Sequential systemic treatment in patients with hepatocellular carcinoma

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Summary
Background: Hepatocellular carcinoma (HCC) is one of the most lethal cancers. After many years of stagnation, there are now several systemic treatments available for patients with HCC.

Aim: To analyse the feasibility and efficacy of sequential systemic treatments in patients with HCC in clinical practice.

Methods: In this multicentre study, patients who were treated with novel systemic therapies for HCC between 2014 and 2019 at two referral centres, Hannover Medical School, Germany, and Medical University of Vienna, Austria, were included.

Results: Overall, 85 patients were included of which 76 patients (89.4%) received more than one and a maximum of five systemic treatment lines. The most common therapy sequence was sorafenib (n = 72; 84.7%) followed by regorafenib (n = 37; 48.7%), whereas 11 patients were initially treated with lenvatinib (12.9%). Other second-line treatments included pembrolizumab, nivolumab, cabozantinib and ramucirumab. Hepatic function deteriorated during sequential systemic treatment in 48.6% of the patients as defined by an increase in at least one Child-Pugh point. Median overall survival (mOS) from the start of first systemic treatment was 35 months for patients with sequential systemic treatment compared to 9 months for patients with one systemic treatment line (P < 0.001). Patients previously treated with surgical/locoregional therapies had a longer mOS compared to patients with initial systemic treatment (66 vs 25 months; P = 0.020).

Conclusions: Sequential systemic treatment is feasible and effective in selected patients with HCC in clinical practice. Our study underlines the critical importance of well-preserved liver function for successful administration of sequential systemic therapy.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the second leading cause of cancer-related death. The prognosis is still dismal.\textsuperscript{1,2} The multityrosine kinase inhibitor sorafenib has been the only approved agent for patients with advanced HCC for almost a decade based on a prolongation of median overall survival (mOS) from 7.9 to 10.7 months.\textsuperscript{3} In the last few years, several systemic treatment options have emerged including the tyrosine kinase inhibitors (TKIs) lenvatinib, regorafenib, cabozantinib and the vascular endothelial growth factor receptor 2 (VEGFR-2) inhibitor ramucirumab.\textsuperscript{4-7} Immune checkpoint inhibitor monotherapies have failed to show a statistically significant improvement in overall survival (OS) in the first- and second-line setting in phase III trials.\textsuperscript{8,9} In contrast, the combined immunotherapy/VEGF inhibition inhibitor ramucirumab and bevacizumab has recently shown superior activity in first-line treatment compared to sorafenib in the phase III IMbrave150 trial and will likely become the new standard of care in first line.\textsuperscript{10}

These numerous novel systemic agents approved in the first- and second-line setting offer a variety of sequential treatment opportunities, which are already being implemented in current guidelines.\textsuperscript{11} So far, there are no prospective clinical studies investigating sequential therapy in HCC, but post hoc analysis from phase-III trials and some real-life studies provided first evidence that sequential treatment will improve mOS in HCC.\textsuperscript{4,12-16}

In this multicentre study, we aimed to investigate the feasibility and efficacy of sequential systemic treatments with the currently available and recently approved drugs in a real life cohort.

PATIENTS AND METHODS

Patient population and data selection

Local data arrays including patients with HCC treated at the two referral centres, Hannover Medical School, Germany, and Medical University of Vienna, Austria, were screened for patients who were treated with at least one novel systemic therapy including lenvatinib, regorafenib, cabozantinib, ramucirumab, pembrolizumab, nivolumab and/or durvalumab between 2014 and 2019. Patients treated only with one systemic agent (sorafenib or lenvatinib) between 2014 and 2019 served as control. Patient data were retrospectively evaluated for baseline characteristics, therapeutic procedures and adverse events (AEs) of first-line systemic treatments. mOS was analysed from first, second and third systemic treatment until last follow-up or death. Median progression-free survival (mPFS) was analysed from first systemic therapy until last follow-up, progression or death, whichever occurred first. Radiological response was assessed according to modified Response Evaluation Criteria in Solid Tumors. Systemic treatment lines were defined as the switch of systemic therapy upon progression or intolerable side effects. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the appropriate institutional review committee of Hannover Medical School and Medical University of Vienna.

