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City of Hope®

Follicular Lymphoma: Treatment updates, emerging therapies, and survivorship

2/4/2017: San Francisco

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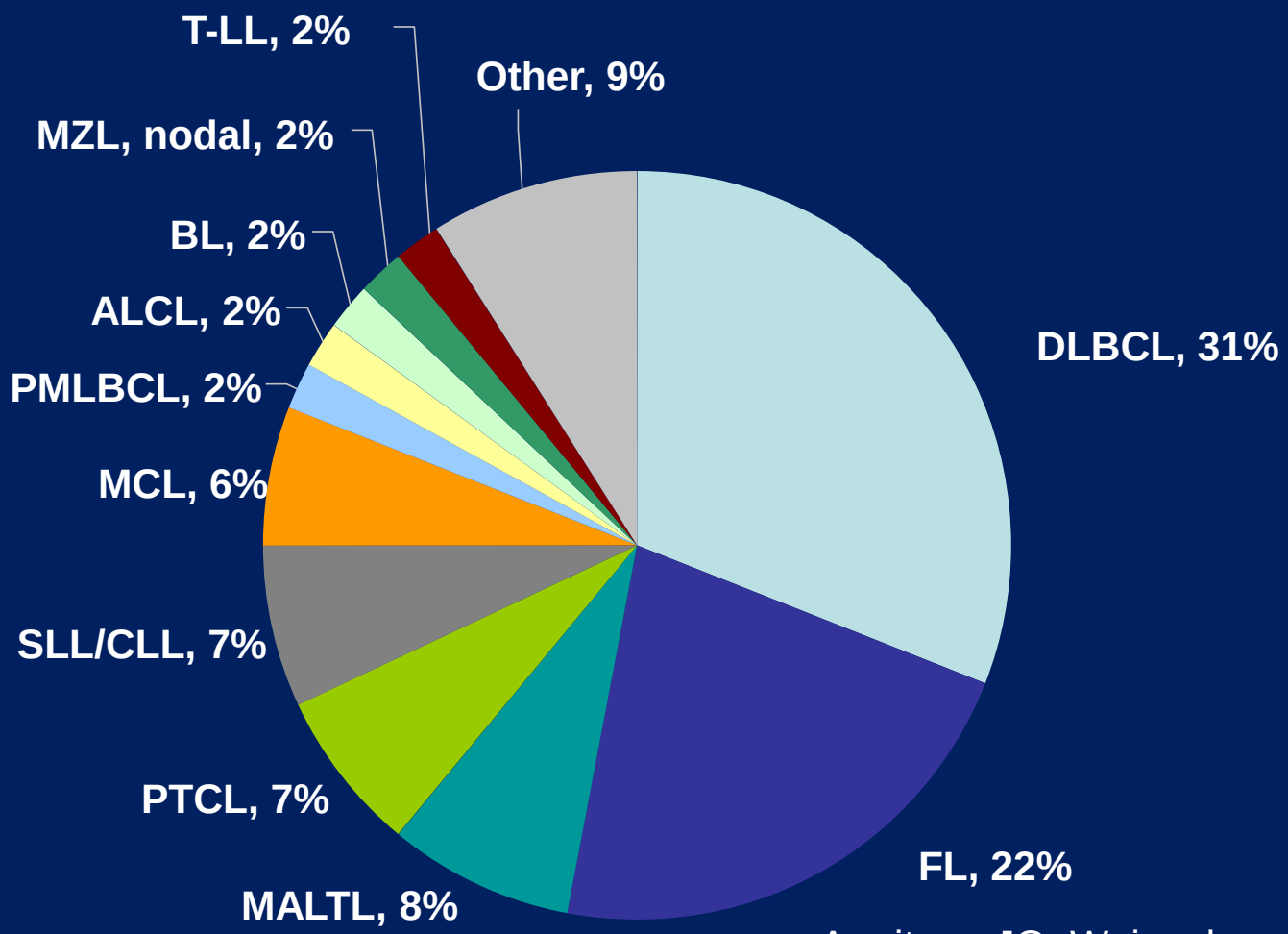
Most Common NHLs



Armitage JO, Weisenburger DD. *J Clin Oncol*. 1998;16:2780-2795.

Follicular NHL

2nd most common NHL

22,000 new cases/yr, median age 60

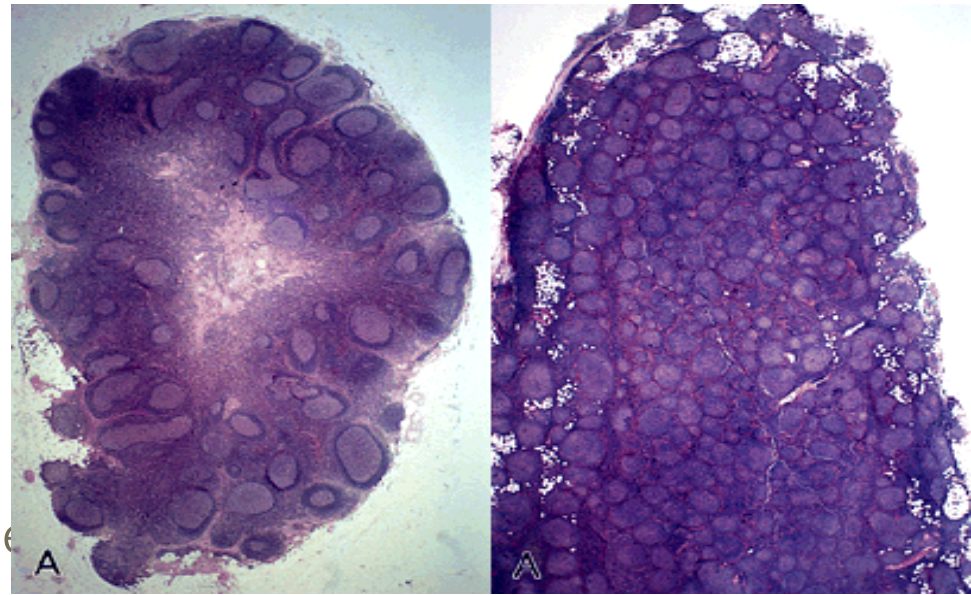
Normal counterpart germinal center B cell

Graded by # large cells

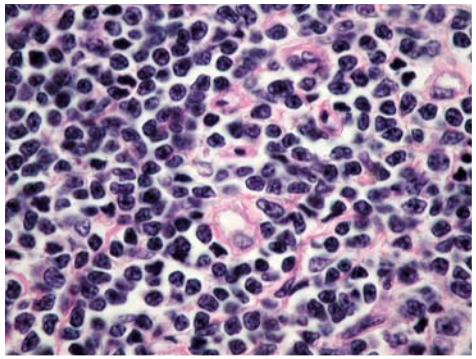
Grade I, II indolent

Gr IIIa*/b aggressive

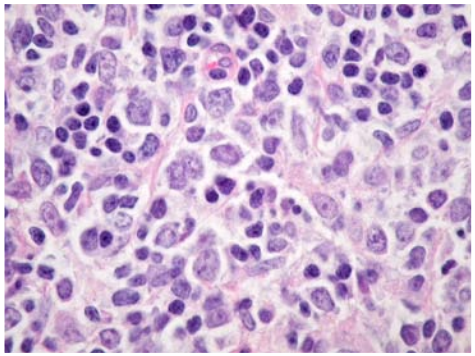
(Gr IIIb ≈ DLBCL)



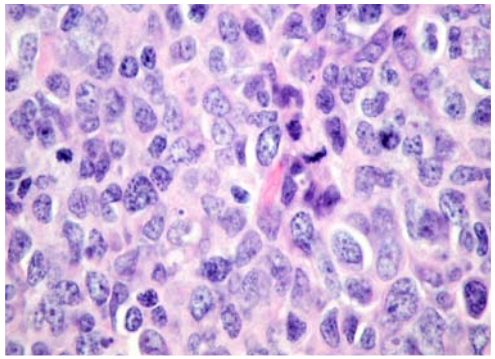
Follicular Lymphoma Grading: Berard Criteria



Grade 1



Grade 2



Grade 3

Natural history of follicular NHL

Spontaneous remissions occur

Waxing and waning disease

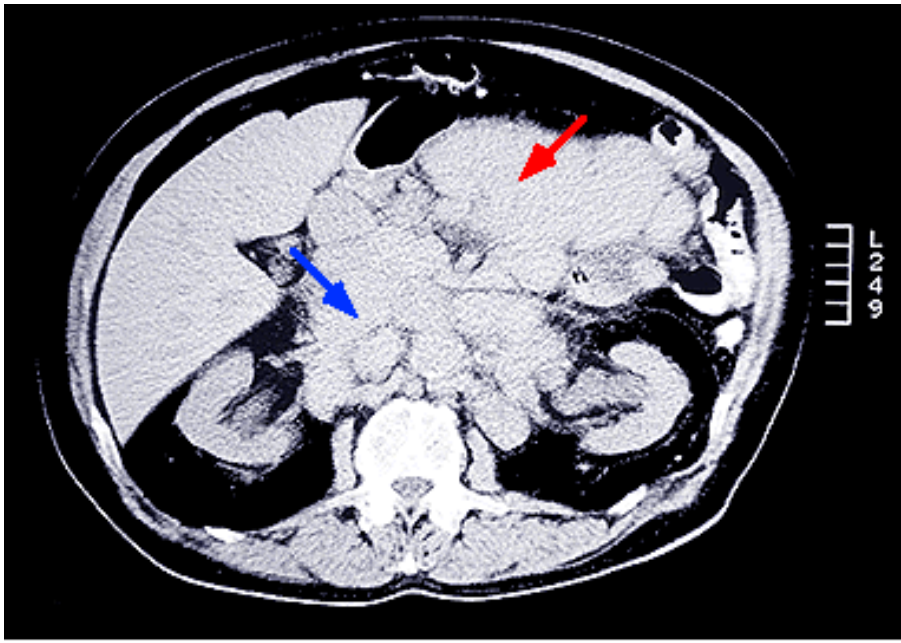
May do well for years without need for treatment

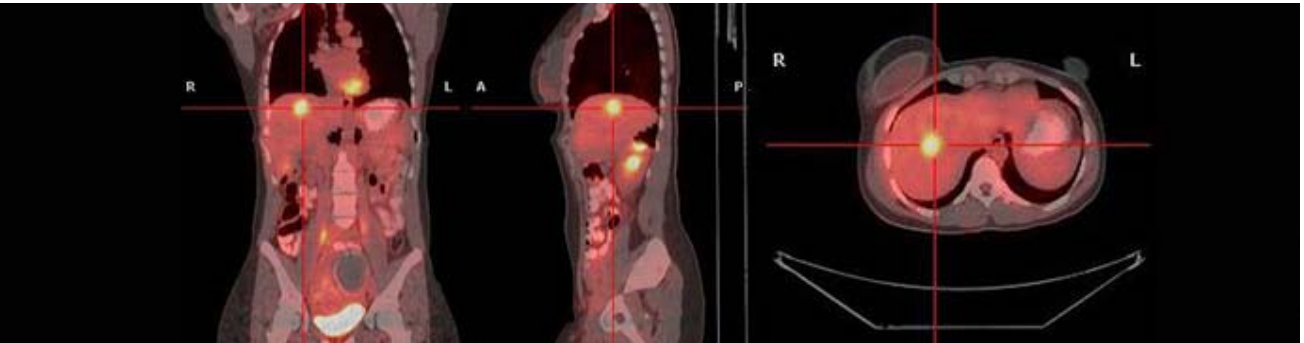
Transformation to aggressive NHL

- 1-4% per year

Usual Clinical presentation

- Painless lymphadenopathy, waxing and waning
- B symptoms uncommon
- Abdominal, retroperitoneal masses
- Spleen involved (40%)
- Marrow frequently involved (>70%)
- Extranodal sites (except the marrow) uncommon.
- Elevated LDH uncommon
- Stage III/IV in over 80% of patients





Early Stage Follicular Lymphoma

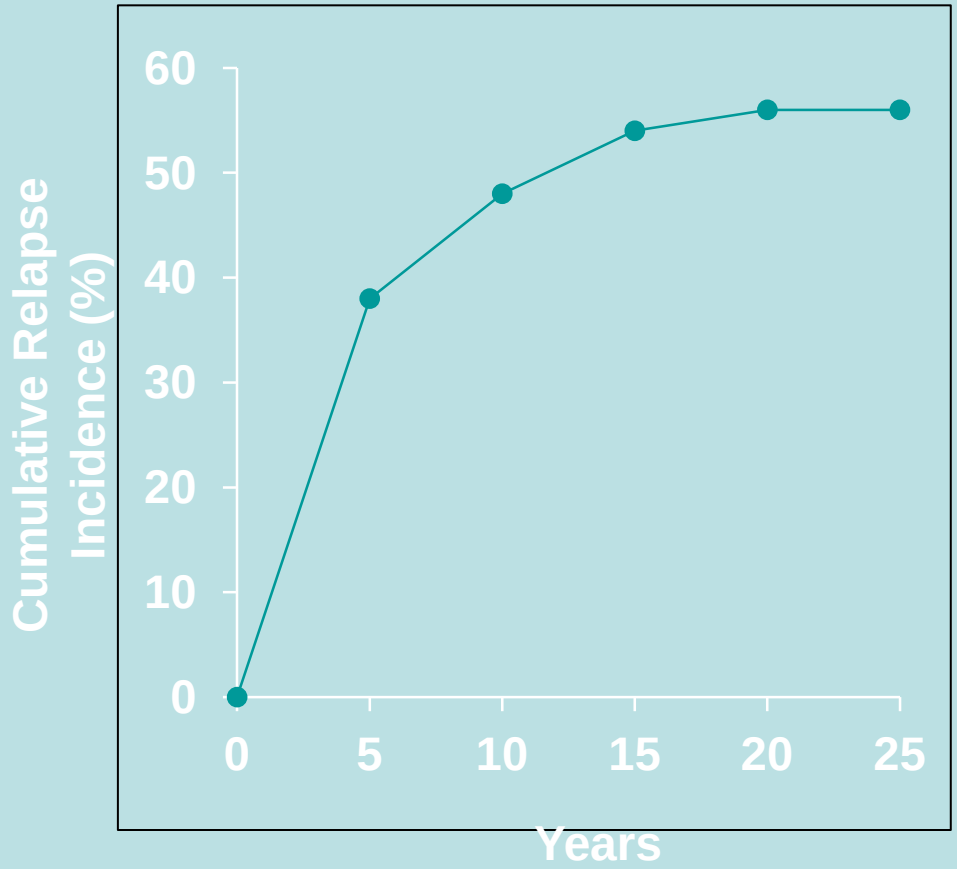
24 Gy IFRT is a potentially curative approach

10-yr PFS/OS: 45-60%/60-80%

CURE in many patients!

Radiation Therapy for Stage I and II Follicular Lymphoma

- A database review 460 patients (St. Margaret's, Toronto) of long-term outcome of involved field RT over a 31-year period
- Local disease control was excellent, although most relapses occurred at distant locations



Peterson PM et al. *Proc Am Soc Clin Oncol*. 2004;23:561. Abstract 6521.

Table 1. Tumor cell surface targets and potential therapies

Category	Target	Potential agents
Anti-CD20 mAbs, type I	CD20	Rituximab
	CD20	Ofatumumab
	CD20	Veltuzumab
	CD20	Ocaratuzumab
	CD20	Ublituximab
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Other mAbs	CD22	Epratuzumab*
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	CD37	BI 836826
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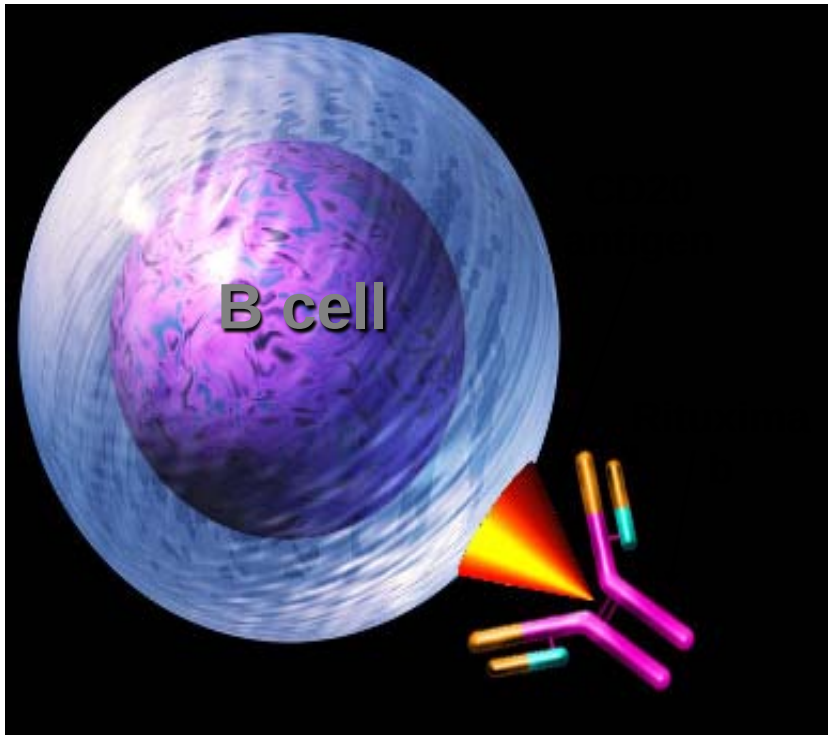
	CD25	ADCT-301
	CD19/CD22	DT2219ARL

ADCs, antibody-drug conjugates.
*No longer in development in NHL.

Adapted from Sehn, L Hematology 2016, p. 284

Monoclonal Antibody for Low-Grade NHL: Rituximab



- Rituximab
  - Chimeric molecule with a murine antigen binding domain
  - Human κ constant region
  - Human IgG1 constant region
- CD20 antigen
  - Hydrophobic, 35 kD phosphoprotein
  - Expressed only on B lineage cells
  - Present in more than 90% of B-cell lymphomas
  - Important for cell cycle initiation and differentiation
  - Does not shed or rapidly modulate off cell surface

Rituximab for Untreated Low-grade NHL

Investigator	No. of patients	CR%	PR%
Solal-Céligny 1999	50	31	28
Hainsworth 2000	39	5	49

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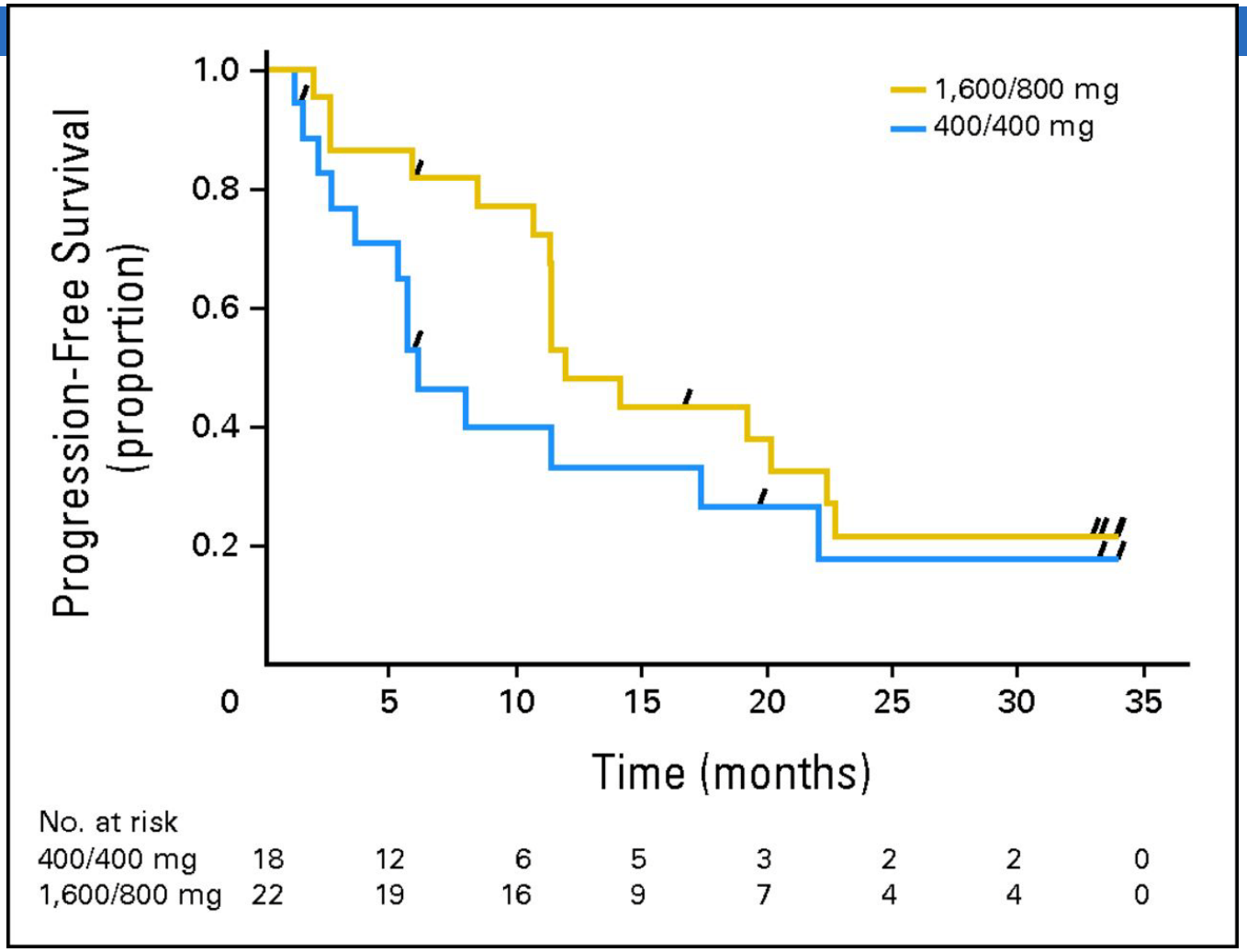
Phase II GAUGUIN
40 PATIENTS (34 FL)



Gilles A. Salles et al. JCO 2013;31:2920-2926

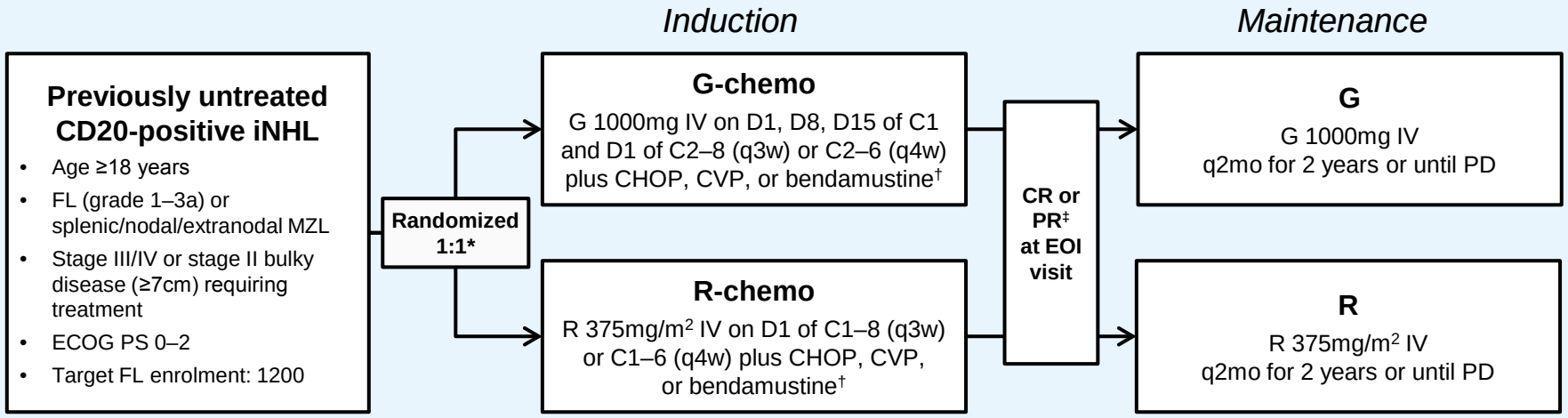
Obinutuzumab-based induction and maintenance prolongs progression-free survival (PFS) in patients with previously untreated follicular lymphoma: primary results of the randomized Phase III GALLIUM study

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

Study design

International, open-label, randomized Phase III study



Primary endpoint

- PFS (INV-assessed in FL)

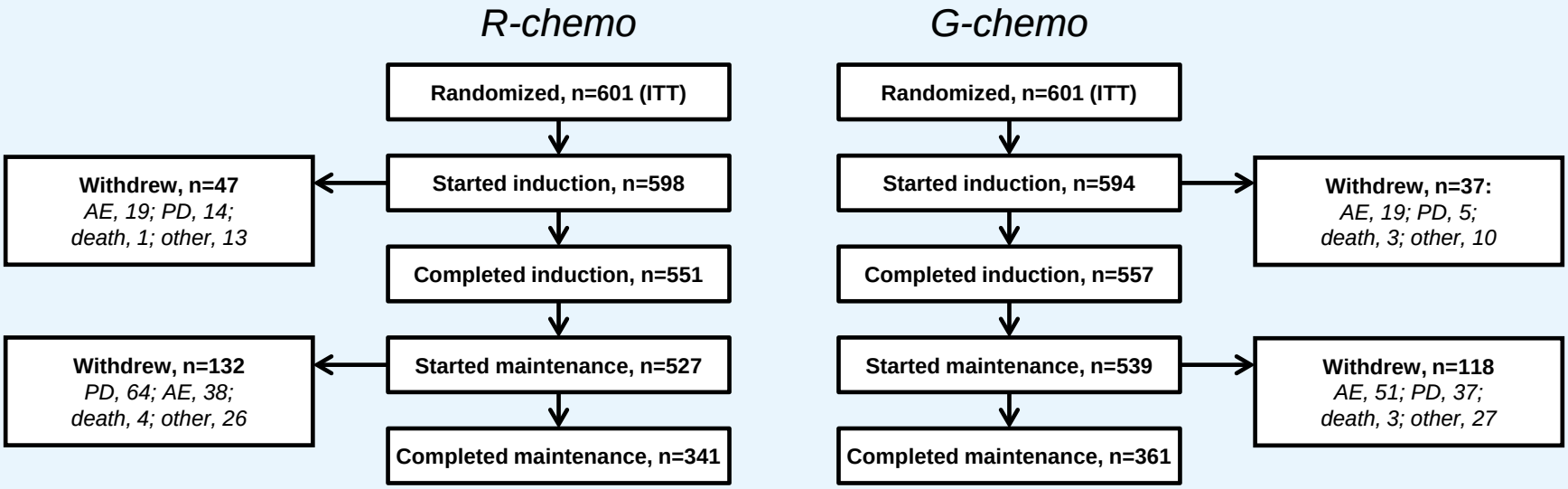
Secondary and other endpoints

- 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

Patient disposition (FL)

