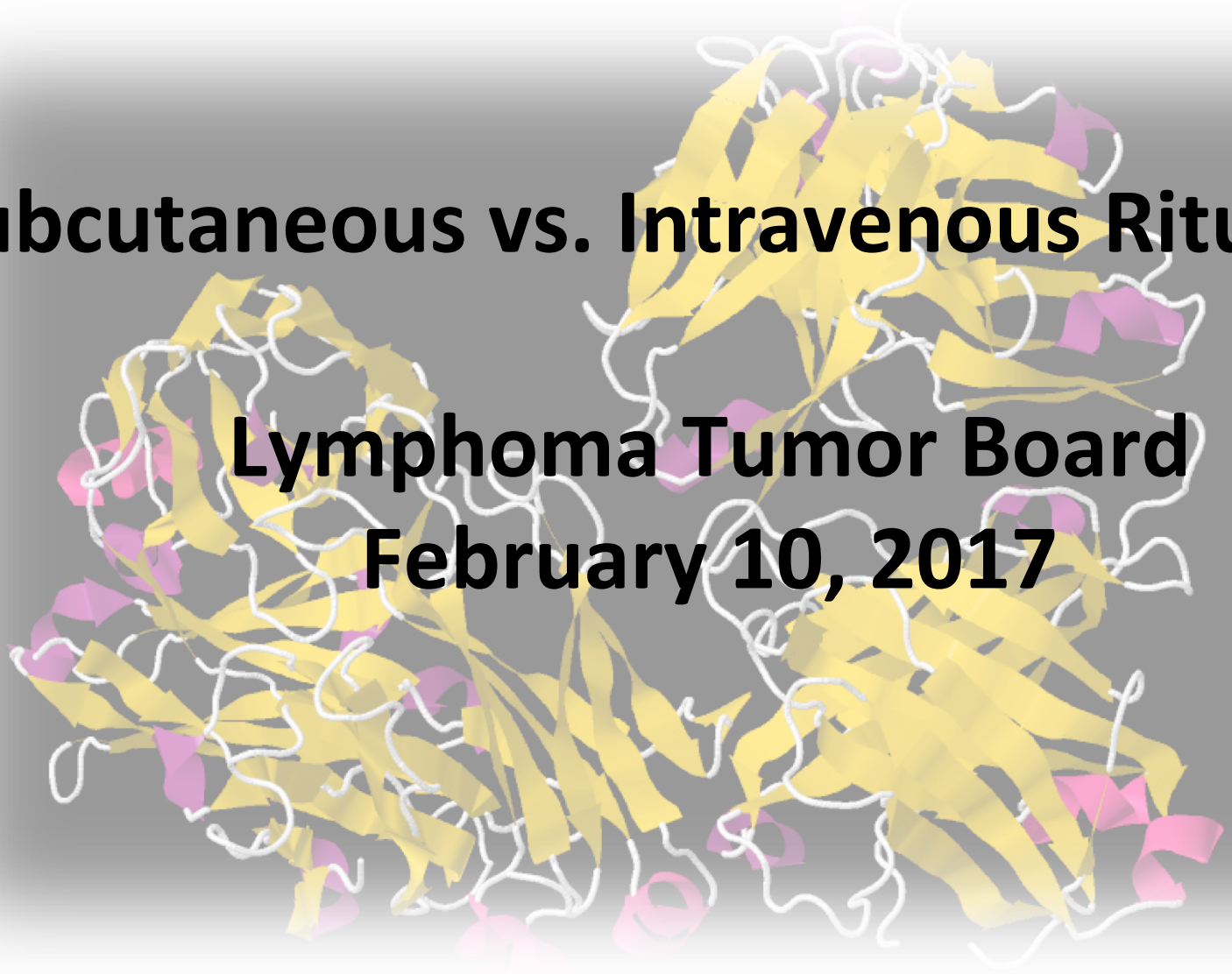
Subcutaneous vs. Intravenous Rituximab



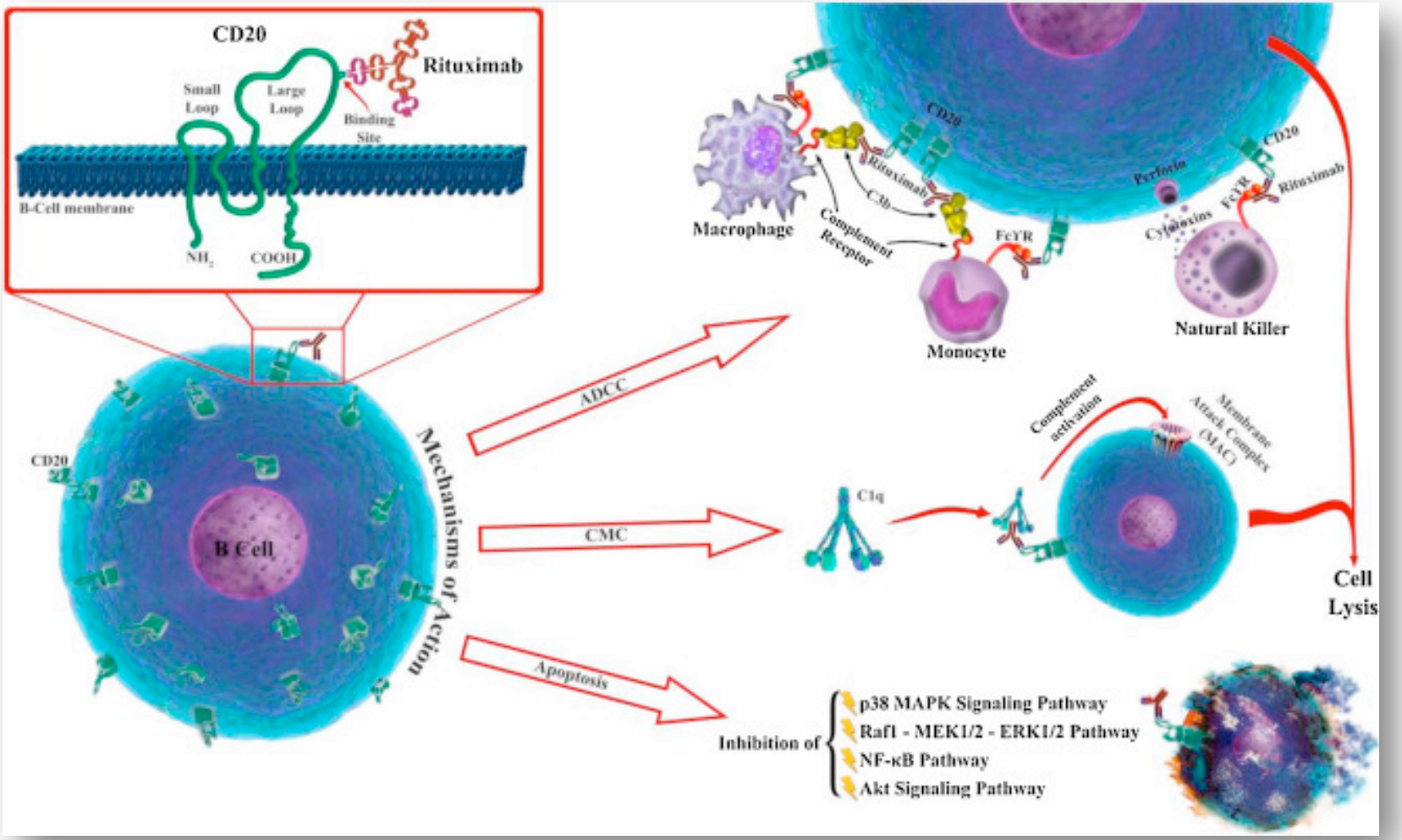
Lymphoma Tumor Board
February 10, 2017

Rituximab

- Monoclonal antibody against CD20
- Approved in 1997 and placed on the WHO list of essential medicines
- Used to treat NHL, CLL, rheumatoid arthritis, SLE, idiopathic thrombocytopenic purpura, and pemphigus vulgaris
- Common side effects usually occur within two hours of rituximab 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 are (1) antibody dependent cellular cytotoxicity (ADCC), (2) complement mediated cytotoxicity (CMC), and (3) apoptosis; subset panel illustrates a schematic view of CD20 structure and rituximab."

