5 Minute JournalClub

Key ASH Presentations
Issue 6, 2012

Single-Agent PCI-32765 in Previously Treated MCL and Rituximab/ Fludarabine/Cyclophosphamide in Newly Diagnosed MCL

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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

- Consider the inclusion of single-agent romidepsin in the treatment algorithm for relapsed or refractory peripheral T-cell lymphoma.
- Integrate new and existing therapeutic strategies into the best-practice management of diffuse large B-cell lymphoma.
- Apply the results of emerging clinical research to the selection of optimal systemic therapy for patients with relapsed/refractory mantle-cell lymphoma.
- Recall new data with investigational agents demonstrating promising activity in non-Hodgkin lymphomas.

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

This past Friday 8 clinical investigators ventured to Miami for our annual post-ASH lymphoma Think Tank. Over the course of more than 6 fascinating hours together we focused on a multitude of topics and as always recorded the proceedings, which will be available as an enduring activity in the coming months. While our engineers are busy de-umming (our little secret) and editing the audio, we thought we would hold you over with a taste of some of the new ASH NHL papers that were fodder for discussion and debate during Friday's lymphoma extravaganza.

1. Lenalidomide/rituximab

The so-called R-squared regimen of the immunomodulatory agent lenalidomide (len) and rituximab (R) has generated considerable excitement among investigators, and at ASH we saw the results from a Phase II trial evaluating this combination alone or with dexamethasone for patients with relapsed indolent NHL or mantle-cell lymphoma (MCL) considered to be resistant to R. Of the 48 patients treated on the trial more than a third had a response, and the median progression-free survival was 18 months. These findings have raised hopes that len might help overcome R resistance and that in select populations such as the elderly this combination might become an alternative to aggressive treatment of relapsed disease — for example, with autologous stem cell transplant (ASCT).

2. Two papers on MCL

Another ASH NHL highlight was the presentation of a Phase II study of PCI-32765, an oral irreversible Bruton's tyrosine kinase inhibitor, as a single agent in relapsed/refractory MCL. The results are compelling, as two thirds of the 39 patients in the study had objective responses and 35 remain on treatment. Importantly, none stopped therapy due to toxicity. Many investigators now have patients in their practices on trials who have experienced obvious prolonged benefit with this agent, and as a result significant excitement surrounds it and other small molecules, like the PI3 kinase inhibitor CAL-101 that is also under active investigation in a variety of NHL subtypes.

The rarity of MCL has made the definition of treatment benefits a challenge, and another important study reported at ASH attempted to better establish the effects of R in this disease. This effort from the UK evaluated the combination of fludarabine and cyclophosphamide with or without R, and while a high rate of infection was observed in these patients receiving fludarabine, substantial improvements in response rate and an almost doubling of progression-free survival reinforced the value of adding the CD20 antibody, which is now used routinely up front and often as maintenance treatment.

3. Two studies of diffuse large B-cell lymphoma (DLBCL)

Previous research with dose-adjusted EPOCH with R has shown promising results in untreated DLBCL, and this **Phase IV trial** of 81 patients with poor-prognosis disease (age-adjusted IPI of 1 or higher) reported an encouraging 62% 5-year progression-free survival rate. An ongoing Phase III Intergroup trial is comparing EPOCH-R to R-CHOP.

One of the biggest disappointments at ASH came from the much-awaited **Phase III SWOG study** comparing conditioning R/BEAM (carmustine, etoposide, cytarabine, melphalan) to ^{131}I-tositumomab/BEAM for patients with DLBCL about to undergo ASCT. The trial results were flat-out negative, confounding the positive findings observed in the Phase II setting and forcing investigators back to the drawing board to look at higher doses of radioimmunotherapy as pretransplant conditioning.

