5 Minute JournalClub

Hematologic Oncology
Issue 1, 2013

Phase I/II Dose-Escalation Trial of Daratumumab for Relapsed/ Refractory Multiple Myeloma

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Clinical Oncology (ASCO) and European Hematology Association (EHA) annual meetings, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they are aware of crucial practice-altering findings. Unlike ASCO, EHA does not offer access to any of the poster or plenary presentations from the annual meeting via the Internet. This creates an almost insurmountable obstacle for clinicians in community practice because not only are they confronted almost overnight with thousands of new presentations and data sets, but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on novel agents in multiple myeloma from the latest ASCO and EHA meetings, including expert perspectives on how these new evidence-based concepts may 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

- Appraise recent data on therapeutic advances and potentially practice-changing clinical data in multiple myeloma, and consider this information in clinical practice.
- Evaluate the preliminary safety profiles and response outcomes observed in studies of next-generation proteasome inhibitors, immunomodulatory agents and novel antibodies alone or in combination with approved systemic treatments for patients with relapsed/refractory multiple myeloma.
- Assess the benefits and risks of carfilzomib in combination with an alkylating or immunomodulatory agent for patients with newly diagnosed multiple myeloma.
- Determine the effectiveness and tolerability of pomalidomide in combination with low-dose dexamethasone for patients with relapsed or refractory multiple myeloma and adverse cytogenetics or renal impairment.

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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: September 2013
Expiration date: September 2014

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

Antonio Palumbo, MD

The revolution in treatment of multiple myeloma (MM) that occurred over the better part of the last decade is evident in the waiting room of every medical oncologist. Thanks to regimens that include immunomodulatory agents (IMiDs) — particularly lenalidomide (len) — and proteasome inhibitors, specifically bortezomib (bz), along with the widespread utilization of bisphosphonates, it is no longer uncommon to see patients on active treatment for 10 years or more. Of course much is still to be done with this challenging disease, and I met with a leader in the field, Dr Antonio Palumbo, for his take on where we are today and where we might be heading.

For some time Dr Palumbo has been a vocal proponent, along with many other MM investigators, of using the most effective therapies as early as possible in the disease course — often for prolonged durations. Based on his research and that of many others, for younger patients his standard is triple-agent induction followed by high-dose chemotherapy and autologous stem cell transplant and then long-term maintenance treatment. On the flip side, Dr Palumbo has taken a leadership role in the use of preemptive dose reductions for the elderly, allowing for longer-term therapy as opposed to what he calls "short flashes of treatment."

From this clinical framework, Dr Palumbo commented on several new data sets from the ASCO and the European Hematology Association (EHA) annual meetings, attempting to better define the role of the 2 most recently approved agents for MM — carfilzomib

(cz) and pomalidomide (pom) — and several other promising candidates in the later stages of development.

1. Cz triplets

At ASCO this year we saw more on CRd (cz/len/low-dose dexamethasone [lddex]), a cousin of RVD (len/bz/dex), currently one of the most commonly used IMiD/proteasome inhibitor induction regimens.

The final report from the Phase Ib/II trial in relapsed/refractory disease led by Dr Michael Wang that started it all in 2008 demonstrated excellent tolerability with CRd — particularly a lack of significant peripheral neuropathy — and impressive efficacy in patients with extensive prior treatment.

These findings inspired Dr Andrzej Jakubowiak and colleagues to launch an up-front trial that was again reported at ASCO. The antitumor activity in this study is interesting because the depth of response increased with more treatment, and by a median of 22 cycles 87% of patients had achieved a VGPR or better. In keeping with his approach of maximizing the depth of response as early in the disease course as possible, Dr Palumbo is hopeful that accumulating data on CRd and other cz-based up-front regimens will result in an important step forward in induction treatment.

In that context, Dr Palumbo presented at EHA the initial results from a **Phase II up-front trial** evaluating the CCd regimen (cz/cyclophosphamide [cy]/lddex), which resembles another major induction triplet in current practice, CyBorD (cy, bz and dex). CCd was not only well tolerated, but the efficacy seemed equivalent if not superior to that of the bz-based approach.

