I Linfomi Non-Hodgkin a cellule B: novità nella terapia con anticorpi antiCD20

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Disclosures – Umberto Vitolo

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Consultant	N/A
Major Stockholder	N/A
Conferences/ Educational Activities	Janssen, Roche, Celgene, Takeda, Gilead
Scientific Advisory Board	Janssen, Roche

Treatment with antiCD20 in B-cell lymphomas

Consolidated results

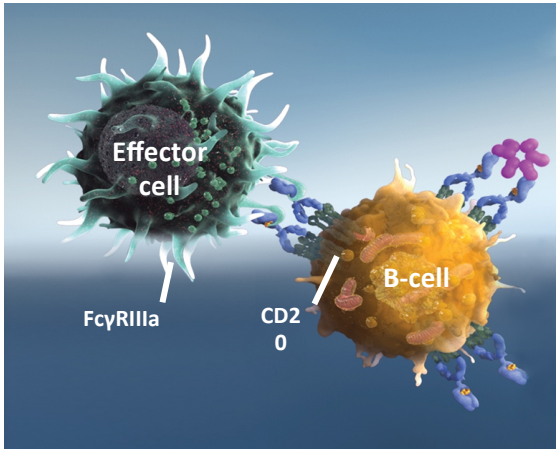
New antiCD20 antibodies

Association with IMIDs

New modality of administration of antiCD20 antibodies

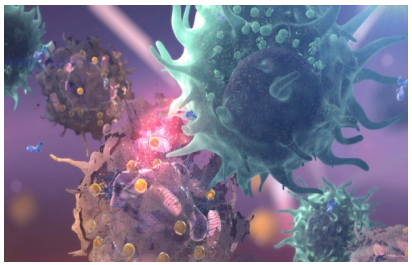
Future development

Anti-CD20 mAbs elicit B-cell death through three major mechanisms

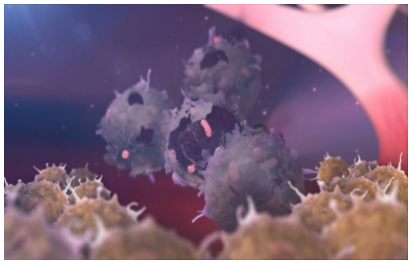


- Three major mechanisms of anti-CD20 mAb activity are[1-4]:
  - intercellular interactions such as antibody-dependent cellular cytotoxicity
  - internal cell-killing mechanisms, such as classical apoptosis or Direct Cell Death
  - complement-dependent cytotoxicity.
- There are 2 different anti-CD20 antibodies: type I and type II.

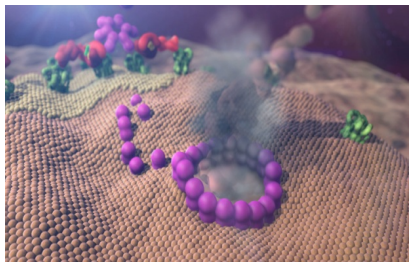
Antibody-dependent cellular cytotoxicity (ADCC)



Direct Cell Death



Complement-Dependent Cytotoxicity (CDC)



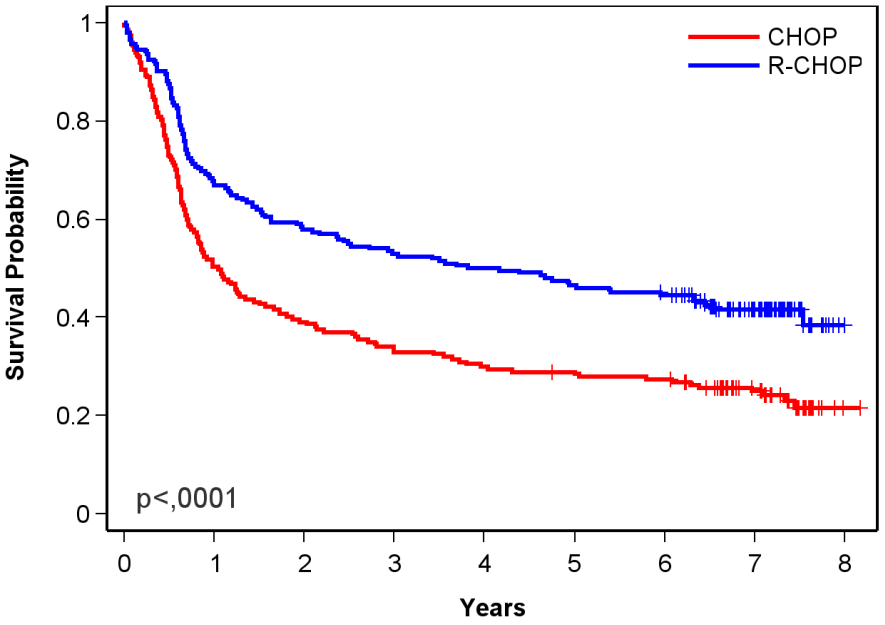
1. Mossner E et al. Blood. 2010; 115(22): 4393-4402; 2. Cragg MS. Blood. 2004; 103(7): 2738-2743; 3. Niederfellner G et al. Blood. 2011; 118(2): 358-367; 4. Alduaij W, et al. Blood. 2011; 117(17): 4519–4529.

Long-term results of the GELA study

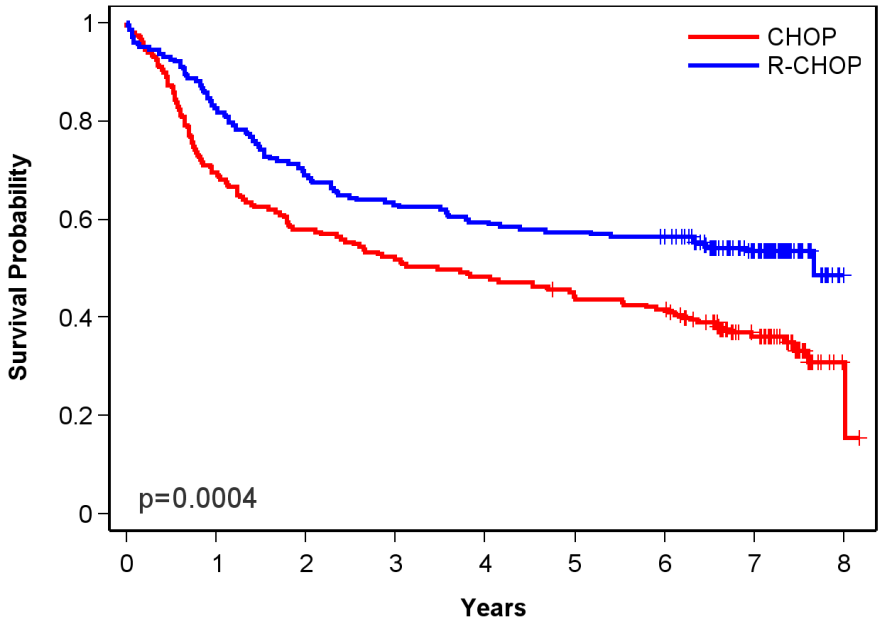
LNH-98.5 study

R-CHOP vs. CHOP in Older Patients with Diffuse Large B-Cell Lymphoma

EFS – Median follow-up 7 y
42% vs. 24%

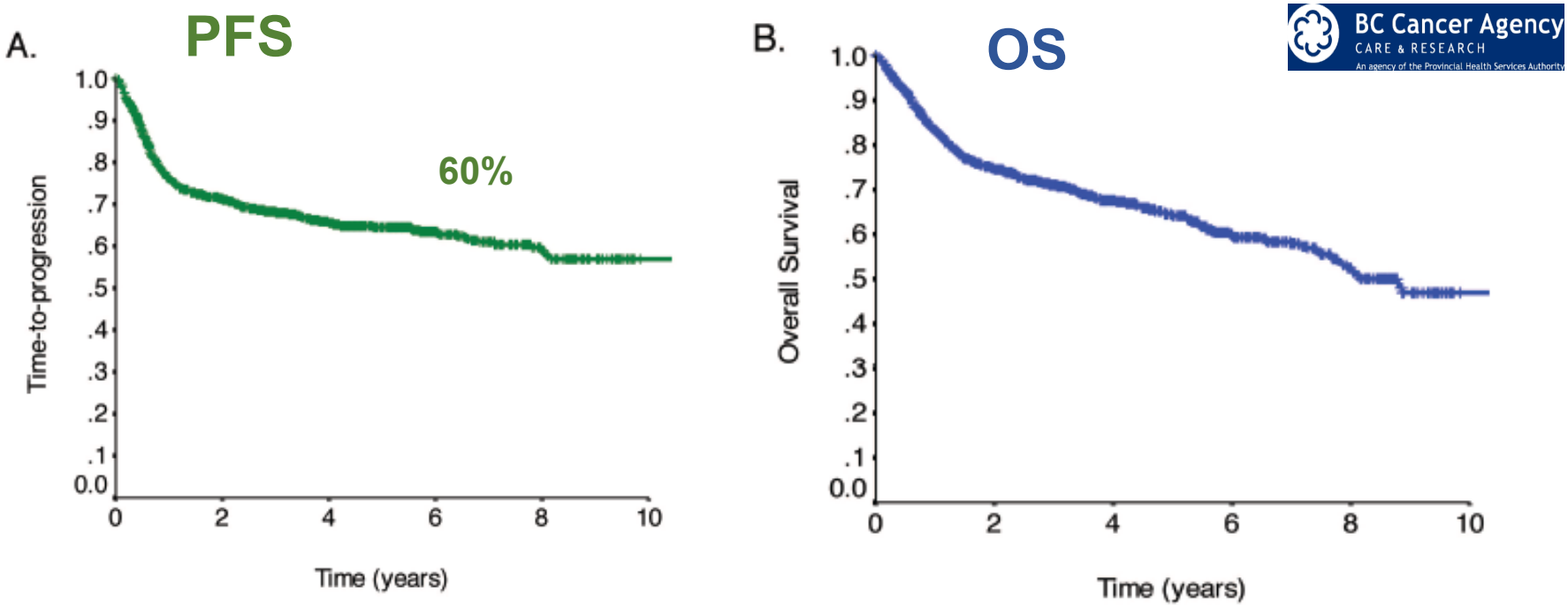


OS – Median follow-up 7 y
>50% vs. 35%



What outcome can we expect with R-CHOP in DLBCL ?

Patients with DLBCL treated with R-CHOP-21 at BCCA (n=1476)

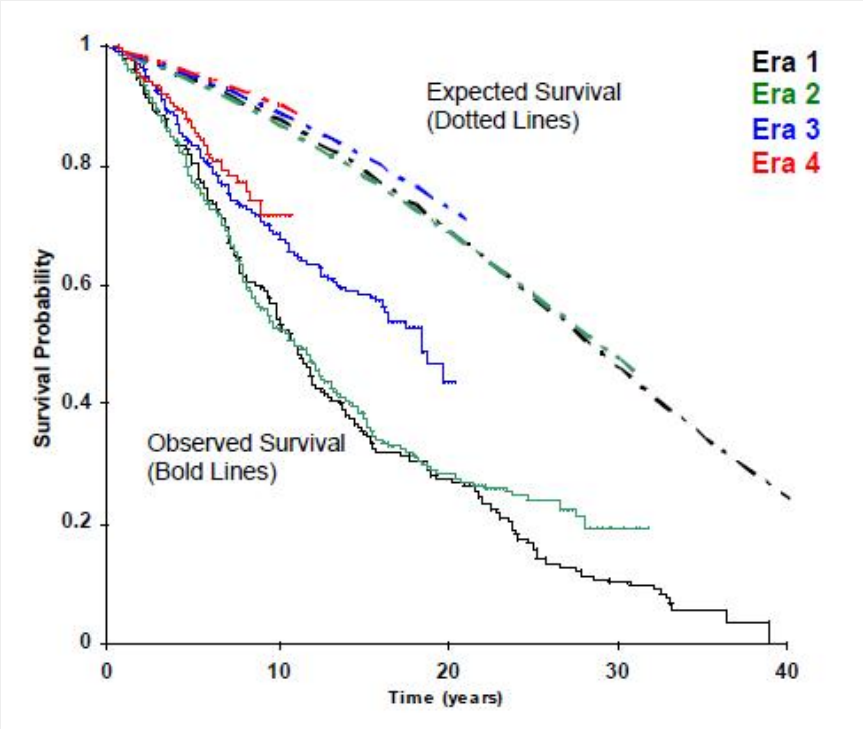


Main role of first line therapy and low activity of salvage treatment

BC Cancer Agency Database Sehn Hematology 2012

Improvements in survival in FL during 4 decades: the Stanford University experience on 1334 pts

Era 1 (1960-1975): pre-anthracycline (median FU 11.1 yrs)
Era 2 (1976-1986): anthracycline (median FU 8.6 yrs)
Era 3 (1987-1996): aggressive chemotherapy/purine analogs (median FU 11.3 yrs)
Era 4 (1997-2003): Rituximab (median FU 6.1 yrs)

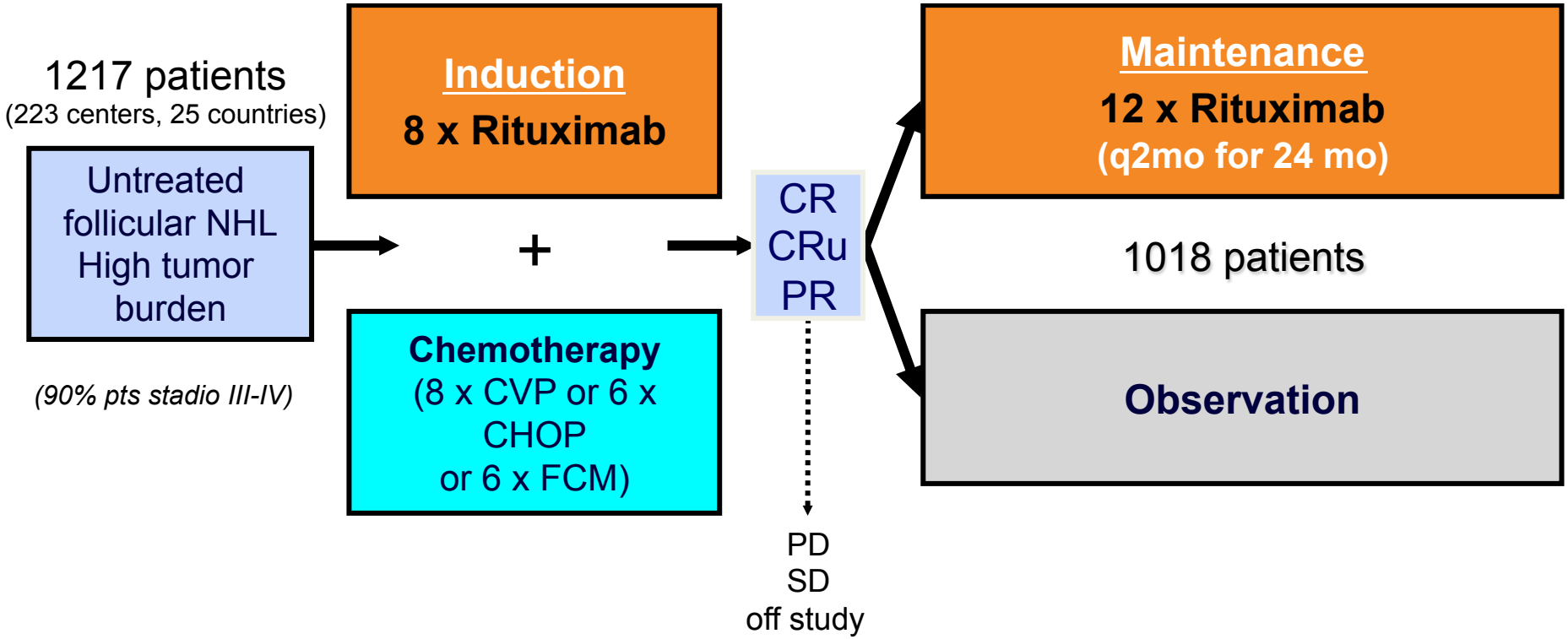


Improvements in OS exceeded improvements in survival in the general population in the same period

