

# Rituximab SC

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Presentation to the  
Oncologic Drugs Advisory Committee

March 29, 2017

Genentech

# Rituximab SC

## Development Rationale

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Nancy Valente, MD  
Head of Global Hematology Development  
Genentech

# Rationale for Rituximab SC Development

## Decreasing Patient Treatment Burden

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- 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

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- 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

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- 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<sup>®</sup> recombinant (hyaluronidase human injection), approved in 2005 - >1 million doses administered

# Regulatory Framework

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- 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

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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

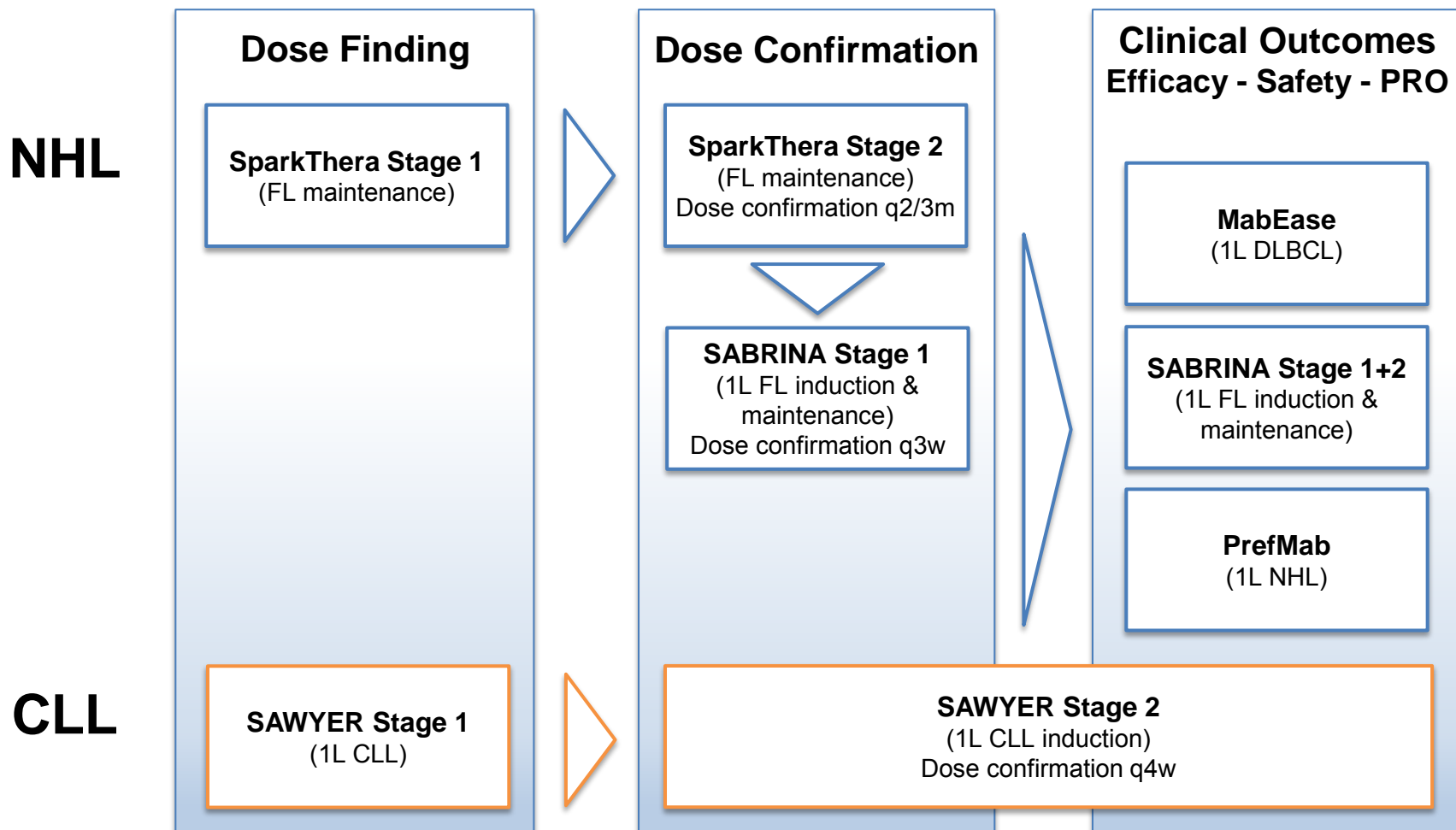
2250 Patients Enrolled (1579 Patients Treated with Rituximab SC)

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

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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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## **Rituximab SC Development Rationale**

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*Genentech*

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## **Rituximab SC Clinical Perspective**

**Andrew Davies, BSc BM PhD FRCP**

Associate Professor in Medical Oncology,  
University of Southampton, UK

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## **Rituximab SC Clinical Pharmacology**

**Peter Morcos, PharmD**

Clinical Pharmacologist  
*Genentech*

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## **Rituximab SC Clinical Development Concluding Remarks**

**Axel Boehnke, MD**

Global Development Team Leader  
*Genentech*

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# Consultants

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## John Gericitano, MD, PhD

Clinical Director, Lymphoma Outpatient Services, Lymphoma Service/Developmental Therapeutics Clinic, Department of Medicine, Memorial Sloan-Kettering Cancer Center

## Donald Mager, PharmD, PhD

Professor of Pharmaceutical Sciences,  
University at Buffalo, SUNY

# Rituximab SC

## Clinical Perspective

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Andrew Davies, BSc BM PhD FRCP

Associate Professor in Medical Oncology,  
University of Southampton, UK

# Disclosures

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- **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

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- ~72,000 new NHL cases each year and ~570,000 patients living with the disease in the US<sup>1</sup>
- ~19,000 new cases of CLL, ~120,000 living with disease in the US<sup>1,2</sup>
- 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

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

<sup>2</sup> Jain N et al, Blood 2016

# Rituximab

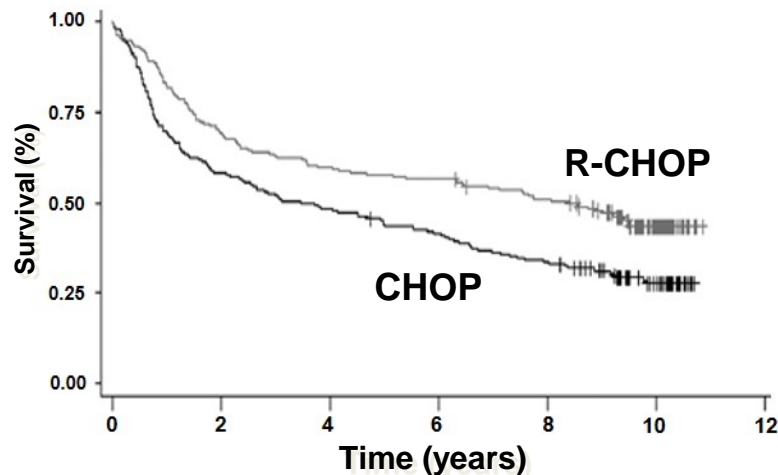
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- Since 1997, rituximab (Rituxan®/MabThera®) has been approved for use in 135 countries worldwide
  - Over 4.4 million patients have been treated in clinical practice
- Approved standard of care (NCCN Guidelines) based on 20 years of clinical evaluation:
  - 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)

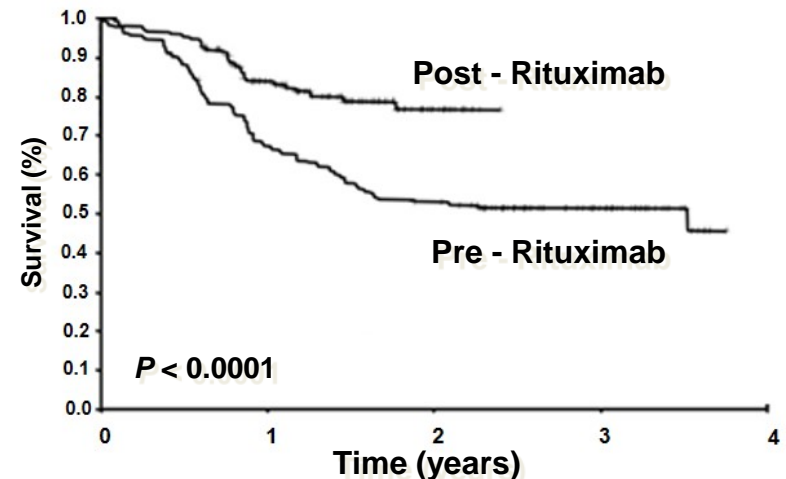


# Rituximab-based Therapy Has Changed the Course of DLBCL

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



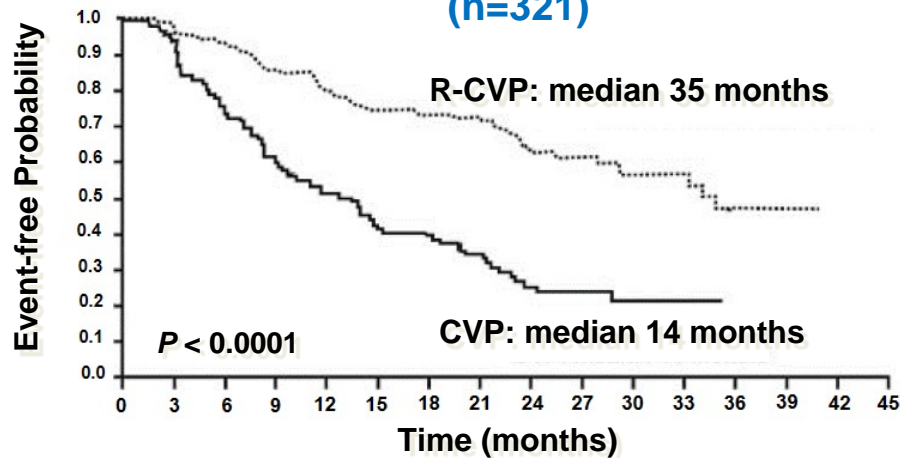
Overall survival by treatment era  
all patients in British Columbia<sup>2</sup>  
(n=292)



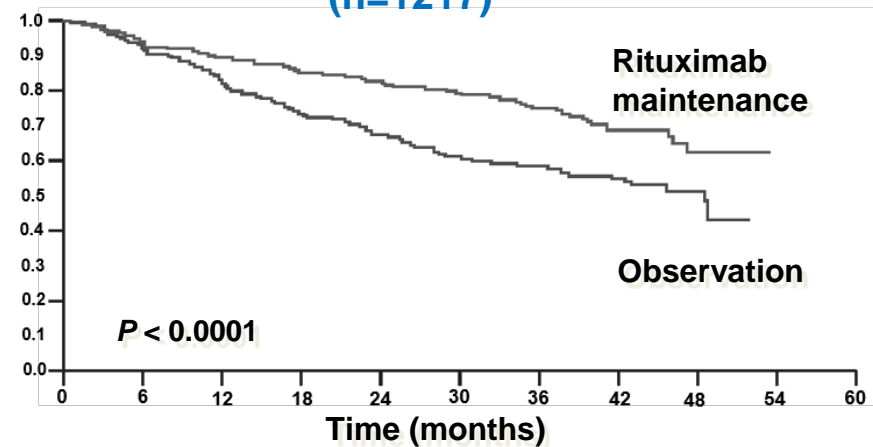
<sup>1</sup> Coiffier et al. Blood. 2010 Sep 23;116(12):2040-5. <sup>2</sup> Sehn et al. J Clin Oncol. 2005;23(22):5027-5033.

