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ORIGINAL ARTICLE

The interval between progression and therapy initiation is the key prognostic parameter in relapsing diffuse large B cell lymphoma: analysis from the Czech Lymphoma Study Group database (NIHIL)

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Abstract

Relapsing diffuse large B cell lymphomas (rDLBCL) represent a heterogeneous disease. This heterogeneity should be recognized and reflected, because it can deform the interpretation of clinical trial results. DLBCL patients with the first relapse and without CNS involvement were identified in the Czech Lymphoma Study Group (CLSG) database. Interval-to-therapy (ITT) was defined as the time between the first manifestation of rDLBCL and the start of any treatment. The overall survival (OS) of different ITT cohorts (< 7 vs. 7–21 vs. > 21 days) was compared. In total, 587 rDLBCLs (51.8% males) progressed with a median of 12.8 months (range 1.6 to 152.3) since the initial diagnosis (2000–2017). At the time of relapse, the median age was 67 years (range 22–95). First-line therapy was administered in 99.3% of the patients; CHOP and anti-CD20 were given to 69.2% and 84.7% of the patients, respectively. The salvage immune/chemotherapy was administered in 88.1% of the patients (39.2% platinum-based regimen). The median ITT was 20 days (range 1–851), but 23.2% of patients initiated therapy within 7 days. The 5-year OS was 17.4% (range 10–24.5%) vs. 20.5% (range 13.5–27.4%) vs. 42.2% (range 35.5–48.8%) for ITT < 7 vs. 7–21 vs. > 21 days ($p < 0.001$). ITT was associated with B symptoms (p 0.004), ECOG ($p < 0.001$), stage (p 0.002), bulky disease (p 0.005), elevated LDH ($p < 0.001$), and IPI ($p < 0.001$). The ITT mirrors the real clinical behavior of rDLBCL. There are patients (ITT < 7 days) with aggressive disease and a poor outcome. Conversely, there are rDLBCLs with ITT ≥ 21 days who survive for a long time.

Keywords Diffuse large B cell lymphoma · Prognosis · Relapse · Therapy

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Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphomas (NHL) in adults, reaching around 40% of all newly diagnosed cases [1] worldwide. Despite its aggressive course, there is a 40–50% chance of patients being cured with conventional immunochemotherapy. Therapy combination is usually based on anthracyclines and monoclonal antibody anti-CD20 [2–6]. On the other hand, there is a similar share of patients who develop recurrent disease, including around 10% of cases progressing during therapy, and another 30–40% of patients relapsing after remission [7, 8]. Patients with recurrent DLBCL survive globally with approximately a median 12 months after relapse, but this group of patients is very heterogeneous. The patients who relapsed beyond 12 months from diagnosis had a better outcome (median OS 37.8 months) compared with patients with primary refractory disease (median OS 7.0 months) or patients who relapsed within 12 months (median OS 12.5 months) [8]. Up till now, the majority of deaths (76%) in DLBCL patients have been attributed to lymphoma, and only the minority (24%) to non-cancer causes [5].

There is an urgent need of efficient therapy for relapsing patients. Just as a matter of interest, despite intensive research and the testing of many new molecules and treatment combinations, no significant clinical success has been identified in this area. As of December 2018, the official Database of Clinical Trials (https://www.clinical.trials.gov) had registered roughly 450 interventional clinical studies dealing with DLBCL (for patients ≥ 18 years) starting in the period from January 1, 2000, to December 1, 2018, and having the status: "enrolling, recruiting, active non-recruiting, completed, terminated, or suspended." Of this number, 300 studies have focused on relapsed or refractory disease [9].

Clinical trials are a modern, rational, and, undoubtedly, efficient medical research tool that has brought major progress in many fields of medicine. However, clinical trials can only fulfill this task under the following conditions: (1) the design of the clinical trial responds correctly to the scientific aims and (2) the population of the study patients does not differ significantly from the usual relevant population. However, selection bias can subvert the randomization process, leading to biased estimates of treatment effects and misleading conclusions. Restricted randomization can increase the risk of selection [10]. The inclusion/exclusion criteria of the majority of study protocols struggle to define the "optimal" study population, resulting more or less in the selection of atypical cases in the framework of a specific diagnosis. It can be said, generally, that the more aggressive the disease (lymphoma), the greater the risk of distortion of the study population compared with that of real patients.

Inclusion/exclusion (selection) criteria are widely acknowledged selection barriers for enrollment in clinical studies. Another obstacle is represented by many time-consuming procedures required during the screening period. For a long time, the screening period was not reflected as a selection factor. Twenty-eight days formally defined per protocol seems to be a sufficient time for all procedures, but too long for some patients with rapidly progressing lymphoma to wait for study treatment. Just recently, the diagnosis-to-treatment interval was reported as a strong prognostic parameter in newly diagnosed DLBCL patients [11].

Regarding the abovementioned facts, we analyzed patients with the initial recurrence of DLBCL in the context of the time between relapse diagnosis and therapy initiation. The cutoff points were selected on the basis of two reasons. The time point of < 7 days is important because DLBCL patients requiring therapy within 1 week usually move from enrollment into clinical trials; on the opposite end of the spectrum, the cutoff is ≥ 21 days, which is related to the minimum technological time necessary for the manufacture and administration of CAR-Ts, which seems to be a currently highly promising treatment modality [12, 13].

Methods

Patients

The prospectively maintained CLSG database "NIHIL" (Czech Lymphoma Study Group; Govtrial NT 03199066) was used as a data source for this retrospective analysis. In total, 4980 patients with diffuse large B cell lymphomas (DLBCLs) initially diagnosed between 2000 and 2017 were registered in the database as of October 2018. For the retrospective analysis, patients with the first progression or relapse of DLBCL, with valid records on therapy and without documented CNS involvement, were included ($n = 587$). The consort diagram depicting patient selection is shown in Fig. 1.

CLSG is a free association of university centers and authorized hematological and oncological non-academic centers in the Czech Republic. The CLSG database of non-Hodgkin lymphomas (NIHIL) has prospectively maintained data of newly diagnosed lymphoma patients and covers approximately 85% of all adult non-skin NHL cases (age ≥ 18 years) in the Czech Republic [14]. The patients signed an informed consent with data collection and storage before the data was entered into the NIHIL database. The diagnosis of DLBCL was established locally, but confirmation of the diagnosis was given by the hemopathologists in the university centers according to the 2008 edition of the WHO classification of lymphoid neoplasms [15]. Cell of origin (COO) determination (GCB vs. non-GCB) has been routinely used in recent years in accordance with the Hans algorithm [16].

