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ORIGINAL REPORT

Comparison of Subcutaneous Versus Intravenous Administration of Rituximab As Maintenance Treatment for Follicular Lymphoma: Results From a Two-Stage, Phase IB Study

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ABSTRACT

Purpose
This two-stage phase IB study investigated the pharmacokinetics and safety of subcutaneous (SC) versus intravenous (IV) administration of rituximab as maintenance therapy in follicular lymphoma.

Patients and Methods
In stage 1 (dose finding), 124 patients who responded to rituximab induction were randomly assigned to SC rituximab (375 mg/m^2, 625 mg/m^2, or an additional group at 800 mg/m^2) or IV rituximab (375 mg/m^2). The objective was to determine an SC dose that would yield a rituximab serum trough concentration (C_{trough}) in the same range as that of IV rituximab. In stage 2, 154 additional patients were randomly assigned (1:1) to SC rituximab (1,400 mg) or IV rituximab (375 mg/m^2) given at 2- or 3-month intervals. The objective was to demonstrate noninferior rituximab C_{trough} of SC rituximab relative to IV rituximab 375 mg/m^2.

Results
Stage 1 data predicted that a fixed dose of 1,400 mg SC rituximab would result in a serum C_{trough} in the range of that of IV rituximab. Noninferiority (ie, meeting the prespecified 90% CI lower limit of 0.8) was then confirmed in stage 2, with geometric mean $C_{trough\ SC}$:$C_{trough\ IV}$ ratios for the 2- and 3-month regimens of 1.24 (90% CI, 1.02 to 1.51) and 1.12 (90% CI, 0.86 to 1.45), respectively. Overall safety profiles were similar between formulations (in stage 2, 79% of patients experienced one or more adverse events in each group). Local administration-related reactions (mainly mild to moderate) occurred more frequently after SC administration.

Conclusion
The fixed dose of 1,400 mg SC rituximab predicted by using stage 1 results was confirmed to have noninferior C_{trough} levels relative to IV rituximab 375 mg/m^2 dosing during maintenance, with a comparable safety profile. Additional investigation will be required to determine whether the SC route of administration for rituximab provides equivalent efficacy compared with that of IV administration.

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INTRODUCTION

Rituximab (MabThera/Rituxan), a chimeric anti-CD20 monoclonal antibody, is effective and well tolerated in patients with B-cell lymphoproliferative disorders, including non-Hodgkin lymphoma and chronic lymphocytic leukemia.[1-5] For patients with follicular lymphoma (FL), induction with rituximab plus chemotherapy followed by rituximab maintenance is the mainstay of therapy.[5-8]

Rituximab is typically infused intravenously (IV) over many hours[9] and thus, subcutaneous (SC) administration of rituximab, which could substantially shorten administration time, is being investigated. SC administration was made possible by hyperconcentrating rituximab (12-fold) compared with the IV formulation and including the enzyme recombinant human hyaluronidase (rHuPH20) as an excipient.[10,11] rHuPH20 temporarily cleaves hyaluronan fibers in the interstitial tissue, thereby facilitating the SC injection of large volumes, as demonstrated in other settings.[11-15] Switching from IV to SC administration may also improve adverse event (AE) profiles, increase patient convenience, and improve cost-effectiveness, as previously shown by the introduction of trastuzumab

and alemtuzumab SC administration.[16,17] Delivery of rituximab via the SC route is suited to the use of a fixed dose, a relatively recent concept for administration of monoclonal antibodies, supported by growing evidence for a minimal influence of body weight on exposure variability for these agents.[18]

For the clinical development of SC rituximab, we hypothesized that an SC dose that achieved noninferior serum trough concentrations (C_{trough}) would result in at least the same degree of target-site saturation and, hence, at least the same efficacy as IV dosing. To the best of our knowledge, SparkThera (A Pharmacokinetic Study of Subcutaneous and Intravenous MabThera [Rituximab] in Patients With Follicular Lymphoma; BP22333; two-stage, phase IB) was the first clinical study to investigate SC rituximab as maintenance therapy in patients with FL. SparkThera incorporated a customized pharmacokinetic model that allowed comparison of SC and IV administration under controlled conditions. Here, we describe the design and final results of the study.

PATIENTS AND METHODS

Patients

Eligible patients were age ≥ 18 years with CD20-positive FL grades 1, 2, or 3a; life expectancy ≥ 6 months; and Eastern Cooperative Oncology Group performance status ≤ 2. Patients must have demonstrated a partial or complete response following induction treatment with IV rituximab given alone or with chemotherapy. Eligible patients received one or more doses of IV rituximab as maintenance therapy and had one or more doses remaining. Exclusion criteria included recent infections or a history of hepatitis B.

An FL maintenance population was chosen because pharmacokinetic variability was expected to be lower than the induction setting as a result of the lower tumor load in responders eligible for maintenance. Before final dose selection, exposure to SC rituximab was limited to a single administration to prevent potential underexposure of patients being maintained in remission with IV rituximab.

Study Design and Treatment

SparkThera was an open-label, multicenter, phase IB study of SC rituximab as maintenance treatment in patients with FL (Figs 1 and 2). The study was conducted in 22 countries around the world (in Europe, Canada, South America, Asia-Pacific, and the Middle East) and was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The independent ethics committee at each study center approved the study protocol. Rituximab was provided as a 10-mL solution with a concentration of 120 mg/mL rituximab (F. Hoffmann-La Roche, Basel, Switzerland) and 2,000 U/mL rHuPH20.

Patients were enrolled onto either stage 1 or stage 2 (Figs 1 and 2) by using a block-size randomization scheme, stratified by their maintenance regimen (every 2 *v* every 3 months). SC rituximab was required to be injected into the abdomen at a single site.

