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ABSTRACTS

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9. ERYTHROPOIETIC REMITTING ACTIVITY OF THE IMMUNOMODULATORY THALIDOMIDE ANALOG CC5013 (REVIMID™) IN PATIENTS WITH MYELODYSPLASTIC SYNDROME (MDS): RESULTS OF A PHASE I/II TRIAL

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Thalidomide improves erythropoiesis in approximately 20% of patients with MDS, but is limited by cumulative neurological toxicity.^[1,2] CC5013 (Revimid™) is an immunomodulatory (IMiD) derivative which displays 100-fold greater suppression of TNF α generation, and lacks the neurologic effects of the parent compound.^[3,4] The pharmacologic effects of CC5013 derive from its multiple relevant biological targets including its action as an inhibitor of cellular response to receptor-initiated trophic signals (e.g., insulin-like growth factor-I, vascular endothelial growth factor [VEGF], cyclooxygenase-2), and blockade of constitutive NF- κ B transactivation.^[3] As a result, CC5013 suppresses the generation of inflammatory cytokines, alters cell adhesion while suppressing apoptosis inhibitory proteins

(e.g., cFLIP, cIAP) and promoting sensitivity to death-receptor initiated programmed cell death. We have shown that CC5013 abrogates mitogenic response to VEGF in AML cells by inhibiting ligand-induced activation of phosphatidylinositol-3' kinase/Akt signaling and down-regulating VEGF gene transcription, and selectively promotes adhesion of MDS mononuclear and CD34⁺ cells to bone marrow stroma while enhancing susceptibility to fas ligand induced cell death.^[5] These findings indicate that CC5013 selectively suppresses proliferation of MDS clones by inhibiting VEGF-induced autocrine signals, corresponding angiogenic response and restoring stromal cell adhesion.

To evaluate the remitting potential of CC5013 in MDS, we performed a Phase I/II trial in patients with red blood cell (RBC) transfusion-dependent (i.e., >4 units/8 wks) or symptomatic anemia (hemoglobin [Hgb]<9 g/dl) with neutropenia or thrombocytopenia less than NCI-Common Toxicity Criteria (CTC) defined grade 4. Patients received treatment with either 25 mg or 10 mg CC5013 in a continuous oral daily dosing schedule, or 10 mg/day \times 21 days following by 1 week treatment hiatus (i.e., 'Syncopated Schedule'). Drug tolerance was assessed at 4 week intervals and response was assessed according to the International Working Group (IWG) criteria after 16 weeks of study treatment. Forty-two patients have been registered for study treatment, and 25 are evaluable for response after completing 8 weeks or more of study treatment. Among non-evaluable patients, 10 are too early (i.e., <8 weeks); 5 discontinued treatment prematurely (<4 weeks) due to unrecognized autoimmune hemolytic anemia, [1] consent withdrawal [2] or myelosuppression [2]; and succumbed to two infectious complications unrelated to study treatment. Median age is 74 years [range: 51–85]. FAB types include RA [12], RARS [7], RAEB [5], and RAEB-t [1] with corresponding IPSS categories of Low/Intermediate (Int)-1, 21 patients; Int-2/High, 4 patients. Eight patients (32%) failed prior treatment with thalidomide. Myelosuppression, characterized by >grade 3 NCI-CTC or 50% decrease in leukocyte and platelet counts [9 pts], or grade 3 fatigue [n=1] necessitated dose reduction in each of the ten subjects receiving the 25 mg dose, compared to 9 of 13 patients receiving the continuous 10mg schedule. Interval to limiting myelosuppression was dose dependent, median number of weeks at 25 mg/d, 4+2 (range, 3–8); versus 10 mg/d, 13+6 weeks (range 2–20). Grade 1 or 2 adverse effects were uncommon and limited to transient scalp pruritus [8 patients] or urticaria [2 patients], diarrhea [6 patients], joint pain [4 patients], hypothyroid [1 patient], and fatigue [2 patients]. Sixteen (64%) of

25 evaluable patients experienced an IWG-defined erythroid response, including major responses (i.e., transfusion-independence or >2 g Hgb increase) in 12 patients, and >50% decrease in RBC transfusions in 4 patients. Response rate was greater in patients with RA or RARS (14/19, 75%), Low/Int-1 IPSS risk score (15/21, 71%), and 5q31–33 interstitial chromosome deletion (8/8). Among 13 patients with an abnormal karyotype, 9 (69%) experienced a major cytogenetic response, including restoration of a normal karyotype in 8 patients. Responses were associated with normalization of blast percentage in 2/6 patients (33%), reduced grade of bone marrow (BM) cytologic dysplasia, and 50% to >40-fold improvement in BM CFU-GEMM and BFU-E formation. Bone marrow (BM) apoptotic index increased 2.5 to 5-fold and microvessel density (MVD) and BM plasma VEGF decreased in responding patients, whereas MVD increased in non-responders. The preliminary results of this study indicate that CC5013 has remarkable erythropoietic and cytogenetic remitting activity in patients with Low/Int-1 risk MDS. The increase in apoptotic index, restoration of colony-forming capacity, and suppression of clonal karyotypic abnormalities suggest that CC5013 promotes extinction of sensitive myelodysplastic clones. Myelosuppression is common and directly related to dose and cumulative drug exposure. Two multicenter phase II studies are underway to define the erythroid response rate in patients with the 5q-syndrome or non-5q- Low/Int-1 MDS.

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10. FUTURE DIRECTIONS IN THE TREATMENT OF TRANSFUSIONAL IRON OVERLOAD IN MYELODYPLASTIC SYNDROMES: FOCUS ON ICL670

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Approximately 80% of myelodysplastic syndromes (MDS) patients develop anemia, and many develop iron overload from chronic red blood cell (RBC) transfusion dependence. Evidence-based recommendations for iron chelation in MDS are limited and are primarily derived from uncontrolled studies of patients with other forms of acquired anemia and transfusional iron overload. The advanced age of the MDS population, limitations on survival due to disease evolution or co-morbidities, and the presence of organ damage related to secondary hemochromatosis weigh heavily in the decision by both doctors and patients to initiate chelation. In MDS patients, desferrioxamine (DFO) can reduce iron body stores as measured by serum ferritin or MRI-imaging of liver iron concentration, and may improve cytopenias in selected patients with prolonged treatment.^[1] However, subcutaneous continuous infusion of the drug using a portable pump is demanding and may adversely impact compliance and long-term efficacy. One study of 11 patients showed that twice daily subcutaneous bolus injection of DFO elicited levels of urinary iron excretion that were not statistically different from a subcutaneous infusion of 2 grams over 12 hours.^[2] In an extension phase of this study, 9 MDS patients with ongoing RBC transfusion requirements exhibited declining serum ferritin levels over 20 months of follow-up.^[3] Although bolus DFO may be an option for poorly compliant individuals with MDS, more data are needed to evaluate efficacy in this group. The oral iron chelator deferiprone (L1), approved for use in Europe, is generally recommended in the setting of clinical trials for patients with intolerance or an unsatisfactory response to DFO.^[4] Potential adverse effects of L1 therapy include nausea/vomiting, fluctuating liver enzymes, arthralgias, agranulocytosis, and zinc deficiency. L1 was evaluated in a subset of patients with