Safety, pharmacokinetic, pharmacodynamic, and efficacy data for the oral MEK inhibitor trametinib: a phase 1 dose-escalation trial

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Summary

Background **Inhibition of MEK stops cell proliferation and induces apoptosis; therefore, this enzyme is a key anticancer target. Trametinib is a selective, orally administered MEK1/MEK2 inhibitor. We aimed to define the maximum tolerated dose and recommended phase 2 dose of trametinib and to assess its safety, pharmacokinetics, pharmacodynamics, and response rate in individuals with advanced solid tumours.**

Methods **We undertook a multicentre phase 1 study in patients with advanced solid tumours and adequate organ function. The study was in three parts: dose escalation to define the maximum tolerated dose; identification of the recommended phase 2 dose; and assessment of pharmacodynamic changes. Intermittent and continuous dosing regimens were analysed. Blood samples and tumour biopsy specimens were taken to assess pharmacokinetic and pharmacodynamic changes. Adverse events were defined with common toxicity criteria, and tumour response was measured by Response Evaluation Criteria In Solid Tumors. This study is registered with ClinicalTrials.gov, number NCT00687622.**

Findings **We enrolled 206 patients (median age 58·5 years, range 19–92). Dose-limiting toxic effects included rash (n=2), diarrhoea (n=1), and central serous retinopathy (n=2). The most common treatment-related adverse events were rash or dermatitis acneiform (n=165; 80%) and diarrhoea (87; 42%), most of which were grade 1 and 2. The maximum tolerated dose was 3 mg once daily and the recommended phase 2 dose was 2 mg a day. The effective half-life of trametinib was about 4 days. At the recommended phase 2 dose, the exposure profile of the drug showed low interpatient variability and a small peak:trough ratio of 1·81. Furthermore, mean concentrations in plasma were greater than the preclinical target concentration throughout the dosing interval. Pathway inhibition and clinical activity were seen, with 21 (10%) objective responses recorded.**

Interpretation **The recommended phase 2 dose of 2 mg trametinib once a day is tolerable, with manageable side-effects. Trametinib's inhibition of the expected target and clinical activity warrants its further development as a monotherapy and in combination.**

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Introduction

The MAPK pathway incorporates the enzymes RAS, RAF, ERK, and MEK. In this pathway, membrane-bound receptors signal to proteins that regulate cell proliferation and survival. The MAPK pathway is constitutively activated in many tumour types, including those *BRAF*^{V600} mutations and some RAS mutations.[1–3] MEK has emerged as a key anticancer target because inhibition of this enzyme blocks cell proliferation and induces apoptosis.[4–7]

Trametinib is a reversible, highly selective allosteric inhibitor of MEK1/MEK2 (also known as MAP2K1 and MAP2K2) activation and kinase activity, with a half-maximum inhibitory concentration (IC_{50}) of 0·7–0·9 nmol/L.[8] In enzymatic and cellular studies, trametinib inhibited kinase activity of MEK1 and MEK2, prevented RAF-dependent MEK phosphorylation, and prolonged inhibition of phosphorylated ERK (a substrate of MEK).[8] In-vitro studies undertaken in 94 different cancer cell lines showed cytotoxic responses in seven of ten BRAF^{V600}-mutant cells lines at nanomolar concentrations.[8] Cell lines and mouse xenograft models with activating mutations in RAS were also sensitive to trametinib.[6] Pharmacokinetic profiling in mice indicated a mean effective half life ($t_{1/2}$) of 33 h, with a low peak:trough ratio (around 1·6–2·8) after single or repeat dosing of trametinib.[8]

We undertook an open-label phase 1 study to ascertain the maximum tolerated dose of trametinib in human beings for the first time, and to define the recommended phase 2 dose and regimen of this agent for patients with advanced solid tumours. We also aimed to establish pharmacokinetic, pharmacodynamic, and efficacy data for trametinib in selected tumour types.

Methods

Study design

We undertook this phase 1 study in three parts (appendix, p 1). In part one, we identified the maximum tolerated dose of trametinib by safety, pharmacokinetic, and

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pharmacodynamic assessments in patients with solid tumours. We assessed three regimens of trametinib, administered orally as tablets: (1) once a day for 21 days, followed by a 7-day break (21/7 regimen); (2) a loading dose on day 1 and day 2, or day 1 only, followed by continuous once-daily dosing (loading dose regimen); and (3) continuous once-daily dosing without a loading dose (once-daily regimen). Treatment cycles for all regimens were 28 days. Part one took place at three institutions: Sarah Cannon Research Institute (Nashville, TN, USA), University of Colorado (Aurora, CO, USA), and University of Pennsylvania (Philadelphia, PA, USA).

In part two, we assessed the safety and efficacy of the recommended phase 2 dose of trametinib in patients with melanoma, pancreatic cancer, non-small-cell lung cancer, colorectal cancer with mutations in *KRAS* or *BRAF*, or any cancer with a mutation in *BRAF*. In part three, we characterised the biologically active dose range of trametinib by analysis of changes in pharmacodynamic markers in tumour biopsy samples from baseline to day 15. Parts two and three were undertaken at the three sites in part one and at additional sites listed in the appendix (p 1).

Patients

Full eligibility criteria are presented in the appendix (p 2). In brief, patients were eligible for the study if they had any advanced solid tumour or lymphoma, had received an unlimited number of previous treatments, and had no history of retinal vein occlusion, central serous retinopathy (defined as fluid accumulation between the retinal pigment epithelium and the outer segment of the eye), or glaucoma diagnosed within 1 month. We allowed those with brain metastases treated previously with gamma knife or radiation to enrol 2 or 4 weeks after radiation treatment, respectively. Individuals with untreated brain metastases were not eligible.

