

Rituximab SC

Presentation to the
Oncologic Drugs Advisory Committee

March 29, 2017

Genentech

Rituximab SC

Development Rationale

Nancy Valente, MD
Head of Global Hematology Development
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Rationale for Rituximab SC Development

Decreasing Patient Treatment Burden

- Rituximab Subcutaneous (SC) is a simpler, faster option for delivery of rituximab clinical benefit
 - Shortens administration time
 - SC injection 5 - 7 minutes versus IV infusion 1.5 - 4 hours
 - Reduces the burden on patients and providers
 - Ready-to-use fixed dosing versus BSA-adjusted dosing
 - Administered using a needle and syringe
 - Has the potential to relieve strain on infusion centers and allow greater patient access

Rituximab SC

Same Antibody, Different Route of Administration

- Contains the same rituximab antibody as currently approved RITUXAN®
 - After maximal concentrating, larger than traditional SC injection
- Required combination with recombinant human hyaluronidase to optimize SC dosing and facilitate volume of injection
- Both components are previously approved drugs; safety and effectiveness has been established individually
- Extensive product testing demonstrates no alteration in the stability or activity of rituximab due to formulation change

Recombinant Human Hyaluronidase Permeation Enhancer

- Depolymerizes hyaluronan at the injection site; a natural barrier to fluid dispersion
 - Effect is local, rapid and transient, short, half-life (30 minutes)
 - Increases dispersion and absorption of the rituximab antibody
 - Decreases swelling and induration
 - Restoration of hyaluronan in 24-48h: no long term impact
- Small amount (<0.3mg); not detected in systemic circulation
- Hylenex[®] recombinant (hyaluronidase human injection), approved in 2005 - >1 million doses administered

Regulatory Framework

- PK bridging is a common regulatory approach to apply the known effectiveness of an approved product to a formulation change
- Rituximab SC development approach expands this framework to include:
 - Clinical evaluation of safety and effectiveness
 - Patient preference

Rituximab SC Development Program

PK-Clinical Bridging Approach

The development program objectives comparing SC to IV formulations:

1. Establish non-inferior exposure
2. Establish comparability of effectiveness and safety
3. Evaluate patient satisfaction/preference for route of administration

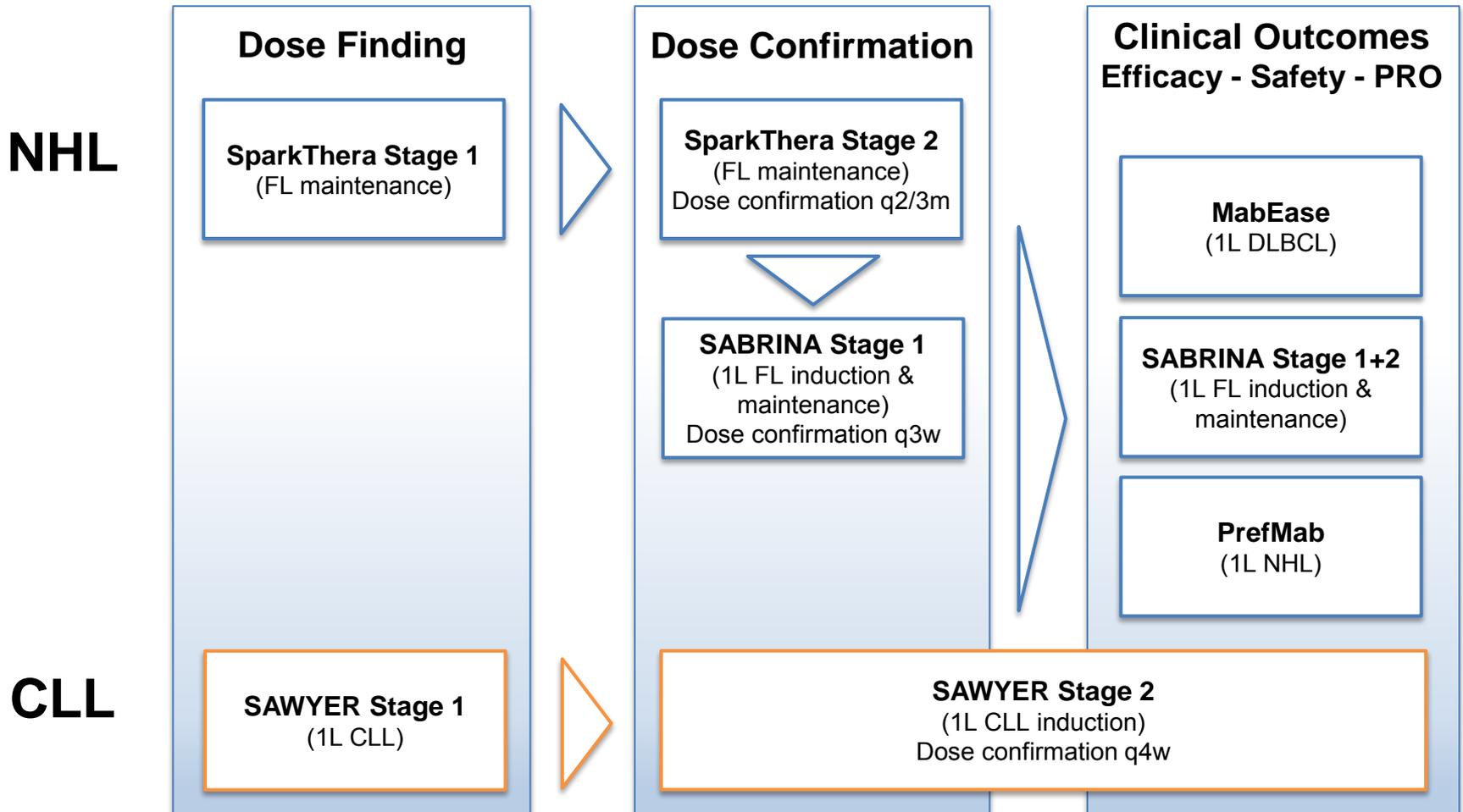
Rituximab SC Development Overview

2250 Patients Enrolled (1579 Patients Treated with Rituximab SC)

PK-Clinical Bridging						
Study	Disease State	n	PK	Clinical		Patient Reported Outcomes
				Efficacy	Safety	
SparkThera	FL Maintenance	281	✓		✓	
SABRINA	FL Induction & Maintenance	410	✓	✓	✓	
SAWYER	CLL	240	✓	✓	✓	
MabEase	DLBCL	576		✓	✓	✓
PrefMab	Lymphoma (FL & DLBCL)	743			✓	✓

Rituximab SC

Integrated PK-Clinical Bridging Development Plan



Rituximab SC Proposed Indications

Rituximab SC is intended to be used in adults for the treatment of:

- Follicular lymphoma (FL)
- Diffuse large B-cell lymphoma (DLBCL)
- Chronic lymphocytic leukemia (CLL)

Agenda

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Clinical Perspective

Andrew Davies, BSc BM PhD FRCP
Associate Professor in Medical Oncology,
University of Southampton, UK

Rituximab SC
Clinical Pharmacology

Peter Morcos, PharmD
Clinical Pharmacologist
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Rituximab SC
Clinical Development
Concluding Remarks

Axel Boehnke, MD
Global Development Team Leader
Genentech

Consultants

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Donald Mager, PharmD, PhD

Professor of Pharmaceutical Sciences,
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Disclosures

- **Celgene**: Research funding; Advisory Board; Honorarium
- **Roche**: Advisory Boards; Honorarium; Research support
- **Gilead**: Advisory Boards; Honorarium; Research support
- **Takeda**: Advisory Boards; Honorarium; Research support, Travel to scientific conferences
- **CTI**: Advisory Boards; Honorarium; Travel to scientific conferences
- **Mundipharma**: Advisory Boards; Honorarium; Travel to scientific conferences
- **GSK**: Research support
- **Bayer**: Research support
- **Janssen**: Honorarium; Research support
- **Karyopharma**: Advisory Board; Research support
- **Pfizer**: Research support; Honorarium

B-cell Malignancies

NHL and CLL

- ~72,000 new NHL cases each year and ~570,000 patients living with the disease in the US¹
- ~19,000 new cases of CLL, ~120,000 living with disease in the US^{1,2}
- DLBCL and follicular are most common types of NHL
- Follicular and CLL are incurable relapsing/remitting course; treated with a series of therapies over lifetime
- Majority of patients treated with chemotherapy in combination with rituximab

¹ SEER Cancer Stat Facts: Chronic Lymphocytic Leukemia. National Cancer Institute. Bethesda, MD, <http://seer.cancer.gov/statfacts/html/clyl.html>

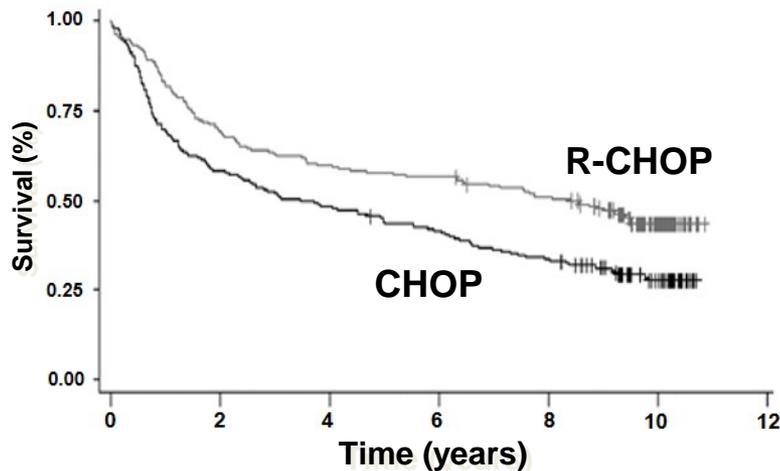
² Jain N et al, Blood 2016

Rituximab

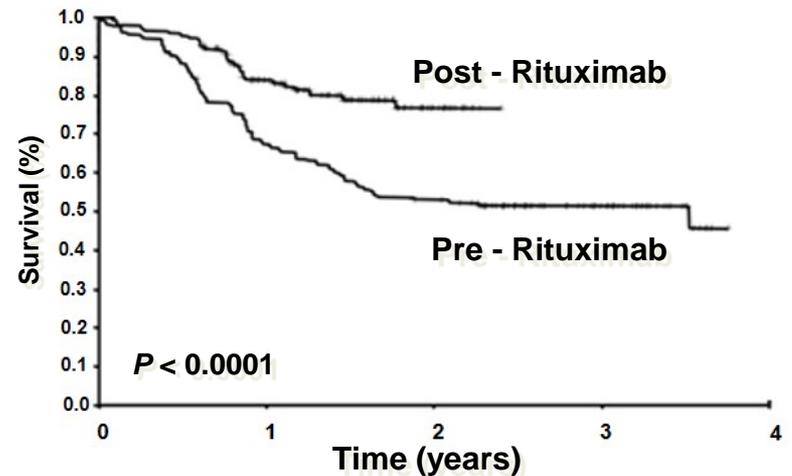
- Since 1997, rituximab (Rituxan[®]/MabThera[®]) has been approved for use in 135 countries worldwide
 - Over 4.4 million patients have been treated in clinical practice
- Approved standard of care (NCCN Guidelines) based on 20 years of clinical evaluation:
 - Well-characterized B-cell depleting mechanism of action
 - Prolonged PFS and OS for various types of B-cell malignancies
 - Well-established safety and efficacy profile
- Listed as an essential medicine by the World Health Organization (WHO)

Rituximab-based Therapy Has Changed the Course of DLBCL

At 10 years, the addition of rituximab to R-CHOP increased overall survival by 16%¹
(n=399)



