Drugs
https://doi.org/10.1007/s40265-025-02215-8

ADISINSIGHT REPORT

Avutometinib and Defactinib: First Approval

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Accepted: 7 July 2025

Abstract
Avutometinib and defactinib (AVMAPKI™ FAKZYNJA™ CO-PACK) is a co-packaged rapidly accelerating fibrosarcoma (RAF)/mitogen-activated protein kinase kinase (MEK) inhibitor (avutometinib) and focal adhesion kinase (FAK)/proline-rich tyrosine kinase-2 (Pyk2) inhibitor (defactinib) being developed by Verastem Oncology for the treatment of RAS/MAPK pathway-driven cancers. In May 2025, avutometinib and defactinib was approved in the USA for the treatment of adult patients with *KRAS*-mutated recurrent low-grade serous ovarian cancer (LGSOC) who have received prior systemic therapy. This article summarizes the milestones in the development of avutometinib and defactinib leading to this first approval for *KRAS*-mutated recurrent LGSOC.

Digital Features for this AdisInsight Report can be found at https://doi.org/10.6084/m9.figshare.29486009.

Avutometinib and Defactinib (AVMAPKI™ FAKZYNJA™ CO-PACK): Key Points

A co-packaged RAF/MEK inhibitor and FAK/Pyk2 inhibitor being developed by Verastem Oncology for the treatment of RAS/MAPK pathway-driven cancers

Received its first approval on 8 May 2025 in the USA

Approved for the treatment of adult patients with KRAS-mutated recurrent LGSOC who have received prior systemic therapy

1 Introduction

Avutometinib (AVMAPKI™) is a rapidly accelerating fibrosarcoma (RAF)/mitogen-activated protein kinase kinase (MEK) inhibitor that potently inhibits MEK1/2 kinase activities and induces formation of dominant negative RAF/MEK complexes, thereby blocking the compensatory activation of MEK by RAF proteins [1]. RAF and MEK proteins are upstream regulators of the rat sarcoma oncogene (RAS)-regulated RAF/MEK/extracellular signal-regulated kinase (ERK), mitogen-activated protein kinase (MAPK) signaling pathway, which promotes cell proliferation, differentiation, survival and migration [2]. Defactinib (FAKZYNJA™) is an inhibitor of focal adhesion kinase (FAK) and also inhibits proline-rich tyrosine kinase-2 (Pyk2), which is the other member of the FAK family of nonreceptor protein tyrosine kinases [3]. FAK integrates signals from integrin and growth factor receptors to regulate cell proliferation, survival, migration and invasion, and has been shown to mediate resistance to multiple cancer agents [3].

Avutometinib and defactinib are being developed by Verastem Oncology for the treatment of RAS/MAPK pathway-driven cancers. Avutometinib is being developed under license from Chugai Pharmaceutical and defactinib is being developed under license from Pfizer. Based on the results of the phase II RAMP 201 trial (NCT04625270) [4], avutometinib co-packaged with defactinib was granted accelerated approval in the USA for the treatment of adult patients with *KRAS*-mutated recurrent low-grade serous ovarian cancer (LGSOC) who have received prior systemic therapy [5, 6]. The approval was based on tumour response rate and duration of response [5]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