We undertook this study in accordance with all applicable regulatory requirements, including good clinical practice guidelines, and the independent ethics committee for every trial centre approved the study. We followed the guiding principles of the Declaration of Helsinki. All patients provided written informed consent.

Procedures

In part one, we used an accelerated titration scheme, in which only one patient was required to complete one cycle (28 days) of treatment before dose escalation.[9] At the second occurrence of a grade 2 toxic effect, or the first occurrence of either one dose-limiting toxic effect or one grade 2 ocular or cardiac toxic effect during the first cycle, escalation then followed a standard 3+3 design. We defined the maximum tolerated dose as the highest dose at which one or fewer of six patients had a dose-limiting toxic effect during the first cycle. We regarded the maximum tolerated dose as the recommended phase 2 dose unless a lower dose with superior tolerability provided adequate exposure and biological activity. We graded toxic effects according to National Cancer Institute criteria.[10] We defined dose-limiting toxic effects during the first 28 days (cycle one) of treatment as follows: grade 4 haematological toxic effects; grade 3 thrombocytopenia with bleeding; grade 3 or 4 non-haematological toxic effects (including rash, nausea, and vomiting if uncontrolled with supportive care); treatment delay of 14 days or more because of unresolved toxic effects; grade 2 or higher non-haematological toxic effects judged dose-limiting by the investigator and medical monitor; a concentration of troponin greater than the upper limit of normal; and a calcium phosphorus product greater than $4{\cdot}4\ mmol^2\ L^{-2}$ ($55\ mg^2\ dL^{-2}$), based on preclinical toxicology findings.

All patients underwent physical examination, electrocardiography, laboratory assessments, ophthalmic examination, left-ventricular ejection fraction measurement by echocardiography or multigated acquisition scan, and disease assessments using Response Evaluation Criteria In Solid Tumors (RECIST), version 1.0. We did these tests at baseline and repeated them throughout the study. Full details of assessments are presented in the appendix (pp 2–3).

For analysis of concentrations in plasma of trametinib, we obtained blood samples during the first cycle of treatment on days 1 and 15 before administration of the dose and at hourly or part-hourly intervals from 0·25 h up to 24 h after the dose was given. We also gathered samples before the dose was administered on day 3, 4, or 5, and day 8, 15, and 22 during cycle one, and at the beginning of subsequent cycles. To characterise the range of biologically active doses, we gave patients in the third part of the study run-in once-daily doses of 0·5 mg, 1 mg, or 2 mg for days 1–15, followed by either 2 mg or 2·5 mg a day (QD15/QD regimen).

We obtained paired tumour biopsy specimens before treatment and on day 15. All patients received either 2 mg or 2·5 mg a day of trametinib after the day 15 biopsy. We analysed biopsy specimens for changes in phosphorylated ERK, Ki67 (a marker of cell proliferation), and p27 (a cyclin-dependent kinase inhibitor encoded by *CDKN1B*).[11] In part one of the study, obtaining tissue biopsy specimens was optional.

Statistical analysis

We tested no formal hypotheses in this study; analyses were descriptive and exploratory. We included patients in analyses if they received at least one dose of trametinib. We did power model analyses to assess dose proportionality (appendix, p 3).[12] We used SAS (version 9.1). The data cutoff was June 7, 2011.

This study is registered with ClinicalTrials.gov, number NCT00687622.

Role of the funding source

This study was funded, initiated, administered, and sponsored by GlaxoSmithKline, which also provided data

analysis. The study was designed by the sponsor in collaboration with JRI, LF, GE, KF, HAB, and WAM. All authors had access to all study data, contributed to data interpretation, and had responsibility for the decision to submit for publication. The Article was written by JRI with contributions from all authors, including employees of the sponsor.

Results

Between July 31, 2008, and Oct 5, 2010, 206 patients were enrolled and received at least one dose of trametinib (table 1). More than half had received three or more previous regimens. Various primary tumour types were included, and melanoma, non-small-cell lung cancer, colorectal cancer, and pancreatic cancers were the most frequent. Data for patients with melanoma are presented elsewhere.[13] At the data cutoff, all but six (3%) patients had discontinued study treatment, most typically for progressive disease (n=148; 72%); 18 (9%) discontinued because of adverse events.

Patients were enrolled into 21 cohorts (table 2). Cohorts 1–12 formed the first part of the study (dose escalation), the second part (assessment of the recommended phase 2 dose) contained cohorts 13 and 14, and in the third part (to test the biologically active dose range), cohorts 15–21 participated. The first trametinib-related adverse events were grade 1 acneiform rash and grade 1 diarrhoea and the first dose-limiting toxic effect was grade 3 rash (table 2).

	Patients (n=206)
Age (years)	58·5 (19–92)
Sex	
Men	112 (54%)
Women	94 (46%)
ECOG performance status*	
0	98 (48%)
1	107 (52%)
Previous lines of treatment	
0	11 (5%)
1–2	51 (25%)
≥3	144 (70%)
Tumour types	
Melanoma (cutaneous or unknown primary)	81 (39%)
Non-small-cell lung	30 (15%)
Colonic or rectal	28 (14%)
Pancreatic	26 (13%)
Uveal melanoma	16 (8%)
Others†	25 (12%)

Data are number (%) or median (range). ECOG=Eastern Cooperative Oncology Group. *One patient had an ECOG performance status of 2. †Ovarian (n=4), papillary thyroid (n=4), carcinoid (n=2), and anal, appendiceal, breast, endometrial or uterine, hepatocellular, nasopharyngeal, neuroendocrine, oral, pleiomorphic, prostate, renal cell, soft palate, soft-tissue sarcoma, squamous cell, and thyroid (all n=1).

