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CADTH PCODR FINAL CLINICAL GUIDANCE REPORT

Clinical Report

Decitabine and Cedazuridine (INQOVI)

Taiho Pharma Canada, Inc.

Indication: The treatment of adult patients with 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) and intermediate-1, intermediate-2, and high-risk IPSS groups.

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AAMAC	Aplastic Anemia & Myelodysplasia Association of Canada
AE	Adverse event
AML	Acute myeloid leukemia
ATG	Anti-thymocyte globulin
BSA	Body-surface area
CDA	Cytidine deaminase
CMML	Chronic myelomonocytic leukemia
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DAC	Drug Advisory Committee
DC	Dose confirmation
Del(5q)	Deletion 5q
DNMT	DNA methyltransferase
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EPO	Erythropoietin
ESA	Erythropoiesis-stimulating agents
FAB	French-American-British
FDC	Fixed-dose confirmation
G-**CSF**	Granulocyte colony stimulating factor
GVHD	Graft-versus-host disease
HI	Hematologic improvement
HMA	Hypomethylating agent
HRQoL	Health-related quality of life
HSCT	Hematopoietic stem cell transplant
ICT	Iron chelation therapy
IPSS	International Prognostic Scoring System
IPSS-R	Revised International Prognostic Scoring System
IRC	Independent Review Committee

IWG	International Working Group
LFS	Leukemia-free survival
LLSC	Leukemia & Lymphoma Society of Canada
LSM	Least squares mean
mCR	Marrow complete response
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network
OCC	Odette Cancer Center
OH-CCO	Ontario Health Cancer Care Ontario
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamic
PFS	Progression-free survival
PK	Pharmacokinetic
PMH	Princess Margaret Hospital
PR	Partial response
QoL	Quality of life
RBC	Red blood cell
RCT	Randomized controlled trial
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
TI	Transfusion independent
WHO	World Health Organization

1 Guidance In Brief

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding the decitabine and cedazuridine combination (Inqovi) for adult patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (FAB) (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 (IPSS) groups. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on a systematic review of the literature conducted by the Clinical Guidance Panel (CGP) and the CADTH Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background of Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input, a summary of submitted Provincial Advisory Group Input, and a summary of submitted Registered Clinician Input are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The purpose of this review is to evaluate the efficacy and safety of the decitabine and cedazuridine combination, referred to as decitabine and cedazuridine from here on, in 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 (IPSS) groups. The funding request aligns with the Health Canada indication. The Health Canada Notice of Compliance was granted for decitabine and cedazuridine on July 7, 2020.

Decitabine and cedazuridine is a novel, oral, fixed-dose cytotoxic combination antineoplastic composed of decitabine, a DNA methyltransferase inhibitor, and the cytidine deaminase inhibitor cedazuridine. Decitabine and cedazuridine is given as a 35/100 mg fixed dose oral tablet once daily for 5-days at the beginning of every 28-day cycle until disease progression or unacceptable toxicity.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The CADTH systematic review included two randomized controlled trials (RCTs); ASCERTAIN (n = 133) and ASTX727-01-B (n = 80).[1,2] A summary of the trials and results is provided below.

ASCERTAIN

ASCERTAIN was a Phase III, multicenter, randomized, open-label, 2-period, 2-sequence crossover study comparing oral decitabine and cedazuridine (also referred to as ASTX727 in the study publications) and intravenous (IV) decitabine as treatment for adult patients with MDS or CMML. The primary objective was to establish decitabine AUC equivalence of 5-day dosing between oral decitabine and cedazuridine and IV decitabine. Eligible patients were randomized to receive either decitabine and cedazuridine followed by crossover to IV decitabine, or the opposite sequence.[1]

To be eligible, patients had to have previously treated or untreated, de novo or secondary MDS, including all FAB subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and CMML), and subjects with MDS IPSS intermediate-1, intermediate-2, or high-risk MDS, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Patients were permitted to have treatment with one prior cycle of hypomethylating agent (HMA; decitabine or azacitidine), provided that treatment was not within four weeks of study treatment.[1]

Eligible patients were randomized 1:1 to receive oral decitabine and cedazuridine (35/100 mg) in cycle 1 followed by IV decitabine (20 mg/m^2) via 1-hour infusion in cycle 2 (Sequence A), or IV decitabine (20 mg/m^2) via 1-hour infusion in cycle 1 followed by oral decitabine and cedazuridine (35/100 mg) in cycle 2 (Sequence B). After completion of the first 2 treatment cycles, subjects continued to receive treatment with oral decitabine and cedazuridine in 28-day cycles until disease progression, unacceptable toxicity, treatment discontinuation for other reasons, or withdrawal from the study. A total of 133 subjects were randomized 1:1 to Sequence A (n = 66), or Sequence B (n = 67). Randomization was stratified by IPSS risk category.[1]

The primary endpoint of the trial was the total 5-day (total cycle) AUC exposures of decitabine after treatment with decitabine and cedazuridine versus IV decitabine, calculated as the ratios of treatment least squares mean (LSM) for decitabine and cedazuridine relative to IV decitabine. The two treatments were to be considered equivalent if the two-sided 90% confidence interval (CI) of the 5-day decitabine AUC_{0-24} ratio of LSM for decitabine and cedazuridine relative to IV decitabine was contained entirely within the range of 0.80 – 1.25. Secondary endpoints included safety as assessed by patient-reported and investigator-assessed AEs, clinical response (overall response rate [ORR], complete response [CR], partial response [PR], marrow complete response [mCR], and hematologic improvement [HI]) based on International Working Group (IWG) 2006 MDS response criteria,[3] red blood cell (RBC) or platelet transfusion independence (TI), leukemia-free survival (LFS), defined as the number of days from the date of randomization to the date when bone marrow or peripheral blood blasts reach ≥20%, or death from any cause, and overall survival (OS), defined as the number of days from the date of randomization to the date of death from any cause, as well as other pharmacokinetic (PK) and pharmacodynamic (PD) parameters.[1]

A total of 173 subjects were screened for eligibility, with 138 randomized, and 133 receiving treatment (66 to Sequence A, and 67 to Sequence B). The median age was 70.0 years (range = 44 to 85 years) in Sequence A and 72.0 years (range = 49 to 88 years) in Sequence B. In both groups, the majority of patients were Caucasian (90.9% and 91.0%) males (63.6% and 67.2%) and had an ECOG performance status of 1 (62.1% and 55.2%). Sequence A had a higher incidence of IPSS intermediate-2 and high-risk patients compared to Sequence B (21.2% and 21.2% vs 17.9% and 10.4%, respectively). The weight of the trial patients ranged from 45.0 kg to 157.9 kg. No exclusion criteria were applied to body weight or body-surface area (BSA). In line with the inclusion/exclusion criteria, the majority of patients did not have prior treatment with HMAs.[1]

Efficacy

The results for the primary and secondary efficacy outcomes from the ASCERTAIN trial are summarized in Table 1. As of the March 2019 data cut off, the median duration of follow up was 155 days (5.1 months) and [redacted].[4] The ASCERTAIN trial is still ongoing for patient follow up.[1,5] [redacted].[6] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

As of the March 2019 data cut off, the ASCERTAIN trial met its primary endpoint by demonstrating that the 5-day AUC_{0-24} ratio of geometric LSM for decitabine and cedazuridine relative to IV decitabine was 98.93% (90% CI: 92.66, 105.6). The two-sided 90% CI is contained entirely within the prespecified range of 0.80 to 1.25 for the primary analysis, indicating equivalent decitabine exposure between oral decitabine and cedazuridine and IV decitabine. Secondary analyses of 5-day AUC at various time points confirmed the results of the primary analysis of 5-day AUC_{0-24}.[7]

As of the first data cut off on March 19, 2019, clinical response outcomes were considered preliminary. Complete response was observed in 9.0% to 13.4% of subjects, however, response data was not available for 32 (24%) of subjects, with an additional 28.4% to 45.5% achieving mCR. The ORR (CR + PR + mCR + HI) ranged from 44.8% to 64.4%.[1,7] [redacted][5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Transfusion independence results were also considered preliminary due to the short follow up period of the March 19, 2019 data cut off. Of the 133 treated subjects, one-third (32.7%) who were RBC transfusion dependent at baseline were RBC TI for any

consecutive greater than or equal to 56-day period post-baseline. Similarly, 30% of platelet transfusion dependent subjects became platelet TI for any greater than or equal to 56-day period post-baseline.[1,7] [redacted].[5]

[redacted].[5] [redacted].[8] [redacted] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

As with LFS, the median OS was not reached at 12.7 months follow up, and only 33 patients had died.[5] Subgroup analysis of intermediate-2 and high-risk MDS patients demonstrated a median OS of 13.94 and 14.37 months, respectively. Patients with prior anticancer therapy (n = 30), and those who received subsequent hematopoietic stem cell transplant (HSCT; n = 33) demonstrated a median OS of 14.37, and 16.44 months, respectively.[8] As of the April 14, 2021 data cut-off, 58 events had occurred and the median OS was 31.76 (28.04, not estimable). At this updated analysis, the median OS was not reached in the intermediate-1 (31.76, not estimable) and CMML (19.79, not estimable) IPSS groups. The median OS was 23.28 (13.05, 29.23) in the intermediate-2 risk group, and 15.45 (10.55, 26.60) in the high-risk group.

Limitations and Potential Sources of Bias

The major limitations and potential sources of bias associated with the ASCERTAIN trial, based on the CADTH Methods Team's critical appraisal of the evidence, are summarized below. The complete list is available in Section 6.

- The ASCERTAIN trial used an open-label study design and therefore treatment assignment was unblinded. This study design has the potential for performance and detection biases in subjective outcomes, including safety and efficacy outcomes of response as awareness of treatment could result in overreporting of (adverse events) AEs by patients, probing by investigators, delaying confirmation of progression and inflating response rates and LFS/OS. Detection bias was minimized by the independent review committee (IRC) assessment for clinical response on the basis of quantifiable variables as per the 2006 IWG MDS Response Criteria.
- At the time of the first data analysis (database cutoff of March 19, 2019), the efficacy outcome data were immature ([redacted]), also resulting in preliminary data for important outcomes of clinical response ([redacted]), and transfusion independence. Overall interpretation of these outcomes at the primary data cutoff is limited due to the short follow up time (median follow up of only 155 days [5.1 months]). A second analysis of efficacy endpoints was performed using all available data up to the data cutoff for the second analysis ([redacted]), in which all patients were evaluable for clinical response, however, this is believed to be too short for analysis of survival outcomes in this population. Thus, there is uncertainty in the reported efficacy outcomes of the ASCERTAIN trial. The April 2021 data cut off provided updated efficacy data where the median OS and LFS had been reached.
- Paired analysis was only conducted for the primary endpoint using the primary PK population using ANOVA models that included treatment, period, and sequence as fixed effects, and subject nested in sequence as a random effect. Following crossover, since both treatment arms received decitabine and cedazuridine, the true efficacy and safety between IV decitabine and decitabine and cedazuridine cannot be confirmed although PK equivalence was demonstrated, suggesting there may be limited differences on these outcomes. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*
- [redacted] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*
- Decitabine and cedazuridine was not compared to relevant comparators in the trial, and therefore there is a lack of direct comparison to relevant agents used to treat MDS such as azacitidine. The sponsor submitted an Indirect Treatment

Comparison (ITC), for intermediate-2 and high-risk populations which included some relevant comparators; however, since the sponsor submitted ITC did not identify any comparative evidence for intermediate-1 or CMML populations (erythropoiesis-stimulating agents [ESAs], RBC transplant/iron chelation therapy [ICT], lenalidomide, etc.), comparative efficacy remains unknown for these patient groups (see Section 7 for further details).

- Health-related quality of life (HRQoL) was not assessed in the ASCERTAIN trial, and therefore the impact of decitabine and cedazuridine on quality of life (QoL) remains unknown.

ASTX727-01-B

ASTX727-01-B was a two-phased international, randomized, phase II, two-cycle, two-sequence crossover trial that evaluated the pharmacokinetics, pharmacodynamics, and safety of either sequence of oral decitabine and cedazuridine followed by IV decitabine or IV decitabine followed by decitabine and cedazuridine.

Eligible patients were age ≥18 years, intermediate-1, intermediate-2- or high-risk MDS, or CMML, ECOG performance status 0 to 2, adequate and renal function, and no evidence of active second malignancy. One prior cycle of either decitabine or azacitidine was allowed, but no other cytotoxic chemotherapy was permitted within 2 weeks of starting study treatment. Patients with prior allo-HSCT were eligible if they were free of graft-versus-host disease (GVHD) and off immunosuppressive therapy at the time of enrollment.[9,10]

Patients were initially randomized 1:1 to receive 1 of 2 treatment sequences during the first two cycles: oral decitabine and cedazuridine daily for 5 days in cycle 1, followed by IV decitabine daily for 5 days in cycle 2 (sequence A); or IV decitabine in cycle 1, followed by the oral drug in cycle 2 (sequence B). The study was conducted in two stages; a dose-confirmation (DC) stage where oral decitabine and cedazuridine was received as two separate capsules, and following the preliminary PK analysis, a single tablet fixed-dose combination (FDC). All patients received oral treatment from cycle 3 onwards.[9]

The primary endpoints of the ASTX727-01-B trial was oral/IV decitabine exposure over 5 days, DNA demethylation of oral decitabine and cedazuridine vs IV decitabine from the first 2 cycles, and ORR using IWG 2006 MDS criteria. Secondary end points included efficacy outcomes of duration of response, transfusion independence, time to acute myeloid leukemia (AML) defined as the number of days from the date the subject received the first dose of study treatment to the date of MDS progression to AML as defined by ≥20% blasts in bone marrow or peripheral blood, or death from any cause, and overall survival defined as the number of days from the date the subject received the first dose of study treatment to the date of death (regardless of cause), other PK measurements, and safety.[9]

A total of 138 patients were screened, and 86 patients were randomized, including 52 into the DC cohort, and 34 into the FDC cohort. Of the 86 randomized, only 80 were treated, as two patients in the DC cohort, and four patients in the FDC cohorts did not receive any study treatment and were excluded from all analyses. Overall, 41 patients were randomized to receive treatment sequence A, and 39 were randomized to treatment sequence B. At data cutoff (June 5, 2018), 67 patients had discontinued treatment (n=41 [82%] in the DC cohort; n=26 [86.7%] in the FDC cohort), with a similar proportion remaining on treatment (n=13; 9 [18%] and 4 [13%] patients in the DC and FDC cohorts, respectively). The primary reason for treatment discontinuation in both groups was disease progression (14 [28%] and 7 [23.3%] in the DC, and FDC cohorts, respectively). Twelve patients (15%) overall discontinued treatment for stem cell transplant. Patients received a median of 7 treatment cycles (range = 1 to 29),[9]

Baseline characteristics were generally balanced across the randomized treatment sequences in each cohort. The median age of all participants was 71 years, and the majority were male (76%), of Caucasian ethnicity (93%), and most subjects had an ECOG performance status score of 0 (44%) or 1 (48%); however, a greater proportion of subjects in Sequence A were ECOG performance status 0 (48.8% vs. 38.5%), while a greater proportion of patients in Sequence B were ECOG 1 (51.3% vs. 43.9%). A total of 7 (9%) patients overall had ECOG performance status of 2. Almost half (48%) of all patients were RBC transfusion dependent at baseline. The majority of patients were IPSS intermediate-1 risk (44%), while 24% were intermediate-2, and 11% and 21% were high-risk and CMML, respectively.

Efficacy

The results for the primary and secondary efficacy outcomes from the ASTX727-01-B trial are summarized in Table 1. At the data cut off, the median follow-up was 24.3 months.[9]

In the primary paired analysis, the 5-day decitabine AUC_{last} oral/IV geometric LSM ratios were 93.5 (80% CI, 82.1- 106.5) and 97.6 (80% CI, 80.5-118.3) in the DC and FDC cohorts, respectively, falling within the prespecified CI limits of 75 to 133, and 65-153.9.[9] This demonstrates that both the DC and FDC administrations achieved decitabine AUC exposure equivalent to IV decitabine at 20 mg/m^2.

As of the June 5, 2018, data cut off, ORR was seen in 48 patients (60%), including 17 (21%) with CR, a PR rate of 0, and a mCR rate of 22%. A total of 16.3% of subjects showed HI in one or more lineage(s). Of the 17 patients with CR, 12 experienced disease progression, with a median duration of response (DOR) of 13.3 months (95% CI: 6.5, 13.8).[9]

At the time of the analysis, of the 38 patients who were RBC transfusion dependent at baseline, 19 (50%) became TI, and of the 12 patients who were platelet transfusion dependent at baseline, 6 (50%) became TI.[9]

Of the 80 subjects included in the ASTX727-01-B trial, 47 (58.8%) progressed to AML or death, and data were censored for the remaining 33 subjects (41.3%). The median time to AML or death for the overall population treated was 12.1 months (95% CI, 5.9, NE).

As of the June 5, 2018, data cutoff, 50% of subjects had died. Median overall survival for all patients treated was 18.3 months (95% CI, 9.1-not estimable).[2,9]

Limitations and Potential Sources of Bias

The major limitations and potential sources of bias associated with the ASTX727-01-B trial based on the CADTH Methods Team's critical appraisal of the evidence are summarized below. Given the similar design of the phase II ASTX727-01-B and phase III ASCERTAIN trial, the CADTH Methods Team identified similar limitations and potential sources of bias for the ASTX727-01-B trial as the ASCERTAIN trial, which should be considered when interpreting the trial results. The complete list is available in Section 6.

- This was an open-label study, in which treatment assignment was not blinded for patients or investigators, increasing the risk of performance and detection biases. Awareness of treatment received by patients and investigators may result in overreporting of AEs by patients and probing by investigators if known or suspected to be related to the treatment and delaying confirmation of progression by the investigator, thereby inflating response and survival outcomes. Detection bias was minimized by the IRC assessment for clinical response on the basis of quantifiable variables as per the 2006 IWG MDS Response Criteria.
- Paired analysis was only conducted for the primary endpoint using the primary PK population. Following crossover, since both treatment arms received decitabine and cedazuridine, the true efficacy and safety between IV decitabine and decitabine and cedazuridine cannot be confirmed, although PK equivalence was demonstrated, suggesting there may be limited differences on these outcomes.
- The primary objective of the ASTX727-01-B trial was PK and sample size/power calculations were based on PK outcomes. Efficacy outcomes, critical to the review, were not controlled for multiplicity or considered for sample size calculations and thus, the study was not powered for these outcomes and the secondary results must be interpreted as exploratory.
- HRQoL was not assessed in the ASTX727-01-B trial, and therefore the impact of decitabine and cedazuridine on QoL remains unknown.

ASCERTAIN and ASTX727-01-B Pooled Harms Outcomes

Pooled safety data from the Phase II ASTX727-01-B trial and the Phase III ASCERTAIN study were submitted in the original NDA based on the June 5, 2018, and March 19, 2019, data cuts. Overall, 205 (98.6%) patients included in the pooled analysis experienced at least one treatment emergent adverse event (TEAE). The most common TEAEs of any grade that occurred in all subjects were thrombocytopenia (52.4%), neutropenia (51.4%), anemia (39.4%), and fatigue (38.9%). The most frequent grade ≥ 3 AEs in the overall population included thrombocytopenia (50.0%), neutropenia (45.7%), anemia (33.7%), febrile neutropenia (27.9%), and leukopenia (22.6%). The most common non-fatal serious adverse events (SAEs) occurring in >5% of subjects in the overall

decitabine and cedazuridine population across all cycles included febrile neutropenia (26%), pneumonia (10.6%), and sepsis (6.7%).[11]

As of the safety update [redacted], a total of 147 patients had discontinued treatment. Of these, 11 (5.3%) patients discontinued treatment, and one patient withdrew from the study due to AEs. A total of 81 subjects in the pooled analysis had died as of the [redacted] with only four occurring during the treatment period, and five deaths were due to AEs. The cause of death was unknown for the majority of patients who died (n = 40; 19.2%), followed by AEs (n = 23; 11.1%), and progressive disease (n = 13; 6.3%) across the ASTX727-01-B and ASCERTAIN trials.[11] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 1: Highlights of Key Outcomes

	ASCERTAIN	ASTX727-01-B	
	Overall Population (N = 133)	DC Cohort (N= 40)	FDC Cohort (N= 24)
Primary Outcome			
5-day AUC Decitabine Exposures, Ratio (%; CI)			
Primary Paired	98.93 (92.66, 105.6)	93.52 (82.10, 106.5)	97.59 (80.48, 118.3)
Sensitivity Unpaired	97.99 (91.84, 104.5)	92.48 (81.37, 105.1)	102.45 (85.35, 123.0)
Sensitivity Paired	97.74 (91.58, 104.3)	-	-
Key Secondary Outcomes			
Clinical Response, n (%)*			
ORR	81 (60.9)	48 (60)	
CR	28 (21.1)	17 (21)	
PR	0	0	
mCR	43 (32.3)	18 (22)	
HI	10 (7.5)	13 (16)	
RBC/Platelet TI, n (%)*			
RBC-TI Post-Treatment			
≥ 56 days	[redacted]	11 (50.0)	8 (50.0)
≥ 112 days		-	-
Platelet TI Post-Treatment			
≥ 56 days	[redacted]	3 (42.9)	3 (60.0)
≥ 112 days		-	-
LFS/Time to AML, months*			
Median (95% CI)	[redacted]	12.1 (5.9, NE)	
OS, months*			
Median (95% CI)	[redacted]	18.3 (9.1, NE)	
Pooled Harms Outcomes (N = 208) (All cycles Decitabine and cedazuridine), n (%)	**Original NDA**	**Safety Update***	
AE (any grade)	203 (97.6)	205 (98.6)	
TEAE	203 (97.6)	205 (98.6)	
Grade ≥3 TEAE	168 (80.8)	181 (87.0)	
WDAE	1 (0.5)	1 (0.5)	

AE = adverse event; AML = acute myeloid leukemia; AUC = area under the curve; CI = confidence interval; CR = complete response; HI = hematological improvement; LFS = leukemia-free survival; mCR = marrow complete response; NE = not estimable; ORR = overall response rate; OS = overall survival; PR = partial response; RBC = red blood cell; TEAE = treatment-emergent adverse event, TI = transfusion independent; WDAE = withdrawal due to adverse event.

*Data cut off: April 14, 2021 for ASCERTAIN, otherwise March 19, 2019 and June 5, 2018 data cut offs for ASCERTAIN and ASTX727-01-B trials, respectively

Sources: ASCERTAIN Clinical Study Report, ASTX727-01-B Clinical Study Report[2], Garcia-Manero 2020[9]; April 2021 Efficacy Data Update[6].

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

The Leukemia & Lymphoma Society of Canada (LLSC) and Aplastic Anemia & Myelodysplasia Association of Canada (AAMAC) provided a joint input on decitabine and cedazuridine (Inqovi) for MDS. Information was gathered through an online survey created by AAMAC. A total of 42 patients responded to the survey, however two were not included due to incomplete data. Of the remaining 40 respondents, 34 identified as patients with MDS, while six were caregivers of MDS patients. One respondent had experience with decitabine and cedazuridine. Responses to the survey were collected from August 4, 2020, to September 25, 2020.

From the patient perspective, MDS symptoms and receiving intravenous or injected MDS treatments were reported to have a significant or large impact on the ability to travel, exercise, work, conduct household chores, fulfill family obligations, and spend time with family and friends. Most patients had treatment experience with azacitidine, followed by Eprex®, blood transfusion, and stem cell transplant for MDS. Side effects associated with MDS treatments administered intravenously or through subcutaneous injections that were most commonly rated to be completely or relatively intolerable included injection-site rash or pain and bruising; sleep problems; fatigue/lack of energy; constipation; and dry mouth. Overall, patients with MDS value having access to new treatments and seek treatments that are effective, have minimal and tolerable side effects, and prolong quality of life. Patients prefer oral agents over injected/infused treatments as they may be administered at home, which mitigates the need to travel to treatment centres and the pain, discomfort, skin irritation, bruising, and soreness that commonly accompanies injected/infused treatments.

Provincial Advisory Group (PAG) Input

Input was obtained from nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Sequencing and priority of treatment

Economic factors:

- None

Registered Clinician Input

Three registered clinician inputs were provided for the review of decitabine and cedazuridine (Inqovi) for MDS: one from an individual oncologist (Alberta) and two group inputs (Ontario)—two clinicians on behalf of Ontario Health Cancer Care Ontario (OH-CCO) Hematology Cancer Drug Advisory Committee (DAC) and five clinicians from Odette Cancer Centre and Princess Margaret Hospital (OCC/PMH). The two Ontario clinician groups reported having experience administering decitabine and cedazuridine, whereas the Alberta clinician did not have experience. All clinicians noted that the patient population in the reimbursement request aligns with the need in their clinical practice.

Current treatments for MDS are administered based on risk sub-type and cytogenetic or familial pre-dispositions. Erythropoietin stimulating agents (e.g., darbepoetin) are used for low or intermediate-1 risk MDS patients, while azacitidine is used in intermediate-2 or high-risk MDS patients. Lenalidomide may be used for MDS patients with a deletion 5q chromosome change. Azacitidine or hydroxyurea (specifically in patients who are transplant ineligible) may be used for CMML patients. Hematopoietic stem cell transplant or high-dose chemotherapy may be used in MDS patients with good fitness but are not standard treatments. Decitabine has Health Canada approval but is not currently marketed for higher risk MDS in Canada. The OH-CCO DAC and Alberta clinicians noted that decitabine and cedazuridine would replace azacitidine in all eligible patients. However, the OCC/PMH clinicians stated that decitabine and cedazuridine would not supplant current treatments in lower risk disease but could replace azacitidine in the higher risk disease patients and those unable to tolerate or travel to receive azacitidine. All clinicians felt it is clinically reasonable to use decitabine and cedazuridine as a bridge to HSCT or intensive chemotherapy (with curative intent). The Ontario clinician groups noted

there is no evidence to support sequencing of azacitidine and decitabine and cedazuridine; whereas the Alberta clinician stated there is evidence for switching in the setting where azacitidine is still working but not sequencing in the traditional sense of switching due to a lack or loss of response.

Summary of Supplemental Questions

In the absence of direct evidence comparing decitabine and cedazuridine to relevant treatments, the sponsor provided an unpublished ITC/NMA comparing decitabine and cedazuridine to azacitidine, BSC, conventional care regimens (CCR), and LDAC for the treatment of intermediate-1, intermediate-2, and high-risk MDS, and CMML.[12]

The analyses were conducted in a Bayesian framework and considered three possible evidence networks: 1) C-DEC Synthetic Trial; where OS outcome data was incorporated with historical IV decitabine data, 2) Limited Network; where the results of the AZA-001 trial were excluded on the assumption that the OS benefit from this trial has not been reproduced in real-world evidence studies, and 3) Full Network; where the complete evidence network of all available and eligible trials was considered.[12] A key limitation to the NMA is that the Limited and Full network scenarios assumed equivalence of oral decitabine and cedazuridine to IV decitabine, and that data from the decitabine and cedazuridine trials was not included in these networks. Additionally, the ITC/NMA did not evaluate the Intermediate-1 and CMML populations and it was assumed that the results would hold across IPSS groups, however, this should be interpreted with caution and may not be generalizable in Canadian clinical practice. Results of the ITC/NMA suggested that decitabine and azacitidine were no different in any network scenario with regards to OS, with the exception of the full evidence network where azacitidine was favoured over decitabine and BSC. Both azacitidine and decitabine were favoured over BSC for all clinical response outcomes, and there was no difference between azacitidine and decitabine, however the results demonstrated significant imprecision evidenced by wide CIs.

Due to severe limitations identified in the sponsor provided ITC/NMA, including the small size and structure of the network, which had no closed loops, concerns of heterogeneity across study populations with regard to IPSS groups, and the clinical and methodological assumptions made including the assumption of equivalence between oral decitabine and cedazuridine and IV decitabine, as well as the omission of decitabine and cedazuridine in two of three network scenarios, and imprecision of results, caution must be taken when interpreting the comparative efficacy estimates.

Comparison with Other Literature

The CADTH Clinical Guidance Panel and the CADTH Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of Generalizability of Evidence for Decitabine and cedazuridine

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="4">Population</td><td>Age and comorbidities</td><td>ASCERTAIN: Median age of MDS patients was 71.0 years (range: 44 – 88). A total of 93 patients (69.9%) were 65 to 84 years of age.[1,7]

ASTX727-01-B: The median age of MDS patients was 71.0 (range: 32 – 90).[9]

There was no reported information from the ASCERTAIN or ASTX727-01-B trials on patient comorbidities.</td><td>Is the age of included patients in the ASCERTAIN and ASTX727-01-B trials representative of what would be seen in clinical practice?

Can the results be applied to patients with comorbidities?</td><td>Yes, the age of patients in the two trials would be representative of patients seen in clinical practice.</td></tr>
<tr><td>MDS Classification</td><td>The ASCERTAIN and ASTX727-01-B trials included patients with all FAB subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and CMML).[1,7,9]</td><td>Is the FAB or the WHO classification system more widely used in Canada? How would this impact the results of the ASCERTAIN and ASTX727-01-B trials?</td><td>The WHO classification system is used more widely in Canada; however, the use of the FAB system would not impact the results as reported in the trials.</td></tr>
<tr><td>ECOG PS</td><td>ASCERTAIN: Patients were included in the trial if they had an ECOG PS of 0 or 1.[1,7]
<table>
<tr><th>ECOG</th><th>Sequence A (n=66)</th><th>Sequence B (n=67)</th><th>Total (n=133)</th></tr>
<tr><td>0</td><td>25 (37.9)</td><td>30 (44.8)</td><td>55 (41.4)</td></tr>
<tr><td>1</td><td>41 (62.1)</td><td>37 (55.2)</td><td>78 (58.6)</td></tr>
</table>
ASTX727-01-B: Patients were included in the trial if they had an ECOG PS of 0 to 2.[9]
<table>
<tr><th>ECOG</th><th>Sequence A (n=41)</th><th>Sequence B (n=39)</th><th>Total (n=80)</th></tr>
<tr><td>0</td><td>20 (48.8)</td><td>15 (38.5)</td><td>35 (43.8)</td></tr>
<tr><td>1</td><td>18 (43.9)</td><td>20 (51.3)</td><td>38 (47.5)</td></tr>
<tr><td>2</td><td>3 (7.3)</td><td>4 (10.3)</td><td>7 (8.8)</td></tr>
</table></td><td>Can the results be applied to patients with ECOG PS 2 or higher?</td><td>Yes, the results can be applied to patients with ECOG PS 2. Clinical judgement should be applied to patients with an ECOG PS higher than 2 when making treatment decisions.</td></tr>
<tr><td>IPSS Risk Category</td><td>The IPSS scoring system was used in both the ASCERTAIN and ASTX727-01-B trials.
Low-risk patients are not included in the funding request.

ASCERTAIN: Few patients with low-risk MDS and CMML were included in the trial.[1,7]
<table>
<tr><th>IPSS</th><th>Sequence A (n=66)</th><th>Sequence B (n=67)</th><th>Total (n=133)</th></tr>
<tr><td>Low</td><td>4 (6.1)</td><td>7 (10.4)</td><td>11 (8.3)</td></tr>
<tr><td>Int-1</td><td>29 (43.9)</td><td>30 (44.8)</td><td>59 (44.4)</td></tr>
</table></td><td>As IPSS-R is more commonly used in Canadian clinical practice, how would the eligibility of patients differ based on classification using IPSS-R?

Are the results of the trials generalizable to patients with IPSS low-risk or CMML?</td><td>The IPSS remains a readily accessible tools that clinicians are very familiar with.

The CGP does not feel that the results of the trials are generalizable to patients with IPSS low-risk and CMML since there exists significant uncertainty about the therapeutic benefit of decitabine and cedazuridine in that patient population.</td></tr>
</table>

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		Int-2 14 (21.2) 12 (17.9) 26 (19.5) **High** 14 (21.2) 7 (10.4) 21 (15.8) **CMML** 5 (7.6) 11 (16.4) 16 (12.0) **ASTX727-01-B:** No low-risk MDS patients were included in the study.[9] **IPSS** | **Sequence A (n=41)** | **Sequence B (n=39)** | **Total (n=80)** **Low** - - - **Int-1** 19 (46.3) 16 (41.0) 35 (43.8) **Int-2** 9 (22.0) 10 (25.6) 19 (23.8) **High** 5 (12.2) 4 (10.3) 9 (11.3) **CMML** 8 (19.5) 9 (23.1) 17 (21.3)		
	Prior Treatments	The funding request includes patients that are previously treated, or untreated. **ASCERTAIN:** Patients were excluded if they had prior treatment with more than 1 cycle of azacitidine or decitabine and cedazuridine.[1,7] **Prior HMA** | **Sequence A (n=66)** | **Sequence B (n=67)** | **Total (n=133)** **AZA** 3 (4.5) 3 (4.5) 6 (4.5) **DEC** 3 (4.5) 1 (1.5) 4 (3.0) **ASTX727-01-B:** Patients were excluded if they had previous treatment with at least 2 courses of decitabine and cedazuridine or azacitidine.[9] **Prior HMA** | **Sequence A (n=41)** | **Sequence B (n=39)** | **Total (n=80)** **AZA** 3 (7.3) 1 (2.6) 4 (5.0) **DEC** 0 (0) 3 (7.7) 3 (3.8)	Are the trial results generalizable to patients who have received > 1 cycle of HMA or other therapy?	Yes, the results can be applied to patients who received more than one cycle of HMA therapy, as long as they did not progress on the prior HMA.
Intervention	Administration of intervention	In both the phase II and III trials,[1,7,9] oral decitabine and cedazuridine (35 mg/100 mg) was compared to IV decitabine (20 mg/m2), which has Health Canada approval but is not marketed or used in Canadian clinical practice. The primary endpoint was to determine PK equivalency between the two options.	Are the equivalence findings from the phase II and III trials acceptable? Would IV decitabine be used if decitabine and cedazuridine were recommended for reimbursement due to the equivalence demonstrated?	The trials do provide convincing evidence that IV decitabine is equivalent to decitabine and cedazuridine. IV decitabine does not have any advantage over decitabine and cedazuridine based on the available evidence and there no reason to believe or argument

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
				to justify to reimbursement for IV decitabine if decitabine and cedazuridine were to be reimbursed.
Comparator	Relevant comparators	The ASCERTAIN and ASTX727-01-B trials did not include a comparison to other relevant treatments for this patient population in Canada (i.e., azacitidine).[1,7,9] The sponsor submitted a NMA comparing decitabine and cedazuridine and IV decitabine (assuming equivalence to decitabine and cedazuridine) to relevant comparators such as azacitidine. However, there were a number of limitations and the NMA failed to demonstrate clinical efficacy of decitabine IV or decitabine and cedazuridine when compared to BSC or azacitidine.[12]	Did the NMA sufficiently demonstrate clinical benefit for decitabine and cedazuridine compared to relevant treatments for MDS patients?	There was significant uncertainty in the reported results of the NMA, and thus the comparative efficacy of decitabine and cedazuridine to relevant comparators remains unknown. Furthermore, patients with intermediate-1 and CMML were not included in the NMA, and thus no conclusions can be drawn on the comparative efficacy of decitabine and cedazuridine to comparators for these patient subgroups.
Outcomes	Appropriateness of primary and secondary outcomes	The primary endpoint for both the phase II ASTX727-01-B and phase III ASCERTAIN trial was the PK outcome of 5-day AUC by central assessment. Secondary outcomes included %LINE-1 methylation, ORR, hematologic improvement, leukemia-free survival, OS, and transfusion independence, however there was no control for multiple testing and thus, these results can only be considered exploratory.[1,7,9]	Were the selection of PK/PD endpoints appropriate, and of clinical relevance to this indication and therapeutic setting?	The endpoints selected were appropriate and of clinical relevance, however the limitations such as lack of control for multiple testing and a direct comparator does introduce uncertainty in the reported clinical efficacy.
Setting	Countries participating in the trial	The ASCERTAIN and ASTX727-01-B trials were conducted in two countries (Canada and the United States).[1,7,9]	There are no national treatment guidelines in Canada. Are there any known differences in the practice patterns or treatment guidelines between Canada and the United States, and which guidelines are typically followed in Canada?	The CGP does not anticipate significant differences in practice patterns between other participating countries and Canada. The results can be applied to Canadian patients.

