Rituximab Sottocute: è un passo avanti?

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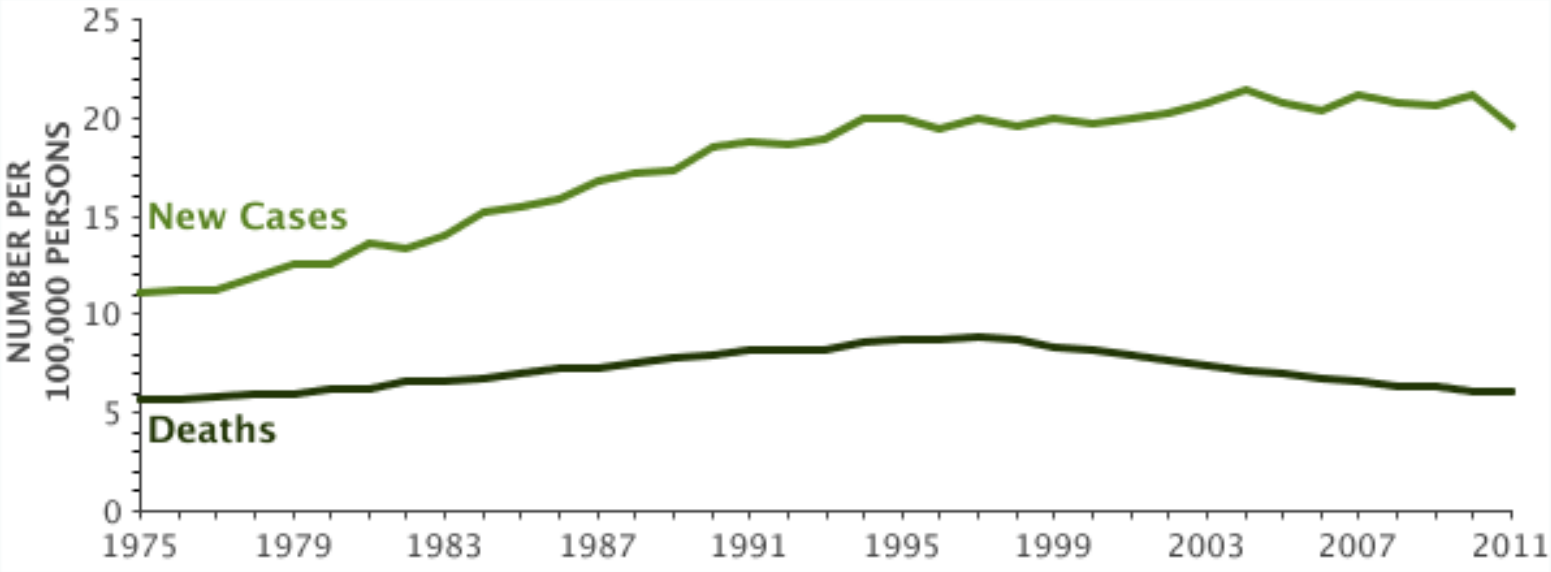
Epidemiology of Lymphomas

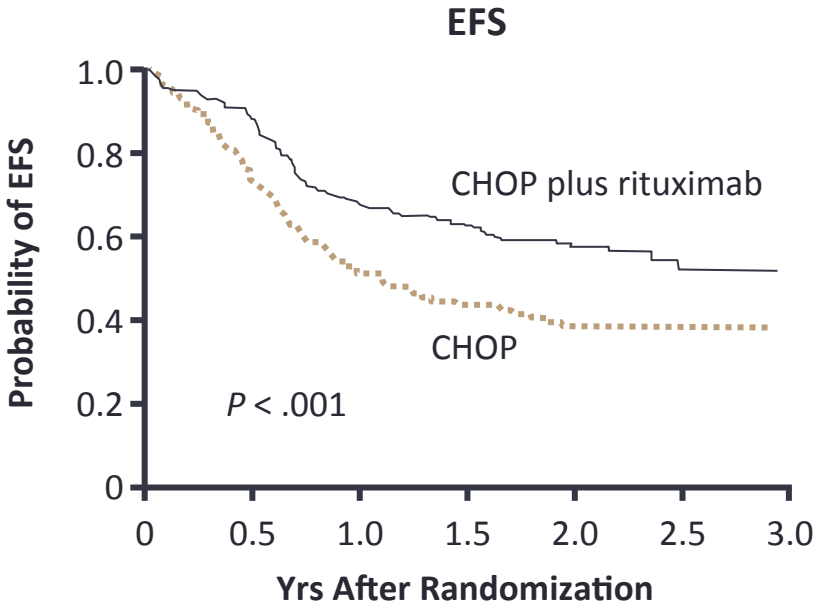
New Cases, Deaths and 5-Year Relative Survival View Data Tab



Year	1975	1980	1985	1990	1994	1998	2002	2006
5-Year Relative Survival	45.8%	49.1%	52.4%	49.7%	52.8%	61.0%	69.3%	70.3%

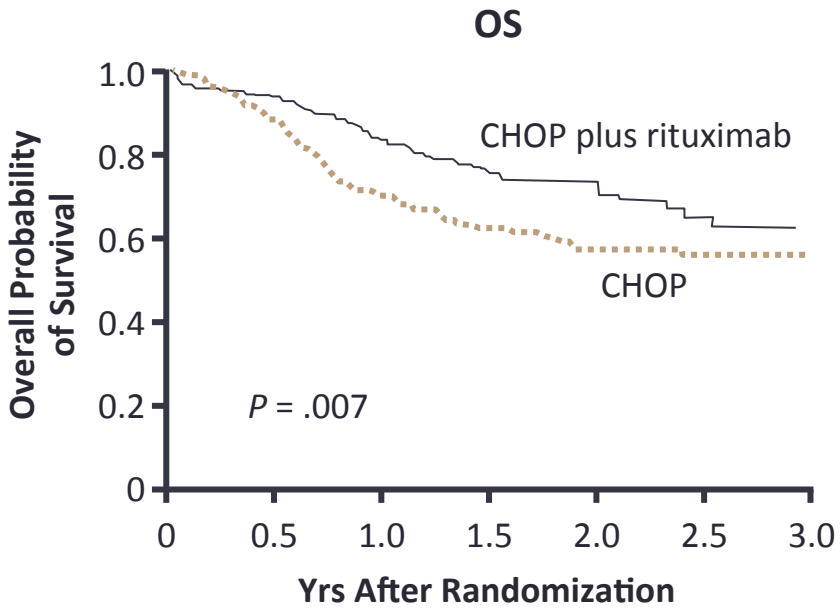
SEER 9 Incidence & U.S. Mortality 1975-2011, All Races, Both Sexes. Rates are Age-Adjusted.

CHOP ± Rituximab in DLBCL: 3-Yr Survival Results (GELA LNH-98.5 Study)



Pts at Risk, n

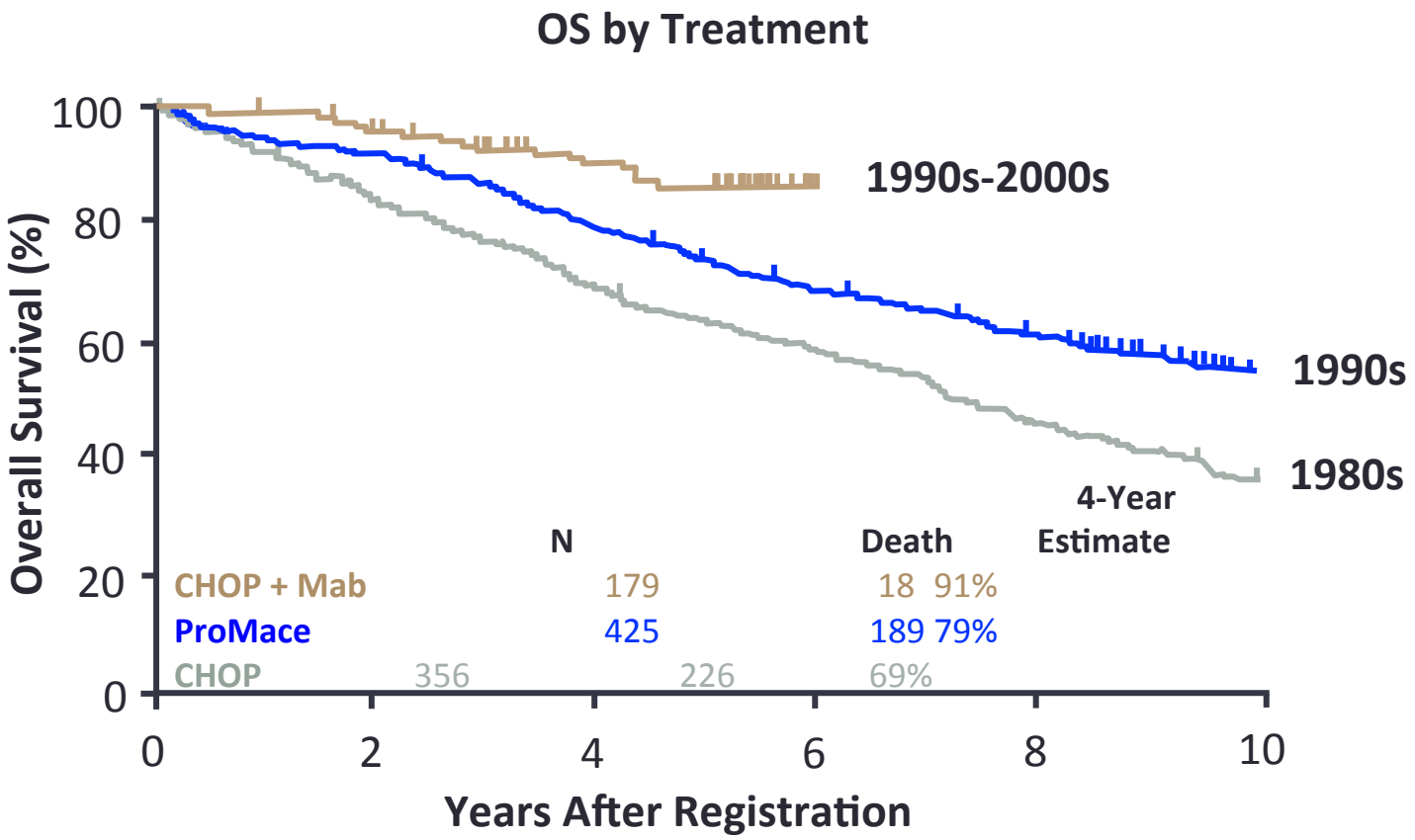
CHOP plus rituximab	202	177	137	108	63	19
CHOP	197	144	101	72	42	17



Pts at Risk, n

CHOP plus rituximab	202	187	167	118	64	21
CHOP	197	171	136	96	58	16

Improving Survival of Follicular NHL: Impact of Antibody-Based Therapy



Fisher RI, et al. J Clin Oncol. 2005; 23:8447-8452.

Success of Rituximab

1999	2002	2004	2006	2009	2012
R-mono in II rel FL	R-CHOP in DLBCL	R-CVP in FL	R-maint in rel/ref FL	R-chemo in FL	R-maint in I line FL + R-chemo in CLL

Is it possible to improve the R-side of ICT?

