City of Hope

Multidisciplinary Approaches to Cancer Symposium

Frontline Therapy of Early Stage Hodgkin Lymphoma

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City of Hope

Disclosures

- Grant/Research Support from BeiGene, and Bristol Myers Squibb.
- Consultant for SeaGen, and ADC Therapeutics
- On the Speakers' Bureau for Seagen.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of nivolumab and brentuximab vedotin will be discussed

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

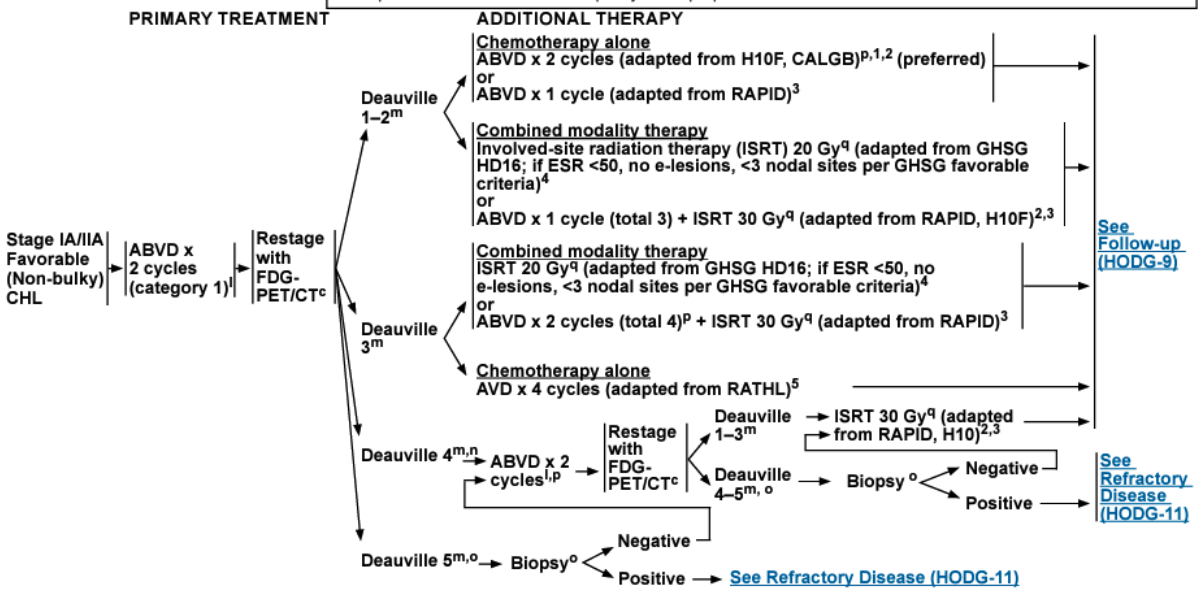
- *Disparities in outcomes of Hodgkin's Lymphoma in different socioeconomic status groups.*
- *Clinical Trial enrollment in minority populations.*

Introduction

- Hodgkin lymphoma is highly curable
    - Best chance is with initial therapy – *important not to undertreat!*
- Early stage (stage I-II) HL has an excellent prognosis (cure rate 80-95%)
- Can we decrease toxicity of therapy without compromising efficacy?
    - De-escalation of therapy?
    - Omission of radiation?
    - Incorporation of novel agents?
    - Better disease assessments?

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

Important Considerations:
- Selection of treatment (combined modality therapy or chemotherapy alone) should be based on 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 progression free survival (PFS)/freedom from progression (FFP), but no difference in overall survival.
- Most patients will benefit from multidisciplinary team input prior to final treatment decisions.



For footnotes, see HODG-3A

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

For references 1–5, see HODG-7A

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Hodgkin Lymphoma (Age ≥18 years)

NCCN Guidelines Index
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Discussion

CLINICAL PRESENTATION:
Stage I/II Unfavorable CHL[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 on 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.
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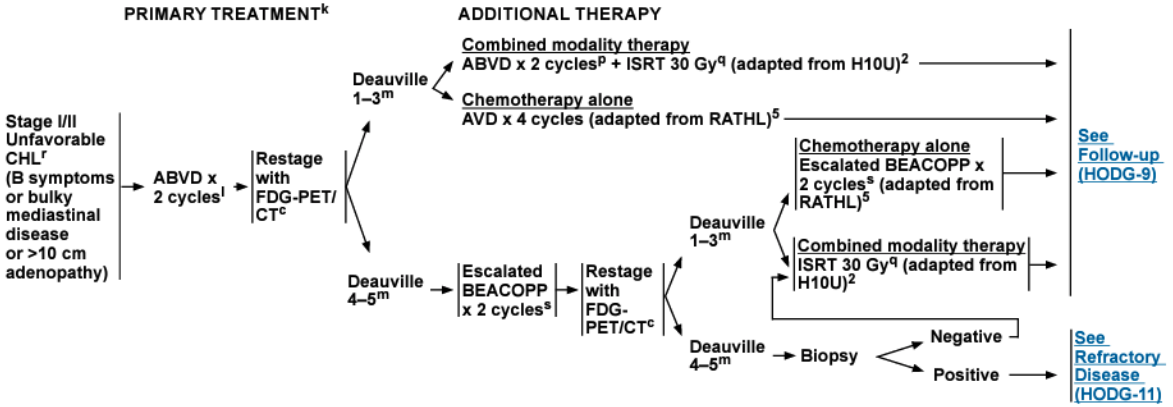

Special considerations for Deauville 4–5 after ABVD x 2 cycles:
- The degree of abnormality of a Deauville 4 score is quite variable and may influence further therapy. If only focally positive on interim FDG-PET, it may be appropriate to continue with ABVD and then repeat the FDG-PET scan. Scans that remain positive warrant a biopsy and/or treatment escalation. If a post-chemotherapy FDG-PET is only focally positive, consolidation RT may be considered, especially if a biopsy is not feasible. See Principles of Radiation Therapy (HODG-D 2 of 12).
- A Deauville 5 score would warrant a biopsy to inform subsequent therapy. If a biopsy is not feasible, treatment should be escalated.