Tan D, et al; Blood 2013

Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial

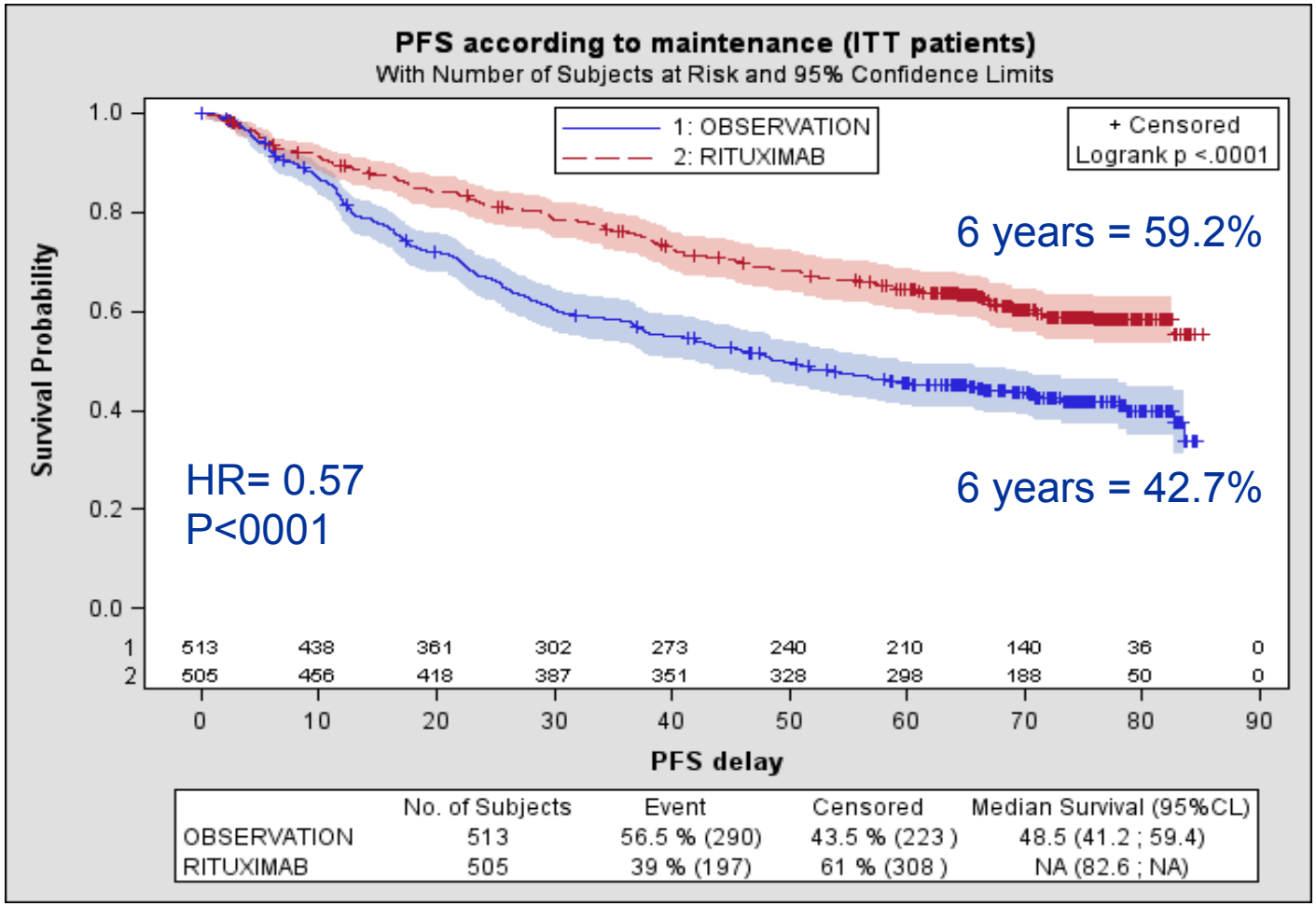
Gilles Salles, John Francis Seymour, Fritz Offner, Armando López-Guillermo, David Belada, Luc Xerri, Pierre Feugier, Réda Bouabdallah, John Vincent Catalano, Pauline Brice, Dolores Caballero, Corinne Haioun, Lars Moller Pedersen, Alain Delmer, David Simpson, Sirpa Leppa, Pierre Soubeyran, Anton Hagenbeek, Olivier Casasnovas, Tanin Intragumtornchai, Christophe Fermé, Maria Gomes da Silva, Catherine Sebban, Andrew Lister, Jane A Estell, Gustavo Milone, Anne Sonet, Myriam Mendila, Bertrand Coiffier, Hervé Tilly



(Median follow-up 3 years)

Salles GA, et al. Lancet 2011;377:42-51.

PRIMA 6 years follow-up
Progression free survival from randomization



Salles et al. ASH 2013

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Consolidated results

New antiCD20 antibodies

Association with IMIDs

New modality of administration of antiCD20 antibodies

Future development

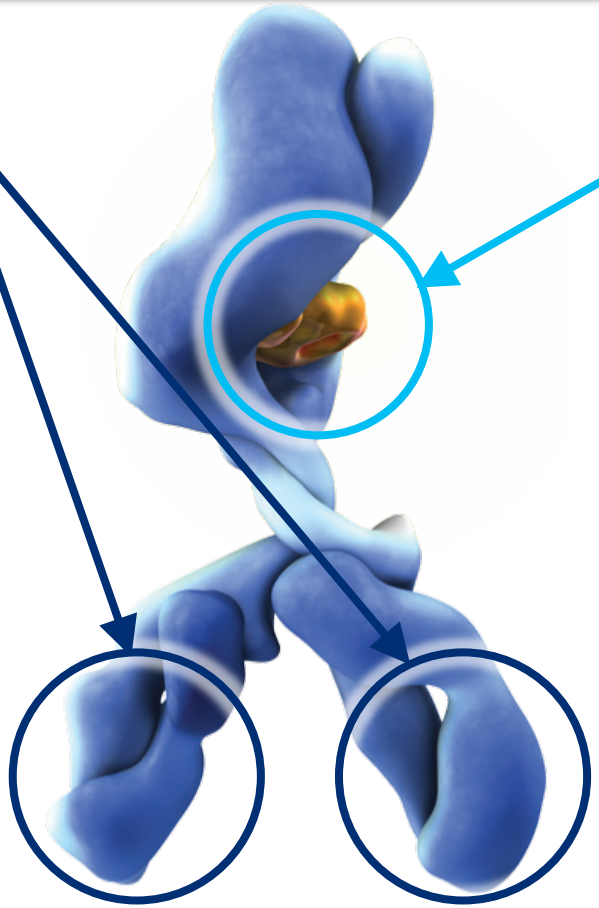
Novel Anti-CD20 MoAbs for Relapsed/ Refractory Indolent NHL

MoAb	Phase	Efficacy
Ofatumumab	I/II	Dose (ORR): 300 mg (63%), 500 mg (33%), 700 mg (20%), 1000 mg (50%)
	II	ORR: 11%, 6-mo PFS in 116 patients with rituximab-refractory FL
Veltuzumab	I/II	IV administration: ORR: 44%; CR: 27% DOR in patients with FL: 19.7 mos Subcutaneous administration: ORR: 53% CR: 20% in patients with indolent NHL
Ocrelizumab	I/II	ORR: 38%; PFS: 11.4 mos in patients with FL
GA101	II	Low dose (400 mg; n = 18): 17% ORR High dose (1600/800 mg; n = 22): 55% ORR

GA101: Designed for increased antibody-dependent cellular cytotoxicity (ADCC) and Direct Cell Death

Type II anti-CD20 mAb[1]

Increased Direct Cell Death[2]



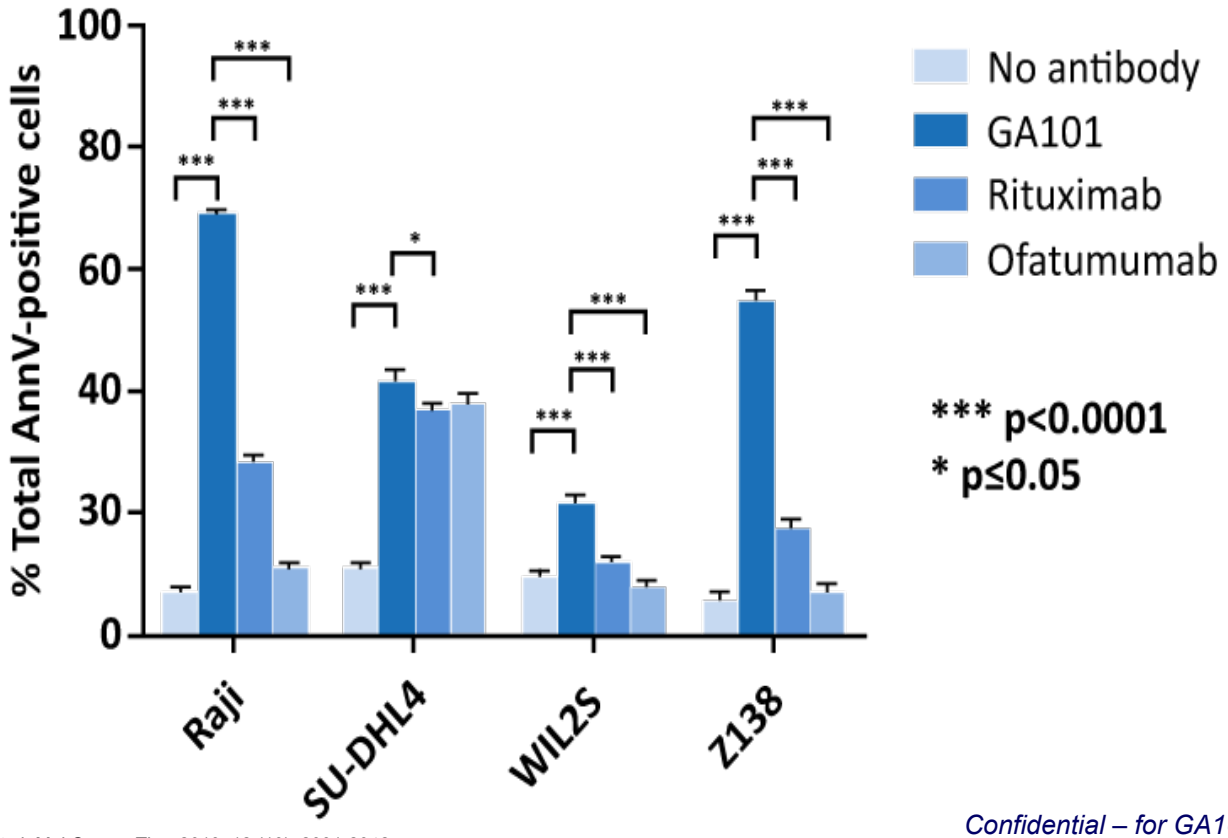
Glycoengineered Fc region[2]

Increased antibody-dependent cellular cytotoxicity (ADCC)[2]

Extensive clinical development program to evaluate the superiority of GA101 over rituximab in multiple head-to-head trials

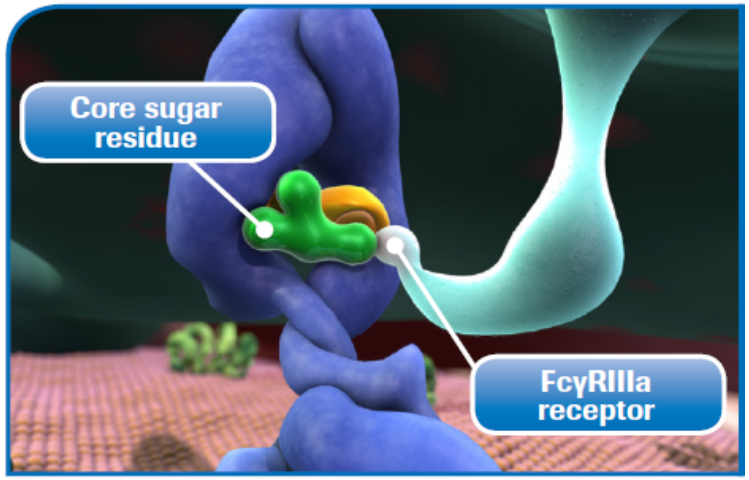
1. Niederfellner G, et al. Blood 2011; 118:358–367. 2. Mössner E, et al. Blood 2010; 115:4393–4402.

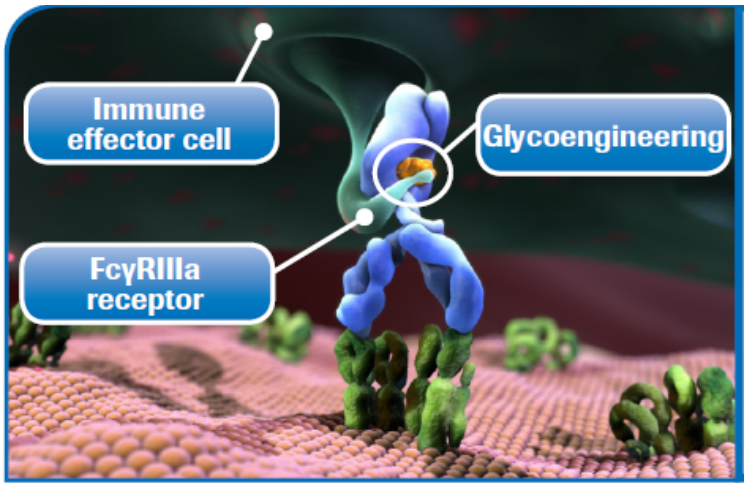
Induction of direct cell death GA101-, Rituximab-, and Ofatumumab-mediated direct cell death assessed in four CD20-expressing cell lines Raji, SUDHL4, Wil2S, and Z138



Herter S, et al. Mol Cancer Ther 2013; 12 (10): 2031-2042.

GA101: Designed through glycoengineering to increase affinity to, and activation of, immune effector cells



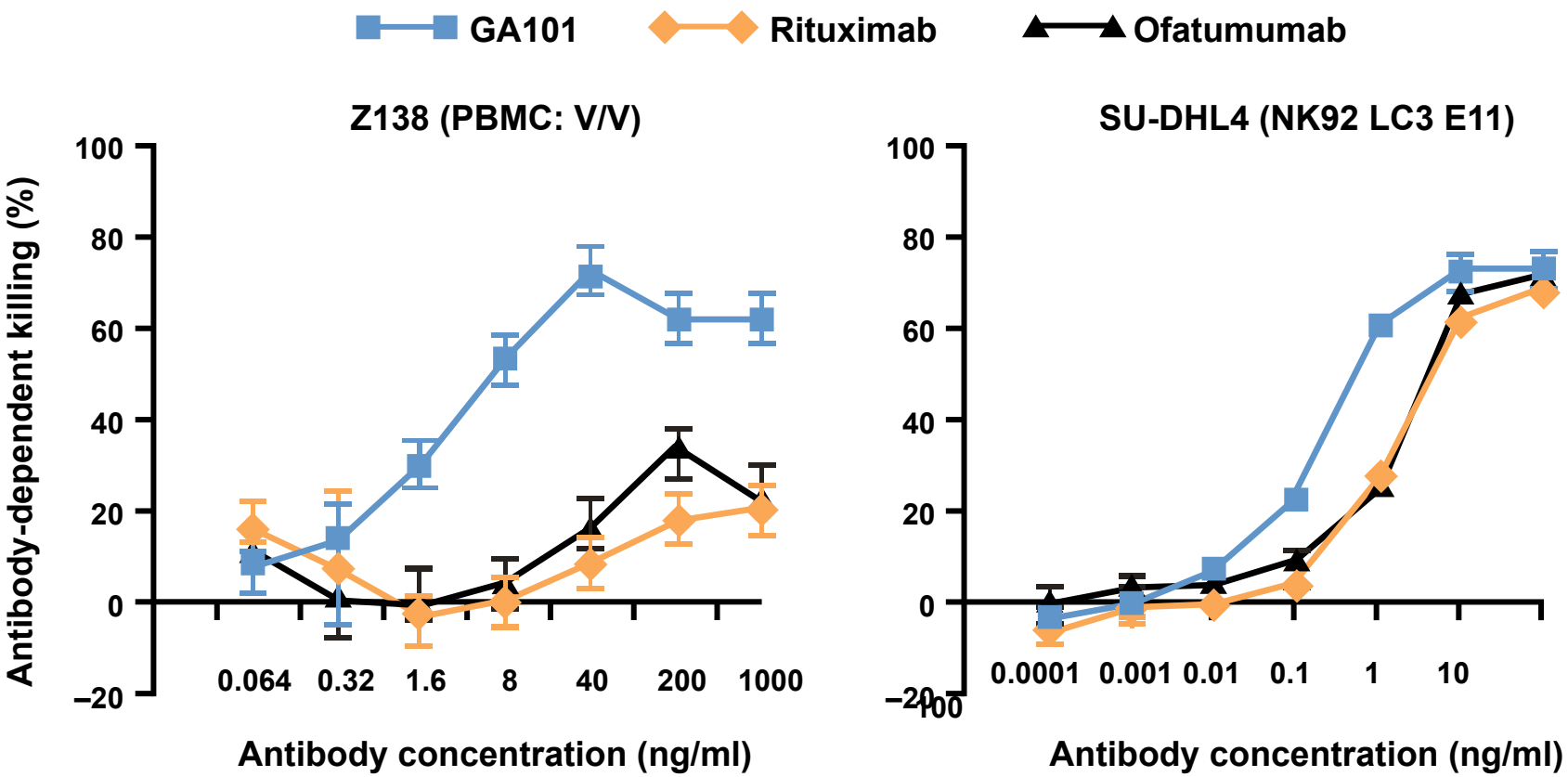


- The presence of certain sugar residues on the Fc region of an antibody may interfere with its ability to bind to immune effector cells[1,2]
- Removal of these sugars via glycoengineering may increase binding affinity between the Fc region of therapeutic antibodies and the Fc receptors on immune effector cells, such as macrophages and natural killer cells[3]
- In preclinical studies, glycoengineering of the Fc region of GA101 has demonstrated up to a 100-fold increase in ADCC over non-glycoengineered mAbs[2,3]

