5 Minute JournalClub

POST-ASH Issue 6, 2013

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CME Information

LEARNING OBJECTIVES

- Recall emerging clinical research data on the efficacy and safety of lenalidomide in combination with R-CHOP for the treatment of diffuse large B-cell lymphoma (DLBCL) or as single-agent therapy for bortezomib-refractory mantle-cell lymphoma (MCL).
- Compare and contrast the benefits and risks of bendamustine/rituximab versus R-CHOP and R-CVP in the first-line treatment of advanced indolent non-Hodgkin lymphoma or MCL.
- Evaluate the efficacy and safety of the novel agent ibrutinib in relapsed/refractory DLBCL and MCL.

CREDIT DESIGNATION STATEMENT

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CME Information (Continued)

FACULTY DISCLOSURES
The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Advisory Committee: Celgene Corporation, Cephalon Inc, Genentech BioOncology, Millennium: The Takeda Oncology Company, Roche Laboratories Inc; *Contracted Research:* Abbott Laboratories, Cephalon Inc, Genentech BioOncology.

5 MinuteJournalClub

POST-ASH Issue 6, 2013

More ASH lymphoma papers... and another perspective on the disease from a very unusual patient

In-depth interviews with clinical investigators occasionally veer into unexpected territory, and this was the case last fall during a fascinating conversation I had with lung cancer researcher Dr David Carbone. Like many similar sessions, our discussion focused in part on reviewing instructive personal cases, and during one in particular in which the patient required a laparoscopic thoracotomy, Dr Carbone casually mentioned that he himself had once undergone that procedure. My ears twitched to attention and in an instant we were deep inside an amazing and profound story.

David's father was the late Dr Paul Carbone, the legendary founder of the Eastern Cooperative Oncology Group and a former pioneering clinical investigator who along with others at the NCI and then the University of Wisconsin helped develop new chemotherapy regimens for breast cancer, Hodgkin lymphoma and diffuse large B-cell lymphoma (DLBCL). Following in his father's inspiring footsteps, David tracked through Johns Hopkins Medical School and then the NCI, after which he joined the medical oncology faculty at

Vanderbilt. In 1999, at the age of 40, while shaving he noticed that the veins in his neck were markedly distended, which he self-diagnosed as superior vena cava syndrome. The cause he soon learned was mediastinal large cell lymphoma, and with 4 children under the age of 14 the younger Dr Carbone accelerated into action. Fortunately, the regimen developed in part by his father, CHOP (rituximab was not quite on board then), along with radiation therapy did the trick and he remains free of recurrence to this day (and recently joined the faculty of the Ohio State Buckeyes).

However, while the end result was a positive one, the experience affected him deeply. After hearing about chemotherapy all his life and prescribing it for many years, David was shocked by its debilitating effects, including "end-to-end" mucositis along with profound fatigue and nausea mixed in with an uncomfortable postop recovery. This eloquent man becomes virtually speechless in trying to describe the suffering and despair engendered by CHOP, although like others who have traveled this difficult path, the experience instantly rearranged his priorities, and one of his fondest memories took place a year after finishing treatment when this former workaholic took off for 2 weeks to visit Sicily with his dad, mom and sister.

Thinking back on this conversation and Dr David Carbone's real-life perspectives, one could expect that he and CHOP survivors everywhere will welcome the day that chemotherapy becomes an afterthought in lymphoma management, and while we may not yet be there, the current evolution of systemic treatment toward selective novel biologic agents — some of which are noteworthy for

impressive efficacy and a relative lack of side effects — is in full swing and offering more promise than ever before. Here are a few of the most compelling ASH reports in that regard:

1. "R-squared CHOP" in DLBCL and more on lenalidomide (len) alone in mantle-cell lymphoma (MCL)

The R-squared regimen of len/rituximab (lenR) has generated considerable excitement in early trials of chronic lymphocytic leukemia and follicular lymphoma (FL), and the known single-agent activity of len in DLBCL led to a natural interest in partnering this immunomodulatory agent with standard R-CHOP. At ASH we saw **2 important Phase II trials** demonstrating impressive overall response rates (95 of 100 patients combined) with this regimen. Of perhaps greater interest, when the results were analyzed by cell of origin, the addition of len appeared to be more effective for patients with activating B-cell (ABC) versus germinal center B-cell-like DLBCL.

While these 2 major DLBCL molecular subtypes were identified more than 10 years ago, up until now this information has been more theoretical than practical. However, a new Intergroup trial (ECOG-E1412) randomly assigning patients with previously untreated DLBCL to R-CHOP or R-squared CHOP will mandate that all patients have their tumors genotyped for cell of origin. The results will be analyzed to definitely assess whether cell of origin is a useful predictive factor.

Another related ASH paper by Dr Andre Goy helped to expand our knowledge base by confirming the activity of len monotherapy in relapsed/refractory MCL. These results from the Phase II EMERGE trial documented a 28% objective response rate for heavily pretreated patients and may help pave the way for this useful agent to be approved in this setting where more options are sorely needed.

2. More on ibrutinib in DLBCL and MCL

A presentation by the NCI's Dr Wyndham Wilson revealed impressive response rates in relapsed/refractory DLBCL with this Bruton tyrosine kinase inhibitor as monotherapy. Importantly, and further strengthening the case for genotyping, benefit was generally confined to patients with the ABC subtype, of whom partial responses were seen in 12 of 29 compared to only 1 of 20 patients with the germinal center B-cell-like subtype of DLBCL. While these findings clearly do not yet have implications for clinical practice, it seems certain that they will play a significant role in informing future research paradigms.

Similarly, in MCL we saw an **update from a Phase II study** originally presented at ASH 2011 further confirming the unprecedented objective response rate (68%) with ibrutinib monotherapy in relapsed/refractory disease. Needless to say, there is extensive enthusiasm for this agent, which has recently been designated as a "breakthrough therapy" by the FDA.

3. Bendamustine/rituximab (BR) as induction therapy in FL and MCL

As reflected by the central role of the BR backbone in current Phase III FL and MCL cooperative group trials, it can be surmised that this novel regimen has largely replaced R-CHOP and R-CVP in the minds of many. This trend got started at ASH 2009 when we were treated to the first results from the German StiL trial in which BR outperformed R-CHOP, and at ASH 2012 Dr Ian Flinn presented **data from the Bright** study, another major related Phase III effort comparing BR to R-CHOP or R-CVP as first-line therapy for FL and MCL. In this instance BR was found to be roughly equivalent in FL, with a modest advantage observed for patients with MCL, and while these results are not likely to shift practice one way or the other, they do confirm that BR is at least as effective as R-CHOP and provide additional perspectives on the relative tradeoffs of these regimens.

Related to the choice of induction treatment, **an interesting Phase II ECOG report** in MCL focused on the VcR-CVAD regimen, which incorporates bortezomib, cyclophosphamide and rituximab (VcR) with the modified hyper-CVAD chemotherapy backbone without methotrexate/cytarabine. Overall the treatment was well tolerated with high response rates (94%). However, it seems more likely that the role of bortezomib as part of up-front therapy will be defined by the ongoing Phase II ECOG-E1411 trial of BR alone or with bortezomib followed by R maintenance alone or with len for patients with previously untreated MCL.

Next, on the final issue of this series, we check out ASH papers in chronic myelogenous leukemia, for which the never-ending avalanche of new data sets has resulted in 3 newly approved agents in the past year.

Neil Love, MD
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Combination of Lenalidomide with R-CHOP (R2CHOP) Is Well Tolerated and Effective as Initial Therapy for Aggressive B-Cell Lymphomas — A Phase II Study [1]

Rituximab-CHOP21 plus Lenalidomide (LR-CHOP21) Is Effective and Feasible in Elderly Untreated Diffuse Large B-Cell Lymphoma (DLBCL): Results of Phase II REAL07 Study of the Fondazione Italiana Linfomi (FIL) [2]

[1] **Nowakowski GS et al.**
Proc ASH 2012;Abstract 689.

[2] **Chiappella A et al.**
Proc ASH 2012;Abstract 903.

Combination of Lenalidomide with R-CHOP (R2CHOP) Is Well Tolerated and Effective as Initial Therapy for Aggressive B-Cell Lymphomas — A Phase II Study

Nowakowski GS et al.

Proc ASH 2012;Abstract 689.

Background

- R-CHOP21 is the standard treatment for untreated diffuse large B-cell lymphoma (DLBCL), but this treatment fails for a significant proportion of patients.
- Lenalidomide monotherapy exhibits about a 30% overall response rate in relapsed/refractory DLBCL (*Ann Oncol* 2011;22:1622).
  - Higher response rates have been recorded with the nongerminal center B-cell-like (non-GCB) subtype than with the germinal center B-cell-like (GCB) subtype (*Cancer* 2011;117:5058).
- A Phase I study demonstrated that 25 mg of lenalidomide (days 1-10) can be safely combined with R-CHOP21 as initial therapy for aggressive B-cell lymphomas (*Leukemia* 2011;25:1877).
- **Study objective:** To assess the efficacy and safety of lenalidomide with R-CHOP (R2CHOP) in patients with newly diagnosed aggressive B-cell lymphomas.

Nowakowski GS al. *Proc ASH* 2012;Abstract 689.

Phase II Study Design

Eligibility (N = 51)

- Newly diagnosed CD20-positive Stage II to IV DLBCL or Grade III follicular lymphoma
- No history of life-threatening or recurrent thrombosis or embolism unless receiving anticoagulation therapy during treatment

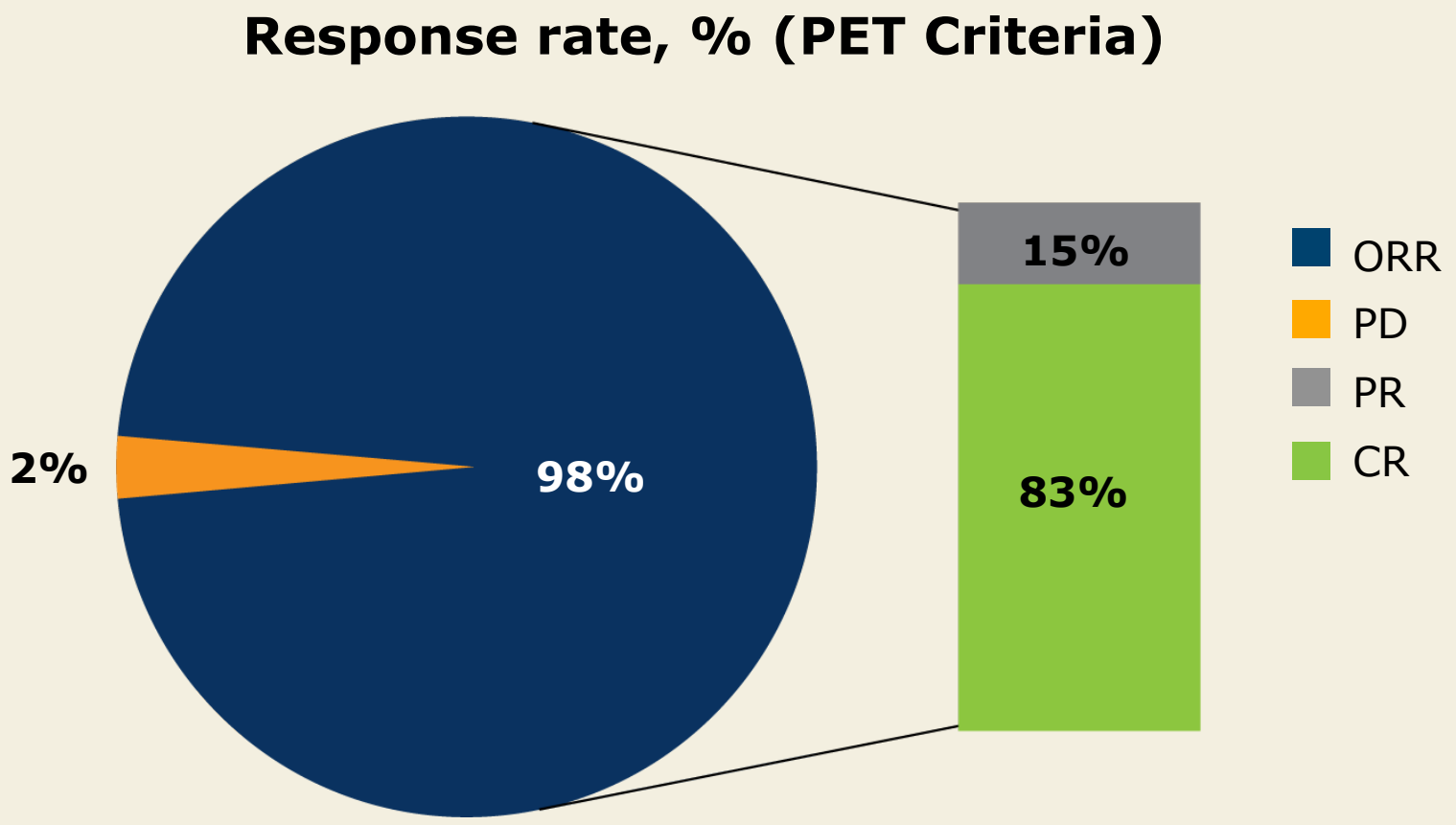
↓

R2CHOP (6 cycles, 21 d each):*
Lenalidomide 25 mg PO, d1-10,
rituximab (375 mg/m^2), cyclophosphamide (750 mg/m^2),
doxorubicin (50 mg/m^2), vincristine (1.4 mg/m^2) IV, d1
and prednisone (100 mg/m^2) PO, d1-5

* Pegfilgrastim (6 mg SC) administered on d2 of each cycle and aspirin (325 mg PO) administered daily

Nowakowski GS al. *Proc ASH* 2012;Abstract 689.

