Myelodysplastic Syndromes without Deletion 5q Cytogenetic Abnormality and REVLIMID® (lenalidomide)

<*Revlimid_D*>

INTRODUCTION

Myelodysplastic syndromes (MDS) are a group of heterogeneous hematologic disorders characterized by one or more blood cytopenias secondary to bone marrow dysfunction.

MDS occur in 5 per 100,000 people in the general population, increasing with age to between 22 and 45 per 100,000 in people over 70 years of age, then increasing even further with age (National Comprehensive Cancer Network 2008). There is a slightly higher incidence in males than females (Cortes JE et al. 2005).

The exact etiology of primary (*de novo*) MDS (80 – 90% of all cases) is unknown, but it has been suggested that cumulative exposure to toxins in the environment, genetic differences in response to leukemia causing factors, and an aging immune system may increase the risk of developing *de novo* MDS. Secondary MDS may be linked to genetic factors, exposure to benzene, insecticides, pesticides, smoking, radiation, bone marrow transplantation or some anti-neoplastic drugs (for example, alkylating agents) (Cortes JE et al. 2005).

Although approximately 50% of patients with MDS are asymptomatic at the time of diagnosis, over 80% present with anemia (typically normo- or macrocytic), 50% have neutropenia, and 30% have thrombocytopenia. Signs and symptoms of MDS are related to the degree of hematopoietic failure and lineage affected (Cortes JE et al. 2005).

Clonal chromosomal abnormalities are detected in 50-60% of de novo patients with MDS and 75-80% of patients with secondary MDS. The most frequent chromosomal abnormalities are interstitial deletion of the long arm of chromosome 5 (5q-); monosomy 7; trisomy 8; deletion of the long arm of chromosome 20 (20q-); and loss of the Y chromosome (-Y). Deletions can be isolated or associated with one or more cytogenetic abnormalities. When there are 3 or more cytogenetic abnormalities, the condition is defined as complex. Complex karyotypes and chromosome 7 abnormalities carry a poor prognosis, whereas normal karyotypes, -Y, 5q-, or 20q- are associated with a favorable outcome (Cortes JE et al. 2005). For clarification, 5q- syndrome is a subset of deletion 5q (5q-).

Several classification systems for MDS are in use. The French-American-British (FAB) classification system categorizes patients into five types according to morphologic characteristics and the percentage of immature cells in the bone marrow and the peripheral blood. These subtypes consist of: refractory anemia (RA); RA with ringed sideroblasts (RARS); RA with excessive blasts (RAEB); RAEB in transformation (RAEB-t) and chronic myelomonocytic leukemia (CMML) (Cortes JE et al. 2005).

The World Health Organization (WHO) classification focuses on blast count, extent of cytopenias, and cytogenetics to further refine the classification system in an effort to better predict overall prognosis of MDS. Accordingly, the WHO guidelines lower the threshold of myeloblasts required to make the diagnosis of AML from 30% to 20%, eliminating the RAEB-t subtype. RAEB patients are separated into those with < 10% blasts (RAEB-1) and those with >

10% blasts (RAEB-2). Refractory cytopenias with multilineage dysplasia (RCMD) without or with ringed sideroblasts (RCMD-RS) have been added to further distinguish patients with altered morphology of more than one myeloid cell type (multilineage dysplasia) from those with erythroid dysplasia only (RA and RARS). A new subtype of MDS includes patients with isolated del(5q) MDS. Patients with the del(5q) abnormality have a relatively good prognosis. Unclassifiable (MDS-U) is also added, whereas CMML is removed from the MDS category and placed in a group of myeloid disorders with features of both myelodysplastic and myeloproliferative diseases (MDS/MPD) (Vardiman JW et al. 2002).

The International Prognostic Scoring System (IPSS) predicts survival in MDS based on cytogenetics, percentage of marrow blasts, and the number of cytopenias. Survival and progression rates to acute myeloid leukemia (AML) are estimated based on the total score, the lower the score, the higher the estimated survival. Scores for the risk categories are: LOW=0; INT-1=0.5-1.0; INT-2=1.5-2.0; HIGH $\geq$ 2.5. Depending on the IPSS score, median survival ranges from 3.5 to 5.7 years (Greenberg et al. 1997).

