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ADISINSIGHT REPORT

Savolitinib: First Approval

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Abstract
Savolitinib (Orpathys®; HUTCHMED, AstraZeneca) is a receptor tyrosine kinase mesenchymal epithelial transition factor (MET) inhibitor being developed for the treatment of metastatic non-small cell lung cancer (NSCLC), papillary and clear cell renal cell carcinoma (RCC), gastric cancer and colorectal cancer. Based on the results of a pivotal phase II trial in patients with NSCLC/pulmonary sarcomatoid carcinoma, savolitinib was recently granted approval in China (conditional on the results of a phase III trial) for the treatment of metastatic NSCLC with MET exon 14-skipping alterations in patients who have progressed after or who are unable to tolerate platinum-based chemotherapy. This article summarizes the milestones in the development of savolitinib leading to this first approval.

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Savolitinib (Orpathys®): Key points

A MET tyrosine kinase inhibitor is being developed by HUTCHMED and AstraZeneca for the treatment of metastatic NSCLC, papillary and clear cell RCC, gastric cancer and colorectal cancer

Received its first approval (conditional) on 22 June 2021 in China

Approved for use in metastatic NSCLC with MET exon 14-skipping alterations in patients who have progressed after or who are intolerant to platinum-based chemotherapy

1 Introduction

Savolitinib (Orpathys®) is a receptor tyrosine kinase mesenchymal epithelial transition factor (MET) inhibitor being developed by HUTCHMED (China) Ltd. (HUTCHMED) and AstraZeneca for the treatment of various cancers. Activation of MET by the binding of the endogenous ligand hepatocyte growth factor triggers various downstream signalling pathways that are involved in cell proliferation, survival and migration. Amplification or mutation of the MET gene is a hallmark of many solid tumours including non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), gastric and oesophageal carcinoma, and medulloblastoma. Indeed, certain tumours appear to depend on sustained MET activity for proliferation and survival (known as oncogene addiction) while in others, activation of MET is a secondary event that potentiates malignant progression of already transformed cells (oncogene expedience) [1]. MET exon 14-skipping (METex14) is a mutation present in 1–3% of NSCLC tumours that renders the receptor less susceptible to ubiquitination and subsequent proteasomal degradation, resulting in sustained MET activation and oncogenesis.

Clinical trials are underway evaluating savolitinib alone or in combination for the treatment of NSCLC with METex14-skipping alterations or that is epidermal growth factor receptor (EGFR)-mutant positive, MET-driven papillary RCC and MET-amplified gastric carcinoma. The drug is conditionally [2] approved in China for the treatment of patients with NSCLC with METex14-skipping alterations that has progressed after platinum-based chemotherapy, or who are intolerant to platinum-based chemotherapy [3]. The recommended starting dose of savolitinib is 600 mg orally once daily for patients weighing ≥ 50 kg, or 400 mg once daily for patients weighing < 50 kg, until disease progression or unacceptable toxicity. The drug should be taken immediately after a meal at the same time each day [4].

