Impact of vincristine dose reduction on outcomes of patients with aggressive B-cell lymphoma treated with (R)-CHOP

Diffuse large B-cell Lymphoma (DLBCL) is the most common type of lymphatic neoplasia with an incidence in Europe of 4.92 cases per 100.000 population per year.[1,2] Treatment for patients with DLBCL includes conventional chemotherapy like the CHOP protocol (cyclophosphamide, doxorubicin, vincristine [VCR], prednisone).[3] The addition of the anti-CD20 antibody rituximab (R) to chemotherapy improved overall survival (OS) and disease-free survival of patients with DLBCL, leading to long-term survival rates of up to 70% for all patients.[4,5] Since the publication of the POLARIX trial, which reported a progression-free survival (PFS) benefit for polatuzumab vedotin as replacement for vincristine in R-CHOP (pola-R-CHP) while showing similar rates of adverse events, this vincristine-free regimen represents an additional treatment option.[6] R-CHOP is given in four to eight cycles depending on patient's age and the individual risk score according to the International Prognostic Index (IPI) with intervals of 14 or 21 days.[7]

Even though R-CHOP achieves excellent response rates, treatment-related side effects can have severe impact on quality of life (QoL).[8] One of the most common side effects with relevant dose-limiting toxicity is peripheral polyneuropathy (PNP), mainly caused by VCR and symptoms can be categorized into sensory, motor, autonomic and cranial neuropathy.[9] VCR is a vinca alkaloid, whose pharmacodynamics relies on anti-microtubule activity.[10] Unfortunately, only very limited evidence of effective treatment options for chemotherapy-induced PNP exists and physicians often face the dilemma of dose reduction or omission of VCR while fearing attenuated efficacy.[11] Hence, dose reduction of VCR is performed regularly in clinical practice but its impact on patient outcomes is unclear.[12–14] In order to provide more evidence regarding this field of investigation, we performed a *post hoc* analysis of the RICOVER-60 trial, investigating the impact of dose reduction/omission of VCR on the outcome of older patients with aggressive B-cell lymphoma. The RICOVER-60 trial (*clinialcaltrials gov. Identifier: NCT00052936*, *EU-20243*) randomly assigned (1:1:1:1) 1,222 older patients (aged 61–80 years) with newly diagnosed CD20-positive aggressive B-cell lymphoma to receive six or eight cycles of CHOP chemotherapy every 2 weeks with or without eight biweekly doses of rituximab. Prephase therapy consisted of 1 mg VCR as absolute dose and 100 mg per day of prednisone over 7 days. Decisions concerning VCR dose reduction or omission in any particular treatment cycle were left to the local investigator. The primary endpoint of the RICOVER-60 trial was event-free survival (EFS), secondary endpoints were PFS and OS.

Patients who received less or more than the planned number of treatment cycles (6 or 8), who received VCR not according to protocol (more than 2 mg or vinblastine instead of VCR), for whom the VCR dose was unknown or patients with missing documentation were excluded from further analyses. Subgroup analyses were performed for patients of the best treatment arm of the RICOVER-60 trial, which was six cycles of CHOP and eight cycles of rituximab (6xCHOP-14 + 8xR).

VCR dose reductions were common and were observed in 51% of all patients. VCR was reduced significantly more often in female (P<0.001) and older patients (P=0.010). Other disease characteristics were equally distributed between patients with and without VCR dose reductions (Table 1). These differences in age and sex distribution for patients with VCR reduction were observed across all levels of dose reductions (≥80-<100%, >50-80%, 50% or <50% of planned VCR dose; *data not shown*). Patient characteristics of the group that was treated with the best treatment arm, i.e. 6xCHOP-14 + 8xR, and their relation to VCR reduction showed matching results to the whole study population (*data not shown*). As expected from the typical VCR toxicity profile, VCR dose reductions were more common in patients with higher grades of reported PNP (*Online Supplementary Table S1*).