Similarly, at ASCO and then again at EHA we were treated to **data on CMP** (cz/melphalan/prednisone) as up-front therapy for elderly patients. Again there was significant activity and good tolerability, and while Dr Palumbo believes that both alkylating agent combinations with cz are effective, in his view cyclophosphamide-based regimens are the way forward because of better tolerability.

With the rapid emergence of impressive up-front data with cz regimens, it will be interesting to see whether regulatory agencies, investigators and payers will require direct head-to-head trials against bz-based treatments to see a change in practice. In this regard, the NCCN now lists **CRd as a category 2A up-front option**.

2. Pom/lddex

In December 2012 at ASH Dr Meletios Dimopoulos presented initial findings from the Phase III MM-003 trial documenting an overall survival benefit with the use of pom/

lddex for patients with relapsed/refractory MM. At ASCO and EHA **the results were updated**, and **subset data from this seminal effort** provided evidence of safety and efficacy in patients with moderate renal impairment and modest activity in patients with adverse cytogenetic profiles. In commenting on these studies, Dr Palumbo stated his belief that this regimen provides useful clinical responses in 30% to 50% of patients with disease progressing on len. He also predicted greater long-term benefit if pom/lddex were used earlier in the disease course, ideally soon after progression on another IMiD.

3. Monoclonal antibodies (mAbs)

The recent emergence of 2 distinct compounds with preliminary activity in MM may soon make this disease fertile ground for the regular use of mAbs. The first agent is elotuzumab, which targets the CS1 antigen, and at ASCO and then again at EHA we got more information from Dr Sagar Lonial's **Phase II trial** combining this drug with len and lddex. While this mAb has no single-agent activity, the combination resulted in an eye-popping median PFS of 25.8 months, and one wonders whether we are looking at the myeloma version of "R squared" in lymphoma (len/rituximab). However, Dr Palumbo cautions us to take a conservative view and hold our excitement until Phase III data are available.

Daratumumab, another FDA breakthrough designation recipient, is an anti-CD38 antibody that has shown significant single-agent activity, including an encouraging 31% clinical response rate in a single-arm **Phase I/II dose-escalation study** presented at ASCO and updated at EHA. In Dr Palumbo's eyes CD38 may be as important in MM as CD20 is in lymphoma, and while he won't speculate as to whether the efficacy of this agent will even come close to what we have seen with rituximab in lymphoma, he is enthusiastic about this potential and recently began entering patients on trials of this agent in his own clinic.

4. Oral proteasome inhibitors

The promise of all-oral combination regimens has many excited about MLN9708 (ixazomib), which has a similar structure to bz but lacks the inconvenience of subcutaneous or IV administration. At ASCO Dr Shaji Kumar presented more from an **expanded Phase I study** of ixazomib demonstrating similar efficacy to what has been observed with bz but with improved tolerability. In that regard, Dr Palumbo is particularly interested in seeing this and other oral agents studied in elderly patients for whom the ease of drug delivery might allow more prolonged treatment and greater disease control.

Over the next few years, we shall see if the next generation of new agents and strategies typified by these EHA and ASCO papers bump ahead outcomes similarly to the initial introduction of IMiDs and proteasome inhibitors, but MM investigators including Dr Palumbo seem determined to push the disease at the least into CML-like control and maybe even cure. Next on this series we consider a number of summer papers on CLL, and one data set in particular that may signal a major shift in choice of anti-CD20 antibody in this disease.

