Claims

1. Use of a water-insoluble controlled-release pattern recognition receptor agonist ("PRRA") or its pharmaceutically acceptable salt or a pharmaceutical composition comprising such water-insoluble controlled-release PRRA or its pharmaceutical acceptable salt for the manufacture of a medicament for the treatment of cancer, wherein the water-insoluble controlled-release PRRA is to be administered by intra-tumoral administration into a solid tumor or lymphoma, which intra-tissue administration results in local inflammation, wherein the water-insoluble controlled-release PRRA comprises a plurality of PRRA moieties, which PRRA moieties are resiquimod covalently and reversibly conjugated to a carrier moiety, which carrier is a PEG-based hydrogel, and wherein PRRA is released from the water-insoluble controlled-release PRRA with a release half-life under physiological conditions of at least 3 days.

2. The use of claim 1, wherein intra-tumoral administration of the water-insoluble controlled-release PRRA in a dose X induces a more than 1.5-fold increase in the percent of antigen-presenting cells in tumor draining lymph nodes 7 days following said administration than intra-tumoral administration of a dose of 0.5 to 1.5 X of the corresponding free PRRA.

3. The use of claim 1 or 2, wherein the cancer is selected from the group consisting of liquid tumors, solid tumors and lymphomas.

4. The use of any one of claims 1 to 3, wherein the cancer is selected from the group consisting of lip and oral cavity cancer, oral cancer, liver cancer/hepatocellular cancer, primary liver cancer, lung cancer, lymphoma, malignant mesothelioma, malignant thymoma, skin cancer, intraocular melanoma, metastasic squamous neck cancer with occult primary, childhood multiple endocrine neoplasia syndrome, mycosis fungoides, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, ovarian cancer, pancreatic cancer, parathyroid cancer, pheochromocytoma, pituitary tumor, adrenocortical carcinoma, AIDS-related malignancies, anal cancer, bile duct cancer, bladder cancer, brain and nervous system cancer, breast cancer, bronchial adenoma/carcinoid, gastrointestinal carcinoid tumor,

carcinoma, colorectal cancer, endometrial cancer, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, gallbladder cancer, gastric (stomach) cancer, gestational trophoblastic tumor, head and neck cancer, hypopharyngeal cancer, islet cell carcinoma (endocrine pancreas), kidney cancer/renal cell cancer, laryngeal cancer, pleuropulmonary blastoma, prostate cancer, transitional cell cancer of the renal pelvis and ureter, retinoblastoma, salivary gland cancer, sarcoma, Sezary syndrome, small intestine cancer, genitourinary cancer, malignant thymoma, thyroid cancer, Wilms' tumor and cholangiocarcinoma.

5. The use of any one of claims 1 to 4, wherein local inflammation is an at least 1.5-fold increase in the levels of at least four proteins selected from the group consisting of TNFα, IL-1β, IL-10, IL-6, MCP-1, MIP-1α, MIP-1β, MIP-2α, MIP-3α, IP-10 and KC compared to baseline tissue measured 3 days after intra-tumoral administration.

6. The use of any one of claims 1 to 5, wherein local inflammation is an at least 2-fold increase in the expression levels of at least four proteins selected from the group consisting of TNFα, IL-1β, IL-10, IL-6, MCP-1, MIP-1α, MIP-1β, MIP-2α, MIP-3α, IP-10 and KC compared to baseline tissue measured 3 days after intra-tumoral administration.

7. The use of any one of claims 1 to 4, wherein local inflammation is an at least 1.5-fold increase in the expression levels of at least four mRNAs selected from the group consisting of *TNF*, *IL1A*, *IL1B*, *IL10*, *IL6*, *IL12B*, *CCL2*, *CCL8*, *CCL3*, *CCL4*, *CXCL2*, *CCL20*, *CSF2*, pan-*IFNA* subtype members, *IFNB1*, *IL18*, *CCL5*, *CXCL10* and *CXCL1* compared to baseline tissue measured 3 days after intra-tumoral administration.

