and 9 comprise a subfamily of TLRs which are located in endosomal or lysosomal compartments of immune cells such as dendritic cells and monocytes. In contrast to TLR7 and 9 which are highly expressed on plasmacytoid dendritic cells (pDC), TLR8 is mainly expressed on myeloid DC (mDC) and monocytes. This subfamily mediates recognition of microbial nucleic acids, such as single stranded RNA. Agonists of TLR8 stimulate the production of various inflammatory cytokines including interleukin-6, interleukin-12, tumor necrosis factor-alpha, and interferon-gamma. Such agonists also promote the increased expression of co-stimulatory molecules such as CD40, CD80, CD83, and CD86, major histocompatibility complex molecules, and chemokine receptors. The type I interferons, IFNα and IFNβ, are also produced by cells upon activation with TLR8 agonists.

[05] Small, low-molecular weight (less than 400 Daltons) synthetic imidazoquinoline compounds which resemble the purine nucleotides adenosine and guanosine were the first TLR7 and TLR8 agonists to be identified. A number of these compounds have demonstrated anti-viral and anti-cancer properties. For example, the TLR7 agonist imiquimod (ALDARA™) was approved by the U.S. Food and Drug Administration as a topical agent for the treatment of skin lesions caused by certain strains of the human papillomavirus. Imiquimod may also be useful for the treatment of primary skin cancers and cutaneous tumors such as basal cell carcinomas, keratoacanthomas, actinic keratoses, and Bowen's disease. The TLR7/8 agonist resiquimod (R-848) is being evaluated as a topical agent for the treatment of human genital herpes.

[06] Doxorubicin is a drug used in cancer chemotherapy. It is an anthracycline antibiotic, closely related to the natural product daunomycin, and like all anthracyclines it works by intercalating DNA. Doxorubicin is commonly used in the treatment of a wide range of cancers, including hematological malignancies, many types of carcinoma, and soft tissue sarcomas.

SUMMARY OF THE INVENTION

[07] The present ~~invention~~disclosure is directed generally to a combination therapy comprising administration of a benzo[b]azepine TLR8 agonist and one or more additional treatment modalities such as an anti-cancer agent (e.g., doxorubicin) for use in treating, alleviating, or preventing cancer, preferably solid tumors (such as sarcomas, carcinomas, and lymphomas), and for other uses including the treatment of leukemias, the treatment of certain skin conditions or

diseases, such as atopic dermatitis, the treatment of infectious diseases, preferably viral diseases, and for use as adjuvants in vaccines formulated for use in cancer therapy and in the treatment of infectious diseases. Specifically, the present ~~invention~~disclosure is directed to methods and compositions comprising a benzo[b]azepine TLR8 agonist, VTX-2337, and doxorubicin. In ~~preferred embodiments~~some examples, VTX-2337 and doxorubicin are used for the treatment of cancer and the cancer is selected from the group consisting of ovarian cancer, breast cancer, head and neck cancer, renal cancer, bladder cancer, hepatocellular cancer, colorectal cancer, melanoma, and lymphoma, or any combination thereof.

[07a] In one aspect, there is provided a pharmaceutical composition for use in a combinational therapy of treating ovarian cancer in a subject, comprising a formulation including a benzo[b]azepine TLR8 agonist and a pharmaceutically acceptable carrier, wherein the combinational therapy further comprises an effective amount of doxorubicin, and the TLR8 agonist is 2-amino-N,N-dipropyl-8-(4-(pyrrolidine-1-carbonyl)phenyl)-3H-benzo[b]azepine-4-carboxamide or a pharmaceutically acceptable salt thereof.