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

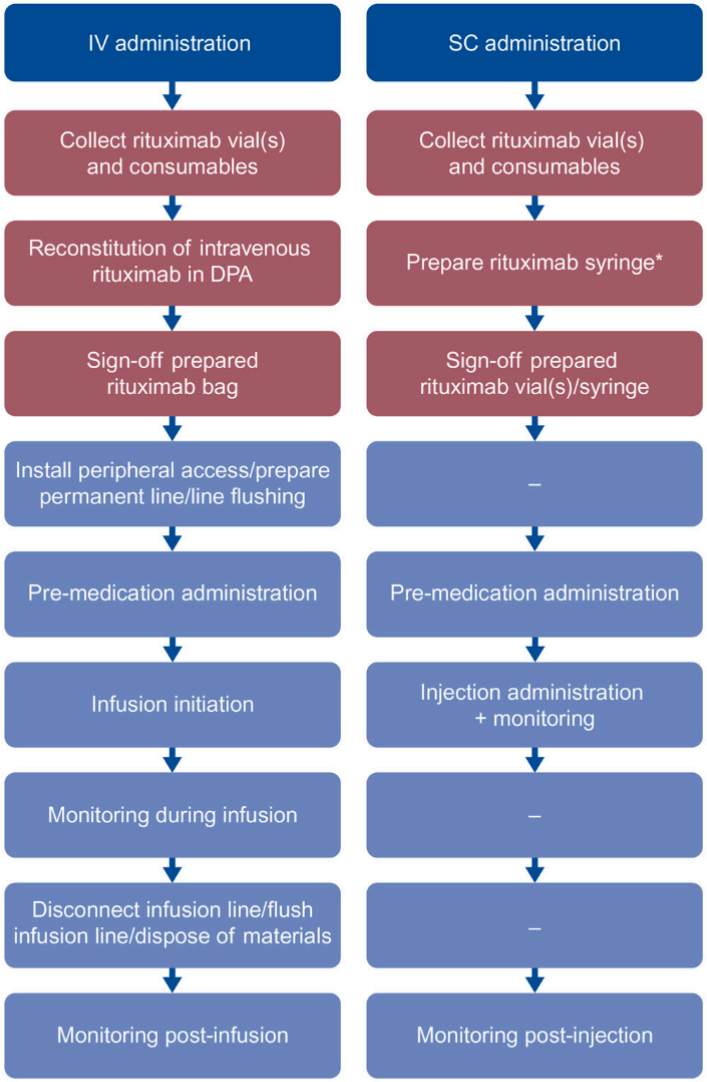
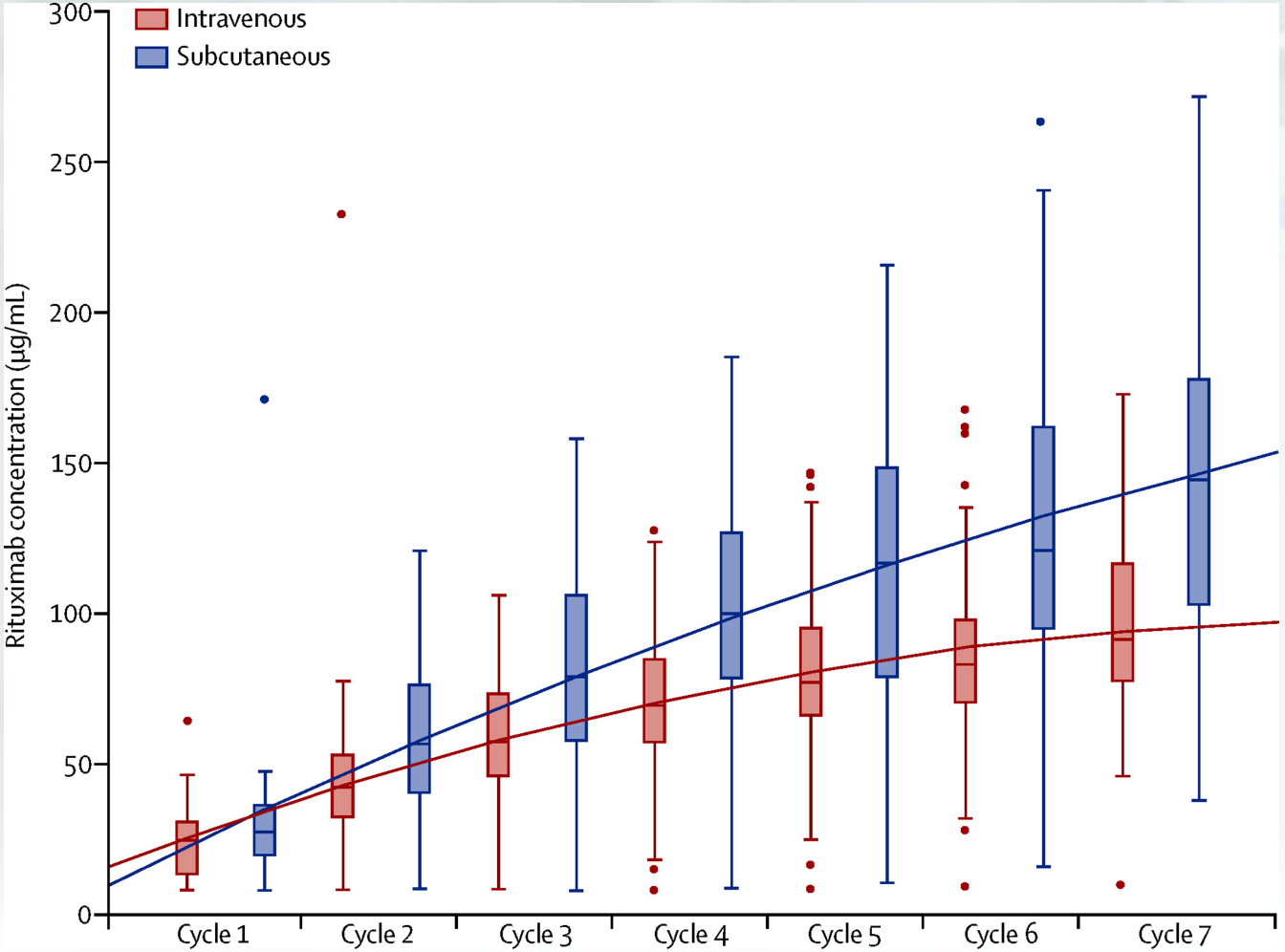