Table 1: **Baseline characteristics**

Pharmacokinetic modelling based on data from cohorts 1–4 predicted that steady state was not achieved during the first treatment cycle with the 21/7 regimen, because of the prolonged effective $t_{1/2}$ of trametinib, but could be achieved in the first cycle with addition of loading doses followed by once-daily dosing (loading dose regimen). The 7-day break in the 21/7 regimen was therefore removed in favour of continuous daily dosing with a loading dose. The loading dose regimen of two 10 mg a day loading doses followed by 3 mg continuous daily dose (10/10/3) exceeded the maximum tolerated dose. Dose-limiting toxic effects of grade 3 diarrhoea, grade 3 rash, and grade 2 central serous retinopathy were seen with this regimen (table 2), with retinopathy and diarrhoea reported within the first 2 days.

Further analysis of pharmacokinetic data showed that steady state could be achieved during the first treatment cycle without loading doses. Thus, loading doses were

	Dose (mg)	Patients (n)	DLTs and adverse events
21/7 regimen (first part of study)			
1	0·125	2	..
2	0·25	1	..
3	0·5	2	Grade 1 rash and diarrhoea (neither DLTs)
4	1	2	..
5	2	3	Grade 3 rash
Loading dose regimen (first part)			
6	10/10/3	4	Grade 2 central serous retinopathy, grade 3 diarrhoea, grade 3 rash
7	6/6/2	6	..
8	8/8/2·5	7	..
9	6/2	4	..
Once-daily regimen (first part)			
10	3	12	..
11	4	3	Grade 2 central serous retinopathy
12	2·5	9	..
Once-daily regimen (second part)			
13	2	62	..
14	2·5	50	..
QD15/QD regimen (third part)			
15	0·5/2	6	..
16	0·5/2·5	6	..
17	1/2	7	..
18	1/2·5	5	..
19	2	8	..
20	2/2·5	4	..
21	2·5	3	..

21/7 regimen=once-daily dosing for 21 days, followed by 7 days without drug. Loading dose regimen=one or two loading doses followed by continuous once-daily dosing. Once-daily regimen=continuous once-daily dosing. QD15/QD regimen=doses of ≤2·5 mg once a day for days 1–15 (run-in dose) followed by either 2 mg or 2·5 mg once a day. DLTs=dose-limiting toxic effects.

Table 2: **Dosing scheme and early adverse events and DLTs**

removed and the resulting once-daily regimen was investigated in cohorts 10–12. In three patients given a daily dose of 4 mg, a grade 2 dose-limiting toxic effect of central serous retinopathy was recorded on day 8 (table 2). Although this event did not meet criteria for declaring a protocol-defined maximum tolerated dose, escalation was halted because of the early onset of this dose-limiting toxic effect and the risk of further central serous retinopathy events. Thus, 3 mg once a day was declared the maximum tolerated dose, with no dose-limiting toxic effects noted during the first cycle in the 12 patients treated. However, beyond the first treatment cycle, one patient was withdrawn from this dose level because of fatigue, five needed dose interruptions, and two had dose reductions. Owing to concerns about the long-term tolerability of the 3 mg daily dose, 2 mg and 2·5 mg once a day were assessed further in expansion cohorts to aid determination of the recommended phase 2 dose.

Safety data for all patients in the study were combined. Table 3 shows treatment-related adverse events that arose at any time in the study with a frequency of at least 5%. Only two grade 4 treatment-related adverse events were noted (rash and thrombocytopenia, with a daily dose of 2·5 mg), and one grade 5 event was reported (sudden death with the 2·0 mg daily dose). Of 70 patients receiving a dose of 2 mg a day, eight (11%) had grade 3 treatment-related events, seven of which arose during the first treatment cycle. Furthermore in this subgroup, eight (11%) individuals needed dose reductions due to adverse events, three of which happened during the first cycle of treatment, whereas 25 (40%) of 62 patients needed reductions at the 2·5 mg daily dose. The most typical adverse event leading to dose reduction at either dose was rash.

Skin-related toxic effects were the most frequent treatment-related adverse events in the study (table 3), in particular, rash or dermatitis acneiform, which was mainly on the face, scalp, chest, and back. Onset happened within 4 weeks in 46 (66%) patients who received the 2 mg a day dose. Occurrence of treatment-related rash or dermatitis acneiform of grade 2 or higher was proportional to dose, arising less frequently in patients receiving 2 mg a day (n=25, 36%) compared with those on 2·5 mg daily (30, 48%) or 3 mg a day (seven, 58%). Skin dryness, fissures, paronychia, and pruritus were also seen. No events of squamous-cell carcinoma or other proliferative skin lesions were recorded.

Diarrhoea, the next most common non-haematological adverse event (table 3), was predominantly grade 1 (all doses combined and 2 mg a day) and was manageable with standard treatments. Peripheral oedema was reported in about a third of all patients, periorbital oedema less frequently. No occurrences higher than grade 2 were reported for either oedema event at 2 mg a day.

