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MEK Inhibition in *KRAS* Mutated NSCLC: Quo vadis?

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Introduction

Lung cancer continues to be the leading cause of cancer deaths worldwide [1]. Approximately 85% of lung cancers are histologically classified as non-small cell lung cancer (NSCLC) of which adenocarcinoma is the most frequent subtype. *KRAS* (v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) is one of the most commonly mutated genes in human cancers [2]. *KRAS* mutations are the most common oncogenic driver mutations in adenocarcinoma of the lung and can be found in up to a quarter of patients [3,4]. The vast majority (95%) are associated with a history of nicotine use. In NSCLC, *KRAS* mutations most often occur in codons 12 and 13 and with a lower frequency in codon 61 [4]. The predominant mutations are G12C, G12V and G12D [5]. The *KRAS* G12C mutation is present in approximately 13% of patients with NSCLC [2]. *KRAS* mutations do generally not overlap with other oncogenic mutations. *KRAS* mutant NSCLC has been reported to be associated with shorter median overall survival (OS) and lower two-year survival rates, however, there is conflicting data on the prognostic significance of *KRAS* mutations [6-8].

The RAS proteins regulate signal transduction by activating different effectors, thereby controlling various cellular functions. There are three genes related to human tumors in the *RAS* gene family: Harvey rat sarcoma viral oncogene (*HRAS*), *KRAS* and Neuroblastoma rat sarcoma viral oncogene (*NRAS*), which are located on chromosomes 11, 12, and 1, respectively [9]. Among them, *KRAS* by far represents the most important one. The KRAS protein is missing a "pocket" for small-molecule binding rendering drug development more difficult for targeted treatment. For decades, numerous efforts were made to target KRAS and its downstream pathways. The best-known downstream pathway is the mitogen activated protein kinase (MAPK)-pathway, which consists of the RAS-rapidly accelerated fibrosarcoma (RAF)-extracellular signal-regulated kinase (MEK)-ERK signaling cascade (Figure 1). However, when activated, KRAS relays on upstream signals from cell surface receptors to additional downstream pathways, including PI3K-AKT-mTOR, RALGDS-RAL and TIAM-RAC, that also control normal cell function and proliferation and add further complexity for drug development.

The first class of drugs directed to KRAS were the farnesyltransferase inhibitors (FTIs) tipifarnib, lonafarnib and second-generation salirasib. However, these trials were unsuccessful, in part due to the compensatory effect of the enzyme geranyltransferase, that among others processes KRAS to let it bind to cell membranes and to exert its activity. MEK is a serine/threonine kinase, a downstream signal of KRAS and BRAF. Activated RAF activates MEK, which activates ERK and other transcription factors promoting cell cycle progression and cell proliferation. MEK1/MEK2 inhibitors, selumetinib (AZD6244, ARRY-142886) and trametinib (GSK1120212, JTP-74057) as monotherapy didn't improve outcomes of patients with *KRAS* mutant NSCLC [10,11]. A potential reason may be that MEK inhibitors induce drug resistance by increased upstream signaling leading to ERK signaling activation [12].

The rationale for performing the SAKK 19/16 trial was the unmet need to treat patients with *KRAS* mutated lung cancer [13]. The trial was developed based on preclinical and clinical evidence, that MEK-Inhibition plus chemotherapy may improve outcomes [14-17], although there have also

