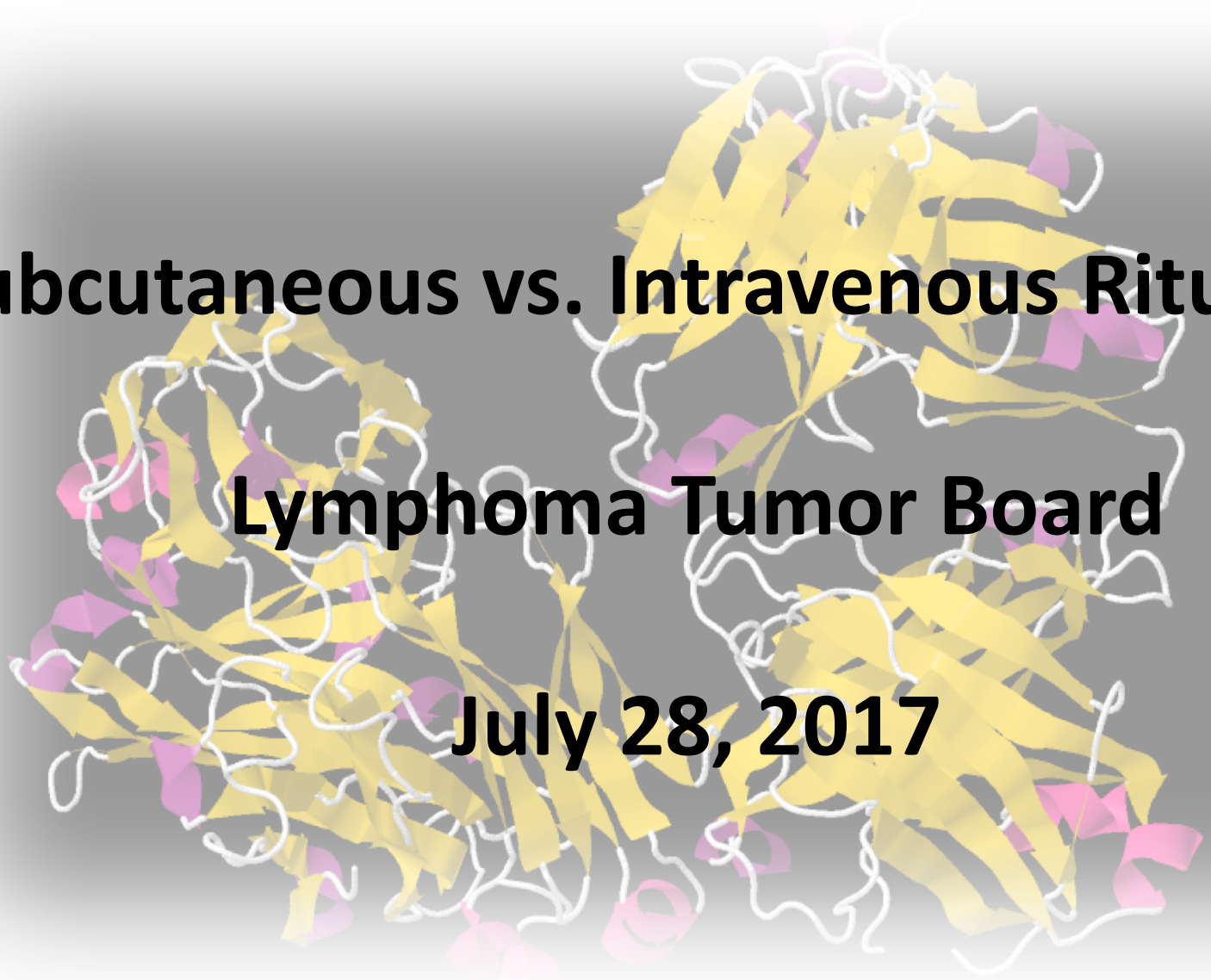


Subcutaneous vs. Intravenous Rituximab

Lymphoma Tumor Board

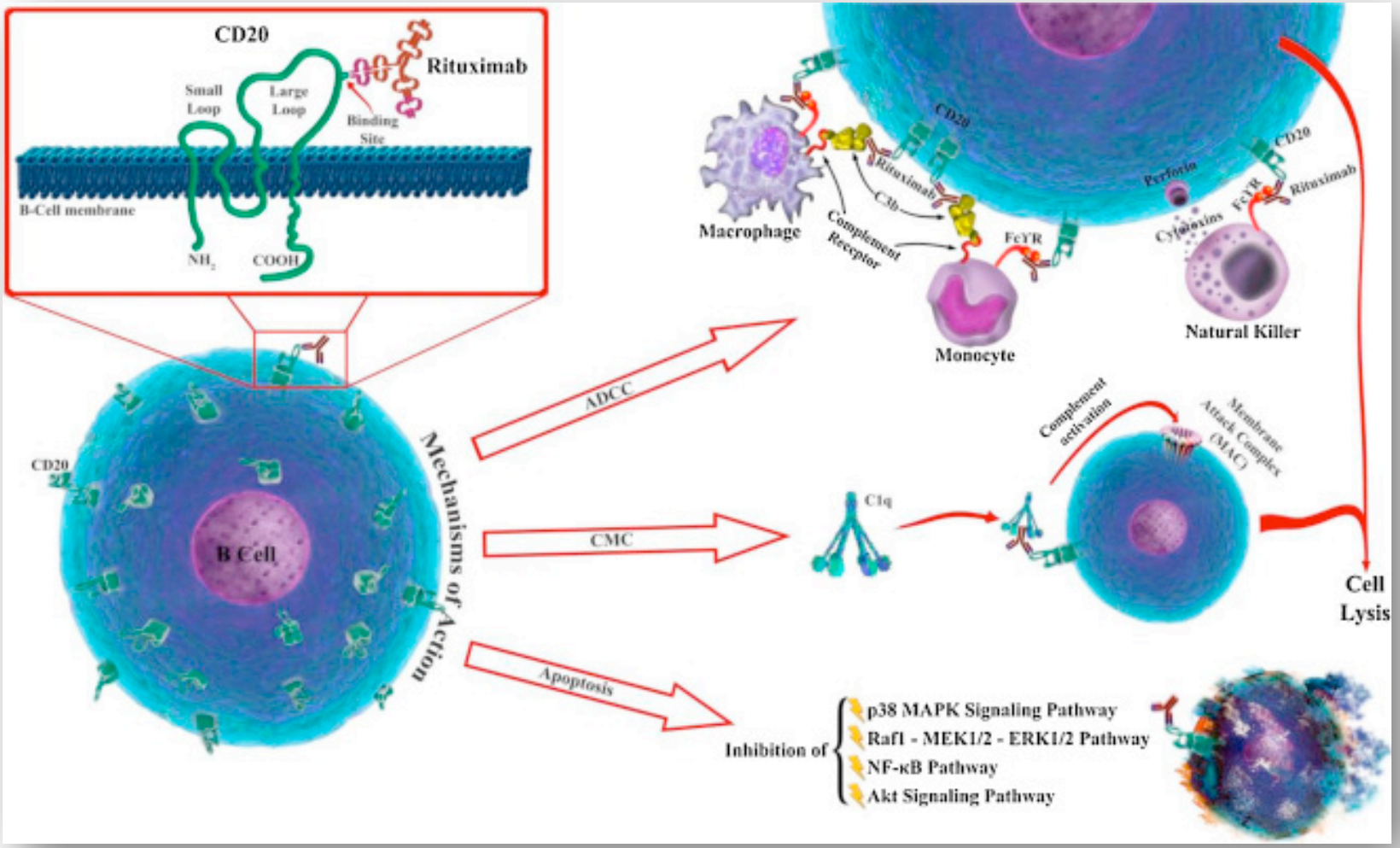
July 28, 2017

Rituximab

- Monoclonal antibody against CD20
- Approved by US FDA in 1997; added to WHO List of Essential Medicines
- Used to treat B-NHL, CLL, rheumatoid arthritis, SLE, idiopathic thrombocytopenic purpura, and pemphigus vulgaris
- Common side effects usually occur within two hours of infusion.
- Acute side effects include:
  - Rash/urticaria
  - Pruritis
  - Hypotension
  - Dyspnea