[08] Preferably, VTX-2337 is formulated at a concentration of from about 0.001 mg/ml to about 50 mg/ml, from about 0.01 mg/ml to about 50 mg/ml, from about 0.5 mg/ml to about 50 mg/ml, from about 1 mg/ml to about 40 mg/ml, or from about 2 mg/ml to about 15 mg/ml. In certain ~~embodiments~~examples, VTX-2337 is formulated at a concentration of from about 0.5 mg/ml to about 10 mg/ml, from about 0.5 mg/ml to about 8 mg/ml, from about 0.5 mg/ml to about 6 mg/ml, from about 0.5 mg/ml to about 4 mg/ml, or from about 0.5 mg/ml to about 2 mg/ml. In certain ~~embodiments~~examples, VTX-2337 is formulated at a concentration of about 0.5 mg/ml, about 1 mg/ml, about 2 mg/ml, about 4 mg/ml, about 6 mg/ml, about 8 mg/ml, about 10 mg/ml, about 15 mg/ml, about 20 mg/ml, about 25 mg/ml, about 30 mg/ml, about 40 mg/ml, or about 50 mg/ml. Preferably, the formulation comprises about 1-30%, 5-15%, or 5-10% weight/volume (w/v) of a cyclodextrin, preferably a β-cyclodextrin, and most preferably sulfobutylether β-cyclodextrin. In certain ~~embodiments~~examples, the formulation comprises 1%, 5%, 10%, 15%, 20%, 25%, or 30% w/v of a cyclodextrin, preferably a β-cyclodextrin, and most preferably sulfobutylether β-cyclodextrin. In a particular ~~embodiment~~example, the formulation is an aqueous solution comprising VTX-2337 at a concentration of at least 2 mg/ml. In a further ~~embodiment~~example, the formulation comprises 15% w/v of a cyclodextrin, preferably a β-cyclodextrin, and most preferably sulfobutyl ether β-

cyclodextrin. In preferred ~~embodiments~~examples, the formulation is suitable for injection in a mammal, preferably a human. In particular ~~embodiments~~examples, injection is by a subcutaneous route, an intramuscular route, or transdermal route. In certain ~~embodiments~~examples, the formulation is suitable for intravenous administration.

[09] Preferably, the reconstituted formulation is suitable for injection in a mammal, preferably a human. In particular ~~embodiments~~examples, injection is by a subcutaneous route, an intramuscular

route, or transdermal route. In certain ~~embodiments~~examples, the formulation is suitable for intravenous administration.

[010] Also disclosed are~~The present invention further provides~~ methods for the treatment of cancer by administering to a subject, preferably a human subject, doxorubicin and TLR8 agonist VTX-2337, which contains a cyclodextrin. In a preferred ~~embodiment~~example, VTX-2337 is administered in combination with one or more additional treatment modalities, where the modalities are selected from a chemotherapeutic agent, a cytokine, an antibody, hormonal therapy, or radiation therapy. In one ~~embodiment~~example, VTX-2337 is administered as part of a regimen for the treatment of a solid tumor. In a further ~~embodiment~~example, the solid tumor is a form of cancer selected from among ovarian cancer, breast cancer, head and neck cancer, renal cancer, bladder cancer, hepatocellular cancer, colorectal cancer, or lymphoma, or any combination thereof. In one ~~embodiment~~example, VTX-2337 is administered as part of a regimen for the treatment of a lymphoma. In one ~~embodiment~~example, the lymphoma is Hodgkin's lymphoma. In another ~~embodiment~~example, the lymphoma is non-Hodgkin's lymphoma. In another ~~embodiment~~example, VTX-2337 is used as a vaccine adjuvant for the treatment of cancer. In certain ~~embodiments~~examples of the methods for the treatment of cancer, VTX-2337 is administered by injection or intravenously. In particular ~~embodiments~~examples, injection is by a subcutaneous route, an intramuscular route, or a transdermal route. In a particular ~~embodiment~~example, the formulation is administered by subcutaneous injection.

