Passive Immunotherapy: Targeting tumor cells

CD20 in Lymphoma and Chronic Lymphocytic Leukemia: Groundwork and outlook

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Disclosures – Umberto Vitolo

Research Support/P.I.	Roche, Celgene
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Conferences/ Educational Activities	Janssen, Roche, Celgene, Takeda, Gilead
Scientific Advisory Board	Janssen, Roche, Celgene

Treatment with antiCD20 in B-cell lymphomas and CLL

Consolidated results

New antiCD20 antibodies

Association with IMIDs

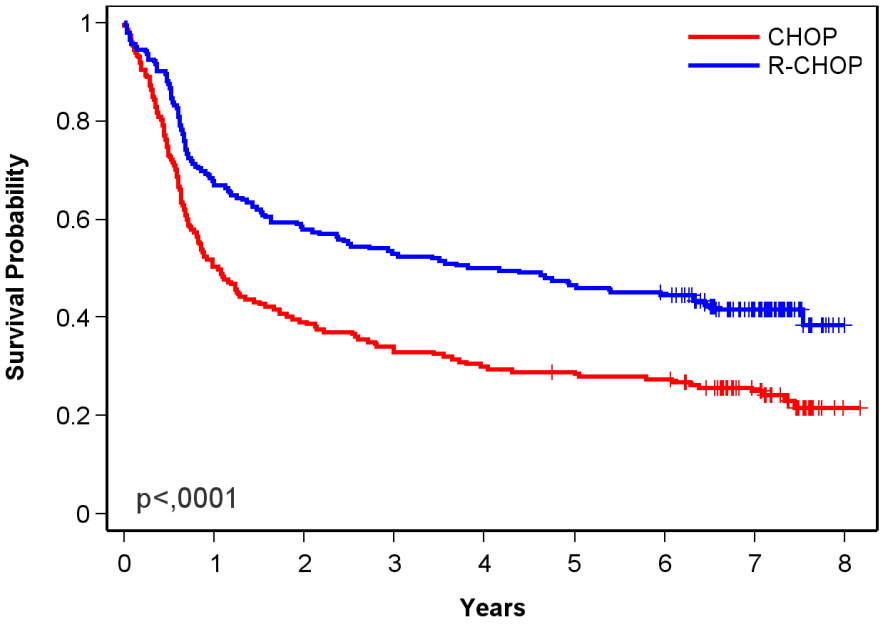
Future development

Long-term results of the GELA study

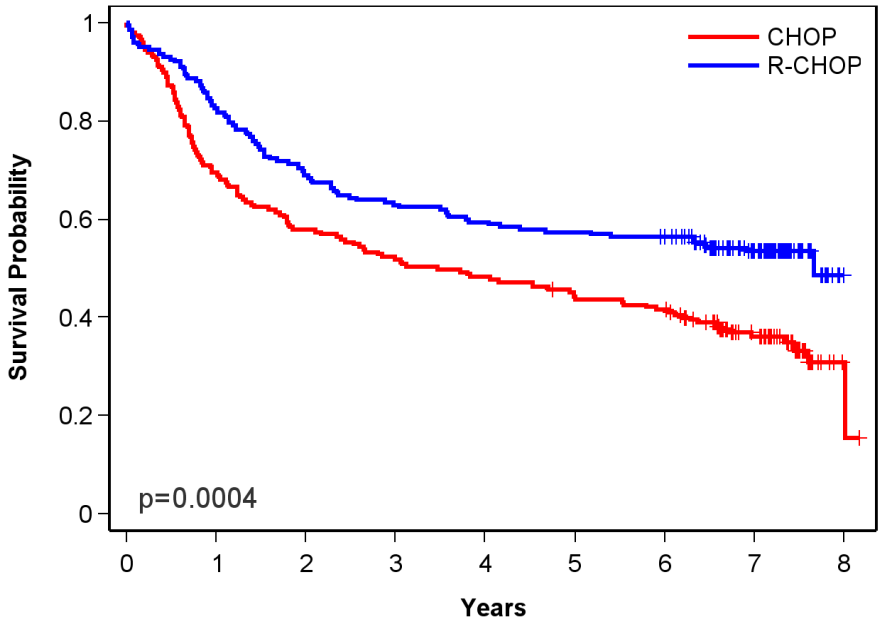
LNH-98.5 study

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

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

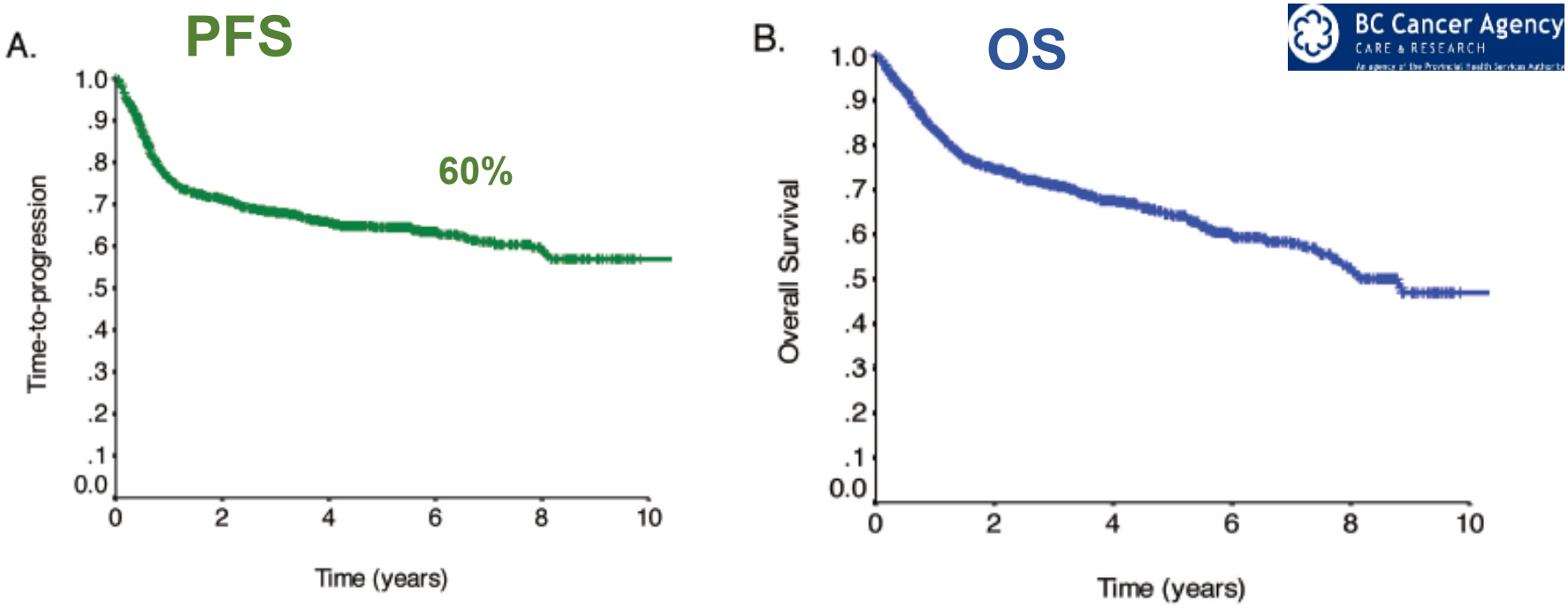


OS – Median follow-up 7 y
>50% vs. 35%



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

R-chemotherapy first-line induction

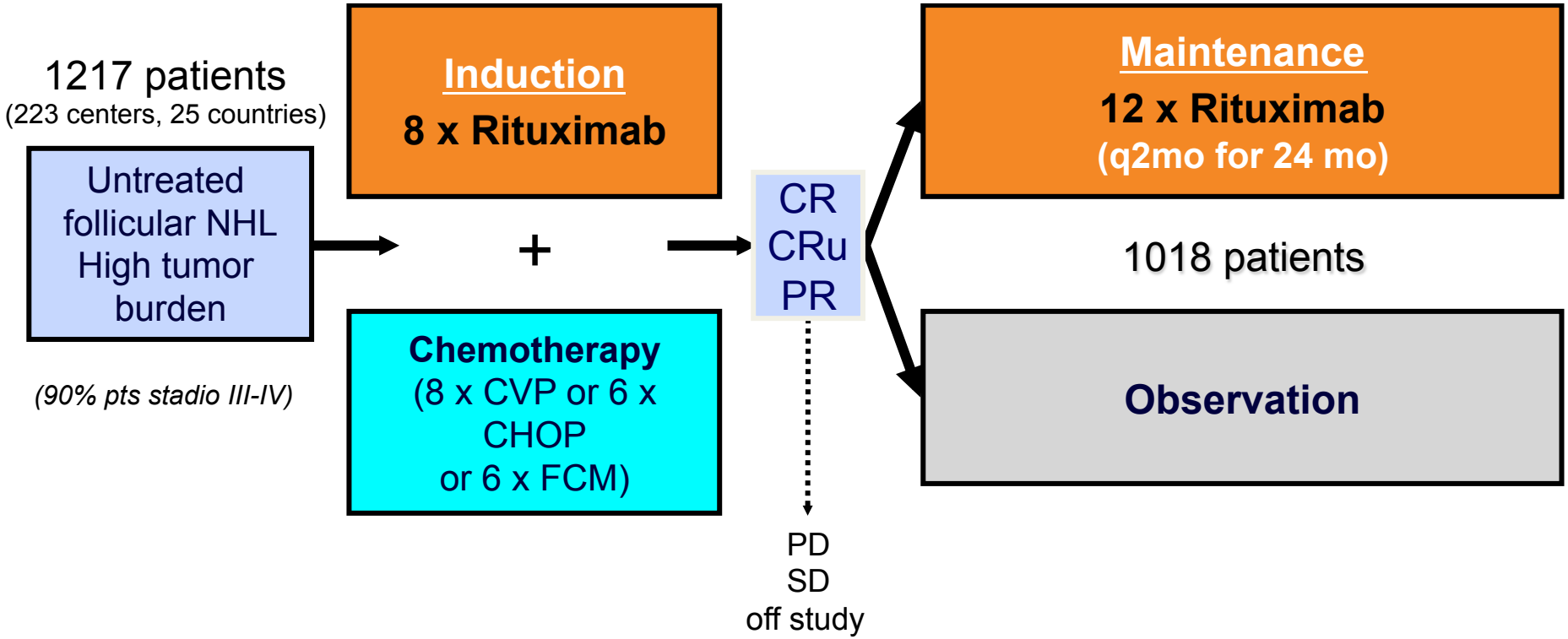
- Addition of Rituximab to chemotherapy improves treatment response (both overall and complete responses)
- Addition of Rituximab to chemotherapy prolongs PFS
- Addition of Rituximab to chemotherapy allows better survival and better control of the disease

Study	Regimen	FU	ORR (%)	CR (%)	Overall survival (%)		*p*-value
					Control	Rituximab	
Marcus R *Blood 2005*	CVP vs R-CVP	4 yrs	57 vs 81	10 vs 41	77	83	0.029
Hiddemann W *Blood 2005*	CHOP vs R-CHOP	5 yrs	90 vs 96	17 vs 20	84	90	0.0493
Herold M *JCO 2007*	MCP vs R-MCP	4 yrs	75 vs 92	25 vs 49	74	86	0.0205
Salles G *Blood 2008*	CHVP/IFN vs R-CHVP/IFN	5 yrs	86 vs 94	44 vs 73	79	84	0.025 (high-risk pts)

Shulz H, et al: Cochrane Database Syst Rev, 2007
Sacchi S, et al: Cancer, 2007

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)

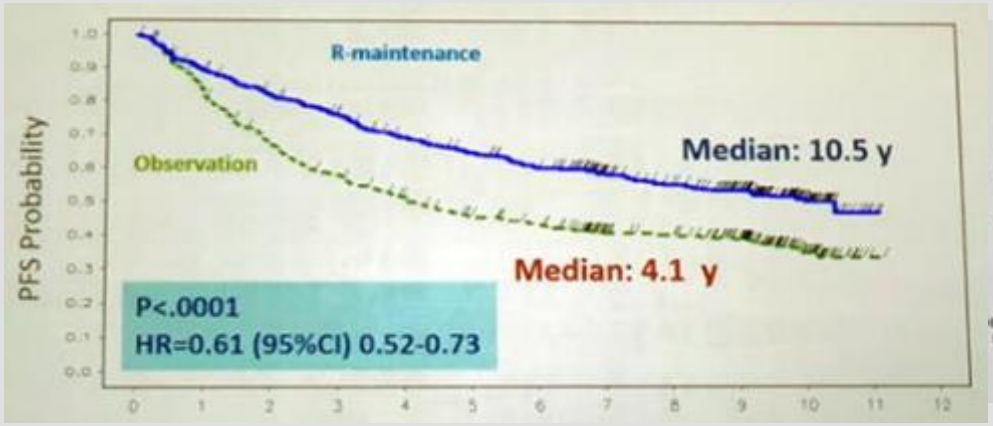
Salles GA, et al. Lancet 2011;377:42-51.

