CLINICAL INVESTIGATION

Translational biomarker in oncology early clinical development: decision case study for MEK inhibitors in healthy volunteer studies

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Biomarkers of drug activity are increasingly important tools in oncology early drug development, particularly in this era of targeted therapies. In early development, their main use is to help select the best drugs and/or dosing regimens to progress in development. The case study demonstrates how a biomarker of molecular target activity was developed in a preclinical setting and translated into the clinic to assess the 'proof of mechanism' for two competing MEK inhibitors, CH4987655 and RO5068760. Inhibition of ERK phosphorylation (pERK) was measured using a surrogate tissue, *ex vivo* phorbol 12-myristate 13-acetate-stimulated peripheral blood mononuclear cells. CH4987655 demonstrated concentration-dependent pERK inhibition with exposures covering pERK inhibition from the no effect level to near maximum effect of 100%. However, RO5068760 demonstrated a rather modest pERK inhibition of only 55%. The biomarker demonstrated CH4987655 was superior in terms of MEK inhibition and the potential for therapeutic effects enabled the choice to progress only CH4987655 into further clinical development.

Keywords: biomarkers • exposure–response relationship • oncology • translational medicine

Biomarkers in oncology early clinical development

A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention [1]. Implementing biomarkers in clinical trials is a major aspect of translational medicine that will improve decision making in clinical drug development [2]. Implications of these statements have intuitive appeal as a means of streamlining drug development processes in several ways:

- Prognostic biomarkers of therapeutic response enable the selection of patients most likely to have positive outcomes with a particular therapy. Two examples of oncology drugs with validated predictive biomarkers include Herceptin® (for HER2+ patients with breast cancer) and Gleevec® (for Philadelphia chromosome-positive patients with chronic myelogenous leukemia);

- Response biomarkers enable the measurement of effect in response to a particular drug therapy and may also help in optimizing the drug's dose and dosing schedule. Response biomarkers are typically measures of activity at the molecular target, or of biochemical or functional effects on the tumor, and can be expected to change after short durations of therapy before any structural effects on the tumor can be detected. One example of such a marker is FDG-PET imaging as an early response biomarker for patients with gastrointestinal

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(GI) stoma tumor;

- Safety biomarkers determine the likelihood of observing a clinically significant adverse event (AE). Examples include elevated liver enzymes (AST and ALT) for assessment of hepatoxicity and QT prolongation for assessment of cardiotoxicity.

While it is desirable to have biomarkers that are true surrogates of efficacy, in early clinical development it is more realistic to rely on markers of target, pathway or pharmacological effects. Although there may be uncertainty about their true ability to predict clinical benefit, they are helpful in defining potential doses and supporting development decisions. Establishing doses with minimal and maximal effects on the biomarker can be used to justify dose regimens for subsequent trials and showing that a lack of activity at the target would stop development. Establishing a link between changes in the biomarker and the tumor response in preclinical models can be used to identify target levels of drug effect on the biomarker, provide confidence regarding the potential success and suitability of molecules and/or doses in subjects and support continued development or increased investment. Indeed, in early clinical development all decisions are ultimately made using biomarkers, whether it is plasma exposures, a finding of a few clinical responses or, as described here, a marker of target effects.

The role of biomarkers in early oncology drug development, as described above, is extensively discussed in current literature; however, more examples of case studies are needed [3–6]. The intention of the current article is to present one such case study in early oncology drug development. This article illustrates how a biomarker for MAPK pathway inhibitors was rationally developed in the laboratory based on the molecular mechanism of action, proven in preclinical models by linking activity to tumor growth inhibition (TGI) and, subsequently, brought forth in early clinical studies to validate MEK target suppression or determine 'proof-of-mechanism' in humans. The validation of MEK target suppression for MAPK pathway inhibitors had important implications in early oncology portfolio 'go–no go' decisions, as well as molecule selection.