[011] In certain ~~embodiments~~examples of the methods for treating cancer, VTX-2337 is administered to the subject at a dose of about 0.02 to 10 mg/kg (e.g., about 0.05-0.075 mg/kg, or about 0.04 to 5 mg/kg) body weight of the subject. In certain ~~embodiments~~examples, VTX-2337 is administered at a dose of about .02 mg/kg, about 0.05 mg/kg, about 1 mg/kg, about 2 mg/kg, or about 5 mg/kg. For example, assuming the subject has a body weight of about 70 kg, VTX-2337 is administered at a dose of about 1.4 mg-700 mg (e.g., 3.5 mg-5.25 mg, or about 2.8-350 mg). In certain further ~~embodiments~~examples, VTX-2337 is administered to the subject on a weekly or biweekly basis.

[011a] In another aspect, there is provided a pharmaceutical pack or kit comprising one or more first containers filled with a liquid or lyophilized form of a formulation of a benzo[b]azepine TLR8 agonist and one or more second containers filled with doxorubicin, wherein the TLR8 agonist is 2-amino-N,N-dipropyl-8-(4-(pyrrolidine-1-carbonyl)phenyl)-3H-benzo[b]azepine-4-carboxamide or a pharmaceutically acceptable salt thereof.

[012] Also disclosed is~~The present invention also provides~~ a pharmaceutical pack or kit comprising one or more containers filled with a liquid or lyophilized VTX-2337 and an anti-cancer agent (e.g., doxorubicin) of the invention for the treatment of cancer or one or more symptoms thereof. The liquid or lyophilized VTX-2337 and an anti-cancer agent (e.g., doxorubicin) can be packed in the same of different containers of the kit. Preferably, the formulation of VTX-2337 comprises about

1-30%, 5-15%, or 5-10% w/v of a cyclodextrin, preferably a β-cyclodextrin, and most preferably sulfobutylether β-cyclodextrin. In certain ~~embodiments~~examples, the formulation VTX-2337 comprises 2%, 5%, 10%, 15%, 20%, 25%, or 30% w/v of a cyclodextrin, preferably a β-cyclodextrin, and most preferably sulfobutylether β-cyclodextrin. In a particular ~~embodiment~~example, the formulation is an aqueous formulation of VTX-2337. Preferably, VTX-2337 is formulated at a concentration of at least 2 mg/ml and the formulation, whether aqueous or a reconstituted lyophilized formulation, is suitable for subcutaneous injection in a mammal, preferably a human.

[013] In one ~~embodiment~~example, VTX-2337 is formulated at a concentration of at least 2 mg/ml. Moreover, the formulation is suitable for administration to the subject, where the subject is preferably a human, by injection and is by subcutaneous, intramuscular, or transdermal injection. In certain ~~embodiments~~examples, VTX-2337 is administered to the subject at a dose of about 0.02 to 10 mg/kg, at a dose of about 0.04 to 5 mg/kg or at a dose of about 0.05-0.075 mg/kg. In certain further ~~embodiments~~examples, VTX-2337 is administered to the subject on a weekly or biweekly basis.

[014] In a preferred ~~embodiment~~example, VTX-2337 is administered in combination with one or more additional treatment modalities, where the modalities are selected from a chemotherapeutic agent, a cytokine, an antibody, hormonal therapy, or radiation therapy. The present invention also provides methods for the treatment of infectious disease is caused by a virus, where the virus is a hepatitis virus.

[015] In a preferred ~~embodiment~~example, doxorubicin is formulated for injection, most preferably intravenous administration. In certain ~~embodiments~~examples, VTX-2337 of the invention is formulated for administration by an intradermal, a transdermal, a subcutaneous, or an intramuscular route.

[016] In certain ~~embodiments~~examples of the methods for treating cancer, doxorubicin is administered to the subject at a dose of from about 0.02 to 10 mg/kg of body weight or about 0.04 to 5 mg/kg of body weight of the subject.