Statistical analysis

Statistical analyses were performed using SPSS 26.0 (SPSS Inc). Differences between categorical variables were calculated using Pearson’s Chi-square test. Continuous data were represented as median with interquartile ranges (IQR). Continuous, related data were tested for differences using the Wilcoxon test. A probability (P) value of less than 0.05 was considered statistically significant. OS was assessed using the Kaplan-Meier estimation. Comparison was made using the Log rank (Mantel-Cox) test.

RESULTS

Demographics

Overall, 85 patients with HCC, who were treated with at least one novel systemic therapy including lenvatinib, regorafenib, cabozantinib, ramucirumab, pembrolizumab, nivolumab and/or durvalumab between 2014 and 2019 at the Hannover Medical School, Germany, and Medical University of Vienna, Austria, were included into this study. The majority of the patients was diagnosed with liver cirrhosis (n = 60; 71.4%). Alcoholic liver disease (ALD) was the most frequent underlying liver disease in patients with liver cirrhosis (n = 26; 43.3%), whereas no patient without liver cirrhosis was diagnosed with (ALD) (P = 0.001). In these patients, nonalcoholic fatty liver disease (NAFLD) was the most frequent diagnosis (n = 7; 29.1%). Most patients were classified as CPS A (n = 50; 75.8%), followed by patients classified as CPS B (n = 15; 22.7%). Only one patient was classified CPS C (n = 1; 1.5%). Accordingly, most patients were either classified ALBI grade 1 (n = 29; 40.8%) or ALBI grade 2 (n = 42; 57.7%), whereas only one patient was classified ALBI grade 3 (1.4%). In total, most patients were diagnosed with three HCC lesions (n = 31; 42.5%) with a median diameter of the largest lesion of 45 mm (IQR 25-90). Patients with liver cirrhosis had smaller (41.5 mm [22.25-71] vs 77.5 mm [IQR 40-106]) but more HCC lesions (≥3:31.1% [n = 18] vs n = 0) compared to patients without cirrhosis. Vascular invasion and extrahepatic disease were present in 36.4% and 42.5% of all patients respectively. The rates of vascular invasion were similar for patients with cirrhosis and without cirrhosis, whereas significantly more patients had extrahepatic disease in the noncirrhotic cohort (59.1% vs 33.9%; P = 0.042). The median AFP level was 13.1 µg/L (4.15-263.6) and was not significantly different between cirrhotic and noncirrhotic patients.

Regarding Barcelona Clinic Liver Cancer (BCLC) staging system, most patients were staged BCLC C (n = 54; 77.1%). Only one patient was classified BCLC D (1.4%) and 15 patients were classified BCLC B (21.4%). The reasons to treat patients at intermediate stage disease...
(BCLC B) with systemic therapies rather than locoregional therapies were either refractoriness to transarterial chemoembolisation (TACE) or transarterial radioembolisation (TARE) as defined by lack of response, advanced hepatic dysfunction (CPS B, 8-9 points, CPS C) or very large tumour nodules (>7 cm). Demographic details are represented in Table 1.

### 3.2 Systemic treatments

While 31 patients (36.5%) received systemic treatment as the first tumour-specific treatment, most patients (n = 54; 63.5%) were previously treated with surgical, ablative or locoregional therapies, whereas TACE was most frequently used (n = 27; 31.8%) (Table 1). The reasons to switch locoregional to systemic therapy was most often disease progression and lack of response to TACE (n = 50; 92.6%) followed by deterioration of liver function or other complications to locoregional therapy (n = 4; 7.4%). Progression of HCC lesions in number (n = 28; 51.9%) and size (n = 27; 50%) was very frequent followed by extrahepatic disease progression (n = 19; 35.2%). In contrast, progression in terms of vascular invasion was less frequent (n = 19; 35.2%). Compared to patients with initial systemic treatment, patients with prior treatment had significantly lower AFP levels (AFP ≤200 µg/L: n = 36; 87.8% vs n = 16; 57.1%; P = 0.004) and had significantly smaller HCCs (≤5 cm: n = 29; 72.5% vs n = 10; 37.0%; P = 0.004), whereas there were no differences in hepatic function or BCLC stage (Table 2).

Among all 85 patients, 76 patients (89.4%) were treated with more than one systemic agent with a maximum of five systemic treatment lines. Overall, 32 patients (37.6%) have received three, ten patients (11.8%) four and two patients (2.4%) five lines of therapy. The first systemic therapy was most often switched or stopped due to tumour progression (n = 45; 64.3%) or toxicity (n = 23; 32.9%). In two patients, the first systemic treatment was stopped due to a long-lasting partial tumour response to sorafenib and one of those patient had a complete response to sorafenib. Treatment algorithms are summarised in Table 3 and Figure S1.