1. Ferrara C, *et al. J Biol Chem 2006; 281:5032–5036; 2.* Ferrara C, *et al. Proc Natl Acad Sci U S A 2011; 108:12669–12674 3.* Mossner E *et al. Blood. 2010;115(22):* 4393-4402

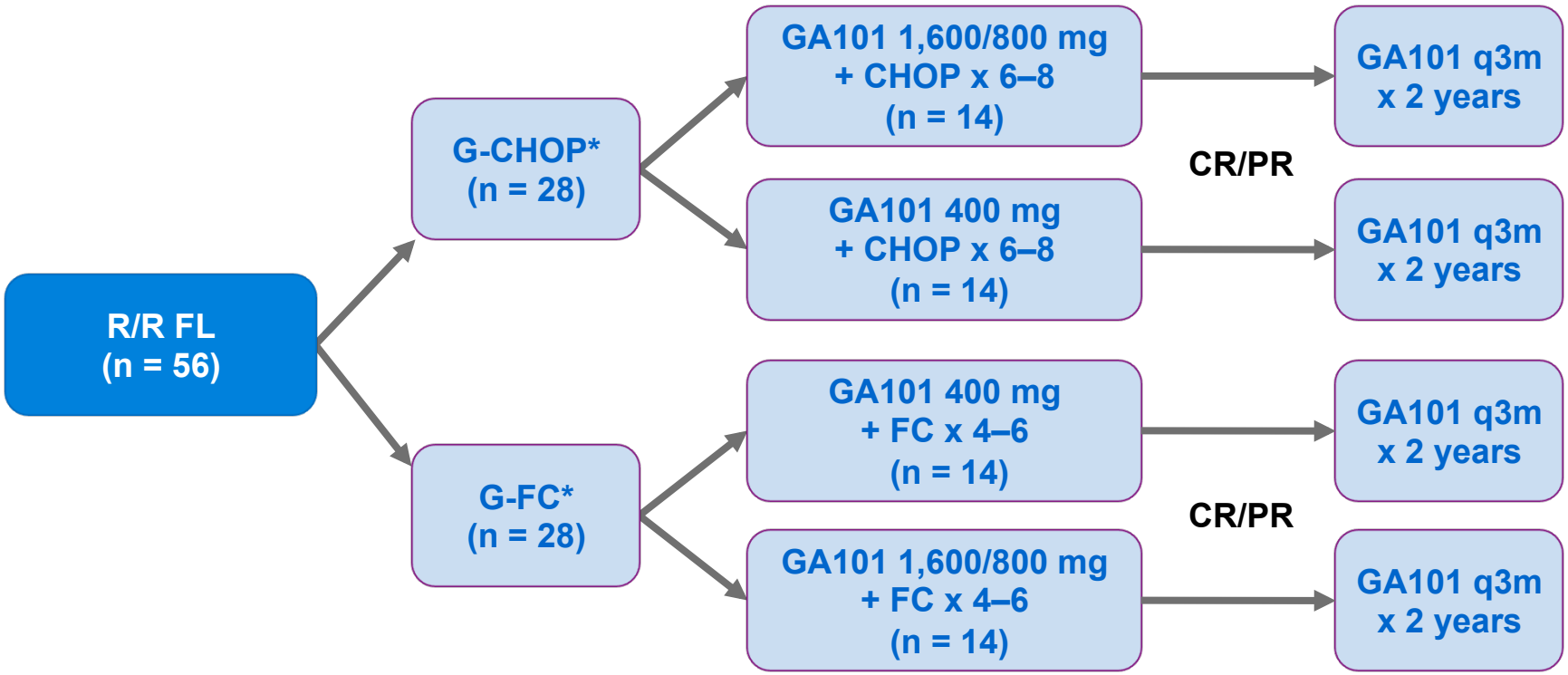
GA101-induced ADCC

GA101 exhibited up to 100-fold higher ADCC potency than rituximab and ofatumumab on Z138 and SU-DHL4 cell lines



ADCC, antibody-dependent cell-mediated cytotoxicity; PBMC, peripheral blood mononuclear cells
Herter S, *et al.* Poster presentation at ASH 2010 (Abstract 3925).

Obinutuzomab (GA101) plus CHOP or FC in relapsed/refractory Follicular Lymphoma: results of the Gaudì study



Radford J, et al; Blood 2013

Obinutuzumab (GA101) plus CHOP or FC in relapsed/refractory follicular lymphoma: results of the GAUDI study (BO21000)

The overall response rate was 96% with G-CHOP and 93% with G-FC

	G-CHOP						G-FC					
	400/400 mg (n = 14)		1600/800 mg (n = 14)		Total (n = 28)		400/400 mg (n = 14)		1600/800 mg (n = 14)		Total (n = 28)	
Patients	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
ORR	13	93	14	100	27	96	14	100	12	86	26	93
CR	2	14	9	64	11	39	11	79	3	21	14	50
PR	11	79	5	36	16	57	3	21	9	64	12	43
SD	1	7	0	0	1	4	0	0	0	0	0	0
PD	0		0	0	0	0	0	0	1	7	1	4

	Treatment-related (all grades)					
	400/400 mg (n = 14)		1600/800 mg (n = 14)		Total (n = 28)	
Patients	No.	%	No.	%	No.	%
G-CHOP						
Neutropenia	4	29	8	57	12	43
Febrile neutropenia	—		1	7	1	4
Thrombocytopenia	—		1	7	1	4
Anemia	3	21	3	21	6	21
Leukopenia	—		1	7	1	4
G-FC						
Neutropenia	9	64	5	36	14	50
Febrile neutropenia	—		1	7	1	4
Thrombocytopenia	2	14	4	29	6	21
Anemia	1	7	—		1	4
Leukopenia	—		1	7	1	4

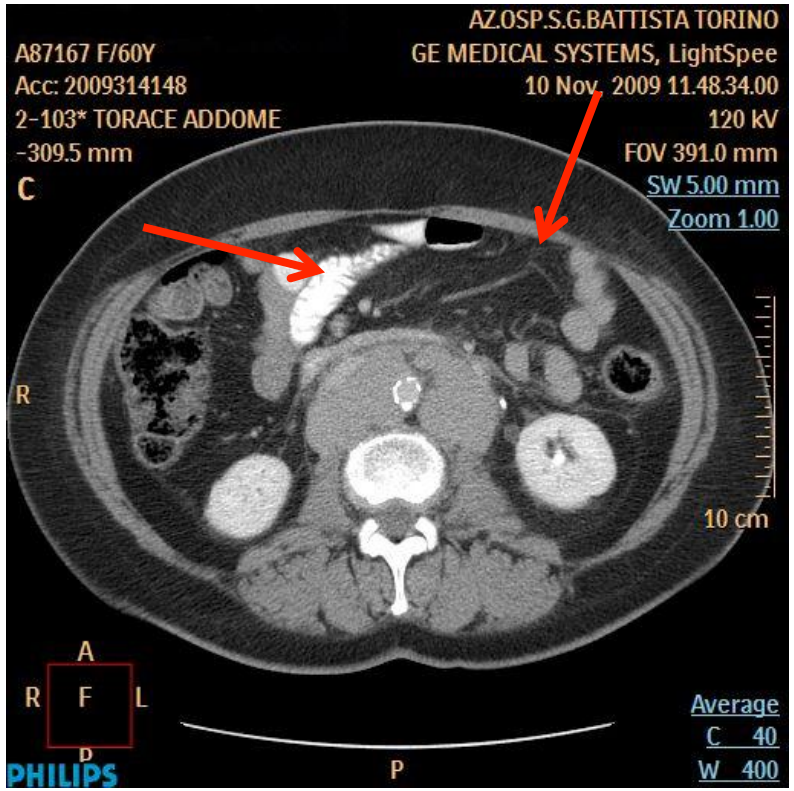
Grade 3-4 neutropenia:

43% of pts in the G-CHOP and 50% in the G-FC

Acceptable safety profile but G-FC was associated with more AEs than G-CHOP

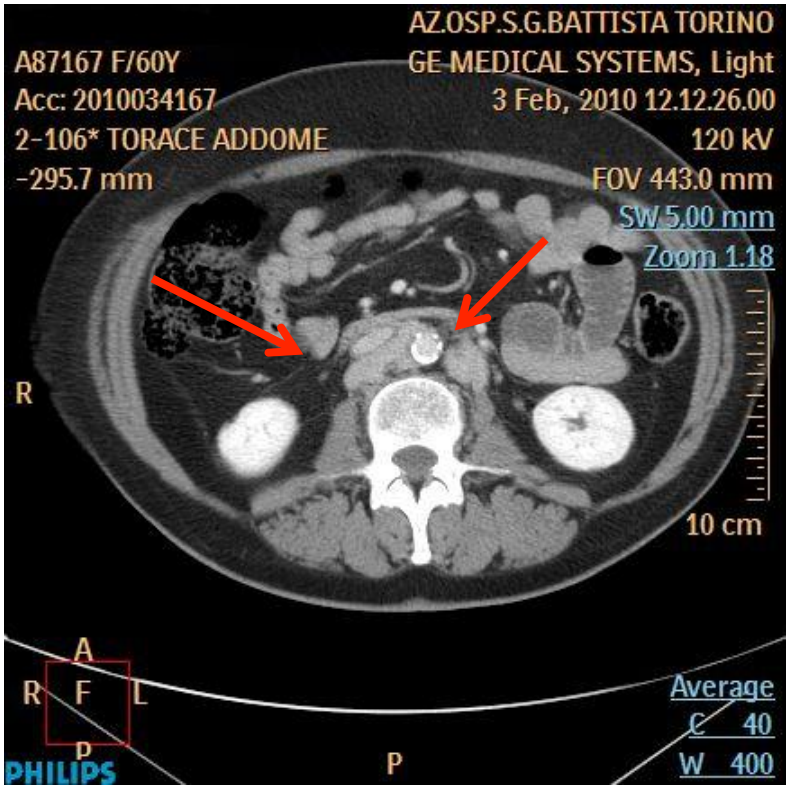
Radford J, Blood 2013

GAUDI STUDY: Turin experience 11 patients



BASELINE CT

INTERIM CT after 4 cycles GA101- FC

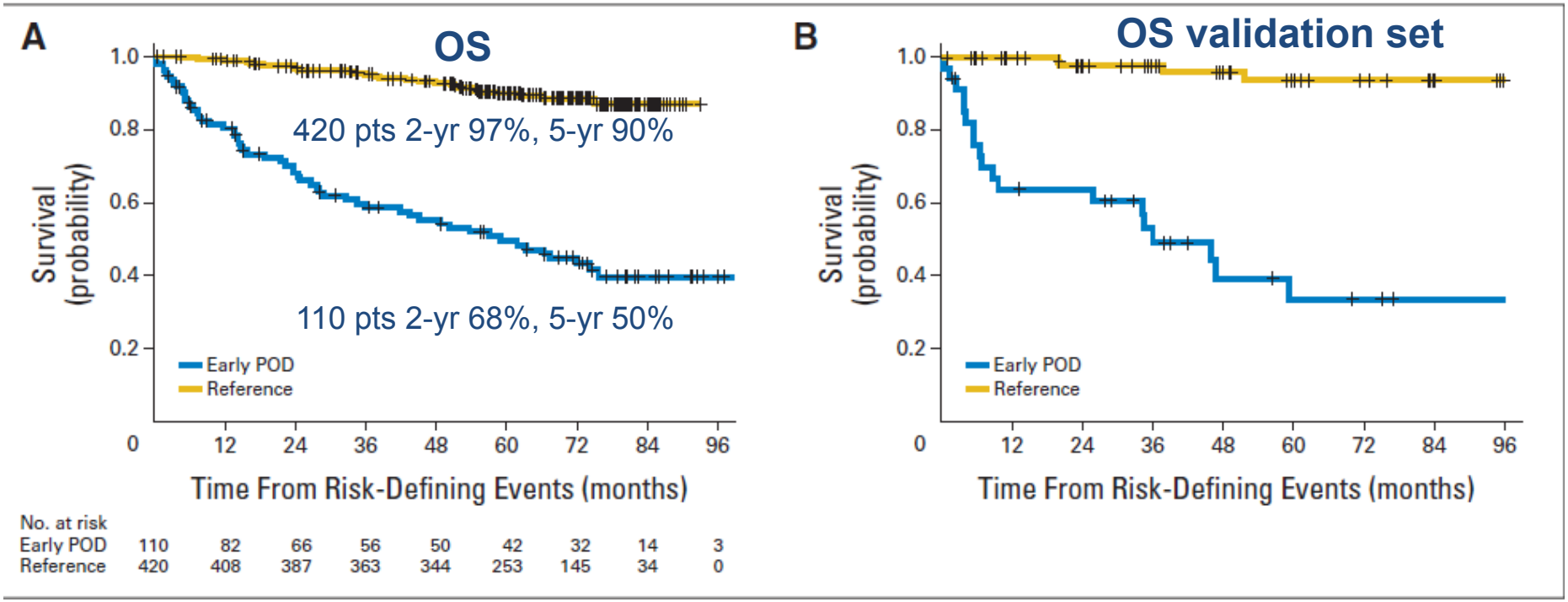


VOLUME 33 · NUMBER 23 · AUGUST 10 2015

JOURNAL OF CLINICAL ONCOLOGY

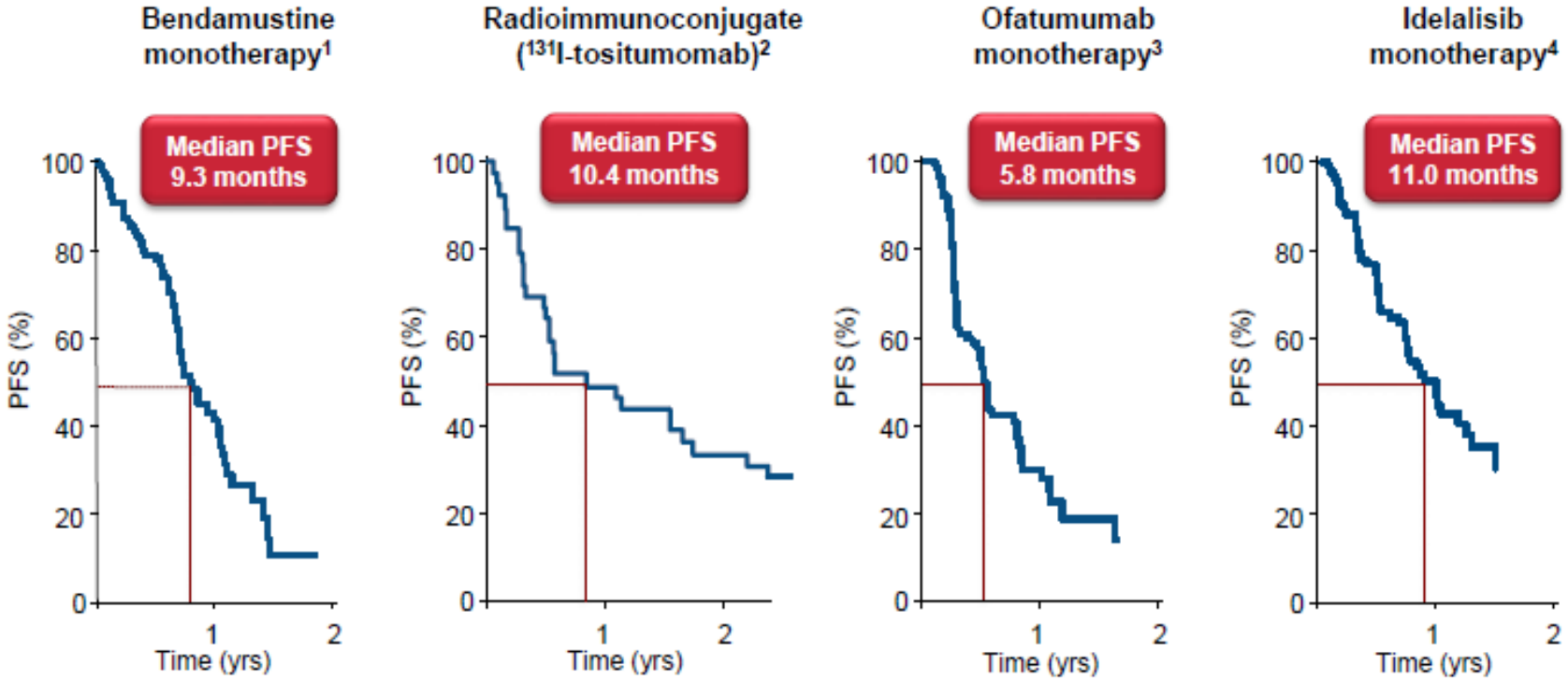
ORIGINAL REPORT

Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study



Casulo C et al, JCO 2015

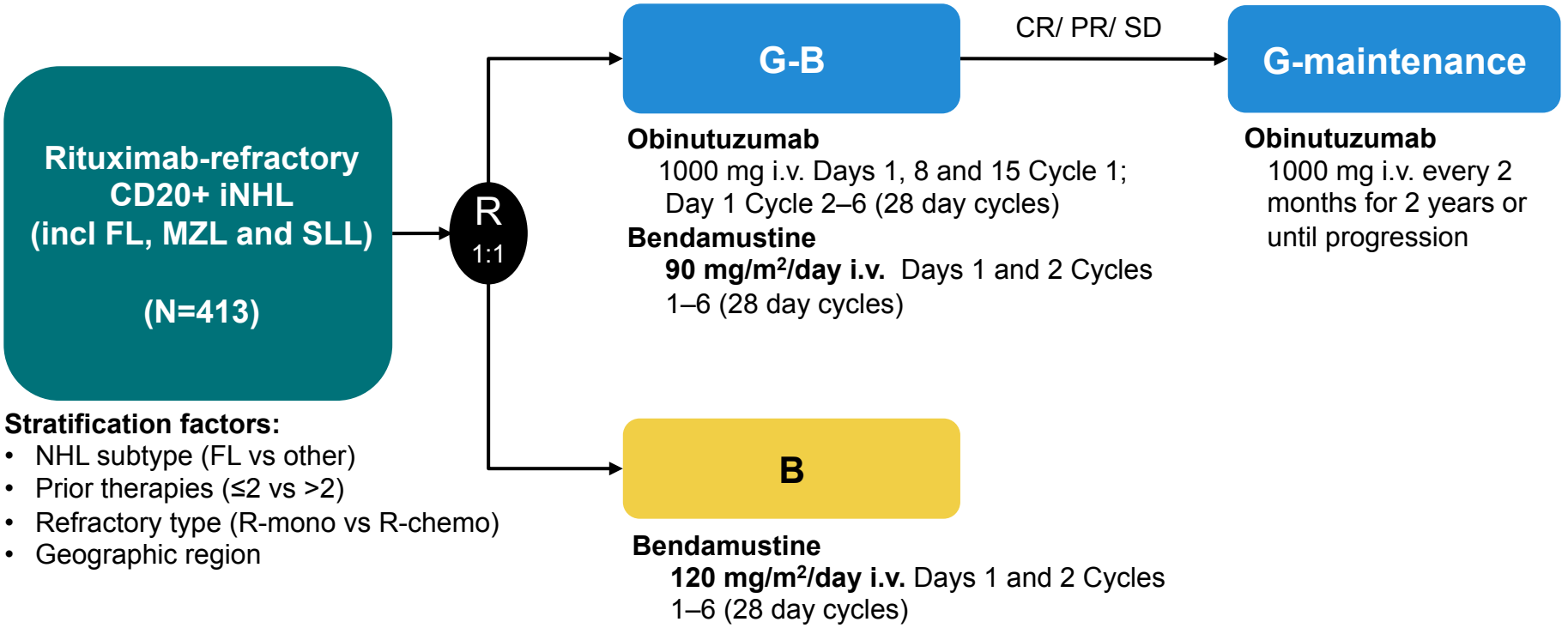
Limited options are available for Relapsed – Refractory iNHL not eligible to transplant



iNHL, indolent non-Hodgkin lymphoma; SoC, standard of care

1. Kahl et al. Cancer 2010;116:106–14
2. Horning et al. J Clin Oncol 2005;23:712–9
3. Czuczman et al. Blood 2012;119:3698–704
4. Gopal et al. N Engl J Med 2014;370:1008–18

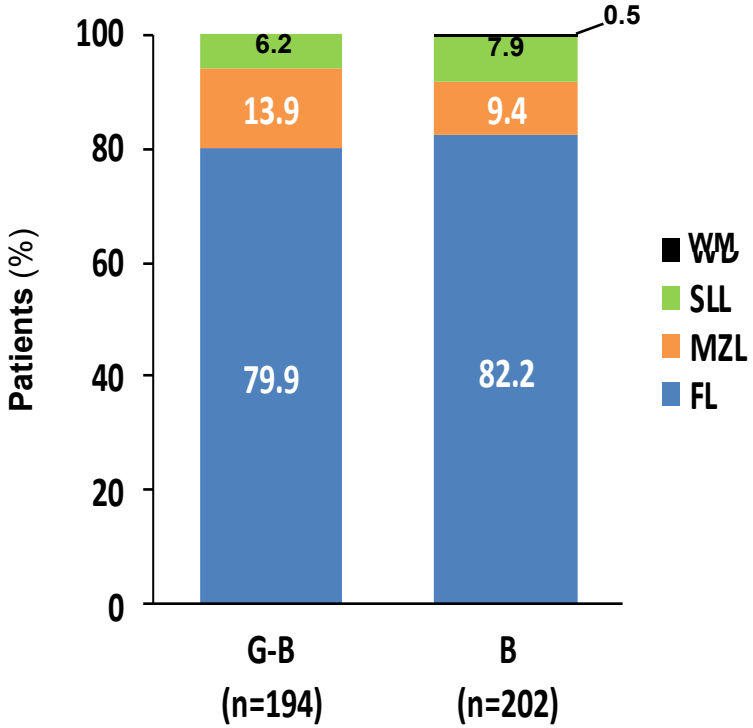
GADOLIN: Study design (NCT01059630)



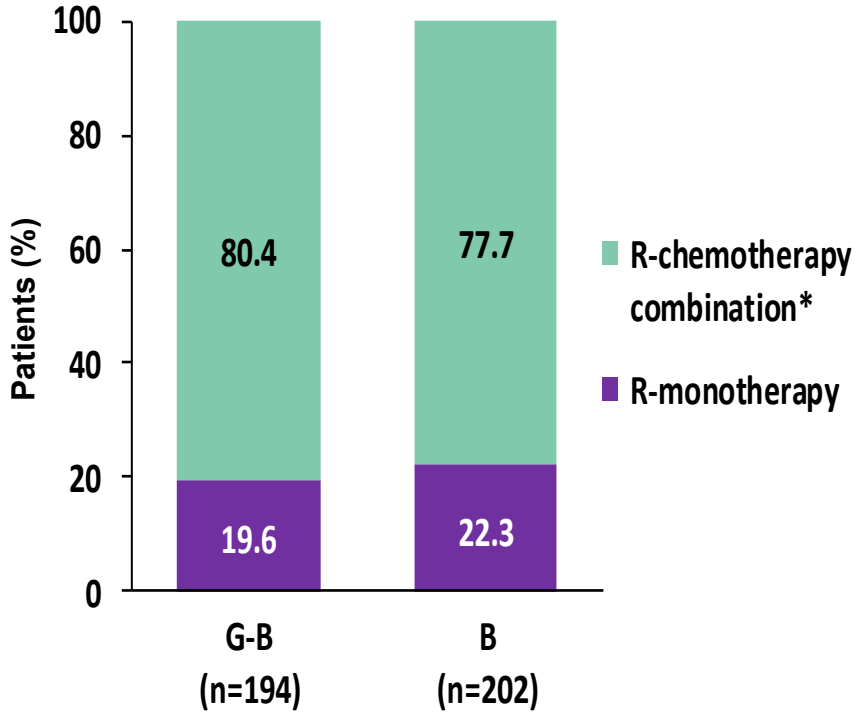
Primary endpoint	PFS as assessed by an IRF
Secondary endpoints	PFS as assessed by investigator, OS, end-of-induction response, best overall response, ORR, CRR, duration of response, EFS, DFS, safety, PK profile, pharmacoeconomics, PROs
***Safety plan**	Early safety interim analysis conducted by a DSMB after 20 patients received Cycle 1 to evaluate for overt excess toxicity resulting in protocol modifications to be considered

GADOLIN: Baseline disease characteristics

Lymphoma subtype



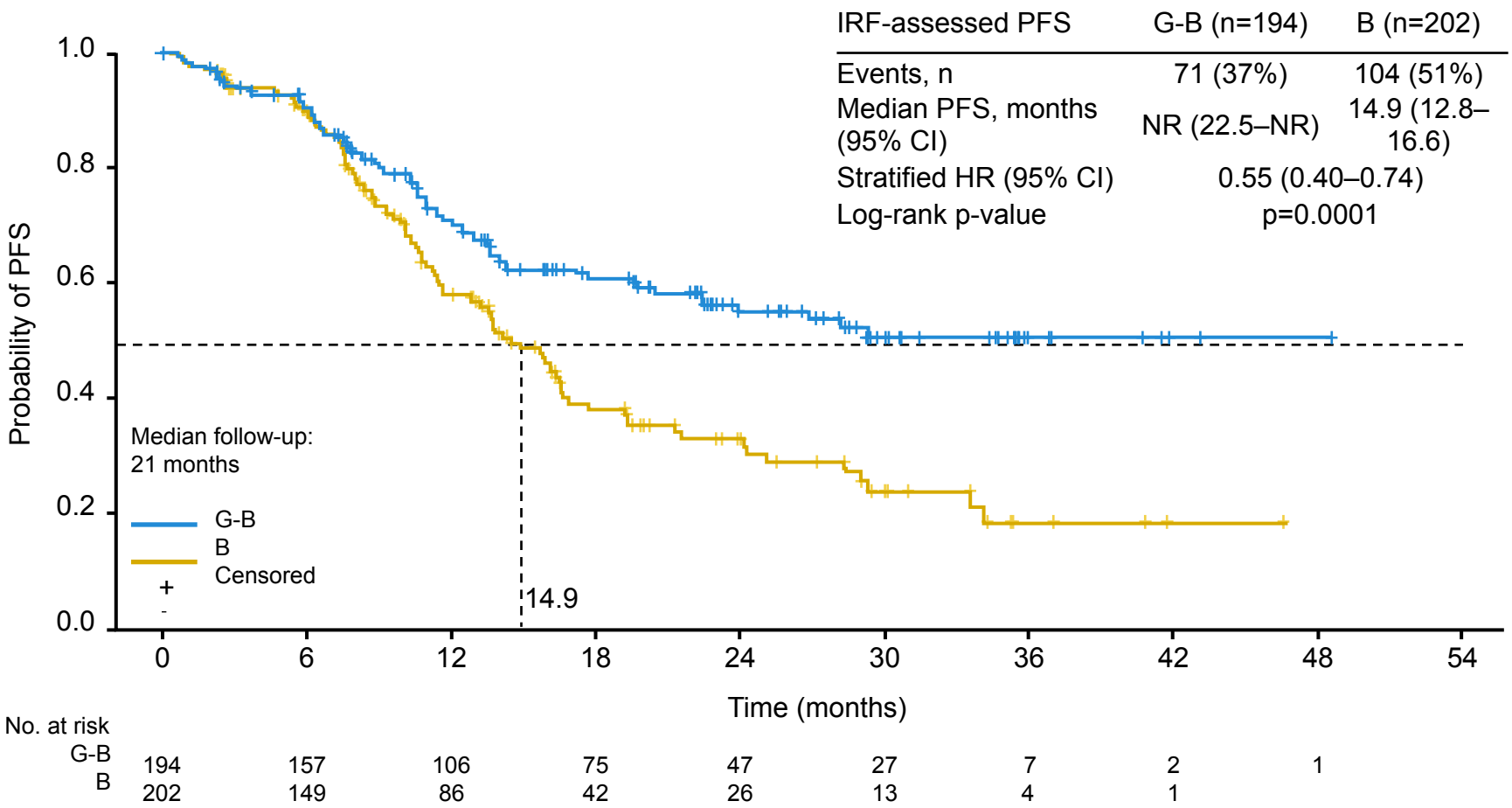
Rituximab-refractory type



* Including patients who relapsed during or within 6 months of R-maintenance following R-chemotherapy

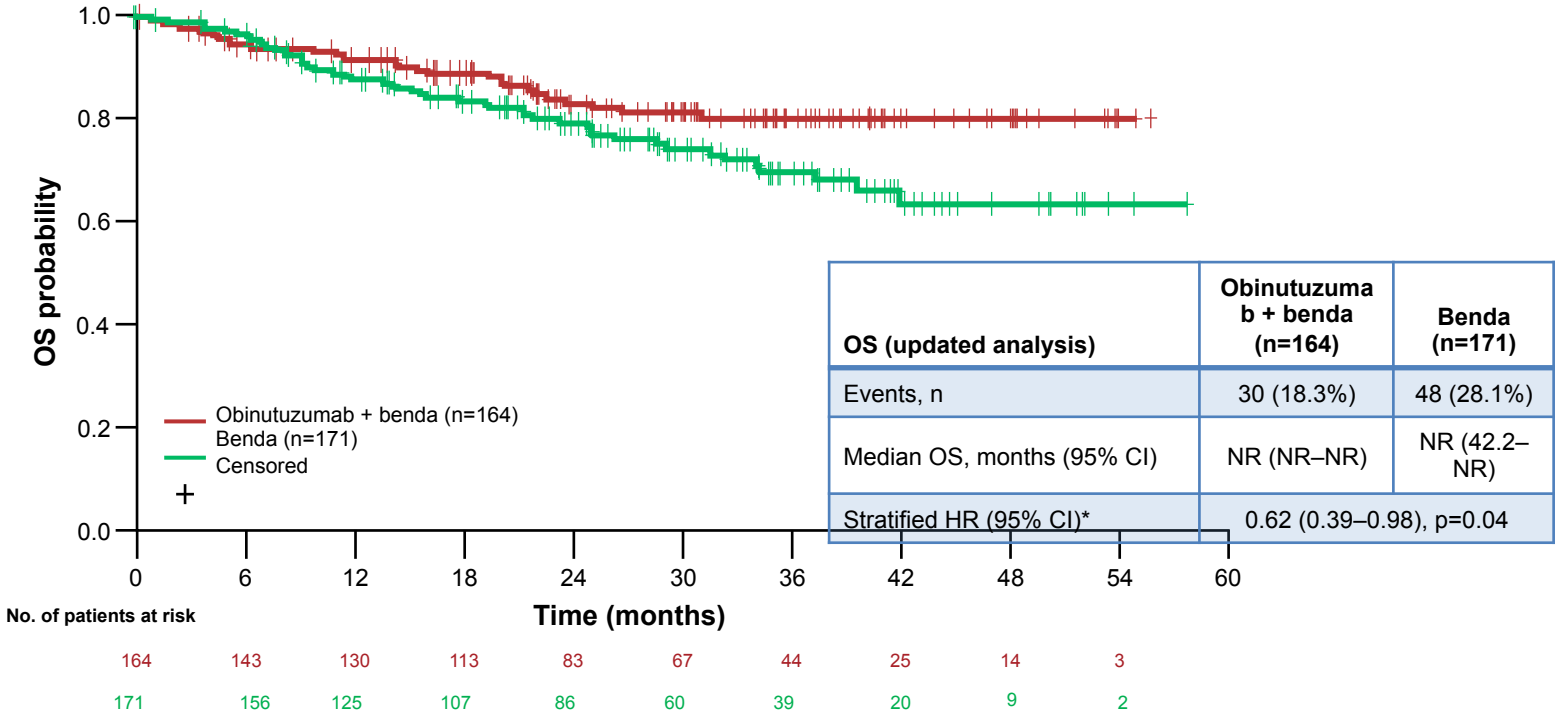
FL, follicular lymphoma; MZL, marginal zone lymphoma including extranodal, nodal and splenic; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

GADOLIN primary outcome: IRF-assessed PFS



IRF, independent radiology facility; HR, hazard ratio; CI, confidence interval; NR, not reached.

