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Imids(TM) Activity Against Multiple Myeloma Cells Presented at The American Society of Hematology Meeting

CAUTION

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ADVANCE/ SAN FRANCISCO, Dec. 5 /PRNewswire/ --
Celgene Corporation (Nasdaq: CELG) -- Researchers from Dana-Farber Cancer Institute and Harvard Medical School presented data results at the 42nd annual meeting of the American Society of Hematology on laboratory studies evaluating the activity of Celgene's IMiDs on multiple myeloma cells. The five abstracts presented suggest that IMiDs may be beneficial in the treatment of multiple myeloma.

The data demonstrate a dose dependent effect of IMiDs on multiple myeloma cells and show their impact at the molecular level on multiple myeloma cell growth. In addition, the data highlight that the IMiDs were found to have direct anti-tumor effects that include enhancement of multiple myeloma cell death (apoptosis) and cell cycle arrest. These compounds were also synergistic with other anti-myeloma agents in some of the cell lines studied.

"These results support previously reported data and demonstrate growing evidence for direct activity of the IMiDs against human multiple myeloma cells," said Kenneth C. Anderson, MD, Professor of Medicine in the Department of Adult Oncology at Dana-Farber Cancer Institute and Harvard Medical School. "The results from these studies provide the framework for a new biologically-based treatment paradigm, using these agents either alone or in combination with conventional therapies, to achieve improved outcome in this disease."

IMiDs are structural analogs of thalidomide that have significantly greater immunomodulatory activity in-vitro while not demonstrating teratogenicity in animal models. In addition, in a Phase I healthy human volunteer trial, they did not display thalidomide's sedative effect. This class of compounds are immunomodulatory drugs that have been reported to enhance T-cell proliferation and interleukin (IL)-2 production. In the same report, the IMiDs were also shown to be potent inhibitors of inflammatory

cytokines that include TNF-alpha and IL-1beta while stimulating the anti-inflammatory cytokine IL-10. IMiDs, including Celgene's current lead clinical candidate CDC-501, are covered by several issued and pending patents in the U.S. and internationally.

According to David I. Stirling, Ph.D., Chief Scientific Officer of Celgene Corporation and one of the researchers involved in these studies, "These findings support our basic understanding of the biologic activity of these compounds as well as the scientific rationale for initiating Phase I/II clinical development with our lead IMiD in myeloma patients. The lead compound, currently in clinical trials in myeloma patients, was selected on the overall activity demonstrated in these and other test systems as well as on the toxicological and pharmacological properties of the compounds."

These in-vitro studies assessed the effect of IMiDs on specific cell types and signal pathways of multiple myeloma cells. The IMiDs studied were found to be dose-dependent inhibitors of human multiple myeloma cell line proliferation and cells harvested directly from myeloma patients.

Results from Dr. Anderson's group show that IMiDs induced proliferation of anti-CD3 primed T-cells in samples harvested from normal donors and multiple myeloma patients in a dose dependent manner. Increased cell killing of patient multiple myeloma cells by autologous peripheral blood mononuclear cells (PBMCs) treated with IMiDs (51.6 percent) was observed. Further, the data pointed to a role for IMiDs in the natural killer cell (NK/LAK) signaling pathway for mediated killing of multiple myeloma cells compared to non-drug treated controls.

Results of anti-angiogenic activity tests show that IMiDs have a direct growth inhibiting and possible anti-angiogenic effect on multiple myeloma cells which may be selective to cell types. Researchers showed that re-treatment with IMiDs results in a dramatic inhibition of VEGF induced MAPK signaling, as well as multiple myeloma cell death which was assessed by DNA laddering. IMiDs did not inhibit growth of human umbilical venous endothelial cells (HUVEC) or the formation of tubular structures of HUVECs in gel assays.

The IMiDs were also tested against multiple cell lines resistant to conventional chemotherapeutic agents, such as doxorubicin, melphalan and dexamethasone. The IMiDs showed dose-dependent inhibition of proliferation of drug resistant multiple myeloma cells, which suggests an independent mechanism of action of the IMiDs compared to conventional treatments.

Based on these results, Celgene, in collaboration with Dr. Anderson's group, also presented data on the activity of one IMiD on multiple myeloma cells. The data demonstrate that the IMiD induces arrest of multiple myeloma cell line growth in a dose dependent manner as measured in HS-Sultan cells and multiple myeloma sensitive cells (MM.1S). Further, the IMiD was used in combination with conventional chemotherapuetic agents doxorubicin, dexamethasone, cisplatinum and 5FU on HS-Sultan and MM.1S cells. Results

showed that when used in combination with 5FU and dexamethasone, the IMiD increased HS-Sultan cell arrest to 90 percent and 51 percent respectively in comparison to 60 percent and 21 percent when these drugs are used alone. The IMiD was found to significantly decrease gene expression including c-myc, (70 percent), integrin beta7 (40 percent), cell cycle protein p38 and elongation factor 1alpha (50 percent). These results show that the IMiD can accentuate the growth arrest typically seen with current myeloma treatments and suggest that its mechanism of action may involve changes in transcription factor activation.

About Multiple Myeloma
There are approximately 40,000 people in the United States living with multiple myeloma and 13,000 new cases of multiple myeloma are diagnosed each year in the United States, making it the second most common blood cancer. Incurable with conventional chemotherapy, multiple myeloma is a malignant cancer of the plasma cells, which are a type of white blood cell found in many tissues of the body, but mainly in the bone marrow. As the cancer grows it destroys normal bone tissue, causing pain and crowding out normal blood cell production. There are nearly 11,000 deaths expected during 2000, according to the Multiple Myeloma Research Foundation.

Celgene Corporation, headquartered in Warren, New Jersey, is an independent biopharmaceutical company engaged in the discovery, development and commercialization of small molecule drugs for cancer and immunological diseases. Please feel free to visit the Company's website at www.celgene.com.

This release contains certain forward-looking statements which involve known and unknown risks, delays, uncertainties and other factors not under the Company's control which may cause actual results, performance or achievements of the Company to be materially different from the results, performance or other expectations implied by these forward-looking statements. These factors include results of current or pending research and development activities, actions by the FDA and other regulatory authorities, and those factors detailed in the Company's filings with the Securities and Exchange Commission such as 10K, 10Q and 8K reports.

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