1202 FL pts enrolled and randomized to treatment



- *Median follow-up = 34.5 mo; maintenance ongoing in 114 pts (R-chemo, 54; G-chemo, 60)*
- *ITT population* = 1202 pts; safety population† = 1192 pts*

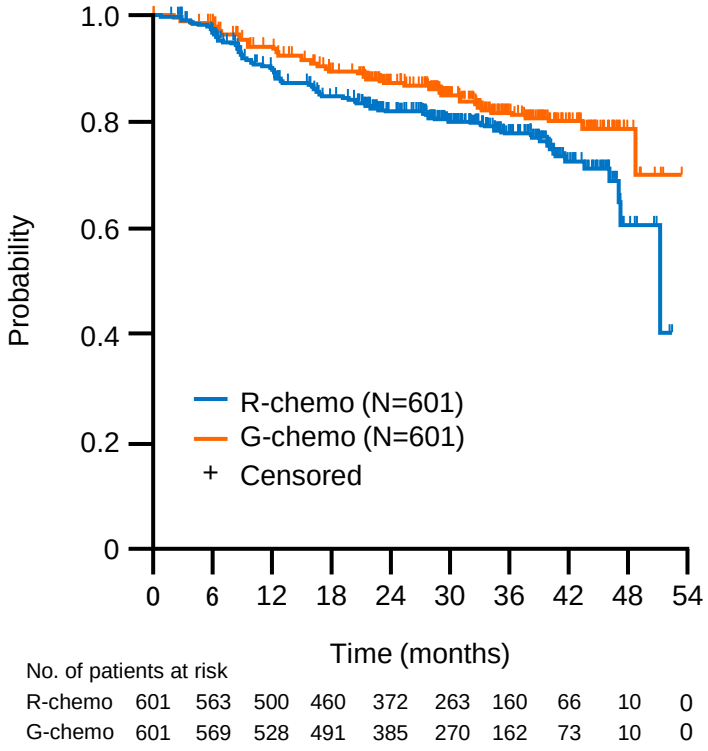
*All randomized FL pts (R-chemo, 601; G-chemo, 601); †All randomized pts who received any amount of study drug (R-chemo, 597; G-chemo, 595)

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

IRC-assessed PFS (FL)



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

	R-chemo, n=601	*G-chemo, n=601*
Pts with event, n (%)	125 (20.8)	93 (15.5)
3-yr PFS, % (95% CI)	77.9 (73.8, 81.4)	81.9 (77.9, 85.2)
HR (95% CI), p-value*	0.71 (0.54, 0.93), p=0.0138	

Median follow-up: 34.5 months

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

Conclusions

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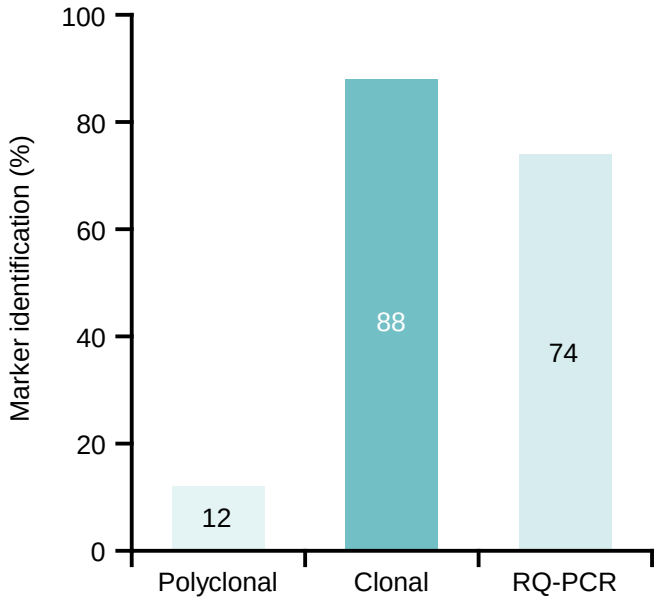
- G-chemo + maintenance superior to R-chemo + maintenance in untreated advanced FL patients at interim efficacy analysis
  - Clinically meaningful improvement in PFS: 34% reduction in risk; HR=0.66
  - PFS result supported by other time-to-event endpoints
- Non-fatal AEs were higher in the G arm
  - IRRs, cytopenias, and infection
- Fatal AEs more common in patients on bendamustine in both arms
- G-based therapy significantly improves outcome compared with R-based therapy and should now be considered as a first-line treatment for FL

MRD assessment: marker identification

- Sample shipment to central lab
- Central MRD lab
  - Marker identification (t(14;18), *IGH*, *IGL*)
    - 88% with clonal marker
  - Large scale RQ-PCR
    - 74% with an RQ-PCR assay sensitivity 10^{-5}
  - Standardized evaluation and reporting
- MRD status
  - Negative: no clone detected in blood and/or BM
  - Positive: clone detected in blood and/or BM

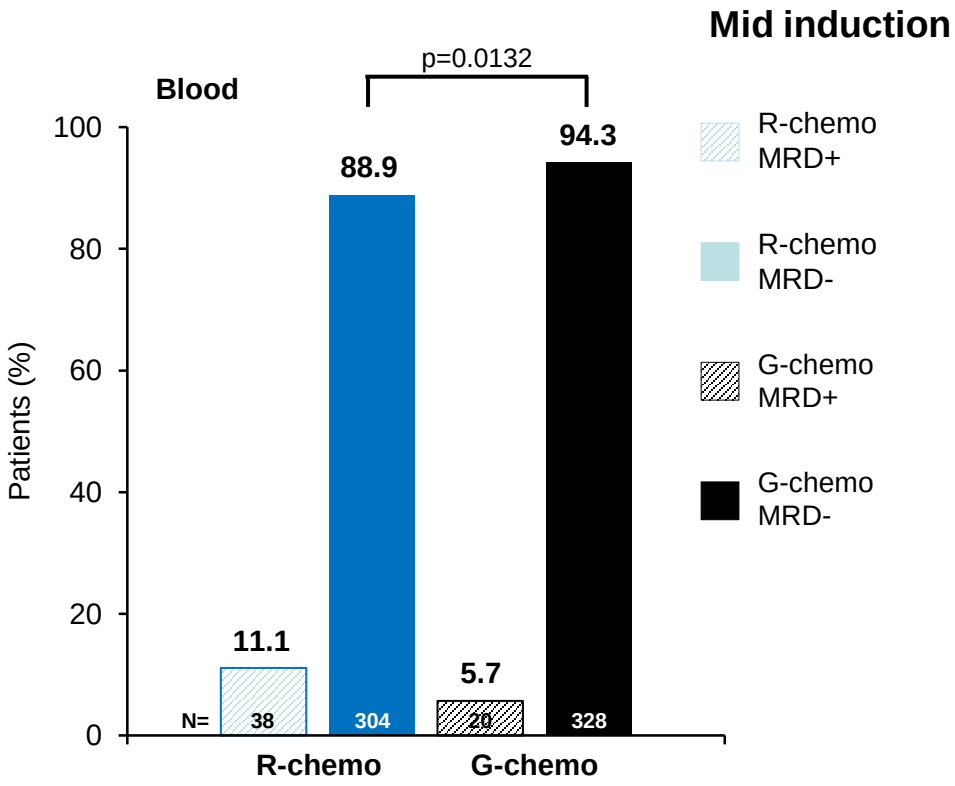


ESLHO european scientific foundation of laboratory hemato oncology

EuroMRD

RQ-PCR, real-time quantitative polymerase chain reaction

MRD status by treatment arm at mid-induction (in blood)



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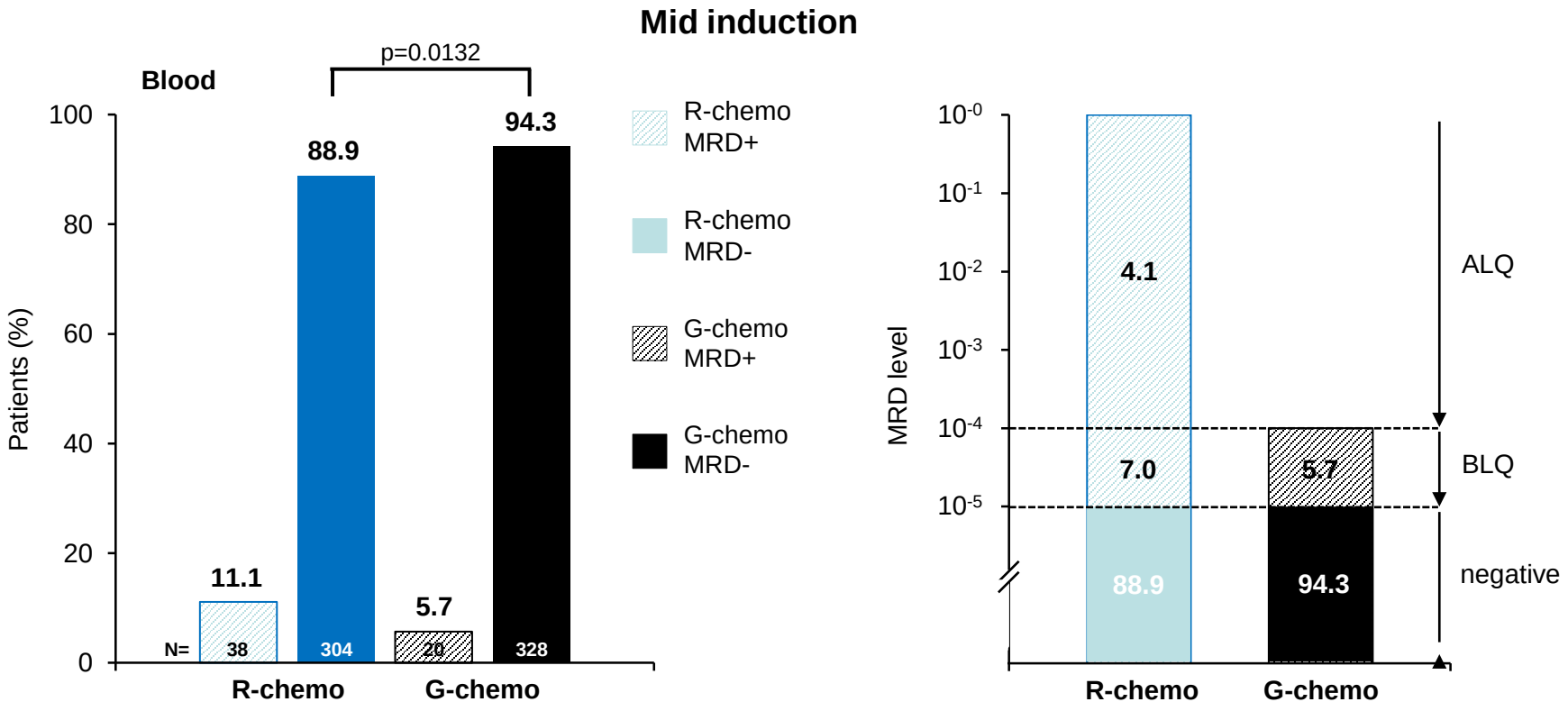
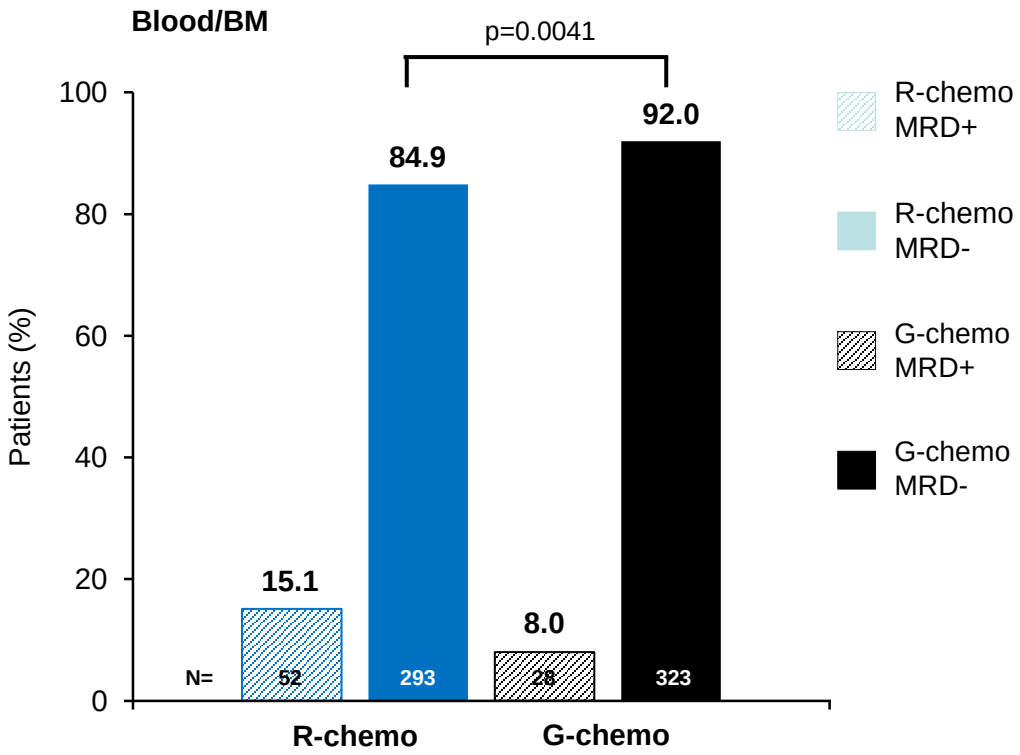
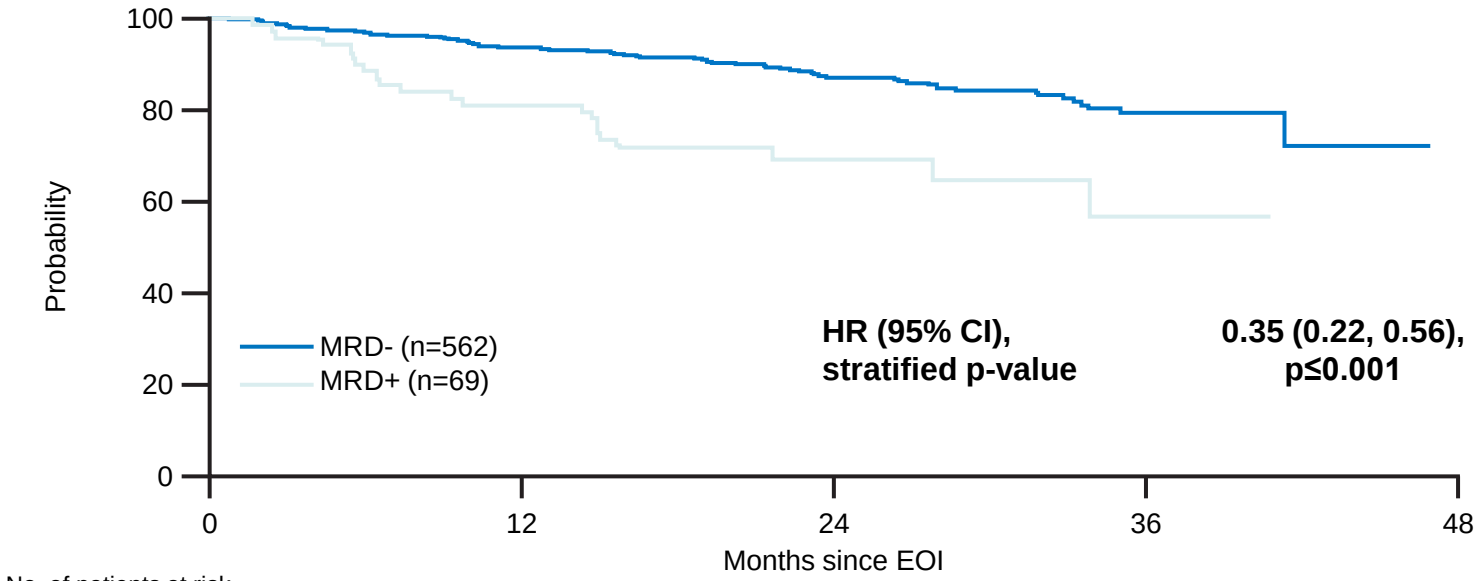


ALQ, above limit of quantification; BLQ, below limit of quantification

MRD status at end of induction



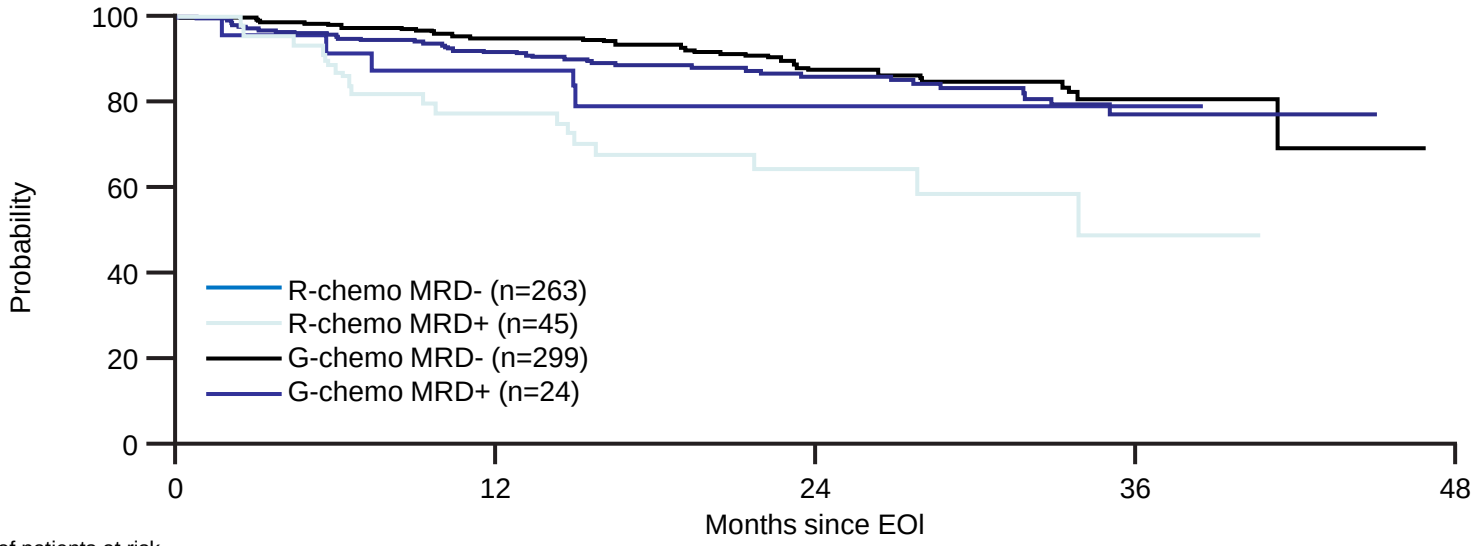
PFS from end of induction by MRD status (patients receiving maintenance)



No. of patients at risk

MRD-	562	535	503	408	287	170	72	9	0
MRD+	69	60	54	43	18	13	5	0	0

PFS from end of induction by treatment arm and MRD status (patients receiving maintenance)



No. of patients at risk

R-chemo MRD-	263	244	230	185	134	77	31	4	0
R-chemo MRD+	45	38	33	27	12	10	4	0	0
G-chemo MRD-	299	291	273	223	153	93	41	5	0
G-chemo MRD+	24	22	21	16	6	3	1	0	0

Conclusions

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- Molecular response rate in both G-chemo and R-chemo arm is high
- Consistently higher MRD response rates observed with obinutuzumab across compartments and chemotherapy partners
- Obinutuzumab may compensate for lower activity of the chemotherapy backbone
- The majority of the MRD response can already be observed at MI
  - MRD kinetics show a faster and deeper response with obinutuzumab-based regimens
- MRD response at EOI is prognostic for PFS and identifies prognostic subgroups after immuno-chemotherapy
- Future analysis will include MRD assessments during maintenance and follow-up across both arms

Table 1. Tumor cell surface targets and potential therapies

Category	Target	Potential agents
Anti-CD20 mAbs, type I	CD20	Rituximab
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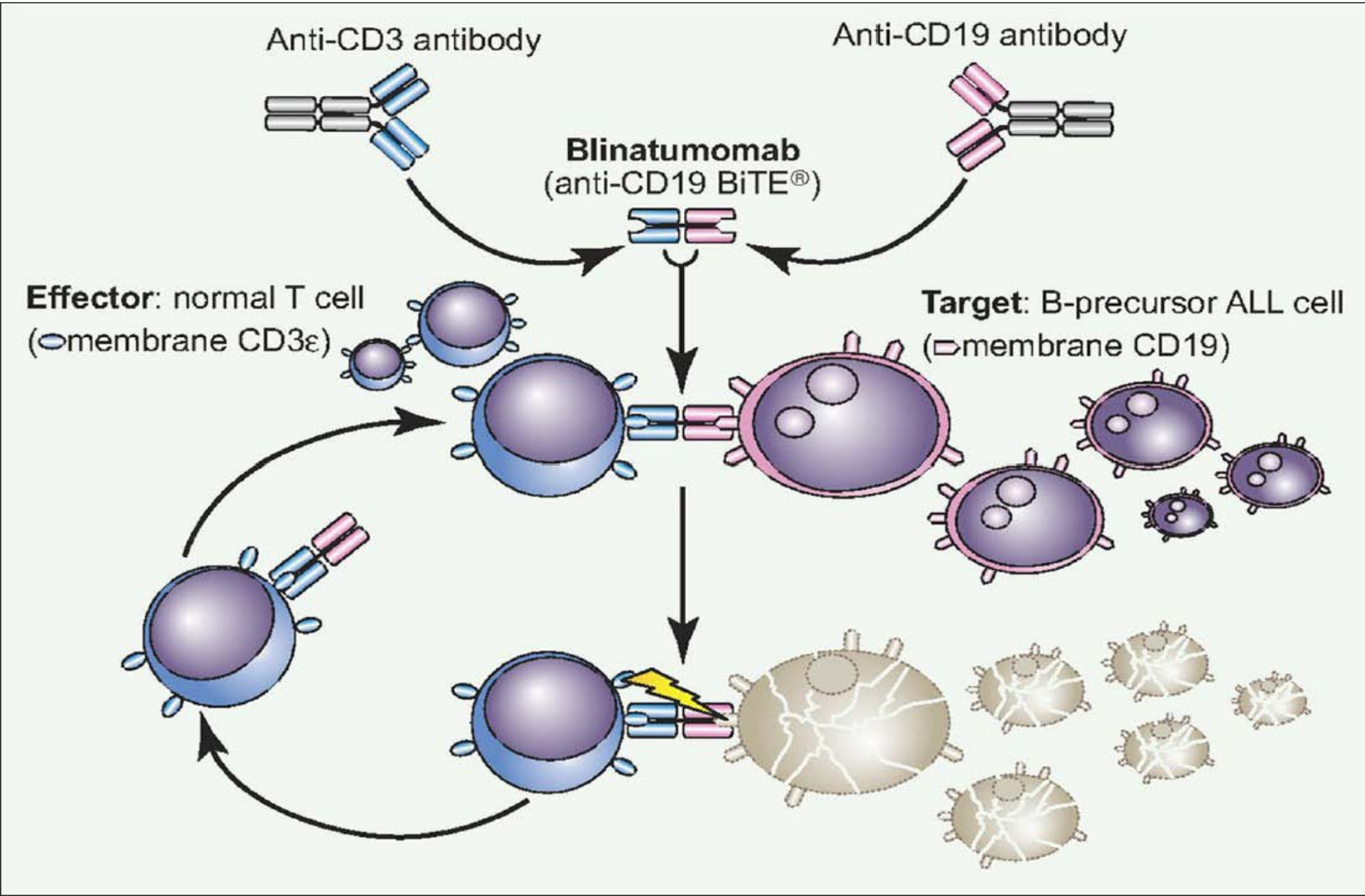
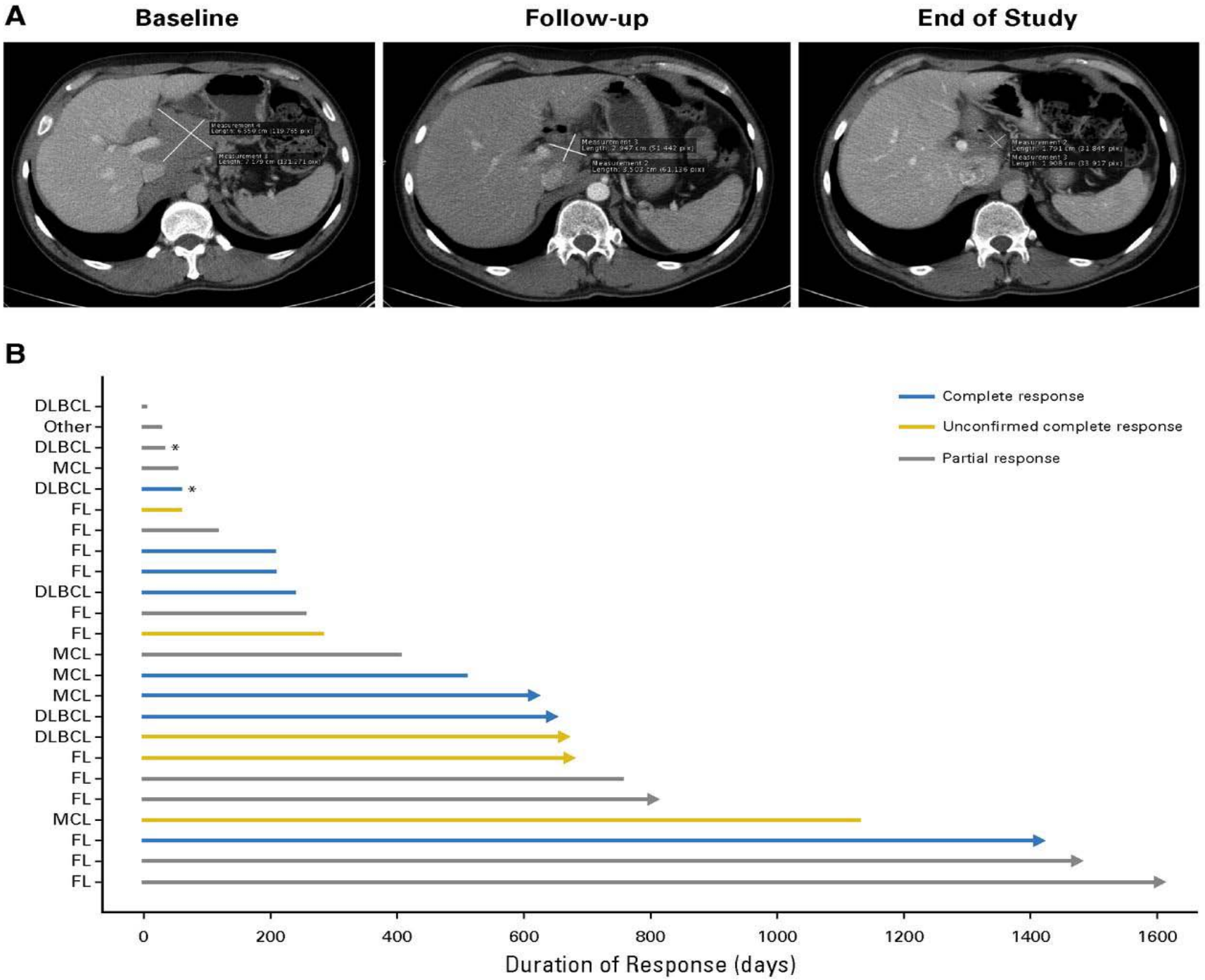
Adapted from Sehn, L Hematology 2016, p. 284

