





that discussed or mentioned during the first 1 to 2 cycles of subcutaneous treatment compared with later cycles included thrombocytopenia, neutropenia, anemia, nausea, vomiting, injection site erythema/pain/bruising/reaction, constipation, petechiae, dizziness, anxiety, hypokalemia, and insomnia. There did not appear to be any adverse reactions that increased in frequency over the course of treatment.

Overall, adverse reactions were qualitatively similar between the intravenous and subcutaneous studies. Adverse reactions that appeared to be specifically associated with the intravenous route of administration included infusion site reactions (e.g. erythema or pain) and catheter site reactions (e.g. infection, erythema, or hemorrhage).

In clinical studies of either subcutaneous or intravenous Azacitidine, the following serious adverse reactions occurring at a rate of <5% (and not described in Tables 2 or 3) were reported:

**Blood and lymphatic system disorders:** agranulocytosis, bone marrow failure, pancytopenia splenomegaly.

**Cardiac disorders:** atrial fibrillation, cardiac failure, cardiac failure congestive, cardiorespiratory arrest, congestive cardiomyopathy.

**Eye disorders:** eye hemorrhage

**Gastrointestinal disorders:** diverticulitis, gastrointestinal hemorrhage, melena, perirectal abscess.

**General disorders and administration site conditions:** catheter site hemorrhage, general physical health deterioration, systemic inflammatory response syndrome.

**Hepatobiliary disorders:** cholecystitis.

**Immune system disorders:** anaphylactic shock, hypersensitivity.

**Infections and infestations:** abscess limb, bacterial infection, cellulitis, blastomycosis, injection site infection, Klebsiella sepsis, neutropenic sepsis, pharyngitis streptococcal, pneumonia Klebsiella, sepsis, septic shock, Staphylococcal bacteremia, Staphylococcal infection, toxoplasmosis.

**Metabolism and nutrition disorders:** dehydration.

**Musculoskeletal and connective tissue disorders:** bone pain aggravated, muscle weakness, neck pain.

**Neoplasms benign, malignant and unspecified:** leukemia cutis.

**Nervous system disorders:** cerebral hemorrhage, convulsions, intracranial hemorrhage.

**Renal and urinary disorders:** loin pain, renal failure.

**Respiratory, thoracic and mediastinal disorders:** hemoptysis, lung infiltration, pneumonitis, respiratory distress.

**Skin and subcutaneous tissue disorders:** pyoderma gangrenosum, rash pruritic, skin induration.

**Surgical and medical procedures:** cholecystectomy.

**Vascular disorders:** orthostatic hypotension.

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## 6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of Azacitidine. 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.

- Interstitial lung disease
- Tumor lysis syndrome
- Injection site necrosis
- Sweet's syndrome (acute febrile neutrophilic dermatosis)
- Necrotizing fasciitis (including fatal cases)
- Differentiation syndrome
- Pericardial effusion
- Pericarditis
- Cutaneous vasculitis

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Based on its mechanism of action and findings in animals, Azacitidine can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no data on the use of azacitidine in pregnant women. Azacitidine was teratogenic and caused embryo-fetal lethality in animals at doses lower than the recommended human daily dose *(see Data)*. Advise pregnant women of the potential risk to the fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

#### Data

##### Animal Data

Early embryotoxicity studies in mice revealed a 44% frequency of intrauterine embryonal death (increased resorption) after a single IP (intraperitoneal) injection of 6 mg/m<sup>2</sup> (approximately 8% of the recommended human daily dose on a mg/m<sup>2</sup> basis) azacitidine on gestation day 10. Developmental abnormalities in the brain have been detected in mice given azacitidine on or before gestation day 15 at doses of ~3-12 mg/m<sup>2</sup> (approximately 4%-16% the recommended human daily dose on a mg/m<sup>2</sup> basis).

In rats, azacitidine was clearly embryotoxic when given IP on gestation days 4-8 (postimplantation) at a dose of 6 mg/m<sup>2</sup> (approximately 8% of the recommended human daily dose on a mg/m<sup>2</sup> basis), although treatment in the preimplantation period (on gestation days 1-3) had no adverse effect on the embryos. Azacitidine caused multiple fetal abnormalities in rats after a single IP dose of 3 to 12 mg/m<sup>2</sup> (approximately 8% the recommended human daily dose on a mg/m<sup>2</sup> basis) given on gestation day 9, 10, 11 or 12. In this study azacitidine caused fetal death when administered at 3-12 mg/m<sup>2</sup> on gestation days 9 and 10, average live animals per litter was reduced to 9% of control at the highest dose on gestation day 9. Fetal anomalies included: CNS anomalies (exencephaly/encephalocele), limb anomalies (micromelia, club foot, syndactyly, oligodactyly), and others (micrognathia, gastroschisis, edema, and rib abnormalities).

