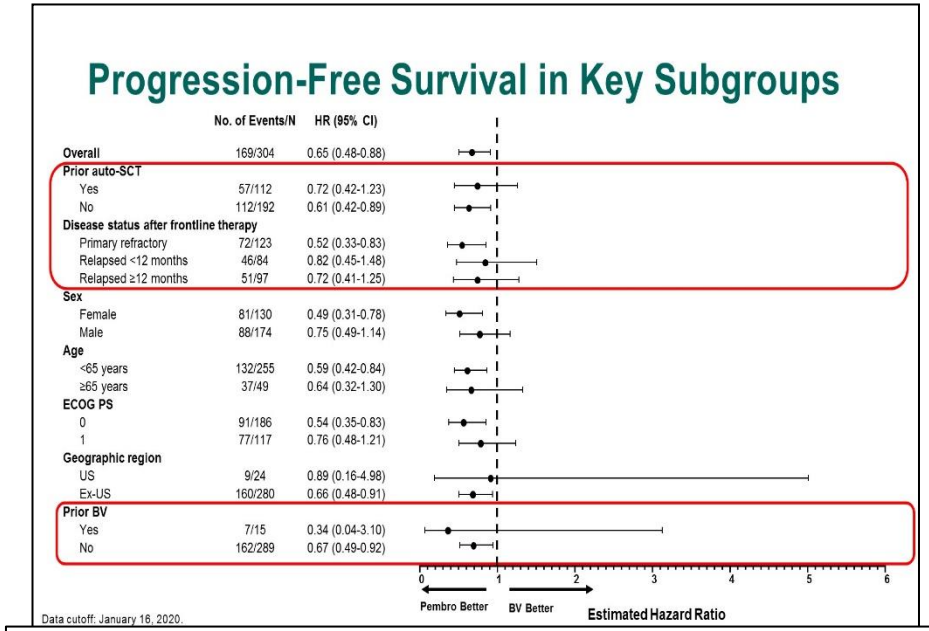
Secondary End Points: PFS per BICR by IWG 2007 criteria excluding clinical and imaging data following auto-SCT or allo-SCT; ORR by BICR per IWG 2007; PFS per investigator review; DOR; safety

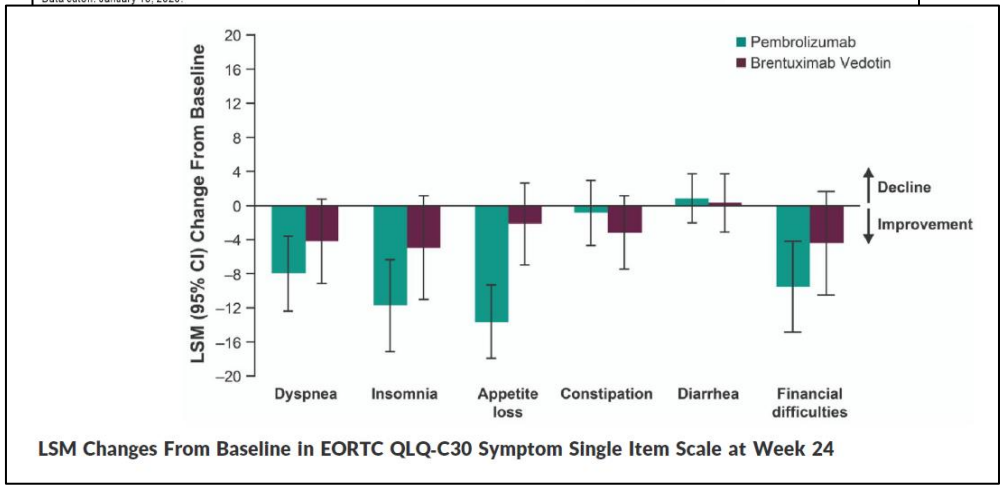
Kuruvilla et Lancet Oncol 2021

Keynote-204: Results

ORR: 65.6 % (P) vs 54.2% (BV) P=0.02, CR 24% in both







Kuruvilla et al Lancet Oncol 2021

Zinzni et al ICML 2021 # 193

Harnessing the Immune System in management of CHL
Incorporating novel agents into treatment

Front-line

- Early stage
  - Ongoing studies to define its potential to reduce chemo/RT
- Advanced stage
  - Improving upon ABVD, BV-AVD

Second-line

- Combination of novel agents
- Novel agents plus chemotherapy

Post-ASCT (in remission)

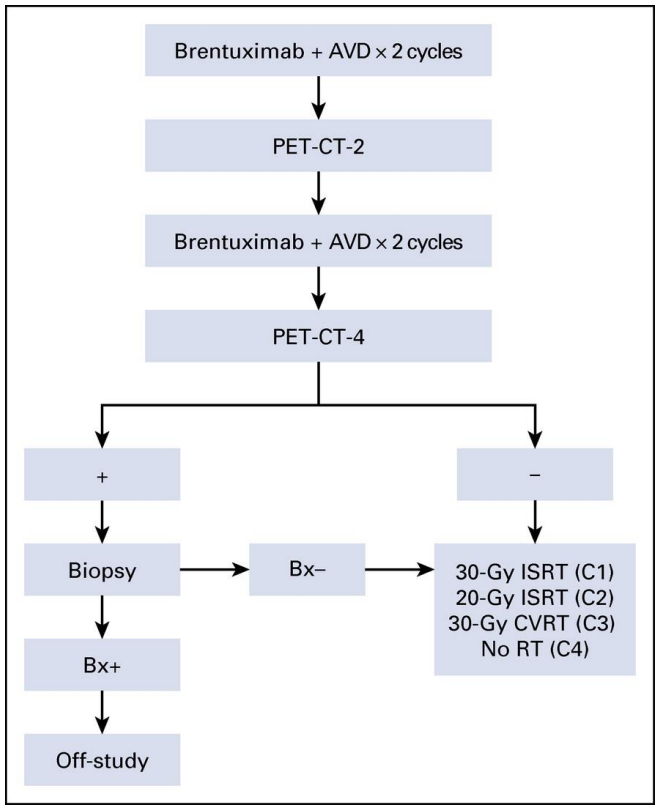
- Maintenance for high risk pts

Post-ASCT (relapse or refractory)

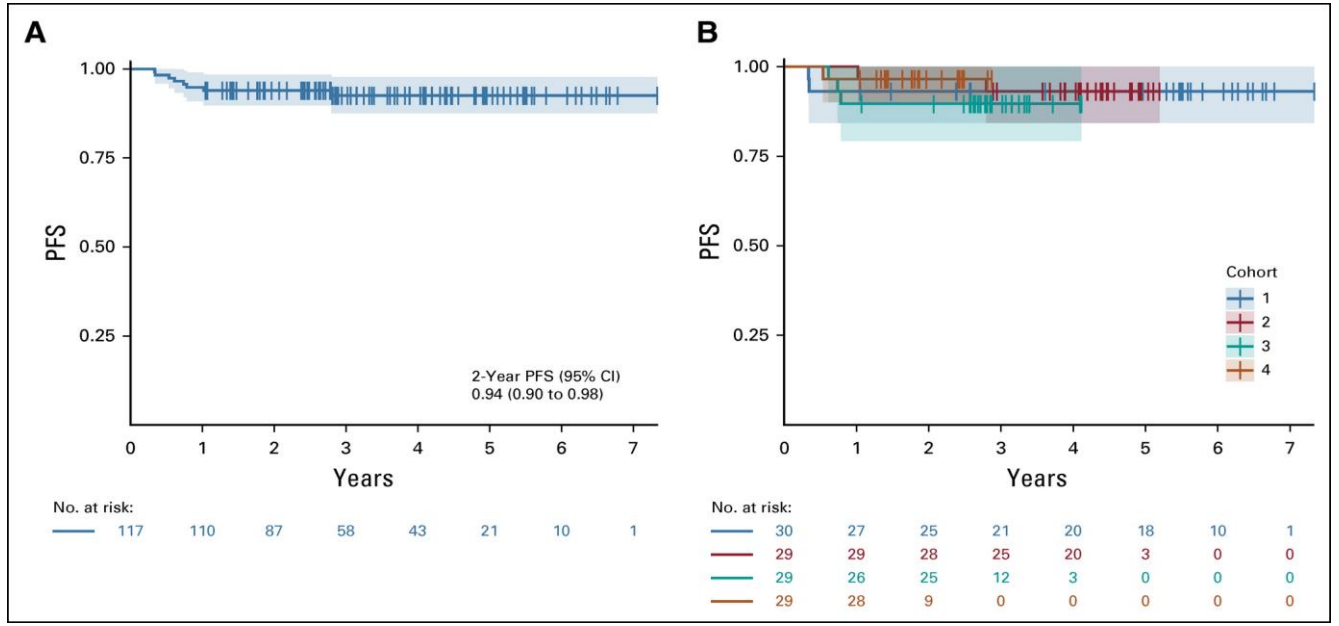
- Emerging therapies

ESHL-U: Can RT be avoided if BV-AVD used?

Bulk disease defined by MSKCC criteria (7 cm in maximal transverse or coronal diameter on CT)
Not required for cohorts 1 and 2 but was required for cohorts 3 and 4.



Kumar et al J Clin Oncol 2021

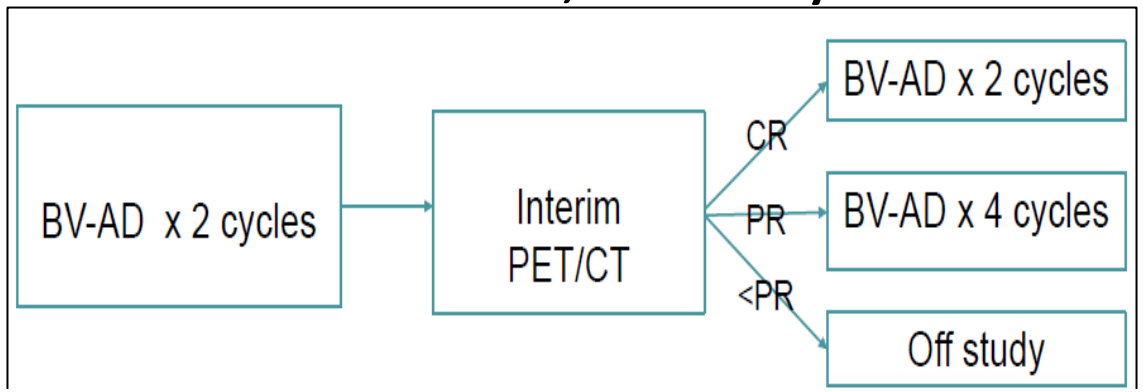


	% CR	% 2y PFS	Median f/u (yrs)
Cohort 1	93	93	5.9
Cohort 2	100	97	4.5
Cohort 3	93	90	2.5
Cohort 4	97	97	2.2

ESHL: Can RT be avoided if BV-AD used [ICML 2021-Abramson, #198]

No GCSF

No Vinblastine, No Bleomycin



Adverse Events of Special Interest

- **Peripheral sensory neuropathy**
  - 19 (56%) patients had any PSN, and was grade 1 in 17 (50%), and grade 2 in 2 (6%) patients. There was no grade 3-4 toxicity.
  - Thirteen have resolved completely at a median of 1.8 months, though follow up remains brief.
- **Neutropenia**
  - 8 (24%) patients had any neutropenia, but only 2 (6%) had grade 3 neutropenia and there was no grade 4 neutropenia.
  - There were no cases of neutropenic fever.
  - No patients received growth factor support.

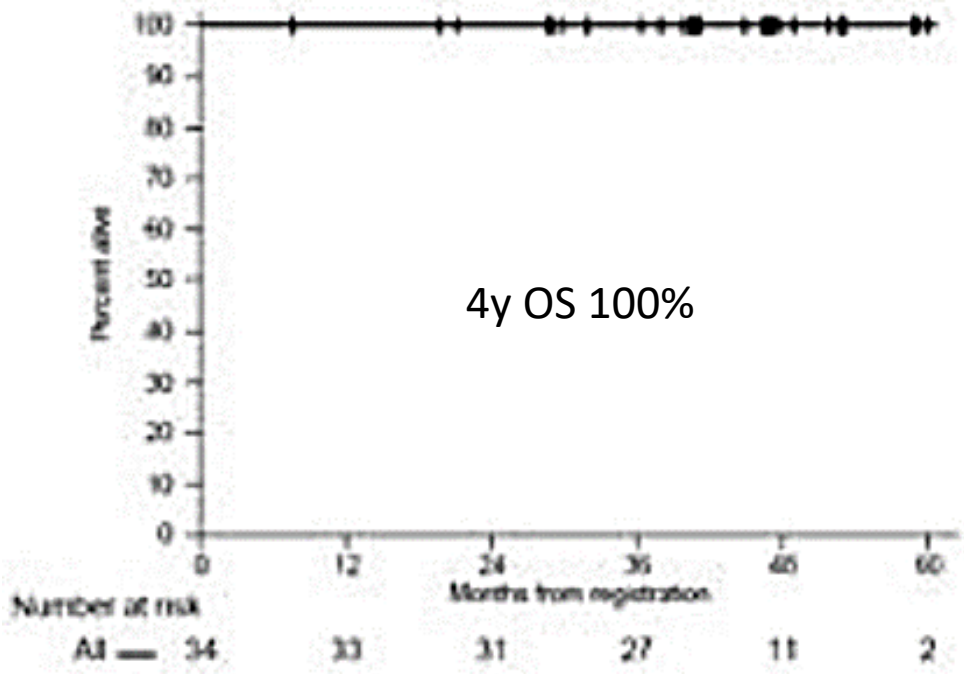
Patient Characteristics

	N=34
Age (range)	36 (range 18-63)
Sex, Female	23 (68%)
Stage	
IA	3 (9%)
IB	1 (3%)
IIA	29 (85%)
IIB	1 (3%)
GHSG Risk Group	
Early favorable	18 (53%)
Early unfavorable	16 (47%)
ECOG PS	
0	30 (88%)
1	4 (12%)
Histology	
Nodular sclerosis	17 (50%)
Mixed cellularity	1 (3%)
Lymphocyte rich	3 (9%)
Classical HL, NOS	13 (38%)
Total treatment cycles	
4	32 (94%)
6	2 (6%)

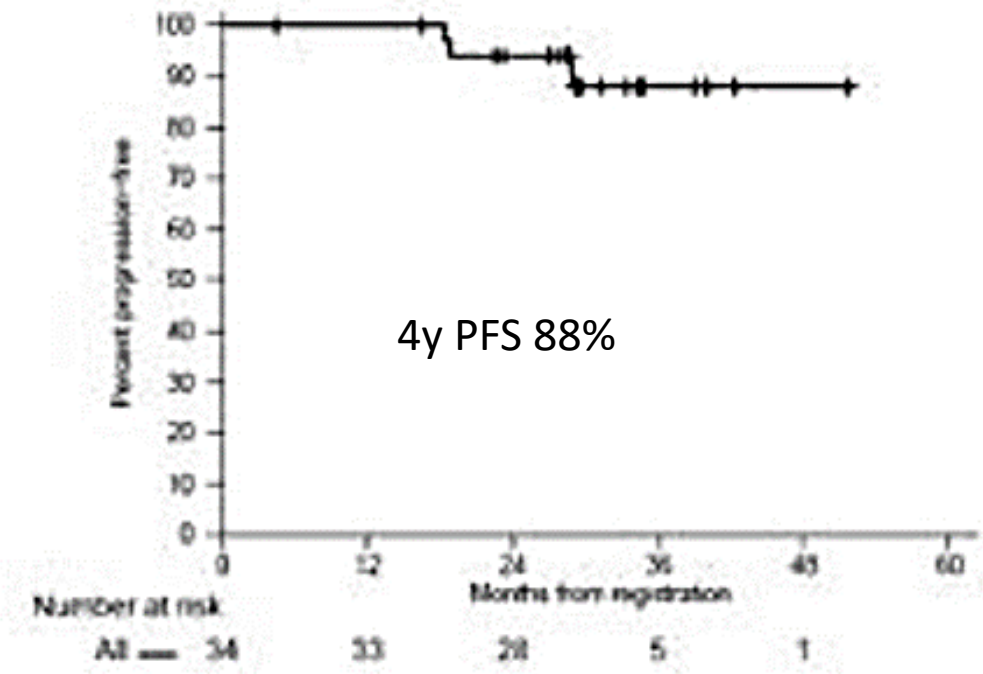
Results

	Interim (post cycle 2)	End of treatment
Overall Response	**100%** 90% CI [92-100]	**100%** 90% CI [92-100]
Complete Response	**94%** 90% CI [83,99]	**100%** 90% CI [92-100]
Partial Response	**6%** 90% CI [1,17]	**0%** 90% CI [0,8]