Bispecific T-cell Engager: Mechanism of action




A
Baseline
Follow-up
End of Study
B
Complete response
Unconfirmed complete response
Partial response
DLBCL
Other
DLBCL
MCL
DLBCL
FL
FL
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FL
DLBCL
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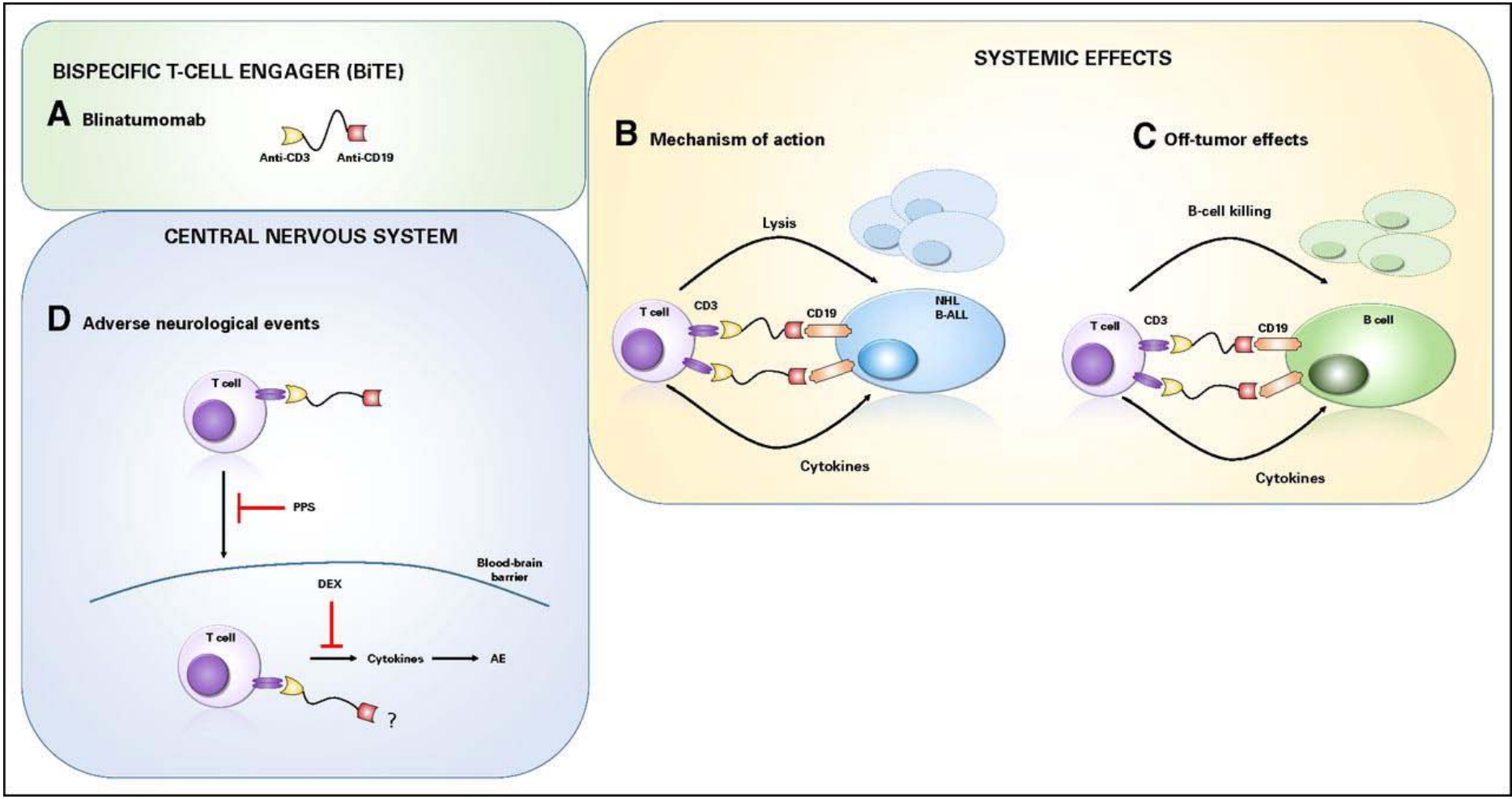
FL
MCL
MCL
MCL
DLBCL
DLBCL
FL
FL
FL
MCL
FL
FL
FL
0
200
400
600
800
1000
1200
1400
1600
Duration of Response (days)

Blinatumomab (BITE) side effects



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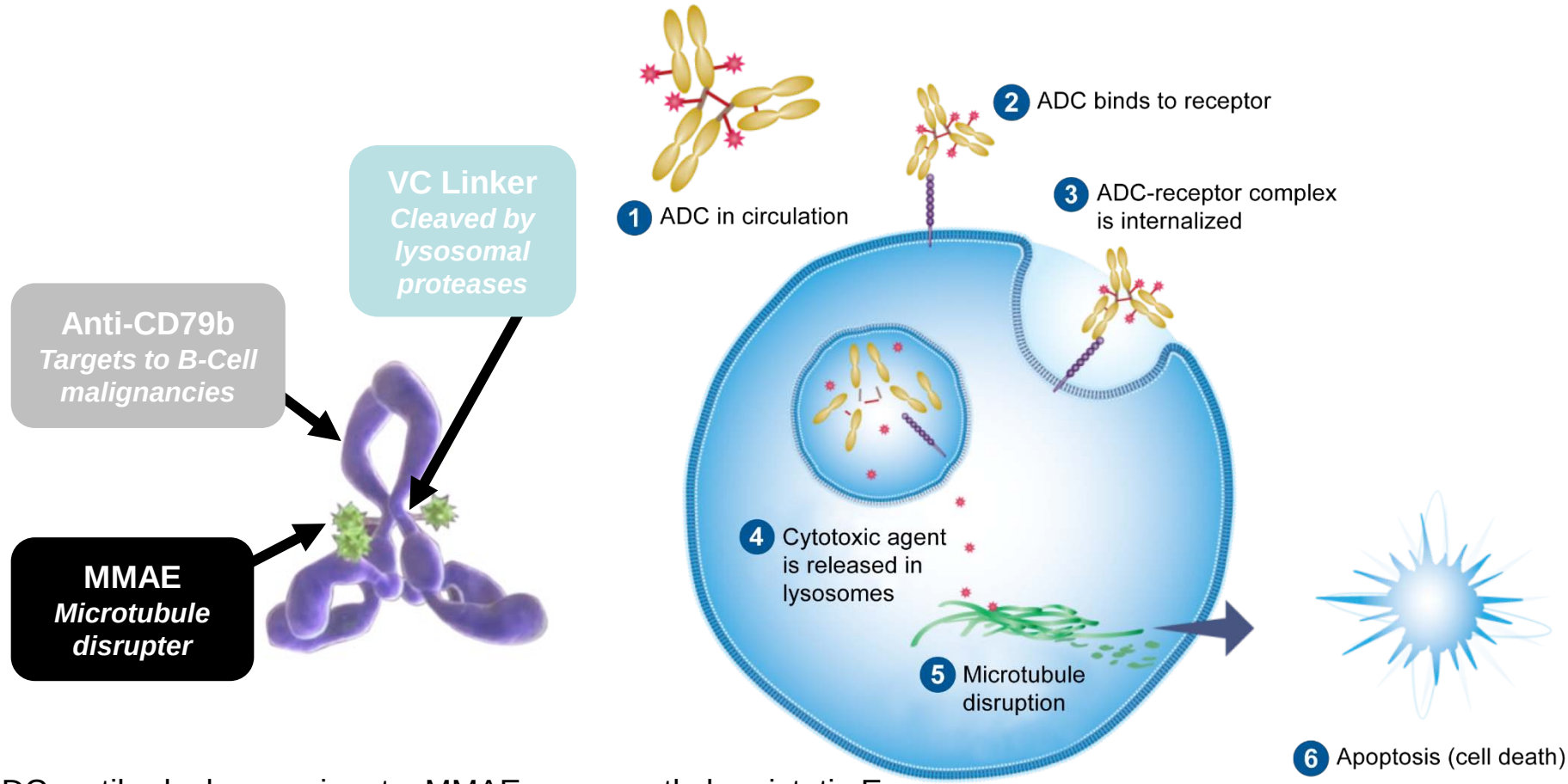
Polatuzumab Vedotin (CD79b-ADC)

- ADC comprising potent microtubule inhibitor MMAE conjugated to CD79b monoclonal antibody via a protease-cleavable peptide linker



ADC, antibody drug conjugate; MMAE, monomethyl auristatin E

Polatuzumab Vedotin Combined with Obinutuzumab for Patients with Relapsed or Refractory Non-Hodgkin Lymphoma: Preliminary Safety and Clinical Activity of a Phase Ib/II Study

Tycel Phillips[1], Mark Brunvand[2], Andy Chen[3], Oliver Press[4], James Essell[5], Annalisa Chiappella[6], Catherine Diefenbach[7], Surai Jones[8], Jamie Hirata[8], Ian Flinn[9]

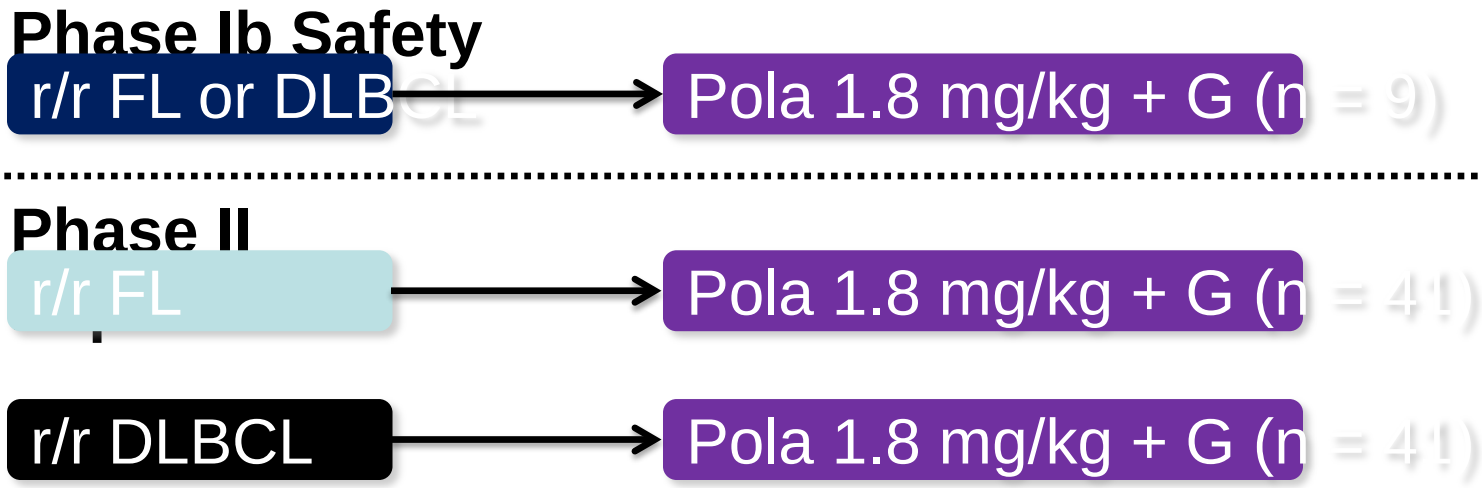
[1]Department of Internal Medicine, Division of Hematology and Oncology, University of Michigan Medical School, Ann Arbor, MI; [2]Colorado Blood Cancer Institute, Denver, CO; [3]Oregon Health and Science University, Portland, OR; [4]Fred Hutchinson Cancer Research Center, Seattle, WA;[5]Oncology Hematology Care, Inc, Cincinnati, OH; [6]Azienda Ospedaliera Universitaria Città della Salute e dellaScienza di Torino, Torino, Italy; [7]New York University School of Medicine/NYU Perlmutter Cancer Center, NewYork, NY; [8]Genentech, Inc., South San Francisco, CA; [9]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN

ROMULUS study

- Ongoing, multicenter, open-label phase Ib/II study in relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma (FL)
- Previously reported results showed clinical activity for polatuzumab vedotin (Pola) 2.4 mg/kg + rituximab (RTX) in patients with R/R DLBCL and FL treated until progression[1]
- Pooled analysis comparing Pola doses (2.4 mg/kg vs 1.8 mg/kg) and duration of treatment (8 cycles vs treatment to progression) suggested tolerability may be improved with 1.8 mg/kg and ≤ 8 cycles treatment[2]
- Here we present data from Pola 1.8 mg/kg + obinutuzumab (G) cohorts
- G is a glycoengineered type II anti-CD20 mAb with greater direct cell death induction and antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) activity than RTX[3,4]

1. Morschhauser ASH 2014; 2. Advani ASCO 2015; 3. Herter et al. 2013; 4. Mössner et al. 2010

ROMULUS Study Design (G-containing Cohorts)



- **Pola (1.8 mg/kg, Day 2 in cycle 1; Day 1 in subsequent cycles)**
- **G (1000 mg, Days 1, 8 and 15 in cycle 1; Day 1 in subsequent cycles)**
- **For total of eight 21-day cycles**

Primary endpoint

- Evaluation of antitumor activity based on PET-CT at end of treatment by Lugano criteria

Data as of 26 July 2016; median (range) time of follow up 4.6 (0.4–15.4) months for FL patients and 2.8 (0.1-11.8) months for DLBCL patients

PET-CT, positron emission tomography–computed tomography

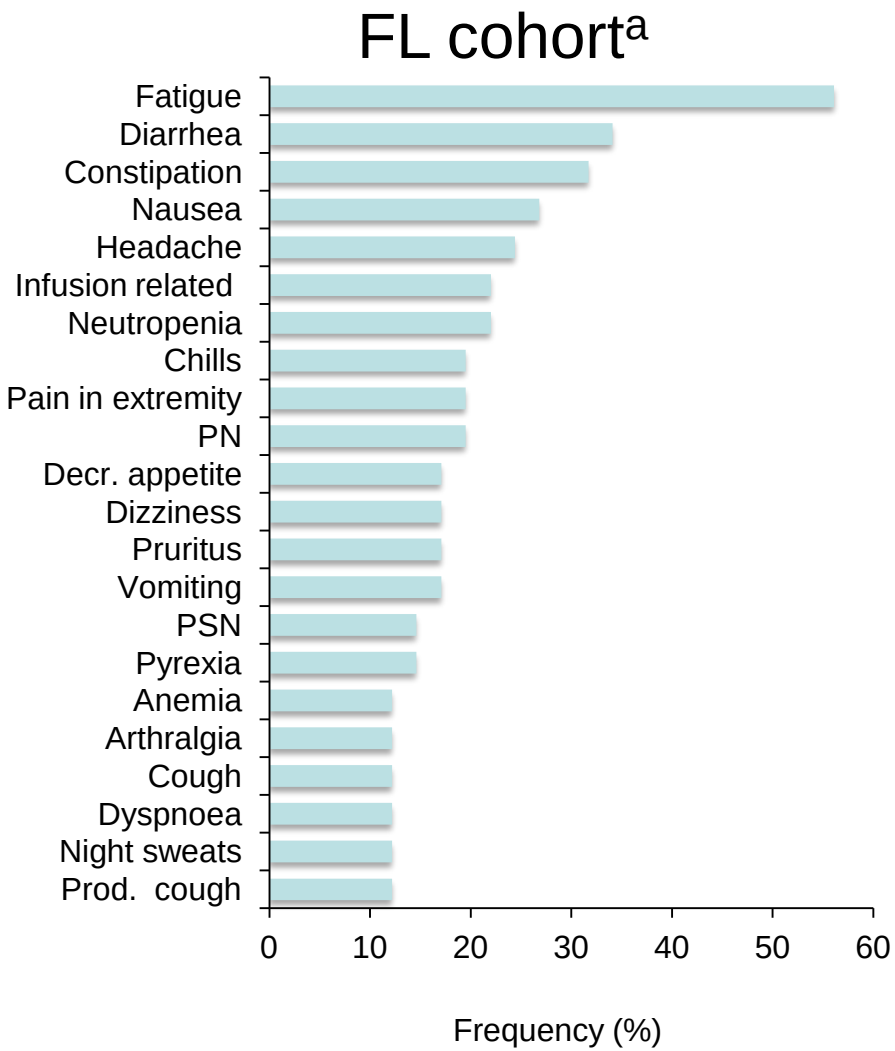
https://www.clinicaltrials.gov/ct2/show/NCT01691898.

Grade 3 or 4 Adverse Events (≥ 5% across cohorts)

	FL (N=41)	DLBCL (N=45)	Total (N=86)
Any grade 3-4 AEs, n (%)	20 (48.8)	26 (57.8)	46 (53.5)
Neutropenia	7 (17.1)	10 (22.2)	17 (19.8)
Infections	6 (14.6)	6 (13.3)	12 (14)
Anemia	3 (7.3)	3 (6.7)	6 (7)
Thrombocytopenia	1 (2.4)	4 (8.9)	5 (5.8)

- Neutropenia was most common grade 3–4 treatment emergent adverse event
- Febrile neutropenia reported in 2 patients with DLBCL
- No treatment discontinuations were for neutropenia
- No clear pattern for the infections, with some bacterial and some viral infections

Adverse Events in > 10% of patients



[a]Safety population (N=41), includes adverse events of all grades;
[b]Safety population (N=45), adverse events of all grades; Decr., decreased; PN, peripheral neuropathy; Prod., productive; PSN, peripheral sensory neuropathy

Frequency (%)

Data Cut-Off: 26 JUL 2016

Download this presentation: http://tago.ca/TPHI

Peripheral Neuropathy (per SMQ)[a]

	FL (N=41)	DLBCL (N=45)
History of prior PN, n (%)	15 (37)	16 (36)
Ongoing PN at Study Entry, n (%)[b]	13 (32)	16 (36)
All Grades, n (%)	17 (42)	11 (24)
Grade 2, n (%)	7 (17)	7 (16)
Median time to Onset, mo. (Q1–Q3)		
First PN Event	2.3 (0.7–2.8)	1.5 (1.3–4.1)
Grade 2 PN Event	3.9 (2.8–4.5)	2.1 (2.1–4.2)
Led to Pola Discontinuation, n (%)	2 (4.9)	2 (4.4)
Led to Pola Dose Reduction, n (%)	5 (12.2)	3 (6.7)

- At time of data cut off, 14 patients experienced Grade 2 PN
  - 11 ongoing (3 of 11 discontinued treatment)
  - 3 recovered within 19-23 days after dose reduction

[a]Peripheral neuropathy = System organ class term
[b]All Grade 1 per protocol eligibility criteria

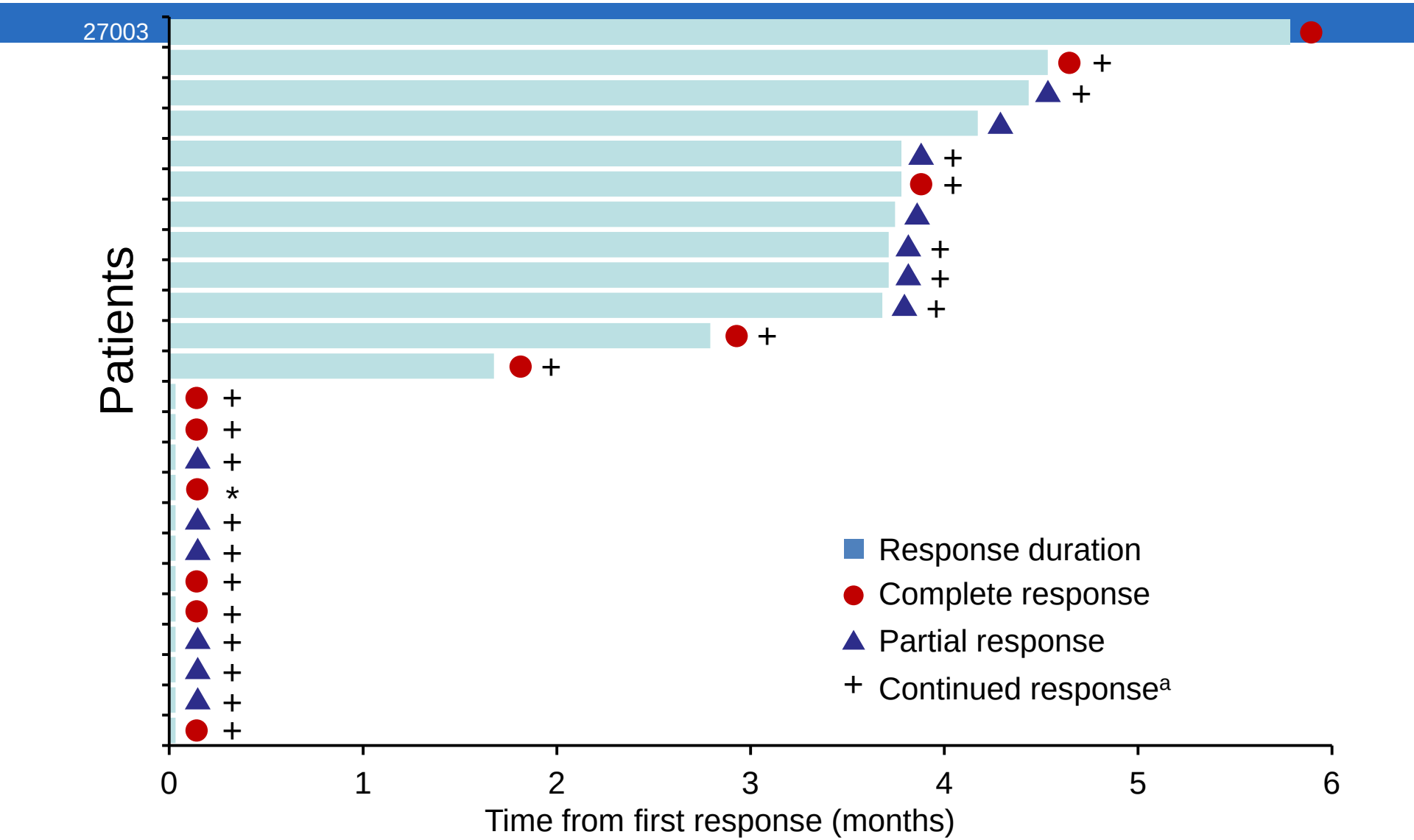
SMQ, Standardized MedDRA Queries

Investigator-Assessed Best Responses by Lugano Criteria[a]

	FL (N=35)	DLBCL (N=43)
Objective response, n (%)	**24 (69)**	**17 (40)**
Complete Response	11 (31)	9 (21)
[90% CI]	[19–47]	[11–34]
Partial Response	13 (37)	8 (19)
[90% CI]	[24–52]	[10–31]
Stable disease, n (%)	4 (11)	0
Progressive disease, n (%)	1 (3)	18 (42)
Unable to evaluate, n (%)	6 (17)[b]	8 (19)[c]

[a]Patients who received ≥1 dose of study treatment; assessment per Lugano Criteria (Cheson 2014)
[b]No Pola dose due to IRR from G, taken off-study (n=2); no PET assessment (n=2); taken off-study due to neutropenia before assessment (n=1); fatal pneumonia before assessment (n=1)
[c]Died before assessment (n=1); PD not by PET (n=4); not assessed due to hospitalization / taken off study (n=2); W/D consent / not dosed (n=1)

