Trends-in-Medicine

April 2005
by Lynne Peterson

SUMMARY

Celgene has a winner in Revlimid, which is almost certainly approvable. ♦ The DVTs and cardiac side effects make Revlimid not as clean as originally thought. ♦ Use of Millennium's Velcade will take a hit initially when Revlimid is approved because Revlimid is easier to administer and will probably be less expensive – but every multiple myeloma patient will eventually get both of these drugs. ♦ Use of Celgene's Thalomid (thalidomide) will be more affected by Revlimid in the U.S. than in Europe. In the U.S., doctors are eager to move Revlimid ahead of thalidomide, but in Europe, cost will triage the three drugs (thalidomide, Revlimid, and Velcade – in that order). ♦ Combination therapy is the future. Eventually, doctors expect to give Velcade+Revlimid+something else. Treatment of myeloma may become like treating HIV – a cocktail that makes it a chronic disease.

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INTERNATIONAL MYELOMA WORKSHOP

Sydney, Australia
April 10-14, 2005

Myeloma experts from around the world attended the 10th International Myeloma Workshop, including more than 150 from the U.S. Multiple myeloma (MM) is the second most common cancer of the blood, representing ~1% of all cancers and 2% of all cancer deaths. There are 15,000 new cases of multiple myeloma diagnosed each year and 50,000 total cases being treated at the present time in the U.S. The median age of multiple myeloma patients is 60, and the disease is more common in African-Americans than Caucasians. Median survival is 3-4 years with conventional therapy, and 4-5 years with high-dose therapy and transplant, but multiple myeloma remains incurable.

Key therapies for multiple myeloma today include:

- Celgene's Thalomid (thalidomide), usually plus dexamethasone (thal/dex).
- Millennium's Velcade (bortezomib).
- Melphalan (GlaxoSmithKline's Alkeran). However, MM is often resistant to cytotoxic agents like melphalan.
- Autologous stem cell transplantation.

The real future of multiple myeloma therapy is likely to be combinations of agents, experts agreed. Among the combinations being tested are:

- **Based on gene profiling:** Velcade+Kosan's 17-AAG. A Phase I-II trial is ongoing with 5 of 7 patients showing a response.
- **Based on cell signaling:**
  - Velcade+HDAC inhibitor. A speaker described this as "the most exciting combination for the future."
  - Velcade+Revlimid. A speaker said, "I think this is a prototype for the future.
  - Two companies agreed enough to allow a joint study of two new agents early. Ten of 11 patients who were resistant to either Velcade or Revlimid or both when given as single agents responded, with 3 CRs, 5 marked PRs, and 2 minimal responses."
- **Based on correlative science:** Velcade+Johnson & Johnson's SCIO-469 (a p38 MAP Kinase inhibitor). A multiple center trial is ongoing. Patients are given two cycles SCIO-469 by itself, and if there is no response, Velcade is added, with even Velcade resistant patients eligible.

Questions were raised whether combination therapy would "burn bridges" and leave nothing to treat patients with relapsed disease, and experts said this is something that has to be watched, but they suggested the promise is greater than

the risk. One commented, "You can go back and recombine drugs, and get people who failed one or another and then add something else, and get a response. It is an evolving process to tell what we can and cannot do, and what kind of resistance we will have at the end of the day." Another said, "We have patients with a response who drop off due to toxicity, and we can retreat those patients and get a response with a newer agent. But some may have untoward effects on marrow function. We may not see it in that drug, but when we move to melphalan or doxorubicin (Johnson & Johnson's Doxil) it may raise its ugly head, so we have to be careful using these drugs willy-nilly up front." A third expert said, "Is combination therapy going to yield unexpected results and unexpected synergies because these drugs have so many different targets? If you combine them, it is not like one pathway plus another pathway. It is like five pathways plus five other pathways ...Dosing and schedules will be variable. I'm impressed that the data show that even if a patient is resistant to one, you can restore sensitivity with arsenic (Cell Therapeutics' Trisenox), so it is more complicated than 1+1."

New therapies and future directions

Several new agents are in development. Dr. Kenneth Anderson, Director of the Jerome Lipper Multiple Myeloma Center at Harvard Medical School, commented, "You will hear a lot about novel agents here…I doubted we would ever see this…I think we are likely to see one new drug for multiple myeloma approved by the FDA per year until further notice…Our job is to put them together. Some of this is already happening…I think it is an unprecedented and very exciting time in multiple myeloma." Dr. James Berenson of the Institute for Myeloma and Bone Cancer Research in West Hollywood CA offered a baseball analogy, "There is no Gleevec (Novartis, imatinib – which has shown dramatic results in CML) for multiple myeloma today. There are some singles or doubles but no home runs."

Other comments about novel agents in development included:

- **GlaxoSmithKline's GW-786034.** A poster concluded that preclinical studies warrant further study of this indazolylpyrimidine.

Novel Therapies in Development to Target Myeloma Cells

Targeting the MM cell	Targeting the MM cell and the BM milieu	Targeting the BM milieu
IF-1 inhibitors	Millennium's Velcade (bortezomib)	IKK inhibitors
CD-40 antibodies	Celgene's Thalomid and Revlimid	P38 MAP Kinase inhibitors (e.g., Johnson & Johnson's SCIO-469)
Kosan Biosciences' geldanamycin (17-AAG)	Merck's SAHA	
PK-11195	Novartis's valatanib (PTK-787)	
Novartis's Smac mimetic peptide	Cell Therapeutics' Trisenox	
Telomestatin		

- **IKK inhibitors.** A University of Pittsburgh study found IKK inhibitors or MAP Kinase inhibitors may be useful in the future with Velcade, dexamethasone, Revlimid, or Kosan's 17-AAG.
- **Johnson & Johnson/Scios's SD-208.** A poster offered a preclinical rationale for this TGV-β Receptor 1 kinase inhibitor.
- **Nereus Pharmaceuticals' salinosporamide (NPI-0052).** Preclinical data on this agent, from a marine microorganism, indicated it is active in Velcade-resistant myeloma cells. A speaker described NPI-0052 as "different from a proteasome inhibitor," adding, "It will go into clinical trials later this year."
- **Novartis's Smac peptide.** A speaker said this will come to multiple myeloma as part of its first-in-man experience.
- **ProConn Biotech's PRO-001.** This Israeli company is working on an anti-FGFR3, and preclinical data support further clinical study.