- Severe side effects include:
  - Reactivation of hepatitis B
  - Progressive multifocal leukoencephalopathy
  - Toxic epidermal necrolysis

Rituximab - mechanism of action



The three major independent mechanisms: (1) antibody-dependent cellular cytotoxicity (ADCC), (2) complement-mediated cytotoxicity (CMC), and (3) apoptosis.
Subpanel illustrates schematic view of rituximab binding to CD20.

Rituximab – SABRINA Trial

PLOS ONE

RESEARCH ARTICLE

Time Savings with Rituximab Subcutaneous Injection versus Rituximab Intravenous Infusion: A Time and Motion Study in Eight Countries

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Rituximab – SABRINA Trial

Table 1

*Time Savings with Rituximab SC Injection

Country	Active HCP time† (mean)			Expected HCP time reduction for yr 1 of treatment, hrs	Patient chair time (mean)		Expected annual chair time savings for 50 pts, 8-hr days
	Difference, min (IV vs SC)	% reduction	% time savings achieved in treatment room		Difference, min (IV vs SC)	% reduction	
AU	6.8 (22.9 vs 16.1)	30	51	0.9	146.3 (197.5 vs 51.3)	74	121.9
BR	15.6 (31.2 vs 15.6)	50	87	2.1	204.7 (268.2 vs 63.5)	76	170.6
FR	17.6 (41.4 vs 23.8)	42	88	2.3	182 (278.3 vs 96.4)	65	151.7
IT	16.1 (38.3 vs 22.2)	42	85	2.1	280.1 (326.3 vs 46.2)	86	233.4
RU	17.1 (30.0 vs 12.9)	57	79	2.3	244.5 (269.6 vs 25.2)	91	203.7
SL	8.9 (18.3 vs 9.4)	49	76	1.2	126.1 (196.4 vs 70.3)	64	105.1
SP	7.0 (26.3 vs 19.3)	27	4	0.9	252.9 (300.3 vs 47.4)	84	210.7
UK	38.4 (88.7 vs 50.3)	43	66	5.1	200.3 (238.8 vs 38.5)	84	166.9

* 95% confidence intervals will be presented at the conference.

† Treatment room + drug preparation area

Rituximab – SABRINA Trial

Effectiveness

Stage 1 of SABRINA (Davies et al. 2014, n=127) found that, compared with intravenous rituximab, fixed dose subcutaneous rituximab:

- was pharmacokinetically non-inferior for the primary outcome of ratio of observed mean rituximab serum trough concentrations (C_{trough}) between the groups at induction cycle 7 (1.62, 90% confidence interval [CI] 1.36 to 1.94).
- was associated with a similar overall response rate (84% with intravenous rituximab compared with 90% with subcutaneous rituximab); however, the trial was not powered to detect differences between the groups.

Safety

- In SABRINA, the most common adverse events in the intravenous and subcutaneous rituximab groups were neutropenia (35% in both groups), nausea (23% and 29% respectively) and constipation (26% and 23% respectively).
- The summary of product characteristics for rituximab subcutaneous injection states that, during the development programme, the safety profile of the subcutaneous injection was comparable to that of the intravenous infusion, with the exception of local injection site reactions.
- In SABRINA, administration-related reactions were more common with subcutaneous rituximab compared with intravenous rituximab (50% compared with 32% respectively; statistical analysis not reported). More than 90% of these reactions were mild-to-moderate.