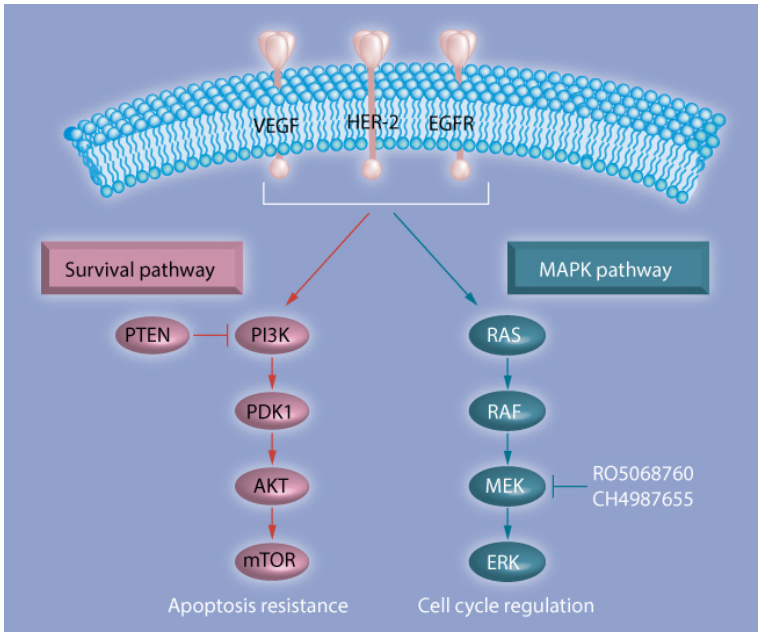

Figure 1. MAPK cell signaling pathway and its downstream effectors are shown on the right side. RO5068760 and CH4987655 inhibit the phosphorylation of ERK, thereby blocking constitutive activation of the MAPK pathway in tumor cells.

MAPK signaling pathway & MEK inhibitors

The Ras/Raf/MEK/ERK (MAPK) pathway represents one of the best characterized signaling pathways involved in the development and progression of human cancers (Figure 1).

This pathway, via the Ras/Raf/MEK/ERK signal cascade, is responsible for transmitting and amplifying mitogenic signals from the cell membrane to the nucleus. Thereafter, the activated transcription factors regulate gene expression and induce activities relevant to the fate of the cell. Deregulation of the MAPK pathway that leads to constitutive activation may be sufficient to transform normal cells into cancer cells. Aberrant receptor tyrosine kinase activation and Ras and/or B-Raf mutations (frequently found in human cancers), represent a major factor in determining abnormal cell growth control [7]. Oncogenic Ras mutations can be found in approximately 30% of all human cancers. The highest incidences of Ras mutations are found in adenocarcinomas of the pancreas (90%), colon (50%) and lung (30%) [8]. Mutations in B-Raf have been detected in 66% of primary melanomas and less frequently in other tumors, such as colon (12%), ovarian (30%) and papillary thyroid cancers (30–70%) [9–11]. Aberrant activation of the MAPK pathway also correlates with tumor progression and poor prognosis in various cancer patients, such as breast, colorectal, prostate, renal cell carcinoma, non-small-cell lung cancer (NSCLC) and melanoma. Therefore, there are several key components of the MAPK pathway that are attractive targets for development of therapeutic agents in cancer [12,13].

Although mutations in MEK1 and MEK2 (MEK1/2) were not observed with frequency in cancers, overexpression of MEK is sufficient to induce cellular

transformation. So far, the only known substrates of MEK1/2 are ERK1/2. This unusual substrate specificity places MEK1/2 at a critical point in the signal transduction cascade, which allows them to integrate many extracellular signals into the MAPK pathway. Targeting MEK1/2 with a small molecule inhibitor could prevent all upstream aberrant oncogenic activations (RTK, Ras and B-Raf) and, as such, is a target of much interest in oncology.

To date, promising results were reported in early trials for Raf and/or MEK inhibitors, although resistance may invariably occur following initial response [14]. Moreover, the use of MEK inhibitors as monotherapy may be limited to a subset of cancer patients with specific gene mutations, while dual Raf and MEK inhibitors could be more promising based on multiple mechanisms of inhibition [15].

The current case study presents the results of two MAPK pathway inhibitors, specifically MEK inhibitors CH4987655 and RO5068760. Both molecules are pure MEK inhibitors that demonstrated no activity against any other kinases. Since ERK is the sole substrate of MEK, it is expected that any observed activities of these two molecules are directly related to the actions of MEK inhibition.

Biomarker assay

The assay for the measurement of pERK was initially developed and tested in preclinical mice and monkey models. Prior to use in the clinic, the assay was validated in *in vitro* experiments for a selected range of drug concentrations using healthy volunteer blood donors. In the clinical studies, approximately 2 ml blood samples were taken at the following time points, time-matched to pharmacokinetic (PK) blood collection: 0 (pre-dose), 1, 2, 4, 6, 8, 12 and 24 h post-dose. Blood samples were stimulated with phorbol 12-myristate 13-acetate (PMA) to activate the MAPK pathway in the blood cells. Following PMA stimulation, blood cells were fixed with formaldehyde and red blood cells were lysed by the addition of a Triton X-100/PBS solution to a final concentration of 0.1%, which allows samples to maintain their *in vivo* MEK/ERK status. The resulting cells were stained with two antibodies (antihuman CD3 and antiphospho-ERK1/2). The CD3 antibody was used to identify T-lymphocytes, thus allowing pERK levels to be analyzed only in gated CD3-positive lymphocyte populations. The pERK level was measured by flow cytometry [16].