GADOLIN: Analysis of OS



OS (updated analysis)	Obinutuzumab + benda (n=164)	Benda (n=171)
Events, n	30 (18.3%)	48 (28.1%)
Median OS, months (95% CI)	NR (NR–NR)	NR (42.2–NR)
Stratified HR (95% CI)*	0.62 (0.39–0.98), p=0.04	

- At updated analysis cut-off **(01 May 2015)** 48/171 (28.1%) patients with FL in the benda arm and 30/164 (18.3%) in the Obinutuzumab + benda arm had died
- Results suggest an emerging survival benefit for Obinutuzumab + benda versus benda alone in the FL population

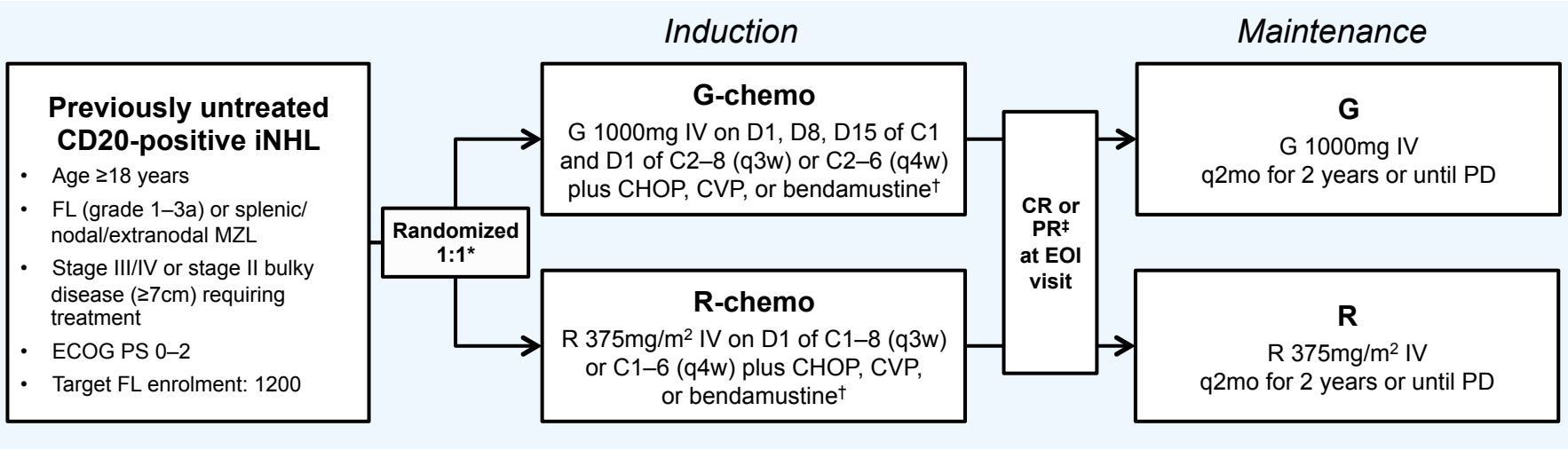
*Stratification factors: refractory type (R vs R-chemo), prior therapies (≤2 vs >2)

Benda, bendamustine; CI, confidence interval; FL, follicular lymphoma; HR, hazard ratio; NR, not reached; OS, overall survival

Trněný M, et al. EHA June 2016. Oral presentation

Obinutuzumab-Based Induction and Maintenance Prolongs Progression-Free Survival (PFS) in Patients with Previously Untreated Follicular Lymphoma: Primary Results of the Randomized Phase 3 GALLIUM Study

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

Marcus R et al, ASH 2016. Oral presentation

Baseline patient and disease characteristics (FL)

Characteristic	*R-chemo, n=601*	*G-chemo, n=601*
Median age, years (range)	58 (23–85)	60 (26–88)
Male, % (n)	46.6% (280)	47.1% (283)
Ann Arbor stage at diagnosis, % (n)		
I	1.3% (8)*	1.7% (10)†
II	7.4% (44)*	6.9% (41)†
III	35.0% (209)*	34.8% (208)†
IV	56.3% (336)*	56.7% (339)†
FLIPI risk group, % (n)		
Low (0–1)	20.8% (125)	21.3% (128)
Intermediate (2)	37.1% (223)	37.3% (224)
High (≥3)	42.1% (253)	41.4% (249)
B symptoms, % (n)	34.3% (206)‡	33.4% (201)
Bone marrow involvement, % (n)	49.3% (295)†	53.7% (318)§
Extranodal involvement, % (n)	65.9% (396)	65.2% (392)
Bulky disease (≥7cm), % (n)	45.2% (271)‡	42.5% (255)‡
Median (range) time from diagnosis to randomization, months	1.4 (0–168.1)	1.5 (0.1–121.6)¶

*n=597; †n=598; ‡n=600; §n=592; ¶n=598, value not determined in three pts

Marcus R et al, ASH 2016. Oral presentation

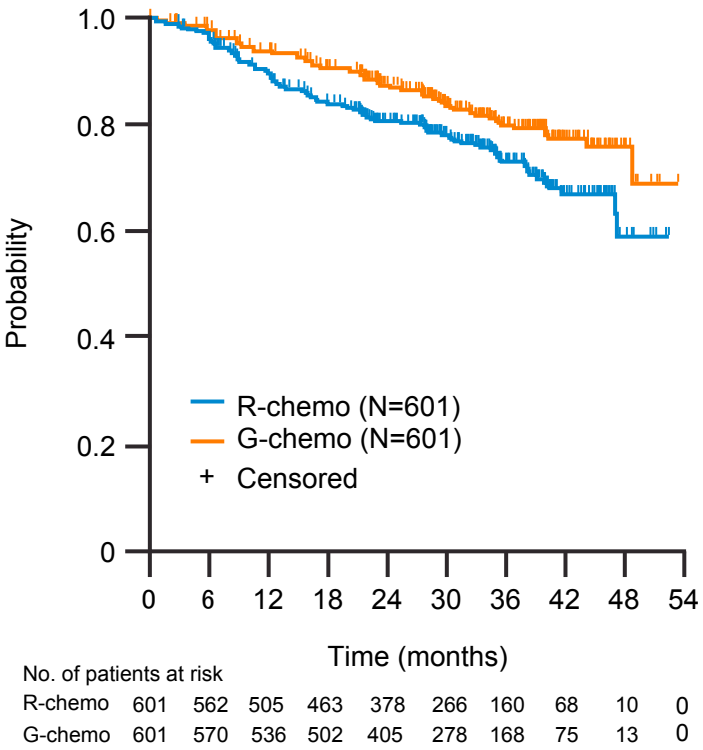
Response rates at end of induction (FL)*

	CT (by investigator)	
% (n); 95% CI	*R-chemo, n=601*	*G-chemo, n=601*
ORR	**86.9% (522); 83.9, 89.5**	**88.5% (532); 85.7, 91.0**
CR	**23.8% (143); 20.4, 27.4**	**19.5% (117); 16.4, 22.9**
PR	63.1% (379)	69.1% (415)
SD	1.3% (8)	0.5% (3)
PD	4.0% (24)	2.3% (14)
Not evaluable / missing	3.5% (21) / 4.3% (26)	4.0% (24) / 4.7% (28)

*INV-assessed using the Revised Response Criteria for Malignant Lymphoma (Cheson BD, et al. J Clin Oncol 2007)
INV, investigator

Marcus R et al, ASH 2016. Oral presentation

INV-assessed PFS (FL; primary endpoint)



No. of patients at risk

R-chemo	601	562	505	463	378	266	160	68	10	0
G-chemo	601	570	536	502	405	278	168	75	13	0

*Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region

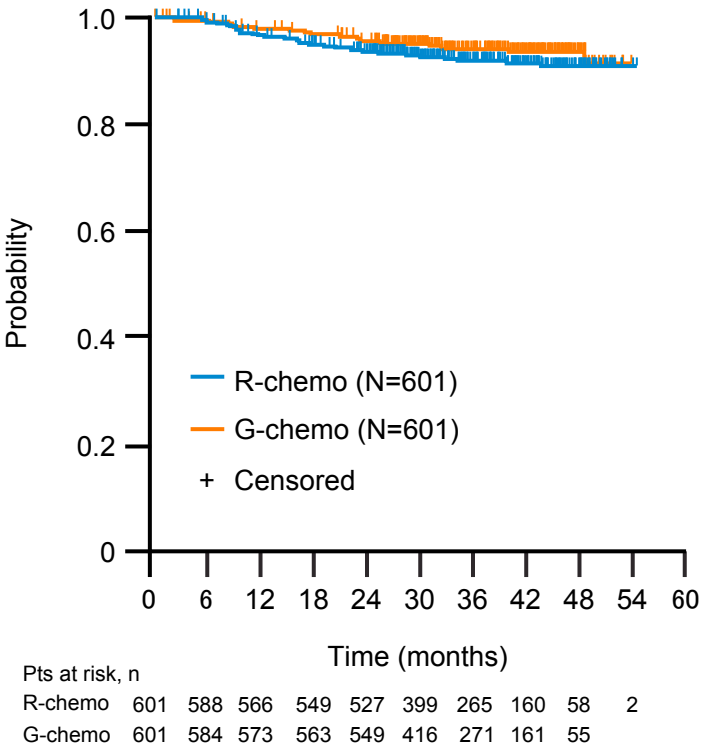
	R-chemo, n=601	*G-chemo, n=601*
Pts with event, n (%)	144 (24.0)	101 (16.8)
3-yr PFS, % (95% CI)	73.3 (68.8, 77.2)	80.0 (75.9, 83.6)
HR (95% CI), p-value*	0.66 (0.51, 0.85), p=0.0012	

Median follow-up: 34.5 months

34% reduction in the risk of progression or death

Marcus R et al, ASH 2016. Oral presentation

OS (FL)



	R-chemo, n=601	*G-chemo, n=601*
Pts with event, n (%)	46 (7.7)	35 (5.8)
3-yr OS, % (95% CI)	92.1 (89.5, 94.1)	94.0 (91.6, 95.7)
HR (95% CI), p-value*	0.75 (0.49, 1.17), p=0.21	

Median follow-up: 34.5 months

*Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region

Marcus R et al, ASH 2016. Oral presentation

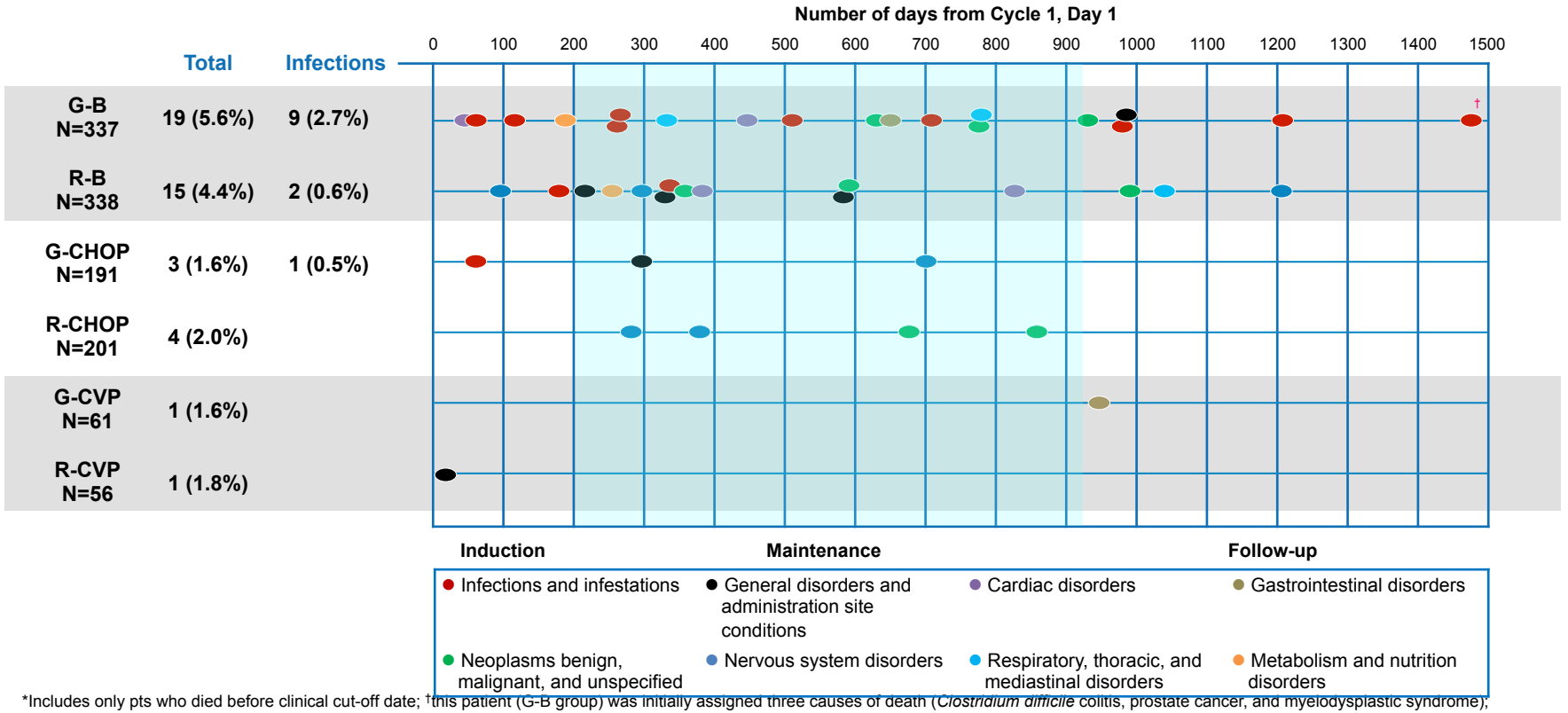
Safety summary (FL)

% (n)	R-chemo (n=597)	G-chemo (n=595)
Any AE	98.3% (587)	99.5% (592)
Grade ≥3 AEs (≥5% in either arm)	67.8% (405)	74.6% (444)
Neutropenia	37.9% (226)	43.9% (261)
Leucopenia	8.4% (50)	8.6% (51)
Febrile neutropenia	4.9% (29)	6.9% (41)
IRRs*	3.7% (22)	6.7% (40)
Thrombocytopenia	2.7% (16)	6.1% (36)
Grade ≥3 AEs of special interest by category (selected)		
Infections†	15.6% (93)	20.0% (119)
IRRs‡	6.7% (40)	12.4% (74)
Second neoplasms§	2.7% (16)	4.7% (28)
SAEs	39.9% (238)	46.1% (274)
AEs causing treatment discontinuation	14.2% (85)	16.3% (97)
Grade 5 (fatal) AEs	3.4% (20)	4.0% (24)**
Median (range) change from baseline in IgG levels at end of induction, g/l¶	-1.46 (-16.4–9.1)††	-1.50 (-22.3–6.5)‡‡

*As MedDRA preferred term; †All events in MedDRA System Organ Class 'Infections and Infestations'; ‡Any AE occurring during or within 24h of infusion of G or R and considered drug-related; §Standardized MedDRA query for malignant or unspecified tumors starting 6 mo after treatment start; ¶Ig levels were measured during screening, at EOI and end of maintenance and during follow-up; **Includes patient who died after clinical cut-off date from AE starting before cut-off date; ††n=472; ‡‡n=462

Marcus R et al, ASH 2016. Oral presentation

Grade 5 (fatal) AEs by treatment (FL)*



*Includes only pts who died before clinical cut-off date; †this patient (G-B group) was initially assigned three causes of death (*Clostridium difficile* colitis, prostate cancer, and myelodysplastic syndrome); *Clostridium difficile* colitis was the most acute, so the patient has been assigned to the 'Infections and infestations' category and the number of fatal AEs in G-B pts in neoplasms SOC reduced from 5 to 3

Marcus R et al, ASH 2016. Oral presentation

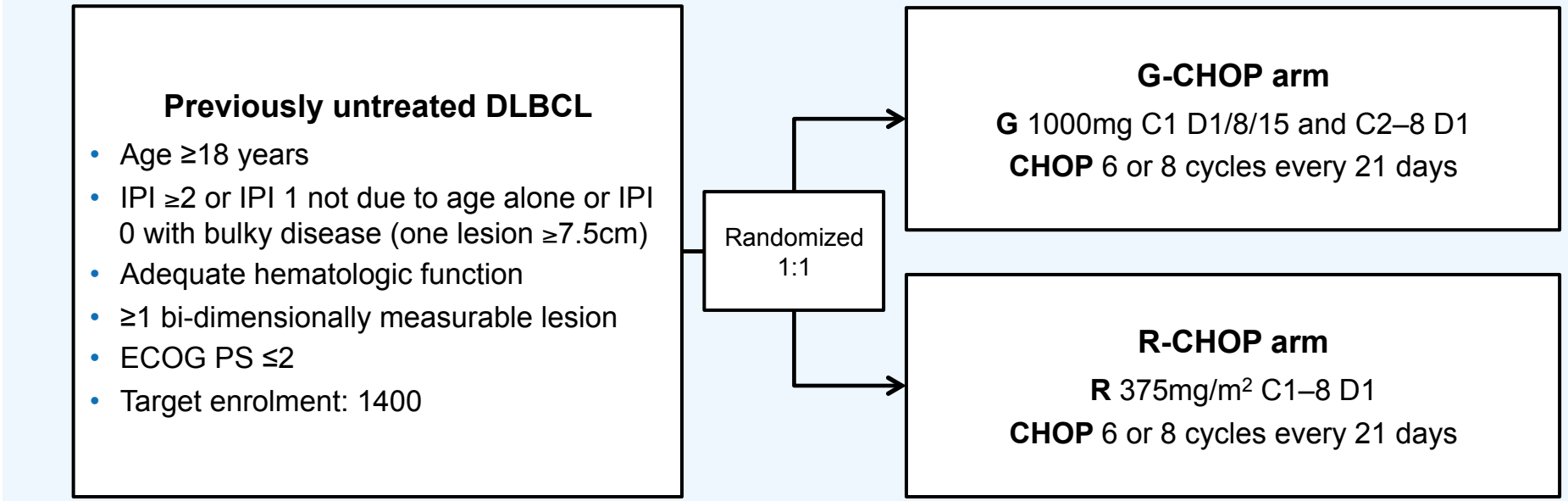
How to improve R-CHOP results in DLBCL

…substitute with different antiCD20 antibody

The GOYA study:

International, open-label, randomized Phase III study in 1L DLBCL pts

- *Scientific support from the Fondazione Italiana Linfomi*



- Number of CHOP cycles pre-planned in advance for all pts at each site
- Randomization stratification factors: planned number of CHOP cycles, IPI, geographic region

Vitolo et al. ASH 2016. Abstract 470.