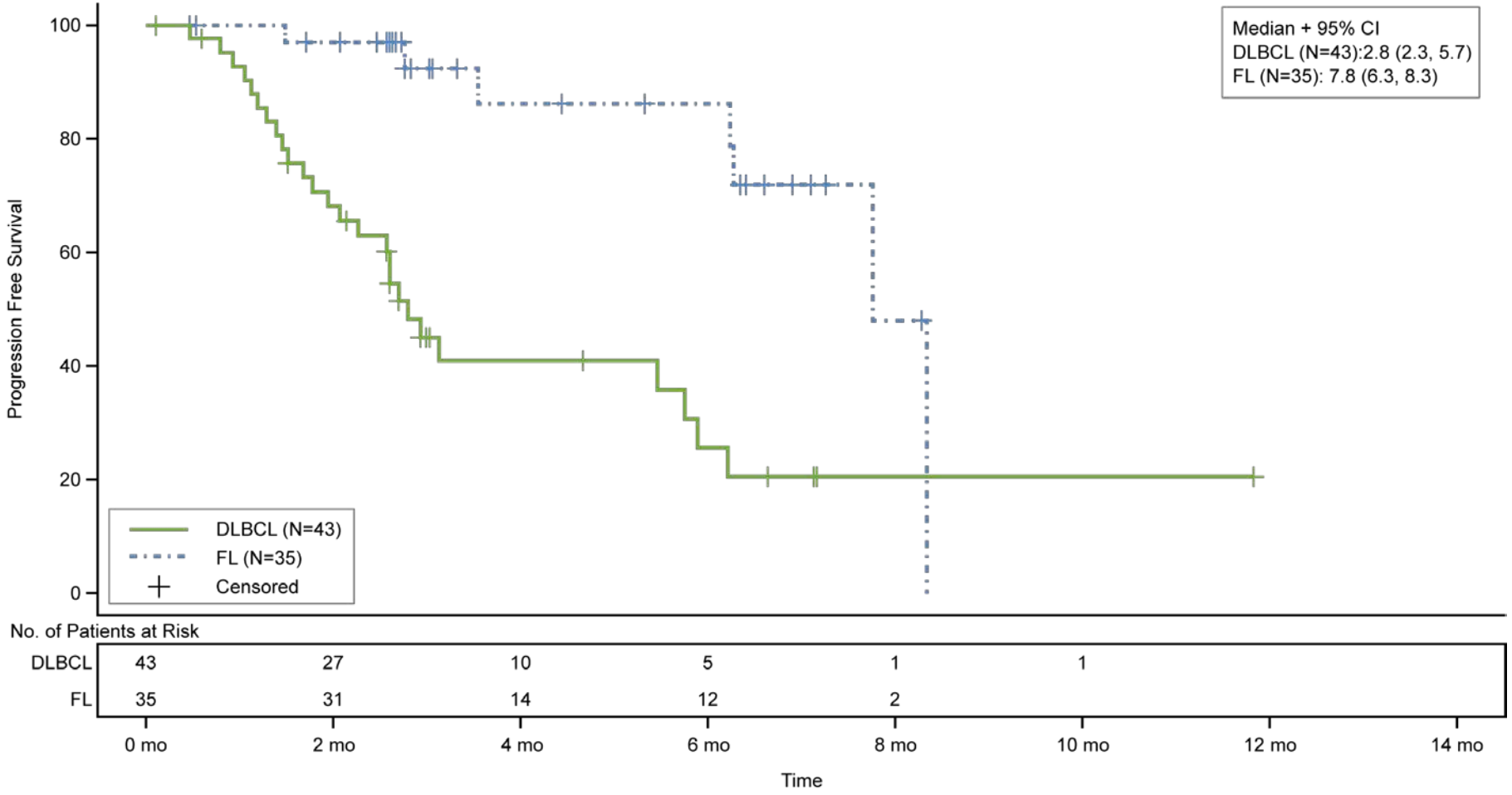
Duration of Response by PET-CT: FL G + Pola (1.8 mg/kg)



[a] Patients in continued response as of last follow up; those without + have progressed/relapsed;
*patient had only 1 assessment before being taken off study

Data Cut-Off: 26 JUL 2016

Progression Free Survival



Conclusions

- Early results from ongoing study show that novel combination of Pola (1.8 mg/kg with fixed duration of ≤ 8 cycles) plus G has acceptable safety profile
  - Most AEs were Grade 1–2
  - Peripheral neuropathy was not a major issue
- Evidence of clinical activity in r/r FL or DLBCL pts who were heavily pretreated or refractory to last prior regimen
  - Best objective response (by Lugano criteria) observed in 69% and 40% of FL and DLBCL pts
  - Median PFS of 7.8 months in FL patients and 3 months in DLBCL patients
- Pola 1.8 mg/kg + RTX/G in combination with chemo and non-chemo compounds are currently being explored in DLBCL and FL

Polatuzumab vedotin Combined with Bendamustine and Rituximab or Obinutuzumab in R/R FL or R/R DLBCL: Preliminary Results of a Phase Ib/II Study

Alex F. Herrera,[1] Matthew J. Matasar,[2] Sarit Assouline,[3] Manali Kamdar,[4] Amitkumar Mehta,[5] Isabelle Fleury,[6] Won Seog Kim,[7] Tae Min Kim,[8] Francesc Bosch,[9] John Radford,[10] Lilian Bu,[11] Wan-Jen Hong,[12] Laurie H. Sehn[13]

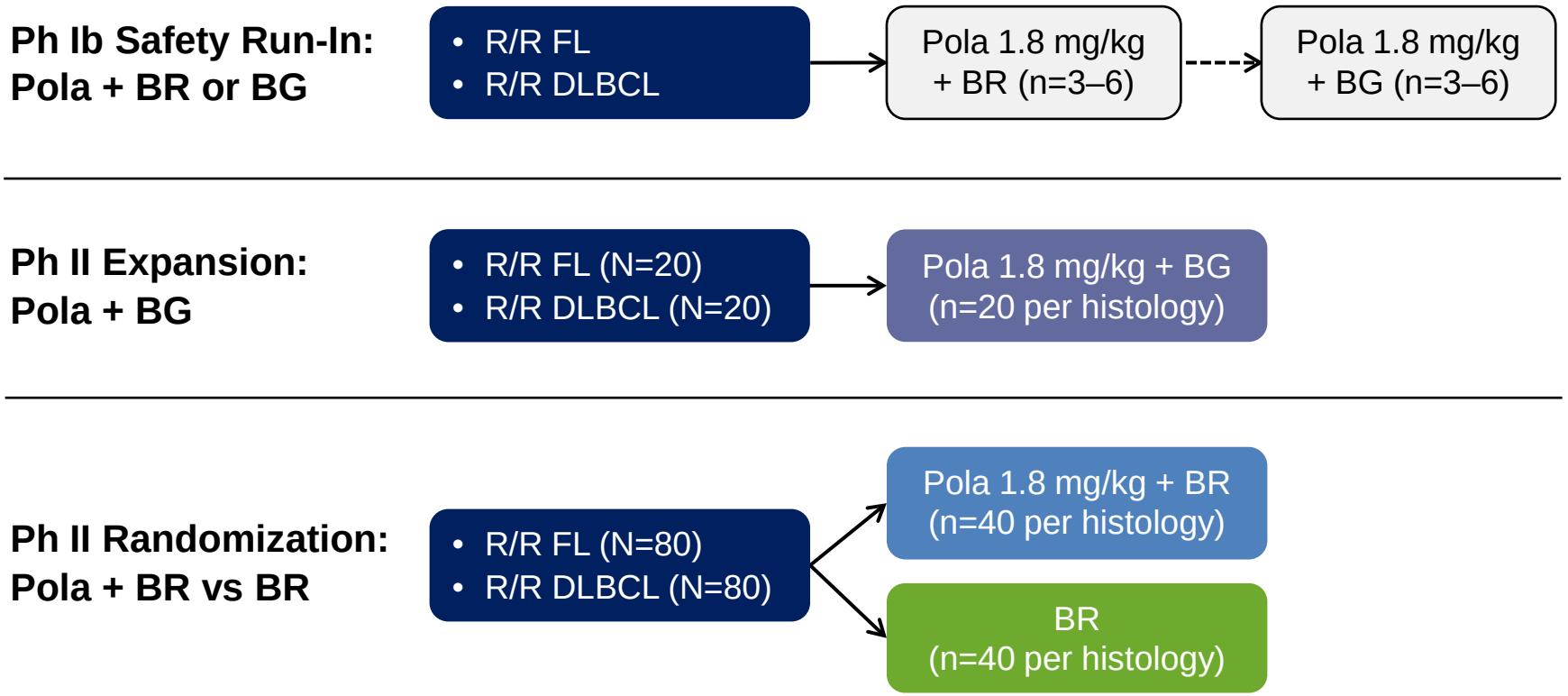
[1]City of Hope, Duarte, CA; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]Jewish General Hospital, Montreal, Canada; [4]University of Colorado, Denver, CO; [5]Department of Medicine, University of Birmingham, Birmingham, AL; [6]Department of Hematology, Maisonneuve-Rosemont Hospital and University of Montreal, Montreal, Canada; [7]Samsung Medical Center, Seoul, South Korea; [8]Seoul National University Hospital, Seoul, South Korea; [9]Hospital Universitari Vall d'Hebron, Barcelona, Spain;[10]The University of Manchester and the Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK; [11]Roche, Shanghai, China; [12]Genentech, Inc., South San Francisco, CA; [13] Centre for Lymphoid Cancer, BC Cancer Agency, Vancouver, Canada

Abstract #4194, Session 626, Monday, December 5th 2016, 6:00 – 8:00pm, Hall GH

GO29365: Introduction

- Patients with transplant ineligible R/R FL and R/R DLBCL have poor outcomes and more effective treatments are needed
- Polatuzumab vedotin (Pola) is an ADC that targets delivery of MMAE to cells expressing CD79b
- Pola combined with R has previously demonstrated promising response rates in patients with R/R FL and R/R DLBCL (ROMULUS)
- Preliminary data are presented from:
  - Phase Ib safety run-in for Pola + BR or BG in R/R FL and R/R DLBCL
  - Phase II expansion for Pola + BG in R/R DLBCL

Study Design

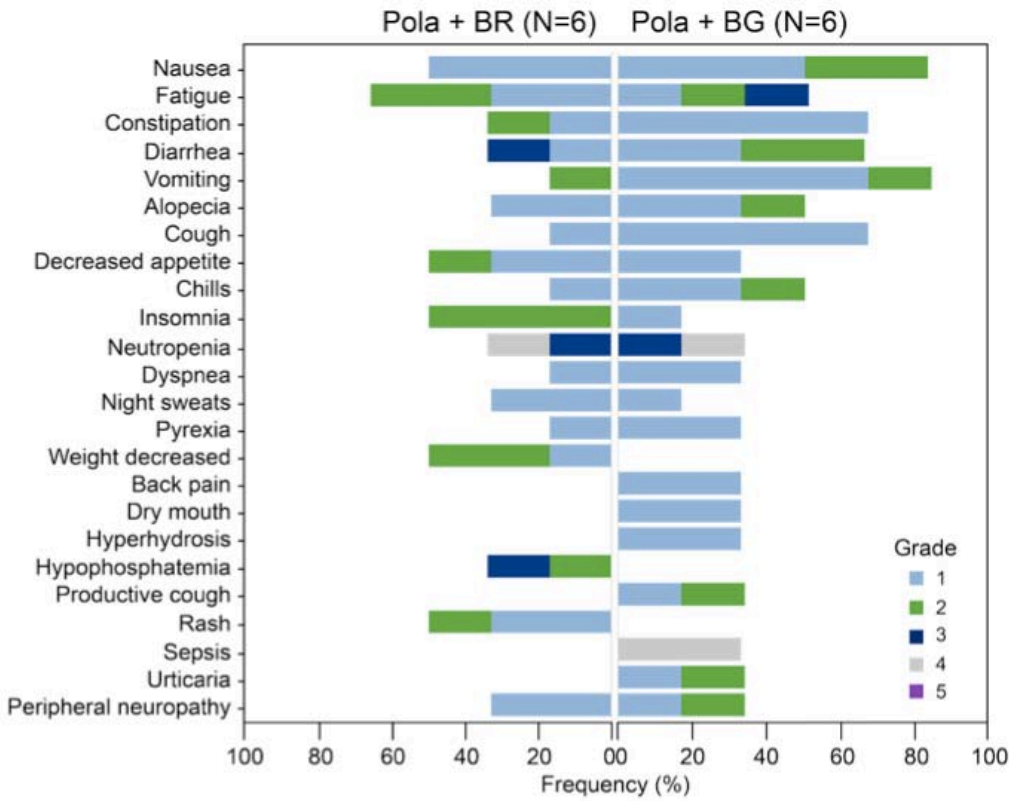


R (375 mg/m^2) D1 of each cycle or G (1000 mg) D1, D8, D15 in cycle 1 then D1 of each subsequent cycle plus B (90 mg/m^2) D2 and D3 in cycle 1 then D1 and D2 in each subsequent cycle. Pola (1.8 mg/kg) D2 of cycle 1, then D1 of each subsequent cycle. FL: Tx administered every 28 das x 6 cycles. DLBCL: Tx administered every 21 days x 6 cycles.

Baseline Characteristics

Characteristic	Phase Ib: Safety Run-In				Phase II: Expansion
	R/R FL		R/R DLBCL		R/R DLBCL
	Pola + BR (N=6)	Pola + BG (N=6)	Pola + BR (N=6)	Pola + BG (N=6)	Pola + BG (N=20)
Median age (range)	68 (54–73)	63.5 (42–73)	65 (58–79)	71 (53–84)	65.5 (30–86)
ECOG PS, n (%) **0** **1** **2**	 3 (50) 3 (50) 0	 3 (50) 3 (50) 0	 2 (33) 4 (67) 0	 1 (17) 4 (67) 1 (17)	 5 (21) 12 (57) 3 (14)
Median # of prior therapies (range)	2 (1–3)	3 (1–3)	2 (1–2)	2 (1–4)	3 (1–5)
Refractory to last prior tx n, (%)	3 (50)	2 (33)	5 (83)	4 (67)	17 (85)
FLIPI1, n (%) **Low (0–1)** **Intermediate (2)** **High (3–5)**	 0 4 (67) 2 (33)	 1 (17) 1 (17) 4 (67)	N/A	N/A	N/A
FLIPI2, n (%) **Low (0–1)** **Intermediate (2)** **High (3–5)**	 0 4 (67) 2 (33)	 1 (17) 2 (33) 3 (50)	N/A	N/A	N/A
IPI, n (%) **Low (0–1)** **Low-intermediate (2)** **High-intermediate/high (3–5)**	N/A	N/A	 1 (17) 4 (67) 1 (17)	 1 (17) 1 (17) 4 (67)	 3 (15) 2 (10) 15 (75)

FL: Most Common Adverse Events (> 20%)



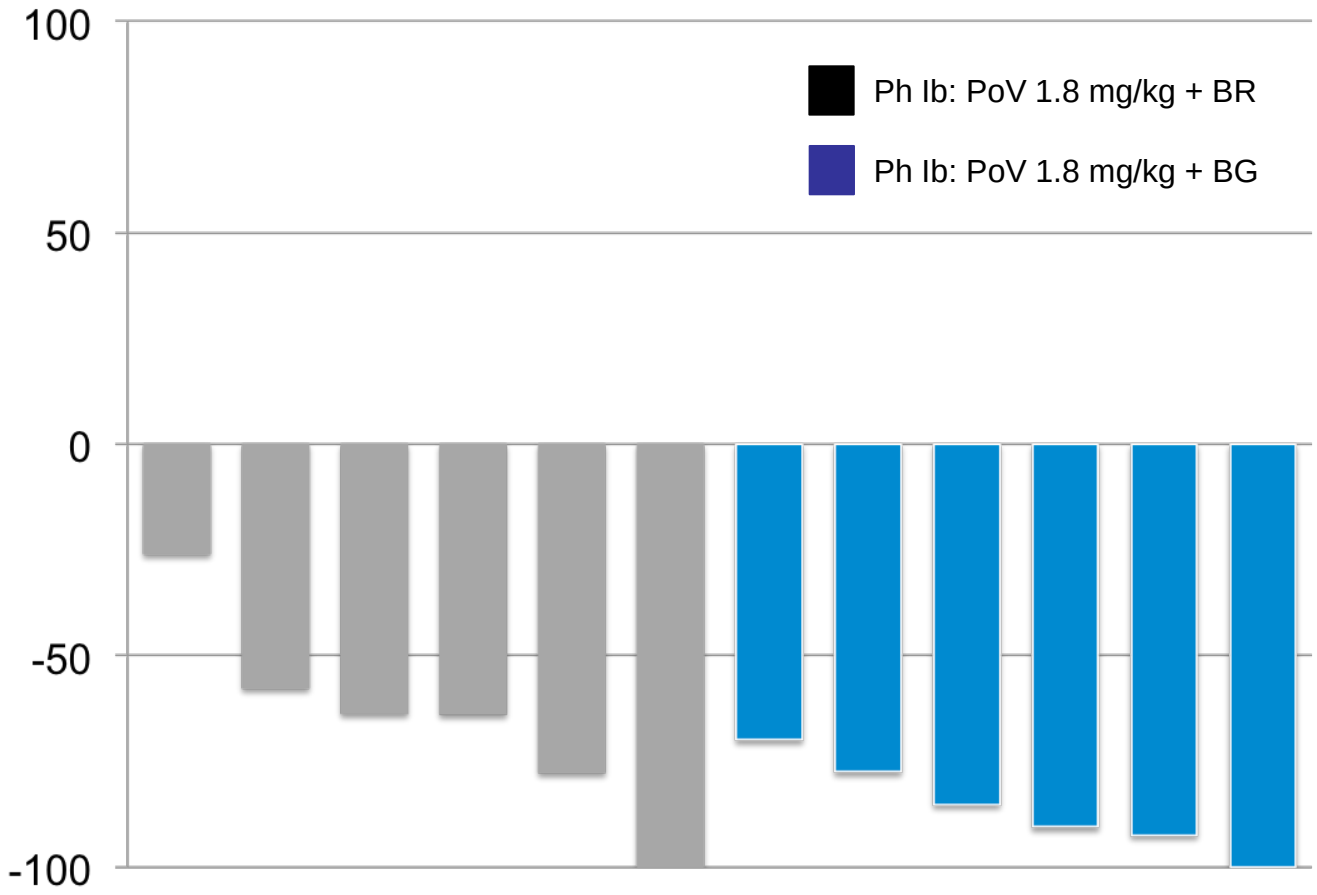
- GI toxicity and fatigue were the most common AEs, but majority were low grade and manageable
- Most common Grade 3/4 AEs were neutropenia, sepsis and thrombocytopenia
- AEs led to discontinuation of bendamustine in 1 patients due to Grade 3 thrombocytopenia
- Treatment-emergent peripheral neuropathy was reported in 4 of 12 (33%) patients and did not lead to study treatment interruption or discontinuation

Best Objective Response by PET/CT

	Pola + BR	Pola + BG	Pola + BR/BG
R/R FL	N=6	N=6	N=12
ORR, n (%)	6 (100)	6 (100)	12 (100)
CR	5 (83)	5 (83)	10 (83)
PR	1 (17)	1 (17)	2 (17)
R/R DLBCL	N=6	N=26**	N=32
ORR, n (%)	3 (50)	16 (61)	19 (59)
CR	2 (33)	10 (38)	12 (39)
PR	1 (17)	6 (23)	7 (22)***
SD, n (%)	0	2 (8)	2 (6)
PD, n (%)	2 (33)	4 (15)	6 (19)
Missing or UE, n (%)	1 (17)	4 (15)	5 (16)

*Response assessment according to modified Lugano 2014 criteria (if available);
**Includes Phase Ib and Phase II expansion pts who received Pola + BG;
***1 pt achieved a CMR by PET scan but did not have a confirmatory bone marrow biopsy

FL: Percent Change in SPD at Best Response Assessment



Conclusions

- Pola 1.8 mg/kg combined with BR or BG has an acceptable safety profile in pts with R/R FL and R/R DLBCL
- Preliminary evaluation of efficacy showed promising responses in heavily pre-treated R/R FL and R/R DLBCL pts; data on pts with longest follow-up suggest that responses can be durable
- Enrollment has completed for the Phase II expansion evaluating Pola + BG in R/R FL (N=20) and Phase II randomization portions of the study comparing Pola + BR vs BR in R/R FL (N=80) and R/R DLBCL (N=80). Results from these arms of the study will be presented at a future meeting

Table 3. Tumor microenvironment targets and potential therapies

Category	Target	Potential Agents
Immunomodulatory agents	Multiple	Lenalidomide
Immune checkpoint inhibitors	PD-1	Pidilizumab
	PD-1	Nivolumab
	PD-1	Pembrolizumab
	PD-1	MEDI-0680
	PD-L1	Durvalumab
	PD-L1	Atezolizumab
	CTLA-4	Ipilimumab
Other immunomodulatory agents	CD47	TTI-621
	CD137	Urelumab
	KIR	Lirilumab

Original Article

PI3Kδ Inhibition by Idelalisib in Patients with Relapsed Indolent Lymphoma

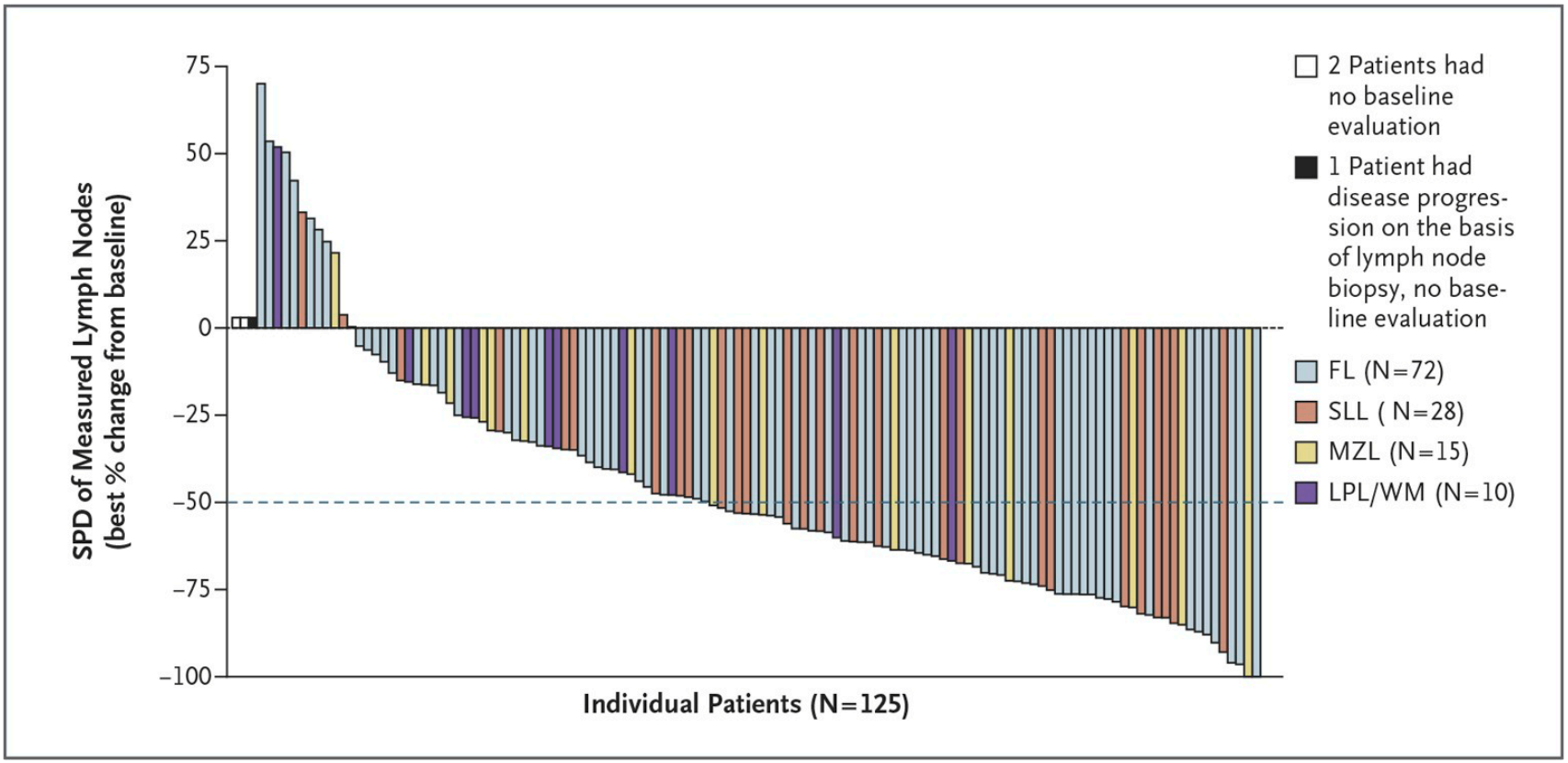
Ajay K. Gopal, M.D., Brad S. Kahl, M.D., Sven de Vos, M.D., Ph.D., Nina D. Wagner-Johnston, M.D., Stephen J. Schuster, M.D., Wojciech J. Jurczak, M.D., Ph.D., Ian W. Flinn, M.D., Ph.D., Christopher R. Flowers, M.D., Peter Martin, M.D., Andreas Viardot, M.D., Kristie A. Blum, M.D., Andre H. Goy, M.D., Andrew J. Davies, M.R.C.P., Ph.D., Pier Luigi Zinzani, M.D., Ph.D., Martin Dreyling, M.D., Dave Johnson, B.S., Langdon L. Miller, M.D., Leanne Holes, M.B.A., Daniel Li, Ph.D., Roger D. Dansey, M.D., Wayne R. Godfrey, M.D., and Gilles A. Salles, M.D., Ph.D.