Median f/u 46 months



4y OS 100%

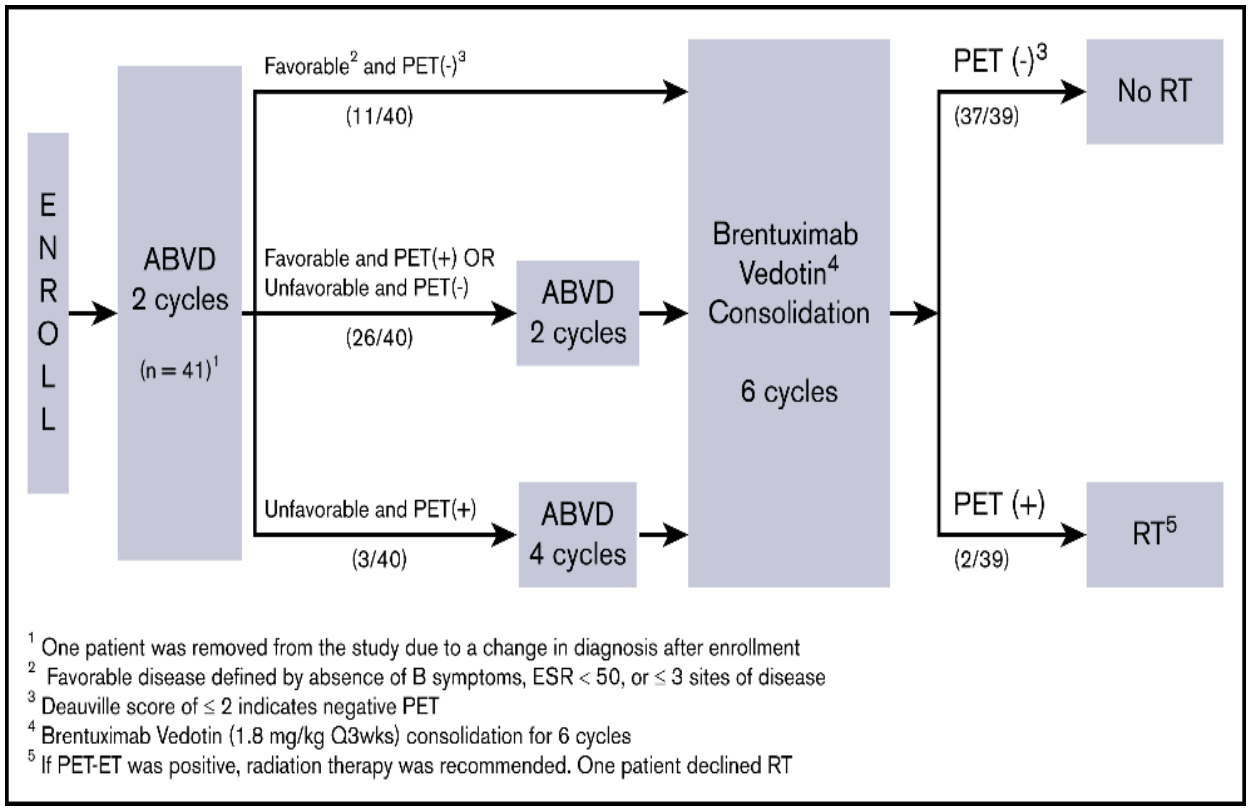


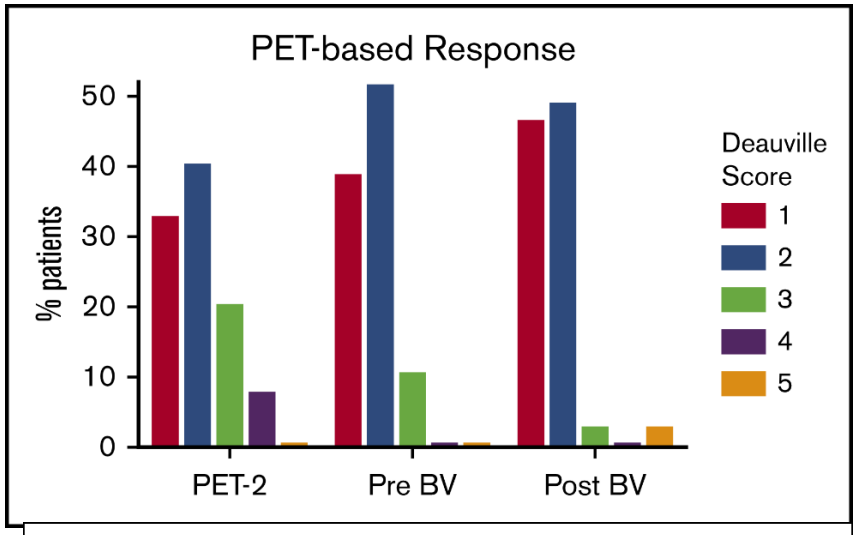
4y PFS 88%

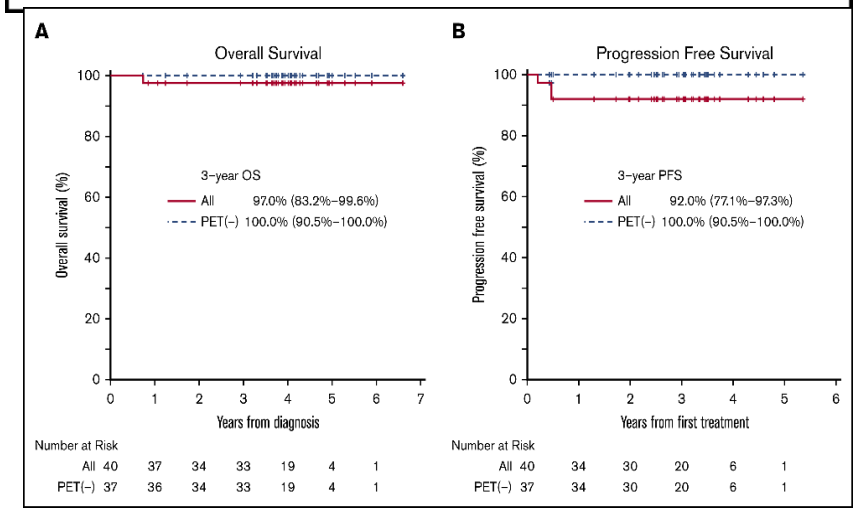
A phase II trial using this regimen plus nivolumab in limited stage HL is currently enrolling (ClinicalTrials.gov NCT03646123).

ESHL: Can RT be avoided
ABVD followed by BV consolidation (PET adapted)

median 29 years, 58% female, 45% unfavorable disease, 98% had stage II disease



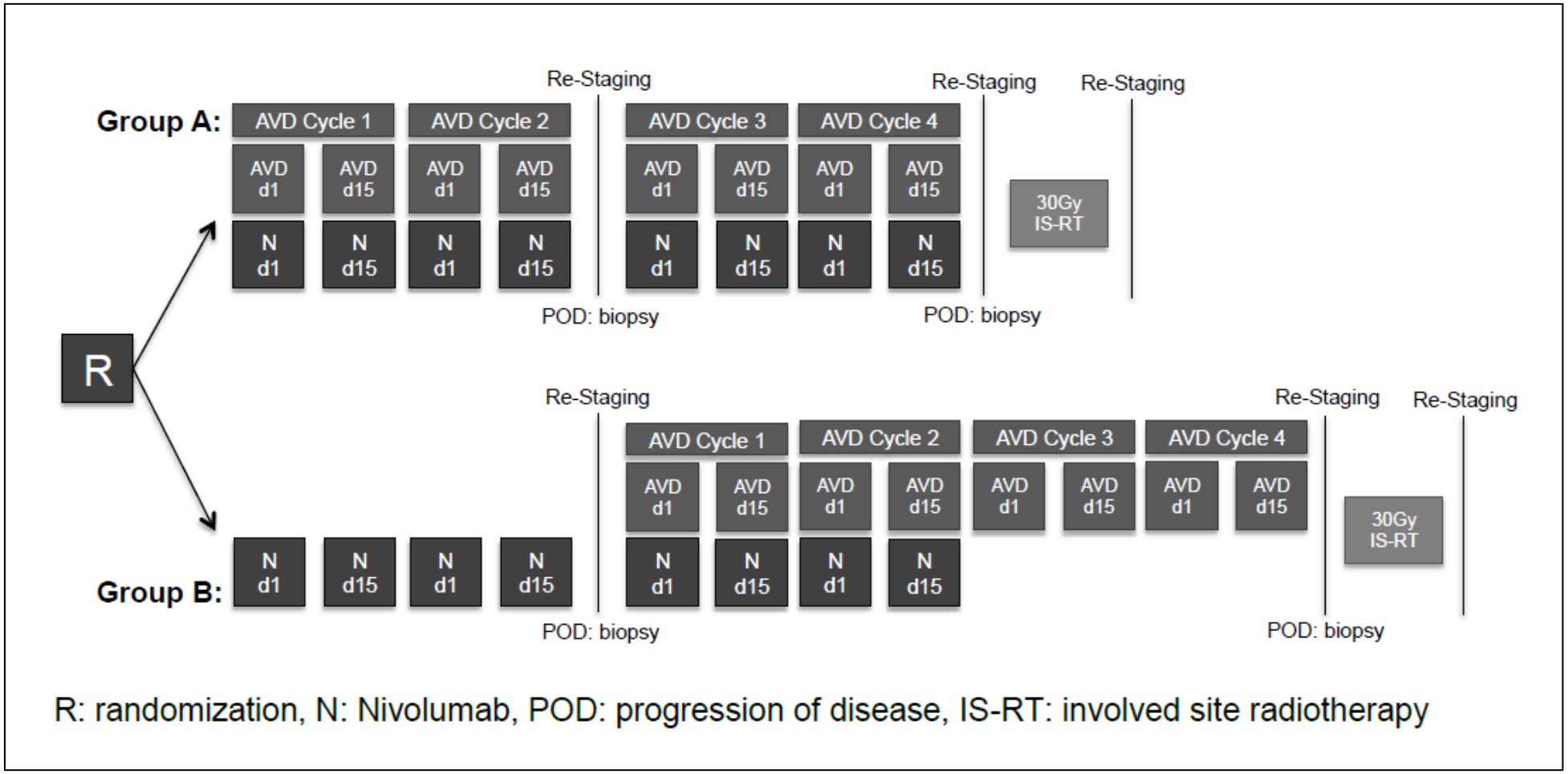




Median f/u 47 months

Park et al Blood Advances 2020

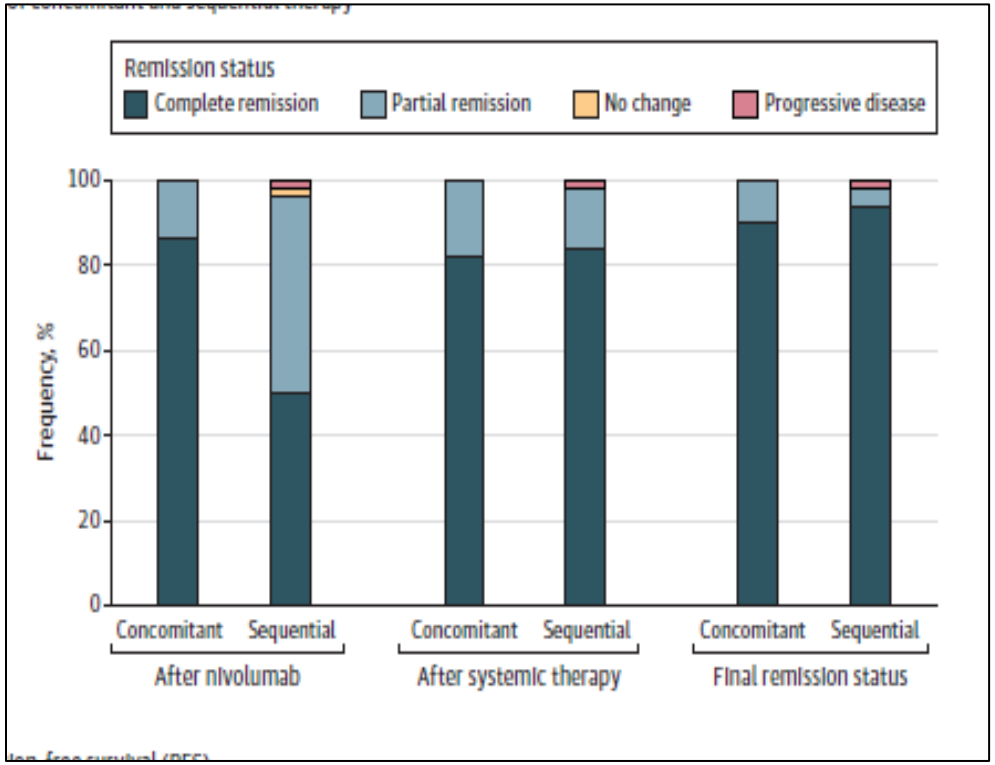
Efficacy of Nivolumab + AVD +ISRT in Early-Stage Unfavorable cHL
The Randomized Phase 2 GHSG NIVAHL Trial

