Safety of switching from intravenous to subcutaneous rituximab during first-line treatment of patients with non-Hodgkin lymphoma: the Spanish population of the MabRella study

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Summary

Rituximab is a standard treatment for non-Hodgkin diffuse large B-cell (DLBCL) and follicular (FL) lymphomas. A subcutaneous formulation was developed to improve the resource use of intravenous rituximab, with comparable efficacy and safety profiles except for increased administration-related reactions (ARRs). MabRella was a phase IIIb trial to assess the safety of switching from intravenous to subcutaneous administration of rituximab during first-line induction/maintenance for DLBCL or FL, focusing on ARRs. Efficacy, satisfaction and quality of life were also assessed. Patients received subcutaneous rituximab plus standard induction chemotherapy for DLBCL or FL for 4–7 cycles, and/or every 2 months maintenance monotherapy for FL for 6–12 cycles. The study included 140 patients: DLBCL, n = 29; FL, n = 111. Ninety-five percent of patients experienced adverse events, reaching grade ≥3 in 38.6% and were serious in 30.0%. AARs occurred in 48.6%, mostly (84.9%) at the injection site, with only 2.1% of patients reaching grade 3. The end-of-induction complete/unconfirmed complete response rate was 69.6%. After a median follow-up of 33.5 months, median disease-/event-/progression-free and overall survivals were not attained. The Rituximab Administration Satisfaction Questionnaire showed improvements in overall satisfaction and the EuroQoL-5D a good quality-of-life perception at induction/maintenance end. Therefore, switching to subcutaneous rituximab showed no new safety issues and maintained efficacy with improved satisfaction and quality of life.

Keywords: non-Hodgkin diffuse large B-cell lymphoma, follicular lymphoma, rituximab, safety, administration-related reactions.
Rituximab, a chimeric murine/human monoclonal antibody with specific affinity for the transmembrane CD20 protein present on the surface of B lymphocytes (Tedder & Engel, 1994), induces the death of rituximab-coated target cells through complement-dependent cellular cytotoxicity, antibody-dependent cellular cytotoxicity and potential apoptosis induction or enhanced chemotherapy sensitivity (Weiner, 2010). Its effectiveness as a single agent and in conjunction with chemotherapy has made rituximab a standard of care for first-line treatment of non-Hodgkin lymphomas, such as diffuse large B-cell (DLBCL) and follicular lymphomas (FL) (Dreyling et al, 2016; National Comprehensive Cancer Network (NCCN), 2017).

Rituximab was initially approved for administration in Non-Hodgkin Lymphoma (NHL) at a dose of 375 mg/m² body surface area as 1-5- to 6-h intravenous infusions [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000165/human_med_000897.jsp&mid=WCOb01ac058001d124; https://www.accessdata.fda.gov/scripts/cder/index.cfm?event=overview.process&ApplNo=103705]. The main inconveniences of rituximab intravenous administrations were the requirement for intravenous access, long infusion times and infusion-related side effects. A subcutaneous formulation was therefore developed to overcome these inconveniences, simplify administration, improve convenience and reduce both the incidence of severe administration-related reactions and costs, including 12 times more concentrated rituximab to reduce the injection volume and a recombinant human hyaluronidase to improve drug dispersion and absorption with limited swelling and pain (Shipilberg & Jackisch, 2013; Davies et al, 2017a).

The subcutaneous formulation enabled non-inferior rituximab trough concentrations to be achieved after a fixed-dose administration of 1400 mg, with a similar adverse event (AE) profile except for the expected increase in local administration reactions (Salar et al, 2014). Further evaluations of the subcutaneous formulation of rituximab confirmed its non-inferior pharmacokinetics (Davies et al, 2014, 2017b), along with an efficacy comparable to intravenous rituximab and no new safety concerns (Lugtenburg et al, 2017; Davies et al, 2017b). Switching from intravenous to subcutaneous dosing shortens the administration time of rituximab to approximately 5 min (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000165/human_med_000897.jsp&mid=WCOb01ac058001d124; https://www.accessdata.fda.gov/scripts/cder/index.cfm?event=overview.process&AppNo=761064), which can improve treatment convenience for patients and reduce resource burden for healthcare providers. Indeed, recent studies have reported that subcutaneous rituximab entails considerable reductions in administration, chair/bed use, active healthcare professional and overall hospital times (De Cock et al, 2016; Lugtenburg et al, 2017), without affecting the patients’ perception of their treatment and the time they had to talk to healthcare providers (Lugtenburg et al, 2017). Data from subcutaneous rituximab administration showed it to be a preferable treatment formulation for patients (Rummel et al, 2017), with improved treatment convenience, satisfaction and effect on daily living (De Cock et al, 2016; Rummel et al, 2017). Based on the accumulated clinical data, subcutaneous rituximab was approved and is currently available for the treatment of patients with DLBCL and FL (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000165/human_med_000897.jsp&mid=WCOb01ac058001d124; https://www.accessdata.fda.gov/scripts/cder/index.cfm?event=overview.process&AppNo=761064). Nonetheless, all patients must receive at least one full dose of intravenous rituximab before starting subcutaneous dosing as a precaution for better handling of potential administration reactions, which most frequently occur at the first administration of rituximab (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000165/human_med_000897.jsp&mid=WCOb01ac058001d124; https://www.accessdata.fda.gov/scripts/cder/index.cfm?event=overview.process&AppNo=761064).

In view of the above, this study aimed to provide further information on the safety of switching rituximab administration from the intravenous to the subcutaneous route, primarily focusing on administration-related reactions (ARRs) due to the expected change in their profile after switching, and secondarily on grade ≥3 adverse events (AEs), grade ≥3 ARRs and serious adverse events (SAEs). Treatment efficacy was also assessed as a secondary objective, along with patient satisfaction and quality of life.

**Methods**

**Study design and participants**

MabRella was an umbrella study comprising three local, open-label, single-arm, phase IIIb trials conducted in Spain, Italy and North Africa. The Spanish MabRella trial was conducted at 39 hospitals according to Helsinki Declaration, Good Clinical Practice and national regulations. The appropriate ethics committee approved the study, and all patients gave their written informed consent. Eligible patients were aged 18–80 years, with histologically confirmed CD20+ non-Hodgkin DLBCL or grade 1–3a FL and Eastern Cooperative Oncology Group performance status ≤3. Patients must have received ≥1 full dose (375 mg/m²) of intravenous rituximab as first-line induction/maintenance and be capable of receiving ≥4 additional induction cycles for DLBCL/FL or ≥6 additional maintenance cycles for FL. The main exclusion criteria included transformed lymphoma or stage 3b FL, primary central nervous system lymphoma, transformation to a Burkitt lymphoma, primary effusion lymphoma or primary mediastinal, testicular or cutaneous DLBCL, and history of another malignancy that could affect protocol compliance or result interpretation. Detailed inclusion/exclusion criteria are described in the Appendix S1.
Procedures

All patients switched from intravenous to subcutaneous rituximab (MabThera; Roche Registration Limited, Welwyn Garden City, UK). Paracetamol and diphenhydramine, or alternative antihistamine premedication was recommended 30–60 min prior to rituximab administration. Each cycle included a single subcutaneous rituximab injection, administered at 1400 mg (11.7 ml) over 5–6 min in the outpatient setting, and no dose modification was considered in the study protocol.

