CLAIMS

WHAT IS CLAIMED IS:

1. Use of:

(a) tirapazamine;

(b) a hypoxia-inducing agent or an embolizing agent, wherein the embolizing agent embolizes one or more blood vessels supplying a solid tumor by trans-arterial embolization, and wherein the hypoxia-inducing agent otherwise creates a localized region of hypoxia in the solid tumor; and

(c) an immune checkpoint inhibitor of PD-1 or PD-L1 in the manufacture of a medicament for a combination therapy for enhancing an immune response to a solid tumor in a subject, wherein the immune checkpoint inhibitor is an antibody.

2. The use of claim 1, wherein the combined use of the tirapazamine and the trans-arterial embolization induces necrosis of the solid tumor.

3. The use of claim 1, wherein the hypoxia-inducing agent is a vascular disrupting agent.

4. The use of claim 3, wherein the vascular disrupting agent is 5, 6-dimethylxantheonone-4-acetic acid (DMXAA), or a stilbene.

5. The use of claim 3, wherein the vascular disrupting agent is selected from the group consisting of: combretastatin, cis-3,4′,5-trimethoxy-3′-aminostilbene (stilbene 5c), and cis-3,4′,5-trimethoxy-3′-hydroxystilbene (stilbene 6c).

6. The use of claim 1, wherein the hypoxia-inducing agent is an anti-angiogenic agent.

7. The use of claim 1, wherein the immune checkpoint inhibitor is a monoclonal antibody.

8. The use of claim 7, wherein the monoclonal antibody is selected from the group consisting of: nivolumab, pembrolizumab, atezolizumab, and MEDI4736.

9. The use of claim 1, wherein the solid tumor is a tumor selected from the group consisting of: hepatocellular carcinoma, cholangiocarcinoma, metastatic colorectal cancer in

liver, lung cancer, breast cancer, colorectal cancer, bladder cancer, head and neck cancer, ovarian cancer, and pancreatic cancer.

10. The use of claim 1, wherein the combined use of the tirapazamine, the trans-arterial embolization, and the immune checkpoint inhibitor exhibit a synergistic effect in treating a proliferative disorder in the subject.

11. The use of claim 1, wherein the combined use of the tirapazamine, the trans-arterial embolization, and the immune checkpoint inhibitor exhibit a synergistic effect, wherein the synergistic effect comprises a size reduction of a second tumor greater than a corresponding size reduction achieved in the absence of the combined use of the tirapazamine and the trans-arterial embolization.

12. The use of claim 1, wherein the combined use of the tirapazamine and the trans-arterial embolization induces necrosis of at least 60% of the solid tumor.

13. The use of claim 1, wherein the combined use of the tirapazamine and the trans-arterial embolization induces necrosis of at least 70% of the solid tumor.

14. A kit for use in combination therapy for enhancing an immune response to a solid tumor in a subject, the kit comprising:

(a) tirapazamine;

(b) a hypoxia-inducing agent or an embolizing agent, wherein the embolizing agent is configured to embolize one or more blood vessels supplying a solid tumor by trans-arterial embolization, and wherein the hypoxia-inducing agent otherwise creates a localized region of hypoxia in the solid tumor; and

(c) an immune checkpoint inhibitor of PD-1 or PD-L1, wherein the immune checkpoint inhibitor is an antibody.

15. The kit of claim 14, wherein the hypoxia-inducing agent is a vascular disrupting agent.

16. The kit of claim 15, wherein the vascular disrupting agent is 5, 6-dimethylxantheonone-4-acetic acid (DMXAA), or a stilbene.

17. The kit of claim 15, wherein the vascular disrupting agent is selected from the group consisting of: combretastatin, cis-3,4′,5-trimethoxy-3′-aminostilbene (stilbene 5c), and cis-3,4′,5-trimethoxy-3′-hydroxystilbene (stilbene 6c).

18. The kit of claim 14, wherein the hypoxia-inducing agent is an anti-angiogenic agent.

19. The kit of claim 14, wherein the immune checkpoint inhibitor is a monoclonal antibody.

20. The kit of claim 19, wherein the monoclonal antibody is selected from the group consisting of: nivolumab, pembrolizumab, atezolizumab, and MEDI4736.

21. The use of claim 1, wherein the hypoxia-inducing agent is combretastatin A4 phosphate.

22. The kit of claim 14, wherein the hypoxia-inducing agent is combretastatin A4 phosphate.