Sorafenib was the most common first-line treatment (n = 72; 84.7%) and only eleven patients were treated with lenvatinib in the front-line (12.9%). Median duration of sorafenib treatment was 4 months (IQR 2-7), with a maximum duration of 76 months. In second-line, regorafenib was the most common treatment (n = 37; 48.7%), followed by immunotherapy. Treatment with cabozantinib, ramucirumab, lenvatinib and others was less frequently used in second-line. In third- to fifth-line settings all of the above-mentioned agents were used, but immune checkpoint inhibitors were most frequently administered in patients previously treated with sorafenib and regorafenib. Among patients treated with immunotherapy in the subsequent-line settings, 11 out of 33 patients (33.3%) available for response assessment according to mRECIST had a radiological response and two patients achieved a complete response (6.1%). Response was durable with a median duration of response of 6 (IQR 3-14) months. Patient- and tumour-specific characteristics of

| TABLE 1 Patients characteristics of the study population |
|-----------------------------------------------|
| Characteristics | Total | n | % |
|---|---|---|---|
| Total | 85 | 100 |
| Gender | | | |
| Male | 65 | 76.5 |
| Female | 20 | 23.5 |
| Aetiology | | | |
| ALD | 26 | 30.6 |
| Hepatitis C | 16 | 18.8 |
| Hepatitis B | 8 | 9.4 |
| NAFLD | 14 | 16.5 |
| Others | 21 | 24.7 |
| Cirrhosis | | | |
| Yes | 60 | 71.4 |
| No | 24 | 28.6 |
| CPS | | | |
| A | 50 | 75.8 |
| B | 15 | 22.7 |
| C | 1 | 1.5 |
| ALBI | | | |
| 1 | 29 | 40.8 |
| 2 | 41 | 57.7 |
| 3 | 1 | 1.4 |
| Number of lesions | | | |
| 1 | 12 | 16.4 |
| 2 | 11 | 15.1 |
| 3 | 31 | 42.5 |
| >3 | 19 | 26.0 |
| AFP | | | |
| >200 µg/L | 17 | 24.6 |
| ≤200 µg/L | 52 | 75.4 |
| Extrahepatic disease | | | |
| Yes | 34 | 42.5 |
| No | 46 | 57.5 |
| Vascular invasion | | | |
| Yes | 28 | 36.4 |
| No | 49 | 63.6 |
| Initial treatment | | | |
| LT | 1 | 1.2 |
| Resection | 19 | 22.4 |
| Localablative | 6 | 7.1 |
| TACE | 27 | 31.8 |
| TARE | 1 | 1.2 |
| Systemic | 31 | 36.5 |
| BCLC | 0 | 0 | (Continues)
patients treated with immunotherapy in the subsequent line setting are summarised in Table S1.

Compared to a control cohort of 106 patients treated with only one systemic agent from 2014 to 2019 (n = 97 sorafenib, n = 9 lenvatinib), patients with more than one systemic treatment line had significantly lower BCLC stages (P < 0.001), lower AFP levels (P = 0.008), less frequently vascular invasion (P = 0.001), less HCC lesions (P < 0.001) and were more frequently CPS A (P = 0.003) and ALBI grade 1 (P = 0.001) (Table 4).

3.3 | Toxicities

Toxicities of the first-line treatments are summarised in Table S2. The overall rate of AEs (56.9% vs 63.6%) was not different between sorafenib and lenvatinib in the first-line setting (P = 0.712). The most common AEs for sorafenib were hand-foot-skin-reaction (HFSR; 26.4%), diarrhoea (19.4%), fatigue (15.3%) and hepatic encephalopathy (18.2%). Similarly, treatment with lenvatinib in the first-line was associated with HFSR (18.2%), fatigue (18.2%) and hepatic encephalopathy (18.2%). In contrast, there were no events of diarrhoea, but decrease in appetite was apparent in 27.3% of the patients treated with lenvatinib. One patient treated with pembrolizumab in first-line developed a dermatitis and bronchiolitis.

