CLAIMS

WHAT IS CLAIMED IS:

1. Use of:

(a) a hypoxia-activated bioreductive agent (HABA);

(b) a hypoxia-inducing agent or an embolizing agent; and

(c) an immune checkpoint inhibitor in the manufacture of a medicament for enhancing an immune response to a solid tumor in a subject.

2. The use of claim 1, wherein the hypoxia-activated bioreductive agent is tirapazamine.

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 DMXAA, a stilbene, or a stilbene derivative.

5. The use of claim 4, wherein the stilbene derivative is selected from the group consisting of: combretastatin, combretastatin derivatives, cis-3,4′,5-trimethoxy-3′-aminostilbene (stilbene 5c), cis-3,4′,5-trimethoxy-3′-hydroxystilbene (stilbene 6c), and a prodrug morpholino-carbamate derivative of stilbene 5c.

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

7. The use of claim 1, wherein the hypoxia-activated agent and the hypoxia-inducing agent are to be administered in amounts effective to induce necrosis of at least 75% of the solid tumor.

8. The use of claim 1, wherein the embolizing agent embolizes one or more blood vessels supplying the solid tumor.

9. The use of claim 1, wherein the immune checkpoint inhibitor is an inhibitor of PD-1, PD-L1, or CTLA-4.

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

11. The use of claim 10, wherein the monoclonal antibody is selected from the group consisting of: nivolumab, pembrolizumab, atezolizumab, MEDI4736, and ipilimumab.

12. 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.

13. The use of claim 1, wherein the immune checkpoint inhibitor is effective in maintaining the solid tumor at a size that is less than 50% of a pre-treatment size for at least 6 months.

14. The use of claim 1, wherein the combination of the HABA, the embolizing agent, and the immune checkpoint inhibitor exhibit a synergistic effect in treating a proliferative disorder in the subject.

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

(a) a hypoxia-activated bioreductive agent (HABA);

(b) a hypoxia-inducing agent or an embolizing agent; and

(c) an immune checkpoint inhibitor.

16. The kit of claim 15, wherein the HABA is tirapazamine.

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

18. The kit of claim 17, wherein the vascular disrupting agent is DMXAA, a stilbene, or a stilbene derivative.

19. The kit of claim 18, wherein the stilbene derivative is selected from the group consisting of: combretastatin, combretastatin derivatives, cis-3,4′,5-trimethoxy-3′-aminostilbene (stilbene 5c), cis-3,4′,5-trimethoxy-3′-hydroxystilbene (stilbene 6c), and a prodrug morpholino-carbamate derivative of stilbene 5c.

20. The kit of claim 15, wherein the hypoxia-inducing agent is an anti-angiogenic agent.

21. The kit of claim 15, wherein the immune checkpoint inhibitor is an inhibitor of PD-1, PD-L1, or CTLA-4.

22. The kit of claim 21, wherein the immune checkpoint inhibitor is a monoclonal antibody.

23. The kit of claim 22, wherein the monoclonal antibody is selected from the group consisting of: nivolumab, pembrolizumab, atezolizumab, MEDI4736, and ipilimumab.