Radiology

TACE Treatment in Patients with Sorafenib-treated Unresectable Hepatocellular Carcinoma in Clinical Practice: Final Analysis of GIDEON[1]

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Purpose: To evaluate transarterial chemoembolization (TACE) use prior to and concomitantly with sorafenib in patients with unresectable hepatocellular carcinoma (HCC) across different global regions.

Materials and Methods: GIDEON is an observational registry study of more than 3000 HCC patients. Patients with histologically, cytologically, or radiographically diagnosed HCC, and for whom a decision had been made to treat with sorafenib, were eligible. Patients were enrolled into the registry from 39 countries beginning in January 2009, with the last patient follow-up in April 2012. Detailed data on treatment history, treatment patterns, adverse events, and outcomes were collected. All treatment decisions were at the discretion of the treating physicians. Documented approval from local ethics committees was obtained, and all patients provided signed informed consent. Descriptive statistics, including minimum, median, and maximum, were calculated for metric data, and frequency tables for categorical data. Kaplan-Meier estimates with 95% confidence intervals were calculated for survival end points.

Results: A total of 3202 patients were eligible for safety analysis, of whom 2631 (82.2%) were male. Median age was 62 years (range, 15–98 years). A total of 1511 (47.2%) patients underwent TACE prior to sorafenib; 325 (10.1%) underwent TACE concomitantly. TACE prior to sorafenib was more common in Japan and Asia-Pacific compared with all other regions (362 [71.3%] and 560 [60.3%] vs 12–209 [13.3%–37.1%]). Adverse events were reported in 2732 (85.3%) patients overall, with no notable differences in the incidence of adverse events, regardless of TACE treatment history. Overall survival was 12.7 months in prior-TACE patients, 9.2 months in non–prior-TACE patients, 21.6 months in concomitant-TACE patients, and 9.7 months in non–concomitant-TACE patients.

Conclusion: Global variation exists in TACE use in sorafenib-treated HCC patients. The combination of TACE with sorafenib appears to be a well-tolerated and viable therapeutic approach.

Online supplemental material is available for this article.

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide (1). HCC is a complex disease of liver cancer with underlying liver dysfunction, commonly arising from viral infections and cirrhosis (2). Therefore, HCC treatment is challenging and effectively amounts to the management of two separate diseases. Treatment decisions in HCC are based on the severity of the cancer and the remaining degree of liver functionality (3). Most patients present with advanced stages of HCC that are incurable with surgical resection. According to most guidelines, transarterial chemoembolization (TACE) is the first-line treatment for patients with intermediate stage HCC that is large or multinodular, unresectable, and without vascular invasion or extrahepatic spread (4–6). Sorafenib (Nexavar; Bayer Pharma, Berlin, Germany) is an oral multikinase inhibitor with antiangiogenic activity and is the only approved systemic treatment for advanced HCC (6). Sorafenib is recommended as a first-line therapy for patients with extensive disease; with confirmed metastasis; who cannot benefit from resection, transplantation, or additional local-regional therapies (LRTs); and who have preserved liver function (6). Currently, TACE and sorafenib are the only noncurative treatments for advanced HCC that have been shown to provide a survival benefit in HCC patients (7–9).

While TACE is widely used in the management of HCC, there is no single, globally accepted therapeutic algorithm for TACE use or for assessment of the response to TACE in clinical practice (10), although scoring systems have been recently developed to inform TACE initiation (selection for transarterial chemoembolization treatment, or STATE) and retreatment (assessment for re-treatment with TACE, or ART) (11,12). However, not all patients who undergo TACE derive clinical benefit, and patients may experience tumor recurrence (13,14). Recurrence may occur because of the proangiogenic effects of hypoxia resulting from TACE-induced necrosis at the tumor site (13). The antiangiogenic effect of sorafenib has the potential to synergistically offset this effect of TACE, and multiple trials have shown promising safety and efficacy data on the use of TACE combined with sorafenib in HCC patients (15–19).

Global investigation of therapeutic decisions in hepatocellular carcinoma and of its treatment with sorafenib (GIDEON) is a nonrandomized observational registry study undertaken to evaluate the safety of sorafenib in patients with unresectable HCC in clinical practice (20). The GIDEON study design allowed for the collection of a large, robust, and clinically relevant global dataset, with a preplanned range of subanalyses across patient subgroups. Data on the use of TACE prior to or concomitantly with sorafenib were collected to allow assessment of TACE and sorafenib use and associated safety and outcomes in a clinical practice setting. The GIDEON study began enrolling patients in 2009 and was completed in 2012, with more than 3000 sorafenib-treated patients enrolled from 39 countries in five global regions. Findings from two interim analyses have been previously reported in approximately 500 and 1500 patients (21,22). Here, we report data from the final analyses of GIDEON.

Advances in Knowledge

- The use of transarterial chemoembolization (TACE) prior to sorafenib varied globally and was more common in Japan (362 of 508; 71.3%) and Asia-Pacific (560 of 928; 60.3%) than in United States (209 of 563; 37.1%) and Europe (368 of 1113; 33.1%).
- Overall, 325 (10.1%) patients underwent TACE concomitant with sorafenib therapy; drug-eluting bead TACE was more commonly used than lipiodol-based TACE in the United States (31/73; 42.5%) and Europe (19/52; 36.5%) compared with other regions (range 0/13–3/125; 0–2.4%).
- The overall safety profile of sorafenib was consistent, irrespective of concomitant TACE administration.
- In this observational study, overall survival in patients treated with sorafenib and concomitant TACE was 21.6 months (95% confidence interval: 18.0, not estimable) compared with 9.7 months (95% confidence interval: 9.2, 10.4) in nonconcomitantly treated patients.