AUC = area under the curve; BSC = best supportive care; CGP = Clinical Guidance Panel; CMML = chronic myelomonocytic leukemia; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FAB = French-American-British; HMA = hypomethylating agent; IPSS = international prognostic scoring system; IPSS-R = international prognostic scoring system revised; IV = intravenous; MDS = myelodysplastic syndrome; NMA = network meta-analysis; ORR = objective response rate; OS = overall survival; PD = pharmacodynamic; PK = pharmacokinetic; WHO = World Health Organization

1.2.4 Interpretation

Burden of Illness and Need

MDS is a rare hematological malignancy characterized by progressive cytopenia and is associated with a decreased quality of life and life expectancy. It has an estimated annual incidence of 1 to 5 cases/100,000.[13,14] Myelodysplastic syndromes typically affects elderly with a median age between 65 and 70 years.[15] The therapeutic options are aimed at improving life expectancy, decrease transfusion-dependence and improving quality of life. The current standard of care of patients with intermediate to high risk MDS and CMML in Canada is treatment with the HMA azacitidine. Azacitidine treatment has been shown in clinical trials to improve survival and QoL. However, azacitidine is given subcutaneously so patients have to come 7 consecutive days 1 week every 4 weeks in the hospital to receive their injection. This places a significant burden on both patients and family and potentially prevents patients with mobility access or who are living in remote community to access the treatment. Decitabine and cedazuridine is a cytotoxic combination antineoplastic composed of decitabine, a DNA methyltransferase inhibitor and the cytidine deaminase inhibitor cedazuridine that is given at fixed oral doses. It meets an unmet need by providing a more manageable oral route which has the potential to improve access to effective treatment.

Effectiveness

The evidence of the effectiveness of decitabine and cedazuridine in the treatment of patients with intermediate-1, intermediate-2, and high-risk MDS and CMML is derived from two trials, the phase 2, open-label, crossover ASTX727-01-B (NTC02103478) and the phase III, randomized, crossover, open-label ASTX727-02 (ASCERTAIN; NCT03306264) trial.[7,9] Both trials were designed with a primary objective to test the pharmacodynamic and pharmacokinetic profile of decitabine and cedazuridine. Neither of these trials directly compared the effectiveness of decitabine and cedazuridine to that of azacitidine. There does not exist a randomized study directly comparing the effectiveness of decitabine and cedazuridine to azacitidine for patients with *de novo* or secondary MDS or CMML.

The phase III ASCERTAIN trial is a multicenter, randomized, open-label, crossover study primary designed to compare the pharmacokinetic and pharmacodynamic profile of decitabine and cedazuridine to IV decitabine monotherapy, a drug that is approved by but not marketed in Canada. Clinical effectiveness was a secondary endpoint. In the study, patients were randomized to receive fixed-dose oral decitabine and cedazuridine for 5 days in cycle 1 followed by IV decitabine daily for 5 days in cycle 2 vs IV decitabine daily for 5 days in cycle 1, followed by oral decitabine and cedazuridine. Patients from both arms received decitabine and cedazuridine for 5 days in all subsequent 28 days cycles. Eligible patients include adult patients with MDS, including previously treated and *de novo* MDS as well as secondary MDS, with the following French American-British subtypes: refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts. Patients with CMML were also included. Patients with MDS and CMML were IPSS of either intermediate-1, intermediate-2 and high-risk groups. The ASCERTAIN trial convincingly demonstrates that decitabine and cedazuridine has comparable pharmacokinetic and pharmacodynamic with 5-day decitabine and cedazuridine to IV decitabine ratio of 5-day Area Under the Curve ($AUC_{0\text{-}24}$) of 98.93% CI: 92.7, 107.5). As well, the difference in pharmacodynamic activity between decitabine and cedazuridine and IV decitabine was minimal as measured by mean maximum percentage Long Interspersed Nucleotide Elements-1 (LINE-1) demethylation with a decitabine and cedazuridine-IV decitabine mean maximum percentage LINE-1 demethylation differences of -0.730% (95% CI: -2.838, 1.378) and -0.818 (95% CI: -2.890, 1.255) in cycles 1 and 2, respectively. The clinical effectiveness outcomes were secondary endpoints and, by virtue of the study design, did not allow direct comparison with neither best supportive care (BSC) nor SC azacitidine monotherapy nor IV decitabine. The study did demonstrate clinical effectiveness with overall response rate of 60.9% (95% CI; 52.1, 69.2) and complete response of 21.1% (95% CI: 14.5, 29.0). The percentage of patients achieving transfusion-independence for any consecutive ≥ 56-day period post-baseline were [redacted] and [redacted] for RBC and platelets, respectively.[7] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

The results of the phase II ASTX727-01-B are in keeping with the results of the ASCERTAIN trial both in terms of pharmacokinetic, pharmacodynamic as well as clinical efficacy. Thus, the 5-day oral decitabine and cedazuridine vs IV decitabine $AUC_{0\text{-}t}$ ratio was 93.52% (80% CI: 82.1, 106.5) and 97.59% (80% CI: 80.5, 118.3) in the two stages of the trial, well within the prespecified limits of 75-

133% and 65-154%. The efficacy results also parallel those of the ASCERTAIN trial with an overall response rate of 60% (95% CI: 48.4, 70.8) and with a CR rate of 17.5% (95% CI: 9.9, 27.6).[9]

Overall, the combined results of both the ASCERTAIN and ASTX727-01 trials do demonstrate confidently that, in patients with MDS and CMML, decitabine and cedazuridine at a dose of 100mg/35mg/ 1 tablet x 5 days every 28 days is pharmacologically equivalent to IV decitabine given at a dose of 20mg/m2 1 h IV infusion x 5 days since both exhibit comparable pharmacokinetic and pharmacodynamic profile. The studies also show evidence of the clinical efficacy of decitabine and cedazuridine in this patient population. The magnitude of the clinical efficacy compared to the standard of care could not be measured with the results of these trials alone given the lack of direct comparison.

The estimation of the clinical efficacy and safety of decitabine and cedazuridine relative to azacitidine in patients with intermediate-1 to high risk MDS and CMML was performed through an indirect comparison using a NMA that was sponsored by the submitter.[12] The NMA compared the treatment of patients with intermediate-1 to high-risk MDS and CMML of 5 days oral decitabine and cedazuridine with 7 days SC azacitidine, which corresponds to the adopted Canadian standard of care. For this analysis, data were combined from the key trials testing the clinical efficacy of decitabine and azacitidine: the ASCERTAIN, AZA-001, CALGB-9221, EORTC 06011 and D0007 trials (Fenaux 2009, Garcia-Manero 2019, Kantarjian 2006, Lubbert 2011, Silverman 2002).[7,16-19] The submitter produced three evidence networks: 1) decitabine and cedazuridine synthetic trial, where the OS treatment effect of decitabine and cedazuridine from the ASCERTAIN trial were compared to historical control derived from the D007 trial (Kantarjian, 2006)[17]; 2) Limited network, where the results of the AZA-001 trial were excluded on the assumption that the OS benefit from this trial were not reproduced in the real-world evidence, and 3) Full Network, where the complete evidence network of all eligible trials were considered. The submitted NMA assumed for the second and third network analyses that decitabine and cedazuridine and IV decitabine are clinically equivalent and used IV decitabine trial data, which was considered a fair assumption given the comparable pharmacokinetic and pharmacodynamic results discussed above.

The NMA of the decitabine and cedazuridine [redacted][20]

[redacted][12] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

[redacted].[12] *(Non-*

disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

All three network scenarios showed that [redacted] However, it must be noted that [redacted] The decitabine trials included patients with lower risk MDS, and the [redacted] on clinically important survival outcomes with this advantage makes it difficult to conclude similar effectiveness to azacitidine. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Overall, the NMA may suggest that decitabine and cedazuridine (assuming clinical equivalence to IV decitabine) is [redacted] for the management of patients with MDS, and it also suggests that [redacted][12] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

The population included in the systematic literature review only partially reflect the population for which funding for decitabine and cedazuridine is sought since the AZA-001 trial, which enrolled the greatest number of patients treated with azacitidine, did not include patients with intermediate-1 MDS nor patients with CMML. Furthermore, the CALBG-9221 trial did not specify the IPSS status of enrolled patients and the relevant comparator in the lower risk patient population (e.g., lenalidomide, anti-thymocyte globulin [ATG], cyclosporin A) were not included in the analysis so there remains uncertainly in the therapeutic benefit of azacitidine in patients with IPSS INT-1 MDS and with CMML.

Safety

Data on the safety profile of decitabine/cedaruzidine was assessed in the ASCERTAIN and ASTX727 trial. Decitabine and cedazuridine was overall quite well tolerated with only 1 patient treated with decitabine and cedazuridine having had to be discontinued because of adverse events (compared to 2 who were treated with azacitidine. Although serious adverse events were more frequent with oral decitabine and cedazuridine compared to IV decitabine (35.9% vs 28%), there was no clinically notable difference between decitabine and cedazuridine and IV decitabine with respect to the proportion of patients who experienced any grade AE. The toxicity profile of decitabine and cedazuridine overall paralleled the toxicity profile expected from other HMAs with increased cytopenia. There was a concern about gastrointestinal toxicities with decitabine and cedazuridine, given Its route of administration, but there were no clinically notable differences between oral decitabine and cedazuridine and IV decitabine.[7] The most common adverse events included cytopenias (thrombocytopenia and neutropenia).

The comparison of the safety/toxicity profile of decitabine and cedazuridine to IV decitabine/SC azacitidine through the NMA was limited in scope since only the hematological toxicities were considered. Both the limited network and full network NMA showed that, as expected, both decitabine and azacitidine are associated with increased hematological toxicities compared with BSC and that there were not consistent, significant differences in hematological toxicities between the two treatments.

1.3 Conclusions

The sponsor submitted a request for oral decitabine and cedazuridine as an alternative to the SC azacitidine formulation for the treatment of patients with INT-1 to high-risk MDS and CMML. The CGP conclude that there is no net clinical benefit of oral decitabine and cedazuridine in the treatment of adult patients with INT-1 to high risk MDS and CMML. The CGP does recognize the value derived from an oral formulation over a SC one, which is likely to improve access and compliance to a broader population of eligible patients, including elderly, disabled or patients living in remote locations. The extent of the potential benefits of the oral formulation could not be assessed with the evidence provided. The CGP recognizes that the benefit of an oral formulation is made more prescient with the COVID-19 crisis, and this should be considered in the final appraisal of the drug. Overall, the CGP feel that decitabine and cedazuridine is a viable alternative to SC azacitidine for patients who are elderly, disabled, or living in remote locations, potentially at the expense of lower clinical efficacy.

There does not exist any study directly comparing the clinical effectiveness and safety of decitabine and cedazuridine with SC azacitidine. Instead, the conclusion is based on 1) Phase II and III studies that convincingly demonstrate that oral decitabine and cedazuridine and IV decitabine exhibit equivalent pharmacokinetic and pharmacodynamic profiles in addition to equivalent safety profile and 2) an NMA that combined the results of a series of phase III RCTs to compare azacitidine, BSC, and other standard of care therapies to decitabine and cedazuridine and IV decitabine, which demonstrated that IV decitabine is comparable to decitabine and cedazuridine in terms of clinical effectiveness and safety, although the CGP noted that there was a signal that decitabine and cedazuridine may not be as effective as azacitidine. The CGP felt that the analysis does not allow to assess the effectiveness of decitabine and cedazuridine relative to azacitidine in patients with INT-1 MDS and CMML since these patients were excluded from the azacitidine trials.

The CGP noted that there was no data on HRQoL presented for decitabine and cedazuridine; given the comparable toxicity profile, the CGP thinks that it is fair to assume that the QoL related to the use of this drug would be comparable, given the oral mode of delivery, although this would have needed to be confirmed empirically.

Table 3: CADTH Clinical Guidance Panel Response to Provincial Advisory Group Implementation Questions

PAG Implementation Questions	CGP Response
Currently Funded Treatments	
PAG seeks an additional comparison of decitabine and cedazuridine with azacitidine in higher risk MDS subtypes as well as azacitidine and hydroxyurea for some patients with CMML. Also, PAG seeks an additional comparison of decitabine and cedazuridine with lenalidomide in patients with deletion 5q chromosome change MDS. Furthermore, PAG seeks an additional comparison of decitabine and cedazuridine with HSCT for MDS.	**Decitabine and cedazuridine compared to azacitidine in higher risk MDS subtypes:** The sponsor submitted a NMA comparing decitabine to azacitidine in intermediate-2 and high-risk MDS patients, however it was subject to a number of limitations resulting in significant uncertainty in the reported results. Thus, the magnitude of the clinical benefit, if any, of decitabine and cedazuridine compared to azacitidine remains unknown. **Decitabine and cedazuridine compared to azacitidine and hydroxyurea in CMML patients:** The sponsor-submitted NMA attempted to include CMML patients, however subgroup analyses were not possible and thus, it was assumed the results of the NMA were similar across IPSS subgroups and CMML patients. Hydroxyurea was not included as a comparator. Thus, the comparative effectiveness of decitabine and cedazuridine to azacitidine and hydroxyurea in CMML patients remains unknown. **Decitabine and cedazuridine compared to lenalidomide:** Comparison to lenalidomide was not possible in the NMA due to lack of available evidence, and as such comparative effectiveness remains unknown. For patients with deletion 5q, lenalidomide would be the preferred regimen due to better available evidence.

PAG Implementation Questions	CGP Response
	Decitabine and cedazuridine compared to HSCT for MDS: HSCT is the only curative option for patients with MDS, and as such decitabine and cedazuridine would not replace HSCT for patients eligible for HSCT. However, decitabine and cedazuridine could be used as a bridge to transplant.
Eligible Patient Population	
PAG is seeking clarity on whether the following patients would be eligible for treatment with decitabine and cedazuridine: • Patients who experienced prior HSCT • Candidates for intensive induction chemotherapy • Patients who are candidates for HSCT • Patients previously treated with a hypomethylating agent • Patients with ECOG PS ≥ 2	• Patients who experienced prior HSCT were not excluded from eligibility from the decitabine and cedazuridine trials per protocol, however no patients included in the trials with decitabine and cedazuridine actually received prior HSCT, so the CGP is unable to comment on the effectiveness of decitabine and cedazuridine in this patient population. • Candidates for intensive induction chemotherapy: Patients who are candidates for intensive induction chemotherapy could be eligible for decitabine and cedazuridine based on patient preference. • Patients who are candidates for HSCT: Patients who are candidates for HSCT could use decitabine and cedazuridine as a bridge to transplant. • Patients previously treated with a hypomethylating agent: Patients treated with a HMA that have had a response could switch, but not those who have progressed on a HMA as there is no evidence to support the use of another HMA upon progression. • Patients with ECOG PS ≥ 2: Patients with ECOG PS 2 or higher would be eligible for treatment with decitabine and cedazuridine.
If treatment with decitabine and cedazuridine were recommended for reimbursement, PAG noted a time-limited need and seeks confirmation from pERC that patients currently on azacitidine may switch for the convenience of an oral therapy and patients with deletion 5q MDS treated with lenalidomide would be able to access decitabine and cedazuridine.	Patients on azacitidine may switch to decitabine and cedazuridine if they have not progressed based on patient preference. Patients with deletion 5q MDS who progress on lenalidomide could be considered for treatment with decitabine and cedazuridine due to the limited treatment alternatives upon progression for these patients.
PAG noted potential indication creep in the following scenarios: use of decitabine and cedazuridine in second line after azacitidine, use of decitabine and cedazuridine for the treatment of AML where azacitidine is available and patients with low-risk MDS.	• Use of decitabine and cedazuridine in second line after azacitidine: There is no evidence to support the use of decitabine and cedazuridine in second line after azacitidine. • Decitabine and cedazuridine for the treatment of AML: Patients with AML were excluded from the trial, and thus there is no evidence to support the use of decitabine and cedazuridine over azacitidine in this patient population. • Low-risk MDS: There is no evidence to support the use of decitabine and cedazuridine in patients with low-risk MDS.
Implementation Factors	
The sponsor indicated that best response may take longer than 4 cycles. Cycles are repeated every 28-days in the absence of hematologic toxicities not attributed to active disease and blood counts show absolute neutrophil count of at least 1.0 × 10^9/L and platelets are at least 50 × 10^9/L, or when they return to pre-treatment levels. The sponsor advised to delay or reduce the dose per cycle for hematologic toxicity. PAG is seeking a clear definition of “continuing treatment as long as the patient continues to benefit.”	Patients should be treated for at least 6 months in the absence of progressive disease or unacceptable toxicity. If the patient is stable or improves, then treatment should continue. Treatment should be discontinued if there is progressive disease, unacceptable toxicity, or due to patient preference.

PAG Implementation Questions	CGP Response
PAG is seeking advice on dose reduction since it may not be possible with a single tablet strength unless skipping days is recommended.	Per the product monograph, one tablet if taken daily for 5 days in each 28-day cycle. Three dose reductions are possible, the first being one tablet once daily through days 1 to 4, a second dose reduction would be one tablet once daily through days 1 to 3, and a third dose reduction would be one tablet one daily on days 1, 3, and 5. In practice, some clinicians may choose to extend a cycle.
There is concern with possible drug wastage because dose reduction involves reducing the number of tablets per cycle (e.g., go from 5 days to 4 days to 3 days). The product monograph outlines a blister pack of 5 tablets with one blister card in a carton. PAG is seeking clarity on the packaging and whether this blister card can be cut to accommodate dose reduction and whether tablets can be used for another patient.	Decitabine and cedazuridine is packaged in a blister pack containing 5 tablets per box. The blister card can be cut by the pharmacy to dispense fewer tablets to accommodate dose reductions. Any remaining blistered tablets that have been cut can be subsequently used for other MDS patients if the tablets remain within the individual blister seal.
Sequencing and Priority of Treatments	
PAG is seeking to confirm the place in therapy and sequencing with decitabine and cedazuridine including the scenarios below: • Options after treatment failure with decitabine and cedazuridine • Use decitabine and cedazuridine as a bridge to HSCT or intensive chemotherapy (with curative intent) to achieve disease and symptom control and thus improve fitness • Sequencing with azacitidine (e.g., does failure of one hypomethylating agent precludes the use of another in subsequent lines)? • For patients with deletion 5q- MDS who are currently on lenalidomide and progress, is there evidence to inform whether these patients would be eligible for decitabine oral upon progression • For patients who have low risk MDS and are treated with EPO +/- G-CSF, is there evidence to inform whether these patients would be eligible for decitabine oral upon progression?	• Options after treatment failure with decitabine and cedazuridine: While there is no standard of care in this setting, options could include BSC, clinical trials, hydroxyurea, and induction chemotherapy. • Use decitabine and cedazuridine as a bridge to HSCT or intensive chemotherapy (with curative intent): Decitabine and cedazuridine could be used as a bridge to HSCT, and possibly intensive chemotherapy, however, the latter is typically not done. • Sequencing with azacitidine: Decitabine and cedazuridine would not be sequenced with azacitidine; failure on one HMA precludes the use in subsequent line. • For patients with deletion 5q- MDS who are currently on lenalidomide and progress: Decitabine and cedazuridine would be used in these patients. • For patients with low risk MDS and have progressed after treatment with EPO +/- G-CSF: There is no evidence to use decitabine and cedazuridine in low-risk patients, unless the low-risk patients have progressed to higher risk MDS of intermediate-1 or higher.

BSC = best supportive care; ECOG = Eastern Cooperative Oncology Group; EPO = erythropoietin; G-CSF = granulocyte colony stimulating factor; HSCT = hematopoietic stem cell transplant; MDS = myelodysplastic syndromes; PAG = Provincial Advisory Group; pERC = pCODR Expert Review Committee; PS = performance status.

2 Background Clinical Information

2.1 Description of the Condition

Myelodysplastic syndromes are a heterogenous group of malignant clonal stem cell disorders in which the bone marrow does not produce enough healthy, mature blood cells. Abnormal (dysplastic), immature blood cells (blasts) accumulate within the bone marrow and blood, decreasing the amount of healthy, functional blood cells in the body. As such, MDS is characterized by ineffective hematopoiesis and cytopenia due to proliferation of abnormal and immature blood cells, and frequent cytogenetic abnormalities. Symptoms of MDS arise as a result of the underlying ineffective hematopoiesis and can include anemia, neutropenia, or thrombocytopenia depending on the type of blood cells affected, as well as general symptoms of fatigue, bleeding, frequent infections, fever, and malaise.

Diagnosis of MDS is typically suspected due to the presence of abnormal blood counts and is confirmed by bone marrow aspiration and biopsy. The number and degree of cell line dysplasia along with the blast counts and cytogenetics are used to diagnose and classify MDS. The blast counts have prognostic significance, with higher percent blasts indicating more severe disease. Death from MDS often occurs from infections or hematological complications associated with cytopenia, or due to progression to AML, which occurs in approximately 30% of MDS patients.[21-23]

Myelodysplastic syndromes most commonly arise *de novo*, with no predisposing hematological disorders. A number of risk factors have been identified that predispose to MDS, including exposure to high-dose radiation, long-term exposure to benzene, petroleum products, fertilizers or pesticides.[21,22,24] MDS can also arise from prior exposure to chemotherapy or radiotherapy (therapy related MDS).[21] As many as 40 to 70% of *de novo* MDS diagnoses exhibit cytogenetic abnormalities. Poor karyotypes include -7, inv(3)/t(3q)/del(3q), -7/del(7q) and complex cytogenetics (3 or more abnormalities) and are associated with a worse prognosis.[22,25,26]

MDS occurs most frequently in the elderly, with the estimated median age of diagnosis between 65 to 70 years. In Canada, MDS is believed to affect between 10,000 and 40,000 Canadians, with an estimated 1,800 to 5,900 new cases per year and tends to develop more often in men than in women. Among patients older than 65 years, the estimated incidence ranges from 75 to 162 patients per 100,000.[22,27] The median survival for MDS ranges from 0.4 to 8.8 years depending on the subtype and severity of the disease, and is approximately 1 to 3 years overall.[22,24,27]

The 2016 World Health Organization (WHO) classification for myeloid neoplasms is the widely accepted classification system used for MDS.[28] A number of prognostic scores have been developed to better risk-stratify patients with MDS. The IPSS is widely used and adopted in the setting of clinical trials to risk-stratify patients and guide treatment decisions.[29] According to the IPSS, patients with MDS are classified into four risk categories based on their cumulative score from three prognostic indicators including: the percentage of blast cells in the bone marrow, the type of chromosomal changes in the marrow cells, and the presence of one or more cytopenias (see Table 4). Patients are classified into the following IPSS risk categories based on their corresponding score: low risk (IPSS risk score 0), intermediate-1 risk (IPSS risk score 0.5 to 1.0), intermediate-2 risk (IPSS risk score 1.5 to 2.0), and high risk (IPSS risk score ≥2.5).

Table 4: International Prognostic Scoring System for MDS

Factor	Notes	Value	IPSS Score
Blasts (percent)	-	<5	0
		5 to 10	0.5
		11 to 20	1.5
		21 to 30	2
Cytogenetics	• Normal • -Y only • del(5q) only • del(20q) only	Good	0

Factor	Notes	Value	IPSS Score
	Abnormalities other than good or poor	Intermediate	0.5
	• Complex • 3 or more abnormalities • Abnormal chromosome 7	Poor	1
Cytopenias*	• Hemoglobin <10 g/dL • Absolute neutrophil count <1,500 cells/μL • Platelet count <100,000 μL	0 or 1	0
		2 or 3	0.5

*Each cytopenia counts as a value of 1
Source: Greenberg et al., 1997[29]

The revised IPSS (IPSS-R) is a more recent prognostic score that includes 5 prognostic factors (blasts, cytogenetics, hemoglobin, neutrophil count, and platelet count), which are scored and totaled to designate patients to IPSS-R risk categories of very low (score less than or equal to 1.5), low (score greater than 1.5 to 3), intermediate (greater than 3 to 4.5), high (greater than 4.5 to 6), and very high (greater than 6). It is a more discriminate score compared to the IPSS and places a greater emphasis on cytogenetics. The IPSS also included patients who had greater than 20-30% blasts, who would currently be classified as AML and IPSS-R excludes this group. The IPSS-R is widely adopted in the clinical setting but has not replaced the IPSS in the setting of clinical trials and to inform funding decisions.[24]

2.2 Accepted Clinical Practice

Treatment decisions are based on the classification of MDS subtype, risk-stratification based on the prognostic score, patient's symptoms, comorbidities and patient's preference. The main goal of treatment is to relieve symptom burden and avoid further complications, improve blood counts, reduce transfusion dependence, improve QoL, delay progression to AML, and extend survival. There are currently no national Canadian guidelines for the management of MDS, although the recommendations from the National Comprehensive Cancer Network (NCCN) for the management of MDS provide a good reference to Canadian clinicians.

Patients who have low-risk IPSS (low to intermediate-1 IPSS) and who are asymptomatic typically do not receive any active treatment and are observed until progression. There are no treatments that have been showed to improve clinical outcomes in these patients with low-risk MDS.[24] Patients with low-risk MDS and who are symptomatic, most commonly from anemia, will typically be offered supportive treatment with RBC transfusions and ICT or, if eligible, ESAs (darbepoetin or erythropoietin), alone or in combination with granulocyte colony stimulating factors (G-CSF). The majority of MDS patients (approximately 80%) will become dependent on regular RBC transfusions throughout their disease.[30] While RBC transfusion is burdensome and does not modify the disease, it may promote a better QoL.[31] In Canada, patients with a serum erythropoietin (EPO) level less than 500 mU/mL and/or a requirement of less than or equal to 2 RBC units per month, ESAs ± G-CSF are recommended.[22] Responses to ESAs is greater in patients with serum EPO levels lesser than 200 mU/mL.[30] Reported median duration of response to ESAs is around 1 to 2 years.[31] It has been suggested that the use of ESAs may provide a favorable survival impact in MDS,[30,32] although this has not been shown in any randomized study.[33]

Other Health Canada approved therapies for low- to intermediate-1 risk MDS include lenalidomide as first-line treatment for patients with del(5q) or other chromosomal changes, although this treatment is not funded in all jurisdictions in Canada. Immunosuppressive therapy with ATG and cyclosporine, may also be considered in low-risk MDS patients that have a hypocellular bone marrow (hypoplastic MDS).[22,24,34]

Patients with higher-risk MDS (IPSS intermediate-2 or high-risk) have a poorer prognosis with survival ranging from a few months to less than 1.5 years.[24] Treatment is aimed at reducing cytopenias, and prolonging survival (by preventing transformation to AML). Patients who are not candidates for HSCT for reasons such as of age and/or comorbidities or lack of suitable donors, are treated with hypomethylating agents (HMAs), either azacitidine (Vidaza) or decitabine (Dacogen). Hypomethylating agents are DNA methyltransferase (DNMT) inhibitors that suppress methylation to modify gene expression in MDS. Currently, the only marketed HMA in Canada for the treatment of MDS is azacitidine, which is mostly listed as a restricted benefit with specified criteria are met (Alberta, British Columbia, Ontario, Prince Edward Island, and Saskatchewan).[35-39] Decitabine is approved, but not marketed in Canada.

According to the Health Canada product monograph, azacitidine is given at a dose of 75 mg/m^2 subcutaneously per day for six (6-0-0) to seven days, with or without a two days pause in the case of the 7 days regimen (5-0-2 vs 7-0-0) every 28 days, with assessment of response by repeat of the bone marrow biopsy typically after 6 cycles of therapy.[16,19,40] Patients who demonstrate response, either with stable disease or complete or partial recovery of normal hematopoiesis will continue on azacitidine. The treatment with azacitidine is associated with prolonged survival and improved overall and hematologic response rates, with a median OS of 24.5 months with azacitidine compared to 15 months with conventional care (HR = 0·58; 95% CI 0.43 - 0.77; *P* = 0.0001).[16,19] Decitabine is given at a dose of 20 mg/m^2 IV daily for five days, every 28 days and is also continued for the duration of response. Decitabine offers improved survival versus best supportive care of RBC transfusions in intermediate-1, intermediate-2, high-risk, and CMML patients.[17,41] Decitabine and azacitidine are considered clinically comparable, with decisions to use one or the other based on availability and cost considerations. Both HMAs require a burdensome and strict dosing schedule with frequent visits to infusion clinics which may result in non-compliance or early discontinuation. Beyond decitabine and azacitidine, there are no superior, relevant, alternatives to HMAs for patients that are not eligible for transplant.

Hematopoietic stem cell transplantation remains the only potentially curative option for MDS patients and is therefore the preferred first-line therapeutic option. Eligible patients will often receive bridge-to-transplant therapy with HMAs or intensive chemotherapy with cytarabine prior to HSCT, with trade-offs between optimal cytoreduction in the case of elevated blast count and minimal treatment-related toxicity. The majority of patients are ineligible for this option due to high morbidity and mortality, lack of viable human leukocyte antigen donors, and is typically reserved for younger, more fit patients.[42,43]

There is currently no standard of care for patients with the CMML subtype of MDS. Treatment decisions follow the recommendations set for MDS patients, based on CMML risk level.[44,45] The HMA azacitidine is sometimes used in some CMML patients, despite not having an approved indication. Hydroxyurea is also used in highly proliferative CMML (white blood cell count ≥13 x 10^9/L) for cytoreduction.[46,47] Treatment with imatinib mesylate may be considered in rare patients with t(5:12) or other PDGFRβ mutations, but is not publicly funded.[22] Patients with higher-risk CMML who are otherwise fit will receive allogeneic stem cell transplantation after having received high-dose chemotherapy.

Decitabine is a nucleoside metabolic inhibitor that is believed to exert its antineoplastic effects after phosphorylation and direct incorporation into DNA and inhibition of DNMT, causing hypomethylation of DNA and cellular differentiation and/or apoptosis.[48] Cytidine deaminase (CDA) is an enzyme that is responsible for the degradation of cytidine nucleosides, including the cytidine analog decitabine, and high levels of CDA in the gastrointestinal tract and liver rapidly degrade these nucleosides and prohibit or limit their oral bioavailability. Cedazuridine inhibits CDA, and the oral administration of cedazuridine with decitabine increases the systemic exposure of decitabine via inhibition of first pass metabolism of decitabine in the gut and liver by CDA. On July 7th, 2020, decitabine and cedazuridine (Inqovi) was issued a NOC for the treatment of for treatment of adult patients with MDS including previously treated and untreated, de novo and secondary MDS with the following FAB subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and CMML) and intermediate-1, intermediate-2, and high-risk IPSS groups. This report focuses on evidence from the ASCERTAIN (ASTX727-02) phase III trial,[7] and the ASTX727-01-B phase II trial,[9] which were both open-label, randomized, 2-cycle, 2-sequence crossover studies comparing decitabine-cedazuridine (oral) with decitabine (IV).

3 Summary of Patient Advocacy Group Input

The Leukemia & Lymphoma Society of Canada (LLSC) and Aplastic Anemia & Myelodysplasia Association of Canada (AAMAC) provided a joint input on decitabine and cedazuridine (Inqovi) for MDS. Information was gathered through an online survey created by AAMAC. The survey was created in English and made available on August 4, 2020 and closed on September 25, 2020. The survey was translated into French by LLSC and made available on August 13, 2020 and closed on September 25, 2020. Both English and French surveys were created using Survey Monkey and promoted by LLSC and AAMAC through various social media channels and by email. The survey asked for input from patients with experience with treatments for MDS including decitabine and cedazuridine. There was a total of 42 respondents—39 and three respondents for the English and French surveys, respectively; however, two of the respondents of the French survey were not included in the input due to incomplete data (responses only provided for the demographic information and no other questions). Therefore, 40 respondents were included in the input—39 respondents and one respondent for the English and French surveys, respectively. There were 34 patient respondents: 23 identified themselves as someone living with MDS and 11 identified themselves as a MDS survivor or a survivor of a MDS-related blood cancer. There were six caregiver respondents (individuals providing care to a person with MDS); however, input specific to the caregiver role was not provided. One respondent had experience with decitabine and cedazuridine. Nineteen respondents identified as female, 20 as male, and one did not specify. All respondents lived in Canada except for one who lived in the United States. Respondents lived in the following provinces (province: n): Ontario: 12, Alberta: 8, Nova Scotia: 8, British Columbia: 6, Quebec: 4, and Manitoba: 1. The ages of all respondents (patient and caregivers) ranged from 48 to 82 with the specific age group of 76-82 years old having the most number of respondents (n=13). The breakdown for the reported age groups (age group: n) was 48-54 years old: 5, 55-61 years old: 5, 62-68 years old: 7, 69-75 years old: 8, and 76-82 years old: 13.

From the patient perspective, MDS symptoms and receiving intravenous or injected MDS treatments were reported to have a significant or large impact on the ability to travel, exercise, work, conduct household chores, fulfill family obligations, and spend time with family and friends. Most patients had treatment experience with azacitidine, followed by, eprex, blood transfusion, and stem cell transplant for MDS. Side effects associated with MDS treatments administered intravenously or through subcutaneous injections that were most commonly rated to be completely or relatively intolerable included injection-site rash or pain and bruising; sleep problems; fatigue/lack of energy; constipation; and dry mouth. It was noted that many patients may live relatively far from treatment centres; thus, receiving treatment is often accompanied by out-of-pocket expenses such as parking, mileage/gas, meals/food, other transportation (taxis, public transit, etc.), and lodging/accommodations. Majority of respondents noted having a negative experience with injected/infused MDS treatments. Input from a 71-year-old female who had experience with decitabine and cedazuridine for seven to 12 months noted that she did not find the treatment effective, the side effects were difficult to tolerate, and her quality of life was low. The side effects she experienced from decitabine and cedazuridine included pneumonia, dyspnea, febrile neutropenia, upper respiratory tract infection, cough, dizziness, nausea, diarrhea, decrease or loss of appetite, and headache. Headache and decrease or loss of appetite were rated to be the most tolerable; alternatively, pneumonia was the only side effect rated to be completely intolerable. Overall, patients with MDS value having access to new treatments and seek treatments that are effective, have minimal and tolerable side effects, and prolong quality of life. Patients prefer oral agents over injected/infused treatments as they may be administered at home, which mitigates the need to travel to treatment centres and the pain, discomfort, skin irritation, bruising, and soreness that commonly accompanies injected/infused treatments.

LLSC and AAMAC voiced their support for new MDS treatments that can be taken at home to reduce hospital visits and noted that the route of administration is an undeniable component of the patient experience. Oral therapies provide patients with more convenience, which is especially significant for those who are negatively impacted by the need to receive treatment in a hospital or clinic. Correspondingly, patients highlighted that the COVID-19 pandemic has impacted the ability to travel and their treatment schedule. Namely, treatment administration may be delayed due to self-isolation periods following travel to the region of the treatment centre. Additionally, patients expressed concerns about contracting COVID-19 as a result of entering a clinic/hospital for injection or infusion.

Of note, quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient groups.

3.1 Condition and Current Therapy Information

3.1.1 Patients Experiences

Symptoms associated with MDS were reported to have impacted or limited day-to-day activities. The following MDS symptoms were reported to have a "5-significant impact" or "4-large impact" on the following day-to-day activities (listed in order of the number of ratings by respondents): ability to travel (19), ability to exercise (17), ability to work (14), ability to conduct household chores (12), ability to fulfill family obligations (9), and ability to spend time with family and friends (8). One respondent noted "*the ability to travel is compounded by COVID-19. Upon return from overseas trip, the self-isolation period means my treatment schedule (azacitidine) could not be resumed in a timely fashion*."

3.1.2 Patients' Experiences with Current Therapy

Table 5 reports various MDS treatments and the number of respondents who had experience with respective treatments. Most respondents had treatment experience with azacitidine (10 responses), followed by eprex (six responses), blood transfusion (five responses), and stem cell transplant (four responses). The remaining reported treatments had been experienced by one respondent. Of note, three respondents reported not having received treatment for MDS at the time of the survey.

Table 5: Current Treatments for MDS

MDS Treatment	Number of Respondents with Treatment Experience
Azacitidine (Vidaza) for injection or infusion/IV	10
Eprex	6
Blood transfusion	5*
Stem cell transplant	4
Decitabine (Dacogen) for infusion/IV	1
Oral decitabine (INQOVI) tablets	1
ATG plus cyclosporine	1
Hydroxyurea	1
Epoetin Alfa Syringe injection	1
hATG	1
Oral chemotherapy	1
Lenalidomide	1
Revlimid	1

ATG = anti-thymocyte globulin; hATG = horse anti-thymocyte globulin.
*One respondent reported transfusion plus exjade as treatment for MDS.

