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Recent Advances in MEK Inhibitors Targeting ERK Signaling in Gastric Cancer: Genetic Alterations, Clinical Trials, and Resistance Mechanisms

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ABSTRACT

Gastric cancer continues to be one of the leading causes of cancer-related deaths around the globe, with a rising incidence in Asia. The mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) signaling pathway engages in regulating cell proliferation, survival, differentiation and its aberration is involved in gastric tumorigenesis. This review provides a comprehensive knowledge on MEK1/2 inhibitors key upstream regulators of ERK and their therapeutics relevance in gastric cancer. We summarize the mutation profiles of MAP2K1, MAP2K2, KRAS, and BRAF genes, and explore the pharmacodynamics, clinical efficacy, and limitations of several MEK inhibitors, including trametinib, selumetinib, and refametinib. Particular emphasis is placed on resistance mechanisms both intrinsic and acquired highlighting adaptive pathway activations such as PI3K/AKT and EGFR/HER2 signaling. Additionally, combination therapies involving MEK inhibitors with STAT3, DNMT1, or SHP2 inhibitors are discussed for their potential to overcome drug resistance. This review also elucidates the impact of MEK inhibition on ERK protein dynamics, cell cycle arrest, and apoptosis in gastric tumorigenesis. Overall, targeting the ERK axis through MEK inhibition emerges as a promising therapeutic strategy, especially in genetically defined subsets of patients. Future advances depend on precision oncology approaches integrating genomic profiling and rational drug combinations.

Keywords: Gastric cancer, MAPK pathway, ERK, Cancer therapeutics, MEK inhibitors, Drug resistance.

INTRODUCTION

Cancer is one of the most fatal diseases worldwide, characterized by uncontrolled cell growth, proliferation, invasion, and metastasis. In 2022, around ~20 million new cases and ~9.8 million cancer-related deaths were reported. The incidence and mortality distribution of the top six cancer types are given in Fig. 1 for both sexes (https://gco.iarc.fr/today). These cancers account for ~45% of new cases and ~50% of cancer deaths, and stomach cancer is at fifth position in both scenarios.

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The incidence of gastric/stomach cancer cases is ~9.7 lakhs worldwide, and the most number of cases are in Asia, i.e., 71.4%, and mortality is ~6.60 lakhs worldwide, and most number of deaths, 70.1% are also reported in Asia region (Bray et al., 2024). In India, the incidence and mortality rate of gastric cancer cases are 9.3% and 12.5% respectively (https://gco.iarc.fr/today). It is expected that by the year 2030, the new cases of gastric cancer will increase by 22.8% worldwide and 26.0% in India (Fig.1). The estimated number of deaths will also increase by 23.4% worldwide and 26.1% in India (Morgan et al., 2022; Yang et al., 2023; Bray et al., 2024).

