

First interim analysis of the GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib) non-interventional study

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SUMMARY

Aims: Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib (GIDEON), a global, non-interventional, surveillance study, aims to evaluate the safety of sorafenib in all patients with unresectable hepatocellular carcinoma (uHCC) under real-life practice conditions, particularly Child-Pugh B patients, who were not well represented in clinical trials. **Methods:** Treatment decisions are determined by each physician according to local prescribing guidelines and clinical practice. Patients with uHCC who are candidates for systemic therapy, and for whom a decision has been made to treat with sorafenib, are eligible for inclusion. Demographic data and medical and disease history are recorded at entry. Sorafenib dosing and adverse events (AEs) are collected throughout the study. **Results:** From January 2009 to April 2011, >3000 patients from 39 countries were enrolled. The prespecified first interim analysis was conducted when the initial approximately 500 treated patients had been followed up for ≥ 4 months; 479 were valid for safety evaluation. Preplanned subgroup analyses indicate differences in patient characteristics, disease aetiology and previous treatments by region. Variation in sorafenib dosing by specialty are also observed; Child-Pugh status did not appear to influence the starting dose of sorafenib. The type and incidence of AEs was consistent with findings from previous clinical studies. AE profiles were comparable between Child-Pugh subgroups. **Discussion:** The GIDEON study is generating a large, robust database from a broad population of patients with uHCC. First interim analyses have shown global and regional differences in patient characteristics, disease aetiology and practice patterns. Subsequent planned analyses will allow further evaluation of early trends.

Introduction

Liver cancer is the fifth most prevalent neoplasm worldwide but the second most common cause of cancer-related mortality in men (1). In women, it is the seventh most common cancer but the sixth leading cause of cancer-related death (1). This is in part because of the poor prognosis for many patients, more than 70% of whom present with advanced disease (2,3). The highest incidence of liver cancer is found in East and South-East Asia and in middle and West Africa (1). Although the incidence rate in more developed regions of the world is lower, including central Europe and the USA, liver cancer

incidence rates in the developed world are increasing (1). The global incidence of hepatocellular carcinoma (HCC) is predicted to continue to increase until a plateau is reached in 2015–2020 (2). Risk factors for the development of HCC include hepatitis B viral (HBV) and hepatitis C viral (HCV) infection, high alcohol intake, obesity and diabetes (1,4).

HCC treatments have developed rapidly over the last two decades in parallel with significant developments in diagnosis, surveillance, staging system and tumour assessment criteria. However, the majority of patients present with unresectable HCC (uHCC). Current non-surgical treatment options include loco-regional treatment (LRT), for example transarterial

What's known

- Currently, there is no global consensus on the management of patients with uHCC. A worldwide study of regional uHCC treatment practices is therefore needed to advance the management of uHCC
- The oral multikinase inhibitor sorafenib is the only systemic therapy indicated for the treatment of uHCC, but data from Child-Pugh B patients are limited

What's new

- The non-interventional GIDEON study is evaluating sorafenib in uHCC under real-life clinical practice conditions and therefore includes a broader patient demographic than that represented in controlled clinical trials
- GIDEON allows global variations in uHCC management to be evaluated in a single robust study, and the prespecified first interim analysis results highlight differences in patient and disease characteristics, aetiology, and risk factors for uHCC, and sorafenib dosing, by region and physician specialty
- The type and incidence of AEs is as expected and appears to be similar in Child-Pugh A and B patients

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chemoembolisation (TACE) and ablation therapy, although it is recognised that these have maximal effect for smaller tumours without vascular invasion (5–8).

Two placebo-controlled Phase III studies (SHARP and Asia-Pacific) have demonstrated that the oral multikinase inhibitor sorafenib (Nexavar®; Bayer HealthCare Pharmaceuticals, Berlin, Germany; Onyx Pharmaceuticals, San Francisco, CA) significantly improves overall survival in patients with uHCC (9,10). Sorafenib is the first systemic anticancer agent to be indicated for patients with uHCC and is currently recommended for selected patients with Child-Pugh A or B liver function and unresectable disease who are unsuitable for liver transplantation (5,8). Sorafenib is also indicated in patients with local disease unsuitable for surgery because of performance status or comorbidity, and for patients with metastatic disease (5).

