ORIGINAL PAPER

IJCP THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib): second interim analysis

R. Lencioni,[1] M. Kudo,[2] S.-L. Ye,[3] J.-P. Bronowicki,[4] X.-P. Chen,[5] L. Dagher,[6] J. Furuse,[7] J. F. Geschwind,[8] L. Ladrón de Guevara,[9] C. Papandreou,[10] T. Takayama,[11] S. K. Yoon,[12] K. Nakajima,[13] R. Lehr,[14] S. Heldner,[15] A. J. Sanyal[16]

SUMMARY

Background: GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma [HCC] and Of its treatment with sorafeNib) is a global, prospective, non-interventional study undertaken to evaluate the safety of sorafenib in patients with unresectable HCC in real-life practice, including Child-Pugh B patients who were excluded from clinical trials. **Methods:** Patients with unresectable HCC, for whom the decision to treat with sorafenib, based on the approved label and prescribing guidelines, had been taken by their physician, were eligible for inclusion. Demographic data and disease/medical history were recorded at entry. Sorafenib dosing and adverse events (AEs) were collected at follow-up visits. The second interim analysis was undertaken when ~1500 treated patients were followed up for ≥ 4 months. **Results:** Of the 1571 patients evaluable for safety, 61% had Child-Pugh A status and 23% Child-Pugh B. The majority of patients (74%) received the approved 800 mg initial sorafenib dose, regardless of Child-Pugh status; however, median duration of therapy was shorter in Child-Pugh B patients. The majority of drug-related AEs were grade 1 or 2, and the most commonly reported were consistent with previous reports. The incidence and nature of drug-related AEs were broadly similar across Child-Pugh, Barcelona Clinic Liver Cancer (BCLC) and initial dosing subgroups, and consistent with the overall population. **Conclusions:** Consistent with the first interim analysis, overall safety profile and dosing strategy are similar across Child-Pugh subgroups. Safety findings also appear comparable irrespective of initial sorafenib dose or BCLC stage. Final analyses in > 3000 patients are ongoing.

What's known

- The oral multikinase inhibitor sorafenib significantly improves overall survival in patients with uHCC. However, pivotal studies generally included only patients with preserved liver function; therefore, investigation of sorafenib in wider patient groups is needed.
- GIDEON is a global, non-interventional study evaluating uHCC patients treated with sorafenib in clinical practice, thereby allowing a broad evaluation of patient subgroups, including those with advanced liver dysfunction.

What's new

- The second interim analysis of the GIDEON study has now been completed in > 1500 uHCC patients treated with sorafenib in clinical practice.
- Consistent with the first interim analysis conducted in ~500 patients, these data highlight that the safety profile of sorafenib appears to be comparable across Child-Pugh and BCLC subgroups in real-life practice.
- Safety findings also appear to be similar, irrespective of the initial sorafenib dose.

Background

Hepatocellular carcinoma (HCC) is now the third leading cause of cancer-related death and the fifth most common malignancy in men; the seventh in women (1,2). The major risk factors for HCC include chronic hepatitis C and hepatitis B viral infections, as well as alcohol consumption, non-alcoholic steatohepatitis and diabetes (3,4). The vast majority (70–90%) of HCC cases occur in the context of liver cirrhosis (5), and consequently many patients present with hepatic dysfunction and experience a high rate of comorbidity. HCC is therefore a heterogeneous disease in terms of aetiology as well as clinical presentation and behaviour, thus presenting challenges for disease management (6).

Most patients with HCC present with unresectable disease (uHCC) that cannot be managed by surgery. Non-surgical locoregional treatment options, such as image-guided ablation and transarterial chemoembolisation, are not suitable for all patients and are associated with high rates of recurrence (7–9). At present, there is no global standardisation of treatment for uHCC, although systemic therapies may offer a new alternative in the treatment of uHCC.

Sorafenib is a multikinase inhibitor used for the treatment of uHCC (10). Two Phase III studies (SHARP and Asia-Pacific) demonstrated significant improvements in overall survival in uHCC patients, the majority of whom had Child-Pugh A (11,12), and sorafenib is suggested as first-line therapy in HCC patients with advanced-stage disease (13).