Treatment-related ocular toxic effects were recorded in 31 (15%) patients, including three events of central

	Grade 1		Grade 2		Grade 3		Grade 4		Total	
	2 mg once daily (n=70)	Total (n=206)	2 mg once daily (n=70)	Total (n=206)	2 mg once daily (n=70)	Total (n=206)	2 mg once daily (n=70)	Total (n=206)	2 mg once daily (n=70)	Total (n=206)
Any events	20 (29%)	55 (27%)	39 (56%)	102 (50%)	8 (11%)	37 (18%)	0	2 (<1%)	68 (97%)	197 (96%)
Skin-related toxic effects*	34 (49%)	81 (39%)	25 (36%)	74 (36%)	4 (6%)	16 (8%)	0	1 (<1%)	63 (90%)	172 (83%)
Rash or dermatitis acneiform	34 (49%)	81 (39%)	22 (31%)	69 (33%)	3 (4%)	14 (7%)	0	1 (<1%)	59 (84%)	165 (80%)
Diarrhoea	24 (34%)	63 (31%)	7 (10%)	22 (11%)	1 (1%)	2 (<1%)	0	0	32 (46%)	87 (42%)
Fatigue	13 (19%)	37 (18%)	7 (10%)	23 (11%)	1 (1%)	8 (4%)	0	0	21 (30%)	68 (33%)
Peripheral oedema	18 (26%)	47 (23%)	2 (3%)	12 (6%)	0	1 (<1%)	0	0	20 (29%)	60 (29%)
Nausea	14 (20%)	46 (22%)	4 (6%)	11 (5%)	0	0	0	0	18 (26%)	57 (28%)
Vomiting	5 (7%)	23 (11%)	3 (4%)	10 (5%)	1 (1%)	1 (<1%)	0	0	9 (13%)	34 (17%)
Pruritus	10 (14%)	19 (9%)	4 (6%)	10 (5%)	0	0	0	0	14 (20%)	29 (14%)
Dry skin, chapped skin, or skin fissures	11 (16%)	31 (15%)	4 (6%)	7 (3%)	0	0	0	0	15 (21%)	38 (18%)
Decreased appetite	6 (9%)	14 (7%)	1 (1%)	5 (2%)	0	1 (<1%)	0	0	7 (10%)	20 (10%)
Ocular toxic effects†	6 (9%)	26 (13%)	0	4 (2%)	1 (1%)	1 (<1%)	0	0	7 (10%)	31 (15%)
Mucosal inflammation	3 (4%)	11 (5%)	0	4 (2%)	0	0	0	0	3 (4%)	15 (7%)
Constipation	2 (3%)	8 (4%)	1 (1%)	3 (1%)	0	0	0	0	3 (4%)	11 (5%)
Left-ventricular dysfunction or ejection fraction decreased	2 (3%)	5 (2%)	4 (6%)	9 (4%)	1 (1%)	2 (<1%)	0	0	7 (10%)	16 (8%)
Periorbital oedema	5 (7%)	10 (5%)	0	1 (<1%)	0	0	0	0	5 (7%)	11 (5%)
Thrombocytopenia	1 (1%)	8 (4%)	0	1 (<1%)	0	1 (<1%)	0	1 (<1%)	1 (1%)	11 (5%)
Dry mouth	2 (3%)	10 (5%)	0	0	0	0	0	0	2 (3%)	10 (5%)

Data are number of patients (%). The most frequent (≥5%) adverse events are shown. *Includes acne, dermatitis acneiform, dermatitis psoriasiform, erythaema, genital rash, palmar-plantar erythrodysesthesia, rash, erythaematous rash, follicular rash, generalised rash, macular rash, maculopapular rash, pruritic rash, pustular rash, seborrhoeic dermatitis, and skin exfoliation. †Includes blurred vision, central serous retinopathy (chorioretinopathy), dry eye, eye naevus, glaucoma, increased intraocular pressure, photophobia, reduced visual acuity, retinal haemorrhage (retinal vein occlusion), and visual impairment.

Table 3: **Treatment-related adverse events**

serous retinopathy and one of retinal vein occlusion (table 3). The retinopathy events arose during loading dose and once-daily regimens (10/10/3 mg, 6/6/2 mg, and 4 mg a day) and all three resolved on withdrawal of trametinib; none were rechallenged. The retinal vein occlusion happened with a daily dose of 2 mg in the seventh cycle of treatment.

A treatment-related fall in left-ventricular ejection fraction and left-ventricular dysfunction were noted in 16 (8%) patients across the entire study: most were grade 2 or lower (table 3). Of two grade 3 events, one resolved on discontinuation of trametinib and the other arose in the setting of progressive disease without follow-up assessment.

Seven (3%) patients had treatment-related serious adverse events but no one event happened more than once. Within the entire study, 21 patients died within 28 days of their last dose of study drug, all due to the disease under study or disease-related complications.

Trametinib was absorbed rapidly; median time to maximum concentration (T_{max}) for one 2 mg dose was 1·5 h. The effect of loading doses was negligible with respect to the maximum concentration (C_{max}) of trametinib and area under the curve (AUC) at day 15, and therefore data from loading dose and once-daily regimens were pooled for repeat-dose analysis according to once-daily dose level (table 4). The effective $t_{1/2}$ was about 4 days. AUC and C_{max} on day 15 rose in proportion to dose (figure 1; appendix, p 3) and median T_{max} ranged from 1·75–2·05 h (table 4). By contrast with single-dose pharmacokinetic data, relatively low interpatient variability was associated with parameters (between-subject coefficient of variation 22–49%) at day 15. At 2 mg a day, trametinib showed a mean peak:trough ratio

