INQOVI® (decitabine and 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 two 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). [Mescher,2020;p2,para2(entire);figure13-2][Weiskopf,2016;p1,col2,para1,ln1-8;p2,col2,para1,ln5] The myelodysplastic syndromes (MDS) are a group of disorders related to abnormal functioning of the hematopoietic stem cells, giving rise to a variety of cytopenias (anemia, thrombocytopenia, and leukopenia) in the peripheral blood.[Mescher,2020;p1,para1,ln1-2][Aster,2020;p2,para3,ln6-8;p17,para5,ln1-3;p18,para3,ln1-3][Young,2020;p23,para3,ln1-2;p26,para3,ln1-3]The blood cells that do form are either malformed or undergo apoptosis before they can develop into mature, functioning cells.[Aster,2020;p17,para5,ln

Chronic myelomonocytic leukemia (CMML) is also a disease of he em cells and has characteristics of MDS. Historically, CMML was once consid de MDS as part of the French-American-British (FAB) morphologi diagnosis (**Table 1**). [Gangat,2016;p77,col1,para5,ln2-10] Recently, it h an MDS overlap syndrome because of the commonalities it sha ,ln1-5] [Elmariah,2019;p154,col1,para1,ln1-5][Patnaik,2018;p824,col1,para1,ln2- 017;p711,col2,para2,ln4-5]

CMML is characterized by an abnormal exp monocytic compartment in the bone marrow, resulting in a persistent els of monocytes) within the peripheral blood.[Itzykson,2017;p711,col1 ol2,para3,ln2;p824,col1,para1,ln3-6;p826,col2,para2,ln1-2;p827,table1,ln1-2][Elmariah,2019;p155,c

Symptomology

The sym DS and CMML is still largely undetermined. Patients may present wit as fatigue, shortness of breath, or pallor), neutropenia (manife ections), or thrombocytopenia (manifested as easy bruising, frequent epistaxis, o [Aster,2020;p18,para3,ln1-3][Young,2020;p27,para2,ln1-2][Elmariah,2019;p154,col2,para2,ln2-9] [Patnaik,2018;p825,c a1,ln7-13] In the past, MDS was often referred to as “refractory anemia” or “pre-

leukemia" because patients usually present with treatment-resistant ane… …of MDS cases develop into overt acute myeloid leukemia (AML). [Aste… …n1-2][Gangat,2016;p76,para2,ln2-3][Bennett,2005;pS3,col1,para1,ln14;pS4,col1,para2,ln4-5][G… …0-12]

Epidemiology

MDS and CMML are rare diseases affecti… …y population.[Aster,2020;p20,para1,ln1][Young,2020;p26,para1… …2][Itzykson,2017;p711,col2,para5,ln1][Elmariah,2019;p154… …24,col2,para2,ln1] Both diseases have a peak incidence occurring with ad… …s and have a slight male predominance.[Aster,2020;p20,para… …2] [Elmariah,2019;p154,col2,para2,ln1-2][Patnaik,2019;p824,col2,para2,ln… …5,ln1-4] In the United States, the overall, age-adjusted incidenc… …MML are 4.3 and 0.5 per 100,000 persons annually, respectively.[… …1][SEER_technical_notes;p1,para1,ln2-3] However, the incidence rates rise to 2… …00 persons annually, respectively, for adults aged 70 to 79 years.[SEE… …ble30.2][SEER_technical_notes;p1,para1,ln2-3] It has been suggested that population-based estimat… …MDS in the United States may underrepresent the true incidence and prevalence rates as a result of underreporting to cancer registries.[Cogle,CurreHaemMaligRep,2015;p273,col1,para2,ln22-27;p273,col2,para2,ln9-14]

Prognosis for both diseases varies widely, but it can be very poor, ranging from a few months to several years.[Aster,2020;p21,para2,ln1][Young,2020;p28,para4,ln1-2][Gangat,2016;p76,para2,ln3-4][Elmariah,2019;p154,col2,para1,ln5;p156,col1,para1,ln1-5][Itzykson,2017;p715,col1,para3,ln2-3] The median survival of patients with MDS is approximately 6 years, but those who are diagnosed at later stages of disease have survival rates of approximately 6 months.[Bennett,2005;pS4,col1,para2,ln10-12] Age greater than 70 years at time of diagnosis is also associated with decreased survival (**Figure 1**).[Greenberg,1997;p2086,table4][Greenberg,2012;p2456,table1;p2459,table5;p2460,table6]

Risk Stratification

The International Prognostic Scoring System (IPSS) is the tool most commonly used to stratify patients with MDS into groups according to outcomes expected (survival and progression to AML) with supportive care alone.[Steensma,2018;p2,table1;p2,col1,para2,ln1-3;p2,col2,para2,ln4-5] In the original (1997) version, there were 4 risk groups (low, intermediate-1, intermediate-2, and high); in the revised (2012) version, there are 5 risk groups (very low, low, intermediate, high, and very high).

