24-3-2017

3rd Postgraduate Lymphoma Conference

New anti-CD20 monoclonal antibodies

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Comprehensive Cancer Center Ulm

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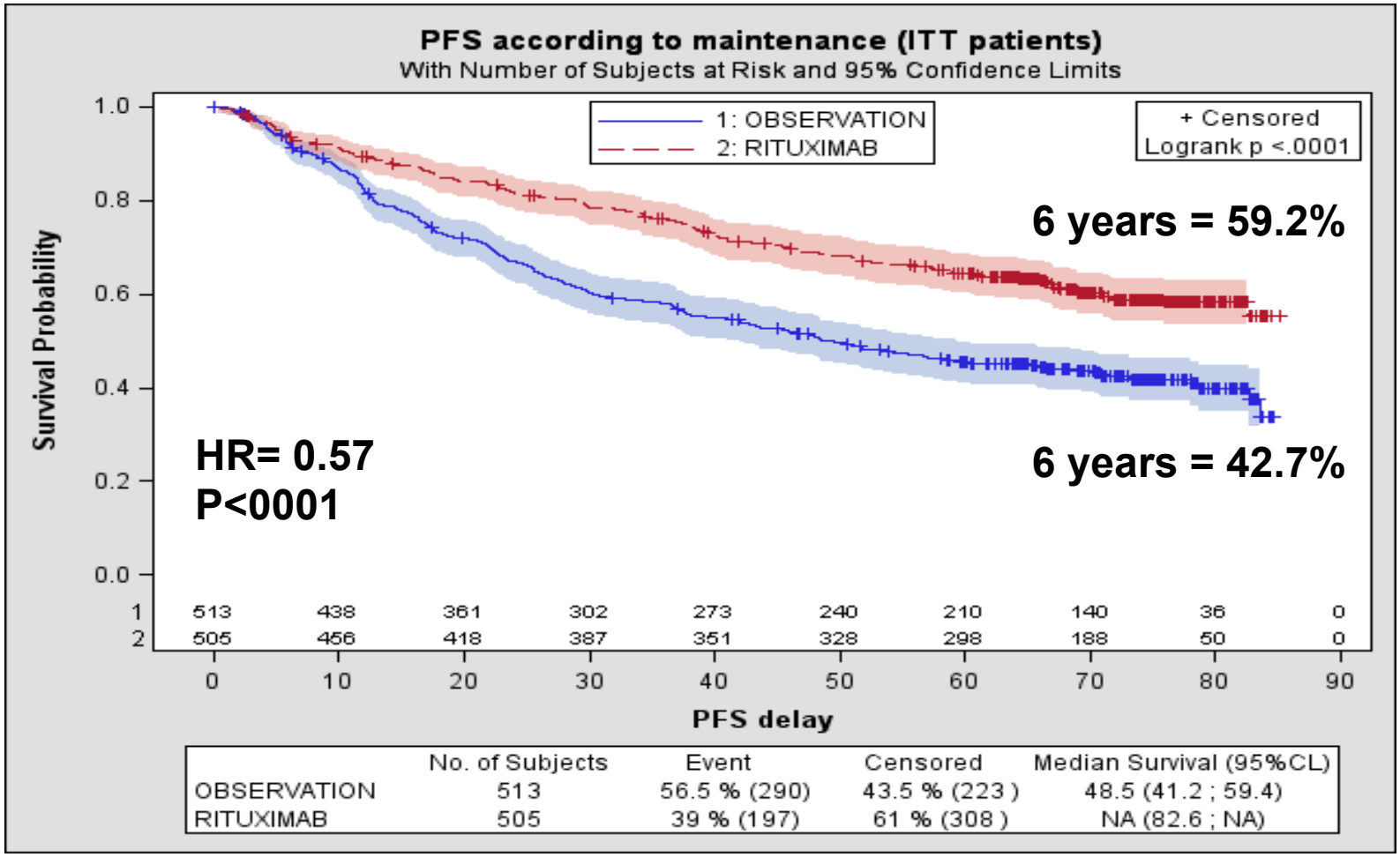
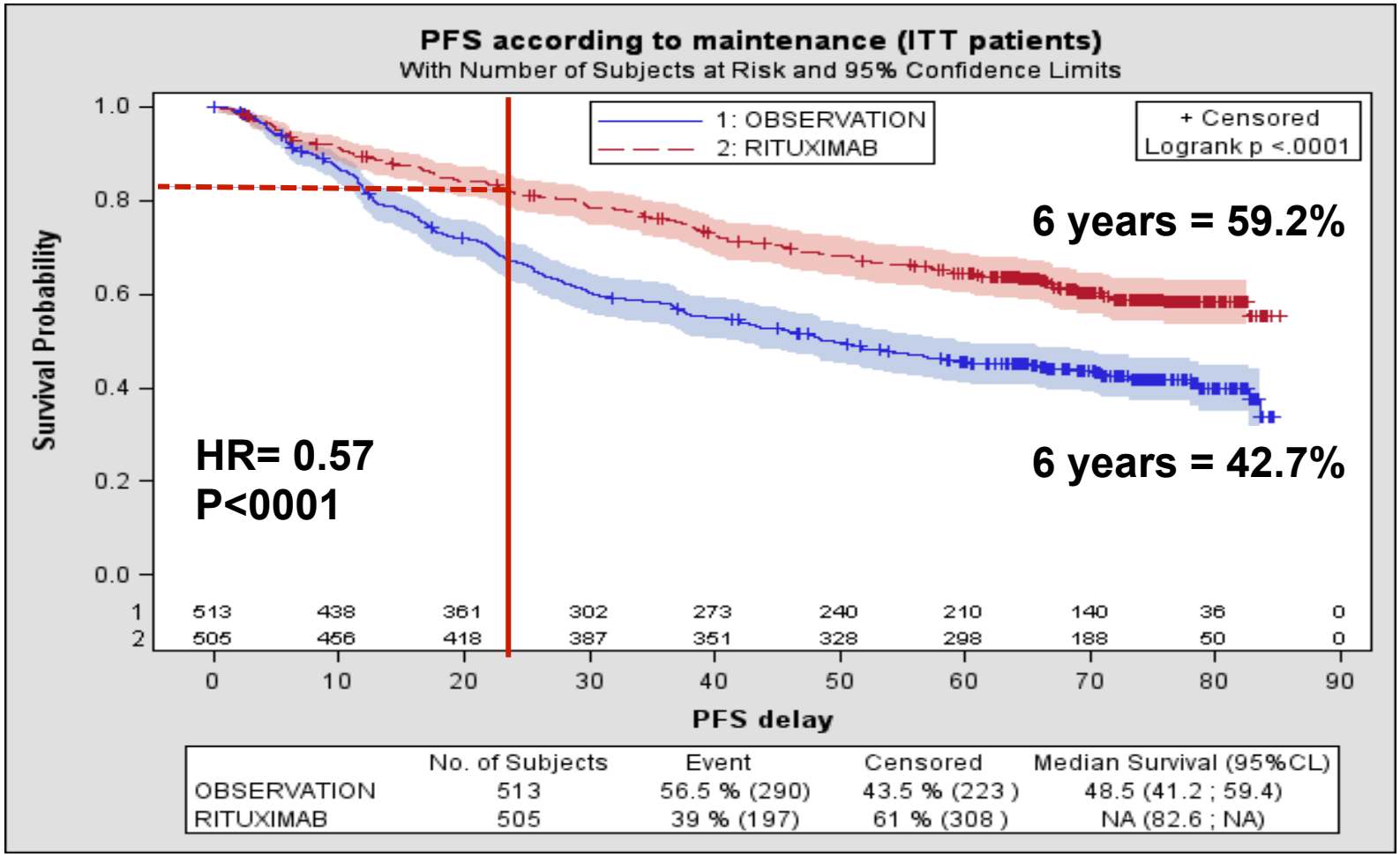
Follicular lymphoma – where are we standing today?

What we can achieve …….. PRIMA data



PRIMA Studie, Salles et al., Lancet Oncology

FL – PRIMA data



PRIMA Studie, Salles et al., Lancet Oncology

Follicular lymphoma – where are we standing today?

Around every fifth FL patient has a dismal prognosis!

Follicular lymphoma – where are we standing today?

How to improve?
New antibodies?

Follicular lymphoma – where are we standing today?

New antibodies?

Obinutuzumab - Quite new, but probably practice changing!

Plenary Session - ASH

Obinutuzumab-based induction and maintenance prolongs progression-free survival (PFS) in patients with previously untreated follicular lymphoma: primary results of the randomized Phase III GALLIUM study

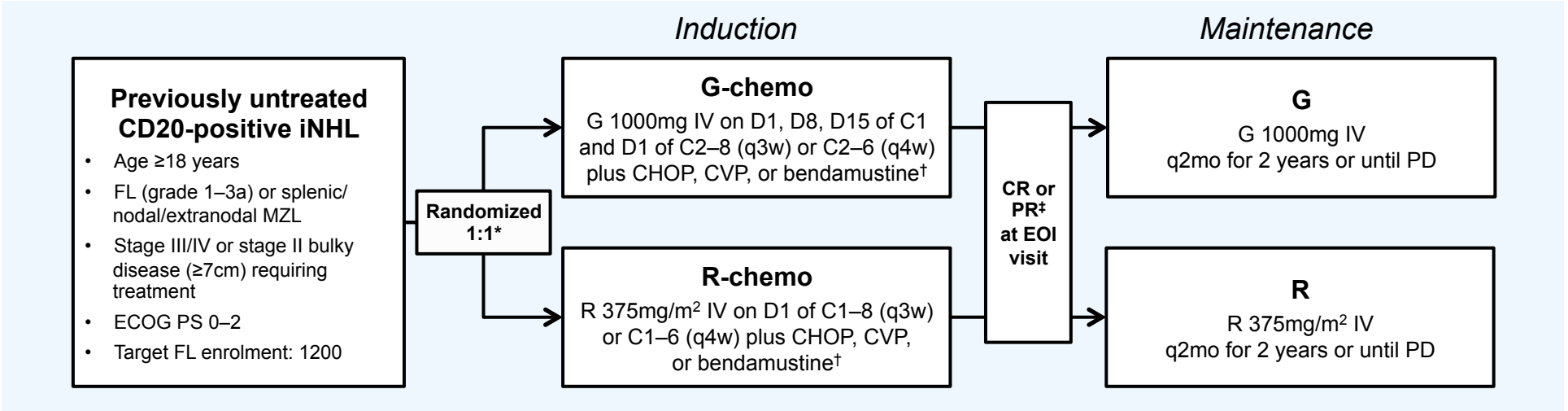
Robert Marcus,[1] Andrew Davies,[2] Kiyoshi Ando,[3] Wolfram Klapper,[4] Stephen Opat,[5] Carolyn Owen,[6] Elizabeth Phillips,[7] Randeep Sangha,[8] Rudolf Schlag,[9] John F Seymour,[10] William Townsend,[7] Marek Trněný,[11] Michael Wenger,[12] Günter Fingerle-Rowson,[13] Kaspar Rufibach,[13] Tom Moore,[13] Michael Herold,[14] Wolfgang Hiddemann[15]