### 8.2 Lactation

#### Risk Summary

There is no information regarding the presence of azacitidine in human milk, the effects of Azacitidine on the breastfed infant, or the effects of Azacitidine on milk production. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for azacitidine in animal studies *[see Nonclinical Toxicology (13.1)]* and the potential for serious adverse reactions in nursing infants from Azacitidine, advise patients not to breastfeed during treatment with Azacitidine and for 1 week after the last dose.

### 8.3 Females and Males of Reproductive Potential

Based on its mechanism of action and findings in animals, Azacitidine can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

#### Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating azacitidine.

#### Contraception

##### Females

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with azacitidine and for 6 months after the last dose.

##### Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with azacitidine and for 3 months after the last dose.

#### Infertility

Based on animal data, azacitidine could have an effect on male or female fertility *[see Nonclinical Toxicology (13.1)]*.

### 8.4 Pediatric Use

Effectiveness and safety of azacitidine in pediatric patients with MDS have not been established.

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### 8.5 Geriatric Use

Of the total number of patients in Studies 1, 2 and 3, 62% were 65 years and older and 21% were 75 years and older. No overall differences in effectiveness were observed between these patients and younger patients. In addition, there were no relevant differences in the frequency of adverse reactions observed in patients 65 years and older compared to younger patients.

Of the 179 patients randomized to azacitidine in Study 4, 68% were 65 years and older and 21% were 75 years and older. Survival data for patients 65 years and older were consistent with overall survival results. The majority of adverse reactions occurred at similar frequencies in patients < 65 years of age and patients 65 years of age and older.

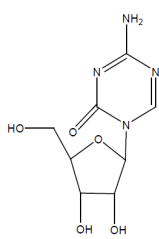
Elderly patients are more likely to have decreased renal function. Monitor renal function in these patients *[see Dosage and Administration (2.7) and Warnings and Precautions (5.4)]*.

### 10 OVERDOSAGE

One case of overdose with Azacitidine was reported during clinical trials. A patient experienced diarrhea, nausea, and vomiting after receiving a single intravenous dose of approximately 290 mg/m<sup>2</sup>, almost 4 times the recommended starting dose. The events resolved without sequelae, and the correct dose was resumed the following day. In the event of overdose, the patient should be monitored with appropriate blood counts and should receive supportive treatment, as necessary. There is no known specific antidote for Azacitidine overdose.

### 11 DESCRIPTION

Azacitidine for injection contains azacitidine, which is a nucleoside metabolic inhibitor. Azacitidine is 4-amino-1-β-D-ribofuranosyl-5-triazin-2(1H)-one. The structural formula is as follows:



The empirical formula is C<sub>6</sub>H<sub>7</sub>N<sub>5</sub>O<sub>5</sub>. The molecular weight is 244. Azacitidine is a white to off-white solid. Azacitidine was found to be insoluble in acetone, ethanol, and methyl ethyl ketone; slightly soluble in ethanol/water (50/50), propylene glycol, and polyethylene glycol; sparingly soluble in water, water saturated octanol, 5% dextrose in water, N-methyl-2-pyrrolidone, normal saline and 5% Tween 80 in water; and soluble in dimethylsulfoxide (DMSO).

The finished product is supplied in a sterile form for reconstitution as a suspension for subcutaneous injection or reconstitution as a solution with further dilution for intravenous infusion. Vials of Azacitidine for injection contain 100 mg of azacitidine and 100 mg mannitol as a sterile lyophilized powder.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Azacitidine is a pyrimidine nucleoside analog of cytidine. Azacitidine is believed to exert its antineoplastic effects by causing hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow. The concentration of azacitidine required for maximum inhibition of DNA methylation *in vitro* does not cause major suppression of DNA synthesis. Hypomethylation may restore normal function to genes that are critical for differentiation and proliferation. The cytotoxic effects of azacitidine cause the death of rapidly dividing cells, including cancer cells that are no longer responsive to normal growth control mechanisms. Non-proliferating cells are relatively insensitive to azacitidine.