Materials and Methods

The GIDEON study is sponsored by Bayer Healthcare Pharmaceuticals and Onyx Pharmaceuticals, an Amgen subsidiary. J.A.M., R.L., M.K., S.L.Y., and A.P.V. are members of the Global Steering and Publication Committee for the GIDEON study; they were involved in the development of the GIDEON protocol and in data review and interpretation. J.A.M., R.L., M.K., S.L.Y., A.P.V., J.P.B., X.P.C., L.D., J.F., J.F.H.G., L.L.d.G., C.P., A.J.S., T.T., and S.K.Y. were responsible for the provision of patients and data acquisition. K.N., R.L., and S.H. are employees of Bayer

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Abbreviations:
DEB = drug-eluting bead
GIDEON = global investigation of therapeutic decisions in hepatocellular carcinoma and of its treatment with sorafenib
HCC = hepatocellular carcinoma
LRT = local-regional therapy
TACE = transarterial chemoembolization

Author contributions:
Guarantors of integrity of entire study, J.F.G., L.D., L.L.d.G., A.J.S., S.K.Y., K.N., S.H., R.L.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, M.K., J.A.M., S.L.Y., K.N.; clinical studies, J.F.G., M.K., J.A.M., A.P.V., X.P.C., L.D., J.F., L.L.d.G., A.J.S., T.T., S.L.Y., S.K.Y., K.N.; experimental studies, J.F.G.; statistical analysis, A.J.S., R.L.; and manuscript editing, J.F.G., M.K., J.A.M., A.P.V., J.P.B., L.D., J.F., C.P., A.J.S., T.T., S.L.Y., K.N., S.H.

Conflicts of interest are listed at the end of this article.

Healthcare and were the lead medical advisor, internal statistician, and global study manager, respectively. All authors had access to relevant data and had control of which data were included in the manuscript. The final decision on manuscript content rested with the authors who are not Bayer employees. The GIDEON protocol is available at *https://www.clinicaltrials.gov/ct2/show/NCT00812175?term=NCT00812175&rank=1*, and a synopsis of the study results is publicly available at *http://pharma.bayer.com/en/research-and-development/*. The required documented approval from the appropriate ethics committees and institutional review boards was obtained for all participating centers prior to the study. All patients provided signed, informed consent to be included in the registry. The GIDEON study began enrolling patients in January 2009 and was completed in April 2012.

Patients with a histologic, cytologic, or radiographic diagnosis of unresectable HCC and with a life expectancy of more than 8 weeks were included in the GIDEON study. Exclusion criteria were based on locally approved product information for sorafenib.

Comprehensive case report forms were used to collect patient data. Information on demographics, baseline disease characteristics, previous therapies, and initial sorafenib dose was recorded at the patients' initial visits. Subsequent follow-up visits were at the discretion of the treating physicians, during which data regarding sorafenib dose (including any modifications or discontinuation), concomitant treatments, adverse events, and outcomes (including death) were collected. The independent contract research organization Kantar Health (Munich, Germany) was responsible for data capture, data management, data quality review, and statistical reporting, overseen by Bayer Healthcare Pharmaceuticals.

All treatment decisions, including the administration of treatments concomitantly with sorafenib, were determined entirely at the discretion of the treating physicians. As such, the type, schedule, and other aspects of TACE were not dictated by the study protocol.