[1]Division of Diagnostic Imaging and Intervention, Pisa University Hospital and School of Medicine, Pisa, Italy
[2]Department of Gastroenterology and Hepatology, Kinki University School of Medicine, Osaka, Japan
[3]Liver Cancer Institute and Zhongshan Hospital, Fudan University, Shanghai, China
[4]Department of Gastroenterology and Hepatology, INSERM U954, University Hospital, University of Lorraine, Nancy, France
[5]Hepatic Surgery Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[6]Policlínica Metropolitana, Caracas, Venezuela
[7]Kyorin University School of Medicine, Mitaka, Tokyo, Japan
[8]Vascular and Interventional Radiology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[9]Hospital Angeles Clínica Londres, Mexico City, Mexico
[10]University Hospital of Larissa, Larissa, Greece
[11]Department of Digestive Surgery, Nihon University School of Medicine, Tokyo, Japan
[12]The Catholic University of Korea, Seoul, Korea
[13]Global Medical Affairs, Bayer HealthCare Pharmaceuticals, Montville, NJ, USA
[14]Clinical Statistics, Bayer HealthCare Pharmaceuticals, Montville, NJ, USA
[15]Global Medical Affairs and Pharmacovigilance, Bayer HealthCare Pharmaceuticals, Berlin, Germany
[16]Virginia Commonwealth University Medical Center, Richmond, VA, USA

Int J Clin Pract, May 2014, **68**, 5, 609–617. doi: 10.1111/ijcp.12352

Correspondence to:
Professor Riccardo Lencioni, Division of Diagnostic Imaging and Intervention, Pisa University Hospital and School of Medicine, Pisa, Italy
Tel.: +39 050 997 321
Fax: +39 050 996 561
Email: riccardo.lencioni@med.unipi.it

ClinicalTrials.gov identifier: NCT00812175

Disclosures
Riccardo Lencioni has participated in a speaker bureau with Bayer; Jean-Pierre Bronowicki has a consulting role with Bayer; Junji Furuse has a consulting role with Bayer, has participated in a speaker bureau with Bayer and has received a research grant from Bayer; Jeff F. Geschwind has a consulting role with Bayer and has received a research grant from Bayer; Laura Ladrón de Guevara has a consulting role with Bayer; Christos Papandreou has a consulting role with Bayer and has received a travel grant from Bayer; Keiko Nakajima is an employee of Bayer and has stock ownership with Bayer; Robert Lehr and Stephanie Heldner are employees of Bayer; Masatoshi Kudo, Sheng-Long Ye, Xiao-Ping Chen, Lucy Dagher, Tadatoshi Takayama, Seung Kew Yoon and Arun J. Sanyal have no financial interests to disclose.

GIDEON (Global Investigation of therapeutic DEcisions in HCC and Of its treatment with sorafeNib) is a prospective, non-interventional study undertaken to fulfil postapproval commitments to licensing agencies (14). The primary objective of GIDEON is to evaluate the safety of sorafenib in uHCC patients under real-life clinical practice conditions and to gather more comprehensive data on the use of sorafenib in patients with Child-Pugh B liver function, who were excluded from the randomised clinical trials (11,12). In general, clinical trials in HCC include only patients with preserved liver function (15), as severe liver dysfunction associated with Child-Pugh B or Child-Pugh C status represents a competing cause of death and may confound results (11).

GIDEON is one of the largest studies undertaken in patients with uHCC, allowing for a broad evaluation of patient subgroups. Multiple predefined subanalyses were therefore undertaken, focusing on potentially predictive or prognostic factors, including Child-Pugh score, Barcelona Clinic Liver Cancer (BCLC) stage and aetiology.

The first interim analysis of GIDEON was performed per protocol when ~500 patients had been enrolled; 479 patients were evaluated (16). Recently published findings of this preliminary analysis highlighted regional variations in patient characteristics, underlying disease aetiology and sorafenib dosing patterns, as well as consistent safety findings across Child-Pugh patients (16).

The second interim analysis of GIDEON was performed per protocol once ~1500 patients had been treated and followed up for ≥ 4 months. Here, we present clinically relevant findings of this analysis, including safety findings across Child-Pugh, BCLC and initial sorafenib dose subgroups (17–19).

Methods

Study design and objectives

GIDEON includes patients who are candidates for systemic therapy and in whom the decision to treat with sorafenib has been made under real-life practice conditions, including patients with Child-Pugh B liver function. Full details of the study design have been previously published (14).

Two interim analyses were preplanned, the first when 500 patients had been followed up for ≥ 4 months, and the second when 1500 patients had reached this point. The final analysis is scheduled at 12-month follow-up following the enrolment of 3000 sorafenib-treated patients (14).

Patients

Eligible patients are those diagnosed histologically, cytologically or radiographically with uHCC, who have a life expectancy of > 8 weeks and in whom the decision to treat with sorafenib has been made by their physician (14). Further inclusion criteria are outlined in the previously published study design report (14). Exclusion criteria are based on the local product information for sorafenib (14). All patients provided informed and signed consent, and the study is being conducted according to established recommendations and regulations relating to non-interventional and postauthorisation safety studies (20) and according to Good Clinical Practice. Documented approval from appropriate ethics committees and institutional review boards was obtained in accordance with local laws, regulations and organisations.

