Preference for subcutaneous or intravenous administration of rituximab among patients with untreated CD20+ diffuse large B-cell lymphoma or follicular lymphoma: results from a prospective, randomized, open-label, crossover study (PrefMab)

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Background: The aim of this study was to evaluate patient preference and satisfaction for the subcutaneous (s.c.) versus intravenous (i.v.) formulation of rituximab given with chemotherapy in previously untreated patients with CD20+ diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma (FL).

Patients and methods: Patients received eight cycles of rituximab according to 2 schedules: Arm A received 1 cycle rituximab i.v. (375 mg/m²) and 3 cycles rituximab s.c. (1400 mg) then 4 cycles rituximab i.v.; Arm B received 4 cycles rituximab i.v. (375 mg/m²) then 4 cycles rituximab s.c. (1400 mg). Alongside rituximab, both arms received 6–8 cycles of chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP), cyclophosphamide, vincristine, prednisone (CVP), or bendamustine as per standard local practice). Preference for s.c. or i.v. administration was evaluated using the Patient Preference Questionnaire (PPQ) at cycles 6 and 8. Patient satisfaction and convenience were assessed using the Cancer Therapy Satisfaction Questionnaire (CTSQ), and Rituximab Administration Satisfaction Questionnaire (RASQ) at cycles 4 and 8.

Results: At the primary data cut-off (19 January 2015), the intent-to-treat population comprised 743 patients. The majority had DLBCL (63%) and baseline characteristics were balanced between arms. At cycle 8, 81% of patients completing the PPQ preferred rituximab s.c. Preference was not impacted by treatment sequence or disease type. Patient satisfaction as measured by RASQ was higher for s.c. versus i.v. CTSQ scores were similar between arms. Adverse events were generally balanced between administration routes and no new safety signals were detected.

Conclusion: Most previously untreated patients with CD20+ DLBCL or FL preferred s.c. to i.v. rituximab administration. Patient satisfaction with rituximab treatment was generally greater with s.c. administration.

Registered clinical trial number: NCT01724021 (ClinicalTrials.gov).

Key words: rituximab, chemotherapy, subcutaneous, DLBCL, FL
**Introduction**

Randomized controlled trials have established the efficacy and safety of rituximab in combination with chemotherapy in patients with indolent and aggressive forms of non-Hodgkin lymphoma (NHL) [1–5]. Rituximab is conventionally administered by intravenous (i.v.) infusion over 1.5–6 h [6, 7]. A subcutaneous (s.c.) formulation of rituximab, allowing fixed-dose delivery over ~5 min, can simplify administration, improve patient convenience, and reduce healthcare-associated costs [8–11]. Pharmacokinetic studies have confirmed that rituximab s.c. 1400 mg produces serum levels non-inferior to the standard i.v. 375 mg/m² dose [12, 13], and have led to the approval of rituximab s.c. for NHL in Europe and elsewhere [14]. End-of-treatment response rates and safety were also comparable between rituximab s.c. and i.v. (in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP)) in patients with diffuse large B-cell lymphoma (DLBCL) [15].

While data indicate that switching to s.c. from i.v. rituximab reduces healthcare resource burden and patient treatment time [8], patient preferences and perceptions have not been explicitly investigated. PrefMab evaluated patient preference for the s.c. or i.v. formulation of rituximab when given with chemotherapy in previously untreated patients with CD20+ DLBCL or follicular lymphoma (FL).

**Methods**

**Study design and treatment**

PrefMab (NCT01724021) is an international, phase IIIb, prospective, multi-center, open-label crossover study. The cut-off date for the primary analysis was 19 January 2015. Patients were randomized to receive eight cycles of rituximab in combination with chemotherapy: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone (CVP), or bendamustine in 14– to 28-day cycles following standard practice at each treatment center (Figure 1). The first dose of rituximab (cycle 1) was given i.v. for all patients. Patients in Arm A then received three cycles of rituximab i.v. followed by four cycles of rituximab 375 mg/m² i.v. Patients in Arm B received three further cycles of rituximab 375 mg/m² i.v. and then four cycles of rituximab 1400 mg s.c.

