Safety of sitagliptin in treatment of hepatocellular carcinoma in chronic liver disease patients

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Safety of sitagliptin in treatment of hepatocellular carcinoma in chronic liver disease patients

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Abstract

Background & Aims: Systemic therapies for hepatocellular carcinoma (HCC) treatment have limited efficacy and poor safety. Dipeptidyl peptidase-4 inhibitors were initially developed and approved as treatment for type 2 diabetes, yet oral administration of sitagliptin has recently been shown to improve naturally occurring tumour immunity in animal models of HCC.

Methods: We conducted a phase Ib clinical trial to evaluate the impact of a preoperative 3-week DPP4 inhibitor (sitagliptin) treatment in HCC patients undergoing liver resection. The primary objective was to evaluate the safety of a sitagliptin treatment in each of the three groups of patients, according to an escalating dosage of sitagliptin (100, 200 and 600 mg/d). Secondary objectives included the assessment of DPP4 activity, cytokine expression in plasma samples and circulating immune populations.

Results: Fourteen patients were included and analysed. In all three dose groups, no severe adverse event related to sitagliptin was reported. A significant inhibition of DPP4 activity was observed upon sitagliptin treatment, which prevented the N-terminal truncation of CXCL10, leading to a mobilization of circulating CD8+ T cells and eosinophils. Immunochemistry analysis showed a lymphoid infiltration in all tumour samples with the presence of a population of CXCR3+ T cells in all but one of the tumours. Positivity for CXCL10 (IP10) and CCR3 in tumour and/or stroma cells was found in all resection pieces.

Conclusion: In summary, sitagliptin can be used safely in patients with chronic liver disease and HCC, and could be tested in phase 2 trial, as an adjuvant in combination with others drugs, for the treatment of HCC patients.

*These authors contributed equally to this work.

KEYWORDS
dipeptidyl peptidase 4, hepatocellular carcinoma, leucocyte trafficking, neoadjuvant therapy, sitagliptin

KEY POINTS

- Sitagliptin as a neoadjuvant treatment in hepatocellular carcinoma.
- Sitagliptin as an immunotherapy in hepatocellular carcinoma.
- Safety of Sitagliptin in chronic liver disease patients with hepatocellular carcinoma.
- Sitagliptin improves leucocyte trafficking in hepatocellular carcinoma

1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer, and third most common cause of cancer-related mortality worldwide.[1] While the early screening of HCC by abdominal ultrasound allows a curative therapy (liver resection, thermo-ablation or liver transplantation) in around two-thirds of cases, other HCCs are usually treated by palliative (TACE) or supportive care.[2] In the absence of screening, more than two-thirds of HCCs are treated either by supportive care or by the only available chemotherapies, sorafenib or regorafenib, antigiogenic drugs with limited efficacy and poor safety.[3] New therapies based on anti-PD1/PDL1 strategies showed encouraging results, especially in combination with antiangiogenic drugs.[4]

Dipeptidyl peptidase 4 (DPP4, also known as CD26) is an enzyme that can remove the first two amino acids from a protein possessing a proline or alanine in the penultimate N-terminal position.[5] In particular, it can truncate the incretin hormones glucosedependent insulinotropic polypeptide (GIP) and glucagonlike peptide-1 (GLP-1), leading to the formation of antagonist forms. Building on this observation, DPP4 inhibitors were developed and approved as treatments for type 2 diabetes.[6] Various chemokines, including CXCL10, CCL11, are also substrates of DPP4, and are important to immune cell trafficking.[5,7]

In previous works, we reported that DPP4 inhibition through oral administration of sitagliptin improved naturally occurring tumour immunity in animal models of melanoma, colorectal carcinoma, as well as HCC. While this improved tumour control was due to increased T cell recruitment through perservation of functional CXCL10 in melanoma and colorectal carcinoma,[8] DPP4 inhibition efficacy in HCC models was driven by and increased eosinophil migration into tumours, mediated by CCL11 and tumour expression of IL-33.[9]

To extend these findings, we conducted a phase Ib clinical trial (ClinicalTrials.gov Identifier: NCT02650427, Figure S1) to evaluate the impact of a pre-operative 3-week DPP4 inhibitor (sitagliptin) treatment in HCC patients undergoing liver resection. The primary objective was to evaluate the safety of a sitagliptin treatment in each of the three groups of patients, according to an escalating dosage of sitagliptin (100, 200 and 600 mg/d). The secondary objectives included the assessment of DPP4 activity, cytokine expression in plasma samples and circulating immune populations in the first two treatment groups (100 and 200 mg daily).

2 | METHODS

2.1 | Study setting and patients

This study was a prospective, open-labelled, monocentric pilot phase Ib clinical trial with dose escalation approved by the Comité de protection des personnes Ile-de-France 3 (CPP IDF 3) and by the Agence nationale de sécurité du médicament (ANSM), and sponsored by Institut national de la santé et de la recherche médicale (Inserm). Participants were patients with HCC for whom a curative surgery was planned in La Pitié Salpêtrière hospital, Paris, France. Inclusion criteria were as follows: above 18 years of age, diagnosis of HCC BCLC A stage, for which surgery has been chosen as curative treatment and no cirrhosis or Child A cirrhosis. Exclusion criteria were as follows: HIV infection, portal hypertension (oesophageal varices, platelet count 100,000, splenomegaly), diabetes and impaired liver or renal function.