[c] See Principles of FDG-PET/CT (HODG-A).
[k] Individualized treatment may be necessary for patients >60 years and patients with concomitant disease. See Management of CHL in Adults >60 Years (HODG-E).
[l] See Principles of Systemic Therapy (HODG-C).
[m] See FDG-PET 5-Point Scale (Deauville Criteria) (HODG-A, 2 of 2).
[p] Consider PFTs after 4 cycles of ABVD.
[q] See Principles of Radiation Therapy (HODG-D).
[r] NCCN Unfavorable Factors include bulky mediastinal or >10 cm disease, B symptoms, ESR ≥50, and >3 sites of disease (see HODG-B).
[s] Escalated BEACOPP is an option only for those aged <60 y.

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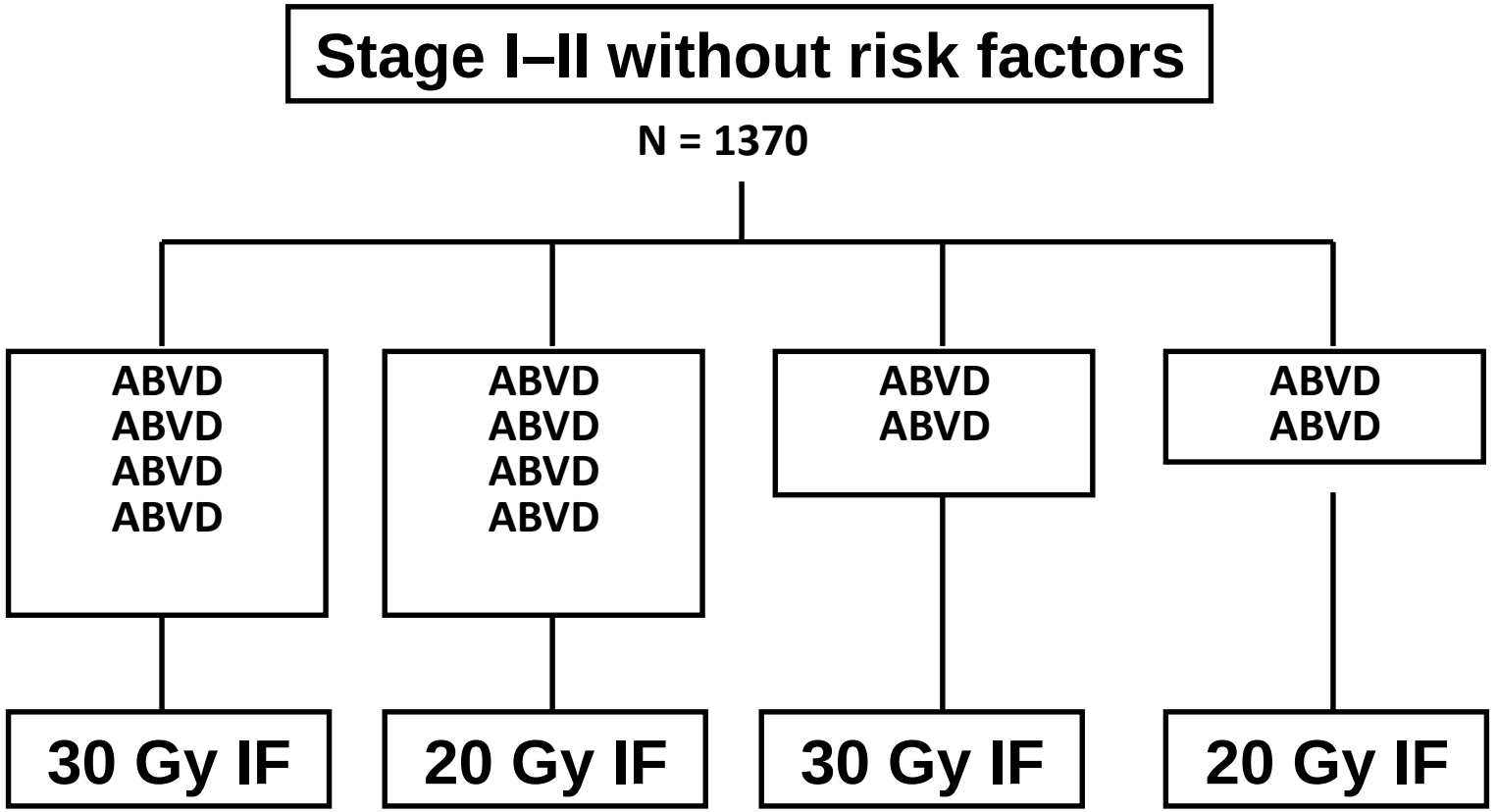
For references 2 and 5 see HODG-7A

Low-risk Disease: GHSG HD10



Engert A et al. N Engl J Med 2010

Low-risk Disease: GHSG HD10

Outcome	Treatment Group			
	Group 1: 4×ABVD + 30 Gy IFRT (N=298)	Group 2: 4×ABVD + 20 Gy IFRT (N=298)	Group 3: 2×ABVD + 30 Gy IFRT (N=295)	Group 4: 2×ABVD + 20 Gy IFRT (N=299)
Response — no. of patients (%)*				
Complete remission with or without residual radiologic abnormalities	287 (96.3)	288 (96.6)	287 (97.3)	288 (96.3)
Partial remission	2 (0.7)	2 (0.7)	3 (1.0)	1 (0.3)
No change	1 (0.3)	0	0	1 (0.3)
Progression	0	1 (0.3)	3 (1.0)	2 (0.7)
Unknown	8 (2.7)	7 (2.3)	2 (0.7)	7 (2.3)
First relapse†	15 (5.0)	16 (5.4)	21 (7.1)	19 (6.4)
Survival rate — % (95% CI)‡				
At 5 years				
Overall survival	96.9 (94.2–98.4)	97.3 (94.6–98.6)	96.6 (93.7–98.1)	96.6 (93.7–98.1)
Freedom from treatment failure	92.8 (89.1–95.3)	93.1 (89.4–95.5)	90.9 (86.8–93.8)	91.2 (87.1–94.1)
Progression-free survival	93.9 (90.3–96.2)	93.2 (89.5–95.6)	90.8 (86.7–93.7)	91.6 (87.6–94.4)
At 8 years				
Overall survival	94.4 (90.2–96.8)	94.7 (90.9–97.0)	93.6 (89.6–96.1)	95.1 (91.7–97.2)
Freedom from treatment failure	87.2 (81.3–91.4)	89.9 (85.2–93.1)	85.5 (79.5–89.8)	85.9 (80.2–90.1)
Progression-free survival	88.4 (82.6–92.4)	90.0 (85.4–93.2)	85.4 (79.4–89.8)	86.5 (80.9–90.6)

