



## Nivolumab with doxorubicin, vinblastine, and dacarbazine in older adults with classic Hodgkin lymphoma: do S1826 results hold up in the real world?

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**Nivolumab with doxorubicin, vinblastine, and dacarbazine in older adults with classic Hodgkin lymphoma: do S1826 results hold up in the real world?**

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**Running head:** NAVD in OA with cHL

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**Abstract**

Older adults (OA,  $\geq 60$  years) with classic Hodgkin lymphoma (cHL) have historically experienced inferior outcomes compared to younger patients. Nivolumab in combination with doxorubicin, vinblastine, and dacarbazine (NAVD) has demonstrated high efficacy in clinical trials, but real-world data in OA are limited. We conducted a multicenter retrospective study across 20 centers in patients with newly diagnosed advanced stage cHL treated with NAVD and analyzed outcomes in OA across the aging spectrum. Among 327 total patients, 81 (25%) were  $\geq 60$  years, with most OA presenting with stage IV disease (58%) and B symptoms (57%). Any-grade and  $\geq$ grade 3 AEs occurred in 88% and 67% of OA, respectively. Prophylactic growth factors were used in most OA (82%) which led to low rates of febrile neutropenia (12%) and infection (12%) despite 52%  $\geq$ grade 3 neutropenia. Immune-related AEs occurred in 29% (12%  $\geq$ grade 3) and treatment was discontinued due to toxicity in 10% of OA. Interim overall (ORR) and complete response rates (CRR) were 100% and 81.6%, end-of-treatment rates were 88% and 82.6%, respectively. At a median follow-up of 12.6 months, 1-year progression-free survival (PFS) and overall survival (OS) in OA were 91.5% and 98.6%, respectively. OS was inferior in OA compared with patients  $< 60$  years, with a trend towards inferior PFS. These findings demonstrate that in OA eligible for anthracycline based therapy, NAVD is highly effective with manageable toxicity. Results are largely comparable to clinical trials, supporting NAVD as a preferred frontline regimen in routine practice.

**Keywords:** Hodgkin lymphoma, nivolumab, checkpoint inhibitor therapy, elderly, frontline therapy

## Introduction

Older adults (OA) defined as those aged 60 years or older comprise approximately a quarter of newly diagnosed cases of classic Hodgkin lymphoma (cHL)<sup>1,2</sup>. Outcomes for OA with cHL are historically inferior to those of younger patients, particularly in advanced disease<sup>1-5</sup>.

Comorbidities, treatment-related toxicity, and disease biology uniquely affect treatment tolerability and outcomes in this population.<sup>3,6</sup> The incorporation of targeted agents such as brentuximab vedotin (BV) and checkpoint inhibitors such as nivolumab into frontline treatment regimens have improved outcomes in newly diagnosed, advanced stage cHL<sup>7,8</sup>. Nivolumab in combination with doxorubicin, vinblastine and dacarbazine (NAVD), in particular, has been widely adopted in clinical practice in the U.S. for frontline treatment of OA with advanced stage cHL based on the subset analysis of S1826 study (n = 50) showing an unprecedented 1-year progression-free survival (PFS) of 93% and 1-year overall survival of 95% after NAVD in this patient population which remained durable on longer-term follow up<sup>9</sup>. Another phase 2 study showed that NAVD was a highly effective and well-tolerated frontline regimen in OA with cHL (n=40) across a wide range of geriatric impairments<sup>10</sup>. Although NAVD has shown favorable efficacy and tolerability in clinical trials, real-world safety and efficacy data in older adults are lacking. Patients enrolled in trials are generally fitter than those in clinical practice, hence the toxicity profile of drugs appears significantly different in the real world compared to what is reported in trials<sup>11,12</sup>. We therefore evaluated outcomes and adverse events in OA with cHL treated with frontline NAVD across 20 academic centers.

## Methods

### Patients

This multicenter retrospective cohort study included adult patients (≥18 years) with newly diagnosed, histologically confirmed, cHL treated with NAVD as standard of care frontline therapy between January 1, 2023, and October 1, 2025, at one of the participating 20 United

States (U.S) sites<sup>13</sup>. This study reports the safety profile and outcomes in OA who were defined as age  $\geq 60$  years<sup>2,4,14</sup>. The study protocol was approved by the University of Utah Institutional Review Board as well as each contributing institute's review board.

Clinical and treatment data were retrospectively abstracted from the medical record at all participating sites. The safety evaluable cohort received at least 1 cycle of NAVD. The efficacy evaluable cohort included patients who completed 6 cycles of treatment with end of treatment (EOT) PET-CT response assessment (excluding those still actively receiving therapy) or patients who were intended to complete treatment but died or discontinued due to progressive disease or AEs prior to the completion of the 6 cycles. Patients with stage III and IV disease were included. Epstein-Barr virus (EBV) positivity was defined as positive EBV-encoded small RNAs (EBER) in situ hybridization (EBER-ISH) within the tissue sample. Response assessment was performed by the treating investigator according to the Lugano 2014 criteria<sup>15</sup>. AEs were retrospectively abstracted from the electronic medical record, including oncology clinic notes, infusion records, laboratory results, hospitalization records, and other relevant clinical documentation. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was used to grade toxicities where sufficient clinical information was available. The primary endpoint was PFS, defined as the time from start of NAVD treatment to disease progression or death with patients alive and in remission censored at last follow up. Secondary endpoints included end of treatment (EOT) overall response rate (ORR), complete response rate (CRR), interim ORR and CRR, and overall survival (OS; defined as the time from start of NAVD treatment to death from any cause).

### Statistical analysis

Baseline characteristics, clinicopathological characteristics, treatment characteristics, and chemotherapy- and immune-related adverse events were summarized using descriptive statistics for this cohort of OA and compared to patients  $<60$  years of age. Continuous variables

were summarized as means (standard deviations) if normally distributed and as medians (interquartile ranges) if skewed. Categorical variables were summarized as count and percentages. PFS and OS were estimated using a Kaplan-Meier estimator and compared between age subgroups via the log-rank test. A multivariable logistic model was used to evaluate the associations between baseline clinicopathological features and CRR. A Cox proportional hazard (PH) model was used to assess the associations between baseline clinicopathological features and PFS. The PH assumption was assessed using Schoenfeld residuals and complementary log-log survival plots; no violations were identified<sup>16</sup>. We performed variable selection through univariable analysis to prevent overfitting, and covariates with a p value  $\leq 0.1$  were included in the multivariable analysis, including patient demographic and clinical features known to be prognostic in cHL.

Absolute standardized mean differences (ASMDs) were used to assess differences in baseline characteristics, treatments, and adverse events across age groups. ASMDs provide a standardized measure of the magnitude of between-group differences and are not subjected to false negatives due to low study power or false positives due to multiple hypothesis testing. ASMD values  $<0.10$  were considered negligible,  $0.10$  to  $0.25$  were considered small, and  $>0.25$  were considered meaningful differences. When comparing outcomes across age groups in OA, the subgroup of patients 70-79 years of age ( $n=32$ ) and those 80 years and older ( $n=9$ ) were combined due to low number of patients 80 years and older. This combined group of patients 70 years and older was compared to those 60-69 years of age. All analyses were conducted using R version 4.4.1 (R Foundation for Statistical Computing).

## Results

### Baseline characteristics

Among 327 total patients, a total of 81 patients (25%) were  $\geq 60$  years of age. Results from the entire cohort have been published previously (13). This report described outcomes in OA across the aging spectrum and compares baseline characteristics and survival between OA and patients  $< 60$  years of age. Median age of the OA cohort was 70 years (range 60-88 years), 70% were male, and 90% were Caucasian (**Table 1**). Among OA, 49% were 60-69 years of age, 40% were 70-79 years and 11% were  $\geq 80$  years of age. Most OA had nodular sclerosis subtype (71%), stage IV disease (58%), B symptoms at diagnosis (57%), and extranodal involvement (61%). Among patients with complete data, 48% had an International Prognostic Score (IPS) of 4-7, 39% had EBV positivity in the biopsy tissue ( $n=27/69$ ), and 10% had history of an autoimmune disease. EBV was detectable in peripheral blood in 65% (20/31) of cases, but it was not tested in the vast majority. When compared to patients 60-69 years of age, OA 70 years and older tended to have lower incidence of B symptoms (68% vs 46%, ASMD 0.44), slightly higher rates of impaired performance status (13% vs 22%, ASMD 0.26) and higher incidence of nodular sclerosis subtype (58% vs 80%, ASMD 0.7) (**table 1 and supplementary table 1**).

The median number of NAVD cycles was 6 (range 1-6). G-CSF was given in 82% of OA (primary prophylaxis in  $n=48$ , 73%) with no significant difference in usage patterns between those 60-69 years of age vs 70 years and above (**table 2 and supplementary table 2**).

Treatment is ongoing in 13% of patients ( $n=11$ ).

### Safety

All patients were safety evaluable. In OA, one or more treatments were interrupted (any length) in 28% with a median delay of 10 days (range 4-49 days) (**Table 2**). Adverse events (AEs) were the most common reason for treatment interruption (94%). Chemotherapy dose was reduced in 25% (20/81), most frequently vinblastine due to neuropathy (20%, 16/81). Any treatment was

discontinued in 28% (21/81), with vinblastine being the most frequently discontinued drug (19%, 15/81). Nivolumab was discontinued in 17% (14/81) of patients, all due to suspected or known irAEs. All therapy was discontinued in 10% (8/81) due to toxicity (supplementary table 11), median number of cycles in these patients was 5 (range 1-5.5). Among OA, treatment interruption (32% vs 24%, ASMD 0.18) and discontinuation (31% vs 26%, ASMD 0.09) were similar between patients 60-69 years and those 70 years and older respectively, however treatment reduction rates were higher in patients  $\geq 70$  years (32% vs 20% for 60-69 years, ASMD 0.27). Median duration of treatment interruption was also higher in patients  $\geq 70$  years (13 vs 7.5 days for 60-69 years, ASMD 0.58). **(supplementary table 2).**

Any grade AE and any grade 3 or higher AE ( $\geq G3$ ) were observed in 88% and 67% of patients, respectively. Treatment related AEs are summarized in **Table 3**. Nausea (37%), infection (27%), and neuropathy (25%) were the most common non-hematologic AEs. Febrile neutropenia occurred in 12% of patients, with most patients requiring hospitalization (11%). The most common non-hematologic  $\geq G3$  AEs included infection (12%), hepatotoxicity (6%), and neuropathy (5%). Among hematological toxicities, neutropenia occurred in 63% (52%  $\geq G3$ ). Grade 3 or greater anemia or thrombocytopenia occurred in 14% and 4%, respectively. Hospitalization for an AE occurred in 29%, most of which were for a chemotherapy-related AE (17%), including one intensive care unit (ICU) admission. Median duration of hospitalization was 5.5 days (range 1-16 days).

Among OA, patients  $\geq 70$  years had lower rates of any grade nausea (32% vs 43% for patients 60-69 years, ASMD 0.22), any grade neuropathy (20% vs 30%, ASMD 0.23), any grade diarrhea (5% vs 15%, ASMD 0.34), but slightly higher rates of  $\geq G3$  non-hematologic AEs (37% vs 28%, ASMD 0.21) compared to those between 60 and 69 years of age (**supplementary table 3**). Rates of any grade neutropenia (56% vs 70%, ASMD 0.29) and  $\geq G3$  hematologic AEs (51% vs 63%, ASMD 0.23) were slightly lower in patients  $\geq 70$  years, with similar rates of febrile neutropenia (12% vs 13%, ASMD 0.01).