[1]Kings College Hospital, London, United Kingdom; [2]Cancer Research UK Centre, University of Southampton, Southampton, United Kingdom; [3]Tokai University School of Medicine, Isehara, Kanagawa, Japan; [4]University of Kiel, Kiel, Germany; [5]Monash Health and Monash University, Melbourne, Australia; [6]Foothills Medical Centre and Tom Baker Cancer Centre, Calgary, AB, Canada; [7]Cancer Research UK and UCL Cancer Trials Centre, London, United Kingdom; [8]Cross Cancer Institute, Edmonton, AB, Canada; [9]Gemeinschaftspraxis Dr. Rudolf Schlag/Dr. Björn Schöttker, Würzburg, Germany; [10]Peter MacCallum Cancer Centre, Melbourne, Australia; [11]Charles University, Prague, Czech Republic; [12]Genentech Inc, South San Francisco, CA, USA; [13]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [14]HELIOS-Klinikum, Erfurt, Germany; [15]Ludwig-Maximilians-University, Munich, Germany

GLSG NCRI National Cancer Research Institute OSHO

Study design

International, open-label, randomized Phase III study



Primary endpoint

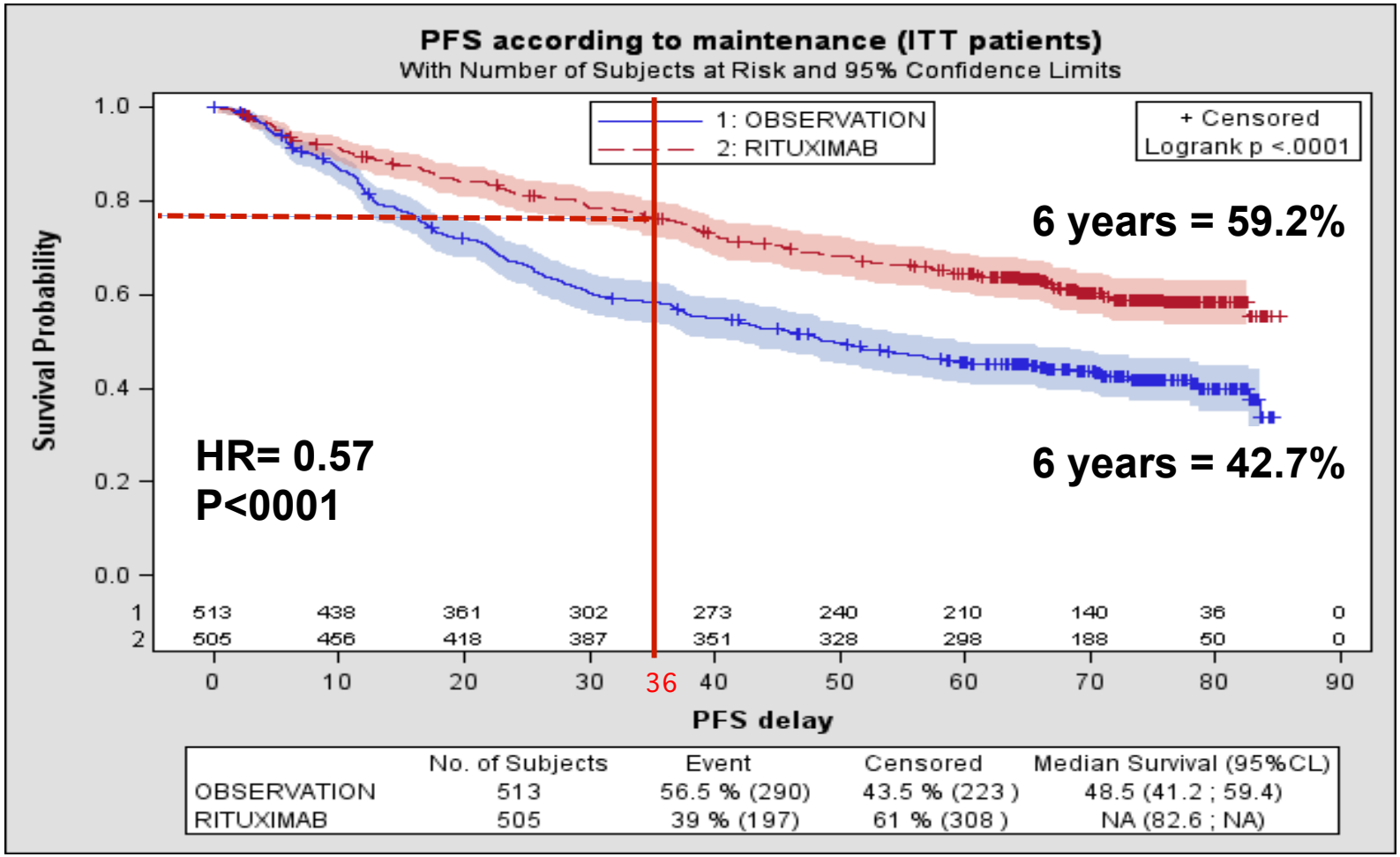
- PFS (INV-assessed in FL)

Secondary and other endpoints

- PFS (IRC-assessed)§
- OS, EFS, DFS, DoR, TTNT
- CR/ORR at EOI (+/− FDG-PET)
- Safety

*FL and MZL pts were randomized separately; stratification factors: chemotherapy, FLIPI (FL) or IPI (MZL) risk group, geographic region; †CHOP q3w × 6 cycles, CVP q3w × 8 cycles, bendamustine q4w × 6 cycles; choice by site (FL) or by pt (MZL); ‡Pts with SD at EOI were followed for PD for up to 2 years; §Confirmatory endpoint

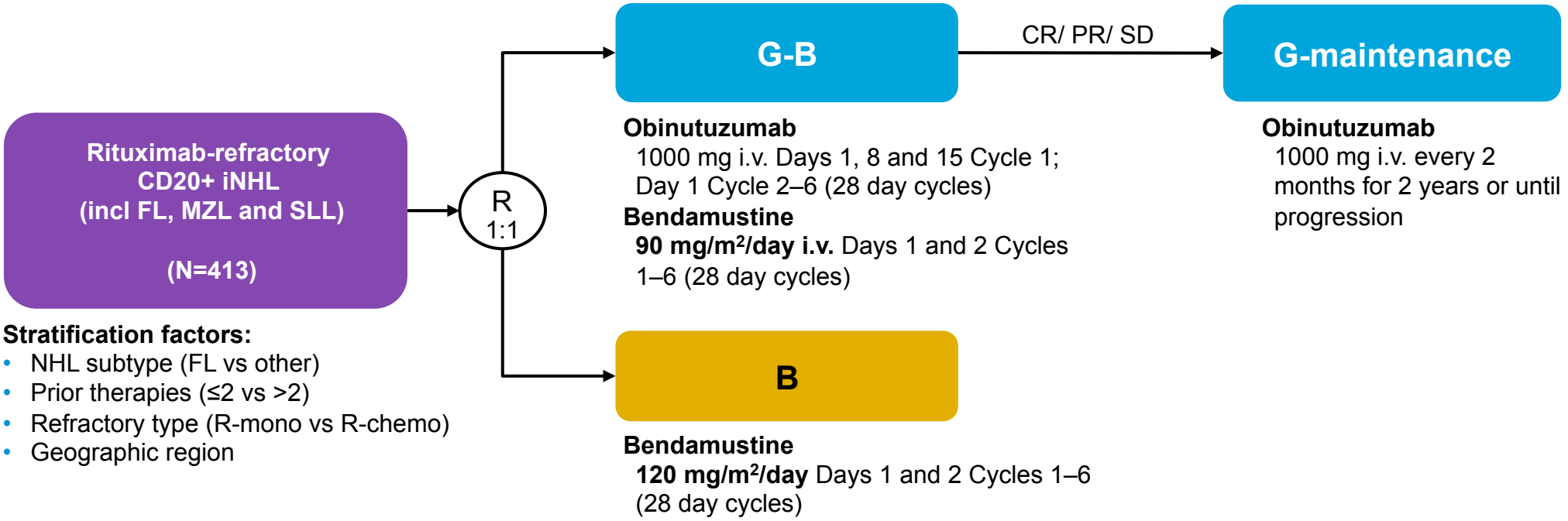
Rituximab refractory – not that rare!