# Rituximab-based Therapy Has Changed the Course of Follicular Lymphoma

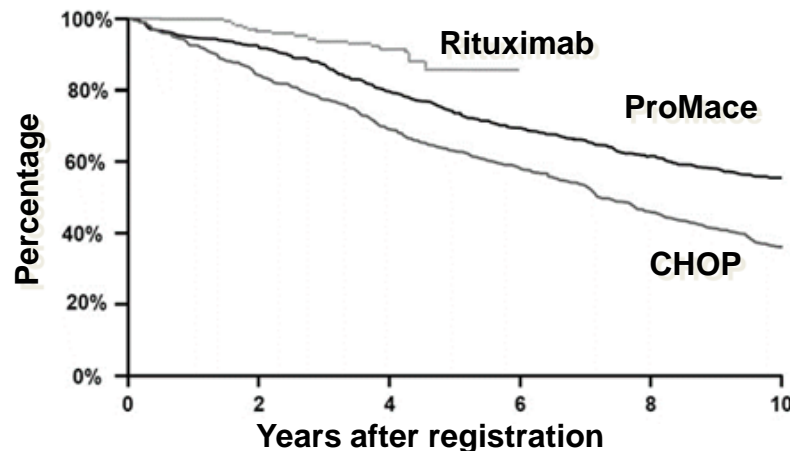
Event free survival, induction therapy<sup>1</sup>  
(n=321)



Event free survival, maintenance therapy<sup>2</sup>  
(n=1217)

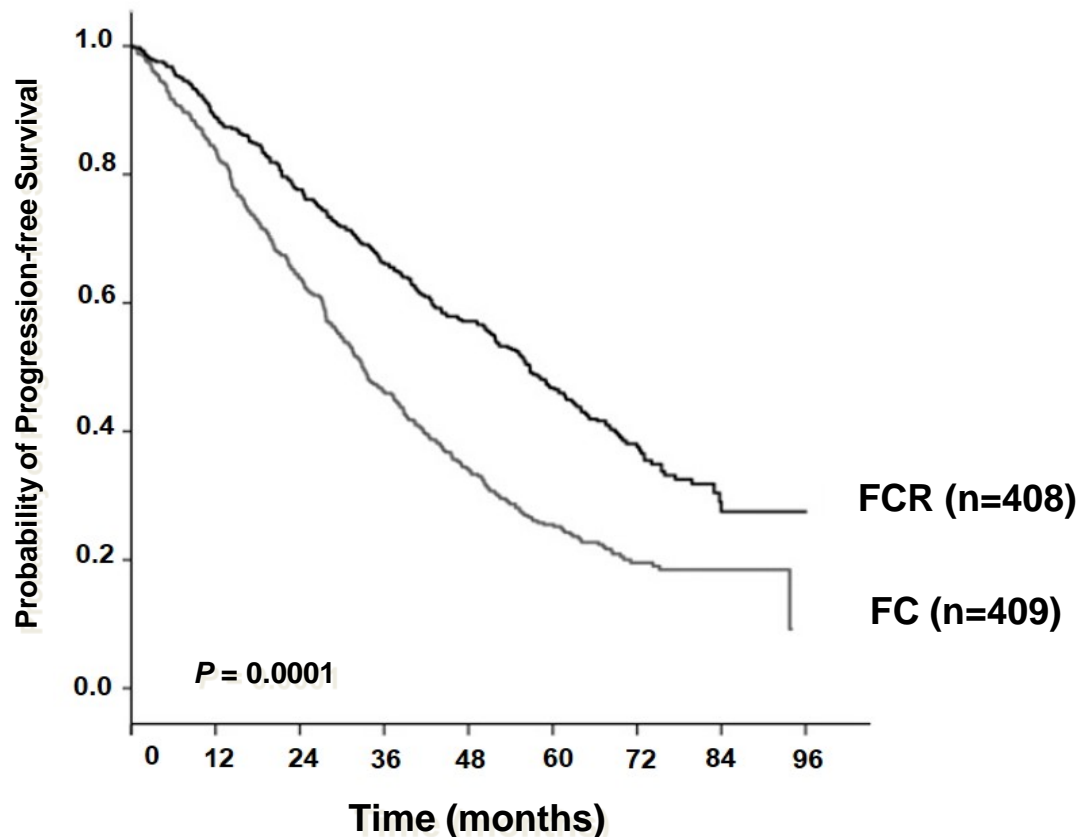


Overall survival by treatment, patients with FL<sup>3</sup> (n=960)



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

Progression free survival,  
CLL8 Study at median FU of almost 6 years<sup>1</sup>



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

# Rituximab IV Administration

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- 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

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- 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

# Agenda

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# Rituximab SC

## Clinical Pharmacology

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Peter Morcos, PharmD  
Clinical Pharmacologist  
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# Rituximab SC

## Clinical Development Program Objectives

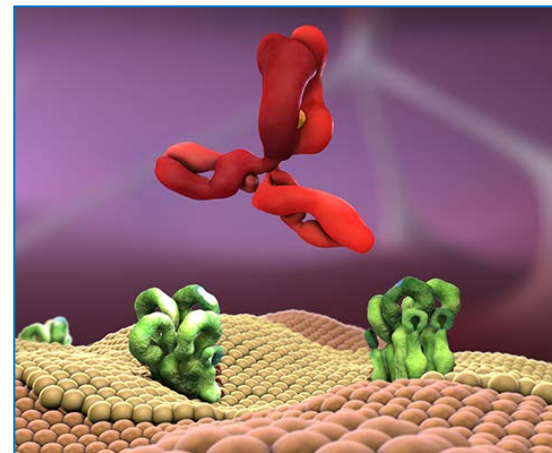
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The clinical program objectives comparing SC to IV formulations:

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

# Rituximab SC PK Bridging Approach

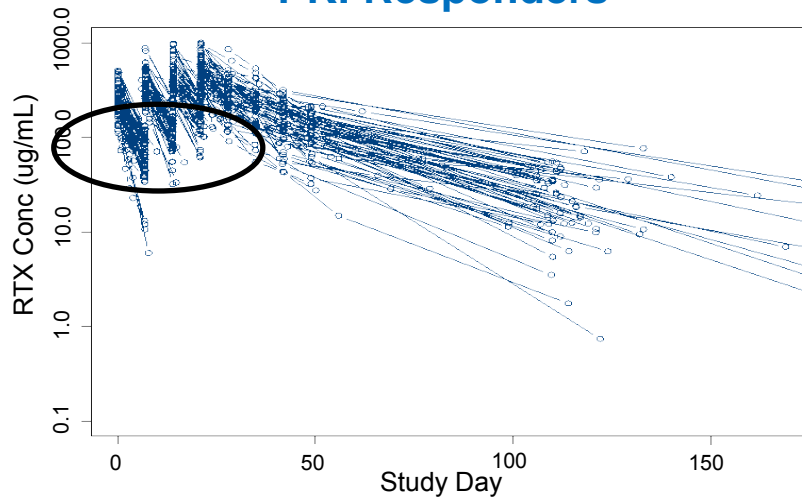
- Same anti-B-cell monoclonal antibody in both formulations (IV and SC)
- Rituximab exerts its anti-B-cell action upon binding to its target, CD20, on the surface of malignant B-cells
- By ensuring serum  $C_{\text{trough}}$  levels following rituximab SC are at least as high as IV then similar target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