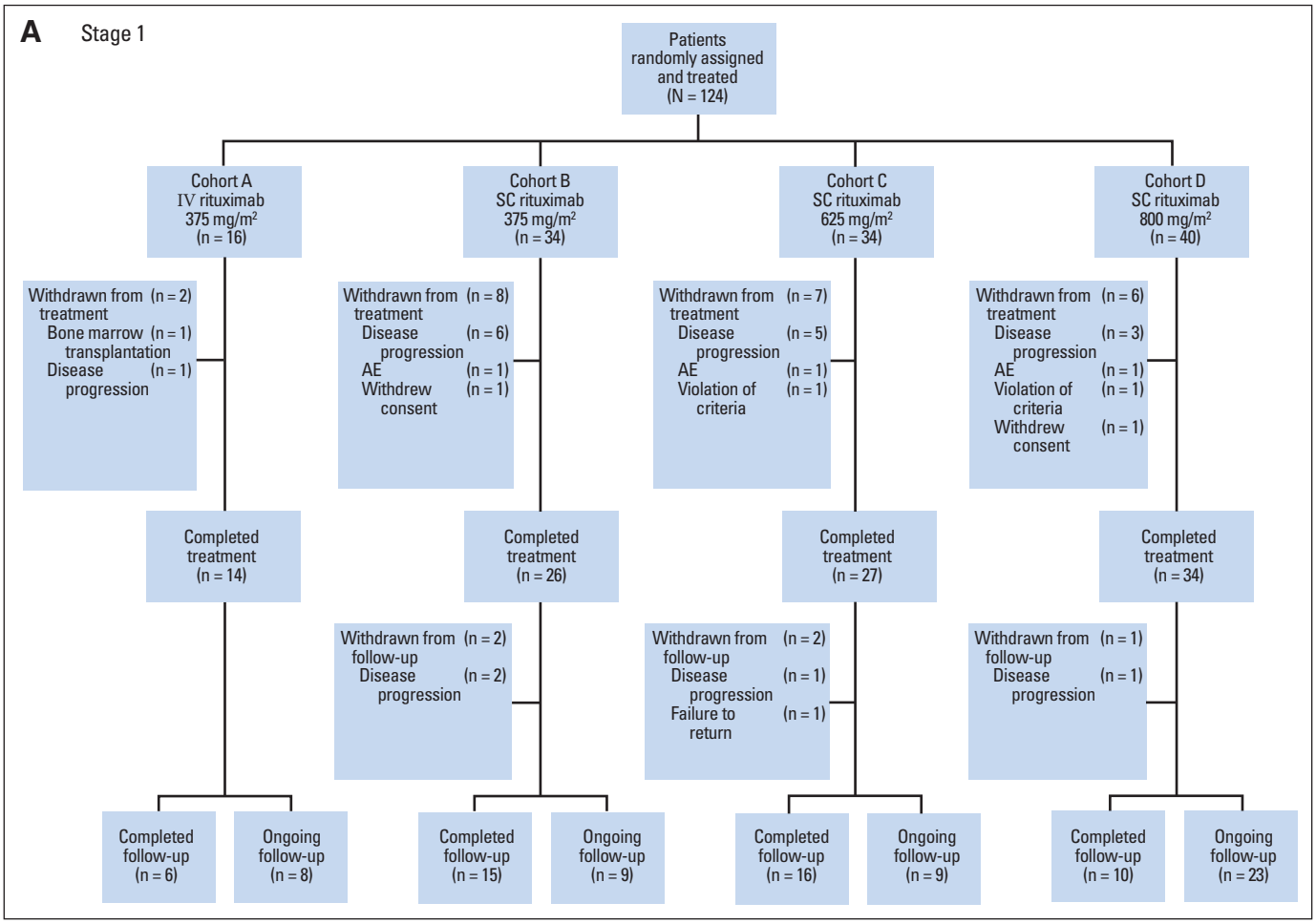

Fig 1. CONSORT diagram for (A) stage 1 of the SparkThera study. AE, adverse event; SC, subcutaneous. (Continued on following page)

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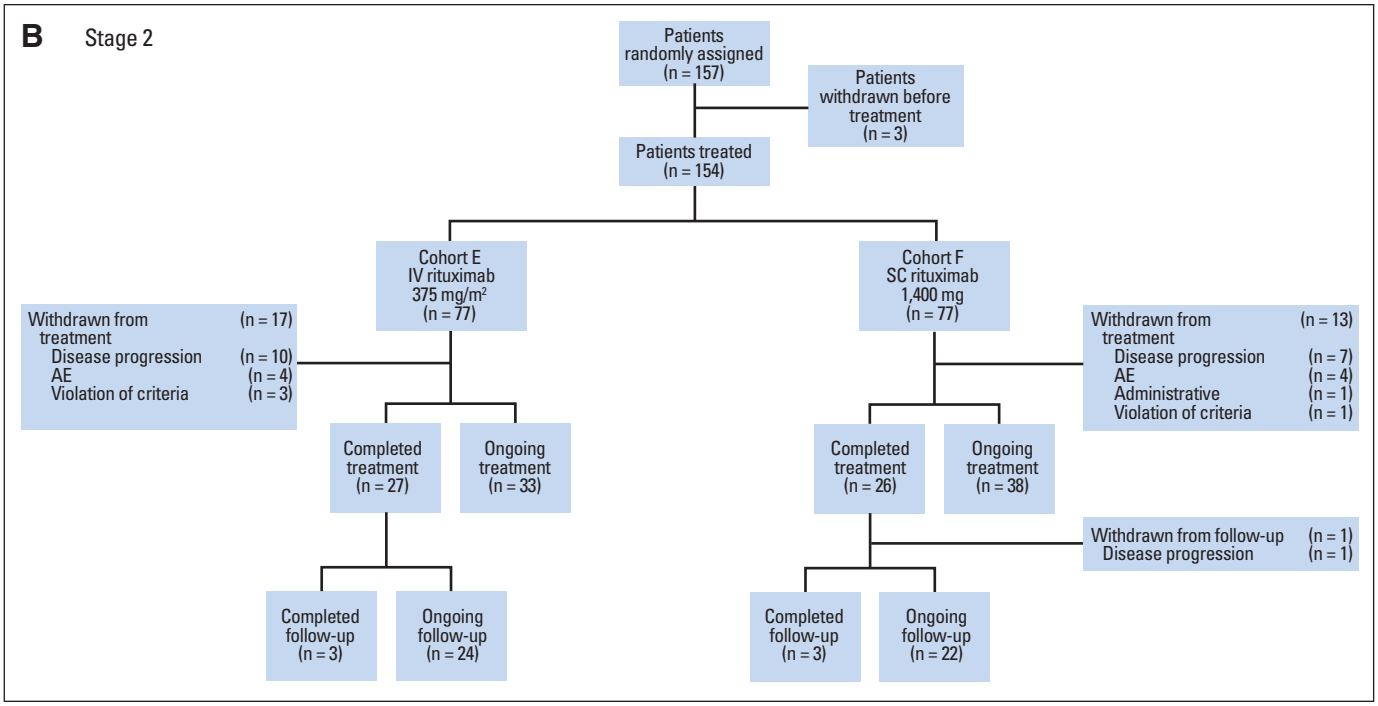

Fig 1. (Continued) CONSORT diagram for (B) stage 2 of the SparkThera study. AE, adverse event; IV, intravenous; SC, subcutaneous.