### 12.2 Pharmacodynamics

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### 12.3 Pharmacokinetics

The pharmacokinetics of azacitidine were studied in 6 adult patients with MDS following a single 75 mg/m<sup>2</sup> subcutaneous dose and a single 75 mg/m<sup>2</sup> intravenous dose.

#### Absorption

Azacitidine is rapidly absorbed after subcutaneous administration; the peak plasma azacitidine concentration of 750 ± 403 ng/ml occurred in 0.5 hour after subcutaneous administration.

#### Distribution

The bioavailability of subcutaneous azacitidine relative to intravenous azacitidine is approximately 89%, based on area under the curve. Mean volume of distribution following intravenous dosing is 76 ± 26 L. Mean apparent subcutaneous clearance is 167 ± 49 L/hour and mean half-life after subcutaneous administration is 41 ± 8 minutes. The AUC and C<sub>max</sub> of subcutaneous administration of azacitidine in 21 patients with cancer were approximately dose proportional within the 25 to 100 mg/m<sup>2</sup> dose range. Multiple dosing at the recommended dose-regimen does not result in drug accumulation with intravenous or subcutaneous administration.

#### Elimination

##### Metabolism

An *in vitro* study of azacitidine incubation in human liver fractions indicated that azacitidine is not metabolized by the cytochrome P450 (CYP) enzymes. Azacitidine undergoes spontaneous hydrolysis and deamination mediated by cytidine deaminase.

#### Excretion

Published studies indicate that urinary excretion is the primary route of elimination of azacitidine and its metabolites. Following intravenous administration of radioactive azacitidine to 5 cancer patients, the cumulative urinary excretion was 85% of the radioactive dose. Fecal excretion accounted for <1% of administered radioactivity over 3 days. Mean excretion of radioactivity in urine following subcutaneous administration of <sup>14</sup>C-azacitidine was 50%. The mean elimination half-lives of total radioactivity (azacitidine and its metabolites) were similar after intravenous and subcutaneous administrations, about 4 hours.

#### Specific Populations

The effects of hepatic impairment, gender, or race/ethnicity on the pharmacokinetics of intravenous and subcutaneous azacitidine have not been studied.

#### Pediatric Patients

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#### Patients with Renal Impairment

In adult patients with cancer, the pharmacokinetics of azacitidine in 6 patients with normal renal function (CL<sub>cr</sub> >80 mL/min) and 6 patients with severe renal impairment (CL<sub>cr</sub> <30 mL/min) were compared following daily subcutaneous dosing (Days 1 through 5) at 75 mg/m<sup>2</sup>/day. Severe renal impairment increased azacitidine exposure by approximately 70% after single and 41% after multiple subcutaneous administrations. This increase in exposure was not correlated with an increase in adverse events. The exposure was similar to exposure in patients with normal renal function receiving 100 mg/m<sup>2</sup>.

#### Drug-Drug Interactions

No normal clinical drug interaction studies with azacitidine have been conducted.

#### *In vitro* Studies

*Cytochrome P450 (CYP) Enzymes:* An *in vitro* study at azacitidine concentrations up to 100 μM (IV C<sub>max</sub> = 10.6 μM) in human liver microsomes indicated that azacitidine does not cause any inhibition of CYP isoforms CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, or CYP2E1 at clinically achievable concentrations.

*In vitro* studies with human cultured hepatocytes indicate that azacitidine at concentrations of 1.0 μM

to 100 μM does not induce CYP 1A2, 2C19, or 3A4/5.

*Transporter Systems:* An *in vitro* study with LLC-PK1 cells expressing P-glycoprotein (P-gp) indicated that azacitidine is not a substrate or inhibitor of P-gp.

Azacitidine does not inhibit, breast cancer resistance protein (BCRP), organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptides (OATP) OATP1B1 and OATP1B3, or organic cation transporter (OCT) OCT2 at clinically relevant concentrations.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The potential carcinogenicity of azacitidine was evaluated in mice and rats. Azacitidine induced tumors of the hematopoietic system in female mice at 2.2 mg/kg (6.6 mg/m<sup>2</sup>; approximately 8% the recommended human daily dose on a mg/m<sup>2</sup> basis) administered IP three times per week for 52 weeks. An increased incidence of tumors in the lymphoreticular system, lung, mammary gland, and skin was seen in mice treated with azacitidine IP at 2.0 mg/kg (6.0 mg/m<sup>2</sup>; approximately 8% the recommended human daily dose on a mg/m<sup>2</sup> basis) once a week for 50 weeks. A tumorigenicity study in rats dosed twice weekly at 15 or 60 mg/m<sup>2</sup> (approximately 20%-80% the recommended human daily dose on a mg/m<sup>2</sup> basis) revealed an increased incidence of testicular tumors compared with controls.