During induction therapy, cycles were repeated every 14, 21 or 28 days, depending on the combination chemotherapy selected according to clinical practice, for 4–7 cycles (Figure S1). FL patients who achieved at least a partial response at week 4–6 after induction were eligible for maintenance single-agent subcutaneous rituximab. During maintenance therapy, subcutaneous rituximab was administered every 2 months for up to 2 years.

After ending the study treatment, patients entered in a post-treatment follow-up, with study visits every 3 and 6 months during its first and second year, respectively. Safety continued to be monitored and efficacy assessments (e.g., tumour response, survival) were conducted according to local practice.

Further details on study assessments are shown in the Appendix S1.

Statistical analyses

The primary endpoint analysis included the incidence of ARRs, defined as treatment-related AEs within 24 h of subcutaneous rituximab administration. The proportion of patients experiencing at least one ARR was estimated with its 95%-Clopper-Pearson confidence interval (CI). Sample size calculation was based on a previous study that reported the imprecision of approximately ±5%, 139 evaluable patients were deemed necessary to address the primary study objective.

Secondary endpoint analyses included the incidence of grade ≥3 AEs, grade ≥3 ARRs and SAEs. Other secondary endpoint analyses included the calculation of treatment response rates 4–6 weeks after induction, disease-free survival in patients achieving complete response, event-free survival, progression-free survival and overall survival. Time-to-event endpoint analyses were performed using the Kaplan–Meier method. Additionally, treatment satisfaction and patient quality of life were assessed according to Rituximab Administration Satisfaction Questionnaire (RASQ) and EuroQol-5D (EQ-5D) scores, respectively. Further details are provided in the Appendix S1.

Results

Patient disposition and baseline characteristics

A total of 160 patients were screened between November 2013 and August 2014, 20 of whom were screening failures (Fig 1). Thus, 140 patients (29 with DLBCL and 111 with FL) were evaluable for the study. Baseline Characteristics of these patients are described in Table I.

Study treatment

Patients started receiving intravenous rituximab after a median (interquartile range, IQR) of 1.2 (0.5–2.1) months from the diagnosis of DLBCL or FL [DLBCL, 0.5 (0.3–1.2) months; FL, 1.3 (0.7–3.6) months]. All patients with DLBCL switched from intravenous to subcutaneous rituximab during induction, mostly at cycles 2–3 (cycle 2, n = 8; cycle 3, n = 14). However, 84 (75.7%) of the 111 patients with FL switched to subcutaneous rituximab during the maintenance treatment, mainly at cycles 1 (n = 23) and 2 (n = 22), compared to 27 (24.3%) who switched during the induction treatment, mainly at cycle 2 (n = 12). Two of the latter patients only received induction treatment with subcutaneous rituximab, and 25 continued to receive it during the subsequent maintenance treatment. Thus, a total of 56 patients received induction treatment with subcutaneous rituximab (induction, n = 31; induction and maintenance, n = 25) and 109 maintenance treatment (induction and maintenance, n = 25; maintenance, n = 84) (Fig 1).

The median (IQR) number of induction cycles in patients with DLBCL and FL were 6.0 (4.0–6.0) and 6.0 (5.0–7.0), respectively (Table II). Induction chemotherapy was CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) in all DLBCL patients. In FL patients, the main induction chemotherapies included CHOP (52.3%), bendamustine (22.5%) and CVP (cyclophosphamide, vincristine and prednisone; 4.5%); chemotherapy regimen was not recorded in 16 (14.4%) patients. FL patients who underwent maintenance treatment received a median (IQR) of 11.0 (8.0–12.0) cycles (Table II).

Study treatment discontinuation was only reported in 8 patients with DLBCL and 16 with FL due to disease progression (DLBCL, n = 4; FL, n = 20), investigator decision (DLBCL, n = 0; FL, n = 3), patient request/consent withdrawal (DLBCL, n = 1; FL, n = 1), death (DLBCL, n = 1; FL, n = 1), or other reasons (DLBCL, n = 2; FL, n = 1).

Safety

A total of 133 (95.0%) patients experienced at least one of the 1162 AEs reported throughout the study (DLBCL, 93.1%; FL, 95.5%), which most frequently included erythema, neutropenia and asthenia (Table III). AEs were grade ≥3 in 54
(38.6%) patients (DLBCL, 48.3%; FL, 36.0%), most frequently neutropenia and febrile neutropenia, and were considered related to subcutaneous rituximab by the treating physicians in 76 cases (54.3%; DLBCL, 37.9%; FL, 58.6%), most frequently erythema and neutropenia (Table III). Study treatment was delayed in 32 (22.9%) patients due to AEs (DLBCL, 13.8%; FL, 25.2%), interrupted in one (0.7%; DLBCL, 0.0%; FL, 0.9%) and permanently discontinued in one (0.7%; DLBCL, 0.0%; FL, 0.9%); treatment withdrawal in the latter patient was due to pneumonia pneumococcal (Table III). A total of 976 (84.0%) of the 1162 AEs resolved (DLBCL, 83.3%; FL, 84.1%), 17 (1.5%) resolved with sequelae (DLBCL, 1.6%; FL, 1.4%), 40 (3.4%) were unresolved but improving (DLBCL, 2.1%; FL, 3.7%), 123 (10.6%) persisted as unresolved (DLBCL, 11.5%; FL, 10.4%), 3 (0.3%) were fatal (DLBCL, 1.0%; FL, 0.1%) and another (0.1%) worsened (DLBCL, 0.0%; FL, 0.1%); the outcome of 2 (0.2%) AEs was unknown (DLBCL, 0.5%; FL, 0.1%).

