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1.14.1.3 Draft Labeling Text

The draft package insert for generic drug product, Decitabine for Injection, 50 mg/vial is provided in this section.

The SPL is also provided electronically in the corresponding section.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DECITABINE FOR INJECTION safely and effectively. See full prescribing information for DECITABINE FOR INJECTION.

DECITABINE for injection, for intravenous use
Initial U.S. Approval: 2006

------------------------INDICATIONS AND USAGE----------------------------

Decitabine for Injection is a nucleoside metabolic inhibitor indicated for treatment of adult patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups. (1)

-------------------- DOSAGE AND ADMINISTRATION --------------------

- Three Day Regimen: Administer decitabine for injection at a dose of 15 mg/m^2 by continuous intravenous infusion over 3 hours repeated every 8 hours for 3 days. Repeat cycle every 6 weeks. (2.1)
- Five Day Regimen: Administer decitabine for injection at a dose of 20 mg/m^2 by continuous intravenous infusion over 1 hour repeated daily for 5 days. Repeat cycle every 4 weeks. (2.1)

----------------- DOSAGE FORMS AND STRENGTHS --------------------

For Injection: 50 mg of decitabine as a lyophilized powder in a single-dose vial for reconstitution. (3)

----------------------------CONTRAINDICATIONS----------------------------

None. (4)

---------------------- WARNINGS AND PRECAUTIONS -------------------

- Neutropenia and Thrombocytopenia: Perform complete blood counts and platelet counts. (5.1)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of reproductive potential of the potential risk to a fetus and to use effective contraception (5.2, 8.1, 8.3)

--------------------------- ADVERSE REACTIONS ----------------------------

Most common adverse reactions (> 50%) are neutropenia, thrombocytopenia, anemia, and pyrexia. (6.1)

-------------------- USE IN SPECIFIC POPULATIONS ---------------------

Lactation: Advise not to breastfeed. (8.2)

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-845-0689 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2022

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Decitabine for Injection is indicated for treatment of adult patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Pre-Medications and Baseline Testing

Consider pre-medicating for nausea with antiemetics.

Conduct baseline laboratory testing: complete blood count (CBC) with platelets, serum hepatic panel, and serum creatinine.

Decitabine for Injection Regimen Options

Three Day Regimen

Administer decitabine for injection at a dose of 15 mg/m^2 by continuous intravenous infusion over 3 hours repeated every 8 hours for 3 days. Repeat cycles every 6 weeks upon hematologic recovery (ANC at least 1,000/ µL and platelets at least 50,000/ µL) for a minimum of 4 cycles. A complete or partial response may take longer than 4 cycles. Delay and reduce dose for hematologic toxicity *[see Dosage and Administration (2.2)]*.

Five Day Regimen

Administer decitabine for injection at a dose of 20 mg/m^2 by continuous intravenous infusion over 1 hour daily for 5 days. Delay and reduce dose for hematologic toxicity *[see Dosage and Administration (2.2)]*. Repeat cycles every 4 weeks upon hematologic recovery (ANC at least 1,000/ µL and platelets at least 50,000/ µL) for a minimum of 4 cycles. A complete or partial response may take longer than 4 cycles.

Patients with Renal or Severe Hepatic Impairment

Treatment with decitabine for injection has not been studied in patients with pre-existing renal or hepatic impairment. For patients with pre-existing renal or hepatic impairment, consider the potential risks and benefits before initiating treatment with decitabine for injection.

2.2 Dosage Modifications for Adverse Reactions

Hematologic Toxicity

If hematologic recovery from a previous decitabine for injection treatment cycle requires more than 6 weeks, delay the next cycle of decitabine for injection therapy and reduce decitabine for injection dose temporarily by following this algorithm:

Recovery requiring more than 6, but less than 8 weeks: delay decitabine for injection dosing for up to 2 weeks and reduce the dose temporarily to 11 mg/m^2 every 8 hours (33 mg/m^2/day, 99 mg/m^2/cycle) upon restarting therapy.

Recovery requiring more than 8, but less than 10 weeks: Perform bone marrow aspirate to assess for disease progression. In the absence of progression, delay decitabine for injection dosing for up to 2 more weeks and reduce the dose to 11 mg/m^2 every 8 hours (33 mg/m^2/day, 99 mg/m^2/cycle) upon restarting therapy, then maintain or increase dose in subsequent cycles as clinically indicated.