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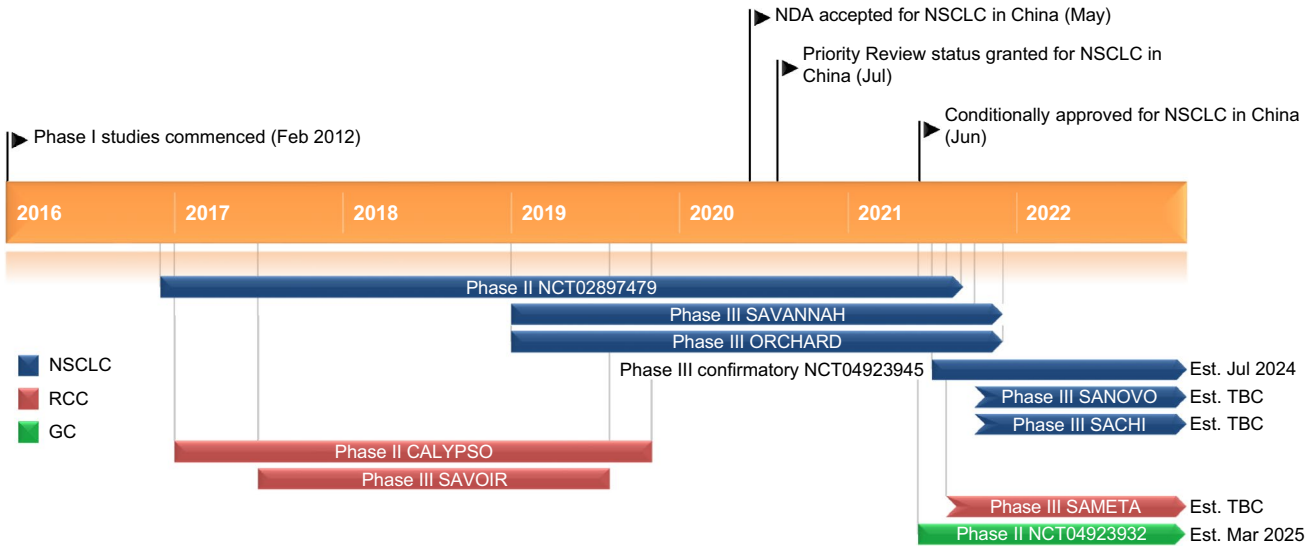


Key Milestones in the development of savolitinib, *GC* gastric cancer, *NDA* new drug application, *NSCLC* non-small cell lung cancer, *RCC* renal cell carcinoma

1.1 Company Agreements

In December 2011, HUTCHMED (then known as Hutchison China MediTech Ltd. [5]) granted a global license to AstraZeneca for the co-development and commercialization of savolitinib. Under the terms of the agreement Hutchmed will lead the development of the drug in China, and the two companies will share development costs. AstraZeneca will lead and finance the development of savolitinib in other parts of the world [6].

In August 2016 this agreement was amended, with HUTCHMED agreeing to contribute up to US $50 million to the joint development costs of the global pivotal phase III study in MET-driven papillary RCC (in return for increased royalties), with the aim of accelerating the global development of savolitinib and to cover multiple MET-driven solid tumour indications. All other provisions of the 2011 agreement remain unchanged [7].

2 Scientific Summary

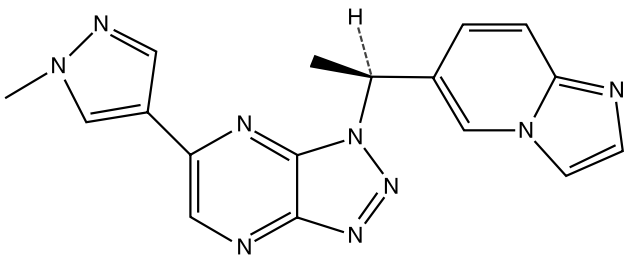
2.1 Pharmacodynamics

Savolitinib inhibited the tyrosine kinase activity of recombinant c-Met with an IC_{50} of 4 nM in vitro. When assessed against a panel of 22 gastric tumour cell lines, the drug selectively inhibited growth of cell lines with high MET expression (SNU-5, SNU-638, Hs746T, SNU-620, GTL16, IM95m; EC_{50} 0.6–14.7 nM). Incubation of Hs746T cells with savolitinib was associated with reductions in markers of activation of MET signaling (i.e. phosphorylated c-Met, ERK1/2 and AKT), suggesting that the antiproliferative effect of the drug is mediated via inhibition of phosphorylated c-Met and downstream signalling through the ERK and AKT pathways [8].

In vivo in a murine Hs746T xenograft model, administration of once daily oral savolitinib 0.3, 1 or 2.5 mg/kg for 16 days produced tumour growth inhibition values of 17% (not significant), 74% and 97% (both $p < 0.001$), respectively. Tumours harvested after administration of single oral doses of savolitinib 0.3, 1 and 2.5 mg/kg had 63%, 81% and 94% reductions in phosphorylated c-Met levels, respectively, after 4 h, and 39%, 76% and 88% after 8 h [8].