Long Term Follow-up of the PRIMA Study: Half of Patients Receiving Rituximab Maintenance Remain Progression Free at 10 Years

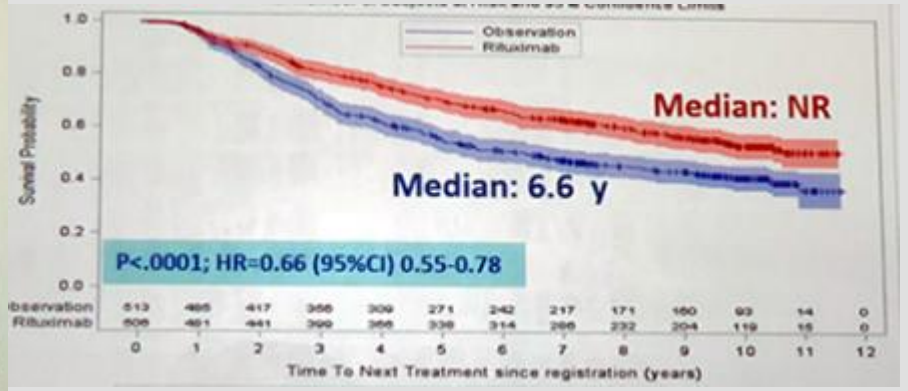
ASH

Median follow-up 9 years

Median PFS



Median TTNT

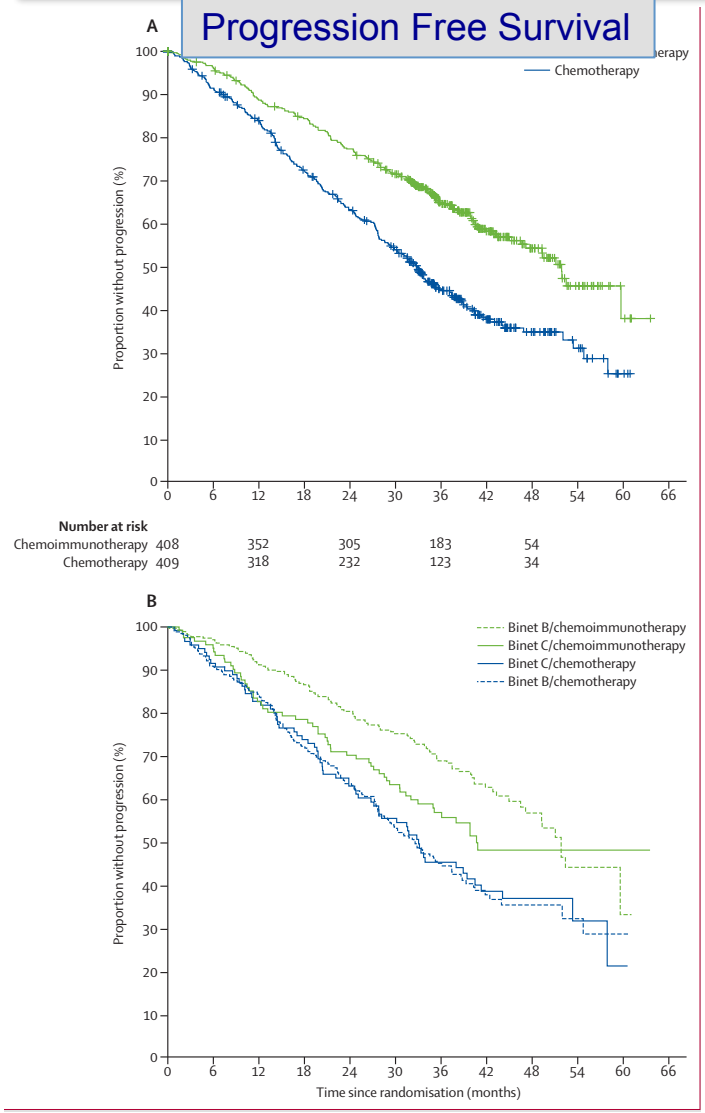


- 51% of pts in R-maintenance arm (vs 35%) free of disease progression
- Benefit of R-maintenance was significant in all patient strata
- Median TTNT not reached in Rituximab maintenance arm with 53% pts not having received a new treatment (vs 41%)
- No new safety signals were indentified with additional 4 years of FU
- OS was identical (80%) in each arm
- **Obtaining truly durable response with 1st line induction and R-maintenance remains an appealing treatment strategy for FL pts**

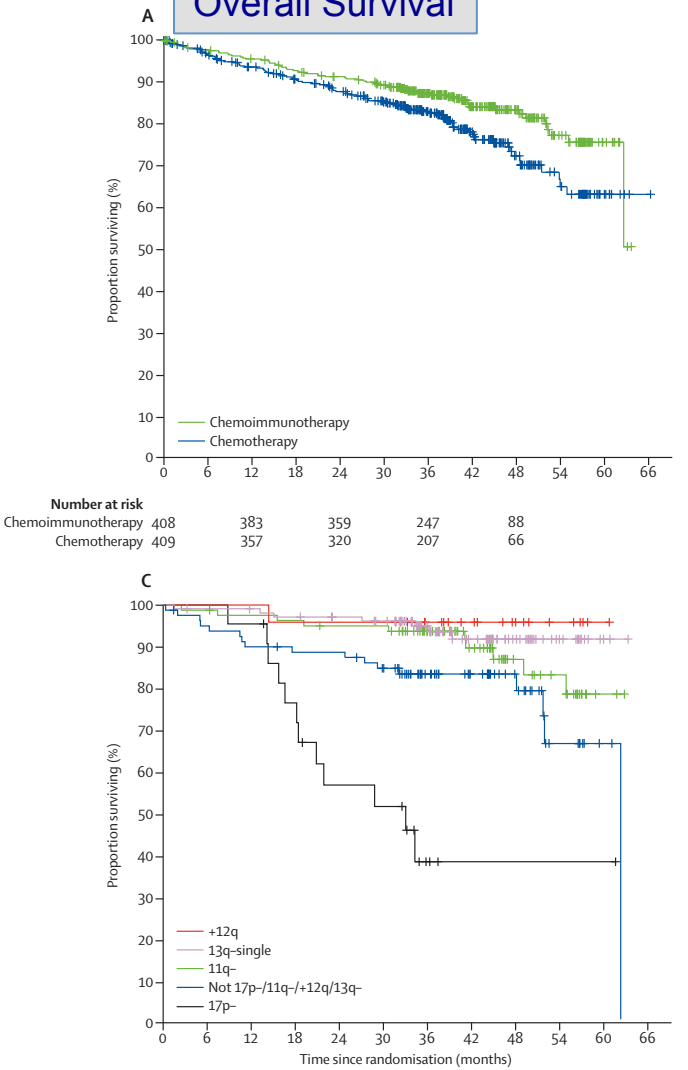
Salles G, et al; Blood 2017 (abs)

Addition of Rituximab to Fludarabine and Cyclophosphamide in patients with chronic lymphoytic leukemia: a randomized open-label phase III trial

Progression Free Survival



Overall Survival



Hallek M et al. Lancet 2010; 376;1164–1174.

Treatment with antiCD20 in B-cell lymphomas and CLL

Consolidated results

New antiCD20 antibodies

Association with IMIDs

Future development

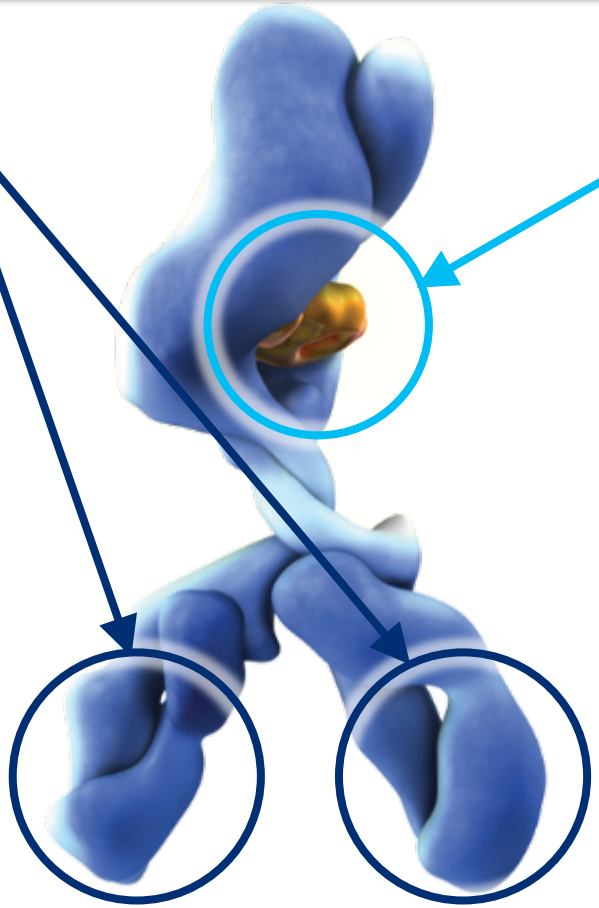
Novel Anti-CD20 MoAbs for Relapsed/ Refractory Indolent NHL

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]



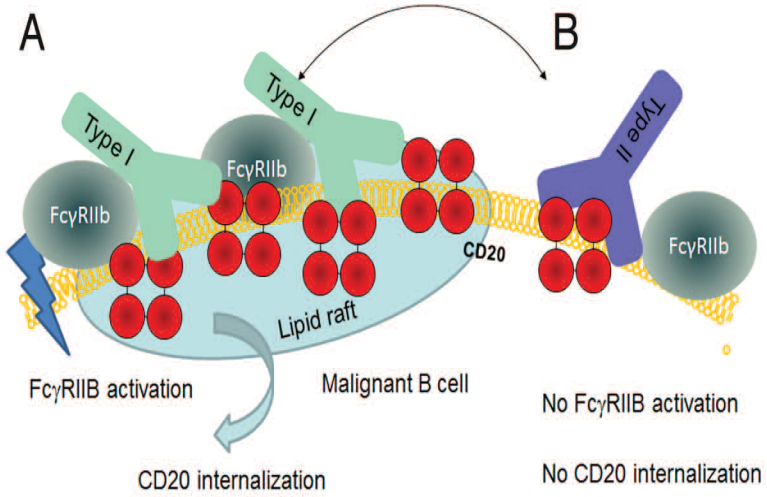
Glycoengineered Fc region[2]

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.

Hypothetical model for CD20 binding of Type I and Type II CD20 antibodies explaining the impact of FcγRIIb on internalization



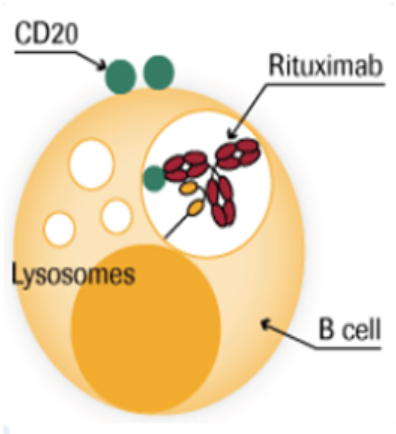
A) Type I antibodies such as Rituximab may bind to CD20 in a conformation that allows simultaneous binding to FcγRIIb and subsequent signaling followed by internalization in lipid rafts.

B) Type II antibodies such as GA101 may bind in a conformation that does not allow simultaneous binding to FcγRIIb, thus resulting in reduced internalization.

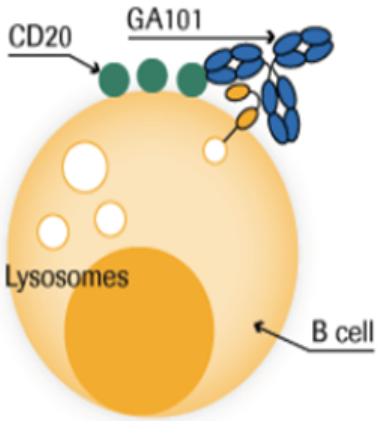
Klein C, et al. MAbs 2013; 5(1): 22-33.

CD20 internalisation

Rituximab (Type I)



GA101 (Type II)



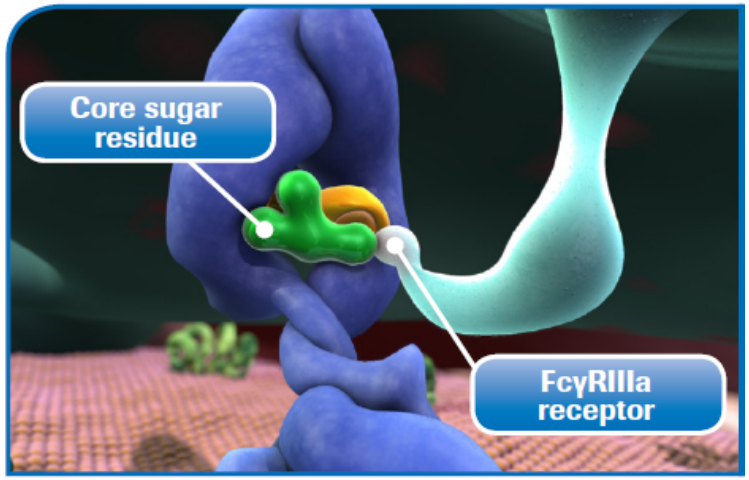
Type I-anti-CD20 mAbs could mediate the internalisation of CD20 into B Cells.

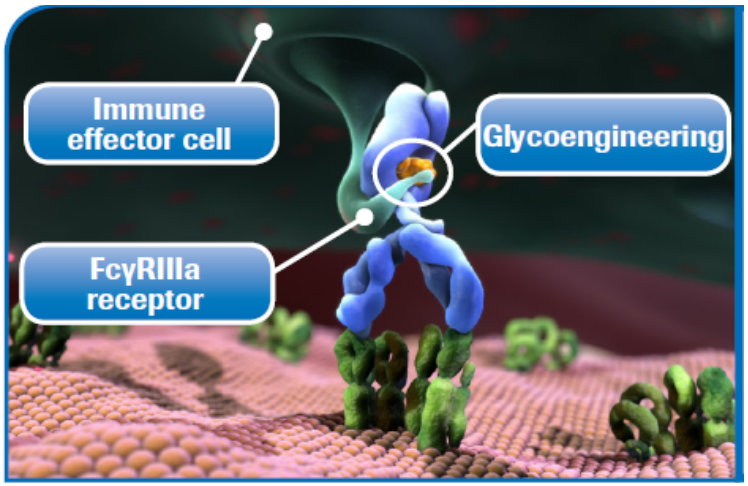
- **May lead to degradation of the mAb-CD20 complex.**
- **Occurred more rapidly in CLL and MCL cells than in FL and DLBCL cells.**
- **There may, therefore, be less CD20 molecules available on the B-cell surface to bind to mAb in MCL and CLL.**

Type II-anti-CD20 mAbs remain almost exclusively on the cell surface and do not internalise.

CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; FL, follicular lymphoma; DLBCL, diffuse large B cell lymphoam.
Graphical elaboration from text data, Beers SA, et al. Seminars Hematol 2010; 47(2):107-114; Beers SA, et al. Blood. 2010; 115(25): 5191-5201.