The Global Investigation of therapeutic DEcisions in HCC and Of its treatment with sorafeNIB (GIDEON) study is the largest prospective, non-interventional study undertaken in patients with uHCC. The study was initiated to fulfil the post-approval commitment to licensing agencies 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, resulting in limited data for patients with more severe liver dysfunction (11). The primary objective of GIDEON is to evaluate the safety of sorafenib in uHCC patients under real-life clinical practice conditions (12). Importantly, the GIDEON study is inclusive of the diverse HCC population from 39 countries, thus allowing both global and regional evaluation of prognostic and predictive factors.

The robust database provided by GIDEON on treatment patterns and outcomes for uHCC patients who are candidates for systemic therapy is a unique resource to further study multiple patient subgroups and physicians' practice patterns around the world. Thus, the GIDEON study can generate data that could better inform treatment choices and ultimately improve outcomes for patients with uHCC. Results from the first interim analysis are presented in this paper.

Methods**Study design and objectives**

GIDEON is a global, non-interventional, surveillance study in which assignment to a particular therapy is not mandated by a study protocol but is decided by the participating physician, as previously described (13). The primary objective is to

evaluate the safety of sorafenib in patients with uHCC who are candidates for systemic therapy and in whom a decision to treat with sorafenib has been made in real-life practice conditions. The secondary objectives include efficacy and duration of therapy with sorafenib. Objectives will be evaluated in a variety of patient subsets, both globally and across regions.

The first patient entered the study in 2009 and the last patient was enrolled in April 2011, 20 months before the anticipated date. Two preplanned interim analyses were defined based on prespecified numbers of patients who are treated with sorafenib and followed for at least 4 months, the first interim at 500 patients and the second interim at 1500 patients. The final analysis is planned 12 months after enrolment of the 3000th treated patient (12).

The study is being conducted according to established regulations and recommendations relating to the conduct of a non-interventional study, according to Good Clinical Practice where applicable to a non-interventional study, and according to relevant local laws, regulations and organisations, with documented approval from appropriate ethics committee(s)/institutional review board as required (12).

Patients

Eligible patients must have histologically, cytologically or radiographically diagnosed uHCC and a life expectancy of >8 weeks. They must also have provided signed, informed consent, and the local physician must have decided to treat them with sorafenib. Radiographic diagnosis is based on findings from multidimensional dynamic computed tomography (CT), CT hepatic arteriography/CT arterial portography, or magnetic resonance imaging. Patient exclusion criteria are based on the approved local product information for sorafenib (12). Patients who received at least one dose of sorafenib and underwent at least one follow-up assessment after start of treatment are evaluable for safety.

Data collection

All data are collected using case report forms, as previously described (12). Dosage details and duration of sorafenib treatment are determined for each patient, and data for discontinuation are summarised. Adverse events (AEs) and serious AEs (SAEs) are graded according to the Common Terminology Criteria for Adverse Events version 3.0; other safety variables are summarised descriptively.

Statistical methods

Based on previously conducted large, global, multi-centre sorafenib studies for HCC, overall incidence

rates of approximately 1–2% had been observed for AEs of interest for further safety monitoring. Approximately 3000 treated patients will provide an 84% chance of observing an AE, with a true incidence of 1% in at least 25 patients. An overall sample size of 3000 patients was therefore considered sufficient for evaluation of safety of both the overall population and specific subgroups (12). All baseline and safety data are summarised using descriptive statistics. Preplanned subgroup analyses of safety data were performed, stratified by region and physician specialty for multiple data points, such as patient demographics and treatment history.

Results

Patients

Per protocol, the first planned interim analysis was initiated when the initial approximately 500 treated patients had been followed for at least 4 months. Based on these criteria, the cut-off date used for the first interim analysis was 11 April 2010. A total of 511 patients have been enrolled from 140 sites. Patients have been enrolled from 39 countries across five regions: Europe, Latin America, the USA, Japan and Asia-Pacific (Figure 1). Of these, 479 were evaluable for safety analyses. Thirty-two patients were excluded from the safety analyses, as they did not receive sorafenib treatment or received sorafenib but had no post-baseline evaluation.