Enrolled patients received 100 mg (n = 5), 200 mg (n = 5) or 600 mg (n = 4) of sitagliptin (Januvia®, Merck) daily during the time awaiting surgery after liver biopsy (28 ± 7 days) (Figure 1). The inclusion of patients started in February 2016. End of inclusion of the first five patients who were given 100 mg/d of sitagliptin occurred in July 2016. Then, the second group of five patients who were given 200 mg/d of sitagliptin was enrolled from July 2016 to June 2017; the third group of four patients who were given 600 mg/d of sitagliptin from January 2018 to May 2018 (Figure 2). All participants gave written informed consent prior to inclusion in the study, in agreement with the principles set out in the WMA Declaration of Helsinki and the Department of Health and Human Services Belmont Report.

2.2 | Visits and blood samples

Patients were evaluated during six visits: after selection and before recruitment and inclusion (V0); at start of sitagliptin treatment (V1);

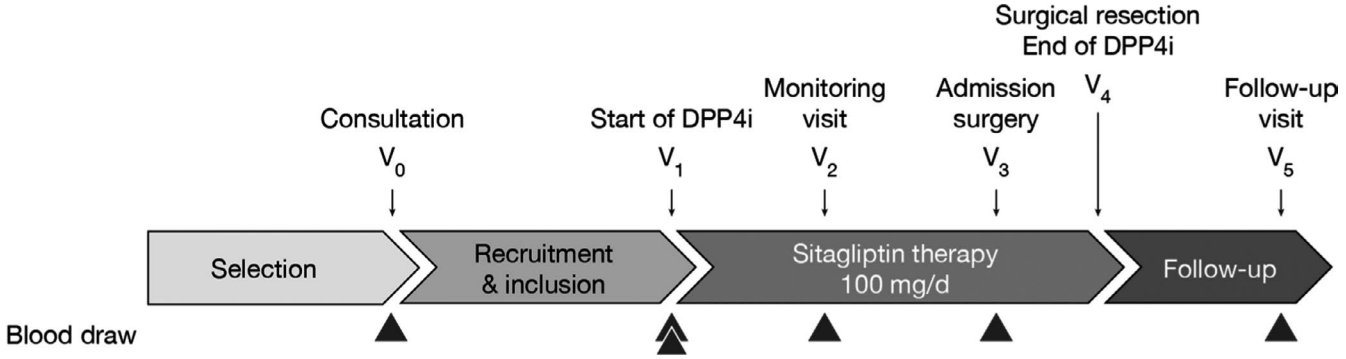


FIGURE 1 Study design of the clinical trial HCC-DPPIV (C15-41). Five patients with histologically proven HCC for whom curative surgery was planned were enrolled at visit 0 (V0). At V1, after liver biopsy they started treatment with the DPP4i sitagliptin (Januvia, Merck, 100 mg per day). The five following patients received 200 mg per day, and the last four patients will receive 600 mg per day. Treatment was continued until the day before surgery (21 ± 7 days of treatment). Blood samples were collected twice during treatment (V2 and V3) and 3 to 5 days after surgery (V5)

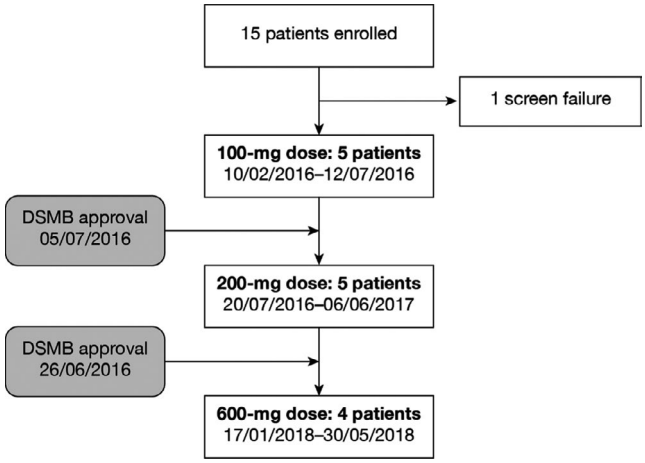


FIGURE 2 Trial flow chart

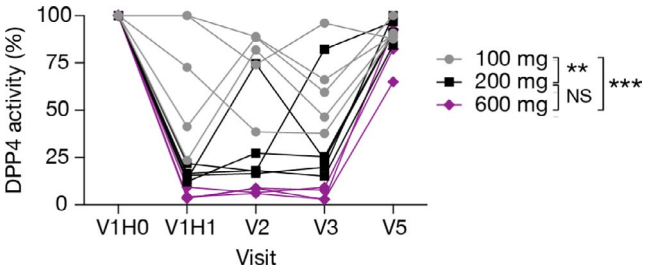


FIGURE 3 Plasmatic DPP4 activity, measured in plasma and plotted as percentage of V1H0 values. Each line corresponds to one patient. NS, not significant; $^{**}P < .01$, $^{***}P < .001$ Significance was determined using mixed effect model followed by Tukey's multiple comparison test

