parenteral therapy also increases contact with medical settings with increased infection risk. Because DNA methyltransferase inhibitors are rapidly degraded by cytidine deaminase in the gut and liver, oral availability has only been recently possible.

SUMMARY

[0011a] In an aspect, there is provided a use of a composition comprising an effective amount of cedazuridine and an effective amount of decitabine, in the manufacture of a medicament for treating myelodysplastic syndromes (MDS) in a subject in need thereof,

wherein the effective amount of cedazuridine and the effective amount of decitabine to be administered increases survival and/or leukemia-free survival of the subject to about 130% to about 400% relative to survival or leukemia-free survival, respectively, obtained by treatment with a hypomethylating agent alone; and/or provides the subject with a survival and/or leukemia-free survival of at least about 28, 30, 32, or 34 months.

[0011b] In another aspect, there is provided the use of a composition comprising an effective amount of cedazuridine and an effective amount of decitabine, in the manufacture of a medicament for treating lower-risk MDS in a subject in need thereof,

wherein the effective amount of cedazuridine and the effective amount of decitabine to be administered increases survival and/or leukemia-free survival of the subject to about 130% to about 400% relative to survival or leukemia-free survival, respectively, obtained by treatment with a hypomethylating agent alone; and/or provides the subject with a survival and/or leukemia-free survival of at least about 28, 30, 32, or 34 months.

[0011c] In another aspect, there is provided the use of a composition comprising an effective amount of cedazuridine and an effective amount of decitabine, in the manufacture of a medicament for treating chronic myelomonocytic leukemia (CMML) in a subject in need thereof,

wherein the effective amount of cedazuridine and the effective amount of decitabine to be administered increases survival and/or leukemia-free survival of the subject to about 130% to about 400% relative to the survival or leukemia-free survival, respectively, obtained by treatment with a hypomethylating agent alone; and/or provides the subject with a survival and/or leukemia-free survival of at least about 28, 30, 32, or 34 months.

[0011d] In another aspect, there is provided the use of a composition comprising an effective amount of cedazuridine and an effective amount of decitabine, in the manufacture of a medicament for treating MDS or CMML in a subject having a *TP53* mutation in need thereof, wherein the effective amount of cedazuridine and the effective amount of decitabine to be administered increases survival and/or leukemia-free survival of the subject to about 130% to about 400% relative to survival or leukemia-free survival, respectively, obtained by treatment with a hypomethylating agent alone; and/or provides the subject with a survival and/or leukemia-free survival of at least about 20, 22, 24, 26, 28, 30, 32, 34, or 36 months for a subject with a mono-allelic *TP53* mutation or at least about 10, 12,14, 16,18, or 20 months for a subject with a bi-allelic *TP53* mutation.

[0011e] In another aspect, there is provided a kit comprising one or more doses (e.g., 1, 2, 3, 4, or 5) of an effective amount of cedazuridine (e.g., 100 mg) and one or more doses (e.g., 1, 2, 3, 4, or 5) of an effective amount of decitabine (e.g., 35 mg) for the use as defined above.

[0011f] In another aspect, there is provided a combination comprising one or more doses (e.g., 1, 2, 3, 4, or 5) of an effective amount of cedazuridine (e.g., 100 mg) and one or more doses (e.g., 1, 2, 3, 4, or 5) of an effective amount of decitabine (e.g., 35 mg) for the use as defined above.

[0012] Provided according to embodiments of the disclosure are methods of treating myelodysplastic syndromes (MDS), including higher-risk MDS or lower-risk MDS, in a subject in need thereof. In some examples, such methods include administering to the subject an effective amount of cedazuridine and an effective amount of decitabine, thereby treating the MDS. In some examples, administering an effective amount of cedazuridine and an effective amount of decitabine increases the subject's survival (e.g., overall median survival) to about 130% to about 400% relative to survival obtained by treatment with a hypomethylating agent alone. In some examples, the MDS is lower-risk MDS. In some examples, the MDS is chronic myelomonocytic leukemia (CMML).

[0013] In some examples, administering an effective amount of cedazuridine and an effective amount of decitabine increases the MDS subject's survival to about 200% to about 400%, relative to survival obtained when the subject only receives best supportive care (BSC).