8. The use of any one of claims 1 to 4 or 7, wherein local inflammation is an at least 2-fold increase in the expression levels of at least four mRNAs selected from the group consisting of *TNF*, *IL1A*, *IL1B*, *IL10*, *IL6*, *IL12B*, *CCL2*, *CCL8*, *CCL3*, *CCL4*, *CXCL2*, *CCL20*, *CSF2*, pan-*IFNA* subtype members, *IFNB1*, *IL18*, *CCL5*, *CXCL10* and *CXCL1* compared to baseline tissue measured 3 days after intra-tumoral administration.

9. The use of any one of claims 1 to 8, wherein intra-tumoral administration is intra-tumoral injection.

10. The use of any one of claims 1 to 9, wherein the treating of the cancer in addition to the administration of the water-insoluble controlled-release PRRA includes the administration of at least one cancer therapeutic.

11. The use of claim 10, wherein the cancer therapeutic is selected from the group consisting of cytotoxic/chemotherapeutic agents, immune checkpoint inhibitors or antagonists, immune checkpoint agonists, multi-specific drugs, antibody-drug conjugates (ADC), radionuclides or targeted radionuclide therapeutics, DNA damage repair inhibitors, tumor metabolism inhibitors, pattern recognition receptor agonists, protein kinase inhibitors, chemokine and chemoattractant receptor agonists, chemokine or chemokine receptor antagonists, cytokine receptor agonists, death receptor agonists, CD47 or SIRPa antagonists, oncolytic drugs, signal converter proteins, epigenetic modifiers, tumor peptides or tumor vaccines, heat shock protein (HSP) inhibitors, proteolytic enzymes, ubiquitin and proteasome inhibitors, adhesion molecule antagonists, and hormones including hormone peptides and synthetic hormones.

12. The use of claim 11, wherein the cancer therapeutic is a cytokine receptor agonist.

13. A water-insoluble controlled-release PRRA or the pharmaceutically acceptable salt thereof, wherein said water-insoluble controlled-release PRRA releases one or more PRRA and wherein intra-tumoral administration into a solid tumor or lymphoma of said controlled-release PRRA causes local inflammation, wherein the water-insoluble controlled-release PRRA comprises a plurality of PRRA moieties, which PRRA moieties are resiquimod covalently and reversibly conjugated to a carrier moiety, which carrier is a PEG-based hydrogel, and wherein PRRA is released from the water-insoluble controlled-release PRRA with a release half-life under physiological conditions of at least 3 days.

14. The water-insoluble controlled-release PRRA or the pharmaceutically acceptable salt thereof of claim 13, wherein intra-tumoral administration of the water-insoluble

controlled-release PRRA in a dose X induces a more than 1.5-fold increase in the percent of antigen-presenting cells in tumor draining lymph nodes 7 days following said administration than intra-tumoral administration of a dose of 0.5 to 1.5 X of the corresponding free PRRA.

15. The water-insoluble controlled-release PRRA or the pharmaceutically acceptable salt thereof of claim 13 or 14, wherein local inflammation is an at least 1.5-fold increase in the levels of at least four proteins selected from the group consisting of TNFα, IL-1β, IL-10, IL-6, MCP-1, MIP-1α, MIP-1β, MIP-2α, MIP-3α, IP-10 and KC compared to baseline tissue measured 3 days after intra-tumoral administration.

16. The water-insoluble controlled-release PRRA or the pharmaceutically acceptable salt thereof of any one of claims 13 to 15, wherein local inflammation is an at least 2-fold increase in the levels of at least four proteins selected from the group consisting of TNFα, IL-1β, IL-10, IL-6, MCP-1, MIP-1α, MIP-1β, MIP-2α, MIP-3α, IP-10 and KC compared to baseline tissue measured 3 days after intra-tumoral administration.

17. The water-insoluble controlled-release PRRA or the pharmaceutically acceptable salt thereof of claim 13 or 14, wherein local inflammation is an at least 1.5-fold increase in the expression levels of at least four mRNAs selected from the group consisting of *TNF*, *IL1A*, *IL1B*, *IL10*, *IL6*, *IL12B*, *CCL2*, *CCL8*, *CCL3*, *CCL4*, *CXCL2*, *CCL20*, *CSF2*, pan-*IFNA* subtype members, *IFNB1*, *IL18*, *CCL5*, *CXCL10* and *CXCL1* compared to baseline tissue measured 3 days after intra-tumoral administration.