36 months = Induction plus Maintenance plus 6 months

PRIMA Studie, Salles et al., Lancet Oncology

GADOLIN: Study Design



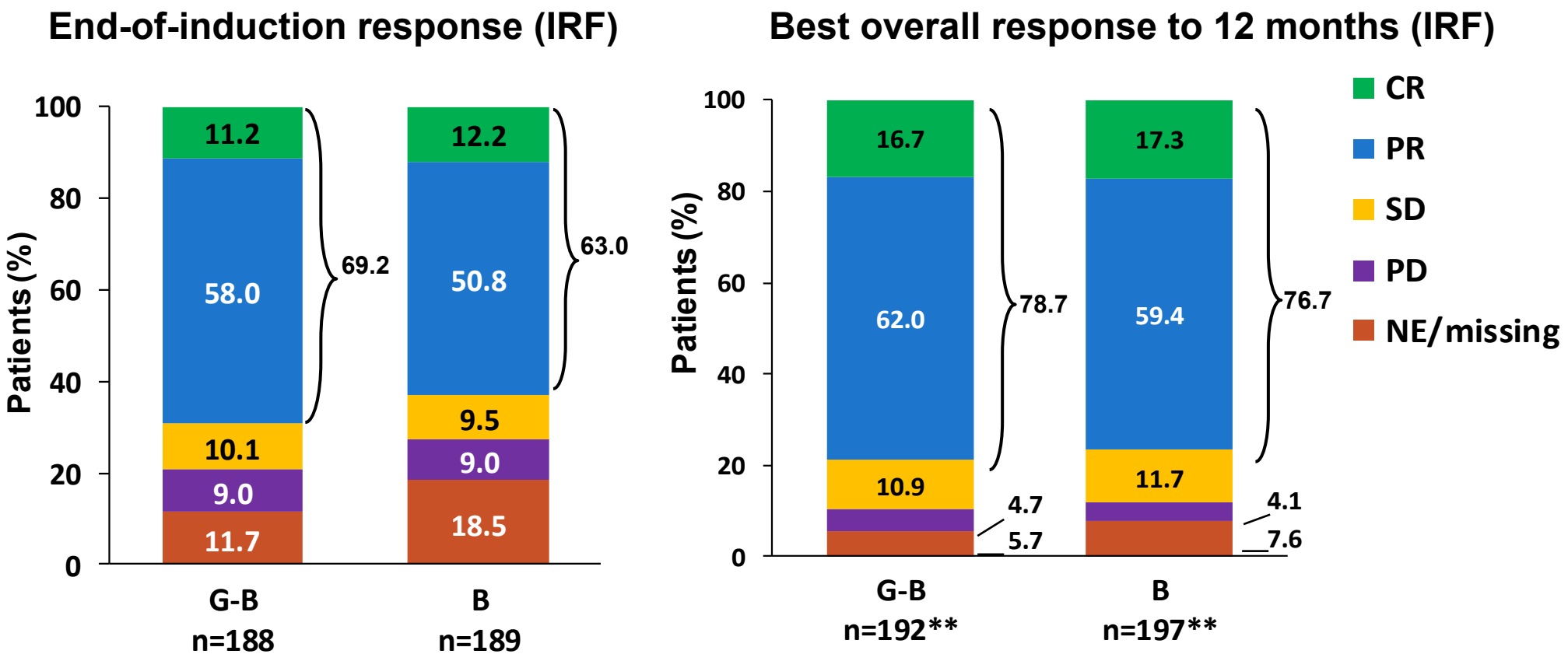
Stratification factors:

- NHL subtype (FL vs other)
- Prior therapies (≤2 vs >2)
- Refractory type (R-mono vs R-chemo)
- Geographic region

- International, randomized, open-label study
- 81% (n=321) of 396 iNHL pts enrolled had FL
- Response monitored by CT scan post-induction, then every 3 months for 2 years, then every 6 months (modified Cheson criteria 2007)

iNHL, indolent non-Hodgkins lymphoma; G-B, obinutuzumab plus bendamustine; G, obinutuzumab

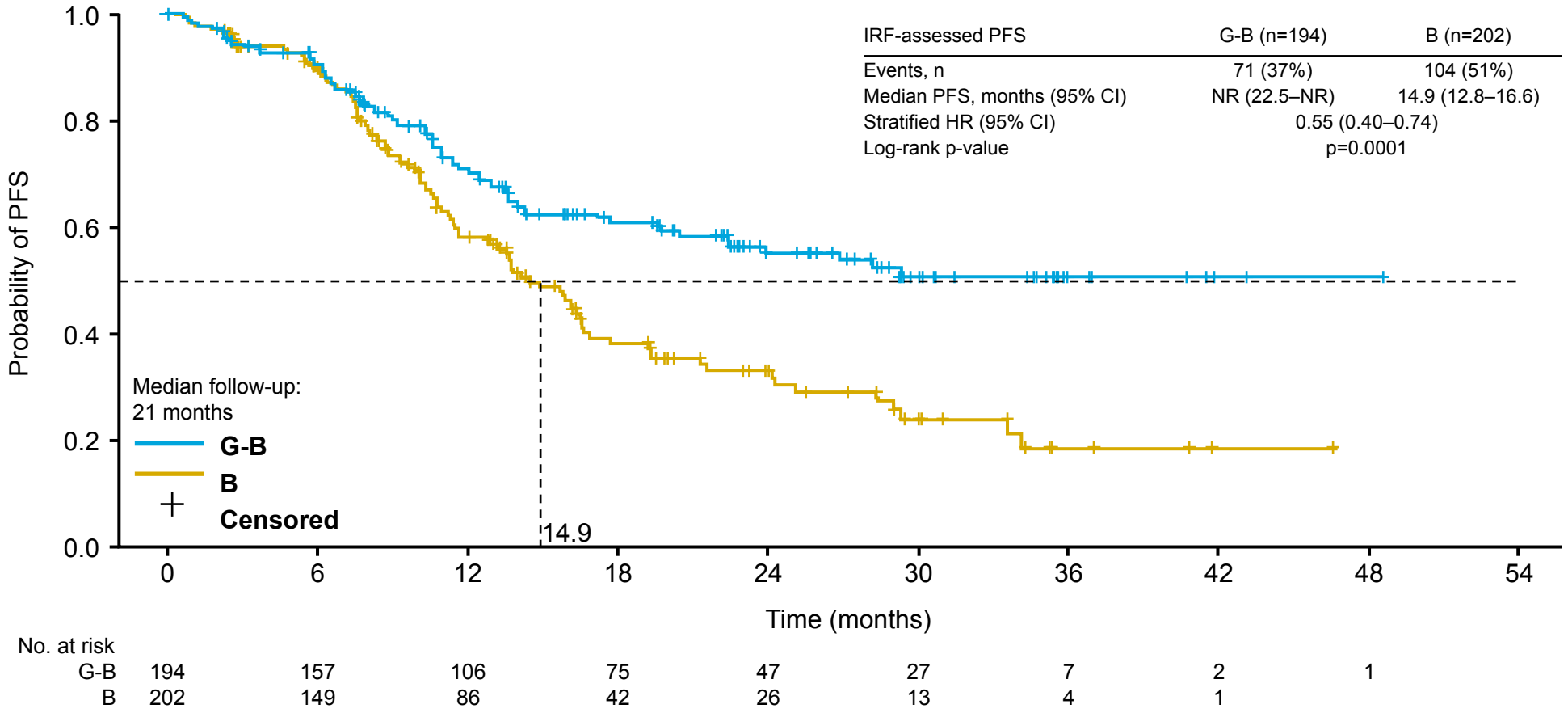
GADOLIN: Response



- 19 patients still in induction (G-B, n=6; B, n=13)*

* Patients ongoing in induction therapy are excluded from analysis. Patients with end of induction response assessment performed >60 days after last induction dose shown as missing.
** Best overall response excludes ongoing patients who have not yet reached the first response assessment.
IRF, independent radiology facility

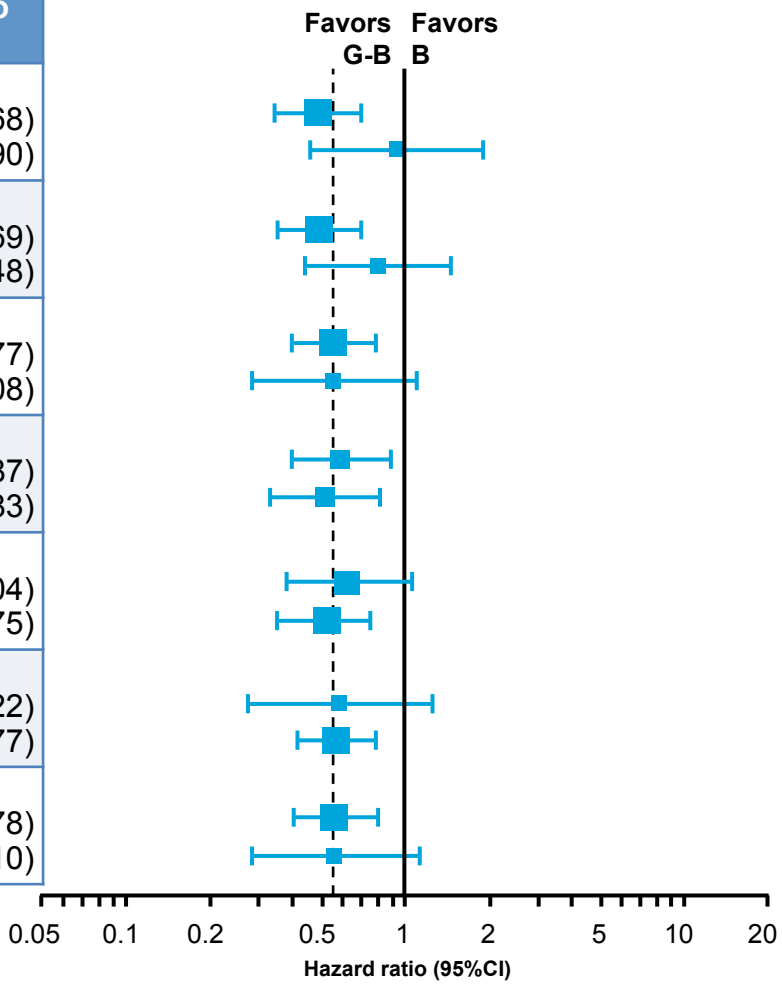
GADOLIN: Primary endpoint PFS (IRC)



IRC, independent review committee; HR, hazard ratio; CI, confidence interval; NR, not reached