CELGENE'S Revlimid (lenalidomide)

Celgene had a strong presence at this meeting and sponsored an education workshop the first day of the meeting. A speaker said, "My prediction is this agent (Revlimid) will quickly become part of the initial management of multiple myeloma."

Celgene submitted Revlimid to the FDA for the treatment of MDS on April 7, 2005. The company is in the midst of data collection and will file Revlimid for multiple myeloma "in 2005" for second-line therapy. Two data sets are being prepared for Revlimid in MM: (1) the data which formed the basis of the decision to stop the trial (the data presented at this meeting), and (2) additional, scrubbed data collected from the participating sites after the initial cut point.

Company officials were very upbeat and optimistic about the outlook at the FDA, and they appear to have reason to be. Revlimid is being developed in multiple myeloma under a Special Protocol Assessment (SPA). Under an SPA, the company and the FDA agree on a regulatory path, which is usually a tougher path, but one which, if the conditions are met, almost assures approval unless safety problems crop up. In this case, the Revlimid trials met the FDA pre-specified endpoint – and exceeded it by the trial being stopped – so approval looks pretty much like a done deal.

Will Revlimid require an FDA Advisory Committee? Probably not unless the FDA wants input on how to prevent the thrombosis. The Agency may decide to ask a panel for their advise on recommendations on the need for prophylactic therapy with an anticoagulant.

Phase III Revlimid+dexamethasone data

The preliminary results of two randomized, double-blind, placebo-controlled, Phase III Special Protocol Assessment trials (MM-009 and MM-010) of Revlimid in relapsed and refractory multiple myeloma were presented at the meeting. The efficacy looked good, and experts described the results as "phenomenal," "very, very positive," "fabulous," and "very exciting." The principal investigator for the North American MM-009 trial, Dr. Donna Weber of M.D. Anderson Cancer Center, said the message from this trial is: "It is clear patients are benefiting from the combination of Revlimid plus dexamethasone. I hope this will lead to approval, so Revlimid can be available to all patients, not just patients in clinical trials. People are stable longer on this combination."

Together, the trials enrolled a total of 705 patients from 97 sites – the MM-009 trial in the U.S. and Canada (354 patients) and the MM-010 trial in Europe, Israel, and Australia (351 patients). Both trials compared 25 mg/kg Revlimid+ dexamethasone to placebo+dexamethasone. The primary end-point was TTP. The survival endpoint has not been reached in either arm yet. The trials were unblinded when the independent data monitoring committee determined that TTP in each trial exceeded the pre-specified stopping value of $p<.0015$ and recommended that all patients in the trials be offered Revlimid. The results of the two trials were remarkably consistent with each other.

However, toxicity (DVTs/PEs) also is more of an issue than expected. There was no significant hepatic toxicity with Revlimid, but sources were surprised by the thrombosis rate – 13.6% in North America. Dr. Weber said, "No one had any inkling; we were surprised there may be a clot issue because we didn't know about it. That's why we do the trials…What we should do about it is still uncertain…There is no consensus on prophylactic therapy for Revlimid+dexamethasone. Since the two trials had slightly different results, it is not clear…I think there is some question, and further analysis on this and other studies would bring the question to light…The international trial and the North American trial had different thrombosis results, and the international trial was not very different from the baseline in multiple myeloma patients generally." Other experts suggested that all Revlimid/ dexamethasone patients should be on aspirin, but Dr. Weber isn't convinced of that yet.

There also may be some cardiac toxicity with Revlimid. The cardiovascular events in the North American trial were a surprise as well. Dr. Weber tried to put them in perspective: "Cardiovascular events were rare, but in the North American trial they were seen in the Revlimid arm but not at all with dexamethasone, so there is a small tendency to Grade 3-4 cardiac events…But in the international trial, both arms saw events, and they were extremely rare in both arms."

Other points that were made about these trials and Revlimid in general include:

- **Data timing.** The data reported in these trials are not from a very recent data cut. The North American trial covered patients through May 2004, and the interim analysis was in July 2004. The international trial covered patients through August 2004, and the interim analysis was in September 2004. The independent data monitoring committee (IDMC) didn't see the data until its regularly-scheduled meeting in February, at which time it decided the trial met the unblinding point ($p<0.0015$). That's a long time between cut points and action.

- **Optimal dose.** An investigator said the best dose of Revlimid probably will vary from patient to patient, but he believes it is in the 25-30 mg range. He explained, "The important point is that there is no MTD up to 50 mg when given continuously. Beyond that myelosuppression occurred but was manageable…Some patients need to be started at a lower dose (than 30 mg)…but we need to look at the data overall to see who those patients are…It appears that patients with a lot of prior chemotherapy don't tolerate the higher (30 mg) dose…The Phase II and III trials attempted to define an upper limit and leave a broad spectrum of doses in between."

- **Dose adjustments.** About 30% of the patients in the trials had their dose adjusted, so concerns may be valid that doctors may need to experiment to find the correct clinical dose, as they did with thalidomide. Furthermore, when Revlimid is given with drugs other than dexamethasone – which is likely – the dose may need to be adjusted even more.

- **Comparison to Velcade.** The results of these trials are similar to the Velcade APEX trial, but you can't compare the studies directly.

- **Markers for Revlimid toxicity.** Asked if there is a marker for patients who will have higher toxicity with Revlimid, an investigator said, "Clearly, there is more toxicity with thalidomide than with Revlimid…(Dr.) Donna Weber reported high levels of homocysteine in patients who develop thrombosis…so she recommends vitamin B-12, folic acid, and aspirin, and we employ that…It is easy and reasonable to do… With Revlimid, the number of DVTs is very small…and it was in patients also on dexamethasone."

