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Inqovi® (35 mg decitabine and 100 mg cedazuridine): An Oral, Fixed-Dose Combination Treatment for Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia

OVERVIEW OF MYELODYSPLASTIC SYNDROMES AND CHRONIC MYELOMONOCYTIC LEUKEMIA

Pathophysiology

Hematopoietic (or blood-making) stem cells in the myeloid tissue (bone marrow) give rise to 2 major lineages of progenitor blood cells: lymphoid cells (which migrate to the lymph tissue to become T, B, and natural killer cells) and myeloid cells (which develop in the bone marrow to become erythrocytes, neutrophils, eosinophils, basophils, monocytes, and platelets).[1,2] The myelodysplastic syndromes (MDS) are a group of disorders related to abnormal functioning of

INQOVI INDICATIONS

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

INQOVI IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Myelosuppression

Fatal and serious myelosuppression can occur with INQOVI. Based on laboratory values, new or worsening thrombocytopenia occurred in 82% of patients, with Grade 3 or 4 occurring in 76%. Neutropenia occurred in 73% of patients, with Grade 3 or 4 occurring in 71%. Anemia occurred in 71% of patients, with Grade 3 or 4 occurring in 55%. Febrile neutropenia occurred in 33% of patients, with Grade 3 or 4 occurring in 32%. Myelosuppression (thrombocytopenia, neutropenia, anemia, and febrile neutropenia) is the most frequent cause of INQOVI dose reduction or interruption, occurring in 36% of patients. Permanent discontinuation due to myelosuppression (febrile neutropenia) occurred in 1% of patients. Myelosuppression and worsening neutropenia may occur more frequently in the first or second treatment cycles and may not necessarily indicate progression of underlying MDS.

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Table 1. The French-American-British Morphology Group Classification for Myelodysplastic Syndromes[9,14,30]

Subtype	Acronym	% blasts in bone marrow	% blasts in peripheral blood	Other bone marrow characteristics
Refractory anemia	RA	<5%	<1%	Reticulocytopenia in peripheral blood
Refractory anemia with ringed sideroblasts	RARS			≥15% all nucleated cells in the bone marrow are ringed sideroblasts
Refractory anemia with excess of blasts	RAEB	5%-20%	<5%	NA
Chronic myelomonocytic leukemia	CMML			Monocytosis (monocytes > 1×10^9/L)
Refractory anemia with excess of blasts in transformation	RAEB-t	21%-30%	>5%	NA

NA, not applicable.

the hematopoietic stem cells of the myeloid lineage, giving rise to a variety of cytopenias (anemia, thrombocytopenia, and leukopenia) in the peripheral blood.[1,3,4] The blood cells that do form are either malformed or undergo apoptosis before they can develop into mature, functioning cells.[3]

Chronic myelomonocytic leukemia (CMML) is also a disease of hematopoietic stem cells and has characteristics of MDS. Historically, CMML was considered a type of high-grade MDS as part of the French-American-British morphologic criteria used for MDS diagnosis (**Table 1**).[5] Recently, it has been categorized as a myelodysplastic and myeloproliferative overlap syndrome because of the commonalities the diseases share.[5-8] Besides the dysplasia (or morphological changes) of the myeloid cells seen in MDS, CMML is characterized by an abnormal expansion of the granulomonocytic compartment in the bone marrow, resulting in a persistent monocytosis (high levels of monocytes) within the peripheral blood.[6-8]

Symptomology

The symptomology for both MDS and CMML varies widely between individuals. Patients may present with symptoms of anemia (fatigue, shortness of breath, or pallor), neutropenia (recurrent infections), and/or thrombocytopenia (easy bruising, frequent epistaxis, or petechiae). However, it is also possible for patients to be asymptomatic except for 1 or more of the cytopenic laboratory findings identified during routine checkup. MDS was once referred to as "refractory anemia" or "preleukemia" because patients usually present with treatment-resistant anemia and about 30% develop overt acute myeloid leukemia (AML).[3,5,9,10]

Epidemiology

MDS and CMML are rare diseases that primarily affect elderly patients.[3,4,6,7] The peak incidence for both diseases is in people aged greater than 70 years, and there is a slight male predominance.[3,4,6,7] In the United States, the overall age-adjusted incidence rates for MDS and CMML are 4.3 and 0.5 per 100,000 persons annually, respectively.[11,12] The incidence rates rise to 26.3 and 3.3 per 100,000 persons annually, respectively, for adults aged 70 to 79 years.[11,12] It has been suggested that population-based estimates of MDS in the United States may underrepresent true incidence rates due to underreporting to cancer registries.[13]

Prognosis for both diseases varies widely, but it can be very poor, ranging from a few months to several years.[3-6,8] The median survival of patients with MDS is approximately 6 years, but those who receive diagnoses at later stages of disease have survival rates of approximately 6 months.[9] Patient age greater than 70 years at time of diagnosis is also associated with decreased survival (**Figure 1**).[14,15]

Risk Stratification

The International Prognostic Scoring System (IPSS) is the tool most commonly used to stratify patients with MDS according to outcomes expected (survival and progression to AML) with supportive care alone.[16] In the original version of the IPSS scoring system, there are

INQOVI IMPORTANT SAFETY INFORMATION (*continued*)

Warnings and Precautions (*continued*)

Myelosuppression (*continued*)

Fatal and serious infectious complications can occur with INQOVI. Pneumonia occurred in 21% of patients, with Grade 3 or 4 occurring in 15%. Sepsis occurred in 14% of patients, with Grade 3 or 4 occurring in 11%. Fatal pneumonia occurred in 1% of patients, fatal sepsis in 1%, and fatal septic shock in 1%.

