haematologica
Journal of the Ferrata Storti Foundation

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Received: November 9, 2026.
Accepted: November 16, 2026.

Citation: Reid W. Merryman. Closing the age gap: real-world outcomes of N-AVD for older patients with classic Hodgkin lymphoma.
Haematologica. 2026 Nov 26. doi: 10.3324/haematol.2026.302293 [Epub ahead of print]

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Closing the age gap: real-world outcomes of N-AVD for older patients with classic Hodgkin lymphoma

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Conflicts of Interests: RWM - Advisory board: Genmab, Bristol Myers Squibb, Abbvie, Ipsen, KITE, Pfizer, AstraZeneca. Consulting: Abbvie, Third Bridge. Honararia: Genmab, Abbvie. Institutional research funding: Merck, Bristol Myers Squibb, Genmab, Genentech/ Roche.

In this issue, Torka and colleagues report encouraging real-world outcomes for older patients with classic Hodgkin lymphoma (cHL) receiving first-line treatment with N-AVD (nivolumab, doxorubicin, vinblastine, and dacarbazine).[1] This study, which represents the largest analysis of N-AVD treatment in older patients, supplements two prospective clinical trials[2,3] and further strengthens the argument that N-AVD should be the preferred regimen for most older patients with advanced stage cHL.

Historically, older patients with cHL have had inferior outcomes compared to younger patients driven by increased morbidity and mortality, reduced tolerance of standard therapies, and less favorable disease biology.[4,5] Most older patients with advanced cHL can be cured with anthracycline-based chemotherapy, but tolerability is a critical issue. Treatment with 6 cycles of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) in older patients is avoided due to high rates of bleomycin lung toxicity in this population. Substituting brentuximab vedotin (BV) for bleomycin did not resolve the issues of treatment-related toxicity for older patients. In the ECHELON-1 trial which compared BV-AVD to ABVD, the PFS benefit observed in other populations was not seen in older patients likely due to higher rates of treatment discontinuation and more frequent adverse events with BV-AVD.[6] Unfit older patients who are not candidates for anthracycline-based combination therapy have particularly poor outcomes. In recent years, the outlook for older patients has changed with the development of N-AVD as an initial treatment option for cHL. In the phase III S1826 trial, N-AVD was associated with both improved efficacy and tolerability compared to BV-AVD.[7] In a subset analysis of 99 patients aged ≥ 60, who represented 10% of trial enrollment, the benefit was particularly pronounced with an improvement in 2-year PFS (89% vs 64%, p=0.001) and a reduction in the rate of non-relapse mortality (6% vs 16%).[3] A phase II trial of N-AVD in 40 older patients (aged ≥60 years) with untreated cHL also reported outcomes that were significantly better than historical controls (3-year PFS of 79% and 3-year OS of 97%).[2] While these results are very encouraging, two key questions remain. Do these findings extend beyond the highly selected trial patients to those treated in the “real-world?” And does efficacy and tolerability vary by age and fitness among older patients?

To address these questions, Torka and colleagues conducted an in-depth subgroup analysis of older patients from a previously assembled real-world cohort of 327 patients who received first-line N-AVD across 20 U.S. sites. The older patient subgroup comprised 81 patients and represented 25% of the overall cohort. The median age within the older adult cohort was 70 (range 60-88), which is slightly higher than in the S1826 and phase II trial populations (median age 66 in both cohorts), and included 40 (49%) patients aged 60-69, 32 (40%) aged 70-79, and 9 (11%) aged 80+. The larger size of this cohort allowed for a breakdown by decade among older patients, an approach that was not feasible in the smaller trial datasets.

N-AVD treatment was feasible, but more challenging to administer among older patients. Compared to younger patients, those aged 60 or older experienced more frequent hospitalizations due to AEs (29% vs 19%), more frequent dose reductions (26% vs 8%), and more frequent treatment discontinuation (26% vs 11% of patients discontinued at least one component of N-AVD). Nevertheless, 90% of patients were able to complete 6 cycles of therapy. Among the 10% who discontinued all treatment early, the median number of cycles received

was 5. Among older patients, rates of treatment delays and treatment discontinuation were similar among patients aged 60-69 and patients ≥70, while dose reductions were more common in patients ≥70 (32% vs 20%). Growth factor support use was more common in older patients compared to younger patients (82% vs 58%) with most older patients receiving growth factor as primary prophylaxis. With this frequent growth factor support, rates of febrile neutropenia in older patients were similar to those seen in younger patients (12% vs 9%).

Despite the increased challenges of N-AVD administration among older patients, efficacy was excellent. The end-of-treatment overall and complete metabolic response rates in older patients were 88% and 83%, respectively. With a median follow-up of 12.6 months, the 1-year PFS was 92% and the 1-year OS was 99%. Similar to S1826, there was a numerical trend toward inferior PFS among older patients compared to younger patients (log-rank p=0.071), but the gap in outcomes is smaller than in historical series with BV-AVD or ABVD treatment.[4,5,8] Similar efficacy outcomes were seen for patients in their 60s and 70s, but PFS appeared to be slightly inferior in the small cohort of patients aged 80 and older (1-year PFS 76%), although larger cohorts are needed to better define outcomes in very elderly patients.

While efficacy results are excellent with N-AVD, there are still significant challenges for this population. Many older patients are not candidates for anthracycline-based treatment due to comorbidities or fitness. There remains no standard treatment approach for frail or unfit patients and currently available treatments generally have limited curative potential.[9,10] As such, determining candidacy for curative-intent therapies has huge consequences and there are not validated geriatric or frailty scores that can aid physicians and patients with this critical decision. Even among fit older patients, there are important opportunities for toxicity mitigation. A wave of response-adapted trials that selectively de-escalate therapy based on early clearance of minimal residual disease (MRD) are enrolling patients or in development (NCT 06745076). Because older patients experience greater toxicity, they may be among those who might benefit most from this approach.

This study provides additional support for N-AVD as a preferred treatment approach among clinically selected older patients. Longer follow-up is needed to define durability of response and to identify delayed adverse events, which may be different among older patients. Important unmet needs remain including better treatment options for frail or very elderly patients who cannot receive anthracycline-based therapy and remain underrepresented in both trials and real-world data sets. Nevertheless, N-AVD has emerged as a major step forward for the treatment of older patients with cHL.

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