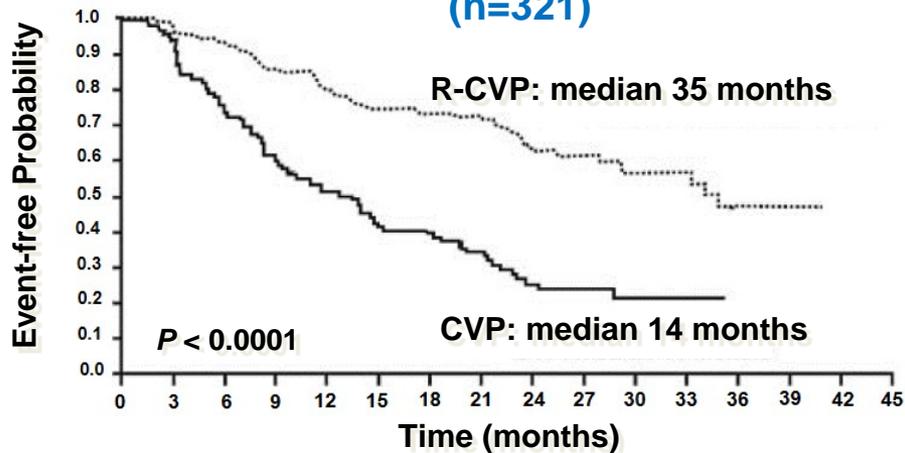
Overall survival by treatment era
all patients in British Columbia²
(n=292)



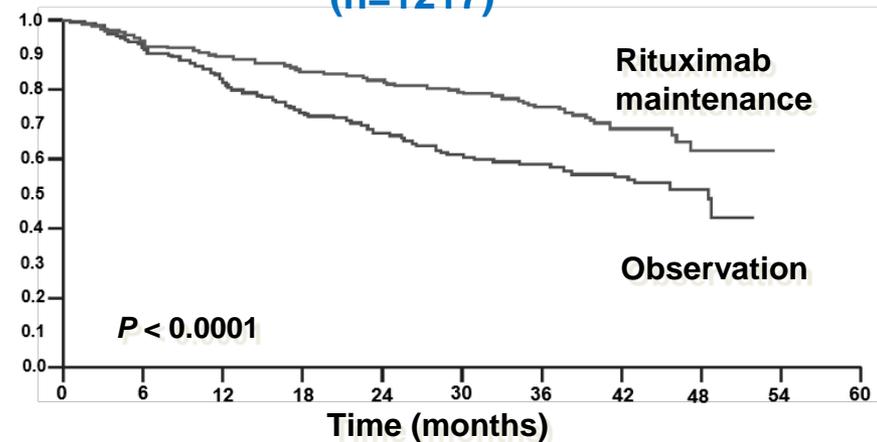
¹ Coiffier et al. Blood. 2010 Sep 23;116(12):2040-5. ² Sehn et al. J Clin Oncol. 2005;23(22):5027-5033.

Rituximab-based Therapy Has Changed the Course of Follicular Lymphoma

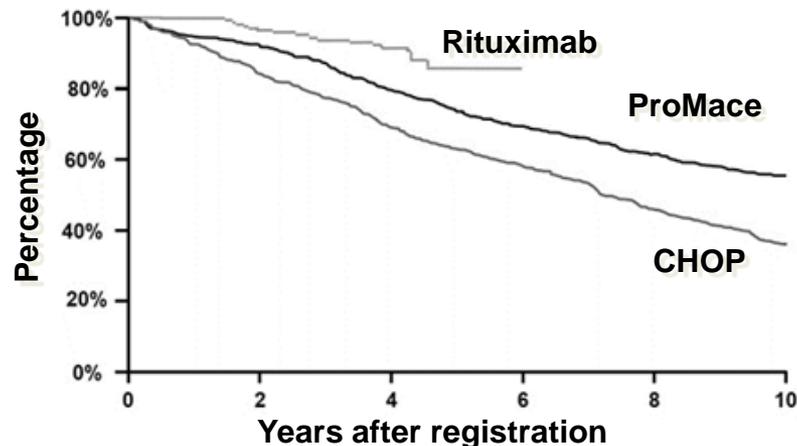
Event free survival, induction therapy¹
(n=321)



Event free survival, maintenance therapy²
(n=1217)

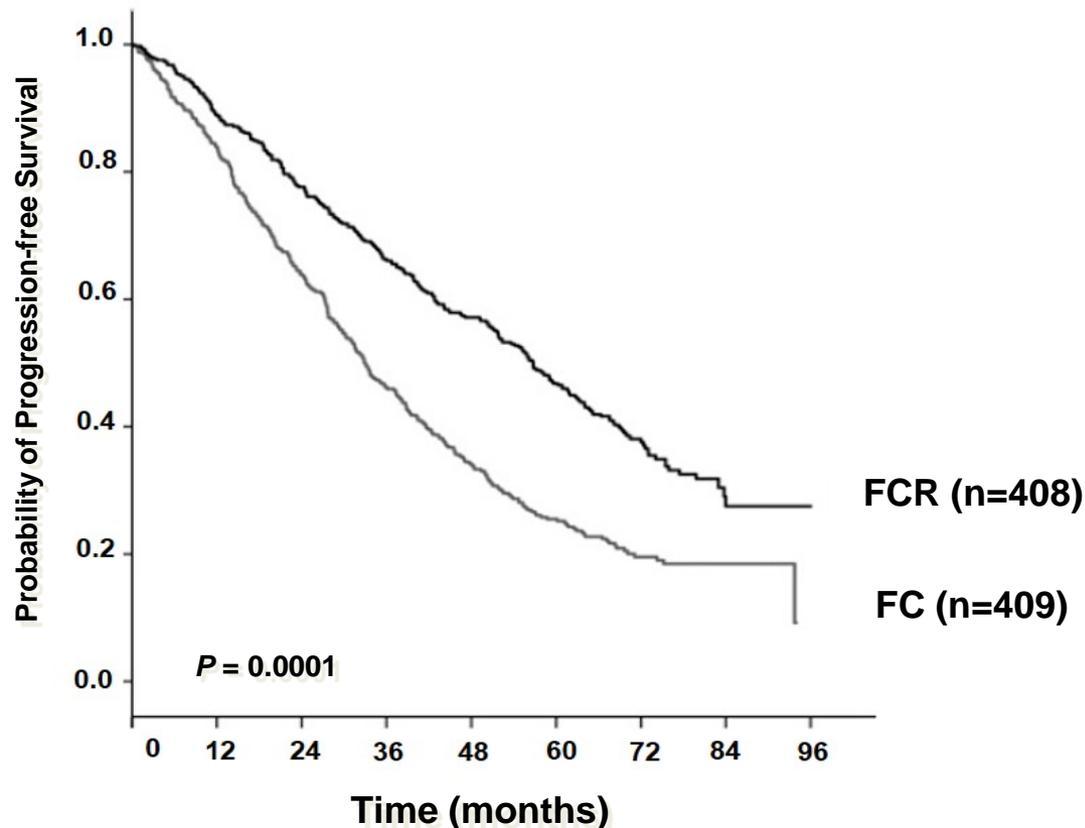


Overall survival by treatment, patients with FL³ (n=960)



Rituximab-based Therapy Has Changed the Course of Chronic Lymphocytic Leukemia

Progression free survival,
CLL8 Study at median FU of almost 6 years¹



¹ K Fischer et al. Blood. 2016 Jan 14;127(2):208-15.

Rituximab IV Administration

- Infusion time of 1.5 to 4 hours
- Preparation of patient, cannulation, serial vital sign measurement and observation
- Requires calculation of dose based on body surface area (BSA) for each patient
 - Dilution with fluid to a specific concentration
- Repeated cannulation over treatment course (up to 2.5 years) and lifetime

Comparison of Rituximab SC to IV

IV administration	SC administration
Patient-specific dosing based on height and weight	Fixed dosing for all patients (no dose calculation required)
Prepare and dilute into IV bag	Ready to use vial
Infusion time: 1.5 to 4 hours	Injection time: 5-7 minutes



Rituximab SC

Offers Meaningful Clinical Benefits

- Builds on the depth of experience of rituximab IV and provides an improved patient experience
- Offers a simpler, faster and less invasive treatment experience for patients
- Reduces the amount of time patients spend in clinic
- Patients prefer the SC route of administration
- Reduces the burden on healthcare providers, helping improve capacity in infusion centers

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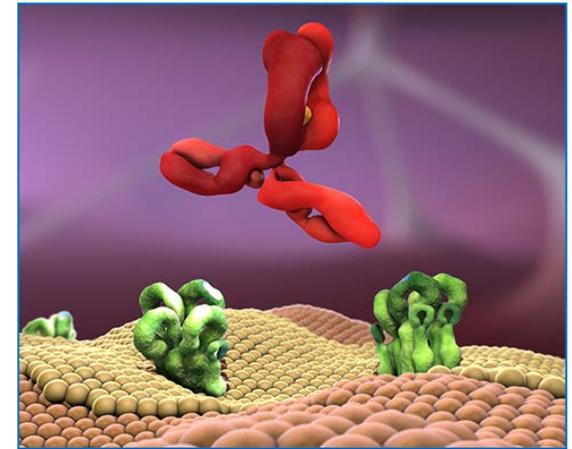
Clinical Development Program Objectives

The clinical program objectives comparing SC to IV formulations:

1. Establish non-inferior exposure
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Rituximab SC PK Bridging Approach

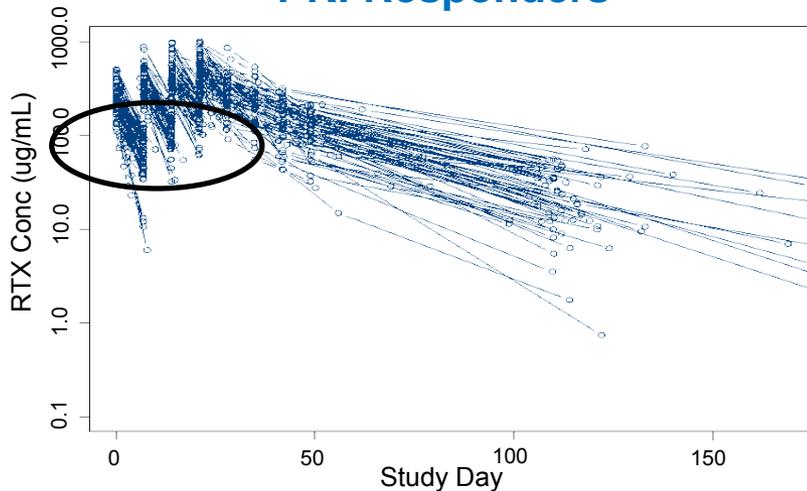
- Same anti-B-cell monoclonal antibody in both formulations (IV and SC)
- Rituximab exerts its anti-B-cell action upon binding to its target, CD20, on the surface of malignant B-cells
- By ensuring serum C_{trough} levels following rituximab SC are at least as high as IV then similar target occupancy may be expected
- Same anti-B-cell activity should be achieved, regardless of the route of administration