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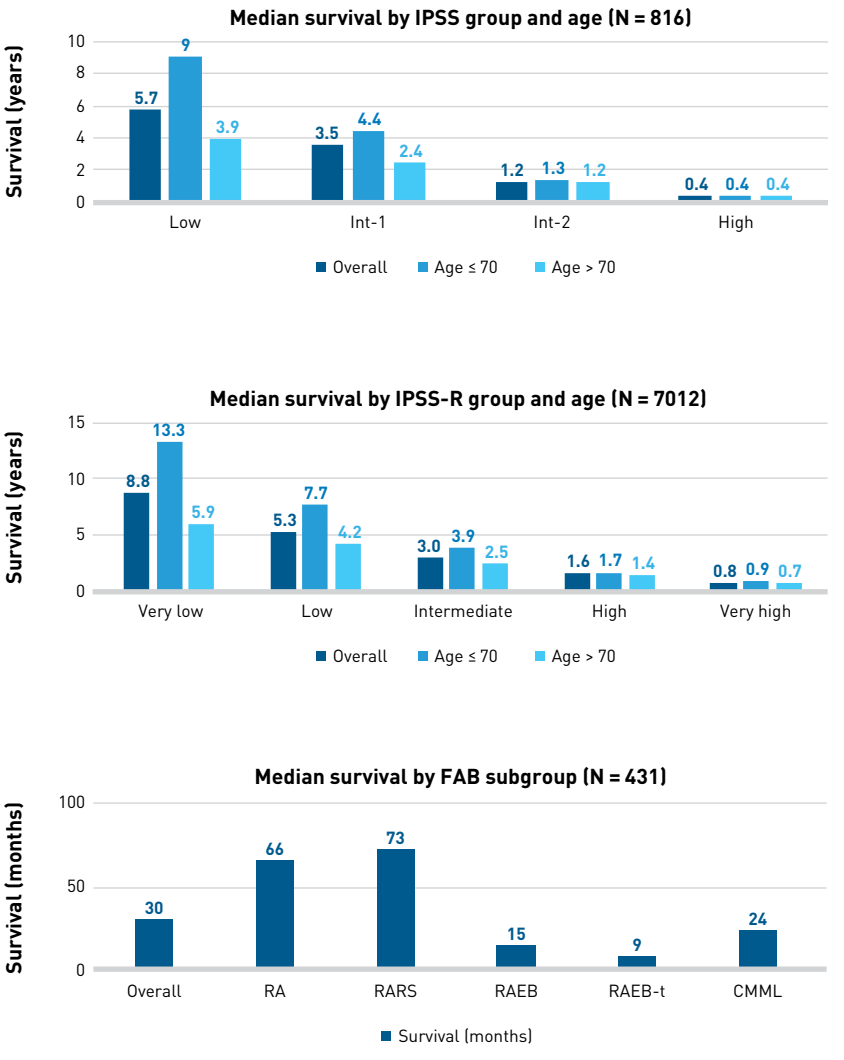
4 risk groups: low, intermediate-1, intermediate-2, and high.[14] In the revised version (IPSS-R), there are 5 risk groups: very low, low, intermediate, high, and very high.[15] In both systems, prognostic category is defined based on the presence of specific cytogenetic (karyotype) abnormalities, proportion of blasts in the marrow, and type and degree of cytopenias (hemoglobin levels, platelet counts, and absolute neutrophil counts; see **Tables 2** and **3**).[14-17] The effect of age can be used to adjust prognosis in both models.[14,15] Additional parameters that can be factored into the IPSS-R prognosis include the patient's performance status and serum levels of ferritin, lactate dehydrogenase, and β_2-microglobulin. However, these clinical features are believed to have a minor effect relative to the other parameters within the model.[15]

Both the IPSS and IPSS-R systems are still operational and form the basis of guideline-based treatment approaches for patients with MDS.[16,18] The distribution of patients fitting into each of the IPSS prognostic risk categories was estimated by an international study that analyzed a subset of patients with MDS (**Figure 2**).[15] However, it has been noted that prognostic accuracy of these models tends to be widely variable, with many patients having poorer clinical outcomes than originally predicted at time of diagnosis.[17]

MDS can also be more broadly categorized as "lower risk" or "higher risk." The lower-risk group includes IPSS low, IPSS intermediate-1, IPSS-R very low, and IPSS-R low. The higher-risk group includes IPSS intermediate-2, IPSS high, IPSS-R high, and IPSS-R very high. The IPSS-R intermediate grouping can fall into either lower risk or higher risk, depending on an individual patient's constellation of clinical metrics.[18]

Figure 1. Survival Stratified by IPSS, IPSS-R, FAB Classification, and Age[14,15,31]



CMML, chronic myelomonocytic leukemia; FAB, French-American-British classification system; Int-1, intermediate-1; Int-2, intermediate-2; IPSS, International Prognostic Scoring System; IPSS-R, IPSS, revised; RA, refractory anemia; RAEB, RA with excess blasts; RAEB-t, RAEB in transformation; RARS, RA with ringed sideroblasts.