[017] Also disclosed is~~The present invention also provides~~ a method of treating cancer with a low-dose formulation of a benzo[b]azepine TLR8 agonist. The method comprising administering to a subject in need thereof a benzo[b]azepine TLR8 agonist at a dose below 0.007 mg/kg/week, e.g., between 0.002 mg/kg/week to 0.006 mg/kg/week. In one ~~embodiment~~example, the benzo[b]azepine TLR8 agonist is 2-amino-N,N-dipropyl-8-(4-(pyrrolidine-1-carbonyl)phenyl)-3H-

benzo[b]azepine-4-carboxamide. The method may include administering benzo[b]azepine TLR8 agonist as the only active ingredient or further include administering a second therapeutic agent such as an anti-cancer drug in combination with the low-dose formulation of the benzo[b]azepine TLR8 agonist. The second therapeutic agent can be another benzo[b]azepine TLR8 agonist or a drug molecule disclosed herein (e.g., doxorubicin, gemcitabine, or cyclophosphamide). The method can also be carried out in combination with one or more additional treatment modalities (e.g., radiation therapy) in a regiment for the treatment of cancer.

[018] Also disclosed is~~In another aspect, the invention also provides~~ a subcutaneous dosage form comprising a benzo[b]azepine TLR8 agonist for the treatment of cancer in a subject, wherein the subcutaneous dosage form, upon administration to a human at a dosage of 2-4 mg/m^2 of the agonist, provides an $AUC_{0\text{-}inf}$ of the agonist of about 55 to about 90 h*ng/mL, e.g., about 60 to about 80 h*ng/mL.

[019] Also disclosed is~~In yet another aspect, the invention also provides~~ a subcutaneous dosage form comprising a benzo[b]azepine TLR8 agonist for the treatment of cancer in a subject, wherein the subcutaneous dosage form, upon administration to a human at a dosage of 2-4 mg/m^2 of the agonist, provides a C_{max} of the agonist of about 10 to about 30 ng/mL, e.g., about 15 to about 25 ng/mL.

[020] Also disclosed is~~The invention also provides~~ a pharmaceutical composition including a liquid or lyophilized formulation of benzo[b]azepine TLR8 agonist (e.g.,VTX-2337) and an anti-cancer agent (e.g., doxorubicin). The formulation of the agonist and the anti-cancer agent can be in the same pharmaceutical composition or in different compositions, in which case, the formulation of the agonist and the anti-cancer agent can be administered concurrently or sequentially.

[021] The above description sets forth rather broadly the more important features of the present invention in order that the detailed description thereof that follows may be understood, and in order that the present contributions to the art may be better appreciated. Other objects and features of the present invention will become apparent from the following detailed description considered in conjunction with the examples.

DESCRIPTION OF THE FIGURES

[022] Figure 1A is a set of FACS images acquired on hematolymphoid cells from NSG-HIS mice. NSG mice received cord blood derived human hematopoietic CD34+ stem cells. Level of

Claims

1. A pharmaceutical composition for use in a combinational therapy of treating cancer in a subject, comprising a formulation including a benzo[b]azepine TLR8 agonist and a pharmaceutically acceptable carrier, wherein the combinational therapy further comprises an effective amount of doxorubicin, and the TLR8 agonist is 2-amino-N,N-dipropyl-8-(4-(pyrrolidine-1-carbonyl)phenyl)-3H-benzo[b]azepine-4-carboxamide or a pharmaceutically acceptable salt thereof.

2. The pharmaceutical composition for use of claim 1, wherein the cancer is a solid cancer selected from the group consisting of ovarian cancer, breast cancer, head and neck cancer, renal cancer, bladder cancer, hepatocellular cancer, colorectal cancer, lymphoma, and any combination thereof.

3. The pharmaceutical composition for use of any of claims 1-2, wherein the cancer is ovarian cancer.

4. The pharmaceutical composition for use of any of claims 1-3, wherein the TLR8 agonist formulation and the doxorubicin are administered concurrently or sequentially.

5. The pharmaceutical composition for use of any of claims 1-3, wherein the TLR8 agonist formulation and the doxorubicin are administered sequentially and the administrations of the TLR8 agonist formulation and the doxorubicin are separated by 5 days.