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



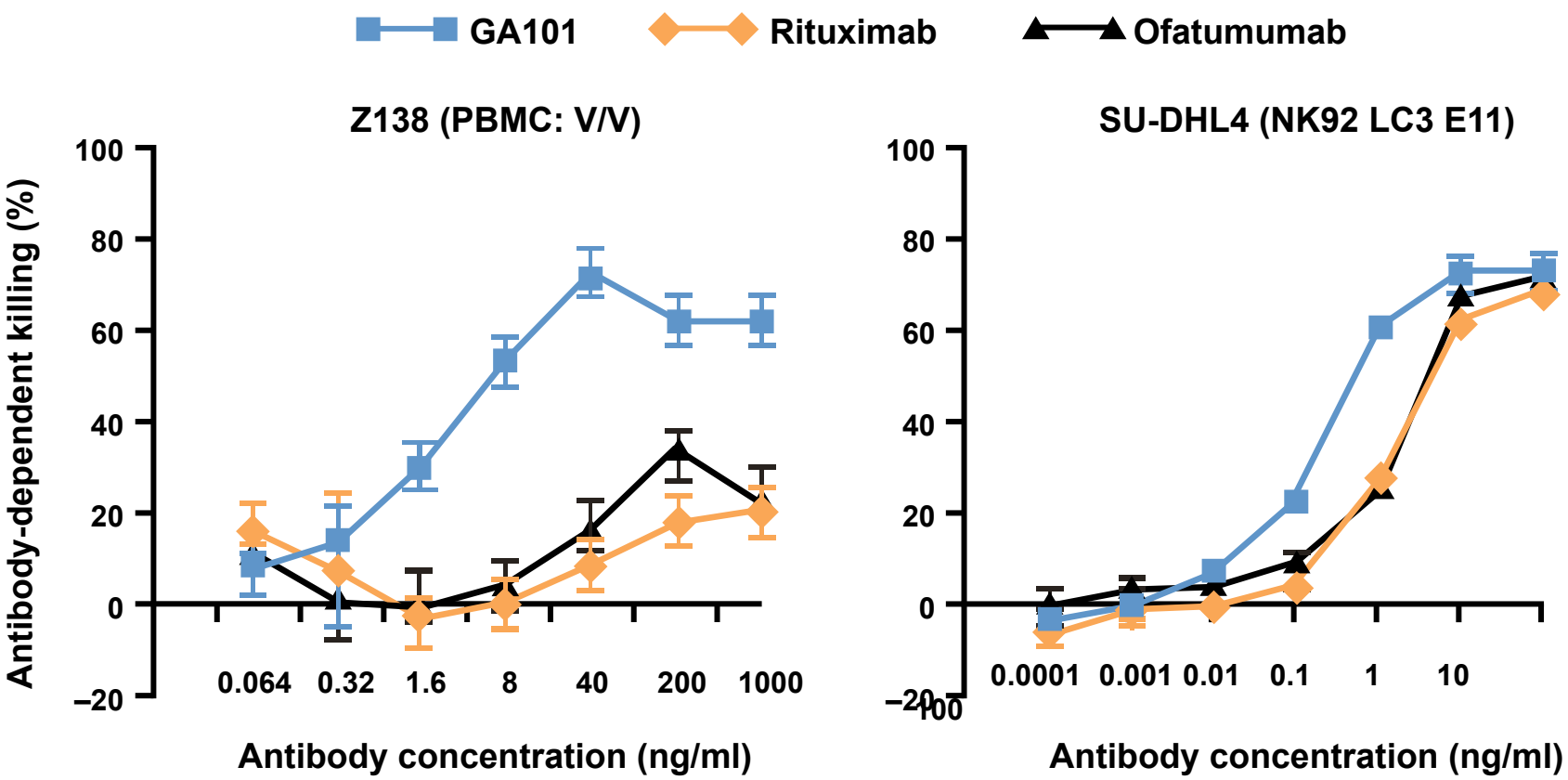


- The presence of certain sugar residues on the Fc region of an antibody may interfere with its ability to bind to immune effector cells[1,2]
- Removal of these sugars via glycoengineering may increase binding affinity between the Fc region of therapeutic antibodies and the Fc receptors on immune effector 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

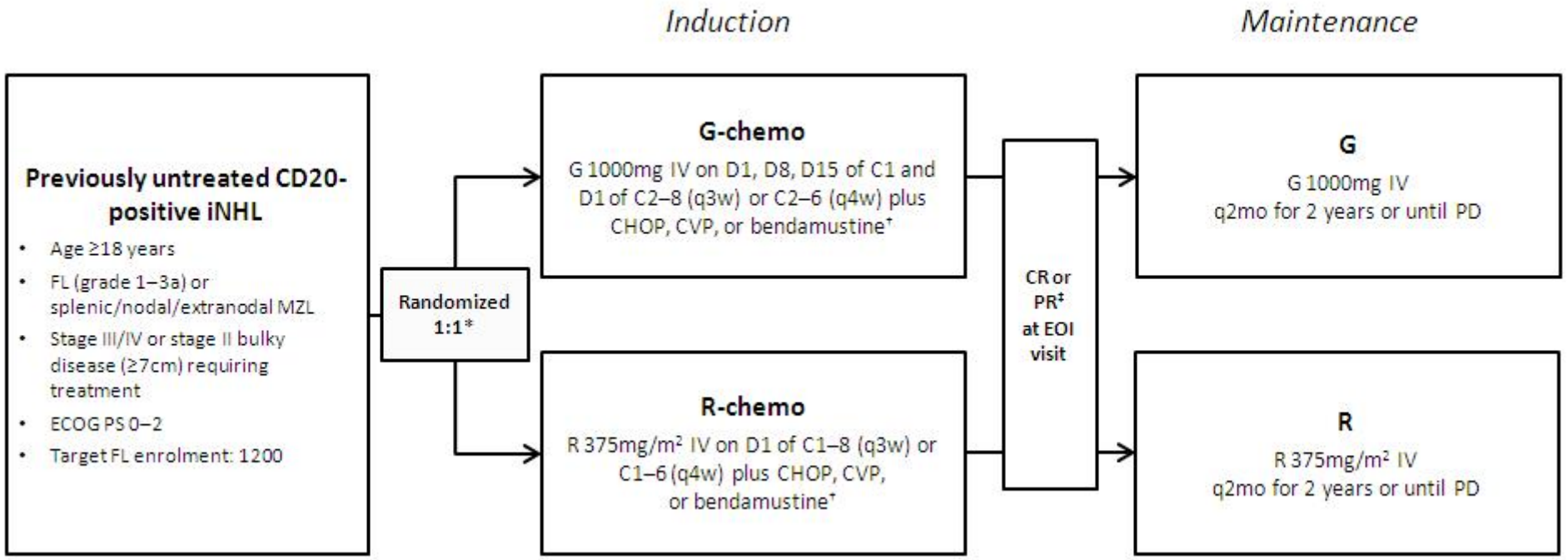
GA101-induced ADCC

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).

Obinutuzumab for the First-Line Treatment of Follicular Lymphoma

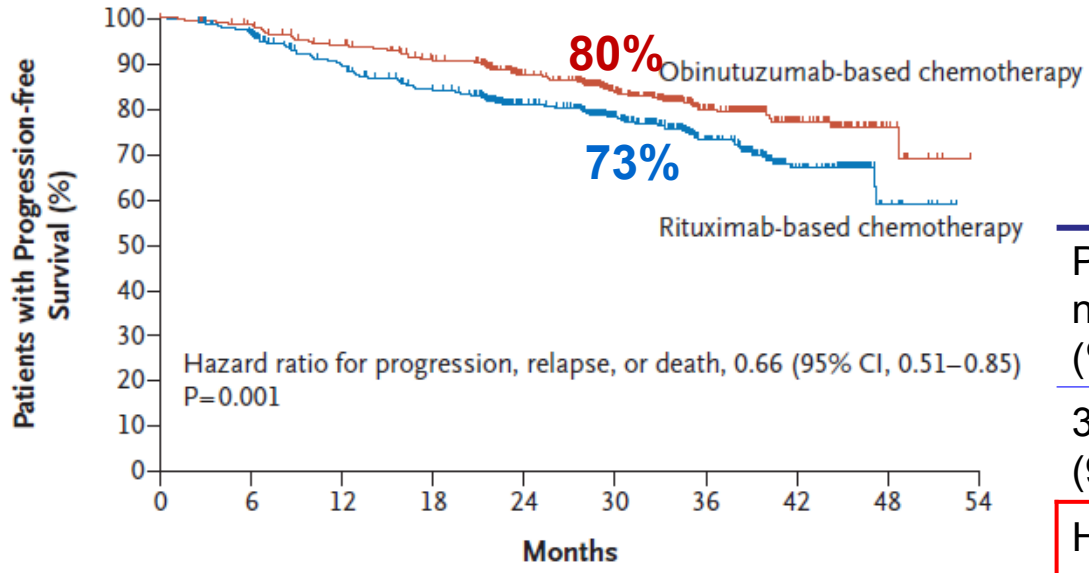


- **1202 enrolled pts**
- Median age 58-60 years (range 23-88)

Marcus R, et al; NEJM 2017

Obinutuzumab for the First-Line Treatment of Follicular Lymphoma

3-yrs PFS
Median FU 34.5 months



	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	

34% reduction in the risk of progression, relapse or death

Marcus R, et al; NEJM 2017

Obinutuzumab for the First-Line Treatment of Follicular Lymphoma

Event	Overall Trial†		Induction Phase		Maintenance and Observation Phases	
	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=548)	Rituximab Group (N=535)
No. of events	10,311	9343	7012	6533	3002	2578
Patients with ≥1 adverse event — no. (%)						
Any event	592 (99.5)	587 (98.3)	580 (97.5)	577 (96.6)	501 (91.4)	458 (85.6)
Event of grade 3 to 5	444 (74.6)	405 (67.8)	357 (60.0)	336 (56.3)	205 (37.4)	169 (31.6)
Event of grade 5‡	24 (4.0)	20 (3.4)§	4 (0.7)	3 (0.5)	10 (1.8)	10 (1.9)
Patients with ≥1 serious adverse event — no. (%)	274 (46.1)	238 (39.9)	166 (27.9)	144 (24.1)	134 (24.5)	110 (20.6)
Treatment-related adverse event — no. (%)						
Any event	564 (94.8)	547 (91.6)	—	—	—	—
Event leading to withdrawal of treatment	75 (12.6)	65 (10.9)	—	—	—	—
Event leading to any dose reduction	103 (17.3)	89 (14.9)	—	—	—	—
Serious adverse event leading to withdrawal of treatment — no. (%)	44 (7.4)	36 (6.0)	—	—	—	—
Serious adverse event leading to dose reduction — no. (%)	12 (2.0)	10 (1.7)	—	—	—	—

- **More pts in GA101-group had grade 3-5 AE or SAEs** but AEs that led to the discontinuation of treatment were similar in the 2 arms

Marcus R, et al; NEJM 2017

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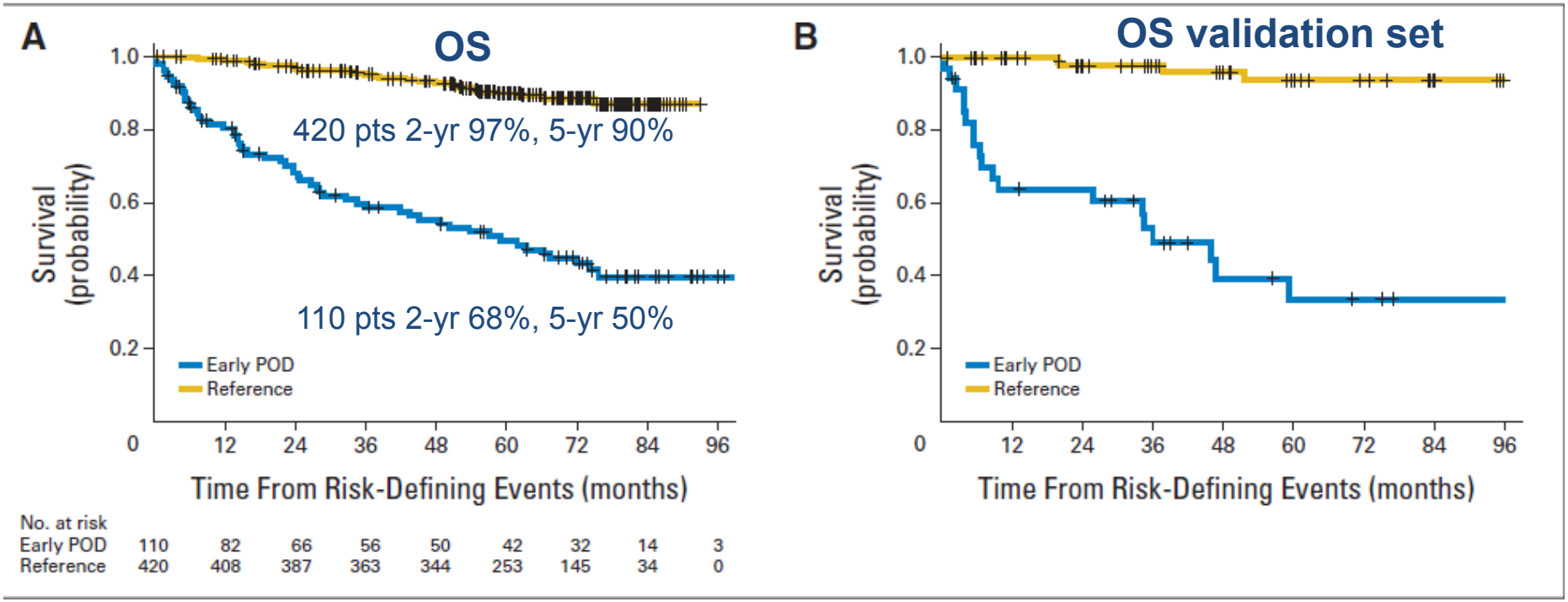
ORIGINAL REPORT

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

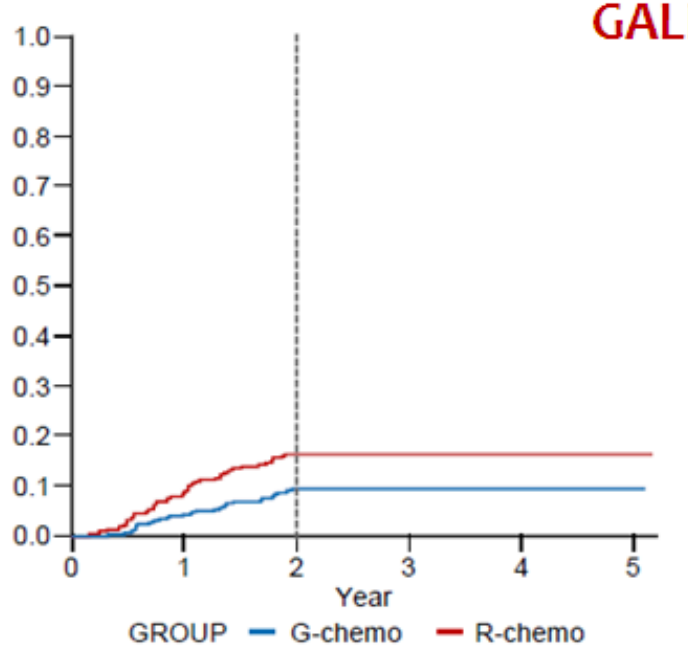


Casulo C et al, JCO 2015

Early Disease Progression Predicts Poorer Survival in Patients with Follicular Lymphoma (FL) in the GALLIUM Study

ASH

GALLIUM: POD24



	R-chemo, N=601	G-chemo, N=601	Risk reduction G-chemo vs R-chemo
POD24 events*, %	16.7	9.7	41.5%†
POD24 events, n	72	43	

