Rituximab SC
Development Rationale

Nancy Valente, MD
Head of Global Hematology Development
Genentech
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 administrated
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
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)

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease State</th>
<th>n</th>
<th>PK</th>
<th>Clinical Efficacy</th>
<th>Clinical Safety</th>
<th>Patient Reported Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SparkThera</td>
<td>FL Maintenance</td>
<td>281</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>SABRINA</td>
<td>FL Induction &amp;</td>
<td>410</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAWYER</td>
<td>CLL</td>
<td>240</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>MabEase</td>
<td>DLBCL</td>
<td>576</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>PrefMab</td>
<td>Lymphoma (FL &amp;</td>
<td>743</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td></td>
<td>DLBCL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Rituximab SC
Integrated PK-Clinical Bridging Development Plan

**Dose Finding**
- **NHL**
  - SparkThera Stage 1 (FL maintenance)
- **CLL**
  - SAWYER Stage 1 (1L CLL)

**Dose Confirmation**
- **NHL**
  - SparkThera Stage 2 (FL maintenance)
    - Dose confirmation q2/3m
  - SABRINA Stage 1 (1L FL induction & maintenance)
    - Dose confirmation q3w
- **CLL**
  - SAWYER Stage 2 (1L CLL induction)
    - Dose confirmation q4w

**Clinical Outcomes**
- Efficacy - Safety - PRO
  - MabEase (1L DLBCL)
  - SABRINA Stage 1+2 (1L FL induction & maintenance)
  - PrefMab (1L NHL)
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

<table>
<thead>
<tr>
<th>Agenda Item</th>
<th>Speaker Name, Title/Position</th>
</tr>
</thead>
</table>
| **Rituximab SC Development Rationale** | Nancy Valente, MD  
Head of Global Hematology Development  
*Genentech* |
| **Rituximab SC 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  
*Genentech* |
| **Rituximab SC Clinical Development Concluding Remarks** | Axel Boehnke, MD  
Global Development Team Leader  
*Genentech* |
Consultants

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

Andrew Davies, BSc BM PhD FRCP
Associate Professor in Medical Oncology,
University of Southampton, UK
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 US\(^1\)
• ~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

\(^2\) 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 Columbia\(^2\) (n=292)

Rituximab-based Therapy Has Changed the Course of Follicular Lymphoma

Event free survival, induction therapy\(^1\) (n=321)

- R-CVP: median 35 months
- CVP: median 14 months

\(P < 0.0001\)

Event free survival, maintenance therapy\(^2\) (n=1217)

- Rituximab maintenance
- Observation

\(P < 0.0001\)

Overall survival by treatment, patients with FL\(^3\) (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

![Graph showing progression free survival with FCR (n=408) and FC (n=409) with p-value 0.0001.]

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

<table>
<thead>
<tr>
<th>IV administration</th>
<th>SC administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-specific dosing based on height and weight</td>
<td>Fixed dosing for all patients (no dose calculation required)</td>
</tr>
<tr>
<td>Prepare and dilute into IV bag</td>
<td>Ready to use vial</td>
</tr>
<tr>
<td>Infusion time: 1.5 to 4 hours</td>
<td>Injection time: 5-7 minutes</td>
</tr>
</tbody>
</table>
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
## Agenda

<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
</table>
| **Rituximab SC Development Rationale** | Nancy Valente, MD  
Head of Global Hematology Development  
*Genentech* |
| **Rituximab SC 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  
*Genentech* |
| **Rituximab SC Clinical Development Concluding Remarks** | Axel Boehnke, MD  
Global Development Team Leader  
*Genentech* |
Rituximab SC
Clinical Pharmacology

Peter Morcos, PharmD
Clinical Pharmacologist
Genentech
Rituximab SC
Clinical Development Program Objectives