Translational aspects of biomarkers

CH4987655

CH4987655 (MW: 565.28) is a potent, highly selective ATP noncompetitive MEK inhibitor that exhibits an excellent selectivity profile [17]. CH4987655 inhibits Raf/MEK/ERK cascading enzymatic activity with an IC_{50} of 5.2 nM (2.9 ng/ml). In *in vitro* cell growth assays, CH4987655 specifically inhibited the phosphorylation of ERK, which led to a significant growth inhibition of cell lines from NSCLC and pancreatic cancer. In *in vivo* xenograft models, daily oral administration of CH4987655 showed strong antitumor activity against various tumors including NSCLC, pancreatic cancer and hepatocellular carcinoma. After treatment with CH4987655, 100% TGI or regression was observed in most xenograft models when dosed daily with at least 3 mg/kg for 14 days [18].

In preclinical species, CH4987655 was characterized by rapid absorption and low systemic clearance with an apparent half-life ($t_{1/2}$) of 11 and 8.54 h in rats and monkeys, respectively. Plasma protein binding was high (>98.9%) across species, including humans. Biliary excretion via glucuronidation (UGT1A1, UGT1A3 and UGT1A8) is the main metabolism pathway.

RO5068760

RO5068760 (MW: 647.45), a substituted hydantoin, represents a new class of potent, highly selective, non-ATP competitive MEK inhibitor. In cell-free systems, RO5068760 inhibits MEK1 with an IC_{50} of 25 nM (16 ng/ml). *In vitro*, RO5068760 selectively inhibits MEK1/2 kinase activity as evidenced by the significant reduction in phosphorylation levels of ERK1/2, the only known substrates of MEK1/2. *In vivo*, RO5068760 induced significant TGI and/or regression in nude mice bearing a broad range of human tumor xenografts including human colorectal, breast, melanoma and NSCLC carrying a B-Raf or Ras mutation. After treatment with RO5068760, 100% TGI or regression was observed in most xenograft models when dosed twice daily (b.i.d.) with at least 100 mg/kg for 14 days [19].

In preclinical species, RO5068760 was characterized by low to moderate clearance and intermediate volume of distribution. The $t_{½}$ was approximately 2–4 h. Bioavailability ranged from 16% (monkeys) to 60% (rats and mice). Metabolism by CYP450 3A4 to two major metabolites is the main metabolism pathway. Elimination of RO5068760 appears to be primarily through biliary excretion in rats.

Bench to bedside

As described above, *in vivo* animal studies for both CH4987655 and RO5068760 demonstrated significant antitumor activities in a number of relevant xenograft models. Although the two molecules were

studied in different laboratories and animal studies were not conducted head-to-head, similar efficacy experiments were performed. The results of these experiments were presented differently, but they convey very similar messages. The efficacy experiments included assessments of drug effects measured at different levels: change in pERK in surrogate tissue peripheral blood mononuclear cell (PBMC), change in pERK in target tumor tissue and change in tumor size. *In vivo* antitumor activities of CH4987655 and RO5068760 were both evaluated using a range of oral doses. Both molecules showed statistically significant TGI (~100%) in tumor-bearing mice for treated mice, compared with vehicle-treated control mice.

For CH4987655, antitumor activities were tested for five doses, up to 6 mg/kg, dosed at a continuous once-daily (q.d.) schedule for 2 weeks. A dose of approximately 1 mg/kg demonstrated approximately 100% TGI. Samples were analyzed for drug concentrations and pERK was determined in both tumor and plasma using western blotting for tumor samples and FACS analysis for blood samples. The results demonstrated similar dose dependency for tumor volume, pERK in tumor and pERK in PBMC, suggesting that inhibition of pERK formation in PBMCs may serve as a good biomarker for tumor volume [18]. For RO5068760, antitumor activities were tested for five doses, up to 200 mg/kg, dosed at a continuous b.i.d. schedule for 2 weeks. A dose of 100 mg/kg demonstrated approximately 100% TGI with a corresponding extent of inhibition of pERK in PBMC and tumor after a single 100 mg/kg dose [15]. Thus pERK inhibition in PBMC for both molecules was near 100% at doses demonstrating >100% TGI. PK simulations of RO5068760 and CH4987655 at dose levels with approximately 100% TGI showed that daily steady state concentrations were above the IC_{50} for inhibition of pERK formation for at least 12 h. Overall, the results supported the use of inhibition of pERK formation in PBMC to serve as a biomarker for drug effect and that achieving exposures above the IC_{50} for more than 12 h may be associated with significant TGI.