N Engl J Med
Volume 370(11):1008-1018
March 13, 2014

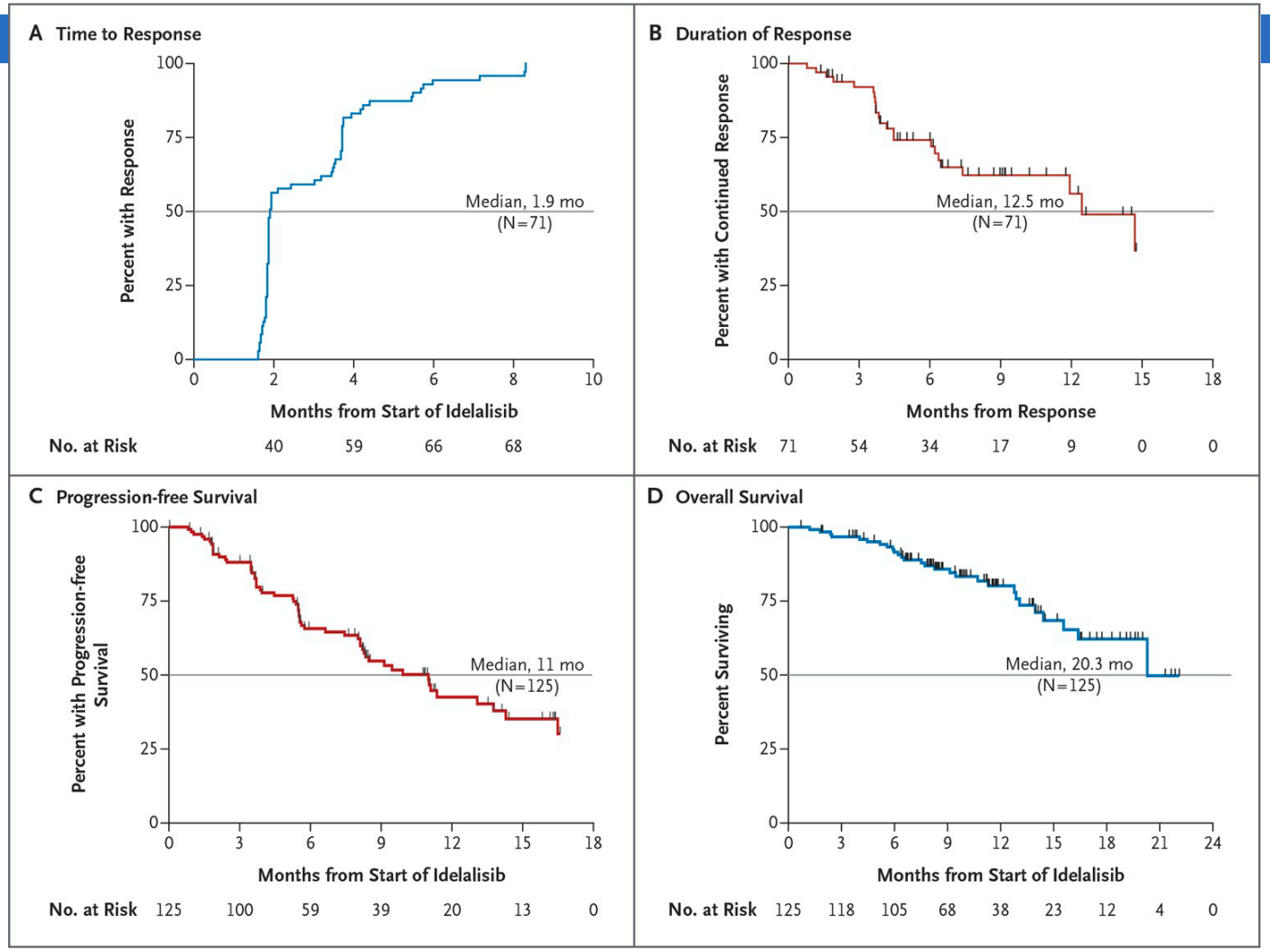
Study Overview

- **Idelalisib, which inhibits PI3K isoform delta, produced antitumor responses in nearly 60% of pretreated patients with indolent non-Hodgkin's lymphomas.**
- **Responses lasted a median of 11 months.**
- **Grade 3 or higher toxic effects were seen in 13 to 27% of patients.**

Best Overall Response.



Kaplan–Meier Curves for Secondary End Points.



Adverse Events during Treatment.

Table 2. Adverse Events during Treatment.*

Event or Abnormality	Grade	
	Any	≥3
	no. (%)	
Adverse event	103 (82)	68 (54)
Diarrhea	54 (43)	16 (13)
Nausea	37 (30)	2 (2)
Fatigue	37 (30)	2 (2)
Cough	36 (29)	0
Pyrexia	35 (28)	2 (2)
Decreased appetite	22 (18)	1 (1)
Dyspnea	22 (18)	4 (3)
Abdominal pain	20 (16)	3 (2)
Vomiting	19 (15)	3 (2)
Upper respiratory tract infection	18 (14)	0
Weight decreased	17 (14)	0
Rash	16 (13)	2 (2)
Asthenia	14 (11)	3 (2)
Night sweats	14 (11)	0
Pneumonia	14 (11)	9 (7)
Peripheral edema	13 (10)	3 (2)
Headache	13 (10)	1 (1)
Hematopoietic laboratory abnormality		
Decreased neutrophils	70 (56)	34 (27)
Decreased hemoglobin	35 (28)	2 (2)
Decreased platelets	32 (26)	8 (6)
Chemical laboratory abnormality		
Increased ALT	59 (47)	16 (13)
Increased AST	44 (35)	10 (8)
Increased alkaline phosphatase	28 (22)	0
Increased bilirubin	13 (10)	0

* Included are adverse events and selected laboratory abnormalities that occurred during treatment in 10% or more of the 125 patients in the study, regardless of whether the event was related to the study drug. Adverse events that occurred during treatment are classified according to the preferred term in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 15.1. Patients who had multiple events within the same preferred-term category were counted once in that category. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

Gopal AK et al. N Engl J Med 2014;370:1008-1018

Conclusions

- **In this single-group study, idelalisib showed antitumor activity with an acceptable safety profile in patients with indolent non-Hodgkin's lymphoma who had received extensive prior treatment.**

- Gilead Sciences has stopped six clinical trials using its drug idelalisib (*Zydelig*) in combination with other cancer drugs on account of a higher rate of serious adverse events, including death, the US Food and Drug Administration (FDA) said today.
- The announcement follows the recent decision by European Union (EU) regulators to review idelalisib in response to an increased rate of serious adverse events such as death in three clinical trials that combined the Gilead Sciences drug with other cancer drugs.
- Idelalisib is approved in the United States to treat relapsed chronic lymphocytic leukemia (CLL) in combination with rituximab; relapsed follicular B-cell non-Hodgkin lymphoma, which is classified as indolent; and relapsed small lymphocytic lymphoma. The agency cautioned today that clinicians should not prescribe the drug for patients with previously untreated CLL.
- The six clinical trials in question involved small lymphocytic lymphoma, CLL, and indolent non-Hodgkin lymphoma, the FDA said. The latter two cancers figured into the three trials scrutinized by EU regulators.
- The FDA said it is reviewing the findings of the six clinical trials stopped by Gilead Sciences.
- More information about today's FDA announcement is available on the agency website.

Table 3. Tumor microenvironment targets and potential therapies

Category	Target	Potential Agents
Immunomodulatory agents	Multiple	Lenalidomide
Immune checkpoint inhibitors	PD-1	Pidilizumab
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	PD-L1	Durvalumab
	PD-L1	Atezolizumab
	CTLA-4	Ipilimumab
Other immunomodulatory agents	CD47	TTI-621
	CD137	Urelumab
	KIR	Lirilumab

SAKK
WE BRING PROGRESS TO CANCER CARE

Nordic Lymphoma Group
Dedicated to promoting research in treatment, biology and epidemiology of malignant lymphomas in the Nordic countries
NLG

Rituximab Plus Lenalidomide Versus Rituximab Monotherapy in Untreated Follicular Lymphoma Patients in Need of Therapy

First Analysis of Survival Endpoints of the Randomized Phase-2 Trial SAKK 35/10

Eva Kimby, Stephanie Rondeau, Anna Vanazzi, Bjorn Ostenstad, Ulrich JM Mey, Daniel Rauch, Björn E Wahlin, Felicitas Hitz, Micaela Hernberg, Ann-Sofie Johansson, Peter de Nully Brown, Hans Hagberg, Andrés JM Ferreri, Andreas Lohri, Urban Novak, Thilo Zander, Hanne Bersvendsen, Mario Bargetzi, Walter Mingrone, Fatime Krasniqi, Stephan Dirnhofer, Hanne Hawle, Simona Berardi, Michele Ghielmini and Emanuele Zucca

Background and rationale

- Long-term remissions with rituximab in patients with follicular lymphoma (FL) in previous trials from the SAKK[1,2] and NLG[3]
- OS similar to immunochemotherapy
- Promising results from single-arm studies of rituximab plus lenalidomide[4]

[1] **Martinelli et al. J Clin Oncol. 2010**
[2] **Taverna et al. J Clin Oncol. 2016**
[3] **Kimby et al. Leuk Lymphoma. 2008, 2015**
[4] **Fowler et al. Lancet Oncol. 2014**

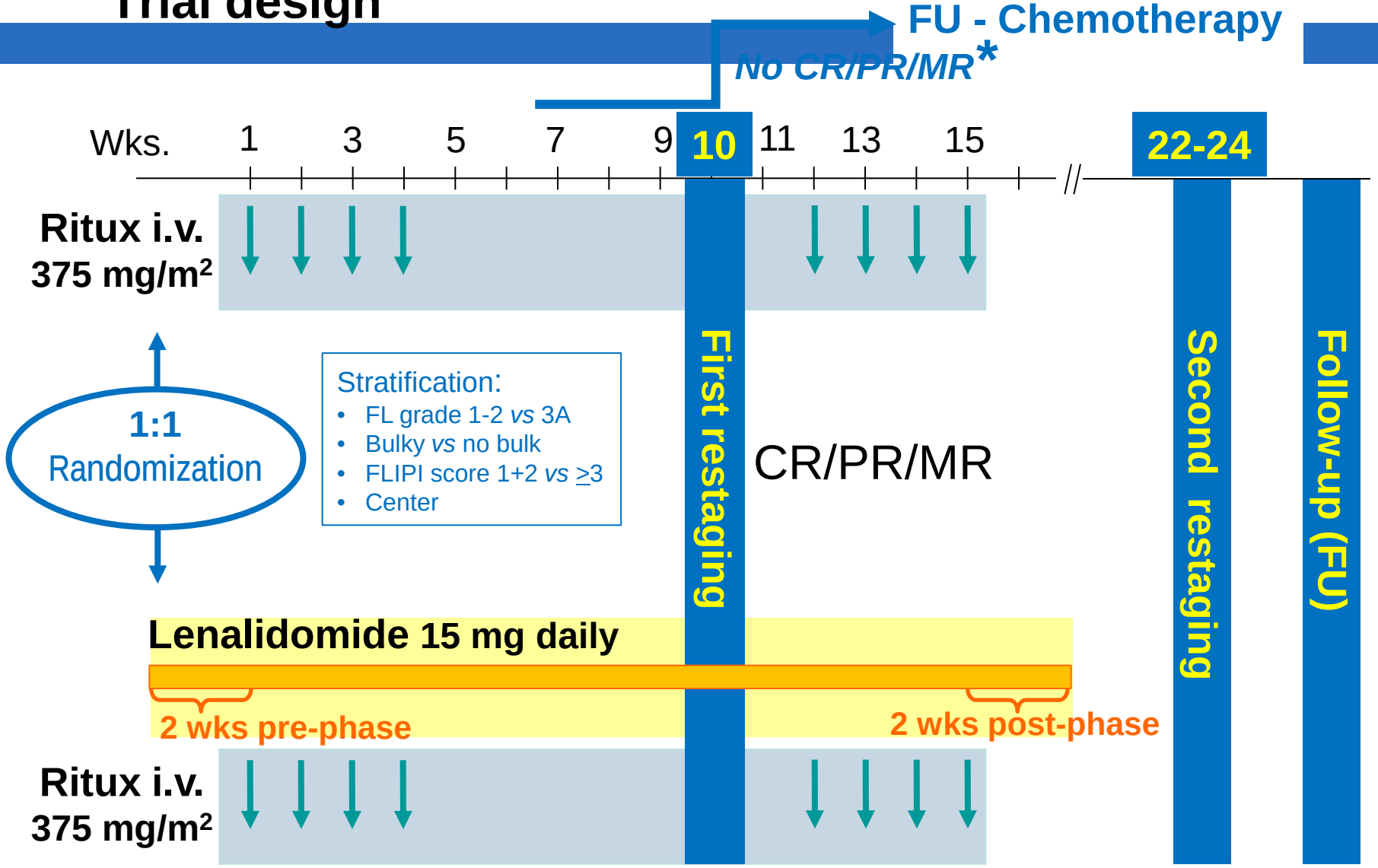
Objective of SAKK 35/10

- A randomized phase-2 study in FL patients
  - Previously untreated and requiring therapy

- Comparing the activity of
  - **Rituximab** + **lenalidomide** (**RL**)

    versus
  - **Rituximab** (**R**) **monotherapy**

Trial design



*MR >25% decrease in SPD

Main inclusion criteria

- Histologically confirmed FL grade 1, 2, 3A
- No previous systemic therapy
- In need of systemic therapy

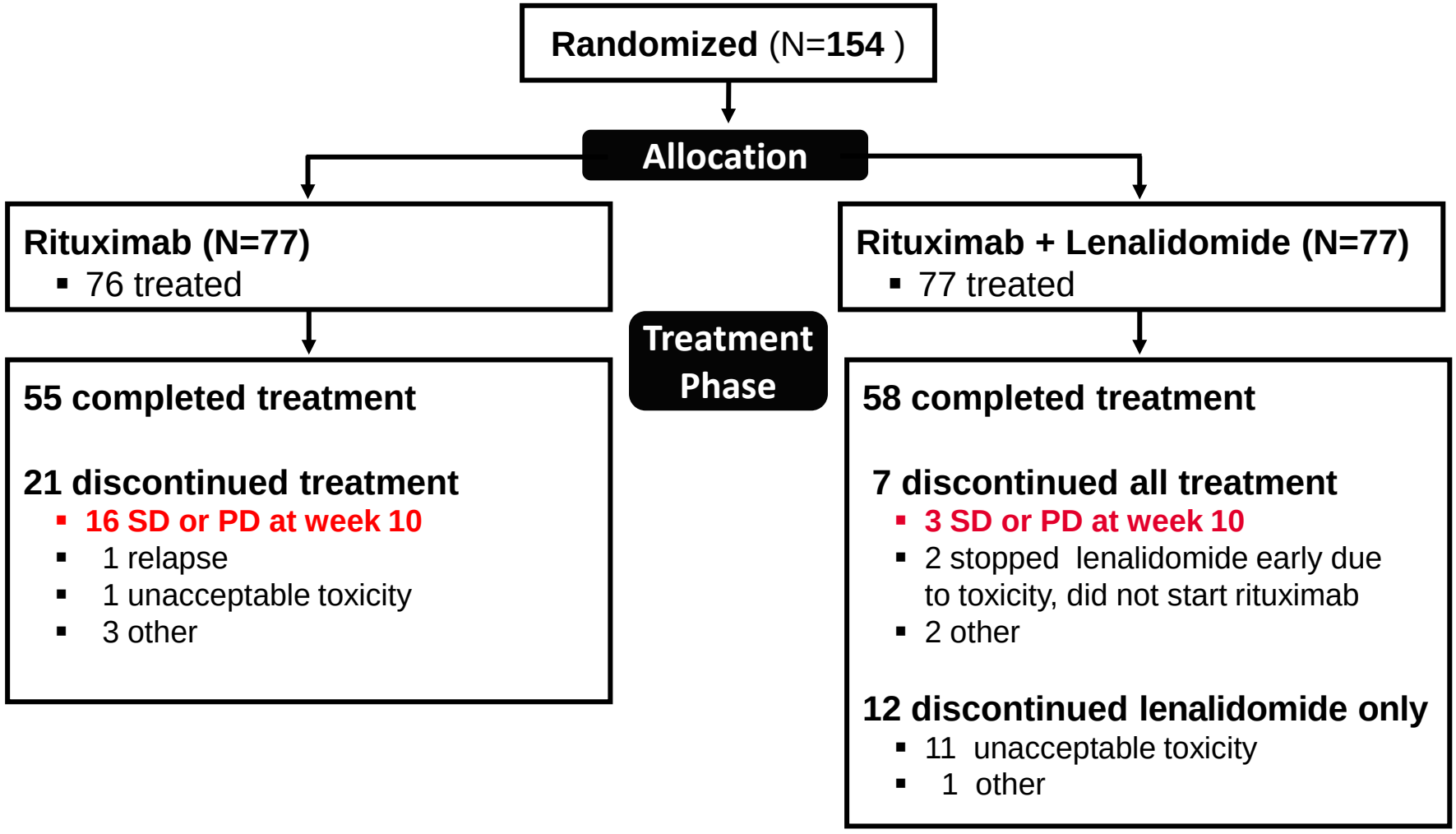
At least one of the following:

- Symptomatic enlarged LN, spleen or other FL manifestations
- Clinically significant progression ≥ 6 months
- Bulky disease ≥ 6 cm in long diameter
- Clinically significant progressive anemia/thrombocytopenia due to FL (Hb <100 g/L and/or PLT <100 x 10^9/L)
- B-symptoms

Patient characteristics

	Rituximab (N=77)	Rituximab + Lenalidomide (N=77)
Sex		
- **Female**	40 (52%)	42 (55%)
- **Male**	37 (48%)	35 (45%)
Age (years)		
Median (Min, Max)	**63** (29, 85)	**61** (26, 80)
Stage		
- **II**	**8** (10%)	**11** (14%)
- **III**	**29** (38%)	**29** (38%)
- **IV**	**40** (52%)	**37** (48%)
FLIPI		
- **Low risk**	**15** (19%)	**21** (27%)
- **Intermediate risk**	**26** (34%)	**20** (26%)
- **High risk**	**36** (47%)	**36** (47%)

Consort diagram



Results

Assessment of **primary endpoint** [CR/CRu] at week 23

- Addition of lenalidomide to rituximab results in a significantly higher CR/CRu rate (IRR: 61% vs 36%) with increased but manageable toxicity

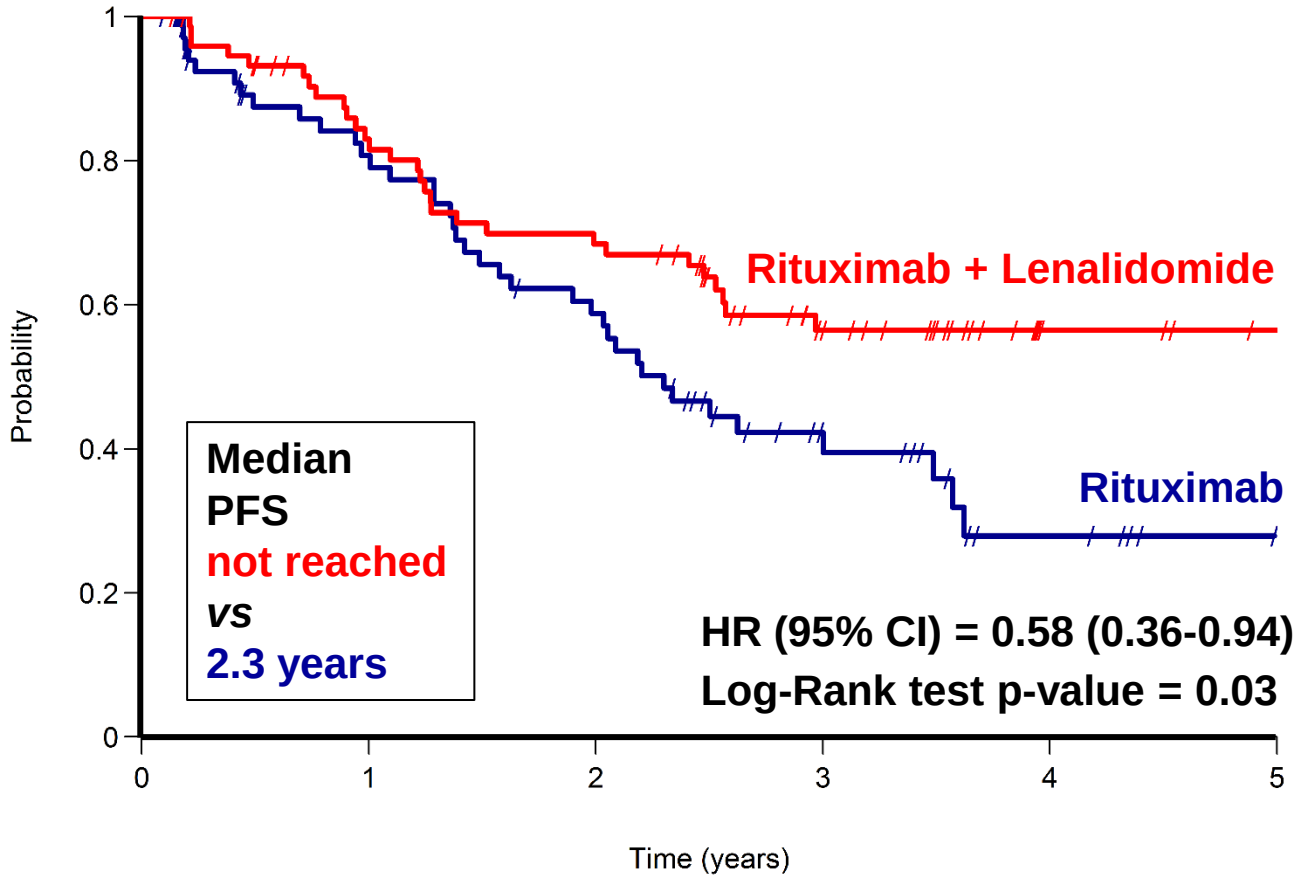
Kimby et al. Blood 2014.124 (21):799, Zucca et al. Hematol Oncol 2015. 33 (s1):105

Now the **analysis of secondary endpoints**

at a median follow-up of 3.5 years

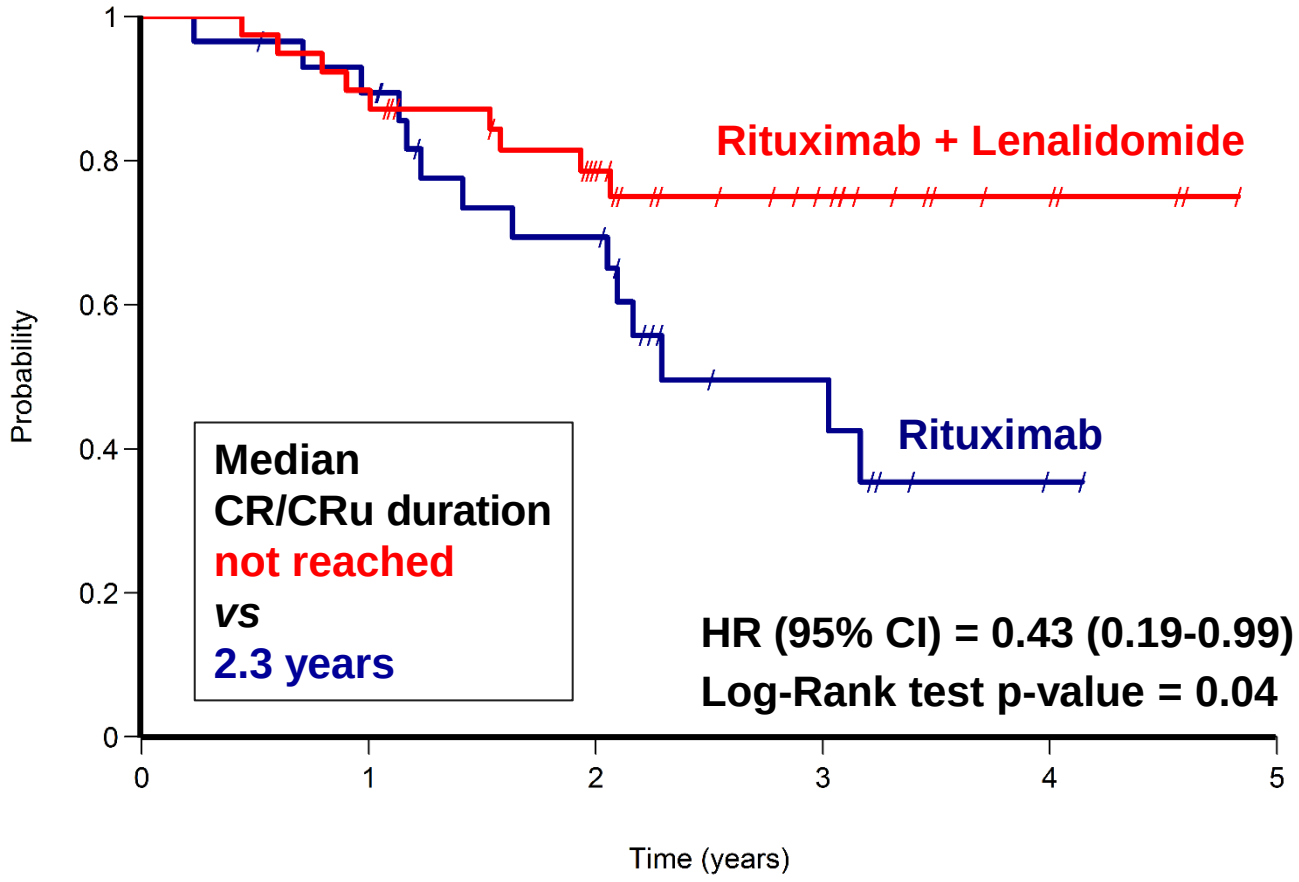
- Progression-free survival (PFS)
- Time to next anti-lymphoma treatment (TTNT)
- CR/CRu duration
- CR/CRu rate at 30 months (CR_{30})
- Overall survival (OS)