- **Survival.** Survival was a secondary endpoint in the trials, but analyzing it may be difficult since the trials were unblinded and crossovers are allowed. As with the APEX trial (which led to Velcade's approval), patients in the dexamethasone-only arm of the Phase III Revlimid trials who progressed were allowed to enter an unblinded "companion" study in which they could receive Revlimid. When the trial was stopped, all patients were offered Revlimid. A Celgene official said a "very high percentage of dex-only patients went into the companion trial, and that will affect this. The trials may not show a survival advantage at the end of the day."

Doctors are likely to be disappointed if there is a lack of survival data. One said, "I'll be looking for differences in survival data. I hope TTP translates to overall survival." (NOTE: A study reported at this meeting found that median survival from first relapse was 1.2 years before Velcade or the combination of thalidomide+dexamethasone were introduced.)

➢ **TTP.** When will TTP be reached in the Revlimid+ dexamethasone arms of the MM-009 and MM-010 trials? A source said, "It is too premature to say. They are approaching the medians, but it is hard to know."

➢ **Missing data.** There were 354 patients in the North American arm, but the data only cover 340 patients.

➢ **Prior thalidomide use.** Asked how many patients in the trials had prior exposure to thalidomide, Dr. Weber said, "About 45%-50% of patients who had prior thalidomide treatment responded to Revlimid, and 15%-20% of prior thalidomide patients responded to dexamethasone alone – and there were CRs in that group. We think many of those patients had been resistant to thalidomide."

Revlimid Phase III Trials

Measurement	North American Trial MM-009 (n=354)		International Trial MM-010 (n=351)	
	25 mg Revlimid + 40 mg dexamethasone n=170	Placebo + 40 mg dexamethasone n=170	25 mg Revlimid + 40 mg dexamethasone n=176	Placebo + 40 mg dexamethasone n=175
Primary endpoint: TTP	Not reached at >15 months	5 months (20 weeks) (p<.00001)	Not reached at >11 months	5 months (20 weeks) (p<.00001)
Demographics				
Disease Stage 3	66%	67%	65%	63%
Mean time from diagnosis	3.6 years	3.9 years	4.2 years	4.6 years
Prior anti-MM regimens ≥2	52%	54%	64%	64%
Prior Velcade therapy	~10%		~10%	
Prior thalidomide therapy	~45%		~45%	
Prior dexamethasone therapy	~60%		~60%	
Prior SCT	~60%		~60%	
Efficacy results				
CR+PR	51.3% (p=.001)	22.9%	47.6%	18.4% (p=.001)
CR	19.5%	3.8%	9.1%	1.2%
PR	31.8%	19.8%	38.4%	17.1%
SD	46.1%	63.7%	N/A	N/A
PD	2.6%	13.4%	N/A	N/A
Safety results				
DVT (all)	11.2%	2.9%	4.7%	2.9%
Pulmonary embolism (all)	2.4%	0.6%	3.5%	1.2%
DVT+PE (all)	13.6%	3.5%	8.2%	4.1%
Grade 3-4 adverse events				
Atrial fibrillation	4.7%	0	0.6%	1.8%
CHF	2.4%	0	0.6%	0
Diarrhea	2.4%	0	2.4%	1.2%
Cytopenias	~15%			
Adverse events leading to dose reduction	29.4%	17.6%	42.6%	27.4%
Adverse events leading to discontinuation	21.2%	11.8%	16.5%	13.7%
Reasons for discontinuation				
Total discontinuations	38%	67%	38%	59%
PD	15%	47%	16%	41%
Adverse events	12%	8%	6%	6%
Patient decline	4%	5%	10%	5%
Stable disease	2%	3%	0	1%
Death	2%	0.6%	6%	6%
Other	3%	3%	0	0.6%

➢ **Anticoagulation.** Patients in these trials were not allowed to take aspirin for their multiple myeloma, but they might have taken it for other reasons; that wasn't monitored. Most sources predicted that Revlimid will need to be given with an anticoagulant – either warfarin, LMWH, or aspirin – but there is no agreement yet on which anticoagulant is preferable. Most sources believe that aspirin will be the choice in the end. Patients on warfarin who take Revlimid do experience spikes (and valleys) in INR measurement, but a Celgene official did not think this is related to the drug. Rather, he suggested it is due to other disease-related factors (diet, not eating, etc).

During the meeting, Celgene sent a letter to the SWOG investigators advising them that all patients in their trial need to be notified and put on aspirin (because of a high incidence of DVTs in that trial).

➢ **CRs.** The CR rate does ***not*** include near-CRs. There are some near CRs, but they were listed as PRs, though they may be moved to CR in the future as the data are further analyzed. Thus the response rate could improve with further analysis.

➢ **Duration of response.** Sources said a response that lasts ≥12 months is considered a "long-response" in the relapse setting for salvage therapy, and a minority of patients (~33%) achieve that currently. An expert estimated that 50% of Velcade patients are "long responders." Asked if there was any anecdotal information on when the disease returns after patients come off Revlimid+dexamethasone therapy, Dr. Weber said, "We don't have that data. Many patients seem to have some progression when the dose of dexamethasone was backed off, and those patients may well respond to pushing the dex…We have no inkling at this time."

➢ **Hematologic adverse events.** In the international trial, Grade 3-4 cytopenias, especially neutropenia, were described as "common," but Grade 3-4 neutropenic fever was uncommon in both arms.

➢ **Future trial designs.** If and when Revlimid is approved, what will be the control arm in future MM trials? Speakers agreed it is unlikely to be 40 mg dexamethasone because of the high level of toxicity with that regimen, but it could be lower dose dexamethasone. An expert said, "The days of high dose dex are probably numbered. I predict that Revlimid and thalidomide should be approved (for multiple myeloma) this year, and that will re-set the control arms as we go forward." Another expert said, "This is a tough one. You don't want to raise the bar so high for new drugs that it makes it impossible to get them through. I like the approach of using whatever is left over…It wouldn't hurt to have three or four different controls that we would accept."

