



THINKSTOCK

## PRODUCT DEVELOPMENT

## OPTIMISM FOR A2A

BY STEPHEN HANSEN, ASSOCIATE EDITOR

Once considered solely a neurology target, the adenosine pathway has attracted interest in immuno-oncology based on its ability to control whether immune cells adopt a stimulatory or suppressive phenotype. The early results from A2A receptor antagonists first developed for neurological disease are a mixed bag. But several companies are persevering with new approaches intended to boost efficacy.

Sosei Group Corp. EVP and Chief R&D Officer Malcolm Weir told BioCentury the presence of A2A receptors on immune cells had been known for over a decade, but “it was with the advent of checkpoint inhibitors that the potential for clinical significance of this mechanism flourished.”

When adenosine binds to the adenosine A2A receptor (ADORA2A), CD8+ T cells and other lymphocytes decrease production of pro-inflammatory cytokines and increase production of immunosuppressive ones.

A2A receptor activation also up-regulates other immune checkpoints on T cells, such as PD-1, and increases forkhead box P3 (FOXP3) expression in CD4+ T cells, which steers them toward an immunosuppressive Treg phenotype.

At least five companies, including Sosei, are developing ADORA2A inhibitors for cancer.

The first signs of efficacy in the clinic came from Corvus Pharmaceuticals Inc.’s CPI-444 at the American Association for Cancer Research (AACR) meeting last April. The company reported initial efficacy data from an ongoing open-label Phase I/Ib trial showing one partial response in each of three cohorts in renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC) and colorectal cancer.

The trial is testing CPI-444 as monotherapy, and in combination with PD-L1 inhibitor Tecentriq atezolizumab from the Genentech Inc. unit of Roche. The patients all have pretreated, advanced cancers, including some that have relapsed or not responded to previous immunotherapies.

The company has since expanded the RCC and NSCLC cohorts, and in January reported updated data from 46 evaluable patients in the RCC cohort showing a disease control rate (DCR) of 36% for monotherapy, and four partial responses and a DCR of 50% for the combination. Final data are expected this year.

On March 5, however, Merck & Co. Inc. ended a 10-patient Phase I trial of A2A antagonist preladenant. The study was testing preladenant as monotherapy and in combination with Keytruda pembrolizumab to treat advanced solid tumors.

On ClinicalTrials.gov, the pharma said the data “did not support study endpoints.” The primary endpoint was dose-limiting toxicities; the secondary endpoint was overall response rate (ORR). Merck declined to be interviewed and has not disclosed whether one or both endpoints were missed.

Michel Detheux, CEO of iTeos Therapeutics S.A., noted preladenant was originally developed for Parkinson’s disease, and said A2A receptor inhibitors originally developed for neurological indications may not be potent enough in cancer.

Levels of extracellular adenosine, which competes with the inhibitors, are about 25 times higher in tumors than in healthy tissues, according to Detheux.

As a result, he thought it would be necessary to up the dosing of repurposed neurology compounds, which could cause toxicities. In

mouse models, high doses of brain-permeable A2A antagonists cause hyperexcitation and sleep disturbances similar to caffeine, which is also an A2A inhibitor.

Detheux cautioned it isn't clear whether the same neurotoxicity would translate into humans, but he said at high enough doses, "it could be like drinking 10 cups of coffee."

iTeos has designed its preclinical A2A antagonist EOS100850 to have a long occupancy on the receptor so that it can better inhibit A2A activity in the presence of high adenosine concentrations. EOS100850 is also excluded from the CNS. The compound is expected to enter the clinic this year in undisclosed cancer indications.

CPI-444, which is licensed from Vernalis plc, is brain-permeable and was originally developed to treat ADHD and other neurology indications.

President and CEO Richard Miller said Corvus has not observed dose-limiting neurotoxicities in any of its trials of CPI-444, which has been administered to about 250 cancer patients. He added that penetrating the brain could be a benefit if it enabled CPI-444 to access brain metastases.

Neither was he concerned about the discontinuation of Acorda Therapeutics Inc.'s tozadenant to treat PD on Nov. 20 after Phase III data revealed several cases of agranulocytosis, including some associated with fatal sepsis events. At the time, tozadenant was the most advanced clinical stage A2A antagonist.

Miller, Weir and Detheux noted other A2A antagonists with clinical or commercial experience have not shown toxicity similar to tozadenant.

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These include CPI-444 and Nouriasit istradefylline from Kyowa Hakko Kirin Co. Ltd., which was approved in Japan in 2013 and has been used to treat thousands of PD patients. In a Japanese Phase III trial of Nouriasit in PD, the most common adverse events were nasopharyngitis and dyskinesia.

“We’re evaluating our compound in patients who have had a lot of bone marrow injury in the past, and even in our cases, we see no neutropenia or anything like that, no infections,” Miller said.

