World Journal of Hepatology

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World J Hepatol 2022 July 27; 14(7): 1438-1458

DOI: 10.4254/wjh.v14.i7.1438

ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Observational Study

Polymorphism AGT2 (rs4762) is involved in the development of dermatologic events: Proof-of-concept in hepatocellular carcinoma patients treated with sorafenib

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Specialty type: Oncology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Cheng H, China; Sahin TT, Turkey
A-Editor: Vasudevan A

Received: November 9, 2021
Peer-review started: November 9, 2021
First decision: January 9, 2022
Revised: January 24, 2022
Accepted: July 6, 2022
Article in press: July 6, 2022
Published online: July 27, 2022

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Abstract

BACKGROUND

Dermatologic adverse events (DAEs) are associated with a better outcome in patients with hepatocellular carcinoma (HCC) irrespective of the therapeutic agent received. The exact mechanisms associated with the development of DAEs are unknown although several studies point to direct toxicity of tyrosine kinase inhibitors (TKIs) to the skin or an immune-mediated reaction triggered by the oncologic treatment. As is the case in other conditions, individual genetic variants may partially explain a higher risk of DAEs.

AIM

To evaluate the contribution of several gene variants to the risk of developing DAEs in HCC patients treated with TKIs.

METHODS

We first analyzed 27 single-nucleotide polymorphisms (SNPs) from 12 genes selected as potential predictors of adverse event (AE) development in HCC patients treated with sorafenib [Barcelona Clinic Liver Cancer 1 (BCLC1) cohort]. Three additional cohorts were analyzed for *AGT1* (rs699) and *AGT2* (rs4762) polymorphisms-initially identified as predictors of DAEs: BCLC2 (n = 79), Northern Italy (n = 221) and Naples (n = 69) cohorts, respectively. The relation between SNPs and DAEs and death were assessed by univariate and multivariate Cox regression models, and presented with hazard ratios and their 95% confidence intervals (95%CI).

RESULTS

The BCLC1 cohort showed that patients with arterial hypertension (AHT) (HR = 1.61; P value = 0.007) and/or *AGT* SNPs had an increased risk of DAEs. Thereafter, *AGT2* (rs4762) AA genotype was found to be linked to a statistically significant increased probability of DAEs (HR = 5.97; P value = 0.0201, AA *vs* GG) in the Northern Italy cohort by multivariate analysis adjusted for BCLC stage, ECOG-PS, diabetes and AHT. The value of this genetic marker was externally validated in the cohort combining the BCLC1, BCLC2 and Naples cohorts [HR = 3.12 (95%CI: 1.2-8.14), P value = 0.0199, *AGT2* (rs4762) AA *vs* AG genotype and HR = 2.73 (95%CI: 1.18-6.32) P value = 0.0188, *AGT2* (rs4762) AA *vs* GG genotype]. None of the other gene variants tested were found to be associated with the risk of DAE development.

CONCLUSION

DAE development in HCC patients receiving TKIs could be explained by the *AGT2* (rs4762) gene variant. If validated in other anti-oncogenic treatments, it might be considered a good prognosis

marker.

Key Words: HCC; Early DAE; Single-nucleotide polymorphisms; *AGT1* (rs699); *AGT2* (rs4762), Tyrosine kinase inhibitors

Core Tip: Dermatologic adverse events (DAEs) are associated with a better outcome in patients with hepatocellular carcinoma (HCC) irrespective of the therapeutic agent received. Our study shows that DAE development in these patients can be explained by individual genetic variants in the *AGT2* gene. *AGT2* (rs4762) AA genotype was associated with DAE risk in the Northern Italy cohort and was externally validated in a cohort combining the BCLC1, BCLC2 and Naples cohorts. Therefore, DAE development in HCC patients receiving TKIs can be explained by the *AGT2* (rs4762) gene variant. If validated in other anti-oncogenic treatments, it might be considered a good prognosis marker.

Citation: Sapena V, Iavarone M, Boix L, Facchetti F, Guarino M, Sanduzzi Zamparelli M, Granito A, Samper E, Scartozzi M, Corominas J, Marisi G, Díaz A, Casadei-Gardini A, Gramantieri L, Lampertico P, Morisco F, Torres F, Bruix J, Reig M. Polymorphism AGT2 (rs4762) is involved in the development of dermatologic events: Proof-of-concept in hepatocellular carcinoma patients treated with sorafenib. *World J Hepatol* 2022; 14(7): 1438-1458
URL: https://www.wjgnet.com/1948-5182/full/v14/i7/1438.htm
DOI: https://dx.doi.org/10.4254/wjh.v14.i7.1438

INTRODUCTION

Treatment-related dermatologic adverse events (DAEs) are reported in a great number of oncological therapies. The profile and timing of on-target skin adverse events (AEs) varies across treatments and cancer types. In this regard, hand-foot skin reaction (HFSR) reported in patients receiving tyrosine kinase inhibitor (TKI) therapy resembles the already described hand-foot syndrome (HFS) described in patients treated with cytotoxic chemotherapies[1,2]. Moreover, several studies have described the association between DAE development and better patient outcome, and this association has been reported for different therapies [TKI, monoclonal antibody directed against EGFR[3] or immunotherapy [4,5] and different cancer types such as colorectal, renal, prostate, non-small cell lung and breast cancer as well as melanoma and hepatocellular carcinoma (HCC)][6]. Therefore, it appears that the association between DAE development and better patient outcome is observed regardless of cancer type or oncological treatment.

Although there are several hypotheses explaining the potential mechanisms of DAE development, the exact mechanisms remain unknown. Previous studies postulated that direct toxicity of TKIs to the skin could depend on drug secretion into eccrine glands[7] somehow copying the already described detection of doxorubicin in the sweat of treated patients[8]. Apart from other speculative explanations, inhibition of proangiogenic pathways could potentially prevent vascular repair mechanisms from functioning correctly and causing HFSR in high pressure areas that may be repeatedly exposed to subclinical trauma[9]. This would be applicable mainly to anti-angiogenic treatments but would leave other therapies out. Considering other drug treatments, a study on immune checkpoint inhibitors (ICIs) therapy in non–small cell lung cancer patients suggested that T cells would recognize antigens shared by both lung tumors and skin[10]. Consequently, treatment would target both organs thus leading to tumor regression associated with autoimmune skin toxic effects. However, the low frequency of tumors harboring potent neoantigens clearly compromises the rationale of this hypothesis. More recently, a study published by Ruiz-Pinto and colleagues[11] described the association between *CDH4* genetic variants with the risk of developing capecitabine-induced HFS. In that study, *CDH4* gene downregulation negatively impacted skin barrier function.

In 2018, we demonstrated that 91.6% of HCC patients who received sorafenib and achieved complete radiological response also developed DAEs within the first 2 mo of treatment[12,13]. Recently published data obtained in our group allowed us to identify the potential role of TKI in peripheral immune cell population profile modification towards a more pro-inflammatory behavior and phenotype[14]. Thus, we envision skin toxicity as a consequence of an immune-mediated reaction triggered by the oncologic treatment in patients prone to developing this side effect.

In order to uncover potential mechanisms underlying individual genetic susceptibility to AEs with clinical implications for risk prediction, we first analyzed 27 Single-Nucleotide Polymorphisms (SNPs) in 12 different genes as potential predictors of AE development in a Barcelona Clinic Liver Cancer 1 (BCLC1) cohort of 82 HCC patients treated with sorafenib. Upon identification of the potential relevance

of the angiotensin genes, which include *AGT1* (rs699) and *AGT2* (rs4762), as predictors of DAEs, we further explored the association in three additional cohorts: a second BCLC cohort (n = 79), a Northern Italy cohort (n = 221) and a Naples cohort (n = 69).

MATERIALS AND METHODS

Four cohorts of patients were analyzed in this study, two prospective cohorts from BCLC1 and BCLC2, and two additional cohorts from Northern Italy [Milan, Bologna, Meldola (FC) and Cagliari Hospitals] and Naples (Figure 1).

The study was approved by the institutional review board of each center (HCB/2009/4755, HCB/2015/0352, Ethical Board 2 480_2018 and CE/2014/193) and complied with the provisions of the Good Clinical Practice guidelines and the Declaration of Helsinki. A Data Transfer Protocol (DTP) was written according to the European regulation [General Data Protection Regulation (GDPR) 2016/679] and approved by each cohort responsible.

Patient eligibility

BCLC1 cohort: This cohort included patients referred to BCLC between February 2009 and March 2015 for sorafenib treatment.

Inclusion criteria were: (1) HCC diagnosed according to EASL guidelines[15]; (2) advanced HCC following the BCLC staging system or patients with earlier stages who could not benefit from treatments of higher priority; (3) normal liver or compensated cirrhosis with preserved liver function (Child-Pugh score ≤ 7 points without clinical ascites and/or encephalopathy; (4) performance status 0-1; (5) controlled arterial hypertension (AHT) and/or stable peripheral vascular disease; (6) adequate hematologic profile (platelet count > 60 × 10^9/L; hemoglobin > 8.5 g/dL; and prothrombin time > 50%); (7) adequate hepatic function (albumin > 2.8 g/dL; total bilirubin ≤ 3 mg/dL; and alanine and aspartate aminotransferases ≤ 5 times the upper limit of the normal range); and (8) adequate renal function (serum creatinine ≤ 1.5 times the upper limit of the normal range).

Exclusion criteria were: (1) Myocardial infarction in the last year or active ischemic heart disease; (2) acute variceal bleeding in the last month; (3) severe peripheral arterial disease; (4) arrhythmia under treatment with drugs different from beta-blockers or digoxin; (5) uncontrolled ascites; and (6) encephalopathy. All patients provided written informed consent before enrolment.