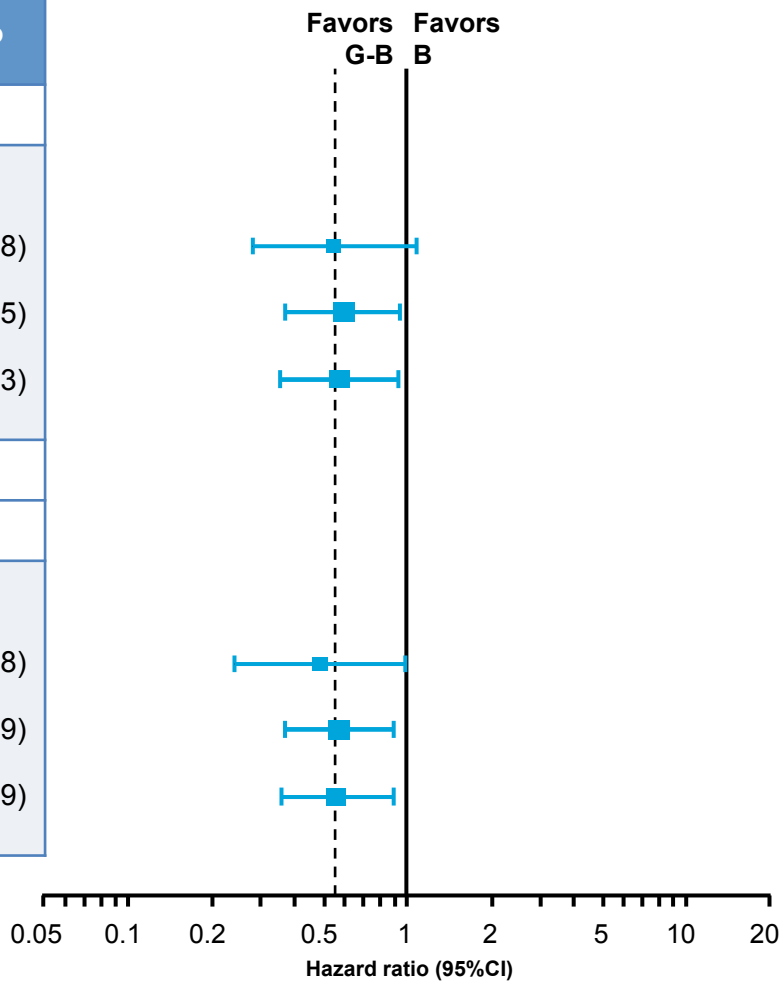
GADOLIN: PFS according to subgroups

Subgroup	Total n	G-B (n=194) n	G-B (n=194) Events	B (n=202) n	B (n=202) Events	Hazard ratio (95%CI)
Follicular lymphoma						
Yes	321	155	54	166	90	0.49 (0.35–0.68)
No	75	39	17	36	14	0.94 (0.46–1.90)
No. of prior therapies						
≤2	312	154	51	158	83	0.49 (0.34–0.69)
>2	84	40	20	44	21	0.80 (0.43–1.48)
Refractory type						
Rituximab + chemotherapy	313	156	57	157	82	0.55 (0.39–0.77)
Rituximab monotherapy	83	38	14	45	22	0.55 (0.28–1.08)
Sex						
Male	228	110	41	118	57	0.58 (0.39–0.87)
Female	168	84	30	84	47	0.52 (0.33–0.83)
Bulky disease at BL						
Yes (>6 cm)	136	66	27	70	37	0.63 (0.38–1.04)
No (≤6 cm)	257	128	44	129	67	0.51 (0.35–0.75)
B symptoms at BL						
Yes	58	30	12	28	16	0.57 (0.27–1.22)
No	335	163	59	172	87	0.55 (0.40–0.77)
Double refractory status						
Yes	311	147	55	164	87	0.56 (0.40–0.78)
No	85	47	16	38	17	0.55 (0.28–1.10)



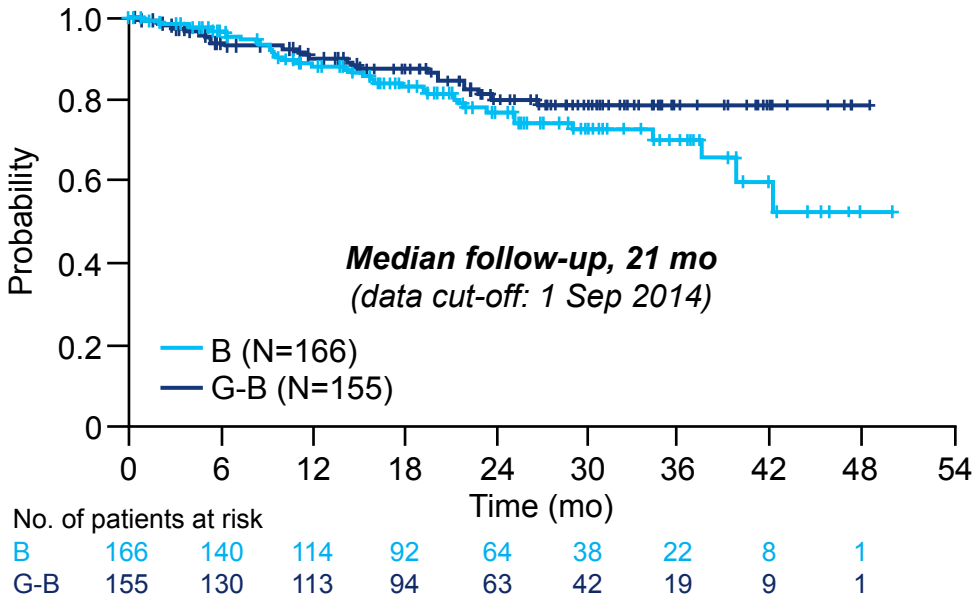
GADOLIN:
PFS according to “Rituximab-refractory type”

Subgroup	Total n	G-B (n=194) n	G-B (n=194) Events	B (n=202) n	B (n=202) Events	Hazard ratio (95%CI)
IRF-assessed						
Refractory to						
R-mono	83	38	14	45	22	0.55 (0.28–1.08)
R-chemo induction	162	76	29	86	42	0.59 (0.36–0.95)
R-maintenance after (R)chemo induction	146	76	28	70	39	0.57 (0.35–0.93)
Investigator-assessed						
Refractory to						
R-mono	83	38	12	45	23	0.49 (0.24–0.98)
R-chemo induction	162	76	33	86	48	0.57 (0.37–0.89)
R-maintenance after (R)chemo induction	146	76	31	70	43	0.56 (0.35–0.89)



GADOLIN FL: overall survival

OS primary analysis

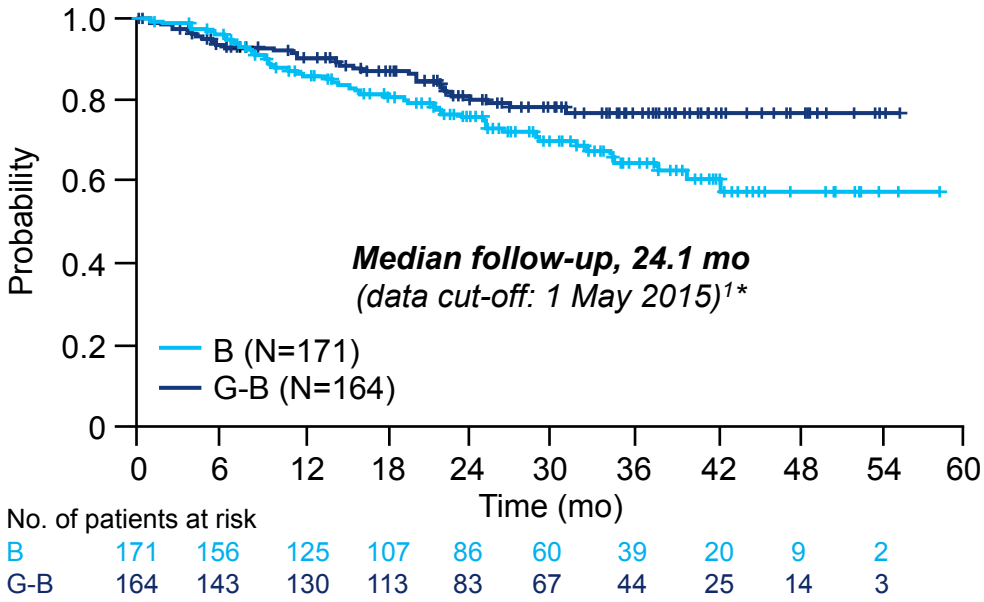


No. of patients at risk

B	166	140	114	92	64	38	22	8	1	
G-B	155	130	113	94	63	42	19	9	1	

	B (n=166)	G-B (n=155)
Pts with event, n (%)	36 (21.7)	25 (16.1)
Median OS (mo)	NR (39.8, NR)	NR (NR, NR)
HR (95% CI); stratified†	**0.71 (0.43, 1.19); p=0.20**	

OS update as per US PI



No. of patients at risk

B	171	156	125	107	86	60	39	20	9	2	
G-B	164	143	130	113	83	67	44	25	14	3	

	B (n=171)	G-B (n=164)
Pts with event, n (%)	48 (28.1)	30 (18.3)
Median OS (mo)	NR (42.2, NR)	NR (NR, NR)
HR (95% CI); stratified†	**0.62 (0.39, 0.98); p=0.04‡**	

*90-day safety update; †stratification factors: refractory type (R vs R-chemo), prior therapies (≤2 vs >2); ‡NS, per protocol planned analysis