Any grade irAE occurred in 24 patients (29%) with  $\geq$ G3 irAEs in 9 patients (11%) and a total of 30 irAE events (**Table 4**). The most common irAEs included inflammatory arthritis (6%, 1%  $\geq$ G3), hypothyroidism (6%), hepatotoxicity (5%, 4%  $\geq$ G3), rash (4%), pneumonitis (4%, 2%  $\geq$ G3), colitis (2%), and adrenal insufficiency (2%, 1%  $\geq$ G3). One patient each had autoimmune neutropenia (G1), myocarditis ( $\geq$ G3), sarcoidosis of lung/skin (G2), and HLH in the setting of CVID ( $\geq$ G3). A dose interruption for an irAE occurred in 20% of patients (n=14/71) with a median interruption of 14 days (range 14-42 days). Nivolumab was discontinued in 14 patients due to irAEs. Overall, 38% (16/42) of patients with available data required steroids for a suspected or confirmed irAE at any time (n=11 oral, n=7 intravenous [IV], n=2 topical, more than one modality used in 4 patients) with resolution of irAEs in 82% (n=18/22). Eleven patients (14%) required continued therapy (n=4 thyroid hormone supplementation, n=5 steroids including hydrocortisone, n=1 medical therapy for heart failure, n=1 unknown). Of patients with a history of prior autoimmune disease (n=8), 1 patient with a history of rheumatoid arthritis (RA) developed immune related colitis and a RA flare and 1 patient with a history of hypothyroidism required an increased thyroid hormone dose.

### Efficacy

Among all older adults (n=81), 86.5% (n=71) had an interim PET-CT after 2-4 cycles. The ORR and CRR at interim PET-CT were 100% and 81.6%, respectively. In the efficacy evaluable population with PET-CT available (n=75; 5 lost to follow-up, one patient died prior to EOT scan), the EOT ORR and CRR were 88% and 82.6%, respectively (**supplementary Table 4**). The median follow up was 12.6 months (range 0.5-32.4 months). 1-year PFS was 91.5%, CI 84.4%-99.1%) and 1-year OS was 98.6%, CI 95.8%-100%) (**Figure 1**). Outcomes were similar among patients 60-69 years of age and those  $\geq$ 70 years of age (**supplementary table 5**,

**supplementary figure 1).** For patients  $\geq 80$  years of age, 1-year PFS was 76.2% (95% CI 33.2%- 93.5%) and 1-year OS was 88.9% (95% CI 43.3%- 98.4%, **supplementary figure 2).** Among the 8 patients with progression/relapse, 5 were primary refractory. 7 patients were started on second line therapy (1 awaiting biopsy). 79 patients are alive at data cut off with two deaths. One death occurred due to lymphoma progression during salvage therapy and one patient died during cycle 1 of NAVD with the cause of death being unknown.

#### *Impact of baseline characteristics on outcomes*

Univariable and multivariable analyses were performed to identify whether baseline clinicopathological or disease characteristics were associated with CRR or PFS. Univariable analysis showed that presence of lymphopenia was associated with lower odds of achieving complete response; however, this distinction was lost in multivariable analysis. No other baseline features were identified to be predictive of response (**Figure 2 and supplementary Table 6**). In the univariable Cox analysis for PFS, again the presence of lymphopenia (HR 5.4, 95% CI: 1.3-21.9,  $p=0.019$ ) was associated with significantly inferior PFS (**Figure 3**). Due to limited number of events (progression/death), multivariable analysis could not be performed for PFS.

#### *Comparison of baseline characteristics, treatment patterns and outcomes between OA and patients <60 years*

Compared to patients aged <60 years, OA had higher frequency of mixed cellularity subtype (22% vs 11%, ASMD 0.41), ECOG 2-4 (18% vs 3%, ASMD 0.48), EBV positivity (39% vs 21%, ASMD 0.40), EBV PCR positivity in blood (65% vs 41%, ASMD 0.48), IPS 4-7 (48% vs 23%, ASMD 0.53), and low albumin (52% vs 39%, ASMD 0.24) (**supplementary table 7**).

Patients less than 60 years of age tended to get G-CSF less commonly [58% (143/246) vs 82% (66/81) of OA, ASMD 0.53] and most often as secondary prophylaxis [52% (74/143) vs 27%

(18/66) in OA]. Rates of treatment interruption were similar (28% vs 25%, ASMD 0.08) between younger and older patients; however rates of treatment reduction (26% vs 8%, ASMD 0.54) and discontinuation (26% vs 11%, ASMD 0.53) were higher in OA (**supplementary table 8**).

Interestingly, nausea was reported more commonly in younger patients (61% vs 37%, ASMD 0.5, **supplementary table 9**), while overall incidence of  $\geq$ G3 non-hematologic AEs was slightly higher in OA (32% vs 22%, ASMD 0.24). Incidence of neutropenia was slightly higher in younger patients (74% vs 63%, ASMD 0.24), likely due to lower use of primary prophylactic G-CSF; however, rates of febrile neutropenia were similar (9% vs 12%, ASMD 0.12). Overall incidence of  $\geq$ G3 hematologic toxicities was similar between patients <60 years and  $\geq$ 60 years of age (57% vs 54%, ASMD 0.05). There was no major difference in the frequency of irAEs among OA and patients <60 years of age (**supplementary table 9**).

When comparing efficacy, 1-year PFS was slightly inferior in older adults (91.5%, CI 84.4%-99.1%) compared to patients <60 years of age (95.5%, CI 92.2%-98.9%), although the difference did not reach statistical significance (log-rank  $p=0.071$ ). 1-year OS was inferior in older adults (98.6%, CI 95.8%-100%) compared to patients <60 years of age (100%,  $p=0.011$ ) (**Figure 1**). OS curves were significantly different by log-rank test ( $p=0.011$ ), driven by late events beyond 12 months.

## Discussion

In this large, real-world cohort of older adults treated with NAVD, we report excellent PFS and OS at the 1-year mark. Notably, rates of  $\geq$ G3 AEs including infections, neuropathy and irAEs remained low and manageable and there were no definite treatment related deaths. About a quarter of patients did require treatment delays or dose reduction in chemotherapy though rate of treatment discontinuation remained low at 10%. Although survival in older adults significantly improved with NAVD compared to historical data<sup>14,17,18</sup>, OS remained inferior to patients <60

years of age with a trend towards inferior PFS. Among older adults, adverse event profile and response rates were similar between the age groups of 60-69 years and  $\geq 70$  years. These data suggest that NAVD should be the favored choice of therapy in most older adults with newly diagnosed cHL with the exception of those rare cases with absolute contraindications to anthracycline- or checkpoint inhibitor-based therapy.

When comparing our cohort (n=81) with the OA cohort treated on the S1826 clinical trial (n=50), baseline characteristics of patients were overall similar; patients in our cohort were slightly older (median age 70 years vs 66.2 years). Rates of neutropenia were higher in our cohort 63% (52%  $\geq G3$ ) vs 53% (49%  $\geq G3$ ) in S1826, however febrile neutropenia rates were similar (12%). In our cohort, 82% patients received G-CSF prophylaxis (73% primary prophylaxis) compared to 71% of OA treated on S1826. In a separate phase 2 study of OA with cHL treated with NAVD, the proportion of patients receiving prophylactic G-CSF was similar to our cohort with a lower rate of  $\geq G3$  neutropenia (30%) albeit with comparable rates of febrile neutropenia (8%)<sup>10</sup>. Taken together, these data suggest that primary or at least early secondary prophylaxis should be strongly considered in all OA on NAVD to mitigate risk of febrile neutropenia. Rates of irAEs appeared comparable between our real-world cohort and those reported in clinical trials (**supplementary table 10**) with similar rates of nivolumab discontinuation (17% vs 14%) and overall treatment discontinuation (10% vs 10%). While S1826 excluded patients with autoimmune conditions, we did have 8 such patients of which 2 experienced a disease flare suggesting that patients with well controlled select autoimmune conditions could receive NAVD judiciously. The 1-year PFS in S1826 was 93%, and the 1-year OS was 96% which is quite similar to our observation in this real-world cohort of OA (91.5% and 98.6% respectively). Strengths of this study include a large, multi-center, geographically diverse cohort with detailed treatment, toxicity and irAE data, including among patients with preexisting autoimmune disease. Limitations include those inherent to a retrospective study design. Unlike prospective clinical trials, in which adverse events are systematically solicited, graded, and assessed for

attribution, routine clinical documentation may incompletely capture lower-grade or transient toxicities and does not consistently document treatment relatedness. We therefore focused on selected clinically significant toxicities known to be associated with NAVD and relied on available clinical documentation and laboratory data for retrospective grading and attribution. Hematologic toxicities were more comprehensively ascertainable from laboratory records, whereas symptoms such as fatigue and lower-grade non-hematologic toxicities were more difficult to reliably assess and were therefore not used for direct comparisons with S1826. Consequently, comparisons of adverse events between our real-world cohort and S1826 should be interpreted cautiously, particularly for grade 1–2 non-hematologic toxicities, and should not be considered equivalent to prospectively collected clinical-trial AE data. Nevertheless, the real-world data provide complementary information regarding clinically significant toxicity and treatment tolerability across the aging spectrum, including patients in their 70s and 80s who may be underrepresented in clinical trials. Fitness assessments were not available which hampers our ability to identify which patients were most vulnerable to AEs and require a priori dose modifications and additional support. Older adults did fairly well in our cohort regardless of age, supporting use of NAVD even in patients over 80 years of age; however, it is possible that these patients were selected to assure tolerability based on baseline fitness. Most patients were treated at academic institutions, and response assessments were performed locally by treating providers rather than through centralized review; however, uniform response assessment criteria were used across all participating sites. We observed FDG uptake on interim and EOT scans in patients who have not had progression, which suggests that the positive PET-CT may be due to non-specific inflammatory uptake as reported in prior datasets <sup>8,10,13</sup>, however data regarding follow up biopsies is not available. Finally, follow-up duration was relatively short, and updated analyses will be reported in the future to allow comparison with the reported outcomes of patients treated on S1826.

Despite our real-world data closely corroborating the excellent overall performance of NAVD in OA with cHL, several unmet needs and unanswered questions remain in this patient population. Most studies, including the current study, have very limited number of octogenarians, hence data regarding efficacy and AE profile of NAVD in this cohort is still lacking. Patients whose cardiac function or other comorbidities precludes anthracycline use have inferior outcomes and would benefit from enrollment in clinical trials evaluating non-chemotherapy or 'chemotherapy-lite' approaches<sup>19,20</sup>. Lastly, we are yet to identify a validated prognostication measure that can be applied uniformly in older adults with cHL. The Hasenclever and Diehl International Prognostic score was not predictive of outcomes in the current study, similar to previous studies of older adults with cHL<sup>6,10,21</sup>. Prior real-world analyses and population-based studies demonstrate that presence of comorbidities as measured by cumulative illness rating scale-geriatrics (CIRS-G) score, impaired functionality as measured by activities of daily living and instrumental activities of daily living, and/or geriatric syndromes is associated with worse OS in OA with cHL<sup>6,22</sup>. However, retrospective studies are unsuited for analysis of fitness parameters due to significant under-reporting of impairments. Fitness assessments were not performed on the S1826 study. Torka et al reported that there was no correlation between baseline geriatric impairments and survival outcomes or toxicities with NAVD; however, patients were relatively fit in this small phase 2 study<sup>10</sup>. The simplified geriatric assessment (sGA) pioneered by the Fondazione Italiana Linfomi for OA with diffuse large B cell lymphoma has not been validated in cHL.<sup>23</sup> An important future direction includes creation of prospective databases that collect patient fitness characteristics in addition to baseline demographics and disease characteristics. Correlation of these variables with survival, adverse events, patient reported outcomes and health resource utilization with better inform appropriate therapeutic selection and identify patients for clinical trials who are not suited for current SOC paradigms such as NAVD.

Overall, our data reinforces the use of NAVD as the preferred frontline option for older adults with advanced stage cHL. Our real-world data recapitulates findings of the pivotal S1826 trial with 1-year PFS and OS of 91.5% and 98.6%, respectively, despite patients being older. Importantly, rate of AEs, especially IrAEs remained similar, with low rates of treatment discontinuation due to toxicities.