Rituximab – SABRINA Trial

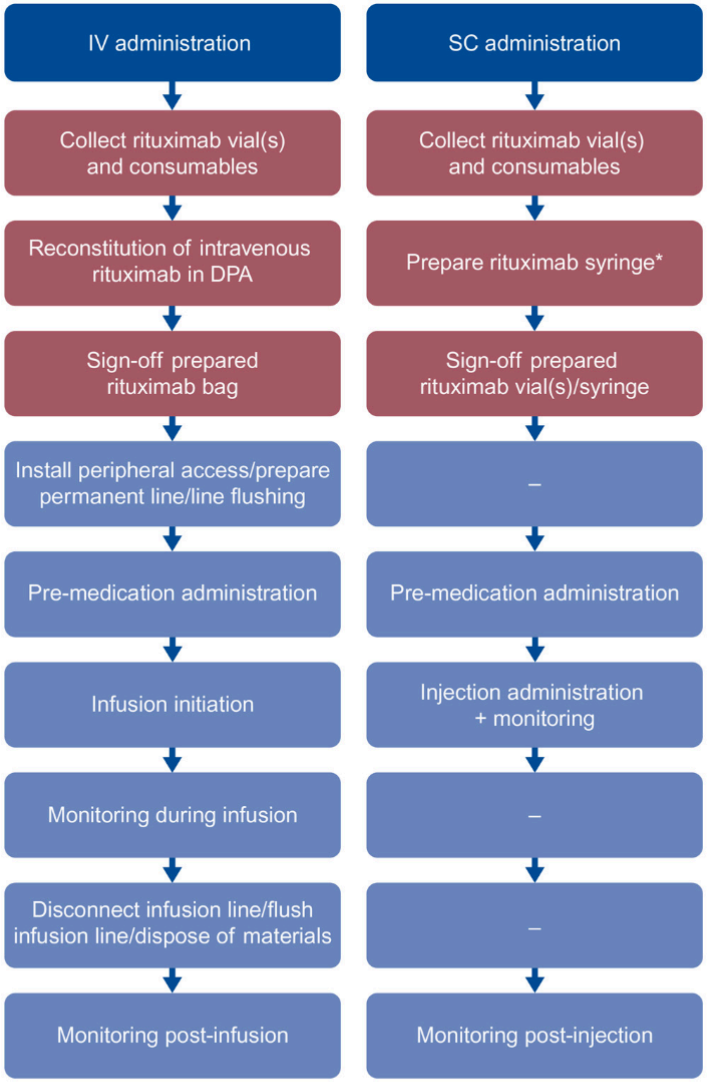
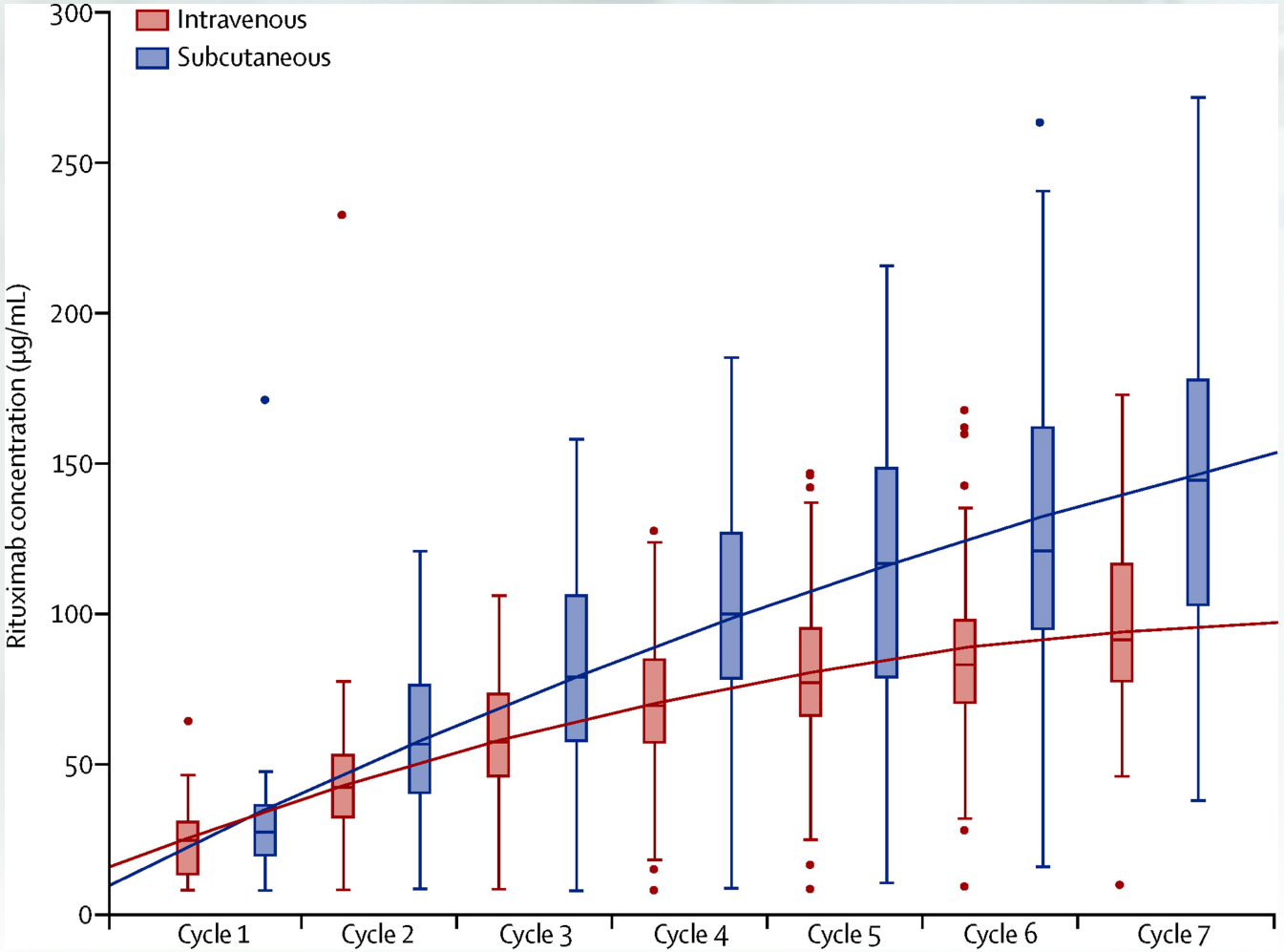


Fig 1. Chronological listing of tasks measured. DPA tasks are in red and treatment room tasks are in blue. *Rituximab syringe can be filled either in the pharmacy (43%), or in a special aseptic DPA within the day oncology unit (57%). IV, intravenous; SC, subcutaneous; DPA, drug preparation area.

Pharmacokinetics and safety of subcutaneous rituximab in follicular lymphoma (SABRINA): stage 1 analysis of a randomised phase 3 study



Rituximab – SABRINA Trial

Table 3. Tumour response rates at the end of induction

Patients, n (%)	Rituximab iv + CT (n = 64)	Rituximab sc + CT (n = 63)
Overall response	54 (84.4)	57 (90.5)
CR/CRu	19 (29.7)	29 (46.0)
PR	35 (54.7)	28 (44.4)
Stable disease	3 (4.7)	2 (3.2)
Progressive disease	1 (1.6)	0 (0.0)
Missing, invalid, or not evaluated*	6 (9.4)	4 (6.3)

CR = complete response; CRu = unconfirmed complete response; CT = chemotherapy; iv = intravenous; n = number of patients; PR = partial response; sc = subcutaneous

**Patients with nonevaluated, invalid, or missing response assessments are classified as nonresponders. A response was classified as invalid if the response assessment was >56 days after the last rituximab intake, after the first rituximab intake of the maintenance phase, or after the start of new antilymphoma treatment.*

http://www.newevidence.com/oncology/stage-1-results-of-the-phase-iii-sabrina-study-comparing-subcutaneous-versus-intravenous-administration-of-rituximab-in-combination-with-chemotherapy-in-patients-with-previously-untreated-follicular-l/