In both systems, prognostic category is defined based on the presence of ic (karyotype) abnormalities, proportion of blasts in the marrow, and penias (hemoglobin levels, platelet counts, and absolute neutrophil c id **3**).[Greenberg,1997;p2084,col1,para1,ln5-11;p2085,table3;p2086,figure6;p2080,col2 1-12;p2084,figure4A;p2081,col1,para3,ln1;p2081,col1,para3,ln7-14;p2086,tabl [Greenberg,2012;p2458,table4;p2462,table8&table9;p2462,figure7;p2 l2,para3(entire);p2458,col1,para1(entire); p2458,col1,para2,ln1-6][Steensma,2018;p2,col1,para2,ln7-13] The effect of age is also considered in both systems and can adjustment to survival prediction after the prognostic category has be determined.[Greenberg,1997;p2 e)][Greenberg,2012;p2461,figure6,including_footnote;p2460,table6;p246 3,col1,para3,ln1-8;p2463,col1 optional parameters that can be made to the International P tem, Revised (IPSS-R) survival prognosis include the patient's d serum levels of ferritin, lactate dehydrogenase, and β_2-microglo hese features are believed to have a minor effect relative to the other parameters w e model.[Greenberg,2012;p2458,col2,para2,ln1-9;p2462,table8;p2463,col1,para4,ln1-4;ln9-13]

Both the IPSS and IPSS-R systems are still operational and form the basis of guideline-based treatment approaches for patients with MDS.[Steensma,2018;p4,figure1][LLS,2019;p13,para2,ln1-3] However, it has been noted that many patients classified as "lower risk" end up doing far worse clinically than the prognostic tool indicator predicted.[Zeidan,2019;p8,col2,para3,ln1-3]

MDS can be more broadly categorized as "lower risk" or "higher risk."[LLS,2019;p14,table6] The "lower risk" group includes IPSS low, IPSS intermediate-1, IPSS-R very low, and IPSS-R low.[LLS,2019;p14,table6] The "higher risk" group includes IPSS intermediate-2, IPSS high, IPSS-R high, and IPSS-R very high.[LLS,2019;p14,table6] The IPSS-R intermediate grouping can fall into either "lower risk" or "higher risk" depending on an individual patient's constellation of clinical metrics.[LLS,2019;p14,table6] 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**).[Greenberg,2012;p2455,col1,para2(entire);p2456,table1]

Pharmacotherapy for MDS

IPSS risk stratification categories, as well as patient-specific risk factors (age, performance status, and comorbidities) form the basis of guideline-based treatment algorithms

for MDS.[Steensma,2018;p4,figure1][Bates,2020;p15,figure_e154-1] [Montalban-Bravo,2018;p134,col2,figure3;p135,col2,para4,ln1-3;p136,col2,para2,ln1-2;ln8-9; p137,col1,para1,ln6-7;p140,col2,para2,ln1-2] For lower-risk patents, treatment goals are to achieve hematologic improvement using immunomodulators, erythropoiesis-stimulating agents (ESAs) with or without growth factor support, immunosuppressive therapy, and hypomethylating agents.[Bates,2020;p15,para3(entire)] For higher-risk patients, treatment goals are to change the disease course by use of allogeneic hematopoietic stem-cell transplant, the only curative option.[Bates,2020;p21,para1(entire)] However, since many patients with MDS are not candidates for transplant, similar therapies that are utilized in lower-risk patients are employed in attempt to improve quality of life and to prolong survival.[Bates,2020;p21,para1(entire)] Historically, CMML has received the same treatment approach as MDS.[Elmariah,2019;p154,col2,para1,ln1-2;p157,col[illegible],ln1-6;p157,col2,para2,ln1-3;p158,col1,para2,ln1-4;p158,col2,para2,ln1-2;p160,col2,para2,ln1-2] [Patnaik,2018;p8[illegible]4;p836,col1,para4,ln2;p836,col2,para1,ln1-8] [Itzykson,2017;p716,col2,para3,ln1-2]

Few drugs carry an FDA-approved indication specifi[illegible];p76,para2,ln9] [Steensma,2018;p1,col2,para2,ln1-6] These drugs include lenalidom[illegible], and decitabine (DEC).[Lenalidomide_PI;psect1.2(entire)] [Azacitidine_PI;sect1.1(entir[illegible]NQOVI_PI,sect1(entire)] Therapeutics used off-label in the treatment [illegible]isk MDS include immunosuppressive therapies such as e[illegible]globulin, cyclosporine A, or tacrolimus.[Steensma,2018;p3,col2,para2,ln1-6[illegible] globulin_PI;sect1(entire)][CyclosporineA_PI[illegible]][Tacrolimus_PI;sect1.1(entire)]

The only curati[illegible]n allogeneic stem cell transplant; however, many patients do not q[illegible]t due to their advanced age at the time of diagnosis.[Pa[illegible]Platzbecker,2019;p1096,col1,para1,ln1-4][Gangat,2016;p76,para2,ln9-11;p86,col2[illegible]] Supportive care is a central part of guideline-directed treatment for ML[illegible]herapies to treat anemia (red blood cell transfusions, luspatercept-aamt, epoetin alf[illegible]bepoetin alfa), bleeding (platelet transfusions and hemostatic agents such as aminocaproic acid, as well as other antifibrinolytics), neutropenia (granulocyte-monocyte colony-stimulating factor), and iron overload (chelators such as deferoxamine and deferasirox) (**Table 4**).[Steensma,2018;p5,col2,para3,ln1-4][Gangat,2016;p82,figure1][Platzbecker,2019;p1098,col1,para2,ln1-4;ln6-9;p1098,col2,para3,ln1-4;p1098,col2,para4,ln3-4;p1099,figure3;p1100,figure4;p1100,col2,para2,ln1;ln4-6][Luspatercept_PI;sect11,para1,ln1]