Data collection and analyses

All data were collected using case report forms as previously outlined (14). All adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Patients who received at least one dose of sorafenib and underwent at least one follow-up assessment were evaluable for safety.

Target enrolment was based on an overall sample of 3000 patients, the number determined sufficient for comprehensive evaluation of safety for the overall population, as well as specified subgroups (14). All baseline and safety data are summarised with descriptive statistics (14).

Results

Patient demographics and disease characteristics at study entry

In the second interim analysis, 1571 patients were eligible for safety analysis. The study population included patients across all BCLC stages and Child-Pugh status groups. The majority of patients (61%) had Child-Pugh A, with 23% having Child-Pugh B, and most had BCLC stage C (54%). The median age of the study population was 62, and the majority of patients were men (82%) (Table 1).

Patient demographics and disease characteristics were generally similar between patients receiving an initial sorafenib dose of 400 or 800 mg. Disease characteristics were also broadly comparable across Child-Pugh and BCLC subgroups (Table 1). There was some variation in prior treatment across Child-Pugh subgroups, as a greater proportion of Child-Pugh A patients had received prior locoregional treatment compared with Child-Pugh B (61% vs. 45%). Transarterial chemoembolisation was the most common locoregional treatment in both Child-Pugh A and Child-Pugh B patients and across all BCLC stages (Table 1).

Table 1 Patient demographics, disease characteristics and prior treatment by initial sorafenib dose, Child-Pugh status and BCLC stage

		Initial sorafenib dose*		Child-Pugh status†,‡			BCLC stage†,§			
	Total	400 mg	800 mg	A (< 7)	B (7–9)	C (> 9)	A	B	C	D
Patients, n (% of total)	1571 (100)	347 (22)	1161 (74)	957 (61)	367 (23)	35 (2)	115 (7)	298 (19)	851 (54)	92 (6)
Median age, years (range)	62 (18–98)	63 (19–89)	62 (18–98)	64 (18–94)	61 (23–86)	58 (39–82)	67 (33–87)	66 (25–98)	60 (18–89)	61 (33–82)
Gender, n (%)										
Men	1285 (82)	279 (80)	963 (83)	790 (83)	297 (81)	29 (83)	76 (66)	238 (80)	724 (85)	72 (78)
Women	286 (18)	68 (20)	198 (17)	167 (17)	70 (19)	6 (17)	39 (34)	60 (20)	127 (15)	20 (22)
ECOG PS, n (%)†,¶										
0	627 (40)	106 (31)	499 (43)	478 (50)	96 (26)	5 (14)	65 (57)	178 (60)	302 (36)	23 (25)
1	670 (43)	170 (49)	472 (41)	370 (39)	171 (47)	19 (54)	43 (37)	98 (33)	412 (48)	29 (32)
≥ 2	183 (12)	44 (13)	133 (11)	68 (7)	75 (20)	10 (29)	4 (4)	19 (6)	94 (11)	40 (44)
TNM status, n (%)†,**										
I	105 (7)	28 (8)	62 (5)	67 (7)	25 (7)	4 (11)	63 (55)	27 (9)	7 (1)	3 (3)
II	177 (11)	43 (12)	124 (11)	128 (13)	34 (9)	3 (9)	30 (26)	101 (34)	27 (3)	4 (4)
III	534 (34)	109 (31)	417 (36)	327 (34)	142 (39)	12 (34)	14 (12)	139 (47)	322 (38)	27 (29)
IV	561 (36)	129 (37)	411 (35)	352 (37)	113 (31)	12 (34)	5 (4)	13 (4)	440 (52)	52 (57)
Extrahepatic spread, n (%)†	612 (39)	141 (41)	453 (39)	382 (40)	127 (35)	11 (31)	1 (1)	5 (2)	503 (59)	50 (54)
Prior surgery, n (%)	294 (19)	66 (19)	221 (19)	218 (23)	34 (9)	1 (3)	13 (11)	59 (20)	168 (20)	7 (8)
Prior LRT, n (%)††	871 (55)	221 (64)	610 (53)	585 (61)	166 (45)	9 (26)	76 (66)	178 (60)	466 (55)	36 (39)
Prior TACE, n (%)	722 (46)	183 (53)	511 (44)	485 (51)	140 (38)	7 (20)	58 (50)	151 (51)	388 (46)	29 (32)

BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; LRT, locoregional treatment; TACE, transarterial chemoembolisation; TNM, tumour node metastasis. *Data missing for eight patients; data not shown for 55 patients (4%) who received an initial dose of 100, 200 or 600 mg sorafenib. †Recorded at study entry (which is defined as start of therapy and is indicated by the initial visit). ‡Child-Pugh status unknown for five patients; 207 patients not evaluable and not tabulated. §Data missing for 13 patients; 202 patients not evaluable and not tabulated. ¶Data missing for 91 patients. **Data missing for 14 patients; 180 patients not evaluable and not tabulated. ††Patients may have received more than one prior treatment. Other LRT received included radiofrequency ablation (15%), hepatic arterial infusion (5%), percutaneous ethanol injection (4%) and other (9%).

