Research Article
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Characteristics and outcomes of immunotherapy-related liver injury in patients with hepatocellular carcinoma versus other advanced solid tumours

Ciro Celsa[1,2,†], **Giuseppe Cabibbo**[2,†], Claudia A.M. Fulgenzi[1,3], Bernhard Scheiner[1,4], Antonio D'Alessio[1,5], Giulia F. Manfredi[1,5], Naoshi Nishida[6], Celina Ang[7], Thomas U. Marron[7], Anwaar Saeed[8], Brooke Wietharn[9], Matthias Pinter[4], Jaekyung Cheon[10], Yi-Hsiang Huang[11], Pei-Chang Lee[12], Samuel Phen[13], Anuhya Gampa[14], Anjana Pillai[15], Caterina Vivaldi[16], Francesca Salani[15,16], Gianluca Masi[15], Natascha Roehlen[17], Robert Thimme[17], Arndt Vogel[18,19], Martin Schönlein[20], Johann von Felden[21], Kornelius Schulze[21], Henning Wege[21], Peter R. Galle[22], Masatoshi Kudo[6], Lorenza Rimassa[23,24], Amit G. Singal[13], Paul El Tomb[25], Susanna Ulahannan[25], Alessandro Parisi[26], Hong Jae Chon[10], Wei-Fan Hsu[27], Bernardo Stefanini[28], Elena Verzoni[29], Raffaele Giusti[30], Antonello Veccia[31], Annamaria Catino[32], Giuseppe Aprile[33], Pamela Francesca Guglielmini[34], Marilena Di Napoli[35], Paola Ermacora[36], Lorenzo Antonuzzo[37], Ernesto Rossi[38], Francesco Verderame[39], Fable Zustovich[40], Corrado Ficorella[41], Francesca Romana Di Pietro[42], Nicola Battelli[43], Giorgia Negrini[44], Francesco Grossi[45], Roberto Bordonaro[46], Stefania Pipitone[47], Maria Banzi[48], Serena Ricciardi[49], Letizia Laera[50], Antonio Russo[51], Ugo De Giorgi[52], Luigi Cavanna[53], Mariella Soraru[54], Vincenzo Montesarchio[55], Paola Bordi[56], Leonardo Brunetti[3], Carmine Pinto[48], Melissa Bersanelli[56], Calogero Cammà[2], Alessio Cortellini[1,3,‡], David J. Pinato[1,5,*,‡]

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Background & Aims: Immune-related liver injury (irLI) is commonly observed in patients with cancer treated with immune checkpoint inhibitors (ICIs). We aimed to compare the incidence, clinical characteristics, and outcomes of irLI between patients receiving ICIs for hepatocellular carcinoma (HCC) *vs.* other solid tumours.
Methods: Two separate cohorts were included: 375 patients with advanced/unresectable HCC, Child-Pugh A class treated with first-line atezolizumab+bevacizumab from the AB-real study, and a non-HCC cohort including 459 patients treated with first-line ICI therapy from the INVIDIa-2 multicentre study. IrLI was defined as a treatment-related increase of aminotransferase levels after exclusion of alternative aetiologies of liver injury. The incidence of irLI was adjusted for the duration of treatment exposure.
Results: In patients with HCC, the incidence of any grade irLI was 11.4% over a median treatment exposure of 4.4 months (95% CI 3.7-5.2) *vs.* 2.6% in the INVIDIa-2 cohort over a median treatment exposure of 12.4 months (95% CI 11.1-14.0). Exposure-adjusted-incidence of any grade irLI was 22.1 per 100-patient-years in patients with HCC and 2.1 per 100-patient-years in patients with other solid tumours (p <0.001), with median time-to-irLI of 1.4 and 4.7 months, respectively. Among patients who developed irLI, systemic corticosteroids were administered in 16.3% of patients with HCC and 75.0% of those without HCC (p <0.001), and irLI resolution was observed in 72.1% and 58.3%, respectively (p = 0.362). In patients with HCC, rates of hepatic decompensation and treatment discontinuation due to irLI were 7%. Grade 1-2 irLI was associated with improved overall survival only in patients with HCC (hazard ratio 0.53, 95% CI 0.29-0.96).
Conclusions: Despite higher incidence and earlier onset, irLI in patients with HCC is characterised by higher rates of remission and lower requirement for corticosteroid therapy (*vs.* irLI in other solid tumours), low risk of hepatic decompensation and treatment discontinuation, not negatively affecting oncological outcomes.

Introduction

The advent of immune checkpoint inhibitors (ICIs) has revolutionised the management of patients with advanced stage cancer, dramatically improving their survival outcomes. Since the approval of ipilimumab for the treatment of metastatic melanoma in 2011,[1] oncological indications for ICI therapy rapidly expanded to most solid tumours either as mono or combination therapy. Particularly, in advanced hepatocellular carcinoma (HCC), the use of ICI-based therapies has led to an

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* Corresponding author. Address: Department of Surgery & Cancer, Imperial College London, Hammersmith Hospital, Du Cane Road, W12 0HS, London, UK; Tel.: +44 0207 5942799.
E-mail address: david.pinato@imperial.ac.uk (D.J. Pinato).
† Equally contributed as first author
‡ Equally contributed as senior authors
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increase in overall survival (OS), now reaching approximately 20 months in contemporary trials.[2–4]

Approval of ICIs in HCC has represented a clinical breakthrough in a disease invariably characterised by poor survival outcomes in advanced stages, dictated by the lack of highly effective systemic treatments and by the nearly universal co-existence of cirrhosis. The mechanism of action of ICI therapy relies on the inhibition of immune checkpoint molecules, including programmed death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) leading to anti-cancer immune reconstitution.

The PD-1 and CTLA-4 pathway are physiologically involved in spontaneous immune tolerance.[5] Direct inhibition of these pathways may result in the development of a spectrum of adverse events of immune-inflammatory nature that are termed immune-related adverse events (irAEs). Although toxicity can affect any organ, the most commonly reported irAEs involve skin, endocrine system, and digestive tract, including the liver.[6] The occurrence of irAEs may have a detrimental impact on the outcomes of patients with cancer due to the life-threatening nature of irAEs and the risk of temporary or permanent discontinuation of life-prolonging treatment.

The incidence of any grade immune-related liver injury (irLI) is estimated to be between 1% and 15% in randomised-controlled trials (RCTs), being higher with combinations of anti-PD-1/PD-L1 plus anti-CTLA-4 or chemotherapy than with monotherapies.[7–9] Clinical presentation is highly heterogeneous ranging from asymptomatic derangement of liver function tests to liver failure and, rarely, death.[10–12]

Incidence of ICI-induced liver injury is variable in patients with HCC and – like other solid tumours – is strongly dependent upon type of drug and treatment regimen, with higher risk being recorded for anti-PD-1/PD-L1 plus anti-CTLA-4.[13,14] However, in patients with a high prevalence of cirrhosis, irLI deserves further attention due to the greater risk of hepatic decompensation, liver failure and death. Unfortunately, RCT data is limited to frequency of irAE and severity according to CTCAE criteria, with little insight into clinical characterisation of irLI, management strategies and impact on clinical outcomes. Moreover, it is unknown whether irLI is more frequent or might have a more severe clinical course in patients with HCC compared to those receiving ICIs for other oncological indications: a point of greater consequence in routine practice and drug development.

To address this gap in knowledge, this study was designed with the aim of comparing incidence, clinical characteristics and outcomes of irLI between two prospective cohorts of patients receiving ICIs for HCC or for other oncological indications.

Patients and methods

HCC cohort

Consecutive patients with unresectable HCC who received atezolizumab plus bevacizumab as routine clinical care in 20 tertiary care centres across Europe, the USA and Asia from January 2019 to January 2023 were enrolled in a prospectively maintained database, as previously described.[15,16] For the aim of this study, we included only patients who received atezolizumab plus bevacizumab as first-line systemic treatment with available data on immune-related liver toxicity. Patients with Child-Pugh class B or C cirrhosis and patients who received combination treatments including anti-CTLA-4 were excluded. Demographic, clinical and biochemical characteristics, including age, sex, Eastern Cooperative Oncology Group-performance status (ECOG-PS), Barcelona Clinic Liver Cancer stage, presence of cirrhosis, aetiology of liver disease, Child-Pugh score, and baseline serum alanine aminotransferase (ALT), alkaline phosphatase, bilirubin, albumin, international normalised ratio (INR) levels and platelet count were recorded. Abnormal baseline ALT and bilirubin levels were defined as levels higher than 1.5x the upper limit of normal (ULN). Atezolizumab and bevacizumab were administered according to the schedule reported in the IMbrave150 RCT.[2] Treatment was administered following a multidisciplinary assessment and according to the local practice of each participating institution. Toxicity management, including dose modifications, was carried out in accordance with the summary of product characteristics for the two agents. Treatment was continued until disease progression or unacceptable toxicity.