First-in-man studies

Traditionally, first-in-man (FIM) oncology studies are conducted in patients. However, the toxicity profile of some cytostatic agents can allow FIM studies in healthy volunteers. The preclinical toxicity profiles allowed both CH4987655 and RO5068760 to be administered as a single dose in healthy volunteers. Preclinical toxicities of concern were only observed after multiple dosing and they included ocular and gall bladder toxicities. In both cases, special safety assessments such as eye tests and ultrasound were performed prior to testing the next higher dose. This is an effective way to obtain a quick pharmacodynamic (PD) read-out with respect to target suppression and also presented the opportunity to characterize the PK, PD and safety/tolerability of the molecules without the confounding factors that exist in patient populations. Confounding factors include decreased organ function, the effect of concomitant medications and disease-related AEs. The FIM studies for both CH4987655 and RO5068760 were conducted in healthy volunteers with measurement of target suppression in PBMCs. Proof of mechanism was determined by inhibition of pERK phosphorylation pre- and postdrug administration. The single-dose clinical study design for both CH4987655 and RO5068760 was nearly identical with the exception of molecule-specific PK and/or safety measurements. The studies were conducted in parallel and at the same clinical site. This arrangement reduced factors that would have contributed to variabilities in PK, PD and safety assessments. Since the biomarker assessments were an essential component of the study, PD samples were diligently handled and processed by the site technicians. Where possible, the same technicians were used to ensure consistency, especially with regards to the steps involving sample PMA-stimulation and fixation with formaldehyde. These were critical pre-analysis procedures that influenced the measurement of drug effects. The results of the studies were reported in Lee *et al.* [20–22].

For CH4987655, pERK inhibition was exposure dependent and greater than 80% inhibition at higher doses. As shown in Figure 2A, the PK–PD relationship was characterized by an inhibitory E_{max} model (E_{max}: ~100%; IC_{50}: 40.6 ng/ml using nonlinear mixed effect modeling) [20,21]. For RO5068760, pERK inhibition was relatively modest with a mean maximal pERK suppression of only 55%. As shown in Figure 2B, the RO5068760 concentration did not span the full concentration range for complete characterization of the exposure-effect E_{max} relationship but exploratory model fitting still enabled an estimate of IC_{50}. Acknowledging the high uncertainty of the parameter estimate, the IC_{50} was approximately 1600 ng/ml [22].

Results of other MEK inhibitors in clinics

Currently, several MEK inhibitors have been evaluated as single agent and/or combination therapy in advanced solid tumor and/or hematological malignancies (e.g., PD0325901, XL518/GDC-0973, AZD6244 [ARRY-142886], AZD8330 [ARRY-704], GSK1120212, ARRY-438162, TAK733, AS703026, E6201, RDEA-119 and WX554).

In a more advanced Phase I patient study for AZD6244, pERK activities in PBMC was also used to assess molecular response and proof of mechanism. At maximum tolerated dose (75-mg capsule), a dose with manageable safety and tolerability profile, the results showed positive signals of clinical activities for patients with V600E metastatic melanoma. At this dose one patient showed a complete response and ten (out of 55) patients experienced stable disease for at least 16 weeks. Together with a favorable PK and PD profile, the prolonged anticancer activity suggested further evaluation at 75 mg in Phase II trials. The relationship between drug exposure and pERK inhibition was characterized by an E_{max} model with an EC_{50} of 352 ng/ml and E_{max} of 91%, indicating a potential for approximately 100% inhibition. At 75 mg, the C_{max} on day 8 was 1439 ng/ml, suggesting approximately 100% pERK inhibition at this dose level [23]. The published single dose concentration–time profiles for AZD6244 can be used to simulate concentration–time profiles after multiple dosing, which suggest that at the dose with clinical responses, plasma concentrations are above IC_{50} for at least 8 h each day, similar to the data from nonclinical studies of CH4987655 and RO5068760. These recent clinical findings together with preclinical findings strengthens the rational basis of using pERK inhibition in PBMC as a translational biomarker for molecule selection in early oncology drug development.

