Claims

1. A combination, comprising:

(i) an effective amount of a targeted therapeutic against a cancer, wherein said targeted therapeutic is capable of binding to a tumor antigen specifically or preferably in comparison to a non-tumor antigen, wherein said tumor antigen is selected from the group consisting of: PD-1, PDL1, and variants thereof; and

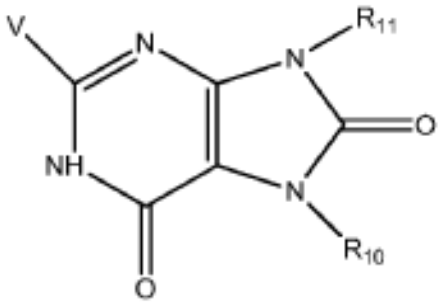
(ii) an effective amount of an immunotherapeutic that is capable of activating a human plasmacytoid dendritic cell, myeloid dendritic cell, or NK cell, or a combination thereof, wherein said immunotherapeutic is the compound 4-amino-2-(ethoxymethyl)-a,a-di-methyl-1H-imidazo[4,5-c]quinoline-1-ethanol,

wherein said targeted therapeutic and said immunotherapeutic are not covalently linked to each other.

2. A combination, comprising:

(i) an effective amount of a targeted therapeutic against a cancer, wherein said targeted therapeutic is capable of binding to a tumor antigen specifically or preferably in comparison to a non-tumor antigen, wherein said tumor antigen is selected from the group consisting of: PD-1, PDL1, and variants thereof; and

(ii) an effective amount of an immunotherapeutic that is capable of activating a human plasmacytoid dendritic cell, myeloid dendritic cell, or NK cell, or a combination thereof, wherein said immunotherapeutic has a structure of Formula (II):



(II)

wherein V is $–NR_6R_7$, wherein each of R_6 and R_7 is independently hydrogen, alkyl, alkenyl, alkoxy, alkylamino, dialkylamino, alkylthio, arylthio, --alkyl-hydroxyl, --alkyl-C(O)-O-R_9, --alkyl-C(O)-R_9, or –alkyl-O-C (O) -R_9, wherein R_9 is hydrogen, alkyl, alkenyl, halogen, or haloalkyl;
R_{10} and R_{11} are independently hydrogen, alkyl, alkenyl, aryl, haloalkyl, heteroaryl, heterocyclyl, or cycloalkyl, each of which is optionally substituted by one or more substituents selected from the group consisting of hydroxyl, alkoxy, alkyl, alkenyl, alkynyl, halogen, --$N(R_5)_2$, --alkoxy-alkyl, --alkoxy-alkenyl, --C(O)-alkyl, --C(O)-O-alkyl, --C(O)-$N(R_5)_2$, aryl, heteroaryl, --CO-aryl, and –CO-heteroaryl, wherein each R_5 is independently hydrogen, alkyl, haloalkyl, --alkyl-aryl, or –alkyl-heteroaryl.

3. The combination of claim 1 or 2, wherein said targeted therapeutic is capable of binding to a tumor cell specifically or preferably in comparison to a non-tumor cell.

4. The combination of claim 3, wherein said tumor cell is of a carcinoma, a sarcoma, a lymphoma, a myeloma, or a central nervous system cancer.

5. The combination of any one of claims 1 to 4, wherein said targeted therapeutic comprises an immunoglobulin, a protein, a peptide, a small molecule, a nanoparticle, or a nucleic acid.

6. The combination of any one of claims 1 to 4, wherein said targeted therapeutic comprises an antibody, or a functional fragment thereof.

7. The combination of claim 6, wherein said antibody is selected from the group consisting of: MPDL3280A, Lambrolizumab, CT-011, MK-3475, BMS-936559, MED14736, and MSB0010718C.

8. The combination of claim 6, wherein said targeted therapeutic comprises a Fab, Fab', F(ab')2, single domain antibody, T and Abs dimer, Fv, scFv, dsFv, ds-scFv, Fd, linear antibody, minibody, diabody, bispecific antibody fragment, bibody, tribody, sc-diabody, kappa (lamda) body, BiTE, DVD-Ig, SIP, SMIP, DART, or an antibody analogue comprising one or more CDRs.

9. The combination of claim 1, wherein said targeted therapeutic comprises a nanoparticle or an aptamer.

10. The combination of any one of claims 1 to 9, wherein said immunotherapeutic is capable of binding specifically to human TLR7 and/or TLR8.

11. The combination of claim 1, consisting of said targeted therapeutic, said immunotherapeutic, and one or more additional therapeutic agents selected from the group consisting of: a chemotherapeutic agent, an antimetabolite, an inhibitor of topoisomerase I and II, an alkylating agent, a microtubule inhibitor, an antiandrogen agent, a GNRh modulator and mixtures thereof.

12. The combination of any one of claims 1 to 11, further comprising an effective amount of an additional therapeutic agent.

13. The combination of claim 12, wherein said additional therapeutic agent is an anticancer agent.

14. The combination of claim 13, wherein said anticancer agent is an antimetabolite, an inhibitor of topoisomerase I and II, an alkylating agent, a microtubule inhibitor, an antiandrogen agent, a GNRh modulator or mixtures thereof.