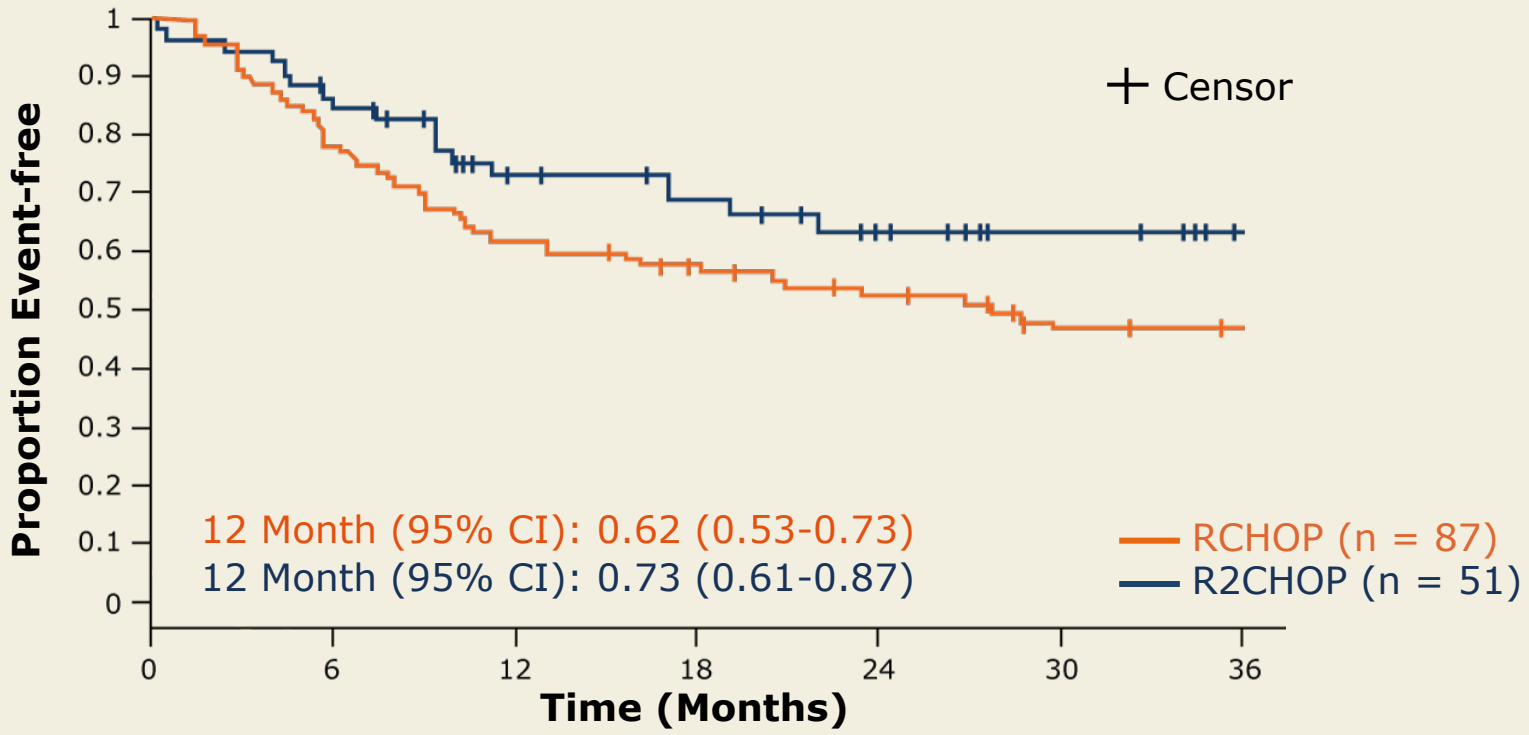
Response to R2CHOP



- Evaluable patients (n = 47)
- 4/51 patients were not evaluable (3 refusals, 1 death before evaluation)

With permission from Nowakowski GS al. *Proc ASH* 2012;Abstract 689.

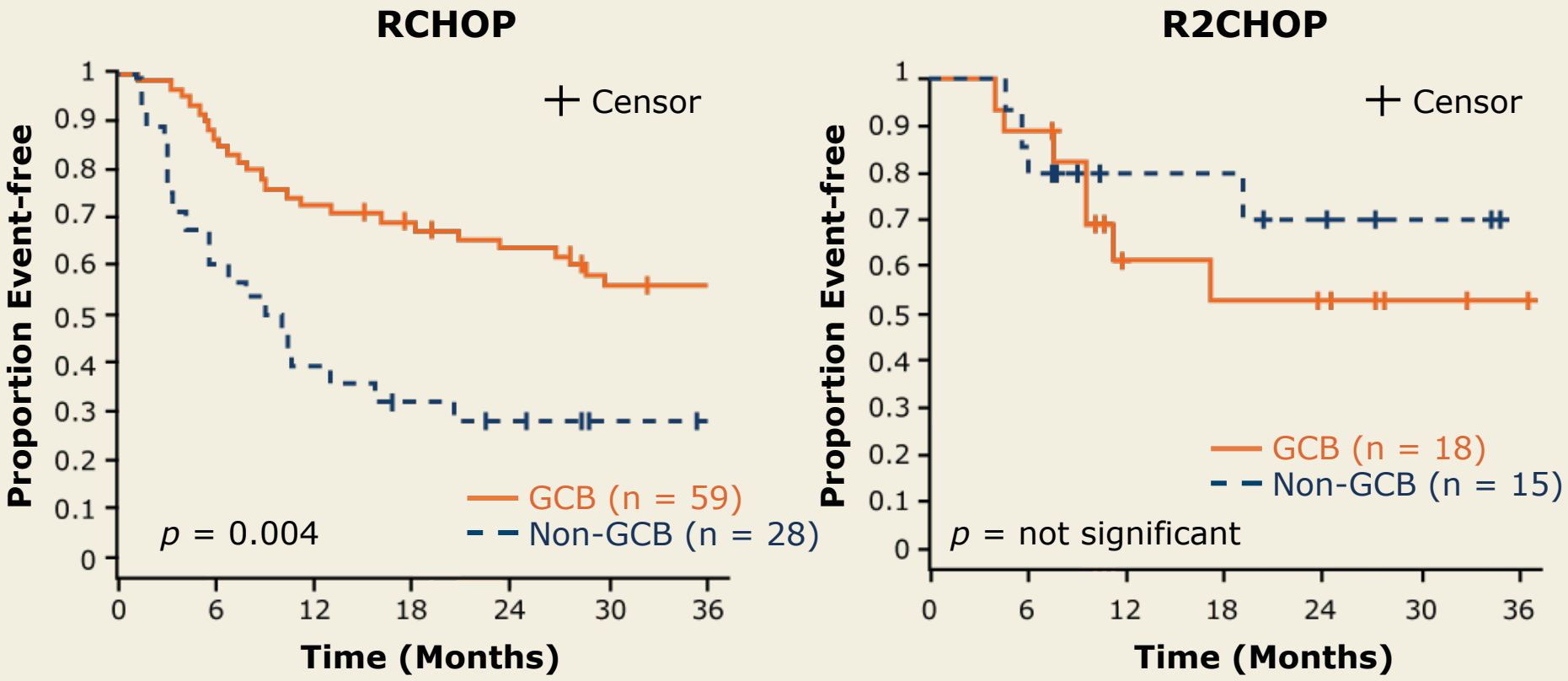
Progression-Free Survival (PFS) with R2CHOP versus R-CHOP Case-Matched Controls



- R-CHOP case-matched controls: Patients with Stage II (n = 20), III (n = 14) and IV (n = 53) DLBCL (same eligibility criteria) identified in the MCR lymphoma database; no difference in clinical characteristics

With permission from Nowakowski GS al. *Proc ASH* 2012;Abstract 689.

PFS by GCB versus Non-GCB Subtype with R2CHOP versus R-CHOP



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Select Adverse Events

Adverse event (n = 51)	Grade 3	Grade 4
Hematologic		
Neutropenia	18%	70%
Thrombocytopenia	20%	20%
Anemia	17%	2%
Infection		
Neutropenic fever	10%	0%
Pneumonia	4%	0%
Sepsis	0%	2%
Venous thrombosis	0%	2%

Grade 4 neutropenia was common; infectious complications were rare; Grade 4 thrombocytopenia was not accompanied by bleeding complications; 1 death due to perforation/sepsis

Nowakowski GS al. *Proc ASH* 2012;Abstract 689.

Author Conclusions

- R2CHOP is well tolerated, including in elderly patients.
- Efficacy of R2CHOP appears to be promising when compared to that of R-CHOP.
- Addition of lenalidomide to R-CHOP may ameliorate the negative effect of the non-GCB phenotype on outcome.
- A randomized study is required to evaluate R2CHOP versus R-CHOP
  - ECOG-E1412 is in development

Nowakowski GS al. *Proc ASH* 2012;Abstract 689.

Investigator Commentary: R2CHOP Is Well Tolerated and Effective as Initial Therapy for Aggressive B-Cell Lymphomas

Single-agent lenalidomide (Len) has a response rate of approximately 30% for relapsed DLBCL. This activity is more robust in patients with the ABC cell of origin as opposed to the GCB cell of origin subtype.

The addition of Len to R-CHOP in this study showed an overall response rate of 98% and a complete response rate of 83%, which is impressive. A comparison of PFS to that for a matched historical control group of patients who received R-CHOP indicated a benefit with the addition of Len. When the results were analyzed by cell of origin, the addition of Len appeared to be more effective for patients with the non-GCB or ABC subtype of DLBCL.

From a toxicity standpoint, it appears that the addition of Len increased the incidence of Grade 3 and 4 neutropenia and thrombocytopenia. But this did not translate into any serious adverse events for patients.

The Eastern Cooperative Oncology Group will conduct a randomized Phase II trial for more than 200 patients with untreated DLBCL, and patients will be randomly assigned to R2CHOP or R-CHOP. Cell of origin subtyping will be performed for all patients, and outcomes will be analyzed by cell of origin.

Interview with Brad S Kahl, MD, January 17, 2013

Rituximab-CHOP21 plus Lenalidomide (LR-CHOP21) Is Effective and Feasible in Elderly Untreated Diffuse Large B-Cell Lymphoma (DLBCL): Results of Phase II REAL07 Study of the Fondazione Italiana Linfomi (FIL)

Chiappella A et al.

Proc ASH 2012;Abstract 903.

Background

- Lenalidomide monotherapy exhibits significant activity in relapsed aggressive B-cell non-Hodgkin lymphoma and has synergistic activity with rituximab and chemotherapy in vitro.
- Therefore, a Phase I/II trial of lenalidomide and R-CHOP21 (LR-CHOP21) was initiated for elderly patients with untreated DLBCL.
- The dose-finding Phase I portion of the study established lenalidomide at 15 mg (days 1-14) as the maximum tolerated dose (MTD) in combination with R-CHOP21 (*Ann Oncol* 2011;22(S4):Abstract 331a).
- **Study objective:** To assess the efficacy and safety of LR-CHOP21 in elderly patients with untreated DLBCL.

Chiappella A et al. *Proc ASH* 2012;Abstract 903.

REAL07 Phase II Study Eligibility and Endpoints

Eligibility (N = 49*)
- Age 60-80 y, fit - CD20+ DLBCL or Grade IIIb FL - Ann Arbor Stage II-IV - IPI: Low-intermediate/intermediate-high/high risk - No peripheral neuropathy, CNS disease or recent DVT - No prior chemotherapy or prior malignancies in past 3 years

* Includes 9 patients treated at MTD in Phase I

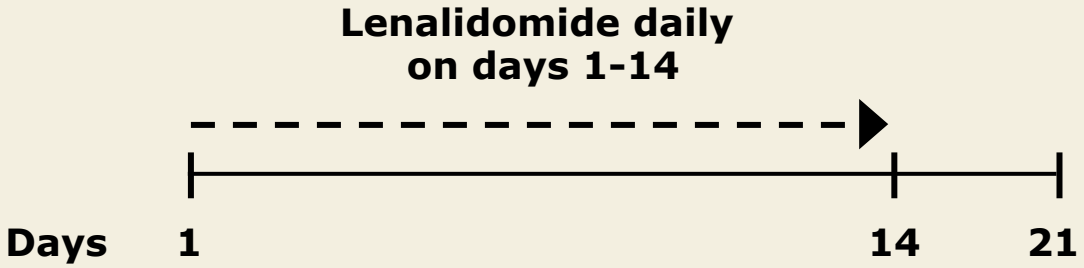
Primary endpoints: Overall response rate (ORR) and complete response (CR)

Secondary endpoints: Included 2-year overall survival (OS) and 2-year progression-free survival (PFS)

Chiappella A et al. *Proc ASH* 2012;Abstract 903.