INVIDIa-2 cohort

Data on patients treated with ICIs for advanced stage cancers other than HCC were extracted from the INfluenza Vaccine Indication During therapy with ICIs (INVIDIa-2) study database. INVIDIa-2 was a multicentre prospective observational trial aiming to investigate the effectiveness and safety of influenza vaccine administration in patients with advanced cancer undergoing systemic treatment with ICI-based regimens from October 1, 2019, to January 31, 2020, at 82 Italian Oncology Units as previously reported.[17,18] For the aim of this study, we included only patients who received single-agent, first-line, PD-1/PD-L1 checkpoint inhibitor monotherapy with available data on immune-related liver toxicity. Patients who received a combination of two or more immunotherapy agents or chemo-immunotherapy combinations were excluded. Demographic, clinical and biochemical characteristics, including age, sex, ECOG-PS, location of primary tumour, liver metastases, pre-existent chronic liver disease and baseline serum ALT and bilirubin levels were recorded.

Outcomes

The overarching objective of the present study was to describe and evaluate differences in incidence, management strategies and clinical outcomes of irLI experienced during ICI-based treatments across the HCC and the INVIDIa-2 cohorts. To satisfy this aim, we assessed irLI of any grade, grade 1-2 and grade 3-4 separately.

IrLI was defined as an increase in the serum levels of ALT and/or aspartate aminotransferase (AST) deemed to be treatment-related and it was graded according to the National Cancer Institute CTCAE v5.0. In patients with abnormal ALT levels (*i.e.* >1.5x ULN) before treatment, irLI was graded according to the severity of baseline derangement, as reported by CTCAE v5.0 criteria. Attribution of causality of liver toxicity was based on the assessment of treating physicians at each centre and on the exclusion of alternative aetiologies of liver injury, including viral infections (new infection or reactivation from major or minor hepatotropic viruses, including HAV, HBV, HCV, HDV, HEV, CMV, EBV, HSV), active alcohol use disorder, autoimmune aetiology, drugs other than ICIs and disease progression. All HBsAg-positive patients received antiviral treatment with nucleos(t)ide analogues during immunotherapy as per clinical

guidelines. All HBsAg-positive patients who experienced an increase in ALT and/or AST underwent quantitative HBV-DNA assessment to exclude HBV reactivation, while all HBsAg negative, anti-HBc positive patients underwent periodic HBsAg assessment every 3 months.

The primary study endpoint was determination of the exposure-adjusted incidence rate (EAIR) of irLI in the two cohorts. A time-adjusted endpoint was chosen to weight the rate of irLI for the duration of ICI treatment exposure, given the known relationship between incidence of toxicity and duration of ICI exposure.[19]

For the EAIR analysis, treatment exposure was computed considering the time interval between ICI treatment start and the date of irLI occurrence for patients experiencing irLI, and the time interval between ICI treatment start and the date of treatment interruption for patients not experiencing irLI. The treatment exposure interval for patients whose treatment was ongoing at the data cut-off date was censored at the date of last clinical follow-up.

Secondary outcomes included the cumulative rate of irLI, time-to-irLI, duration of irLI, requirement for and duration of systemic corticosteroid treatment, mortality related to irLI and the cumulative rate of other irAEs.

Time-to-irLI was defined as the time interval between the date of ICI treatment start and the date of irLI occurrence. The duration of irLI was defined as the time interval between the date of irLI start and the date of the resolution of irLI to grade ≤1. We explored, in separate analyses, irLI duration among patients who experienced resolution to grade ≤1 only and including all patients by censoring alive patients with unresolved irLI at the date of last clinical follow-up.

In patients with HCC, hepatic decompensation was defined as the occurrence of ascites, portal hypertensive bleeding or hepatic encephalopathy.

IrAEs are considered bona fide pharmacodynamic effects which are known to be associated with improved clinical outcomes across different cancer types, including HCC.[20,21] However, different irAEs may carry differential clinical implications depending on the primary tumour sites and the targeted organs, with skin and thyroid toxicities being among those linked to improved oncological outcomes as opposed to respiratory and liver toxicity, which carry independent negative prognostic impact due to their impact on organ function.[20,22,23] Acknowledging the multifaceted relationship between irAEs and outcomes, we assessed the impact of irLI of any grade, grade 1-2 irLI and grade 3-4 irLI on OS, progression-free survival (PFS) and objective response rate (ORR), comparing patients experiencing irLI with those who experienced no irAEs in each analysis.

OS was calculated from the date of initiation of ICI to the date of death and/or last follow-up. PFS was calculated from the date of initiation of ICI to the date of disease progression and/or death. Patients who did not experience disease progression were censored at the date of last radiological assessment for PFS, while patients alive at the data cut-off date were censored at the date of last clinical follow-up for OS. ORR was defined as the proportion of patients who achieved, as the best response to ICI, a complete or partial response compared to patients who initially experienced stable or progressive disease as measured by RECIST v1.1 criteria.[24] Because emergence of AEs is time-dependent,[25] we further evaluated the association between irLI and risk of death and disease progression/death, considering the development of irLI as a time-varying covariate.

Statistical analysis

Continuous variables were reported as median and range or IQR. Categorical variables were reported as absolute count and percentages. Differences between continuous variables were evaluated with Mann-Whitney *U* test, while differences between categorical variables were evaluated with the $\chi 2$ test.

The outcome of interest (irLI) was reported as frequency and exposure-adjusted incidence rate. Incidence rates per 100 patient-years (PY) were calculated by dividing the total number of patients experiencing irLI events by the sum of all patients' time (in 100 years) of exposure during the treatment period. To compare the EAIR between the two cohorts, a Poisson regression model was used, with number of events as the dependent variable and log (exposure time) as the offset variable. Time to event endpoints, including survival intervals, were computed with the Kaplan-Meier method and compared with the log-rank test. Given the limited sample size of subgroups, the ORRs were reported as crude rates with binomial 95% CIs. Duration of follow-up was calculated according to the reverse Kaplan-Meier method.

Cox proportional-hazards regression was used for the analysis of the risk of death (OS) and the risk of disease progression/death (PFS), and to compute the hazard ratios with 95% CIs. Cox proportional-hazards regression was also used for the time-dependent supplementary analysis. Logistic regression analysis was used for the analysis of ORR and to compute odds ratios (ORs) with 95% CIs.

All *p* values were two-sided and confidence intervals set at the 95% level, with significance pre-defined as <0.05. Analyses were performed using the R-studio software, R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, the MedCalc® Statistical Software version 20 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021) and the SPSS statistics software version 23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp).

Ethical considerations

The study was conducted according to the ethics guidelines in the Declaration of Helsinki. For the HCC cohort, ethical approval to conduct this study was granted following review of the study protocol by the Imperial College Tissue Bank (Reference Number R16008) and locally by the ethical committee of each participating site. For the INVIDIa-2 cohort, Local Institutional Review Board approval was required for each centre for inclusion in the study. Written informed consent was obtained for all prospectively enrolled patients.

Results

Baseline

At the time of data cut-off (15th June 2023), 790 patients treated with atezolizumab plus bevacizumab were included in the HCC cohort. After removing patients not meeting the inclusion criteria (Fig. 1), 375 patients were retained for analyses. Patients' distribution across centres is reported in Table S1.

