adverse effects leading to discontinuation of treatment. Chemotherapeutic agents are usually reserved for patients who have failed BCG therapy. Chemotherapy is typically applied intravesically to concentrate the chemotherapeutic agent at the tumor sites and eliminate any residual tumor after resection while avoiding systemic exposure of the drug.

One such chemotherapeutic agent used in clinical trials for treating bladder cancer is gemcitabine. Gemcitabine (2',2'-difluorodeoxycytidine) is a pyrimidine analogue with activity against metastatic bladder cancer. Gemcitabine has also been used in clinical trials to treat superficial bladder cancers and NMIBC by instillation in the bladder with various weekly schedules. Gemcitabine is typically instilled over 1 to 2 hours once or twice a week for several weeks at doses typically ranging from 500 to 2000 mg in up to 100 ml of saline.

It is known that such formulations are voided from the bladder before full efficacy is achieved. The short dwell times of 1 to 2 hours limit therapeutic benefit. In addition, high concentrations (40 mg/ml) and high doses (up to 2 grams per instillation) are used in an attempt to achieve therapeutic tissue levels in order to try to overcome the dwell time limitations. However, intravesical administration of high doses of gemcitabine can lead to significant systemic absorption and cause gastrointestinal, bladder and bone marrow toxicity further limiting the clinical utility in addition to local tolerability issues.

The literature also reports that intravenous systemic administration of gemcitabine by bolus injection, e.g., over 1 to 2 minutes, is better tolerated by patients than slow intravenous infusion, e.g., over 90 minutes. This suggests that prolonged exposure to gemcitabine increases toxicity and should be avoided.

Accordingly, there remains a need for improved drug delivery methods and systems for treating bladder cancer. For example, there remains a need to administer therapeutic levels of gemcitabine to patient over sustained periods while avoiding or mitigating toxicity and tolerability issues that have been observed to limit the clinical utility of gemcitabine.

Brief Summary

The present disclosure provides ~~In one aspect,~~ a medicament ~~is provided~~ which comprises gemcitabine for use in the treatment of bladder cancer by locally administering the gemcitabine into the bladder of a patient to achieve a sustained concentration of the gemcitabine in the urine in the bladder sufficient to produce a therapeutic concentration of the gemcitabine in the bladder tissues, wherein the local administration into the patient's bladder is at a mean average amount of from 1 mg/day to about 300 mg/day of the gemcitabine free base equivalent (FBE).

In one aspect of the present disclosure, there is provided a medicament comprising gemcitabine for use in the treatment of bladder cancer by locally administering the gemcitabine into the bladder of a patient to achieve a sustained concentration of the gemcitabine in the urine in the bladder sufficient to produce a therapeutic concentration of the gemcitabine in the bladder tissues,

wherein the locally administering into the patient's bladder is at a mean average amount of from 1 mg/day to about 300 mg/day of the gemcitabine (FBE).

In another aspect of the present disclosure, there is provided a use of gemcitabine in the manufacture of a medicament for the treatment of bladder cancer in a patient, wherein the medicament is to be locally administered into the bladder of the patient to achieve a sustained concentration of the gemcitabine in the urine in the bladder sufficient to produce a therapeutic concentration of the gemcitabine in the bladder tissues, wherein the locally administering into the patient's bladder at a mean average amount of from 1 mg/day to about 300 mg/day of the gemcitabine (FBE).

In embodiments, the local administer into the patient's bladder is at a mean average amount of from 1 mg/day to 200 mg/day of the gemcitabine (FBE), from 5 mg/day to 100 mg/day of

the gemcitabine (FBE), from 10 mg/day to 50 mg/day of the gemcitabine (FBE), or from 15 mg/day to 25 mg/day of the gemcitabine (FBE). In one case, the locally administering into the patient's bladder is at a mean average amount of about 20 mg/day of the gemcitabine (FBE). The local administer into the patient's bladder may be continuous or intermittent. In embodiments, the continuous or intermittent administration is over a period from 1 day to 30 days, from 1 day to 14 days, or from 1 day to 7 days.

In a preferred embodiment, the gemcitabine is delivered into the bladder from an intravesical drug delivery device which continuously releases the gemcitabine into the urine in the bladder over a sustained period. In another embodiment, the gemcitabine is delivered into the bladder from a coating substance applied to the bladder, which coating substance (e.g., a mucoadhesive formulation) releases the gemcitabine into the urine in the bladder over a sustained period. In still another embodiment, a liquid form of the gemcitabine is pumped into the bladder over a sustained period through a urethral or suprapubic catheter which is deployed into the bladder.

The present disclosure also provides ~~In another aspect,~~ a drug delivery device ~~is provided~~ for administering gemcitabine to a patient in need of treatment of bladder cancer by intravesically administering gemcitabine into the bladder of the patient to achieve a sustained concentration of the gemcitabine in urine in the bladder sufficient to produce a therapeutically effective concentration of the gemcitabine in the tissues of the bladder.

In another aspect of the present disclosure, there is provided a drug delivery device comprising a medicament as hereinbefore described, configured to release the gemcitabine when the drug delivery device is inserted into the bladder.