Sixty-eight (48.6%, 95% CI 40.1–57.1%) patients exhibited at least one of the 218 reported ARRs (DLBCL, 34.5%, 95% CI 18.6–54.3%; FL, 52.3%, 95% CI 42.6–61.7%). Thirty-three (15.1%) ARRs were generalized and/or remote from the injection site (DLBCL, 57.9%; FL, 11.1%), while 185 (84.9%) were localized at the injection site (DLBCL, 42.1%; FL, 88.9%). Patients most frequently exhibited erythema, injection site erythema and presyncope (Table III). Only four grade 3 ARRs were reported in 3 (2.1%) patients (DLBCL, 0.0%; FL, 2.7%; Table III); no grade ≥4 ARR was reported (Table IV). The grade 3 ARRs included injection site pain, injection site reaction, paresthesia oral and presyncope (Table IV).

Eighty-two SAEs were experienced by 42 (30.0%) patients (DLBCL, 37.9%; FL, 27.9%), most frequently febrile neutropenia, neutropenia and pneumonia (Tables III and V), and 3 (2.1%) were fatal (DLBCL, 6.9%; FL, 0.9%); gastrointestinal haemorrhage, brain neoplasm and sepsis (Table III). Sepsis was the only fatal AE related to subcutaneous rituximab.

Efficacy

Treatment response. Response to induction treatment with subcutaneous rituximab was assessed in the 56 patients who received it throughout the study (DLBCL, n = 29; FL, n = 27; Fig 1). The complete response rate (i.e., complete...
response [CR] plus unconfirmed complete response [CRu]) was 69.6% (DLBCL, 65.5%; FL, 74.1%): CR 64.3% (DLBCL, 62.1%; FL, 66.7%) and CRu 5.4% (DLBCL, 3.4%; FL, 7.4%). Partial response, stable disease and disease progression rates were 7.1% (DLBCL, 3.4%; FL, 11.1%), 1.8% (DLBCL, 0.0%; FL, 3.7%) and 12.5% (DLBCL, 17.2%; FL, 7.4%), respectively. Response was reported as 'unable to assess' or 'not evaluable' in 5 (8.9%) patients (DLBCL, 13.8%; FL, 3.7%).

**Survival assessments.** After a median (IQR) of 33.5 (30.9–35.8) months [DLBCL, 27.6 (25.3–30.3) months; FL, 34.1 (32.7–36.1) months], disease-free survival in patients achieving CR/CRu was not reached in either the overall population or according to lymphoma type (i.e., DLBCL and FL) (Figure S2A). Similarly, median event-free, progression-free and overall survivals were not reached in either the overall population or according to lymphoma type (i.e., DLBCL and FL) (Figure S2B–D).

**Patient-reported outcomes**

**Treatment satisfaction.** The RASQ was completed by 133 (95.0%) patients at the screening/baseline visit after the last dose of intravenous rituximab before switching to subcutaneous rituximab, and showed satisfaction with intravenous rituximab. After induction treatment with subcutaneous rituximab, the RASQ was completed by 38 (67.9%) of the 56 patients who received such induction treatment, and showed satisfaction with subcutaneous rituximab. Higher mean scores were observed in all RASQ domains at the end of induction, especially in the psychological, impact on daily living, convenience and satisfaction domains, suggesting improvements after switching to subcutaneous rituximab (Fig 2A). Similar results were achieved when RASQ scores were analysed according to lymphoma type (i.e., DLBCL and FL) (Fig 2B, C).

In addition, 89 (81.7%) of the 109 patients who received maintenance treatment with subcutaneous rituximab completed the RASQ at the end of maintenance. Mean RASQ scores in these patients also suggested a positive effect in the psychological, impact on daily living, convenience and satisfaction domains after switching to subcutaneous rituximab (Fig 2D).

**Quality of life.** Thirty-four (60.7%) of the 56 patients who received induction treatment with subcutaneous rituximab completed the EQ-5D questionnaire at the end of induction. Most patients reported no problems with mobility, self-care or

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Table I. Baseline patient characteristics

| Patient characteristics | DLBCL (N = 29) | FL (N = 111) | Total (N = 140) |
|-------------------------|----------------|-------------|----------------|
| Median age, years (IQR) | 66.8 (51.7–72.0) | 59.9 (50.4–69.2) | 61.6 (51.4–69.7) |
| Male, n (%)             | 12 (41.4)       | 53 (47.7)   | 65 (46.4)       |
| Caucasian, n (%)        | 29 (100)        | 110 (99.1)  | 139 (99.3)      |
| Mean body weight, kg (+SD) | 68.0 ± 15.5   | 73.4 ± 15.1* | 72.3 ± 15.3*   |
| Mean body mass index, kg/cm² (+SD) | 25.6 ± 4.6 | 27.2 ± 4.8* | 26.8 ± 4.8*   |
| ECOG performance status, n (%) |                  |             |                |
| ECOG 0                  | 20 (69.0)       | 90 (81.1)   | 110 (78.6)     |
| ECOG 1                  | 7 (24.1)        | 19 (17.1)   | 26 (18.6)      |
| ECOG 2                  | 1 (3.4)         | 2 (1.8)     | 3 (2.1)        |
| ECOG 3                  | 1 (3.4)         | 0 (0.0)     | 1 (0.7)        |
| Median time from diagnosis, months (IQR) | 2.0 (1.1–2.5) | 9.3 (5.8–14.7) | 8.0 (2.4–13.2) |
| IPI score for DLBCL patients, n (%) |                  |             |                |
| Low risk                | 12 (41.4)       |             |                |
| Low-intermediate risk    | 3 (10.3)        |             |                |
| High-intermediate risk   | 6 (20.7)        |             |                |
| High risk               | 8 (27.6)        |             |                |
| Grade of FL, n (%)       |                  |             |                |
| Grade 1                 | –               | 38 (34.2)   | –              |
| Grade 2                 | –               | 51 (45.9)   | –              |
| Grade 3a                | –               | 22 (19.8)   | –              |
| FLIPI score for FL patients, n (%)† |                  |             |                |
| Low risk                | –               | 23 (24.2)   | –              |
| Intermediate risk        | –               | 37 (38.9)   | –              |
| High risk               | –               | 35 (36.8)   | –              |

DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; IPI, International Prognostic Index; IQR, interquartile range; SD, standard deviation.

*Missing data, n = 3.
†Missing data, n = 16.
do their usual activities, as well as no pain/discomfort or anxiety/depression (Table VI). They rated their health state with a mean score of about 75 in a visual analogue scale, ranging from 0 (i.e., worst imaginable health state) to 100 (i.e., best imaginable health state), denoting a good perception of their quality of life. Mean index of preference values (tariffs) were 0-8–0-9 on a scale from 0 (i.e., death) to 1 (i.e., best health state), which also denoted a good health state.