2.2 Pharmacokinetics

Administration of single oral 200, 400 and 600 mg doses of savolitinib to fasted Chinese male volunteers ($n = 3$ per dose) produced C_{max} values of 1020, 2230 and 3500 ng/ml, respectively, after 0.5–1 h (t_{max}). AUC_{0-inf} was 3850, 11,500 and 14,300 h • ng/ml, respectively.



Chemical structure of savolitinib

Features and properties of savolitinib	
Alternative names	Orpathys®, AZD-6094, HMP-504, HMPL-504, Volitinib
Class	Antineoplastics, imidazoles, pyrazines, pyrazoles, pyridines, triazoles
Mechanism of action	Met tyrosine kinase inhibitor
Route of administration	Oral
Pharmacodynamics	IC_{50} 4 nmol/L for tyrosine kinase activity of recombinant c-Met
Pharmacokinetics	C_{max} 2230 and 3500 ng/ml, after single oral 400 and 600 mg doses, t_{max} 0.5–1 h AUC_{0-inf} 11,500 and 14,300 h • ng/ml, $t_{½}$ 9.72 and 5.97 h, apparent clearance 36.2 and 43.7 L/h; AUC increased by 17.6% and tmax from 2 to 4 h when given with food compared to the fasted state
Adverse events	
Most frequent	Nausea, vomiting, diarrhoea, oedema, fatigue/weakness, loss of appetite, hypoalbuminemia, anaemia, abnormal liver function, rash
Occasional	
Rare	Prolonged QT interval on ECG, severe allergic/hypersensitivity reactions
ATC codes	
WHO ATC code	L01X-E
EphMRA ATC code	L1H
Chemical name	1-[(1S)-1-(imidazo[1,2-a]pyridin-6-yl)ethyl]-6-(1-methyl-1H-pyrazol-4-yl)-1H-1,2,3-triazolo[4,5-b]pyrazine

The terminal elimination half-life ($t_{½}$) was 6.17, 9.72 and 5.97 h, respectively, apparent volume of distribution during the terminal phase was 431, 467 and 398 L, respectively, and apparent clearance was 52.8, 36.2 and 43.7 L/h, respectively. Also in Chinese male volunteers ($n = 16$), administration of a single 600 mg dose of savolitinib with a high fat, high calorie meal did not affect C_{max}, but increased AUC by 17.6% and t_{max} from 2 to 4 h, compared to the fasted state [9].

Approximately 23% of a 600 mg dose of savolitinib was recovered from urine (≈ 13.1%) and faeces (≈ 10.0%) up to 48 h post-dose; unchanged drug and two metabolites (HMPL-504-M2 and HMPL-504-M3) were recovered in varying amounts in both urine and faeces [9].

No pharmacokinetic studies have been conducted in special populations such as the elderly, children and patients with renal or hepatic impairment [4].

2.3 Therapeutic Trials

2.3.1 NSCLC

Savolitinib as monotherapy had promising activity in Chinese patients with advanced NSCLC with METex14-skipping alterations, including pulmonary sarcomatoid carcinoma, in a phase II trial conducted in China (NCT02897479). Seventy patients were enrolled and treated with savolitinib at the recommended dose. At data cut-off (3 August 2020) the objective response rate was 49.2% in the independent review committee-assessed tumour response evaluable set ($n = 61$, primary endpoint) after median follow-up of 17.6 months. All responses observed were partial. The median time to response and duration of response were 1.4 months and 8.3 months, respectively, and the disease control rate was 93·4%. Median overall survival was 12.5 months [10].