The patient stage was determined by the treating physician according to the Ann Arbor criteria, and more

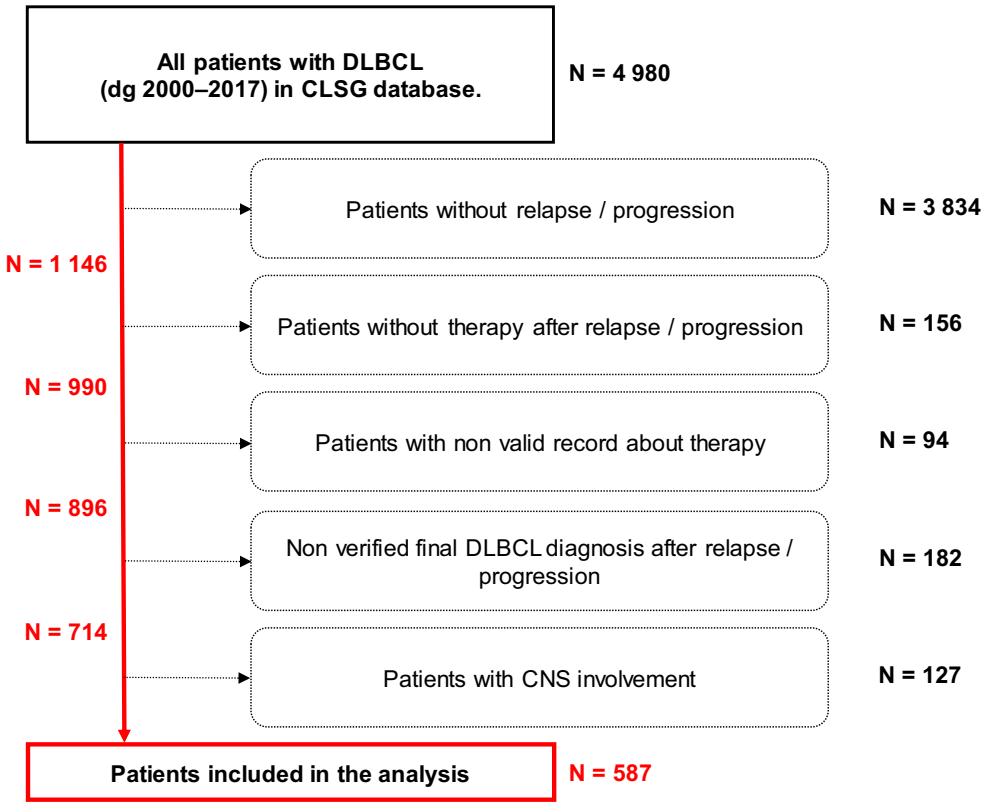

Fig. 1 Consort diagram of selection of patient data from the CLSG database

recently, Czech Lymphoma Study Group staging recommendations have also been used [17, 18]. The initial rigorous staging included at least a thoracic and abdominal CT scan and unilateral bone marrow biopsy. PET (positron emission tomography) or PET/CT has only been used in recent years. A complete blood count and LDH (lactate dehydrogenase) level were performed and recorded in the database. Response to treatment was assessed by Cheson criteria 1999 or 2007 depending on the availability of PET scans [19, 20]. The treatment and outcomes, including response, time to progression, and survival, were collected annually. The enrolled patients were followed until their death, withdrawal of consent, or loss of follow-up. The date of relapse or progression was defined as the first documented manifestation of a relapse (clinical symptoms or radiological finding or the date of biopsy confirming DLBCL relapse).

According to the time between the diagnosis of relapse and the start of therapy, we compared the OS (overall survival) in patients with therapy initiation in <7 days and patients who were treated later. From a practical point of view, an analysis of three time intervals (≥ 7 days or 7–21 and >21 days) was added. To avoid potential treatment-related bias, the sub-analysis of patients treated exclusively with R-CHOP at the first line was performed. The patients assigned to the R-CHOP cohort had to receive at least 3 cycles of R-CHOP-21; intrathecal or systemic CNS-prophylaxis (high-dose methotrexate, high-dose cytosine-arabinoside) was allowed, as was pre-phase therapy (coming from high-dose corticosteroids to a combination consisting of cyclophosphamide, vincristine, and prednisolone).

Statistical analysis

Standard descriptive statistics were used to characterize the sample data set. A comparison of the categorical parameters was performed using the Fisher exact (chi-square) test. In the case of continuous variables, the Mann-Whitney or Kruskal-Wallis test was used. The overall survival (OS) was estimated using the Kaplan-Meier method and all point estimates were accompanied by 95% confidence intervals. The OS was defined as the time from diagnosis of relapse to death from any cause. PFS (progression-free survival) was not calculated in spite of reported data that it can be used as a surrogate and point for the OS [21]. Patients who had not died were censored at the date of their last update. The comparison of the OS between different subgroups was carried out by means of the logrank test. The level of statistical significance was set at $\alpha = 0.05$.

Results

Overall analysis

In total, 587 patients with the first recurrence of DLBCL (including 109 progressions during first-line therapy) relapsed within a wide range of time from 1.6 to 152.3 months (median 12.8 months) after the initial diagnosis. For this whole cohort, the median time between the diagnosis of progression and the start of therapy was 20 days (range 1–851 days). Therapy had to be started within 1 week (< 7 days) in 23.2% of the cases with recurrent DLBCL (rDLBCL). The detailed distribution of the intervals between progression and therapy initiation (interval-to-therapy = ITT) is depicted in Fig. 2. The median follow-up from the initial diagnosis was 5.2 years (range 0.4–17.6) for living patients, while 385 patients died. First-line therapy (including chemotherapy, monoclonal antibody, and/or radiotherapy) was administered in 99.3% of the patients. The most frequent chemotherapy backbone was CHOP (cyclophosphamide, doxorubicine, vincristine, and prednisone) in 69.2% of the cases, and monoclonal anti-CD20 antibody was given to 84.7% of the patients (usually with chemotherapy). The therapy of the first relapse/progression of DLBCL was based on systemic immuno/chemotherapy in 88.1% of the patients, and 39.2% of the patients received platinum-based regimens (ESHAP, ESAP, DHAP, ICE). In the second line, 114 (19.4%) patients were autotransplanted, and 9 patients (1.53%) underwent allogeneic stem cell transplantation (allo-SCT).