REAL07 Phase II Study Design

Treatment cycles



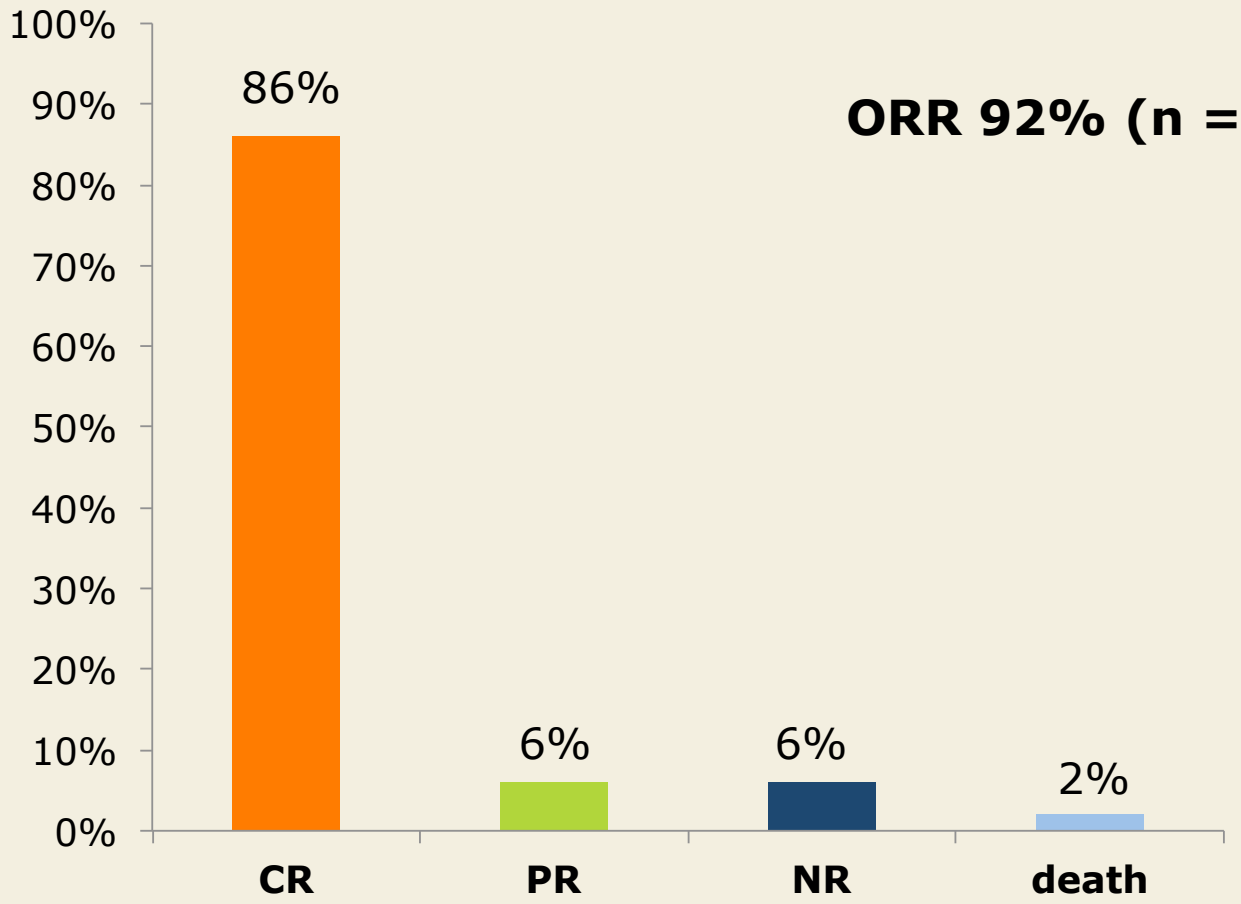
Lenalidomide at MTD:
15 mg daily on days 1-14 (Vitolo U, ASH 2010)

(↑) Rituximab	**375 mg/m^2**
Cyclophosphamide	**750 mg/m^2**
Doxorubicin	**50 mg/m^2**
Vincristine	**1.4 mg/m^2 (capped at 2.0 mg)**
Prednisone	**40 mg/m^2 on days 1-5**

Prophylaxis included: GCSF or PEG-GCSF, low-molecular-weight heparin or low-dose aspirin, co-trimoxazole

Chiappella A et al. *Proc ASH* 2012;Abstract 903.

Final Response After 6 Cycles of LR-CHOP21



ORR 92% (n = 49)

PR = partial response; NR = no response

Chiappella A et al. *Proc ASH* 2012;Abstract 903.

Select Adverse Events

Adverse event	Grade 3	Grade 4
Hematologic*		
Leukocytopenia	15%	13%
Neutropenia	9%	22%
Febrile neutropenia	3%	1%
Thrombocytopenia	6%	7%
Anemia	4%	<0.5%
Nonhematologic†		
Cardiac	2%	0%
Neurological	4%	0%
Infection	2%	0%
DVT	2%	0%

* Recorded in 277 cycles of treatment; † In the population of 49 patients

Chiappella A et al. *Proc ASH* 2012;Abstract 903.

Author Conclusions

- Lenalidomide with R-CHOP21 is highly effective, with an ORR of 92% and a CR (PET-negative) of 86% in elderly patients with DLBCL.
- With limited follow-up, these results (data not shown) compare favorably to historical R-CHOP21 data (*NEJM* 2002;346(4):235
  - 2-year OS rate: 92% vs 70%
  - 2-year PFS rate: 73% vs 57%
- LR-CHOP21 induced a high 2-y PFS rate of 65%, even in patients with poor-risk disease (data not shown).
- The addition of lenalidomide to R-CHOP21 is safe without unexpected toxicities and does not impair the dose and timing of R-CHOP.
- These encouraging data warrant a future Phase III randomized trial comparing LR-CHOP21 to R-CHOP21 in elderly patients with untreated DLBCL.

Chiappella A et al. *Proc ASH* 2012;Abstract 903.

Investigator Commentary: Phase II REAL07 Study of LR-CHOP21 in Elderly Patients with Untreated DLBCL

This Phase II trial investigated the addition of lenalidomide to R-CHOP21 for elderly patients with DLBCL. One reason why the combination of lenalidomide and rituximab may be synergistic is that it may restore the ability of the immune system to attack cancer cells. Malignant cells have the ability to repel immune cells in the tumor microenvironment. In vitro, lenalidomide can overcome that inhibition and restore normal immunomodulatory synapse formation.

The results showed a high complete response rate of 86% and a 2-year PFS of 73%, which is better than historical controls. This study provides evidence that the addition of lenalidomide to an R-CHOP backbone is beneficial. Randomized trials will provide a definitive answer and are in the planning stage.

Interview with Brad S Kahl, MD, January 17, 2013

Phase II Multicenter Study of Single-Agent Lenalidomide in Subjects with Mantle Cell Lymphoma Who Relapsed or Progressed After or Were Refractory to Bortezomib: The MCL-001 Study (EMERGE™ Trial)

Goy A et al.

Proc ASH 2012;Abstract 905.

Background

- Relapsed/refractory mantle-cell lymphoma (MCL) is characterized by frequent chemoresistance and limited treatment options.
- There is no standard therapy for patients for whom bortezomib (BTZ) has failed.
- Phase II studies have shown activity and tolerability with single-agent lenalidomide in relapsed/refractory aggressive non-Hodgkin lymphomas, including MCL (*Ann Oncol* 2011;22:1622, *Br J Haematol* 2009;145:344).
- **Study objective:** To assess the safety and efficacy of single-agent lenalidomide in patients with MCL that has relapsed or is refractory to BTZ.

Goy A et al. *Proc ASH* 2012;Abstract 905.

Phase II EMERGE Study Design

Eligibility (N = 134)

- MCL diagnosis reviewed by central pathology
- Disease progression on prior anthracycline (or mitoxantrone), cyclophosphamide, rituximab, BTZ
- BTZ failure: Relapsed/progressed ≤12 mo from last dose after CR/PR or refractory with <PR after ≥2 cycles

→ Lenalidomide: 25 mg, d1-21, q28d*

* Until disease progression or unacceptable toxicity, CT every 2 cycles; follow-up CT every 90 d

Aspirin or low-molecular-weight heparin prophylaxis for patients at high risk

Primary endpoints: Overall response rate and duration of response

Secondary endpoints: CR, PFS, TTP, OS and safety

Goy A et al. *Proc ASH* 2012;Abstract 905.

Response to Lenalidomide

Response (n = 134)	Central review	Investigator review
Overall response rate*	28%	32%
CR/CRu	8%	16%
PR	20%	16%
Stable disease	29%	27%
Progressive disease	26%	32%
Median DOR	16.6 mo	18.5 mo
Median DOR for CR/CRu	16.6 mo	26.7 mo

* No response assessments available for 23 pts (central review) and 12 pts (investigator review)

- Maximum DOR was 29+ months at data cutoff

Goy A et al. *Proc ASH* 2012;Abstract 905.

Efficacy of Lenalidomide

Efficacy parameter (n = 134)	Central review	Investigator review
Median time to response	2.2 mo	2.0 mo
Median time to CR/CRu	3.7 mo	5.6 mo
Median PFS	4.0 mo	3.8 mo
Median OS*	19.0 mo	

* Median follow-up = 9.9 months

Goy A et al. *Proc ASH* 2012;Abstract 905.

Efficacy Subgroup Analysis (Central Review)

Characteristics	ORR	Median DOR
High MIPI (n = 39)	26%	7.7 mo
High tumor burden* (n = 77)	29%	14.8 mo
Bulky disease† (n = 44)	30%	14.8 mo
Refractory to BTZ (n = 81)	27%	20.5 mo
Refractory to last prior therapy (n = 74)	27%	26.7 mo
Prior high-dose or high-intensity treatment (n = 44)	27%	16.7 mo

* At least 1 lesion ≥5 cm in diameter or at least 3 lesions ≥3 cm in diameter by central radiology review
† At least 1 lesion ≥7 cm by central radiology review

Goy A et al. *Proc ASH* 2012;Abstract 905.

Select Adverse Events

Adverse event (n = 134)	Overall	Grade 3/4
Hematologic		
Neutropenia	49%	43%
Thrombocytopenia	36%	27%
Anemia	31%	11%
Leukopenia	15%	7%
Febrile neutropenia	6%	7%
Nonhematologic		
Fatigue	34%	7%
Diarrhea	31%	6%

Overall incidence of other AEs: Tumor flare reaction (Grade 1/2): 10%; deep vein thrombosis: 4%; pulmonary embolism: 2%; second primary malignancy: 5%

Goy A et al. *Proc ASH* 2012;Abstract 905.

Author Conclusions

- The EMERGE trial confirmed lenalidomide efficacy with an ORR of 28% (CR/CRu 8%); median DOR 16.6 months.
- These results were obtained in a population with heavily pretreated MCL: Median 4 prior therapies (range, 2-10), two thirds refractory to BTZ, more than half with high tumor burden, one third with bulky disease and one third received prior transplant (data not shown).
- Safety profile was manageable and consistent with other studies of lenalidomide in non-Hodgkin lymphoma.
- Lenalidomide demonstrated rapid (median time to response, 2 months) and durable efficacy in patients with MCL for whom prior therapies that included BTZ had failed.

Goy A et al. *Proc ASH* 2012;Abstract 905.

Investigator Commentary: Phase II EMERGE Study of Lenalidomide in Relapsed/Refractory MCL

EMERGE is a multicenter, registration trial investigating single-agent lenalidomide in relapsed/refractory MCL. The results of this study will determine whether lenalidomide receives FDA approval in MCL.

The overall response rate to single-agent lenalidomide was 28%, which is respectable. The response rates are not as exciting in the ibrutinib era where responses in the 50% to 70% range are being observed in relapsed MCL. The progression-free survival of 4 months is not impressive, but the median duration of response was approximately 17 months, which suggests that in patients who do respond, the responses are durable.

Toxicities were similar to what had been previously observed with lenalidomide and included neutropenia, thrombocytopenia and a low rate of venous thromboembolic disease.

My hope is that lenalidomide does receive approval in this setting. MCL is incurable, and we need more treatment options for patients with this disease.

Interview with Brad S Kahl, MD, January 17, 2013

The Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib (PCI-32765), Has Preferential Activity in the ABC Subtype of Relapsed/Refractory De Novo Diffuse Large B-Cell Lymphoma (DLBCL): Interim Results of a Multicenter, Open-Label, Phase 2 Study

Wilson WH et al.

Proc ASH 2012;Abstract 686.

Background

- Survival of activated B-cell-like (ABC) but not germinal center B-cell-like (GCB) DLBCL cell lines is sustained by "chronic active" B-cell receptor (BCR) signaling.
- Constitutive activation of NFκB leads to activation of a prosurvival program in ABC DLBCL.
- Mutations in the BCR subunit CD79B and in the adaptor protein for toll-like receptors, MYD88, occur more frequently in ABC than GCB DLBCL and could lead to the activation of NFκB and chronic BCR signaling in ABC DLBCL.
- Ibrutinib is a first-in-class oral inhibitor of Bruton tyrosine kinase (BTK), a kinase in the BCR pathway.
- **Study objective:** Evaluate the efficacy and safety of ibrutinib in relapsed/refractory DLBCL.

Wilson WH et al. *Proc ASH* 2012;Abstract 686.