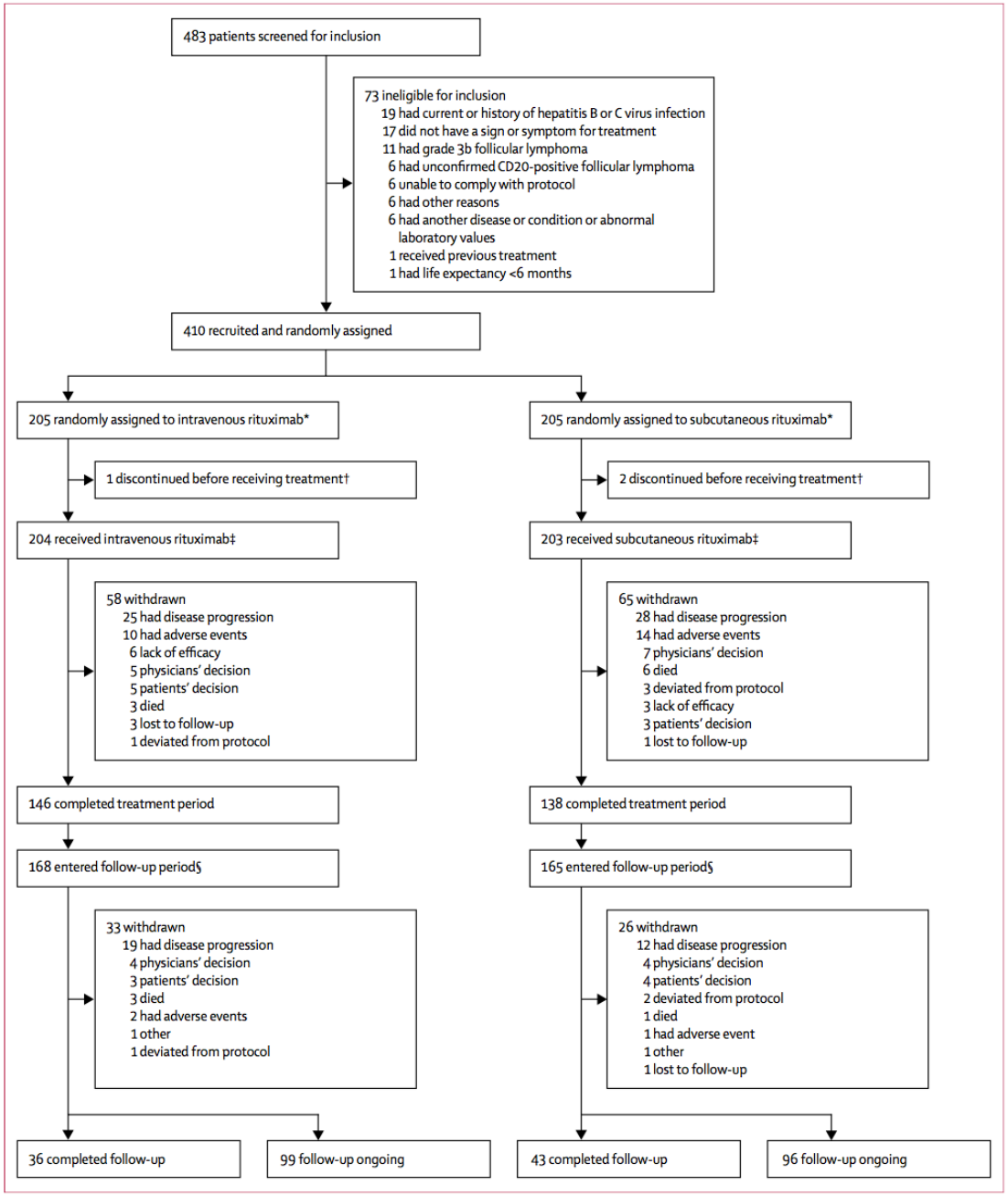


Figure 1: **Trial profile**

*Intention-to-treat population. †Three patients (one in the intravenous group and two in the subcutaneous group) discontinued before receiving treatment and were excluded from the safety population. ‡Six patients in the rituximab subcutaneous group discontinued after cycle 1 and were analysed in the intravenous group in the safety population. §Only patients who completed the treatment period or discontinued for reasons other than withdrawal of consent, disease progression, death, or loss to follow-up are included in the follow-up period.

	Intravenous rituximab (n=205)	Subcutaneous rituximab (n=205)
Age (years)	57 (46–65)	56 (48–64)
Sex		
Male	106 (52%)	85 (41%)
Female	99 (48%)	120 (59%)
Bodyweight (kg)	75 (65–85)	72 (61–85)
Height (cm)	168 (162–176)	167 (160–172)
Body surface area	1·8 (1·7–2·0)	1·8 (1·6–2·0)
Low (≤1·73 m²)	56 (27%)	85 (41%)
Medium (1·74 m² to ≤1·92 m²)	77 (38%)	58 (28%)
High (>1·93 m²)	72 (35%)	62 (30%)
Ethnic origin		
n	187	190
White	160 (86%)	164 (86%)
Asian	11 (6%)	10 (5%)
Other race	14 (7%)	13 (7%)
Native American or Alaskan	1 (1%)	3 (2%)
Black	1 (1%)	0
Follicular lymphoma grade		
1	45 (22%)	67 (33%)
2	109 (53%)	93 (46%)
3a	42 (20%)	35 (17%)
3*	9 (4%)	9 (4%)
FLIPI score		
Low	44 (21%)	42 (20%)
Intermediate	66 (32%)	73 (36%)
High	95 (46%)	90 (44%)
Bulky disease†	76 (37%)	93 (45%)
First-line chemotherapy		
CHOP	130 (63%)	132 (64%)
CVP	75 (37%)	73 (36%)
CHOP cycles		
n	131	128
6	43 (33%)	55 (43%)
8	76 (58%)	65 (51%)
Lactate dehydrogenase > upper limit of normal	59 (29%)	59 (29%)
Rituximab cycles		
n	210	197
6	191 (91%)	186 (94%)
8	188 (90%)	179 (91%)
20	146 (70%)	138 (70%)

Data are median (IQR) or n (%). Because of rounding or missing data, some percentages might not total 100%. FLIPI=Follicular Lymphoma International Prognostic Index. CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisolone. CVP=cyclophosphamide, vincristine, and prednisolone. *Not otherwise specified. †Nodal or extranodal (except the spleen) mass ≥7 cm in its greatest diameter.

