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Principal Authors: Kim Grant
Tricia L. Hanlon
Jeffrey D. Berk, PhD, MBA
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Executive Summary

Hematology-Oncology Thought Leader Panel #26, published January 2011, captures the opinions of 6 experts (4 US, 1 Italian, 1 German) who specialize in multiple myeloma. They provide insight into the practice-changing ramifications of the data presented at ASH 2010.

Drugs discussed in this report:

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Report Highlights

Standard of Care

- Multiple myeloma has been transformed into a chronic but still life threatening disease. Initial response rates to standard of care are very high. Revlimid, Velcade and dexamethasone gives a 100% response rate, with the very good partial response rate being 75%. From a commercial standpoint, this means that the population that can benefit from any one targeted therapeutic is going to be rather small, and limited to non-community settings. MM should be thought of as one indication for a new product, but frankly, all targeted therapies are going to be tried very far down the salvage tree, and certainly for the next decade, proteasome inhibitors and IMiDs will remain the backbone of myeloma therapy. Targeted therapies will be adjunctive, and introduction of pomalidomide in lenalidomide refractory patients is going to push newer targeted therapy to 4th line by default. If MM is the only indication, a targeted therapy is not going to be a profitable drug.

- Today, standard risk myeloma (low tumor mass, low disease activity after transplant) should get bortezomib-based induction and one transplant.

- High risk (patients who have not achieved a CR at 3-months post-transplant) should get Revlimid maintenance. If no CR on Revlimid alone, maintenance should be Revlimid + Velcade.

- All things being equal on efficacy and safety, American hematologists are in the peculiar position where they are compensated for administering drug infusions. So they choose parenteral products. Generally in Europe the fewer procedures performed, the less it costs the healthcare system, and physicians aren’t paid an administration fee, so orals are preferred over parenterals.

- The tertiary care hematologists have already switched high risk patients to aggressive PI or IMiD for as long as the patient can tolerate the regimen, because they know that these patients are not going to do well otherwise; and frankly, aren’t going to do well anyway.

Unmet Need / New Therapeutics
The key unmet need in multiple myeloma are therapies that increase survival in high risk patients. In the past ten years, survival in standard risk patients has doubled from 3-4 years, to 6 years for elderly and 8-10 years for younger patients. Over the course of the decade, there has been virtually no change in survival for the high risk patient.

Durability of response (PFS) in treatment naive MM patients has barely budged in the past decade. The increase even with newer therapies has been from a baseline of 30-36 months to today's 40 months. Ballpark, an increase of 15-18 months PFS on top of that will be impressive.

Proteasome inhibitor, IMiD, melphalan and dexamethasone will remain the backbone of MM treatment. All newer agents must obviate the need for chemotherapy and/or transplant or they are not going to be used.

The side effect profile of a regimen becomes more important in the community setting than it is in tertiary care. This drives the community hematologist’s preference for Velcade-Dex, Revlimid-Dex or thalidomide-Dex, as opposed to triplets.

**Risk Stratification**

Caris / Signal Genetics’ MyPRS is the first commercially available gene array that can risk stratify MM patients. As of TODAY, risk stratification can allay fear for standard risk patients, but cannot point to optimal therapeutic choice for high-risk patients. The hope is that once targeted therapy catches up with the diagnostic, it will make it easier for the community hematologist to choose appropriate therapy.

PET scanning can be diagnostic for risk stratification, but the biggest hurdle to universal adoption is that community physicians can’t interpret them as readily as they can a PET scan of a solid tumor.

**Transplant**

Transplant as 1st-line therapy for multiple myeloma is going to remain standard of care whenever possible. All of the drug regimens we discuss in this report have better results in the patients who underwent transplant than in the cohorts who did not.
Allogeneic transplant is best suited for medically fit patients under the age of 70. They can expect 2-3 years post-transplant where they will be free of myeloma therapy.

Autologous transplant upfront of an allogeneic transplant failed to demonstrate a survival advantage over the tandem Allo. There was a 20% mortality rate for the auto-allo transplant vs 10% mortality associated with the tandem allo transplant.

**Anticoagulation**

- The use of anticoagulation for the secondary prevention of thromboembolic events (strokes, deep vein thrombosis, pulmonary embolism etc.) is given to about 10% of cancer patients. Notably, 100% of patients who are on IMiDs and can tolerate anticoagulation receive either warfarin or low molecular weight heparin. Panelists have been slow to adopt new oral direct thrombin inhibitors (Pradaxa; dabigatran, Xarelto; rivaroxaban) because their manufacturers carefully avoided putting cancer patients on registration trials. With the approval of these drugs for SPAF (secondary prevention of atrial fibrillation), we expect to see more focus on the hem/onc setting.

- Defibrotide is a mild anticoagulant, currently not approved in the US, which is used for the treatment of vaso-occlusive disease. In trials it produces a 40% reduction in VOD.

**Skeletal Related Events**

- Xgeva (denosumab) was approved for the prevention of skeletal related events in breast and prostate cancer in 4Q2010. One German panelist shared that his group is able to get reimbursement for patients who failed (had an event) bisphosphonates, either pamidronate or zoledronic acid. Taking the reimbursement issue off the table, his perspective was that the sub-q was much easier to dose, and the acute toxicity is less with Xgeva. He perceives Xgeva as much more potent and less apt to cause osteonecrosis. So that is our “N = 1” for this report.

**Proteasome Inhibitors**
Velcade (bortezomib) remains the 1st-line induction therapy for transplant eligible patients. In countries that will pay more for drug therapy Revlimid is more often going to be co-administered in treatment naive patients. In others, Velcade (+ DEX) has a dominant hold on the new patient market. Velcade induction, with twice-weekly infusion, is likely to remain the key platform of 1st-line therapy for MM in older patients.

Physicians are likely to dose adjust to once-weekly Velcade in patients who don’t tolerate twice weekly. Bortezomib qw is associated with lower risk of severe neuropathy. The reason this hasn’t gained more traction is that while the less frequent dosing doesn’t show a significant drop in efficacy, there is a directional decrease. The effect on practice is going to be full dose (d 1,4,8 11) for the first 4 cycles, and then reduction to qw for patients where neuropathy is problematic.

Carfilzomib is not going to displace bortezomib as the 1st-line proteasome inhibitor in the first two years after launch. As experience evolves, its somewhat better efficacy, and clearly superior safety profile, will move it ahead. Clearly the degree of neuropathy associated with carfilzomib is lower than bortezomib, which justifies using carfilzomib in bortezomib-intolerant myeloma patients. However, there are too few CRs and PRs in patients on carfilzomib to impress our Panel enough to make carfilzomib their first choice PI right out of the gate. The overall response rate was 26% vs. 18% in Velcade refractory patients.

Carfilzomib is an irreversible protease inhibitor, differentiating it from bortezomib. It has a better safety profile both on neuropathy and platelets. Carfilzomib causes less peripheral neuropathy than tiw bortezomib, but it is not “zero”. One panelist estimated the neuropathy rate on carfilzomib to be 15%. Net, while all of our panelists expect carfilzomib to be better than bortezomib on this dimension, it is important to realize that there is an underlying level of peripheral neuropathy in MM patients, and thus regardless of how good carfilzomib is, it will not appear “perfect”. Regarding platelet release, carfilzomib appears to block that process to a lesser extent than does bortezomib.

The renal toxicity signal with carfilzomib is real. The drug causes a significant amount of Gr-2 reduction in creatinine clearance. Proteolix says this is due to “tumor lysis”, but more likely it is due to a metabolic effect on the kidney.

FDA will probably grant accelerated approval for carfilzomib as salvage therapy. The only real risk to this is because even though it produced an 18% response rate in bortezomib refractory MM, here was some disagreement amongst our panelists on the durability of these responses. One said the PFS was only about 4 months, when considering all comers. Another said 9 months if one speaks only of the patients who had an initial response to carfilzomib.
The overall tolerability profile will make carfilzomib a better choice for maintenance than bortezomib, but orally dosed lenalidomide will be a more convenient choice for the patient for maintenance.

**IMiD**

- Revlimid (+melphalan + prednisone) is the 1<sup>st</sup>-line therapy of choice for younger, transplant ineligible MM. Lenalidomide causes significant fatigue, hematotoxicity and increased thromboembolic risk, but is less associated with neuropathy than bortezomib.

- Lenalidomide 4-cycles also appears to be beneficial as induction in both younger and older transplant eligible patients. It will challenge bortezomib, but the stroke risk is problematic for LEN.

- Revlimid maintenance after melphalan/prednisone/Revlimid induction (a.k.a. MPRR) is superior to MPR induction alone. Maintenance therapy in the transplants, at 4-years, the PFS for MPRR = 70% vs. 35% for MPR. Until the Revlimid + Velcade maintenance data matures, MPRR is going to be standard of care maintenance in MM. The “consensus” is that maintenance should be used in high risk patients; i.e., those who did not achieve a CR at 3-months post transplant. The maintenance period is undetermined, but most patients will get tired of LEN maintenance before they progress.

- Secondary cancers called extramedullary plasmacytomas are probably real. These plasmacytomas behave differently than the original myeloma and are very difficult to treat, but the risk/benefit (double the PFS at 4-years) still strongly favors LEN use.

- We do not expect generic competition to Revlimid, even once the exclusivity on Revlimid lapses. The reason is because it will be too expensive for a generic manufacturer to field a monitoring program similar to RevAssist.

- Celgene will file Actimid for use in lenalidomide relapsed/refractory MM during 2H2011. The company is actively differentiating Actimid by positioning it as the go-to drug in Revlimid failures. They are not letting investigators run 1<sup>st</sup>-line studies with pomalidomide. With Actimid as the go-to drug for lenalidomide failures, it will be thalidomide that is pushed aside. FDA is probably going to require PFS data, meaning that response rate in the LEN rel/ref patient cohort is not going to suffice for approval of Actimid.
Pomalidomide is an iterative improvement over lenalidomide, increasing the CR rate by about 20%. It does seem to have a much better safety profile - less fatigue, hematotoxicity (and no increase in neuropathy) vs LEN.

Pomalidomide is going to be a direct threat to carfilzomib because of the high response rate being seen with Celgene’s drug in bortezomib failures.

Low-dose pomalidomide is marginally effective in the treatment for anemia associated with JAK2V617F-positive myelofibrosis. Best results reported at ASH 2010 were in the absence of marked splenomegaly.

**HDAC**

HDAC inhibition will add marginal synergism to doublet and triplet regimens based on foundational PIs and/or IMiDs. We do not see these as 1st-line agents. HDAC inhibitors should help to overcome resistance to proteasome inhibitors. Their target is the aggresome, putting a second hit on the proteasome pathway. In practice their efficacy is very synergistic with bortezomib, but because aggresomes are ubiquitous, each HDAC has dose limiting systemic toxicities. In addition, HDAC inhibitors also have an epigenetic mechanism, which compliments the activity of IMiDs.

Zolinza (vorinostat) will be filed 3Q2011 for use in combination with bortezomib based on the Ph-III Vantage 088 and Ph-IIb Vantage 095 trials. This will give Zolinza a two-year time to market advantage over panobinostat.

Vorinostat efficacy / tolerability appears to be better when combined with lenalidomide than bortezomib. This highlights that the epigenetic mechanism is independent from the aggresome inhibition. There is less consensus that the synergistic power is as good here, but the question is the efficacy AND safety of the combinations.

The gastrointestinal toxicity associated with vorinostat is a very significant hurdle to combining it with bortezomib. Some (not all) of our panelists felt that the GI toxicity was more difficult to manage than the platelet toxicity seen with rival panobinostat. Patients don’t phone up the physician when their platelets are low. They do when they have dyspepsia.

Ph-III trials for panobinostat in MM are just beginning. Pano is thus about two years behind vorinostat.
Panobinostat, in contrast to vorinostat, is probably a better partner with bortezomib based on efficacy. 70% response rates are being reported when added to bortezomib / DEX, vs 50% for bortezomib / DEX. But, bortezomib prevents the release of platelets, and panobinostat exacerbates thrombocytopenia by killing the megakaryocytes. This could be a deal-killer for panobinostat, and won’t be known until the Ph-III trial progresses for a couple more years. Panobinostat was not tolerated in Ph-I trials with lenalidomide, and that combination will not be pursued.

With the exception, perhaps, of the salvage setting, Celgene does not appear to have the desire to couple Istodax (romidepsin) with an IMiD for MM. They seem content to develop Istodax for lymphoma. The way salvage would work is that instead of encouraging the physician to abandon LEN altogether, and thus burn their pomalidomide option too early, adding Istodax to Revlimid might at least for a while re-establish control.

**CS-1**

LEN +/- elotuzumab in LEN naive pts produced extremely impressive responses. The RR = 60% for LEN alone, but 90% for the LEN + ELO combination. For perspective, usually one can expect a 15% increase from second agent, not a 50% increase. The mechanism of action appears to be both ADCC (antibody dependent cytotoxicity) + a second apoptotic signal. Now for the “other perspective” - this was only a 20-patient trial, so had 1-2 patients swung the other way, nobody would be getting excited about this result. Furthermore, elotuzumab has no single agent activity, and no activity when combined with bortezomib. Net, while interesting, and there are good mechanistic reasons why elotuzumab should synergize with IMiDs, elotuzumab has a long way to go before it is established as part of a 1st-line LEN regimen. The key endpoint will be reduction in transplants.

**CD38**

Daratumumab mediates MM cell killing via complement dependent cytotoxicity (CDC), antibody dependent cellular cytotoxicity (ADCC) and apoptosis. CD38 is commonly expressed in MM, making an anti-CD38 approach particularly attractive. However... the efficacy data with daratumumab thus far are quite immature.

**CD56**
Lorvotuzumab is an anti-CD56 drug conjugate that delivers its chemotherapy by targeting CD56 on the cell surface. A number of tumors, including MM, small-cell lung cancer, Merkel cell carcinoma, ovarian, carcinoid, and other neuroendocrine tumors express CD56. Roughly 50% of MM tumors overexpress CD56. In practice, an anti-CD56 may not be as effective as an anti-CD38 approach, but because CD56 is more limited to MM cells, this may have less off-target effects.

Anti-CD56 causes immunosuppression. In MM an active immune system is critical. Impairing the immune system’s ability to deal with MM may be counter-productive.

CD138

BT062 is a CD138-specific immunoconjugate comprised of the chimerized anti-CD138 MAb, nBT062, and the cytotoxic agent maytansinoid, DM4. It is expected to have the properties of a very safe chemotherapy. In terms of development timing, this MAb trails BMS/Facet’s elotuzumab.

FGFR3

Anti-FGFR3 is the only targeted therapy in clinical development for multiple myeloma. FGFR3 expression is closely associated with the t(4;14) translocation, and this mutation is closely associated with poor prognosis. The role for an FGFR inhibitor is going to be limited to a small subset of MM patients who both have overexpression, and who have not adequately responded to standard PI / IMiD based approaches. About 10% of MM patients overexpress FGFR3.

Dovitinib is an FGFR, PDGFR and VEGFR inhibitor in Ph-II trials in rel/ref MM. TKI258 demonstrated efficacy in murine xenograft models of MM with and without FGFR3 expression, suggesting that TKI258 may offer therapeutic benefit to multiple myeloma patients with or without t(4;14) translocation. Thus patients with and without this mutation are being included in this trial. The dosing regimen is 500mg/day, 5 days on 2 days off in 28 day cycles.

A Phase I clinical trial evaluating Anti-FGFR3 for t(4;14)-positive multiple myeloma is ongoing.
IL6

- IL6 inhibition (e.g., with CNTO-328) does not appear to have, at least in-vitro, the same “knock out” efficacy as does anti-CD38.

RAF / MEK

- RAF is known to be mutated in 10% of patients with high-risk myeloma. MEK, downstream in the RAF pathway, should be a good target. MEK inhibitors to date appear to have ocular toxicity as a class effect. Net, it remains to be seen if any will be viable for this indication.
Key Findings

Therapeutics

Proteasome Inhibitors

Velcade; bortezomib (Millennium)

- Velcade (bortezomib) remains the 1st-line induction therapy for transplant eligible patients. In countries that will pay more for drug therapy Revlimid is more often going to be co-administered in treatment naive patients. In others, Velcade (+ DEX) has a dominant hold on the new patient market.

“I do think the majority of people would favor using Velcade in newly diagnosed patients. I do think that many people are choosing to go with the combination of Velcade and Revlimid, certainly in the United States. Outside of the United States that is a very difficult economic proposition and I think Velcade is probably the favorite. I don’t know if the marketing backs it up or not but that is my sense. So Velcade I think has still got a dominant hold on the popular imagination for newly diagnosed patients. Then there is certainly a lot of Revlimid use as well, particularly in countries like the US where you can get both together”.

“I think actually it was a great meeting for the transplant aspect of myeloma. So 1a data about bortezomib being the best or being a good induction for transplant eligible patients seems to be solid”.

"I think actually it was a great meeting for the transplant aspect of myeloma. So 1a data about bortezomib being the best or being a good induction for transplant eligible patients seems to be solid".
Velcade induction, with twice-weekly infusion, is likely to remain the key platform of 1st-line therapy for MM in older patients. Physicians are likely to dose adjust to once-weekly Velcade in patients who don’t tolerate twice weekly.

“I think (carfilzomib) is going to get used up front and then eventually it will probably be used in the maintenance setting. So you are saying it is going to displace bortezomib up front? I would say, well actually, if you had asked me last year I would have said yes, but now with the idea that with changing bortezomib dosing you can get away from the neuropathy and still get the efficacy it might be a whole different story. So the critical thing there is do you believe that once weekly bortezomib...? I think it is. Its close; it is good enough for government work”.

“Is everybody going to move to bortezomib once weekly? No, I don’t think so. I think the bortezomib twice weekly will remain a key platform. I think bortezomib will remain the first choice proteasome inhibitor. I think the new boronate peptides coming through the pipeline are very interesting. I think carfilzomib will be approved and will be a widely used proteasome inhibitor, but I think it will be used in the context of bortezomib intolerance and/or bortezomib failure. I will be surprised if it knocks bortezomib off of its perch. At the end of the day myeloma patients who walk in the door who are sick as stink and need three drug therapy are typically metabolically ill. They will have renal failure and will have all these other issues. You want a drug that is going to work that you have a very clear understanding of the toxicity profile”.

Specifically, pairing bortezomib with either melphalan/prednisone (VMP) or thalidomide/prednisone (VTP) results in favorable response rates among older patients with multiple myeloma. The overall response rate was 80% for VMP therapy and 81% for VTP therapy; complete remission rates were 20% and 27%. Gr-3+ neutropenia was 39% in the VMP arm and 22% in the VTP arm. Grade 3+ cardiac toxicity was 0% in the VMP arm and 8% with VTP. Grade-3 to grade-4 peripheral neuropathy frequency was 5% in the VMP group and 9% in the VTP group.

“There was, I think, a remarkable study that basically contrasted and compared various induction approaches in the European context. I think
these are not necessarily combinations that would be first choice in the US. There are some important lessons to be learned from them. Maria-Victoria Mateos in a randomized prospective fashion I think pretty convincingly showed that a proteasome inhibitor with an alkylator as induction followed by an IMiD, if all you have is thalidomide, is the way to go in her randomized trial. So you had a randomized trial in older patients where she compared various regimens, showed that thalidomide plus Velcade plus steroid induction therapy in the elderly was very active but not particularly well tolerated. She showed that VMP was better tolerated”.

- Bortezomib qw is associated with lower risk of severe neuropathy. The reason this hasn’t gained more traction is that while the less frequent dosing doesn’t show a significant drop in efficacy, there is a directional decrease. The effect on practice is going to be full dose (d 1,4,8 11) for the first 4 cycles, and then reduction to qw for patients where neuropathy is problematic.

“Was there a dose modification with bortezomib? The plenary session had the Spanish study in regards to bortezomib/melphalan/prednisone vs. bortezomib/thalidomide/prednisone so MPT vs. MPV. I think there because the Spanish have shown that when you reduce your bortezomib to once a week you reduce your risk of severe neuropathy significantly. I think but that I don’t know how much traction is going to – I would have thought that when this was presented last year that I was going to start seeing almost everybody getting bortezomib once-a-week and I haven’t seen that happen. Is that because people are afraid of losing the response? Yes. But I have changed my practice. I think with this it was presented in the plenary session. It is getting a lot of press, so I think we are going to get more people getting maybe not initially at the first four cycles but then in the subsequent cycles people are going to reduce the bortezomib to once-a-week”.

“For a guy like you who is thinking in terms of going to the bortezomib once-a-week but in the back of your mind you have this concern about loss of efficacy. I personally don’t think so. I think that the efficacy is the same. Personally I think for induction it is probably going to be the same. And the only persons that you are going to do 1, 4, 8 and 11 are those who you want to get a rapid response on. I think for most people with high-risk disease everybody is going to get triple therapy which is going to be bortezomib, lenalidomide and dexamethasone. I think that is the way I think things are feeling”.
Velcade has gained traction as part of induction therapy in myeloma patients who have transplant.

“I think for myeloma the idea that bortezomib is important for induction therapy for myeloma is, again, at least a theme that is getting traction. It is getting traction because the randomized trials from both the French and the Italian was positive, they continue to be positive. Although lenalidomide and even with the RBD with lenalidomide, bortezomib, dexamethasone and transplant those results look good. I think this bortezomib is the appropriate induction for transplant is a theme that carries some weight”.

At an Onyx dinner meeting one of our Panelists was told that carfilzomib was going to be studied in CLL and lymphoma; whereas because of its neurotoxicity Velcade couldn’t be developed for these indications.

“I went to an Onyx dinner thing where they presented some brief data. I was impressed by the fact that, one, the responses were as good if not a little bit better if I remember correctly and much, much less toxicity. They are really going to mine it for other diseases than Velcade has done so far because of neurotoxicity”.

Velcade is not going to be part of a maintenance standard of care during the patent life of the drug.

“Now, would we recommend going Velcade plus Revlimid maintenance and I think that is the data that probably we may need to wait for it to mature a little bit and would somebody do a Velcade Revlimid vs. Revlimid maintenance to show what was better or not and that is going to take many years to be done and data available. But for now I think I see Revlimid as becoming standard of maintenance and Velcade may be considered. There is a Hovon study which has looked at Velcade maintenance also with some
positive results. But will the Velcade maintenance become standard of care, probably we will have to wait and see”.

carfilzomib (Proteolix / Onyx)

- Carfilzomib is not going to displace bortezomib as the 1st-line proteasome inhibitor in the first two years after launch. As experience evolves, its somewhat better efficacy, and clearly superior safety profile, will move it ahead. Clearly the degree of neuropathy associated with carfilzomib is lower than bortezomib, which justifies using carfilzomib in bortezomib-intolerant myeloma patients. However, there are too few CRs and PRs in patients on carfilzomib to impress our Panel enough to make carfilzomib their first choice PI right out of the gate. The overall response rate was 26% vs. 18% in Velcade refractory patients.

“The interesting question to me is will it knock bortezomib out of its primary position. I don’t see that yet. I think that remains to be seen. It will be used in the context of bortezomib intolerance and/or bortezomib failure”.

“When I looked at the carfilzomib CRs and PRs they didn’t knock my socks off. No, I think you are right. I think if you look at carfilzomib response in Velcade refractory patient and I could be off by percent or two but the numbers are so small it doesn’t matter too much. But I think it was an overall 18 percent response in Velcade refractory patient, truly refractory, and 26 percent in Velcade exposed patients. And there were 13% PR and 13% or so MR. So what it tells me is that the drug works. I think that is true that it works in refractory patients. Is it good enough that it needs to be still evaluated? I am no so sure yet about it. I agree, and you didn't make me bias. I agree with you”.

“Personally I just couldn’t see carfilzomib pushing ahead of bortezomib. I cannot imagine that. I agree with you. If you look at the side effects I have used and worked with the development of bortezomib and I am maybe a
little bit too attached to the drug but besides neuropathy, which can be controlled well with adjustment of the dose and adjustment of the timing, bortezomib is a really well-tolerated drug. In order to develop a better proteasome inhibitor or to replace Velcade that drug needs to be superior in efficacy."

“If we are talking about first line treatment, let’s say from a marketing point of view this is exactly the issue. The issue is if carfilzomib will prove to be superior in terms of efficacy towards bortezomib at this point the answer is yes. So you will see carfilzomib taking over bortezomib. If the efficacy will not be significantly different from bortezomib, at that point for cost reasons we will make carfilzomib still present on the market because anyway you would always try a different compound before saying there is nothing else to do. But generally speaking this will not substitute bortezomib. So carfilzomib will have a niche. I think generally speaking there is no question that carfilzomib will have a niche in the market. If it will be a big one at that point it needs to be a significant increase in efficacy over bortezomib”.

“I am wondering what the practicing physician will decide to do regarding the fact that they don’t have a head-to-head comparison of carfilzomib. This is in the up front setting: so carfilzomib vs. bortezomib up front. Carfilzomib is probably going to get approved as salvage therapy because it works for patients who have relapsing off bortezomib”.

“I think you are right that carfilzomib isn’t the answer. It is not going to knock bortezomib off its perch. The analogy is if bortezomib is thalidomide is carfilzomib Revlimid? I don’t think that is true. I think that they are very different. I think carfilzomib still will have a role”.

“I have got to tell you I think carfilzomib is going to get approved as an agent for bortezomib-intolerant patients. I think you are clearly seeing that it is well-tolerated in the sense that it doesn’t have the same degree of neuropathy that bortezomib does. The thing that is a little disconcerting is that there aren’t a bundle of CRs in there. There aren’t an overwhelming PR or better rate. There clearly is clinical benefit in some patients but it is not the sort of between your eyes observation that we saw for example with pomalidomide where pomalidomide is clearly working in lenalidomide failure and indeed in Velcade failure. The pomalidomide data are frankly to
my mind anyway much more impressive than carfilzomib. Having said that, I think carfilzomib is an important addition and it is a proof of concept that second generation proteasome inhibitors are a) approvable in my view, and b) they have a role”.

- The other initial use for carfilzomib will be in patients who achieved only a PR on bortezomib. The advantage to switching to carfilzomib is that physicians don’t want to abandon a class that has produced some positive result.

“Generally speaking my impression is that I do not see many physicians changing treatment because they did not reach a CR. If you reach a response rate you are happy of that and basically you keep going even though a PR rate is not the maximum expectation you might have. I do see much more room in a situation where an unmet medical need where you have progressive disease. Your patient is not going anywhere. You are trying to get some kind of response but you do not reach any kind of response. At that point you are willing to add another agent. I think these are the market niches certainly present for HDAC inhibitors, and to some extent at the same time are present for carfilzomib. Carfilzomib should have a better market niche from this point of view because generally speaking can be a substitute to the bortezomib. So from this point of view you might have the broader thinking of using a different regimen. Let’s say I have a second relapse of bortezomib, giving minimal response, I am not going anywhere, I might change to a carfilzomib combination”.

- As with bortezomib / REV / DEX, carfilzomib / REV / DEX in the upfront setting produces a 100% response rate, with encouraging very good PRs and better.

“The carfilzomib/Rev/dex combination in the upfront setting. That is again quite interesting and is more or less a copy from the V/R/D data seeing some 100% overall response. Encouraging depth of response regarding very good partial and better”.
Carfilzomib is an irreversible protease inhibitor, differentiating it from bortezomib. It has a better safety profile both on neuropathy and platelets. Carfilzomib causes less peripheral neuropathy than tiw bortezomib, but it is not “zero”. One panelist estimated the neuropathy rate on carfilzomib to be 15%. Net, while all of our panelists expect carfilzomib to be better than bortezomib on this dimension, it is important to realize that there is an underlying level of peripheral neuropathy in MM patients, and thus regardless of how good carfilzomib is, it will not appear “perfect”. Regarding platelet release, carfilzomib appears to block that process to a lesser extent than does bortezomib.

“It is an irreversible proteasome inhibitor and that makes it fundamentally different to bortezomib”.

“There are two major issues related to carfilzomib. One is the difference in the safety profile. So from this point of view the lack of peripheral neuropathy is the major safety difference with Velcade. Also, a better hematologic toxicity in comparison to bortezomib is a major safety difference from bortezomib”.

“One of my patients clearly had grade 3 neuropathy on the clinical trial and actually had to have a dose reduction”.

“I think it is about 15 percent”.

“I think carfilzomib data is nicely maturing. I am encouraged with the fact that the side effect profile seems to be really coming along better than what I would expect”.

“I believe that carfilzomib as a single agent or in combination with dexamethasone will be better tolerated than bortezomib. I think efficacy will
be at least as good as bortezomib. Is it going to combine with other drugs as
good as bortezomib, I think we need studies”.

- The overall safety profile suggests that hematologists will have more leeway to
increase the dose of carfilzomib than they do with bortezomib.

I think if you want a picture of the drug one issue is certainly much better
safety profile and the other issue is probably the opportunity to increase the
dose since we do have such a good safety profile. This could probably
increase also the efficacy of the carfilzomib. If you want to make a picture of
the situation the conclusion is there is proven better safety profile of this
drug. We might see in the future, but this is a question mark and it is data to
be validated, but it could also have some increase in efficacy because we
might have the opportunity to increase the dose that we have been seeing
until now.

- FDA will probably grant accelerated approval for carfilzomib as salvage therapy.
The only real risk to this is because even though it produced an 18% response rate
in bortezomib refractory MM, here was some disagreement amongst our panelists
on the durability of these responses. One said the PFS was only about 4 months,
when considering all comers. Another said 9 months if one speaks only of the
patients who had an initial response to carfilzomib.

“This is not actually a correct statement because, first of all, the PFS is around
eight months and four months is just taking in consideration patients who
didn’t have a significant response to the immediate stop of the drug. So
generally speaking to some extent I would probably question the opposite
issue in the sense that probably the PFS looks quite convincing. Eight
months seem to be a very good PFS data and the opportunity to use it for let’s
say a sort of maintenance approach would probably improve those data. I
wouldn’t be that concerned about this statement of four months due to early
discontinuation of the drug”.