Omitting radiation - RAPID

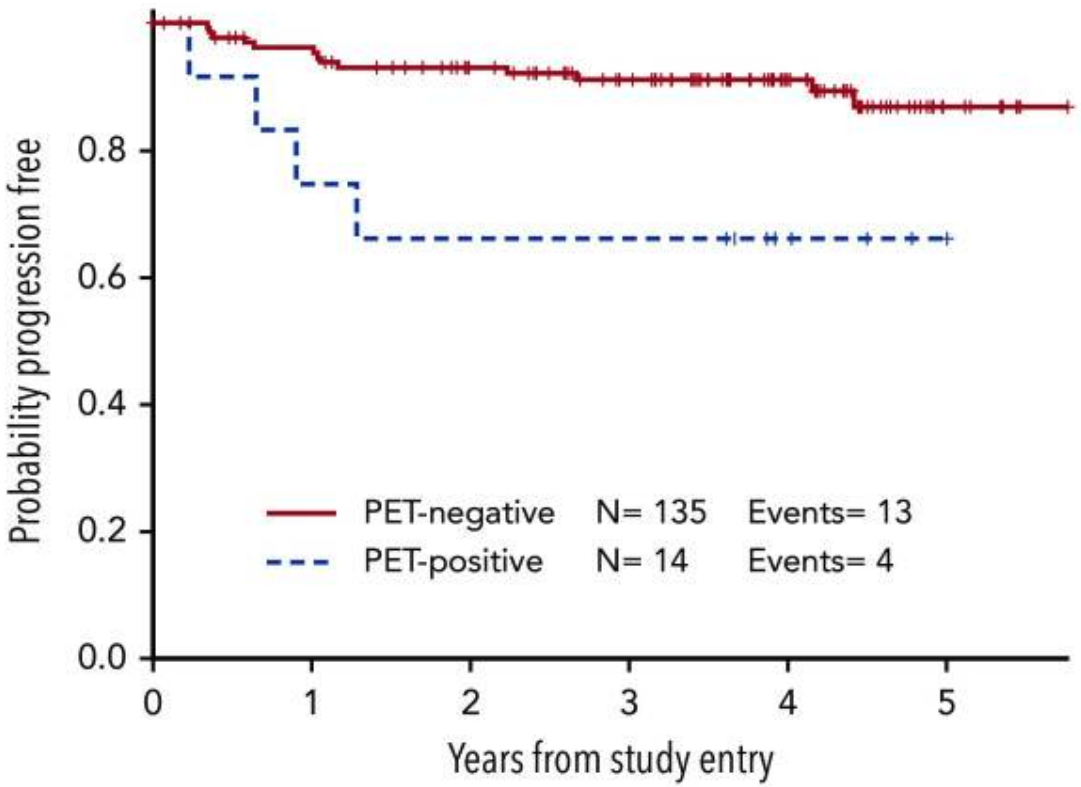
UK study – ABVD x 3 for non-bulky stage IA/IIA HL followed by PET (n=602)

- PET3 negative (defined as Deauville 1 or 2) – randomized to IFRT vs. no tx
- 3y PFS 94.6 vs 90.8% for patients with negative PET3
- **Did not meet non-inferiority threshold, but 3y PFS not statistically different (94.6 vs. 90.8%)**

CALGB 50604

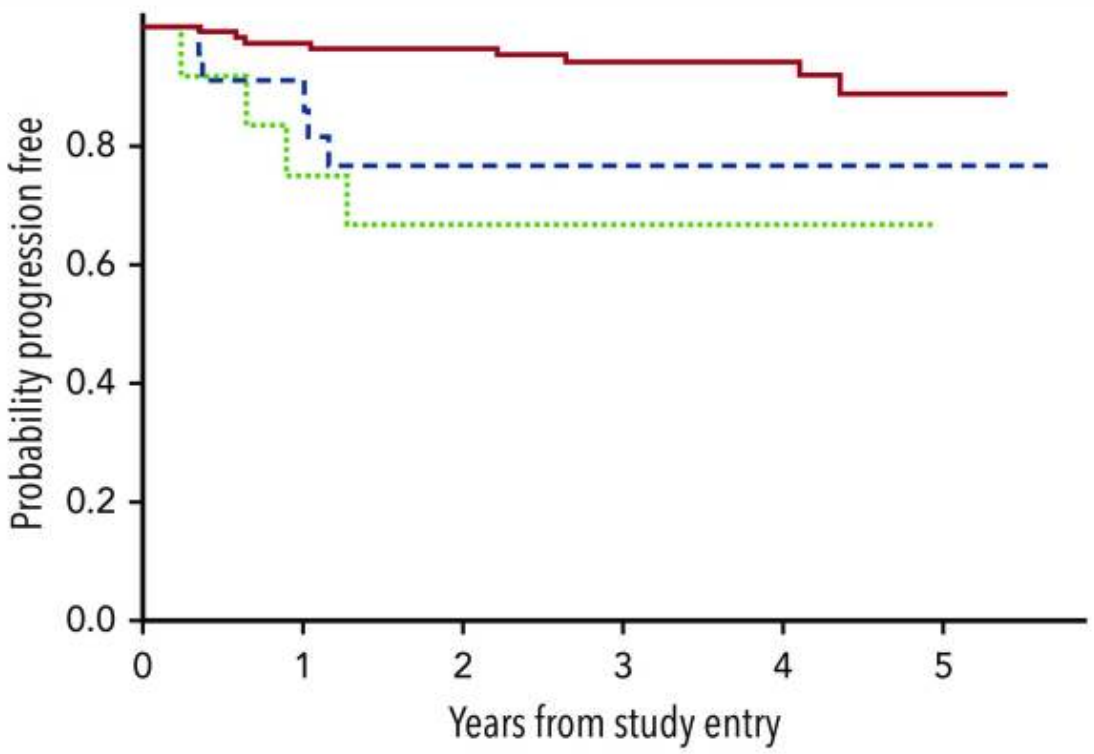
- US trial – ABVD x 4 (PET-adapted) for stage I/II non-bulky HL (n=149)
- ABVD x 2→ PET/CT (PET2)
    - DS 1-3 -> ABVD x 2 (total 4)
    - Otherwise eBEACOPP x 2 + 30.6 Gy IFRT
- **3y PFS 91% for PET2-negative patients**

