



Tunlametinib: First Approval

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Abstract

Tunlametinib (科露平[®]) is an oral, selective, mitogen-activated protein kinase kinase 1 and 2 (MEK 1/2) inhibitor being developed by Shanghai KeChow Pharma, Inc. for the treatment of solid tumours with RAS and RAF mutations, including melanoma, non-small cell cancer (NSCLC), colorectal cancer (CRC) and neurofibromatosis type 1 (NF1) plexiform neurofibromas. In March 2024, tunlametinib was granted conditional approval in China (based on surrogate endpoints) for use in patients with *NRAS*-mutated advanced melanoma who have failed anti-PD-1/PD-L1 treatment. This article summarizes the milestones in the development of tunlametinib leading to this first approval for the treatment of solid tumours with RAS and RAF mutations.

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Tunlametinib (科露平[®]): Key Points

An oral selective MEK 1/2 inhibitor being developed by Shanghai KeChow Pharma, Inc for the treatment of solid tumours with RAS and RAF mutations, including melanoma, NSCLC, CRC and NF1 plexiform neurofibromas

Received its first approval (conditional approval) on 15 March 2024 in China

Approved for use in patients with *NRAS*-mutated advanced melanoma who have failed anti-PD-1/PD-L1 treatment

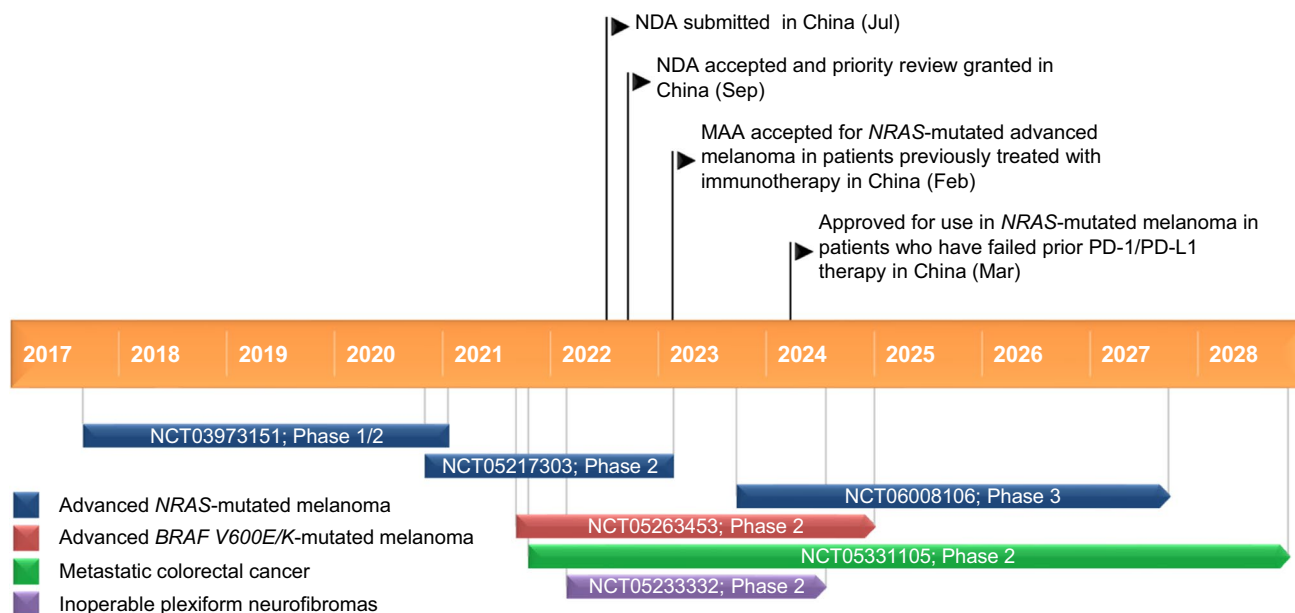
1 Introduction

The mitogen-activated protein kinase (MAPK)/extracellular regulated protein kinases (ERK) signalling pathway (also known as the RAS/RAF/MEK/ERK signalling pathway) controls cell proliferation, survival and differentiation [1, 2]. Within the MAPK/ERK pathway, activated RAF phosphorylates and activates mitogen-activated protein kinase kinase 1 and 2 (MEK 1/2), resulting in downstream phosphorylation and activation of ERK1 and ERK2, which then triggers activation of targets associated with cell transcription, proliferation, differentiation and metabolism [1, 2]. Aberrant activation of the MAPK/ERK signalling pathway due to mutations in *KRAS*, *NRAS* and *BRAF* has been identified in > 20% of solid malignancies, including melanoma, non-small cell lung cancer (NSCLC), pancreatic cancer, and colorectal cancer (CRC) [3–6]; consequently, targeting the MAPK/ERK signalling pathway is a promising therapeutic approach [1, 2]. In the last decade, numerous MEK inhibitors have been investigated for use in tumours with RAS and RAF mutations, but poor exposure and drug toxicity issues have limited drug efficacy (mainly due to limited potency and/or an unfavourable pharmacokinetic profile) and few have been approved by regulatory agencies worldwide [1, 2]. Thus there is a need for MEK inhibitors that have good potency and improved efficacy and toxicity [2].