Figure 1

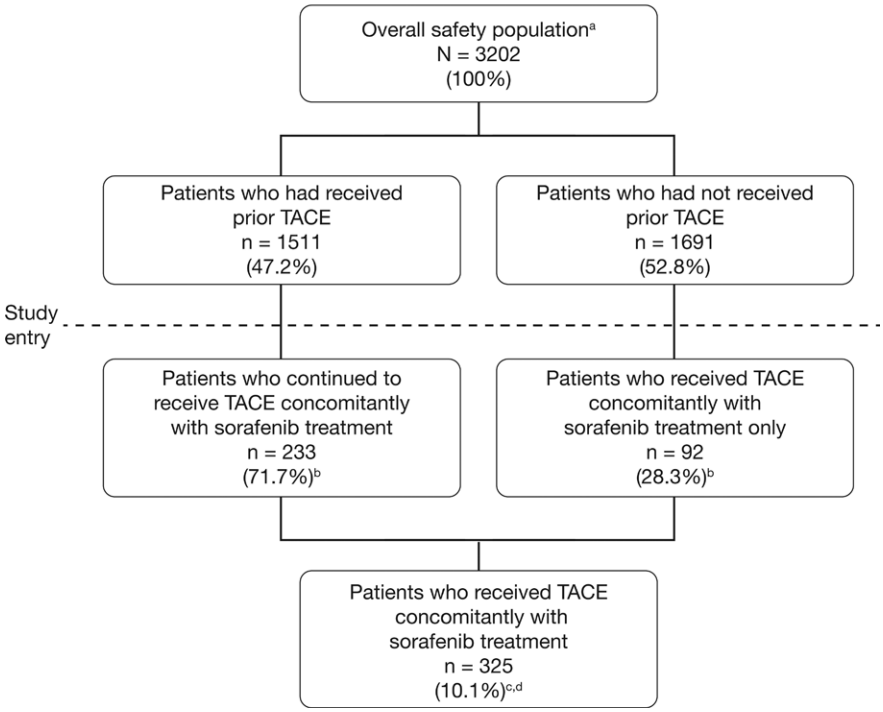

Figure 1: Flowchart of patient selection in GIDEON. [a]Safety population includes all patients who received at least one dose of sorafenib and underwent at least one follow-up assessment after the start of sorafenib treatment. [b]Expressed as a percentage of patients who received TACE concomitantly with sorafenib treatment. [c]Expressed as a percentage of overall safety population. [d]89.9% of the overall patient population did not receive concomitant TACE.

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (National Cancer Institute, Bethesda, Md), and the likely relationship of sorafenib to any adverse event was documented as part of the case report form. Patients who received at least one dose of sorafenib and underwent at least one follow-up examination were evaluable for safety.

The primary objective of GIDEON was to evaluate the safety of sorafenib in patients with HCC under real-life practice conditions. Secondary objectives included evaluating sorafenib efficacy, duration of therapy, and treatment practice across various clinically relevant subsets of patients. Full details of the GIDEON study design and rationale have previously been published (20).

Enrollment was planned for 3000 patients, which was deemed sufficient for full safety evaluation of the overall study population, as well as for specific subgroups that were preplanned in the study design, including analysis based on treatment history, Child-Pugh score, and geographic region (20). The final analysis was performed 12 months after the 3000th patient was enrolled. All baseline and safety data are summarized by using descriptive statistics, including mean, standard deviation, minimum, quartiles, median, and maximum calculated for metric data, and frequency tables for categorical data. Kaplan-Meier estimates and curves were calculated for survival end points.

Results

Patient Disposition

Overall, 3202 patients were eligible for and included in the safety analysis (Fig 1).

Table 1

Use of Prior and Concomitant Therapies by Region

Therapy	Asia-Pacific (*n* = 928)	Europe (*n* = 1113)	Latin America (*n* = 90)	United States (*n* = 563)	Japan (*n* = 508)	Total (*n* = 3202)
Prior therapy						
All LRTs	624 (67.2)	484 (43.5)	25 (27.8)	278 (49.4)	429 (84.4)	1840 (57.5)
TACE*	560 (60.3)	368 (33.1)	12 (13.3)	209 (37.1)	362 (71.3)	1511 (47.2)
Lipiodol based	505 (90.2)	218 (59.2)	10 (83.3)	85 (40.7)	298 (82.3)	1116 (73.9)
DEB	16 (2.9)	133 (36.1)	2 (16.7)	83 (39.7)	6 (1.7)	240 (15.9)
No. of TACE treatments†						
1	228 (40.7)	174 (47.3)	10 (83.3)	124 (59.3)	76 (21.0)	612 (40.5)
2	116 (20.7)	92 (25.0)	1 (8.3)	55 (26.3)	67 (18.5)	331 (21.9)
≥3	216 (38.6)	102 (27.7)	1 (8.3)	30 (14.4)	219 (60.5)	568 (37.6)
Ablation						
Radiofrequency ablation‡	119 (12.8)	166 (14.9)	16 (17.8)	65 (11.5)	195 (38.4)	561 (17.5)
Percutaneous ethanol injection§	25 (2.7)	59 (5.3)	0	6 (1.1)	59 (11.6)	149 (4.7)
Hepatic arterial infusion‖	48 (5.2)	11 (1.0)	2 (2.2)	22 (3.9)	96 (18.9)	179 (5.6)
Radiation						
Externa#	123 (13.3)	14 (1.3)	0	27 (4.8)	29 (5.7)	193 (6.0)
Radioembolization**	1 (0.1)	1 (< 0.1)	0	2 (0.4)	0	4 (0.1)
Surgery	225 (24.2)	172 (15.5)	5 (5.6)	53 (9.4)	220 (43.3)	675 (21.1)
Systemic therapy	46 (5.0)	42 (3.8)	0	19 (3.4)	59 (11.6)	166 (5.2)
Concomitant therapy						
TACE	125 (13.5)	52 (4.7)	13 (14.4)	73 (13.0)	62 (12.2)	325 (10.1)
Lipiodol based	100 (80.0)	26 (50.0)	12 (92.3)	21 (28.8)	50 (80.6)	209 (64.3)
DEB	3 (2.4)	19 (36.5)	0	31 (42.5)	0	53 (16.3)
No. of TACE treatments						
1	90 (9.7)	35 (3.1)	9 (10.0)	48 (8.5)	43 (8.5)	225 (7.0)
2	24 (2.6)	10 (0.9)	3 (3.3)	19 (3.4)	9 (1.8)	65 (2.0)
≥3	11 (1.2)	7 (0.6)	1 (1.1)	6 (1.1)	10 (2.0)	35 (1.1)
Ablation						
Radiofrequency ablation	14 (1.5)	14 (1.3)	5 (5.6)	12 (2.1)	8 (1.6)	53 (1.7)
Percutaneous ethanol injection	2 (0.2)	3 (0.3)	0	0	0	5 (0.2)
Hepatic arterial infusion	34 (3.7)	1 (< 0.1)	0	1 (0.2)	18 (3.5)	54 (1.7)
Radiation						
External	33 (3.6)	13 (1.2)	0	14 (2.5)	23 (4.5)	83 (2.6)
Radioembolization	0	2 (0.2)	0	1 (0.2)	0	3 (< 0.1)
Surgery	8 (0.9)	2 (0.2)	1 (1.1)	4 (0.7)	3 (0.6)	18 (0.6)

Note.—Data in parentheses are percentages.