INQOVI IMPORTANT SAFETY INFORMATION (*continued*)

Warnings and Precautions (*continued*)

Myelosuppression (*continued*)

Obtain complete blood cell counts prior to initiation of INQOVI, prior to each cycle, and as clinically indicated to monitor response and toxicity. Administer growth factors and anti-infective therapies for treatment or prophylaxis as appropriate. Delay the next cycle and resume at the same or reduced dose as recommended.

Table 2. The International Prognostic Scoring System Criteria Used in Myelodysplastic Syndromes[14,15,18]

IPSS						
Score	**0**	**0.5**	**1.0**	**1.5**	**2.0**	**> 2.0**
Category	**Low**	**Int-1**		**Int-2**		**High**
BM blasts (%)	< 5	5-10		11-20	21-30	
Cytogenetic group[a]	Good	Int	Poor			
Cytopenias[b]	0/1	2/3				

IPSS-R												
Score	**0**	**0.5**	**1.0**	**1.5**	**2.0**	**3.0**	**3.5**	**4.5**	**5.0**	**5.5**	**6.0**	**> 6.0**
Category	**Very low**				**Low**		**Intermediate**		**High**			**Very high**
BM blasts (%)	≤ 2		> 2 and < 5		5-10	> 10						
Cytogenetic group[a]	Very good		Good		Intermediate	Poor	Very poor					
Cytopenias												
Hemoglobin[c]	≥ 10		8 to < 10		< 8							
Platelets[d]	≥100	50 to < 100	< 50									
ANC[d]	≥ 0.8	< 0.8										

ANC, absolute neutrophil count; BM, bone marrow; IPSS, International Prognostic Scoring System; IPSS-R, IPPS, revised.

[a]Cytogenetic (karyotype) group determined based on presence of specific mutations.

[b]A cytopenia in the IPSS system was defined as (1) hemoglobin < 10 g/dL, (2) platelets <100,000/µL, and/or (3) ANC < 1500/µL.

[c]Hemoglobin values are g/dL.

[d]Platelet and ANC values are 10^9/L.

TREATMENTS FOR MDS

IPSS categories, as well as patient-specific risk factors (age, performance status, and comorbidities), form the basis of guideline-based treatment algorithms for patients with MDS.[16,19,20] For lower-risk patients, the treatment goal is to achieve hematologic improvement using immunomodulators, erythropoiesis-stimulating agents with or without growth factor support, immunosuppressive therapy, and hypomethylating agents. Allogeneic hematopoietic stem-cell transplant (allo-HSCT) is the recommended treatment for higher-risk patients. Pharmacotherapies that are utilized in lower-risk patients are also employed in higher-risk patients.[20] Participation in clinical trials with experimental single or combination agents is encouraged following treatment failure in this patient population.[6] Historically, CMML has received the same treatment approach as MDS.[6-8]

Few drugs are FDA approved for MDS.[5,16,21] The only curative option for MDS is an allo-HSCT; however, many patients do not qualify for transplant due to their older age at the time of diagnosis.[5,7,22] Supportive care is a central part of guideline-directed treatment for MDS and includes therapies to treat anemia, bleeding, neutropenia, and iron overload.[4,5,16,22]

As the currently available therapeutics for treating MDS or CMML are not considered curative, MDS and CMML are lifelong diseases that can present substantial challenges to patients and their caregivers. Many agents used in the treatment of MDS and CMML are

INQOVI IMPORTANT SAFETY INFORMATION (*continued*)

Warnings and Precautions (*continued*)

Embryo-Fetal Toxicity

INQOVI can cause fetal harm. Advise pregnant women of the potential risk to a fetus. Advise patients to use effective contraception during treatment and for 6 months (females) or 3 months (males) after last dose.

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Table 3. Cytogenetic Prognostic Groups Used Within the IPSS and IPSS-R Systems[14,15]

	IPSS			IPSS-R				
	Cytogenetic prognostic group			Cytogenetic prognostic group				
Mutation type[a]	Good	Intermediate	Poor	Very good	Good	Intermediate	Poor	Very poor
Normal	•				•			
del(5q)	•				•			
del(7q)						•		
del(11q)				•				
del(12p)					•			
del(20q)	•				•			
i(17q)						•		
inv(3)/t(3q)/del(3q)							•	
–7			•				•	
+8		•				•		
+19						•		
–Y	•			•				
Other single abnormalities		•				•		
Double abnormalities		•			• including del(5q)	•	• including –7/del(7q)	
Complex abnormalities			• (≥3)				• (3)	• (>3)

Del, deletion; i, isochromosome; inv, inversion; IPSS, International Prognostic Scoring System; IPSS-R, IPSS, revised; t, translocation.

[a]A patient with MDS is placed in a cytogenetic prognostic group based on the presence of at least 1 of the genetic abnormalities listed for that group.

parenterally administered; thus, frequent visits to infusion sites (clinic or hospital) are required to receive care. Orally administered agents may help with this.[23,24]

Inqovi (35 mg decitabine and 100 mg cedazuridine) was approved by the FDA under priority review on July 7, 2020.[24,25] Inqovi is an oral therapy that is indicated for the treatment of adult patients with MDS, including previously treated and untreated, de novo and secondary MDS with the French-American-British subtypes of refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and CMML and intermediate-1, intermediate-2, and high-risk IPSS groups.[21]

Hypomethylating Agents

Hypomethylating agents (HMAs) exert their cytotoxic action by a mechanism known as hypomethylation.[26] This process is described in detail in **Figure 3**.[26]

