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Docket Number	9516-825-888	Type a plus sign (+) inside this box 6	+

INVENTOR(s) APPLICANT(s)			
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TITLE OF THE INVENTION (280 characters max)

ORAL DOSAGE FORMS OF CYTIDINE ANALOGS AND METHODS OF USE THEREOF

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ENCLOSED APPLICATION PARTS (*check all that apply*)

☒ Specification	*Number of Pages*	79	☐ Applicant claims small entity status, see 37 CFR §1.27			
☒ Drawing(s)	*Number of Sheets*	17	☐ Other (specify)			
TYPE	*NO. FILED*	LESS	EXTRA	EXTRA RATE		FEE
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Respectfully submitted,

Signature _____

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REGISTRATION NO. *(if appropriate)* 35,203

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☐ Additional inventors are being named on separately numbered sheets attached hereto.

Total number of cover sheet pages. 1

PROVISIONAL APPLICATION FILING ONLY

ORAL DOSAGE FORMS OF CYTIDINE ANALOGS AND METHODS OF USE THEREOF

I. FIELD

[0001] Provided herein are pharmaceutical dosage forms comprising cytidine analogs, or their salts, solvates, hydrates, precursors, and/or derivatives thereof, for oral administration in subjects. Also provided are methods for making the dosage forms and for using the dosage forms to treat cancer and disorders related to abnormal cell proliferation.

II. BACKGROUND

[0002] Cancer is a major worldwide public health problem; in the United States alone, approximately 570,000 cancer-related deaths were expected in 2005. *See, e.g.*, Jemal *et al.*, *CA Cancer J. Clin.* 55(1):10-30 (2005). Many types of cancer have been described in the medical literature. Examples include cancer of the blood, bone, lung (*e.g.*, non-small-cell lung cancer and small-cell lung cancer), colon, breast, prostate, ovary, brain, and intestine. The incidence of cancer continues to climb as the general population ages and as new forms of cancer develop. A continuing need exists for effective therapies to treat subjects with cancer.

[0003] Myelodysplastic syndromes (MDS) refers to a diverse group of hematopoietic stem cell disorders. MDS affects approximately 40,000-50,000 people in the U.S. and 75,000-85,000 subjects in Europe. MDS may be characterized by a cellular marrow with impaired morphology and maturation (dysmyelopoiesis), peripheral blood cytopenias, and a variable risk of progression to acute leukemia, resulting from ineffective blood cell production. *See, e.g.*, *The Merck Manual* 953 (17th ed. 1999); List *et al.*, *J. Clin. Oncol.* 8:1424 (1990).

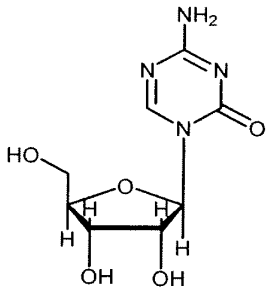
[0004] MDS are grouped together because of the presence of dysplastic changes in one or more of the hematopoietic lineages including dysplastic changes in the myeloid, erythroid, and megakaryocytic series. These changes result in cytopenias in one or more of the three lineages. Subjects afflicted with MDS may develop complications related to anemia, neutropenia (infections), and/or thrombocytopenia (bleeding). From about 10% to about 70% of patients with MDS may develop acute leukemia. In the early stages of MDS, the main cause of cytopenias is increased programmed cell death (apoptosis). As the disease progresses and converts into leukemia, a proliferation of leukemic cells

overwhelms the healthy marrow. The disease course differs, with some cases behaving as an indolent disease and others behaving aggressively with a very short clinical course that converts into an acute form of leukemia. The majority of people with higher risk MDS eventually experience bone marrow failure. Up to 50% of MDS patients succumb to complications, such as infection or bleeding, before progressing to AML.

[0005] An international group of hematologists, the French-American-British (FAB) Cooperative Group, classified MDS into five subgroups, differentiating them from acute myeloid leukemia. *See, e.g.*, *The Merck Manual* 954 (17th ed. 1999); Bennett J. M., *et al.*, *Ann. Intern. Med.*, 103(4): 620-5 (1985); and Besa E. C., *Med. Clin. North Am.* 76(3): 599-617 (1992). An underlying trilineage dysplastic change in the bone marrow cells of the patients is found in all subtypes. Information is available regarding the pathobiology of MDS, certain MDS classification systems, and particular methods of treating and managing MDS. *See, e.g.*, U.S. Patent No. 7,189,740 (issued March 13, 2007), which is incorporated by reference herein in its entirety.