6. The pharmaceutical composition for use of claim 1, wherein the cancer is ovarian cancer, and the doxorubicin is a pegylated liposomal form of doxorubicin.

7. The pharmaceutical composition for use of claim 6, wherein the doxorubicin is administered intravenously.

8. The pharmaceutical composition for use of any of claims 1-7, wherein the subject is a mammal.

9. The pharmaceutical composition for use of any of claims 1-8, wherein the TLR8 agonist formulation is injected by a subcutaneous route, an intravenous route, an intramuscular route, or transdermal route.

10. The pharmaceutical composition for use of any of claims 1-8, wherein the TLR8 agonist formulation is administered subcutaneously.

11. The pharmaceutical composition for use of any of claims 1-10, wherein the TLR8 agonist formulation is dosed to provide a concentration of the TLR8 agonist of from 0.02 to 10 mg/kg or from 0.04 to 5 mg/kg body weight of the subject.

12. The pharmaceutical composition for use of any of claims 1-10, wherein the TLR8 agonist formulation is dosed to provide a concentration of the TLR8 agonist of 0.02 mg/kg, 0.05 mg/kg, 0.075 mg/kg, 0.1 mg/ kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg, or 5 mg/kg body weight of the subject.

13. The pharmaceutical composition for use of any of claims 1-10, wherein the TLR8 agonist formulation is dosed to provide a concentration of the TLR8 agonist of from 2.5 to 3.5 mg/m^2 of body surface area of the subject.

14. The pharmaceutical composition for use of any of claims 1-10, wherein the TLR8 agonist formulation is dosed to provide a concentration of the TLR8 agonist of between 0.002 mg/kg and 0.006 mg/kg body weight of the subject.

15. The pharmaceutical composition for use of any of claims 1-14, wherein the TLR8 agonist formulation is administered to the subject on a weekly or biweekly basis.

16. The pharmaceutical composition for use of any of claims 3-15, wherein the doxorubicin is administered at a dose of from 0.02 to 10 mg/kg of body weight or from 0.04 to 5 mg/kg of body weight of the subject.

17. The pharmaceutical composition for use of any of claims 1-16, wherein the TLR8 agonist formulation further comprises from 1% to 30%, from 5% to 15%, or from 5% to % weight/volume of a cyclodextrin.

18. The pharmaceutical composition for use of any of claims 1-16, wherein the TLR8 agonist formulation further comprises about 1%, about 5%, about 10%, about 15%, about 20%, about 25%, or about 30% weight/volume of a cyclodextrin.

19. The pharmaceutical composition for use of any of claims 1-16, wherein the TLR8 agonist formulation further comprises about 15% w/v of a cyclodextrin.

20. The pharmaceutical composition for use of any of claims 17-19, wherein the cyclodextrin is a beta-cyclodextrin.

21. The pharmaceutical composition for use of claim 20, wherein the cyclodextrin is a sulfobutyl ether β-cyclodextrin.

22. The pharmaceutical composition for use of any of claims 1-21, wherein the doxorubicin is in a pegylated liposomal form.

23. The pharmaceutical composition for use of any of claims 1-22, wherein the TLR8 agonist formulation contains from 0.01 to 50 mg/ml of the TLR8 agonist.

24. The pharmaceutical composition for use of any of claims 1-22, wherein the TLR8 agonist formulation contains from 0.5 mg/ml to 50 mg/ml, from 1 mg/ml to 40 mg/ml, or from 2 mg/ml to 15 mg/ml of the TLR8 agonist.

25. The pharmaceutical composition for use of any of claims 1-22, wherein the TLR8 agonist formulation contains from 0.5 mg/ml to 10 mg/ml, from 0.5 mg/ml to 8 mg/ml, from 0.5 mg/ml to 15 mg/ml, from 0.5 mg/ml to 4 mg/ml, or from 0.5 mg/ml to 2 mg/ml of the TLR8 agonist.