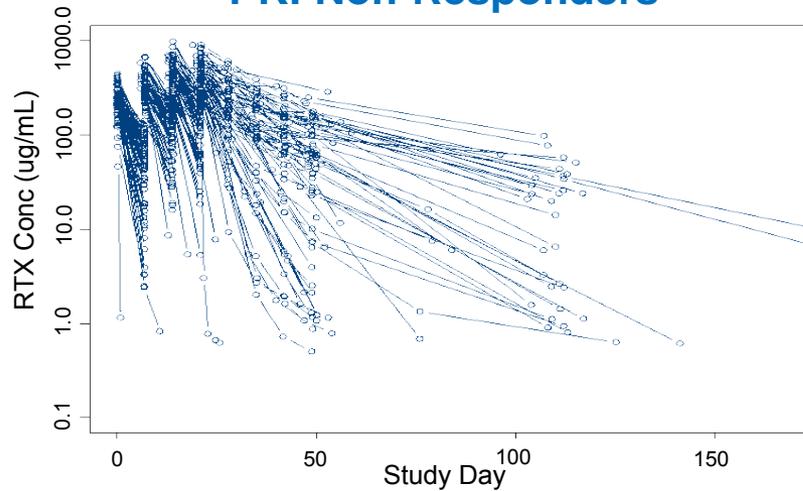
Rituximab IV

C_{trough} Association with B-cell Depletion

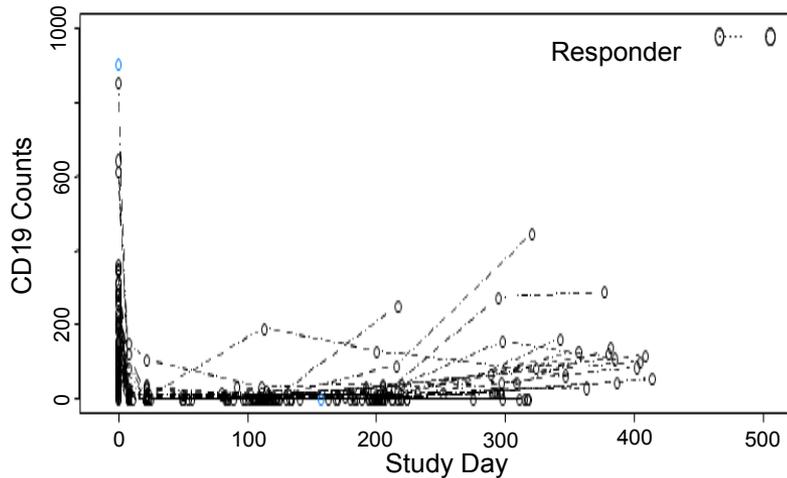
PK: Responders



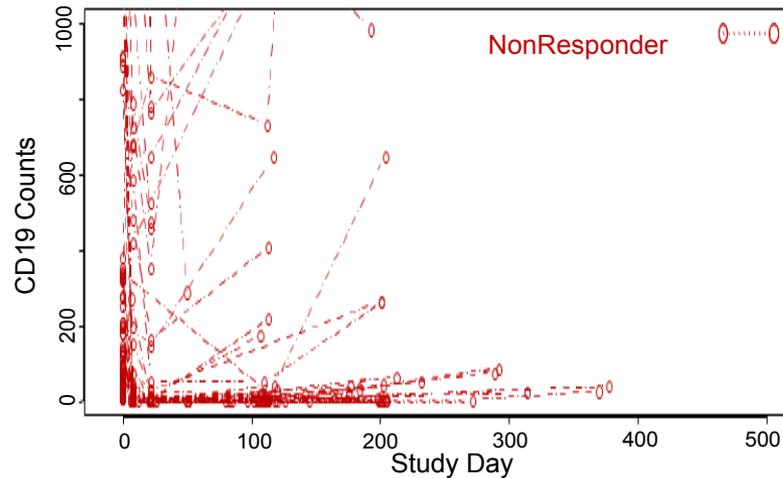
PK: Non-Responders



B-cells Depletion Profile: Responders



B-cells Depletion Profile: Non-Responders



Clinically Relevant PK Endpoints for Bridging

C_{trough} at steady-state (Primary PK endpoint)

- Considers mode of action
- Associated with clinical outcomes¹⁻⁹

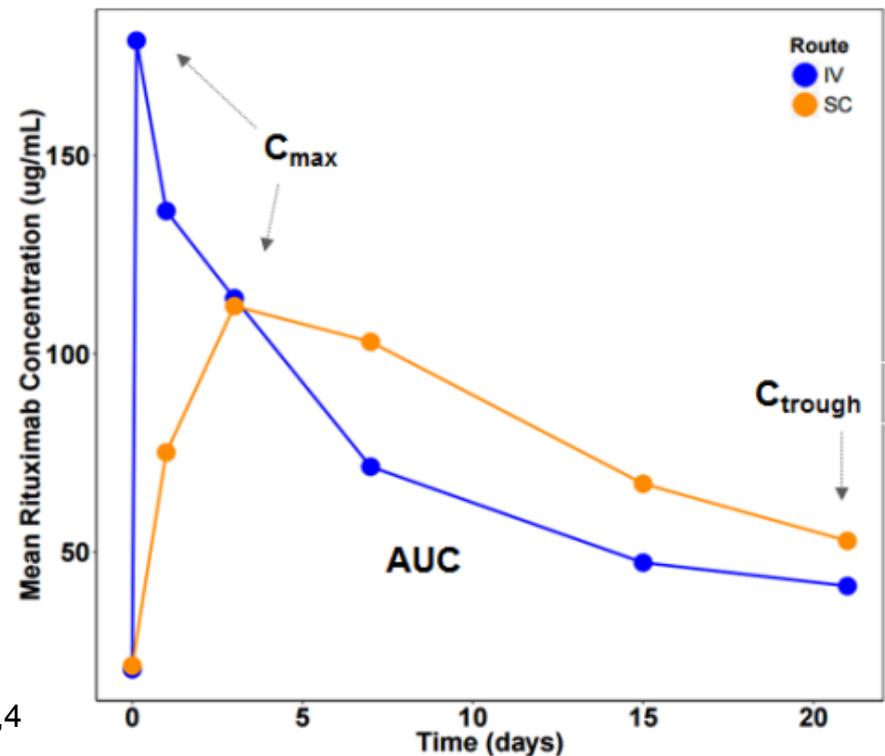
AUC at steady-state (Secondary PK endpoint)

- Provides exposure information over the course of the treatment cycle
- Correlates with C_{trough}

C_{max}

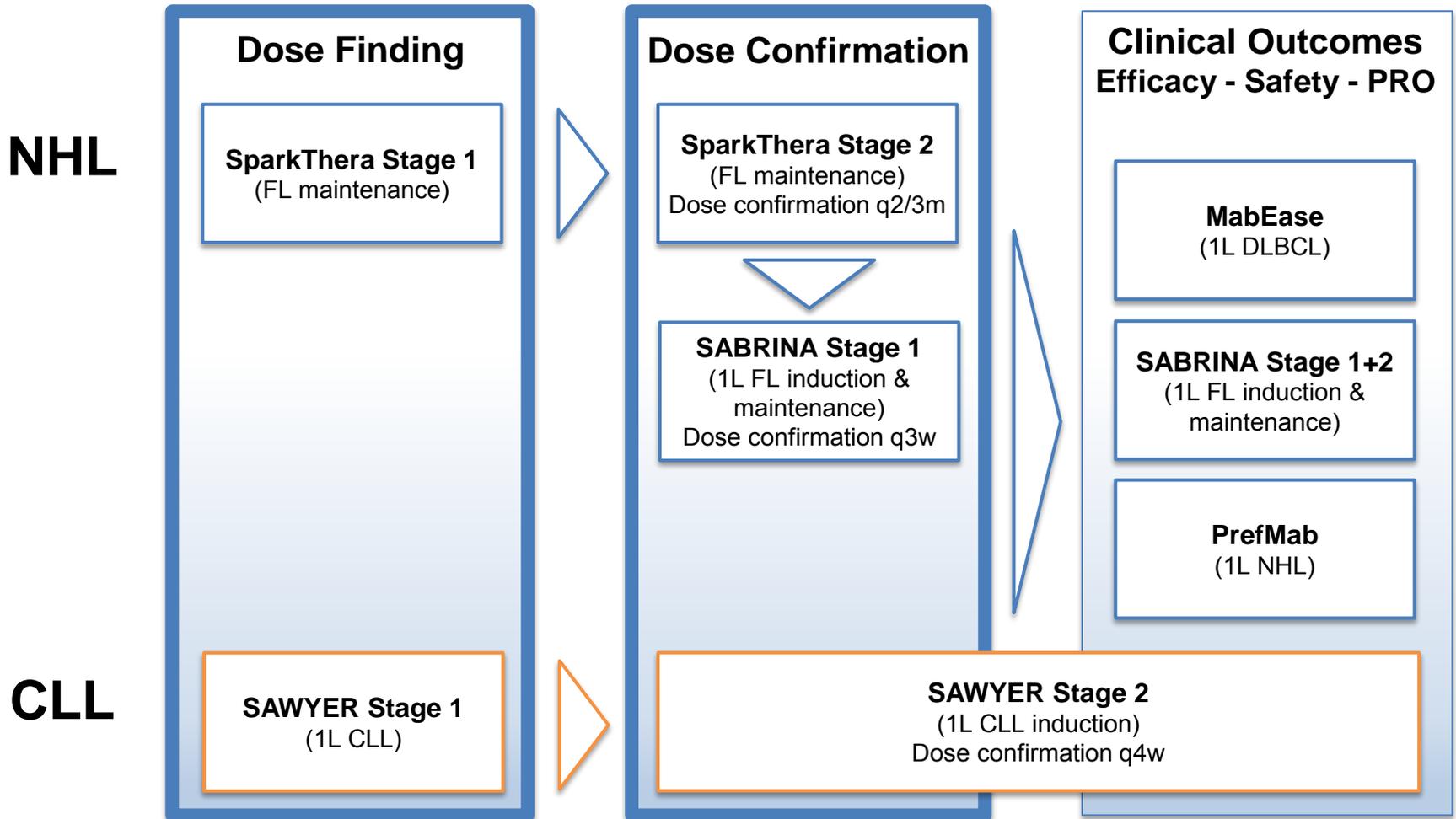
- C_{max} after IV is not subject to distribution and elimination effects
- Not clearly correlated with outcomes^{1,4}

Serum Concentration-Time Profile



Rituximab SC

Integrated PK-Clinical Bridging Development Plan

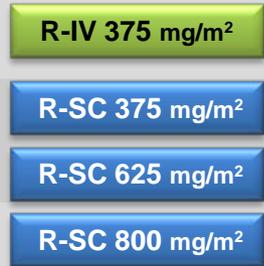


Rituximab SC Dose Finding Studies

To match rituximab IV NHL dose (375 mg/m²)

SparkThera Stage 1

FL receiving rituximab maintenance
n=124



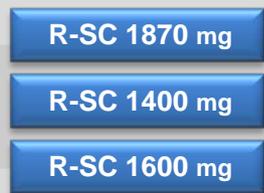
Complete 2 years

9
months
FU

To match rituximab IV CLL dose (500 mg/m²)

SAWYER Stage 1

CLL receiving R-FC
n=64



4 years
FU



Standard Rituximab IV
NHL or CLL



Rituximab SC

M&S* predicted non-inferiority of:

- Rituximab SC 1400 mg (NHL)
- Rituximab SC 1600 mg (CLL)

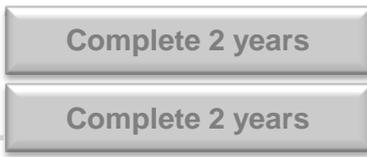
Rituximab SC Dose Confirmation Studies

PK Non-Inferiority of Rituximab SC Across Dosing Schedules

NHL dose at q2/3m (observed data and M+S)

SparkThera Stage 2

FL receiving rituximab maintenance
n=154

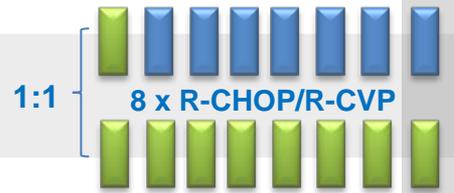


9 months FU

NHL dose at q3w (observed data)

SABRINA Stage 1

Untreated patients with FL
n=127

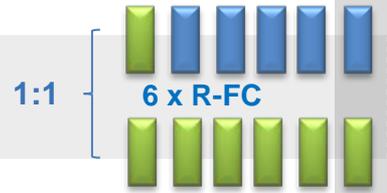


2 years FU

CLL dose q4w (observed data)

SAWYER Stage 2

Untreated patients with CLL
n=176



4 years FU

Standard Rituximab IV

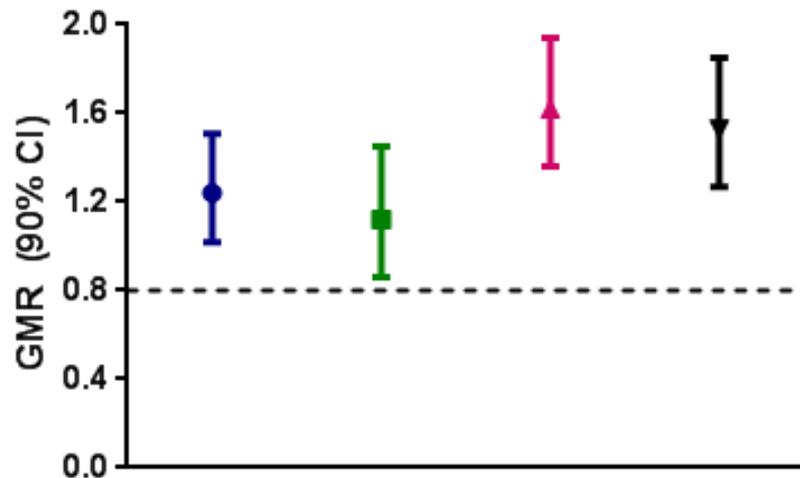
Rituximab SC Selected Doses

Assessment of steady-state C_{trough}^*

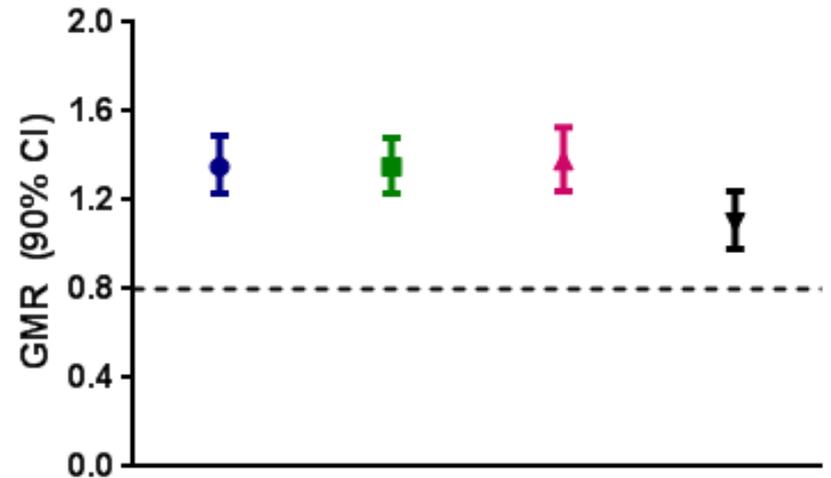
*Powered for non-inferiority using the standard lower 90% CI boundary (0.8) for the GMR of SC/IV [FDA Guidance]