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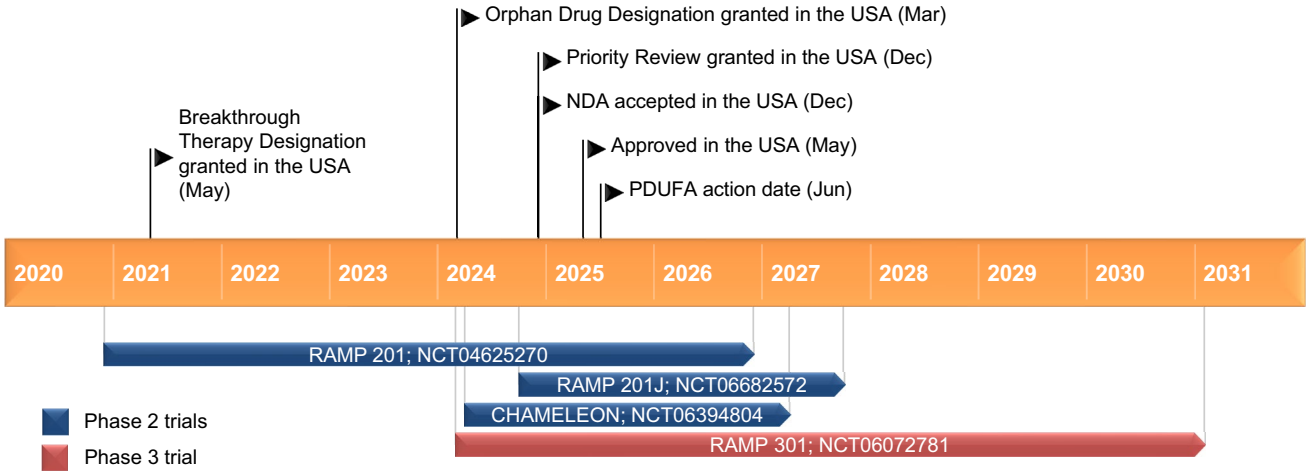
Published online: 05 August 2025



Key milestones in the development of avutometinib and defactinib combination, focusing on its use in patients with *KRAS*-mutated recurrent low-grade serous ovarian cancer who have received prior systemic therapy. *NDA* New Drug Application, *PDUFA* Prescription Drug User Fee Act

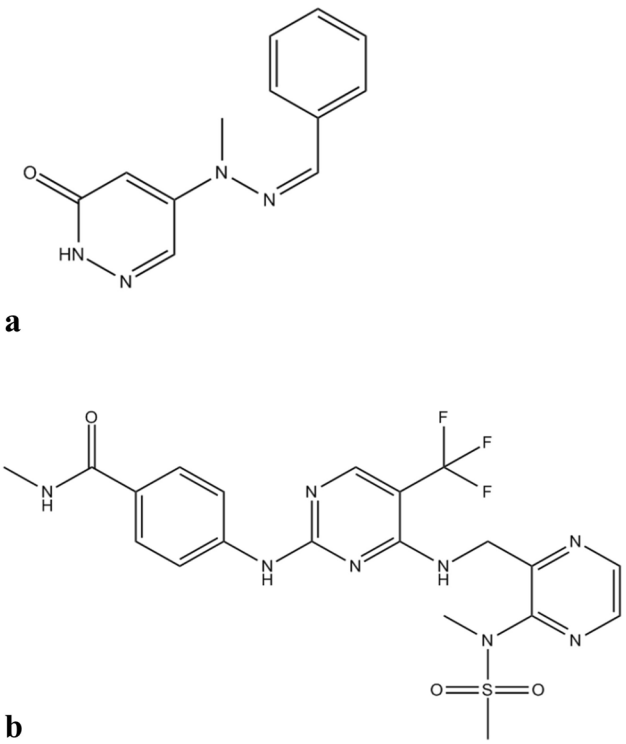
The recommended dosage of avutometinib is 3.2 mg (four 0.8 mg capsules) twice weekly (day 1 and day 4) and the recommended dosage of defactinib is 200 mg (one tablet) twice daily. Each should be taken orally with food for the first 3 weeks of each 4-week cycle until disease progression or unacceptable toxicity occurs [5].

The New Drug Application for avutometinib and defactinib for the treatment of adult patients with recurrent LGSOC who received at least one prior systemic therapy and have a *KRAS* mutation was accepted by the US FDA in December 2024 and Priority Review was granted [7]. Orphan Drug Designation for avutometinib alone or in combination with defactinib for the treatment of all patients with recurrent LGSOC had been granted in March 2024 [8]. Earlier, in May 2021, avutometinib and defactinib had been granted Breakthrough Therapy Designation in recurrent LGSOC regardless of *KRAS* status after one or more prior lines of therapy, including platinum-based chemotherapy [9].

Avutometinib and defactinib combination therapy is in ongoing phase I/II development for the treatment of other solid tumours, including non-small cell lung cancer (NSCLC), pancreatic cancer, gynaecological cancer, melanoma, gastric cancer, colorectal cancer, thyroid cancer and glioblastoma.

