



**COMMENT**

# Searching for treatments for non-G12C-*KRAS* mutant cancers

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*KRAS* mutations drive a wide variety of cancers. Drugs targeting the protein product of *KRAS*<sup>G12C</sup> mutations are currently being evaluated show preliminary efficacy in clinical trials. A clinical trial of VS-6766, a dual RAF–MEK inhibitor, has reported early single agent activity in non-G12C mutated *KRAS* driven cancers.

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**MAIN**

*KRAS* mutations are commonly associated with a range of solid tumours and haematological malignancies.<sup>1</sup> Initial attempts to drug *KRAS* proved challenging due to the high affinity of *KRAS* to GTP and the relative abundance of GDP/GTP in human cellular tissue.<sup>2</sup> This led a plethora of efforts to target downstream effectors such as RAF, MEK, PI3K, AKT, mTOR and the combination of these signalling nodes,<sup>1–3</sup> but these approaches have not led to registration of a drug or drug combinations in the setting of *KRAS* mutant (*KRAS*<sup>M</sup>) cancers. There has however been significant progress in developing drugs directly targeting protein products of specific subsets of *KRAS* mutations i.e. *KRAS*<sup>G12C</sup>. These inhibitors (sotorasib and adagrasib) have shown promising activity in non-small cell lung cancer (NSCLC) with *KRAS*<sup>G12C</sup> mutations<sup>4,5</sup> and will no doubt be further explored in registration enabling studies.

Guo et al. reported a Phase 1b dose-escalation, basket expansion study of a dual RAF–MEK inhibitor, VS-6766 (previously known as CH5126766 and RO5126766), which showed promising anti-tumour activity in patients with solid tumours and multiple myeloma harbouring non-G12C-*KRAS* mutations.<sup>6</sup> There are several interesting aspects to this study.

Firstly, the drug has interesting pharmacological properties. It is a MEK inhibitor but also blocks in-complex (CRAF–MEK) phosphorylation of MEK,<sup>7</sup> leading to reduction of phosphorylation of both MEK and ERK as demonstrated in pre- and post-treatment biopsies. This is distinct to a reduction of phosphorylation of ERK but not MEK caused by currently licensed MEK inhibitors. The inhibition of signalling in two distinct nodes in the MEK–ERK signalling network by a single drug may explain the preliminary single agent efficacy of VS-6766 reported.

Secondly, the authors have exploited an unusually long half-life of the drug of approximately 50 hours (which is significantly longer than other RAF or MEK inhibitors) to run pharmacokinetic simulations to predict drug concentrations and design a twice a week dosing schedule. The highly intermittent twice a week schedule established in the trial enables patients to tread the fine line between efficacy and toxicity. Further, a dose modification strategy to drop to three-weeks on-one week off rather

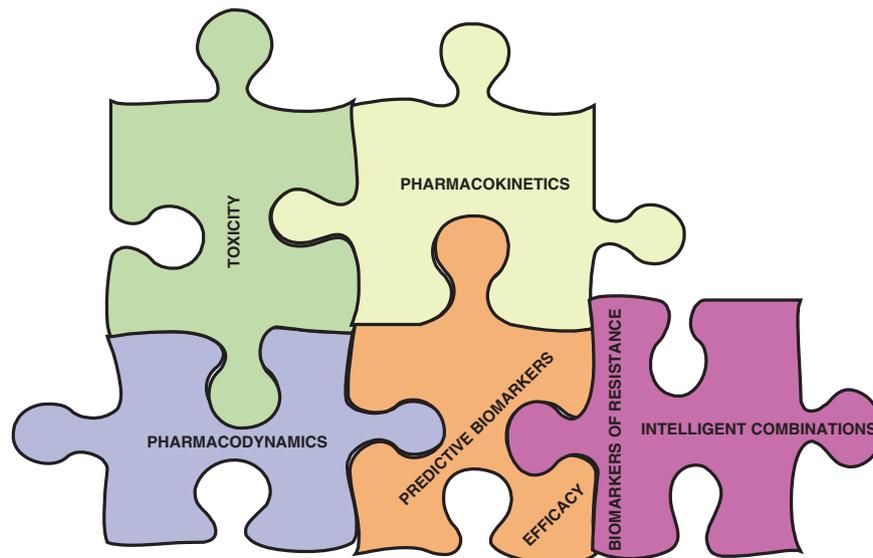
than reducing the dose of the drug is different from dose modification strategies commonly used in combination studies of targeted agents.<sup>8</sup> This reflects previous preclinical studies by the group where they had studied the importance of maximal inhibition of MEK signalling in *KRAS*<sup>M</sup> models.<sup>9</sup> The intermittent schedule has significantly improved the therapeutic index of the drug compared with previous studies that explored continuous dosing schedules.<sup>10</sup>

Finally, the authors have demonstrated single agent activity in a variety of *KRAS*<sup>M</sup> cancers in a cohort of heavily pre-treated patients. Of note, they have demonstrated partial responses in 3/10 patients with *KRAS*<sup>M</sup> NSCLC as a single agent and interestingly two of the three patient who responded had *KRAS*<sup>G12V</sup> mutations. Given there are no *KRAS* targeted therapies for *KRAS*<sup>G12V</sup> mutations, VS-6766 could be explored further in this disease space both as a single agent or in combination. Of note, 3/5 patients with *RAS/RAF* mutations with gynaecological cancers responded to treatment. There is considerable excitement and activity of MEK inhibitors (trametinib and binimetinib) in low grade serous ovarian cancer (LGSOC).<sup>11,12</sup> The combination study of VS-6766 with defactinib have shown promising activity in Phase 1 studies with expansions in LGSOC<sup>13</sup> and randomised a Phase 2 trial is exploring the activity of the combination in LGSOC is ongoing (NCT04625270). Further, an interesting response was seen in patient with *KRAS*<sup>G12V</sup> driven multiple myeloma. While anecdotal responses of MEK inhibitors have been noted in myeloma,<sup>14</sup> this further confirms response of this agent in an independent cancer type driven by *KRAS* mutations.

Attention to detail of pharmacokinetics, pharmacodynamics, toxicity and predictive biomarkers of efficacy are part of the pharmacological audit trail and remain critical to successful development of targeted therapy<sup>15</sup> (Fig. 1). The trial by Guo et al.<sup>6</sup> has defined a backbone of a highly intermittent schedule of novel RAF–MEK inhibitor VS-6766. Multiple early Phase clinical trials of combinations with this VS-6766 are currently ongoing with agents such as everolimus (NCT02407509) and defactinib (NCT03875820). Randomised studies of the combination of VS-6766 and defactinib to explore efficacy of the combination in *KRAS*<sup>M</sup> LGSOC (NCT04625270) and NSCLC (NCT04620330) are currently ongoing.

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**Fig. 1 The Pharmacological Audit Trial.** Crucial elements in the pharmacological audit trail that are key to optimise dosing schedules and use predictive biomarkers to accelerate early clinical development.

### AUTHOR CONTRIBUTIONS

C.G. and U.B. contributed to the writing of the manuscript.

### ADDITIONAL INFORMATION

**Ethics approval and consent to participate** Not applicable.

**Data availability** Not applicable.

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