twice during treatment (V2 and V3); at day of surgery (corresponding to treatment end, V4); and 3-5 days after sitagliptin discontinuation/surgery (V5). Six blood samples were collected for each patient: one at V0, two at V1 (one before (V1H0) and one 1 h after the first pill (V1H1)), one at V2, one at V3 and one at V5. Liver biopsy was performed at V1.

Plasma was collected in BD P800 tubes containing ethylenediamine tetraacetic acid (EDTA) and a DPP4 inhibitor to prevent extracorporeal cleavage of CXCL10. Blood collected in sodium heparin tubes was used for monitoring DPP4 activity and for performing flow cytometry. Plasma samples were stored at −80°C until analysis.

2.3 | Flow cytometry

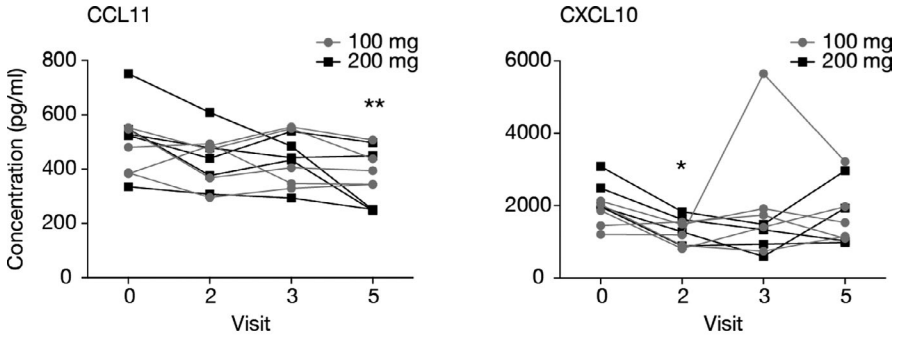
Fluorochromeconjugated antibodies used were anti-hCD56 (clone TULY56, eBioscience), -hCD3 (clone UCHT1, BD Biosciences), -hCD8b (clone SIDI8BEE, eBioscience), -hCD19 (clone HIB19, BD Bioscience), -hCD4 (clone OKT4, eBioscience), -hCD14 (clone 61D3, eBioscience), -hSiglec-8 (clone 7C9, BioLegend), -hCD16 (clone B73.1, BD Bioscience), -hCD45 (clone HI30, BD Bioscience), -hCD193 (CCR3) (clone eBio5E8-G9-B4, eBioscience), -hCD86 (clone 2331, BD Bioscience) and -hCD279 (clone MIH4, BD Bioscience). Flow cytometry was done with a MACSQuant Analyzer 10 (Miltenyi Biotec) and computer analysis was performed with FlowJo (Treestar).

2.4 | Luminex assay and DPP4 activity

For the detection of human IL-4, IL-5, IL-13, CXCL10, CCL11, IFN-γ, TNF-α, Millipex MAP human cytokine/chemokine magnetic bead panel (MCYTOMAG-70K, Merck) was used. Plates were read in a Magpix System (Merck). Computer analysis was done with Millipex Analyst 5.1 software. DPP4 activity was measured in plasma with the DPPIV-Glo Protease Assay (Promega).

2.5 | CXCL10 quantification

Human plasma concentration of total (R&D clone 33036), long ($CXCL10_{1-77}$, AbD Serotec clone 12 010) and short ($CXCL10_{3-77}$, AbD



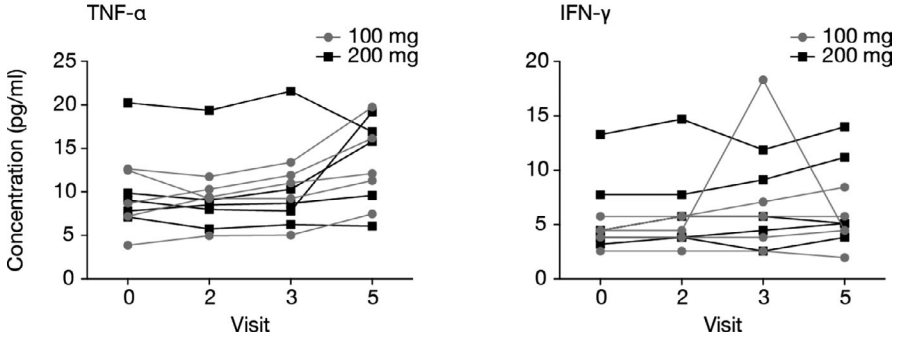


FIGURE 4 Plasmatic levels of cytokines. Plasmatic levels of CCL11, CXCL10, TNF-α and IFN-γ were quantified by Luminex technology. Results for IL-4, IL-5 and IL-13 were below the limit of detection. NS, not significant; *$P < .05$, **$P < .01$. Significance was determined using Friedman test followed by Dunn's post-test