In addition, 88 (80-7%) of the 109 patients who received maintenance treatment with subcutaneous rituximab completed the EQ-5D at the end of maintenance. Most of them also reported no problems in walking about, self-caring or doing their usual activities, as well as no pain/discomfort or anxiety/depression (Table VI). Their rating of the health state on the visual analogue scale was good, showing a mean value of 73-9 on a scale from 0 (i.e., worst imaginable health state) to 100 (i.e., best imaginable health state). Moreover, the index of preference values (tariffs) denoted a good health state, as the mean value was 0-9 on a scale from 0 (i.e., death) to 1 (i.e., best health state).

**Discussion**

The results of this phase IIIb study showed that switching from intravenous to subcutaneous rituximab was well tolerated and did not raise new safety concerns. Although 95% of patients experienced at least one AE, they reached grade ≥3 in 38-6% and were SAEs in 30-0%. ARRs were reported in 48-6% and reached grade 3 in 2-1%; no grade ≥4 ARR was reported throughout the study. These data showed that although ARRs were commonly experienced, their intensity was mostly mild to moderate (i.e., grade 1–2). In addition, while only 15-1% of the reported ARRs were generalized and/or remote from the injection site, most ARRs (84-9%) were localized at the injection site. Among these, the only ARRs reported in more than 5% of patients were erythema, injection site erythema and presyncope. In addition, most of these ARRs resolved spontaneously, as drug delay was only reported in one patient and no treatment discontinuation was required. These safety results, including the 48-6% of ARRs and the 7-9% presentation of injection site erythema, are in line with the acceptable safety profile reported in clinical trials that assessed subcutaneous rituximab administration (Salar et al., 2014; Davies et al., 2014, 2017b; Rummel et al., 2017; Lugtenburg et al., 2017). The SABRINA (FL) and MabEase (DLBCL) trials showed the occurrence of ARRs in 20-9–48-2% of patients during up to 7 cycles of subcutaneous rituximab for the first-line induction treatment of FL and DLBCL, mainly manageable mild to moderate events – only reaching grade 3 in 2-7–3-1% of patients –, which most frequently included injection-site reactions (≥5%), such as erythema, pruritus, rash, pain, bruising, discoloration, hematoma, hypertrophy, induration or inflammation/swelling (Lugtenburg et al., 2017; Davies et al., 2017b). Although the PrefMab (FL and DLBCL) trial reported lower rates of ARRs, ranging from 10-4% to 21-1% and with few overall cases of
Table III. Overview of safety results

| Variable                                      | DLBCL (N = 29) | FL (N = 111) | Total (N = 140) |
|-----------------------------------------------|----------------|--------------|-----------------|
|                                               | Any grade      | Grade ≥ 3    | Any grade       | Grade ≥ 3    | Any grade       | Grade ≥ 3    |
| **AEs, n (%)**                                | 27 (93-1)      | 14 (48-3)    | 106 (95-5)      | 40 (36-0)    | 133 (95-0)      | 54 (38-6)    |
| Erythema                                      | 3 (10-3)       | 0 (0-0)      | 34 (30-6)       | 0 (0-0)      | 37 (26-4)       | 0 (0-0)      |
| Neutropenia                                   | 10 (34-5)      | 9 (31-0)     | 22 (19-8)       | 20 (18-0)    | 32 (22-9)       | 29 (20-7)    |
| Asthenia                                      | 6 (20-7)       | 1 (3-4)      | 25 (22-5)       | 0 (0-0)      | 31 (22-1)       | 1 (0-7)      |
| Respiratory tract infection                   | 4 (13-8)       | 1 (3-4)      | 21 (18-9)       | 3 (2-7)      | 25 (17-9)       | 4 (2-9)      |
| Diarrhoea                                     | 6 (20-7)       | 0 (0-0)      | 16 (14-4)       | 1 (0-9)      | 22 (15-7)       | 1 (0-7)      |
| Anaemia                                       | 7 (24-1)       | 1 (3-4)      | 6 (5-4)         | 1 (0-9)      | 13 (9-3)        | 2 (1-4)      |
| Febrile neutropenia                           | 6 (20-7)       | 6 (20-7)     | 7 (6-3)         | 6 (5-4)      | 13 (9-3)        | 12 (8-6)     |
| Viral upper respiratory tract infection        | 2 (6-9)        | 0 (0-0)      | 19 (17-1)       | 0 (0-0)      | 21 (15-0)       | 0 (0-0)      |
| Paraesthesia                                   | 5 (17-2)       | 0 (0-0)      | 9 (8-1)         | 0 (0-0)      | 14 (10-0)       | 0 (0-0)      |
| Nausea                                        | 5 (17-2)       | 0 (0-0)      | 8 (7-2)         | 0 (0-0)      | 13 (9-3)        | 0 (0-0)      |
| Abdominal pain                                | 1 (3-4)        | 0 (0-0)      | 13 (11-7)       | 1 (0-9)      | 14 (10-0)       | 1 (0-7)      |
| Back pain                                     | 3 (10-3)       | 1 (3-4)      | 13 (11-7)       | 0 (0-0)      | 16 (11-4)       | 1 (0-7)      |
| Cough                                         | 1 (3-4)        | 0 (0-0)      | 13 (11-7)       | 0 (0-0)      | 14 (10-0)       | 0 (0-0)      |
| Pyrexia                                       | 2 (6-9)        | 0 (0-0)      | 12 (10-8)       | 0 (0-0)      | 14 (10-0)       | 0 (0-0)      |
| Vomiting                                      | 3 (10-3)       | 0 (0-0)      | 4 (3-6)         | 0 (0-0)      | 7 (5-0)         | 0 (0-0)      |
| Upper respiratory tract infection             | 3 (10-3)       | 0 (0-0)      | 9 (8-1)         | 0 (0-0)      | 12 (8-6)        | 0 (0-0)      |
| Lymphopenia                                   | 3 (10-3)       | 0 (0-0)      | 1 (0-9)         | 0 (0-0)      | 4 (2-9)         | 0 (0-0)      |
| **Rituximab-related AEs, n (%)**              | 11 (37-9)      | 3 (10-3)     | 65 (58-6)       | 19 (17-1)    | 76 (54-3)       | 22 (15-7)    |
| Erythema                                      | 3 (10-3)       | 0 (0-0)      | 34 (30-6)       | 0 (0-0)      | 37 (26-4)       | 0 (0-0)      |
| Neutropenia                                   | 1 (3-4)        | 1 (3-4)      | 14 (12-6)       | 13 (11-7)    | 15 (10-7)       | 14 (10-0)    |
| **ARRs, n (%)†**                              | 10 (34-5)      | 0 (0-0)      | 58 (52-3)       | 3 (2-7)      | 68 (48-6)       | 3 (2-1)      |
| Erythema                                      | 3 (10-3)       | 0 (0-0)      | 32 (28-8)       | 0 (0-0)      | 35 (25-0)       | 0 (0-0)      |
| Injection site erythema                       | 0 (0-0)        | 0 (0-0)      | 11 (9-9)        | 0 (0-0)      | 11 (7-9)        | 0 (0-0)      |
| Presyncope                                    | 2 (6-9)        | 0 (0-0)      | 1 (0-9)         | 1 (0-9)      | 3 (2-1)         | 1 (0-7)      |
| **SAEs, n (%)‡**                              | 11 (37-9)      | 11 (37-9)    | 31 (27-9)       | 28 (25-2)    | 42 (30-0)       | 39 (27-9)    |
| Febrile neutropenia                           | 6 (20-7)       | 6 (20-7)     | 6 (5-4)         | 5 (4-5)      | 12 (8-6)        | 11 (7-9)     |
| Neutropenia                                   | 3 (10-3)       | 3 (10-3)     | 7 (6-3)         | 7 (6-3)      | 10 (7-1)        | 10 (7-1)     |
| Pneumonia                                     | 2 (6-9)        | 2 (6-9)      | 2 (1-8)         | 2 (1-8)      | 4 (2-9)         | 4 (2-9)      |
| **AEs leading to withdrawal, n (%)‡**          | 0 (0-0)        | 0 (0-0)      | 1 (0-9)         | 0 (0-0)      | 1 (0-7)         | 0 (0-0)      |
| Pneumonia pneumococcal                        | 0 (0-0)        | 0 (0-0)      | 1 (0-9)         | 0 (0-0)      | 1 (0-7)         | 0 (0-0)      |
| **Fatal AEs, n (%)‡**                         | 2 (6-9)        | 2 (6-9)      | 1 (0-9)         | 1 (0-9)      | 3 (2-1)         | 3 (2-1)      |
| Gastrointestinal haemorrhage                  | 1 (3-4)        | 1 (3-4)      | 0 (0-0)         | 0 (0-0)      | 1 (0-7)         | 1 (0-7)      |
| Brain neoplasm                                | 1 (3-4)        | 1 (3-4)      | 0 (0-0)         | 0 (0-0)      | 1 (0-7)         | 1 (0-7)      |
| Sepsis                                       | 0 (0-0)        | 0 (0-0)      | 1 (0-9)         | 1 (0-9)      | 1 (0-7)         | 1 (0-7)      |