Confirmed PK Non-Inferiority Across Established Dosing Schedules

C_{trough} (Primary Endpoint)



AUC (Key Secondary Endpoint)



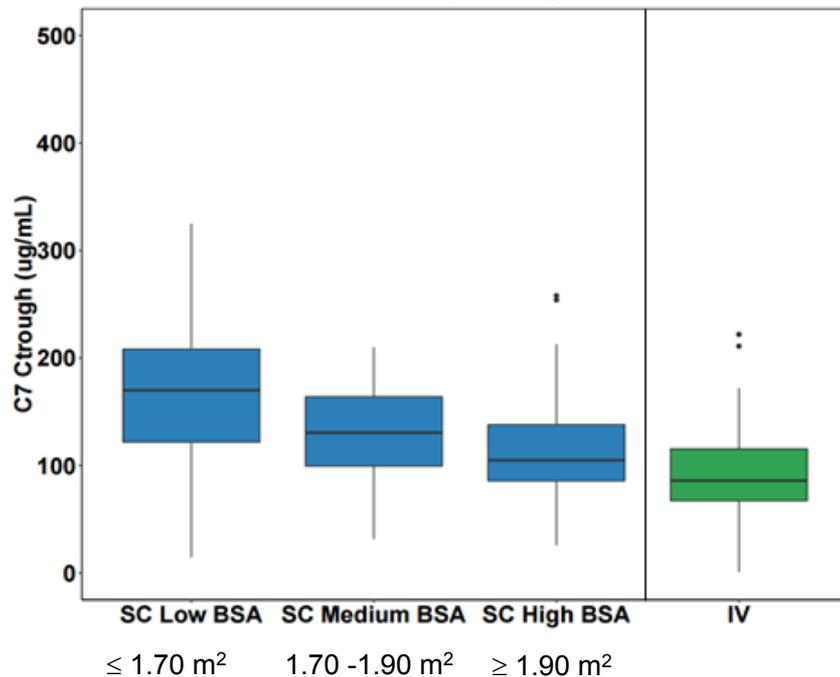
● SparkThera NHL (q2m)¹ ■ SparkThera NHL (q3m)¹ ▲ SABRINA NHL (q3w)² ▼ SAWYER CLL (q4w)²

GMR: geometric mean ratio for SC/IV
Lower boundary of the 90% CI of the GMR R^{SC}/R^{IV} pre-specified as non-inferiority margin

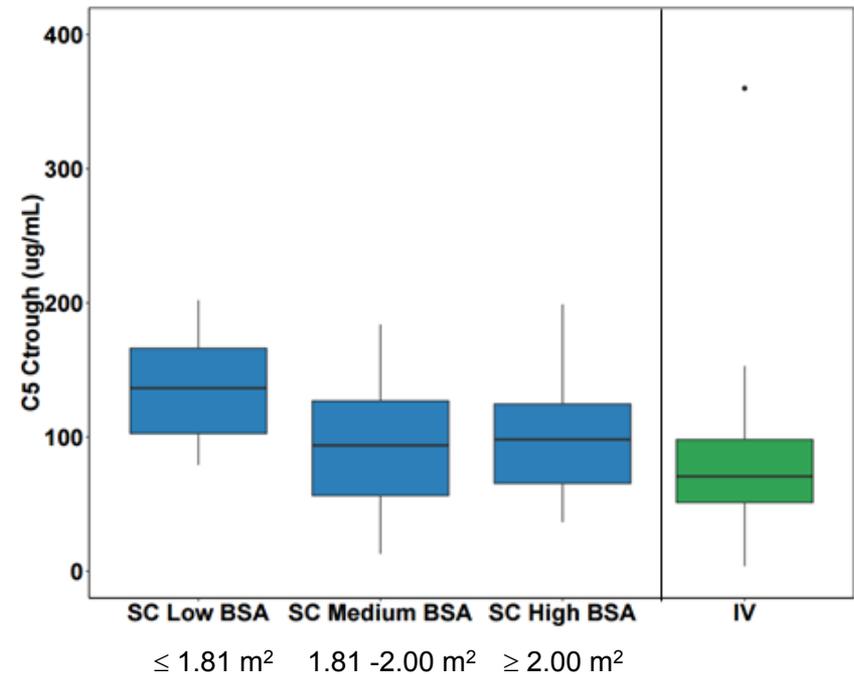
¹ Estimated by population PK; ² Calculation of observed data

Fixed SC Doses Demonstrate Non-Inferior Exposure Across the Entire BSA Range

SABRINA (NHL)



SAWYER (CLL)

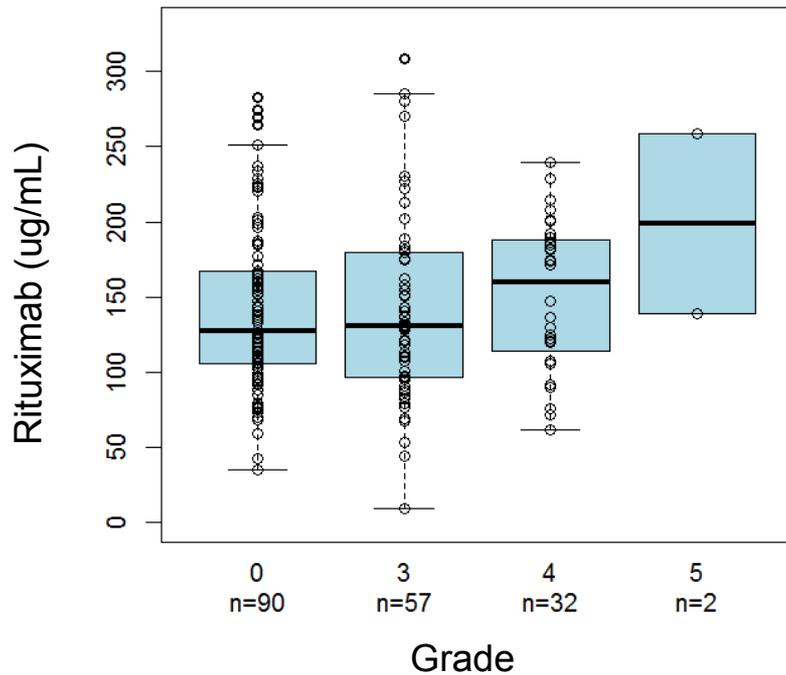


SABRINA BSA range 1.34-2.51 m²; SAWYER Stage 2 BSA range 1.41-2.42 m²

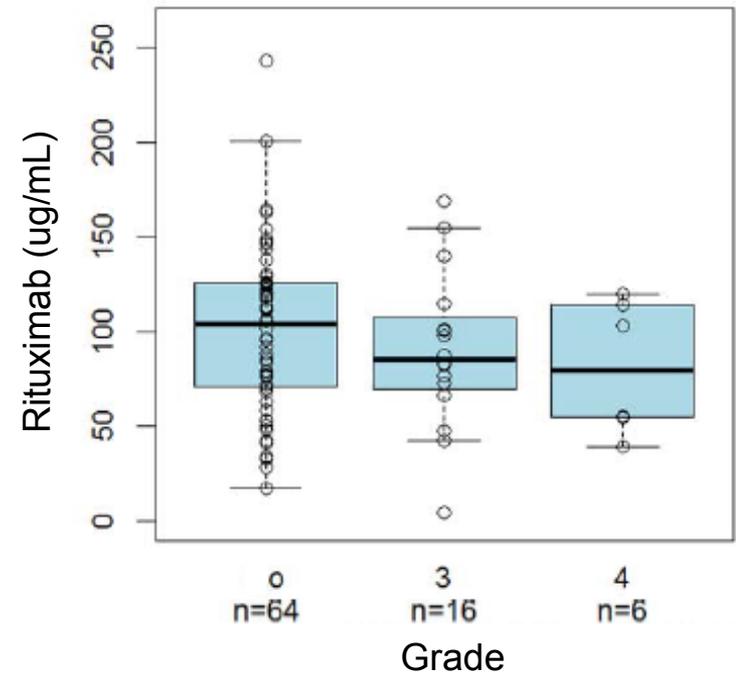
Boxplots: upper whisker extends from the hinge to the highest value that is within 1.5×IQR of the hinge, where IQR is the inter-quartile range, or distance between the first and third quartiles. The lower whisker extends from the hinge to the lowest value within 1.5×IQR of the hinge. Data beyond the end of the whiskers are outliers and plotted as points

Safety Events for Rituximab SC Not Correlated with Exposure (Grade ≥ 3 AE)

SABRINA (NHL)



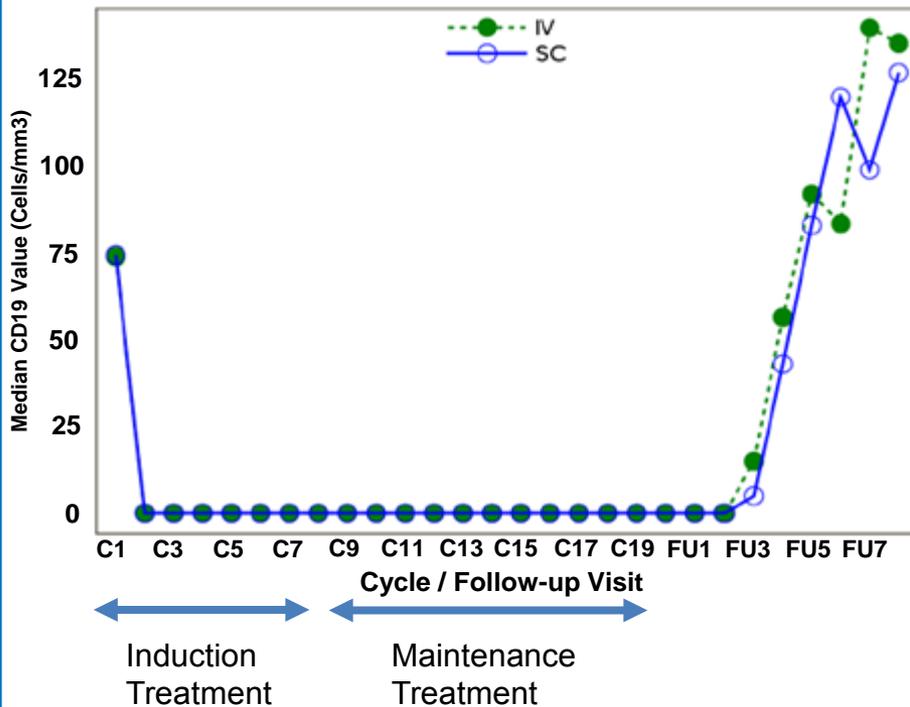
SAWYER (CLL)