Table 6 reports the side effects experienced with current treatments for MDS that were administered intravenously or through subcutaneous injections that were rated to be "1-completely intolerable" or "2-relatively intolerable." The side effects most commonly rated to be "1-completely intolerable" or "2-relatively intolerable" were injection-site rash or pain and bruising (10 respondents); sleep problems (nine respondents); fatigue/lack of energy, constipation, and dry mouth (eight respondents each). Namely, seven respondents reported that they experienced injection-site pain or significant discomfort as a result of azacitidine injections; five respondents rated this pain as a 4, on a scale from "1-no discomfort and/or pain" to "5-being significant discomfort and/or pain."

Table 6: Completely or Relatively Intolerable Side Effects Associated with Current Treatments for MDS

MDS Treatment Side Effects Rated as Completely or Relatively Intolerable	Number of Respondents who Rated the Side Effect as Completely or Relatively Intolerable
Injection site rash or pain and bruising	10
Sleep problems	9
Fatigue/lack of energy (asthenia)	8
Constipation	8
Dry mouth	8
Joint pain (arthralgia)	7
Dry skin	7
Stomach pain	6
Mouth sores	6
Insomnia/sleep problems	6
Decrease or loss of appetite	5
Dizziness	5
Vomiting	5
Nausea	5
Headache	4
Increased urination	4
Increased thirst	3
Diarrhea	3
Cough	2
Fever	2

The patient groups highlighted discomfort, skin irritation, bruising, and soreness to be other problems associated with injections (those in bold). As noted by patients in their own words:

- *"RBC Transfusion. **Discomfort** in my port area due to frequent use."*
- *"Just the **skin irritation** of the area as the days increase."*
- *"Just the normal **bruising and discomfort**"*
- *"Bruising swelling of stomach **very sore**"*
- *"Hard to find the right spot of my vine (sic)"*

The schedule for MDS treatments administered intravenously or through injection was reported to impact or limit day-to-day activities. Namely, there was a "4-large impact" or "5-significant impact" on the following day-to-day activities (listed in order of the number of ratings): travel (16), work (12), exercise (11), fulfilling family obligations (9), spending time with family and friends (9), and conducting household chores (8).

Respondents were asked if their current or previous treatment for MDS is/was administered in a hospital or clinic, if so, how far did they have to travel (one-way) to receive treatment? Most respondents were located 0 to 25 kilometres (10 responses) and 26 to 50 kilometres (eight responses) from the centre of treatment administration. One respondent each, reported being 260 kilometres and 400 kilometres from the centre of treatment administration. Two respondents reported having to arrange for lodging in order to accommodate their infusion schedule. Respondents were asked if they had any other out-of-pocket expenses related to their treatment/infusion schedule; the following expenses were reported (listed in order of the number of ratings): parking (19), mileage/gas (15), meals/food (9), other transportation (taxis, public transit, etc.) (3), and lodging/accommodations (2).

The patient groups also highlighted the non-monetary difficulties associated with travelling to treatment centres. Traffic, use of public transit, and the fatigue/weakness experienced when commuting were highlighted in the following quotations:

- *"Traffic congestion at rush hours / appointment times"*
- *"Daughter drives to treatments while on summer break. Will have to apply for Handi-Transit in the fall."*
- *"Heavy traffic especially in winter months"*
- *"Yes, too crowded in the skytrain so that I had to stand and feel tired."*
- *"Weakness."*

Respondents were asked to discuss other relevant experiences with injected/infused treatments for their MDS, one respondent indicated a positive experience as they stated, "*it was overall, a **good experience**."* However, more respondents indicated a negative experience, which is reflected in the following quotations. Of note, the patient groups highlighted the lack of confidence, bruising, loss of appetite/fatigue, severing of the ulna nerve, infections, pain, and two attacks of GVHD (those in bold).

- *"Fatigue, hives during infusion."*
- *"With aggressive MDS the lack of options to extend prognosis is extremely worrying. Plus the delay in availability as new treatments get approved elsewhere and take much longer in Canada and then Nova Scotia. Being told if I'm lucky a maximum life left of 24 months **does not leave me feeling very confident**."*
- *"Very sore **and bruised stomach** from injections. **Loss of appetite and fatigue** especially week following. Takes 3 hours or more each of 7 days of treatments."*
- *"when I had pics in my arm they kept coming out. The final time it was jammed in it **severed my ulna nerve** and now I have trouble (pain, cold) with my two fingers of my right hand. They tried to fix it with surgery, but the surgery didn't work."*
- *"my father was able to stay with me during his treatments however it was **very tiring for him** to make the 260 km trip one way to get near the hospital"*
- *"**Infections** requiring hospitalization"*
- *"**Pain** non understanding dr"*
- *"Rejet de la greffe ensuite infusion lymphocytes et 2 crises de GVH en 1 mois" (Rejection of the transplant followed by infusion of lymphocytes and **2 attacks of GVHD** in 1 month)*

3.1.3 Impact on Caregivers

The input noted that there were six caregiver respondents; however, there was no direct information detailing the specific impact on caregivers.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for New Therapies

On a scale from "1-not important" to "5-very important", respondents were asked to rate how important it is to them to have access to new treatments for MDS. One respondent rated "1-not important", two respondents rated 3, six respondents rated 4, and 25 respondents rated "5-very important."

The need for an oral agent was particularly expressed during the current COVID-19 pandemic. It was highlighted that some Canadians affected by a blood cancer have expressed concerns about travelling to hospitals or clinics for treatments and question whether it is safe to do so. Namely, 18 respondents reported that they would be concerned about contracting COVID-19 as a result of visiting a clinic/hospital to receive an injection or infusion.

3.2.2 Patient Experiences to Date

One respondent, a 71 year old female, had experience with decitabine and cedazuridine for seven to 12 months. From her personal experience, she did not find the treatment effective and rated its effectiveness "1-not effective" on a scale from 1 to 5. The respondent rated her quality of life a 2 while on the treatment on a scale from "1-low/seriously impacted" to "5-high/normal living".

The respondent reported the side effects as being difficult to tolerate, rating it a 2 on a scale from "1-completely intolerable" to "5-very tolerable". When asked to describe the side effects and experience, she responded "*low counts and frequent infections*".

Table 7 reports the side effects experienced by the one female patient when she received decitabine and cedazuridine and the associated rating of tolerability on a scale from "1-completely intolerable" to "5-very tolerable". Headache and decrease or loss of appetite were rated to be the most tolerable; alternatively, pneumonia was the only side effect rated to be completely intolerable.

Table 7: Tolerability of Side Effects Associated with Decitabine and cedazuridine

MDS Treatment Side Effects	Rating of Tolerability
Pneumonia	1
Shortness of breath (dyspnea)	2
Febrile neutropenia	2
Upper respiratory tract infection	2
Cough	2
Dizziness	2
Nausea	3
Diarrhea	3
Decrease or loss of appetite	4
Headache	4

3.3 Companion Diagnostic Testing

None to report.

3.4 Additional Information

LLSC and AAMAC highlighted that MDS can progress to AML in about one third of people and there is a subgroup of MDS patients that carry a gene variant called GFI136N that are resistant to azacitidine or decitabine treatment and very rapidly develop AML. Additionally, LLSC and AAMAC support the use of new treatments for MDS that can be taken at home to reduce hospital visits. The route of administration is an undeniable component of the patient experience. Oral therapies provide patients with more convenient treatment options, which is especially significant for those who are negatively impacted by the need to receive treatment in a hospital or clinic.

4 Summary of Provincial Advisory Group (PAG) Input

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the CADTH website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Sequencing and priority of treatment

Economic factors:

- None

Please see below for more details.

4.1 Currently Funded Treatments

There is variation across standard of care for myelodysplastic syndromes (MDS) according to the subtypes. Low or intermediate-1 risk MDS is treated with ESA's (e.g., darbepoetin) +/- G-CSF for patients with an EPO level <500 and for patients receiving <2 units RBC transfusions/month. For all other intermediate-2 or high-risk MDS, azacitidine is the standard of treatment. Lenalidomide is available in some jurisdictions for MDS with deletion 5q chromosome change. Additionally, azacitidine is used for the treatment of Chronic Myelomonocytic Leukemia (CMML) is a French-American-British (FAB) subtype of MDS. Hydroxyurea is available as treatment for CMML for patients who are not transplant-candidates, and azacitidine may be offered to some of these patients also (e.g., treatment of CMML with 10-29% blasts, intermediate-2 or high-risk type according to the CMML-specific prognostic scoring system, treatment of relapsed CMML following an allogeneic stem cell transplant). Hematopoietic stem cell transplant (HSCT) or high-dose chemotherapy can be offered to some MDS patients with good fitness but are not standard in this population.

PAG noted that the phase III ASCERTAIN study and phase I/II ASTX727-01-B study compared oral decitabine and cedazuridine to intravenous (IV) decitabine monotherapy. PAG noted that IV decitabine monotherapy is approved but not marketed in Canada (IV decitabine monotherapy is no longer available in Canada). PAG seeks an additional comparison of decitabine and cedazuridine with azacitidine in higher risk MDS subtypes as well as azacitidine and hydroxyurea for some patients with CMML. Also, PAG seeks an additional comparison of decitabine and cedazuridine with lenalidomide in patients with deletion 5q chromosome change MDS. Furthermore, PAG seeks an additional comparison of decitabine and cedazuridine with HSCT for MDS.

4.2 Eligible Patient Population

The reimbursement request is decitabine and cedazuridine for the treatment of adult patients with MDS including previously treated and untreated, de novo and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and CMML and intermediate-1, intermediate-2, and high-risk IPSS groups).

In view of the characteristics of the included patient population and exclusion criteria in the ASCERTAIN and ASTX727-01-B studies, PAG is seeking clarity on whether the following patients would be eligible for treatment with decitabine and cedazuridine:

- Patients who experienced prior HSCT
- Candidates for intensive induction chemotherapy
- Patients who are candidates for HSCT
- Patients previously treated with a hypomethylating agent

- Patients with ECOG PS ≥2

If treatment with decitabine and cedazuridine were recommended for reimbursement, PAG noted a time-limited need and seeks confirmation from pERC that patients currently on azacitidine may switch for the convenience of an oral therapy and patients with deletion 5q MDS treated with lenalidomide would be able to access decitabine and cedazuridine.

PAG noted potential indication creep in the following scenarios: use of decitabine and cedazuridine in second line after azacitidine, use of decitabine and cedazuridine for the treatment of AML where azacitidine is available and patients with low-risk MDS.

4.3 Implementation Factors

The recommended dose is 1 tablet containing 100 mg of cedazuridine and 35 mg of decitabine taken orally once daily on days 1 through 5 of each 28-day cycle for a minimum of 4 cycles. The sponsor indicated that best response may take longer than 4 cycles. Cycles are repeated every 28-days in the absence of hematologic toxicities not attributed to active disease and blood counts show absolute neutrophil count of at least 1.0×10^9/L and platelets are at least 50×10^9/L, or when they return to pre-treatment levels. The sponsor advised to delay or reduce the dose per cycle for hematologic toxicity. PAG is seeking a clear definition of "continuing treatment as long as the patient continues to benefit." PAG is seeking advice on dose reduction since it may not be possible with a single tablet strength unless skipping days is recommended. PAG acknowledged that once daily dosing for 5 days is an enabler to implementation.

PAG noted that decitabine and cedazuridine is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings. As such, PAG identified the oral route of administration, in which patients could easily use in the community, as an enabler.

PAG noted that decitabine and cedazuridine involves increased pharmacy and nursing resources for monitoring adverse effects and adherence. When first starting treatment with decitabine and cedazuridine, cytopenias may lead to increased blood work and increase in supportive care drugs such as antibiotics. There is concern with possible drug wastage because dose reduction involves reducing the number of tablets per cycle (e.g., go from 5 days to 4 days to 3 days). The product monograph outlines a blister pack of 5 tablets with one blister card in a carton. PAG is seeking clarity on the packaging and whether this blister card can be cut to accommodate dose reduction and whether tablets can be used for another patient.

4.4 Sequencing and Priority of Treatments

PAG is seeking to confirm the place in therapy and sequencing with decitabine and cedazuridine including the scenarios below:

- Options after treatment failure with decitabine and cedazuridine
- Options after treatment failure with azacitidine
- Use decitabine and cedazuridine as a bridge to HSCT or intensive chemotherapy (with curative intent) to achieve disease and symptom control and thus improve fitness
- Sequencing with azacitidine (e.g., does failure of one hypomethylating agent precludes the use of another in subsequent lines)?
- For patients with deletion 5q- MDS who are currently on lenalidomide and progress, is there evidence to inform whether these patients would be eligible for decitabine oral upon progression
- For patients who have low risk MDS and are treated with EPO +/- G-CSF, is there evidence to inform whether these patients would be eligible for decitabine oral upon progression?

4.5 Companion Diagnostic Testing

None.

4.6 Additional Information

None.

5 Summary of Registered Clinician Input

Three registered clinician inputs were provided for the review of decitabine and cedazuridine (Inqovi) for MDS: one from an individual oncologist (Alberta) and two group inputs (Ontario)—two clinicians on behalf of Ontario Health Cancer Care Ontario (OH-CCO) Hematology Cancer Drug Advisory Committee (DAC) and five clinicians from Odette Cancer Centre and Princess Margaret Hospital (OCC/PMH). The two Ontario clinician groups reported having experience administering decitabine and cedazuridine, whereas the Alberta clinician did not have experience. All clinicians noted that the patient population in the reimbursement request aligns with the need in their clinical practice. Currently available MDS treatments vary across provincial formularies and are administered based on risk sub-type and cytogenetic or familial pre-dispositions. Erythropoietin stimulating agents (e.g., darbepoetin) are used for low or intermediate-1 risk and azacitidine for intermediate-2 or high-risk MDS patients. Lenalidomide may be used for MDS patients with a del(5q) chromosome change. Azacitidine or hydroxyurea (specifically in patients who are transplant ineligible) may be used for CMML. Hematopoietic stem cell transplant or high-dose chemotherapy may be used in MDS patients with good fitness but are not standard treatments. The OCC/PMH clinicians noted that less than 10% of patients with lower risk MDS and clinically significant cytopenias may be candidates for immunosuppressive therapy. Decitabine has Health Canada approval but is not currently marketed for higher risk MDS in Canada. Companion diagnostic testing is not required for decitabine and cedazuridine; however, cytogenetic testing is needed for risk stratification and calculation of the IPSS and IPSS-R. All clinicians indicated a preference for the IPSS-R; nevertheless, the original IPSS is currently used in most parts of Canada as funding for azacitidine is based on this scoring system (only for intermediate-2 and high-risk disease).

All clinicians noted that the criteria of the pivotal trials (ASCERTAIN study and the ASTX727-01-B) are reasonable and may be applied in clinical practice. All clinicians would not limit or extend decitabine and cedazuridine to any specific subgroups. The safety, tolerability, and efficacy of decitabine and cedazuridine and azacitidine were noted to be comparable based on randomized phase 2 studies comparing decitabine and azacitidine of lower risk disease. However, decitabine and azacitidine have not been directly compared in a randomized trial for higher risk disease. The OH-CCO DAC and Alberta clinicians noted that decitabine and cedazuridine would replace azacitidine in all eligible patients. However, the OCC/PMH clinicians stated that decitabine and cedazuridine would not supplant current treatments in lower risk disease but could replace azacitidine in the higher risk disease patients and those unable to tolerate or travel to receive azacitidine. The OH-CCO DAC clinicians support administering one cycle of azacitidine in patients waiting to gain access to decitabine and cedazuridine. All clinicians felt that the oral administration of decitabine and cedazuridine and the potential for at-home administration is particularly beneficial for resourcing and patient quality of life, which benefits clinical staff and patients. Namely, this is favourable for patients who experience difficulties or are unable to travel due to mobility limitations, travel considerations, or COVID-19 concerns. Decitabine and cedazuridine may improve compliance and clinical outcomes as many MDS patients are currently treated with azacitidine, which requires seven consecutive visits every 28 days for intravenous or subcutaneous administration.

Decitabine and cedazuridine was recommended to be discontinued for excessive toxicity or progressive disease but continued indefinitely if working. The clinicians suggested to follow the key response criteria used to guide discontinuation of other HMAs such as measures of hematologic function (blood count [e.g., regular CBCs] and bone marrow [aspiration and biopsies]) and clinical improvement (energy, well-being, and reduced infections). The OCC/PMH clinicians specified that response is typically assessed at six months, and the Alberta clinician noted there is no set time for bone marrow assessments. All clinicians were not aware of any direct evidence to inform treatment options following progression on decitabine and cedazuridine. The OH-CCO DAC clinicians noted that palliative/supportive measures could be implemented but currently there are no disease modifying alternatives, and the Alberta clinician stated that there is evidence with azacitidine, which has demonstrated equivalence to decitabine and cedazuridine. All clinicians noted there is limited evidence to support the use of decitabine and cedazuridine following azacitidine failure. However, the OH-CCO DAC clinicians indicated it would be reasonable to allow patients currently on azacitidine to switch to decitabine and cedazuridine on a time-limited basis. All clinicians felt it is clinically reasonable to use decitabine and cedazuridine as a bridge to HSCT or intensive chemotherapy (with curative intent); namely, the OCC/PMH and Alberta clinicians noted that evidence could be extrapolated from azacitidine in current practice. The Ontario clinician groups noted there is no evidence to support sequencing of azacitidine and decitabine and cedazuridine; whereas the Alberta clinician stated there is evidence for switching in the setting where azacitidine is still working but not sequencing in the traditional sense of switching due to a lack or loss of response.

Please see below for details from the clinician input(s).

5.1 Current Treatment(s)

CADTH identified the following currently available treatments for MDS according to risk sub-types.

- Low or intermediate-1 risk MDS: ESAs (e.g., darbepoetin) with or without G-CSF for patients with an EPO level <500 and for patients receiving <2 units RBC transfusions per month.
- all other intermediate-2 or high-risk MDS: azacitidine.

CADTH identified the following currently available treatments for MDS according to cytogenetic or familial risk:

- MDS with del 5q chromosome change: lenalidomide is available in some jurisdictions.
- CMML—FAB subtype of MDS: azacitidine.
    - Azacitidine may be offered to some of these patients as well
        - CMML with 10-29% blasts
        - Intermediate-2 or high-risk type according to the CMML-specific prognostic scoring system
        - Relapsed CMML following an allogeneic stem cell transplant
    - CMML patients who are not transplant-candidates: hydroxyurea

Hematopoietic stem cell transplant or high-dose chemotherapy can be offered to some MDS patients with good fitness but are not standard treatments. The two Ontario clinician groups agreed with the treatments identified above by CADTH. The OCC/PMH clinicians added that some selected patients (<10%) with lower risk MDS may be candidates for immunosuppressive therapy if they have clinically significant cytopenias. Hypomethylating agents like decitabine and cedazuridine, decitabine (monotherapy), or azacitidine are not currently reimbursed therapies for lower risk MDS in Ontario despite evidence for clinical benefit. Thus, clinicians use azacitidine in lower risk patients with clinically significant cytopenias if the drug can be accessed compassionately. Decitabine has Health Canada approval but is not currently marketed in Canada for higher risk MDS. The Alberta clinician noted they have access to azacitidine for treatment of high risk MDS and CMML and lenalidomide for treatment of low risk MDS, whereas ESAs are only accessed by private insurance coverage (e.g., Blue Cross). Additionally, hydroxyurea is available for the patient population of the reimbursement request in those with an increasing white cell count and/or splenomegaly.

5.2 Eligible Patient Population

All clinicians noted that the patient population in the reimbursement request aligns with the need in their clinical practice and the inclusion and exclusion criteria of the pivotal trials (ASCERTAIN and ASTX727-01-B) are reasonable and may be applied in clinical practice. Accordingly, they would not extend or limit decitabine and cedazuridine to any specific subgroups of patients. However, the OH-CCO DAC clinicians specified a need for treatment of intermediate-1 MDS, for which azacitidine is currently not funded in Ontario. The OCC/PMH clinicians noted that they have treatment algorithms in both lower risk and higher risk MDS and both populations were included in the pivotal trials. They specified that in lower risk of disease and CMML-1, they would use decitabine and cedazuridine in patients with transfusion dependent disease, symptomatic anemia, significant cytopenias not targetable by ESAs, or following ESA failure (e.g., following treatment of thrombocytopenia) as decitabine and cedazuridine provides high levels of RBC TI (50%) and platelet TI (35-40%). Additionally, they would use decitabine and cedazuridine in del5q patients following lenalidomide failure. They noted that access to decitabine and cedazuridine is highly favourable as there are no approved therapies for the lower risk disease and CMML-1 population (other than lenalidomide for del5q MDS, which accounts for 5% of MDS). For the higher risk of disease, they would use decitabine and cedazuridine in patients who should be treated with a HMA if they are ineligible for allogeneic stem cell transplant or as a bridge and cytoreductive agent towards an allogeneic stem cell transplant; additionally, in patients who do not tolerate azacitidine and who are unwilling or unable to receive azacitidine (e.g., unable to travel to treatment centre).

5.2.1 Which scoring system is best used to identify intermediate and high-risk patients? Is it the original IPSS or is it the revised IPSS?

All clinicians preferred the IPSS-R to identify intermediate and high-risk patients. Nevertheless, the two Ontario clinician groups noted that the original IPSS is currently used in Ontario (and most parts of Canada) as funding for azacitidine is based on this scoring

system (only for intermediate-2 and high-risk disease). The OH-CCO DAC clinicians noted that the pivotal trials used the original IPSS for risk stratification of patients. The OCC/PMH clinicians specified that the IPSS-R is better for risk stratification and the scoring systems are slightly different; for instance, a score of > 3.5 is typically used to identify higher risk patients with the IPSS-R. The Alberta clinician prefers the IPSS-R as it includes transfusion requirements and is dynamic.

5.3 Relevance to Clinical Practice

The two Ontario clinician groups reported having experience administering decitabine and cedazuridine; whereas, the Alberta clinician did not have experience. The OH-CCO DAC clinicians prefer decitabine and cedazuridine over subcutaneous azacitidine as it is an oral take-home drug and noted there are no specific contraindications. The OCC/PMH clinicians stated that decitabine and cedazuridine would not supplant current treatments in lower risk disease but provide a treatment option once standard first-line treatments fail (and patients remain transfusion dependent or seriously cytopenic). However, decitabine and cedazuridine could replace azacitidine in higher risk disease for patients unable to tolerate azacitidine or unable to travel for azacitidine. They also noted that decitabine and cedazuridine could provide an effective and potentially disease modifying therapy in patients with intermediate-1 risk disease that are upstaged to higher risk disease by the IPSS-R (e.g., high and very high risk or IPSS-R score >3.5) and for CMML patients that do not qualify for azacitidine. The Alberta clinician would use decitabine and cedazuridine in all patients who are currently receiving or will receive single agent azacitidine and noted that the criteria for azacitidine administration in Alberta are quite broad. Nevertheless, they noted that azacitidine still needs to be available despite decitabine and cedazuridine demonstrating equivalence to other HMAs in clinical trials.

All the clinicians indicated that the safety, tolerability, and efficacy of decitabine and cedazuridine and azacitidine are comparable. The OCC/PMH clinicians stated that decitabine (by default decitabine and cedazuridine, which has equivalent PK, PD, and toxicity to IV decitabine 20 mg/m^2 IV x five days) has demonstrated comparable response rates and survival with a slightly higher rate of transfusion independence compared with azacitidine in some randomized phase 2 studies of lower risk disease. However, decitabine and azacitidine have never been directly compared in a randomized trial for higher risk disease but a SEER/MEDICARE interrogation by Zeidan et al., and a NMA by Almasri et al., demonstrate identical OS between azacitidine and decitabine. The OH-CCO DAC clinicians stated that the side effect profiles are similar with no additional resource implications for decitabine and cedazuridine. The Alberta clinician stated that decitabine and cedazuridine has been shown to be equivalent to subcutaneously administered HMAs.

All the clinicians felt that the oral administration of decitabine and cedazuridine and the potential for at-home administration is particularly beneficial for resourcing and patient quality of life, which benefits clinical staff and patients. Namely, this would benefit patients who experience difficulties or are unable to travel to clinics to receive subcutaneously injected or IV infused treatments due to mobility limitations, travel considerations (e.g., method of transportation, distance, parking, and related financial hardships), or COVID-19 concerns. Decitabine and cedazuridine may improve compliance and clinical outcomes as many patients with MDS are currently treated with azacitidine, which requires seven consecutive visits every 28 days for intravenous or subcutaneous administration. The OH-CCO DAC clinicians noted that 50% of transfusion dependent patients were rendered transfusion independent in the pivotal trial(s), which significantly reduces time spent in treatment/transfusion units.

5.3.1 What are the key response criteria factors and timing of evaluation for clinical benefit to determine when to discontinue decitabine and cedazuridine?

Decitabine and cedazuridine was recommended to be discontinued (not remitting with dose reduction or schedule adjustment) for excessive toxicity or progressive disease but continued indefinitely if working (i.e., patients with stable bone marrow disease accompanied by hematologic and/or clinical improvement). The two Ontario clinician groups suggested to follow key response criteria used to guide discontinuation of other HMAs (azacitidine) for discontinuation of decitabine and cedazuridine. Response assessments included measures of hematologic function (blood count [e.g., regular CBCs] and bone marrow [aspiration and biopsies]) and clinical improvement (energy, well-being, and reduced infections). The OH-CCO DAC clinicians stated the evaluation for clinical benefit should align with current practice for azacitidine; namely, similar frequency of blood count monitoring. The OCC/PMH clinicians specified that response is typically assessed at six months with a repeat bone marrow; whereas the Alberta clinician noted there is no set time to perform bone marrow assessments.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

The OH-CCO DAC clinicians stated there are no other treatments to sequence decitabine and cedazuridine with as there are no available data; therefore, decitabine and cedazuridine would replace azacitidine and not be used sequentially. However, they support patients receiving one cycle of azacitidine while waiting to access decitabine and cedazuridine (e.g., in Ontario through the exceptional access program [EAP]) as the pivotal trials allowed prior azacitidine treatment (of note, only in the dose confirmation stage of the phase 2 pivotal trial: ASTX727-01-B).

5.4.1 Is there evidence to inform treatment options after progression on decitabine and cedazuridine?

All clinicians were not aware of any direct evidence to inform treatment options following progression on decitabine and cedazuridine. The OH-CCO DAC clinicians noted that palliative/supportive measures could be implemented but currently there are no disease modifying alternatives. The OCC/PMH clinicians added that clinical trials are underway to investigate adding venetoclax or other targeted agents. The Alberta clinician stated there is no direct evidence with decitabine and cedazuridine but there is for azacitidine, which has demonstrated equivalence.

5.4.2 What evidence is there to support the use of decitabine and cedazuridine for MDS treatment following treatment failure with azacitidine?

All the clinicians noted there is limited evidence to support use of decitabine and cedazuridine for MDS treatment following treatment failure with azacitidine. The OH-CCO DAC clinicians specified there is limited evidence as the phase 3 pivotal trial (ASCERTAIN) only allowed one cycle of azacitidine. However, based on quality of life and resource utilization benefits, it would be reasonable to allow patients who are currently on azacitidine to switch to decitabine and cedazuridine on a time-limited basis. The OCC/PMH clinicians noted that a few azacitidine-treated patients were enrolled in earlier clinical studies, but it is unclear if they experienced treatment failure with azacitidine.

5.4.3 What evidence is available to use decitabine and cedazuridine as a bridge to HSCT or intensive chemotherapy (with curative intent)?

All clinicians felt it is clinically reasonable to use decitabine and cedazuridine as a bridge to HSCT or intensive chemotherapy (with curative intent). The OCC/PMH and Alberta clinicians noted that evidence could be extrapolated from azacitidine in current practice. The OCC/PMH clinicians attributed this to azacitidine and decitabine and cedazuridine working similarly as cytotoxic and hypomethylating agents. In some respects, decitabine and cedazuridine may work as a faster cytotoxic agent and be particularly effective in MDS patients with elevated blasts.

5.4.4 What evidence is available to support sequencing of azacitidine, decitabine and cedazuridine?

The two Ontario clinician groups noted there is no evidence to support sequencing of azacitidine and decitabine and cedazuridine. The OH-CCO DAC clinicians stated there is no biological rationale for sequencing and the oral route of administration of decitabine and cedazuridine is likely favoured by patients. The OCC/PMH clinicians would select one HMA alone for higher risk disease and not offer the alternate in cases of disease progression or loss of response. In lower risk of disease, there is some evidence for using three days of decitabine or five days of azacitidine alone. It is not clear if there is benefit from extending the schedule in patients who progress from lower risk to higher risk disease if HMA exposed. The Alberta clinician stated there is evidence for switching in the setting where azacitidine is still working but not sequencing in the traditional sense of switching due to a lack or loss of response.

5.5 Companion Diagnostic Testing

No companion diagnostic test is required for decitabine and cedazuridine. However, the OCC/PMH clinicians stated that cytogenetic testing is needed for risk stratification and calculation of the IPSS and IPSS-R. They highlighted that the turnaround time for cytogenetics in Ontario is “woefully long;” thus, improving this resource is critical. They also noted that next generation sequencing as a method of upstaging lower risk disease could help identify patients in need of a HMA who are not currently qualified according to the IPSS.

5.6 Additional Information

None to report.

6 Systematic Review

6.1 Objectives

The primary objective of this systematic review is to evaluate the efficacy and safety of oral decitabine and cedazuridine compared to standard of care for the treatment of adult patients with MDS including previously treated and untreated, de novo and secondary MDS of all FAB subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and CMML) and intermediate-1, intermediate-2, and high-risk IPSS groups.

Supplemental Issues and Comparison with Other Literature most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7 and section 8.

- **Supplemental Issue:** The CADTH review team identified no trials directly comparing decitabine and cedazuridine to relevant comparators for patients with MDS. In the absence of a direct head-to-head comparisons, the sponsor submitted a NMA comparing oral decitabine and cedazuridine to decitabine, azacitidine, and best supportive care in patients with intermediate and high-risk MDS. Refer to section 7 for the summary and critical appraisal of the sponsor submitted NMA.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the CADTH Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the CADTH Methods Team are provided in Appendix A.

Table 8: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*†	Outcomes
Published or unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of decitabine and cedazuridine should be included.	Adult patients with previously treated and untreated, de novo, or secondary MDS of all FAB subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and CMML) and IPSS Intermediate-1, Intermediate-2, and high-risk groups. Subgroups: • Number and type of prior treatments (e.g., azacitidine, HSCT) • Mutations (including but not limited to: SF3B1, TET2, SRSF2, ASXL1, DNMT3A, TP53) • Time from completion/failure on prior treatment (for applicable patients) • Risk category (based on IPSS and/or IPSS-R) including % blasts, and cytopenias	Oral combination of decitabine and cedazuridine	**Intermediate-1 risk MDS:** • BSC (ESAs, RBC/ICT) • Lenalidomide (for patients with del(5q)) • HMAs (such as azacitadine if patients have significant cytopenias or don't seem fit for other treatments) **Intermediate-2 or high-risk MDS:** • HMAs (Decitabine, Azacitidine) • High-dose chemotherapy **For CMML subtype:** • Azacitidine • Hydroxyurea • Imatinib • High-dose chemotherapy	**Efficacy:** • **OS** • **ORR, CR, mCR, and PR** • PFS • **Hematologic improvement** • **RBC/platelet transfusion independence** • **HRQoL** • Time to AML • Transplantation rate/HSCT **Safety:** • AEs (AEs of interest include GI toxicity) • SAEs • WDAE • Deaths

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*†	Outcomes
	• Transfusion dependence • Age • Comorbidities • ECOG PS			

AE = adverse event; AML = acute myeloid leukemia; ATG = anti-thymocyte globulin; BSC = best supportive care; CMML = chronic myelomonocytic leukemia; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ESA = erythropoiesis-stimulating agents; FAB = French-American-British; HMA = hypomethylating agent; HSCT = hematopoietic stem cell transplantation; HRQoL = health-related quality of life; ICT = iron chelation therapy; IPSS = International Prognostic Scoring System; IPSS-R = Revised International Prognostic Scoring System; LINE-1 = Long Interspersed Nucleotide Elements; mCR = marrow complete response; MDS = myelodysplastic syndromes; ORR = overall response rate; OS = overall survival; PR = partial response; RBC = red blood cell; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

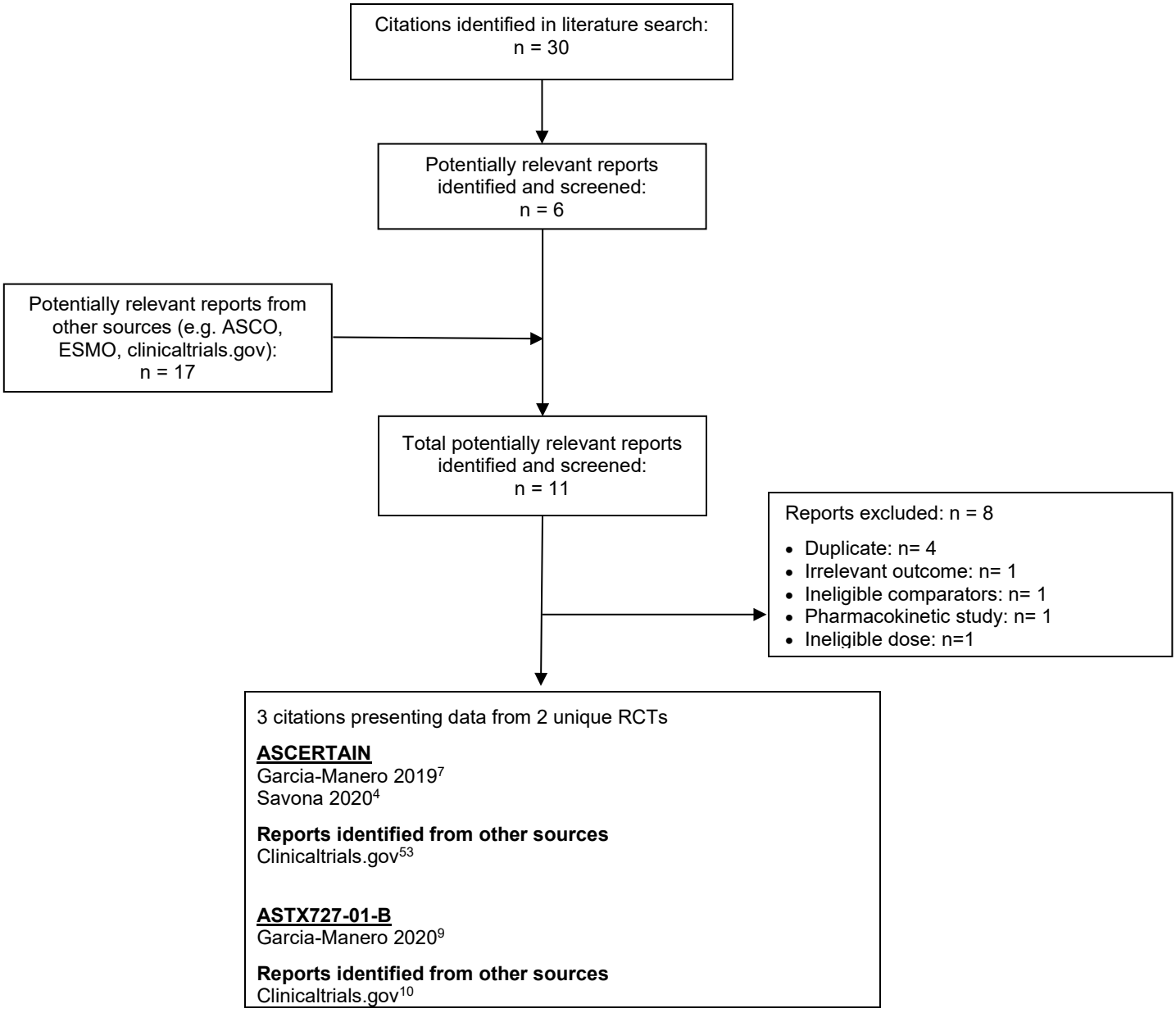
† The CGP noted that decitabine and cedazuridine would not replace HSCT in the MDS patient population, which is considered the only curative option for eligible patients. The sponsor clarified decitabine and cedazuridine is intended for use in transplant ineligible patients or may be used as a bridge to transplant, and thus the CGP agreed that HSCT would not be included as a relevant comparator.[8]

6.3 Results

6.3.1 Literature Search Results

Of the 42 potentially relevant reports identified, two studies were included in the pCODR systematic review[7,9] and 8 studies were excluded. Studies were excluded because they were duplicate references[49-53] were not the study type of interest,[54] did not include a relevant comparator[55] or did not include an appropriate dose.[56]

Figure 1: Flow Diagram for Study Selection



Note: Additional data related to ASCERTAIN and ASTX727-01-including Clinical Summary,[57] Clinical Study Reports,[1,2] Updated Efficacy and Safety Reports,[5,6,11] Indirect treatment comparison,[12,20] and Checkpoint Responses[8] were also obtained through requests to the Sponsor by CADTH

6.3.2 Summary of Included Studies

The CADTH systematic review included two RCTs (ASCERTAIN and ASTX727-01-B)[7,9]. Both studies were open-label, two-cycle, two-sequence crossover trials.