AEs, adverse events; ARRs, administration-related reactions; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; SAEs, serious adverse events.

*Details on AEs and rituximab-related AEs of any grade with frequency ≥ 10% in the overall, DLBCL, or FL populations are shown.
†Details on ARRs and SAEs of any grade with frequency ≥ 5% in the overall, DLBCL, or FL populations are shown.
‡All AEs leading to withdrawal and fatal AEs are described.

erythema (1.8%) or injection site erythema (1.5%), the differences in trial design should be noted, as this trial used a crossover approach of intravenous and subcutaneous rituximab administration with the latter being administered for up to 3–4 cycles (Rummel et al., 2017). With regard to maintenance treatment for FL, the SparkThera trial also supported an acceptable and manageable safety profile, with 31% of patients experiencing ARRs after subcutaneous rituximab injection for up to 2 years, which were mainly mild to moderate, rarely required treatment, and most commonly included erythema (13%), injection site erythema (5%) and myalgia (5%) (Salar et al., 2014). In addition, a post-marketing single-centre assessment of the safety profile of subcutaneous rituximab for B-cell NHL also supported that most subcutaneous injections administered in daily practice were well-tolerated, with 39% of patients developing ARRs over 1–7 injections per patient; these were mainly mild reactions that generally resolved without treatment, and included erythema, local pain, haematoma, cellulitis, pruritus and dizziness (Sanchez-Gonzalez et al., 2018).

With regard to the type of lymphoma, erythema also was the most frequently observed ARRs in patients with DLBCL and FL, though its incidence was almost three times higher in FL patients (DLBCL, 10.3%; FL, 28.8%). Among other
Table IV. Frequency of patients with administration-related reactions

| ARRs, n (%) | DLBCL (N = 29) | FL (N = 111) | Total (N = 140) |
|-------------|----------------|--------------|----------------|
|             | Any grade | Grade 3* | Any grade | Grade 3* | Any grade | Grade 3* |
| Erythema    | 3 (10-3) | 0 (0-0) | 32 (28-8) | 0 (0-0) | 35 (25-0) | 0 (0-0) |
| Injection site erythema | 0 (0-0) | 0 (0-0) | 11 (9-9) | 0 (0-0) | 11 (7-9) | 0 (0-0) |
| Presyncope  | 2 (6-9) | 0 (0-0) | 1 (0-9) | 1 (0-9) | 3 (2-1) | 1 (0-7) |
| Oedema      | 1 (3-4) | 0 (0-0) | 3 (2-7) | 0 (0-0) | 4 (2-9) | 0 (0-0) |
| Injection site pain | 0 (0-0) | 0 (0-0) | 4 (3-6) | 1 (0-9) | 4 (2-9) | 1 (0-7) |
| Pain        | 0 (0-0) | 0 (0-0) | 4 (3-6) | 0 (0-0) | 4 (2-9) | 0 (0-0) |
| Injection site discomfort | 1 (3-4) | 0 (0-0) | 2 (1-8) | 0 (0-0) | 3 (2-1) | 0 (0-0) |
| Nausea      | 1 (3-4) | 0 (0-0) | 2 (1-8) | 0 (0-0) | 3 (2-1) | 0 (0-0) |
| Inflammation | 0 (0-0) | 0 (0-0) | 3 (2-7) | 0 (0-0) | 3 (2-1) | 0 (0-0) |
| Rash        | 0 (0-0) | 0 (0-0) | 3 (2-7) | 0 (0-0) | 3 (2-1) | 0 (0-0) |
| Haematoma   | 0 (0-0) | 0 (0-0) | 3 (2-7) | 0 (0-0) | 3 (2-1) | 0 (0-0) |
| Injection site reaction | 0 (0-0) | 0 (0-0) | 3 (2-7) | 1 (0-9) | 3 (2-1) | 1 (0-7) |
| Burning sensation | 0 (0-0) | 0 (0-0) | 3 (2-7) | 0 (0-0) | 3 (2-1) | 0 (0-0) |
| Injection site oedema | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 2 (1-4) | 0 (0-0) |
| Skin reaction | 1 (3-4) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 2 (1-4) | 0 (0-0) |
| Parasthesia  | 1 (3-4) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 2 (1-4) | 0 (0-0) |
| Pruritus     | 0 (0-0) | 0 (0-0) | 2 (1-8) | 0 (0-0) | 2 (1-4) | 0 (0-0) |
| Abdominal pain  | 0 (0-0) | 0 (0-0) | 2 (1-8) | 0 (0-0) | 2 (1-4) | 0 (0-0) |
| Dyspepsia    | 1 (3-4) | 0 (0-0) | 0 (0-0) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Muscle fatigue | 1 (3-4) | 0 (0-0) | 0 (0-0) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Musculoskeletal pain | 1 (3-4) | 0 (0-0) | 0 (0-0) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Pain in extremity | 1 (3-4) | 0 (0-0) | 0 (0-0) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Anemia       | 1 (3-4) | 0 (0-0) | 0 (0-0) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Headache     | 1 (3-4) | 0 (0-0) | 0 (0-0) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Neutropenia  | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Abdominal pain lower | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Diarrhoea    | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Parasthesia oral | 0 (0-0) | 0 (0-0) | 1 (0-9) | 1 (0-9) | 1 (0-7) | 1 (0-7) |
| Administration site erythema | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Administration site pain | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Discomfort   | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Feeling hot  | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Infusion site pain | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Injection site bruising | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Injection site discolouration | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Injection site haematoma | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Injection site papule | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Edema peripheral | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Puncture site erythema | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Puncture site pain | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Puncture site reaction | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Pyrexia      | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Herpes zoster | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Otitis media acute | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Upper respiratory tract infection | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Decreased appetite | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Back pain    | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Somnolence   | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Dyspnoea     | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Dermatitis   | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |
| Urticaria    | 0 (0-0) | 0 (0-0) | 1 (0-9) | 0 (0-0) | 1 (0-7) | 0 (0-0) |