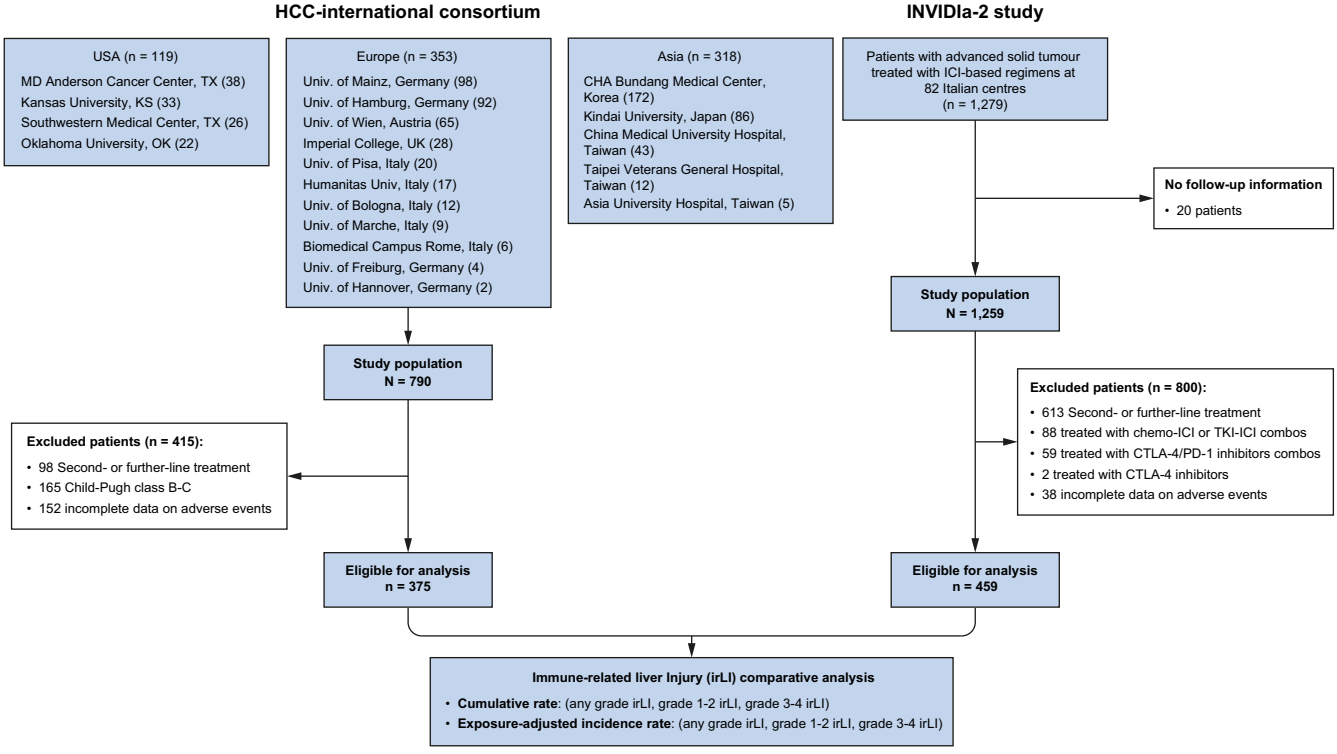

Fig. 1. Flowchart illustrating the patient selection process. Flowchart of the selection process for patients with unresectable HCC treated with first-line atezolizumab plus bevacizumab (HCC cohort) and patients with advanced stage solid tumours other than HCC treated with first-line anti-PD-1/anti-PD-L1 agents (INVIDIa-2 cohort). Anti-PD-1, anti-programmed death-1; anti-PD-L1, anti-programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; irLI, immune-related liver injury; TKI, tyrosine kinase inhibitor.

Table 1 shows the baseline characteristics of these patients: median age was 69.8 years and 78% of patients were male. Most patients (64%) were of ECOG-PS 0 and 62% belonged to Barcelona Clinic Liver Cancer stage C. Cirrhosis was present in 72% of patients and HCV infection was the most common aetiology, in 35% of patients. Most patients had preserved liver function before atezolizumab plus bevacizumab commencement, as shown by bilirubin, albumin and INR levels. Approximately 20% of patients had abnormal ALT levels (*i.e.* >1.5x ULN) at baseline.

The INVIDIa-2 cohort included 1,258 patients treated with ICIs for tumours other than HCC. After removing patients not meeting the inclusion criteria (Fig. 1), 459 patients treated with single-agent, first-line, anti-PD-1/PD-L1 therapy were retained for analyses. Patients' distribution across centres is reported in Table S2. Baseline characteristics of these patients are shown in Table 2. Median age was 71 years, 70% of patients were male and most patients (61%) had ECOG-PS 0. Non-small cell lung cancer and melanoma were the most common tumours in approximately 60% and 25% of patients, respectively, and only 10% of the overall cohort had liver metastases. Baseline bilirubin and ALT levels were within normal range in 98% of patients and only 2% had evidence of pre-existent chronic liver disease. Among immunotherapy treatments, pembrolizumab was used in 92%, nivolumab in 5% and avelumab in 2%.

Outcomes

In the HCC cohort, after a median follow-up time of 9.0 months (95% CI 8.0-10.5), 43 patients (11.4%) experienced any grade irLI, with a median treatment exposure time of 4.4 months (95% CI 3.7-5.2). Grade 3-4 irLI events were observed in 16 (4.3%) patients. As shown in Table 1, no significant differences in baseline characteristics were observed between patients who developed irLI and those who did not, except for AFP levels, which were significantly higher in patients who developed irLI. The proportion of patients with abnormal baseline ALT levels was 25.9% in patients who developed grade 1-2 irLI and 31.2% in patients who developed grade 3-4 irLI. No cases of HBV reactivation or HBsAg seroreversion were observed in patients with HCC.

In the INVIDIa-2 cohort, after a median follow-up time of 19.5 months (95% CI 18.9-19.9), 12 patients (2.6%) experienced any grade irLI, with a median treatment exposure time of 12.4 months (95% CI 11.1-14.0). Grade 3-4 irLI events were observed in 5 (1.1%) patients. No significant differences in baseline characteristics were observed between patients who developed irLI and those who did not (Table 2).

The incidence of other irAEs in the two cohorts is reported in Table 3. Patients in the INVIDIa-2 cohort showed a higher frequency of endocrine, lung and skin irAEs compared to patients with HCC.

Fig. 2 shows the EAIR of irLI in the two cohorts. Exposure-adjusted incidence of any grade irLI was higher in the HCC cohort (22.1 per 100-PY) compared to the INVIDIa-2 cohort (2.1 per 100-PY), as well as for grade 1-2 irLI (14.2 *vs.* 1.2 per 100-PY, respectively) and for grade 3-4 irLI (8.6 *vs.* 0.9 per 100-PY, respectively). irLI events occurred earlier in the HCC cohort compared to the INVIDIa-2 cohort, with a median

Table 1. Baseline characteristics of 375 patients with unresectable/advanced hepatocellular carcinoma treated with atezolizumab plus bevacizumab as first-line systemic therapy, stratified according to the development of irLI.

	Overall, n = 375	No irLI, n = 332 (88.5%)	Any grade irLI, n = 43 (11.5%)	*p* value
Age, (years)				
Median (range)	69.8 (24-89)	70.1 (24-89)	67.4 (39-87)	0.178
Elderly (≥70 yr)	187 (49.9)	169 (50.9)	18 (41.9)	0.265
Sex				
Male	291 (77.6)	255 (76.8)	36 (83.7)	0.307
ECOG-PS				
0	240 (64.0)	208 (62.7)	32 (74.4)	0.131
1	119 (31.7)	110 (33.1)	9 (20.9)	
2	11 (2.9)	10 (3.0)	1 (2.3)	
n.a.	5 (1.3)	4 (1.2)	1 (2.3)	
BCLC				
A	26 (6.9)	25 (7.5)	1 (2.3)	
B	113 (30.1)	94 (28.3)	19 (44.2)	0.625
C	232 (61.9)	209 (63.0)	23 (53.5)	
n.a.	4 (1.1)	4 (1.2)	0 (0.0)	
Portal vein thrombosis	91 (24.2)	81 (24.4)	10 (23.3)	0.261
AFP (ng/ml), median (IQR)	74 (1,742.2)	70.6 (1,656.6)	107.2 (2,996.0)	0.030
Cirrhosis	270 (72.0)	238 (71.7)	32 (74.4)	0.883
Aetiology of liver disease				
HBV	74 (19.7)	66 (19.9)	8 (18.6)	0.844
HCV	131 (34.9)	114 (34.3)	17 (39.5)	0.502
Alcohol	103 (27.5)	88 (26.5)	15 (34.9)	0.252
MASLD	56 (14.9)	48 (14.5)	8 (18.6)	0.473
Other	21 (4.0)	18 (5.4)	3 (7.0)	0.760
Child-Pugh score				
5	219 (58.4)	190 (57.2)	29 (67.4)	0.202
6	156 (41.6)	142 (42.8)	14 (32.6)	
Baseline bilirubin level, >1.5 ULN	24 (6.4)	21 (6.3)	3 (7.0)	0.925
Baseline ALT level, >1.5 ULN	74 (19.7)	62 (18.7)	12 (27.9)	0.341
Baseline albumin levels (g/dl)				
Median (IQR)	3.7 (0.7)	3.7 (0.7)	3.7 (0.7)	0.670
n.a.	3 (0.7)	3 (0.9)	0 (0)	
Baseline INR levels				
Median (IQR)	1.1 (0.2)	1.1 (0.2)	1.1 (0.1)	0.328
n.a.	62 (16.5)	58 (17.5)	4 (6.4)	
Baseline platelet levels (10^9xL)				
Median (IQR)	178 (127)	177 (125)	186 (131)	0.768
n.a.	16 (4.3)	16 (4.8)	0 (0)	

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; BCLC, Barcelona Clinic Liver Cancer; ECOG-PS, Eastern Cooperative Oncology Group-Performance status; INR, international normalised ratio; irLI, immune-related liver injury; MASLD, metabolic dysfunction associated steatotic liver disease; ULN, upper limit of normal.
Continuous variables are reported as median (IQR) and compared by using Mann-Whitney *U* test. Categorical variables are reported as absolute number (percentage) and compared by $\chi 2$ test. *p* values <0.05 were considered statistically significant.

time-to-any grade irLI of 1.4 (range 0.1-25.5) and 4.7 months (range 0.9-12.8), a median time-to-grade 1-2 irLI of 1.8 (range 0.4-24.7) and 3.2 months (range 0.9-12.8), and a median time-to-grade 3-4 irLI of 0.8 (range 0.1-25.5) and 5.3 months (range 2.7-9.0), respectively.