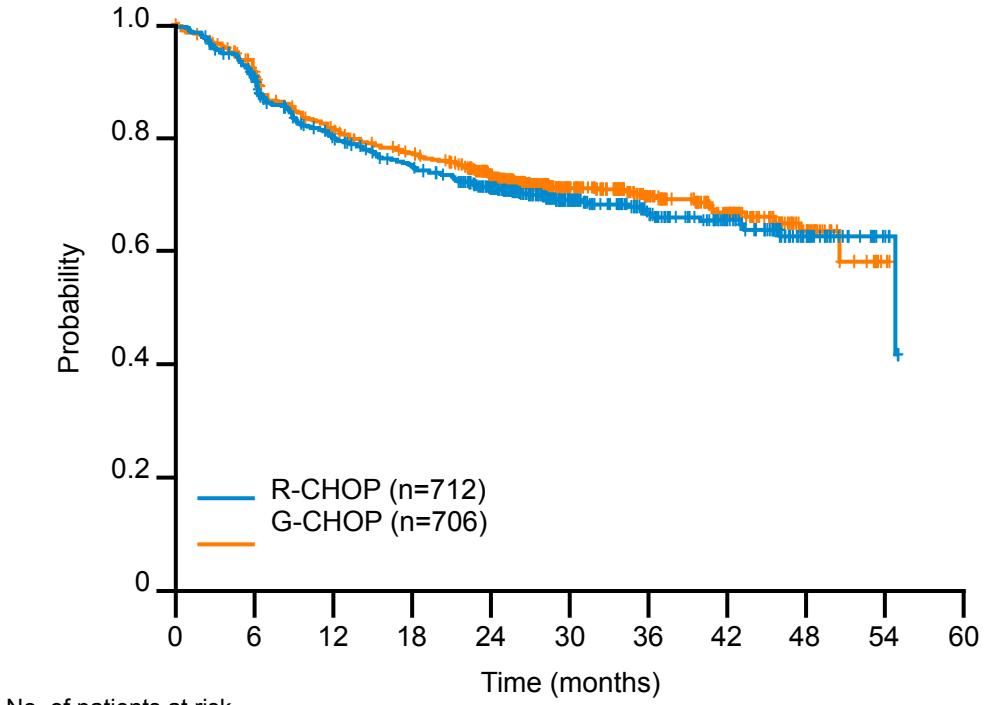
Baseline patient and disease characteristics

% (n)	R-CHOP, n=712	G-CHOP, n=706
Median age, years (range)	62.0 (18–83)	62.0 (18–86)
Female	46.2% (329)	47.7% (337)
Ann Arbor stage at diagnosis		
I–II	24.1% (171)	24.1% (170)
III–IV	75.9% (540)	75.9% (536)
ECOG PS*		
0	46.3% (330)	46.0% (325)
1	39.7% (283)	41.5% (293)
2	13.8% (98)	12.2% (86)
IPI		
Low/low-intermediate	57.4% (409)	53.3% (376)
High-intermediate	27.0% (192)	31.3% (221)
High	15.6% (111)	15.4% (109)
Extranodal involvement (>1 site)	33.7% (240)	37.3% (263)
Bone marrow involvement	10.9% (77)	10.9% (76)
Bulky disease (≥7.5cm)	36.9% (262)	37.1% (261)
COO subtype in evaluable pts (n=933)†		
GCB	58.2% (269)	57.5% (271)
ABC	25.5% (118)	26.5% (125)
Unclassified	16.2% (75)	15.9% (75)

*ECOG PS 3: R-CHOP, n=1; G-CHOP, n=1
†Missing COO classifications due to: restricted Chinese export license, n=252; CD20+ DLBCL not confirmed, n=102; missing/inadequate tissue, n=131

Investigator-assessed PFS (primary endpoint)

Kaplan-Meier plot of investigator-assessed PFS by treatment arm



No. of patients at risk

R-CHOP	712	616	527	488	413	227	142	96	41	6
G-CHOP	706	622	540	502	425	240	158	102	39	2

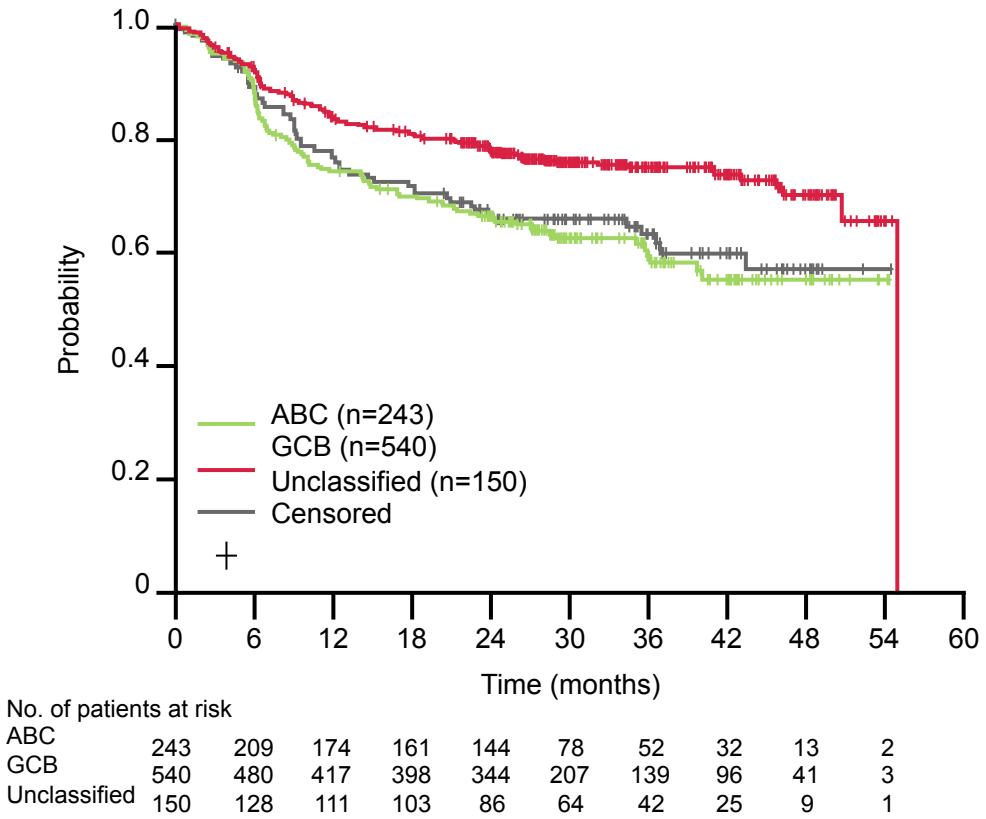
	R-CHOP, n=712	G-CHOP, n=706
Pts with event, n (%)	215 (30.2)	201 (28.5)
1-yr PFS, %	79.8	81.6
2-yr PFS, %	71.3	73.4
3-yr PFS, %	66.9	69.6
HR (95% CI), p-value*	0.92 (0.76, 1.11), p=0.3868	

Median follow-up: 29 months

*Stratified analysis; stratification factors: IPI score, number of planned chemotherapy cycles

Investigator-assessed PFS by cell of origin*

Kaplan-Meier plot of investigator-assessed PFS by COO



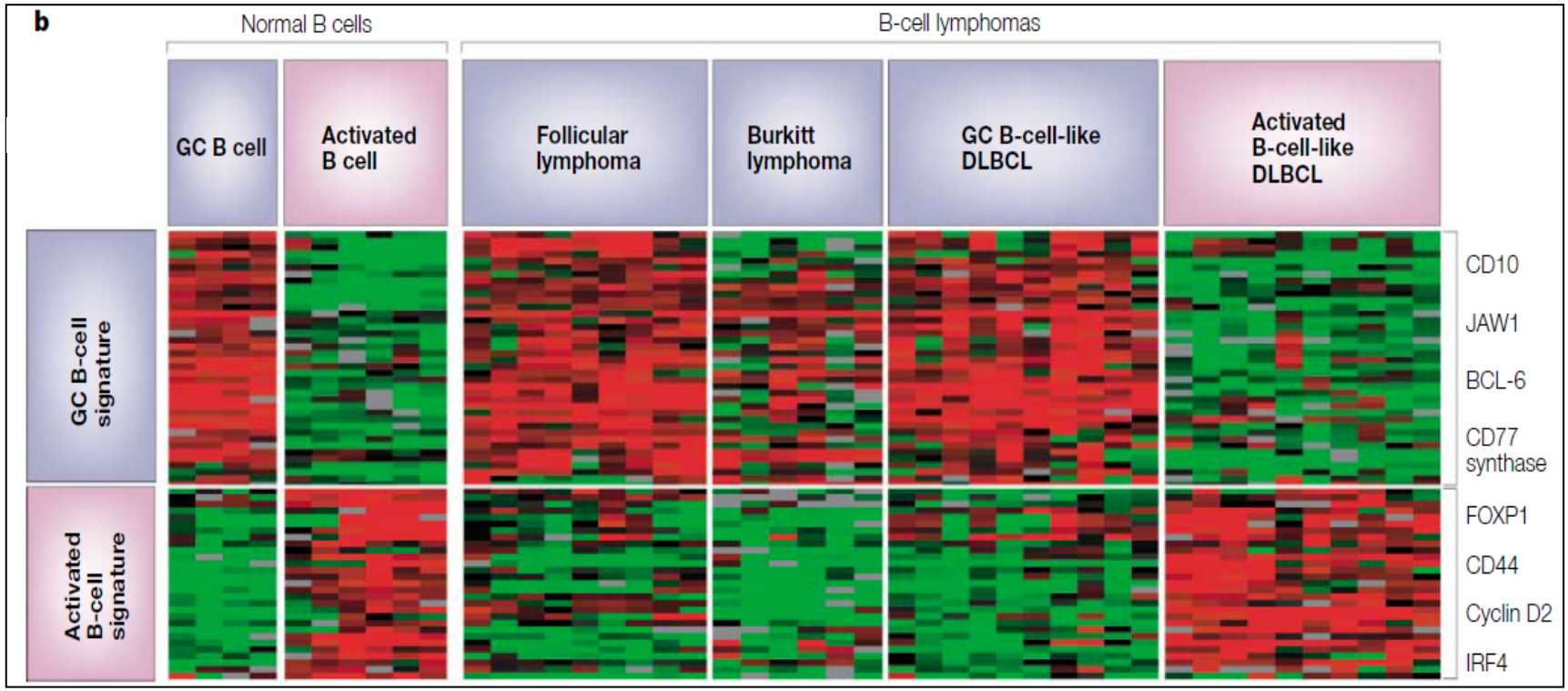
	ABC, n=243	*GCB, n=540*	*Unclassified, n=150*
Pts with event, n (%)	92 (37.9)	129 (23.9)	54 (36.0)
2-yr PFS, %	66.4	78.0	65.9
3-yr PFS, %	59.3	75.0	63.2

HR (95% CI)	
ABC vs GCB	1.70 (1.30, 2.23)
Unclassified vs GCB	1.57 (1.14, 2.16)

*Exploratory analysis; COO classification determined for 933 pts by gene expression profiling assay (Nanostring); missing COO classifications due to: restricted Chinese export license, n=252; CD20+ DLBCL not confirmed, n=102; missing/inadequate tissue, n=131; PFS HR=0.82 (0.64, 1.04) in pts with COO classification; PFS HR=1.18 (0.85, 1.64) in pts without COO classification

FL and GCB DLBCL patients share similar biology

FL and GCB DLBCL both arise from germinal centre B cells and share a similar gene expression profile



Schaffer et al, Nature Rev Immunol, 2002

Treatment with antiCD20 in B-cell lymphomas

Consolidated results

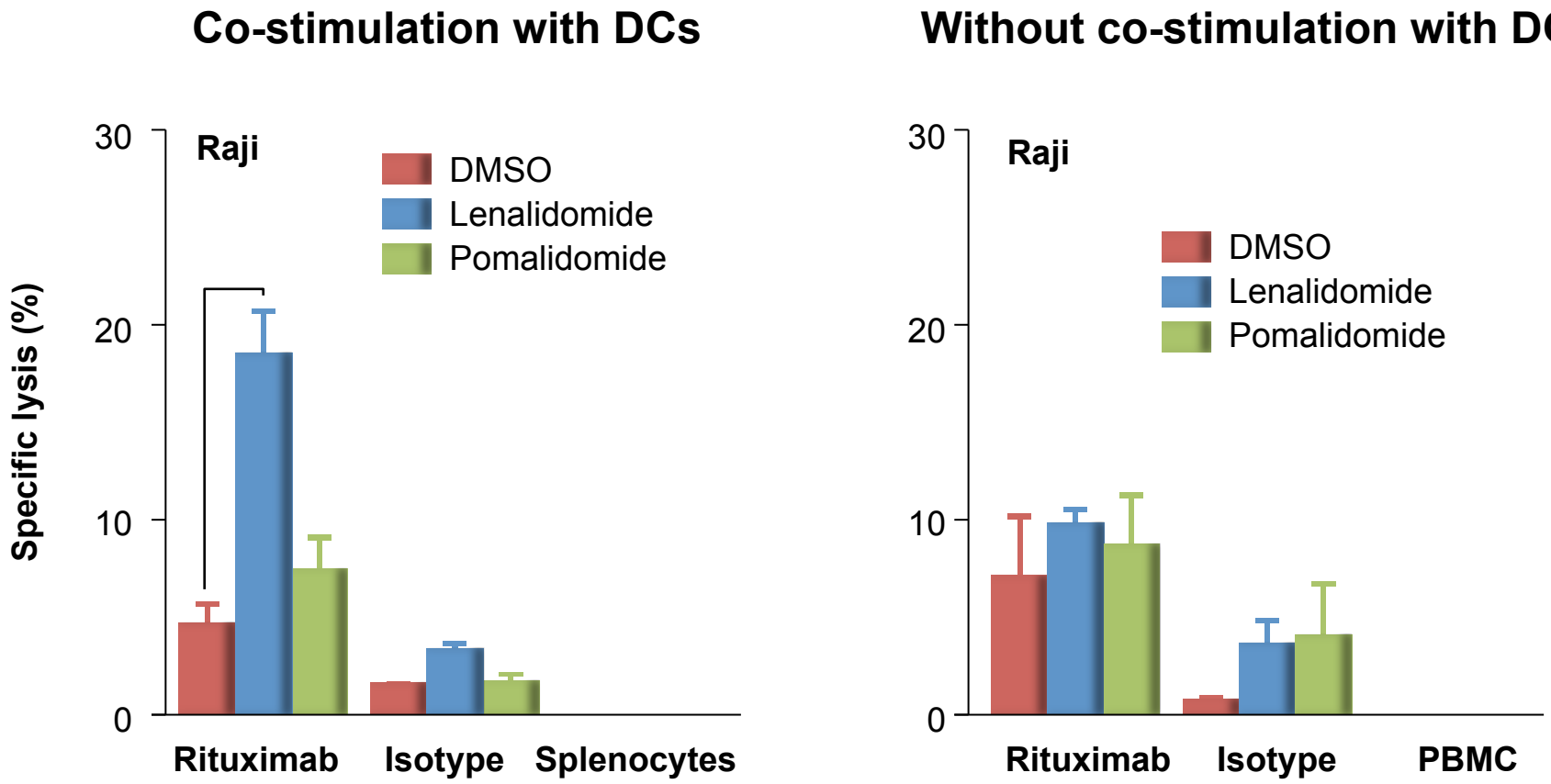
New antiCD20 antibodies

Association with IMIDs

New modality of administration of antiCD20 antibodies

Future development

IMiD enhancement of rituximab-dependent ADCC ex vivo is mediated via co-stimulation of NK-cells by DCs



Provides rationale for R2 regimen

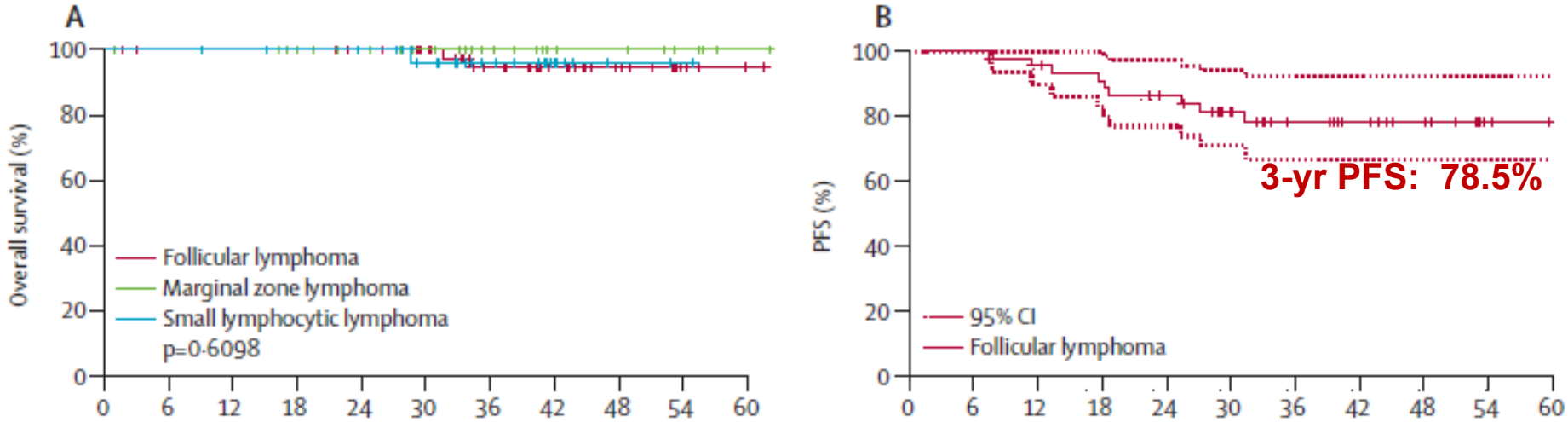
Data is represented by means with error bars showing mean ± 1.0 SE.