ARRs, administration-related reactions; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma.

*No grade ≥ 4 ARR was reported throughout the study.
ARRs with incidence ≥5%, injection site erythema was more frequently reported in patients with FL (DLBCL, 0.0%; FL, 9.9%) and presyncope in those with DLBCL (DLBCL, 6.9%; FL, 0.9%). When considering the frequencies of other AEs in these patient populations, it was found that FL patients also reported much higher rates of viral upper respiratory tract infection (DLBCL, 6.9%; FL, 17.1%), cough (DLBCL, 3.4%; FL, 11.7%) and abdominal pain (DLBCL, 3.4%; FL, 11.7%), while DLBCL patients reported much higher rates of neutropenia (DLBCL, 34.5%; FL, 19.8%), anaemia (DLBCL, 24.1%; FL, 5.4%), febrile neutropenia (DLBCL, 20.7%; FL, 6.3%), paraesthesia (DLBCL, 17.2%; FL, 8.1%), nausea (DLBCL, 17.2%; FL, 7.2%), vomiting (DLBCL, 10.3%; FL, 3.6%) and lymphopenia (DLBCL, 10.3%; FL, 0.9%). Although the interim analysis of pooled data from the three local trials within the global umbrella MabRella study showed that the safety profile of subcutaneous rituximab was generally comparable between FL and DLBCL patients, it also showed that patients with FL more frequently exhibited erythema and those with DLBCL more commonly presented neutropenia (Panizo et al., 2016, 2017) and anaemia (Panizo et al., 2017). However, the MabRella study was descriptive and was not designed to compare the AEs exhibited in patients with DLBCL and FL. Indeed, the number of patients with DLBCL was much lower than that of FL, which might affect the assessment of comparisons between groups of patients. In addition, while all patients with DLBCL received CHOP chemotherapy along with rituximab, those with FL received more variable chemotherapy regimens or even maintenance with rituximab monotherapy in many cases. Thus, the chemotherapy received with rituximab might explain the higher rates of febrile neutropenia and other haematological toxicities in DLBCL patients, while the corticosteroid component of the CHOP regimen might have contributed to the less frequent occurrence of cutaneous events, such as erythema and injection site erythema. In addition, the longer treatment administration in patients with FL, mainly over maintenance therapy, might have entailed a higher detection of AEs by the investigators, including cough, abdominal pain and viral infections. It should be noted, though, that the chemotherapy regimen was not reported in 14% of FL patients and other factors, such as the impact of potential differences in premedication administration, cannot be ruled out. Therefore, the assessment of the safety profile according to the type of lymphoma warrants further evaluation in future comparative studies.

The safety profile of subcutaneous rituximab contributed to adequate treatment administration, which was discontinued mostly as a result of disease progression and only as a result of an AE in one patient with FL. Indeed, patients with DLBCL or FL received a median of 6 induction cycles and those with FL received a median of 11 maintenance cycles. By ensuring non-inferior rituximab serum trough concentrations after subcutaneous rituximab injection versus intravenous administration, target-receptor occupancy would be maintained, and therefore the same degree of anti-B-cell activity would be expected (Davies et al., 2014, 2017b; Salar et al., 2014). Hence, switching from intravenous to the subcutaneous formulation would not impair the clinical efficacy of rituximab. This is in line with the efficacy results observed in the present study, in which complete response rates (i.e., CR plus CRu) to induction therapy were over 65%, ranging from 65.5% in patients with DLBCL to 74.1% in those with FL. In addition, after a median follow-up of 33.5 months, median event-free, progression-free and overall survivals were not reached. Although our findings should be considered with