With regard to outcome, patients who received 2 mg of VCR in each of the six of eight cycles (n=391) were compared for survival differences to patients with any reduction in VCR dosage (n=405). EFS, PFS and OS were not different between both groups. These results were confirmed in multivariable analyses adjusted for IPI factors, sex and age (Figure 1A-C) and were also observed for the subgroup treated within the 6xCHOP-14 + 8xR study arm (Figure 1D-F). In further analyses, EFS, PFS and OS were compared between patients receiving 100% of the intended VCR dose and the subgroups that received ≥80-<100%, >50-<80%, 50% or <50% of planned VCR dose. There were no differences in EFS, PFS and OS between these VCR dosing subgroups for all analyzed patients (*Online Supplementary Figure S1A-C*) and for patients of the 6xCHOP-14 + 8xR arm (*Online Supplementary Figure S1D-F*), even if VCR was reduced to less than 50% of the intended dose.

Since some study centers used 1 mg of VCR in every cycle as standard dose, we compared outcomes of patients receiving 2 mg of VCR in all cycles to outcomes of patients

Table 1. Patient characteristics according to administered vincristine dose.

Characteristics	Without VCR reduction 391 (49%)	With VCR reduction 405 (51%)	Total 796 (100%)
Sex, N (%)			
Male#	236 (60)	193 (48)	429 (54)
Female	155 (40)	212 (52)	367 (46
Age in years#, N (%)			
61-65	170 (43)	134 (33)	304 (38)
66-70	121 (31)	134 (33)	255 (32)
71-75	76 (19)	96 (24)	172 (22)
76-80	24 (6)	41 (10)	65 (8)
LDH >UNV, N (%)	182 (47)	195 (48)	377 (47)
ECOG >1, N (%)	39 (10)	40 (10)	79 (10)
Stage 3/4, N (%)	191 (49)	205 (51)	396 (50)
Extralymph. inv., N (%)	207 (53)	208 (51)	415 (52)
Extralymph. inv. >1, N (%)	64 (16)	61 (15)	125 (16)
IPI, N (%)			
1	133 (34)	125 (31)	258 (32)
2	106 (27)	116 (29)	222 (28)
3	99 (25)	115 (28)	214 (27)
4,5	53 (14)	49 (12)	102 (13)
Bulky disease ≥7.5 cm, N (%)	149 (38)	153 (38)	302 (38)
B symptoms, N (%)	123 (31)	133 (33)	256 (32)
BM involvement, N (%)	20 (5)	19 (5)	39 (5)
Reference pathology, N (%)			
DLBCL	302 (79)	323 (81)	625 (80)
other B-cell lymphoma	78 (20)	69 (17)	147 (19)
other	2 (1)	5 (1)	7 (1)
VCR in prephase*, N (%)			
0 mg	24 (6)	22 (5)	46 (6)
>0 and ≤1 mg	231 (59)	264 (66)	495 (62)
>1 mg	134 (34)	117 (29)	251 (32)

*Some missing values; #sex: *P*<0.001, age groups: *P*=0.010 for patients without VCR reduction (n=391) *vs.* patients with VCR reduction (n=405). VCR: vincristine; LDH: lactate dehydrogenase; UNV: upper normal value; ECOG: Eastern Cooperative Oncology Group performance status; IPI: International Prognostic Index; BM: bone marrow; extralymph.: extralymphatic; inv.: involvement; DLBCL: diffuse large B-cell lymphoma.

who received 1 mg of VCR in each cycle. EFS, PFS and OS did not differ between both groups when analyzing all patients (Figure 2A-C) and patients of the 6xCHOP-14 + 8xR treatment arm (Figure 2D-F), supporting the notion that 1.4 mg/m^2 of VCR may be an excessive dose for most patients and not only for patients developing VCR-induced side effects.

Because the IPI score correlates directly with prognosis,[15] we speculated that patients with higher IPI scores might have an additional benefit of higher cumulative VCR doses. However, when analyzing EFS, PFS and OS according to IPI groups (1, 2, 3, 4–5) of all 796 patients, no differences were found between patients with and without VCR reduction/omission (*Online Supplementary Figure S2A-D; data for EFS and OS not shown*). This indicates that even in patients with high-risk aggressive B-cell lymphoma, dose reduction of VCR has no bearing on survival outcomes.

