unstable in the acidic gastric environment. Previous attempts to develop oral dosage forms of cytidine analogs have required enteric coating of the drug core to protect the active pharmaceutical ingredient (API) from what was understood and accepted to be therapeutically unacceptable hydrolysis in the stomach, such that the drug is preferably absorbed in specific regions of the lower gastrointestinal tract, such as the jejunum in the small intestine. *See, e.g.*, Sands, *et al.*, U.S. Patent Publication No. 2004/0162263 (App. No. 10/698,983). In addition, a generally accepted belief in the art has been that water leads to detrimental hydrolytic degradation of cytidine analogs during formulation, subsequently affecting the stability of the API in the dosage form. As a result, coatings applied to the drug core for prospective oral delivery of cytidine analogs have previously been limited to organic solvent-based systems to minimize exposure of the API to water.

[0014] A great need remains for oral formulations and dosage forms of cytidine analogs, such as, *e.g.*, 5-azacytidine, to potentially permit, *inter alia*, more advantageous dosing amounts or dosing periods; improved pharmacokinetic profiles, pharmacodynamic profiles, or safety profiles; evaluation of the benefits of long-term or maintenance therapies; development of improved treatment regimens that maximize biologic activity; use of cytidine analogs for treating new diseases or disorders; and/or other potential advantageous benefits.

IV. SUMMARY

[0015] Disclosed herein are pharmaceutical compositions comprising cytidine analogs, wherein the compositions release the API substantially in the stomach upon oral administration. Also disclosed are methods for making the compositions, and methods for using the compositions to treat diseases and disorders including cancer, disorders related to abnormal cell proliferation, and hematologic disorders, among others. In one aspect, the present invention refers to a pharmaceutical composition for oral administration comprising a therapeutically effective amount of 5-azacytidine, wherein the composition is a tablet comprising a non-enteric coating, with the proviso that the composition does not comprise an enteric coating. In another aspect, the present invention refers to a pharmaceutical composition comprising a therapeutically effective amount of 5- azacytidine,

wherein the composition for use in treating a disease or disorder associated with abnormal cell proliferation, wherein the composition is prepared for oral administration, and wherein the composition is a tablet comprising a non-enteric coating, with the proviso that the composition does not comprise an enteric coating.

[0016] In certain examples, the cytidine analog is 5-azacytidine. In other examples, the cytidine analog is 5-aza-2'-deoxycytidine (decitabine or 5-aza-CdR). In yet other examples, the cytidine analog is, for example: l-β-D-arabinofuranosylcytosine (Cytarabine or ara-C); pseudoisocytidine (psi ICR); 5-fluoro-2'-deoxycytidine (FCdR); 2'-deoxy-2',2'-difluorocytidine (Gemcitabine); 5-aza-2'-deoxy-2',2'-difluorocytidine; 5-aza-2'-deoxy-2'-fluorocytidine; l-β-D-ribofuranosyl-2(1*H*)-pyrimidinone (Zebularine); 2',3'-dideoxy-5-fluoro-3'-thiacytidine (Emtriva); 2'-cyclocytidine (Ancitabine); l-β-D-arabinofuranosyl-5-azacytosine (Fazarabine or ara-AC); 6-azacytidine (6-aza-CR); 5,6-dihydro-5-azacytidine

(dH-aza-CR); N^4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine (Capecitabine); N^4-octadecyl-cytarabine; elaidic acid cytarabine; or their derivatives or related analogs.

[0017] Certain examples herein describe compositions that are single unit dosage forms comprising a cytidine analog. Certain examples herein disclose compositions that are non-enteric-coated. Certain examples herein describe compositions that are tablets comprising a cytidine analog. Certain examples herein disclose compositions that are capsules comprising a cytidine analog. The capsules may be, *e.g.*, a hard gelatin capsule or a soft gelatin capsule; particular examples describe hydroxypropyl methylcellulose (HPMC) capsules. In certain examples, the single unit dosage forms optionally further contain one or more excipients. In certain examples, the tablets optionally further contain one or more excipients. In other examples, the capsules optionally further contain one or more excipients. In certain examples, the composition is a tablet that effects an immediate release of the API upon oral administration. In other examples, the composition is a tablet that effects a controlled release of the API substantially in the stomach. In certainexamples, the composition is a capsule that effects an immediate release of the API upon oral administration. In other examples, the composition is a capsule that effects a controlled release of the API substantially in the stomach. In particularexamples, the tablet contains a drug core that comprises a cytidine analog, and optionally further contains a coating of the drug core, wherein the coating is applied to the drug core using an aqueous solvent, such as, for example, water, or non-aqueous solvent, such as, for example ethanol.

[0018] Certain examples herein disclose methods of making formulations of cytidine analogs intended for oral delivery. Further disclosed are articles of manufacture containing packaging material, an oral formulation of a cytidine analog, and a label that indicates that the formulation is for the treatment of certain diseases or disorders including, *e.g.*, a cancer, a disorder related to abnormal cell proliferation, a hematologic disorder, or an immune disorder.