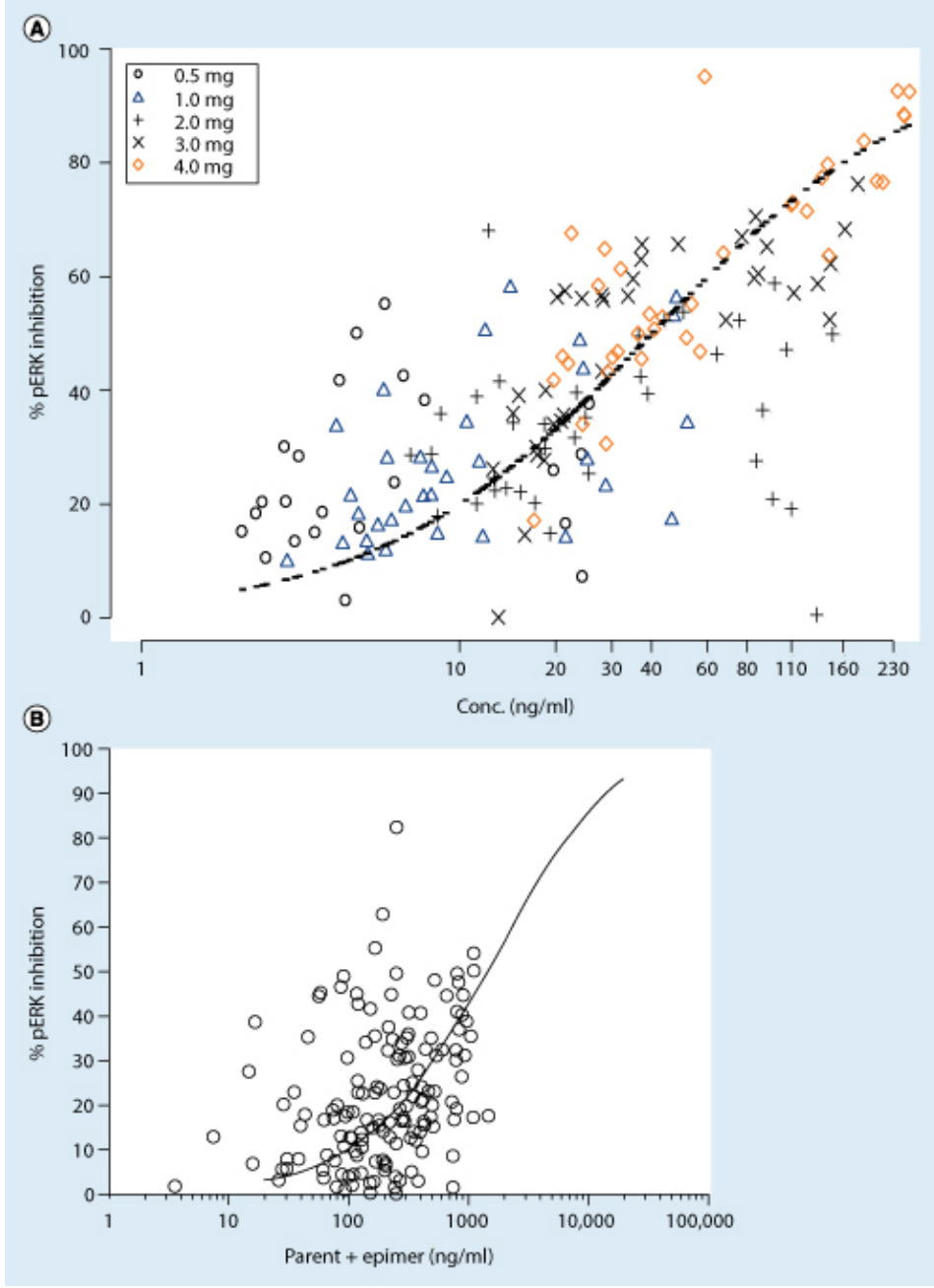

Figure 2. Relationships between drug concentration and extent of ERK phosphorylation inhibition were characterized by a direct pharmacological model, the E_{max} model.
(A) CH4987655, **(B)** RO5068760.
Figures reproduced from [21] **(A)** and [22] **(B)**.

Role of biomarker in decision making for CH4987655 & RO5068760

Go–no go decisions for each molecule were defined based on safety, PK and PD criteria. The safety profiles must not suggest any AEs deemed unacceptable in humans. Molecules must demonstrate acceptable PK variabilities and characteristics allowing for a convenient q.d. or b.i.d. dosing schedule. Exposures should approximate the effective exposure range observed in preclinical models. Importantly, molecules must demonstrate PD, that is, pERK inhibition in PBMCs that were above the threshold indicative of activity as suggested by preclinical models, as well as clinical data for other MEK inhibitors.