➢ **More data.**

- The median duration of response is not available yet but it is at least >6 weeks. This data may be available at ASCO 2005.
- At ASCO, the new Revlimid data will be an update of the Phase III trials (MM-009 and MM-010) through at least December 31, 2004, and perhaps through February 2005. A Celgene official said, "There is absolutely no reason to think the numbers will change."
- Survival data were described as "too immature," but it is likely to be presented at the American Society of Hematology (ASH) 2005 (***not*** the European Hematology Association meeting in June 2005).

Single-agent Revlimid data

Revlimid also appears to work as a single agent – without dexamethasone. Dr. Paul Richardson presented the data from

Preliminary Results of Revlimid MM-014 Trial

Measurement	30 mg Revlimid n=222
Primary endpoint: Myeloma response (CR+PR)	25%
Stable disease	71%
Secondary endpoint: **Safety**	
≥1 treatment-related adverse event	96%
Treatment-emergent peripheral neuropathy (any grade)	5%
Upper respiratory infection	23%
Fatigue	18%
Pyrexia	18%
Diarrhea	16%
Dyspnea	15%
Nausea	15%
Constipation	14%
Cough	14%
Other secondary endpoints	
Median TTP	22.4 weeks (~5.2 months) (range 1.8-66 weeks)
Duration of response	Ongoing, no results yet
Survival	Ongoing, no results yet
Time to first skeletal-related event	Ongoing, no results yet
Serious adverse events	
Pneumonia	1%
Febrile neutropenia	4%
Renal failure	4%
Thrombocytopenia	4%
Neutropenia	3%
Pyrexia	3%
Dehydration	3%
Renal failure, acute	3%
Anemia	2%
DVT	2%
Adverse events leading to discontinuation	
Neutropenia	40%
Thrombocytopenia	23%
Fatigue	5%
Anemia	5%

the single-agent, open-label, multicenter, 222-patient MM-014 trial of 30 mg Revlimid in relapsed and refractory MM patients. Of these patients, 41% had prior Velcade therapy, 44% had prior transplantation, and 80% had prior thalidomide. As of the cutoff date of February 14, 2005, 51 patients were ongoing in the study. In terms of response, 10 patients were not evaluable.

The Revlimid outlook

Doctors were impressed with the Revlimid data, but doctors did not believe the Revlimid data will be sufficient to guide them in its use. Doctors really haven't worked out how to choose among Velcade, Revlimid, and thalidomide when all three agents are available. They will be looking for data from the additional trials. Meanwhile, they will experiment themselves or put all Revlimid patients in clinical trial.

Because of the easier adverse event profile, patients are expected to stay on Revlimid longer than they stay on thalidomide. A source said, "We have patients who've been on Revlimid three and a half years. Revlimid is extremely well-tolerated, and we are not seeing the things that make patients stop thalidomide."

Other general comments on the outlook for Revlimid included:

- *U.S.:* "The issue of safety will color usage. We need more follow-up to know how to use Revlimid. The responses need to be durable. The response can't be weeks instead of months. The dose in the trials is not what we may actually give. With thalidomide, the company insisted 800 mg would be the dose, but we had to reduce it. Will we have to reduced the Revlimid dose as well? That is something we will have to be very careful with Revlimid because of the effect on bone. And if Revlimid compromises function it will limit our future choices. From a study of Revlimid+dexamethasone in 30 patients, we can't say Revlimid should be used as front-line therapy. I also can't see moving Revlimid front-line based on the Phase III data. We could do harm and turn on the disease. It could be there is just a short response, followed by relapse. We saw that in stem cell transplantation."
- *Finland:* "I'm keenly waiting for Revlimid, but cost could be an issue."
- *Spain:* "An oral medication is more comfortable for patients."

➢ **Impact on Velcade.** Sources said Velcade is primarily used second-line (at first relapse), but there is significant use front-line, and sources estimated that from 5%-50% of their multiple myeloma patients are currently on Velcade, though non-U.S. doctors are at the low end of that range. Sources suggested Revlimid is likely to be used ahead of Velcade because of the ease of administration. Doctors are predicting that they will try Revlimid first, and give Velcade when patients fail Rev/dex.

- *New York doctor:* "I would use Revlimid before Velcade because Revlimid is easier to give."
- *Georgia doctor:* "If the Revlimid results are comparable or better than Velcade, then patients would prefer Revlimid…But there are no data to show what the right way to go is in choosing between Velcade and Revlimid."
- *U.S. doctor:* "It will be patient-specific. Patients who need a rapid response and are in deep trouble will get Velcade. Patients with more gradual disease who want an oral agent will get Revlimid."
- *U.S. doctor:* "Velcade is mainly second-line, some first-line, rarely alone. There is a lot of low-dose Doxil used with Velcade. With Velcade we knew what dose to use. We don't know the Revlimid dose. I think Revlimid development was rushed."
- *California hematologist:* "I currently use Velcade mostly second- or third-line, for about 10% of my multiple myeloma patients, and my use has been increasing slightly. Before using Revlimid I want to see more detailed data and published manuscripts. But from what I hear, it is remarkable. Most Velcade patients are far along in their disease and have a hard time with the Velcade, so I would consider Revlimid before Velcade. Revlimid also sounds like a replacement for thalidomide, but I think there will still be a role for both."

Some doctors said they plan to split their use between Velcade and Revlimid in thalidomide failures, giving Velcade to patients with more aggressive disease and Revlimid to patients with less aggressive or less symptomatic disease. The preference is for using Revlimid ahead of Velcade because of the ease of administration, assuming the cost is lower than Velcade.

➢ **Impact on thalidomide.** Sources estimated that about half of their myeloma patients are on thalidomide. Most doctors hope and believe there will still be a role for thalidomide. However, they generally plan to replace thalidomide with Revlimid in their practices, so they aren't really sure where thalidomide will be used, except perhaps in Revlimid failures. An Australian doctor said, "I think both Revlimid and thalidomide have activity and are complementary. They are like a BMW and a Mercedes. I don't know which I would choose. I hope this meeting will answer this question." A U.S. doctor said, "Thalidomide won't go away, but Revlimid will replace it as the preferred drug…The potential is for Revlimid to be use in thalidomide failures. Intuitively, most people think that will work." A New York doctor said, "Thalidomide may still have a role. Thalidomide failures can respond to Revlimid, but I'm not sure the opposite is true." Dr. Weber commented, "Revlimid appears to have a slightly different side effect profile…We need to sort out whether it works in refractory thalidomide patients and, later,

whether thalidomide works in refractory Revlimid patients… You don't want to lose a drug in the armamentarium."