First, all 587 rDLBCLs were divided into two subgroups (136 vs. 451 patients) according to the interval-to-therapy (< 7 days vs. ≥ 7 days). The baseline characteristics of patients at first relapse according to ITT are presented in Table 1. There were many differences between cohorts in B symptoms, clinical stage, performance status (ECOG), elevated LDH, distribution of bulky disease, IPI score, and in the proportion of patients with early/late DLBCL progression (Table 1). The overall survival (OS) was significantly better in the subgroup of patients with therapy initiation ≥ 7 days with median 1.6 years (range 1.1–2.0) vs. 0.6 years (range 0.5–0.8; 95% CI; $p < 0.001$), and the corresponding 5-year OS was 34.1% (range 29.1–39.2%) vs. 17.4% (range 10.3–24.5%; 95% CI; $p < 0.001$). The survival curves are depicted in Fig. 3.

Furthermore, patients with early vs. later start of therapy (< 7 vs. ≥ 7 days) differed subtly in therapy of the first relapse. From the treated patients, chemotherapy was given in 93.4% vs. 89.8% of the cases (p 0.243); monoclonal antibody anti CD20 was received by 65.4% vs. 74.3% of the patients (p 0.049). On the other hand, radiotherapy was administered in 25% vs. 27.3% (p 0.659) of the patients, whereas autologous stem cell transplantation (auto-SCT) was performed in 16.9% vs. 20.2% (p 0.459) and allo-SCT in 0% vs. 2% (p 0.0126) of the cases. Response to salvage therapy was significantly different between ITT subgroups (< 7 vs. ≥ 7 days) with 25.0% vs. 43.0% complete remissions, 8.1% vs. 11.5% partial remissions, 8.8% vs. 5.5% stable disease, and 32.4% vs. 28.4% progressions ($p < 0.001$). There were 35/136 (25.7%) and 52/451 (11.5%) patients, respectively, with an unevaluable response in corresponding ITT groups (< 7 vs. ≥ 7 days).

Interestingly, there were various impacts of the interval-to-therapy initiation on the particular IPI subgroups. In the low-risk IPI cohort, there was a 5-year OS of 35.7% (range 10.6–60.8) vs. 60.0% (range 48.5–71.6) for < 7 and ≥ 7 days ITT (p 0.088; 95% CI), whereas in the high-risk IPI subgroup, a 5-

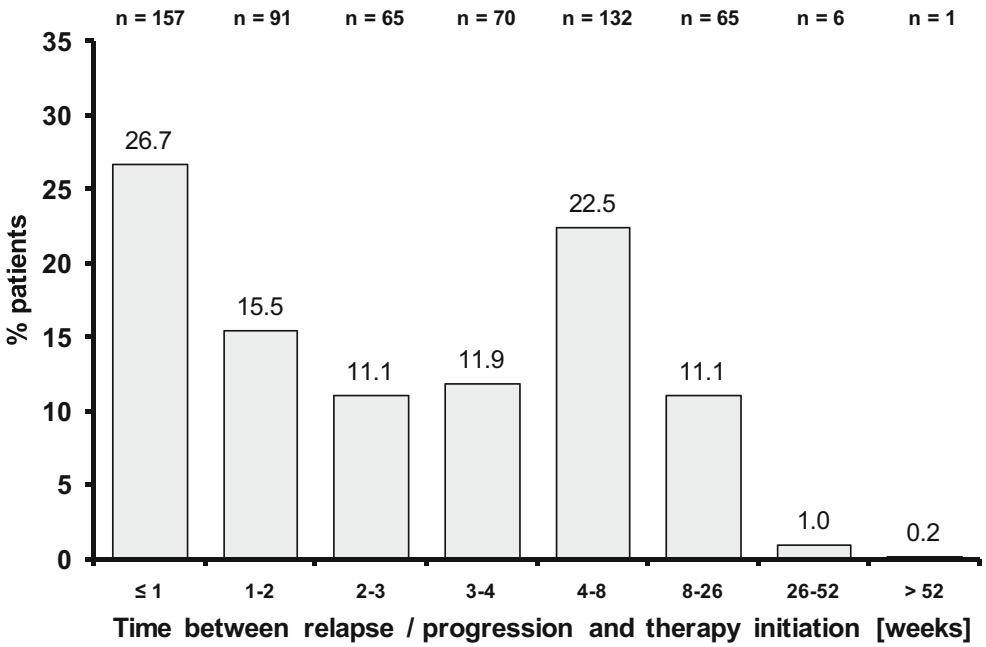

Fig. 2 Distribution of patients at 1st relapse of DLBCL according to the ITT (interval-to-therapy)

Table 1 Baseline characteristics of patients at the 1st first relapse/progression of DLBCL

Characteristics*, *n* (%)	Time between relapse/progression and therapy initiation		*p* value**
	< 7 days (*n* = 136)	≥ 7 days (*n* = 451)	
Sex			
Male	78 (57.4)	226 (50.1)	0.143
Age			
Median (min–max)	68 years (22–95)	67 years (24–93)	0.193
≥ 65 years	86 (63.2)	267 (59.2)	
B symptoms			
Yes	43 (32.8)	97 (21.9)	*0.015*
Stage			
I	15 (11.4)	83 (18.9)	*0.031*
II	26 (19.7)	95 (21.7)	
III	21 (15.9)	88 (20.1)	
IV	70 (53.0)	172 (39.3)	
BM			
Yes	11 (8.8)	40 (9.1)	0.999
Extranodal involvement			
0	22 (16.7)	72 (16.1)	0.893
≥ 1	110 (83.3)	375 (83.9)	
ECOG PS			
0	19 (14.4)	115 (26.3)	*< 0.001*
1	57 (43.2)	204 (46.7)	
2	30 (22.7)	83 (19.0)	
3	18 (13.6)	27 (6.2)	
4	8 (6.1)	8 (1.8)	
Bulky disease			
< 1.9 cm	2 (1.9)	40 (10.3)	*0.001*
2.0–4.9 cm	42 (39.3)	180 (46.4)	
5.0–7.4 cm	20 (18.7)	82 (21.1)	
7.5–9.9 cm	18 (16.8)	34 (8.8)	
≥ 10 cm	25 (23.4)	52 (13.4)	
LDH			
≤ ULN	24 (19.2)	145 (33.6)	*0.002*
IPI score			
Low risk	15 (12.4)	83 (20.2)	*0.001*
Low-intermediate risk	28 (23.1)	118 (28.7)	
High-intermediate risk	30 (24.8)	121 (29.4)	
High risk	48 (39.7)	89 (21.7)	
Relapse/progression diagnosis			
< 12 months	76 (55.9)	192 (42.6)	*0.008*
≥ 12 months	60 (44.1)	259 (57.4)	
Cell of origin***			
GC phenotype (*n* = 46)	14 (43.8)	32 (39.0)	0.675
Non GC phenotype (*n* = 68)	18 (56.3)	50 (61.0)	