1.1 Company Agreements

In July 2012, Verastem entered into a licensing agreement with Pfizer for the exclusive worldwide development and commercialization rights for defactinib [10]. Under the terms of agreement, Verastem is solely responsible for global product development of defactinib [10]. In January 2020, Verastem Oncology entered into a licensing agreement with Chugai Pharmaceuticals for the exclusive worldwide development and commercialization rights for avutometinib [11].



Chemical structure of **a)** avutometinib and **b)** defactinib

2 Scientific Summary

2.1 Pharmacodynamics

Avutometinib simultaneously blocks both the RAF and MEK kinases in the RAF/MEK/ERK (MAPK) signalling pathway, while defactinib is an inhibitor of both FAK and Pyk2, both members of the FAK family of non-receptor tyrosine kinases [5].

In vitro, avutometinib inhibited MEK1/2 and ERK1/2 phosphorylation and tumour proliferation and increased the level of phosphorylated FAK [5, 12]. In patients with solid tumours, avutometinib inhibited MEK and ERK phosphorylation, reduced cell proliferation, increased apoptosis and demonstrated promising preliminary anti-tumour activity [13, 14]. Defactinib inhibited FAK autophosphorylation in vitro and in murine xenograft models [5, 12] but demonstrated minimal anti-tumour activity in patients with solid tumours [15, 16].

Preclinical studies demonstrated strong synergistic effects of combined avutometinib and defactinib, including enhanced inhibition of cell proliferation in vitro and anti-tumour activity in murine models and patient-derived xenograft models [5, 12, 17]. In the first-in-human, phase I FRAME trial (NCT03875820), the combination of avutometinib and defactinib demonstrated promising clinical activity in patients with solid tumours including LGSOC, NSCLC and colorectal cancer [18].

Features and properties of avutometinib and defactinib

	Avutometinib	Defactinib
Alternative names	AVMAPKI™; CH 5127566; CH-5126766; CKI-27; R-7304; Raf/MEK inhibitor VS-6766; RG 7304; RO-5126766; VS-6766	FAKZYNJA™; defactinib hydrochloride; PF-04554878; PF-4554878; VS-6063
Class	Antineoplastics, Benzopyrans, Ethers, Fluorinated hydrocarbons, Ketones, Pyridines, Pyrimidines, Small molecules, Sulfonamides	Amines, Antineoplastics, Benzamides, Fluorinated hydrocarbons, Pyrazines, Pyrimidines, Small molecules, Sulfones
Mechanism of action	Mitogen-activated protein kinase inhibitors; Raf kinase inhibitors	Focal adhesion protein tyrosine kinase inhibitors
Route of administration	Oral	Oral
Pharmacodynamics	Simultaneously blocks both RAF and MEK kinases in the RAF/MEK/ERK signalling pathway; inhibits MEK and ERK phosphorylation, reduces tumour proliferation and increases apoptosis	Inhibits both FAK and Pyk2, members the FAK family of non-receptor tyrosine kinases; inhibits FAK autophosphorylation in vitro and in vivo
Pharmacokinetics	Dose proportional exposure over 0.1–5 mg dose range; median T_{max} ≈2 h (fasted state); 99% bound to plasma proteins; mean Vd 25 L; primarily metabolized by CYP3A4 and non-enzymatic degradation; mean CL 0.3 L/h; mean $t_{½}$ 51 h	Dose proportional exposure over 12.5–450 mg dose range; median T_{max} ≈4 h (fed state); 90% bound to plasma proteins; mean Vd 1560 L; primarily metabolized by CYP3A4 and CYP2C9; mean CL 69 L/h; mean $t_{½}$ 9 h
Most common TRAEs[a]	Nausea, increased CPK, diarrhoea, peripheral oedema, fatigue, vomiting, blurred vision, rash, dermatitis acneiform, increased bilirubin/hyperbilirubinaemia, increased AST, dry skin, anaemia	
ATC codes		
WHO ATC code	L01 (Antineoplastic Agents), L01X (Other Antineoplastic Agents)	L01 (Antineoplastic Agents), L01X-E (Protein Kinase Inhibitors)
EphMRA ATC code	L1 (Antineoplastics), L1X (All Other Antineoplastics)	L1 (Antineoplastics); L1H (Protein Kinase Inhibitor Antineoplastics)
Chemical name	3-[[3-fluoro-2-(methylsulfamoylamino)pyridin-4-yl] methyl]-4-methyl-7-pyrimidin-2-yloxychromen-2-one	Benzamide, N-methyl-4-((4-(((3-(methyl(methylsulfonyl)amino)-2-pyrazinyl)methyl) amino)-5-(trifluoromethyl)-2-pyrimidinyl)amino)-