The primary objective of stage 1 was to identify a dose of SC rituximab that yielded a serum C_{trough} in the range achieved with IV rituximab (dose finding). In stage 2, the primary objective was to demonstrate the noninferiority of C_{trough} (described in Statistical Analysis) in patients administered SC rituximab at the dose determined from stage 1 versus IV rituximab.

The variation in the number of prestudy treatment cycles patients had received, residual rituximab serum concentrations from IV infusions administered before study entry, and the effects of the underlying crossover from IV to SC administration limited the value of using measured data and necessitated a modeling approach. C_{trough} was selected as the primary pharmacokinetic parameter because it was expected to reflect the degree of target-site saturation during the entire dosing interval. Secondary end points of both stages included assessments of area under the concentration-time curve (AUC), safety, immunogenicity, and B-lymphocyte levels.

Dose selection for stage 1 was supported by bioavailability data for SC rituximab from a preclinical animal model and the known bioavailability of other monoclonal antibodies after SC administration in humans (40% to 100%).[19,20] Patients were randomly assigned (2:2:1) to a single dose of either SC rituximab (375 or 625 mg/m^2) or IV rituximab (375 mg/m^2). Following an interim analysis, an SC rituximab 800 mg/m^2 cohort was opened to support selection of the fixed dose for stage 2 by enabling interpolation over a wider range of exposure (further rationale in the Data Supplement).

The first patients treated with each of the SC rituximab doses were evaluated for safety and tolerability for $\geq$ 4 days before a second patient was treated. After a single SC or IV dose, all patients continued IV rituximab until completion of 2 years of maintenance. Following selection of the final SC dose, patients randomly assigned to an SC dose group could choose to receive any remaining doses as SC rituximab, provided they had completed at least 1 year of maintenance with IV rituximab.

In stage 2, patients were randomly assigned 1:1 to the fixed SC dose determined in stage 1 (1,400 mg) or to the IV dose of 375 mg/m^2 until 2 years of maintenance was completed. After treatment completion, patients in both stages were observed for 9 months at 3-month intervals.

Assessments and Evaluations

Pharmacokinetics and pharmacodynamics. Blood samples for pharmacokinetic analyses were drawn from all patients throughout the study until the last follow-up visit (9 months after the last maintenance dose) for rituximab and during the first cycle in patients receiving SC rituximab for rHuPH20. Pharmacokinetic sampling times, assays, power calculations, and data modeling are detailed in the Data Supplement. Blood samples for measuring CD19$^+$ B lymphocytes were taken before each rituximab administration and at each follow-up visit.

Safety and immunogenicity. Safety and tolerability data were collected throughout the study. AEs were summarized by using the Medical Dictionary for Regulatory Activities (MedDRA) and were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Any AE that occurred during or within 24 hours of treatment and was considered to be related to rituximab by the investigator was defined as an administration-related reaction (ARR).

Samples for measuring antirituximab and anti-rHuPH20 antibodies were collected throughout the study. Details on sampling and assays can be found in the Data Supplement. Assessments and procedures were identical for both stages of the study unless otherwise specified.

Dose Interpretation With Pharmacokinetic Analysis

Stage 1. Pharmacokinetic data from patients receiving IV and SC rituximab in stage 1 of the study were included in a population pharmacokinetic model (described in the Data Supplement). This model was initially derived from six clinical studies in the non-Hodgkin lymphoma induction setting[21] and allowed comparison of SC and IV administration of rituximab under similar conditions. After stage 1, the model was used to simulate an SC rituximab fixed dose that would result in noninferior C_{trough} compared with IV rituximab 375 mg/m^2 during a 2- or 3-month maintenance regimen in a population with a body surface area (BSA) of 1.92 $\pm$ 0.247 m^2.

Stage 2. At the end of stage 2, the population pharmacokinetic parameters were updated by using the combined data from both stages. Individual pharmacokinetic parameters derived from the updated model were combined with a hypothetical sequence of induction (IV or SC; every 2 months or every 3 months during maintenance) to generate individual predicted serum concentration profiles. From these profiles, C_{trough} and AUC over the dosing interval (AUC_τ), were calculated by model-independent means at cycle 2 of maintenance. A noninferiority test then compared rituximab C_{trough} and AUC_τ levels with both routes of administration.

