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Five-year results of short-course brentuximab vedotin combined with chemotherapy and radiation in early stage, unfavorable Hodgkin lymphoma

RUNNING HEAD: Five-Year Results of BV-AVD in Early Stage, Unfavorable Hodgkin Lymphoma

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To the Editor:

The standard of care in the treatment of patients with newly-diagnosed, early stage (ES), unfavorable risk (UF) Hodgkin lymphoma (HL) is combined modality therapy (CMT) with chemotherapy and radiation (RT) or full-course chemotherapy.¹⁻³ While the majority of patients with ES UF HL can be cured upfront, 10-15% still relapse. In addition, balancing efficacy with late toxicities, including cardiovascular disease (CVD) and secondary malignancies (SMs), is critical.⁴⁻⁶ To increase curability and minimize treatment exposure in ES UF HL, we conducted an investigator-initiated trial of short-course brentuximab vedotin (BV) with doxorubicin, vinblastine, and dacarbazine (AVD) followed by four consolidative RT approaches with de-escalating dose and field.⁷ We hypothesized that the inclusion of BV would enhance the efficacy of initial chemotherapy and facilitate the reduction of full-course chemotherapy and RT exposure. This treatment program resulted in a 96% end of treatment complete response (CR) rate and 2-year progression-free (PFS) and overall survival (OS) rates of 94% and 99%, respectively.⁷ We now present final five-year survival and evaluate baseline metabolic tumor volume (MTV) and interim positron emission tomography/computed tomography (PET/CT) as prognostic factors.

Study design and eligibility were previously described.⁷ The study was approved by the institutional review board (IRB) at each participating institution and registered at clinicaltrials.gov as NCT01868451. Patients aged 18-60 years with untreated, stage I/II HL were enrolled in four sequential cohorts. In cohort 1, eligible patients had any of the following UF risk factors: bulky mediastinal mass ($>1/3$ mediastinal mass ratio on posterior-anterior chest X-ray or ≥ 10 cm by CT imaging in transaxial plane), erythrocyte sedimentation rate (ESR) ≥ 50 mm/h or ESR ≥ 30 mm/h in patients with B symptoms, extranodal involvement, >2 lymph node sites (as defined by German

Hodgkin Study Group), or infradiaphragmatic disease. In cohort 2, the same criteria were applied, except that disease bulk was updated to reflect the externally validated Memorial Sloan Kettering (MSK) bulk definition,⁸ namely a lymph node mass at any site with a maximal transverse or coronal diameter >7 cm. In cohorts 3 and 4, all patients were required to have bulk by MSK criteria. All patients received four cycles of BV-AVD. PET scans were performed at baseline and after two and four cycles, with scans interpreted using the 5-point scale, with a Deauville score of 1, 2, or 3 considered negative. Patients with biopsy-proven PET-4–positive disease were removed from the study. Depending on the cohort, patients received one of four RT strategies (30-Gy involved site RT [ISRT] in cohort 1, 20-Gy ISRT in cohort 2, 30-Gy consolidation-volume radiotherapy [CVRT] in cohort 3, and no RT in cohort 4).

The primary outcome of this report is five-year PFS and OS. Stratification by baseline MTV and interim PET-2 scan was performed. Baseline MTV was measured using the 41% maximum standard uptake value method in 84 patients with available imaging for MTV calculations. For MTV and PET-2 estimates, given the small sample size and few number of events, five-year time to progression (TTP) was also estimated. The study was not powered to compare each cohort, and differences between cohorts are exploratory and hypothesis-generating.

From 2013 to 2019, one-hundred seventeen patients enrolled. Median age was 32 years, 98% of patients had stage II disease, and 86% had disease bulk by MSK criteria. Additional characteristics are shown in **Table 1**. Across all cohorts, 99% (116 of 117) completed the planned four cycles of BV-AVD, with one patient coming off study after one cycle due to grade 3 hypertension and peripheral neuropathy. In the cohorts with planned RT (cohorts 1-3), 94% (82 of 87) received the

planned RT. Among the five patients who did not, two refused, two had biopsy-confirmed primary refractory disease, and one received proton-beam RT off study.