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Table V. Frequency of patients with serious adverse events

| SAEs, n (%) | DLBCL (N = 29) | FL (N = 111) | Total (N = 140) |
|------------|---------------|-------------|----------------|
| Fever      | 6 (20.7)      | 6 (5.4)     | 12 (8.6)       |
| Neutropenia| 3 (10.3)      | 7 (6.3)     | 10 (7.1)       |
| Pneumonia  | 2 (6.9)       | 2 (1.8)     | 4 (2.9)        |
| Respiratory tract infection | 1 (3.4) | 3 (2.7) | 4 (2.9) |
| Gastroenteritis | 0 (0.0) | 3 (2.7) | 3 (2.1) |
| Abdominal pain | 0 (0.0) | 2 (1.8) | 2 (1.4) |
| Pneumonia pneumococcal | 0 (0.0) | 2 (1.8) | 2 (1.4) |
| Urosepsis | 0 (0.0)       | 2 (1.8)     | 2 (1.4)        |
| Gastrointestinal disorder | 1 (3.4) | 0 (0.0) | 1 (0.7) |
| Gastrointestinal haemorrhage | 1 (3.4) | 0 (0.0) | 1 (0.7) |
| Intestinal obstruction | 1 (3.4) | 0 (0.0) | 1 (0.7) |
| Pyrexia    | 1 (3.4)       | 0 (0.0)     | 1 (0.7)        |
| Escherichia bacteraemia | 1 (3.4) | 0 (0.0) | 1 (0.7) |
| Influenza  | 1 (3.4)       | 0 (0.0)     | 1 (0.7)        |
| Malnutrition | 1 (3.4) | 0 (0.0) | 1 (0.7) |
| Back pain  | 1 (3.4)       | 0 (0.0)     | 1 (0.7)        |
| Brain neoplasm | 1 (3.4) | 0 (0.0) | 1 (0.7) |
| Venous thrombosis | 1 (3.4) | 0 (0.0) | 1 (0.7) |
| Agranulocytosis | 0 (0.0) | 1 (0.9) | 1 (0.7) |
| Atrial fibrillation | 0 (0.0) | 1 (0.9) | 1 (0.7) |
| Vertigo    | 0 (0.0)       | 1 (0.9)     | 1 (0.7)        |
| Abdominal pain upper | 0 (0.0) | 1 (0.9) | 1 (0.7) |
| Enteritis  | 0 (0.0)       | 1 (0.9)     | 1 (0.7)        |
| Paraeesthesia oral | 0 (0.0) | 1 (0.9) | 1 (0.7) |
| Umbilical hernia | 0 (0.0) | 1 (0.9) | 1 (0.7) |
| Cellulitis | 0 (0.0)       | 1 (0.9)     | 1 (0.7)        |
| Enterobacter bacteraemia | 0 (0.0) | 1 (0.9) | 1 (0.7) |
| Lung infection | 0 (0.0) | 1 (0.9) | 1 (0.7) |
| Sepsis     | 0 (0.0)       | 1 (0.9)     | 1 (0.7)        |
| Urinary tract infection | 0 (0.0) | 1 (0.9) | 1 (0.7) |
| Toxicity to various agents | 0 (0.0) | 1 (0.9) | 1 (0.7) |
| Hypomagnesemia | 0 (0.0) | 1 (0.9) | 1 (0.7) |
| Gastric neoplasm | 0 (0.0) | 1 (0.9) | 1 (0.7) |
| Malignant melanoma | 0 (0.0) | 1 (0.9) | 1 (0.7) |
| Prostate cancer | 0 (0.0) | 1 (0.9) | 1 (0.7) |
| Presyncope | 0 (0.0)       | 1 (0.9)     | 1 (0.7)        |
| Syncope    | 0 (0.0)       | 1 (0.9)     | 1 (0.7)        |
| Prostatitis | 0 (0.0) | 1 (0.9) | 1 (0.7) |
| Haemoptysis | 0 (0.0) | 1 (0.9) | 1 (0.7) |
| Pulmonary mass | 0 (0.0) | 1 (0.9) | 1 (0.7) |

DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; SAEs, serious adverse events.
Fig 2. Rituximab Administration Satisfaction Questionnaire scores throughout the study. Scores at screening/baseline and end of induction in the overall (A), diffuse large B-cell lymphoma (B), and follicular lymphoma (C) populations. Scores at screening/baseline and end of maintenance for follicular lymphoma (D). IV, intravenous; SC, subcutaneous. [Colour figure can be viewed at wileyonlinelibrary.com]
Subcutaneous Rituximab for Non-Hodgkin Lymphoma

Table VI. EuroQoL 5D assessment at the end of induction and maintenance

| EQ-SD                | Induction       | Maintenance     |
|----------------------|-----------------|-----------------|
|                      | DLBCL (N = 14)  | FL (N = 20)     | Total (N = 34) | FL (N = 88) |
| **Mobility, n (%)**   |                 |                 |               |             |
| I have no problems in walking about | 9 (64-3)       | 15 (78-9)*      | 24 (72-7)*     | 64 (72-7)    |
| I have slight problems in walking about | 4 (28-6)       | 3 (15-8)*       | 7 (21-2)*     | 11 (12-5)   |
| I have moderate problems in walking about | 0 (0-0)        | 1 (5-3)*        | 1 (3-0)*    | 12 (13-6)   |
| I have severe problems in walking about | 0 (0-0)        | 0 (0-0)*        | 0 (0-0)*    | 1 (1-1)     |
| I am unable to walk about | 1 (7-1)         | 0 (0-0)*        | 1 (3-0)*    | 0 (0-0)     |
| **Self-care, n (%)**  |                 |                 |               |             |
| I have no problems washing or dressing myself | 11 (84-6)*     | 18 (94-7)*      | 29 (90-6) †   | 81 (93-1)*   |
| I have slight problems washing or dressing myself | 1 (7-7)*       | 1 (5-3)*        | 2 (6-3)†   | 4 (4-6)*     |
| I have moderate problems washing or dressing myself | 0 (0-0)*       | 0 (0-0)*        | 0 (0-0)†  | 2 (2-3)*     |
| I have severe problems washing or dressing myself | 1 (7-7)*       | 0 (0-0)*        | 1 (3-1)†   | 0 (0-0)     |
| **Usual activities, n (%)** |                 |                 |               |             |
| I have no problems doing my usual activities | 8 (57-1)       | 13 (68-4)*      | 21 (63-6)*   | 65 (75-6)†   |
| I have slight problems doing my usual activities | 4 (28-6)       | 4 (21-1)*       | 8 (24-2)*    | 10 (11-6)†   |
| I have moderate problems doing my usual activities | 1 (7-1)        | 2 (10-5)*       | 3 (9-1)*    | 10 (11-6)†   |
| I have severe problems doing my usual activities | 0 (0-0)        | 0 (0-0)*        | 0 (0-0)*†  | 1 (1-2)*     |
| I am unable to do my usual activities | 1 (7-1)         | 0 (0-0)*        | 1 (3-0)*†   | 0 (0-0)     |
| **Pain/discomfort, n (%)** |                 |                 |               |             |
| I have no pain or discomfort | 7 (50-0)       | 10 (52-6)*      | 17 (51-5)*    | 50 (57-5)*   |
| I have slight pain or discomfort | 4 (28-6)       | 6 (31-6)*       | 10 (30-3)*    | 26 (29-9)†   |
| I have moderate pain or discomfort | 2 (14-3)       | 3 (15-8)*       | 5 (15-2)*    | 10 (11-5)†   |
| I have extreme pain or discomfort | 1 (7-1)         | 0 (0-0)*        | 1 (3-0)*     | 1 (1-1)*     |
| **Anxiety/depression, n (%)** |                 |                 |               |             |
| I am not anxious or depressed | 10 (71-4)      | 10 (52-6)*      | 20 (60-6)*   | 48 (55-2)*   |
| I am slightly anxious or depressed | 2 (14-3)       | 6 (31-6)*       | 8 (24-2)*    | 25 (28-7)*   |
| I am moderately anxious or depressed | 1 (7-1)        | 3 (15-8)*       | 4 (12-1)*    | 11 (12-6)*   |
| I am severely anxious or depressed | 1 (7-1)        | 0 (0-0)*        | 1 (3-0)*     | 3 (3-4)*     |
| Your health state today (VAS), mean ± SD | 75-9 ± 21-9 | 75-0 ± 13-6 | 75-4 ± 17-2 | 73-9 ± 21-3* |
| Index of preference values (tariffs), mean ± SD | 0-8 ± 0-4* | 0-9 ± 0-1* | 0-8 ± 0-3† | 0-9 ± 0-1† |