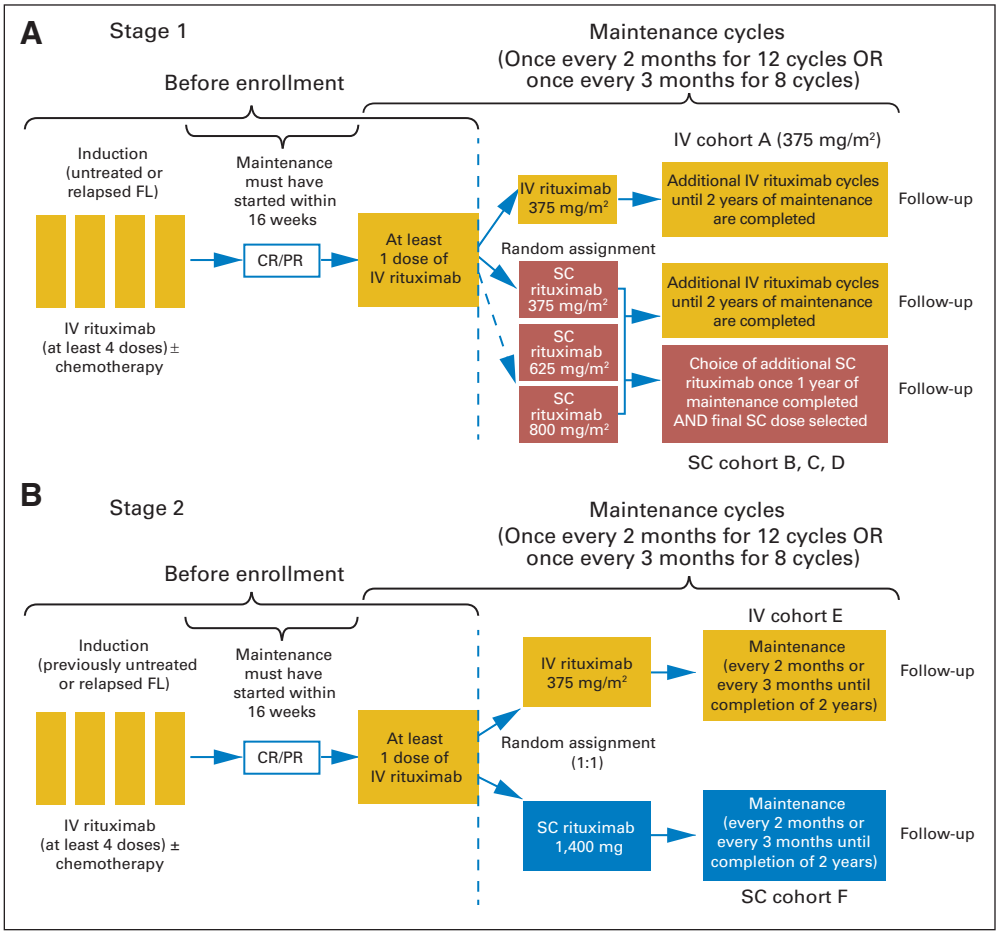

Fig 2. Study design for (A) stage 1 and (B) stage 2. CR, complete response; FL, follicular lymphoma; IV, intravenous; PR, partial response; SC, subcutaneous.

Statistical Analysis

In stage 1, sample size was based on the model's precision of estimation: 30 patients per SC group and 15 patients per IV group. In stage 2, the sample size of 70 patients per treatment arm was based on rituximab C_{trough} levels. Noninferiority would be considered confirmed if the lower boundary of the two-sided 90% CI of the geometric mean ratio $C_{trough\ SC}$:$C_{trough\ IV}$ was more than 0.8.

Pharmacokinetic analyses included all patients with available assessments. The safety analysis included all patients who had received one or more doses of SC rituximab or IV rituximab within the study. B-cell levels and safety variables were summarized descriptively.

RESULTS

Patients

In stage 1, 124 patients were randomly assigned (Fig 1), and at analysis (May 11, 2012), 101 patients (81%) had completed treatment, 49 (40%) continued in follow-up, and 47 (38%) had completed the study.

In stage 2, 157 patients were randomly assigned (Fig 1); at analysis, 38 (49%) SC and 33 (42%) IV patients were receiving treatment, 22 (28%) SC and 24 (30%) IV patients continued in follow-up, and six (4%) had completed the study. Median treatment duration on study was 14.8 months (range, 0 to 19 months) for SC rituximab and 13.8 months (range, 0 to 19 months) for IV rituximab.

Baseline characteristics were similar across treatment groups in both stages of the study (Table 1). SC rituximab injections of 1,400 mg (n = 537) had a median duration of administration of 5.9 minutes (range, 2.0 to 13.4 minutes).

Pharmacokinetics

Rituximab time course profiles for stage 1 patients (SC: 375 mg/m², n = 33; 625 mg/m², n = 33; 800 mg/m², n = 37; IV: 375 mg/m², n = 15) with sufficient pharmacokinetic data indicated that an SC dose of 625 to 800 mg/m² would result in C_{trough} levels in the range of those achieved with the standard IV dose of 375 mg/m² (Fig 3). Absolute bioavailability of the SC formulation was estimated at 65%.

By using the pharmacokinetic model, which combined C_{trough} data from all dose-finding groups, serum C_{trough} and AUC_{τ} values were simulated 100 times by comparing IV rituximab 375 mg/m² with fixed doses of SC rituximab between 1,100 and 1,400 mg and assuming a BSA distribution of 1.92 ± 0.24 m². Dose selection was performed on C_{trough} concentrations at cycle 2 of maintenance.

The model predicted that a fixed SC dose of 1,400 mg would yield a noninferior serum C_{trough} and comparable AUC compared with IV rituximab, regardless of BSA or whether rituximab was given every 2 or every 3 months (Data Supplement). A dose of 1,400 mg was selected for assessment in stage 2 to ensure that all patients, including those at

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Table 1. Baseline Patient Demographic and Disease Characteristics

Characteristic	Stage 1								Stage 2			
	SC						IV		SC		IV	
	375 mg/m^2 (n = 34)		625 mg/m^2 (n = 34)		800 mg/m^2 (n = 40)		375 mg/m^2 (n = 16)		1,400 mg (n = 77)		375 mg/m^2 (n = 77)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age, years												
Median	56.0		58.5		63.0		57.0		58.0		58.0	
Range	30-83		35-81		23-82		35-82		36-77		28-87	
Female sex	19	56	16	47	20	50	10	63	45	58	45	58
Body surface area, m^2												
Median	1.9		1.8		1.9		1.8		1.8		1.8	
Range	1.4-2.3		1.5-2.5		1.5-2.3		1.4-2.1		1.4-2.4		1.4-2.4	
Time from diagnosis, months												
Median	16		24		12		13		12		13	
Range	5-159		8-151		6-185		8-136		7-200		5-262	
Best response prior to study entry												
Complete response	19	56	18	53	21	53	11	69	41	53	45	58
Complete response unconfirmed	6	18	6	18	6	15	—		5	6	3	4
Partial response	9	26	10	29	13	33	5	31	31	40	29	38
ECOG performance status												
0	28	82	31	91	38	95	14	88	69	91*	71	92
1	6	18	3	9	2	5	2	13	7	9*	5	6
2	—		—		—		—		—		1	1
Follicular lymphoma grade												
1	14	41	17	50	13	33	6	38	30	39	29	38
2	18	53	13	38	17	43	6	38	31	40	28	36
3a	2	6	4	12	8	20	2	13	16	21	19	25
Not known†	—		—		2	5	2	13	—		1	1

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IV, intravenous; SC, subcutaneous.
*Evaluable patients, n = 76.
†Grade 3b excluded.

the upper end of the BSA range, would achieve an SC:IV C_{trough} ratio of at least 0.8. Considering the clinical evidence that rituximab has a wide therapeutic window[22,23] and has an established efficacy and safety profile in B-cell lymphomas,[3,24] preventing underdosing in all patient subgroups was considered to be the first priority.