26. The pharmaceutical composition for use of any of claims 1-22, wherein the TLR8 agonist formulation contains about 0.01 mg/ml, about 0.5 mg/ml, about 1 mg/ml, about 2 mg/ml, about 4 mg/ml, about 15 mg/ml, about 8 mg/ml, about 10 mg/ml, about 15 mg/ml, about 20 mg/ml, about 25 mg/ml, about 30 mg/ml, about 40 mg/ml, or about 50 mg/ml of the TLR8 agonist.

27. A pharmaceutical pack or kit comprising one or more first containers filled with a liquid or lyophilized form of a formulation of a benzo[b]azepine TLR8 agonist and one or more second containers filled with doxorubicin, wherein the TLR8 agonist is 2-amino-N,N-dipropyl-8-(4-

(pyrrolidine-1-carbonyl)phenyl)-3H-benzo[b]azepine-4-carboxamide or a pharmaceutically acceptable salt thereof.

28. The pharmaceutical pack or kit of claim 27, wherein the TLR8 agonist formulation is an aqueous formulation.

29. The pharmaceutical pack or kit of claim 27 or 28, wherein the TLR8 agonist formulation contains from 0.01 to 50 mg/ml of the TLR8 agonist.

30. The pharmaceutical pack or kit of any of claims 27-29, wherein the doxorubicin is in a pharmaceutically acceptable salt form.

31. The pharmaceutical pack or kit of any of claims 27-30, wherein the doxorubicin is in a pegylated liposomal form.

Claims

1. A pharmaceutical composition for use in a combinational therapy of treating ovarian cancer in a subject, comprising a formulation including a benzo[b]azepine TLR8 agonist and a pharmaceutically acceptable carrier, wherein the combinational therapy further comprises an effective amount of doxorubicin, and the TLR8 agonist is 2-amino-N,N-dipropyl-8-(4-(pyrrolidine-1-carbonyl)phenyl)-3H-benzo[b]azepine-4-carboxamide or a pharmaceutically acceptable salt thereof.

2. The pharmaceutical composition for use of claim 1, wherein the TLR8 agonist formulation and the doxorubicin are administered concurrently or sequentially.

3. The pharmaceutical composition for use of any of claims 1-2, wherein the TLR8 agonist formulation and the doxorubicin are administered sequentially and the administrations of the TLR8 agonist formulation and the doxorubicin are separated by 5 days.

4. The pharmaceutical composition for use of claim 1, wherein the doxorubicin is a pegylated liposomal form of doxorubicin.

5. The pharmaceutical composition for use of claim 4, wherein the doxorubicin is administered intravenously.

6. The pharmaceutical composition for use of any of claims 1-5, wherein the subject is a mammal.

7. The pharmaceutical composition for use of any of claims 1-6, wherein the TLR8 agonist formulation is injected by a subcutaneous route, an intravenous route, an intramuscular route, or transdermal route.

8. The pharmaceutical composition for use of any of claims 1-5, wherein the TLR8 agonist formulation is administered subcutaneously.

9. The pharmaceutical composition for use of any of claims 1-8, wherein the TLR8 agonist formulation is dosed to provide a concentration of the TLR8 agonist of from 0.02 to 10 mg/kg or from 0.04 to 5 mg/kg body weight of the subject.

10. The pharmaceutical composition for use of any of claims 1-8, wherein the TLR8 agonist formulation is dosed to provide a concentration of the TLR8 agonist of 0.02 mg/kg, 0.05 mg/kg, 0.075 mg/kg, 0.1 mg/ kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg, or 5 mg/kg body weight of the subject.

11. The pharmaceutical composition for use of any of claims 1-8, wherein the TLR8 agonist formulation is dosed to provide a concentration of the TLR8 agonist of from 2.5 to 3.5 mg/m^2 of body surface area of the subject.