[0006] Nucleoside analogs have been used clinically for the treatment of viral infections and cancer. Most nucleoside analogs are classified as anti-metabolites. After they enter the cell, nucleoside analogs are successively phosphorylated to nucleoside 5'-mono-phosphates, di-phosphates, and tri-phosphates. In most cases, nucleoside tri-phosphates are the chemical entities that inhibit DNA or RNA synthesis, either through competitive inhibition of polymerases or through incorporation of the modified nucleotides into DNA or RNA sequences. Nucleosides may also act as di-phosphates.

[0007] 5-Azacytidine (National Service Center designation NSC-102816; CAS Registry Number 320-67-2), also known as azacitidine, AZA, or 4-amino-l-β-D-ribofuranosyl-1,3,5-triazin-2(l*H*)-one, is currently marketed as the drug product VIDAZA®. 5-Azacytidine is a nucleoside analog, more specifically a cytidine analog. 5-Azacytidine is an antagonist of its related natural nucleoside, cytidine. 5-Azacytidine and 5-aza-2'-deoxycytidine (also known as decitabine, an analog of deoxycytidine) are also antagonists of deoxycytidine. A structural difference between these cytidine analogs and their related natural nucleoside is the presence of a nitrogen at position 5 of the cytosine ring in place of a carbon. 5-Azacytidine may be defined as having the molecular formula $C_8H_{12}N_4O_5$, a molecular weight of 244.21 grams per mole, and the following structure:



5-Azacytidine.

[0008] Other members of the class of cytidine analogs include, for example: l-β-D-arabinofuranosylcytosine (Cytarabine or ara-C); 5-aza-2'-deoxycytidine (Decitabine or 5-aza-CdR); 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; and elaidic acid cytarabine.

[0009] After its incorporation into replicating DNA, 5-azacytidine or 5-aza-2'-deoxycytidine forms a covalent complex with DNA methyltransferase. DNA methyltransferase is responsible for reproducing the methylation patterns in the daughter strands. Inhibition of DNA methyltransferase by a cytidine analog leads to DNA hypomethylation, thereby reestablishing the anti-proliferative signals extinguished by DNA hypermethylation in malignant cells, such as morphologically dysplastic and immature hematopoietic cells. The cytotoxic effects of these cytidine analogs cause the death of rapidly dividing cells, including cancer cells, that are no longer responsive to normal cell growth control mechanisms.

[0010] 5-Azacytidine and 5-aza-2'-deoxycytidine have been tested in clinical trials and showed significant anti-tumor activity, such as, for example, in the treatment myelodysplastic syndromes (MDS), acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), acute lymphocytic leukemia (ALL), and non Hodgkin's lymphoma (NHL). *See, e.g.*, Aparicio *et al.*, *Curr. Opin. Invest. Drugs* 3(4): 627-33 (2002). 5-Azacytidine has undergone NCI-sponsored trials for the treatment of MDS and has been approved for treating all FAB subtypes of MDS. *See, e.g.*, Kornblith *et al.*, *J. Clin. Oncol.* 20(10): 2441-2452 (2002); Silverman *et al., J. Clin. Oncol.* 20(10): 2429-

2440 (2002). 5-Azacytidine may alter the natural course of MDS by diminishing the transformation to AML through its cytotoxic activity and its inhibition of DNA methyltransferase. In a Phase III study, 5-azacytidine significantly prolonged survival and time to AML transformation or death in elderly subjects. *See, e.g.,* Silverman *et al., Blood* 106(11): Abstract 2526 (2005).

[0011] 5-Azacytidine and other cytidine analogs are approved for subcutaneous (SC) or intravenous (IV) administration to treat various proliferative disorders. Oral dosing of cytidine analogs would be more desirable and convenient for patients and doctors, *e.g.*, by eliminating injection-site reactions that may occur with SC administration and/or by permitting improved patient compliance. However, oral delivery of cytidine analogs has proven difficult due to combinations of chemical instability, enzymatic instability, and/or poor permeability. For example, cytidine analogs have been considered acid labile and 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.

[0012] 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 demethylation or gene re-expression; use of cytidine analogs for treating new diseases or disorders; and/or other potential advantageous benefits.

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