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LEADING ARTICLE

The Biology and Clinical Development of MEK Inhibitors for Cancer

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Abstract The mitogen-activated protein kinase kinases (MAPKK) MEK1 and MEK2 are integral members of the MAPK/ERK signaling pathway and are of interest in the development of anti-cancer therapeutics. The MAPK/ERK pathway is dysregulated in more than 30 % of cancers, predominately by mutations in RAS and BRAF proteins, and MEK serves as a potential downstream target for both of these. The biology of MEK inhibition is complex, as the molecule is differentially regulated by upstream RAS or RAF. This has impacted on the past development of MEK inhibitors as treatments for cancer and may be exploited in more rational, molecularly selected drug development plans in the future. The role of MEK in cancer and the mechanism of action of MEK inhibitors is reviewed. Furthermore, MEK inhibitors that are available in standard practice, as well as those most advanced in clinical development, are discussed. Finally, next steps in the development of MEK inhibitors are considered.

Key Points

MEK1 and MEK2 are integral elements of the mitogen-activated protein kinase (MAPK)/ERK pathway and are important molecules for targeted therapy drug development in cancer.

The activity of MEK inhibitors is differentially regulated by upstream activation of RAS as opposed to BRAF, and the activity of MEK inhibitors will be structure dependent.

Trametinib was the first MEK1/2 inhibitor approved for cancer therapy; however, several other MEK inhibitors have demonstrated interesting activity as single agents as well as in combination with other cancer therapies.

1 Introduction

With the development of clinical sequencing platforms for cancer genotyping, the role for oncogene-targeted therapies has grown rapidly. Mutations in multiple growth pathways have been identified and there is a growing list of small molecules that have been successfully developed as targeted therapies for cancer. Here we focus on the role of MEK in cancer biology and review agents in clinical development that target MEK. We further discuss the

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benefits and downsides of combination strategies involving the inhibition of MEK.

2 Role of MEK in Cancer

The mitogen-activated protein kinase (MAPK) pathway plays a critical role in multiple cellular functions and is constitutively activated in a wide range of human cancers. Canonical MAPK signaling results from activation of receptor tyrosine kinases (RTKs) on the cell surface such as the epidermal growth factor receptor, HER kinases, MET and the fibroblast-growth factor receptor [1]. Upon activation of an RTK by a mitogen (growth factors, cytokines, etc.), RTKs generally undergo dimerization and transphosphorylation, leading to their activation. Thereafter, small adaptor proteins, such as SHC, son of sevenless (SOS), and GRB, associate with activated RTKs recruiting guanine nucleotide exchange factors (GEF). At the cell membrane, these GEFs activate RAS GTP-ases (H-, K-, N-RAS) by promoting the exchange of GDP for GTP by RAS [2, 3]. When GTP is bound, RAS-GTP triggers activation signals down multiple growth pathways including MAPK as well as phosphoinositide 3-kinase (PI3K)/AKT and RalGEF-Ral [4, 5]. RAS activity is regulated under physiologic conditions due to an inherent low-level GTP-ase activity of the RAS protein that facilitates a normal exchange of GTP to GDP, eventually extinguishing signaling by RAS GTP.

After RAS activation, RAF kinases (A- B-, C-RAF [RAF-1]) are recruited to the cell membrane in association with RAS [6, 7], are differentially phosphorylated [8], and undergo dissociation from RAF kinase inhibitory protein [9]. RAFs are activated via phosphorylation of homo- or heterodimer RAF complexes [6], and then act as serine/threonine MAPK kinase kinases (MAPKKK), directly activating MAPKK (MEK1/MEK2) [10]. Among RAF isoforms, B-RAF has been associated with a much higher potency for MEK phosphorylation relative to other isoforms. Other MAPKKK proteins also exist and can modulate MEK activity via phosphorylation. Notable examples of this include MAP3K8 (*COT/Tpl2*) and PAK1, which have both been implicated in cancer processes [11].

After MEK activation, MEK acts as an MAPKK via dual-specificity tyrosine and serine/threonine kinase activity on MAPK (ERK1/ERK2) [12]. ERKs are the only known phosphorylation targets of MEKs. The consequences of ERK activation by different MEK isoforms (e.g. MEK1 vs. MEK2) are under investigation; however, potential differences are not yet clearly relevant in the development of MEK inhibitors for cancer therapy. Phosphorylated MAPK/ERK proteins function as serine/threonine kinases, activating many cytoplasmic and nuclear mediators such as kinases, phosphatases, and transcription factors. The activity of signal transduction via RAF-MEK-ERK, and eventual downstream ERK output, is dependent on scaffold proteins notably including the IQGAP family. Of the three IQGAP members, IQGAP1 is understood the best; more than 90 partner molecules have been found that associate with IQGAP1, including many oncogenic proteins [13]. In the context of scaffold support, activated ERK then facilitates multiple cellular processes such as cell proliferation, motility, differentiation, and survival. Examples of downstream ERK targets include cell cycle proteins such as cyclin D, transcription factors such as MYC and FOS, as well as the regulatory protein families SPRY and DUSP, which mediate negative feedback on the MAPK pathway [14, 15].

While canonical signaling through the MAPK pathway appears uni-linear at first glance, feedback regulation of the pathway and cross-talk between MAPK proteins and other pathways, such as PI3K, c-Jun N-terminal kinase (JNK), nuclear factor (NF)-κB, p38, and others, complicate attempts to develop inhibitors of this pathway as anticancer agents [16, 17]. Feedback regulation of the MAPK pathway has recently gained interest due to the development of inhibitors of oncogenic MAPK component proteins such as V600E BRAF. After suppression of oncogenic BRAF, a rebound of ERK activity eventually results in resistance to upstream BRAF inhibition. This has been attributed to relief of BRAF inhibitor-induced physiologic ERK-dependent feedback via SPRY and DUSP activity, reactivation of RTK by ligand binding, increased Ras-GTP, and generation of physiologic RAF dimers that are insensitive to selective V600E BRAF inhibitors [18]. Similar feedback, as well as cross-talk with other pathways, may influence the ability of MEK inhibitors to effectively inhibit their targets as well (Fig. 1).

The importance of the MAPK pathway is emphasized by the recurrent mutations found in RTKs that activate this pathway as well as the specific signaling components that make it up. The MAPK pathway is activated in at least 30 % of human cancers through activating mutations in RAS or BRAF [19]. Of these, aberrant RAS activity plays a major role, with RAS mutations being commonly associated with carcinomas of the pancreas (63–90 %), colon (36–50 %), lung (19–30 %), and melanoma (15–20 %) [20, 21]. Mutations in RAS are frequently found in codons 12, 13, and 61, with variability by RAS isoform and cancer histology [22]. KRAS mutations occur at codon 12 at a frequency of approximately 80 %, while many fewer mutations occur in codon 61. This contrasts with NRAS, where codon 61 is mutated in 60 % of cases, while less than 35 % are mutated at codon 12. Mutation frequency in HRAS is less polarized, with a nearly 50 % split between