Progression-free survival



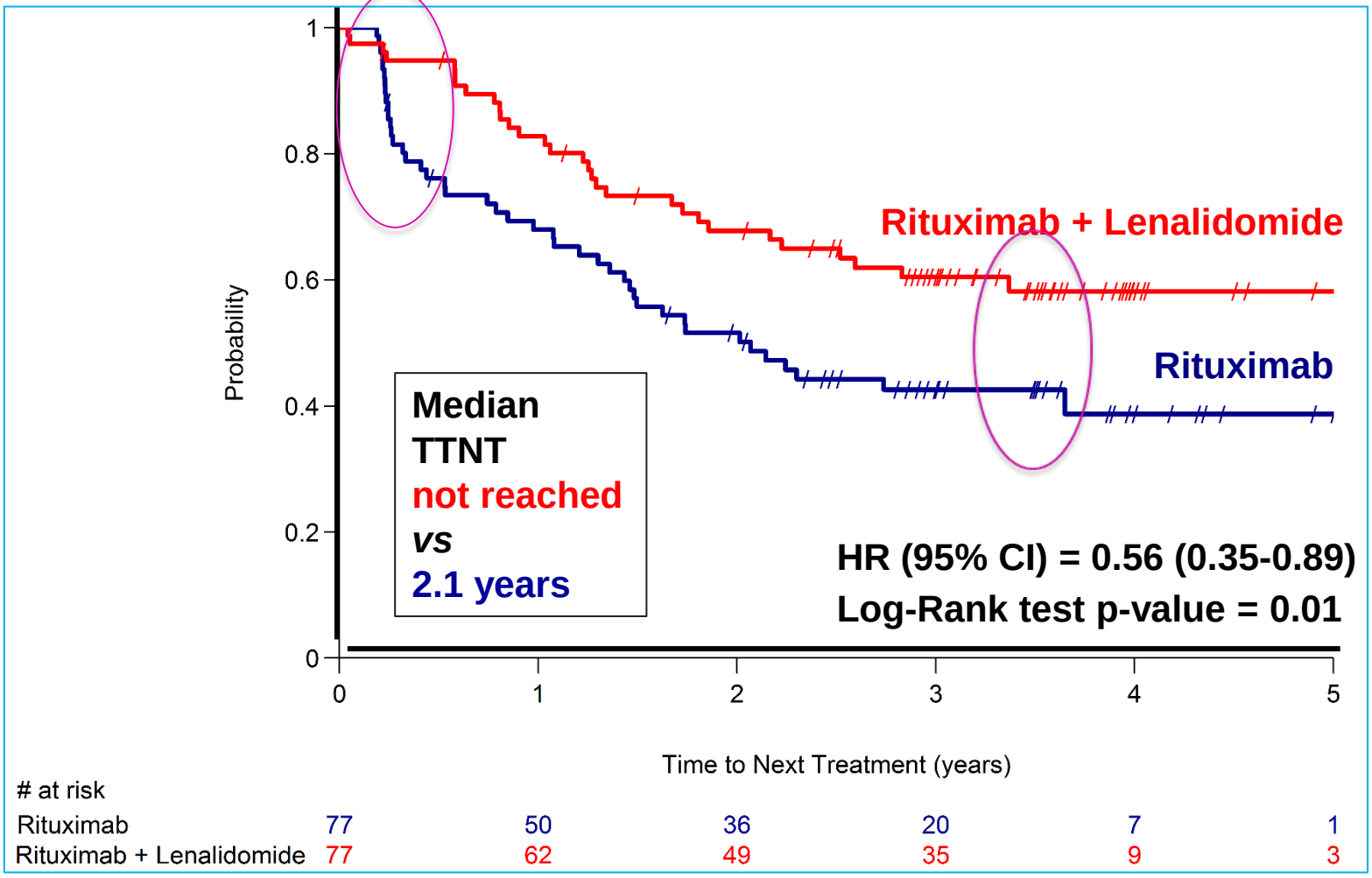
# at risk						
Rituximab	77	48	34	15	5	0
Rituximab + Lenalidomide	77	57	47	26	6	3

CR/CRu duration



# at risk						
Rituximab	30	25	17	7	1	0
Rituximab + Lenalidomide	43	35	24	13	5	0

Time to new therapy



Conclusions

Addition of lenalidomide to rituximab

- Increased the CR/CRu rate significantly at week 23 (primary endpoint).
- A significant difference seen also in CR_{30} and response duration.
- Both PFS and TTNT were significantly prolonged.
- The good OS in both arms suggests that chemotherapy-free strategies should be further explored

Table 3. Tumor microenvironment targets and potential therapies

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Immune checkpoint inhibitors	PD-1	Pidilizumab
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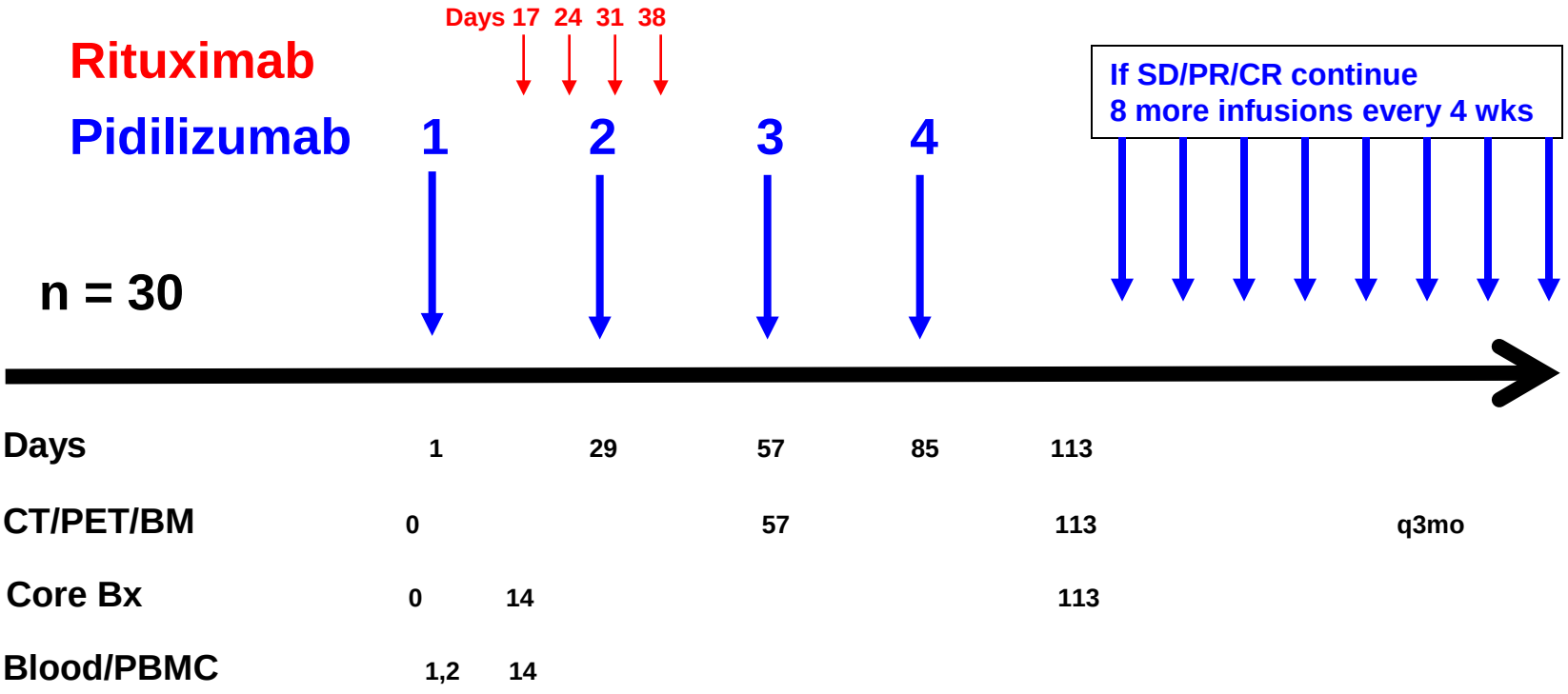
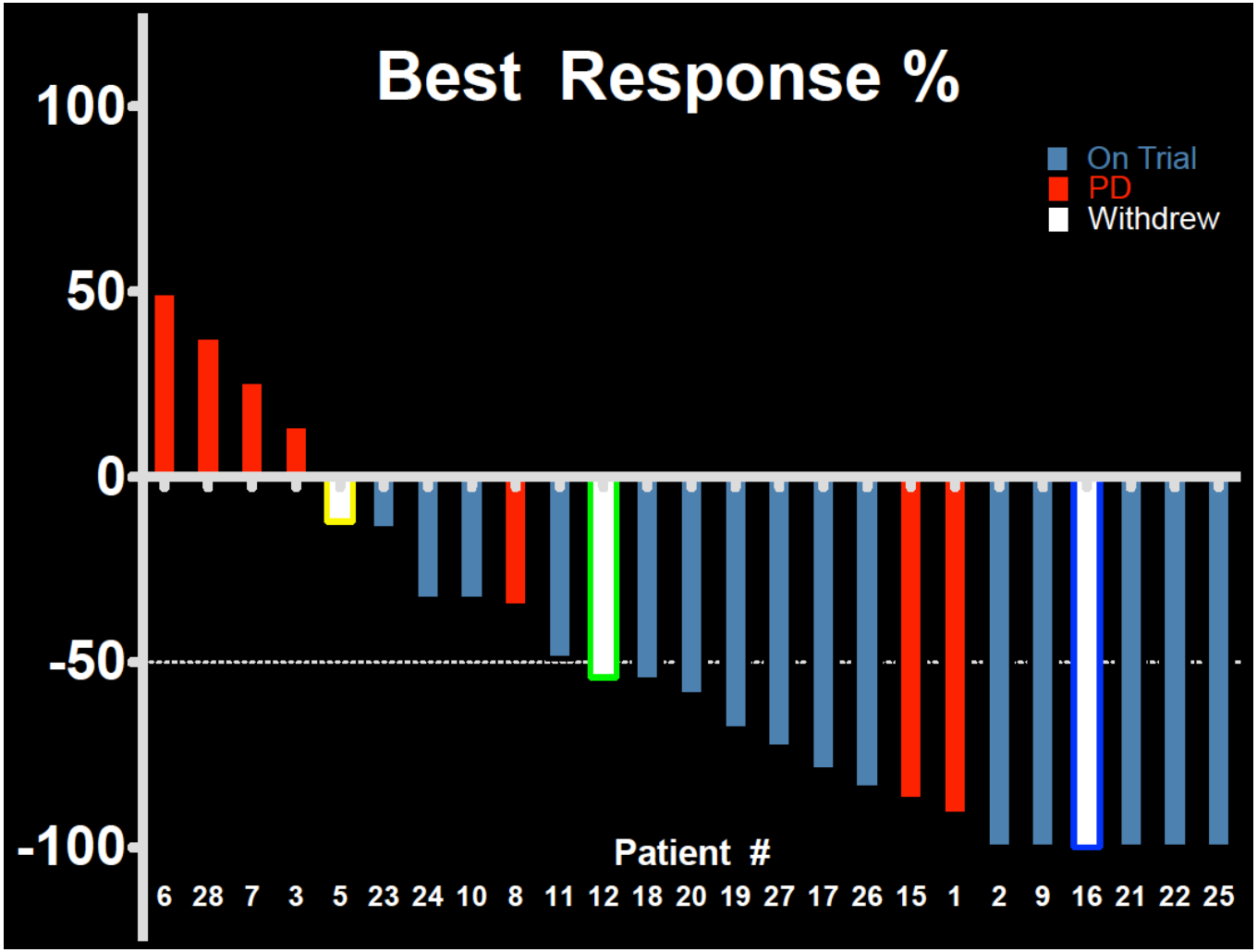
	PD-1	Pembrolizumab
	PD-1	MEDI-0680
	PD-L1	Durvalumab
	PD-L1	Atezolizumab
	CTLA-4	Ipilimumab
Other immunomodulatory agents	CD47	TTI-621
	CD137	Urelumab
	KIR	Lirilumab

Pidilizumab (anti-PD1) + rituximab in relapsed follicular lymphoma (FL) patients



Pidilizumab (CT-011) – iv infusion at 3.0 mg/kg/cycle q4 weeks for up to 12 cycles **Rituximab** - iv infusion at a dose of 375 mg/m^2 weekly for 4 weeks

Pidilizumab + Rituximab – Best response



Summary of clinical results

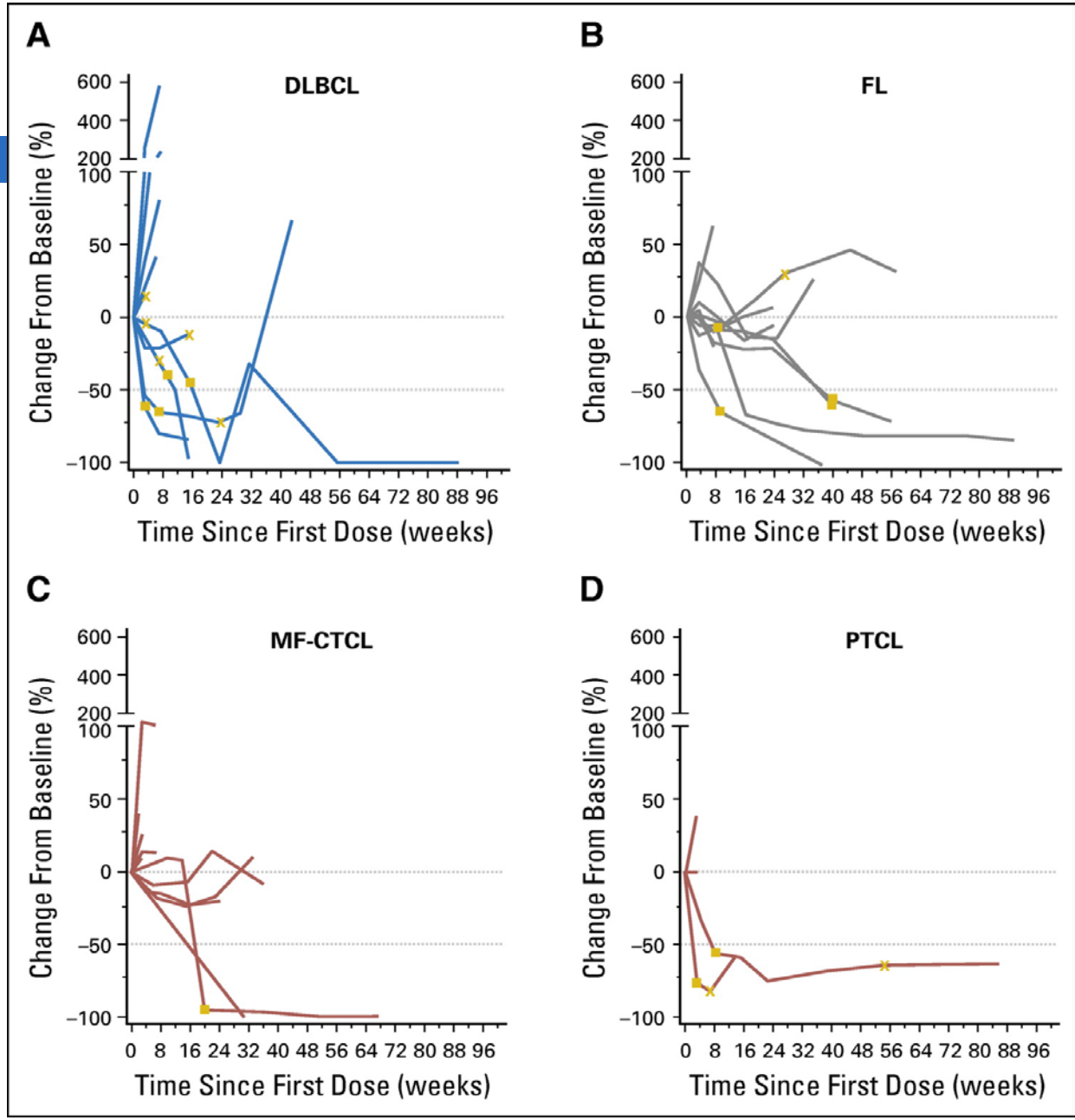
- Pidilizumab + Rituximab therapy is well tolerated, there were no grade/4 or autoimmune adverse events noted.
- Highly effective in relapsed, rituximab-sensitive follicular lymphoma with an ORR of 66% and CR of 52%
- Compares favorably to previous rituximab retreatment data (e.g. ORR of 40% & CR of 11% - Davis et al, *J Clin Oncol* 2000)

Westin et al. [Neelapu, Kwak] Lancet Oncol, 2014

Table 3. Tumor microenvironment targets and potential therapies

Category	Target	Potential Agents
Immunomodulatory agents	Multiple	Lenalidomide
Immune checkpoint inhibitors	PD-1	Pidilizumab
	PD-1	Nivolumab
	PD-1	Pembrolizumab
	PD-1	MEDI-0680
	PD-L1	Durvalumab
	PD-L1	Atezolizumab
	CTLA-4	Ipilimumab
Other immunomodulatory agents	CD47	TTI-621
	CD137	Urelumab
	KIR	Lirilumab

Nivolumab in NHL



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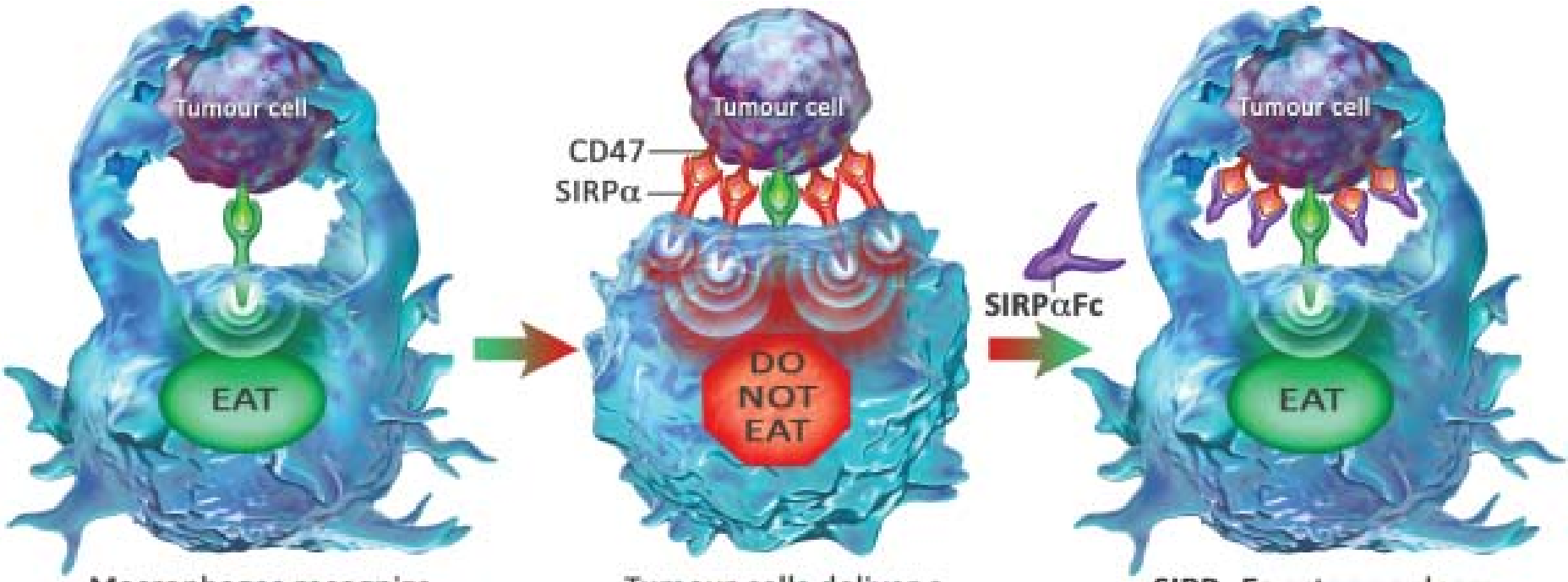
	CD137	Urelumab
	KIR	Lirilumab

CD47: Don't Eat Me!



Macrophages recognize pro-phagocytic (EAT) signals on tumour cells

Tumour cells deliver a DO NOT EAT signal through CD47 binding to SIRPα

SIRPαFc acts as a decoy receptor blocking the inhibitory CD47 signal

Table 2. Key intracellular pathway and epigenetic targets and potential therapies

Category	Target	Potential agents
BTK inhibitors	BTK	Ibrutinib
	BTK	Acalabrutinib
	BTK	ONO/GS-4059
	BTK	BGB-3111
	BTK	CC-292
PI3K inhibitors	PI3Kδ	Idelalisib
	PI3K δ and γ	Duvelisib
	PI3K δ and α	Copanlisib
	PI3Kδ	TGR1202
Syk inhibitors	Syk	Fostamatinib*
	Syk	Entospletinib
BCL2 inhibitors	BCL2	Venetoclax
MDM2 inhibitors	MDM2	Idasanutlin
	MDM2	DS-3032b
Epigenetic modifiers	EZH2	Tazemetostat
	EZH2	CPI-1205
	EZH2	GSK2816126

*No longer in development in NHL.

Background

- Most patients with follicular lymphoma (FL) will eventually relapse after initial chemoimmunotherapy[1,2]
- Relapsed FL is incurable and novel therapeutic options are needed[3]
- Ibrutinib, a potent oral BTK inhibitor,[4] has shown activity in other B-cell malignancies (CLL/SLL, MCL, WM)[5-7]
- Preliminary data have indicated that ibrutinib has activity in treatment naïve and relapsed/refractory FL[8-10]

1. Ladetto M, et al. *Blood.* 2008;111:4004-4013.
2. Van Oers M, et al. *J Clin Oncol*. 2010;28:2853-2858.
3. Coiffier B, et al. *Lancet Oncol.* 2011;12:773-784.
4. Honigberg LA, et al. *Proc Natl Acad Sci USA*. 2010;107:13075-13080.
5. Brown JR, et al. *Blood.* 2015;126:1751. Abstract 3331.
6. Wang ML, et al. *Blood.* 2015;126:739-745.
7. Treon SP, et al. *New Engl J Med*. 2015;372:1430-1440.
8. Advani RH, et al. *J Clin Oncol*. 2013;31:88-94.
9. Bartlett N, et al. *Blood*. 2014;124:Abstr 800.
10. Fowler N, et al. *Blood*. 2015;126:470-470.

BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; SLL, small lymphocytic leukemia; WM, Waldenström's macroglobulinemia.

FLR2002 (DAWN, NCT01779791): Phase 2 Open-Label Study

Patients with previously treated FL
- 2 or more prior lines of therapy, including ≥ 1 rituximab-containing regimen
- Progressed on last prior line of chemoimmunotherapy (< 12 months)

Oral ibrutinib 560 mg daily

Treatment until PD or toxicity

- Primary end point: IRC-assessed overall response rate
  - Target: ORR 38%, ruling out ORR 18%
- Secondary end points: DOR and safety of ibrutinib, PFS, OS, time to response, resolution of B-cell lymphoma-related symptoms, biomarkers
- Amendment: Allow for continuation of ibrutinib in patients with radiographic PD who are clinically stable or improving or exhibiting signs of tumor flare (pseudo-PD) [Abstract# 2980]

DOR, duration of response; IRC, independent review committee; OS, overall survival; PD, progressive disease; PFS, progression-free survival.

Patient Characteristics at Baseline (1)

	All Treated Patients (N = 110)
Median age (range), years	61.5 (28-87)
Male, n (%)	67 (60.9)
ECOG performance status, n (%)	
0	55 (50.0)
1	55 (50.0)
FLIPI score, n (%)[a]	
0-1	21 (19.1)
2	25 (22.7)
3-5	64 (58.2)

[a]Derived at baseline.

ECOG, Eastern Cooperative Oncology Group performance status; FLIPI, Follicular Lymphoma International Prognostic Index.

Patient Characteristics at Baseline (2)

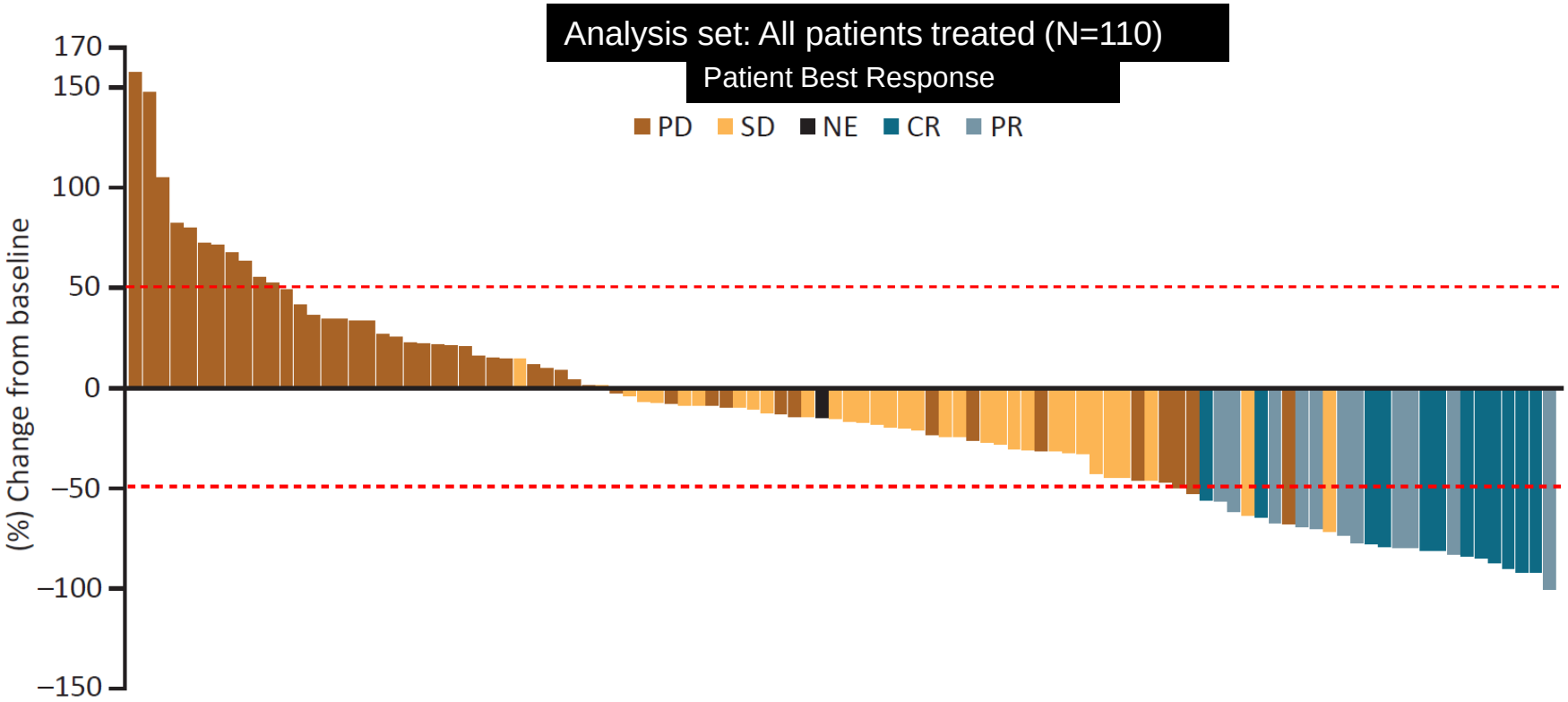
	All Treated Patients (N = 110)
Refractory disease, n (%)[a,b]	45 (40.9)
Bulky disease (> 6 cm), n (%)	21 (19.1)
Prior lines of therapy, n (%)	
Median (range)	3 (2-13)
2	49 (44.5)
3-6	53 (48.2)
> 6	8 (7.3)
Median time (range) from initial diagnosis, months	52.16 (6.9-312.6)
Median time (range) from end of last therapy to first dose, months	4.24 (0.5-32.4)

[a] Refractory disease was defined as failure to achieve at least partial response to the last regimen prior to study entry.
[b] 94/110 (85%) patients had progressed within 6 months on last prior line of therapy.