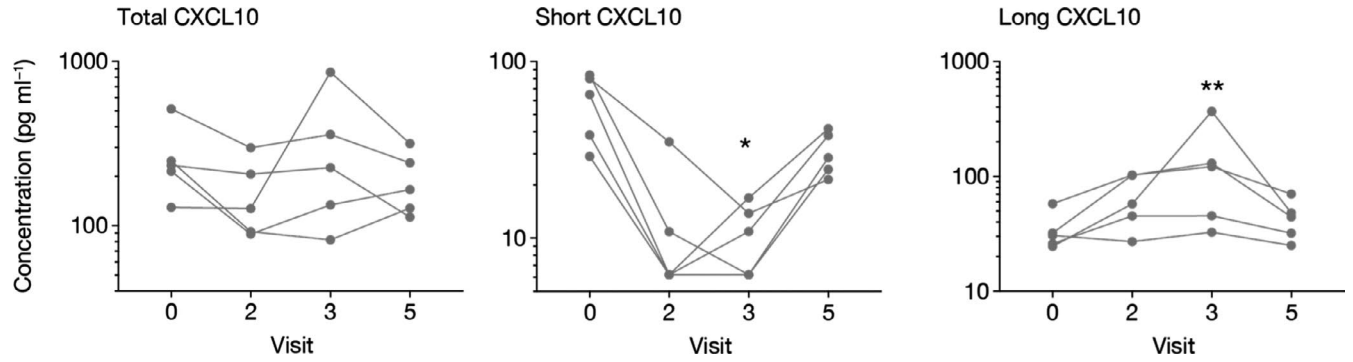


FIGURE 5 Quantification of long, short and total forms of CXC10 in plasma. Plasma levels of the long form of CXCL10 (CXCL101-77) and the short form of CXCL10 (CXCL103-77) were quantified by Simoa immunoassays. Each line corresponds to one patient from the first group. *$P < .05$, **$P < .01$ Significance was determined using Friedman test followed by Dunn's post-test

Serotec clone 09852) CXCL10 was measured using Simoa technology (Quanterix). Simoa assays were carried out as previously described (205).

2.6 | Histology

The immunostaining procedure was performed on formalin fixed, deparaffinised, 3µm thick sections using Ventana Benchmark Ultra platform (Roche Diagnostics, France) and the visualization system Optiview (Roche Diagnostics) according to manufacturer's instructions. The following primary antibodies were used: mouse monoclonal anti-CXCR3 antibody (dilution 1/150; clone 49801; ref. MAB160, R&D Systems, MN) with the following antigen retrieval (CC1, 8 min, 95°C) and antibody incubation time of 60 min at 20°C; rabbit polyclonal anti-IP10 (dilution 1/100; ref. ab9807, Abcam, France) with the following antigen retrieval (CC2, 8 min, 95°C) and antibody incubation time of 60 min at 20°C; rabbit polyclonal anti-DPP4 (dilution 1/500; ref. ab28340, Abcam) with the following antigen retrieval (CC1, 8 min, 95°C) and antibody incubation time of 28 min at 20°C; rabbit monoclonal anti-CCR3 (dilution 1/100; clone Y31; ref. ab32512, Abcam) with the following antigen retrieval (CC1, 8 min, 95°C) and antibody incubation time 60 min at 20°C.

Each marker was semi-quantitatively assessed according a four-level scale: negative, slightly positive (+), moderately positive (++), strongly positive (+++).

2.7 | Statistical analysis

Statistical analyses were performed with Prism v. 8 (Graphpad). Friedman's test followed by Dunn's post-test were used to compare visits (reference visit was V1H0 for Figure 3, and V0 for Figures 4 and 5). Two-way analysis of variance was used to compare dose groups. Statistical tests were two-sided, and P values < .05 were considered significant.

TABLE 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• 18 years of age at day of inclusion • For women, a negative blood pregnancy test before inclusion. Note: this test will be done only to women of childbearing age and non-menopausal. • HCC based on medical imaging with indication of liver resection and without contra-indication of preoperative liver biopsy. • Minor resection not exceeding 2 liver segments. • No cirrhosis or cirrhosis with a Child-Pugh score Class A. • Informed consent prior to study entry. • Affiliation to health policy insurance.	• HIV Infection • Renal impairment (CrCl <60 mL/min). • Compromised liver function (Child Pugh B, MELD Score >9) • Indirect sign of portal hypertension (oesophageal varices, splenomegaly, platelet count <100 000/mm^3) • Need for hepatic resection (> 2 segments) • Treatment by digoxin (digitalis) within 6 months of starting treatment • History of severe hypersensitivity reaction (such as anaphylactic shock or angioedema) to sitagliptin • Diabetes • Pregnancy or absence of an effective contraception for women • Deprivation of liberty by judicial or administrative decision, person subject to a legal protection measure • Living conditions suggesting an inability to track all scheduled visits by the protocol • Life expectancy <3 months

3 | RESULTS

Patients with HCC and planned liver resection that met the inclusion criteria (Table 1) were selected and evaluated during six visits (Figure 1). From February 2016 and September 2018, of 15 patients enrolled, 14 were included: the first five patients received 100 mg of sitagliptin daily, the next five received 200 mg daily and the last four received 600 mg daily (Figure 2).