Table 1: **Baseline characteristics in stages 1 and 2 of SABRINA**

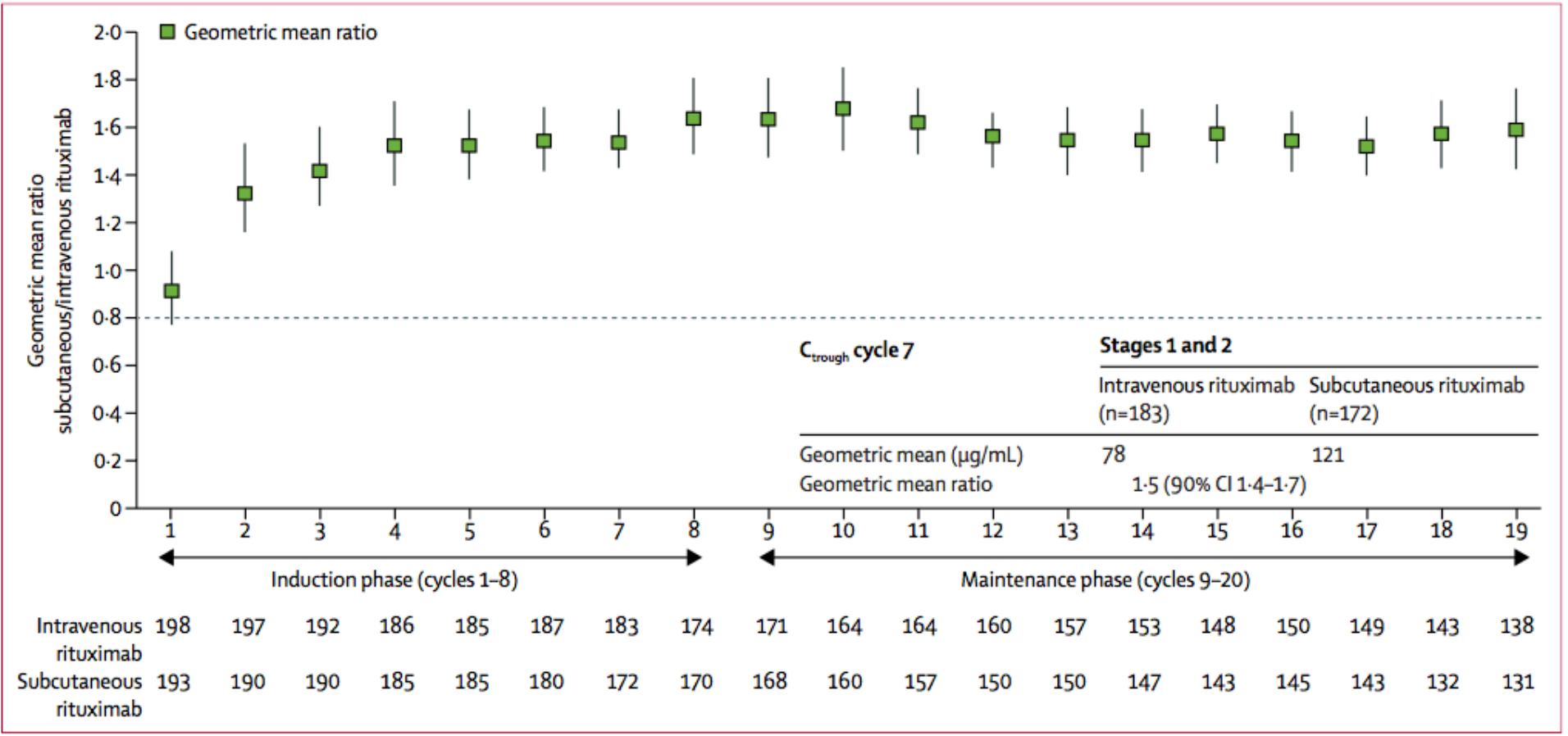


Figure 2: **Observed C_{trough} geometric mean ratios of subcutaneous rituximab and intravenous rituximab during treatment for stages 1 and 2 of the SABRINA study**
Bars represent 90% CIs. Data points correspond to the C_{trough} for each cycle (ie, cycle 19 is pre-dose cycle 20). C_{trough}=trough serum concentrations.

	Intravenous rituximab	Subcutaneous rituximab
Overall pooled data		
n	205	205
Overall response	174 (84·9%; 79·2–89·5)	173 (84·4%; 78·7–89·1)
Complete response (confirmed or unconfirmed)	66 (32·2%; 25·9–39·1)	66 (32·2%; 25·9–39·1)
Body surface area		
Low body surface area		
n	56	85
Overall response	50 (89·3%; 78·1–96·0)	67 (78·8%; 68·6–86·9)
Complete response (confirmed or unconfirmed)	21 (37·5%; 24·9–51·5)	33 (38·8%; 28·4–50·0)
Medium body surface area		
n	77	58
Overall response	62 (80·5%; 69·9–88·7)	51 (87·9%; 76·7–95·0)
Complete response (confirmed or unconfirmed)	23 (29·9%; 20·0–41·4)	16 (27·6%; 16·7–40·9)
High body surface area		
n	72	62
Overall response	62 (86·1%; 75·9–93·1)	55 (88·7%; 78·1–95·3)
Complete response (confirmed or unconfirmed)	22 (30·6%; 20·2–42·5)	17 (27·4%; 16·9–40·2)
Chemotherapy regimen		
CHOP		
n	130	132
Overall response	112 (86·2%; 79·0–91·6)	116 (87·9%; 81·1–92·9)
Complete response (confirmed or unconfirmed)	45 (34·6%; 26·5–43·5)	41 (31·1%; 23·3–39·7)
CVP		
n	75	73
Overall response	62 (82·7%; 72·2–90·4)	57 (78·1%; 66·9–86·9)
Complete response (confirmed or unconfirmed)	21 (28·0%; 18·2–39·6)	25 (34·2%; 23·5–46·3)

Data are n (response rates [ie, percentages of patients]; 95% CI) at the end of induction. Low body surface area is ≤1·73 , medium body surface area is 1·74 m^2 to ≤1·92 m^2, high body surface area is >1·93 m^2.
CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone. CVP=cyclophosphamide, vincristine, prednisolone or prednisolone.

***Table 2*: Response rates overall and by subgroup**

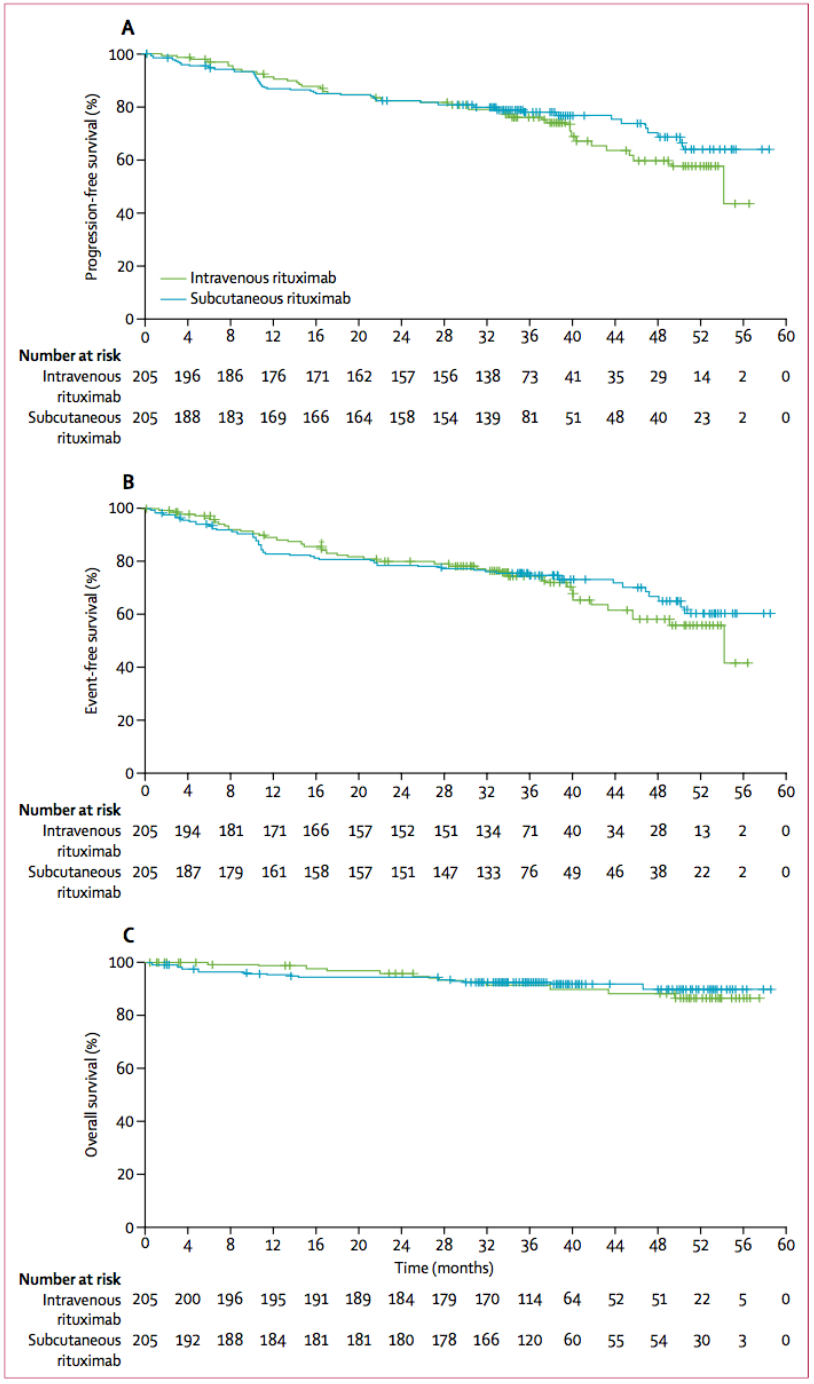


Figure 3: **Kaplan-Meier plots of progression-free (A), event-free (B), and overall (C) survival in the intention-to-treat population**

	Intravenous rituximab* (n=210)	Subcutaneous rituximab (n=197)
Adverse events	199 (95%)	189 (96%)
Serious adverse events	72 (34%)	73 (37%)
Grade ≥3 adverse events	116 (55%)	111 (56%)
Administration-related reaction	73 (35%)	95 (48%)

Data are n (%). *Includes adverse events from six patients in the subcutaneous rituximab group who withdrew after cycle 1 (intravenous rituximab for all patients) and were analysed in the intravenous group in the safety-analysis population.