“No, I want to drive back to carfilzomib a little bit because I feel I want to be
very fair to it because I think it is a good drug. I think carfilzomib what I liked
at the presentation that David Siegel gave was that it was very comprehensive. It was very full. I loved the fact that he got a response rate of 18 percent in the bortezomib refractory patients. That was really cool. I think that puts it in the ballpark to get accelerated approval. I want to be careful about one thing that I didn’t like though. I did not understand why the progression free survival was so short. That was disappointing to me. 

Yes. Do you mean in those patients who were already refractory to bortezomib? No, the whole study. If you were at the presentation that David Siegel gave the progression free survival was 3.7 months. That is not long and that is going to be a very tough sell to the agency. And help me understand what had those patients seen as prior therapy that might account for that very short progression free survival? They were all relapsed and refractory, although some of them were not classically relapsed and refractory. They were defined by an oddity of the protocol. My point is if your progression free survival is that short you have got to have very, very clean tight data around those patients to explain it because frankly if you have a progression free survival of five or six months with a response rate of about 25 percent and a response rate in the relapse refractory population of 18 percent then to my mind you are home and you have got it. The problem is that if you have got a response rate like that but it doesn’t appear very durable because the progression free survival is so short, you get my point. I think carfilzomib is going to be approved come what may. The only question I think there is, is whether it is from the randomized trial that is ongoing right now, which is carfilzomib, lenalidomide, and dexamethasone (CRd) versus lenalidomide and dexamethasone (Rd) or is it from accelerated approval this year by virtue of the strength of the phase II data? The phase II data to me I think are in play. I think they are real. I think they have a chance of being accelerated approval. Do I think it is a slam dunk? I don’t think so. I don’t think it is 100 percent actually. I am not sure I completely understand that short progression free survival. Was that carfilzomib monotherapy at that point? Yes it was. To be fair it was carfilzomib monotherapy plus low dose dexamethasone for the pre-med”.

- The overall tolerability profile will make carfilzomib a better choice for maintenance than bortezomib, but orally dosed lenalidomide will be a more convenient choice for the patient for maintenance.

“As maintenance is concerned carfilzomib is better tolerated than bortezomib. So it is a plus in terms of maintenance, both as an IV route of administration and this is a minus in comparison to lenalidomide or other IMiD compounds”.
LEN/DEX +/- carfilzomib is ongoing.

“The randomized trial that is ongoing right now, which is carfilzomib, lenalidomide, and dexamethasone (CRd) versus lenalidomide and dexamethasone (Rd)”

The renal toxicity signal with carfilzomib is real. The drug causes a significant amount of Gr-2 reduction in creatinine clearance. Proteolix says this is due to "tumor lysis", but more likely it is due to a metabolic effect on the kidney.

“I think that the challenges in the early phase trials were that I am not sure that they reached what I would define MTD in the very early phase I work that they did with Bob Orlowski. I think that the phase IIs then were somewhat challenged by the fact that they saw some complex toxicology signals early. This renal signal was real and they dealt with it very well. They hydrated, they administered dexamethasone. They called it tumor lysis. Frankly I find that a bit of a stretch. I think that the reality is that it has a metabolic effect at the level of the kidney. I think that it is an irreversible proteasome inhibitor and that makes it fundamentally different to bortezomib. But I think they have gotten around it and I think you can safety administer carfilzomib to most patients. But the renal signal is real and they would be foolish to underestimate that. What they presented in their data was grade 3 creatinines, low, low, low rates. But grade 2 creatinines, the upper limit of normal for a CTC grade 2 is 3 ½ the upper limit of normal which is 4 ½. So to downgrade 1/2s is something they need to be carful about because you don’t want to do that in myeloma because kidney disease is real. So you are trading off neuropathy for? Potentially for nephrotoxicity.

**CEP18770 (Cephalon) / MLN-9708 (Millennium)**

Both CEP-18770 and MLN-9708 actually may displace bortezomib (one day). They are both oral compound (a positive for patients, a negative for hematologists in the US who are paid to administer drugs) and specifically in the case of MLN-9708 has a
superior pharmacokinetic/pharmacodynamic profile than bortezomib, with much faster on and faster off. Therefore it might have a better therapeutic index.

“The Cephalon oral inhibitor could be equal. If it is equal I think it could push Velcade out because simply it is oral. And Millennium I guess had an oral as well. Yeah. I think that is going to be the next step. Whoever develops an oral drug, an oral inhibitor which is equal and not just in phase I/II, which shows really efficacy identical to single agent Velcade in randomized study, will win the race. I think Cephalon is doing right. I think they have a pretty good product and we will see how it goes. When we talk about oral then it will be a big difference compared to intravenous. However, we always have to think about oncologists and their practices. Depending on all development of the payments through the Medicare and things like that the question is what will happen with the oral drugs. Although the flipside of that is you have a lot of patients who are traveling long distances. That is true. You cannot use oral drug if oncologists don’t want to use it. Your point is well made. Yeah. I think it is both ways. How it stands at the present and looking at the thalidomide history of Revlimid I think oral drug which has no more side effects or equal side effects to Velcade and same efficacy at the present at this moment will beat Velcade”.

“I suspect that the other boronic-acid peptides are the ones to watch and the ones I mean in those regard I think Cephalon have an interesting compound”.

“I think at the same time Millennium have a new orally bioavailable boronate MLN9708 which I think you should keep your eye on because I think that is a very exciting new compound. Touch on that because all I really took from that when I saw it was that it was orally available. Yeah but it has got a much superior pharmacokinetics and pharmacodynamics profile to bortezomib, much faster, much faster on and faster off, therefore it might have a better therapeutic index and I am always struck by key thinkers in this area and their comments and particularly impressive man is Avram Hershko who you
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may know of. He is a Nobel laureate and basically Avram has always said to me “be careful of the irreversible proteasome inhibitors I am not convinced they are going to be the same as the boronate peptides because of this whole construct that you want something that reversible rather than irreversible.” He is much more excited chemically by 9708 than he is the other ones. I think that is very interesting particularly from someone as erudite and with insight as full as Avram”.

“I think it will be important. Again, all things considered, efficacy and lack of toxicity are going to be the gold standard. That being equal and I think oral regimen will be important. It will be convenient. Now convenience or lack of it will come down to frequency. With Velcade being given twice a week for two weeks is very inconvenient. If it becomes one-a-week it is less inconvenient. But if it is oral like Revlimid, currently one of the criteria used to select between Revlimid and Velcade ends up being the convenience that Velcade is oral, do it and come back in a month. So I think oral regimens would be attractive if available for proteasome inhibitors providing efficacy and toxicity are on the favorable side”.

**NPI-0052 (Nereus)**

- NPI-0052 is an irreversible proteasome inhibitor derived from Salinispora. As with other irreversible inhibitors, e.g. carfilzomib, NPI-0052 causes significant nephrotoxicity.

“The reason I can speak with authority about the nephrotoxicity is with the NPI-0052 (Nereus Pharmaceuticals) compound, which we are working with, is another irreversible proteasome inhibitor. It is in a different class. It is not an epoxy ketone. It is a salinispora. It is from Salinispora basically. It is a naturally derived product. It is clearly nephrotoxic. This is, I think, a feature of the irreversible proteasome inhibitors. I think they are nephrotoxic. The point is why wouldn’t you see something. You cannot irreversibly block a proteasome in a living system and expect it to be free ride”.
**IMiD**

*Revlimid; lenalidomide (Celgene) / Thalomid; thalidomide (Celgene)*

- Revlimid (+melphalan + prednisone) is the 1st-line therapy of choice for younger, transplant ineligible MM. Lenalidomide causes significant fatigue, hematotoxicity and increased thromboembolic risk, but is less associated with neuropathy than bortezomib.

“What we actually see when we are combining lenalidomide with dexamethasone and adriamycin, although not much, but we have seen patients with thromboembolic events. We started with using a continuous infusion of adriamycin. We have now switched to push infusion. Currently we are doing four times in 24 hours. So we see some thromboembolic events. None are really life threatening. Most are actually associated with indwelling catheters. But this is what we see. I think that is a specific adverse effect. So if we have the chance to figure out patients who are at high risk for VTE, they should preferably be excluded from the Revlimid/doxorubicin combination. On the other hand, we do not see any neuropathy. I think currently we do not get any very promising remission in myeloma without seeing specific adverse effects. But I think that they can be managed. In our hands thromboembolism associated with Rev is less severe than the neuropathy that we saw with bortezomib/cyclophosphamide/dexamethasone combination. So I think Revlimid has a place in first line therapy and is not fully understood whether we need additional drug in addition to DEX. But we think that remission quality with adding a third drug, a conventional chemotherapy, might be better than seeing Rev/DEX alone”.

“I think lenalidomide in combination with melphalan and prednisone could be and probably will be one of the standards of care in patients who are not candidates for transplant”.

“I still think the melphalan/prednisone/Velcade has an excellent profile toxicity wise and efficacy wise. But I cannot say that Revlimid responses will be or are inferior. I think Revlimid has an advantage in a sense that it has not produced neuropathy, but on the other side produces more hematotoxicity in
combination with melphalan, particularly in older patients who are mostly patients who are not candidates for transplant, could be harder to tolerate. And Revlimid/DEX I don’t think it is good enough as a first line unless there are really limiting factors for use of other combinations.

- Lenalidomide 4-cycles also appears to be beneficial as induction in both younger and older transplant eligible patients. It will challenge bortezomib, but the stroke risk is problematic for LEN.

“Interesting is the long-term follow up of the lenalidomide, the ECOG E4A03. David Siegel’s abstract where the people who even over 70, so 65-70 and less than 70 who got four cycles of Revlimid followed by transplant are doing very well”.

“Just to clarify, are these patients being prepared for transplant? Absolutely. But let's do this the other way around. So more or less an Allo study, but we have a risk stratification of doing it in very favorable vs. less favorable. So we do not want to transplant patients who will be doing very well even with tandem transplant. But all patients receive one unique high-dose melphalan (Alkeran) and then either Auto/Allo or second high-dose melphalan. Yes, all patients go to transplant”.

- Revlimid maintenance after melphalan/prednisone/Revlimid induction (a.k.a. MPRR) is superior to MPR induction alone. In the transplants, at 4-years, the PFS for MPRR = 70% vs. 35% for MPR. Until the Revlimid + Velcade maintenance data matures, MPRR is going to be standard of care maintenance in MM. The “consensus” is that maintenance should be used in high risk patients; i.e., those who did not achieve a CR at 3-months post transplant. The maintenance period is undetermined, but most patients will get tired of LEN maintenance before they progress.

“I do think what is happening is that many patients and physicians who see their patients not in a complete remission after three months post-transplant have opted to the idea that we should give you maintenance for a period of time. I don’t think it is going to be until progression. I think people are going
to get sick and tired of it. It will be interesting to see how this unfolds. I do get the feeling that different to what you are saying I get the feeling that maintenance is being adopted much more readily. Now remember, before it wasn’t hardly ever done. So maintenance lenalidomide definitely has much more acceptability than maintenance thalidomide, despite the fact that there were three randomized trials for maintenance thalidomide”.

“The second study I think which was of equal importance was the Palumbo study, which was the MP vs. MPR vs. MPRR where RR means MPR plus Revlimid maintenance. And there were a number of aspects of this study which I am sure we will discuss, but one part which is important from this first point I am making is that the MPR vs. MPRR the MPRR was better suggesting that if you give Revlimid maintenance on a long-term basis it provides a better outcome. I think both of these studies, the Mateos – the plenary study, and Palumbo study establishes maintenance as being a critical factor. Before you move along just clarify. MPR is melphalan, prednisone and Revlimid. And the MPRR is...? Melphalan, prednisone and Revlimid. Exactly the same as the other one, but then patients got Revlimid maintenance. And so that study was a study that shows that the first and the second that maintenance does provide benefit. And this study also the point ends up being that some sort of maintenance does. Now common between the two studies is that patients who got thalidomide in one study was Revlimid alone in another study did well making a point in my mind and I think in the general community is that Revlimid maintenance or some immunomodulatory maintenance is important. And so I don’t think anybody is going to use thalidomide maintenance unless the other drug is not available in the country. And so from that angle Revlimid maintenance also ends up being important. So that is the bottom line”.

“I think the main message I would say that came out of ASH, more in general than specifics, but either way was I would say about maintenance therapy. I think there were two major presentations both focused on maintenance therapy. They were critical sort of in some ways driving what we may be doing moving forward. So there were two studies. One was the actually a plenary presentation, which between you and I, I wasn’t sure why it was a plenary session. I was not one of the reviewers so I can comment. But it was. There was a study where they compare VTP vs. VMP and those two arms in general didn’t show significant differences with toxicity differences. The main importance of that study was that in the maintenance they give patients
Velcade with thalidomide vs. Velcade with dexamethasone. And what this showed was that patients who got Velcade with thalidomide did better than who got Velcade with dexamethasone. This was very infrequent maintenance. It was just once every three months, a cycle every three months. So very tolerable and doable regimen. And so whether this particular regimen is to be used moving forward or not is a different issue and we can discuss that. But what it established was that maintenance does have a role in this disease and these are the patients who were not transplanted. They were patients who got regular treatment. So post standard dose therapy, not standard therapy but standard dose therapy, maintenance has a role. That is what I think shows and establishes”.

“From my standpoint it doesn’t really change practice because I practice with maintenance. I think before we had enough data to proceed with maintenance. The question was always what kind of maintenance? First, maintenance treatment was actually established by a SWOG. It was almost 15 years ago, Jim Berenson’s study which showed that prednisone if you are able to give up to three years will improve survival. And then came a British study with interferon, which was not really, I think, an attractive study because nobody can go with long interferon. And then came thalidomide. There were definitely several European studies with maintenance with thalidomide with or without transplant and then Bart Barlogie did total therapy 2 and then total therapy 3, which showed that patients who received thalidomide maintenance actually live longer. The problem with the thalidomide maintenance is that when they relapse after that they live shorter than patients who did not get thalidomide. And that is the problem that I have with thalidomide. Maintenance with Velcade is also I think becoming very popular and in my practice I use it. Of course, maintenance with Velcade goes once a week which now is becoming more and more a way to give Velcade because of Palumbo’s study showing reduction in neuropathy. Maintenance with Revlimid I think will become a little bit more complicated because of its hematotoxicity. So I think maintenance with Revlimid needs to be figured out dose and schedule”.

“I think the myeloma theme came out pretty clear that a) maintenance is going to be important because then you have the non-transplant study, Palumbo’s study, where he did the Revlimid maintenance followed a non-
transplant and that the people getting Revlimid maintenance are doing better. I think that just tells you that even for the transplant and the non-transplant candidate prolonged therapy with Revlimid is going to be important. That I think is one big take home message that we are still trying to fit in. Particularly what to do with the patients who are being transplanted now? You wonder what are we going to do with all those patients who got transplanted and are one-year out of their transplant? Are they going to go back to their physicians and say I want to go on Revlimid? It is going to be interesting to see what happens”.

“I think for practical purposes, so the question is what did you hear at ASH that is going to change the practice over the next two years, although we didn't hear it at ASH I think Revlimid maintenance post-transplant is probably one”.

“I think the most important theme, which will have some impact on transplant, was the issue of post-transplant therapies from myeloma. That in itself is a whole theme. There are two large trials now for lenalidomide maintenance. One which was presented in a poster session CALGB 100-104, and Dr. McCarthy just presented the demographic. That the study the DSMB closed it because Revlimid showed a significant benefit in time to progression. So although it wasn’t presented at ASH officially it was presented demographically and I think it is important also because it is the first time the American Intergroup beats the French. The French presented the consolidation Revlimid at the meeting and that also showed that by giving consolidation Revlimid you could upgrade your response but the fact that maintenance Revlimid makes a difference, I think will change the patterns of practice enormously in the US. Up until now thalidomide had three randomized trials that had been presented all showing that there was a benefit in regards to progression free survival; some of them showing benefits for survival. Thalidomide is a lot harder to get than Revlimid. So now a lot of the practicing physicians will have to decide what do I do with my post transplant patients? Should I put them all on Revlimid? Should I watch them? I think that is a major change that has happened”.
Maintenance strategies that include an IMiD + proteasome inhibitor are interesting, but not robust enough at this point to be practice changing. The complete response rate increased from 23% up to 42% for both VT and VP maintenance therapy. The conclusion is that in the maintenance setting, bortezomib + IMiD is better than bortezomib + steroid. Lenalidomide + bortezomib appears to be a superb combination for maintenance; especially in the 70+ year old patient. This cohort did extremely well.

“But was very interesting was that she showed that bortezomib plus thalidomide as a maintenance strategy appeared to be the best combination going forward. She showed that in the maintenance setting Velcade and steroid alone was not as good as Velcade plus IMiD, thalidomide. So very interesting series of questions were answered by the trial. And very impressively she showed that maintenance really mattered. And as I saw that the jump for me, the question was okay that was done with thalidomide, and I am assuming because of when the trial started, but now you have lenalidomide available. You took the words out of my mouth because I was so sorry that our RVD presentation actually was unfortunately only poster-based because we would have complimented as an oral session at least what else is on the podium. The fact is that Revlimid plus Velcade is a superb combination and it is the obvious choice if you are not going to use MP (melphalan-prednisone). And what we showed in our study was a significant group of older patients, because you had a large, not a lot, but a significant number of patients over the age of 70, and they basically did extremely well. I think you are quite right that the observation is proteasome inhibitor plus the right IMiD may be an entirely different story. I think the message was very positive in regards that maintenance matters, choice of induction strategy matters with less toxicity being important, and staying on treatment of some form or another is very critical. The old sort of paradigm of an IMiD alone as maintenance seems to be being challenged head on by the fact that the combination of Velcade and IMiD appears to be superior”.

“I would not suggest that this study says that Velcade/thalidomide is THE maintenance regimen but it at least confirms the role of maintenance in this setting. But the Richardson data is much less mature. Correct. Do you extrapolate, and thus use Revlimid plus bortezomib in maintenance or do you wait for the trial? I would actually go and take another step before coming to that”.
“Now, would we recommend going Velcade plus Revlimid maintenance and I think that is the data that probably we may need to wait for it to mature a little bit and would somebody do a Velcade Revlimid vs. Revlimid maintenance to show what was better or not and that is going to take many years to be done and data available. But for now I think I see Revlimid as becoming standard of maintenance and Velcade may be considered”.

➢ We do not expect generic competition to Revlimid, even once the exclusivity on Revlimid lapses. The reason is because it will be too expensive for a generic manufacturer to field a monitoring program similar to RevAssist.

“So once lenalidomide is available as a generic, or will it ever be? I think it will be. So how is your hospital formulary going to manage specifically that issue? With the Revlimid it will be again a problem of who is going to do that with all the paperwork and the RevAssist program and things like that. I am not sure who is going to jump. I don’t know logistically how that will be resolved. So that could be an obstacle to the availability of Revlimid through other sources but Celgene”.

➢ Secondary cancers called extramedullary plasmacytomas are probably real. These plasmacytomas behave differently than the original myeloma and are very difficult to treat, but the risk/benefit (double the PFS at 4-years) still strongly favors LEN use.

“I heard of some concerns about these secondary cancers that were developed directionally higher in the lenalidomide patients. I am not surprised with that. I think people start talking about that now more. I don’t know last year when we talked about that if I mentioned concern. My concern is more relapses of myeloma with IMiDs. I have more concerns with the thalidomide than Revlimid because Revlimid was not used as thalidomide. But if you are in practice and you see those patients when they relapse especially after longer use of thalidomide they have significant number of what is called extramedullary plasmacytomas. Those plasmacytomas behave differently from original myeloma. They are very hard to treat. They behave like metastatic malignancies; very hard to treat and they are very deadly.”
Concern about secondary cancers I think is there probably more with Revlimid than thalidomide because of the very nature of ways of how Revlimid works and the potency of the drug itself.

“I think lenalidomide and the secondary cancer story is a bit of a storm in a tea cup to be perfectly honest with you. I think people are living longer so you are seeing these issues. You have got to be very careful about what I call ascertainment bias. What happens here is that if you are on lenalidomide on one of the trials you are followed very carefully for as long as it takes. If you are on the placebo arm and you progress if you are crossed over to lenalidomide, which a proportion of patients are but not all, you will continue to be followed but arguably not necessarily as carefully as the primary group. Certainly in the placebo arm if you come off and go and get salvage elsewhere with another/different cocktail all the study sites care about is whether or not you are alive or dead. The details of what then happens are a bit of catch-if catch-can. You may or may not know what happened to the patient. So you can see how an ascertainment bias could get in the mix. Irrespective of that, the numbers are very small, but there does seem to be something there. That something may in fact because that there is an underlying vulnerability to second cancers in myeloma patients period. And I agree with that. I think it is clear-cut and we know that. Two, is it possible that prolonged lenalidomide exposure over three or four years in a very, very small number of patients say in that risk population of less than 1 percent can develop some second B-cell process that is atypical? Well yeah maybe it is but if it is it ain’t going to change what I am going to do because lenalidomide has changed the therapeutic landscape. It is giving people 70 percent progression free survival at four years versus 35 percent. It is giving people survivals post-transplant that are unprecedented. So my overall assessment is storm in a teacup”.

“We didn’t see it with thalidomide. I think it says heads up and buyer beware. Obviously everybody is looking at this and we need to figure it out. At least it did not impact survival in the first two years”.

- Trials looking at combinations of lenalidomide with a variety of antibodies seem to suggest that LEN generates stronger signals than does bortezomib in similar
combination studies. The recommendation to companies developing MAbs for salvage therapy in MM is that they should be looking to combine with lenalidomide.

“Lenalidomide seems to be the ideal partner for the antibodies from everything I have seen so far. Velcade certainly is helpful, but Velcade alone doesn’t seem to generate quite as strong a signal as lenalidomide does”.

**Actimid; pomalidomide (Celgene)**

- Celgene will file Actimid for use in lenalidomide relapsed/refractory MM during 2H2011. The company is actively differentiating Actimid by positioning it as the go-to drug in Revlimid failures. They are not letting investigators run 1st-line studies with pomalidomide. With Actimid as the go-to drug for lenalidomide failures, it will be thalidomide that is pushed aside. FDA is probably going to require PFS data, meaning that response rate in the LEN rel/ref patient cohort is not going to suffice for approval of Actimid.

<table>
<thead>
<tr>
<th>Refractory to:</th>
<th>N</th>
<th>CR (%)</th>
<th>VGPR (%)</th>
<th>PR (%)</th>
<th>SD (%)</th>
<th>PD (%)</th>
<th>RR (%)</th>
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<td>10</td>
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<td>2(20%)</td>
<td>3(30%)</td>
<td>4(40%)</td>
<td>0</td>
<td>6(60%)</td>
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<tr>
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<td>1(5%)</td>
<td>7(35%)</td>
<td>9(45%)</td>
<td>3(15%)</td>
<td>8(40%)</td>
</tr>
<tr>
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<td>0</td>
<td>2(13%)</td>
<td>4(25%)</td>
<td>6(38%)</td>
<td>4(25%)</td>
<td>6(38%)</td>
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“That data remains strong. That space has not changed. It is not commercially available but they will probably look for an approval some time next year. I wonder if they can get it approved based on just responses on lenalidomide failures. I don’t think so. I think they are going to have to do a randomized trial, but we will see. Celgene does not want to position it in competition to lenalidomide. Right. So the idea that we are going to get pomalidomide up front studies at this moment in time is probably unlikely. Cannibalism. There is no reason for them to do that. Yeah. And it is what it is. The data that we have is the data that we will get”.
“I think pomalidomide in a lenalidomide world is huge because I think what you are going to see is that lenalidomide is used up front and in truth the pomalidomide will start to go right into lenalidomide failure where as thalidomide currently will sort of increasingly get pushed sideways. Pomalidomide is awesome. It is quite frankly in my experience the best of thalidomide and the best of Revlimid put into one to be perfectly honest with you. I am pretty sure you did this other presentation that really tickled me and that was the combination of thalidomide and Revlimid overcoming thalidomide resistance. To me I don’t get why you would do that. I would stick with pomalidomide. The bottom line is thalidomide is toxic and it is unpredictable. So combining Revlimid and thalidomide, I mean yeah sure if you are stuck and you can’t get pomalidomide I suppose you could do it. But you know what that is actually a neat little thought because if you can’t get pomalidomide that is what I might do if I was looking to overdrive resistance to either of the two alone and I was stuck. I would use low dose Revlimid and low dose thalidomide”.

“You know Celgene is trying to give a role to pomalidomide as basically third, so another agent in patients resistant to lenalidomide. This is the role of pomalidomide. Pomalidomide is a little bit more effective than lenalidomide. That has some other side effects like hematologic toxicity. But I think what will be very much the use of pomalidomide will be, again, in those kind of niche that we were talking about before for carfilzomib and HDAC inhibitor. This would be the perfect agent to use if you want something or in condition where lenalidomide is already completely resistant. Probably with time pomalidomide will move earlier on”.

“I think the first usage is going to be in patients who have relapsed after Revlimid and after Velcade. So it would be third line therapy. Whether they are refractory to Revlimid or not, I think we will have to wait and see how the studies will end up being done. But I am sure they would be the patients who are exposed to Revlimid. I don’t expect a study being done that compares directly to Revlimid. And in absence to that they will be Revlimid exposed patient. An easier study would be a nonrandomized study to take Revlimid refractory patient and show the drug works. But that is again many ifs and buts and FDA in the middle”.
“Pomalidomide is clearly working in lenalidomide failure and indeed in Velcade failure. The pomalidomide data are frankly to my mind anyway much more impressive than carfilzomib. *So the pomalidomide data, what is the mechanism? Why do you think it is working so much better than lenalidomide?* I think there are a couple of points to make. I think that if you look at it from a molecular point of view – it sort of just dawned on me as I was looking at the molecular structures – it is the best of thalidomide and the best Revlimid because it combines the carbonyl and amine in the phthaloyl ring. Everyone said “what about combining thalidomide and Revlimid? Wouldn’t that be an exciting trial?” The reality is the pomalidomide does exactly that as one agent. *Interesting.* I think that it is really interesting drug. I think it clearly works thalidomide failure. That was never a question. But the fact that it is working so consistently in Revlimid failure is really unexpected. I don’t think any of us expected to see that strength of signal. You mentioned carfilzomib as it being oversold. I think that is the challenge for carfilzomib. When you have got single agent response rates from pomalidomide of 35 to 40 percent in combination, I should say, even with dexamethasone in the face of true lenalidomide and true Velcade failure, that is an impressive signal. And it is extremely well tolerated too, which is the other message. I think pomalidomide is probably going to be the next FDA approved IMiD. I don’t think it is going to be too long. I think it could be within the next couple of years. Carfilzomib, I think will probably get an approval as well, probably in the same sort of time frame. But I think pomalidomide is moving very quickly forward.”

“I am wondering at the end of the day how are you going to really practice. So you have a patient who is relapsing from a CR with a minimal monoclonal peak. Your first choice is probably going to be Revlimid because it is oral and you may or may not give them dexamethasone. So now you have something that is going to make them respond 80 percent of the time. So you get another year out of it, a year-and-a-half, and they are relapsing again. And then you say are you going to add perifosine, are you going to add HuLuc? You are probably not. You are probably going to say let me give them Velcade. And then you are going to say, okay, I am going to give them Velcade. Do I give them Velcade single agent or do I give them Velcade with one of these new partners? That may be where it fits, particularly in patients with symptomatic relapses. *So by that point we are looking at basically a*
fourth line kind of therapy? Correct. So they will probably get some degree of response but a short period of time and there are going to be a lot more toxicities. And if pomalidomide becomes available then you can say guess who is going to be the default? It is going to be pomalidomide. A lot of it is going to be it depends how they market the drug and whether pomalidomide is on the market or not“.

Pomalidomide is an iterative improvement over lenalidomide, increasing the CR rate by about 20%. It does seem to have a much better safety profile - less fatigue, hematotoxicity (and no increase in neuropathy) vs LEN.

“Honestly speaking, I am not looking also at the data. Some people are saying, well, pomalidomide is completely different. In my opinion if you look at the efficacy lenalidomide stays at thalidomide as pomalidomide stays at lenalidomide. So every time you increase the efficacy a little bit with the novel agent but you are not really changing the world because you are not doubling the CR rate where basically increase of 15 to 20 percent, a response rate with the newer agent. So the efficacy is not changing the world. It is better, but it is not dramatically better and that is the perfect agent and I think Celgene will do everything possibly to position that agent in that respect. It is the perfect agent to use in lenalidomide resistant patient”.

“I am currently treating two patients with Pom/adromycine/dex and I can see that tolerability is really excellent. They do not have any of these adverse effects that are associated with Len. No neurotoxicity, no hematoxicity and no fatigue. So it is really outstanding how those patients are doing who are receive P/A/D. So I think there is no real medical reason for holding Pom for the majority of myeloma subjects. I think if we look into the upfront data that was presented it was really very interesting. And it should be continued to be further developed. But I think it will not happen as long as lenalidomide has any success in the earlier lines of treatment“.

“The pomalidomide data when I looked at responses in lenalidomide refractory patients, it seemed like there was 25 or perhaps 30 percent
response rate. Close to that. That seemed very good to me. It is good. I think it is good. I think pomalidomide data are not new actually. There was a paper recently published by Mayo Clinic on pomalidomide and I think that will be in a range of 20 to 25 percent in lenalidomide resistance. I think those are good data. I think it is very encouraging. I don’t think pomalidomide is a different mechanism. I think it is just a more potent drug. I think that honestly when you look at the side effects of pomalidomide, at least by what was published from Mayo, it doesn’t look like the side effects will be overwhelming compared to lenalidomide. So my feeling is that pomalidomide could actually start replacing Revlimid as mainstay treatment”.

