

CLAIMS

What is claimed is:

1. Use of an antimetabolite in the manufacture of a medicament for~~A method of~~ treating a urothelial carcinoma of the lower tract in an individual~~comprising administering to the individual an effective amount of an antimetabolite~~, wherein the antimetabolite is to be delivered locally to the bladder, wherein the urothelial carcinoma of the lower tract is muscle invasive bladder cancer.
2. The method-use of claim 1, wherein the individual is unfit for radical cystectomy.
3. The method-use of claim 1 or 2, wherein the individual cannot tolerate systemic chemotherapy and/or chemotherapy with an agent other than the antimetabolite.
4. The method-use of any one of claims 1-3, wherein the individual does not receive a radical cystectomy.
5. Use of an antimetabolite in the manufacture of a medicament for~~A method of~~ treating a urothelial carcinoma of the lower tract in an individual~~comprising administering to the individual an effective amount of an antimetabolite~~, wherein the antimetabolite is to be delivered locally to the bladder, wherein the urothelial carcinoma of the lower tract is non-muscle invasive bladder cancer.
6. Use of a combination of an antimetabolite with a second agent in the manufacture of a medicament for~~A method of~~ treating a urothelial carcinoma of the lower tract in an individual~~comprising administering to the individual an effective amount of an antimetabolite~~, wherein the antimetabolite is to be delivered locally to the bladder,~~wherein the method further comprises administering to the individual an effective amount of a second agent.~~

7. The ~~method-use~~ of any of claims 1-6, wherein the antimetabolite is a nucleoside analog.
8. The ~~method-use~~ of any one of claims 1-7, wherein the antimetabolite is gemcitabine.
9. The ~~method-use~~ of claim 8, wherein the gemcitabine is to be delivered continuously to the bladder of the individual for 24 hours to 6 weeks.
10. Use of an antimetabolite in the manufacture of a medicament for~~A method of~~ bladder preservation in an individual ~~comprising delivering an effective amount of gemcitabine locally to the bladder,~~ wherein the antimetabolite is gemcitabine, wherein gemcitabine is to be delivered continuously to the bladder of the individual for 24 hours to 6 weeks, wherein the individual has a urothelial carcinoma of the lower tract.
11. The ~~method-use~~ of any one of claims 8-10, wherein the gemcitabine is to be delivered continuously to the bladder of the individual for a period of 24 hours to three weeks.
12. The ~~method-use~~ of any one of claims 8-11, wherein the gemcitabine is to be delivered continuously to the bladder of the individual for 7 days.
13. The ~~method-use~~ of any one of claims 8-11, wherein the gemcitabine is to be delivered continuously to the bladder of the individual for 3 weeks.
14. The ~~method-use~~ of any one of claims 8-13, wherein the ~~method-use~~ comprises a first gemcitabine delivery period and a second gemcitabine delivery period.
15. The ~~method-use~~ of claim 14, wherein the first and second gemcitabine delivery periods are each 7 days.
16. The ~~method-use~~ of claim 14, wherein the first and second gemcitabine delivery periods are each 3 weeks.

17. The ~~method-use~~ of any one of claims 14-16, wherein the first and second gemcitabine delivery periods are separated by a rest period of 14 days.

18. The ~~method-use~~ of any of claims 1-17, wherein the antimetabolite is to be delivered in a first phase of the delivery at a first release rate followed by a second phase of the delivery having a second release rate.

19. The ~~method-use~~ of any of claims 1-18, wherein the antimetabolite is to be delivered at a dose of from about 1 mg/day to about 300 mg/day.

20. The ~~method-use~~ of any of claims 1-19, wherein the concentration of antimetabolite in the urine is from about 0.1 µg/mL to about 200 µg/mL during the delivery period.

21. The ~~method-use of~~ claim 20, wherein the concentration of antimetabolite in the urine is from about 1 µg/mL to about 10 µg/mL during the delivery period.

22. The ~~method-use~~ of claim 20, wherein the concentration of antimetabolite in the urine is about 10 µg/mL during the delivery period.