*All characteristics in subgroups are known in more than 88% of patients, with exception of bulky disease (78%)

**Fisher exact test or Mann-Whitney test

***Cell of origin is known in 19.4% of patients (*n* = 114)

year OS of 5.6% (range 0.1–12.4) vs. 8.2% (range 1.1–15.4; $p < 0.001$; 95% CI) was observed. On the other hand, no differences were found in low-intermediate and high-intermediate risk IPI.

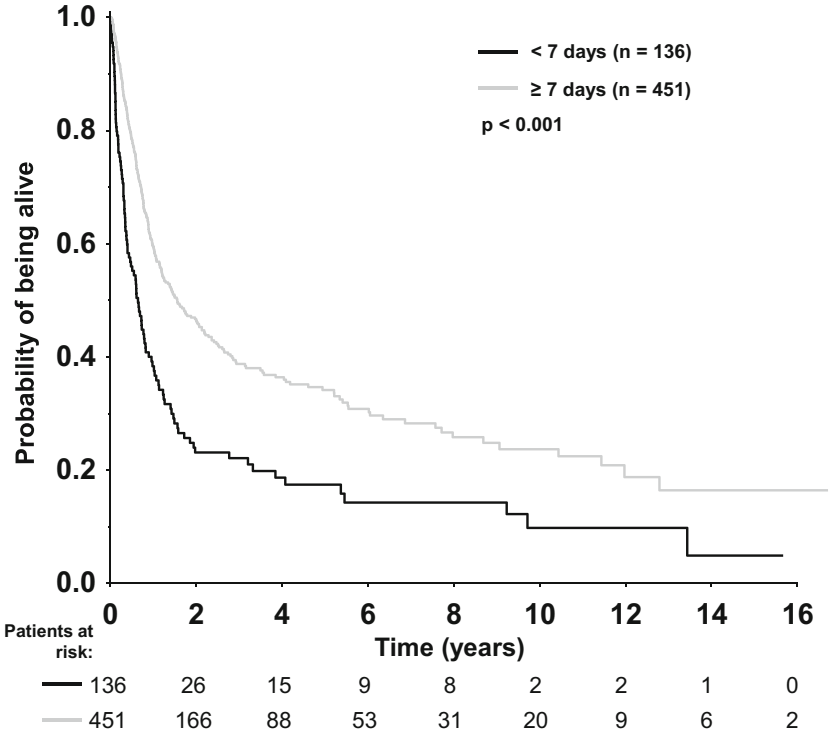

Fig. 3 Overall survival from 1st relapse/progression of DLBCL according to the ITT (interval-to-therapy)

Despite the fact that the proportion of early relapses (< 12 months) was significantly higher in the subgroup ITT < 7 days (55.9% vs. 44.1%; p 0.008; Table 1), the ITT remained significant in both of the subgroups < 12 vs. ≥ 12 months. For 268 patients with early relapse (< 12 months), there was a 5-year OS 16.0% (7.0–24.9) vs. 25.1% (18.3–31.9%) for ITT < 7 vs. ≥ 7 days (95% CI; $p < 0.001$). The 319 patients who relapsed later (≥ 12 months) displayed 5-year OS 18.8% (7.3–30.2) vs. 41.1% (34.0–48.2; $p < 0.001$; 95% CI) for the same ITT groups. Data are shown in Supplementary Figure S1 and in Supplementary Table S1.

We also analyzed ITT (< 7 days vs. later) in different subgroups by age (< 65 vs. ≥ 65 years). In 234 younger patients (< 65 years), the 5-year OS was 32.6% (17.6–47.6) vs. 45.9% (38.1–53.7) for ITT < 7 vs. ≥ 7 days, and 8.8% (2.2–15.4) vs. 24.9% (18.4–31.3) in older people (95% CI; $p < 0.001$). The results are provided in Supplementary Figure S2 and Supplementary Table S2.

Sub-analysis of patients with R-CHOP in the first line

In the sub-analysis of 349 patients treated in the first line with R-CHOP, there were two cohorts (75 vs. 274 patients) according to ITT (< 7 days vs. ≥ 7 days). The median follow-up was 4.9 years for surviving patients, and there were 213 deaths. The overview of baseline characteristics is depicted in Table 2. Again, B symptoms, performance status (ECOG), LDH level, and IPI score were significantly different between subgroups in favor of patients with therapy start ≥ 7 days. Conversely, the clinical stage lost its significance, and the male gender seemed to be associated with an urgent start of therapy with borderline significance. Similar to the overall analysis, the R-CHOP cohort with a therapy start within 7 days had a worse 5-year OS, 16.9% (range 6.9–26.9) vs. 35.9% (range 29.2–42.6) ($p < 0.001$; 95% CI). The overall survival differences are shown in Fig. 4.

Sub-analysis of < 7 vs. 7–21 vs. ≥ 21 days

Additionally, we compared three different ITTs: < 7 days vs. 7–21 days vs. ≥ 21 days. The similar baseline clinical and laboratory parameters were identified as significantly different among subgroups (B symptoms, clinical stages, ECOG, bulky disease, LDH level, and IPI score) as shown in Table 3. A shorter interval between relapse and treatment was associated with a worse prognosis. The overall survival at 5 years for three interval subgroups (< 7 days vs. 7–21 days vs. ≥ 21 days) was 17.4% (range 10.3–24.5%) vs. 20.5% (range 13.5–27.4%) vs. 42.2% (range 35.5–48.8%; 95% CI; $p < 0.001$). The relevant data is depicted in Fig. 5.