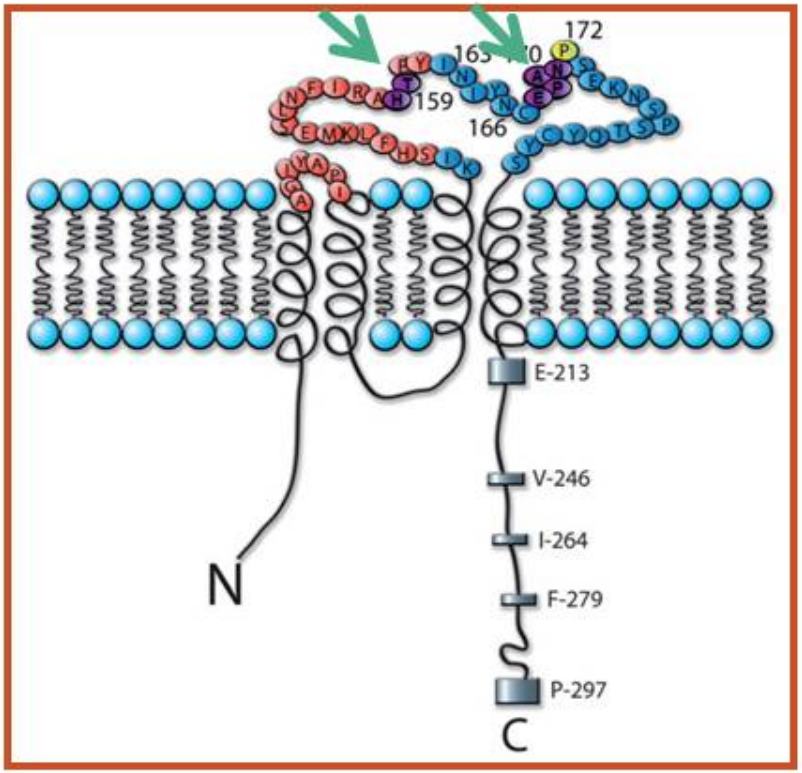
1. http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125486s013lbl.pdf (aufgerufen 21.6.2016)

Follicular Lymphoma

„Newer“ antibodies?

Ublituximab: Glycoengineered Anti-CD20 mAb

- Type 1 chimeric IgG1 mAb
- Unique binding sequence on CD20 (**Green** arrows in figure)
- Potential advantages over current standards of care:
  - Glycoengineered for enhanced ADCC
  - Activity in "low" CD20 expressing cell lines
- Single agent responses observed in rituximab refractory patients[1]



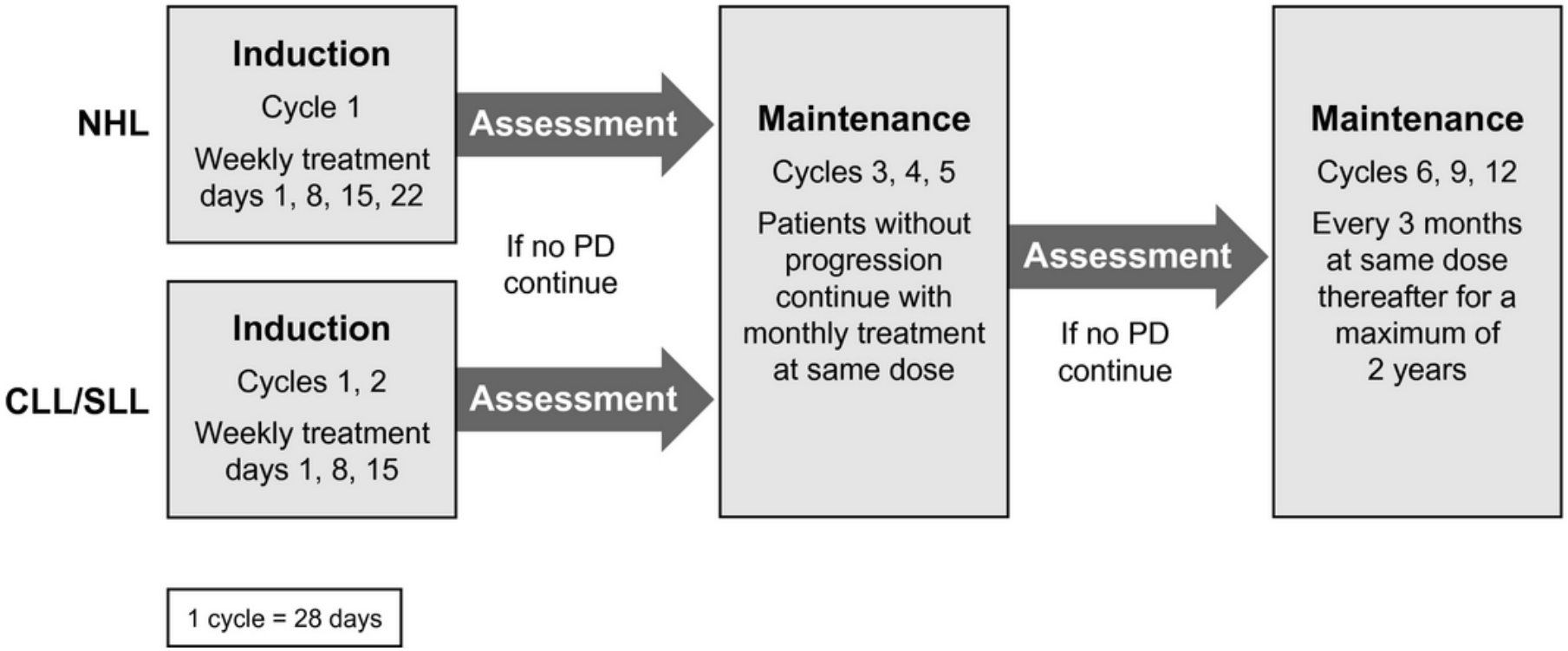
Source: Adapted from Ruuls et al 2008

(1) O'Connor et al, ASCO 2014

bjh research paper

A phase 1/2 trial of ublituximab, a novel anti-CD20 monoclonal antibody, in patients with B-cell non-Hodgkin lymphoma or chronic lymphocytic leukaemia previously exposed to rituximab

Ahmed Sawas,[1] Charles M. Farber,[2] Marshall T. Schreeder,[3] Mazen Y. Khalil,[4] Daruka Mahadevan,*[5] Changchun Deng,[1] Jennifer E. Amengual,[1] Petros G. Nikolinakos,[6] Jill M. Kolesar,[7] John G. Kuhn,[8] Peter Sportelli,[9] Hari P. Miskin[9] and Owen A. O'Connor[1]



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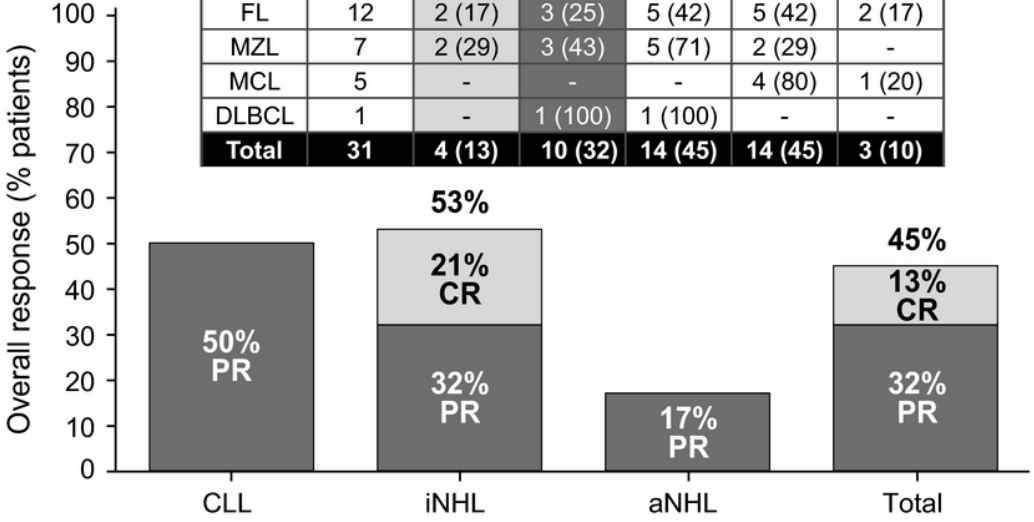
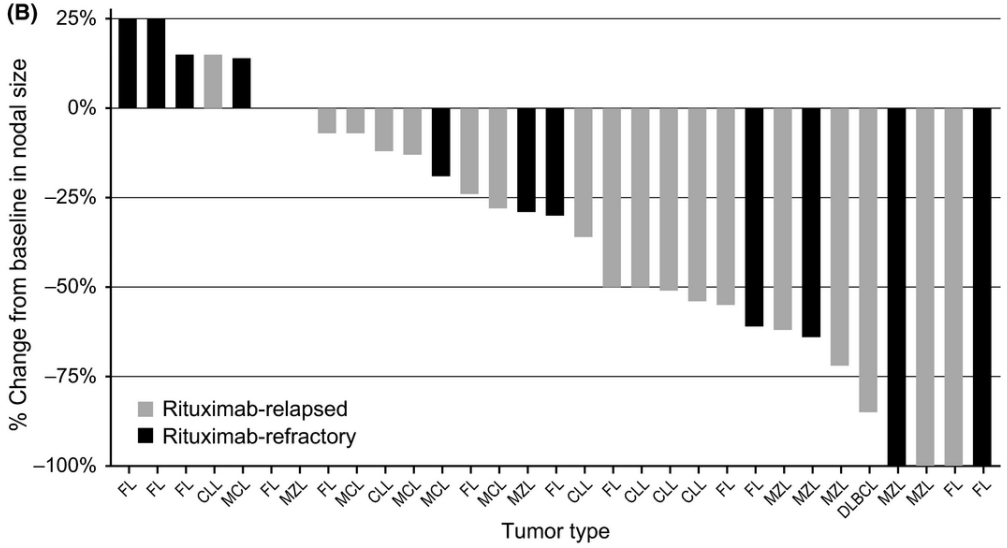
(A)

Type	Pts (*n*)	CR *n* (%)	PR *n* (%)	ORR *n* (%)	SD *n* (%)	PD *n* (%)
CLL	6	-	3 (50)	3 (50)	3 (50)	-
FL	12	2 (17)	3 (25)	5 (42)	5 (42)	2 (17)
MZL	7	2 (29)	3 (43)	5 (71)	2 (29)	-
MCL	5	-	-	-	4 (80)	1 (20)
DLBCL	1	-	1 (100)	1 (100)	-	-
Total	**31**	**4 (13)**	**10 (32)**	**14 (45)**	**14 (45)**	**3 (10)**