- Dosing
- Administration
- Efficacy

More appropriate use of rituximab

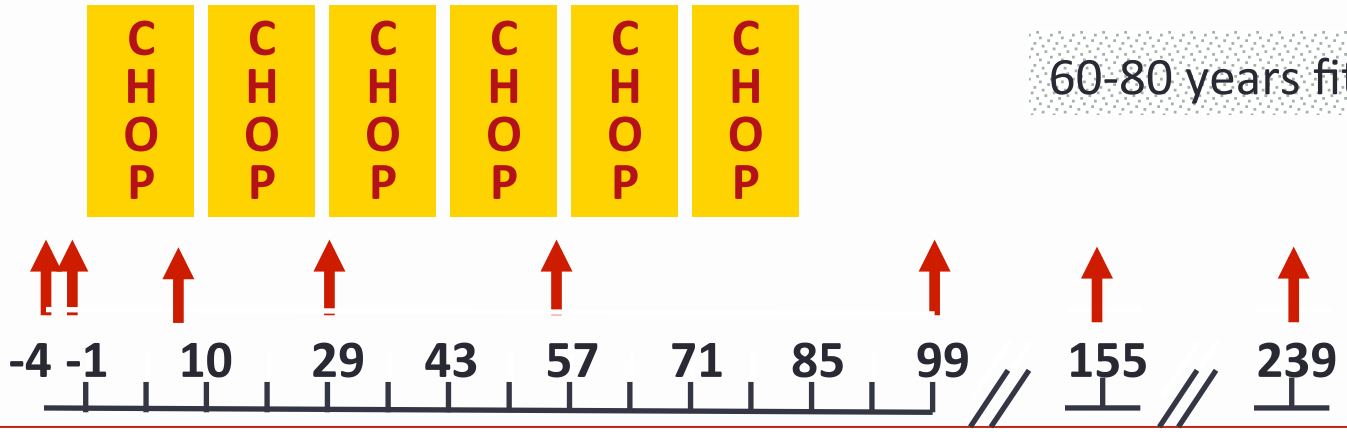
SMART-E –R-CHOP-14 TRIAL

- ✓ RCHOP 14 is not superior to RCHOP 21 (2 prospective trials)
- ✓ Pharmakokinetics of RCHOP 14 → plateau R – serum level not until cycle 5

AIM:

- ✓achieve high R levels early
- ✓manitain R serum levels over a prolonged period

SMARTE- R-CHOP-14 (8 x R)



Pfreundschuh

SMART-E-R-CHOP *vs* RCHOP 14 (RICOVER 60)

RETROSPECTIVE MATCHED COMPARISON (*data in percent)

	ALL PATIENTS						IPI 3-5		
	N^	CR*	PD*	G 3-4 Infect*	EFS*	OS*	N^	EFS *	OS*
SMARTE	99	84	5.6	3.3°	67.5	81.4	50	69°	78
RICOVER 60	306 ⚠	78	3	6.6°	66.5	78.1	123	54°	67

° p significant

⚠ → more high risk cases in SMARTE

Pharmakokinetic analysis:
earlier maximal R level in SMARTE vs RICOVER (2nd vs 6th course)

Pfreundschuh

RCHOP & GENDER

ORIGINAL ARTICLE: CLINICAL

Prognostic role of gender in diffuse large B-cell lymphoma treated with rituximab containing regimens: a Fondazione Italiana Linfomi/Grupo de Estudos em Moléstias Onco-Hematológicas retrospective study

Angelo M. Carella[1], Carmino A. de Souza[2], Stefano Luminari[3], Luigi Marcheselli[3], Annalisa Chiappella[4], Alice Di Rocco[5], Marina Cesaretti[3], Andrea Rossi[6], Luigi Rigacci[7], Gianluca Gaidano[8], Francesco Merli[9], Michele Spina[10], Caterina Stelitano[11], Stefan Hohaus[12], Anna Barbui[6], Benedetta Puccini[7], Eliana C. Miranda[2], Annalisa Guida[3] & Massimo Federico[3]

1793 DLBCL PTS 2001-2007

- ✓All treated with R-CT
- ✓53% males
- ✓5-yr PFS 76 % (whole cohort)
- ✓Male gender significant univariate - HR 1.52
- ✓Male gender significant multivariate adjusted by IPI

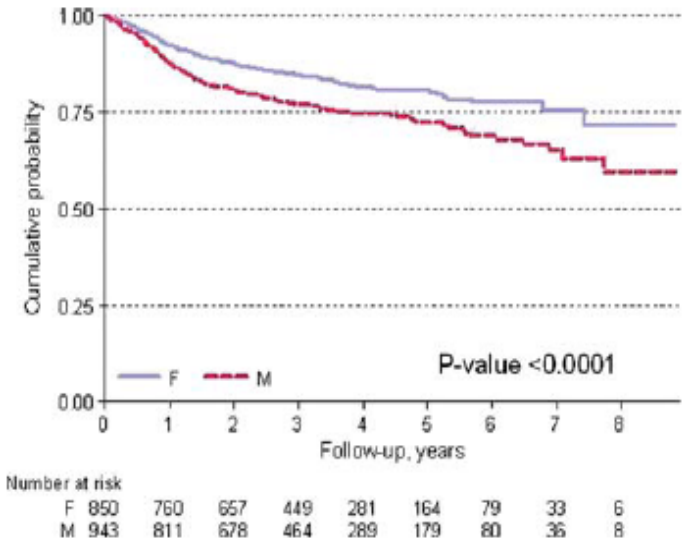
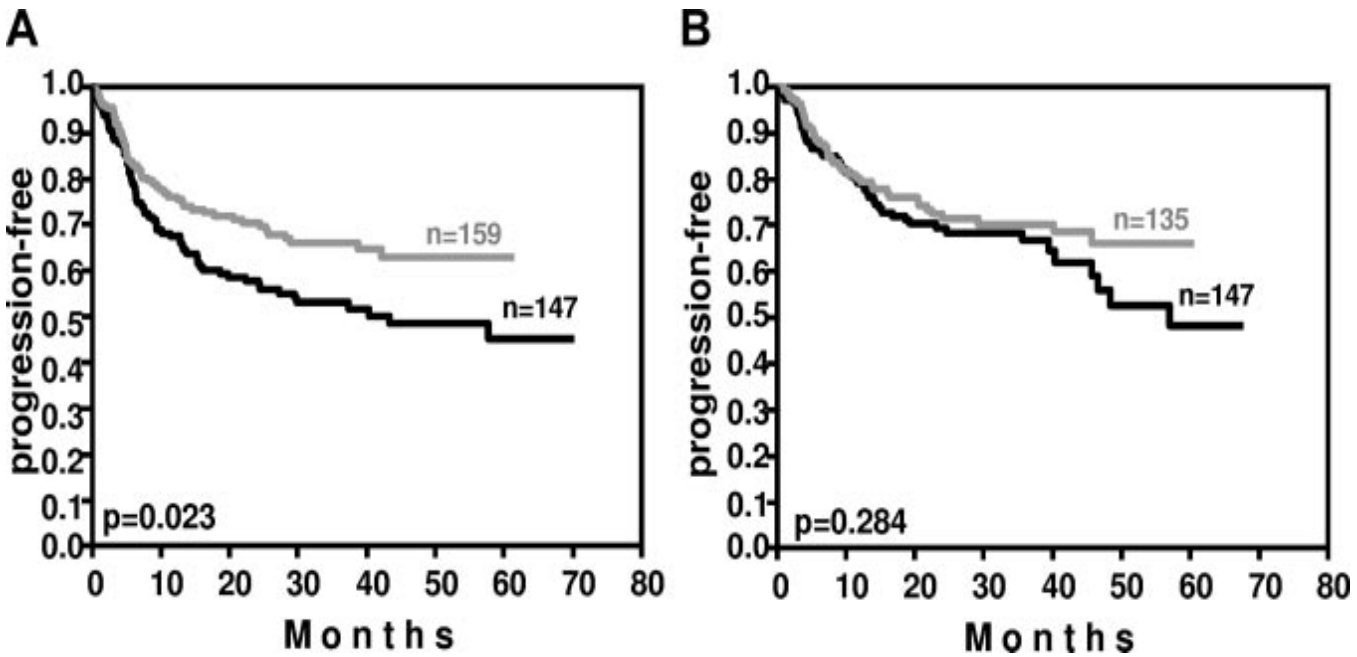


Figure 1. OS stratified by gender.

Impact of weight in R- pharmacokinetic

Impact of weight on PFS in RICOVER 60



Weight within lower quartile (female ≤ 60, male ≤ 73 Kg)

Weight within upper quartile (female ≥ 70, male ≥ 89 Kg)

Muller

blood

Role of gender & weight

20 pts RCHOP 14 RICOVER 60

Blood samples

10 min pre-R → 1 wk - 3,6,9 mos post R

	Clearance ml/h	Half life days
Male	**12.6**	**24.7**
	p0.03	*p0.03*
Female	**8.21**	**30.7**

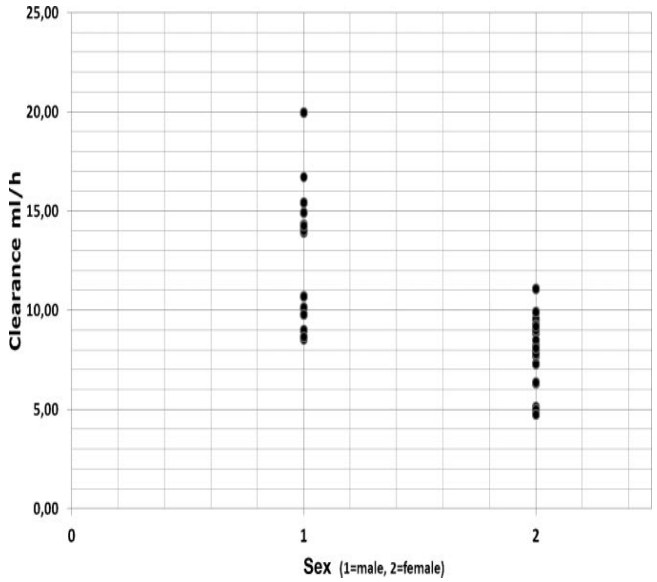


Table 4. Impact of weight on rituximab clearance and serum $t_{1/2\beta}$ in elderly male patients with DLBCL

	Median	Median + 25%	Median − 25%
Weight	88.8 kg	111.0 kg	66.6 kg
Clearance, mL/h	12.43	15.90	8.96
$t_{1/2\beta}$	527.0	412.0	731.3

Table 5. PFS rates of female and male patients treated in the RICOVER-60 trial with CHOP-14 with and without rituximab

	CHOP-14	R-CHOP-14
2-year PFS, % (95% CI)		
Female patients (n = 287/285)	62 (56-68)	77 (72-82)
Male patients (n = 325/325)	61 (56-67)	71 (66-76)
Difference	1.0 (0.7-1.3)	5.7 (5.4-6.0)
3-year PFS, % (95% CI)		
Female patients (n = 287/285)	60 (53-66)	75 (70-81)
Male patients (n = 325/325)	55 (49-60)	68 (62-73)
Difference	5.1 (4.8-5.5)	7.7 (7.4-8.0)
4-year PFS, % (95% CI)		
Female patients (n = 287/285)	50 (42-58)	72 (65-78)
Male patients (n = 325/325)	49 (42-56)	64 (58-70)
Difference	0.9 (0.3-1.5)	7.6 (7.2-8.0)

What are the challenges faced for IV administration?

IV infusion times for rituximab are long; inconveniencing patients

Preparation, premedication, monitoring and observation of patients are time-consuming tasks for healthcare professionals

IV infusion of treatments presents a challenge to organisational capacity

IV infusion is associated with a higher PK variability, and is a poor indicator of optimal drug exposure*

Salar A, *et al*. ASH 2010. Abstract 2858 (poster).
* Golay J. et al, mAbs 5:6, 1–12; November/December 2013
* Cartron G. et al, Clin Cancer Res 2011;17:19-30

SC Rituximab: Physicochemical Properties

Rituximab S.C. :

Same molecule of rituximab i.v.