Non-hematologic Toxicity

Delay subsequent decitabine for injection treatment for any the following nonhematologic toxicities and do not restart until toxicities resolve:

Serum creatinine greater than or equal to 2 mg/dL

Alanine transaminase (ALT), total bilirubin greater than or equal to 2 times upper limit of normal (ULN)

Active or uncontrolled infection

2.3 Preparation and Administration

Decitabine for injection is a cytotoxic drug. Follow special handling and disposal procedures.[1]

Aseptically reconstitute decitabine for injection with room temperature (20 ℃ to 25 ℃) 10 mL of Sterile Water for Injection, USP. Upon reconstitution, the final concentration of the reconstituted decitabine for injection solution is 5 mg/mL. You must dilute the reconstituted solution with 0.9% Sodium Chloride Injection or 5% Dextrose Injection prior to administration. Temperature of the diluent (0.9% Sodium Chloride Injection or 5% Dextrose Injection) depends on time of administration after preparation.

For Administration Within 15 Minutes of Preparation

If decitabine for injection is intended to be administered within 15 minutes from the time of preparation,
to
Injection or 5% Dextrose Injection to a final concentration of 0.1 mg/mL to 1 mg/mL. Discard unused portion.

For Delayed Administration

If decitabine for injection is intended to be administered after 15 minutes of preparation, dilute the
to
to a final concentration of 0.1 mg/mL to to
solution must be used within 4 hours from the time of preparation. Discard unused portion.

Use the diluted, refrigerated solution within 4 hours from the time of preparation or discard.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if there is evidence of particulate matter or discoloration.

3 DOSAGE FORMS AND STRENGTHS

For Injection: 50 mg of decitabine as a sterile, white to almost white lyophilized powder in a single-dose vial for reconstitution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Fatal and serious myelosuppression occurs in decitabine-treated patients. Myelosuppression (anemia, neutropenia, and thrombocytopenia) is the most frequent cause of decitabine dose reduction, delay, and discontinuation. Neutropenia of any grade occurred in 90% of decitabine-treated patients with grade 3 or 4 occurring in 87% of patients. Grade 3 or 4 febrile neutropenia occurred in 23% of patients. Thrombocytopenia of any grade occurred in 89% of patients with grade 3 or 4 occurring in 85% of patients. Anemia of any grade occurred in 82% of patients. Perform complete blood count with platelets at baseline, prior to each cycle, and as needed to monitor response and toxicity. Manage toxicity using dose-delay, dose-reduction, growth factors, and anti-infective therapies as needed *[see Dosage and Administration (2.2)]*. Myelosuppression and worsening neutropenia may occur more frequently in the first or second treatment cycles and may not necessarily indicate progression of underlying MDS.

5.2 Embryo-Fetal Toxicity

Based on findings from human data, animal studies and its mechanism of action, decitabine can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1) and Nonclinical Toxicology (13.1)]*. In preclinical studies in mice and rats, decitabine caused adverse developmental outcomes including embryo-fetal lethality and malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception while receiving decitabine and for 6 months following the last dose. Advise males with female partners of reproductive potential to use effective contraception while receiving treatment with decitabine and for 3 months following the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

Myelosuppression [*see Warnings and Precautions (5.1)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of decitabine was studied in 3 single-arm studies (N = 66, N = 98, N = 99) and 1 controlled supportive care study (N = 83 decitabine, N = 81 supportive care). The data described below reflect exposure to decitabine in 83 patients in the MDS trial. In the trial, patients received 15 mg/m^2 intravenously every 8 hours for 3 days every 6 weeks. The median number of decitabine cycles was 3 (range 0 to 9).

Most Common Adverse Reactions: neutropenia, thrombocytopenia, anemia, fatigue, pyrexia, nausea, cough, petechiae, constipation, diarrhea, and hyperglycemia.

Adverse Reactions Most Frequently 1%) Resulting in Clinical Intervention and or Dose Modification in the Controlled Supportive Care Study in the Decitabine Arm:

Discontinuation: thrombocytopenia, neutropenia, pneumonia, Mycobacterium avium complex infection, cardio-respiratory arrest, increased blood bilirubin, intracranial hemorrhage, abnormal liver function tests.