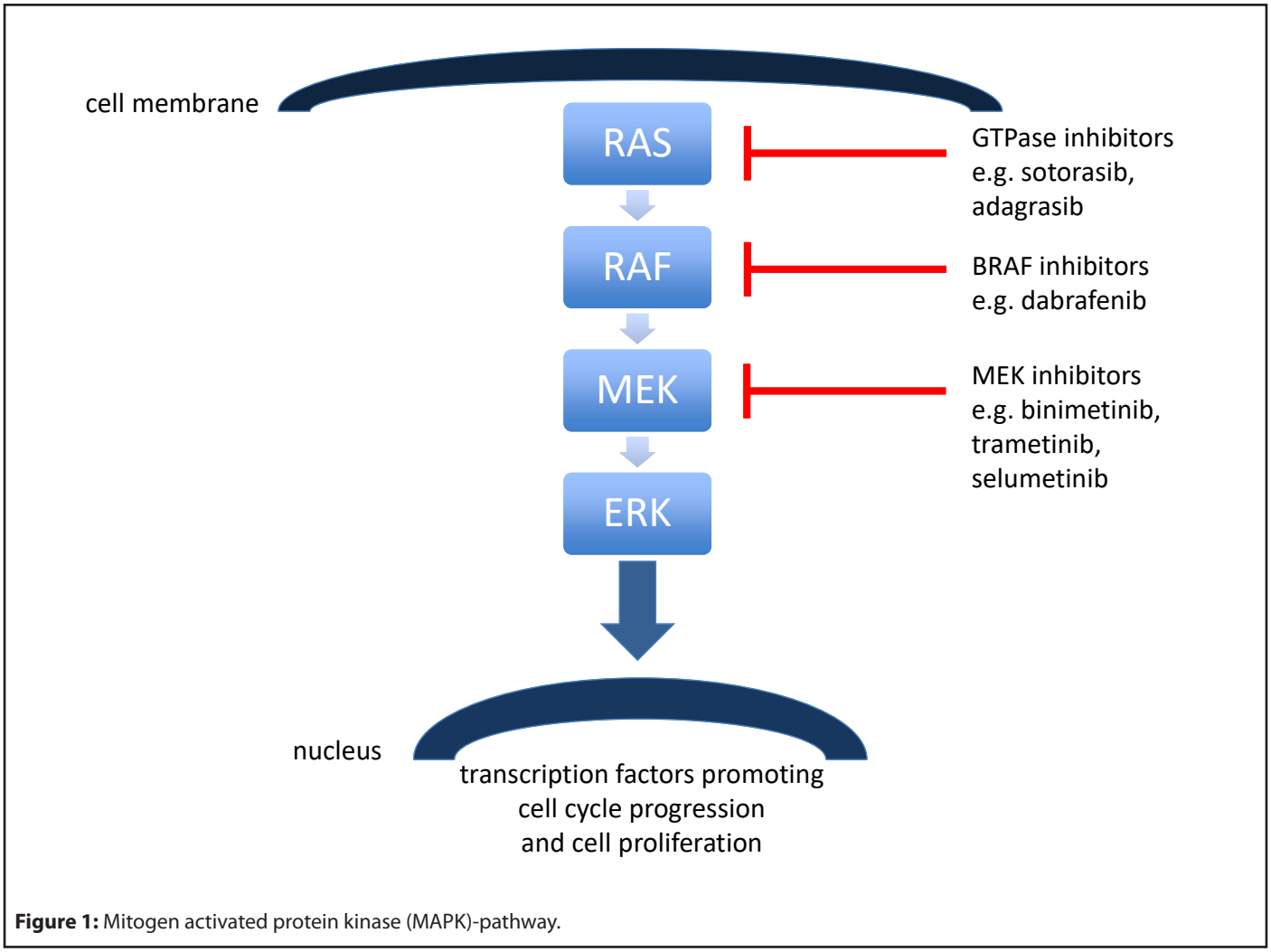

Figure 1: Mitogen activated protein kinase (MAPK)-pathway.

been disappointing results such as in the SELECT-1 trial, which showed no benefit for the addition of selumetinib to docetaxel as second-line therapy for advanced *KRAS* mutant NSCLC [10]. At time of start of the SAKK 19/16 trial, a cisplatin combination was recommended as first-line treatment in advanced and metastatic NSCLC based on a meta-analysis by Ardizzoni et al. [18]. Pemetrexed and cisplatin were therefore chosen as chemotherapy backbone in combination with binimetinib (MEK162). Binimetinib is an oral inhibitor of the MAPK kinases MEK1 and MEK2. The aim of the SAKK 19/16 trial was to determine the recommended phase 2 dose of binimetinib and assess early anti-tumor activity. Cisplatin, pemetrexed and binimetinib were administered for 4 cycles followed by a binimetinib and pemetrexed maintenance until disease progression (PD) or unacceptable toxicity. The protocol suggested maintenance pemetrexed as standard treatment given a randomized phase III trial previously has demonstrated a survival benefit [19]. For binimetinib an intermittent schedule (d1-14 q21 days) was chosen because MEK inhibitors have shown to be more active as pulsatile instead of continuous treatment in preclinical studies [20]. Eligible patients had treatment naive, metastatic or locally advanced NSCLC unsuitable for curative treatment and a *KRAS* mutation (codon 12, 13 or 61). Eighteen patients were enrolled. The primary endpoint were dose-limiting toxicities (DLT), and two different dose levels of binimetinib (30 and 45 mg BID) were explored. Secondary endpoints included adverse events (AE) and objective response rate (ORR), progression-free survival (PFS) and OS. DLT did not occur in the nine evaluable patients. Thus, 45mg binimetinib BID was declared to be the maximum tolerated dose (MTD). In 9 out of 10 patients treated at the MTD at least one serious adverse event (SAE) occurred. The most common treatment-related grade 3 (G3) AE of all 16 evaluable patients for safety were lung infection (25%), fatigue (19%) and anemia (19%). Of the 10 patients who received binimetinib at the MTD fatigue (30%), nausea (20%), anemia (20%), hypertension (20%) and lung infection (20%) were the most common G3 AEs. The ORR was 29% (95% CI, 35-87) in all 14 evaluable patients and 33% (95% CI, 7-70) in the nine patients treated at the MTD. PFS and OS in the MTD group were 5.7 months (95% CI, 1.1-14.0) and 6.5 months (95% CI, 1.8–not reached).