At the time of data cut-off, 31 out of 43 patients (72.1%) who developed irLI in the HCC cohort and 7 out of 12 patients (58.3%) who developed irLI in the INVIDIa-2 cohort experienced resolution to grade ≤1 of irLI ($p = 0.362$). The duration of irLI was longer among patients from the INVIDIa-2 cohort than those from the HCC cohort in both the analyses including only patients who experienced resolution to grade ≤1 (3.6 months [95% CI 0.4–7.9] *vs.* 1.1 months [95% CI 0.7–1.5]) and all the patients who experienced irLI (6.6 months [95% CI 0.4-7.9] *vs.* 0.9 months [95% CI 0.7–1.4]).

Steroid treatment (with doses higher than 10 mg of prednisone or equivalent) was given in 7 out of 43 patients (16.3%) in the HCC cohort and in 9 out of 12 patients (75.0%) in the INVIDIa-2 cohort (p <0.001). Further details on characteristics and duration of steroid treatment are reported in Table S3. Steroid therapy was administered for grade 3-4 irLI events in 5 out of 7 patients in the HCC cohort and in 5 out of 9 patients in the INVIDIa-2 cohort. Median duration of systemic steroids was 2.3 months (95% CI 0.8-4.0) and 1.5 months (95% CI 0.4-4.9) in the HCC and INVIDIa-2 cohorts, respectively.

Resolution without steroids occurred in 26 out of 31 patients (83.9%) whose irLI resolved in the HCC cohort and in 1 out of 7 patients (14.3%) whose irLI resolved in the INVIDIa-2 cohort.

In the HCC cohort, irLI was associated with hepatic decompensation in 3 patients (7.0%) all of whom developed ascites. Overall, irLI resulted in treatment delay in 7 patients (16.3%) and in permanent treatment discontinuation in 3 patients (7.0%). Death with unresolved irLI occurred in 7 (16.3%) and 2 (16.7%) patients in the HCC and INVIDIa-2 cohorts, respectively. No death could be directly attributed to irLI in either cohort.

In the HCC cohort, patients who developed any grade irLI had a median OS of 19.7 months (95% CI 15.0-not reached; 43 events) compared to 15.4 months (95% CI 13.0-19.6; 119 events) in patients who did not experience irAEs (Fig. 3A). The

Table 2. Baseline characteristics of 459 patients with advanced stage solid tumours other than HCC treated with single anti-PD-1/anti-PD-L1 agents as first-line systemic therapy (INVIDIa-2 cohort), stratified according to the development of irLI.

	Total, n = 459	No irLI, n = 447 (97.4%)	Any grade irLI, n = 12 (2.6%)	*p* value
Age, (years)				
Median (range)	71 (20–93)	71 (20–93)	70 (53-92)	0.789
Elderly (≥70 yr)	247 (53.8)	241 (53.9)	6 (50)	
Gender				
Male	323 (70.4)	312 (69.8)	11 (91.7)	0.102
ECOG-PS				0.269
0	280 (61.0)	274 (61.3)	6 (50.0)	
1	150 (32.7)	146 (32.7)	4 (33.3)	
≥2	20 (4.3)	18 (4.0)	2 (16.7)	
n.a.	9 (1.9)	9 (2.0)	—	
Primary tumour				
NSCLC	276 (60.1)	267 (59.7)	9 (75.0)	0.305
Melanoma	131 (28.5)	129 (28.9)	2 (16.7)	
Renal cell carcinoma	16 (3.5)	16 (3.6)	—	
Urothelial	11 (2.4)	11 (2.5)	—	
H&N	7 (1.5)	6 (1.3)	1 (8.3)	
Others	18 (3.9)	18 (4.0)	—	
Liver metastases	47 (10.2)	45 (10.1)	2 (16.7)	0.457
Baseline bilirubin levels				
>1.5x ULN	7 (2.1)	7 (2.2)	—	0.693
n.a.	131 (28.5)	126 (28.2)	5 (41.7)	
Baseline ALT levels				
>1.5x ULN	9 (2.5)	9 (2.6)	—	0.647
n.a.	99 (21.6)	95 (21.2)	4 (33.3)	
Pre-existent liver disease, yes	9 (1.9)	8 (1.8)	1 (8.3)	0.107
HBV	2 (0.4)	1 (0.2)	1 (8.3)	
HCV	3 (0.6)	3 (0.7)	—	
Non-viral	4 (0.9)	4 (0.9)	—	
Anti-PD-1/PD-L1 agents				0.344
Pembrolizumab	424 (92.4)	412 (92.2)	12 (100)	
Nivolumab	24 (5.2)	24 (5.4)	0 (0)	
Avelumab	11 (2.4)	11 (2.4)	0 (0)	

ALT, alanine aminotransferase; anti-PD-1, anti-programmed death-1; anti-PD-L1, anti-programmed death-ligand 1; ECOG-PS, Eastern Cooperative Oncology Group-Performance status; H&N, head and neck; HCC, hepatocellular carcinoma; irLI, immune-related liver injury; NSCLC, non-small cell lung carcinoma; ULN, upper limit of normal.
Continuous variables are reported as median (interquartile range) and compared by using Mann-Whitney *U* test. Categorical variables are reported as absolute number (percentage) and compared by $\chi 2$ test. *P* values <0.05 were considered statistically significant.

Table 3. IrAEs in 375 patients with unresectable/advanced HCC treated with Atezolizumab plus Bevacizumab as first-line systemic therapy (HCC cohort) and in 459 patients with advanced stage solid tumours other than HCC treated with single anti-PD-1/anti-PD-L1 agents as first-line systemic therapy (INVIDIa-2 cohort).

	HCC (n = 375)			Non-HCC (n = 459)		
	Any grade (%)	Grade 1-2 (%)	Grade 3-4 (%)	Any grade (%)	Grade 1-2 (%)	Grade 3-4 (%)
Gastrointestinal	42 (11.2)	33 (8.8)	9 (2.4)	47 (10.2)	37 (8.1)	10 (2.2)
Endocrine	11 (2.9)	10 (2.6)	1 (0.3)	41 (8.9)	39 (8.5)	2 (0.4)
Skin	37 (9.9)	36 (9.6)	1 (0.3)	58 (12.6)	56 (12.2)	2 (0.4)
Lung	3 (0.8)	2 (0.5)	1 (0.3)	15 (3.3)	10 (2.2)	5 (1.1)
Neuromuscolar and rheumatologic	14 (3.7)	11 (2.9)	3 (0.8)	27 (5.9)	26 (5.7)	1(0.2)

Anti-PD-1, anti-programmed death-1; anti-PD-L1, anti-programmed death-ligand 1; HCC, hepatocellular carcinoma; irAEs, immune-related adverse events.
Categorical variables are reported as absolute number (percentage).

emergence of grade 1-2 irLI was significantly associated with longer survival (hazard ratio 0.53, 95% CI 0.29-0.96), while no significant associations were observed between any grade irLI or grade 3-4 irLI and OS. Notably, these results were confirmed also by time-dependent Cox regression analysis (Table 4). Median PFS was 8.0 months (95% CI 4.2-17.6; 28 events) in patients who developed any grade irLI and 7.4 months (95% CI 6.1-8.5; 178 events) in patients who did not experience irAEs (Fig. 3B). No significant associations between any grade irLI, grade 1-2 irLI or grade 3-4 irLI and PFS were observed, including when considering the development of irLI as a time-varying covariate (Table 4). ORRs were 35.9% (95% CI 21.2-52.8), 44.0% (95% CI 24.4-65.1), 21.4% (95% CI 4.6-50.8) and 22.9% (95% CI 17.7-28.9) in patients with any grade irLI, grade 1-2 irLI, grade 3-4 irLI and in those without irAEs, respectively. Grade 1-2 irLI was associated with a significantly higher probability of achieving tumour response (OR 2.64, 95% CI 1.13-6.16), while no significant associations were found for any grade irLI (OR 1.88, 95% CI 0.91-3.87) and grade 3-4 irLI (OR 0.92, 95% CI 0.25-3.40).