Follow-up: Clinical and laboratory assessments were performed monthly and radiologic tumor evaluation at week 4 and every 8 wk thereafter. Unscheduled visits due to AEs occurred according to patients' needs.

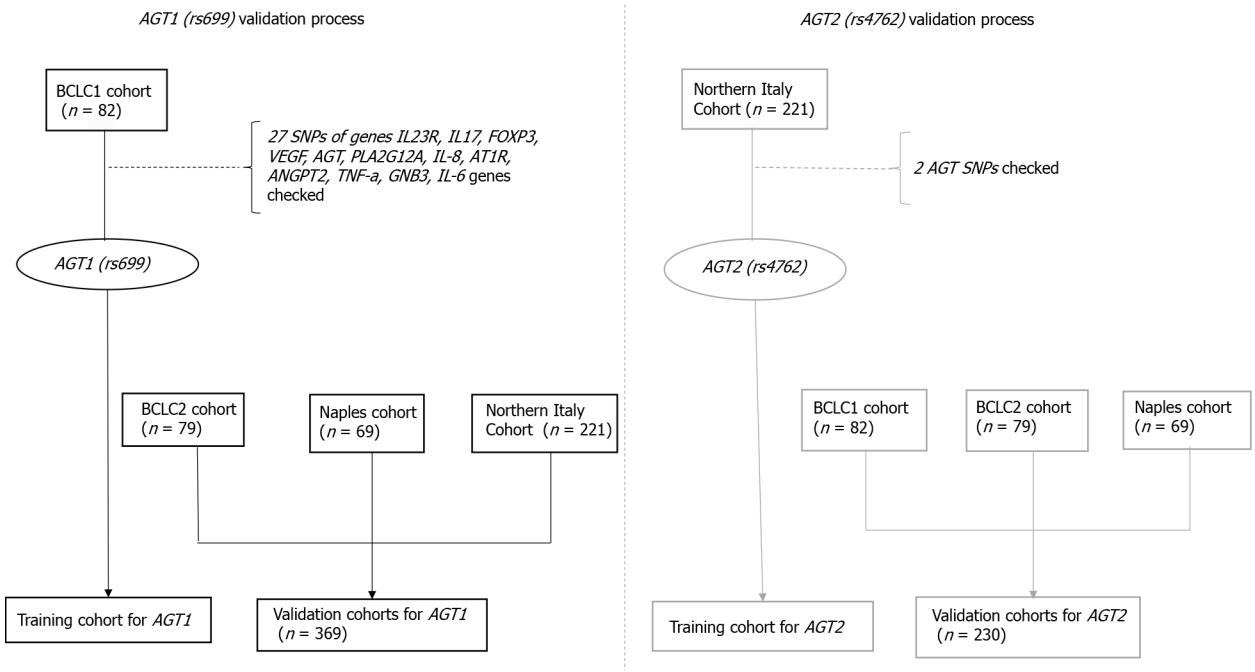
DAEs were graded according to version 3.0 of the CTCAE of the National Cancer Institute, during treatment and 30 days after the last dose. We focused on DAEs within the first 60 days (eDAE) +/-7 days of treatment, which determined dose modification.

BCLC2 cohort: This cohort included patients referred to BCLC between June 2015 and August 2018 for sorafenib treatment.

The inclusion and exclusion criteria as well as the follow-up of this cohort were the same as for the BCLC1 cohort.

Northern Italy cohort: The Northern Italy cohort included patients with HCC treated with sorafenib prospectively enrolled between July 2008 and June 2018 in four tertiary centers in Italy whose data have already been published in several multicenter studies on sorafenib treatment[16,17]. Briefly, all patients with advanced HCC or intermediate-stage HCC refractory to or unsuitable for locoregional therapies, either histologically proven or diagnosed according to the AASLD guidelines (American Association for the Study of Liver Diseases 2005) and receiving sorafenib were eligible for analysis. Exclusion criteria were those established by the Italian Medicines Agency (AIFA), *i.e.*, a performance status score > 2 and clinical decompensation. All patients received sorafenib with the standard schedule (400 mg bid continuously) with dose reduction applied as clinically indicated.

Follow-up: Follow-up consisted of a physical examination and complete blood count every 3 wk and Computed Tomography (CT) /Magnetic Resonance Imaging (MRI) scanning every 8 wk or as clinically indicated. Each visit included the recording of AEs, clinical laboratory tests, physical examination, and assessment of vital signs. At any time during treatment, the patient could have direct access to physicians for AE management. Safety was assessed in all patients who received at least one dose of sorafenib; AEs were graded according to the National Cancer Institute's Common Terminology Criteria (version 3.0 CTCAE). Hepatic function deterioration was defined as a Child-Pugh score increase ≥ 2 points, which was evaluated at each visit and at predefined time points of week 12 and 24 of therapy. In line with the aim of the study, independently of clinical practice, we focused on the AEs which determined dose modification within the first 30 and 60 days of treatment, respectively. Treatment with sorafenib was continued until disease progression, unacceptable toxicity, or death. In each patient, the



DOI: 10.4254/wjh.v14.i7.1438

Figure 1 Study flowchart.

medical history, physical examination, blood cell count, serum chemistry, coagulation and alpha-fetoprotein levels were obtained at baseline and every 4 wk thereafter.

Naples cohort: This cohort included patients referred to the Gastroenterology Unit of the University Hospital Federico II of Naples between January 2014 and December 2019 for sorafenib treatment.

Inclusion criteria were: (1) HCC diagnosed according to EASL guidelines[15]; (2) advanced HCC following the BCLC staging system or patients with earlier stages who could not benefit from treatments of higher priority; (3) normal liver or compensated cirrhosis with preserved liver function (Child-Pugh score ≤ 7 points without clinical ascites and/or encephalopathy; (4) performance status 0-1; (5) controlled AHT and/or stable peripheral vascular disease; (6) adequate hematologic profile (platelet count > 30 × 10^3/L; hemoglobin > 8.5g/dL; and INR < 1.7; (7) adequate hepatic function (albumin > 2.8 g/dL; total bilirubin < 3 mg/dL; and alanine and aspartate aminotransferases < 5 times the upper limit of the normal range); and (8) adequate renal function (serum creatinine < 1.5 times the upper limit of the normal range).

Exclusion criteria were: (1) Myocardial infarction in the last year or active ischemic heart disease; (2) acute variceal bleeding in the last month; (3) severe peripheral arterial disease; (4) arrhythmia under treatment with drugs different from beta-blockers or digoxin; (5) uncontrolled ascites; and (6) encephalopathy. All patients provided written informed consent before enrolment.

Follow-up: Clinical and laboratory assessments were performed monthly and radiologic tumor evaluation at week 8 and every 8 wk thereafter. Unscheduled visits due to AEs occurred according to patients' needs.

DAEs were graded according to version 3.0 of the CTCAE of the National Cancer Institute, during treatment and 30 days after the last dose. We focused on DAEs within the first 60 days (eDAE)+/-7 days of treatment, which determined dose modification.

Genomic DNA (gDNA) purification: gDNA was purified from isolated peripheral blood mononuclear cells (PBMCs) in the BCLC cohorts of patients and from 500 mL of whole frozen blood in the Naples cohort. gDNA purification was performed using the PureLink gDNA mini kit (Invitrogen, Thermo Fisher Scientific) following the manufacturer's instructions.

Patient genotyping

BCLC1 cohort: Patients were genotyped for a series of SNPs in *IL23R, IL17, FOXP3, VEGF, AGT, PLA2G12A, IL-8, AT1R, ANGPT2, TNF-a, GNB3,* and *IL-6* genes. SNPs were selected according to reported associations with susceptibility to cardiovascular disease, hypertension, stroke, inflammatory pathways or even cancer development. The genes and SNPs analyzed are detailed in Supplementary Table 1.

Twenty ng of gDNA were used for each SNP reaction. All SNPs were evaluated by means of TaqMan predesigned genotyping assays (Applied Biosystems, Thermo Fisher Scientific) and the procedure was performed following the manufacturer's instructions. A list of assays used is specified in Supplementary Table 2.

Briefly, TaqMan® MGB probes from the genotyping assay provide a fluorescent signal for the amplification of each allele. SNP genotyping uses a 60 s extension time at 60ºC for 40 cycles. Real-time PCR software plots the results of the allelic discrimination data as a scatter plot of Allele 1 (VIC® dye) *vs* Allele 2 (FAM™ dye). Each well of the 96-well reaction plate is represented as an individual point on the allelic discrimination plot. Positive controls were used for each homozygote and heterozygote genotype.

Patients from the BCLC2, Northern Italy and Naples cohorts were genotyped for 2 SNPs of the AGT-gene [*AGT1* (rs699) and *AGT2* (rs4762)] using the TaqMan endpoint-genotyping assay, following the same techniques as previously described.

Statistical analysis

The statistical methods and analysis of this study were performed by Víctor Sapena and reviewed by Ferran Torres from the Hospital Clínic de Barcelona.

Quantitative variables are expressed as median and interquartile range [IQR 25th-75th percentiles]. Categorical variables are described as absolute frequencies and percentages (%).

Time to event variables are expressed as median and 95% confidence intervals (95%CI) using the Kaplan-Meier method. The log-rank test was used to compare Kaplan-Meier curves. Univariate and multivariate Cox regression models were used to estimate Hazard Ratios (HR) and 95%CI to evaluate the increased probability of developing grade II or early dermatologic events (eDAEs), dermatologic events (DAEs) or death according to each SNP. The multivariate adjusting factors were previously selected according to their clinical relevance, and these were BCLC stage (A or B *vs* C), ECOG-PS (0 *vs* ≥ 1), history of AHT (No *vs* Yes) and history of diabetes (No *vs* Yes). An analysis using 67 days as the landmark timepoint was used to calculate overall survival (OS) according to eDAE.