In parts B and D of the multi-arm, multi-drug combination TATTON study (NCT02143466), savolitinib plus osimertinib had promising efficacy in patients with locally advanced/metastatic, MET-amplified/overexpressed, EGFR-mutant NSCLC and disease progression after prior treatment with an EGFR-tyrosine kinase inhibitor. In Part B, 138 patients received osimertinib 80 mg plus savolitinib 300 or 600 mg once daily depending on bodyweight. In Part D, 42 patients who had not received prior treatment with a third-generation EGFR-tyrosine kinase inhibitor, and who were T790M-negative, received osimertinib plus savolitinib 300 mg. Patients in part B were further subdivided into those previously treated with a third generation EGFR-tyrosine kinase inhibitor ($n = 69$), and those who were third generation EGFR-tyrosine kinase inhibitor naïve and T790M negative ($n = 51$) or positive ($n = 18$), The objective response rate was 33, 65 and 67%, respectively, with median progression-free survival of 5.5, 9.1 and 11.1 months, respectively. In part D the objective response rate was 62% and median progression-free survival was 9.0 months [11].

2.3.2 Papillary Renal Cell Carcinoma

Savolitinib as monotherapy had promising activity as treatment for MET-driven papillary RCC in the global, active comparator-controlled phase III SAVOIR trial (NCT03091192). Patients with MET-driven, unresectable and locally advanced/metastatic papillary RCC were randomized to savolitinib at the recommended dose ($n = 33$) or sunitinib 50 mg once daily in 6-week cycles, comprising 4 weeks of treatment then 2 weeks without treatment ($n = 27$). Recruitment to the study was closed early when

the results of a concurrent molecular epidemiology study indicated MET-driven status was not a negative predictor for treatment outcome, and thus the trial would be unlikely to detect a difference in efficacy between the two treatment groups. Fifty-two percent of patients in the savolitinib group had progression events compared to 74% in the sunitinib group (not significant) and median progression-free survival was 7.0 months and 5.6 months, respectively (primary endpoint). Nine (27%) savolitinib recipients died compared to 13 (48%) in the sunitinib group. Median overall survival was not reached and 13.2 months, respectively [12].

In a prior global phase II study (NCT02127710), savolitinib demonstrated activity in patients with MET-driven papillary RCC but not in those with MET-independent disease. Patients were treated with savolitinib 600 mg once daily until progression or when treatment discontinuation criteria were met. Of 109 patients treated, 44 (40%) had MET-driven papillary RCC. The objective response rate was 7% in the overall treatment population, but was significantly higher in the MET-driven subgroup than in the MET-independent subgroup (18% vs 0%; $p = 0.002$). All responses observed were partial. Median progression-free survival was significantly longer in patients with MET-driven papillary RCC than in those with MET-independent disease (6.2 vs 1.4 months; $p = 0.001$) [13].

Savolitinib in combination with durvalumab demonstrated clinical activity in the phase II CALYPSO study (NCT02819596) in patients with metastatic papillary RCC unselected for MET status. Patients ($n = 41$) were treated with savolitinib 600 mg once daily plus durvalumab 1500 mg once every 4 weeks, with a median follow-up of 26.8 months. In the overall population the confirmed response rate was 29% with a median progression-free survival of 4.9 months. Among those patients with MET-driven papillary RCC ($n = 14$), the confirmed response rate was 57% with a duration of response of 9.4 months. Median progression-free survival was 10.5 months and overall survival was 27.4 months [14].

The randomized multi-drug, phase II SWOG study (NCT02761057) in patients with papillary RCC unselected for MET status included a savolitinib arm, however, accrual was stopped and the arm closed after an interim analysis showed a hazard ratio > 1 for progression-free survival in this group and one other which randomized patients to sunitinib [15].