CALGB 50604 Results



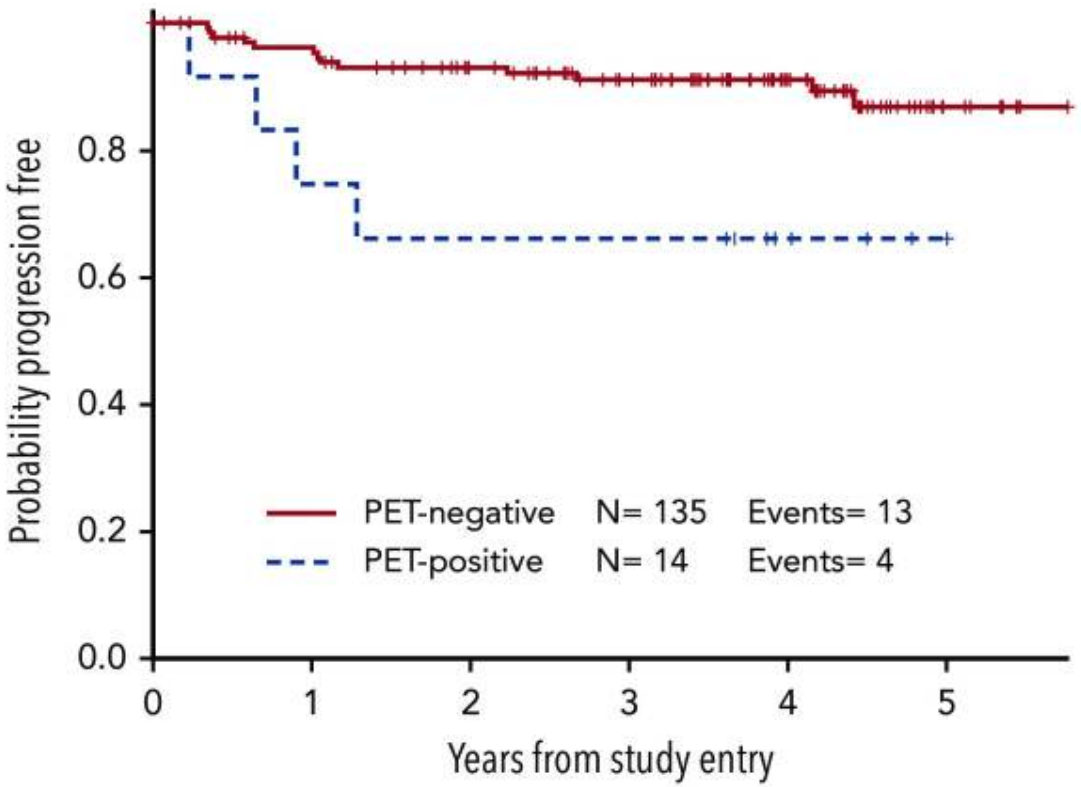
	1-year	2-year	3-year
PET-negative	.96 (.91-.98)	.93 (.87-.96)	.91 (.84-.95)
PET-positive	.75 (.41-.91)	.67 (.34-.86)	.67 (.34-.86)

*95% CI in parenthesis



PET Grade	N	Events	3-year PFS (95% CI)
1-2	113	8	.94 (.87-.97)
3	22	5	.77 (.52-.90)
4-5	14	4	.67 (.34-.86)

CALGB 50604 Results



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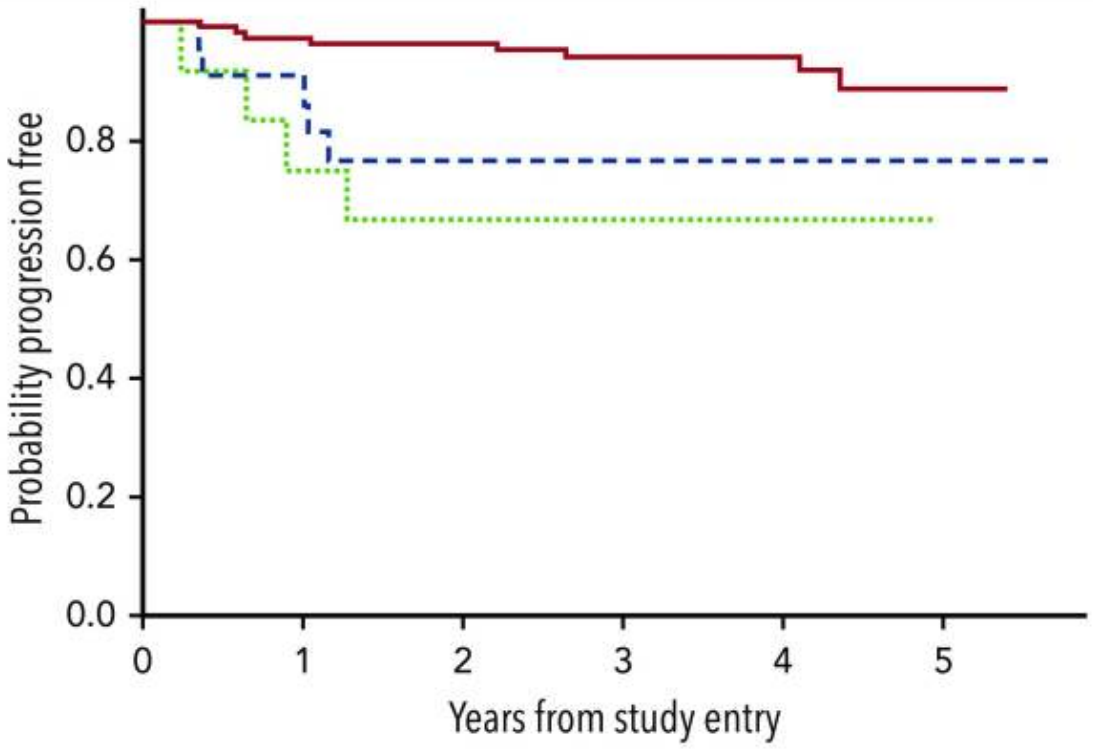