Fig 1. Chronological listing of tasks measured. DPA tasks are in red and treatment room tasks are in blue. *Rituximab syringe can be filled either in the pharmacy (43%), or in a special aseptic DPA within the day oncology unit (57%). IV, intravenous; SC, subcutaneous; DPA, drug preparation area.

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/

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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

Antonio Salar, Irit Avivi, Beate Bittner, Reda Bouabdallah, Mike Brewster, Olivier Catalani, George Follows, Andrew Haynes, Florence Hourcade-Potelleret, Andrea Janikova, Jean-François Larouche, Christine McIntyre, Michael Pedersen, Juliana Pereira, Pakeeza Sayyed, Ofer Shpilberg, and Gayane Tumyan

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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.

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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.

J Clin Oncol 32:1782-1791.

Study Design

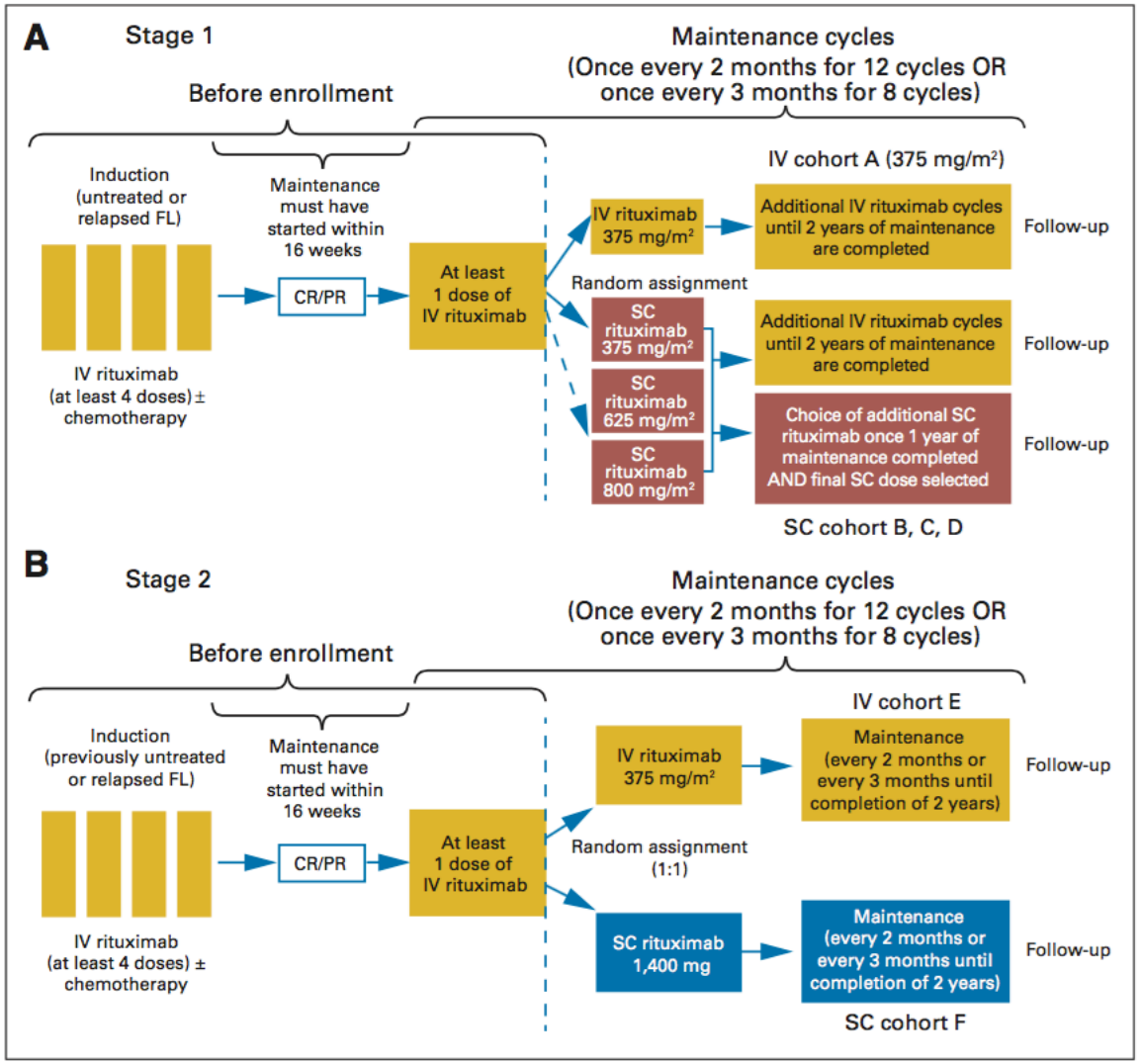


Fig 2. Study design for (A) stage 1 and (B) stage 2. CR, complete response; FL, follicular lymphoma; IV, intravenous; PR, partial response; SC, subcutaneous.

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

Variable	SC 375 mg/m^2 (n = 34) No.	SC 375 mg/m^2 (n = 34) %	SC 625 mg/m^2 (n = 34) No.	SC 625 mg/m^2 (n = 34) %	SC 800 mg/m^2 (n = 40) No.	SC 800 mg/m^2 (n = 40) %	IV 375 mg/m^2 (n = 16) No.	IV 375 mg/m^2 (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