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**

- **RTX Conc (ug/mL)**
  - 1000.0
  - 100.0
  - 10.0
  - 1.0
  - 0.1

- **Study Day**
  - 0
  - 50
  - 100
  - 150

**PK: Non-Responders**

- **RTX Conc (ug/mL)**
  - 1000.0
  - 100.0
  - 10.0
  - 1.0
  - 0.1

- **Study Day**
  - 0
  - 50
  - 100
  - 150

**B-cells Depletion Profile: Responders**

- **CD19 Counts**
  - 0
  - 100
  - 500
  - 200
  - 300
  - 400

- **Study Day**
  - 0
  - 100
  - 200
  - 300
  - 400
  - 500

**B-cells Depletion Profile: Non-Responders**

- **CD19 Counts**
  - 0
  - 100
  - 500
  - 200
  - 300
  - 400

- **Study Day**
  - 0
  - 100
  - 200
  - 300
  - 400
  - 500

Clinically Relevant PK Endpoints for Bridging

\[ C_{\text{trough}} \text{ at steady-state (Primary PK endpoint)} \]
- Considers mode of action
- Associated with clinical outcomes\(^1\text{-}^9\)

\[ \text{AUC at steady-state (Secondary PK endpoint)} \]
- 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\(^1,^4\)

Serum Concentration-Time Profile

Rituximab SC
Integrated PK-Clinical Bridging Development Plan

**NHL**
- **Dose Finding**
  - SparkThera Stage 1
    - (FL maintenance)

**Dose Confirmation**
- SparkThera Stage 2
  - (FL maintenance)
  - Dose confirmation q2/3m
- SABRINA Stage 1
  - (1L FL induction & maintenance)
  - Dose confirmation q3w
- Clinical Outcomes
  - Efficacy - Safety - PRO
    - MabEase
      - (1L DLBCL)
    - SABRINA Stage 1+2
      - (1L FL induction & maintenance)
    - PrefMab
      - (1L NHL)

**CLL**
- SAWYER Stage 1
  - (1L CLL)

**Dose Confirmation**
- SAWYER Stage 2
  - (1L CLL induction)
  - Dose confirmation q4w
Rituximab SC Dose Finding Studies

To match rituximab IV NHL dose (375 mg/m²)
SparkThera Stage 1
FL receiving rituximab maintenance
n=124

To match rituximab IV CLL dose (500 mg/m²)
SAWYER Stage 1
CLL receiving R-FC
n=64

M&S* predicted non-inferiority of:
• Rituximab SC 1400 mg (NHL)
• Rituximab SC 1600 mg (CLL)

*Modeling and Simulation
**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

### NHL dose at q3w (observed data)
- **SABRINA Stage 1**
  - Untreated patients with FL
  - n=127
  - 8 x R-CHOP/R-CVP

### CLL dose q4w (observed data)
- **SAWYER Stage 2**
  - Untreated patients with CLL
  - n=176
  - 6 x R-FC

**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

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

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)**

- **Graph Details:**
  - **Axes:** Rituximab (ug/mL) vs. Grade
  - **Boxes:** Inter-quartile range (IQR)
  - **Black Lines:** Median values
  - **Whiskers:** 1.5*IQR
  - **Circles:** Individual values

**SAWYER (CLL)**

- **Graph Details:**
  - **Axes:** Rituximab (ug/mL) vs. Grade
  - **Boxes:** Inter-quartile range (IQR)
  - **Black Lines:** Median values
  - **Whiskers:** 1.5*IQR
  - **Circles:** Individual values

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
- $C_{\text{trough}}$ (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

<table>
<thead>
<tr>
<th>Topic</th>
<th>Speaker</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rituximab SC Development Rationale</strong></td>
<td>Nancy Valente, MD</td>
<td>Genentech</td>
</tr>
<tr>
<td><strong>Rituximab SC Clinical Perspective</strong></td>
<td>Andrew Davies, BSc BM PhD FRCP</td>
<td>University of Southampton, UK</td>
</tr>
<tr>
<td><strong>Rituximab SC Clinical Pharmacology</strong></td>
<td>Peter Morcos, PharmD</td>
<td>Genentech</td>
</tr>
<tr>
<td><strong>Rituximab SC Clinical Development</strong></td>
<td>Axel Boehnke, MD</td>
<td>Genentech</td>
</tr>
</tbody>
</table>
Rituximab SC
Clinical Development