The level of significance was set at the two-tailed 5% level and all analyses and data base integration structure were performed with SAS 9.4 software (SAS Institute, Cary, NC, United States).

RESULTS

This study included 82 patients from the BCLC1 cohort, 79 from the second BCLC2 cohort, 221 from the Northern Italy cohort, and 69 from the Naples cohort.

Baseline characteristics

Tables1, 2 and 3 describe the characteristics, OS and follow-up at the time of locking the database (December 2019) and the AE rates of all patients included in the study.

BCLC1 cohort: All but 2 (2.4%) patients were cirrhotic. A total of 54 (65.9%) patients had Hepatitis C Virus (HCV) and 10 (12.2%) had Hepatitis B Virus (HBV). Ninety-three percent of patients were asymptomatic (ECOG-PS 0) and 40 (48.8%) were BCLC B that failed or had a contraindication to loco-regional treatment, 70 (85.4%) were Child-Pugh class A. Twenty-two (26.8%) had vascular invasion, and 24 (29.3%) had extra-hepatic spread. AHT was present in 45.1% of patients and diabetes in 26.8%. Seventy-seven patients (93.9%) started sorafenib treatment at 800 mg.

BCLC2 cohort: All but 5 (6.3%) patients were cirrhotic. A total of 38 (48.1%) patients had HCV and 6 (7.6%) had HBV. Ninety-three percent of patients were asymptomatic (ECOG-PS 0) and 36 (45.6%) were BCLC B that failed or had a contraindication to loco-regional treatment, 63 (79.8%) were Child-Pugh class A. Twenty-six (32.9%) had vascular invasion, and 27 (34.2%) had extra-hepatic spread. AHT was present in 45.6% of patients and diabetes in 35.4%. Seventy-seven patients (97.4%) started sorafenib treatment at 800 mg.

Northern Italy cohort: All patients were cirrhotic. A total of 111 (50.2%) patients had HCV and 46 (20.8%) had HBV. Seventy percent of patients were asymptomatic (ECOG-PS 0) and 76 (34.4%) were BCLC B that failed or had a contraindication to loco-regional treatment, 207 (93.7%) were Child-Pugh class A. Sixty-one (27.6%) had vascular invasion, and 79 (35.8%) had extra-hepatic spread. AHT was present in 29.4% of patients and diabetes in 27.6%. One hundred ninety-seven patients (89.1%) started sorafenib treatment at 800 mg.

Naples cohort: All but 1 (1.5%) patient were cirrhotic. A total of 44 (63.7%) patients had HCV and 12 (17.4%) had HBV. All patients were asymptomatic (ECOG-PS 0) and 20 (29%) were BCLC B that failed or had a contraindication to loco-regional treatment, 58 (84.1%) were Child-Pugh class A. Thirty-one (44.9%) had vascular invasion, and 23 (33.3%) had extra-hepatic spread. AHT was present in 65.2% of patients and diabetes in 33.3%. All patients started sorafenib treatment at 800 mg.

Table 1 Baseline characteristics of patients included in each cohort

	BCLC1 cohort	BCLC2 cohort	Northern Italy cohort	Naples cohort
Patients, *n*	82	79	221	69
Gender (Male)	73 (89.02)	67 (84.81)	184 (83.26)	60 (86.96)
Age (Years)	63 (56-71)	63 (56-72)	69 (60-74)	70 (60-74)
AGT1 (rs699)				
AA	26 (31.71)	25 (31.65)	72 (32.58)	22 (31.88)
AG	34 (41.46)	35 (44.3)	101 (45.7)	38 (55.07)
GG	22 (26.83)	19 (24.05)	47 (21.27)	9 (13.04)
NA	0 (0)	0 (0)	1 (0.45)	0 (0)
AGT2 (rs4762)				
AA	5 (6.1)	3 (3.8)	5 (2.26)	0 (0)
AG	16 (19.51)	10 (12.66)	44 (19.91)	15 (21.74)
GG	61 (74.39)	66 (83.54)	172 (77.83)	54 (78.26)
AHT (Yes)	37 (45.12)	36 (45.57)	65 (29.41)	45 (65.22)
Diabetes (Yes)	22 (26.83)	28 (35.44)	61 (27.6)	23 (33.33)
HBV (Yes)	10 (12.2)	6 (7.59)	46 (20.81)	12 (17.39)
HCV (Yes)	54 (65.85)	38 (48.1)	111 (50.23)	44 (63.77)
HIV (Yes)	2 (2.44)	1 (1.27)	3 (1.36)	0 (0)
Child-Pugh				
A: 5-6	70 (85.37)	63 (79.75)	207 (93.67)	58 (84.06)
B: 7-9	10 (12.2)	11 (13.93)	14 (6.33)	10 (14.49)
Not applicable	2 (2.44)	5 (6.33)	0 (0)	1 (1.45)
ECOG-PS (0)	77 (93.9)	74 (93.67)	155 (70.14)	69 (100)
Ascites (Yes)	11 (13.41)	9 (11.39)	25 (11.31)	14 (20.29)
Encephalopathy (Yes)	0 (0)	0 (0)	11 (4.98)	0 (0)
Extrahepatic spread (Yes)	24 (29.27)	27 (34.18)	79 (35.75)	23 (33.33)
Vascular Invasion (Yes)	22 (26.83)	26 (32.91)	61 (27.6)	31 (44.93)
BCLC (A[1] or B / C)	42 (51.22) / 40 (48.78)	36 (45.57) / 43 (54.43)	76 (34.39) / 145 (65.61)	20 (28.99) / 49 (71.01)
Alpha-fetoprotein (ng/mL)	20.5 (7-212.5)	25 (8-228)	100.5 (10-869)	98 (5-1903)
Hemoglobin basal (g/dL)	13.8 (12.95-14.95)	13.1 (11.9-14.5)	12.5 (11.2-14)	13 (11.9-13.9)
Prothrombin time (%)	88.3 (76.5-95.6)	76 (65-88)	NA	84.5 (76-100)
International normalized ratio	NA	NA	1.1 (1-1.22)	1.13 (1.03-1.24)
Total bilirubin (mg/dL)	1 (0.8-1.6)	1.1 (0.6-1.7)	0.9 (0.72-1.3)	0.95 (0.7-1.4)
AST (UI/L)	78 (46-119)	54 (34-84)	NA	52 (35-80)
ALT (UI/L)	72 (35-106.5)	44 (25-65)	43 (23-56)	42 (32-55)
GGT (UI/L)	134.5 (93.5-285.5)	143 (83-264)	NA	96 (48-204)
Albumin (mg/L)	38.5 (35-43)	40 (35-43)	38 (35-40)	3.6 (3.3-4)
Initial dosage of sorafenib (mg)				
400	5 (6.1)	2 (2.6)	19 (8.6)	0 (0)
600	0 (0)	0 (0)	5 (2.26)	0 (0)
800	77 (93.9)	77 (97.4)	197 (89.14)	69 (100)

Descriptive statistics are frequencies (%) or median (IQR: Interquartile range), as appropriate. AHT: Arterial Hypertension; HCV: Hepatitis C Virus; HBV: Hepatitis B Virus; HIV: Human immunodeficiency virus; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma glutamyl transpeptidase; IQR: Interquartile range; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; BCLC: Barcelona Clinic Liver Cancer; INR: International normalized ratio; NA: Not available.
[1]5 BCLC A patients.

Adverse events

The rate of DAEs at any time point in the BCLC1, BCLC2, Northern Italy and Naples cohorts were 51.2 %, 35.4%, 14.5% and 39.1%, respectively (Table 3). The incidence of eDAEs in the BCLC1 cohort was 40.2% and was 27.8%, 12.7% and 36.2% in the BCLC2, Northern Italy and Naples cohorts, respectively.

The distribution of patients with a history of diabetes and AHT who did or did not develop eDAEs or DAEs in each cohort and the association between DAEs and AHT are summarized in Supplementary Tables 4 and 5, respectively.

The association between DAEs and a history of AHT was statistically significant in the BCLC1 cohort, with a HR = 1.96 (95%CI: 1.05-3.65; *P* value = 0.04) and confirmed when all patients were analyzed as a unique cohort with a HR = 1.61 (95%CI: 1.14-2.28; *P* value = 0.007).

Follow-up and Overall survival

BCLC1 cohort: The median follow-up was 18.6 mo (IQR: 10.3-34.2) and 75 (91.5%) patients died. Ninety-eight percent of deaths were due to HCC-related causes. The median treatment duration and OS were 9.1 (IQR: 4.1-17.5) and 18.8 mo (95%CI: 14.7-23.6), respectively.

BCLC2 cohort: The median follow-up was 13.1 mo (IQR: 6.6-22.4) and 47 (59.5%) patients died. Ninety-seven percent of deaths were due to HCC-related causes. The median treatment duration and OS were 5.9 (IQR: 2.1-13.5) and 18.3 mo (95%CI: 13.1-26.4), respectively.

Northern Italy cohort: The median follow-up was 12.7 mo (IQR: 6.1-25.9) and 180 (81.4%) patients died. Sixty-five percent of deaths were due to HCC-related causes. The median treatment duration and OS were 8.5 (IQR: 2.6-20.8) and 14.3 mo (95%CI: 11.8-18), respectively.

Naples cohort: The median follow-up was 9.9 mo (IQR: 4.5-18.3) and 57 (82.6%) patients died. Eighty-four percent of deaths were due to HCC-related causes. The median treatment duration and OS were 8.1 (IQR: 3.7-17) and 9.9 mo (95%CI: 7.7-12.8), respectively.

