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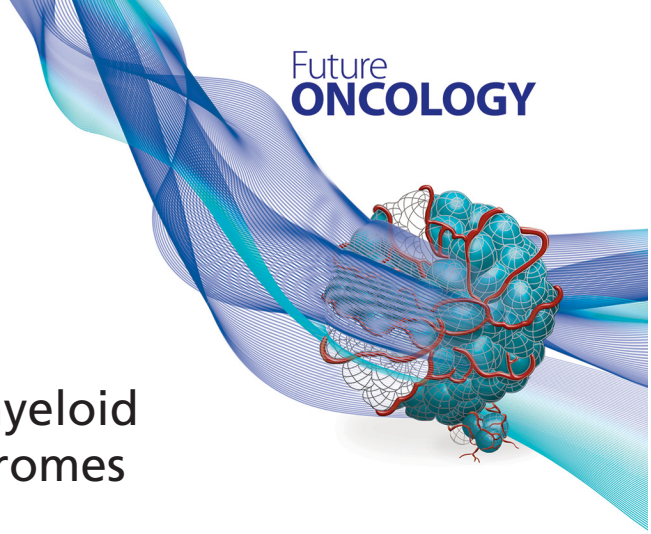

The path to approval for oral hypomethylating agents in acute myeloid leukemia and myelodysplastic syndromes

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Two oral hypomethylating agents, oral azacitidine (CC-486) and decitabine/cedazuridine (ASTX727), have recently entered the clinical domain. CC-486 has been shown to improve overall survival as maintenance therapy for older patients with acute myeloid leukemia in complete remission, whereas the combination of decitabine with cedazuridine, a cytidine deaminase inhibitor, is indicated for the treatment of adult patients with myelodysplastic syndromes and chronic myelomonocytic leukemia with intermediate-1, or higher, International Prognostic Scoring System risk. This article briefly summarizes the clinical development of both drugs, the pivotal studies that led to their approval and some of the issues faced in extending the use of these drugs to other indications.

Lay abstract: One of the key challenges in treating acute myeloid leukemia is to prevent relapse after remission has been achieved. This means that developing an effective maintenance treatment is very important. Maintenance treatment is given for a prolonged period and so it needs to be easy to give and well tolerated. Oral azacitidine is an example of this type of treatment and is the first drug that has been shown to improve survival as maintenance therapy for acute myeloid leukemia patients. This article describes the key studies that led to the approval of this important therapy.

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Acute myeloid leukemia (AML) is a heterogeneous myeloid malignancy characterized by acquired genetic and epigenetic mutations, resulting in impaired differentiation of hematopoietic precursors and enhanced growth and survival of myeloid progenitors. Conventional cytotoxic induction and consolidation chemotherapy, often followed by allogeneic hematopoietic cell transplantation (allo-HCT) for patients at higher risk of relapse, has been the standard of care for AML. A proportion of patients with AML are not eligible for allo-HCT due to older age, comorbidities, donor limitations or patient/physician preference. After completing intensive chemotherapy (IC), observation is usually recommended if allo-HCT is not possible or contraindicated.

Maintenance therapy is the term ascribed to lower-intensity treatment aimed at preventing relapse and prolonging remission. Recently, the benefit of maintenance therapy with CC-486 in prolonging survival in patients with AML in first remission was demonstrated in a randomized Phase III study. Therefore, on 2 September 2020 the US FDA approved CC-486 for maintenance treatment of adult patients with AML who have achieved first complete remission (CR) or CR with incomplete blood count recovery (CRi) after intensive induction chemotherapy and who are unable to complete intensive curative therapy. This approval provides an opportunity for oral hypomethylating agents to be used more broadly in the postremission setting and to be explored in a variety of new indications for patients with myeloid and other malignancies.

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Determination of bioavailability & the optimal dose schedule for CC-486

Due to the short plasma half-life of azacitidine [1] and cell cycle-restricted DNA incorporation [2], a newly formulated oral agent allowing extended dosing schedules had the theoretical advantage of enhancing the exposure to cycling malignant cells to azacitidine. To validate the bioavailability of CC-486, a pilot study was conducted in four patients with solid malignant tumors, AML or myelodysplastic syndromes (MDS). Patients received a single CC-486 dose of 60 or 80 mg [3]. All four patients showed measurable plasma concentrations of azacitidine. The 80-mg dose was tolerable, with 17% bioavailability compared with subcutaneous (SC) exposure. No severe drug-related toxicities were observed.