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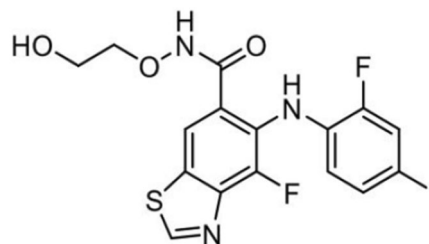
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Key milestones in the development of tunlametinib for use in cancer. *MAA* marketing authority application, *NDA* new drug application

Tunlametinib (科露平®) is an oral, selective MEK1/2 inhibitor being developed by Shanghai KeChow Pharma, Inc. for the treatment of solid tumours with RAS and RAF mutations, including melanoma, non-small cell cancer (NSCLC), colorectal cancer (CRC) and neurofibromatosis type 1 (NF1) plexiform neurofibromas [7–9]. In March 2024, tunlametinib was granted conditional approval in China (based on surrogate endpoints) for use in adult patients with *NRAS*-mutated advanced melanoma who have failed anti-PD-1/PD-L1 treatment [7, 8]. Confirmation that the patient's tumour sample carries *NRAS* mutations using a validated detection method is required before starting treatment with tunlametinib. An independent third-party designated by Shanghai KeChow Pharma, Inc should conduct an audit using the investigational companion diagnostic test to confirm that the patient is carrying the *NRAS* mutation and can continue to take the drug. The recommended dose of tunlametinib is 12 mg twice daily (approximately 12 h apart) with or without food. A missed dose can be taken provided if it is 8 h or more before the next dose; if the time to the next dose is < 8 h, the missed dose should not be taken [9]. Warnings and precautions related to tunlametinib treatment include decreased left ventricular ejection fraction (LVEF; baseline LVEF should be higher than the lower limit of normal and LVEF should be checked regularly during

treatment), skin toxicity, ocular toxicity, interstitial lung disease, gastrointestinal reactions and increased blood creatine phosphokinase (CPK). Dose reductions, treatment interruption or treatment discontinuation may be required to manage decreased LVEF (including symptomatic congestive heart failure), ocular toxicity, pneumonia, rash, increased blood CPK and other grade 2–4 adverse reactions that are intolerable. Tunlametinib should be used with caution in patients with impaired liver function or with moderate/severe renal impairment. Pregnant women should not take tunlametinib and effective contraceptive measures should be taken by men and by women of childbearing potential during tunlametinib treatment and for 30 days after the last dose. Breastfeeding is not advised during tunlametinib treatment and within 30 days of the last dose [9].



