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

Bernhard Scheiner,1,2,3 Daniel Roessler,1,4 Samuel Phen,4 Mir Lim,4 Katharina Pomej,1,2 Tiziana Pressiani,5 Antonella Cammarota,6 Thorben W. Fründt,7 Johann von Felden,7 Kornelius Schulze,7 Vera Himmelsbach,8 Fabian Finkelmeier,8 Ansgar Deibel,9 Alexander R. Siebenhäuser,10,11 Kateryna Shmanko,12 Pompilia Radu,13,14 Birgit Schwach-Aeppler,15 Matthias P. Ebert,15,16,17 Andreas Teufel,16,18 Angela Djann,19 Florian Hucke,20 Lorenz Balcar,2,12 Alexander B. Philipp,2 David Hsiehchen,4 Marino Venerito,21 Friedrich Sinner,21 Michael Trauner,1 Antonio D’Alessio,6,22 Claudia A.M. Fulgenzi,22,23 David J. Pinato,22,24 Markus Peck-Radosavljevic,20 Jean-François Dufour,13 Arndt Weinmann,12 Andreas E. Kremer,9,25 Amit G. Singal,4 Enrico N. De Toni,3 Lorenza Rimassa,5,6,3, Matthias Pinter1,2,*

1Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; 2Liver Cancer (HCC) Study Group Vienna, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; 3Department of Medicine II, University Hospital, LMU Munich, Munich, 81377, Germany; 4Department of Medicine, UT Southwestern Medical Center, Dallas TX USA; 5Medical Oncology and Hematology Unit, Humanitas Cancer Center, RCCS Humanitas Research Hospital, Via Manzoni 56, 20089 Rozzano (Milan), Italy; 6Department of Biomedical Sciences, University of Eastern Piedmont, Novara, Italy; 7Department of Internal Medicine, Gastroenterology & Hepatology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; 8Department of Gastroenterology, Hepatology and Endocrinology, University Hospital Zurich and University Zurich, Zurich, Switzerland; 9Department of Medical Oncology and Hematology, University Hospital Zurich and University Zurich, Zurich, Switzerland; 10Department of Medical Oncology and Hematology, Cantonal Hospital Schaffhausen, Schaffhausen, Switzerland; 11Department of Internal Medicine I, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany; 12Hepatology-Department of Biomedical Research, University of Bern, Bern, Switzerland; 13Department of Visceral Surgery and Medicine, Inselspital, University of Bern, Bern, Switzerland; 14Department of Internal Medicine II, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; 15Clinical Cooperation Unit Healthy Metabolism, Center for Preventive Medicine and Digital Health Baden-Württemberg (CPDBW), Heidelberg University, Mannheim, Germany; 16Division of Gastroenterology, Hepatology, Endocrinology and Metabolism, Medical University of Innsbruck, Innsbruck, Austria; 17Internal Medicine and Gastroenterology (IMuG), including Centralized Emergency Service (ZAE), Klinikum Klagenfurt am Wörthersee, Klagenfurt, Austria; 18Department of Gastroenterology, Hepatology and Infectious Diseases, Otto-Von-Guericke University Hospital, 39120 Magdeburg, Germany; 19Department of Surgery & Cancer, Imperial College London, Hammersmith Hospital, London, UK; 20Department of Medical Oncology, University Campus Bio-Medico of Rome, Italy; 21Division of Oncology, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy; 22Department of Medicine I, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany

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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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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;6,7 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 melanoma9 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.

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
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-line (n = 29, 50%) 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.

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

|                      | ICI-1                  | ICI-2                  |
|----------------------|------------------------|------------------------|
|                      | (n = 58; 100%)         | (n = 58; 100%)         |
| **Age (years), mean ± SD** | 65.0±9.0               | 68.2±9.4               |
| **Sex, male**        | 41 (71%)               | -                      |
| **Viral etiology**   |                        |                        |
| 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        | 20 (34%)               | -                      |
| (TACE, SIRT, radiation) |                    |                        |
| Systemic             | 22 (38%)               | -                      |
| **Macrovascular invasion** |                      |                        |
| Systemic             | 21 (36%)               | 21 (36%)               |
| **Extrahepatic metastases** |                  |                        |
| Systemic             | 29 (50%)               | 34 (59%)               |
| **BCLC stage**       |                        |                        |
| A                    | 13 (22%)               | 10 (17%)               |
| B                    | 44 (76%)               | 48 (83%)               |
| C                    | 1 (2%)                 | 0                      |
| **Alpha-fetoprotein (IU/ml)** | 54.3 (5.7-902.2)      | 182.2 (5.8-7907.4)     |
| **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%)               |
| Dual ICI combination | 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, transcatheter arterial embolization; TT, targeted therapy; VEGF, vascular endothelial growth factor.**

* Missing ICI-1: n = 1.
** Missing ICI-1: n = 2 and ICI-2: n = 4.
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

| 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.
modulating the immunosuppressive tumor immune microenvironment through different mechanisms.\textsuperscript{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.\textsuperscript{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). In conclusion, our results demonstrate that the use of ICI-1 and ICI-2.

|                     | ICI-1       | Any grade | Grade 3–4* |
|---------------------|-------------|-----------|------------|
| Infusion/allergic reaction | 6 (10%) | 1 (2%) | —         |
| Arthritis/arthritis/myalgia   | 5 (9%) | — | 4 (7%) |
| Diarrhea/colitis       | 4 (7%) | 1 (2%) | 6 (10%) |
| Pruritus               | 4 (7%) | — | 2 (3%) |
| Mucositis/stomatitis  | 2 (3%) | 1 (2%) | 2 (3%) |
| Hepatitis             | 2 (3%) | — | 4 (7%) |
| Dermatological        | 3 (5%) | — | 4 (7%) |
| Arterial hypertension | 6 (10%) | 2 (3%) | 3 (5%) |
| 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%) |
| Nephritis             | 1 (2%) | — | —         |
| Cough                 | 1 (2%) | — | —         |
| Sinusitis             | 1 (2%) | — | —         |
| Thrombocytopenia      | 2 (3%) | — | —         |
| Hypertriglyceridemia  | 1 (2%) | — | —         |
| Palmar-plantar erythrodyssthesia | 1 (2%) | — | 2 (3%) |
| Fatigue               | 3 (5%) | — | 9 (16%) |
| 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%) |
| Ulcer bleeding        | — | — | 1 (2%) |
| Hypothyroidism        | — | — | 1 (2%) |
| Hypophysitis          | — | — | 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.

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.\textsuperscript{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
BOR, best overall response; CR, complete response; DCR, disease control rate; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease; TRAEs, treatment-related adverse events; TTP, time-to-progression.

Financial support
D.J.P. acknowledges the infrastructural support provided by Imperial Experimental Cancer Medicine Centre, Cancer Research UK Imperial Centre, the Imperial College BRC and the Imperial College Healthcare NHS Trust Tissue Bank.

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, Bay. AC has nothing to disclose.

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