Patient characteristics at baseline

Demographics and baseline characteristics for patients evaluable for safety analyses are presented by region and by leading physician specialty in Table 1. Based on this first interim analysis, Asia-Pacific countries enrolled the most patients. The distribution of males/females was generally similar across geographic regions, except for Latin America. Patients in Asia-Pacific were relatively younger than those in other regions.

Primary physician specialty

Overall, hepatologists/gastroenterologists (Hep/GIs) were the most common treating physicians (52%) for patients with uHCC. Medical oncologists (Med Oncs) treated 35% of patients across all regions. Other treating specialties were less commonly reported: surgery (7%), traditional Chinese medicine (2%), radiology (1%) and anaesthesiology (1%). Baseline characteristics were generally similar between patients treated by Hep/GIs and those treated by Med Oncs.

Prior locoregional treatment

Overall, 55% of patients received prior LRT (Table 1). TACE was the most commonly received LRT, with 44% of all patients receiving prior TACE compared with only 15%, 5% and 3% of patients receiving prior radiofrequency ablation, hepatic arterial infusion and percutaneous ethanol injection, respectively.

Prior locoregional treatment by region

Wide regional variation was observed in the use of prior LRT. In Japan all patients received LRT prior to sorafenib treatment; however, in Asia-Pacific, the USA and Europe, 68%, 46% and 45% of patients received prior LRT, respectively. TACE was the most commonly received LRT in each region, although with considerable regional variation. Prior TACE treatment was more frequent in Japan (90%) and Asia-Pacific (62%) and less common in Europe (27%) and Latin America (22%).

Disease characteristics at study entry

Disease characteristics at study entry (defined as start of sorafenib therapy, indicated by the initial visit) are provided in Table 2. Patients were enrolled across all Barcelona Clinic Liver Cancer (BCLC) stages. The majority of patients (53%) had BCLC stage C; however, 19% of patients had BCLC stage B, and 10% and 6% had stage A and D, respectively. More

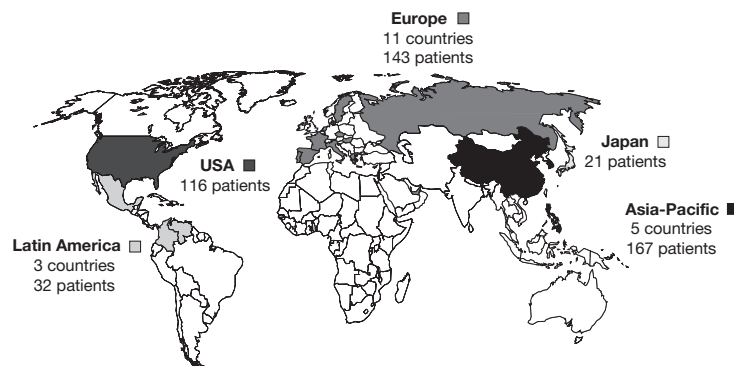


Figure 1 Distribution of patients included in the first interim analysis, by region

Table 1 Demographic and baseline characteristics

	Total	Geographic regions					Specialty*	
		Asia-Pacific	Europe	USA	Latin America	Japan	Hep/GI†	Med Onc
Patients, <i>n</i> (% of total)	479 (100)	167 (35)	143 (30)	116 (24)	32 (7)	21 (4)	248 (52)	168 (35)
Median age, years	62	54	68	62	65	70	60/67	61
Gender, <i>n</i> (%)								
Male	392 (82)	144 (86)	125 (87)	89 (77)	15 (47)	19 (90)	210 (85)	134 (80)
Female	87 (18)	23 (14)	18 (13)	27 (23)	17 (53)	2 (10)	38 (15)	34 (20)
ECOG PS, <i>n</i> (%)‡,§								
0	181 (38)	51 (31)	69 (48)	41 (35)	5 (16)	15 (71)	114 (46)	40 (24)
1	199 (42)	78 (47)	50 (35)	43 (37)	22 (69)	6 (29)	93 (38)	75 (45)
≥2	62 (13)	14 (8)	22 (15)	22 (19)	4 (12)	0	36 (15)	23 (14)
Prior LRT, <i>n</i> (%)¶	264 (55)	114 (68)	64 (45)	53 (46)	12 (38)	21 (100)	132 (53)	88 (52)
Prior TACE, <i>n</i> (%)	212 (44)	104 (62)	39 (27)	43 (37)	7 (22)	19 (90)	107 (43)	68 (40)
Prior RFA, <i>n</i> (%)	72 (15)	17 (10)	35 (25)	8 (7)	6 (19)	6 (29)	45 (18)	20 (12)
Prior HAI, <i>n</i> (%)	26 (5)	14 (8)	2 (1)	6 (5)	2 (6)	2 (10)	17 (7)	4 (2)
Prior PEI, <i>n</i> (%)	15 (3)	4 (2)	8 (6)	0	0	3 (14)	12 (5)	2 (1)