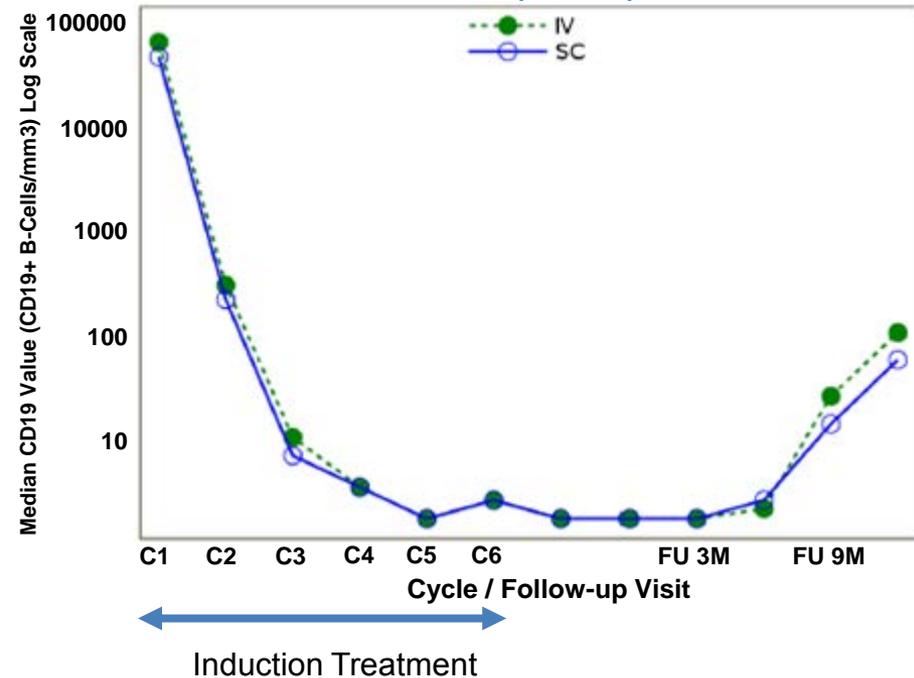
Boxes: inter-quartile range (IQR)
Black lines: Median values
Whiskers: 1.5*IQR
Circles: individual values

Pharmacodynamics: Highly Consistent B-cell Depletion/Repletion with Rituximab SC and IV

SABRINA (NHL)



SAWYER (CLL)



Clinical Pharmacology Summary

- PK bridging confirmed fixed SC doses which correspond to approved IV dosing schedules
- C_{trough} (and AUC) non-inferiority confirmed in both NHL and CLL for approved IV doses and schedules and across the entire BSA range
- Pharmacodynamic results demonstrate consistent and durable depletion and repletion kinetics of B-cells during the course of treatment

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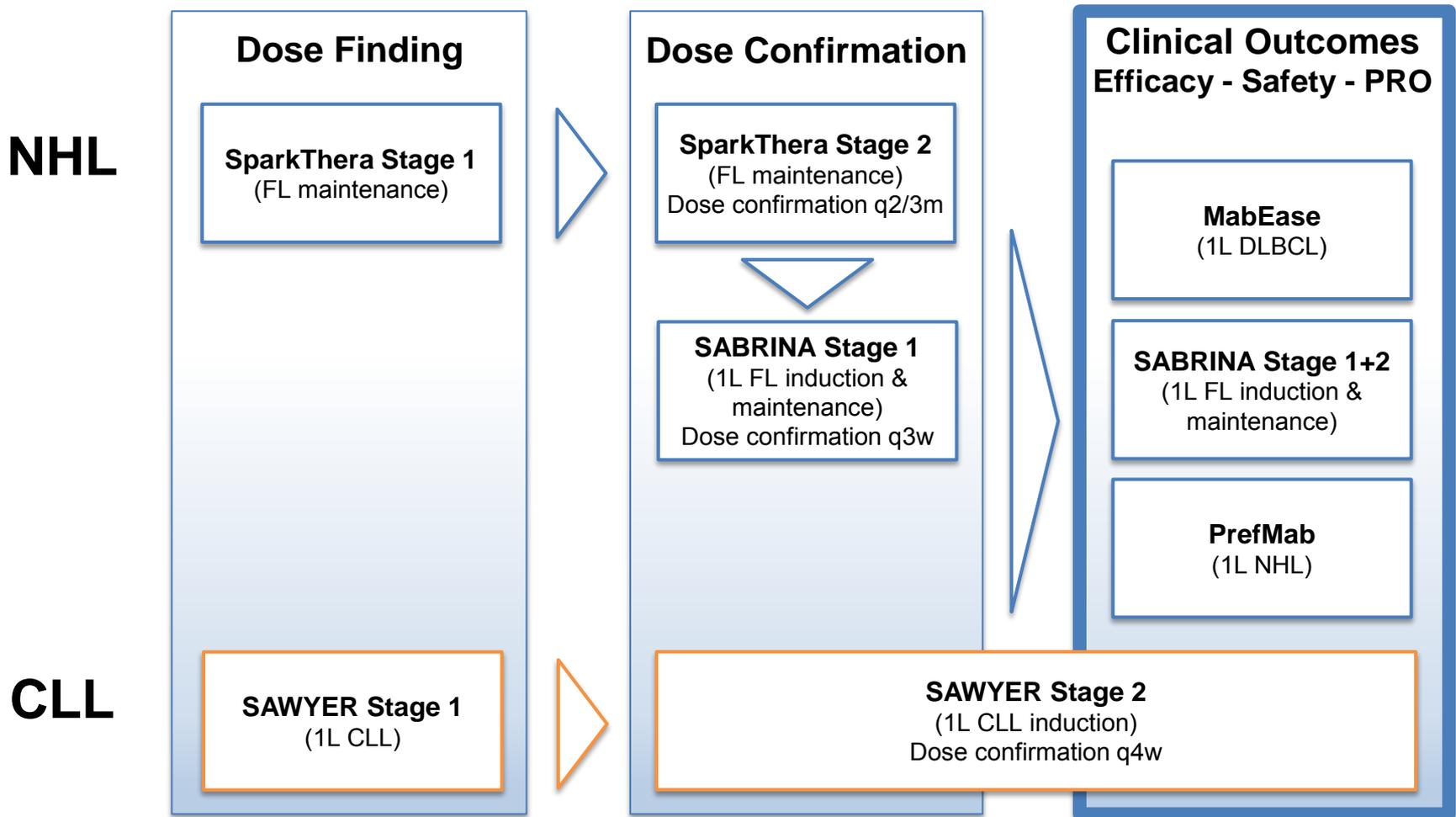
Clinical Development Program Objectives

The clinical program objectives comparing SC to IV formulations:

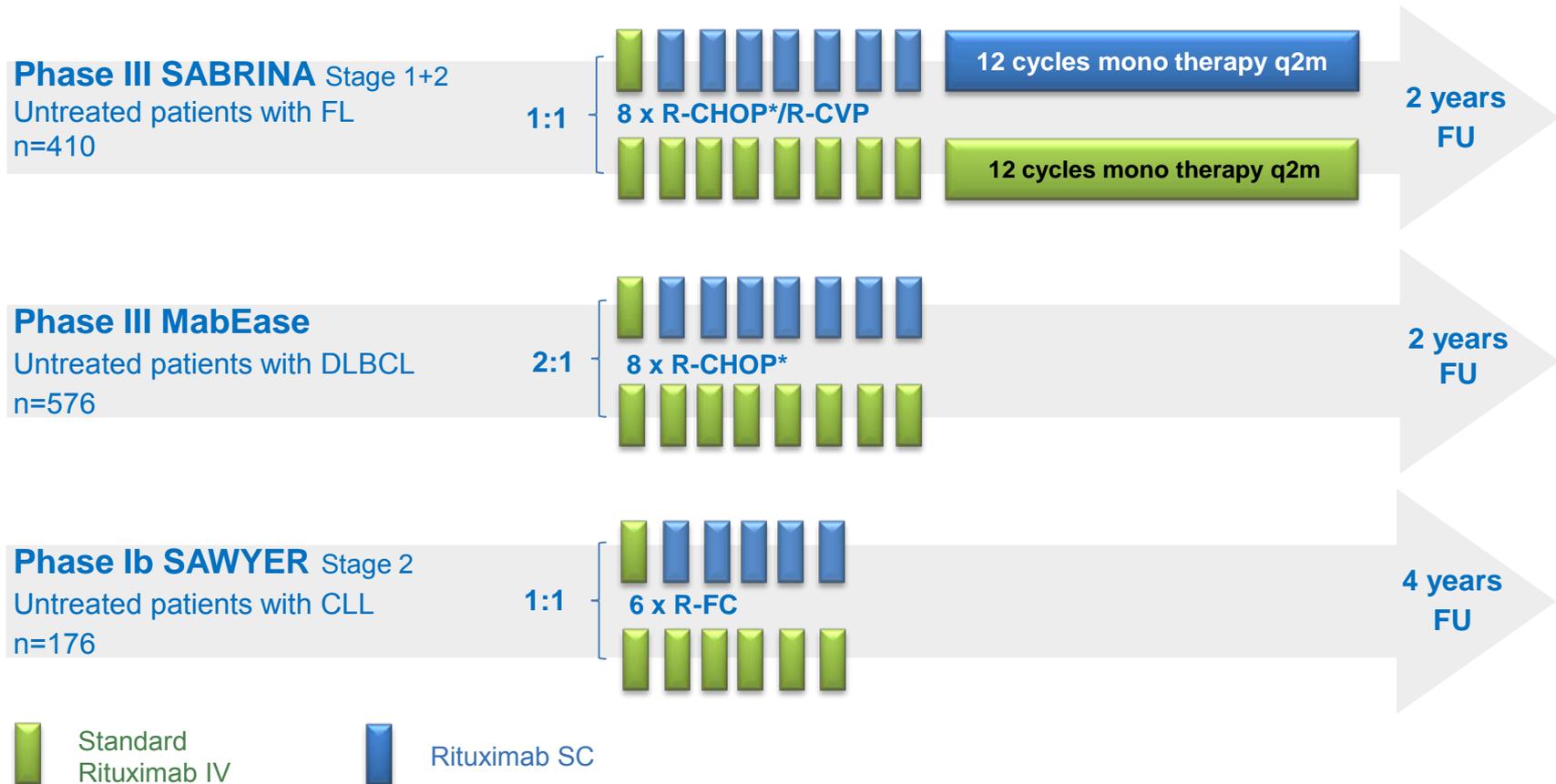
1. Establish non-inferior exposure through Pharmacokinetic (PK)-clinical bridging
2. Establish comparability of effectiveness and safety
3. Evaluate patient satisfaction/preference for route of administration

Rituximab SC

Integrated PK-Clinical Bridging Development Plan

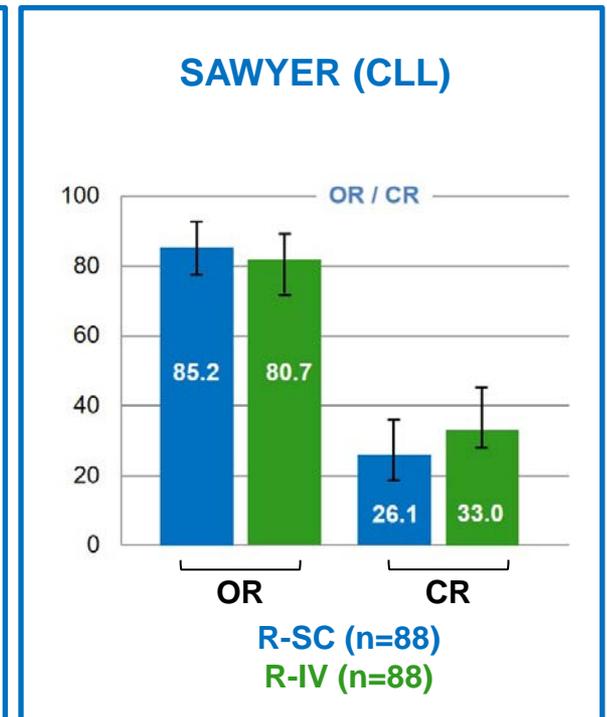
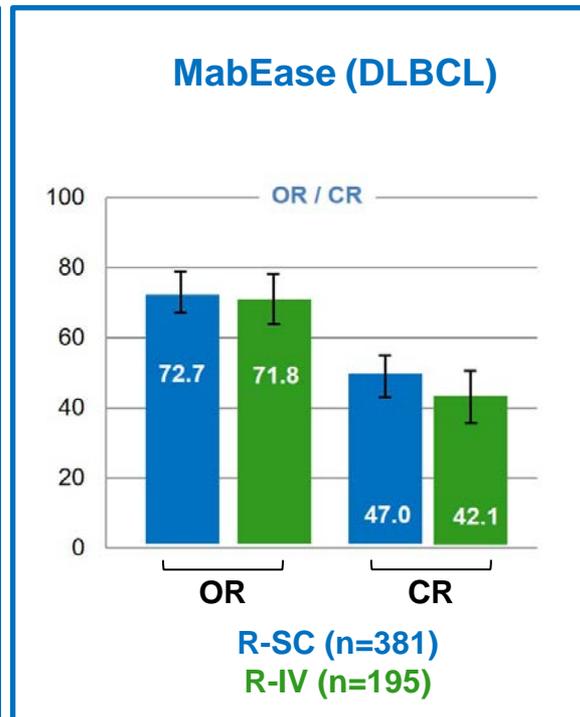
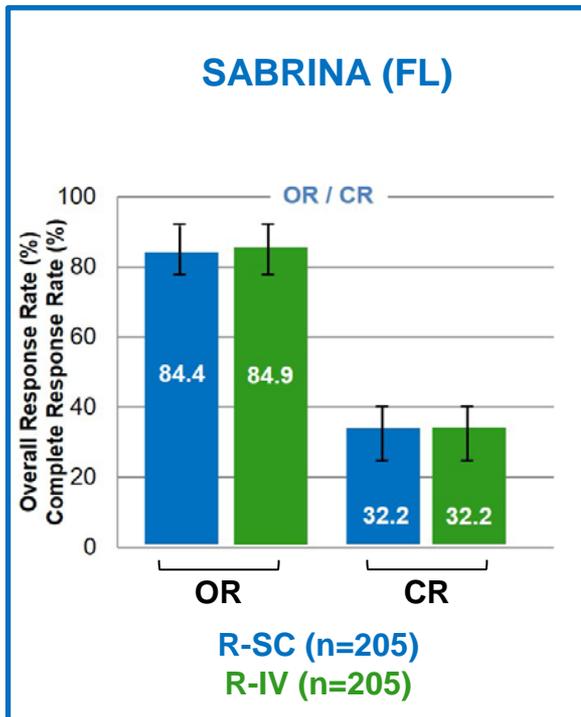