The mutagenic and clastogenic potential of azacitidine was tested in *in vitro* bacterial systems Salmonella typhimurium strains TA100 and several strains of trpE8, *Escherichia coli* strains WVP14 Pro, WP3103P, WP3104P, and CC103; in *in vitro* forward gene mutation assay in mouse lymphoma cells and human lymphoblast cells; and in an *in vitro* micronucleus assay in mouse L5178Y lymphoma cells and Syrian hamster embryo cells. Azacitidine was mutagenic in bacterial and mammalian cell systems. The clastogenic effect of azacitidine was shown by the induction of micronuclei in L5178Y mouse cells and Syrian hamster embryo cells.

Administration of azacitidine to male mice at 9.9 mg/m<sup>2</sup> (approximately 9% the recommended human daily dose on a mg/m<sup>2</sup> basis) daily for 3 days prior to mating with untreated female mice resulted in decreased fertility and loss of offspring during subsequent embryonic and postnatal development. Treatment of male rats 3 times per week for 11 or 16 weeks at doses of 15-30 mg/m<sup>2</sup> (approximately 20%-40% the recommended human daily dose on a mg/m<sup>2</sup> basis) resulted in decreased weight of the testes and epididymides, and decreased sperm counts accompanied by decreased pregnancy rates and increased loss of embryos in mated females. In a related study, male rats treated for 16 weeks at 24 mg/m<sup>2</sup> resulted in an increase in abnormal embryos in mated females when examined on day 2 of gestation.

## 14 CLINICAL STUDIES

### 14.1 Myelodysplastic Syndromes (MDS)

Study 1 was a randomized, open-label, controlled trial carried out in 53 U.S. sites compared the safety and efficacy of subcutaneous Azacitidine plus supportive care with supportive care alone ("observation") in adult patients with any of the five FAB subtypes of myelodysplastic syndromes (MDS): refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMoL). RA and RARS patients were included if they met one or more of the following criteria: required packed RBC transfusions; had platelet counts ≤ 50.0 x 10<sup>9</sup>/L; required platelet transfusions; or were neutropenic (ANC <1.0 x 10<sup>9</sup>/L with infections requiring treatment with antibiotics. Patients with acute myelogenous leukemia (AML) were not intended to be included. Supportive care allowed in this study included blood transfusion products, antibiotics, antiemetics, analgesics and antipyretics. The use of hematopoietic growth factors was prohibited. Baseline patient and disease characteristics are summarized in Table 6; the 2 groups were similar.

Azacitidine was administered at a subcutaneous dose of 75 mg/m<sup>2</sup> daily for 7 days every 4 weeks. The dose was increased to 100 mg/m<sup>2</sup> if no beneficial effect was seen after 2 treatment cycles. The dose was decreased and/or delayed based on hematologic response or evidence of renal toxicity. Patients in the observation arm were allowed by protocol to cross over to Azacitidine if they had increases in bone marrow blasts, decreases in hemoglobin, increases in red cell transfusion requirements, or decreases in platelets, or if they required a platelet transfusion or developed a clinical infection requiring treatment with antibiotics. For purposes of assessing efficacy, the primary endpoint was response rate (as defined in Table 7).

Of the 191 patients included in the study, independent review (adjudicated diagnosis) found that 19 had the diagnosis of AML at baseline. These patients were excluded from the primary analysis of response rate, although they were included in an intent-to-treat (ITT) analysis of all patients randomized. Approximately 55% of the patients randomized to observation crossed over to receive Azacitidine treatment.