Concentrating the rituximab 12-fold (MabThera i.v. : 10 mg/ml MabThera s.c: 120 mg/ml) **resulting in volume of 11.7 ml** (=1400:120)

Addition of hyaluronidase as permeation enhancer

Efforts have been made to concentrate the dose of rituximab IV; however, volume of 11.7 ml still remain too large to be effectively administered SC without permeation enhancer

rHuPH20 Gen2 =

2000 U / ml (2000 x 11,7 ml = 23400 U)

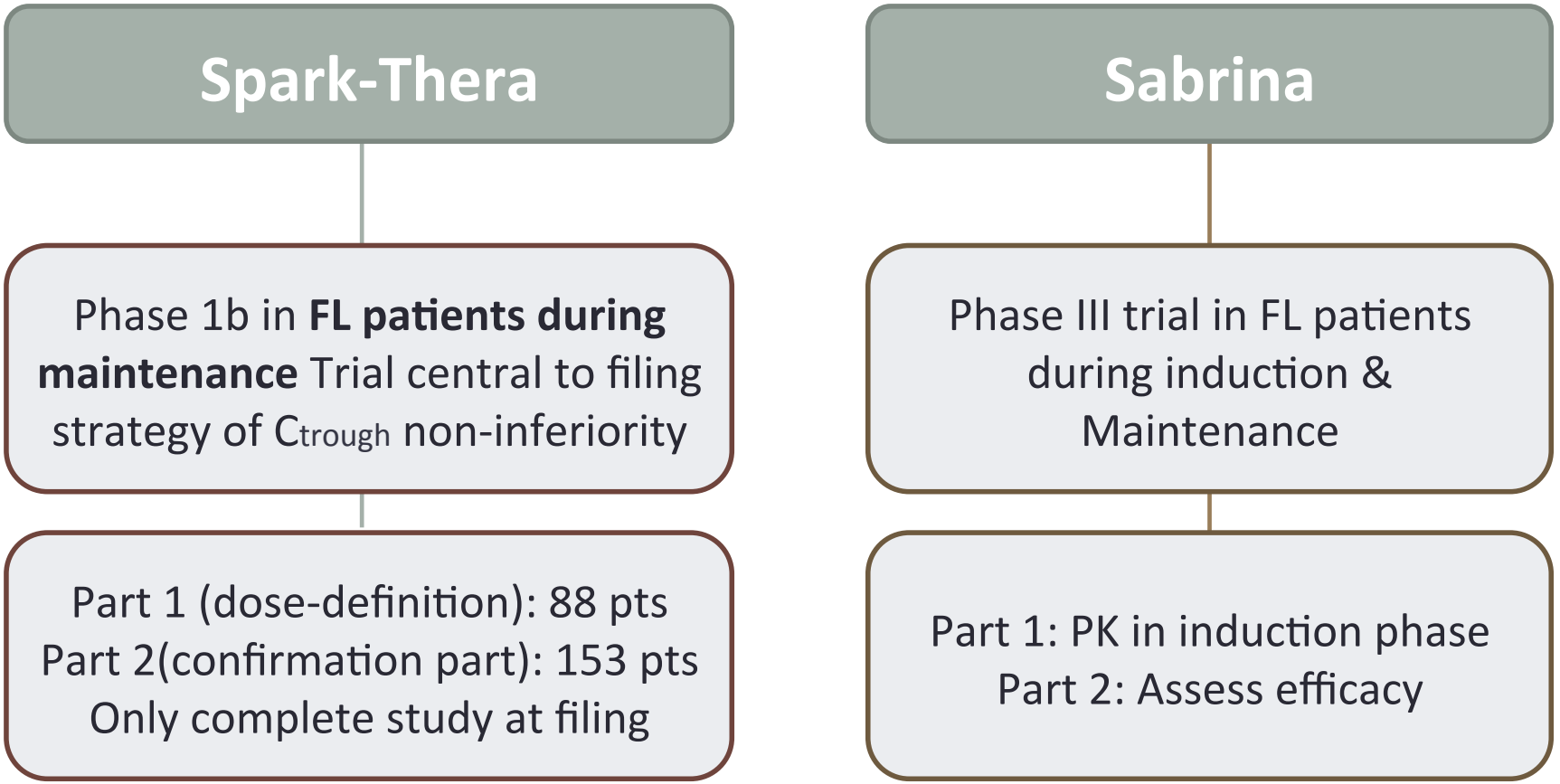
Classified as a novel permeation enhancer

No therapeutic effect

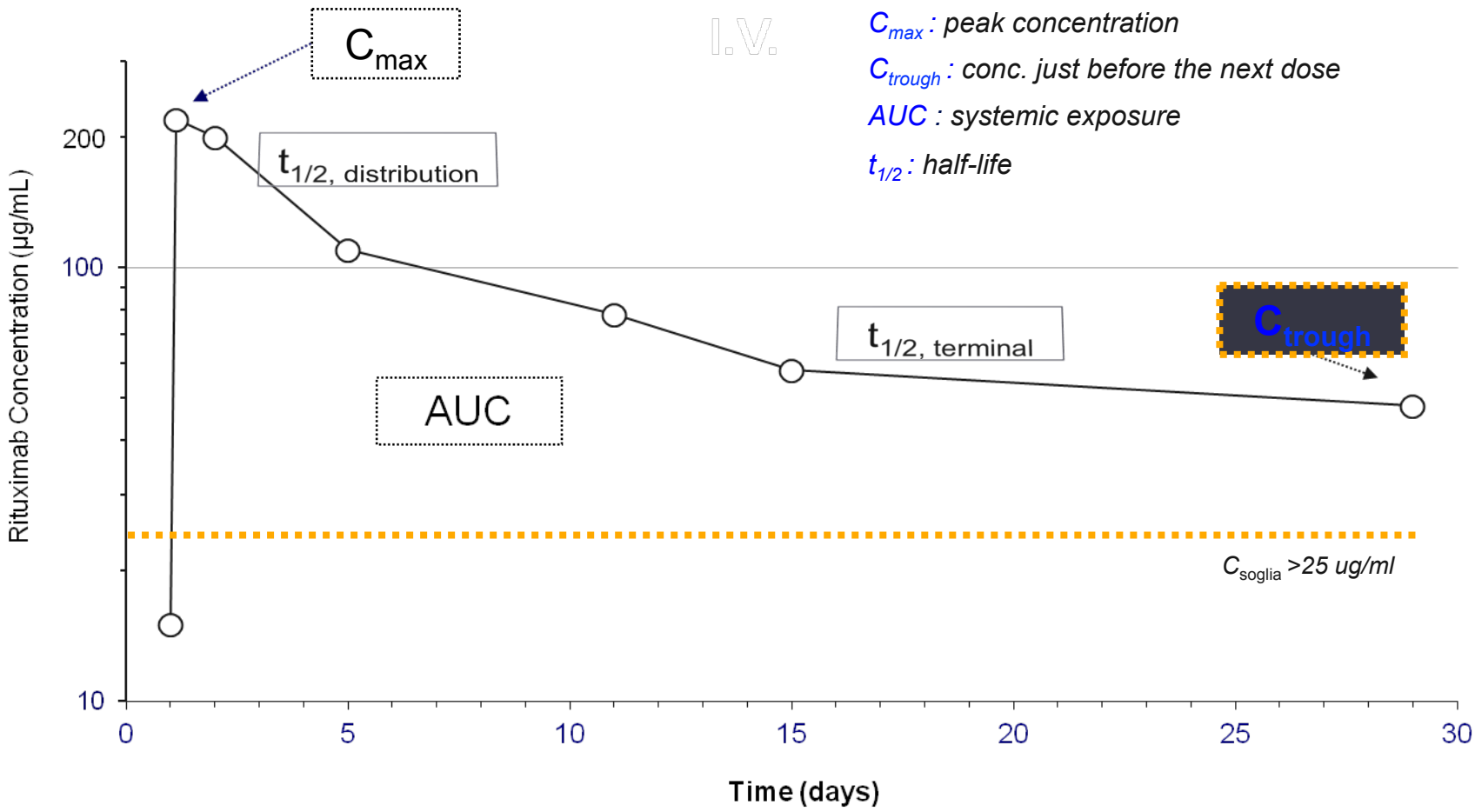
Transient and reversible impact

Salar A, *et al. Blood* 2010; 116:Abstract 2858 (Poster presentation).

NHL Registration Clinical Development Plan Based on 2 studies

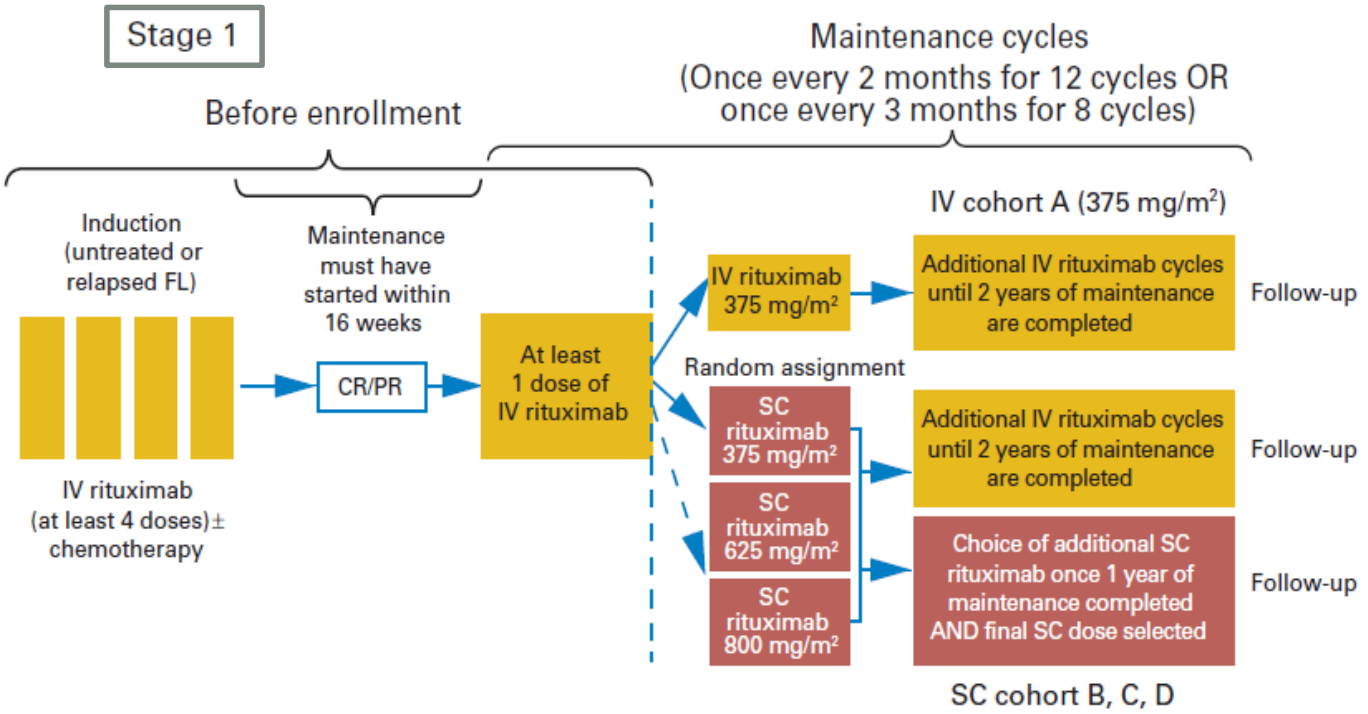


Rituximab disposition after Intravenous administration



The most important PK paramenter of rituximab is C_{trough}

A Comparison of Subcutaneous Versus Intravenous Administration of Rituximab as Maintenance Treatment for Follicular Lymphoma: Results from a Two-Stage, Phase Ib Study SPARK-THERA STUDY



- **Primary Objective:** to determine a SC rituximab dose that results in non-inferior Ctrough levels compared to an IV rituximab dose of 375 mg/m2
- Non- inferiority = 90% CI of R-SC/R-IV C_{trough} ratio above 0.8