* Data missing for 327 patients.

† Based on number of patients who received TACE.

‡ Data missing for 338 patients.

§ Data missing for 353 patients.

‖ Data missing for 341 patients.

Data missing for 3009 patients.

** Data missing for 3198 patients.

TACE subgroups comprised patients who had received TACE treatment prior to sorafenib (47.2%), patients who had not received prior TACE treatment (52.8%), patients who received TACE treatment concomitantly with sorafenib (10.1%), and patients who did not receive concomitant TACE treatment (*n* = 2877; 89.9%). Of the patients who received concomitant TACE treatment, the majority (71.7%) had also received prior TACE treatment.

Use of Prior and Concomitant Therapies

In total, 57.5% of patients had received LRT prior to study entry, although with regional variation. Overall, TACE was the most common prior LRT received (Table 1). Lipiodol (Guebert, Villepinte,

Table 2

Baseline Demographics and Disease Characteristics at Study Entry by Prior and Concomitant TACE

Characteristic	No Prior TACE (n = 1691)	Prior TACE (n = 1511)	No Concomitant TACE (n = 2877)	Concomitant TACE (n = 325)	Overall (n = 3202)*
No. of men	1349 (79.8)	1282 (84.8)	2362 (82.1)	269 (82.8)	2631 (82.2)
Median age (y)†	62 (18–98)	62 (15–90)	63 (15–98)	58 (18–88)	62 (15–98)
Median body mass index (kg/m^2)†	24.8 (13.9–58.0)	23.8 (14.1–45.1)	24.2 (13.9–58.0)	24.7 (17.2–43.2)	24.2 (13.9–58.0)
Etiology‡					
Hepatitis B	522 (30.9)	648 (42.9)	1030 (35.8)	140 (43.1)	1170 (36.5)
Hepatitis C	545 (32.2)	508 (33.6)	938 (32.6)	115 (35.4)	1053 (32.9)
Alcohol use	483 (28.6)	351 (23.2)	761 (26.5)	73 (22.5)	834 (26.0)
Nonalcoholic steatohepatitis	55 (3.3)	35 (2.3)	80 (2.8)	10 (3.1)	90 (2.8)
BCLC stage§					
A	120 (7.1)	106 (7.0)	192 (6.7)	34 (10.5)	226 (7.1)
B	282 (16.7)	352 (23.3)	536 (18.6)	98 (30.2)	634 (19.8)
C	915 (54.1)	749 (49.6)	1526 (53.0)	138 (42.5)	1664 (52.0)
D	115 (6.8)	58 (3.8)	161 (5.6)	12 (3.7)	173 (5.4)
Child-Pugh status‖					
A	950 (56.2)	1018 (67.4)	1737 (60.4)	231 (71.1)	1968 (61.5)
B	403 (23.8)	263 (17.4)	611 (21.2)	55 (16.9)	666 (20.8)
C	58 (3.4)	16 (1.1)	68 (2.4)	6 (1.8)	74 (2.3)
Metastatic lesion					
HCC confined to liver	731 (43.2)	689 (45.6)	1228 (42.7)	192 (59.1)	1420 (44.3)
Vascular invasion	427 (25.3)	285 (18.9)	660 (22.9)	52 (16.0)	712 (22.2)
Extrahepatic spread	650 (38.4)	622 (41.2)	1180 (41.0)	92 (28.3)	1272 (39.7)

Note.—Unless otherwise indicated, data are number of patients and data in parentheses are percentages.

* Reflects patients with and those without prior TACE or patients with and those without concomitant TACE.

† Data in parentheses are the range.

‡ Data missing/not available for seven patients.

§ BCLC = Barcelona Clinic Liver Cancer. Data missing for four patients and not evaluable for 501 patients.

‖ Score missing for one patient and not evaluable for 493 patients.

France)-based TACE was generally more common than drug-eluting beads (DEB) TACE; however, DEB TACE was more common in the United States and Europe compared with all other regions. Other LRTs used prior to study entry included radiofrequency ablation, percutaneous ethanol injection, and hepatic artery infusion, which also varied regionally (Table 1).

The use of TACE concomitant with sorafenib was similar across the regions, although lower in Europe compared with elsewhere (Table 1). Overall, for concomitant TACE, lipiodol-based TACE was more common than DEB TACE (64.3% vs 16.3%), except for in the United States, where DEB TACE was more common (42.5% vs 28.8%). Concomitant use of treatments other than TACE was reported rarely, with external radiation being the most frequent (2.6%) (Table 1). A small number of patients underwent TACE after sorafenib discontinuation (4.3%), most commonly in Japan (11.8%) (Table E1 [online]).