“I would certainly think that if it was on the list to be picked I would put it as number one for me. I think its activity demonstrated by two studies presented, Gertz and Martha Lacy clearly suggests it is a very active drug number one. Number two, it has shown clear efficacy in real refractory setting in patients who are refractory to lenalidomide. 30% response in that setting. I personally had patients who were refractory to everything and got the drug and responded. So there is a clear signal about its activity and activity that is superior than Revlimid. And it’s tolerated quite well. It is the same toxicity that we see with Revlimid. A little bit more here and there, but I think it is very clearly effective drug. I think from those angles, both convenience of dosing – oral dosing and efficacy I think it has really good potential. I would think that is the number one new drug that I would watch for going forward and I really look forward to using it. Truthfully in current setting, and this is confidential what I am saying, but my personal bias about it is that I think we all are, and not just me personal, but my colleagues here too. We are clearly distressed that the drug is not available for the patients who are right now relapsing and dying. It looks so promising. I think it is a good drug. That would be my first pick”.

➢ Pomalidomide is going to be a direct threat to carfilzomib because of the high response rate being seen with Celgene’s drug in bortezomib failures.

“You mentioned carfilzomib as it being oversold. I think that is the challenge for carfilzomib. When you have got single agent response rates from pomalidomide of 35 to 40 percent in combination, I should say, even with
dexamethasone in the face of true lenalidomide and true Velcade failure, that is an impressive signal. And it is extremely well tolerated too, which is the other message. I think pomalidomide is probably going to be the next FDA approved IMiD. I don’t think it is going to be too long. I think it could be within the next couple of years. Carfilzomib, I think will probably get an approval as well, probably in the same sort of time frame. But I think pomalidomide is moving very quickly forward”.

- Low-dose pomalidomide is marginally effective in the treatment for anemia associated with JAK2V617F-positive myelofibrosis. Best results reported at ASH 2010 were in the absence of marked splenomegaly. Combined response rate using IWG-MRT criteria was 25% (95% CI, 16-34%) and ranged between 11% and 42% among the four treatment arms. Response appears to be predicted by early drug-induced basophilia. Pomalidomide also appears to improve thrombocytopenia in most subjects with baseline platelets <100 x 10e9/L but is not active in controlling disease-associated splenomegaly. Grade 3/4 adverse events (regardless of attribution) included anemia (10%), thrombocytopenia (9%), leukopenia (9%), fatigue (7%), dyspnea (5%), thrombosis (4%), diarrhea (4%) and hyperglycemia (4%).

“Pomalidomide is not yet commercially available. They have to do the study looking at pomalidomide for Revlimid failures. That is going to be their licensing trial. So pomalidomide is not going to be on the market probably for one or two years unless they get the myelofibrosis indication. If they get the myelofibrosis indication similar to what happen when Revlimid was approved for MDS but not for myeloma, I would say that many people won’t have access to pomalidomide unless they have myelofibrosis because it won’t be reimbursed”.
HDAC

- HDAC inhibition will add marginal synergism to doublet and triplet regimens based on foundational PIs and/or IMiDs. We do not see these as 1st-line agents. HDAC inhibitors should help to overcome resistance to proteasome inhibitors. Their target is the aggresome, putting a second hit on the proteasome pathway. In practice their efficacy is very synergistic with bortezomib, but because aggresomes are ubiquitous, each HDAC has dose limiting systemic toxicities. In addition, HDAC inhibitors also have an epigenetic mechanism, which compliments the activity of IMiDs.

“I don’t really understand why some of these companies are making these huge investments in drugs without doing some smaller phase II type of randomized pilot studies to figure out if it is real or not. So let me turn you to the HDAC inhibitors. Same story. Same story. I think of all the people you talk to my sense is that I am one of the least positive people about those. I again don’t see much evidence that they are active. I don’t see much evidence that they have single agent activity or even necessarily combination activities”.

“At least of course the HDAC inhibitors because that is what they target is the aggresome. And I think that is huge potentially. But I do think that toxicity matters because if you have got an escape pathway that the aggresome is being upregulated through by which normal tissues probably respond as well you have got to be careful about what you see in terms of side effects. What has impressed about the HDACs is that they are potent with bortezomib, very potent. My own clinical experience with them has been exactly that; great combination conceptually and practically, but the big issue is minimizing side effects”.

“It is the aggresome induction that makes sense to couple the HDAC inhibitors with a proteasome inhibitor? Exactly”.

“You touched on the fact that the mechanism by which the HDAC inhibitor is working is targeting this aggresome. To some extent, yes. Not completely
though because there is clearly an epigenetic mechanism as well. *So it is the epigenetic mechanism that makes sense to couple the HDAC inhibitors with lenalidomide? Yeah*.

- Monotherapy efficacy will be close to irrelevant to the choice of HDAC inhibitor. Rather the drivers will be combination efficacy, tolerability, dose form convenience, cost of drug and, at least in the US, how much the hematologist will make for prescribing.

“I personally think that we would hopefully have the choice because the reality is in myeloma patients you see both. What I would like to see is vorinostat approved and I would like to see panelists approved and I could pick my potion. Quite seriously because I think they are different. I like them both because I think they are different toxicologically. But they are very importantly quite, there is this code of passion that says cleaner drugs are better, but I am not entirely convinced about that. You need drugs that are multi-targeted. In myeloma our big success stories have been with multitargeted drugs; the cleaner the drug that less useful it is being. I think that I like both vorinostat and panobinostat. I think they are both important drugs. I think the fascinating point to me is that vorinostat may be a better partner with Revlimid and panobinostat, LBH, maybe a better partner with Velcade. That is kind of neat. That gives us a nice set of options to play with”.

*Zolinza; vorinostat (Merck)*

- Zolinza (vorinostat) will be filed 3Q2011 for use in combination with bortezomib based on the Ph-III Vantage 088 and Ph-IIb Vantage 095 trials. This will give Zolinza a two-year time to market advantage over panobinostat. Vantage 088: Phase III randomized double-blind study (N=742 planned accrual) of bortezomib plus vorinostat or placebo in MM patients aged ≥18 years with progressive disease after 1–3 prior treatment regimens. Patients who had previously received bortezomib must have achieved MR, PR, or complete response (CR; eg, not bortezomib-refractory). Vantage 095: Phase IIb international open-label study (N=142 planned accrual) of vorinostat plus bortezomib in RR MM patients aged ≥18 years who had received ≥2 prior treatment regimens. Patients must have been refractory to bortezomib and relapsed while taking, refractory to, intolerant of, or ineligible for other MM therapies including at least 1 IMiD (thalidomide or lenalidomide).
“As far as I know, vorinostat is almost going to the end of the phase III studies while the LBH is not at that stage. So vorinostat looks to be much early on the LBH”.

“They are banking on the vorinostat/bortezomib story. We haven’t seen the definitive results. My guess is that they are hedging their bets in case that they don’t get the signal they want, they still have something they can do with the drug because they have invested a significant amount of money on that drug. Now mechanistically I understand the use of the HDAC inhibitors to perhaps do a second hit on the aggresome... Yeah, it makes a huge amount of sense. We all agree that it is really a lot of sense but you know the road to hell is paved with things that made sense and didn’t make it. All right, that is fair. I think what is going to happen with vorinostat in combination with bortezomib will depend on the randomized trial and it is going to have to be a major difference for people to be able to accept the extra cost and the extra toxicity”.

“I don’t think any of them will be in monotherapy. Do they have a role in treatment of multiple myeloma? It all will depend how you combine them. I think they do. I think they could find some place but the question is which combination will they fit into. When I look at the combinations I see Velcade really as the main drug in most of the combinations that will be used in multiple myeloma. For some reason because of maybe different mode of action or different mechanism, it looks like it combines well with a lot of other drugs. So that is what the Merck study is? Right. And that is what the direction will be. The danger in that always is like everything else it is overexposure or overutilization of one drug. So we all were fooled by the initial experience of Velcade which combines really nicely with everything else? And are we now pushing drugs that naturally will not combine? Well, you have to do study and find out. So can you speak to any of the data that Merck spoke about in terms of VANTAGE? Are you impressed or not? I think it is too early. I guess the main program is in combination with bortezomib. But they also had at least one poster looking at vorinostat plus lenalidomide plus dexamethasone. Right. And vorinostat originally was planned to be combined with Velcade because of presumed alternative proteasome pathway which is called aggresome. So I think vorinostat was introduced as a possible drug that will block aggresome pathway and will allow so proteasome pathway will be blocked completely. The theory is that there was some escape from a proteasome blockage by bortezomib through this aggresome alternative pathway. I think but theoretically it makes sense”.
Vorinostat efficacy / tolerability appears to be better when combined with lenalidomide than bortezomib. This highlights that the epigenetic mechanism is independent from the aggresome inhibition. There is less consensus that the synergistic power is as good here, but as we’ve highlighted before, the question is the efficacy AND safety of the combinations.

“The vorinostat data was awesome. The best vorinostat data that I saw, I am a bit biased because we are involved in it, but is the lenalidomide/vorinostat data. It was gorgeous. And that points to the other mechanism which is the epigenetics. And essentially by epigenetic mechanisms at play you gene silence; and we have seen great results with lenalidomide plus vorinostat in myeloma. I was very pleased with that”.

“I am not sure that the combination with Revlimid makes scientific sense.

”Because it is not completely shutting down that proteasome pathway? Right. So I am not sure what will be biological based or explanation for that combination. So that is a shot in the dark? I think it is a shot in the dark”.

“One of the panelists before you made a comment about the HDAC combinations and he said to me that he thought that the combination of vorinostat looked better with lenalidomide than vorinostat plus bortezomib, and he said, but if you took panobinostat that looks better combined with bortezomib. So he was saying combine vorinostat with lenalidomide and panobinostat with bortezomib. Can you comment on that? Yeah, these are certainly the data presented at ASH. Generally speaking is true, but I didn’t make too much of this. These are small cohorts of patients when you start to see two different court of patients in one phase II studies ten percent PR than in the other it is very difference to say that A is superior to B. It is not randomized. It is a simple size. Relapsed patients have different disease features. So it is very difficult to say. Generally speaking it is true that lenalidomide seems to be more effective with vorinostat and bortezomib with LBH”.
The gastrointestinal toxicity associated with vorinostat is a very significant hurdle to combining it with bortezomib. Some (not all) of our panelists felt that the GI toxicity was more difficult to manage than the platelet toxicity seen with rival panobinostat. Patients don’t phone up the physician when their platelets are low. They do when they have dyspepsia.

"Vorinostat plus bortezomib is real. I think those trials will come through, but I think the toxicity is a big challenge”.

“I personally think the drug is pretty hard to tolerate. Because of the gastrointestinal issue with Vorinostat? Right”.

“Vorinostat has a lot of GI toxicity. Which, I think, is going to be the one that will make it extremely difficult. So is GI toxicity harder for you to manage as a physician? It will be much harder because it is a lot easier to monitor platelets than to start treating diarrhea. And the patient calls the physician a lot more because of diarrhea than because of platelet counts”.

(Takes the counter point of view): "If I have to make comment between the two drugs I would pay much more attention, honestly speaking, to the safety profile. And from this point of view vorinostat seems to be better than LBH. Because you would prefer to have the GI toxicity versus the thrombocytopenia? Yeah. But in our experience it seems more feasible the use of vorinostat. It seems sometimes a little bit troublesome, the use of LBH. I don’t have any general data. This is just personal experience of what we do in our clinic”.

The caution to Merck is that physicians are likely to keep going with bortezomib or lenalidomide if these drugs produced a PR. They are only likely to add the HDAC if patients are not responding to these foundation drugs.
“Generally speaking my impression is that I do not see many physicians changing treatment because they did not reach a CR. If you reach a response rate you are happy of that and basically you keep going even though a PR rate is not the maximum expectation you might have. I do see much more room in a situation where an unmet medical need where you have progressive disease. Your patient is not going anywhere. You are trying to get some kind of response but you do not reach any kind of response. At that point you are willing to add another agent. I think these are the market niches certainly present for HDAC inhibitors, and to some extent at the same time are present for carfilzomib”.

Merck / Celgene are co-sponsoring NCT01038388, a 35 pt Ph-I study evaluating vorinostat + lenalidomide + bortezomib + dexamethasone (RVD) in 1st-line multiple myeloma. This highlights the tension between companies on the one side, trying to find an ever increasing market for their drugs, and physicians/payers/patients on the other questioning the incremental value of the second, third or fourth component of the regimen.

“Fortunately or unfortunately, however you want to take it, a lot of this is going to be predicated on the notion of “where can I market this drug”? I think a lot of this from the practicing physician perspective is it going to be is it worth the extra cost and the extra toxicity. I have to say I think it is a little bit of the same thing that we are seeing with induction treatment that people who started double therapy, triple therapy and when they are getting to quadruple therapy they are getting to the point of diminishing return. So the addition of an alkylator to triple therapy adds toxicity and does not necessarily push you to increase cures. Now mind you, I think what we are going to see is a little bit – so on an individual note and I am starting to hear my colleagues say they feel the same – is the idea of recapturing control or recapturing response may start gathering some momentum in the myeloma space. What does that mean? So you are following a patient with myeloma and lenalidomide maintenance, for example, or on bortezomib maintenance and they have a mild increase in their paraprotein peak. So rather than saying oh you failed this treatment I am going to change classes of drug, you are going to add another drug that is going to be synergistic to the drug that is starting to develop resistance to the disease to try an capture control”.
panobinostat (Novartis)

- Ph-III trials for panobinostat in MM are just beginning. Pano is thus about two years behind vorinostat.

“So is LBH in phase III trials yet? I am not aware of this honestly speaking because I know if the phase II. If they are, they are really at the beginning of the phase III”.

- Panobinostat, in contrast to vorinostat, is probably a better partner with bortezomib based on efficacy. Many Panelists mentioned that panobinostat appears to, at least in-vitro, synergize better with bortezomib than do vorinostat or romidepsin. 70% response rates are being reported when added to bortezomib / DEX, vs 50% for bortezomib / DEX. But, bortezomib prevents the release of platelets, and panobinostat exacerbates thrombocytopenia by killing the megakaryocytes. This could be a deal-killer for panobinostat, and won’t be known until the Ph-III trial progresses for a couple more years. Panobinostat was not tolerated in Ph-I trials with lenalidomide, and that combination will not be pursued.

“I am a bit more encouraged by the recent panobinostat data. I don’t think vorinostat showed me anything that I would be excited about. But I have colleagues that swear blind it works in some of their patients. Panobinostat, the same thing; I am more encouraged recently that they had a 70 percent response rate at the MDV with Velcade is encouraging. But Velcade and dexamethasone alone is 50 percent and it is not that far off statistically. My guess is those drugs have a modest effect. We do see some activity of them in our mouse model which we think is quite predictive. My guess is they have some effect but it is not a dramatic one. The differences will be subtle and the side effects are not insignificant. I guess again I would be a little bit surprised if they end up being major drugs in myeloma. But you know I hope I am proved wrong”.

“I think panobinostat in contrast to vorinostat is probably a better partner with bortezomib overall in my experience. I think that panobinostat is more challenging to give with lenalidomide based on the phase I studies that have
been done to data. In fact, they won’t be pursued because there were too many side effects. My feeling is that you will see vorinostat as an idea partner with lenalidomide going forward and also with bortezomib but perhaps not to the extent that was perhaps originally envisaged. And panobinostat will be a partner of choice with bortezomib going forward as well. I think that is an important positive”.

“The mechanism of thrombocytopenia is very important. We have thrombocytopenia with bortezomib which clinically doesn’t really create much of a problem for us because it is not based on the cytotoxic or effect of bortezomib. It is just a problem with the release of thrombocytes or platelets formed from the megakaryocyte. However, if you have a drug which has a cytotoxic effects on megakaryocytes, then you have a problem because it will produce complications of bleeding and other complications from thrombocytopenia itself. So does panobinostat fit that latter category? I think all drugs from that group probably are more toward later than first one but the problem will be how can you combine that with the bortezomib if it produces thrombocytopenia and how to combine with Revlimid which also produces thrombocytopenia”.

“With myeloma most of the patients who come with myelomas, unless we start treating earlier, they don’t come in really good performance status. And a lot of them are older patients. So it is possible that we can use them earlier because of side effects but I don’t think that will be the deciding moment. Because if you have toxic drug in old patients with multiple myeloma if you use in first, second or third line it will be very hard to use it”.

“These three HDAC inhibitors seem to be in play at the meeting in relation to multiple myeloma. How do you distinguish between them? I think the most important will be side effects. I think effectiveness I am not sure there will be a significant difference. I know about studies for vorinostat for some time and honestly every time when I talk to people who are doing those studies they were all very concerned with the side effects of vorinostat. Right. So I am not sure. I don’t have enough information or enough data to talk about the other two but if anything comes which is less toxic and has significant activity in the sense of HDAC inhibition and blocking alternative proteasome
pathway or ubiquitin-proteasome pathway (UPP) I think that the drug could be a hit”.

“Other than that, I think of the newer targets and newer drugs that I think of: an HDAC inhibitor would be interesting. Which one will be more interesting? Again, only time will tell. I might have picked panobinostat without having very strong argument why. But I think it has very good in vitro efficacy that makes it an interesting agent going forward, but certainly it is a very important target. Can you speak to the in vitro efficacy? How do you distinguish it between the other HDACs? It is not as much as distinguishing because I don’t think we have clear… it is not as objective as being more subjective”.

“How do you differentiate between the three? I think it is going to be tolerability mainly. So if they all three send for approval together at the same time I think they will probably look very similar in my mind. There is less data from romidepsin for various reasons than the other two. But there were enough data in panobinostat looks very good and interesting. I think it would be very hard to write now pick one versus another in my mind as being superior. You just made a comment that there is something interesting about panobinostat. How does that stand out? The in vitro data looked very intriguing. So it is in vitro data where we see synergism. It is a little better studied drug in vitro, but vorinostat because it is approved clinically it has gone to clinical phase III study sooner than panobinostat. And in terms of synergy we are looking at how they work in concert with the proteasome inhibitors? Correct. With Velcade basically, yeah”.

“Why is panobinostat fast-tracked? I am wondering because the phase II data in combination with Velcade looked like the response rates were higher. But, it is going to be interesting to see what the definitive data looks like”.

“Why is panobinostat fast-tracked? I am wondering because the phase II data in combination with Velcade looked like the response rates were higher. But, it is going to be interesting to see what the definitive data looks like”.
“What did you think of the HDAC inhibitors? The HDACs are the other story I was going to share with you because I think the HDAC story is unfolding. I think that vorinostat is clearly doing more than we expected but I think at the same time what is really interesting is looking at agents like panobinostat because they may be quite different, but let’s see. Panobinostat may be better tolerated and may be easier to administer because it is a three times a week drug, but the panobinostat data are quite interesting”.

“You mentioned perifosine. I will be honest nobody has really expressed any great enthusiasm. I think the Novartis drug panobinostat will get more traction”.

“What is the role and is there a particular pharmacotherapy right now or particular drug that stands out as the best option you see coming through the clinic in terms of HDACs for myeloma? There are three of them as you know. One is vorinostat and the second one is panobinostat and romidepsin is a third one. I think the most advanced probably because it started first is the vorinostat study. It is already in phase III which is ongoing and there is also a phase II study. I don’t think any data is clearly available although all three have phase II data that looks quite exciting”.

**Istodax; romidepsin (Celgene / Gloucester)**

- With the exception, perhaps, of the salvage setting, Celgene does not appear to have the desire to couple Istodax (romidepsin) with an IMiD for MM. They seem content to develop Istodax for lymphoma. The way salvage would work is that instead of encouraging the physician to abandon LEN altogether, and thus burn their pomalidomide option too early, adding Istodax to Revlimid might at least for a while re-establish control.

“Let me stick with the Celgene theme for a moment. They have their own HDAC inhibitor now, with romidepsin, Istodax. Does it make sense for them to couple this with their IMiD? I think it does make sense. But, one, they don’t have all
the money in the world. Two, there is concern about how much bang you get for your buck. So romidepsin has a very good space in T-cell lymphomas probably. The studies you would need to do to say okay we will put romidepsin to make Revlimid a better drug, I don't know. The front line space in myeloma is so good now for them. It is either Revlimid/dexamethasone or VRD. They have the maintenance. You could think well maybe they want to do maintenance with romidepsin in people who have failed lenalidomide. I think they will still continue to explore it in the salvage setting. So I think investigators are going to probably look at trying to explore romidepsin in other combinations, but I don't think Celgene is going go for it”.

“So there you could think about so what do they want to do with romidepsin? So Celgene will say well rather than burn pomalidomide let’s do lenalidomide intensification. If that doesn’t work then let’s do lenalidomide plus romidepsin or lenalidomide plus Biaxin. You understand? And the physician will like that and the patients will like that because, one, at least a part of the treatment they know what price they are paying for it, the toxicity price. And for the drug companies the incentive is that they are going to be able to continue to sell the drug in the same space”.

(From last panel): Istodax (romidepsin) is really intriguing to our Panel because while vorinostat and panobinostat are closely related, romidepsin is structurally unrelated and inhibits different HDAC subgroups. Thus the Panel is eagerly awaiting results from Celgene’s Ph-II trial of bortezomib +/- romidepsin in myeloma (NCT00765102). Celgene’s acquisition of Gloucester is only tangentially based on the MM category (see AML/MDS) but there is preclinical data to show that romidepsin adds to the efficacy of lenalidomide in MM.

“This other new kid on the block, which everyone sort of really is keeping an eye on was romidepsin, the old depsipeptide, which you may know Celgene bought Gloucester. I think that in that context, they already got a lymphoma indication but I think to be honest with you romidepsin is quite an interesting drug and we are certainly interested in studying it in myeloma. Why should it be different than panobinostat? They are totally different constructs. Panobinostat and vorinostat are in the same class and romidepsin is completely different. So just in the way that you have very
different proteasome inhibitors and so on you are going to see different HDACs”.

“I guess you are assuming that this Gloucester purchasing has to do with Celgene’s strategy for myeloma. I actually think that it probably has more to do with the strategy for MDS... (But) preclinical data would say that it would be effective for MDS in a combination of a 5 azacitidine, or it would be effective in myeloma in combination with lenalidomide”.

(From last panel): Initial results coming from Australia suggest that romidepsin + bortezomib has a distinctly different toxicity profile vs. both panobinostat and vorinostat: less thrombocytopenia, less fatigue, and (according to one Panelist) a better cardiac profile. We believe that the QTc prolongation seen with romidepsin will turn out to be similar to that seen with vorinostat and panobinostat.

“I am not very well aware of romidepsin’s pitfalls or toxicity problems that could be major. I think all HDAC inhibitors as a group do have cardiac toxicity which is QTc prolongation. And actually the precursor of panobinostat had a problem and I think that didn't go further. Then panobinostat, which other name is LBH which is what I know it better as, has probably similar connection but less severe. And so I think romidepsin is similarly but I think myeloma studies need to be done on a little bit larger scale for us to know if there is anything more specific. Because number one, it will be given with Velcade and, number two, it will be given to myeloma patients; which are different than CTCL or other situations where it has been used. I think whether romidepsin has different toxicity profile in myeloma with Velcade and if it is different than other drugs we will have to wait and see. I am sure it has the same QT problem as others. And is the QTc prolongation notably worse for vorinostat than panobinostat or the other way around? I think one is being careful for both. I think from the available data in my mind I don't think I would say one is better or worse than the other in that regard. So panobinostat very close attention is being given so that it is captured if there is any problem quite well but it doesn't tell me that it is worse compared to the other. That is not how I read the data so far”.
“I don’t think it has been mined properly in myeloma so we are going to see. But essentially the initial trials with romidepsin plus Velcade in Australia are quite promising. Very different toxicities to panobinostat and vorinostat. Miles Prince’s group in Melbourne have really led the charge there and certainly the combination has been associated with the different toxicity: less thrombocytopenia, less fatigue, obviously being very focused on the cardiac issues”.

CS-1

**elotuzumab; HuLuc63 (Bristol-Myers Squibb / Abbott)**

- LEN +/- elotuzumab in LEN naive pts produced extremely impressive responses. The RR = 60% for LEN alone, but 90% for the LEN + ELO combination. For perspective, usually one can expect a 15% increase from second agent, not a 50% increase. The mechanism of action appears to be both ADCC (antibody dependent cytotoxicity) + a second apoptotic signal. Now for the “other perspective” - this was only a 20-patient trial, so had 1-2 patients swung the other way, nobody would be getting excited about this result. Furthermore, elotuzumab has no single agent activity, and no activity when combined with bortezomib. Net, while interesting, and there are good mechanistic reasons why elotuzumab should synergize with IMiDs, elotuzumab has a long way to go before it is established as part of a 1st-line LEN regimen. The key endpoint will be reduction in transplants.

“I think that the elotuzumab data are really interesting and I think they are real. I can speak directly to it because we are the lead enroller to the trial so a lot of my patients are on that study and they have all benefited. It is real. The thing that I would share with you is that they are all Revlimid naive so what you are seeing is a 60 percent response rate from Revlimid but the elotuzumab is adding to it pushing you into the nineties. I think it is not just the natural killer; it is not the ADCC because it is just too quick. I think there is more going on. I thought there was a nice poster by Andrzej Jakubowiak, which made that point. What he looked at was the safety and efficacy of elotuzumab in combination with bortezomib and he showed a very robust response rate that I think was favorable. Personally, my take on this is that it is without a doubt more than just an ADCC thing. I think ADCC is part of it,
but I honestly think there is a dual apoptotic signaling. There is some other mechanism by which elotuzumab is doing its damage. Patients with myeloma have low NK levels anyway. So if they have got low NK levels anyway, you do stimulate them obviously with the IMiD, that is a given. But to say it is just ADCC effect that is leading to this extraordinary synergy doesn’t make sense because the responses we are seeing are rapid. They are within the first two cycles. The other thing is candidly that we got dexamethasone with it. They get dexamethasone as well. Dexamethasone is hardly good for natural killer cells. It is a lympholytic agent. I think there is more than just the ADCC effect. In any event, however it is working and I think it is probably a mix of the two, the reality is that it is a very good addition. It is well-tolerated. We have defined a dose which is 10 mg per kilo. It is well-tolerated in the context of the appropriate infusional pre-medications. I firmly believe it is the first of a basketful of monoclonals that are coming through. They include this one, elotuzumab; I think it is going to be lead”.

“Elotuzumab targets a cell surface receptor that is way over expressed in myeloma in other tissues. CS1. CS1. And yet the single agent activity is dismal, I mean it is zero. So are you excited about that? Well, maybe. When you give it with Revlimid there is a very high response rate. They have 95 percent, but it is 20 patients and are we joining the BMS phase III trials? No, we are not. We don’t think the evidence is all that compelling right now that this is an active drug. Is that because it was such a small trial? Because on its own it doesn’t do anything and then the 95 percent response rate is in 20 patients. So one or two either way it becomes 60 percent and it doesn’t look very different from Revlimid alone. So I guess we weren’t convinced. I hope it does work, but I guess we weren’t convinced enough to throw our eggs in the basket yet. Although I must say with that one we were intrigued. I think that 95 percent is intriguing. I wouldn’t say we are not joining because we have no faith in the drug. So we are intrigued by it and we are looking forward to seeing the result but it is somewhat disconcerting. With Velcade it doesn’t do anything. On its own it doesn’t do anything. There are some theoretical reasons that Revlimid might work. It might upregulate cell surface receptors and things like that. So potentially they are synergistic. On its own it doesn’t look like it is all that active. Although the comment that other panelists made to me was that normally when you take lenalidomide – and my recollection is that these were lenalidomide-naïve patients – so normally if you give lenalidomide plus anything else as the doublet you may expect a 50 percent increase over the response you would have originally gotten from lenalidomide itself. The lenalidomide/dexamethasone randomized phase III trial in lenalidomide-naïve patients had a 65 to 68 percent response rate. So 20 patients, what is that, that is 14 out of 20,
something like that you would expect just with the drugs alone. And they are saying, hey we have got 18 out of 20 or 19 out of 20. It is a lot of faith to put in one or two patients swaying it. I guess I am being Scottish here and taking the negative viewpoint, which is that I have yet to see a drug with no single agent activity become suddenly a big success in patients. But we will see. I guess I am in the doubt that is going to work camp for that one. If I were BMS I wouldn't be investing in a phase III trial right now. I don't really understand why some of these companies are making these huge investments in drugs without doing some smaller phase II type of randomized pilot studies to figure out if it is real or not”.

“I think the fair comment is elotuzumab is very, very interesting. Elotuzumab single agent no activity or let's say very small activity. Elotuzumab with lenalidomide extraordinary good activity. Elotuzumab with bortezomib average activity. So here I think if you see the difference of response, elotuzumab plus lenalidomide is extraordinarily higher in comparison to elotuzumab plus bortezomib. And the old limitation we were seeing before different studies, relapsed patient, if this is characteristic, the difference is really extraordinary because when you move from 50 to 90 percent PR rate you are almost doubling. This is not the 10 or 15 percent difference in response rate you might see between vorinostat and LBH. So from this point of view with all the limitations of the phase II study the difference seems really, really quite important. There is a question mark. The question mark is to some extent you might have some bias by patient selection. These studies are not big. They are under 50 patients. So there could be major bias in that you might by chance to have a good prognosis patient. But if you do not have a major bias in those studies the signal is the same seems pretty important. I would be quite enthusiastic on the drug. If, again, you don’t have a bias around but done by the fact that in 40 patients you might have a selection of good prognosis patients or whatever. What is important to stress on elotuzumab is that when you see all the other agents you are playing games with different in 15 to 20 percent rate of response. Here you have a difference of almost 50 percent. This is something you usually do not see. Let’s put it this way”.