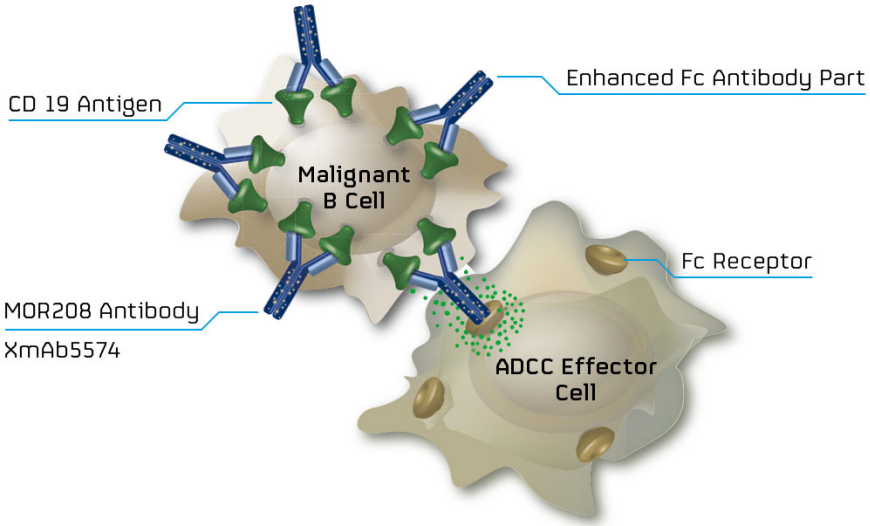


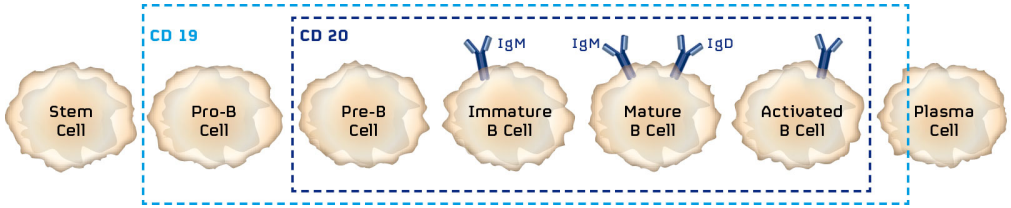
(B)



Subgroup analyses of diffuse large B-cell lymphoma (DLBCL) and indolent lymphoma cohorts from a phase IIa study of single-agent MOR208 in patients with relapsed or refractory non-Hodgkin's lymphoma (R-R NHL)

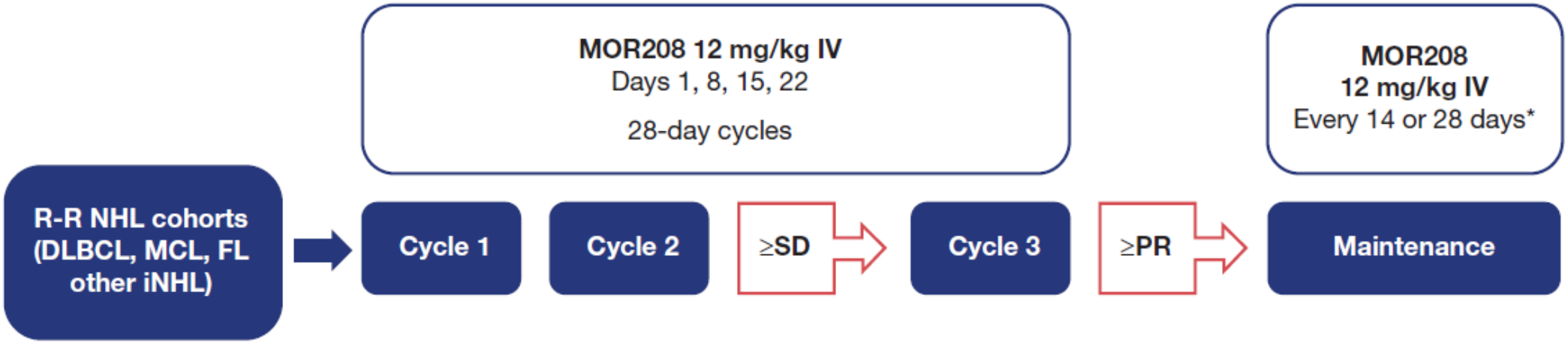
Wojciech Jurczak, Pier Luigi Zinzani, Gianluca Gaidano, Andre Goy, Mariano Provencio, Zsolt Nagy, Tadeusz Robak, Kami J. Maddocks, Christian Buske, Sumeet Ambarkhane, Mark Winderlich, Maren Dirnberger-Hertweck, Jan Endell, and Kristie A Blum





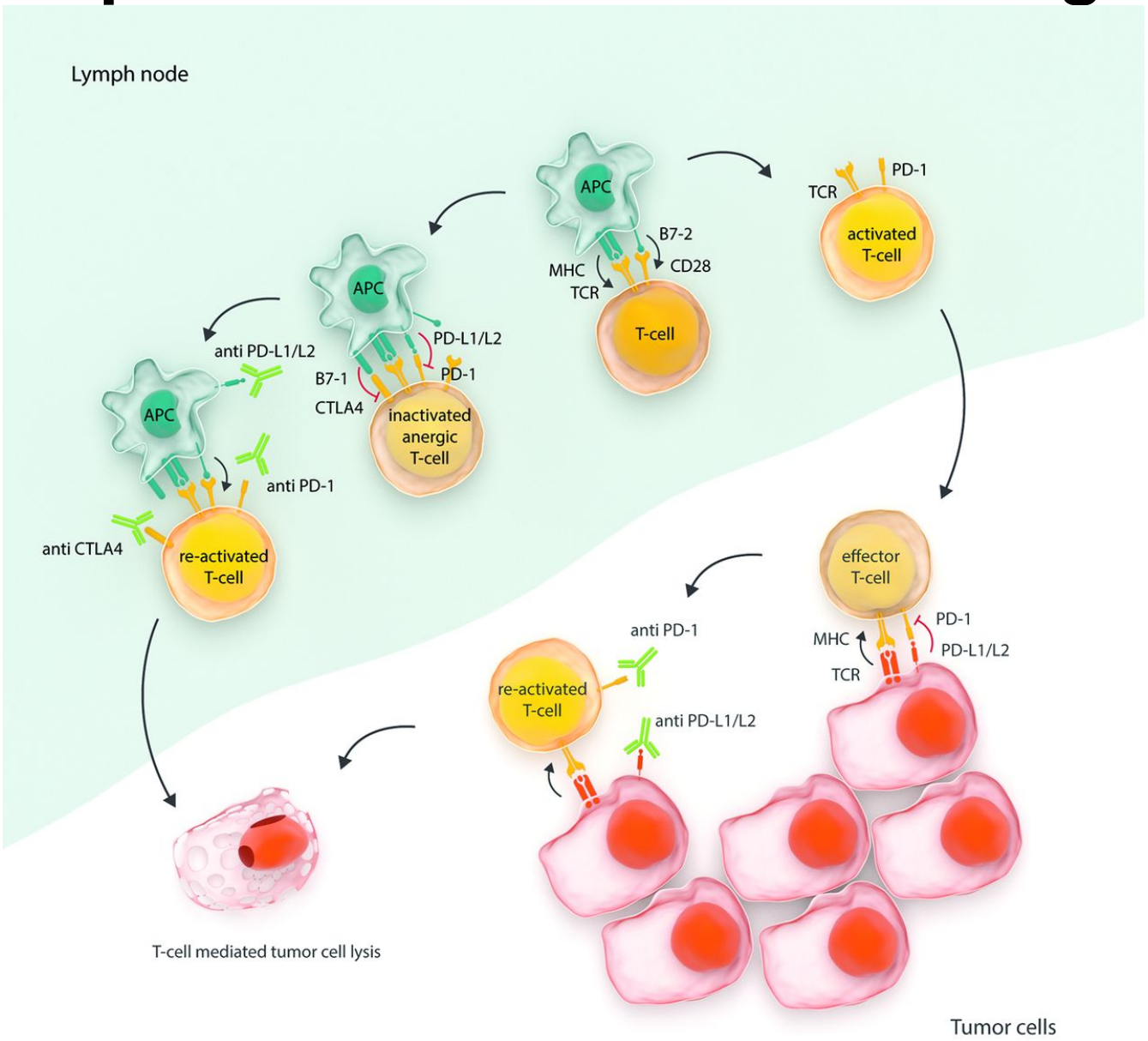
Methods

Figure 1. Study design and treatment



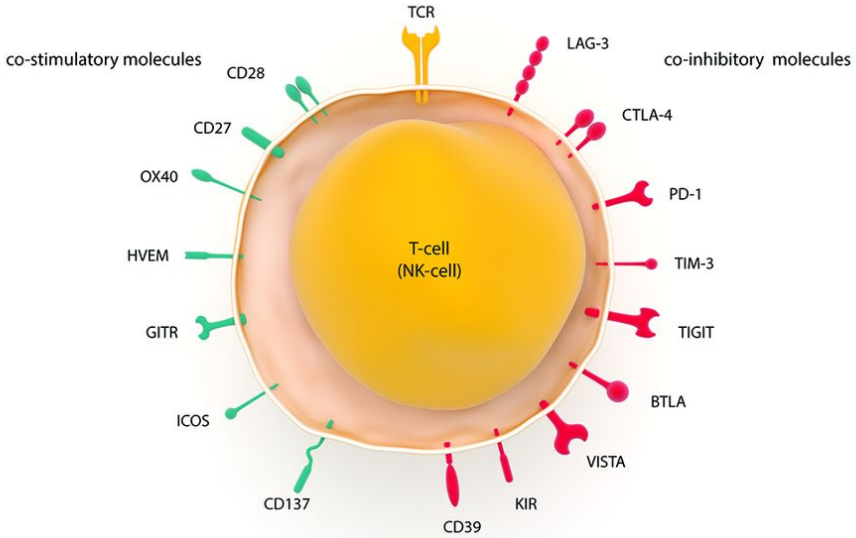
*Until disease progression. DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; iNHL, indolent non-Hodgkin's lymphoma; IV, intravenous infusion; MCL, mantle cell lymphoma; PR, partial response; R-R relapsed or refractory; SD, stable disease

