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Abstract# 3224

Apoptotic Signaling Induced by Immunomodulatory Thalidomide Analogs (Imids) in Human Multiple Myeloma Cells: Therapeutic Implications. Nicholas Mitsiades*,[1] Constantine S. Mitsiades*,[1] Vassiliki Poulaki*,[2] Masaharu Akiyama*,[1] Yu-Tzu Tai*,[1] Boris K. Lin*,[1] Toshiaki Hayashi*,[1] Lawrence Catley*,[1] Teru Hideshima*,[1] Dharminder Chauhan*,[1] Steven P. Treon*,[1] Kenneth C. Anderson.[1] *[1]Department of Adult Oncology, Dana Farber Cancer Institute, Boston, MA; [2]Massachusetts Eye and Ear Infirmary, Boston, MA.*

Thalidomide (Thal) achieves responses even in the setting of refractory multiple myeloma (MM). Although increased angiogenesis in MM bone marrow and the anti-angiogenic effect of Thal formed the empiric basis for its use in MM, Thal and its immunomodulatory analogs (IMiDs) may also inhibit the production of cytokines in the bone marrow and stimulate NK cell anti-MM immunity. Our prior studies have also demonstrated that IMiD1 (Celgene, Warren, NJ) is several-fold more potent than Thal in inhibiting the growth of MM cells and directly induces apoptosis in the MM.1S MM cell line. We therefore investigated further the mechanism of its pro-apoptotic activity, in particular the role of caspases and the pro-survival transcription factor NF-kB. Using a colorimetric activity assay, we found that IMiD1 induced caspase-8, but not caspase-9, activity in MM.1S cells. Moreover, the caspase-8 specific inhibitor IETD-FMK, but not the caspase 9 inhibitor LEHD-FMK, protected MM.1S cells from IMiD1-induced cell death. Caspase-8 is a key mediator of death receptor-mediated apoptosis and can be inhibited by the anti-apoptotic proteins cIAP2 and FLIP. We found that IMiD1 sensitized MM.1S cells to low concentrations of Fas-crosslinking Ab CH11, and downregulated cIAP2 and FLIP, but not Bcl-2, protein expression. The constitutive activity of NF-κB, a pro-survival transcription factor that upregulates cIAP2 and FLIP expression in various models, was also decreased upon treatment with IMiD1, as was the expression of another NF-kB target gene, the adhesion molecule ICAM-1. IMiD1 also blocked the stimulatory effect of Insulin-like Growth Factor (IGF)-1 on NF-κB activity and cIAP2 and FLIP protein levels. Importantly, IMiD1 potentiated the anti-MM activity of dexamethasone and the proteasome inhibitor PS341 (Millennium, Cambridge, MA). These studies both delineate the mechanisms of action of IMiD1 against MM cells in vitro and form the basis for clinical trials of these agents, alone and coupled with conventional and other novel therapies, to improve outcome in MM.

Abstract# 3225

A Phase 1 Study of Oral CC5013, an Immunomodulatory Thalidomide (Thal) Derivative, in Patients with Relapsed and Refractory Multiple Myeloma (MM). P.G. Richardson,[1] R.L. Schlossman,[1] T. Hideshima,[1] F. Davies,[1] R. LeBlanc,[1] L. Catley,[1] D. Doss*,[1] K.A. Kelly*,[1] M. McKenney*,[1] J. Mechlowicz*,[1] A. Freeman*,[1] R. Deocampo*,[1] R. Rich*,[1] J. Ryoo*,[1] D. Chauhan,[1] N. Munshi,[1] E. Weller*,[1] S. Thomas*,[2] J. Zeldis,[2] K.C. Anderson.[1] *[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Celgene Inc., Warren, NJ, USA.*