In the INVIDIa-2 cohort, 444 and 449 patients were included in the OS and PFS analysis, respectively (none of the excluded patients due to missing follow-up information were among those who experienced irAEs including irLI). Median OS was

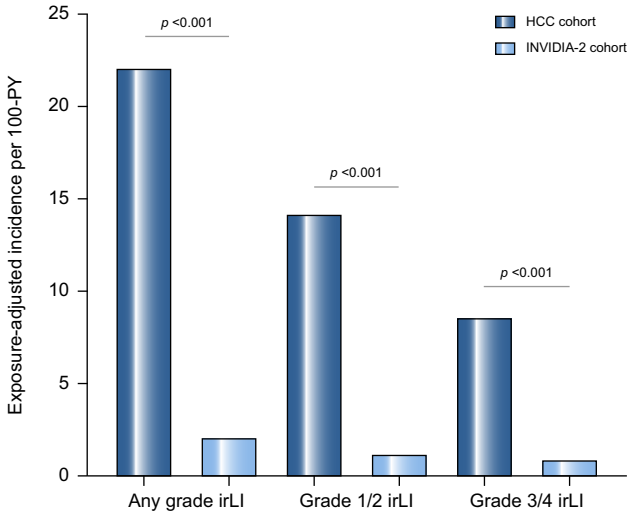

Fig. 2. Exposure-adjusted incidence rate of irLI in patients with HCC and in patients with advanced stage solid tumours other than HCC treated with first-line ICI-based therapy. Columns represent exposure-adjusted incidence rates per 100 patient-years. Exposure-adjusted incidence rates between the two cohorts were compared by using a Poisson regression model, with number of events as the dependent variable and log (exposure time) as the offset variable. *p* values <0.05 were considered statistically significant. HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; irLI, immune-related liver injury; PY, patient-years.

22.7 months (95% CI 16.3-not reached; 5 events) in patients who experienced any grade irLI and 27.9 months (95% CI 18.7-not reached; 101 events) in patients who did not experience irAEs (Fig. 3C). Median PFS was 16.3 months (95% CI 16.2-not reached; 6 events) in patients who experienced any grade irLI and 12.6 months (95% CI 9.4-18.3; 141 events) in patients who did not experience irAEs (Fig. 3D). No significant associations between any grade irLI, grade 1-2 irLI or grade 3-4 irLI and OS or PFS were observed, including when considering the development of irLI as a time-varying covariate (Table 4). ORRs were 72.7% (95% CI 39.1-93.9), 66.7% (95% CI 22.2-95.7), 80.0% (95% CI 28.3-99.5) and 35.3% (95% CI 29.0-41.2) in patients with any grade irLI, grade 1-2 irLI, grade 3-4 irLI and in those without irAEs, respectively. IrLi of any grade (OR 4.89, 95% CI 1.26-18.97) were associated with a significantly higher probability of achieving tumour response, while no associations were found for grade 1-2 irLI (OR 3.67, 95% CI 0.65-20.48) and grade 3-4 irLI (OR 7.34, 95% CI 0.80-66.81).

Discussion

IrLI during treatment with ICIs is relatively common in patients with cancer.[7] Although often identified because of elevation in ALT/AST levels, correct identification remains challenging since no specific diagnostic criteria exist and a definitive diagnosis is mainly based on the exclusion of alternative causes of liver injury.[26]

IrLI is particularly relevant in patients with HCC due to the high proportion of patients with pre-existing liver dysfunction. The high proportion of patients who present with higher baseline ALT/AST levels is a challenge to an accurate diagnosis of irLI. In addition, the onset of irLI may negatively impact oncological outcomes, resulting in treatment discontinuation and the need for high-dose steroid use, a universally advocated disease-modifying therapy which may cause long-term sequelae from metabolic disturbances and immunosuppression.

Our study shows that irLI occurred in 11.5% of patients with HCC and in only 2.6% of patients with advanced stage solid tumours, rates that are superimposable to those reported in IMbrave150 for HCC (2, 3), and in meta-analyses inclusive of solid tumours (2%).[7] Moreover, our results are similar to those reported in a recent cohort study of 1,500 patients with cancer treated with ICIs, where higher rates of hepatic AEs were observed in patients with liver cancer compared to those with non-hepatic primary malignancies.[27]

As expected, the two cohorts we compared were different in terms of baseline characteristics. Patients with HCC had a higher prevalence of cirrhosis and a higher prevalence of abnormal liver function tests at the time of treatment initiation compared with patients with tumours other than HCC. Conversely, patients from the INVIDIa-2 cohort had a lower proportion of intrahepatic tumour burden, with only 10% prevalence of liver involvement at the time of treatment initiation. Intrinsic differences in baseline characteristics and differential responsiveness to ICIs are likely determinants of the difference in the median duration of treatment exposure: three times shorter in patients with HCC compared with patients with other tumours (4 *vs.* 12 months).

Despite this difference, we confirmed a 10-fold higher incidence and earlier onset of irLI in patients with HCC *vs.* those with non-hepatic primary malignancies after adjustment for the duration of treatment exposure, with adjusted incidence rates of 22.1 and 2.1 per 100-PY, respectively. Acknowledging the difference between the two cohorts, this is the first study that, to the best of our knowledge, provides clear estimates of a treatment exposure-adjusted comparison for the incidence of irLI in patients with HCC and in those with other advanced stage cancers.

The prospective design of the two cohorts we evaluated allowed us to assess clinically relevant characteristics related to irLI, in terms of its duration, management, impact on treatment discontinuation, liver decompensation and mortality.

Despite the higher incidence observed in patients with HCC, irLI was associated with resolution in more than 70% of patients, with only 16% of patients with HCC receiving steroid treatment, mostly due to grade 3-4 events. Moreover, we found that up to 80% of patients with HCC who experienced resolution of irLI did not receive steroid treatment. The lower use of steroids in patients with HCC compared to those with other advanced stage tumours probably reflects the propensity of treating physicians to avoid steroid treatment in patients with advanced chronic liver disease or cirrhosis. In addition to the potential detrimental effect on the antitumor efficacy of ICIs, the use of steroids in patients with cirrhosis could be associated with a potential increase in the risk for infections, as previously demonstrated in patients with tumours other than HCC receiving high-dose steroids for irAEs [28] and its safety in this setting remains to be explored.[29]

Another practice-informing message emerging from our study is that efficacy outcomes were not negatively affected by the development of irLI. In fact, hepatic decompensation, a driver of mortality in these patients competing with cancer progression[30,31] occurred only in 7% of patients with HCC who experienced irLI. Permanent treatment discontinuations due to irLI were also low at 7%.