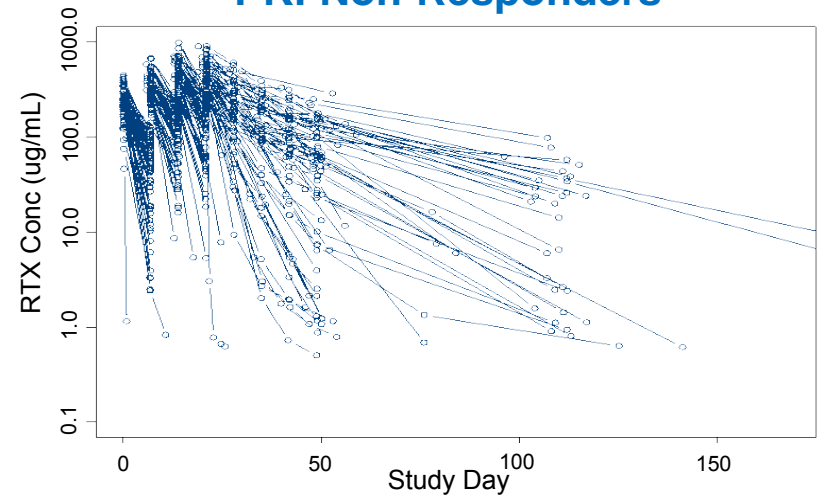
# Rituximab IV

## $C_{\text{trough}}$ Association with B-cell Depletion

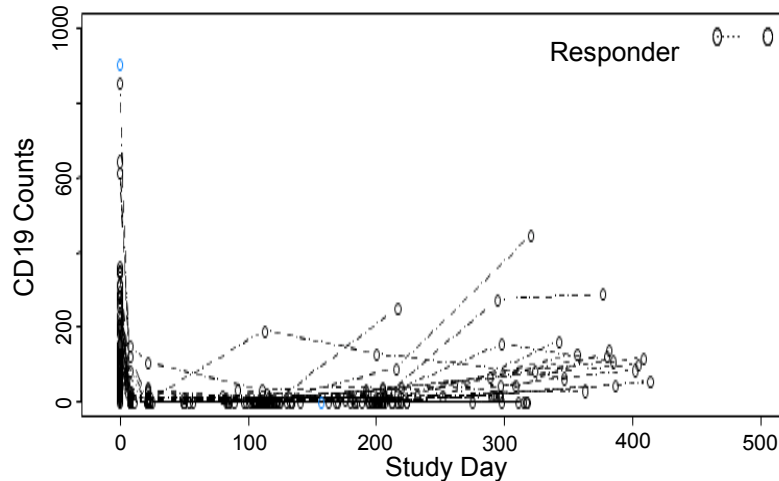
PK: Responders



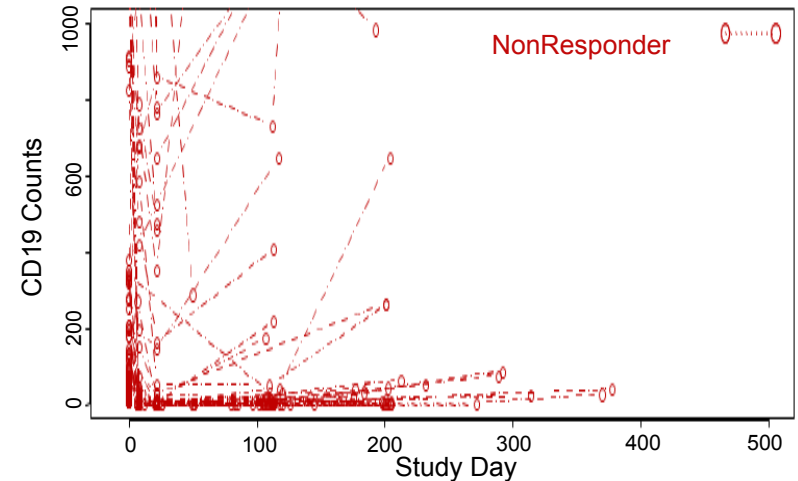
PK: Non-Responders



B-cells Depletion Profile: Responders



B-cells Depletion Profile: Non-Responders



# Clinically Relevant PK Endpoints for Bridging

## $C_{\text{trough}}$ at steady-state (Primary PK endpoint)

- Considers mode of action
- Associated with clinical outcomes<sup>1-9</sup>

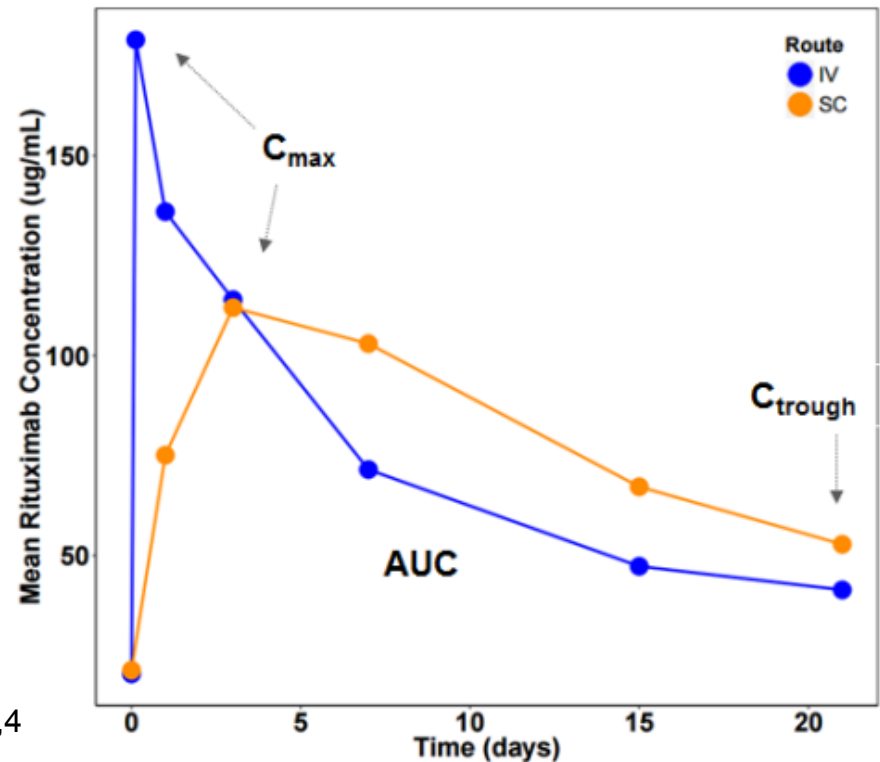
## AUC at steady-state (Secondary PK endpoint)

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

## $C_{\text{max}}$

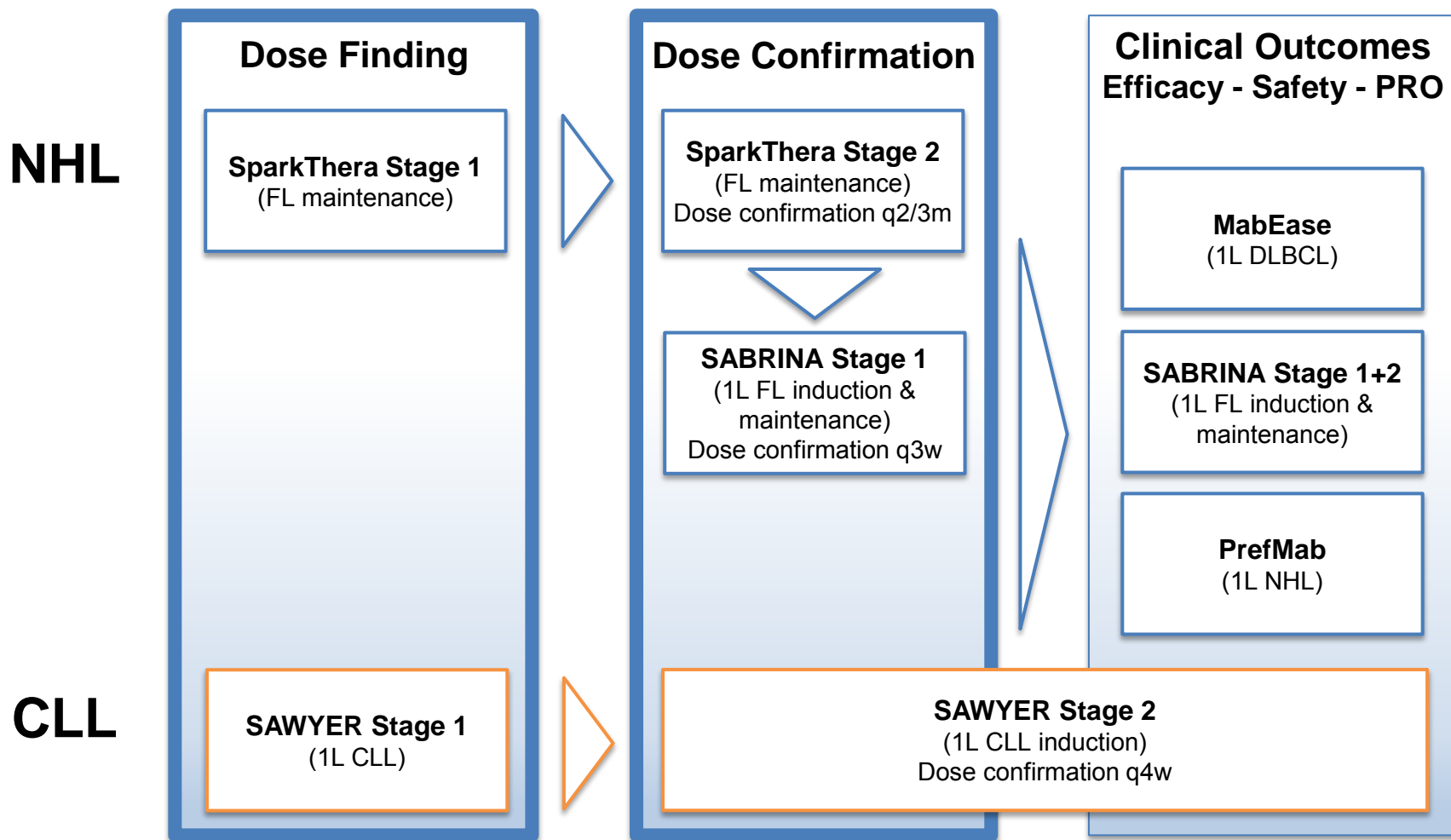
- $C_{\text{max}}$  after IV is not subject to distribution and elimination effects
- Not clearly correlated with outcomes<sup>1,4</sup>

## 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/m<sup>2</sup>)*

## SparkThera Stage 1

FL receiving rituximab maintenance  
n=124



R-IV 375 mg/m<sup>2</sup>

R-SC 375 mg/m<sup>2</sup>

R-SC 625 mg/m<sup>2</sup>

R-SC 800 mg/m<sup>2</sup>

Complete 2 years

9  
months  
FU

*To match rituximab IV CLL dose (500 mg/m<sup>2</sup>)*

## SAWYER Stage 1

CLL receiving R-FC  
n=64



R-SC 1870 mg

R-SC 1400 mg

R-SC 1600 mg

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

1:1

Complete 2 years

Complete 2 years

9  
months  
FU

### NHL dose at q3w (observed data)

#### SABRINA Stage 1

Untreated patients with FL  
n=127

1:1

8 x R-CHOP/R-CVP

12 cycles mono therapy q2m

12 cycles mono therapy q2m

2 years  
FU

### CLL dose q4w (observed data)

#### SAWYER Stage 2

Untreated patients with CLL  
n=176

1:1

6 x R-FC

4 years  
FU

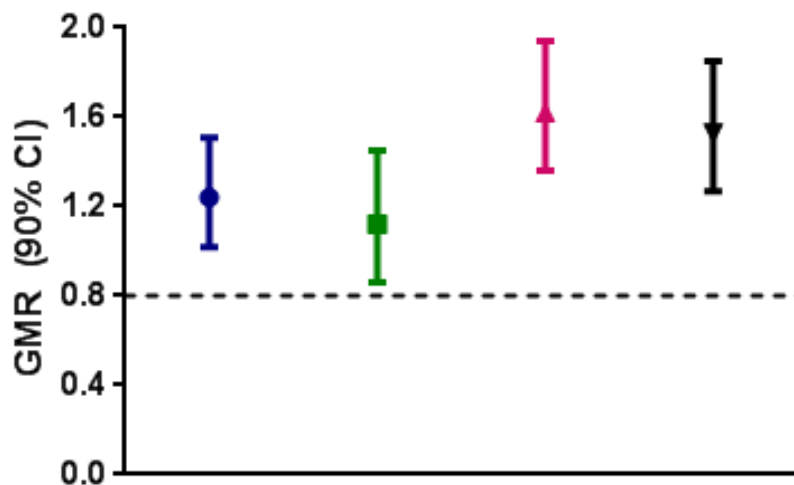
 Standard  
Rituximab IV

 Rituximab SC  
Selected Doses

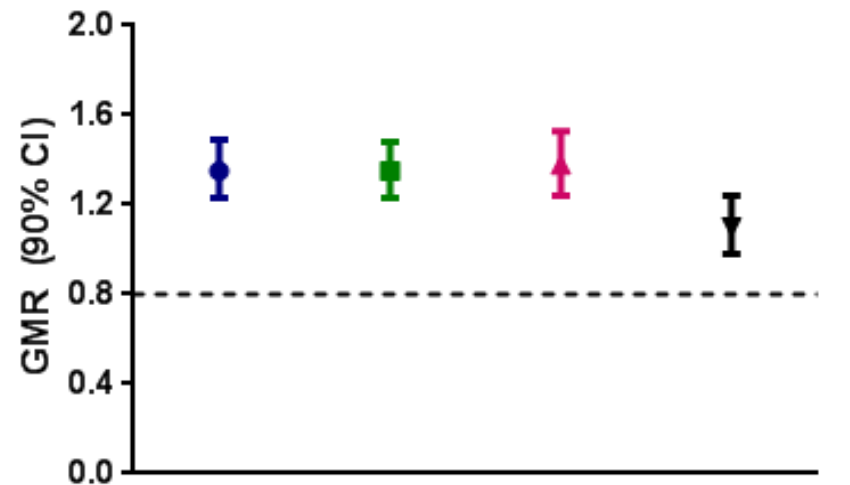
Assessment  
of steady-state  
 $C_{trough}^*$