***Table 3*: Summary of adverse events in stages 1 and 2 of SABRINA (safety population)**

	Intravenous rituximab (n=210)*						Subcutaneous rituximab (n=197)					
	Overall	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Overall	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Gastrointestinal disorders												
Nausea	46 (22%)	31 (15%)	15 (7%)	..	..	..	62 (31%)	42 (21%)	20 (10%)	..	..	..
Constipation	55 (26%)	37 (18%)	17 (8%)	1 (<1%)	..	..	49 (25%)	30 (15%)	19 (10%)	..	..	..
Diarrhoea	33 (16%)	25 (12%)	6 (3%)	2 (1%)	..	..	35 (18%)	23 (12%)	9 (5%)	3 (2%)	..	..
Vomiting	26 (12%)	14 (7%)	10 (5%)	2 (1%)	..	..	27 (14%)	13 (7%)	14 (7%)	..	..	..
Abdominal pain	26 (12%)	19 (9%)	5 (2%)	2 (1%)	..	..	28 (14%)	19 (10%)	9 (5%)	..	..	..
General disorders and administration-site conditions												
Fatigue	37 (18%)	28 (13%)	7 (3%)	2 (1%)	..	..	39 (20%)	27 (14%)	12 (6%)	..	..	..
Pyrexia	33 (16%)	21 (10%)	11 (5%)	1 (<1%)	..	..	30 (15%)	20 (10%)	9 (5%)	1 (1%)	..	..
Asthenia	27 (13%)	19 (9%)	8 (4%)	..	..	..	34 (17%)	25 (13%)	7 (4%)	2 (1%)	..	..
Injection-site erythema	..	..	..	..	..	..	26 (13%)	25 (13%)	1 (1%)	..	..	..
Blood and lymphatic system disorders												
Neutropenia	57 (27%)	8 (4%)	5 (2%)	24 (11%)	20 (10%)	..	63 (32%)	4 (2%)	7 (4%)	24 (12%)	28 (14%)	..
Anaemia	27 (13%)	15 (7%)	12 (6%)	..	..	..	30 (15%)	11 (6%)	10 (5%)	9 (5%)	..	..
Leucopenia	23 (11%)	8 (4%)	10 (5%)	2 (1%)	3 (1%)	..	12 (6%)	3 (2%)	1 (1%)	6 (3%)	2 (1%)	..
Febrile neutropenia	13 (6%)	..	..	8 (4%)	5 (2%)	..	15 (8%)	1 (1%)	..	9 (5%)	3 (2%)	2 (1%)
Nervous system disorders												
Paraesthesia	26 (12%)	21 (10%)	5 (2%)	..	..	..	31 (16%)	26 (13%)	5 (3%)	..	..	..
Peripheral neuropathy	30 (14%)	16 (8%)	13 (6%)	1 (<1%)	..	..	23 (12%)	13 (7%)	7 (4%)	3 (2%)	..	..
Headache	18 (9%)	12 (6%)	6 (3%)	..	..	..	26 (13%)	19 (10%)	7 (4%)	..	..	..
Musculoskeletal and connective tissue disorders												
Arthralgia	20 (10%)	14 (7%)	6 (3%)	..	..	..	25 (13%)	18 (9%)	6 (3%)	1 (1%)	..	..
Back pain	25 (12%)	12 (6%)	11 (5%)	2 (1%)	..	..	18 (9%)	6 (3%)	11 (6%)	1 (1%)	..	..
Bone pain	16 (8%)	9 (4%)	7 (3%)	..	..	..	19 (10%)	13 (7%)	5 (3%)	1 (1%)	..	..
Pain in extremities	11 (5%)	7 (3%)	4 (2%)	..	..	..	19 (10%)	17 (9%)	2 (1%)	..	..	..
Infections and infestations												
Upper-respiratory-tract infection	21 (10%)	7 (3%)	14 (7%)	..	..	..	29 (15%)	11 (6%)	17 (9%)	1 (1%)	..	..
Urinary tract infection	29 (14%)	5 (2%)	22 (10%)	1 (<1%)	..	1 (<1%)	15 (8%)	1 (1%)	12 (6%)	2 (1%)	..	..
Nasopharyngitis	21 (10%)	11 (5%)	10 (5%)	..	..	..	19 (10%)	13 (7%)	6 (3%)	..	..	..
Pneumonia	9 (4%)	..	3 (1%)	2 (1%)	3 (1%)	1 (<1%)	21 (11%)	1 (1%)	11 (6%)	9 (5%)	..	..
Skin and subcutaneous tissue disorders												
Alopecia	22 (10%)	10 (5%)	11 (5%)	1 (<1%)	..	..	28 (14%)	13 (7%)	14 (7%)	1 (1%)	..	..
Pruritus	25 (12%)	13 (6%)	11 (5%)	1 (<1%)	..	..	19 (10%)	14 (7%)	5 (3%)	..	..	..
Rash	14 (7%)	8 (4%)	6 (3%)	..	..	..	19 (10%)	14 (7%)	5 (3%)	..	..	..
Respiratory, thoracic, and mediastinal disorders												
Cough	28 (13%)	14 (7%)	13 (6%)	1 (<1%)	..	..	45 (23%)	29 (15%)	16 (8%)	..	..	..
Dyspnoea	16 (8%)	6 (3%)	6 (3%)	2 (1%)	2 (1%)	..	22 (11%)	12 (6%)	8 (4%)	2 (1%)	..	..

Data are n (%). Further information about use of granulocyte-colony stimulating factor and neutropenia is in the appendix. *Includes adverse events from six patients in the subcutaneous rituximab group who withdrew after cycle 1 (intravenous rituximab for all patients) and were analysed in the intravenous group in the safety-analysis population.

***Table 4*: Most common adverse events (in ≥10% patients) and grade 3 or higher adverse events (in >2% patients) in stages 1 and 2 of SABRINA**

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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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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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.

J Clin Oncol 32:1782-1791.