Sorafenib administration

Table 2 summarises sorafenib administration for the overall study population and by initial dose and Child-Pugh and BCLC subgroups. Overall, the majority of patients received the approved initial dose of 800 mg (74%). The median daily dose across all patients was 693 mg.

A slightly higher percentage of patients who received an initial sorafenib dose of 400 mg had treatment duration of ≤ 4 weeks compared with those who initially received 800 mg (20% vs. 16%). Patients with an initial dose of 400 mg also had lower median treatment duration (9.7 weeks) compared with those with an initial dose of 800 mg (12.3 weeks).

A similar proportion of patients across Child-Pugh subgroups received the recommended 800 mg initial dose, although the median daily dose was slightly higher in Child-Pugh B (721 mg) compared with Child-Pugh A patients (680 mg). However, median duration of sorafenib therapy was less in Child-Pugh B (8.6 weeks) than in Child-Pugh A patients (13.7 weeks) and shorter with increasing Child-Pugh B scores: B7 (9.0 weeks), B8 (8.5 weeks) and B9 (6.7 weeks).

Initial sorafenib dose and median daily dose were broadly consistent across BCLC stages. However, patients with BCLC stage C tended to have a shorter duration of treatment (10.1 weeks) than patients with BCLC stage B (16.3 weeks) and BCLC stage A (19.6 weeks) (Table 2).

Safety assessments

Safety data from the overall population are presented in Tables 3–5. Overall, 83% of patients experienced a treatment-emergent AE, with 64% in total reporting a drug-related AE. The majority of drug-related AEs were grade 1 or 2, and only 9% of patients experienced a drug-related serious AE (SAE) (Table 3). The most commonly observed drug-related AEs across all patients were diarrhoea, hand-foot skin reaction and fatigue (Table 5).

The incidence of AEs and drug-related AEs was comparable between Child-Pugh A and Child-Pugh B patients (Table 3). The majority of drug-related AEs were grade 1 or 2 in both Child-Pugh A and Child-Pugh B patients. However, there was a higher percentage of SAEs and drug-related SAEs, and a higher rate of

Table 2 Summary of sorafenib administration by initial sorafenib dose, Child-Pugh status and BCLC stage

Sorafenib administration	Total (n = 1571)	Initial sorafenib dose		Child-Pugh status*,†					BCLC stage*,‡			
		400 mg (n = 347)	800 mg (n = 1161)	A (< 7) (n = 957)	B (7) (n =196)	B (8) (n = 96)	B (9) (n = 69)	B (7–9) (n = 367)	C (> 9) (n = 35)	A (n = 115)	B (n = 298)	C (n = 851)	D (n = 92)
Duration of treatment ≤ 4 weeks, n (%)§,¶	265 (17)	69 (20)	183 (16)	120 (13)	43 (22)	21 (22)	20 (29)	86 (23)	16 (46)	15 (13)	26 (9)	150 (18)	27 (29)
Median treatment duration, weeks	11.7	9.7	12.3	13.7	9.0	8.5	6.7	8.6	4.1	19.6	16.3	10.1	7.2
Median daily dose, mg**,††	693.0	400.0	800.0	680.0	718.0	729.0	749.0	721.0	679.5	696.5	669.0	718.0	800.0
Initial dose of 800 mg/day, n (%)‡‡	1161 (74)	NA	1161 (100)	733 (77)	143 (73)	66 (69)	46 (67)	260 (71)	24 (69)	77 (67)	227 (76)	659 (77)	67 (73)

BCLC, Barcelona Clinic Liver Cancer; NA, not available. *At start of therapy. †Child-Pugh status unknown for five patients; 207 patients not evaluable and not tabulated; six patients documented as having Child-Pugh B but specific score not recorded. ‡Data missing for 13 patients; 202 patients not evaluable and not tabulated. §Time in weeks from initial visit to last dosing date (for ongoing patients to last visit date) +1. ¶1283 patients received > 4 weeks of sorafenib treatment and data missing for 23 patients. **Determined within patient based on actual days on study drug (interruptions excluded). ††Based on 1243 patients. ‡‡402 patients received ≤ 600 mg/day and data missing for eight patients.

treatment discontinuation because of AEs, in Child-Pugh B compared with Child-Pugh A patients.

The most frequent drug-related AEs across Child-Pugh subgroups were consistent with findings in the overall population and comparable across Child-Pugh subgroups (Table 5). Diarrhoea, hand-foot skin reaction and fatigue were the most frequently observed drug-related AEs in both Child-Pugh A and Child-Pugh B patients. However, a lower incidence of skin toxicity was observed in Child-Pugh B patients compared with Child-Pugh A patients (15% vs. 29%). No unexpected AEs were observed in patients with more severe liver dysfunction.