*Other specialties not tabulated included surgery (*n* = 35), radiology (*n* = 6), anaesthesiology (*n* = 4) and traditional Chinese medicine (*n* = 10); †Hep/GI population comprised 178 patients treated by hepatologists and 70 patients treated by gastroenterologists; ‡Recorded at study entry (which is defined as start of therapy and is indicated by the initial visit); §Data missing for 37 patients; ¶Data missing for one patient.

ECOG PS, Eastern Cooperative Oncology Group performance status; GI, gastroenterologist; HAI, hepatic arterial infusion; Hep, hepatologist; LRT, locoregional treatment; Med Onc, medical oncologist; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transarterial chemoembolisation.

patients had tumour, node, metastasis (TNM) stage III and IV disease (37% and 35%, respectively) than stage I (6%) or II (14%).

As might be anticipated, the majority of patients in the overall population had Child-Pugh A status (*n* = 278; 58%) and there were fewer Child-Pugh B patients (*n* = 134; 28%). Subgroup analyses of disease characteristics at study entry suggest differences in many prognostic and predictive factors across regions and by treating-physician specialty (Table 2).

Disease characteristics by region

Some regional variation was observed: patients in Asia-Pacific tended to have more advanced HCC based on BCLC and TNM status at study entry than in other regions (Table 2). In Asia-Pacific, 74% of patients had BCLC stage C disease and 50% had TNM stage IV disease compared with 24–51% and 13–43%, respectively, across other regions. Extrahepatic spread was also observed within considerably more patients in Asia-Pacific (60%) than in other regions (16–34%).

There was some regional variation observed in Child-Pugh status (Table 2). A higher percentage of patients (60–76%) in Asia-Pacific, Europe and Japan had less advanced liver disease (i.e. Child-Pugh A) than in either the USA (41%) or Latin America (44%).

Differences in the aetiology of underlying liver disease were observed across regions (Table 2). The majority of patients in Asia-Pacific had HBV infection (84%), whereas HCV infection was more common in Europe (33%) and the USA (50%). A greater proportion of patients in Europe (42%) and the USA (34%) had alcoholic liver disease compared with other regions (16–19%). Thus, the major aetiologies for uHCC were HCV and alcoholic liver disease in Europe and the USA and HBV in Asia-Pacific.

Disease characteristics by physician specialty

Based on subgroup analyses by leading physician specialty, variations in disease characteristics were also seen between patients principally treated by Med Oncs and those treated by Hep/GIs (Table 2). Med Oncs tended to treat a greater number of patients with advanced HCC (64% of patients had BCLC stage C or D; 46% of patients had TNM stage IV) compared with Hep/GIs (59% of patients had BCLC stage C or D; 28% of patients had TNM stage IV). Hep/GIs treated more patients with Child-Pugh B status compared with Med Oncs (32% and 20%, respectively).