“What I don't like in studies like this is that from the beginning, from the phase I, you are combining the drug with something else. What I would like to see is, first, to find out if a single drug as an agent has any activity in myeloma. So the question is now are they trying to use this as a way for
delivering lenalidomide or something else into the plasma cells. Or they
think that this is a drug that combines well with lenalidomide? I never really
figured out what the idea was. If you want to combine with lenalidomide
then I think you owe to show activity of the single drug first and then try to
combine with others. So that is why I am a little bit uneasy with this
combination”.

“That I think of all the things that you are thinking about what new things
you felt, oh this is going to become – if you look at the data, remember these
are lenalidomide-naïve patients. So the big question is how much more does
elotuzumab add to lenalidomide? There is not a randomized trial of this.
They just did it in combination. Response rates were dramatic. I am thinking
obviously where they are going to position. I think they are going to have to
do a randomized trial plus or minus the monoclonal antibody to show that
there is an enhanced response rate and that there is an improvement in PFS.
What I don't know is whether they are going to explore at the same time the
front line setting”.

“I think what they want to do is try to bump out the transplant. I would say,
okay, let’s say the addition of this drug can obviate the need for a transplant.
Is that wishful thinking? I believe there will be people looking at that. I think
it is a valid question. Again, it is a question of how much are you willing to
pay for it”.

“I think what is really interesting to see is elotuzumab combination from the
Richardson data actually. While there is one important caveat, that prior
lenalidomide treated patients were excluded. So the data looks pretty much
okay. Overall response rate was some 80% and some 30% at least with some
partial response. They were not really heavily pretreated. Less than 50%
were bortezomib and around 50% thalidomide. But what is appealing
regarding this particular combination is that it is free of genotoxic drugs. So
we have a first combination of antibody plus IMiD plus dexamethasone. I
think that this is quite appealing. But the real efficacy cannot be determined
by this small study not including real subjects certainly who have not
received Len before. Around about 50% of either bortezomib or thalidomide
is nothing”.
The purported mechanism of action for elotuzumab, the enhancement of natural killer cells, is probably not the whole story. CS1 is expressed on NK cells, and treating with elotuzumab probably kills them. Thus, there is probably a signal transduction mechanism at play, more than an apoptotic or pan-cytotoxic mechanism.

“I have to tell you, I am not convinced, for example, with CS1 that the mechanism is what it is touted to be, which is the enhancement of natural killer cell effects. Actually CS1 is expressed on natural killer cells. So why would you see CS1 targeting antibody therapy working through that mechanism because presumably natural killer cells are going up in smoke. So I think to be candid with you it is probably much more to do with signal transduction than a dual apoptotic or a pancytotoxic effect on the tumor cells. I think that is probably much more like it. In any event, the monoclonal antibody story is strong”.

**CD38**

*daratumumab; HuMax-CD38 (GenMab)*

Daratumumab mediates MM cell killing via complement dependent cytotoxicity (CDC), antibody dependent cellular cytotoxicity (ADCC) and apoptosis. CD38 is commonly expressed in MM, making an anti-CD38 approach particularly attractive. However... the efficacy data with daratumumab thus far are quite immature.

“Plasma cells make CD56 and CD38 and CD138. I guess the question is whether a monoclonal antibody directed against those targets will be cytotoxic or not. I don’t think anybody has come along with an antibody yet and said here if we use our naked antibody, or even immunoconjugate antibody and we bind these cell surface receptors in a patient that myeloma goes away. That is the problem. A lot of those trials are very immature. They are just starting now: CD56, CD38, CD138; these are all cell surface antibodies that are good targets for that kind of therapy. It is just that
nobody has shown clinically that they are active yet. We have a trial right now we just opened with an anti-CD38 antibody because we think it is worth exploring. But whether these will activate VDCC or be directly cytotoxic or just do nothing we can’t tell”.

“I think the next one in the pipeline that is looking promising is CD38, Genmab compound. That is on my list. I think that is really interesting”.

“I think those make sense. I think if you want to target really then you target something that is specific or at least very present on plasma cells. How effective those monoclonal drugs will be is always a big question. But at least logically I think it makes sense. And maybe some of those, some will show to be effective, some maybe will show to be a new Rituxan or Zevalin or some of those combinations”.

“I am going to say too premature”.

“I think CD38 has a great appeal that is much more universal. I like Genmab. I think they are a good company. They are these Danish guys. They are good and they know what they are doing. They have done some good work in other areas and they are well organized in their discipline and they have got a very good study group on the Genmab program. It is all basically Nordic and European right now. We are going to get involved as it comes across the ocean but the fact is that what I have seen in the CD38 program has been encouraging”.

“We are now talking about a situation where basically there is, honestly speaking, no answer. Basically from your list of compounds, we do have very good preclinical data, very good theoretical mechanism of action, but no clinical data. Fair enough. As you know, preclinical data might become quite opposite in the clinic. So if you want to ask me do you think this is something that is going to move on my comment is that those drugs have, as you said, an
excellent mechanism of action and excellent preclinical data. I did not see at present any clinical data to make a judgment. It is not like elotuzumab where you have phase II studies with a 90 percent PR. I need to see something like that before say we might have something with a high chance to hit the market”.

- NCT00574288 is a Ph-I/II trial of HuMax-CD38 monotherapy in patients with multiple myeloma relapsed or refractory to at least 2 different cytoreductive therapies and without further established treatment options.

“Whether CD138 comes through remains to be seen. Possibly CD38 is another target as opposed to CD138. We will have to see. I think it depends on bystander effects and so forth. I think the antibody stories are emerging”.

**CD56**

**lorvotuzumab; IMGN901 (ImmunoGen)**

- Lorvotuzumab is an anti-CD56 drug conjugate that delivers its chemotherapy by targeting CD56 on the cell surface. A number of tumors, including MM, small-cell lung cancer, Merkel cell carcinoma, ovarian, carcinoid, and other neuroendocrine tumors express CD56. Roughly 50% of MM tumors overexpress CD56. In practice, an anti-CD56 may not be as effective as an anti-CD38 approach, but because CD56 is more limited to MM cells, this may have less off-target effects.

“I like more what Usher did with the lorvotuzumab when he used it as a monotherapy, the anti-CD56. It is a drug conjugate. That will give you an answer of yes or no. We have activity, we can do something with this drug or it is a completely useless drug. _Yeah, I really liked that_. This drug, at least what I like, and I think Usher and other guys were doing the right thing, is let’s find first activity as a monotherapy or in parallel we can combine with others and see if we have any activity. I think this is the right way to go”.
“CD56 we have looked at and we have been part of that study group and CD56 I still think we need to keep chasing because it is a marker of bad prognosis. I would be very happy to see the landscape open up to allow a CD56 targeting antibody in the mix. But I have to tell you that I am not sold that CD56 is going to be easier or better than CD38”.

“That one I think is of interest because of CD56 is a potential good target. The problem with CD38 as a target is that there are a lot of other cells that express it. So you can assume that the toxicity profile might be better for a CD56 targeted agent”.

“We have about some 50% of myelomas expressing CD56. And CD56 expression is correlated with an adverse prognosis. Some of our colleagues in our department of pathology here have done this work. I think this really something where a patients could be benefited by such an approach since they have an adverse prognosis. And it is a substantial number of patients who could get the beneficial effects. 50% is more if we get back to the FGFR3 story of 10%”.

- Anti-CD56 causes immunosuppression. In MM an active immune system is critical. Impairing the immune system’s ability to deal with MM may be counter-productive.

“I think the one thing here and the caveat with all of these is that they target the immune system and NK immunity may be important in myeloma. *So tell me more about that because that brings up things like MAGE.* I think none of the vaccines are yet ready for prime time. Although, I think eventually we will have some degree of exploration of vaccine therapy for myeloma probably as an adjuvant to stuff that we do. Now I think the same thing with the monoclonal antibody, most of us think that to be able to control the disease we are going to need to either reduce the tumor burden and stimulate the immune system whichever way we can come up with. The problem with drugs at the same time eliminate or impair the immune system’s ability to deal with the disease may actually end up being counterproductive. *Give me an example of a drug.* Like Campath, for example, not for CLL but Campath for ALL in the transplant setting. Campath for myeloma in the transplant setting despite the fact that myeloma cells are actually CD22 positive some of them it didn’t work. ATG has activity in vitro
for myeloma. ATG can kill myeloma cells. But again, unfortunately it did not work. This is just exploring the CD56 issue immediately. So here I would say the problem with the CD56 story in myeloma is it may not work because of the fact that that you may be eliminating the immune system”.

**CD138**

**BT-062 (Biotest / ImmunoGen)**

- BT062 is a CD138-specific immunoconjugate comprised of the chimerized anti-CD138 MAb, nBT062, and the cytotoxic agent maytansinoid, DM4. It is expected to have the properties of a very safe chemotherapy. In terms of development timing, this MAb trails BMS/Facet’s elotuzumab.

“I think those make sense. I think if you want to target really then you target something that is specific or at least very present on plasma cells. How effective those monoclonal drugs will be is always a big question. But at least logically I think it makes sense. And maybe some of those, some will show to be effective, some maybe will show to be a new Rituaxan or Zevalin or some of those combinations”.

“To me there was a very sexy molecule that came from a small German company called Biotest and they have the CD138. Right. And they hooked that with the maytansinoid. So I think of that like a rocket with a warhead on top of it. Yeah, I think that will be interesting. I have to look at that to see if I can get that drug to do clinical trials. Is something like that always going to be used in heavily pretreated refractory patients? Yeah, at the present time, in this moment I would say you have to look at the end of line. But if it shows activity it can move very fast. That is something that could change the landscape. I like the idea”.

“So there was another drug that stood out and this was simply based on a phase I trial. The company was called Biotest. I guess ImmunoGen is their partner and they had a CD138 which they hook up with the maytansinoid. That is interesting. It is interesting in that it is a novel target”.

“I think the elotuzumab data with Revlimid appears interesting. It is a very high response rate. Again, there is a lot more work to do to get somewhere but I think it appears more novel. I think we do need an antibody which ends up being a less toxic molecule. I think it would be something I would look for. The other antibodies too, I think CD138 and CD40 are both interesting. But I think CS1 has a little more data currently which is attractive”.

FGFR3

- Anti-FGFR3 is the only targeted therapy in clinical development for multiple myeloma. FGFR3 expression is closely associated with the t(4;14) translocation, and this mutation is closely associated with poor prognosis. The role for an FGFR inhibitor is going to be limited to a small subset of MM patients who both have overexpression, and who have not adequately responded to standard PI / IMiD based approaches. About 10% of MM patients overexpress FGFR3.

“It is about 10%. So we are doing some lab experiments in cell lines as well as patient derived samples. My perception is that we are currently facing a real breakthrough. I think that this may add to some 10% of all myeloma patients, maybe, but again I think that it is too early to conclude that this is a really important target”.

“The only one we are going to have a targeted therapy for is FGFR3 subset. Whether that will even work or not we don’t know yet. We have some trials open and addressing it now, but other than that we are still kind of shooting in the dark a little bit”.
“It is the only one where we know there is a kinase involved and there is a mutation involved in some patients; therefore, a kinase inhibitor or cell surface antibody-based therapy. There are two trials open, which I think are public and I don’t think it is a secret, they are open as well and known publicly. One is with Novartis small molecule tyrosine kinase inhibitor, dovitinib, and the other one is with Genentech’s monoclonal antibody. Those are the only truly targeted therapies. I mean you brought the example of EGFR and NSCLC. That kind of specificity, those are the only targeted therapies being employed. But whether they work or not is a completely open question because these are initiating genetic events that presumably at some point may be supplanted by subsequent change in the genome that makes them less important over time. So whether you can still turn that off and affect the tumor overall it is much more akin to the EGFR story. You are never going to respond to these drugs if you don’t have kinase over-amplification but even when you have it you may still not respond. That is what we will learn from these trials if there is any credence to the hypothesis if this is still a driver that will be switched off”.

“There were a couple of other of these FGF inhibitors. What is the relevance to multiple myeloma? Is it a worthwhile target? I think it could be a relevant target. I am not sure that it will be a major target. I think everybody is looking at different things and I think we are looking at too many targets. The question is how much you can combine anymore. I think it is reasonable to look into. At the present I don’t see it as major”.

“I think where Leif is absolutely right is that we need to be very careful when we are studying drugs like PI3 kinase inhibitors, MEK inhibitors, FGFR3 inhibitors and so forth that we don’t miss the signal in subpopulations of patients. But that is not quite the same thing as I think what he is saying. I think he is sort of saying we need to precisely identify in a particular patient the presence of a mutation and then generate a cocktail that goes specifically after it. It is very elegant scientifically; in the clinic very difficult to translate. I think we have seen FGFR3 experiences go forward which have been singularly disappointing. The Chiron compound of old is the one that I know
best and that actually came from Leif himself and from Suzanne Trudel and Keith and that study was a bust and we saw nothing. Now whether or not we are going to be able to enrich populations to such a degree in the relapse refractory setting, which is the classic sort of phase I environment, where we can discern a signal I don’t know”.

**dovitinib (Novartis)**

- Dovitinib is an FGFR, PDGFR and VEGFR inhibitor in Ph-II trials in rel/ref MM. TKI258 demonstrated efficacy in murine xenograft models of MM with and without FGFR3 expression, suggesting that TKI258 may offer therapeutic benefit to multiple myeloma patients with or without t(4;14) translocation. Thus patients with and without this mutation are being included in this trial. The dosing regimen is 500mg/day, 5 days on 2 days off in 28 day cycles.

**Anti-FGFR3 MAb (Genentech)**

- A Phase I clinical trial evaluating Anti-FGFR3 for t(4;14)-positive multiple myeloma is ongoing.

**HSP90**

- Our panel is uniformly negative on the potential for HSP90 inhibitors to be coupled with standard myeloma regimens. They are just too toxic.

    “Anything interesting on the HSP90 front? I never believed in that. I don’t see anything new. I just didn’t believe in the theory”.

    “I don’t think they work”. 
**Tanespimycin (Bristol-Myers Squibb)**

- The Ph-III program is currently on hold because the formulation isn’t optimized and there is clearly a signal that the drug is aggravating Velcade associated neuropathic toxicity. Panelists working with the drug believe the program is halted.

“I keep it simple. I mean Kosan, tanespimycin (KOS-953) which is BMS now – as far as I know because I haven’t been involved with the trials – but what I have seen and heard it sounds as if that has been halted. Other companies have them in trials but I haven’t heard anything publicly from anybody that suggests that they have good activity at this point”.

“I think the HSP90 story which you didn’t get a chance to speak on hopefully we will be seeing stuff rebooting there because at the meeting there was clearly a signal about how HSP90 inhibition can aggravate toxicity”.

“I don’t know if BMS is coming back with any other drugs from the Kosan group of HSP90s. But my sense is that they had very good activity and it has always just been trouble finding a way to safely dose them. Formulate them, yeah. I think that is the thing it is a good target. I think there is data that actually came out of our group, phase II data, that it works well. Again, it is going to be in combination in my mind, not as a single agent, and in combination with Velcade than anything else. The issue would be can it overcome Velcade resistance. Our phase II data shows that yes this combination given to patients who are Velcade refractory has potential to overcome the resistance mechanism and be effective. But I think the formulation and dosaging and those things I think are to some point slowing down the phase III study that I think will need to be done or will be done to answer it”.
**NVP-AUY922 (Novartis / Vernalis)**

- AUY922 is the first HSP90 inhibitor in development from Novartis partnership with Vernalis. The drug is in Ph-I trials for solid tumors and some hematologic cancers. Because of its potency AUY922 may be more tolerable than tanespimycin at therapeutic doses, but there isn’t enough clinical data do be definitive. AUY-922 is parenteral, and there is a pre-clinical candidate, further back in development that is oral.

  “The bottom line is that it is a good agent but I don’t think it is going forward for myeloma that I am aware of. We will have to wait and see where it would be and would it be in some other malignancy that it will be investigated. But as a general class if it is HSP90 inhibitor that is going to be tolerable, I think it will have activity in myeloma. Now whether the class will be pursued or not, I would not know yet”.

**AKT**

**Perifosine (Keryx / Aeterna Zentaris)**

- Keryx has begun a Ph-III registration trial of Velcade + dexamethasone +/- perifosine in relapsed/refractory multiple myeloma. The trial will enroll approximately 400 patients. The primary endpoint is progression-free survival and secondary endpoints include overall response rate, overall survival and safety. Our Panelists are expecting only marginal benefit. Our panel doesn’t think that perifosine is going to be successful, and they suggest that other AKT inhibitors (without specifying which) may be better.

  “Perifosine I have not been that impressed by, but there are other companies with other drugs that I think might show a little bit more promise. That is a space we certainly can do more clinical trials in and investigate”.  

“There are many phase III studies. So there are two other targets which I am not picking at the moment, although I might. One is HSP90, of course, and the second one being AKT inhibitor, perifosine. Both are actually on the fringe of starting a phase III study”.

“What was new in terms of perifosine? I don’t know. I hear about that drug for so long and I don’t see really any movement on the clinical side. I don’t believe in the drug. Fair enough. I didn’t either. I know people who are pushing it, but I just don’t see it”.

“It is quite interesting to see that the more targeted the approach is in myeloma the lesser is the single agent activity. So the success of the IMiDs and the proteasome inhibitors is because I think they are not really targeted. In contrast, they are targeting several cancer promoting pathways. That is a very consistent message with what many of your colleagues have said. I think that if we really would see that targeting one special pathway is worthwhile do this would be promising and would of course move the field forward and going more into depth to elucidate that there is some myelomas being AKT dependent or RAS/RAF dependent. But I think that translation from basic knowledge to real working drugs is still far ahead of us”.

“Now the PI3 kinase/AKT inhibitors, I think we are just beginning to learn a little bit about them now. I do think there is likely to be some evidence of activity there but we just don’t have enough clinical data yet to really know for sure”.
CD66b

**BW 250 / 183** (*°Y anti-CD66 radioimmunoconjugate; Southampton University Hospitals NHS Trust)

- Plasma cells express CD66. Southampton University Hospital has advanced into Ph-II trials an anti-CD66 radioimmunoconjugate consisting of the murine IgG1 monoclonal antibody BW250/183 labeled with yttrium Y 90. BW 250/183 binds to a 95 kD nonspecific cross-reacting antigen (CD66b or NCA-95) on granulocytes, selectively delivering a cytotoxic dose of Y 90 beta radiation to CD66b-expressing cells. CD66b, a member of the carcinoembryonic antigen family with an unknown function, appears early in the differentiation of granulopoietic cells and is expressed on the cell surface of almost all human granulocytes and their more mature precursors.

“Is targeting the bone with a conjugate going to be close enough or do I physically need to be targeting the cell surface on the bone marrow cells. Not necessarily. If we have some of those bone-seeking radiopharmaceuticals, so it is holmium or Samarium EDTMP, it is close enough actually and you get myeloablation. You actually need transplant to overcome myelotoxicity.

“What we have actually done, it was not really antibody coupled but it was bone-seeking radiopharmaceuticals. So it was a similar approach. I think bringing such meaningful drug into bone marrow compartment may be really helpful to overcoming drug resistance and to get myeloablation before an Allo or Auto transplant. So I think that these are quite interesting approaches and we should learn more about them. I am not sure whether this will be open to a majority of subjects. But I think that it is really worthwhile to go for this special approach. Hopefully we will be able to do some radio immunoconjugates regarding an anti-CD66 antibody with our colleagues from radiopharmaceutical department. So this would be a similar way to go for myeloablation in subjects who have seen a large number of pretreatments. So this is currently done as a myeloablative approach in
acute myeloid leukemia, AML. And there are some things that plasma cells may also express CD-66”.

**IGF-1**

(From last report): IGF-1 is the 2nd most important growth receptor in multiple myeloma. The main problem with IGF-1 inhibitors for MM is that nobody has developed one that can be used without excess toxicity, but this remains a very good target, either for combination or for monotherapy.

“We looked some time ago, actually a long time ago into IGF1 receptors and I think that was left. But I saw several papers recently and I think there was at least one poster that are looking at IGF1 receptors. Those are probably the second most important growth receptors in multiple myeloma cells. So I think people are going back to that and looking. It is not directly environment but it is a growth potential. I need you to touch more on that. The context is that there have been a number of companies that – I mean Pfizer has reported a lot of toxicity with their IGF1 inhibitor. That is true but I think that is the main problem with IGF1 compounds that it looks like nobody developed a compound that can be used without excess toxicity. But I think in multiple myeloma whoever comes with a possible tolerable compound to block IGF1 receptors, or at least IGF1 pathway, could come with a very, very good drug to combine with others or maybe even as a single agent. Have you seen anybody starting a clinical trial in myeloma yet? No. There was somebody, and I don’t remember who, but somebody started I think it was phase I and I started actually being interested in it and then it was stopped. I think it is toxicity. And I agree with you in terms of the potential efficacy. I just haven’t seen a single one of these drugs that avoids the class toxicity. Right. But I am sure there will be in the future”.

**IL6**
**CNTO-328 (Centocor)**

- IL6 inhibition (e.g., with CNTO-328) does not appear to have, at least in-vitro, the same “knock out” efficacy as does anti-CD38.

  “And there are others in the mix as well. IL-6, CNTO328 is also good. It is not quite the same thing. It is not quite the same sort of knock-out blow but it is the concept of an antibody working on the microenvironment”.

**RAF / MEK**

- RAF is known to be mutated in 10% of patients with high-risk myeloma. MEK, downstream in the RAF pathway, should be a good target. MEK inhibitors to date appear to have ocular toxicity as a class effect. Net, it remains to be seen if any will be viable for this indication.

  “We know the genetic subtypes that are high risk, of course, but we haven’t narrowed down to specific mutations or mechanisms that we understand well enough to be able to target yet. The whole genome sequencing has been disappointing in some ways because it hasn’t after some 40-odd myeloma genomes we know now, we still haven’t pinpointed a specific reproducible common mutation that we can go after with targeting. I mean they did find that the genome’s RAF was mutated in 10 percent of patients. So that is something that hasn’t been explored yet”.

  “In the genome sequencing 8 percent of patients have a RAF mutation”.

**Vaccines**
MAGE-A3 A15 (GlaxoSmithKline)

A MAGE vaccine by itself is not immunogenic enough to be a therapeutic for MM. MAGE is expressed in enough myeloma cells to make a MAGE-A3 vaccine, acting as a Trojan Horse, to deliver a warhead conjugated to it.

“*What do you think of MAGE? I think it is the first of many potential vaccines or proteins that will be explored in myeloma. As a vaccine it is not very good because it is not very immunogenic. I think it is expressed in enough myeloma cells that it will be relevant. So using it as a target, particularly if you can put it together with something that actually gets incorporated into the myeloma cells and kills it. So it can serve either as a Trojan horse or I think as a vaccine by itself it is not going to work. But I think it is going to open the door to other vaccines. If I stay with the Trojan horse concept then you are going to couple that with some maytansine or some other...? Perhaps, your anticancer of choice. And then if you are thinking about a better therapeutic vaccine what comes to mind? I can only tell you that there are other antigens that are being explored. I can’t go into details*.”

“To be honest I’m not really aware of any vaccination data in myeloma that has entered large scale clinical trials. I am only aware of the indolent lymphoma, but myeloma – no good idea about it”.

Habits & Practice

Standard of Care

Multiple myeloma has been transformed into a chronic but still life threatening disease. Initial response rates to standard of care are very high. Revlimid, Velcade and dexamethasone gives a 100% response rate, with the very good partial response rate being 75%. From a commercial standpoint, this means that the
population that can benefit from any one targeted therapeutic is going to be rather small, and limited to non-community settings. MM should be thought of as one indication for a new product, but frankly, all targeted therapies are going to be tried very far down the salvage tree, and certainly for the next decade, proteasome inhibitors and IMiDs will remain the backbone of myeloma therapy. Targeted therapies will be adjunctive, and introduction of pomalidomide in lenalidomide refractory patients is going to push newer targeted therapy to 4th line by default. If MM is the only indication, a targeted therapy is not going to be a profitable drug.

"Myeloma is a disease that cannot be cured still but can be really turned into chronic disease. I mentioned that, and it was almost five years ago in Whistler at the meeting and the Charlie Schiffer and some people criticized me because they said that I am dreaming. Now we are seeing that. So we are able with the different combinations to really prolong life of patients with the multiple myeloma. We are turning multiple myeloma into chronic disease. So our main goal is not anymore to increase response rate from 92 to 94 or do little tweaks of the numbers. I think our main goal now should be to keep patient’s quality of life at a good level. And I am concerned that long-term use of hematotoxic drugs can really start producing long-term complications. I think Revlimid maintenance will be interesting and I think we will use it. The question will be, again, how long, which dose, and what will be long-term side effects? When you look at the thalidomide, we use thalidomide as maintenance and I would use thalidomide without any limitations until I saw patients relapsing with very aggressive myelomas”.

“None of these targeted therapies, and again we can discuss quite a few things, but none of these targeted agents will be pushed in as a first line therapy for approval. I think they will have to come in down the line before they climb up. And that is what I think. The main reason is with the current agent, for example, I already did our study here at Farber and with our collaborators, Revlimid, Velcade and dexamethasone and it gives 100 percent response rate. And it gives 75 percent very good PR rate. So can I propose adding an antibody to it up front? Well there are studies being done on antibodies, or example HSP90 inhibitor or HDAC or something, theoretically yes. But practically it would be a very difficult study to improve upon 75 percent very good PR given that CR rate is still around 30 percent it is a much harder hurdle to cross and a longer study to do even it was justified from a toxicity point of view. One will have to be sure about toxicity with the three drugs to make it a four drug regimen. To give an example, RVD was combined with Cytoxan which is an approved drug and no big deal it still
needed a phase I study to see what dose of Cytoxan would be. After all was said and done the current results for CRVD is no better than RVD already. So I think for a new drug to be added up front I would say that is not going to be very easy”.

“I don’t know if we talked about this last year, but I mean I think this issue about getting drugs that are not very good by themselves and combining them with bortezomib to make bortezomib a better drug – the way I am practicing now is you give single agent bortezomib or single agent lenalidomide in the patient who is in the relapse setting. Then, if they are progressing on that you give them drugs that you know work together. You give them Revlimid and dexamethasone. I guess if you look at the paradigm of Velcade and Doxil, how much is it being used in the salvage setting? It is not a lot. And you have a randomized trial that says that Velcade and Doxil – and Doxil is an active agent, much more active than all the other ones we have. So what do people still do? They do Velcade and when it stops working they go either to Revlimid or they combine Revlimid and Velcade, the two active drugs, or they combine it with an alkylator. Particularly you can think about that Velcade is going to become generic”.

“This is another one that their strategy is going to be “we can make Velcade or Revlimid a better drug” but by itself it wasn’t a homerun. I think the one thing about this is it really is devoid of toxicity. Again, the interesting thing is going to be is whether the difference that they showed is going to be in the long run confirmed by a phase III randomized trial in which it will actually make a difference in survival, or even in progression free survival. And how they are pricing it is going to be another big issue. Particularly you can start thinking about now a myeloma who is going on Revlimid maintenance and is relapsing, think about how much money they have spent with their three years of Revlimid. And now they are going to go on these other drugs. I think in the next five years we are going to see a plethora of these combinations of Velcade/Revlimid with any agent that really by itself cannot stand alone. The one that is going to be successful are those that can show, look you know we really do get responses and these responses are durable and we can reduce toxicity to a minimum degree. I have to say that none of the ones that I have seen so far have impressed me”.

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“I think as always you have a highly intelligent observation in the sense that an interesting and provocative position from Leif. I think the truth of it is though that we are not CML and we know that, myeloma is a highly heterogeneous disease with marked variation in disease biology, not just between patients but within a patient. I think that is the critical point. So what you are looking at is what I consider backbone agents that provide you with a platform to provide the kind of multtargeted sort of cluster bomb effect that does the job of covering most of the bases. I think frankly the IMiD proteasome inhibitor partnership is vital. I think it is the cornerstone with glucocorticoids. Now alkylator and anthracyclines and so forth may compliment that, but we know from old the limitations of conventional chemotherapy. I think where Leif is absolutely right is that we need to be very careful when we are studying drugs like PI3 kinase inhibitors, MEK inhibitors, FGFR3 inhibitors and so forth that we don’t miss the signal in subpopulations of patients. But that is not quite the same thing as I think what he is saying. I think he is sort of saying we need to precisely identify in a particular patient the presence of a mutation and then generate a cocktail that goes specifically after it. It is very elegant scientifically; in the clinic very difficult to translate. I think we have seen FGFR3 experiences go forward which have been singularly disappointing. The Chiron compound of old is the one that I know best and that actually came from Leif himself and from Suzanne Trudel and Keith and that study was a bust and we saw nothing. Now whether or not we are going to be able to enrich populations to such a degree in the relapse refractory setting, which is the classic sort of phase I environment, where we can discern a signal I don’t know. I have a distinct feeling that a lot of these more targeted approaches are going to have to be tested much earlier in disease if we are ever going to be able to see a signal. Truthfully in a relapse refractory patients who has got highly aggressive and heavily pretreated disease to try and discern a signal for a small molecule inhibitor like that is very hard. I think that we are going to see various strategies going forward of combinations with small molecule inhibitors added to sort of fundamental platforms. But I am not sold that we are going to have a sort of Gleevec type approach with a very specific target pulled out and then be able to see dramatic responses. This disease doesn’t behave like that. It is not just variations between patients it is within the patient as well. That is what I am so struck by, which is frankly humbling to be honest with you. Say something more about this variation within the patient. In other words, take me through say a mutational analysis on one patient. What we realize and we know this from gene expression profile and disease in different settings is that it changes across the course of the natural history of the disease within a patient. We know that also from the way the disease behaves in a patient it is not linear. This is not like AML. It is not even like CML for that matter. It is a highly complex beast. Is there any mutational
an analysis that you would recommend or suggest to me where you can have similar, very durable responses if a patient is so lucky as to have that mutation? I think that could be seen. I mean that is possible. I just think it is not going to be a large number of populations in each case or not as many of patients in each case that is going to make it quite difficult. I think that as we go forward what we are going to see is a continued construct of a platform basis that goes forward and a combination strategy that is built in where I think what we can do is start to discern subsets of patients within study populations and just look for particularly responsive ones in that group. Whether or not we are going to restrict entry of trials or restrict patient’s entry into trials based upon them having the mutation or not is a slightly more difficult question because in reality that from a practical point of view is quite difficult to do. I think it is a great goal and I think we may get there in a few years. But I think we have got a little bit of a ways to go to be honest with you”.