ADCC, antibody-dependent cellular cytotoxicity; DC, dendritic cell; DMSO, dimethyl sulfoxide; IMiD, immunomodulatory drug; NK, natural killer; PBMC, peripheral blood mononuclear cells; SE, standard error.

Reddy N, et al. Br J Haematol. 2007;140:36-45.

Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase 2 trial

110 pts (Jun 2008 – Aug 2011): 50 FL, 30 MZL and 30 SLL.



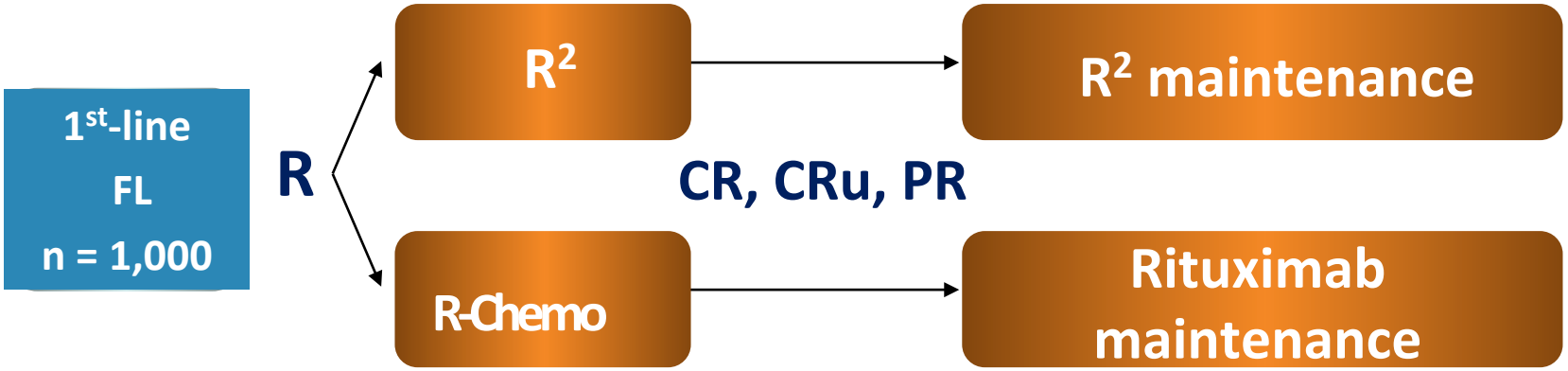
- 3-year OS: 96.1%
- Median PFS for Follicular Lymphoma pts not reached at 40.6 months
- **89% Bcl2+ pts at diagnosis achieved molecular remission after 6 cycles**

- Most common grade 3-4 haematological toxicity was neutropenia: 35% of pts
- Most common grade 3-4 non-haematological toxicities were: muscle pain (9%), rash (8%), dyspnoea or pulmonary symptoms (5%), fatigue (5%), thrombosis (5%)

Fowler NH, et al: Lancet Oncol 2014

RELEVANCE trial: Rituximab and Lenalidomide vs any chemotherapy

International, phase 3, multi-centre, randomized study
(Frank Morchhauser, Nathan Fowler)



- **R-Chemo** according to investigator choice of **R-CHOP, R-CVP, R-B**
- **R + Lenalidomide 20 mg x 6 cycles; if CR then 10 mg; if PR 20 mg x further 3-6 cycles and then 10 mg for up to 18 cycles**
- Co-primary end-points
  - surrogate end-point: CR/CRu rate at 1.5 years
  - PFS

NCT01476787. Available from: http://clinicaltrials.gov.

Phase 2 Studies of R2-CHOP in Front-line DLBCL

MAYO CLINIC

Agent	Dose	Route	Day of Cycle
Lenalidomide	25 mg	po	1-10
Rituximab	375 mg/ m^2	IV	1
Cyclophosphamide	750 mg/ m^2	IV	1
Doxorubicin	50 mg/ m^2	IV	1
Vincristine	1.4 mg/ m^2	IV	1
Prednisone	100 mg/ m^2	po	1-5
Pegfilgrastim	*6 mg*	*SC*	*2*
Aspirin	*325 mg*	*po*	*daily*

FONDAZIONE FIL ITALIANA LINFOMI

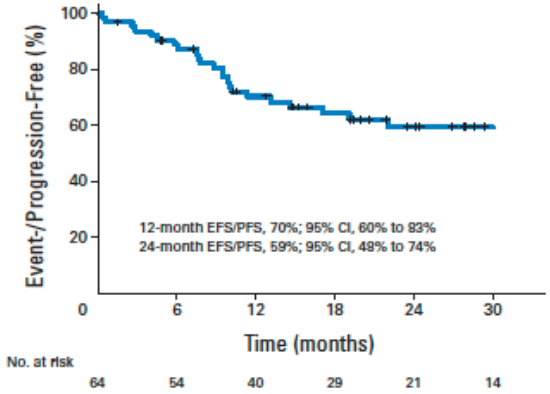
Agent	Dose	Route	Day of Cycle
Lenalidomide	15 mg	po	1-14
Rituximab	375 mg/ m^2	IV	1
Cyclophosphamide	750 mg/ m^2	IV	1
Doxorubicin	50 mg/ m^2	IV	1
Vincristine	1.4 mg/ m^2	IV	1
Prednisone	40 mg/ m^2	po	1-5
Pegfilgrastim	-	-	-
LMWH prophylaxis		*SC*	*daily*

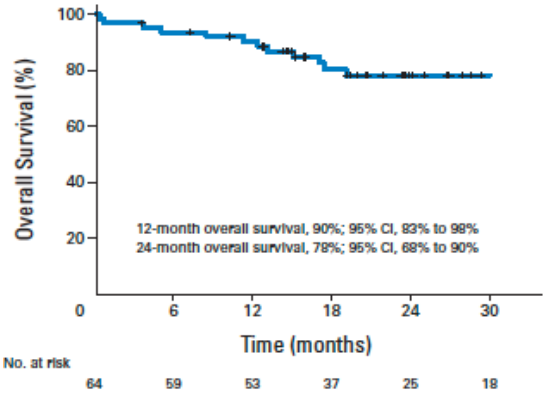
Nowakowski, et al. *J Clin Oncol*. 2015;33:251-257.
Vitolo, et al. *Lancet Oncol*. 2014;15:730-737.

Phase 2 Studies of R2-CHOP in Front-line DLBCL

MAYO CLINIC

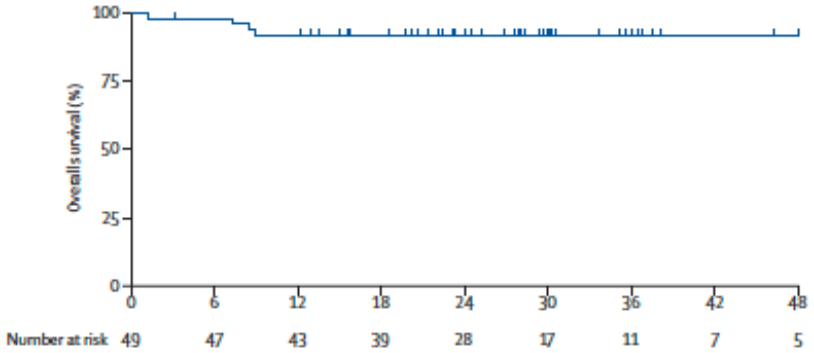
N=60
ORR 98%
CR 80%

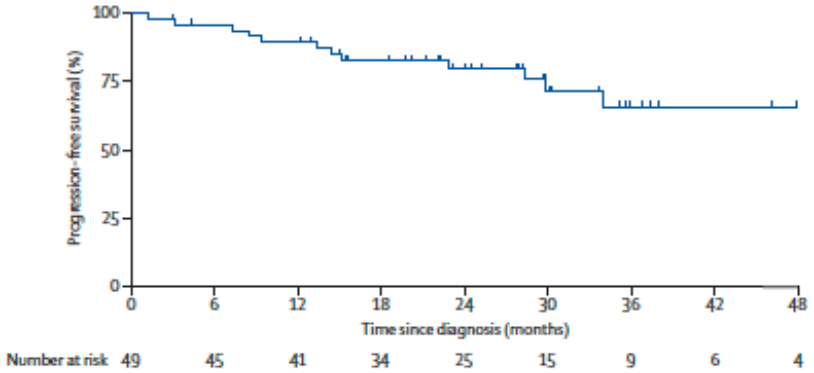




FONDAZIONE FIL ITALIANA LINFOMI

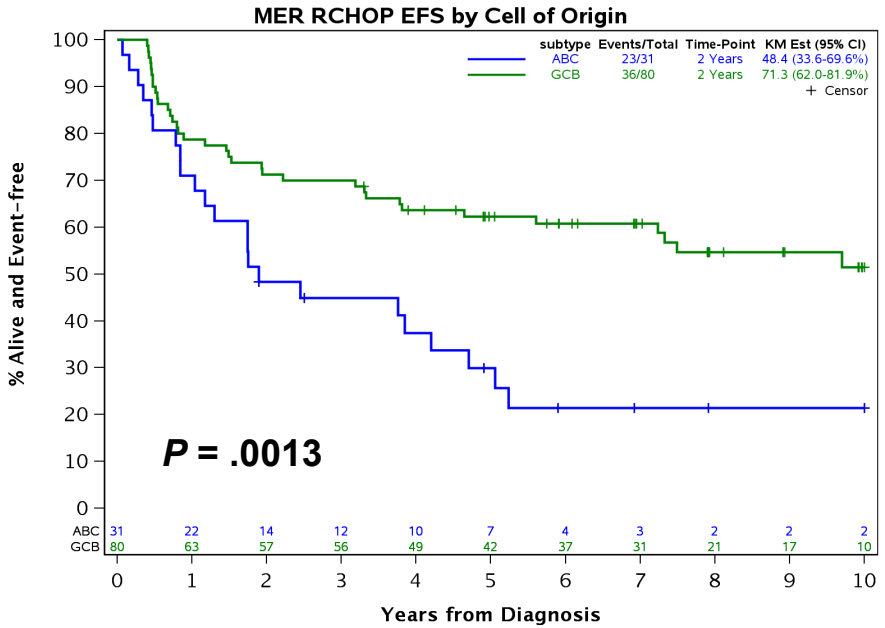
N=49
ORR 92%
CR 86%

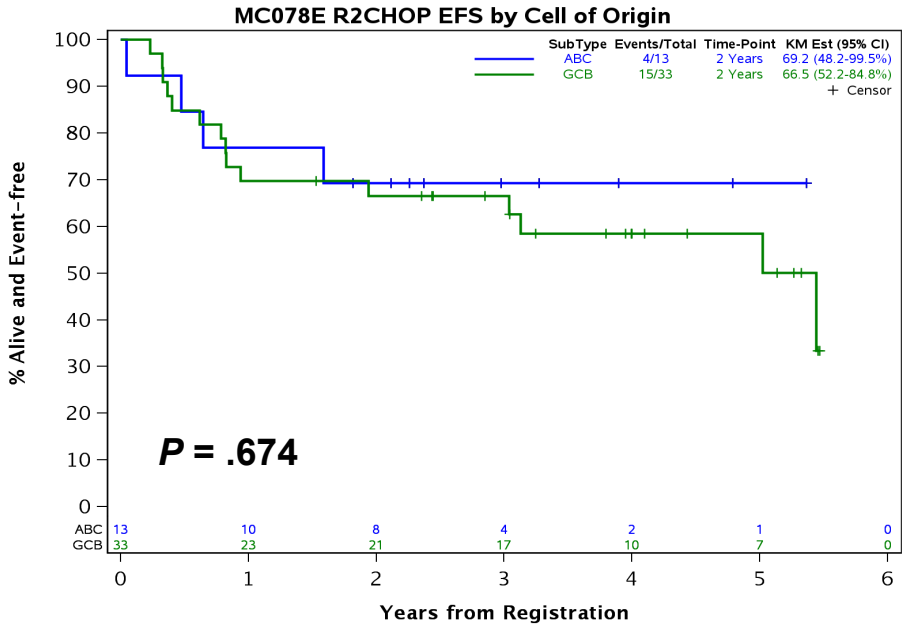




Nowakowski, et al. *J Clin Oncol*. 2015;33:251-257.
Vitolo, et al. *Lancet Oncol*. 2014;15:730-737.

Phase 2 Study of R2-CHOP in Newly Diagnosed DLBCL by COO by Nanostring Assay: EFS



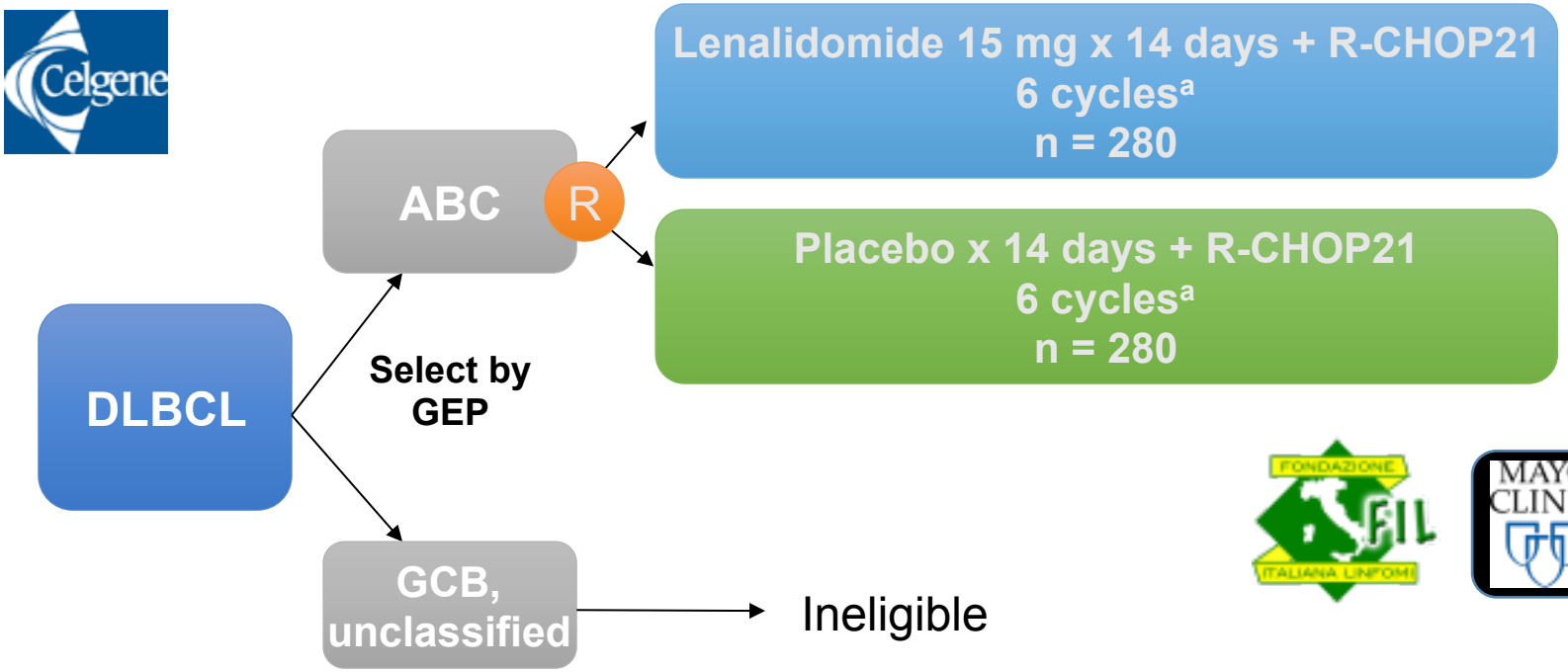


Cohort	N	GCB		ABC		Unclassified	
		n (%)	EFS24	n (%)	EFS24	n (%)	EFS24
MER R-CHOP	124	80 (65%)	71%*	31 (25%)	48%	13 (10%)	46%
MC078E R^2-CHOP	50	33 (66%)	67%#	13 (26%)	69%	4 (8%)	50%

Nowakowski et al. ASH 2016. Abstract 3035.