- G-chemo was associated with a reduced relative risk of a POD24 event by 42% compared to R-chemo: **demonstration of the superiority of G-chemo over R-chemo**
- Post-progression survival for POD24 pts appeared to be similar in the 2 arms: **suggestion that post-progression survival is not compromised by 1st line G-chemo**

Launonen A, et al; ASH 2017

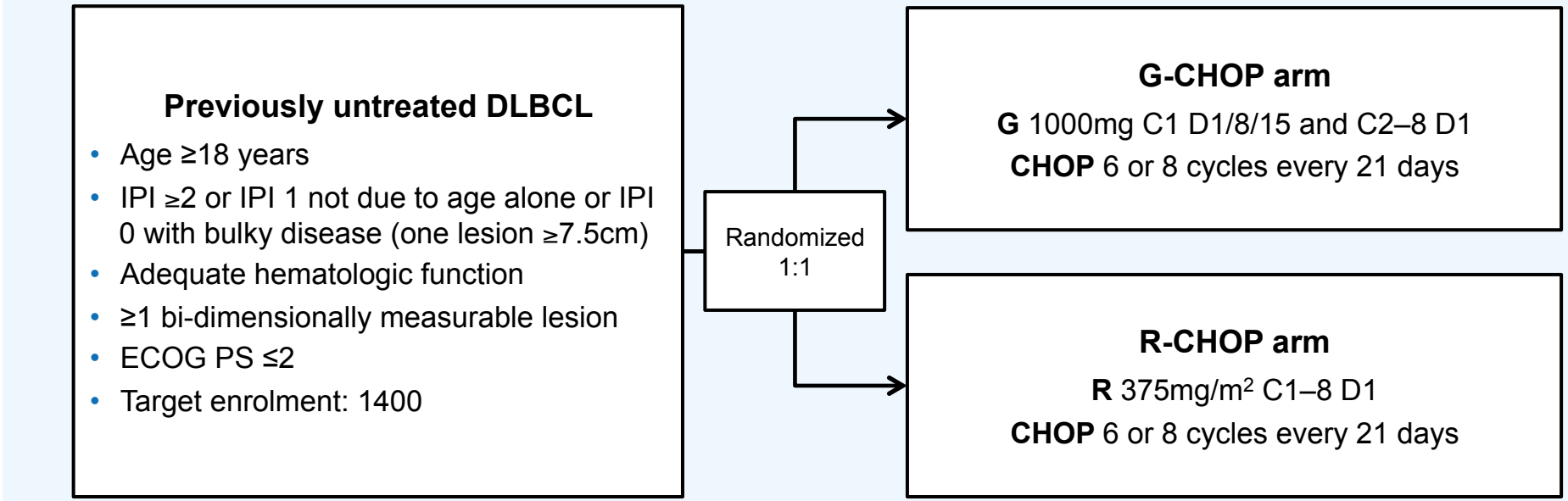
How to improve R-CHOP results in DLBCL

…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*

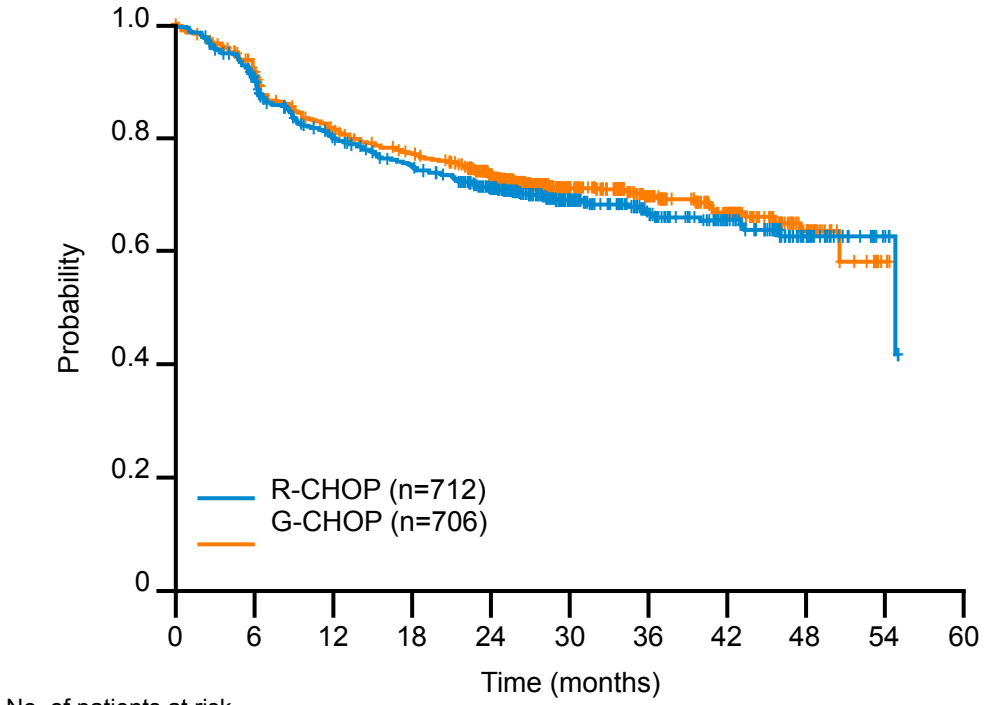


- Number of CHOP cycles pre-planned in advance for all pts at each site
- Randomization stratification factors: planned number of CHOP cycles, IPI, geographic region

Vitolo et al. ASH 2016. Abstract 470.

Investigator-assessed PFS (primary endpoint)

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



No. of patients at risk

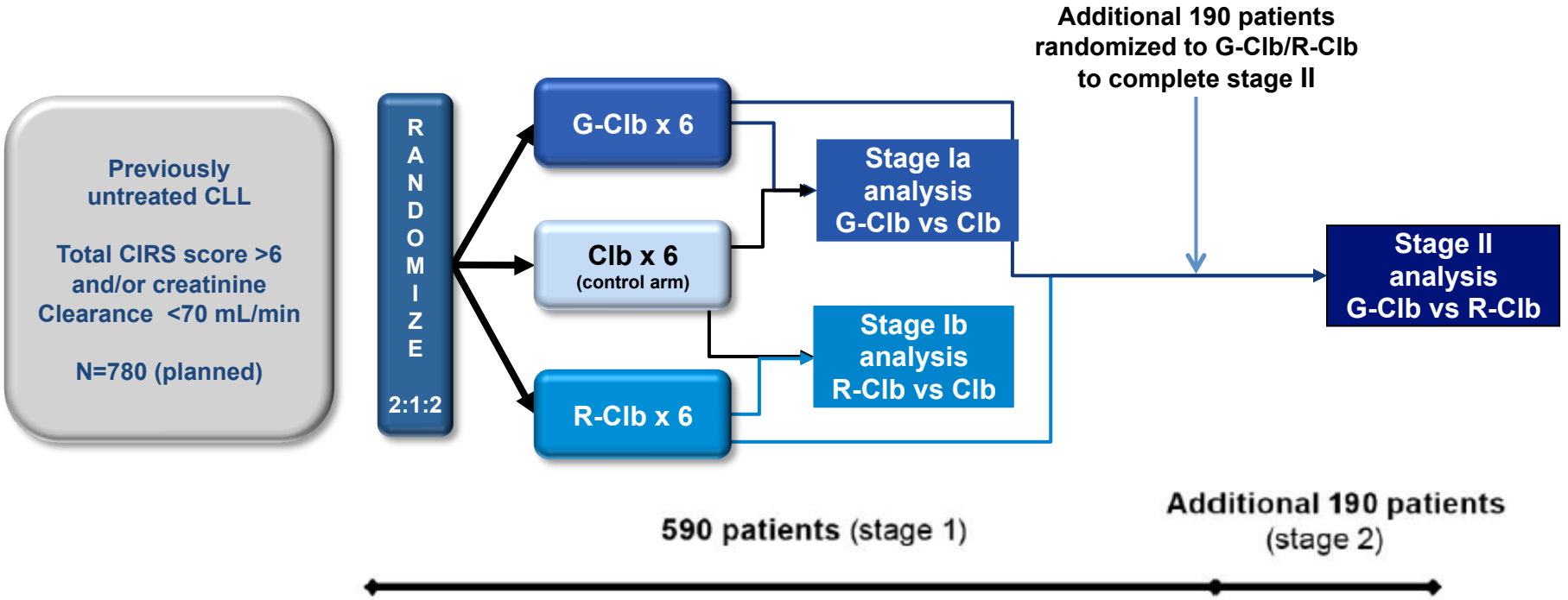
R-CHOP	712	616	527	488	413	227	142	96	41	6
G-CHOP	706	622	540	502	425	240	158	102	39	2

	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

CLL11: Obinutuzomab plus Chlorambucil in patients with CLL and coexisting conditions

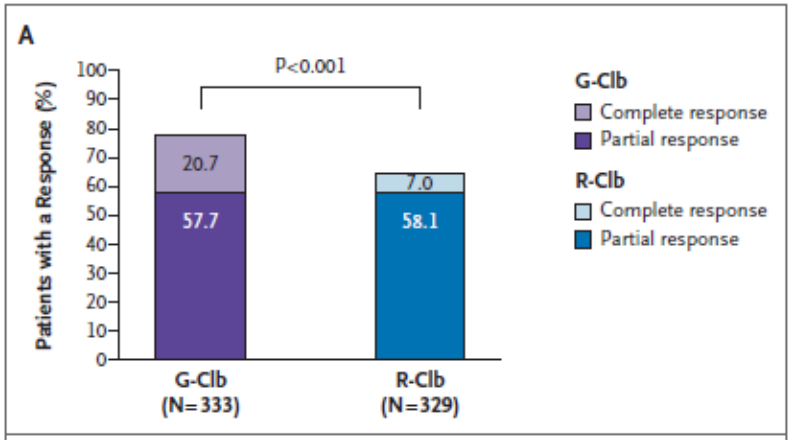


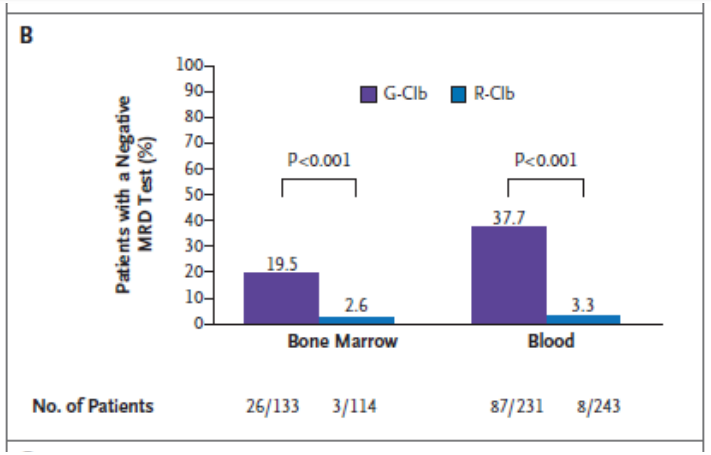
- **GA101: 1000 mg days 1, 8, and 15 cycle 1; day 1 cycles 2–6, every 28 days**
- **Rituximab: 375 mg/m2 day 1 cycle 1, 500 mg/m2 day 1 cycles 2–6, every 28 days**
- **Chlorambucil: 0.5 mg/kg day 1 and day 15 cycle 1–6, every 28 days**
- **Patients with progressive disease in the Clb arm were allowed to cross over to G-Clb**

Adapted from Supp. Material - Goede et al., N Engl J Med.* 2014 Jan 8

NCT01010061 - http://www.clinicaltrials.gov/ct2/show/NCT01010061?term=NCT01010061&rank=1, Last Access Jan 2014

CLL11 stage II : Response Rate and Progression free Survival





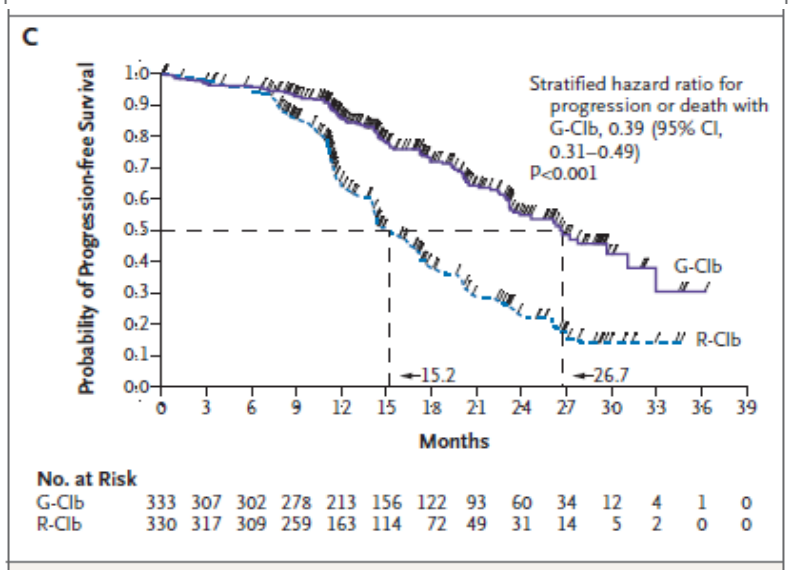
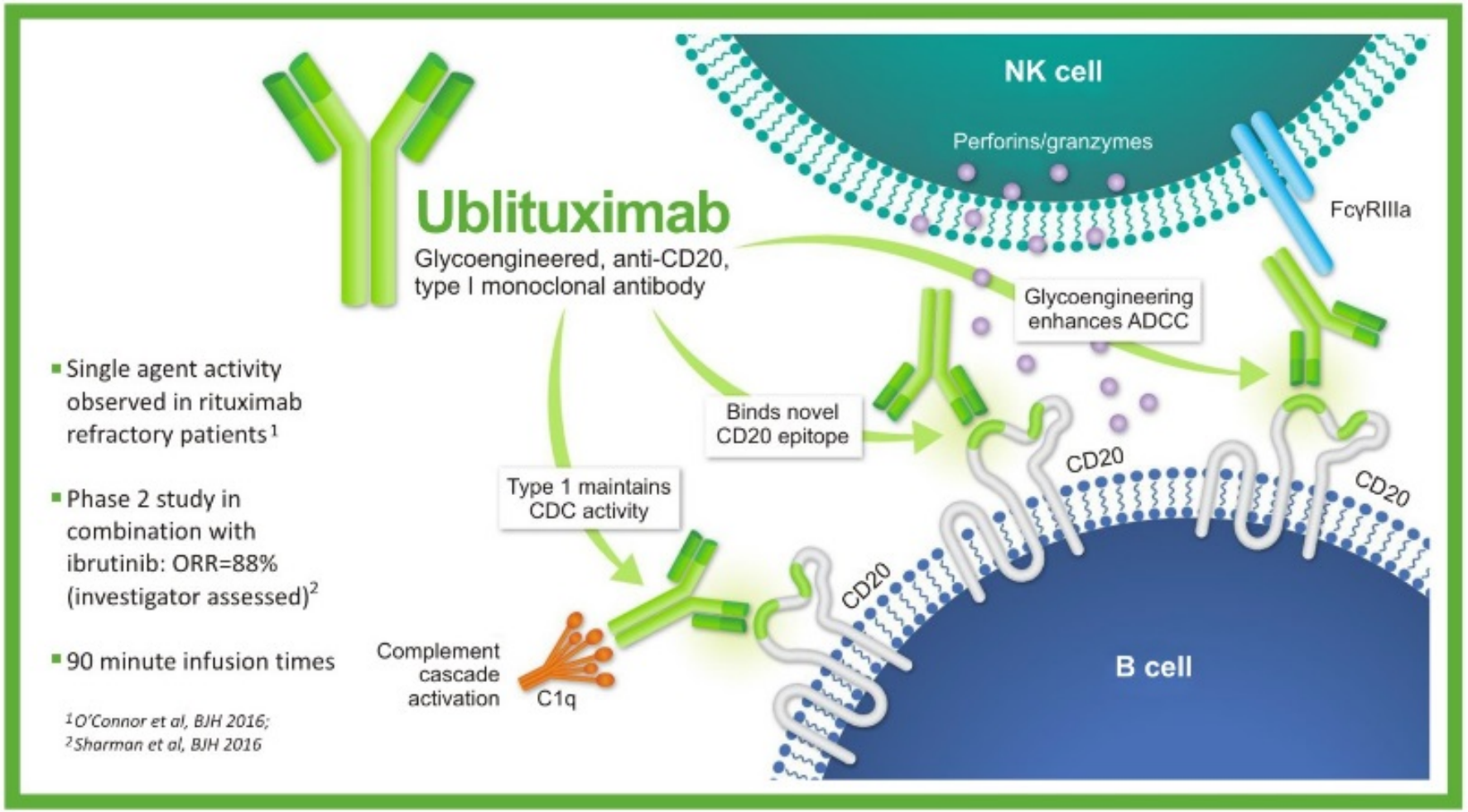