Sorafenib administration

Sorafenib administration data from the overall population are presented in Table 3. Overall, 76% of patients received the approved initial daily dose of

Table 2 Disease characteristics

	Geographic regions						Specialty	
	Total (n = 479)	Asia-Pacific (n = 167)	Europe (n = 143)	USA (n = 116)	Latin America (n = 32)	Japan (n = 21)	Hep/GI (n = 248)	Med Onc (n = 168)
BCLC staging^{*,†}, n (%)								
Stage A	47 (10)	1 (1)	20 (14)	17 (15)	8 (25)	1 (5)	21 (8)	20 (12)
Stage B	92 (19)	19 (11)	32 (22)	21 (18)	11 (34)	9 (43)	55 (22)	25 (15)
Stage C	253 (53)	123 (74)	73 (51)	43 (37)	9 (28)	5 (24)	129 (52)	98 (58)
Stage D	29 (6)	7 (4)	7 (5)	11 (9)	3 (9)	1 (5)	17 (7)	10 (6)
TNM stage^{*,‡}, n (%)								
Stage I	31 (6)	2 (1)	10 (7)	14 (12)	5 (16)	0	15 (6)	8 (5)
Stage II	69 (14)	13 (8)	17 (12)	18 (16)	11 (34)	10 (48)	41 (17)	16 (10)
Stage IIIa	121 (25)	44 (26)	39 (27)	30 (26)	7 (22)	1 (5)	69 (28)	37 (22)
Stage IIIb	15 (3)	3 (2)	4 (3)	7 (6)	0	1 (5)	8 (3)	7 (4)
Stage IIIc	40 (8)	14 (8)	16 (11)	8 (7)	2 (6)	0	20 (8)	15 (9)
Stage IV	167 (35)	83 (50)	40 (28)	31 (27)	4 (13)	9 (43)	69 (28)	78 (46)
Extrahepatic spread [*] , n (%)	193 (40)	101 (60)	49 (34)	32 (28)	5 (16)	6 (29)	88 (35)	84 (50)
Child-Pugh status[§], n (%)								
A	278 (58)	101 (60)	100 (70)	47 (41)	14 (44)	16 (76)	149 (60)	91 (54)
B	134 (28)	44 (26)	30 (21)	41 (35)	15 (47)	4 (19)	80 (32)	34 (20)
C	11 (2)	1 (1)	2 (1)	8 (7)	0	0	5 (2)	5 (3)
CLIP score[¶], n (%)								
0	30 (6)	5 (3)	11 (8)	7 (6)	6 (19)	1 (5)	16 (6)	10 (6)
1	93 (19)	19 (11)	39 (27)	19 (16)	7 (22)	9 (43)	53 (21)	26 (15)
2	99 (21)	30 (18)	33 (23)	20 (17)	8 (25)	8 (38)	60 (24)	23 (14)
3	75 (16)	27 (16)	20 (14)	22 (19)	4 (13)	2 (10)	48 (19)	20 (12)
4–6	68 (14)	34 (20)	15 (10)	15 (13)	3 (9)	1 (5)	46 (19)	16 (10)
Aetiology of underlying liver disease^{**}, n (%)								
Hepatitis B	194 (41)	140 (84)	25 (17)	23 (20)	1 (3)	5 (24)	89 (36)	77 (46)
Hepatitis C	146 (30)	12 (7)	47 (33)	58 (50)	17 (53)	12 (57)	82 (33)	44 (26)
Alcohol	138 (29)	29 (17)	60 (42)	40 (34)	5 (16)	4 (19)	84 (34)	42 (25)
Liver cirrhosis^{††}, n (%)								
Yes ^{‡‡}	327 (68)	111 (66)	104 (73)	78 (67)	20 (63)	14 (67)	197 (79)	86 (51)
No	107 (22)	42 (25)	27 (19)	25 (22)	10 (31)	3 (14)	34 (14)	62 (37)

*Recorded at study entry (which is defined as start of therapy and is indicated by the initial visit); †Data missing for six patients and not evaluable for 52 patients; ‡Data missing for six patients and not evaluable for 30 patients; §Data missing for five patients and not evaluable for 51 patients; ¶Data missing for seven patients and not evaluable for 107 patients; **Patients could have >1 underlying liver disease; other aetiologies included non-alcoholic steatohepatitis, metabolic factors and haemochromatosis; ††Data missing for one patient and unknown for 47 patients; ‡‡Includes clinical, histologic or radiologic diagnosis.

BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; TNM, tumour, node, metastasis.

800 mg sorafenib, while 24% of patients received an initial daily dose of <800 mg. The majority of patients were treated for >4 weeks (75%). However, treatment duration data based on interim analyses are preliminary, as data will also reflect the point at which patients started the study relative to the timing of database cut-off.