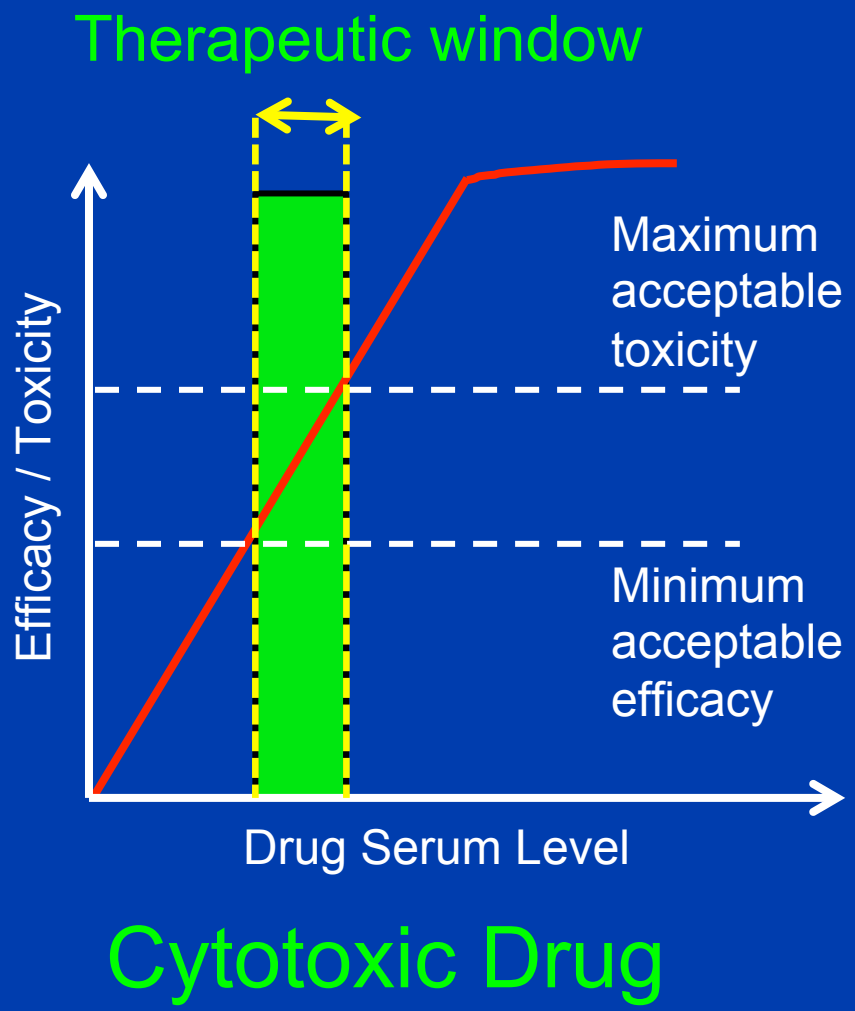
SPARK-THERA STUDY stage1

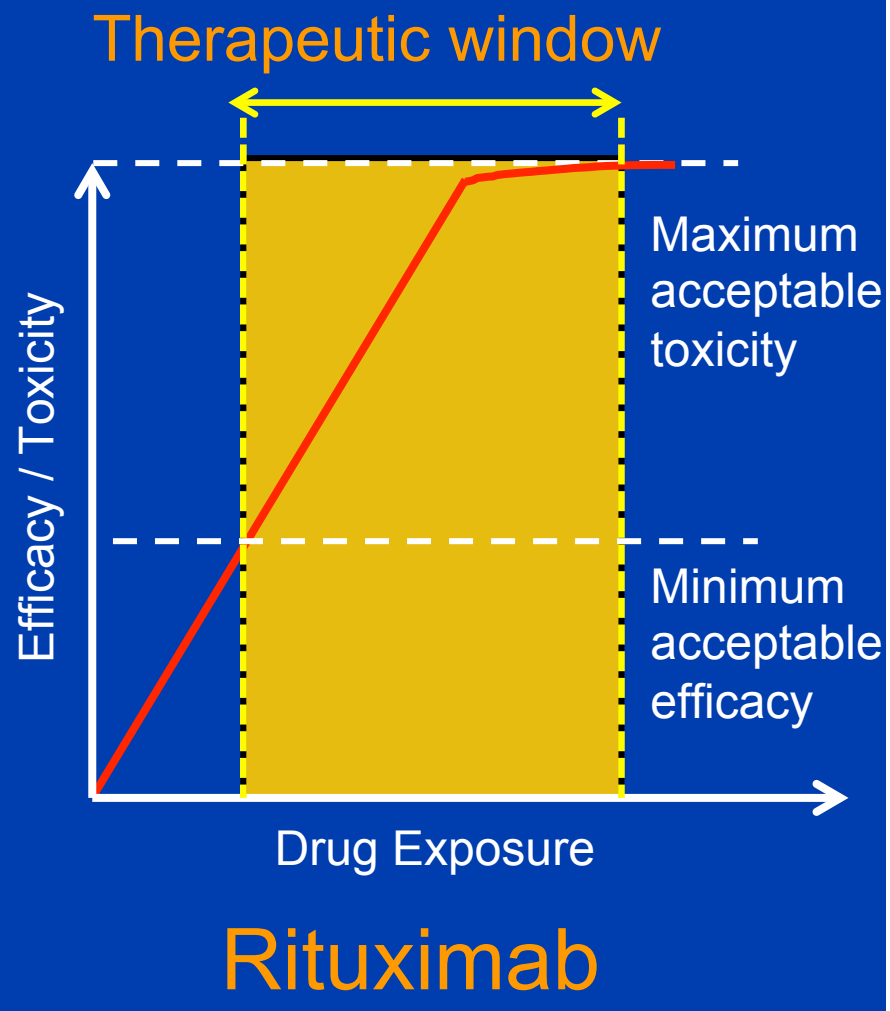
Cohort	Regimen	PK parameter, mean ± standard deviation (n)		
		C_{trough} (µg/ml)	AUC_{0-57} (day ·µg/ml)	AUC_{0-85} (day ·µg/ml)
375 mg/m² IV	q2m	45.2 ± 32.5 (8)	4,830 ± 1,550 (9)	–
	q3m	14.6 ± 6.76 (5)	–	4,300 ± 946 (7)
375 mg/m² SC	q2m	19.1 ± 11.7 (15)	2,380 ± 944 (17)	–
	q3m	13.8 ± 10.0 (11)	–	2,880 ± 1,240 (16)
625 mg/m² SC	q2m	42.5 ± 18.0 (15)	4,530 ± 1,580 (18)	–
	q3m	15.6 ± 9.76 (9)	–	4,130 ± 1,700 (15)
800 mg/m² SC	q2m	52.1 ± 21.0 (16)	5,120 ± 2,010 (20)	–
	q3m	19.9 ± 11.8 (7)	–	5,740 ± 1,710 (18)

- Rituximab C_{trough} on Day 28 and AUC in patients administered 625 mg/m² Rituximab SC were comparable to those in patients given Rituximab intravenously (375 mg/m²)

Salar A, *et al*. ASH 2010; Abstract 2858

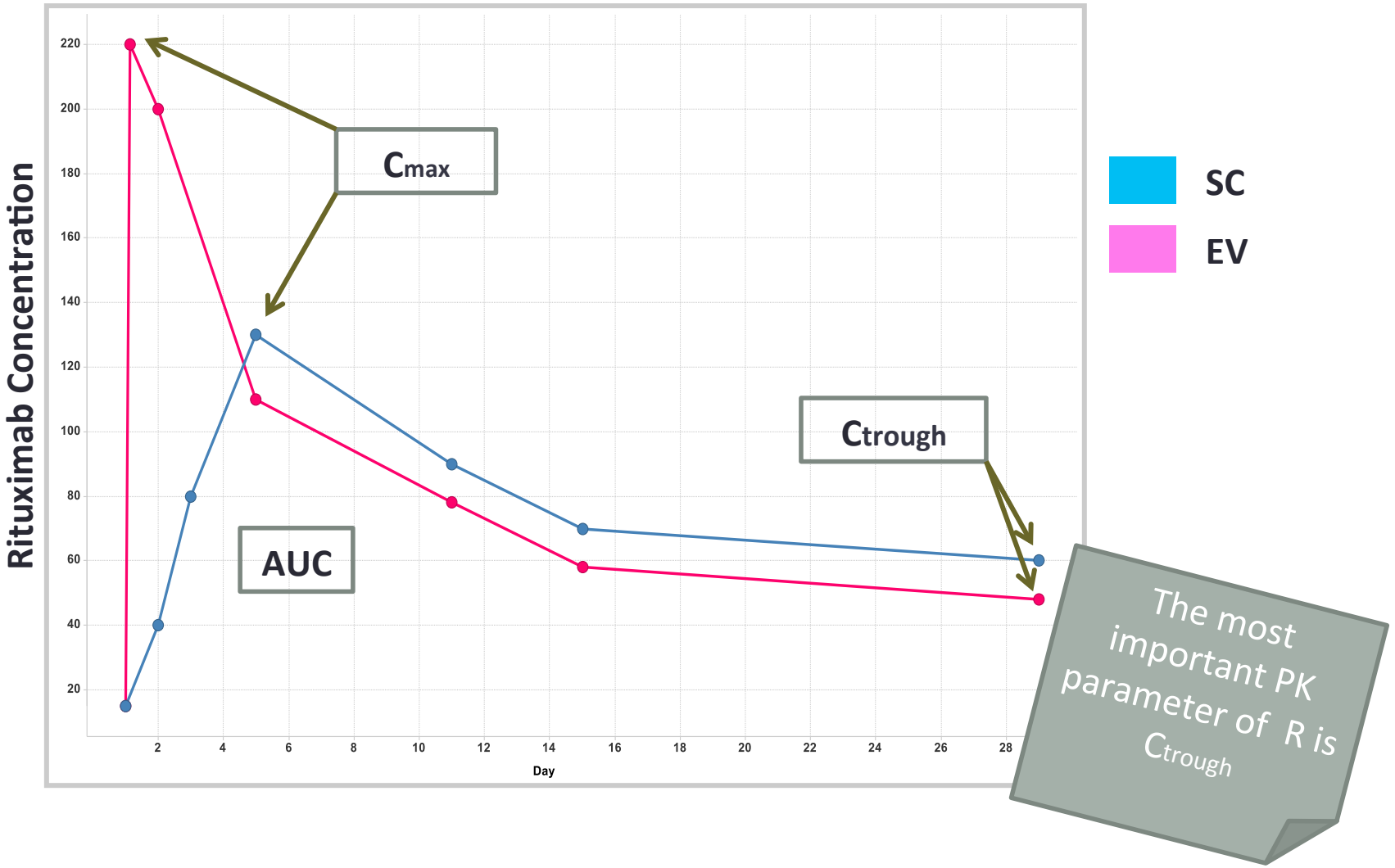
Therapeutic Windows: Cytotoxic Drugs vs Rituximab





Rituximab SC fixed Dose

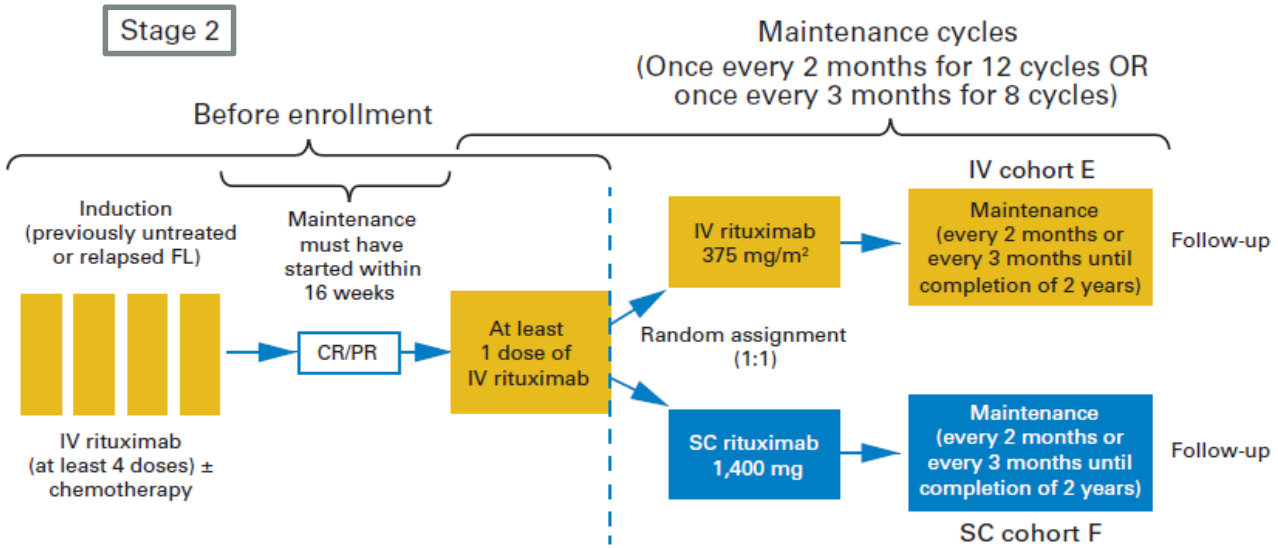
The fixed dose has been calculated from the PK results of the dose-finding stage of BP22333 (SparkThera trial)



