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Pooled safety analysis of BAY 43-9006 (sorafenib) monotherapy in patients with advanced solid tumours: Is rash associated with treatment outcome?

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ABSTRACT

In this analysis of the safety and efficacy of BAY 43-9006 (sorafenib) – a novel, oral multi-kinase inhibitor with effects on tumour and its vasculature – pooled data were obtained from four phase I dose-escalation trials. Time to progression (TTP) was compared in patients with/without ⩾grade 2 skin toxicity/diarrhoea. Grade 3 hand–foot skin reactions (HFS; 8%) and diarrhoea (6%) were common. At the recommended 400 mg bid dose for phase II/III trials (RDP), 15% of patients experienced grade 2/3 HFS, and 24% experienced grade 2/3 diarrhoea. Sorafenib induced stable disease for ⩾6 months in 12% of patients (6% stabilized for ⩾1 year). Patients receiving sorafenib doses at or close to the RDP, who experienced skin toxicity/diarrhoea, had a significantly increased TTP compared with patients without such toxicity ($P < 0.05$). Sorafenib was well tolerated at the RDP, and induced sustained disease stabilization, particularly in patients with skin toxicity/diarrhoea.

1. Introduction

Eukaryotic cell function is regulated by complex and coordinated arrays of growth-regulatory genes, including those for cytokines and growth factors. The GTPase Ras relays cytokine and growth factor signals from the cell surface to the nucleus via the Raf/MEK/ERK pathway.[1] Raf has an important role in regulating normal cellular growth, differentiation and apoptosis, and is implicated in tumourigenesis.[2,3] B-Raf knockout mice die mid-gestation due to increased endothelial cell

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apoptosis and vascular defects,[2] while blocking C-Raf (Raf-1 or c-Raf-1) inhibits cellular proliferation and VEGF-mediated angiogenesis.[2,4] The *b-raf* V599E mutation is present in 63% of malignant melanomas;[4] 40% of sporadic colorectal tumours with high microsatellite instability;[5] 38% of papillary thyroid carcinomas;[6] and some non-small-cell lung carcinomas (NSCLCs).[4] Activating *ras* mutations result in aberrant signalling via Raf, and are common in human solid tumours of the pancreas (90%), colorectum (45%), lung (NSCLC: 35%), liver (30%), skin (melanoma: 15%) and kidney (10%).[1,2,7–9] Aberrant signalling via Ras and Raf can also result from overexpression, amplification or mutational activation of upstream vascular endothelial (VEGFR), platelet-derived (PDGFR-β), and epidermal (EGFR) growth factor receptors.[2,10,11]

The management of advanced solid tumours is limited by the fact that they are often refractory to current treatments, including radiotherapy and chemotherapy, and have a generally poor prognosis. Therefore, there is an urgent need to develop more effective drugs to stabilize/slow the progression of advanced solid tumours. Novel targeted agents that interfere with either EGF/VEGF–receptor interactions or Raf/MEK/ERK signalling downstream of EGFR/VEGFR have shown promising clinical activity against several advanced solid tumour types.[1,12,13] In contrast to standard chemotherapies, targeted agents are also generally well tolerated.[14,15] Interestingly, the improved clinical activity of novel agents targeting the EGF pathway may correlate with the appearance of skin rash.[16,17] If confirmed, this relationship may be useful in predicting treatment response and/or ensuring optimal dose titration.

BAY 43-9006 (sorafenib) is a novel, orally administered multi-kinase inhibitor with effects on the tumour and vasculature. In biochemical assays, it is a potent inhibitor of Raf-1, wild-type B-Raf and V599E *b-raf* kinases, and proangiogenic VEGFR-2, VEGFR-3, and PDGFR-β tyrosine kinases.[18,19] Sorafenib also inhibits phosphorylation of Flt3, c-KIT, and p38α – a member of the MAPK family.[18,19] In xenograft models, sorafenib inhibited the growth of human colon, pancreatic and NSCLC tumours carrying *b-raf* or *k-ras* mutations.[20] It also significantly inhibited neovascularization in human xenograft models of colon (HT-29 and Colo205) and breast cancer (MDA-MB-231).[19] Furthermore, sorafenib monotherapy demonstrated promising efficacy (e.g., advanced refractory renal and hepatocellular carcinoma), particularly at doses $\geqslant$200 mg bid, and favourable safety in four phase I dose-escalation trials, in which different dosing schedules were evaluated.[21–26]

In the present analysis, data were pooled from these trials to provide an overview of the safety and efficacy of sorafenib monotherapy in patients with advanced cancer. Since Raf, a target for sorafenib, is a downstream effector of EGFR, we also investigated the relationship between skin toxicity/diarrhoea and time to progression (TTP).