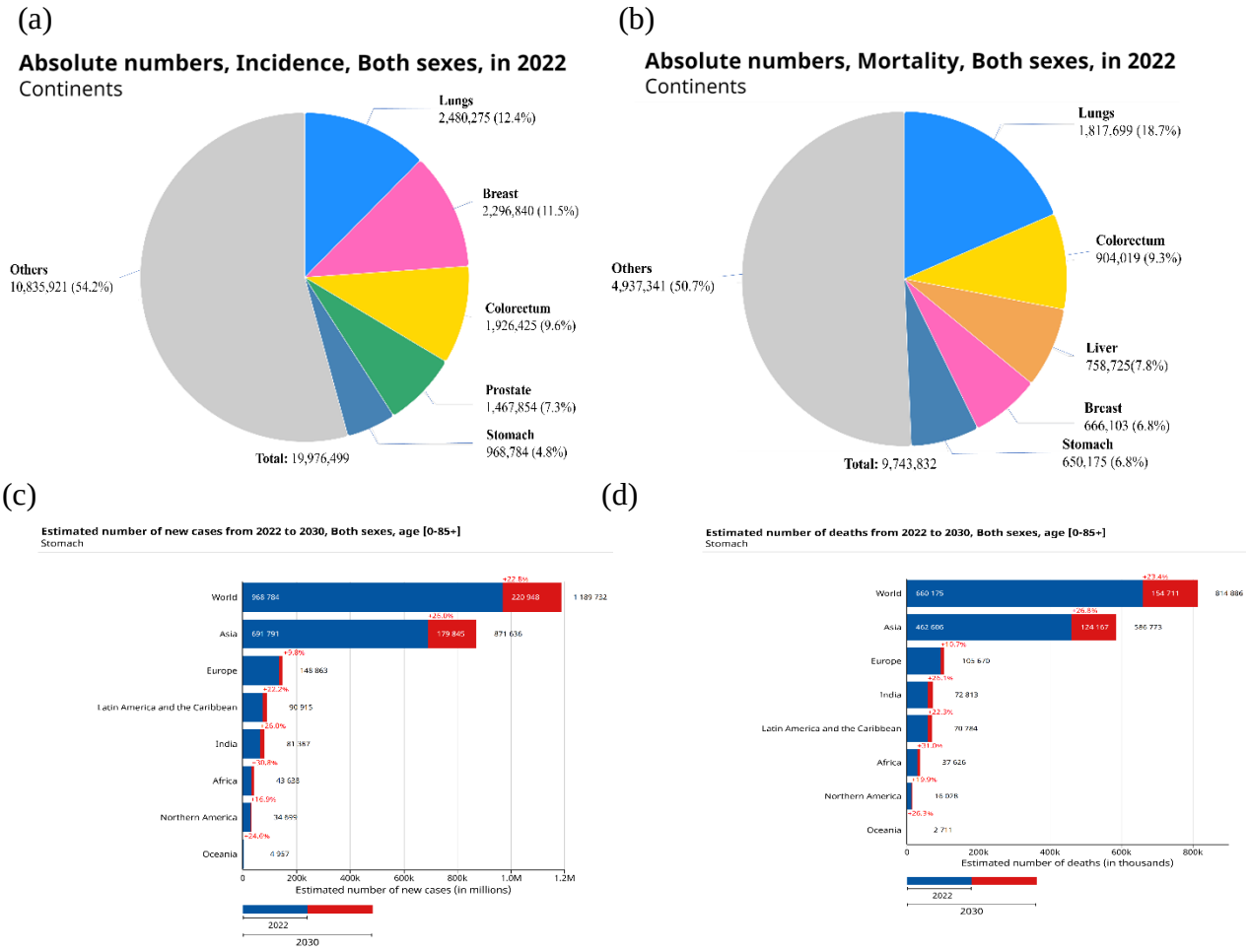

Fig 1. Incidence (a) and mortality (b) of all the cancers worldwide. Estimated number of new cases from 2022 to 2030 (c) and estimated number of deaths from 2022 to 2030 (d). Source: GLOBOCAN 2022 (https://gco.iarc.fr/).

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GENE ALTERATION PROFILES OF MAP2K1 (MEK1), MAP2K2 (MEK2), KRAS AND BRAF GENE IN GASTRIC CANCER

Mutation is the major cause of constitutive RAS/RAF/MEK/ERK pathway activation. The gene alteration frequency of the MAP2K1 (MEK1), MAP2K2 (MEK2) KRAS, and BRAF genes in 13 different types of gastric cancer studies are shown in figure 2 (Fig 2). This study contains 3621 total number of samples and the alterations include mutation, copy number variations, amplification, and deep deletion in the MAP2K1 (MEK1), MAP2K2 (MEK2), KRAS, and BRAF genes. This study includes 3621 total number of samples. Gene alteration was reported in 1% of the MAP2K1 (MEK1) gene, 1% of the MAP2K2 (MEK2) gene, 13% in the KRAS gene, and 2% in the BRAF gene out of 3621 total sample studied. (Fig. 2). Each MAP2K1, MAP2K2, KRAS, and BRAF mutation profile in gastric cancer is shown in figure 3. Mutation involved are given in Table 1.