MabThera IV administration vs SC

Mabthera IV	Mabthera SC
About 700mg containing 375mg/mq administered in 2,5-4,5 hours	11.7 ml containing 1400 mg administered in 6 minutes
Concentrate for solution for infusion	Ready to use liquid formulation
Rituximab at a concentration of 10 mg/ mL (total 500 mg or 100 mg)	Rituximab at a concentration of 120 mg/mL (total 1400 mg)
To be diluted in glucosate or saline solution to a calculated concentration of 1 to 4 mg/ml prior to administration	Must not be diluted prior to administration
The drug product is a sterile, clear, colourless liquid	The drug product is a sterile, colorless to yellowish, clear to opalescent liquid
Vials: colorless 50 ml or 10 ml vials	Vials: colorless 11.7 mL vials

SPARK-THERA STUDY stage2



Stage 1 identified a flat dose of 1.400 mg rituximab SC for non-inferiority testing

Stage 2: N = 154 (IV, n = 77; SC, n = 77)

Stage 2 primary endpoint: Non-inferiority of rituximab SC C_{trough} compared with IV

- Protocol-specified non-inferiority limit was an SC:IV C_{trough}, ratio of 0.8

Secondary endpoints included: PK (AUC) and safety

Salar A, et al. J Clin Oncol doi:10.1200/JCO.2013.52.2631, 2014

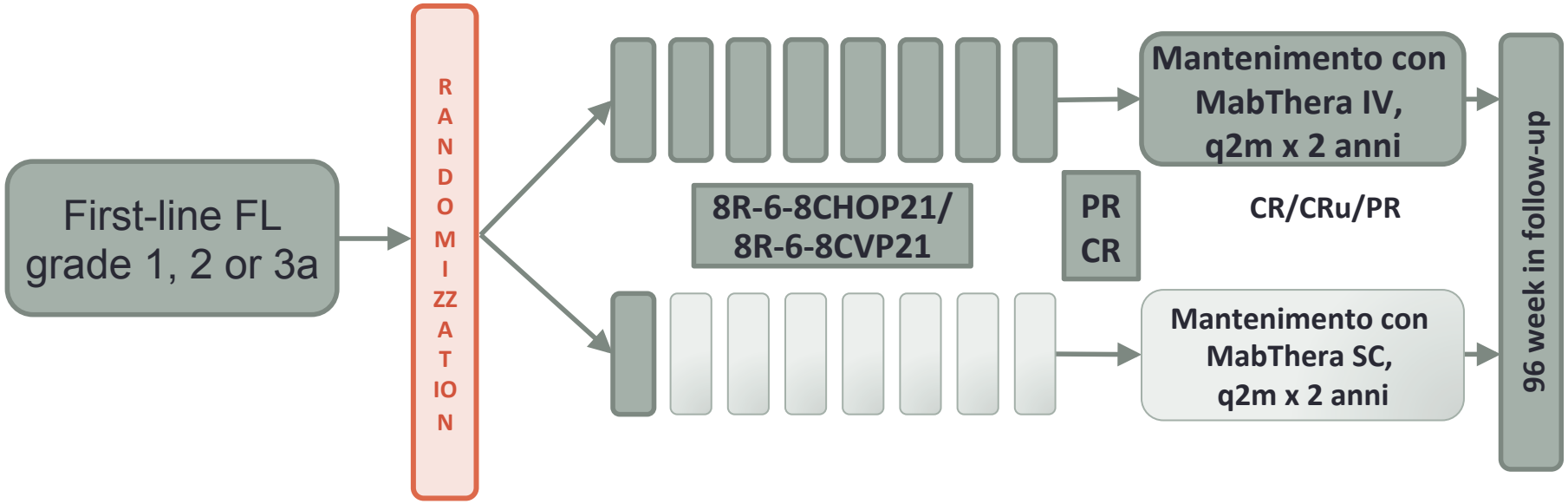
SPARK-THERA STUDY stage2: AEs

AE, n (%)	SC 1400 mg (n=77)	IV 375 mg/m^2 (n=77)
Any AE	61 (79)	61 (79)
Leading to withdrawal from treatment	4 (5)	4 (5)
Leading to temporary dose modification/interruption	8 (10)	7 (9)
Grade 3 (severe) AE	14 (18)	13 (17)
Serious AE	9 (12)	11 (14)
Leading to withdrawal	2 (3)	2 (3)
Leading to temporary dose modification/interruption	2 (3)	0 (0)
Related to treatment	2 (3)	1 (1)
Treatment-related AE	37 (48)	19 (25)
Leading to withdrawal from treatment	2 (3)	2 (3)
Leading to temporary dose modification/interruption	5 (6)	3 (4)
ARRs*	24 (31)	3 (4)
Erythema	10 (13)	–
Injection-site erythema	4 (5)	–
Myalgia	4 (5)	–

Overall safety profiles were similar for SC vs IV. Local administration-related reactions (ARRs; mainly mild-to-moderate) were more frequent with MabThera SC

Salar A, et al. J Clin Oncol doi:10.1200/JCO.2013.52.2631, 2014

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



- **Stage 1**, N = 127 (rituximab IV, n = 64; rituximab SC, n = 63)
- Stratified by FLIPI, chemotherapy and region: 40 pts in each arm (63%) received R-CHOP
- **Stage 1 primary endpoint:** *non-inferiority PK* of the SC:IV C_{trough} ratio at cycle 7 of induction (limit for non-inferiority was SC:IV C_{trough} ratio > 0.8)
- **Secondary endpoints:** other PK endpoints, safety, efficacy and pharmacoeconomic parameters

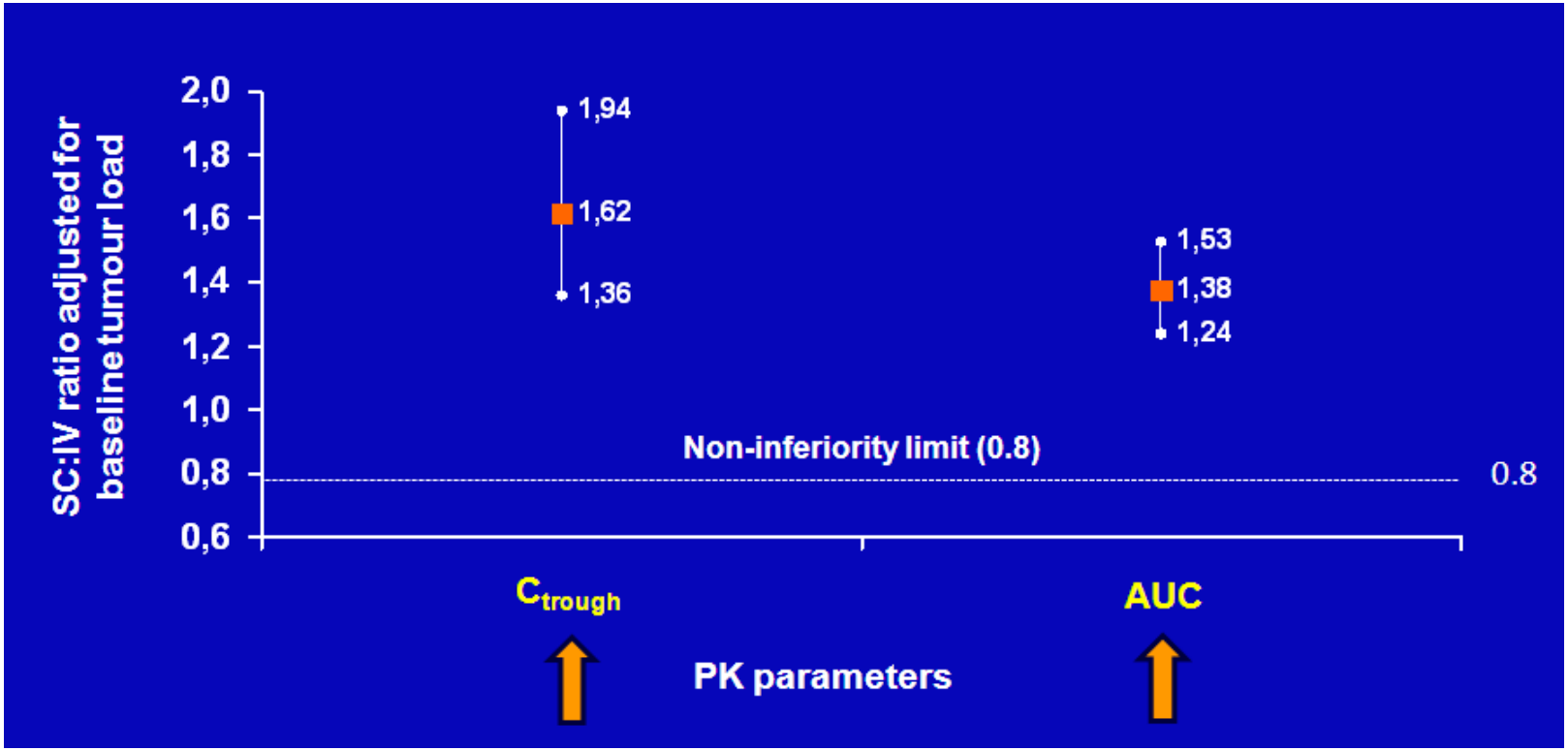
Davies A, the Lancet Oncology, vol15march2014

SABRINA STUDY stage1: PK endpoint

Primary PK endpoint was met: SC:IV C_{trough} ratio of 1.62 (90% CI: 1.36, 1.94)

Therefore, SC rituximab (1,400 mg) is non-inferior to IV rituximab (375 mg/m^2)

SC:IV AUC ratio 1.38 [90% CI: 1.24, 1.53]) is also non-inferior



Davies A, the Lancet Oncology, vol15march2014

SABRINA STUDY stage1: Efficacy

	Intravenous rituximab plus chemotherapy (n=64)		Subcutaneous rituximab plus chemotherapy (n=63)	
	Investigator assessment	Independent review	Investigator assessment	Independent review
Overall response	54 (84%)	56 (88%)	57 (90%)	54 (86%)
CR or CRu	19 (30%)	12 (19%)	29 (46%)	17 (27%)
PR	35 (55%)	44 (69%)	28 (44%)	37 (59%)
Stable disease	3 (5%)	1 (2%)	2 (3%)	4 (6%)
Progressive disease	1 (2%)	0	0	2 (3%)
Missing or invalid*	6 (9%)	7 (11%)	4 (6%)	3 (5%)

	Overall response (CR, CRu, PR)		Complete response (CR or CRu)	
	Intravenous rituximab plus chemotherapy	Subcutaneous rituximab plus chemotherapy	Intravenous rituximab plus chemotherapy	Subcutaneous rituximab plus chemotherapy
Overall	54/64 (84%)	57/63 (90%)	19/64 (30%)	29/63 (46%)
Low BSA*	15/16 (94%)	22/26 (85%)	5/16 (31%)	14/26 (54%)
Medium BSA*	20/26 (77%)	15/16 (94%)	7/26 (27%)	8/16 (50%)
High BSA*	18/21 (86%)	20/21 (95%)	7/21 (33%)	7/21 (33%)
Male	27/33 (82%)	25/26 (96%)	7/33 (21%)	11/26 (42%)
Female	27/31 (87%)	32/37 (86%)	12/31 (39%)	18/37 (49%)
CHOP	34/40 (85%)	37/40 (93%)	13/40 (33%)	17/40 (43%)
CVP	20/24 (83%)	20/23 (87%)	6/24 (25%)	12/23 (52%)

