5 Minute JournalClub

POST-ASH Issue 6, 2013

Combination of Lenalidomide with R-CHOP for Aggressive B-Cell Lymphomas

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual American Society of Hematology (ASH) meeting is unmatched in its importance with regard to advancements in hematologic cancer and related disorders. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results and new information lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across virtually all malignant and benign hematologic disorders. As online access to posters and plenary presentations is not currently available, a need exists for additional resources to distill the information presented at the ASH annual meeting for those clinicians unable to attend but desiring to remain up to date on the new data released there. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists, hematologists and hematology-oncology fellows in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

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.

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FACULTY — 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.

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This activity is supported by educational grants from Celgene Corporation, Genentech BioOncology/Biogen Idec, Millennium: The Takeda Oncology Company, Seattle Genetics and Teva Oncology.

Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: May 2013
Expiration date: May 2014

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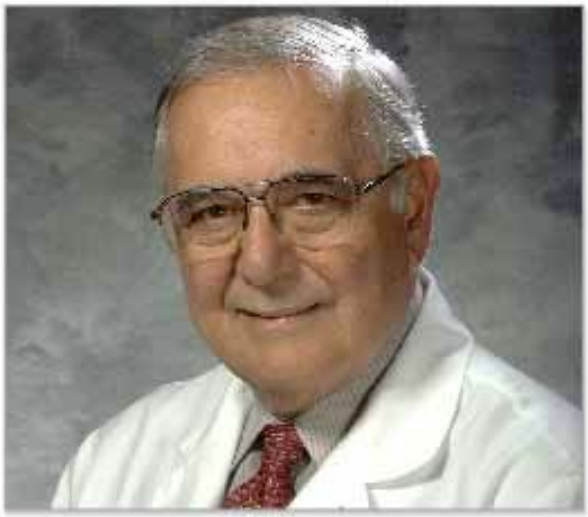
POST-ASH Issue 6, 2013

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

To go directly to slides and commentary for this issue, **click here**.

David Carbone, MD, PhD

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.



Paul Carbone, MD

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. (**Click here for more of this story.**)

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.

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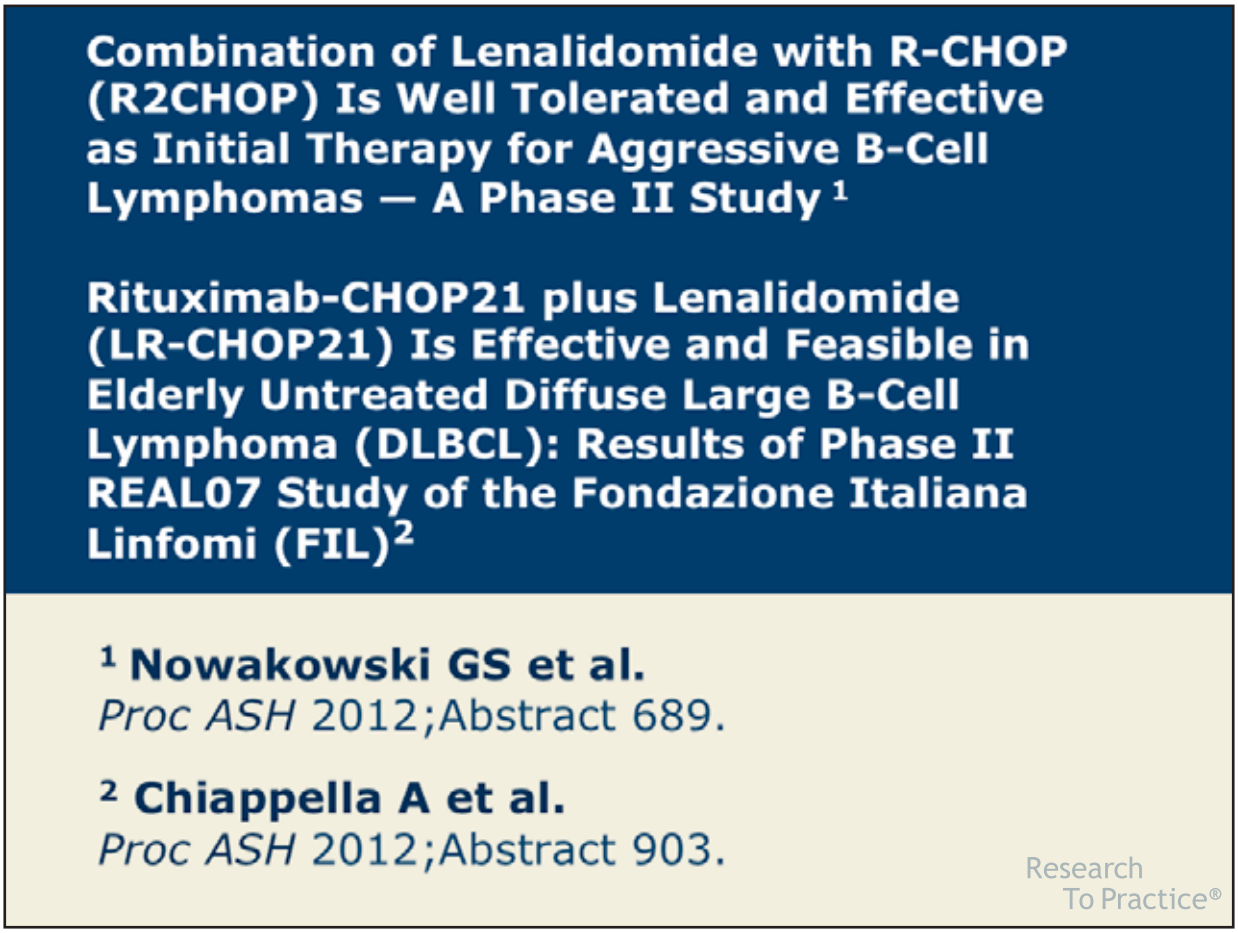
Combination of Lenalidomide with R-CHOP for Aggressive B-Cell Lymphomas