~~23. The method of any of claims 1-22, wherein the antimetabolite concentration in the plasma of the individual is less than about 1 µg/mL.~~

~~24. The method of any of claims 1-23, wherein upon delivery of antimetabolite the ratio of antimetabolite in the urine to antimetabolite in the plasma of the individual is greater than about 500:1.~~

~~23~~5. The ~~method-use~~ of any of claims 1-~~22~~4, comprising
a) a first antimetabolite delivery period, wherein the concentration of antimetabolite in the urine of the individual is at least about 0.1 µg/mL;

b) a rest period; and

c) a second antimetabolite delivery period, wherein the concentration of antimetabolite in the urine of the individual is greater than about 0.1 µg/mL.

~~26. The method of 25, wherein the concentration of antimetabolite in the urine is greater than about 1 µg/mL for at least half of the rest period.~~

247. The ~~method-use~~ of any one of claims ~~1-5 and 7-231-26~~, ~~wherein further comprising administering to the individual~~ an effective amount of a second agent is to be administered to the individual.

258. The ~~method-use~~ of claim ~~6 or 2427~~, wherein the second agent is to be delivered systemically.

269. The ~~method-use~~ of claim ~~6 or 2427~~, wherein the second agent or second chemotherapeutic agent is to be delivered locally.

~~30. The method of 29, wherein the antimetabolite and the second agent are delivered via a single delivery device.~~

2731. The ~~method-use~~ any one of claims ~~248-2630~~, wherein the second agent is an immunomodulating agent.

2832. The ~~method-use~~ of claim ~~2731~~, wherein the immunomodulating agent is an immune checkpoint inhibitor.

2933. The ~~method-use~~ of claim ~~2832~~, wherein the immune checkpoint inhibitor is an inhibitor of an immune checkpoint protein selected from the group consisting of PD-L1, CTLA4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, B- and T-lymphocyte attenuator (BTLA), Killer inhibitory

receptor (KIR), GAL9, TIM3, A2AR, LAG-3, phosphatidylserine, CD27, TNF- α , CD33, Siglec-5, Siglec-7, Siglec-9, and Siglec-11.

~~34. The method of claim 32, wherein the immunomodulating agent is an agonist of a costimulatory immune molecule.~~

~~35. The method of claim 34, wherein the costimulatory immune molecule is selected from the group consisting of CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, IL-10, TGF-beta, TOR receptor, and glucocorticoid-induced TNFR-related protein GITR.~~

~~36. The method of claim 27-30, wherein the second agent is a second chemotherapeutic agent.~~

~~37. The method of claim 36, wherein the chemotherapeutic agent is selected from the group consisting of paclitaxel, docetaxel, and oxaliplatin.~~

308. The ~~method-use~~ of any of claims 1-~~2937~~, wherein the individual does not receive radiation therapy.

319. The ~~method-use~~ of any one of claims 1-~~2938~~, wherein the ~~method-use~~ further comprises radiation therapy.

~~3240~~. The ~~method-use~~ of any of claims 1-~~3139~~, wherein the antimetabolite is to be delivered in a neoadjuvant setting.

~~3341~~. The ~~method-use~~ of any of claims 1-~~3139~~, wherein the antimetabolite is to be delivered in an adjuvant setting.

~~42. The method of any of claims 1-41, further comprising a third therapy comprising surgery, wherein delivery of antimetabolite to the individual is initiated at the time of the surgery.~~

3443. The ~~method-use~~ of any of claims 1-3342, wherein the antimetabolite is to be delivered into the bladder by an intravesicular ~~delivery~~ device.

3544. The ~~method-use~~ of claim 3443, wherein the intravesicular device contains 100 mg to 500 mg of gemcitabine.

3645. The ~~method-use~~ of claim 3544, wherein the intravesicular device contains 225 mg of gemcitabine.

~~46. The method of any of claims 43-45, wherein the intravesicular device comprises a housing configured for intravesicular insertion; and a dosage form comprising antimetabolite, wherein the housing holds the dosage form and is configured to release antimetabolite in an amount effective for the treatment of a urothelial carcinoma of the lower tract.~~

~~47. The method of any one of claims 43-46, wherein the intravesicular drug delivery device comprises a housing defining a reservoir;
a first unit contained within the reservoir, the first unit comprising an antimetabolite; and
a second unit contained within the reservoir in a position distinct from the first unit, wherein the second unit comprises a functional agent that facilitates in vivo release of the antimetabolite from the housing.~~