Sorafenib administration by region

Based on these preliminary findings, regional variation in dosing was observed. In Asia-Pacific, 66% of patients received sorafenib for >4 weeks compared with 77–97% of patients in other regions. Therefore,

patients in Asia-Pacific tended to stop sorafenib therapy earlier than patients in other regions. The lowest median daily dose was given in Japan (521 mg) and the USA (564 mg). Patients in Asia-Pacific, Europe and Latin America tended to receive a much higher median daily dose (710–800 mg).

Sorafenib administration by physician specialty

Variations in sorafenib dosing patterns were seen across physician specialties (Table 3). A greater percentage of Hep/GIs initiated sorafenib therapy at 800 mg/day compared with Med Oncs (83% and 65%, respectively), and Hep/GIs gave a higher

Table 3 Summary of sorafenib administration stratified by region, specialty and Child-Pugh status

Sorafenib administration	Geographic regions						Specialty		Child-Pugh status*, †	
	Total (n = 479)	Asia-Pacific (n = 167)	Europe (n = 143)	USA (n = 116)	Latin		Hep/GI (n = 248)	Med Onc (n = 168)	Child-Pugh A (n = 278)	Child-Pugh B (n = 134)
					America (n = 32)	Japan (n = 21)				
Duration of treatment, n (%)‡, §										
≤4 weeks	106 (22)	50 (30)	25 (17)	26 (22)	1 (3)	4 (19)	53 (21)	40 (24)	47 (17)	44 (33)
>4–8 weeks	87 (18)	32 (19)	23 (16)	22 (19)	5 (16)	5 (24)	44 (18)	28 (17)	45 (16)	29 (22)
>8–12 weeks	72 (15)	24 (14)	20 (14)	22 (19)	3 (9)	3 (14)	32 (13)	32 (19)	38 (14)	19 (14)
>12–16 weeks	53 (11)	14 (8)	19 (13)	10 (9)	5 (16)	5 (24)	35 (14)	15 (9)	34 (12)	10 (7)
>16–20 weeks	56 (12)	11 (7)	26 (18)	10 (9)	5 (16)	4 (19)	22 (9)	22 (13)	44 (16)	7 (5)
>20–24 weeks	30 (6)	9 (5)	8 (6)	9 (8)	4 (13)	0	16 (6)	12 (7)	20 (7)	8 (6)
>24–28 weeks	25 (5)	11 (7)	7 (5)	6 (5)	1 (3)	0	13 (5)	9 (5)	18 (6)	2 (1)
>28 weeks	38 (8)	10 (6)	10 (7)	10 (9)	8 (25)	0	24 (10)	7 (4)	27 (10)	10 (7)
Median daily dose¶, **, mg	692	710	779	564	800	521	774	570	624	800
Initial dose of 800 mg/day††, n (%)	363 (76)	133 (80)	114 (80)	69 (59)	31 (97)	16 (76)	206 (83)	109 (65)	221 (79)	100 (75)
Permanent discontinuation of sorafenib because of AEs, n (%)	133 (28)	49 (29)	36 (25)	37 (32)	2 (6)	9 (43)	81 (33)	34 (20)	69 (25)	53 (40)

*At start of therapy; †Data missing for five patients and not evaluable for 51 patients; ‡Time in weeks from initial visit to last dosing date (for ongoing patients to last visit date) + 1; §Data missing for 12 patients; ¶Determined per patient based on actual days on study drug (interruptions excluded); **Based on 367 patients; †† 114 patients received ≤ 600 mg/day and data missing for two patients.

AE, adverse event; GI, gastroenterologist; Hep, hepatologist; Med Onc, medical oncologist.

median daily dose than Med Oncs (774 mg and 570 mg, respectively).

Sorafenib administration by Child-Pugh status

Sorafenib administration based on Child-Pugh classification was also assessed (Table 3). Duration of treatment was generally shorter in Child-Pugh A than in Child-Pugh B patients. A greater number of Child-Pugh A patients received treatment for >8 weeks compared with Child-Pugh B patients (65% vs. 42%). These preliminary data suggest that patients with advanced Child-Pugh status tended to stop sorafenib treatment earlier than patients with less advanced disease. However, a number of Child-Pugh B patients were treated for longer periods, and 7% and 10% of Child-Pugh B and Child-Pugh A patients, respectively, received >28 weeks of sorafenib therapy.