Patient Baseline Demographics and Disease Characteristics at Study Entry

Baseline demographics and disease characteristics at study entry for prior and concomitant TACE treatment use are shown in Table 2. Disease etiology was similar across all patient subgroups, although variations in Child-Pugh and Barcelona Clinic Liver Cancer stage were observed, as patients who had never received TACE treatment tended to have more severe liver disease at the start of sorafenib therapy compared with those who received prior or concomitant TACE treatment. Vascular invasion was less common in patients who had received prior or concomitant TACE treatment compared with those who had not (Table 2). Extrahepatic spread was lower in patients treated concomitantly with TACE compared with all other subgroups.

Sorafenib Administration

The median daily dose of sorafenib was lower in patients previously treated with TACE compared with those who had not been previously treated with TACE (603.0 mg vs 757.0 mg) (Table 3). The median daily dose of sorafenib was also lower in concomitantly treated TACE patients compared with nonconcomitantly treated patients (587.0 mg vs 698.5 mg). The overall median duration of sorafenib therapy was 15.0 weeks, although it was notably longer

in patients who underwent concomitant TACE (36.4 weeks) compared with patients who did not undergo concomitant TACE (13.1 weeks) (Table 3).

Safety

Overall, treatment-emergent adverse events were reported in 85.3% of patients and drug-related adverse events were reported in 66.0% of patients, with little variation across patient subgroups (Table 4). Serious adverse events and drug-related serious adverse events were reported in 43.3% and 9.3% of patients, respectively. Serious adverse events occurred in 33.5% of patients who underwent concomitant TACE, compared with 44.4% of those who did not. Overall, the most frequent treatment-emergent adverse events (occurring in ≥ 10% of patients) included diarrhea (30.6%), hand-foot skin reaction (27.1%), and fatigue (23.7%) (Table 4). Patients who received concomitant TACE treatment had slightly increased incidences of diarrhea (37.8%) and hand-foot skin reaction (41.5%), compared with the overall study population (30.6% and 27.1%, respectively), but a slightly lower incidence of fatigue (21.8% vs 23.7%). Adverse events resulting in permanent discontinuation of sorafenib were

Table 3

Administration of Sorafenib

Characteristic	No Prior TACE (*n* = 1691)	Prior TACE (*n* = 1511)	No Concomitant TACE (*n* = 2877)	Concomitant TACE (*n* = 25)	Overall (*n* = 3202)*
Daily dose					
No. of patients†	1492	1365	2576	281	2857
Median dose (mg)‡	757.0	603.0	698.5	587.0	688.0
Mean dose (mg)‡	643.1	587.4	621.4	571.6	616.5
Duration of therapy					
No. of patients	1639	1491	2805	325	3130
Median duration (wk)§	13.3	16.7	13.1	36.4	15.0
Mean duration (wk)§	22.8	25.3	21.8	42.6	24.0

* Reflects patients with and those without prior TACE or patients with and those without concomitant TACE.

† Patients for whom dosing data are available.

‡ Average daily dose determined within patient-based actual days on study drug excluding interruptions.

§ Treatment duration is the time from initial visit to last dosing date.

Table 4

Summary of Sorafenib Safety Profile and Incidence of Most Common Treatment-emergent Adverse Events Occurring in 10% or More of Patients

Characteristic	No Prior TACE (*n* = 1691)	Prior TACE (*n* = 1511)	No Concomitant TACE (*n* = 2877)	Concomitant TACE (*n* = 325)	Overall (*n* = 3202)*
Adverse events					
Total (all grades)	1430 (84.6)	1302 (86.2)	2444 (84.9)	288 (88.6)	2732 (85.3)
Drug related	1037 (61.3)	1075 (71.1)	1871 (65.0)	241 (74.2)	2112 (66.0)
Serious (all grades)	811 (48.0)	576 (38.1)	1278 (44.4)	109 (33.5)	1387 (43.3)
Drug-related serious (all grades)	151 (8.9)	146 (9.7)	277 (9.6)	20 (6.2)	297 (9.3)
Grade 3 or 4	497 (29.4)	519 (34.3)	905 (31.5)	111 (34.2)	1016 (31.7)
Drug-related grade 3 or 4	359 (21.2)	395 (26.1)	677 (23.5)	77 (23.7)	754 (23.5)
Grade 5	519 (30.7)	279 (18.5)	742 (25.8)	56 (17.2)	798 (24.9)
Drug-related grade 5	31 (1.8)	15 (1.0)	44 (1.5)	2 (0.6)	46 (1.4)
Resulting in permanent discontinuation of sorafenib	504 (29.8)	500 (33.1)	937 (32.6)	67 (20.6)	1004 (31.4)
Incidence of most common adverse events, all grades					
Diarrhea	502 (29.7)	479 (31.7)	858 (29.8)	123 (37.8)	981 (30.6)
Hand-foot skin reaction	352 (20.8)	517 (34.2)	734 (25.5)	135 (41.5)	869 (27.1)
Fatigue	416 (24.6)	344 (22.8)	689 (23.9)	71 (21.8)	760 (23.7)
Anorexia	250 (14.8)	233 (15.4)	440 (15.3)	43 (13.2)	483 (15.1)
Abdominal pain	236 (14.0)	212 (14.0)	398 (13.8)	50 (15.4)	448 (14.0)
Liver dysfunction	217 (12.8)	178 (11.8)	366 (12.7)	29 (8.9)	395 (12.3)
Rash/desquamation	203 (12.0)	188 (12.4)	337 (11.7)	54 (16.6)	391 (12.2)
Nausea	190 (11.2)	130 (8.6)	279 (9.7)	41 (12.6)	320 (10.0)
Hypertension	141 (8.3)	168 (11.1)	269 (9.4)	40 (12.3)	309 (9.7)
Fever	88 (5.2)	103 (6.8)	158 (5.5)	33 (10.2)	191 (6.0)

Note.—Data are number of patients and data in parentheses are percentages. SAE = serious adverse event.