To determine the maximal tolerated dose of CC-486, a Phase I study was conducted (AZA PH US 2007 CL 005) in patients with MDS, chronic myelomonocytic leukemia (CMML) or AML [4]. A total of 41 patients received SC azacitidine (75 mg/m^2) on days 1–7 of cycle 1, followed by CC-486 (120 to 600 mg) days 1–7 of subsequent cycles. Pharmacokinetic (PK) and pharmacodynamic (PD) profiles were compared between cycles 1 and 2. Adverse events (AEs) and hematologic responses were recorded. Crossover to SC azacitidine was permitted for nonresponders who received at least six cycles of CC-486.

Dose-limiting toxicity (grade-3/4 diarrhea) occurred in two of three patients at the 600-mg dose level, resulting in 480 mg being declared the maximal tolerated dose. The most common grade-3/4 AEs were diarrhea (12%), nausea (7%), vomiting (7%), febrile neutropenia (20%) and fatigue (10%). The mean relative oral bioavailability ranged from 6.3 to 20%. The maximal PD effect of oral and SC azacitidine, as assessed by DNA hypomethylation in peripheral blood, occurred on day 15 of each cycle. As a single agent, CC-486 demonstrated impressive activity among patients with MDS and CMML, with the overall response rate (i.e., CR, hematological improvement [HI] or red blood cell [RBC]- or platelet-transfusion independence [TI]) being 35% in previously treated patients and 73% in those with treatment-naive disease.

Pharmacokinetic & pharmacodynamic properties of CC-486

Two Phase I studies evaluated the PK characteristics of CC-486 in subjects with MDS, CMML and AML. High inter-subject variability in area under the curve (AUC_∞) and C_{max} was seen. CC-486 was rapidly absorbed (within 1 h), with little or no effect of food on PK parameters [5]. CC-486 had modest oral bioavailability (6.3–20%). Clearance was mainly hepatic and extrahepatic, with minimal renal clearance [4]. The cumulative azacitidine exposures with CC-486 at a dose of 300 mg daily for 14 or 21 days per 28-day cycle were equivalent to 38 and 57%, respectively, of the cumulative exposure of SC azacitidine administered for 7 days per cycle [6].

Dynamic changes in DNA methylation after SC azacitidine and CC-486 were similar, with maximal hypomethylation achieved on day 15 and methylation levels returning to near-baseline values by the end of each cycle. Notably, CC-486 induced less demethylation than the SC formulation [4]. PK and PD studies were also conducted in a cohort of 59 patients sequentially assigned to one of four extended CC-486 dosing schedules: either 300 mg once daily for 14 or 21 days or 200 mg twice daily (bd) for 14 or 21 days each 28-day cycle [7]. The 300-mg once-daily and the 200-mg bd schedules both reduced global DNA methylation in whole blood at all measured time points (days 15, 22 and 28 of the treatment cycle). Maximal hypomethylation was seen at 22 days. CC-486 exposures and extent of DNA hypomethylation were significantly correlated. Patients who had a hematologic response had significantly greater reductions in methylation than nonresponding patients. These data showed that extended dosing schedules of CC-486 could sustain epigenetic effects throughout the treatment cycle.

CC-486 in lower-risk MDS

Part 2 of AZA PH US 2007 CL 005 evaluated extended duration CC-486 dosing in patients with lower-risk MDS [6]. Patients received CC-486 at a dose of 300 mg daily for 14 (n = 28) or 21 days (n = 27) in repeated 28-day cycles. The median patient age was 72 years and 75% had International Prognostic Scoring System intermediate-1 risk MDS. The median duration of treatment was seven cycles for the 14-day dosing schedule and six cycles for the 21-day schedule. The overall response rate (CR or partial response [PR], RBC- or platelet-TI or HI) was 36% among patients receiving 14-day dosing and 41% in patients receiving 21-day dosing. RBC-TI rates were similar for both dosing schedules (31 and 38%, respectively). CC-486 was generally well tolerated. These studies concluded that extended dosing schedules of CC-486 could provide effective treatment for patients with lower risk MDS.