Introduction: Thalidomide (thal) has a broad spectrum of biologic effects and significant clinical activity against multiple myeloma (MM). CC-5013, a small molecule derivative of thal and a member of the immunomodulatory drug (IMiD) class, is more potent than thal in mediating direct, cytokine-related and immunomodulatory effects against human MM cell lines and patient (pt) derived cells *in vitro* . Animal studies of CC-5013 have shown anti-MM activity and anti-angiogenic effects, with minimal toxicity. Moreover, this agent has a favorable safety profile in normal human volunteers. **Methods:** A phase I study has been performed in pts with refractory or relapsed MM to identify the maximum tolerated dose and to evaluate the safety of CC-5013 given orally for up to 4 weeks at 5 mg/day (d), 10 mg/d, 25 mg/d and 50 mg/d. Secondary objectives included evaluation of response to CC-5013, as well as pharmacokinetics and identification of surrogate markers to aid in defining mechanisms of action. Pts tolerating drug and without progression were permitted to continue on therapy beyond 28d as part of an extension phase for up to 1 year. **Results:** 26 pts (median age 57y, range 40-70y) have been enrolled; 16 had undergone prior autologous stem cell transplantation and 16 had received prior thal, with a median of 3 prior regimens (range 2-6). All pts had relapsed MM and 18 were refractory to salvage therapy. 2 pts were removed from study on the first day of treatment due to rapid disease progression with renal dysfunction that rendered them ineligible. The first group of 3 pts were treated for 28 d at 5 mg/d without any dose limiting toxicity (DLT). The second cohort of 3 pts commenced therapy at 10 mg/d. In 1 pt, DLT was encountered with grade (G) 2 fever as well as G3 leukopenia and neutropenia, resulting in removal from study before d 28. 2 pts tolerated drug and 3 additional pts were treated at 10 mg/d with no attributable toxicity within the first 28d. In the third cohort of 3 pts at 25mg/d, drug was well tolerated within the first 28d but G3 and G4 thrombocytopenia and neutropenia occurred during the second month, resulting in 2 pts being removed from study. In the fourth cohort at 50mg/d, the first 3 pts tolerated treatment without DLT in the first 28d, but subsequent G3 myelosuppression in the extension phase prompted dose reduction and GCSF support. To date, a further 8 pts have been treated at 50mg/d to better define toxicity and outcome. No DLT has been encountered within the first 28d, and no significant somnolence, constipation or neuropathy has been seen in any cohort. Median duration of therapy is currently 2 months [range 1 week - 9 months] and 16 pts continue on treatment. Maximal paraprotein reductions seen during therapy in pts who have received ≥ 28d of treatment are summarized below:

Dose[mg]	pts [n]	< 25%	≥25%<50%	≥50%	progression
5	3	-	2	1	-
10	5	-	-	1	4
25	3	1	2	-	-
50	8	2	3	3	-
(subtotals)	(19)	(3)	(7)	(5)	(4)

Best responses in paraprotein with a reduction of ≥ 25% have been seen in 12 of 19 evaluable pts (63%) and <25% in an additional 3 pts. **Conclusion:** This study shows that CC-5013 has anti-tumor activity and acceptable toxicity in pts with relapsed and refractory MM, and provides the framework for future phase II trials in MM.

Abstract# 3226

Results of Phase I Study of CC-5013 for the Treatment of Multiple Myeloma (MM) Patients Who Relapse after High Dose Chemotherapy (HDCT). Maurizio Zangari,[1] Guido Tricot,[1] Jerome Zeldis,[2] Paul Eddlemon*,[1] Fariba Saghafifar*,[1] Bart Barlogie.[1] *[1]Myeloma and Transplantation Research Center, University of Arkansas for Medical Sciences, Little Rock, AR, USA; [2]Celgene, Warren, NJ, USA.*

Despite the 40%-50 complete response rate and increased survival achieved by high dose chemotherapy, there is a clear need to further improve treatment outcome in MM. We report results from a single center, open label, escalating dose, phase I-study of the thalidomide derivative CC-5013. Four different daily dose levels (5/10/25/50 mg) were tested. All patients were treated for four weeks. In the absence of dose-limiting toxicity (DLT) or evidence of disease progression (PD), patients could be entered on an extension study, which allowed further dose escalations. The maximum dose allowed in this study was 50 mg/day. If at any level one of the first 3 patients experienced DLT, the cohort was expanded to 6 patients; if 2 patients experienced DTL in the same cohort, no further dose escalation was allowed. Fifteen patients were enrolled; 6 were males. Median age was 62 years (43-73); median β-2 microglobulin was 2.6 mg/l (1.4-6.4), median CRP 0.24 mg/l (.09 to 3.7). Ten had chromosome 13 abnormalities on cytogenetic analysis. All patients had chemorefractory disease having relapsed after at least one HDCT (range 1 to 3) with a median of 10 prior cycles of chemotherapy (range 3 to 80). No responses were seen at the 5 and 10 mg level. However, 2 of the 3 patients, who started at 10 mg and were subsequently escalated on the extension study to 25 and 50 mg, respectively, achieved a > 50% paraprotein response with a decrease in BM plasmacytosis of 50% in one patient, while the other continued to show < 5% bone marrow plasma cells. One patient at the 25 mg level had stable paraprotein and bone marrow plasmacytosis for 5 months, while discontinuation of therapy was required in 2 patients (one syncope; one PD). Six patients started at 50 mg/day; 3 are still on study, one with stable, one with > 25% and one with> 50 % in both paraprotein level and bone marrow plasmacytosis; 2 patients experienced DLT (thromboembolism and profound thrombocytopenia) and one PD. Six patients continue on this study after 2, 2, 4, 5, 6 and 6 months, five at 50 mg/day and one at 25 mg/day dose. Five of these patients have experienced a > 50% drop in platelet count. The initial platelet count in these 5 patients was > 140,000/μl and their bone marrow biopsy cellularity > 30%. We conclude that 20% of these heavily pretreated MM patients showed a > 50% paraprotein reduction with a concomitant bone marrow response. Responses were only observed at the 25 and 50 mg dose. However, the thalidomide derivative appears to also cause significant myelosuppression even in patients with adequate platelet counts and bone marrow cellularity before the start of treatment. It also has the potential to cause cardiovascular problems such as thromboembolism and syncope. Neurologic toxicity is minimal.