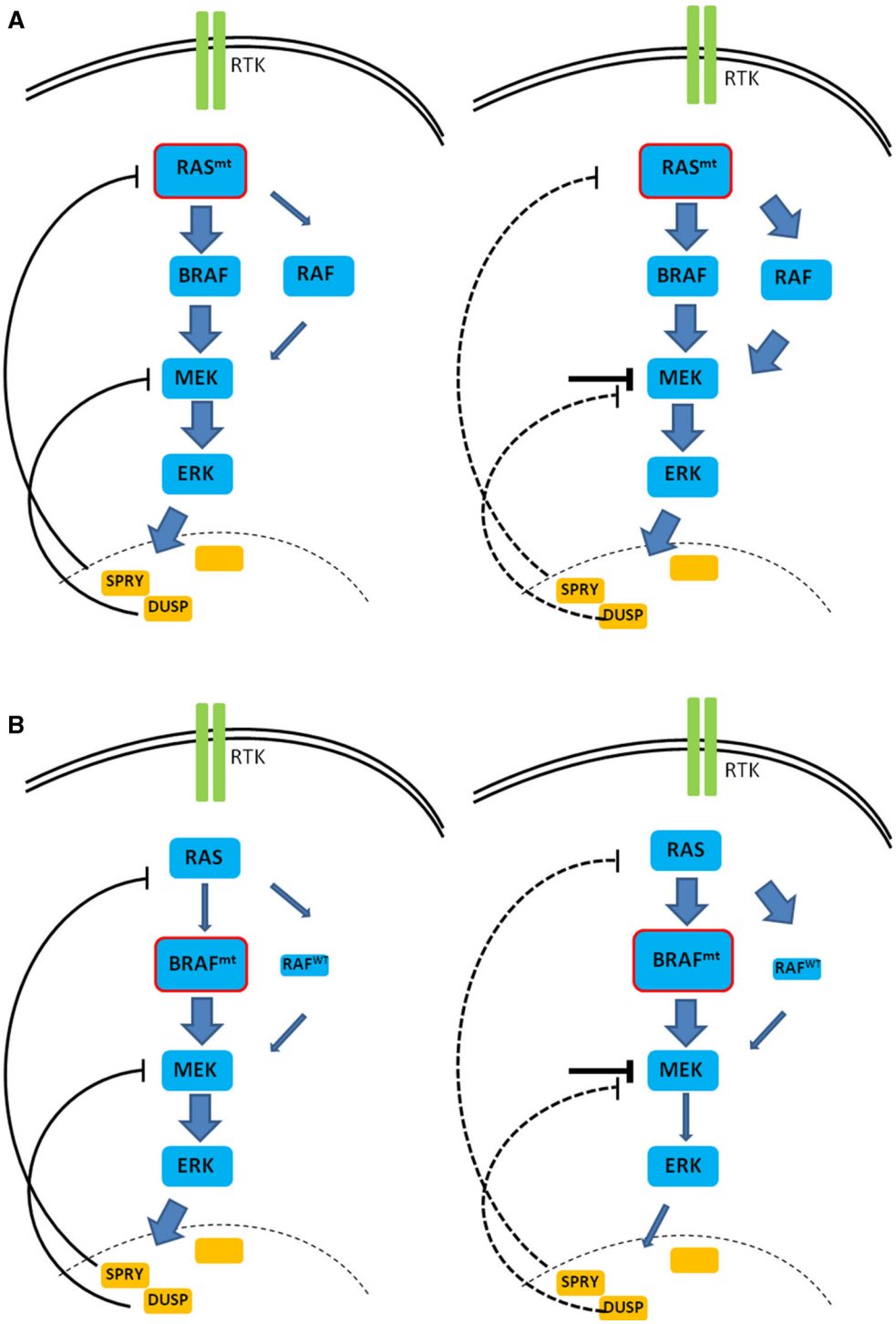

Fig. 1 Inhibition of MEK with a small-molecule inhibitor leads to induction of a feedback loop, via SPRY and DUSP proteins, and reactivation of the MAPK pathway. RAS mutant (**a**) but not BRAF mutant (**b**) tumors exhibit a relative abundance of wild-type RAF proteins. Thus, in RAS mutant tumors, MEK inhibitor-induced feedback mediates activation of wild-type RAF proteins (predominately CRAF) through the formation of CRAF–MEK complexes. This results in feedback phosphorylation of MEK and an eventual increase in downstream MAPK pathway activation. BRAF mutant tumors exhibit a relative lack of wild-type RAF proteins, attenuating feedback-induced ERK reactivation. *$BRAF^{mt}$* mutant BRAF, *RAS^{mt}* mutant RAS, *RTK* receptor tyrosine kinase

codons 12 and 61, though the incidence of HRAS mutation in human cancers is much less frequent than K- and NRAS [21]. The association of some of these mutations with specific cancer types has been determined to be due to particular genetic insults. For example, ionizing radiation skews toward RAS Q61 mutations via the formation of pyrimidine dimers, as seen in cutaneous melanoma [23], whereas chemical carcinogenesis, by tobacco smoking, leads to the development of the DNA adducts and bias toward RAS G12 mutations, as commonly seen in non-small-cell lung cancer (NSCLC) [24].

BRAF is the most frequently mutated protein kinase in human malignancies [25]. Mutations of BRAF have been characterized as approximately 50 % of driver mutations in cutaneous melanoma [25, 26], and several other tumor types such as 10–15 % of colorectal carcinomas [25], 3 %

of NSCLC [27], 3 % of breast cancers [28], 20–50 % of serous ovarian cancers [29–31], and 29–69 % of papillary thyroid cancers [32, 33]. The presence of mutations in BRAF has also been correlated with an unfavorable prognosis [34, 35]. Why BRAF, as opposed to ARAF or CRAF, is recurrently mutated is not clear. However, structural analysis of BRAF suggests that a single mutation in V600 can introduce a stable mutated catalytic site of the BRAF protein, whereas multiple mutations would be predicted to be required for a stable mutated form of ARAF or CRAF [36, 37].

Oncogenic mutations in MEK are much less frequent than RAS or BRAF mutations; ERK mutations have not been described. In NSCLC, mutations in MEK1 (Q56P, K57N, D67N) have been described as constituting less than 1 % of mutations [38]. In melanoma, mutations in MEK1 and MEK2 have been described in up to 8 % of patient samples [39], and appear to co-exist with mutations in RAS and BRAF in some cases [40]. In the setting of anti-cancer treatment directed toward BRAF, MEK mutations as secondary resistance mechanisms have also been observed. After treatment with a selective BRAF inhibitor in V600E BRAF cell lines and patient samples, mutations in MEK1 C121S, F129L, and P124L as well as MEK2 C125S have conferred resistance to inhibitors of both BRAF and MEK [41–44]. Similarly, after a combination strategy of BRAF and MEK inhibitors, a MEK2 Q60P mutation has been observed in a post-treatment patient sample [45].

3 Mechanism of Action of MEK Inhibitors

MEK, the MAPK kinase, is a dual-specific tyrosine and serine/threonine kinase, with ERK being the only known phosphorylation target. Regulation of MEK is via phosphorylation by RAF on serine residues in the catalytic domain at codons 217 and 221 [46]. Stoichiometric analysis of phosphorylation on MEK by RAF confirms that RAF facilitates phosphorylation at both sites with rapid kinetics, ruling out intrinsic autophosphorylation of MEK protein. All RAFs are able to phosphorylate MEKs; however, the degree of MEK activation that results is variable: BRAF is the most potent, followed by CRAF and ARAF [10].

RAF-mediated activation of MEK is differentially regulated in KRAS and BRAF mutant molecular environments, as illustrated by the differential anti-proliferative effects of various MEK inhibitors and especially in the variable activity of the small-molecule MEK inhibitors that have been brought into clinic to date [47–50]. This difference may be partly understood by dissecting the feedback induced via inhibition of the MAPK pathway at different levels (Fig. 1). In the setting of MEK inhibition of KRAS mutant cells, release of feedback on upstream RTK by SPRY and DUSP leads to physiologic signaling through MAPK (due to abundant wild-type RAF), resulting in an increase of phosphorylated MEK [50, 51]. This is in contrast to V600 BRAF mutant cells where the low level of wild-type RAF does not lead to increased MEK phosphorylation, thus allowing persistent suppression of MEK [49, 51]. In KRAS mutant cells, BRAF-CRAF heterodimers have been described as the predominant RAF complexes as depletion of B- or ARAF, but not CRAF, has been linked to MEK phosphorylation after MEK inhibitor treatment, leading to downstream ERK phosphorylation and reactivation of the MAPK pathway with an impact on the anti-neoplastic effect [46, 52].

In this context, the mechanism of MEK inhibition by different small molecules has the potential to determine impact the anti-neoplastic effect (Fig. 2). Two mechanisms for MEK inhibition then become obvious, one being inhibition of RAF phosphorylation activity of MEK or an allosteric association of an inhibitor with MEK impeding the conformational shift induced by phosphorylation on serine 217 and 221. Some data to support such models exist in which MEK inhibitors have been described to directly inhibit RAF phosphorylation of MEK, [49, 53] though the exact mechanism has been unclear.

