expectancy or death from metastatic disease. Approximately 350,000 patients in the US and EU are currently undergoing treatment for unresolved tumors.

[0005] NMIBC is typically treated with intravesicular BCG, which elicits a nonspecific local immune response against the tumor cells. BCG elicits a nonspecific massive local inflammatory reaction in the bladder wall, and elevated appearance of cytokines can be detected in the urine of BCG-treated patients. BCG is internalized by antigen-presenting cells, such as macrophages, but also by urothelial tumor cells, which result in an altered gene expression of these cells. Additionally, none of the available chemotherapeutic agents, including gemcitabine, cisplatin, and valrubicin, that are currently explored in clinical trials for treating bladder cancer are targeted therapeutics.

[0006] Sirolimus (INN/USAN), also known as rapamycin, is an immunosuppressant drug used to prevent rejection in organ transplantation; it is especially useful in kidney transplants. It prevents activation of T cells and B cells by inhibiting their response to interleukin-2 (IL-2). The mode of action of sirolimus is to bind the cytosolic protein FK-binding protein 12 (FKBP12), and the sirolimus-FKBP12 complex in turn inhibits the mammalian target of sirolimus (mTOR) pathway by directly binding the mTOR Complex1 (mTORC1).

[0007] Albumin-based nanoparticle compositions have been developed as a drug delivery system for delivering substantially water insoluble drugs. *See*, for example, U.S. Pat. Nos. 5,916,596; 6,506,405; 6,749,868, and 6,537,579, 7,820,788, and 7,923,536. Abraxane®, an albumin stabilized nanoparticle formulation of paclitaxel, was approved in the United States in 2005 and subsequently in various other countries for treating metastatic breast cancer. It was recently approved for treating non-small cell lung cancer in the United States, and has also shown therapeutic efficacy in various clinical trials for treating difficult-to-treat cancers such as bladder cancer and melanoma. Albumin derived from human blood has been used for the manufacture of Abraxane® as well as various other albumin-based nanoparticle compositions.

[0008] The disclosures of all publications, patents, patent applications and published patent applications referred to herein are hereby incorporated herein by reference in their entirety.

SUMMARY

[0009] In one aspect, there is provided use of a composition comprising nanoparticles comprising a limus drug and an albumin in the manufacture of a medicament for treating bladder cancer in an individual, wherein the medicament is to be administered to the individual in combination with an effective amount of Bacillus Calmette-Guérin (BCG).

[0009a] Also disclosed are methods of treating bladder cancer in an individual, comprising administering to the individual an effective amount of a composition comprising nanoparticles comprising an mTOR inhibitor (such as a limus drug). In some embodiments,

CLAIMS

What is claimed is:

1. Use of a composition comprising nanoparticles comprising a limus drug and an albumin in the manufacture of a medicament for treating bladder cancer in an individual, wherein the medicament is to be administered to the individual in combination with an effective amount of Bacillus Calmette-Guérin (BCG).

2. The use of claim 1, wherein the composition is to be administered intravesicularly.

3. The use of claim 1 or 2, wherein the bladder cancer is non-muscle-invasive bladder cancer.

4. The use of any one of claims 1-3, wherein the bladder cancer is refractory to treatment with mitomycin C or interferon.

5. The use of any one of claims 1-4, wherein the composition is at a dose of 5 mg to 500 mg limus drug.

6. The use of claim 5, wherein the composition is at a dose of 30 mg to 400 mg limus drug.

7. The use of claim 5 or 6, wherein the composition is at a volume of 20 ml to 150 ml.

8. The use of any one of claims 5-7, wherein the composition is to be administered intravesicularly and retained in the bladder for 30 minutes to 4 hours.

9. The use of any one of claims 1-8, wherein the BCG is to be administered intravesicularly.

10. The use of claim 9, wherein the BCG is to be administered at a dose of 8 mg to 100 mg.

11. The use of any one of claims 1-10, wherein the limus drug is sirolimus.

12. The use of any one of claims 1-11, wherein the nanoparticles in the composition have an average diameter of no greater than 200 nm.

13. The use of any one of claims 1-12, wherein the limus drug in the nanoparticles is coated with albumin.

14. The use of any one of claims 1-13, wherein the bladder cancer is urothelial carcinoma.

15. The use of any one of claims 1-14, wherein the bladder cancer is a high grade bladder cancer.

16. The use of any one of claims 1-15, wherein the individual is human.

17. The use of any one of claims 1-16, wherein the individual has a high level of one or more of: p-S6K, pAKT, p-4EBP1, Ki67, p53, p63, Stathmin, Tau, SPARC, p73, c-myc, and cyclin D1.