Abstract# 3227

A Single Subcutaneous Dose of an Osteoprotegerin (OPG) Construct (AMGN-0007) Causes a Profound and Sustained Decrease of Bone Resorption Comparable to Standard Intravenous Bisphosphonate in Patients with Multiple Myeloma. P. Greipp,[1] T. Facon,[2] C.D. Williams,[3] A. Lipton,[4] X. Mariette*,[5] J.-P. Fermand,[6] J. Berenson,[7] J.-L. Harousseau,[8] R. Alexanian,[9] A. Nakanishi*,[10] D. Holloway*,[10] C.R. Dunstan*,[10] P.J. Bekker*.[10] *[1]Mayo Clinic, Rochester, MN; [2]CHU de Lille, Lille, France; [3]Christie Hospital, Manchester, United Kingdom; [4]Hershey Medical Center, Hershey, PA; [5]CHU de Bicetre, Paris, France; [6]Hopital Saint-Louis, Paris, France; [7]Cedars Sinai Med Ctr, Los Angeles, CA; [8]Hopital Hotel Dieu, Nantes, France; [9]MD Anderson Med Ctr, Houston, TX; [10]Amgen Inc, Thousand Oaks, CA.*

Bone destruction causes significant morbidity in most patients with multiple myeloma (MM). Cytokines released during bone destruction promote myeloma cell proliferation and survival. OPG is a potent inhibitor of osteoclastic bone destruction. A randomized, double-blind, double-dummy, active-controlled, single-dose, dose escalation study is being conducted to determine the safety and effect on bone resorption of AMGN-0007 in MM patients with radiological confirmed lytic bone lesions. Patients were randomized (3:1 ratio) to receive a single dose of either AMGN-0007 SC or pamidronate (PAM; 90 mg IV) and were followed for 57 days. Medications or other diseases affecting bone metabolism and chemotherapy within 28 days of dosing were exclusion criteria. Biological activity of AMGN-0007 was assessed by measurement of the surrogate marker of bone resorption, urinary N-telopeptide of collagen (NTX). Preliminary data indicate that SC AMGN-0007 caused a rapid, sustained dose-dependent decrease in NTX/creatinine levels (nmol Bone Collagen Equivalents/mmol creatinine). No patients dropped out due to adverse events. Two patients in the 1.0 mg/kg AMGN-0007 group had albumin-adjusted serum calcium levels of 7.4 and 7.5 mg/dL at day 8, but there were no clinical sequelae. In conclusion, a single SC dose of AMGN-0007 suppressed bone resorption as indicated by a rapid, sustained, and profound decrease of urinary NTX/creatinine in MM patients. Changes were comparable to those with PAM. AMGN-0007 was well tolerated.

Urinary NTX/Creatinine levels after AMGN-0007 or PAM

Study Drug				
AMGN-0007	**Baseline NTX**; *Mean (SD)*	**Percent Change from Baseline NTX**; *Mean (SE)*		
SC (mg/kg)	Day 0	Day 1	Day 8	Day 29
0.1 (n=3)	46.3 (33.1)	-11.7 (20.2)	-20.5 (20.3)	-2.8 (6.4)
0.3 (n=4)	27.3 (16.2)	-28.6 (5.3)	-53.7 (11.9)	-44.8 (9.9)
1.0 (n=7)	27.8 (11.7)	-37.9 (14.2)	-56.1 (7.0)	-58.8 (6.6)
3.0 (n=6)	27.8 (17.2)	-32.5 (12.6)	-46.4 (14.7)	-34.7 (16.9)

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