2. Patients and methods

2.1. Patient selection

Patients recruited into the four phase I sorafenib trials (A–D) utilized in this pooled analysis were aged $\geqslant$16 years and had histologically documented advanced and/or metastatic solid tumours that were refractory to standard curative therapies. These patients also had an Eastern Co-operative Oncology Group (ECOG) performance status $\leqslant$2, and life expectancy $\geqslant$12 weeks. Recruited patients had clinically and/or radiologically evaluable disease; adequate bone marrow, hepatic, and renal function; and normal haemostatic function (i.e., prothrombin time/activated partial thromboplastin time).

Patients were excluded if they were pregnant or lactating; experienced severe cardiovascular disorders within 6 months prior to recruitment; received chemotherapy or radiotherapy within 4 weeks of enrolment. Patients considered by the investigator to have any medical condition or psychological or social problems that might affect study participation and/or evaluations were also excluded.

All patients provided written informed consent in accordance with federal and institutional guidelines. These phase I trials received institutional ethics committee approval, and were conducted in accordance with good clinical practice and the Declaration of Helsinki.

2.2. Study design

Data were pooled from four sorafenib dose-escalation trials (A–D) in patients with advanced refractory solid tumours. Trial A was conducted at the Dana-Farber Cancer Institute, Brigham and Women's Hospital and Massachusetts General Hospital Cancer Center, Boston, MA, and the University of Southern California/Kenneth Norris Comprehensive Cancer Center, Los Angeles, CA, between October 2001 and February 2003. Trial B was performed at the Jules Bordet Institute, Brussels, Belgium between December 2000 and December 2002. Trial C was conducted at the Princess Margaret Hospital, Toronto, and Juravinski Cancer Center in Hamilton, ON, Canada, between December 2000 and January 2003. Trial D was performed at the West German Cancer Center, University of Essen, Germany between July 2000 and February 2003. Trials A–D were designed to evaluate the safety [dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), potential long-term toxicities], pharmacokinetics, and preliminary anti-tumour activity (optimum dosing schedule, impact of biomarkers, biologically active dose range, effects on tumour progression) of sorafenib monotherapy. This pooled analysis will focus on the safety (adverse events, DLTs and MTD), tumour response, and TTP data from the sorafenib phase I program.

Tumour response and progression were evaluated as described previously,[21–26] in accordance with the Response Evaluation Criteria in Solid Tumours (RECIST).[27]

The dose-escalation schedule for these phase I trials is depicted in Fig. 1. The treatment cycles lasted 14 days (7 days on/7 days off) in Trial A, 28 days (21 days on/7 days off) in Trial B, and 35 days (28 days on/7 days off) in Trial C.

In Trial D, patients received a starting dose of 50 mg on Day 1 of a weekly treatment cycle. After an initial period of dose escalation according to a once-weekly single-dosing schedule, further dose escalations were achieved by bid administration, and then continued by doubling the number of treatment days per week (Day 1, Days 1 and 2, Days 1–4, continuous dosing). If any patient developed DLT during a given treatment cycle, three additional patients were enrolled at that dose level. If two of the additional patients experienced DLT, dose