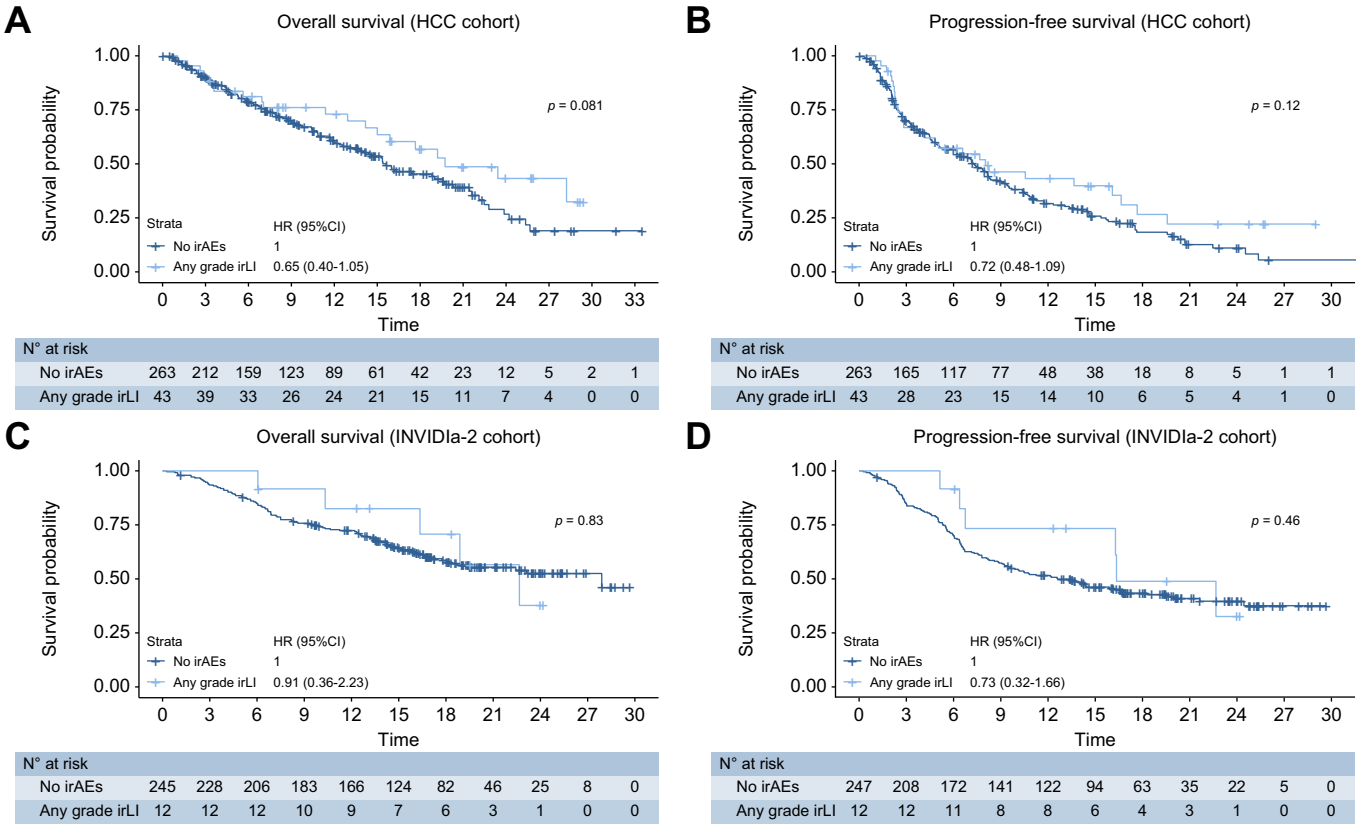

Fig. 3. Kaplan Meier survival estimates according to the experience of any grade irLI across the HCC and the INVIDIa-2 cohort HCC cohort. (A) OS; patients who experience any grade irLI, median 19.7 months (95% CI 15.0-not reached; 43 events) *vs.* patients who experience no irAEs, median 15.4 months (95% CI 13.0-19.6; 119 events); (B) PFS; patients who experience any grade irLI, median 8.0 months (95% CI 4.2-17.6; 28 events) *vs.* patients who experience no irAEs, median 7.4 months (95% CI 6.1-8.5; 178 events). INVIDIa-2 cohort. (C) OS; patients who experience any grade irLI, median 22.7 months (95% CI 16.3-not reached; 5 events) *vs.* patients who experience no irAEs, median 27.9 months (95% CI 18.7-not reached; 101 events); (D) PFS; patients who experience any grade irLI, median 16.3 months (95% CI 16.2-not reached; 6 events) *vs.* patients who experience no irAEs, median 12.6 months (95% CI 9.4-18.3; 141 events). Due to missing follow-up information, 444 and 449 patients from the INVIDIa-2 cohort were respectively included in the OS and PFS analysis; none of the excluded patients experienced irAEs, including irLI. OS and PFS were calculated according to Kaplan-Meier method and statistical significance was tested using log-rank test (*p* values shown in plot). *p* values <0.05 were considered statistically significant. irAEs, immune-related adverse events; irLI, immune-related liver injury; OS, overall survival; PFS, progression-free survival.

When evaluating the association between the development of irLI and efficacy outcomes in HCC, we found that patients with grade 1-2 irLI had significantly longer OS in time-adjusted analysis and a significantly higher probability of achieving ORR compared to patients who did not develop irAEs. Conversely, both OS and ORR were not significantly different when stratifying patients according to the development of any grade irLI or grade 3-4 irLI. Overall, these results are in line with those of previously published studies[21 32,33] and a recently presented exploratory analysis of the HIMALAYA study,[34] demonstrating the positive association between treatment-emerging adverse events, particularly irAEs, and treatment efficacy in patients with HCC.

However, these findings also pose a relevant question regarding the biological and clinical significance of mild increases in liver cytolytic enzymes during ICI treatment in patients with HCC. It could be speculated that, rather than the expression of immune-related liver toxicity, a mild increase in aminotransferase levels could occur as a result of tumour cells lysis in patients responding to ICIs, as suggested by the significant association we found between grade 1-2 irLI and ORR. Alternatively, other possible mechanisms could be related to a higher T-cell infiltration, leading to an overproduction of proinflammatory cytokines by intrahepatic immune cells, as previously suggested by data from a clinical trial evaluating tremelimumab in patients with active HCV infection.[35] Interestingly, we found that patients with HCC who developed liver injury had significantly higher baseline AFP levels, leading us to speculate whether the higher expression of this recognised tumour-associated antigen may be somewhat linked to the poorly understood relationship between ALT elevation and response.

In the absence of translational analyses on patients' T-cell responses, which could be the aim of future studies, our results underline that the mere increase of ALT and/or AST in patients with HCC superimposed on cirrhosis receiving ICIs might represent an imperfect diagnostic tool to correctly identify immune-related toxicity. Equally, our data support the view that a conservative wait-and-see strategy or temporary treatment delay represent a reasonable choice in patients developing a mild increase (*i.e.* grade 1-2) of aminotransferase levels during ICI treatment, sparing patients from unnecessary steroid therapy without compromising efficacy outcomes.

We acknowledge several limitations to our study. First, it should be emphasised that a comparative study of this kind,

Table 4. Association between irLI and risk of progression/death or risk of death.

	HCC cohort		INVIDIA-2	
	Risk of disease progression/death, HR (95% CI)	**Risk of death, HR (95% CI)**	**Risk of disease progression/death, HR (95% CI)**	**Risk of death, HR (95% CI)**
All grade irLI Yes *vs.* No irAEs	0.72 (0.48-1.09)	0.65 (0.40-1.05)	0.73 (0.32-1.66)	0.91 (0.36-2.23)
G1/G2 irLI Yes *vs.* No irAEs	0.61 (0.36-1.03)	0.53 (0.29-0.96)	0.59 (0.18-1.78)	0.58 (0.14-2.36)
G3/G4 irLI Yes *vs.* No irAEs	0.93 (0.52-1.69)	0.94 (0.45-1.93)	1.05 (0.33-3.29)	1.46 (0.46-4.6)
	Time-adjusted risk of disease progression/death, HR (95% CI)	**Time-adjusted risk of death, HR (95% CI)**	**Time-adjusted risk of disease progression/death, HR (95% CI)**	**Time-adjusted risk of death, HR (95% CI)**
All grade irLI Yes *vs.* No irAEs	0.75 (0.50-1.11)	0.66 (0.41-1.07)	1.01 (0.32-3.19)	0.86 (0.21-3.52)
G1/G2 irLI Yes *vs.* No irAEs	0.63 (0.37-1.05)	0.53 (0.29-0.97)	1.53 (0.38-6.22)	2.46 (0.78-7.81)
G3/G4 irLI Yes *vs.* No irAEs	0.95 (0.53-1.70)	0.81 (0.39-1.67)	1.17 (0.47-2.87)	1.41 (0.57-3.48)

Anti-PD-1, anti-programmed death-1; anti-PD-L1, anti-programmed death-ligand 1; HCC, hepatocellular carcinoma; HR, hazard ratio; irAEs, immune-related adverse events; irLI, immune-related liver injury.
Association between irLI and risk of progression/death or risk of death in patients with unresectable/advanced HCC treated with atezolizumab plus bevacizumab as first-line systemic therapy (HCC cohort) and in patients with advanced stage solid tumours other than HCC treated with single anti-PD-1/anti-PD-L1 agents as first-line systemic therapy (INVIDIa-2 cohort), by Cox regression model and by Cox time-dependent regression model with irLI as a time-varying covariate.

although balanced in terms of treatment line and patients' staging relies on the comparison of two cohorts of patients with intrinsically different baseline features and treatment characteristics. The INVIDIa-2 dataset included patients with exquisitely immunogenic tumours including PD-L1-overexpressing non-small cell lung cancer and malignant melanoma: two oncological diagnoses where PD-1 blocking agents are characterised by higher response rates and potential for long-term survivorship. In addition to that, INVIDIa-2 assessed patients receiving ICIs with an enrolment window ranging from October 2019 to January 2020, however, patients who had started the ICI treatment up to May 2019 were allowed to enter the study, creating therefore a further positive selection of the study population. Secondly, differences in treatment regimens should also be considered as a key difference amongst groups. Patients with tumours other than HCC received single-agent anti-PD-1/PD-L1 treatment, while those with HCC received anti-PD-L1 plus VEGF combination treatment. However, bevacizumab does not cause direct liver injury,[36] leading to a low risk in overestimation of the incidence of irLI in patients with HCC. With bevacizumab being a highly uncommon cause of drug-induced liver injury, the potential for a relationship between bevacizumab exposure and liver decompensation is improbable and remains to be established in future studies. Thirdly, because the HCC and INVIDIa-2 cohorts were accrued with different primary research questions, types of corticosteroids utilized could be reconstructed only for patients with HCC. Whilst a pairwise comparison of types of corticosteroids utilized to treat irLi was not possible, our choice to compare rates of steroid utilization based on a 10 mg prednisone dose reflects a commonly used threshold utilized in the reporting of clinical trials, including landmark immunotherapy studies in HCC.[2,4,14] Finally, this is a real-world study conducted in multiple sites in different countries, lacking central adjudication of toxicity outcomes, with management of irLI that could have been different according to local clinical practice, especially in terms of criteria for administering steroid treatment. Reporting of irAEs, including irLI, was not a primary endpoint for the INVIDIa-2 cohort. Therefore, the inter-rater heterogeneity in outcome definitions and in the management of irLI could be difficult to explore and to explain. Moreover, as for all studies conducted in a real-world setting, the quality of data registration cannot be as high as in RCTs, as also demonstrated by the exclusion of patients due to incomplete data on adverse events in both cohorts.

In conclusion, this prospective comparative international multicentre study of patients with advanced stage solid tumours treated with first-line ICI-based treatment demonstrated that irLI is significantly more common and it occurs earlier in patients with HCC compared to patients with other tumours, although it does not negatively affect the outcomes of these patients in terms of need for steroid treatment, hepatic decompensation, treatment discontinuation and efficacy outcomes. Finally, our results underline the need for a multidisciplinary management of patients treated with ICIs, requiring an integrated collaboration between specialties involved in liver cancer management in order to optimize the management of side effects of ICI treatments and to improve patient outcomes.