Dose Delayed: neutropenia, pulmonary edema, atrial fibrillation, central line infection, febrile neutropenia.

Dose Reduced: neutropenia, thrombocytopenia, anemia, lethargy, edema, tachycardia, depression, pharyngitis.

Table 1 presents all adverse reactions occurring in at least 5% of patients in the decitabine group and at a rate greater than supportive care.

Table 1 Adverse Reactions Reported in 5% of Patients in the Decitabine Group and at a Rate Greater than Supportive Care in the Controlled Trial in MDS

	Decitabine N = 83 (%)	**Supportive Care N = 81 (%)**
Blood and lymphatic system disorders		
Neutropenia	75 (90)	58 (72)
Thrombocytopenia	74 (89)	64 (79)
Anemia NOS	68 (82)	60 (74)
Febrile neutropenia	24 (29)	5 (6)
Leukopenia NOS	23 (28)	11 (14)
Lymphadenopathy	10 (12)	6 (7)

	Decitabine N = 83 (%)	Supportive Care N = 81 (%)
Thrombocythemia	4 (5)	1 (1)
Cardiac disorders		
Pulmonary edema NOS	5 (6)	0 (0)
Eye disorders		
Vision blurred	5 (6)	0 (0)
Gastrointestinal disorders		
Nausea	35 (42)	13 (16)
Constipation	29 (35)	11 (14)
Diarrhea NOS	28 (34)	13 (16)
Vomiting NOS	21 (25)	7 (9)
Abdominal pain NOS	12 (14)	5 (6)
Oral mucosal petechiae	11 (13)	4 (5)
Stomatitis	10 (12)	5 (6)
Dyspepsia	10 (12)	1 (1)
Ascites	8 (10)	2 (2)
Gingival bleeding	7 (8)	5 (6)
Hemorrhoids	7 (8)	3 (4)
Loose stools	6 (7)	3 (4)
Tongue ulceration	6 (7)	2 (2)
Dysphagia	5 (6)	2 (2)
Oral soft tissue disorder NOS	5 (6)	1 (1)
Lip ulceration	4 (5)	3 (4)
Abdominal distension	4 (5)	1 (1)
Abdominal pain upper	4 (5)	1 (1)
Gastro-esophageal reflux disease	4 (5)	0 (0)
Glossodynia	4 (5)	0 (0)
General disorders and administrative site disorders		
Pyrexia	44 (53)	23 (28)
Edema peripheral	21 (25)	13 (16)
Rigors	18 (22)	

	Decitabine N = 83 (%)	Supportive Care N = 81 (%)
Hepatobiliary disorders		
Hyperbilirubinemia	12 (14)	4 (5)
Infections and infestations		
Pneumonia NOS	18 (22)	11 (14)
Cellulitis	10 (12)	6 (7)
Candidal infection NOS	8 (10)	1 (1)
Catheter related infection	7 (8)	0 (0)
Urinary tract infection NOS	6 (7)	1 (1)
Staphylococcal infection	6 (7)	0 (0)
Oral candidiasis	5 (6)	2 (2)
Sinusitis NOS	4 (5)	2 (2)
Bacteremia	4 (5)	0 (0)
Injury, poisoning and procedural complications		
Transfusion reaction	6 (7)	3 (4)
Abrasion NOS	4 (5)	1 (1)
Investigations		
Cardiac murmur NOS	13 (16)	9 (11)
Blood alkaline phosphatase NOS increased	9 (11)	7 (9)
Aspartate aminotransferase increased	8 (10)	7 (9)
Blood urea increased	8 (10)	1 (1)
Blood lactate dehydrogenase increased	7 (8)	5 (6)
Blood albumin decreased	6 (7)	0 (0)
Blood bicarbonate increased	5 (6)	1 (1)
Blood chloride decreased	5 (6)	1 (1)
Protein total decreased	4 (5)	3 (4)
Blood bicarbonate decreased	4 (5)	1 (1)
Blood bilirubin decreased	4 (5)	1 (1)
Metabolism and nutrition disorders		
Hyperglycemia NOS	27 (33)	16 (20)
Hypoalbuminemia	20 (24)	14 (17)
Hypomagnesemia	20 (24)	6 (7)
Hypokalemia	18 (22)	10 (12)
Hyponatremia	16 (19)	13 (16)
Appetite decreased NOS	13 (16)	12 (15)
Anorexia	13 (16)	8 (10)
Hyperkalemia	11 (13)	3 (4)
Dehydration	5 (6)	4 (5)
Musculoskeletal and connective tissue disorders		
Arthralgia	17 (20)	8 (10)
Pain in limb	16 (19)	8 (10)
Back pain	14 (17)	5 (6)
Chest wall pain	6 (7)	1 (1)