Sub-analysis according to cell of origin

The data on 114/587 (19.4%) patients with the first relapse of DLBCL was available for the analysis according to the COO. The GCB ($n = 46$; 40.4%) and non-GCB ($n = 68$; 59.6%) subtypes of DLBCL were evaluated at the initial diagnosis. There were no differences in terms of gender, age, B symptoms,

Table 2 Baseline characteristics of patients at the 1st relapse/progression of DLBCL treated with first-line R-CHOP

Characteristics*, *n* (%)	Time between relapse/progression and therapy initiation		*p* value**
	< 7 days (*n* = 75)	≥ 7 days (*n* = 274)	
Sex			
Male	47 (62.7)	137 (50.0)	0.067
Age			
Median (min–max)	67 years (22–86)	67 years (32–83)	0.813
< 65 years	29 (38.7)	103 (37.6)	0.894
≥ 65 years	46 (61.3)	171 (62.4)	
B symptoms			
Yes	25 (33.8)	59 (21.9)	*0.046*
No	49 (66.2)	211 (78.1)	
Stage			
I	9 (12.0)	53 (19.8)	0.102
II	13 (17.3)	61 (22.8)	
III	12 (16.0)	50 (18.7)	
IV	41 (54.7)	104 (38.8)	
BM			
Yes	6 (8.6)	19 (7.2)	0.798
Extranodal involvement			
0	10 (13.5)	52 (19.0)	0.309
≥ 1	64 (86.5)	222 (81.0)	
ECOG PS			
0	9 (12.3)	81 (30.0)	*0.010*
1	37 (50.7)	125 (46.3)	
2	15 (20.5)	40 (14.8)	
3	8 (11.0)	18 (6.7)	
4	4 (5.5)	6 (2.2)	
Bulky disease			
< 1.9 cm	2 (3.3)	26 (11.0)	0.081
2.0–4.9 cm	22 (36.7)	101 (42.6)	
5.0–7.4 cm	11 (18.3)	50 (21.1)	
7.5–9.9 cm	9 (15.0)	25 (10.5)	
≥ 10 cm	16 (26.7)	35 (14.8)	
LDH			
≤ ULN	11 (16.2)	87 (33.1)	*0.007*
> ULN	57 (83.8)	176 (66.9)	
IPI score			
Low risk	8 (11.9)	50 (19.6)	*0.007*
Low-intermediate risk	15 (22.4)	70 (27.5)	
High-intermediate risk	15 (22.4)	80 (31.4)	
High risk	29 (43.3)	55 (21.6)	

*All characteristics in subgroups are known in more than 88% of patients, with exception of bulky disease (80%)

**Fisher exact test or Mann-Whitney test

clinical stage, bone marrow and extranodal involvement, ECOG, bulky disease, LDH activity, or IPI score between the GCB and non-GCB groups (Supplementary Table S3). Interestingly, there were no survival differences between GCB and non-GCB recurrent DLBCL. The 5-year OS was 43% (28.1–58.0%) vs. 36.1% (21.1–51.1%; 95% CI) for the GCB and non-GCB subgroups ($p = 0.758$).

The distribution of the GCB and non-GCB phenotype in subgroups according to the time between diagnosis of relapse and therapy initiation (< 7 days vs. ≥ 7 days) was similar (Table 1). A similar observation was made in the R-CHOP-treated patients, and there was also no association of GCB/non-GCB distribution according to ITT < 7 days vs. 7–21 days vs. > 21 days (data not shown).

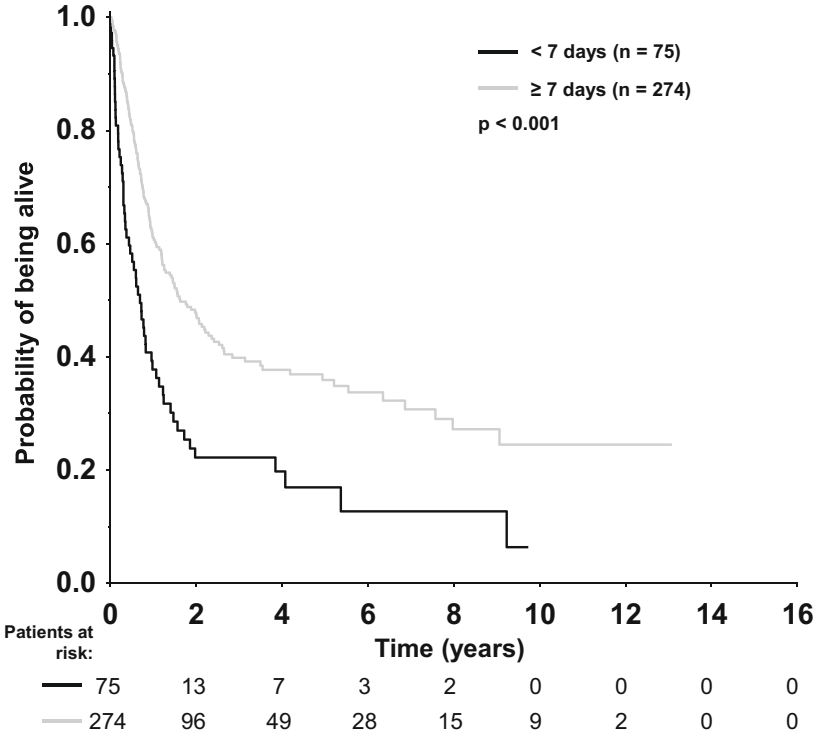

Fig. 4 Overall survival from relapse/progression (R-CHOP in the first line) according to ITT (interval-to-therapy) < 7 days vs. ≥ 7 days

Discussion

Relapsing and/or refractory DLBCL represents a major medical problem. But a relapse itself does not mean the same for every relapsing patient. It was observed, even in the study focused on "refractory" DLBCLs with extremely poor survival (median OS 6.3 months), that there was a small subgroup of patients (about 20%) who remained alive for more than 2 years [22].

Our population-based retrospective analysis brings evidence that the interval between the diagnosis of relapse and start of therapy is an important prognostic parameter that can be helpful for better recognition of the heterogeneity of recurrent DLBCL. Our study also indirectly confirms similar results reported in newly diagnosed DLBCLs in US, Canadian, and European cohorts of patients [11, 23]. We fully agree with the statement presented by Maurer et al. that "the urgency to start therapy appears to be a function of disease aggression" [11]. The significance of ITT is intimately related to the selection bias of the clinical trials. Generally, patient selection bias has been highlighted many times as a concern in clinical trials [10, 24]. Almost 30% of DLBCL patients were excluded from clinical trial participation based on inclusion/exclusion criteria, despite the fact that the trial population finally included more patients with advanced disease, B symptoms, and bulky infiltrates compared with the real-world patients [25].