Patient characteristics are shown in Table 2. Population consisted in 11 men and 3 women, median age was 68.5 years and median BMI was 25.7 kg/m^2. Eight (57%) of patients had biopsy-proven cirrhosis (Metavir F4 score at the histological analysis of the liver) and causes of chronic liver disease were chronic viral infection (HBV in 6 patients and HCV in 5 patients) or alcohol consumption in three patients. The median duration of sitagliptin treatment was 19.5 (range 14-28) days. All patients underwent surgery within 28 days except one patient (patient 11) for whom therapeutic strategy changed for radiological chemoembolization.

In the three groups of doses, no severe adverse effect related to sitagliptin was reported (Table 3). No hypoglycaemia (Table S1), pancreatitis or premature discontinuation occurred. Among severe adverse effects (grade 4) non-related to the treatment, we found three elevation of liver enzymes just after liver resection, one post-operative hypoxaemia, one pre-operative bradycardia, one post-operative pneumonia and one wrist fracture. Most common low-grade adverse effects were asthenia and fever.

DPP4 activity was assessed in plasma samples throughout visits in patients in the three groups (100, 200 and 600 mg daily). A significant inhibition of DPP4 activity was observed upon sitagliptin treatment, starting 1 h after the first pill taken (V1H1) (Figure 3). Notably, this inhibition was more dramatic and more consistent in the 200-mg and 600-mg groups compared to the 100-mg group, with an approximate 25% (100-mg group), 75% (200-mg group) and 95% (600-mg group) DPP4 inhibition.

Plasma levels of different cytokines in the first two groups showed a significant decrease in CCL11 levels at V5 and CXCL10 at V2 in both groups. No significant modification of TNF-α or IFN-γ was observed (Figure 4).

To identify which form of CXCL10 was affected by this decrease, long, short and total forms of CXCL10 upon sitagliptin treatment for the first group (100-mg dose) was measured. Again, total CXCL10 levels were decreased at V2, indicating that sitagliptin prevented the truncation of CXCL10, preserving the long agonist form at the expense of short antagonist form (Figure 5). No correlation was found between CXCL10 levels and ASAT and ALAT levels (Table S2).

We then evaluated the modifications of circulating immune cells upon treatment by flow cytometry in all groups. We observed a modest reduction in the number of circulating CD8$^+$ T cells and a decrease in the percentage of circulating eosinophils (Figure 6). Eosinophils found in the blood of patients showed a reduced expression of the chemokine receptor CCR3 upon treatment with DPP4i.

Histological analysis of the 13 tumours resections showed a median tumour size of 30 (range 17-180) mm. All tumours were HCCs, with all but one of the resections being considered complete. Four tumours were encapsulated, 11 tumours were moderately differentiated, one was well differentiated, one was poorly differentiated and four patients showed evidence of vascular embolism. Immunochemistry analysis showed a lymphoid infiltration in all tumour samples with presence of population of CXCR3$^+$ T cells in all but one of the tumours. Positivity for CXCL10 (IP10) and CCR3 in tumour and/or stroma cells was found in all resection pieces (Figure 7 and Table 4).

At the end of the study, 2 patients died with death being attributed to tumoral disease. Of the 12 patients alive, 2 (16.7%) had a local tumour recurrence after a mean follow-up of 18 months after liver resection.

4 | DISCUSSION

Sitagliptin has recently been shown to improve naturally occurring tumour immunity in animal models of HCC and a synergistic

TABLE 2 Patient characteristics

Patient	2	3	4	5	6	7	8
Gender	M	M	M	M	M	M	M
Age (years)	56	73	60	60	68	38	77
BMI (kg/m^2)	22.8	21.7	26.4	18.6	26.7	27	29.4
Liver disease	HCV UT	HBV UT	OH	HCV cured	HCV cured	HBV UT	OH/ NASH
Viral Load (UI/mL)	< 12	< 10	-	-	-	10^6	-
Antiviral therapy	SOF+LED +RIBA	TNF	-	-	-	ETV	-
Cirrhosis	No F1	Yes ChildA	No F0	Yes ChildA	Yes ChildA	Yes ChildA	Yes ChildA
ASAT/ALAT (UI/mL)	26/16	89/28	28/25	32/28	33/27	55/73	26/31
Total Bilirubin (μmol/L)	10	11	9	12	10	7	6
GFR CKD-EPI (mL/min)	88	71	78	98	63	115	83
Albumin (g/L)	42	39	33	42	47	38	38
Platelets (10^9/L)	142	102	348	148	281	122	161
Prothrombin Rate (%)	97	80	84	97	98	76	84
AFP (μg/L)	127	36	8	4	97	4	5
Number of HCC nodules	1	1	1	2	1	1	1
BCLC	A	A	A	A	A	A	A
Previous HCC treatment	Naive	Naive	Naive	RF	Naive	Naive	Naive
Sitagliptin (days)	22	25	15	28	26	21	15

Note: Statistics are given as number of patients with characteristics (percentage) for binary variable, median (range) for continuous variables.
Abbreviations: AFP, alpha-foetoprotein; BCLC, Barcelona clinic liver cancer; GFR, glomerular filtration rate; HCC, hepatocellular carcinoma; OH, alcohol; SAE, severe adverse event; ttt, treatment duration; UT, under treatment.