[Deferoxamine_PI;p1,para1,ln1;p1,para5(entire)][Deferasirox_PI;sect1.1(entire);sect11,para1,ln1;sect12.1,para1,ln1-2]31[Epoetin_PI;sect1.3(entire)][Darbepoetin_PI;sect1.2(entire)][AminocaproicAcid_PI;p1,IndicationsAndUses,para1(entire)]

Because the currently available therapeutics for treating MDS or CMML are not considered curativeMDS and CMML are lifelong diseases that impart challenges to patients, providers, and payers. Because most agents used in the treatment of MDS and CMML are parenterally administered, frequent visits to the clinic or hospital are required to receive care. Orally administered agents can help lessen visits to the clinic or hospital to receive treatment infusions for MDS.[Lowder,2015;p1084,col2,para3,ln1-9][PressRelease_INQOVI_FDA,2020;p1,para1,2(entire)]

On July 7th 2020, INQOVI® (decitabine and cedazuridine), was approved by the FDA under Priority Review.[PressRelease_INQOVI_FDA,2020;p1,dateline;p1,para1(entire);para6,ln1][PressRelease_INQOVI_Taiho,2020;p1,para1,ln1-2;para2(entire);para4,ln2] INQOVI® is an oral therapy that is indicated for the treatment of adult patients with MDS, including previously treated and untreated, de novo and second... with the following FAB subtypes (refractory anemia, refractory anemia with ri... refractory anemia with excess blasts, and CMML and intermedia... nd high-risk IPSS groups.[Inqovi_PI;sect1(entire);sect11,para3,ln1-2]

Hypomethylating Agents

Hypomethylating agents (HMAs), such a... abine, exert their cytotoxic action by a mechanism known as l... process is described in detail in **Figure 3.**[Karahoca,2013;p2,col1,para3,ln11-13;p2... col2,para1,ln1-3;p2,col2,para1,ln6-7;p3,col1,para2,ln6-10;p9,col2,para3,ln1-5][Izar,20...

Azacitidine

Azacitidine is a... e analog of cytidine. It is believed to exert its antineoplastic eff... ethylation of DNA and direct cytotoxicity on abnormal hematopoiet... rrow. The concentration of azacitidine required for maximum inhibiti... n in vitro does not cause major suppression of DNA synthesis. Hypom... estore normal function to genes that are critical for differentiation and proliferatio... ytotoxic 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. Azacitidine must be administered subcutaneously.[Azacitidine_PI;sect12.1,para1(entire);sect1.1(entire);sect2.1(entire)]

Decitabine

Decitabine is also pyrimidine nucleoside analog of cytidine.[Lowder,2015;p1083,col1,para1,ln20-21][Karahoca,2013;p1,col1,para1,ln4-5;p1,col1,para1,ln1][Rodwell,2020;p2,para3,ln1] . It 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 and/or apoptosis.[Decitabine_PI;sect12.1,para1,ln1-3] Decitabine has been shown to induce hypomethylating both in vitro and in vivo.[Decitabine_PI;sect12.2,para1,ln1] In vitro, decitabine inhibition of DNA methylation is achieved at concentrations that do not cause major suppression of DNA synthesis.[Decitabine_PI;sect12.1,para1,ln3-5] 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. Non-proliferating cells are relatively insensitive to decitabine.[Decitabine_PI;psect12.1,para1,ln5-9]]

Cytidine Deaminase & Cytidine Deaminase Inhibitors

Cytidine deaminase (CDA) is an enzyme that catalyze tidine, including the cytidine analog decitabine. High levels of C inal tract and liver degrade decitabine and limit its oral bioavaila a CDA inhibitor . Administration of cedazuridine with decitabi posure of decitabine.[Inqovi_PI;sect12.1,para2(entire)] A sch cedazuridine's mechanism of action is shown in Figure 4.

INQOVI®

INQOVI® is a fix decitabine, and cedazuridine[Inqovi_PI;sect3,ln1] . In patients administere sage of INQOVI®, the maximum change from baseline in the eotide elements-1 (LINE-1) demethylation was observed at Day 8, wi ecovery of LINE-1 methylation to baseline at the end of the treatment he exposure-response analyses, a relationship between an increase in 5-day cumula y decitabine exposure and a greater likelihood of some adverse reactions (e.g., any grade neutropenias, thrombocytopenia) was observed in clinical studies.[Inqovi_PI;sect12.2(entire)]

Clinical Studies of INQOVI®

INQOVI® was evaluated in Study ASTX727-01-B (NCT0210378) and Study ASTX727-02 (NCT03306264).[Inqovi_PI;sect14,para1,ln1-2;sect14,para5,ln1-2] Results of these clinical studies have been summarized in **Tables 6** and **7**, respectively. These trials demonstrated that INQOVI® given as an oral fixed-dose combination tablet of 35 mg decitabine and 100 mg cedazuridine produces comparable pharmacokinetics (measured as area under the concentration-time curve [AUC] and peak plasma concentration [C_{max}] values), pharmacodynamics (measured as depth of hypomethylation using LINE-11 demethylation assays), clinical efficacy (measured as complete response [CR] and transfusion independence), and toxicity profiles compared with IV decitabine administered at doses adjusted to the patient's BSA.[Garcia-Manero,Blood,2020;p680,col2,para1(entire)][Inqovi_PI;sect6.1,para2(entire)]