We observed that more than 42% of the patients with first relapse of DLBCL had to start systemic therapy within 2 weeks, and nearly 30% of the cases even within only 1 week. Supposing that the minimum time needed for screening procedures is usually about 7–10 days, approximately 30–40% of the DLBCLs with first recurrence have no or a very limited chance to enter the clinical trial based on this simple parameter and regardless of other inclusion/exclusion criteria. At the same time, the 5-year overall survival was significantly better in the subgroup of patients with therapy initiation ≥ 7 days (34.1% vs. 17.4%). In accordance with the results published by Maurer et al., a shorter time to therapy also correlates with adverse disease-related factors, including more B symptoms, advanced clinical stage, poorer performance status (ECOG), elevated LDH, bulky disease, and higher IPI score [26]. Clinical trials usually require extended screening periods and may be unintentionally enriched with lymphoma patients who exhibit less aggressive clinical behavior with a better prognosis.

Our dataset of rDLBCL patients was roughly similar to real-world published data. The median age at first progression in our cohort was 67 years vs. 64–71 years in the published analyses [26, 27]. First-line therapy with CHOP backbone was received by 69.2% of the patients in our cohort, compared with 68% of patients treated by RCHOP. The platinum-based salvage therapy of the first relapse/progression was administered to 39.1% of our patients, whereas 32% of the DLBCLs were treated with R-DHAP or R-DHAX across the European analysis. Additionally, 19.4% vs. 16.6% of patients were consolidated with stem cell transplantation [28]. In our analysis, we did not collect and analyze additional socioeconomic and system-related variables (education level, marital

Table 3 Baseline characteristics of patients at the 1st relapse/progression of DLBCL

Characteristics*, *n* (%)	Time between relapse/progression and therapy initiation			*p* value**
	< 7 days (*n* = 136)	7–21 days (*n* = 166)	≥ 21 days (*n* = 285)	
Sex				
Male	78 (57.4)	81 (48.8)	145 (50.9)	0.304
Age				
Median (min–max)	68 years (22–95)	68 years (31–88)	67 years (24–93)	0.307
< 65 years	50 (36.8)	67 (40.4)	117 (41.1)	0.689
≥65 years	86 (63.2)	99 (59.6)	168 (58.9)	
B symptoms				
Yes	43 (32.8)	45 (27.6)	52 (18.6)	*0.004*
No	88 (67.2)	118 (72.4)	228 (81.4)	
Stage				
I	15 (11.4)	22 (13.8)	61 (21.9)	*0.002*
II	26 (19.7)	32 (20.0)	63 (22.7)	
III	21 (15.9)	27 (16.9)	61 (21.9)	
IV	70 (53.0)	79 (49.4)	93 (33.5)	
BM				
Yes	11 (8.8)	20 (12.3)	20 (7.2)	0.208
Extranodal involvement				
0	22 (16.7)	19 (11.7)	53 (18.6)	0.163
≥ 1	110 (83.3)	143 (88.3)	232 (81.4)	
ECOG PS				
0	19 (14.4)	33 (20.5)	82 (29.7)	< *0.001*
1	57 (43.2)	73 (45.3)	131 (47.5)	
2	30 (22.7)	34 (21.1)	49 (17.8)	
3	18 (13.6)	15 (9.3)	12 (4.3)	
4	8 (6.1)	6 (3.7)	2 (0.7)	
Bulky disease				
< 1.9 cm	2 (1.9)	12 (8.6)	28 (11.2)	*0.005*
2.0–4.9 cm	42 (39.3)	61 (43.9)	119 (47.8)	
5.0–7.4 cm	20 (18.7)	29 (20.9)	53 (21.3)	
7.5–9.9 cm	18 (16.8)	13 (9.4)	21 (8.4)	
≥ 10 cm	25 (23.4)	24 (17.3)	28 (11.2)	
LDH				
≤ ULN	24 (19.2)	34 (21.1)	111 (41.1)	< *0.001*
> ULN	101 (80.8)	127 (78.9)	159 (58.9)	
IPI score				
Low risk	15 (12.4)	17 (11.3)	66 (25.4)	< *0.001*
Low-intermediate risk	28 (23.1)	40 (26.5)	78 (30.0)	
High-intermediate risk	30 (24.8)	55 (36.4)	66 (25.4)	
High risk	48 (39.7)	39 (25.8)	50 (19.2)	

*All characteristics in subgroups are known in more than 88% of patients, with exception of bulky disease (78%)

**Fisher exact test or Mann-Whitney test

status, income, distance to treating hospital, etc.) and their impact on lymphoma outcome [23]. On the other hand, the published data show that socioeconomic parameters play only a marginal role compared with the time to therapy initiation [23, 26]. In spite of the difference in the analysis design and patient population, we present interval-to-treatment results in the rDLBCL very similar to Maurer et al. The cohort from Mayo prospectively enrolled 162 patients (median age 64 years) who initiated aggressive salvage with DHAP and were designated for transplant. Our retrospective analysis included 587 patients (median age 67 years), who were treated with various aggressive platinum-based regimens (ESHAP,

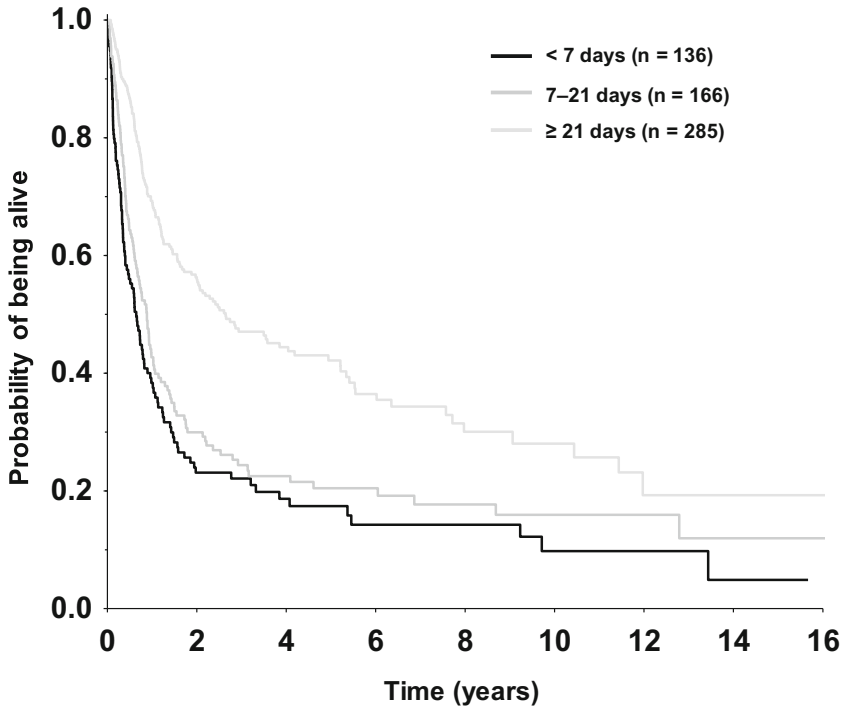

Fig. 5 Overall survival from the first relapse/progression according to cell of origin (COO)