TABLE 3 Severe adverse events

Dose	Patient	Severe adverse event(s)
100 mg	4	ALT Increase (V5)
	6	Post-operative hypoxia (V5)
200 mg	8	Pre-operative bradycardia (V4)
	11	Left wrist fracture (V2)
300 mg	12	Post-operative pneumonia (V5)/ALT Increase (V5)
	13	ALT Increase (V5)/AST Increase (V5)
	14	Obstruction in the resection lodge (V5)

effect has been established with immune therapies.[8,9] This phase 1b study showed that DPP4 inhibition by oral sitagliptin is safe at the three tested escalating doses (100, 200, 600 mg daily) in a population of with HCC-associated chronic liver disease patients, with no adverse event related to the drug. Additionally, we confirmed that oral sitagliptin treatment, by inhibiting DPP4 activity, modulates the expression of the DPP4 substrates CXCL10 and CCL11. Particularly, sitagliptin preserves the long active form of CXCL10 and decreases the short antagonist form of CXCL10. This therapeutic effect seems to be associated with a decrease in circulating CD8$^+$ T cells and a reduction in circulating eosinophils. Some supplementary functional analyses of peripheral or intra-tumoral T cells need to be done in future studies, including analysis of traffic regulatory T cells.

We confirmed by histological analyses of the tumours that CXCR3$^+$ T cells are involved in antitumor immunity and that CXCL10 chemokine is present in the tumour environment. The use of a drug that enhances active forms of CXCL10 to promote CXCR3$^+$ cytotoxic T cells could be an efficient strategy for treatment of HCC, as a neoadjuvant drug to improve the efficacy of the other treatments.

We made the choice of evaluating the impact of sitagliptin in the treatment of HCC, as neoadjuvant therapy, since (i) we previously reported efficacy in reducing tumour volume in animal models[8,9]; (ii) There are no drugs approved in this clinical setting; and (iii) combined therapies with various targets should be more efficacious than monotherapy.[10] This phase 1b study was only devoted to the evaluation of the safety of escalating dose of sitagliptin. This treatment is currently administrated

9	10	11	12	13	14	15	Statistic
F	M	F	M	F	M	M	11 M (78%)
70	53	57	77	72	69	82	68.5 (38-82)
25	25	31	28	36	21	21	25.7 (21-36)
HBV	HBV UT	HBV UT	HCV cured	HCV cured	HBV UT	OH	
< 10	< 10	< 10	-	-	< 10	-	
-	ETV	ETV	-	-	ETV	-	
Yes ChildA	No F3	Yes ChildA	Yes ChildA	N0 F3	No F2	No F2	8 (57%)
38/18	32/25	142/136	26/24	25/23	51/70	44/38	
6	11	17	7	5	12	15	
79	97	112	88	111	106	83	
39	45	28	43	33	42	36	
198	126	149	209	147	173	236	
87	101	76	103	92	87	98	
38 220	142	6450	5	128	19	19	
1	1	2	1	1	1	1	
A	A	A	A	A	A	A	
Naive	Naive	Naive	Naive	Surgery RF	Naive	Naive	
20	14	16	28	19	18	14	19.5 (14-28)