6.3.2.1 Detailed Trial Characteristics

The summary of the trials and select characteristics are presented in Table 9.

Table 9: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes

ASCERTAIN/ASTX727-02 (NCT03306264)[7,53]
 	
Characteristics:
Multicenter, randomized (1:1), open-label, crossover, phase III trial
 	
• N randomized = 138 (Sequence A: n = 69; Sequence B: n = 69)
• N treated = 133 (Sequence A: n = 66; Sequence B: n = 67)
 	
Setting:
37 study sites in two countries (Canada and the United States)
 	
Patient Enrolment Dates
February 8, 2018 to January 8, 2019
 	
Data cut-off:
March 19, 2019
 	
Database lock:
May 20, 2019
 	
Status:
Ongoing
 	
Final Analysis Date:
TBD
 	
Funding:
Astex Pharmaceuticals, Inc.
	Key Inclusion Criteria:
	• Men or women aged ≥ 18 years who are candidates for IV decitabine
	  ○ In North America: Participants with MDS previously treated or untreated with de novo or secondary MDS, including all FAB subtypes (RA, RARS, RAEB, RAEB-t, and CMML), and subjects with IPSS intermediate-1, -2, or high-risk MDS
	  ○ In Europe: Participants with de novo or secondary AML, as defined by the WHO criteria, who are not candidates for standard induction chemotherapy (Protocol amendment following latest data cut-off)
	• ECOG PS 0 to 1
	• Adequate hepatic function defined as total or direct bilirubin ≤ 2 x ULN, AST/SGOT and ALT/SGPT ≤ 2.5 x ULN
	• Adequate renal function defined as serum creatinine ≤ 1.5x ULN or calculated creatinine clearance or glomerular filtration rate > 50 mL/min per 1.73 m^2 of body surface area for subjects with creatinine levels above institutional normal
	• No major surgery within 30 days of first study treatment
	• Life expectancy ≥ 3 months
	• One prior cycle of HMA was allowed
	
	Key Exclusion Criteria:
	• Prior treatment with > 1 cycle of azacitadine or decitabine
	• Cytotoxic chemotherapy or prior azacitidine or decitabine within 4 weeks of first dose of study treatment
	• Concurrent MDS therapies, including lenalidomide, EPO, cyclosporine/tacrolimus, G-CSF, GM-CSF, etc.
	• Life-threatening illness or severe organ system dysfunction, such as uncontrolled CHF or COPD
	• Prior malignancy except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, prostate cancer or breast cancer
		Intervention:
		Oral decitabine and cedazuridine daily for 5 days in cycle 1, followed by IV decitabine daily for 5 days in cycle 2 (Sequence A)
		
		Comparator:
		IV decitabine daily for 5 days in cycle 1, followed by oral decitabine and cedazuridine daily for 5 days in cycle 2 (Sequence B)
			Primary:
			• Total 5-day decitabine AUC equivalence
			
			Secondary:
			• LINE-1 demethylation
			  ○ Additional secondary PK parameters
			• Clinical response
			  ○ MDS/CMML: Number of participants with CR, mCR, PR, hematologic improvement)
			  ○ AML: Number of participants with CR, CRp, and CRi
			• RBC transfusion independence
			• Platelet transfusion independence
			• Leukemia-free survival
			• OS
			• AEs

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	under control with hormone therapy, or other cancer from which the subject has been disease free for at least 2 years		
Study ASTX727-01-B (NCT02103478)[9] **Characteristics:** Two-stage, multicenter, randomized, open-label, randomized (1:1), open-label, crossover, phase II trial • N randomized = 86 patients (52 patients entered the DC stage; 52 patients entered FDC stage) • N treated = 50 patients in the DC group, 30 patients in the FDC group **Setting** 17 study sites in two countries (four in Canada, 13 in the United States) **Patient Enrolment Dates** December 30, 2015 to May 29, 2017 **Data cut-off:** June 5, 2018 **Database lock:** September 4, 2018 **Status:** Complete **Final Analysis Date:** TBD **Funding:** Astex Pharmaceuticals, Inc.	**Key Inclusion Criteria:** • Age ≥ 18 years • IPSS intermediate-1, -2- or high-risk MDS, or CMML • ECOG PS ≤ 2 • Adequate hepatic (≤ 2 x ULN for bilirubin, and ≤ 2.5x ULN for AST and ALT) and renal (≤ 1.5 x ULN for serum creatinine or > 50 mL/min per 1.73 m^2) function • No evidence of active second malignancy • No major surgery within 2 weeks of starting study treatment • One prior cycle of either decitabine or azacitidine was permitted • No cytotoxic chemotherapy within 2 weeks of starting study treatment • Prior allo-HSCT were eligible if they were free of graft-versus-host disease and were no longer using immunosuppressive therapy at enrollment **Key Exclusion Criteria:** • Previous treatment with ≥ 2 cycles of decitabine (all stages) or azacitidine (DC stage only) • Treatment with investigational therapy within 2 weeks of study treatment • Uncontrolled medical disease(s) or active, uncontrolled infection • Diagnosed with AML • Active uncontrolled gastric or duodenal ulcer • Known history of HIV or hepatitis C or B	**Intervention:** Oral decitabine/ cedazuridine daily for 5 days in cycle 1, followed by IV decitabine daily for 5 days in cycle 2 (Sequence A) **Comparator:** IV decitabine daily for 5 days in cycle 1, followed by oral decitabine and cedazuridine in cycle 2 (Sequence B)	**Primary:** • Oral/IV decitabine exposure over 5 days • DNA demethylation of oral decitabine and cedazuridine vs IV decitabine from the first 2 cycles • ORR **Secondary:** • Safety (incidence and severity of AEs) • DOR • Hematological improvement • RBC transfusion independence • Time to AML • OS • Other PK parameters

AE = adverse event; ALT = Alanine aminotransferase; AML = acute myeloid leukemia; AST = aspartate aminotransferase; AUC = area under the curve; CHF = congestive heart failure; CMML = chronic myelomonocytic leukemia; COPD = chronic obstructive pulmonary disease; CR = complete response; CRi = complete remission with incomplete hematologic recovery ; CRp = complete remission with incomplete platelet recovery; DC = dose-confirmation; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EPO = erythropoietin; FAB = French, American, British; FDC = fixed-dose combination; G-CSF = granulocyte colony stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; HIV = human immunodeficiency virus; HMA = hypomethylating agent; HSCT = hematopoietic stem cell transplant; IPSS = International Prognostic Scoring System; LINE-1 = long interspersed nuclear elements; mCR = marrow complete response; MDS = myelodysplastic syndromes; ORR = overall response rate; OS = overall survival; PK = pharmacokinetic; PR = partial response; PS = performance status; RA = refractory anemia; RAEB = refractory anemia with excess blasts; RAEB-t = refractory anemia with excess blasts in transformation; RARS = refractory anemia with ringed sideroblasts; RBC = red blood cell; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal; WHO = World Health Organization.

Source: Garcia-Manero 2020[9]; Garcia-Manero 2019[7]; clinicaltrials.gov[53];ASTX727-02 Clinical Study Report[1]; ASTX727-01-B Clinical Study Report[2]

a) Trials

ASCERTAIN Trial

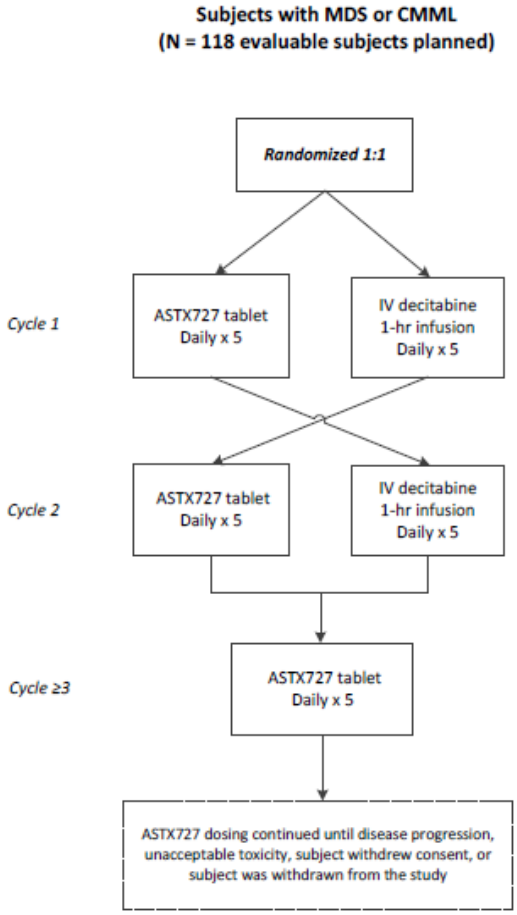
Screening, Eligibility Criteria, and Randomization

ASCERTAIN is an ongoing international, multicenter, randomized, open-label, two-cycle, two-sequence crossover, phase III trial comparing oral decitabine and cedazuridine and IV decitabine in IPSS intermediate-1, -2, or high-risk MDS, or CMML patients. The primary study objective was to establish the total 5-day AUC_{0-24} exposures between oral decitabine and cedazuridine and IV decitabine, with secondary objectives to assess the long term safety and efficacy of decitabine and cedazuridine.[1,57,58] The trial was conducted across 37 sites in two countries, including seven sites in Canada from which 23 patients were treated (Alberta = 3; Ontario = 14; Quebec = 2; Nova Scotia = 4).[1,58,59]

Key eligibility criteria for the ASCERTAIN study are summarized in Table 9. Briefly, eligible patients included male and female adults (≥ 18 years) diagnosed with previously treated or untreated, de novo or secondary MDS, including all FAB subtypes, and IPSS intermediate-1, intermediate-2, or high-risk MDS, or CMML who were eligible to receive IV decitabine, and had an ECOG performance status of 0 to 1.[57,60] One prior cycle of either decitabine or azacitidine was allowed, but no other cytotoxic chemotherapy was permitted within 4 weeks of first dose of study treatment.[1] Prior treatment with other MDS therapies (lenalidomide, EPO, G-CSF, etc.) was permitted, provided that completion was at least 1 week prior to first dose of study treatment.[53] It is unclear what proportion of patients were eligible for HSCT at baseline.

The design of the ASCERTAIN trial is shown in Figure 2 below. Patients were randomized 1:1 via computer-generated randomization schedule to one of two treatment sequences (oral decitabine and cedazuridine in Cycle 1 and IV decitabine Cycle 2 [Sequence A], or IV decitabine in Cycle 1 and oral decitabine and cedazuridine in Cycle 2 [Sequence B]) for the first two cycles.[7] Following completion of the first two treatment cycles, subjects continued to receive oral decitabine and cedazuridine in 28-day cycles until disease progression, unacceptable toxicity, treatment discontinuation for various reasons, or withdrawal.[58,60]

Figure 2: Study Design of the ASCERTAIN Trial



Source: Clinical Study Report[1]

Study Endpoints and Statistical Analysis

Analysis Set(s):

The All Subject Analysis Set included all screened subjects, including those who did not meet the study entry criteria, and was only used for screening displays.[1] The Randomized Subject Analysis Set included all subjects who were randomized into the study. Subjects were included in the treatment group according to their randomly assigned treatment sequence.[1]

Efficacy Analysis and Safety Analysis Sets were used to analyze all safety and efficacy outcomes and included data from all subjects who received any amount of study treatment. No data exclusion was permitted due to protocol deviations in the Efficacy and Safety Analysis Sets. Efficacy variables based on the efficacy analysis set (clinical response, transfusion independence, LFS, OS) were summarized using descriptive statistics, and no comparisons between treatment sequences were performed.[1]

Efficacy analyses for PK endpoints were conducted in two PK analysis sets were used to analyze PK data: The Primary Endpoint PK Analysis Set (primary paired population) and the Overall PK Analysis Set (overall unpaired sensitivity population). The primary endpoint PK analysis set, used to calculate the decitabine 5-day $AUC_{0\text{-}24}$, included subjects who received full dose of decitabine and cedazuridine within 3 hours of intended dosing with no vomiting occurring within 6 hours of dosing, or IV decitabine (both treatments on days 1 through 5), and had to have at least one evaluable $AUC_{0\text{-}24}$ measurement. The overall PK (sensitivity) analysis set included

additional subjects who may have not been included in the primary endpoint PK analysis set and that received any amount of study treatment.[1]

Study Endpoints and Statistical Analyses:

The primary endpoint of the ASCERTAIN study was the total 5-day AUC exposure of decitabine following treatment with oral decitabine and cedazuridine (100/35 mg) vs. IV decitabine (20 mg/m^2).[7,53] Total 5-day AUC_{0-24} was selected as the primary endpoint for the study as steady state decitabine exposure after oral decitabine and cedazuridine is reached on day 2 and does not increase through day 5. Serial blood samples (3 mL each) were collected for PK analysis throughout the day on days 1, 2, and 5 for decitabine and cedazuridine, and on days 1 and 5 for IV decitabine. A mixed-effect ANOVA model including treatment, period (cycle), and sequence as fixed effects, and subject as a random effect was performed on the natural logarithm transformed (ln-transformed) 5-day cumulative AUC_{0-24} parameter for plasma decitabine from ASTX727 versus IV decitabine 20 mg/m^2 1-hour infusion. Model outputs included calculations of least squares mean (LSM), LSM differences between treatments, and the standard error. The 90% CIs for the ratios of treatment LSM for ASTX727 relative to IV decitabine were calculated for the parameters of 5-day AUC_{0-24} (and secondary AUC parameters) using ln-transformed data. Ln-transformed results were back-transformed to the original scale by exponentiation to obtain geometric LSM for each treatment and geometric LSM ratios of 5-day AUC_{0-24} of oral versus IV treatment. The LSM were expressed as a ratio relative to the LSM of IV decitabine for the comparison of ASTX727 relative to IV decitabine. The two treatments (ASTX727 and IV decitabine) were to be considered equivalent if the two-sided 90% CI of the 5-day decitabine AUC_{0-24} ratio of LSM for ASTX727 relative to IV decitabine (oral/IV) was contained entirely within the range of 0.80 – 1.25 specified in the Sample Size calculation below.[1]

Secondary endpoints for this study that were relevant to the systematic review included:

- **Clinical response:** Clinical response was conducted by medical review of peripheral blood and bone marrow sample collections including percentage of peripheral blood blasts; bone marrow blasts; neutrophils; platelets; hemoglobin level; and days from the most recent RBC or platelet transfusion and assessed by the investigator and IRC using the IWG 2006 MDS Response Criteria (Table 10).[1,3,7] Rates of CR, PR, mCR, HI, and ORR (CR+PR+mCR+HI), and mCR with HI were estimated using sample proportions and 95% Wald CI based on the number of subjects.[1]

Table 10: IWG 2006 MDS Response Criteria

Category	Response Criteria
Complete Response (CR)	**The following for 4 weeks:** • **Peripheral**: Normal peripheral counts with persistent granulocyte count ≥1.0×10^9/L, platelet ≥100×10^9/L and Hgb ≥11 g/dL. No blasts. • **Marrow**: Normal bone marrow with persistent marrow blasts ≤5%. Persistent dysplasia will be noted.
Partial Response (PR)	**The following for 4 weeks:** • **Peripheral:** Normal peripheral counts with granulocyte count ≥1.0×10^9/L, platelet count ≥100×10^9/L, and Hgb ≥11 g/dL. No blasts. • **Marrow:** Normal bone marrow and marrow blasts >5% but were reduced by 50% or more.
Marrow Complete Response (mCR)	**The following for 4 weeks:** • Reduction of bone marrow blasts to ≤5% and decrease by 50% or more without normalization of peripheral counts.
Hematological Improvement (HI)	**Lasts at least 8 weeks:** • **Erythroid Response** (Major Response) – Hemoglobin increase ≥1.5 g/dL in the absence of RBC transfusion. • **Platelet Response** (Major Response) – Absolute increase of platelet count from <20 to >20×10^9/L and by at least 100%, or if more than 20×10^9/L, by an absolute increase of at least 30×10^9/L in the absence of platelet transfusion. • **Neutrophil Response** (Major Response) – Granulocyte increase ≥100%, and by an absolute increase ≥0.5×10^9/L

Source: Adapted from Cheson 2006[3]

- **RBC or platelet TI:** Transfusion independence (RBC or platelet) was defined as no transfusion for 56 consecutive days or more after the first dose of study treatment while maintaining hemoglobin greater than or equal to 8 g/dL (RBC TI) or maintaining platelets greater than or equal to 20×10^9/L (platelet TI). The same analyses were performed for 84-day and 112-day TI. Transfusion (RBC and platelet) requirements were obtained at baseline and monthly during Cycles 1 and 2 and monthly thereafter until the 30-day follow-up visit. Hemoglobin and platelet count were collected as part of the complete blood count and were obtained weekly during Cycles 1 and 2 then biweekly in Cycle 3 and beyond. Post-treatment TI rate was calculated separately for RBC TI and platelet TI as the number of subjects who were transfusion independent post-treatment (n) among those who were transfusion dependent at baseline (N). The 95% Wald CI for TI rates was provided.[1]
- **Leukemia-Free Survival**: LFS was defined as the number of days from the date of randomization to the date of MDS progression to AML (defined as detection of ≥ 20% blasts after two consecutive reports based on peripheral blood or after the first report based on bone marrow), or the date of death from any cause Peripheral blood and bone marrow aspirate or biopsy were collected and used for assessment of progression to AML. Bone marrow aspirate or biopsy was performed at Screening, on or before Day 1 of Cycles 3, 5, 7, then every 3 months during the first year and every 6 months thereafter. Subjects who have bone marrow or peripheral blood blasts greater than or equal to 20% at baseline will be censored at the date of randomization, and subjects without a time to AML event as described above will be censored on the date of last contact. Leukemia-free survival was assessed using the Kaplan-Meier method.[1] Subjects who received subsequent anticancer therapy were not censored in the analysis.[8]
- **Overall Survival:** OS was defined as the number of days from the day the subject was randomly assigned to study treatment to the date of death (regardless of cause). Subjects were followed for survival until withdrawal of consent or until they were lost to follow up. Subjects without documentation of death will be censored on the last date of contact or the last date subject was confirmed alive, whichever is later. Median OS and 95% CIs were assessed, and OS was summarized using the Kaplan-Meier method.[1]
- **Safety:** Safety was assessed by subject-reported and investigator-observed AEs, along with physical examination, clinical laboratory tests (hematology, chemistry, and urinalysis), vital signs, concomitant medications, ECOG performance status, and electrocardiogram within the Safety Analysis Set. Adverse events were mapped using the Medical Dictionary for Regulatory Activities (MedDRA), v22.0, and were assessed for severity using the Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Safety and AEs was summarized using descriptive statistics.[1]

No HRQoL or PRO outcomes were assessed during this study.

Database Cut-Off:

The database cut-off for the ASCERTAIN trial was March 19, 2019, representing a median follow-up of 155 days (5.1 months).[1,58]

Interim and Final Analyses:

No interim analyses were planned for this study. Two formal analyses were planned for this study. The first analysis was performed after all evaluable subjects had completed Cycles 1 and 2 and included analyses of all PK endpoints, and all available clinical response, TI, and safety data up to the data cutoff date of March 19, 2019. A second analysis will be performed after all subjects completed at least 6 months of follow up, or permanently discontinued treatment prior to 6 months of follow up from their first treatment dose.[1] The initial March 19, 2019 data cut, as well as an updated analysis with a data cut of [redacted] including longer term analysis of efficacy and safety data were provided to CADTH. Regular ongoing analyses are being conducted until median OS is reached, with the most recent periodic data cut in [redacted]).[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

An updated summary analysis was provided to CADTH by the sponsor based on an updated efficacy data cutoff of April 14, 2021 when the median OS was reached. Only OS and AMLFS/LFS outcomes were provided.[6] Response and safety endpoints were not updated and are therefore not included. The methodology and analysis of the additional data cut follow that of the original CSR.

Power Calculation and Sample Size:

The sample size for this study was based on a primary endpoint analysis of 5-day AUC in the ASTX727-01 study which showed an estimate of intra-subject coefficient of variation of 0.5. A conservative coefficient of variation of 0.55 was chosen to calculate the sample size for the ASCERTAIN study. The total of 118 evaluable subjects planned for the primary analysis included in the 2 one-sided equivalence tests for the geometric mean ratio of decitabine and cedazuridine 5-day $AUC_{0\text{-}24}$ relative to IV decitabine 5-day

AUC_{0-24} was to provide 90% power at the statistical significance level of 0.05, when the true ratio of geometric means is 1.0, the coefficient of variation under an unlogged scale is 0.55, and the 90% CI equivalence limits for the ratio of geometric means are 0.80 and 1.25. Assuming 10% of subjects may not be evaluable for PK assessments in Cycles 1 and 2, approximately 132 subjects were planned to be randomized.[1]

No secondary efficacy endpoints, which are of primary interest for this review, were controlled for multiplicity, nor were they used in the calculation of sample size.

Protocol Amendments:

A total of two regional trial protocol amendments occurred, which are summarized in Table 11. Neither of the protocol amendments were believed to affect subject safety or scope of the study. At the time of the March 19, 2019 data cutoff, all patients had been enrolled under the original version of the protocol. The protocol was amended once more on December 10, 2019 to enroll an additional 70 patients in the European Union with AML. As of the March 19, 2019 data cutoff, no subjects were enrolled under that amendment.[1] It is worth noting that AML patients are included in the IV decitabine label in the European Union.[61]

Table 11: Summary of Protocol Amendments in the ASCERTAIN Trial

Amendment Number (Date) No. Patients recruited	Changes Made in the Amendment
Amendment 1.1 (not implemented; 18 January 2018) **0**	• Removed statement in Section 9.6 Missed Evaluations per request from Health Canada: "If rescheduling becomes, in the investigator's opinion, medically unnecessary because the evaluation would occur too close to the next scheduled evaluation, it may be omitted." • Removed statement in Section 14.1.3 Ongoing Communication of Safety information During the Study per request from Health Canada: "This does not include safety issues that could be mitigated by simple changes in the protocol decided by the SSC…such as limiting the eligibility criteria or reducing the decitabine and cedazuridine dose or dosing schedule."
Amendment 1.2 (22 May 2018) **23**	Per request from Health Canada: • Clarified that the decitabine and cedazuridine tablet will be given by mouth. • Added text to distinguish between the decitabine and cedazuridine tablet formulations used in Phase 2 and Phase 3 (referencing nonclinical study Bioduro Study Report APL-FFS-PK-20170522-01 to indicate similarity). • Clarified that pregnancy is to be reported up to 90 days after the last dose. • Text added to indicate the Sponsor shall maintain study records for up to 25 years

Source: Clinical Study Report[1]

Fifteen protocol deviations occurred, of which none were believed to affect the study outcomes or conclusions, the majority of which were related to study procedures and missing or uncollected PK/PD samples. Protocol deviations are summarized in Table 12. Upon review of potentially important protocol deviations by the CADTH Methods Team, none were considered to have a significant impact on study outcomes or conclusions.

Table 12: ASCERTAIN Important Protocol Deviations by Subject

Subject No.	Deviation Category	Deviation Description
202-014	Study Procedures	C2D5 IV decitabine end of infusion (EOI) and EOI 5±1 min PK blood draws were missed due to difficulty placing the line. Day 5 data not used.
202-018	Study Procedures	C2D1 IV decitabine EOI infusion PK sample not collected, 5 min EOI PK sample not collected.
208-013	Study Procedures	C2D8 blood draw for *LINE-1* methylation missed.
210-001	Study Drug Administration	94 mL of decitabine was administered rather than 108 mL.
217-003	Study Procedures	C2D4 PK blood samples not collected.
219-002	Eligibility Criteria	1 cycle of azacitidine taken prior to enrollment with 27-day washout period prior to dosing (protocol required minimum 28-day washout) (Exclusion Criterion #4).
223-002	Safety	SAE (AE#1 myocardial infarction – not related) not reported to Astex Drug Safety within 24 hr.
226-004	Study Procedures	C2D5 4-hr, 6-hr, and 8-hr PK blood samples not collected.
227-001	Safety	SAE (AE#2 febrile neutropenia – related to ASTX727) not reported to Astex Drug safety within 24 hr.
228-001	Study Procedures	C1D1 end of infusion and 0.25 hr post IV infusion samples not collected.
228-003	Study Procedures	C1D1 1 hr sample missing. C1D5 0.5 hr sample missing.
234-001	Study Procedures	C2D3 EOI PK sample not drawn.
314-003	Study Procedures	C2D5 30 min post-dose PK sample drawn but misplaced in the lab.
317-001	Safety	SAE (AE#6 febrile neutropenia – related to ASTX727) not reported to Astex Drug Safety within 24 hr.
317-002	Eligibility Criteria	Hospitalization for suspected febrile neutropenia for more than 2 days within 30 days of screening (Exclusion Criterion #2).

Source: Clinical Study Report[1]

Funding:

The ASCERTAIN trial was funded by Astex Pharmaceuticals, Inc. The primary publication of the trial is anticipated in Q3 2021 after median OS is reached.[62] The role of the funder in relation to the conduct and reporting of the trial was not reported.

ASTX727-01-B Trial

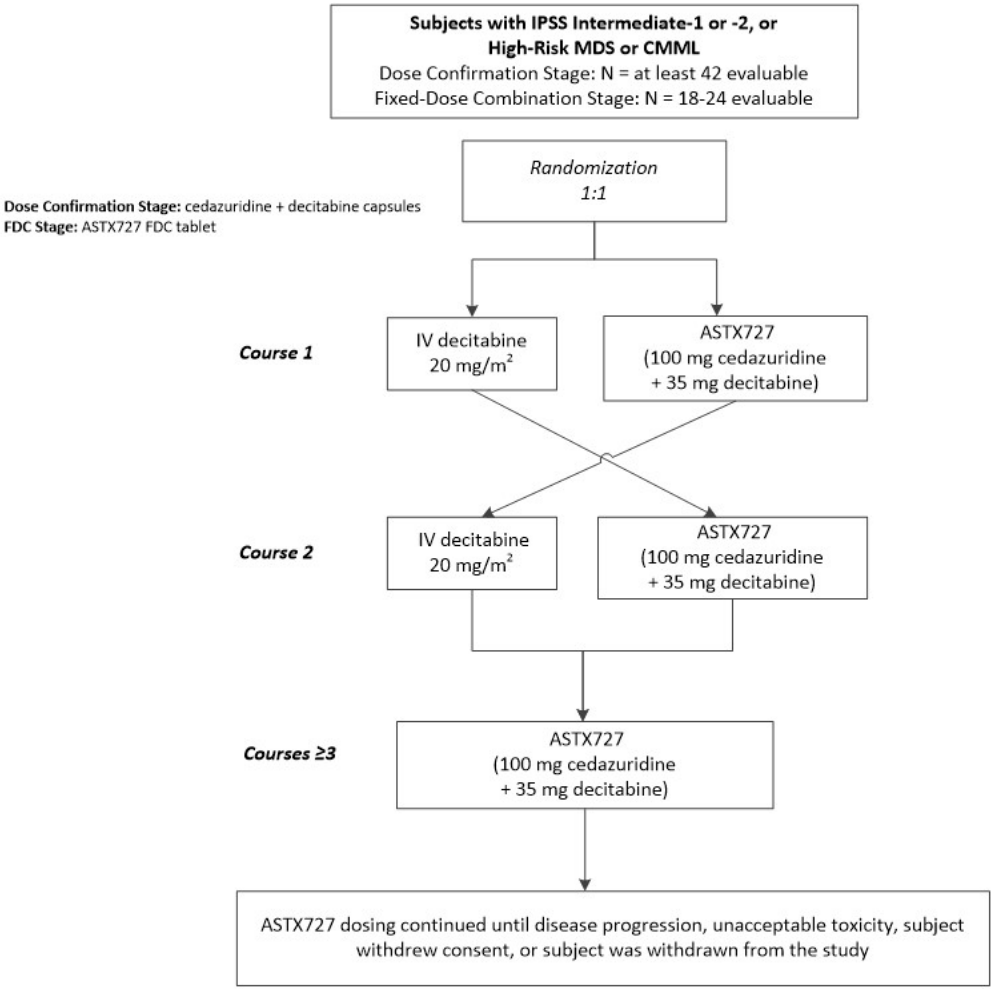
Screening, Eligibility Criteria, and Randomization

ASTX727-01-B was a two-phased international, randomized, phase I and II, two-cycle, two-sequence crossover trial that evaluated the pharmacokinetics, pharmacodynamics of DNA demethylation, and safety of either sequence of oral decitabine and cedazuridine followed by IV decitabine or IV decitabine followed by decitabine and cedazuridine in the first two randomized treatment cycles, and then to assess the long-term efficacy and safety of oral decitabine and cedazuridine after long-term treatment with the oral drug as a single arm.[9] The trial was conducted in 17 sites in two countries, including four sites in Canada, from which 16 patients were treated (Alberta = 2; Ontario = 10; Quebec = 4).[59]

The design of ASTX727-01-B is depicted in Figure 3, and key eligibility criteria are outlined. Briefly, eligible patients included adults (≥ 18 years), with IPSS intermediate-1, intermediate-2- or high-risk MDS, or CMML, ECOG performance status 0 to 2, and no evidence of active second malignancy. One prior cycle of either decitabine or azacitidine was allowed, but no other cytotoxic chemotherapy was permitted within 2 weeks of starting study treatment. Patients with prior allo-HSCT were eligible if they were free of GVHD and off immunosuppressive therapy at the time of enrollment.[9,10]

Eligible patients were randomized 1:1 to receive one of two treatment sequences during the first two 28-day cycles: oral decitabine and cedazuridine (35 mg/100 mg) daily for 5 days in cycle 1, followed by IV decitabine (20 mg/m^2) daily for 5 days in cycle 2 (sequence A); or IV decitabine (20 mg/m^2) in cycle 1, followed by the oral decitabine and cedazuridine (35 mg/100 mg) in cycle 2 (sequence B). Subjects were stratified according to IPSS risk level. Patients with CMML were randomized to the IPSS intermediate-2/high-risk category. In a first DC stage, patients received oral decitabine and oral cedazuridine as separate capsules. After preliminary PK analyses in this cohort showed comparable decitabine exposure of oral and IV decitabine, a second cohort was randomized to either sequence A or B using the FDC tablet containing the two drugs at the same doses (FDC stage). Cycles were repeated every 28 days. All patients received oral treatment from cycle 3 onwards.[9]

Figure 3: Study Design of the ASTX727-01-B Trial



Source: Clinical Study Report[2]

Study Endpoints and Statistical Analyses

Analysis Set(s):

Multiple analysis sets were used in the ASTX727-01-B trial, depending on the outcome evaluated. The All Subject Analysis Set included all randomized (enrolled) subjects, including those who did not receive any study treatment. This analysis set was only used for analysis of subject disposition.[2]

For the primary endpoint, the Primary PK Analysis Set (primary paired population) included all randomized subjects who received two courses of treatment and who had sufficient plasma concentration data to allow AUC_{0-t} determination for each treatment course. As an additional sensitivity analysis, all subjects with available oral or IV course data (not necessarily matched or paired) were included (unpaired analysis).[2]

The Efficacy and Safety Analysis Sets contained all randomized subjects who received any amount of study treatment,[9] and was used for all efficacy and safety related outcomes. No data exclusion was permitted due to protocol deviations in the Efficacy and Safety Analysis Sets.[2]

Study Endpoints and Statistical Analyses:

The primary endpoints of the phase II ASTX727-01-B study included:

- **Oral/IV Decitabine 5-day AUC:** Oral/IV decitabine exposure over 5 days was the primary endpoint for this phase II study, as assessed by 5-day decitabine AUC at various timepoints.[9] Analysis of Variance was performed on natural log-transformed decitabine 5-day AUC_{last}. Secondary AUC analyses were also conducted from time 0 to 24 hours post-dose and to infinity were also performed for all patients who received ≥1 cycle of treatments.[2]
- **Response Rate:** Response rates were defined by the IWG 2006 MDS Response Criteria (see Table 10),[3] and assessed by independent medical monitors by review of peripheral blood and bone marrow. Subjects were counted only once for best response according to the following hierarchy: CR, PR, mCR, and any HI.[2,9]

Secondary study endpoints included:

- **Duration of Response:** DOR was assessed using the Kaplan-Meier method for calculating DOR only for responders, separately for CR, PR, mCR, and for overall best response (CR, PR, and mCR combined) from the first time a response category (CR, PR, and mCR) was initiated to the date of disease progression which was defined as the earliest date of death or end of response (AML conversion, disease progression date, last treatment date, or study exit date). In the absence of progressive disease, subjects were censored on the last date of disease assessment.[2]
- **RBC/platelet TI:** Transfusion independence was defined as no transfusion for 56 consecutive days or more after treatment.[2] Patients were defined as transfusion dependent at baseline if there was documentation of 2 units or more of transfusion within 56 days of the first study treatment. [2]
- **Time to AML:** Time to AML was defined as the number of days from the date the subject received the first dose of study treatment to the date of MDS progression to AML as defined by greater than or equal to20% blasts in bone marrow (based on first date recorded) or peripheral blood (based on date of second consecutive record) or death from any cause. The event date of time to AML was based on the earlier of the date of death or conversion to AML. Subjects without a time to AML event as described above were censored on the date of last contact.[2]
- **Overall Survival:** OS was defined as the number of days from the date the subject received the first dose of study treatment to the date of death (regardless of cause). Subjects without documentation of death were censored on the last date of contact or the last date subject was confirmed alive, whichever was later. Overall survival was assessed using the Kaplan-Meier method. [2]
- **Safety:** Safety was assessed by subject-reported and investigator-observed AEs, along with physical examination, electrocardiogram, and clinical laboratory tests. Adverse events were reported using the CTCAE v4.0.[9]

No HRQoL or patient reported outcomes were assessed in the ASTX727-01-B study.

Database Cut-off:

The database cut-off for the ASTX727-01-B trial was 05 June 2018, representing a 24.3-month follow-up (range: 12.0-29.2).[9,58]

Interim and Final Analyses:

No interim analyses were planned for this study. Final analyses were performed following database lock.[2]

Power Calculation and Sample Size:

Sample size was estimated separately for the DC and FDC stages. The target sample size was based on an equivalence test of the mean decitabine 5-day AUC of oral decitabine and cedazuridine vs. IV decitabine using two one-sided tests on data from the 2-cycle,

2-sequence crossover design. For the DC cohort, a target enrollment of 42 patients was calculated to achieve 86% power at a 10% significance level when the true ratio of the means was 1.0, the coefficient of variation on the original scale was 0.5, and the equivalence limits of the mean ratio were 0.75 and 1.33. For the FDC cohort, the target sample size of 18 to 24 evaluable patients was calculated to provide 75% to 88% power at a 10% significance level when the true ratio of the means was 1.0, the coefficient of variation on the original scale was 0.55, and the equivalence limits for the ratio of means were 0.65 and 1.539. In the DC and FDC cohorts, approximately 50 and 30 patients were allowed to be treated to compensate for non-evaluable patients in the preliminary PK analyses. Equivalence between DC and FDC treatments was achieved if the ratio of the geometric LSM and its 80% CI were fully contained within the prespecified CI limits of 75 to 133 in the dose-confirmation cohort and 65 to 153.9 in the FDC cohort.[9]

Protocol Amendments:

A total of four protocol amendments occurred and are summarized in Table 13. Nine subjects were enrolled under the original protocol.[2]

Table 13: Summary of Amendments in the ASTX727-01-B Trial

Amendment Number (Date) No. Patients recruited	Changes Made in the Amendment
Amendment 1 (November 24, 2014) **35**	• Modified Phase 1 study design from 6+6 to 3+3 to allow earlier dose escalation (applicable only to Phase 1). • Eliminated requirement for hematology assessments on Days 2-5 in Courses 1 and 2, to reduce burden of assessments.
Amendment 2 (September 23, 2015) **53**	• Added PK assessments on Days 2, 3, and 4 during oral decitabine and cedazuridine course in DC Stage to estimate PK over 5 dosing days. • Added content of administrative letters #2, #3, #4.
Amendment 3 (July26, 2016) **33**	• Added FDC stage to confirm FDC tablet formulation yields PK and PD data similar to data for IV decitabine and to gather additional efficacy and safety data with the FDC. • Added content of administrative letter #5.
Amendment 4 (April 6, 2017) **0**	• Require transition of long-term ongoing subjects in DC Stage from cedazuridine and oral decitabine capsules to the FDC tablet. • Added content of administrative letter #6.