Figure 2. Response Rates and Progression-free Survival with Obinutuzumab–Chlorambucil versus Rituximab–Chlorambucil.

Panel A shows response rates at 3 months after the end of treatment. Complete response included complete response with incomplete bone marrow recovery; partial response included nodular partial response. Panel B shows molecular response rates; MRD denotes minimal residual disease. Panel C shows progression-free survival, as assessed by the site investigators. P values were calculated with the use of a stratified log-rank test. G-Clb denotes obinutuzumab–chlorambucil, and R-Clb rituximab–chlorambucil.

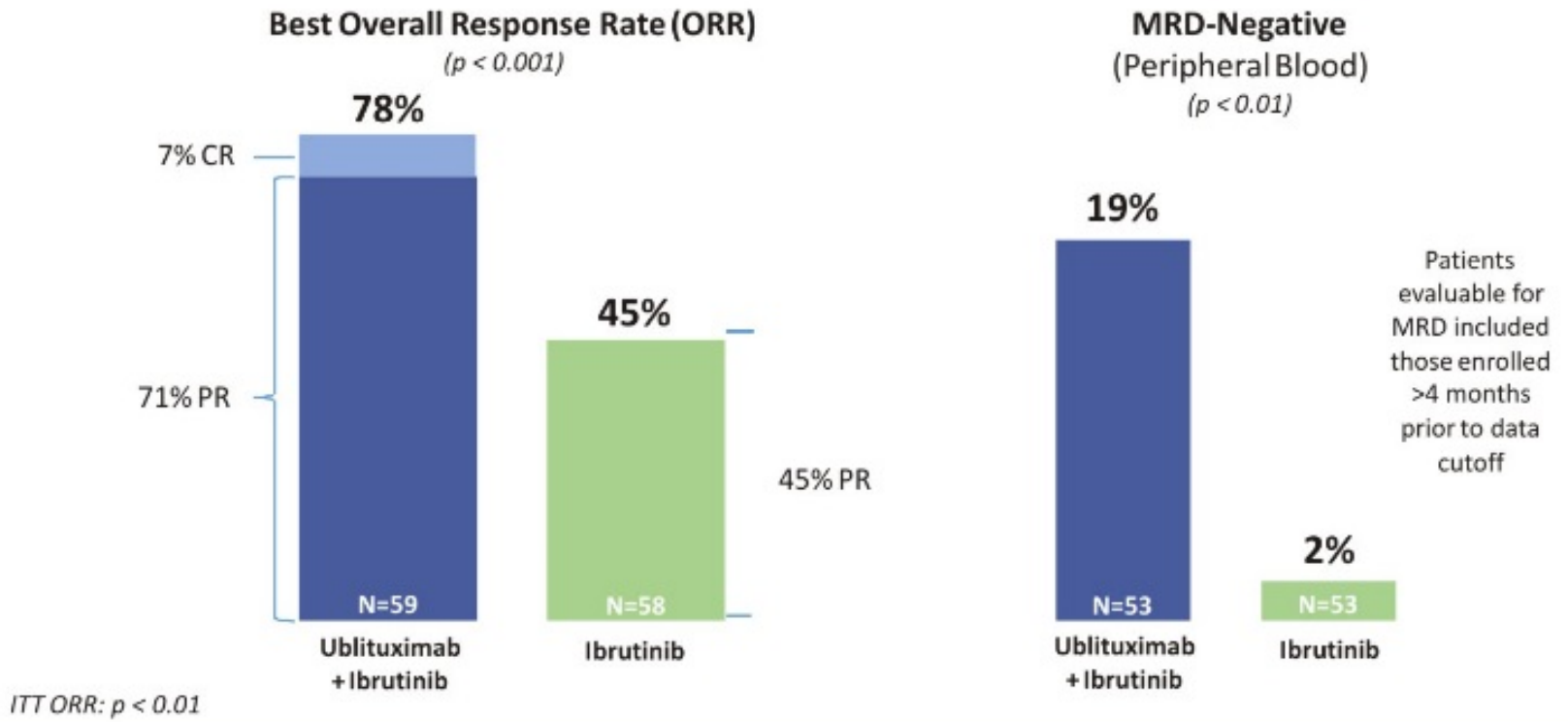
Goede et al., N Engl J Med.* 2014 Jan 8

Ublituximab: Differentiating Anti CD20 mAB's
Novel Type 1, Chimeric Anti CD 20



GENUINE Trial: Ublituximab + IB versus IB

Efficacy: IRC Assessed ORR, CR, & MRD-Negativity



Treatment with antiCD20 in B-cell lymphomas and CLL

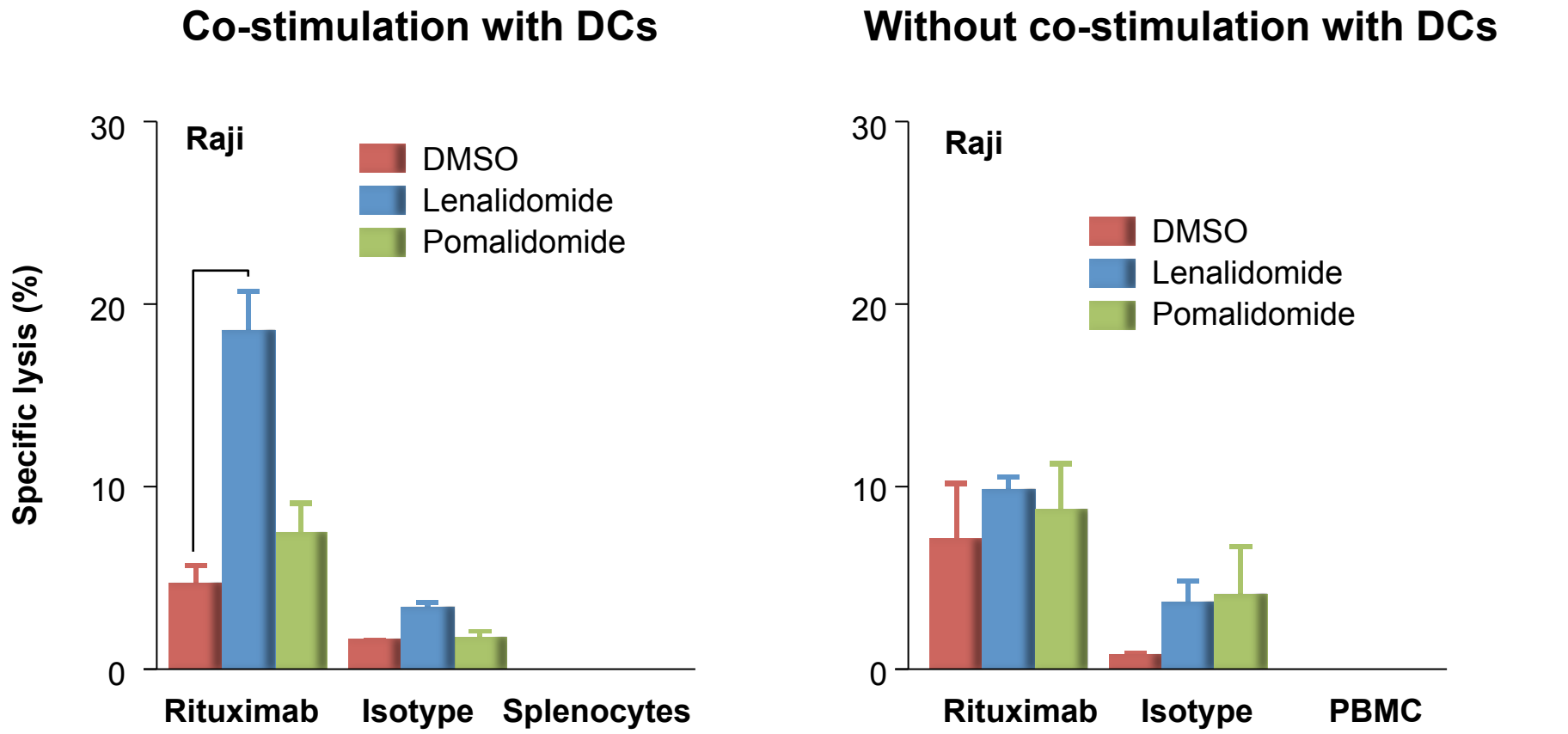
Consolidated results

New antiCD20 antibodies

Association with IMIDs

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

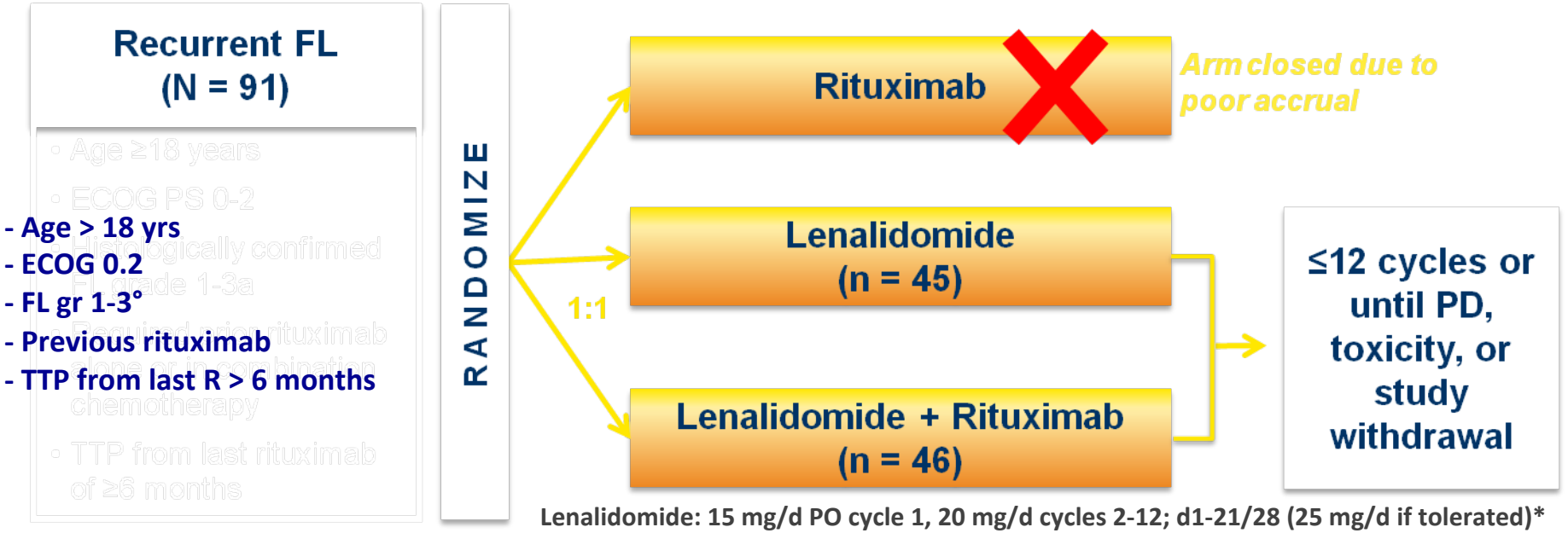
Data is represented by means with error bars showing mean ± 1.0 SE.

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.