18. The water-insoluble controlled-release PRRA or the pharmaceutically acceptable salt thereof of any one of claims 13, 14 or 17, wherein local inflammation is an at least 2-fold increase in the expression levels of at least four mRNAs selected from the group consisting of *TNF*, *IL1A*, *IL1B*, *IL10*, *IL6*, *IL12B*, *CCL2*, *CCL8*, *CCL3*, *CCL4*, *CXCL2*, *CCL20*, *CSF2*, pan-*IFNA* subtype members, *IFNB1*, *IL18*, *CCL5*, *CXCL10* and *CXCL1* compared to baseline tissue measured 3 days after intra-tumoral administration.

19. The water-insoluble controlled-release PRRA or the pharmaceutically acceptable salt thereof of any one of claims 13 to 18, wherein intra-tumoral administration is intra-tumoral injection.

20. A pharmaceutical composition comprising one or more water-insoluble controlled-release PRRA or the pharmaceutically acceptable salt thereof of any one of claims 13 to 19 and at least one excipient.

21. The water-insoluble controlled-release PRRA or the pharmaceutically acceptable salt thereof of any one of claims 13 to 19 or the pharmaceutical composition of claim 20 for use as a medicament for the treatment of cancer.

22. The water-insoluble controlled-release PRRA or the pharmaceutically acceptable salt thereof or the pharmaceutical composition for use of claim 21, wherein the cancer is selected from the group consisting of lip and oral cavity cancer, oral cancer, liver cancer/hepatocellular cancer, primary liver cancer, lung cancer, lymphoma, malignant mesothelioma, malignant thymoma, skin cancer, intraocular melanoma, metastasic squamous neck cancer with occult primary, childhood multiple endocrine neoplasia syndrome, mycosis fungoides, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, ovarian cancer, pancreatic cancer, parathyroid cancer, pheochromocytoma, pituitary tumor, adrenocortical carcinoma, AIDS-related malignancies, anal cancer, bile duct cancer, bladder cancer, brain and nervous system cancer, breast cancer, bronchial adenoma/carcinoid, gastrointestinal carcinoid tumor, carcinoma, colorectal cancer, endometrial cancer, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, gallbladder cancer, gastric (stomach) cancer, gestational trophoblastic tumor, head and neck cancer, hypopharyngeal cancer, islet cell carcinoma (endocrine pancreas), kidney cancer/renal cell cancer, laryngeal cancer, pleuropulmonary blastoma, prostate cancer, transitional cell cancer of the renal pelvis and ureter, retinoblastoma, salivary gland cancer, sarcoma, Sezary syndrome, small intestine cancer, genitourinary cancer, malignant thymoma, thyroid cancer, Wilms' tumor and cholangiocarcinoma.

23. The water-insoluble controlled-release PRRA or the pharmaceutically acceptable salt thereof or the pharmaceutical composition for use of claim 21 or 22, wherein the treatment of cancer in addition to the administration of the water-insoluble controlled-release PRRA includes the administration of at least one cancer therapeutic.

24. The water-insoluble controlled-release PRRA or the pharmaceutically acceptable salt thereof or the pharmaceutical composition for use of claim 23, wherein the cancer therapeutic is selected from the group consisting of cytotoxic/chemotherapeutic agents, immune checkpoint inhibitors or antagonists, immune checkpoint agonists, multi-specific drugs, antibody-drug conjugates (ADC), radionuclides or targeted radionuclide therapeutics, DNA damage repair inhibitors, tumor metabolism inhibitors, pattern recognition receptor agonists, protein kinase inhibitors, chemokine and chemoattractant receptor agonists, chemokine or chemokine receptor antagonists, cytokine receptor agonists, death receptor agonists, CD47 or SIRPa antagonists, oncolytic drugs, signal converter proteins, epigenetic modifiers, tumor peptides or tumor vaccines, heat shock protein (HSP) inhibitors, proteolytic enzymes, ubiquitin and proteasome inhibitors, adhesion molecule antagonists, and hormones including hormone peptides and synthetic hormones.

25. The water-insoluble controlled-release PRRA or the pharmaceutically acceptable salt thereof or the pharmaceutical composition for use of claim 23 or 24, wherein the cancer therapeutic is a cytokine receptor agonist.