# Efficacy and safety of immune checkpoint inhibitor rechallenge in individuals with hepatocellular carcinoma

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**Background & Aims:** We investigated the efficacy and safety of immune checkpoint inhibitor (ICI) rechallenge in patients with hepatocellular carcinoma (HCC) who received ICI-based therapies in a previous systemic line.

**Methods:** In this international, retrospective multicenter study, patients with HCC who received at least two lines of ICI-based therapies (ICI-1, ICI-2) at 14 institutions were eligible. The main outcomes included best overall response and treatment-related adverse events.

**Results:** Of 994 ICI-treated patients screened, a total of 58 patients (male, n = 41; 71%) with a mean age of 65.0±9.0 years were included. Median systemic treatment lines of ICI-1 and ICI-2 were 1 (range, 1-4) and 3 (range, 2-9), respectively. ICI-based therapies used at ICI-1 and ICI-2 included ICI alone (ICI-1, n = 26, 45%; ICI-2, n = 4, 7%), dual ICI regimens (n = 1, 2%; n = 12, 21%), or ICI combined with targeted therapies/anti-VEGF (n = 31, 53%; n = 42, 72%). Most patients discontinued ICI-1 due to progression (n = 52, 90%). Objective response rate was 22% at ICI-1 and 26% at ICI-2. Responses at ICI-2 were also seen in patients who had progressive disease as best overall response at ICI-1 (n = 11/21; 52%). Median time-to-progression at ICI-1 and ICI-2 was 5.4 (95% CI 3.0-7.7) months and 5.2 (95% CI 3.3-7.0) months, respectively. Treatment-related adverse events of grade 3-4 at ICI-1 and ICI-2 were observed in 9 (16%) and 10 (17%) patients, respectively.

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**Conclusions:** ICI rechallenge was safe and resulted in a treatment benefit in a meaningful proportion of patients with HCC. These data provide a rationale for investigating ICI-based regimens in patients who progressed on first-line immunotherapy in prospective trials.

**Impact and implications:** Therapeutic sequencing after first-line immune checkpoint inhibitor (ICI)-based therapy for advanced hepatocellular carcinoma (HCC) remains a challenge as no available second-line treatment options have been studied in immunotherapy-pretreated patients. Particularly, the role of ICI rechallenge in patients with HCC is unclear, as data from prospective trials are lacking. We investigated the efficacy and safety of ICI-based regimens in patients with HCC pretreated with immunotherapy in a retrospective, international, multicenter study. Our data provide the rationale for prospective trials investigating the role of ICI-based regimens in patients who have progressed on first-line immunotherapy.

## Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and a leading cause of cancer-related mortality worldwide.[1] Most patients become candidates for systemic therapy at some point during the course of the disease. The systemic treatment landscape of HCC has changed rapidly over the last years.[2] Several immune checkpoint inhibitors (ICIs) have been added to the treatment armamentarium in the United States after receiving conditional approval for sorafenib-pretreated patients following promising phase II data.[3] The combination of atezolizumab/bevacizumab was the first ICI-based regimen to meet its primary survival endpoints *vs.* sorafenib in a phase III trial, and consequently became the standard of care in systemic front-line treatment.[2,4,5] Only recently, the combination of durvalumab/tremelimumab was shown to be superior to sorafenib in terms of overall survival in a phase III trial, and durvalumab alone was non-inferior to sorafenib;[6] thus, both will likely be added as additional first-line options upon approval.[7]

Sequencing after first-line immunotherapy is currently empirical in HCC and largely based on clinical characteristics and toxicity profiles, as well as local regulations and drug availabilities.[2,8] The role of subsequent ICI use in ICI-pretreated patients with HCC is unclear, as data from prospective trials are lacking. Successful ICI rechallenge in a subset of patients has been reported in other solid tumors, including melanoma[9] and renal cell carcinoma,[10,11] providing the rationale for evaluating this strategy also in patients with HCC.

In this international, retrospective, multicenter study, we investigated the efficacy and safety of ICI-based regimens in patients with HCC who had received ICIs in a previous line of systemic therapy.