In a series of elegant modeling and functional experiments, Hatzivassiliou et al. [46] have described a mechanism for differential potency of different MEK inhibitors. Using crystal structures and serine mutagenesis of MEK, they demonstrated that formation of a strong hydrogen bond by higher potency MEK inhibitors to serine 212 of MEK disrupts the hydrogen-bond network between the serine 212 side chain, the activation loop helix, and the glutamate 114 of the α-C helix of the MEK protein. This prevents access of RAF to serine 217 of MEK, decreases phosphorylation, and stabilizes the RAF-MEK complex. RAF-MEK complexes are specific to wild-type RAF as V600 BRAF signals downstream as a monomer [54]. As such, this RAF-MEK stabilization has a more powerful anti-neoplastic effect in KRAS mutant models. This is consistent with previous reports, which have also described an interaction of MEK inhibitors with serine 212 [55, 56]. In V600E BRAF models, a correlation was observed between high MEK inhibitor-binding affinity and MEK inhibition due to the high basal MEK activity in V600 BRAF cancers [46]. This high binding affinity was described as secondary to interactions between a high-affinity binding MEK inhibitor and the α-C helix and catalytic loop of MEK. These data are also consistent with previous experiments demonstrating the differential activation of MEK by V600 BRAF versus wild-type RAF in (B- and CRAF) in KRAS mutant models [57, 58]. These experiments suggest that the chemical structure of different MEK inhibitors could be rationally tailored in their clinical

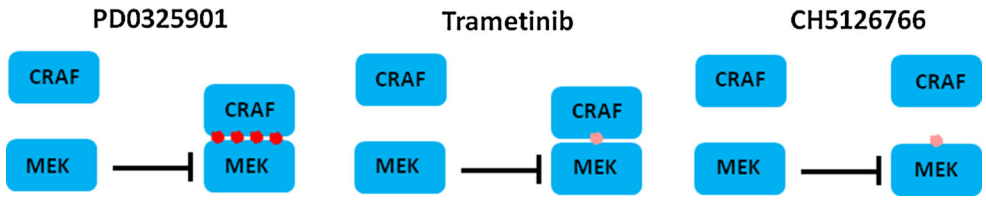

Fig. 2 In KRAS mutant tumors, the MEK inhibitor PD0325901 leads to formation of CRAF–MEK complexes, resulting in MEK phosphorylation and reactivation of the MAPK pathway. Trametinib induces formation of CRAF–MEK complexes, but inhibits MEK phosphorylation by CRAF (by inducing a conformational change in MEK). CH5126766 does not induce relevant CRAF/MEK interaction (by increasing dissociation of MEK from CRAF), thereby preventing phosphorylation of MEK. As a result, both trametinib and CH5126766 lead to more sustained ERK phosphorylation relative to older-generation MEK inhibitors such as PD0325901

benefit as anti-neoplastic activity could be predicted prior to dosing of human subjects based on BRAF or KRAS mutation.

The activity of MEK inhibitors in the setting of mutant RAS has been further elucidated by Lito et al. [59] in the specific setting of KRAS mutant tumors. By administering the MEK inhibitors PD0325901, selumetinib, and refametinib in conjunction with a library of doxycycline-inducible short hairpin RNAs against components of RAS effector pathways, they identified CRAF as the primary mediator of MEK activation in KRAS mutant tumors. Further, after blockade of ERK signaling, as by MEK inhibitor treatment, CRAF was observed to robustly reactivate and mediate rebound in ERK phosphorylation in KRAS as compared with V600E BRAF mutant cells. Using an engineered FLAG-MEK1, they found that treatment with allosteric MEK inhibitors in the setting of RAS mutant cell lines leads to formation of RAF-MEK complexes (predominately CRAF-MEK), whereas this is not the case in BRAF mutant cells. This RAF-MEK complex is then less sensitive to MEK inhibition in terms of reduction of phosphorylated ERK as compared with the free MEK observed in the BRAF mutation setting. Thus, MEK inhibitors activate CRAF by relieving ERK-dependent negative feedback and cause the formation of CRAF-MEK complexes, leading to attenuation of MEK inhibition in KRAS mutant tumors.

Thereafter, Lito et al. [59] show that the efficacy of MEK inhibition in the RAS mutation setting can be modulated by two approaches that are exemplified by newer MEK inhibitors: trametinib and CH5126766, a novel MEK inhibitor. Using surface plasmon resonance to define the dissociation constant of MEK1 with B- or CRAF, they show that trametinib reduces the formation of RAF-MEK complexes. This is despite a proposed similar mechanism of action of trametinib to the older MEK inhibitor PD0325901 in inhibiting the catalytic activity of MEK. Interruption of RAF-MEK complexes then leads to reduction in phosphorylated ERK rebound and prevention of MAPK reactivation. In contrast, CH5126766 does not inhibit the catalytic site of MEK and promotes RAF-MEK complexes, yet also inhibits ERK rebound. Using a structure guided approach, Lito et al. [59] demonstrated that CH5126766 interacts with serine 222 and asparagine 221 on MEK. This prevents MEK phosphorylation by CRAF, leading to MEK inhibitor-bound, dephosphorylated MEK binding to RAF and a subsequent increase of RAF-MEK complexes. Notably, this model of CH5126766 activity is, to some extent, at odds with the model proposed by Hatzivassiliou et al. [46]. The different findings are potentially explained by the fact that Lito et al. [59] completely solved the ternary structure of CH5126766-bound MEK1, as opposed to a limited structure used previously, showing that CH5126766 forms interactions at multiple positions beyond serine 212 of MEK and displaces the activation segment of MEK1. Nevertheless, both of these models will likely be useful in the future development of more potent MEK inhibitors.

4 Approved and Investigational MEK Inhibitors of Significance in Clinical Development

The first generation of MEK1/2 inhibitors, such as CI-1040, demonstrated poor exposure in human subjects, limiting their utility [60]. Second-generation inhibitors, such as PD325901, overcame this problem, but had a poor safety profile, with dose-limiting toxicities such as neurological and eye toxicities [61]. Subsequent generations of MEK inhibitors are now being investigated and appear to be more potent and more tolerable. The agents that are furthest along in clinical development are compared in Table 1 and reviewed here.

4.1 Trametinib Dimethyl Sulfoxide (GSK1120212B, JTP-74057)

4.1.1 Preclinical Data

Trametinib dimethyl sulfoxide (trametinib) is an allosteric, non-ATP competitive inhibitor of both MEK isoforms (half maximal inhibitory concentration [IC_{50}] of MEK1: 0.7,

Table 1 Comparison of MEK inhibitors in development

Drug	IC_{50} MEK1	$T_{½}$	Manufacturer
Trametinib	0.7 ηM	108 h[a]	GlaxoSmithKline
Selumetinib	10 ηM	12 h	AstraZeneca
Cobimetinib	4.2 ηM	49 h[b]	Genentech
Refametinib	19 ηM	12 h	Bayer
Binimetinib	12 ηM	8 h	Novartis
Pimasertib	Undisclosed	Undisclosed	EMD Serono
RO4987655	5.2 ηM	12 h	Roche

IC_{50} half maximal inhibitory concentration, $T_{½}$ half-life

[a] 4.5 days

[b] 2.0 days

MEK2: 0.9 ηM) [49]. Trametinib inhibits phosphorylation by RAF on serine 217 of MEK1 and suppresses phosphorylated ERK. The MEK kinase-specific suppressive activity of trametinib has been broadly validated across a panel of kinases [62]. Trametinib has also shown differential activity against BRAF and NRAS mutants, as compared with wild-type, cell lines and xenografts [62, 63].