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## **Tables and figures**

### **Tables**

Table 1. Baseline characteristics of older adults with cHL treated with NAVD

Table 2. Treatment characteristics of older adults with cHL treated with NAVD

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Table 4. Frequency of immune-related adverse events among older adults with cHL treated with at least one cycle of NAVD

**Table 1. Baseline characteristics of older adults with cHL treated with NAVD**

| Characteristic                                 | Overall, n=81<br>N (%) | 60-69 years, n=40<br>(49%) | 70-79 years,<br>n=32 (40%) | 80 years and<br>above, n=9<br>(11%) |
|------------------------------------------------|------------------------|----------------------------|----------------------------|-------------------------------------|
| <b>Age at diagnosis</b>                        |                        |                            |                            |                                     |
| Median (Range)                                 | 70 (60– 88)            | 63.5 (60 - 69)             | 74.5 (70 - 79)             | 83 (80 - 88)                        |
| <b>Male</b>                                    | 57 (70%)               | 31 (78%)                   | 19 (59%)                   | 7 (78%)                             |
| <b>Race</b>                                    |                        |                            |                            |                                     |
| Caucasian                                      | 71 (90%)               | 34 (87%)                   | 28 (90.3%)                 | 9 (100%)                            |
| African American                               | 3 (4%)                 | 0 (0%)                     | 3 (9.7%)                   | 0                                   |
| Asian                                          | 1 (1.3%)               | 1 (3%)                     | 0                          | 0                                   |
| Other                                          | 4 (5%)                 | 4 (10%)                    | 0                          | 0                                   |
| <b>Ethnicity</b>                               |                        |                            |                            |                                     |
| Hispanic                                       | 16 (20%)               | 9 (24%)                    | 5 (16%)                    | 2 (25%)                             |
| <b>History of autoimmune condition, (n=81)</b> | 8 (10%)                | 4 (10%)                    | 1 (3.1%)                   | 3 (33%)                             |
| <b>B Symptoms present</b>                      | 46 (57%)               | 27 (67%)                   | 13 (40.6%)                 | 6 (67%)                             |
| <b>Bulky Disease</b>                           | 8 (10%)                | 5 (12%)                    | 3 (9.4%)                   | 0                                   |
| <b>Ann Arbor Stage</b>                         |                        |                            |                            |                                     |
| III                                            | 34 (42%)               | 17 (42%)                   | 12 (37.5%)                 | 5 (56%)                             |
| IV                                             | 47 (58%)               | 23 (58%)                   | 20 (62.5%)                 | 4 (44%)                             |
| <b>ECOG PS (n=80)</b>                          |                        |                            |                            |                                     |
| 0-1                                            | 65 (82%)               | 34(87%)                    | 24(77%)                    | 7(78%)                              |
| 2-4                                            | 14(18%)                | 5(13%)                     | 7(23%)                     | 2(22%)                              |
| <b>cHL Subtype, (n=49)</b>                     |                        |                            |                            |                                     |
| Lymphocyte depleted                            | 1 (2%)                 | 0 (0.0%)                   | 1 (4%)                     | 0                                   |
| Lymphocyte rich                                | 2 (4%)                 | 2 (11%)                    | 0                          | 0                                   |
| Mixed cellularity                              | 11 (22%)               | 6 (32%)                    | 5 (20%)                    | 0                                   |
| Nodular sclerosis                              | 35 (71%)               | 11 (58%)                   | 19 (76%)                   | 5(100%)                             |
| <b>EBV-positive in biopsy, (n=69)</b>          | 27 (39%)               | 15 (43%)                   | 10 (36%)                   | 2(33%)                              |
| <b>IPS Score, (n=80)</b>                       |                        |                            |                            |                                     |
| 0-3                                            | 42 (53%)               | 19(47%)                    | 20(65%)                    | 3(33%)                              |
| 4-7                                            | 38 (48%)               | 21(53%)                    | 11(35%)                    | 6(67%)                              |
| <b>Labs</b>                                    |                        |                            |                            |                                     |
| LDH, Median (Range), (n=76)                    | 222 (108-1,296)        | 222.0 (117-1,296)          | 228.0 (108-720)            | 226 (138-426)                       |
| WBC, Median (Range)                            | 6.6(0.9-19.4)          | 5.6 (1.4-14.3)             | 7.0 (0.9-16.3)             | 10.5 (5-19.4)                       |
| HGB, Median (Range)                            | 11.6 (7.0-16.1)        | 11.3 (7.1-16.1)            | 12.2 (7.0-16.1)            | 11.2 (9.3-14.2)                     |
| Normal albumin                                 | 39 (48%)               | 19 (48%)                   | 18 (56%)                   | 2 (22%)                             |
| Lymphopenia                                    | 20 (24%)               | 10 (25%)                   | 6 (19%)                    | 4 (44%)                             |
| ESR, Median (range), (n=73)                    | 47 (1-130)             | 60(1-130)                  | 46 (5-130)                 | 39(6-130)                           |
| <b>Extranodal involvement</b>                  | 49(61%)                | 25(63%)                    | 19 (60%)                   | 5(55%)                              |
| 1                                              | 24 (30%)               | 10 (25%)                   | 13 (41%)                   | 1(11%)                              |
| ≥ 2                                            | 25 (31%)               | 15 (38%)                   | 6 (19%)                    | 4(44%)                              |

**Abbreviations:** cHL=Classic Hodgkin Lymphoma; NS =Nodular Sclerosis; ECOG PS = Eastern Cooperative Oncology Group performance status; EBV=Epstein-Barr Virus, as measured by EBV-ISH by

IHC on tumor pathology; LDH=Lactate Dehydrogenase; WBC= White Blood Cell; HGB = Hemoglobin; ESR = Erythrocyte Sedimentation Rate; IPS= international prognostic score. Bulky disease defined as tumor size  $\geq 7.5$  cm. Denominator is out of N=81 patients except where otherwise noted.

**Table 2. Treatment characteristics of older adults with cHL treated with NAVD**

| Treatment Characteristic                    | Overall, n=81<br>N (%) | 60-69 years,<br>n=40 | 70-79 years,<br>n=32 | 80 years and<br>above, n=9 |
|---------------------------------------------|------------------------|----------------------|----------------------|----------------------------|
| <b>G-CSF use</b>                            | N=66 (82%)             | N=31(77%)            | N=27(84%)            | N=8(89%)                   |
| Primary ppx                                 | 48 (73%)               | 22 (71%)             | 21 (78%)             | 5 (62%)                    |
| Secondary ppx                               | 18 (27%)               | 9 (29%)              | 6 (22%)              | 3 (38%)                    |
| <b>Treatment Interrupted</b>                | 23 (28%)               | 13 (32%)             | 10 (31%)             | 0                          |
| <b>Duration of treatment interruption</b>   |                        |                      |                      |                            |
| Median (Range), days                        | 10(4 - 49)             | 7.5 (4 - 21)         | 13 (4- 49)           | NA                         |
| <b>Reason for treatment delay</b>           |                        |                      |                      |                            |
| Infection/febrile neutropenia               | 4(24%)                 | 2(22%)               | 2(25%)               | 0                          |
| Other AE                                    | 6(35%)                 | 1(11%)               | 5(63%)               | 0                          |
| Neutropenia                                 | 6(35%)                 | 5(56%)               | 1(13%)               | 0                          |
| Pt preference/logistics                     | 1(6%)                  | 1(11%)               | 0                    | 0                          |
| <b>Treatment Reduction*</b>                 |                        |                      |                      |                            |
| Doxorubicin Reduced                         | 14(17%)                | 6(15%)               | 6(19%)               | 2(22%)                     |
| Vinblastine Reduced                         | 16(20%)                | 6(15%)               | 8(25%)               | 2(22%)                     |
| Dacarbazine Reduced                         | 12(15%)                | 2(5%)                | 8(25%)               | 2(22%)                     |
| Unknown                                     | 2(2%)                  | -                    | -                    | -                          |
| <b>Reason for treatment reduction*</b>      |                        |                      |                      |                            |
| Neuropathy                                  | 6(7%)                  | 3(7%)                | 3(9%)                | 0                          |
| Cytopenias                                  | 5(6%)                  | 2(5%)                | 2(6%)                | 1(11%)                     |
| Treatment-related Hepatotoxicity            | 3(2%)                  | 2(5%)                | 1(3%)                | 0                          |
| Fatigue                                     | 8(10%)                 | 1(2%)                | 6(19%)               | 1(11%)                     |
| Other                                       | 4(5%)                  | 1(2%)                | 2(6%)                | 1(11%)                     |
| <b>Treatment Discontinued</b>               | 21(28%)                | 11(31%)              | 5 (17%)              | 5(62%)                     |
| <b>Treatment Discontinuation*</b>           |                        |                      |                      |                            |
| Nivolumab                                   | 14(17%)                | 8(20%)               | 3(9%)                | 3(33%)                     |
| Doxorubicin                                 | 12(15%)                | 7(17%)               | 3(9%)                | 2(22%)                     |
| Vinblastine                                 | 15(19%)                | 8(20%)               | 4(12%)               | 3(33%)                     |
| Dacarbazine                                 | 11(14%)                | 6(15%)               | 3(9%)                | 2(22%)                     |
| All therapy                                 | 8(10%)                 | 5(12%)               | 2(6%)                | 1(11%)                     |
| Unknown                                     | 7(9%)                  | -                    | -                    | -                          |
| <b>Reason for Treatment Discontinuation</b> |                        |                      |                      |                            |
| Toxicity                                    | 18/21(86%)             | 9/11(82%)            | 5/5 (100%)           | 4/5 (80%)                  |
| Other†                                      | 2                      | 2                    | 0                    | 0                          |

**Abbreviations:** G-CSF=Granulocyte Colony-Stimulating Factor; ppx=prophylaxis; AE=adverse event; Pt=patient. Primary prophylaxis refers to empiric use of G-CSF. Secondary prophylaxis refers to addition of G-CSF in response to infection or neutropenia. Cytopenias include anemia, thrombocytopenia or neutropenia with decision for treatment modification at discretion of treating physician. Patients included in this table received at least 1 cycle of treatment.

\*Percentages are given among all patients, excluding unknown

†One patient self-discontinued therapy and was lost to follow up, one pt had doxorubicin discontinued due to prior anthracycline use

**Table 3. Frequency of select adverse events among older adults with cHL treated with at least one cycle of NAVD**

| <b>Adverse Event</b>                                      | <b>Overall,<br/>n=81<br/>N (%)</b> | <b>60-69 years,<br/>n=40</b> | <b>70-79 years,<br/>n=32</b> | <b>80 years<br/>and above,<br/>n=9</b> |
|-----------------------------------------------------------|------------------------------------|------------------------------|------------------------------|----------------------------------------|
| <b>Non-Hematologic Toxicity</b>                           |                                    |                              |                              |                                        |
| Nausea                                                    | 30 (37%)                           | 17 (43%)                     | 10 (31%)                     | 3(33%)                                 |
| Any infection                                             | 22 (27%)                           | 9 (23%)                      | 9 (28%)                      | 4(44%)                                 |
| Neuropathy                                                | 20 (25%)                           | 12 (30%)                     | 7 (23%)                      | 1(11%)                                 |
| Diarrhea                                                  | 8 (10%)                            | 6 (15%)                      | 2 (6%)                       | 0                                      |
| <b>Grade <math>\geq</math> 3 Non-Hematologic Toxicity</b> | 26 (32%)                           | 11(28%)                      | 12(38%)                      | 3(33%)                                 |
| Infection                                                 | 10 (12%)                           | 6(15%)                       | 2(6%)                        | 2(22%)                                 |
| Hepatotoxicity                                            | 5 (6%)                             | 2(5%)                        | 3(9%)                        | 0                                      |
| Neuropathy                                                | 4 (5%)                             | 2(5%)                        | 2(6%)                        | 0                                      |
| Nausea                                                    | 2 (2%)                             | 0                            | 1 (3%)                       | 1 (11%)                                |
| Diarrhea                                                  | 1 (1%)                             | 1(3%)                        | 0(3%)                        | 0                                      |
| <b>Febrile neutropenia</b>                                | 10 (12%)                           | 5(13%)                       | 4(13%)                       | 1(11%)                                 |
| Cycle, median (range)                                     | 1 (1 - 5)                          | 1 (1 - 5)                    | 1 (1 - 1)                    | 1 (1 - 1)                              |
| Hospitalization                                           | 9 /10(90%)                         | 5/5(100%)                    | 3/4(75%)                     | 1/1(100%)                              |
| <b>Hematologic toxicity</b>                               |                                    |                              |                              |                                        |
| Neutropenia                                               | 51 (63%)                           | 28(70%)                      | 19(59%)                      | 4(44%)                                 |
| <b>Grade <math>\geq</math> 3 Hematologic Toxicity</b>     | 46 (57%)                           | 25 (63%)                     | 16 (50%)                     | 5(56%)                                 |
| Neutropenia                                               | 42 (52%)                           | 24(60%)                      | 15(47%)                      | 3(33%)                                 |
| Anemia                                                    | 11 (14%)                           | 5(1%)                        | 6(19%)                       | 0                                      |
| Thrombocytopenia                                          | 3 (4%)                             | 2(5%)                        | 1(3%)                        | 0                                      |