Davies A, the Lancet Oncology, vol15march2014

SABRINA STUDY stage2: Safety Results

	Rituximab	
	IV	**SC**
AE	92%	93%
AEs grade ≤2	88%	90%
Patients with at least one toxicity of Grade ≥3 (%)	47%	49%
SAE **Infections** **Febrile neutropenia**	26% 8% 6%	29% 10% 4%
ARRs	33%	47%

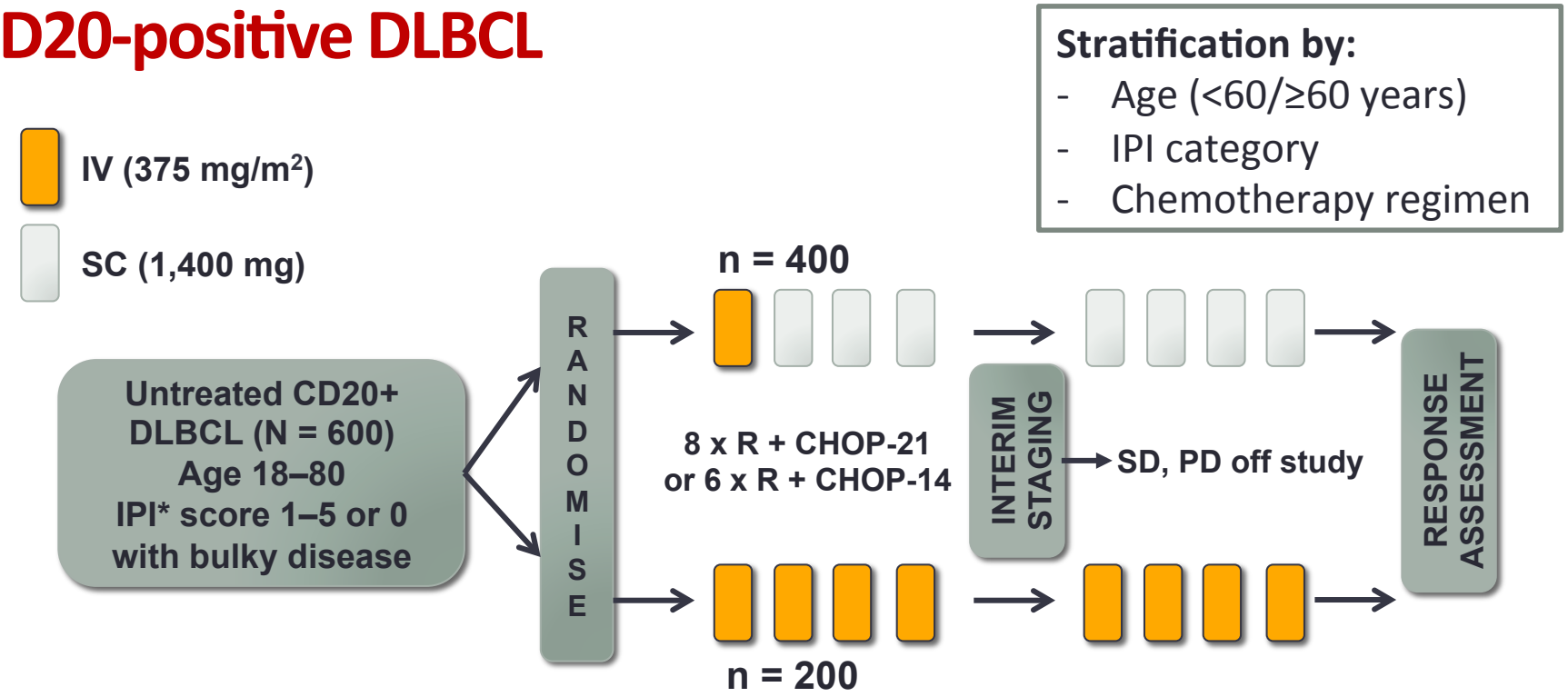
SABRINA STUDY stage2: Response Rate

	Rituximab	
	IV (n. 205)	**SC (n. 205)**
ORR	84 % (78.7 - 89.1%)	83 % (77.6 - 88.2%)
CR/CRu	31.7%	32.7%

ORR and CR Rate indicate that switching to the SC route of administration does not impair rituximab's anti-lymphoma activity (follow-up 14.4 months)

Davies A, abs 5054, EHA Milano 12-15 june 2014

MabEase: Comparative, randomised (2:1), multicentre, open-label, phase IIIb study in previously untreated CD20-positive DLBCL

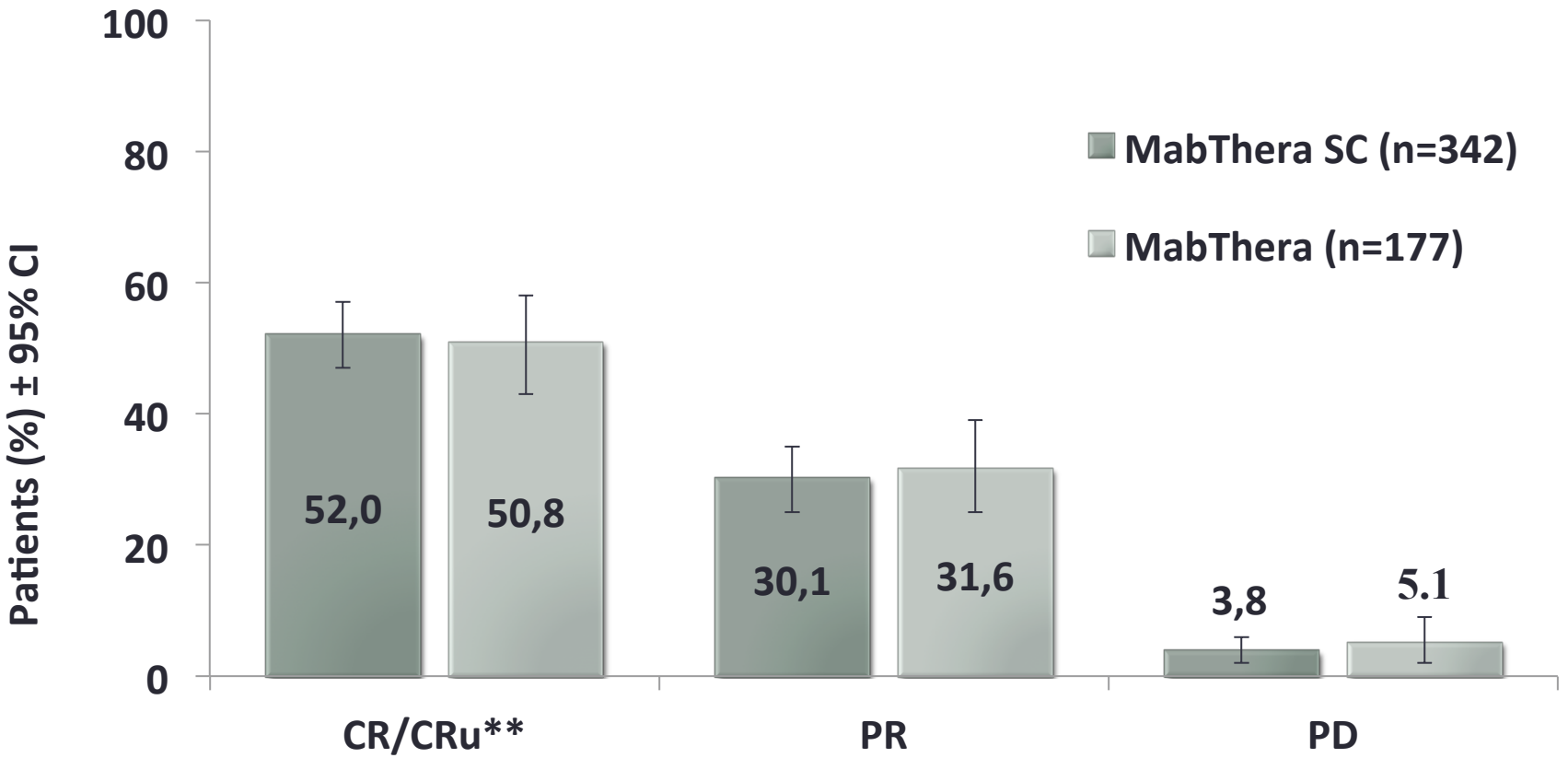


Primary objective: efficacy (CR) 4–8 weeks after the end of treatment

Secondary objectives: patient satisfaction with Rituximab SC vs Rituximab administered intravenously in patients with DLBCL, efficacy (EFS, DFS, PFS and OS from randomisation), safety

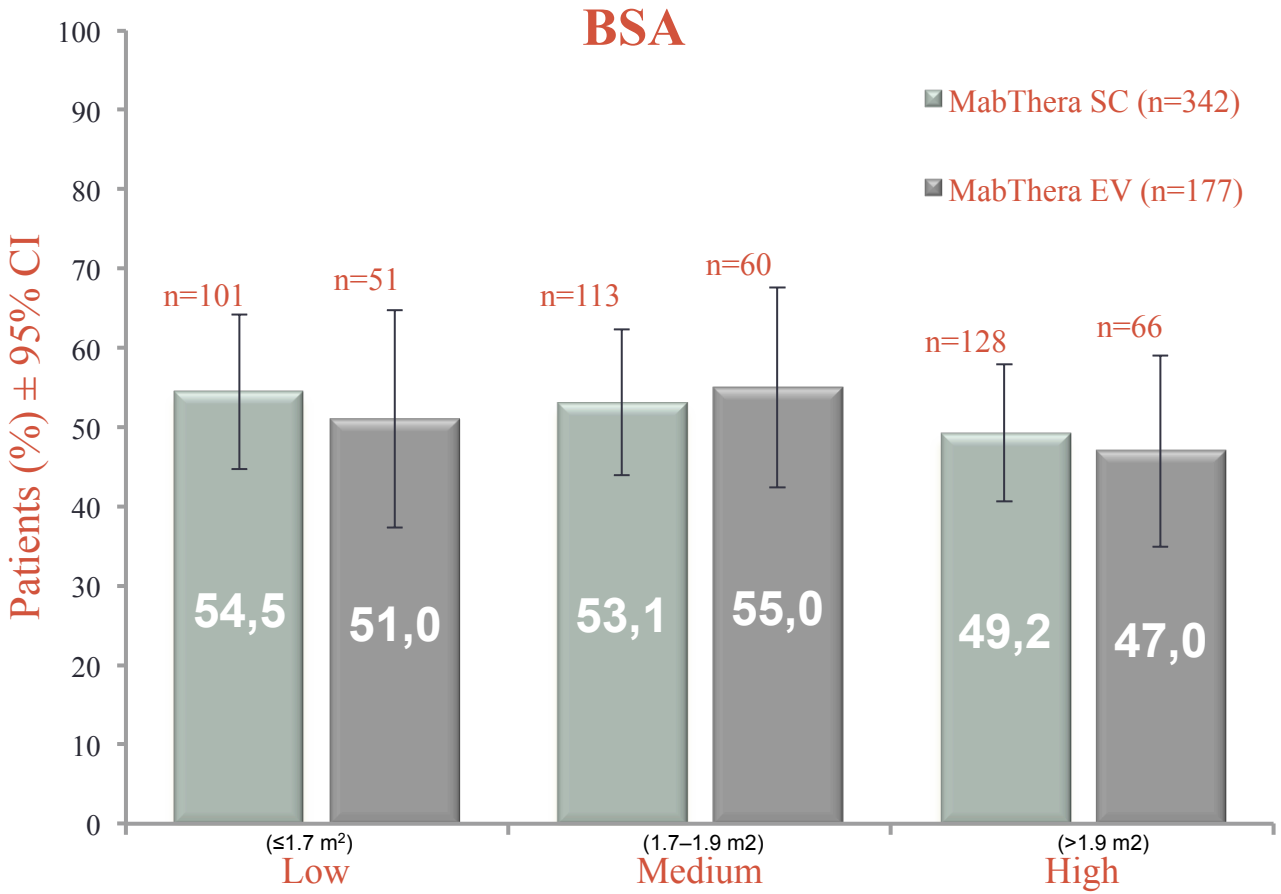
Lugtenburg P et al. Abs S484 , presented at EHA Vienna 11-14 june 2015