When analyzing the age groups according to VCR dose reduction, no impact of VCR dosage on survival outcomes was observed within age groups of 61-65 years, 66-70 years and 71-75 years. Interestingly, a significant benefit in survival rates occurs for patients from 76–80 years of age in whom VCR was reduced or omitted at any time (*Online Supplementary Figure S2E-H; data for EFS and OS not shown*). These findings suggest that the reduction of potential VCR toxicity may have had a higher impact on survival than its additional cytostatic effect in 76–80-year-old patients with aggressive B-cell lymphoma. This is of special interest as this patient group (>75 years) is usually underrepresented in clinical trials and our data therefore support attempts of VCR dose reduction in >75-year-old patients as full dosing of VCR might be harmful in this vulnerable patient group.

In a sensitivity analysis, we compared survival outcomes of

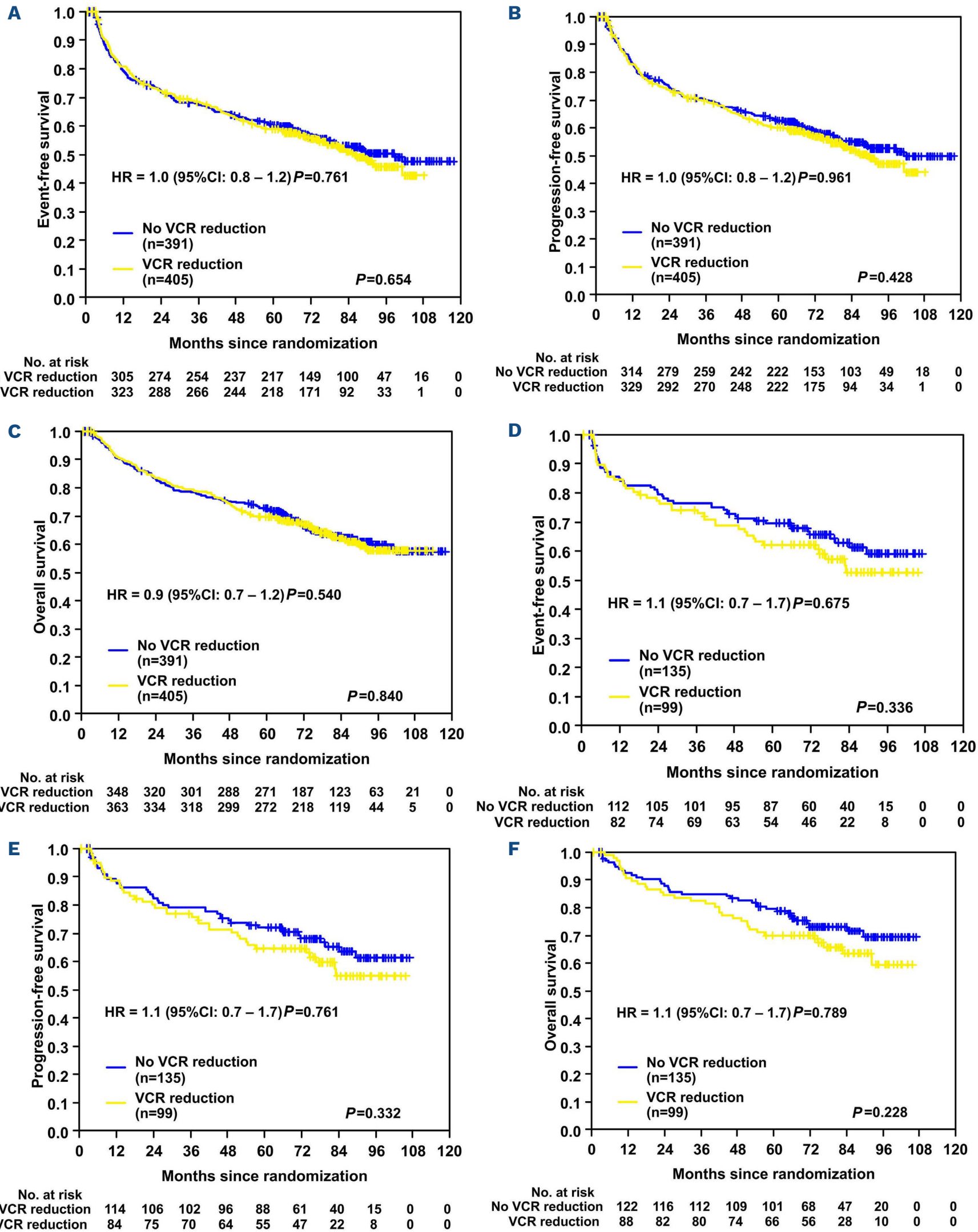

Figure 1. Survival outcomes for patients with and without vincristine reduction. (A, D) Event-free, progression-free (B, E) and overall survival (C, F) of all 796 patients (A–C) and of 234 patients treated with the best treatment arm 6xCHOP-14 + 8xR (D–F) participating in the RICOVER-60 trial according to their vincristine (VCR) dose (not reduced *vs.* reduced) are shown. Log-rank *P* values, hazard ratios adjusted for International Prognostic Index factors, sex and age, 95% confidence intervals and the *P* value from the multivariable Cox Model for VCR dose are presented. CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; 6xCHOP-14 + 8xR: 6 cycles of CHOP and 8 cycles of rituximab.