## Patients and methods

### Patients

In this international, retrospective multicenter study, patients with histologically or radiologically diagnosed HCC who received at least two lines of ICI-based therapies (ICI-1, ICI-2) at 14 institutions in Austria, Germany, Italy, Switzerland, United Kingdom, and the United States were considered. Patients who received two lines of different ICIs alone or as combination therapy and patients who received the same ICI at ICI-1 and ICI-2 but with a different combination partner were eligible. Patients were allowed to receive one or more treatments between ICI-1 and ICI-2.

Patients who received ICIs in a curative setting as (neo) adjuvant treatment before/after resection or ablation, and patients who received loco-regional therapies as the main treatment but in combination with ICIs were not included. The retrospective analysis was approved by the Ethics Committee of the Medical University of Vienna.

### Assessments and outcomes

Main outcomes included investigator-assessed best overall response (BOR) and treatment-related adverse events (TRAEs) according to Common Terminology Criteria for Adverse Events version 5.0. Objective response rate (ORR) was defined as the proportion of patients with complete response (CR) or partial response (PR) as BOR. Disease control rate (DCR) was defined as the proportion of patients achieving CR/PR or stable disease (SD) as BOR. Further outcomes included time-to-progression (TTP) as well as overall survival (OS).

### Statistical analysis

Data on baseline characteristics, radiological tumor evaluation, and TRAEs were summarized using descriptive statistics. Median duration of treatment was defined as time from the date of treatment initiation until the date of last administration; patients who were still receiving immunotherapy at data cut-off were censored. Patients who had at least one follow-up imaging were evaluable for assessment of BOR and TTP. TTP was defined as the time from the date of treatment initiation until the date of first radiologically confirmed tumor progression; patients
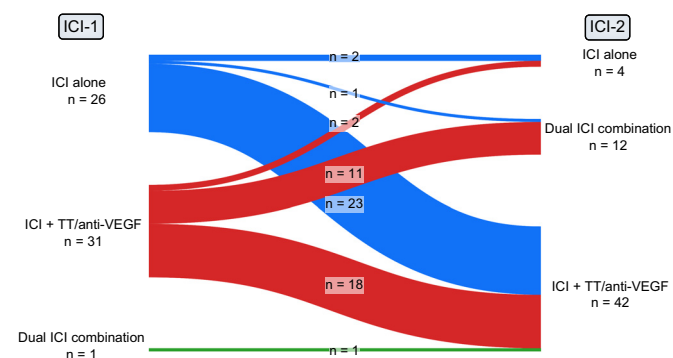


**Fig. 1. Type of immune checkpoint inhibitor regimen used at first and second line of ICI treatment.** ICI, immune checkpoint inhibitor; ICI-1, first line of ICI treatment; ICI-2, second line of ICI treatment; TT, targeted therapy, VEGF, vascular endothelial growth factor.
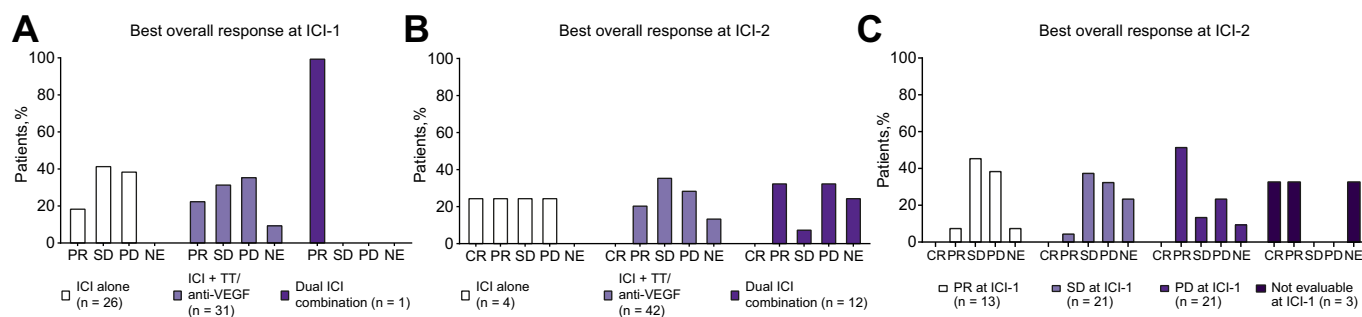
**Fig. 2. BOR at ICI-1 and ICI-2 line in selected patient populations.** (A) BOR at ICI-1 according to type of therapy received at ICI-1, (B) BOR at ICI-2 according to type of therapy received at ICI-2, and (C) BOR at ICI-2 according to BOR at ICI-1. BOR, best overall response; CR, complete response; ICI, immune checkpoint inhibitor; ICI-1, first line of ICI treatment; ICI-2, second line of ICI treatment; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TT, targeted therapy, VEGF, vascular endothelial growth factor.