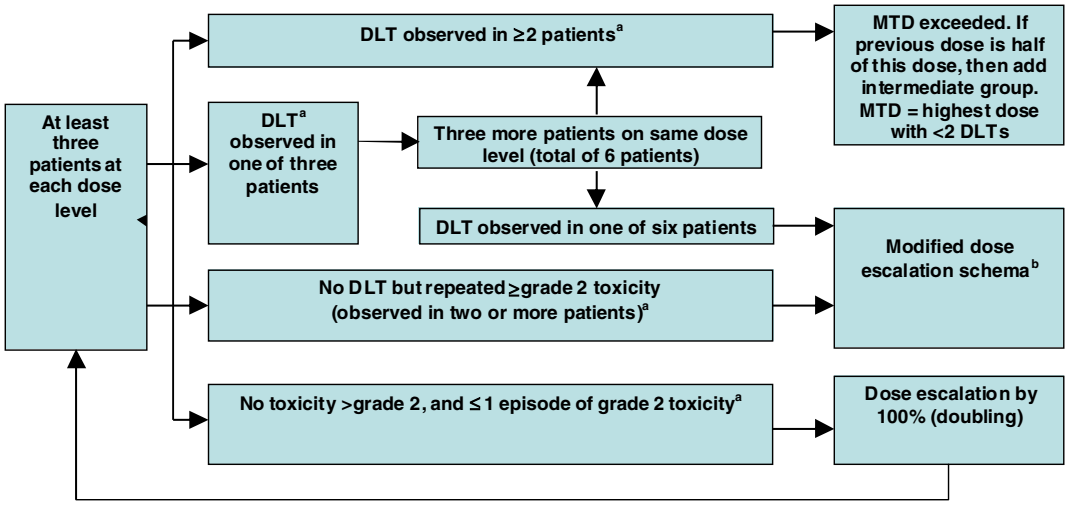

Fig. 1 – Dosing schedule for phase I sorafenib monotherapy trials A–D. [a]Within the treatment cycle. [b]Dose escalations according to the following sequence: 50%, 33%, 25% and 25% thereafter, using a dosage that provides the closest approximation of this increment. DLT, dose-limiting toxicity; MTD, maximum tolerated dose.

escalation was stopped and the previous dose was determined as the MTD for sorafenib (Fig. 1). Up to 10 patients could be enrolled at the declared MTD to obtain additional safety data at the recommended dose.

In each trial, sorafenib was administered orally until the occurrence of unacceptable toxicity, withdrawn consent, or death. Treatment was also discontinued if tumour progression occurred, and a final visit took place within 2 weeks of establishing progression.

2.3. *Safety evaluations*

Toxicity was evaluated and graded in Trials A–D according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.[28] DLTs were defined as clinically significant haematological toxicity (⩾grade 3) for >5 days, or non-haematological toxicity (⩾grade 3) considered by the investigator to warrant withholding study medication, and to be at least possibly related to study drug.

2.4. *Efficacy evaluations*

Pooled TTP data were evaluated for each dose of sorafenib. Tumour responses were evaluated according to RECIST criteria.[27] The duration of response (i.e., time elapsing from the initial measurement of complete or partial response [CR, PR] to the first observation of recurrent disease or progressive disease [PD]) was documented objectively. The duration of stabilized disease (SD) was defined as the time interval from the start of therapy until the criteria for disease progression were first met. The same method of assessment and the same techniques were used to characterize each reported lesion at baseline and during follow-up.

Toxicity–efficacy interactions were evaluated by comparing TTP in patients who experienced skin toxicity/diarrhoea (i.e., ⩾grade 2) with those who did not (i.e., none or ⩽grade 2). Skin toxicity comprised hand–foot skin reaction (HFS) and rash.

2.5. *Statistical analyses*

No formal sample size estimations were performed in these primarily descriptive phase I safety and tolerability trials. Summary statistics were utilized for pooled demographic variables and TTP analyses. Patients who received at least one dose of sorafenib and had post-treatment data available were included in the pooled safety assessments. In each trial, efficacy data were pooled from the intention-to-treat (ITT) cohort, which comprised all patients with at least one assessment after the start of sorafenib treatment.

3. Results

3.1. *Patients' characteristics*

The median age of the 179 patients was 57 years (range 18–79 years). Most participants were male (56%) with advanced refractory colorectal (38%) or gastrointestinal (13%) solid tumours, and an ECOG performance status of 0–1 at baseline. Almost all patients had received surgery (92%) and chemotherapy (98%) prior to study entry, and 39% had received radiotherapy (Table 1).

3.2. *Dose escalation*

The sorafenib doses administered were <100, 100, 200, 400, 600 and 800 mg bid. In addition, a dose of 300 mg bid was administered in Trial B. DLTs were not observed in any patient on a non-continuous dosing schedule (Trials A–C). On the continuous dosing schedule (Trial D), one patient each from the 100 and 200 mg bid cohorts experienced a DLT (grade 3 pancreatitis and grade 3 diarrhoea, respectively). At the 800 mg bid dose, two of six patients reported DLTs of grade 3 diarrhoea, and an additional patient experienced grade 3 fatigue. Because the prior dose level of 400 mg bid was not associated with significant toxicity, an intermediate dose of 600 mg bid sorafenib was investigated. At this dose, four of

Table 1 – Demographic and clinical characteristics of patients participating in the sorafenib phase I program