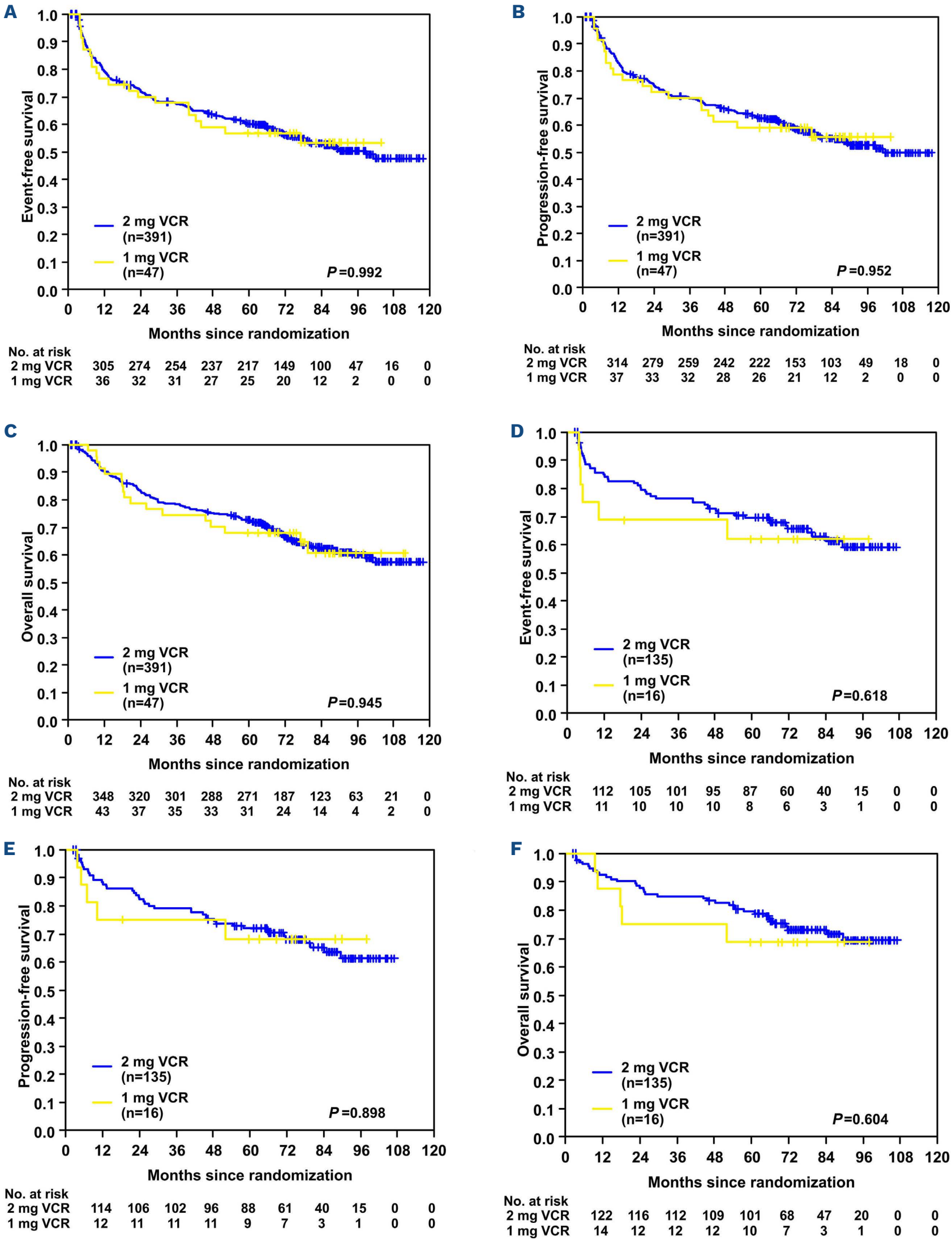

Figure 2. Comparison of survival outcomes in patients who received 1 mg *versus* 2 mg of vincristine in all cycles. (A, D) Event-free, (B, E) progression-free and (C, F) overall survival of 438 patients treated with 6/8xCHOP-14 ± 8xR (A–C) and of 151 patients treated with 6xCHOP-14 + 8xR (D–F) participating in the RICOVER-60 trial according to their vincristine (VCR) dose (2 mg *vs.* 1 mg in each of the 6/8 cycles) are shown. Log-rank *P* values are presented. CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; 6CHOP-14 ± 8xR: 6 cycles of CHOP and 8 cycles of rituximab.

patients from the two dosing subgroups (with or without VCR dose reduction) separately, depending on the application of VCR during prephase (>0 and ≤1 mg or >1 mg), since this may act as confounding factor. We found no differences in PFS, EFS or OS (*data not shown*) between both groups regardless of VCR dosing during the prephase.

We further investigated the influence of toxicities caused by co-administered chemotherapeutic agents. Considering only patients of the 6xCHOP-14 + 8xR arm who received fully dosed chemotherapy (cyclophosphamide ≥95%), there was no difference in PFS related to VCR reduction. There was, however, a non-significant (*P*=0.114) PFS difference with regard to VCR reduction in the small subgroup of patients in whom additional reduction of chemotherapy (cyclophosphamide <95%) was necessary, indicating that only after reduction of other chemotherapeutic agents, reduction of VCR might have an influence on outcomes.

When analyzing the influence of body surface area (BSA) on PNP, VCR reduction and survival outcomes, no correlation between BSA and maximal developed PNP grade was found. Interestingly, VCR was more often reduced in patients with lower BSA. However, VCR reduction (yes *vs*. no) had no impact on survival endpoints (EFS, PFS and OS) regardless of BSA (*data not shown*).