DC = dose-confirmation; FDC = fixed dose combination; PD = pharmacodynamic; PK = pharmacokinetic.
Source: Clinical Study Report[2]

Astex noted six important protocol deviations that were considered to potentially affect subject safety or the primary study endpoint.[2] Upon review of potentially important protocol deviations by the CADTH Methods Team, none were considered to have a significant impact on study outcomes or conclusions.

Funding:

The trial was funded by Astex Pharmaceuticals, Inc. Two authors were directly employed by the sponsor and did not contribute to the collection of data. A total of seven other authors disclosed conflicts of interest as reported support from the sponsor in the form of research funding, honoraria, and consulting or advisory fees. Medical writing and editorial assistance were provided by BioScience Communications and were funded by Astex.[9]

b) Populations

ASCERTAIN Trial

The Efficacy/Safety Analysis Set (all treated subjects) was used to summarize the baseline characteristics of patients included in the ASCERTAIN trial and are shown in Table 14 below. A total of 133 patients were randomized to either Sequence A (oral decitabine and cedazuridine followed by IV decitabine; n=66) or Sequence B (IV decitabine followed by oral decitabine and cedazuridine; n=67). Baseline characteristics were generally balanced between treatment sequences. The median age of patients in the trial was 71 years (range = 44 to 88), and greater than half of patients were male (65%), with the majority of subjects of Caucasian ethnicity (91%). The majority of subjects overall had an ECOG PS of 1 (58.6% overall; 62.1% vs 55.2% in Sequence A and B, respectively). No body weight or BSA limitations were placed on subject eligibility in this trial. As such, the median body weight was 83.1 kg (range = 45 to 158).

There was a notably lower representation of CMML patients in the Sequence A cohort compared to Sequence B (7.6% vs 16.4%), and a noticeably higher representation of IPSS high-risk patients in Sequence A compared to Sequence B (21.2% vs 10.4%). Overall, the median time since diagnosis was 83 days, however, was numerically different between groups (48 days vs 144 days in Sequence A and B, respectively). No patients had received prior HSCT, and the majority of patients had not received prior anticancer therapy, nor prior HMA, as per the inclusion criteria of the study. Rates were similar between treatment sequences with 21.2% vs. 23.9% of patients in Sequences A and B receiving prior anticancer therapy. Prior HMA therapy consisting of one cycle of decitabine or azacitidine was only received by 6 (4.5%) and 4 (3%) of patients overall, respectively. The proportion of patients eligible for HSCT at baseline was not reported.

Following medical review of the study data at the April 14, 2021 data cutoff, changes were made to the baseline IPSS categorization. Some patients were originally misclassified due to some sites use of the IPSS-R (vs IPSS). Six patients from the low-risk group were reclassified, five to the intermediate-1 group, and one to the intermediate-2 group. The total number of patients in each IPSS risk group was 5, 64, 27, 21, and 16 in the low-risk, intermediate-1, intermediate-2, high-risk, and CMML groups, respectively.[6] The low-risk population was not of interest for this review.

Table 14: Demographic and Baseline Characteristics of the ASCERTAIN Trial (Efficacy/Safety Analysis Set)

Baseline Characteristic	Sequence A (n=66)	Sequence B (n=67)	Total (n=133)
Age (years)			
Mean (SD)	68.7 (10.22)	70.7 (8.40)	69.7 (9.37)
Median (range)	70 (44-85)	72 (49-88)	71 (44-88)
18 – 64	21 (31.8)	15 (22.4)	36 (27.1)
65 – 84	43 (65.2)	50 (74.6)	93 (69.9)
≥85	2 (3.0)	2 (3.0)	4 (3.0)
Sex			
Male	42 (63.6)	45 (67.2)	87 (65.4)
Female	24 (36.4)	22 (32.8)	46 (34.6)
Race			
White	60 (90.9)	61 (91.0)	121 (91.0)
Black/African American	1 (1.5)	3 (4.5)	4 (3.0)
Asian	2 (3.0)	1 (1.5)	3 (2.3)
Not Reported	3 (4.5)	2 (3.0)	5 (3.8)
Body Weight (kg)			
Mean (SD)	82.30 (19.175)	85.15 (18.154)	83.74 (18.652)
Median (range)	79.20 (45-157.9)	84.81 (50.5-127.4)	83.10 (45-157.9)
BSA (m^2)			
Mean (SD)	1.96 (0.253)	2 (0.254)	1.98 (0.253)
Median (range)	1.93 (1.45-2.9)	2.02 (1.5-2.6)	1.99 (1.4-2.9)
ECOG PS			

Baseline Characteristic	Sequence A (n=66)	Sequence B (n=67)	Total (n=133)
0	25 (37.9)	30 (44.8)	55 (41.4)
1	41 (62.1)	37 (55.2)	78 (58.6)
IPSS Classification*			
Low Risk	4 (6.1)	7 (10.4)	11 (8.3)
Int-1	29 (43.9)	30 (44.8)	59 (44.4)
Int-2	14 (21.2)	12 (17.9)	26 (19.5)
High Risk	14 (21.2)	7 (10.4)	21 (15.8)
Transfusion Dependence			
RBCs	26 (39.4)	26 (38.8)	52 (39.1)
Platelets	6 (9.1)	4 (6.0)	10 (7.5)
Disease			
MDS	61 (92.4)	56 (83.6)	117 (88.0)
CMML	5 (7.6)	11 (16.4)	16 (12.0)
Time Since Diagnosis (Days)			
Median (Range)	48.0 (5-5,606)	144.0 (11-5,550)	83.0 (5-5,606)
Mean (SD)	444.8 (1002.54)	651.5 (1109.85)	548.9 (1059.04)
Bone Marrow Blasts (%)			
Mean (SD)	6.0 (4.80)	5.9 (4.19)	6.0 (4.48)
Median (Range)	4.5 (0-19)	5.0 (1-18)	5.0 (0-19)
>5% Bone Marrow Blasts	26 (42.6)	27 (41.5)	53 (42.1)
Prior Anticancer Therapy			
Yes	14 (21.2)	16 (23.9)	30 (22.6)
No	52 (78.8)	51 (76.1)	103 (77.4)
Prior HMA Therapy			
Prior azacitidine	3 (4.5)	3 (4.5)	6 (4.5)
Prior decitabine	3 (4.5)	1 (1.5)	4 (3.0)

CMML = chronic myelomonocytic leukemia; ECOG = Eastern Cooperative Oncology Group; IPSS = International Prognostic Scoring System; MDS = myelodysplastic syndrome; PS = performance status; RBC = red blood cell

NOTE: Data are n (%) unless otherwise specified

*CMML patients not included, and low risk patients were eligible according to the FAB classification criteria in the decitabine label

Source: Garcia-Manero 2019[7]; Clinical Study Report[1]; ASTX727 Efficacy Update[5]

Study ASTX727-01-B

Demographic and baseline characteristics based on the efficacy and safety analysis sets of patients included in the ASTX727-01-B trial are summarized in Table 15. A total of 80 patients were randomized and treated in the Efficacy/Safety Analysis set (52 to the DC cohort, and 34 to the FDC cohort).[9] Baseline characteristics were generally balanced across the randomized treatment sequences in each cohort. The median age of all participants was 71 years, and the majority were male (76%), of Caucasian ethnicity (93%), and most subjects had an ECOG performance status of 0 (44%) or 1 (48%), however, a greater proportion of subjects in Sequence A were ECOG PS 0 (48.8% vs. 38.5%), while a greater proportion of patients in Sequence B were ECOG 1 (51.3% vs. 43.9%). A total of 7 (9%) patients overall had ECOG performance status of 2. No exclusion criteria were applied to weight, therefore a wide range of body weight and BSA were included, however patients in Sequence A had a numerically lower median body weight than those in Sequence B (78.8 kg vs. 86.2 kg).[2] Almost half (48%) of all patients were RBC transfusion dependent at baseline. The majority of patients were IPSS intermediate-1 risk (44%), while 24% were intermediate-2, and 11% and 21% were high-risk and CMML, respectively. The FDC cohort had a higher proportion of patients who were intermediate-1 (50% vs. 40%) and CMML (27% vs. 18%) but had fewer high-risk patients than the DC cohort (3% vs. 16%). No patients were IPSS high-risk in Sequence B of the FDC cohort.

Table 15: Demographic and Baseline Characteristics of the ASTX727-01-B Trial, Efficacy/Safety Analysis Set

Characteristic	DC Cohort			FDC Cohort			Phase 2 Overall		
	Sequence A (n = 25)	Sequence B (n = 25)	Total (n = 50)	Sequence A (n = 16)	Sequence B (n = 14)	Total (n = 30)	Sequence A (n = 41)	Sequence B (n = 39)	Total (n = 80)
Age									
Mean (SD)	69.3 (11.2)	70.2 (10.5)	69.7 (10.7)	69.9 (12.1)	69.4 (9.0)	69.6 (10.6)	69.5 (11.38)	69.9 (9.85)	69.7 (10.6)
Median (range)	69 (32-87)	72 (41-86)	71.5 (32-87)	71 (40-90)	70 (53-82)	70.5 (40-90)	71 (32-90)	71 (41-86)	71 (32-90)
Sex									
Male	20 (80)	21 (84)	41 (82)	12 (75)	8 (57)	20 (67)	32 (78.0%)	29 (74.4%)	61 (76)
Female	5 (20)	4 (16)	9 (18)	4 (25)	6 (43)	10 (33)	9 (22.0%)	10 (25.6%)	19 (24)
Ethnic Origin									
White	24 (96)	22 (88)	46 (92)	14 (88)	14 (100)	28 (93)	38 (92.7%)	36 (92.3%)	74 (93)
Black/African American	1 (4)	1 (4)	2 (4)	0 (0)	0 (0)	0 (0)	1 (2.4%)	1 (2.6%)	2 (2.5)
Other	0 (0)	2 (8)	2 (4)	2 (12)	0 (0)	2 (7)	2 (4.9%)	2 (5.1%)	4 (5)
Body Weight (kg)									
Median (range)	82 (40-122)	87 (55-118)	85 (40-122)	76 (49-100)	83 (42-98)	80 (42-100)	78.8 (40-122)	86.20 (42-118)	83 (40-122)
BSA (m^2)									
Mean (SD)	1.9 (0.3)	2.0 (0.2)	2.0 (0.3)	1.9 (0.2)	1.9 (0.3)	1.9 (0.2)	1.92 (0.26)	1.99 (0.23)	1.95 (0.25)
ECOG PS									
0	13 (52)	9 (36)	22 (44)	7 (44)	6 (43)	13 (43)	20 (48.8%)	15 (38.5%)	35 (44)
1	9 (36)	15 (60)	24 (48)	9 (56)	5 (36)	14 (47)	18 (43.9%)	20 (51.3%)	38 (48)
2	3 (12)	1 (4)	4 (8)	0 (0)	3 (21)	3 (10)	3 (7.3%)	4 (10.3%)	7 (9)
Disease and IPSS Category									
MDS Intermediate-1	10 (40)	10 (40)	20 (40)	9 (56)	6 (43)	15 (50)	19 (46.3%)	16 (41.0%)	35 (44)
MDS Intermediate-2	6 (24)	7 (28)	13 (26)	3 (19)	3 (21)	6 (20)	9 (22.0%)	10 (25.6%)	19 (24)
MDS High-Risk	4 (16)	4 (16)	8 (16)	1 (6)	0 (0)	1 (3)	5 (12.2%)	4 (10.3%)	9 (11)
CMML	5 (20)	4 (16)	9 (18)	3 (19)	5 (36)	8 (27)	8 (19.5%)	9 (23.1%)	17 (21)
Transfusion Dependence									
RBCs	9 (36)	13 (52)	22 (44)	11 (69)	5 (36)	16 (53)	20 (48.8%)	18 (46.2%)	38 (48)
Platelets	4 (16)	3 (12)	7 (14)	4 (25)	1 (7)	5 (17)	8 (19.5%)	4 (10.3%)	12 (15)
Bone Marrow Blasts (%)									
Mean (SD)	7.9 (5.73)	7.6 (5.69)	7.7 (5.65)	5.9 (3.27)	5.4 (3.28)	5.7 (3.23)	7.1 (4.95)	6.8 (5.02)	7.0 (4.95)
Median (Range)	7.0 (0-19)	9.0 (0-17)	7.5 (0-19)	6.0 (0-12)	4.8 (1-12)	5.0 (0-12)	7.0 (0-19)	5.0 (0-17)	6.0 (0-19)
>5% Bone Marrow Blasts	14 (60.9)	14 (56)	28 (58.3)	8 (53.3)	5 (35.7)	13 (44.8)	22 (57.9%)	19 (48.7%)	41 (53.2)
Prior HMA Therapy (n)									
Prior azacitidine	2	0	2	1	1	2	3	1	4
Prior decitabine	0	1	1	0	2	2	0	3	3

BSA = body surface area; DC = dose confirmation; FDC = fixed dose combination; ECOG = Eastern Cooperative Oncology Group; IPSS = International Prognostic Scoring System; RBC = red blood cell

Data are n (%) unless otherwise specified

Source: Garcia-Manero 2020[9]; Clinical Study Report[2]

c) Interventions

ASCERTAIN Trial

Treatment Dosing Schedule

Patients were randomized to one of two treatment sequences for the first two treatment cycles: fixed-dose oral decitabine and cedazuridine 35 mg/100 mg in Cycle 1 followed by crossover to 20 mg/m^2 of IV decitabine in Cycle 2 (Sequence A), or 20 mg/m^2 of IV decitabine in Cycle 1 followed by decitabine and cedazuridine 35 mg/100 mg in Cycle 2 (Sequence B).[7] IV decitabine was delivered by continuous 1-hour infusion based on BSA in accordance with the 5-day regimen in the US prescribing information.[60] Both treatments were administered daily for five days at the beginning of each 28-day cycle at the study center. All patients received oral decitabine and cedazuridine from Cycle 3 onwards until disease progression (requiring alternative therapy), unacceptable toxicity, treatment discontinuation or study withdrawal.[58] Of the 133 subjects dosed, 129 (97%) received at least 2 cycles of treatment. At the time of the March 19, 2019 data cut off, [redacted] while at the [redacted] data cutoff, patients received a median of 8 cycles of treatment (range = 1 to 18),[4] [redacted].[1,5,8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Dose Modifications, Interruptions, or Reductions

Dose reductions were not permitted in Cycles 1 or 2 for either oral decitabine and cedazuridine or IV decitabine. If a dose reduction was required in Cycle 3 or beyond, the number of dosing days in the cycle was decreased. Dose delays were permitted for up to 2 weeks for recovery of blood counts. Subjects were instructed to fast from food and non-clear liquids at least two hours before and after dosing with decitabine and cedazuridine. No dietary restrictions were in place for the IV decitabine cycles.[1]

[redacted][1] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Concomitant Therapies

Subjects were instructed not to take drugs that might alter gastric pH, such as antacids, proton pump inhibitors, or H_2 antagonists, within 4 hours of oral decitabine and cedazuridine. Investigators were permitted to perform diagnostic testing and to prescribe supportive treatment(s) at their discretion, including blood and platelet transfusions, and treatment for infection. Antibiotics were permitted to prevent or manage febrile neutropenia according to institutional standard practice. Short-term use of G-CSF for febrile neutropenia was permitted at the discretion of the treating physician. In addition to growth factors, and anti-infective treatments, other concomitant medications of special interest included anti-emetics, and hydroxyurea given to reduce high counts during study treatment and not as part of a subsequent anti-leukemia treatment, as well as chemotherapy, immunotherapy, or any experimental therapy.[1]

Study ASTX727-01-B

Treatments

Patients were randomized to receive either oral decitabine and cedazuridine (35 mg/100 mg) daily for 5 days in cycle 1, followed by crossover to IV decitabine (20 mg/m^2) daily for 5 days in cycle 2 (sequence A); or IV decitabine (20 mg/m^2) in cycle 1, followed by crossover to oral decitabine and cedazuridine (35 mg/100 mg) in cycle 2 (sequence B). Cycles were repeated every 28 days. All

patients received oral treatment from Cycle 3 onwards. Patients received a median of 7 treatment cycles (range = 1 to 29),[9] which was greater than the ASCERTAIN trial, however the ASCERTAIN trial is still ongoing and only had 5.1 months follow up at the March 19, 2019 data cut off.

Dose Modifications, Interruptions, or Reductions

Dose reduction was not permitted in the first 2 cycles but was permitted from cycle 3 onwards by reducing the number of days of oral treatment. Dose delay at the discretion of the investigator was permitted to allow for count recovery in case of drug-related myelosuppression.[9] Dose reductions in the DC stage were accomplished by reducing the dose of decitabine while maintaining cedazuridine at 100 mg/dose and retaining the 5-day schedule. Conversely, dose reductions in the FDC stage/cohort were accomplished by reducing the number of days the FDC tablet was administered in the schedule.[2]

All patients received treatment until disease progression, unacceptable toxicity, or withdrawal by patient or investigator for other reasons. Subjects were instructed to fast from food and non-clear liquids at least two hours before and after dosing with decitabine and cedazuridine. No dietary restrictions were in place for the IV decitabine cycles. Overall, 32 patients (40%) had one or more dose reductions and 41 patients (51%) had one or more cycles delayed.[9]

Concomitant Therapies

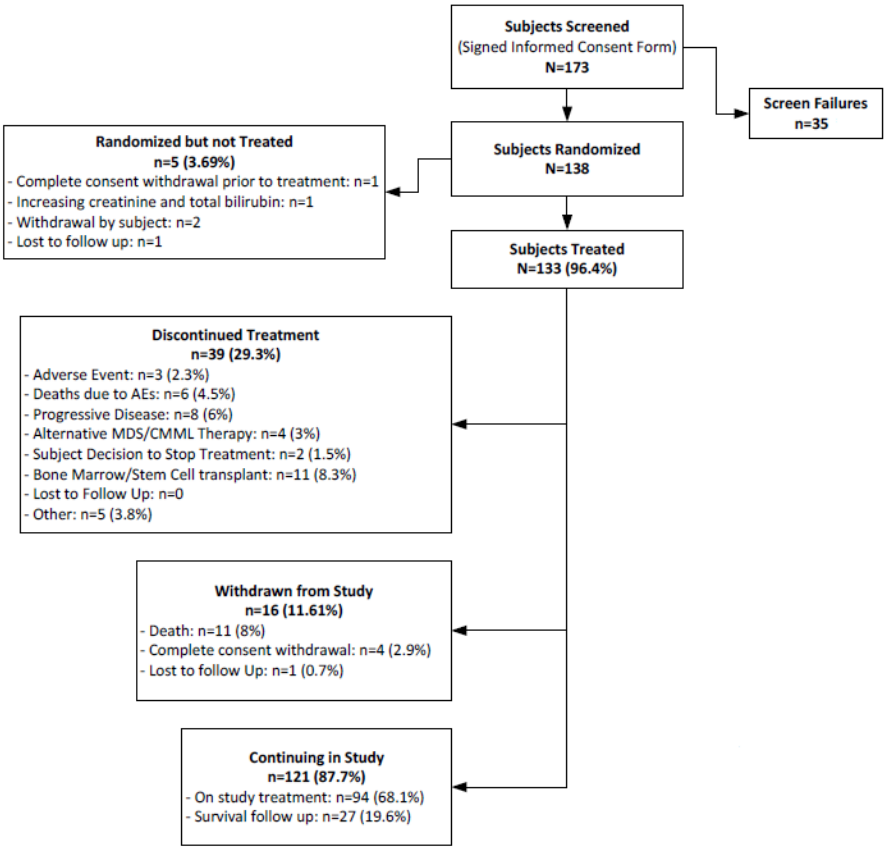
Supportive treatments including hydration, antiemetics, blood and platelet transfusions were permitted at investigator discretion and according to study center standards. Antibiotics were permitted to prevent or manage septic events. Short-term use of growth factors was not to be routinely used but were permitted at the discretion of the treating physician.[2]

d) Patient Disposition

ASCERTAIN Trial

The patient disposition for the ASCERTAIN trial is presented in Figure 4. A total of 173 subjects were screened for participation, of which 35 (20%) failed screening. The main reasons for screening failure were patients not candidates for IV decitabine (n = 14), and inability to understand and comply with study procedures (n = 9).[8] The remaining 138 patients were randomized to a treatment sequence (N=69 each to Sequence A and Sequence B). Five of these patients did not receive study treatment, resulting in a total of 66 patients in sequence A, and 67 patients in Sequence B. As of the data cutoff date (19 March 2019), 87.7% of patients were continuing the study, with 68.1% still receiving study treatment, and almost 20% of patients had entered the follow-up and were off study treatment. The follow up time ranged from 57 to 397 days, with a median follow up of 155 days (5.1 months).[1] [redacted]. Other reasons for treatment discontinuation are outlined in Figure 4 below. [redacted][1] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Figure 4: Patient Disposition in the ASCERTAIN Trial



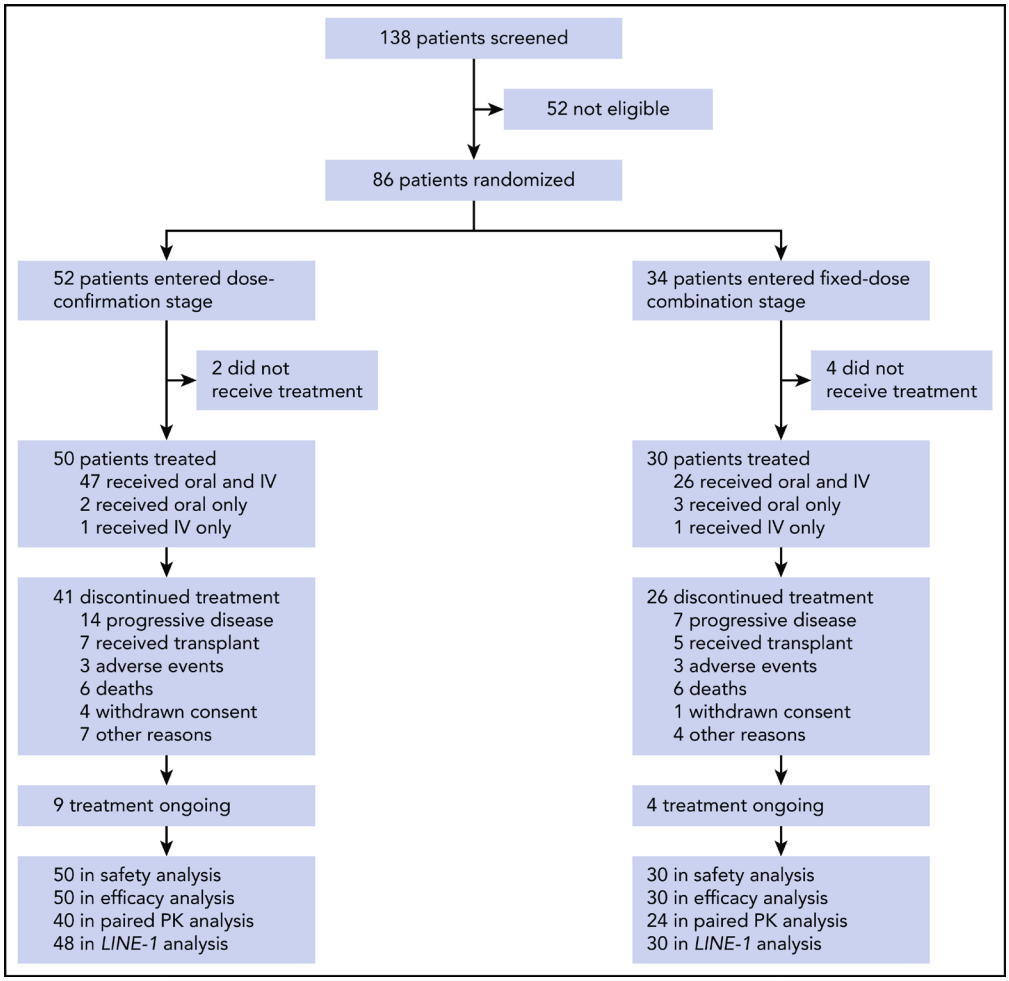
AE = adverse event; CMML = chronic myelomonocytic leukemia; MDS = myelodysplastic syndromes.
Source: Clinical Study Report[1]

Study ASTX727-01-B

The patient disposition for the ASTX727-01-B trial is presented in Figure 5. Screening of 138 patients identified 52 ineligible subjects. The main reasons for ineligibility were inability to understand and comply with study procedures (n = 15), not candidates for HMAs in the dose escalation stage (n = 15), and diagnosis of AML (n = 11).[8] A total of 86 patients were randomized, including 52 into the DC cohort, and 34 into the FDC cohort. Of the 86 randomized, only 80 were treated, as two patients in the DC cohort, and four patients in the FDC cohorts did not receive any study treatment and were excluded from all analyses. Reasons randomized patients did not receive their assigned treatment sequence included misdiagnosis (n=1), ineligibility due to elevated liver enzymes (n=2), progressive disease (n=1), death (n=1), and withdrawal of consent prior to treatment initiation (n=1). A total of 50 patients were included in the DC cohort (n=25 in sequence A, and n=25 in sequence B), while 30 patients were included in the FDC cohort (n=16 in sequence A, and n=14 in sequence B). Overall, 41 patients were randomized to receive treatment sequence A (oral decitabine and cedazuridine in cycle 1, followed by crossover to IV decitabine daily for 5 days in cycle 2), and 39 were randomized to treatment sequence B (IV decitabine in cycle 1, followed by crossover to oral decitabine and cedazuridine in cycle 2).[9]

At data cutoff (June 5, 2018), 67 patients had discontinued treatment (n=41 [82%] in the DC cohort; n=26 [86.7%] in the FDC cohort), with a similar proportion remaining on treatment (n=13; 9 [18%] and 4 [13%] patients in the DC and FDC cohorts, respectively). The primary reason for treatment discontinuation in both groups was disease progression (14 [28%] and 7 [23.3%] in the DC, and FDC cohorts, respectively). Twelve patients (15%) overall discontinued treatment for stem cell transplant. All patients that received treatment were included in the efficacy and safety analyses.[9]

Figure 5: Patient Disposition in the ASTX727-01-B Trial



DC = dose-confirmation; FDC = fixed-dose combination.

Source: Garcia-Manero 2020.[9] Reprinted from Blood, Vol 136(6), Garcia-Manero G, Griffiths EA, Steensma DP, et al., Oral cedazuridine/decitabine for MDS and CMML: a phase 2 pharmacokinetic/pharmacodynamic randomized crossover study, Pages 674-683, Copyright 2020, with permission from The American Society of Hematology.

e) Limitations/Sources of Bias

ASCERTAIN Trial

The ASCERTAIN trial is an ongoing study. Overall, there were no major concerns with the conduct of the ASCERTAIN trial. The design of the trial was appropriate given the aim of the study to examine the equivalence between oral decitabine and cedazuridine and IV decitabine. The crossover design fit the main objective and endpoint of the study (i.e., PK parameters), which did not require a large population to observe significant differences between treatments, however, there were no relevant comparators to assess comparative efficacy of decitabine and cedazuridine in the Canadian treatment landscape. Randomization was well conducted, and treatment assignments were determined through a computer-generated randomization schedule. The study protocol was approved by governing institutional review boards or ethics committees at each study center prior to implementation, and the study was conducted in accordance with the ICH Good Clinical Practice guidelines, and applicable regulatory requirements. Overall, the methods used to conduct the ASCERTAIN trial were considered acceptable, however, the CADTH Methods Team identified the following limitations and potential sources of bias that should be considered when interpreting the trial results:

- The ASCERTAIN trial used an open-label study design and therefore treatment assignment was unblinded. This study design has the potential for performance and detection biases in subjective outcomes, including safety and efficacy outcomes of response as awareness of treatment could result in overreporting of AEs by patients, probing by investigators, and delaying confirmation of progression, inflating response rates and LFS/OS. Detection bias was minimized by the IRC assessment for clinical response on the basis of quantifiable variables as per the 2006 IWG MDS Response Criteria.
- The ASCERTAIN trial employed a simple randomized crossover design. A frequent issue with crossover trials is the carryover effect. In the ASCERTAIN trial, the authors believe that no carryover of IV decitabine was expected due to the time to steady state of each drug. Additionally, the bias due to the carryover effect between Cycles 1 and 2 was reduced by presenting results separately by cycle for AEs to minimize the influence of the carryover effect. Time between dosing of each cycle was considered the washout period (i.e., days 6 to 28 of each cycle). Other than this, ASCERTAIN did not include any other washout period between cycles, and therefore sufficient time for carryover to disappear was not possible, which may have further diminished potential carryover effects.
- Paired analysis was only conducted for the primary endpoint using the primary PK population using ANOVA models that included treatment, period, and sequence as fixed effects, and subject nested in sequence as a random effect. Following crossover, since both treatment arms received decitabine and cedazuridine, the true efficacy and safety between IV decitabine and decitabine and cedazuridine cannot be confirmed although PK equivalence was demonstrated, suggesting there may be limited differences on these outcomes.
- The primary PK outcome of 5-day decitabine exposure is an appropriate and clinically relevant endpoint for determining equivalence between decitabine and cedazuridine and IV decitabine. ASCERTAIN was not designed to demonstrate superiority or non-inferiority to relevant comparators, or to compare efficacy or safety of decitabine and cedazuridine to IV decitabine. Therefore, efficacy outcomes, which are of primary interest alongside safety for this review, were assessed as secondary outcomes and were not controlled for multiplicity. The trial was not powered to test specific efficacy hypotheses, and sample size calculations were not based on establishing efficacy. Thus, efficacy outcomes should be interpreted as exploratory in nature.
- At the time of the first data analysis (database cutoff of March 19, 2019), the efficacy outcome data were immature [redacted], also resulting in preliminary data for important outcomes of clinical response [redacted] and transfusion independence. Overall interpretation of these outcomes is limited due to the short follow up time (median follow up of only 155 days [5.1 months]). A second analysis of efficacy endpoints was performed using all available data up to the data cutoff for the second analysis [redacted], in which all patients were evaluable for clinical response, however, this is believed to be too short for analysis of survival outcomes in this population. Thus, there is uncertainty in the reported efficacy outcomes of the ASCERTAIN trial. [redacted]

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

- [redacted]. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*
- HRQoL was not assessed in the ASCERTAIN trial, and therefore the impact of decitabine and cedazuridine on QoL remains unknown.
- Decitabine and cedazuridine was not compared to relevant comparators in the trial, and therefore there is a lack of direct comparison to relevant agents used to treat MDS such as azacitidine. The sponsor submitted an ITC, for intermediate-2 and high-risk which included some relevant comparators, however this did not include any comparative evidence for intermediate-1 or CMML populations (ESAs, RBC/ICT, lenalidomide, etc.), so comparative efficacy remains unknown for these patient groups (see Section 7 for further details).
- A total of [redacted] patients received [redacted] which may not be generalizable to the MDS population in Canada. [redacted].[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

ASTX727-01-B Trial

Overall, study ASTX727-01-B was a well conducted phase I/II study that had a sufficient length of follow-up for assessment of efficacy and safety outcomes (24.3 months). ASTX727-01-B was the first phase II study to demonstrate the equivalence of decitabine and cedazuridine with standard IV decitabine. The study protocol was approved by regional institutional review boards, and the study was conducted in accordance with Good Clinical Practice guidelines, local regulatory requirements, and ethical principles as per the Declaration of Helsinki.[9] The CADTH Methods Team did not identify any major concerns with the ASTX727-01-B study other than that it was a PK study, and therefore did not compare decitabine and cedazuridine to relevant treatments and did not have a primary focus on efficacy outcomes. Given the similar designs of the phase II ASTX727-01-B trial and phase III ASCERTAIN trial, the CADTH Methods Team identified very similar limitations and potential sources of bias for the ASTX727-01-B trial as the ASCERTAIN trial which should be considered when interpreting the trial results:

- The ASTX727-01-B trial was a crossover trial aimed at assessing equivalence of decitabine and cedazuridine and IV decitabine, and therefore no comparative evidence is available for decitabine and cedazuridine versus other relevant treatments.
- This was an open-label study, in which treatment assignment was not blinded for patients or investigators, increasing the risk of performance and detection biases. Awareness of treatment received by patients and investigators may result in overreporting of AEs by patients and probing by investigators if known or suspected to be related to the treatment and delaying confirmation of progression by the investigator thereby inflating response, and survival outcomes. Detection bias was minimized by the IRC assessment for clinical response on the basis of quantifiable variables as per the 2006 IWG MDS Response Criteria.
- Patients were randomized 1:1 to Sequence A or B, in either the DC stage where they received separate decitabine and cedazuridine capsules, or FDC stage where they received a single decitabine and cedazuridine tablet. Although the randomization method was adequately conducted, randomized numbers were not equal between DC and FDC cohorts, and the relatively small number of patients in the FDC cohort may have impacted the validity and reliability of the results.
- The DC stage of the study consisted of a different administration mode (multiple capsules, as opposed to a single formulation), which may impact adherence and proper dosing and is not the intended formulation as per the product monograph.[63] The direction of the effect in which this may impact results is unknown. Additionally, the efficacy outcomes of this study were pooled for the DC and FDC stages, which has the potential to influence study outcomes.
- Time between dosing of each cycle was considered the washout period (i.e., days 6 to 28 of each cycle) and the potential for carryover effects may influence the results in favour of the treatment received first.
- Paired analysis was only conducted for the primary endpoint using the primary PK population. Following crossover, since both treatment arms received decitabine and cedazuridine, the true efficacy and safety between IV decitabine and decitabine and cedazuridine cannot be confirmed although PK equivalence was demonstrated, suggesting there may be limited differences on these outcomes.
- The primary objective of the ASTX727-01-B trial was PK and sample size/power calculations were based on PK outcomes. Efficacy outcomes, critical to the review, were not controlled for multiplicity or considered for sample size calculations and thus, the study was not powered for these outcomes and the secondary results must be interpreted as exploratory.
- HRQoL was not assessed in the ASTX727-01-B trial, and therefore the impact of decitabine and cedazuridine on QoL remains unknown.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

ASCERTAIN Trial

Pre-specified efficacy and safety outcomes of interest for the systematic review (Table 8) included OS, clinical response (ORR, CR, mCR, PR), progression-free survival (PFS), HI, TI, HRQoL, time to AML, transplantation rate/HSCT, and safety (AEs, SAEs, WDAEs and deaths). Progression-free survival, and HRQoL were not evaluated in the ASCERTAIN trial. Transplantation rate was considered the proportion of patients who discontinued treatment for HSCT. In the absence of PFS, LFS was reported in the ASCERTAIN trial, which was deemed a relevant clinical outcome for this report.