12. The pharmaceutical composition for use of any of claims 1-8, wherein the TLR8 agonist formulation is dosed to provide a concentration of the TLR8 agonist of between 0.002 mg/kg and 0.006 mg/kg body weight of the subject.

13. The pharmaceutical composition for use of any of claims 1-12, wherein the TLR8 agonist formulation is administered to the subject on a weekly or biweekly basis.

14. The pharmaceutical composition for use of any of claims 1-13, wherein the doxorubicin is administered at a dose of from 0.02 to 10 mg/kg of body weight or from 0.04 to 5 mg/kg of body weight of the subject.

15. The pharmaceutical composition for use of any of claims 1-14, wherein the TLR8 agonist formulation further comprises from 1% to 30%, from 5% to 15%, or from 5% to % weight/volume of a cyclodextrin.

16. The pharmaceutical composition for use of any of claims 1-14, wherein the TLR8 agonist formulation further comprises about 1%, about 5%, about 10%, about 15%, about 20%, about 25%, or about 30% weight/volume of a cyclodextrin.

17. The pharmaceutical composition for use of any of claims 1-14, wherein the TLR8 agonist formulation further comprises about 15% w/v of a cyclodextrin.

18. The pharmaceutical composition for use of any of claims 15-17, wherein the cyclodextrin is a beta-cyclodextrin.

19. The pharmaceutical composition for use of claim 18, wherein the cyclodextrin is a sulfobutyl ether β-cyclodextrin.

20. The pharmaceutical composition for use of any of claims 1-19, wherein the doxorubicin is in a pegylated liposomal form.

21. The pharmaceutical composition for use of any of claims 1-20, wherein the TLR8 agonist formulation contains from 0.01 to 50 mg/ml of the TLR8 agonist.

22. The pharmaceutical composition for use of any of claims 1-20, wherein the TLR8 agonist formulation contains from 0.5 mg/ml to 50 mg/ml, from 1 mg/ml to 40 mg/ml, or from 2 mg/ml to 15 mg/ml of the TLR8 agonist.

23. The pharmaceutical composition for use of any of claims 1-20, wherein the TLR8 agonist formulation contains from 0.5 mg/ml to 10 mg/ml, from 0.5 mg/ml to 8 mg/ml, from 0.5 mg/ml to 15 mg/ml, from 0.5 mg/ml to 4 mg/ml, or from 0.5 mg/ml to 2 mg/ml of the TLR8 agonist.

24. The pharmaceutical composition for use of any of claims 1-20, wherein the TLR8 agonist formulation contains about 0.01 mg/ml, about 0.5 mg/ml, about 1 mg/ml, about 2 mg/ml, about 4 mg/ml, about 15 mg/ml, about 8 mg/ml, about 10 mg/ml, about 15 mg/ml, about 20 mg/ml, about 25 mg/ml, about 30 mg/ml, about 40 mg/ml, or about 50 mg/ml of the TLR8 agonist.

25. A pharmaceutical pack or kit comprising one or more first containers filled with a liquid or lyophilized form of a formulation of a benzo[b]azepine TLR8 agonist and one or more second containers filled with doxorubicin, wherein the TLR8 agonist is 2-amino-N,N-dipropyl-8-(4-(pyrrolidine-1-carbonyl)phenyl)-3H-benzo[b]azepine-4-carboxamide or a pharmaceutically acceptable salt thereof.

26. The pharmaceutical pack or kit of claim 25, wherein the TLR8 agonist formulation is an aqueous formulation.

27. The pharmaceutical pack or kit of claim 25 or 26, wherein the TLR8 agonist formulation contains from 0.01 to 50 mg/ml of the TLR8 agonist.

28. The pharmaceutical pack or kit of any of claims 25-27, wherein the doxorubicin is in a pharmaceutically acceptable salt form.

29. The pharmaceutical pack or kit of any of claims 25-28, wherein the doxorubicin is in a pegylated liposomal form.