Decitabine

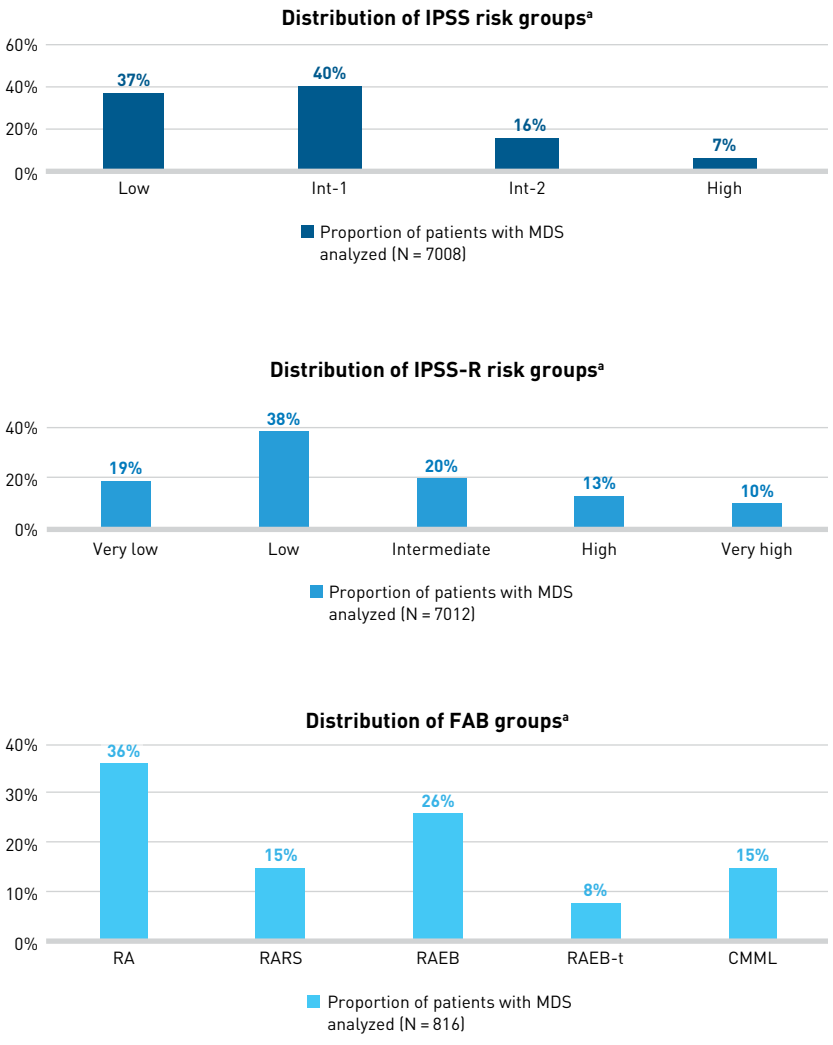
Decitabine is an azapyrimidine nucleoside analogue of cytidine.[23,26,27] It is believed to exert its antineoplastic effects after phosphorylation and direct incorporation into DNA, where it inhibits DNA methyltransferase and causes hypomethylation. DNA hypomethylation causes cellular differentiation and/or apoptosis. Decitabine has been shown

INQOVI IMPORTANT SAFETY INFORMATION (*continued*)

Adverse Reactions

Serious adverse reactions in > 5% of patients included febrile neutropenia (30%), pneumonia (14%), and sepsis (13%). Fatal adverse reactions included sepsis (1%), septic shock (1%), pneumonia (1%), respiratory failure (1%), and one case each of cerebral hemorrhage and sudden death.

Figure 2. Approximate Distributions of IPSS, IPSS-R, and FAB Groups[9,14,15]



CMML, chronic myelomonocytic leukemia; FAB, French-American-British classification system; Int-1, intermediate-1; Int-2, intermediate-2; IPSS, International Prognostic Scoring System; IPSS-R, IPSS, revised; MDS, myelodysplastic syndromes; RA, refractory anemia; RAEB, RA with excess blasts; RAEB-t, RAEB in transformation; RARS, RA with ringed sideroblasts.

[a]Data are from international registries.

to induce hypomethylation both in vitro and in vivo. In vitro, decitabine inhibition of DNA methylation is achieved at concentrations that do not cause major suppression of DNA synthesis. Decitabine-induced hypomethylation in cancer 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. Nonproliferating cells are relatively insensitive to decitabine.

Cytidine Deaminase and Cytidine Deaminase Inhibitors

Cytidine deaminase (CDA) is an enzyme that catalyzes the degradation of cytidine, including the cytidine analogue decitabine. High levels of CDA in the gastrointestinal tract and liver degrade decitabine and limit its oral bioavailability. Cedazuridine is a CDA inhibitor (CDAi), and coadministration of cedazuridine with decitabine increases systemic exposure of decitabine.[21] A schematic representation of cedazuridine's mechanism of action is shown in **Figure 4**.[21,23,28]

INQOVI

Inqovi is an oral, fixed-dose combination of decitabine, an HMA, and cedazuridine, a CDAi.[21] In patients administered the recommended dosage of Inqovi, the deepest level of hypomethylation achieved, measured as the maximum change from baseline in the long interspersed nucleotide element-1 (LINE-1) demethylation, was observed at day 8, with less than complete recovery of LINE-1 methylation to baseline at the end of the

INQOVI IMPORTANT SAFETY INFORMATION (*continued*)

Adverse Reactions (*continued*)

The most common adverse reactions (≥20%) were fatigue (55%), constipation (44%), hemorrhage (43%), myalgia (42%), mucositis (41%), arthralgia (40%), nausea (40%), dyspnea (38%), diarrhea (37%), rash (33%), dizziness (33%), febrile neutropenia (33%), edema (30%), headache (30%), cough (28%), decreased appetite (24%), upper respiratory tract infection (23%), pneumonia (21%), and transaminase increased (21%). The most common Grade 3 or 4 laboratory abnormalities (≥50%) were leukocytes decreased (81%), platelet count decreased (76%), neutrophil count decreased (71%), and hemoglobin decreased (55%).