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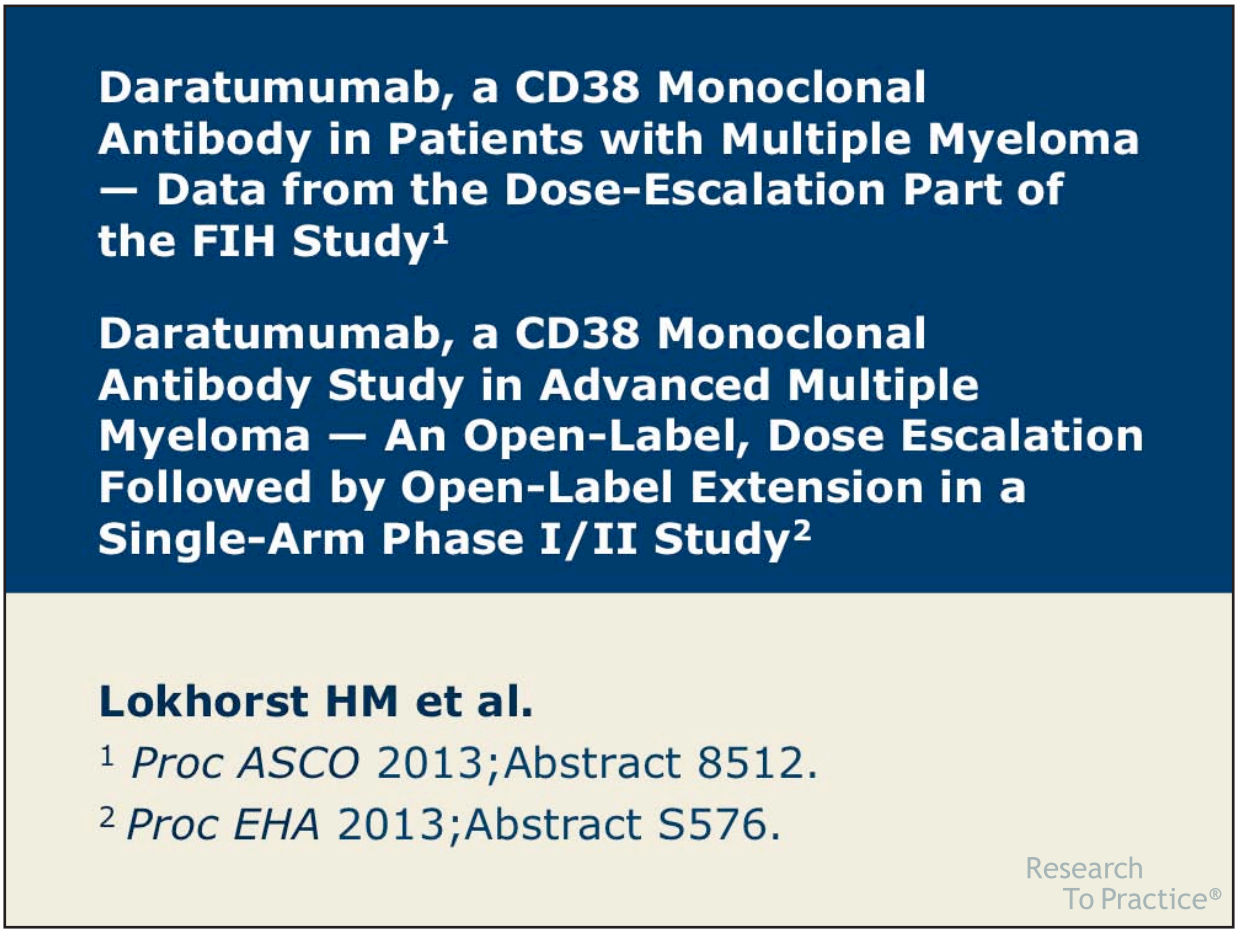
Phase I/II Dose-Escalation Trial of Daratumumab for Relapsed/Refractory Multiple Myeloma

Presentations discussed in this issue

Lokhorst HM et al. **Daratumumab, a CD38 monoclonal antibody in patients with multiple myeloma — Data from the dose-escalation part of the FIH study.** *Proc ASCO* 2013;**Abstract 8512**.

Lokhorst HM et al. **Daratumumab, a CD38 monoclonal antibody study in advanced multiple myeloma — An open-label, dose escalation followed by open-label extension in a single-arm Phase I/II study.** *Proc EHA* 2013;**Abstract S576**.

Slides from presentations at ASCO 2013/EHA 2013 and transcribed comments from a recent interview with Antonio Palumbo, MD (8/20/13)



Background

- Daratumumab is a human CD38 monoclonal antibody with broad-spectrum killing activity.
- It effectively mediates killing of CD38-expressing tumor cells via complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity and apoptosis.
- Daratumumab has shown promising activity in the treatment of relapsed or refractory multiple myeloma (MM) (*Proc EHA* 2012; Abstract 1143).
- This investigational agent has received breakthrough designation by the FDA for relapsed and refractory MM.
- **Study Objective:** Present efficacy and safety results from a dose-escalation study (part 1) of daratumumab in patients with relapsed or relapsed and refractory MM.

