Immunogenic cell death—the next frontier in cancer immunotherapy

Phosphatlin Therapeutics is harnessing immunogenic cell death (ICD) as an alternative mechanism to existing cancer immunotherapy strategies. PT-112, Phosphatlin's lead ICD inducer, is in phase 2 clinical trials for metastatic castration-resistant prostate cancer, and could be applicable to other indications, including rare and refractory forms of cancer.

Phosphatlin Therapeutics is a privately held, clinical stage pharmaceutical company developing best-in-class small molecule inducers of immunogenic cell death (ICD), a novel oncology immunotherapy modality. ICD is a form of cell death in the tumor microenvironment that can activate a patient’s immunity and direct it to mount a tumor-specific immune response.

Phosphatlin holds an exclusive global license to ‘phosphaplatins’, a family of small molecule ICD inducers designed to avoid the toxicity and drug resistance issues often associated with chemotherapeutic regimens. The company’s lead compound, PT-112, has completed phase 1 clinical studies as both a monotherapy and in combination therapy with PD-1/L1 immune checkpoint inhibition, and is in a phase 2 clinical trial in metastatic castration-resistant prostate cancer.

“We believe our immunogenic small molecule provides a safe and attractive means of harnessing the body’s own immune system to engender an ongoing anti-cancer response,” said Robert Fallon, Phosphatlin’s President and CEO. “Our compounds are uniquely designed to offer a safe and effective alternative to patients with rare and refractory forms of cancer.”

Harnessing ICD for cancer immunotherapy

The unprecedented clinical success of novel cancer immunotherapies in certain cancer types has fundamentally disrupted the oncology space. However, the majority of patients still may not benefit from these treatments, highlighting the need for new strategies to fully realize the potential of immunotherapy in cancer.

Most immunotherapies have focused on either enhancing the T cell response by targeting inhibitory pathways with immune checkpoint inhibitors, or by targeting T cells to cancer cells using chimeric antigen receptor T cells or bispecific antibodies. Given the crucial role the adaptive immune response plays in fighting cancer, identifying additional cancer immunomodulatory mechanisms that could be harnessed for therapeutic purposes has become a priority.

ICD is a form of cell death that triggers an immune response and can be pharmacologically induced. When tumor cells succumb to ICD, the dying cells release immune-stimulatory molecules called damage-associated molecular patterns (DAMPs), which constitute a heterogeneous group of molecules not normally presented upon cell death, including ATP, the cell surface exposure of calreticulin, and release of nuclear proteins such as HMGB1. These molecules bind to antigen-presenting cells such as dendritic cells and lead to T cell infiltration, an immune response in the tumor microenvironment and tumor suppression.

PT-112—a platinum-containing immunotherapy agent

Phosphatlin is leading the development of phosphaplatin, a class of stable pyrophosphate/platinum conjugates that exhibit cytotoxicity towards cancer cells while sparing healthy cells. Lead compound PT-112 has a unique hybrid mechanism of action (MOA)—both cytotoxic and immunomodulating—that distinguishes it from other anti-cancer agents on the market. Upon being absorbed by the tumor cell, PT-112 triggers cancer cell death in such a way that the subsequent release of DAMPs promotes a tumor-specific immune response with the potential for ongoing tumor suppression (Fig. 1).

The risk of developing resistance to PT-112 is reduced due to its pleiotropic ICD-inducing MOA, which is not subject to DNA-repair drug resistance pathways, and to the amplification of long-term immune response. Phosphaplatins do not readily de-ligate under physiological conditions, and are soluble and stable in aqueous solution, making them easy to administer systemically.

Owing to its pyrophosphate moiety, PT-112 also exhibits osteotropism, leading to its enhanced accumulation in mineralized bone. This unique characteristic of PT-112 has clear potential within the treatment of cancers that originate in or metastasize to the bone, including metastases common in prostate, lung and breast cancers, as well as some hematological malignancies such as multiple myeloma.

PT-112 has demonstrated single-agent activity, as well as in combination with a PD-L1 immune checkpoint inhibitor, with favorable tolerability and safety profiles in three phase 1 studies. A phase 2 clinical study of PT-112 in metastatic castration-resistant prostate cancer is currently underway, and a second one is planned in thymoma/thymic carcinoma, for which PT-112 holds Orphan Drug Designation. Durable responses to single-agent PT-112 among thoracic cancer and prostate cancer patients, as well as multiple myeloma patients, have been reported at major medical conferences.

Expanding collaborations

Backed by a strong intellectual property position, Phosphatlin is advancing its R&D portfolio through collaborations including a clinical collaboration with Pfizer and Merck KGaA on a combination study of PT-112 and avelumab in solid tumors, and a sub-licensing agreement for Greater China study of PT-112 and avelumab in solid tumors, as well as multiple myeloma patients, have been reported at major medical conferences.

CONTACT
Taylor B. Young, Senior Director of Strategic Development
Phosphatlin Therapeutics Inc.
New York, NY, USA
Tel: +1 646-974-6456
Email: tyoung@phosplatin.com

www.nature.com/biopharmdeal | March 2021 | 817