Decisions regarding treatment are based on performance status, age, patient's preference, concomitant illnesses and the potential to tolerate potentially intensive therapies in this largely older population. NCCN-recommended treatment approaches for patients with IPSS Low/Intermediate-1 risk disease include: lenalidomide for patients with deletion 5q abnormalities; recombinant human erythropoietin for patients with serum erythropoietin levels $\leq$500mU/mL (with or without granulocyte colony-stimulating factor); with azacitidine, decitabine and lenalidomide considered for patients with non-deletion 5q cytogenetics, or clinical trials for patients who do not respond. Patients with higher Epo levels should be considered for cyclosporine, with or without anti-thymocyte globulin (ATG). For non-responders recommendations include azacitidine, decitabine clinical trials or treatment with lenalidomide considered for patients with non-deletion 5q cytogenetics, then ATG or a clinical trial if no effect noted. High-risk (IPSS Int-2/High) patients should receive intensive chemotherapy, with transplant when appropriate. Supportive care should be provided at all stages (National Comprehensive Cancer Network 2008).

FDA-approved drugs for certain patients with MDS include lenalidomide (Revlimid®) (Revlimid Prescribing Information, January 2009), 5-azacitidine (Vidaza®) (Vidaza Prescribing Information, August 2008), administered by intravenous infusion (in the US) or subcutaneous injection and decitabine (Dacogen™) (MGI Pharma 2006), delivered intravenously.

CLINICAL EXPERIENCE with LENALIDOMIDE in MYELODYSPLASTIC SYNDROMES WITHOUT DELETION 5Q CYTOGENETIC ABNORMALITY

The Tables section summarizes published reports using lenalidomide in non-deletion 5q MDS patients. The first study (MDS-001) reports the use of lenalidomide as single-agent therapy in three different dosing regimens to treat transfusion-dependent or symptomatic anemia (List et al. 2005). Based on results from this study, two additional studies were conducted to evaluate lenalidomide in transfusion-dependent MDS: MDS-003 for Low/Int-1 risk IPSS MDS with deletion 5q with or without additional cytogenetic abnormalities and MDS-002 for Low/Int-1 risk IPSS MDS with normal or other cytogenetic abnormalities (List A et al. 2006; Raza et al. 2008; Raza et al. 2006). A case report in non-deletion 5q MDS (Tubb et al. 2007) is also included in the Table as well as A summary of a Phase I study evaluating the combination of lenalidomide and azacitidine in higher-risk MDS (Sekeres et al. 2008a; Sekeres et al. 2008b).

MDS-001

List et al. evaluated lenalidomide daily doses of 25 mg, 10 mg given continuously, or 10 mg for the first 21 days of each 28-day cycle in 43 MDS patients who were transfusion-dependent or had symptomatic anemia (List et al. 2005). All patients were either refractory to recombinant erythropoietin therapy or had high levels of endogenous erythropoietin. Response was assessed at 16 weeks. Twenty-four of 43 (56%) patients had a hematological response and 20/32 patients who required transfusions, achieved transfusion independence (TI). The median time to response was dose-dependent, from 9 weeks in the 25mg cohort to 11.5 weeks in the 10mg for 21-day cohort. The median increase in hemoglobin from baseline was 5.3g/dL (range, 4.4-8.7). At 81 weeks, the median duration of response had not been reached (range, 13-101+ weeks).

The cytogenetic pattern correlated significantly with hematologic response: 83% of 12 patients with a deletion of 5q3l.l had a response, compared with 57% of 23 patients with a normal karyotype and 12% of 8 patients with other cytogenetic abnormalities (p=0.007). Thirty-one of the 43 patients (72%) had normal or non del 5q karyotypes. Twenty patients presented with clonal cytogenetic abnormalities and 11 achieved cytogenetic responses. Of the 10 patients who had complete cytogenetic responses, nine had del(5)(q31.1). The median time to cytogenetic response was eight weeks (range, 8 to 24).