# Confirmed PK Non-Inferiority Across Established Dosing Schedules

$C_{\text{trough}}$  (Primary Endpoint)



AUC (Key Secondary Endpoint)



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

GMR: geometric mean ratio for SC/IV

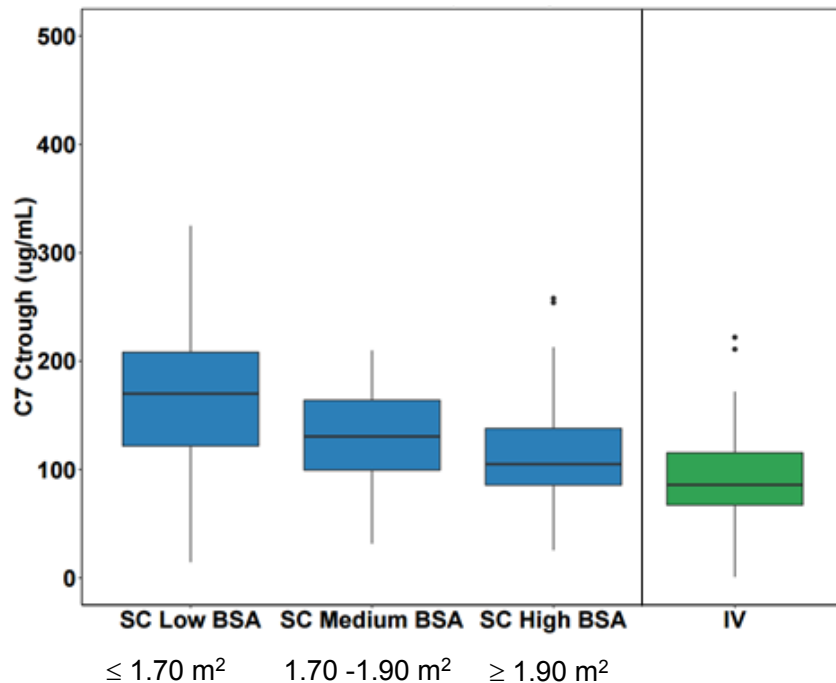
Lower boundary of the 90% CI of the GMR  $R^{\text{SC}}/R^{\text{IV}}$  pre-specified as non-inferiority margin

<sup>1</sup> Estimated by population PK; <sup>2</sup> Calculation of observed data

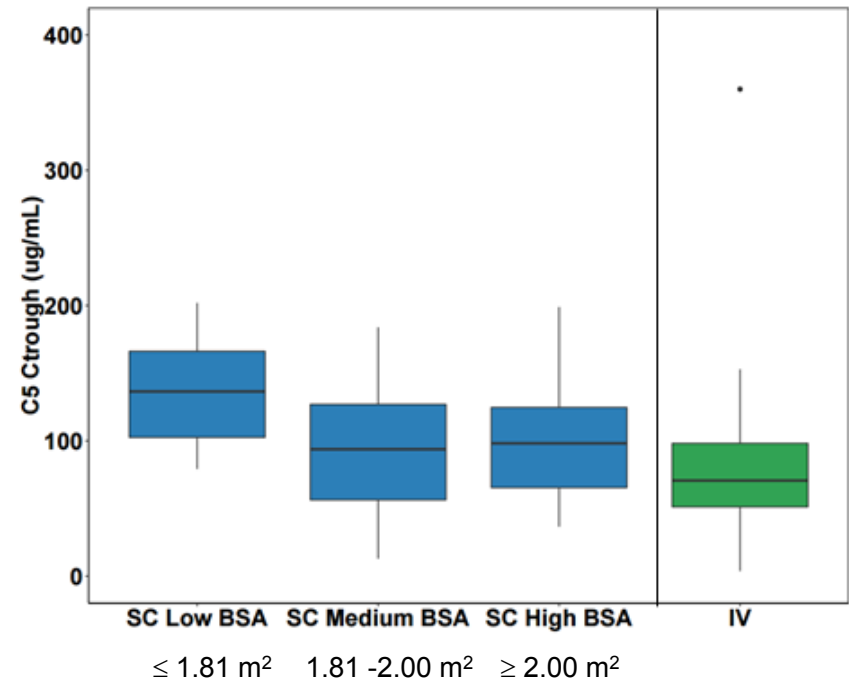


# Fixed SC Doses Demonstrate Non-Inferior Exposure Across the Entire BSA Range

## SABRINA (NHL)



## SAWYER (CLL)

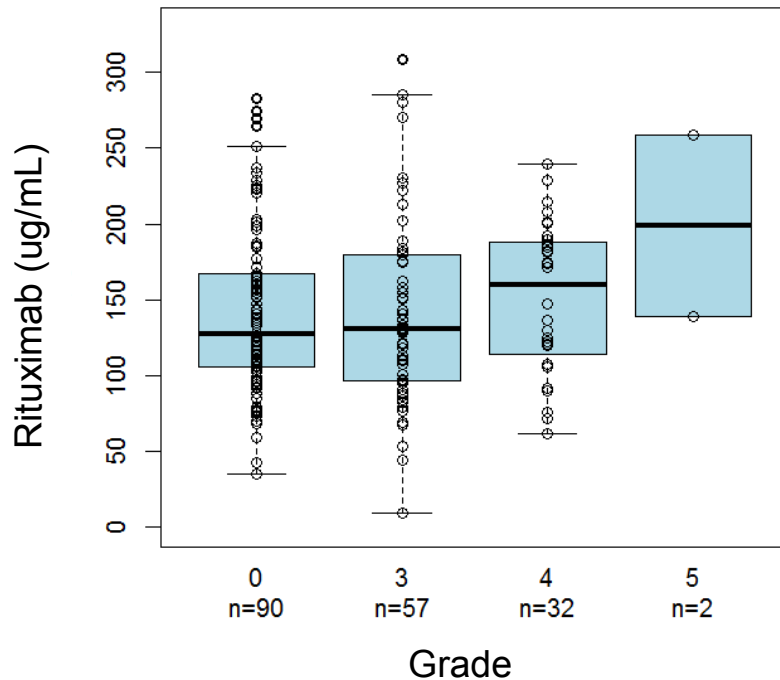


SABRINA BSA range  $1.34 - 2.51 \text{ m}^2$ ; SAWYER Stage 2 BSA range  $1.41 - 2.42 \text{ m}^2$

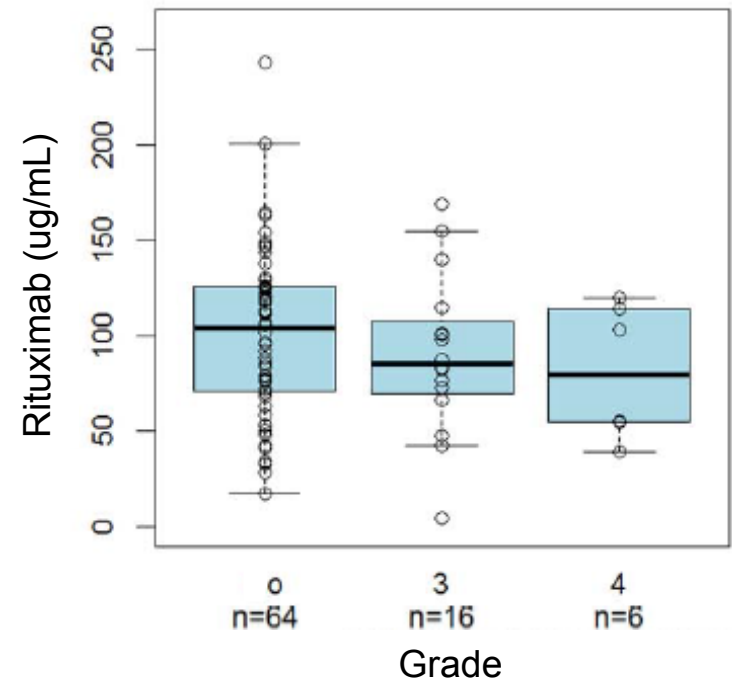
Boxplots: upper whisker extends from the hinge to the highest value that is within  $1.5 \times \text{IQR}$  of the hinge, where IQR is the inter-quartile range, or distance between the first and third quartiles. The lower whisker extends from the hinge to the lowest value within  $1.5 \times \text{IQR}$  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 $\geq 3$ AE)

SABRINA (NHL)



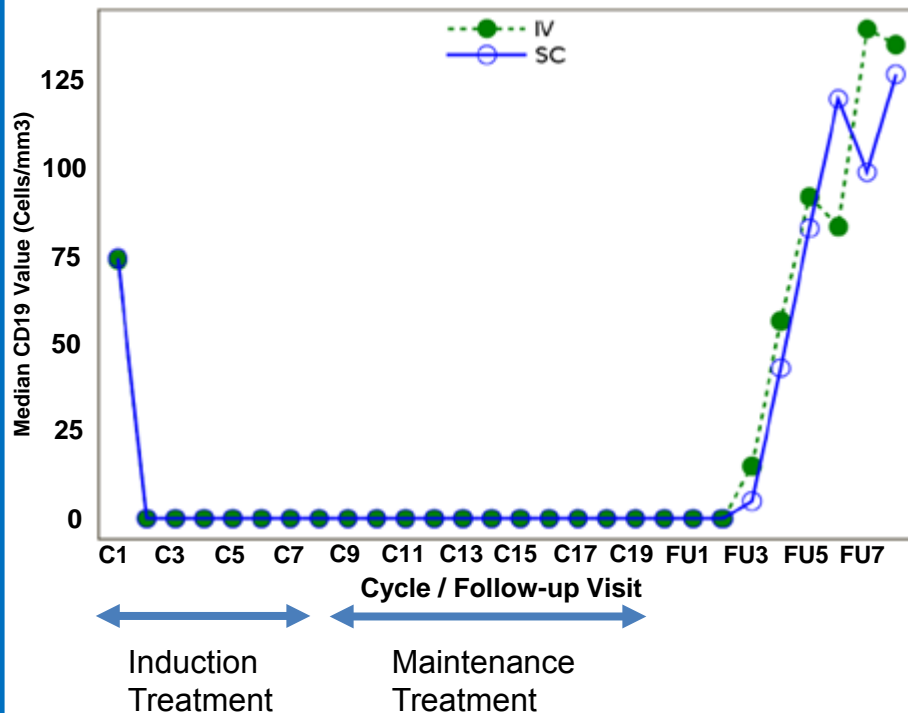
SAWYER (CLL)