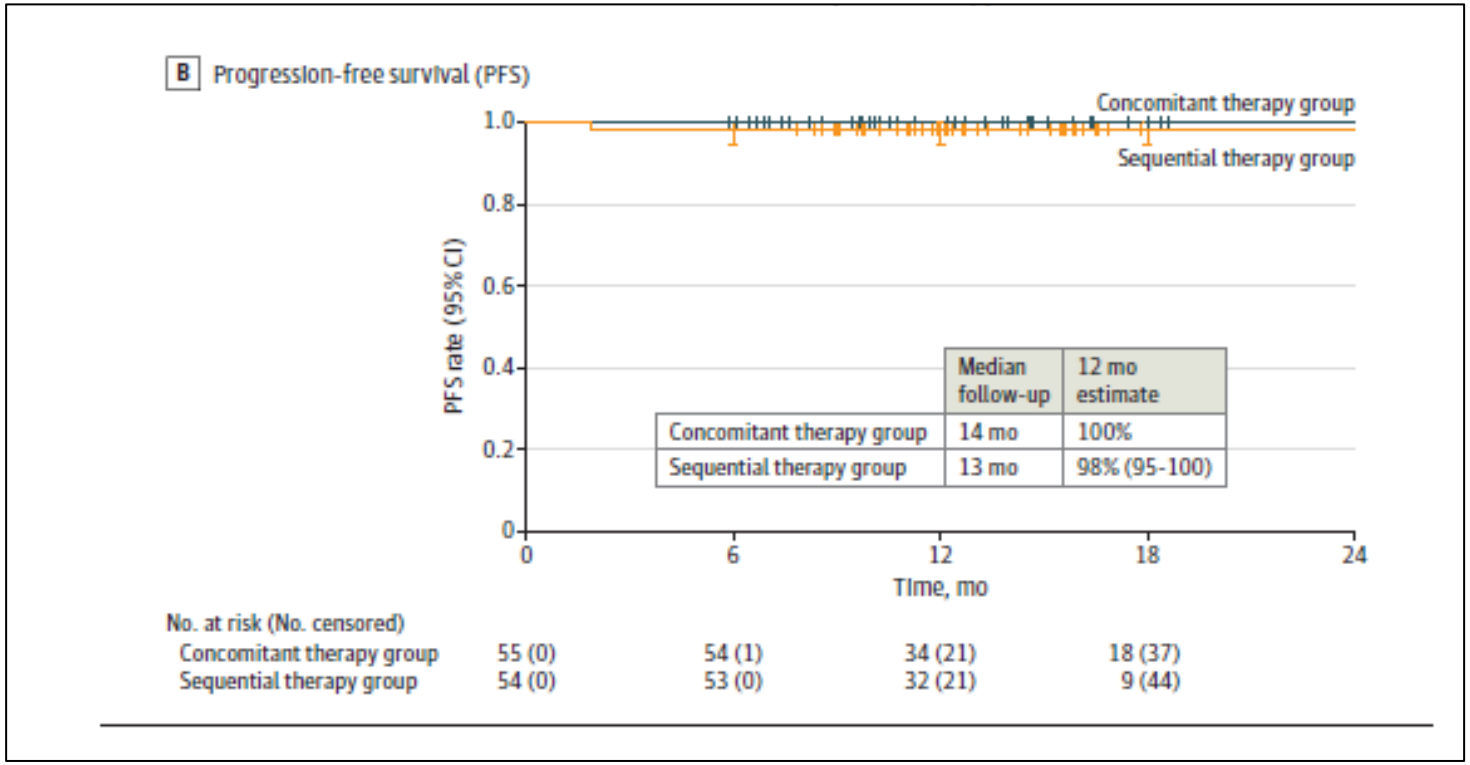


Brockelmann et al Jama Oncology 2020

Results
Randomized Phase 2 German Hodgkin Study Group NIVAHL Trial

Median follow-up 14 mo

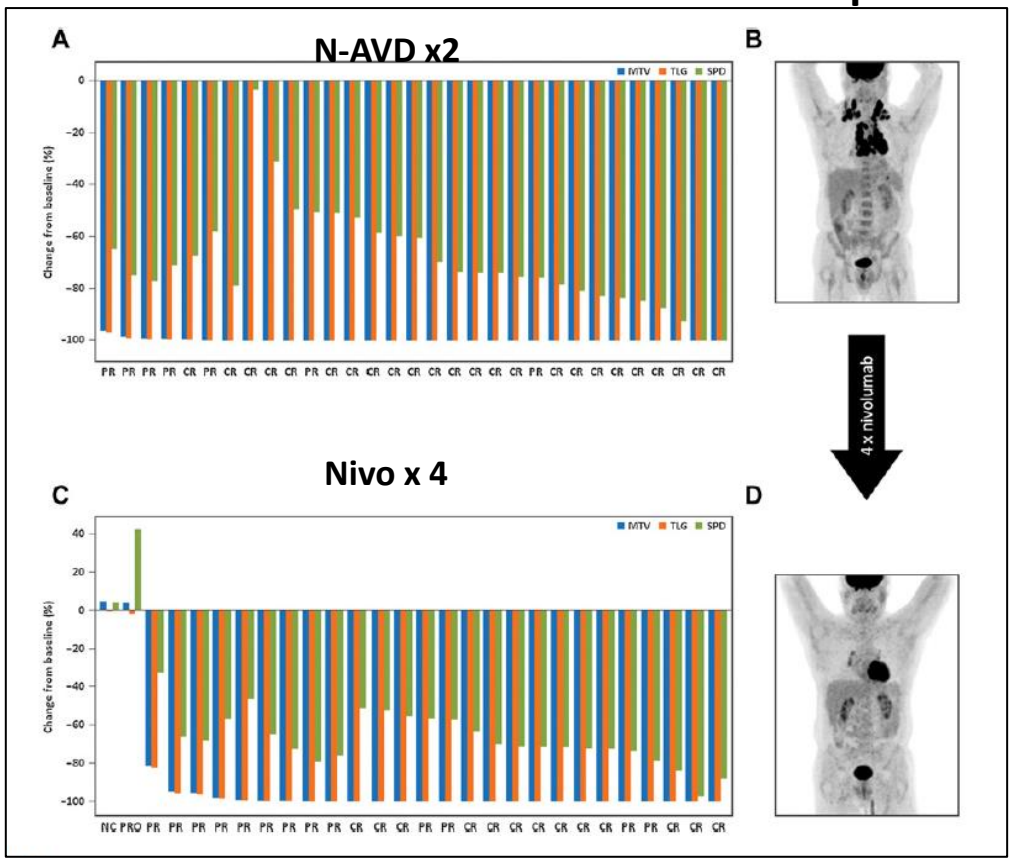




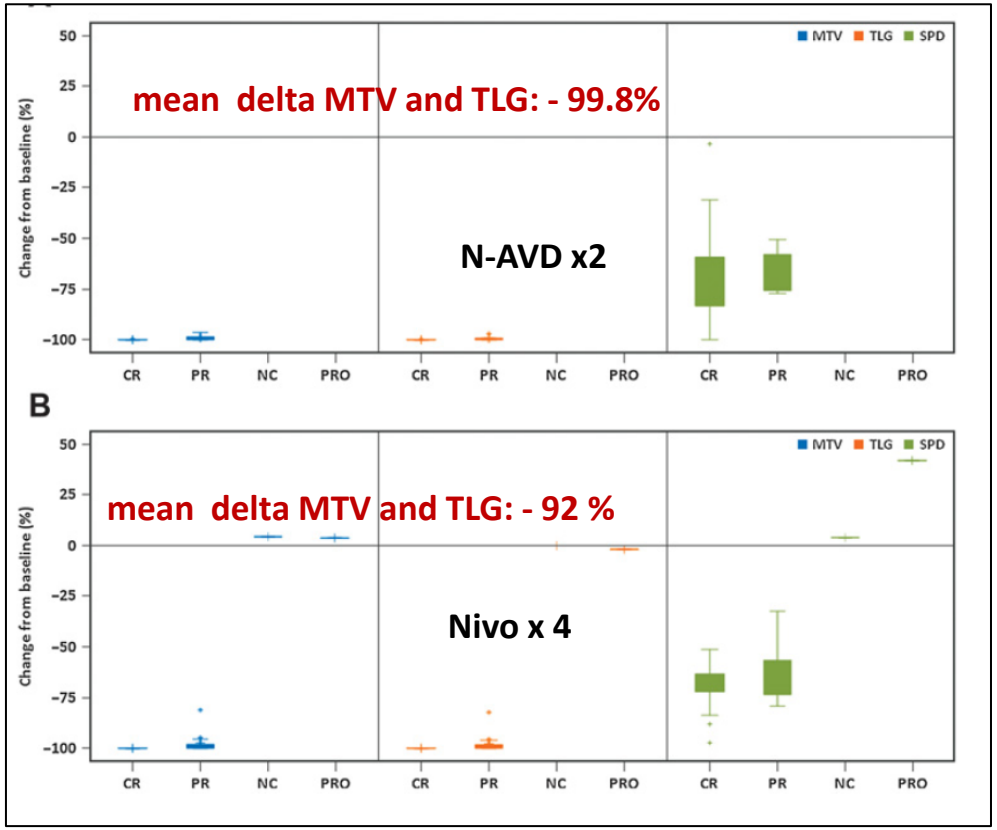
Brockelmann et al Jama Oncology 2020

Early Response to PD-1 Blockade in ESHL (U): NIVAHL Trial

Decrease in tumor burden at interim response



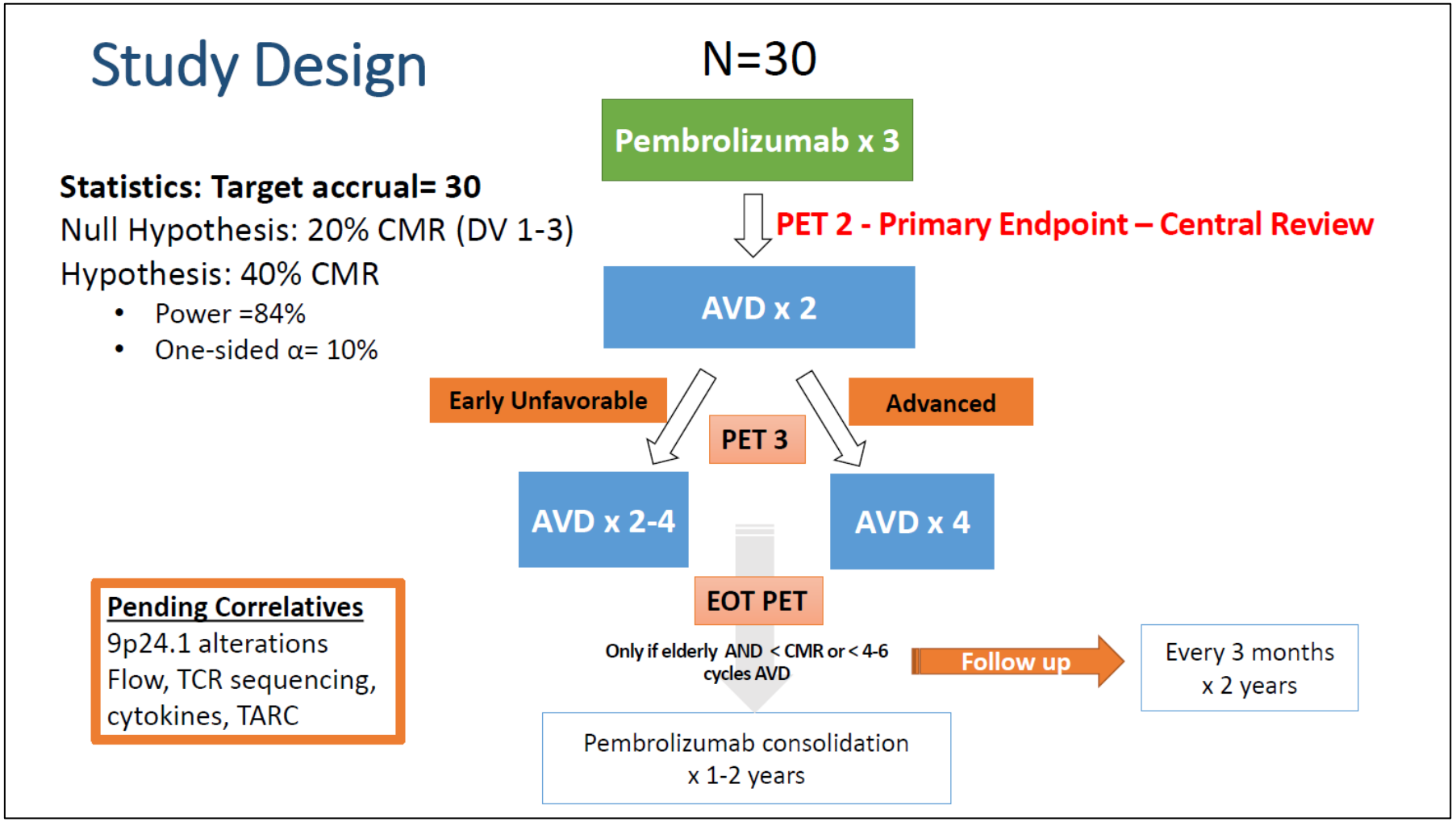
Wider spread of SPDs compared with MTV/ TLG



Tailored first-line treatment could benefit from more continuous parameters such as DMTV.
Achieving a PR by established criteria with substantial MTV reduction may be considered sufficient for de-escalation.

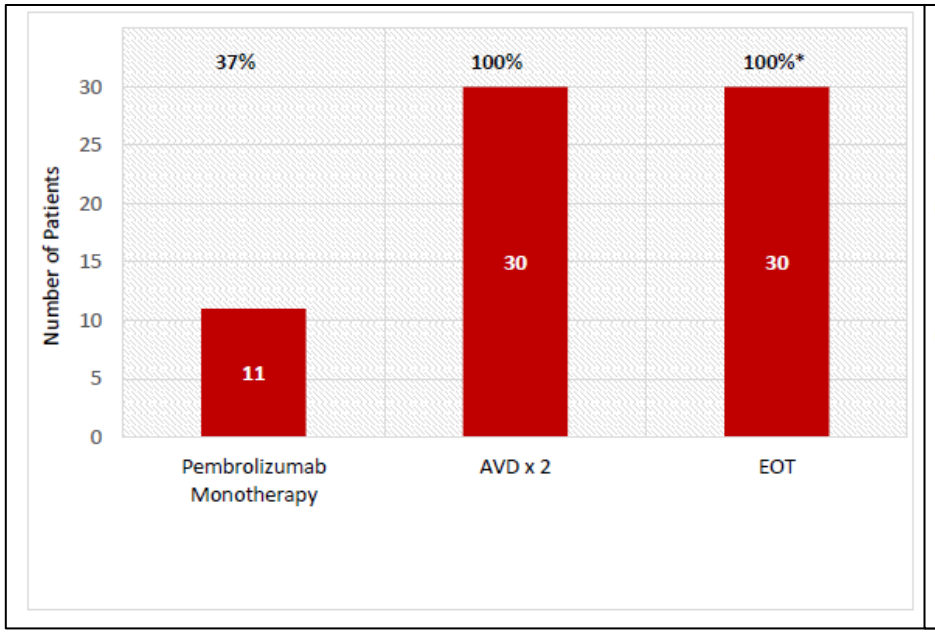
Voltin et al CCR 2020

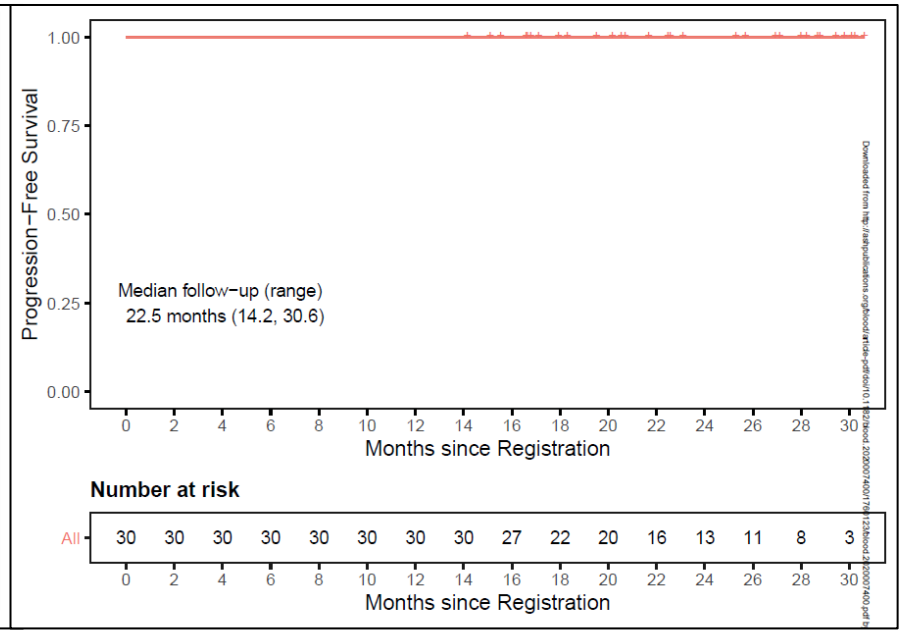
NU16H08: Phase II study of PET-directed frontline therapy with pembrolizumab and AVD for patients with cHL (No RT)

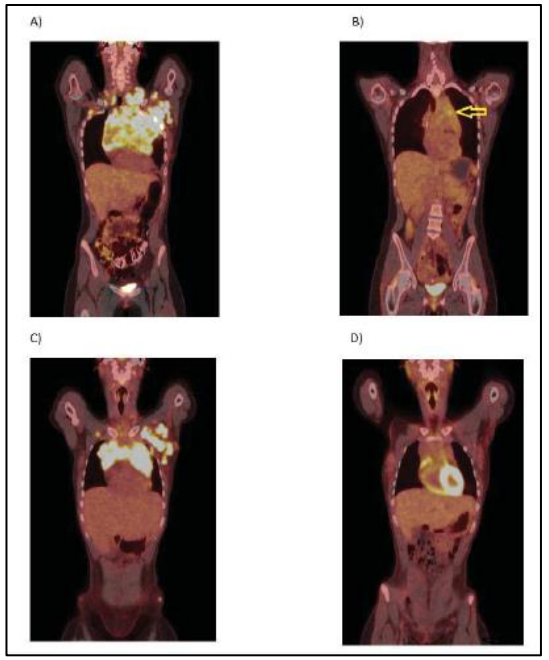


NU16H08: Phase II study of PET-directed frontline therapy with pembrolizumab and AVD for patients with cHL (No RT)

Median f/u: 22.5 months

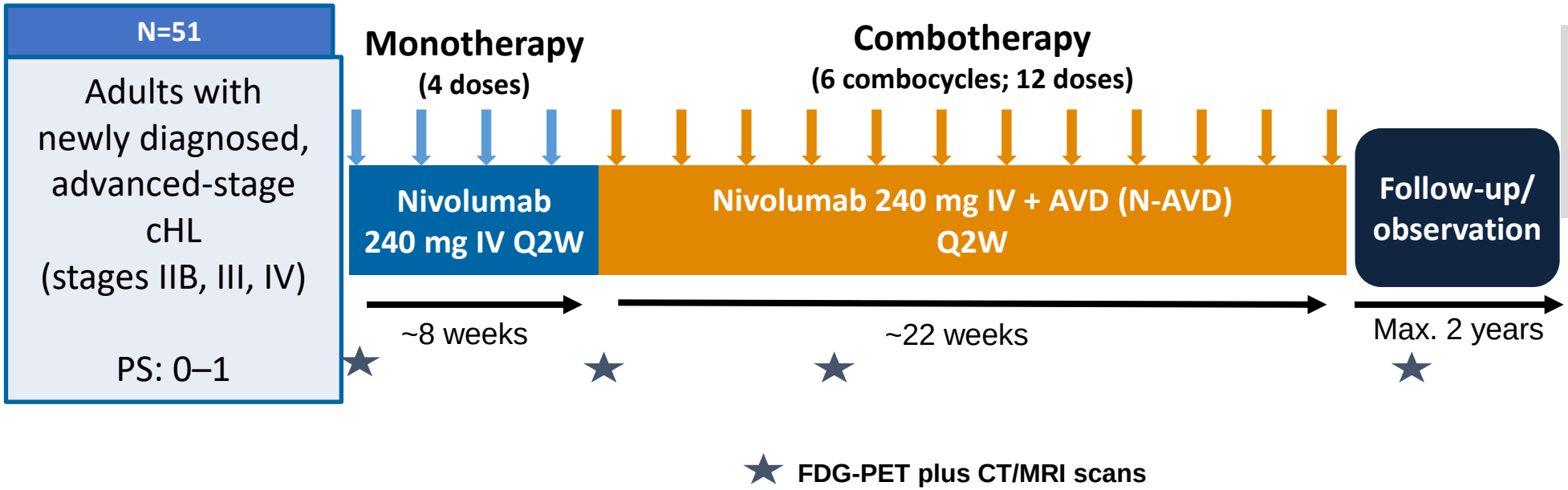






Allen et al Blood 2020

Advanced Stage cHL: Frontline therapy
Phase 2 CheckMate 205: Study Design



Primary endpoint

Safety and tolerability (G3–5 treatment-related AEs)

Additional endpoints

- Discontinuation rate
- CR and ORR by IRC
- CR and ORR by investigator
- mPFS
- OS

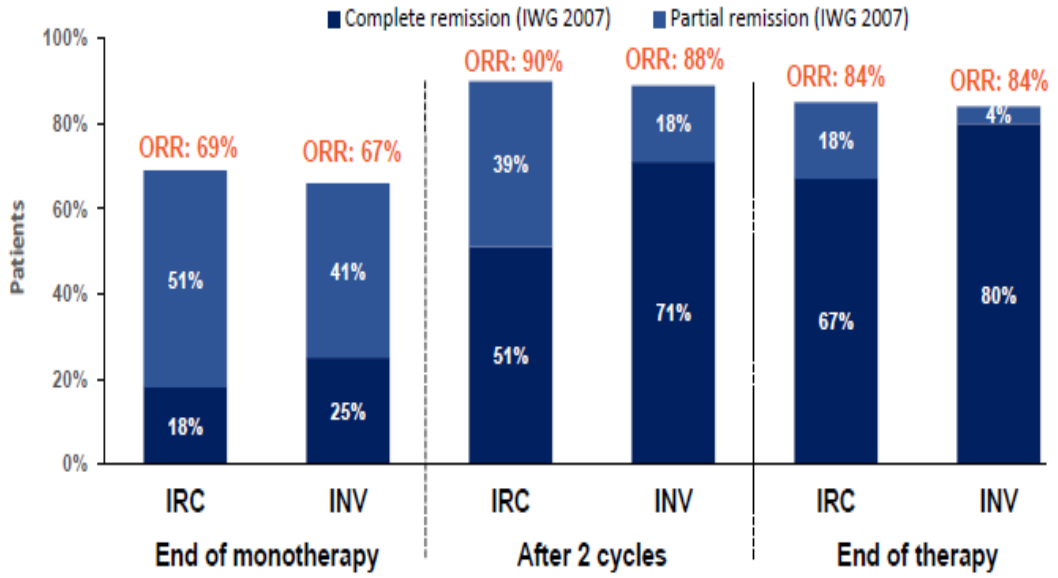
- At database lock (Oct 2017), median duration of follow-up was 11.1 months

N= 51 y, median age 37 y, Stage 4: 57%, IPS >/=3: 49%, B symptoms 80%

Ramchandren et al Lancet Oncol 2019

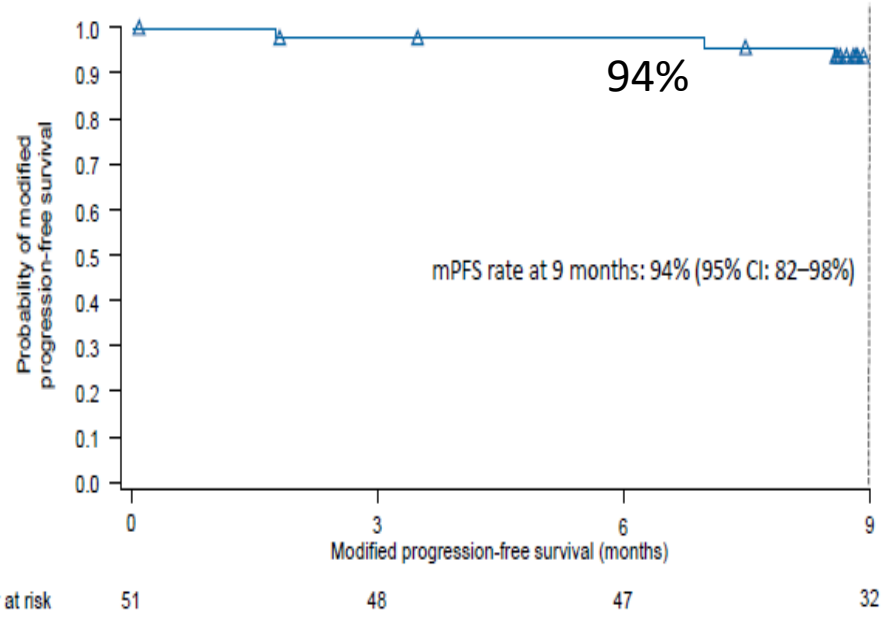
Results

Response per IRC and Investigator – ITT population



- At end of therapy, ORR per investigator for the ITT population was 84%, with 80% of patients achieving CR
- Five patients were non-evaluable at end of therapy

Modified Progression-Free Survival per IRC



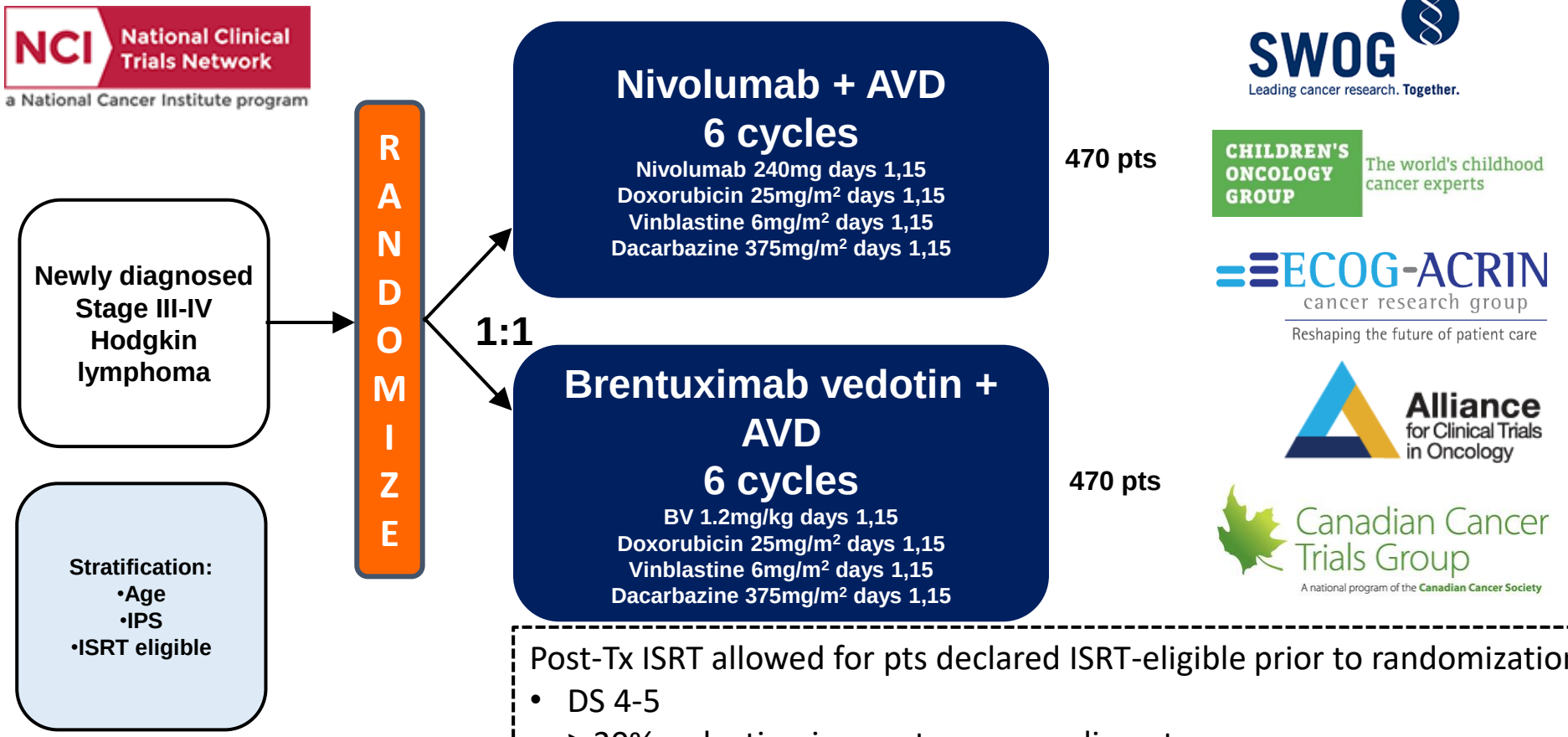
- Modified PFS was defined here as time to progression, death, or first subsequent systemic therapy in patients not achieving CR at end of therapy
- Minimum follow-up was 9.4 months