	Decitabine N = 83 (%)	Supportive Care N = 81 (%)
Musculoskeletal discomfort	5 (6)	0 (0)
Myalgia	4 (5)	1 (1)
Nervous system disorders		
Headache	23 (28)	11 (14)
Dizziness	15 (18)	10 (12)
Hypoesthesia	9 (11)	1 (1)
Psychiatric disorders		
Insomnia	23 (28)	11 (14)
Confusional state	10 (12)	3 (4)
Anxiety	9 (11)	8 (10)
Renal and urinary disorders		
Dysuria	5 (6)	3 (4)
Urinary frequency	4 (5)	1 (1)
Respiratory, thoracic and Mediastinal disorders		
Cough	33 (40)	25 (31)
Pharyngitis	13 (16)	6 (7)
Crackles lung	12 (14)	1 (1)
Breath sounds decreased	8 (10)	7 (9)
Hypoxia	8 (10)	4 (5)
Rales	7 (8)	2 (2)
Postnasal drip	4 (5)	2 (2)
Skin and subcutaneous tissue disorders		
Ecchymosis	18 (22)	12 (15)
Rash NOS	16 (19)	7 (9)
Erythema	12 (14)	5 (6)
Skin lesion NOS	9 (11)	3 (4)
Pruritis	9 (11)	2 (2)
Alopecia	7 (8)	1 (1)
Urticaria NOS	5 (6)	1 (1)
Swelling face	5 (6)	0 (0)
Vascular disorders		
Petechiae	32 (39)	13 (16)
Pallor	19 (23)	10 (12)
Hypotension NOS	5 (6)	4 (5)
Hematoma NOS	4 (5)	3 (4)

In a single-arm MDS study (N=99), decitabine was dosed at 20 mg/m^2 intravenously, infused over one hour daily, for 5 consecutive days of a 4-week cycle. Table 2 presents all adverse reactions occurring in at least 5% of patients.

Table 2 Adverse Reactions Reported in 5% of Patients in a Single-arm Study[*]

	Decitabine N = 99 (%)
Blood and lymphatic system disorders	
Anemia	31 (31)
Febrile neutropenia	20 (20)
Leukopenia	6 (6)
Neutropenia	38 (38)
Pancytopenia	5 (5)
Thrombocythemia	5 (5)
Thrombocytopenia	27 (27)
Cardiac disorders	
Cardiac failure congestive	5 (5)
Tachycardia	8 (8)
Ear and labyrinth disorders	
Ear pain	6 (6)
Gastrointestinal disorders	
Abdominal pain	14 (14)
Abdominal pain upper	6 (6)
Constipation	30 (30)
Diarrhea	28 (28)
Dyspepsia	10 (10)
Dysphagia	5 (5)
Gastro-esophageal reflux disease	5 (5)
Nausea	40 (40)
Oral pain	5 (5)
Stomatitis	11 (11)
Toothache	6 (6)
Vomiting	16 (16)
General disorders and administration site conditions	
Asthenia	15 (15)
Chest pain	6 (6)
Chills	16 (16)
Fatigue	46 (46)
Mucosal inflammation	9 (9)
Edema	5 (5)
Edema peripheral	27 (27)
Pain	5 (5)
Pyrexia	36 (36)
Infections and infestations	
Cellulitis	9 (9)
Oral candidiasis	6 (6)
Pneumonia	20 (20)

	Decitabine N = 99 (%)
Sinusitis	6 (6)
Staphylococcal bacteremia	8 (8)
Tooth abscess	5 (5)
Upper respiratory tract infection	10 (10)
Urinary tract infection	7 (7)
Injury, poisoning and procedural complications	
Contusion	9 (9)
Investigations	
Blood bilirubin increased	6 (6)
Breath sounds abnormal	5 (5)