4.1.2 Pharmacokinetics and Drug Metabolism

Dose escalation of trametinib resulted in a maximum tolerated dose of 3 mg continuous daily dosing and a recommended phase II dose (RP2D) of 2 mg daily [63]. Fasting pharmacodynamic monitoring demonstrated dose proportionality up to 6 mg daily, with an effective half-life of approximately 4.5 days. Steady state drug levels were reached by day 15 of dosing. At 2 mg daily, on day 15, the mean area under the curve (AUC) over 24 h was 376 ng·h/mL and maximum concentration (C_{max}) was 23 ng/mL. The trough concentrations ranged from a mean of 10.0 to 18.9 ng/mL. Trametinib exhibits non-cytochrome P450 (CYP)-mediated metabolism, primarily via deacetylation and glucuronidation.

4.1.3 Clinical Experience

In a phase I study of 206 patients with advanced solid tumors, a response rate (RR) for trametinib was determined as 10 % [63]. Within a melanoma-only cohort of the study, 97 patients were treated. These included V600E/K BRAF (total of 36 patients, 30 BRAF inhibitor naive), wild-type BRAF (39 patients), BRAF status unknown (six patients), and uveal (16 patients) [64]. An RR of 33 % was determined for BRAF inhibitor-naive patients with median progression-free survival (PFS) of 5.7 months. In BRAF wild-type patients, the RR was 10 %; no responses were observed in patients with uveal melanoma.

The phase III METRIC study subsequently evaluated trametinib as compared with dacarbazine (DTIC) or paclitaxel in patients with melanoma harboring a V600E/K BRAF mutation [65]. A total of 322 patients were randomized in a two-to-one ratio favoring trametinib. Cross-over to trametinib was allowed at progression of disease. A median PFS of 4.8 months was determined in the intention-to-treat population of the trametinib-treated arm versus 1.5 months ($p < 0.001$) for the DTIC- or paclitaxel-treated arm. An early suggestion of improvement in survival with trametinib as compared with chemotherapy was also noted, with an immature hazard ratio (HR) for death of 0.54 (95 % confidence interval [CI] 0.32–0.92, $p = 0.01$) despite cross-over of nearly half of the study population.

Combination therapy with inhibitors of BRAF and MEK via dabrafenib and trametinib has also been explored. In a phase I/II study, doses of 150 mg twice daily of dabrafenib and 2 mg daily of trametinib were found to be the RP2D. Only patients with V600E/K BRAF-mutant melanoma were enrolled, and the phase II portion of the study evaluated doses of 150 and 2 mg (dabrafenib/trametinib) as well as 150 and 1 mg compared with dabrafenib 150 mg twice daily. An improvement in both RR (76 vs. 54 %, $p = 0.03$.) and PFS (9.4 vs. 5.8 months, $p < 0.001$) was observed when dabrafenib and trametinib (150/2) were compared with dabrafenib monotherapy [66]. Additionally, fewer adverse events for the combination were observed when compared with dabrafenib alone, including the development of squamous cell carcinoma (7 vs. 19 %). Of note, pyrexia (71 vs. 26 %) was increased with the combination. Based on this, the drug combination was approved by the US FDA in 2014.

Data from the phase III clinical trial of dabrafenib and trametinib combination therapy versus dabrafenib and placebo are eagerly awaited. In January 2014, a communication from the drug manufacturer GlaxoSmithKline revealed that the primary endpoint of PFS had been met. The median PFS was described as 9.3 months in the dabrafenib and trametinib arm as compared with 8.8 months in the dabrafenib arm (HR 0.75, $p = 0.035$). The combination therapy was described to have an RR of 67 versus 51 % for dabrafenib. Toxicity was similar to the previously described phase II results. Data on overall survival (OS) were not yet mature [67].

4.1.4 Safety Profile

Common toxicities for trametinib were similar across studies, with the dominant events in skin (rash), gastrointestinal (diarrhea), general (edema), and constitutional (fatigue) systems [63–65]. Dose-limiting toxicities were similar but were also observed to include central serous retinopathy. At doses of 2 mg, skin toxicity was observed at a rate of 48–91 % across studies and diarrhea with an incidence of 28–58 %. Other notable toxicities at 2 mg

included cardiac toxicity (ejection fraction reduction or ventricular dysfunction in 3–21 % of patients), ocular toxicity (blurred vision, reversible chorioretinopathy or retinal vein occlusion in 6–21 % of patients), hepatitis (7–15 % of patients), and pneumonitis (<5 %).

4.2 Selumetinib (AZD6244, ARRY-142886)

4.2.1 Preclinical Data

Selumetinib is a selective, ATP non-competitive inhibitor of MEK1 and MEK2 at an IC_{50} of approximately 10–14 ηM [50, 68]. Selumetinib is metabolized to *N*-desmethyl AZD6244, a compound with greater MEK-inhibiting capacity, three times greater downstream ERK suppression and three times greater reduction of cell viability relative to the parent compound. The selectivity of selumetinib for MEK has been documented against a panel of kinases up to concentrations of 10 μM [68]. Selumetinib has anti-tumor activity in BRAF and NRAS mutant preclinical models including cell lines and xenografts from melanoma, pancreatic, lung, colon, breast, and hepatocellular carcinoma [50, 68, 69].

4.2.2 Pharmacokinetics and Drug Metabolism

The initial formulation of selumetinib was an oral suspension requiring reconstitution from free base in an aqueous solution of sulphobutylether β-cyclodextrin (Captisol®) [70]. Despite pharmacological animal studies suggesting good oral bioavailability, absorption was dose limited and drug administration was inconvenient. The drug was therefore reformulated as the hydrogen sulfate salt (AZD6244 Hyd-Sulfate). Subsequent studies suggest dose-proportional bioavailability [71]. Steady-state pharmacokinetic evaluation suggests a C_{max} of approximately 1 h, a half-life of 12 h, and time-independent kinetics based on comparison of day 1 and day 15 drug levels. Excretion of selumetinib is predominantly via the feces, with the majority of metabolites undergoing glucuronidation. Selumetinib is metabolized by CYP, with predominant activity by CYP1A2, 2C19, and 3A4 [72].

4.2.3 Clinical Experience

Phase I experience with selumetinib confirmed RP2D of 100 mg twice daily on a 28-day administration schedule [71]. Selumetinib was then evaluated in a wide range of unselected but MAPK-activated enriched tumors including biliary, colorectal, pancreatic, NSCLC, and melanoma. In patients with melanoma, a similar RR (5.8 %) and PFS (2.5 months) were observed for selumetinib as compared with temozolomide [73]. In patients with BRAF mutant tumors, the RR was 11.1 %, which is not different from that for temozolomide. In patients with pancreatic cancer, OS in the second line after gemcitabine with selumetinib or capcitabine was found to be similar (5.4 months) [74]. In patients with NSCLC who had progressed through at least two prior lines of treatment, selumetinib appeared similar to pemetrexed in terms of median PFS (3 months) [75]. Similarly, in colorectal cancer, PFS of selumetinib was similar to capecitabine (2.8 months) [76]. In patients with biliary tract cancers who had progressed on one line of prior chemotherapy, a single-arm phase II study suggested a RR of 12 % and PFS of 3.7 months [77]. In previously untreated patients with advanced hepatocellular carcinoma, median time to progression was 8 weeks; three transient objective tumor responses were observed [78]. In an open-label phase II study of patients with low-grade serous carcinoma of the ovary, a disease commonly characterized by mutations in BRAF, an RR of 15 % was observed. This was considered useful when compared with the historical standard of care with chemotherapy where responses are very rare [79].

