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Depleting arginine as a first-line cancer therapy

Polaris Pharmaceuticals is evaluating its lead therapeutic protein—pegargiminase, a novel targeted cancer therapy that depletes circulating arginine—in combination with standard chemotherapies and immuno-oncology drugs in various cancers, including hepatocellular carcinoma and mesothelioma.

Polaris Pharmaceuticals, Inc. (a subsidiary of Polaris Group) is a biopharmaceutical company specializing in the research and development of novel treatments for cancer. Pegargiminase (ADI-PEG 20) is a potential first-in-class targeted cancer therapy in late-stage clinical development for a wide range of cancers, including hepatocellular carcinoma (HCC) and malignant pleural mesothelioma (MPM). Pegargiminase is well tolerated, both as a monotherapy and as part of a combination therapy.

"Preclinical data revealed various biochemical mechanisms that provide compelling rationales for combining pegargiminase with other agents, and we are exploring these potential synergies in our global clinical trial program," said John Bomalaski, MD and EVP of medical affairs at Polaris.

"Evidence suggests pegargiminase induces metabolic changes that can make cancer cells more susceptible to conventional chemotherapies, and this has been borne out in clinical studies, which show combination therapy can significantly enhance the efficacy of first-line therapy. We are also exploring a potential strong synergy with cancer immunotherapy drugs."

Based in San Diego, California, USA, Polaris Pharmaceuticals collaborates with major pharmaceutical companies and more than 40 cancer centers worldwide. The multinational Polaris Group also includes high-quality in-house current good manufacturing practice (cGMP) manufacturing through wholly owned subsidiaries. Its global clinical trial program is supported by a highly experienced management team and renowned scientific advisors, including James Allison, who was awarded the 2018 Nobel Prize in Physiology or Medicine for his pioneering work on cancer immunotherapy.

Targeting arginine metabolism

Pegargiminase is a PEGylated therapeutic protein based on a microbial enzyme, arginine deiminase (ADI). It converts extracellular arginine into citrulline, thus blocking the external supply of this important nutrient to cancer cells (**Fig. 1**).

Arginine is an amino acid that is required for protein synthesis and cell survival. Cancer cells need high amounts of arginine for growth and proliferation. When the external supply of arginine is restricted, cancer cells must produce enough arginine internally via the urea cycle not only to maintain normal cellular functions, but also to support their rapid rates of growth and replication. This process requires the cancer cells to spend energy (ATP). Arginine deprivation also gives rise to a host of conditions within cancer cells, including increased autophagy, increased apoptosis, increased eukaryotic stress and altered gene expression. Healthy cells are unaffected by the depletion of circulating arginine because they are able to convert citrulline back into arginine through the urea cycle.

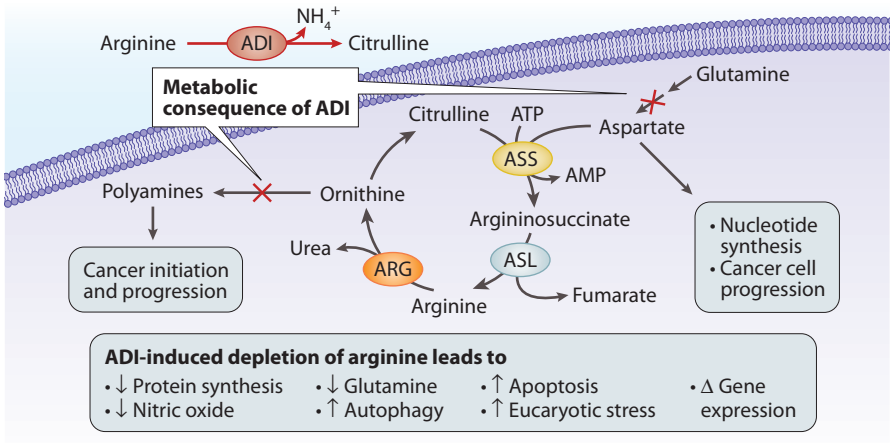

Fig. 1 | Pegargiminase converts extracellular arginine into citrulline. Cancer cells are therefore blocked from receiving this external supply of important nutrient. ADI, arginine deiminase; ARG, arginase; ASL, argininosuccinate lyase; ASS1, argininosuccinate synthetase.

There are multiple cancers with reduced expression of argininosuccinate synthetase (ASS1), the rate-limiting enzyme in internal arginine synthesis in the urea cycle. In these cancers, pegargiminase can be very effective as a monotherapy. For cancer cells with normal or even elevated levels of ASS1, pegargiminase has demonstrated strong synergy when used in combination with other systemic treatments.

Pivotal combination therapy trials

Two pivotal clinical trials are currently underway to assess the efficacy of pegargiminase in combination with standard chemotherapies, with potential marketing approvals planned for HCC and MPM by 2020.

A global phase 2 registration study (NCT02102022) designed to support accelerated approval for pegargiminase in combination with folinic acid (leucovorin), fluorouracil and oxaliplatin (FOLFOX) in HCC patients who have failed at least two lines of prior systemic treatments. Led by the Memorial Sloan Kettering Cancer Center (New York, USA), the single-arm, open-label study was expanded from a phase 1 clinical study after promising efficacy results were seen.

"Pegargiminase plus FOLFOX is showing more favorable efficacy compared to historic controls and the combination remains well tolerated," said Bomalaski. "We are committed to developing an effective treatment for the third line or later for HCC patients who have no approved treatment option."

Meanwhile, patients with MPM are taking part in ATOMIC-Meso (NCT02709512), a pivotal phase 2/3 study led by Barts Cancer Institute (London, UK). Based on data from a phase 1b study, the multicenter, randomized, double-blind trial is assessing pegargiminase in combination with pemetrexed and cisplatin, the current first-line standard-of-care chemotherapies for MPM. The study is using an adaptive biomarker-driven design with an interim analysis to be conducted at the end of phase 2.

Promising pipeline

Proof of principle for the efficacy of pegargiminase in combination with first-line therapies has also been demonstrated in other indications, including non-small-cell lung cancer, pancreatic cancer and acute myeloid leukemia. A phase 2 trial of pegargiminase in combination with gemcitabine and docetaxel for the treatment of soft tissue sarcoma is also currently underway.

Potential synergies with checkpoint inhibitors are also being explored in a phase 1 trial of pegargiminase in combination with pembrolizumab for the treatment of advanced solid tumors and in upcoming trials with dual checkpoint inhibition.

contact
John S. Bomalaski, MD and EVP of Medical Affairs
Polaris Pharmaceuticals, Inc.
San Diego, CA, USA
Tel: +1-858-452-6688 ext 114
Email: jbomalaski@polarispharma.com