Nivolumab monotherapy followed by N-AVD well tolerated

Safety profile of N-AVD was consistent with monotherapy, with no new safety signals

Ramchandren et al Lancet Oncol 2019

S1826: A Phase III Randomized Trial of Nivolumab or Brentuximab Vedotin Plus AVD in Patients (Age ≥ 12 Years) With Newly Diagnosed Advanced Stage cHL



- Primary endpoint: PFS
- Secondary endpoints: EFS, OS, CR

Post-Tx ISRT allowed for pts declared ISRT-eligible prior to randomization with EOT:

- DS 4-5
- ≥ 30% reduction in max transverse diameter

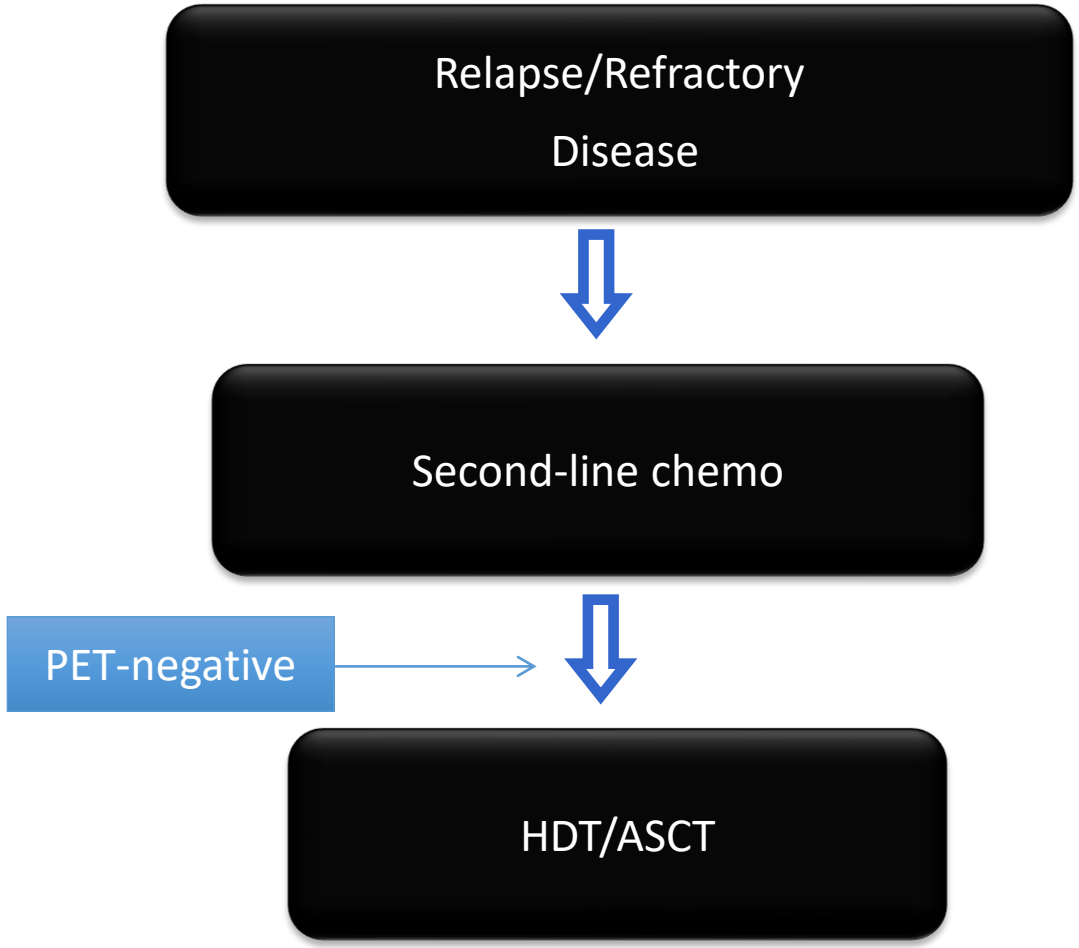
AND

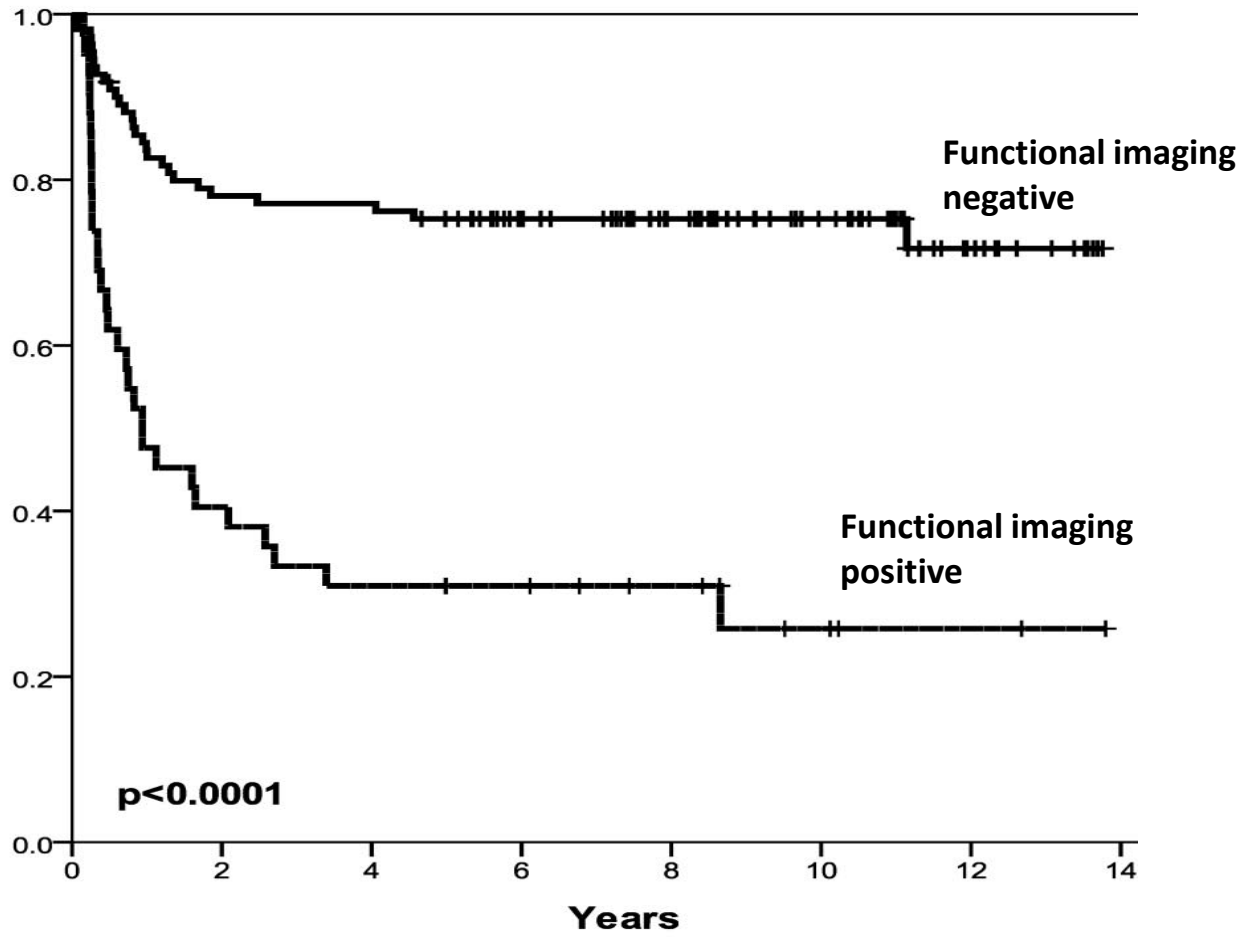
- Residual LN ≥ 2.5cm

OR

- Residual extranodal lesion > 1cm

Pre-transplant PET – most consistent prognostic factor for relapsed/refractory HL



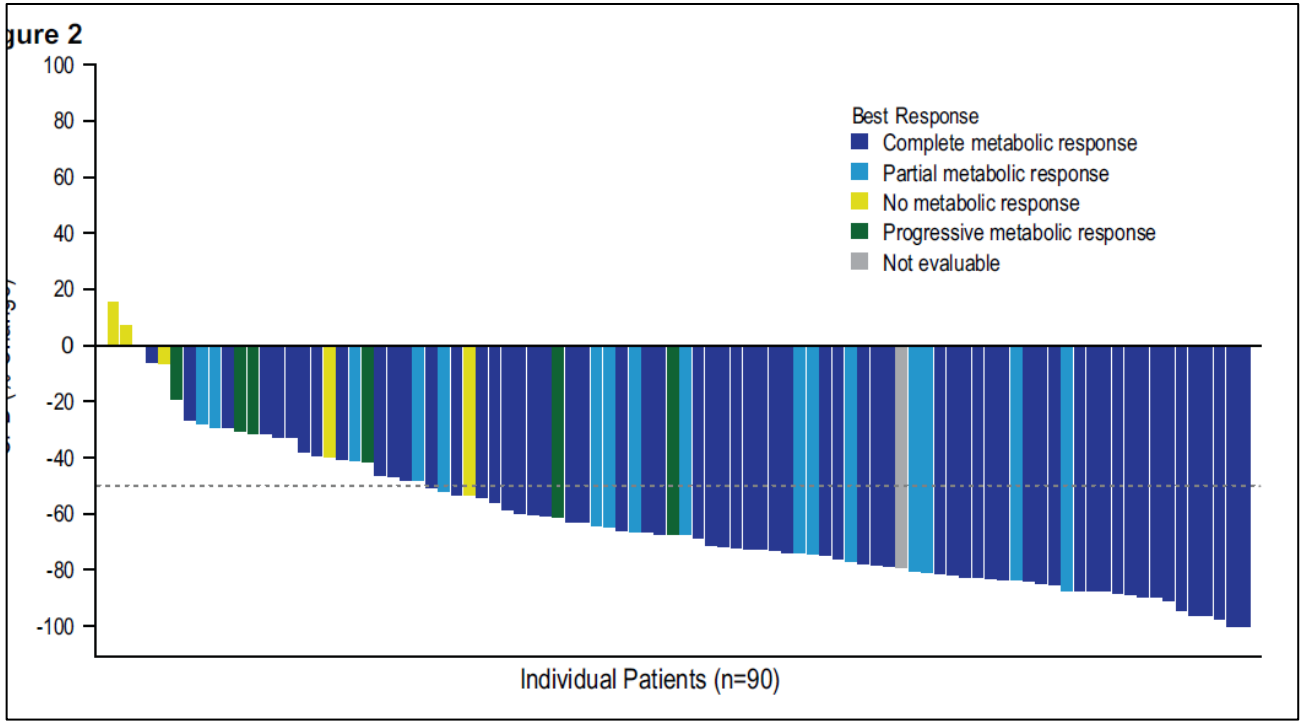


Schmitz, et al. Lancet. 2002; Lynch, et al. Lancet. 1993; Moskowitz AJ et al. Blood 2010

Contemporary second-line regimens: PET negative rate ~67-80%

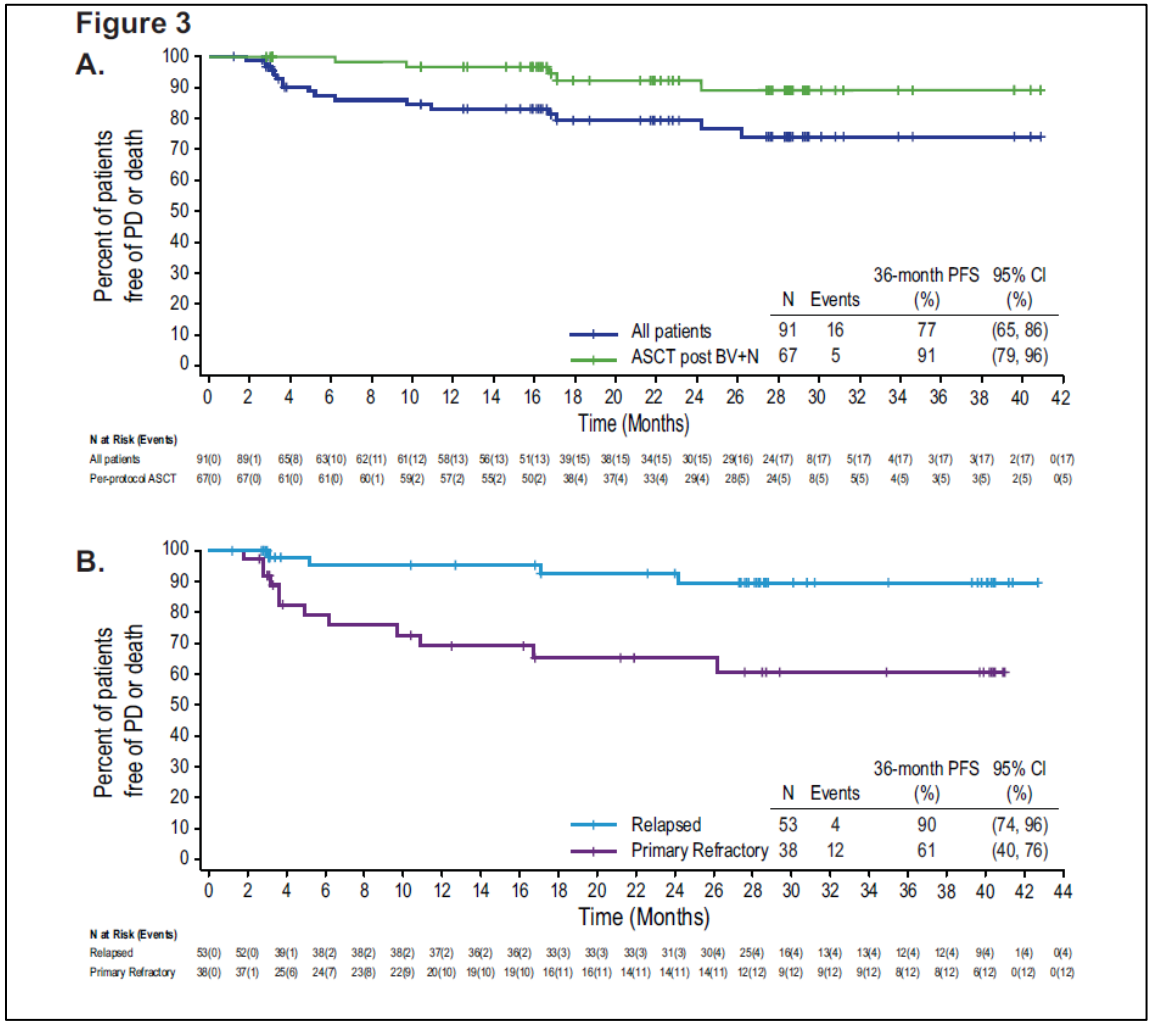
	Regimen	n	% PET-neg	PFS	Reference
Sequential BV and chemo	BV->augICE	65	83% 27% (BV alone)	73% @ 6 y	Moskowitz, et al. Blood 2017; ASH 2019
	BV->ICE	56	66% 43% (BV alone)	67% @ 2 y	Herrera, et al. Ann Oncol 2018
Combined BV and chemo	BV-benda	55	74%	62.6% @ 2 y 69.8% for ASCT pts	LaCasce, et al. Blood 2018
	BV plus: ICE DHAP ESHAP Gem	 39 61 66 42	 69% 79% 70% 67%	 69% @ 1 y 76% @ 2 y 71% @ 30 mo Too soon	 Stamatoullas, et al. ASH 2019 Hagenbeek, et al. ASH 2018 Garcia-Sanz, et al. Ann Oncol 2019 Cole, et al. Lancet Oncol 2018
BV plus **CPI**	BV-nivolumab	91	67%	79% @ 2 y 93% @3y for ASCT pts	Advani, et al Blood 2021

BV-Nivo as First salvage in R/R HL: 3y follow up



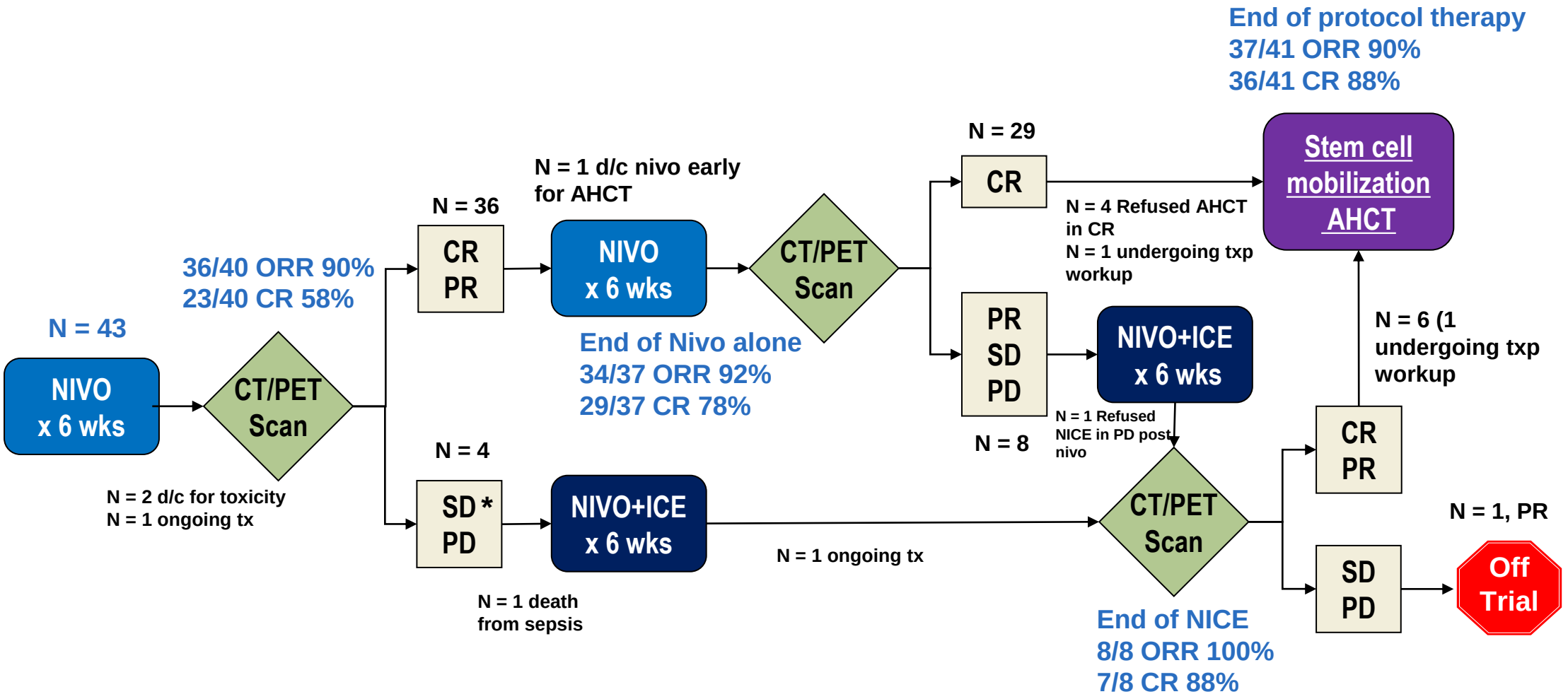
3-year follow-up of phase 1/2 study (N = 91)