MDS-002

The efficacy of lenalidomide in treating 214 MDS patients with normal or non del 5q karyotypes is being evaluated by Raza et al. in an ongoing multi-center phase II study, initiated July 2003 (Raza et al. 2008; Raza et al. 2006). The starting dose of lenalidomide was 10 mg daily on days 1-21 of a 28-day cycle. In September 2003, the dose schema was amended to 10 mg continuous daily dosing. On central review, Low-or Int-1-risk IPSS scores were confirmed in 168 (79%) patients, 8 (4%) had Int-2 or High-risk IPSS and IPSS scores were not centrally classified in 38 (18%) patients. Using the FAB subtype, by central review, the classification was as follows: RA (22%), RARS (40%), RAEB (11%), CMML (9%), RAEB-t (2%), AML (1%). The median age of the patients was 72 years (range 27-94). Twenty-seven percent of patients had baseline neutropenia <1500/ul, while 20% had baseline thrombocytopenia <100,000.

Transfusion independence (TI) was defined as the number of days from initiation of study treatment until the day after the last RBC transfusion that proceeded the first 8-week response period. Twenty-six percent of patients achieved TI and an additional 37 patients achieved a ≥ 50% decrease in transfusion requirements, for an overall hematological improvement in 43% using the modified International Working Group (IWG) 2000 criteria. The median peak increase in hemoglobin was 3.2 g/dL for patients who achieved TI (range 1-9.8) with a median time to TI of 4.8 weeks. Forty-five percent of the responding patients achieved a hemoglobin concentration of ≥ 12 g/dL for a median of 13.3 g/dL (range 12-18 g/dL). Among patients who achieved TI, 90% of patients began their TI period by 16.9 weeks. After a median follow-up of 76 weeks (range 16-173 weeks) the median duration of TI was 41 weeks (range 8.0 – 136.4). TI was continued in 35/56 (63%) for at least 6 months and 20/56 (36%) maintained TI for over a year.

Of the 47 patients (22%) who had abnormal karyotypes at baseline, 9 (19%) had a cytogenetic response, with 4 achieving complete responses. Responding karyotypes included trisomy 8 (n=3), -Y (n=3), deletion 11q (n=2) and deletion 17p (n=1). There were no significant differences in TI rates with respect to age, gender, FAB type, IPSS category, cytogenetic pattern or cytopenia within the first 16 weeks. Using the IWG 2006 criteria, 23 patients achieved TI (defined as no transfusions administered for ≥ 8 weeks) and an additional 17 patients achieved a decrease from baseline in RBC transfusion requirement, for an overall hematological improvement in 30%

(40/133). For patients who did not achieve TI, hemoglobin response was achieved in 30 patients, for an overall erythroid response rate of 33%. Hemoglobin response was defined as an increase of ≥ 1.5 g/dL maintained for at least 8 weeks.

Myelosuppression often occurred early in treatment course, with 43% of grade 3 or 4 hematologic events occurring within the first 8 weeks of therapy. Grade ≥3 neutropenia and thrombocytopenia was noted in 30% and 25% of patients, respectively, occurring less frequently than in patients with del 5q (study MDS-003). A total of 117 patients required a dose adjustment during the course of lenalidomide therapy. The median time to dose adjustment was 7 weeks (range, <1-80 wks). Other side effects were of low or moderate severity and included rash, pruritus, constipation, diarrhea, fatigue, peripheral edema and nausea. Deep vein thrombosis (DVT) occurred in 2 patients and no pulmonary embolism was reported. Autoimmune hemolytic anemia (AIHA) developed in 6 patients after a median of 29 days of study treatment (range 8-153) leading to withdrawal of lenalidomide in 3 patients. The patients with reported AIHA were either non-responders (n=5) or a minor responder (n=1).

There were 21 reported deaths with one death attributed to urosepsis/septic shock and another to respiratory failure, both possibly treatment related. Others were due to disease progression (n=6), cardiac arrest (n=4), pneumonia (n=2), renal failure (n=2), multi-organ failure (n=1), hepatic failure (n=2), respiratory failure (n=1), septic shock (n=1) and unknown (n=1). Over the duration of the study, 10 (5%) patients experienced progressive disease marked by a ≥ 50% increase in marrow blasts and a worsening of FAB subtype and/or disease transformation to acute leukemia (n=9; 4%).