	Decitabine N = 99 (%)
Skin and subcutaneous tissue disorders	
Dry skin	8 (8)
Ecchymosis	9 (9)
Erythema	5 (5)
Night sweats	5 (5)
Petechiae	12 (12)
Pruritus	9 (9)
Rash	11 (11)
Skin lesion	5 (5)
Vascular disorders	
Hypertension	6 (6)
Hypotension	11 (11)

* In this single arm study, investigators reported adverse events based on clinical signs and symptoms rather than predefined laboratory abnormalities. Thus, not all laboratory abnormalities were recorded as adverse events.

No overall difference in safety was detected between patients > 65 years of age and younger patients in these MDS trials. No significant differences in safety were detected between males and females. Patients with renal or hepatic dysfunction were not studied. Insufficient numbers of non-White patients were available to draw conclusions in these clinical trials.

Serious adverse reactions that occurred in patients receiving decitabine not previously reported in Table 1 and Table 2 include:

Allergic Reaction: hypersensitivity (anaphylactic reaction)

Blood and Lymphatic System Disorders: myelosuppression, splenomegaly

Cardiac Disorders: myocardial infarction, cardio-respiratory arrest, cardiomyopathy, atrial fibrillation, supraventricular tachycardia

Gastrointestinal Disorders: gingival pain, upper gastrointestinal hemorrhage

General Disorders and Administrative Site Conditions: chest pain, catheter site hemorrhage

Hepatobiliary Disorders: cholecystitis

Infections and Infestations: fungal infection, sepsis, bronchopulmonary aspergillosis, peridiverticular abscess, respiratory tract infection, pseudomonal lung infection, Mycobacterium avium complex infection

Injury, Poisoning and Procedural Complications: post procedural pain, post procedural hemorrhage

Nervous System Disorders: intracranial hemorrhage

Psychiatric Disorders: mental status changes

Renal and Urinary Disorders: renal failure, urethral hemorrhage

Respiratory, Thoracic and Mediastinal Disorders: hemoptysis, lung infiltration, pulmonary embolism, respiratory arrest, pulmonary mass

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of decitabine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

syndrome (acute febrile neutrophilic dermatosis)

Differentiation syndrome

Interstitial lung disease

7 DRUG INTERACTIONS

Drug interaction studies with decitabine have not been conducted. In vitro studies in human liver microsomes suggest that decitabine is unlikely to inhibit or induce cytochrome P450 enzymes. In vitro metabolism studies h1 0 TJTc[(in)] TJETQq0.00000912 0 612 792 reW* nBT/F1 12 Tf1 0 0 1 4l73 46(62

There are no data on the presence of decitabine or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions from decitabine in a breastfed child, advise women not to breastfeed while receiving decitabine and for at least 2 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Conduct pregnancy testing of females of reproductive potential prior to initiating decitabine.

Contraception

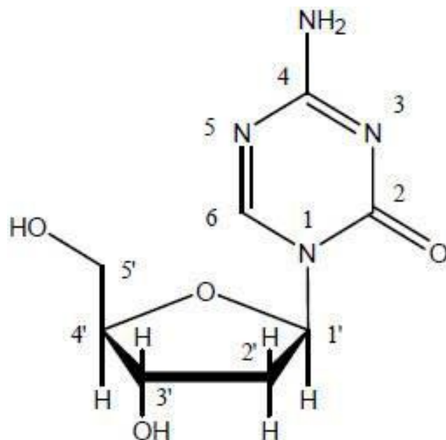
Females

Decitabine can cause fetal harm when administered to pregnant women [*see Use in Specific*

Breastfed

11 DESCRIPTION

Decitabine is a nucleoside metabolic inhibitor. Decitabine is a fine, white to almost white powder with the molecular formula of $C_8H_{12}N_4O_4$ and a molecular weight of 228.21. Its chemical name is 4-amino-1-(2-deoxy- -D-erythro-pentofuranosyl)-1,3,5-triazin-2(1*H*)-one and it has the following structural formula:



Decitabine is slightly soluble in ethanol/water (50/50), methanol/water (50/50) and methanol; sparingly soluble in water and soluble in dimethylsulfoxide (DMSO).