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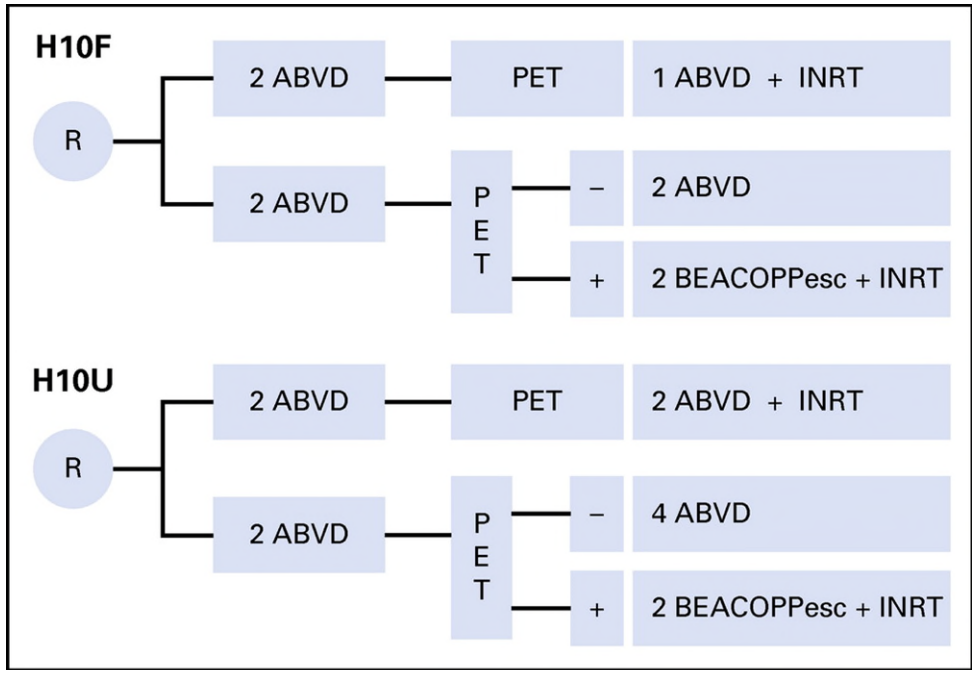
EORTC/LYSA/FIL H10

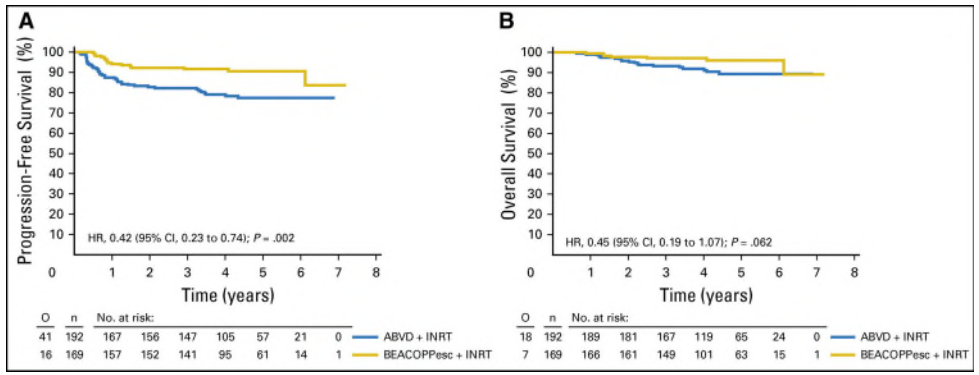
European trial of ABVD followed by PET-adapted tx

- PET2+ (DS 3+) randomized to eBEACOPP + INRT vs. ABVD + INRT
- PET2- randomized to ABVD alone vs. ABVD + INRT
- In both – favorable pts had less ABVD post PET2
  - Pts getting no radiation had ABVD x 4 total vs. ABVD x 6 total
  - PET-negative patients getting radiation got ABVD x 3 -> INRT vs. ABVD x 4 -> INRT

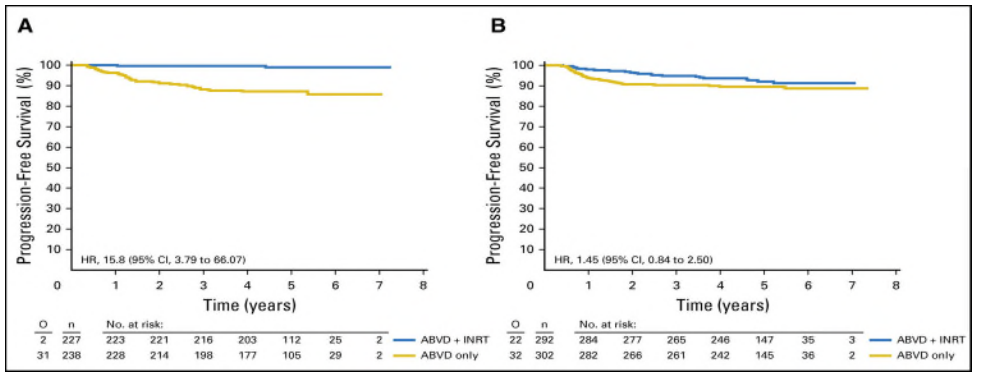


EORTC/LYSA/FIL HD10

PET2+ cohort:



PET2- cohort:



5y PFS:

PET2+: 77.4% with ABVD + INRT, 90.6% with eBEACOPP + INRT

PET2-: 99% with ABVD + INRT, 87.1% with ABVD alone (favorable)

92.1% with ABVD + INRT, 89.6% with ABVD alone (unfavorable)

GHSG HD17

- eBEACOPP x 2 + ABVD x 2 followed by IFRT vs no XRT (n=1100)
    - Half of patients randomized to IFRT
    - In other half, IFRT given only for PET4+
- 5y PFS 97.7% (IFRT) vs. 95.9%
    - 5y PFS 96% for bulky disease with PET4-adapted approach!