Studies to Investigate Efficacy



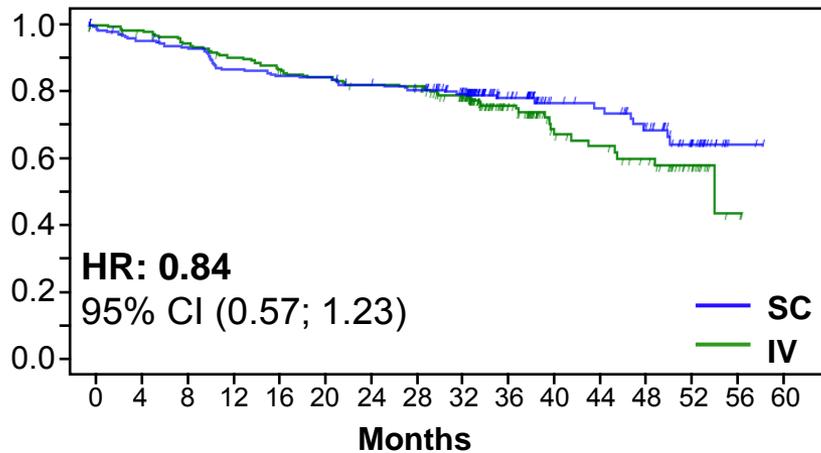
* 6-8 cycles of CHOP

Comparable OR and CR Rates End of Induction

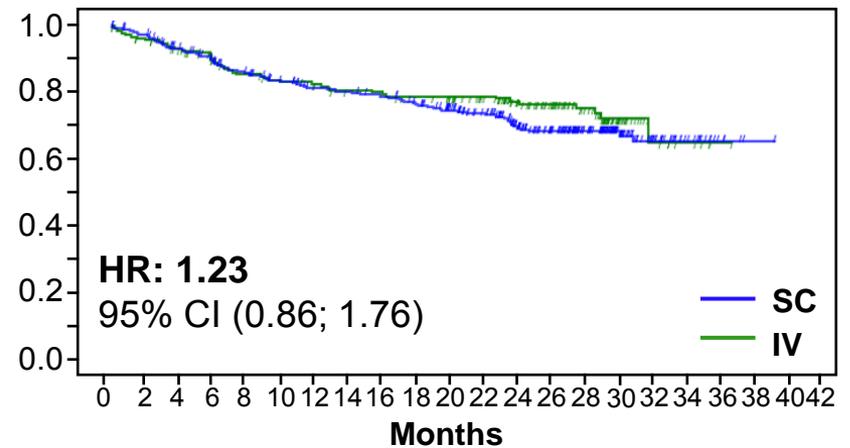


Comparable Progression-free Survival (PFS)

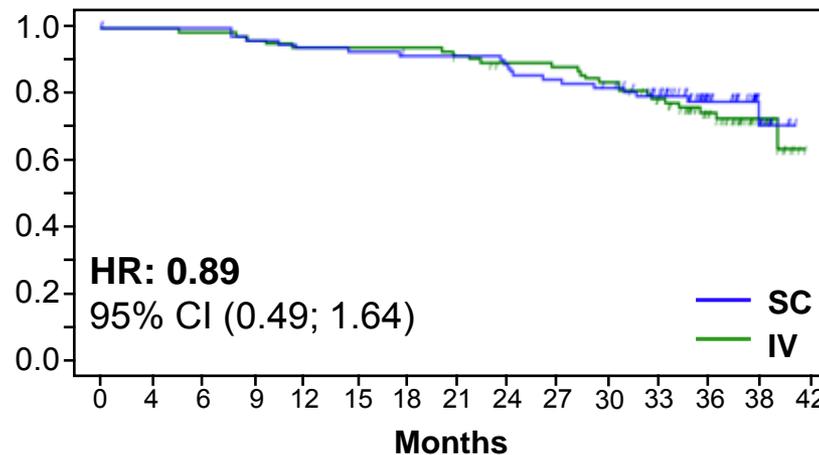
SABRINA (FL, median FU of ~37 months)



MabEase (DLBCL, median FU of ~28 months)

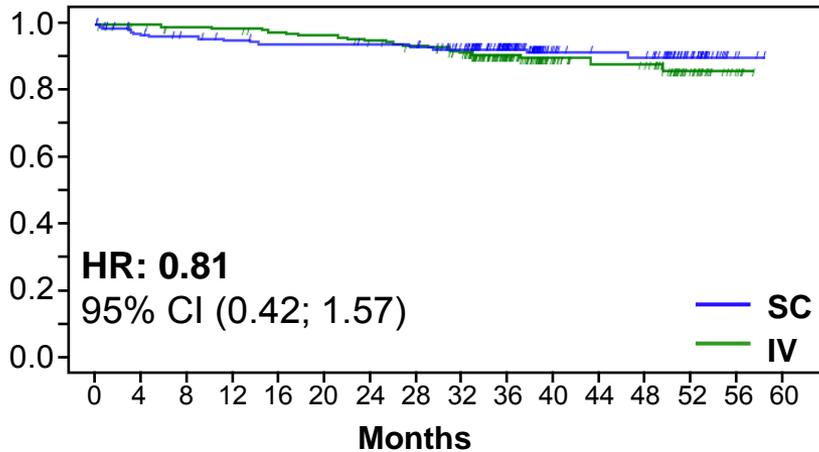


SAWYER (CLL, Median FU of ~36 months)

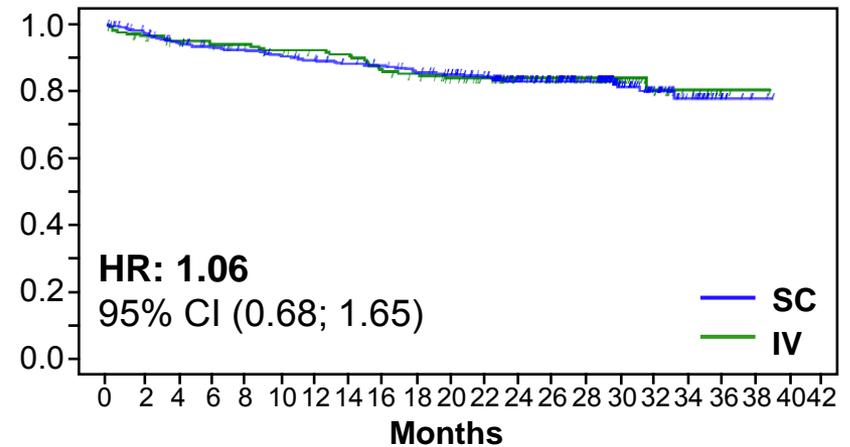


Comparable Overall Survival (OS)

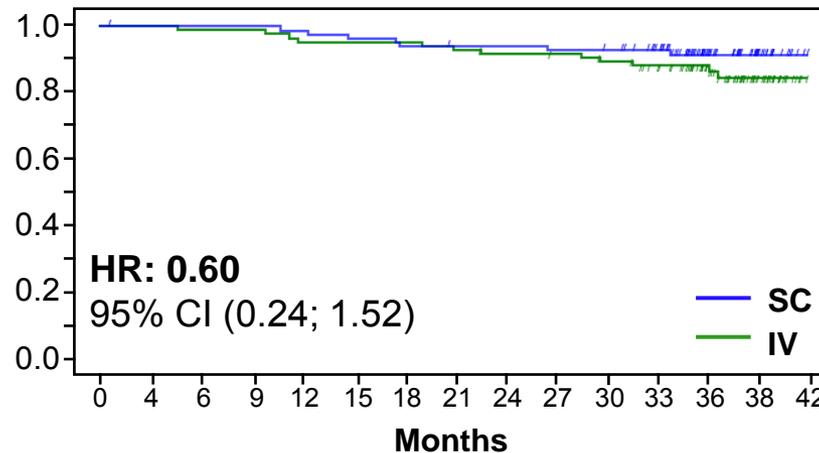
SABRINA (FL, median FU of ~37 months)



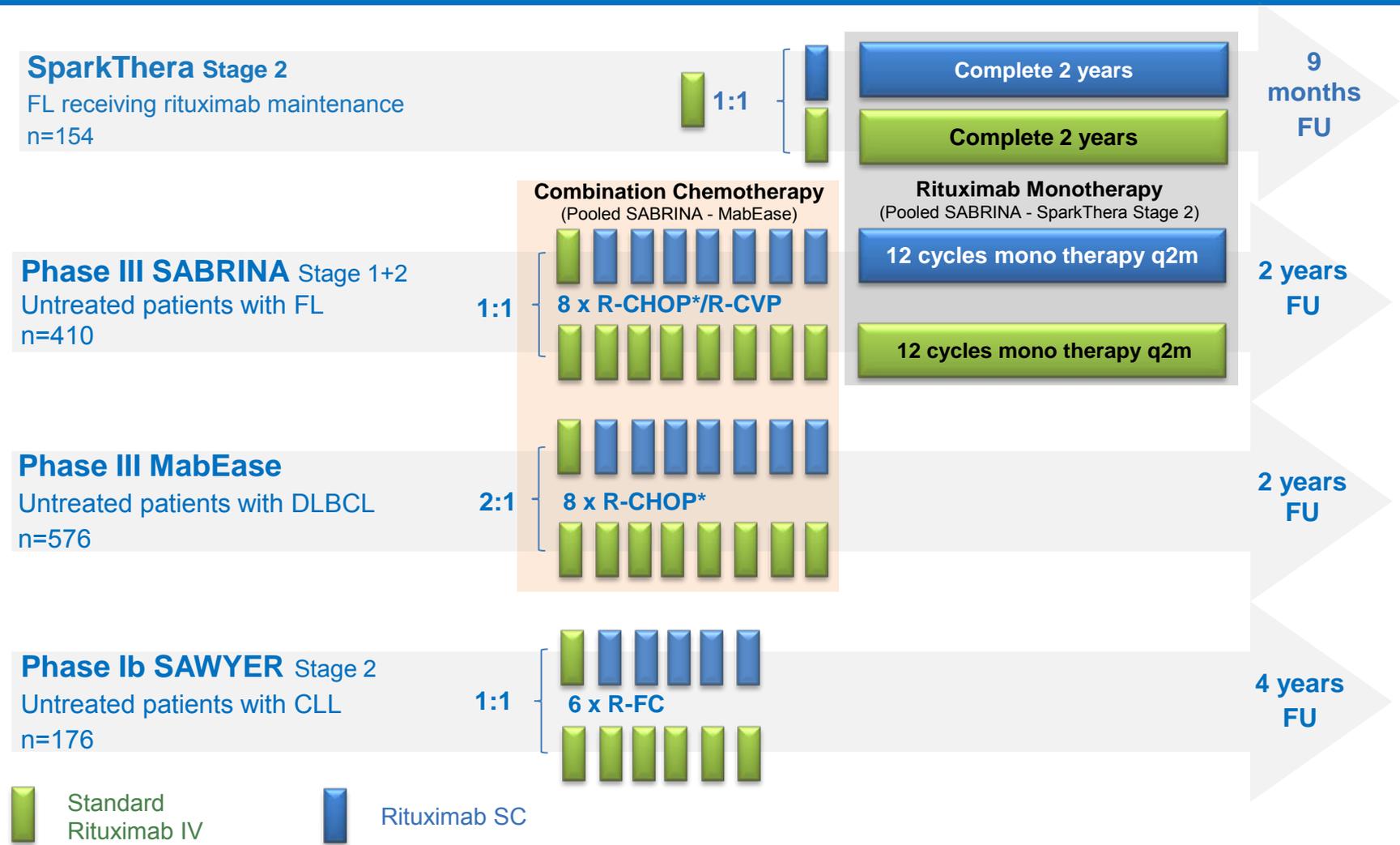
MabEase (DLBCL, median FU of ~28 months)



