Orpathys approved in China for lung cancer

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Orpathys approved in China for patients with lung cancer and MET gene alterations

First-in-class approval in China in this setting and first regulatory approval for the oral, potent and highly selective MET tyrosine kinase inhibitor

AstraZeneca and HUTCHMED's *Orpathys* (savolitinib) has been granted conditional approval in China to treat patients with non-small cell lung cancer (NSCLC) with MET exon 14 skipping alterations who have progressed following prior systemic therapy or are unable to receive chemotherapy.

This approval follows a priority review designation by the Center for Drug Evaluation of China's National Medical Products Administration (NMPA) and marks the first global regulatory approval for the oral, potent, and highly selective MET tyrosine kinase inhibitor (TKI).

More than a third of the world's lung cancer patients are in China and, among those with NSCLC, approximately 2-3% have tumours with MET exon 14 skipping alterations, a targetable mutation in the MET gene.[1-3] This mutation is more common (13-22%) among patients with pulmonary sarcomatoid carcinoma (PSC), a rare and aggressive subtype of NSCLC usually resistant to chemotherapy.[1,4]

The approval by the NMPA was based on positive results from a single-arm Phase II trial conducted in China in patients with NSCLC with this mutation, including patients with the PSC subtype. *Orpathys* demonstrated robust anti-tumour activity based on an independent review of objective response rate (ORR) in the trial's primary endpoint and its disease control rate (DCR). Continued approval is contingent upon the successful completion of a confirmatory trial in this patient population.

Dave Fredrickson, Executive Vice President, Oncology Business Unit, said: "This approval makes *Orpathys* the only targeted medicine approved for these biomarker-selected patients in China, and it adds another novel medicine to our already diverse lung cancer portfolio. We are proud that this first-ever regulatory approval of *Orpathys* is in China, where we have a long-standing commitment to improving patient outcomes and working with the right partners to achieve that goal. Alongside HUTCHMED, we look forward to the continued development of this medicine across a range of cancers where MET alterations and amplification are drivers of tumour growth and treatment resistance."

Christian Hogg, Chief Executive Officer, HUTCHMED, said: "It is with great pleasure that today we announce the first regulatory approval of *Orpathys* globally, HUTCHMED's third self-discovered oncology drug to be commercialized. Our collaboration with AstraZeneca in 2011 has been an important driver in the development of this novel targeted oncology drug, involving both a China-based biotech and a global pharmaceutical company. This approval is a testament to the perseverance and scientific ingenuity of this long-standing alliance, and we are hopeful that this is only the beginning of the progress we can achieve for patients with MET-altered tumours."

In the Phase II trial, at a median follow up of 17.6 months, *Orpathys* demonstrated an ORR of 42.9% (95% confidence interval [CI] 31.1-55.3) and median progression-free survival (PFS) of 6.8 months (95% CI 4.2-9.6) in the overall trial population. PFS was clinically meaningful across subgroups, and ORR results were consistent regardless of prior treatment or tumour histology, including in patients with the PSC subtype (40.0%, 95% CI 21.1-61.3) and patients

with other NSCLC subtypes (44.4%, 95% CI 29.6-60.0). DCR in the overall trial population was 82.9% (95% CI 72.0-90.8).

The safety and tolerability profile of *Orpathys* was consistent with previous trials, and no new safety signals were identified. Most adverse events (AEs) were Grade 1–2 and resolved with dose modification or discontinuation. Grade 3 or higher AEs occurred in 45.7% of patients, and treatment-related serious AEs occurred in 24% of patients. One treatment-related death was reported from tumour lysis syndrome in a patient with PSC.

Results from the Phase II trial were presented during the American Society of Clinical Oncology ASCO20 Virtual Scientific Program in May 2020, and updated results were published in *The Lancet Respiratory Medicine* in June 2021.

As part of the joint global development programme with HUTCHMED, *Orpathys* is being evaluated in combination with *Tagrisso* and other medicines to address tumour mechanisms of resistance in NSCLC in the ORCHARD and SAVANNAH Phase II trials for the combinations to provide longer duration of benefit, and as a treatment for other MET-driven tumours, including papillary renal cell carcinoma, and gastric and gastroesophageal junction cancers.