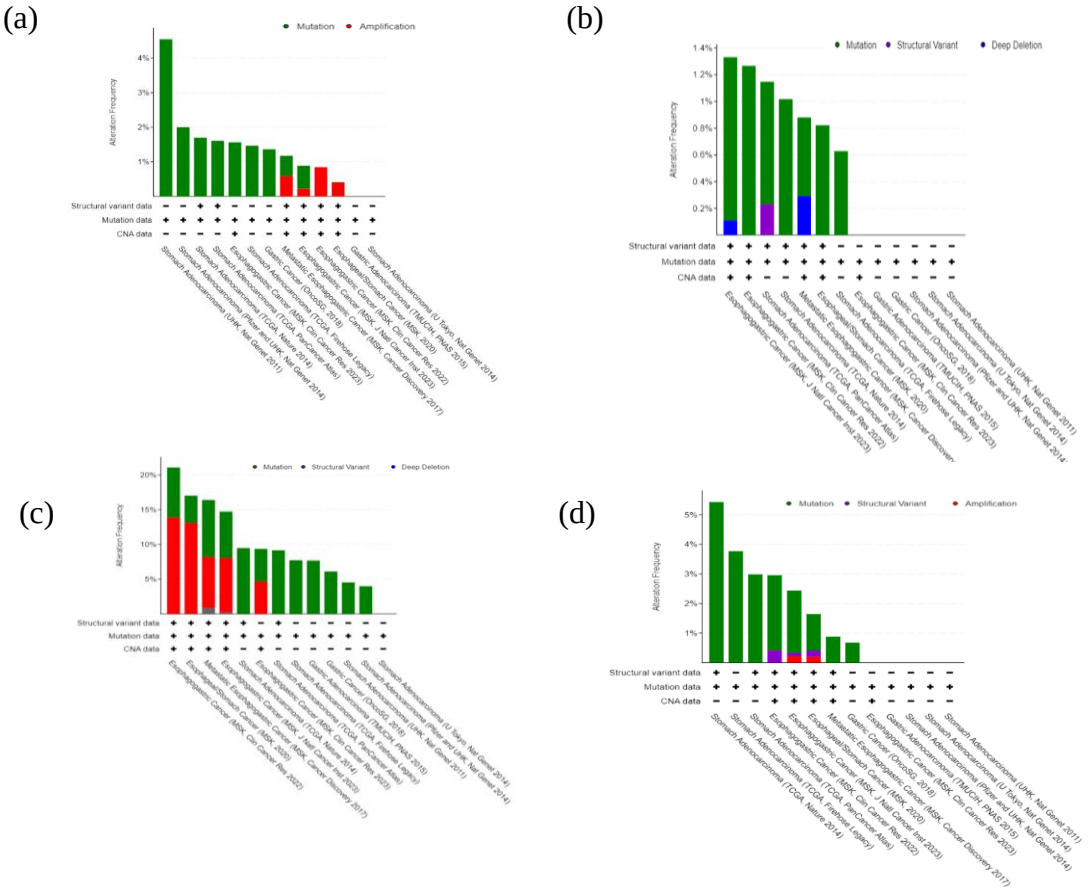

Fig 2. Fig represents the gene alteration profiles of (a). MAP2K1 (MEK1), (b). MAP2K2 (MEK2), (c) KRAS, (d). BRAF. Mutation (Green), Amplifications (Red) Structural variant (Purple) Deep deletion (Blue). Data adapted from the cbioportal.org

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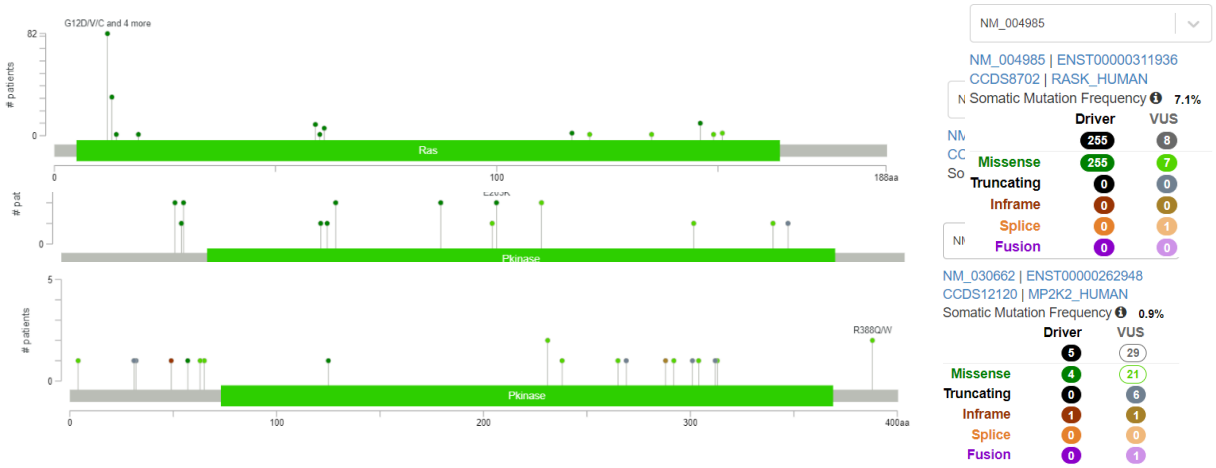
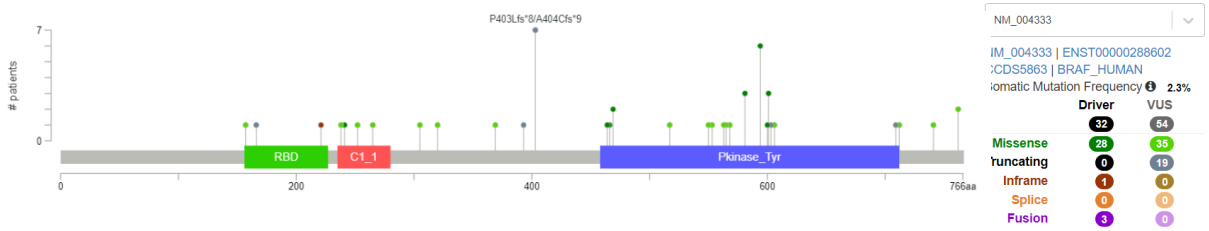
.a). MAP2K1 (MEK1) mutations in gastric cancer

b). MAP2K2 (MEK2) mutations in gastric cancer



c). K-RAS mutation in gastric cancer



d). B-RAF mutation in gastric cancer

Fig 3. Representation of particular mutation at sites a) MAP2K1 gene, b) MAP2K2 gene, c) KRAS gene and d) BRAF gene. Data adapted from the cbioportal.org

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Table 1. Mutation status in gastric cancer types. Data adapted from the cbioportal.org

Cancer Type	MEK1 mutations	MEK2 mutations	K-Ras mutations	B-Raf mutations
Stomach Adenocarcinoma	F53L, K57T, K57N, F53L, C121S, G128V, G128S, L177M, V224M, L332V, R201C, A32Gfs*16	C125S, F57V, R388W, Q49_K63del, A32Gfs*16	A146T, R149K, Q61H, R135T, A59T, A59E R135T, A59E, G12D, R151T, G12S, G12V, V14I, A146V, A59T, K117N, X151_splice	A762V, A305V, G563C, E741D, H568D, A320T, A712T, V369A, T241M, D594E, D594V, N581S, D594N, K601E, K601T, A404Cfs*9, P403Lfs*8, G393*, R603*
Tubular Stomach Adenocarcinoma	E203K, C121S, K340Afs*2	H292R, P269Rfs*58	A59T, G12C, G12D	-
Papillary Stomach Adenocarcinoma	-	-	G12D	-
Esophagogastric Adenocarcinoma	P124Q	R231C	G12C, G12V, G12L, P121H, Q61H	BRAF intragenic
Poorly Differentiated Carcinoma of the Stomach	R295K	R231C, R303Afs*24	A146V, A146T, R295K, G12R	D594G, D594N
Intestinal Type Stomach Adenocarcinoma	G128V	-	A59T G12D, G12S, G12V	A320T, A712T, A762V
Diffuse Type Stomach Adenocarcinoma	-	-	G12D, G12V, G13D, Q61H	A305V
Signet Ring Cell Carcinoma of the Stomach	-	-	G12D, G13D	G469A, G265R
Mucinous Stomach Adenocarcinoma	-	-	G12D, G13D	H568D, A404Cfs*9
Adenocarcinoma of the Gastroesophageal Junction	-	-	G12D, G13D, L19F, Q61H	K601E, L553R, R252Q, Q709Pfs*7