4. Two papers on T-cell lymphoma

At ASH Dr Bertrand Coiffier presented an update of the Phase II pivotal study evaluating the selective inhibitor of histone deacetylase romidepsin in relapsed or refractory peripheral T-cell lymphoma (PTCL). This trial, which led to the FDA approval in this setting, evaluated 130 patients across PTCL subgroups, and these findings reveal higher response rates among individuals with the most common forms of the disease. This suggests that romidepsin may perhaps have more activity in common PTCL subtypes than initial data suggested.

In cutaneous T-cell lymphoma we saw the results of a Phase II trial investigating the interesting sequence of pegylated liposomal doxorubicin (PLD) — which has been shown to have high response rates and is known to concentrate in the skin — followed by the synthetic retinoid bexarotene (Bex). Perhaps because the study selected for patients with more aggressive disease, a 41% response rate (lower than reported in other trials) was observed with PLD and Bex did not increase the rate or duration of response. With the current shortage of PLD, not many patients are being treated with this agent.

Next up on this ASH series we go back to multiple myeloma and new reports on effective long-term disease control in older patients on continuing therapy.

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Single-Agent PCI-32765 in Previously Treated MCL and Rituximab/Fludarabine/Cyclophosphamide in Newly Diagnosed MCL

Presentation discussed in this issue

Wang L et al. **The Bruton's tyrosine kinase inhibitor PCI-32765 is highly active as single-agent therapy in previously-treated mantle cell lymphoma (MCL): Preliminary results of a Phase II trial.** *Proc ASH* 2011;**Abstract 442**.

Rule S et al. **The addition of rituximab to fludarabine and cyclophosphamide (FC) improves overall survival in newly diagnosed mantle cell lymphoma (MCL): Results of the randomised UK National Cancer Research Institute (NCRI) trial.** *Proc ASH* 2011;**Abstract 440**.

Slides from presentations at ASH 2011 and transcribed comments from recent interviews with Brad S Kahl, MD (3/9/12) and Owen A O'Connor, MD, PhD (2/3/12)

The Bruton's Tyrosine Kinase Inhibitor PCI-32765 is Highly Active as Single-Agent Therapy in Previously-Treated Mantle Cell Lymphoma (MCL): Preliminary Results of a Phase II Trial[1]

The Addition of Rituximab to Fludarabine and Cyclophosphamide (FC) Improves Overall Survival in Newly Diagnosed Mantle Cell Lymphoma (MCL): Results of the Randomised UK National Cancer Research Institute (NCRI) Trial[2]

[1] **Wang L et al.**
Proc ASH 2011;Abstract 442.
[2] **Rule L et al.**
Proc ASH 2011;Abstract 440.

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The Bruton's Tyrosine Kinase Inhibitor PCI-32765 Is Highly Active as Single-Agent Therapy in Previously-Treated Mantle Cell Lymphoma (MCL): Preliminary Results of a Phase II Trial

Wang L et al.

Proc ASH 2011;Abstract 442.

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Background

- Bruton's tyrosine kinase (Btk) is a central mediator of B-cell receptor signaling, essential for normal B-cell development.
- PCI-32765 is an irreversible inhibitor of Btk that induces apoptosis and blocks cellular migration and adhesion in malignant B cells.
- A Phase I trial showed that treatment with PCI-32765 resulted in objective responses in patients with relapsed B-cell or MCL (*ASH* 2010;Abstract 964).
- **Objective:**
  - Report the preliminary efficacy and safety results of an ongoing Phase II trial of single-agent PCI-32765 in patients with previously treated MCL (PCYC-1104 trial).

Wang L et al. *Proc ASH* 2011;Abstract 442.

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PCYC-1104 Study Method

- PCYC-1104 is a Phase II trial of single-agent PCI-32765 (560 mg PO daily x 28-day continuous cycles) in patients with relapsed or refractory MCL who were either bortezomib naïve or bortezomib exposed.
- Bortezomib-naïve and bortezomib-exposed cohorts were analyzed separately and tumor response was evaluated every 2 cycles by 2007 NHL IWG criteria.
- Safety analysis includes patients (n = 39) who have initiated treatment and have reported 1 adverse event (AE).
- Efficacy analysis includes patients (n = 24) who have undergone at least 1 tumor follow-up assessment.