- ORR: 85%
- CR: 67%
- 3-year PFS: 77%
  - 91% in patients who progressed to auto-SCT
- 3-year OS: 93%



Advani et al Blood 2021

PET-adapted Nivolumab or Nivolumab plus ICE as First Salvage Therapy in Relapsed/Refractory CHL (ASH 2020 Herrera et al # 239)

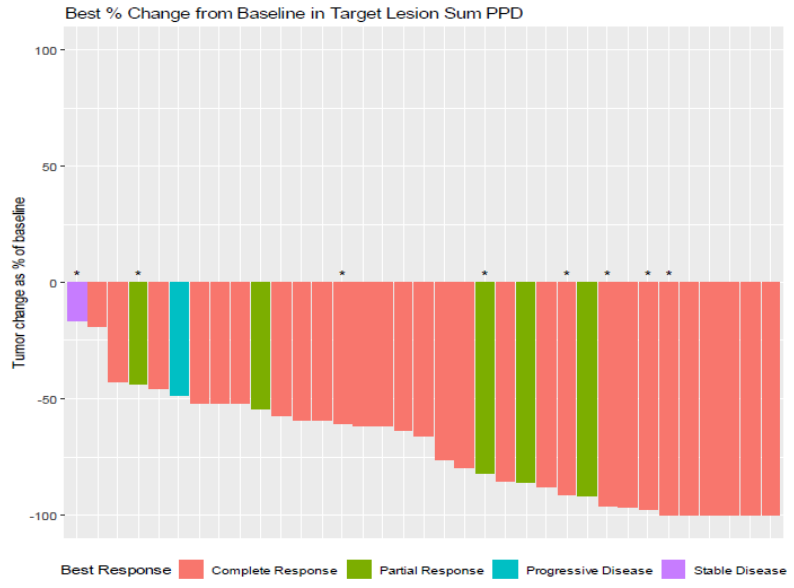


Courtesy Herrera et al ASH 2019

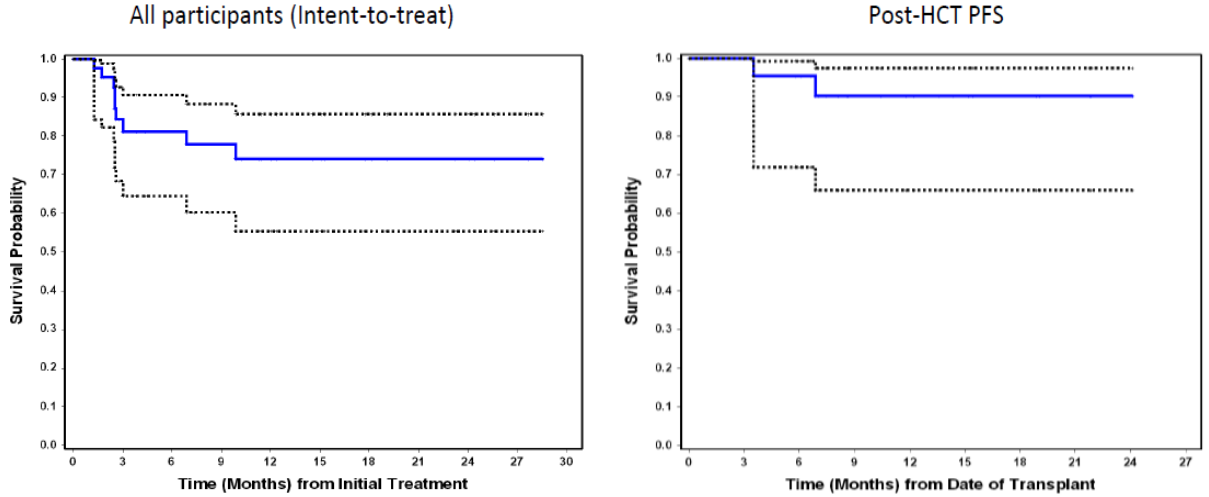
Results

Best Change in Tumor Size From Baseline

*Asterisks indicate participants treated with Nivo + ICE



Progression-Free Survival



- Median follow-up: 12 months (range: 0.5-28.6)
- 1 year PFS: 74% (95% CI: 55 - 86)
- Median follow-up: 9 months

PET-adapted sequential Nivo +/- ICE resulted in a high CR rate and bridged most pts to transplant without traditional chemo

Unexpectedly high CR rate (70%) using Nivo as first salvage therapy

Nivo+ICE is tolerable and effective in patients not in CR after Nivo alone

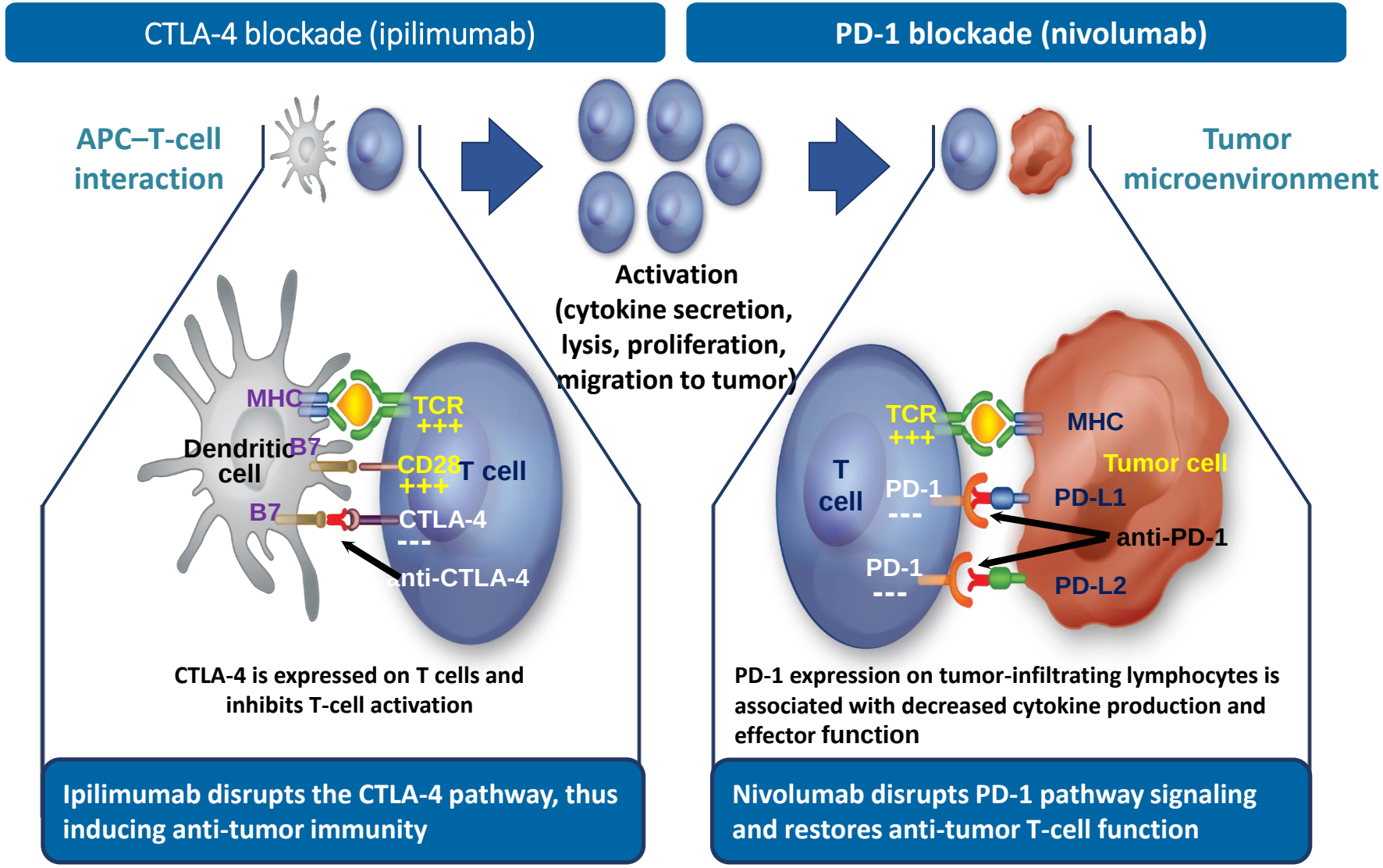
No unexpected safety signals with Nivo or Nivo+ICE in 2nd-line setting

PD-1 blockade with Nivo can be an effective bridge to ASCT independent of BV

Courtesy Herrera et al ASH 2019

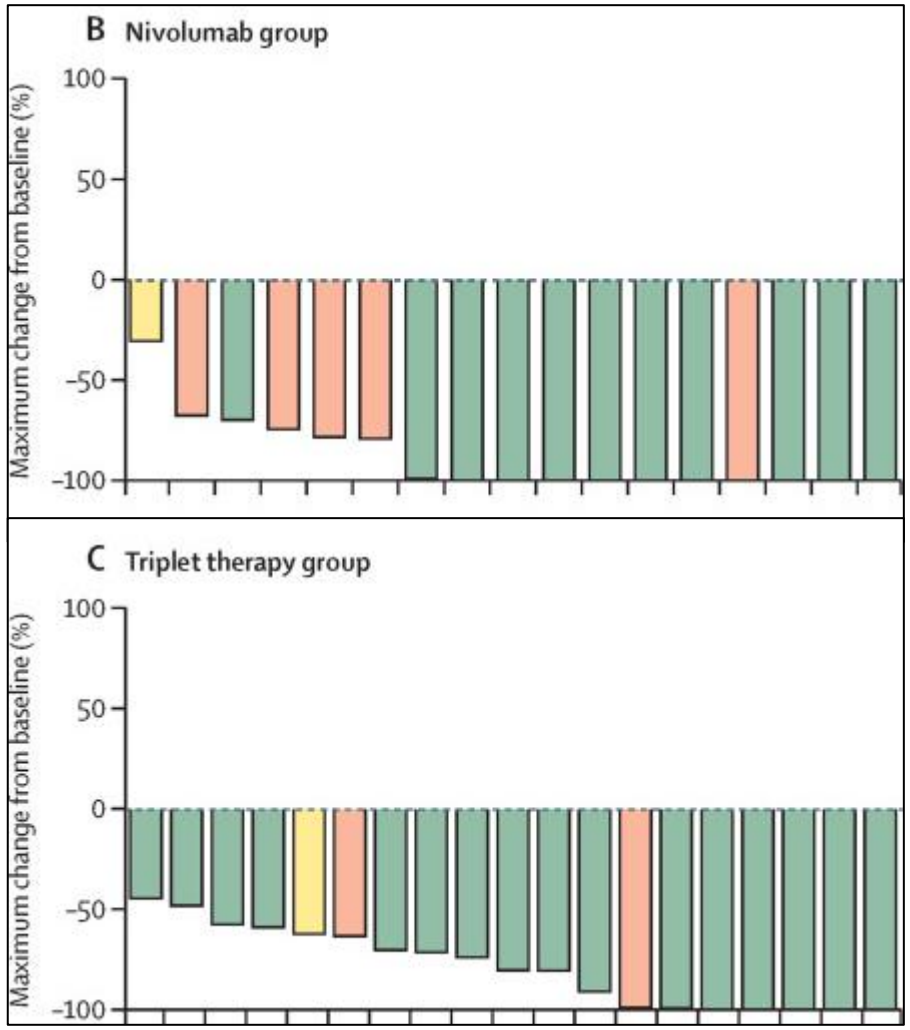
Nivolumab and Ipilimumab
Two Immune Checkpoint Inhibitors

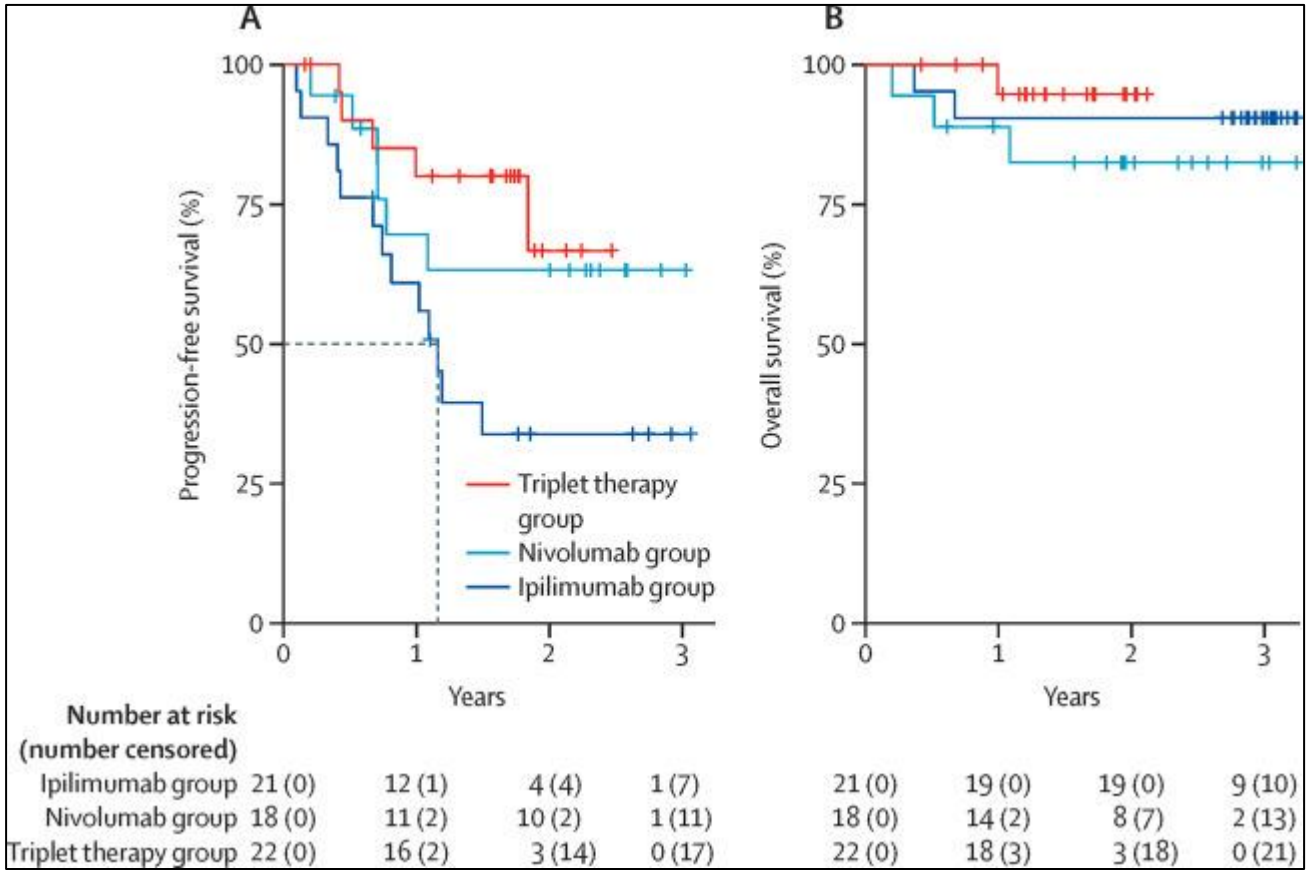
CD68 the ligand for CTLA-4 is also expressed by HRS cells and may trigger CTLA-4 mediated T cell suppression.



Courtesy Ansell et al. ASH 2016 abstract #183

Doublet or Triplet Therapy in Relapsed/Refractory cHL





E4412 Phase 2 Currently Accruing Doublet vs Triplet

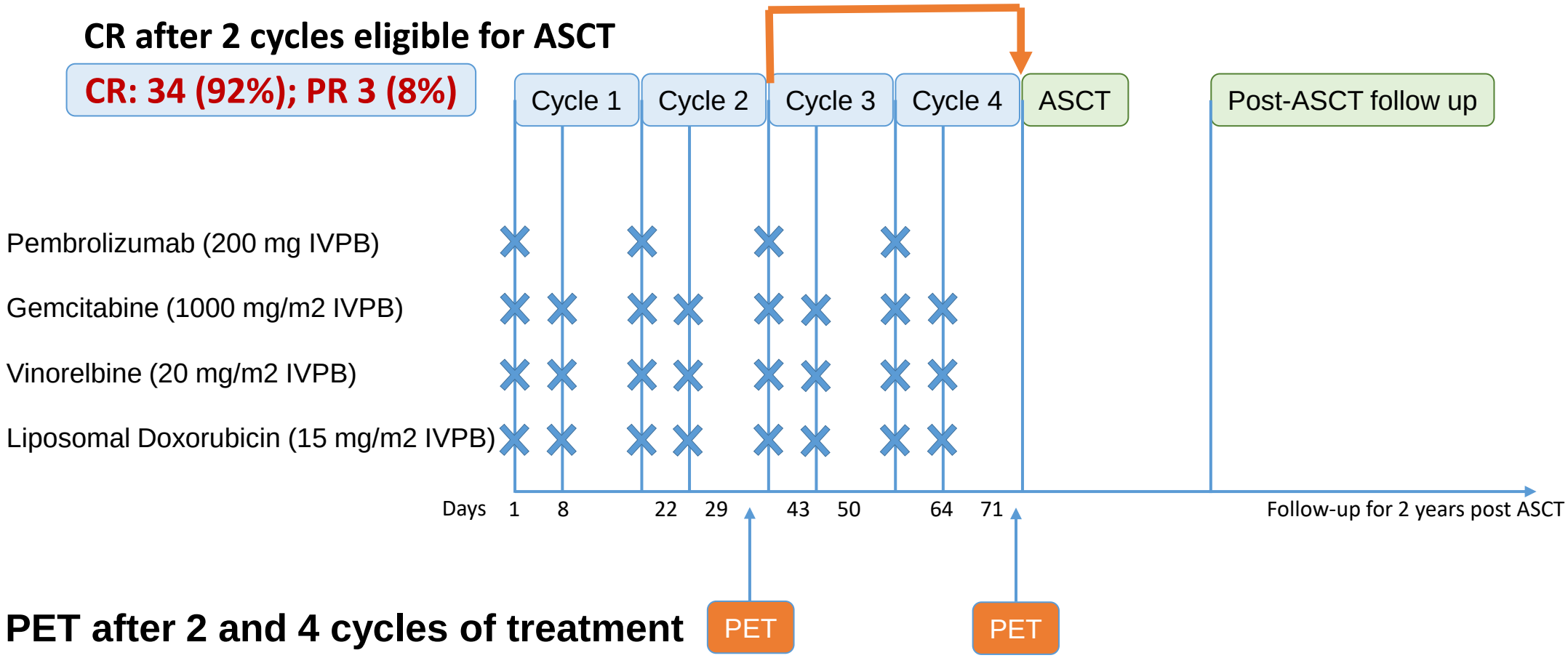
Diefenbach et al Lancet Hematology 2020

Phase II Study of Pembrolizumab Plus GVD As Second-Line Therapy for **Relapsed** or Refractory CHL [ASH 2020: Moskowitz et al, #470]