Overall survival according to eDAE

Using a landmark timepoint of 60 (+7) days and excluding 17 patients with less than 60 (+7) days of follow-up, the median OS in eDAE and in non-eDAE patients was 21.6 mo (95%CI: 12.7-28.2) and 14.8 mo (95%CI: 9.9-17.6) in BCLC1, 19.5 mo (95%CI: 8-24.2) and 14.2 mo (95%CI: 8.9-30.5) in BCLC2, 15.9 mo (95%CI: 8.3-40.6) and 12.1 mo (95%CI: 9.6-16.6) in the Northern Italy cohort, 12.4 mo (95%CI: 7.86-21.14) and 6.8 mo (95%CI: 2.7-8.7) in the Naples cohort, respectively.

Single-nucleotide polymorphisms (SNPs)

BCLC1 cohort: Supplementary Table 1 describes the assessed SNPs in this cohort. Of all SNPs analyzed, only the *AGT1* (rs699) AA genotype had a significant estimated increase in the probability of eDAE with a HR = 2.31 (95%CI: 1.03-5.14; *P* value = 0.04; AA *vs* AG) in the univariate model and a HR = 2.3 (95%CI: 1.02-5.16; *P* value = 0.04; AA *vs* AG) in the multivariate model (Table 4). For DAEs at any time point, *AGT1* (rs699) AA genotype showed a significant estimated increase in the probability of DAEs with a HR = 2.7 (95%CI: 1.27-5.75; *P* value = 0.01; AA *vs* AG) in the univariate model and a HR = 2.68 (95%CI: 1.25-5.77; *P* value = 0.01; AA *vs* AG) in the multivariate model. No other polymorphism showed a significant association with general AEs or specifically DAE or eDAE development in the BCLC1 cohort.

Allele distribution of Single-nucleotide polymorphisms (SNPs) AGT1 (rs699) and AGT2 (rs4762)

Allele distributions of *AGT1* (rs699) and *AGT2* (rs4762) are summarized in Table 1. There were no significant differences between the included cohorts (*P* value 0.5 and 0.2 for *AGT1* rs699 and *AGT2* rs4762, respectively). Thus, the present cohorts are comparable in terms of genetic variants.

AGT1 (rs699) and AGT2 (rs4762) influence in the development of DAE and eDAE

Tables 4 and 5 describe the Cox regression models for eDAE and DAE development by *AGT1* (rs699) and *AGT2* (rs4762), respectively. The results of the BCLC1 cohort are mentioned above.

BCLC2 cohort: The *AGT1 (rs699)* did not show a significant association with DAEs. By contrast, the *AGT2* (rs4762) AA genotype was associated with a significant increased risk of eDAE with a HR = 4.43 (95%CI: 1.01-19.39; *P* value = 0.048; AA *vs* GG) in the univariate analysis, and showed a trend in the multivariate model with a HR = 4.24 (95%CI: 0.95-19.06]; *P* value = 0.06; AA *vs* GG), Table 5.

Table 2 Overall survival of each cohort by single-nucleotide polymorphisms

		SNP alleles (A/G)	Patients at risk	Events	Median OS (95%CI), months	*P* value (log-rank)
BCLC1cohort			82	75	18.81 (14.76-23.58)	
BCLC2 cohort			79	47	18.32 (13.05-26.44)	
Northern Italy cohort			221	180	14.3 (11.84-17.99)	
Naples cohort			69	57	9.9 (7.69-12.82)	
BCLC1 cohort	*AGT1* (rs699)		82	75		0.16
		AA	26	23	18.73 (11.84-41.4)	
		AG	34	33	18.43 (10.75-22.76)	
		GG	22	19	18.81 (9.67-30.42)	
	AGT2 (rs4762)		82	75		0.4
		AA	5	5	41.34 (0.39-74.12)	
		AG	16	15	13.95 (7.3-23.87)	
		GG	61	55	19.11 (14.86-24.47)	
BCLC2 cohort	*AGT1* (rs699)		79	47		0.15
		AA	25	15	23.74 (7.46-26.5)	
		AG	35	19	21.74 (11.15-33.77)	
		GG	19	13	6.64 (3.42-30.29)	
	AGT2 (rs4762)		79	47		0.3
		AA	3	1	NE (13.61-NE)	
		AG	10	5	30.29 (3.88-32.69)	
		GG	66	41	16.41 (8.78-23.74)	
Northern Italy cohort	*AGT1* (rs699)		220	179		0.5
		AA	72	58	13.58 (10.92-19.2)	
		AG	101	83	17.59 (10.85-20.68)	
		GG	47	38	12.43 (8.81-20.68)	
	AGT2 (rs4762)		221	180		0.7
		AA	5	2	NE (1.94-NE)	
		AG	44	36	14.3 (7.46-20.68)	
		GG	172	142	14.9 (11.25-18.09)	
Naples cohort	*AGT1* (rs699)		69	57		0.7
		AA	22	19	12.66 (6.15-18.25)	
		AG	38	31	8.32 (4.9-11.71)	
		GG	9	7	10.95 (2.6-21.83)	
	AGT2 (rs4762)		69	57		0.6
		AG	15	11	9.8 (2.89-24.93)	
		GG	54	46	10.1 (7.14-12.82)	

NE: Not estimable; OS: Overall survival; 95%CI: 95% confidence interval; SNP: Single-nucleotide polymorphisms; BCLC: Barcelona clinic liver cancer.

Northern Italy cohort: In this cohort, the *AGT2* (rs4762) AA genotype showed a statistically significant increased probability of eDAE both in the univariate analysis (HR = 4.54 [95%CI: 1.05-19.64]; *P* value = 0.04; AA *vs* GG) and in the multivariate analysis (HR = 5.15 [95%CI: 1.17-22.63]; *P* value = 0.03; AA *vs* GG).

Table 3 Follow-up and evolutionary events in the included patients of each cohort

	BCLC1cohort	BCLC2cohort	Northern Italy cohort	Naples cohort
Patients, *n*	82	79	221	69
Follow-up (mo)	18.58 (10.33-34.17)	13.05 (6.64-22.36)	12.73 (6.05-25.88)	9.87 (4.51-18.25)
Treatment duration (mo)	9.06 (4.11-17.46)	5.95 (2.14-13.52)	8.52 (2.56-20.78)	8.06 (3.72-16.97)
Adverse Events				
Gastrointestinal (Yes)	35 (42.68)	27 (34.18)	23 (10.41)	38 (55.07)
Dermatologic (Yes)	42 (51.22)	28 (35.44)	32 (14.48)	27 (39.13)
Early Dermatologic (Yes)	33 (40.24)	22 (27.85)	28 (12.67)	25 (36.23)
Performance status deterioration (Yes)	44 (53.66)	46 (58.23)	53 (23.98)	0 (0)
Cardiovascular (Yes)	18 (21.95)	14 (17.72)	16 (7.24)	16 (23.19)
Dermatologic and Cardiovascular simultaneously (Yes)	7 (8.54)	5 (6.33)	0 (0)	10 (14.49)
Other (Yes)	48 (58.54)	34 (43.04)	45 (20.36)	65 (94.2)
Death (Yes)	75 (91.46)	47 (59.49)	180 (81.44)	57 (82.61)
Cause of death				
HCC	74 (98.67)	46 (97.87)	118 (65.56)	48 (84.21)
Not HCC related	0 (0)	1 (2.13)	58 (32.22)	9 (15.79)
Others[1]	1 (1.33)	0 (0)	4 (2.22)	0 (0)

Descriptive statistics are frequencies (%) or median (IQR: Interquartile range), as appropriate. AE: Adverse events; DAE: Dermatological adverse events; eDAE: early Dermatological adverse events.

[1]Other causes of Exitus are: 1 Sudden death, 4 unknown.

Naples cohort: In the Naples cohort, none of the SNPs showed a significant effect on DAE or eDAE development.

Validation of the AGT2 (rs4762) value identified in the Northern Italy cohort in the large cohort combining all cohorts but the Northern Italy one

The results in the individual cohorts suggested that the inconclusive results obtained in the BCLC and Naples cohorts could be due to a limited sample size. Thus, we combined these cohorts into a single cohort that would match the Northern Italy sample size.

This analysis showed that *AGT2* (rs4762) was significantly associated with DAE development with a HR = 2.94 (95%CI: 1.14-7.6; *P* value = 0.03; AA *vs* AG) and HR = 2.49 (95%CI: 1.08-5.73; *P* value = 0.03; AA *vs* GG) in univariate models, and HR = 2.85 (95%CI: 1.1-7.39; *P* value = 0.03; AA *vs* AG) and HR = 2.48 (95%CI: 1.08-5.72; *P* value = 0.03; AA *vs* GG) in multivariate models (Table 5).

Influence ofAGT2 (rs4762) in DAE and eDAE development after adjusting for baseline tumor burden, liver function, performance status and comorbidities

Table 5 shows the multivariate analyses adjusted for baseline BCLC stage, ECOG-PS, diabetes and AHT in the same model, considering diabetes and AHT together and each one separately. The multivariate analysis adjusted for baseline BCLC stage, ECOG-PS, diabetes and AHT showed a statistically significant increased risk in the probability of eDAE in patients harboring *AGT2* (rs4762) AA genotype in the Northern Italy cohort (HR = 8.51, 95%CI: 1.78-40.54; *P* value = 0.007; AA *vs* GG; and HR = 5.61, 95%CI: 1.01-31.12; *P* value = 0.048; AA *vs* AG).