[0014] In some examples, administering an effective amount of cedazuridine and an effective amount of decitabine to a subject with MDS provides the subject with a survival of

at least about 28, 30, 32, 34, or 36 months. In some examples, administering an effective amount of cedazuridine and an effective amount of decitabine to a subject with MDS provides the subject with a leukemia-free survival of at least about 26, 28, 30, 32, or 34 months.

[0015] In some method examples of the disclosure, treatment of lower-risk MDS includes treatment of a lower-risk MDS subject as determined by the International Prognostic Scoring System (IPPS), including the Low and Intermediate-1 subgroups. In some method examples of the disclosure, treatment of lower-risk MDS includes treatment of a lower-risk MDS subject as determined by the International Prognostic Scoring System-Revised (IPPS-R), including the Very Low, Low, and Intermediate subgroups. In some method examples of the disclosure, treatment of lower-risk MDS includes treatment of a lower-risk MDS subject as determined by the WHO Classification-based Prognostic Scoring System (WPSS), including the Very Low, Low, and Intermediate subgroups. In some method examples of the disclosure, treatment of

lower-risk MDS includes treatment of a lower-risk MDS subject as determined by the French-American-British (FAB) criteria.

[0016] In some examples of the disclosure, administering an effective amount of cedazuridine and an effective amount of decitabine to a subject includes administering to a subject cedazuridine and decitabine in one or more oral dosage forms. In some examples, administering an effective amount of cedazuridine and an effective amount of decitabine to a subject includes administering a single solid oral dosage form that includes cedazuridine and decitabine.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] Figure 1 shows patient randomization and disposition. CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome.

[0018] Figures 2A-2B show mean plasma decitabine concentration-time profiles following single and multiple doses of IV decitabine and Oral decitabine/cedazuridine on Days 1, 2, and 5. Linear and semi-log scales. A: Mean plasma decitabine concentration-time profiles on days 1, 2, and 5. B: Lower limit of quantification (LLOQ) of plasma decitabine concentration-time profiles on days 1, 2, and 5.

[0019] Figure 3 is a Kaplan-Meier plot for leukemia-free survival of the subjects in a Phase 3 trial for the use of oral decitabine/cedazuridine to treat MDS.

[0020] Figure 4 is a Kaplan-Meier plot for the overall survival of the subjects in a Phase 3 trial for the use of oral decitabine/cedazuridine to treat MDS.

[0021] Figure 5 is a Kaplan-Meier plot for leukemia-free survival of the subjects with CMML or Int-1 or low risk MDS in a Phase 3 trial for the use of oral decitabine/cedazuridine to treat MDS.

[0022] Figure 6 is a Kaplan-Meier plot for the overall survival of the subjects with CMML or Int-1 or low risk MDS in a Phase 3 trial for the use of oral decitabine/cedazuridine to treat MDS.

[0023] Figure 7 shows a Kaplan-Meier plot for the *TP53* mutation population compared to the wild-type population.

[0024] Figure 8 shows a Kaplan-Meier plot for the mono-allelic *TP53* mutation population compared to the bi-allelic *TP53* population.

What is claimed is:

1. Use of a composition comprising an effective amount of cedazuridine and an effective amount of decitabine, in the manufacture of a medicament for treating MDS or CMML in a subject having a *TP53* mutation in need thereof,
wherein the effective amount of cedazuridine and the effective amount of decitabine to be administered increases survival and/or leukemia-free survival of the subject to about 130% to about 400% relative to survival or leukemia-free survival, respectively, obtained by treatment with a hypomethylating agent alone; and/or provides the subject with a survival and/or leukemia-free survival of at least about 20, 22, 24, 26, 28, 30, 32, 34, or 36 months for a subject with a mono-allelic *TP53* mutation or at least about 10, 12,14, 16,18, or 20 months for a subject with a bi-allelic *TP53* mutation.

2. The use according to claim 1, wherein the effective amount of cedazuridine and the effective amount of decitabine are to be administered on days 1-5 of a 28-day cycle.

3. The use according to claim 1, wherein the effective amount of cedazuridine and the effective amount of the decitabine are present in a solid oral dosage form that comprises 100 mg cedazuridine, 35 mg decitabine, and at least one pharmaceutically acceptable excipient.

4. The use according to claim 1,
wherein the effective amount of cedazuridine and the effective amount of decitabine to be administered increases survival and/or leukemia-free survival of the subject to about 200% to about 400% relative to survival or leukemia-free survival, respectively, obtained by providing best supportive care alone.