Presentations discussed in this issue

Nowakowski GS et al. **Combination of lenalidomide with R-CHOP (R2CHOP) is well-tolerated and effective as initial therapy for aggressive B-cell lymphomas — A Phase II study.** *Proc ASH* 2012;**Abstract 689**.

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

Slides from presentations at ASH 2012 and transcribed comments from a recent interview with Brad S Kahl, MD (1/17/13)



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/m²), cyclophosphamide (750 mg/m²),
doxorubicin (50 mg/m²), vincristine (1.4 mg/m²) IV, d1
and prednisone (100 mg/m²) 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.

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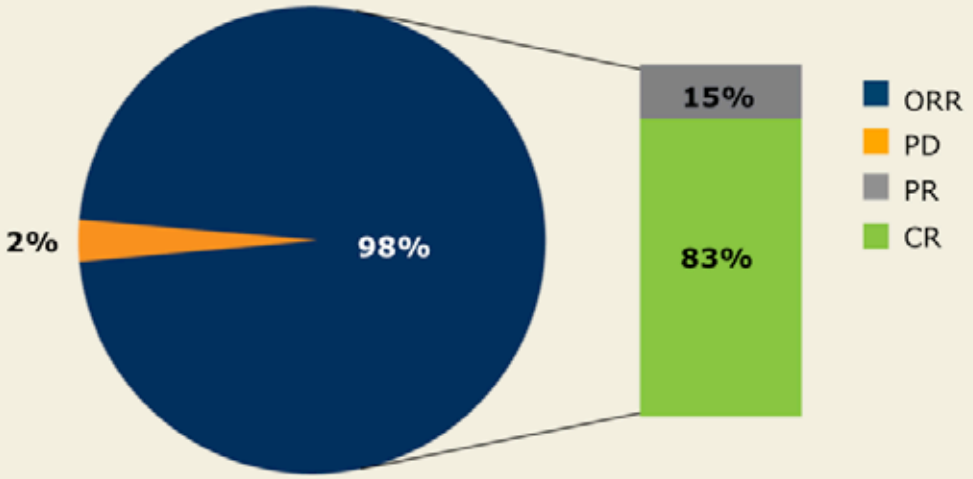
Response to R2CHOP

Response rate, % (PET Criteria)



- 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.

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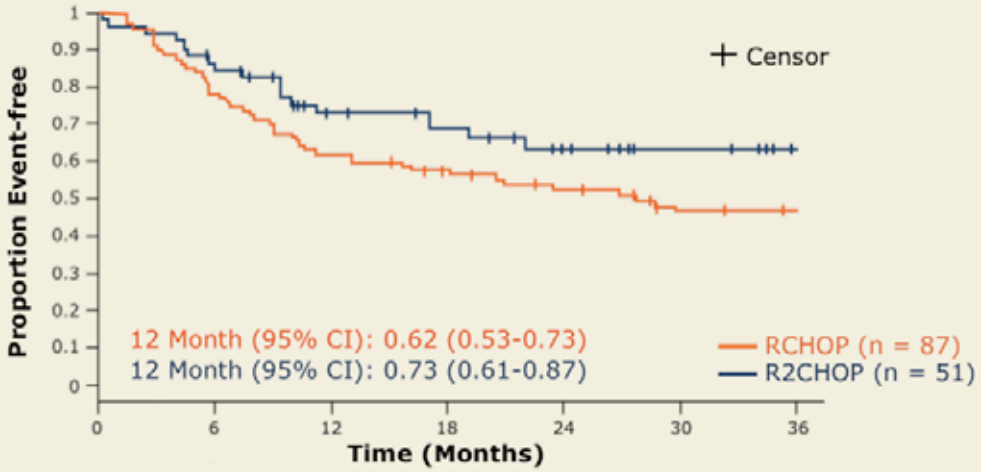
Progression-Free Survival (PFS) with R2CHOP versus R-CHOP Case-Matched Controls