Study Design – SparkThera Trial

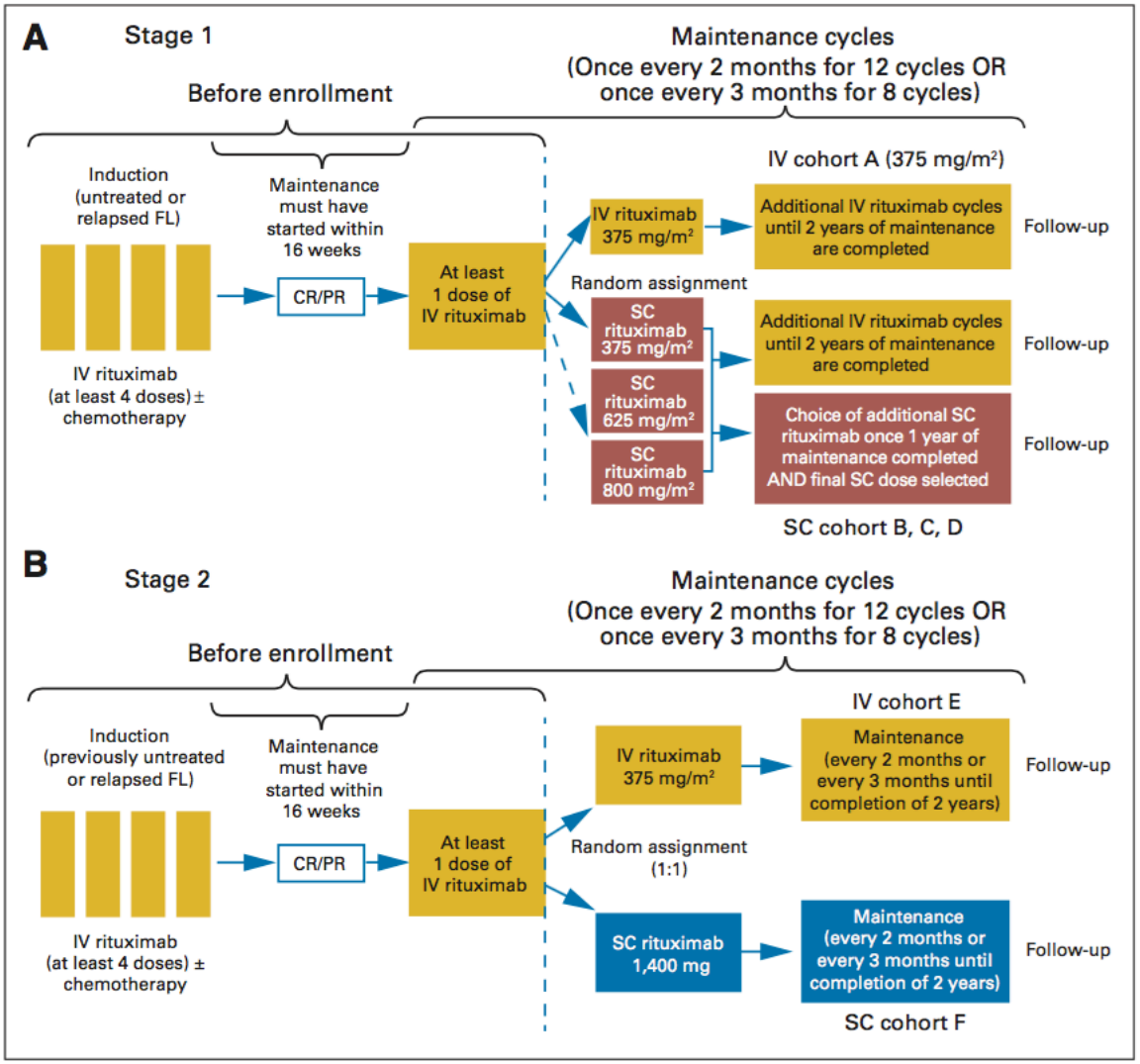

Fig 2. Study design for (A) stage 1 and (B) stage 2. CR, complete response; FL, follicular lymphoma; IV, intravenous; PR, partial response; SC, subcutaneous.

Safety results and AEs – SparkThera Trial

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.

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ORIGINAL ARTICLE

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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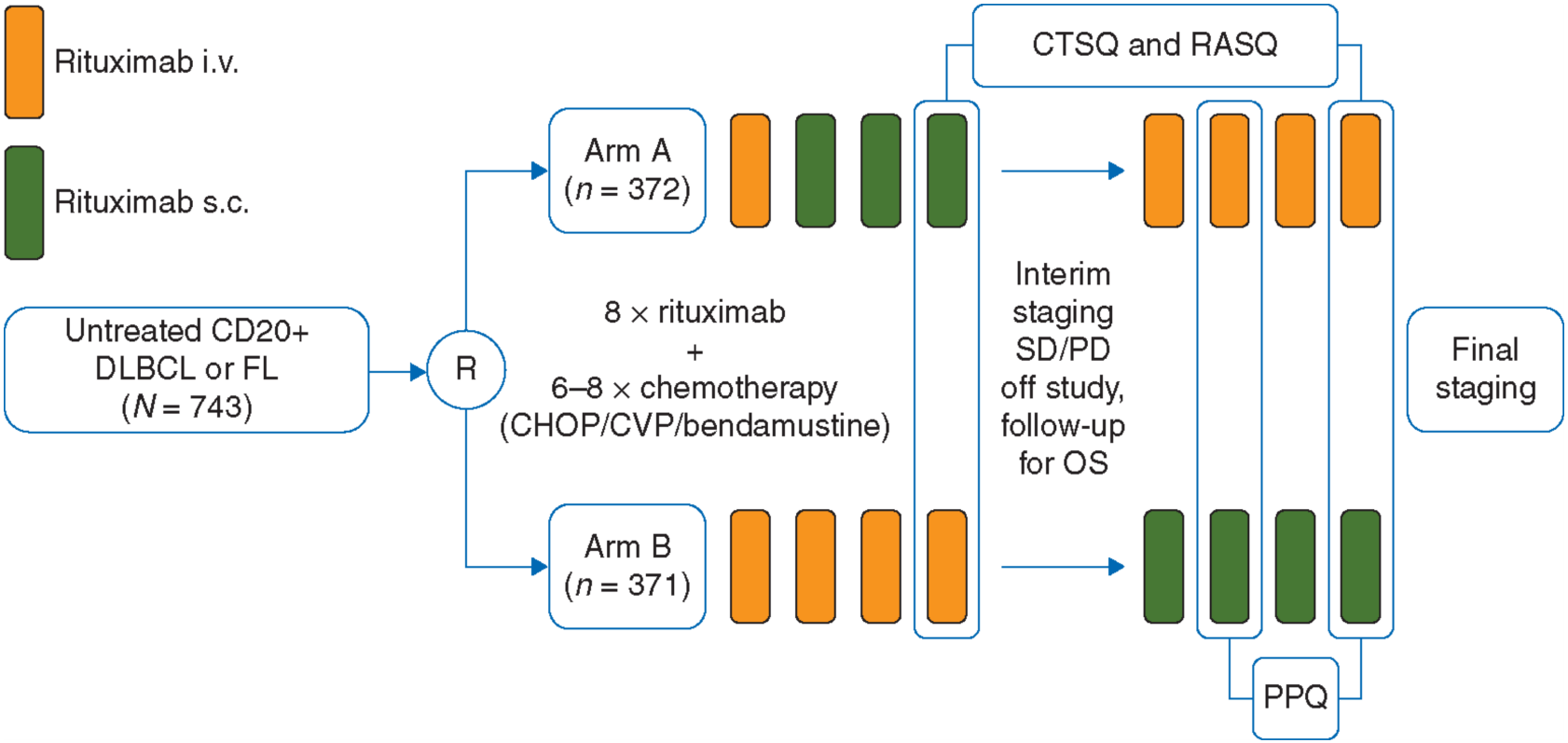
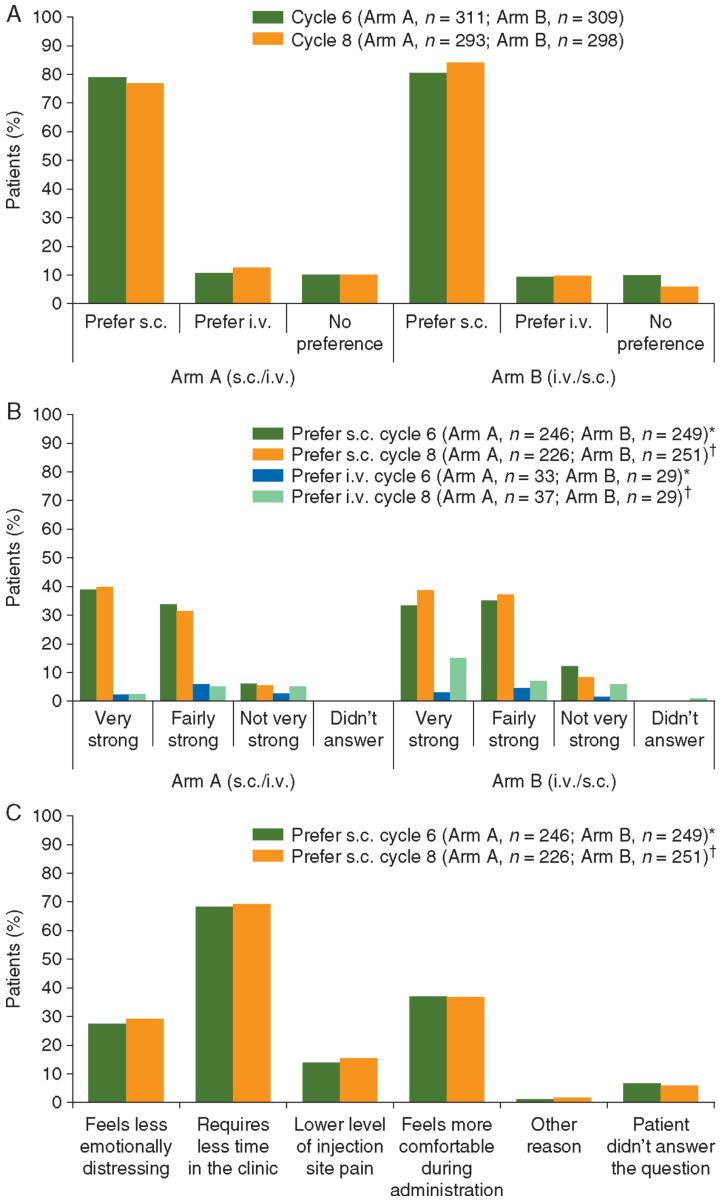
Study Design – PrefMab