Although DLT was not observed, the high rates of SAEs and the significant proportion of patients not evaluable for DLT indicate tolerability issues, that were most likely mainly

chemotherapy-related. As the patients with *KRAS* mutations generally have a significant history of nicotine use resulting in relevant comorbidities and impaired performance status, retrospectively, carboplatin likely might have been a better tolerable choice.

In summary, the addition of binimetinib to a cisplatin-based first-line chemotherapy seems to be feasible with no DLT at a dose of 45 mg binimetinib BID, although the high rates of SAEs should be taken into account. However, no sign of improved anti-tumor activity of the treatment combination of cisplatin, pemetrexed and binimetinib as first-line therapy in *KRAS* mutated metastatic NSCLC was observed.

MEK Inhibition in *KRAS* Mutant NSCLC – Quo vadis?

In a more recent phase I study by Fung et al., binimetinib was investigated in combination with carboplatin and pemetrexed as chemotherapy backbone in patients with stage IV non-squamous NSCLC [21]. No prior chemotherapy was allowed. Unlike in the SAKK 19/16 trial, patients with *KRAS* wild type, sensitizing *EGFR* mutations or *ALK*-fusions or high PD-L1 levels were eligible if previously treated with the respective tyrosine kinase inhibitors (TKIs) or immune checkpoint inhibitors. In this study 6 cycles of binimetinib, carboplatin and pemetrexed were administered followed by a maintenance therapy with pemetrexed/binimetinib until PD. Whereas binimetinib in the SAKK 19/16 trial was administered for 14 days in a 21-day cycle, in the study by Fung et al. binimetinib was administered for days 1-5 in cycle 1 followed by chemotherapy on day 8 and binimetinib from day 8-26. In the following cycles (21 day-cycles) binimetinib was given continuously BID except for a washout period 2 days prior to the next chemotherapy (except for dose level -1, in which binimetinib was administered on days 1-14 of each cycle starting from cycle 2). Aim of the study was to determine the recommended phase 2 dose and to assess safety. With their schedule of binimetinib, two patients reached a DLT event at 45 mg BID (elevated alanine aminotransferase (ALT) for longer than 7 days and G3 ocular toxicity) resulting in a recommended dose of 30mg binimetinib BID. AEs of any grade occurred in all 13 enrolled patients with eight patients developing a G3/4 AE. In total, 12/13 patients were evaluated for efficacy with an ORR of 50% (95% CI, 21.1-78.9) by investigator assessment and of 33.4% by independent review (95% CI, 9.9-65.1). The median PFS was 4.5 months (95% CI, 2.6-NA). Seven patients enrolled in this study harbored a *KRAS* mutation, among those the ORR was 57.1% by investigator assessment and 28.6% by independent review. Although disease control rate (DCR) was 100% in patients harboring a *KRAS* mutation and ORR were slightly higher in *KRAS* mutated patients no meaningful conclusion can be drawn from this small sample size with regards to activity of the combination. In addition, no information on the PFS in the *KRAS* mutated subgroup was provided. Despite the DLTs, the study by Fung et al. showed a slightly more manageable toxicity profile compared to the SAKK 19/16 trial, which used a cisplatin combination (G3 or higher AE rate of 61.5% versus 66.7% in the SAKK 19/16 trial). The ORR of the two studies is comparable and lack a clear signal of additional activity of binimetinib in this situation that is in line with previous studies evaluating other MEK inhibitors with platinum-doublet chemotherapy [22-24].