Wang L et al. *Proc ASH* 2011;Abstract 442.

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Efficacy Results (Abstract Only)

Response	Bortezomib naïve (n = 12)	Bortezomib exposed (n = 12)
Objective response rate (ORR)	58%	75%
ORR (all patients, n = 39)	67%	

- 35 out of 39 patients (90%) remain on PCI-32765
- Four patients have discontinued PCI-32765
  - Progressive disease (n = 3)
  - Investigator decision (n = 1)

Wang L et al. *Proc ASH* 2011;Abstract 442.

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AEs (Abstract Only)

Event	Patients (n = 39)
Grade >3 AEs potentially related to PCI-32765	11%
Serious AEs (SAEs)	21%
SAEs potentially related to PCI-32765 Rash Febrile neutropenia	 3% 3%
Death*	3%

* Patient (n = 1) did not receive PCI-32765 due to rapid disease progression.

- No patient has discontinued treatment due to AEs.
- Grade 1 or 2 diarrhea, fatigue and nausea have been the most frequently reported AEs.

Wang L et al. *Proc ASH* 2011;Abstract 442.

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Author Conclusions (Abstract Only)

- Preliminary data from the PCYC-1104 Phase II trial suggest that PCI-32765 induces a high response rate in patients with relapsed or refractory MCL.
- PCI-32765 is well tolerated.
- Phase III trials of PCI-32765 in patients with MCL are planned.

Wang L et al. *Proc ASH* 2011;Abstract 442.

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Investigator Commentary: The Btk Inhibitor PCI-32765 Is Highly Active as Single-Agent Therapy in Pretreated Patients with MCL: Preliminary Results

Without question, targeting unique biological features of large B-cell lymphoma such as Btk has become attractive. One of the first such drugs targeting the downstream components of the B-cell receptor inhibited the Syk kinase. The Btk inhibitor is actually downstream of the Syk kinase and has proved to be a target that has produced significant benefits in several large B-cell lymphomas.

In patients with MCL who had received prior bortezomib therapy, ORR was a little higher compared to bortezomib-naïve patients. The difference is, however, too small to make major dogmatic comments regarding the impact of prior bortezomib on the response rate. Achieving a response rate of 67% is significant in this patient population that has been exposed to prior chemotherapies, especially considering the observation that none of the patients discontinued treatment because of secondary AEs. It will be interesting to see duration data on how long these beneficial responses last.

Interview with Owen A O'Connor, MD, PhD, February 3, 2012

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The Addition of Rituximab to Fludarabine and Cyclophosphamide (FC) Improves Overall Survival in Newly Diagnosed Mantle Cell Lymphoma (MCL): Results of the Randomised UK National Cancer Research Institute (NCRI) Trial

Rule S et al.

Proc ASH 2011;Abstract 440.

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Background

- The role of rituximab in the treatment of mantle-cell lymphoma (MCL) is unclear.
- Prior studies showed improved response rates to chemotherapy in combination with rituximab.
- The survival benefit of rituximab is less reliable due to heterogeneity among the trials (*Cochrane Database Syst Rev* 2007;4:CD003805; *Blood* 2011;118:4808).
- **Current study objective**: Assess the efficacy and safety of fludarabine and cyclophosphamide with or without rituximab in the treatment of MCL.

Rule S et al. *Proc ASH* 2011;Abstract 440.