Phase II Study Design

Eligibility (N = 70)

- Relapsed/refractory de novo DLBCL
- Progressive disease (PD) after ASCT or ineligible for ASCT
- Archival tissue for central review
- No primary mediastinal DLBCL, transformed DLBCL or CNS involvement

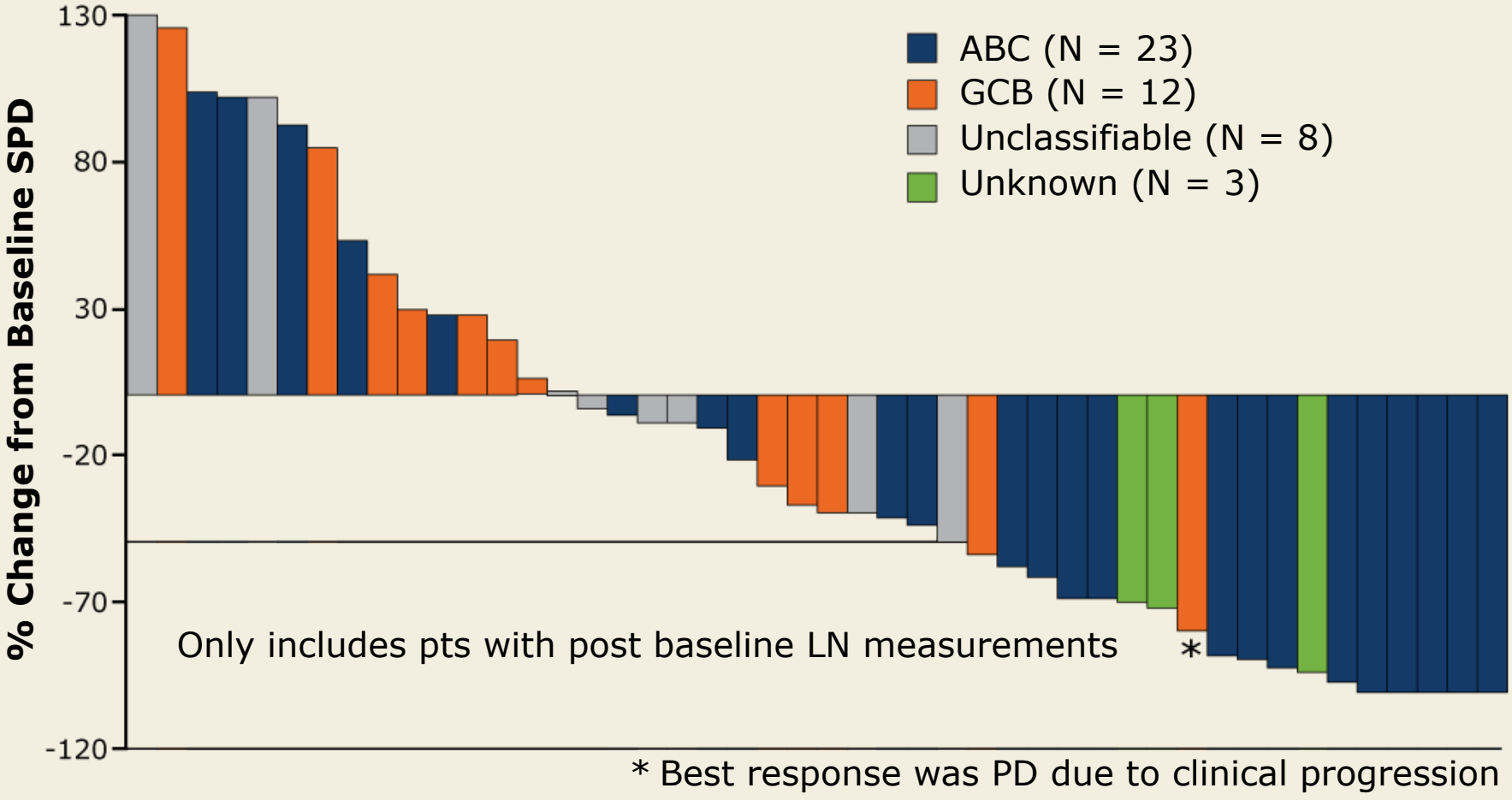
→ Ibrutinib: 560 mg/d, PO

ASCT = autologous stem cell transplant

- Gene expression profiling of biopsy tissues using Affymetrix arrays to identify DLBCL subtype (ABC, GCB, unclassifiable)
- Mutations in tumor samples analyzed by PCR and DNA sequencing
- ABC DLBCL tumors analyzed for mutations in CD79B, MYD88 and CARD11 genes

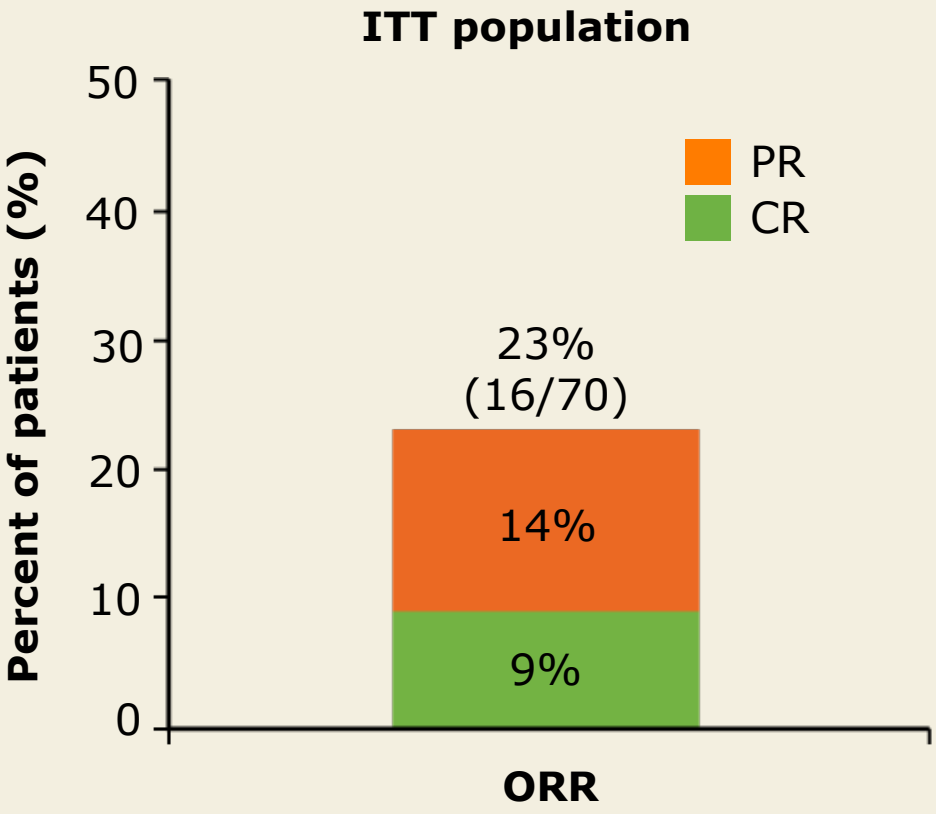
Wilson WH et al. *Proc ASH* 2012;Abstract 686.

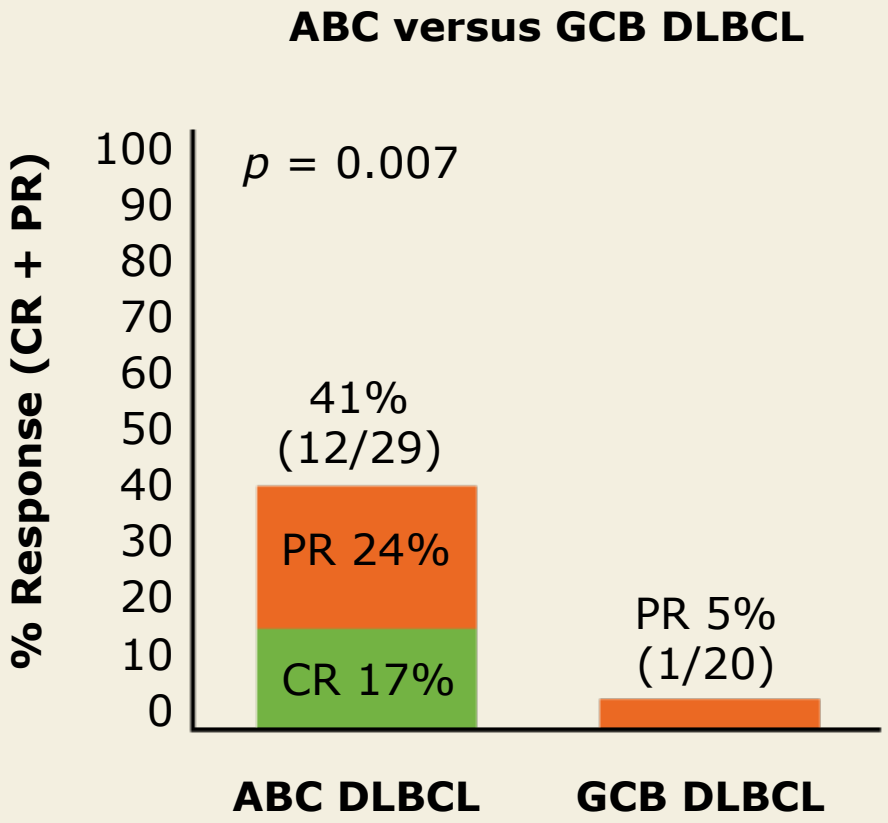
Waterfall Plot of Maximum Decrease in Bidimensional Measurements



With permission from Wilson WH et al. *Proc ASH* 2012;Abstract 686.

Response to Ibrutinib

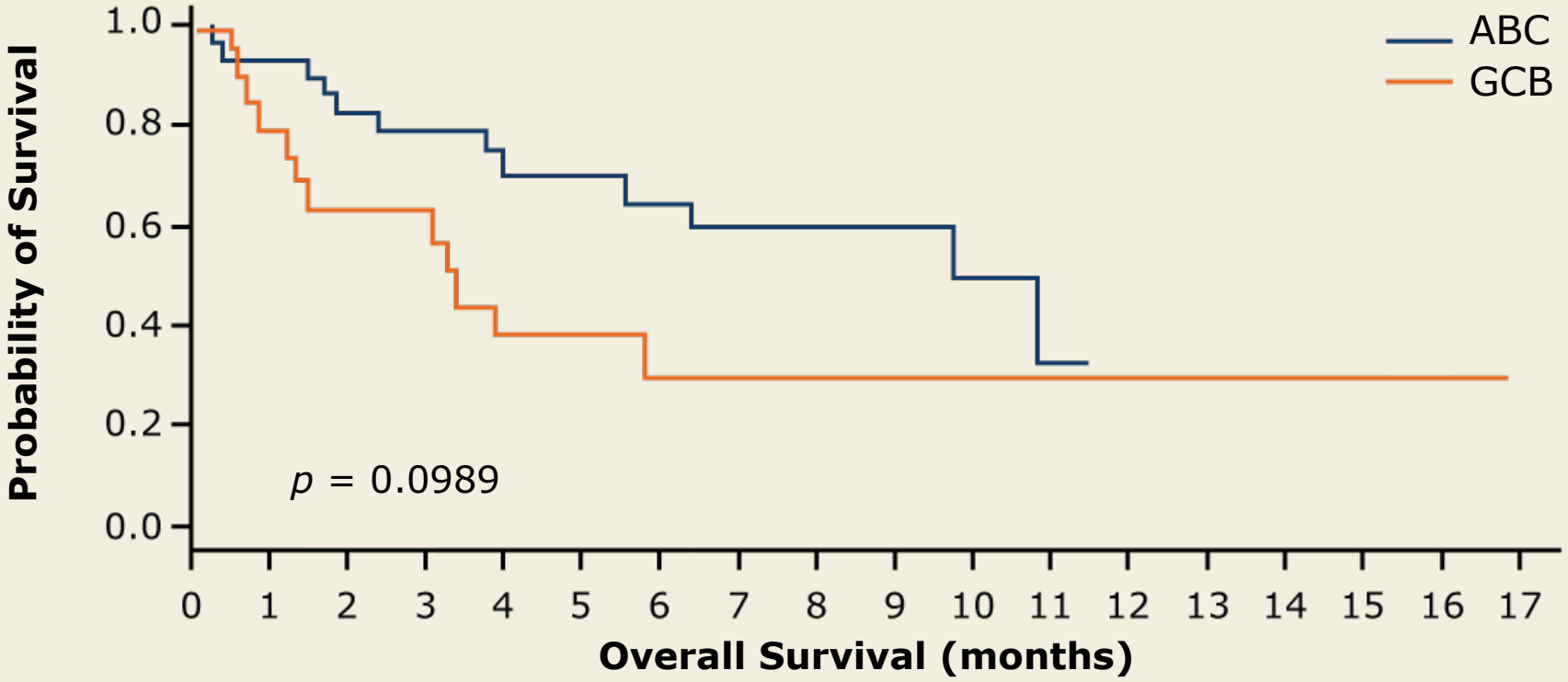




ORR = overall response rate; PR = partial response; CR = complete response

With permission from Wilson WH et al. *Proc ASH* 2012;Abstract 686.