ASTX727-01-B

Highlights ASTX727-01-B (NCT0210378), a phase II clinical trial of INQ®, are provided in **Table 6**.[Inqovi_PI;sect14,para1,ln1-2][Garcia-Manero,2020;p675,col2,para2,ln1;p674,abst OVI® (35 mg decitabine and 100 mg cedazuridine, administered orally) was decitabine (dosed according to BSA at 20 mg/m^2 and given as a 1 ndomized cross-over design (N = 80).[Garcia-Manero,2020;p675,col2,para2,ln1-2;p676 ,ln7-12;p677,col1,para1,ln1-6;p676,table1][Inqovi_PI;sect14,para1,ln1-2] For cycl cipants received either INQOVI® orally in cycle 1 and IV decitabi erse, with IV decitabine in cycle 1 and INQOVI® orally in cycle 2.[Gar ,ln6-11;677,col1,para1,ln1-6] All patients received INQOVI® from cycle 20;p677,col1,para1,ln5-6] Peak (C_{max}) decitabine plasma concentrations fter the start of the IV infusion and 1 hour after oral administratio ero,2020;p679,col2,para4(entire)] Cumulative 5-day AUC from time zero (n able concentration of DEC were similar between orally administere citabine, with an oral to IV ratio of 93.5% in the dose-confirmation me and cedazuridine were administered as 2 separate oral capsules ed dose combination cohort (where decitabine and cedazuridine were admi er in 1 tablet).[Garcia-Manero,2020;p677,col1,para1,ln6-12;p679,col2,para3,ln5-9] The 80% CIs for both ra ncluded the null (82.1% to 106.5% and 80.5 to 118.3, respectively).[Garcia-Manero,2020;p679,col2,para3,ln5-9] The depth of demethylation produced by orally administered INQOVI® emulated that of IV decitabine, with a difference between the two of less than 1% and the 95% CI containing the null (zero).[Garcia-Manero,2020;679,col2,para5(entire)]

Because all patients in this study received orally administered INQOVI® at some point during cycles 1 and 2 and then from cycle 3 onward, clinical response rates observed are suggestive of INQOVI®'s efficacy. [INQOVI_PI;p19,table6] 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%).[INQOVI_PI;p19,para1,ln1-3] Sixty-four percent of patients who were transfusion independent at baseline maintained transfusion independence during any consecutive 56-day postbaseline period (25/39).[INQOVI_PI;p19,para1,ln3-4] 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.[INQOVI_PI;p19,table6]

There were no notable increases in gastrointestinal adverse events observed with orally administered INQOVI® versus IV decitabine administered during the first 2 cycles.[Garcia-Manero,2020;p680,col1,para3,ln4-6] Incidences of other adverse effects were also similar for [illegible] IV in the first 2 cycles.[Garcia-Manero,2020;p680,col1,para3,ln2-4]

ASTX727-02

Preliminary results of ASTX727-02 (NCT03306264), a p[illegible] INQOVI® (the ASCERTAIN trial are summarized in **Table [illegible]**

[https://clinicaltrials.gov/ct2/show/NCT03306264;p2,table,col3;p2,para2,ln1]][Aste[illegible]let3,ln1;p2,para3(entire)]

ASCERTAIN was designed to establish bioequiv[illegible]e oral combination of INQOVI® (decitabine-cedazuridine 35 mg, 1[illegible]me dosed according to BSA at 20 mg/m^2.[https://clinicaltrials.gov/ct2/show/NCT033[illegible]ded to the list] [INQOVI_PI;p19,para2,ln4-5] Study participants (N = 133) recei[illegible]nistered INQOVI® in cycle 1 and IV decitabine in cycle 2 or the r[illegible]bine administered in cycle 1 and INQOVI® given in cycle 2.[INQOVI_P[illegible]cle 3 onward, all participants received INQOVI®.[INQOVI_P[illegible]

The 5[illegible] ratio of oral to IV was 99% (90% CI, 93%-106%).[Inq[illegible] As with the phase II study (ASTX727-01B), all patients in ASCERTAIN [illegible]rally administered INQOVI® at some point during cycles 1 and 2 and then from cycle 3 [illegible]ward; thus, clinical response rates observed are suggestive of INQOVI®'s efficacy. CR was observed in 21% of patients across both cohorts.[INQOVI_PI;p21,table8] Conversion from transfusion dependence at baseline to transfusion independence during any consecutive 56-day postbaseline period occurred in 30 of 57 patients (53%).[INQOVI_PI;p21,para1,ln1-2] Sixty-three

percent of patients who were transfusion independent at baseline maintained transfusion independence during any consecutive 56-day postbaseline period (48/76).[34][INQOVI_PI;p21,para1,ln2-4] 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.[INQOVI_PI;p21,table8]

Drug Interaction Studies

In vitro studies in human liver microsomes suggest that decitabine is unlikely to inhibit or induce cytochrome P450 enzymes. In vitro met metabolism studies have suggested that decitabine is not a substrate for human liver cytochrome P450 enzymes.[Decitabine_PI;sect7(entire)]