**Patients**

Eligible patients were aged 18–80 years with previously untreated DLBCL or FL requiring therapy, ≥1 lesion with largest dimension ≥1.5 cm by computed tomography (CT), and Eastern Cooperative Oncology Group performance status ≤3. Detailed exclusion criteria are provided in the supplementary data, available at *Annals of Oncology* online.

The study was carried out in accordance with the International Conference on Harmonization E6 guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki, together with local laws and regulations. The protocol was approved by independent institutional review boards and ethics committees. All patients provided written informed consent.

**Study assessments**

The primary objective of overall patient preference for rituximab s.c. or i.v. was assessed using a Patient Preference Questionnaire (PPQ) that recorded preference as ‘s.c.’, ‘i.v.’, or ‘no preference’ after rituximab therapy in cycles 6 and 8 (Figure 1), and rated preference on a 3-point scale as ‘very strong’, ‘fairly strong’, or ‘not very strong’. Patients were also asked to provide two main reasons for their treatment preference: ‘feels less emotionally distressing’, ‘requires less time in the clinic’, ‘lower level of injection-site pain’, ‘feels more comfortable during administration’, or ‘other reason’.

Secondary objectives included comparison of administration routes in terms of patient satisfaction and convenience, administration time, safety, and efficacy. Patient satisfaction was assessed using the validated Cancer Treatment Satisfaction Questionnaire (CTSQ) [16] and the validated Rituximab Administration Satisfaction Questionnaire (RASQ) [17] at cycles 4 and 8 (CTSQ before and RASQ after rituximab administration; Figure 1). Details of the questionnaires are shown in the supplementary data, available at *Annals of Oncology* online. Both questionnaires were scored from 0 (worst) to 100 (best). Administration time was evaluated from start to end of either s.c. injection or i.v. infusion and was summarized by site and treatment sequence group. Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Complete response (CR) or CR unconfirmed

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**Figure 1.** Study design. CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CTSQ, Cancer Therapy Satisfaction Questionnaire; CVP, cyclophosphamide, vincristine, prednisone; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; i.v., intravenous; OS, overall survival; PPQ, patient preference questionnaire; R, randomized; RASQ, Rituximab Administration Satisfaction Questionnaire; s.c., subcutaneous; SD/PD, stable disease/progressive disease.
(CRu) rates 4–8 weeks after the last dose of induction treatment were assessed using CT scans according to either original international working group (IWG) criteria for response assessment of lymphoma [18] or institutional standards. Progression-free survival (PPS) was defined as the time from randomization to the first occurrence of progression or relapse, according to the IWG response criteria or other country standards, or death from any cause.

Data analyses

PPQ, CTSAQ, and RASQ data were analyzed in the intent-to-treat (ITT) group of all randomized patients. Safety data were analyzed in patients who received at least one dose of rituximab. Proportions of patients preferring s.c. over i.v. rituximab, with corresponding 95% confidence intervals (CIs), were estimated. CTSAQ, RASQ, and administration time data were summarized and presented by treatment group. PFS was assessed using the Kaplan–Meier methodology.

In the absence of prior data on rituximab s.c., the proportion of patients likely to prefer rituximab s.c. was projected to be 60% with a 3.6% margin of error. On this basis, 720 patients would be needed to assess preference, with a 95% CI would be 56.4–63.6%. Following a planned interim analysis, in which the observed preference rate for s.c. was higher (>80%), the sample size requirement was reduced to 560 patients, with approximately 700 randomized.

Results

Study population

At the data cut-off for the primary analysis, there were 743 ITT patients: 372 in Arm A and 371 in Arm B, and 371 and 369 in the respective safety populations. Table 1 summarizes the baseline patient and disease characteristics, together with the chemotherapy regimens, which were balanced between treatment arms.

The patient flow is shown in supplementary Figure S1, available at Annals of Oncology online. The numbers of patients discontinuing immunotherapy prematurely were comparable between arms, as were the numbers of patients discontinuing the study. The most common reason for discontinuing treatment was AEs (52 patients) and for discontinuing the study was death [53 patients (5/ 273 FL; 48/465 DLBCL), most commonly due to progressive disease (19 patients) and AEs (17 patients)].