15. The combination of claim 14, wherein said additional therapeutic agent is a chemotherapeutic agent selected from the group consisting of tamoxifen, raloxifene, anastrozole, exemestane, letrozole, imatanib, paclitaxel, cyclophosphamide, lovastatin, minosine, gemcitabine, cytarabine, 5-fluorouracil, methotrexate, docetaxel, goserelin, vincristine, vinblastine, nocodazole, teniposide etoposide, gemcitabine, epothilone, vinorelbine, camptothecin, daunorubicin, actinomycin D, mitoxantrone, acridine, doxorubicin, epirubicin, or idarubicin.

16. The combination of any one of claims 1 to 15, wherein said immunotherapeutic is of an amount that is capable of:

(1) inducing IFN-α in a enriched human blood DCs;

(2) inducing TNF-α in a enriched human blood DCs; and/or

(3) inducing IL-12-α in a enriched human blood DCs.

17. The combination of any one of claims 1 to 16, wherein the effective amount of the immunotherapeutic in the combination does not cause substantial toxicity.

18. The combination of any one of claims 1 to 17, wherein said effective amount of said immunotherapeutic is in an oral formulation and in a dose of between about 0.0005 mg/kg, 0.0006 mg/mg/kg, 0.0007 mg/kg, 0.0008 mg/kg, 0.0009 mg/kg, 0.001 mg/kg, 0.002 mg/kg, 0.003 mg/kg, 0.004 mg/kg, 0.005 mg/kg, 0.006 mg/kg, 0.007 mg/kg, 0.008 mg/kg, 0.009 mg/kg, or 0.01 mg/kg, to about 0.02 mg/kg, all inclusive, twice per week.

19. The combination of any one of claims 1 to 17, wherein said effective amount of said immunotherapeutic is in an intravenous formulation and in a dose of between about 0.0005 mg/kg, 0.0006 mg/kg, 0.0007 mg/kg, 0.0008 mg/kg, 0.0009 mg/kg, 0.001 mg/kg, 0.002 mg/kg, 0.003 mg/kg, 0.004 mg/kg, 0.005 mg/kg, or 0.006 mg/kg to about 0.015 mg/kg, all inclusive, weekly.

20. Use of the combination of any one of claims 1 to 19 in the manufacture of a medicament for the treatment of tumor.

21. Use of the combination of any one of claims 1 to 19 in the manufacture of a medicament for the treatment of abnormal cell proliferation.

22. The use of claim 21, wherein said abnormal cell proliferation comprises a pre-cancerous lesion.

23. The use of claim 21, wherein said abnormal proliferation is of cancer cells.

24. The use of claim 23, wherein said cancer is selected from the group consisting of: breast cancer, colorectal cancer, diffuse large B-cell lymphoma, endometrial cancer, follicular lymphoma, gastric cancer, glioblastoma, head and neck cancer, hepatocellular cancer, lung cancer, melanoma, multiple myeloma, ovarian cancer, pancreatic cancer, prostate cancer, and renal cell carcinoma.

25. The use of any one of claims 20 to 24, wherein the medicament comprises an oral formulation comprising said immunotherapeutic in a dose of between about 0.0005 mg/kg, 0.0006 mg/mg/kg, 0.0007 mg/kg, 0.0008 mg/kg, 0.0009 mg/kg, 0.001 mg/kg, 0.002 mg/kg, 0.003 mg/kg, 0.004 mg/kg, 0.005 mg/kg, 0.006 mg/kg, 0.007 mg/kg, 0.008 mg/kg, 0.009 mg/kg, or 0.01 mg/kg, to about 0.02 mg/kg, all inclusive, twice per week.

26. The use of any one of claims 20 to 24, wherein the medicament comprises an oral formulation comprising said immunotherapeutic in a dose of up to about 0.0005mg/kg, 0.0006 mg/kg, 0.0007 mg/kg, 0.0008 mg/kg, 0.0009 mg/kg, 0.001 mg/kg, 0.002 mg/kg, 0.003 mg/kg, 0.004 mg/kg, 0.005 mg/kg, 0.006 mg/kg, 0.007 mg/kg, 0.008 mg/kg, 0.009 mg/kg, or 0.01 mg/kg, twice per week.

27. The use of any one of claims 20 to 24, wherein the medicament comprises an intravenous formulation comprising said immunotherapeutic in a dose of between about 0.0005 mg/kg, 0.0006 mg/kg, 0.0007 mg/kg, 0.0008 mg/kg, 0.0009 mg/kg, 0.001 mg/kg, 0.002 mg/kg, 0.003 mg/kg, 0.004 mg/kg, 0.005 mg/kg, or 0.006 mg/kg to about 0.015 mg/kg, all inclusive, weekly.

28. The use of any one of claims 20 to 24, wherein the medicament comprises an intravenous formulation comprising said immunotherapeutic in a dose of up to about 0.003 mg/kg, 0.004 mg/kg, 0.005 mg/kg, or 0.006 mg/kg, to about 0.01 mg/kg, weekly.

29. The use of any one of claims 20 to 28, wherein said immunotherapeutic has a local concentration that is between about 0.005 μg/ml to about 12 μg/ml.

30. The use of any one of claims 20 to 28, wherein said immunotherapeutic has a local concentration that is between about 0.05 μg/ml, 0.1 μg/ml, 0.15 μg/ml, 0.2 μg/ml, 0.3 μg/ml, or 0.4 μg/ml, to about 0.5 μg/ml.

31. A kit, comprising the combination of any one of claims 1 to 19.