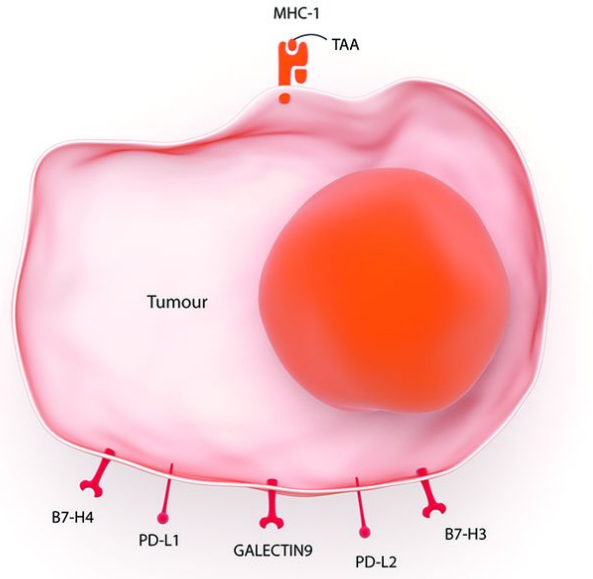
Checkpoint Inhibitors - fascinating new concept

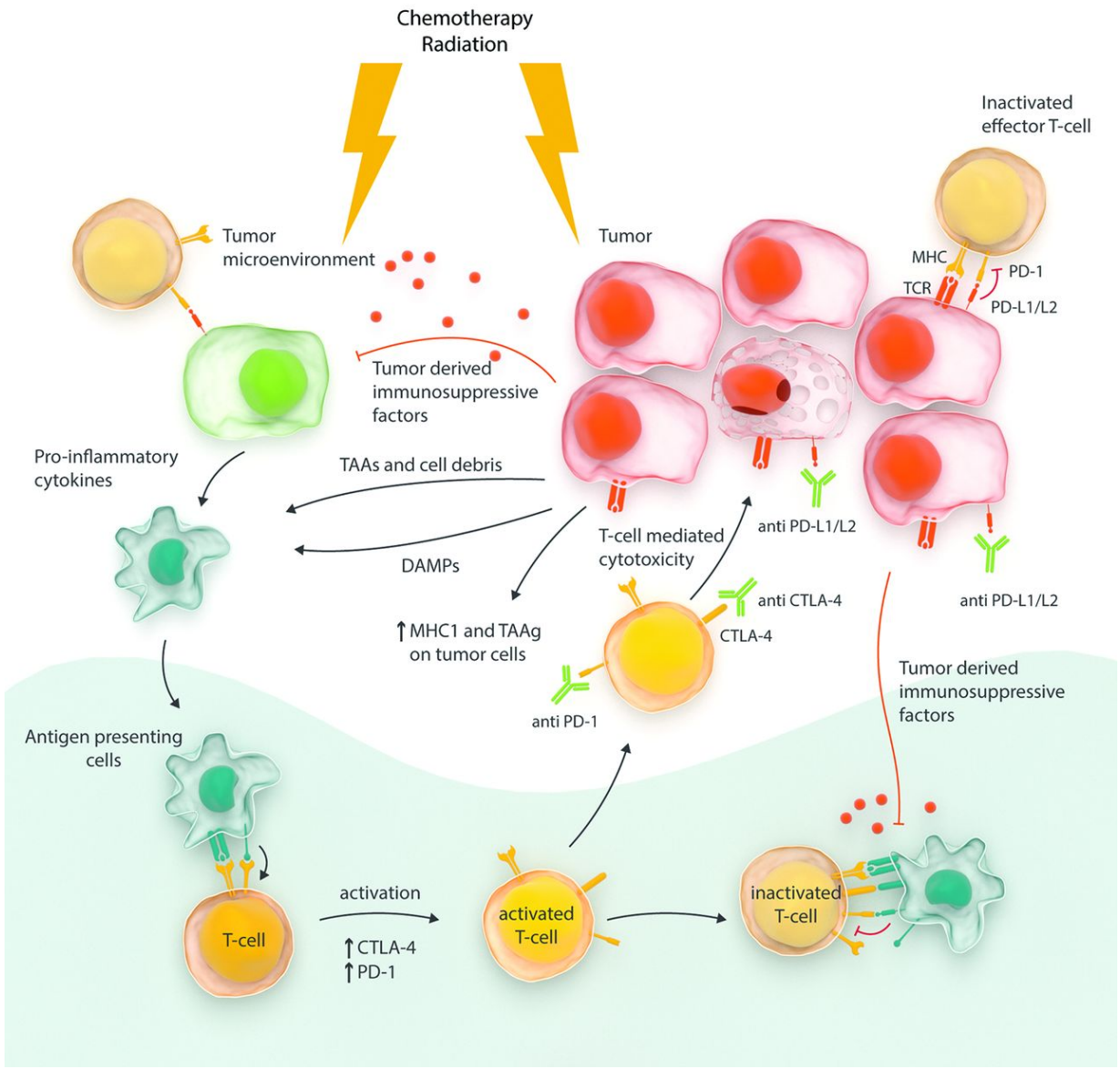


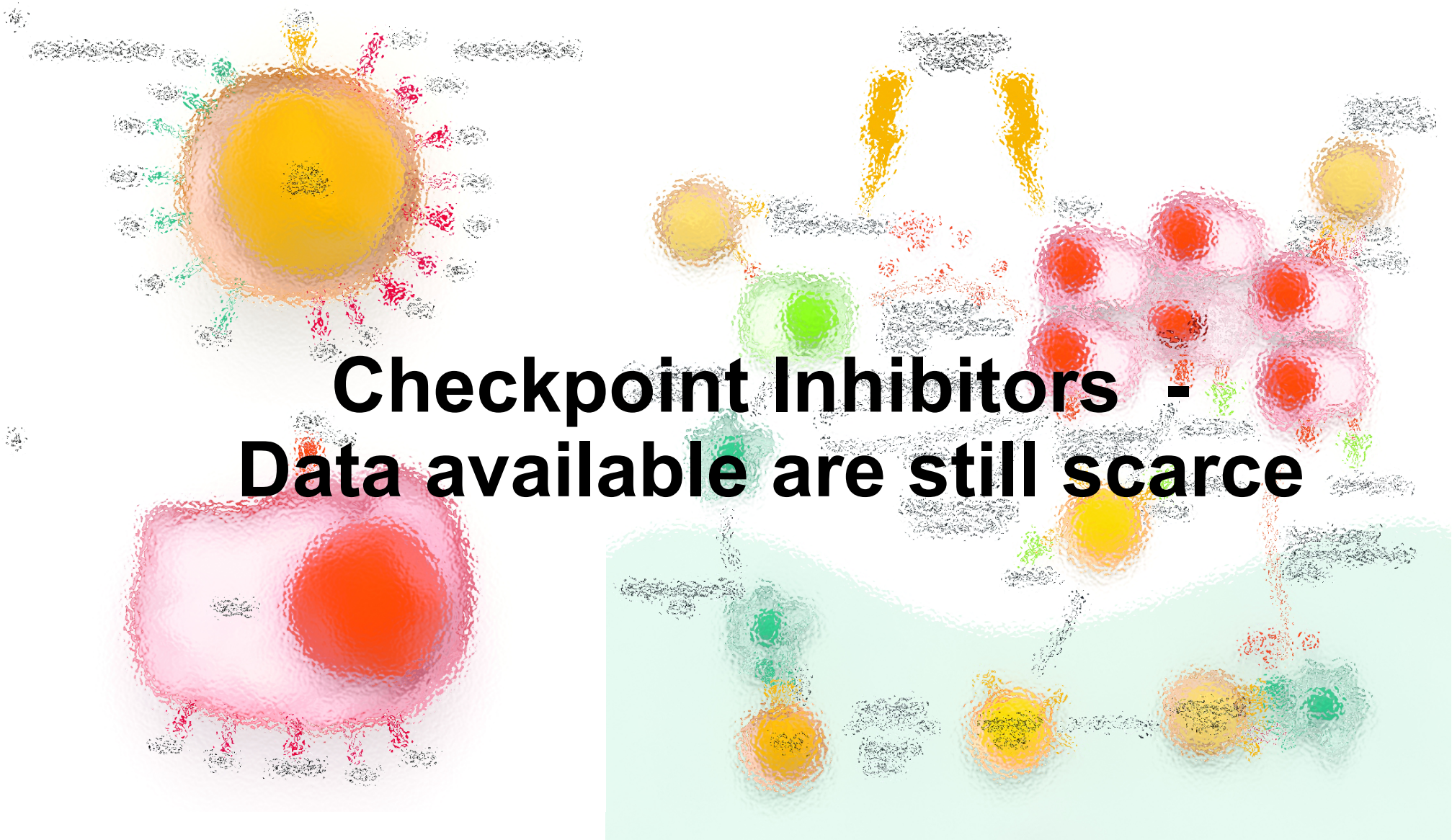
Ida Hude et al. Haematologica 2017;102:30-42

Checkpoint Inhibitors - much to come!