Hepatic function slightly deteriorated with increasing lines of systemic treatment as assessed by CPS and ALBI score. In 48.6% of the patients, there was an increase in at least one CPS point. Accordingly, there were in trend more patients with CPS B/C cirrhosis after the last systemic treatment compared to initial systemic treatment (41.9% vs 24.2%; P = .068; Figure S2A). Similarly, median ALBI score raised significantly from −2.46 to −2.24 (P = 0.003) and accordingly fewer patients were classified as ALBI grade 1 (ALBI grade 1: 35.9% vs 40.8%; P = 0.103; Figure S2B,C).

3.4 | Response and survival

Radiological response assessment to the first systemic treatment was available for 70 patients (82.4%). Overall response rate (ORR) to first systemic therapy was 12.8% (n = 9), whereas eight patients had a partial response and one patient had a complete response respectively. The patient with the complete response was on sorafenib-treatment. Among the patients with a partial response, five patients were treated with sorafenib and three patients were treated with lenvatinib, leading to an ORR of 8.3% for sorafenib and 27.3% for lenvatinib. Half of the patients (n = 36; 51.4%) had progressive disease upon the first imaging control. Accordingly, the median PFS was 3 months (Figure 1A). However, mOS from the first systemic therapy was 35 months in total (Figure 1B). Control patients with only one systemic treatment line had
a significantly shorter mOS with 9 months compared to 35 months for patients treated with at least two systemic agents ($P < 0.001$; Figure 1C). Patients who were first treated with surgical, ablative or locoregional therapies had a significantly longer mOS from the start of first systemic treatment compared to therapy-naïve patients ($66 \pm 25$ months; $P = 0.020$) (Figure 1D). mOS from the start of the second and the third systemic treatment was 22 and 16 months respectively. For patients treated with two systemic treatment lines, mOS from the second systemic treatment was 18 and 22 months for patients treated with more than two systemic lines ($P = 0.308$).

4 | DISCUSSION

This is to our knowledge the largest real-life, multicentre study investigating sequential systemic therapies in selected caucasian patients with HCC. We show that sequential therapy is feasible and correlates with a long survival in selected patients. The mOS of 35 months from the first systemic treatment was very encouraging compared to historical data of 11-14 months.$^{3,17}$ The patients in our study were treated with at least one of the novel systemic therapeutics including lenvatinib, regorafenib, cabozantinib, ramucirumab or immune checkpoint inhibitors.

In our study, most patients were treated with sorafenib in the first line (84.7%), whereas 12.9% of the patients were initially treated with lenvatinib. Lenvatinib is an oral TKI that has been tested within the phase III REFLECT study in comparison to sorafenib. The primary endpoint was to show noninferiority and was reached with a mOS of 13.6 vs 12.3 months for lenvatinib vs sorafenib (hazard ratio [HR] 0.92; 95% confidence interval 0.79–1.06). These results led to the approval of the European Medicines Agency (EMA) in August 2018 as an alternative to sorafenib in the first-line setting. In contrast to sorafenib, however, there are very few real-life data for lenvatinib treatment. In our study, AEs were similar between sorafenib and lenvatinib (56.9% vs 63.6%) in agreement with the observation in the REFLECT trial. Toxicities were typical for TKIs such as HFSR (18.2%), fatigue (18.2%) hepatic encephalopathy (18.2%) and decreased appetite (27.3%). Similar to our study, fatigue was one of the most common AEs in a small real-life study including 14 patients.$^{18}$ Regarding efficacy, the ORR was higher for patients treated with lenvatinib compared to sorafenib (27.3% vs 8.3%) and thus also in agreement with the REFLECT data (24.1% vs 9.2%).

Cabozantinib, another TKI, showed a prolongation of mOS over placebo in patients who progressed on sorafenib or were intolerable to sorafenib in the CELESTIAL trial (8.0–10.2 months [HR 0.7, $P = 0.0049$]). Based on these results, cabozantinib was approved by the EMA in November 2018.$^{6}$ For patients with TKI-associated AEs and high AFP levels, treatment with the VEGFR-2 antibody ramucirumab represents a good option in the second-line setting. In the phase III REACH-2 study mOS was improved from 7.3 to 8.5 months (HR 0.71, $P = 0.0199$) in patients with AFP-levels ≥400 μg/L who have previously been treated with sorafenib, so that ramucirumab was granted EMA approval in June 2019.$^{7}$ In our study, cabozantinib and ramucirumab were administered only in seven (8.2%) and in three patients (3.5%), respectively, due to their only recently granted approvals.