Additional analyses

In a secondary analysis of the MDS-002 multicenter trial, List et al. determined the rate of TI and duration of response according to transfusion burden prior to study (≤ 4 vs. > 4 units of RBCs in the 8 weeks prior to study), MDS disease duration (≤ 2 vs. > 2 years since initial diagnosis, and age (≤ 60 vs. > 60 years) (List et al. 2008b; List et al. 2008a). The rate of TI was significantly higher among the 60 patients with low transfusion burden and short MDS duration compared to the 154 patients with greater transfusion burden and longer disease duration (43% vs. 19%, $p < 0.001$). The rate of TI was also higher among the 29 patients ≤ 60 years of age compared to the 186 patients > 60 years of age (41% vs. 24%; p=0.069). The median duration of response among patients with low transfusion burden and short disease duration was 10 months (95% CI 5.2-not reached; range 1.9-39.5) compared to 9.5 months (95% CI 4.9-14.0- range 2.0-37.1) among patients with greater transfusion burden and longer disease duration. A highly significant ($p < 0.0001$) association between baseline transfusion burden and the frequency of TI response was also demonstrated.

A retrospective analysis examined the correlations between baseline thrombocytopenia (defined as a platelet count < 150,000/μL) and/or neutropenia (defined as absolute neutrophil count (ANC) < 2,000/μL) and changes in platelet and ANC counts during treatment with achievement of TI in the MDS-003 and MDS-002 studies (Sekeres et al. 2007b; Sekeres et al. 2008c). In transfusion-dependent, lower-risk MDS patients with del5q, a decrease in platelets of ≥ 50% within the first 8 weeks of treatment correlated with a higher likelihood of achievement of TI, regardless of baseline platelet count. A similar correlation with TI was found in patients with a normal baseline neutrophil count. TI occurred in 82% of patients in whom ANC decreased by ≥ 75%, compared with 51% in whom ANC remained stable or decreased by < 75%. In contrast, multivariate analyses showed no relationship between the development of cytopenias and response among lower-risk MDS patients without del5q cytogenetic abnormality.

PK-002

List et al evaluated lenalidomide (10 or 15 mg daily) alone or combined with recombinant erythropoietin (rhu-EPO) in 39 patients with low-risk MDS (32 with normal or non del 5q cytogenetics) who previously failed EPO therapy (List et al. 2007). The potential benefit of the combination and the relationship between lenalidomide pharmacokinetics (PK) and treatment-related cytopenias were also assessed. Single dose and steady-state fasting PK were evaluated on Days -7 and +14, respectively for patients receiving the 10 mg dose. All patients were refractory to recombinant erythropoietin therapy. Response was assessed after 16 weeks of lenalidomide monotherapy. Non-responders and minor responders were offered the combination of lenalidomide and erythropoietin for a minimum of 8 weeks.

Among the 39 patients receiving lenalidomide therapy, seven were diagnosed with del5q MDS, the remaining 32 were non-del 5q. Of the 33 patients that completed the monotherapy phase, 11 (33%) achieved a hematological response consisting of 9 major and 2 minor erythroid responses. Sixteen patients proceeded to the combination phase and 4 (25%) achieved erythroid responses (2 major and 2 minor). PK analyses showed no evidence of drug accumulation after 14 days of treatment. Lenalidomide area under the curve (AUC) was highest in patients with reduced creatinine clearance. There was no significant difference in steady-state lenalidomide concentration, AUC, or C_{max} in patients with $\geq 50\%$ vs. $< 50\%$ decrease in ANC or platelet count during the first 28 days of treatment. However, mean AUC inversely correlated with the interval to $\geq 50\%$ reduction in platelet count ($p= 0.04$). Most common adverse events included grade ≥ 3 neutropenia in 28/39 (72%) patients and thrombocytopenia in 23/39 (59%) patients. The authors concluded that lenalidomide has pro-erythropoietic activity in primary EPO-non-responders, which may be improved with the addition of EPO.

Findings from this study were subsequently reported after all 39 patients had completed the monotherapy phase (Lancet et al. 2008). Erythroid response occurred in 14 (36%) patients treated with monotherapy. Mean baseline serum EPO in responders was higher compared to non-responders (1177 vs. 530 mU/mL, respectively). At Week 16, 18 patients proceeded to the combination phase and 5 (28%) achieved an erythroid response. Mean Week 16 serum EPO in responders was lower than in non-responders (339 vs. 1116 mU/mL, respectively). A higher rate of erythroid response during the combination phase occurred in patients with serum EPO < 500 mU/mL (33% vs. 17%). The authors concluded that erythroid response to lenalidomide was serum EPO-dependent in transfusion-dependent cytokine failures.