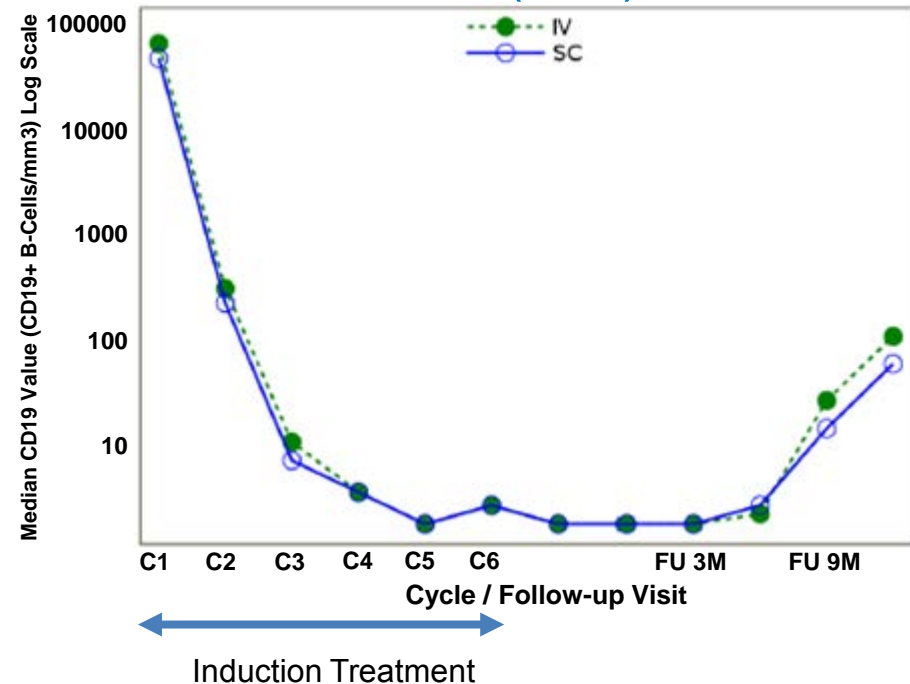
Boxes: inter-quartile range (IQR)  
Black lines: Median values  
Whiskers: 1.5\*IQR  
Circles: individual values

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

## SABRINA (NHL)



## SAWYER (CLL)



# Clinical Pharmacology Summary

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- PK bridging confirmed fixed SC doses which correspond to approved IV dosing schedules
- $C_{\text{trough}}$  (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

# Agenda

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# Rituximab SC

## Clinical Development

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Global Development Team Leader  
Genentech

# Rituximab SC

## Clinical Development Program Objectives

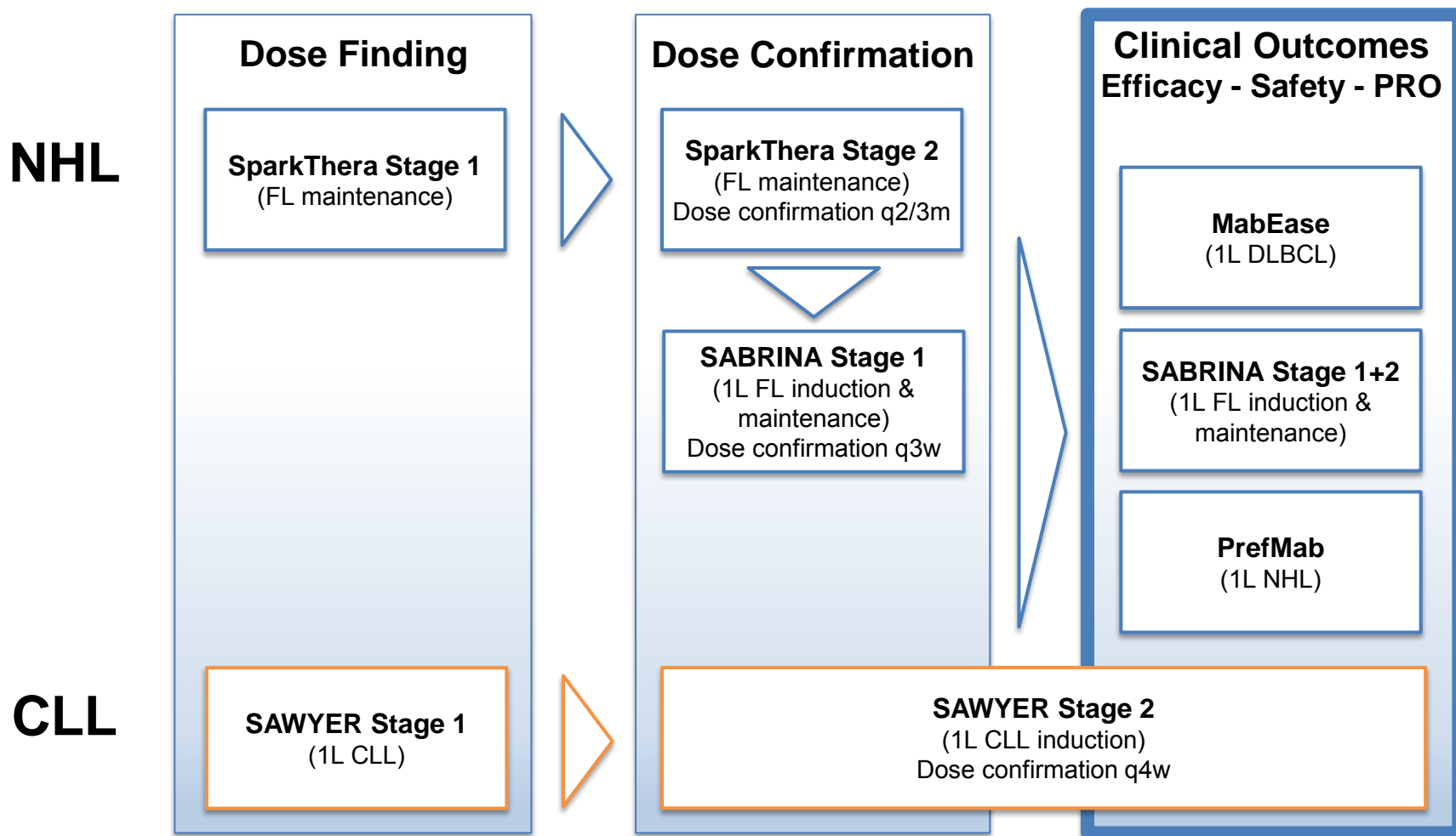
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The clinical program objectives comparing SC to IV formulations:

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



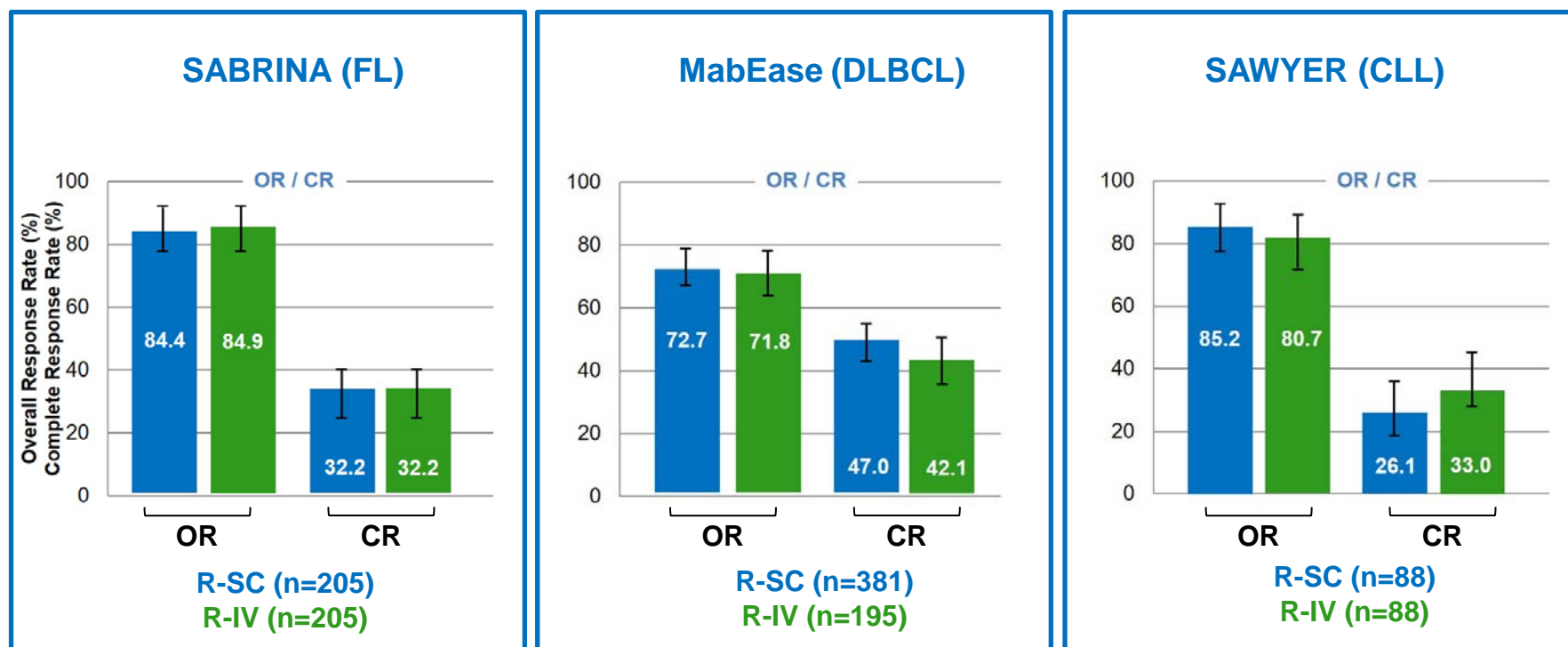


# Studies to Investigate Efficacy



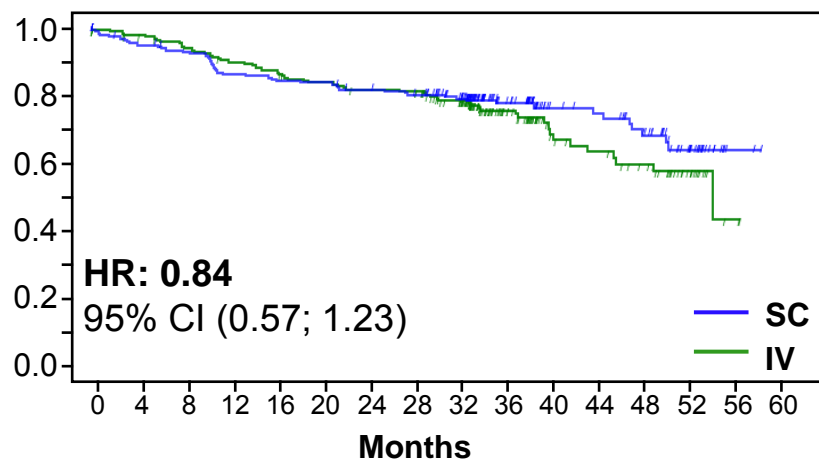
\* 6-8 cycles of CHOP

# Comparable OR and CR Rates End of Induction

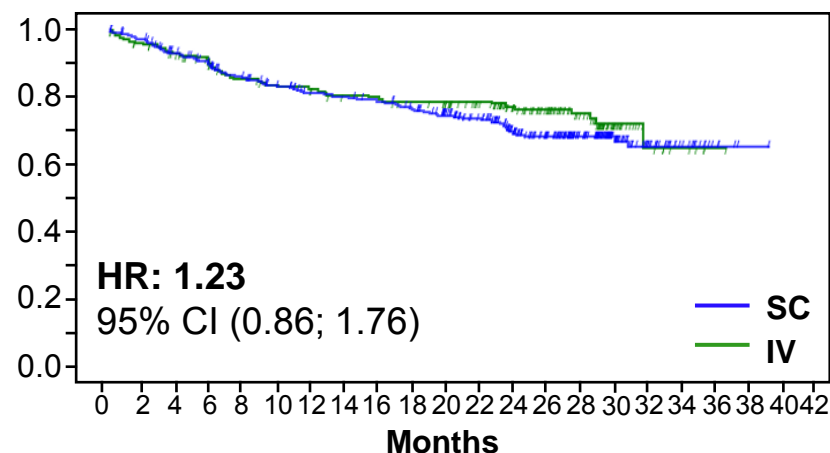


# Comparable Progression-free Survival (PFS)

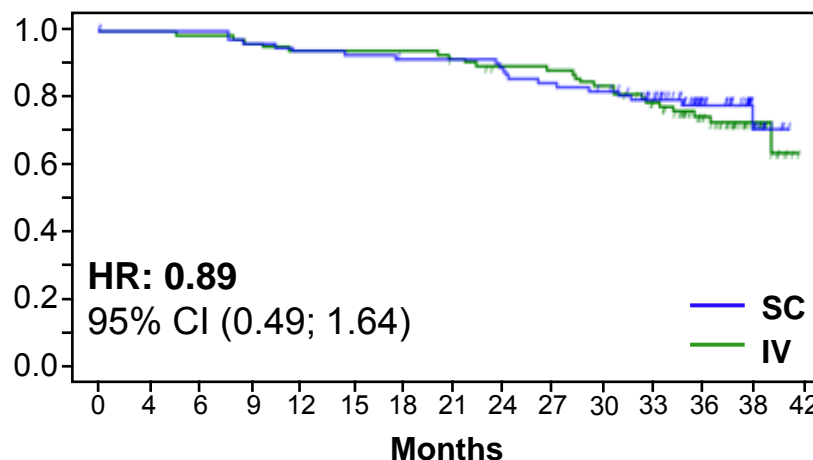
**SABRINA (FL, median FU of ~37 months)**



**MabEase (DLBCL, median FU of ~28 months)**

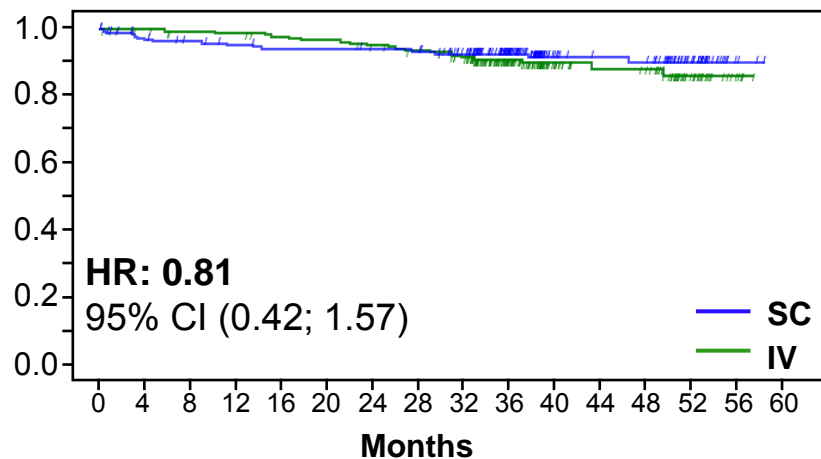


**SAWYER (CLL, Median FU of ~36 months)**

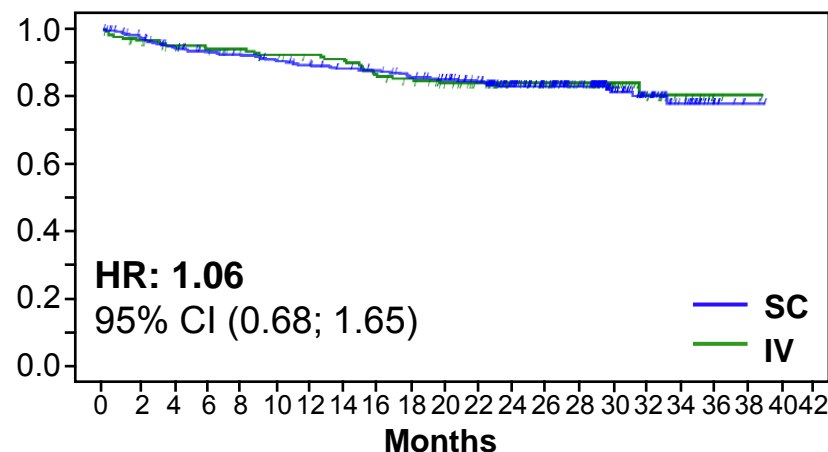


# Comparable Overall Survival (OS)

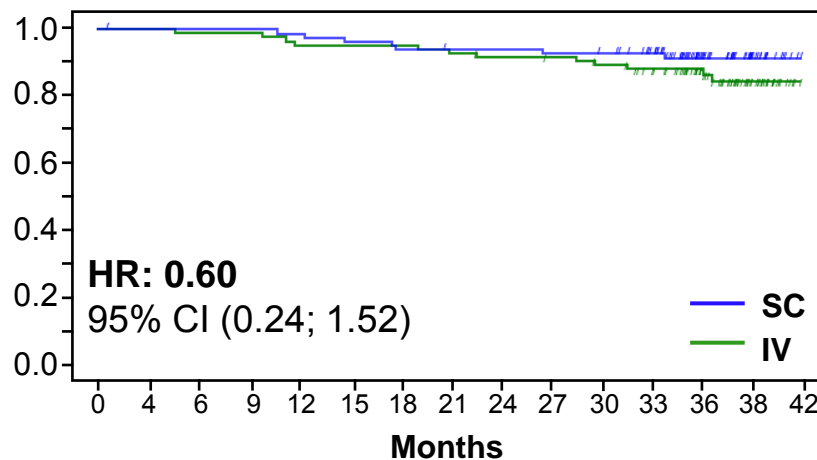
SABRINA (FL, median FU of ~37 months)



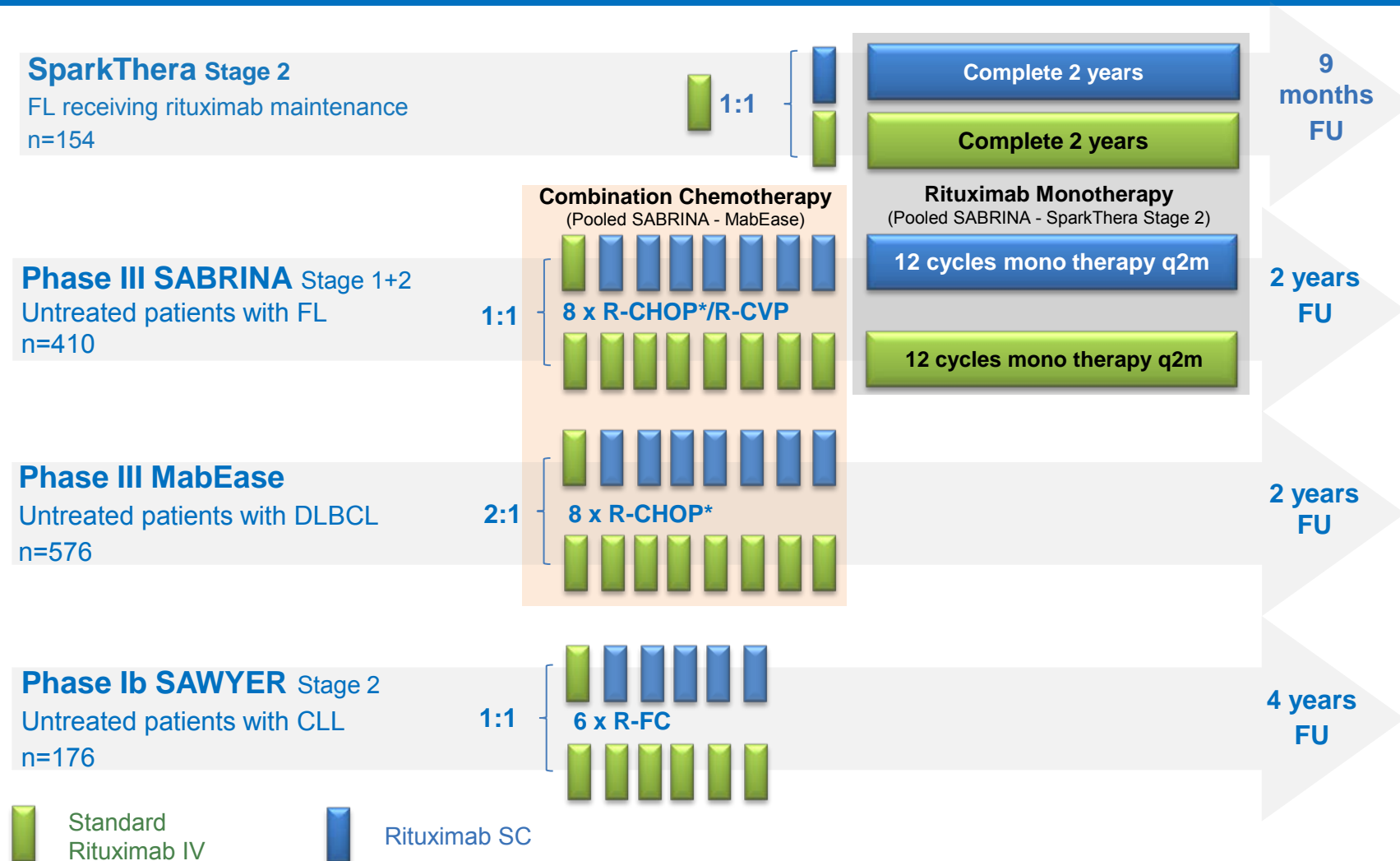
MabEase (DLBCL, median FU of ~28 months)