Disposition and Exposure

	All Treated Patients (N = 110)
Median treatment duration (range), months	**7.0 (1-37+)**
Median duration of follow-up (range), months	27.7 (1.1-37.1)
Study treatment phase disposition, n (%)	
Discontinued study treatment	110 (100)
Primary reason for discontinuation	
Progressive disease or relapse	72 (65.5)
Rolled into long-term extension study (NCT01804686)	13 (11.8)
Physician decision	10 (9.1)
Adverse event	7 (6.4)
Death	4 (3.6)
Withdrawal of consent	3 (2.7)
Lost to follow-up	1 (0.9)

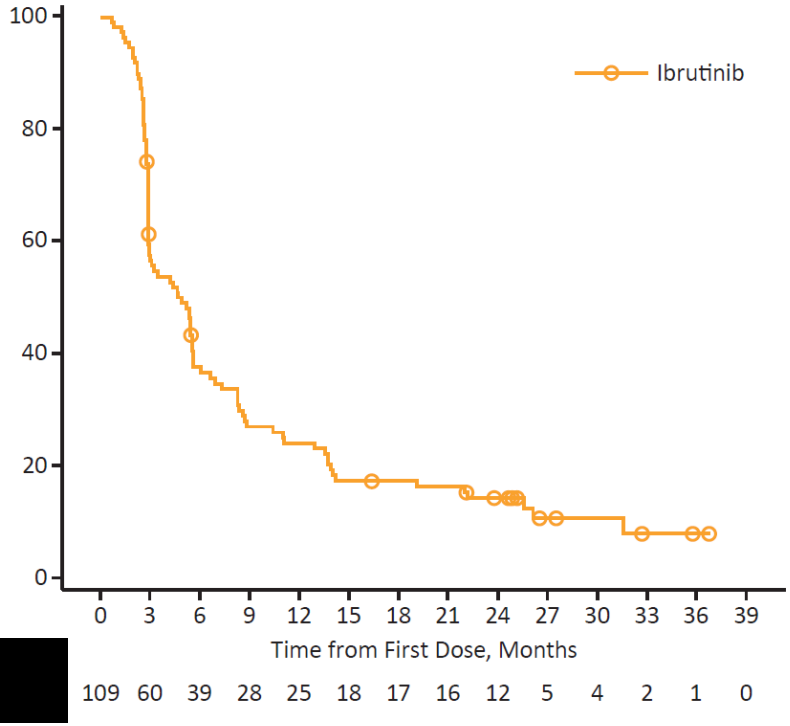
Percent Change in Tumor Size With Single-Agent Ibrutinib



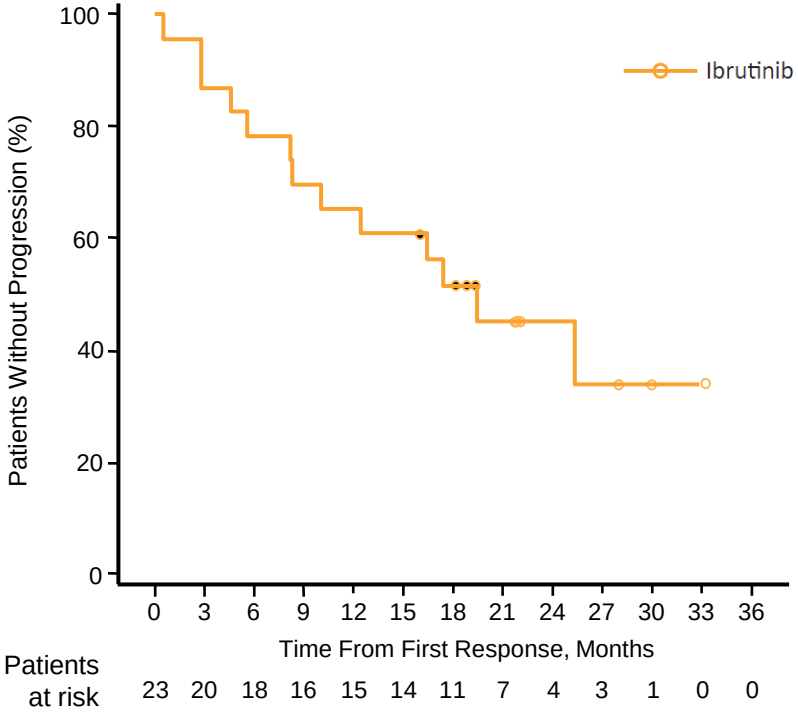
- 63% of patients had a reduction in tumor size
- Tumor size decreased ≥ 50% in 25% of patients

Progression-Free Survival and Duration of Response

Progression-Free Survival



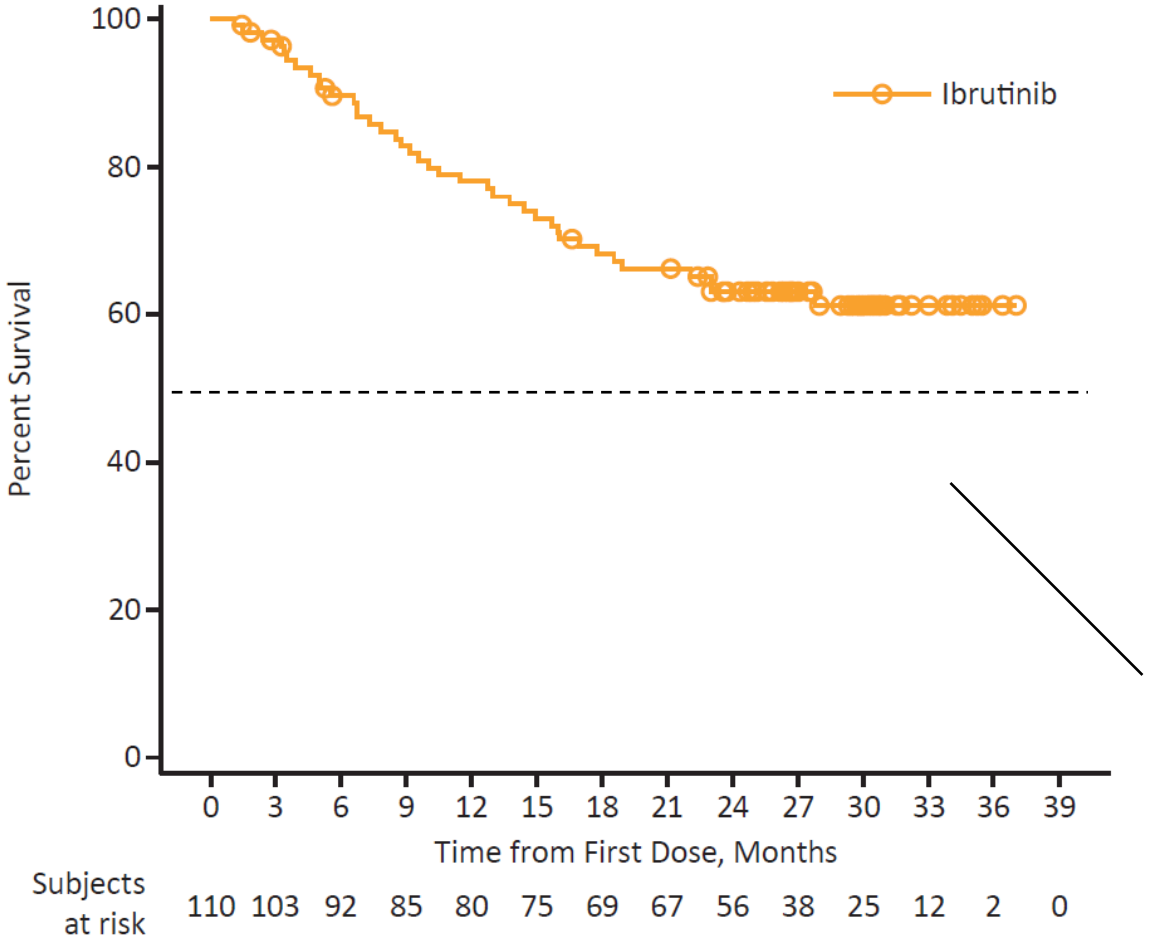
Duration of Response



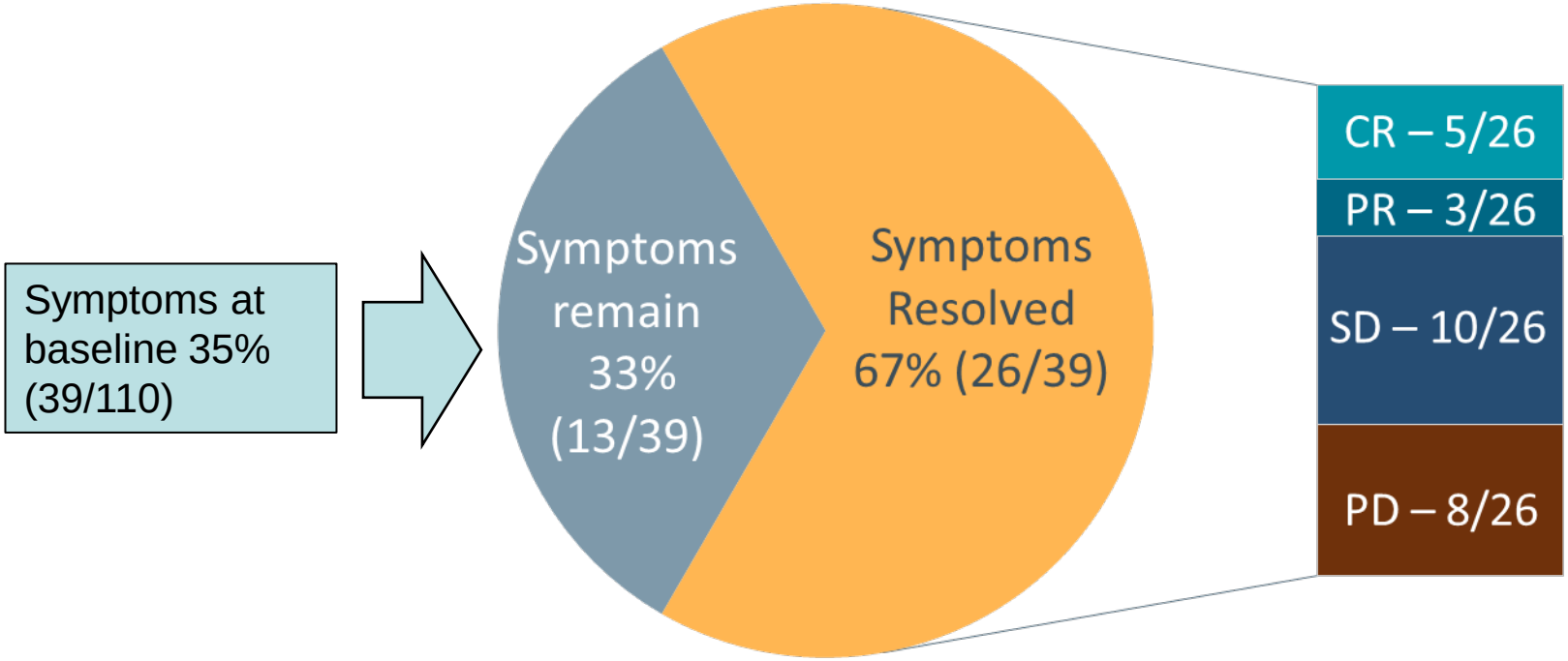
Median PFS 4.6 months

Median DOR 19.4 months

Overall Survival



Resolution of Lymphoma Symptoms With Single-Agent Ibrutinib



- Median time to resolution was 0.7 months (95% CI, 0.7-1.4), duration of symptom resolution of 10.4 months (95% CI, 6.5-NE)
- Clinical benefit was observed in patients without radiological response

Conclusions

- Single-agent ibrutinib achieved an ORR of 20.9% (CI 13.7-29.7) in chemoimmunotherapy-refractory FL
  - Study did not rule out ORR < 18%
  - DOR = 19 months
  - Disease control rate (ORR + SD for ≥ 6 months) was 33.6%
- Some patients experienced symptom improvement without a radiographic response
- AEs were consistent with prior studies of ibrutinib
- Potential biomarkers may identify ibrutinib responders
- Ongoing studies:
  - BR or R-CHOP +/- ibrutinib in relapsed/refractory FL
  - Rituximab plus ibrutinib in untreated FL

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	BTK	Acalabrutinib
	BTK	ONO/GS-4059
	BTK	BGB-3111
	BTK	CC-292
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	PI3K δ and γ	Duvelisib
	PI3K δ and α	Copanlisib
	PI3Kδ	TGR1202
Syk inhibitors	Syk	Fostamatinib*
	Syk	Entospletinib
BCL2 inhibitors	BCL2	Venetoclax
MDM2 inhibitors	MDM2	Idasanutlin
	MDM2	DS-3032b
Epigenetic modifiers	EZH2	Tazemetostat
	EZH2	CPI-1205
	EZH2	GSK2816126

*No longer in development in NHL.

Phase 2 Study of Venetoclax plus Rituximab or Randomized Venetoclax plus Bendamustine + Rituximab (BR) versus BR in Patients with Relapsed/ Refractory Follicular Lymphoma: CONTRALTO Study- Interim Data

Pier Luigi Zinzani[1], Max S. Topp[2], Sam L.S. Yuen[3], Chiara Rusconi[4], Isabelle Fleury[5], Barbara Pro[6], Giuseppe Gritti[7], Michael Crump[8], Wanling Hsu[9], Elizabeth Punnoose[9], James Hilger[9], Mehrdad Mobasher[9], Wolfgang Hiddemann[10]

1. Institute of Hematology “L. e A. Seràgnoli”, University of Bologna, Bologna, Italy; 2. Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Germany; 3. Department of Haematology, Calvary Mater Newcastle, NSW Australia; 4. Division of Hematology, Niguarda Hospital, Milan, Italy; 5. Department of Hematology, Maisonneuve-Rosemont Hospital and University of Montreal, Montreal, Canada; 6. Robert H. Lurie Comprehensive Cancer Center Chicago, Il, USA; 7. Ospedale Papa Giovanni XXIII, Hematology and BMT Unit, Bergamo, Italy; 8. Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada; 9. Genentech, Inc., South San Francisco, CA, USA; 10. Department of Internal Medicine III, Klinikum der Universität München, Munich, Germany

American Society of Hematology
San Diego, CA, December 5, 2016

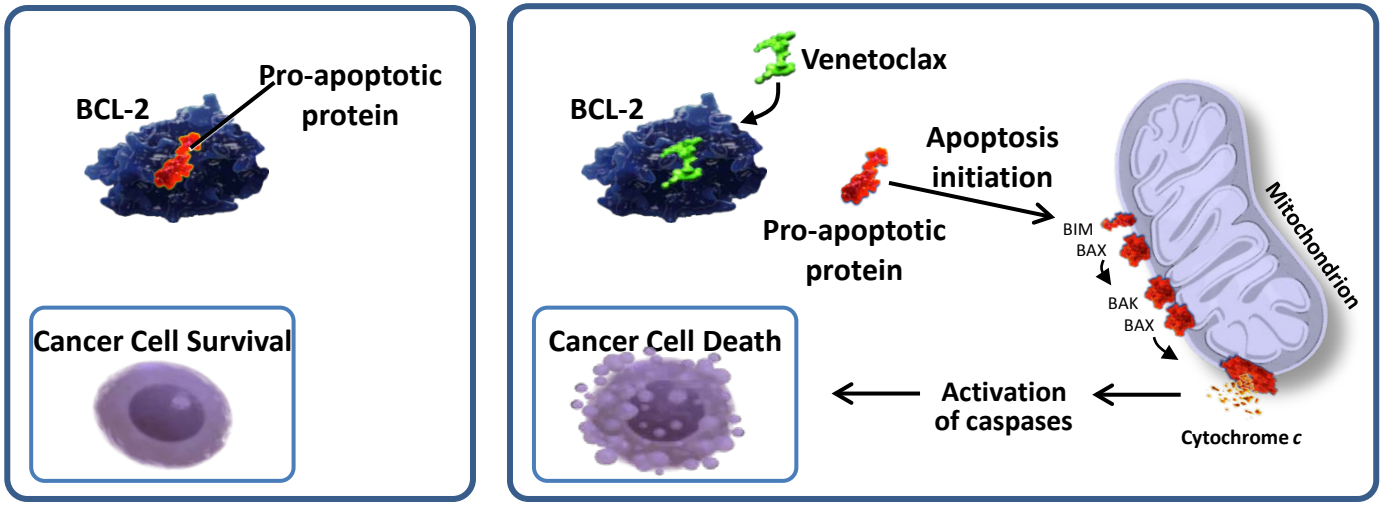
Background: Mechanism of Action and Early Data

FL is characterized by overexpression of BCL-2, which dysregulates the intrinsic apoptotic pathway and is associated with chemotherapy resistance[1–4]

Venetoclax (VEN), a selective, potent oral BCL-2 inhibitor, is in development for the treatment of B-cell malignancies

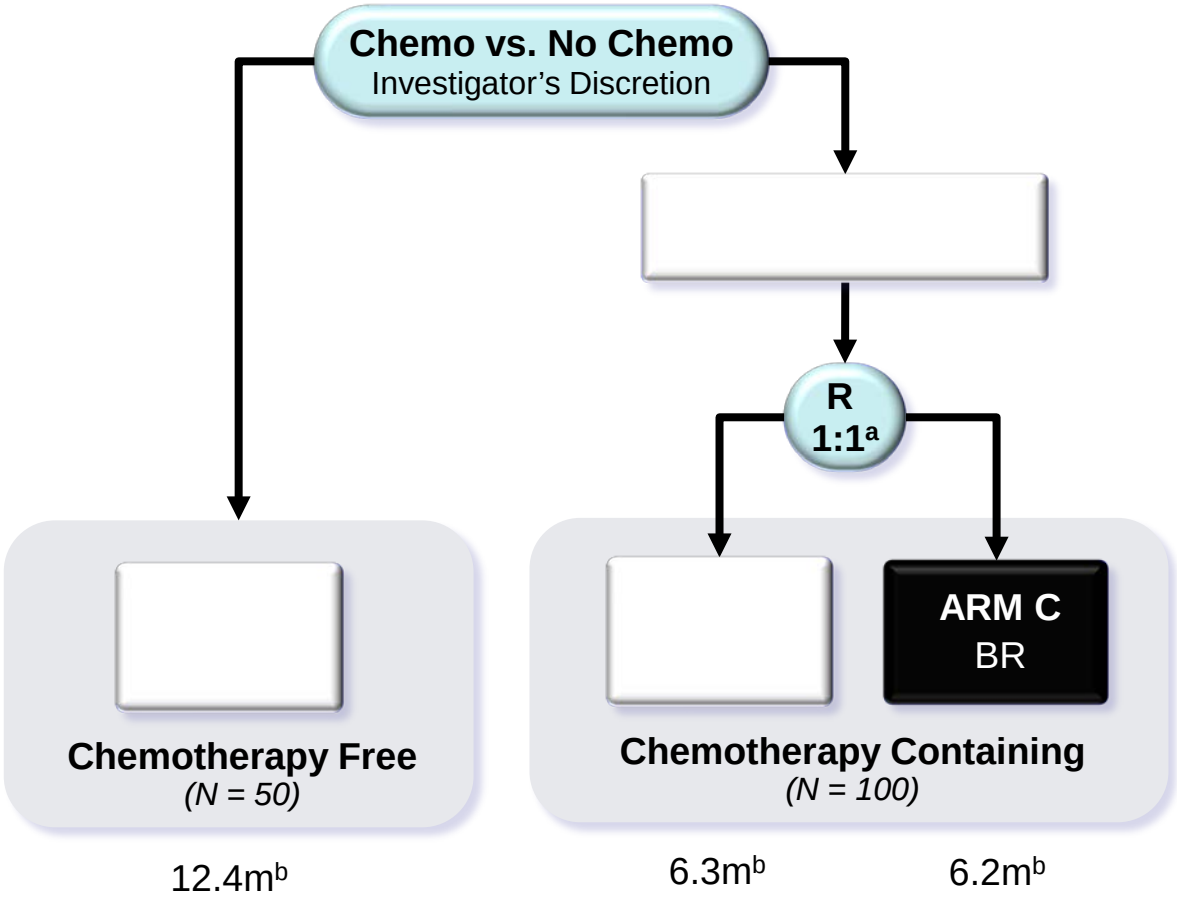
- Preclinical[5] and early clinical[6] data suggest addition of VEN to R or bendamustine may improve responses over R or chemotherapy alone
- Phase 1 of VEN monotherapy showed an ORR of 38% in FL[7]
- Dose finding study with VEN + BR investigated doses of VEN 50–1200 mg with no MTD[6]

Restoration of apoptosis through BCL-2 inhibition



CONTRALTO Phase 2 Study Design

VEN + R and randomized VEN + BR vs BR alone in patients with R/R FL, Grade 1–3a



Key inclusion criteria

- Age ≥18 yrs
- Confirmed R/R FL (Gr 1–3a)
- Treated with ≥1 line of prior therapy for FL
- Adequate marrow, coagulation, renal, and hepatic function
- No history of bendamustine-refractory disease
- No CNS lymphoma

Primary Endpoint

- PET-CR rate by IRC at end of induction (Cheson 2014)

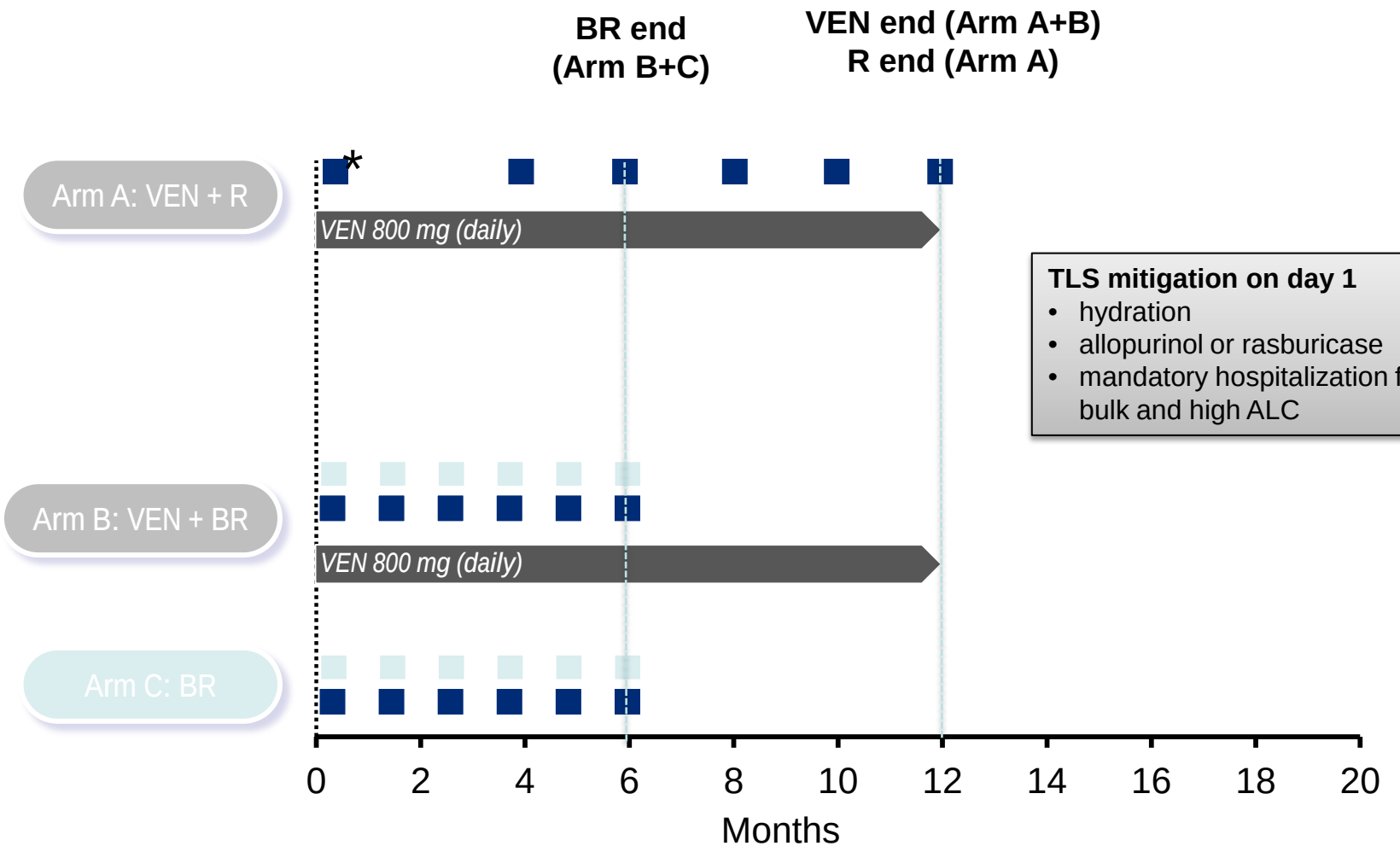
Secondary Endpoints

- CR rate (PET and CT) by investigator at end of induction and 1 year
- ORR
- PFS
- Safety

a Stratified: DOR to prior tx (≤12m vs. >12m) Disease burden (high vs. low)

b median months on study so far (ongoing)

Dosing Schedule by Arm and Time on Study (Ongoing)



TLS mitigation on day 1
- hydration
- allopurinol or rasburicase
- mandatory hospitalization for pts with bulk and high ALC

Blue circles represent the median, and the lines are for the associated range
*R administered on Days 1, 8, 15 and 22.
28-day cycles

Venetoclax	Daily over period indicated	800 mg daily
Rituximab	D1 of period indicated	375 mg/m²
Bendamustine	D1 + D2 of period indicated	90 mg/m²