Table 6. Baseline Demographics and Disease Characteristics

	Azacitidine (N=99)	Observation (N=92)
<b>Gender (n%)</b>		
Male	72 (72.7)	60 (65.2)
Female	27 (27.3)	32 (34.8)
<b>Race (n%)</b>		
White	93 (93.9)	85 (92.4)
Black	1 (1.0)	1 (1.1)
Hispanic	3 (3.0)	5 (5.4)
Asiani/Oriental	2 (2.0)	1 (1.1)
<b>Age (years)</b>		
N	99	91
Mean ± SD	67.3 ± 10.39	68.0 ± 10.23
Range	31 - 92	35 - 88
<b>Adjudicated MDS diagnosis at study entry (n%)</b>		
RA	21 (21.2)	18 (19.6)
RARS	6 (6.1)	5 (5.4)
RAEB	38 (38.4)	39 (42.4)
RAEB-T	16 (16.2)	14 (15.2)
CMMoL	8 (8.1)	7 (7.6)
AML	10 (10.1)	9 (9.8)
<b>Transfusion product used in 3 months before study entry (n%)</b>		
Any transfusion product	70 (70.7)	59 (64.1)
Blood cells, packed human	66 (66.7)	55 (59.8)
Platelets, human blood	15 (15.2)	12 (13.0)
Hetastarch	0(0.0)	1(1.1)
Plasma protein fraction	1(1.0)	0(0.0)
Other	2(2.0)	2(2.2)

Table 7. Response Criteria

	RA	RARS	RAEB	RAEB-T	CMMoL
<b>Complete Response (CR), duration ≥ 4 weeks</b>	<b>Marrow</b>	<5% blasts			
	<b>Peripheral Blood</b>	Normal CBC if abnormal at baseline Absence of blasts in the peripheral circulation			
<b>Partial Response (PR), duration ≥ 4 weeks</b>	<b>Marrow</b>	No marrow requirements ≥50% decrease in blasts Improvement of marrow dyspoiesis			
	<b>Peripheral Blood</b>	≥50% restoration in the deficit from normal levels of baseline white cells, hemoglobin and platelets if abnormal at baseline No blasts in the peripheral circulation For CMMoL, if WBC is elevated at baseline, a ≥75% reduction in the excess count over the upper limit of normal			

The overall response rate (CR + PR) of 15.7% in Azacitidine-treated patients without AML (16.2%

for all Azacitidine randomized patients including AML) was statistically significantly higher than the response rate of 0% in the observation group (p<0.0001) (Table 8). The majority of patients who achieved either CR or PR had either 2 or 3 cell line abnormalities at baseline (79%; 11/14) and had elevated bone marrow blasts or were transfusion dependent at baseline. Patients responding to Azacitidine had a decrease in bone marrow blasts percentage, or an increase in platelets, hemoglobin or WBC. Greater than 90% of the responders initially demonstrated these changes by the 5<sup>th</sup> treatment cycle. All patients who had been transfusion dependent became transfusion independent during PR or CR. The mean and median duration of clinical response of PR or better was estimated as 512 and 330 days, respectively; 75% of the responding patients were still in PR or better at completion of treatment. Response occurred in all MDS subtypes as well as in patients with adjudicated baseline diagnosis of AML.

Table 8. Response Rates

	Azacitidine (N=89)	Observation Before Crossover (N=83)	
<b>Response</b>	<b>n (%)</b>	<b>n (%)</b>	<b>P value</b>
Overall (CR+PR)	14 (15.7)	0 (0.0)	(<0.0001)
Complete (CR)	5 ( 5.6)	0 ( 0.0)	(0.06)
Partial (PR)	9 (10.1)	0 ( 0.0)	--

Patients in the observation group who crossed over to receive Azacitidine treatment (47 patients) had a response rate of 12.8%.

Study 2, a multi-center, open-label, single-arm study of 72 patients with RAEB, RAEB-T, CMMoL, or AML, was also carried out. Treatment with subcutaneous Azacitidine resulted in a response rate (CR + PR) of 13.9%, using criteria similar to those described above. The mean and median duration of clinical response of PR or better was estimated as 810 and 430 days, respectively; 80% of the responding patients were still in PR or better at the time of completion of study involvement. In Study 3, another open-label, single-arm study of 48 patients with RAEB, RAEB-T, or AML, treatment with intravenous Azacitidine resulted in a response rate of 18.8%, again using criteria similar to those described above. The mean and median duration of clinical response of PR or better was estimated as 389 and 281 days, respectively; 67% of the responding patients were still in PR or better at the time of completion of treatment. Response occurred in all MDS subtypes as well as in patients with adjudicated baseline diagnosis of AML in both of these studies. Azacitidine dosage regimens in these 2 studies were similar to the regimen used in the controlled study.

