Intra-tumoural hypoxia is common in solid tumours. Hypoxic tumour cells usually display enhanced resistance to standard chemotherapies which target rapidly dividing cells. The use of artificial oxygen carriers may represent a novel approach to counter the intra-tumoural hypoxic effect. We study the therapeutic strategies and the underlying mechanism of the Investigational New Drug, YQ23, a stabilized non-polymeric diaspertin cross-linked tetrameric hemoglobin. We have previously reported that YQ23 could effectively inhibit intrahepatic and lung metastases in hepatocellular carcinoma after hepatectomy and partial hepatic ischemic reperfusion injury. Using live cell imaging studies, we show for the first time, that YQ23 could be preferentially uptaken in slow-growing hypoxic cells via receptor(s)-mediated endocytosis. Importantly, YQ23 displays tumour growth inhibition in vivo, in particularly when used as an adjunct to other chemotherapeutics (standard of care). YQ23 is active against the hypoxic tumour cells in multiple advanced and refractory solid tumours such as hepatocellular carcinoma, triple negative breast cancer, pancreatic cancer, colorectal cancer, and esophageal cancer. The anti-cancer activity is associated with oxidative-stressed induced mitochondrial dysfunction and increased ROS generation, leading to irreversible DNA damage and hence intrinsic apoptosis. We also revealed that YQ23 could significantly inhibit angiogenesis through the Hypoxic Inducible Factor 1 alpha signaling pathway. All together, we have identified the therapeutic strategies of the investigational new drug, YQ23, which shows enhanced anti-tumour activity in multiple advanced hypoxic solid tumours. Our findings suggest a strategy for targeting the slower-growing, drug resistant populations of tumour cells for improved cancer treatment.