Chemical structure of tunlametinib

2 Scientific Summary

2.1 Pharmacodynamics

Tunlametinib inhibits MEK 1/2 kinase activity, which blocks downstream ERK signalling pathways, inhibiting the ERK protein in tumour cells, inducing cell cycle arrest at the G0/G1 phase and inducing tumour cell apoptosis [9]. In cell-free enzyme assays, tunlametinib at 10 $\mu\text{mol/L}$ showed a high selectivity for MEK1 (complete inhibition; no inhibition of numerous other kinases tested) and significant inhibitory activity (IC_{50} 1.9 nM) against MEK1/MAP2K1(h) kinase [2]. Tunlametinib showed 18.5-fold greater inhibitory activity against MEK1/MAP2K1(h) kinase compared with binimetinib (IC_{50} 12.1 vs 223.7 nM) [2]. In vitro, tunlametinib inhibited cell proliferation (IC_{50} 0.67–59.89 nM) in RAS- or RAF-mutated melanoma, colon, lung cancer and myeloma cell lines, but had minimal effect (IC_{50} 252.04 to > 1000 nM) on the proliferation of RAS-mutated LOX and RAF-mutated PANC-1 tumour cell lines, RAS/RAF wild-type tumour cell lines and normal cell lines [2, 9]. The inhibitory activity of tunlametinib in cell lines with RAS or RAF mutations was similar to that of trametinib (GSK212) and 10- to 100-fold greater than that of selumetinib (AZD6244) [2]. ERK phosphorylation levels of *BRAF*-mutated melanoma A375 cells decreased dose-dependently after treatment with tunlametinib 0.1–100 nmol/L and was almost completely blocked with tunlametinib 100 nmol/L. Tunlametinib dose-dependently increased the proportion of G0/G1 phase in A375 cells and induced apoptosis of COLO 205 cells in vitro [2]. In vivo, administration of tunlametinib 1–9 mg/kg once daily dose-dependently inhibited tumour growth and ERK phosphorylation in *BRAF/KRAS*-mutated melanoma and CRC or *BRAF/KRAS* wild type cell line-derived xenograft models, and tunlametinib 1 mg/kg once daily significantly (tumour growth inhibition > 79%; $p < 0.05$ vs vehicle) inhibited tumour growth in four *BRAF*-mutated CRC patient-derived xenograft models [2]. The combination of tunlametinib with *BRAF*, *KRAS*^{G12C} and *SHP2* inhibitors or docetaxel showed a synergistic inhibitory effect on tumour cell proliferation in *BRAF/KRAS*-mutated melanoma, CRC or NSCLC cell lines in vitro and tumour growth in *BRAF/KRAS*-mutated cell line-derived xenograft models [2].

2.2 Pharmacokinetics

The pharmacokinetics of tunlametinib in patients with melanoma were generally dose-proportional after administration of single and multiple oral doses of tunlametinib 0.5–18 mg twice daily in a phase 1 trial (NCT03973151) [9,

10]. Tunlametinib was rapidly absorbed after oral administration, and peak concentrations were reached at a median 1 h. Steady state was achieved after 8 days' administration of tunlametinib 12 mg twice daily; at steady state, C_{max} was 122 ng/mL, C_{trough} was 8.87 ng/mL and AUC_{τ} was 360 ng·h/mL. The accumulation ratio was 1.66. Food has no clinically relevant effect on the absorption of tunlametinib [9]. Tunlametinib is highly bound (99.7%) to human plasma proteins. The mean V_d was ≈ 1940 L. Tunlametinib is primarily metabolized in the liver by CYP2C9 and to a lesser extent by CYP2C8 and CYP3A4. The mean CL/F was ≈ 51.9 L/h and the mean $t_{1/2}$ was ≈ 26.2 h. Tunlametinib is excreted via faeces (59.6% of a total dose), urine (28.3%) and the lungs (2.8%) [9].