Decitabine for Injection, for intravenous use, is a sterile, white to almost white lyophilized powder supplied in a clear colorless glass single-dose vial. Each single-dose glass vial contains 50 mg decitabine, 68 mg monobasic potassium phosphate (potassium dihydrogen phosphate) and 11.6 mg sodium hydroxide. Sodium hydroxide and/or hydrochloric acid are used for pH adjustment.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Decitabine is believed to exert its antineoplastic effects after phosphorylation and direct incorporation into DNA and inhibition of DNA methyltransferase, causing hypomethylation of DNA and cellular differentiation or apoptosis. Decitabine inhibits DNA methylation in vitro, which is achieved at concentrations that do not cause major suppression of DNA synthesis. Decitabine-induced hypomethylation in neoplastic cells may restore normal function to genes that are critical for the control of cellular differentiation and proliferation. In rapidly dividing cells, the cytotoxicity of decitabine may also be attributed to the formation of covalent adducts between DNA methyltransferase and decitabine incorporated into DNA. Non-proliferating cells are relatively insensitive to decitabine.

12.2 Pharmacodynamics

Decitabine has been shown to induce hypomethylation both in vitro and in vivo. However, there have been no studies of decitabine-induced hypomethylation and pharmacokinetic parameters.

12.3 Pharmacokinetics

Pharmacokinetic (PK) parameters were evaluated in patients. Eleven patients received 20 mg/m^2 infused over 1 hour intravenously (treatment Option 2). Fourteen patients received 15 mg/m^2 infused over 3 hours intravenously (treatment Option 1). PK parameters are shown in Table 3. Plasma concentration-time profiles after discontinuation of infusion showed a biexponential decline. The clearance (CL) of decitabine was higher following treatment Option 2. Upon repeat doses, there was no systemic accumulation of decitabine or any changes in PK parameters. Population PK analysis (N=35) showed that the cumulative AUC per cycle for treatment Option 2 was 2.3-fold lower than the cumulative AUC per cycle following treatment Option 1.

Table 3 Mean (CV% or 95% CI) Pharmacokinetic Parameters of Decitabine

Dose	C_{max} (ng/mL)	AUC_{0-INF} (ng h/mL)	$T_{1/2}$ (h)	CL (L/h/m^2)	$AUC_{Cumulative}$ (ng h/mL)
15 mg/m^2 3- hr infusion every 8 hours for 3 days					

(ng h/mL

Demographic or Other Patient Characteristic	Decitabine N = 89	Supportive Care N = 81
Platelet Transfusion Status n (%)		
Independent	69 (78)	62 (77)
Dependent	20 (22)	19 (23)
IPSS Classification n (%)		
Intermediate-1	28 (31)	24 (30)
Intermediate-2	38 (43)	36 (44)
High Risk	23 (26)	21 (26)
FAB Classification n (%)		
RA	12 (13)	12 (15)
RARS	7 (8)	4 (5)
RAEB	47 (53)	43 (53)
RAEB-t	17 (19)	14 (17)
CMML	6 (7)	8 (10)

Patients randomized to the decitabine arm received decitabine intravenously infused at a dose of 15 mg/m^2 over a 3-hour period, every 8 hours, for 3 consecutive days. This cycle was repeated every 6 weeks, depending on the clinical response and toxicity. Supportive care consisted of blood and blood product transfusions, prophylactic antibiotics, and hematopoietic growth factors. The study endpoints were overall response rate (complete response + partial response) and time to AML or death. Responses were classified using the MDS International Working Group (IWG) criteria; patients were required to be RBC and platelet transfusion independent during the time of response. Response criteria are given in **Table 5**.

Table 5 Response Criteria for the Controlled Trial in MDS*

Complete Response (CR) 8 weeks	**Bone Marrow**	**On repeat aspirates:** • < 5% myeloblasts • No dysplastic changes
	Peripheral Blood	**In all samples during response:** • Hgb > 11 g/dL (no transfusions or erythropoietin • ANC growth factor) • Platelets (no thrombopoietic agent) • No blasts and no dysplasia
Partial Response (PR) 8 weeks	**Bone Marrow**	**On repeat aspirates:** • 50% decrease in blasts over pretreatment values OR • Improvement to a less advanced MDS FAB classification
	Peripheral Blood	**Same as for CR**

*Cheson BD, Bennett JM, et al. Report of an International Working Group to Standardize Response Criteria for MDS. *Blood.* 2000; 96:3671-3674.

