Progression-free survival at 24 months (PFS24) and subsequent outcome for patients with diffuse large B-cell lymphoma (DLBCL) in the real-world setting

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other anticancer medications, may improve treatment still further in future.

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Progression-free survival at 24 months (PFS24) and subsequent outcome for patients with diffuse large B-cell lymphoma (DLBCL) in the real-world setting

With great interest, we read the article by Maurer et al., in which the *Surrogate Endpoint for Aggressive Lymphoma* (SEAL) collaboration reported that diffuse large B-cell lymphoma (DLBCL) patients who are enrolled in randomized clinical trials and remain alive without progression at 24 months from the onset of treatment with the first-line anthracycline-based immunochemotherapy (PFS24), have excellent outcomes, with an overall survival (OS) comparable to the general population [1]. Using PFS24 as a surrogate end point in clinical trials compared with the classic OS may allow a faster approval of effective new drugs for hemato-oncologic patients with unmet medical needs. However, in the end, these new drugs will be applied not only to DLBCL patients in randomized clinical trials but also to a substantial amount of 'real-world' patients, who are excluded from trials for several reasons such as patient preference, socioeconomic circumstances, distant homes, older age and comorbidities [2, 3]. To answer the question how the data from the SEAL collaboration compare with 'real-world', we would like to report the population-based survival data from our HemoBase registry, which is a > 10-year cohort from 2005 to 2018, including all 558 patients diagnosed with DLBCL treated in the province of Friesland, The Netherlands [4]. In addition, as this database contains fully complete parameters, we can provide insight in causes of death after PFS24.

In our cohort, 474 (85%) patients received anthracycline-containing immuno-chemotherapy. Median age was 67 years (range 18–93) and 70% of patients were >60 years, which is older than patients from the SEAL cohort (52% >60) [1]. Patients were 56% male, 48% had an elevated lactate dehydrogenase, 53% had stage III–IV disease and 13% had an Eastern Cooperative Oncology Group performance status of 2–4. The International Prognostic Index was 0–1 in 37%, 2 in 26%, 3 in 21% and 4–5 in 16% and comparable to the SEAL cohort. 319 patients (67%) achieved PFS24. The subsequent OS at 3, 5 and 7 years was 91.2%, 85.5% and 71.6%, respectively (Figure 1A). After PFS24, 28/319 patients (9%) had relapsed disease and 57/319 patients (18%) died. Causes of death were relapsed lymphoma (19%), cardiovascular events (23%), second malignancies (25%) and other (8%). In 25% of cases, the cause of death was unknown—the majority of these patients were >80 years old (Figure 1B).

In conclusion, although patients in clinical trials differ substantially from those in the general population, OS in our 'real-world' cohort did not differ from OS in the SEAL cohort for PFS24 patients in the first 5 years, supporting the use of PFS24 as a surrogate end point. However, after 5 years, in comparison with clinical trial patients, there was a slight decline in survival. Even years after PFS24, fatal relapses occurred. Also, a notable number of

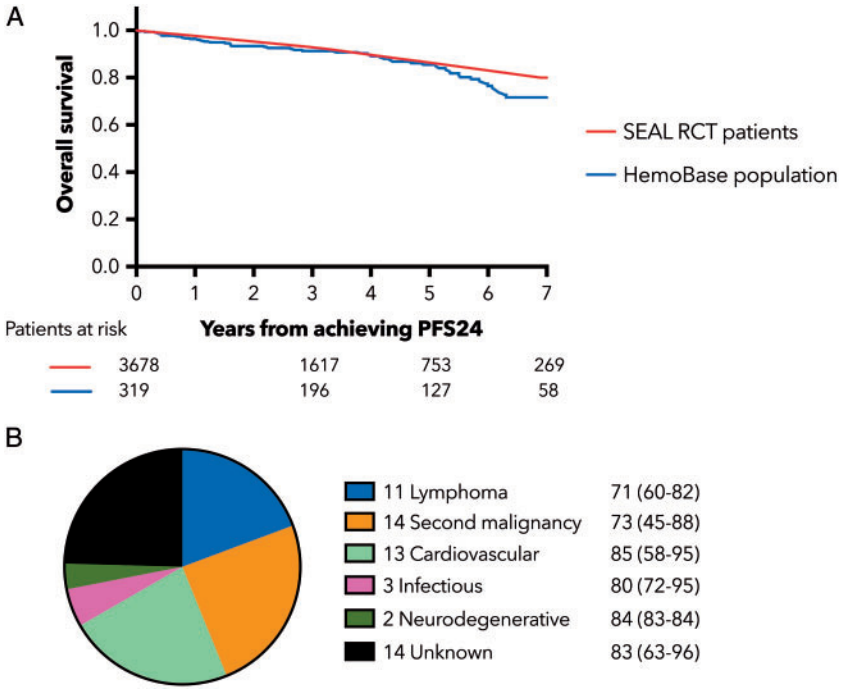

Figure 1. Overall survival (OS) from achieving progression-free survival at 24 months (PFS24) and causes of death. (A) OS from PFS24 of the 319 HemoBase patients [blue (online) line] who were progression free at 24 months after initiating treatment versus the 3678 *Surrogate Endpoint for Aggressive Lymphoma* (SEAL) patients [red (online) line] is shown. (B) Causes of death are divided into six subgroups. Besides each subgroup, the median age (with range) at the time of death of patients in the subgroup is shown. RCT, randomized clinical trial.

deaths may have been related to previous DLBCL treatment with immuno-chemotherapy, e.g. cardiovascular events and second malignancies. However, these patients represent an older population with more comorbidities. Longer follow-up of the SEAL collaboration data and comparison to our cohort will give more insight into these important events for all patients.

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