Child-Pugh score did not seem to influence the starting dose of sorafenib, and at least 75% of patients in both Child-Pugh A and Child-Pugh B groups received the recommended initial daily dose of 800 mg sorafenib (79% and 75%, respectively). Overall, the dosing strategy for Child-Pugh B patients did not appear to be different from that for Child-Pugh A patients.

Safety assessments

Safety data from this first interim analysis are preliminary; however, the overall safety profile of sorafenib in this first interim analysis was consistent with that reported in previous clinical studies and no unforeseen AEs were reported (Tables 4 and 5). A total of 87% of patients reported at least one AE. Drug-related AEs were experienced by 319 patients (67%): 41% with grade 1 or 2 events and 25% with grade 3 or 4 events. Overall, 42% of patients (n = 201) experienced SAEs and 11% experienced drug-related SAEs. Study drug was permanently discontinued as a result of AEs in 28% of patients. This was because of a variety of AEs, each with a relatively low incidence in the overall population. The most commonly reported AEs in the overall population included diarrhoea, hand-foot skin reaction, fatigue, rash/desquamation and anorexia (Table 5). Hand-foot skin reaction and fatigue were the most commonly reported grade 3 or 4 AEs within the study population.

AE profiles were comparable between subgroups of Child-Pugh status (Table 4). The overall incidence of treatment-emergent AEs was slightly higher in Child-Pugh B patients than in Child-Pugh A patients (91% vs. 84%, respectively); however, the incidence of drug-related AEs was similar in both Child-Pugh A

Table 4 Treatment-emergent adverse events by Child-Pugh status

Treatment-emergent adverse events, n (%)	Total (n = 479)	Child-Pugh status at start of therapy		
		Child-Pugh A (<7) (n = 278)	Child-Pugh B (7–9) (n = 134)	Child-Pugh C (>9) (n = 11)
AEs (all grades)	415 (87)	234 (84)	122 (91)	10 (91)
AEs (grade 3 or 4)	194 (41)/43 (9)	98 (35)/19 (7)	70 (52)/20 (15)	4 (36)/2 (18)
Drug-related AEs (all grades)	319 (67)	193 (69)	84 (63)	6 (55)
Drug-related AEs (grade 3 or 4)	110 (23)/12 (3)	66 (24)/7 (3)	31 (23)/5 (4)	3 (27)/0
SAEs* (all grades)	201 (42)	93 (33)	80 (60)	7 (64)
Drug-related SAEs* (all grades)	51 (11)	28 (10)	22 (16)	0
AEs resulting in permanent discontinuation of sorafenib†	133 (28)	69 (25)	53 (40)	5 (45)
Deaths‡	114 (24)	49 (18)	50 (37)	4 (36)

*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 dose of study drug. AE, adverse event; SAE, serious adverse event.

Table 5 Treatment-emergent adverse events in ≥5% of the total study population

n (%)	Treatment-emergent adverse events (n = 479)		Treatment-emergent drug-related adverse events (n = 479)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Any adverse event	415 (87)	161 (34)	319 (67)	109 (23)
Diarrhoea	132 (28)	10 (2)	114 (24)	8 (2)
Hand-foot skin reaction	126 (26)	26 (5)	124 (26)	26 (5)
Fatigue	81 (17)	27 (6)	51 (11)	16 (3)
Rash/desquamation	73 (15)	12 (3)	63 (13)	12 (3)
Anorexia	55 (11)	24 (5)	39 (8)	7 (1)
Abdominal pain	53 (11)	20 (4)	-	-
Liver dysfunction	42 (9)	11 (2)	-	-
Nausea	41 (9)	5 (1)	25 (5)	4 (1)
Ascites	39 (8)	24 (5)	-	-
Hyperbilirubinemia	38 (8)	22 (5)	-	-
Hypertension	36 (8)	12 (3)	29 (6)	9 (2)
Alopecia	29 (6)	0	28 (6)	0
Vomiting	29 (6)	3 (1)	-	-
Weight loss	28 (6)	4 (1)	-	-
Fever	25 (5)	2 (<1)	-	-
Encephalopathy	25 (5)	10 (2)	-	-