	Trial A *n* (%)	Trial B *n* (%)	Trial C *n* (%)	Trial D *n* (%)	Trials A–D *n* (%)
Number of patients	23	44	43	69	179
Median age (years)	55	58	52	60	57
Age range (years)	32–74	42–79	33–70	18–75	18–79
Male:female [*n* (%)]	13:10 (57:43)	25:19 (57:43)	18:25 (42:58)	44:25 (64:36)	100:79 (56:44)
Malignancy					
CRC	8 (35)	15 (34)	17 (40)	28 (41)	68 (38)
Ovarian	0	1 (2)	10 (23)	1 (1)	12 (7)
Breast	0	7 (16)	1 (2)	4 (6)	12 (7)
HCC	0	1 (2)	0	9 (13)	10 (5)
Pancreas	2 (9)	0	3 (7)	1 (1)	6 (3)
Renal	1 (4)	7 (16)	2 (5)	1 (1)	11 (6)
GI other	4 (17)	2 (5)	4 (9)	13 (19)	23 (13)
Melanoma	0	2 (5)	0	1 (1)	3 (2)
NSCLC	2 (9)	1 (2)	0	0	3 (2)
Other/CUP	6 (3)	8 (18)	6 (14)	11 (16)	31 (17)
ECOG performance status					
0	7	12	23	26	68 (38)
1	11	30	12	36	89 (49)
2	5	2	8	7	22 (12)
Previous therapy					
Surgery	19	41	38	64	162 (92)
Chemotherapy	23	44	42	67	176 (98)
Radiotherapy	8	22	18	22	70 (39)

ECOG, Eastern Co-operative Oncology Group.

14 patients (29%) experienced at least one dose-limiting skin toxicity during the initial 5-week treatment/observation period. Therefore, sorafenib 400 mg bid was established as the MTD and the recommended dose for future phase II/III trials (i.e., RDP).

3.3. *Safety*

In the pooled safety population ($n = 179$), the most commonly reported treatment-emergent adverse events were fatigue (51%), anorexia (43%), diarrhoea (41%), nausea (36%) and HFS (25%) (Table 2). The majority of adverse events were mild to moderate. The most common grade 3 toxicities were HFS (8%) and diarrhoea (6%) (Table 2).

A small proportion of patients experienced drug-related diarrhoea at dose levels <400 mg bid, which was usually mild (Fig. 2A). Approximately 40% of patients experienced diarrhoea at a dose level of 400 mg bid, which increased in intensity upon further dose escalation, and was dose limiting at 800 mg bid. The incidence of grade 2/3 diarrhoea at the RDP was 24% (Fig. 2A).

Few patients reported drug-related HFS at dose levels <300 mg bid. However, there was an increase in the frequency and severity of HFS from sorafenib 300–600 mg bid,

Table 2 – Incidences of treatment-emergent adverse events in the phase I program ($n = 179$), according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 and worst grade

Adverse event	Incidence	Worst NCI-CTC Grade		
		1	2	3
	n (%)	*n* (%)	*n* (%)	*n* (%)
Fatigue	91 (51)	37 (21)	22 (12)	3 (2)
Anorexia	76 (43)	48 (27)	22 (12)	6 (3)
Diarrhoea	73 (41)	33 (18)	30 (17)	10 (6)
Nausea	64 (36)	43 (24)	17 (10)	4 (2)
Other skin reactions	59 (33)	40 (22)	18 (10)	1 (1)
Hand–foot skin reaction	45 (25)	16 (9)	14 (8)	15 (8)
Alopecia	33 (18)	25 (14)	6 (3)	2 (1)
Rash	32 (18)	14 (8)	14 (8)	4 (2)
Stomatitis	21 (12)	13 (7)	8 (5)	0 (0)
Elevated bilirubin[a]	20 (11)	4 (2)	7 (4)	9 (5)
Pancreatitis	3 (2)	0 (0)	0 (0)	3 (2)

a Transient laboratory abnormalities.