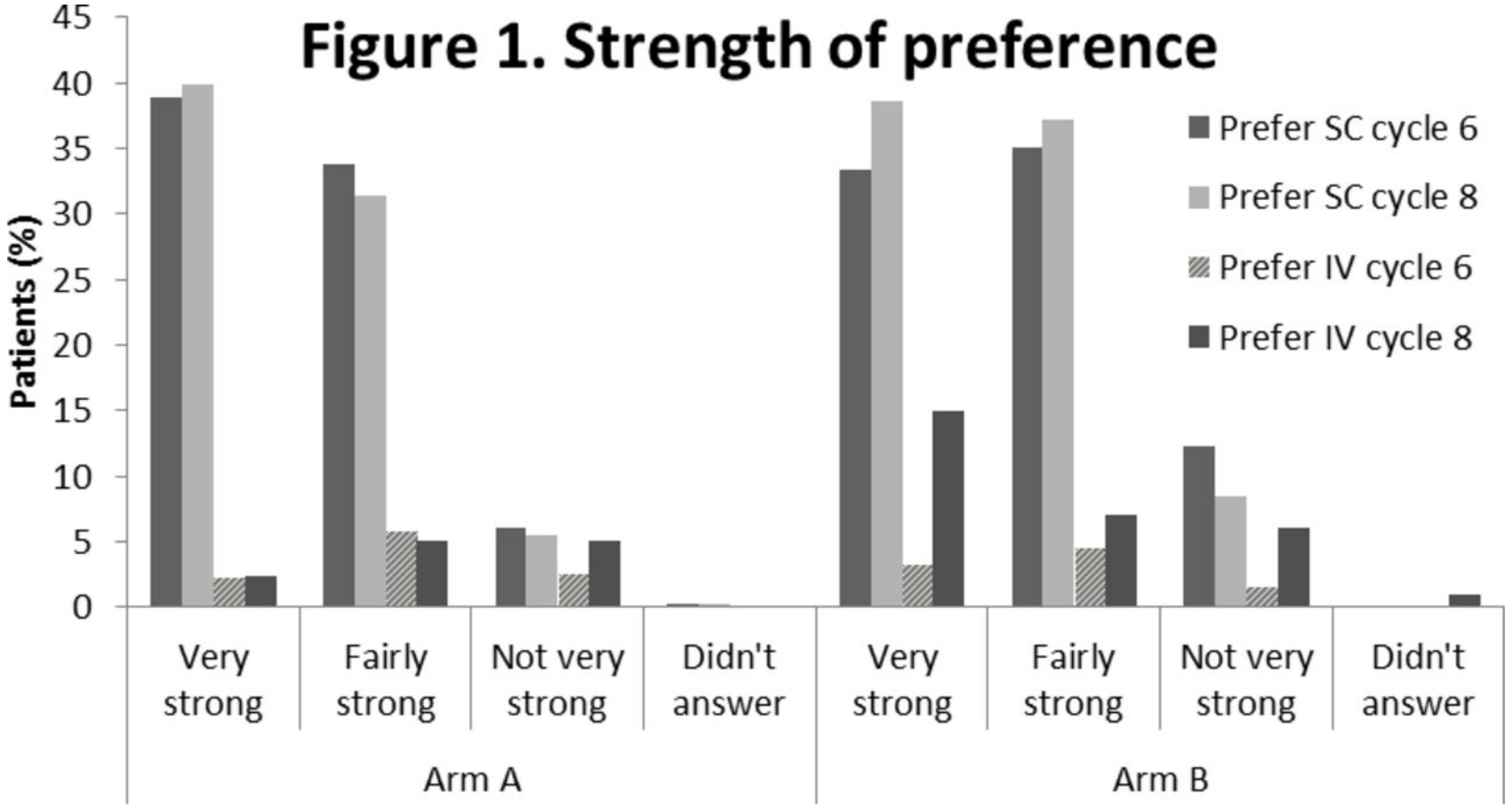
Variable	SC 1,400 mg (n = 77) No.	SC 1,400 mg (n = 77) %	IV 375 mg/m^2 (n = 77) No.	IV 375 mg/m^2 (n = 77) %
Stage 2 Patients Experiencing AEs				
Any AE	61	79	61	79
Leading to withdrawal from treatment	4	5	4	5
Leading to temporary dose modification or interruption	8	10	7	9
Grade 3 (severe) AEs	14	18	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.

Prefmab: Final Analysis of Patient Preference for Subcutaneous Versus Intravenous Rituximab in Previously Untreated CD20+ Diffuse Large B-Cell Lymphoma and Follicular Lymphoma

Mathias Rummel, Tae Min Kim, Caterina Plenteda, Enrico Capochiani, Maria Mendoza, Rodney Smith, Stuart Osborne and Andrew Grigg

Blood 2015 126:3972;



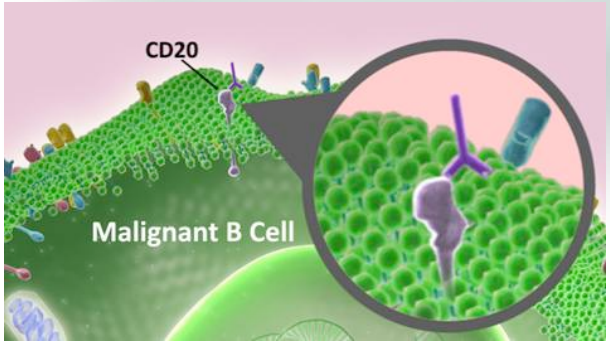
Mathias Rummel et al. Blood 2015;126:3972

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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