RAS/RAF/MEK/ERK SIGNALLING PATHWAYS

The MAPK signaling pathway plays a vital role in the invasion and metastasis of gastric cancer. It is typically involved in critical cellular processes like cell proliferation, death, differentiation, migration, invasion and responds to extracellular stimuli (Montagut & Settleman, 2009). However, when abnormally regulated, the MAPK pathway can contribute to the occurrence and progression of cancer, including gastric cancer. Despite many studies investigating the relationship between MAPK signaling and cancer metastasis and invasion, there has been less focus on its roles in gastric

cancer specifically. An insight into this relationship is crucial for developing individualized therapeutic strategies and biomarkers for early diagnosis of gastric cancer (Wong et al., 2018; Barbosa et al., 2021).

The activation of ERK1/2, which is a part of the MAPK signaling pathway, involves a cascade of proteins that communicates signals from surface receptor of the cell to the nucleus affecting gene expression. ERK signaling pathway begins when cell surface receptors, particularly receptor tyrosine kinases, detect external signals and subsequently activate adapter proteins like GRB2. The adapter protein recruits SOS, a guanine nucleotide exchange factor that activates the small GTPase Ras. Upon activation, Ras triggers Raf's kinase activity, which subsequently phosphorylates and activates MEK. MEK then completes this signaling cascade by phosphorylating and activating ERK. This sequential mechanism allows cells to transform external stimuli into internal cellular reactions. In the cytoplasm, ERK targets multiple downstream effectors, including kinases like RSK (Ribosomal S6 Kinase) and MNK (MAP kinase-interacting serine/threonine-protein kinase). These target proteins are vital for regulating protein synthesis, gene control, and cell survival. ERK also modulates enzymes such as cPLA2, which are essential for lipid signaling pathways and inflammatory processes. Additionally, ERK influences the cellular architecture and morphology by phosphorylating proteins that regulate cell adhesion and migration, as well as key regulatory molecules involved in metabolism and other cellular activities. Through these diverse targets, ERK allows cells to adapt rapidly and dynamically to environmental stimuli within the cytoplasmic environment. (F. Liu et al., 2018; Bahar et al., 2023; Song et al., 2023).

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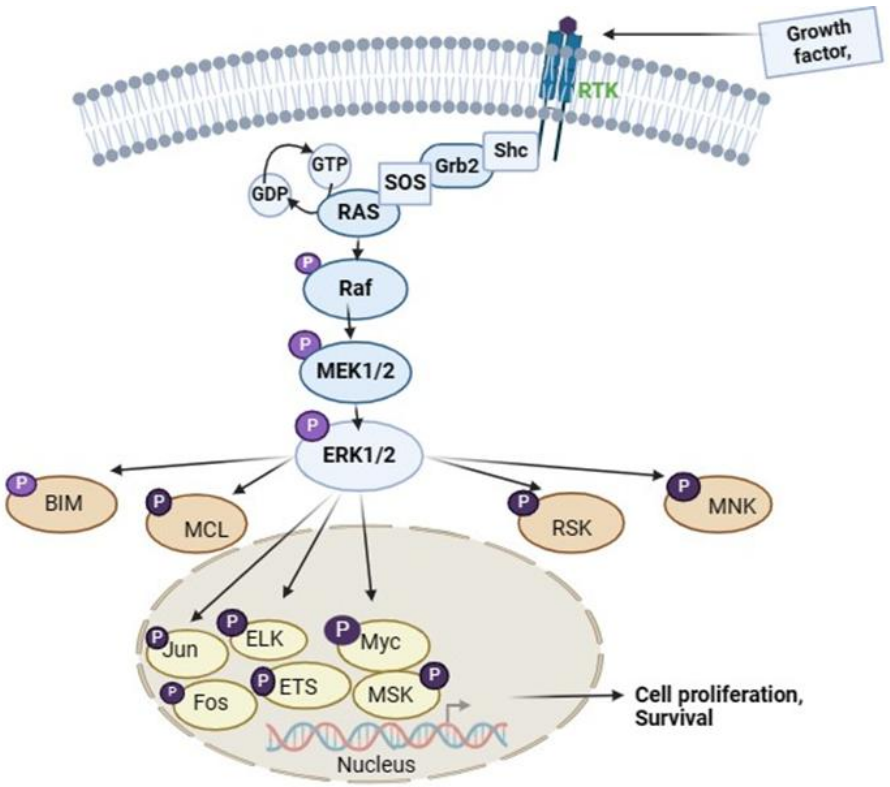

Fig 4. Pathway elucidating the activation of MAPK and downstream effectors of ERK in the cytoplasm and nucleus which can phosphorylate key regulatory proteins involved in cell metabolism and other cellular processes (L. Liu et al., 2010).