The stage 2 primary end point was met; SC rituximab 1,400 mg achieved noninferior C_{trough} compared with IV rituximab 375 mg/m^2. Geometric mean $C_{trough\ SC}$:$C_{trough\ IV}$ ratios were 1.24 and 1.12 for the 2- and 3-month regimens, respectively (Fig 4), and the lower limits of the two-sided 90% CI (1.02 and 0.86, for the 2-month and 3-month regimens, respectively) exceeded the protocol-specified noninferiority limit ($C_{trough\ SC}$:$C_{trough\ IV}$ ratio of 0.8; Fig 4). The geometric mean AUC over the dosing interval $AUC_{\tau\ SC}$:$AUC_{\tau\ IV}$ ratio was 1.35, and the lower limit of the two-sided 90% CI was 1.23 for both 2- and 3-month regimens, indicating that AUC_τ after SC rituximab was at least as high as that after IV rituximab (Fig 4). C_{trough} and AUC_τ geometric mean values are provided in the Data Supplement.

Pharmacodynamics

$CD19^+$ B lymphocytes were depleted at enrollment and throughout the study for all patients, as expected during maintenance. Evidence of B-cell repletion was observed 9 months after the last rituximab (IV or SC) administration, but at the time of analysis, patient numbers were too small for any conclusions (only six patients had completed the 9-month follow-up visit).

Safety and Immunogenicity

In stage 1, the proportion of patients experiencing AEs and severe AEs was similar between the SC and IV groups (Table 2). The majority of AEs were grade 1 or 2. Comparing events after a single cycle allowed direct comparison of SC versus IV administration (in contrast to overall events, in which patients had received both SC and IV rituximab). The most common AE in the single cycle of randomly assigned treatment and throughout stage 1 was ARR (more frequent with SC rituximab). Serious adverse events (SAEs) were experienced by 13% of patients receiving IV 375 mg/m^2 and 15%, 15%, and 8% of patients receiving SC 375, 625, or 800 mg/m^2, respectively. Three SAEs (one in each of the SC cohorts) led to withdrawal from treatment (none were considered related to study treatment and all occurred when patients had received further cycles by IV infusion). There were no fatal AEs or other deaths in stage 1.

A total of 15, 12, and 16 eligible patients receiving SC rituximab 375, 625, and 800 mg/m^2, respectively, in stage 1 (40%) chose SC administration for their remaining maintenance treatment. This choice was not actively encouraged, but investigators reminded patients of the option. The incidence of AEs in these patients was similar to that of other patients in stage 1 (who received only one dose of SC rituximab) but with fewer ARRs reported.

In stage 2, 61 patients (79%) in each group experienced one or more AEs (Table 2), with reports of severe AEs balanced between the groups: 13 (17% for IV rituximab 375 mg/m^2) versus 14 (18% for SC rituximab

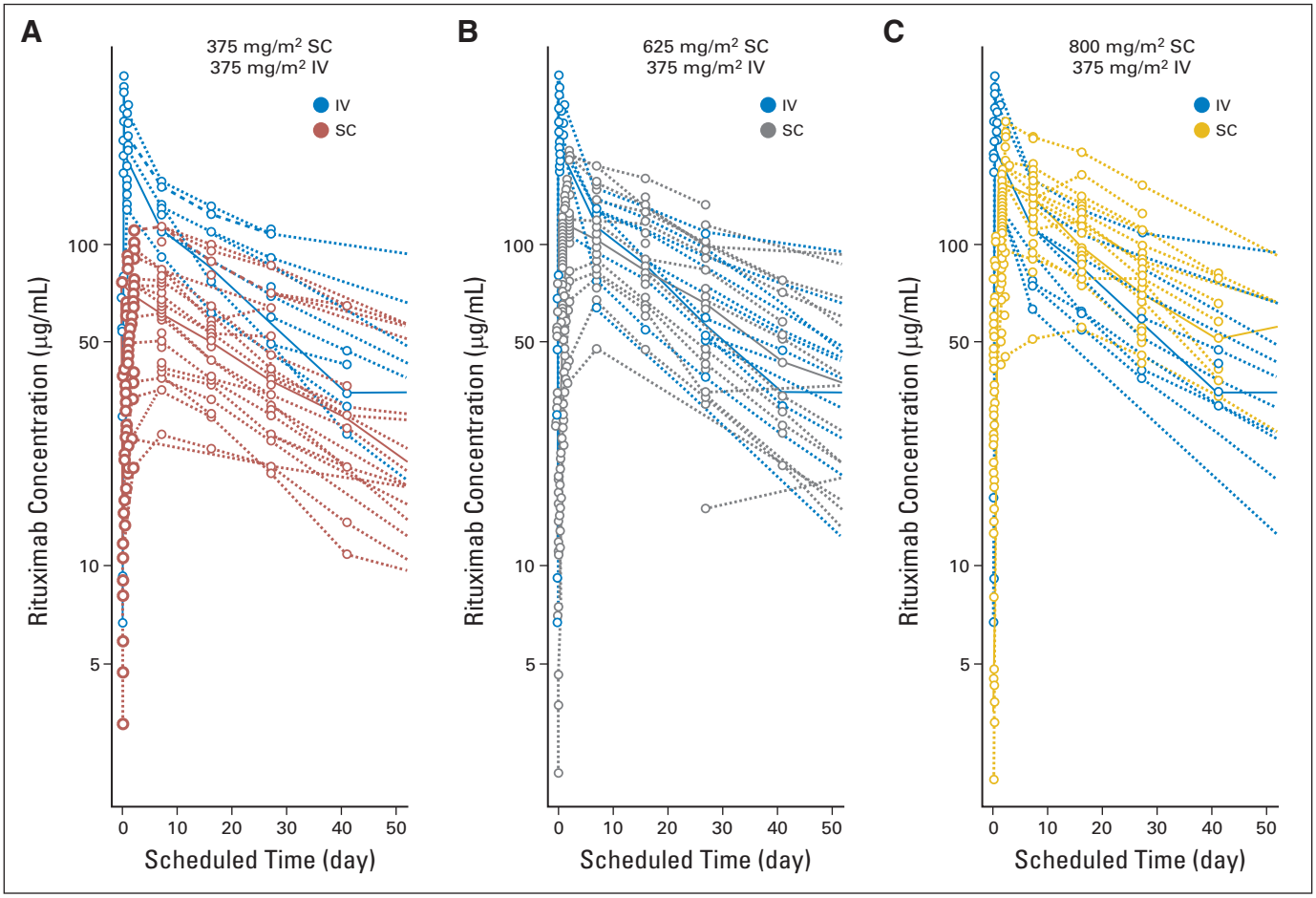

Fig 3. Observed mean (± standard deviation) of rituximab serum concentration-time profiles in stage 1. (A) 375 mg/m^2 subcutaneous (SC) and 375 mg/m^2 intravenous (IV); (B) 625 mg/m^2 SC and 375 mg/m^2 IV; (C) 800 mg/m^2 SC and 375 mg/m^2 IV. The dotted lines represent the individual time course profiles. The solid lines represent the median time course profile.