2.3.3 Gastric Cancer

Savolitinib as monotherapy demonstrated promising efficacy as second or third-line therapy for metastatic gastric cancer in the VIKTORY trial (NCT02299648). This trial classified patients according to clinical sequencing, focusing on various biomarker groups, including MET amplification and MET overexpression, to guide assignment of targeted treatment. Two savolitinib treatment arms were planned, one evaluating the drug as monotherapy at a dose of 800 mg/day in patients with MET amplification ($n = 20$, arm 4) and one evaluating savolitinib plus docetaxel in patients with MET overexpression (arm 5); however, enrolment into the latter was stopped early after promising efficacy was observed in the savolitinib monotherapy arm. In the savolitinib monotherapy arm, progression-free survival at 6 weeks (primary endpoint) was 80% and the overall response rate was 50%. All responses observed were partial [16].

2.4 Adverse Events

Tolerability data for savolitinib are available from five clinical trials involving a total of 345 cancer patients who received the drug as monotherapy, of whom 338 received at least the recommended dose. Among the latter, 20.4% stopped treatment because of adverse reactions which included oedema (4.7%), nausea (3.6%), vomiting (3.6%), fever (3.8%), increased aspartate aminotransferase (AST) levels (2.4%), increased alanine aminotransferase (ALT) levels (2.1%), fatigue/weakness (1.8%), decreased appetite (1.5%), anaemia (1.5%), skin rash (1.5%) and abnormal liver function (1.2%) [4].

Adverse reactions (≥ 1%) that led to dosage reductions included oedema (4.4%), elevated ALT levels (3.6%), elevated AST levels (3.3%), nausea (1.5%), fatigue/asthenia (1.2%), fever (1.2%) and abnormal liver function (1.2%). Permanent discontinuation of savolitinib because of adverse reactions occurred in 11.8% of patients and included abnormal liver function (3.8%), vomiting (1.5%), elevated ALT levels (2.1%), fatigue (1.2%), oedema (1.2%), elevated AST levels (1.2%) and severe allergic reactions (1.2%) [4].

Adverse events occurring in patients treated with savolitinib at at least the recommended dose included nausea (all grades 44.7%, ≥ grade three 1.5%), vomiting (31.5%, 1.5%), diarrhoea (13.6%, 0.6%), oedema (40.5%, 3.8%), fatigue/weakness (31.1%, 4.4%), loss of appetite (21.0%, 1.2%), hypoalbuminemia (17.2%, 1.2%), anaemia (16.6%, 3.3%), fever (15.7%, 1.2%), abnormal liver function (11.8%, 5.6%), rash (9.5%, 0.6%) and severe hypersensitivity reactions (1.5%, 1.2%). Laboratory abnormalities occurring in patients treated with savolitinib at at least the recommended dose included elevated AST levels (18.0%, 6.2%), elevated ALT levels (16.3%, 5.9%), elevated blood alkaline phosphatase levels (7.1%, 0%), elevated blood bilirubin levels (7.1%, 0.6%), increased γ-glutamyltransferase levels (4.7%, 1.2%) and prolonged QT interval on ECG (3.0%, 0%) [4].