Cedazuridine is not a substrate of cytochrome P450 (CYP) 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 (OAT) AT1, OAT3, OATP1B1, OAPT1B3, and OATP2B; or the organic cation transporters OCT2. Cedazuridine does not inhibit MATE1, MATE2-K, OAT1, OAT3, OATP1 OCT2, or the breast cancer resistance protein efflux transporter (BCP 10(entire)]

Decitabine had no clinically meaningful effect on t f cedazuridine. Cedazuridine increased the exposure of decitabine. T INQOVI® with proton pump inhibitors (PPI's) had no clinically exposure to decitabine or cedazuridine. [Inqovi_PI;sect12.3;para7-8(entire)] [Inqov

Conclusions

INQOVI®, a fixed-do decitabine combined with cedazuridine, a cytidine deaminase inhib similar pharmacokinetics and pharmacodynamics to IV decitabine d nt BSA. INQOVI® as an oral treatment may represent an important -centered care for patients with MDS, as it allows for at-home me n.

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Tables and Figures

Table 1. The French-American-British Morphology Group Cla… Myelodysplastic Syndromes[Bennett,1982;p192,table1;p195,para8(entire);p197… …ol1,para1,ln4-5;ln9-11;p2081,col1,para2,ln1-12][Bennett,2005;pS4,col2,para2,ln3-11]

Subtype	Acronym	% Blasts in Bone Marrow	% …	…e Marrow Characteristics
Refractory Anemia	RA	<5%		…iculocytopenia 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%	n/a
Chronic Myelomonocytic Leukemia				Monocytosis (monocytes > 1 x 10^9/L)
Refractory Anemi… Excess of B… Transf…		21%-30%	>5%	n/a

Table 2. The International Prognostic Scoring System Criteria Used in Myelodysplastic Syndromes[Greenberg,1997;p2080,col2,para2,ln5-8;p2085,table3][Greenberg,2012;p2458,table3,table4][LLS,20 ,table6]

IPSS												
Score	**0**	**0.5**	**1.0**	**1.5**	**2.0**	**>2**						
Category	**Low**	**Int-1**		**Int-2**								
BM Blasts (%)	<5	5-10		11-20								
Cytogenetic Group[a]	Good	Int										
Cytopenias[b]	0/1											
IPSS-R												
Score	**0**	**0.5**	**1.0**	**1.5**	**2.0**				**5.0**	**5.5**	**6.0**	**>6.0**
Category	**Very Low**								**High**			**Very High**
BM Blasts (%)	≤2		>2 and <5					>10				
Cytogenetic Group[a]	Very Good		Good					Very Poor				
Cytopenias												
Hemoglobin[c]	≥10							<8				
Platelets[d]	≥100	50						<50				
ANC[d]	≥0.8							<0.8				
Broad Risk Categories												
IPSS						Higher Risk						
IPSS-R			Lower Risk						Higher Risk			

ANC,absolut narrow; Int, intermediate; IPSS, International Prognostic Scoring System; IPSS-R, Internatio , Revised.

[a]Cytogene determined based on presence of specific mutations.
[b]A cytopenia em was defined as 1) hemoglobin <10 g/dL; 2) platelets <100,000/µL; and/or 3) ANC <1500/µL.
[c]Hemoglobin v dL.
[d]Platelet and ANC ues are 10^9/L.

Table 3. Cytogenetic Prognostic Groups Used Within the IPSS and IPSS-R Systems

[Greenberg,2012;p2457,table2][Greenberg,1997;p2080,table1_footnote;p2084,figure4A]

Mutation Type[a]	IPSS			IPSS-R				
	Cytogenetic Prognostic Group			Cytogenetic Prog				
	Good	Intermediate	Poor	Very Good	Good	Inte		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; inv, in… …rognostic Scoring System; IPSS-R, International Prognostic Scoring System, Revised; t, transl…

[a]A patient … …genetic prognostic group based on the presence of at least 1 of the genetic abnormalities listed fo…

Table 4. Therapeutic Agents Used in Supportive Care of MDS.

[Steensma,2018;p1,col2,para2,ln1-6;p4,figure1][Young,2020;p30,para2,ln2-7][Epoetin_PI;sect1.3(entire);sect2.4,bullet1, bullet3][Darbepoetin_PI;sect1.2(entire);sect11(entire)][Luspatercept_PI;p1,col1,para2(entire);sect1.2(entire);sect11,ln1] [AminocaproicAcid_IV_PI;Description,para3,ln1;IndicationsAndUsage,para1(entire)][AminocaproicAcid_oral_PI;p1,para4,ln1;para5,ln1;p2,para5,ln1][Deforoxamine_PI;p1,ln5-7;p1,para1,ln1-2;para5(entire)][Deferasirox_PI;sect1.1(entire);sect11,ln1]

Agent	Route of Administration		Mechanism of Action/Therapeutic Class	
	Parenteral	Oral		
Epoetin alpha Darbepoetin alfa	• (SQ, IV)		Erythropoiesis-stimulating agent	
Luspatercept-aamt	• (SQ)		RBC maturation	agent and ≥ 2 or more units over 8 eeks in adult patients with very low- to intermediate-risk MDS-RS or with MDS/MPN-RS-T
Aminocaproic acid	• (IV)	• (Tab, S		Control bleeding that is refractory to platelet transfusion
Deferoxamine	• (SQ, IV, IM)			Iron overload
Deferasirox			ator	