AST aspartate aminotransferase, *CL* clearance, *CPK* creatine phosphokinase, *ERK* extracellular signal-regulated kinase, *FAK* focal adhesion kinase, *MEK* mitogen activated protein kinase/ERK, *Pyk2* proline-rich tyrosine kinase-2, $t_{½}$ estimated elimination half-life, T_{max} time to peak plasma concentration, *TRAEs* treatment-related adverse events, *Vd* volume of distribution

[a]When used in avutometinib + defactinib combination therapy

2.2 Pharmacokinetics

2.2.1 Avutometinib

The systemic exposure of avutometinib is dose proportional after single doses ranging from 0.1–5 mg (0.03–1.6 times the approved recommended dosage) [5]. There is no significant accumulation of avutometinib at the approved recommended dosage. Peak plasma concentrations (C_{max}) are reached in a median time of ≈2 h under fasted conditions. Administration of avutometinib with a high-fat meal had no significant effect on area under the concentration-time curve (AUC) and decreased C_{max} by 29%. In vitro, avutometinib is highly (99%) bound to plasma proteins. At steady state, avutometinib has an apparent mean volume of distribution of 25 L [5].

Avutometinib is primarily metabolized by CYP3A4 and non-enzymatic degradation [5]. Following administration of a single radiolabeled dose of avutometinib 2.4 mg, 52% of the dosed total radioactivity was excreted in the urine (3.2% unchanged) and 39% was excreted in the faeces (9.5% unchanged). Avutometinib has a mean apparent oral clearance rate of 0.3 L/h and a mean estimated elimination half-life of 51 h [5].

Sex, age (21–87 years), race, body weight (40–169 kg), mild or moderate renal impairment and mild hepatic impairment have no clinically meaningful impact on the pharmacokinetics of avutometinib [5]. The effects of severe renal impairment or moderate to severe hepatic impairment on the pharmacokinetics of avutometinib are unknown [5].

Avutometinib is a substrate of CYP3A4, P-glycoprotein and BCRP in vitro [5]. No clinically significant differences in avutometinib pharmacokinetics were observed when coadministered with itraconazole (a strong CYP3A4 inhibitor). Avutometinib AUC decreased by 34% with no clinically significant change in C_{max} following coadministration with phenytoin (a strong CYP3A4 inducer) [5].

2.2.2 Defactinib

Defactinib demonstrates dose-proportional exposure over the dose range of 12.5–450 mg (0.06–2.25 times the approved recommended dosage) [5]. At the approved recommended dosage, defactinib accumulates ≈1.5-fold. The median time to C_{max} under fed conditions is ≈4 h. Administration of defactinib with a high-fat meal increased AUC by 2.7-fold and increased C_{max} by 1.9-fold. In vitro, 90% of defactinib is bound to human plasma proteins. The apparent mean volume of distribution of defactinib at steady state is 1560 L [5].

Defactinib is primarily metabolized by CYP3A4 and CYP2C9 [5]. The two major metabolites (M2 and M4) represent 92% and 28% of exposure at steady state, respectively. Following administration of a single radiolabeled dose of defactinib 400 mg, 87% of the total radioactivity was excreted in the faeces (52% unchanged) and 7.6% was excreted in the urine (0.8% unchanged). The clearance rate of defactinib is 69 L/h and the mean estimated elimination half-life is 9 h [5].

The pharmacokinetics of defactinib are not impacted to a clinically meaningful extent based on age, sex, race, body weight, mild or moderate renal impairment or mild hepatic impairment [5]. The effect of severe renal impairment or moderate to severe hepatic impairment on defactinib pharmacokinetics is unknown [5].