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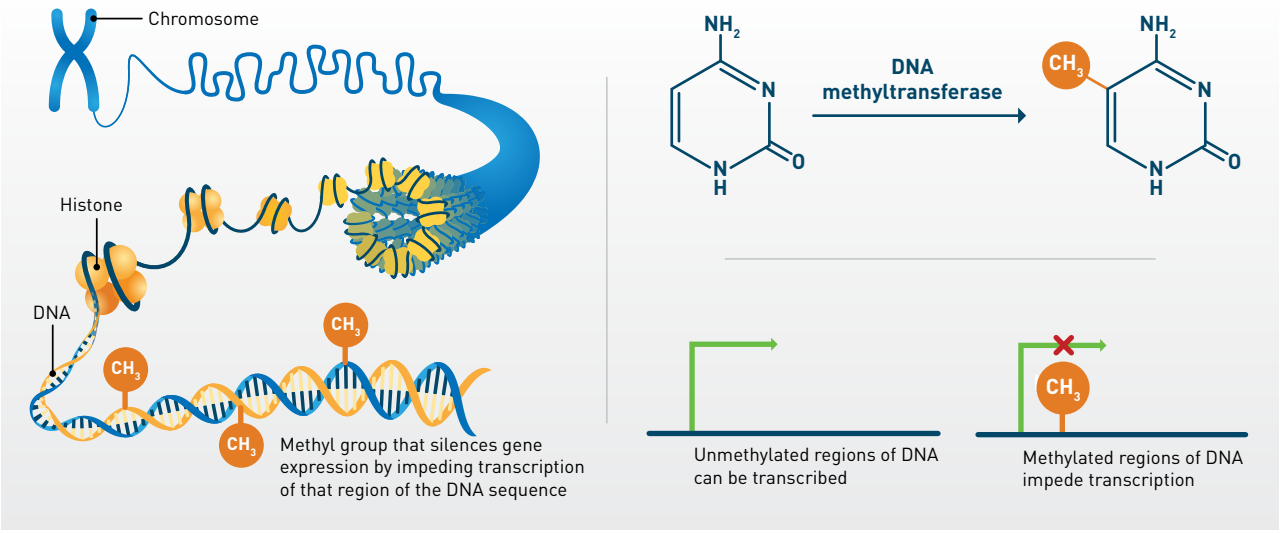
Figure 3. Mechanism of DNA Methylation and Gene Silencing



In the setting of malignancy, tumor suppressor genes encoded within DNA can become silenced through a process called hypermethylation. During this process, enzymes called DNA methyltransferases (DNMTs) catalyze the attachment of methyl groups to certain nucleoside bases within the DNA structure, impeding that region's ability to be read in the DNA sequence. Hypomethylation is a way to reverse the process of gene silencing, allowing for the expression of important tumor suppressor genes that normally function to survey the cell growth process for abnormalities.[26] Mutations can activate DNMTs, resulting in increased methylation (and silencing) of genes that help control cellular differentiation and proliferation. The result is uncontrolled cell growth.[32] This reduced expression of genes in cancerous cells allows their continued growth and survival.[23] In myelodysplastic syndromes, the p15 tumor suppressor gene is frequently hypermethylated, causing a reduction in its ability to monitor malignant transformation of cells.[26] Hypomethylating agents, such as decitabine, can reactivate tumor suppressor genes by inhibiting the action of aberrant DNMTs.[26,32] During DNA methylation, a methyl ($-CH_3$) group is transferred from a molecule called S-adenosyl-L-methionine onto the 5-position of the cytosine ring within a cytosine-phosphate-guanine dinucleotide (CpG) base-pairing region of a gene. The reaction is catalyzed by a DNA methyltransferase enzyme. After a CpG section of a gene is methylated, it cannot be transcribed (ie, it is silenced).[26]

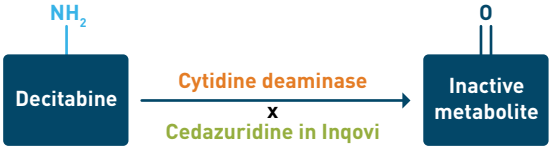
DNA © VectorMine / Adobe Stock / Modified by Julianne Costello

treatment cycle. Based on the exposure-response analyses, a relationship between an increase in 5-day cumulative daily decitabine exposure and a greater likelihood of some adverse reactions (eg, any grade of neutropenias and/or thrombocytopenia) was observed in clinical studies.[21]

Clinical Studies of Inqovi

Inqovi was evaluated in study ASTX727-01-B (NCT02103478) and in study ASTX727-02 (NCT03306264).[21] Results of these clinical studies have been summarized in **Table 4**[21] and **Table 5**,[21] respectively. Inclusion criteria for both trials was a diagnosis of MDS or CMML with any French-American-British classification or IPSS intermediate-1, intermediate-2, or high-risk prognostic score. Both

Figure 4. Deamination and Deactivation of Decitabine by Endogenous Cytidine Deaminases[21,23,28]



INQOVI IMPORTANT SAFETY INFORMATION (*continued*)

Use in Specific Populations

Lactation

Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with INQOVI and for at least 2 weeks after the last dose.