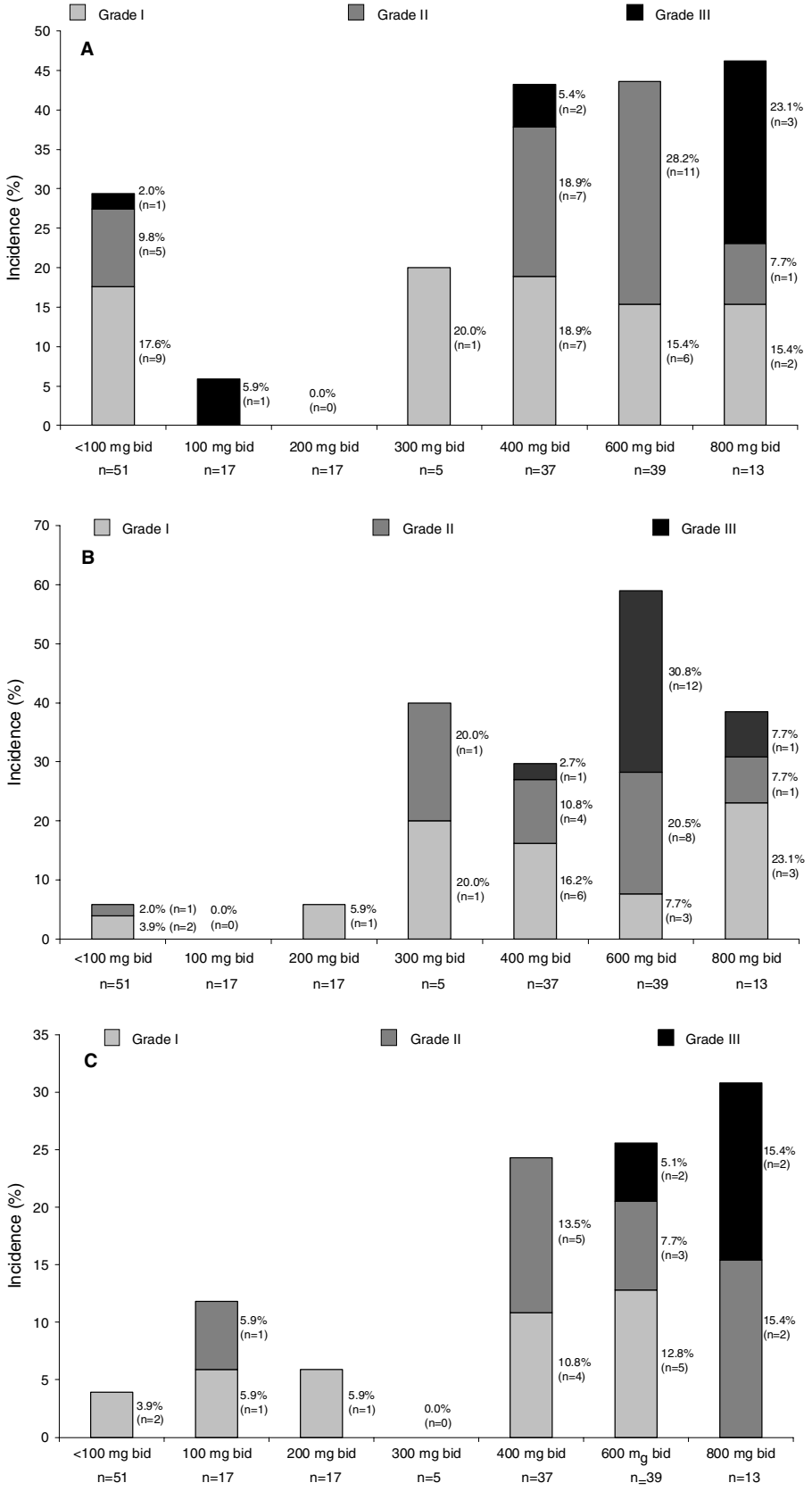

Fig. 2 – A–E Incidence and severity (NCI-CTC version 2.0 worst grade) of common drug-related treatment-emergent adverse events with increasing doses of sorafenib in phase I monotherapy trials A–D: (A) diarrhoea; (B) hand–foot skin reaction; (C) rash; (D) alopecia; (E) fatigue.