Defactinib is a substrate of CYP3A4, CYP2C9, P-glycoprotein and BCRP, an inhibitor of CYP3A4, CYP2C9, P-glycoprotein, BCRP, OATP1B1, OATP1B3 and MATE2-K, and an inducer of CYP2B6 and CYP1A2 in vitro [5]. Defactinib may also inhibit UGT1A1 at clinically relevant concentrations. Concomitant use of defactinib with itraconazole (a strong CYP3A4 inhibitor) increases defactinib exposure. Coadministration of defactinib with strong CYP3A4 inducers or proton pump inhibitors decreases defactinib exposure [5].

2.3 Therapeutic Trials

2.3.1 Low-Grade Serous Ovarian Cancer

Combination therapy with avutometinib and defactinib was associated with high response rates in patients with recurrent LGSOC participating in the phase II RAMP 201 trial (NCT04625270) [4, 19]. At initial data cutoff (6 April 2023), the efficacy evaluable population (part A) comprised 60 patients with *KRAS*-mutant ($n = 30$) or *KRAS*-wildtype ($n = 30$) LGSOC [19]. Overall, the confirmed objective response rate (ORR) was 45% in the avutometinib and defactinib combination therapy group and 10% in the avutometinib monotherapy group. Among patients with *KRAS*-mutant disease, the ORR was 60% with combination therapy and 13% with avutometinib monotherapy. Among patients with *KRAS*-wildtype disease, the ORR was 29% with combination therapy and 6% with avutometinib monotherapy. Median time to response was 5.5 months in the combination therapy group and 7.3 months in the avutometinib monotherapy group. Median duration of response (DOR) and progression-free survival (PFS) were not reached [19].

In the primary analysis (data cutoff 30 June 2024; median follow-up 13.6 months), the combination of avutometinib and defactinib resulted in clinically meaningful responses in patients with recurrent LGSOC [4]. The confirmed ORR was 31% with avutometinib and defactinib combination therapy and 17% with avutometinib monotherapy. Corresponding ORRs in patients receiving combination therapy and

Key clinical trials of avutometinib and defactinib

Drug(s)	Indication	Phase	Status	Location(s)	Identifier	Sponsor
Avutometinib, defactinib	LGSOC	III	Recruiting	Multinational	RAMP 301; NCT06072781	Verastem Oncology
Avutometinib, defactinib	LGSOC	II	Active, not recruiting	Multinational	RAMP 201; NCT04625270	Verastem Oncology
Avutometinib, defactinib	LGSOC	II	Recruiting	Japan	RAMP 201J; NCT06682572	Verastem Oncology
Avutometinib, defactinib, letrozole	LGSOC	II	Recruiting	USA	CHAMELEON; NCT06394804	Memorial Sloan Kettering Cancer Center
Avutometinib, defactinib	NSCLC	II	Completed	Multinational	RAMP 202; NCT04620330	Verastem Oncology
Avutometinib, defactinib, nivolumab	NSCLC	II	Recruiting	USA	NCT06495125	Emory University
Avutometinib, defactinib, sotorasib	NSCLC	I/II	Recruiting	Multinational	RAMP 203; NCT05074810	Amgen, Verastem Oncology
Avutometinib, defactinib, gemcitabine, nab-paclitaxel	Pancreatic cancer	Ib/IIa	Recruiting	USA	RAMP 205; NCT05669482	Verastem Oncology
Avutometinib, defactinib	Gynaecological cancer	II	Recruiting	USA	DURAFAK; NCT05512208	University of Oklahoma
Avutometinib, defactinib	Gynaecological cancer	II	Recruiting	USA	NCT05787561	Memorial Sloan Kettering Cancer Center
Avutometinib, defactinib	Uveal melanoma	II	Active, not recruiting	USA	NCT04720417	Thomas Jefferson University
Avutometinib, defactinib, encorafenib	Melanoma	Ib/II	Recruiting	USA	DETERMINE; NCT06194929	University of Utah
Avutometinib, defactinib	Gastric cancer	II	Recruiting	USA	NCT06487221	Columbia University
Avutometinib, defactinib, cetuximab	Colorectal cancer	II	Recruiting	USA	NCT06369259	M.D. Anderson Cancer Center
Avutometinib, defactinib	Thyroid cancer	II	Recruiting	USA	NCT06007924	Memorial Sloan Kettering Cancer Center
Avutometinib, defactinib, temozolomide	Brain tumours	I/II	Recruiting	England	5G-RUBY; NCT06630260	The Institute of Cancer Research
Avutometinib, defactinib	Glioblastoma	I	Recruiting	USA	NCT05798507	Emory University
Avutometinib, defactinib	Solid tumours	I	Active, not recruiting	England	FRAME; NCT03875820	The Institute of Cancer Research