In a particular embodiment, the drug delivery device includes a housing configured for intravesical insertion, and a dosage form comprising gemcitabine, wherein the housing holds the dosage form and is configured to release the gemcitabine into the bladder in an amount therapeutically effective for the treatment of the prostate, wherein the device is configured to release gemcitabine into the bladder at a mean average amount of from 1 mg/day to about 300 mg/day of the gemcitabine. In a preferred embodiment, the housing releases the gemcitabine without a predefined release aperture. In a particular version of this preferred embodiment, the housing releases the gemcitabine by diffusion through a drug permeable polymeric wall. The housing which contains and controllably releases the gemcitabine may be elastically deformable between a retention shape configured to retain the device in a patient's bladder and a deployment shape for passage of the device through the patient's urethra.

In a further aspect of the present disclosure, there is provided a drug delivery device comprising:

a housing configured for intravesical insertion; and

a dosage form comprising gemcitabine,

wherein the housing holds the dosage form and is configured to release the gemcitabine into the bladder in an amount therapeutically effective for the treatment of the bladder,

wherein the device is configured to release gemcitabine into the bladder at a mean average amount of from 1 mg/day to about 300 mg/day of the gemcitabine.

The present disclosure also provides~~In still another aspect,~~ methods of treating bladder cancer are provide by locally administering the gemcitabine into the bladder of a patient to achieve a sustained concentration of the gemcitabine in the urine in the bladder sufficient to produce a therapeutic concentration of the gemcitabine in the bladder tissues. In embodiments, the

local administration into the patient's bladder is at a mean average amount of from 1 mg/day to about 300 mg/day of the gemcitabine (FBE). In one embodiment, the method further includes administering at least a second therapeutic agent to the patient. The second therapeutic agent may be administered intravesically. In another embodiment, the method further includes administering urea or another solubility altering agent into the bladder in an amount effective to enhance or otherwise alter solubilization of the gemcitabine. In embodiments, the second therapeutic agent and/or the solubility altering agent is released from an intravesical device which releases the gemcitabine.

In a further aspect of the present disclosure, there is provided a use of gemcitabine in the manufacture of a medicament for the treatment of bladder cancer in a patient, wherein the medicament is to be intravesically administered into the bladder of the patient to achieve a sustained concentration of the gemcitabine in urine in the bladder sufficient to produce a therapeutically effective concentration of the gemcitabine in the tissues of the bladder.

Brief Description of the Drawings

FIGS. 1A-1B illustrate one embodiment of an intravesical drug delivery device that may be used for administering gemcitabine as described herein.

FIGS. 2A-2B illustrate another embodiment of an intravesical drug delivery device that may be used for administering gemcitabine as described herein.

FIGS. 3A-3C illustrate still another embodiment of an intravesical drug delivery device that may be used for administering gemcitabine as described herein.

FIGS. 4A-4B illustrate a method of inserting an intravesical drug delivery device into the bladder of a patient for local administration of gemcitabine as described herein.

FIG. 5A illustrates a material applied to the inner surface of the bladder wall for local administration of gemcitabine as described herein.

FIG. 5B illustrates a method of applying a coating material onto to the inner surface of the bladder wall for local administration of gemcitabine as described herein.

FIG. 6 illustrates a method of applying a liquid drug or drug formulation into the bladder.

FIG. 7 illustrates the concentration of gemcitabine in the prostate after bladder perfusion and intravenous administration.

FIG. 8 illustrates the plasma levels of gemcitabine after bladder perfusion and intravenous administration.

FIG. 9 illustrates ^{14}C gemcitabine concentration in the bladder after bladder perfusion and intravenous administration.

FIGS. 10A-C illustrate one embodiment of an intravesical drug delivery device for releasing gemcitabine via permeation disks. **FIG. 10A** is a plan view of the device. **FIG. 10B** is a cross-sectional view of one of the four drug reservoir modules of the device shown in **FIG. 10A**, showing the drug tablets and permeation disks of each module. **FIG. 10C** is a

20. The medicament of any one of claims 1 to 6, wherein the locally administering comprises pumping a liquid form of the gemcitabine into the bladder through a urethral or suprapubic catheter which is deployed into the bladder.

21. The medicament of claim 20, wherein the locally administering into the patient's bladder is continuous or intermittent over a period from 1 day to 7 days.

22. Use of gemcitabine in the manufacture of a medicament for the treatment of bladder cancer in a patient, wherein the medicament is to be locally administered into the bladder of the patient to achieve a sustained concentration of the gemcitabine in the urine in the bladder sufficient to produce a therapeutic concentration of the gemcitabine in the bladder tissues, wherein the locally administering into the patient's bladder is at a mean average amount of from 1 mg/day to about 300 mg/day of the gemcitabine (FBE).

23. The use of claim 22, wherein the locally administering into the patient's bladder is at a mean average amount of from 1 mg/day to 200 mg/day of the gemcitabine (FBE).

24. The use of claim 22, wherein the locally administering into the patient's bladder is at a mean average amount of from 5 mg/day to 100 mg/day of the gemcitabine (FBE).

25. The use of claim 22, wherein the locally administering into the patient's bladder is at a mean average amount of from 10 mg/day to 50 mg/day of the gemcitabine (FBE).