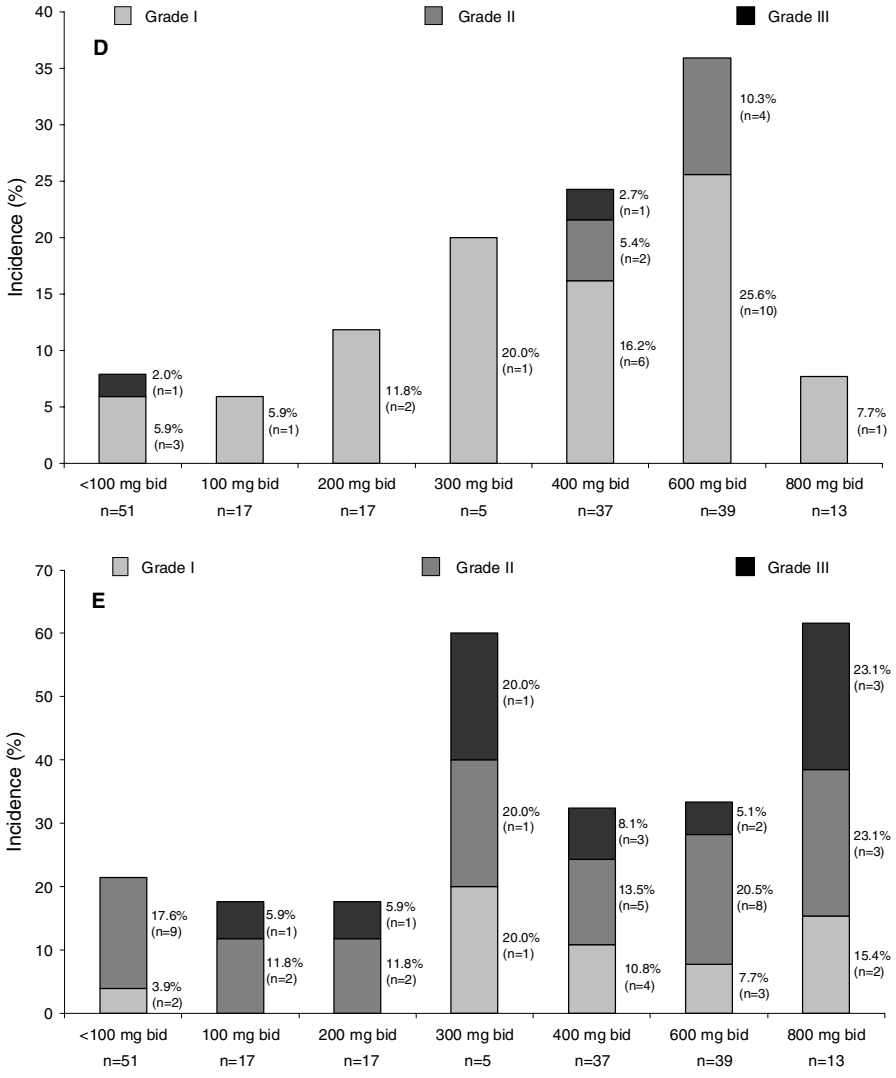

Fig. 2 – continued.

at which dose HFS became dose limiting (Fig. 2B). At the RDP, approximately 15% of patients experienced grade 2/3 HFS (Fig. 2B).

Drug-related rash was rarely reported as an additional skin reaction at doses <200 mg bid (Fig. 2C). However, at higher doses there was an increase in the severity but not the frequency of rash. At the RDP, the incidence of rash was similar to that for HFS, but did not reach grade 3 (Fig. 2B and C).

A small number of patients (⩽10% of all patients) experienced drug-related grade 1 alopecia across all dose levels. Only few patients experienced grade 3 alopecia, the incidence of which was not related to the applied dose (Fig. 2D).

A small number of patients had dose-limiting grade 3 fatigue across all levels of continuous dosing (Fig. 2E) without any clear relationship to the applied sorafenib dose.

In total, 42% of patients experienced skin toxicity (i.e., rash and HFS) or diarrhoea ⩾grade 2 in severity during the course of the phase I program (Table 3). The rate of skin toxicity/diarrhoea grade 2 occurrence was estimated to be 53% during the first year by using standard Kaplan–Meier methodology. The cumulative incidence in Table 3 reflects the estimated probability of toxicity, assuming that patients were treated until the endpoint without interruption. Thus, in approximately half of

Table 3 – Onset rates and cumulative incidences of diarrhoea or skin toxicity of ⩾grade 2 (National Cancer Institute Common Toxicity Criteria) in the sorafenib phase I program

Endpoint	Number of patients at risk of events	Number of events	Incidence (%)	Cumulative Incidence (%)
Day 7	179	16	8.9	8.9
Day 14	163	27	16.6	24.0
Day 30	136	11	8.1	30.2
Day 90	125	15	12.0	38.5
Day 180	110	6	5.5	45.2
Day 360	26	1	3.8	53.1
Entire study	179	76	42.5	n.d.

n.d., not done.

Table 4 – Overall duration of treatment (time to progression) for each sorafenib dose level achieved during the phase I program, and proportions of patients experiencing progression at specified treatment intervals

Dose level	*n*	Time to progression (months)				Proportion of patients progressing within each treatment interval [*n* (%)]			
		Range	Median	Mean	SD	<3 months	3–<6 months	6–<12 months	⩾12 months
<100 mg bid continuous	51	0.2–24.6	1.9	4.0	5.3	34 (67)	9 (17)	4 (8)	4 (8)
100 mg bid continuous	17	0.3–15.2	2.4	3.4	3.8	12 (71)	3 (18)	1 (5)	1 (5)
200 mg bid continuous	17	0.7–21.3	1.9	4.5	5.7	12 (71)	2 (12)	1 (5)	2 (12)
300 mg bid continuous	5	0.7–7.1	1.6	2.4	2.7	4 (80)	0 (0)	1 (20)	0 (0)
400 mg bid continuous	37	0.0–14.3	2.3	3.8	3.7	22 (59)	5 (13)	8 (22)	2 (5)
600 mg bid continuous	39	0.4–14.5	2.3	3.7	3.5	24 (61)	8 (20)	5 (13)	2 (5)
800 mg bid continuous	13	0.3–9.1	1.2	2.4	2.8	10 (77)	1 (7)	2 (15)	0 (0)
<200 mg bid continuous	68	0.2–24.6	2.1	3.8	4.9	46 (68)	12 (18)	5 (7)	5 (7)
⩾200 mg bid continuous	111	0.0–21.3	2.2	3.6	3.8	72 (65)	15 (14)	16 (14)	8 (7)
All doses	179	0.0–24.6	2.1	3.7	4.3	118 (66)	28 (16)	22 (12)	11 (6)

the patients who experienced skin toxicity/diarrhoea, these side-effects appeared within the first 2 weeks of treatment.