Overall Survival in ABC and GCB DLBCL



	ABC (n = 29)	GCB (n = 20)
Median OS	9.76 mo	3.35 mo

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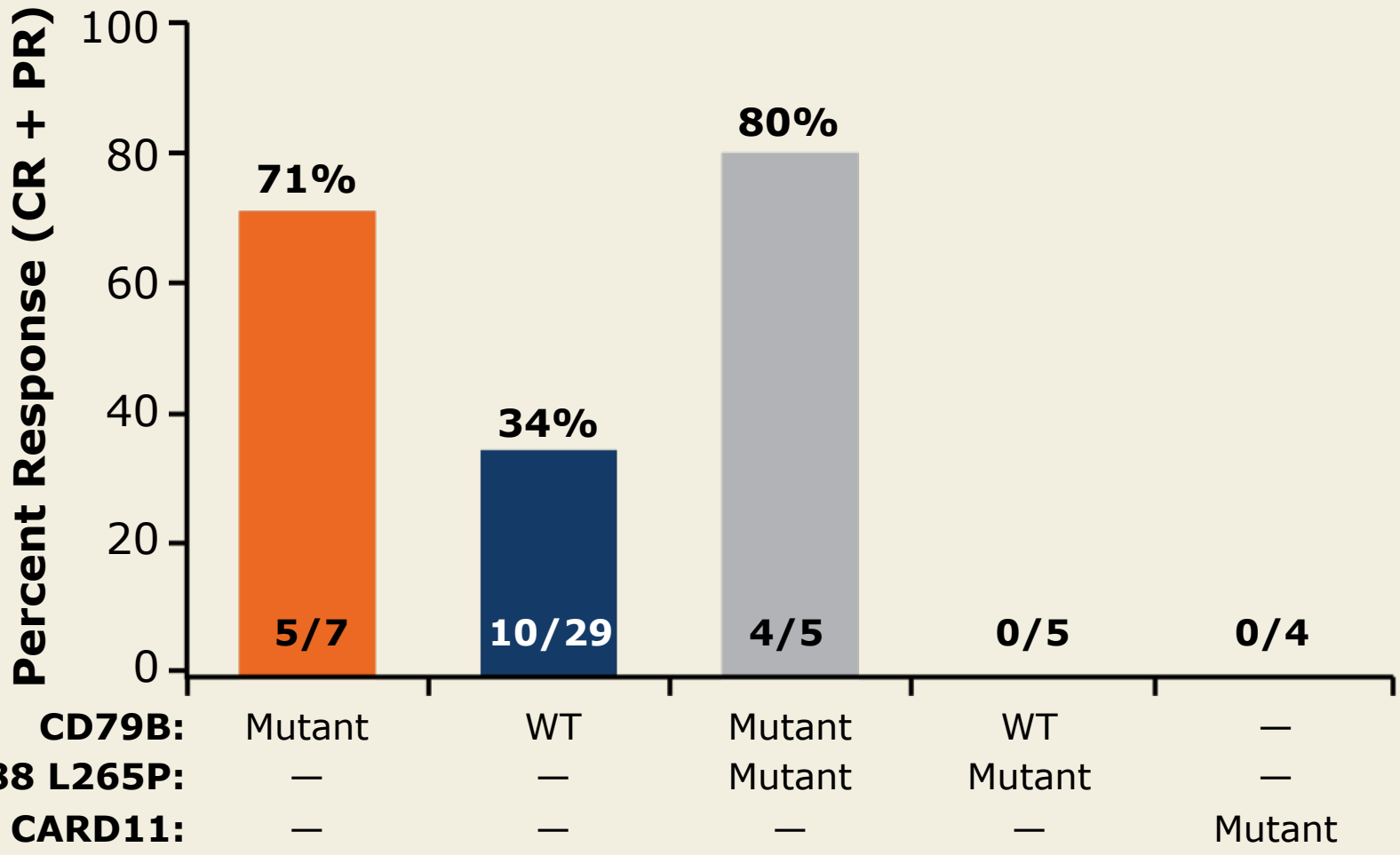
Response of CD79B-, MYD88- and CARD11-Mutant ABC DLBCL to Ibrutinib



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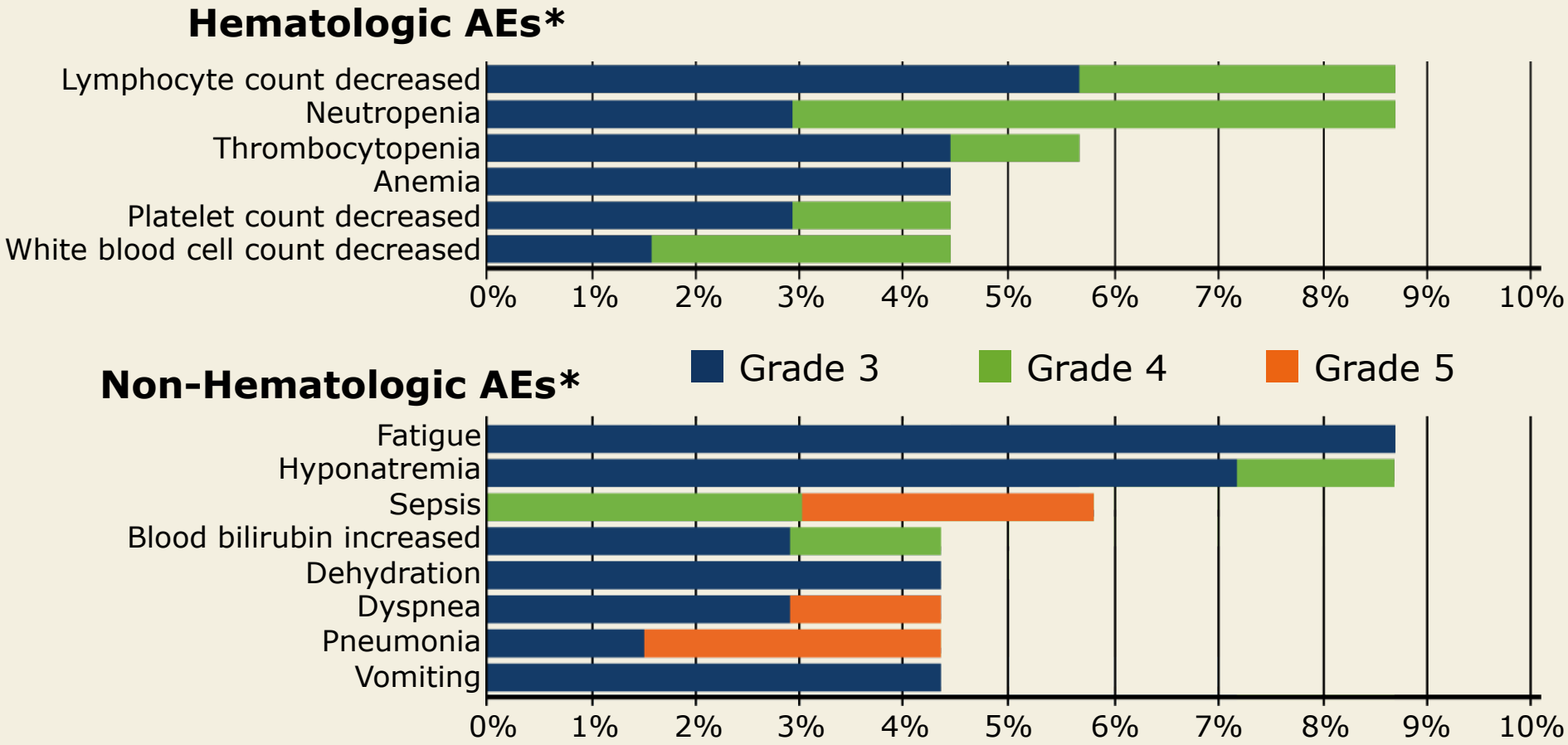
Grade ≥3 Adverse Events



* >3% incidence (unrelated and related to ibrutinib)

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Author Conclusions

- Ibrutinib induced a high response rate in relapsed/refractory ABC DLBCL.
- Ibrutinib had marginal activity in GCB DLBCL, supporting the ABC DLBCL molecular subtype as a biomarker for activity.
- CD79B-mutant tumors responded frequently to ibrutinib, suggesting that it inhibits "chronic active" BCR signaling in ABC DLBCL.
- Ibrutinib response did not require CD79B mutation, suggesting that BCR pathway addiction can occur by other means in ABC DLBCL.
- CARD11-mutant tumors were resistant, suggesting that ibrutinib response requires upstream BCR signaling.
- Tumors harboring only MYD88 L265P mutation were resistant to ibrutinib, suggesting a BCR-independent pathway to ABC DLBCL.
- Ibrutinib was associated with a favorable safety profile.

Wilson WH et al. *Proc ASH* 2012;Abstract 686.

Investigator Commentary: Phase II Study of Ibrutinib in the ABC Subtype of Relapsed/Refractory DLBCL

The oral BTK inhibitor ibrutinib is one of the most dynamite drugs in lymphoid cancers. The drug is active in chronic lymphocytic leukemia/ small lymphocytic lymphoma and mantle-cell lymphoma. Its activity in follicular lymphoma is less well defined.

In DLBCL, the activity of ibrutinib is selective based on the cell of origin. The overall activity of ibrutinib in an unselected population in this study was not impressive. However, when patients were classified according to the cell of origin subtype, the overall response rate (ORR) for those with the ABC subtype was approximately 40%, whereas the ORR for those with the GCB subtype was 5%.

This is an example of how a better understanding of the biology of the disease can lead to a more rational selection of patients for treatment with targeted agents. The preferential activity of ibrutinib in ABC DLBCL has implications not only for relapsed/refractory disease but also for the design of trials that may be initiated with ibrutinib in the front-line treatment of the disease.

Interview with Brad S Kahl, MD, January 17, 2013

Interim Results of an International, Multicenter, Phase 2 Study of Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib (PCI-32765), in Relapsed or Refractory Mantle Cell Lymphoma (MCL): Durable Efficacy and Tolerability with Longer Follow-Up

Wang M et al.

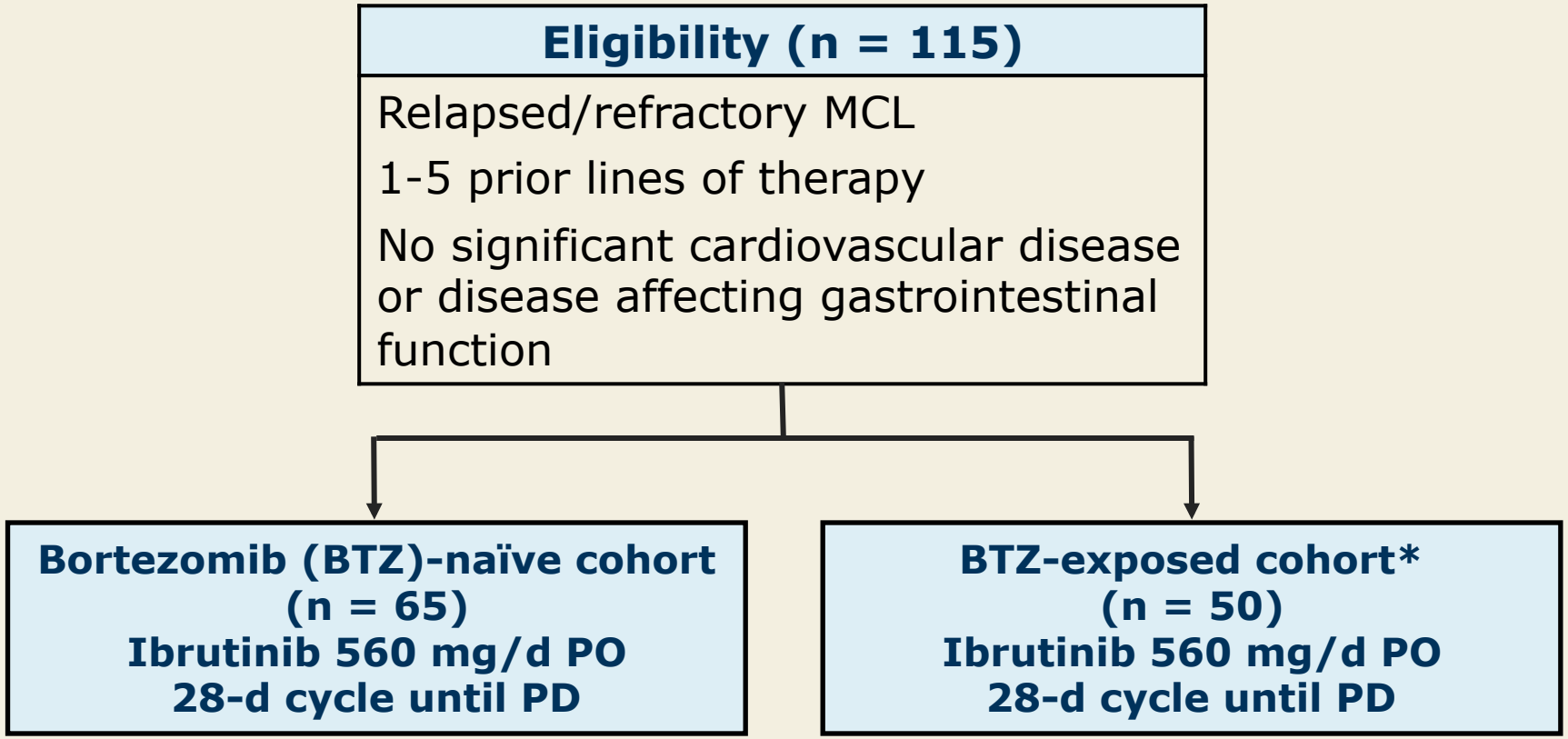
Proc ASH 2012;Abstract 904.