without radiologically confirmed tumor progression were censored at the date of last imaging. OS was defined as the time from treatment start until date of death; patients who were still alive were censored at the date of last contact. Survival curves were calculated using the Kaplan-Meier method. Statistical analyses were performed using IBM SPSS Statistics version 26.0 (SPSS Inc., Chicago, IL). Fig. 1 was created using the software sankeyMATIC freely available at https://sankeymatic.com and Fig. 2 was created using GraphPad Prism 9 (GraphPad Software, LLC, San Diego, US). Median follow-up time was calculated using the reverse Kaplan-Meier method.

## Results

### Patients

Of the 994 ICI-treated patients with HCC screened, 58 (6%) patients were put on another ICI-based regimen between March 2019 and March 2022 after prior ICI discontinuation and were thus included in this analysis. Detailed patient characteristics at start of ICI-1 and ICI-2 are displayed in Table 1. Most patients had well-preserved liver function (Child-Pugh A) at ICI-1 (n = 55, 95%) and ICI-2 (n = 50, 86%). The majority had BCLC stage C at ICI-1 (n = 44, 76%) and ICI-2 (n = 48, 83%). Forty-two (72%) patients received any prior HCC treatment before immunotherapy. Most patients received ICI-1 as first- (n = 36, 62%) and ICI-2 as second- (n = 29, 50%) line systemic therapy. Seventeen patients (29%) received at least one systemic line between ICI-1 and ICI-2. ICI-based regimens used at ICI-1 and ICI-2 are shown in Table S1 and Fig. 1. Fifty-two patients (90%) discontinued ICI-1 due to radiological progression, 4 (7%) because of adverse events, one (2%) due to clinical progression, and another one (2%) due to patient preference. Median duration of ICI-1 and ICI-2 was 5.4 (95% CI 4.3-6.5) months and 3.6 (95% CI 2.4-4.9) months, respectively. Median duration from ICI-1 discontinuation to ICI-2 initiation was 1.3 (95% CI 0.4-2.1) months.

### Efficacy

Median estimated follow-up from ICI-1 was 25.1 (95% CI 20.8-29.4) months. Twenty-six patients (45%) died during the observation period. Median OS from initiation of systemic first-line, start of ICI-1, and start of ICI-2 was 47.0 (95% CI 39.9-54.2) months, 39.8 (95% CI 33.7-45.9) months, and 12.0 (95% CI 7.5-16.5) months, respectively. BOR at ICI-1 was CR/PR/SD/progressive disease (PD)/not evaluable in 0 (0%)/13 (22%)/21 (36%)/21 (36%)/3 (5%) patients, corresponding to an ORR and DCR of 22% and 59%, respectively. BOR at ICI-2 was CR/PR/SD/PD/not evaluable in 1 (2%)/14 (24%)/17 (29%)/17 (29%)/9 (16%) patients, corresponding to an ORR and DCR of 26% and 55%, respectively (Table 2). One patient (2%) had an objective response at both ICI-1 and ICI-2.