Pharmacokinetic Outcomes

5-Day AUC

The primary endpoint of the ASCERTAIN study was 5-day decitabine exposure. Results of the primary analysis of the primary endpoint of decitabine AUC_{0-24} exposure equivalence were confirmed by paired and unpaired sensitivity and secondary analyses at

various timepoints. The Primary PK Analysis Set included 123 subjects in the paired primary population. A mixed-effect ANOVA model analysis was performed on the natural logarithm transformed (ln-transformed) 5-day cumulative AUC_{0-24} parameter for plasma decitabine from decitabine and cedazuridine vs IV decitabine 20 mg/m^2.[1]

Decitabine AUC results for the primary paired, and paired and unpaired sensitivity analyses are presented in Table 16 and Figure 6. The paired primary population included 123 patients; five less than the paired sensitivity analysis due to data quality issues.[1] The primary analysis shows that the 5-day AUC_{0-24} ratio of geometric LSM for oral decitabine and cedazuridine relative to IV decitabine was 98.93% (90% CI: 92.66, 105.6).[7] The two-sided 90% CI is contained entirely within the prespecified range of 0.80 to 1.25 for the primary analysis, indicating equivalent decitabine exposure between oral decitabine and cedazuridine and IV decitabine. Secondary analyses of 5-day AUC at various time points confirmed the results of the primary analysis of 5-day AUC_{0-24}.[7]

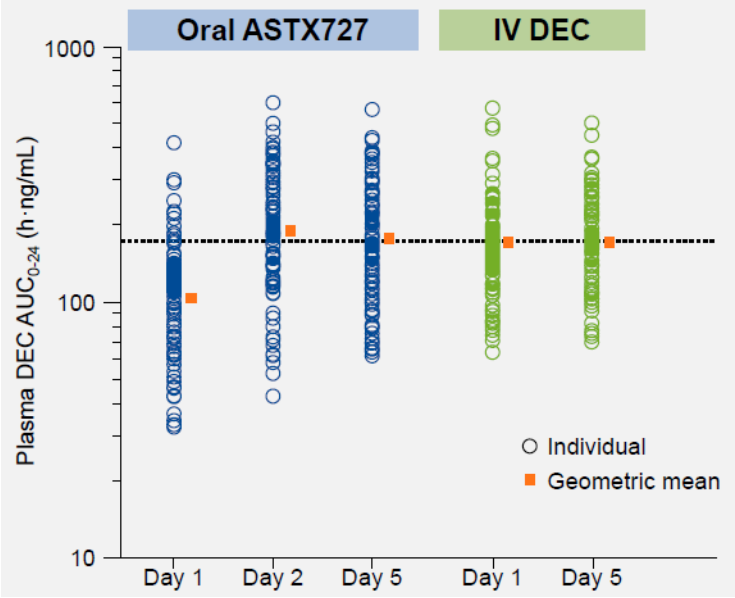
Table 16: 5-Day Decitabine AUC_{0-24} Equivalence Assessment (Primary Endpoint PK Analysis Set)

		AUC Parameter (h*ng/mL)	IV Decitabine N	IV Decitabine Geo. LSM	Oral ASTX727 N	Oral ASTX727 Geo. LSM	Ratio (%) of Geo. LSM (90% CI)[a]		Intra-Subject (CV%)
Primary	**Paired**	**5-day AUC_{0-24}**	**123**	**864.94**	**123**	**855.69**	**98.93**	**(92.66, 105.6)**	**31.7**
Sensitivity	Unpaired	5-day AUC_{0-24}	131	865.82	128	848.40	97.99	(91.84, 104.5)	32.2
	Paired	5-day AUC_{0-24}	128	869.96	128	850.32	97.74	(91.58, 104.3)	32.2

CI=confidence interval; IV=intravenous; Geo. LSM=Geometric Least Squares Means.
Bold=primary analysis of the primary PK endpoint.
Test treatment=Oral ASTX727 FDC tablet (100 mg cedazuridine and 35 mg decitabine).
Reference treatment=20 mg/m^2 IV infusion (1 hr) of decitabine.
[a] Analysis is based on ANOVA model with treatment, cycle, and sequence as fixed effects, and subject nested in sequence as a random effect (ratio is Oral/IV).

Source: Garcia-Manero 2019[7]; Clinical Study Report[1], Clinical Summary[57]

Figure 6: Plasma Decitabine Concentration after Treatment with Decitabine and cedazuridine and IV Decitabine



Source: Garcia-Manero 2019[7,59]

Efficacy Outcomes

Clinical Response Outcomes (ORR, CR, mCR, PR)

Clinical response to treatment was assessed by IRC- and investigator-assessment using the IWG 2006 MDS Response Criteria (see Table 9).[3] [redacted]. Response data were preliminary given the data cutoff date (March 19, 2019) and is summarized for all subjects regardless of randomized treatment sequence. [redacted] in Table 18. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

As of the March 19, 2019 data cut off, 32 subjects (24%) were not evaluable for best response due to insufficient duration of follow up, or to lack of follow-up response data. Of all subjects evaluable for response, 11.9% ([redacted] experienced CR [redacted][7] Partial response was not seen in any subjects. An additional 45.5% of subjects achieved mCR, including mCR with HI in up to 13.9% of subjects. Hematologic improvement alone was only recorded in 7 (6.9%) of subjects. A total of 28 (27.7%) of subjects had stable disease. The resulting ORR was 64.4% in subjects evaluable for response (48.9% in all subjects).[7] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 17: Analysis of Best Clinical Response Rate (Efficacy Analysis Set)

[redacted]

Source: Clinical Study Report[1]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

[redacted]. The median duration of follow-up was 12.6 months compared to 155 days (5.1 months) in the original analysis. The CR rate was 21.1%, with an ORR of 61%, both improved from the preliminary response analysis (9.0% and 48.9%, respectively). Only 10 patients (7.5%) experienced HI in one or more lineages.[4] [redacted].[5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Duration of Response

[redacted].[5] The median duration of CR was 7.5 months (range = 1.6 to 17.5 months)[4] [redacted].[5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 18: ASCERTAIN Updated Analysis of Best Response (Efficacy Analysis Set)

[redacted]

Source: ASTX727 Efficacy Update[5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Subgroup Analysis –Response by Disease Type

[redacted].[5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 19: Best Response in MDS vs CMML (Efficacy Analysis Set)

[redacted]

Source: ASTX727 Efficacy Update[5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Transfusion Independence

Transfusion independence results were preliminary due to the short follow-up period as of the data cutoff date (March 19, 2019). Summary data for RBC and platelet TI by sequence for 56, 84, and 112 consecutive days at any time post-baseline are shown in Table 20. Of 52 subjects who were RBC transfusion dependent at baseline, 32.7% were RBC TI for any consecutive 56-day or more period post-baseline. Similarly, 30% of subjects were platelet TI over any 56-day or more period post-baseline for subjects with platelet transfusion dependence at baseline as of the March 19, 2019, data cutoff. Rates of RBC and platelet TI decreased over time, with 21% and 15% of patients achieving post-treatment TI of greater than or equal to 84 and 112 days, respectively.[7]

Table 20: Transfusion Independence Post-Baseline for Subjects with Transfusion Dependence at Baseline (Efficacy Analysis Set; N = 133)

	≥56 Days (8 weeks)		≥84 Days (12 weeks)		≥112 Days (16 weeks)	
	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
RBC Transfusion Dependent at Baseline (n = 52) Post-Treatment TI	17 (32.7)	[redacted]	11 (21.2)	[redacted]	8 (15.4)	[redacted]
Platelet Transfusion Dependent at Baseline (n = 10) Post-Treatment TI	3 (30.0)	[redacted]	1 (10)	[redacted]	1 (10)	[redacted]

RBC = red blood cell; TI = transfusion independent.
Data cut off: March 19, 2019

Source: Garcia-Manero 2019[7]; Clinical Study Report[1] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

[redacted].[5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 21: Transfusion Independence Post-Baseline for Subjects with Transfusion Dependence at Baseline

[redacted]

Source: ASTX727 Efficacy Update[5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Of the 57 subjects who were RBC or platelet transfusion dependent at baseline, 30 (53%) achieved TI,[4] and [redacted].[5] At 112 days 33% of patients were RBC or platelet TI following treatment.[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Subgroup Analysis – Transfusion Dependence by Response Category

[redacted][5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 22: Transfusion Dependence by Response (Efficacy Analysis Set; N=133)

[redacted]

Source: ASTX727 Efficacy Update[5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Leukemia-Free Survival

Leukemia-free survival was assessed for the Efficacy Analysis Set and was not assessed at the preliminary March 19, 2019 data cutoff. [redacted].[5] [redacted][6] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Figure 7: Kaplan-Meier Estimate for Leukemia-Free Survival (Efficacy Analysis Set)

[redacted]

Source: ASTX727-02 Efficacy Update[5]; April 2021 Efficacy Data Update[6] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Subgroup Analysis – LFS by IPSS Risk Category

[redacted][6] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 23: Leukemia-Free Survival for Subjects with IPSS Intermediate-1, Intermediate-2, and High Risk (Efficacy Analysis Set)

[redacted]

Source: Checkpoint Responses[8]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Figure 8: Kaplan-Meier Plot for Leukemia-Free Survival by IPSS Category (Efficacy Analysis Set)

[redacted]

Source: Checkpoint Responses[8]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Figure 9: Kaplan-Meier Plot for AMLFS by IPSS Category (April 14, 2021 Update)

Source: April 2021 Efficacy Data Update[6]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Subgroup Analysis – LFS by Prior Line of Therapy

[redacted].[8]

Table 24: Leukemia-Free Survival for Subjects With and Without Prior Anticancer Therapy (Efficacy Analysis Set)

[redacted]

Source: Checkpoint Responses[8]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Figure 10: Leukemia-Free Survival for Subjects With and Without Prior Anticancer Therapy (Efficacy Analysis Set)

[redacted]

Source: Checkpoint Responses[8]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Subgroup Analysis – LFS by Subsequent HSCT

[redacted].[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 25: Leukemia-Free Survival by Subsequent HSCT (Efficacy Analysis Set)

[redacted]

Source: Checkpoint Responses[8]
Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Figure 11: Kaplan-Meier Plot for Leukemia-Free Survival by Subsequent HSCT (Efficacy Analysis Set)

[redacted]

Source: Checkpoint Responses[8]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Overall Survival

Overall survival was not assessed at the preliminary March 19, 2019 data cutoff. [redacted][5] [redacted][8] [redacted][6] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Figure 12: Kaplan-Meier Estimate for Overall Survival (Efficacy Analysis Set)

[redacted]

Source: ASTX727-02 Efficacy Update[5,8]; [redacted][6] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Subgroup Analysis – OS by IPSS Risk Category

[redacted][8] [redacted][6] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 26: Overall Survival for Subjects with IPSS Intermediate-1, Intermediate-2, and High Risk (Efficacy Analysis Set)

[redacted]

Source: Checkpoint Responses[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Figure 13: Kaplan-Meier Plot for Overall Survival by IPSS Category (Efficacy Analysis Set)

[redacted]

Source: Checkpoint Responses[8]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Figure 14: Kaplan-Meier Plot for Overall Survival by IPSS Category (April 14, 2021 Update)

Source: April 2021 Efficacy Data Update[6]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Subgroup Analysis – OS by Prior Anticancer Therapy

[redacted][8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 27: Overall Survival for Subjects with and Without Prior Anticancer Therapy (Efficacy Analysis Set)

[redacted]

Source: Checkpoint Responses[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Figure 15: Kaplan-Meier Plot for Overall Survival for Subjects with and Without Prior Anticancer Therapy (Efficacy Analysis Set)

[redacted]

Source: Checkpoint Responses[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Subgroup Analysis – OS by Subsequent HSCT

[redacted].[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 28: Overall Survival by Subsequent HSCT (Efficacy Analysis Set)

[redacted]

Source: Checkpoint Responses[8]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Transplantation Rate

[redacted].[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Harms Outcomes

There was a total of 133 subjects included in the Safety Analysis Set. [redacted].[1] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

[redacted] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 29: Overview of Adverse Events in the ASCERTAIN Trial (Efficacy Analysis Set)

[redacted]

Source: Clinical Study Report[1]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Adverse Events

[redacted][1] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

The most frequently occurring AEs in cycles 1 or 2 for decitabine and cedazuridine and IV decitabine overall were thrombocytopenia (43.8% vs 37.9%), neutropenia (35.4% vs 31.8%), and anemia (36.9% vs 31.8%). Incidence of AEs was generally lower for decitabine and cedazuridine in cycles 3 or later compared with IV decitabine.[7]

Table 30: Adverse Events Reported in ≥5% of Subjects – All Grades (Safety Analysis Set)

[redacted]

Source: Clinical Study Report[1]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

[redacted][1]*(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 31: Related Adverse Events in ≥ 2% of Subjects – All Grades (Safety Analysis Set)

[redacted]

Source: Clinical Study Report[1]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

[redacted][1] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 32: Grade ≥3, and Related Adverse Events Reported in ≥2% of Patients in the ASCERTAIN Trial (Safety Analysis Set)

[redacted]

Source: Clinical Study Report[1]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Adverse Events of Special Interest – Gastrointestinal AEs

There were no clinically notable differences between decitabine and cedazuridine and IV decitabine were observed with regard to GI disorders. [redacted].[1] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Serious Adverse Events

[redacted][1] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 33: Serious Adverse Events in >1 Subject (Safety Analysis Set)

[redacted]

Source: Clinical Study Report[1]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Withdrawals Due to Adverse Events and Deaths

[redacted].[5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

ASTX727-01-B Trial

Pre-specified efficacy and safety outcomes of interest for the systematic review (Table 8) included OS, clinical response (ORR, CR, mCR, PR), PFS, HI, TI, HRQoL, time to AML, transplantation rate/HSCT, and safety (AEs, SAEs, WDAEs and deaths). Outcomes of interest to this review including PFS, HRQoL, and rate of HSCT were not evaluated in the ASTX727-01-B trial. Relevant outcomes assessed in the ASTX727-01-B trial included clinical response, time to AML, which was deemed of importance to this review, OS, and harms outcomes. The only efficacy outcomes in the ASTX727-01-B trial that was evaluated by subgroups of interest in the systematic review (Table 8) were clinical response and OS by genetic mutation status, however these were omitted from the report due to the limited population. No other efficacy outcomes included subgroup analyses.

Pharmacokinetic Outcomes

5-Day AUC

The primary endpoint of the ASTX727-01-B trial was 5-day decitabine exposure. The primary oral/IV AUC from time 0 to last measurable concentration (AUC_{last}) analysis was conducted in patients who successfully received and provided sufficient PK samples from the first two randomized cycles of oral and IV decitabine. Pharmacokinetic AUC results are shown in Table 34. In the primary paired analysis, the 5-day decitabine AUC_{last} oral/IV geometric LSM ratios were 93.5 (80% CI, 82.1- 106.5) and 97.6 (80% CI, 80.5-118.3) in the DC and FDC cohorts, respectively, falling within the prespecified CI limits of 75 to 133, and 65-153.9.[9] This demonstrates that both the DC and FDC administrations achieved decitabine AUC exposure equivalent to IV decitabine at 20 mg/m^2. Results of the primary paired analysis were supported by the secondary unpaired population, where the LSM ratio of oral:IV and the 80% CI also fell within the prespecified range.[9]

Table 34: Decitabine AUC for oral Decitabine and cedazuridine vs IV Decitabine

Parameter	IV geometric LSM	Oral geometric LSM	LSM ratio (oral/IV)	80% CI	Intrapatient CV%
Primary paired population					
5-d AUC_{last}, ng × hr per mL (primary end point)					
DC cohort (n = 40)	802.81	750.82	93.52	82.10-106.5	47.0
FDC cohort (n = 24)	745.26	727.29	97.59	80.48-118.3	53.8
Secondary unpaired population					
5-d AUC_{last}, ng × hr per mL					
DC cohort	795.41 (n = 42)	735.62 (n = 48)	92.48	81.37-105.1	48.4
FDC cohort	742.26 (n = 26)	760.43 (n = 28)	102.45	85.35-123.0	52.7
5-d AUC_{24}, h/ng per mL					
DC cohort	794.73 (n = 40)	753.68 (n = 45)	94.83	83.97-107.1	43.5
FDC cohort	696.90 (n = 20)	846.82 (n = 26)	121.51	97.15-152.0	59.1
5-d AUC_{∞}, ng × hr per mL					
DC cohort	794.73 (n = 40)	733.26 (n = 42)	92.27	81.27-104.7	44.6
FDC cohort	687.08 (n = 40)	845.57 (n = 26)	121.30	97.00-151.7	59.1

AUC = area under the curve; DC = dose confirmation; FDC = fixed dose combination
Data cut off: June 5, 2018
Source: Garcia-Manero 2020.[9] Reprinted from Blood, Vol 136(6), Garcia-Manero G, Griffiths EA, Steensma DP, et al., Oral cedazuridine/decitabine for MDS and CMML: a phase 2 pharmacokinetic/pharmacodynamic randomized crossover study, Pages 674-683, Copyright 2020, with permission from The American Society of Hematology.

Efficacy Outcomes

Clinical Response

The evaluation of response was based on IWG 2006 MDS Response Criteria,[3]. A summary of best response for all patients, regardless of treatment sequence is provided in Table 35 below. Overall response was seen in 48 patients (60%), including 17 (21%) with CR, a PR rate of 0, and a mCR rate of 22%. A total of 16.3% of subjects (13 of 80) showed HI in one or more lineage(s). A total of 40% of subjects showed no response. Clinical response results outcomes of CR, PR, and ORR of the ASTX727-01-B were similar to the [redacted] data cut off in the ASCERTAIN trial, despite the shorter follow up time. The population of the ASTX727-01-B trial included patients with ECOG performance status 2, did not include low-risk patients, and had more patients who were dependent on RBC transfusions compared to the ASCERTAIN population. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Duration of Response

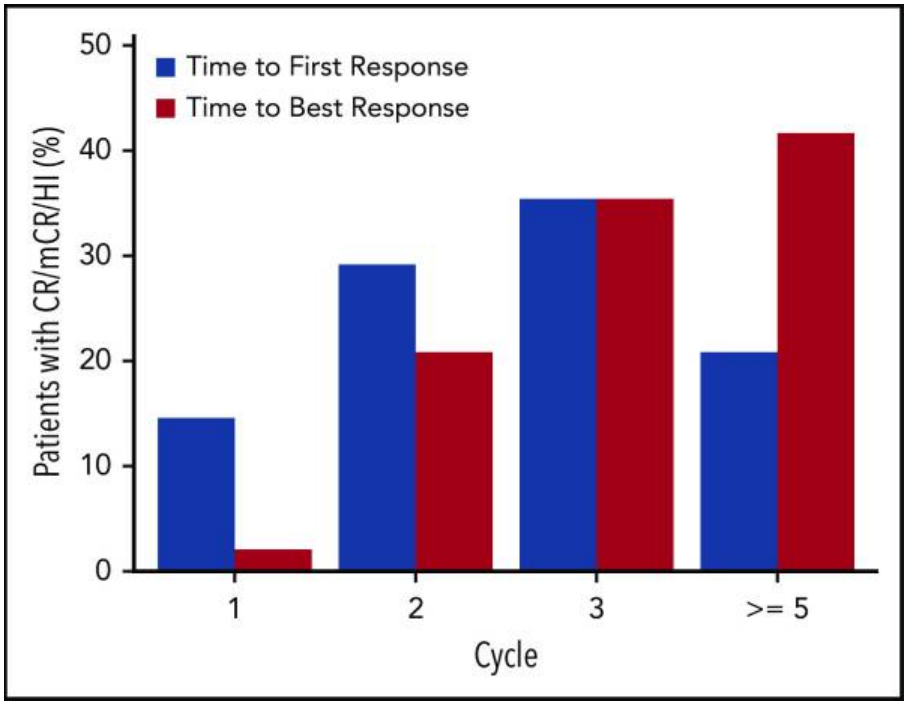
As of the June 5, 2018 data cutoff, 12 of the 17 patients with CR experienced disease progression, with a median DOR of 13.3 months (95% CI: 6.5, 13.8).[9] Of the 18 subjects with mCR, 7 (38.9%) progressed. Median duration of response for subjects with a best response of mCR was 397 days (13.1 months, range = 4.6 months to not evaluable).[2] The time to first response and time to best response by cycle is shown in Figure 14.

Table 35: Analysis of Best Response in the ASTXZ727-01-B Trial (Overall Population)

Type of response	Phase 2 overall (N = 80)	
	n (%)	95% CI
CR	17 (21)	13-32
PR	0	
mCR mCR with HI	18 (22) 6 (7)	14-33 3-16
HI HI-E HI-N HI-P	13 (16) 8 (10) 2 (2) 11 (14)	9-26 4-19 0-9 7-23
Overall response* (CR + PR + mCR + HI)	48 (60)	48-71
No response	32 (40)	29-52

*Patients are counted only once with their best response as per the table hierarchy.
CR = complete response; HI = hematologic improvement; HI-E = erythroid response; HI-N = neutrophil response; HI-P = platelet response; mCR = marrow complete response; PR = partial response.
Data cut off: June 5, 2018
Source: Garcia-Manero 2020.[9] Reprinted from Blood, Vol 136(6), Garcia-Manero G, Griffiths EA, Steensma DP, et al., Oral cedazuridine/decitabine for MDS and CMML: a phase 2 pharmacokinetic/pharmacodynamic randomized crossover study, Pages 674-683, Copyright 2020, with permission from The American Society of Hematology.

Figure 16: Time to Best Response (Overall Population)



CR = complete response; HI = hematologic improvement; mCR = marrow complete response
Data cut off: June 5, 2018
Source: Garcia-Manero 2020.[9] Reprinted from Blood, Vol 136(6), Garcia-Manero G, Griffiths EA, Steensma DP, et al., Oral cedazuridine/decitabine for MDS and CMML: a phase 2 pharmacokinetic/pharmacodynamic randomized crossover study, Pages 674-683, Copyright 2020, with permission from The American Society of Hematology.

Transfusion Independence

Transfusion dependence results are summarized in Table 36. Of 38 patients who were RBC transfusion dependent at baseline, 19 (50%) became TI. Of the 12 patients who were platelet transfusion dependent at baseline, 6 (50%) became TI.[9] These results were generally consistent with the results of the ASCERTAIN trial at 56 days, despite more patients being RBC transfusion dependent at baseline in the ASTX727-01-B trial.

Table 36: Transfusion Independence for 56 Days for Subjects Transfusion Dependent at Baseline

Type of Transfusion	Status		Dose Confirmation Stage (N=50)	Fixed-Dose Combination Stage (N=30)	Phase 2 Overall (N=80)
Red Blood Cell	Baseline Dependent	N[a]	22	16	38
	Post-treatment Independence	n[b]	11 (50.0%)	8 (50.0%)	19 (50.0%)
		95% CI[c]	(28.2, 71.8)	(24.7, 75.3)	(33.4, 66.6)
Platelet	Baseline Dependent	N[a]	7	5	12
	Post-treatment Independence	n[b]	3 (42.9%)	3 (60.0%)	6 (50.0%)
		95% CI[c]	(9.9, 81.6)	(14.7, 94.7)	(21.1, 78.9)

[a] N=Number of subjects who were transfusion dependent (ie, received 2 or more transfusions within 56 days of first dose of any study medication and have sufficient follow-up time).
[b] n=Number of subjects who became transfusion independent (ie, were transfusion free for any 56-day period post-baseline).
[c] The 95% CI is the Clopper-Pearson confidence interval.

Data cut off: June 5, 2018
Source: Clinical Study Report[2]

Time to AML or Death

Time to AML or death for patients in study ASTX727-01-B is summarized in Table 37. Of the 80 subjects, 47 (58.8%) reached the event (AML or death), and data were censored for the remaining 33 subjects (41.3%). The median time to AML or death for the overall population treated was 12.1 months (95% CI, 5.9, NE).[9] This is comparable to the ASCERTAIN trial where the median LFS was [redacted] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 37: ASTX727-01-B Time to AML or Death

Characteristics	Dose Confirmation Stage (N=50)	Fixed-Dose Combination Stage (N=30)	Phase 2 Overall (N=80)
Number of Subjects, (n (%))			
Censored	22 (44.0%)	11 (36.7%)	33 (41.3%)
Event	28 (56.0%)	19 (63.3%)	47 (58.8%)
K-M Estimate (Days, (95% CI))			
25th percentile	203.0 (96.0, 348.0)	110.0 (38.0, 273.0)	177.0 (96.0, 273.0)
Median	582.0 (274.0, NE)	315.0 (237.0, NE)	364.0 (305.0, 645.0)
75th percentile	NE (654.0, NE)	NE (352.0, NE)	NE (645.0, NE)

Data cut off: June 5, 2018
Source: Clinical Study Report[2]

Subgroup Analysis – Time to AML or Death by IPSS Risk Category

[redacted].[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 38: Time to AML or Death for Subjects with IPSS Intermediate-1, Intermediate-2, and High-Risk MDS

[redacted]

Source: Checkpoint Responses[8]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Subgroup Analysis – Time to AML or Death by Prior Line of Therapy

[redacted].[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 39: Time to AML or Death for Subjects With and Without Prior Anticancer Therapy

[redacted]

Source: Checkpoint Responses[8]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Subgroup Analysis – Time to AML or Death by Subsequent HSCT

[redacted].[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 40:Time to AML or Death by Subsequent HSCT

[redacted]

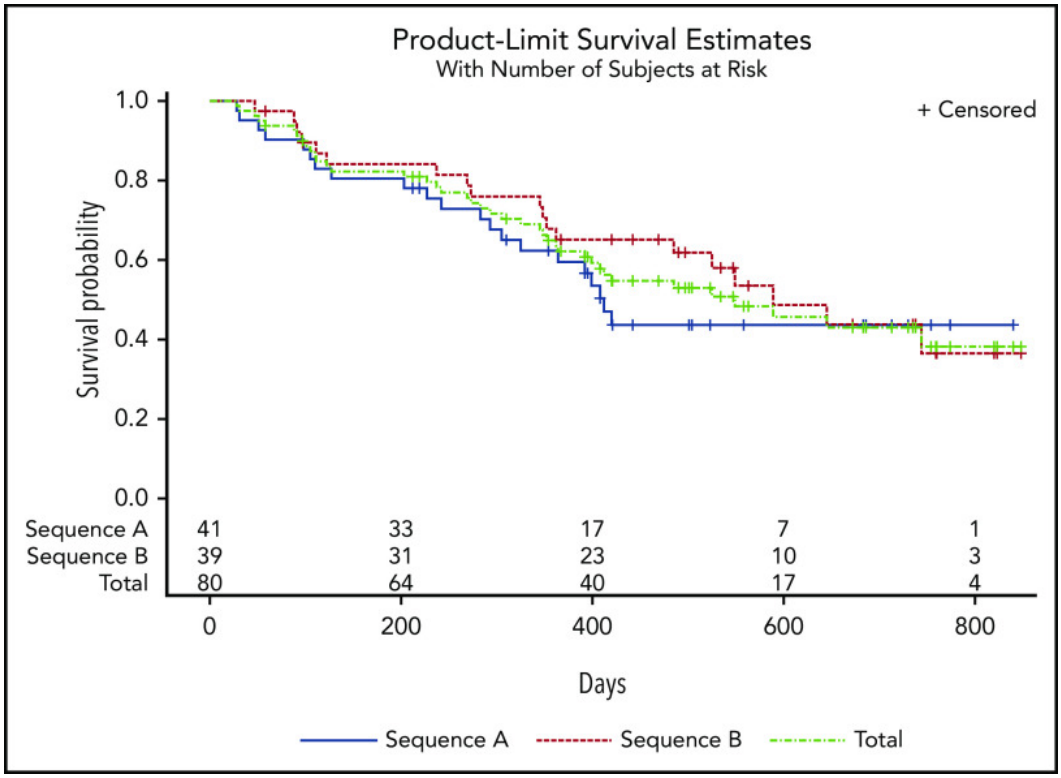
Source: Checkpoint Responses[8]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Overall Survival

As of the June 5, 2018 data cutoff, 50% of subjects had died. Median overall survival for all patients treated was 18.3 months (95% CI, 9.1-not estimable).[2,9] Kaplan-Meier curves for each treatment sequence, and the overall efficacy analysis set is shown in Figure 15.

The ASTX727-01-B study had nearly one year longer follow-up compared to the ASCERTAIN trial (24.3 months vs. [redacted][8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Figure 17: ASTX727-01-B Kaplan-Meier Estimate for Overall Survival



Data cut off: June 5, 2018

Source: Garcia-Manero 2020.[9] Reprinted from Blood, Vol 136(6), Garcia-Manero G, Griffiths EA, Steensma DP, et al., Oral cedazuridine/decitabine for MDS and CMML: a phase 2 pharmacokinetic/pharmacodynamic randomized crossover study, Pages 674-683, Copyright 2020, with permission from The American Society of Hematology.

Subgroup Analysis – OS by IPSS Risk Category

[redacted].[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 41: Overall Survival for Subjects with IPSS Intermediate-1, Intermediate-2, and High-Risk MDS

[redacted]

Source: Checkpoint Responses[8]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Subgroup Analysis – OS by Prior Line of Therapy

[redacted].[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR*

Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Table 42: Overall Survival for Subjects With and Without Prior Anticancer Therapy

[redacted]

Source: Checkpoint Responses[8] (Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Subgroup Analysis – OS by Subsequent HSCT

Median OS for patients with or without subsequent HSCT is summarized in Table 43. As of the updated efficacy analysis (November 1, 2019), median OS was 21.21 months in patients with subsequent HSCT, and was 19.36 months in patients who did not have subsequent HSCT.[8]

Table 43: Overall Survival by Subsequent HSCT

[redacted]

Source: Checkpoint Responses[8]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Transplantation Rate

At the June 5, 2018 data cut off, a total of 12 (15%) of patients received HSCT, and discontinued study treatment.[2]

Harms Outcomes

A summary of AEs in the phase II ASTX727-01-B trial are shown in Table 44. Overall, the incidence of AEs in Cycles 1 and 2 (including AEs Grade ≥3) was similar between IV decitabine and decitabine and cedazuridine (92% vs 92.3%, respectively). At the June 5, 2018 cutoff the median follow-up was 24.3 months (range = 12 to 29.2 months). Five patients discontinued treatment due to AEs, however these were not considered related to treatment.[9]

Table 44: Summary of Subjects Experiencing Adverse Events: All AEs and Related AEs – Phase 2 Overall

	All Adverse Events Phase 2 Overall Number (%) of Subjects		
	IV Decitabine Course 1 or 2 (N=75)	ASTX727[a] Course 1 or 2 (N=78)	ASTX727 Total[b] (N=78)
Subjects with any Adverse Event	69 (92.0%)	72 (92.3%)	75 (96.2%)
Subjects with any Grade ≥3 Adverse Event	44 (58.7%)	45 (57.7%)	65 (83.3%)
Subjects with AE Leading to Discontinuation of Study Treatment	1 (1.3%)	1 (1.3%)	6 (7.7%)
Subjects with any Serious Adverse Event	21 (28.0%)	28 (35.9%)	52 (66.7%)
Death	2 (2.7%)	3 (3.8%)	9 (11.5%)
Other Serious Adverse Event	19 (25.3%)	25 (32.1%)	43 (55.1%)
Subjects with any Related Adverse Event	34 (45.3%)	35 (44.9%)	52 (66.7%)
Subjects with any Grade ≥3 Related Adverse Event	24 (32.0%)	21 (26.9%)	37 (47.4%)
Subjects with AE Leading to Discontinuation of Study Treatment	0	0	2 (2.6%)
Subjects with any Related Serious Adverse Event	4 (5.3%)	6 (7.7%)	12 (15.4%)
Death	0	0	1 (1.3%)
Other Serious Adverse Event[c]	4 (5.3%)	6 (7.7%)	11 (14.1%)

Denominator in each column is number of subjects who received at least one dose of the corresponding study drug (ASTX727 or IV decitabine).
Adverse events were coded using MedDRA version 21.0 and graded using CTCAE 4.0.
[a] Subjects received cedazuridine + oral decitabine capsules or the ASTX727 FDC tablet.
[b] Includes all ASTX727 (oral) courses: either Course 1 or 2, and Courses ≥3.
[c] Excluding subjects with SAEs that led to death.

Data cut off: June 5, 2018
Source: Clinical Study Report[2]

Adverse Events

The most common treatment emergent AEs (TEAE) in the ASTX727-01-B trial are summarized in Table 45 below. All grade, and grade ≥ 3 AEs are presented by treatment cycle for all treated patients. The proportion of patients who reported at least one TEAE in cycles 1 and 2 was similar for IV decitabine (92%) and oral decitabine and cedazuridine (92.3%), but higher in all decitabine and cedazuridine cycles (96%). The most common TEAEs for decitabine and cedazuridine were neutropenia (46.2%), thrombocytopenia (43.6%), fatigue (33.3%), and febrile neutropenia (29.5%).[2,9]

Grade ≥ 3 Adverse Events

The most common grade ≥ 3 TEAEs in the ASTX727-01-B trial are summarized in Table 45 below. Incidence of grade ≥ 3 TEAEs was also similar between courses at 59% and 58% for IV decitabine and oral decitabine and cedazuridine, respectively. The most frequently occurring grade ≥ 3 TEAEs were all slightly higher in the IV course than in the oral course and included neutropenia (IV: 27% vs oral: 21%), thrombocytopenia (IV: 28% vs oral: 23%), and febrile neutropenia (IV: 16% vs oral: 12%). A higher incidence of dyspnea was reported in the decitabine and cedazuridine groups (n = 12; 15.4 vs 2.7% (2/75) in IV decitabine cycles 1 or 2, however these were all grades 1 or 2, and deemed not related to study treatment.[2,9]

Table 45: Treatment-Emergent AEs During Cycles 1 and 2, and the Entire Phase 2 Study

Preferred term, n (%)	IV decitabine cycle 1 or 2 (n = 75)	Oral cedazuridine/ decitabine cycle 1 or 2 (n =78)	All oral cedazuridine/ decitabine cycles (n = 78)
Patients with ≥1 TEAE	69 (92)	72 (92)	75 (96)
Most common TEAEs (≥20% of patients)			
Neutropenia	22 (29)	17 (22)	36 (46)
Thrombocytopenia	24 (32)	23 (29)	34 (44)
Fatigue	10 (13)	15 (19)	26 (33)
Febrile neutropenia	12 (16)	9 (12)	23 (29)
Nausea	11 (15)	13 (17)	22 (28)
Diarrhea	9 (12)	10 (13)	22 (28)
Leukopenia	9 (12)	10 (13)	21 (27)
Dizziness	8 (11)	9 (12)	20 (26)
Anemia	11 (15)	10 (13)	19 (24)
Constipation	12 (16)	14 (18)	19 (24)
Dyspnea	2 (3)	12 (15)	19 (24)
Patients with grade ≥3 TEAEs	44 (59)	45 (58)	65 (83)
Most common grade ≥3 TEAEs (≥10% of patients)			
Neutropenia	20 (27)	16 (21)	36 (46)
Thrombocytopenia	21 (28)	18 (23)	30 (38)
Febrile neutropenia	12 (16)	9 (12)	23 (29)
Leukopenia	8 (11)	7 (9)	19 (24)
Anemia	9 (12)	9 (12)	17 (22)
Pneumonia	5 (7)	7 (9)	10 (13)
Sepsis	1 (1)	4 (5)	8 (10)

TEAE = treatment emergent adverse event.
Data cut off: June 5, 2018
Source: Garcia-Manero 2020.[9] Reprinted from Blood, Vol 136(6), Garcia-Manero G, Griffiths EA, Steensma DP, et al., Oral cedazuridine/decitabine for MDS and CMML: a phase 2 pharmacokinetic/pharmacodynamic randomized crossover study, Pages 674-683, Copyright 2020, with permission from The American Society of Hematology.

Adverse Events of Special Interest – Gastrointestinal AEs

Gastrointestinal AEs, such as nausea, vomiting, and diarrhea observed in this study were all Grades 1 or 2 and similar in incidence between oral decitabine and cedazuridine and IV dosing, and no notable increase in GI AEs was observed with oral decitabine and cedazuridine vs IV decitabine in the two first randomized cycles.[2,9]

Serious Adverse Events

Table 46 shows the SAEs for all subjects in the Phase II study. The SAEs with highest incidence for decitabine and cedazuridine Total (all oral courses) were febrile neutropenia (25.6%), sepsis (10.3%), and pneumonia (9%). The majority of related SAEs were Grade 3, with only 3 being Grade 4 or 5.[2]

Table 46: Serious Adverse Events (≥ 5% of Subjects) – Phase 2 Overall

	Phase 2 Overall		
SOC/Preferred Term	IV Decitabine Course 1 or 2 (N=75)	ASTX727 Course 1 or 2 (N=78)	ASTX727 Total[a] (N=78)
Total Number of SAEs	30	42	127
Number of subjects who reported at least one SAE	21 (28.0%)	28 (35.9%)	52 (66.7%)
Febrile Neutropenia	9 (12.0%)	8 (10.3%)	20 (25.6%)
Sepsis	1 (1.3%)	4 (5.1%)	8 (10.3%)
Pneumonia	5 (6.7%)	5 (6.4%)	7 (9.0%)
Cellulitis	0	2 (2.6%)	4 (5.1%)
Pyrexia	0	0	4 (5.1%)

Denominator is number of subjects who received at least one dose of study treatment. SAEs are treatment emergent.
Subjects are counted only once for each AE PT.
PTs are coded using MedDRA v21.0.
[a] Data sorted in descending order of incidence for ASTX727 Total (all oral courses).