1,400 mg) patients. There were no deaths during the study, but one patient in the SC group died as a result of disease progression after withdrawal. The SC group had a higher rate of treatment-related AEs (48% *v* 25%) than the IV group, primarily as a result of a higher incidence of grade 1 or 2 ARRs (by prerequisite, events listed as ARRs were considered related by the investigator) in the SC rituximab group (31% *v* 4%), with erythema (13%) being the most common. No true anaphylactic reactions and no occurrences of cytokine release syndrome or tumor lysis syndrome were reported after SC rituximab administration.

Antirituximab antibodies were not detected in stage 1. In stage 2, one patient (SC rituximab) tested positive during his first study cycle (predose, days 22 and 85). Further samples were not taken as the patient's disease progressed, leading to withdrawal from the study. Anti-rHuPH20 antibodies were detected in six patients (stage 1) and

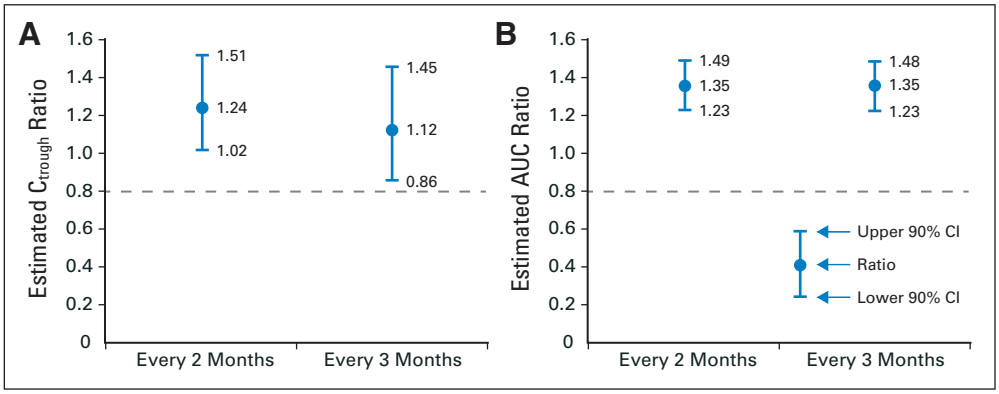

Fig 4. (A) Serum trough concentration (C_{trough}) and (B) area under the concentration-time curve over the dosing interval (AUC_τ) ratios by treatment regimen in stage 2.

Table 2. Safety Results for Stage 1 and Stage 2 of the SparkThera Study

Variable	SC 375 mg/m² (n = 34) No.	SC 375 mg/m² (n = 34) %	SC 625 mg/m² (n = 34) No.	SC 625 mg/m² (n = 34) %	SC 800 mg/m² (n = 40) No.	SC 800 mg/m² (n = 40) %	IV 375 mg/m² (n = 16) No.	IV 375 mg/m² (n = 16) %
Stage 1 Patients Experiencing AEs During the Single Treatment Cycle of SC or IV Rituximab								
Any AE	15	44	17	50	21	53	7	44
Leading to withdrawal from treatment	0	0	0	0	0	0	0	0
Leading to temporary dose modification or interruption	1	3	1	3	3	8	0	0
Grade 3 (severe) AEs	2	6	0	0	2	5	1	6
Serious AEs	0	0	1	3	1	3	1	6
Leading to withdrawal from treatment	0	0	0	0	0	0	0	0
Leading to temporary dose modification or interruption	0	0	0	0	1	3	0	0
Related to treatment	0	0	0	0	0	0	0	0
AEs leading to death	0	0	0	0	0	0	0	0
Treatment-related AEs	9	26	11	32	13	33	1	6
Leading to withdrawal from treatment	0	0	0	0	0	0	0	0
Leading to temporary dose modification or interruption	1	3	0	0	0	0	0	0
Administration-related reactions	7	21	8	24	9	23	1	6
Erythema*	2	6	5	15	0	0	0	0
Rash*	2	6	0	0	1	3	0	0
Dry mouth*	1	3	0	0	0	0	1	6

Variable	SC 1,400 mg (n = 77) No.	SC 1,400 mg (n = 77) %	IV 375 mg/m² (n = 77) No.	IV 375 mg/m² (n = 77) %
Stage 2 Patients Experiencing AEs				
Any AE	61	79	61	79
Leading to withdrawal from treatment	4	5	4	5
Leading to temporary dose modification or interruption	8	10	7	9
Grade 3 (severe) AEs	14	18	13	17
Serious AEs	9	12	11	14
Leading to withdrawal from treatment	2	3	2	3
Leading to temporary dose modification or interruption	2	3	0	0
Related to treatment	2	3	1	1
AEs leading to death	0	0	0	0
Treatment-related AEs	37	48	19	25
Leading to withdrawal from treatment	2	3	2	3
Leading to temporary dose modification or interruption	5	6	3	4
Administration-related reactions	24	31	3	4
Erythema*	10	13	—	
Injection-site erythema*	4	5	—	
Myalgia*	4	5	—	

NOTE. AEs that occurred only once may be included in more than one category in this table.
Abbreviations: AE, adverse event; IV, intravenous; SC, subcutaneous; SparkThera study, A Pharmacokinetic Study of Subcutaneous and Intravenous MabThera (Rituximab) in Patients With Follicular Lymphoma.
*Most common events reported by ≥ 5% of patients in any one treatment group.

seven patients (stage 2) at multiple time points, including before SC rituximab. The presence of antidrug antibodies was not observed to correlate with worsening of safety.

DISCUSSION

In SparkThera, a pharmacokinetic model incorporating stage 1 data predicted that a fixed 1,400-mg SC rituximab dose would provide noninferior C_{trough} levels compared with standard IV dosing. This was confirmed in stage 2: a fixed 1,400-mg SC dose was noninferior to IV maintenance dosing for 2- and 3-month regimens. Because rituximab has a wide therapeutic window,[22,25] fixed dosing in adults is feasible if the dose is sufficient to prevent underdosing while maintaining an acceptable safety profile. The 1,400-mg SC dose should be viewed in the context that bioavailability estimated by using stage 1 data was 65%. To avoid underdosing individual patients, dose selection considered the variability of the pharmacokinetic data (Figs 3 and 4). Furthermore, because the lower limit of the 90% CI of the C_{trough} ratio (SC:IV) for the 3-month regimen was marginally above the threshold at 0.86, a lower dose would have failed the noninferiority test.