	Patients (n)	AUC_{0-24} (ng h^{-1} mL^{-1})	C_{max} (ng/mL)	T_{max} (h)	C_{24} (ng/mL)	AR	$T_{1/2}$ eff (h)
0·125 mg	2	17·8, 14·6	1·21, 1·58	1·0, 1·5	0·66, 0·58	NA, NA	NA, NA
0·25 mg	1	31·4	2·08	1·5	1·16	NA	NA
0·5 mg	2	60·2, 98·9	3·91, 5·38	2·08, 1·0	2·21, 4·29	NA, 10·2	NA, 161
1 mg	2	245, 95·1	15·8, 7·96	0·75, 1·5	8·44, 19·1	18·3, 7·80	296, 121
2 mg	13*	370 (22% [256–500])	22·2 (28% [14·0–32·9])	1·75 (1·0–3·0)	12·1 (19% [8·26–16·9])	5·97 (33% [4·03–11·5])	90·2 (36% [58·4–183])
2·5 mg	16†	410 (41% [215–865])	24·1 (49% [12·4–63·2])	2·0 (1·0–10·2)	15·1 (52% [6·86–40·5])	4·39 (83% [1·02–13·1])	57·6 (137% [4·01–210])
3 mg	16‡	540 (38% [261–968])	33·4 (41% [15·6–60·9])	2·05 (0·5–10·0)	17·9 (44% [7·77–35·5])	5·93 (85% [1·50–18·0])	86·1 (106% [15·1–291])
4 mg	3§	946, 546	62·8, 43·8	1·0, 1·5	17·0 (103% [8·01–42·8])	3·46, 2·40	48·8, 30·9

Data are combined for both loading and continuous dosing regimens. Data listed for individuals if n≤2 and as geometric mean (CVb% [range]) if n≥3. T_{max} reported as median (range). AUC_{0-24}=area under the curve for 0–24 h. C_{max}=maximum concentration. T_{max}=time taken to reach maximum concentration. C_{24}=concentration after 24 h. AR=accumulation ratio. $T_{1/2}$ eff=effective half-life, calculated as –0·693*tau/(ln[1–{1/AR}]). CVb%=between-subject coefficient of variation. NA=not applicable. *n=11 for AUC_{0-24}, $T_{1/2}$ eff, and AR; n=12 for C_{max} and T_{max}. †n=14 for AUC_{0-24}. ‡n=13 for AR and $T_{1/2}$ eff; n=14 for AUC_{0-24}. §One patient omitted from analysis (with the exception of C_{24}) because drug was withheld and incomplete dosing information was available, so pharmacokinetic variables are only calculated for two patients.

Table 4: **Pharmacokinetic parameters after repeat once-daily dose administration of trametinib (day 15)**

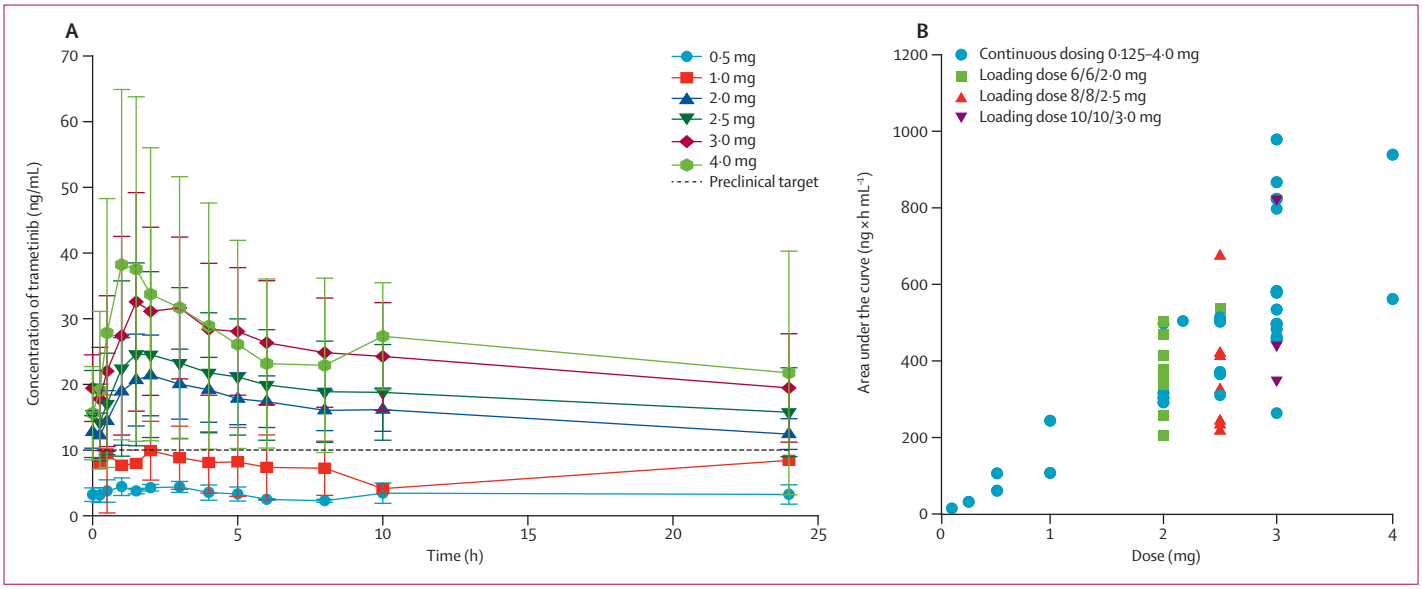

Figure 1: **Pharmacokinetic profiles for trametinib at day 15**

(A) Mean concentration of trametinib over time. Error bars show SD. Dashed line shows preclinical target concentration (10·4 ng/mL, the estimated mean inhibitory concentration at which 50% growth occurs) for four *BRAF*-mutant melanoma cell lines. (B) Dose-proportionality of trametinib after repeated doses.