OTHER DATA

Phase I Study (Lenalidomide and Azacitidine Combination)

A Phase I combination study of lenalidomide and azacitidine in patients with higher-risk MDS was conducted to determine maximum tolerated dose (MTD) and dose limiting toxicity (DLT) of this combination (Sekeres et al. 2008a; Sekeres et al. 2008b; Sekeres et al. 2007a). Clinical outcomes of this combination were also assessed using modified IWG 2006 criteria. A total of 19 patients were enrolled; 1 patient was excluded for AML diagnosis at entry, and 18 patients were evaluated for response. Median age was 68 years, median time from MDS diagnosis was 5 weeks, and a majority of patients had higher-risk disease per IPSS. Patients were treated in a 3+3 design at 6 different dose levels consisting of 2 different dosing schedules of subcutaneously administered azacitidine (75 mg/m^2 daily days 1-5 or 50 mg/m^2 daily days 1-5 and 8-12) and 3

different dosing schedules of orally administered lenalidomide (5 mg daily days 1-14, 5 mg daily days 1-21, or 10 mg daily days 1-21).

Safety findings revealed no DLTs reached through all dosing cohorts and MTD was not reached. Median ANC decrease was 21% and median platelet decrease was 1%, with mean decrease of 20%. A delay in cycle 2 occurred in 2 patients due to neutropenia. Grade 3/4 non-hematologic toxicities included 2 cases of febrile neutropenia and a single case each of atrial fibrillation, monocular blindness, basal cell skin carcinoma, CNS hemorrhage, shortness of breath and perforated appendix.

Overall response rate was 72% consisting of 7 complete responses, 1 partial response, 3 hematologic improvements and 2 complete bone marrow responses. The "go forward" dose was identified as 75 mg/m^2 daily days 1-5 azacitidine in combination with 10 mg daily of lenalidomide days 1-21 for this higher-risk IPSS population, based on the observed safety profile, and response rate. Additional response data are expected. A study of concomitant versus sequential dosing strategies with azacitidine and lenalidomide is planned.

Case Report

Tubb et al reported responses that were first noted after discontinuation of lenalidomide therapy in three MDS patients including one with non-del 5q cytogenetic abnormality (Tubb et al. 2007). Time to TI among these three patients varied from 1 to 4 months after discontinuation of lenalidomide therapy. A 16-month duration of TI was observed starting one month after discontinuation of therapy in an 82-year-old male with 45X, -Y karyotype MDS who underwent a 6 month trial with lenalidomide. Prior to the start of therapy, this patient had an RBC transfusion requirement of 2 units/4 weeks.

DOSAGE and ADMINISTRATION

The recommended starting dose of REVLIMID® (lenalidomide) for patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities is 10 mg daily (Revlimid Prescribing Information, January 2009).

Dosing is continued or modified based upon clinical and laboratory findings. *Please refer to the accompanying Package Insert for recommended dose adjustments during treatment, based on platelet and absolute neutrophil counts*. Laboratory monitoring for cytopenias during treatment for MDS should be performed weekly during the first 8 weeks of REVLIMID® (lenalidomide) treatment and at least monthly thereafter.

SAFETY ISSUES with LENALIDOMIDE in MYELODYSPLASTIC SYNDROMES

Giagounidis et al presented practical recommendations on the management of hematological and non hematological adverse events in MDS patients treated with lenalidomide (Giagounidis et al. 2008).

These recommendations were developed by an international group of MDS specialists in January 2007 (Giagounidis et al. 2008). Overall, a stringent strategy for the management of hematological and non-hematological adverse events due to the treatment of lenalidomide was recommended. Recommendations of the panel include the following:

Hematologic:

- Weekly blood counts of neutrophils for the first 2 months and bi-weekly monitoring for up to 5 weeks;
- Co-administration of G-CSF may be included if the ANC reaches <1000/uL or lenalidomide can be temporarily discontinued;
- Interruption of lenalidomide if platelets fall < 25,000/uL without platelet support;
- Consider phlebotomy (depending on ferritin levels) in patients with polycythemia and either continue or interrupt lenalidomide therapy;
- VTE prophylaxis is not generally recommended in patients with MDS.
    - In the event of VTE, consider dose interruption of lenalidomide, treat VTE, and carefully re-introduce lenalidomide once stable anti-coagulation is established

Non-Hematologic:

- Most rashes resolve over time and lenalidomide does not necessarily need to be discontinued.
    - A course of antihistamines proves effective in treating the majority of rashes and 10 mg of prednisone for 14 days can be administered if antihistamines prove unsuccessful.
    - Lenalidomide should be interrupted for persistent/severe rashes until the rash resolves
    - Lenalidomide can be restarted without rash recurrence
- Rule out anemia or auto-immune disorders in cases of common non-specific symptoms including: fatigue, pruritis, diarrhea, nausea and muscle cramps
- Generally screen for thyroid-stimulating hormone (TSH) and compare baseline level to levels during treatment
- Diarrhea should be treated symptomatically after ruling out other underlying causes
    - If due to lactose content in lenalidomide capsules, use of lactase supplementation may be helpful

Adverse events reported from published non-del 5q myelodysplastic syndrome studies are noted in the Table.

The incidence of hematological toxicities differed between the non-del and del 5q study populations.

- In MDS-003 (del 5q with or without additional cytogenetic abnormalities) neutropenia (59%) and thrombocytopenia (62%) were the most frequently reported adverse events. Grade 3 and 4 neutropenia occurred in 53% of patients, and grade 3 or 4 thrombocytopenia occurred in 50%. The next most common adverse events included diarrhea (49%), pruritus (42%), rash (36%), and fatigue (31%) (Revlimid Prescribing Information, January 2009)
- In MDS-001 (primary MDS, included patients with both normal and abnormal karyotypes) grade 3 or 4 neutropenia and thrombocytopenia were dose-dependent and necessitated treatment interruption/reduction in 58% of patients (List et al. 2005).
- In MDS-002 (normal or non-del 5q karyotype) neutropenia and thrombocytopenia have occurred in 30% and 25% of patients respectively. Myelosuppression occurred early in treatment course with 43% of grade 3 or 4 hematologic adverse event occurring with the first 8 weeks of therapy (Raza et al. 2008).

ONGOING CLINICAL TRIALS of LENALIDOMIDE in MYELODYSPLASTIC SYNDROMES

Clinical Trial	Location
A Phase I Study of Lintuzumab Combined With Lenalidomide in Patients With Myelodysplastic Syndromes (MDS)	Memorial Sloan-Kettering Cancer Center *(multiple locations)*
Study of Idarubicin + Cytarabine and Lenalidomide in Patients With Myelodysplastic Syndrome (MDS), Acute Myeloid Leukemia (AML)	H. Lee Moffitt Cancer Center, FL
A Phase 1 Dose Escalating Trial of Bortezomib in Combination With Lenalidomide in Patients With Myelodysplasia (Low to Intermediate-1 Risk Category)	Dana Farber Cancer Institute, MA *(multiple locations)*
Lenalidomide and Azacitidine in Treating Patients With Advanced Myelodysplastic Syndromes	H. Lee Moffitt Cancer Center, FL *(multiple locations)*
Study of Oral CC-5013 (Lenalidomide; Revlimid) in Myelodysplastic Syndromes	H. Lee Moffitt Cancer Center, FL
Efficacy Study of Revlimid® and Low Dose Continuously Administered Melphalan to Treat Higher Risk Myelodysplastic Syndromes (REMMYDYS)	Odette Cancer Center, Toronto, Canada
A Safety and Efficacy Study to Evaluate AMG 531 Treatment in Subject With Myelodysplastic Syndrome Receiving Revlimid	Amgen Sponsored *(multiple locations)*
Revlimid and Azacitidine for Treating Advanced Myelodysplastic Syndrome (MDS)	East Melbourne, Victoria, Australia
Study of the Efficacy and Safety of Lenalidomide in Combination With Cyclosporine A in Patients With Myelodysplastic Syndromes	Weill Cornell Medical College, NY
A Dose Range Finding Study of Lenalidomide in Non-5q Chromosome Deletion in Low and Intermediate Risk Myelodysplastic Syndrome (MDS) Patients	Thomas Jefferson University, PA
Lenalidomide and Recombinant Human Stem Cell Factor for Treatment of Myelodysplasia	Peter MacCallum Cancer Centre - Victoria, Australia
Lenalidomide in Comb w/Rituximab for Pts w/CD5+/CD20+ Hem Malig Who Relapse/Progress After Rituximab	H. Lee Moffitt Cancer Center

*Accessed on 02-02-09. Please refer to www.clinicaltrials.gov for updates or further information regarding these clinical trials.