Ann Oncol. 2016;28(4):836-842. doi:10.1093/annonc/mdw685

Patient Preference – PrefMab



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Safety of Subcutaneous Administration of Rituximab during the First-Line Treatment of Patients with Non-Hodgkin Lymphoma: The MabRella Study

Table 1. Summary of safety (overall safety population)

AEs, n (%)	Total (n=336)	FL (n=205)	DLBCL (n=131)
Any-grade AE*	282 (84)	180 (88)	102 (78)
Neutropenia	95 (28)	43 (21)	52 (40)
Asthenia	48 (14)	27 (13)	21 (16)
Erythema	44 (13)	40 (20)	4 (3)
Pyrexia	39 (12)	23 (11)	16 (12)
Diarrhea	38 (11)	21 (10)	17 (13)
ARRs	75 (22)	60 (29)	15 (12)
Drug-related AE	119 (35)	86 (42)	33 (25)
Grade ≥3 AE†	135 (40)	78 (38)	57 (44)
Neutropenia	82 (24)	41 (20)	41 (31)
Febrile neutropenia	20 (6)	10 (5)	10 (8)
Drug-related grade ≥3 AE	39 (12)	27 (13)	12 (9)
SAE	97 (29)	53 (26)	44 (34)
Any AE leading to withdrawal	11 (3)	9 (4)	2 (2)
Fatal AE	11 (3)	4 (2)	7 (5)

*AEs with incidence ≥10% overall are shown; †Grade ≥3 AEs with incidence ≥5% are shown

Carlos Panizo *et al*. Blood 2016;128:2971

Safety of Subcutaneous Administration of Rituximab during the First-Line Treatment of Patients with Non-Hodgkin Lymphoma: The MabRella Study

Table 2. Summary of safety in FL patients completing ≥1 cycle of rituximab SC induction or maintenance

AEs, n (%)	Patients completing ≥1 cycle of induction (n=84)	Patients completing ≥1 cycle of maintenance (n=190)
Any-grade AE*	64 (76)	155 (82)
Neutropenia	31 (37)	20 (11)
Pyrexia	12 (14)	13 (7)
Anemia	10 (12)	3 (2)
Asthenia	10 (12)	17 (9)
Paresthesia	10 (12)	7 (4)
Erythema	8 (10)	34 (18)
Cough	4 (5)	22 (12)
ARRs	12 (14)	51 (27)
Drug-related AE	24 (29)	72 (38)
Grade ≥3 AE†	37 (44)	48 (25)
Neutropenia	30 (36)	16 (8)
Febrile neutropenia	7 (8)	3 (2)
Drug-related grade ≥3 AE	15 (18)	14 (7)
SAE	23 (27)	33 (17)
Any AE leading to withdrawal	2 (2)	7 (4)
Fatal AE	2 (2)	2 (1)

*AEs with incidence ≥10% are shown; †Grade ≥3 AEs with incidence ≥5% are shown

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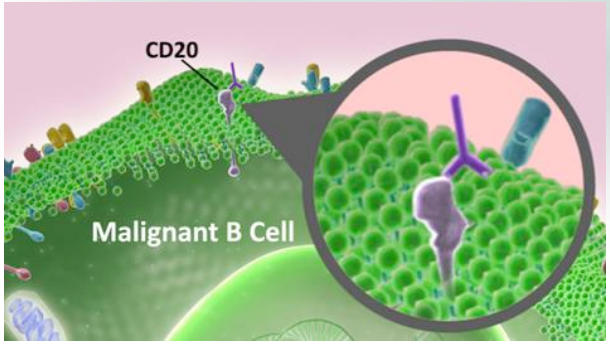
Other CD20-specific monoclonal antibodies

- Ocrelizumab
  - Humanized (90%-95% human) B cell-depleting agent.

- Ofatumumab (HuMax-CD20)
  - Fully human B cell-depleting agent.

- Third-generation anti-CD20s such as obinutuzumab have a glycoengineered Fc fragment (Fc) with enhanced binding to Fc gamma receptors, which increase ADCC (antibody-dependent cellular cytotoxicity). This strategy for enhancing a monoclonal antibody's ability to induce ADCC takes advantage of the fact that the displayed Fc glycan controls the antibody's affinity for Fc receptors.



Rituximab binding to CD20. The CD20 proteins are sticking out of the cell membrane, and rituximab, the Y-shaped antibody, is binding to the CD20 proteins."

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