Lokhorst HM et al. *Proc ASCO* 2013;Abstract 8512.

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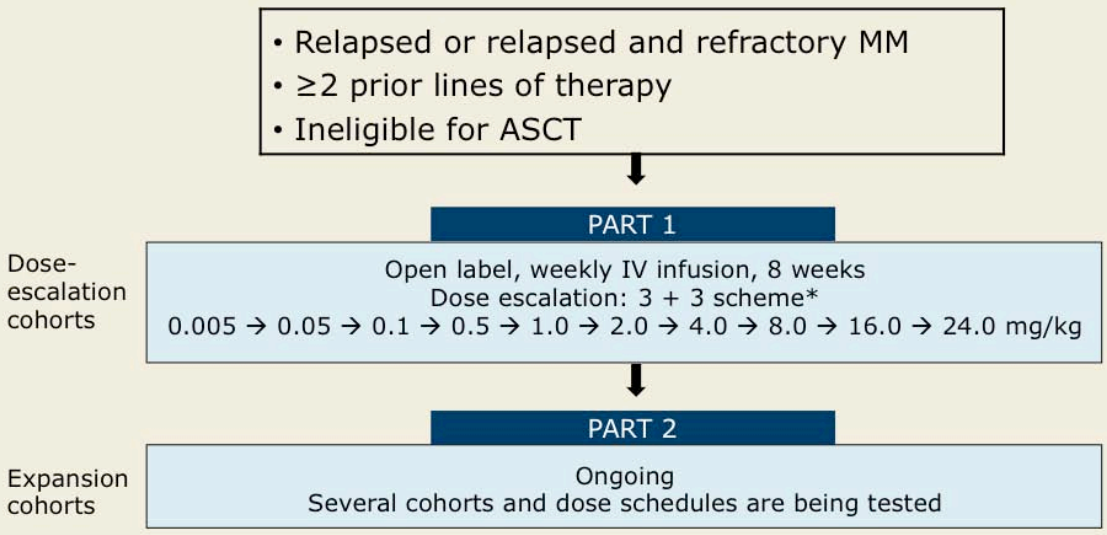
Phase I/II Study Design



* Start with predose at 10% of the full dose, maximum 10 mg; 3 weeks delay after first full dose

Lokhorst HM et al. *Proc ASCO* 2013;Abstract 8512.

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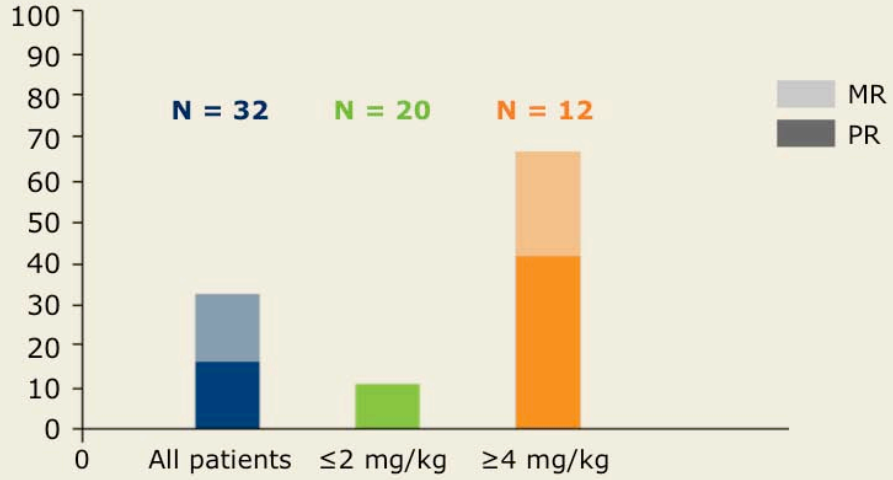
IMWG Response to Daratumumab



- Of all patients, 10 (31%) achieved a clinical response: 5 patients (15.5%) achieved a partial response (PR) and 5 patients (15.5%) achieved a minor response (MR).
- In the ≥4 mg/kg cohort, 8 patients (67%) achieved a clinical response: 5 patients (42%) achieved a PR and 3 patients (25%) achieved an MR.