A Phase III placebo-controlled trial in lower-risk MDS was conducted (AZA-MDS-003; ClinicalTrials.gov: NCT01566695) comparing CC-486 with placebo in patients with RBC-transfusion-dependent anemia and thrombocytopenia [8]. The primary end point was RBC-TI lasting for at least 56 days. Key secondary end points were

overall survival (OS), at least 84 days of RBC-TI, and HI in erythroid and platelet lineages. The planned enrolment was 386 patients; however, the study was halted early due to an observed excess of early deaths in the CC-486 arm, potentially due to neutropenia-related complications. The final sample size was 216 patients [8]. CC-486 met the primary end point of RBC-TI (31% of patients in the CC-486 arm, compared with 11% in the placebo arm). CC-486 also resulted in durable improvements in hemoglobin and platelet counts. No difference in survival was seen.

CC-486 in AML

A total of 23 patients with AML (13 patients with *de novo* disease and ten with AML secondary to MDS) were treated in the AZA PH US 2007 CL 005 study [9]. Of eight patients treated with CC-486 at a dose of 120–600 mg daily for 7 days, three achieved a response (38%), including two with marrow CR and one with marrow PR. Of 15 patients treated with CC-486 in extended dosing schedules (300 mg daily or 200 mg bd for 14 or 21 days), seven achieved a response (47%), including four with HI, four with RBC-TI, one with platelet-TI and three with marrow PR. No patients achieved CR or PR. One response was also observed in a patient failing prior injectable demethylating agent therapy. The most common AEs were gastrointestinal (GI). The most common higher-grade AEs (grade 3/4) were febrile neutropenia (35%), pneumonia (17%), syncope (17%) and nausea (13%).

Phase III study of CC-486 as maintenance therapy in AML

Maintenance therapy for patients with AML in first remission was considered a suitable setting for a new orally administered epigenetic drug. Maintenance therapy in AML was an area of unmet need. The goal of postremission therapy is to target measurable residual disease (MRD) with the goal of prolonging remission. The term 'maintenance' has mainly been intended to represent postremission therapy that is less intensive than consolidation chemotherapy.

For patients with AML who were in remission after IC and not candidates for allo-HCT, there were no competing agents with demonstrated capacity to prolong OS. Although maintenance therapy with parenteral azacitidine has been shown to prolong disease-free survival in older AML patients [10], the potential to double the cycle exposure with a 14-day CC-486 schedule and to more conveniently deliver therapy for more cycles than with injectable hypomethylating agents was an important consideration in the design of the QUAZAR AML-001 study, and may have played a significant role in it being positive for OS (see below).

Compared with parentally administered azacitidine, CC-486 had the advantage of being a conveniently administered formulation that was well tolerated in the extended dosing schedules used in Phase I studies, with evidence that it could sustain DNA hypomethylation across the treatment cycle. Furthermore, as noted above, CC-486 was likely to be continued for more cycles than parenterally administered therapy, due to its greater convenience. The current standard of care postchemotherapy for those not proceeding to transplant was observation; therefore, the maintenance study could be conducted using CC-486 as a single agent versus placebo. The target population included patients with AML aged 55 years or older, in whom allo-HCT was less likely to be performed than in younger patients. Patients were required to commence CC-486 within 120 days of achieving first CR or CRi, in order to avoid enrolling patients with a lower likelihood of relapse, which would have reduced the event rate in the studied population.

The QUAZAR AML-001 study randomized 472 patients in a 1:1 ratio to CC-486, 300 mg daily, or placebo for 14 days per 28-day cycle [11]. The 14-day schedule was chosen as it was considered to be more tolerable than the 21-day schedule used in the Phase I studies. The 21-day schedule produced more severe cytopenic complications, which was considered to be undesirable in patients whose leukemia was in remission. Where there was evidence of early progression, however, a 21-day schedule was allowed (see below).

The primary end point was OS. Secondary end points included relapse-free survival (RFS) and health-related quality of life. Patients had received a variety of induction regimens that included at least cytarabine and an anthracycline. More than one cycle of induction was permitted in order to achieve remission. Receipt of consolidation therapy was not a prerequisite for study entry, such that patients deemed unfit to receive any further consolidation therapy could receive maintenance therapy with CC-486.