The safety profiles for both CH4987655 and

RO5068760 were acceptable. CH4987655 single doses up to 4 mg were well tolerated. As expected for MEK inhibitors, epithelial and GI types of AEs were observed, such as diarrhea, abdominal pain, acne, upper abdominal pain and flatulence. This was consistent with preclinical toxicology data and reported AEs from other MEK inhibitors in the clinic and the drug's mechanism of action [24]. Both epithelial and GI AEs were dose dependent, with increasing frequency and severity at higher doses. The PK profiles for CH4987655 and RO5068760 were different. CH4987655 demonstrated rapid absorption with a median t_{max} of 1 h and a disposition phase with a terminal elimination $t_{1/2}$ of approximately 25 h. Exposures were dose proportional and the variabilities were low for both C_{max} and AUC. RO5068760 was absorbed with a median t_{max} of 2 h. The disposition was biphasic with a mean terminal elimination $t_{1/2}$, ranging from 5 to 9 h. RO5068760 variability was moderate to high, ranging from 38 to 62% for C_{max} and from 41 to 69% AUC. Statistical analysis demonstrated a lack of dose proportionality within the dose range of 50–800 mg.

The PD profiles for CH4987655 and RO5068760 were different. They spanned a different range of pERK inhibition and were, therefore, discriminatory. CH4987655 demonstrated dose- and concentration-dependent pERK inhibition in PBMCs with exposures of CH4987655 up to 4-mg dose covering pERK inhibition from the no effect level to near the maximum effect of 100%. However, RO5068760 demonstrated rather modest pERK inhibition of only 55% up to the highest dose of 800 mg. Although they covered different ranges of pERK inhibition, it is the extent of pERK inhibition following multiple dosing at steady-state which is relevant, since the drug is expected to