After a median follow-up of 5.5 years (interquartile range, 4.9–7.1), the five-year PFS (**Figure 1A**) and OS were 92% (95% CI, 0.87–0.97) and 98% (95% CI, 0.96–1.00), respectively. For cohorts 1-4, the five-year PFS was 93% (95% CI, 0.84-1.00) for cohort 1 (30-Gy ISRT), 93% (95% CI, 0.84-1.00) for cohort 2 (20-Gy ISRT), 90% (95% CI, 0.79-1.00) for cohort 3 (30-Gy CVRT), and 93% (95% CI, 0.84-1.00) for cohort 4 (no RT) (**Figure 1B**). Most progression events (6 of 9) were refractory disease within nine months of treatment initiation at the initial site of disease. Of the other three events, there were two relapses within three years and one late relapse at 6.5 years. The late relapse was at distant sites to the original site of disease (below the diaphragm). For cohorts 1-4, the five-year OS was 100%, 97% (95% CI, 0.89-1.0), 96% (95% CI, 0.87-1.00), and 100%, respectively. There were two deaths. One patient with relapsed HL who received allogeneic transplant died of transplant- and disease-related factors. The second patient died of a car accident in remission.

Stratifying patients by the median MTV of 150 cm³, the five-year PFS/TTP for high MTV was 91%/91% versus 98%/100% for low MTV (P=0.2 for TTP). Stratifying patients by interim PET-2, the five-year PFS/TTP for PET-2–positive disease was 79%/79% versus 94%/95% for PET-2–negative disease (P=0.04 for TTP). To evaluate baseline MTV in conjunction with interim PET-2 scan, we formed four treatment groups: (1) MTV-low/PET-2–negative, (2) MTV-low/PET-2–positive, (3) MTV-high/PET-2–negative, and (4) MTV-high/PET-2–positive. The five-year

PFS/TTP for each group was 97%/100%, 100%/100%, 95%/95% and 60%/60%, ($P=0.01$ for TTP) (Figure 2).

Despite tremendous advancements in treating HL, 10-15% of patients still relapse. Management of ES UF disease remains particularly challenging, as patients often have bulky disease in need of urgent treatment, and disease often overlies key organs at risk for late toxicities from RT. While CMT produces the highest tumor control rates for ES UF HL, it has not demonstrated improved survival over chemotherapy-alone regimens, and late effects of CMT, in particular CVD and SMs, remain significant contributors to morbidity and mortality in survivors.^{5,9} Still, chemotherapy alone, especially with increasing cumulative exposure, is an independent risk factor for CVD and SMs.^{4,5,9} Therefore, trials that limit both RT and chemotherapy exposure yet maintain high disease cure rates are pivotal moving forward. Our trial attempts this balance of efficacy and late toxic effects.

For ES UF disease, multiple treatment paradigms have been described.^{1-3,10-12} Long-term followup of the H10U trial, which employed a PET-adapted CMT approach, demonstrated a 10-year PFS of 91.4% in the standard CMT arm.¹ Similarly, long-term followup of patients with stage II disease in the RATHL trial, which allowed stage IIB or IIA with adverse features, demonstrated a seven-year PFS of 84.7% using a PET-adapted full-course chemotherapy approach.¹³ Several more recent trials have also focused on ES UF disease. These include CALGB 50801, a full-course ABVD chemotherapy, PET-adapted approach omitting RT in patients with PET-2 negative disease,¹⁰ the BREACH trial, which used four cycles of BV-AVD and 30-Gy ISRT,¹¹ and the NIVAHL trial, which used four cycles of nivolumab-AVD and 30-Gy ISRT.¹² Inclusion criteria differ slightly for

each of these trials, making comparisons challenging (NIVAHL notably excluded patients with stage IIB and a large mediastinal mass and/or extranodal disease). In addition, these trials, like ours, are relatively small with shorter follow up compared to the much larger RATHL and H10 trials, each of which enrolled over 500 patients and have nearly 10 years of follow up. Still, despite these caveats, each reported impressive response rates and PFS estimates. Notably, all of the above trials include either full course chemotherapy or abbreviated treatment with radiation.