Table 4. Results of Study ASTX727-01-B[21]

Intervention

Participants randomized 1:1 to sequence A or sequence B

Sequence A

Cycle No.	Route	Agent	Duration
Cycle 1	IV	Decitabine	Days 1-5 of 28-day cycle
Cycle 2	Oral	Inqovi	Days 1-5 of 28-day cycle
Cycle 3+	Oral	Inqovi	Days 1-5 of 28-day cycle

Sequence B

Cycle No.	Route	Agent	Duration
Cycle 1	Oral	Inqovi	Days 1-5 of 28-day cycle
Cycle 2	IV	Decitabine	Days 1-5 of 28-day cycle
Cycle 3+	Oral	Inqovi	Days 1-5 of 28-day cycle

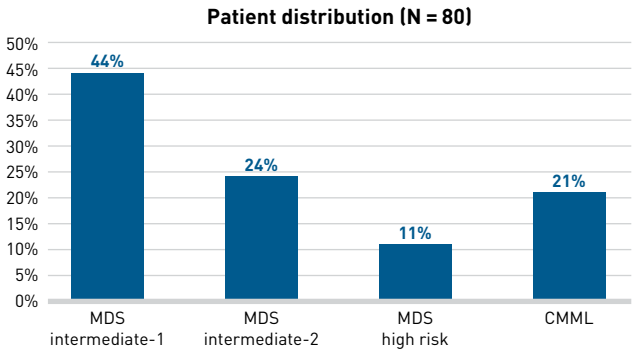
Doses:
Oral (Inqovi): 35 mg decitabine; 100 mg cedazuridine
IV: 20 mg/m^2 decitabine over 1 hour

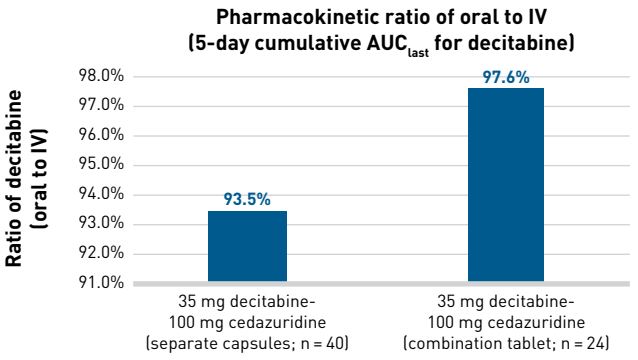
Pharmacokinetic data collected:
- Serial plasma decitabine concentrations from predose to postdose (postdose was 24 hours for oral and 8 hours for IV). AUC_{last} was defined as time 0 to last measurable concentration.

Pharmacodynamic data collected:
- DNA methylation at screening, on day 1 (predose), and then on days 8, 15, and 22

Efficacy data collected include:
- CR
- Conversion from transfusion dependence to transfusion independence

Results





Efficacy data (N = 80)	
CR (95% CI)	18% (10, 28)
Median duration of CR—months (range)[a]	8.7 months (1.1 - 18.2)
Median time to CR—months (range)	4.8 months (1.7 - 10.0)
Transitioned from transfusion dependence[b] at baseline to independence after treatment	49% (20/41)
Remained transfusion independent[c] from baseline to after treatment	64% (25/39)

AUC, area under the concentration time curve; CR, complete response; CMML, chronic myelomonocytic leukemia; IV, intravenous; MDS, myelodysplastic syndromes.

[a]From start of CR until relapse or death.

[b]Red blood cells and/or platelets.

[c]Transfusion independence is defined as having no red blood cells or platelets transfusion for 8 consecutive weeks.

INQOVI IMPORTANT SAFETY INFORMATION (*continued*)

Use in Specific Populations (*continued*)

Renal Impairment

No dosage modification of INQOVI is recommended for patients with mild or moderate renal impairment (creatinine clearance [CLcr] of 30 to 89 mL/min based on Cockcroft-Gault). Due to the potential for increased adverse reactions, monitor patients with moderate renal impairment (CLcr 30 to 59 mL/min) frequently for adverse reactions. INQOVI has not been studied in patients with severe renal impairment (CLcr 15 to 29 mL/min) or end-stage renal disease (ESRD: CLcr < 15 mL/min).

Please see full Prescribing Information.

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Table 5. Preliminary Results of Study ASTX727-02[21]

Intervention

Participants randomized 1:1 to sequence A or sequence B

Sequence A

Cycle No.	Route	Agent	Duration
Cycle 1	Oral	Inqovi	Days 1-5 of 28-day cycle
Cycle 2	IV	Decitabine	Days 1-5 of 28-day cycle
Cycle 3+	Oral	Inqovi	Days 1-5 of 28-day cycle