IM, intramuscular; MDS, m DS-RS, myelodysplastic syndrome with ringed sideroblasts; MPN-RS-T, myeloproliferative n and thrombocytosis; RBC, red blood cell; Soln, oral solution; SQ, subcutaneous; Tab, t

Table 6. Results of Study ASTX727-01-B (a Phase II Trial of INQOVI®)

[Inqovi_PI;sect14,para1,ln1-2;ln3-8;table5,row1;row17-21;para3-4(entire);table6]

Intervention

Participants randomized 1:1 to Sequence A or Sequence B

Sequence A

Cycle No.	Route	Agent(s)	Duration
Cycle 1	IV	decitabine	x 5d
Cycle 2	Oral	INQOVI®	x 5d
Cycle 3+	Oral	INQOVI®	x 5d

Sequence B

Cycle No.	Route	Agent(
Cycle 1	Oral	IN
Cycle 2	IV	
Cycle 3+	Ora	d

Doses

Oral (INQ , 100 mg cedazuridine
IV: 20 mg/m hour

Pharmacokinetic ollected:

- 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.

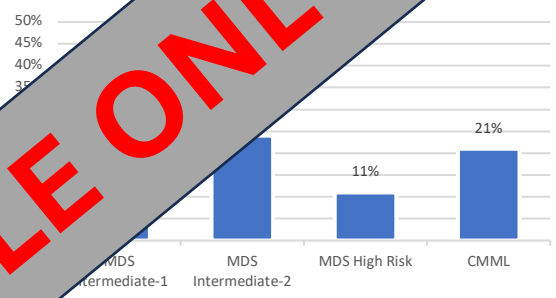
Pharmacodynamic Data Collected:

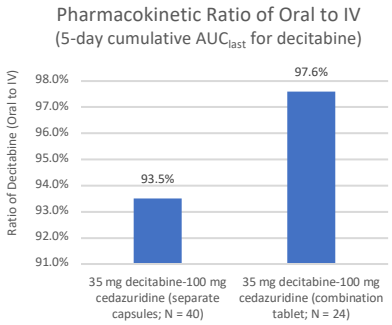
- DNA methylation at screening, on day 1 (predose), and then on days 8, 15, and 22

Efficacy Data Collected:

- CR
- Conversion from transfusion dependence to transfusion independence

Results





Efficacy Data (N = 80)	
CR	18%
Transfusion dependence to independence after treatment	49% (20/41)
Remained transfusion dependent from baseline to after treatment	64% (25/39)
Median duration of CR	8.7 months
Median time to CR	4.8 months

AUC,area under the concentration-time curve; C_{max}, peak plasma concentration; CR, complete response; CMML, chronic myelomonocytic leukemia; IV, intravenous; MDS, myelodysplastic syndromes.

Table 7. Preliminary Results of Study ASTX727-02 (a Phase III Trial of INQOVI®)[Inqovi_PI;sect12.3,para2,ln5-7;sect14,para5,ln1-2;ln4-8;table7,row1;row15-20;para7-8(entire);table8]

Intervention

Participants randomized 1:1 to Sequence A or Sequence B

Sequence A

Cycle No.	Route	Agent(s)	Duration
Cycle 1	Oral	INQOVI®	x 5d
Cycle 2	IV	decitabine	x 5d
Cycle 3+	Oral	INQOVI®	x 5d

Sequence B

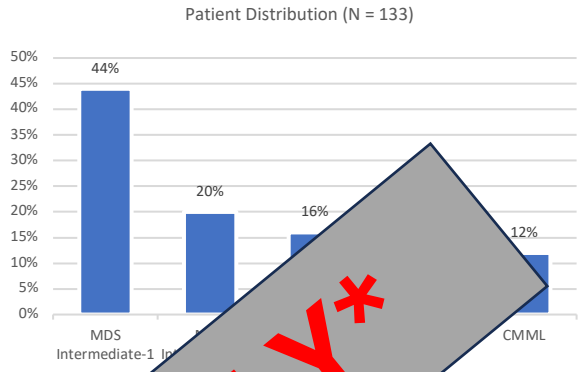
Cycle No.	Route	Agent(s)	Duration
Cycle 1	IV	decitabine	x 5d
Cycle 2	Oral	INQOVI®	x 5d
Cycle 3+	Oral	INQOVI®	x 5d

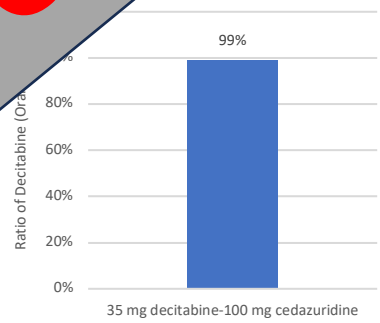
Doses
Oral (INQOVI®): 35 mg DEC, 100 mg cedazuridine
IV: 20 mg/m^2 decitabine over 1 hour