Checkpoint Inhibitors - Data available are still scarce

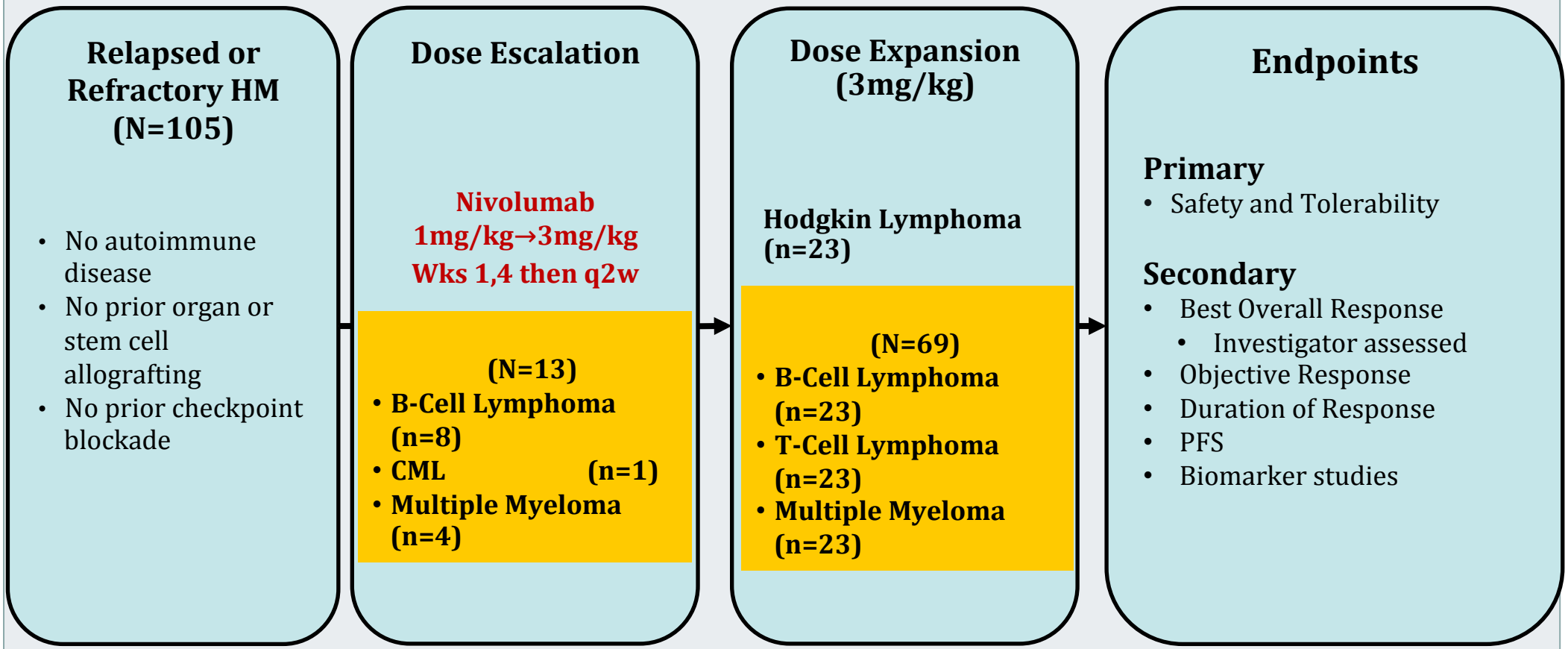
Ida Hude et al. Haematologica
2017;102:30-42

Nivolumab in Patients with Relapsed or Refractory Lymphoid Malignancies and Classical Hodgkin Lymphoma: Updated Results of a Phase 1 Study (CA209-039)

**John Timmerman, MD,[1] Philippe Armand, MD, PhD,[2] Alexander Lesokhin, MD,[3]
Ahmad Halwani, MD,[4] Michael Millenson, MD,[5] Stephen J. Schuster, MD,[6]
Martin Gutierrez, MD,[7] Emma Scott, MD,[8] Deepika Cattry, MS,[3]
Gordon Freeman, PhD,[2] Bjoern Chapuy, MD, PhD,[2] Azra Ligon, PhD,[9]
Scott Rodig, MD, PhD,[9] Lili Zhu, MS,[10] Joseph Grosso, PhD,[10] Jason Simon,PhD,[10]
Margaret Shipp, MD,[2] Adam Cohen, MD,[6] Daniel Lebovic, MD,[11]
Madhav Dhodapkar, MD,[12] David Avigan, MD,[13] Ivan Borrello, MD,[14]
Stephen Ansell, MD, PhD[15]**

[1]Jonsson Comprehensive Cancer Center, University of California, Los Angeles, CA; [2]Dana-Farber Cancer Institute, Boston, MA; [3]Memorial Sloan Kettering Cancer Center, New York, NY; [4]University of Utah Huntsman Cancer Institute, Salt Lake City, UT; [5]Fox Chase Cancer Center, Philadelphia, PA; [6]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; [7]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ; [8]Oregon Health and Science University, Portland, Oregon; [9]Brigham and Women's Hospital, Boston, MA; [10]Bristol-Myers Squibb, Princeton, NJ; [11]University of Michigan Hematology, Ann Arbor, MI; [12]Yale Cancer Center, New Haven, CT; [13]Beth Israel Deaconess Medical Center, Boston, MA; [14]Johns Hopkins University School of Medicine and the Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; [15]Mayo Clinic, Rochester, MN

Study Design

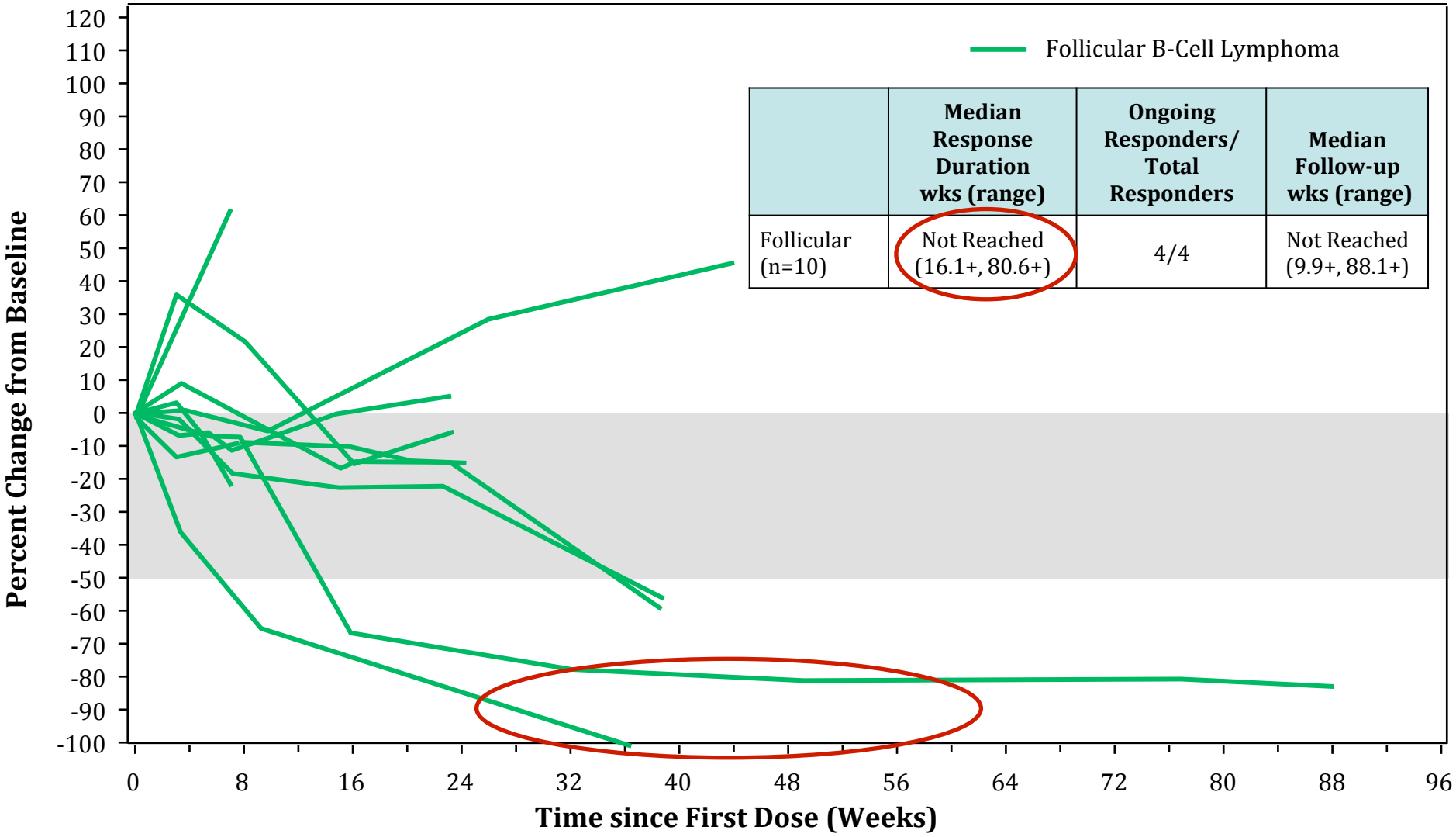


Best Overall Response

	Objective Response Rate, n (%)	Complete Responses, n (%)	Partial Responses, n (%)	Stable Disease n (%)
B-Cell Lymphoma* (n=29)	8 (28)	2 (7)	6 (21)	14 (48)
Follicular Lymphoma (n=10)	4 (40)	1 (10)	3 (30)	6 (60)
Diffuse Large B-Cell Lymphoma (n=11)	4 (36)	1 (9)	3 (27)	3 (27)
T-Cell Lymphoma† (n=23)	4 (17)	0 (0)	4 (17)	10 (43)
Mycosis Fungoides (n=13)	2 (15)	0 (0)	2 (15)	9 (69)
Peripheral T-Cell Lymphoma (n=5)	2 (40)	0 (0)	2 (40)	0 (0)
Multiple Myeloma (n=27)	0 (0)	0 (0)	0 (0)	18 (67)
Primary Mediastinal B-Cell Lymphoma (n=2)	0 (0)	0 (0)	0 (0)	2 (100)

*includes other B-cell lymphoma (n=8)
†includes other cutaneous T-cell lymphoma (n=3) and other non-cutaneous T-cell lymphoma (n=2)

Follicular Lymphoma Patient Responses



	Median Response Duration wks (range)	Ongoing Responders/ Total Responders	Median Follow-up wks (range)
Follicular (n=10)	Not Reached (16.1+, 80.6+)	4/4	Not Reached (9.9+, 88.1+)

Many Thanks