The clinical activity of selumetinib was more impressive when patients were selected based on mutational status of KRAS or BRAF. In melanoma, trials including patients with both BRAF V600E and BRAF wild-type tumors in particular have been pursued. In V600E BRAF patients, a phase II combination of DTIC with and without selumetinib reported a significant improvement in the PFS of patients treated with selumetinib as opposed to placebo: 5.6 months versus 3.0 months ($p = 0.021$), respectively. No improvement in OS was seen, and toxicity consistent with both agents was observed [80]. In a phase II study of selumetinib in BRAF V600E melanoma stratified by phosphorylated AKT (high vs. low), no responses were seen in the AKT high cohort, whereas a 20 % RR was observed in the AKT low cohort [81]. In BRAF wild-type melanoma, the combination of docetaxel with selumetinib had a similar PFS to docetaxel alone (4 months). The RR for the combination was higher, but toxicity was also increased [82]. In uveal melanoma, a chemotherapy-resistant melanoma subtype where mutations in the G-coupled protein receptors *GNAQ* and *GNA11* are found in 85 % of tumors eventually leading to MAPK activation [83], tumor regression and RR were found to be 50 and 15 %, respectively [84]. In KRAS mutant NSCLC, the combination of docetaxel and selumetinib showed a significantly improved RR (37 vs. 0 %, $p < 0.0001$) and PFS (5.3 vs. 2.1 months, $p = 0.014$). OS was not improved, and toxicity was greater with the combination treatment [85].

Finally, selumetinib appears to influence the biology of thyroid cancer. In iodine-refractory papillary thyroid cancer, a median PFS of 32 weeks was observed. In patients with tumors harboringV600E BRAF mutation, PFS was

longer (33 vs. 11 weeks) [86]. Further, a phase II study was performed in which selumetinib was administered with the intent of reversing refractory status to radioiodine in patients with metastatic thyroid cancer [87]. In four of nine patients with BRAF mutant tumors and five of five patients with NRAS mutant tumors, treatment with selumetinib led to increased uptake of iodine-124. In 8 of 12 patients, the dosimetry threshold for radioiodine therapy was reached and, in these eight patients, five patients experienced partial response (PR) and three patients experienced stable disease (SD). All of these patients demonstrated decreased levels of serum thyroglobulin levels, with a mean reduction of 89 %.

4.2.4 Safety Profile

The most common adverse events reported in human trials of selumetinib include fatigue (71 %), nausea (54 %), vomiting (27 %), diarrhea (48.2), edema (43 %), and dyspnea (29 %) [71]. Serious adverse events associated with selumetinib have notably included hypoxia (<1 %), pyrexia (<1 %), and visual disturbances (including serous retinal detachment, 10 %).

4.3 Cobimetinib (GDC-0973, XL518)

4.3.1 Preclinical Data

Cobimetinib is a potent and highly selective allosteric inhibitor of MEK1/2, with a MEK1 IC_{50} of 4.2 ηM [88]. Efficacy in vivo has been demonstrated in BRAF and KRAS mutant cell lines [88, 89]. Cobimetinib showed inhibition of tumor growth in a dose-dependent fashion up to 10 mg/kg in Colo205 (V600E BRAF) tumor xenografts. Pharmacodynamic parameters estimated the 50 % knockdown concentration (KC_{50}) as 0.39 μM. Total concentration required for tumor stasis was 0.05 μM [90]. An estimated IC_{50} after single doses of cobimetinib of phosphorylated ERK in xenograft mice were 0.78 and 0.52 μmol/L in tumor models WM-266-4 and A375, respectively. Multiple dosing increased the IC_{50} [91].

4.3.2 Pharmacokinetics and Drug Metabolism

Cobimetinib has exhibited variable absorption in cancer patients. Absolute bioavailability of cobimetinib is described as 46.2 %, with mean clearance of 11.7 L/h. The half-life of cobimetinib is described as demonstrating dose-proportional and time-independent pharmacokinetics, with a half-life of 2.0 days [92]. A high-fat diet delays absorption with prolonged time to C_{max} (T_{max}) but does not affect exposure or AUC. Overall, oral administration of cobimetinib is not affected by food or gastric pH.

4.3.3 Clinical Experience

In the phase I monotherapy study of cobimetinib, multiple schedules were evaluated with maximum tolerated doses of cobimetinib established as 100 mg 14 days on/14 days off and 60 mg 21 days on/7 days off [93]. No efficacy data of cobimetinib as a single agent in the treatment of human cancers have been released to date. However, cobimetinib has been evaluated in multiple schedules in combination with the V600 BRAF inhibitor vemurafenib [94]. A multi-factorial dose-escalation phase I study was pursued in which vemurafenib at both 720 or 960 mg twice daily was evaluated with cobimetinib at 60, 80, or 100 mg in schedules including 14 days on/14 days off, 21 days on/7 days off, or continuously. Two dose levels were expanded, including vemurafenib 720 mg and 960 mg twice daily plus cobimetinib 60 mg daily 21 days on/7 days off. When assessing benefit in patients previously treated with vemurafenib, a 15 % RR and 43 % SD rate were observed in the expansion arms. The median PFS for patients who had previously progressed on vemurafenib was 2.8 months. In those patients not previously treated with BRAF inhibitors, an RR of 85 and 10 % complete RR was observed. In BRAF inhibitor-untreated patients, the median PFS was not reached at a median follow-up of 10 months.

4.3.4 Safety Profile

Common adverse events associated with single-agent cobimetinib include diarrhea, rash, pruritus, nausea, vomiting, blurred and impaired vision, fatigue, and abdominal pain [93]. In combination with vemurafenib, the most frequent adverse events observed included diarrhea (48 %), non-acneiform rash (35 %), nausea (32 %), photosensitivity/sunburn (29 %), fatigue (28 %), and liver test abnormality (25 %) [94].

4.4 Refametinib (BAY 86-9766, RDEA119)

4.4.1 Preclinical Data

Refametinib is a potent, non-ATP-competitive, highly selective allosteric inhibitor of MEK1 and MEK2 with an IC_{50} of 19 and 47 ηmol/L, respectively. Refametinib has exhibited activity against V600E BRAF mutant cell lines, with 50 % growth inhibition concentration (GI_{50}) values ranging from 40 to 84 ηmol/L, and tumor reduction in A375 melanoma, Colo205 colorectal, and OCIP19 pancreatic carcinoma xenografts [95, 96].

4.4.2 Pharmacokinetics and Drug Metabolism

Refametinib demonstrates a median T_{max} of 2 h with an elimination half-life ($T_{½}$) of 12 h after single dosing. Dose-

proportional C_{max} and steady-state AUC were observed between a 2–100 mg dosing range on a daily schedule [97].

4.4.3 Clinical Experience

The RP2D of refametinib is 100 mg daily [97]. Activity was observed in the phase I study in BRAF and KRAS mutant tumors. Refametinib was also dose escalated in combination with gemcitabine 1,000 mg/m^2 daily, where an RP2D of 30 mg twice per day was determined [98].

4.4.4 Safety Profile

Common treatment-related adverse events include dermatologic toxicity such as primarily acneiform dermatitis (33 %), maculopapular rash (20 %), as well as nausea (29 %), vomiting (26 %), diarrhea (32 %), edema (28 %), and fatigue (26 %) [97].

4.5 Binimetinib (MEK162, ARRY-438162)

4.5.1 Preclinical

Binimetinib inhibits MEK1 and MEK2 in a potent and selective non-ATP competitive manner ($IC_{50} = 12$ ηM). Binimetinib has been documented to inhibit proliferation and reduce tumor volume in KRAS, NRAS, and BRAF mutant as well as non-MAPK activities in vitro and in vivo cell line and tumor models [99].

4.5.2 Pharmacokinetics and Metabolism

The pharmacokinetics of binimetinib are linear, and the drug exhibits moderate oral bioavailability in all species tested. It is highly protein bound in plasma and somewhat more distributed in plasma than blood. Binimetinib has multiple routes of metabolism; however, glucuronidation (predominately through UGT1A1) appears to be most common, with excretion nearly evenly split between urine and feces. Binimetinib has limited effects on relevant CYP enzyme family members. The human $T_{½}$ is approximately 8 h [100].