In vitro, tunlametinib is not an inhibitor of CYP3A4, CYP1A2, CYP2D6, CYP2C8 and CYP2B6. While tunlametinib is an inhibitor of CYP2C9 and CYP2C19, the effect is not clinically significant [9]. Tunlametinib is not a substrate of the transporters OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K, or of P-gp and BCRP in vitro and is not an inhibitor of OCT2 and MATE2-K. While tunlametinib is an inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, MATE1, P-gp and BCRP in vitro, the effect is not clinically significant [9]. Clinical drug-drug interaction studies have not been formally conducted for tunlametinib; however, co-administration with inhibitors and inducers of CYP2C9 should be avoided [9].

2.3 Therapeutic Trials

Tunlametinib showed good efficacy in adult patients with advanced *NRAS*-mutated melanoma in a multicentre open label phase 2 trial (NCT05217303) conducted in China [11]. At data cut-off (19 February 2023; median follow-up 12.8 months), objective response rate (ORR) assessed by independent radiological review committee (IRRC) [primary endpoint] in patients receiving tunlametinib 12 mg twice daily ($n = 95$; full analysis set) was 35.8% [all partial response (PR)]. Median duration of response (DOR) was 6.1 months, median progression-free survival (PFS) was 4.2 months, disease control rate (DCR) was 72.6% and median overall survival (OS) was 13.7 months. In the subgroup of patients who had previously received anti-PD1/PD-L1 therapy ($n = 64$), ORR was 40.6%, median DOR was 6.3 months, median PFS was 4.1 months, DCR was 70.3% and median OS was 12.3 months [9, 11]. In patients who had not been treated with immunotherapy previously ($n = 31$), ORR was 25.8% [11]. Overall, tumor response and survival outcomes were sustained at a median follow-up of 24.4 months [12]. Eligible patients had histologically or cytologically confirmed unresectable stage III or IV melanoma, with documented *NRAS* mutations at baseline. In

patients with central laboratory-confirmed *NRAS* mutations ($n = 95$), *NRAS* mutations were observed at Q61 (78.9%), G12 (15.8%) and G13 (5.3%). Median age at baseline was 58 years, most patients had stage IV melanoma (85.3%) and most (73.7%) had received prior systemic treatment (chemotherapy, immunotherapy, or both). Treatment was administered in 21-day cycles and continued until unacceptable toxicity, disease progression, consent withdrawal, death, or when clinical benefits were outweighed by the risks of treatment. If patients experienced treatment-related adverse events (TRAEs) requiring dose modification, dose reductions (one-level: 9 mg twice daily; two-level: 6 mg twice daily) were recommended. At data cut-off, 4 patients remained on treatment [11].

In a phase 1 dose-escalation and dose expansion trial (NCT03973151) of tunlametinib in 42 adult patients with advanced *NRAS*-mutated melanoma conducted in China, PR was only seen in the tunlametinib 9, 12, 15 and 18 mg twice daily groups [13]. In the cohort of patients ($n = 15$) receiving tunlametinib 12 mg twice daily confirmed ORR was 26.7%, DCR was 86.7%, median DOR was 2.9 months and median PFS was 3.6 months patients. Eligible patients had histologically or cytologically confirmed

unresectable stage III or IV melanoma, with documented *NRAS* mutations at baseline tested by centralized laboratories. Median age at baseline was 56 years and most patients had stage IV melanoma ($n = 37$). Tunlametinib 0.5–18 mg was administered twice daily in the dose-escalation phase and 12 mg twice daily in the dose-expansion phase [13].