ESAP, DHAP, ICE) in 39.2% of the cases only; 19.4% of the patients were finally autotransplanted. Despite the differences in the study design, patients with short interval-to-therapy (0–6 days in the Mayo cohort or < 7 days in our analysis) had a median OS similar in both datasets 6.7 months vs. 0.6 years (= 7.2 months) [26].

The interval-to-therapy for the initial diagnosis or relapse of DLBCL varies across studies. Maurer et al. reported a median interval-to-therapy of 15 days (0–155) for MER (Molecular Epidemiology Resource) patients, whereas 23 days were reported (0–215) for the LYSA (Lymphoma Study Association) cohort for initially diagnosed DLBCL [26]. Another analysis in newly diagnosed DLBCL reported a median of 37 days from diagnosis to treatment [23]. The ITT difference between our results and the data published by Maurer (median of 20 vs. 6 days) can be caused by a different design of study in rDLBCL.

In our analysis, we observed a 5-year OS of 42% (35.5–48.8%; 95% CI) in the subgroup of rDLBCL patients with an ITT of > 21 days. This observation is interesting in the context of the introduction of chimeric antigen receptor (CAR) T cell therapy. Anti-CD19 chimeric antigen receptor (CAR) T cell (CD19-CAR-T) therapy demonstrates impressive responses, including complete responses in approximately 40–60% of recurrent aggressive lymphomas [12, 13, 29–31]. One of the limitations of this promising new treatment strategy is the technology time necessary for manufacturing and logistics, which require at least 3 weeks. In the phase II study, the ORR after axicabtagene ciloleucel (axi-cel) administration was 82%, with 54% complete remissions in rDLBCL. The median of the treatment duration was 11 months and median progression-free survival was 6 months. The median OS was not reached with a follow-up at 27 months, but there was calculated 50.5% OS at 24 months [29]. In spite of promising results with CAR-T, it is necessary to note that the subgroup of rDLBCL of our study with interval-to-therapy initiation > 21 days also showed remarkably good survival.

Interestingly, we could not find any association between the COO subtype of DLBCL and interval-to-therapy. Our results are, however, limited by the lack of COO classification on the whole cohort (only 19.4% of the samples were classified), and COO evaluation came from the initial diagnosis samples. It is assumed that the COO subtype does not change after the treatment of DLBCL [32]. On the other hand, an increased number of molecular mutations or amplification were observed in relapsed patients compared with diagnostic biopsies from the same patient [33].

We can conclude that the time between progression and therapy initiation is (ITT) a strong prognosis predictor that is recognized easily in common daily practice, and we also demonstrated its consistency across various populations (patients < 65 vs. ≥ 65 years, early vs. late relapses). We agree that this parameter is one of the most potent selection biases of DLBCL clinical trials. Patients with refractory DLBCL, generally considered to have a poor prognosis but healthy enough to wait for study testing or drug preparation for weeks,

represent a selected subgroup with a more favorable clinical disease. Despite the difference between published studies, we can generally summarize that patients having to start their therapy urgently (within days) represent a subgroup with a very poor prognosis. Conversely, patients with the same DLBCL who can wait for several weeks for treatment have incomparably better survival rates. These facts should be taken into account in basic molecular research and in the clinical testing of new drugs.

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Compliance with ethical standards

Conflict of interest Author J. A. declares that she has no conflict of interest. Author M. J. declares that he has no conflict of interest. Author B. Z. declares that he has no conflict of interest. Author C. R. declares that she has no conflict of interest. Author C. V. declares that he has no conflict of interest. Author K. N. declares that she has no conflict of interest. Author K. P. declares that he has no conflict of interest. Author B. K. declares that she has no conflict of interest. Author H. J. declares that she has no conflict of interest. Author B. D. has received consulting honoraria from Roche, Takeda, Gilead Sciences, Janssen-Cilag, and Debiopharm. Author P. V. has received speaker honoraria from Roche and Gilead Sciences, and consulting for Roche and Takeda. Author P. R. declares that he has no conflict of interest. Author P. J. declares that he has no conflict of interest. Author D. J. declares that he has no conflict of interest. Author M. H. declares that she has no conflict of interest. Author T. M. has received speaker honoraria from Janssen, Gilead Sciences, Takeda, Bristol-Myers-Squibb, Amgen, Abbvie, Roche, Morphosys, Incyte. Consulting and Advisory for Takeda, Bristol-Myers-Squibb, Incyte, Abbvie, Amgen, Roche, Gilead Sciences, Janssen, Celgene, Morphosys.