With permission from Lokhorst HM et al. *Proc ASCO* 2013;Abstract 8512.

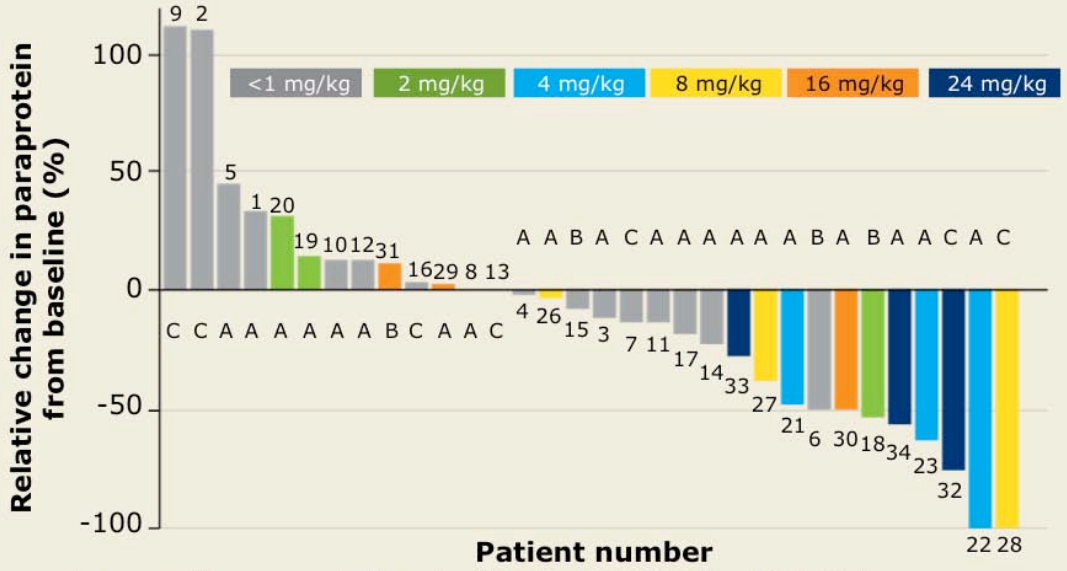
Summary of Response

Cohort mg/kg (n)	Max reduction in M component (%)		Max reduction in difference between involved and uninvolved FLC (%)	Max reduction in plasma cells in bone marrow biopsy (%) [Baseline value, %]	Response according to IMWG†
	Serum	Urine			
4 (3)	49 100 64	* 87 *	* 96 *	80 [12.5] 89 [23] 97 [19]	MR PR PR
8 (3)	4 39 *	* * *	* * *	-29 [14] 93 [7.5] —	SD MR NE
16 (3)	-3 50 *	* * -12	-12 88 55	— 100 [31.5] 100 [2]	PD PR SD
24 (3)	* 29 68‡	* * 93	80‡ * 94	51 [18.5] 17 [3.0] 91 [17.0]	PR MR PR

* No measurable disease/normal at baseline; † Evaluation based on maximum reduction in M component or FLC; ‡ Follow-up still ongoing
FLC = free light chain; SD = stable disease; NE = not evaluable; — = data not available

Lokhorst HM et al. *Proc ASCO* 2013;Abstract 8512.

Maximal Change in Paraprotein



A = serum M-component; B = urine M-component; C = Free Light Chains

- 47% of patients treated with 8 weeks of daratumumab at doses of ≤24 mg/kg showed a reduction in paraprotein.