Exposure to rituximab is summarized in supplementary Table S1, available at Annals of Oncology online. Almost all patients completing 8 cycles of treatment received the planned rituximab dose. By nature of the study design, the cumulative dose of rituximab s.c. tended to be higher in Arm B than in Arm A, while the cumulative dose of rituximab i.v. tended to be higher in Arm A than Arm B. The median administration time per cycle was 6 min for each s.c. dose (cycles 2–8) and ranged from 170–240 min for i.v. administration (cycles 1–8; supplementary Figure S2, available at Annals of Oncology online).

Patient preference

The PPQ was completed by 620 and 591 patients at cycles 6 and 8, respectively. Regardless of treatment sequence, the majority of patients at each time-point preferred s.c. administration; 79%–81% expressed an overall preference at cycle 6 and 77%–84% at cycle 8, with 68%–73% at cycle 6 and 71%–76% at cycle 8 expressing a ‘very strong’ or ‘fairly strong’ preference (Figure 2). The most commonly identified reasons were ‘requires less time in the clinic’ (68%–69%), ‘feels more comfortable during administration’ (37%), and ‘feels less emotionally distressing’ (28%–29%; Figure 2).

The preference observed in the ITT population was seen across subgroups according to type of lymphoma and risk category (IPI or FLIPI), age, chemotherapy regimen, and sex (supplementary Table S2, available at Annals of Oncology online). Patient

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**Table 1. Baseline patient and disease characteristics (safety population)**

<table>
<thead>
<tr>
<th></th>
<th>Arm A (n = 371)</th>
<th>Arm B (n = 369)</th>
<th>Total (n = 740)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (IQR)</td>
<td>60 (50–68)</td>
<td>60 (51–70)</td>
<td>60 (51–69)</td>
</tr>
<tr>
<td>Age &lt;60 years</td>
<td>181 (49)</td>
<td>179 (49)</td>
<td>360 (49)</td>
</tr>
<tr>
<td>Age ≥60 years</td>
<td>190 (51)</td>
<td>190 (52)</td>
<td>380 (51)</td>
</tr>
<tr>
<td>Male</td>
<td>184 (50)</td>
<td>189 (51)</td>
<td>373 (50)</td>
</tr>
<tr>
<td>Female</td>
<td>187 (50)</td>
<td>180 (49)</td>
<td>367 (50)</td>
</tr>
<tr>
<td>DLBCL</td>
<td>235 (63)</td>
<td>230 (62)</td>
<td>465 (63)</td>
</tr>
<tr>
<td>FL</td>
<td>136 (37)</td>
<td>137 (37)</td>
<td>273 (37)</td>
</tr>
<tr>
<td>Median body surface area, m² (IQR)</td>
<td>1.77 (1.62–1.99)</td>
<td>1.80 (1.64–1.98)</td>
<td>1.79 (1.63–1.98)</td>
</tr>
</tbody>
</table>

**IPI risk group**

- Low: 86 (37) vs 82 (36): 168 (36)
- Low to intermediate: 65 (28) vs 65 (28): 130 (28)
- Intermediate to high: 53 (23) vs 49 (21): 102 (22)
- High: 31 (13) vs 34 (15): 65 (14)

**FLIPI risk group**

- Low (0–1): 29 (21) vs 33 (24): 62 (23)
- Intermediate (2): 50 (37) vs 51 (37): 101 (37)
- High (≥3): 57 (42) vs 53 (39): 110 (40)

**Chemotherapy regimen**

- Bendamustine: 63 (17) vs 63 (17): 126 (34)
- Bendamustine-21 × 6: 2 (1%) vs 0: 2 (1%)
- Bendamustine-21 × 8: 1 (1%) vs 2 (1%): 3 (1%)
- Bendamustine-28 × 6: 52 (14) vs 50 (14): 102 (14)
- Bendamustine-28 × 8: 8 (2) vs 11 (3): 19 (3)
- CHOP: 284 (77) vs 282 (77): 566 (77)
- CHOP-14 × 6: 26 (7) vs 23 (6): 49 (7)
- CHOP-14 × 8: 2 (1%) vs 3 (1%): 5 (1%)
- CHOP-21 × 6: 110 (30) vs 117 (32): 227 (31)
- CHOP-21 × 8: 143 (39) vs 137 (37): 280 (38)
- CHOP-28 × 8: 3 (1%) vs 2 (1%): 5 (1%)
- CVP: 24 (6) vs 24 (7): 48 (7)
- CVP-21 × 6: 2 (1%) vs 4 (1%): 6 (1%)
- CVP-21 × 8: 20 (5) vs 19 (5): 39 (5)
- CVP-28 × 6: 1 (1%) vs 0: 1 (1%)
- CVP-21 × 3 + CHOP-21 × 3: 1 (1%) vs 1 (1%): 2 (1%)

Values are n (%) unless stated otherwise.