## Table 1. Patient characteristics at ICI-1 and ICI-2.

| | ICI-1 (n = 58; 100%) | ICI-2 (n = 58; 100%) |
|---|---|---|
| Age (years), mean ± SD | 65.0±9.0 | 68.2±9.4 |
| Sex, male | 41 (71%) | — |
| Viral etiology | 24 (41%) | — |
| Child-Pugh stage | | |
| A | 55 (95%) | 50 (86%) |
| B | 2 (3%) | 8 (14%) |
| C | 1 (2%) | 0 |
| ECOG PS* ≥1 | 10 (17%) | 24 (41%) |
| Treatment prior to ICI-1 | | |
| Surgery | 25 (43%) | — |
| Ablation | 7 (12%) | — |
| Loco-regional (TACE, SIRT, radiation) | 20 (34%) | — |
| Systemic | 22 (38%) | — |
| Macrovascular invasion | 21 (36%) | 21 (36%) |
| Extrahepatic metastases | 29 (50%) | 34 (59%) |
| BCLC stage | | |
| B | 13 (22%) | 10 (17%) |
| C | 44 (76%) | 48 (83%) |
| D | 1 (2%) | 0 |
| Alpha-fetoprotein (IU/ml)**, median (IQR) | 54.3 (5.7-902.2) | 182.2 (5.8-7,907.4) |
| Line of ICI therapy, median (range) | 1 (1-4) | 3 (2-9) |
| Type of ICI regimen | | |
| ICI alone | 26 (45%) | 4 (7%) |
| Dual ICI combination | 1 (2%) | 12 (21%) |
| ICI plus TT/anti-VEGF | 31 (53%) | 42 (72%) |
| Reason for discontinuation of ICI-1 | | |
| Radiological progression | 52 (90%) | — |
| Toxicity | 4 (7%) | — |
| Other | 2 (3%) | — |

BCLC, Barcelona-Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ICI, immune checkpoint inhibitor; ICI-1, first line of ICI treatment; ICI-2, second line of ICI treatment; SIRT, selective internal radiotherapy; TACE, transarterial chemoembolization; TT, targeted therapy; VEGF, vascular endothelial growth factor.
* Missing ICI-1: n = 1.
** Missing ICI-1: n = 2 and ICI-2: n = 4.

**Table 2. Main efficacy outcomes at ICI-1 and ICI-2.**

| | ICI-1 | ICI-2 |
|---|---|---|
| **Best overall response** | | |
| CR | 0 | 1 (2%) |
| PR | 13 (22%) | 14 (24%) |
| SD | 21 (36%) | 17 (29%) |
| PD | 21 (36%) | 17 (29%) |
| N/E | 3 (5%) | 9 (16%) |
| ORR (CR+PR) | 13 (22%) | 15 (26%) |
| DCR (CR+PR+SD) | 34 (59%) | 32 (55%) |
| TTP, median (95%CI) | 5.4 (3.0-7.7) months | 5.2 (3.3-7.0) months |

CR, complete response; DCR, disease control rate; ICI-1, first line of ICI treatment; ICI-2, second line of ICI treatment; N/E, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TTP, time-to-progression.

Median TTP was 5.4 (95% CI 3.0-7.7) months (ICI-1) and 5.2 (95% CI 3.3-7.0) months (ICI-2), respectively (Table 2). Responses at ICI-2 were also seen in patients who had PD as BOR at ICI-1 (n = 11/21; 52%), and who received ICI monotherapy at ICI-2 (n = 2/4; 50%) (Fig. 2). Characteristics of individual patients who achieved a CR/PR at ICI-2 are displayed in Table 3.

In the subgroup of patients receiving atezolizumab/bevacizumab at ICI-1 (n = 17; 29%), 2 (12%) and 15 (88%) patients were treated with ICI monotherapy and combinatorial regimens at ICI-2, respectively (Table S2). The ORR and DCR at ICI-2 in this subgroup were 18% (n = 3) and 53% (n = 9), respectively. In patients who were treated with atezolizumab/bevacizumab at ICI-2 (n = 29; 50%), ORR and DCR were 24% (n = 7) and 52% (n = 15), respectively.