and B patients (69% vs. 63%, respectively). The incidence of grade 3 or 4 drug-related events was consistent, with 23–24% of grade 3 and 3–4% of

grade 4 events experienced by patients in each of the Child-Pugh A and B subgroups. Drug-related SAEs occurred in 10% of Child-Pugh A and 16% of Child-Pugh B patients. The rate of discontinuation of sorafenib because of AEs, regardless of any causal relationship with sorafenib, was higher in patients with Child-Pugh B status (40%) than in patients with Child-Pugh A status (25%). The safety profile of Child-Pugh B patients was generally consistent with the overall safety profile.

Discussion

The GIDEON study is, to date, the largest, prospective, non-interventional global study to investigate the treatment of patients with uHCC in the real world and reflects participating physicians' current practice. Data have been collected from a wide uHCC population, and the study database allows analyses of global and regional differences in patient characteristics, disease aetiology, underlying liver disorders and practice patterns.

Demographic data for patients in the first interim analysis of this study were consistent with findings from previously reported epidemiological HCC studies (14,15). The first interim analyses of the GIDEON study highlight notable regional differences in patient and disease characteristics, aetiology and risk factors of uHCC. Global variations in the aetiology of HCC, in particular HBV and HCV, have been previously reported (2,16). TACE is the current standard of care for patients with multinodular, intermediate-stage uHCC (13,17) and this is reflected in the patterns of TACE used in this first interim analysis. Interestingly,

regional variations are observed with patients in Japan and Asia-Pacific receiving more prior TACE than in other regions. This is the first time that variations in the management of uHCC in real-life practice have been evaluated in a single robust study with consistent methodology.

In this interim analysis, dosing differences based on non-clinical factors such as region and specialty are observed; however, Child-Pugh status does not appear to be a factor for sorafenib dosing patterns. The sorafenib dosing findings in this study are preliminary. Sorafenib dosing will continue to be evaluated in the GIDEON study, with the aim of optimising sorafenib treatment. It will be important to further explore reasons for these differences in sorafenib usage (between Med Oncs and Hep/GIs, and across regions).

The safety profile reported in this first interim analysis is consistent with that previously published from randomised clinical trials, with no unexpected AEs (9,10). The most commonly reported drug-related AEs reflect the findings of previous clinical studies of sorafenib in patients with uHCC. In the SHARP and Asia-Pacific studies, diarrhoea, fatigue and hand-foot skin reactions were also the most commonly reported drug-related AEs (9,10).

The safety profile observed in the GIDEON first interim analysis is generally similar in both Child-Pugh A and B patients. Overall, Child-Pugh B score does not appear to be associated with an increased incidence of drug-related AEs, compared with Child-Pugh A. These interim safety results support published data from clinical studies of patients with HCC on the safety of sorafenib in Child-Pugh B patients, in which there was no major difference in the incidence/grade of AEs between Child-Pugh A and B patients (11,18–20).

The results from this first interim analysis are preliminary and should be interpreted accordingly. Observational studies have their limitations, principally in the lack of a control arm and randomised study population; nonetheless, results from the GIDEON study provide the opportunity to evaluate a wide range of data in uHCC patients and sorafenib use globally. Initial findings provide an interesting insight into real-life clinical practice. The study is ongoing with final analyses planned 12 months after enrolment of the 3000th treated patient (12). Future reports will provide further

evidence that may help inform treatment choices and contribute to the advancement of HCC management.

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Author contributions

RL, MK, S-LY and JAM are members of the Global Steering and Publication Committee for the GIDEON study and have been involved in discussion and modification of the GIDEON protocol, and in data review and interpretation. RL was responsible for the conception and design of the manuscript. RL, MK, S-LY, JAM, J-PB, X-PC, LD, JF, JFG, LL de G, CP, AJS, TT and SKY were all responsible for the provision of patients/data acquisition. All authors provided critical review of the manuscript, and approved the final version for publication. KN is the sponsor study physician adviser and has contributed to data analysis and interpretation. FC is the study statistician and has contributed to statistical analysis. SH is responsible for the global study management and for the supervision of the set-up and conduct of the study.

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