Sequence B

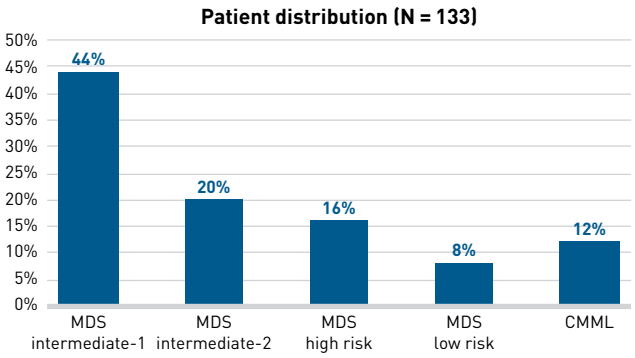
Cycle No.	Route	Agent	Duration
Cycle 1	IV	Decitabine	Days 1-5 of 28-day cycle
Cycle 2	Oral	Inqovi	Days 1-5 of 28-day cycle
Cycle 3+	Oral	Inqovi	Days 1-5 of 28-day cycle

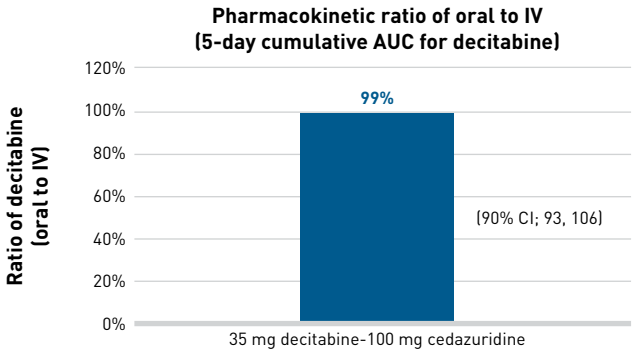
Doses:
Oral (Inqovi): 35 mg decitabine; 100 mg cedazuridine
IV: 20 mg/m^2 decitabine over 1 hour

Pharmacokinetic data collected:
- Decitabine 5-day AUC

Efficacy data collected:
- CR
- Conversion from transfusion dependence to transfusion independence

Results





Efficacy data (N = 133)	
CR (95% CI)	21% (15, 29)
Median duration of CR—months (range)[a]	7.5 months (1.6 - 17.5)
Median time to CR—months (range)	4.3 months (2.1 - 15.2)
Transitioned from transfusion dependence[b] at baseline to independence after treatment	53% (30/57)
Remained transfusion independent[c] from baseline to after treatment	63% (48/76)

AUC, area under the concentration time curve; CR, complete response; CMML, chronic myelomonocytic leukemia; IV, intravenous; MDS, myelodysplastic syndromes.

[a]From start of CR until relapse or death.

[b]Red blood cells and/or platelets.

[c]Transfusion independence is defined as having no red blood cells or platelets transfusion for 8 consecutive weeks.

studies were open-label, randomized, 2-cycle, 2-sequence crossover studies. The trials demonstrated that Inqovi given as an oral fixed-dose combination tablet of 35 mg decitabine and 100 mg cedazuridine produces comparable area under the concentration time curve (AUC) values compared with intravenous (IV) decitabine administered at 20 mg/m^2 of body surface area (BSA) given during the first 2 cycles. Depth of hypomethylation using LINE-1 demethylation assays and toxicity profiles were also similar. Following the crossover period, all patients received Inqovi until disease progression, unacceptable toxicity, or study withdraw. Clinical efficacy end points such as complete response (CR) and transfusion dependence were also recorded.[21,28]

ASTX727-01-B

Study ASTX727-01-B (NCT02103478) was a phase 1/2 clinical trial of Inqovi in which Inqovi (35 mg decitabine and 100 mg cedazuridine, administered orally) was compared with IV decitabine (dosed according to BSA at 20 mg/m^2 and given as a 1-hour infusion) in a randomized crossover design (N = 80).[21,28] For cycles 1 and 2, study participants received either Inqovi orally in cycle 1 and IV decitabine in cycle 2 or

the reverse, with IV decitabine in cycle 1 and Inqovi orally in cycle 2. All patients received Inqovi from cycle 3 onward.

Peak decitabine plasma concentrations were achieved at similar time points regardless of route of administration (at 1 hour after the start of the IV infusion and at 1 hour after oral administration of Inqovi). Cumulative 5-day AUC values from time 0 (predose) to last measurable concentration of decitabine were similar between orally administered Inqovi and IV decitabine, with an oral-to-IV ratio of 93.5% in the dose-confirmation cohort (where decitabine and cedazuridine were administered as 2 separate oral capsules) and 97.6% in the fixed-dose combination cohort (where decitabine and cedazuridine were administered together in 1 tablet). The 80% CIs for both ratios included the null (82.1%-106.5% and 80.5%-118.3%, respectively). The depth of demethylation produced by orally administered Inqovi emulated that of IV decitabine, with a difference between the 2 agents of about 1% and the 95% CI containing the null (0).[28]

Because all patients in the study received orally administered Inqovi during cycles 1 or 2 and then from cycle 3 onward, clinical response rates observed could primarily be attributed to Inqovi's efficacy. CR was observed in 18% of patients across both cohorts. Conversion from transfusion dependence at baseline to transfusion independence during any consecutive 56-day postbaseline period occurred in 20 of 41 patients (49%). Sixty-four percent of patients who were transfusion independent at baseline maintained transfusion independence during any consecutive 56-day postbaseline period (25/39). The median duration of CR (defined as the start of CR to disease relapse or death) was 8.7 months, and median time to CR was 4.8 months.[21]

There were no notable increases in gastrointestinal adverse events observed with orally administered Inqovi versus IV decitabine administered during the first 2 cycles. Incidences of other adverse effects were also similar for oral and IV in the first 2 cycles.[28]