## Safety

In total, 31 (53%) patients developed at least one TRAE at ICI-1 and 28 (48%) patients at ICI-2, respectively; grade 3-4 TRAEs were observed in 9 (16%) and 10 (17%) patients at ICI-1 and ICI-2, respectively. Three patients (5%) experienced grade 3-4 TRAEs at both ICI-1 and ICI-2. No treatment-related deaths were recorded. Eight (14%) and seven (12%) required systemic corticosteroid treatment at ICI-1 and ICI-2, respectively, and one patient (2%) received systemic corticosteroids at both ICI-1 and ICI-2. Four (7%) and two (3%) patients discontinued treatment due to toxicity at ICI-1 and ICI-2, respectively. TRAEs at ICI-1 and ICI-2 are summarized in Table 4.

## Discussion

In this international, retrospective, multicenter study, an ORR of 26% and a DCR of 55% was observed in patients with HCC who received an ICI-based regimen after prior exposure to ICIs. ICI rechallenge was safe, even in patients who experienced high-grade TRAEs or required corticosteroids at ICI-1.

Several conclusions can be derived from our study. Firstly, the fact that we had to screen 994 patients in order to include 58 eligible patients (6%) suggests that ICI rechallenge is currently an uncommon practice in HCC, likely because of the lack of evidence and approval. However, there is a scientific rationale supporting the use of ICI-based therapies, particularly combinatorial regimens, in patients with primary or acquired resistance to a prior ICI regimen. For instance, upgrading from ICI monotherapy to combination treatment (*i.e.*, dual ICI treatment or ICI plus tyrosine kinase inhibitors/anti-VEGF [vascular endothelial growth factor]) or using a different combination than the previous ICI regimen may restore the efficacy of immunotherapy by synergistically

**Table 3. Details of patients with a response at ICI-2.**

| Patient # | Type of ICI-1 | Line of ICI-1 | BOR at ICI-1 | Reason for discontinuation of ICI-1 | Time between ICI-1 and ICI-2 (months) | Type of ICI-2 | Line of ICI-2 | BOR at ICI-2 |
|---|---|---|---|---|---|---|---|---|
| 1 | Pembrolizumab | 3 | PR | Progression | 5.4 | Atezolizumab/bevacizumab | 6 | PR |
| 2 | Atezolizumab/bevacizumab | 1 | N/E | Adverse event | 0.5 | Pembrolizumab | 2 | CR |
| 3 | Nivolumab | 2 | PD | Adverse event | 0.9 | Pembrolizumab | 3 | PR |
| 4 | Pembrolizumab | 4 | PD | Progression | 6.5 | Atezolizumab/bevacizumab | 6 | PR |
| 5 | Pembrolizumab | 1 | PD | Progression | 3.3 | Atezolizumab/bevacizumab | 2 | PR |
| 6 | Nivolumab | 3 | PD | Progression | 22.8 | Atezolizumab/bevacizumab | 6 | PR |
| 7 | Pembrolizumab | 1 | PD | Progression | 1.1 | Atezolizumab/bevacizumab | 2 | PR |
| 8 | Pembrolizumab | 2 | PD | Progression | 5.6 | Pembrolizumab/lenvatinib | 4 | PR |
| 9 | Nivolumab | 2 | PD | Progression | 18.8 | Atezolizumab/bevacizumab | 4 | PR |
| 10 | Nivolumab/lenvatinib | 1 | SD | Adverse event | 0.5 | Nivolumab/ipilimumab | 2 | PR |
| 11 | Atezolizumab/bevacizumab | 2 | PD | Progression | 0.7 | Nivolumab/ipilimumab | 3 | PR |
| 12 | Nivolumab/lenvatinib | 1 | PD | Progression | 0.5 | Nivolumab/ipilimumab | 2 | PR |
| 13 | Atezolizumab/Bevacizumab | 2 | PD | Progression | 10.2 | Nivolumab/ipilimumab | 5 | PR |
| 14 | Pembrolizumab/bavituximab | 1 | PD | Progression | 1.1 | Pembrolizumab/bevacizumab | 2 | PR |
| 15 | Pembrolizumab/bavituximab | 1 | N/E | Patient's preference | 0.7 | Atezolizumab/bevacizumab | 2 | PR |