On the basis of previous clinical investigations with high-dose rituximab,[22,25] the fixed-dose approach for SC administration was not expected to result in a greater risk of AEs. This was supported by a post hoc analysis of AEs by BSA showing comparable AE profiles for SC and IV (Data Supplement), even with approximately 35% higher mean AUC for SC rituximab 1,400 mg versus IV rituximab 375 mg/m^2. In addition, an analysis of AEs, SAEs, and severe AEs by BSA performed in stage 2 revealed similar incidence in both SC- and IV-treated patients within any given BSA category (Table 3 and Data Supplement).

Overall, the safety profiles of the SC and IV formulations were comparable. No unexpected AEs were observed with SC dosing (including the incidence of severe AEs, SAEs, and AEs leading to withdrawal of treatment), and the profile was similar following SC or IV treatment. There were no treatment-related fatal AEs in either group. Common AEs related to rituximab, including infections, arthralgia, and nausea, were observed at rates in line with the established safety profile. A higher proportion of patients receiving SC rituximab experienced ARRs (mostly grade < 2), but this was not unexpected, and treatment was rarely required. A degree of expectancy bias in the study was difficult to avoid, especially because the SC formulation was introduced into an ongoing regimen. Furthermore, increased ARRs have been reported with SC formulations of other monoclonal antibodies.[26]

SparkThera had a heterogeneous patient profile, but several other studies have shown that the safety profile of rituximab during maintenance therapy is similar regardless of treatment setting (first-line or relapse) or dosing interval for maintenance.[5,27-31] Continual B-cell depletion was observed with both SC and IV rituximab, indicating that rituximab mode of action[32] was unchanged by route of administration. Immunogenicity data were limited but encouraging, with few positive cases for antirituximab and anti-rHuPH20 antibodies, and there was no apparent correlation with safety.

Table 3. Stage 2 Patients With One or More AE, SAE, or Grade ≥ 3 AE, According to BSA

Variable	IV Rituximab 375 mg/m^2 (n = 77)		SC Rituximab 1,400 mg (n = 77)		Total (N = 154)	
	No. of Patients With Event	%	No. of Patients With Event	%	No. of Patients With Event	%
AE						
Low BSA	22 of 26	85	19 of 26	73	41 of 52	79
Medium BSA	17 of 23	74	18 of 22	82	35 of 45	78
High BSA	22 of 28	79	24 of 29	83	46 of 57	81
SAE						
Low BSA	2 of 26	8	1 of 26	4	3 of 52	6
Medium BSA	5 of 23	22	2 of 22	9	7 of 45	16
High BSA	4 of 28	14	6 of 29	21	10 of 57	18
Grade ≥ 3 AE						
Low BSA	2 of 26	8	2 of 26	8	4 of 52	8
Medium BSA	4 of 23	17	3 of 22	14	7 of 45	16
High BSA	7 of 28	25	9 of 29	31	16 of 57	28

NOTE. There was an increase in incidence of serious adverse events (SAEs) with greater body surface area (BSA) in the subcutaneous (SC) rituximab group (4%, 9%, and 21% for low, medium, and high BSA, respectively). A similar trend was observed in the intravenous (IV) rituximab group. Low BSA, ≤ 1.70 m^2; medium BSA, > 1.70 m^2 to < 1.90 m^2; high BSA, ≥ 1.90 m^2.
Abbreviation: AE, adverse event.

Our study demonstrates that a fixed dose of SC rituximab 1,400 mg achieves noninferior serum C_{trough} levels relative to standard IV dosing in the maintenance setting, with a comparable safety profile. Ongoing trials (including the phase III SABRINA study; A Study of MabThera [Rituximab] Subcutaneous Vs. MabThera [Rituximab] Intravenous in Patients With Follicular Non-Hodgkin's Lymphoma)[33] will provide additional insight regarding whether this C_{trough} noninferiority translates into comparable efficacy as in other phase I studies evaluating SC administration of therapeutics.[34,35]

SparkThera provides an indicator of patient preference in the 43 stage 1 patients that chose SC rituximab for their remaining maintenance treatment. Furthermore, the annual amount of chair time saved per center by patients switching to SC rituximab has been estimated to range from 109 to 219 8-hour days, and the potential benefits for patients and health care systems are being investigated further.[36] Together, these findings suggest that SC administration of rituximab will improve the convenience of this drug, although additional investigation will be required to determine whether the SC route provides equivalent efficacy compared with that of IV administration.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Coiffier B, Lepage E, Briere J, et al: CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 346:235-242, 2002

2. Hiddemann W, Kneba M, Dreyling M, et al: Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: Results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 106:3725-3732, 2005

3. Marcus R, Imrie K, Solal-Celigny P, et al: Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol 26:4579-4586, 2008

4. Hallek M, Fischer K, Fingerle-Rowson G, et al: Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: A randomised, open-label, phase 3 trial. Lancet 376:1164-1174, 2010

5. Salles G, Seymour JF, Offner F, et al: Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): A phase 3, randomised controlled trial. Lancet 377:42-51, 2011

6. Dreyling M, Ghielmini M, Marcus R, et al: Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 22:vi59-vi63, 2011

7. Ghielmini M, Vitolo U, Kimby E, et al: ESMO Guidelines consensus conference on malignant lymphoma 2011 part 1: Diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL). Ann Oncol 24:561-576, 2013

8. National Comprehensive Cancer Network: Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas, version 1.2014. http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf

9. Vogel WH: Infusion reactions: Diagnosis, assessment, and management. Clin J Oncol Nurs 14:E10-E21, 2010

10. Salar A, Bouabdallah R, McIntyre C, et al: A two-stage phase Ib study to investigate the pharmacokinetics, safety and tolerability of subcutaneous rituximab in patients with follicular lymphoma as part of maintenance treatment. Blood 116, 2010 (abstr 2858)

11. Bookbinder LH, Hofer A, Haller MF, et al: A recombinant human enzyme for enhanced interstitial transport of therapeutics. J Control Release 114:230-241, 2006

12. Frost GI: Recombinant human hyaluronidase (rHuPH20): An enabling platform for subcutaneous drug and fluid administration. Expert Opin Drug Deliv 4:427-440, 2007