European doctors said they generally use thalidomide for patients who relapse, not front-line because of cost. These sources all indicated Revlimid would be used in thalidomide failures, since the cost of Revlimid will be higher than thalidomide. A U.K. doctor said, "The big question with Revlimid is cost. The initial data look very promising, but if you have to anticoagulate with warfarin or LMWH, you lose the (cost) advantage – unless you can just give aspirin." A German doctor said, "Revlimid is interesting, but I want to see German studies on it. Revlimid won't replace thalidomide initially because of cost, but it will be used ahead of Velcade if it is less expensive than Velcade."

Other comments about the future of thalidomide included:

- "Patients who fail thalidomide may be responsive to Revlimid…We hope that both agents remain active and available for patients with multiple myeloma."
- "I see them as two distinct drugs, despite the subtle chemical differences. They behave differently, have different toxicity profiles…We see thalidomide failures who benefit from Revlimid, and I've seen the opposite as well. So there is room for both."
- "They are separate drugs, and it is important that both be available. But, from my perspective, drugs like Velcade, thalidomide, and Revlimid are not competing. We will find that we want a strategy so we don't 'burn our bridges.' We don't want to use so much thalidomide that we burn the bridge of using Velcade down the track and vice versa. So, we need to work out a good paradigm to manage all the options so we don't have interacting toxicities. I think we will find the combinations are better…Thalidomide might be better combined with drugs that are more myelosuppressive."
- "Anecdotally, we tend to use thalidomide later in the disease rather than early…When we had patients who progressed on Revlimid and we didn't give a washout period because the disease was progressing quickly, what we were very impressed by was that five of six patients had very quick responses that we don't see with thalidomide or thal/dex…Maybe these drugs (thalidomide and Revlimid) are quite different, and there might be some additive effect or synergisms with both drugs."
- "Using lower doses of Revlimid and thalidomide might overcome resistance to either…In that spirit, I would suggest thalidomide+Revlimid is worth testing together …We might be able to use very low doses of thalidomide and avoid the neuropathy. That is at least worth testing."
- "Thalidomide won't go away. There is more peripheral neuropathy with thalidomide but less cytopenia and less myelosuppression."
- *(Myeloma patient on thalidomide):* "My disease is progressing slowly and I'm starting to have some neuropathy, so I would probably switch from thalidomide to Revlimid."

➢ **Combination therapy.** Sources predicted combination therapy will be the standard in the future, but doctors don't yet know which combinations and in which order. There are already a lot of trials ongoing with Revlimid, including combination trials, but many more are likely to be instituted as doctors work to figure out the new treatment paradigms. Dr. Weber said, "People will be combining agents and trying to decide which combination to use and how to use it…You are not replacing one with the other…You can decide when to use each…You have to consider the side effects with each patient, a patient's difficulties, and then tailor therapy to each patient. That is part of the art of medicine."

➢ **The cost issue.** Cost is likely to be an issue in the U.S. as well, but perhaps less of an issue than in Europe. Will insurance companies pay for Velcade+Revlimid? Sources predicted they will want ***published*** Phase II data first. Two knowledgeable sources predicted Revlimid will be priced slightly less than Velcade. They explained that Velcade costs ~$25,000 every six months or $4,167/month, thalidomide ~$2,000/month, and Revlimid will fall in the middle at ~$3,333/month. A Celgene official said the average annual cost of thalidomide per patient is $15,000, and the average patient takes the drug for 170 days. This would put the average cost per patient monthly at $2,679. This official said there have been no thalidomide price increases in the past seven months.

A Celgene official said 15%-20% of thalidomide currently is provided free of charge to Medicare and Medicaid patients, but that is likely to change now that thalidomide is included in a CMS demonstration project. In 2006, it is expected to be included in Medicare drug coverage.

Combining Revlimid and MILLENNIUM'S Velcade

Preliminary results of a Phase I dose-finding pilot study of the combination of Velcade plus Revlimid (without dexamethasone) were presented by Dr. Paul Richardson of Dana Farber Cancer Institute. The primary objective was safety and

Design of Velcade+Revlimid Combination Pilot Study

	Revlimid 5 mg	Revlimid 10 mg	Revlimid 15 mg	Revlimid 20 mg
Velcade 1.0 mg/m^2	Cohort 1	Cohort 3	Cohort 5	Cohort 7
Velcade 1.3 mg/m^2	Cohort 2	Cohort 4	Cohort 6	Cohort 8
Demographics				
Mean number of prior therapies	4			
Prior SCT	66%			
Prior Velcade	33%			
Prior Revlimid	17%			

identification of the MTD and the recommended dose for a Phase II trial. The secondary objectives are response, assessment of PK, and surrogate markers. So far, 12 patients have been enrolled. Once the MTD is determined, an additional 10 patients will be enrolled at that dose. Dr. Richardson concluded, "There is an encouraging safety profile." A source suggested the MTD is likely to be 15 mg Revlimid+1.0 mg/m^2 Velcade.

Side Effects in Velcade+Revlimid Pilot Study

Cohort	Adverse event	Number of patients	Responses
1	Grade 4 neutropenia	3	1 PR, 2 MR
2	Grade 4 thrombocytopenia	3	1 CR, 2 PR
3	Grade 3 neutropenia	3	3 PR
4	1 hyponatremia 1 DVT Grade 2 rash	N/A	N/A

Once Dr. Richardson's pilot, dose-finding study of combination Revlimid/Velcade determines the MTD, Dr. Weber said she hopes to start a Revlimid+Velcade+ dexamethasone trial.