Table: Summary of Lenalidomide Clinical Studies in Myelodysplastic Syndromes Without Deletion 5q Cytogenetic Abnormality

CITATION	DISEASE/NUMBER OF PATIENTS	STUDY DESIGN/ DOSE/DURATION	RESPONSE	SAFETY/ TOLERABILITY
MDS-002 (Raza et al. 2008) CU 4746	MDS w/ normal or non deletion 5q31 karyotype N=214 Med age: 72 yrs (range, 27-94) Transf dep (> 2 RBC U/8 wks) FAB types[A]: ▪ RA: 47 ▪ RARS: 86 ▪ RAEB: 24 ▪ RAEB-t: 5 ▪ CMML: 20 ▪ AML: 1 IPSS risk groups: ▪ Low: 92 ▪ Int-1: 76 ▪ Int-2/High: 8 ▪ Unclassified: 38 Abn Karyotype: ▪ Trisomy 8: 3 ▪ -Y: 3 ▪ Del 11q: 2 ▪ Del 17p: 1	Multi-center, phase II *LEN:* ▪ 10mg d 1-21 q 28d cycle (n=114) ▪ Amended to 10mg continuous daily (n=100) ▪ Dose adj allowed (n=117)	***IWG 2000 Criteria*** **Eryth Resp**: ▪ 93 (43%) ▪ RR not signif diff btwn FAB types or IPSS **TI:** ▪ 26% ▪ Med TTR= 4.8 wks ▪ Med DOR= 41 wks (w/ 36% > 52 wks) ▪ Med peak ↑ in Hgb = 3.2 g/dl (range, 1.0-9.8) **PD/Transformation** ▪ 10 (5%) ▪ DOT (3-85 wks) ***IWG 2006 Criteria*** **Eryth Resp**: ▪ 70/214 (33%) **TI:** ▪ 23/214 (17%) **Transf Resp (TR):** ▪ 40/133 (30%) **Hgb Resp (HgbR):** ▪ 30/81 (37%)	Most common Gr 3/4 AEs ▪ Neutropenia (30%) ▪ Thrombocytopenia (25%) ▪ Rash (4%) ▪ Fatigue (4%) ▪ Pruritus (1%) ▪ Constipation (1%) ▪ Diarrhea (1%) ▪ Peripheral Edema (1%) ▪ Nausea (1%) ▪ AIAH (6pts) ▪ DVT (2pt) 21 deaths due to: ▪ Septic shock: 1 ▪ Respir failure; 1 ▪ PD: 6 ▪ Cardiac arrest :4 ▪ Pneumonia: 2 ▪ Renal failure: 2 ▪ MOF: 1 ▪ UNK: 1 ▪ Hepatic fail: 2
MDS-001 (List et al. 2005) Internal Reference: CU3707	Primary MDS w/ Symptomatic Anemia or Transf Dep N=43 Med age: 72 yrs (range 28-85) Hgb < 10g/dl or transf req ≥ 4 U/8wks Resist to recombinant epo tx or endogenous epo levels > 500 mU/mL Prior tx: ▪ 30% failed Thal ▪ 77% failed Epo FAB Types: ▪ RA: 20 ▪ RARS: 13 ▪ RAEB: 8 ▪ RAEB-t: 1 ▪ CMML:1 IPSS categories: ▪ Low/Int-1: 38 ▪ Int-2/High: 5	Randomized, open label *LEN:* ▪ 25 mg/d qd ▪ 10 mg/d qd ▪ 10 mg/d x 21d q 4 wks (sync) Final resp assessed after 16 wks	Modified IWG Resp must be sustained for 8 consecutive wks **Eryth Resp**: ▪ OR= 24(56%) ▪ Med ↑ Hgb= 5.3g/dl ▪ Med Hgb= 13.2 ±1.4g/dl (range 11.5-15.8) in responders ▪ Med TTR: 9-11.5 wks-dose-depend ▪ Med DOR: not reached, > 48wks (range 13-101+ wks) ▪ Resp-independ FAB / IPSS categories ▪ Resp highest in del5q31.1 (83%) vs normal (57%) or other (12%) karyotypes **TI**: ▪ 20/32(63%) w/ prior TD Cytogen Resp: ▪ OR= 11/20 w/ clonal abn ▪ CR= 10/11 ▪ 10/12 (83%) del 5q31.1 pts w/ response, 9=CR ▪ Med TTR: 8wks (range, 8-24)	AEs Gr 1-2 ▪ Pruritus 28% ▪ Diarrhea 8 (19%) AEs ≥ Gr 3 Neutropenia ▪ 25 mg/d: 77% ▪ 10 mg/d: 62% ▪ 10 mg sync: 59% Thrombocytopenia ▪ 25 mg/d: 54% ▪ 10 mg/d: 54% ▪ 10 mg sync: 53% 3 deaths, none thought to be tx-related ▪ Cholecystitis w/ rupture ▪ Splenic infarct ▪ Pneumonia w/o neutropenia