* Reflects patients with and those without prior TACE or patients with and those without concomitant TACE.

Figure 2

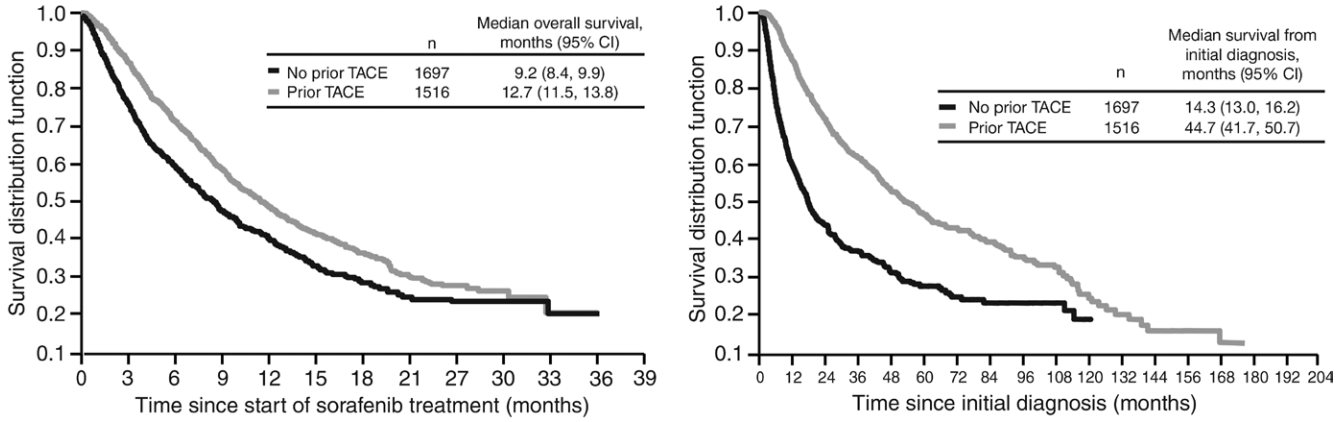

Figure 2: Graphs show **(a)** overall survival and **(b)** survival time from initial diagnosis to death in patients who received prior TACE treatment versus patients who had not received prior TACE treatment. *CI* = confidence interval.

Figure 3

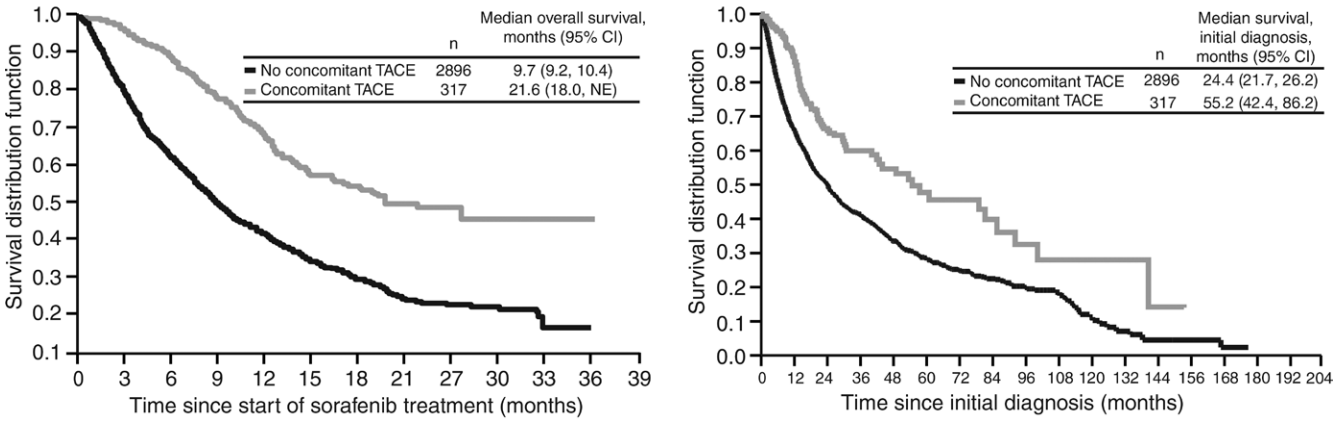

Figure 3: Graphs show **(a)** overall survival and **(b)** survival time from initial diagnosis to death in patients who received TACE treatment concomitantly with sorafenib and patients who had not received concomitant TACE treatment. *CI* = confidence interval, *NE* = not evaluable.

least common in concomitantly treated TACE patients compared with other subgroups (20.6% vs 29.8%–33.1%).