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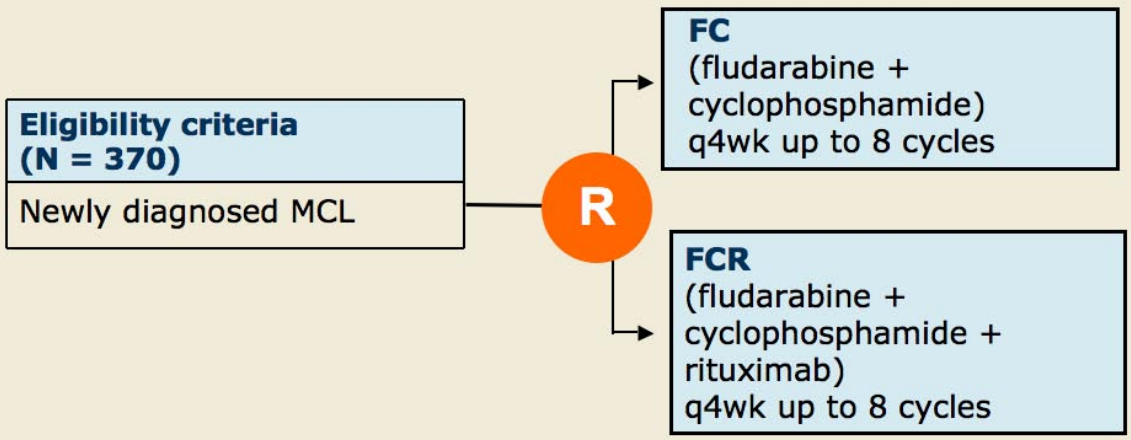
Study Design



Rule S et al. *Proc ASH* 2011;Abstract 440.

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Efficacy of FCR versus FC (Abstract Only)

Outcome	FCR	FC	HR	*p*-value
Overall response rate CR + CRu	90.6% 64.7%	79.8% 46.9%	NR	0.01 0.002
Progressive disease	5.8%	11.9%	NR	NR
Median progression-free survival	30.6 mo	16.1 mo	0.56	<0.001
Median overall survival	45.7 mo	37 mo	0.72	0.03

HR = hazard ratio; CR = complete response; CRu = unconfirmed complete response

Median follow-up 38.8 months

Rule S et al. *Proc ASH* 2011;Abstract 440.

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Grade 3/4 Adverse Events and Causes of Death (Abstract Only)

Adverse event (N = 370)	Incidence
Neutropenia	51.4%
Leucopenia	45.8%
Thrombocytopenia	23.3%
Anemia	12.9%
Infections	11.8%

- One patient had Grade 3 renal toxicity.
- Significantly more patients in the FCR arm had Grade 3/4 leukopenia, thrombocytopenia.
- Most common cause of death: Lymphoma.
- Death due to other causes: FCR 29%, FC 24%.
  - Almost half were infection related.
- Eleven patients died of secondary cancer, 4 due to AML.
- Death without disease progression: FCR 14%, FC 10%.

Rule S et al. *Proc ASH* 2011;Abstract 440.

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Author Conclusions

- The addition of rituximab to FC chemotherapy leads to a significant improvement in both progression-free survival and overall survival with an acceptable level of additional toxicity.
- A significant number of patients who received FC-based chemotherapy died of nonlymphoma-related causes while in remission.

Rule S et al. *Proc ASH* 2011;Abstract 440.

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Investigator Commentary: The Addition of Rituximab to FC Improves Overall Survival in Newly Diagnosed MCL: Results of the UK NCRI Trial

This study was performed in a fairly representative group of patients with MCL and showed major clinical benefits with the addition of rituximab to FC. This is important because previous studies in MCL had raised questions about the value of adding rituximab to the chemotherapy regimen. This trial should help to put uncertainties about the addition of rituximab to chemotherapy to rest. The observation that both treatment arms had significant rates of infections, with some leading to death, is notable. Despite the fact that the efficacy of the FCR regimen was reasonably good, a high rate of infection-related toxicity is associated with fludarabine-based therapy in older patients with MCL.

Although these data demonstrated the value of adding rituximab to FC, the toxicity profile leads me to believe that FC is not the appropriate chemotherapy backbone for older patients with MCL.

The Kluin-Nelemans study showed unequivocally that R-CHOP is a better induction choice than FCR. Hence, rituximab should be added to either CHOP or bendamustine when treating MCL in older patients.

Interview with Brad S Kahl, MD, March 9, 2012