4.5.3 Clinical Experience

Binimetinib is dosed as 45 or 60 mg daily or twice daily [100, 101]. In a phase II study of binimetinib in melanoma, a 20 % RR was observed for both patients with advanced NRAS mutant and those with BRAF mutant melanoma [101]. The activity of binimetinib is also being evaluated in biliary tract tumors, where a PR and a complete response have been observed. Notably, these patients were found not to harbor RAS- or RAF-activating mutations [102]. Results from a combination phase I/II study of binimetinib with the selective BRAF inhibitor LGX818 have also described a dosing regimen of LGX818 at 450 mg daily with binimetinib 45 mg twice daily as a tolerable regimen. Early indications of efficacy for this combination in melanoma have described an RR of 71 % was seen in patients with non-previously treated BRAF mutant disease as well as 22 % in those who were previously treated with a BRAF inhibitor [103].

4.5.4 Safety

Frequently reported adverse events associated with binimetinib include rash (79 %), diarrhea (32 %), edema (32 %), nausea (43 %), fatigue (29 %), and vomiting (36 %) [102].

4.6 Pimasertib (AS703026, MSC1936369B)

4.6.1 Preclinical

Pimasertib is a selective and potent oral ATP uncompetitive inhibitor of MEK1 and MEK2 that has demonstrated antitumor activity in multiple preclinical models, with special focus on RAS-driven tumors (myeloma, pancreas, lung, colon cancers) [104, 105]. Biomarker analysis of 12-*O*-Tetradecanoylphorbol-I3-acetate-stimulated (MAPK-activated) leukocytes indicated a consistent inhibition of ERK phosphorylation by pimasertib [105]. Further, pimasertib has shown a potential for combination therapy. Studies with PI3K pathway inhibitors or various chemotherapies have shown synergistic activity on tumor growth inhibition [106].

4.6.2 Pharmacokinetics and Metabolism

Human pharmacokinetic data have not been publicly disclosed regarding pimasertib. One study evaluating drug exposure in murine brain and glioblastoma models has suggested a T_{max} in the brain of 1 h associated with a 90 % inhibition of phosphorylated ERK [107].

4.6.3 Clinical Activity

Pimasertib has been evaluated in several RAS and RAF mutant tumors. In a phase I study of pimasertib with 5-fluorouracil (5-FU), irinotecan, and leucovorin, dose-limiting toxicity limited the escalation of pimasertib, and this combination was abandoned [108]. Other combination approaches have included dose escalation with the PI3K/mammalian target of rapamycin (mTOR) inhibitor SAR245409 and gemcitabine. In combination with SAR245409, doses of pimasertib 60 mg twice daily with 70 mg of SAR245409 was determined to be the RP2D, with PRs being observed in patients with KRAS mutant colorectal carcinoma and low-grade ovarian cancer [109].

Activity of pimasertib has also been observed in combination with gemcitabine in pancreatic carcinoma. In combination with gemcitabine, pimasertib 60 mg twice daily, continuous dosing was deemed the RP2D; PR was observed in 19 % of patients, and SD for greater than 3 months was seen in 25 % of patients [110].

4.6.4 Safety

Toxicity has yet to be widely reported; however, common toxicities have been similar to MEK inhibitor class effects and include retinal vein occlusion, ocular events, diarrhea, asthenia, edema, vomiting, and nausea.

4.7 RO4987655

4.7.1 Preclinical

RO4987655 is a potent, highly selective non-ATP-competitive inhibitor of MEK1 and MEK2. Anti-tumor activity in preclinical models of melanoma, pancreatic carcinoma, and colorectal cancer has been observed with RO4987655 as a single agent as well as in combination with chemotherapies such as paclitaxel, gemcitabine, and cisplatin [111].

4.7.2 Pharmacokinetics and Metabolism

RO4987655 demonstrates dose-proportional pharmacokinetics by C_{max} and AUC as well as rapid bioavailability, with a median T_{max} of approximately 1 h (range 0.5–2) [112]. The human mean terminal $T_{½}$ was demonstrated as 12 h with an effective $T_{½}$ of 9 h. RO4987655 demonstrates biphasic elimination with multiple routes of elimination; however, renal elimination is minimal. The major metabolite of RO4987655 is a ring-open structure, although oxidative metabolites are also observed.

4.7.3 Clinical Activity

RO4987655 has been evaluated in several expansion arms of the phase I dose-escalation study including melanoma, NSCLC, and colorectal carcinoma [113]. Among patients with melanoma, four of 18 (24 %) BRAF mutant and four of 20 (20 %) BRAF WT had a response, with PR as best response in these cohorts. Among patients with KRAS mutant NSCLC, two of 18 patients had response (all PR), while none of the 18 patients with KRAS mutant colorectal carcinoma had a response.

4.7.4 Safety

Toxicities observed with RO4987655 have been similar to those described with other MEK inhibitors [113]. Common toxicities have included those that were skin related (rash and acneiform dermatitis), gastrointestinal disorders (nausea, vomiting, diarrhea), ocular (serous retinal detachment and blurred vision), and general (peripheral edema and asthenia). The majority of grade 3–4 adverse events included asymptomatic increase of creatine phosphokinase (23 %), rash (16 %), diarrhea (8 %), folliculitis (7 %), super-infected dermatitis (1 %), and serous retinal detachment (7 %).

5 Next Steps for MEK Inhibitors

With the approval of trametinib, MEK inhibition has entered the clinical area as a standard of care option. Multiple studies are ongoing with MEK inhibitors as single agents (Table 2). Beyond V600 BRAF, other melanoma subtypes may also be sensitive enough to MEK monotherapy to justify approval of MEK inhibitors for clinical practice. In other molecular subsets, such as RAS mutant histologies, this question is more open.

A robust preclinical literature suggests that combining MEK inhibition may be additive or synergistic with other treatments. While monotherapy with MEK inhibition does have interesting activity in several diseases, combination strategies with other treatment approaches such as chemotherapy, targeted therapy, and immunotherapy also appear promising. Table 3 describes ongoing combination trials with MEK inhibitors. To date, the development of these approaches has been limited by toxicity, and this highlights an important difference between MEK inhibition and V600 BRAF inhibition. Mutation of BRAF at V600 generates a new enzyme target for drug development. This tumor-specific mutation facilitates a wider 'therapeutic window', allowing administration of a much higher dosage of BRAF inhibition prior to the development of dose-limiting toxicity [114]. This is in contrast to MEK inhibition, which targets the physiologic MAPKK proteins on which nearly all cells depend to some degree. As such, the therapeutic window for MEK inhibition is much smaller than for V600 BRAF and limits dose escalation.

This difference in mutant versus physiologic protein targets manifests particularly in the setting of combination therapy. For reasons that have been well described previously [19, 54], combination approaches of V600 BRAF and MEK inhibition are synergistic and reduce the toxicity of BRAF inhibition alone [66]. However, synergy is not necessarily expected with other combinations (e.g. MEK inhibitor plus PI3K, AKT inhibitor or chemotherapy, etc.). This has borne out in phase I studies where it has not been possible to optimally dose escalate MEK inhibitors with other drugs and the observed efficacy has been limited [115, 116].