Outcomes

Median overall survival was 12.7 months (95% confidence interval [CI]: 11.5, 13.8) in patients who received prior TACE treatment and 9.2 months (95% CI: 8.4, 9.9) in patients who had not received prior TACE treatment (Fig 2a). Patients who had received TACE treatment prior to sorafenib had a notably longer median time from initial diagnosis to death than patients who had not received prior TACE treatment (44.7 months [95% CI: 41.7, 50.7] vs 14.3 months [95% CI: 13.0, 16.2]) (Fig 2b). Concomitantly treated TACE patients had a median overall survival of 21.6 months (95% CI: 18.0, not estimable) and a median time from initial diagnosis to death of 55.2 months (95% CI: 42.4, 86.2), while nonconcomitantly treated patients had a median overall survival time of 9.7 months (95% CI: 9.2, 10.4) and a median time from initial diagnosis to death of 24.4 months (95% CI: 21.7, 26.2) (Fig 3a, 3b). Overall survival was longer in concomitantly treated patients across Barcelona Clinic Liver Cancer stages (Fig 4).

Discussion

The large database generated from systematic data collection in GIDEON offers an opportunity to assess global patterns of LRT use in the treatment of HCC in clinical practice. Final analyses of GIDEON highlighted that almost half of patients received TACE treatment

Figure 4

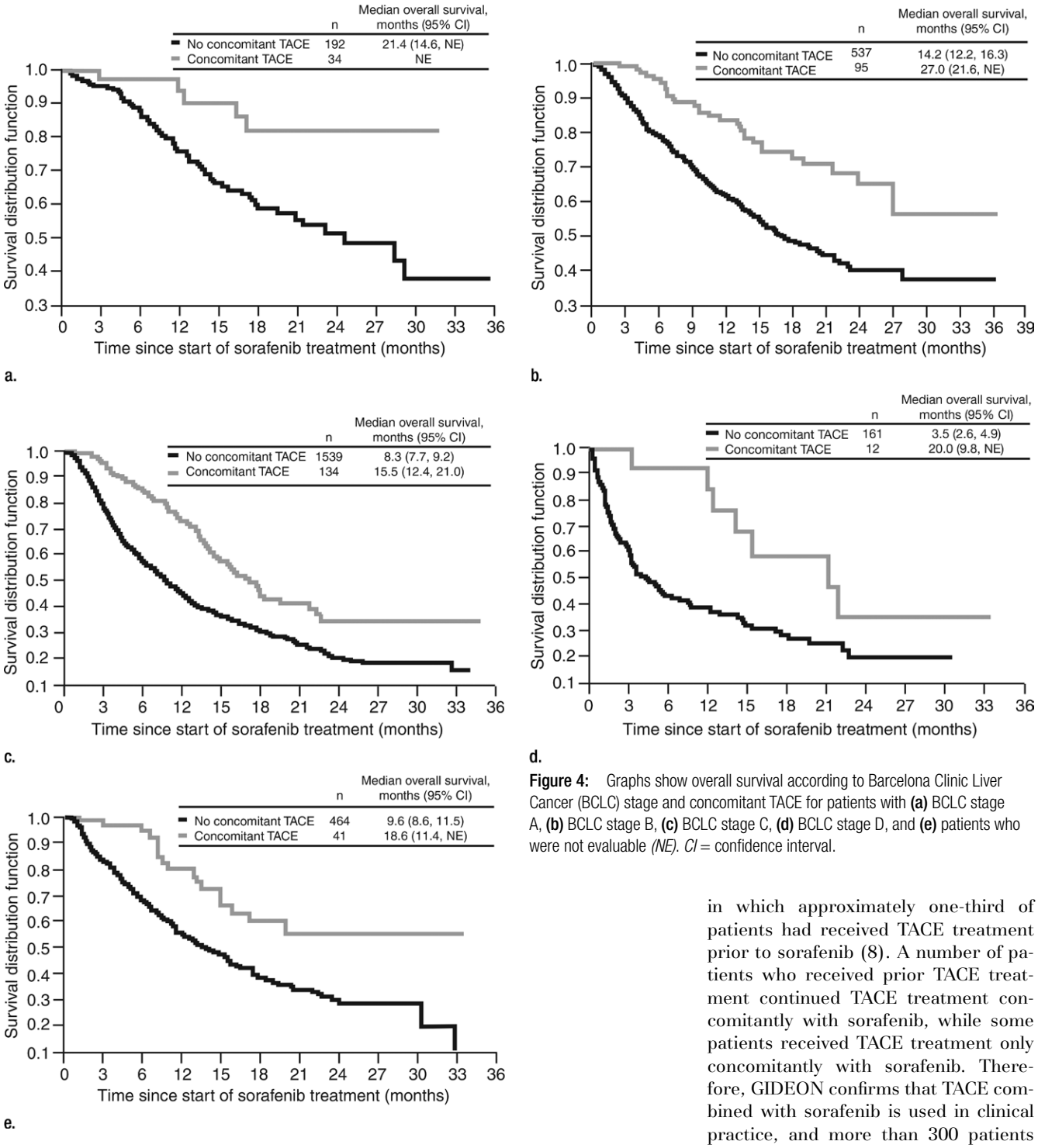

Figure 4: Graphs show overall survival according to Barcelona Clinic Liver Cancer (BCLC) stage and concomitant TACE for patients with **(a)** BCLC stage A, **(b)** BCLC stage B, **(c)** BCLC stage C, **(d)** BCLC stage D, and **(e)** patients who were not evaluable *(NE)*. *CI* = confidence interval.