[0019] Certain examples herein disclose methods of using the formulations disclosed herein to treat diseases or disorders including, *e.g.*, cancer, disorders related to abnormal cell proliferation, hematologic disorders, or immune disorders, among others. In certain examples , the formulations of cytidine analogs are orally administered to subjects in need thereof to treat a cancer or a hematological disorder, such as, for example, MDS, AML, ALL, CML, NHL, leukemia, or lymphoma; or a solid tumor, such as, for example, sarcoma, melanoma, carcinoma, or cancer of the colon, breast, ovary, gastrointestinal system, kidney,

lung (*e.g.*, non-small-cell lung cancer and small-cell lung cancer), testicle, prostate, pancreas or bone. In certain examples, the formulations of cytidine analogs are orally administered to subjects in need thereof to treat an immune disorder. In certain examples, the oral formulations disclosed herein are co-administered with one or more therapeutic agents to provide a synergistic therapeutic effect in subjects in need thereof. In certain examples, the oral formulations described herein are co-administered with one or more therapeutic agents to provide a resensitization effect in subjects in need thereof. The co-administered agents may be a cancer therapeutic agent, as described herein. In certain examples, the co-administered agent(s) may be dosed, *e.g.*, orally or by injection.

[0020] In particular examples, there are disclosed tablets containing 5-azacytidine and methods for making and using the tablets to treat cancer, disorders related to abnormal cell proliferation, or hematologic disorders. In certain examples, the tablets optionally further contain one or more excipients such as, for example, glidants, diluents, lubricants, colorants, disintegrants, granulating agents, binding agents, polymers, and/or coating agents. Examples of ingredients useful in preparing certain formulations provided herein are described in, *e.g.*, Etter *et al.*, U.S. Patent Application Publication No. 2008/0057086 (App. No. 11/849,958), which is incorporated herein by reference in its entirety.

[0021] Specific examples herein disclose, *inter alia*, pharmaceutical compositions comprising a therapeutically effective amount of 5-azacytidine, wherein the composition releases the 5-azacytidine substantially in the stomach following oral administration to a subject. Further examples disclose the aforementioned compositions, which: are immediate release compositions; do not have an enteric coating (*i.e.*, are non-enteric-coated); are tablets; are capsules; further comprise an excipient selected from any excipient disclosed herein; further comprise a permeation enhancer; further comprise d-alpha-tocopheryl polyethylene glycol 1000 succinate; further comprise a permeation enhancer in the formulation at about 2% by weight relative to the total weight of the formulation; are essentially free of a cytidine deaminase inhibitor; are essentially free of tetrahydrouridine; have an amount of 5-azacytidine of at least about 40 mg; have an amount of 5-azacytidine of at least about 400 mg; have an amount of 5-azacytidine of at least about 1000 mg; achieve an area-under-the-curve value of at least about 200 ng-hr/mL following oral administration to a subject; achieve an area-under-the-curve value of at least about 400 ng-hr/mL following oral administration to a subject; achieve a maximum plasma concentration of at least about 100 ng/mL following oral administration to a subject; achieve a maximum plasma concentration

of at least about 200 ng/mL following oral administration to a subject; achieve a time to maximum plasma concentration of less than about 90 minutes following oral administration to a subject; and/or achieve a time to maximum plasma concentration of less than about 60 minutes following oral administration to a subject.

[0022] Specific examples herein disclose a pharmaceutical composition for oral administration comprising a therapeutically effective amount of 5-azacytidine, which releases the 5-azacytidine substantially in the stomach and achieves an area-under-the-curve value of at least about 200 ng-hr/mL following oral administration.

[0023] Specific examples herein disclose a pharmaceutical composition for oral administration comprising a therapeutically effective amount of 5-azacytidine, which releases the 5-azacytidine substantially in the stomach and achieves an area-under-the-curve value of at least about 400 ng-hr/mL following oral administration.

[0024] Specific examples herein disclose a pharmaceutical composition for oral administration comprising a therapeutically effective amount of 5-azacytidine, which releases the 5-azacytidine substantially in the stomach and achieves a maximum plasma concentration of at least about 100 ng/mL following oral administration.

[0025] Specific examples herein disclose a pharmaceutical composition for oral administration comprising a therapeutically effective amount of 5-azacytidine, which releases the 5-azacytidine substantially in the stomach and achieves a maximum plasma concentration of at least about 200 ng/mL following oral administration.

[0026] Specific examples herein disclose a pharmaceutical composition for oral administration comprising a therapeutically effective amount of 5-azacytidine, which releases the 5-azacytidine substantially in the stomach and achieves a time to maximum plasma concentration of, *e.g.*, less than about 6 hr, less than about 5 hr, less than about 4 hr, less than about 3 hr, less than about 2.5 hr, less than about 2 hr, less than about 1.5 hr, less than about 1 hr, less than about 45 min, or less than about 30 min following oral administration. In specific embodiments, the presence of food may affect (*e.g.*, extend) the total exposure and/or time to maximum plasma concentration.