DLBCL, diffuse large B-cell lymphoma; EQ-5D, EuroQoL 5D; FL, follicular lymphoma; SD, standard deviation; VAS, visual analogue scale.

*Missing data, n = 1.
†Missing data, n = 2.

caution due to the fact that the study was primarily designed to assess treatment safety and the limited data on post-induction response assessment, results from other clinical trials also showed that the subcutaneous formulation enabled rituximab efficacy to be maintained during first-line treatment of these types of lymphomas (Rummel et al, 2017; Lugtenburg et al, 2017; Davies et al, 2017b). Indeed, CR/CRu rates observed after receiving 3–7 cycles of subcutaneous rituximab within induction first-line treatment ranged from 32-2% to 45% in patients with FL to 50-6–57% in those with DLBCL (Rummel et al, 2017; Lugtenburg et al, 2017). In addition, median disease-free, event-free, progression-free and overall survivals were not reached over a median follow-up of 35–37 months (Lugtenburg et al, 2017; Davies et al, 2017b).

Moreover, patient satisfaction according to RASQ scores suggested improvements in psychological, impact on daily living, convenience and overall satisfaction domains at the end of both the induction and maintenance treatments. These improvements are in line with those seen when administering subcutaneous rituximab for first-line DLBCL and FL in the PrefMab and MabEase studies (Rummel et al, 2017; Lugtenburg et al, 2017). In addition, their results also supported that subcutaneous administration did not affect patients’ perception on the time they had to talk about their illness or treatment with the healthcare provider, which is also in agreement with our findings. Furthermore, as in our study, most patients in the PrefMab and MabEase studies preferred subcutaneous over intravenous administration of rituximab (Rummel et al, 2017; Lugtenburg et al, 2017), mainly due to the shorter time required in the clinic (Rummel et al, 2017).

These benefits translated into a good perception of patient quality of life according to the EQ-5D questionnaire. Thus, most patients reported no problems with mobility, self-care, performing their usual activities, and no pain/discomfort or anxiety/depression at the end of induction or maintenance treatment. Their rating of health state in the visual analogue scale was good, with an average score of approximately 75 on a scale where 0 is the worst imaginable health state and 100 is the best.
100 is the best imaginable state, and the index preference values (tariffs) also denoted good health, with average values of 0.8-0.9 on a scale where 0 is death and 1 is the best health state. The use of another version of the EQ-5D during the administration of subcutaneous rituximab maintenance monotherapy to FL patients also reported an overall perception of their health state and quality of life (Fargier et al, 2018). Hence, most patients expressed no problems in mobility, self-care or performing their usual activities. Similarly, more than half reported no anxiety/depression and nearly half no pain/discomfort.

We acknowledge that the study has some limitations that should be considered when interpreting its findings. These include the non-comparative nature of the study, which only provides descriptive data on patients switching from intravenous to subcutaneous rituximab during first-line treatment of DLBCL and FL. In addition, this switching may have occurred at any time during the administration of standard rituximab-based regimens and the disease was then followed up according to local practice, increasing the variability of our patient sample. However, this study was designed as a pragmatic trial and was therefore intended to reproduce daily practice as much as possible, including the potential switch to subcutaneous rituximab after at least one intravenous rituximab administration and its concomitant administration within routine clinical practice regimens. Likewise, there was no central review of response assessments, and although current guidelines recommend positron emission tomography scans to increase the accuracy of treatment response assessments (Cheson et al, 2014), their use could not be mandated due to their limited availability in clinical practice. In addition, although the study findings suggest positive effects on patients’ satisfaction and quality of life, we acknowledge that the lower availability of data after induction may have introduced bias, the study was not primarily designed for their assessment and effects of confounding factors cannot be ruled out; the results should therefore be considered as suggestive and deserve further assessment to achieve stronger evidence.

In conclusion, switching from intravenous to subcutaneous rituximab was well tolerated during the first-line treatment of non-Hodgkin DLBCL and FL, with an expected AE profile that did not raise new safety concerns. Although ARRs were frequently reported, they were mainly driven by mild to moderate injection-site reactions – reflecting the expected change when switching to subcutaneous administration – and resolved spontaneously. In addition, switching to subcutaneous rituximab formulation did not seem to impair the clinical efficacy of rituximab, with complete response rates (i.e., CR plus CRu) to induction therapy of over 65% and non-attainment of median disease-free, event-free, progression-free and overall survival during a median follow-up of 33-5 months. Most patients preferred subcutaneous dosing and satisfaction seemed to improve after switching to subcutaneous rituximab – especially in terms of psychological status, impact on daily living, convenience and overall satisfaction. Furthermore, treatment benefits translated into a good perception of patient quality of life according to the EQ-5D questionnaire at the end of both induction and maintenance treatments. Nonetheless, additional data on the safety and efficacy of switching from intravenous to subcutaneous rituximab would be desirable to optimize the daily management of patients with DLBCL and FL, as well as improving treatment satisfaction and patient quality of life.

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Author contribution

R.G.M., C.Q., E.P.P., A.D.G., C.P.L., T.V.R., A.M.M.C., J.M.A.P. and C.P. contributed to the acquisition of data. All authors contributed to data interpretation and revised the manuscript critically for important intellectual content. In addition, all authors provided their final approval of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Roche data sharing statement

Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche’s criteria for eligible studies are available at: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx. For further details on Roche’s Global Policy on the
Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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