The same analysis was performed for *AGT2* (rs4762) AA genotype and DAE development. A statistically significant increased risk in the probability of DAE was observed in the Northern Italy cohort (HR = 5.97, 95%CI: 1.32-27.01; *P* value = 0.02; AA *vs* GG) and when considering all but the Northern Italy cohort together as a unique cohort (HR = 3.12, 95%CI: 1.2-8.14; *P* value = 0.02; AA *vs* AG, and HR = 2.73, 95%CI: 1.18-6.32: *P* value = 0.02; AA *vs* GG).

AGT1 (rs699) and AGT2 (rs4762) influence on survival

No statistically significant effect on survival was found for *AGT1* (rs699) or *AGT2* (rs4762) using univariate or multivariate models in any cohort or combination thereof (Supplementary Table 6 and

Table 4 Cox regression models for eDAE and DAE by *AGT1* (rs699)

Event	Centre	*AGT1* (rs699)	HR (95%CI)	*P* value	HR (95%CI) adjusted by BCLC + ECOG-PS	*P* value	HR (95%CI) adjusted by BCLC + ECOG-PS + AHT + DM	*P* value	HR (95%CI) adjusted for AHT + DM	*P* value	HR (95%CI) adjusted for DM	*P* value	HR (95%CI) adjusted for AHT	*P* value
eDAE	BCLC1 cohort	AA vs AG	2.31 (1.03-5.14)	0.04	2.3 (1.02-5.16)	0.04	2.34 (1.02-5.37)	0.04	2.33 (1.03-5.24)	0.04	2.45 (1.1-5.5)	0.03	2.24 (1-5.03)	0.049
		AA *vs* GG	1.68 (0.71-3.97)	0.2	1.69 (0.71-4)	0.2	1.64 (0.69-3.93)	0.3	1.65 (0.69-3.92)	0.3	1.75 (0.74-4.13)	0.2	1.62 (0.68-3.87)	0.3
		AG *vs* GG	0.73 (0.29-1.85)	0.5	0.73 (0.29-1.89)	0.5	0.7 (0.27-1.82)	0.5	0.71 (0.28-1.79)	0.5	0.71 (0.28-1.8)	0.5	0.72 (0.29-1.84)	0.5
	BCLC2 cohort	AA *vs* AG	0.66 (0.25-1.76)	0.4	0.63 (0.24-1.7)	0.4	0.71 (0.26-1.93)	0.5	0.72 (0.27-1.93)	0.5	0.72 (0.27-1.91)	0.5	0.68 (0.25-1.83)	0.5
		AA *vs* GG	1.13 (0.32-4.01)	0.9	1.08 (0.3-3.84)	0.9	1.35 (0.37-4.95)	0.7	1.36 (0.38-4.9)	0.7	1.32 (0.37-4.72)	0.7	1.13 (0.32-4)	0.9
		AG *vs* GG	1.71 (0.55-5.3)	0.4	1.7 (0.55-5.28)	0.4	1.89 (0.6-5.91)	0.3	1.89 (0.6-5.9)	0.3	1.85 (0.6-5.74)	0.3	1.66 (0.53-5.17)	0.4
	Northern Italy cohort	AA *vs* AG	0.8 (0.33-1.95)	0.6	0.75 (0.3-1.86)	0.5	1.02 (0.4-2.61)	0.9	0.96 (0.39-2.36)	0.9	0.83 (0.34-2.02)	0.7	0.91 (0.37-2.23)	0.8
		AA *vs* GG	0.9 (0.31-2.6)	0.8	0.71 (0.24-2.1)	0.5	0.96 (0.31-2.98)	0.9	1.22 (0.4-3.73)	0.7	0.96 (0.33-2.8)	0.9	1.12 (0.37-3.36)	0.8
		AG *vs* GG	1.12 (0.42-3.01)	0.8	0.95 (0.35-2.58)	0.9	0.94 (0.33-2.69)	0.9	1.27 (0.46-3.49)	0.7	1.15 (0.43-3.12)	0.8	1.23 (0.45-3.34)	0.7
	Naples cohort	AA *vs* AG	1.26 (0.54-2.95)	0.6	1.21 (0.51-2.86)	0.7	1.35 (0.56-3.27)	0.5	1.36 (0.57-3.25)	0.5	1.23 (0.52-2.93)	0.6	1.44 (0.61-3.39)	0.4
		AA *vs* GG	1.26 (0.34-4.66)	0.7	1.18 (0.31-4.43)	0.8	1.33 (0.35-5)	0.7	1.34 (0.36-4.96)	0.7	1.27 (0.34-4.68)	0.7	1.35 (0.37-5)	0.7
		AG *vs* GG	1 (0.28-3.51)	0.9	0.97 (0.28-3.43)	0.9	0.98 (0.28-3.49)	0.9	0.99 (0.28-3.49)	0.9	1.03 (0.29-3.65)	0.9	0.94 (0.27-3.3)	0.9
	BCLC2 cohort + Naples cohort + Northern Italy cohort	AA *vs* AG	0.87 (0.52-1.47)	0.6	0.85 (0.51-1.43)	0.5	0.84 (0.5-1.41)	0.5	0.85 (0.51-1.43)	0.6	0.87 (0.52-1.47)	0.6	0.85 (0.51-1.43)	0.6
		AA *vs* GG	1.05 (0.54-2.04)	0.9	0.95 (0.49-1.86)	0.9	0.92 (0.47-1.81)	0.8	1.01 (0.52-1.97)	0.9	1.05 (0.54-2.04)	0.9	1.01 (0.52-1.97)	0.9
		AG *vs* GG	1.2 (0.65-2.22)	0.6	1.12 (0.61-2.08)	0.7	1.1 (0.59-2.05)	0.8	1.18 (0.64-2.18)	0.6	1.2 (0.65-2.22)	0.6	1.18 (0.64-2.18)	0.6
	BCLC1 cohort + Naples cohort + Northern Italy	AA *vs* AG	1.35 (0.84-2.17)	0.2	1.35 (0.84-2.18)	0.2	1.33 (0.82-2.15)	0.2	1.31 (0.81-2.11)	0.3	1.35 (0.84-2.18)	0.2	1.3 (0.81-2.1)	0.3

	cohort	AA *vs* GG	1.19 (0.67-2.12)	0.6	1.13 (0.6-2.01)	0.7	1.08 (0.6-1.93)	0.8	1.1 (0.61-1.97)	0.8	1.19 (0.67-2.12)	0.6	1.09 (0.61-1.96)	0.8
		AG *vs* GG	0.88 (0.5-1.55)	0.7	0.83 (0.47-1.48)	0.5	0.81 (0.46-1.43)	0.5	0.84 (0.48-1.48)	0.6	0.88 (0.5-1.55)	0.7	0.84 (0.48-1.48)	0.6
	BCLC1cohort + BCLC2 cohort + Naples cohort	AA *vs* AG	1.32 (0.81-2.15)	0.3	1.29 (0.79-2.11)	0.3	1.3 (0.79-2.12)	0.3	1.31 (0.81-2.14)	0.3	1.33 (0.82-2.17)	0.3	1.31 (0.8-2.13)	0.3
		AA *vs* GG	1.4 (0.75-2.6)	0.3	1.38 (0.7-2.57)	0.3	1.44 (0.77-2.69)	0.3	1.45 (0.78-2.7)	0.2	1.46 (0.79-2.72)	0.2	1.38 (0.74-2.57)	0.3
		AG *vs* GG	1.06 (0.58-1.94)	0.9	1.06 (0.58-1.95)	0.9	1.11 (0.6-2.03)	0.8	1.1 (0.6-2.02)	0.8	1.1 (0.6-2.01)	0.8	1.06 (0.58-1.94)	0.9
DAE	BCLC1 cohort	AA *vs* AG	2.7 (1.27-5.75)	0.01	2.68 (1.25-5.77)	0.01	2.52 (1.16-5.47)	0.02	2.6 (1.21-5.57)	0.01	2.82 (1.32-6.06)	0.008	2.5 (1.17-5.35)	0.02
		AA *vs* GG	1.26 (0.62-2.58)	0.5	1.24 (0.61-2.55)	0.6	1.11 (0.53-2.31)	0.8	1.13 (0.55-2.35)	0.8	1.3 (0.63-2.66)	0.5	1.12 (0.54-2.32)	0.8
		AG *vs* GG	0.47 (0.21-1.05)	0.06	0.46 (0.2-1.06)	0.07	0.44 (0.19-1.01)	0.053	0.44 (0.19-0.98)	0.045	0.46 (0.2-1.03)	0.06	0.45 (0.2-1.01)	0.052
	BCLC2 cohort	AA *vs* AG	0.98 (0.43-2.2)	0.9	0.94 (0.42-2.13)	0.9	0.99 (0.43-2.26)	0.9	1.01 (0.45-2.3)	0.9	1.03 (0.45-2.32)	0.9	0.95 (0.42-2.16)	0.9
		AA *vs* GG	1.89 (0.59-6.04)	0.3	1.78 (0.55-5.76)	0.3	2.08 (0.63-6.85)	0.2	2.18 (0.67-7.03)	0.19	2.08 (0.65-6.66)	0.2	1.88 (0.59-6.01)	0.3
		AG *vs* GG	1.94 (0.64-5.9)	0.2	1.89 (0.62-5.77)	0.3	2.12 (0.69-6.49)	0.19	2.15 (0.7-6.57)	0.18	2.02 (0.66-6.15)	0.2	1.98 (0.65-6.05)	0.2
	Northern Italy cohort	AA *vs* AG	0.89 (0.39-2.06)	0.8	0.85 (0.37-1.98)	0.7	1.01 (0.42-2.41)	0.9	1 (0.42-2.33)	0.9	0.91 (0.39-2.11)	0.8	0.95 (0.41-2.22)	0.9
		AA *vs* GG	0.62 (0.25-1.57)	0.3	0.54 (0.21-1.37)	0.2	0.6 (0.23-1.6)	0.3	0.74 (0.28-1.92)	0.5	0.64 (0.25-1.62)	0.4	0.7 (0.27-1.79)	0.5
		AG *vs* GG	0.7 (0.3-1.62)	0.3	0.63 (0.27-1.48)	0.2	0.6 (0.25-1.43)	0.2	0.74 (0.32-1.72)	0.5	0.71 (0.3-1.63)	0.4	0.73 (0.31-1.69)	0.5
	Naples cohort	AA *vs* AG	1.29 (0.57-2.92)	0.5	1.23 (0.54-2.81)	0.6	1.35 (0.58-3.15)	0.5	1.38 (0.6-3.17)	0.5	1.23 (0.54-2.81)	0.6	1.49 (0.66-3.4)	0.3
		AA *vs* GG	1.38 (0.38-5.03)	0.6	1.28 (0.35-4.73)	0.7	1.45 (0.39-5.36)	0.6	1.49 (0.41-5.41)	0.6	1.39 (0.38-5.05)	0.6	1.51 (0.41-5.51)	0.5
		AG *vs* GG	1.07 (0.31-3.72)	0.9	1.04 (0.3-3.62)	0.9	1.08 (0.31-3.77)	0.9	1.08 (0.31-3.79)	0.9	1.13 (0.32-3.96)	0.9	1.01 (0.29-3.52)	0.9
	BCLC2 cohort + Naples cohort + Northern Italy cohort	AA *vs* AG	1 (0.62-1.61)	0.9	0.98 (0.61-1.57)	0.9	0.95 (0.59-1.54)	0.9	0.97 (0.6-1.56)	0.9	1.01 (0.63-1.62)	0.9	0.96 (0.6-1.55)	0.9
		AA *vs* GG	1.13 (0.61-	0.7	1.04 (0.56-1.92)	0.9	0.98 (0.53-1.81)	0.9	1.05 (0.57-1.95)	0.9	1.12 (0.61-2.07)	0.7	1.05 (0.57-1.95)	0.9