Revlimid management strategies

Revlimid patient management strategies were discussed by Dr. Mohamed Hussein of the Cleveland Clinic. He said their experience with Revlimid indicates it is well-tolerated as a single agent, "The challenge in the next few months to years will be figuring out which lab values mean something clinically…We would not want to cut the dose or cause delays in an effective drug when it is not necessary."

Ongoing Revlimid trials

- **CALGB-011.** This is a 544-patient Phase III U.S. trial. The principal investigator is Dr. McCarthy.
- **ECOG-040.** This randomized, Phase III, 412-patient, U.S. trial recently opened, and 56 patients have been enrolled so far. An investigator said the trial is "accruing rapidly." The trial compares 25 mg Revlimid+dexamethasone x 4 to Revlimid+low dose dexamethasone x 4. The investigator said the trial is "very similar to the thal/dex randomized trial." The principal investigator is Dr. Vincent Rajkumar of the Cleveland Clinic. In this trial, patients who fail Revlimid will then receive thalidomide.
- **SWOG-088.** This 500-patient, double-blind, placebo-controlled, Phase III trial in the U.S. The principal investigator is Dr. Jeffrey Zonder of the Barbara Ann Karmanos Cancer Institute in Detroit.
- **SWOG S-0232.** This is testing Revlimid+dexamethasone vs. placebo+dexamethasone in newly diagnosed MM patients in the U.S. A speaker said, "Of the first eight patients entering, four experienced DVT with Revlimid/dexamethasone, and there was no prophylactic aspirin."

Cleveland Clinic Experience with Revlimid Patient Management

Measurement	MM-014 trial: Revlimid as a single agent	DVd-R Trial Revlimid combination therapy (Doxil, vincristine, dexamethasone, 10 mg Revlimid)
Patients	22	46
Disease	Relapsed with refractory features	75% refractory 25% relapsed
Neutropenia	Mostly Grade 1-2 Grade 3 mostly with longer term use but not associated with neutropenic fever	Grade 3-4 in patients with neutrophil counts of <1000. Not associated with neutropenic fever
Neutropenia management strategy	No specific therapy needed. Can use growth factor or reduce dose	Recovered with response. Did not need growth factor therapy over the long run
Thrombocytopenia	All Grade 2, noted early	Grade 3
Thrombocytopenia management strategy	No need for cell component support, dose reduction or limiting starting dose	Not specified
Elevated liver enzymes	Grade 1-2 (asymptomatic, rare, recovered with drug discontinuation)	---
ALT management strategy	Delay therapy until enzymes return to normal. Dose reduction does not appear to change the course.	---
Clinical adverse events	No DVT Fatigue in 40% of patients Constipation in <5% of patients, mostly Grade 1 Neuropathy in <5% of patients without baseline neuropathy	Fatigue Neuropathy Grade 1-2 Constipation Rash when combined with sulfa agents and uncommonly with penicillin DVT in <10% of patients on aspirin
Clinical management strategy	Dose reduction was not necessary for any clinical adverse events	Not specified
Optimal dose: still under evaluation	25 mg/day x 21 days q 28 days	10 mg/day x 21 days q 28 days

- **PI-020.** This is an open-label, 58-patient Phase I study of Revlimid+Velcade in the U.S. The principal investigator is Dr. Paul Richardson.
- **PI-030.** This is a 35-patient Phase II study of Biaxin+Revlimid+dexamethasone for newly diagnosed MM patients in the U.S. The principal investigator is Dr. Ruben Niesvizky of New York Presbyterian Hospital, Weill Medical College of Cornell University.
- **PI-026.** A multi-center, open-label, trial of 51 patients in Italy of melphalan+prednisone+Revlimid as induction therapy in elderly newly diagnosed MM patients.
- **MM-011.** This 50-patient Phase I U.S. trial is testing DVd+Revlimid in relapsed/refractory MM.
- **Germany.** A Phase I/II multicenter trial of Revlimid+doxorubicin+dexamethasone (RAD) in relapsed or refractory MM being conducted in Germany.
- Single-arm, open label safety and efficacy study of Revlimid monotherapy for relapsed MM from studies THAL-003, MM-009, and MM-010.

CELGENE'S Thalomid (thalidomide)

A speaker discussed cardiovascular complications with thalidomide in multiple myeloma and possible strategies for avoiding them. It is information that may be useful for Revlimid as well.

On DVTs, he observed:

- "There is a much higher incidence of DVT in newly diagnosed patients than in relapsed or refractory patients."
- "We tried giving low-dose Coumadin (warfarin), but there was no difference (in DVTs) in patients who got Coumadin and those who didn't."
- "We tried Lovenox (Sanofi-Aventis, enoxaparin) through the induction (~100 days), and DVTs were the same: 15% in thalidomide+Lovenox and 15% with thal/dex."
- "The development of DVTs does not appear to affect overall survival (in MM patients)."

On sinus bradycardia, he said, "In 200 patients, bradycardia was observed only in the thalidomide arm, and it was observed early in treatment: 53% had bradycardias, 19% had Grade ≥2, and 2.5% required a pacemaker."

Another speaker commented that APC resistance may be the most useful test for predicting thrombosis with thalidomide.

CELL THERAPEUTICS' Trisenox (arsenic trioxide)

In a Phase I study, the response rate for the 11 evaluable patients was 63%: good PR 18.2%, poor PR 45.5%, stable disease 27.3%, and no response 9.1%. Only three patients progressed on therapy.

Unexpected findings in this trial included:

- Ascorbic acid (vitamin C) appears to blunt the toxicity of Trisenox, especially fluid retention and fatigue. Ascorbic acid not only sensitizes cells to Trisenox but also potentates Trisenox. Oral vitamin C may not offer the same benefits as IV ascorbic acid. A speaker said, "The oral kinetics (of ascorbic acid) are very different than IV, and we think the kinetics of ascorbic acid may be important." Another expert said, "There are in vitro data emerging that Velcade becomes resistant in the face of vitamin C. Whether that is true in vivo will be tested soon, so this issue is very complex."
- The degree of clinical response generally plateaued after two cycles, even though in vitro sensitivity was unchanged. A speaker said, "Our suspicion is that MM cells don't change, don't become more resistant to Trisenox. What happens, we think, is myeloma's micro-environment adapts to Trisenox. It may be that the important drugs to combine with Trisenox are those drugs that further target the microenvironment, and that may significantly increase the efficacy of this drug."
- Disease progression on treatment was uncommon.