Although *KRAS* is the oncogene most frequently mutated in human cancer, targeting the RAS-RAF-MEK-ERK pathway remains a challenge. Most recently, the focus of drug development laid on the codon variant in the KRAS protein G12C accounting for 39% of *KRAS* mutations in NSCLC, followed by G12V (21%) and G12D (17%) [5]. The incidence of $KRAS^{G12C}$ is therefore similar to the one of *EGFR* mutations in a Western European population. Recently, sotorasib, a covalent $KRAS^{G12C}$ inhibitor locking KRAS in its inactive GDP-bound state by irreversibly binding to the switch II pocket [25], was evaluated in the CodeBreaK 100 study in patients with previously treated advanced or metastatic $KRAS^{G12C}$ mutated cancer (n=129) [26]. The ORR for patients with NSCLC (59/129 patients) was 32.2% (95% CI, 20.62-45.64) and the DCR 88.1% (95% CI, 77.07-95.09). AEs of G3 or higher were reported in 52.7% of all patients (68/129 patients). These results led to accelerated approval of sotorasib for advanced and metastatic NSCLC by the FDA in May 2021. Sotorasib is currently investigated further in several ongoing studies. Adagrasib is another $KRAS^{G12C}$ inhibitor currently in clinical development. It is a potent inhibitor that irreversibly and selectively binds $KRAS^{G12C}$ and locks it in its inactive state. Seventy-nine pretreated patients with NSCLC were enrolled in the KRYSTAL-1 trial and received adagrasib 600mg BID. Of 51 patients evaluable for efficacy 23 patients (45%) showed a partial remission and 26 patients had stable disease [27]. Sotorasib and adagrasib have also recently shown early signs of activity in $KRAS^{G12C}$ mutated colorectal cancer in combination with panitumumab and cetuximab, respectively [28,29]. However, the results of the prespecified analysis of the CodeBreaK100 trial for previously treated $KRAS^{G12C}$ mutant colorectal cancers showed a modest anti-tumor activity and manageable safety but did not reach the benchmark with an ORR of 9.7% (6/62 patients, 95% CI, 3.6-19.9) [30]. Given these recent developments with selective $KRAS^{G12C}$ inhibitors demonstrating activity in a further subset of *KRAS* mutated NSCLC patients as well as the emergence of immunotherapy (which has significant activity particularly in the subset of *KRAS* mutated NSCLC) [31], the two first-line trials investigating binimetinib plus chemotherapy discussed above have to be viewed in this new context and the question arises: Quo vadis MEK inhibition in *KRAS* mutated NSCLC?

There are numerous approaches ongoing targeting various components of the RAS-RAF-MEK-ERK pathway: HL-085, a novel ATP non-competitive MEK inhibitor is explored in a phase I trial (ClinicalTrials.gov Identifier: NCT03990077). In addition, pulse MEK inhibition combined with CTLA-4 blockade may prolong the survival time of *KRAS* mutant tumors in mice, possibly due to T-cell activation and increased CTLA-4 expression resulting from pulse therapy. Furthermore, the combination of a MEK- and RAF-inhibitor may also be promising as currently

investigated in a phase I trial of LXH254 and trametinib as well as belvarafenib combined with cobimetinib (ClinicalTrials.gov Identifier: NCT02974725 and NCT03284502). Finally, VS-6766 (RO5126766), a novel targeted drug that inhibits both MEK and RAF, is being evaluated in a phase II clinical study (ClinicalTrials.gov Identifier: NCT04620330). SHP2 plays a crucial role in *KRAS* mutation-driven tumors. It is involved in the downstream signal transduction of various growth factors and cytokines. The combination of SHP2 with MEK inhibitors resulted in a synergistic effect to control tumor growth in *KRAS* mutant NSCLC xenograft models [32]. A single drug phase I study and a clinical trial in combination with pembrolizumab are ongoing (ClinicalTrials.gov Identifier: NCT03634982, ClinicalTrials.gov Identifier: NCT04418661).

Since the inhibition of the MAPK-pathway activates the PI3K-pathway, reducing *KRAS* mutated cell sensitivity to MEK inhibitors, an approach to target the PI3K-AKT-mTOR- and RAF-MEK-ERK-pathways simultaneously could be promising, but potentially results in increased toxicity. Likewise, if in *KRAS* mutant NSCLC MEK is inhibited, STAT3 is activated via fibroblast growth factor receptor and Janus kinase, thus combined inhibition of MEK and Janus kinase has shown to result in tumor regression [33]. Finally, as ERK is the final kinase in the MAPK-pathway, the resistance of *KRAS* mutated tumors to RAF or MEK inhibitors is frequently caused by ERK feedback activation. Combined inhibition of ERK may be another strategy to prevent drug resistance. Currently, ERK inhibitors such as JSI-1187-01 and ASN007 are in phase I clinical trials (ClinicalTrials.gov Identifier: NCT04418167 and NCT03415126), respectively.

In summary, MEK inhibitors could still play a role in the future in the treatment of *KRAS* mutated advanced NSCLC patients and may find their place as combination partners with other targeted agents given the complexity of the RAS-RAF-MEK-ERK-pathway and/or immunotherapy. Results of ongoing respective trials are eagerly awaited.

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