Relatively little use of eBEACOPP in U.S. but data are very compelling.

RATHL

PET-adapted randomized trial for stage II-IV HL to test de-escalation of bleomycin in patients with an interim negative PET2 with ABVD (n=1203)

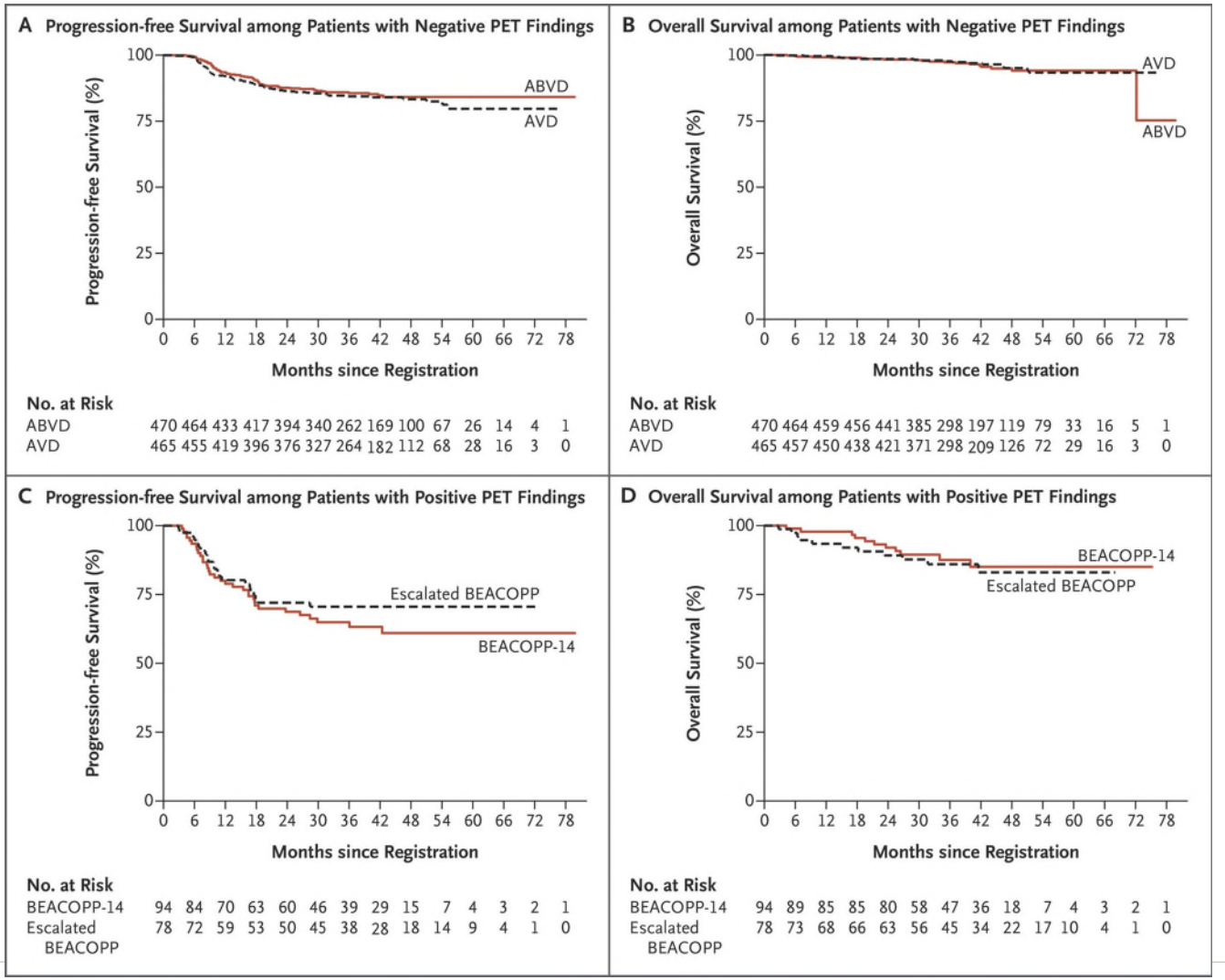
- 42% stage II

ABVD x 2 -> PET/CT scan

- DS 1-3: randomized to ABVD x 4 (total 6) vs. AVD x 4 (no bleomycin)
- DS 4-5: eBEACOPP vs BEACOPP14

RATHL Outcomes

- For PET2-negative pts:
  - 3y PFS 85.7% vs. 84.4% (ABVD vs. ABVD->AVD)
- **3y PFS 90% for PET2-negative stage II patients**



Novel Agents for 1L Early Stage HL

BV (and soon to be nivo) are widely used for 1L stage III-IV HL

Yet 1L tx for stage I-II HL largely built around ABVD +/- IFRT

- What about incorporating these?