Table 2 Selection of MEK inhibitor monotherapy studies

Phase	Name of drug	Disease indication	ClinialTrials.gov number	Sponsor
I	Trametinib	Hepatic dysfunction	NCT02070549	NCI
I	Selumetinib	QTc interval in healthy male volunteer	NCT02056392	AstraZeneca
I	Selumetinib	Hepatic dysfunction	NCT02063230	AstraZeneca
I	Selumetinib	Neurofibromatosis type 1 and inoperable plexiform neurofibromas	NCT01362803	NCI
I	Binimetinib	Hepatic dysfunction	NCT02050815	Novartis
I	Pimasertib	Solid tumors (bioavailability)	NCT01992874	EMD Serono
I	Pimasertib	Solid tumors—Japanese subjects	NCT01668017	Merck KGaA
I/II	Selumetinib	Pediatric glioma (low grade)	NCT01089101	Pediatric brain tumor consortium
I/II	Selumetinib	Pediatric glioma (low grade)	NCT01386450	NCI
I/II	Binimetinib	Acute myeloid leukemia	NCT02089230	MD Anderson Cancer Center
I/IIa	Trametinib	Pediatric cancer/plexiform neurofibromas	NCT02124772	GlaxoSmithKline
II	Trametinib vs. 5FU–leucovorin or capecitabine	Biliary cancer	NCT02042443	SWOG
II	Trametinib	Rare BRAF V600E mutant cancers	NCT02034110	GlaxoSmithKline
II	Trametinib	Oral cavity squamous cell cancer	NCT01553851	Washington University School of Medicine
II	Trametinib	Triple negative breast cancer kinome response	NCT01467310	UNC Lineberger Comprehensive Cancer Center
II	Selumetinib	DLBCL	NCT01278615	NCI
II	Refametinib	RAS mutant hepatocellular carcinoma	NCT01915589	Bayer
II	Binimetinib	MAPK-activated solid and hematologic cancers	NCT01885195	Novartis
II	Pimasertib vs. dacarbazine	NRAS mutant melanoma	NCT01693068	EMD Serono
II/III	Trametinib	Low-grade ovarian cancer or peritoneal cavity cancer	NCT02101788	GOG
IIa	Trametinib	Biliary cancer	NCT01943864	GlaxoSmithKline
III	Binimetinib vs. dacarbazine	NRAS mutant melanoma	NCT01763164	Novartis
III	Binimetinib vs. chemotherapy	Low-grade serous ovarian cancer	NCT01849874	Array BioPharma

DLBCL diffuse large B-cell lymphoma, *GOG* Gynecologic Oncology Group, *MAPK* mitogen-activated protein kinase, *NCI* National Cancer Institute, *QTc* corrected QT, *SWOG* Southwest Oncology Group, *UNC* University of North Carolina, *5-FU* 5-fluorouracil

[a] 4.5 days

[b] 2.0 days

The utility of MEK inhibition will also have to be closely considered in the setting of a new class of immunotherapeutic agents that are of increasing interest in cancer treatment. These immune-checkpoint blockade approaches, such as anti-CTLA-4, anti-PD1 and anti-PD-L1 antibodies, rely on an activated T-cell response as the anti-tumor agent. Laboratory experiments have suggested that inhibition of MEK may have immune-dampening effects via blockade of the MAPK pathway during T-cell activation. Whether the combination of MEK inhibitors and immunotherapy is an appropriate approach for optimal anti-tumor effect will have to be closely investigated [117]. Thus, much is yet to be learned regarding the combining of MEK inhibitors with chemotherapy and immunotherapy [118].

With these caveats, MEK inhibition is clearly an important area of drug development that has advanced tremendously over the past decade. While the development of MEK inhibitors as single agents may be appropriate in some settings, it seems likely that combination approaches with other agents will be the most highly efficacious strategies in many cancers. Furthermore, it may be that the dosing schedule of MEK inhibitors is an important consideration in their clinical utility. Preclinical models have suggested that intermittent dosing approaches may be more appropriate to avoid genetic and molecular feedback resistance through the MAPK pathway [119]. Clearly, further research into these areas will be required to optimize the utility of MEK inhibition in the treatment of patients with cancer.

Table 3 Selection of MEK combination studies

Phase	Name of drugs (molecular targets)	Disease indication	ClinialTrials.gov number	Sponsor
I	Trametinib (MEK)-radiation	RAS or RAF mutant malignancies	NCT02015117	NCI
I	Trametinib-dabrafenib-ipilimumab (MEK-BRAF-CTLA-4 concurrent)	BRAF mutant melanoma	NCT01767454	GlaxoSmithKline
I	Trametinib-dabrafenib (BRAF-MEK-CTLA-4)	BRAF mutant melanoma	NCT01940809	NCI-CTEP (Dana-Farber Cancer Hospital)
I	Trametinib-dabrafenib-MEDI4736 (MEK-BRAF-PD-L1)	BRAF mutant melanoma	NCT02027961	MedImmune
I	Trametinib-dabrafenib-pembrolizumab (MEK-BRAF-PD-1)	BRAF mutant melanoma	Not yet registered	Merck
I	Trametinib-dabrafenib-AT13387 (BRAF-MEK-Hsp90)	BRAF mutant melanoma	NCT02097225	NCI-CTEP (Massachusetts General Hospital)
I	Trametinib-carboplatin-paclitaxel (MEK-chemotherapy)-radiation	NSCLC	NCT01912625	NCI-CTEP (MD Anderson Cancer Center)
I	Trametinib-dabrafenib-ipilimumab (MEK-BRAF-CTLA-4 sequential)	BRAF mutant melanoma	NCT01940809	NCI-CTEP (Dana-Farber Cancer Hospital)
I	Trametinib-GSK2256098 (MEK-FAK)	Solid tumors/mesothelioma	NCT01938443	GlaxoSmithKline
I	Trametinib-GSK2141795 (MEK-AKT)	Solid tumors	NCT01138085	GlaxoSmithKline
I	Trametinib-pazopanib (MEK-VEGFR/PDGFR/Raf)	Thyroid cancer, soft-tissue sarcoma, and cholangiocarcinoma	NCT01438554	Sidney Kimmel Comprehensive Cancer Center
I	LY2875358-trametinib (RAF-MEK)	Solid tumors	NCT01287546	Eli Lilly and Company
I	LY2835219-other drugs including trametinib (CDK4/6-MEK)	NSCLC	NCT02079636	Eli Lilly and Company
I	Selumetinib-cisplatin-gemcitabine (MEK-chemotherapy)	Biliary cancer—Japanese subjects	NCT01949870	AstraZeneca
I	Selumetinib – first-line chemotherapy (MEK-chemotherapy)	NSCLC	NCT01809210	AstraZeneca
I	Selumetinib-thoracic radiation	NSCLC	NCT01146756	Christie Hospital NHS Foundation Trust
I	Selumetinib-docetaxel (MEK-chemotherapy)	Solid tumors/NSCLC—Japanese subjects	NCT01605916	AstraZeneca
I	Selumetinib, erlotinib, MK2206, sunitinib, lapatinib	NSCLC, SCLC, thymic carcinoma	NCT01306045	NCI
I	Refametinib-gemcitabine (MEK-chemotherapy	Solid tumors—Asian subjects	NCT01764828	Bayer
I	Binimetinib-idarubicin-cytarabine (MEK-chemotherapy)	Acute myeloid leukemia	NCT02049801	NCI (Stanford University)
I	Binimetinib-FOLFOX (MEK-chemotherapy)	Colorectal cancer	NCT02041481	NCI (City of Hope Medical Center)
I	Binimetinib-gemcitabine-oxaliplatin (MEK-chemotherapy)	Biliary cancer	NCT02105350	University Health Network, Toronto
I	Binimetinib-paclitaxel (MEK-chemotherapy)	Epithelial ovarian, fallopian tube, or peritoneal cancer	NCT01649336	Array BioPharma
I	Pimasertib-SAR405838 (MEK-HDM2)	Solid tumors	NCT01985191	Sanofi
I	Pimasertib	Solid tumors—Japanese subjects	NCT01668017	Merck KGaA