Affiliations

[1]Department of Surgery & Cancer, Imperial College London, Hammersmith Hospital, Du Cane Road, W120HS London, UK; [2]Gastroenterology and Hepatology Unit, Department of Health Promotion, Mother & Child Care, Internal Medicine & Medical Specialties, University of Palermo, Italy; [3]Operative Research Unit of Oncology, Fondazione Policlinico Universitario Campus Bio-Medico, Via Alvaro del Portillo, 200 - 00128 Roma, Italy; [4]Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; [5]Division of Oncology, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy; [6]Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka, Japan; [7]Department of Medicine, Division of Hematology/Oncology, Tisch Cancer Institute, Mount Sinai Hospital, New York, NY, USA; [8]Department of Medicine, Division of Hematology & Oncology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA; [9]Department of Medicine, Division of Medical Oncology, Kansas University Cancer Center, Kansas City,

Kansas, USA; [10]Medical Oncology, Department of Internal Medicine, CHA Bundang Medical Center, CHA University, Seongnam, Korea; [11]Healthcare and Services Center, Taipei Veterans General Hospital, Taipei, Taiwan; Division of Gastroenterology and Hepatology, Taipei Veterans General Hospital, Taipei, Taiwan; Institute of Clinical Medicine, Faculty of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan; [12]Division of Gastroenterology and Hepatology, Taipei Veterans General Hospital, Taipei, Taiwan; Faculty of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan; [13]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA; [14]Section of Gastroenterology, Hepatology & Nutrition, The University of Chicago Medicine 5841 S. Maryland Ave, 60637 Chicago, IL, USA; [15]Unit of Medical Oncology 2, Azienda Ospedaliero- Universitaria Pisana, Pisa, Italy; [16]Scuola Superiore Sant'Anna Pisa, Interdisciplinary Research Center "Health Science", Pisa, Italy; [17]Department of Medicine II (Gastroenterology, Hepatology, Endocrinology and Infectious Diseases), Freiburg University Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany; [18]Hannover Medical School, Hannover, Germany; [19]Longo Family Chair in Liver Cancer Research, Division of Gastroenterology and Hepatology, Toronto General Hospital, Medical Oncology, Princess Margaret Cancer Centre, Schwartz Reisman Liver Research Centre, Toronto, Canada; [20]Department of Oncology, Hematology and Bone Marrow Transplantation with Section of Pneumology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [21]Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [22]University Medical Center Mainz, Department of Internal Medicine I, Mainz, Germany; [23]Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, 20072 Pieve Emanuele, Milan, Italy; [24]Medical Oncology and Hematology Unit, Humanitas Cancer Center, IRCCS Humanitas Research Hospital, Via Manzoni 56, 20089 Rozzano, Milan, Italy; [25]Medical Oncology/TSET Phase 1 Program, Stephenson Cancer Center, University of Oklahoma, Oklahoma City; [26]Department of Oncology, Università Politecnica delle Marche, Azienda Ospedaliero-Universitaria delle Marche, 60126 Ancona, Italy; [27]Center for Digestive Medicine, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan; [28]Department of Medical and Surgical Sciences, University of Bologna, Italy; [29]SS. Oncologia Genitourinaria, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; 30. Medical Oncology Unit, Sant'Andrea Hospital, Roma, Italy; [31]Medical Oncology, Santa Chiara Hospital, Trento, Italy; [32]Medical Thoracic Oncology Unit, IRCCS Istituto Tumori "Giovanni Paolo II", Bari, Italy; [33]Department of Oncology, San Bortolo General Hospital, Vicenza, Italy; [34]SC Oncologia, AO SS Antonio e Biagio e C. Arrigo, Alessandria, Italy; [35]UC Oncologia Medica Uro-Ginecologica, Istituto Nazionale Tumori "Fondazione G. Pascale", IRCCS, Napoli, Italy; [36]Dipartimento di Oncologia, Presidio Ospedaliero Universitario Santa Maria della Misericordia, Azienda sanitaria universitaria integrata Friuli Centrale, Udine, Italy; [37]Medical Oncology Unit, University Hospital Careggi, Firenze, Italy; [38]Medical Oncology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [39]Oncology Department, Ospedali Riuniti Villa Sofia Cervello, Palermo, Italy; [40]UOC Oncologia di Belluno, Dipartimento di Oncologia Clinica, AULSS 1 Dolomiti, Ospedale S.Martino, Belluno, Italy; [41]Department of Biotechnological and Applied Clinical Sciences, St Salvatore Hospital, University of L'Aquila, L'Aquila, Italy; [42]U.O.C. Oncologia, Istituto Dermopatico dell'Immacolata IDI-IRCCS, Roma, Italy; [43]UOC Oncologia, Ospedale Generale Provinciale di Macerata, ASUR Marche Area Vasta 3, Macerata, Italy; [44]Medical Oncology Unit, Papa Giovanni XXIII Hospital, Bergamo, Italy; [45]Medical Oncology Department, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [46]Medical Oncology Unit, ARNAS Garibaldi, Catania, Italy; [47]Medical Oncology Unit, University Hospital of Modena e Reggio Emilia, Italy; [48]Medical Oncology Unit, AUSL-IRCCS of Reggio Emilia, Reggio Emilia, Italy; [49]Medical Oncology, San Camillo Forlanini Hospital, Roma, Italy; [50]Medical Oncology, Ospedale Generale Regionale F Miulli, Acquaviva delle Fonti, Puglia, Italy; [51]Dipartimento di Discipline Chirurgiche, Oncologiche e Stomatologiche, Università degli Studi di Palermo, Palermo, Italy; [52]Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy; [53]Oncologia Medica, ASL di Piacenza, Piacenza, Italy; [54]Medical Oncology, Camposampiero Hospital, AULSS 6 Euganea, Padova, Italy; [55]UOC Oncologia, Ospedale Monaldi, Azienda Ospedaliera Specialistica dei Colli, Napoli, Italy; [56]Medical Oncology Unit, Medicine and Surgery Department, University of Parma, Parma, Italy

Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EAIR, exposure-adjusted incidence rate; ECOG-PS, Eastern Cooperative Oncology Group-performance status; ICIs, immune checkpoint inhibitors; INR, international normalised ratio; irAEs, immune-related adverse events; irLI, immune-related liver injury; OR, odds ratio; ORR, objective response rate; OS, overall survival; PD-1, programmed death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PY, patient-years; RCT, randomised-controlled trials; ULN, upper limit of normal.

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Conflicts of interest

CiC received speaker fees and advisory board honoraria from AstraZeneca, Eisai, Merck Sharp & Dohme, Ipsen and travel support from Roche. GC received has served as a consultant or on advisory boards for Bayer, Eisai, Ipsen, MSD, AstraZeneca, Roche. AD received educational support for congress attendance from Roche. JvF received advisory board fees from Roche. HW received lecture fees and advisory board honoraria from Roche, Bayer, Ipsen, Eisai, BMS. PRG reports a consulting or advisory role and received honoraria from AdaptImmune, AstraZeneca, Bayer, Bristol Myers Squibb, Eisai, Ipsen, Lilly, Merck Sharp & Dohme, Roche, and Sirtex; has been on a speakers bureau for AstraZeneca, Bayer, Bristol Myers Squibb, Eisai, Ipsen, Lilly, Merck Sharp & Dohme, Roche, and Sirtex; has received research funding from Bayer and Roche; has provided expert testimony for Lilly; and has received travel or accommodation expenses from AstraZeneca, Bayer, Bristol Myers Squibb, Eisai, Ipsen, Lilly, and Roche. AV reports honoraria for speaker, consultancy and advisory role from Roche, AstraZeneca, EISAI, Bayer, Merck, Bristol Myers Squibb, Merck Sharp & Dohme, Incyte, PierreFabre, Ipsen, and Sanofi. BSc received travel support from Gilead, Ipsen and AbbVie. SU reports advisory role for Eisai, Astra Zeneca, IgM biosciences and received institutional support for research, all funds to institution, from AbbVie, Inc, Adlai Nortye, ArQule, Inc, AstraZeneca, Atreca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene Corporation, Ciclomed LLC, Erasca, Evelo Biosciences, Inc., Exelexis, G1 Therapeutics, Inc, GlaxoSmithKline GSK, IGM biosciences, Incyte, Isofol, Klus Pharma, Inc., Macrogenics, Merck Co. Inc, Mersana Therapeutics, OncoMed Pharmaceuticals, Inc. Pfizer, Regeneron, Inc., Revolution Medicines, Inc., Synermore Biologics Co, Takeda, Tarveda Therapeutics, Tesaro, Tempest, Vigeo Therapeutics Inc. LR received consulting fees from AstraZeneca, Basilea, Bayer, BMS, Eisai, Exelixis, Genenta, Hengrui, Incyte, Ipsen, IQVIA, Jazz Pharmaceuticals, MSD, Nerviano Medical Sciences, Roche, Servier, Taiho Oncology, Zymeworks; lecture fees from AstraZeneca, Bayer, BMS, Eisai, Incyte, Ipsen, Merck Serono, Roche,Servier; travel expenses from AstraZeneca; and institutional research funding from Agios, AstraZeneca, BeiGene, Eisai, Exelixis, Fibrogen, Incyte, Ipsen, Lilly, MSD, Nerviano Medical Sciences, Roche, Zymeworks. AGS has served on advisory boards or as consultant for Genentech, AstraZeneca, Eisai, Bayer, Exelixis, BMS, Roche, Glycotest, Exact Sciences, FujiFilm Medical Sciences, GRAIL. MS received accommodation expenses from Janssen, Ipsen, BMS, Astellas, Pfizer and personal fees from Janssen. PE received honoraria speaker from MSD, BMS, Astellas and Gentili and served on advisory board for Ipsen and MSD. ER had a role as consultant for Bristol Myers Squibb, MSD, Novartis, Pierre Fabre, Immunocore and Pfizer. MB was hired as employee of Pfizer Srl after the paper was drafted and concluded. AC received grants for consultancies/advisory boards from BMS, MSD, OncoC4, IQVIA, Roche, GSK, AstraZeneca, Access Infinity, Ardelis Health and AlphaSight. He also received speaker fees from AstraZeneca, EISAI, Pierre-Fabre, MSD. DJP received lecture fees from ViiV Healthcare, Bayer Healthcare, BMS, Roche, Eisai, Falk Foundation, travel expenses from BMS and Bayer Healthcare; consulting fees for Mina Therapeutics, EISAI, Roche, DaVolterra, Mursla, Exact Sciences and