Phase II treatment protocols that have been tried with Trisenox in relapsed/refractory MM include:

- **Initial study.** 0.15 mg/kg IV over 2 hours daily for 30 days. Responses were seen in 3 of 14 patients.
- **Single agent multicenter study.** 0.25 mg/kg Trisenox by 1-2 hour infusion 5 days a week, with 2 weeks on followed by 2 weeks off. Responses were seen in 33% of the 24 patients.
- **Combination study TAD.** 0.25 and 0.35 mg/kg Trisenox twice weekly times 8, followed by a 3-week rest (11-week cycle). Patients also got ascorbic acid and dexamethasone. Six patients experienced Grade 3 toxicities (fatigue, hyperglycemia, headache, neutropenia, dehydration, syncope, burning at the IV site), and one patient had Grade 4 sensory neuropathy. Responses were seen in 30% of patients (2 near CRs, 4 PRs).
- **DATA trial.** This study is ongoing in newly-diagnosed, high risk MM patients and relapsed/refractory patients who have failed either Trisenox or Thalomid with Trisenox+ascorbic acid+100 mg Thalomid+dexamethasone in 16-week cycles. All patients have responded. Bacteria and pneumonia have been issues, and they are being addressed with antibiotics. DVT looks like an issue which may be able to be controlled by the addition of aspirin.

Key issues for Trisenox use in MM include:

- Monitoring potassium and magnesium.
- Renal disruption.
- Fluid retention/pulmonary edema.
- Monitoring QTc prolongation. There is some QT prolongation with Trisenox, but that may not pose a regulatory issue. A speaker said, "The only time we saw statistically significant QT prolongation was in Cycle 1, with an average prolongation of 30 ms. This was not clinically apparent – no arrhythmias and no other cardiac-related symptoms – and we never stopped any doses for QTc prolongation…QTc intervals actually got shorter compared to baseline with Cycles 5 and 6." At a workshop on QT prolongation (sponsored jointly by the FDA and the Drug Information Agency) in January 2003, an FDA official commented that a mean QT prolongation >20 ms generally would make a drug not approvable "unless it is arsenic trioxide and treats leukemia" – or perhaps multiple myeloma.

Future directions for Trisenox include:

- Trisenox+Velcade. A Phase I/II trial is ongoing in relapsed/refractory MM patients.
- Trisenox+pegylated Doxil+ascorbic acid (DAC). A pilot study is underway with a weekly regimen of Trisenox (0.35 mg/kg after an initial 2 doses in Week 1 of 0.25 mg/kg).
- Trisenox+liposomal doxorubicin+ascorbic acid. A prospective, open-label, non-randomized, Phase II trial is scheduled to begin "shortly."

Patients who may benefit from Trisenox combination therapy were described as: patients with significant neuropathy, patients with relapsed/refractory MM and renal failure, and patients who have failed chemotherapy, steroids, thalidomide, and/or Velcade. Patients who may benefit from TAD (an alkylator-free regimen of Trisenox+ascorbic acid+dexamethasone) were described as those with significant (2+) neuropathy. Patients who may benefit from MAC therapy (a steroid free regimen of melphalan+ascorbic acid+Trisenox) were described as those with severe steroid myopathy, a history of intolerance to steroids, an infectious disease, diabetes, elderly (≥70 years), or renal insufficiency.

MILLENNIUM'S Velcade (bortezomib) (marketed by Johnson & Johnson outside the U.S.)

Dr. Paul Richardson of Dana Farber Cancer Institute reviewed data from the Phase II Velcade SUMMIT and CREST trials, and he presented new data from the randomized, Phase III APEX trial on which the FDA based approval of Velcade. This was the first trial in which the FDA accepted TTP as a surrogate endpoint for survival as a meaningful endpoint in a clinical trial. He concluded that the APEX trial showed Velcade to be superior to high dose dexamethasone overall as well as in second-line therapy for patients in their first relapse.

A statistically significant difference in the incidence of a herpes zoster side effect was reported with Velcade, and Dr. Richardson recommended prophylactic use of acyclovir. He said, "There was no increase in other atypical infections. We are not seeing a higher incidence of viral infections of other forms. The use of acyclovir is highly effective as a prophylactic, and there have been no life-threatening herpes zoster infections."

Peripheral neuropathy also was an issue in APEX, but 69% of patients had underlying peripheral neuropathy at baseline, and he said there is a clear correlation between drug-induced neuropathy and the patient's previous neurotoxicity profile. Patients with severe underlying neuropathy or a prior history of diabetes are more at risk.

He recommended:

- For Grade 1 neuropathy with pain – reduce the dose.
- For Grade 2 with pain – withholding the drug until the toxicity resolves.
- For Grade 3 – discontinue Velcade.

Velcade Trials

Measurement	SUMMIT trial	CREST trial	APEX trial
Number of patients	202	56	669
Overall response	35%	38% at 1.3 mg/m^2 30% at 1.0 mg/m^2	38%
CR	10%	---	6%
Median TTP	7 months	---	7 months

APEX Trial Results

Measurement	Velcade n=333	Dexamethasone n=336	p-value
Treatment time	273 days	280 days	---
Discontinued for PD	29%	52%	---
CR	6%	1%	---
Near CR (nCR)	7%	N/A	---
PR	25%	16%	---
Overall response	38%	18%	---
Median TTP	43 months	43 months	---
1-year survival	80%	66%	.005
Patients at first relapse (n=251)			
Median TTP	7 months	5.6 months	.0021
1-year survival	89%	72%	.0098
CR	6%	2%	---
Grade 3 adverse events	75%	60%	---
Grade 4 adverse events	14%	16%	---
Significant bleeding	4%	5%	---
Herpes zoster	13%	5%	---

A trial of a half-dose of Velcade (0.7 mg) + 10% melphalan four times a month (instead of four times every three weeks) in front-line MM patients is starting. A researcher said, "I was very impressed with the safety of that combination, and the response rate was very high…There is a rationale for combining these drugs at a lower dose."