prior to sorafenib. The observed use of sorafenib following TACE was consistent with the pivotal phase III Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol trial, which demonstrated the efficacy of sorafenib and in which approximately one-third of patients had received TACE treatment prior to sorafenib (8). A number of patients who received prior TACE treatment continued TACE treatment concomitantly with sorafenib, while some patients received TACE treatment only concomitantly with sorafenib. Therefore, GIDEON confirms that TACE combined with sorafenib is used in clinical practice, and more than 300 patients received this combination. The patterns of TACE use prior to sorafenib varied regionally, consistent with previous reports, particularly in the frequency of

prior TACE and number of prior TACE treatments received per patient (23).

Lipiodol-based TACE was the predominant choice and more common than DEB TACE, perhaps unsurprisingly as DEB is a relatively new method (13,24); for example, DEB TACE was not approved by the China Food and Drug Administration to be the choice of TACE agent except for use in clinical trials. DEB TACE use varied globally and was more common in Western regions. These data may reflect regional variations or delays in the uptake of DEB TACE, and patterns may alter as further safety and efficacy data in representative patient populations are reported (25–27).

With respect to disease characteristics, patients without a history of TACE treatment tended to be at a more advanced stage of disease, likely reflecting that patients with an earlier disease stage may be more likely to receive TACE treatment. Some patients receiving concomitant TACE treatment had extrahepatic spread (28%) or vascular invasion (16%), somewhat contrary to TACE treatment guidelines, which recommend TACE use in intermediate noninvasive HCC (28).

Safety findings in GIDEON were consistent with the known safety profile of sorafenib. There was no evidence of unanticipated adverse events or adverse event patterns in TACE-treated patients, and safety was similar in patients treated with TACE and those never treated with TACE. The combination of TACE with sorafenib appeared to be well tolerated, and safety profiles were broadly similar irrespective of the pattern of TACE use. Sorafenib administration data revealed that duration of sorafenib treatment was longest in patients who received concomitant TACE treatment (over 36 weeks), highlighting the feasibility of the combination.

Patients who received prior TACE treatment tended to have a slightly longer overall survival time compared with those who had not received prior TACE treatment. However, these outcomes data must be interpreted with caution, given the variations in disease characteristics between patients who received prior or concomitant TACE treatment and those never treated with TACE. Patients who underwent a combination of TACE with sorafenib had a longer overall survival compared with all other subgroups. However, data must be interpreted with caution as only a relatively low number of patients received concomitant TACE treatment compared with the other subgroups, and the majority of patients who received concomitant TACE treatment had also received TACE treatment prior to sorafenib.

A number of studies have reported that the combination of sorafenib and TACE resulted in improved overall survival in patients with advanced HCC (17,19,29,30). However, a further study reported no benefit of sorafenib when given sequentially to patients who had responded to TACE (31). Ongoing trials will hopefully help to address key questions in relation to this combination in patients with advanced as well as intermediate stage HCC, including the optimal timing of sorafenib in relation to TACE and the influence of patient characteristics on the safety and efficacy of this combination (32).

Overall, the final analysis of GIDEON highlights global variations in TACE treatment patterns, as observed in the previous interim analysis (21). GIDEON data suggest that although prior TACE and TACE concomitant with sorafenib are tolerable and feasible, consistent with previous reports, variations exist in clinical practice, including the use of different TACE methodologies across global regions. GIDEON data may also reflect variations in decisions regarding when TACE should be performed and when TACE should be stopped (refractory), and thus when systemic therapy should be initiated (10). Repeated courses of TACE with no objective response may detract from the administration of potentially effective systemic therapy as a result of a lack of evidence-based guidelines (33). Further, scoring systems that better inform TACE retreatment are likely to prove useful in improving the approach to TACE use (11,34). The findings from GIDEON provide support for the standardization of TACE treatment practices and the publication of evidence-based guidelines to inform clinical decisions. Moreover, outcomes of HCC patients treated with TACE followed or not followed by sorafenib and the influence of timing to initiate **s**orafenib, or OPTIMIS, is an ongoing, prospective, observational study that will further evaluate the use of TACE and sorafenib in clinical practice.

Because GIDEON is an observational registry study, it is inherently limited by the lack of a randomized, controlled population. In addition, its observational nature means the study is also limited by the potential for selection bias and an inability to control for possible confounding factors. As such, it cannot evaluate if sorafenib in combination with TACE provided a benefit over TACE alone, and the descriptive statistics used do not allow for conclusive analysis of outcomes, so outcomes data must be interpreted with caution. However, GIDEON provides an opportunity to evaluate and understand global treatment patterns in clinical practice for the treatment of unresectable HCC. These data can be used to inform best practice and, ultimately, improve patient treatment and outcomes.

In conclusion, the findings from GIDEON in more than 3000 sorafenib-treated HCC patients highlight that global variation exists in LRT use for the treatment of HCC and in the technical aspects of TACE. Importantly, no safety concerns were noted in the use of TACE treatment either prior to or concomitant with sorafenib treatment. Therefore, TACE treatment prior to and/or concomitant with sorafenib appears to be a viable therapeutic approach in the treatment of unresectable HCC.

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