**Table 4. Frequency of immune-related adverse events among older adults with cHL treated with at least one cycle of NAVD**

| Immune-Related Events (irAEs)                                                                                                                                                                                                                                                                                                                                                       | Adverse | Overall (N=81) | 60–69 years (n=40) | 70–79 years (n=32) | ≥80 years (n=9) |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|----------------|--------------------|--------------------|-----------------|
| <b>Any-grade irAE*</b>                                                                                                                                                                                                                                                                                                                                                              |         | 24 (29.6)      | 13 (32.5)          | 8 (25.0)           | 3 (33.3)        |
| Inflammatory arthritis†                                                                                                                                                                                                                                                                                                                                                             |         | 5 (6.2)        | 4 (10.0)           | 0                  | 1 (11.1)        |
| Hypothyroidism                                                                                                                                                                                                                                                                                                                                                                      |         | 5 (6.2)        | 3 (7.5)            | 1 (3.1)            | 1 (11.1)        |
| Hepatotoxicity                                                                                                                                                                                                                                                                                                                                                                      |         | 4 (4.9)        | 2 (5.0)            | 2 (6.3)            | 0               |
| Rash                                                                                                                                                                                                                                                                                                                                                                                |         | 3 (3.7)        | 1 (2.5)            | 1 (3.1)            | 0               |
| Pneumonitis                                                                                                                                                                                                                                                                                                                                                                         |         | 3 (3.7)        | 2 (5.0)            | 1 (3.1)            | 0               |
| Colitis                                                                                                                                                                                                                                                                                                                                                                             |         | 2 (2.5)        | 1 (2.5)            | 1 (3.1)            | 0               |
| Adrenal insufficiency                                                                                                                                                                                                                                                                                                                                                               |         | 2 (2.5)        | 0                  | 2 (6.3)            | 0               |
| Sarcoidosis (lung/skin)                                                                                                                                                                                                                                                                                                                                                             |         | 1 (1.2)        | 0                  | 1 (3.1)            | 0               |
| Neutropenia                                                                                                                                                                                                                                                                                                                                                                         |         | 1 (1.2)        | 0                  | 0                  | 1 (11.1)        |
| Fatigue                                                                                                                                                                                                                                                                                                                                                                             |         | 1 (1.2)        | 1 (2.5)            | 0                  | 0               |
| <b>Grade ≥3 irAE</b>                                                                                                                                                                                                                                                                                                                                                                |         | 9 (11.1)       | 5 (12.5)           | 4 (12.5)           | 0               |
| Hepatotoxicity                                                                                                                                                                                                                                                                                                                                                                      |         | 3 (3.7)        | 1 (2.5)            | 2 (6.3)            | 0               |
| Pneumonitis                                                                                                                                                                                                                                                                                                                                                                         |         | 2 (2.5)        | 1 (2.5)            | 1 (3.1)            | 0               |
| Inflammatory arthritis                                                                                                                                                                                                                                                                                                                                                              |         | 1 (1.2)        | 1 (2.5)            | 0                  | 0               |
| Adrenal insufficiency                                                                                                                                                                                                                                                                                                                                                               |         | 1 (1.2)        | 0                  | 1 (3.1)            | 0               |
| Myocarditis                                                                                                                                                                                                                                                                                                                                                                         |         | 1 (1.2)        | 1 (2.5)            | 0                  | 0               |
| HLH in setting of baseline CVID                                                                                                                                                                                                                                                                                                                                                     |         | 1 (1.2)        | 0                  | 0                  | 0               |
| <b>Hospitalization for AE (n=77)</b>                                                                                                                                                                                                                                                                                                                                                |         | 22 (28.6)      | 11 (28.9)          | 8 (28.6)           | 3 (33.3)        |
| Chemotherapy-related                                                                                                                                                                                                                                                                                                                                                                |         | 13/22 (59.1)   | 6/11 (54.5)        | 4/8 (50.0)         | 2/3 (66.7)      |
| irAE-related                                                                                                                                                                                                                                                                                                                                                                        |         | 5/22 (22.7)    | 3/11 (27.3)        | 2/8 (25.0)         | 0               |
| Other causes                                                                                                                                                                                                                                                                                                                                                                        |         | 4/22 (18.2)    | 2/11 (18.2)        | 0                  | 1/3 (33.3)      |
| Duration of hospitalization, median days (range)                                                                                                                                                                                                                                                                                                                                    |         | 5.5 (1–16)     | 3 (1–15)           | 7 (4–10)           | 14 (8–16)       |
| <b>ICU admission for AE(n=70)</b>                                                                                                                                                                                                                                                                                                                                                   |         | 1 (1.4)        | 1 (3.3)            | 0                  | 0               |
| Chemotherapy-related                                                                                                                                                                                                                                                                                                                                                                |         | 0              | 0                  | 0                  | 0               |
| <u>Abbreviations:</u> AE=adverse event, ICU=intensive care unit, <b>HLH</b> =hemophagocytosis lymphohistiocytosis, CVID=common variable immunodeficiency. Patients included in this table received at least 1 cycle of treatment with NAVD.<br>*30 total irAE events in 24 pts, †Inflammatory arthritis includes specifically: sacroiliitis (n=1) and polymyalgia rheumatica (n=1). |         |                |                    |                    |                 |

**Figures**

Figure 1. Outcomes of patients treated with NAVD stratified by age.

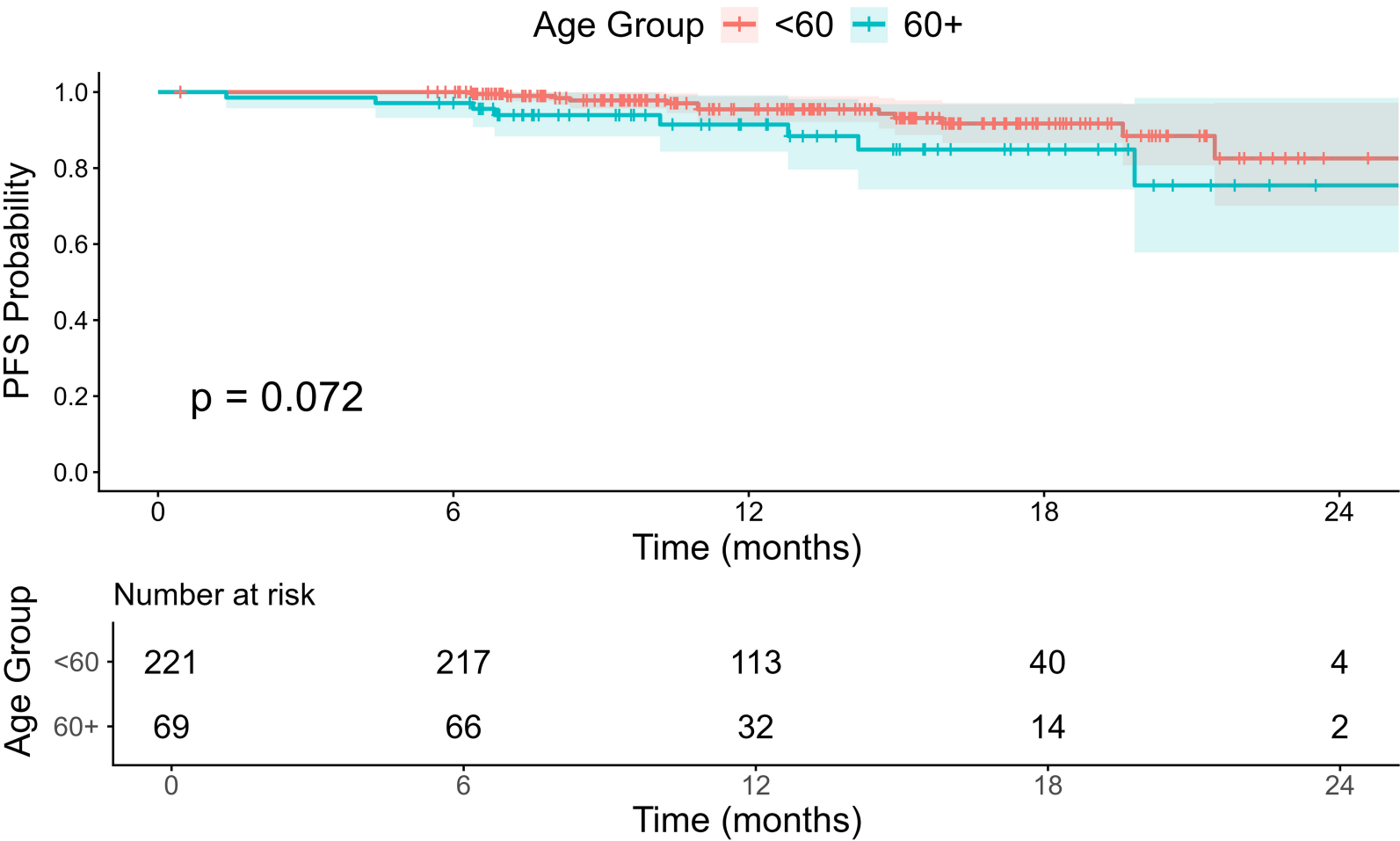
A) Progression free survival among patients stratified by age  $\geq 60$  years and  $<60$  years

B) Overall survival among patients stratified by age  $\geq 60$  years and  $<60$  years.

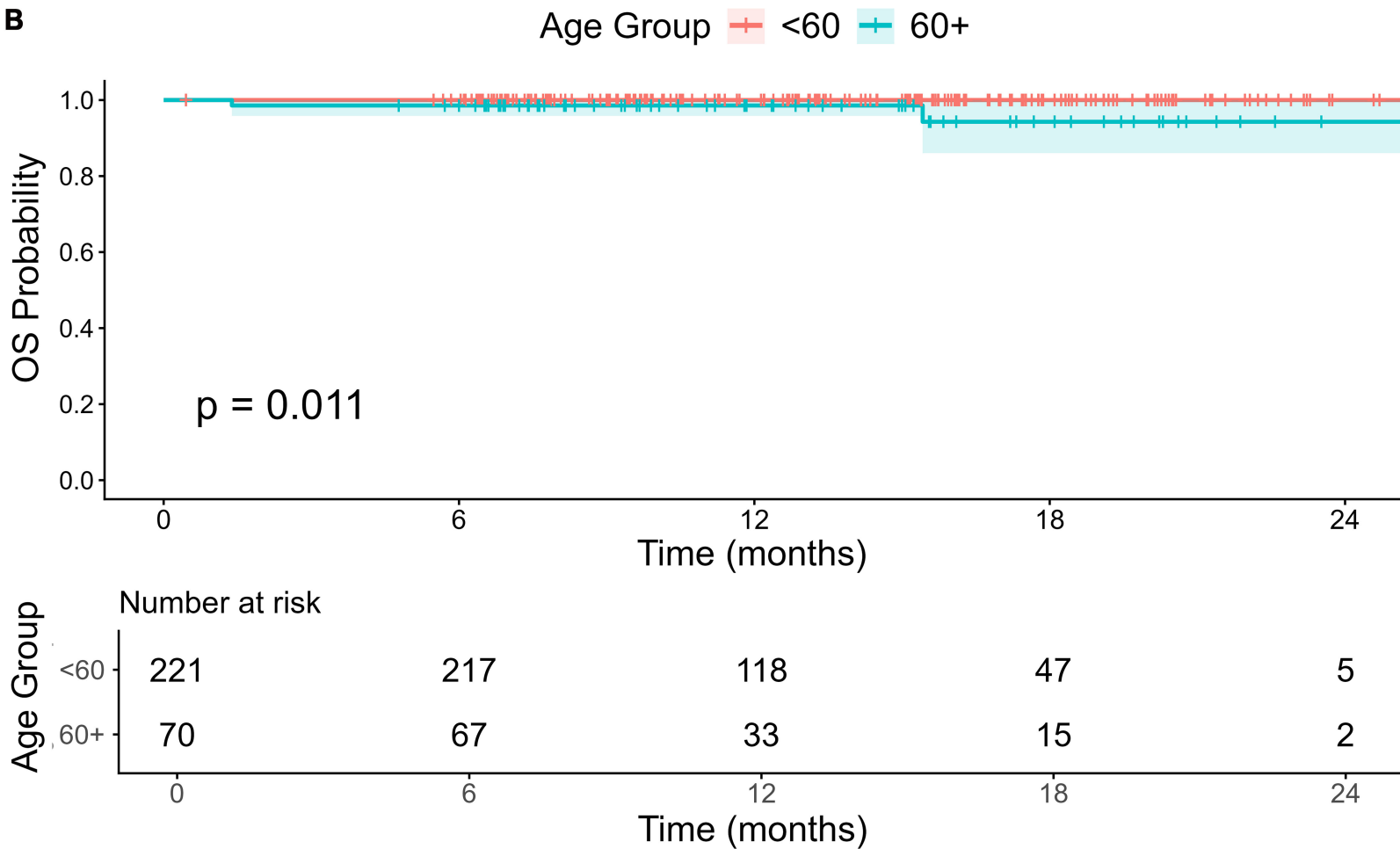
Figure 2. Univariate analysis of predictors of complete response in older adults with cHL