Axel Boehnke, MD
Global Development Team Leader
Genentech
Rituximab SC
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

**NHL**

- **Dose Finding**
  - SparkThera Stage 1
    - (FL maintenance)

- **Dose Confirmation**
  - SparkThera Stage 2
    - (FL maintenance)
    - Dose confirmation q2/3m
  - SABRINA Stage 1
    - (1L FL induction & maintenance)
    - Dose confirmation q3w

**CLL**

- **Dose Finding**
  - SAWYER Stage 1
    - (1L CLL)

- **Dose Confirmation**
  - SAWYER Stage 2
    - (1L CLL induction)
    - Dose confirmation q4w

**Clinical Outcomes**

- Efficacy - Safety - PRO
  - MabEase
    - (1L DLBCL)
  - SABRINA Stage 1+2
    - (1L FL induction & maintenance)
  - PrefMab
    - (1L NHL)
Studies to Investigate Efficacy

**Phase III SABRINA** Stage 1+2
Untreated patients with FL
n=410

1:1
8 x R-CHOP*/R-CVP
12 cycles mono therapy q2m
2 years FU

**Phase III MabEase**
Untreated patients with DLBCL
n=576

2:1
8 x R-CHOP*
12 cycles mono therapy q2m
2 years FU

**Phase Ib SAWYER** Stage 2
Untreated patients with CLL
n=176

1:1
6 x R-FC

Standard Rituximab IV
Rituximab SC

* 6-8 cycles of CHOP

41
Comparable OR and CR Rates End of Induction

SABRINA (FL)

R-SC (n=205)
R-IV (n=205)

OR / CR

84.4 84.9
32.2 32.2

MabEase (DLBCL)

R-SC (n=381)
R-IV (n=195)

OR / CR

72.7 71.8
47.0 42.1

SAWYER (CLL)

R-SC (n=88)
R-IV (n=88)

OR / CR

85.2 80.7
26.1 33.0
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)

HR: 0.84
95% CI (0.49; 1.64)

HR: 0.89
95% CI (0.57; 1.64)

HR: 1.23
95% CI (0.86; 1.76)
Comparable Overall Survival (OS)

SABRINA (FL, median FU of ~37 months)

Months

<table>
<thead>
<tr>
<th>Months</th>
<th>SC</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0.95</td>
<td>0.95</td>
</tr>
<tr>
<td>12</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>16</td>
<td>0.80</td>
<td>0.80</td>
</tr>
<tr>
<td>20</td>
<td>0.70</td>
<td>0.70</td>
</tr>
<tr>
<td>24</td>
<td>0.60</td>
<td>0.60</td>
</tr>
<tr>
<td>28</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>32</td>
<td>0.40</td>
<td>0.40</td>
</tr>
<tr>
<td>36</td>
<td>0.30</td>
<td>0.30</td>
</tr>
<tr>
<td>40</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>44</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>48</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>52</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>56</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>60</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

HR: 0.81
95% CI (0.42; 1.57)

MabEase (DLBCL, median FU of ~28 months)

Months

<table>
<thead>
<tr>
<th>Months</th>
<th>SC</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0.95</td>
<td>0.95</td>
</tr>
<tr>
<td>12</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>16</td>
<td>0.80</td>
<td>0.80</td>
</tr>
<tr>
<td>20</td>
<td>0.70</td>
<td>0.70</td>
</tr>
<tr>
<td>24</td>
<td>0.60</td>
<td>0.60</td>
</tr>
<tr>
<td>28</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>32</td>
<td>0.40</td>
<td>0.40</td>
</tr>
<tr>
<td>36</td>
<td>0.30</td>
<td>0.30</td>
</tr>
<tr>
<td>40</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>44</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>48</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>52</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>56</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>60</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

HR: 1.06
95% CI (0.68; 1.65)

SAWYER (CLL, Median FU of ~36 months)