In the nucleus, ERK phosphorylates various transcription factors including Elk-1, c-Jun, c-Fos, and ATF2, which are critical for gene expression regulation. Through phosphorylation of these transcription factors, ERK enhances the transcription of genes involved in cellular proliferation, differentiation, and survival (Fig 4). ERK also influences other nuclear proteins like MSK1/2, which modify histones and reorganize chromatin structure to affect gene expression programs. These nuclear functions are essential for maintaining long-term cellular responses to external signals mediated by the ERK signaling pathway (Gonzalez-Hormazabal et al., 2018; Mezynski et al., 2021).

MEK INHIBITORS IN THERAPEUTICS

MEK inhibitors have made significant strides in cancer therapy, progressing through pre-clinical, clinical, and approved stages. In the pre-clinical setting, numerous MEK inhibitors have exhibited promising activity in cellular and animal models (Cheng & Tian, 2017). These inhibitors selectively

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target and inhibit MEK1/2, essential components of the MAPK/ERK signaling pathway (P.-K. Wu & Park, 2015). For instance, several MEK inhibitors demonstrated growth inhibition in cell lines and tumor growth suppression in mouse xenograft studies (Table 2) (De La Puente et al., 2016). Moving into the clinical stage, various MEK inhibitors have undergone clinical trials to determine their toxicity and potency in cancer patients. These trials have explored MEK inhibitors as monotherapy or in combination with other anticancer agents (Ram et al., 2023). Examples include CI-1040, PD0325901, Selumetinib, MEK162, AZD8330, and TAK-733 (Cheng & Tian, 2017). Pimasertib has demonstrated promising drug absorption and distribution characteristics along with effective target suppression in patients diagnosed with solid tumors. However, certain MEK inhibitors like CI-1040 have faced difficulties due to limited water solubility and rapid clearance from the body (Table 3) (Ram et al., 2023).

Multiple MEK inhibitors have gained regulatory approval from FDA for treating specific cancer types (Ram et al., 2023). The approved medications include trametinib, cobimetinib, selumetinib, and binimetinib. Both trametinib and cobimetinib are authorized for treating melanoma patients with BRAF V600E/K mutations, with cobimetinib being administered alongside vemurafenib (Cheng & Tian, 2017). Selumetinib is approved for pediatric patients with neurofibromatosis type 1 and inoperable plexiform neurofibromas, and binimetinib is also approved for BRAF V600E/K-mutated melanoma (Table 4). These approvals underscore the clinical benefits of MEK inhibition in certain cancer types, and ongoing research aims to broaden their applications in cancer therapy (McCubrey et al., 2012; Della Pepa et al., 2015).

Table 3. MEK inhibitors in pre-clinical trials.

MEK Inhibitor	Target	Mode Of Action	Research Progress
CInQ-03	MEK1/2	Decrease ERK phosphorylation (D. J. Kim et al., 2013)	Undergoing preclinical study
G-573	MEK	Inhibition of p-ERK (Choo et al., 2010)	Undergoing preclinical study
PD184161	MEK	Inhibits phosphorylation of ERK1/2 (Yung et al., 2004; Klein et al., 2006)	Undergoing preclinical study

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PD318088	MEK1	Non-ATP competitive MEK1 Inhibitor (S. Han et al., 2005)	Undergoing preclinical study
PD98059	MEK1	Non-ATP competitive MEK1 Inhibitor (Dudley et al., 1995; Cerioni et al., 2003; Di Paola et al., 2010)	Undergoing preclinical study
RO5068760	MEK1	Non-ATP competitive MEK1/2 Inhibitor (Daouti et al., 2010; L. Lee et al., 2010)	Undergoing preclinical study
U0126	MEK1/2	Non-ATP competitive MEK1/2 Inhibitor (Dokladda et al., 2005)	Undergoing preclinical study
SL327	MEK1/2	Suppress phosphorylation of MEK1/2 (W. Wang et al., 2017)	Undergoing preclinical study

Table 4. Approved drugs as per the official website of the U.S food and drug administration. Source: https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases

BRAF/MEK inhibitor combinations approved by FDA	**Treatment for Cancer type**	**Manufacturer**
Zelboraf (Vemurafenib) with Cotellic (Cobimetinib)	Melanoma whose tumors have *BRAF* V600E and V600K mutation.	Roche Molecular Systems, Inc.
Braftovi (Encorafenib) with Mektovi (Binimetinib)		bioMérieux Inc.
Tecentriq (atezolizumab) with Cotellic (cobimetinib) and Zelboraf (vemurafenib)		Foundation Medicine, Inc.
Tafinlar (dabrafenib) with Mekinist (Trametinib)	Non-Small Cell Lung Cancer (NSCLC) Tissue with BRAF V600E mutations	Life Technologies Corporation
Braftovi (Encorafenib) with Mektovi (Binimetinib)		Foundation Medicine, Inc.
Tafinlar (dabrafenib) with Mekinist (Trametinib)	Anaplastic Thyroid Cancer (ATC) – Tissue with *BRAF* V600E mutations	Life Technologies Corporation