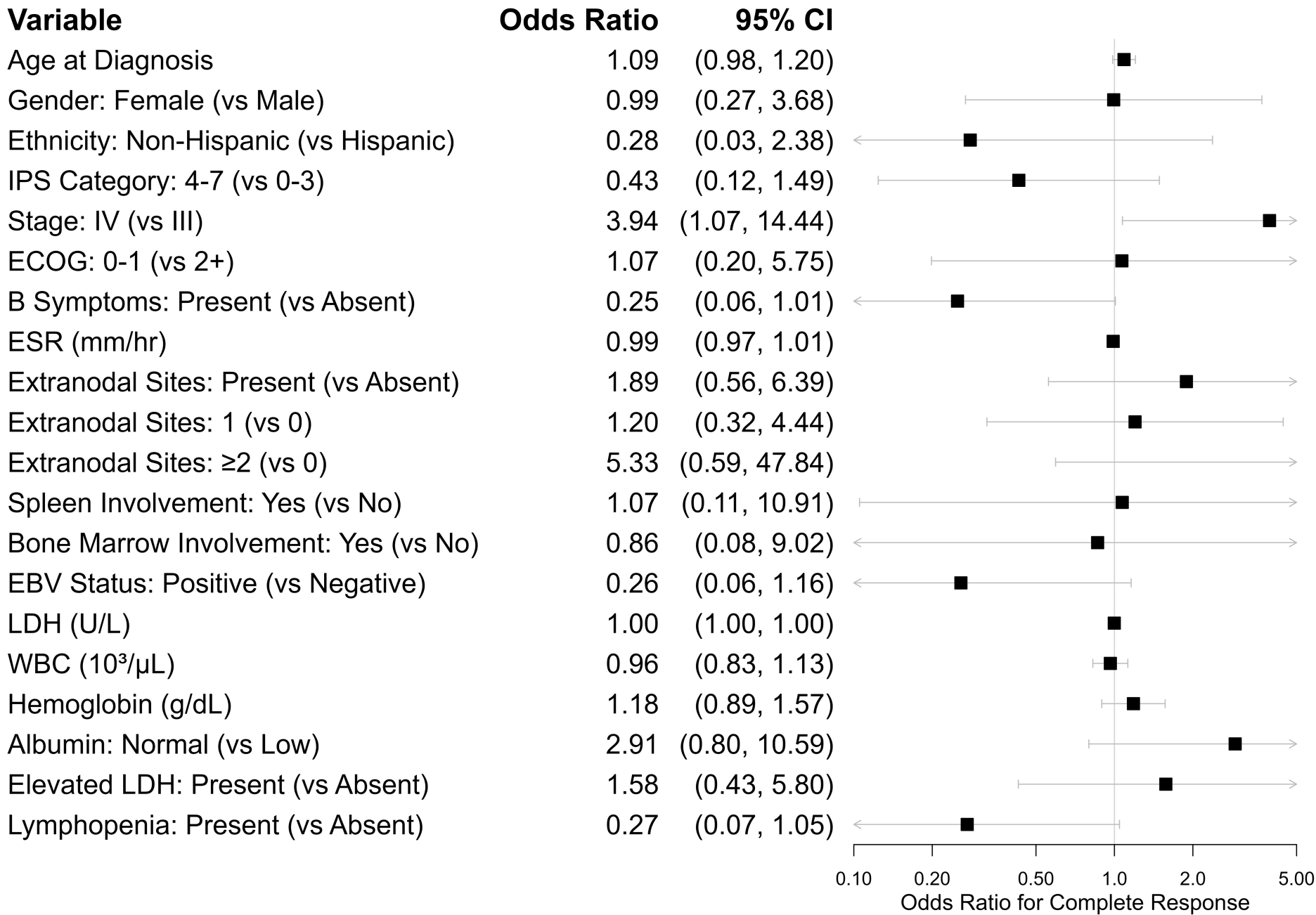
Figure 3. Univariate analysis of predictors of progression-free survival in older adults with cHL

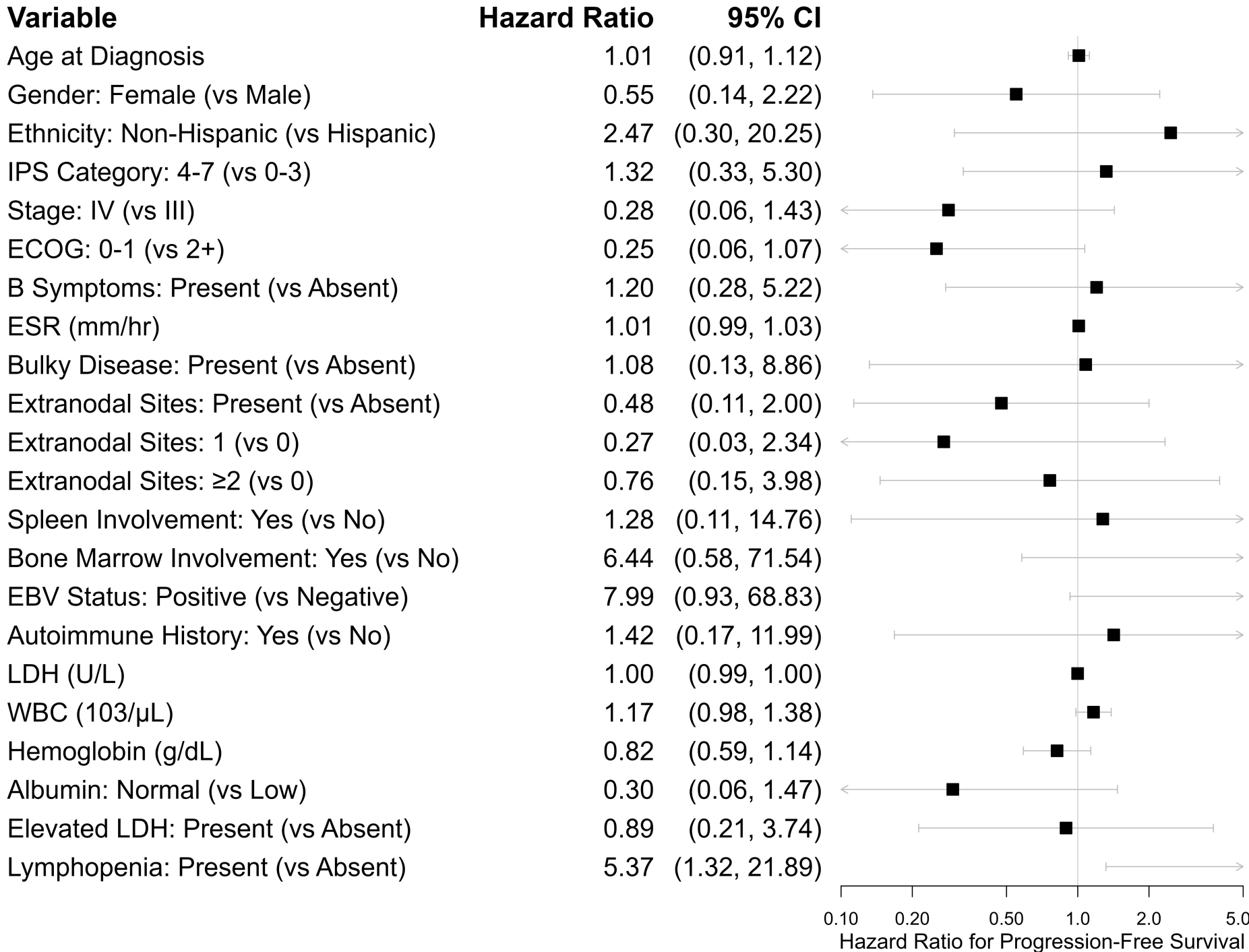
**A** Kaplan-Meier Curve for PFS by Age Group



Kaplan-Meier Curve for OS by Age Group







## **Nivolumab with Doxorubicin, Vinblastine, and Dacarbazine (NAVD) in Older Adults with Classic Hodgkin Lymphoma: Do S1826 Results Hold Up in the Real World?**

### **Supplementary Appendix**

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Supplementary Table 11. Specific toxicities leading to treatment discontinuation (n=8)

Supplementary Figure 1. Outcomes of OA with cHL treated with NAVD stratified by age. A) Progression free survival among patients stratified by age 60-69 years and  $\geq 70$  years, and B) Overall survival among patients stratified by age 60-69 years and  $\geq 70$  years.

Supplementary Figure 2. Outcomes of patients  $\geq 80$  years of age treated with NAVD. A) Progression free survival, and B) Overall survival

**Supplementary Table 1. Comparison of baseline characteristics of patients 60-69 years and ≥70 years of age treated with NAVD**

| Characteristic                                 | 60-69 years,<br>n=40<br>(49%) | ≥70 years,<br>n=41 (51%) | ASMD |
|------------------------------------------------|-------------------------------|--------------------------|------|
| <b>Age at diagnosis</b>                        |                               |                          |      |
| Median (Range)                                 | 63.5 (60 - 69)                | 76(70 - 88)              |      |
| <b>Male</b>                                    | 31 (78%)                      | 26 (63%)                 | 0.31 |
| <b>Race</b>                                    |                               |                          |      |
| Caucasian                                      | 34 (87%)                      | 37(93%)                  | 0.68 |
| African American                               | 0 (0%)                        | 3(8%)                    |      |
| Asian                                          | 1 (3%)                        | 0                        |      |
| Other                                          | 4 (10%)                       | 0                        |      |
| <b>Ethnicity</b>                               |                               |                          | 0.15 |
| Hispanic                                       | 9 (24%)                       | 7(18%)                   |      |
| <b>History of autoimmune condition, (n=81)</b> | 4 (10%)                       | 4(10%)                   | 0.02 |
| <b>B Symptoms present</b>                      | 27 (68%)                      | 19 (46%)                 | 0.44 |
| <b>Bulky Disease</b>                           | 5 (13%)                       | 3(7%)                    | 0.17 |
| <b>Ann Arbor Stage</b>                         |                               |                          | 0.02 |
| III                                            | 17(42%)                       | 17 (41%)                 |      |
| IV                                             | 23(58%)                       | 24 (59%)                 |      |
| <b>ECOG PS (n=80)</b>                          |                               |                          | 0.26 |
| 0-1                                            | 34(87%)                       | 31(78%)                  |      |
| 2-4                                            | 5(13%)                        | 9(22%)                   |      |
| <b>cHL Subtype, (n=49)</b>                     |                               |                          | 0.70 |
| Lymphocyte depleted                            | 0 (0%)                        | 1(3%)                    |      |
| Lymphocyte rich                                | 2 (11%)                       | 0 (0%)                   |      |
| Mixed cellularity                              | 6 (32%)                       | 5 (17%)                  |      |
| Nodular sclerosis                              | 11 (58%)                      | 24(80%)                  |      |
| <b>EBV-positive in biopsy, (n=69)</b>          | 15 (43%)                      | 12(29.2%)                | 0.16 |
| <b>IPS Score, (n=80)</b>                       |                               |                          | 0.20 |
| 0-3                                            | 19(47%)                       | 23 (58)                  |      |
| 4-7                                            | 21(53%)                       | 17 (43)                  |      |
| <b>Labs</b>                                    |                               |                          |      |
| LDH, Median (Range), (n=76)                    | 222 (117-1,296)               | 228 (108-720)            | 0.13 |
| WBC, Median (Range)                            | 5.6 (1.4-14.3)                | 7.3 (0.9-19.3)           | 0.51 |
| HGB, Median (Range)                            | 11.3 (7.1-16.1)               | 12.1 (7.0-16.1)          | 0.14 |
| Normal albumin                                 | 19 (48%)                      | 20(49%)                  | 0.03 |
| Lymphopenia                                    | 10 (25%)                      | 10(24%)                  | 0.01 |
| ESR, Median (range), (n=73)                    | 60(1-130)                     | 45(5-130)                | 0.11 |
| <b>Extranodal involvement</b>                  | 25(63%)                       | 24(59%)                  | 0.08 |
| 1                                              | 10 (25%)                      | 14(34%)                  | 0.30 |
| ≥ 2                                            | 15 (38%)                      | 10(25%)                  |      |