Due to the unclear benefit VCR adds to the CHOP regimen, VCR seems to be a reasonable choice as an exchange partner in future studies investigating the efficacy and safety of new drugs in the treatment of aggressive lymphomas. This is supported by the recently published, international phase III POLARIX trial, which evaluated the replacement of vincristine (as part of standard R-CHOP) with polatuzumab vedotin in patients with previously untreated intermediate- or high-risk DLBCL.[6]

Taken together, we here present the largest analysis of a phase III trial regarding VCR reduction in patients with aggressive B-cell lymphoma so far. Dose reduction of VCR due to toxicity in older patients with aggressive B-cell lymphoma treated with CHOP-14 seems to have no impact on survival outcomes (EFS, PFS and OS).

Major conclusions are: i) VCR reduction due to toxicity had no impact on outcomes of patients with aggressive B-cell lymphoma treated within the RICOVER-60 trial, ii) even in patients of the highest IPI risk group, VCR reduction had no influence on outcomes, iii) no survival differences were observed for patients who received only 1 mg VCR by institutional standards as compared to patients who received 2 mg of VCR in every cycle.

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Contributions

MP, MZ, BA, DKM, MB and IK developed the concept and design of the study. BA and MZ performed statistical analysis. All authors interpreted the data. MB, DKM, BA, IK, KC and MZ wrote the initial draft of the manuscript. MB, NS, VL, MZ, ML and BA reviewed the first draft. All authors gave their final approval of the manuscript. Data analysis and interpretation, writing of the paper, and decision to submit were left to the authors' discretion and were not influenced by third parties.

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Data-sharing statement

Additional data can be made available upon reasonable request to the corresponding author.

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