26. The use of claim 22, wherein the locally administering into the patient's bladder is at a mean average amount of from 15 mg/day to 25 mg/day of the gemcitabine (FBE).

27. The use of claim 22, wherein the locally administering into the patient's bladder is at a mean average amount of about 20 mg/day of the gemcitabine (FBE).

28. The use of any one of claims 22 to 27, wherein the locally administering into the patient's bladder is continuous over a period from 1 day to 30 days.

29. The use of any one of claims 22 to 27, wherein the locally administering into the patient's bladder is intermittent over a period from 1 day to 30 days.

30. The use of any one of claims 22 to 27, wherein the locally administering into the patient's bladder is intermittent or continuous over a period from 1 day to 14 days.

31. The use of any one of claims 22 to 27, wherein the locally administering into the patient's bladder is continuous over a period from 1 day to 7 days.

32. The use of any one of claims 22 to 27, wherein the gemcitabine is to be delivered into the bladder from an intravesical drug delivery device which continuously releases the gemcitabine into the urine in the bladder over a sustained period.

33. The use of claim 32, wherein the intravesical drug delivery device continuously releases the gemcitabine into the urine in the bladder over a period of 1 day to 14 days.

34. The use of claim 33, wherein the intravesical drug delivery device comprises a housing which contains and controllably releases the gemcitabine and is elastically deformable between a retention shape configured to retain the device in a patient's bladder and a deployment shape for passage of the device through the patient's urethra.

35. The use of claim 34, wherein the gemcitabine contained in the housing is in a non-liquid form.

36. The use of claim 35, wherein the non-liquid form is selected from the group consisting of tablets, granules, semisolids, capsules, and combinations thereof.

37. The use of claim any one of claims 22 to 27, wherein the gemcitabine is to be delivered into the bladder from a coating substance applied to the bladder, which coating substance releases the gemcitabine into the urine in the bladder over a sustained period.

38. The use of claim 37, wherein the coating substance comprises a mucoadhesive formulation.

39. The use of claim 38, wherein the locally administering into the patient's bladder is continuous over a period from 1 day to 14 days.

40. The use of claim 38, wherein the locally administering into the patient's bladder is continuous over a period from 1 day to 7 days.

41. The use of any one of claims 22 to 27, wherein the locally administering comprises pumping a liquid form of the gemcitabine into the bladder through a urethral or suprapubic catheter which is deployed into the bladder.

42. The use of claim 41, wherein the locally administering into the patient's bladder is continuous or intermittent over a period from 1 day to 7 days.

~~22~~43. A drug delivery device comprising a medicament according to any one of ~~the preceding~~ claims 1 to 21, configured to release the gemcitabine when the drug delivery device is inserted into the bladder.

~~23~~44. Use of gemcitabine in the manufacture of a medicament for the ~~A method of administering a drug to a patient in need of~~ treatment of bladder cancer in a patient, wherein the medicament is to be intravesically administered ~~the method comprising: intravesically administering gemcitabine~~ into the bladder of the patient to achieve a sustained concentration of the gemcitabine in urine in the bladder sufficient to produce a therapeutically effective concentration of the gemcitabine in the tissues of the bladder.

~~24~~45. The ~~method~~ use of claim ~~23~~44, wherein ~~further comprising administering at least~~ a second therapeutic agent is to be further administered to the patient.

~~25~~46. The ~~method~~ use of claim ~~24~~45, wherein the second therapeutic agent is to be administered intravesically.

~~26~~47. The use ~~method~~ of claim ~~23~~44, wherein ~~further comprising administering~~ urea or another solubility altering agent is to be further administered into the bladder in an amount effective to enhance or otherwise alter solubilization of the gemcitabine.

~~27~~48. The ~~method~~ use of claim ~~26~~47, wherein the urea or other solubility altering agent is released from an intravesical device releasing the gemcitabine.

~~2849~~. A drug delivery device comprising:

a housing configured for intravesical insertion; and

a dosage form comprising gemcitabine,

wherein the housing holds the dosage form and is configured to release the gemcitabine into the bladder in an amount therapeutically effective for the treatment of the bladder,

wherein the device is configured to release gemcitabine into the bladder at a mean average amount of from 1 mg/day to about 300 mg/day of the gemcitabine.

~~2950~~. The device of claim ~~2849~~, wherein the housing releases the gemcitabine by diffusion through a drug permeable polymeric wall.

~~3051~~. The device of claim ~~2849~~, wherein the housing releases the gemcitabine without a predefined release aperture.

~~3152~~. The device of claim ~~2849~~, wherein the housing comprises a release orifice in communication with a drug reservoir in which the gemcitabine is contained along with (i) a viscosity enhancing agent, (ii) an osmotic agent, or (iii) a combination of a viscosity enhancing agent and an osmotic agent.

~~3253~~. The device of claim ~~3152~~, wherein the gemcitabine is provided in a first region comprising one or more tablets and the osmotic agent and/or viscosity enhancing agent is/are provided in a second region comprising one or more tablets, wherein the first and second regions are discrete spaces within the drug reservoir.