**Abbreviations:** cHL=Classic Hodgkin Lymphoma; NS =Nodular Sclerosis; ECOG PS = Eastern Cooperative Oncology Group performance status; EBV=Epstein-Barr Virus, as measured by EBV-ISH by IHC on tumor pathology; LDH=Lactate Dehydrogenase; WBC= White Blood Cell; HGB = Hemoglobin; ESR = Erythrocyte Sedimentation Rate; IPS= international prognostic score. Bulky disease defined as tumor size ≥ 7.5 cm.

**Supplementary Table 2. Comparison of treatment characteristics of older adults 60-69 years and ≥70 years of age treated with NAVD**

| Treatment Characteristic                    | 60-69 years,<br>n=40 (49%) | ≥70 years,<br>n=41 (51%) | ASMD |
|---------------------------------------------|----------------------------|--------------------------|------|
| <b>G-CSF use</b>                            | 31 (77%)                   | 35 (85%)                 | 0.20 |
| Primary ppx                                 | 22 (71%)                   | 26 (74%)                 | 0.07 |
| Secondary ppx                               | 9 (29%)                    | 9 (26%)                  |      |
| <b>Treatment Interrupted</b>                | 13 (32%)                   | 10 (24%)                 | 0.18 |
| <b>Duration of treatment interruption</b>   |                            |                          |      |
| Median (Range), days                        | 7.5 (4 - 21)               | 13 (4 - 49)              | 0.58 |
| <b>Reason for treatment delay</b>           |                            |                          |      |
| Infection/febrile neutropenia               | 2(22%)                     | 2(25%)                   |      |
| Other AE                                    | 1(11%)                     | 5(63%)                   |      |
| Neutropenia                                 | 5(56%)                     | 1(13%)                   |      |
| Pt preference/logistics                     | 1(11%)                     | 0                        |      |
| <b>Treatment Reduction*</b>                 | 8 (20%)                    | 13 (32%)                 | 0.27 |
| Doxorubicin Reduced                         | 6(15%)                     | 8(20%)                   |      |
| Vinblastine Reduced                         | 6(15%)                     | 10(24%)                  |      |
| Dacarbazine Reduced                         | 2(5%)                      | 10(24%)                  |      |
| Unknown                                     | -                          | -                        |      |
| <b>Reason for treatment reduction*</b>      |                            |                          |      |
| Neuropathy                                  | 3(7%)                      | 3(7%)                    |      |
| Cytopenias                                  | 2(5%)                      | 3(7%)                    |      |
| Treatment-related Hepatotoxicity            | 2(5%)                      | 1(2%)                    |      |
| Fatigue                                     | 1(2%)                      | 7(17%)                   |      |
| Other                                       | 1(2%)                      | 3(7%)                    |      |
| <b>Treatment Discontinued</b>               | 11(31%)                    | 10(26%)                  | 0.09 |
| <b>Treatment Discontinuation*</b>           |                            |                          |      |
| Nivolumab                                   | 8(20%)                     | 6(14%)                   |      |
| Doxorubicin                                 | 7(17%)                     | 5(12%)                   |      |
| Vinblastine                                 | 8(20%)                     | 7(17%)                   |      |
| Dacarbazine                                 | 6(15%)                     | 5(12%)                   |      |
| All therapy                                 | 5(12%)                     | 3(7%)                    |      |
| Unknown                                     | -                          | -                        |      |
| <b>Reason for Treatment Discontinuation</b> |                            |                          |      |
| Toxicity                                    | 9/11(82%)                  | 9/10 (90%)               |      |
| Other†                                      | 2                          | 0                        |      |

**Supplementary Table 3. Comparison of select adverse events of older adults 60-69 years and ≥70 years of age treated with NAVD**

**3A**

| <b>Adverse Event</b>                      | <b>60-69 years,<br/>n=40 (49%)</b> | <b>≥70 years,<br/>n=41 (51%)</b> | <b>ASMD</b> |
|-------------------------------------------|------------------------------------|----------------------------------|-------------|
| <b>Non-Hematologic Toxicity</b>           |                                    |                                  |             |
| Nausea                                    | 17 (43%)                           | 13(32%)                          | 0.22        |
| Any infection                             | 9 (23%)                            | 13(32%)                          | 0.21        |
| Neuropathy                                | 12 (30%)                           | 8(20%)                           | 0.23        |
| Diarrhea                                  | 6(15%)                             | 2(5%)                            | 0.34        |
| <b>Grade ≥ 3 Non-Hematologic Toxicity</b> | 11(28%)                            | 15(37%)                          | 0.21        |
| Infection                                 | 6(15%)                             | 4(10%)                           |             |
| Hepatotoxicity                            | 2(5%)                              | 3(7%)                            |             |
| Neuropathy                                | 2(5%)                              | 2(5%)                            |             |
| Nausea                                    | 0                                  | 2(5%)                            |             |
| Diarrhea                                  | 1(3%)                              | 0(0%)                            |             |
| <b>Febrile neutropenia</b>                | 5(13%)                             | 5(12%)                           | 0.01        |
| Cycle, median (range)                     | 1 (1 - 5)                          | 1 (1 - 1)                        |             |
| Hospitalization                           | 5/5(100%)                          | 4/5(80%)                         |             |
| <b>Hematologic toxicity</b>               |                                    |                                  |             |
| Neutropenia                               | 28(70%)                            | 23(56%)                          | 0.29        |
| <b>Grade ≥ 3 Hematologic Toxicity</b>     | 25 (63%)                           | 21(51%)                          | 0.23        |
| Neutropenia                               | 24(60%)                            | 18(44%)                          |             |
| Anemia                                    | 5(1%)                              | 6(10%)                           |             |
| Thrombocytopenia                          | 2(5%)                              | 1(2%)                            |             |

**3B**

| <b>IRAE</b>                                                           | <b>60-69 years,<br/>n=40 (49%)</b> | <b>≥70 years,<br/>n=41 (51%)</b> | <b>ASMD</b> |
|-----------------------------------------------------------------------|------------------------------------|----------------------------------|-------------|
| <b>Any Grade IRAE</b>                                                 | 13(33%)                            | 11(27%)                          | 0.12        |
| Inflammatory arthritis†                                               | 4(10%)                             | 1(2%)                            |             |
| Hypothyroidism                                                        | 3(8%)                              | 2(5%)                            |             |
| Rash                                                                  | 1(3%)                              | 2(5%)                            |             |
| Colitis                                                               | 1(3%)                              | 1(2%)                            |             |
| Hepatotoxicity                                                        | 2(5%)                              | 2(5%)                            |             |
| Pneumonitis                                                           | 2(5%)                              | 1(2%)                            |             |
| Adrenal insufficiency                                                 | -                                  | 2(5%)                            |             |
| Sarcoidosis of lung/skin                                              | -                                  | 1(2%)                            |             |
| Neutropenia                                                           | -                                  | -                                |             |
| Fatigue                                                               | 1(3%)                              | -                                |             |
| <b>Grade ≥3 IRAE</b>                                                  | 5(13%)                             | 4(10%)                           | 0.09        |
| Hepatotoxicity                                                        | 1(3%)                              | 2(5%)                            |             |
| Pneumonitis                                                           | 1(3%)                              | 1(2%)                            |             |
| Inflammatory arthritis                                                | 1(3%)                              | -                                |             |
| HLH in setting of baseline CVID                                       | -                                  | -                                |             |
| Adrenal insufficiency                                                 | -                                  | 1(2%)                            |             |
| Myocarditis                                                           | 1(3%)                              | -                                |             |
| <b>Hospitalization required for AE, (n=77)</b>                        | 11(29%)                            | 11(27%)                          | <0.01       |
| Chemotherapy-related                                                  | 6/11(55%)                          | 4/11(36%)                        |             |
| irAE-related                                                          | 3/11(27%)                          | 2/11(18%)                        |             |
| Others                                                                | 2/11(18%)                          | 0                                |             |
| <b>Duration of hospitalization, median<br/>number of days (range)</b> | 3 (1 - 15)                         | 7.5 (4 – 16)                     | 0.79        |
| ICU admission for AE, (n=70)                                          | 1(3%)                              | 0                                |             |

**Supplementary Table 4. Interim and EOT PET-CT responses among all older patients treated with NAVD**

| <b>Interim PET* (n=71)</b>         | <b>N (%)</b> | <b>1-year PFS (95% CI)</b> |
|------------------------------------|--------------|----------------------------|
| ORR                                | 71 (100%)    | 95.5 (89.4-100)            |
| CR                                 | 58 (81.6%)   | 94.5 (87.3-100)            |
| PR                                 | 11 (15%)     |                            |
| Not performed                      | 7            |                            |
| <b>End of treatment PET (n=75)</b> |              |                            |
| ORR                                | 66 (88%)     | 97.2 (92-100)              |
| CR                                 | 62 (82.6%)   | 96.9 (91-100)              |
| PR                                 | 4 (5%)       |                            |
| SD†                                | 0            |                            |
| PD                                 | 6 (8%)       |                            |
| Mixed response†                    | 3 (4%)       |                            |
| Missing/unknown                    | 6            |                            |

**Abbreviations:** CR=complete response; ORR=overall response rate, CR + partial response (PR); SD=stable disease; PD=progressive disease; PFS= progression free survival; CI= confidence interval. 6 patients did not have an EOT scan due to loss to follow up, or death prior to response assessment. Response assessment determined by the treating investigator at each site according to Lugano 2014 criteria.

\*Interim PET-CT was performed after 2 (n=51), 3 (n=15) or 4 (n=4) cycles. Unknown n=1

†All patients with mixed response have not yet had PD.

**Supplementary Table 5. Comparison of EOT PET-CT responses among older patients treated with NAVD based on age group of 60-69 years, 70-79 years and ≥80 years**

| Cohort                          | EOT PET         | 60-69 Years of Age, Count (%) | 70-79 Years of Age, Count (%) | ≥80 Years of Age, Count (%) |
|---------------------------------|-----------------|-------------------------------|-------------------------------|-----------------------------|
| Recipients of ≥1 cycles of NAVD | CR              | 28 (75.6)                     | 28 (90.3)                     | 6 (85.7)                    |
|                                 | PR              | 3 (8.1)                       | 1 (3.2)                       | 0                           |
|                                 | PD              | 3 (8.1)                       | 2 (6.4)                       | 1 (8.5)                     |
|                                 | SD              | 0                             | 0                             | 0                           |
|                                 | Mixed Response  | 3 (8.1)                       | 0                             | 0                           |
|                                 | Unknown/Missing | 3                             | 1                             | 2                           |
|                                 | ORR             | 31 (83.7)                     | 29 (93.5)                     | 6 (85.7)                    |

**Abbreviations:** CR=complete response; ORR=overall response rate, CR + partial response (PR); SD=stable disease; PD=progressive disease; PFS= progression free survival; CI= confidence interval. 6 patients did not have an EOT scan due to loss to follow up, or death prior to response assessment. Response assessment determined by the treating investigator at each site according to Lugano 2014 criteria.