Regarding immune checkpoint inhibition, both the phase III Checkmate-459 and Keynote-240 study have demonstrated a clinically meaningful survival prolongation in the first-line and in the second-line setting for the programmed cell death protein 1 (PD-1) inhibitors nivolumab and pembrolizumab respectively.$^{8,9}$ Moreover, the results of the phase III IMbrave150 study provided very recently evidence for efficacy of immunotherapy in combination with anti-VEGF treatment with a significant survival benefit for the PDL1-inhibitor atezolizumab in combination with bevacizumab compared to sorafenib (mOS not reached vs 13.2 months, HR 0.58, $P = 0.0006$).$^{10}$ In our study, immune checkpoint inhibitors were frequently used in our patients in all lines of treatments. Impressively, patients treated with immunotherapy in the second or even further lines had an overall response rate of 33.3% and a durable median response of 6 months. Our results therefore support previous real-life data that provided evidence for clinical efficacy and a good safety profile of immune checkpoint inhibition in patients with HCC.$^{19}$

### TABLE 3 Description of systemic therapies and treatment lines

| Therapy | Total | Sorafenib | Lenvatinib | Regorafenib | Cabozantinib | Pembrolizumab | Nivolumab | Durvalumab | Ramucirumab | Others |
|---------|-------|-----------|-----------|------------|-------------|--------------|-----------|------------|------------|--------|
| 1st line | n 85  | 72  | 11  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |
| % 100  | 84.7 | 12.9 | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |
| 2nd line | n 76  | 3  | 8  | 37  | 1  | 10  | 8  | 3  | 6  | 1  |
| % 89.4 | 3.9 | 10.5 | 48.7 | 1.3 | 13.2 | 10.5 | 3.9 | 7.9 | 1  | 1  |
| 3rd line | n 32  | 1  | 7  | 3  | 14  | 6  | 1  | 1  | 1  | 1  |
| % 37.6 | 3.1 | 21.9 | 9.4 | 43.8 | 18.8 | 3.1 | 1  | 1  | 1  | 1  |
| 4th line | n 10  | 1  | 4  | 2  | 2  | 1  | 1  | 1  | 1  | 1  |
| % 11.8 | 10.0 | 40.0 | 20.0 | 20.0 | 10.0 | 10.0 | 1  | 1  | 1  | 1  |
| 5th line | n 2  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |
| % 2.4 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |

Note: Others: tivantinib, nintedanib, FOLFOX, XELOX, XELIRI.
from the start of sorafenib followed by sequential treatment with regorafenib.\textsuperscript{12} Accordingly, several small, mostly Asian co-
horts with less than 50 patients and one systematic review and
meta-analysis including 809 patients demonstrated a prolonged
survival in patients treated with regorafenib following sorafenib
compared to historical controls.\textsuperscript{13-16,20} Furthermore, other real-life
studies demonstrated in line with our findings a long mOS par-
cularly for patients receiving even further treatment following
regorafenib.\textsuperscript{13,14}

The variety of effective systemic treatments offer novel options
for an early treatment stage migration from locoregional to systemic
therapies. This might be especially true in patients who did not re-
spond to local therapies such as TACE and TARE.\textsuperscript{21} We could demon-
strate that particularly pre-treated patients had a significantly longer
mOS from first systemic treatment compared to treatment-naïve
patients in accordance to a previous report.\textsuperscript{22} Further studies with
larger population sizes are strongly requested to analyse the impact
of sequential treatment in patients with initial systemic treatments
and vs surgically or locally pre-treated patients.

One challenge to sequential systemic therapy in HCC is the de-
cline of liver function over the course of the disease. Previous studies
have shown, that not only local therapies can lead to a deterioration
of liver function, but that liver function also decreased under sys-
temic therapy. In the phase III REFLECT study a considerable num-
ber of CPS A patients deteriorated to CPS B at the end of first line
treatment; patients classified as CPS A6 and treated with lenvatinib
and sorafenib time to deterioration to CPS B (≥7 points) was 15.9 and
23.7 months respectively.\textsuperscript{23} Similarly, a decrease in hepatic function
as assessed by CPS and ALBI score was evident in our study. These
data strongly suggest that liver synthesis parameters need to be
carefully monitored during systemic treatment as liver function can
deteriorate as it has been observed after locoregional treatments
such as TACE.\textsuperscript{23} The deterioration of hepatic function is specifically
crucial in patients with a restricted hepatic function due to an under-
lying liver cirrhosis. Important to note, in our study, patients with and
without liver cirrhosis received similarly often sequential systemic
treatments (n = 53 [88.3\%] vs n = 19 [82.6\%]; P = 0.491) and we
did not observe more frequent hepatic decompensations in patients
with liver cirrhosis. Nevertheless, the influence of multiple systemic
treatments should be particularly carefully observed in patients with
liver cirrhosis.