“I guess the honest answer is I think what is happening with a lot of these compounds or products is that since a) they don’t work across the board, and b) they are going to be very expensive, c) a lot of companies are starting to see this paradigm, for example, of getting a biomarkers that is going to predict response to a drug is what many insurance companies and providers want. If you think about Avastin you give it to everybody and only so many people respond. That means you throw away most of the money you are using or the EGF receptor in regards to lung cancer. I still think these are interesting concepts. I don’t think these things are at the grasp of the primary oncologist or the primary hematologist. I am waiting to see this further. To me it is going to be at least for the next two to three years people who relapse with myeloma doctors are going to continue to do what they have done always and say what did you get before? You haven’t gotten this, so let me give you this. And I don’t see them saying let’s see if you have the 4,14. Partly because the drugs aren’t going to be available for the person in the community. So whether you have any of these gene products that may be abnormal in which there is a potential inhibitor, the one you talked about specifically, unless they show a large trial that this is going to be important to do and it makes a difference versus not having to think of just giving whatever comes in your mind, most practicing physicians won’t even worry about it, particularly because the test is not going to be cheap”.
“I am wondering at the end of the day how are you going to really practice. So you have a patient who is relapsing from a CR with a minimal monoclonal peak. Your first choice is probably going to be Revlimid because it is oral and you may or may not give them dexamethasone. So now you have something that is going to make them respond 80 percent of the time. So you get another year out of it, a year-and-a-half, and they are relapsing again. And then you say are you going to add perifosine, are you going to add HuLuc? You are probably not. You are probably going to say let me give them Velcade. And then you are going to say, okay, I am going to give them Velcade. Do I give them Velcade single agent or do I give them Velcade with one of these new partners? That may be where it fits, particularly in patients with symptomatic relapses. So by that point we are looking at basically a fourth line kind of therapy? Correct. So they will probably get some degree of response but a short period of time and there are going to be a lot more toxicities. And if pomalidomide becomes available then you can say guess who is going to be the default? It is going to be pomalidomide. A lot of it is going to be it depends how they market the drug and whether pomalidomide is on the market or not”.

➢ Today, standard risk myeloma (low tumor mass, low disease activity after transplant) should get bortezomib-based induction and one transplant.

➢ High risk (patients who have not achieved a CR at 3-months post-transplant) should get Revlimid maintenance. If no CR on Revlimid alone, maintenance should be Revlimid + Velcade.

“I am still trying to figure out where it stands. I actually see maintenance being adopted much more commonly than what I thought would have happened. That is despite the fact that I would say that most of us who are going out distributing the information that we have about maintenance have been extremely cautious about how that information gets distributed. For sure, I have not been a blind proponent of it. I know Phil McCarthy has not. And Celgene definitely has not. So I can’t tell you that there are all these people out there banging the drum of maintenance. I do think what is happening is that many patients and physicians who see their patients not in a complete remission after three months post-transplant have opted to the idea that we should give you maintenance for a period of time. I don’t think it is going to be until progression. I think people are going to get sick and tired
of it. It will be interesting to see how this unfolds. I do get the feeling that different to what you are saying I get the feeling that maintenance is being adopted much more readily. Now remember, before it wasn’t hardly ever done. So maintenance lenalidomide definitely has much more acceptability than maintenance lenalidomide despite the fact that there were three randomized trials for maintenance thalidomide”.

➢ All things being equal on efficacy and safety, American hematologists are in the peculiar position where they are compensated for administering drug infusions. So they choose parenteral products. Generally in Europe the fewer procedures performed, the less it costs the healthcare system, and physicians aren’t paid an administration fee, so orals are preferred over parenterals.

“I have many hematology friends here in the US in community practices. They say to me if the agents have about the same efficacy they are likely to choose a product that they can infuse because they are getting paid to do that and Medicare pays for that as well unlike oral medications where there is much more patient responsibility. Is that just an American thing? Yes. Absolutely, yes. What is the world like in Italy? No because here to some extent is completely the opposite. Here everything is public and I am talking about Europe generally speaking. There is no need to make X drug extra procedures to increase your income. Here the fewer procedures you do the less expensive it is on your public system and the more everybody is happy. So from the European point of view things are completely different. If you have something that is oral you can take the hospital care out and your patient is costing less. This is a major plus from an economical point of view for all of Europe. To this point, lenalidomide was immediately approved by NICE and bortezomib was not. Bortezomib was approved by NICE with the limitation of only paying for patients with responses. So this is a very peculiar situation of private practice where the more you do the more is your rank income, so you try to do as much as you can in order to increase your income”.

➢ The tertiary care hematologists have already switched high risk patients to aggressive PI or IMiD for as long as the patient can tolerate the regimen, because they know that these patients are not going to do well otherwise; and frankly, aren’t going to do well anyway.
“So until it can point you to a treatment... For us it (genomic screening) changed our treatment. We go, you know what, you are high risk we can’t do hit-and run-therapy. We can’t treat you for four months and then give you a transplant and then stop because there is no way in heck that you are going to live a long time if that is all we do. You are going to have to go on Velcade and Revlimid and we are going to have to keep you on as long as we possibly can if we have any chance of overcoming this. But I don’t know that the community is thinking those ways still at this time”.

Unmet Need / New Therapeutics

➢ The key unmet need in multiple myeloma are therapies that increase survival in high risk patients. In the past ten years, survival in standard risk patients has doubled from 3-4 years, to 6 years for elderly and 8-10 years for younger patients. Over the course of the decade, there has been virtually no change in survival for the high risk patient.

“I suspect we have doubled survival for all standard risk groups. I think ten years ago in 2002 if you were elderly I think you had a three to four year survival and if you were younger you had a five to six year survival. I think certainly for the lower risk groups we are probably double that for both groups. It is probably six years for elderly and ten years for younger. In the high risk myeloma I don’t think we have made a lot of impact frankly one way or the other”.

“The high risk are clearly genomically unstable. They clearly relapse quickly after any therapy, even the most aggressive therapy out there - TT3 they still do badly. If you are a nihilist you would say treat them with something fairly minimalist because nothing works and you are going to put them through a lot for no reason. So those are the problems we have”.

➢ Durability of response (PFS) in treatment naive MM patients has barely budged in the past decade. The increase even with newer therapies has been from a baseline
of 30-36 months to today's 40 months. Ballpark, an increase of 15-18 months PFS on top of that will be impressive.

“We are currently facing very high response rates, but nonetheless we have not seen any breakthroughs. So if you go back a decade, when we did not have any of the novel agents, not at all in first line, we had some between 30-36 months PFS in the first line setting. We now employ one or two novel agents and we come up to 40 months or so. I think it is not really the question of depth of response, but how are we able to prolong events. So relapse, deaths from myeloma, development of extramedullary lesions and so on. So I think depth of response is okay and is amazing to see how the figures rise, but we don’t have a translation into significant longer treatment-free intervals”.

“I think if we have prospective data indicating an extension of lets say 15 or 18 months this would be impressive. So patients would be benefited in the terms that they enjoy longer PFS and would not need ongoing treatment, be it consolidation or maintenance. So it is quality of life and being out of hospital. So lets say 15-18 months up would be excellent”.

➢ Proteasome inhibitor, IMiD, melphalan and dexamethasone will remain the backbone of MM treatment. All newer agents must obviate the need for chemotherapy and/or transplant or they are not going to be used.

“These new monoclonal antibodies I think are possible additional drugs in combination, unless we see single drug that has at least activity as bortezomib did as a single agent. I think they could be potentially useful tool, useful addition to standard treatment. And maybe some of them will help in the sense that they will remove a need for chemotherapy. I see a role for this new monoclonal treatment in this way to really work as adjunct to present treatment and removing a need for chemotherapy or transplant”.

➢ The side effect profile of a regimen becomes more important in the community setting than it is in tertiary care. This drives the community hematologist’s
preference for Velcade-Dex, Revlimid-Dex or thalidomide-Dex, as opposed to triplets.

“It is also very true for the general market that more simple and stupid the more its welcome, especially in the community hospital setting for both Europe and in the US. In other words, when you are in a highly specialized center with many myeloma patients and there is a lot of expertise side effects are not a problem. When you start to go into the smaller community type facilities with fewer melanoma patients safety becomes a much more important concern than efficacy. In that respect a drug with a better safety profile even with a little bit less of efficacy will be certainly chosen. Which side effect is more concerning to you; an impact on platelets or an impact on neuropathy or an impact on gastrointestinal side effects? You see if you reason from point of view of let’s say a general oncologist’s major concern is on the acute side effect, so thrombocytopenia and GI, things that may create a major issue on Friday, Saturday and Sunday. Peripheral neuropathy to that respect is less important because you can always postpone until Monday. From my personally experience I do see this, but it is a psychological issue. You would prefer to have something that is not creating too much trouble. As a general oncologist that faces a hundred different diseases it is not easy. So you do prefer something that is not creating trouble. From this respect VD, RD, TD are popular and it is basically for those safety considerations”.

Risk Stratification

Myeloma Prognostic Risk Signature (MyPRS) (Signal Genetics / Caris)

- Signal Genetics’ MyPRS is the first commercially available gene array that can risk stratify MM patients. As of TODAY, risk stratification can allay fear for standard risk patients, but cannot point to optimal therapeutic choice for high-risk patients. The hope is that once targeted therapy catches up with the diagnostic, it will make it easier for the community hematologist to choose appropriate therapy.
“I think what has changed in the last ten years is we are much better able to predict the high and the low risk groups and, again, to segregate them into different patient populations and clearly the low risk group do well. I mean you see those folks and you feel pretty comfortable telling them, listen that don’t fret, but what kind of therapy you are going to get you are probably going to live a long time no matter what we do. With the high risk people you secretly worry without telling the patient that this isn’t going to be good no matter what you do. I think that is where we are today. **What is the value of having this prognostic risk signature?** I think the main value is prognostic at this point. The main value is you are going to know through that test more than any other that we offer whether your patient is high or truly low risk and will therefore be more reassuring for those who are low risk. I think in academia it would change thinking about how to manage the disease. I don’t think the community is really mature enough now that they would take that information and necessarily change what they do based on it, but it is probably the single most effective test at telling whether your patient is high or low risk at the outset. I personally am supportive the test because I think it is good for the patient and the physician to know going forward whether they are high or low risk. But, I am sure there will be many folks you speak to that say we don’t see the value there yet in terms of whether we will change our treatment or not”.

“Signal Genetics producing the gene expression profiling as a commercial assay to risk stratify myeloma into high risk and standard risk now for the first time there will be, let’s say for the regular physician, the ability to risk stratify patients. Whether it will make a difference or not on what they do is another story. I think it is a watershed moment that there is that ability. **So if you were going to advise the community hematologist on actions to take based on these risk stratifications and choices of first line therapy, second line therapy, etc, what is your take on...?** I think for sure standard risk myeloma should get bortezomib-based induction and one transplant. Then if they are in complete remission the question of do they need maintenance is very appropriate. I would say this would provide strong argument that a patient with standard risk myeloma, low tumor mass, who had low level disease after transplant or had a CR after transplant, should probably be left alone and not be placed on maintenance. The converse to that is people with high tumor mass or high risk gene expression profiling (GEP) signature. They
should probably be placed on maintenance post-transplant. *With Revlimid?*  
If they are not in CR Revlimid alone may not be enough and that they might be a combination maintenance with Revlimid and bortezomib. I think that to me was the practical aspect to that”.

**PET Scan**

- PET scanning can be diagnostic for risk stratification, but the biggest hurdle to universal adoption is that community physicians can't interpret them as readily as they can a PET scan of a solid tumor.

“I don’t know where it stands, but I think the other thing that came out was the issue of PET scanning. So whether or not PET scans should be considered standard. *Comment on that because others have as well.* I think what came out is that PET scans could be effective because the trial that the Spaniards showed that it seemed to be helpful. I think what also came out loud and clear is that there is no standardization about the way PET scans are performed or read in North America. That in itself is probably the biggest barrier for universal use of PET scanning. It is still not considered standard. It is still not universally reimbursed. I think eventually it will be but the way I am looking at it is that probably somebody on the national level will have to create a task force to develop a guideline of how PET scans should be done and read in myeloma. And then after having done that they will have to look and see how it works. The Medicare Demonstration Project, I can’t say I have seen the definitive results, but I don’t think it was dramatically positive. And what happens, at least when I speak with community physicians, is many of them will tell you this really wasn’t really very helpful for me. It probably has more to do with the fact that the community radiologist doesn’t know how to read PET scans in myeloma patients because they read them like in regular solid tumors and there is a difference. *Very good.* Whether PET scanning for myeloma will be able to go out into the community I think is still a question.

**Transplant**
Transplant as 1st-line therapy for multiple myeloma is going to remain standard of care whenever possible. All of the drug regimens we discuss in this report have better results in the patients who underwent transplant than in the cohorts who did not.

“I think the next question that comes up, again to the myeloma theme, is the issue of transplant versus no transplant as up front therapy. Although a lot was said about all these new drugs I think the realization is that although the response rate is high it is not as high as when you do it with transplant. The French and the Italian presented their novel therapy induction, either one or two transplants followed by some form of maintenance and those results are dramatically good. You are talking about progression free survivals of 80 percent at three years or at four years. You don’t get that when you don’t do the transplant component. So my feeling is that at least for the next foreseeable future, three to five years, transplant will be still part of front line therapy for many patients and for those who opt not to get transplanted up front they will do it as part of a salvage. I think that theme is pretty much established”.

Allogeneic transplant is best suited for medically fit patients under the age of 70. They can expect 2-3 years post-transplant where they will be free of myeloma therapy.

“Allogeneic transplant. I think that it is still a matter of debate. Who is the right patient, or the patient who will benefit the most? Medically fit active subjects up to say 65-70 years of age. I think they really have the option for some two and a half or three years without medical treatment”.

Autologous transplant upfront of an allogeneic transplant failed to demonstrate a survival advantage over the tandem Allo. There was a 20% mortality rate for the auto-allo transplant vs 10% mortality associated with the tandem allo transplant.
“I think the other practical aspect that came out of ASH is that the role of allogeneic transplant still remains I would say investigational. That was the large CTN trial showing that there was no defined benefit for an auto-allo up front as compared to a tandem auto”.

“There was the CTN trial that basically said allo failed and tandem allo-auto was associated with 10 percent treatment related mortality which was interesting to see in a prospective randomized trial across experienced transplant centers. That I think poured a lot of cold water on tandem auto-allo. I think the allo field really needs an injection of new ideas. I think otherwise frankly with the exception of the Bruno data, which is almost an anomaly now because it is so positive it just doesn’t make sense because everything else is so negative. The control arm being a fifty-fifty match just also doesn’t make biological sense. It just unfortunately brings the whole Bruno study – I am not saying it is a fraud because I don’t think it is. I just don’t think it is representative for whatever reason. In any event, allo really needs something new. And what is that going to be? I think it means a lot of things. I think it needs novel therapies up front, in the middle and out back. And I think it needs immunomodulatory therapy, proteasome inhibition, mTOR inhibition. All of these strategies need to be integrated into allo because otherwise it is going to die. The CTN trial was just negative. The reality was and is that basically the autologous transplant followed by the allo arm did substantially worse actually. So in the treatment related mortality was 20 percent. I think twice that which it was in the auto arm. I think there is going to be a major rethink there”.

**Anticoagulation**

*Warfarin, LMWH, Pradaxa (dabigatran), Xarelto (rivaroxaban)*

- Anticoagulation for the secondary prevention of thromboembolic events (strokes, deep vein thrombosis, pulmonary embolism etc.) is given to about 10% of cancer patients. Notably, 100% of patients who are on IMiDs and can tolerate anticoagulation receive either warfarin or low molecular weight heparin. Panelists have been slow to adopt new oral direct thrombin inhibitors (Pradaxa; dabigatran, Xarelto; rivaroxaban) because their manufacturers carefully avoided putting cancer
patients on registration trials. With the approval of these drugs for SPAF (secondary prevention of atrial fibrillation), we expect to see more focus on the hem/onc setting.

“How big of an issue is thrombotic events in your myeloma patients and are you using anything beyond warfarin or low molecular weight heparin? At this moment in time we are just doing warfarin and low molecular weight heparin. For the first time we are starting to have a discussion when the new oral anticoagulants become available, what should we do. We have cautioned that reality is that none of these oral agents have been tested in the cancer setting so that both the toxicity and the efficacy in regards to thrombosis associated with transplant may be totally different than where these things are going to be indicated which is in atrial fibrillation due to valvular disease. It kind of amazes me that none of these companies have taken on a cancer trial yet. I think they will but I think they wanted to get the drug on the market and trying to get the drug on the market with a cancer trial they were probably cautioned against it. Because you may have more adverse events? Right because of the degree of adverse events that you are going to have”.

“Final question and this is far different than anything we have been talking about. I run a number of different therapeutic panels and one of them deals with antithrombics and all of those guys are cardiologists. I have the sense that thrombosis, and this is my paradigm but this is where I am going to look for your insight, but that DVTs and these embolisms are a big problem for these cancer patients and all I am doing is talking to cardiologists. Take the last couple of minutes and talk to me about your unmet needs for antithrombotics. They are huge. Right now we have got the empiricism of aspirin versus Coumadin versus low molecular weight heparin. We need randomized trials that are a little more exhaustive than we have. Right now we basically have a lot of descriptive experiences. I think aspirin is real. I think that Antonio Palumbo has well done an earnest effort looking at thrombosis and so far have told us a few things. One, that bortezomib is protective. Two, that aspirin in most patients does a reasonable job particularly if there is not too much in the way of steroid or other cytotoxics in the mix. But the reality is that if you want to look for level of evidence type, if you want to look at sort of VISTA, APEX, MM09, MM010 type evidence for antithrombotics in myeloma we really don’t have it. We need to. I think there will be some work being done. Ideally oral and ideally targeting endothelial cells surface interactions because that is where the action seems to be. What is your familiarity with either these direct thrombin inhibitors or the factor Xa
inhibitors? I think that institutionally experience is limited because we are very traditional. I think that aspirin and low molecular heparin remain our number ones. The use of the new anti-Xa inhibitors and so on has been very limited. I think there is an opportunity for studies interesting that area. We will be potentially working with J&J and some of their compounds. Not me directly but colleagues of mine will be looking at that”.

“I got an e-mail just the other day asking us to join a trial in myeloma with one of the oral anticoagulants. So what is your current perspective on these drugs? I think it would be awesome to have them. I mean I honestly think we are just a bit lazy as oncologists. We put people on Revlimid and thalidomide and we know they have got 10 percent DVT rate, we are just too lazy to monitor Coumadin on all of them. There is obviously the risk/benefit profile too, but I think if we had an oral drug that didn’t require monitoring and you could put people on I think we would all sleep better at night thinking about our patients on Revlimid and thalidomide. I say bring them on is my opinion about that. What would you venture is…? Our market for those is so small compared to what they are really going to do. What percentage of cancer patients in your opinion should be on any sort of anticoagulation? I think it is probably pretty high. In myeloma the DVT rate is 10 percent. I am not sure what it is in other tumors, but I think it is probably as high or higher in many other solid tumor types. So I suspect there are a lot of cancer patients out there if you have a non-monitoring, non-injectable oral anticoagulant, I think it would be quite a good market for that. But is the reason that you use them associated with drug toxicity? In other words, is it the IMiD that is raising that risk? Yeah, without the IMiDs, the risk is lowered to 3 or 4 percent. It is not very high. So it is the IMiDs that is raising it. But in the solid tumor sphere it is, again, I don’t know the facts and figures, but there is a fairly high DVT rate in some malignancies I believe. But that is not my area of expertise. I am guessing. But something like pancreatic cancer, for example, I would think there might be some uptake of that”.

“We are using low molecular weight heparin throughout all patients. I personally have no experience with some with the upcoming novel oral drugs. Second, patients with myeloma have an inherently high risk of DVT compared to non-myeloma patients and even higher than in solid cancers, lets say except prostate and pancreatic. Third, we are administering anticoagulants to all subjects who have at least one specific risk factor as outlined in the leukemia paper by Palumbo two years ago.
“It is a big problem because it really interferes with quality of life. It interferes with the treatment. It actually also is a cost problem because those episodes cost society a lot. So it is a big problem. And it is becoming more and more of a problem in oncology. We just had a direct thrombin inhibitor, Pradaxa, dabigatran, approved in the US for SPAF and I saw just today Xarelto, which is rivaroxaban, was filed also for SPAF. Are you using any of these newer agents versus warfarin yet? I am not because they are not approved. For DVT? I would. Warfarin is taking a lot of our time. It is very time consuming and it is very cumbersome. Patients are waiting for a replacement to warfarin for years. I think the FDA needs to really react relatively fast if there is strong data. And there is strong data when you look at the NEJM. I look at all those things and there is very strong data and I think they should approve as soon as possible. I think it is a big deal in the oncology practice”.

“I think we will come along. This is really a personal opinion. I don’t have a lot of data. I think they will certainly represent a major replacement of warfarin. They could certainly have a major role in cancer patients. I don’t know why at present but those companies are very much concentrating in hip replacement and not very concentrated, as far as a I can tell, in some niche disease like myeloma. So we would try to have some experience in this but they were pretty much reluctant. That is because they are so afraid that there is going to be a higher bleeding (or mortality) rate in the cancer patients. I think that is why they are so afraid of putting their drugs into the oncology patients. I can see the issue but I think there is a major marketing issue more than really a scientific issue. What do you mean by a major marketing issue? At present they want to go into the major anticoagulation market. This was my impression. Now they want surgery, general surgery, and general medicine. This is where they are concentrating the effort to hit the market. Then when it will be established in that situation they will try to open up in other niche situations by myeloma or cancer. For 100 myeloma patients who you treat what percentage of those patients do you have on anticoagulant therapy? You see myeloma is very peculiar because if you use IMiDs 100 percent of them. But again, we are in an old fashioned use of anticoagulation. We are mainly using heparin and low molecular weight when we do have a high risk patient. I don’t know if this is another reason. But basically with IMiDs I have, let’s say, 100 percent of patients with bortezomib probably none of them. What if I had asked you the question for the hematology community as a whole would you venture a guess as to what percentage of
patients are on an anticoagulant? Not many. Probably more in the US. Here, not many. But the risk of DVT is not low because at least 10% patients with cancer do have a DVT. But generally speaking I do see in the practice the use of anticoagulation if you have a high risk of thrombosis. Otherwise I really do not see them use a lot of anticoagulation. You would say 10 percent DVT everybody on anticoagulation. It really is not working this way at least in Italy. We do use anticoagulation when there is high risk of that otherwise we try to skip it”.

Dasovas; defibrotide (Gentium)

- Defibrotide is a mild anticoagulant, currently not approved in the US, which is used for the treatment of vaso-occlusive disease. In trials it produces a 40% reduction in VOD.

“There was a really nice bundle of data that was presented on defibrotide. I don’t know if you followed that at all. That is in veno occlusive disease. And the reason I am going to touch on it, I mean obviously I am involved, but most importantly there is actually a myeloma piece to this. Defibrotide data, there is now randomized prospective trial in prevention which won the VonBeckham award at the EBMT in Vienna, which is the best clinical research in 2010. It was awesome. It was a 400 randomized trial, patient trial randomized between controls and defibrotide. And what was seen, and this is sort of the sweet spot, was not only a significant reduction VOD, a 40 percent reduction of VOD. Now this was not a shock necessarily to us because it was a hypothesis that we thought we should look at and we were proven right, but is there was a highly significant reduction in GVHD. And that we presented updates from our treatment IND, we presented updates from our safety data base and we did a meta-analysis across all the prospective trials. All of those were positive. So we had a poster for safety, which was awesome, over 400 patients worth of data, a meta-analysis that was also awesome and positive. That was a poster looking at different patient studies and comparing them to a carefully controlled and well-organized historical control. And then we did a treatment IND, which I didn’t realize it was going to be such a highlight but it was actually picked as one of the highlights of ASH by ASH because what we showed was that the treatment IND was in over 200 patients – understand what that is, that was a perspective phase II but it was across 60 centers. It was again all the same criteria, severe VOD, etc, multi-organ failure. The results were actually better than the control trial. That to me was very interesting because when you
take a drug like that into the sick population and move it out into different centers you would actually expect the numbers to worsen wouldn’t you? Right. Yeah, I don’t know if you know much about VOD but it is a horrible disease and kills quickly. My point is the numbers were actually better and the survivorship and CR rates were really robust. So what was really exciting for us was to see that in the community setting, if you will, across 60 centers in the transplant community the data were actually stronger than we saw in the control trial. So how far in advance of the actual transplant is this dose given? It isn’t. That is the point it is given in reaction to VOD. So this is treatment. The prophylactic trial was the proof of principle trial because it could not be done in a randomized fashion. Once VOD strikes you can’t randomize to nothing because it kills. Mortality is in excess of 80 percent. How can you offer a patient sitting there nothing versus something in which the survivorship is around 40 or 50 percent? It is just unethical. So what you do in the established disease you do controlled trials, historically controlled, and in prophylaxis you do prevention with randomization and that is why we are so excited by the pediatric trial because it is a large well-organized study, multicenter EBMT and it was strongly positive. So because of that we don’t need to worry about proof of principle anymore. We now have that. We now look hard at the treatment data and the treatment data were very positive. Not only were they positive for safety and outcome, but what is really interesting was the GVHD rate was low as well. The reason I bring that back down around DF, rather bring DF back to myeloma is because DF amongst a number of things that it does is a pleiotropic piece of DNA. One of the most interesting things it does is it targets heparinase. We have shown that in a single arm, phase I trial with Antonio Palumbo we did MP, thal, plus defibrotide. Not only was there a very low rate of thrombosis, you weren’t allowed to get aspirin or low molecular weight heparin because it is an antithrombotic. We also saw an enhanced progression-free survival with low toxicity. Very interesting. Isn’t that interesting? So my thinking in the allo world to get back because you might say where on earth am I going with this, my point about the allo world is we need to revisit the allo world with the right drugs. My view is that you do minis but you do them with smart GVHD prophylaxis, you use bortezomib, you use IMiDs and then you integrate novel new agents like defibrotide into that mix to sort of try and move it all in the right direction. You have got to reduce for treatment related mortality. You can’t have 20 percent death rate. That is unacceptable. And you have got to enhance efficacy”.

Skeletal Related Events
Xgeva / Prolia (denosumab; Amgen)

- Xgeva (denosumab) was approved for the prevention of skeletal related events in breast and prostate cancer in 4Q2010. One German panelist shared that his group is able to get reimbursement for patients who failed (had an event) bisphosphonates, either pamidronate or zoledronic acid. Taking the reimbursement issue off the table, his perspective was that the sub-q was much easier to dose, and the acute toxicity is less with Xgeva. He perceives Xgeva as much more potent and less apt to cause osteonecrosis. So that is our “N = 1” for this report.

“We are currently starting to use RANK ligands. It has been approved in Germany or in the EU just in Oct or November maybe. We are currently treating some patients with Prolia who fail conventional bisphosphonates. But I think that it is still too early to really get an impression. We are currently treating most patients with pamidronate, 60-90 mg every four weeks and in the outpatient department it is still zoledronate. We have not the reimbursement situation that everybody may receive Prolia, so we have to ask the patient's insurances if they really have bone disease that becomes worse during treatment and mostly we succeed. But it is not a general option to treat patients with RANK ligand inhibitors. If I took the reimbursement question out of the equation, so on just a medical basis what do you see differently in terms of your use of a bisphosphonate vs. a RANK ligand inhibitor? What are the pros and cons of each from a medical standpoint? I think it is the ease of administration. You don’t need to do it intravenously with RANKL. It causes less acute toxicity. You have maybe a little less osteonecrosis. And the compound is significantly more potent than conventional bisphosphonates. I think that we will see a move of Prolia towards at least second line treatment along with let’s say second line systemic treatment for myeloma. I think more and more patients will get this drug.

“Why are these bone protecting agents not used in prevention of the initial skeletal related events. Why do you wait until there has been an event before patients are being put on these agents? I think that we will change to use the drugs differentially as soon as we have seen promising up-front data regarding myeloma. Up to now it is more or less confined to solid tumors that receive the majority of beneficial events regarding RANKL inhibitors. It is just a matter of time”.
Thought Leader Interviews

Interview OHIID02532

Interview Topics

Multiple Myeloma

Physician Demographics

TL # 10553
Specialty: Hematology
Geography: Boston, MA
Interview date = 01/04/2011

Interview Transcript

I saw a lot of your presentations at ASH; some of the best. You were very busy and I didn’t really feel like there was an opportunity to come say hello in person.

You are so nice to say that Jeff. I really appreciate it. Which ones did you see because I love your feedback?