**Supplementary Table 6. Multivariate logistic regression of complete response rate among all older cHL patients treated with NAVD**

|                      | <b>Odds Ratio (95% CI)</b> |
|----------------------|----------------------------|
| Stage IV             | 4.762 (0.687–33.029)       |
| Lymphopenia: Present | 0.211 (0.026–1.696)        |
| EBV: Positive        | 0.259 (0.039–1.736)        |
| B symptoms: Present  | 0.448 (0.064–3.162)        |
| Age at diagnosis     | 1.189 (0.997–1.417)        |

**Supplementary Table 7. Comparison of baseline characteristics of patients  $\geq 60$  years and  $< 60$  years of age**

| Characteristic                          | $\geq 60$ years, n=81<br>N (%) | $< 60$ years, n=246<br>N (%) | ASMD     |
|-----------------------------------------|--------------------------------|------------------------------|----------|
| <b>Age at diagnosis, Median (Range)</b> | 70 (60– 88)                    | 30 (18 - 59)                 |          |
| <b>Male</b>                             | 57 (70%)                       | 129 (52%)                    | 0.37     |
| <b>Race</b>                             |                                |                              | 0.48     |
| White                                   | 71 (90%)                       | 172 (73%)                    |          |
| African American                        | 3 (4%)                         | 25 (11%)                     |          |
| Asian                                   | 1 (1.3%)                       | 14 (6%)                      |          |
| Other                                   | 4 (5%)                         | 20 (8%)                      |          |
| <b>Ethnicity, Hispanic</b>              | 16 (20%)                       | 43 (18%)                     | 0.07     |
| <b>History of autoimmune condition</b>  | 8 (10%)                        | 17 (7%)                      | 0.10     |
| <b>B Symptoms present</b>               | 46 (57%)                       | 126 (51%)                    | 0.11     |
| <b>Bulky Disease</b>                    | 8 (10%)                        | 80 (33%)                     | 0.58     |
| <b>Ann Arbor Stage</b>                  |                                |                              |          |
| III                                     | 34 (42%)                       | 94 (38%)                     | 0.08     |
| IV                                      | 47 (58%)                       | 152 (62%)                    |          |
| <b>ECOG PS</b>                          |                                |                              |          |
| 0-1                                     | 65 (82%)                       | 224(97%)                     | 0.48     |
| 2-4                                     | 14(18%)                        | 8(3%)                        |          |
| <b>cHL Subtype</b>                      |                                |                              | 0.41     |
| Lymphocyte depleted                     | 1 (2%)                         | 0                            |          |
| Lymphocyte rich                         | 2 (4%)                         | 4 (2%)                       |          |
| Mixed cellularity                       | 11 (22%)                       | 20 (11%)                     |          |
| Nodular sclerosis                       | 35 (71%)                       | 160 (87%)                    |          |
| <b>EBV-positive</b>                     | 27 (39%)                       | 46 (21%)                     | 0.40     |
| <b>IPS Score, (n=80)</b>                |                                |                              |          |
| 0-3                                     | 42 (53%)                       | 185(77%)                     | 0.53     |
| 4-7                                     | 38 (48%)                       | 55(23%)                      |          |
| <b>Labs</b>                             |                                |                              |          |
| LDH, Median (Range), (n=76)             | 222 (108 – 1,296)              | 238 (115 - 1,474)            | 0.09     |
| WBC, Median (Range)                     | 6.6 (0.9 – 19.4)               | 10.2 (1.5 - 33.5)            | 0.81     |
| HGB, Median (Range)                     | 11.6 (7.0 – 16.1)              | 12 (6.4 - 16.2)              | 0.12     |
| Low albumin                             | 42 (52%)                       | 97 (39%)                     | 0.24     |
| Lymphopenia                             | 20 (24%)                       | 60 (25%)                     | $< 0.01$ |
| ESR, Median (range), (n=73)             | 47 (1 – 130)                   | 48 (1 - 130)                 | $< 0.01$ |
| <b>Extranodal involvement</b>           | 49 (61%)                       | 153 (62%)                    | 0.03     |
| 1                                       | 24 (30%)                       | 88 (36%)                     | 0.14     |
| $\geq 2$                                | 25 (31%)                       | 65 (26%)                     |          |

**Abbreviations:** cHL=Classic Hodgkin Lymphoma; NS =Nodular Sclerosis; ECOG PS = Eastern Cooperative Oncology Group performance status; EBV=Epstein-Barr Virus, as measured by EBV-ISH by IHC on tumor pathology; LDH=Lactate Dehydrogenase; WBC= White Blood Cell; HGB = Hemoglobin; ESR = Erythrocyte Sedimentation Rate; IPS= international prognostic score. Bulky disease defined as tumor size  $\geq 7.5$  cm.

**Supplementary Table 8: Comparison of treatment characteristics of patients ≥60 years and <60 years of age with cHL treated with NAVD**

| Treatment Characteristic                    | ≥60 years n=81<br>N (%) | <60 years n=246<br>N (%) | ASMD |
|---------------------------------------------|-------------------------|--------------------------|------|
| <b>G-CSF use</b>                            | 66 (82%)                | 143 (58%)                | 0.53 |
| Primary ppx                                 | 48 (73%)                | 68 (48%)                 | 0.52 |
| Secondary ppx                               | 18 (27%)                | 74 (52%)                 |      |
| <b>Treatment Interrupted</b>                | 23 (28%)                | 61 (25%)                 | 0.08 |
| <b>Duration of treatment interruption</b>   |                         |                          | 0.25 |
| Median (Range), days                        | 10 (4 - 49)             | 7.5 (2 - 42)             |      |
| <b>Reason for treatment delay</b>           |                         |                          |      |
| Infection/febrile neutropenia               | 4 (24%)                 | 14 (33%)                 |      |
| Other AE                                    | 6 (35%)                 | 9 (21%)                  |      |
| Neutropenia                                 | 6 (35%)                 | 8 (19%)                  |      |
| Pt preference/logistics                     | 1 (6%)                  | 8 (19%)                  |      |
| <b>Treatment Reduction*</b>                 | 21 (26%)                | 19 (8%)                  | 0.50 |
| Doxorubicin Reduced                         | 14 (17%)                | 7(3%)                    |      |
| Vinblastine Reduced                         | 16 (20%)                | 19(8%)                   |      |
| Dacarbazine Reduced                         | 12 (15%)                | 5(2%)                    |      |
| Unknown                                     | 2 (2%)                  | -                        |      |
| <b>Reason for treatment reduction*</b>      |                         |                          |      |
| Neuropathy                                  | 6 (7%)                  | 10(4%)                   |      |
| Cytopenias                                  | 5 (6%)                  | 1(0.4%)                  |      |
| Treatment-related<br>Hepatotoxicity         | 3(2%)                   | 2(0.8%)                  |      |
| Fatigue                                     | 8 (10%)                 | 0                        |      |
| Other                                       | 4 (5%)                  | 1(0.4%)                  |      |
| <b>Treatment Discontinued</b>               | 21 (28%)                | 27 (11%)                 | 0.44 |
| <b>Treatment Discontinuation*</b>           |                         |                          |      |
| Nivolumab                                   | 14 (17%)                | 19 (8%)                  |      |
| Doxorubicin                                 | 12 (15%)                | 6 (2%)                   |      |
| Vinblastine                                 | 15 (19%)                | 12 (5)                   |      |
| Dacarbazine                                 | 11 (14%)                | 7 (3%)                   |      |
| All therapy                                 | 8 (10%)                 | 5 (2%)                   |      |
| Unknown                                     | 7                       | 5                        |      |
| <b>Reason for Treatment Discontinuation</b> |                         |                          |      |
| Toxicity                                    | 18/21(86%)              | 23/27(85%)               |      |
| Other                                       | 2†                      | 2                        |      |

**Abbreviations:** G-CSF=Granulocyte Colony-Stimulating Factor; ppx=prophylaxis; AE=adverse event; Pt=patient. Primary prophylaxis refers to empiric use of G-CSF. Secondary prophylaxis refers to addition of G-CSF in response to infection or neutropenia. Cytopenias include anemia, thrombocytopenia or neutropenia with decision for treatment modification at discretion of treating physician. Patients included in this table received at least 1 cycle of treatment.

\*Percentages are given among all patients, excluding unknown

†One patient self-discontinued therapy and was lost to follow up, one pt had doxorubicin discontinued due to prior anthracycline use

**Supplementary Table 9: Comparison of select adverse events (3A) and Immune related adverse events (3B) in cHL patients treated with NAVD: ≥60 years vs <60 years of age**

**9A**

| <b>Adverse Event</b>                      | <b>≥60 years n=81<br/>N (%)</b> | <b>&lt;60 years n=246<br/>N (%)</b> | <b>ASMD</b> |
|-------------------------------------------|---------------------------------|-------------------------------------|-------------|
| <b>Non-Hematologic Toxicity</b>           |                                 |                                     |             |
| Nausea                                    | 30 (37%)                        | 151 (61%)                           | 0.50        |
| Any infection                             | 22 (27%)                        | 60 (24%)                            | 0.06        |
| Neuropathy                                | 20 (25%)                        | 78 (32%)                            | 0.15        |
| Diarrhea                                  | 8 (10%)                         | 32 (13%)                            | 0.10        |
| <b>Grade ≥ 3 Non-Hematologic Toxicity</b> | 26 (32%)                        | 54 (22%)                            | 0.24        |
| Infection                                 | 10 (12%)                        | 24 (10%)                            | 0.08        |
| Hepatotoxicity                            | 5 (6%)                          | 6(3%)                               |             |
| Neuropathy                                | 4 (5%)                          | 4 (2%)                              |             |
| Nausea                                    | 2 (2%)                          | 5 (2%)                              |             |
| Diarrhea                                  | 1 (1%)                          | 5 (2%)                              |             |
| <b>Febrile neutropenia</b>                | 10 (12%)                        | 21 (9%)                             | 0.12        |
| Cycle, median (range)                     | 1 (1-5)                         | 3 (1- 6)                            |             |
| Hospitalization                           | 9 /10 (90%)                     | 18/21(86%)                          |             |
| <b>Hematologic toxicity</b>               |                                 |                                     |             |
| Neutropenia                               | 51 (63%)                        | 182 (74%)                           |             |
| <b>Grade ≥ 3 Hematologic Toxicity</b>     | 46 (57%)                        | 132 (54%)                           | 0.05        |
| Neutropenia                               | 42 (52%)                        | 122 (50%)                           |             |
| Anemia                                    | 11 (14%)                        | 9 (4%)                              |             |
| Thrombocytopenia                          | 3 (4%)                          | 2 (0.8%)                            |             |