DLC-002 (ROBUST) study design: COO categorization made on nanostring

Sponsor: Celgene Corporation. Team leader: FIL and Mayo Clinic.
PIs: U. Vitolo, T. Witzig.
Writing committee: U. Vitolo, A. Chiappella, M. Spina, T. Witzig, G. Nowakowski.



- Newly diagnosed ABC DLBCL; IPI ≥ 2; ECOG PS ≤ 2; age 18–80 years
- Primary endpoint = PFS; N = 560
- 90% power to detect 60% difference in PFS (control median PFS estimate = 24 months)
- 208 sites expected to be involved

[a]Option for 2 additional rituximab doses after completing treatment regimen (if considered standard of care per local practice). ABC, activated B-cell like; COO, cell of origin ; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal centre B-cell like; GEP, gene expression profile; IPI, International Prognostic Index; PFS, progression-free survival; PI, principle investigator; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone.

NCT02285062.

Treatment with antiCD20 in B-cell lymphomas

Consolidated results

New antiCD20 antibodies

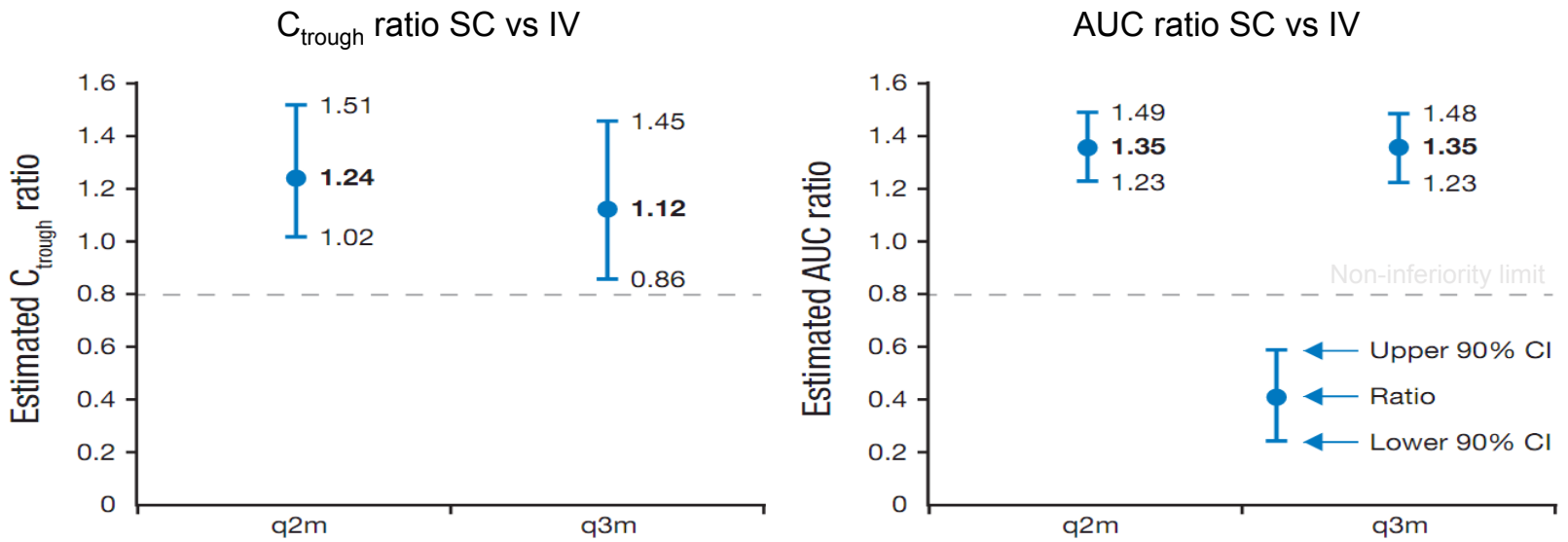
Association with IMIDs

New modality of administration of antiCD20 antibodies

Future development

SparkThera - 1,400 mg fixed dose of Rituximab SC is predicted to be non-inferior to the IV dose of 375 mg/m2

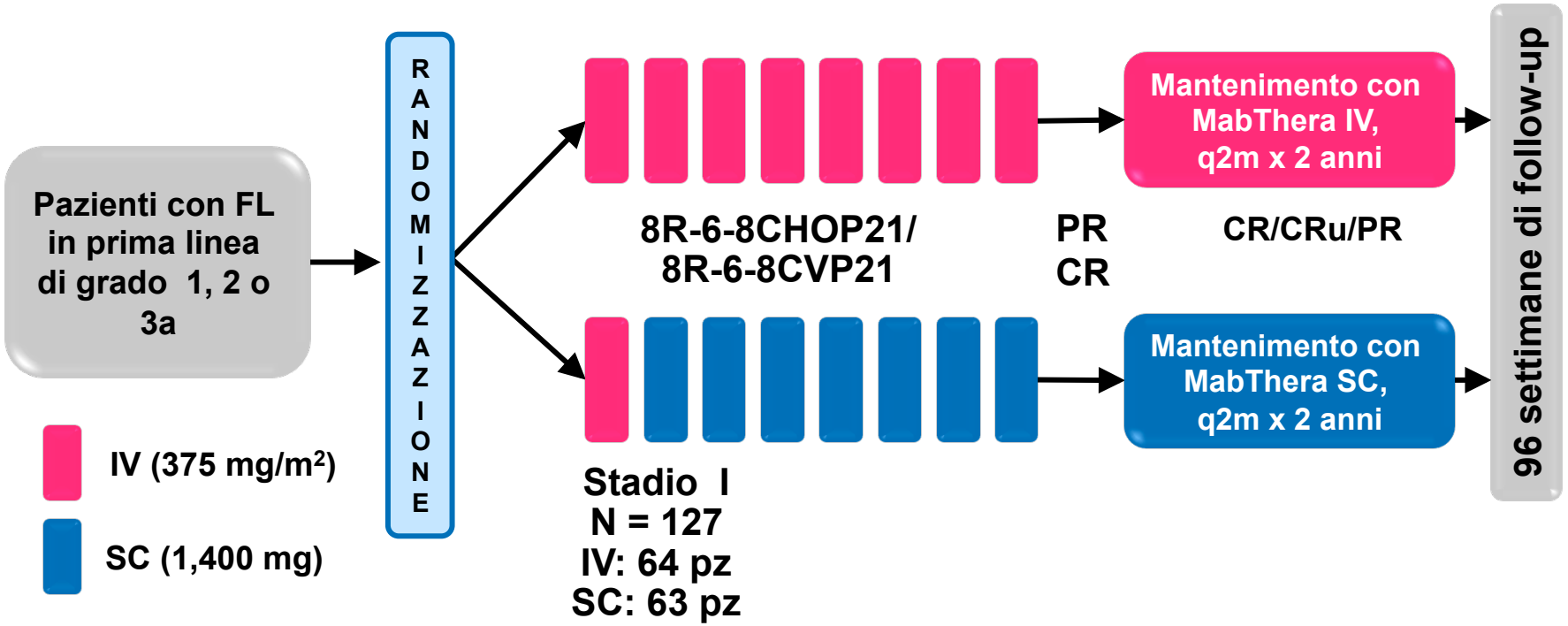
SparkThera: stage 2 PK endpoint primario– Ctrough



- L'endpoint primario di PK (SC:IV C_{trough} ratio) è stato raggiunto : il limite inferiore del' 90% CIs è al di sopra del margine di ***non inferiorità predefinito di 0.8*** per la schedula ***ogni 2 mesi (1.02) e ogni 3 mesi (0.86)***
- Rituximab SC alla dose di 1400 mg è risultato non inferiore a rituximab alla dose di 375 mg/m^2 somministrato per via endovenosa

Salar A et al. J Clin JCO.2013

SABRINA: Conferma della dose e dell'efficacia di rituximab SC nell'induzione e mantenimento nel FL

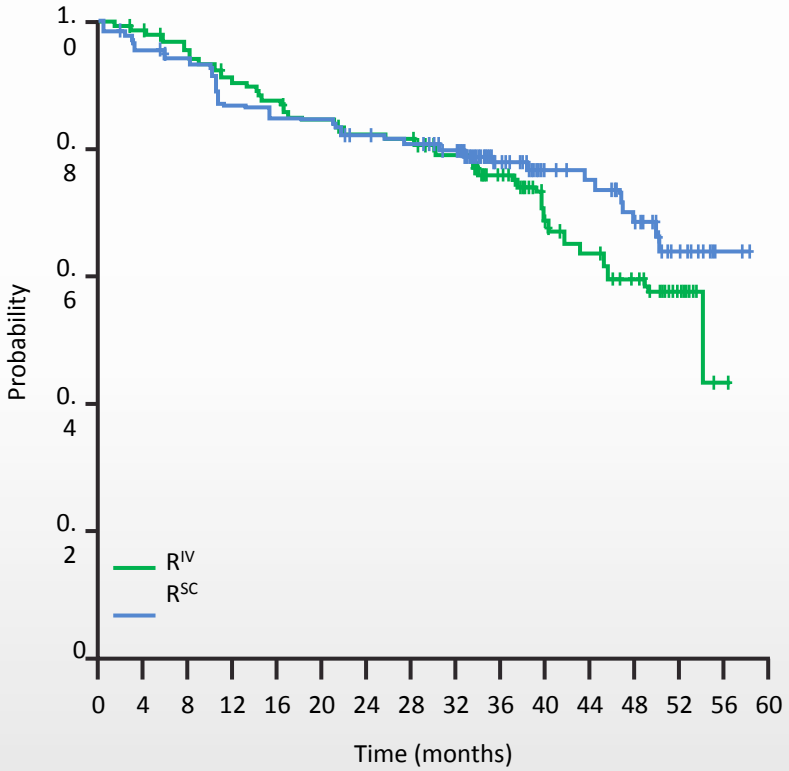


Endpoint primario: PK Ctrough $_{SC:IV}$ ratio maggiore di 0.8, $AUC_{SC:IV}$ ratio > 0.8

Enpoint secondario: efficacia (ORR, CR,Cru, PR) alla fine dell'induzione

Davies A, thelancetoncology, vol15march2014

SABRINA: progression-free survival (ITT)



Patients at risk, n

Rituximab IV	205	196	186	176	171	162	157	156	138	73	41	35	29	14	2	0
Rituximab SC	205	188	183	169	166	164	158	154	139	81	51	48	40	23	2	0

	R^{IV} (n=205)	R^{SC} (n=205)
Patients with event, n (%)	57 (27.8)	50 (24.4)
HR (95% CI), p-value*	0.84 (0.57, 1.23), p=0.3696	

Median follow-up: 37 months

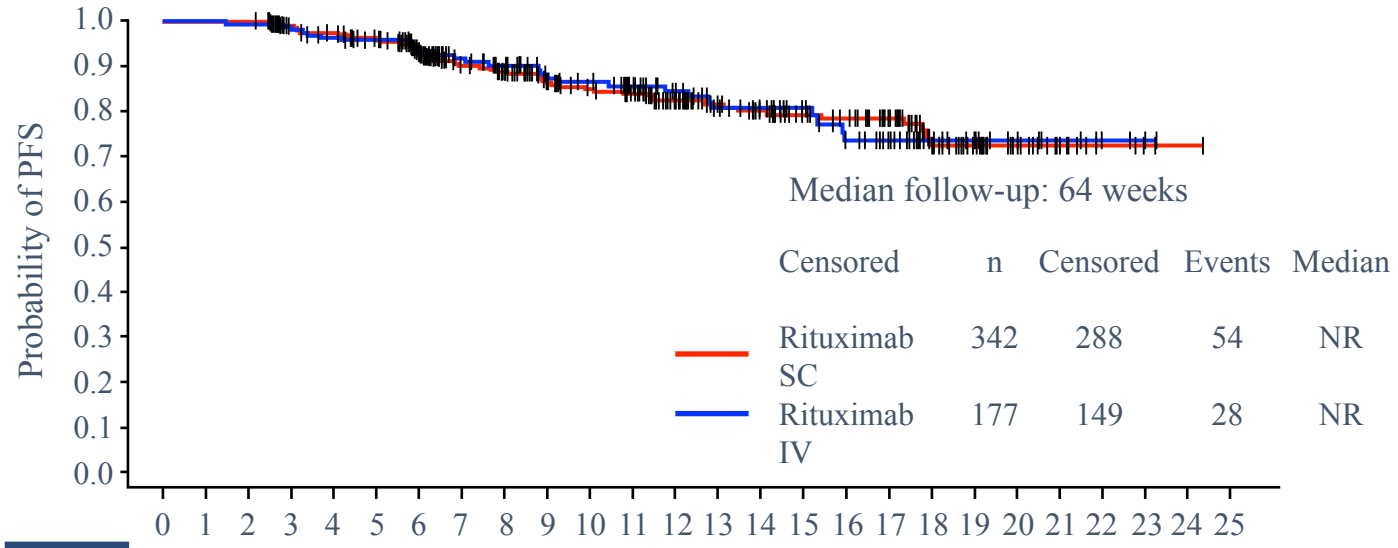
Davies, ASH 2016

SABRINA: safety overview

n (%)	R^{IV} (n=210*)	R^{SC} (n=197*)
Any AE	199 (95)	189 (96)
Grade ≥3 AEs	116 (55)	111 (56)
SAEs	72 (34)	73 (37)
Deaths	22 (10)	14 (7)
AEs leading to death	12 (6)	7 (4)
Deaths due to disease progression	7 (3)	6 (3)
Deaths due to unknown cause	2 (<1)	1 (<1)

Davies, ASH 2016

MabEase: comparative, randomised (2:1), multicentre, open-label, phase IIIb study in previously untreated DLBCL R-CHOP 21/14 with R sc vs iv



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

PFS was comparable between treatment arms

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

Analisi di impatto dei benefici tecnico-organizzativi di una formulazione sottocute nel percorso paziente con linfoma

***Il progetto ha coinvolto 17 centri di Ematologia ed i risultati hanno dimostrato che l'uso di MabThera SC può ridurre*:**

Risultati nell'uso di MabThera SC

Impegno complessivo tempo del paziente	**-59%**
Impegno del personale infermieristico nella gestione del paziente	**-54%**
Impegno del personale per allestimento farmaco	**-54%**
Scarti farmaco	**-94%**

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

Treatment with antiCD20 in B-cell lymphomas

Consolidated results

New antiCD20 antibodies

Association with IMIDs

New modality of administration of antiCD20 antibodies

Future development

Conclusions

- ✓ CD20 is still the best target for monoclonal antibodies in the treatment of B-cell lymphoma
- ✓ Rituximab has changed the outcome of FL and DLBCL
- ✓ Obinutuzumab is the first glycoengeenered antiCD20 antibody with a different mode of action than Rituximab
- ✓ Obinutuzumab has shown a greater clinical activity in FL and CLL
- ✓ Rituximab can be safely combined with Lenalidomide as chemotherapy free regimen in FL or with RCHOP backbone with preliminary good results
- ✓ Rituximab sub cute provides a more friendly mode of administration alllowing to save time for the patient, nurses, pharmacists and overall organization
- ✓ Future developments of antiCD20 include possibly bispecific antibodies allowing to restore T-cell cytotoxic activity against lymphoma cells.