3.4. *Efficacy*

During the course of the four phase I studies, two patients experienced a confirmed PR (patients with hepatocellular carcinoma and renal carcinoma).[22]

However, 12% of patients across all dose levels experienced stabilization (i.e., SD) of previously progressive disease for at least 6 months, and 6% had SD for at least 1 year (Table 4). There was no clear relationship between the individual dose levels and overall duration of treatment (i.e., TTP). It is also worth noting that most patients who received sorafenib 600–800 mg bid experienced a dose reduction to the 400 mg bid dose upon experiencing toxicity, and this may have contributed to the lack of a clear dose-response.

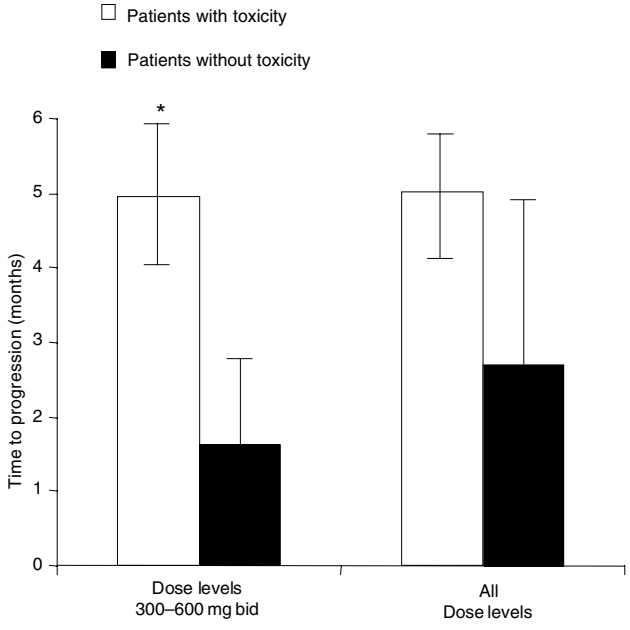

Fig. 3 – Relationship between toxicity and time to progression (TTP). Patients included in this analysis were stratified by skin toxicity/diarrhoea (i.e., ⩾grade 2 vs. none or ⩽grade 2). *P < 0.05 vs. patients exhibiting no toxicity.

3.5. *Relationship between toxicity and efficacy*

It was questioned whether patients experiencing significant skin toxicity/diarrhoea (i.e., ⩾grade 2) might also experience a longer TTP relative to those who did not experience toxicity (none or skin toxicity/diarrhoea <grade 2). Patients experiencing skin toxicity/diarrhoea with sorafenib doses at or close to the RDP (i.e., 300–600 mg bid) had a significantly longer TTP than patients without toxicity ($P < 0.05$; Fig. 3). However, from the pooled data for all doses of sorafenib (i.e., <100–800 mg bid) there was no significant difference in TTP between patients who experienced skin toxicity/diarrhoea and those who did not.

4. Discussion

In this pooled analysis, the majority of drug-related toxicities associated with oral sorafenib administration were mild to moderate in severity, easily manageable, of gastrointestinal or dermatological nature, and unrelated to the dosing schedule. Diarrhoea was the most common gastrointestinal toxicity and was dose limiting in patients receiving the highest sorafenib dose (800 mg bid continuous). Skin toxicity (i.e., HFS and rash) was dose limiting and occurred with mild diarrhoea at sorafenib 600 mg bid continuous. Cumulative toxicity data support the safety of the sorafenib 400 mg bid dose recommended for further clinical phase II/III trials. Significant but manageable toxicity (i.e., NCI-CTC ⩾grade 2) occurred in 42% of patients throughout the phase I monotherapy program. Furthermore, it was estimated that this percentage would have increased to 53% if patients had remained on sorafenib monotherapy without dose reduction for at least 1 year. Toxicity was most likely to occur within the first 2 weeks of treatment.