Background

- Ibrutinib is an orally available BTK inhibitor that induces apoptosis and inhibits cellular migration and adhesion in malignant B cells.
- Preliminary results from the Phase II PCYC-1104-CA trial demonstrated that ibrutinib produced rapid nodal responses, including complete responses, in patients with relapsed or refractory MCL (*Proc ASH* 2011;Abstract 442).
- Treatment with ibrutinib was also associated with the inhibition of MCL cell chemotaxis and adherence (*Proc ASH* 2011;Abstract 954).
- **Study objective:** To provide updated PCYC-1104-CA interim analysis results of the efficacy and safety of single-agent ibrutinib in previously treated MCL.

Wang M et al. *Proc ASH* 2012;Abstract 904.

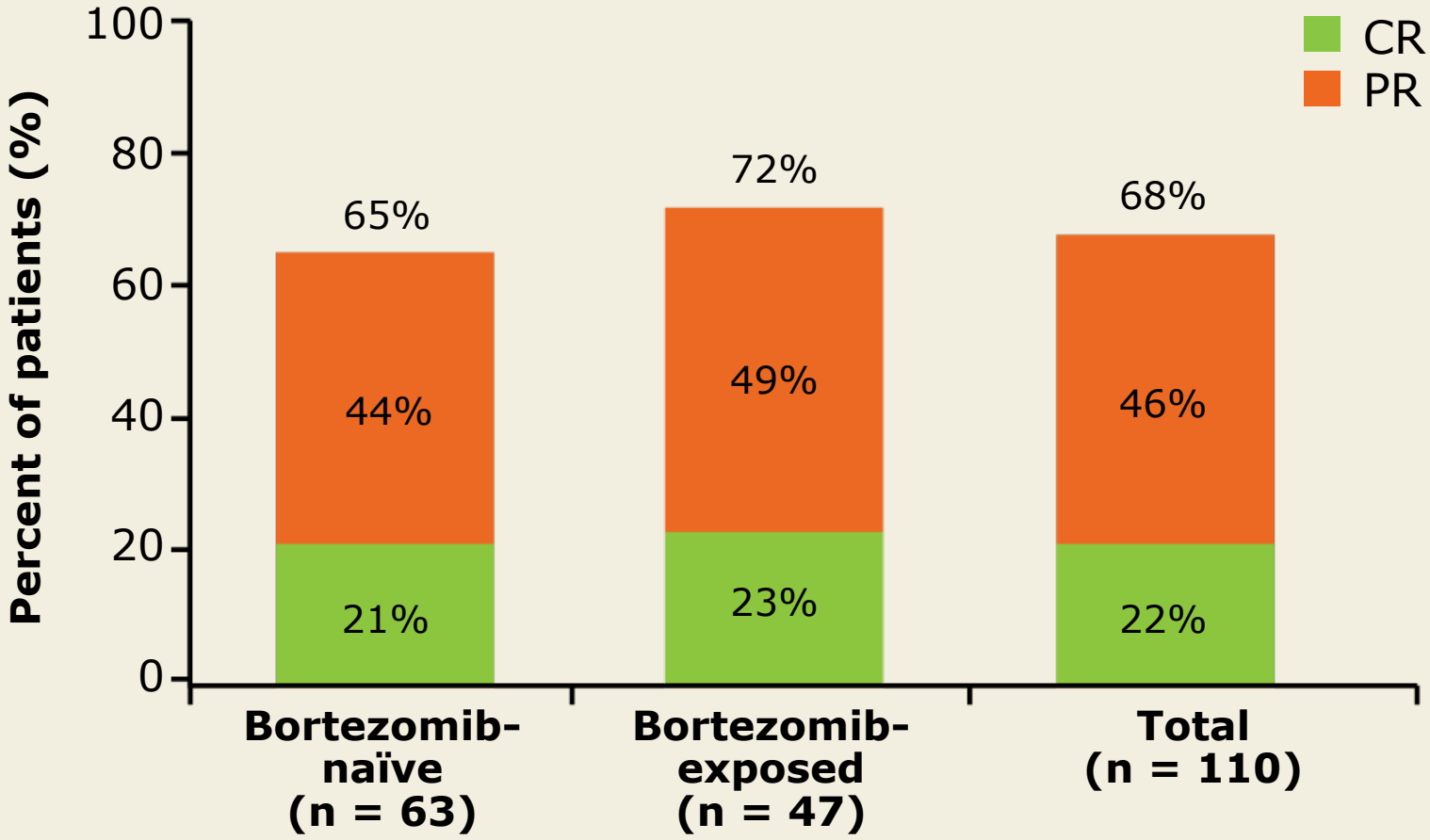
PCYC-1104-CA: Phase II Trial Design



* ≥2 cycles

Wang M et al. *Proc ASH* 2012;Abstract 904.

Best Response



Efficacy population, n = 110. Median follow-up: 9.2 mo

With permission from Wang M et al. *Proc ASH* 2012;Abstract 904.

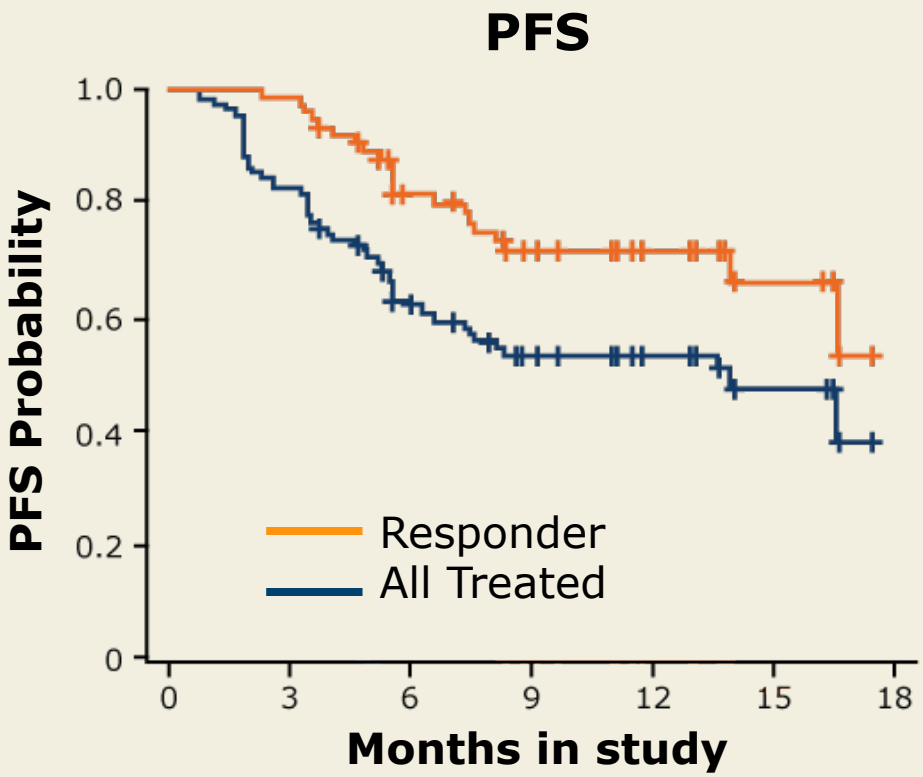
Time to Response (Phenomenon of Incremental Response)

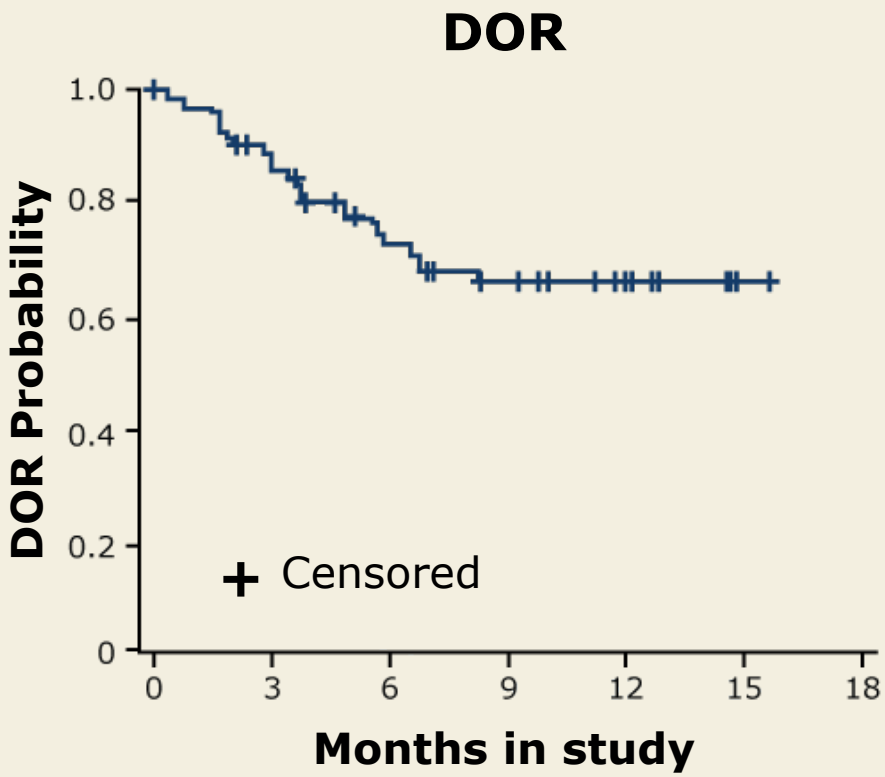
Response	Bortezomib naïve (n = 63)	Bortezomib exposed (n = 47)	Total (n = 110)
Time to PR			
N	37	31	68
Median	1.9 mo	1.8 mo	1.9 mo
Range	1.4-8.1 mo	1.5-9.1 mo	1.4-9.1 mo
Time to CR			
N	13	11	24
Median	5.6 mo	3.9 mo	5.5 mo
Range	1.7-16.4 mo	1.7-11.0 mo	1.7-16.4 mo

PR = partial response; CR = complete response

Wang M et al. *Proc ASH* 2012;Abstract 904.

Progression-Free Survival (PFS)and Duration of Response (DOR)



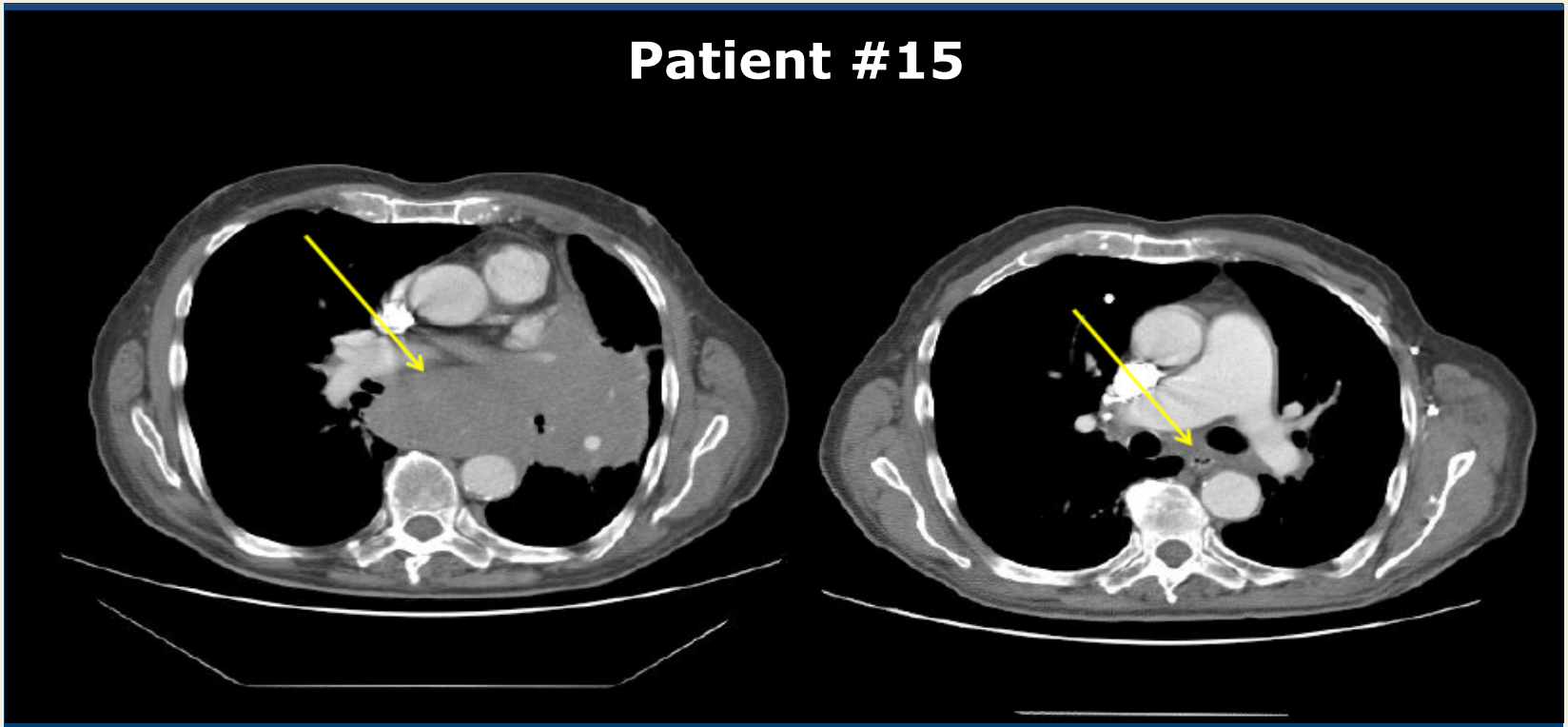


All Treated Population	111
Median PFS (CI 95%) months	13.9 (6.64, NR)