The results from our study are comparable to prior studies for ES UF HL, with five-year PFS for all patients of 92%. Furthermore, cohort 4 in our trial utilized four cycles of BV-AVD *without* RT and still demonstrated a 5-year PFS of 93%. This data is hypothesis-generating and paves the way for larger studies of abbreviated chemotherapy-only approaches with more potent agents, such as BV and anti-PD-1 therapy, to enhance the efficacy of initial systemic therapy and reduce the need for full course treatment and/or RT.

In addition to long-term efficacy, we show the prognostic importance of baseline MTV and interim PET-2. Baseline MTV has previously been shown to prognosticate patients treated in the H10 trial and BREACH trials.^{11,14} In our trial, when baseline MTV is combined with interim PET-2 score, we identify a high-risk group of patients with suboptimal outcomes. Specifically, patients with high MTV and PET-2–positive disease had five-year PFS/TTP of just 60%, clearly inferior to other groups. These results align with prior findings. For example, among all patients in the BREACH trial, two-year PFS was 100% for those with low MTV versus 84.9% for those with high MTV. Similarly, among patients treated on the standard arm in HD10, patients with low MTV/PET-2–negative disease had five-year PFS of 95% versus just 25% for those with high MTV/PET-2–

positive disease. Based on these and our findings, we designed an MTV- and PET-adapted protocol using short-course BV-AVD in patients with ES bulky HL, which is enrolling patients (NCT063377566). In this trial, all patients receive two cycles of BV-AVD followed by a PET scan. Patients with negative interim PET (Deauville 1-3) receive two additional cycles without RT. Patients with positive interim PET (Deauville 4-5) are stratified by baseline MTV using the SUV-4 method—patients with low MTV receive two additional cycles and RT, whereas those with high MTV are transitioned to pembrolizumab-based salvage chemotherapy¹⁵ and RT, recognizing that these patients (high MTV/PET-2–positive disease) are those with suboptimal outcomes and may benefit from early introduction of anti-PD1 therapy.

Our study has important limitations. Each cohort was small and the study was not powered to evaluate differences between each other, limiting the ability to provide firm conclusions regarding short-course BV-AVD without RT. In addition, baseline MTV was not available in all patients, limiting a full analysis. Finally, late effects of treatment require even longer followup and are not measured within this study.

In summary, short-course BV-AVD is highly active in ES UF HL. Baseline MTV and interim PET identify low- and high-risk patients and support prospective testing of MTV- and PET-adapted treatment paradigms.