LENALIDOMIDE + RITUXIMAB in Recurrent FL

Phase II Randomized Multicenter Study of L vs. LR in Recurrent FL (CALGB 50401- Alliance)



Lenalidomide: 15 mg/d PO cycle 1, 20 mg/d cycles 2-12; d1-21/28 (25 mg/d if tolerated)*

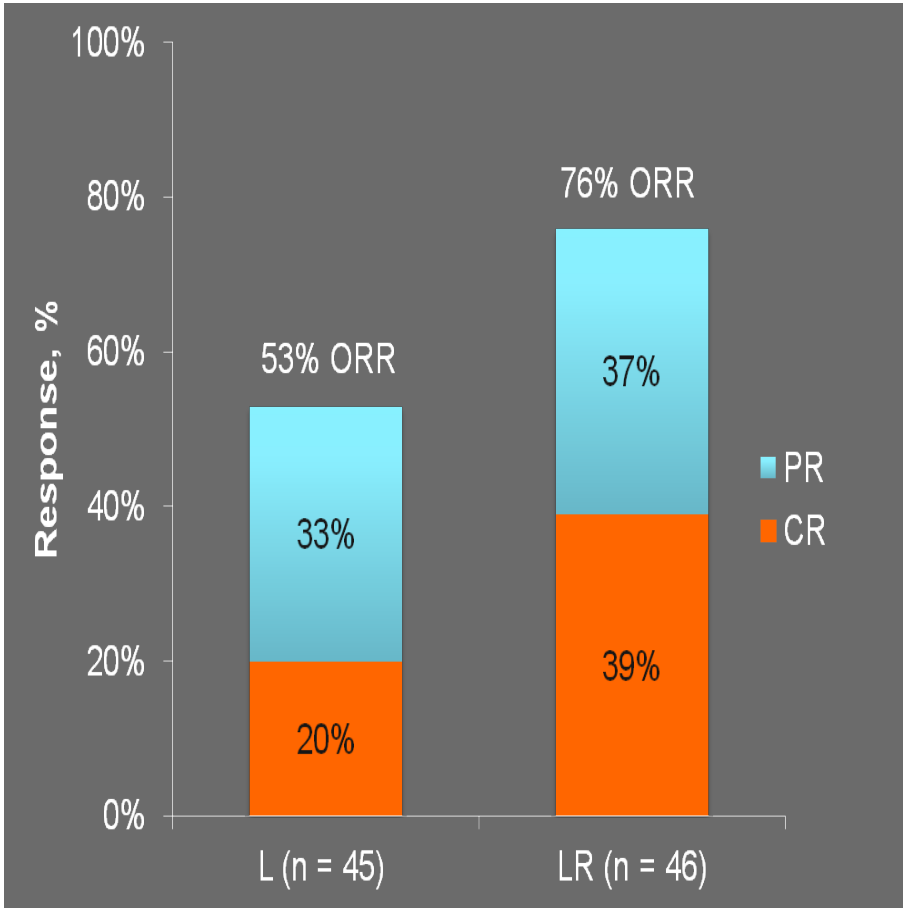
Rituximab: 375 mg/m^2 IV d8, 15, 22, 29 of cycle 1

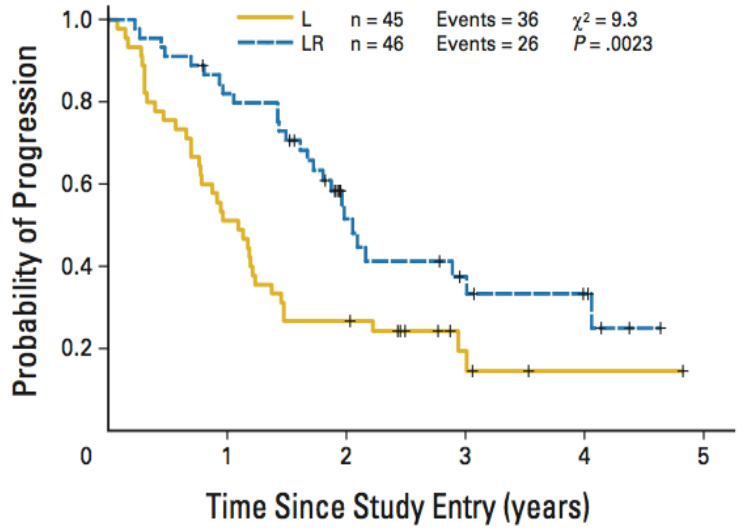
Primary endpoints: ORR and CR†

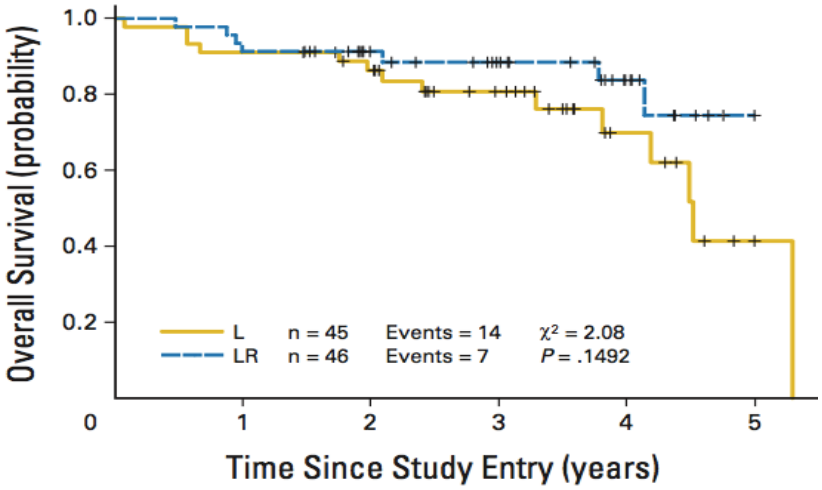
Secondary endpoints: TTP, OS, and safety

Leonard et al. JCO 2015

R2 in relapsed FL







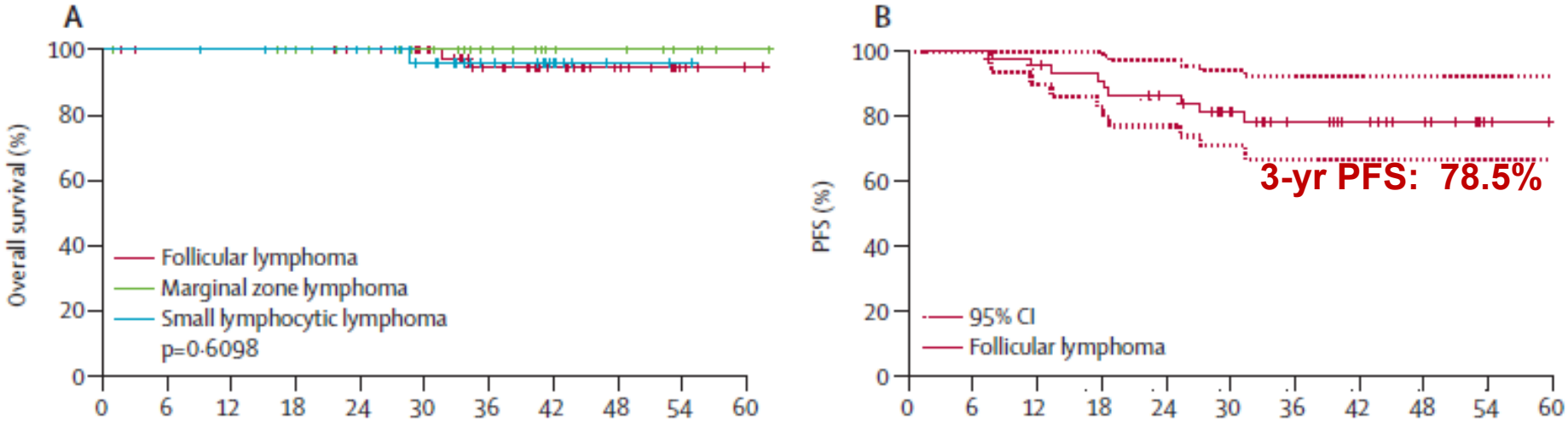
- ORR was significantly improved for LR vs. L (*P*=0.029)

Leonard et al. JCO 2015

Leonard et al. *J Clin Oncol.* 2015; doi: 10.1200/JCO.2014.59.9258. Epub ahead of print.

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.



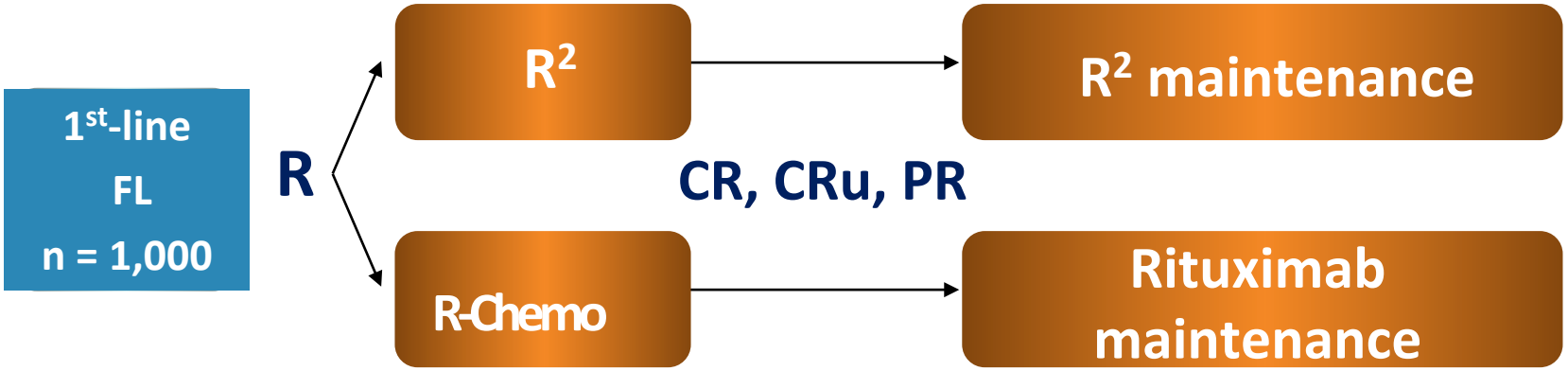
- 3-year OS: 96.1%
- Median PFS for Follicular Lymphoma pts not reached at 40.6 months
- **89% Bcl2+ pts at diagnosis achieved molecular remission after 6 cycles**

- 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

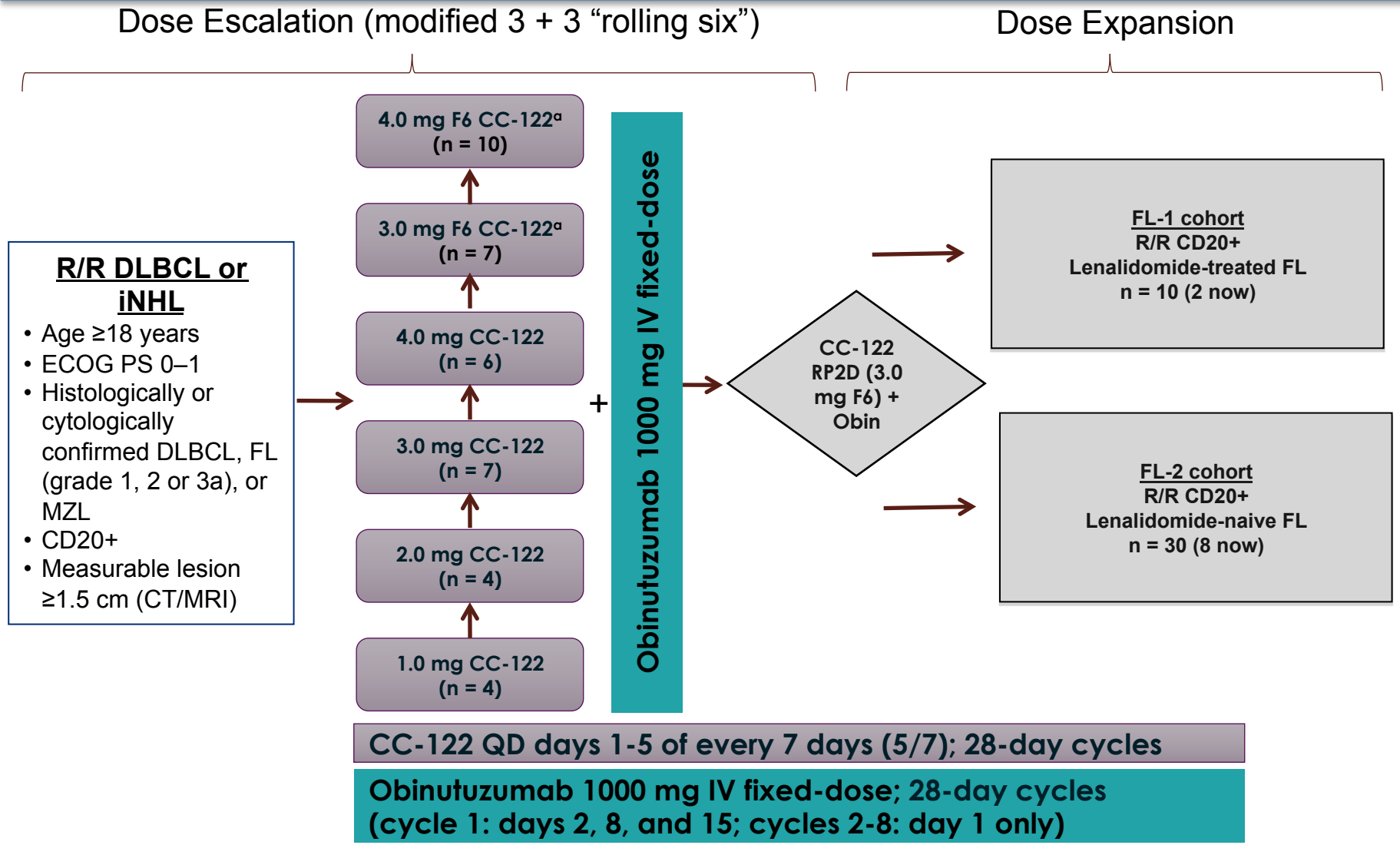
International, phase 3, multi-centre, randomized study
(Frank Morchhauser, Nathan Fowler)



- **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.

OBINUTUZUMAB+CC-122-NHL-001 STUDY DESIGN (NCT00875667; EUDRACT 2014-003333-26)



CT/MRI, computed tomography/magnetic resonance imaging; ECOG PS, Eastern Cooperative Oncology Group performance status; F6, new formulation; IV, intravenous; MZL, marginal zone lymphoma; Obin, Obinutuzumab; QD, every day; RP2D, recommended phase 2 dose.

[a]An alternate dosing schedule with a formulated CC-122 capsule was examined in the 5th and 6th cohorts to assess safety.

Michot JB et et al. ASH 2017.