Ethical approval This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Al-Hamadani M, Habermann TM, Cerhan JR et al (2015) Non-Hodgkin lymphoma subtype distribution, geodeomographic patterns, and survival in the US: a longitudinal analysis of the national cancer data base from 1998 to 2011. Am J Hematol 90:790–795
2. Habermann TM, Weller EA, Morisson VA et al (2006) Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol 24:3121–3127
3. Pfreundschuh M, Trumpel L, Osterborg A et al (2006) CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large B-cell lymphoma: a randomised controlled trial by the MabThera International (MInT) group. Lancet Oncol 7:379–391
4. Sehn LH, Donaldson J, Chhanabhai M, Fitzgerald C, Gill K, Klasa R, MacPherson N, O'Reilly S, Spinelli JJ, Sutherland J, Wilson KS, Gascoyne RD, Connors JM (2005) Introduction of combined CHOP plus rituximab dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. J Clin Oncol 23:5027–5033
5. Howlander N, Mariotto AB, Besson C et al (2017) Cancer-specific mortality, cure fraction, and noncancer causes of death among diffuse large B-cell lymphoma patients in the immunochemotherapy era. Cancer 123:3326–3334
6. Coiffier B, Lepage E, Briére J et al (2002) CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. NEJM 346:235–242
7. Coiffier B, Thieblemont C, Den Van Neste E et al (2010) Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 116:2040–2045
8. Farooq U, Maurer MJ, Thompson CA, Thanarajasingam G, Inwards DJ, Micallef I, Macon W, Syrbu S, Lin T, Lin Y, Ansell SM, Nowakowski GS, Habermann TM, Cerhan JR, Link BK (2017) Clinical heterogeneity of diffuse large B cell lymphoma following failure of front-line immunochemotherapy. Br J Haematol 179:50–60
9. https://www.clinical.trials.gov
10. Kahan BC, REhal S, Cro S (2015) Risk of selection bias in randomised trials. Trials 16:405. https://doi.org/10.1186/s13063-015-0920-x
11. Maurer MJ, Ghesquiéres H, Link BK et al (2018) Diagnosis-to-treatment interval is an important clinical factor in newly diagnosed diffuse large B-cell lymphoma and has implication for Bias in clinical trials. J Clin Oncol 36:1603–1610
12. Kochenderfer JN, Sommerville RPT, Lu T et al (2017) Lymphoma remissions caused by anti-CD19 chimeric antigen receptor T cells are associated with high serum interleukin-15 levels. J Clin Oncol 35(16):1803–1813
13. Abramson J, Gordon L, Palomba ML et al (2018) Updated safety and long-term clinical outcomes in TRANSCEND NHL 001, pivotal trial of lisocabtagen maraleucel (JCAR017) in R/R aggressive NHL. J Clin Oncol 36(15suppl):7505
14. https://www.uzis.cz/cz/mkn/C81-C96.html
15. Swerdlow SH, Campo E, Harris NL et al (2008) WHO classification of tumours of haematopoietic and lymphoid tissues. In: International Agency for Research on Cancer (IARC), 4th edn. Lyon
16. Hans CP, Weisenburger DD, Greiner TC et al (2004) Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 103:275–282
17. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M (1971) Report of the committee on no Hodgkin's disease staging classification. Cancer Res 31:1860–1861
18. Sykorova A, Belada D, Smolej L et al (2010) Staging of non-Hodgkin's lymphoma –recommendations of the Czech Lymphoma Study Group. Klin Onkol 23:146–154
19. Cheson BD, Horning SJ, Coiffier B et al (1999) Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 17(4):1244
20. Cheson BD, Pfistner B, Juweid ME et al (2007) International Harmonization Project on lymphoma. Revised response criteria for malignant lymphoma. J Clin Oncol 25(5):579–586
21. Shi Q, Schmitz N, Ou FS, Dixon JG, Cunningham D, Pfreundschuh M, Seymour JF, Jaeger U, Habermann TM, Haioun C, Tilly H, Ghesquieres H, Merli F, Ziepert M, Herbrecht R, Flament J, Fu T, Coiffier B, Flowers CR (2018) Progression-free survival as a surrogate end point for overall survival in first-line diffuse large B-cell

lymphoma: an individual patient-level analysis of multiple randomized trials (SEAL). J Clin Oncol 36:2593–2602
22. Crump M, Neelapu SS, Farooq U, van den Neste E, Kuruvilla J, Westin J, Link BK, Hay A, Cerhan JR, Zhu L, Boussetta S, Feng L, Maurer MJ, Navale L, Wiezorek J, Go WY, Gisselbrecht C (2017) Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood 130:1800–1808
23. Blunt DN, Smyth L, Gatov E, Nagamuthu C, Buckstein R, Croxford R, Cheung M (2018) Diagnosis to treatment interval in DLBCL is predictive of overal survival in a large, population-based registry. Blood 132:1700
24. Yelland LN, Kahan BC, Dent E, Lee KJ, Voysey M, Forbes AB, Cook JA (2018) Prevalence and reporting of recruitment, randomisation and treatment errors in clinical trials: a systematic review. Clin Trials 15(3):278–285
25. Fatola T, Rutherford SC, Allan JN, Ruan J, Furman RR, Zhengming C, Garcia A, Kong C, Bhavsar EB, Falsenfeld J, Leonard JP, Martin P (2018) Understanding the differences between clinical trial participants and real-world patients with non-Hodgkin lymphoma. Blood 132:2970
26. Maurer MJ, Farooq U, Wahlen MM et al (2018) Short time between progression after immunochemotherapy and initiation of salvage therapy (PTI) is associated with inferior long-term outcomes in patients with relapsed/refractory DLBCL. ASH Annual Meeting; Abstract No 4204
27. Harrysson S, Eloranta S, Ekberg S, Enblad G, Jerkeman M, Hasselblom S, Wahlin BE, Andersson PO, Smedby KE (2018) Incidence and outcome of relapsed/refractory diffuse large B-cell lymphoma (DLBCL) in a population-based cohort of 3165 patients in Sweden. Blood 132:2975
28. Galaznik A, Way N (2018) Patient characteristics and treatment paterns in the first-line and second-line treatment of diffuse large B-cell lymphoma and follicular lymphoma in the United Kingdom, France, and Germany. Blood 132:4232
29. Locke FL, Ghobaldi A, Jacobskon CA et al (2019) Long-term safety and activity of axicabtabene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol 20:31–42
30. Neelapu SS, Locke FL, Bertlett et al (2017) Axicabtagene Ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med 377:2531–2544
31. Schuster SJ, Bishop M, Tam C, Waller EK, Borchmann P, McGuirk J, Jäger U, Jaglowski S, Andreadis C, Westin JR, Fleury I, Bachanova V, Foley SR, Ho PJ, Mielke S, Magenau JM, Holte H, Pantano S, Pacaud LB, Awasthi R, Chu J, Anak Ö, Salles G, Maziarz RT, JULIET Investigators (2019) Tisagenlecleucel in adult relapsed and refractory diffuse large B-cell lymphoma. N Engl J Med 380:45–56
32. Veldman-Jones MH, Lai Z, Wappett M, Harbron CG, Barrett JC, Harrington EA, Thress KS (2015) Reproducible, quantitative, and flexible molecular subtyping of clinical DLBCL samples using the nanostring Countersystem. Clin Cancer Res 21:2367–2378
33. Greenawalt D, Liang WS, Saif S et al (2017) Comparative analysis of primary versus relapse/refractory DLBCL identifies shifts in mutation spectrum. Oncotarget 8:99237–99244