Velcade+Thalomid+dexamethasone (BTD)

A researcher discussed a study that looked at thal/dex vs. triple therapy with Velcade. A speaker said, "We expected more cytopenias than we saw. Combining Velcade with thalidomide may be of use…At the present time it is a confusing picture, and we are not sure what regimen is best."

Measurement	Thalidomide+ dexamethasone n=130	Velcade+ thalidomide+ dexamethasone n=130
Responses (CR+PR)	68%	80%

Future plans for Velcade

These include:

- Combination studies with:
  - Revlimid
  - Kosan's KOS-953 (17-AAG)
  - Johnson & Johnson/Scios's SCIO-469
  - FTI inhibitors
- Genomic and proteomic analysis to individualize therapy
- Integration into current treatment paradigms (e.g., SCT)

BISPHOSPHENATE USE IN MULTIPLE MYELOMA

Bisphosphenates – generally Novartis's Aredia (pamidronate) or Zometa (zoledronic acid) are now routinely used to treat myeloma bone disease. The osteonecrosis of the jaw (ONJ) which was discussed at an FDA advisory panel meeting in March 2005 came up several times at the myeloma meeting. A speaker acknowledged this side effect can occur, but he insisted the benefits continue to outweigh this risk.

Novartis's Myeloma Scientific Advisory Board met in Sydney the day before the conference, and a member said:

- There was a suggestion of delayed progression in myeloma with bisphosphenates. He added, "These are very early data and need follow-up. If there is an anti-tumor effect, perhaps we should be using it in all patients. But we don't have the data, and we have to weigh it against the side effects over time."
- The panel was advising the company on the ONJ issue, and there was a lot of discussion – but no answers – on what to do if a patient develops ONJ.

Dr. James Berenson of the Institute for Myeloma and Bone Cancer Research in West Hollywood CA, who spoke at the FDA advisory committee meeting in March on the problem of ONJ and IV bisphosphenates, made these key points about bisphosphenate use in MM:

- ONJ is rare.
- The vast majority of cases are associated with dental procedures. Maintaining excellent oral hygiene is increasingly recognized as an important part of the care of patients receiving these drugs.
- A dental examination should be considered or done prior to receiving a bisphosphenate to assess dental hygiene.
- While on treatment, patients should avoid dental procedures, if possible.
- It is unclear that discontinuation of these agents changes the course of this disorder. Dr. Berenson said, "We really don't know if stopping the drug is the right thing to do… I've had patients with more severe forms, and patients who could deal with it quite effectively with antibiotics. It varies quite a lot in spectrum."
- For patients who develop ONJ while on treatment, dental therapy may exacerbate the condition. There are no data to suggest whether discontinuation of the drug reduces the risk. Dr. Berenson said, "It is an individual decision between you and the patient…We continue the bisphosphenate if (the ONJ) is not clinically significant…But avoiding dental procedures is a good thing to do. Many of our patients are undergoing dental procedures unnecessarily."
- Oral bisphosphenates do not work as well as IV bisphosphenates in MM. He said, "My belief is that the dose needed in multiple myeloma is too high for oral bisphosphenates."

Dr. Berenson said he has seen six cases of ONJ in his practice. Three of these patients required intermittent antibiotics and remain on bisphosphenate therapy. One patient was recently diagnosed with minor temporary discomfort but was largely resolved with oral clarithromycin (Abbott's Biaxin) and remains on bisphosphenate therapy. Two patients discontinued bisphosphenate use secondary to a significant effect on mastication. In these six patients, the multiple myeloma is in fairly good control: 3 long-term CRs, 1 near CR, and 2 with long-term indolent myeloma requiring no other therapy. He concluded, "We have to weigh the relative risk vs. the potential benefit of the drug."

Doctors asked a speaker how long to keep their patients on a bisphosphenate, but the speaker said there is no clear cut answer. He keeps his patients on an IV bisphosphenate

indefinitely, commenting, "The question is whether these agents will really be ***tumor*** protective."

Renal safety of Zometa+thalidomide

Questions were raised at the American Society of Hematology meeting in December 2004 about the renal safety of Zometa given to patients on thalidomide. A trial was initiated of post-autologous stem cell transplantation in 223 patients randomized to Zometa ± thalidomide. As of February 5, 2005, data were available on 138 patients, and, so far, 9 patients have had Zometa withheld for renal reactions:

- 2 cases were rapidly progressing disease
- 3 patients had it withheld in violation of the protocol. A speaker said, "It is still not clear why this happened, and this is being investigated further."
- 4 had Zometa withheld for criteria: 2 of these were on thalidomide and 2 were not.

The medium number of doses of Zometa is 11 in Arm A and 9 in Arm B. A speaker said, "We think triple therapy with post-transplant Zometa+thalidomide+prednisolone is safe and feasible."

KYPHON'S Kyphoplasty

At two talks at the myeloma conference, a speaker urged doctors to consider kyphoplasty for multiple myeloma patients with vertebral compression fractures, which is the most frequent fracture in MM patients. The Phase III CAFÉ trial is now starting in the U.S. and Europe to evaluate kyphoplasty vs. non-surgical fracture management in the treatment of cancer patients with painful vertebral body compression fractures. Two hundred patients at 30 centers will be enrolled over 12 months. The control patients will have standard non-surgical management, but they may opt for kyphoplasty after 30 days.

MISCELLANEOUS

➢ Haiming Chen PhD of the Institute for Myeloma and Bone Cancer Research in California reported at the meeting his discovery that monocytes can be turned into blood vessels – full, tubular blood vessels capable of carrying blood, such as those used in CABG. There are clear implications with this discovery for stem cell research: It may be that stem cells won't be needed in the future. Other cells may be able to be tricked into changes.

➢ A Phase II study of thalidomide+celecoxib (Pfizer's Celebrex) found that high dose Celebrex (400 mg BID) adds to the anti-myeloma activity of thalidomide but comes at an "unacceptable toxicity."

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