Months

<table>
<thead>
<tr>
<th>Months</th>
<th>SC</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0.95</td>
<td>0.95</td>
</tr>
<tr>
<td>12</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>16</td>
<td>0.80</td>
<td>0.80</td>
</tr>
<tr>
<td>20</td>
<td>0.70</td>
<td>0.70</td>
</tr>
<tr>
<td>24</td>
<td>0.60</td>
<td>0.60</td>
</tr>
<tr>
<td>28</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>32</td>
<td>0.40</td>
<td>0.40</td>
</tr>
<tr>
<td>36</td>
<td>0.30</td>
<td>0.30</td>
</tr>
<tr>
<td>40</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>44</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>48</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>52</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>56</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>60</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

HR: 0.60
95% CI (0.24; 1.52)
Studies to Investigate Safety

**SparkThera Stage 2**
Untreated patients with FL
n=154

**Phase III SABRINA** Stage 1+2
Untreated patients with FL
n=410

**Phase III MabEase**
Untreated patients with DLBCL
n=576

**Phase Ib SAWYER** Stage 2
Untreated patients with CLL
n=176

* 6-8 cycles of CHOP

**Combination Chemotherapy** (Pooled SABRINA - MabEase)
8 x R-CHOP*/R-CVP

**Rituximab Monotherapy** (Pooled SABRINA - SparkThera Stage 2)
12 cycles mono therapy q2m

**Complete 2 years**

**Complete 2 years**

**2 years FU**

**2 years FU**

**4 years FU**

**Standard Rituximab IV**

**Rituximab SC**
# Safety Comparison: Rituximab IV and SC

## NHL Combination Chemotherapy (Pooled SABRINA - MabEase)

<table>
<thead>
<tr>
<th></th>
<th>IV (n=413) No. (%)</th>
<th>SC (n=566) No. (%)</th>
<th>IV (n=255) No. (%)</th>
<th>SC (n=249) No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>380 (92)</td>
<td>533 (94)</td>
<td>208 (82)</td>
<td>202 (81)</td>
</tr>
<tr>
<td>Grade ≥ 3 AEs</td>
<td>208 (50)</td>
<td>322 (57)</td>
<td>73 (29)</td>
<td>67 (27)</td>
</tr>
<tr>
<td>SAEs</td>
<td>120 (29)</td>
<td>204 (36)</td>
<td>55 (22)</td>
<td>48 (19)</td>
</tr>
<tr>
<td>Deaths</td>
<td>42 (10)</td>
<td>65 (11)</td>
<td>14 (5)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>AEs leading to deaths</td>
<td>19 (5)</td>
<td>34 (6)</td>
<td>9 (4)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>AEs leading to treatment discontinuation</td>
<td>25 (6)</td>
<td>34 (6)</td>
<td>9 (4)</td>
<td>14 (6)</td>
</tr>
</tbody>
</table>

## NHL Rituximab Monotherapy (Pooled SABRINA-SparkThera)

<table>
<thead>
<tr>
<th></th>
<th>IV (n=255) No. (%)</th>
<th>SC (n=249) No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>208 (82)</td>
<td>202 (81)</td>
</tr>
<tr>
<td>Grade ≥ 3 AEs</td>
<td>73 (29)</td>
<td>67 (27)</td>
</tr>
<tr>
<td>SAEs</td>
<td>55 (22)</td>
<td>48 (19)</td>
</tr>
<tr>
<td>Deaths</td>
<td>14 (5)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>AEs leading to deaths</td>
<td>9 (4)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>AEs leading to treatment discontinuation</td>
<td>9 (4)</td>
<td>14 (6)</td>
</tr>
</tbody>
</table>

## CLL Combination Chemotherapy (SAWYER)

<table>
<thead>
<tr>
<th></th>
<th>IV (n=89) No. (%)</th>
<th>SC (n=85) No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>81 (91)</td>
<td>82 (96)</td>
</tr>
<tr>
<td>Grade ≥ 3 AEs</td>
<td>63 (71)</td>
<td>59 (69)</td>
</tr>
<tr>
<td>SAEs</td>
<td>29 (33)</td>
<td>25 (29)</td>
</tr>
<tr>
<td>Deaths</td>
<td>4 (4)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>AEs leading to deaths</td>
<td>2 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>AEs leading to treatment discontinuation</td>
<td>7 (8)</td>
<td>9 (11)</td>
</tr>
</tbody>
</table>