The two treatment arms in the study were well balanced. The median age was 68 years (range: 55–86). Although patients with favorable cytogenetic risk were excluded from the study, the population included only 9% with secondary AML and 14% with adverse cytogenetic risk, suggesting enrichment of patients with nonadverse disease characteristics who were less likely to be considered candidates for allo-HCT. The population included patients

who lost fitness and/or candidacy for intensive consolidation therapy; indeed, at study screening, 20% of patients had not received consolidation therapy, whereas 45 and 35% had received one or more than one consolidation cycle, respectively. The study population included patients in CR (81%) or CRi (19%) and 19% had received more than one induction cycle in order to achieve remission. The study included centralized multiparameter flow cytometry in order to assess MRD, which was detected in 46% at study baseline.

With a median follow-up time of 41.2 months, the median OS from randomization was significantly improved with CC-486 versus placebo (24.7 vs 14.8 months; p = 0.0009). Survival benefits were demonstrated across patient subgroups, including those with adverse-risk baseline features such as poor cytogenetic risk, no prior consolidation therapy, CR with incomplete hematologic recovery and MRD positivity. The median RFS was also significantly prolonged with CC-486 (10.2 vs 4.8 months; p = 0.0001).

One notable feature of the QUAZAR AML-001 study was the intensive MRD monitoring program, which included three-monthly bone marrow assessments for 24 months, followed by six-monthly assessments thereafter. This enabled much earlier detection of relapse, explaining the apparently shorter RFS in this study compared with that reported in previous maintenance studies [10]. During MRD surveillance on the QUAZAR AML-001 study, patients with early relapse (5–15% bone marrow blasts) were eligible for an extended dosing schedule of CC-486 (21 days per 28-day cycle). Extended dosing was commenced in 21% of patients receiving CC-486, with CR or CRi being re-established in 23%, compared with 11% in the placebo arm.

Similar to the dose-finding experience, GI toxicity was the most commonly reported AE, with nausea, vomiting and diarrhea reported in approximately 60%. Grade-3/4 GI toxicity, however, was uncommon (≤5%), as were treatment discontinuations due to GI events (5%). Although GI toxicity was more common during the first two cycles, the frequency was less common in subsequent cycles (~15%), likely due to the implementation of prophylactic supportive care measures. Although grade-3/4 neutropenia (41%) and thrombocytopenia (23%) were reported, the rate of febrile neutropenia was low (12%). Patient-reported outcome studies showed no deterioration in quality of life during therapy with CC-486 compared with placebo. Based on the positive efficacy outcome and tolerable safety profile, CC-486 received FDA approval as a new maintenance therapy in AML.

Oral maintenance therapy after allogeneic stem cell transplantation

Relapse is the main cause of treatment failure after allo-HCT in AML, occurring in up to 50% of patients. Currently, no post-transplant maintenance therapy has been approved for AML [12].

The Phase I/II CC-486-AML-002 study investigated the use of CC-486 maintenance after allo-HCT [13]. Adults with MDS or AML in morphologic CR 42–84 days after allo-HCT were included. This was a dose-optimization study that enrolled patients to one of four CC-486 dosing schedules for up to 12 cycles. Of 30 patients, seven received CC-486 once daily for 7 days per cycle (200 mg, n = 3; 300 mg, n = 4) and 23 for 14 days per cycle (150 mg, n = 4; 200 mg, n = 19 [expansion cohort]). Grade-3/4 AEs were infrequent and occurred with similar frequency across regimens. Of 28 evaluable patients, relapse or progressive disease occurred in three of seven patients (43%) receiving 7-day dosing and three of 23 (13%) who had received the 14-day dosing schedule. Estimated 1-year survival rates were 86 and 81% in the 7 and 14-day dosing cohorts, respectively. CC-486 maintenance was generally well tolerated, with low rates of graft-versus-host disease. A randomized controlled trial incorporating CC-486 as maintenance in the post-allo-HCT setting for AML aiming to enroll 324 patients is currently underway (NCT04173533).

Oral hypomethylating agent therapy for MDS

The convenience of CC-486 makes it an attractive option to replace injectable azacitidine in a variety of drug combinations. CC-486, however, has low bioavailability [4] due to rapid clearance by the enzyme CDA, which is ubiquitous in the gut and liver [14]. CC-486 is therefore not bioequivalent to parenteral azacitidine [6].