5. Use of a composition comprising an effective amount of cedazuridine and an effective amount of decitabine, in the manufacture of a medicament for treating myelodysplastic syndromes (MDS) in a subject in need thereof,

wherein the effective amount of cedazuridine and the effective amount of decitabine to be administered increases survival and/or leukemia-free survival of the subject to about 130% to about 400% relative to survival or leukemia-free survival, respectively, obtained by

treatment with a hypomethylating agent alone; and/or provides the subject with a survival and/or leukemia-free survival of at least about 28, 30, 32, or 34 months.

6. The use according to claim 5, wherein the effective amount of cedazuridine and the effective amount of decitabine are to be administered on days 1-5 of a 28-day cycle.

7. The use according to claim 5, wherein the effective amount of cedazuridine and the effective amount of the decitabine are present in a solid oral dosage form that comprises 100 mg cedazuridine, 35 mg decitabine, and at least one pharmaceutically acceptable excipient.

8. The use according to claim 5,

wherein the effective amount of cedazuridine and the effective amount of decitabine to be administered increases survival and/or leukemia-free survival of the subject to about 200% to about 400% relative to survival or leukemia-free survival, respectively, obtained by providing best supportive care alone.

9. Use of a composition comprising an effective amount of cedazuridine and an effective amount of decitabine, in the manufacture of a medicament for treating lower-risk MDS in a subject in need thereof,

wherein the effective amount of cedazuridine and the effective amount of decitabine to be administered increases survival and/or leukemia-free survival of the subject to about 130% to about 400% relative to survival or leukemia-free survival, respectively, obtained by treatment with a hypomethylating agent alone; and/or provides the subject with a survival and/or leukemia-free survival of at least about 28, 30, 32, or 34 months.

10. The use according to claim 9, wherein the effective amount of cedazuridine and the effective amount of decitabine are to be administered on days 1-5 of a 28-day cycle.

11. The use according to claim 9, wherein the effective amount of cedazuridine and the effective amount of the decitabine are present in a solid oral dosage form that comprises 100 mg cedazuridine, 35 mg decitabine, and at least one pharmaceutically acceptable excipient.

12. The use according to claim 9,

wherein the effective amount of cedazuridine and the effective amount of decitabine to be administered increases survival and/or leukemia-free survival of the subject to about 200% to about 400% relative to survival or leukemia-free survival, respectively, obtained by providing best supportive care alone.

13. Use of a composition comprising an effective amount of cedazuridine and an effective amount of decitabine, in the manufacture of a medicament for treating chronic myelomonocytic leukemia (CMML) in a subject in need thereof,

wherein the effective amount of cedazuridine and the effective amount of decitabine to be administered increases survival and/or leukemia-free survival of the subject to about 130% to about 400% relative to the survival or leukemia-free survival, respectively, obtained by treatment with a hypomethylating agent alone; and/or provides the subject with a survival and/or leukemia-free survival of at least about 28, 30, 32, or 34 months.

14. The use according to claim 13, wherein the effective amount of cedazuridine and the effective amount of decitabine are to be administered on days 1-5 of a 28-day cycle.

15. The use according to claim 13, wherein the effective amount of cedazuridine and the effective amount of the decitabine are present in a solid oral dosage form that comprises 100 mg cedazuridine, 35 mg decitabine, and at least one pharmaceutically acceptable excipient.

16. The use according to claim 13,

wherein the effective amount of cedazuridine and the effective amount of decitabine to be administered increases survival and/or leukemia-free survival of the subject to about 200% to about 375% relative to survival or leukemia-free survival, respectively, obtained by providing best supportive care alone.

17. A kit comprising one or more doses (e.g., 1, 2, 3, 4, or 5) of an effective amount of cedazuridine (e.g., 100 mg) and one or more doses (e.g., 1, 2, 3, 4, or 5) of an effective amount of decitabine (e.g., 35 mg) for the use according to claims 1-16.

18. A combination comprising one or more doses (e.g., 1, 2, 3, 4, or 5) of an effective amount of cedazuridine (e.g., 100 mg) and one or more doses (e.g., 1, 2, 3, 4, or 5) of an effective amount of decitabine (e.g., 35 mg) for the use according to claims 1-16.