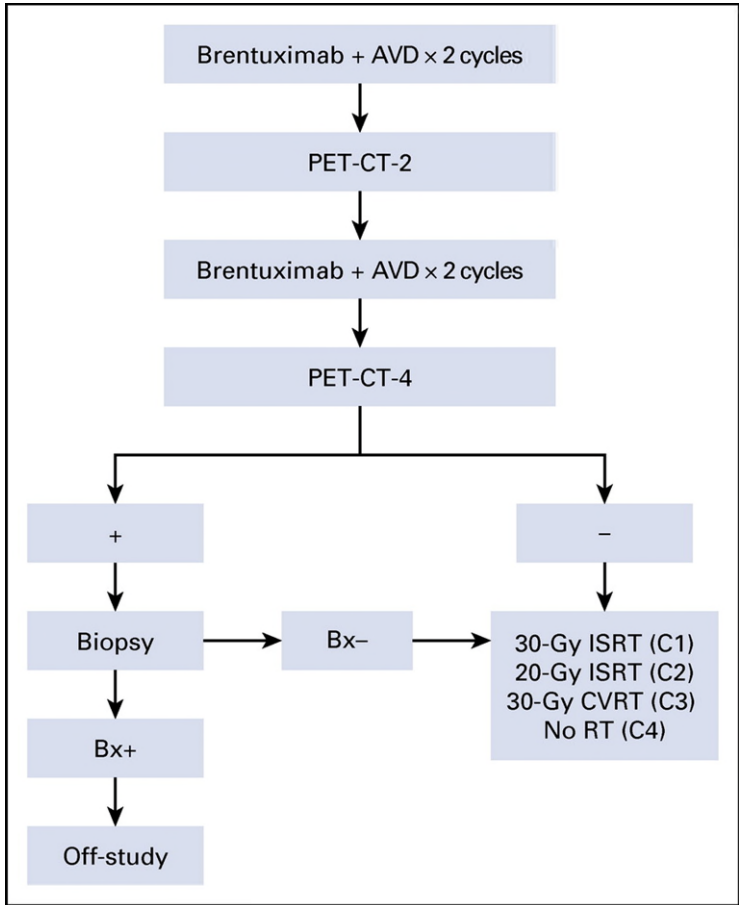
MSKCC Early Stage Trial

Early stage unfavorable HL (n=117)

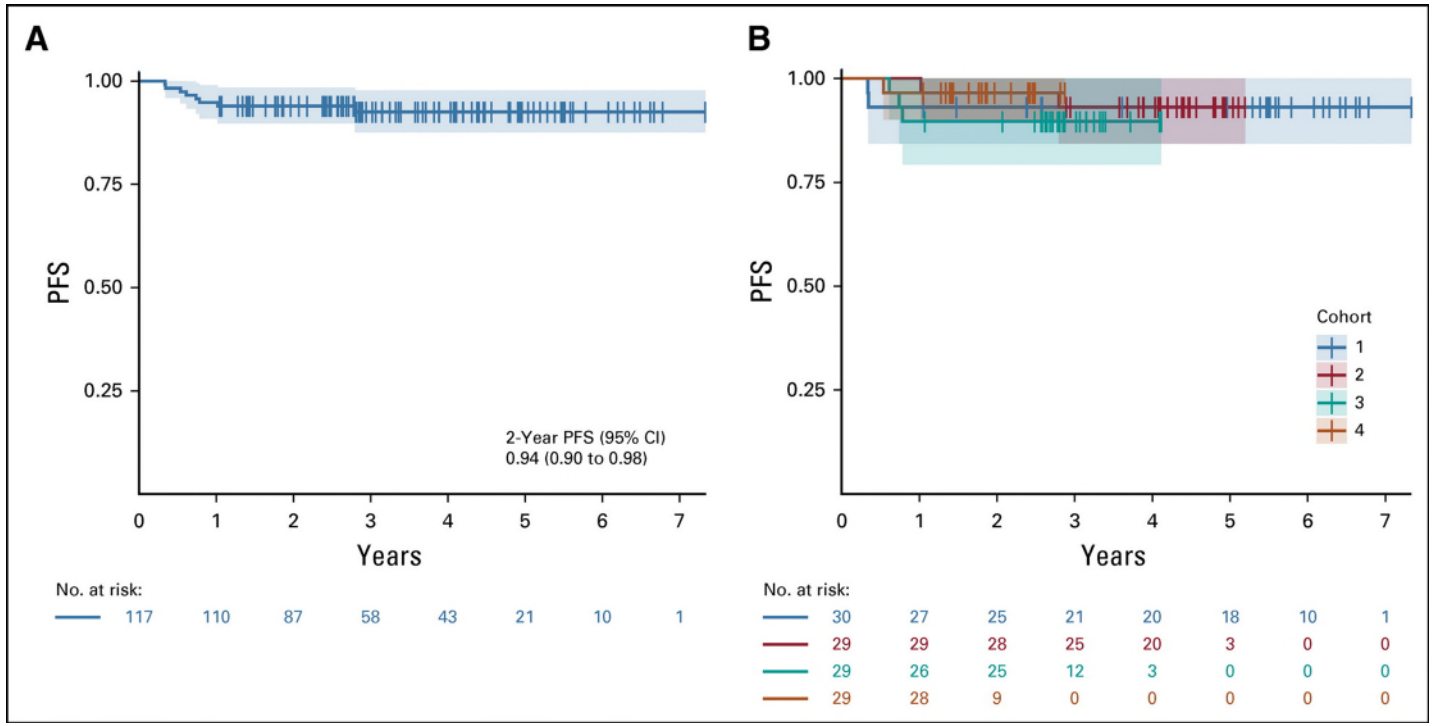
BV + AVD x 4 cycles.

Pts in CR after 4 cycles were randomized to one of following:

- 30 Gy ISRT, 20 Gy ISRT, 30 Gy consolidation-volume RT, no RT
- ***2y PFS 96.6% in cohort 4 (no RT), 4y PFS 93% in cohort 4 at 4y f/u***