Patient Characteristics – 1

Median age (range), years	63 (40–84)	66 (43–82)	61 (35–80)
Male, n (%)	27 (51)	35 (69)	30 (59)
Bulky ≥ 10 cm, n (%)	5 (9)	4 (8)	8 (16)
Ann Arbor Stage, n (%)			
I	3 (6)	5 (10)	3 (6)
II	5 (10)	8 (16)	10 (20)
II	9 (18)	13 (27)	8 (16)
IV	33 (66)	23 (47)	30 (59)
FLIPI category, n (%)			
Low (0–1)	4 (8)	11 (22)	12 (24)
Intermediate (2)	17 (32)	18 (35)	19 (37)
High (≥3)	32 (60)	21 (41)	20 (39)
Unknown	0	1 (2)	0

VEN + R Safety

Diarrhea	21 (40)
IRR	15 (29)
Neutropenia	15 (29)
Nausea	14 (27)
Fatigue	13 (25)
Thrombocytopenia	8 (15)
Vomiting	7 (14)
Abdominal Pain	7 (14)
G3–4 > 5%, n (%)	
Neutropenia	13 (25)
Thrombocytopenia	5 (10)
Diarrhea	3 (6)

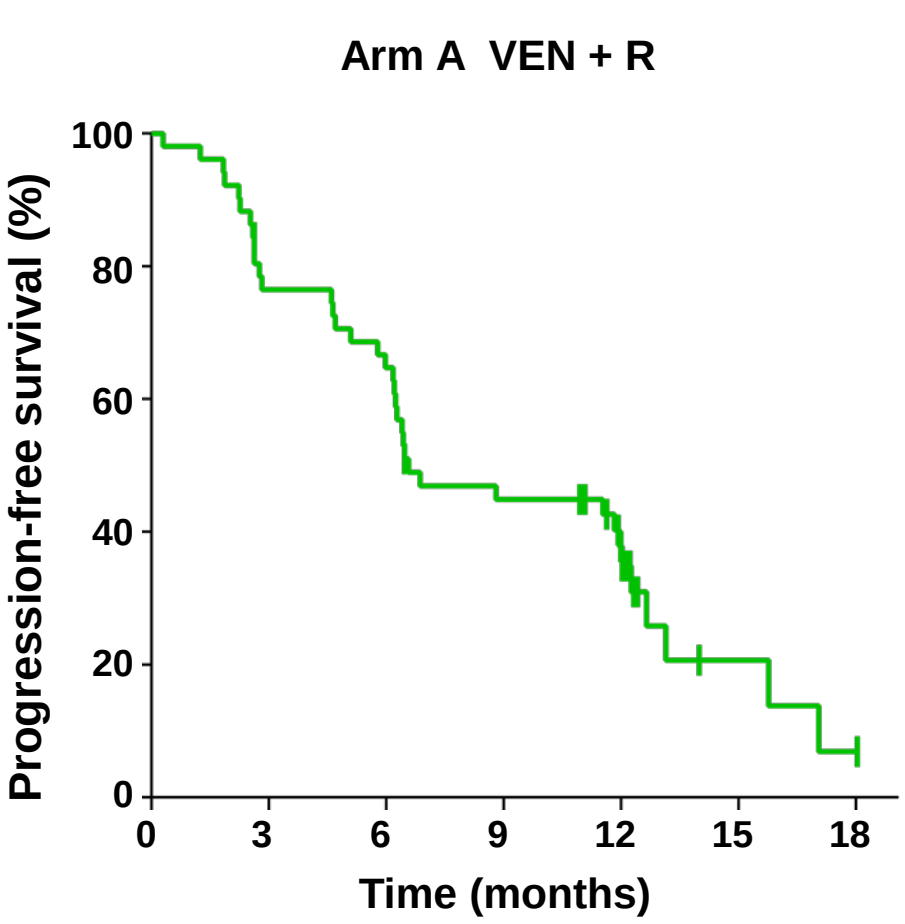
Lab tumor lysis syndrome was seen in 1 pt and was manageable

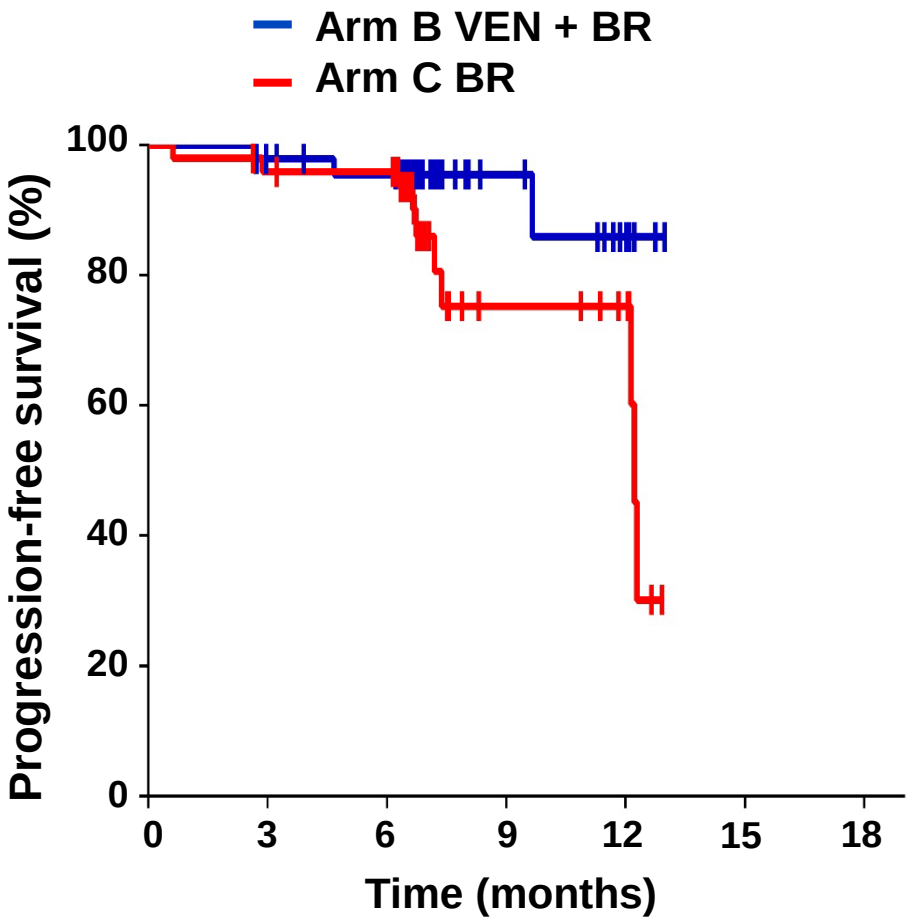
6 deaths on study

- 2 PD
- 1 each of: pulmonary hemorrhage, colitis, myocardial infarction, and unknown cause

Pts with adverse events leading to stopping drug: 5 (10%) total

- VEN: 5 (10%) pts
- R: 2 (4%) of pts





Pts at risk:

(50) (39) (33) (22) (13) (3) (1)

Pts at risk:

(48) (42) (39) (11) (5) - -

(49) (47) (45) (10) (7) - -

Venetoclax (ABT-199/GDC-0199) plus bendamustine and

Conclusions

- VEN combinations result in higher rates of hematologic toxicity, which can be manageable with proactive monitoring
- VEN + R showed responses in R/R FL including complete responses even in patients who were refractory to their last treatment
- Preliminary efficacy data suggest an improvement in PFS when VEN is combined with BR vs. BR alone
- Higher BCL-2 expression may be associated with a higher CR rate of VEN + BR vs. BR, consistent with the mechanism of action of VEN
- Longer follow-up is required to assess VEN + BR as a potential new treatment option, and additional BCL-2 analyses are planned

Table 2. Key intracellular pathway and epigenetic targets and potential therapies

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	BTK	ONO/GS-4059
	BTK	BGB-3111
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Epigenetic modifiers	EZH2	Tazemetostat
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*No longer in development in NHL.

Initial Safety and Efficacy Report from Phase 2 Global, Multicenter Study of Tazemetostat in Patients with Relapsed or Refractory (R/R) NonHodgkin Lymphoma (NHL)

American Society for Hematology 2016 Meeting on Lymphoma Biology

June 19-21, 2016

Franck Morschhauser, MD, Gilles Salles, MD, PhD, Pam McKay, MBChB, FRCP, Steven Le Gouill, MD, PhD, Hervé Tilly, MD, John A. Radford, MD, FRCP, Guillaume Cartron, MD, PhD, Michael J. Dickinson, MBBS, FRACP, FRCPA, Christophe Fruchart, MD, John G Gribben, MD, DSc, Anna Schmitt, MD, Peter Johnson, MA, MD, FRCP, Stephen Opat, MD, Pier Luigi Zinzani, MD, PhD, Patricia Pimentel, Maria Roche, NP, Stephen J. Blakemore, PhD, Alice McDonald, Mark Woodruff, Natalie Michele Warholic, Shelley Knight, Alicia Clawson, Harry Miao, MD, PhD, John Larus, Peter T Ho, MD, PhD, and Vincent Ribrag, MD

Tazemetostat for the Treatment of NHL

For NHL patients refractory to or relapsed from front-line therapy, clinical success diminishes rapidly, underscoring the need for new treatment options

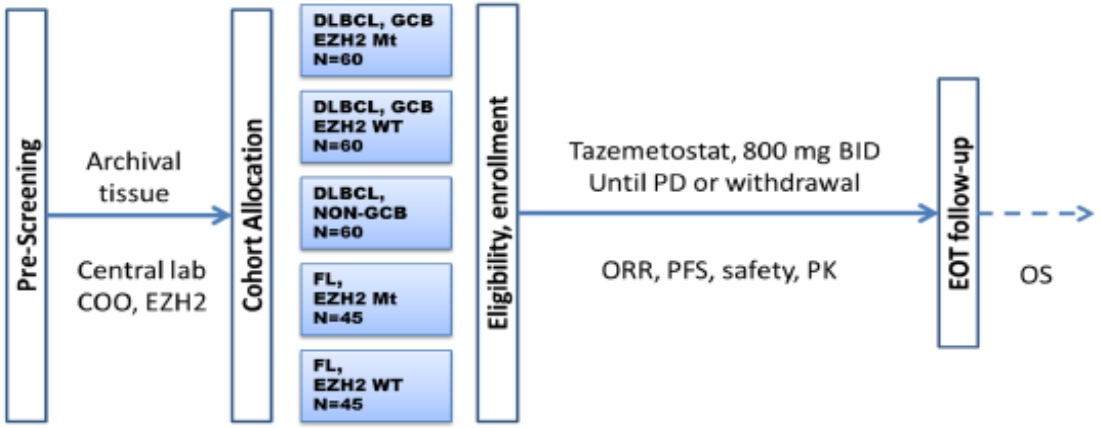
- NHL: one of the most common cancers in the U.S.; approx. 4% of all cancers[1]
  - Diffuse large B-cell lymphoma (DLBCL) is the most common form of NHL; up to 30% of all newly diagnosed cases in U.S.[2]
  - Follicular lymphoma (FL) considered incurable with existing therapies[3]
- EZH2 enzyme plays a critical role in multiple forms of cancer
  - EZH2 is a histone methyltransferase (HMT) that can become an oncogenic driver for NHL and a variety of other solid tumors
  - Preclinical data demonstrate activity in DLBCL cell lines irrespective of mutational status and cell of origin[4]
- Tazemetostat
  - First-in-class and most advanced EZH2 inhibitor in clinical development
  - Orally available small molecule inhibitor discovered and developed by Epizyme
  - Previously reported Phase 1 data demonstrating tazemetostat to be well tolerated with single-agent activity in multiple types of patients with relapsed or refractory (R/R) NHL, as well as certain genetically-defined tumors

[1] ACS, Non-Hodgkins Lymphoma; June 7, 2016
[2] Lymphoma Research Foundation 2016
[3] Gisselbrecht, JCO, 2010.
[4] Epizyme preclinical data, ASH Lymphoma Biology 2016.

Tazemetostat Ongoing Phase 2 NHL Study Design

Study designed to assess clinical activity and safety of tazemetostat in five NHL subtypes and determine potential registration path for each subtype

- Global, multi-center, open-label study in 5 cohorts of patients with R/R DLBCL or FL
  - Patient stratification based on EZH2 mutational status and cell of origin
  - All patients treated with $\geq$ 2 prior therapies
- Primary endpoint: overall response rate
  - Secondary efficacy endpoints include: progression-free survival (PFS) and duration of response
- Study expanded to 270 patients total
  - 60 patients in each DLBCL cohort; 45 patients in each FL cohort



Objective response assessed by IWG-NHL criteria (Cheson 2007); restaging every 8 weeks for 6 cycles, then every 12 weeks thereafter

Phase 2 NHL Study Progress as of Data Cutoff[1]

- ~30% of total study population (n=270) enrolled
  - Approx. 48% of all patients enrolled within the last 5 months
  - Approx. 20% identified to have EZH2 mutations (DLBCL and FL), matching prevalence estimates

- Futility has been surpassed in 4 of 5 study cohorts[2]:
  - FL with wild-type EZH2 cohort not yet reached futility assessment
  1. DLBCL with Germinal Center B-cell (GCB) subtype and EZH2 mutations
  2. DLBCL with GCB subtype and wild-type EZH2
  3. DLBCL with non-GCB subtype (including PMBCL)
  4. FL with EZH2 mutations

- 82 patients evaluable for safety[3], of which 47 patients evaluable for efficacy[4]
  - 35 patients not included in efficacy assessment
    - 19 patients with FL with wild-type EZH2
    - 16 patients too early or data not entered for efficacy assessment

[1] Data cut off as of May 27, 2016
[2] Confirmed by Independent Data Monitoring Committee
[3] Safety data reported from all five study cohorts
[4] Efficacy data on 4 cohorts that surpassed futility confirmed by IDMC

Demographics & Disease Characteristics

Characteristic		DLBCL GCB		DLBCL non-GCB	Follicular Lymphoma		Total
EZH2 status		Mutant	Wild-type		Mutant	Wild-type	
n		7	26	26	4	19	82
Age, median	years	71	66	70	59	60	65
Males		29%	58%	73%	75%	63%	62%
ECOG PS, median (range)		1 (0 - 2)	1 (0 - 2)	1 (0 - 2)	1 (0 - 2)	1 (0 - 2)	1 (0 - 2)
Prior lines of therapy, n (%)	2	1 (14%)	8 (31%)	10 (38%)	1 (25%)	6 (32%)	26 (32%)
	3	4 (57%)	4 (15%)	6 (23%)	1 (25%)	3 (16%)	18 (22%)
	4	1 (14%)	5 (19%)	4 (15%)	0	2 (11%)	12 (15%)
	≥ 5	1 (14%)	8 (31%)	5 (19%)	2 (50%)	8 (42%)	24 (29%)
Refractory to last regimen, n (%)		6 (86%)	13 (50%)	18 (69%)	3 (75%)	9 (47%)	49 (60%)
Prior HSCT		0	23%	15%	50%	58%	28%
Prior RT		29%	42%	19%	50%	26%	30%
Median time from initial diagnosis	years	0.8	2.0	1.5	8.0	5.3	2.0
Median time from last prior therapy	weeks	6.7	15.1	9.1	48.6	91.4	15.2

Data as of 5/27/16

Adverse Events Led to Low Rate of Dose Reductions and Discontinuations

Patients (n=82)	**All Adverse Events (AEs)***	**Treatment-Related AEs**
Adverse Event (any)	65 (79%)	41 (50%)
Grade ≥ 3	23 (28%)	13 (16%)
Serious AE	15 (18%)	8 (10%)
AE Leading to Dose Interruption	18 (22%)	12 (15%)
AE Leading to Dose Reduction	3 (4%)	2 (2%)
AE Leading to Drug Discontinuation	5 (6%)	2 (2%)

* All treatment emergent adverse events that first appear during treatment, which were absent before or which worsen relative to pre-treatment

Data as of 5/27/16

Tazemetostat Demonstrated Favorable Safety Profile in Phase 2 Patients

	All Adverse Events (AEs)*		Treatment-Related AEs	
Patients (n=82) with AE[1]	**All Grades**	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**
Nausea	15 (18%)	0	11 (13%)	0
Cough	11 (13%)	0	1 (1%)	0
Asthenia	9 (11%)	0	8 (10%)	0
Thrombocytopenia	9 (11%)	3 (4%)	7 (9%)	2 (2%)
Fatigue	7 (9%)	3 (4%)	4 (5%)	1 (1%)
Neutropenia	7 (9%)	5 (6%)	6 (7%)	4 (5%)
Constipation	5 (6%)	0	1 (1%)	0
Diarrhoea	5 (6%)	0	3 (4%)	0
Insomnia	5 (6%)	0	2 (2%)	0
Lung infection	5 (6%)	1 (1%)	1 (1%)	0
Vomiting	5 (6%)	0	1 (1%)	0
Hyperglycaemia	4 (5%)	1 (1%)	1 (1%)	0
Lethargy	4 (5%)	0	1 (1%)	0
Urinary tract infection	4 (5%)	0	2 (2%)	0

*All treatment emergent adverse events that first appear during treatment, which were absent before or which worsen relative to the pre-treatment;
[1]All adverse events reported in ≥5% of patients regardless of attribution.

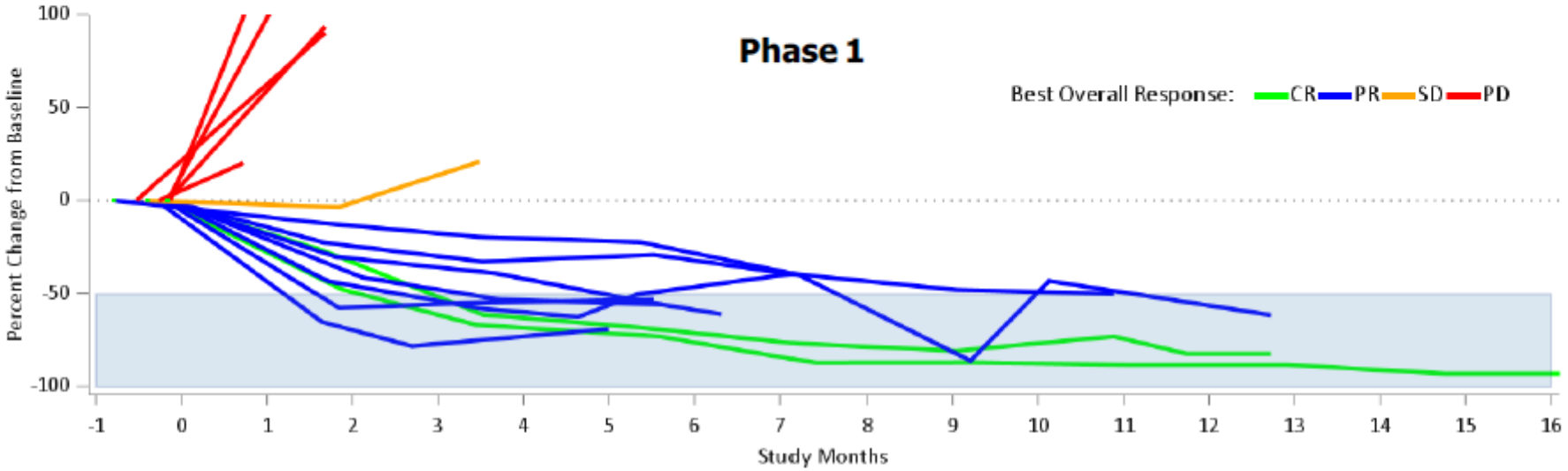
Data as of 5/27/16

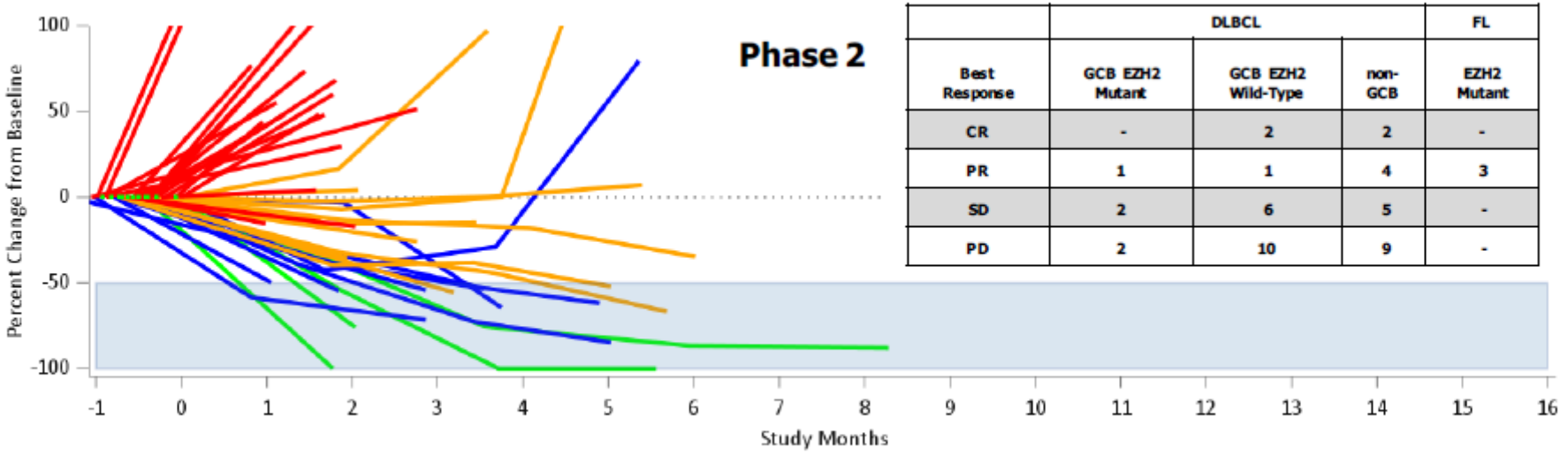
Thrombocytopenia and Neutropenia by Laboratory Results in Phase 2 Patients

Subjects (n=82) with:	
Thrombocytopenia *	9 (11%)
Grade 3	8 (10%)
Grade 4	1 (1%)
Neutropenia *	5 (6%)
Grade 3	2 (2%)
Grade 4	3 (4%)

* Determined by laboratory results, not by investigator assignment
Patients counted only once for their highest toxicity grade observed

Evolution of Tumor Response and Preliminary Efficacy Assessment

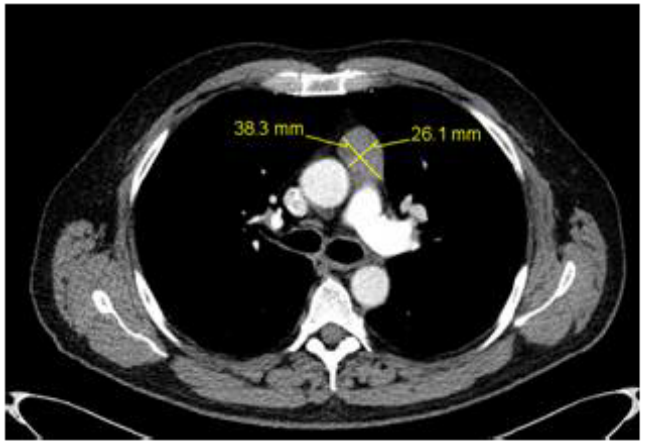




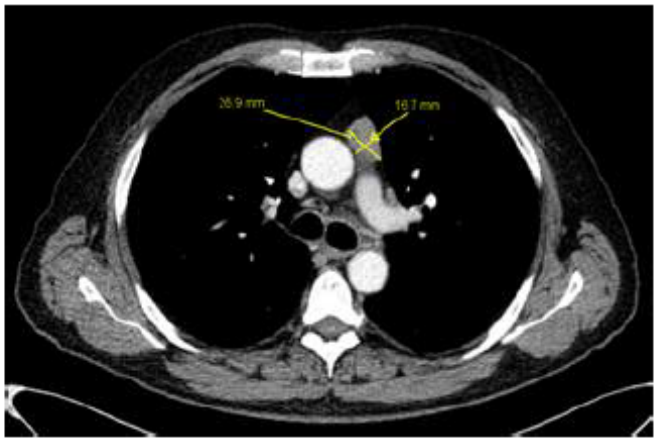
	DLBCL			FL
Best Response	GCB EZH2 Mutant	GCB EZH2 Wild-Type	non-GCB	EZH2 Mutant
CR	-	2	2	-
PR	1	1	4	3
SD	2	6	5	-
PD	2	10	9	-

Phase 1: Ribrag et al., ICML 2015; Phase 2: Data as of 5/27/16 Lines are truncated at greater than ±100%

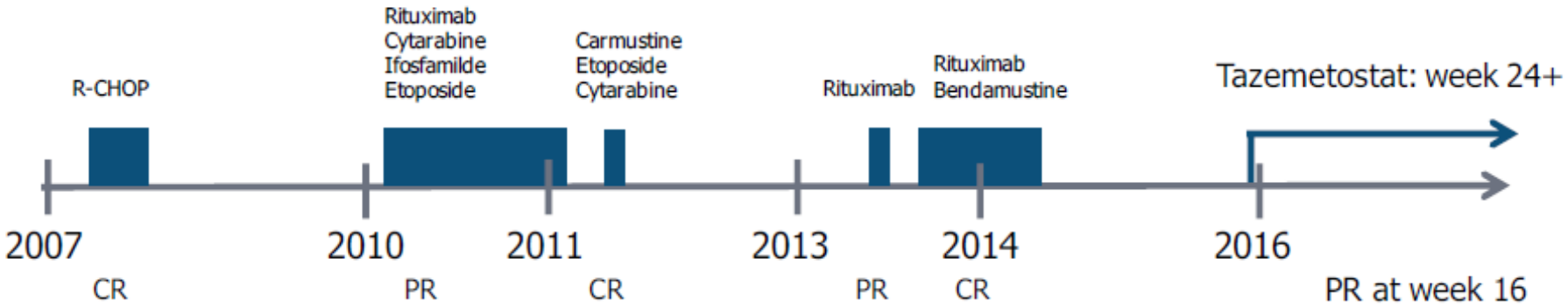
Objective Response in Patient with Follicular Lymphoma with EZH2 Y646N Mutation



Baseline: 38 x 26 = 988



Week 16: 27 x 17 = 459



Data as of 5/27/16