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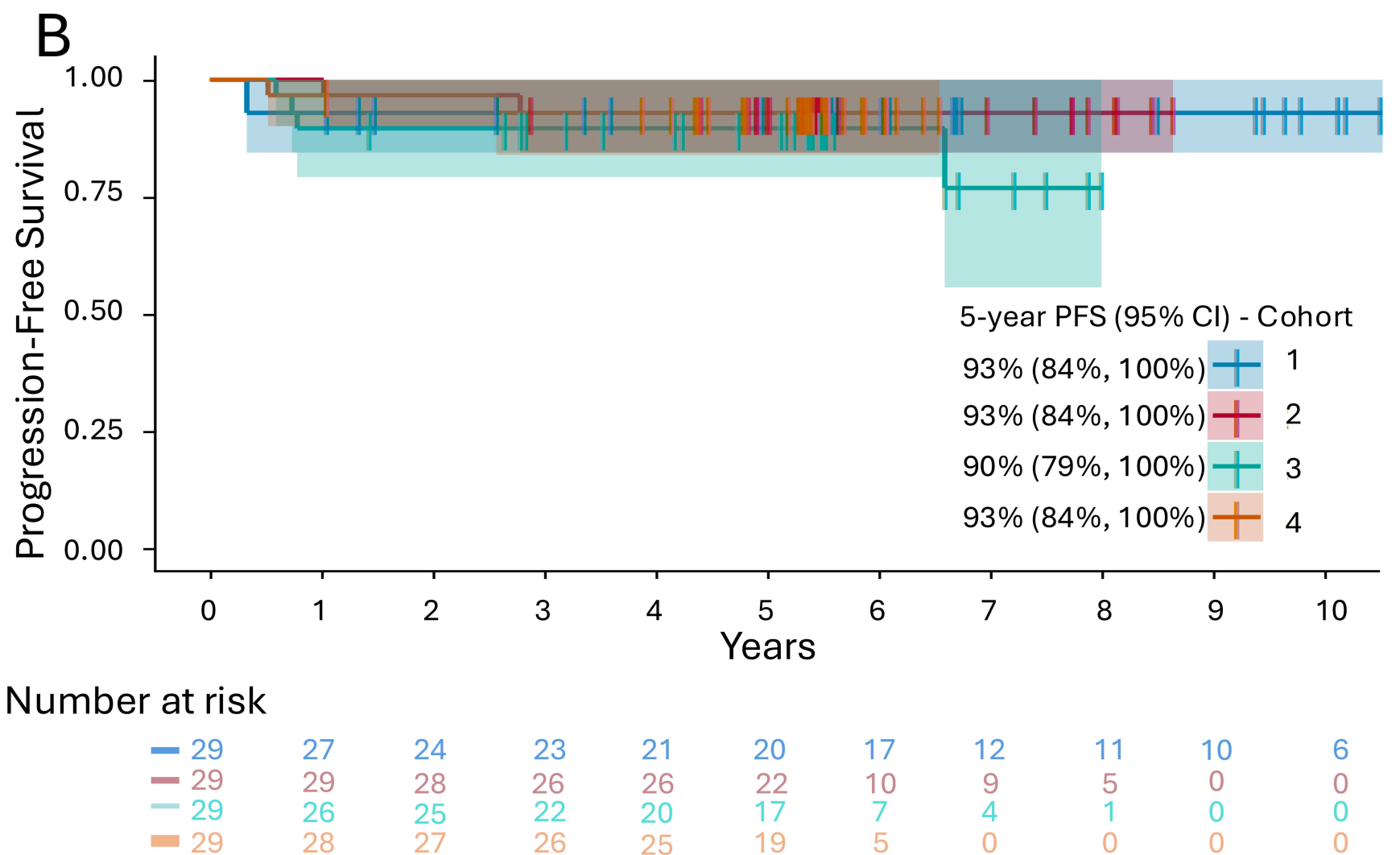
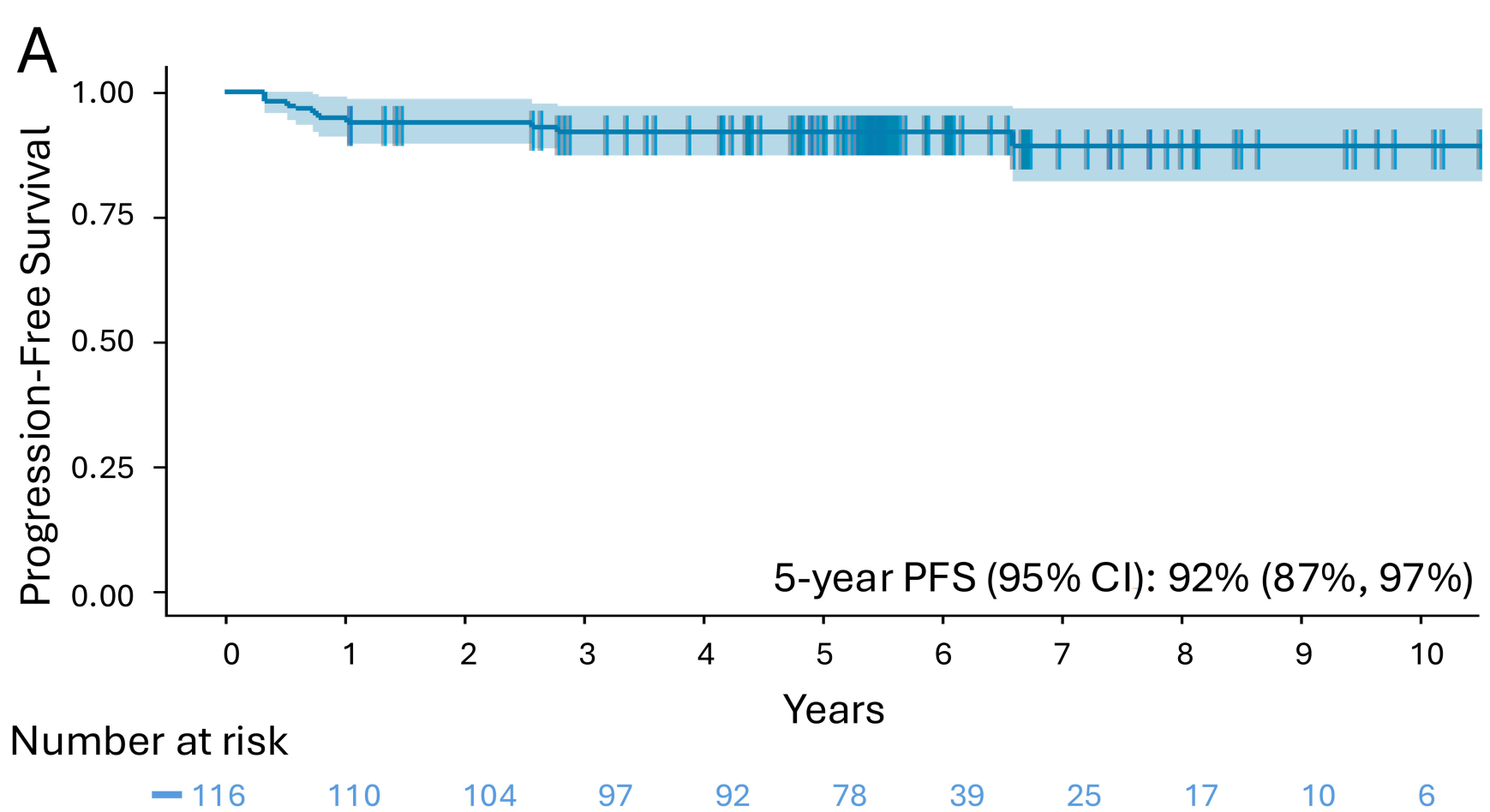