In a phase 1 trial (NCT03781219) of tunlametinib plus vemurafenib in adult patients with advanced *BRAF V600*-mutated solid tumours conducted in China [14], at data cutoff (4 November 2022), ORR was 60.6%, median DOR was 11.3 months and median PFS was 11.7 months in the subgroup of patients with NSCLC ($n = 33$); in the subgroup of patients with mCRC ($n = 24$), ORR was 25.0%, median DOR was 5.5 months and median PFS was 6.2 months [14]. Eligible patients had progressed on or were intolerant to previous standard treatment. Patients were administered twice daily tunlametinib 0.5, 6, 9, 12 or 15 mg plus twice daily vemurafenib 960 mg in 21-day cycles in the dose-escalation phase, and twice daily tunlametinib 12 mg plus vemurafenib 960 mg, tunlametinib 12 mg plus vemurafenib 720 mg or tunlametinib 9 mg plus vemurafenib 720 mg in the dose-expansion phase [14].

Features and properties of tunlametinib

Alternative names	科露平®; HL-085
Class	Aniline compounds; antineoplastics; benzothiazoles; fluorobenzenes; iodobenzenes; small molecules
Mechanism of action	MAP kinase kinase 1/2 inhibitor
Route of administration	Oral
Pharmacodynamics	High selectivity for MEK1 (complete inhibition); IC_{50} 1.9 nM against MEK1/MAP2K1(h) kinase In vitro, ↓ tumour cell proliferation (IC_{50} 0.67–59.89 nM), ↑ the proportion of G0/G1 phase, induced apoptosis in RAS- or RAF-mutated melanoma, colon, lung cancer and myeloma cell lines; minimal effect ($IC_{50} > 1000$ nM) on RAS or RAF wild-type tumour and normal cell lines ↓ ERK phosphorylation, tumour cell growth in vitro and in vivo Synergistic inhibition with BRAF, KRAS ^{G12C} and SHP2 inhibitors or docetaxel on <i>BRAF/KRAS</i> -mutated tumour cell proliferation in vitro and in vivo
Pharmacokinetics (steady state)	Mean C_{max} 122 ng/mL, mean C_{trough} 8.87 ng/mL, median T_{max} 1 h, mean AUC_t 360 ng·h/mL, accumulation ratio 1.66, mean $Vd \approx 1940$ L, mean $CL/F \approx 51.9$ L/h, mean $t_{1/2} \approx 26.2$ h
Adverse events	
Most frequent (any grade)	↑ blood CPK, diarrhoea, facial oedema, peripheral oedema, increased AST, rash, ↑ blood lactate dehydrogenase, anaemia, ↑ ALT, asthenia, hypoalbuminemia, ↑ blood CPK MB, dermatitis acneiform
Occasional (any grade)	left ventricular dysfunction, interstitial lung disease, gastrointestinal bleeding, ocular events
Serious	Rash, hypoalbuminemia, pyrexia, peripheral oedema
ATC codes	
WHO ATC code	L01 (Antineoplastic Agents)
EphMRA ATC code	L1 (Antineoplastics)
Chemical name	4-fluoro-5-(2-fluoro-4-iodoanilino)-N-(2-hydroxyethoxy)-1,3-benzothiazole-6-carboxamide

↑ increase(s), ↓ decrease(s)

Key clinical trials of tunlametinib (Shanghai KeChow Pharma, Inc.)

Drug(s)	Indication	Phase	Status	Location(s)	Identifier
Tunlametinib, combination chemotherapy	Advanced <i>NRAS</i> -mutated melanoma	3	Enrolling	China	NCT06008106; HL-085-301
Tunlametinib	Advanced <i>NRAS</i> -mutated melanoma	2	Completed	China	NCT05217303; HL-085-101-II
Tunlametinib, vemurafenib	Advanced <i>BRAF V600E/K</i> mutated melanoma	2	Ongoing	China	NCT05263453; HL-085-102-II-01
Tunlametinib	Advanced <i>NRAS</i> -mutated melanoma	1/2	Completed	China	NCT03973151; HL-085-101
Tunlametinib, vemurafenib	Metastatic colorectal cancer	2	Ongoing	China	NCT05233332, HL-085-201
Tunlametinib, vemurafenib	<i>BRAF V600E</i> -mutated metastatic colorectal cancer	3	Recruiting	China	NCT06008119; HL-085-304
Tunlametinib, vemurafenib	<i>BRAF V600E</i> -mutated non-small cell lung cancer	2	Recruiting	China	NCT05900219; HL-085-203
Tunlametinib	NF1 and inoperable plexiform neurofibromas	2	Ongoing	China	NCT05331105; HL-085-106-II
Tunlametinib, vemurafenib	Advanced <i>BRAF V600</i> -mutated solid tumours	1	Ongoing	China	NCT03781219; HL-085-102
Tunlametinib	Advanced solid tumours	1	Completed	USA	NCT04683354; HL-085-US-102