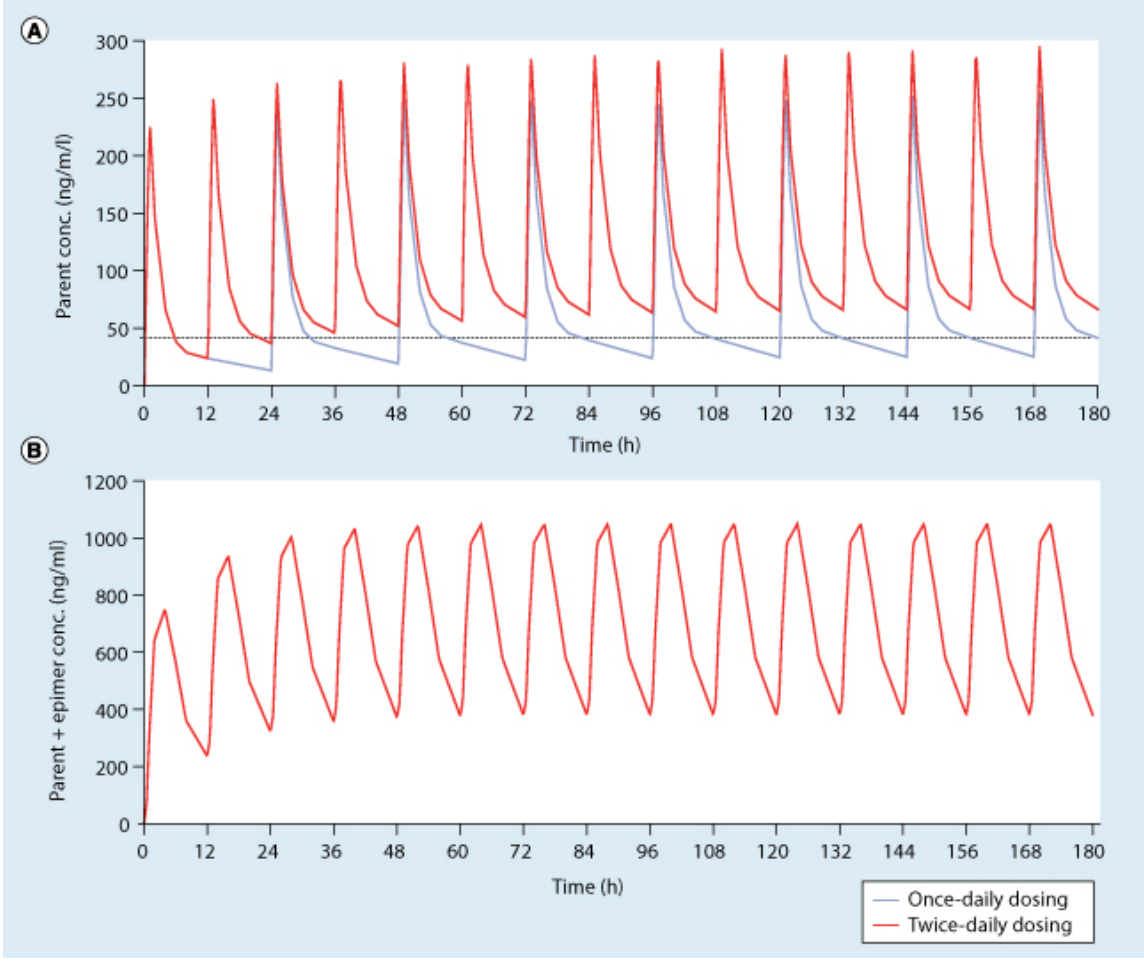

Figure 3. Pharmacokinetic simulations for multiple continuous daily dosing based on characteristics of single dose pharmacokinetic data. (A) CH4987655 dosed on both continuous once-daily and twice-daily schedules. **(B)** RO5068760 dosed on continuous once-daily schedule.
Figures reproduced from [21] **(A)** and [22] **(B)**.

be dosed chronically. Assuming no time-dependent PK, multiple dose simulations are shown in Figure 3. CH4987655 demonstrated that 4 mg dosed b.i.d. will maintain concentration above IC_{50} for 12 h, and 4 mg q.d. will still maintain concentration above IC_{50} for a significant part of the dosing interval. However, multiple dose simulations of RO5068760 demonstrated that even the highest dose of 800 mg dosed b.i.d. does not maintain concentration above IC_{50}. Moreover, due to its less than proportional exposure increase and high PK variability, it was considered very unlikely that higher doses could achieve higher drug concentrations or pERK inhibition. From this perspective, the PD results demonstrated that CH4987655 was superior to that of RO5068760 in terms of MEK inhibition and, therefore, potential for therapeutic effects. The comparative findings between that of CH4987655 versus RO5068760 are summarized in Table 1.

Conclusion

For novel targets such as ERK in the case of CH4987655 or RO5068760, it is the usual situation that limited preclinical and preliminary clinical data support molecule decision and progression in oncology early clinical development. Until late-phase confirmatory data are available to validate the biomarkers, support from preclinical and preliminary clinical data must suffice. The current case study illustrated how a predictive response biomarker was identified and developed in preclinical models and translated into early clinical studies. The marker of drug activity in a surrogate tissue, and indeed a surrogate population, enabled an early decision regarding which molecule was the more promising to develop. For the selected molecule, CH4987655, the pERK inhibition biomarker data also helped determine the potential dosing schedules for the initial efficacy and tolerability studies in patients. For novel drug targets where there are no clinical efficacy data, biomarkers such as inhibition of pERK by MEK inhibitors cannot yet be used as surrogates of clinical benefit. This link can only be established (or refuted) once substantial biomarker and clinical efficacy data are available, ideally for more than one drug. However, although activity on a biomarker of target engagement cannot yet predict eventual clinical outcome, it does at least confirm that CH4987655 is a MEK inhibitor *in vivo* in man, achieves levels of inhibition associated with efficacy in xenograft models and is capable of investigating the potential clinical utility of MEK inhibitors.

The exact level of activity, measured in PBMCs, which correlates to tumor response is not yet known but is currently being explored in a ongoing CH4987655 Phase I patients study. This patient study

Table 1. Summary of comparative preclinical and clinical findings for CH4987655 versus RO5068760.

Molecule	Preclinical findings						Clinical findings		
	MW	*In vitro* IC_{50} (nM [ng/ml])	*In vivo*	BCS class	Absolute bioavailability (%)	Major elimination pathway	Drug interaction liabilities	Dose linearity (AUC, C_{max}; mg)	PK variability (AUC, C_{max}; %)	Clinical IC_{50}, pERK in PBMC (ng/ml)	Simulated drug conc. at steady-state, either q.d. or b.i.d. dosing schedule
CH4987655	565.28	5.2 (2.9)	100% TGI in broad range of xenograft models	I	Rats (84) monkeys (9–17)	Glucuronidation via UGT1A1	CYP3A4 inducer, P-gp inhibiter	Linear, 0.5–4	Low	~41	4 mg b.i.d. maintained concentration above IC_{50}
RO5068760	647.45	25 (16)	100% TGI in broad range of xenograft models	IV	Rats (60) monkeys (16)	Metabolism via CYP3A4	CYP3A4 inducer and substrate	Does not appear linear, 50–800, exposure plateau at higher doses	Moderate to high	~1000	Neither q.d. nor b.i.d. achieved IC_{50}