[0027] Specific examples herein disclose a pharmaceutical composition for oral administration comprising a therapeutically effective amount of 5-azacytidine, which releases the 5-azacytidine substantially in the stomach and achieves a time to maximum plasma concentration of less than about 60 minutes following oral administration.

[0028] Specific examples herein disclose any of the aforementioned compositions, as single unit dosage forms, tablets, or capsules.

[0029] Specific examples herein disclose , *inter alia*, methods for treating a subject having a disease associated with abnormal cell proliferation, comprising orally administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of 5-azacytidine, wherein the composition releases the 5-azacytidine substantially in the stomach following oral administration to the subject. Further examples herein disclose the aforementioned methods, in which: the disease is myelodysplastic syndrome; the disease is acute myelogenous leukemia; the method further comprises co-administering to the subject in need thereof an additional therapeutic agent selected from any additional therapeutic agent disclosed herein; the composition is an immediate release composition; the composition does not have an enteric coating; the composition further comprises a permeation enhancer; the composition further comprises the permeation enhancer d-alpha-tocopheryl polyethylene glycol 1000 succinate; the composition further comprises d-alpha-tocopheryl polyethylene glycol 1000 succinate in the formulation at about 2% by weight relative to the total weight of the formulation; the method further comprises not co-administering a cytidine deaminase inhibitor with the cytidine analog; the composition is a single unit dosage form; the composition is a tablet; the composition is a capsule; the composition further comprises an excipient selected from any excipient disclosed herein; the amount of 5-azacytidine is at least about 40 mg; the amount of 5-azacytidine is at least about 400 mg; the amount of 5-azacytidine is at least about 1000 mg; the method achieves an area-under-the-curve value of at least about 200 ng-hr/mL following oral administration to the subject; the method achieves an area-under-the-curve value of at least about 400 ng-hr/mL following oral administration to the subject; the method achieves a maximum plasma concentration of at least about 100 ng/mL following oral administration to the subject; the method achieves a maximum plasma concentration of at least about 200 ng/mL following oral administration to the subject; the method achieves a time to maximum plasma concentration of less than about 90 minutes following oral administration to the subject; and/or the method achieves a time to maximum plasma concentration of less than about 60 minutes following oral administration to the subject

[0030] Specific examples herein disclose, *inter alia*, pharmaceutical compositions comprising a therapeutically effective amount of 5-azacytidine, wherein the compositions are for treating a disease or disorder associated with abnormal cell proliferation, wherein the

compositions are prepared for oral administration, and wherein the compositions are prepared for release of the 5-azacytidine substantially in the stomach. Further examples herein disclose the aforementioned compositions, which: have an amount of 5-azacytidine of about 40 mg, about 400 mg, or about 1000 mg; are prepared to achieve an area-under-the-curve value of at least about 200 ng-hr/mL or 400 ng-hr/mL following oral administration; are prepared to achieve a maximum plasma concentration of at least about 100 ng/mL or 200 ng/mL following oral administration; are prepared to achieve a time to maximum plasma concentration of less than about 60 minutes or 90 minutes after being administered; are prepared in the form of an immediate release composition; are prepared for oral administration in combination with an additional therapeutic agent selected from any additional therapeutic agent disclosed herein; are for treating myelodysplastic syndrome or acute myelogenous leukemia; further comprise a permeation enhancer; which further comprise the permeation enhancer d-alpha-tocopheryl polyethylene glycol 1000 succinate; are single unit dosage forms; are tablets or capsules; and/or further comprise an excipient selected from any excipient disclosed herein.

[0031] Specific examples herein disclose, *inter alia*, uses of 5-azacytidine for the preparation of a pharmaceutical composition for treating a disease associated with abnormal cell proliferation, wherein the composition is prepared for oral administration, and wherein the composition is prepared for release of the 5-azacytidine substantially in the stomach. Further embodiments herein provide the aforementioned uses, in which: the disease is myelodysplastic syndrome or acute myelogenous leukemia; the amount of 5-azacytidine is selected from any amount disclosed herein; and/or the composition is prepared for immediate release. Further examples disclose, *inter alia*, methods for treating a subject having a disease or disorder provided herein by administering a pharmaceutical compositions provided herein, wherein the treatment results in improved survival of the subject.

V. BRIEF DESCRIPTION OF THE DRAWINGS

[0032] Figure 1 represents processes and steps that may be used to make particular tablets comprising azacitidine for oral dosing; in specific embodiments, one or more steps may be optionally omitted.

[0033] Figure 2 represents human PK profiles following 75 mg/m^2 SC dosing of azacitidine on Days 1 and 7 in a multiple dose escalation study (n = 18). The X-axis represents time; the Y-axis represents azacitidine plasma concentrations (mean $\pm$ SD).