The major limitation of our study is its retrospective nature with
all its potential confounders. Patients that could be treated with
sequential systemic therapy presented with lower tumour burden,
more preserved hepatic function, and were staged more as BCLC B
and C. Patients who were only treated with one systemic line repre-
sented a profoundly different population with a poor prognosis. At
this point in time, it is impossible to propose the best possible se-
quence of systemic treatment in patients with HCC. Moreover, most
second-line treatments have only been evaluated and approved
after failure or intolerance of sorafenib in first-line therapy. With
availability of more effective options in first line such as lenvatinib
or atezolizumab/bevacumab it will be important to determine how

| Characteristics                  | 1 line n % | ≥2 lines n % | P       |
|----------------------------------|------------|-------------|---------|
| Gender                           |            |             |         |
| Male                             | 81 (76.4%) | 60 (80.0%)  | 0.567   |
| Female                           | 25 (23.6%) | 15 (20.0%)  |         |
| Cirrhosis                        |            |             |         |
| Yes                              | 78 (73.6%) | 53 (71.6%)  |         |
| No                               | 28 (26.4%) | 21 (28.4%)  | 0.771   |
| CPS                              |            |             |         |
| A                                | 20 (42.6%) | 43 (75.4%)  |         |
| B                                | 25 (53.2%) | 13 (22.8%)  |         |
| C                                | 2 (4.3%)   | 1 (1.8%)    | 0.003   |
| ALBI                             |            |             |         |
| 1                                | 10 (15.6%) | 26 (40.6%)  |         |
| 2                                | 44 (68.8%) | 37 (57.8%)  |         |
| 3                                | 10 (15.6%) | 1 (1.6%)    | 0.001   |
| Diameter lesion                  |            |             |         |
| >5 cm                            | 31 (53.4%) | 24 (40.7%)  |         |
| ≤5 cm                            | 27 (46.6%) | 35 (59.3%)  | 0.166   |
| Number of lesions                |            |             |         |
| 1                                | 15 (19.7%) | 10 (15.4%)  |         |
| 2                                | 9 (11.8%)  | 10 (15.4%)  |         |
| 3                                | 9 (11.8%)  | 31 (47.7%)  |         |
| >3                               | 43 (56.6%) | 14 (21.5%)  | <0.001  |
| AFP                              |            |             |         |
| >200 µg/L                        | 34 (45.9%) | 15 (24.2%)  |         |
| ≤200 µg/L                        | 40 (54.1%) | 47 (75.8%)  | 0.008   |
| Extrahepatic disease             |            |             |         |
| Yes                              | 32 (38.6%) | 30 (42.3%)  |         |
| No                               | 51 (61.4%) | 41 (57.7%)  | 0.641   |
| Vascular invasion                |            |             |         |
| Yes                              | 53 (63.1%) | 24 (35.3%)  |         |
| No                               | 31 (36.9%) | 44 (64.7%)  | 0.001   |
| BCLC                             |            |             |         |
| 0                                | 0 (0%)     | 0 (0%)      |         |
| A                                | 0 (0%)     | 0 (0%)      |         |
| B                                | 0 (0%)     | 16 (25.0%)  |         |
| C                                | 66 (97.1%) | 47 (73.4%)  |         |
| D                                | 2 (2.9%)   | 1 (1.6%)    | <0.001  |

In our cohort, regorafenib was the most common second-line
treatment. Regorafenib was the first agent that reached an OS ben-
itif over placebo after sorafenib failure with 10.6 vs 7.8 months
(HR 0.62, P < 0.001) within the phase III RESORCE trial and led to
its approval by the EMA in August 2017.\textsuperscript{3} First prospective data on
sequential systemic treatment were provided by a post hoc anal-
ysis of the III RESORCE study, which showed a mOS of 26.0 months

TABLE 4 Patients characteristics by systemic treatment line (1
vs ≥2)
and with which drugs these patients can be treated in subsequent lines of therapy.

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**AUTHORSHIP**

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