LGSOC low-grade serous ovarian cancer, *NSCLC* non-small cell lung cancer

monotherapy were 44% and 23%, respectively, in patients with *KRAS*-mutant disease and 17% and 13%, respectively, in patients with *KRAS*-wildtype disease. Median time to response with combination therapy was 3.7 months. Median DOR was 31.1 months in the combination therapy group and could not be estimated in the monotherapy group. Median PFS in the combination therapy group was 12.9 months (22.0 months in patients with *KRAS*-mutant disease and 12.8 months in patients with *KRAS*-wildtype disease) [4].

RAMP 201 was a randomized, multicentre trial with an adaptive study design [4, 19]. The trial comprised four parts: part A (selection phase), part B (expansion phase), part C (expansion phase combination) and part D (lower dose in combination). Eligibility criteria included histologically confirmed recurrent LGSOC, measurable disease, known *KRAS* status and prior platinum chemotherapy. The combination treatment was determined to be the go-forward regimen and was expanded in part C. Part D explored a lower starting dose of avutometinib in combination with defactinib but was determined to be suboptimal and not pursued. Patients in parts A and B were randomized to receive oral avutometinib 3.2 mg twice weekly plus oral defactinib 200 mg twice daily (combination therapy) or oral avutometinib 4.0 mg twice weekly (monotherapy), each according to a 3 weeks on/1 week off schedule. The primary endpoint was ORR as measured by blinded independent review [4, 19].

The combination of avutometinib with defactinib demonstrated anti-tumour activity in patients with recurrent LGSOC participating in the phase I FRAME trial

(NCT03875820) [18]. The ORR was 42% and the median PFS was 20.1 months [18].

2.3.2 Non-Small Cell Lung Cancer

The combination of avutometinib and defactinib demonstrated clinical activity in previously treated patients with *KRAS G12V* mutant NSCLC participating in the phase II RAMP 202 trial (NCT04620330) [20]. Among evaluable patients enrolled in part A ($n = 35$), there were 2/19 (11%) confirmed ORRs with avutometinib and defactinib combination therapy. Both were partial responses, with durations of 7.9 and 8.5 months (both ongoing at the time of the analysis). There were no confirmed ORRs in the avutometinib monotherapy group. Criteria to proceed to part B (expansion phase) were not met [20].

RAMP 202 was a randomized, open-label, multicentre trial with an adaptive study design [20]. The trial enrolled patients with histologically confirmed, *KRAS*-mutated, advanced NSCLC. All patients had measurable disease, an Eastern Cooperative Oncology Group performance status of 0 or 1 and had received at least one prior systemic therapy (platinum-based chemotherapy and immune checkpoint inhibitor or appropriate therapy for activating mutation). Patients were randomized to receive oral avutometinib 3.2 mg twice weekly plus oral defactinib 200 mg twice daily (combination therapy) or oral avutometinib 4.0 mg twice weekly (monotherapy), each according to a 3 weeks on/1 week off schedule. The primary endpoint was confirmed ORR as measured by blinded independent review [20].

2.3.3 Pancreatic Cancer

Avutometinib and defactinib combined with gemcitabine and nab-paclitaxel demonstrated notable preliminary efficacy in treatment-naïve patients with metastatic pancreatic ductal adenocarcinoma (PDAC) participating in the phase Ib/II RAMP 205 trial (NCT05669482) [21]. At initial data cutoff (14 May 2024), five of the six (83%) patients in dose level 1 with mature follow-up (i.e. all patients enrolled ≥ 6 months prior to data cutoff) achieved an ORR. All responses were partial responses and the median time to response was 4.6 months. All patients in dose level 1 with an elevated CA19-9 at baseline ($n = 5$) experienced a ≥ 60% reduction in CA19-9, with 60% of these patients achieving this reduction within the first 8 weeks of treatment. Follow-up in the other dose levels was immature, with treatment ongoing in most patients (Sect. 2.5) [21].