BOR, best overall response; CR, complete response; ICI-1, first line of ICI treatment; ICI-2, second line of ICI treatment; N/E, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

**Table 4. Treatment-related adverse events at ICI-1 and ICI-2.**

| | ICI-1 | | ICI-2 | |
|---|---|---|---|---|
| | Any grade | Grade 3-4* | Any grade | Grade 3** |
| Infusion/allergic reaction | 6 (10%) | 1 (2%) | – | – |
| Arthritis/arthralgia/myalgia | 5 (9%) | – | 4 (7%) | – |
| Diarrhea/colitis | 4 (7%) | 1 (2%) | 6 (10%) | 1 (2%) |
| Pruritus | 4 (7%) | – | 2 (3%) | – |
| Mucositis/stomatitis | 2 (3%) | 1 (2%) | 2 (3%) | 1 (2%) |
| Hepatitis | 2 (3%) | – | 4 (7%) | 3 (5%) |
| Dermatological | 3 (5%) | – | 4 (7%) | 1 (2%) |
| Arterial hypertension | 6 (10%) | 2 (3%) | 3 (5%) | 1 (2%) |
| Transient ischemic attack | 1 (2%) | 1 (2%) | – | – |
| Scrotal edema | 1 (2%) | 1 (2%) | – | – |
| Amylase/lipase increase | 1 (2%) | 1 (2%) | – | – |
| Proteinuria | 1 (2%) | 1 (2%) | 1 (2%) | 1 (2%) |
| Nephritis | 1 (2%) | – | – | – |
| Cough | 1 (2%) | – | – | – |
| Sinusitis | 1 (2%) | – | – | – |
| Thrombocytopenia | 2 (3%) | – | – | – |
| Hypertriglyceridemia | 1 (2%) | – | – | – |
| Palmar-plantar erythrodysesthesia | 1 (2%) | – | 2 (3%) | 1 (2%) |
| Fatigue | 3 (5%) | – | 9 (16%) | 1 (2%) |
| Epistaxis | 1 (2%) | – | 1 (2%) | – |
| AV block III | 1 (2%) | 1 (2%) | – | – |
| Wound healing impairment | 1 (2%) | – | – | – |
| Hair loss | 2 (3%) | – | 1 (2%) | – |
| Nausea | – | – | 1 (2%) | – |
| Gastritis | – | – | 1 (2%) | 1 (2%) |
| Ulcer bleeding | – | – | 1 (2%) | 1 (2%) |
| Hypothyroidism | – | – | 1 (2%) | – |
| Hypophysitis | – | – | 1 (2%) | 1 (2%) |
| Fever | – | – | 2 (3%) | – |
| Dysphonia | – | – | 1 (2%) | – |

AV, atrioventricular; ICI-1, first line of ICI treatment; ICI-2, second line of ICI treatment.
* No grade 5 treatment-related adverse events were recorded.
** No grade 4 or 5 treatment-related adverse events were recorded.

modulating the immunosuppressive tumor immune microenvironment through different mechanisms.[12–14] This may also be achieved by only switching the combination partner (*i.e.*, TKI/anti-VEGF) while continuing with the same ICI. Indeed, in our cohort, most patients (93%) received combination therapies at ICI-2.

Secondly, patients may benefit from a second ICI regimen, even those with PD as BOR at ICI-1. In fact, ORR was similar at ICI-1 and ICI-2 in our cohort (22% *vs.* 26%), and comparable to ORRs reported for ICI-based combinations in phase III first-line trials.[4,6] Notably, we observed responses in both patients who received ICI monotherapy and combination therapies at ICI-2, as well as in patients with primary resistance (progression as BOR) at ICI-1.