Let's do this in reverse. The elotuzumab, the CS1 data. Let me just give you a break out of how I would like to handle our 30 minutes. I want to do about ten minutes on carfilzomib and pomalidomide and get some sense of how they are going to challenge established therapy. So then the next ten minutes I want to do some of these late stage approaches. Where will elotuzumab synergize? Where will the HDAC synergize? AKT, HSP90 and whatever else you want to add to that group? And then the last ten minutes I want to do some of these really upstream things like the antibody drug conjugates. I am going to break it out that way. But let me tell you the elotuzumab data just really stunned me. I want to find out if that as good as I took away. Let us start with carfilzomib and pomalidomide because each of these drugs are going to have to break into regimens that are very well established. So take those one at a time. How is carfilzomib going to displace or live in a bortezomib world?

So basically great question. It is very interesting. Just to give you my background in carfilzomib. I have referred patients to the trials, I am pretty familiar with the data, but I have not been directly involved with the studies themselves. My sense of carfilzomib is that it is a real drug. I think there is no doubt in my mind about that and it is a nice validation of the proteasome inhibitor concept. I think that the challenges in the early
phase trials were that I am not sure that they reached what I would define MTD in the very early phase I work that they did with Bob Orlowski. I think that the phase IIs then were somewhat challenged by the fact that they saw some complex toxicology signals early. This renal signal was real and they dealt with it very well. They hydrated, they administered dexamethasone. They called it tumor lysis. Frankly I find that a bit of a stretch. I think that the reality is that it has a metabolic effect at the level of the kidney. I think that it is an irreversible proteasome inhibitor and that makes it fundamentally different to bortezomib. But I think they have gotten around it and I think you can safely administer carfilzomib to most patients. But the renal signal is real and they would be foolish to underestimate that. What they presented in their data was grade 3 creatinines, low, low, low rates. But grade 2 creatinines, the upper limit of normal for a CTC grade 2 is 3 ½ the upper limit of normal which is 4 ½. So to downgrade 1/2s is something they need to be careful about because you don’t want to do that in myeloma because kidney disease is real.

So you are trading off neuropathy for?

Potentially for nephrotoxicity. The reason I can speak with authority about the nephrotoxicity is with the NPI-0052 (Nereus Pharmaceuticals) compound, which we are working with, is another irreversible proteasome inhibitor. It is in a different class. It is not an epoxy ketone. It is a salinispora. It is from Salinispora basically. It is a naturally derived product. It is clearly nephrotoxic. This is, I think, a feature of the irreversible proteasome inhibitors. I think they are nephrotoxic. The point is why wouldn’t you see something. You cannot irreversibly block a proteasome in a living system and expect it to be free ride. So I think that the Onyx data that I heard I was very impressed by. I think it is an active drug, but I think they need to be a little bit careful about the toxicology because I don’t know that it is quite as much of a free ride as some of the investigators are saying. My own experience with it from the patients I have referred to the trials one of my patients clearly had grade 3 neuropathy on the clinical trial and actually had to have a dose reduction. On that dose reduction she progressed, but she did initially respond. Now in fairness, she had grade 3 neuropathy because she went to the trial because she had underlying neuropathy from prior bortezomib and thalidomide. So in fairness I am not surprised she got neurotoxicity. But I don’t think the neurotoxicity signal Jeff is zero either. I think it is about 15 percent. She was one of the few patients at the site that I referred her to that had significant neuropathy. I think they are being very honest about the neuropathy signal. I don’t think it is high. I think truthfully it is a less neurotoxic drug and I am quite comfortable with that.

Let me interject. One of the other panelists said that as we look at his whole mechanistic approach to proteasome inhibition that there is a feedback or a leakage of aggresome induction.

Yes.
So do any of these approaches by themselves or can you point me in the direction of how to...and do we couple this with a resistance? Is this a resistance mechanism? And if so, what do you see coming down the pipeline that is going to target that feedback?

At least of course the HDAC inhibitors because that is what they target is the aggresome. And I think that is huge potentially. But I do think that toxicity matters because if you have got an escape pathway that the aggresome is being upregulated through by which normal tissues probably respond as well you have got to be careful about what you see in terms of side effects. What has impressed about the HDACs is that they are potent with bortezomib, very potent. My own clinical experience with them has been exactly that; great combination conceptually and practically, but the big issue is minimizing side effects.

I saw more of vorinostat data. I didn’t see that much panobinostat data.

Yeah, the vorinostat data was awesome. The best vorinostat data that I saw, I am a bit biased because we are involved in it, but is the lenalidomide/vorinostat data. It was gorgeous. And that points to the other mechanism which is the epigenetics. And essentially by epigenetic mechanisms at play you gene silence; and we have seen great results with lenalidomide plus vorinostat in myeloma. I was very pleased with that. I think vorinostat plus bortezomib is real. I think those trials will come through, but I think the toxicity is a big challenge. I think panobinostat in contrast to vorinostat is probably a better partner with bortezomib overall in my experience. I think that panobinostat is more challenging to give with lenalidomide based on the phase I studies that have been done to data. In fact, they won’t be pursued because there were too many side effects. My feeling is that you will see vorinostat as an idea partner with lenalidomide going forward and also with bortezomib but perhaps not to the extent that was perhaps originally envisaged. And panobinostat will be a partner of choice with bortezomib going forward as well. I think that is an important positive.

I need you to address a key question for me and that is you touched on the fact that the mechanism by which the HDAC inhibitor is working is targeting this aggresome.

To some extent, yes. Not completely though because there is clearly an epigenetic mechanism as well.

So it is the epigenetic mechanism that makes sense to couple the HDAC inhibitors with lenalidomide?

Yeah.
It is the aggresome induction that makes sense to couple the HDAC inhibitors with a proteasome inhibitor?

Exactly.

I saw toxicity issue with both of these drugs though.

Yeah.

I don’t know if you can do this but if you had to pick a toxicity profile that you as a clinician were more willing to expose your myeloma patient to would you rather they had the GI toxicity of vorinostat or the platelet toxicity of panobinostat?

I personally think that we would hopefully have the choice because the reality is in myeloma patients you see both. What I would like to see is vorinostat approved and I would like to see panelists approved and I could pick my potion. Quite seriously because I think they are different. I like them both because I think they are different toxicologically. But they are very importantly quite, there is this code of passion that says cleaner drugs are better, but I am not entirely convinced about that. You need drugs that are multi-targeted. In myeloma our big success stories have been with multitargeted drugs; the cleaner the drug that less useful it is being. I think that I like both vorinostat and panobinostat. I think they are both important drugs. I think the fascinating point to me is that vorinostat may be a better partner with Revlimid and panobinostat, LBH, maybe a better partner with Velcade. That is kind of neat. That gives us a nice set of options to play with.

Right. From a reaching the market standpoint, what is in the public domain in terms of targets for approvals? Are these on the same basic timeline?

No, I want to drive back to carfilzomib a little bit because I feel I want to be very fair to it because I think it is a good drug. I think carfilzomib what I liked at the presentation that David Siegel gave was that it was very comprehensive. It was very full. I loved the fact that he got a response rate of 18 percent in the bortezomib refractory patients. That was really cool. I think that puts it in the ballpark to get accelerated approval. I want to be careful about one thing that I didn’t like though. I did not understand why the progression free survival was so short. That was disappointing to me.

Yes. Do you mean in those patients who were already refractory to bortezomib?

No, the whole study. If you were at the presentation that David Siegel gave the progression free survival was 3.7 months. That is not long and that is going to be a very tough sell to the agency.
And help me understand what had those patients seen as prior therapy that might account for that very short progression free survival?

They were all relapsed and refractory, although some of them were not classically relapsed and refractory. They were defined by an oddity of the protocol. My point is if your progression free survival is that short you have got to have very, very clean tight data around those patients to explain it because frankly if you have a progression free survival of five or six months with a response rate of about 25 percent and a response rate in the relapse refractory population of 18 percent then to my mind you are home and you have got it. The problem is that if you have got a response rate like that but it doesn’t appear very durable because the progression free survival is so short, you get my point. I think carfilzomib is going to be approved come what may. The only question I think there is, is whether it is from the randomized trial that is ongoing right now, which is carfilzomib, lenalidomide, and dexamethasone (CRd) versus lenalidomide and dexamethasone (Rd) or is it from accelerated approval this year by virtue of the strength of the phase II data? The phase II data to me I think are in play. I think they are real. I think they have a chance of being accelerated approval. Do I think it is a slam dunk? I don’t think so. I don’t think it is 100 percent actually. I am not sure I completely understand that short progression free survival.

Interesting.

Does that make sense to you?

It does. Was that carfilzomib monotherapy at that point?

Yes it was. To be fair it was carfilzomib monotherapy plus low dose dexamethasone for the pre-med.

So my take away of this is that there are so many possible combinations and some of the synergies on mechanistic grounds I understand or I can picture better than others. So who is ever going to use carfilzomib as monotherapy anyway?

I agree with that. I think that is correct. I think that is why I am very confident that the combination trial will be successful. I am confident about that as long as unexpected toxicology doesn’t emerge. I don’t think it will because I think they have been careful about dosing. It is a well run study, etc, etc. And the CID phase I/II by Ruben Niesvizky I think was good. But I think the interesting question to me is will it knock bortezomib out of its primary position. I don’t see that yet. I think that remains to be seen.
Is everybody going to move to bortezomib once weekly?

No, I don’t think so. I think the bortezomib twice weekly will remain a key platform. I think bortezomib will remain the first choice proteasome inhibitor. I think the new boronate peptides coming through the pipeline are very interesting. I think carfilzomib will be approved and will be a widely used proteasome inhibitor, but I think it will be used in the context of bortezomib intolerance and/or bortezomib failure. I will be surprised if it knocks bortezomib off of its perch. At the end of the day myeloma patients who walk in the door who are sick as stink and need three drug therapy are typically metabolically ill. They will have renal failure and will have all these other issues. You want a drug that is going to work that you have a very clear understanding of the toxicity profile. And I think that the carfilzomib story is still evolving and I think it is has got a ways to go; several years probably of us getting our hands around the drug and getting some experience. My partners and friends who have used it and are really savvy investigators do like Andrzej Jakubowiak and others insist that it is a very well-tolerated drug and I believe them. I think there are a number of stories though that I have had from colleagues in the field as well where they have seen stuff that is weird but I still think there is a lot to be learned.

It is perfect. I want to turn to pomalidomide. Before you dive into that, there were some comments I heard going through the hallways about some people were really concerned about the lenalidomide secondary cancers and other people said to me, come on it is just the mechanism of the drugs, there is more being made out if it, it is just directional so is lenalidomide going to be a first line agent in light of these possible secondary cancers?

I think lenalidomide and the secondary cancer story is a bit of a storm in a tea cup to be perfectly honest with you. I think people are living longer so you are seeing these issues. You have got to be very careful about what I call ascertainment bias. What happens here is that if you are on lenalidomide on one of the trials you are followed very carefully for as long as it takes. If you are on the placebo arm and you progress if you are crossed over to lenalidomide, which a proportion of patients are but not all, you will continue to be followed but arguably not necessarily as carefully as the primary group. Certainly in the placebo arm if you come off and go and get salvage elsewhere with another/different cocktail all the study sites care about is whether or not you are alive or dead. The details of what then happens are a bit of catch-if catch-can. You may or may not know what happened to the patient. So you can see how an ascertainment bias could get in the mix. Irrespective of that, the numbers are very small, but there does seem to be something there. That something may in fact because that there is an underlying vulnerability to second cancers in myeloma patients period. And I agree with that. I think it is clear-cut and we know that. Two, is it possible that prolonged lenalidomide exposure over three or four years in a very, very small number of patients say in that risk population of less than 1 percent can develop some second B-cell process that is atypical? Well yeah maybe it is but if it is it ain’t going to change what I am going to do because lenalidomide has changed the therapeutic landscape. It is giving people 70 percent progression free survival at four years
versus 35 percent. It is giving people survivals post-transplant that are unprecedented. So my overall assessment is storm in a teacup.

Okay, so everything you have said so far in my mind makes it very hard to, and I understand why Celgene would want pomalidomide to move into therapy but what about the rest of us in a lenalidomide world?

I think pomalidomide in a lenalidomide world is huge because I think what you are going to see is that lenalidomide is used up front and in truth the pomalidomide will start to go right into lenalidomide failure where as thalidomide currently will sort of increasingly get pushed sideways. Pomalidomide is awesome. It is quite frankly in my experience the best of thalidomide and the best of Revlimid put into one to be perfectly honest with you.

I am pretty sure you did this other presentation that really tickled me and that was the combination of thalidomide and Revlimid overcoming thalidomide resistance.

To me I don’t get why you would do that. I would stick with pomalidomide. The bottom line is thalidomide is toxic and it is unpredictable. So combining Revlimid and thalidomide, I mean yeah sure if you are stuck and you can’t get pomalidomide I suppose you could do it. But you know what that is actually a neat little thought because if you can’t get pomalidomide that is what I might do if I was looking to overdrive resistance to either of the two alone and I was stuck. I would use low dose Revlimid and low dose thalidomide. Do you remember which session you were at?

It was one of the later ones. It was late in the meeting. I will find it for you because I am sure I have the abstract.

If you could send it to me I would really appreciate it.

I absolutely will do that.

I really like that idea in the sense that – I much prefer pomalidomide but the bottom line is until you can get pomalidomide why not.

So let’s do elotuzumab. I really like the guy who presented that.

You are too kind. I think that the elotuzumab data are really interesting and I think they are real. I can speak directly to it because we are the lead enroller to the trial so a lot of my patients are on that study and they have all benefited. It is real. The thing that I would share with you is that they are all Revlimid naive so what you are seeing is a 60 percent
response rate from Revlimid but the elotuzumab is adding to it pushing you into the nineties. I think it is not just the natural killer; it is not the ADCC because it is just too quick. I think there is more going on. I thought there was a nice poster by Andrzej Jakubowiak, which made that point. What he looked at was the safety and efficacy of elotuzumab in combination with bortezomib and he showed a very robust response rate that I think was favorable. Personally, my take on this is that it is without a doubt more than just an ADCC thing. I think ADCC is part of it, but I honestly think there is a dual apoptotic signaling. There is some other mechanism by which elotuzumab is doing its damage. Patients with myeloma have low NK levels anyway. So if they have got low NK levels anyway, you do stimulate them obviously with the IMiD, that is a given. But to say it is just ADCC effect that is leading to this extraordinary synergy doesn’t make sense because the responses we are seeing are rapid. They are within the first two cycles. The other thing is candidly that we got dexamethasone with it. They get dexamethasone as well. Dexamethasone is hardly good for natural killer cells. It is a lympholytic agent. I think there is more than just the ADCC effect. In any event, however it is working and I think it is probably a mix of the two, the reality is that it is a very good addition. It is well-tolerated. We have defined a dose which is 10 mg per kilo. It is well-tolerated in the context of the appropriate infusional premedications. I firmly believe it is the first of a basketful of monoclonals that are coming through. They include this one, elotuzumab; I think it is going to be lead. I think the next one in the pipeline that is looking promising is CD38, Genmab compound.

*That is on my list.*

I think that is really interesting. And there are others in the mix as well. IL-6, CNT0328 is also good. It is not quite the same thing. It is not quite the same sort of knock-out blow but it is the concept of an antibody working on the microenvironment.

*I want you to do the CD38 from Genmab and the other one. I saw a poster which tickled me and I want to see whether or not I overstated this in my own mind. But there was a CD56 monoclonal called lorvotuzumab. Compare the two. Frankly, if you only had the opportunity to target CD38 or the opportunity to target the CD56 which way would you go?*

CD56 we have looked at and we have been part of that study group and CD56 I still think we need to keep chasing because it is a marker of bad prognosis. I would be very happy to see the landscape open up to allow a CD56 targeting antibody in the mix. But I have to tell you that I am not sold that CD56 is going to be easier or better than CD38. I think CD38 has a great appeal that is much more universal. I like Genmab. I think they are a good company. They are these Danish guys. They are good and they know what they are doing. They have done some good work in other areas and they are well organized in their discipline and they have got a very good study group on the Genmab program. It is all basically Nordic and European right now. We are going to get involved as it comes across the ocean but the fact is that what I have seen in the CD38 program has been encouraging.
There were some JAK inhibitor posters - which seemed a little odd to me, I am used to JAK inhibition in myeloproliferative disorder. But there was a poster from AstraZeneca and a separate poster I believe from BMS both talking about JAK2 inhibitors having activity in myeloma.

That is very interesting. I think it is an interesting target and we will see how it evolves. We are not up to something anything clinically yet, but again, there are sort of two directions in which the field are going. You have got these kind of backbone agents which target multiple things. Then you have got this highly pure approach where you can put together cocktails and small molecules that each individual one hits a particular target like JAK2. Whether or not this results in a better outcome than the bigger, broader, brush strokes will remain to be seen. My suspicion is it will be a mix of the two as we go forward. I think a JAK2 inhibitor in myeloma will have to be in combination. You are absolutely right I don’t think of it as a primary driver of this illness.

Final question and this is far different than anything we have been talking about. I run a number of different therapeutic panels and one of them deals with antithrombotics and all of those guys are cardiologists. I have the sense that thrombosis, and this is my paradigm but this is where I am going to look for your insight, but that DVTs and these embolisms are a big problem for these cancer patients and all I am doing is talking to cardiologists. Take the last couple of minutes and talk to me about your unmet needs for antithrombotics.

They are huge. Right now we have got the empiricism of aspirin versus Coumadin versus low molecular weight heparin. We need randomized trials that are a little more exhaustive than we have. Right now we basically have a lot of descriptive experiences. I think aspirin is real. I think that Antonio Palumbo has well done an earnest effort looking at thrombosis and so far have told us a few things. One, that bortezomib is protective. Two, that aspirin in most patients does a reasonable job particularly if there is not too much in the way of steroid or other cytotoxics in the mix. But the reality is that if you want to look for level of evidence type, if you want to look at sort of VISTA, APEX, MM09, MM010 type evidence for antithrombotics in myeloma we really don’t have it. We need to. I think there will be some work being done. Ideally oral and ideally targeting endothelial cells surface interactions because that is where the action seems to be.

What is your familiarity with either these direct thrombin inhibitors or the factor Xa inhibitors?

I think that institutionally experience is limited because we are very traditional. I think that aspirin and low molecular heparin remain our number ones. The use of the new anti-Xa inhibitors and so on has been very limited. I think there is an opportunity for studies interesting that area. We will be potentially working with J&J and some of their
compounds. Not me directly but colleagues of mine will be looking at that. I don’t know if you saw anything, but are you interested in the transplant arena at all?

Absolutely.

A couple of things. The myeloma sphere obviously there was the CTN trial that basically said allo failed and tandem allo-auto was associated with 10 percent treatment related mortality which was interesting to see in a prospective randomized trial across experienced transplant centers. That I think poured a lot of cold water on tandem auto-allo. I think the allo field really needs an injection of new ideas. I think otherwise frankly with the exception of the Bruno data, which is almost an anomaly now because it is so positive it just doesn’t make sense because everything else is so negative. The control arm being a fifty-fifty match just also doesn’t make biological sense. It just unfortunately brings the whole Bruno study – I am not saying it is a fraud because I don’t think it is. I just don’t think it is representative for whatever reason. In any event, allo really needs something new.

And what is that going to be?

I think it means a lot of things. I think it needs novel therapies up front, in the middle and out back. And I think it needs immunomodulatory therapy, proteasome inhibition, mTOR inhibition. All of these strategies need to be integrated into allo because otherwise it is going to die. The CTN trial was just negative. The reality was and is that basically the autologous transplant followed by the allo arm did substantially worse actually. So in the treatment related mortality was 20 percent. I think twice that which it was in the auto arm. I think there is going to be a major rethink there. There was a really nice bundle of data that was presented on defibrotide. I don’t know if you followed that at all. That is in veno occlusive disease. And the reason I am going to touch on it, I mean obviously I am involved, but most importantly there is actually a myeloma piece to this. Defibrotide data, there is now randomized prospective trial in prevention which won the VonBeckham award at the EBMT in Vienna, which is the best clinical research in 2010. It was awesome. It was a 400 randomized trial, patient trial randomized between controls and defibrotide. And what was seen, and this is sort of the sweet spot, was not only a significant reduction VOD, a 40 percent reduction of VOD. Now this was not a shock necessarily to us because it was a hypothesis that we thought we should look at and we were proven right, but is there was a highly significant reduction in GVHD. And that we presented updates from our treatment IND, we presented updates from our safety data base and we did a meta-analysis across all the prospective trials. All of those were positive. So we had a poster for safety, which was awesome, over 400 patients worth of data, a meta-analysis that was also awesome and positive. That was a poster looking at different patient studies and comparing them to a carefully controlled and well-organized historical control. And then we did a treatment IND, which I didn’t realize it was going to be such a highlight but it was actually picked as one of the highlights of ASH by ASH because what we showed was that the treatment IND
was in over 200 patients – understand what that is, that was a perspective phase II but it was across 60 centers. It was again all the same criteria, severe VOD, etc, multi-organ failure. The results were actually better than the control trial. That to me was very interesting because when you take a drug like that into the sick population and move it out into different centers you would actually expect the numbers to worsen wouldn’t you?

Right.

Yeah, I don’t know if you know much about VOD but it is a horrible disease and kills quickly. My point is the numbers were actually better and the survivorship and CR rates were really robust. So what was really exciting for us was to see that in the community setting, if you will, across 60 centers in the transplant community the data were actually stronger than we saw in the control trial.

So how far in advance of the actual transplant is this dose given?

It isn’t. That is the point. It is given in reaction to VOD. So this is treatment. The prophylactic trial was the proof of principle trial because it could not be done in a randomized fashion. Once VOD strikes you can’t randomize to nothing because it kills. Mortality is in excess of 80 percent. How can you offer a patient sitting there nothing versus something in which the survivorship is around 40 or 50 percent? It is just unethical. So what you do in the established disease you do controlled trials, historically controlled, and in prophylaxis you do prevention with randomization and that is why we are so excited by the pediatric trial because it is a large well-organized study, multicenter EBMT and it was strongly positive. So because of that we don’t need to worry about proof of principle anymore. We now have that. We now look hard at the treatment data and the treatment data were very positive. Not only were they positive for safety and outcome, but what is really interesting was the GVHD rate was low as well. The reason I bring that back down around DF, rather bring DF back to myeloma is because DF amongst a number of things that it does is a pleiotropic piece of DNA. One of the most interesting things it does is it targets heparinase. We have shown that in a single arm, phase I trial with Antonio Palumbo we did MP, thal, plus defibrotide. Not only was there a very low rate of thrombosis, you weren’t allowed to get aspirin or low molecular weight heparin because it is an antithrombotic. We also saw an enhanced progression-free survival with low toxicity.

Very interesting.

Isn’t that interesting? So my thinking in the allo world to get back because you might say where on earth am I going with this, my point about the allo world is we need to revisit the allo world with the right drugs. My view is that you do minis but you do them with smart GVHD prophylaxis, you use bortezomib, you use IMiDs and then you integrate novel new agents like defibrotide into that mix to sort of try and move it all in the right direction. You
have got to reduce for treatment related mortality. You can't have 20 percent death rate. That is unacceptable. And you have got to enhance efficacy.

You have given me a lot to think about today. I really want to thank you.

It is a pleasure.
I would like to debrief on this past ASH. I thought it was from a myeloma standpoint an extremely rich meeting and so there is no way we are going to get to cover everything on my list. There are three areas that I would like to cover with you and then we will do what we can. So basically I want to split this conversation into three pieces. First, I want to get your take on the carfilzomib and pomalidomide data; carfilzomib in relation to bortezomib and pomalidomide in relation to lenalidomide. Maybe the next ten minutes I want to focus on some of the combination strategies people talked about like where will elotuzumab synergize, where will the HDAC synergize. And then there were some really upstream things which caught my attention, some of these antibody drug conjugates and things like that that I want to feel you out on. That is how I am going to break out my thirty minutes. But before we get into that, what is the most interesting thing you took away from the meeting?

I think actually it was a great meeting for the transplant aspect of myeloma. So 1a data about bortezomib being the best or being a good induction for transplant eligible patients seems to be solid. Interesting is the long-term follow up of the lenalidomide, the ECOG E4A03. David Siegel’s abstract where the people who even over 70, so 65-70 and less than 70 who got four cycles of Revlimid followed by transplant are doing very well. I think that important point is there. And on a side note I think the availability now of Signal Genetics producing the gene expression profiling as a commercial assay to risk stratify myeloma into high risk and standard risk now for the first time there will be, let’s say for the regular physician, the ability to risk stratify patients. Whether it will make a difference or not on what they do is another story. I think it is a watershed moment that there is that ability.

So if you were going to advise the community hematologist on actions to take based on these risk stratifications and choices of first line therapy, second line therapy, etc, what is your take on...?
I think for sure standard risk myeloma should get bortezomib-based induction and one transplant. Then if they are in complete remission the question of do they need maintenance is very appropriate. I would say this would provide strong argument that a patient with standard risk myeloma, low tumor mass, who had low level disease after transplant or had a CR after transplant, should probably be left alone and not be placed on maintenance. The converse to that is people with high tumor mass or high risk gene expression profiling (GEP) signature. They should probably be placed on maintenance post-transplant.

*With Revlimid?*

If they are not in CR Revlimid alone may not be enough and that they might be a combination maintenance with Revlimid and bortezomib. I think that to me was the practical aspect to that. I think the other practical aspect that came out of ASH is that the role of allogeneic transplant still remains I would say investigational. That was the large CTN trial showing that there was no defined benefit for an auto-allo up front as compared to a tandem auto.

*Yes.*

I think as you well mentioned and identified, I think when we should focus on what we call the next generation of drugs. And the next generation of drugs we will call carfilzomib, we will say elotuzumab and we will call pomalidomide. I think we discussed last year the pomalidomide data. And I think that data remains strong. That space has not changed. It is not commercially available but they will probably look for an approval some time next year. I wonder if they can get it approved based on just responses on lenalidomide failures. I don’t think so. I think they are going to have to do a randomized trial, but we will see. Celgene does not want to position it in competition to lenalidomide.

*Right.*

So the idea that we are going to get pomalidomide up front studies at this moment in time is probably unlikely.

*Cannibalism. There is no reason for them to do that.*

Yeah. And it is what it is. The data that we have is the data that we will get.
Let me stick with the Celgene theme for a moment. They have their own HDAC inhibitor now, with romidepsin, Istodax. Does it make sense for them to couple this with their IMiD?

I think it does make sense. But, one, they don’t have all the money in the world. Two, there is concern about how much bang you get for your buck. So romidepsin has a very good space in T-cell lymphomas probably. The studies you would need to do to say okay we will put romidepsin to make Revlimid a better drug, I don’t know. The front line space in myeloma is so good now for them. It is either Revlimid/dexamethasone or VRD. They have the maintenance. You could think well maybe they want to do maintenance with romidepsin in people who have failed lenalidomide. I think they will still continue to explore it in the salvage setting. So I think investigators are going to probably look at trying to explore romidepsin in other combinations, but I don’t think Celgene is going go for it.

Let me just take this from a slightly tangential perspective. I saw a lot of update or activity from Merck talking about the VANTAGE study and vorinostat as an addition bortezomib. But they were also talking about a trial, and I don’t know if it was ongoing but they were certainly talking about doing vorinostat in combination with one of the IMiDs.

Yeah. Well how do I say this? Well let me just say it this way: I think vorinostat is trying to find a home. They are banking on the vorinostat/bortezomib story. We haven’t seen the definitive results. My guess is that they are hedging their bets in case that they don’t get the signal they want, they still have something they can do with the drug because they have invested a significant amount of money on that drug.

Now mechanistically I understand the use of the HDAC inhibitors to perhaps do a second hit on the aggresome...

Yeah, it makes a huge amount of sense. We all agree that it is really a lot of sense but you know the road to hell is paved with things that made sense and didn’t make it.

All right, that is fair.

I think what is going to happen with vorinostat in combination with bortezomib will depend on the randomized trial and it is going to have to be a major difference for people to be able to accept the extra cost and the extra toxicity.

So my recollection is they were looking at real salvage population like with three plus prior regimens and they were also looking at a separate trial in less heavily treated. Does one or the others of those make more sense to you for an HDAC?
Not really.

So they are basically, as you put it, hedging bets?

They are hedging bets I think. Fortunately or unfortunately, however you want to take it, a lot of this is going to be predicated on the notion of “where can I market this drug”? I think a lot of this from the practicing physician perspective is it going to be is it worth the extra cost and the extra toxicity. I have to say I think it is a little bit of the same thing that we are seeing with induction treatment that people who started double therapy, triple therapy and when they are getting to quadruple therapy they are getting to the point of diminishing return. So the addition of an alkylator to triple therapy adds toxicity and does not necessarily push you to increase cures. Now mind you, I think what we are going to see is a little bit – so on an individual note and I am starting to hear my colleagues say they feel the same – is the idea of recapturing control or recapturing response may start gathering some momentum in the myeloma space. What does that mean? So you are following a patient with myeloma and lenalidomide maintenance, for example, or on bortezomib maintenance and they have a mild increase in their paraprotein peak. So rather than saying oh you failed this treatment I am going to change classes of drug, you are going to add another drug that is going to be synergistic to the drug that is starting to develop resistance to the disease to try an capture control. So there you could think about so what do they want to do with romidepsin? So Celgene will say well rather than burn pomalidomide let’s do lenalidomide intensification. If that doesn’t work then let’s do lenalidomide plus romidepsin or lenalidomide plus Biaxin. You understand? And the physician will like that and the patients will like that because, one, at least a part of the treatment they know what price they are paying for it, the toxicity price. And for the drug companies the incentive is that they are going to be able to continue to sell the drug in the same space.

Let me do some time management. You mentioned elotuzumab. I saw Paul Richardson’s talk. I think it was like Monday evening.