In an updated analysis (data cutoff 3 Jan 2025), the ORRs for patients in dose levels 1, 0, –1, 1a and 2a were 83%, 100%, 27%, 33% and 25%, respectively [22]. Corresponding disease control rates for ≥ 4 cycles were 83%, 100%, 82%, 56% and 58%, respectively. The maximum tolerated dose has not been reached [22].

RAMP 205 was an open-label, multicentre, single-arm trial that enrolled patients with histologically confirmed newly diagnosed metastatic PDAC with measurable disease, an ECOG performance status of 0 or 1, adequate organ function and no prior treatment for advanced or metastatic disease [21, 22]. Patients were treated in 3 + 3 cohorts with escalating doses of oral avutometinib twice weekly and oral defactinib twice daily, each for 3 out of 4 weeks, in combination with intravenous gemcitabine and intravenous nab-paclitaxel on days 1, 8 and 15 or days 1 and 15 (modified) of a 4-week cycle. They were enrolled in the following dose levels: 1 (avutometinib 2.4 mg, defactinib 200 mg, gemcitabine 800 mg/m^2, nab-paclitaxel 125 mg/m^2), 0 (avutometinib 3.2 mg, defactinib 200 mg, gemcitabine 800 mg/m^2, nab-paclitaxel 100 mg/m^2), – 1 (avutometinib 2.4 mg, defactinib 200 mg, gemcitabine 800 mg/m^2, nab-paclitaxel 100 mg/m^2), 1a (avutometinib 3.2 mg, defactinib 200 mg, gemcitabine 800 mg/m^2, nab-paclitaxel 125 mg/m^2) and 2a (avutometinib 3.2 mg, defactinib 200 mg, gemcitabine 1000 mg/m^2, nab-paclitaxel 125 mg/m^2). The primary endpoint was ORR [21, 22].

2.3.4 Gynaecological Cancer

The combination of avutometinib and defactinib demonstrated preliminary clinical activity in patients with advanced or recurrent mesonephric or mesonephric-like gynaecological cancer participating in a phase II trial (NCT05787561) [23]. According to interim results from stage 1 ($n = 13$), all patients had a reduction in target lesions, with two patients experiencing a confirmed partial response. The response threshold required to advance to stage 2 was exceeded and patients are being enrolled in the expansion phase (Sect. 2.5) [23].

This single-arm trial with a Simon two-stage design enrolled female patients aged ≥ 18 years with histological confirmation of mesonephric or mesonephric-like cancer of the cervix, ovary or endometrium and measurable disease [23]. All patients received oral avutometinib 3.2 mg twice weekly and oral defactinib 200 mg twice daily for the first 3 weeks of every 4-week cycle. The primary endpoint was confirmed response rate (complete or partial response) [23].

2.4 Adverse Events

Combination therapy with avutometinib and defactinib had a manageable tolerability profile in patients with

recurrent LGSOC participating in the RAMP 201 trial (NCT04625270) [4]. At data cutoff (30 June 2024), the most common (incidence > 20%) treatment-related adverse events (TRAEs) of any grade among patients who received avutometinib plus defactinib ($n = 115$) were nausea (67%), increased creatine phosphokinase (60%), diarrhoea (58%), peripheral oedema (53%), fatigue (44%), vomiting (43%), blurred vision (41%), rash (36%), dermatitis acneiform (34%), increased bilirubin/hyperbilirubinaemia (33%), increased aspartate aminotransferase (31%), dry skin (26%) and anaemia (23%). The most common (incidence > 3%) grade ≥ 3 TRAEs were diarrhoea (8%), anaemia (5%) and dermatitis acneiform (4%). Serious TRAEs occurred in 7% of patients. Most adverse events (AEs) were of mild to moderate severity and were managed with dose interruptions and reductions. AEs led to dose interruption, dose reduction and treatment discontinuation in 80%, 37% and 10% of patients, respectively. There were four deaths, none of which were considered to be related to study treatment [4].