Table 3 continued

Phase	Name of drugs (molecular targets)	Disease indication	ClinialTrials.gov number	Sponsor
I/Ib	Binimetinib-erlotinib (MEK-EGFR)	NSCLC	NCT01859026	H. Lee Moffitt Cancer Center and Research Institute
I/II	Trametinib-dabrafenib-navitoclax (MEK-BRAF-Bcl-2)	Solid tumors/BRAF mutant melanoma	NCT01989585	NCI-CTEP (Massachusetts General Hospital)
I/II	Trametinib-palbociclib (MEK-CDK4/6)	Solid tumors/BRAF mutant melanoma	NCT02065063	GlaxoSmithKline
I/II	Trametinib-dabrafenib-metformin (MEK-BRAF-PPAR agonist)	BRAF mutant melanoma	NCT02143050	University of Louisville
I/II	Trametinib-dabrafenib-panitumumab (MEK-BRAF-EGFR)	Colorectal cancer	NCT01750918	GlaxoSmithKline
I/II	Selumetinib-HAART (MEK-anti-viral)	Kaposi's sarcoma (SCART)	NCT01752569	Sheffield Teaching Hospitals NHS Foundation Trust
I/II	Selumetinib-vandetinib (MEK-VEGFR2)	Solid tumors/NSCLC (VanSel-1)	NCT01586624	Cancer Research UK
I/II	Binimetinib-cisplatin-gemcitabine (MEK-chemotherapy)	Biliary cancer	NCT01828034	Memorial-Sloan Kettering Cancer Center
Ib	Cobimetinib-MPDL3280A (MEK-PD-L1)	BRAF and RAS mutant solid tumors/melanoma	NCT01988896	Hoffman-La Roche
Ib	Trametinib-docetaxel (MEK-chemotherapy)	NSCLC–Japanese subjects	NCT01938456	GlaxoSmithKline
Ib	Trametinib-digoxin (MEK-Na/K-ATPase inhibition)	BRAF-wild-type melanoma	NCT02138292	University of Texas Southwestern Medical Center
Ib	Selumetinib – any line chemotherapy	NSCLC	NCT01783197	NCIC Clinical Trials Group
Ib	Vemurafenib- cobimetinib, onartuzumab (BRAF-MEK-MET)	RAS, BRAF mutant tumors/melanoma	NCT01974258	Hoffmann-La Roche
Ib	MEHD7945A-cobimetinib (EGFR-MEK)	KRAS mutant solid tumors	NCT01986166	Genentech
Ib	Vemurafenib-cobimetinib (BRAF-MEK)	BRAF mutant melanoma	NCT01562275	Genentech
Ib	Cobimetinib-Pictilisib (MEK-PI3K)	Solid tumors	NCT00996892	Genentech
Ib	Binimetinib-BYL719 (MEK-PI3K)	Solid tumors	NCT01449058	Novartis
Ib	Binimetinib-LEE011 (MEK-CDK4/6)	NRAS mutant melanoma	NCT01781572	Novartis
Ib/II	Selumetinib-gefitinib (MEK-EGFR)	EGFR mutant NSCLC	NCT02025114	National Taiwan University Hospital
Ib/II	Binimetinib-sotrastaurin (MEK-PKC)	Uveal melanoma	NCT01801358	Novartis
Ib/II	Binimetinib-imatinib (MEK-KIT)	Gastrointestinal stromal tumor	NCT01991379	Memorial-Sloan Kettering Cancer Center
Ib/II	LGX818-binimetinib (BRAF-MEK)	BRAF solid tumors	NCT01543698	Novartis
Ib/II	Binimetinib-panitumumab (MEK-EGFR)	Solid tumors/NRAS mutant tumors	NCT01927341	Novartis
Ib/II	Trametinib-navitoclax (MEK-Bcl-2)	KRAS colorectal cancer	NCT02079740	NCI-CTEP (Massachusetts General Hospital)
Ib/IIa	Trametinib-dabrafenib-AM232 (MEK-BRAF-HDM2)	Melanoma	NCT02110355	Amgen
II (Neoadjuvant)	Trametinib-fluorouracil (MEK-chemotherapy)-Radiation	Rectal cancer	NCT01740648	Ohio State University
II (Neoadjuvant)	Trametinib-dabrafenib (MEK-BRAF)	BRAF mutant melanoma	NCT01972347	Melanoma Institute Australia

Table 3 continued

Phase	Name of drugs (molecular targets)	Disease indication	ClinialTrials.gov number	Sponsor
II (Neoadjuvant)	Trametinib-dabrafenib (MEK-BRAF)	BRAF mutant melanoma	NCT01701037	Vanderbilt-Ingram Cancer Center
II	Trametinib-GSK2141795 (MEK-AKT)	Cervical cancer	NCT01958112	Dana-Farber Cancer Institute
II	Trametinib-GSK2141795 (MEK-AKT)	Triple-negative breast cancer	NCT01964924	NCI
II	Trametinib-GSK2141795 (MEK-AKT)	NRAS and BRAF-wild-type melanoma	NCT01941927	University of California, San Francisco
II	Trametinib-GSK2141795 (MEK-AKT)	Multiple myeloma	NCT01989598	NCI-CTEP (Princess Margaret Hospital)
II	Trametinib-dabrafenib (MEK-BRAF)	BRAF mutant acral melanoma	NCT02083354	GlaxoSmithKline
II	Trametinib-GSK2141795 (MEK-AKT)	Uveal melanoma	NCT01979523	NCI-CTEP (Memorial Sloan-Kettering Cancer Center)
II	Trametinib-GSK2141795 (MEK-AKT)	Endometrial carcinoma	NCT01935973	GOG
II	Trametinib-GSK2141795 (MEK-AKT)	Acute myeloid leukemia	NCT01907815	NCI-CTEP (MD Anderson Cancer Center)
II	Trametinib-dabrafenib (MEK-BRAF)	NSCLC	NCT01336634	GlaxoSmithKline
II	Trametinib-dabrafenib (MEK-BRAF)	BRAF mutant melanoma brain metastases	NCT02039947	GlaxoSmithKline
II	Trametinib-dabrafenib (MEK-BRAF)	BRAF melanoma brain metastases PK	NCT01978236	GlaxoSmithKline
II	Trametinib-dabrafenib (MEK-BRAF)	BRAF inhibitor resistance melanoma	NCT01619774	MD Anderson Cancer Center
II	Trametinib-degarelix-enzalutamide (AR inhibition-MEK)	Prostate cancer	NCT01990196	University of California, Los Angeles
II	Selumetinib-radioactive iodine	Differentiated thyroid cancer (ASTRA)	NCT01843062	AstraZeneca
II	Selumetinib-docetaxel (MEK-chemotherapy)	NSCLC—second line	NCT01750281	AstraZeneca
II	Selumetinib-MK2206 or mFOLFOX (MEK-AKT or MEK-chemotherapy)	Pancreatic cancer	NCT01658943	SWOG
II	Selumetinib, erlotinib, MK2206, sorafenib	NSCLC (BATTLE-2)	NCT01248247	MD Anderson Cancer Center
II	Selumetinib, erlotinib, AZD2014, AZD4547, AZD5363, AZD8931, vandetanib, pemetrexed	NSCLC (SAFIR02_Lung)	NCT02117167	UNICANCER
II	Refametinib-sorafenib (MEK-VEGFR2)	RAS mutant hepatocellular carcinoma	NCT01915602	Bayer
II	LGX818-binimetinib, BKM120, LEE011, BGJ398, INC820 (BRAF + MEK, PI3K, CDK4/6, FGFR, MET)	BRAF mutant melanoma (LOGIC)	NCT01820364	Novartis
II	Pimasertib-SAR245409 (MEK-PI3K/mTOR)	Ovarian cancer	NCT01936363	EMD Serono
II	Pimasertib-gemcitabine (MEK-chemotherapy)	Pancreatic cancer	NCT01016483	Merck KGaA
III (Adjuvant)	Trametinib-dabrafenib (MEK-BRAF)	BRAF mutant melanoma (COMBI-AD)	NCT01682083	GlaxoSmithKline
III	Selumetinib-docetaxel (MEK-chemotherapy)	KRAS mutant NSCLC (SELECT-1)	NCT01933932	AstraZeneca
III	Dacarbazine-selumetinib (chemotherapy-MEK)	Uveal melanoma (SUMIT)	NCT01974752	AstraZeneca
III	LGX818-binimetinib (BRAF-MEK)	BRAF mutant melanoma	NCT01909453	Novartis

CTEP Cancer Therapy Evaluation Program, *EGFR* epidermal growth factor receptor, *GOG* Gynecologic Oncology Group, *NCI* National Cancer Institute, *NCIC* National Cancer Institute of Canada, *NHS* National Health Service, *NSCLC* non-small-cell lung cancer, *PK* pharmacokinetics, *SCLC* small-cell lung cancer, *SWOG* Southwest Oncology Group

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