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STUDY OF MEK INHIBITORS IN GASTRIC CANCER PATIENTS

Selumetinib may be beneficial for patients with advanced gastric cancer who have a high MEK expression, particularly those with KRAS mutations or amplifications. Examination of MEK profile status and its correlation with various genetic alterations in two cohorts of patients with advanced gastric cancer, one cohort from Korea and another from Vietnam, helped to develop a diagnostic tool indicative of RAS pathway activity, which identifies patients who could benefit from MEK inhibition as a treatment strategy. MEK signature was revealing in reacting to selumetinib in gastric cancer cell lines despite the KRAS mutation status. However, it is essential to note that the study did not directly assess the treatment response to selumetinib in patients of Korean cohort that had 125 patients, of which 98 were KRAS wild type and 27 had KRAS alterations, including 10 with KRAS amplifications and 17 with KRAS mutation. MEK signature is high in the altered KRAS group. However, in 8 altered PIK3CA cases, none of the cases were related to a high MEK signature. Among 93 patients in the Vietnamese cohort, 7 were BRAF mutants, and 13 had PIK3CA alteration. The Vietnamese cohort found a higher MEK signature in the altered KRAS group than in the wild type (Ahn et al., 2017). For the effective treatment of KRAS-amplified gastroesophageal cancers, a combination of MEK and SHP2 inhibitors, GSK1120212 and SHP099, respectively, can be employed. It helps to overcome potential resistance to MEK inhibition and more effectively block the KRAS-driven signaling pathways that contribute to cancer cell growth and survival. The study was conducted in a Japanese cohort with adenocarcinoma, in which 30 patients had KRAS amplification and 97 subjects were without KRAS amplification. Five-year survival analysis was done using the Kaplan-Meier method. The KRAS-amplified group showed poor prognosis as compared to the non-KRAS-amplified group (Wong et al., 2018).

MEK INHIBITORS IN OTHER CANCERS TYPE WITH RESPECT TO PATIENT DATA

The HGF/c-MET signaling pathway has been observed to play a key driver in the aggressive and treatment resistance in pancreatic cancer. The activation of this pathway triggers several downstream signaling processes, such as the MAPK/ERK, PI3K/AKT, and STAT3 pathways. These pathways contribute to cancer cell invasion, proliferation, migration and avoidance of cell death, all of which are crucial for tumor growth and metastasis. The use of trametinib, a MEK

inhibitor, disrupts the RAS pathway one of the downstream pathways from HGF/c-MET activation which is frequently mutated and constitutively activated in pancreatic cancer. For the treatment of pancreatic cancer with a combination of stereotactic body radiotherapy with pembrolizumab and trametinib, a phase II was carried out with an open-label, randomized control layout, which enrolled 170 patients with locally recurrent pancreatic ductal adenocarcinoma post-surgery (J. Kim et al., 2024). These patients had tumors with KRAS mutation and characterized by programmed death-ligand 1. One group of patients were treated with a stereotactic body radiation therapy (SBRT) along with pembrolizumab (an immune checkpoint blocker) and trametinib (a MEK blocker), while the second group received SBRT plus gemcitabine (a chemotherapy agent). Patients treated with the SBRT, pembrolizumab, and trametinib combination survived a median of 14.9 months, compared to 12.8 months for those receiving SBRT with gemcitabine. This triple-therapy approach shows promise for patients with locally recurring pancreatic cancer following surgical intervention and was recommended for phase 3 clinical trials for further evaluation (J. Kim et al., 2024). For patients diagnosed with neurofibromatosis type 1 (NF1) who have inoperable plexiform neurofibromas (PN), selumetinib has proven to be a valuable therapeutic option. The response rate reached 68.0%, demonstrating positive outcomes in most treated patients. Additionally, 96.8% of patients achieved disease control, meaning their tumors either shrank or remained stable. Remarkably, only 1.4% of patients experienced disease progression, showing that tumor advancement during treatment was uncommon (Y. Han et al., 2024). In treating metastatic uveal melanoma, selumetinib is employed either alone or combined with the chemotherapy drug paclitaxel. A study involving 77 chemotherapy-naive patients with metastatic uveal melanoma compared continuous selumetinib monotherapy against continuous or intermittent selumetinib plus paclitaxel combinations. While the combination approach extended progression-free survival, overall survival rates remained comparable between single-drug and combination treatments (Sacco et al., 2024).

A clinical study was conducted to examine the safety and effectiveness of combination therapy of refametinib with gemcitabine for advanced pancreatic cancer treatment. The initial phase focused on determining safe dosing levels with 20 enrolled patients receiving both drugs. The subsequent phase evaluated treatment effectiveness using 80 patients who received 50mg of refametinib twice

daily while monitoring safety parameters. The refametinib-gemcitabine combination proved to be well-accepted by patients with advanced pancreatic cancer (Van Laethem et al., 2017). Since RAS mutations are associated with poorer prognoses and may not respond well to certain therapies, exploring combination treatments like refametinib and sorafenib (a medication already approved for HCC) could potentially offer a more effective treatment strategy for RAS-mutant unresectable or metastatic hepatocellular carcinoma (Lim et al., 2018). A combination of drugs often works synergistically or additively, attacking cancer cells through various pathways. Refametinib inhibits the MEK pathway, which is downstream of RAS in the signaling cascade, while sorafenib targets multiple kinases involved in tumor growth and angiogenesis. Combining refametinib with sorafenib might increase the overall therapeutic efficacy compared to either agent alone, possibly leading to better clinical outcomes for patients with RAS-mutated hepatocellular carcinoma (Parhi et al., 2012). In another study, two cohorts comprised patients with RAS mutations where the first cohort(n=16) of patients received refametinib monotherapy while the second cohort(n=16) of patients received a combination therapy of refametinib plus sorafenib. In this subset of patients with *RAS*-mutated hepatocellular carcinoma, combining refametinib with sorafenib lead to a synergistic effect (Lim et al., 2018).