That I think of all the things that you are thinking about what new things you felt, oh this is going to become – if you look at the data, remember these are lenalidomide-naïve patients. So the big question is how much more does elotuzumab add to lenalidomide? There is not a randomized trial of this. They just did it in combination. Response rates were dramatic. I am thinking obviously where they are going to position. I think they are going to have to do a randomized trial plus or minus the monoclonal antibody to show that there is an enhanced response rate and that there is an improvement in PFS. What I don’t know is whether they are going to explore at the same time the front line setting.

Once again, you said that first line is so well established, the responses are so high. How does anybody come in and...?
I think what they want to do is try to bump out the transplant. I would say, okay, let’s say the addition of this drug can obviate the need for a transplant.

*Is that wishful thinking?*

I believe there will be people looking at that. I think it is a valid question. Again, it is a question of how much are you willing to pay for it. I could see – well what is your feeling about what is going to happen with gene expression profiling now becoming commercially available? I think that the community will start exploring the idea of risk stratification and that it actually will have more relevance for the maintenance question than for the induction question. Am I the first key opinion leader you are talking to?

*I have spoken to a number of other people as well.*

Am I the first to talk about risk stratification and the fact that now this test is available?

*I have got a lot of friends who are community hematologists so we actually had these conversations as the meeting. There were a number of things which came up, which surprised me in terms of what was driving choice of therapy and what actions were they taking. As an academic I would say it is all the evidence-based medicine. But you talked about a couple of things which I want to bring them up and then see how it comes together with the evidence-based medicine. These guys said to me given the option if it is a patient who is nearby whatever the therapy, the risk stratification would lead to, if it is basically a wash and I can given a parenteral product, I am doing that. If I am in an academic center and this patient is driving a really long distance I will give them an oral therapy. My take was that until there is a clear-cut advantage of maintenance, like people sort of think there should be an advantage to it, but you are putting people on an added drug with an added toxicity. I didn’t get a sense from the people I spoke to at the meeting, and there were quite a few of them, that people were really sold on maintenance yet.

Which is I have to tell you and I am still trying to figure out where it stands. I actually see maintenance being adopted much more commonly than what I thought would have happened. That is despite the fact that I would say that most of us who are going out distributing the information that we have about maintenance have been extremely cautious about how that information gets distributed. For sure, I have not been a blind proponent of it. I know Phil McCarthy has not. And Celgene definitely has not. So I can’t tell you that there are all these people out there banging the drum of maintenance. I do think what is happening is that many patients and physicians who see their patients not in a complete remission after three months post-transplant have opted to the idea that we should give you maintenance for a period of time. I don’t think it is going to be until progression. I think people are going to get sick and tired of it. It will be interesting to see how this unfolds. I do get the feeling that different to what you are saying I get the feeling that
maintenance is being adopted much more readily. Now remember, before it wasn’t hardly ever done. So maintenance lenalidomide definitely has much more acceptability than maintenance thalidomide, despite the fact that there were three randomized trials for maintenance thalidomide.

*I think that is true. I guess the only other concern I heard raised about the lenalidomide maintenance was secondary malignancy. Some people say well it is an IMiD; what did you expect? What is your reaction?*

We didn’t see it with thalidomide. I think it says heads up and buyer beware. Obviously everybody is looking at this and we need to figure it out. At least it did not impact survival in the first two years.

*Right. Okay, I got ten minutes and I have got a lot of upstream things I want to touch. I am going to put them out, if you like them let me know, otherwise we move along. There was a CD38 from Genmab.*

Are you saying buy, sell or hold? I would say I didn’t see that. I had heard something about it. I am going to say too premature.

*Okay, there was a CD56 molecule which I really thought was cute because it used this monoclonal that...?*

That one I think is of interest because of CD56 is a potential good target. The problem with CD38 as a target is that there are a lot of other cells that express it. So you can assume that the toxicity profile might be better for a CD56 targeted agent.

*Did you see that molecule?*

I heard about it.

*It is IMGN901, lorvotuzumab (ImmunoGen).*

Yeah.

*I have seen these antibody drug conjugates...well for Hodgkin's Seattle Genetics has brentuximab (SGN-35).*
I think the one thing here and the caveat with all of these is that they target the immune system and NK immunity may be important in myeloma.

So tell me more about that because that brings up things like MAGE.

I think none of the vaccines are yet ready for prime time. Although, I think eventually we will have some degree of exploration of vaccine therapy for myeloma probably as an adjuvant to stuff that we do. Now I think the same thing with the monoclonal antibody, most of us think that to be able to control the disease we are going to need to either reduce the tumor burden and stimulate the immune system whichever way we can come up with. The problem with drugs at the same time eliminate or impair the immune system’s ability to deal with the disease may actually end up being counterproductive.

Give me an example of a drug.

Like Campath, for example, not for CLL but Campath for ALL in the transplant setting. Campath for myeloma in the transplant setting despite the fact that myeloma cells are actually CD22 positive some of them it didn’t work. ATG has activity in vitro for myeloma. ATG can kill myeloma cells. But again, unfortunately it did not work. This is just exploring the CD56 issue immediately. So here I would say the problem with the CD56 story in myeloma is it may not work because of the fact that that you may be eliminating the immune system.

What do you think of MAGE?

I think it is the first of many potential vaccines or proteins that will be explored in myeloma. As a vaccine it is not very good because it is not very immunogenic. I think it is expressed in enough myeloma cells that it will be relevant. So using it as a target, particularly if you can put it together with something that actually gets incorporated into the myeloma cells and kills it. So it can serve either as a Trojan horse or I think as a vaccine by itself it is not going to work. But I think it is going to open the door to other vaccines.

If I stay with the Trojan horse concept then you are going to couple that with some maytansine or some other…?

Perhaps, your anticancer of choice.

And then if you are thinking about a better therapeutic vaccine what comes to mind?
I can only tell you that there are other antigens that are being explored. I can’t go into details.

_I have got a couple of minutes left. To bring our conversation to a close of everything we have talked about if you could only have one new therapeutic available to you in the next three years which one would it be and how is it going to get used?_

That is an interesting question. I would have to say carfilzomib over pomalidomide.

**And so how are you going to use carfilzomib?**

I think it is going to get used up front and then eventually it will probably be used in the maintenance setting.

_So you are saying it is going to displace bortezomib up front?_

I would say, well actually, if you had asked me last year I would have said yes, but now with the idea that with changing bortezomib dosing you can get away from the neuropathy and still get the efficacy it might be a whole different story.

_So the critical thing there is do you believe that once weekly bortezomib…?_

I think it is. Its close; it is good enough for government work.

_Okay. I have two questions I want to put in here. One is a philosophical one and this actually comes back to the HDAC we were talking about. So panobinostat, the Novartis HDAC has a lot of thrombocytopenia associated with it and vorinostat has a lot of GI toxicity._

Which, I think, is going to be the one that will make it extremely difficult.

_So is GI toxicity harder for you to manage as a physician?_

It will be much harder because it is a lot easier to monitor platelets than to start treating diarrhea. And the patient calls the physician a lot more because of diarrhea than because of platelet counts.
Got it. Last question. This is totally changing gears on your. How big of an issue is thrombotic events in your myeloma patients and are you using anything beyond warfarin or low molecular weight heparin?

At this moment in time we are just doing warfarin and low molecular weight heparin. For the first time we are starting to have a discussion when the new oral anticoagulants become available, what should we do. We have cautioned that reality is that none of these oral agents have been tested in the cancer setting so that both the toxicity and the efficacy in regards to thrombosis associated with transplant may be totally different than where these things are going to be indicated which is in atrial fibrillation due to valvular disease.

*It kind of amazes me that none of these companies have taken on a cancer trial yet.*

I think they will but I think they wanted to get the drug on the market and trying to get the drug on the market with a cancer trial they were probably cautioned against it.

*Because you may have more adverse events?*

Right because of the degree of adverse events that you are going to have.

Okay. *Is there anything I should have asked you about myeloma coming out of ASH that I didn’t think to bring up?*

I don’t know where it stands, but I think the other thing that came out was the issue of PET scanning. So whether or not PET scans should be considered standard.

*Comment on that because others have as well.*

I think what came out is that PET scans could be effective because the trial that the Spaniards showed that it seemed to be helpful. I think what also came out loud and clear is that there is no standardization about the way PET scans are performed or read in North America. That in itself is probably the biggest barrier for universal use of PET scanning. It is still not considered standard. It is still not universally reimbursed. I think eventually it will be but the way I am looking at it is that probably somebody on the national level will have to create a task force to develop a guideline of how PET scans should be done and read in myeloma. And then after having done that they will have to look and see how it works. The Medicare Demonstration Project, I can’t say I have seen the definitive results, but I don’t think it was dramatically positive. And what happens, at least when I speak with community physicians, is many of them will tell you this really wasn’t really very helpful for me. It probably has more to do with the fact that the community radiologist doesn’t
know how to read PET scans in myeloma patients because they read them like in regular solid tumors and there is a difference.

Very good.

Whether PET scanning for myeloma will be able to go out into the community I think is still a question.

Very good. I know I am out of time. It is really a pleasure catching up with you.
Interview OHIID02534

Interview Topics

Multiple Myeloma

Physician Demographics

TL # 10419
Specialty: Hematology
Geography: Detroit, MI
Interview date = 01/05/2011

Interview Transcript

It is nice to get a chance to debrief with you from ASH 2010. From my standpoint it was an extremely target rich meeting so I am going to have you do some of the prioritization of what you thought was important and I am going to try to do a little of the time management to make sure we stay on 30 minutes. I will tell you the things that jumped out and put these in perspective. How good was the carfilzomib data?

I think carfilzomib data is nicely maturing. I am encouraged with the fact that the side effect profile seems to be really coming along better than what I would expect.

From what I took from many of the presentations is that we really need to be thinking about the doublets, triplets and quads of how these drugs are going to be used. As you look at what we know about bortezomib how it is able to be combined versus carfilzomib, are we simply going to be able to substitute out bortezomib?

That is a good question. I don’t think we have enough data to say something like that. I believe that carfilzomib as a single agent or in combination with dexamethasone will be better tolerated than bortezomib. I think efficacy will be at least as good as bortezomib. Is it going to combine with other drugs as good as bortezomib, I think we need studies.

So when it is available to you, how are you going to sequence it?

I think carfilzomib will be a very interesting drug in patients who were treated previously with the IMiDs. Patients who have significant neuropathy and we see a lot of those patients now in the practice. So I am not gung ho on carfilzomib as first line yet because I think we need more data. But I think in the relapse refractory setting it could be a very useful drug.
Okay. So where does lenalidomide stand in terms of moving into a first line role for multiple myeloma?

I think lenalidomide in combination with melphalan and prednisone could be and probably will be one of the standards of care in patients who are not candidates for transplant. I still think the melphalan/prednisone/Velcade has an excellent profile toxicity wise and efficacy wise. But I cannot say that Revlimid responses will be or are inferior. I think Revlimid has an advantage in a sense that it has not produced neuropathy, but on the other side produces more hematotoxicity in combination with melphalan, particularly in older patients who are mostly patients who are not candidates for transplant, could be harder to tolerate. And Revlimid/dex I don't think it is good enough as a first line unless there are really limiting factors for use of other combinations.

There was some discussion at the meeting, certainly in the hallways that I heard, of some concerns about these secondary cancers that were developed directionally higher in the lenalidomide patients.

I am not surprised with that. I think people start talking about that now more. I don't know last year when we talked about that if I mentioned concern. My concern is more relapses of myeloma with IMiDs. I have more concerns with the thalidomide than Revlimid because Revlimid was not used as thalidomide. But if you are in practice and you see those patients when they relapse especially after longer use of thalidomide they have significant number of what is called extramedullary plasmacytomas. Those plasmacytomas behave differently from original myeloma. They are very hard to treat. They behave like metastatic malignancies; very hard to treat and they are very deadly. Concern about secondary cancers I think is there probably more with Revlimid than thalidomide because of the very nature of ways of how Revlimid works and the potency of the drug itself.

There was the one mechanistic presentation and I wish I could remember who the author was right now, but the essential message was that combination of lenalidomide in that thalidomide patient in some ways overcoming the thalidomide resistance. Had you seen that?

The lenalidomide is overcoming the thalidomide resistance? I am not sure about that. I think that is overreaching. I think if you talk about treatment of patients who were treated with thalidomide and then Revlimid, I don't think it is a matter of overcoming resistance. It is a matter of giving much more potent drug to somebody who receives same type of drug with much less activity.

Okay, well bring pomalidomide into our discussion. Is it that much better than Revlimid?
I think it is better. I don’t think it is that much better. I think that at the end it will be probably replacing Revlimid because of the push by industry than the quality of the drug. The activity of the drug I think is good, but activity of Revlimid is excellent. I think that will depend more on commercial issues than scientific issues.

*So once lenalidomide is available as a generic, or will it ever be?*

I think it will be.

*So how is your hospital formulary going to manage specifically that issue?*

With the Revlimid it will be again a problem of who is going to do that with all the paperwork and the RevAssist program and things like that. I am not sure who is going to jump. I don’t know logistically how that will be resolved. So that could be an obstacle to the availability of Revlimid through other sources but Celgene.

*Got it. So I want to move into a large number of clinical development candidates that I saw at the meeting maybe in no specifically order. The first thing that stood out was I have been watching these VANTAGE studies from Merck for quite some time and Novartis I guess has similar studies with the panobinostat for their HDAC inhibitor. First, from a global standpoint maybe these aren’t good enough as monotherapies but…*

I don’t think any of them will be in monotherapy.

*Do they have a role in treatment of multiple myeloma?*

It all will depend how you combine them. I think they do. I think they could find some place but the question is which combination will they fit into. When I look at the combinations I see Velcade really as the main drug in most of the combinations that will be used in multiple myeloma. For some reason because of maybe different mode of action or different mechanism, it looks like it combines well with a lot of other drugs.

*So that is what the Merck study is?*

Right. And that is what the direction will be. The danger in that always is like everything else it is overexposure or overutilization of one drug. So we all were fooled by the initial experience of Velcade which combines really nicely with everything else? And are we now pushing drugs that naturally will not combine? Well, you have to do study and find out.
So can you speak to any of the data that Merck spoke about in terms of VANTAGE? Are you impressed or not?

I think it is too early.

I guess the main program is in combination with bortezomib. But they also had at least one poster looking at vorinostat plus lenalidomide plus dexamethasone.

Right. And vorinostat originally was planned to be combined with Velcade because of presumed alternative proteasome pathway which is called aggresome. So I think vorinostat was introduced as a possible drug that will block aggresome pathway and will allow so proteasome pathway will be blocked completely. The theory is that there was some escape from a proteasome blockage by bortezomib through this aggresome alternative pathway. I think but theoretically it makes sense. I personally think the drug is pretty hard to tolerate.

Because of the gastrointestinal issue with Vorinostat?

Right. So I am not sure that the combination with Revlimid makes scientific sense.

Because it is not completely shutting down that proteasome pathway?

Right. So I am not sure what will be biological based or explanation for that combination.

So that is a shot in the dark?

I think it is a shot in the dark.

So Novartis, what I glean from their discussions as that they have more of this thrombocytopenia problem?

But that will be always. That is always an issue. The mechanism of thrombocytopenia is very important. We have thrombocytopenia with bortezomib which clinically doesn’t really create much of a problem for us because it is not based on the cytotoxic or effect of bortezomib. It is just a problem with the release of thrombocytes or platelets form the megakaryocyte. However, if you have a drug which has a cytotoxic effects on megakaryocytes, then you have a problem because it will produce complications of bleeding and other complications from thrombocytopenia itself.
So does panobinostat fit that latter category?

I think all drugs from that group probably are more toward later than first one but the problem will be how can you combine that with the bortezomib if it produces thrombocytopenia and how to combine with Revlimid which also produces thrombocytopenia.

*Just from a practical standpoint, how far behind is Novartis versus Merck in terms of getting these phase III programs done?*

I don’t have any information that either of them is close to advanced studies.

*Okay. So as I said, there were a ton of new therapeutic approaches.*

A lot of new antibodies and conjugates.

*Right. So let’s take some of them. First, comment on elotuzumab, the CS1 approach, before we get into the conjugates. So what did you think of elotuzumab?*

I am not convinced that it will give us anything new. Having said that I haven’t dug into the details. But just looking at elotuzumab and at the target they are using, CS1, I think what they decided to do is to look at the target that is expressed in myeloma cells. And you know we tried to do that. We tried a long time ago to use CD20s which were expressed in myeloma cells as a target and we didn’t get anything. I am not sure if that is the right approach. I am not sure that they have enough basic information to say that this CS1 is really important for the plasma cells.

*Although if you were to use that as a targeting approach you are at least increasing the local concentration of whatever warhead you are trying to deliver.*

That is true. But we tried to do those things in many other combinations. I am not sure that it is a silver bullet way. What I don’t like in studies like this is that from the beginning, from the phase I, you are combining the drug with something else. What I would like to see is, first, to find out if a single drug as an agent has any activity in myeloma. So the question is now are they trying to use this as a way for delivering lenalidomide or something else into the plasma cells. Or they think that this is a drug that combines well with lenalidomide?

*Yeah, well I think they are looking at using it as combination.*
I never really figured out what the idea was. If you want to combine with lenalidomide then I think you owe to show activity of the single drug first and then try to combine with others. So that is why I am a little bit uneasy with this combination. I like more what Usher did with the lorvotuzumab when he used it as a monotherapy, the anti-CD56. It is a drug conjugate. That will give you an answer of yes or no. We have activity, we can do something with this drug or it is a completely useless drug.

*Yeah, I really liked that.*

This drug, at least what I like, and I think Usher and other guys were doing the right thing, is let’s find first activity as a monotherapy or in parallel we can combine with others and see if we have any activity. I think this is the right way to go.

*There were a lot of CD38s and CD138s.*

Oh yeah. I think those make sense. I think if you want to target really then you target something that is specific or at least very present on plasma cells. How effective those monoclonal drugs will be is always a big question. But at least logically I think it makes sense. And maybe some of those, some will show to be effective, some maybe will show to be a new Rituxan or Zevalin or some of those combinations.

*So all of these therapies I can’t picture how they are ever going to displace the proteasome inhibitor-based therapies on the one side or the IMiDs on the other side.*

They will not. These new monoclonal antibodies I think are possible additional drugs in combination, unless we see single drug that has at least activity as bortezomib did as a single agent. I think they could be potentially useful tool, useful addition to standard treatment. And maybe some of them will help in the sense that they will remove a need for chemotherapy. And now combination of bortezomib/Revlimid/dexamethasone is a very potent combination which it seems to displace chemotherapy from the treatment for myeloma. I see a role for this new monoclonal treatment in this way to really work as adjunct to present treatment and removing a need for chemotherapy or transplant.

*Two final quick questions. Anything interesting on the HSP90 front?*

I never believed in that. I don’t see anything new. I just didn’t believe in the theory.

*Final question. I am dealing with as an auxiliary issue to some of the oncology discussions the question of how big of a problem is venous thrombosis in your patients and how do you currently manage either the prevention or the treatment?*
It is a big problem because it really interferes with quality of life. It interferes with the treatment. It actually also is a cost problem because those episodes cost society a lot. So it is a big problem. And it is becoming more and more of a problem in oncology.

*We just had a direct thrombin inhibitor, Pradaxa, dabigatran, approved in the US for SPAF and I saw just today Xarelto, which is rivaroxaban, was filed also for SPAF. Are you using any of these newer agents versus warfarin yet?*

I am not because they are not approved.

*For DVT?*

I would. Warfarin is taking a lot of our time. It is very time consuming and it is very cumbersome. Patients are waiting for a replacement to warfarin for years. I think the FDA needs to really react relatively fast if there is strong data. And there is strong data when you look at the *NEJM*. I look at all those things and there is very strong data and I think they should approve as soon as possible. I think it is a big deal in the oncology practice.

*Very good. I want to thank you very much for sharing your thoughts.*

You are welcome.
Interview OHIID02535

Interview Topics

Multiple Myeloma

Physician Demographics
TL # 10638
Specialty: Hematology
Geography: Torino, IT
Interview date = 01/18/2011

Interview Transcript

It is really a pleasure to get to chat with you in person. I see many of your discussions at ASH and ASCO and it is really nice to add you to our international panel. What I want to do is take about 10 minutes to talk about carfilzomib and pomalidomide in relation to bortezomib and lenalidomide, of course. And then I want to speak about some of the newer agents that were discussed at the most recent ASH meeting and get our sense of how they are going to fit into therapy. Finally, at the end I would like to talk about some much more upstream molecules that I saw going through the meeting and get your sense of those as well. With that said, when you think about everything that we know about carfilzomib at this point how does that fit into a world that has bortezomib so well established?

There are two major issues related to carfilzomib. One is the difference in the safety profile. So from this point of view the lack of peripheral neuropathy is the major safety difference with Velcade. Also, a better hematologic toxicity in comparison to bortezomib is a major safety difference from bortezomib.

Will that still be the case when bortezomib is used in a once weekly regimen?

We don't know yet. These data are not released from this point of view. So generally speaking I think if you want a picture of the drug one issue is certainly much better safety profile and the other issue is probably the opportunity to increase the dose since we do have such a good safety profile. This could probably increase also the efficacy of the carfilzomib. If you want to make a picture of the situation the conclusion is there is proven better safety profile of this drug. We might see in the future, but this is a question mark and it is data to be validated, but it could also have some increase in efficacy because we might have the opportunity to increase the dose that we have been seeing until now.
Some panelists before you commented to me that they felt that the progression free survival time that was reported for carfilzomib, it was under four months, and they said that was a bit of a weakness and it raises some concerns about the durability.

This is not actually a correct statement because, first of all, the PFS is around eight months and four months is just taking in consideration patients who didn’t have a significant response to the immediate stop of the drug. So generally speaking to some extent I would probably question the opposite issue in the sense that probably the PFS looks quite convincing. Eight months seem to be a very good PFS data and the opportunity to use it for let’s say a sort of maintenance approach would probably improve those data. I wouldn’t be that concerned about this statement of four months due to early discontinuation of the drug.

That is very helpful. And you are bringing up the maintenance concept. I am not sure you want to start talking about maintenance until we talk about lenalidomide first. So let’s hold off the maintenance for a moment. Do you see carfilzomib having a profile that can realistically push bortezomib out of a first line proteasome position?

Maybe it is not clear to me, but you seem to be confusing two different issues here. One issue is maintenance. As maintenance is concerned carfilzomib is better tolerated than bortezomib. So it is a plus in terms of maintenance, both as an IV route of administration and this is a minus in comparison to lenalidomide or other IMiD compounds. If we are talking about first line treatment, let’s say from a marketing point of view this is exactly the issue. The issue is if carfilzomib will prove to be superior in terms of efficacy towards bortezomib at this point the answer is yes. So you will see carfilzomib taking over bortezomib. To some extent as lenalidomide is taking over thalidomide. If the efficacy will not be significantly different from bortezomib, at that point for cost reasons we will make carfilzomib still present on the market because anyway you would always try a different compound before saying there is nothing else to do. But generally speaking this will not substitute bortezomib. So carfilzomib will have a niche. I think generally speaking there is no question that carfilzomib will have a niche in the market. If it will be a big one at that point it needs to be a significant increase in efficacy over bortezomib.

Given everything that we have seen as next generation products – and let me give you an example – Merck was talking about the VANTAGE study looking at the combination of vorinostat plus bortezomib in patients who either didn’t have a complete response to bortezomib or many of those patients will be bortezomib treated. If you have a patient who are in a first line regimen that contains bortezomib if they give you an inadequate response are you more likely to try a different proteasome or are you going to be more likely to try one of these other combinations, for example and HDAC plus bortezomib?
Not easy to answer because I don’t know. Generally speaking my impression is that I do not see many physicians changing treatment because they did not reach a CR. If you reach a response rate you are happy of that and basically you keep going even though a PR rate is not the maximum expectation you might have. I do see much more room in a situation where an unmet medical need where you have progressive disease. Your patient is not going anywhere. You are trying to get some kind of response but you do not reach any kind of response. At that point you are willing to add another agent. I think these are the market niches certainly present for HDAC inhibitors, and to some extent at the same time are present for carfilzomib. Carfilzomib should have a better market niche from this point of view because generally speaking can be a substitute to the bortezomib. So from this point of view you might have the broader thinking of using a different regimen. Let’s say I have a second relapse of bortezomib, giving minimal response, I am not going anywhere, I might change to a carfilzomib combination. But to be honest, I do see the use of this drug in this setting.

Very good. So let me turn towards the IMiDs. Celgene has to me a very interesting commercial situation in that they own both molecule; lenalidomide and pomalidomide.

And thalidomide.

And thalidomide. Good. You know the lenalidomide story better than or as well as anybody on my panel. I am interested in what is happening with lenalidomide but I am really interested in your assessment of the role of pomalidomide in a world that has so much lenalidomide data available.

You know Celgene is trying to give a role to pomalidomide as basically third, so another agent in patients resistant to lenalidomide. This is the role of pomalidomide. Pomalidomide is a little bit more effective than lenalidomide. That has some other side effects like hematologic toxicity. But I think what will be very much the use of pomalidomide will be, again, in those kind of niche that we were talking about before for carfilzomib and HDAC inhibitor. This would be the perfect agent to use if you want something or in condition where lenalidomide is already completely resistant. Probably with time pomalidomide will move earlier on. Honestly speaking, I am not looking also at the data. Some people are saying, well, pomalidomide is completely different. In my opinion if you look at the efficacy lenalidomide stays at thalidomide as pomalidomide stays at lenalidomide. So every time you increase the efficacy a little bit with the novel agent but you are not really changing the world because you are not doubling the CR rate where basically increase of 15 to 20 percent, a response rate with the newer agent. So the efficacy is not changing the world. It is better, but it is not dramatically better and that this is the perfect agent and I think Celgene will do everything possibly to position that agent in that respect. It is the perfect agent to use in lenalidomide resistant patient.
You mentioned something a little while back that intrigues me. I have many hematology friends here in the US in community practices. They say to me if the agents have about the same efficacy they are likely to choose a product that they can infuse because they are getting paid to do that and Medicare pays for that as well unlike oral medications where there is much more patient responsibility. Is that just an American thing?

Yes. Absolutely, yes.

What is the world like in Italy?

No because here to some extent is completely the opposite. Here everything is public and I am talking about Europe generally speaking. There is no need to make X drug extra procedures to increase your income. Here the fewer procedures you do the less expensive it is on your public system and the more everybody is happy. So from the European point of view things are completely different. If you have something that is oral you can take the hospital care out and your patient is costing less. This is a major plus from an economical point of view for all of Europe. To this point, lenalidomide was immediately approved by NICE and bortezomib was not. Bortezomib was approved by NICE with the limitation of only paying for patients with responses. So this is a very peculiar situation of private practice where the more you do the more is your rank income, so you try to do as much as you can in order to increase your income. On the other side it is also very true for the general market that more simple and stupid the more its welcome, especially in the community hospital setting for both Europe and in the US. In other words, when you are in a highly specialized center with many myeloma patients and there is a lot of expertise side effects are not a problem. When you start to go into the smaller community type facilities with fewer melanoma patients safety becomes a much more important concern than efficacy. In that respect a drug with a better safety profile even with a little bit less of efficacy will be certainly chosen.

Which side effect is more concerning to you; an impact on platelets or an impact on neuropathy or an impact on gastrointestinal side effects?

You see if you reason from point of view of let's say a general oncologist’s major concern is on the acute side effect, so thrombocytopenia and GI, things that may create a major issue on Friday, Saturday and Sunday. Peripheral neuropathy to that respect is less important because you can always postpone until Monday. From my personally experience I do see this, but it is a psychological issue. You would prefer to have something that is not creating too much trouble. As a general oncologist that faces a hundred different diseases it is not easy. So you do prefer something that is not creating trouble. From this respect VD, RD, TD are popular and it is basically for those safety considerations.
Very helpful. One of the panelists before you made a comment about the HDAC combinations and he said to me that he thought that the combination of vorinostat looked better with lenalidomide than vorinostat plus bortezomib, and he said, but if you took panobinostat that looks better combined with bortezomib. So he was saying combine vorinostat with lenalidomide and panobinostat with bortezomib. Can you comment on that?

Yeah, these are certainly the data presented at ASH. Generally speaking is true, but I didn't make too much of this. These are small cohorts of patients when you start to see two different court of patients in one phase II studies ten percent PR than in the other it is very difference to say that A is superior to B. It is not randomized. It is a simple size. Relapsed patients have different disease features. So it is very difficult to say. Generally speaking it is true that lenalidomide seems to be more effective with vorinostat and bortezomib with LBH. But if I have to make comment between the two drugs I would pay much more attention, honestly speaking, to the safety profile. And from this point of view vorinostat seems to be better than LBH.

Because you would prefer to have the GI toxicity versus the thrombocytopenia?

Yeah. But in our experience it seems more feasible the use of vorinostat. It seems sometimes a little bit troublesome, the use of LBH. I don’t have any general data. This is just personal experience of what we do in our clinic.

Do you have a sense of which therapy is more likely to be available first? Are they on the same sort of timing or is one or the other out ahead?

As far as I know, vorinostat is almost going to the end of the phase III studies while the LBH is not at that stage. So vorinostat looks to be much early on the LBH.

So is LBH in phase III trial yet?

I am not aware of this honestly speaking because I know if the phase II. If they are, they are really at the beginning of the phase III.

Okay. I want to turn your attention toward some of the new molecules I saw at the meeting. Elotuzumab I list as a new molecule and obviously that is moving along quite rapidly. I saw the, I think it was the Monday evening session that Paul Richardson did talking about elotuzumab. He seemed really enthusiastic about it. I don’t know if I should be as enthusiastic or not. That is why I am asking you your impression of that molecule?