- **Eligibility**: relapsed or refractory cHL following 1-line of therapy
- **Primary endpoint**: CR (by Deauville 3) rate after 2-4 cycles

CR after 2 cycles eligible for ASCT

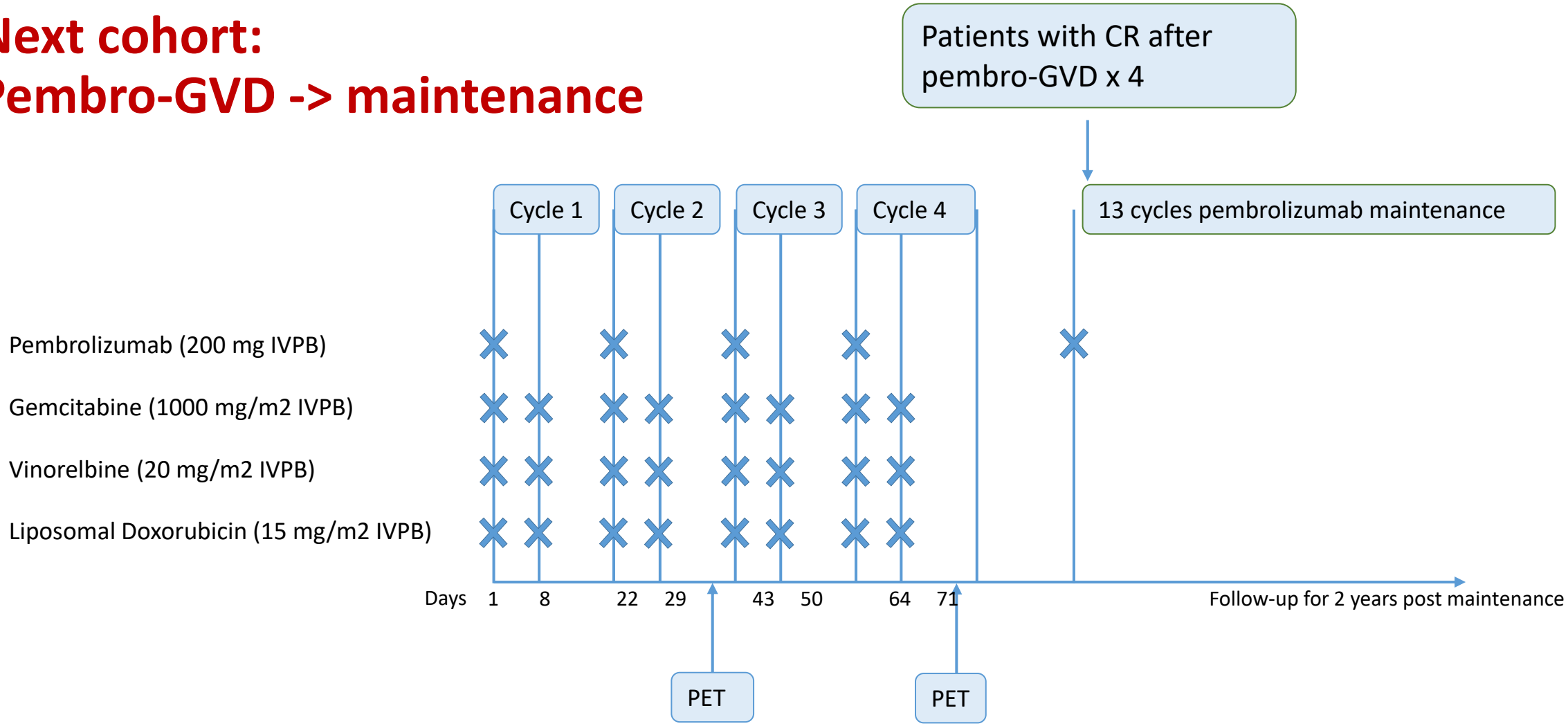
CR: 34 (92%); PR 3 (8%)



PET after 2 and 4 cycles of treatment

Median f/u post-ASCT: 11.2 months (range: 0.95-24 mo), No progressions, well tolerated

Next cohort:
Pembro-GVD -> maintenance

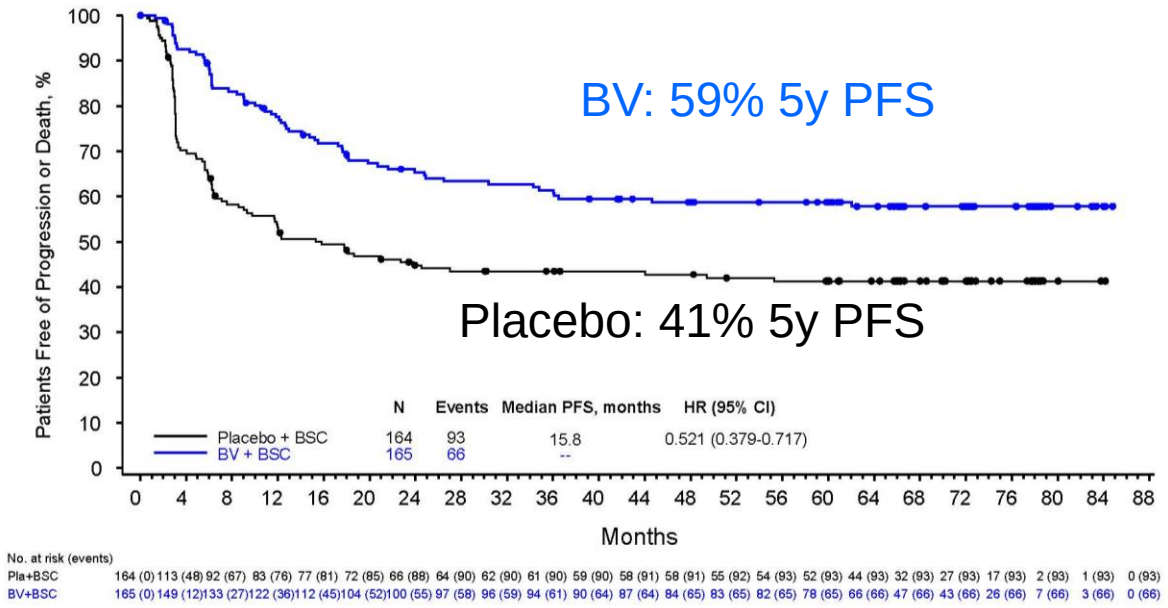


Exploratory: cytokines, immune cell subsets, metabolic tumor volume, ctDNA, 9p24.1 amplification, IHC staining for MHC-I, MHC-II, pd-1, pd-l1, pd-l2, beta-2 microglobulin

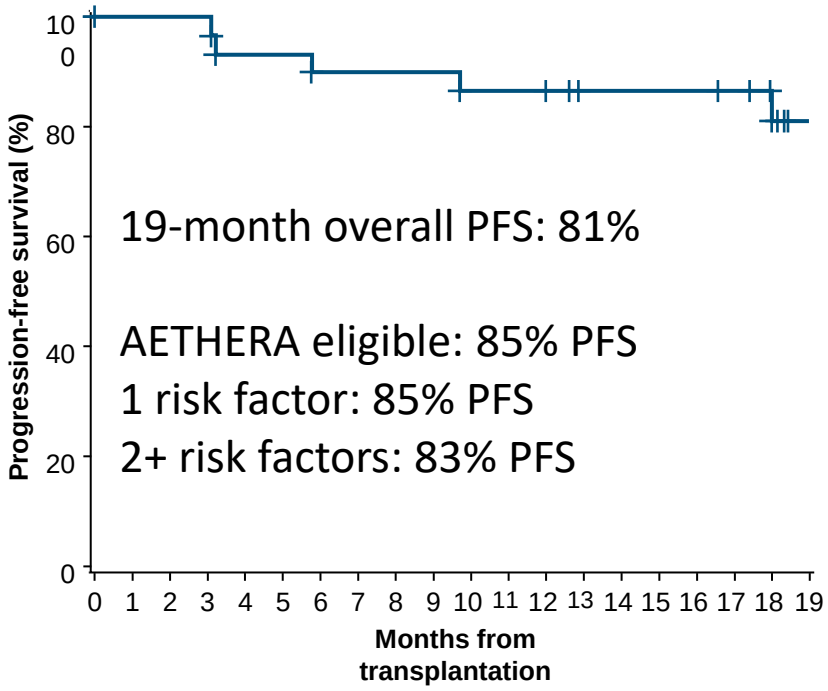
Memorial Sloan Kettering Cancer Center

Consolidation after ASCT in CHL

AETHERA, BV consolidation after ASCT
n = 329 high-risk R/R HL, 16 cycles
85% 2+ risk factors



Pembrolizumab consolidation after ASCT
n = 30 R/R HL, 8 cycles
40% 2+ risk factors



Moskowitz CH, et al Blood 2019, Armand P, et al Blood 2019.

Consolidation with Nivolumab and Brentuximab Vedotin after ASCT in Patients with High-Risk HL [ASH 2020 Herrera et al, #472]

Variable	N (%)
Male gender	34 (58%)
Age, median (range)	30 (18-72)
Primary refractory	18 (31%)
Relapse within 1 year	35 (59%)
Late relapse	6 (10%)
B sx at relapse	14 (24%)
Extranodal dz at relapse	23 (39%)
2 or more salvage regimens	15 (25%)
Disease status at HCT	
Complete response	48 (81%)
Partial response	11 (19%)
Disease status at baseline	
Complete response	53 (90%)
Partial response	6 (10%)
Modified AETHERA risk factors	
1	21 (36%)
2	23 (40%)
3+	14 (24%)
Frontline regimen	
A(B)VD	50 (85%)
ABVD/MOPP	1 (2%)
BV+AVD	2 (3%)
ABVE+PC	6 (10%)
Prior radiation	14 (24%)
Prior BV	30 (51%)
Prior PD-1 blockade	25 (42%)
HCT conditioning regimen	
BEAM	47 (80%)
GemBuMelVorinostat	7 (12%)
Other	5 (8%)

OS 98%

Figure 1: Progression-free survival in all patients (n=59)

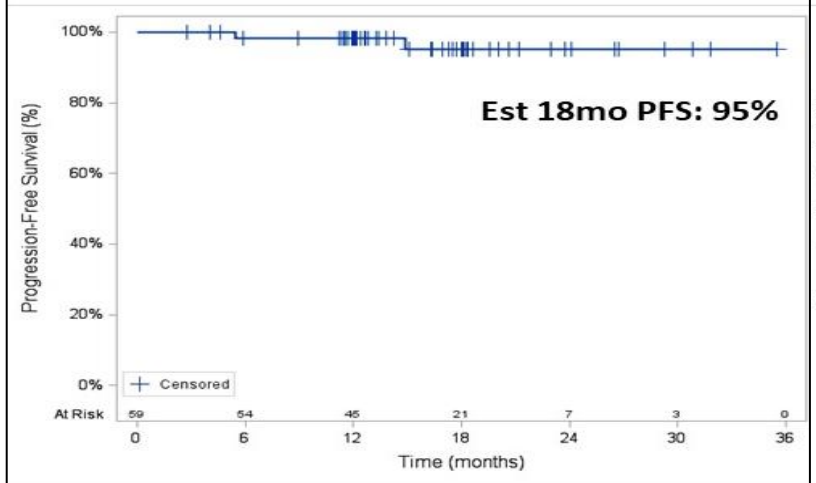
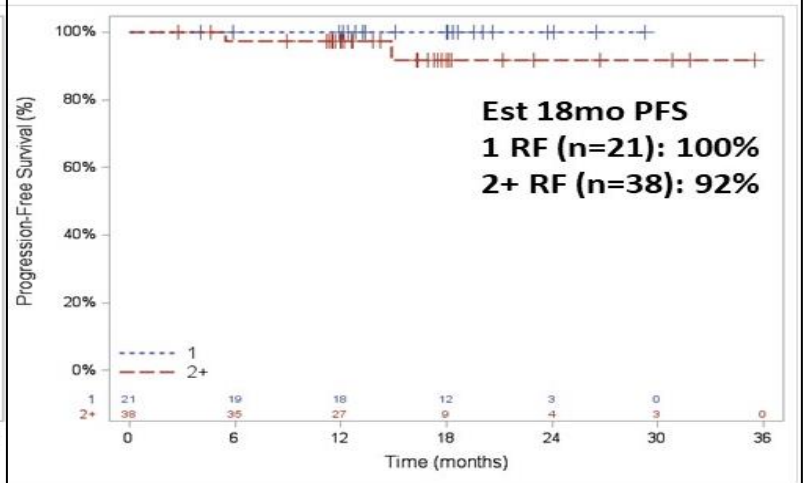


Figure 2: Progression-free survival by number of high-risk factors



Completed all 8 cycles of BV and Nivo	29 (49%)
Early Discontinuation of both BV and Nivo	14 (24%)

More irAE than in pre-AHCT setting (27% requiring steroids)

PD-1 Blockade and Sensitization in ASCT

Retrospective study

Patients (N = 78) with R/R HL who received anti-PD-1 therapy prior to ASCT

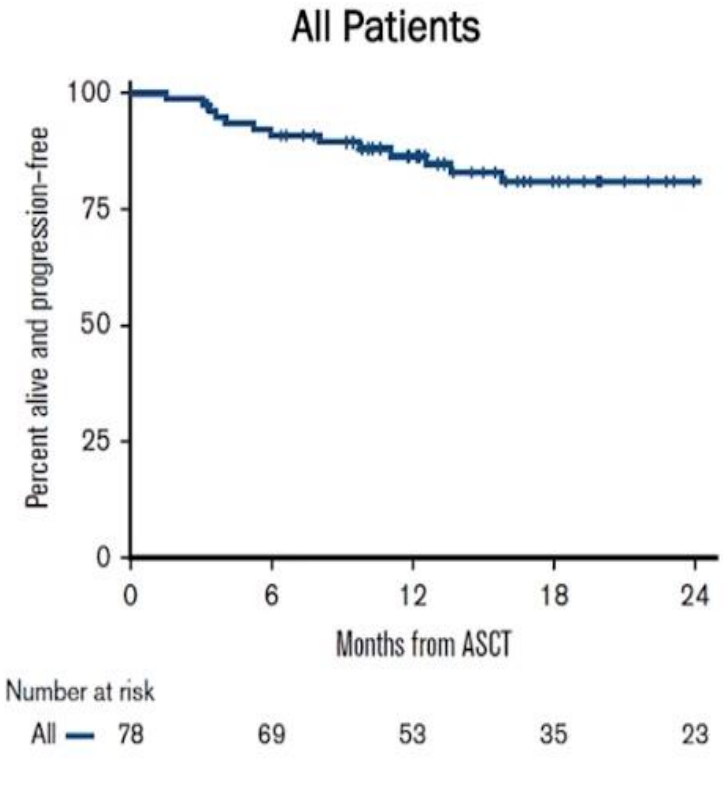
- Had insufficient responses to proceed to ASCT after ≥ 2 systemic therapies
- Were treated with a PD-1 or PD-L1 mAb as third-line or later therapy, and
- Subsequently underwent ASCT before October 2019

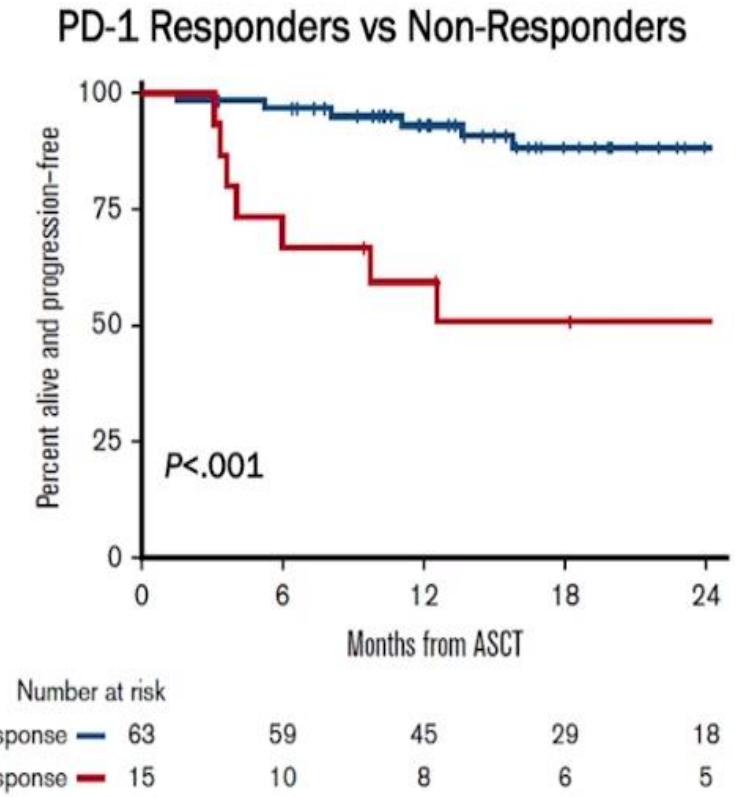
Best Response to Anti-PD-1 Therapy

Best Response	Patients (N = 78)
CR	42%
PR	38%
SD	11%
PD	8%

Response with anti-PD-1 combination vs monotherapy regimen:

- ORR: 100% vs 75%
- CR: 58% vs 33%

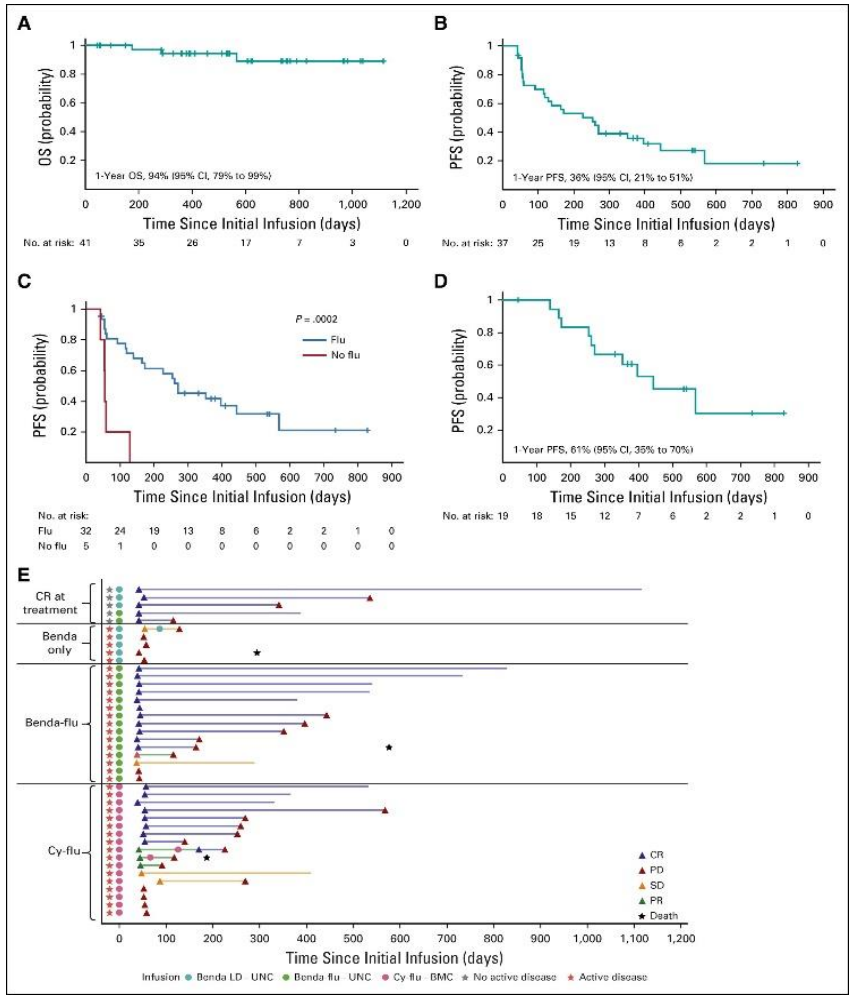


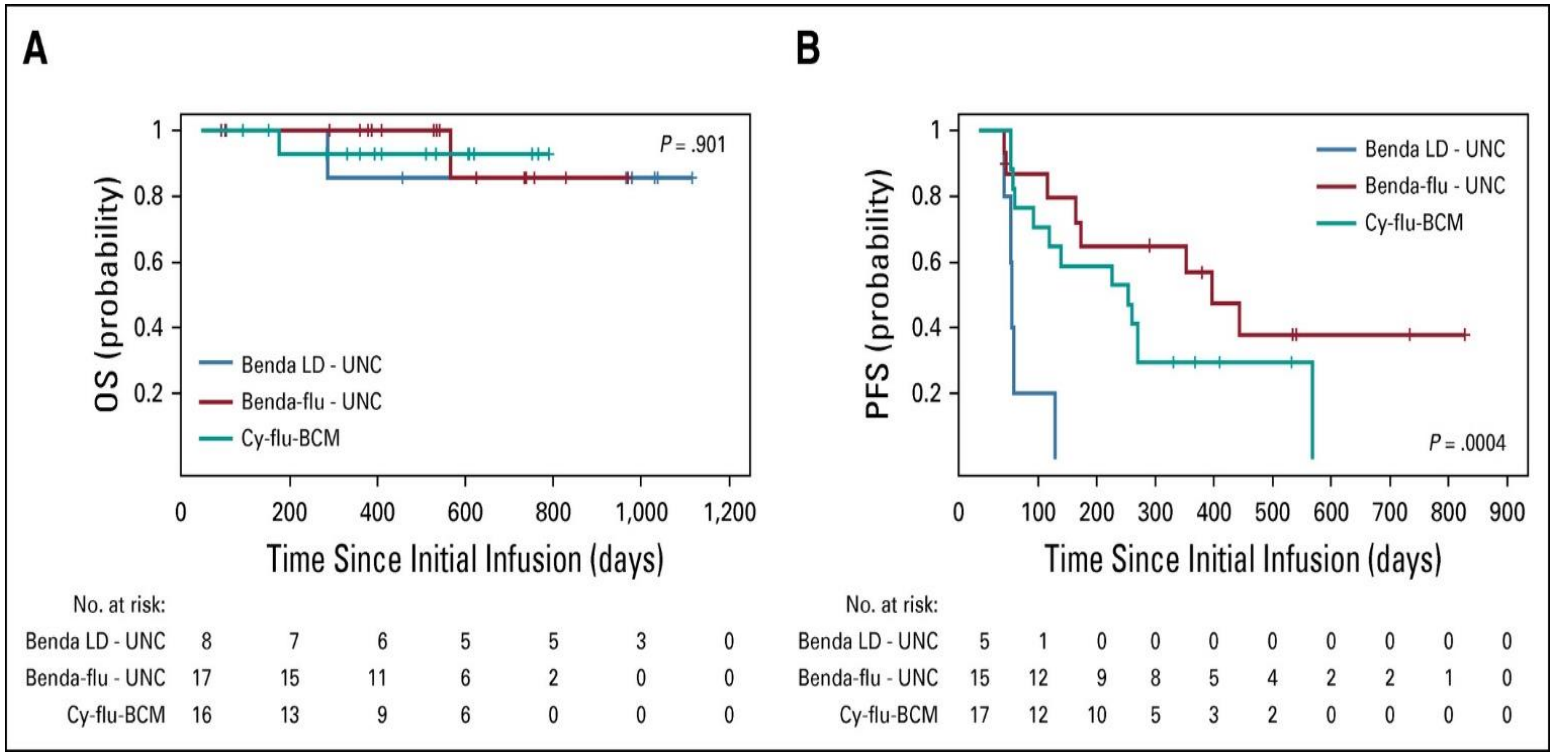


Merryman et al Blood Adv 2021

CAR.CD30-T Cells in Patients with CD30+ Lymphomas Relapsed after Multiple Treatments Including BV

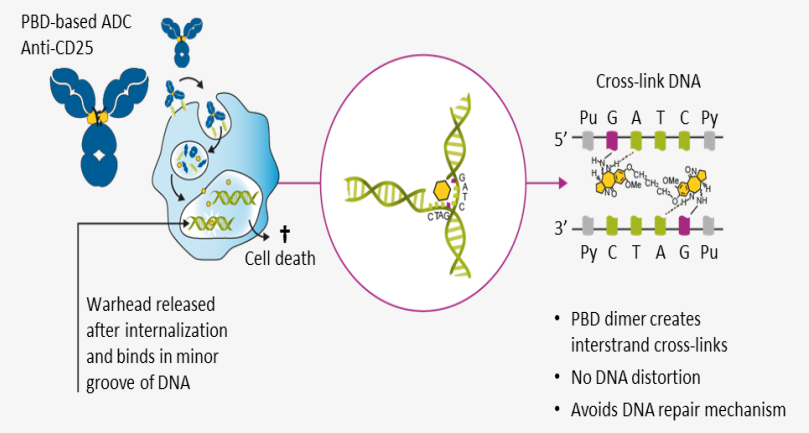
RELY-30 trial (NCT02917083)





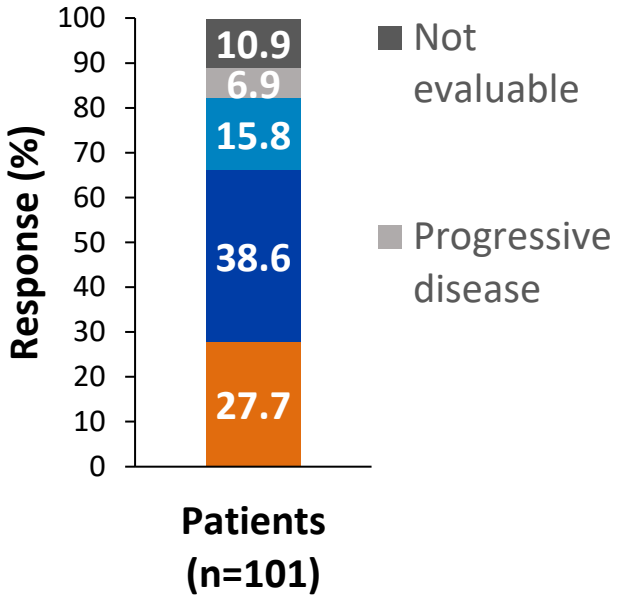
Ramos et al JCO 2020

CAMIDANLUMAB TESIRINE Efficacy and Safety in an Open Label, multicenter, Phase II study in R/R CHL [2021 ICML-Zinzani et al, #75]



- **Camidanlumab tesirine:** human IgG1 anti-CD25 antibody conjugated to a PBD dimer, which cross-links DNAs leading to cell death
- Two potential mechanisms of action in cHL
  - Direct cytotoxicity in CD25+ Reed-Sternberg cells (~60-80% express CD25)
  - Depletion of immunosuppressive

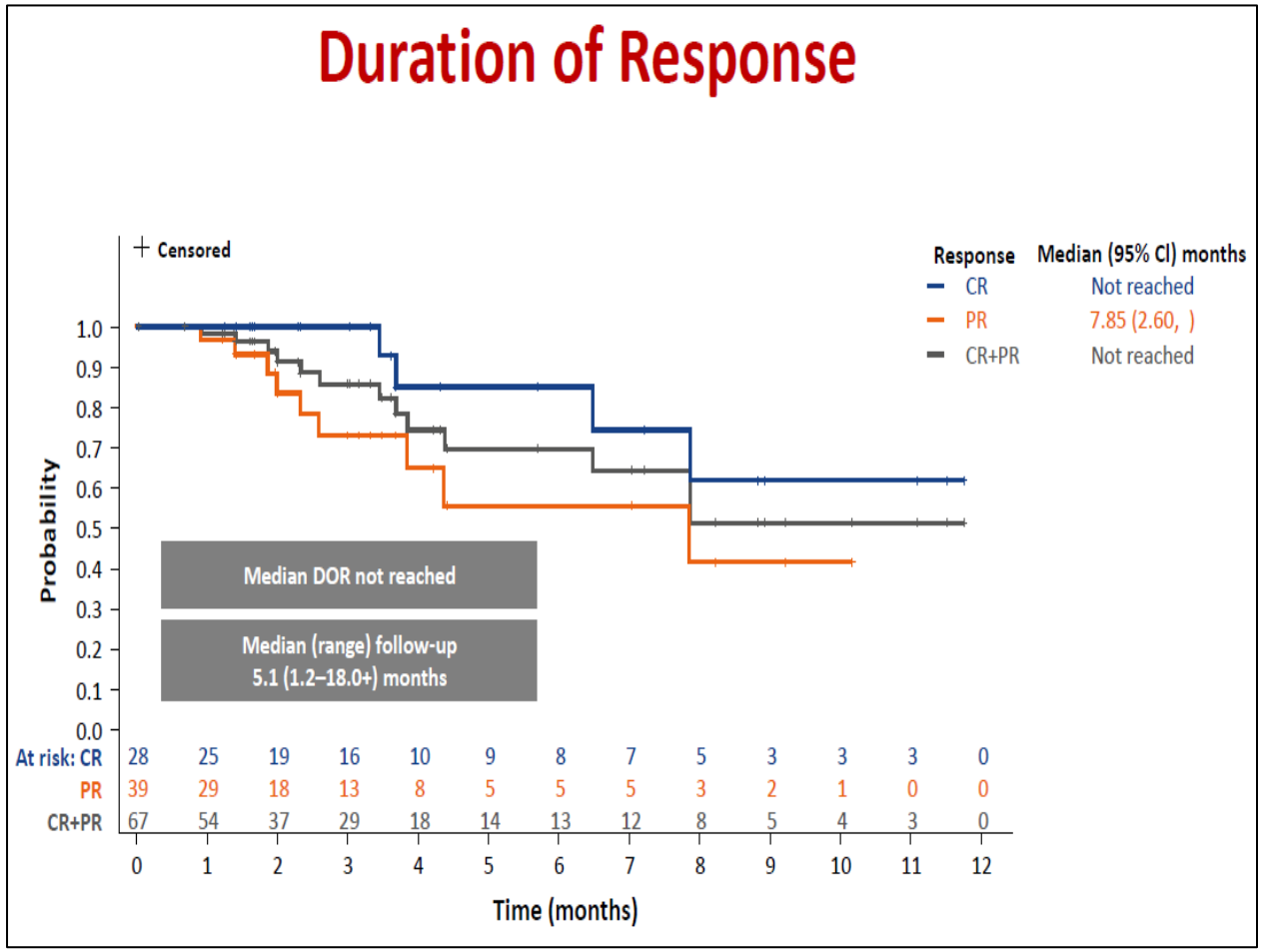
Characteristic		Total (N=117) %
Sex	Male	73 (62.4)
	Female	44 (37.6)
Age, years, median		37 (19, 87)
ECOG status	0	63 (53.8)
	1	48 (41.0)
	2	6 (5.1)
No. prior systemic therapies median (range)		6 (3–19)
Prior BV and PD-1 blockade	BV	116 (99.1)
	PD-1 blockade therapy	117 (100)
	BV and PD-1 blockade therapy	116 (99.1)
Prior HSCT	Autologous	58 (49.6)
	Allogeneic	3 (2.6)
	Both	12 (10.3)
Disease status after last-line systemic therapy	Relapsed	38 (32.5)
	Refractory	66 (56.4)
	Other[d]	13 (11.1)

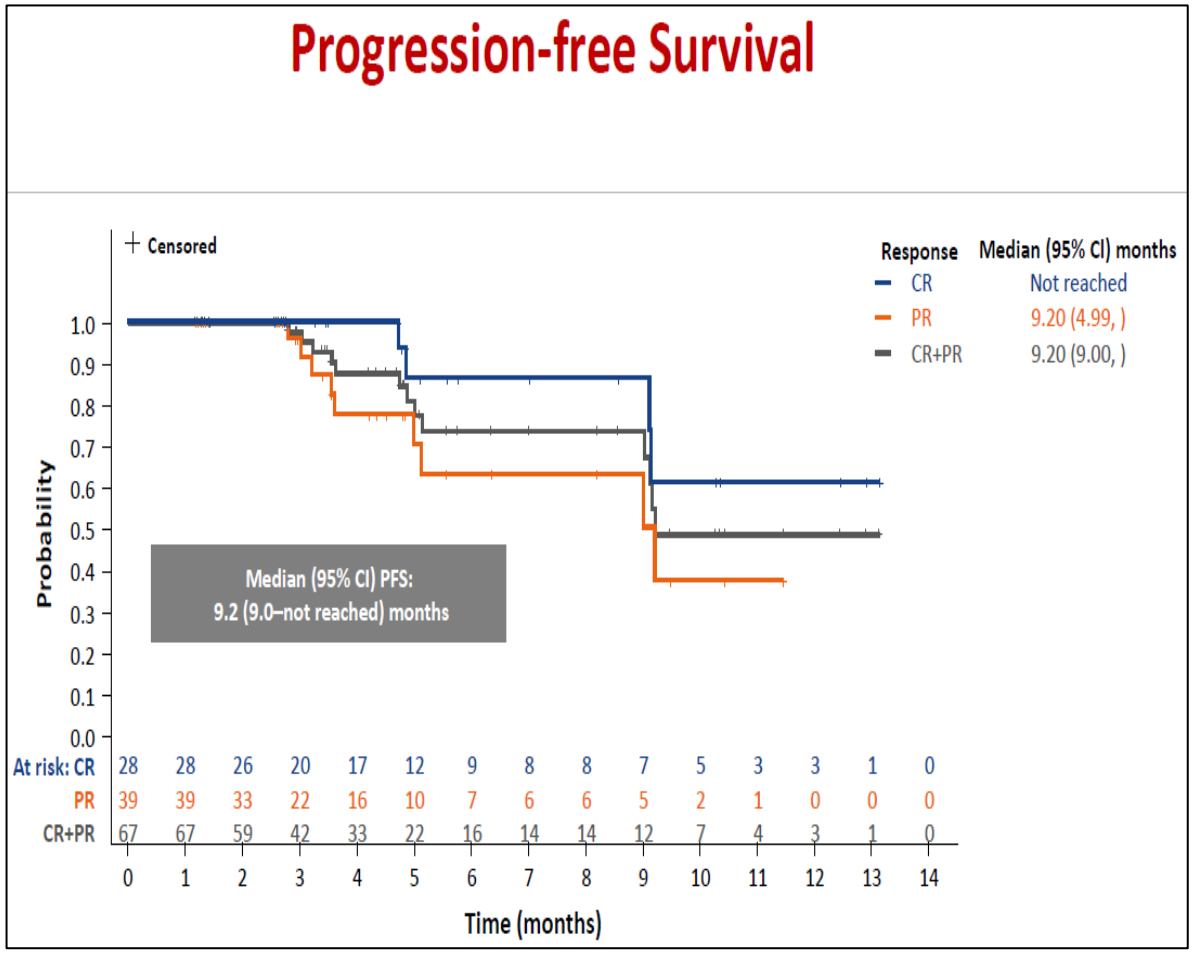


ORR: 66%
CR: 28%

7 pts (6%) Guillain-Barre Syndrome ? Etiology
4 ongoing, 3 recovered

CAMIDANLUMAB TESIRINE



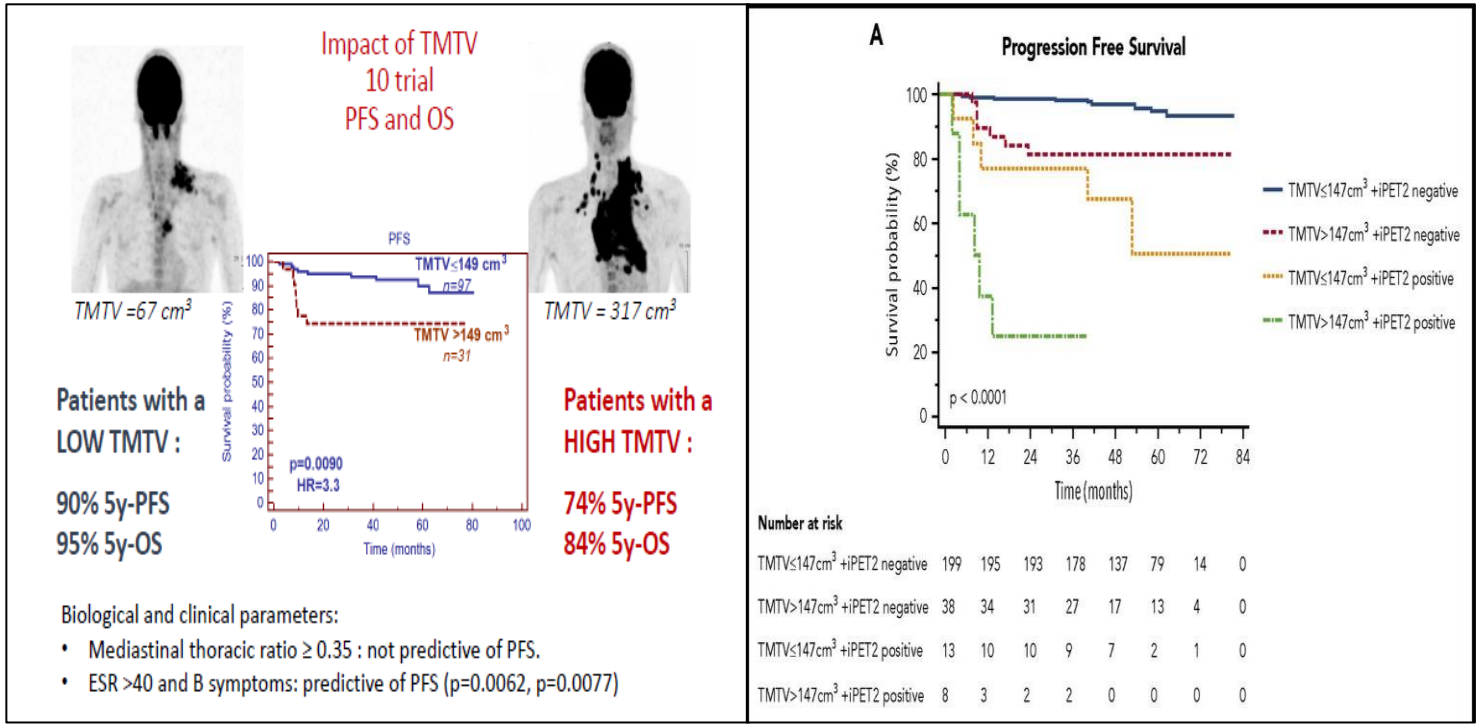


Zinzani et al, ICML 2021, #75

Emerging prognostic markers in HL
Reclassifying patients with ESHL based on functional radiographic markers at presentation (standard arm of the H10 trial)