RESISTANCE TO MEK INHIBITORS

The development of acquired drug resistance is the main obstacle to kinase inhibitor-based targeted therapy. The following are examples of mechanisms of resistance: i) Amplification of target kinase resulting in partial target inhibition; ii) secondary mutation in target kinase preventing drug binding; and iii) phenomenon of bypass signaling pathway because cancer cells can activate secondary survival kinase (Garraway & Jänne, 2012). Mutation is one of the causes of acquired resistance against the receptor tyrosine kinase (RTK). Alternative signaling pathways (bypass pathways) can be activated to maintain cancer cell survival and proliferation even if the targeted RTK is blocked/inhibited. Upregulation of Bcl-2 protein family such as Bcl-2 and Bcl-xL protein levels regulates apoptosis. Increased levels of these proteins in cancer cells can confer resistance to TKIs by inhibiting cell death. These mechanisms can lead to inherent and acquired resistance after the initial treatment response (Jin et al., 2017). In one of the studies, gastric cancer cell line, Okajima, was found to have a novel MEK1 mutation (S72G) which was identified and classified as a novel

activating mutation, which can lead to the growth and survival of cancer cells independent of the normal regulatory mechanisms that control cell proliferation. These mutations conferred the ability to activate the MAPK pathway constitutively and became the cause of resistance against MEK inhibitors (Sogabe et al., 2014).

Research by Choi and colleagues revealed that KRAS-mutated gastric cancer cells (SNU601) initially responded well to MEK inhibitors but gradually developed resistance. The resistance mechanism was traced to increased c-MET activity, which remains unaffected by MEK inhibition. These resistant cells reliant on PI3K/AKT/mTOR signaling pathways for survival and showed heightened vulnerability to dual PI3K/mTOR inhibitors (Choi et al., 2018). In another study, Tsubaki and team examined resistance mechanisms by developing colorectal cancer cell lines resistant to PD0325901 and trametinib. They confirmed resistance by measuring IC50 values, which were substantially higher in resistant compared to parent cell lines. Investigation of the PI3KCA gene revealed M1043V mutation, a known activator of AKT signaling. Treatment with perifosine (an AKT inhibitor) successfully reversed resistance to both MEK inhibitors by blocking AKT activation, indicating that excessive AKT activity drives MEK inhibitor resistance and can be countered with AKT inhibition (Tsubaki et al., 2019). Resistant malignant peripheral nerve sheath tumors (MPNST) cell lines were created using trametinib, TAK-733, and selumetinib. The resistant cells expressed elevated levels of LAMA4 gene expression and its receptors (ITGA1 and ITGB1). This LAMA4/ITGB1 pathway upregulation, along with downstream FAK/SRC protein overexpression, contributed to resistance by reactivating MAPK signaling. Combined FAK/SRC and MEK inhibition proved more effective than individual treatments in reducing cell viability (Gu et al., 2022). Mizukami et. al., observed that MEK1-mutated gastric cancer cells (OCUM-1) showed increased EGFR and HER2 signaling following trametinib treatment. External EGF exposure activated EGFR and HER2 signals, leading to trametinib resistance (Mizukami et al., 2015a). Increased expression of ERBB3 and ERBB2 proteins were observed in selumetinib treated KRAS-mutated lung and colon cancers. MEK inhibition caused MYC-dependent ERBB3 upregulation, resulting in intrinsic drug resistance and ERK reactivation. It is suggested that combining EGFR

and ERBB2 inhibitors (like afatinib) with selumetinib could overcome resistance by reducing pro-apoptotic protein phosphorylation (Sun et al., 2014).