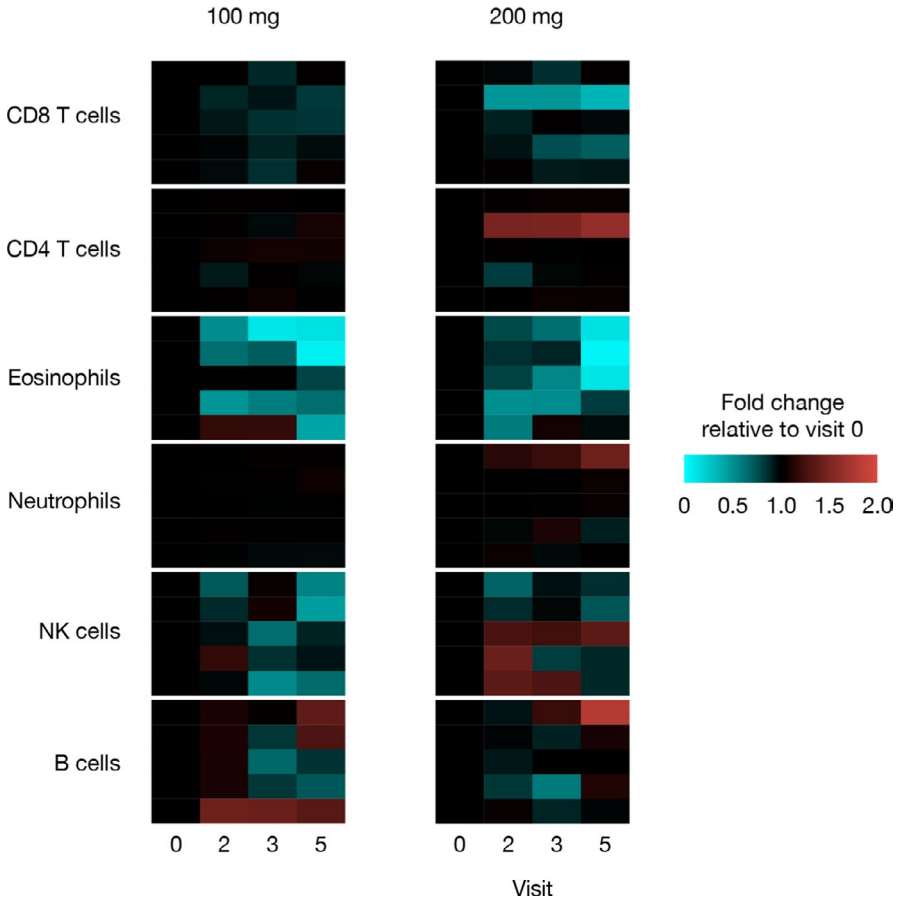


FIGURE 6 Impact of sitagliptin treatment on circulating immune populations. Blood-associated immune cell populations were evaluated by flow cytometry and plotted as fold change relative to V0

TABLE 4 Histological features of resected tumours

Patient	Size (mm)	Capsule	Complete resection	Grade	Differentiation	Vascular embolism	CK19	Necrosis (%)	Eosinophils
2	20	No	Yes	2(3)	moderate	0	–	0	0
3	25	No	Yes	1(1)	good	0	–	0	0
4	180	No	Yes	4(4)	poor	1	–	0	0
5	30	Yes	Yes	2(2)	moderate	0	–	90	+
6	10	Yes	Yes	2(2)	moderate	0	–	10	0
7	30	No	No	2(2)	moderate	0	–		0
8	50	Yes	Yes	2(1)	moderate	0	–	0	0
9	70	No	Yes	2(2)	moderate	1	–	10	0
10	25	No	Yes	2(3)	moderate	0	–	70	0
12	29	No	Yes	2(2)	moderate	0	–	10	0
13	17	No	Yes	2(2)	moderate	1	–	10	0
14	45	Yes	Yes	2(2)	moderate	1	–	10	0
15	35	No	Yes	2(3)	moderate	0	–	30	0