SAWYER (CLL, Median FU of ~36 months)



Studies to Investigate Safety



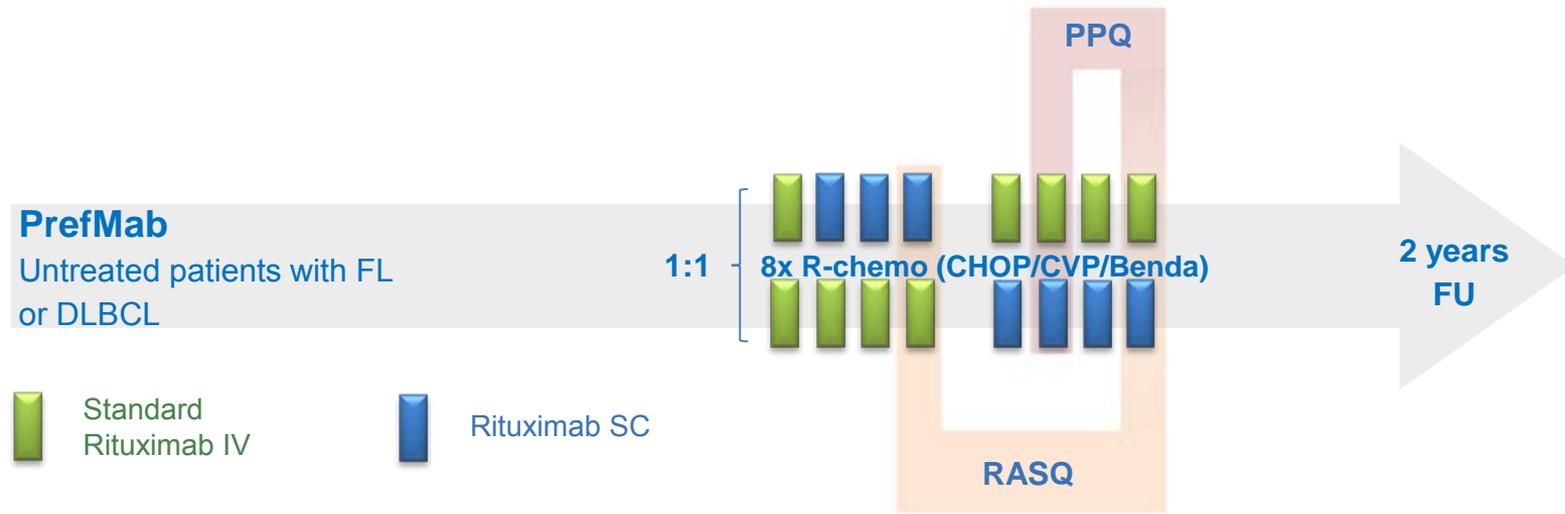
* 6-8 cycles of CHOP

Safety Comparison: Rituximab IV and SC

	NHL Combination Chemotherapy (Pooled SABRINA - MabEase)		NHL Rituximab Monotherapy (Pooled SABRINA-SparkThera)		CLL Combination Chemotherapy (SAWYER)	
	IV (n=413) No. (%)	SC (n=566) No. (%)	IV (n=255) No. (%)	SC (n=249) No. (%)	IV (n=89) No. (%)	SC (n=85) No. (%)
Any AE	380 (92)	533 (94)	208 (82)	202 (81)	81 (91)	82 (96)
Grade ≥ 3 AEs	208 (50)	322 (57)	73 (29)	67 (27)	63 (71)	59 (69)
SAEs	120 (29)	204 (36)	55 (22)	48 (19)	29 (33)	25 (29)
Deaths	42 (10)	65 (11)	14 (5)	9 (4)	4 (4)	5 (6)
AEs leading to deaths	19 (5)	34 (6)	9 (4)	3 (1)	2 (2)	2 (2)
AEs leading to treatment discontinuation	25 (6)	34 (6)	9 (4)	14 (6)	7 (8)	9 (11)
ARRs*	131 (32)	192 (34)	8 (3)	50 (20)	40 (45)	37 (44)

*Administration-related reactions: any AE within 24 hours after treatment and assessed by the investigator as causally related to rituximab IV or SC

Study to Investigate Patient Preference PrefMab (NHL; n=743)



PPQ: Patient Preference Questionnaire

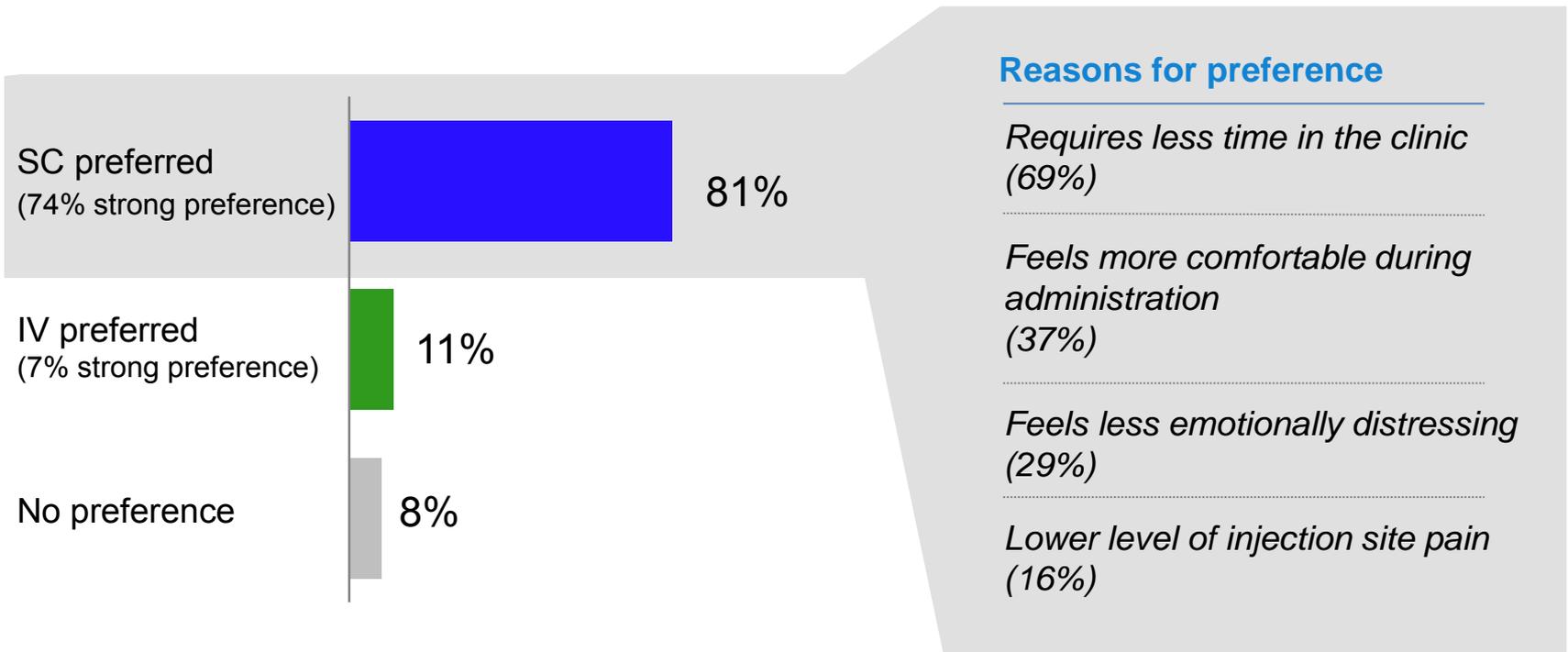
3 simple questions, requiring straight forward decisions

RASQ: Rituximab Administration Satisfaction Questionnaire

20-item questionnaire capturing 5 factors contributing to patients' satisfaction with the rituximab administrations (IV or SC)

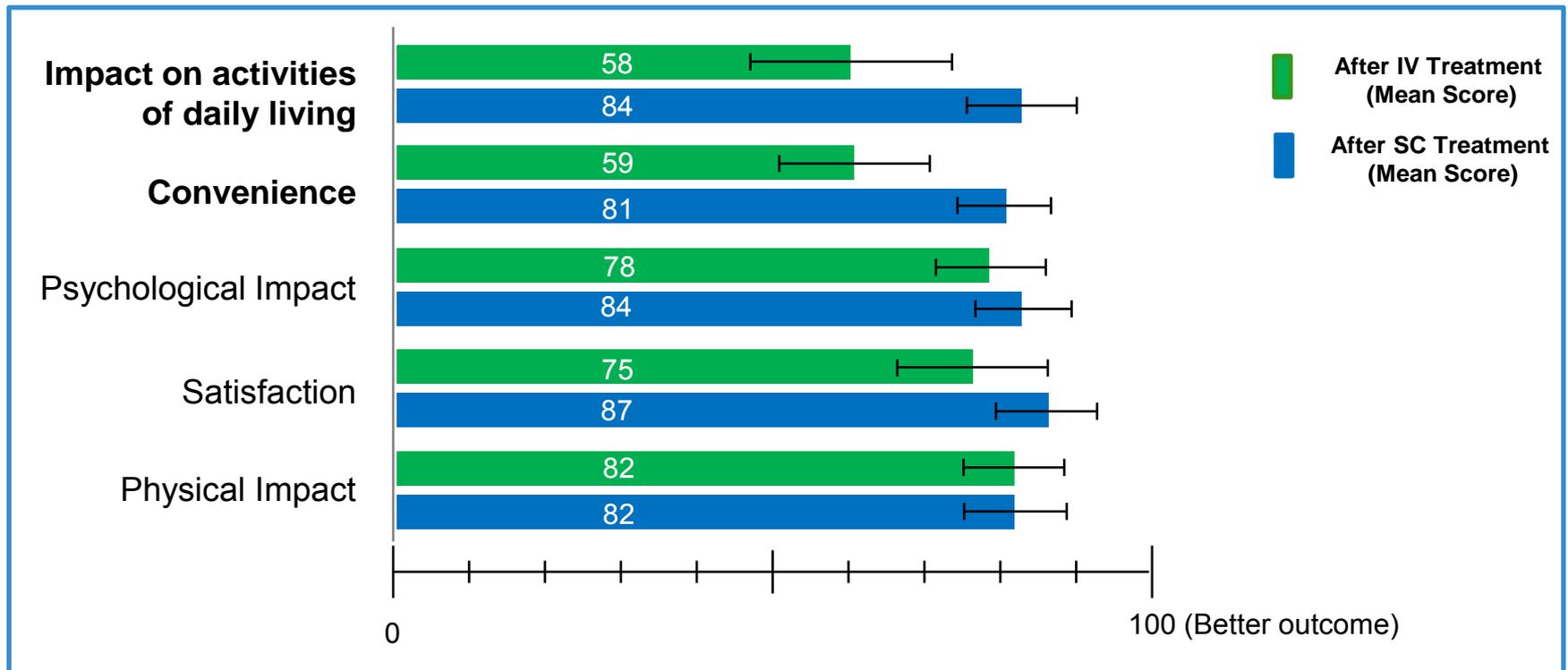
Compelling Patient Preference for Rituximab SC