Decitabine, another DNA methyltransferase inhibitor, is also not readily orally bioavailable, due to rapid inactivation by CDA in the GI tract and liver. The competitive CDA inhibitor tetrahydrouridine (THU) increases the oral bioavailability of decitabine, but THU is unstable in acidic environments, making it pharmaceutically difficult to develop [15,16]. Cedazuridine (CDZ) is an alternative oral inhibitor of CDA and has been shown to safely and effectively increase decitabine exposure following oral administration in preclinical studies [15,17].

The first-in-human dose-escalation trial of oral cedazuridine plus decitabine (ASTX727), concurrently administered at various doses, enrolled 44 patients with previously treated or newly diagnosed MDS or CMML [18]. ASTX727, containing 30–40 mg of decitabine combined with 100 mg of CDZ, was associated with decitabine

exposure and PD activity (as assessed by demethylation of DNA) that were comparable with those of intravenous (iv.) decitabine. ASTX727 achieved decitabine AUC 5-day exposures (oral/iv. ratio) of 81–128%. Clinical responses were similar to those seen with iv. decitabine treatment for 5 days.

A subsequent Phase II study was designed to compare systemic decitabine exposure, demethylation activity and safety in the first two cycles between patients receiving cedazuridine 100 mg/decitabine 35 mg and a standard decitabine schedule of 20 mg/m^2 iv. [19]. A total of 80 patients with MDS or CMML were randomized 1:1 to receive ASTX727 or iv. decitabine in cycle 1, followed by crossover in cycle 2. All patients received ASTX727 in subsequent cycles. ASTX727 was associated with systemic decitabine exposure, DNA demethylation and safety profile that were similar to those of iv. decitabine during the first two cycles. Efficacy was also similar, with 21% of patients achieving a CR and 60% recording a clinical response. The most common grade-3 or more AEs were again hematological: neutropenia (46%), thrombocytopenia (38%) and febrile neutropenia (29%). Notably, GI AEs were predominantly grade 1 or 2 and were reported at similar incidences between oral and iv. dosing in cycles 1 and 2, suggesting no additional GI toxicity with oral treatment, at least during the first two cycles.

These studies led to the ASCERTAIN study, a randomized crossover Phase III study of ASTX727 compared with iv. decitabine [20]. In this study, 138 patients (121 with MDS and 17 with CMML) were randomized 1:1 to either ASTX727 (100/35 mg) in cycle 1 followed by iv. decitabine (20 mg/m^2) in cycle 2, or iv. decitabine in cycle 1 followed by ASTX727 in cycle 2, in order to compare PK and PD (DNA demethylation using the *LINE-1* assay). All patients received ASTX727 from cycle 3 onwards. The study met its end point with high confidence: the oral/iv. 5-day decitabine AUC ratio was 99% (90% confidence interval, 93–106%). All sensitivity and secondary PK AUC analyses confirmed findings from the primary analysis. There was no significant difference in *LINE-1* DNA demethylation between ASTX727 and iv. decitabine (<1% difference in each cycle). The overall response rate (CR, PR, marrow CR and HI) in 101 evaluable patients was 64%, comparing favorably with response rates observed in previous studies of CC-486 in MDS, CMML and AML (30–40%). These results supported the approval, on 7 July 2020, of ASTX727 for adult patients with International Prognostic Scoring System intermediate-1 or higher MDS or CMML.

Conclusion

The pivotal QUAZAR AML-001 AML maintenance study has shown that CC-486 improves both RFS and OS in older patients with AML following IC. There are now two approved oral hypomethylating agents in the clinic. These new drug formulations provide many diverse therapeutic opportunities for patients with AML and MDS. Despite the lower exposure of oral as compared with injectable azacitidine, there is evidence that lowering the dose of a hypomethylating agent (which should decrease cytotoxic effects) and administering the dose over a longer period (which should increase S phase-dependent DNA incorporation) may enhance efficacy [21]. For maintenance therapy after AML, only CC-486 has so far been shown to improve survival in the context of a Phase III trial. ASTX727 has shown promise in clinical studies of patients with MDS and CMML and has better bioavailability and less GI toxicity than CC-486. The mechanism of action and PK exposure of ASTX727, however, are likely to be distinct from those of CC-486 and so a separate validation of ASTX727 in a randomized setting is needed before it can be supported for use as a maintenance option in AML.