2.4 Adverse Events

In the phase 2 trial (NCT05217303) of tunlametinib in adult patients with advanced *NRAS*-mutated melanoma, 100% of patients ($n = 100$) experienced a treatment-related adverse event (TRAE) of any grade; the incidence of TRAEs \geq grade 3 was 68% [11, 13]. The most common adverse reactions ($\geq 15\%$) included diarrhoea [74% (any grade); 4% (\geq grade 3)], facial oedema (64%; 0%), peripheral oedema (62%; 4%), rash (53%; 5%), anaemia (39%; 6%), asthenia (36%; 5%), hypoalbuminemia (34%; 0%), dermatitis acneiform (24%; 7%), vomiting (19%; 0%), hypokalaemia (19%; 4%), pruritus (18%; 0%), palmar-plantar erythrodysesthesia syndrome (17%; 0%), pyrexia (17%; 0%), hypocalcaemia (16%; 0%), increased weight (16%; 1%) and stomatitis (15%; 2%) [9]. The most common laboratory abnormalities (incidence $\geq 15\%$) that worsened from baseline included increased blood CPK (91%; 38%), increased AST (60%; 2%), increased blood lactate dehydrogenase (47%; 0%), increased ALT (40%; 0%), increased blood CPK MB (31%; 0%), increased γ GT (16%; 0%) and increased blood myoglobin (16%; 0%) [9]. Serious TRAEs were reported in 26% of patients, the most common being rash (3%), hypoalbuminemia (3%), pyrexia (2%) and peripheral oedema (2%) [11]. TRAEs led to treatment interruption in 73% of patients, treatment interruption and dose reduction in 50% of patients, dose reduction in 37% of patients and treatment discontinuation in 9% of patients [9, 11].

In the phase 1 trial (NCT03781219) of tunlametinib plus vemurafenib in patients with advanced *BRAF V600*-mutated solid tumours, at cut-off date ($n = 72$ evaluable patients) the most common adverse events were CPK elevation, anaemia and rash [14].

2.5 Ongoing Clinical Trials

A phase 3 trial comparing tunlametinib with investigator-selected chemotherapy in patients with advanced *NRAS*-mutated melanoma who have previously received immunotherapy (NCT06008106) has commenced recruiting [15]. Other ongoing trials, all of which are being conducted in China, are: a phase 2 trial of tunlametinib plus vemurafenib in patients with advanced *BRAF V600E/K*-mutated melanoma (NCT05263453); a phase 2 trial of tunlametinib plus vemurafenib in patients with mCRC (NCT05233332); a phase 2 trial of tunlametinib in patients with NF1 and inoperable plexiform neurofibromas (NCT05331105); and a phase 1 trial of tunlametinib plus vemurafenib in patients with advanced *BRAF V600*-mutated solid tumours (NCT03781219). A phase 3 trial of tunlametinib plus vemurafenib in patients with *BRAF V600E*-mutated mCRC (NCT06008119) and a phase 2 trial of tunlametinib plus vemurafenib in patients with *BRAF V600E*-mutated NSCLC (NCT05900219) are recruiting patients.

3 Current Status

Tunlmetinib received its first approval on 15 March 2024 for the treatment of patients with *NRAS*-mutated advanced melanoma who have failed anti-PD-1/PD-L1 therapy in China [7, 8].

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40265-024-02072-x>.

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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