Benefit was seen in patients who did not meet the criteria for PR or better, but were considered "improved." About 24% of Azacitidine-treated patients were considered improved, and about 2/3 of those lost transfusion dependence. In the observation group, only 5/83 patients met criteria for improvement, none lost transfusion dependence. In all 3 studies, about 19% of patients met criteria for improvement with a median duration of 195 days.

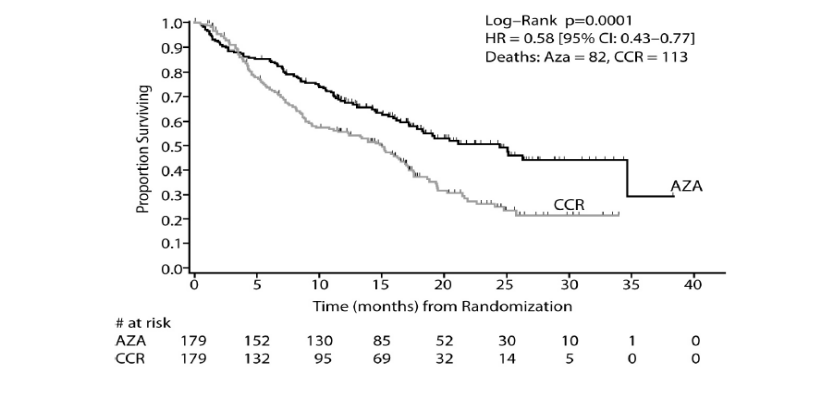
Study 4 was an international, multicenter, open-label, randomized trial in patients with MDS with RAEB, RAEB-T or modified CMMoL according to FAB classification and Intermediate-2 and High risk according to IPSS classification. Of the 358 patients enrolled in the study, 179 were randomized to receive azacitidine plus best supportive care (BSC) and 179 were randomized to receive conventional care regimens (CCR) plus BSC (105 to BSC alone, 49 to low dose cytarabine and 25 to chemotherapy with cytarabine and anthracycline). The primary efficacy endpoint was overall survival.

The azacitidine and CCR groups were comparable for baseline parameters. The median age of patients was 69 years (range was 38-88 years), 98% were Caucasian, and 70% were male. At baseline, 95% of the patients were higher risk by FAB classification: RAEB (58%), RAEB-T (34%), and CMMoL (3%). By IPSS classification, 87% were higher risk: Int-2 (41%), High (47%). At baseline, 32% of patients met WHO criteria for AML.

Azacitidine was administered subcutaneously at a dose of 75 mg/m<sup>2</sup> daily for 7 consecutive days every 28 days (which constituted one cycle of therapy). Patients continued treatment until disease progression, relapse after response, or unacceptable toxicity. Azacitidine patients were treated for a median of 9 cycles (range 1 to 39), BSC only patients for a median of 7 cycles (range 1 to 26), low dose cytarabine patients for a median of 4.5 cycles (range 1 to 15), and chemotherapy with cytarabine and anthracycline patients for a median of 1 cycle (range 1 to 3, i.e. induction plus 1 or 2 consolidation cycles).

In the Intent-to-Treat analysis, patients treated with azacitidine demonstrated a statistically significant difference in overall survival as compared to patients treated with CCR (median survival of 24.5 months vs. 15.0 months; stratified log-rank p=0.0001). The hazard ratio describing this treatment effect was 0.58 (95% CI: 0.43, 0.77).

**Kaplan-Meier Curve of Time to Death from Any Cause:** (Intent-to-Treat Population)



Key: AZA = azacitidine; CCR = conventional care regimens; CI = confidence interval; HR = Hazard Ratio  
Azacitidine treatment led to a reduced need for red blood cell transfusions (see Table 8). In patients treated with azacitidine who were RBC transfusion dependent at baseline and became transfusion independent, the median duration of RBC transfusion independence was 13.0 months.

Table 9. Effect of Azacitidine on RBC Transfusions in Patients with MDS

Efficacy Parameter	Azacitidine plus BSC (n= 179)	Conventional Care Regimens (n= 179)
Number and percent of patients who were transfusion dependent at baseline who became transfusion independent on treatment <sup>1</sup>	50/111 (45.0%) (95% CI: 35.6%, 54.8%)	13/114 (11.4%) (95% CI: 6.2%, 18.7%)
Number and percent of patients who were transfusion-independent at baseline who became transfusion-dependent on treatment	10/68 (14.7%) (95% CI: 7.3%, 25.4%)	28/65 (43.1%) (95% CI: 30.9%, 56.0%)