Neither the incidence nor the severity of drug-related AEs was notably different across BCLC subgroups. SAEs were more frequent in advanced disease but the incidence of drug-related SAEs was similar regardless of BCLC stage (Table 3). The nature of the most frequent drug-related AEs was consistent across all BCLC stages and with the overall population (Table 5).

Safety profiles appeared to be similar regardless of initial dose. The number of drug-related AEs and SAEs, and the number of patients in whom treatment was discontinued because of AEs, were similar across dosing subgroups (Table 4). The type and incidence of the most commonly reported drug-related AEs were also comparable for patients receiving an initial sorafenib dose of either 400 or 800 mg; diarrhoea (26% vs. 25%), hand-foot skin reaction (23% vs. 25%) and fatigue (17% vs. 14%) (Table 5).

Overall, the incidence of AEs, drug-related AEs and SAEs was similar in both older (≥ 65 years) and younger patients (Table 4). Across Eastern Cooperative Oncology Group (ECOG) subgroups, the incidence of SAEs was higher in patients with a greater ECOG score at baseline; however, the incidence of drug-related SAEs was similar (Table 3).

Nearly half of all deaths were HCC-related (40%), with 14% of deaths determined as liver-related and 11% both HCC- and liver-related (Table 6). Generally, the causes of death were similar between Child-Pugh A and Child-Pugh B patients, with HCC-related the most common cause of death.

Discussion

GIDEON is a Phase IV non-interventional study undertaken to evaluate the safety of sorafenib in clinical practice. The GIDEON study population is therefore a heterogeneous one, and multiple subgroup analyses, based on predictive and prognostic factors, were preplanned. The second interim analysis allowed for assessment of overall safety findings in the larger population of > 1500 patients and for

Table 3 Treatment-emergent adverse events by ECOG PS, Child-Pugh status and BCLC stage

Treatment-emergent adverse events, n (%)	Total (n = 1571)	ECOG PS		Child-Pugh status*,†			BCLC stage*,‡			
		≤ 1 (n = 1297)	2 (n = 143)	A (< 7) (n = 957)	B (7–9) (n = 367)	C (> 9) (n = 35)	A (n = 115)	B (n = 298)	C (n = 851)	D (n = 92)
AEs (all grades)	1307 (83)	1066 (82)	121 (85)	780 (82)	326 (89)	30 (86)	82 (71)	244 (82)	718 (84)	76 (83)
AEs (grade 3 or 4)	472 (30)	391 (30)	42 (29)	278 (29)	115 (31)	12 (34)	34 (30)	101 (34)	243 (29)	25 (27)
Drug-related AEs (all grades)	1010 (64)	850 (66)	79 (55)	639 (67)	230 (63)	16 (46)	70 (61)	206 (69)	562 (66)	45 (49)
Drug-related AEs (grade 3 or 4)	366 (23)	315 (24)	26 (18)	228 (24)	80 (22)	8 (23)	29 (25)	84 (28)	187 (22)	19 (21)
SAEs§ (all grades)	587 (37)	435 (34)	83 (58)	278 (29)	206 (56)	22 (63)	27 (24)	94 (32)	324 (38)	51 (55)
Drug-related SAEs§ (all grades)	142 (9)	123 (9)	11 (8)	72 (8)	54 (15)	2 (6)	10 (9)	35 (12)	75 (9)	6 (7)
AEs resulting in permanent discontinuation of sorafenib¶	434 (28)	336 (26)	56 (39)	225 (24)	141 (38)	18 (51)	28 (24)	76 (26)	226 (27)	40 (44)
Deaths**	343 (22)	250 (19)	49 (34)	154 (16)	125 (34)	13 (37)	14 (12)	48 (16)	196 (23)	34 (37)

AE, adverse event; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; SAE, serious adverse event. *At start of therapy. †Child-Pugh status unknown for five patients; 207 patients not evaluable and not tabulated. ‡Data missing for 13 patients; 202 patients not evaluable and not tabulated. §An SAE is defined as any AE occurring at any dose that results in any of the following outcomes: death; life-threatening; hospitalisation or prolongation of existing hospitalisation; persistent or significant disability/incapacity; congenital anomaly/birth defect; medically important event. ¶Any AE. **Deaths while on treatment and up to 30 days after last study medication dose.