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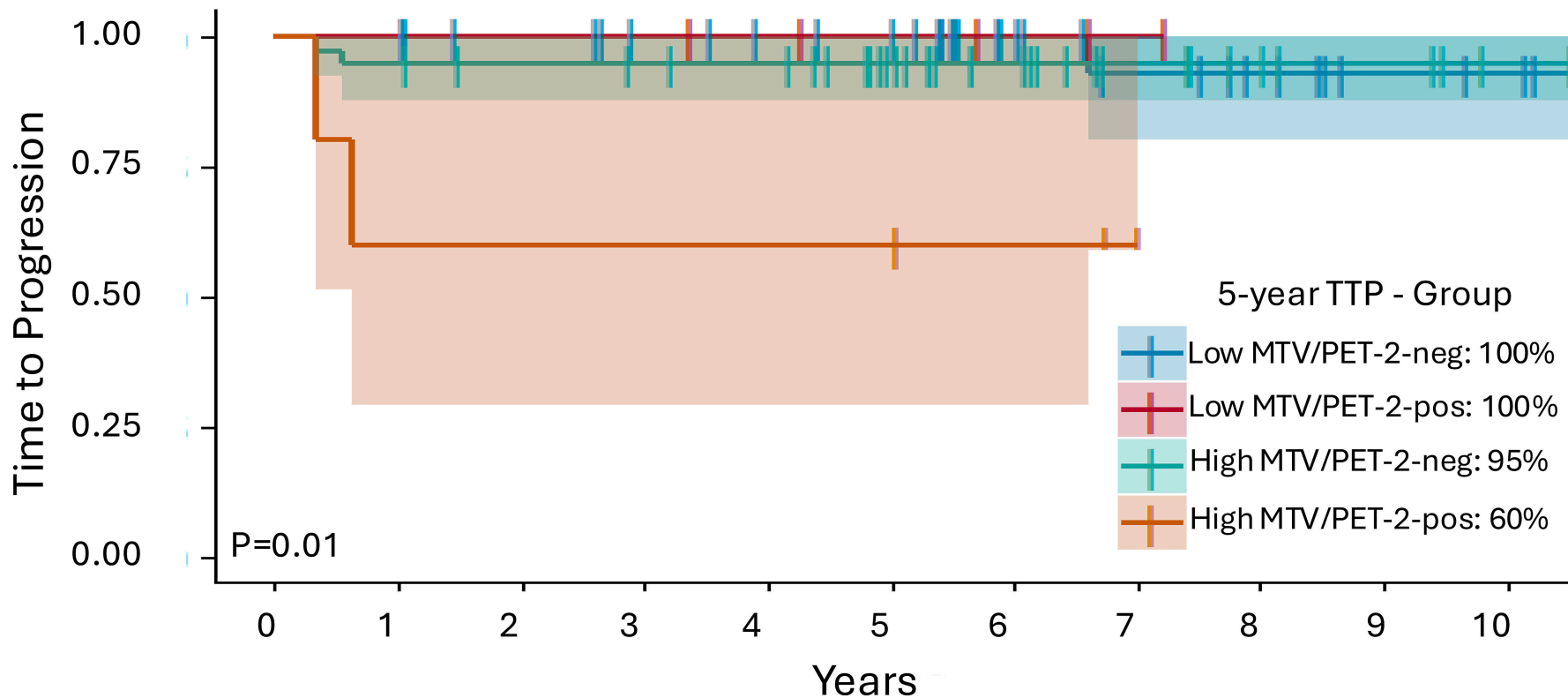
Table 1. Patient Characteristics at Baseline.