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Table: Summary of Lenalidomide Clinical Studies in Myelodysplastic Syndromes Without Deletion 5q Cytogenetic Abnormality

CITATION	DISEASE/NUMBER OF PATIENTS	STUDY DESIGN/ DOSE/DURATION	RESPONSE	SAFETY/ TOLERABILITY
(Sekeres et al. 2008a; Sekeres et al. 2008b) ASH '08 #0221	Higher-risk MDS N=19 Med age: 68 (range 52-78) M/F: 12/7 BL levels: Hgb=9.9g/dl, Plt=69 k/ul, neutrophils=0.84 k/ul, epo=99 MIU/ml, ferritin=893 ng/ml, bone blast %=11 No prior LEN or AZA IPSS categories: ▪ Int-1: 3 pts ▪ Int-2: 9 pts ▪ High: 6 pts ▪ 1 pt del 5q (cohort #4)	Phase I, dose-finding 6 Dosing Cohorts Combination: *LEN:* ▪ 5-10mg/d D 1-14 or 1-21 q28-d cycle x max 7 cycles *AZA:* ▪ 50-75 mg/m^2 d 1-5 ± d 8-12 q 28-d cycle x max 7 cycles	17 eval Resp: ▪ OR= 71% ▪ CR=7 (41%) ▪ PR=1 (6%) ▪ HI=3 (18%) marrow CR=1 (3%	No DLT's MTD not reached Grade 3/4 Non-hem AEs: ▪ atrial fibrillation (1) ▪ monocular blindness (1) ▪ basal cell skin carcinoma (1) ▪ CNS hemorrhage (1) ▪ febrile neutropenia (2) ▪ SOB (1) ▪ perforated appendix (1) Med ANC ↓: 21% Mean Plts ↓: 20%
(Tubb et al. 2007) ASH '07 #1447	Non-del 5q MDS N=1 82 yo male Prior tx: ▪ EPO, 2 U/4 wks Karyotype: ▪ 45 X, -Y IPSS: ▪ Low-risk	Case report *LEN:* *dose n/a x 6 mos*	Time to TI after d/c of LEN: ▪ 1 mo Duration of TI: ▪ 16 mos	Remarks on BM: ▪ Persistent dysplasia

Key: adj= adjustment; AE(s) = adverse event(s); AIHA= Autoimmune hemolytic anemia; AML= acute myeloid leukemia; ANC= absolute neutrophil count; ASCT= autologous stem cell transplant; AZA= azacitidine; BL= baseline; BM= bone marrow; CML= chronic myeloid leukemia; CMML=chronic myelomonocytic leukemia; cytogen= cytogenetic; DLT= dose limiting toxicity; DOR= duration of response; DOT= duration of treatment ; DVT= deep vein thrombosis; EPO= erythropoietin; eryth= erythroid; eval= evaluable; FAB= French American British classification; fail= failure; Gr= grade; HI= hematologic improvement; IPSS=International Prognostic Scoring System; IWG=International Working Group; LEN= lenalidomide; MOF= multi organ failure; mo(s)= month(s); MTD= maximum tolerated dose; n/a= not available; PD= disease progression; plt= platelet; q= every; qd= once daily; RA= refractory anemia; RARS=RA with ringed sideroblasts; RAEB=RA with excess blasts; RAEB-t=RAEB in transformation; resist= resistance; resp= response; respir= respiratory; sync= syncopated; Thal= thalidomide; TI= transfusion independence; transf= transfusion; TTR= time to response; tx= treatment; U= units; UKN= unknown; wks= weeks; yo= year old

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