Preliminary pooled efficacy data from the sorafenib phase I program suggest that it is associated with clinically meaningful and durable stabilization of progressive disease, rather than with tumour regressions. Across all dose levels, 12% of patients experienced stabilization of previously progressive disease for at least 6 months, and 6% were stabilized for

at least 1 year. Tumour biology and the relative contribution of the cellular target(s) of sorafenib to tumour growth might be more relevant for efficacy than the achieved dose intensity. Extensive cross-talk between signalling pathways, together with genetic instability, may enable solid tumours to bypass single molecular blockades. It has been suggested that anticancer drugs acting on a single molecular target may be particularly susceptible to such escape mechanisms.

It is not yet clear which of the intracellular targets of sorafenib (i.e., Raf-1, wild-type B-Raf, mutant *b-raf V599E*, VEGFR-2, VEGFR-3, PDGFR-β, Flt3, c-KIT and p38α)[18,19] contributed most to its observed efficacy in these phase I trials. Although there are currently no available molecular markers predictive of clinical outcome with sorafenib, our preliminary findings raise the possibility that the observed manageable DLTs (i.e., skin toxicity/diarrhoea ⩾grade 2) may have prognostic value. Patients treated with dose levels close to the RDP who experienced skin toxicity/diarrhoea ⩾grade 2 in severity appeared to have a significantly longer TTP than patients without such toxicities. However, this association requires validation in further appropriately designed clinical trials.

One of the main targets of sorafenib (identified by biochemical assays) is Raf kinase, which is a downstream effector molecule of the EGFR signalling pathway. Interestingly, response as a function of skin toxicity has also been reported for inhibitors of EGFR. The association between rash and efficacy was evaluated in patients with metastatic colorectal carcinomas receiving the anti-EGFR (HER-1) monoclonal antibody cetuximab (IM-C225) in combination with irinotecan. Patients who developed acneiform rash and folliculitis involving the face and upper chest had a significantly higher response rate than those who did not develop rash (29% vs. 3%, respectively; $P < 0.001$).[16,29] Furthermore, the severity of rash in patients with NSCLC who received the EGF-RTK inhibitor erlotinib correlated with increased survival.[17] Median survival of patients without rash was 46.5 days, compared with 257 and 597 days for those with grade 1 or grade 2–4 rash, respectively ($P = 0.0001$).[17] It has been suggested that rash commonly associated with EGF-pathway inhibitors could be predictive of treatment outcome, and that the onset of rash could be used for optimal dose titration.[17] Although the specific cytopathic mechanism underlying this particular form of drug-induced rash has not yet been determined, it is likely the result of EGFR inhibition in the skin.[30] Inhibition of EGFR-induced signalling in the skin via Raf kinase inhibition may also explain the skin toxicity (i.e., HFS and rash) associated with sorafenib treatment. Furthermore, inhibitors of the EGF pathway are also associated with an increased incidence of diarrhoea.[30] However, sorafenib may be poorly absorbed and it is likely that it may induce diarrhoea by a direct irritant effect on the gut, particularly at higher doses (data not shown). Alternatively, it is conceivable that antagonism of VEGF signalling by sorafenib (directly via VEGFR-RTK or indirectly via downstream Raf) could also account for the rash associated with sorafenib. The mechanisms underlying the rash associated with sorafenib treatment should, therefore, be investigated further.

Phase I trials have reported considerable inter-individual variability in plasma exposure to sorafenib with multiple dosing.[21–26] It is therefore conceivable that the correlation between toxicity and efficacy observed in the present meta-analysis is simply due to differences in total exposure between the two patient subsets evaluated (i.e., no toxicity vs. skin toxicity/diarrhoea ⩾grade 2). This possibility will need to be addressed and resolved in an appropriately designed follow-up trial evaluating exposure–toxicity, exposure–efficacy, and toxicity–efficacy relationships.

In conclusion, this pooled analysis confirmed that oral sorafenib monotherapy was generally safe and well tolerated and associated with a clinically meaningful stabilization of previously progressive disease in patients with advanced solid tumours. Furthermore, patients who experienced skin toxicity/diarrhoea while receiving sorafenib doses at or close to the RDP apparently gained significantly more benefit than those without toxicity. This relationship should be treated with caution until validated in appropriately designed follow-up investigations.

Conflict of interest statement

Drs. Strumberg, Awada, Hirte, Clark, Seeber, Piccart and Hofstra have all received funding for undertaking phase I trials and/or have acted as consultants/received honoraria from Bayer AG, Wuppertal, Germany/Bayer Pharmaceuticals Corporation, West Haven, CT, USA. Drs. Voliotis, Christensen, Brueckner and Schwartz are all employees of Bayer AG, Wuppertal, Germany/Bayer Pharmaceuticals Corporation, West Haven, CT, USA.

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