Avutometinib and defactinib combination therapy carries warnings for ocular toxicities, serious skin toxicities, hepatotoxicity, rhabdomyolysis and embryo-foetal toxicity [5]. Dose reduction, treatment interruption or permanent discontinuation may be required for ocular toxicities, serious skin toxicities, hepatotoxicity, rhabdomyolysis and other adverse reactions [5]. Consult local prescribing information for more details.

2.5 Ongoing Clinical Trials

In addition to the ongoing RAMP 201 (NCT04625270), RAMP 205 (NCT05669482) and NCT05787561 trials discussed in Sect. 2.3, a number of other company-sponsored and investigator-initiated clinical trials are currently underway. These include, but are not limited to, the following:

2.5.1 Ovarian Cancer

- RAMP 301 (NCT06072781), a multinational, randomized, open-label, phase III trial evaluating the efficacy and tolerability of avutometinib plus defactinib versus investigator's choice of treatment in patients with recurrent LGSOC with or without a *KRAS* mutation who have progressed on a previous platinum-based therapy [24].
- RAMP 201J (NCT06682572), a multicentre, open-label, phase II trial evaluating the efficacy and tolerability of avutometinib plus defactinib in Japanese patients with molecularly profiled recurrent LGSOC.
- CHAMELEON (NCT06394804), a multicentre, phase II trial evaluating the efficacy and tolerability of the combination of avutometinib, defactinib and letrozole in patients with LGSOC.

2.5.2 Non-Small Cell Lung Cancer

- NCT06495125, a multicentre, phase II trial evaluating the efficacy and tolerability of avutometinib plus defactinib in combination with nivolumab in patients with anti-PD1 refractory *LKB1*-mutant advanced NSCLC.
- RAMP 203 (NCT05074810), a multinational, open-label, phase I/II trial evaluating the efficacy and tolerability of avutometinib in combination with sotorasib, with or without defactinib, in patients with *KRAS G12C*-mutant NSCLC.

2.5.3 Other Solid Tumours

- DURAFAK (NCT05512208), a multicentre, open-label, phase II trial evaluating the efficacy and tolerability of avutometinib plus defactinib in patients with recurrent gynaecological cancers, including endometrioid cancer, mucinous ovarian cancer, high-grade serous ovarian cancer and solid gynaecological cancer.
- DETERMINE (NCT06194929), a multicentre, phase Ib/II trial evaluating the efficacy and tolerability of avutometinib plus defactinib, with or without encorafenib, in patients with brain metastases from cutaneous melanoma.
- NCT06487221, a multicentre, phase II trial evaluating the efficacy and tolerability of avutometinib in combination with defactinib in patients with metastatic/unresectable gastric or gastroesophageal junction carcinoma classified as diffuse, poorly cohesive, signet ring cell or mixed type with progression on at least one line of therapy including platinum/fluorouracil chemotherapy [25].
- NCT06369259, an open-label, phase II trial evaluating the anti-tumour activity of avutometinib in combination with defactinib and cetuximab in patients with unresectable, anti-EGFR-refractory, advanced colorectal cancer.
- NCT06007924, a multicentre, phase II trial evaluating the efficacy and tolerability of avutometinib plus defactinib in RAF dimer-driven radioiodine-refractory differentiated thyroid cancer or anaplastic thyroid cancer.
- 5G-RUBY (NCT06630260), a multicentre, open-label, phase I/II trial evaluating the anti-tumour activity and tolerability of avutometinib plus defactinib, with or without temozolomide, in patients with high-grade malignant brain tumours.

3 Current Status

Avutometinib and defactinib received its first approval on 8 May 2025 in the USA for the treatment of adult patients with *KRAS*-mutated recurrent LGSOC who have received prior systemic therapy [6].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40265-025-02215-8.

Declarations

Funding The preparation of this review was not supported by any external funding.

Authorship and Conflict of Interest During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on the article. Changes resulting from any comments received were made by the authors on the basis of scientific completeness and accuracy. Hannah A. Blair is a salaried employee of Adis International Ltd/Springer Nature and declares no relevant conflicts of interest. All authors contributed to this article and are responsible for its content.

Ethics Approval, Consent to Participate, Consent to Publish, Availability of Data and Material, Code Availability Not applicable.

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