Just as ASTX727 cannot be substituted for CC-486 as maintenance therapy in AML, CC-486 cannot be used interchangeably with injectable azacitidine in settings where the latter is already established. In other words, for other disease scenarios where injectable azacitidine is used (e.g., in combination with venetoclax in AML or as a single agent in MDS), properly conducted safety- and efficacy-based studies must be conducted in order to identify the optimal dosing schedule, rather than substituting oral for parenteral azacitidine, based on the fact that CC-486 is not pharmacokinetically equivalent to parenteral azacitidine.

The most obvious consideration would be to use CC-486 in combination with venetoclax for the treatment of older patients with AML. This will, however, require validation that CC-486 combined with venetoclax will produce similar efficacy without increased toxicity. Currently, the approved dosing schedules of oral and injectable azacitidine are 14 and 7 days per cycle, respectively. It is unknown what the optimal dose or schedule of CC-486 in combination with venetoclax would need to be in order to maximize the therapeutic window. Therefore, carefully conducted dose-escalation studies would need to be performed, potentially in patients with relapsed/refractory disease initially. For use in the frontline setting in older patients, CC-486 would need to at least demonstrate noninferiority to parenteral azacitidine in combination with venetoclax. Substituting ASTX727 for iv. decitabine in combination with venetoclax is likely to be more straightforward, as ASTX727 has a very similar PK profile to

that of iv. decitabine and the combination of iv. decitabine with venetoclax has been shown to be efficacious and tolerable in Phase Ib studies [22].

The population in the QUAZAR AML-001 study was limited to patients aged at least 55 years. Patients with core-binding factor AML were excluded. Investigating maintenance therapy in younger patients has the challenge of an increased frequency of allo-HCT, which could confound the interpretation of survival outcomes. One strategy would be to focus on patients less likely to undergo allo-HCT in first remission, such as patients with favorable-risk AML as defined by the European LeukemiaNet. This would include patients with core-binding factor AML, AML with biallelic-mutated *CEBPA* and AML with mutated *NPM1* without *FLT3*-ITD. The major challenge in studying this patient population would be the likelihood of a long study end point, due to the better prognosis for patients in this more favorable AML subgroup. In order to overcome this barrier, such a study could consider the role of MRD as an earlier surrogate of survival outcome.

For drugs with new indications, such as CC-486 or ASTX727 in combination with other agents in situations where parenterally administered hypomethylating agents have not been established, studying hybrid oral combinations would be a very worthwhile initiative. Such combinations could include oral hypomethylating agents with IDH, FLT3 and checkpoint inhibitors. These combinations could be utilized for patients with relapsed/refractory disease, as frontline therapy or in the maintenance setting. Securing registration status, however, could be challenging. It would be highly challenging to demonstrate CC-486 to be superior to injectable azacitidine, either in relapsed/refractory disease or in the frontline setting in older patients unfit for IC. Therefore, the best approach might be to consider an oral hypomethylating agent combined with venetoclax and a targeted inhibitor (e.g., an IDH or FLT3 inhibitor) as part of an 'all-oral' novel triplet combination. This will, of course, require dose-optimization studies to be performed. In the maintenance setting, there is greater opportunity to combine CC-486 with other agents in order to augment survival, highlighted by the fact that the QUAZAR AML-001 study demonstrated that the majority of patients eventually relapsed, even though RFS and OS were prolonged compared with placebo. As shown by QUAZAR AML-001, however, maintenance studies take a long time to conduct and complete, which would be particularly problematic for a new maintenance study if it were limited to a targeted sub-group.

In conclusion, the approval of two new oral hypomethylating agents creates new opportunities, but also new challenges, for patients with AML. Patients are likely to benefit from new drug indications, greater convenience and probably less hospitalization. The potential for extended duration dosing schedules, which could be delivered for many more cycles than is generally feasible with injectable agents, will provide physicians with new opportunities to design treatment schedules that could better target S-phase-dependent leukemic populations. The exact mechanism of action of oral hypomethylating agents remains uncertain and so there is likely to be renewed interest in conducting correlative studies in order to identify 'responder' and 'nonresponder' populations, now that the place of oral hypomethylating agents in the growing armamentarium of AML therapy has been established.