		2.08)											
	AG *vs* GG	1.13 (0.63-2)	0.7	1.06 (0.59-1.89)	0.8	1.02 (0.57-1.83)	0.9	1.09 (0.61-1.94)	0.8	1.12 (0.63-1.99)	0.7	1.09 (0.61-1.95)	0.8
BCLC1 cohort + Naples cohort +Northern Italy cohort	AA *vs* AG	1.43 (0.91-2.24)	0.12	1.43 (0.91-2.24)	0.12	1.39 (0.88-2.19)	0.15	1.36 (0.87-2.14)	0.18	1.44 (0.92-2.26)	0.11	1.35 (0.86-2.12)	0.19
	AA *vs* GG	0.94 (0.57-1.56)	0.8	0.9 (0.54-1.51)	0.7	0.82 (0.49-1.38)	0.5	0.83 (0.49-1.39)	0.5	0.94 (0.57-1.57)	0.8	0.82 (0.49-1.38)	0.5
	AG *vs* GG	0.66 (0.4-1.09)	0.1	0.63 (0.38-1.05	0.08	0.59 (0.36-0.99)	0.04	0.61 (0.37-1.01)	0.052	0.66 (0.4-1.08)	0.1	0.61 (0.37-1.01)	0.053
BCLC1 cohort + BCLC2 cohort + Naples cohort	AA *vs* AG	1.54 (0.98-2.41)	0.06	1.49 (0.95-2.34)	0.08	1.48 (0.94-2.32)	0.09	1.52 (0.97-2.37)	0.07	1.55 (0.99-2.43)	0.055	1.5 (0.96-2.35)	0.07
	AA *vs* GG	1.35 (0.78-2.32)	0.3	1.3 (0.75-2.25)	0.3	1.32 (0.76-2.28)	0.3	1.35 (0.78-2.33)	0.3	1.39 (0.81-2.4)	0.2	1.3 (0.76-2.24)	0.3
	AG *vs* GG	0.88 (0.51-1.51)	0.6	0.87 (0.51-1.5)	0.6	0.89 (0.52-1.54)	0.7	0.89 (0.52-1.54)	0.7	0.9 (0.52-1.54)	0.7	0.87 (0.5-1.49)	0.6

eDAE: early Dermatological adverse events; DAE: Dermatological adverse events; HR: Hazard ratio; 95%CI: 95% confidence interval; BCLC: Barcelona Clinic Liver Cancer; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; AHT: Arterial hypertension; DM: Diabetes mellitus.

Supplementary Table 7).

DISCUSSION

The aim of Precision Oncology is to decide the treatment to be recommended to a specific patient according to the individualized evaluation of the clinical, biochemical and hopefully, molecular profile. It is common to focus all the attention on the genomic abnormalities of cancer to define the best intervention, but it is well known that, patients' genetic background, irrespective of the tumor, is involved in the efficacy and safety of any therapeutic intervention. The best example is the clearance related to the glucuronidation activity resulting in fast and slow elimination of drugs and their metabolites[18]. Response to inflammation or tolerance to antiangiogenic agents is also influenced by genetic background and most cancer treatments have targets affecting several of these separate domains. In some instances, these non-cancer effects may become a surrogate of drug activity and even be correlated with improved outcomes as already described in the introduction.

This multicenter international study explored whether specific genetic variants, as identified by SNP analysis, may be linked to the development of AEs that have been associated with improved outcome. This is not only the case for DAEs in patients with HCC treated with sorafenib[12,19], as has been extensively proven, but also when using other TKIs such as regorafenib[20]. Furthermore, the association of DAEs with improved outcome is also being reported when using chemotherapy or

Table 5 Cox regression models for eDAE and DAE by *AGT2* (rs4762)

Event	Center	*AGT2* (rs4762)	HR (95%CI)	*P* value	HR (95%CI) adjusted for BCLC + ECOG-PS	*P* value	HR (95%CI) adjusted for BCLC + ECOG-PS + AHT + DM	*P* value	HR (95%CI) adjusted for AHT + DM	*P* value	HR (95%CI) adjusted for DM	*P* value	HR (95%CI) adjusted for AHT	*P* value
eDAE	BCLC1 cohort	AA *vs* AG	1.14 (0.22-5.89)	0.9	0.98 (0.19-5.12)	0.9	0.97 (0.18-5.04)	0.9	1.09 (0.21-5.64)	0.9	1.15 (0.22-5.95)	0.9	1.11 (0.21-5.72)	0.9
		AA *vs* GG	0.84 (0.2-3.53)	0.8	0.73 (0.17-3.15)	0.7	0.71 (0.16-3.1)	0.7	0.81 (0.19-3.4)	0.8	0.8 (0.19-3.39)	0.8	0.84 (0.2-3.54)	0.8
		AG *vs* GG	0.73 (0.28-1.91)	0.5	0.74 (0.28-1.94)	0.5	0.74 (0.28-1.97)	0.6	0.74 (0.28-1.94)	0.6	0.7 (0.27-1.82)	0.5	0.76 (0.29-1.98)	0.6
	BCLC2 cohort	AA *vs* AG	3.71 (0.62-22.39)	0.2	3.52 (0.58-21.5)	0.2	4.8 (0.74-31.28)	0.1	4.81 (0.74-31.24)	0.1	4.78 (0.76-29.88)	0.09	4.46 (0.7-28.35)	0.11
		AA *vs* GG	4.43 (1.01-19.39)	0.048	4.24 (0.95-19.06)	0.06	6.14 (1.28-29.55)	0.02	6.28 (1.32-29.95)	0.02	6.25 (1.35-28.89)	0.02	5.34 (1.15-24.86)	0.03
		AG *vs* GG	1.19 (0.35-4.08)	0.8	1.21 (0.35-4.15)	0.8	1.28 (0.37-4.45)	0.7	1.31 (0.38-4.47)	0.7	1.31 (0.38-4.47)	0.7	1.2 (0.35-4.08)	0.8
	Northern Italy cohort	AA *vs* AG	2.72 (0.57-13.1)	0.2	3.21 (0.64-15.99)	0.15	5.61 (1.01-31.12)	0.048	3.43 (0.69-16.96)	0.13	2.69 (0.56-12.97)	0.2	3.2 (0.66-15.6)	0.15
		AA *vs* GG	4.54 (1.05-19.64)	0.04	5.15 (1.17-22.63)	0.03	8.51 (1.78-40.54)	0.007	5.51 (1.25-24.33)	0.02	4.72 (1.09-20.48)	0.04	4.93 (1.13-21.41)	0.03
		AG *vs* GG	1.67 (0.69-4.02)	0.3	1.6 (0.66-3.9)	0.3	1.52 (0.6-3.82)	0.4	1.61 (0.66-3.9)	0.3	1.75 (0.73-4.24)	0.2	1.54 (0.63-3.73)	0.3
	Naples cohort	AG *vs* GG	1.2 (0.48-3.01)	0.7	1.2 (0.48-3.02)	0.7	1.25 (0.5-3.15)	0.6	1.26 (0.5-3.16)	0.6	1.2 (0.48-3)	0.7	1.29 (0.51-3.23)	0.6
	BCLC2 cohort + Naples cohort + Northern Italy cohort	AA *vs* AG	2.76 (0.92-8.27)	0.07	2.95 (0.97-9.84)	0.06	2.78 (0.9-8.56)	0.07	2.61 (0.87-7.86)	0.09	2.75 (0.92-8.25)	0.07	2.61 (0.87-7.86)	0.09
		AA *vs* GG	3.5 (1.27-9.67)	0.02	3.8 (1.36-10.58)	0.01	3.67 (1.31-10.3)	0.01	3.39 (1.22-9.37)	0.02	3.5 (1.27-9.66)	0.02	3.38 (1.22-9.37)	0.02
		AG *vs* GG	1.27 (0.73-9.67)	0.4	1.29 (0.74-2.25)	0.4	1.32 (0.75-2.32)	0.3	1.3 (0.74-2.27)	0.4	1.27 (0.73-2.22)	0.4	1.3 (0.74-2.27)	0.4
	BCLC1 cohort + Naples cohort +Northern Italy cohort	AA *vs* AG	1.66 (0.65-4.9)	0.4	1.63 (0.55-4.85)	0.4	1.53 (0.51-4.57)	0.5	1.54 (0.52-4.57)	0.4	1.66 (0.56-4.9)	0.4	1.54 (0.52-4.57)	0.4
		AA *vs* GG	1.83 (0.67-5.03)	0.2	1.73 (0.63-4.77)	0.3	1.7 (0.62-4.69)	0.3	1.8 (0.65-4.94)	0.3	1.85 (0.67-5.08)	0.2	1.79 (0.65-4.93)	0.3
		AG *vs* GG	1.1 (0.65-1.86)	0.7	1.06 (0.63-1.81)	0.8	1.11 (0.65-1.9)	0.7	1.17 (0.69-1.97)	0.6	1.11 (0.66-1.88)	0.7	1.16 (0.69-1.97)	0.6