A small retrospective study reported acceptable toxicity and an ORR of 16% for dual ICI treatment (anti-CTLA-4 [cytotoxic T-lymphocyte antigen-4] plus anti-PD1 [programmed cell death 1]) in 25 patients with HCC who progressed on prior ICIs.[15] However, in contrast to our cohort, most patients (84%) received prior PD-1 monotherapy, and only one patient was treated with atezolizumab/bevacizumab,[15] the standard of care in systemic front-line treatment.[5] As the most clinically relevant subgroup, 17 patients received atezolizumab/bevacizumab at ICI-1 in our cohort; in these patients, the ORR and DCR were 18% and 53%, respectively, at ICI-2. Atezolizumab/bevacizumab also led to a treatment benefit when given at ICI-2 (ORR, 24%; DCR, 52%).

Thirdly, the safety profile of the second ICI regimen was good, even in patients who experienced high-grade adverse events or required corticosteroids at ICI-1. This is in line with current recommendations suggesting that ICIs may be reinitiated – depending on the severity and site affected – once the adverse event has resolved with or without immunosuppressive treatment.[16]

Limitations of our study include the limited sample size, heterogenous population, retrospective nature, and lack of blinded response assessment at predefined intervals. Some patients received multiple lines of systemic therapy which may have led to selection of patients with less aggressive tumors and well-preserved liver function. However, the selection of a better trial population (*i.e.*, better performance status, compensated liver disease) is a *conditio sine qua non* when investigating later line treatments, and concerns not only our analysis but also large prospective studies testing second- or third-line therapies in HCC. Only patients who are alive with good performance status and well-preserved liver function are eligible for inclusion, while those with deteriorating performance status/liver function would not qualify.[17]

In conclusion, our results demonstrate that the use of ICI-based regimens after prior immunotherapy is feasible and safe, and can lead to a treatment benefit (response and stabilization) in a clinically relevant proportion of patients with HCC. These data provide a rationale for testing ICI-based therapies in patients who progressed on first-line immunotherapy in large prospective trials.

## Abbreviations

## Financial support

## Conflicts of interest

BS received travel support from AbbVie, Ipsen and Gilead. DR has received advisory fees from Bayer and speakers fees as well as travel grants from Ipsen. He is an investigator for Bayer, BMS, Lilly, AstraZeneca and Roche. SP has nothing to disclose. ML has nothing to disclose. KP has nothing to disclose. TP received consulting fees from IQVIA and Bayer; and institutional research funding from Lilly, Roche, Bayer. AC has nothing to disclose. TWF has nothing to disclose. JVF has received advisory board fees from Roche. KS served as consultant for Ipsen and Bayer, and conducts studies for Bayer, Roche, Lilly, MSD, and BMS. VH has nothing to disclose. FF received travel support from Abbvie and Novartis, and speaker fees from Abbvie and MSD. AD has nothing to disclose. ARS has served at advisory boards and received consulting honoraria from AMGEN, AAA, Bayer, BMS, IPSEN, Lilly, Merck, MSD, Pfizer, Roche, Sanofi, and Servier. KS has nothing to disclose.

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Please refer to the accompanying ICMJE disclosure forms for further details.

## Authors' contributions

All authors contributed either to research design (B.S. and M.P.), and/or the data acquisition (B.S., D.R., S.P., M.L., K.P., T.P., A.C., T.W.F., J.v.F., K.S., V.H., F.F., A.D., A.R.S., K.S., P.R., Bi.S., M.P.E., A.T., Ang.D., F.H., L.B., A.B.P., D.H., M.V., F.S., M.T., A.D'A., C.A.M.F., D.J.P., M.P.-R., J.-F.D., A.W., A.E.K., A.G.S., E.N.d.T., L.R., M.P.), analysis (B.S. and M.P.), or interpretation (all authors) of data. B.S. and M.P. drafted the manuscript, which was critically revised by all other authors.

## Data availability statement

The data that support the findings of this study are available from the corresponding author, MP, upon reasonable request.

## Supplementary data

## References

*Author names in bold designate shared co-first authorship*

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