MEK INHIBITORS ON ERK PROTEIN DYNAMICS IN GASTRIC CANCER

ERK is a central regulator in the MAPK/ERK signaling pathway that drives cancer cell progression by promoting proliferation, survival, resistance to apoptosis, and metastatic spread. It also assists in the remodelling of cell metabolism to support continuous cancer cell growth and division. Due to its pivotal role in multiple cellular processes essential for tumor development and maintenance, ERK is often hyperactivated in cancer, making it a potential target for therapeutic intervention. MEK inhibitors function by specifically blocking the MEK enzymes, which are upstream activators of ERK in the MAPK/ERK signaling pathway. By inhibiting MEK, these drugs reduce ERK phosphorylation and activation, leading to a decrease in ERK-mediated signaling. Monotherapy of MEK inhibitors has been rather limited as it does not sufficiently restrain tumor growth in gastric cancer due to the reactivation of alternative signalling pathways. Combined inhibition of JAK2/STAT3 and MEK pathways using fedratinib and trametinib respectively proved a more effective treatment than single-pathway inhibition in suppressing gastrointestinal cancer cell proliferation and inducing cell death both *in vitro* and animal studies (X. Wang et al., 2021). Another study demonstrated synergistic effects when combining AZD6244 (MEK inhibitor) with gefitinib (EGFR inhibitor) in wild-type EGFR gastric cancer cells. This combination significantly inhibited both EGFR-mediated AKT activation and MEK-mediated ERK activation in 6 of 9 tested cell lines. Though, 3 cell lines with developed MET/FGFR was unresponsive to the combined administration. This indicates that the expression and amplification of other receptor tyrosine kinases also play a role in determining the sensitivity of gastric cancer cells to the combination of AZD6244 and gefitinib (Yoon et al., 2009). Gastric cancer cells with the KRAS mutation exhibited selective sensitivity to MEK inhibition compared to cells with both KRAS and PI3K mutations, or those with wild-type KRAS alleles. For KRAS-mutated cell lines, this sensitivity to MEK inhibition suggests that these cancer cells may be more dependent on the MEK/ERK pathway for their growth and survival, indicating a potential "addiction" to these signaling pathways. Therefore, inhibiting MEK could have a pronounced impact on cell viability and might lead to lower ERK activation levels in

KRAS-mutated cell lines as the signal transduction through this pathway is disrupted (Yoon et al., 2009).

MEK inhibition on gastric cancers that are driven by oncogenic MEK1 mutations develops resistance due to upregulation of EGFR and HER2 signals, which can reactivate ERK1/2 signaling pathways. Using OCUM-1 cells, it is shown that combining trametinib with lapatinib could overcome drug resistance. While trametinib initially suppressed ERK1/2 phosphorylation, subsequent EGFR and HER2 activation led to ERK1/2 reactivation. Lapatinib prevented this reactivation by inhibiting EGFR and HER2 signals, enhancing trametinib's growth-inhibitory effects. The use of lapatinib in combination with trametinib is shown to obstruct this resistance by inhibiting the activation of EGFR and HER2 signals, thereby preventing the reactivation of ERK1/2 and elevating the growth inhibitory response of trametinib on OCUM-1 gastric cancer cell line (Mizukami et al., 2015b). Gannon and colleagues tested trametinib on three MAP2K1-mutated cell lines and found it most effective against NCI-H1437 lung adenocarcinoma cells compared to other lung cancer cell lines. *In vivo*, trametinib treatment resulted in little to no tumor growth in mice with NCI-H1437 xenografts, whereas A549 harbouring KRAS mutation survived regardless of the treatment. Similarly, the colorectal cancer cell line SNU-C1 displayed strong sensitivity to trametinib, comparable to the response seen in NCI-H1437 cells. The gastric cancer cell line OCUM-1, with a mutation within the inhibitory alpha helix of MAP2K1, was reported to be sensitive to selumetinib as in comparison to wild-type MAP2K1 gastric cancer cells (Gannon et al., 2016).

TRAIL treatment can lead to the activation of the ERK1/2 pathway. However, when the ERK1/2 pathway is inhibited by a MEK inhibitor, such as U0126, it promotes cell death through increased activation of caspases, a drop in mitochondrial membrane potential, and the downregulation of anti-apoptotic proteins like XIAP, cIAP2, and Mcl-1. Consequently, the inhibition of ERK1/2 signaling by a MEK inhibitor can sensitize gastric cancer cells to TRAIL-induced apoptosis, essentially suggesting that the MEK inhibitor treatment would suppress the phosphorylation (activation) of ERK1/2, enhancing the apoptotic effect of TRAIL on the gastric cancer cells (N. Wu et al., 2021). The inhibition of the MEK using U0126 resulted in the sensitization of gastric cancer cells to

endoplasmic reticulum stress-induced apoptosis, and is linked to the down-regulation of GRP78. By dephosphorylating ERK, the up-regulation of GRP78 is disrupted, which can enhance the apoptotic response to ER stress in gastric cancer cells (Zhang et al., 2009). Inhibition of HGF-mediated cell proliferation and upregulated urokinase plasminogen activator (uPA) expression on gastric cancer cells by PD098059 and SB203580, an MEK and p38 inhibitors suppresses the MAPK pathway proteins, thereby reducing uPA secretion and possibly reduce cancer cell invasion and metastasis (K. H. Lee et al., 2006).

Conclusion

MEK inhibitors show promise as targeted therapies for gastric cancer management, especially in tumors with RAS/RAF mutations or amplification. While preclinical and early clinical studies demonstrate MEK inhibition as potential factor for reducing tumor progression and enhancing apoptosis, monotherapy has limited long-term success due to compensatory signaling and acquired resistance. Combination strategies using MEK inhibitors with other inhibitor targeted agents against proteins like SHP2, EGFR, STAT3, AKT and DNMT1 provide more effective approaches by simultaneously targeting multiple cancer-promoting pathways. MEK inhibitors have shown to modulate ERK protein activity, cell cycle control, and apoptosis induction in both normal and mutated gastric cancer types. However, gastric cancers heterogeneity requires better understanding of molecular subtypes and biomarker-guided treatment selection. Identifying predictive biomarkers and optimizing combination strategies are essential for improving therapeutic effectiveness.

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