Total Metabolic Tumor Volume

$TMTV = \sum MTV_L$



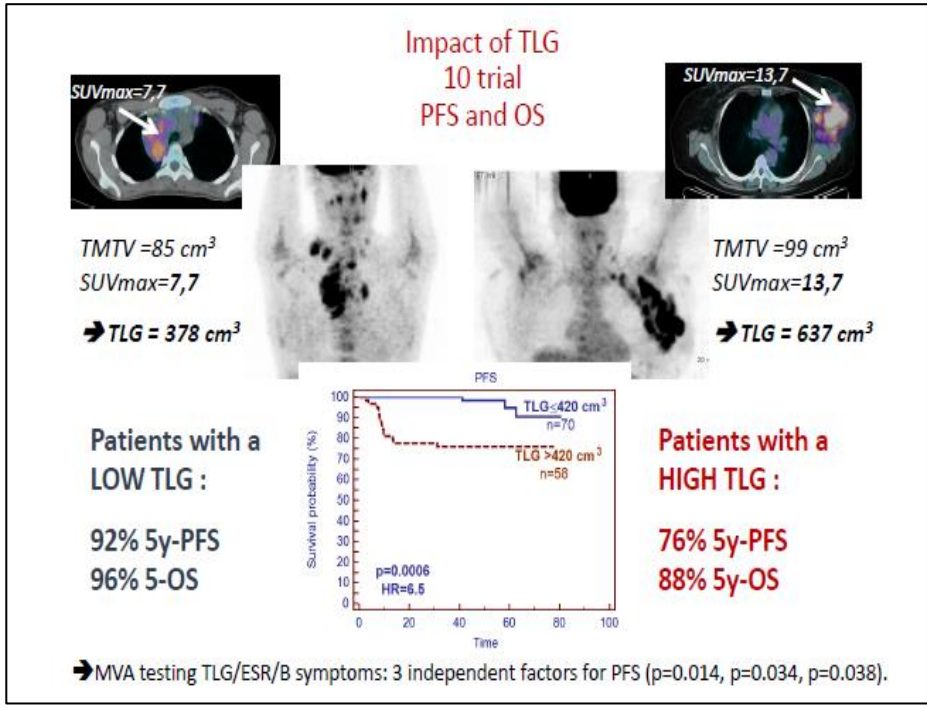
Biological and clinical parameters:

- Mediastinal thoracic ratio ≥ 0.35 : not predictive of PFS.
- ESR >40 and B symptoms: predictive of PFS (p=0.0062, p=0.0077)

Cottereau et al Blood 2018

Total Lesion Glycolysis

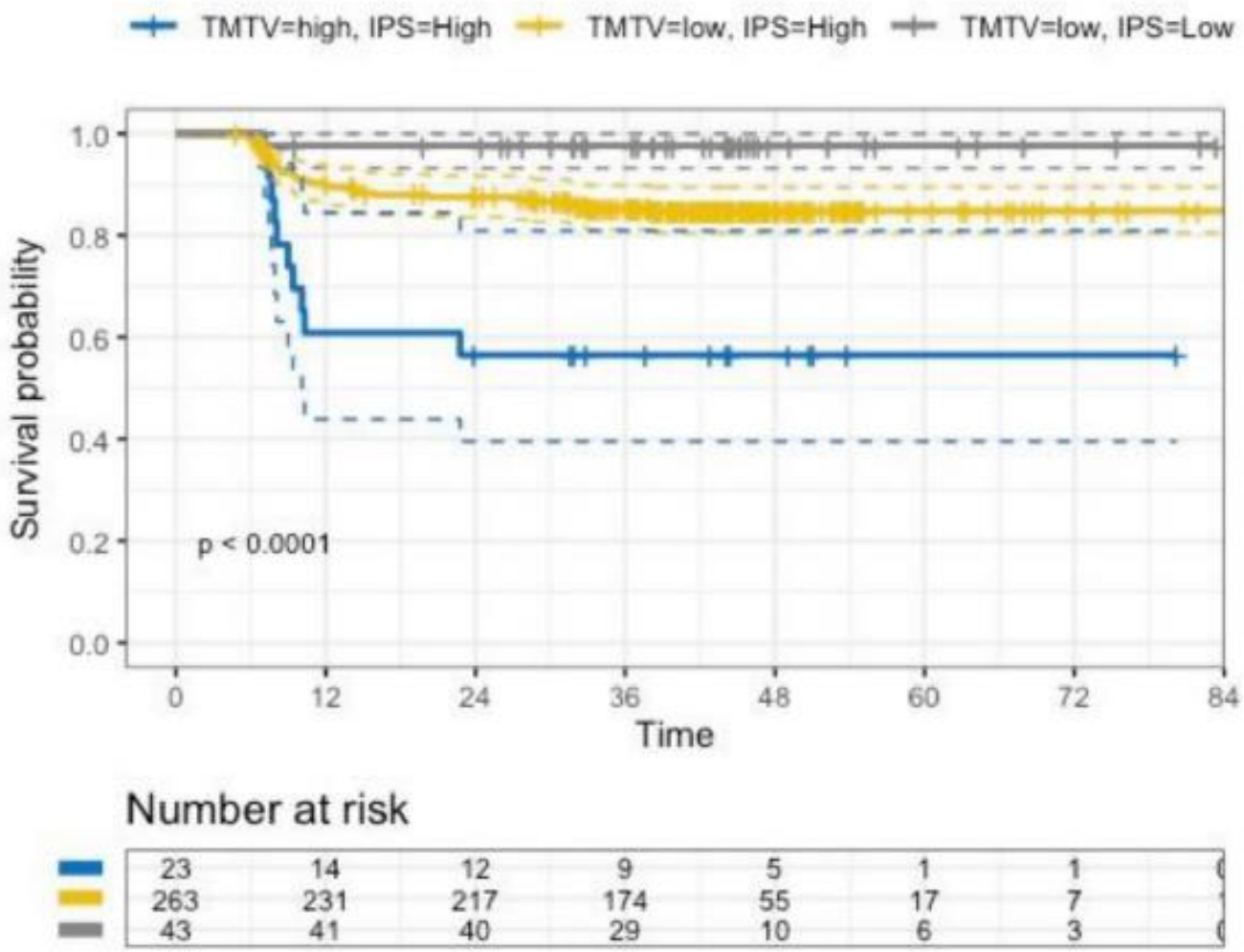
$TLG = \sum (MTV_L \times SUV\ mean_L)$



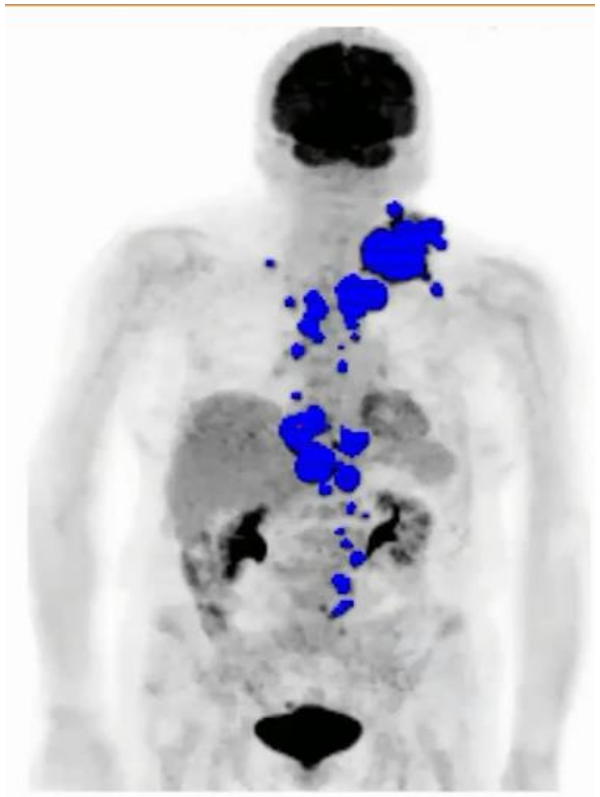
➔MVA testing TLG/ESR/B symptoms: 3 independent factors for PFS (p=0.014, p=0.034, p=0.038).

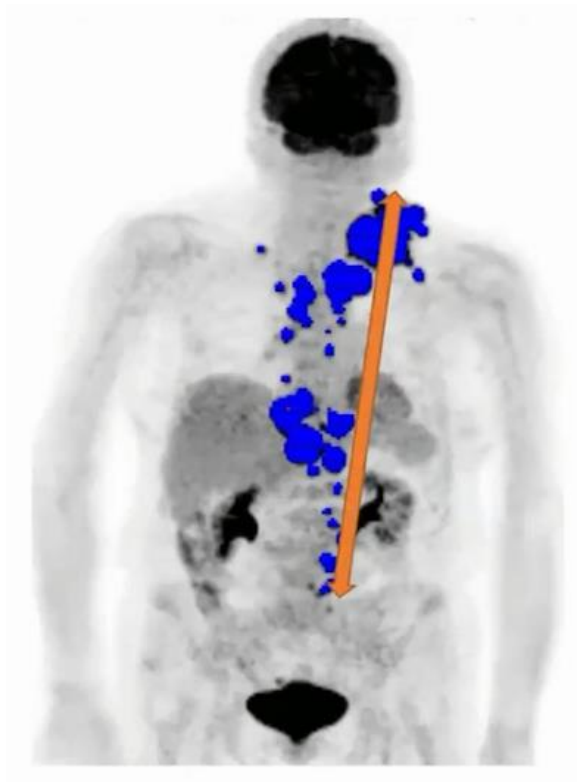
Courtesy Dr Casasnovas ASH 2016

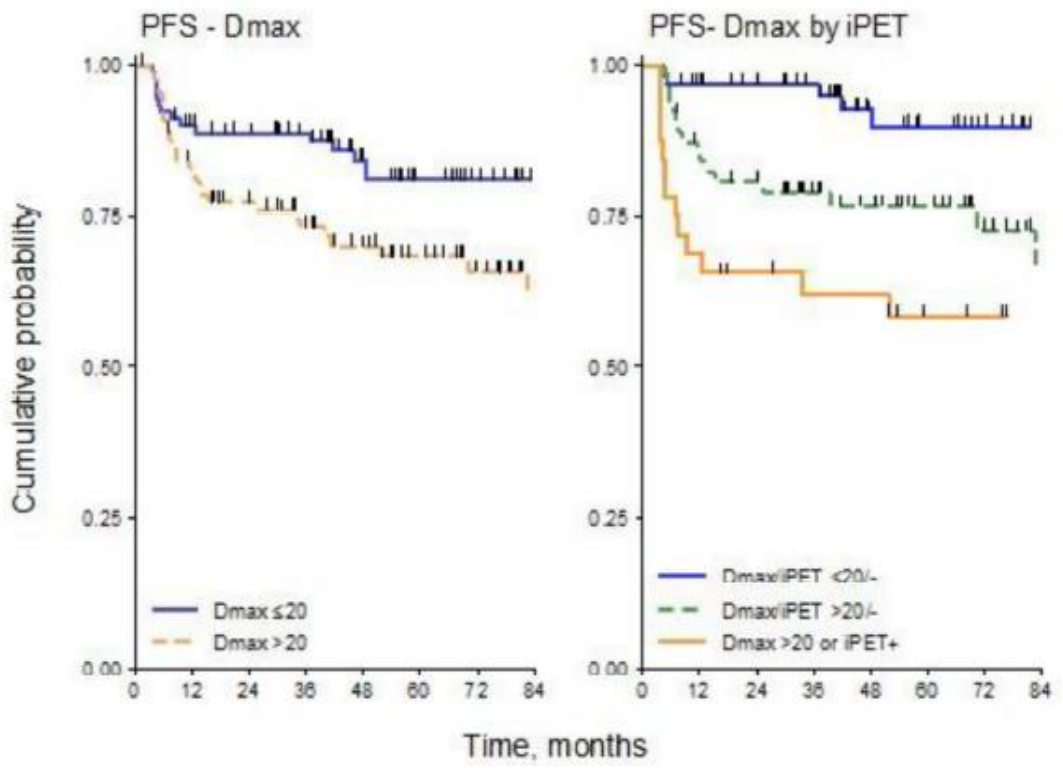
Baseline MTV AND IPS Predict ABVD Failure In Advanced Stage HL with a Negative Interim PET scan after 2 chemotherapy cycles. A Retrospective analysis from the GITIL/FIL HD0607 TRIAL [ICML 2021 Gallamini et al, #19]



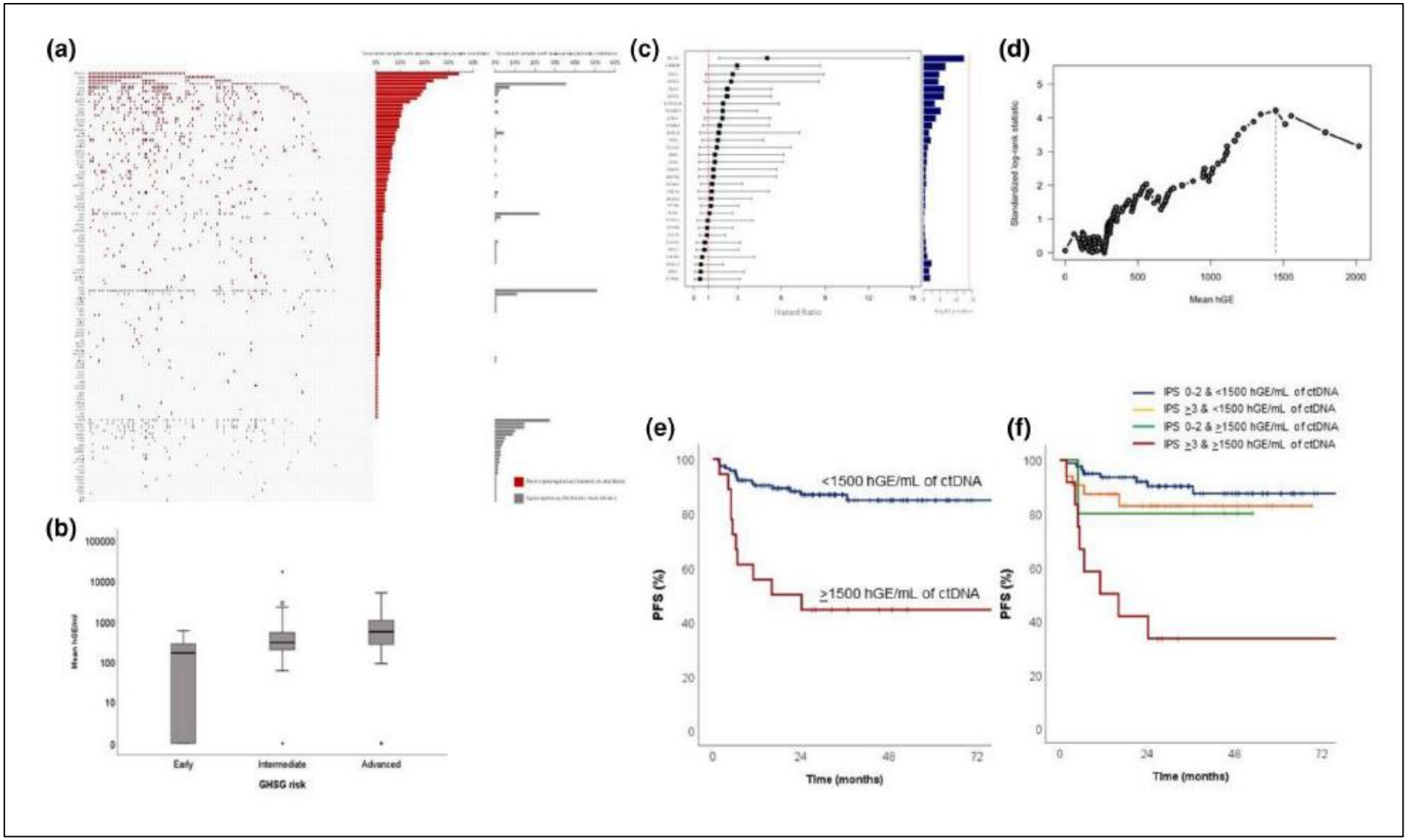
Prognostic Role of Lesion Dissemination Feature (Dmax) Calculated on Baseline PET/CT In HL [ICML 2021 Durmo et al, #20]



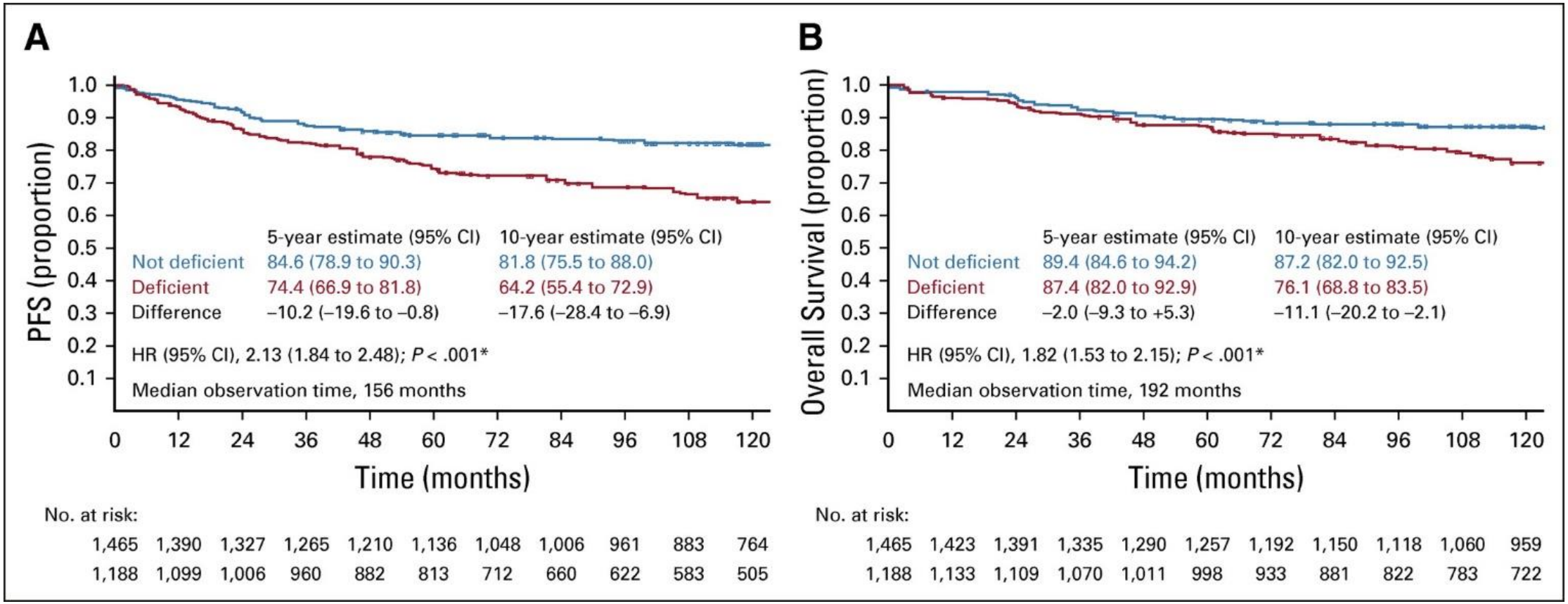




Circulating Tumor DNA is a Prognostic Biomarker in cHL [ICML 2021: Spina et al, #70]



Emerging prognostic markers in CHL
Pretreatment Vitamin D Deficiency (< 30 nmol/L)
Associated With Impaired PFS and OS



Borchmann et al J Clin Oncol 2019

State of the Art: Current and Emerging Treatment of CHL

Balancing Risk With Benefit for the Individual

Highest cure rate with primary therapy

Optimal Survivorship