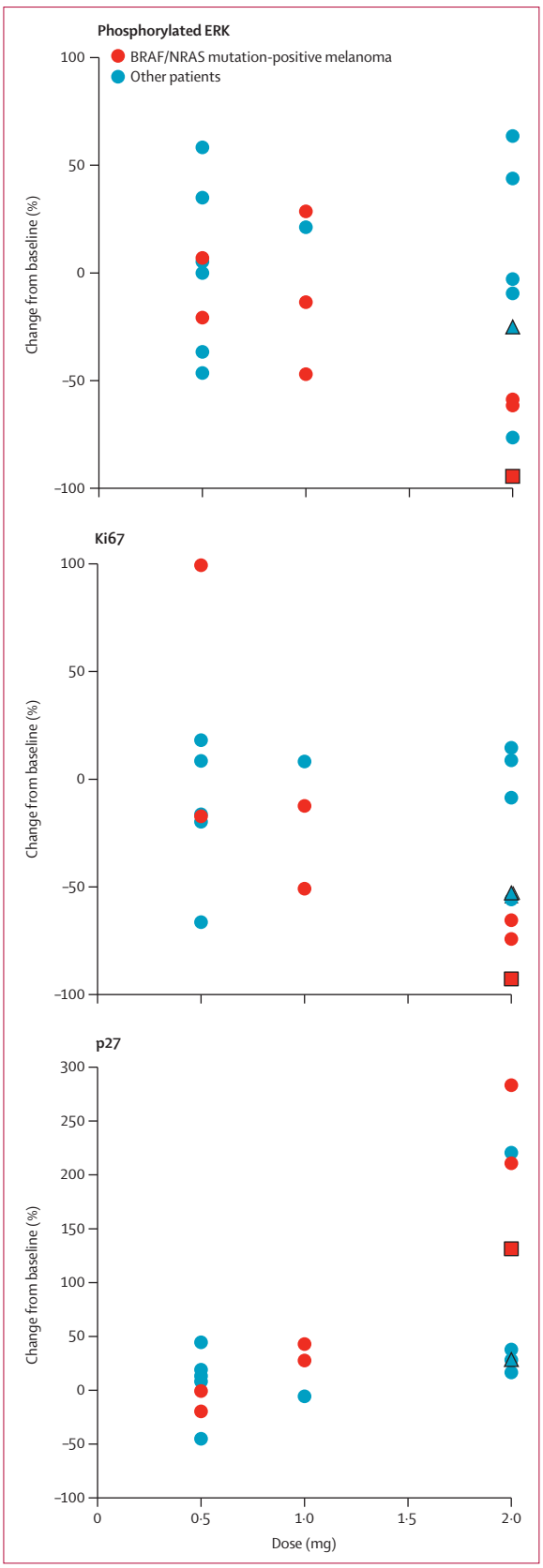

Figure 2: **Pharmacodynamic profiles for trametinib at day 15**
Percentage changes from baseline H-score in all assessable patients are shown. H-score=(3 × % cells stained strongly)+(2 × % cells stained moderately) + (1 × % cells stained weakly). Primary tumour types assessed were pancreas, breast, colon or rectum, ovary, and other. All patients received the dose indicated, except one (triangle) administered 6 mg on day 1 followed by 2 mg once a day, and another (square) administered 6 mg on days 1 and 2 followed by 2 mg a day.

of 1·81 and a mean accumulation ratio of 5·97. The estimated clearance time obtained from repeat-dose pharmacokinetic data was 5·4 L/h. With a 2 mg daily dose, mean plasma concentrations of trametinib exceeded the preclinical target throughout the entire dosing interval (figure 1). The low C_{max} in plasma with the 2 mg a day dose suggests that trametinib is low risk for drug interactions (unpublished data).

Figure 2 shows the change from baseline at day 15 in pharmacodynamic markers for all patients with assessable paired biopsy samples. The median change noted with a daily dose of 2 mg was 30% inhibition of phosphorylated ERK, 54% inhibition of Ki67, and 83% increase of p27. Pathway modulation seemed to be dose-dependent for all three markers in melanoma samples containing BRAF and NRAS mutations. In this subgroup, the median change seen at 2 mg daily was 62% inhibition of ERK phosphorylation, 83% inhibition of Ki67, and 171% increase of p27. Trough concentrations on day 15 were 9·51–18·2 ng/mL in these patients.

The recommended phase 2 dose was chosen based on combined safety, pharmacokinetic, pharmacodynamic, and efficacy data. Because continuous dosing regimens showed an acceptable safety profile, they were assessed further in the second part of the study. The 2 mg once-daily dosing regimen had exposure concentrations above the preclinical target threshold (figure 1), pathway inhibition, and durable objective responses. This dose also showed superior safety and tolerability compared with higher doses, and was therefore selected as the recommended phase 2 dose.

21 (10%) objective responses (18 confirmed) were noted at all dose levels, with the most sensitive population being BRAF-mutant melanoma.[13] Of 26 patients with pancreatic cancer, two partial responses (8%, both confirmed) were reported (figure 3), with treatment duration of 40 and 47 weeks (one *KRAS* mutation-positive, one *KRAS* mutation-unknown; appendix, p 4). 11 (42%) patients with pancreatic cancer had measurable decreases in tumour size. Of 30 patients with non-small-cell lung cancer, two achieved partial responses (7%; both confirmed), both of whom had *KRAS* mutations and remained on study treatment for 21 and 41 weeks (appendix, p 4). A further 16 patients had stable disease and five of these received treatment for 24 weeks or longer. Reductions in tumour size of 6–52% were seen in eight of 22 *KRAS* mutation-positive patients. No objective responses were recorded in 28 patients with colorectal cancer (figure 3). Of 13 with *KRAS* mutations, one person had minor radiographic improvement and received treatment for 31 weeks. Eight other patients with colorectal cancer had stable disease (three *KRAS* mutation-positive, two *KRAS* mutation-negative, three *KRAS* mutation-unknown). Three of five patients without detected *KRAS* mutations had alterations in *BRAF*; one of these had a 13% decrease in tumour size and received study treatment for 31 weeks. *BRAF* mutations were identified in one of four women with