SAWYER (CLL, Median FU of ~36 months)



# Studies to Investigate Safety



\* 6-8 cycles of CHOP

# Safety Comparison: Rituximab IV and SC

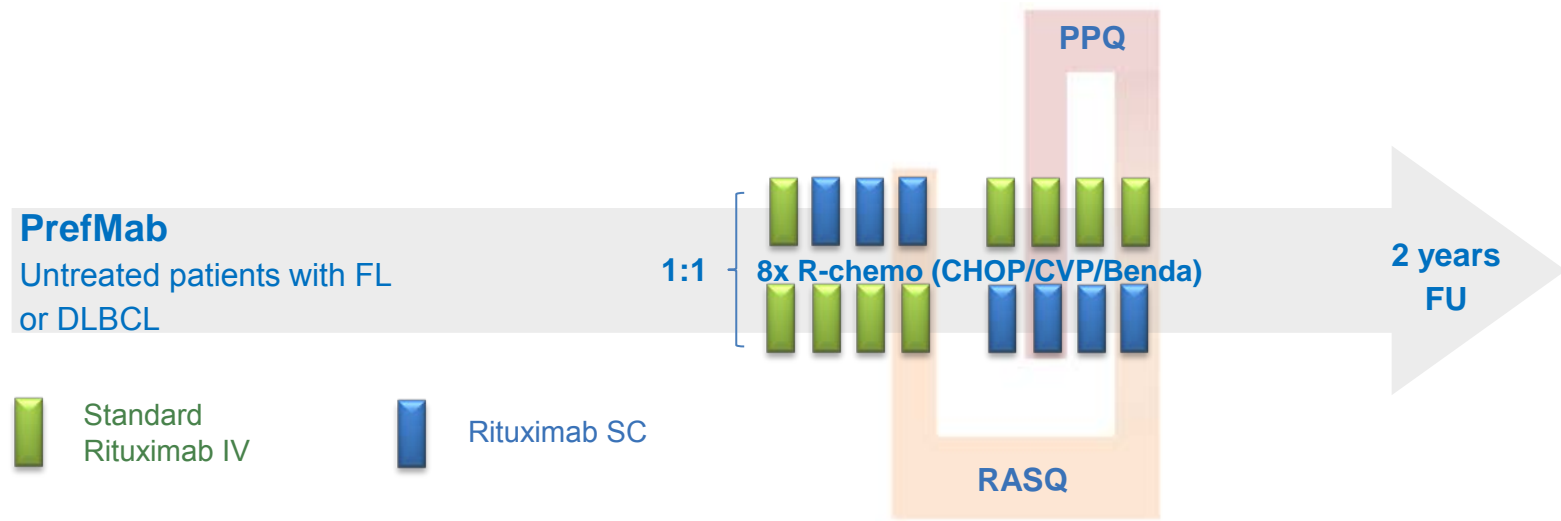
	NHL Combination Chemotherapy (Pooled SABRINA - MabEase)		NHL Rituximab Monotherapy (Pooled SABRINA-SparkThera)		CLL Combination Chemotherapy (SAWYER )	
	IV (n=413) No. (%)	SC (n=566) No. (%)	IV (n=255) No. (%)	SC (n=249) No. (%)	IV (n=89) No. (%)	SC (n=85) No. (%)
<b>Any AE</b>	380 (92)	533 (94)	208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

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### **PPQ: Patient Preference Questionnaire**

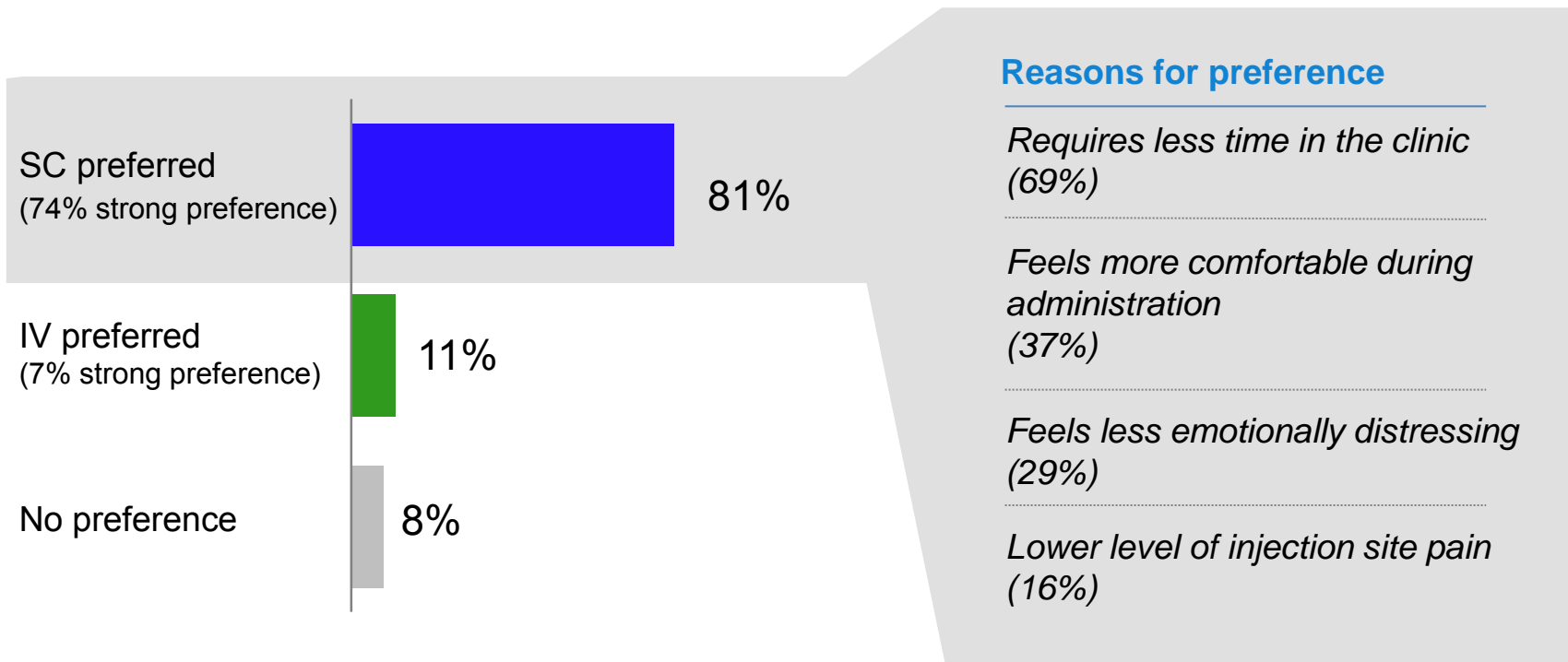
3 simple questions, requiring straight forward decisions

### **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

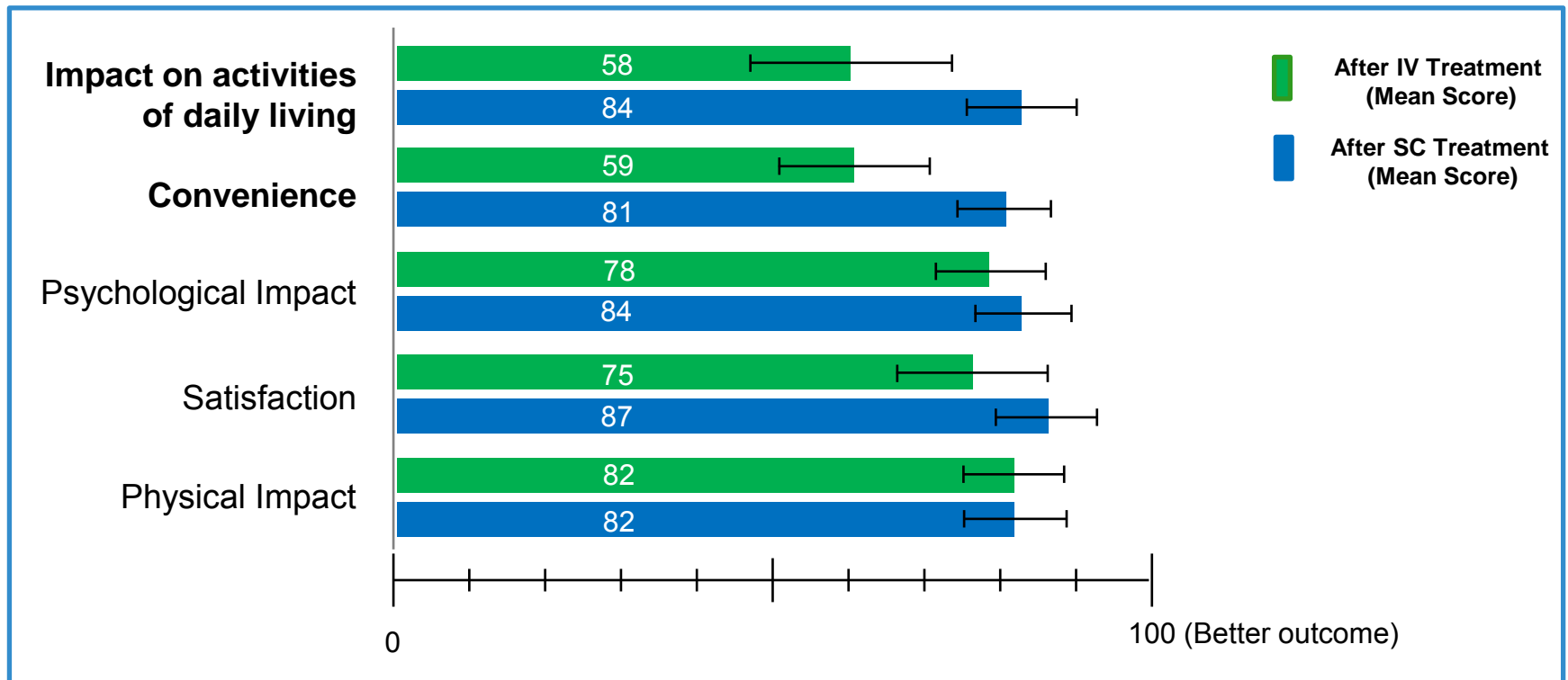
## PrefMab (NHL): PPQ Results at Cycle 8