*Lympoma type was not recorded in two patients.

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CVP, cyclophosphamide, vincristine, prednisone; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; FLIPI, follicular lymphoma international prognostic index; IPI, international prognostic index; IQR, interquartile range.
preference by country is presented in supplementary Figure S3, available at *Annals of Oncology* online.

**Patient satisfaction**

Median CTSQ scores were similar for s.c. and i.v. administration for all domains, and were not affected by treatment sequence (Table 2). Median RASQ scores (any sequence) were higher for s.c. than i.v. rituximab for ‘Psychological Impact’ (87.5 versus 80.0), ‘Impact on Activities of Daily Living’ and ‘Convenience of Therapy’ (both 83.3 versus 58.3), and ‘Satisfaction with Therapy’ (87.5 versus 75.0), and the same (83.3 both routes) for ‘Physical Impact’ (Table 2). The RASQ descriptive question responses suggested that most patients felt that the time taken to administer
rituximab was 'just right', although the proportion was substantially higher for the s.c. group (Figure 3). In general, administration route did not affect patients’ perceived ability to discuss their illness or treatment with the nurse and/or doctor (Figure 3).

Safety

The overall incidence of AEs on or after cycle 2 (all patients received i.v. in cycle 1) was broadly comparable between Arms A and B: treatment-emergent AEs (89% (n = 318) versus 88% (n = 315)), grade ≥3 AEs (41% (n = 146) versus 41% (n = 145)), and serious AEs (SAEs; 28% (n = 99) versus 24% (n = 87)). AEs on or after cycle 2 were also balanced when summarized by s.c. or i.v. administration route (any treatment arm; supplementary Table S3, available at Annals of Oncology online). Grade ≥3 hematologic AEs were balanced between administration routes (s.c. 15% versus i.v. 16%), including grade ≥3 neutropenia and febrile neutropenia (supplementary Table S3, available at Annals of Oncology online). Administration-related reactions (ARRs) were reported in few patients, with erythema and injection site erythema reported by 1.8% and 1.5%, respectively, of patients overall.

Efficacy

Efficacy findings were similar between treatment arms. At data cut-off, response data were available for 310 patients in Arm A and 315 in Arm B. Overall response and CR/CRu rates by treatment arm and lymphoma type are summarized in Table 3. Twenty-two patients had progressive disease (Arm A, 9; Arm B, 13). PFS at 12 months was 92.0% in Arm A and 89.3% in Arm B.

Discussion

This study demonstrated strong patient preference for s.c. versus i.v. administration of rituximab, notably considering rituximab s.c. was administered in a clinical setting as part of a treatment regimen that contained an i.v. chemotherapy component. The most common reasons for preferring rituximab s.c. to i.v. were 'requires less time in the clinic' and 'feels more comfortable during administration'. Similar results were reported for the PrefHer study of s.c. or i.v. trastuzumab in patients with HER2-positive early breast cancer [10, 19].

Overall treatment satisfaction assessed by the CTSQ was similar for rituximab s.c. and i.v. in all three domains, consistent with another randomized evaluation of rituximab s.c. (MABEASE study) in patients with DLBCL [20]. Although, in the MABEASE study patients received either rituximab s.c. or i.v. as part of a rituximab-CHOP regimen for the duration of treatment after cycle 1 and did not cross over. Using the more specific rituximab questionnaire (RASQ), patient satisfaction with s.c. dosing was improved versus i.v. for four of the five domains (‘Psychological Impact’, ‘Impact on Activities of Daily Living’, ‘Convenience of Therapy’, and ‘Satisfaction with Therapy’), with comparable scores for the ‘Physical Impact’ domain; similar results were reported in the MABEASE study [20].