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

Authors' contributions

Study concept and design: CiC, GC, AC, DJP. Analysis and interpretation of data: CiC, GC, AC, DJP. Statistical analyses: CiC, AC. Supervision: AC, DJP. Drafting of the manuscript: CiC, AC, DJP. All the authors were involved in data acquisition and critical revision of the manuscript and they all approved the final version of the manuscript.

Data availability statement

Data, analytic methods and study materials will be made available to other researchers upon reasonable request.

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Supplementary data

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Author names in bold designate shared co-first authorship

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Supplemental information

Characteristics and outcomes of immunotherapy-related liver injury in patients with hepatocellular carcinoma versus other advanced solid tumours

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Table S1. Patients disposition across centres participating in AB-real cohort.

AB-real cohort, Centre	Number	(%)
Kindai University Faculty of Medicine, Osaka, Japan	82	21.9
University Medical Center Mainz, Mainz, Germany	63	16.8
University Medical Center Hamburg-Eppendorf, Hamburg, Germany	50	13.3
Medical University of Vienna, Vienna, Austria	43	11.5
China Medical University Hospital, Taichung, Taiwan	28	7.5
Imperial College, London, United Kingdom	23	6.1
Kansas University Cancer Center, Kansas City, USA	19	5.1
Azienda Ospedaliero- Universitaria Pisana, Pisa, Italy	19	5.1
IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy	17	4.5
IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy	11	2.9
Azienda Ospedaliero-Universitaria delle Marche, Ancona, Italy	7	1.9
Taipei Veterans General Hospital, Taipei, Taiwan	7	1.9
Campus Bio-Medico, Roma, Italy	2	0.5
Freiburg University Medical Center, Freiburg, Germany	2	0.5
Hannover Medical School, Hannover, Germany	1	0.3
University of Texas Southwestern Medical Center, Dallas, USA	1	0.3
Total	375	100.0%

Table S2. Patients disposition across centres participating in INVIDIa-2 cohort.

INVIDIa-2 cohort, Centre	Number	(%)
Azienda Ospedaliero Universitaria di Parma	26	5.7%
IRCCS Istituto Nazionale Tumori, Milano	24	5.2%
Presidio Ospedaliero S Andrea, Roma	20	4.4%
Ospedale Civile S. Chiara, Trento	19	4.1%
IRCCS Giovanni Paolo II, Oncologia Toracica, Bari	18	3.9%
Ospedale San Bortolo, Vicenza	17	3.7%
ASO SS Antonio Biagio Arrigo - Alessandria	16	3.5%
IRCCS Istituto Nazionale Tumori Pascale, Napoli	16	3.5%
Azienda Ospedaliera Santa Maria della Misericordia, Udine	15	3.3%
Azienda Ospedaliera Universitaria Careggi, Oncologia Medica, Firenze	14	3.1%
IRCCS Policlinico Agostino Gemelli, Roma	13	2.8%
Ospedale Villa Sofia-Cervello, Palermo	13	2.8%
Ospedale S Martino, Belluno	12	2.6%
Ospedale S. Salvatore, L-Aquila	9	2.0%
Istituto Dermopatico dell'Immacolata (IDI), Roma	9	2.0%
Ospedale Generale di Macerata	9	2.0%
ASST Papa Giovanni XXIII, Ospedale di Bergamo	8	1.7%
IRCCS Ospedale Maggiore Ca Granda, Milano	8	1.7%
Presidio Ospedaliero Garibaldi-Nesima, Catania	8	1.7%
Azienda Ospdaliero Universitaria di Modena	8	1.7%
IRCCS Azienda Ospedaliera di Reggio Emilia	8	1.7%
Ospedale San Camillo-Forlanini, Roma	8	1.7%
Ospedale Generale Regionale "F. Miulli" - Acquaviva delle Fonti	7	1.5%
AOU P. Giaccone, Palermo	7	1.5%
IRST Amadori, Meldola	7	1.5%
Ospedale Guglielmo da Saliceto, Piacenza	7	1.5%
Ospedale di Camposampiero	6	1.3%
AOU dei Colli, Monaldi, Napoli	6	1.3%
Centro di Riferimento Oncologico (CRO), Aviano	5	1.1%
IRCCS Giovanni Paolo II, Oncologia Tumori Cutanei, Bari	5	1.1%
Ospedale Sacro Cuore di Gesu Fate Bene Fratelli, Benevento	5	1.1%
Azienda Ospedaliera Universitaria Careggi, Radioterapia Oncologica, Firenze	5	1.1%
Ospedale Di Guazzalla	5	1.1%
IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy	5	1.1%
Ospedale Vito Facci, Lecce	5	1.1%
Azienda Ospedaliera Odrine Mauriziano, Torino	5	1.1%
Ospedale SS Cosma e Damiano, Pescia	5	1.1%
IRCCS S Martino, Genova	5	1.1%
Ospedale di Alba-Bra	4	0.9%
Ospedale di Carpi	4	0.9%
Ospedale Papa Giovanni XXIII, Bari	4	0.9%
Ospedale della Versilia, Lido di Camaiore	4	0.9%
AULSS3 Serenissima, Mirano	4	0.9%
IRCCS Sacro Cuore, Don Calabria, Negrar	4	0.9%
Fondazione Poliambulanza, Brescia	4	0.9%
Azienda Ospedaliera S. Maria, Terni	4	0.9%
AOU Mater Domini, Catanzaro	3	0.7%
Ospedale Engles Profili, Fabriano	3	0.7%
IRCCS Maugeri, Pavia	3	0.7%
Presidio Ospedaliero di Saronno	3	0.7%
Nuovo Ospedale Civile di Sassuolo	3	0.7%
Ospedale Maggiore di Trieste	3	0.7%
Presidio Ospedaliero di Brindisi	2	0.4%

Humanitas Cliniche Gavezzeni, Bergamo	2	0.4%
Ospedale San Luca, Lucca	2	0.4%
AOU San Luigi Gonzaga, Orbassano	2	0.4%
Ospedale del Mare, Napoli	2	0.4%
Ospedale San Salvatore ed Ospedale Santa Croce, Pesaro/Fano	2	0.4%
Ospedale S Camillo, Rieti	2	0.4%
Azienda Ospedaliero Universitaria di Verona	2	0.4%
ASST Franciacorta – Chiari, Brescia	1	0.2%
Fondazione Policlinico Campus Bio-Medico	1	0.2%
Istituti Ospidalieri Cremona	1	0.2%
Ospedale di Faenza	1	0.2%
Ospedale Mater Salutis, ULSS9, Scagliera	1	0.2%
Total	459	100.0%

Table S3. Characteristics of corticosteroid therapy for treating immune-related liver injury in 7 patients with hepatocellular carcinoma treated with Atezolizumab+Bevacizumab

AB-real cohort			
Patient	Drug name	Maximum dosage (mg)	Duration of treatment (months)
1	Prednisolone	80	2.3
2	Prednisolone	60	2.2
3	Prednisolone	120	2.4
4	Methylprednisolone	32	0.7
5	Methylprednisolone	125	2.4
6	Prednisolone	30	4.4
7	Prednisolone	40	1.4