## 9B

| IRAE                                                              | ≥60 years n=81<br>N (%) | <60 years n=246<br>N (%) | ASMD |
|-------------------------------------------------------------------|-------------------------|--------------------------|------|
| <b>Any Grade IRAE</b>                                             | 24 (30%)*               | 70 (28%)                 | 0.02 |
| Inflammatory arthritis                                            | 5 (6%) †                | 7 (3%)                   |      |
| Hypothyroidism                                                    | 5 (6%)                  | 26 (11%)                 |      |
| Rash                                                              | 3 (4%)                  | 8 (3%)                   |      |
| Colitis                                                           | 2 (2%)                  | 4 (2%)                   |      |
| Hepatotoxicity                                                    | 4 (5%)                  | 16 (6%)                  |      |
| Pneumonitis                                                       | 3 (4%)                  | 1 (0.4%)                 |      |
| Adrenal insufficiency                                             | 2 (2%)                  | 2 (0.8%)                 |      |
| Sarcoidosis of lung/skin                                          | 1 (1%)                  | -                        |      |
| Neutropenia                                                       | 1 (1%)                  | -                        |      |
| Fatigue                                                           | 1 (1%)                  | -                        |      |
| <b>Grade ≥3 IRAE</b>                                              | 9 (11%)                 | 19 (8%)                  | 0.11 |
| Hepatotoxicity                                                    | 3 (4%)                  | 10                       |      |
| Pneumonitis                                                       | 2 (2%)                  | -                        |      |
| Inflammatory arthritis                                            | 1 (1%)                  | 2                        |      |
| HLH in setting of baseline CVID                                   | 1 (4%)                  | -                        |      |
| Adrenal insufficiency                                             | 1 (1%)                  | 1                        |      |
| Myocarditis                                                       | 1 (1%)                  | -                        |      |
| Type 1 Diabetes                                                   | -                       | 1                        |      |
| Colitis                                                           | -                       | 3                        |      |
| Acute Kidney Injury requiring dialysis                            | -                       | 1                        |      |
| Pancreatitis                                                      | -                       | 1                        |      |
| DRESS                                                             | -                       | 1                        |      |
| <b>Hospitalization required for AE, (n=77)</b>                    | 22 (29%)                | 44 (19%)                 | 0.24 |
| Chemotherapy-related                                              | 13 (17%)                | 17 (38%)                 |      |
| irAE-related                                                      | 5 (7%)                  | 10 (22%)                 |      |
| Others                                                            | 4 (5%)                  | 16 (36%)                 |      |
| <b>Duration of hospitalization, median number of days (range)</b> | 5.5 (1-16)              | 4 (1 - 17)               | 0.49 |
| <b>ICU admission for AE, (n=70)</b>                               | 1 (1.2%)                | 3 (1.2%)                 | 0.01 |
| Chemotherapy related                                              | 0                       | 1                        |      |

Abbreviations: AE=adverse event, ICU=intensive care unit, HLH=hemophagocytosis lymphohistiocytosis, CVID=common variable immunodeficiency, DRESS- Drug reaction with eosinophilia and systemic symptoms. Patients included in this table received at least 1 cycle of treatment with NAVD.

\*30 total irAE events in 24 pts, †Inflammatory arthritis includes specifically: sacroiliitis (n=1) and polymyalgia rheumatica (n=1).

**Supplementary Table 10. Frequency of selected adverse events among older adults treated with NAVD in the RW cohort vs S1826**

| Adverse Event                                | Real world (n=82) (n %) | S1826 (n=49) (n %)      |
|----------------------------------------------|-------------------------|-------------------------|
| <b>Grade ≥ 3 Non-Hematologic Toxicity</b>    |                         |                         |
| Any grade≥3 infection                        | 10 (12%)                | 3 (6%, coded as sepsis) |
| Grade ≥ 3 hepatotoxicity                     | 5 (6%)                  | 3 <sup>†</sup> (6%)     |
| Grade ≥ 3 neuropathy                         | 4 (5%)                  | 0                       |
| Grade ≥ 3 nausea                             | 2 (2%)                  | 0                       |
| Grade ≥ 3 diarrhea                           | 1 (1%)                  | 2 (4%)                  |
| Grade ≥ 3 diarrhea                           | 0                       | 1 (2%)                  |
| Grade ≥ 3 thromboembolic events              | 0                       | 2 (4%)                  |
| <b>Febrile neutropenia</b>                   | 10 (12%)                | 6 (12%)                 |
| <b>Hematologic toxicity</b>                  |                         |                         |
| Neutropenia                                  | 52 (63%)                |                         |
| <b>Grade ≥ 3 Hematologic Toxicity</b>        | 46 (56%)                |                         |
| Neutropenia                                  | 43 (52%)                | 24 (49%)                |
| Anemia                                       | 11 (13%)                | 5 (10%)                 |
| Thrombocytopenia                             | 3 (4%)                  | 2 (4%)                  |
| <b>Immune related adverse events (irAE)*</b> |                         |                         |
| Grade ≥ 3 irAE                               | 9 (12%)                 |                         |
| Hepatotoxicity                               | 3 (4%)                  | 4 <sup>‡</sup>          |
| Pneumonitis                                  | 2 (2%)                  | 1                       |
| Inflammatory arthritis                       | 1 (1%)                  | 0                       |
| HLH in setting of baseline CVID              | 1 (4%)                  | 0                       |
| Adrenal insufficiency                        | 1 (1%)                  | 1                       |
| Myocarditis                                  | 1 (1%)                  | 0                       |
| Colitis                                      | 0                       | 2                       |
| Hypothyroidism                               | 0                       | 1                       |

**Abbreviations:** AE=adverse event, ICU=intensive care unit, HLH=hemophagocytosis lymphohistiocytosis, CVID=common variable immunodeficiency. Patients included in this table received at least 1 cycle of treatment with NAVD.

\*30 total irAE events in 24 pts, †Inflammatory arthritis includes specifically: sacroiliitis (n=1) and polymyalgia rheumatica (n=1).

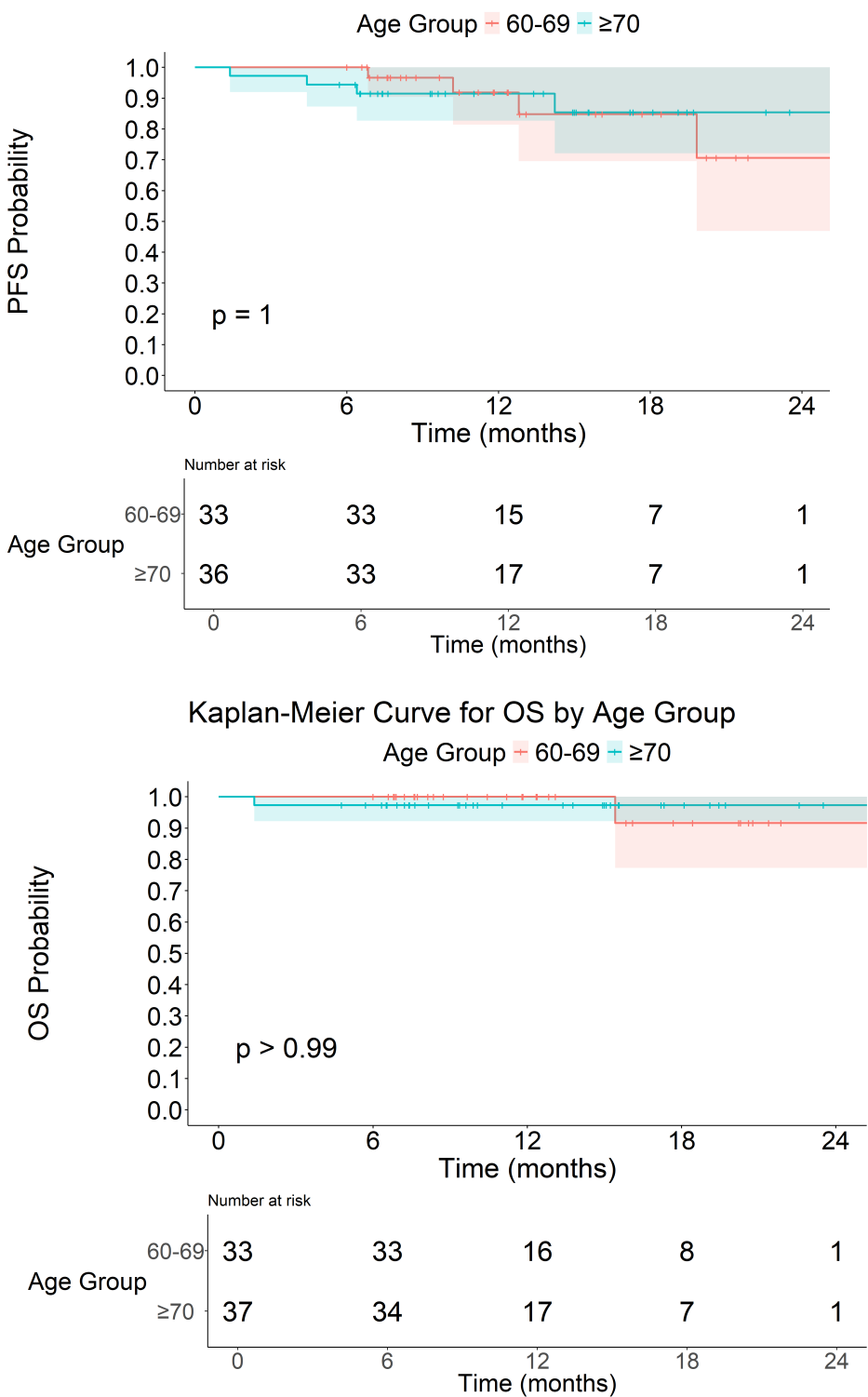
‡ In S1826, IrAE was not specifically coded as hepatitis. These numbers belong to the row 'ALT increased'. We omitted the 'AST increased' numbers since they were lower than 'AST increased' with the assumption that any patient with significant hepatitis is likely to have both AST and ALT increased at the same time.

**Note:** RW AEs were retrospectively ascertained and graded using CTCAE v5.0 where feasible and may be under-ascertained, particularly grade 1–2 non-hematologic toxicities. Comparisons with prospectively collected S1826 data should therefore be interpreted cautiously.

**Supplementary Table 11. Specific toxicities leading to treatment discontinuation (n=8)**

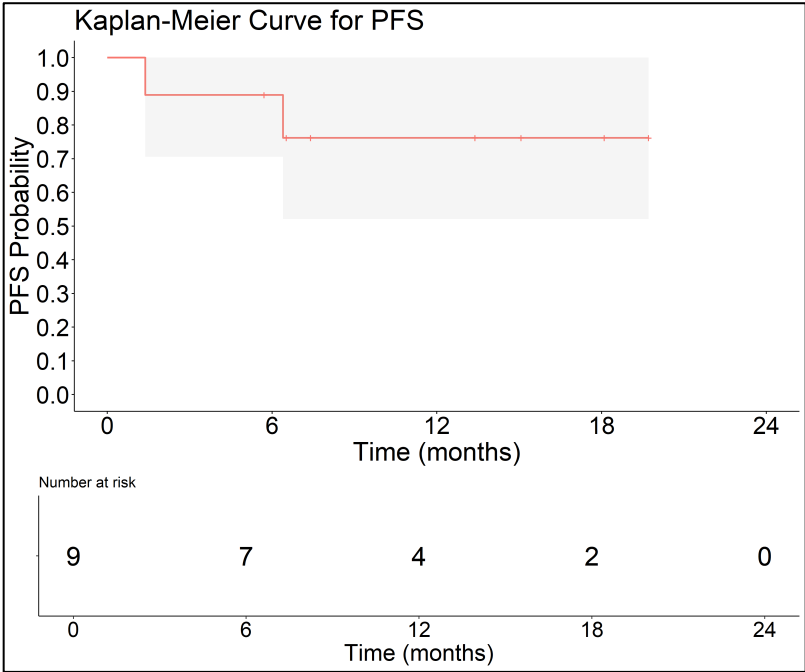
| Toxicity                               | Immune-related?                               | No. of cycles received |
|----------------------------------------|-----------------------------------------------|------------------------|
| Severe pancytopenia                    | Possible                                      | 4                      |
| Myocarditis, neutropenia               | Yes                                           | 3                      |
| Cryptococcal meningitis                | No                                            | 3                      |
| Cytomegalovirus/Giardiasis, neuropathy | Possible for neuropathy (sacral mononeuritis) | 5.5                    |
| Hepatotoxicity                         | Yes                                           | 3                      |
| Hepatotoxicity                         | Yes                                           | Unknown                |
| Grade 3 neuropathy                     | Possible                                      | 4                      |
| Grade 3 neuropathy                     | No                                            | 5                      |

**Supplementary Figure 1. Outcomes of OA with cHL treated with NAVD stratified by age.** A) Progression free survival among patients stratified by age 60-69 years and  $\geq 70$  years, and B) Overall survival among patients stratified by age 60-69 years and  $\geq 70$  years.



**Supplementary Figure 2. Outcomes of patients  $\geq 80$  years of age treated with NAVD. A) Progression free survival, and B) Overall survival**

A)



B)