PrefMab (NHL): PPQ Results at Cycle 8



RASQ Results Support the PPQ Results

PrefMab (NHL)



Rituximab SC Clinical Development Summary

- Builds on the extensive experience with rituximab IV
- Large program enrolling 2250 patients into 5 studies (1579 treated with rituximab SC) demonstrating:
 - Non-inferior exposure after rituximab SC
 - Comparable efficacy of rituximab SC and IV, consistent across 3 randomized controlled studies
 - Comparable safety of rituximab SC and IV
 - Compelling patient preference for rituximab SC

Rituximab SC Post Approval Experience

- Comparability of the safety profile has been further confirmed by post-approval experience
 - First approval in 2014
 - 34,179 patient exposures*
 - No new safety signals

Conclusion

- Rituximab SC reduces the treatment burden for patients
- Rituximab SC has a positive benefit risk profile comparable to that of rituximab IV
- Substantial evidence supports the approval of rituximab SC as treatment option for patients with:
 - Follicular lymphoma (FL)
 - Diffuse large B-cell lymphoma (DLBCL)
 - Chronic lymphocytic leukemia (CLL)

BACK-UP

NHL Pooled Safety Analyses

Adverse Events, Grade ≥ 3 Adverse Events, and Serious Adverse Events by Subgroups (BSA) for NHL

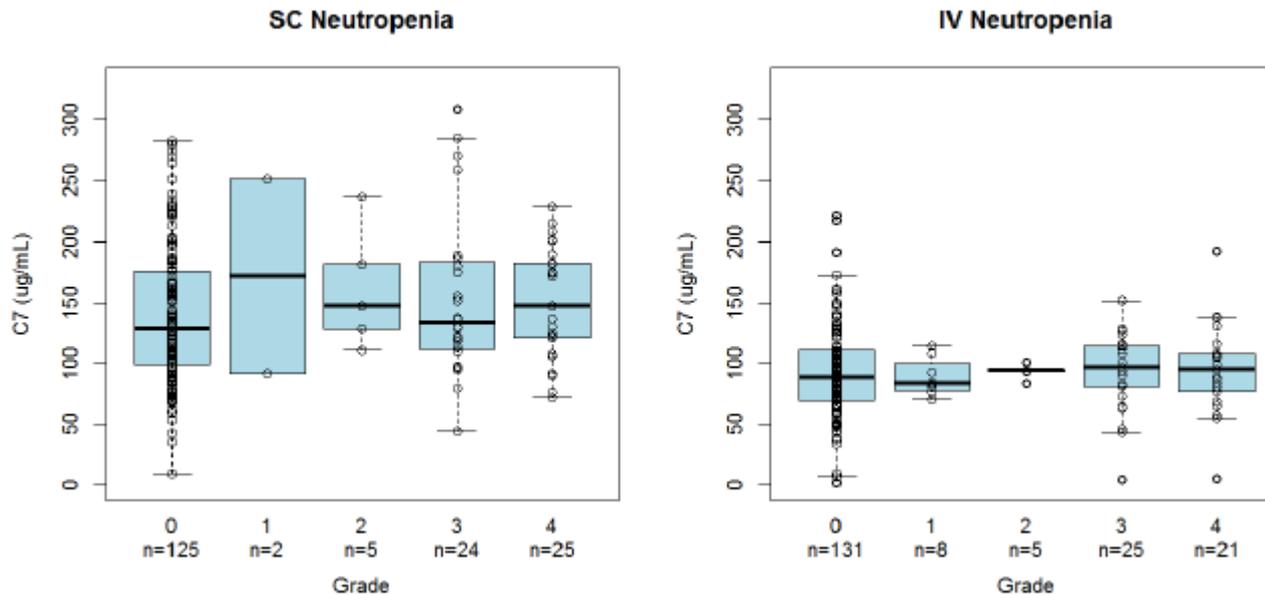
BSA subgroup	Combination Chemotherapy (Pooled SABRINA - MabEase)		Rituximab Monotherapy (Pooled SABRINA - SparkThera Stage 2)	
	IV n/N (%)	SC n/N (%)	IV n/N (%)	SC n/N (%)
Patients with at least one AE				
Low	122/131 (93)	206/217 (95)	71/80 (89)	82/102 (80)
Medium	131/147 (89)	157/169 (93)	72/91 (79)	57/72 (79)
High	127/135 (94)	170/180 (94)	65/84 (77)	63/75 (84)
Patients with at least one Grade≥ 3 AE				
Low	67/131 (51)	145/217 (67)	23/80 (29)	25/102 (25)
Medium	79/147 (54)	93/169 (55)	27/91 (30)	22/72 (31)
High	62/135 (46)	84/180 (47)	23/84 (27)	20/75 (27)
Patients with at least one serious AE (SAE)				
Low	39/131 (30)	90/217 (41)	16/80 (20)	19/102 (19)
Medium	52/147 (35)	63/169 (37)	23/91 (25)	14/72 (19)
High	29/135 (21)	51/180 (28)	16/84 (19)	15/75 (20)

Treatment Discontinuations or Deaths by BSA

	Combination Chemotherapy (Pooled SABRINA - MabEase)		Rituximab Monotherapy (Pooled SABRINA - SparkThera Stage 2)	
	IV N=413 n (%)	SC N=566 n(%)	IV N=255 n (%)	SC N=249 n (%)
AEs Leading to Treatment Discontinuation				
Total Pts with at least one AE (all)	25 (6)	34 (6)	9 (4)	14 (6)
Low BSA	9 (7)	17 (8)	4 (5)	4 (4)
Medium BSA	8 (5)	8 (5)	2 (2)	7 (10)
High BSA	8 (6)	9 (5)	3 (4)	3 (4)
Adverse Events Leading to Death				
Total Pts with at least one AE (All)	19 (5)	34 (6)	9 (4)	3 (1)
Low BSA	8 (6)	20 (9)	4 (5)	2 (2)
Medium BSA	10 (7)	9 (5)	2 (2)	1 (1)
High BSA	1 (1)	5 (3)	3 (4)	0

SABRINA: Neutropenia

Cycle 2 Onwards



Median values are designated by black lines in the center of the boxes

Boxes: inter-quartile range (IQR)

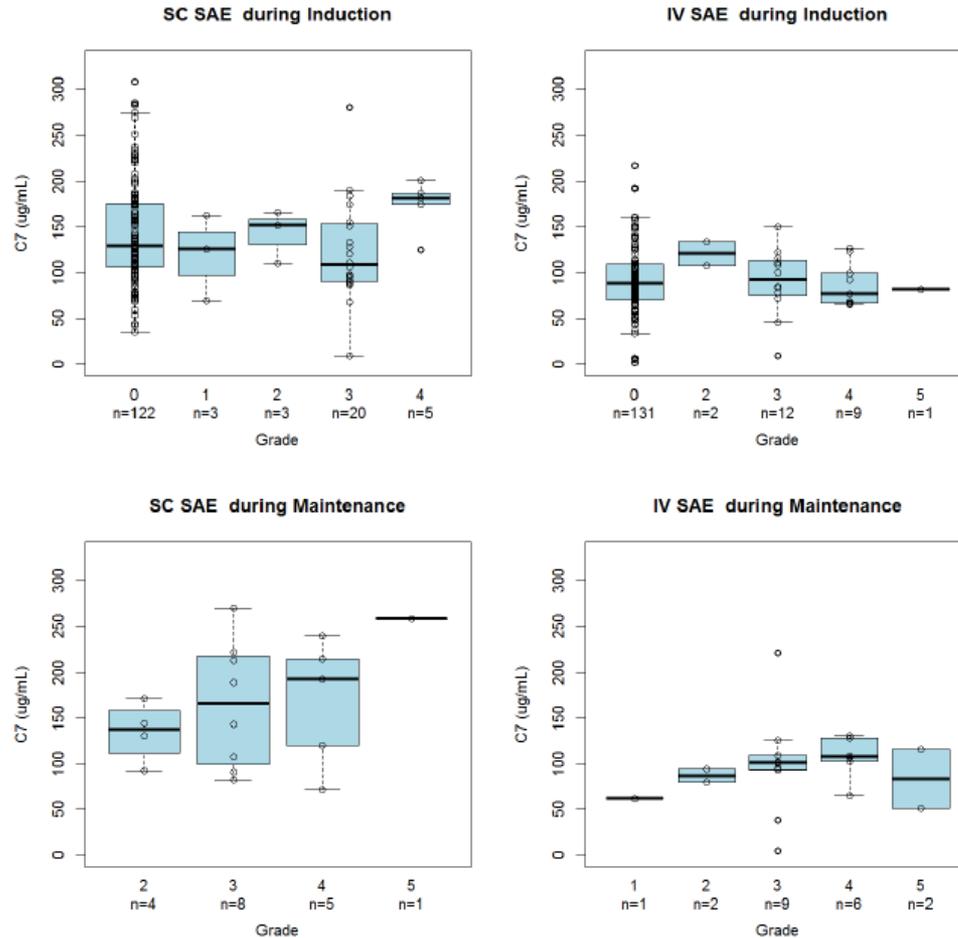
Whiskers represent 1.5*IQR

Circles represent individual values

No evidence of relationship between grades of events and exposure

SABRINA: SAE for Induction and Maintenance Separately

Cycle 2 Onwards

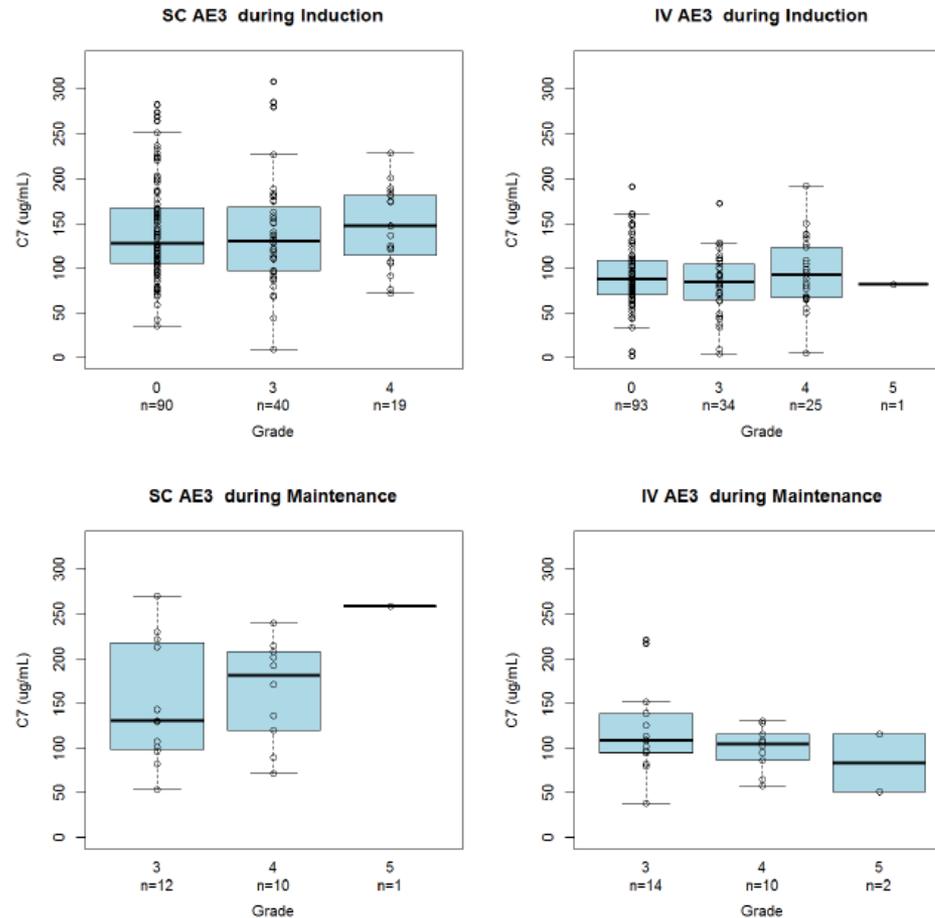


Median values are designated by black lines in the center of the boxes
Boxes: inter-quartile range (IQR)
Whiskers represent 1.5*IQR
Circles represent individual values

No evidence of relationship between grades of events and exposure

SABRINA: Grade ≥ 3 AE for Induction and Maintenance Separately

Cycle 2 Onwards



No evidence of relationship between grades of events and exposure