13. Thomas JR, Wallace MS, Yocum RC, et al: The INFUSE-Morphine study: Use of recombinant human hyaluronidase (rHuPH20) to enhance the absorption of subcutaneously administered morphine in patients with advanced illness. J Pain Symptom Manage 38:663-672, 2009

14. Harb G, Lebel F, Battikha J, et al: Safety and pharmacokinetics of subcutaneous ceftriaxone administered with or without recombinant human hyaluronidase (rHuPH20) versus intravenous ceftriaxone administration in adult volunteers. Curr Med Res Opin 26:279-288, 2010

15. Ismael G, Hegg R, Muehlbauer S, et al: Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I-III breast cancer (HannaH study): A phase 3, open-label, multicentre, randomised trial. Lancet Oncol 13:869-878, 2012

16. Pivot X, Gligorov J, Müller V, et al: Patient preference for subcutaneous versus intravenous adjuvant trastuzumab: Results of the PrefHer Study. 13th St Gallen International Breast Cancer Conference, St Gallen, Switzerland, March 13-16, 2013

17. Stilgenbauer S, Zenz T, Winkler D, et al: Subcutaneous alemtuzumab in fludarabine-refractory chronic lymphocytic leukemia: Clinical results and prognostic marker analyses from the CLL2H study of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 27:3994-4001, 2009

18. Bai S, Jorga K, Xin Y, et al: A guide to rational dosing of monoclonal antibodies. Clin Pharmacokinet 51:119-135, 2012

19. Reff ME, Carner K, Chambers KS, et al: Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood 83:435-445, 1994

20. Velagapudi R, Noertershauser P, Awni W, et al: Bioavailability of adalimumab following subcutaneous injections in rheumatoid arthritis patients. Clin Pharmacol Ther 77:P84, 2005

21. Yin A, Li J, Hurst D, et al: Population pharmacokinetics (PK) and association of PK and clinical outcomes of rituximab in patients with non-Hodgkin's lymphoma. J Clin Oncol 28, 2010 (suppl; abstr e13108)

22. O'Brien SM, Kantarjian H, Thomas DA, et al: Rituximab dose-escalation trial in chronic lymphocytic leukemia. J Clin Oncol 19:2165-2170, 2001

23. Coiffier B, Haioun C, Ketterer N, et al: Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: A multicenter phase II study. Blood 92:1927-1932, 1998

24. Coiffier B, Thieblemont C, Van Den Neste E, et al: 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, 2010

25. Keating M, O'Brien S: High-dose rituximab therapy in chronic lymphocytic leukemia. Semin Oncol 27:86-90, 2000

26. Lundin J, Kimby E, Björkholm M, et al: Phase II trial of subcutaneous anti-CD52 monoclonal antibody alemtuzumab (Campath-1H) as first-line treatment for patients with B-cell chronic lymphocytic leukemia (B-CLL). Blood 100:768-773, 2002

27. Forstpointner R, Unterhalt M, Dreyling M, et al: Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). Blood 108:4003-4008, 2006

28. Ghielmini M, Schmitz SF, Cogliatti SB, et al: Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. Blood 103:4416-4423, 2004

29. Hochster H, Weller E, Gascoyne RD, et al: Maintenance rituximab after cyclophosphamide, vincristine, and prednisone prolongs progression-free survival in advanced indolent lymphoma: Results of the randomized phase III ECOG 1496 Study. J Clin Oncol 27:1607-1614, 2009

30. van Oers MH, Klasa R, Marcus RE, et al: Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: Results of a prospective randomized phase 3 intergroup trial. Blood 108:3295-3301, 2006

31. van Oers MH, Van Glabbeke M, Giurgea L, et al: Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: Long-term outcome of the EORTC 20981 phase III randomized intergroup study. J Clin Oncol 28:2853-2858, 2010

32. Cartron G, Watier H, Golay J, et al: From the bench to the bedside: Ways to improve rituximab efficacy. Blood 104:2635-2642, 2004

33. Davies A, Merli F, Mihaljevic B, et al: Pharmacokinetics (PK), safety and overall response rate (ORR) achieved with subcutaneous (SC) administration of rituximab in combination with chemotherapy were comparable to those achieved with intravenous (IV) administration in patients (pts) with follicular lymphoma (FL) in the first-line setting: Stage 1 results of the phase III SABRINA study (BO22334). Presented at the 54th American Society of Hematology Annual Meeting, Atlanta, GA, December 8-11, 2012 (abstr 1629)

34. Moreau P, Coiteux V, Hulin C, et al: Prospective comparison of subcutaneous versus intravenous administration of bortezomib in patients with multiple myeloma. Haematologica 93:1908-1911, 2008

35. Moreau P, Pylypenko H, Grosicki S, et al: Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: A randomised, phase 3, non-inferiority study. Lancet Oncol 12:431-440, 2011

36. De Cock E, Kritikoi P, Tao S, et al: Time and resource savings with rituximab subcutaneous (SC) injection vs rituximab intravenous (IV) infusion: First results from a time and motion study (T&M). Presented at the 18th European Hematology Association Annual Congress, Stockholm, Sweden, June 13-16, 2013 (abstr 4326)

GLOSSARY TERMS

CD20: cell-surface antigen present on lymphoid B cells. CD20 is a widely used phenotypic marker for typing malignant lymphomas. It is involved in B-cell activation.

Eastern Cooperative Oncology Group performance status: criteria used by doctors and researchers to define the progression of a patient's disease, assessing how the disease affects daily living habits, and to assist in the determination of the appropriate treatment and prognosis.

monoclonal antibody: an antibody that is secreted from a single clone of an antibody-forming cell. Large quantities of monoclonal antibodies are produced from hybridomas, which are produced by fusing single antibody-forming cells to tumor cells. The process is initiated with initial immunization against a particular antigen, stimulating the production of antibodies targeted to different epitopes of the antigen. Antibody-forming cells are subsequently isolated from the spleen. By fusing each antibody-forming cell to tumor cells, hybridomas can each be generated with a different specificity and targeted against a different epitope of the antigen.

pharmacokinetics: a branch of pharmacology that studies the relationship between drug exposure level, time course of exposure, and the overall response of an organism. Although pharmacokinetics is largely applied to drugs, it is also applicable to other compounds such as nutrients, toxins, hormones, etc. Pharmacokinetics is subdivided into absorption and disposition (distribution, metabolism, and excretion) and is generally referred to as ADME (absorption, distribution, metabolism, excretion). With respect to drugs administered, all processes occur in tandem once a drug dose is administered. In clinical trials, phase I studies will typically study pharmacokinetics and safety of the drug.

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