Table 4 Treatment-emergent adverse events by initial sorafenib dose and age

		Initial sorafenib dose		Age	
Treatment-emergent adverse events, n (%)	**Total (n = 1571)**	**400 mg (n = 347)**	**800 mg (n = 1161)**	**< 65 years (n = 883)**	**≥ 65 years (n = 688)**
AEs (all grades)	1307 (83)	318 (92)	940 (81)	713 (81)	594 (86)
AEs (grade 3 or 4)	472 (30)	123 (35)	334 (29)	233 (26)	239 (35)
Drug-related AEs (all grades)	1010 (64)	237 (68)	740 (64)	530 (60)	480 (70)
Drug-related AEs (grade 3 or 4)	366 (23)	84 (24)	274 (24)	172 (20)	194 (28)
SAEs* (all grades)	587 (37)	152 (44)	412 (36)	329 (37)	258 (38)
Drug-related SAEs* (all grades)	142 (9)	33 (10)	101 (9)	60 (7)	82 (12)
AEs resulting in permanent discontinuation of sorafenib†	434 (28)	109 (31)	309 (27)	219 (25)	215 (31)
Deaths‡	343 (22)	84 (24)	248 (21)	199 (23)	144 (21)

AE, adverse event; BCLC, Barcelona Clinic Liver Cancer; SAE, serious adverse event. *An SAE is defined as any AE occurring at any dose that results in any of the following outcomes: death; life-threatening; hospitalisation or prolongation of existing hospitalisation; persistent or significant disability/incapacity; congenital anomaly/birth defect; medically important event. †Any AE. ‡Deaths while on treatment and up to 30 days after last study medication dose.

further evaluation across key clinical subgroups, including initial sorafenib dose, Child-Pugh status and BCLC stage. The final GIDEON analysis, in > 3000 patients, is currently being undertaken and will report data from final analyses across all subgroups.

Results of this second interim analysis, in 1571 patients, are consistent with observations reported in the first interim analysis in 479 patients (16). As previously observed, patient demographics in GIDEON are in line with previous HCC epidemiological reports in terms of age, gender, Child-Pugh status and prior treatment (21,22).

Consistent with the first interim analysis, the majority of patients received the recommended initial dose of sorafenib (800 mg), and had Child-Pugh A status and BCLC stage C. Patients across all BCLC stages and Child-Pugh status subgroups were treated with sorafenib. Nearly 25% of patients had Child-Pugh B status, and based on initial and median dose there was no evidence that the dosing strategy differs between Child-Pugh A and Child-Pugh B patients. However, duration of treatment tended to be less for patients with Child-Pugh B and was increasingly shorter with higher Child-Pugh B scores. Therefore, the dosing patterns observed in the larger patient population of the second interim analysis reflect those previously reported in the first interim analysis.

As reported in the first interim analysis, sorafenib was generally well tolerated in the clinical setting. In line with the SHARP and Asia-Pacific Phase III trials, the majority of drug-related AEs were grade 1 or 2 in nature (11,12). Similarly, the nature of the AEs was consistent with the Phase III trials, with diarrhoea, hand-foot skin reactions, fatigue and rash/desquamation being the most commonly reported drug-related AEs in the GIDEON, SHARP and Asia-Pacific studies, respectively (11,12).

The most commonly reported drug-related AEs across Child-Pugh subgroups were comparable in both type and incidence and were consistent with the overall population, although there was a lower incidence of skin toxicity in Child-Pugh B compared with Child-Pugh A patients.

Generally, drug-related safety findings appeared similar in both younger and older patients and in patients with lower and higher ECOG performance status at baseline. Also, the safety profile of sorafenib did not appear to differ across BCLC stages. Importantly, BCLC represents one of several staging systems used in HCC patients (23), and final analyses from the GIDEON study will allow for further exploration of findings across other staging systems and prognostic variables.

The safety profile of sorafenib appeared to be similar irrespective of initial dose; however, the lower initial dose of 400 mg was associated with a slightly shorter duration of treatment. Interestingly, this is in contrast to a recent Italian observational study in which a lower sorafenib dose was associated with a longer duration of treatment and improved outcomes (24). However, the outcome findings need to be interpreted with caution as the analysis did not account for the notable difference in treatment duration between the lower and higher dosing groups.

In this second interim analysis, study treatment duration findings must be considered preliminary.