Characteristic	Cohort 1, No. (%)	Cohort 2, No. (%)	Cohort 3, No. (%)	Cohort 4, No. (%)	Total, No. (%)
No. of patients	30	29	29	29	117
Age, years, median (range)	31 (18-59)	33 (19-55)	31 (20-58)	30 (20-58)	32 (18-59)
Male	16 (53)	17 (59)	15 (52)	11 (38)	59 (50)
CD30+ HL	30 (100)	29 (100)	28 (97)	28 (97)	115 (98)
CD20+ HL	4 (13)	3 (10)	8 (28)	1 (3)	16 (14)
Stage II	30 (100)	29 (100)	28 (97)	28 (97)	115 (98)
Unfavorable risk factors					
Disease bulk by MSK definition	23 (77)	20 (69)	29 (100)	29 (100)	101 (86)
Disease bulk by traditional CT criteria	12 (40)	9 (31)	6 (21)	7 (24)	32 (27)
Elevated ESR	20 (67)	12 (41)	12 (41)	17 (59)	61 (52)
B symptoms	15 (50)	11 (38)	8 (28)	12 (41)	46 (39)
Extranodal involvement	9 (30)	6 (21)	4 (14)	5 (17)	24 (21)
Nodal sites > 2	13 (43)	21 (72)	10 (34)	22 (76)	66 (56)
Infradiaphragmatic site	1 (3)	1 (3)	1 (3)	1 (3)	4 (3.4)
Anterior mediastinal mass bulk (> 7 cm), cm, median transverse size (range)	12.9 (7.7-16.9)	10.0 (7.2-17.3)	8.7 (7.2-17.5)	9.0 (7.2-16.5)	9.95 (7.2-17.5)
Advanced stage by GHSG criteria	12 (40)	9 (31)	1 (3)	5 (17)	27 (23)
IIBX	6 (20)	7 (24)	0 (0)	3 (10)	16 (14)
IIBE	4 (13)	0 (0)	0 (0)	1 (3)	5 (4)
IIBXE	2 (7)	2 (7)	1 (3)	1 (3)	6 (5)

Figure 1. Progression-free survival of the entire trial (A) and for each treatment cohort (B). All treatment cohorts received BV-AVD x 4 cycles followed by one of our radiation strategies if PET-negative: 30-Gy involved site RT (ISRT) in cohort 1, 20-Gy ISRT in cohort 2, 30-Gy consolidation-volume radiotherapy (CVRT) in cohort 3, and no radiation in cohort 4. The study was not powered to compare radiation strategies.

Figure 2. Time-to-progression estimates among patients based on baseline metabolic tumor volume (MTV) and interim PET scan after 2 cycles of BV-AVD. MTV was measured using the 41% maximum standard uptake value method. The median MTV was 150 cm³, with high or low MTV classified as above or below this value, respectively. All PET scans were interpreted using the 5-point Deauville scale, with a Deauville score of 1, 2, or 3 considered negative. Differences between groups were compared with the log-rank test.





Number at risk

36	36	33	30	28	27	17	12	8	4	3
5	5	5	5	4	3	2	1	0	0	0
38	36	34	33	32	25	18	12	9	6	3
5	8	3	3	3	3	2	0	0	0	0