The only serious adverse event reported for CPI-444 in the trial was one case of grade three nausea and diarrhea.

## ADORA2A ANTAGONISTS FOR CANCER

Selected adenosine A2A receptor (ADORA2A) antagonists in or near the clinic to treat cancer. (A) Phase I trial is in healthy volunteers, and a Phase I/II trial in cancer patients will begin this year; (B) expected to enter the clinic this year; *Source: BCIQ: BioCentury Online Intelligence*

Company	Compound	Phase	Indication
<b>Palobiofarma S.L. / Novartis AG</b> (NYSE:NVS; SIX:NOVN)	PBF-509	Ph I/II	Non-small cell lung cancer (NSCLC)
<b>Sosei Group Corp.</b> (Tokyo:4565) / <b>AstraZeneca plc</b> (LSE:AZN; NYSE:AZN)	AZD4635	Ph I/II	NSCLC
<b>Vernalis plc</b> (LSE:VER) / <b>Corvus Pharmaceuticals Inc.</b> (NASDAQ:CRVS) / <b>Genentech Inc.</b> / <b>Roche</b> (SIX:ROG; OTCQX:RHHBY)	CPI-444	Ph I/II	NSCLC
<b>Arcus Biosciences Inc.</b> (NYSE:RCUS)	AB928	Ph I	Cancer (A)
<b>iTeos Therapeutics S.A.</b>	EOS100850	Preclin	Lymphoma (B)

“Tozadenant is a completely different chemical structure than our compound, so I put this in the category of idiosyncratic, drug-related adverse events,” he added.

The next readout for the class will come in 2Q, when Arcus Biosciences Inc. reports Phase I data for AB928, an antagonist of A2A and A2B receptors.

### COMBINATION STRATEGIES

Corvus and other companies are combining their A2A antagonists with therapies that act on additional targets in the pathway to lower extracellular adenosine levels, which should make the A2A antagonists more effective without increasing the dose.

Two targets that could do the job are ecto-5'-nucleotidase (NT5E; NT; CD73) and ectonucleoside triphosphate diphosphohydrolase 1 (ENTPD1; CD39).

CD73 is up-regulated on tumor cells, stromal cells and endothelial cells in the hypoxic tumor microenvironment and catabolizes AMP to produce extracellular adenosine. CD39 also generates adenosine, but by degrading extracellular ATP.

While CD73 and CD39 aren't the only mechanisms tumors use to produce adenosine, Detheux, Miller and Innate Pharma S.A.'s SVP and CSO Eric Vivier noted the targets are considered primary producers.

This month, Corvus expects to start a Phase I/Ib trial of anti-CD73 mAb CPI-006 in combination with CPI-444 or Keytruda.

Innate is developing mAbs against both targets -- IPH52 for CD39, and IPH53 for CD73.

Vivier told BioCentury that discontinuation of the preladenant study “doesn't tell us anything about the way we are targeting the adenosine pathway.”

“I would say it the other way around. It reinforces our strategy to block the entire pathway by blocking CD39 and increasing ATP in the tumor bed, which promotes antigen presentation by dendritic cells, and also in combination with CD73,” he said.

Sosei’s partner AstraZeneca plc is combining the biotech’s A2A antagonist HTL001071 (AZD4635) with the anti-CD73 mAb MEDI9447 in a Phase Ib/II trial in 98 patients with advanced, EGFR-mutant NSCLC. ClinicalTrials.gov states data are expected in 2021.

AZD4635 is also in a Phase I trial as monotherapy or in combination with anti-PD-L1 mAb Imfinzi durvalumab for solid tumors.

Arcus is also developing a small molecule against CD73. AB680, a small molecule antagonist of CD73, is expected to enter the clinic by mid-year. 

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## COMPANIES AND INSTITUTIONS MENTIONED

**Acorda Therapeutics Inc.** (NASDAQ:ACOR), Ardsley, N.Y.  
**American Association for Cancer Research**, Philadelphia, Pa.  
**Arcus Biosciences Inc.** (NYSE:RCUS), Hayward, Calif.  
**AstraZeneca plc** (LSE:AZN; NYSE:AZN), London, U.K.  
**Corvus Pharmaceuticals Inc.** (NASDAQ:CRVS), Burlingame, Calif.  
**Genentech Inc.**, South San Francisco, Calif.  
**Innate Pharma S.A.** (Euronext:IPH), Marseille, France  
**iTeos Therapeutics S.A.**, Gosselies, Belgium  
**Kyowa Hakko Kirin Co. Ltd.** (Tokyo:4151), Tokyo, Japan  
**Merck & Co. Inc.** (NYSE:MRK), Kenilworth, N.J.  
**Roche** (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland  
**Sosei Group Corp.** (Tokyo:4565), Tokyo, Japan  
**Vernalis plc** (LSE:VER), Winnersh, U.K.