Rituximab s.c. reduced administration times compared with i.v., consistent with findings from previous monoclonal antibody studies [12, 13] and most patients found the shortened administration time more convenient. Despite the shorter duration of administration with rituximab s.c., most patients (79% for both administration routes) felt that they had ‘more than enough time’ to discuss their illness with their healthcare provider, findings also observed in MABEASE [20].

Importantly, there were no differences in efficacy or safety profiles between the routes of administration, consistent with previous studies in patients with FL and DLBCL [12, 13, 15]. Rates of individual ARRs with both routes were low and, although efficacy was not the primary endpoint in this study, response rates and PFS were not impacted by treatment sequence.

In conclusion, these results show that most previously untreated patients with CD20+ DLBCL or FL prefer s.c. over i.v. administration of rituximab. Safety and efficacy do not appear to be impacted when rituximab is administered by the s.c. route. These observations, together with data demonstrating the economic advantages of rituximab s.c. [8], indicate that s.c. rituximab may be the preferred route of administration.

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Table 2. Summary of cancer therapy satisfaction questionnaire and rituximab administration satisfaction questionnaire scores for s.c. and i.v. administration of rituximab with any treatment sequence

<table>
<thead>
<tr>
<th>Domain</th>
<th>Rituximab s.c. (n = 687)</th>
<th>Rituximab i.v. (n = 740)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTSQ Expectations of therapy</td>
<td>n = 627</td>
<td>n = 631</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>85.0 (75.0–95.0)</td>
<td>81.3 (75.0–100.0)</td>
</tr>
<tr>
<td>Feelings about side effects</td>
<td>n = 624</td>
<td>n = 630</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>62.5 (43.8–75.0)</td>
<td>62.5 (43.8–75.0)</td>
</tr>
<tr>
<td>Satisfaction with therapy</td>
<td>n = 623</td>
<td>n = 619</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>85.7 (78.6–92.9)</td>
<td>85.0 (75.0–95.8)</td>
</tr>
<tr>
<td>RASQ Physical impact</td>
<td>n = 619</td>
<td>n = 622</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>83.3 (75.0–91.7)</td>
<td>83.3 (75.0–91.7)</td>
</tr>
<tr>
<td>Psychological impact</td>
<td>n = 612</td>
<td>n = 614</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>87.5 (75.0–95.0)</td>
<td>80.0 (70.0–90.0)</td>
</tr>
<tr>
<td>Activities of daily living</td>
<td>n = 461</td>
<td>n = 433</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>83.3 (83.3–100.0)</td>
<td>58.3 (41.7–83.3)</td>
</tr>
<tr>
<td>Convenience</td>
<td>n = 599</td>
<td>n = 619</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>83.33 (75.0–91.7)</td>
<td>58.33 (41.7–75.0)</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>n = 624</td>
<td>n = 617</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>87.50 (75.0–100.0)</td>
<td>75.0 (62.5–87.5)</td>
</tr>
</tbody>
</table>

CTSQ, Cancer Therapy Satisfaction Questionnaire; IQR, interquartile range; i.v., intravenous; RASQ, Rituximab Administration Satisfaction Questionnaire; s.c., subcutaneous.
Acknowledgements

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Figure 3. Overall responses (any sequence) to descriptive questions in the Rituximab Administration Satisfaction Questionnaire. i.v., intravenous; s.c., subcutaneous.

Table 3. Summary of tumor response results

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>CR/CRu rate (95% CI)</th>
<th>ORR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment sequence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm A</td>
<td>310</td>
<td>51% (46–57%)</td>
<td>94% (90–96%)</td>
</tr>
<tr>
<td>Arm B</td>
<td>315</td>
<td>52% (47–58%)</td>
<td>92% (89–95%)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLBCL</td>
<td>385</td>
<td>56% (51–61%)</td>
<td>91% (88–94%)</td>
</tr>
<tr>
<td>FL</td>
<td>240</td>
<td>45% (39–52%)</td>
<td>95% (91–97%)</td>
</tr>
</tbody>
</table>

CI, confidence interval; CR, complete response; CRu, complete response unconfirmed; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; ORR, overall response rate.

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References