~~48. The method of any one of claims 43-47, wherein the intravesicular drug delivery device comprises a housing which contains and controllably releases the antimetabolite and is elastically deformable between a retention shape configured to retain the device in the individual's bladder and a deployment shape for passage of the device through the individual's urethra.~~

~~49. The method of any one of claims 43-48, wherein the device comprises a drug reservoir lumen bounded by a first wall and a second wall, wherein the first wall is impermeable to the drug and the second wall is permeable to the antimetabolite.~~

~~50. The method of any of claims 43-49, wherein the intravesicular drug delivery device comprises at least two drug reservoir lumens.~~

~~51. The method of any one of claims 43-50 wherein the antimetabolite is released from the device by osmotic pressure.~~

~~52. The method of any one of claims 43-51, wherein the antimetabolite is released from the device by diffusion.~~

~~53. The method of any of claims 43-52, wherein the antimetabolite contained in the housing is in a non-liquid form.~~

~~54. The method of claim 53, wherein the non-liquid form is selected from the group consisting of tablets, granules, powders, semisolids, capsules, and combinations thereof.~~

3755. The ~~method-use~~ of any of claims 6-~~36~~54, wherein the urothelial carcinoma of the lower tract is bladder cancer.

3856. The ~~method-use~~ of claim 3755, wherein the bladder cancer is muscle invasive bladder cancer.

3957. The ~~method-use~~ of claim 3755, wherein the bladder cancer is non-muscle invasive bladder cancer.

~~58. The method of any of claims 1-4, or 6-55, wherein the bladder cancer is locally advanced bladder cancer or metastatic bladder cancer.~~

~~59. The method of any one of claims 5-55, wherein the bladder cancer is carcinoma in situ.~~

~~60. The method of any one of claims 1-55, wherein the bladder cancer is BCG (Bacillus Calmette-Guerin) refractory or BCG resistant cancer or papillary bladder cancer.~~

4061. The method-use of any one of claims 1-~~3960~~, wherein the individual is human.

4162. The method-use of any one of claims 1-4061, wherein the individual is unsuitable for systemic chemotherapy.

4263. The method-use of any one of claims 1-4162, wherein the individual has a compromised immune system.

~~64. The method any one of claims 1-63, wherein the individual has a high level of an immune checkpoint protein.~~

~~65. The method of any one of claims 1-63, wherein the individual has a low level of an immune checkpoint protein.~~

~~66. The method of any one of claims 1-65, wherein the individual has a high level of a nucleoside transporter.~~

~~67. The method of any one of claims 1-65, wherein the individual has a low level of a nucleoside transporter.~~

~~68. — The method of any one of claims 8–67, wherein the method further comprise determining the gemcitabine/metabolite ratio in the urine, wherein a ratio below a threshold value is indicative of effective treatment.~~

~~69. — A kit for treating a urothelial carcinoma of the lower tract in an individual comprising: a) an antimetabolite and b) an immunomodulating agent, wherein the antimetabolite is in a device for local delivery to the bladder.~~

~~70. — A kit for treating a urothelial carcinoma of the lower tract in an individual comprising: a) an antimetabolite and b) a second agent, wherein the antimetabolite is in a device for local delivery to the bladder, wherein the urothelial carcinoma of the lower tract is muscle invasive bladder cancer.~~

~~71. — The kit of claim 70, wherein the second agent is an immunomodulatory agent.~~

~~72. — The kit of claim 69 or 70, wherein the antimetabolite is gemcitabine.~~

~~73. — A delivery device for local delivery of an antimetabolite and a second agent to the bladder of an individual, comprising: a housing containing an antimetabolite and an immunomodulatory agent, wherein the housing is configured to provide local release of the antimetabolite and the second agent into the bladder of the individual.~~

~~74. — The delivery device of claim 73, wherein the antimetabolite is gemcitabine.~~

~~75. — The delivery device of claim 73 or 74, wherein the second agent is an immunomodulatory agent.~~

~~76. — A method of enhancing an immune response against a urothelial carcinoma of the lower tract in an individual comprising administering to the individual an effective amount of an antimetabolite, wherein the antimetabolite is delivered locally to the bladder.~~