All Responded Population	75
Median DOR (CI 95%) months	NR (NR, NR)

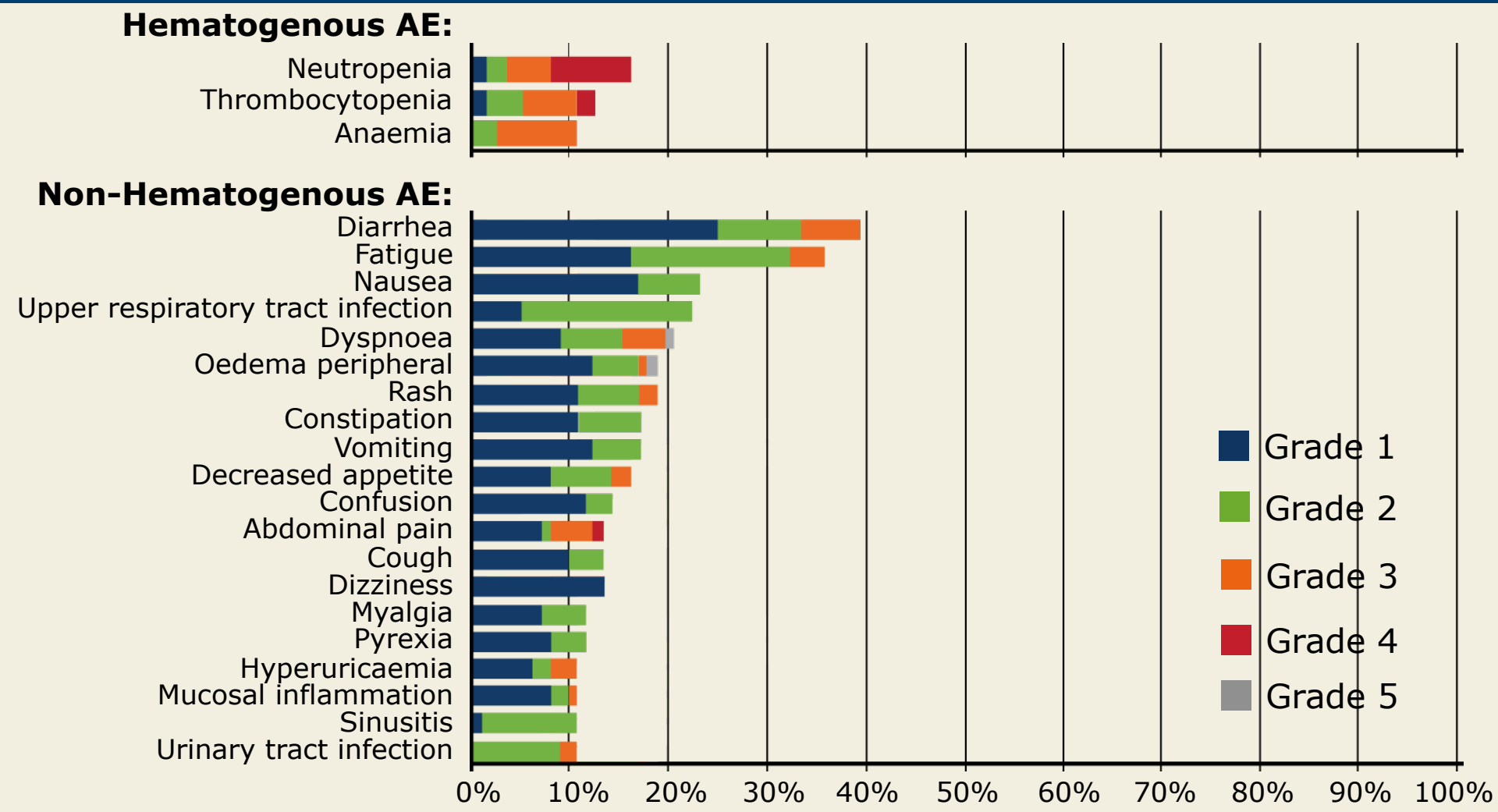
With permission from Wang M et al. *Proc ASH* 2012;Abstract 904.

Case Report: Response After 2 Cycles of Ibrutinib



With permission from Wang M et al. *Proc ASH* 2012;Abstract 904.

Adverse Events (AEs) in >10% of Patients Regardless of Cause



With permission from Wang M et al. *Proc ASH* 2012;Abstract 904.

Author Conclusions

- Ibrutinib demonstrated an unprecedented single-agent overall response rate and a high complete response rate in relapsed/refractory MCL.
- Responses were durable: Median duration of response not reached, median PFS 13.9 months.
- Response improved with longer follow-up with the phenomenon of "incremental response."
- Ibrutinib has a favorable safety profile and is well tolerated. The treatment-emergent AEs were consistent with safety data previously reported.
- Additional studies have been initiated in multiple clinical settings in MCL.

Wang M et al. *Proc ASH* 2012;Abstract 904.

Investigator Commentary: Interim Results of a Phase II Study of Ibrutinib in Relapsed or Refractory MCL

This is a report of the results from a multicenter, Phase II study of single-agent ibrutinib for 115 patients with relapsed/refractory MCL. Similar to the data presented in chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL), ibrutinib produced fantastic responses in MCL. In this cohort of patients with MCL, the ORR was about 70%, and the durability of response was impressive. At 12 months, about 60% of patients were still experiencing disease remission.

In my opinion, the PFS curves across different disease histologies are interesting. The responses to ibrutinib appear to be most durable in CLL/SLL, with the PFS curves holding near the top. In MCL, however, the responses seem to be dropping off somewhat faster. Nonetheless, response to ibrutinib is impressive in MCL. I believe ibrutinib therapy yields better results in comparison to PI3-kinase inhibitors in MCL in terms of response rates and duration of response. Based on this study, it is fair to say that ibrutinib is an extremely impressive drug. Right now, bortezomib is the only agent approved for relapsed disease. About 7 years ago, we thought that the discovery of bortezomib was a tremendous breakthrough. Looking at ibrutinib today, it appears to be twice as effective as bortezomib in this patient population.

Interview with Brad S Kahl, MD, January 17, 2013

An Open-Label, Randomized Study of Bendamustine and Rituximab (BR) Compared with Rituximab, Cyclophosphamide, Vincristine, and Prednisone (R-CVP) or Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) in First-Line Treatment of Patients with Advanced Indolent Non-Hodgkin's Lymphoma (NHL) or Mantle Cell Lymphoma (MCL): The Bright Study

Flinn IW et al.

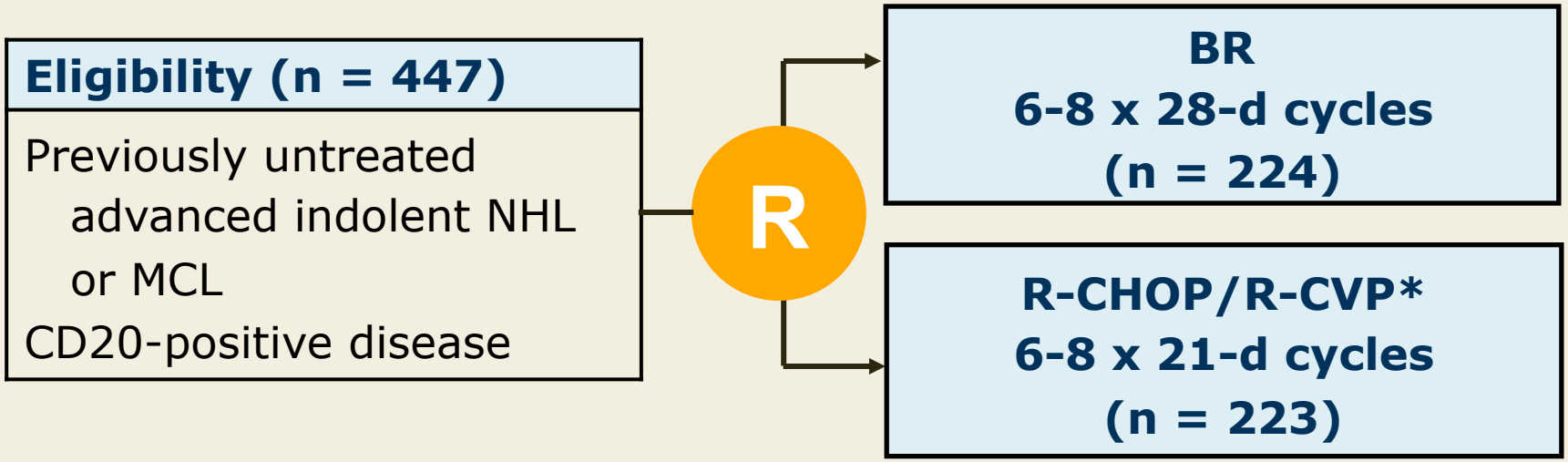
Proc ASH 2012;Abstract 902.

Background

- Bendamustine (B) is an active agent for relapsed and refractory indolent NHL (*Clin Lymphoma Myeloma Leuk* 2010;10:452).
- The Phase III StiL trial demonstrated that the combination of B with rituximab (R) versus R-CHOP as first-line therapy for patients with advanced follicular, indolent and mantle-cell lymphoma (*Lancet* 2013;381:1203):
  - Is tolerable
  - Improves progression-free survival and complete response (CR) rates
- **Study objective:** To compare the efficacy and safety of BR to the standard treatment regimens R-CHOP and R-CVP as first-line therapy for indolent NHL or MCL.

Flinn IW et al. *Proc ASH* 2012;Abstract 902.

Phase III Bright Trial Design



* Determined by investigator prior to randomization

- **Primary endpoint:** Demonstrate noninferiority of CR rate for BR versus R-CHOP/R-CVP (noninferiority margin [ratio]: 0.88)

Flinn IW et al. *Proc ASH* 2012;Abstract 902.

Patient Characteristics (Abstract Only)

Characteristic	BR	R-CHOP/R-CVP
Median age	60 years	58 years
Gender (male)	61%	59%
ECOG PS 0	64%	64%
Lymphoma type		
Indolent	83%	83%
Ann Arbor Stage IV	62%	62%

- Of 447 patients who were randomly assigned:
  - 436 received treatment and were evaluable for safety
  - 419 were evaluable for efficacy

Flinn IW et al. *Proc ASH* 2012;Abstract 902.

CR Rates (Abstract Only)

Population	BR (n = 213)	R-CHOP/R-CVP (n = 206)	Ratio	*p*-value
Evaluable*	31%	25%	1.25	0.0225†
Randomized*	31%	23%	1.34	0.0084†
Randomized (NHL)*	27%	23%	1.16	0.1289†
Randomized (MCL)*	51%	24%	1.95	0.0180‡
Randomized (INV)	31%	18%	1.60	0.0013‡

INV = investigator assessment

* Tumor response by blinded independent review committee (IRC)

† Test for noninferiority

‡ Test for superiority

Flinn IW et al. *Proc ASH* 2012;Abstract 902.

Response Rate and Treatment Outcomes (Abstract Only)

	BR (n = 213)	R-CHOP/R-CVP (n = 206)
Overall response rate	94%	84%
Progressive/relapsed disease or death*	8%	4%
Completed 6 treatment cycles with >96% dose intensity	92%	91%
Dose delays	35%	19%
Dose reductions	22%	29%

* At time of data cutoff

- Independent review committee and INV differed mainly in quality of response (CR versus partial response) rather than in whether a patient was a responder.
- Time-to-event data are immature at time of present analyses.

Flinn IW et al. *Proc ASH* 2012;Abstract 902.

Select Adverse Events (AEs) (Abstract Only)

All AEs (no. of patients [n])	BR (n = 221)	R-CHOP/R-CVP (n = 215)
Nausea	139	102
Fatigue	113	107
Alopecia	8	74
Grade 3 or 4 AEs (n)		
Lymphopenia	137	64
Neutropenia; leukopenia	98; 84	151; 116
Thrombocytopenia; anemia	16; 6	15; 9

- Fatal AEs occurred in 6 patients (BR) and 1 patient (R-CHOP/R-CVP).
- Most common investigator-reported Grade 3 or 4 nonhematologic AEs were infusion-related reactions.

Flinn IW et al. *Proc ASH* 2012;Abstract 902.