ASTX727-02

Study ASTX727-02 (NCT03306264), the ASCERTAIN trial, was a phase 3 clinical trial of Inqovi designed to establish bioequivalence of the fixed-dose oral combination of Inqovi (35 mg decitabine and 100 mg cedazuridine) to IV decitabine dosed according to BSA at 20 mg/m^2.[21,25,29] Study participants (N = 133) received either Inqovi in cycle 1 and IV decitabine in cycle 2 or the reverse, with IV decitabine administered in cycle 1 and Inqovi given in cycle 2. From cycle 3 onward, all participants received Inqovi.[21]

The 5-day AUC decitabine ratio of oral to IV was 99% (90% CI, 93%-106%). As with the phase 2 study (ASTX727-01-B), all patients in ASCERTAIN received orally administered Inqovi during cycles 1 or 2 and then from cycle 3 onward; thus, clinical response rates observed could be primarily attributed to Inqovi's efficacy. CR was observed in 21% of patients across both cohorts. Conversion from transfusion dependence at baseline to transfusion independence during any consecutive 56-day postbaseline period occurred in 30 of 57 patients (53%). Sixty-three percent of patients, who were transfusion independent at baseline, maintained transfusion independence during any consecutive 56-day postbaseline period (48/76). The median duration of CR (defined as the start of CR to disease relapse or death) was 7.5 months, and median time to CR was 4.3 months.[21]

Safety

Serious adverse reactions occurred in 68% of patients who received Inqovi. Serious adverse reactions in more than 5% of patients included febrile neutropenia (30%), pneumonia (14%), and sepsis (13%). Fatal adverse reactions occurred in 6% of patients. These included sepsis (1%), septic shock (1%), pneumonia (1%), respiratory failure (1%) and 1 case each of cerebral hemorrhage and sudden death. Permanent discontinuation due to an adverse reaction occurred in 5% of patients who received Inqovi. The most frequent adverse reactions resulting in permanent discontinuation were febrile neutropenia (1%) and pneumonia (1%). Dose interruptions due to an adverse reaction occurred in 41% of patients who received Inqovi. Adverse reactions requiring dosage interruptions in more than 5% of patients who received Inqovi included neutropenia (18%), febrile neutropenia (8%), thrombocytopenia (6%), and anemia (5%). Dose reductions due to an adverse reaction occurred in 19% of patients who received INQOVI. Adverse reactions requiring dosage reductions in more than 2% of patients who received INQOVI included neutropenia (12%), anemia (3%), and thrombocytopenia (3%). The most common adverse reactions (≥ 20%) were fatigue, constipation, hemorrhage, myalgia, mucositis, arthralgia, nausea, dyspnea, diarrhea, rash, dizziness, febrile neutropenia, edema, headache, cough, decreased appetite, upper respiratory tract infection, pneumonia, and increased transaminase. The most common grade 3 or 4 laboratory abnormalities (≥ 50%) were decreased leukocytes, platelet count decreased, neutrophil count decreased, and hemoglobin decreased.[21]

Drug Interaction Studies

In vitro studies in human liver microsomes suggest that decitabine is unlikely to inhibit or induce cytochrome P450 (CYP450) enzymes. These studies have also suggested that decitabine is not a substrate for CYP450 enzymes.

Cedazuridine is also not a substrate of CYP450 enzymes or of the P-glycoprotein (P-gp) transporter system. It does not induce CYP1A, CYP2B6, CYP2C9, or CYP3A or inhibit CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A, or P-gp. In addition, cedazuridine is not a substrate of the multidrug and toxin extrusion (MATE) transporters MATE1 and MATE2-K; the organic anion transporters (OATs) OAT1, OAT3, OATP1B1, OAPT1B3, and OATP2B; or the organic cation transporters (OCTs) OCT1 and OCT2. Cedazuridine does not inhibit P-gp, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT2, or the breast cancer resistance protein efflux transporter. Cedazuridine is an inhibitor of the CDA enzyme. Coadministration of Inqovi with drugs that are metabolized by CDA may result in increased systemic exposure with potential for increased toxicity of these drugs. Avoid coadministration of Inqovi with drugs that are metabolized by CDA.[21]

Decitabine imparts no clinically meaningful effect on the pharmacokinetics of cedazuridine. However, clinical studies have shown that cedazuridine increases exposure of decitabine, a finding that is desirable for boosting the oral bioavailability of decitabine. The coadministration

Please see additional **Important Safety Information** throughout and accompanying full **Prescribing Information**. The **Prescribing Information** is also available at **https://www.taihooncology.com/documents/78/INQOVI_Prescribing_Information.pdf**.

of Inqovi with proton pump inhibitors has no clinically meaningful effect on exposure to decitabine or cedazuridine. Cedazuridine is an inhibitor of the CDA enzyme. Coadministration of Inqovi with drugs that are metabolized by CDA may result in increased systemic exposure with potential for increased toxicity of these drugs. Avoid coadministration of Inqovi with drugs that are metabolized by CDA.[21]

CONCLUSIONS

MDS is a rare disease affecting primarily elderly adults and is generally associated with a poor prognosis. Limited treatment options exist for patients with MDS, and most options require parenteral administration and visits to the clinic or hospital for treatment. Inqovi is an oral formulation of an HMA (decitabine) combined with a CDAi (cedazuridine) that has demonstrated equivalent systemic exposure and DNA demethylation to that of IV decitabine (dosed according to patient BSA) in clinical trials. Inqovi may represent an important treatment option in patient-centered care for patients with MDS, because it allows for oral, at-home medication administration. •

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