NSCLC, PSC and MET aberrations

Lung cancer is the leading cause of cancer death among men and women, accounting for about one-fifth of all cancer deaths.[2] Lung cancer is broadly split into NSCLC and small cell lung cancer, with 80-85% classified as NSCLC.[5] The majority of NSCLC patients are diagnosed with advanced disease.[6]

PSC is a rare subtype of NSCLC, comprising 0.3-3% of all lung malignancies.[7] Compared with other NSCLC subtypes, PSC patients have a poorer prognosis and limited treatment options.[4,8-9]

MET is a tyrosine kinase receptor.[10] While MET genetic alterations are common in many solid tumours, MET exon 14 skipping alterations are more frequently associated with lung cancer, occurring in approximately 2-3% of patients with NSCLC and 13-22% of patients with PSC.[1,4,11] MET amplification or overexpression is one of the mechanisms of acquired resistance to epidermal growth factor receptor (EGFR) TKIs for metastatic EGFR-mutated NSCLC.[10]

NCT02897479

The single-arm, open-label Phase II trial NCT02897479 assessed the efficacy and safety of *Orpathys* in the treatment of Chinese patients with locally advanced or metastatic PSC or other NSCLC subtypes with MET exon 14 skipping alterations who progressed on prior treatment or were unable to receive chemotherapy.

Patients were treated with weight-based dosing of *Orpathys* once-daily oral tablets (600mg/day or 400mg/day for patients weighing less than 50kg). Treatment continued until disease progression, death, intolerable toxicity, or discontinuation. The trial enrolled 70 patients across multiple centres in China. The primary endpoint was ORR, and key secondary endpoints were PFS, DCR and safety assessment.

Orpathys

Orpathys (savolitinib) is an oral, potent, and highly selective MET TKI that has demonstrated clinical activity in advanced solid tumours. It blocks atypical activation of the MET receptor tyrosine kinase pathway that occurs because of mutations (such as exon 14 skipping alterations or other point mutations) or gene amplification.

Orpathys is currently under clinical development for multiple tumour types, including lung, kidney, and gastric cancers, as a single treatment and in combination with other medicines.

AstraZeneca and HUTCHMED collaboration

In 2011, AstraZeneca and HUTCHMED entered a global licensing agreement to jointly develop and commercialise *Orpathys*. HUTCHMED is responsible for the manufacturing and supply of *Orpathys*, and AstraZeneca is responsible for its commercialisation in China and worldwide. Sales of *Orpathys* will be recognised by AstraZeneca.

AstraZeneca in lung cancer

AstraZeneca is working to bring patients with lung cancer closer to cure through the detection and treatment of early-stage disease, while also pushing the boundaries of science to improve outcomes in the resistant and advanced settings. By defining new therapeutic targets and assessing innovative approaches, the Company aims to match medicines to the patients who can benefit most.

The Company's comprehensive portfolio includes leading lung cancer medicines and the next wave of innovations including *Tagrisso* (osimertinib) and *Iressa* (gefitinib); *Imfinzi* (durvalumab) and tremelimumab; *Enhertu* (trastuzumab deruxtecan) and datopotamab deruxtecan in collaboration with Daiichi Sankyo; *Orpathys* (savolitinib) in collaboration with HUTCHMED; as well as a pipeline of potential new medicines and combinations across diverse mechanisms of action.

AstraZeneca is a founding member of the Lung Ambition Alliance, a global coalition working to accelerate innovation and deliver meaningful improvements for people with lung cancer, including and beyond treatment.

AstraZeneca in oncology

AstraZeneca is leading a revolution in oncology with the ambition to provide cures for cancer in every form, following the science to understand cancer and all its complexities to discover, develop and deliver life-changing medicines to patients.

The Company's focus is on some of the most challenging cancers. It is through persistent innovation that AstraZeneca has built one of the most diverse portfolios and pipelines in the industry, with the potential to catalyse changes in the practice of medicine and transform the patient experience.

AstraZeneca has the vision to redefine cancer care and, one day, eliminate cancer as a cause of death.

AstraZeneca

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Contacts

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