Pharmacokinetic Data Collected:
- decitabine 5-day AUC

Efficacy Data Collected:
- CR
- Conversion from
  transfusion in

Results





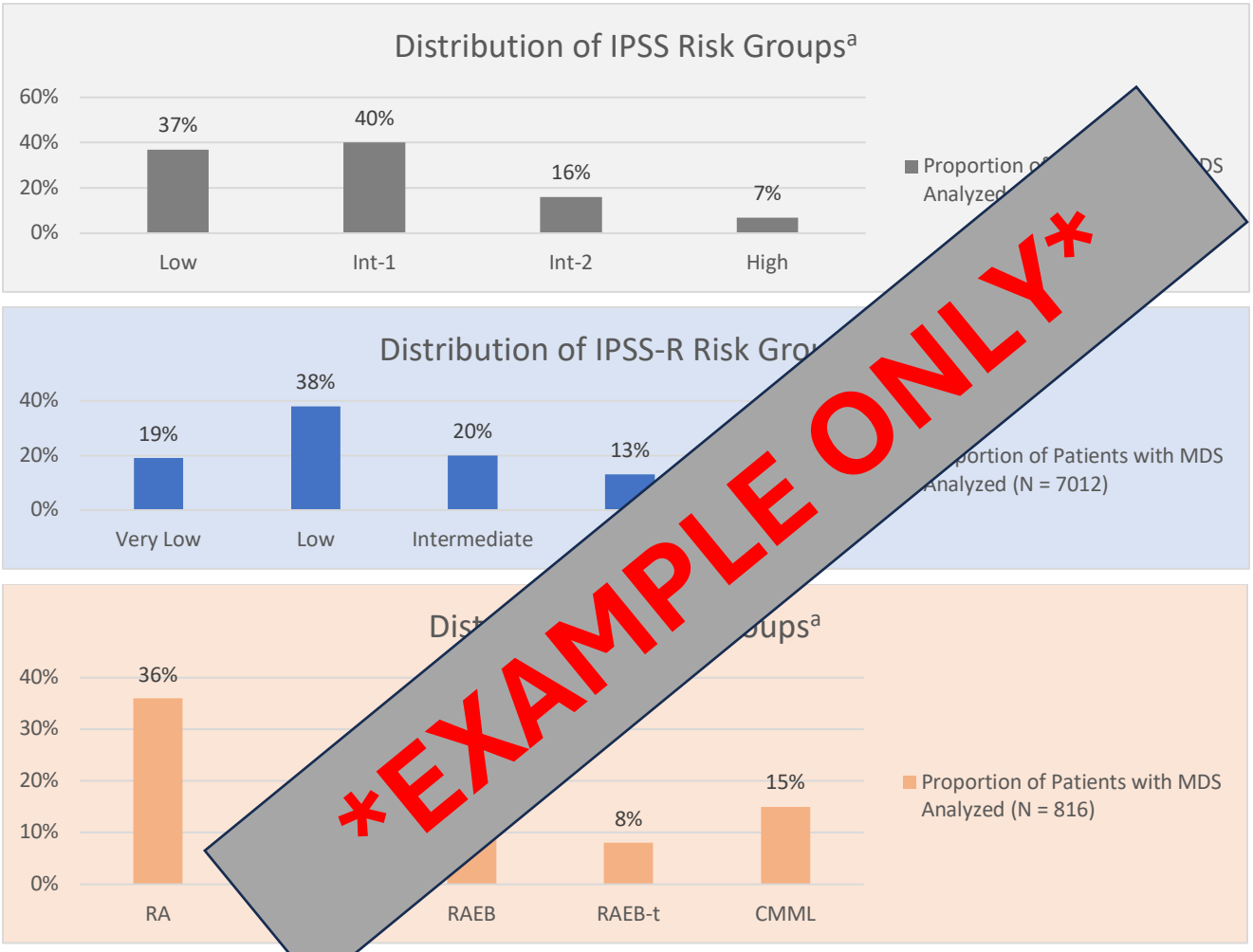
Efficacy Data (N = 133)	
CR	21%
Transfusion dependence to independence after treatment	53% (30/57)
Remained transfusion dependent from baseline to after treatment	63% (48/76)
Median duration of CR	7.5 months
Median time to CR	4.3 months

AUC, area under the concentration-time curve; C_{max}, peak plasma concentration; CR, complete response; CMML, chronic myelomonocytic leukemia; IV, intravenous; MDS, myelodysplastic syndromes.

Figure 1. Survival Stratified by IPSS, IPSS-R, FAB classification, and Age
[Greenberg,1997;p2086,table4][Greenberg,2012;p2456,table1;p2459,table5;p2460,table6][Nosslinger,2001;p2936,table1]

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, International Prognostic Scoring System, Revised; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RAEB-t, refractory anemia with excess blasts in transformation; RARS, refractory anemia with ringed sideroblasts.