BCS: Biopharmaceutical class system; b.i.d.: Twice daily; PBMC: Peripheral blood mononuclear cell; q.d.: Once daily; TGI: Tumor growth inhibition.

will attempt to correlate PBMC pERK activity to tumor pERK activity, both of which will be evaluated for their correlation to FDG-PET results and tumor activity. Correlation to tumor pERK and FDG-PET activities will be evaluated in an identified patient population who are responsive to CH4987655 treatment. The identified patient population may be a specific tumor type, such as advanced melanoma, and/or designated by mutation status, such as advanced melanoma with V600E Braf mutation. This will ensure that the drug effects, as measured by pERK in target tumor tissue, are indeed events that occur in response to inhibiting the dominant dysregulated MAPK cell pathway driving the cancer, and that measurements are performed in a homogeneous patient population. As discussed in 'Translational aspects of biomarkers', correlations between PBMC pERK and tumor pERK and activities were already suggested in xenograft models responsive to MEK inhibitors. To complete this linkage into man, the fully planned pending analysis will explore correlative analysis of PBMC (xenografts) → PBMC (HV) → PBMC (patients) → tumor (patients) → FDG-PET (patients) → tumor response (patients). If in patients PBMC pERK correlates to that of FDG-PET and tumor response, the predictive validity of PBMC pERK as a biomarker for molecule selection in oncology early clinical development will be strengthened.

Assuming the above is confirmed, pERK PBMC can then conveniently be used as a biomarker of drug effects for MEK inhibitors. Since PBMCs are considered normal surrogate tissues in both healthy volunteers and patients, it is expected that PBMC pERK in healthy volunteers will represent PBMC pERK in patients. This argues for the evaluation of biomarkers in healthy volunteers as a means of driving rapid and effective decision making in oncology. Drug safety and toxicities permitting, the advantages of using a single ascending dose, healthy volunteers study to start clinical investigations include:

- Characterization of PK and PD in a homogeneous population without confounding disease factors, thereby reducing sources of variability;
- Faster enrollment and quicker turnaround of PK and PD results, thereby accelerating the understanding of the drug, leading to expedited decision making;
- Avoid the need to expose patients to subactive doses, thereby subsequent patient studies may start at higher doses;
- Understanding of PK properties in advance of patient studies, thereby guiding subsequent patient studies with the optimal dosing regimen.

One consideration might be that clinical safety and toxicities cannot be fully evaluated in a single ascending dose, healthy volunteer study because most safety and toxicities only occur after multiple dosing and the risk–benefit may not allow for this to be tested in healthy volunteers. Despite that, the advantages of first testing in a single dose ascending study in healthy volunteers still provide much valuable PK and PD data, which helps efficiently design the subsequent patients study.

The results of the complete patient biomarker analysis as it relates to clinical activities are anticipated in the near future. In addition, the translational aspects of safety and toxicity are of interest and will also be included in the context of clinical activities. In conclusion, as more is learnt about MEK inhibitors in the clinic, it will become clear which are the most relevant PD parameters driving clinical activities, and how they can best be used to guide targeted therapies in oncology early clinical development.

Future perspective

Translational medicine intends to facilitate the transition of basic science to clinical practice, thereby sharing many of the basic tenets of the discipline of clinical pharmacology. Traditionally, early clinical studies aim to characterize the safety/tolerability and PK, and to define the dose-limiting toxicities and maximum tolerated doses. For targeted therapies, where the targets and their downstream effects are known, biomarkers can be incorporated to demonstrate biological activities (either target modulation or downstream activities). Development of biomarkers with predictive value is critical to facilitate the transition from *in vitro* and experimental animal research to human application. Targeted therapies may utilize this strategy to improve success rate by making critical decisions early in clinical development, which ultimately attempts to maximize efficiency while minimizing expensive late attrition rates. Critical decisions include decision on 'go–no go', selection of the best molecule and recommendation on dose or dosing schedule. The current article presents one case study demonstrating an early strategy in selecting the most promising molecule to move forward in the next clinical phase. With advances in genomics and knowledge of disease pathways, it is expected that translational medicine will continue to be an emerging field that focuses on developing new, effective and safe therapies.

Executive summary

- Targeted therapies (where the targets and their downstream effects are known) and biomarkers can be incorporated in oncology early clinical studies to demonstrate biological activities (either target modulation or downstream activities).
- Strategic implementation of biomarkers for targeted therapies may help maximize efficiency by facilitating critical decisions, such as molecule 'go–no go' selection of best molecule and recommendation of dose or dosing schedule.
- The current case study demonstrated a successful example of molecule selection for a class of compound, MEK inhibitors, in early clinical development.

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