	BCLC1 cohort + BCLC2 cohort + Naples cohort	AA *vs* AG	1.67 (0.55-5.09)	0.4	1.6 (0.53-4.87)	0.4	1.61 (0.53-4.92)	0.4	1.66 (0.55-5.06)	0.4	1.71 (0.56-5.19)	0.4	1.63 (0.54-4.95)	0.4
		AA *vs* GG	1.7 (0.62-4.67)	0.3	1.67 (0.61-4.59)	0.3	1.68 (0.61-4.63)	0.3	1.7 (0.62-4.67)	0.3	1.7 (0.62-4.67)	0.3	1.68 (0.61-4.62)	0.3
		AG *vs* GG	1.01 (0.57-1.81)	0.9	1.04 (0.58-1.86)	0.9	1.04 (0.58-1.86)	0.9	1.02 (0.57-1.82)	0.9	0.99 (0.56-1.78)	0.9	1.03 (0.58-1.84)	0.9
DAE	BCLC1 cohort	AA *vs* AG	2.8 (0.78-10.01)	0.1	2.45 (0.68-8.81)	0.2	2.73 (0.74-9.99)	0.13	3.09 (0.85-11.2)	0.09	2.85 (0.79-10.22)	0.11	2.86 (0.8-10.28)	0.11
		AA *vs* GG	1.82 (0.64-5.16)	0.3	1.61 (0.56-4.64)	0.4	1.89 (0.64-5.57)	0.2	2.12 (0.74-6.1)	0.16	1.79 (0.63-5.08)	0.3	2.03 (0.71-5.78)	0.19
		AG *vs* GG	0.65 (0.27-1.56)	0.3	0.66 (0.27-1.59)	0.4	0.69 (0.28-1.72)	0.4	0.69 (0.28-1.68)	0.4	0.63 (0.26-1.52)	0.3	0.71 (0.29-1.71)	0.4
	BCLC2 cohort	AA *vs* AG	3.83 (0.64-23.05)	0.1	3.71 (0.61-22.68)	0.2	3.91 (0.62-24.73)	0.15	4.05 (0.65-25.33)	0.14	4.49 (0.73-27.55)	0.1	3.79 (0.61-23.44)	0.15
		AA *vs* GG	3.22 (0.75-13.76)	0.1	3.27 (0.74-14.38)	0.1	3.74 (0.82-17.15)	0.09	3.7 (0.82-16.76)	0.09	4.04 (0.91-18)	0.07	3.18 (0.72-14.13)	0.13
		AG *vs* GG	0.84 (0.25-2.8)	0.8	0.88 (0.26-2.96)	0.8	0.96 (0.28-3.24)	0.9	0.92 (0.27-3.06)	0.9	0.9 (0.27-3.01)	0.9	0.84 (0.25-2.8)	0.8
	Northern Italy cohort	AA *vs* AG	2.85 (0.59-13.73)	0.2	3.28 (0.66-16.21)	0.1	4.71 (0.89-24.91)	0.07	3.4 (0.69-16.77)	0.13	2.83 (0.59-13.64)	0.2	3.13 (0.65-15.21)	0.16
		AA *vs* GG	3.68 (0.86-15.63)	0.08	4.15 (0.96-17.87)	0.06	5.97 (1.32-27.01)	0.02	4.41 (1.02-19.03)	0.046	3.97 (0.93-16.94)	0.06	3.8 (0.89-16.16)	0.07
		AG *vs* GG	1.29 (0.55-3.01)	0.6	1.26 (0.54-2.96)	0.6	1.27 (0.53-3.05)	0.6	1.3 (0.55-3.05)	0.6	1.4 (0.6-3.29)	0.4	1.21 (0.52-2.84)	0.7
	Naples cohort	AG *vs* GG	1.12 (0.45-2.77)	0.8	1.11 (0.45-2.76)	0.8	1.12 (0.45-2.79)	0.8	1.13 (0.46-2.82)	0.8	1.12 (0.45-2.77)	0.9	1.16 (0.47-2.88)	0.8
	BCCL2 cohort + Naples cohort + Northern Italy cohort	AA *vs* AG	2.79 (0.93-8.35)	0.07	3.04 (1-9.21)	0.049	2.72 (0.88-8.34)	0.08	2.54 (0.84-7.63)	0.1	2.74 (0.92-8.21)	0.07	2.56 (0.85-7.7)	0.09
		AA *vs* GG	2.96 (1.08-8.13)	0.03	3.27 (1.18-9.05)	0.02	3.07 (1.1-8.56)	0.03	2.81 (1.02-7.73)	0.045	2.94 (1.07-8.07)	0.04	2.83 (1.03-7.78)	0.04
		AG *vs* GG	1.06 (0.62-1.83)	0.8	1.07 (0.62-1.86)	0.8	1.13 (0.65-1.96)	0.7	1.11 (0.64-1.92)	0.7	1.07 (0.62-1.85)	0.8	1.11 (0.64-1.91)	0.7
	BCLC1 cohort + Naples cohort + Northern Italy cohort	AA *vs* AG	2.82 (1.13-7.07)	0.03	2.9 (1.15-7.32)	0.02	2.7 (1.06-6.84)	0.04	2.66 (1.06-6.69)	0.04	2.81 (1.12-7.05)	0.03	2.68 (1.07-6.74)	0.04
		AA *vs* GG	2.86 (1.24-6.58)	0.01	2.84 (1.23-6.54)	0.01	2.85 (1.24-6.57)	0.01	2.94 (1.28-6.77)	0.01	2.91 (1.27-6.7)	0.01	2.94 (1.28-6.77)	0.01
		AG *vs* GG	1.01 (0.61-	0.9	0.98 (0.59-1.63)	0.9	1.06 (0.63-1.77)	0.8	1.1 (0.67-1.83)	0.7	1.04 (0.63-1.71)	0.9	1.1 (0.66-1.82)	0.7

		1.68)											
BCLC1 cohort + BCLC2 cohort + Naples cohort	AA *vs* AG	2.94 (1.14-7.6)	0.03	2.85 (1.1-7.39)	0.03	3.12 (1.2-8.14)	0.02	3.21 (1.23-8.34)	0.02	3.05 (1.18-7.9)	0.02	2.9 (1.12-7.5)	0.03
	AA *vs* GG	2.49 (1.08-5.73)	0.03	2.48 (1.08-5.72)	0.03	2.73 (1.18-6.32)	0.02	2.75 (1.19-6.34)	0.02	2.54 (1.1-5.85)	0.03	2.51 (1.09-5.77)	0.03
	AG *vs* GG	0.85 (0.49-1.48)	0.6	0.87 (0.5-1.52)	0.6	0.87 (0.5-1.53)	0.7	0.86 (0.49-1.5)	0.6	0.83 (0.48-1.45)	0.5	0.87 (0.5-1.51)	0.6

eDAE: early Dermatological adverse events; DAE: Dermatological adverse events; HR: Hazard ratio; 95%CI: 95% confidence interval; BCLC: Barcelona Clinic Liver Cancer; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; AHT: Arterial hypertension; DM: Diabetes mellitus.

immunotherapy not only in liver cancer but also in other tumor types[3-5].

The results of our multicenter study confirm that the genetic background of patients plays a key role in the emergence of specific events that are linked to a distinct outcome under HCC treatment. Previously, different SNPs were reported to be potentially associated with survival outcomes[16,17] while others were identified as significantly associated with a higher likelihood of DAEs affecting the angiotensin gene and its *AGT2* (rs4762) variant.

Our results confirmed that the distribution of the *AGT* genetic variants studied, *AGT1* (rs699) and *AGT2* (rs4762), was comparable across patients from northern and southern Italy and those from Barcelona, and confirmed that the frequency of reference and alternative alleles follow the reported distribution for the European population[21,22].

Although rs699 and rs4762 could not be associated with AHT events in our patients, the most relevant finding is the identification of *AGT2* (rs4762) AA genotype as a predictor of DAE development [HR = 5.97; *P* value = 0.0201] in the Northern Italy cohort and its validation in the remaining 3 cohorts when they were considered as one unique cohort [HR = 3.12 (95%CI: 1.2-8.14); *P* value = 0.02 and HR = 2.73 (95%CI: 1.18-6.32); *P* value = 0.02].