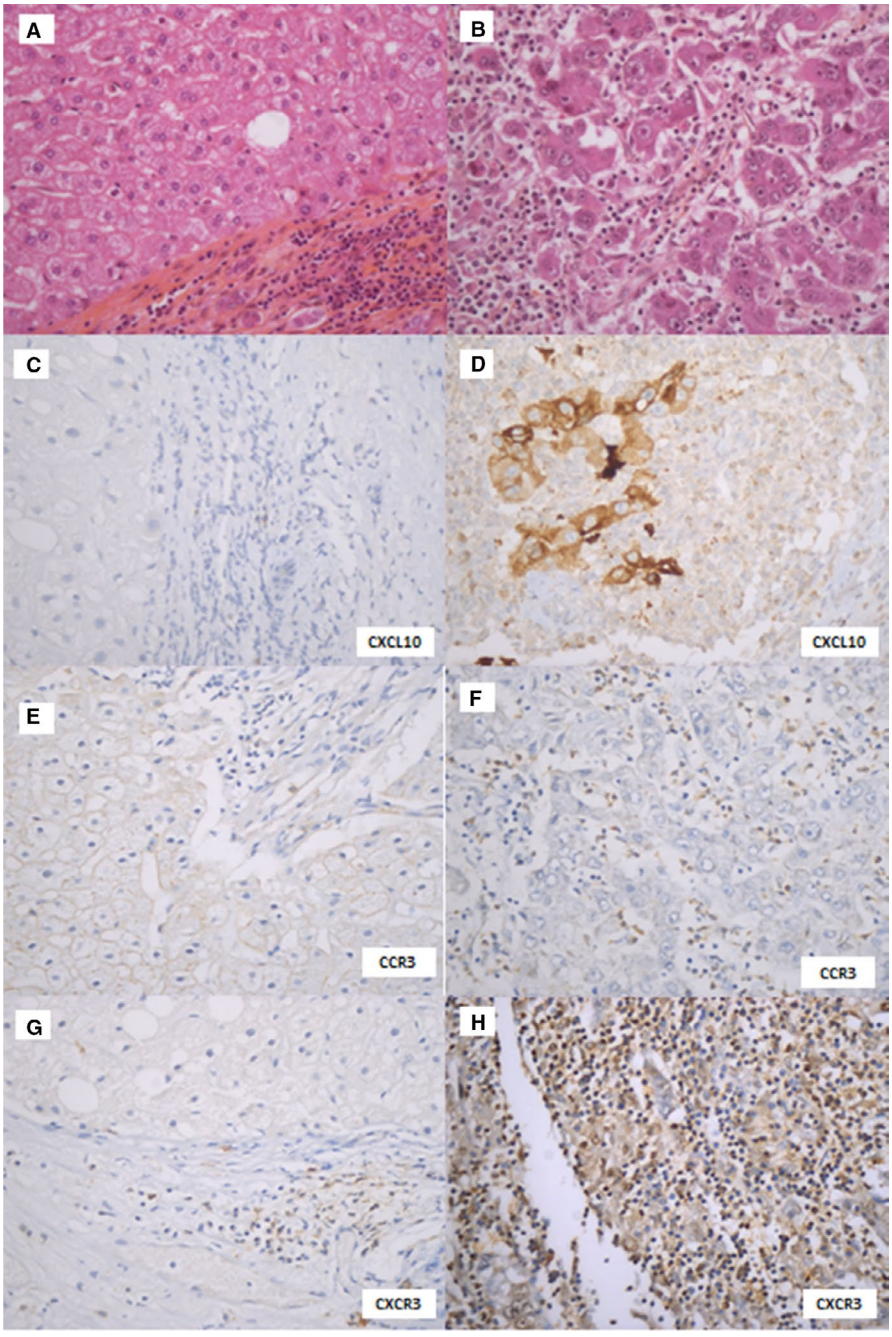


FIGURE 7 Expression of CXCL10, CCR3 and CXCR3 in non tumoral and tumoral liver. Patient no. 6. A, Non tumoral cirrhotic liver (haematein-eosin-saffron, original magnification x400). B, Hepatocelullar carcinoma (haematein-eosin-saffron, original magnification x400). C, Cirrhotic liver: rare inflammatory cells within the fibrous septa faintly express CXCL-10 (immunostaining, original magnification x400). D, Hepatocelullar carcinoma: Tumour cells and stromal cell express CXCL-10 (immunostaining, original magnification x400). E, Cirrhotic liver: inflammatory cells are negative for CCR3 (immunostaining, original magnification x400). F, Hepatocelullar carcinoma: stromal cells express CCR3 (immunostaining, original magnification x400). G, Cirrhotic liver: inflammatory cells are positive for CXCR3 (immunostaining, original magnification x400). H, Hepatocelullar carcinoma: stromal cells express CCR3 (immunostaining, original magnification x400)

Non tumoral liver	Steatosis	Lymphoid infiltration	CXCR3$^+$ T cells	IP10 tumor cells	IP10 stroma	CD26	CCR3 tumor cells	CCR3 stroma
A1F1	S0	+	+	+	+	+	+	+
A2F4	S1	+	+	−	−	+	−	+
A0F0	S1	+	−	+	+	+	−	++
A1F4	S0	+	+	−	+	+	−	++
A1F4	S1	+++	+	+	+	+	−	+++
A1F4	S0	++	+	−	−	+	−	−
A1F4	S3	+	+	−	−	+	++	−
A0F4	S0	+	+	+	−	+	+	−
A0F3	S0	+	+	+	+	+	−	+
A0F4	S0	+	+	−	−	+	++	+
A0F3	S0	+	+	−	−	+	−	+
A1F2	S0	+	+	−	+	+	++	+
A1F2	S0	+	+	+	+	+	−	+

to several millions of type 2 diabetes patients for its effect on incretin hormones, yet the regular dosage is currently 100 mg/d.[6] Our study suggests that higher dosages (200 and 600 mg) are well tolerated since we did not observe significant adverse events which should be attributed to sitagliptin. With a fair safety, the use of high dosage of sitagliptin could be considered for the treatment of HCC, given the dose-dependent effect.

Some systematic reviews reported some correlation between antidiabetic medications and risk of HCC. Metformin showed a beneficial effect on HCC incidence,[11] while insulin or sulphonylureas therapy were associated with higher risk of HCC.[12] Metformin can impede carcinogenesis through indirect (insulin-dependent) and direct (insulin-independent) mechanisms such as the activation of the AMP-activated protein kinase (AMPK) and the inhibition of mTOR activity.[13] Similar meta-analyses are clearly needed to evaluate the association between risk of HCC and gliptin treatments.

In conclusion, sitagliptin treatment decreases DPP4 activity in vivo in patients with chronic liver disease and HCC, allowing the preservation of active form of chemokines (CXCL10), which can have a positive impact on leucocyte trafficking towards the tumour. Some further studies need to be done with control group of patients to better clarify immune modulatory effect of sitagliptin. However, this drug can be used safely in this population of patients and could be tested in phase 2 trial, alone or in combination with others drugs, for the neoadjuvant treatment of HCC patients.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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