Data cut off: June 5, 2018
Source: Clinical Study Report[2]

Withdrawals Due to Adverse Events and Deaths

As of the data cutoff date (05 June 2018), 50% of subjects had died in Phase 2, 48% in the Dose Confirmation Stage, and 53.3% who were in the FDC Stage. A total of 11 patients had an AE with an outcome of death (2 in the IV decitabine, and 9 overall in the decitabine and cedazuridine groups), including four from sepsis or septic shock and two from pneumonia (all considered not related to treatment), and 1 each from respiratory failure, cardiac arrest, sudden death, myocarditis, and small-cell lung cancer.[9]

Pooled Harms Outcomes

Pooled safety data from the Phase II ASTX727-01-B trial and the Phase III ASCERTAIN study were submitted in the original NDA based on the June 5, 2018 and March 19, 2019 data cuts. A summary of SAEs reported in the safety database after the CSR cutoff dates up to 12 October 2019 was also included in the original NDA. Pooled safety data from the original NDA and the 120-day safety update ([redacted]) are summarized below.[11] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Adverse Events

A summary of AEs of all grades occurring in ≥5% of subjects in any group in the integrated population in the original NDA and the Safety Update is presented in Table 47. Of the 208 patients included in the pooled analysis, 205 (98.6%) patients experienced at least one TEAE. There were modest increases in the incidence of AEs between data cutoffs. The most frequently occurring AEs remained blood and lymphatic system disorders (79.3%) including thrombocytopenia (52.4%), neutropenia (51.4%), anemia (39.4%), febrile neutropenia (28.4%), and leukopenia (26.4%). The largest increase in blood and lymphatic system disorders was seen in neutropenia (43.8% to 51.4%).[11]

Table 47: All Adverse Events Occurring in ≥ 5% of Subjects in the Integrated Decitabine and cedazuridine Population (Phase 2 and Phase 3 Subjects)

System Organ Class Preferred term	Number (%) of Patients	
	All cycles Decitabine and cedazuridine Capsules or ASTX727 FDC Tablet (N = 208)	
	Original NDA	Safety Update
Number of subjects who reported at least one TEAE	***203 (97.6)***	***205 (98.6)***
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**155 (74.5)**	**165 (79.3)**
Thrombocytopenia	102 (49.0)	109 (52.4)
Neutropenia	91 (43.8)	107 (51.4)
Anemia	71 (34.1)	82 (39.4)
Leukopenia	50 (24.0)	55 (26.4)
Febrile neutropenia	49 (23.6)	59 (28.4)
GASTROINTESTINAL DISORDERS	**144 (69.2)**	**156 (75.0)**
Nausea	55 (26.4)	60 (28.8)
Constipation	53 (25.5)	62 (29.8)
Diarrhea	48 (23.1)	63 (30.3)
Stomatitis	18 (8.7)	28 (13.5)
Vomiting	18 (8.7)	26 (12.5)
Abdominal pain	17 (8.2)	21 (10.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**116 (55.8)**	**140 (67.3)**
Fatigue	70 (33.7)	81 (38.9)
Asthenia	32 (15.4)	36 (17.3)
Oedema peripheral	26 (12.5)	37 (17.8)
Pyrexia	24 (11.5)	29 (13.9)
Chills	12 (5.8)	16 (7.7)
INFECTIONS AND INFESTATIONS	**107 (51.4)**	**129 (62.0)**
Pneumonia	24 (11.5)	34 (16.3)
Upper respiratory tract infection	17 (8.2)	24 (11.5)
Sepsis	17 (8.2)	20 (9.6)
Septic shock[a]	3 (1.4)	3 (1.4)
Cellulitis	15 (7.2)	21 (10.1)
Urinary tract infection	12 (5.8)	19 (9.1)
Nasopharyngitis[b]	7 (3.4)[b]	11 (5.3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**55 (26.4)**	**78 (37.5)**
Contusion	19 (9.1)	34 (16.3)
Fall	18 (8.7)	23 (11.1)
Skin laceration[b]	7 (3.4)[b]	11 (5.3)
INVESTIGATIONS	**71 (34.1)**	**79 (38.0)**
Alanine aminotransferase increased	26 (12.5)	28 (13.5)
Weight decreased	18 (8.7)	19 (9.1)
Blood creatinine increased	17 (8.2)	21 (10.1)
Aspartate aminotransferase increased	16 (7.7)	18 (8.7)

System Organ Class Preferred term	Number (%) of Patients	
	All cycles Decitabine and cedazuridine Capsules or ASTX727 FDC Tablet (N = 208)	
	Original NDA	Safety Update
Blood bilirubin increased	12 (5.8)	14 (6.7)
Blood alkaline phosphatase increased[b]	10 (4.8)[b]	13 (6.3)
METABOLISM AND NUTRITION DISORDERS	**92 (44.2)**	**103 (49.5)**
Decreased appetite	38 (18.3)	45 (21.6)
Hypocalcaemia	19 (9.1)	20 (9.6)
Hypokalaemia	18 (8.7)	24 (11.5)
Hypomagnesaemia	17 (8.2)	19 (9.1)
Hypoalbuminaemia	16 (7.7)	19 (9.1)
Hyperglycaemia	14 (6.7)	17 (8.2)
Hyponatraemia	13 (6.3)	15 (7.2)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**84 (40.4)**	**110 (52.9)**
Arthralgia	32 (15.4)	43 (20.7)
Back pain	21 (10.1)	27 (13.0)
Myalgia	14 (6.7)	22 (10.6)
Pain in extremity[b]	8 (3.8)[b]	15 (7.2)
Bone pain	9 (4.3)	14 (6.7)
Muscle spasms[b]	4 (1.9)[b]	12 (5.8)
NERVOUS SYSTEM DISORDERS	**84 (40.4)**	**100 (48.1)**
Dizziness	39 (18.8)	48 (23.1)
Headache	35 (16.8)	44 (21.2)
PSYCHIATRIC DISORDERS	34 (16.3)	43 (20.7)
Insomnia	18 (8.7)	22 (10.6)
Anxiety[b]	7 (3.4)[b]	11 (5.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**102 (49.0)**	**122 (58.7)**
Dyspnoea	43 (20.7)	53 (25.5)
Cough	29 (13.9)	43 (20.7)
Oropharyngeal pain	20 (9.6)	22 (10.6)
Epistaxis	14 (6.7)	17 (8.2)
Nasal congestion[b]	10 (4.8)[b]	13 (6.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**68 (32.7)**	**88 (42.3)**
Rash maculo-papular	14 (6.7)	18 (8.7)
Rash[b]	7 (3.4)[b]	14 (6.7)
Alopecia[b]	7 (3.4)[b]	11 (5.3)
VASCULAR DISORDERS	**37 (17.8)**	**46 (22.1)**
Hypertension	11 (5.3)	16 (7.7)
Hypotension	11 (5.3)	14 (6.7)

FDC = fixed dose combination; NDA = New Drug Application; TEAE = treatment emergent adverse event.

[a] Septic shock is included despite occurring at an incidence below the cutoff because of its medical relatedness to sepsis.

[b] Event was below ≥5% cutoff in original NDA.

Source: ASTX727 120-Day Safety Update[11]

Grade 3 or greater AEs are summarized in Table 48. The most frequent Grade ≥ 3 AEs (occurring in >20% of subjects) in the overall decitabine and cedazuridine population across all cycles were the same in the Safety Update as in the original NDA, and included thrombocytopenia, neutropenia, anemia, febrile neutropenia, and leukopenia. As above, there were increases in the incidence of all Grade > 3 AEs at the 120-day safety update ([redacted][11] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 48: Grade ≥ 3 AEs Occurring in ≥ 2% of Subjects in the Decitabine and cedazuridine Integrated Population (Phase 2 and Phase 3 Subjects)

SYSTEM ORGAN CLASS Preferred Term	Number (%) of Subjects All Cycles Cedazuridine and Decitabine Capsules or ASTX727 FDC Tablet (N=208) Original NDA	 Safety Update
Number of subjects who reported at least one Grade ≥3 TEAE	168 (80.8)	181 (87.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	148 (71.2)	161 (77.4)
Neutropenia	88 (42.3)	104 (50.0)
Thrombocytopenia	87 (41.8)	95 (45.7)
Anaemia	59 (28.4)	70 (33.7)
Febrile neutropenia	49 (23.6)	58 (27.9)
Leukopenia	43 (20.7)	47 (22.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	12 (5.8)	16 (7.7)
Fatigue	6 (2.9)	8 (3.8)
Asthenia [a]	3 (1.4)[a]	5 (2.4)
INFECTIONS AND INFESTATIONS	58 (27.9)	68 (32.7)
Pneumonia	21 (10.1)	28 (13.5)
Sepsis	16 (7.7)	20 (9.6)
Septic shock[b]	3 (1.4)	3 (1.4)
Cellulitis	6 (2.9)	8 (3.8)
METABOLISM AND NUTRITION DISORDERS	21 (10.1)	26 (12.5)
Hyponatraemia	5 (2.4)	5 (2.4)
Hypokalaemia	4 (1.9)	5 (2.4)
NERVOUS SYSTEM DISORDERS	9 (4.3)	11 (5.3)
Syncope	5 (2.4)	6 (2.9)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	15 (7.2)	18 (8.7)
Dyspnoea	6 (2.9)	7 (3.4)
Hypoxia [a]	4 (1.9)[a]	6 (2.9)
Respiratory failure [a]	4 (1.9)[a]	5 (2.4)
VASCULAR DISORDERS	10 (4.8)	15 (7.2)
Hypertension [a]	4 (1.9)[a]	6 (2.9)

[a] Event was below ≥2% cutoff in original NDA.
[b] Septic shock is included because of its medical relatedness to sepsis despite occurring at an incidence below the cutoff.

FDC = fixed dose combination; NDA = New Drug Application; TEAE = treatment emergent adverse event.
Source: ASTX727 120-Day Safety Update[11]

The most common related Grade ≥ 3 AEs in the original NDA and 120-day safety update for the overall integrated population were neutropenia (29.8% to 38%), thrombocytopenia (26.4% to 30.8%), leukopenia (17.8% to 19.2%), anemia (15.4% to 20.2%), and febrile neutropenia (7.7% to 9.6%), which increased moderately (Table 49).[11]

Table 49: All Related Grade ≥3 Adverse Events in the ASTX727 Integrated Population (Phase 2 and Phase 3 Subjects)

System Organ Class Preferred Term	Number (%) of Subjects All Cycles Cedazuridine and Decitabine Capsules or ASTX727 FDC Tablet (N=208) Original NDA	 Safety Update
Number of subjects who reported at least one related Grade ≥3 TEAE	99 (47.6)	120 (57.7)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	99 (47.6)	119 (57.2)
Neutropenia	62 (29.8)	79 (38.0)
Thrombocytopenia	55 (26.4)	64 (30.8)
Leukopenia	37 (17.8)	40 (19.2)
Anaemia	32 (15.4)	42 (20.2)
Febrile neutropenia	16 (7.7)	20 (9.6)
Lymphopenia	3 (1.4)	4 (1.9)
Bone marrow failure	1 (0.5)	1 (0.5)
CARDIAC DISORDERS	1 (0.5)	1 (0.5)
Cardiogenic shock	1 (0.5)	1 (0.5)
Myocarditis	1 (0.5)	1 (0.5)
GASTROINTESTINAL DISORDERS	3 (1.4)	5 (2.4)
Colitis	1 (0.5)	1 (0.5)
Diarrhoea	2 (1.0)	3 (1.4)
Gingival bleeding	0	1 (0.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	6 (2.9)	7 (3.4)
Fatigue	4 (1.9)	5 (2.4)
Asthenia	1 (0.5)	1 (0.5)
Pain	1 (0.5)	1 (0.5)
IMMUNE SYSTEM DISORDERS	1 (0.5)	1 (0.5)
Drug hypersensitivity	1 (0.5)	1 (0.5)
INFECTIONS AND INFESTATIONS	13 (6.3)	14 (6.7)
Sepsis	5 (2.4)	5 (2.4)
Pneumonia	2 (1.0)	4 (1.9)
Urinary tract infection	2 (1.0)	2 (1.0)
Bacterial infection	1 (0.5)	1 (0.5)
Bronchopulmonary aspergillosis	1 (0.5)	1 (0.5)
Cellulitis	1 (0.5)	2 (1.0)
Enterobacter infection	1 (0.5)	1 (0.5)
Septic shock[a]	1 (0.5)	1 (0.5)
Pneumonia cytomegaloviral	0	1 (0.5)
Pseudomonal bacteraemia	0	1 (0.5)

FDC = fixed dose combination; NDA = New Drug Application; TEAE = treatment emergent adverse event.
[a] For 1 event of related septic shock that occurred in an ASTX727 cycle (Cycle 2), the investigator attributed causality to the IV decitabine received in Cycle 1.
Source: ASTX727 120-Day Safety Update[11]

Adverse Events of Special Interest – Gastrointestinal AEs

There was a moderate increase in gastrointestinal AEs between the original NDA data cutoffs (June 5, 2018 and March 19, 2019 data cut) and the 120-day Safety Update ([redacted] however the incidence remained low overall with nausea, constipation, and diarrhea remaining the most frequent at 28.8%, 29.8%, and 30.3%, respectively.[11] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Serious Adverse Events

Serious adverse events as of the 120-day safety update are summarized in Table 50. For both the original NDA and the Safety Update, the most common non-fatal SAEs occurring in >5% of subjects in the overall decitabine and cedazuridine population across all cycles included febrile neutropenia (26%), pneumonia (10.6%), and sepsis (6.7%).[11]

Table 50: Non-fatal SAEs Occurring in Any Group in the Integrated Population (Phase 2 and Phase 3 Subjects)

System Organ Class Preferred Term	Number (%) of Subjects All Cycles Cedazuridine and Decitabine Capsules or ASTX727 FDC Tablet (N=208) Original NDA	 Safety Update
Number of subjects who reported at least one non-fatal serious TEAE[a]	102 (49.0)	123 (59.1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	46 (22.1)	58 (27.9)
Febrile neutropenia	43 (20.7)	54 (26.0)
Anaemia	3 (1.4)	3 (1.4)
Thrombocytopenia [b]	1 (0.5)[b]	2 (1.0)
CARDIAC DISORDERS	5 (2.4)	5 (2.4)
Myocardial infarction	2 (1.0)	2 (1.0)
GASTROINTESTINAL DISORDERS	11 (5.3)	14 (6.7)
Gastrointestinal haemorrhage	4 (1.9)	4 (1.9)
Abdominal pain	2 (1.0)	2 (1.0)
Nausea	2 (1.0)	2 (1.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	10 (6.8)	13 (6.3)
Pyrexia	6 (2.9)	6 (2.9)
Asthenia	3 (1.4)	4 (1.9)
Oedema peripheral	2 (1.0)	2 (1.0)
Fatigue [b]	1 (0.5)[b]	2 (1.0)
INFECTIONS AND INFESTATIONS	49 (23.6)	56 (26.9)
Pneumonia	17 (8.2)	22 (10.6)
Sepsis	12 (5.8)	14 (6.7)
Cellulitis	6 (2.9)	8 (3.8)
Bacteraemia	4 (1.9)	4 (1.9)
Urinary tract infection	4 (1.9)	4 (1.9)
Influenza	3 (1.4)	4 (1.9)
Upper respiratory tract infection	3 (1.4)	4 (1.9)
Diverticulitis	2 (1.0)	3 (1.4)
Pharyngitis	2 (1.0)	2 (1.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	4 (1.9)	5 (2.4)
Fall	3 (1.4)	4 (1.9)
METABOLISM AND NUTRITION DISORDERS	5 (2.4)	6 (2.9)
Failure to thrive	2 (1.0)	2 (1.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	4 (1.9)	4 (1.9)
Back pain	2 (1.0)	2 (1.0)
NERVOUS SYSTEM DISORDERS	6 (2.9)	7 (3.4)
Syncope	4 (1.9)	5 (2.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6 (2.9)	7 (3.4)
Dyspnoea	2 (1.0)	2 (1.0)
VASCULAR DISORDERS	5 (2.4)	7 (3.4)
Hypertension	2 (1.0)	2 (1.0)
Embolism[b]	1 (0.5)[b]	3 (1.4)

[a] Excluding AEs with an outcome of death, but including the non-fatal SAEs of subjects who had AEs with outcome of death.

[b] Event was below ≥1% cutoff in original NDA.

Source: ASTX727 120-Day Safety Update[11]

Withdrawals Due to Adverse Events and Deaths

As of the safety update [redacted] data cut off, a total of 147 patients had discontinued treatment. Three additional patients from the integrated population (Phase II and Phase III subjects) discontinued treatment due to AEs between the data cutoffs for the original NDA (June 5, 2018 and March 19, 2019 data cut) and the 120-day Safety Update ([redacted]), and one patient withdrew from the study due to AE. A total of 81 deaths had occurred by the safety update, with 32 occurring between the

data cutoffs for the original NDA and the Safety Update, with only 4 of them occurring in the treatment period. Five of the additional deaths were due to AEs (3 during the treatment period, 2 after the treatment period). One of those 5 subjects died from an AE in an IV decitabine cycle that was not captured in the original NDA. The cause of death was unknown for the majority of patients who died (n = 40; 19.2%), followed by AEs (n = 23; 11.1%), and progressive disease (n = 13; 6.3%).[11] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

6.4 Ongoing Trials

In addition to the completed ASTX727-01-B and ongoing ASTX727-02 trials, additional ongoing studies involving decitabine and cedazuridine to treat MDS are summarized in Table 51. All ongoing studies are funded by Astex Pharmaceuticals (Taiho Pharmaceuticals) and include two open label extension studies, an ongoing dose-finding study, and a pre-emptive therapy study.

Table 51: Ongoing Trials of Decitabine and cedazuridine in MDS

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: An Open-Label, Multicenter, Extension Study for Subjects Who Participated in Prior Clinical Studies of ASTX727 (Standard Dose) (NCT04093570; ASTX727-06) **Characteristics:** Open-label, single group assignment, phase 2 trial **Sample size:** N = 300 **Setting:** 18 study sites in the United States, and 5 study sites in Canada **Patient Enrolment Dates:** September 30, 2019 **Estimated Completion Date:** March 31, 2021 **Funding:** Astex Pharmaceuticals, Inc.	**Key Inclusion Criteria:** • Previous participation in an Astex-sponsored decitabine and cedazuridine clinical trial (including, but not limited to studies ASTX727-01, ASTX727-02, and ASTX727-04) in which the subject was treated with decitabine and cedazuridine and was still on active treatment with decitabine and cedazuridine at the time of study completion • Subject is considered to be benefitting from decitabine and cedazuridine treatment in the opinion of the treating investigator at the time of parent study completion (Subjects must not be withdrawn from the parent study until eligibility for this study is confirmed) **Key Exclusion Criteria:** • Any subject who, in the opinion of the investigator, may have other conditions, organ dysfunction, or for whom safety data from parent study participation suggests the risks of continuing treatment with decitabine and cedazuridine may outweigh the benefits	**Intervention:** ASTX727 (decitabine and cedazuridine)	**Primary:** • Treatment-emergent adverse events **Secondary:** • Time to death from any cause

Study:
Phase 1-2 Study of Low Dose ASTX727 (ASTX727 LD) in Lower Risk MDS
(NCT03502668; ASTX727-03)
 	
Characteristics:
Open-label, randomized, sequential assignment phase 1/2 trial
 	
Sample Size:
	Key Inclusion Criteria:
	• Men or women ≥18 years with IPSS low risk or Int-1 MDS (all subjects). Subjects must have had at least 1 of the following disease-related criteria during the 8 weeks before randomization:
	  ○ RBC transfusion dependence of 2 or more RBC units or Hb of <8.5 g/dL in at least 2 blood counts
	  ○ ANC of <0.5 x 109/L in at least 2 blood counts
		Intervention:
		Decitabine and cedazuridine Low Dose
		
		Comparator:
		Decitabine and cedazuridine Standard Dose
			Primary:
			• Incidence of drug-related Grade ≥3 AEs or DLTs (if any) for each cohort dose/schedule
			• Hematologic response based on normalization of conversion of any baseline cytopenia or anemia
			
			Secondary:

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
N = 160 **Setting:** 20 study sites in the United States **Patient Enrolment Dates:** July 27, 2018 **Estimated Completion Date:** December 2020 **Funding:** Astex Pharmaceuticals, Inc.	○ Platelet counts of <50 x 109/L in at least 2 blood counts • ECOG PS 0 to 2 • Adequate organ function **Key Exclusion Criteria:** • Treatment with any investigational drug or therapy within 2 weeks before study treatment • Treatments for MDS must be concluded 1 month prior to study treatment • Diagnosis of CMML • Poor medical risk because of other conditions such as uncontrolled systemic diseases or active uncontrolled infections • Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, PC or BC under control with hormone therapy, or other cancer from which the subject has been disease free for at least 1 year • Known active infection with HIV or hepatitis viruses		• %LINE-1 methylation change from baseline • Area under the curve • Maximum plasma concentration, time to reach maximum concentration, half life • Hematologic response (Phase 1 only) based on normalization of conversion of any baseline cytopenia or anemia • Time to bone marrow blasts >5% • Leukemia-free survival • OS
Study: ASTX727-06: An Open-Label, Multicenter, Extension Study for Subjects Who Participated in Prior Clinical Studies of ASTX727 (Standard Dose) (NCT04093570) **Characteristics:** Phase II, multicenter, open-label, single group assignment, extension study for subjects who participated in prior ASTX727 clinical studies **Sample Size:** N = 300 (estimated) **Setting:** 23 study sites in 2 countries (5 in Canada, and 18 in the United States) **Patient Enrolment Dates:** September 30, 2019 **Estimated Completion Date:** March 31, 2021 **Funding:** Astex Pharmaceuticals, Inc.	**Key Inclusion Criteria:** • Previous participation in an Astex-sponsored decitabine and cedazuridine clinical trial (including, but not limited to studies ASTX727-01, ASTX727-02, and ASTX727-04) in which the subject was treated with decitabine and cedazuridine and was still on active treatment with decitabine and cedazuridine at the time of study completion as determined by Astex. • Subject is considered to be benefitting from decitabine and cedazuridine treatment in the opinion of the treating investigator at the time of parent study completion (Subjects must not be withdrawn from the parent study until eligibility for this study is confirmed). **Key Exclusion Criteria:** • Any subject who, in the opinion of the investigator, may have other conditions, organ dysfunction, or for whom safety data from parent study participation suggests the risks of continuing treatment with decitabine and cedazuridine may outweigh the benefits	**Interventions:** Decitabine and cedazuridine	**Primary:** • Number of participants with TEAEs **Secondary:** • Time to death from any cause
Study: A Phase I/II Trial of Pre-emptive Therapy With decitabine and cedazuridine to Improve	**Key Inclusion Criteria:** • Diagnosis of MDS based on WHO 2016 classification who have received an allogeneic	**Interventions:** Decitabine and cedazuridine	**Primary:**

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Outcomes in MDS Patients with Measurable Residual Disease Post Allogeneic Hematopoietic Cell Transplant (NCT04742634) **Characteristics:** Phase I/II open-label, non-randomized, sequential assignment clinical trial **Sample Size:** N = 126 **Setting:** One study center in the United States **Patient Enrolment Dates:** April 30, 2021 **Estimated Completion Date:** April 30, 2024 **Funding:** Washington University School of Medicine, and Taiho Oncology, Inc.	HSCT. Any stem cell source, conditioning regimen, and immunosuppression regimen as determined by the treating physician, per institutional guidelines, is permitted. Patients may have received any therapy, or no therapy, prior to transplant • At least 18 years of age • One or more somatically acquired variants that were present prior to transplant detected by the MyeloSeq-HD panel at Day 30 post-transplant, with a variant allele frequency of ≥ 0.5% • ≤ 5 % bone marrow myeloblasts on the Day 30 post-transplant biopsy. • If patient has GVHD, it must be grade 2 or lower. Patients with active grade 3 or higher GVHD are ineligible for the decitabine and cedazuridine arm. Patients with a history of GVHD or with adequately controlled GVHD are eligible. • ECOG performance status ≤ 2 **Key Exclusion Criteria:** • Currently receiving any other investigational agents. • A history of allergic reactions attributed to compounds of similar chemical or biologic composition to decitabine and cedazuridine or other agents used in the study. • Concomitant administration of drugs metabolized by cytidine deaminase • Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia.		• Number of patients with dose-limiting toxicities (Phase I only) • Maximum tolerated dose (Phase I only) • Recommended phase II dose (Phase I only) • PFS (Phase II recommended dose only) • Rate of relapse (Phase II recommended dose only) **Secondary:** • OS • Percentage of patients requiring decitabine and cedazuridine dose adjustment/delay • Percentage of cycles given on time/at dose • Change in mutational MRD disease burden as measured by variant allele frequency cycles

AE = adverse events; AML = Acute myeloid leukemia; ANC = absolute neutrophil count; BC = breast cancer; CMML = chronic myelomonocytic leukemia; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicities; ECOG = Eastern Cooperative Oncology Group; GVHD = graft versus host disease; HSCT = hematopoietic stem cell transplant; IPSS = International Prognostic Scoring System; MDS = myelodysplastic syndromes; MPN = myeloproliferative neoplasms; NR = not reported; NYHA = New York Heart Association; OS = overall survival; PC = prostate cancer; PFS = progression-free survival; PS = performance status; RBC = red blood cell; TEAE = treatment emergent adverse events.

7 Supplemental Questions

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of INQOVI (C-DEC; decitabine and cedazuridine oral tablets) for the treatment of adult patients with MDS including previously treated and untreated, de novo and secondary MDS of all FAB subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and CMML) and intermediate-1, intermediate-2, and high-risk IPSS groups:

- Summary and critical appraisal of a sponsor-submitted ITC/NMA comparing decitabine + cedazuridine to azacitidine, BSC, CCR, and LDAC for the treatment of intermediate-1, intermediate-2, and high-risk MDS, and CMML.

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Summary and Critical Appraisal of Sponsor-Submitted ITC/NMA Comparing Decitabine + Cedazuridine to Azacitidine, BSC, CCR, and LDAC for the Treatment of Intermediate-1, Intermediate-2, and High-Risk MDS and CMML

7.1.1 Objective

The oral combination of decitabine and cedazuridine was approved by the US FDA and Health Canada in July 2020.[64] The phase III ASCERTAIN study and phase I/II ASTX727-01-B study compared oral decitabine and cedazuridine to IV decitabine monotherapy which is approved but not marketed in Canada. Accordingly, PAG has requested comparative data of decitabine and cedazuridine and azacitidine (± hydroxyurea), in patients with higher risk MDS and CMML, as well as lenalidomide (for patients with deletion 5q chromosome changes), and with HSCT; however, the systematic review perfomed by CADTH did not identify any additional trials that directly compared decitabine and cedazuridine to relevant MDS treatments (refer to Section 6).

In the absence of a direct head-to-head comparison of decitabine and cedazuridine to relevant comparators, the sponsor submitted evidence to CADTH in the form of an ITC.[12]

The objective of this section is to summarize and critically appraise the methods and findings of the sponsor-submitted ITC/NMA[12] comparing decitabine and cedazuridine to azacitidine, BSC, conventional care regimens for the treatment of intermediate-1, intermediate-2, and high-risk MDS and CMML.

An updated NMA report was submitted with a revised synthetic network analysis based on the April 14, 2021 data cut-off for the phase III ASCERTAIN trial, which included more mature median AMLFS and median OS data. Analysis methodology did not change.[20]

7.1.2 Findings

Methods

Systematic Review

The objective of the sponsor-submitted ITC/NMA[12] was to estimate the comparative efficacy and safety of decitabine and cedazuridine and azacitidine in the INT1-HR MDS population. The ITC/NMA was based on a systematic literature review, in which the following databases were searched from inception to June 2020: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. Searches were restricted to publications only in English, as well as publications from 2010 to the search date. The reference lists of included studies were also screened for additional relevant studies. The PICOS criteria of the SLR is provided in Table 52. No details concerning dosing, or definition of BSC or conventional care were provided.[12]

Table 52: Inclusion Criteria for the Systematic Literature Review

Clinical PICOS	
Patient population	▪ Adult patients with MDS including previously untreated and treated, de novo and secondary MDS* ▪ MDS of all French-American-British subtypes (refractory anaemia, refractory anemia with ringed sideroblasts, refractory anaemia with excess blasts, refractory anaemia with excess blasts in transformation, and CMML) ▪ INT1, INT2, and HR IPSS groups
Intervention and Comparators	▪ Azacitidine SQ (Vidaza) ▪ Decitabine IV (Dacogen) ▪ ASTX727 (oral cedazuridine/decitabine) ▪ Best supportive care ▪ Conventional care regimens (including chemotherapy)
Outcomes measures	▪ Overall survival (OS) ▪ Progression-free survival (PFS), event-free survival (EFS) ▪ Response rate (ORR, CR, any other form of response) ▪ All other efficacy endpoints (e.g., duration of response, leukemia-free survival, time to leukemic transformation, transfusion dependence) ▪ Any safety endpoints
Study design	▪ Randomized clinical trials (including extension studies) ▪ Sub-group analyses of previously published studies ▪ Systematic reviews and meta-analyses (for cross-checking only) ▪ Pooled analyses (for cross-checking only)

*Studies with mixed populations were included if with more than 50% of patients with intermediate- or high-risk MDS or reporting outcomes among subgroup of patients with intermediate- or high-risk MDS.

CMML = chronic myelomoncytic leukemia; CR = complete response; HR = high risk; INT1 = intermediate 1; INT2 = intermediate 2; IPSS = International Prognositc Scoring System; ORR = objective response rate; SQ = subcutaneous.

Source: Sponsor-submitted ITC/NMA[12]

All abstracts and proceedings identified by the literature search were screened for eligibility. Potentially eligible studies underwent abstract and full-text article screening prior to data extraction. The quality of the included studies was assessed using The Cochrane Collaboration's Risk of Bias Tool.[12] Information regarding key steps of study selection for screening and data extraction, and quality assessment including how many reviewers were involved, and how differences of opinion were settled was not provided.

Indirect Treatment Comparison/Network Meta-Analysis

Analysis

The NMA was conducted using a Bayesian framework. By default, random effects models with non-informative prior distributions were attempted and deemed not feasible due to the small number of studies resulting in non-convergence and unrealistically wide credible intervals (CrI), limiting the ability to model between-study heterogeneity. Model convergence was assessed using trace plots and Gelman-Rubin-Brooks plots of the potential scale reduction factor with a minimum cut off below 1.05 by the final iteration. The number of iterations was 100,000 with a 5000 burn-in period.. Fixed effects models were used and reported as final models.[12]

The primary outcome of the ITC/NMA was survival including OS, AML-free survival (AMLFS), and 12-month OS. No definition for these outcomes was provided. Additional outcomes of interest for the ITC/NMA included clinical response (ORR defined as any of CR, PR and mCR, as well as CR, and HI) as defined by Cheson[3], and safety, with particular interest on neutropenia, anemia, and thrombocytopenia. No pre-planned subgroup analyses or sensitivity analyses were reported. The authors noted the limitation that subgroup analyses of intermediate-1 and CMML patients was not performed as only two trials (ASCERTAIN and D0007) included this population and a connected network could not be formed.[12] Treatment effects were compared using mean differences log(HR) for time to event variables. Comparisons of binary outcomes were compared using OR and conducted on the logit scale. Pooled direct and indirect HR and OR were estimated along with treatment rankings, and probabilities of each comparator being the best of all compared. Most trials included a common BSC reference arm except for ASCERTAIN, and therefore BSC was used as the reference treatment.[12]

Individual patient level data was reconstructed using KM curves using the Guyot approach[65] when HRs for OS and AMLFS were not reported for each trial. Hazard ratios were then estimated using Cox-proportional hazards models with standard errors and entered into the NMA. Proportional hazards assumptions were tested with visual assessment of the KM curves, Schoenfeld residuals and a Kolmogorov-supremum type test. The authors noted that small sample sizes at the end of follow-up caused KM curves to cross which suggested borderline evidence of violation to the proportional hazard assumption; however, no planned methods of addressing non-proportional hazards were mentioned. The deviance information criterion (DIC) was used to compare the goodness-of-fit of competing survival models.[12]

Assumptions

Comparisons of study design, inclusion/exclusion criteria, and patient characteristics were used to assess transitivity, homogeneity, and consistency, however, no information on this process was provided. The authors noted that the transitivity assumption appeared reasonable based on the assessment of trial designs, differences were noted with respect to the patient characteristic included in the trials, primarily with respect to cytogenetic risk, FAB and IPSS classifications.[12]

Scenarios

Given that the ASCERTAIN trial was incomplete at the time of the NMA/ITC report, the authors considered two approaches to assess comparative efficacy and safety of decitabine and cedazuridine: 1) Incorporating the ASCERTAIN data using historical controls, or 2) assuming the equivalence of decitabine and cedazuridine to IV decitabine based on the PK results of the ASCERTAIN trial. To assess the comparative effectiveness of decitabine and cedazuridine and relevant comparators, the authors produced three evidence networks:[12]

- **C-DEC Synthetic Trial**, where the OS treatment effect of decitabine and cedazuridine and relevant comparators was assessed by combining data from the ASCERTAIN trial and a historical control from D0007 (Kantarjian [2006][17]) trial and excluded decitabine IV trials from the network. Clinical response and safety endpoints were not analyzed as the complete ASCERTAIN trial data was not available. The historical control was incorporated using the following steps:
    - The best supportive care arm of the D0007 trial was digitized and the individual patient level data was recreated using the Guyot (2012) approach. This arm serves as the historical control for the ASCERTAIN study data.
    - The ASCERTAIN data, based on the April 2021 data cut, was pooled with the digitized D0007 historical control arm to develop a synthetic trial with BSC and C-DEC study arms.
    - The hazard ratios comparing C-DEC to BSC for OS and AMLFS were estimated using a Cox-proportional hazards model. The resulting hazard ratios were included the synthetic trial network meta-analysis using the Bayesian framework used for the limited and full networks.
- **Limited Network**, where the results of the AZA-001 (Fenaux [2009][16]) trial were excluded on the assumption that the OS benefit from this trial has not been reproduced in real-world evidence studies.
- **Full Network**, where the complete evidence network of all available and eligible trials was considered.

The limited and full network approaches above assumed the equivalence of decitabine and cedazuridine to IV decitabine, and ASCERTAIN data was not included in the analysis.