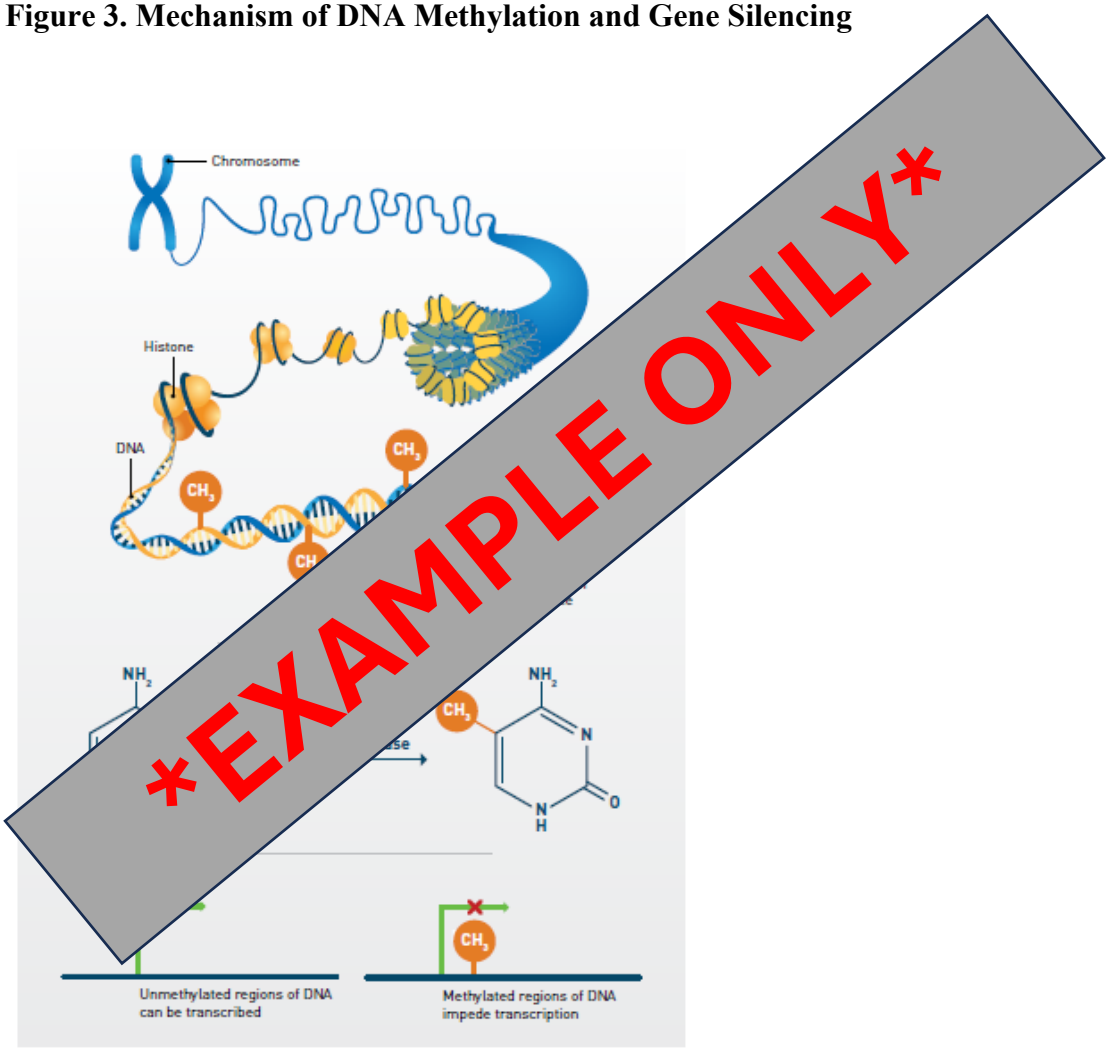
Figure 2. Approximate Distributions of IPSS, IPSS-R, and FAB Groups[Greenberg,2012;p2455,col1,para2(entire);p2456,table1][Bennett,2005;pS6,figure3][Greenberg,1997;p2080,table1;p2081,col2,para2,ln1-3]



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, International Prognostic Scoring System, Revised; MDS, myelodysplastic syndromes; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RAEB-t, refractory anemia with excess blasts in transformation; RARS, refractory anemia with ringed sideroblasts.

[a]Data is from international registries.

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 ***hyper***methylation. 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.[Karahoca,2013;p2,col1,para3,ln13-19] ***Hypo***methylation 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.[Karahoca,2013;p2,col1,para3,ln11-13;p3,col1,para2,ln10-11;p3,table1] Mutations can over-activate DNMTs, resulting in increased methylation (and silencing) of genes that help control cellular differentiation and proliferation. The result is uncontrolled cell growth.[Izar,2020;p37,para5,ln1-4] This reduced expression of genes in cancerous cells allows their continued growth and survival.[Lowder,2015;p1083,col1,para1,ln6-12] In myelodysplastic syndromes, the p15 tumor suppressor gene is frequently hypermethylated, causing a reduction in its ability to monitor malignant transformation of cells.[Karahoca,2013;p3,col1,para2,ln6-10] The hypomethylating agents azacitidine and decitabine can reactivate tumor suppressor genes by inhibiting the action of aberrant DNMTs.[Karahoca,2013;p2,col2,para1,ln1-3;p2,col2,para1,ln6-7;p3,col1,para2,ln6-10;p9,col2,para3,ln1-5] [Izar,2020;p13,para6,ln2-4]

During DNA methylation, a methyl (-CH3) group is transferred from a molecule culled from S-adenosyl-L-methionine onto the 5-position of the cytosine ring within a cyt[illegible]phosphate-guanine dinucleotide (CpG) base pairing region of a gene. The reaction i[illegible]d by a DNA methyltransferase enzyme. After a CpG section of a gene is methylat[illegible]anscribed (it is silenced).[26[Karahoca,2013;p2,col1,para3,ln13-19]]

Figure 4. Deamination and Deactivation of Decitabine by Endoge
Deaminases[Inqovi_PI;sect12.1,para2(entire)][Lowder,2015;p1083,col2,para3,ln8-10][Garci n2-5]
[Decitabine_PI;sect11,figure]