MSKCC Early Stage Trial



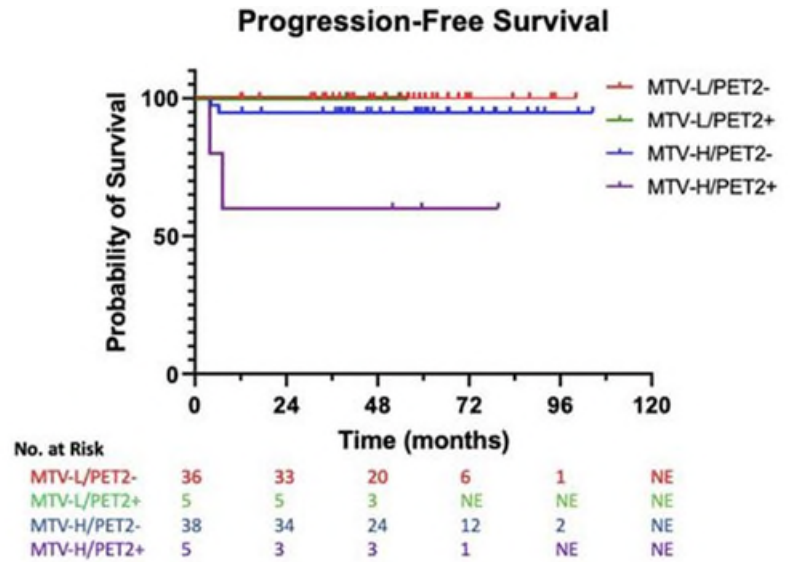


Figure 1. Progression-Free Survival by MTV and PET2 Results. Kaplan-Meier estimates of progression-free survival by baseline metabolic tumor volume (MTV) in combination with PET2 results on a 5-point scale. High MTV was considered volume > 150 cm^3. Positive PET2 was considered Deauville score ≥ 4. MTV-L and MTV-H refer to low and high MTV respectively. PET2+ and PET2- refer to positive and negative PET2, respectively. Note that the MTV-L/PET2+ curve (green) overlaps the MTV-L/PET2- curve (red).

ACCRU-LY1601

- Early stage non-bulky HL
- BV + AVD x 3
    - PET-negative -> nivo x 8
    - PET-positive -> BV + nivo x 4 -> nivo x 8
- N=83, 97% PET/CR after BV-AVD x 3.
- PFS 100% @ 22m!

NIVAHL

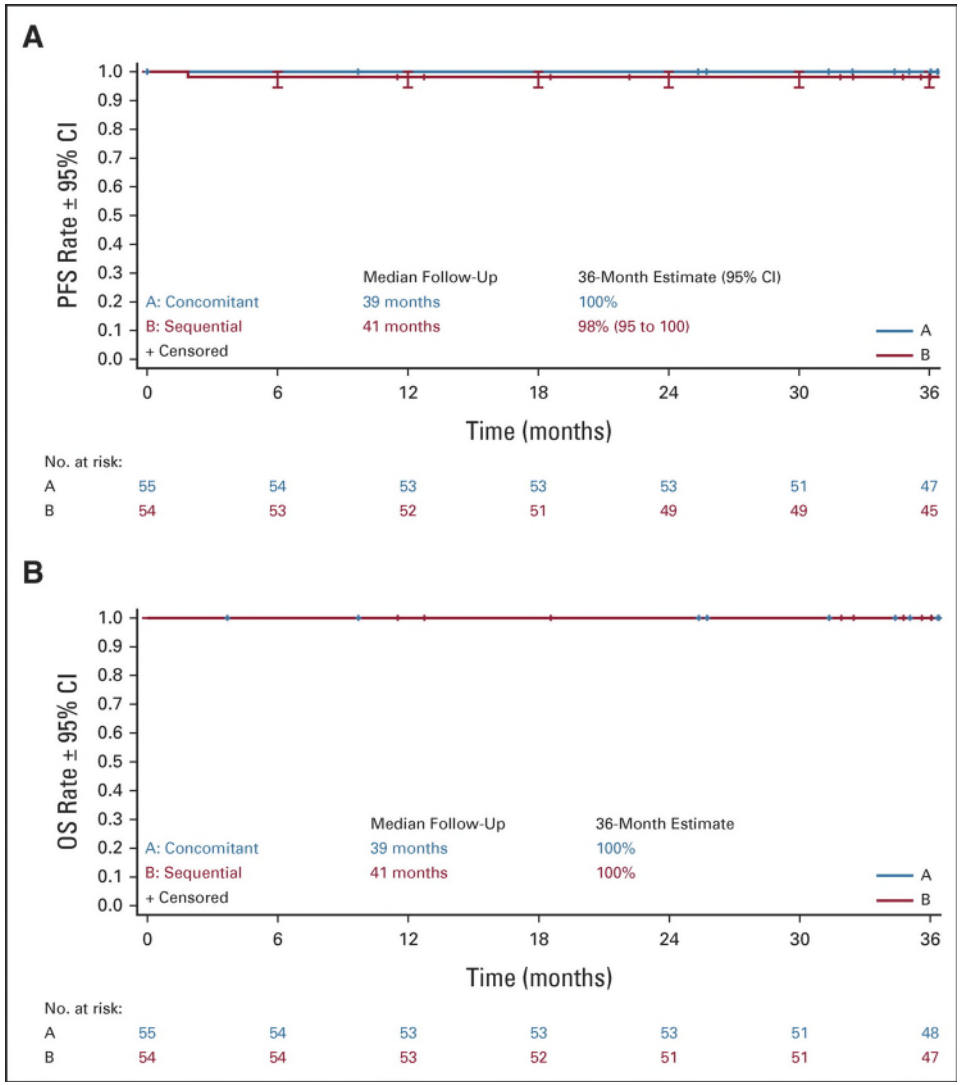
Early stage, unfavorable HL, up to age 60

- N=109, 58% with bulky (5 cm+) disease

Nivo-AVD X 4 -> IFRT 30 Gy

3y PFS 99%, 3y OS 100% (one pt progressed)

- Hypothyroidism in 21%



Clinical Trial Enrollment

- Advances only possible through trials
- Demographic / geographic under-representation still in hematology trials (Casey M, et al. JCO 2022)
- HL has led the way
  - 10.1% non-Hispanic black, 20.3% Hispanic enrollment on AHOD1331 (Castellino SM, et al, NEJM 2022)
  - 25% minority enrollment on SWOG S1826 (nivo-AVD vs. BV-AVD for stage III-IV dz – 994 pts, Herrera AF, et al ASCO 2023)
- Still more work to be done
  - SES predictive of outcomes (Berkman A, et al. Cancer Epidemiol Biomarkers Prev 2019)
  - Efficacy (EFS) in pts treated on trial appear to be comparable but adjust OS worse in HL pts treated on COG trials (Kahn JM, et al, JCO 2019) -- driven by post-relapse mortality

Conclusion

Omission of radiation results in increased relapse with ABVD alone

- **ABVD x 3 or x 4 without IFRT cures probably slightly less than 90%, ? Slightly higher with RATHL (6 cycles)**
- **Individualized decision whether to avoid radiation or not – NNT ~15-30 to prevent one relapse**

Novel therapies (BV, nivo) appear to be very effective but have not become standard yet