The overall response rate (CR+PR) in the ITT population was 17% in decitabine-treated patients and 0% in the SC group (p<0.001) (**see Table 6**). The overall response rate was 21% (12/56) in decitabine-treated patients considered evaluable for response (i.e., those patients with pathologically confirmed MDS at baseline who received at least 2 cycles of treatment). The median duration of response (range) for patients who responded to decitabine was 288 days (116-388) and median time to response (range) was 93 days (55-272). All but one of the decitabine-treated patients who responded did so by the fourth cycle. Benefit was seen in an additional 13% of decitabine-treated patients who had hematologic improvement, defined as a response less than PR lasting at least 8 weeks, compared to 7% of SC patients. Decitabine treatment did not significantly delay the median time to AML or death versus supportive care.

Table 6 Analysis of Response (ITT)

Parameter	**Decitabine N=89**	**Supportive Care N=81**
Overall Response Rate (CR+PR)	**15 (17%)***	**0 (0%)**
Complete Response (CR)	8 (9%)	0 (0%)
Partial Response (PR)	7 (8%)	0 (0%)
Duration of Response		
Median time to (CR+PR) response - Days (range)	93 (55-272)	NA
Median Duration of (CR+PR) response - Days (range)	288 (116-388)	NA

*p-value <0.001 from two-sided Fisher's Exact Test comparing Decitabine vs. Supportive Care.
In the statistical analysis plan, a p-value of 0.024 was required to achieve statistical significance.

All patients with a CR or PR were RBC and platelet transfusion independent in the absence of growth factors.

Responses occurred in patients with an adjudicated baseline diagnosis of AML.

14.2 Single-arm Studies in Myelodysplastic Syndrome

Three open-label, single-arm, multicenter studies were conducted to evaluate the safety and efficacy of decitabine in MDS patients with any of the FAB subtypes. In one study conducted in North America, 99 patients with IPSS Intermediate-1, Intermediate-2, or high-risk prognostic scores received decitabine 20 mg/m^2 as an intravenous infusion over 1-hour daily, on days 1-5 of week 1, every 4 weeks (1 cycle). The results were consistent with the results of the controlled trial and are summarized in **Table 8**.

Table 7 Baseline Demographics and Other Patient Characteristics (ITT)

Demographic or Other Patient Characteristic	**Decitabine N = 99**
Age (years)	
Mean (±SD)	71 ±9
Median (Range: min-max)	72 (34-87)
Sex n (%)	
Male	71 (72)
Female	28 (28)

Demographic or Other Patient Characteristic	Decitabine N = 99
Race n (%)	
White	86 (87)
Black	6 (6)
Asian	4 (4)
Other	3 (3)
Days From MDS Diagnosis to First Dose	
Mean (±SD)	444±626
Median (Range: min-max)	154 (7-3079)
Previous MDS Therapy n (%)	
Yes	27 (27)
No	72 (73)
RBC Transfusion Status n (%)	
Independent	33 (33)
Dependent	66 (67)
Platelet Transfusion Status n (%)	
Independent	84 (85)
Dependent	15 (15)
IPSS Classification n (%)	
Low Risk	1 (1)
Intermediate 1	52 (53)
Intermediate 2	23 (23)
High Risk	23 (23)
FAB Classification n (%)	
RA	20 (20)
RARS	17 (17)
RAEB	45 (45)
RAEB-t	6 (6)
CMML	11 (11)

Table 8 Analysis of Response (ITT)*

Parameter	Decitabine N=99
Overall Response Rate (CR+PR)	**16 (16%)**
Complete Response (CR)	15 (15%)
Partial Response (PR)	1 (1%)
Duration of Response	
Median time to (CR+PR) response - Days (range)	162 (50-267)
Median Duration of (CR+PR) response - Days (range)	443 (72-722$^+$)

* Cheson BD, Bennett JM, et al. Report of an International Working Group to Standardize Response Criteria for MDS. *Blood*. 2000; 96:3671-3674.

$^+$ indicates censored observation

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