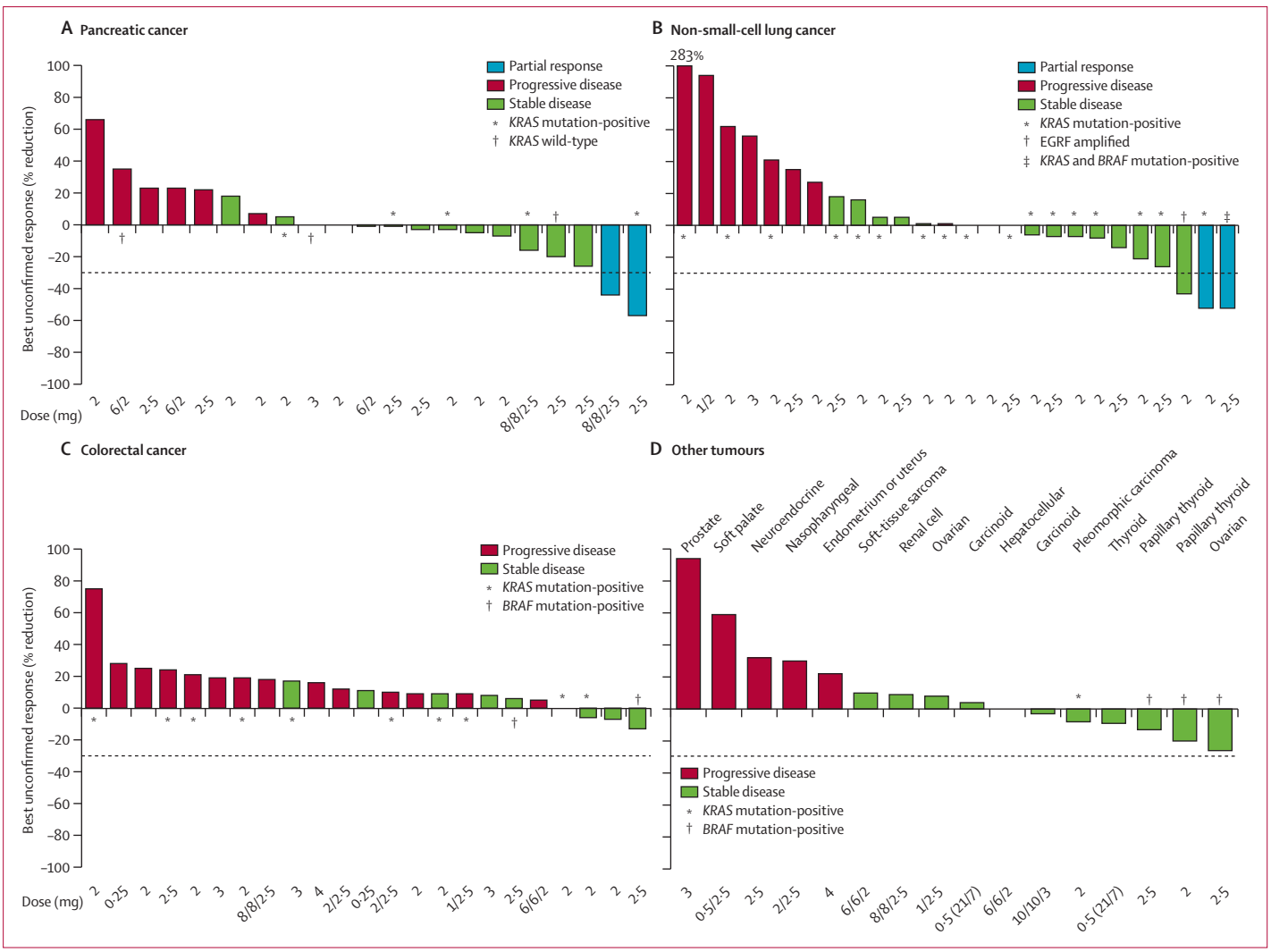

Figure 3: **Waterfall plots of best overall response**

Positive values indicate tumour growth, negative values indicate tumour reduction. Dashed line represents the threshold for partial response. Scans were unavailable for (A) five patients who either had progressive disease (n=4) or withdrew (n=1) before the first disease assessment, (B) four patients who either had progressive disease (n=3) or withdrew (n=1) before the first disease assessment, (C) five patients who either had progressive disease (n=3) or had incomplete scans (n=2), and (D) nine patients who either progressed or died before the first disease assessment (n=7) or had incomplete scans (n=2). Daily dose amounts are shown beneath every bar.

ovarian cancer and two of four patients with papillary thyroid tumours (figure 3). The best response was stable disease for these individuals, and duration of study treatment was 30, 64, and 72 weeks for *BRAF*-mutant ovarian and papillary thyroid patients, respectively (appendix, p 4).

Discussion

Our findings show that trametinib is fairly well tolerated, with the most common adverse events of rash and diarrhoea easily managed. Early dose-limiting events of central serous retinopathy prevented dose escalation beyond 3 mg a day, which was declared the maximum tolerated dose of trametinib on a continuous daily dosing schedule. However, 3 mg a day was tolerated poorly beyond the first cycle of treatment. Thus, on the basis of safety, long-term tolerability, pharmacokinetic, pharmacodynamic, and clinical efficacy data, a daily dose of 2 mg was selected as the recommended phase 2 dose of trametinib.