CC-122-NHL-001: EFFICACY BY NHL TYPE

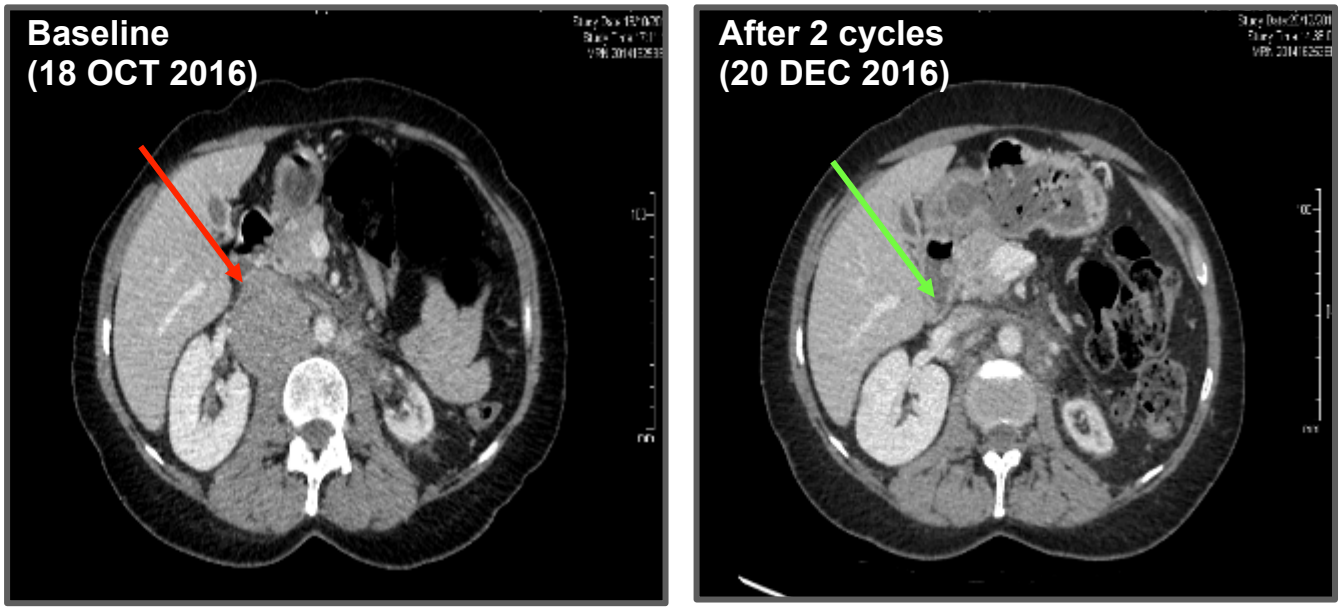
Response by Histology, n (%)	All Patients (N = 44)	DLBCL (n = 19)	FL + MZL[a] (n = 25)
ORR	30 (68)	9 (47)	**21 (84)[b]**
CR	12 (27)	2 (11)	**10 (40)**
PR	18 (41)	7 (37)	**11 (44)**
SD	5 (11)	3 (16)	**2 (8)**
PD	6 (14)	4 (21)	**2 (8)**
Not evaluable/missing	3 (7)	3 (16)	**0**
mPFS (mo, 95% CI)[b]	11.3 (3.7-21.2)	4.7 (1.8-NR)	**16.2 (3.7-NR)**
6-mo PFS (95% CI)[b]	55 (37-70)	40 (16-63)	**68 (42-85)**
mDOR (mo, 95% CI)[b]	19.4 (7.9-NR)	NR	**19.4 (7.9-NR)**

[a]MZL n = 1; [b]3 FL patients with PR were not evaluable for PFS or DOR at the data cutoff
Data cutoff was September 1, 2017

- ORR was 61%, including 12 patients (27%) with a CR
  - DLBCL patients ORR = 47%
  - FL + MZL patients ORR = 72%
- Median time to best response was 57 days (95% CI, 56-113)

CC-122-NHL-001 PATIENT #1011010

- Woman 47 years old with DLBCL/transformed FL
- Molecular profile: TP53, ARID1A and CREBBP mutations
- Previous treatment
  - R-CHOP (refractory)
  - R-DHAP (refractory)
  - EZH2i (Tazemetostat; refractory)



(-) 88 % CR

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

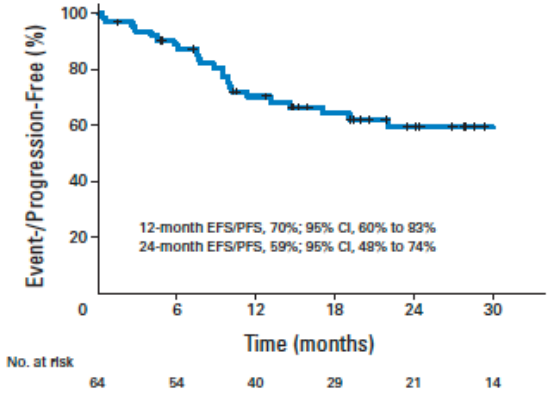
Agent	Dose	Route	Day of Cycle
Lenalidomide	15 mg	po	1-14
Rituximab	375 mg/ m^2	IV	1
Cyclophosphamide	750 mg/ m^2	IV	1
Doxorubicin	50 mg/ m^2	IV	1
Vincristine	1.4 mg/ m^2	IV	1
Prednisone	40 mg/ m^2	po	1-5
Pegfilgrastim	-	-	-
LMWH prophylaxis		*SC*	*daily*

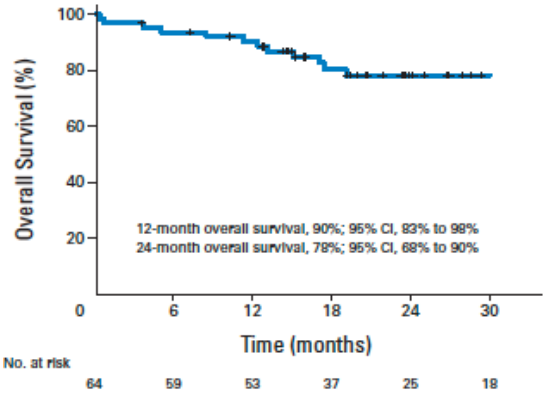
Nowakowski, et al. *J Clin Oncol*. 2015;33:251-257.
Vitolo, et al. *Lancet Oncol*. 2014;15:730-737.

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

MAYO CLINIC

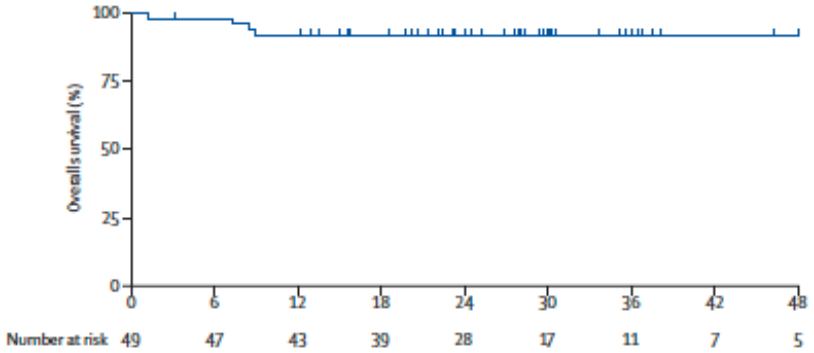
N=60
ORR 98%
CR 80%

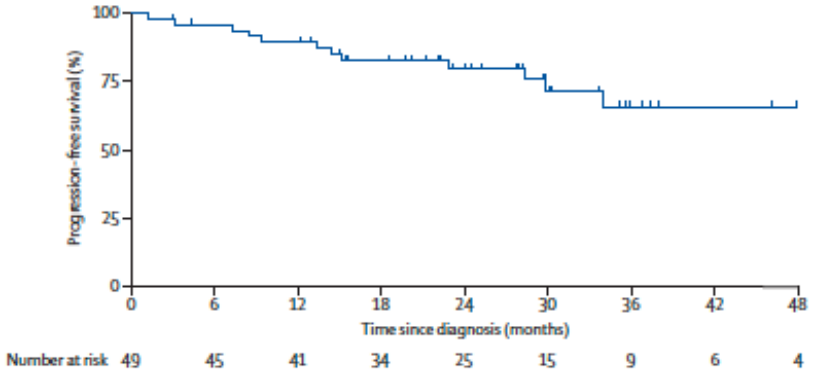




FONDAZIONE FIL ITALIANA LINFOMI

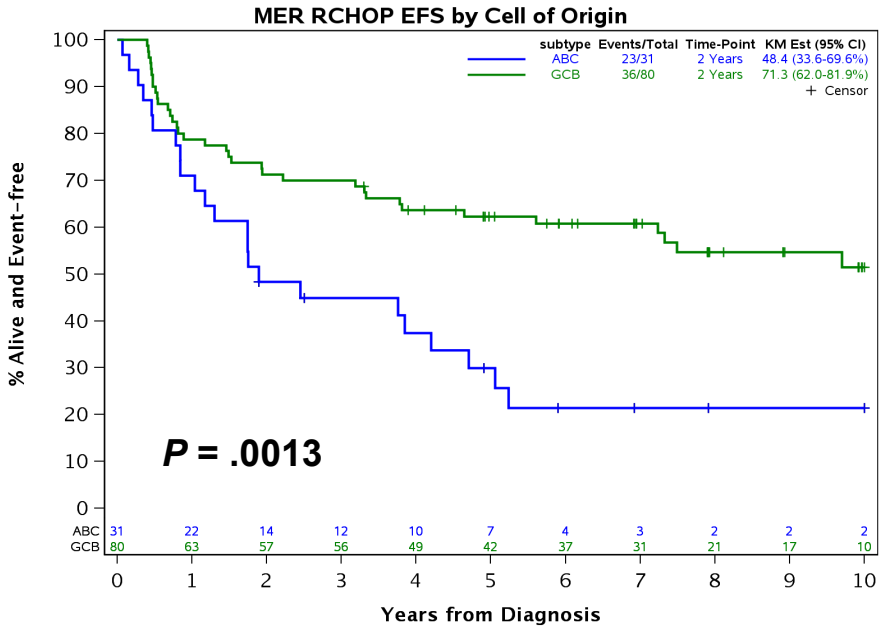
N=49
ORR 92%
CR 86%

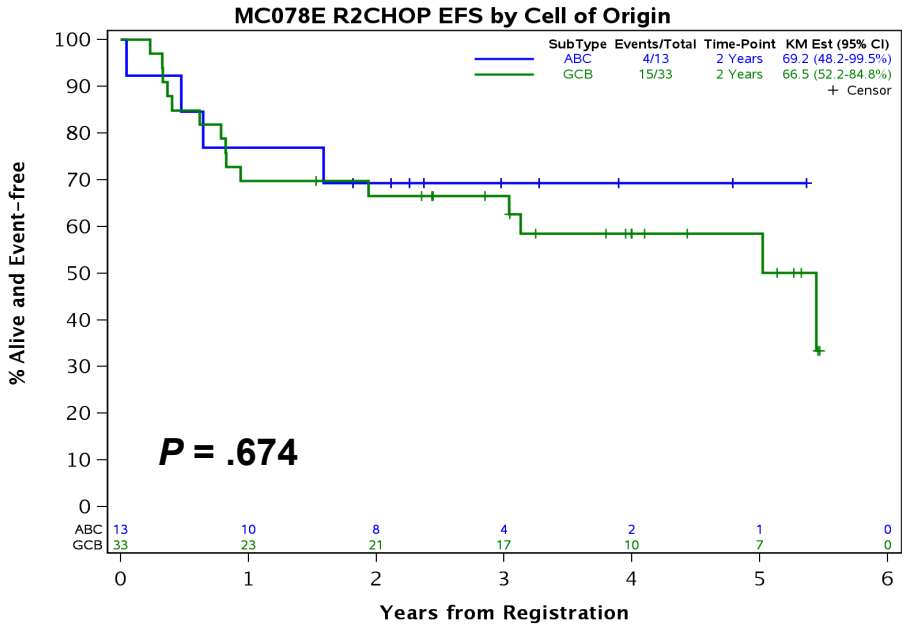




Nowakowski, et al. *J Clin Oncol*. 2015;33:251-257.
Vitolo, et al. *Lancet Oncol*. 2014;15:730-737.

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



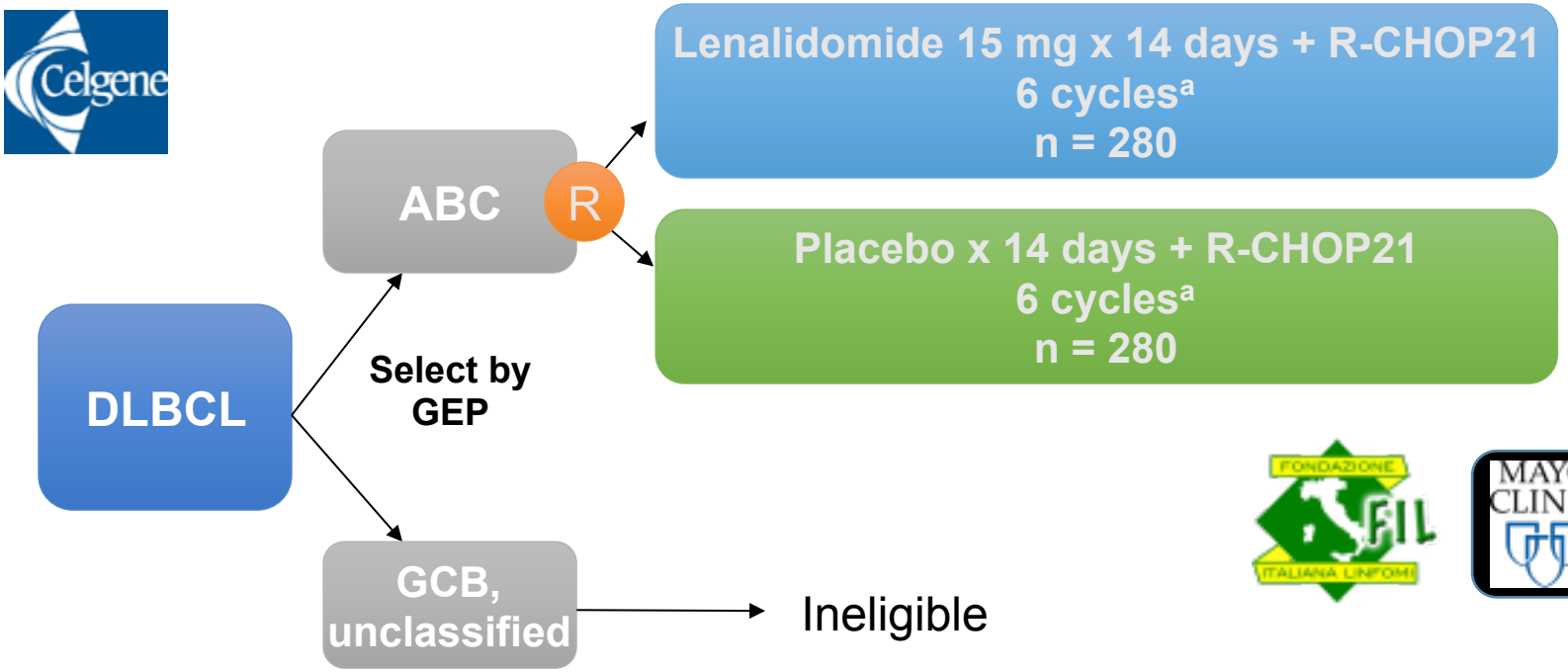


Cohort	N	GCB		ABC		Unclassified	
		n (%)	EFS24	n (%)	EFS24	n (%)	EFS24
MER R-CHOP	124	80 (65%)	71%*	31 (25%)	48%	13 (10%)	46%
MC078E R^2-CHOP	50	33 (66%)	67%#	13 (26%)	69%	4 (8%)	50%