Financial & competing interests disclosure

AH Wei has served on advisory boards for Novartis, Janssen, Amgen, Roche, Pfizer, Abbvie, Servier, Celgene-BMS, Macrogenics, Agios and Gilead; receives research funding from Novartis, AbbVie, Servier, Celgene-BMS, Astra Zeneca and Amgen; serves on speaker's bureaus for AbbVie, Novartis and Celgene; and receives royalty payments from the Walter and Eliza Hall Institute of Medical Research related to venetoclax. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Pharmacokinetic properties, optimal dose & toxicity of CC-486

- CC-486 has low bioavailability (~20% compared with subcutaneous exposure) due to rapid clearance by the enzyme CDA, and is therefore not bioequivalent to parenteral azacitidine.
- Oral administration provides a cumulative azacitidine exposure of 38–57% of that seen with the parenteral formulation.
- The optimal dose is 300 mg daily.
- The most common adverse events are gastrointestinal (GI). These are mostly mild (grade 1–2).

Pharmacodynamic properties of CC-486

- CC-486 causes less DNA demethylation than the subcutaneous formulation.
- Nonetheless, extended dosing schedules of CC-486 result in sustained demethylation throughout the treatment cycle, with maximal demethylation at 22 days.
- CC-486 exposure is significantly correlated with the extent of DNA demethylation.

CC-486 in lower risk myelodysplastic syndromes

- CC-486 has an overall response rate of 30–40% in patients with lower risk myelodysplastic syndromes (MDS).
- Approximately 30% of patients with lower-risk MDS and transfusion-dependent anemia achieve red cell transfusion independence.
- Extended dosing schedules are effective and feasible.

Phase I study of CC-486 in acute myeloid leukemia

- CC-486 showed a modest response rate in patients with acute myeloid leukemia (AML) treated in a small Phase I study.

Phase III study of CC-486 as maintenance therapy in AML

- The Phase III QUAZAR AML-001 study randomized 472 patients aged at least 55 years in a 1:1 ratio to CC-486, 300 mg daily, or placebo for 14 days per 28-day cycle. The primary end point was OS.
- The median overall survival from randomization was significantly improved with CC-486 versus placebo (24.7 vs 14.8 months; $p = 0.0009$). The median relapse-free survival was also significantly prolonged with CC-486 (10.2 vs 4.8 months; $p = 0.0001$).
- Based on the positive efficacy outcome and tolerable safety profile, CC-486 received US FDA approval as a new maintenance therapy in AML.

Oral maintenance therapy after allogeneic stem cell transplantation

- A small Phase I/II study investigated the use of CC-486 maintenance after allogeneic hematopoietic cell transplantation. Azacitidine was well tolerated and resulted in favorable relapse and 1-year survival rates.
- A large randomized controlled trial incorporating CC-486 as maintenance in the postallogeneic hematopoietic cell transplantation setting for AML is currently underway (ClinicalTrials.gov: NCT04173533).

Oral hypomethylating agent therapy for MDS

- Decitabine is also not readily bioavailable, due to rapid inactivation by CDA in the gut and liver.
- Cedazuridine (CDZ) is an oral inhibitor of CDA and increases decitabine exposure.
- Decitabine combined with cedazuridine (ASTX727) is associated with systemic exposure, pharmacodynamic activity and safety profile that are equivalent to those of intravenous decitabine.
- ASTX727 has fewer GI side effects than CC-486.
- In July 2020 ASTX727 was approved for the treatment of International Prognostic Scoring System intermediate-1 or higher-risk MDS or chronic myelomonocytic leukemia.

Conclusion

- The pivotal QUAZAR AML-001 AML maintenance study has shown that CC-486 improves both relapse-free and overall survival in older patients with AML following intensive chemotherapy.
- ASTX727 has shown promise in clinical studies of patients with MDS and chronic myelomonocytic leukemia and has better bioavailability and less GI toxicity than CC-486.
- The potential exists for all-oral therapeutic combinations for AML, for example, including venetoclax and IDH, FLT3 and checkpoint inhibitors; however, these will require carefully conducted validation and dose-finding studies.
- Investigating maintenance therapy in younger AML patients remains a challenge.
- Likely benefits of oral hypomethylating agents in the treatment of AML include new drug indications, greater convenience, less hospitalization and the potential for extended duration dosing schedules.

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