Similar to other MEK inhibitors,[14–16] acneiform rash was the most common treatment-related adverse event. Based on previous experience with EGFR inhibitors[17,18] and other MEK inhibitors,[19] early recognition and supportive treatment strategies make this toxic effect manageable. Diarrhoea was also typical, but was usually self-limiting and manageable with intermittent anti-diarrhoeal agents. In this study, two patients (<1%) had treatment-related grade 3 left-ventricular dysfunction or a decrease in ejection fraction. The mechanism for

Panel: Research in context

Systematic review

We searched PubMed with the terms "MEK inhibitor" and "clinical trial" for publications reporting on any clinical trials of MEK inhibitors in patients with cancer, from Jan 1, 2002, to May 19, 2012. We identified reports of phase 1 and 2 studies of three MEK inhibitors, AZD6244,[14] CI-1040,[15] and PD-0325901,[16] in patients with advanced cancers, which had limited success.

Interpretation

This first-in-human phase 1 study of trametinib was designed to establish the maximum tolerated dose of trametinib and to select and investigate the clinical activity of the recommended phase 2 dose in several tumour types. Trametinib is distinguished from other MEK inhibitors by its unique exposure profile, including a small peak:trough ratio, prolonged effective half-life, and low interpatient variability, which might allow it to overcome the narrow therapeutic index associated with MEK inhibition. Responses with durable clinical benefit were noted in patients with BRAF wild-type melanoma, non-small-cell lung cancer, and pancreatic cancer. In view of our findings, we believe MEK is an important therapeutic target, which can change clinical outcomes for patients with advanced cancer when inhibited effectively.

reduction of left-ventricular ejection fraction in relation to MEK inhibition is unknown, but because cardiac toxic effects have been reported elsewhere for another MEK inhibitor,[20] this adverse event could be a class effect. Monitoring of cardiac function will continue in future studies.

During our study, we recorded three occurrences of central serous retinopathy by optical coherence tomography. Two of these events arose either 1 day after a loading dose or within days of administration of the highest once-daily dose, suggesting that central serous retinopathy could be a toxic effect related to the C_{max} of trametinib. Concomitant drugs or risk factors that predisposed these patients to central serous retinopathy were not identified. Visual acuity of the patient with retinal vein occlusion increased after intraocular treatments of antibodies against VEGF. Ocular toxic effects have been reported in several other studies of MEK inhibitors;[4,14,16,20] therefore, our data suggest that central serous retinopathy and retinal vein occlusion are class effects of MEK inhibitors. The mechanism of these drug-related effects remains unknown and should be monitored in future trials.

Targeting MEK successfully in patients with cancer has been difficult because toxic effects arise either at clinically meaningful exposure concentrations or before these levels are achieved (panel). Compared with previous data for MEK inhibitors,[14–16] trametinib has an unique exposure profile with low interpatient variability. Pharmacokinetic data were generally dose proportional and showed a prolonged effective $t_{1/2}$ (about 4 days), which contributes to trametinib's relatively small peak:trough ratio and flat exposure profile. This exposure profile has the advantage of allowing constant target inhibition with a fairly low C_{max}. While higher exposures could potentially be achieved with intermittent dosing, such schedules of trametinib would probably be limited by the drug's long $t_{1/2}$ and early onset of dose-limiting toxic effects, which we noted in our study. At 2 mg once a day, most patients are predicted to exceed preclinical target exposure concentrations for the entire 24-h dosing interval. These findings suggest the pharmacokinetic properties of trametinib allow the drug to overcome the narrow therapeutic index that has been associated with MEK inhibition.[8,21] Indeed, dose-dependent tumour changes in phosphorylated ERK, Ki67, and p27 consistent with target inhibition were noted. Although too few melanoma biopsy specimens containing BRAF or NRAS mutations were obtained in this study to correlate inhibition of phosphorylated ERK with tumour reduction,[22] these changes were greatest at the recommended phase 2 dose in melanoma patients with RAS or RAF mutations (figure 2).

Proof of concept of MEK inhibition is supported further by responses noted with durable clinical benefit in patients with melanoma,[13] non-small-cell lung cancer, and pancreatic cancer. The early efficacy seen in our first-in-human phase 1 study supports ongoing monotherapy trials in individuals with non-small-cell lung cancer and melanoma. Nevertheless, the greatest potential for trametinib could be in combination with both targeted and cytotoxic chemotherapies, especially in melanoma, pancreatic cancer, and other tumours that contain genetic alterations leading to activation of the MAPK pathway. Studies incorporating inhibition of the MAPK pathway in combination with a BRAF inhibitor are currently underway.[23] Moreover, since MAPK activation might also function as a resistance mechanism after inhibition of other signalling pathways, additional strategies that include combinations with receptor tyrosine kinase inhibitors and dual-pathway inhibition, together with inhibitors of PI3K, AKT, or mTOR, are ongoing.

Contributors

All authors participated in data collection, analysis, and interpretation. The study was designed by GlaxoSmithKline in collaboration with JRI, LF, GE, KF, HAB, and WAM. JRI wrote the report. All authors reviewed and commented on the report at all stages and approved the final version.

Conflicts of interest

JRI has advised on an uncompensated basis and received reimbursement for travel from GlaxoSmithKline. KF has acted as a consultant for GlaxoSmithKline. WAM has acted as a consultant for and received research funding from GlaxoSmithKline. GSF and LAF have received research funding and reimbursement for travel from GlaxoSmithKline. RK has received research funding from GlaxoSmithKline. DJD, DSC, YX, SRM, VGRP, and NTL are employees of GlaxoSmithKline. SN, CB, LH, JCB, GE, MSG, and HAB all declare no conflicts of interest.

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