Table 5 Treatment-emergent drug-related adverse events (any grade) in ≥ 5% of the total study population stratified by initial sorafenib dose, Child-Pugh status and BCLC stage at start of therapy

	Total	Initial sorafenib dose		Child-Pugh status			BCLC stage			
n (%)	Any grade (n = 1571)	400 mg (n = 347)	800 mg (n = 1161)	A (< 7) (n = 957)	B (7–9) (n = 367)	C (> 9) (n = 35)	A (n = 115)	B (n = 298)	C (n = 851)	D (n = 92)
Any adverse event	1010 (64)	237 (68)	740 (64)	639 (67)	230 (63)	16 (46)	70 (61)	206 (69)	562 (66)	45 (49)
Diarrhoea	387 (25)	90 (26)	289 (25)	248 (26)	86 (23)	3 (9)	26 (23)	95 (32)	217 (26)	13 (14)
Hand-foot skin reaction	380 (24)	79 (23)	293 (25)	278 (29)	54 (15)	1 (3)	22 (19)	91 (31)	213 (25)	14 (15)
Fatigue	222 (14)	60 (17)	157 (14)	139 (15)	41 (11)	6 (17)	18 (16)	41 (14)	122 (14)	10 (11)
Rash/desquamation	190 (12)	47 (14)	140 (12)	123 (13)	36 (10)	2 (6)	14 (12)	41 (14)	96 (11)	9 (10)
Anorexia	141 (9)	31 (9)	108 (9)	93 (10)	30 (8)	1 (3)	12 (10)	24 (8)	84 (10)	6 (7)
Hypertension	104 (7)	25 (7)	78 (7)	85 (9)	11 (3)	0	5 (4)	23 (8)	66 (8)	2 (2)
Alopecia	102 (7)	19 (6)	82 (7)	79 (8)	11 (3)	1 (3)	8 (7)	21 (7)	63 (7)	3 (3)
Nausea	93 (6)	26 (8)	65 (6)	51 (5)	18 (5)	2 (6)	10 (9)	6 (2)	44 (5)	9 (10)
Weight loss	74 (5)	14 (4)	60 (5)	45 (5)	15 (4)	1 (3)	11 (10)	18 (6)	34 (4)	3 (3)

BCLC, Barcelona Clinic Liver Cancer.

Table 6 Cause of death*,† while on sorafenib therapy or within 30 days of discontinuing therapy, by Child-Pugh status at study entry

		Child-Pugh status		
Deaths, n (%)	**Total‡ (n = 343)**	**A§ (< 7) (n = 154)**	**B§ (7–9) (n = 125)**	**C (> 9) (n = 13)**
HCC-related	138 (40)	61 (40)	50 (40)	4 (31)
HCC- and liver-related	38 (11)	15 (10)	15 (12)	3 (23)
HCC- and liver-related and MOF	9 (3)	4 (3)	2 (2)	1 (8)
Liver-related	49 (14)	22 (14)	18 (14)	2 (15)
HCC-related and MOF	15 (4)	8 (5)	4 (3)	0
MOF	22 (6)	10 (7)	8 (6)	1 (8)

HCC, hepatocellular carcinoma; MOF, multi-organ system failure. *Incidence > 2% in total population. †Patients may be included in more than one cause of death category. ‡Child-Pugh status missing for one patient. §Data missing for seven Child-Pugh A and seven Child-Pugh B patients.

Final data are needed to fully evaluate duration of treatment, and final outcome analyses will adjust for duration of treatment.

Conclusions

This updated analysis of the GIDEON study confirms the findings from earlier reports. Sorafenib is well tolerated in the clinical setting and safety findings are as anticipated. The safety profile of sorafenib appears to be similar irrespective of Child-Pugh status, BCLC stage or initial sorafenib dose.

The GIDEON study is an observational study and thus is limited by the lack of either a control arm or a randomised study population. However, a non-interventional study provides an opportunity to observe treatment patterns in clinical practice and allows the assessment of a wider patient population than in randomised clinical trials. Thus, while GIDEON is a non-controlled, non-interventional study, the opportunity to evaluate > 3000 patients with uHCC in clinical practice, including patients with a greater degree of liver dysfunction, is of considerable clinical interest and relevance.

The GIDEON study is ongoing, with final analyses planned for 12 months following the recruitment of 3000 treated patients (14). Therefore, reports from interim analyses need to be considered preliminary and results interpreted with caution. Final reports will include updated analysis of safety, both overall and across subgroups, reports on duration of treatment and evaluation of treatment outcomes.

Acknowledgements

The authors would like to thank all participating clinical sites that are contributing to the GIDEON study. All data management-related activities for the GIDEON study are coordinated and overseen by Anja Laske at Bayer HealthCare Pharmaceuticals. The contract research organisation Kantar Health GmbH (Munich, Germany) is responsible for the data management system, data capture, quality review, statistical analysis and report writing. Kieran Davey, PhD, at Complete HealthVizion provided assistance in the preparation and revision of the draft manuscript, funded by Bayer HealthCare Pharmaceuticals. The authors take full responsibility for the scope, direction and content of the manuscript.

The GIDEON study is funded by Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals.