MabEase Study: End of treatment response rate ITT



Lugtenburg P et al. Abs S484 , presented at EHA Vienna 11-14 june 2015

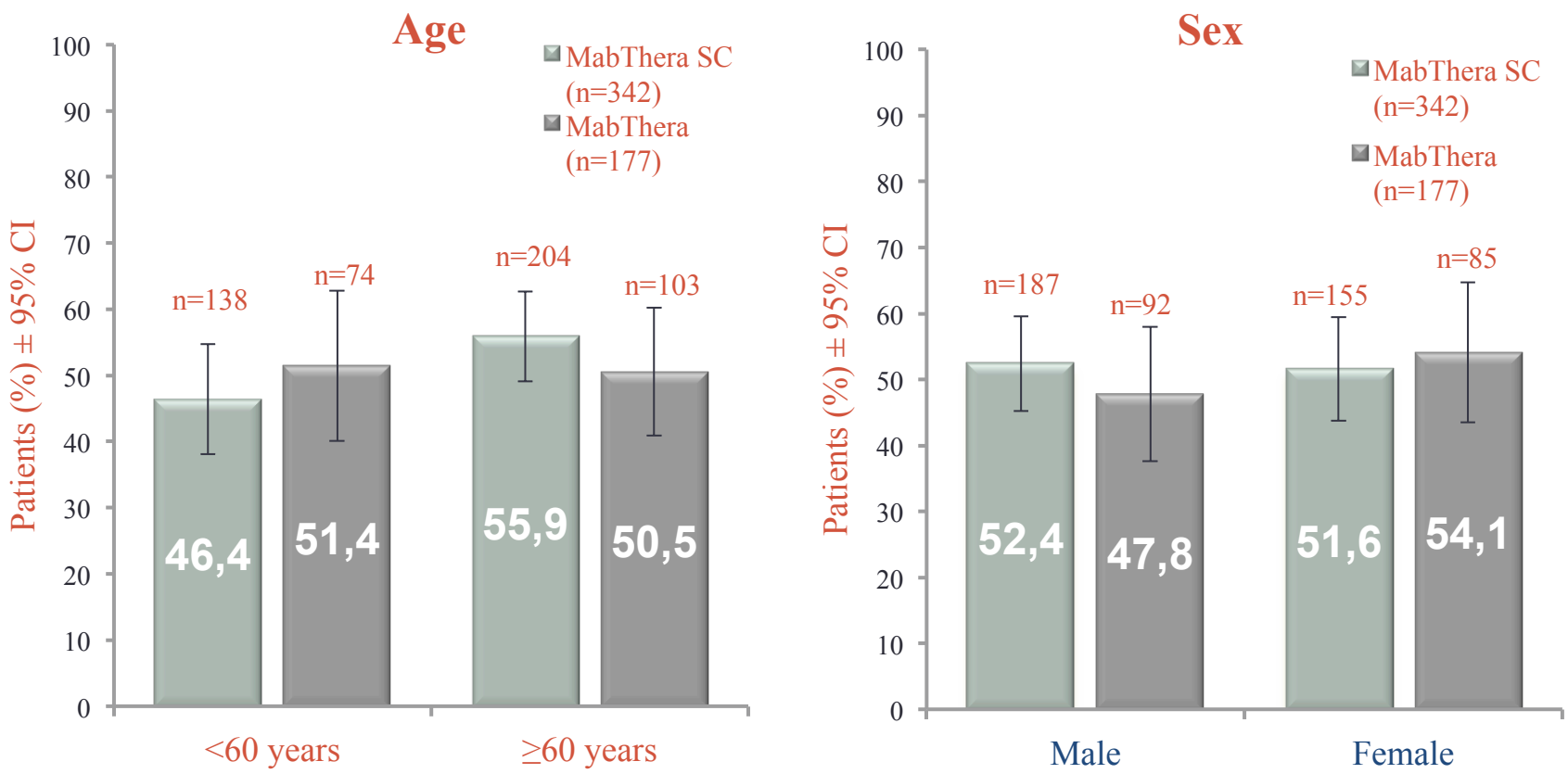
MabEase: CR/CRu* by BSA



End-of-induction CR/CRu was comparable between treatment arms

Lugtenburg P et al. Abs S484 , presented at EHA Vienna 11-14 june 2015

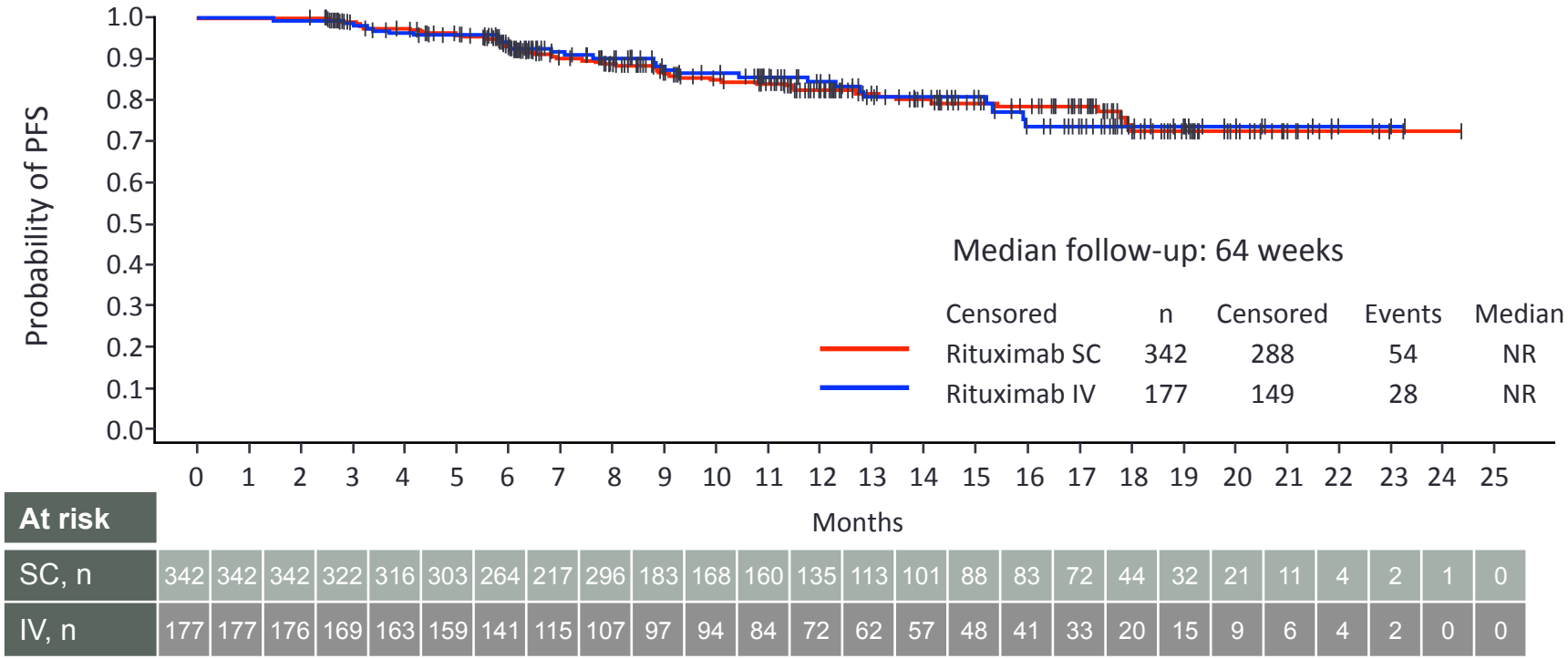
MabEase: CR/CRu* by age and sex (ITT)



End-of-induction CR/CRu was comparable between treatment arms

Lugtenburg P et al. Abs S484 , presented at EHA Vienna 11-14 june 2015

MabEase Study: Progression free survival

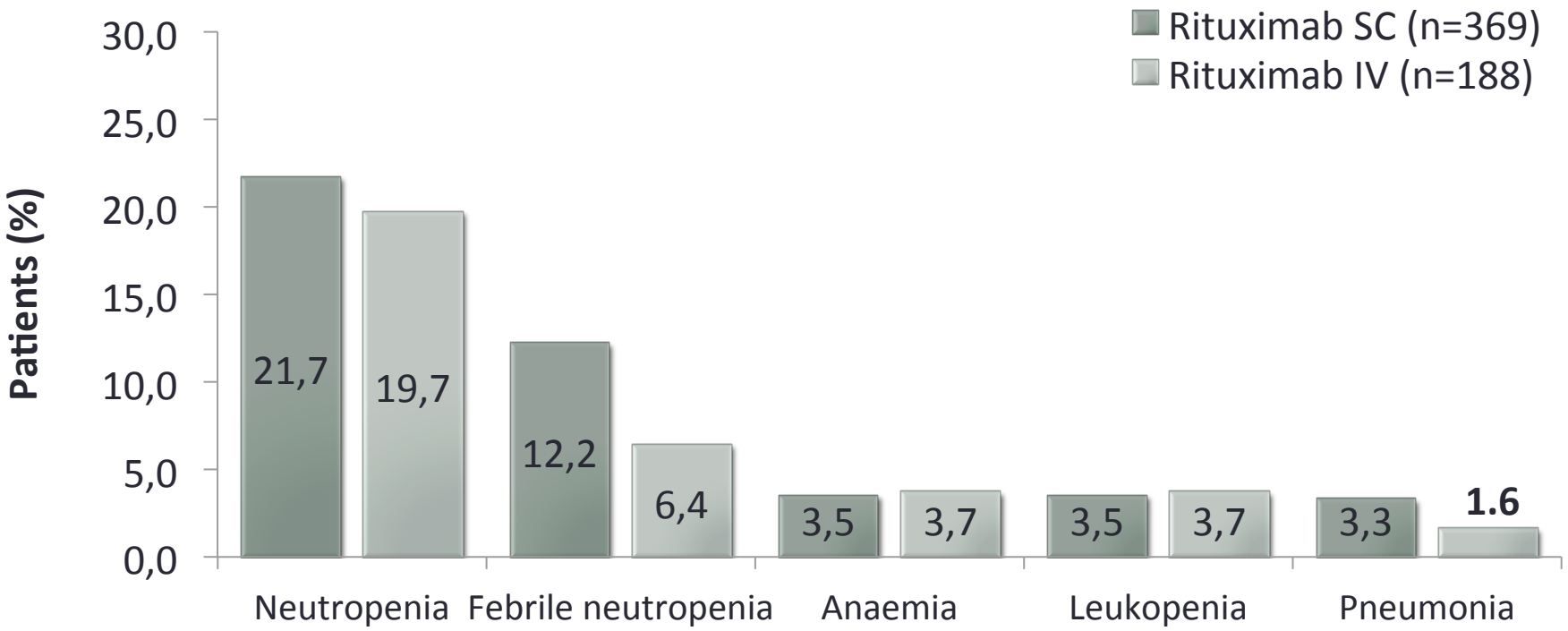


At risk																									
SC, n	342	342	342	322	316	303	264	217	296	183	168	160	135	113	101	88	83	72	44	32	21	11	4	2	1	0
IV, n	177	177	176	169	163	159	141	115	107	97	94	84	72	62	57	48	41	33	20	15	9	6	4	2	0	0