AGT2 (rs4762) is a missense variant that codes for the replacement of threonine by methionine with no reported clear association with blood AGT protein levels. *AGT2* (rs4762) has been associated with renal dysplasia, a potentially benign disease[22]. However, published data suggest that rs4762 may be associated with an increased risk of mortality in patients with heart failure[23] and with the development of intracranial hemorrhage in stroke patients[24]. Available data at this moment do not allow to unequivocally associate an increase in blood AGT levels with rs4762 polymorphism, but it is speculated that it could induce Renin-Angiotensin System (RAS) activation. The RAS is a key regulator of systemic homeostasis by controlling salt-water balance and consequently, blood pressure. Interestingly, several studies have also unveiled the activation of this system in several peripheral tissues (tRAS)[25] and organs including skin and liver[26]. Since activation of tRAS is associated with tissue regeneration, inflammation and fibrosis[27] and considering that all of these are key components of tumor development, tRAS activation is likely to play a role in carcinogenesis. A review by Ager EI and collaborators[28] describes the potential contribution of tRAS activation in cancer development and progression putting the emphasis not only on tumor angiogenesis, but also on inflammation and fibrosis. Considering that the components of the tRAS pathway are also participating in physiological

and pathological wound healing and fibrosis processes that are particularly important in skin homeostasis[29,30], DAE development in our patients with rs4762 AA genotype may be considered a consequence of tRAS activation at the skin level.

The role of genetic variants in the components of the RAS pathway has been extensively reported in the past years and some of these roles involve response to anti-neoplastic treatments, disease prognosis and patient survival. In that sense, it is already known that *ACE* I/D rs4646994, a variant of the Angiotensin-Converting Enzyme (ACE), has been associated with prediction of response to bevacizumab in metastatic breast and colorectal cancer patients[31]. The *AGT*rs5050 GG genotype[32] is reported to be linked to poor prognosis in patients with astrocytoma. A very interesting *in silico* study by Goswami and colleagues analyzed 354 SNPs in the *AGT* gene[33] in order to predict those variants that are pathogenic and how amino acid substitutions would impact protein function. In this study, *AGT2* rs4762 was categorized mainly as a damaging *AGT* SNP with controversial results on its pathogenicity or disease identity. Thus, the importance of genetic variants is determined by the levels and/or functionality of the protein they code for. Along these lines, Feng *et al*[34] proposed that cancer tissue levels of *ACE2* correlates with immune infiltrates and these would affect the prognosis of cancer patients. In another study, Urupet *et al*[35] suggested that low expression of the *AGT* gene and high expression of an HLA-class II gene (*HLADQA1*) were independent predictors associated with response in glioblastoma patients treated with bevacizumab.

AGT2 (rs4762) has been associated with an increased risk of AHT in several studies[36,37] but this association remains controversial as the results could not be confirmed in other series of individuals analyzed[38]. We were not able to identify an association between *AGT2* rs4762 and AHT in our patients not even when analyzing the impact of concomitant medication that the BCLC1 and BCLC2 cohort patients received for AHT that included IEACA (renin angiotensin aldosterone axis inhibitor) (Supplementary Table 8). This could be related to the low frequency of *AGT2* rs4762 in patients who developed this AE [0 (0%) in the BCLC1 and Northern Italy cohorts, 1 (1.27%) in the BCLC2 cohort and 2 (2.9%) in the Naples cohort].

However, in our cohort, the impact of *AGT2* (rs4762) was maintained when the multivariate was adjusted for history of AHT.

To the best of our knowledge, the relationship between *AGT2* rs4762AA genotype and DAE development in HCC patients under sorafenib treatment has not been previously reported. This is a 'proof-of-concept' study to identify a novel genetic marker to screen for patients with good outcome. It would be interesting for our results to be validated in other cancer types besides HCC or even in different therapeutic approaches. If this were to be the case, *AGT2* (rs4762) should be considered a good prognosis marker instead of being only a predictor of DAE development. The retrospective profile of the study did not allow us to assess analysis related to radiological response as the radiological follow-up between the cohorts was different, and this could be seen as a limitation of the study. However, we prefer to be conservative and avoid overestimating the role of DAEs on the radiological outcome.

In conclusion, our findings open the window to explore individual genetic susceptibility as prognostic factors or predictors of treatment outcome, and to unveil novel mechanisms triggered by oncological treatment and their potential link to tumor response and patient survival.

CONCLUSION

DAE development in HCC patients receiving TKIs could be explained by the *AGT2* (rs4762) gene variant. If validated in other anti-oncogenic treatments, it might be considered a good prognosis marker.

ARTICLE HIGHLIGHTS

Research background

In hepatocellular carcinoma (HCC), patients regardless of the chosen treatment, the development of dermatologic adverse events (DAEs) is associated with better outcome. The underlying mechanism of these effects is unknown.

Research motivation

Distinct genetic variants could have an effect to the likelihood of developing DAEs in patients treated with TKIs for advanced HCC.

Research objectives

The objective of this study was to evaluate the association of two specific *AGT* gene single-nucleotide polymorphisms, rs699 and rs4762, in DAE development.

Research methods

Four cohorts were used to assess the effect, as training and external validation, of the effect of *AGT1* (rs699) and *AGT2* (rs4762) on the development of DAEs in patients with advanced HCC.

Research results

AGT2 (rs4762) AA genotype was related to an increased risk of DAEs development in the Northern Italy cohort in a multivariate model adjusted for clinically relevant factors such as BCLC stage, ECOG-PS, diabetes and arterial hypertension (AHT). This effect was externally validated in the validation cohort (combining BCLC1, BCLC2 and Naples cohorts).

Research conclusions

The development of DAEs in patients treated with TKIs for advanced HCC could be explained by the *AGT2* (rs4762) SNP.

Research perspectives

The *AGT2* (rs4762) SNP could be proposed as a valuable predictive marker if a similar effect is found in other anti-oncogenic treatments.

FOOTNOTES

Author contributions: Reig M, Boix L, Iavarone M, Bruix J and Torres F designed the conceptualization; Reig M, Torres F and Sapena V performed the methodology; Sapena V and Torres F performed the formal analysis; Reig M, Boix L, Iavarone M, Bruix J and Sapena V performed the research; Sapena V and Sanduzzi Zamparelli M performed data curation; Sapena V, Boix L and Reig M wrote the original draft; Sapena V, Iavarone M, Boix L, Facchetti F, Guarino M, Sanduzzi Zamparelli M, Granito A, Samper E, Scartozzi M, Corominas J, Marisi G, Diaz A, Casadei-Gardini A, Gramantieri L, Lampertico P, Morisco F, Torres F, Bruix J, Reig M contributed analytic tools and reviewed and edited the manuscript; Reig M, Bruix J, Iavarone M and Morisco F performed expert supervision; Reig M and Iavarone M performed project administration; Reig M, Bruix J and Boix L searched funding acquisition.

Supported by the Bayer Grant, No. JBT-SOR 2013-01; the Instituto de Salud Carlos III, No. PI18/00768, PI15/00145 and PI18/0358; Fondo Europeo de Desarrollo Regional (FEDER) from the European Commission "Una manera de hacer Europa"; Pla estratègic de recerca i innovació en salut (PERIS) Grant, No. PERIS_IPIF19-SLT008/18/00182-RH0; Contratos Predoctorales de Formación en Investigación en Salud (PFIS), No. FI19/00222.

Institutional review board statement: The study was approved by the institutional review board of each center (HCB/2009/4755, HCB/2015/0352, Ethical Board 2 480_2018 and CE/2014/193).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: Víctor Sapena: Travel grants from Bayer; Massimo Iavarone: Bayer, Gilead Sciences, BMS, Janssen, Ipsen, MSD, BTG-Boston Scientific, AbbVie, Guerbet, EISAI, Shionogi; Loreto Boix: Speaker fees from Bayer; Marco Sanduzzi Zamparelli: Speaker fees and travel funding from Bayer; Travel grant from BTG, Eisai and MSD; Mario Scartozzi: Speakers Bureau and Advisory board Bayer, EISAI, MSD, AMGEN, Merck, Sanofi; Alba Díaz: Speaker fees from Bayer; Andrea Casadei-Gardini: Speakers Bureau and Advisory board Bayer, EISAI, MSD, Ipsen, AstraZeneca, GSK; Pietro Lampertico: Speaking bureau/advisor for Abbvie, Eiger, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck/ Merck Sharp & Dohme, MYR Pharma, Roche; Ferran Torres: DSMB fees from Basilea Pharmaceutica International and ROVI; educational fees from Janssen and Ferrer; Jordi Bruix: Consultancy fees from Arqule, Bayer, Novartis, BMS, BTG-Biocompatibles, Eisai, Kowa, Terumo, Gilead, Bio-Alliance/Onxeo, Roche, AbbVie, Merck, Sirtex, Ipsen, Astra-Medimmune, Incyte, Quirem, Adaptimmune, Lilly, Basilea, Nerviano; Research grants from Bayer and BTG; Educational grants from Bayer and BTG; Lecture fees from Bayer, BTG-Biocompatibles, Eisai, Terumo, Sirtex, Ipsen; María Reig: Consultancy fees from Bayer, BMS, Roche, Ipsen, AstraZeneca, UniversalDX and Lilly; Lecture fees from Bayer, BMS, Gilead, Lilly and Roche; Research grants (to the institution) from Bayer, Roche and Ipsen; and the rest of the authors have no conflicts of interest to report.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: Spain

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S-Editor: Ma YJ
L-Editor: Webster JR
P-Editor: Ma YJ

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