Results

Systematic Review

The SLR identified 4,204 citations based on the database search. Of these, 16 citations representing 11 unique RCTs met the inclusion criteria and were included in the SLR, while only five studies were included in the ITC/NMA: ASCERTAIN, AZA-001, CALGB-9221, EORTC 06011, and D0007.[7,16-19] All five studies were phase III randomized controlled trials. Details of the included trials is displayed in Table 53. No information on prior treatment was provided for two trials, and patients were excluded from three trials for prior MDS treatment. Inclusion criteria related to cytogenetics were not reported. Six trials met the eligibility criteria for the systematic review, but not the ITC/NMA, and were excluded as five studies were dose comparison studies, and one study violated the transitivity assumption as it included low and intermediate-1 risk patients.[12]

The baseline characteristics of patients in the five included studies are summarized in Table 54. The authors noted that the studies identified by the SLR were consistent with respect to trial design and inclusion/exclusion criteria. All but one trial included patients aged 18 years or older with intermediate-1, intermediate-2, high risk, or unspecified MDS or CMML.[12]

The median age of patients in studies included in the NMA/ITC ranged from 67 to 71 years. In each trial, most patients were male (range: 64% to 87%) with ECOG PS 0/1 (range, 85% to 96%). The proportion of patients with intermediate-1, intermediate-2, and high risk IPSS score ranged greatly across studies included in the ITC/NMA from 2% to 44%, 11% to 55%, and 9% to 49%, respectively. The authors noted that the EORTC 06011 trial had a notably higher proportion of patients with poor cytogenetic risk (45% to 48% vs. 16% to 30% in the other trials). The results of the authors' risk of bias assessment were presented and showed a low risk of bias with respect to incomplete outcomes, selective reporting, and random sequence allocation, while the risk of performance and detection bias was higher than other biases as trials were not blinded or blinding was not reported. Lastly, risk of bias due to allocation concealment was unclear.[12]

Table 53: SLR Studies Included in the ITC/NMA

Reference	Trial Acronym	Trial Arms	Study Design	Population	Total N	Inclusion Criteria	Exclusion Criteria
Garcia-Manero 2019	ASCERTAIN	CED+DEC and DEC	Phase 2/3 RCT, open-label, multicenter, crossover design	Int-1, Int-2, or High risk MDS and CMML	133	≥18 years ECOG ≤ 1 LE ≥3 months	Prior AZA/DEC
Fenaux 2009	AZA-001	AZA vs. CCR, BSC, and LDAC	Phase 3, open-label, multicenter RCT	Int-2 or high-risk MDS	316	≥18 years ECOG ≤2 LE ≥3 months	Prior AZA, Transplant or Cytotoxic Therapy for MDS
Silverman 2002	CALBG-9221	AZA vs. BSC	Phase 3 RCT, masking NR	Untreated MDS	191	≥15 years ECOG ≤2 LE ≥2 months	Prior treatment for MDS
Lubbert 2011	EORTC 06011	DEC+BSC vs. BSC	Phase 3 multicenter RCT, masking NR	Int-1 or 2 or high risk MDS, ineligible for intensive chemotherapy	233	≥60 years	NR
Kantarjian 2006	D0007	DEC+BSC vs. BSC	Phase 3, open-label, multicenter RCT	MDS	170	≥18 years	NR

AZA = azacitidine; BSC = best supportive care; DEC = decitabine; CED= = cedazuridine; CCR = conventional care regimens; ECOG = Eastern Cooperative Oncology Group; LDAC = low dose cytarabine; MDS = myelodysplastic syndromes; NR = not reported; RCT = randomized controlled trial

Source: Garcia-Manero 2019[7]; Fenaux 2009[16]; Silverman 2002[19]; Lubbert 2011[18]; Kantarjian 2006[17], Sponsor-Submitted ITC/NMA[12]

Table 54. Baseline Characteristics of Patients in RCTs included in the ITC/NMA

	ASCER-TAIN	AZA-001						CALGB 9221		EORTC 06011		D0007	
Characteristic	C-DEC	AZA	LDAC	AZA	CCR	AZA	BSC	AZA	BSC	DEC	BSC	DEC	BSC
Median age (range)	71.0 (44-88)	69 (42-82)	71 (56-85)	69 (42-83)	70 (38-88)	69 (42-83)	70 (50-88)	69 (31-92)	67 (35-88)	69 (70-90)	70 (60-86)	70 (65-76)	70 (62-74)
Male		39 (87)	35 (71)	132 (74)	119 (67)	81 (69)	67 (64)	72 (73)	60 (65)	76 (64)	73 (64)	59 (66)	57 (70)
FAB Class													
RAEB		27 (60)	25 (51)	104 (58)	103 (65)	69 (59)	68 (65)	32 (32)	34 (37)				
RAEB-T		15 (33)	19 (39)	61 (34)	62 (35)	38 (33)	30 (29)	27 (27)	18 (20)	61 (51)	64 (56)	47 (53)	43 (53)
CMML		1 (2.2)	1 (2)	6 (3)	5 (4)	5 (4)	4 (4)	7 (7)	7 (8)	40 (34)	35 (31)	17 (19)	14 (17)
AML		1 (2.2)	1 (2)	1 (1)	1 (1)					10 (8)	4 (4)	6 (7)	8 (10)
Indeterminate		1 (2.2)	3 (6.1)							1 (1)	1 (1)		
RA								5 (5)	20 (22)				
RARS								17 (17)	3 (3)	5 (4)	8 (7)	12 (13)	12 (15)
Other								11 (11)	10 (11)	3 (3)	2 (2)	7 (8)	4 (5)
IPSS Risk													
Low								2 (2)	5 (6)				
INT-1	44%	1 (2)	2 (4)	5 (3)	13 (7)	4 (3)	9 (9)	21 (26)	16 (20)	8 (6.7)	8 (7.0)	28 (31)	24 (30)
INT-2	20%	22 (49)	21 (43)	76 (43)	70 (39)	48 (41)	46 (44)	9 (11)	13 (16)	64 (53.8)	63 (55.3)	38 (43)	36 (44)
HR	16%	19 (42)	21 (43)	82 (46)	85 (48)	57 (49)	46 (44)	7 (9)	8 (10)	46 (38.7)	42 (36.8)	23 (26)	21 (26)
Secondary MDS										15 (12.6)	14 (12.3)	12 (13)	11 (14)
Cytogenetic Risk (poor)		13 (29)	8 (16)	50 (28)	50 (28)	33 (28)	31 (30)			57 (47.9)	51 (44.7)	26 (29)	19 (23)
ECOG PS (0/1)		42 (94)	46 (94)	164 (92)	166 (93)	106 (90)	95 (90)			105 (88.3)	97 (85)	85 (96)	76 (94)
Bone Marrow , median												10 (4-7)	9 (5-16)
HgB, median g/dL		9.6 (7.1-12.2)	9.7 (5.4-14.3)					9.0 (5.3-14.0)	9.3 (5.7-14.0)				

n (%), unless otherwise specified

AML = acute myeloid leukemia; AZA = azacitidine; BSC = best supportive care; C-DEC = cedazuridine + decitabine; CCR = conventional care regimen; CMML = chronic myelomonocytic leukemia; ECOG = Eastern Cooperative Oncology Group; HgB = hemoglobin; IPSS = International Prognostic Scoring System; LDAC = low dose cytarabine; MDS = myelodysplastic syndromes; PS = performance status; RA = refractory anemia; RAEB = refractory anaemia with excess blasts; RAEB-T = refractory anaemia with excess blasts in transformation; RARS = refractory anemia with ringed sideroblasts

Source: Sponsor-submitted ITC/NMA[12]

NMA Results

C-DEC Synthetic Trial:

The synthetic trial evidence scenario used a historical BSC control from the D0007 (Kantarjian [2006]) trial. Data were then combined with the ASCERTAIN trial to facilitate comparisons of decitabine and cedazuridine with azacitidine and BSC.[12] The synthetic trial evidence networks from the original and updated NMA reports, irrespective of outcomes of interest is depicted in Figure 18. [redacted].[20] [redacted].*(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Figure 18: Synthetic Evidence Network

Source: Sponsor-submitted ITC/NMA[12]; Updated Sponsor-submitted ITC/NMA [20]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Survival Outcomes

Table 55 reports the [redacted] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 55: OS and AMLFS Log(HR) for NMA used in the Synthetic ITC/NMA

[redacted]

Source: Sponsor-submitted ITC/NMA[12]; Updated Sponsor-submitted ITC/NMA[20]

The results of the original and updated ITC/NMAs are summarized in Table 56 for the HR (95% CrI) for OS and AMLFS for each pairwise comparison in the synthetic trial scenarios.

In the initial sponsor-submitted ITC/NMA report ([redacted]), only results of OS were displayed for the synthetic network as the ongoing ASCERTAIN trial did not have results for other outcomes of AMLFS, clinical response, and safety at the time of the analysis. [redacted] Hazard ratios above 1 indicate a higher risk of mortality while HRs <1 indicates less risk relative to the comparator. [redacted][12] The forest plot summarizing the results of the synthetic control NMA are shown in Figure 17a. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

[redacted][20]

[redacted].[20] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 56: OS and AMLFS HR NMA and Pairwise Comparison Results

[redacted]

Source: Sponsor-submitted ITC/NMA[12]; Updated Sponsor-submitted ITC/NMA[20]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Figure 19: Synthetic Network OS and AMLFS Forest Plots

Source: Sponsor-submitted ITC/NMA[12]; Updated Sponsor-submitted ITC/NMA[20]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

[redacted].[12] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Limited Network:

In the limited evidence network (Figure 20), the authors excluded results from Fenaux (2009) trial due to the reported OS benefit that has not been replicated in the real-world.12 [redacted].[17-19] The sponsor clarified that the ASCERTAIN trial was not included in the network due to the crossover design of the trial, thus no data from the ASCERTAIN trial was used in the analysis, however, the authors assumed equivalence between decitabine and cedazuridine and IV decitabine. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Figure 20. Limited Evidence Network

Source: Sponsor-submitted ITC/NMA[12]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Survival Outcomes

Table 57 reports the raw outcome data which were used in the NMA of OS and AMLFS.

[redacted][12] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

[redacted][12] The results of the limited NMA for OS are summarized in Table 61. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 57: OS and AMLFS Log(HR) for NMA used in the Limited Evidence ITC/NMA

[redacted]

Source: Sponsor-submitted ITC/NMA[12]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Table 58 reports the raw outcome data which were used in the NMA of 12-month OS. [redacted][12] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 58: 12-Month OS Raw Outcome Data used in the Limited Evidence ITC/NMA

[redacted]

Source: Sponsor-submitted ITC/NMA[12]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

The forest plot summarizing the OS, AMLFS, and 12-month OS results of the limited evidence network are shown in Figure 21a.

Clinical Response Outcomes

Table 59 reports the raw outcome data for clinical response outcomes of ORR, CR, and HI that were used in the NMA.

Table 59: Raw Clinical Response Outcome Data Used in the Limited Evidence ITC/NMA

[redacted]

Source: Sponsor-submitted ITC/NMA[12]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

[redacted][12]

[redacted][12]

[redacted][12] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

The forest plot summarizing the clinical response results of the limited evidence network are shown in Figure 19b.

Safety Outcomes

Table 60 reports the raw safety data for neutropenia, anemia, and thrombocytopenia that were used in the NMA.

Table 60: Raw Safety Outcome Data Used in the Limited Evidence ITC/NMA

[redacted]

Source: Sponsor-submitted ITC/NMA[12]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

The results of the limited evidence NMA for safety outcomes are summarized in Table 61. [redacted][12]

[redacted][12]

[redacted][12] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

The forest plot summarizing the safety results of the limited evidence network are shown in Figure 19c.

Table 61: Limited Network Survival, Response, and Safety HR/OR NMA and Pairwise Comparison Results

[redacted]

Source: Sponsor-submitted ITC/NMA[12]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Figure 21: Limited Network Survival, Response, and Safety Endpoint Forest Plots

[redacted]

Source: Sponsor-submitted ITC/NMA[12]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Full Network:

The full base case evidence network diagram is shown in Figure 22. [redacted] The authors noted that an additional study (NCT01720225[66]) violated the transitivity assumption as the study population included lower risk MDS patients, and was therefore excluded from the network.[12] As with the limited evidence network, the ASCERTAIN trial was unable to be included due to the crossover design, and the authors assumed equivalence between decitabine and cedazuridine and IV decitabine. Thus, no data from the ASCERTAIN trial (decitabine and cedazuridine) was used in the analysis. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor*

requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Figure 22: Full Evidence Network

[redacted]

Source: Sponsor-submitted ITC/NMA[12]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Survival Outcomes

Table 62 reports the raw outcome data which were used in the NMA of OS and AMLFS. The Fenaux (2009) trial was not included in the 12-month OS analysis as these estimates nor Kaplan-Meier curves were reported for the AZA vs BSC comparison, therefore the results are identical to the limited network scenario reported in Table 58.[12]

Table 62: OS and AMLFS Log(HR) for NMA used in the Full ITC/NMA

[redacted]

Source: Sponsor-submitted ITC/NMA[12]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Table 68 reports the OS, AMLFS, and 12-month OS HR/OR NMA results for each comparator relative to BSC. [redacted][12] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 63: Full Network Pairwise Comparison Results (Survival Outcomes)

[redacted]

Source: Sponsor-submitted ITC/NMA[12]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

The forest plot summarizing the OS, AMLFS, and 12-month OS results of the full evidence network are shown in Figure 23aa.

Clinical Response Outcomes

Table 64 reports the raw outcome data for clinical response outcomes of ORR, CR, and HI that were used in the NMA.

Table 64: Raw Clinical Response Outcome Data Used in the Full ITC/NMA

[redacted]

Source: Sponsor-submitted ITC/NMA[12]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Table 68 summarizes the results the OR NMA results for each comparator relative to BSC for clinical response outcomes (ORR, CR and HI). [redacted][12] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 65: Full Network Pairwise Comparison Results (Clinical Response Outcomes)

[redacted]

Source: Sponsor-submitted ITC/NMA[12]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

The forest plot summarizing the clinical response results of the limited evidence network are shown in Figure 21b.

Safety Outcomes

Table 66 reports the raw safety data for neutropenia, anemia, and thrombocytopenia that were used in the full NMA.

Table 66: Raw Safety Outcome Data Used in the Full ITC/NMA

[redacted]

Source: Sponsor-submitted ITC/NMA[12]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

The results of the full NMA for safety outcomes are summarized in Table 68. [redacted][12] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 67: Full Network Pairwise Comparison Results (Safety Outcomes)

[redacted]

Source: Sponsor-submitted ITC/NMA[12]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

The forest plot summarizing the safety results of the limited evidence network are shown in Figure 21c.

Table 68: Full Network Survival, Response, and Safety HR/OR NMA Results

[redacted]

Source: Sponsor-submitted ITC/NMA[12]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Figure 23: Full Network Survival, Response, and Safety Endpoint Forest Plots

Source: Sponsor-submitted ITC/NMA[12]
(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

Critical Appraisal of Indirect Treatment Comparison/Network Meta-Analysis

The sponsor submitted ITC/NMA was critically appraised according to recommendations of the International Society for Pharmacoeconomics and Outcomes Research Task Force on Indirect Treatment Comparisons and Network Meta-Analyses.[67] Details of the quality appraisal are provided in Table 69.

The key limitations of the ITC/NMA include the small size and structure of the network, which had no closed loops, the potential heterogeneity across the trials related to differences in study design and patient characteristics, and the clinical and methodological assumptions made. These limitations resulted in imprecision of estimates and multiple potential sources of bias. The ITC/NMA only provides indirect evidence for the comparison of decitabine and cedazuridine in two of three network scenarios (limited and full evidence networks) as no data from the ACERTAIN trial was included and relies on the assumption of equivalence to IV decitabine. Conversely, the synthetic network scenario included combined ASCERTAIN and D0007 OS and AMLFS data. These limitations are summarized below.

The ITC/NMA was based on a SLR that identified studies according to prespecified inclusion criteria. The literature search was last conducted in 2020, and appeared comprehensive; however, only search terms for decitabine and azacitidine were used, and those related to other relevant comparators in MDS and all IPSS categories were not specified. Moreover, the planned search was restricted to studies published after 2010, and therefore it's possible that, given the lack of innovation in the therapeutic space, some key historical trials involving relevant comparators may be missing. However, studies published before 2010 were identified and included, although no detail was provided on how these studies were identified. There was no list of studies excluded at the full-text stage, and therefore it was not possible to assess whether potentially eligible studies were excluded. The report did however include a list of studies that were included in the SLR but then excluded from the ITC, along with the justification for exclusion. The methods of study selection and data extraction were omitted, so it is unclear whether appropriate methods were followed. The authors' risk of bias assessments concluded that the five included trials had low risk of bias on most domains of the Cochrane Risk of Bias Tool, with the exception of allocation concealment and blinding for most trials, and therefore the risk of performance and detection bias was higher.

Overall, the outcomes assessed were appropriate; however, other important outcomes including PFS, and HRQoL were not considered. Progression-free survival was included as an outcome, and it is assumed that evidence of this outcome was limited. Health related quality of life was not included in the PICOS framework of the SLR. Based on the NMA report, it is unclear whether the outcomes assessed in the included trials were similar with respect to the definitions used and assessment methods (i.e., investigator versus centrally assessed) as this was not reported. The authors also did not report the criteria of the trials used to determine response (complete or partial). There was no mention of duration of follow up or time of assessment of the outcomes in the studies included in NMA. Any differences in outcome assessment and the criteria used for response across included studies may be a source of heterogeneity between studies and have the potential to influence (bias) relative treatment effect estimates.

The authors noted that random effects models were not feasible as there was a small number of studies and sample size in the NMA resulting in non-convergence and wide CrIs, which limits the ability to model between-study heterogeneity. Instead, the authors relied on visual inspection of heterogeneity across trials.

There were other differences in study characteristics across the trials that may also be potential sources of heterogeneity, namely characteristics of the populations in the studies. The EORTC 06011 trial had notably higher proportions of patients with poor cytogenetic risk (range of 44.7% and 47.9% in the EORTC 06011 trial vs. 16% to 30% in all other trials). There were also notable differences in the proportion of patients with different IPSS risk classes in each trial, with intermediate-1 patients ranging from 2% to 44%, intermediate-2 patients ranging from 11% to 55%, and high-risk patients ranging from 9% to 49% across studies. As cytogenetic risk and IPSS category are likely treatment effect modifiers, violation of the transitivity assumption and heterogeneity could be considered. The authors did note that one study, NCT01720225, met the inclusion criteria, but was excluded as violating the transitivity assumption, as the patient population had low risk MDS. Moreover, the authors noted that the small number of available trials limited the ability of the NMA to model between-study heterogeneity or to adjust for the influence of potential treatment effect modifiers by meta-regression. Therefore, the NMA results may be affected by differences in study and patient characteristics across the trials, and the direction of this potential bias is difficult to determine in light of missing information and imbalances in factors that bias in different directions.

The authors noted that in several studies, the OS and AMLFS HR were not reported, therefore digitization of KM curves was required to reconstruct individual patient-level data to estimate HR, which may be susceptible to bias and error. Furthermore, the authors noted that small sample sizes at the end of follow-up caused KM curves to cross which suggested possible violation to the proportional hazard assumption. There was no mention of how the authors handled non-proportional hazards in the analysis. They also noted that several studies reported no patients experiencing objective response or CR in their respective BSC arms, therefore a continuity correction was incorporated to prevent infinite ORs, which resulted in significant imprecision and wide confidence intervals (see response outcomes in Table 61 and Table 65), and so the response results must be interpreted with caution.

In all three scenarios, the available trials formed networks with no closed loops; therefore, it was not possible to validate the transitivity assumption of NMA and check for consistency of results between direct and indirect comparisons. The synthetic trial scenario incorporated a synthetic trial consisting of a historical BSC control arm and the decitabine and cedazuridine group of the ASCERTAIN trial. This involves the assumption that the D0007 BSC control arm is representative and would perform similarly in each study population. Randomization was not preserved within the NMA due to this comparison, which may result in inaccurate, and potentially over-estimated treatment effect of decitabine and cedazuridine. This method was also applied to the updated analyses (April 2021 data cut-off), where the newly available OS and AMLFS from the ASCERTAIN trial was pooled with the digitized D0007 data. Information on the homogeneity of populations for these two trials was not provided, and therefore estimates concerning this synthetic trial are highly uncertain. The results of the synthetic network scenario were consistent for OS between the original ITC/NMA report submitted and the updated analysis based on the April 2021 data cut-off of the ASCERTAIN trial, however, the decitabine and cedazuridine combination was now favoured over BSC in the updated analysis, however given the limitations specified above, these results are at a risk of bias and are uncertain. In the updated NMA analysis, the Silverman 2002 trial was removed from the base case analysis post-hoc as it greatly reduced the comparative efficacy of azacitidine, which ensured more conservative estimates of treatment effect according to the sponsor. This change was considered inappropriate as the Silverman 2002 study met the pre-specified inclusion criteria, and has the potential to introduce further bias. In a scenario analysis with the Silverman 2002 trial included, decitabine and cedazuridine was favoured over azacitidine and BSC, however as previously mentioned, this greatly impacted the comparative efficacy of azacitidine. Coupled with a fairly wide CI, the true direction of benefit and results of comparative efficacy between decitabine and cedazuridine and azacitidine remains uncertain.

In the limited evidence and full evidence networks, the main limitation of the NMA/ITC is the indirectness of the ITC itself and the assumption that oral decitabine and cedazuridine is equivalent to IV decitabine. Although the results of the phase II ASTX727-01-B, and phase III ASCERTAIN trials suggest PK equivalence between the oral decitabine and cedazuridine and IV decitabine, no data or evidence from the decitabine and cedazuridine trials was presented in the limited and full networks for the assumption of clinical equivalence. As previously noted, survival curves were digitized in the limited evidence network, which is susceptible to imprecise estimates. Moreover, they noted that low numbers of events for clinical response outcomes resulted in significant imprecision of response results. In the limited network scenario, the authors excluded the AZA-001 study as it reports an OS benefit that has not been replicated in real world evidence studies. The authors stated that the results of the full evidence network are also susceptible to the same biases of the limited network due to the digitization of curves and limited response events, as well as potential bias due to the inclusion of results from the AZA-001 trial, which was thought to be unrepresentative of the population. The authors believe that the inclusion of this trial in the full evidence network may bias the OS results in favour of azacitidine. This was evidence by the OS results of the full evidence network (i.e., inclusion of AZA-001) favouring azacitidine, while in the limited evidence network, there was no difference between azacitidine and decitabine. The CGP noted that the higher-risk population included in the AZA-001 trial (primarily intermediate-2 and high risk, as well as some AML patients) trial would be expected to have decreased response to treatment and survival; however, this was not the case.

The authors did not conduct any subgroup analyses by IPSS risk category. They noted that analysis of intermediate-1 and CMML patients were not performed as only two trials included these populations and a network could not be constructed. The authors stated that the results of the indirect comparison are assumed to be similar across IPSS risk groups. Given that patients with intermediate-1 generally have less severe disease and also are treated with treatments not included in the SLR or ITC/NMA (lenalidomide, antithymocyte globulin, erythroid stimulating agents, HSCT, etc.) the assumption that patients would respond the same should be interpreted with caution. The same rationale applies for patients with CMML, given that the treatments for these patients are different than what was used in the ITC/NMA.

Overall, the results of the ITC/NMA may not be generalizable to the Canadian context. The reimbursement request for this submission was for treatment of adult patients with MDS including previously treated and untreated, de novo and secondary MDS with the following FAB subtypes and intermediate-1, intermediate-2, and high-risk IPSS groups. The analyses presented for the ITCs were not specified FAB subtype, nor by IPSS risk category, and no analyses for intermediate-1 and CMML patients were conducted due to a lack of available data, which were included in the funding request. The sponsors assumption that the results apply across IPSS risk groups may be challenged. Azacitidine is not an approved treatment for the intermediate-1 and CMML populations; however, it may be given off-label in these patients, and therefore could be considered a relevant treatment option and comparator in Canada. Additionally, no conclusions can be made for other relevant subgroups identified previously by the CGP of this submission (i.e., Genetic mutations, transfusion dependence, age, ECOG PS) as these subgroups were not analyzed in the ITC and may be considered treatment effect modifiers. Outcomes related to other relevant efficacy outcomes (e.g., PFS), and HRQoL were not included in the analyses and therefore no conclusions can be drawn comparing the treatment for these outcomes.

Table 69: Summary and Critical Appraisal of Sponsor-Submitted ITC/NMA Using ISPOR Criteria

ISPOR Questions	Details and Comments
1. Is the population relevant?	Yes, partially. The ITC/NMA did not include low risk, intermediate-1 risk, and CMML patients, where intermediate-1 and and CMML patients are included in the funding request, and therefore does not address key questions for these patients. The AZA-001 trial did not include intermediate-1 or CMML patients and the CALGB-9221 trial did not specify the IPSS status. Subgroup analyses of these populations were not conducted as only two eligible trials included intermediate-1 and CMML patients, and therefore the sponsor stated that results of the ITC were assumed to be similar across IPSS risk and CMML populations, however uncertainty remains in IPSS intermediate-1 and CMML patients.
2. Are any critical interventions missing?	Yes. Relevant comparators for the intermediate-1 (BSC, azacitidine, and lenalidomide; for Del5q patients) and CMML (azacitidine, hydroxyurea, and HSCT) populations were not included. The sponsor acknowledged the use of azacitidine in these populations as off-label and through compassionate or other access programs. Lenalidomide was included in the systematic review search, however trials of lenalidomide were excluded as they included primarily a low-risk population. The sponsor noted that a lack of a common anchor hindered the inclusion of hydroxyurea in the ITC/NMA. It should be noted that the limited and full evidence networks did not include any data for decitabine and cedazuridine, and that equivalence between decitabine and cedazuridine and IV decitabine was assumed for all clinical endpoints based on PK data.
3. Are any relevant outcomes missing?	Yes. The ITC/NMA reported outcomes for survival (OS, AMLFS, 12-month OS), clinical response (ORR, CR, HI), and safety (neutropenia, anemia, and thrombocytopenia), however other important outcomes such as PFS and HRQoL were not included.
4. Is the context (e.g., settings and circumstances) applicable to your population?	Overall, the generalizability of the results to the Canadian context may be limited by the population included in the analysis. The reimbursement request for this submission was for treatment of adult patients with MDS including previously treated and untreated, de novo and secondary MDS with the following FAB subtypes and intermediate-1, intermediate-2, and high-risk IPSS groups. The analyses presented for the ITCs did not include intermediate-1 or CMML patients, and no subgroup analyses by IPSS risk category was presented.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	Yes. The researchers performed a SLR with prespecified PICOS criteria to identify relevant trials, however search terms did not include all relevant comparators and interventions in MDS. The ITC/NMA report described the information sources searched and the search strategies used. However, in the updated analysis of the synthetic network, one study (Silverman 2002) was removed after the analysis as it created a reduced effect of azacitidine, which biases the results.

ISPOR Questions	Details and Comments
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	The included trials formed a connected network; however, there was no closed loops available to evaluate consistency of direct and indirect evidence.
7. Is it apparent that poor quality studies were included thereby leading to bias?	The quality of the included studies was evaluated using the Cochrane Risk of Bias tool. The authors stated that the included trials had a low risk of bias.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	Selective outcome reporting was evaluated as part of the risk of bias assessment and no selective outcome reporting was found for each included trial.
9. Are there systematic differences in treatment effect modifiers (i.e., baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	No treatment effect modifiers were assessed in the ITC/NMA. The individual distributions of patients for most baseline patient and study characteristics were reported (i.e., age, sex [male], FAB class) and were similar between the included studies; however, some differences were noted (proportions of patients with poor cytogenetic risk, and IPSS risk class), however no analyses were conducted. Some information was missing with regards to ECOG PS, transfusion dependence, time since diagnosis, and prior therapy, making it difficult to identify all potential sources of clinical heterogeneity. The ITC/NMA report did not provide a full summary of the eligibility criteria used in each trial.
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	The report did not mention any treatment effect modifiers prior to comparing individual study results, and no analyses were conducted on the basis of treatment effect modifiers.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	Within study randomization was violated for the synthetic network scenario as the comparisons were made between the decitabine and cedazuridine population of ASCERTAIN, and the decitabine arm of D0007. For the limited and full evidence networks, within study randomization was preserved. It does not appear that naïve comparisons were made.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e., closed loops), was agreement in treatment effects (i.e., consistency) evaluated or discussed?	Not applicable. There were no closed loops.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Not applicable. There were no closed loops.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	No, the authors did not attempt to minimize inconsistency or imbalance biases within the analysis. The authors noted that small number of trials and small sample sizes limited the ability of the study to account for heterogeneity in patient populations through meta-regressions and random effects models, and low event rates, particularly in the response analysis, caused substantial imprecision in the indirect estimates of treatment effect.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	Yes, the authors noted that due to small sample size, methods to account for heterogeneity in the populations such as meta-regression and random effects models could not be used.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	Not applicable. Random effects models were not used.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	Not applicable. Meta-regression was not possible due to the small network size, study sample sizes, and no subgroup analyses were conducted.
18. Is a graphical or tabular representation of the evidence network provided with information	Evidence network diagrams were presented for all analyses and scenarios.

ISPOR Questions	Details and Comments
on the number of RCTs per direct comparison?	
19. Are the individual study results reported?	Yes. Where possible, the authors included the n, % for each participant, and the HR/OR from the individual studies for the various outcomes.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	No.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	Yes.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	Yes.
23. Is the impact of important patient characteristics on treatment effects reported?	No
24. Are the conclusions fair and balanced?	Yes, the conclusions were fair and balanced, albeit there was some uncertainty around the results. The authors concluded that the results of the ITC/NMA demonstrated that DEC and AZA were favoured over BSC in terms of survival and clinical response outcomes, but not for safety outcomes. In two of three network scenarios, DEC and AZA were not significantly different from each other with respect to survival, clinical response, and safety, however in the full evidence network, decitabine was associated with a significantly lower OS and AMLFS compared to azacitidine. Results are thought to be biased by the authors due to the inclusion of the AZA-001 trial which included some higher-risk patients and the real-world survival for azacitidine has not been replicated. The CGP noted that it is expected that this higher-risk population would have lower survival and response rates than the results of the AZA-001 study report.
25. Were there any potential conflicts of interest?	No conflict-of-interest information was reported; however, the ITC/NMA was commissioned by the sponsor.
26. If yes, were steps taken to address these?	No.

AMLFS = acute myeloid leukemia-free survival; BSC = best supportive care; CMML = chronic myelomonocytic leukemia; CR = complete response; ECOG = Eastern Cooperative Oncology Group; FAB = French-American-British; HI = hematologic improvement; HR = hazard ratios; HRQoL = health-related quality of life; HSCT = hematopoietic stem cell transplant; IPSS = International Prognostic Scoring System; ITC = indirect treatment comparison; NMA = network meta-analysis; OR = odds ratio; OS = overall survival; ORR = objective response rate; PFS= progression-free survival; PS = performance status; SLR = systematic literature review.

7.1.3 Summary

In the absence of direct evidence comparing ASTX727 to other relevant treatments in MDS patients, the sponsor provided CADTH with an unpublished report comparing decitabine and cedazuridine and/or decitabine to azacitidine, BSC, conventional care regimens for the treatment of intermediate-1, intermediate-2, and high-risk MDS and CMML. This report was later updated to include more mature median OS and AMLFS from the ASCERTAIN trial.Analysis methodology remained the same. A systematic literature search identified five trials that met the eligibility criteria and were included in the ITC/NMA. The trials evaluated the following treatments, all compared to BSC except ASCERTAIN: decitabine and cedazuridine, decitabine, azacitidine, CCR, and LDAC. Treatments were compared with respect to the following endpoints: OS, AMLFS, 12-Month OS, ORR, CR, HI, neutropenia, anemia, and thrombocytopenia. The analyses were conducted in a Bayesian framework and considered three possible evidence networks: 1) C-DEC Synthetic Trial; where OS and AMLFS outcome data from ASCERTAIN was incorporated with historical IV decitabine data, 2) Limited Network; where the results of the AZA-001 trial were excluded on the assumption that the OS benefit from this trial has not been reproduced in real-world evidence studies, and 3) Full Network; where the complete evidence network of all available and eligible trials was considered. Scenarios 2 and 3 assumed equivalence of oral decitabine and cedazuridine and IV decitabine based on PK data from ASTX727-01-B and ASCERTAIN, however the report did not include decitabine and cedazuridine data from the ASCERTAIN trial, nor was there evidence presented for the assumption of clinical equivalence. In the synthetic evidence network, within study randomization was not preserved within the NMA which may result in inaccurate, and potentially over-estimated

treatment effects. Both decitabine and cedazuridine and azacitidine were favoured over BSC with respect to OS, but there was no difference between azacitidine and decitabine and cedazuridine. In the limited evidence network, there was no difference between azacitidine and decitabine with regards to survival outcomes, and azacitidine was only favoured over BSC for AMLFS. In contrast, the full evidence network demonstrated that azacitidine is favoured over decitabine and BSC for OS and AMLFS, while decitabine showed no difference compared to BSC for any survival outcomes. Both azacitidine and decitabine were favoured over BSC for all clinical response outcomes, and there was no difference between azacitidine and decitabine. With regards to safety, rates of thrombocytopenia were higher for decitabine in both the limited and full evidence networks, and both azacitidine and decitabine were associated with higher rates of neutropenia and thrombocytopenia compared to BSC. The key limitations of the ITC/NMA include the small size and structure of the network, which had no closed loops, potential sources of heterogeneity across the trials related to differences in study design and patient characteristics such as the differences in IPSS groups and differences in cytogenetic risk of patients across studies, the lack of ability to use random effects models or meta-regression in the analysis, and the clinical and methodological assumptions made including the assumption of equivalence between oral decitabine and cedazuridine and IV decitabine, as well as the lack of comparative efficacy data for decitabine and cedazuridine which hindered the ability to incorporate the ASCERTAIN trial results in two of three network scenarios. The results of the ITC/NMA should be interpreted with caution considering these limitations.

8 Comparison with Other Literature

The CADTH Clinical Guidance Panel and the CADTH Methods Team did not identify other relevant literature providing supporting information for this review.

9 About this Document

This Clinical Guidance Report was prepared by the CADTH Hematology Clinical Guidance Panel and supported by the CADTH Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on Decitabine and Cedazuridine for the treatment of adult patients with MDS. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant CADTH Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

CADTH considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the Procedures for the CADTH pan-Canadian Oncology Drug Review. The sponsor, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

Appendix 1: Literature Search Strategy and Detailed Methodology

1. Literature search via Ovid platform

Database(s): Cochrane Central Register of Controlled Trials (CENTRAL); Embase (1974 to present); MEDLINE All (1946 to present)

Search Strategy:

#	Searches	Results
1	(inqovi* or ASTX727 or ASTX 727 or C-DEC).ti,ab,kf,kw,hw,nm,rn,ot.	67
2	Decitabine/ or (Decitabine* or dacogen* or NSC 127716 or NSC127716 or "BRN 0617982" or CCRIS 8227 or BRN0617982 or CCRIS8227 or DAC or JNJ 30979754 or JNJ30979754 or 776B62CQ27).ti,ab,ot,kf,kw,hw,nm,rn.	36169
3	(cedazuridine* or E7727 or E 7727 or WHO 10741 or WHO10741 or 39IS23Q1EW).ti,ab,ot,kf,kw,hw,nm,rn.	61
4	2 and 3	59
5	1 or 4	92
6	5 use medall	25
7	5 use cctr	16
8	*cedazuridine plus decitabine/	2
9	(inqovi* or ASTX727 or ASTX 727).ti,ab,kw,dq.	40
10	8 or 9	41
11	*decitabine/ or (Decitabine* or dacogen* or NSC 127716 or NSC127716 or "BRN 0617982" or CCRIS 8227 or BRN0617982 or CCRIS8227 or DAC or JNJ 30979754 or JNJ30979754).ti,ab,kw,dq.	10852
12	*cedazuridine/ or (cedazuridine* or E7727 or E 7727 or WHO 10741 or WHO10741).ti,ab,kw,dq.	39
13	11 and 12	37
14	10 or 13	49
15	14 use oemezd	25
16	15 not (conference abstract or conference review).pt.	8
17	15 not 16	17
18	limit 17 to english language	17
19	limit 18 to yr="2015 -Current"	16
20	6 or 16	33

21	limit 20 to english language	28
22	7 or 21	44
23	remove duplicates from 22	35

2. **Cochrane Central Register of Controlled Trials (CENTRAL)**
   (Searched via Ovid)

3. **Grey literature search via:**

Clinical trials registries:

US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

World Health Organization
http://apps.who.int/trialsearch/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Health Canada's Clinical Trials Database
https://health-products.canada.ca/ctdb-bdec/index-eng.jsp

The European Clinical Trials Register
https://www.clinicaltrialsregister.eu/ctr-search/search

Search: ASTX727 OR inqovi* OR ASTX 727 OR (Decitabine* OR dacogen* OR NSC 127716 OR NSC127716 OR BRN 0617982 OR CCRIS 8227 OR BRN0617982 OR CCRIS8227 OR DAC OR JNJ 30979754 OR JNJ30979754) AND (cedazuridine* OR E7727 OR E 7727 OR WHO 10741 OR WHO10741)

Select international agencies including:

US Food and Drug Administration (FDA)
https://www.fda.gov/

European Medicines Agency (EMA)
https://www.ema.europa.eu/

Search: ASTX727 OR inqovi* OR ASTX 727 OR (Decitabine* OR dacogen* OR NSC 127716 OR NSC127716 OR BRN 0617982 OR CCRIS 8227 OR BRN0617982 OR CCRIS8227 OR DAC OR JNJ 30979754 OR JNJ30979754) AND (cedazuridine* OR E7727 OR E 7727 OR WHO 10741 OR WHO10741)

Conference abstracts:

American Society of Clinical Oncology (ASCO)
https://www.asco.org/

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

American Society of Hematology (ASH)

http://www.hematology.org/

Search: Search: ASTX727 OR inqovi* OR ASTX 727 OR (Decitabine* OR dacogen* OR NSC 127716 OR NSC127716 OR BRN 0617982 OR CCRIS 8227 OR BRN0617982 OR CCRIS8227 OR DAC OR JNJ 30979754 OR JNJ30979754) AND (cedazuridine* OR E7727 OR E 7727 OR WHO 10741 OR WHO10741) – 2015 - 2020

Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the PRESS Peer Review of Electronic Search Strategies checklist (https://www.cadth.ca/resources/finding-evidence/press).[68]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Inqovi (decitabine and cedazuridine). The search was limited to English-language documents but not limited by publication year.

The search is considered up to date as of February 18, 2021.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the Grey Matters: A Practical Tool For Searching Health-Related Grey Literature checklist (https://www.cadth.ca/grey-matters).[69] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trials registries (US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry, Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials, Health Canada Clinical Trials Database, and the European Clinical Trials Registry), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Hematology (ASH), the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the CADTH Clinical Guidance Panel. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

Study Selection

One member of the CADTH Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team made the final selection of studies to be included in the review.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the CADTH Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. [Cite tools used for quality assessment of included studies]. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and CADTH:

- The Methods Team wrote a summary of background clinical information, a systematic review of the evidence, interpretation of the systematic review, and summaries of evidence for supplemental questions.
- The CADTH Clinical Guidance Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- CADTH wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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