Lugtenburg P et al. Abs S484 , presented at EHA Vienna 11-14 june 2015

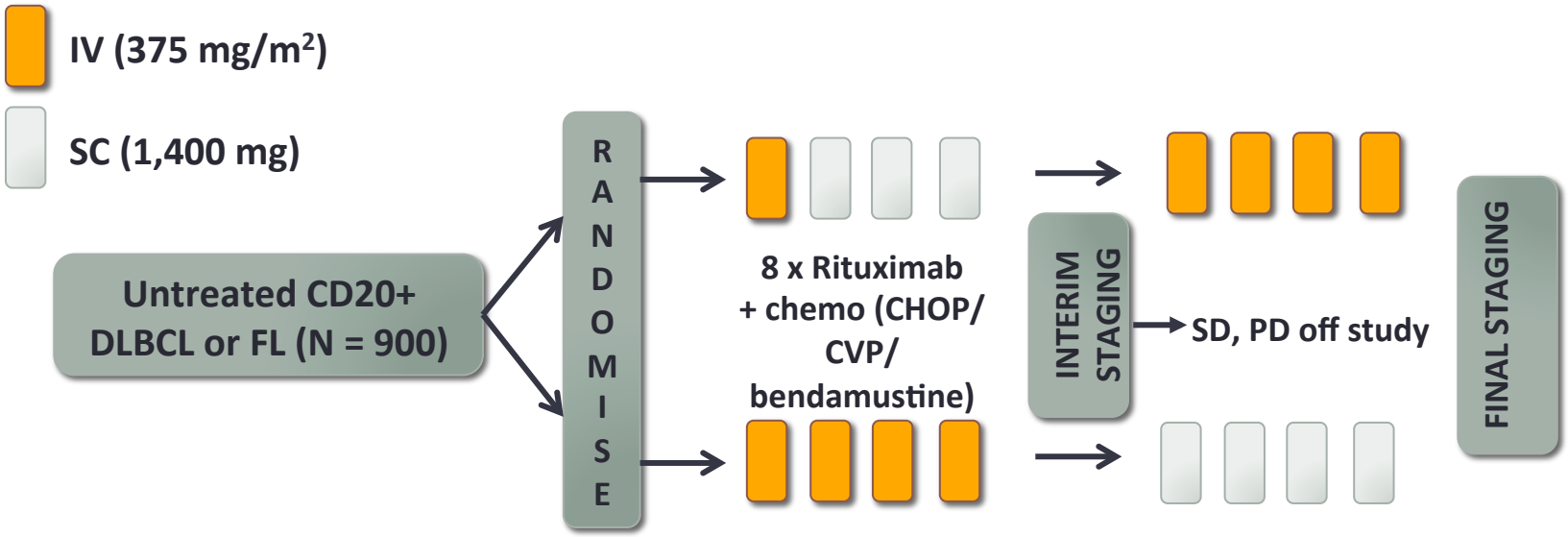
MabEase Study: Adverse events grade ≥3 in cycle 2 or later (safety population)

AE of grade ≥3 in cycle 2 or later	Rituximab SC	Rituximab IV
Total number of patients with ≥1 AE of grade ≥3	195 (52.8%)	93 (49.5%)
Total number of events of grade ≥3	476	229



Lugtenburg P et al. Abs S484 , presented at EHA Vienna 11-14 june 2015

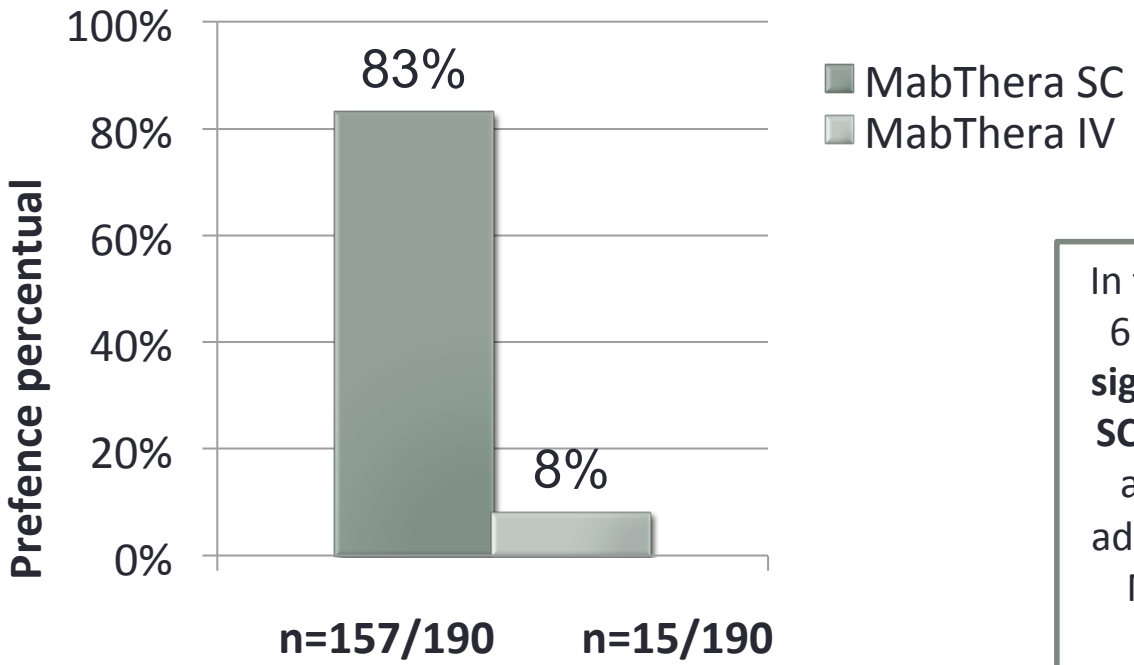
PrefMab (MO28457): Study design



- Primary objective: proportion of patients with a preference for Rituximab SC or Rituximab administered intravenously, to be assessed using a Preference Questionnaire
- Secondary objectives:
  - Safety of Rituximab SC
  - Efficacy (CR including CRu, EFS, DFS, PFS and OS)
  - Comparisons of administration time, patient-assessed satisfaction and convenience using the Cancer Therapy Satisfaction Questionnaire and Rituximab Administration Satisfaction Questionnaire and immunogenicity for Rituximab SC vs Rituximab administered intravenously

Rummel M., abstract presented at 19° EHA Congress, abstract #5054 Haematologica June 2014 99: 1-796, P467

PrefMab (MO28457): Study design



In the study, 83% of patients in Cycle 6 (and 86% in Cycle 8) **expressed a significant preference for Rituximab SC compared to the IV formulation**, after experiencing both modes of administration during induction with MabThera plus chemotherapy in DLBCL and follicular lymphoma.

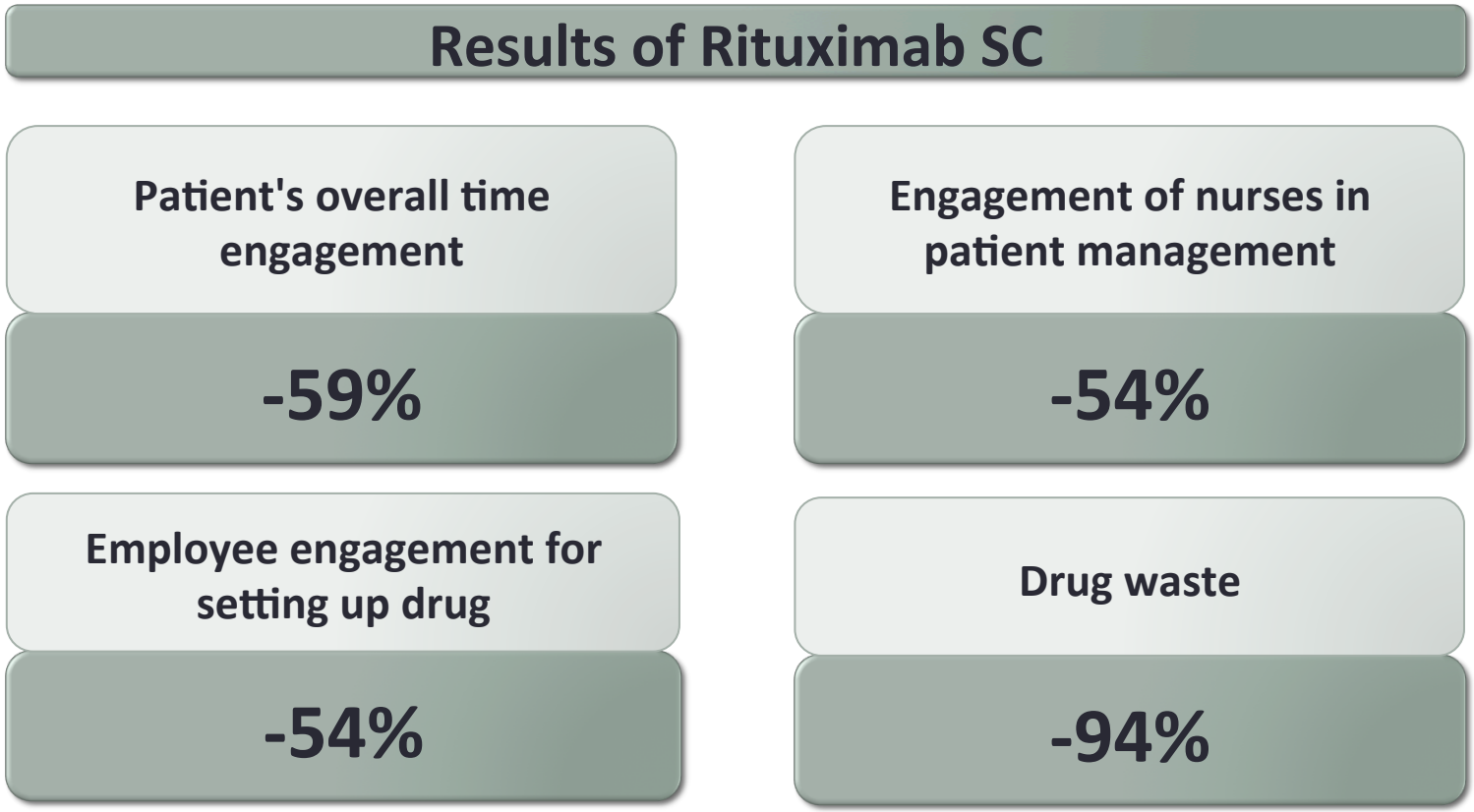
190 patients completed the *Patient Preference Questionnaire* at cycle VI.
Rituximab SC was preferred to Rituximab EV for:

- Less time in hospital **(68%)**
- Less emotic stress **(31%)**
- More comfortable administration **(42%)**

Rummel M., abstract presented at 19° EHA Congress, abstract #5054 Haematologica June 2014 99: 1-796, P467

Impact analysis of the technical and organizational benefits of a subcutaneous formulation in patients with lymphoma path

The project involved 17 centers of Hematology and the results have shown that the use of Rituximab SC can reduce:



Farina M et al. Frammenti Educational 2014; Suppl. 32:3-22 .F

Is it possible to improve the R-side of ICT?

- Dosing: fixed dose grants for a higher exposure to MoAb (ca +30%) and probably removes sex and BMI differences
- Administration: administration time is greatly reduced (better for hospital and for the patient)
- Efficacy: sc therapy is at least as effective as iv administration

Rituximab SC: indication

Linfoma Follicolare (FL)

1L stadio III-IV

Induzione con CHT

Risposta al trattamento

Mantenimento in monoterapia

R/R

Induzione con CHT

Risposta al trattamento

Mantenimento in monoterapia

Linfoma Diffuso a Grandi Cellule B (DLBCL)

Induzione: in combinazione con CHT (CHOP)

FL monoterapia

Stadio III-IV R/R dopo CHT

Leucemia Linfatica Cronica (CLL)

I linea o R/R