Paul Richardson is always enthusiastic. He is an enthusiastic person. But besides this, I think the fair comment is elotuzumab is very, very interesting. Elotuzumab single agent no
activity or let’s say very small activity. Elotuzumab with lenalidomide extraordinary good activity. Elotuzumab with bortezomib average activity. So here I think if you see the difference of response, elotuzumab plus lenalidomide is extraordinarily higher in comparison to elotuzumab plus bortezomib. And the old limitation we were seeing before different studies, relapsed patient, if this is characteristic, the difference is really extraordinary because when you move from 50 to 90 percent PR rate you are almost doubling. This is not the 10 or 15 percent difference in response rate you might see between vorinostat and LBH. So from this point of view with all the limitations of the phase II study the difference seems really, really quite important. There is a question mark. The question mark is to some extent you might have some bias by patient selection. These studies are not big. They are under 50 patients. So there could be major bias in that you might by chance to have a good prognosis patient. But if you do not have a major bias in those studies the signal is the same seems pretty important. I would be quite enthusiastic on the drug. If, again, you don’t have a bias around but done by the fact that in 40 patients you might have a selection of good prognosis patients or whatever.

And this is going to be the same for any of the molecules we talk about now because they are not in randomized large scale trials. So there is a bit of guess work and that is fine.

What is important to stress on elotuzumab is that when you see all the other agents you are playing games with different in 15 to 20 percent rate of response. Here you have a difference of almost 50 percent. This is something you usually do not see. Let’s put it this way.

Okay. What about daratumumab, the CD38 from Genmab? I kind of like that.

Theoretically, we are now talking about a situation where basically there is, honestly speaking, no answer. Basically from your list of compounds, we do have very good preclinical data, very good theoretical mechanism of action, but no clinical data.

Fair enough.

As you know, preclinical data might become quite opposite in the clinic. So if you want to ask me do you think this is something that is going to move on my comment is that those drugs have, as you said, an excellent mechanism of action and excellent preclinical data. I did not see at present any clinical data to make a judgment. It is not like elotuzumab where you have phase II studies with a 90 percent PR. I need to see something like that before say we might have something with a high chance to hit the market.

I want to take the last couple of minutes and ask a question about your real world clinical practice. I also run an anticoagulant thought leader panel and here in the US we finally have
the first of these new oral anticoagulants available as warfarin replacements or as low molecular weight heparin replacements. What is the oncologist’s perspective about the risk of thrombosis? How familiar are you with the direct thrombin inhibitors like dabigatran or the factor Xa inhibitors like rivaroxaban or apixaban?

I think we will come along. This is really a personal opinion. I don’t have a lot of data. I think they will certainly represent a major replacement of warfarin. They could certainly have a major role in cancer patients. I don’t know why at present but those companies are very much concentrating in hip replacement and not very concentrated, as far as I can tell, in some niche disease like myeloma. So we would try to have some experience in this but they were pretty much reluctant.

That is because they are so afraid that there is going to be a higher bleeding (or mortality) rate in the cancer patients. I think that is why they are so afraid of putting their drugs into the oncology patients.

I can see the issue but I think there is a major marketing issue more than really a scientific issue.

What do you mean by a major marketing issue?

At present they want to go into the major anticoagulation market. This was my impression. Now they want surgery, general surgery, and general medicine. This is where they are concentrating the effort to hit the market. Then when it will be established in that situation they will try to open up in other niche situations by myeloma or cancer.

For 100 myeloma patients who you treat what percentage of those patients do you have on anticoagulant therapy?

You see myeloma is very peculiar because if you use IMiDs 100 percent of them. But again, we are in an old fashioned use of anticoagulation. We are mainly using heparin and low molecular weight when we do have a high risk patient. I don’t know if this is another reason. But basically with IMiDs I have, let’s say, 100 percent of patients with bortezomib probably none of them.

What if I had asked you the question for the hematology community as a whole would you venture a guess as to what percentage of patients are on an anticoagulant?

Not many. Probably more in the US. Here, not many. But the risk of DVT is not low because at least 10% patients with cancer do have a DVT. But generally speaking I do see in the practice the use of anticoagulation if you have a high risk of thrombosis. Otherwise I
really do not see them use a lot of anticoagulation. You would say 10 percent DVT everybody on anticoagulation. It really is not working this way at least in Italy. We do use anticoagulation when there is high risk of that otherwise we try to skip it.

Very good. I want to thank you very much. For me it was a very enlightening discussion and it is really a pleasure to add you to our panel.
Interview OHIID02537

Interview Topics
Multiple Myeloma

Physician Demographics
TL # 10639
Specialty: Hematology
Geography: Scottsdale, AZ
Interview date = 01/25/2011

Interview Transcript

I am very familiar with the field so speak as freely as you wish. Let me just say I am really interested especially from the translational side, many of our panelists focus a lot about drugs we have had around for a long time but one of the premises that I am coming into our discussion today with is if I compare myeloma to NSCLC, for example, non-small cell, we are targeting EGFR and EML4-ALK. These are very targeted therapeutic approaches. I feel like myeloma may just be on the cusp of getting to that, but not there yet.

Yeah, we are not that close, but we will get into it I guess. The only one we are going to have a targeted therapy for is FGFR3 subset. Whether that will even work or not we don’t know yet. We have some trials open and addressing it now, but other than that we are still kind of shooting in the dark a little bit.

Ten years ago if I had said to you what is expected survival for standard risk and expected survival for a high risk myeloma patient compare that to today. Just quickly what sort of progress have we made?

I suspect we have doubled survival for all standard risk groups. I think ten years ago in 2002 if you were elderly I think you had a three to four year survival and if you were younger you had a five to six year survival. I think certainly for the lower risk groups we are probably double that for both groups. It is probably six years for elderly and ten years for younger. In the high risk myeloma I don’t think we have made a lot of impact frankly one way or the other.

So is the underlying reason for the high risk having to do with these mutations that have really not yet been identified as the key drivers?
The key drivers of high risk disease, that is true. We know the genetic subtypes that are high risk, of course, but we haven’t narrowed down to specific mutations or mechanisms that we understand well enough to be able to target yet. The whole genome sequencing has been disappointing in some ways because it hasn’t after some 40-odd myeloma genomes we know now, we still haven’t pinpointed a specific reproducible common mutation that we can go after with targeting. I mean they did find that the genome’s RAF was mutated in 10 percent of patients. So that is something that hasn’t been explored yet. The high risk are clearly genomically unstable. They clearly relapse quickly after any therapy, even the most aggressive therapy out there - TT3 they still do badly. If you are a nihilist you would say treat them with something fairly minimalist because nothing works and you are going to put them through a lot for no reason. So those are the problems we have. I think what has changed in the last ten years is we are much better able to predict the high and the low risk groups and, again, to segregate them into different patient populations and clearly the low risk group do well. I mean you see those folks and you feel pretty comfortable telling them, listen that don’t fret, but what kind of therapy you are going to get you are probably going to live a long time no matter what we do. With the high risk people you secretly worry without telling the patient that this isn’t going to be good no matter what you do. I think that is where we are today.

The poster I saw at ASH from Signal Genetics on their myeloma prognostic risk signature how applicable is that to the community physician right now? What sort of decisions are they going to do differently in terms of either induction or whether they use maintenance or not after transplant? What is the value of having this prognostic risk signature?

I think the main value is prognostic at this point. The main value is you are going to know through that test more than any other that we offer whether your patient is high or truly low risk and will therefore be more reassuring for those who are low risk. I think in academia it would change thinking about how to manage the disease. I don’t think the community is really mature enough now that they would take that information and necessarily change what they do based on it, but it is probably the single most effective test at telling whether your patient is high or low risk at the outset. I personally am supportive the test because I think it is good for the patient and the physician to know going forward whether they are high or low risk. But, I am sure there will be many folks you speak to that say we don’t see the value there yet in terms of whether we will change our treatment or not.

So until it can point you to a treatment...

For us it changed our treatment. We go, you know what, you are high risk we can’t do hit-and run-therapy. We can’t treat you for four months and then give you a transplant and then stop because there is no way in heck that you are going to live a long time if that is all we do. You are going to have to go on Velcade and Revlimid and we are going to have to
keep you on as long as we possibly can if we have any chance of overcoming this. But I don’t know that the community is thinking those ways still at this time.

Okay. You made an interesting comment to me in terms of FGFR3. I want to make sure I understood what I think you said: that this was the one therapeutic target that stands out.

So it is the only one where we know there is a kinase involved and there is a mutation involved in some patients; therefore, a kinase inhibitor or cell surface antibody-based therapy. There are two trials open, which I think are public and I don’t think it is a secret, they are open as well and known publicly. One is with Novartis small molecule tyrosine kinase inhibitor, dovitinib, and the other one is with Genentech’s monoclonal antibody. Those are the only truly targeted therapies. I mean you brought the example of EGFR and NSCLC. That kind of specificity, those are the only targeted therapies being employed. But whether they work or not is a completely open question because these are initiating genetic events that presumably at some point may be supplanted by subsequent change in the genome that makes them less important over time. So whether you can still turn that off and affect the tumor overall it is much more akin to the EGFR story. You are never going to respond to these drugs if you don’t have kinase over-amplification but even when you have it you may still not respond. That is what we will learn from these trials if there is any credence to the hypothesis if this is still a driver that will be switched off.

So that is an interesting train of thought as well. So let’s go to the EGFR in non-small cell analogy for a moment. So you can be an EGFR overexpresser but not respond to Tarceva. So as I talk to the myeloma panelists, in particular I was asking questions about this anti-CD56 molecule I saw from ImmunoGen at the meeting. And people say to me, so clearly myeloma is overexpressing CD56. But this drug itself – I guess most people I have spoken to weren’t absolutely thrilled about the data that they saw. So here we have myeloma cells over-expressing, but that is not necessarily translating into a therapeutic target.

Well plasma cells make CD56 and CD38 and CD138. I guess the question is whether a monoclonal antibody directed against those targets will be cytotoxic or not. I don’t think anybody has come along with an antibody yet and said here if we use our naked antibody, or even immunoconjugate antibody and we bind these cell surface receptors in a patient that myeloma goes away. That is the problem. A lot of those trials are very immature. They are just starting now: CD56, CD38, CD138; these are all cell surface antibodies that are good targets for that kind of therapy. It is just that nobody has shown clinically that they are active yet. We have a trial right now we just opened with an anti-CD38 antibody because we think it is worth exploring. But whether these will activate VDCC or be directly cytotoxic or just do nothing we can’t tell. Elotuzumab is another example. So elotuzumab targets a cell surface receptor that is way over expressed in myeloma in other tissues.

CS1.
CS1. And yet the single agent activity is dismal, I mean it is zero. So are you excited about that? Well, maybe. When you give it with Revlimid there is a very high response rate. They have 95 percent, but it is 20 patients and are we joining the BMS phase III trials? No, we are not. We don’t think the evidence is all that compelling right now that this is an active drug.

Is that because it was such a small trial?

Because on its own it doesn’t do anything and then the 95 percent response rate is in 20 patients. So one or two either way it becomes 60 percent and it doesn’t look very different from Revlimid alone. So I guess we weren’t convinced. I hope it does work, but I guess we weren’t convinced enough to throw our eggs in the basket yet. Although I must say with that one we were intrigued. I think that 95 percent is intriguing. I wouldn’t say we are not joining because we have no faith in the drug. So we are intrigued by it and we are looking forward to seeing the result but it is somewhat disconcerting. With Velcade it doesn’t do anything. On its own it doesn’t do anything. There are some theoretical reasons that Revlimid might work. It might upregulate cell surface receptors and things like that. So potentially they are synergistic. On its own it doesn’t look like it is all that active.

Although the comment that other panelists made to me was that normally when you take lenalidomide – and my recollection is that these were lenalidomide-naïve patients – so normally if you give lenalidomide plus anything else as the doublet you may expect a 50 percent increase over the response you would have originally gotten from lenalidomide itself.

The lenalidomide/dexamethasone randomized phase III trial in lenalidomide-naïve patients had a 65 to 68 percent response rate. So 20 patients, what is that, that is 14 out of 20, something like that you would expect just with the drugs alone. And they are saying, hey we have got 18 out of 20 or 19 out of 20. It is a lot of faith to put in one or two patients swaying it. I guess I am being Scottish here and taking the negative viewpoint, which is that I have yet to see a drug with no single agent activity become suddenly a big success in patients. But we will see. I guess I am in the doubt that is going to work camp for that one. If I were BMS I wouldn’t be investing in a phase III trial right now. I don’t really understand why some of these companies are making these huge investments in drugs without doing some smaller phase II type of randomized pilot studies to figure out if it is real or not.

So let me turn you to the HDAC inhibitors.

Same story. Same story. I think of all the people you talk to my sense is that I am one of the least positive people about those. I again don’t see much evidence that they are active. I don’t see much evidence that they have single agent activity or even necessarily combination activities. I am a bit more encouraged by the recent panobinostat data. I don’t
think vorinostat showed me anything that I would be excited about. But I have colleagues that swear blind it works in some of their patients. Panobinostat, the same thing; I am more encouraged recently that they had a 70 percent response rate at the MDV with Velcade is encouraging. But Velcade and dexamethasone alone is 50 percent and it is not that far off statistically. My guess is those drugs have a modest effect. We do some activity of them in our mouse model which we think is quite predictive. My guess is they have some effect but it is not a dramatic one. The differences will be subtle and the side effects are not insignificant. I guess again I would be a little bit surprised if they end up being major drugs in myeloma. But you know I hope I am proved wrong.

Who the patient is that might see Velcade or Revlimid first line?

I think it is very mixed as you have probably ascertained. I do think the majority of people would favor using Velcade in newly diagnosed patients. I do think that many people are choosing to go with the combination of Velcade and Revlimid, certainly in the United States. Outside of the United States that is a very difficult economic proposition and I think Velcade is probably the favorite. I don’t know if the marketing backs it up or not but that is my sense. So Velcade I think has still got a dominant hold on the popular imagination for newly diagnosed patients. Then there is certainly a lot of Revlimid use as well, particularly in countries like the US where you can get both together.

You had mentioned RAF way back. Should I be extrapolating that to MEK and AKT?

All I said was in the genome sequencing that 8 percent of patients have a RAF mutation. Now the PI3 kinase/AKT inhibitors, I think we are just beginning to learn a little bit about them now. I do think there is likely to be some evidence of activity there but we just don’t have enough clinical data yet to really know for sure. Perifosine I have not been that impressed by, but there are other companies with other drugs that I think might show a little bit more promise. That is a space we certainly can do more clinical trials in and investigate.

I guess the last drug class I want to touch on that I have been seeing at myeloma meetings for many years have been these HSP90 inhibitors. There used to be a lot of toxicity associated with the regimens.

I don’t think they work.

Okay.

I keep it simple. I mean Kosan, tanespimycin (KOS-953) which is BMS now – as far as I know because I haven’t been involved with the trials – but what I have seen and heard it
sounds as if that has been halted. Other companies have them in trials but I haven’t heard anything publicly from anybody that suggests that they have good activity at this point. I think that there are a lot of these classes of drugs out there. Unfortunately, there is not really great support that any of them are dramatically active other than carfilzomib and pomalidomide. I mean there are some things that I know work in a few patients that we have in trials that aren’t public yet. I think may offer a little bit more promise than the ones we have talked about but they are still sort of an early stage testing and miles and miles away from commercial application.

*Final question and this is totally tangential from where our discussion has been. I also run an anticoagulants panel and those are guys are just bringing forward these new oral anticoagulants.*

I got an e-mail just the other day asking us to join a trial in myeloma with one of the oral anticoagulants.

*So what is your current perspective on these drugs?*

I think it would be awesome to have them. I mean I honestly think we are just a bit lazy as oncologists. We put people on Revlimid and thalidomide and we know they have got 10 percent DVT rate, we are just too lazy to monitor Coumadin on all of them. There is obviously the risk/benefit profile too, but I think if we had an oral drug that didn’t require monitoring and you could put people on I think we would all sleep better at night thinking about our patients on Revlimid and thalidomide. I say bring them on is my opinion about that.

*What would you venture is…?*

Our market for those is so small compared to what they are really going to do.

*What percentage of cancer patients in your opinion should be on any sort of anticoagulation?*

I think it is probably pretty high. In myeloma the DVT rate is 10 percent. I am not sure what it is in other tumors, but I think it is probably as high or higher in many other solid tumor types. So I suspect there are a lot of cancer patients out there if you have a non-monitoring, non-injectable oral anticoagulant, I think it would be quite a good market for that.

*But is the reason that you use them associated with drug toxicity? In other words, is it the IMiD that is raising that risk?*
Yeah, without the IMiDs, the risk is lowered to 3 or 4 percent. It is not very high. So it is the IMiDs that is raising it. But in the solid tumor sphere it is, again, I don’t know the facts and figures, but there is a fairly high DVT rate in some malignancies I believe. But that is not my area of expertise. I am guessing. But something like pancreatic cancer, for example, I would think there might be some uptake of that.

Okay. I know my time is up. I want to thank you very much. This has been a fantastic first discussion. Will you be at AACR in Orlando?

I am not going to AACR this year. I will be at ASCO.

So hopefully if our paths don’t cross before then I would love to stop by at ASCO and say hello.

Sure or see you on the airplane.
Interview OHIID02538

Interview Topics

Multiple Myeloma

Physician Demographics
TL # 10640
Specialty: Hematology
Geography: Würzburg, GER
Interview date = 01/28/2011

Interview Transcript

Welcome to our Hematology Oncology Thought Leader Panel. What I want to do today, since I've already spoken to several multiple myeloma thought leaders at this point, is bring to you the issues where there was some wiggle room and have you offer your thoughts. I saw a poster at ASH that was yours actually. So that is really where I want to start the discussion. We are very interested in understanding how lenalidomide is pushing into first line, so who are the patients and what combinations will synergize best. As I think about the next generation products, like HDAC inhibitors for example, being coupled up with lenalidomide what are some of the issues that we are going to be facing? So how do you view lenalidomide coming into the first line? What are the indications and what are the contraindications for moving forward?

What we actually see when we are combining lenalidomide with dexamethasone and adriamycin, although not much, but we have seen patients with thromboembolic events. We started with using a continuous infusion of adriamycin. We have now switched to push infusion. Currently we are doing four times in 24 hours. So we see some thromboembolic events. None are really life threatening. Most are actually associated with indwelling catheters. But this is what we see. I think that is a specific adverse effect. So if we have the chance to figure out patients who are at high risk for VTE, they should preferably be excluded from the Revlimid/doxorubicin combination. On the other hand, we do not see any neuropathy. I think currently we do not get any very promising remission in myeloma without seeing specific adverse effects. But I think that they can be managed. In our hands thromboembolism associated with Rev is less severe than the neuropathy that we saw with bortezomib/cyclophosphamide/dexamethasone combination. So I think Revlimid has a place in first line therapy and is not fully understood whether we need additional drug in addition to dex. But we think that remission quality with adding a third drug, a conventional chemotherapy, might be better than seeing Rev/dex alone.
Just to clarify, are these patients being prepared for transplant?

Absolutely. But let's do this the other way around. So more or less an allo study, but we have a risk stratification of doing it in very favorable vs. less favorable. So we do not want to transplant patients who will be doing very well even with tandem transplant. But all patients receive one unique high-dose melphalan (Alkeran) and then either Auto/Allo or second high-dose melphalan. Yes, all patients go to transplant.

Second follow up question. The issue of anticoagulation particularly in the patients who were given IMiDs was highlighted to me by a number of the panelists before you. I am very interested in some of the new oral anticoagulants. I know Pradaxa, dabigatran, just launched here in the US and I am sure that is available in Europe as well. There are factor Xas coming along. So comment from the standpoint of hematology in general and then help me understand if these myeloma patients are more at risk for the DVTs that you focused on or is it simply because of the use of IMiDs?

The first answer is that we are using low molecular weight heparin throughout all patients. I personally have no experience with some with the upcoming novel oral drugs. Second, patients with myeloma have an inherently high risk of DVT compared to non-myeloma patients and even higher than in solid cancers, lets say except prostate and pancreatic. Third, we are administering anticoagulants to all subjects who have at least one specific risk factor as outlined in the leukemia paper by Palumbo two years ago.

Okay very good. If I wanted to look at the dynamic of lenalidomide from the medical standpoint, on the one hand, and a commercial stand point on the other hand, and I wanted to bring in what Celgene is doing with pomalidomide, everything that I see Celgene doing is holding pomalidomide back for salvage in these lenalidomide incomplete responders or failures or some other reason. Is there a medical reason for that is that simply because it is best from a company position?

I am currently treating two patients with Pom/adromycine/dex and I can see that tolerability is really excellent. They do not have any of these adverse effects that are associated with Len. No neurotoxicity, no hematoxicity and no fatigue. So it is really outstanding how those patients are doing who are receive P/A/D. So I think there is no real medical reason for holding Pom for the majority of myeloma subjects. I think if we look into the upfront data that was presented it was really very interesting. And it should be continued to be further developed. But I think it will not happen as long as lenalidomide has any success in the earlier lines of treatment.

When I was at ASH there were countless new therapies that are being developed to combine with lenalidomide. Of everything that you saw put into the public domain, did anything catch
you interest from either a synergistic mechanism standpoint or a tolerability standpoint? For any reason that you can see does anything stand out in your mind as something that is going to fit well in a lenalidomide regimen?

I think what is really interesting to see is elotuzumab combination from the Richardson data actually. While there is one important caveat, that prior lenalidomide treated patients were excluded. So the data looks pretty much okay. Overall response rate was some 80% and some 30% at least with some partial response. They were not really heavily pretreated. Less than 50% were bortezomib and around 50% thalidomide. But what is appealing regarding this particular combination is that it is free of genotoxic drugs. So we have a first combination of antibody plus IMiD plus dexamethasone. I think that this is quite appealing. But the real efficacy cannot be determined by this small study not including real subjects certainly who have not received Len before. Around about 50% of either bortezomib or thalidomide is nothing. Then next is the carfilzomib/Rev/dex combination in the upfront setting. That is again quite interesting and is more or less a copy from the V/R/D data seeing some 100% overall response. Encouraging depth of response regarding very good partial and better. So I think that these are two studies that are quite appealing. But you cannot draw any definite conclusions from those small studies.

Let me come back to the elotuzumab data first. I was at Paul’s presentation and this was the first time I was seeing it. So from an outsider that looked amazing. I think about what I would normally expect to see when adding a drug onto lenalidomide-naïve patients and it is something like 15% response. So if I expect a 60% response from Len-naïve patients upfront and you add a doublet upfront maybe you could expect to see 70% or something like that. So when they showed 90% response in those patients that seemed to me to be very good. So I start to speak to my other panel members and I am all excited. But they say Jeff that was 20 patients. One patient here or there and it is no different. So how should I temper my enthusiasm? I mean you seem pretty encouraged as well.

Yeah absolutely. I think the first point is about patient selection and the second point is really about durability. We are currently facing very high response rates, but nonetheless we have not seen any breakthroughs. So if you go back a decade, when we did not have any of the novel agents, not at all in first line, we had some between 30-36 months PFS in the first line setting. We now employ one or two novel agents and we come up to 40 months or so. I think it is not really the question of depth of response, but how are we able to prolong events. So relapse, deaths from myeloma, development of extramedullary lesions and so on. So I think depth of response is okay and is amazing to see how the figures rise, but we don’t have a translation into significant longer treatment-free intervals.

You mentioned the carfilzomib equivalent to the V/A/D trial. What sort of PFS are we seeing the C/A/D trial and does it meet what you are looking for in terms of improvement the bortezomib regimen? Where I am going with that is, what is an improvement in durability of
response that is going to impress you and are you starting to see that with carfilzomib based regimens?

I think if we have prospective data indicating an extension of lets say 15 or 18 months this would be impressive. So patients would be benefited in the terms that they enjoy longer PFS and would not need ongoing treatment, be it consolidation or maintenance. So it is quality of life and being out of hospital. So lets say 15-18 months up would be excellent.

*Is that realistic with carfilzomib?*

I don't know. I think we have to wait for mature data either in the relapse setting as well as first line.

*So one of the other topics that other panelists have talked about is the use of targeted therapy. Other panelists have said that the other real kinase inhibitor that has shown active in myeloma are some of the FGFR3 approaches. What is the prevalence of FGF in myeloma? Is that a worthwhile target or is that simply an observation?*

It is about 10%. So we are doing some lab experiments in cell lines as well as patient derived samples. My perception is that we are currently facing a real breakthrough. I think that this may add to some 10% of all myeloma patients, maybe, but again I think that it is too early to conclude that this is a really important target. It is quite interesting to see that the more targeted the approach is in myeloma the lesser is the single agent activity. So the success of the IMiDs and the proteasome inhibitors is because I think they are not really targeted. In contrast, they are targeting several cancer promoting pathways.

*That is a very consistent message with what many of your colleagues have said.*

I think that if we really would see that targeting one special pathway is worthwhile do this would be promising and would of course move the field forward and going more into depth to elucidate that there is some myelomas being AKT dependent or RAS/RAF dependent. But I think that translation from basic knowledge to real working drugs is still far ahead of us.

*I'm changing gears here a little bit. I want to bring the concept of vaccine approaches into the treatment of myeloma. What is the most attractive vaccine-based approach and how do you think ultimately such a technology would fit into therapy?*

To be honest I'm not really aware of any vaccination data in myeloma that has entered large scale clinical trials. I am only aware of the indolent lymphoma, but myeloma – no good idea about it.
There were a couple of antibodies that were used as delivery-free vehicles for cytotoxic agents, so these antibody drug conjugates. There was a poster with I think the drug was called lorvotuzumab. It was an anti-CD56. They have maybe a maytansinoid or something like that hooked onto the end of it. How attractive of a concept is that for myeloma?

We have about some 50% of myelomas expressing CD56. And CD56 expression is correlated with an adverse prognosis. Some of our colleagues in our department of pathology here have done this work. I think this really something where a patients could be benefited by such an approach since they have an adverse prognosis. And it is a substantial number of patients who could get the beneficial effects. 50% is more if we get back to the FGFR3 story of 10%. What we have actually done, it was not really antibody coupled but it was bone-seeking radiopharmaceuticals. So it was a similar approach. I think bringing such meaningful drug into bone marrow compartment may be really helpful to overcoming drug resistance and to get myeloablation before an Allo or Auto transplant. So I think that these are quite interesting approaches and we should learn more about them. I am not sure whether this will be open to a majority of subjects. But I think that it is really worthwhile to go for this special approach. Hopefully we will be able to do some radio immunoconjugates regarding an anti-CD66 antibody with our colleagues from radiopharmaceutical department. So this would be a similar way to go for myeloablation in subjects who have seen a large number of pretreatments.

I need to clarify did you say anti-56 or anti-66?

Anti-66. So this is currently done as a myeloablative approach in acute myeloid leukemia, AML. And there are some things that plasma cells may also express CD-66.

This may show my naivety, but when I think about targeting bone I usually think about agents like bisphosphonates like zoledronic acid. So if I am targeting the bone marrow, is targeting the bone with a conjugate going to be close enough or do I physically need to be targeting the cell surface on the bone marrow cells.

Not necessarily. If we have some of those bone-seeking radiopharmaceuticals, so it is holmium or Samarium EDTMP, it is close enough actually and you get myeloablation. You actually need transplant to overcome myelotoxicity.

Have you ever heard Novartis talking about coupling or using the basic structure of zoledronic acid and hooking a linker onto that and hooking a warhead onto the end of that.

Not yet, but it sounds really interesting.
Okay. Maybe I should be going out and getting a patent on that. The other thing that you mentioned was RAF. How relevant are those mutations and what is the status of for example of MEK inhibitors for myeloma?

There are several myeloma samples that take use of these special pathways. They can actually be – those samples can die. They can actually go into apoptosis in cell lines and ex vivo experiments. I think it is all about toxicity when moving this concept into clinic. I’m not sure whether there are some early clinical trials ongoing. We are currently exploring those concepts in the lab, so still in the lab.

The final question on my list is how you are treating the skeletal related events with myeloma? Do you have a preference for the bisphosphonates vs. RANK ligand inhibition? If so why do you prefer one approach vs. the other?

We are currently starting to use RANK ligands. It has been approved in Germany or in the EU just in Oct or November maybe. We are currently treating some patients with Prolia who fail conventional bisphosphonates. But I think that it is still too early to really get an impression. We are currently treating most patients with pamidronate, 60-90 mg every four weeks and in the outpatient department it is still zoledronate. We have not the reimbursement situation that everybody may receive Prolia, so we have to ask the patient’s insurances if they really have bone disease that becomes worse during treatment and mostly we succeed. But it is not a general option to treat patients with RANK ligand inhibitors.

If I took the reimbursement question out of the equation, so on just a medical basis what do you see differently in terms of your use of a bisphosphonate vs. a RANK ligand inhibitor? What are the pros and cons of each from a medical standpoint?

I think it is the ease of administration. You don’t need to do it intravenously with RANKL. It causes less acute toxicity. You have maybe a little less osteonecrosis. And the compound is significantly more potent than conventional bisphosphonates. I think that we will see a move of Prolia towards at least second line treatment along with let’s say second line systemic treatment for myeloma. I think more and more patients will get this drug.

Why are these bone protecting agents not used in prevention of the initial skeletal related events. Why do you wait until there has been an event before patients are being put on these agents?

I think that we will change to use the drugs differentially as soon as we have seen promising up-front data regarding myeloma. Up to now it is more or less confined to solid tumors that receive the majority of beneficial events regarding RANKL inhibitors. It is just a matter of time.
We have covered a lot of ground this evening. Is there anything else that I should have asked you that I should be sure to ask my next thought leader?

Allogeneic transplant. I think that it is still a matter of debate.

Who is the right patient, or the patient who will benefit the most?

Medically fit active subjects up to say 65-70 years of age. I think they really have the option for some two and a half or three years without medical treatment.

I am out of time. My time runs out before my question. It has been a great pleasure to have you share your insights.