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 and CLL

Consolidated results

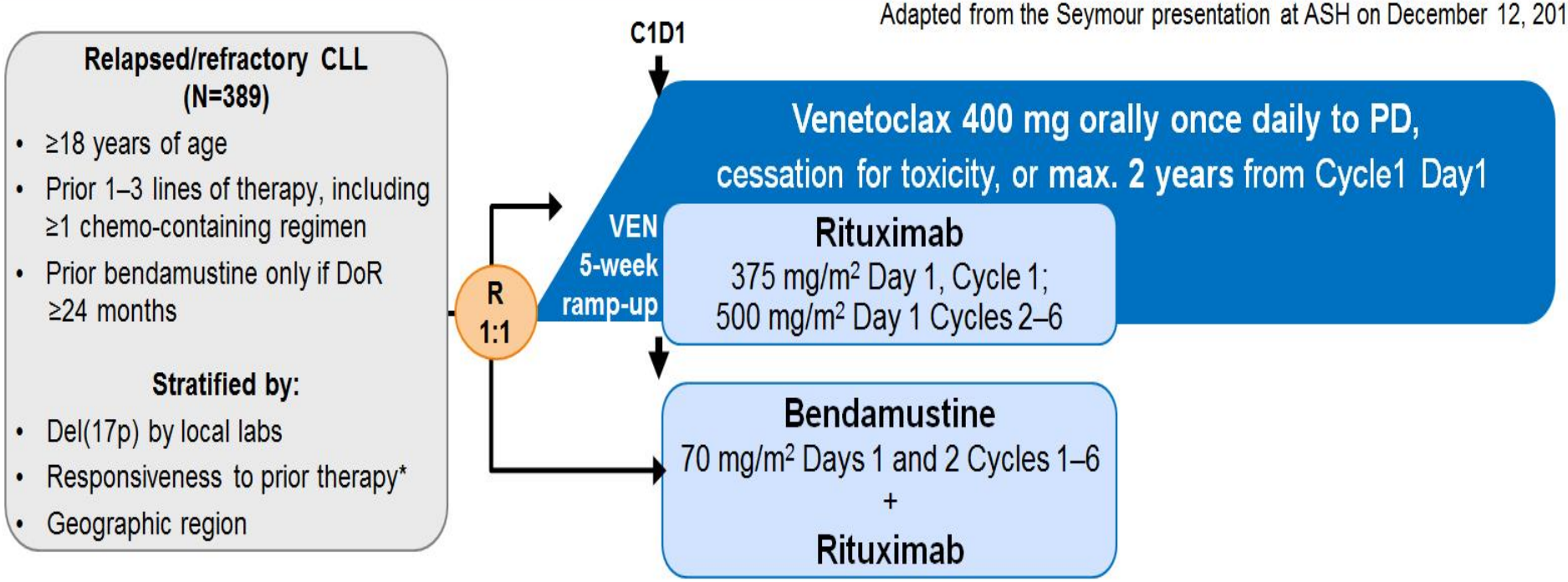
New antiCD20 antibodies

Association with IMIDs

Future development

MURANO Study Design

Adapted from the Seymour presentation at ASH on December 12, 2017



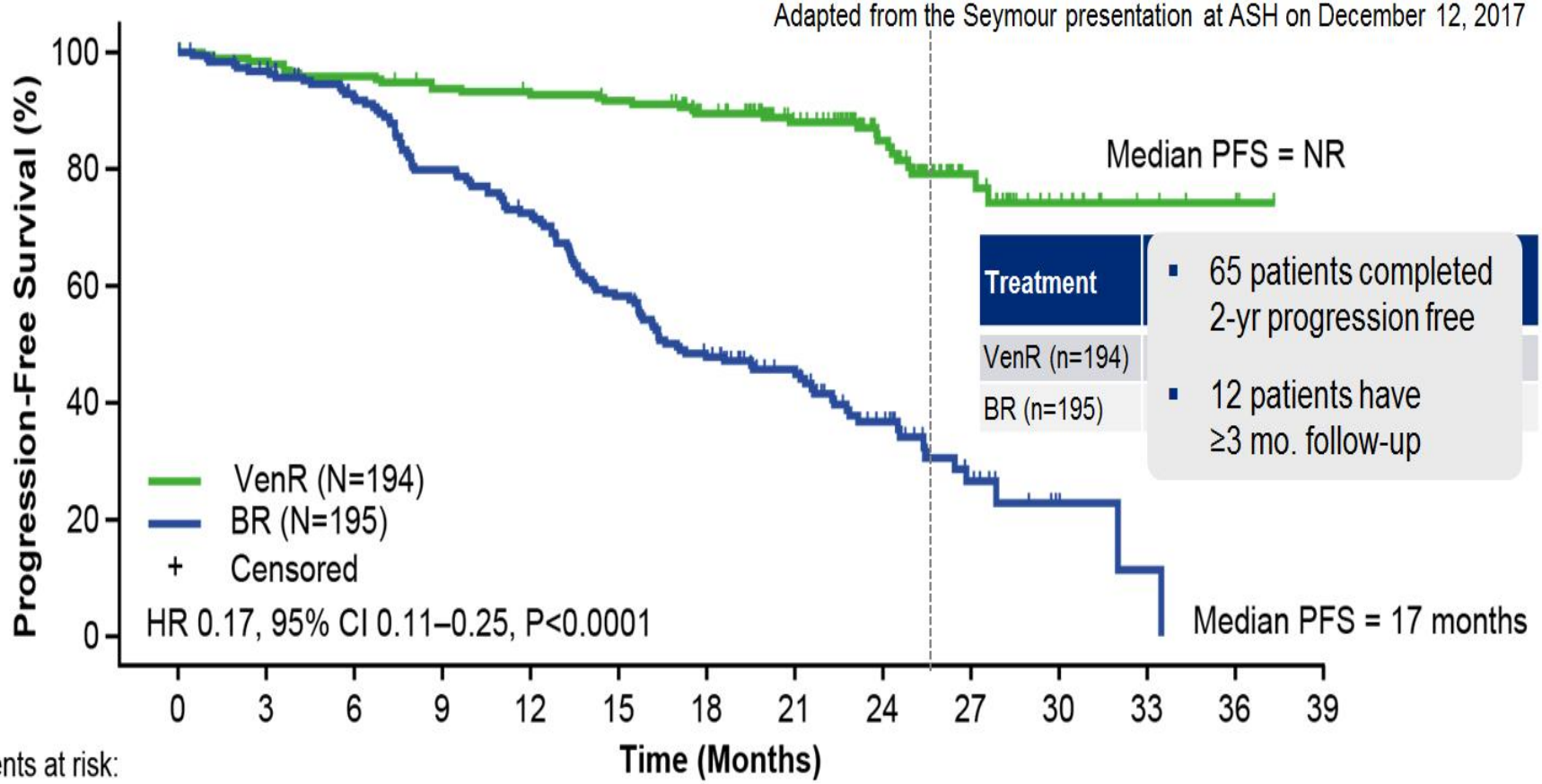
Primary Endpoint	INV-assessed PFS
Major Secondary Endpoints	• IRC-CR ⇒ IRC-ORR ⇒ OS (hierarchical testing) • IRC-assessed PFS and MRD-negativity
Key Safety Endpoints	Overall safety profile, focusing on serious adverse events and Grade ≥3 adverse events
Interim Analysis	Approximately 140 INV-assessed PFS events (75% of total information)

NCT02005471

*High-risk CLL – any of following features: del(17p) or no response to front-line chemotherapy-containing regimen or relapsed ≤12 months after chemotherapy or within ≤24 months after chemoimmunotherapy.

Investigator-Assessed PFS Superior for VenR vs. BR

Adapted from the Seymour presentation at ASH on December 12, 2017



No. of patients at risk:

VenR	194	190	185	179	176	173	157	115	76	33	14	5	3
BR	195	177	163	141	127	102	81	57	35	12	3	1	

- Median (range) duration of follow-up, 23.8 (0.0–37.4) months: Venetoclax + rituximab, 24.8 months; bendamustine + rituximab, 22.1 months

As of 8 May 2017

Phase 1b/2: Obinutuzumab, Ibrutinib, and Venetoclax in CLL - Treatment Naive Cohort: Study Design and Baseline

Inclusion criteria
- TN, symptomatic CLL
- ECOG PS ≤1
- Preserved end-organ and BM function

Exclusion criteria
- Uncontrolled autoimmune thrombocytopenia or anemia
- Clinically apparent Richter's Transformation
- CNS involvement by leukemia
- Use of Warfarin or potent CYP3A4 inhibitors or inducers ≤ 7 days prior to study treatment

Fourteen 28-day cycles OBI+IBR+VEN started sequentially over the first 3 cycles
- C1: OBI (D1: 100mg, D2: 900mg, D8,D15: 1,000mg, C2-8 D1: 1,000mg)
- C2: add IBR in C2 (C2-14 D1-28: 420mg)
- C3: add VEN in C3 with dose escalation according to its US label

Primary objective: MRD (-) CR after C14 are expected in May 2018

Baseline Characteristics, %	N=25	Baseline Characteristics, %	N=25
Median age, yrs (range)	59 (24-77)	**Unmutated IGHV**	71
Male	60	**Complex karyotype**	24
Del(11)q	20	**Trisomy 12**	12
Del(17)p	12	**TLS Risk high**	28
Del(13)q	20	**TLS Risk medium**	72
		TLS Risk low	0

Rogers et al. ASH 2017. Abstract #431

Phase 1b/2: Obinutuzumab, Ibrutinib, and Venetoclax in CLL - Treatment Naive Cohort: Disposition and Efficacy

- With median follow-up of 14.7 mo (range, 7.4-16.1), 22 patients remain on study
  - 1 discontinued treatment after C7 at the discretion of the treating physician
  - 1 after C10 for patient preference
  - 1 after C10 for AEs of neutropenia and colitis (deceased)
- 12 patients completed combination treatment

Responses post-C8, n (%)	N=25	MRD (−) Both*
ORR	24 (96)	14/24 (58%)
CR	5 (20)	8/13 (46)
CRi	8 (32)	
PR	11 (46)	6/11 (55)
SD	0	
PD	0	
NR	1 (4)	

*4-color flow cytometry on PB and BM.

- CRi due to cytopenias with (4/8) or without (4/8) hypocellular marrow
- 6/11 PR patients met count and marrow requirements for CR but had LN >1.5 cm
- All but 1 patients had no morphologic evidence of CLL in bone marrow

Rogers et al. ASH 2017. Abstract #431

UNITY-NHL in US, Italy, Spain, UK, Poland

Bologna, Milan (IEO, San Rafaella), Torino, Rome, Ferrara

DLBCL
R/R Not Transplant Eligible
→ **U2 + Bendamustine**

Follicular
R/R 2+ Prior Lines of Tx
→ **Umbralisib**

SLL
R/R 2+ Prior Lines of Tx
→ **Umbralisib**

Marginal Zone
R/R 1+ Prior anti-CD20
→ **Umbralisib**

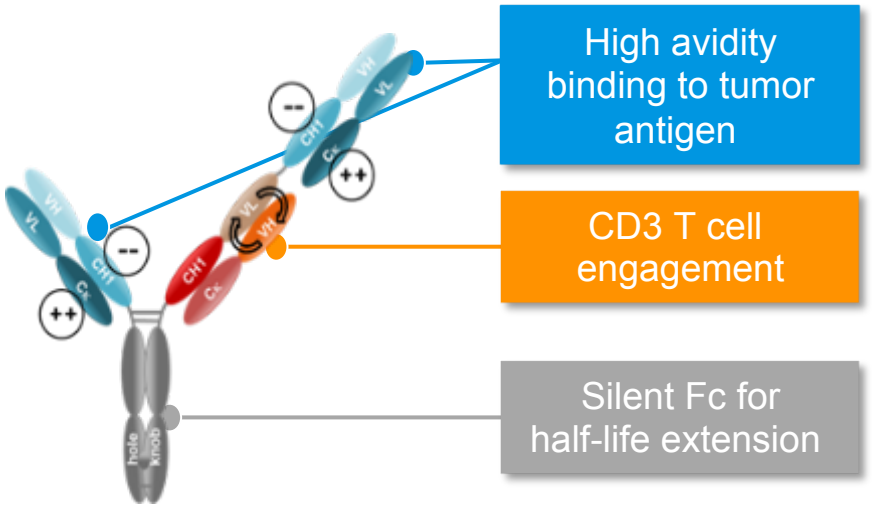
Mantle Cell
BTK-Refractory
→ **Umbralisib**

UNITY NHL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA UMBRALISIB (TGR-1202)
PREVIOUSLY TREATED NHL PATIENTS

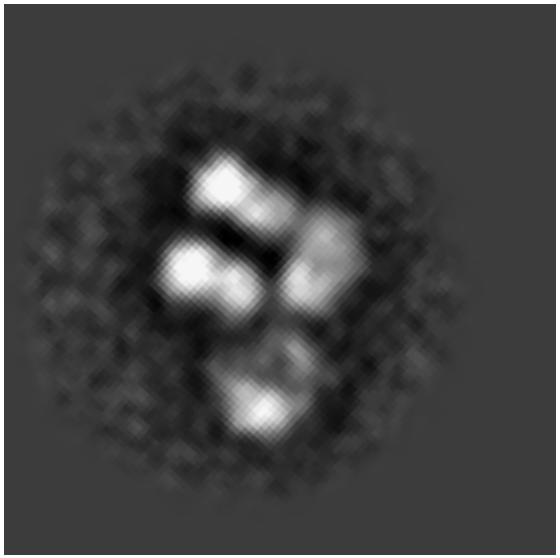
Future Stages to Evaluate…

Structural characteristics of the CD20 CD3 TCB 2:1 format

"2:1" TCB format



Fab range of motion in TCB



- Human/cyno cross-reactive humanized antibody GAZYVA-based CD20 binder and human/cyno cross-reactive humanized antibody CD3 binder
- Bivalency for tumor antigen (CD20); Head-to-tail geometry of CD20 and CD3 binders confers higher potency
- Fc-based TCB for half-life extension (fully silent Fc, P329G LALA); Production using standard processes (CHO)

Conclusions

- ✓ CD20 is still the best target for monoclonal antibodies in the treatment of B-cell lymphoma and CLL
- ✓ Rituximab has changed the outcome of DLBCL, FL and CLL
- ✓ 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 and Obinutuzumab can be safely combined with Lenalidomide as chemotherapy free regimen in FL or with RCHOP backbone with preliminary good results
- ✓ Future developments of antiCD20 include combination with novel small molecules, development of new antiCD20 antibodies and possibly bispecific antibodies allowing to restore T-cell cytotoxic activity against lymphoma cells.

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Scientific Board:
Marco Ladetto (Alessandria)
Umberto Vitolo (Turin)

Turin, September 13-14, 2018

Torino Incontra Centro Congressi