- 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

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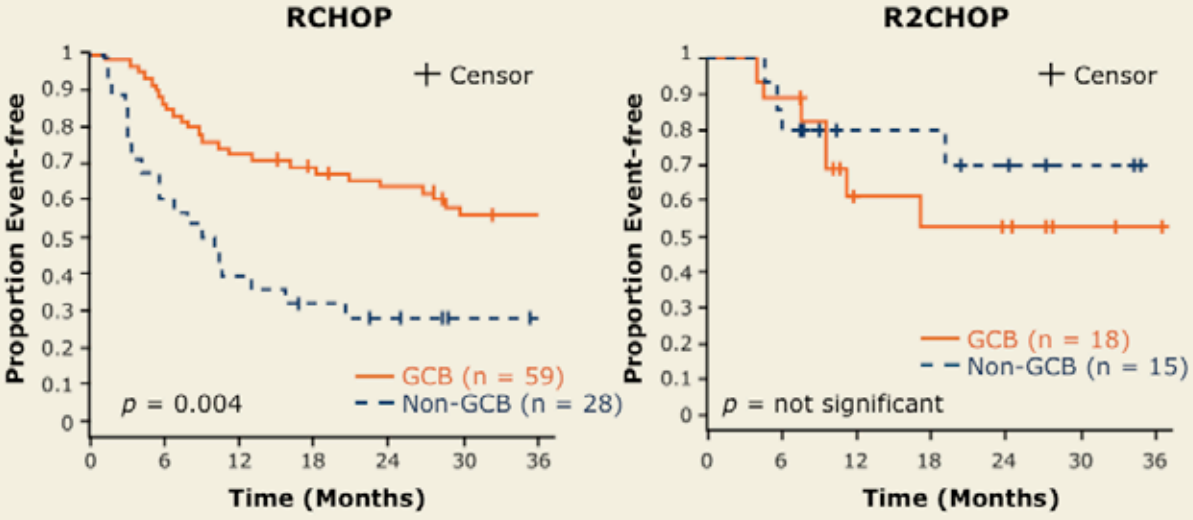
PFS by GCB versus Non-GCB Subtype with R2CHOP versus R-CHOP



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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.

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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.

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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.

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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.

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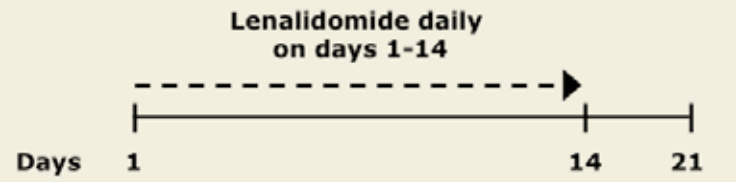
REAL07 Phase II Study Design

Treatment cycles



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

(↑) Rituximab	375 mg/m²
Cyclophosphamide	750 mg/m²
Doxorubicin	50 mg/m²
Vincristine	1.4 mg/m² (capped at 2.0 mg)
Prednisone	40 mg/m² 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.

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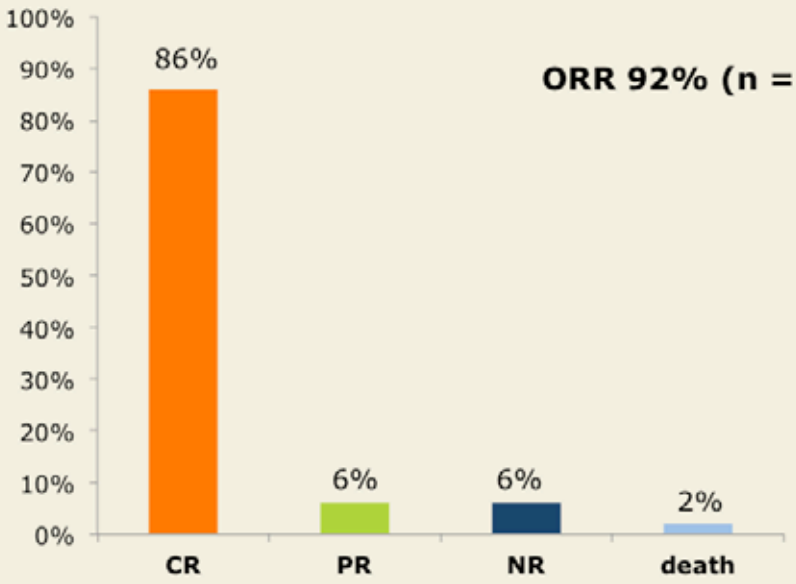
Final Response After 6 Cycles of LR-CHOP21



ORR 92% (n = 49)

PR = partial response; NR = no response

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

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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.

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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.

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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

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