# RASQ Results Support the PPQ Results

## PrefMab (NHL)



# Rituximab SC Clinical Development Summary

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- 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

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- 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

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- 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

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# NHL Pooled Safety Analyses

Adverse Events, Grade  $\geq 3$  Adverse Events, and Serious Adverse Events by Subgroups (BSA) for NHL

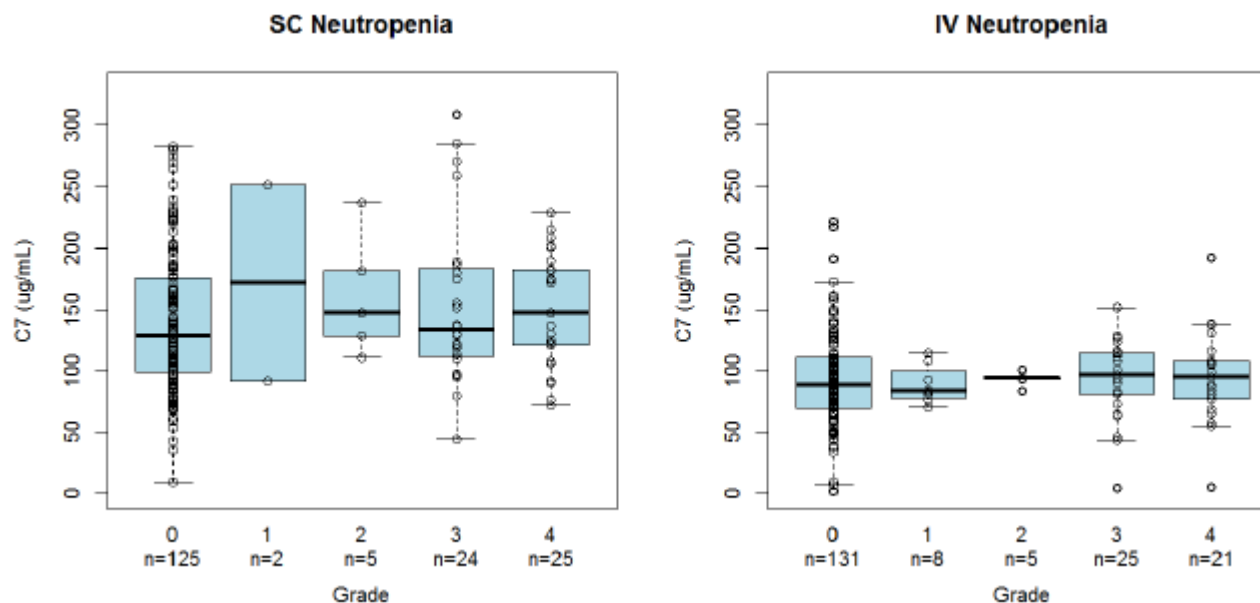
BSA subgroup	Combination Chemotherapy (Pooled SABRINA - MabEase)		Rituximab Monotherapy (Pooled SABRINA - SparkThera Stage 2)	
	IV n/N (%)	SC n/N (%)	IV n/N (%)	SC n/N (%)
<b>Patients with at least one AE</b>				
Low	122/131 (93)	206/217 (95)	71/80 (89)	82/102 (80)
Medium	131/147 (89)	157/169 (93)	72/91 (79)	57/72 (79)
High	127/135 (94)	170/180 (94)	65/84 (77)	63/75 (84)
<b>Patients with at least one Grade<math>\geq 3</math> AE</b>				
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)
<b>Patients with at least one serious AE (SAE)</b>				
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 (%)
<b>AEs Leading to Treatment Discontinuation</b>				
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)
<b>Adverse Events Leading to Death</b>				
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

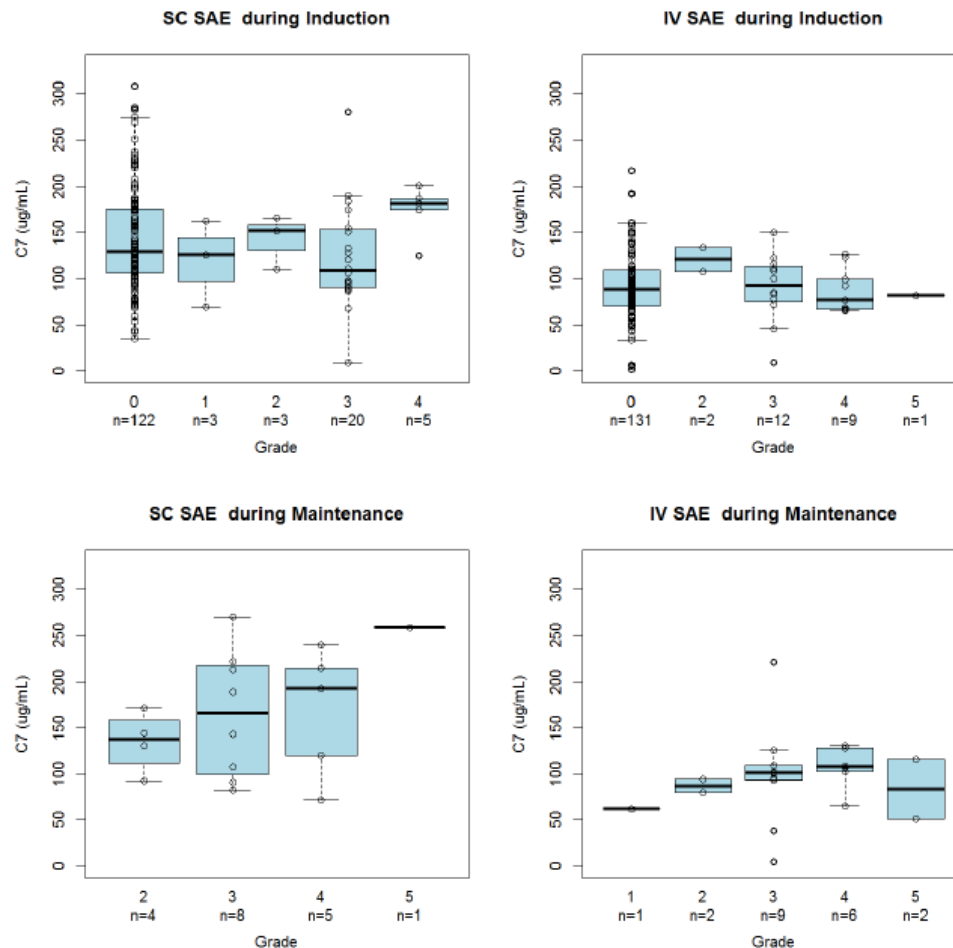
No evidence of relationship between grades of events and exposure



# SABRINA: SAE for Induction and Maintenance

## Separately

### Cycle 2 Onwards

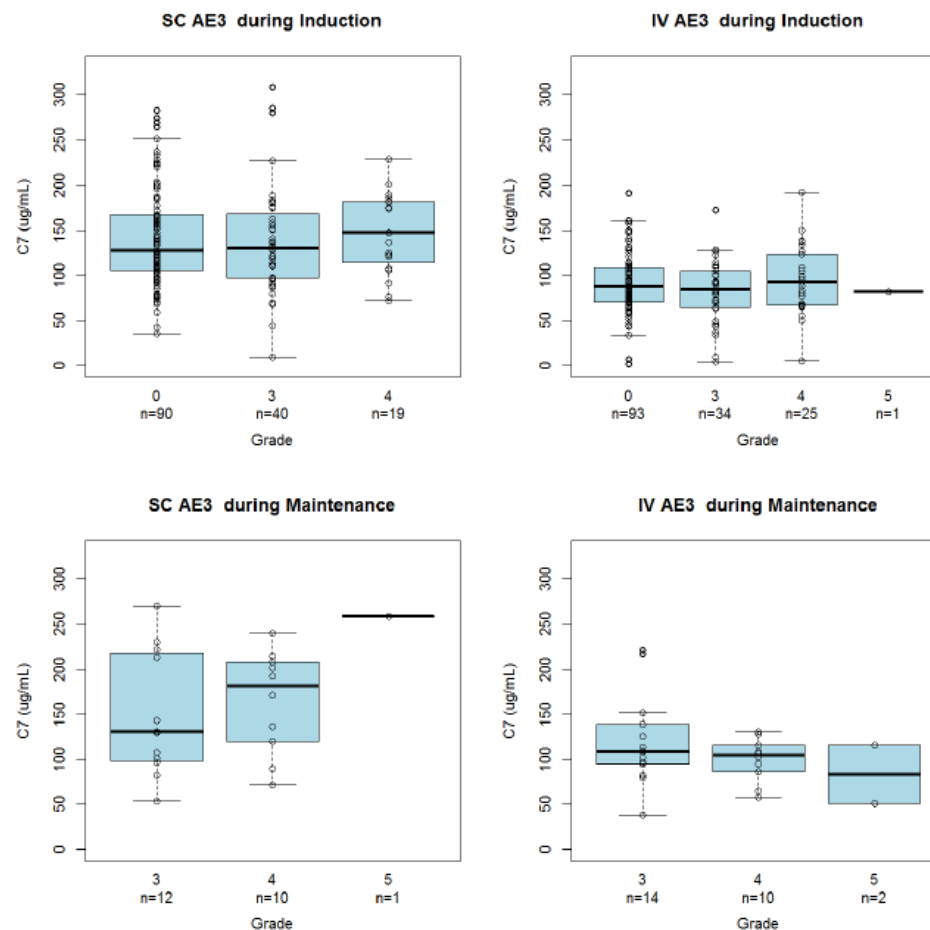


Median values are designated by black lines in the center of the boxes  
Boxes: inter-quartile range (IQR)  
Whiskers represent 1.5\*IQR  
Circles represent individual values

No evidence of relationship between grades of events and exposure

# SABRINA: Grade $\geq 3$ AE for Induction and Maintenance Separately

## Cycle 2 Onwards



No evidence of relationship between grades of events and exposure