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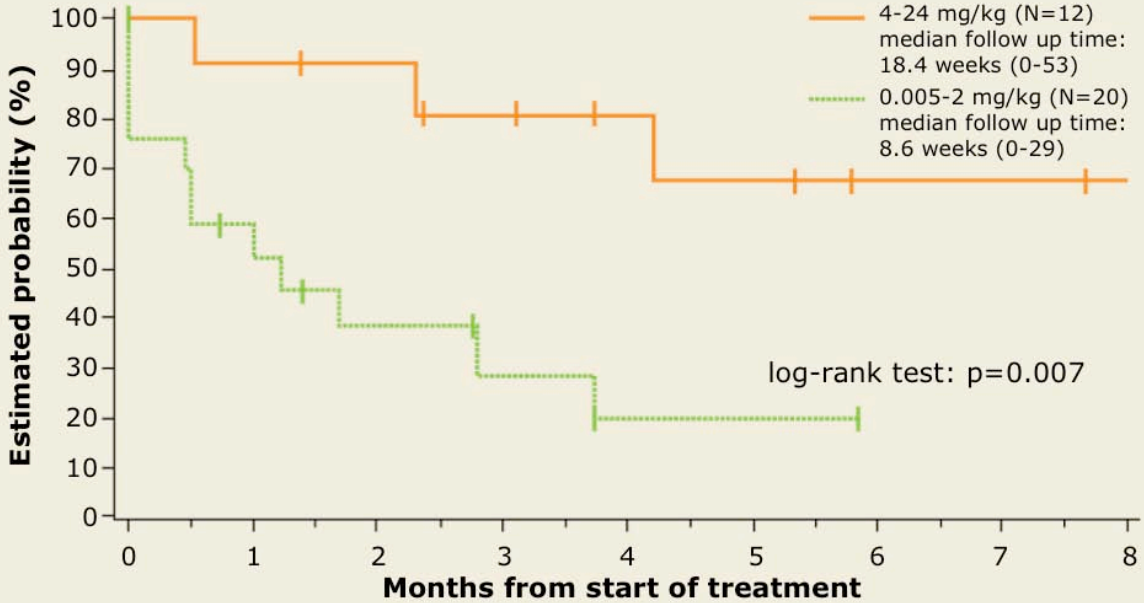
Progression-Free Survival



- Median PFS in the ≥4mg/kg dose groups has not been reached.

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Drug-Related Adverse Events

Adverse event (n = 32)	Patients, %	Grade
Bronchospasm	6%	2, 3
Anemia	3%	3
Thrombocytopenia	3%	4
Aspartate aminotransferase >5.2 times the upper limit of normal	3%	2, 3
Cytokine release syndrome	3%	2

- The most common adverse events reported were infusion-related events (IREs), which occurred mainly during the first full infusion.
- 44% of patients across all dose groups experienced IREs of Grade 1 to 3, of which 2 were Grade 3.

Lokhorst HM et al. *Proc ASCO* 2013;Abstract 8512.

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Author Conclusions

- Daratumumab has a favorable safety profile as monotherapy for patients with relapsed or relapsed and refractory MM.
- 47% (15/32) of patients with heavily pretreated MM who received 8 weeks of daratumumab at doses of ≤24 mg/kg showed a reduction in paraprotein.
- 31% (10/32) of patients who received doses of ≤24 mg/kg achieved a clinical response.
- 67% (8/12) of patients who received doses of ≥4 mg/kg achieved a clinical response.
- Biochemical response was accompanied by clearance of myeloma cells from the bone marrow.
- At higher dose levels, plasma concentrations were close to those predicted (data not shown).

Lokhorst HM et al. *Proc ASCO* 2013;Abstract 8512.

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Author Conclusions (Continued)

- Overall, increased daratumumab exposure correlated with longer PFS.
- Future studies:
  - An 8-mg/kg weekly schedule is currently being explored.
  - Higher doses and different schedules will also be investigated.

Lokhorst HM et al. *Proc ASCO* 2013;Abstract 8512.

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Investigator Commentary: Phase I/II Study of Daratumumab in Relapsed or Refractory MM

CD38 is as important in MM as CD20 is in lymphoma. So the usual question is whether daratumumab will demonstrate efficacy in MM that is equivalent to that seen with rituximab in lymphoma. From this perspective, great expectations surround daratumumab. Presently, several companies are trying to develop new anti-CD38 antibodies.

In this Phase I/II study, about 40% of patients achieved partial responses with daratumumab at a dose of ≥4 mg/kg. This appears to be the therapeutic dose. The median progression-free survival (PFS) was not reached after 8 courses of daratumumab. This was not a study of treatment until disease progression. This Phase I study involved the administration of single-agent daratumumab for only 8 weeks, and therefore the PFS results are interesting. This study also demonstated major reductions in bone marrow plasma cells with daratumumab monotherapy.

Interview with Antonio Palumbo, MD, August 12, 2013

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