*ARRs*<sup>*</sup> = 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 straightforward 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

Reasons for preference

- Requires less time in the clinic (69%)
- Feels more comfortable during administration (37%)
- Feels less emotionally distressing (29%)
- Lower level of injection site pain (16%)

SC preferred (74% strong preference)
81%

IV preferred (7% strong preference)
11%

No preference
8%
RASQ Results Support the PPQ Results
PrefMab (NHL)

Impact on activities of daily living
- After IV Treatment: 84
- After SC Treatment: 58

Convenience
- After IV Treatment: 81
- After SC Treatment: 59

Psychological Impact
- After IV Treatment: 84
- After SC Treatment: 78

Satisfaction
- After IV Treatment: 87
- After SC Treatment: 75

Physical Impact
- After IV Treatment: 82
- After SC Treatment: 82

0 100 (Better outcome)
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

*Data as of October 2016
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

<table>
<thead>
<tr>
<th>BSA subgroup</th>
<th>Combination Chemotherapy (Pooled SABRINA - MabEase)</th>
<th>Rituximab Monotherapy (Pooled SABRINA - SparkThera Stage 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV n/N (%)</td>
<td>SC n/N (%)</td>
</tr>
<tr>
<td>Patients with at least one AE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>122/131 (93)</td>
<td>206/217 (95)</td>
</tr>
<tr>
<td>Medium</td>
<td>131/147 (89)</td>
<td>157/169 (93)</td>
</tr>
<tr>
<td>High</td>
<td>127/135 (94)</td>
<td>170/180 (94)</td>
</tr>
<tr>
<td>Patients with at least one Grade≥3 AE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>67/131 (51)</td>
<td>145/217 (67)</td>
</tr>
<tr>
<td>Medium</td>
<td>79/147 (54)</td>
<td>93/169 (55)</td>
</tr>
<tr>
<td>High</td>
<td>62/135 (46)</td>
<td>84/180 (47)</td>
</tr>
<tr>
<td>Patients with at least one serious AE (SAE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>39/131 (30)</td>
<td>90/217 (41)</td>
</tr>
<tr>
<td>Medium</td>
<td>52/147 (35)</td>
<td>63/169 (37)</td>
</tr>
<tr>
<td>High</td>
<td>29/135 (21)</td>
<td>51/180 (28)</td>
</tr>
</tbody>
</table>
## Treatment Discontinuations or Deaths by BSA

<table>
<thead>
<tr>
<th></th>
<th>Combination Chemotherapy (Pooled SABRINA - MabEase)</th>
<th>Rituximab Monotherapy (Pooled SABRINA - SparkThera Stage 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV N=413 n (%)</td>
<td>SC N=566 n(%)</td>
</tr>
<tr>
<td><strong>AEs Leading to Treatment Discontinuation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Pts with at least one AE (all)</td>
<td>25 (6)</td>
<td>34 (6)</td>
</tr>
<tr>
<td>Low BSA</td>
<td>9 (7)</td>
<td>17 (8)</td>
</tr>
<tr>
<td>Medium BSA</td>
<td>8 (5)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>High BSA</td>
<td>8 (6)</td>
<td>9 (5)</td>
</tr>
<tr>
<td><strong>Adverse Events Leading to Death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Pts with at least one AE (All)</td>
<td>19 (5)</td>
<td>34 (6)</td>
</tr>
<tr>
<td>Low BSA</td>
<td>8 (6)</td>
<td>20 (9)</td>
</tr>
<tr>
<td>Medium BSA</td>
<td>10 (7)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>High BSA</td>
<td>1 (1)</td>
<td>5 (3)</td>
</tr>
</tbody>
</table>
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

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