Author contributions

Riccardo Lencioni, Masatoshi Kudo and Sheng-Long Ye are members of the GIDEON Global Steering Committee and were involved in the GIDEON study design and data interpretation; Keiko Nakajima is the study sponsor physician and contributed to data analysis and interpretation; Riccardo Lencioni, Masatoshi Kudo, Sheng-Long Ye, Jean-Pierre Bronowicki, Xiao-Ping Chen, Lucy Dagher, Junji Furuse, Jeff F. Geschwind, Laura Ladrón de Guevara, Christos Papandreou, Tadatoshi Takayama, Seung Kew Yoon and Arun J. Sanyal were responsible for the provision of patients/data acquisition; Stephanie Heldner supervised the set-up and conduct of the study; Robert Lehr was responsible for statistical analysis; Riccardo Lencioni was responsible for the concept and design of the manuscript. All authors critically reviewed the manuscript and approved the final version for publication.

References

1 Maillard E. [Epidemiology, natural history and pathogenesis of hepatocellular carcinoma]. *Cancer Radiother* 2011; **15**: 3–6. (in French).

2 El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology* 2012; **142**: 1264–73.e1.

3 El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. *Clin Gastroenterol Hepatol* 2006; **4**: 369–80.

4 Gao J, Xie L, Yang WS et al. Risk factors of hepatocellular carcinoma – current status and perspectives. *Asian Pac J Cancer Prev* 2012; **13**: 743–52.

5 Okuda H. Hepatocellular carcinoma development in cirrhosis. *Best Pract Res Clin Gastroenterol* 2007; **21**: 161–73.

6 Thomas MB, Zhu AX. Hepatocellular carcinoma: the need for progress. *J Clin Oncol* 2005; **23**: 2892–9.

7 Bruix J, Sala M, Llovet JM. Chemoembolization for hepatocellular carcinoma. *Gastroenterology* 2004; **127**(Suppl 1): S179–S188.

8 Bruix J, Sherman M. Practice Guidelines Committee American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology* 2005; **42**: 1208–36.

9 Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003; **362**: 1907–17.

10 National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancers (Version 2.2013). http://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. 2012 (accessed June 2013).

11 Cheng AL, Kang YK, Chen Z et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25–34.

12 Llovet JM, Ricci S, Mazzaferro V et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378–90.

13 Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; **53**: 1020–2.

14 Lencioni R, Marrero J, Venook A, Ye SL, Kudo M. Design and rationale for the non-interventional Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib (GIDEON) study. *Int J Clin Pract* 2010; **64**: 1034–41.

15 Ozenne V, Paradis V, Pernot S et al. Tolerance and outcome of patients with unresectable hepatocellular carcinoma treated with sorafenib. *Eur J Gastroenterol Hepatol* 2010; **22**: 1106–10.

16 Lencioni R, Kudo M, Ye SL et al. First interim analysis of the GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib) non-interventional study. *Int J Clin Pract* 2012; **66**: 675–83.

17 Marrero J, Venook A, Kudo M et al. Second interim analysis of GIDEON (Global Investigation of therapeutic DEcisions in unresectable hepatocellular carcinoma and Of its treatment with sorafeNib): subgroup analysis by initial sorafenib dose. Abstract 2192 presented at the Liver Meeting 2011 – The 62nd Annual Meeting of the American Association for the Study of Liver Diseases, San Francisco, CA, USA, 4–8 November 2011.

18 Marrero JA, Lencioni R, Kudo M et al. Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib (GIDEON) second interim analysis in more than 1,500 patients: clinical findings in patients with liver dysfunction. *J Clin Oncol* (*Meeting Abstracts*) 2011; **29**: abs 4001.

19 Lencioni R, Venook A, Marrero J et al. Second interim results of the GIDEON (Global Investigation of therapeutic DEcisions in HCC and Of its treatment with sorafeNib) study: Barcelona Clinic Liver Cancer (BCLC) stage subgroup analysis. Abstract 6500 presented at the ECCO-ESMO, Stockholm, Sweden, 23–27 September 2011.

20 European Medicines Agency. EUDRALEX: the rules governing medicinal products in the European Union. http://ec.europa.eu/enterprise/newsroom/cf/itemdetail.cfm?&item_id=897. 2013 (accessed June 2013).

21 Farinati F, Rinaldi M, Gianni S, Naccarato R. How should patients with hepatocellular carcinoma be staged? Validation of a new prognostic system. *Cancer* 2000; **89**: 2266–73.

22 Tandon P, Garcia-Tsao G. Prognostic indicators in hepatocellular carcinoma: a systematic review of 72 studies. *Liver Int* 2009; **29**: 502–10.

23 Pons F, Varela M, Llovet JM. Staging systems in hepatocellular carcinoma. *HPB (Oxford)* 2005; **7**: 35–41.

24 Iavarone M, Cabibbo G, Piscaglia F et al. Field-practice study of sorafenib therapy for hepatocellular carcinoma: a prospective multicenter study in Italy. *Hepatology* 2011; **54**: 2055–63.

Paper received July 2013, accepted October 2013