Author Conclusions

- Among patients with advanced indolent NHL and MCL, BR produced a CR rate that is noninferior to that of R-CHOP/ R-CVP.
- In the subgroup of patients with MCL, BR produced a significantly higher CR rate (51% versus 24%).
- High overall response rates were achieved in both treatment groups.
- The toxicity profile of BR was distinct from that of R-CHOP/ R-CVP.

Flinn IW et al. *Proc ASH* 2012;Abstract 902.

Investigator Commentary: Phase III Bright Trial of First-Line BR versus R-CHOP or R-CVP for Advanced Indolent NHL or MCL

This was a noninferiority study that demonstrated that BR was not inferior to R-CHOP or R-CVP for all patients. As in the StiL trial, BR was not better than R-CHOP for indolent lymphoma, with comparable response rates. The toxicity profile included more GI toxicities with BR, whereas patients who received R-CHOP or R-CVP experienced more alopecia and neutropenia. I would call this a kind of "toxicity tradeoff." From an efficacy standpoint, BR was comparable to R-CHOP or R-CVP for indolent lymphoma. However, for MCL the BR regimen was a little better than R-CHOP or R-CVP, with a CR of 51% versus 24%. Along with the StiL trial, this study gives me confidence that BR is a better platform or a better backbone for MCL than R-CHOP. I believe the jury is still out for follicular lymphoma or other indolent histologies. The StiL trial demonstrated that BR is somewhat more efficacious than R-CHOP, and this study showed that the 2 regimens are roughly comparable. In either scenario, I'm still comfortable administering front-line BR to my patients because it is not worse than R-CHOP. Since BR is associated with less risk of alopecia than R-CHOP, it is attractive to patients. Also, it allows one to save the anthracycline included in the R-CHOP for later, in case the disease transforms.

Interview with Brad S Kahl, MD, January 17, 2013

Mature Results from ECOG Study E1405 — A Phase II Study of VcR-CVAD with Maintenance Rituximab for Previously Untreated Mantle Cell Lymphoma

Kahl BS et al.

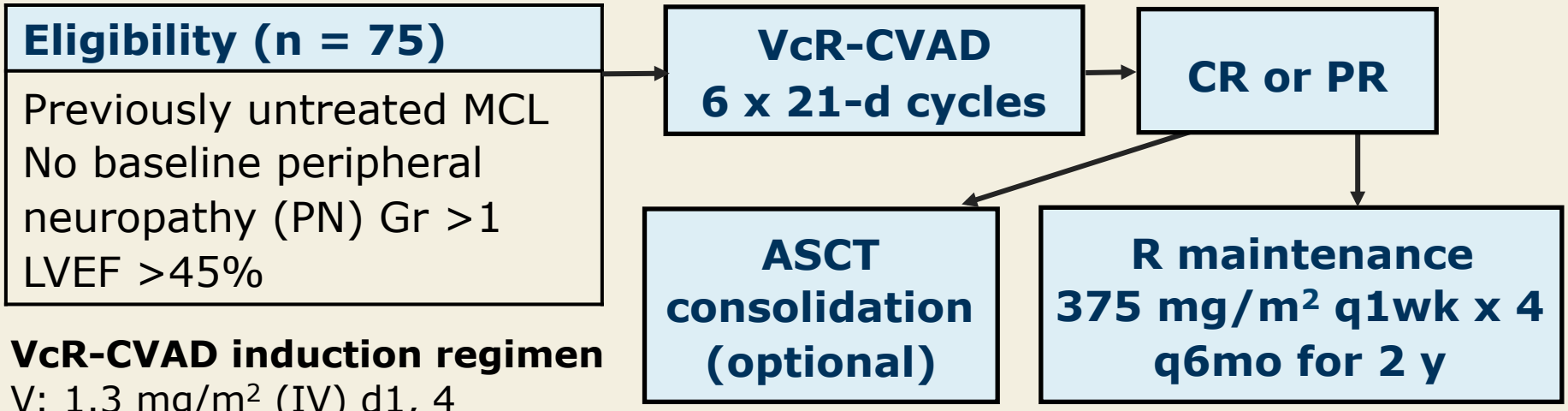
Proc ASH 2012;Abstract 153.

Background

- Mantle-cell lymphoma (MCL) is an incurable, moderately aggressive B-cell malignancy characterized by the presence of the t(11:14) translocation and overexpression of cyclin D1.
- The VcR-CVAD regimen for MCL, which incorporates bortezomib, cyclophosphamide and rituximab (VcR) into induction therapy, followed by maintenance rituximab (R) for 5 years previously demonstrated (*Br J Haemtol* 2011;155:190):
  - Overall response rate (ORR): 90%
    - Complete response (CR): 77%
  - 3-year progression-free survival (PFS) rate: 63%
  - 3-year overall survival (OS) rate: 86%
- **Study objective:** To test the efficacy and safety of VcR-CVAD followed by maintenance rituximab in previously untreated MCL.

Kahl BS et al. *Proc ASH* 2012;Abstract 153.

Phase II ECOG-E1405 Trial Design



VcR-CVAD induction regimen
V: 1.3 mg/m^2 (IV) d1, 4
R: 375 mg/m^2 (IV) d1
Cyclo: 300 mg/m^2 (IV) q12h d1-3
Doxo: 50 mg/m^2 (concurrent IV) d1-2
Vincristine: 1 mg (IV) d3
Dex: 40 mg (PO) d1-4

- **Primary endpoint:** PET-based CR rate with VcR-CVAD induction therapy
  - CR of ≥75% considered promising
- GCSF was administered with each VcR-CVAD cycle

Kahl BS et al. *Proc ASH* 2012;Abstract 153.

Response Rates

Response, n (%)	Eligible population (n = 75)	Fully restaged population (n = 64)*
CR	51 (68%)	51 (80%)
PR	20 (26%)	9 (14%)
PD	2 (3%)	2 (3%)
Nonevaluable	2 (3%)	2 (3%)

PD = progressive disease

* Coded as such because of missing end-of-induction marrow or PET scans for 11 out of 20 eligible patients who experienced PR

- Median follow-up for time to event: 3.6 years

Kahl BS et al. *Proc ASH* 2012;Abstract 153.

Progression-Free Survival (PFS)

Outcome	N = 75
Two-year PFS rate	77%
Three-year PFS rate	74%
Four-year PFS rate	50%

Kahl BS et al. *Proc ASH* 2012;Abstract 153.

Comparison of the 2-Year PFS Rate between Maintenance R and ASCT

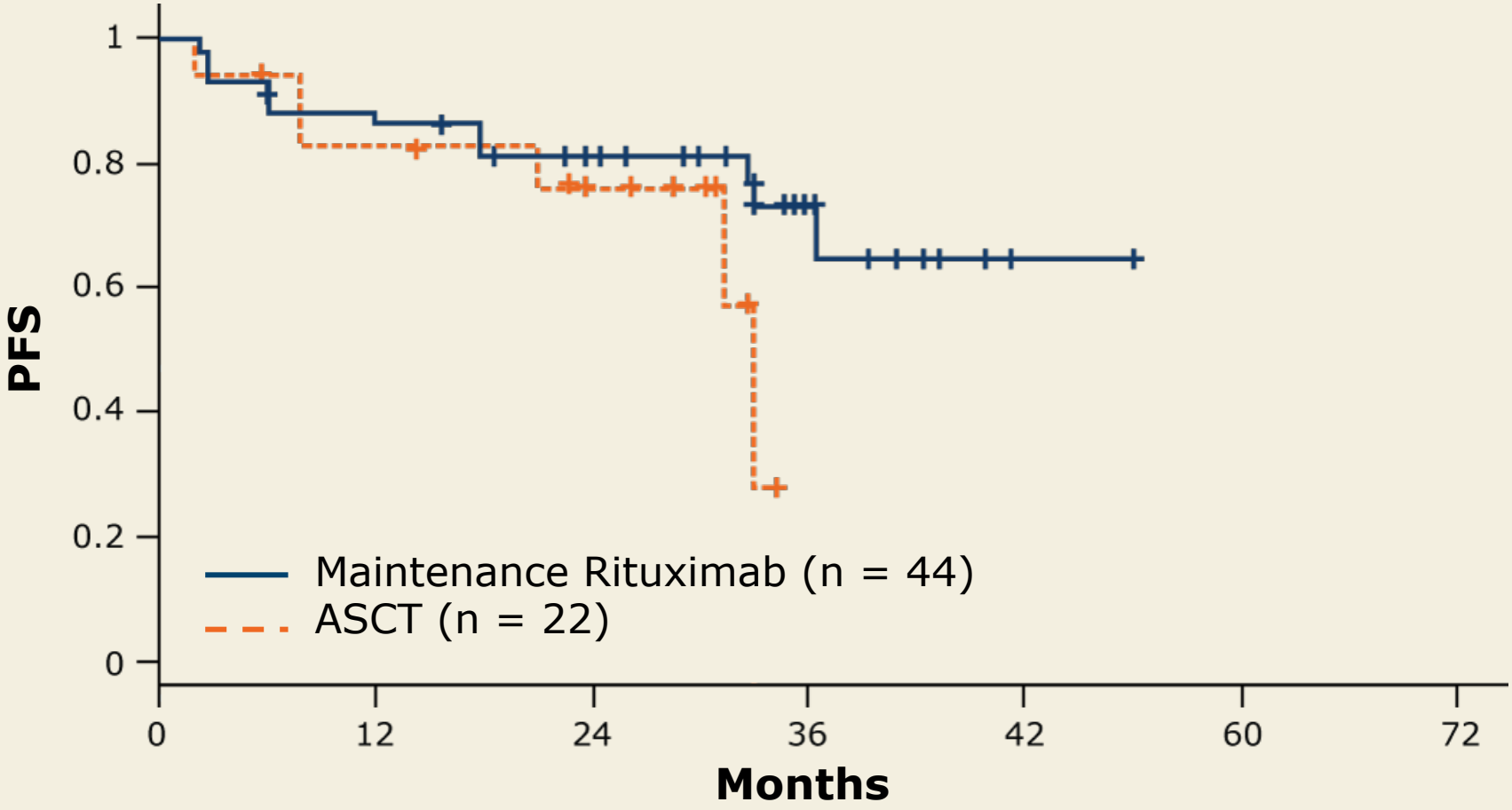
MIPI characteristic	Maintenance R (n = 44)	ASCT (n = 22)
Low	36%	45%
Intermediate	36%	36%
High	20%	14%
Unknown	7%	5%

MIPI = MCL International Prognostic Index

- The median age (range) was
  - Maintenance R: 63 (40-76) years
  - ASCT: 57 (48-68) years

Kahl BS et al. *Proc ASH* 2012;Abstract 153.

Duration of Response



With permission from Kahl BS et al. *Proc ASH* 2012;Abstract 153.

Overall Survival (OS)

Outcome	N = 75
Two-year OS rate	95%
Three-year OS rate	88%
Four-year OS rate	81%

Kahl BS et al. *Proc ASH* 2012;Abstract 153.

Select Adverse Events

	Induction (n = 77)		Maintenance (n = 45)	
	Grade 3	Grade 4	Grade 3	Grade 4
Neutropenia	16%	68%	11%	9%
Thrombocytopenia	23%	43%	2%	0%
Anemia	31%	1%	0%	2%
Infection				
Neutropenic	5%	1%	2%	0%
Nonneutropenic	7%	1%	8%	0%
Febrile neutropenia	9%	3%	2%	0%
Fatigue	9%	1%	4%	0%

- No Grade ≥3 PN or Grade 5 AEs reported

Kahl BS et al. *Proc ASH* 2012;Abstract 153.

Author Conclusions

- The VcR-CVAD regimen was well tolerated.
- In a typical population of patients with MCL, it demonstrated
  - A high overall response rate of 97%
  - A complete response rate of 68% to 80%
- Maintenance rituximab likely enhanced remission durability, performed as well as ASCT consolidation and was well tolerated.
- The randomized Phase II ECOG-E1411 trial of rituximab, bortezomib, bendamustine and lenalidomide for patients (≥60 years) with previously untreated MCL is ongoing to determine the true value of adding bortezomib to conventional therapy.

Kahl BS et al. *Proc ASH* 2012;Abstract 153.

Investigator Commentary: Phase II ECOG-E1405 Trial of VcR-CVAD with Maintenance Rituximab for Previously Untreated MCL

The VcR-CVAD regimen is the modified hyper-CVAD/chemotherapy backbone without methotrexate/cytarabine. The toxicities were in line with what would have been expected in terms of myelosuppression. Because VcR-CVAD includes bortezomib and vincristine, PN was of concern, but no Grade 3 or 4 PN was reported in the study. The CR rate was 68% in the entire population, but restaging was not completed for a few patients because the treating physician didn't get an end-of-study bone marrow evaluation. In the group of patients with complete restaging and all the end-of-treatment tests, the CR rate was 80%, so we believe the results were encouraging. The interesting aspect of the trial was the off-protocol ASCT option due to the trend in the United States for physicians to treat MCL in younger patients intensively. Patients who decided to stay with the protocol received maintenance rituximab for 2 years. We ended up with 44 patients who received maintenance rituximab and 22 patients who opted for ASCT. Interestingly, the patients who received maintenance rituximab fared as well as the patients who received ASCT, with 77% free of disease progression at 2 years. This finding raises a provocative and interesting question about whether some nonintensive strategies might perform as well as intensive strategies for patients with MCL.

Interview with Brad S Kahl, MD, January 17, 2013