Key clinical trials of savolitinib

Drug(s)	Indication	Phase	Status	Location(s)	Sponsor	Identifier
Savolitinib, durvalumab	MET-driven papillary RCC	III	Pending	China	Hutchmed	SAMETA
Savolitinib	NSCLC	III	Recruiting	China	Hutchmed	NCT04923945, CTR2021151
Savolitinib, osimertinib	EGFR mutant NSCLC with MET overexpression	III	Ongoing	China	Hutchmed	SANOVO, CTR20211427
Savolitinib, osimertinib	EGFR-TKI refractory NSCLC with MET-amplification	III	Ongoing	China	Hutchmed	SACHI, CTR20211441
Savolitinib	Gastric cancer, esophagogastric junction adenocarcinoma	II	Recruiting	China	Hutchmed	NCT04923932
Osimertinib, savolitinib	NSCLC	II	Recruiting	Global	AstraZeneca	NCT04606771
Savolitinib, osimertinib, gefitinib, necitumumab, durvalumab, carboplatin, pemetrexed, alectinib, selpercatinib	NSCLC	II	Recruiting	Global	AstraZeneca	NCT03944772, ORCHARD
Savolitinib, osimertinib	NSCLC	II	Recruiting	Global	AstraZeneca, Hutchmed	NCT03778229, SAVANNAH
Savolitinib, sunitinib	Papillary RCC	III	Active, not recruiting	Global	AstraZeneca, Hutchmed	NCT03091192, SAVOIR
Savolitinib, docetaxel	Advanced gastric adenocarcinoma with MET overexpression	II	Completed	Korea	Samsung Medical Center	NCT02447380, VIKTORY
Savolitinib, MEDI4736, tremelimumab	Metastatic RCC	II	Completed	Spain, UK	AstraZeneca	NCT02819596, CALYPSO
Savolitinib	Lung sarcomatoid carcinoma	II	Follow-up ongoing	China	Hutchmed	NCT02897479
Savolitinib	Advanced gastric adenocarcinoma	II	Completed	Korea	Samsung Medical Center	NCT02449551, VIKTORY
Savolitinib, docetaxel	Advanced gastric adenocarcinoma	I/II	Enrolment stopped	Korea	Samsung Medical Center	NCT02447406, VIKTORY
Savolitinib, gefitinib	Safety & PK in patients with NSCLC	I	Completed	China	Hutchmed	NCT02374645
Savolitinib, AZD9291, selumetinib, MEDI4736	Advanced NSCLC	I	Completed	Global	AstraZeneca	NCT02143466
Savolitinib	Papillary RCC	II	Completed	USA, Canada, UK	AstraZeneca	NCT02127710

EGFR epidermal growth factor receptor, *NSCLC* non-small cell lung cancer, *PK* pharmacokinetics, *RCC* renal cell carcinoma, *TKI* tyrosine kinase inhibitor

2.5 Ongoing Clinical Trials

The confirmatory phase III (NCT04923945) trial evaluating savolitinib as monotherapy for advanced or metastatic NSCLC with METex14-skipping alterations in Chinese patients is underway. Chinese phase III registration trials evaluating savolitinib plus osimertinib as first-line treatment for EGFR-mutant MET-driven NSCLC (SANOVO) and as second-line treatment for EGFR-tyrosine kinase inhibitor-refractory NSCLC with MET amplification (SACHI) are underway as is a phase II trial evaluating savolitinib as monotherapy for gastric cancer with MET amplification (NCT04923932). A global phase III trial (NCT04606771) evaluating savolitinib alone or combined with osimertinib as treatment for EGFR-mutant and MET-amplified, advanced NSCLC is currently recruiting patients. In addition, the ongoing phase II SAVANNAH trial (NCT03778229) is evaluating combination therapy with osimertinib and savolitinib in patients with EGFR-mutant, MET-driven, locally advanced or metastatic NSCLC that has progressed on osimertinib [17]. SAVANNAH will be aligned to benefit from molecular profiling in the concurrent multi-drug, phase II ORCHARD platform trial (NCT03944772) in patients with advanced EGFR-mutant NSCLC whose disease has

progressed on first line therapy with osimertinib. Patients enrolled in ORCHARD who have MET-driven EGFR-mutant NSCLC and meet relevant inclusion criteria will be prioritized for inclusion in SAVANNAH [18].

The multinational phase III SAVOIR trial (NCT03091192) in patients with papillary RCC described above [12] is ongoing, and the global phase III SAMETA registration trial evaluating savolitinib combined with durvalumab in MET-driven papillary RCC is expected to commence enrolment in the second half of 2021.

A phase II study evaluating the efficacy of savolitinib in patients with MET-amplified metastatic colorectal cancer detected by cell-free DNA (NCT03592641) is currently recruiting patients at several US centres [19].

3 Current Status

Savolitinib received its first approval on 22 June 2021 in China for the treatment of NSCLC with METex14-skipping alterations in patients who have progressed after or who are intolerant to platinum-based chemotherapy. This approval is conditional [2] upon successful completion of a confirmatory phase III study in this patient population [3].

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Declarations

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Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

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