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Position Paper

Management of immune checkpoint inhibitor in patients with cancer and pre-existing inflammatory bowel disease: Recommendations from the GETAID☆

Aurelien Amiot[a,b,*], David Laharie[c], Georgia Malamut[d], Melanie Serrero[e], Florian Poullenot[c], on behalf of the educational committee of the GETAID[1]

[a] Department of Gastroenterology, Hopitaux Universitaires Bicêtre, AP-HP, Universite Paris Est Creteil, Le Kremlin Bicêtre, France
[b] INSERM, Centre for Research in Epidemiology and Population Health, Institut Gustave Roussy, Université Paris Saclay, Villejuif, France
[c] CHU de Bordeaux, Hôpital Haut-Lévêque, Service d'Hépato-gastroentérologie et oncologie digestive – Université de Bordeaux, F-33000 Bordeaux, France
[d] Department of Gastroenterology, AP-HP-Centre, Université de Paris, Hôpital Cochin, Paris, France
[e] Department of Gastroenterology, University Hospital of Marseille Nord, Aix-Marseille, Marseille University, Marseille, France

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ABSTRACT

Background and aims: There is no consensus on the management of immune checkpoint inhibitor (ICI) for treating cancer in patients with pre-existing inflammatory bowel disease (IBD). The Groupe d'Étude Thérapeutique des Affections Inflammatoires du tube Digestif (GETAID) aimed to provide recommendations on this topic.

Methods: A dedicated working group performed a comprehensive expert-based review of the literature, generated clinical key question and shaped recommendations that were further voted for approval by the educational and scientific committees of the GETAID. Using consensus methods, treatment modalities were defined by vote.

Results: Majority of patients with IBD in clinical remission can be treated with ICI after cancer diagnosis. The rate of relapse or immune-related diarrhoea or colitis upon ICI treatment is up to 39.8% and is maximal with ICI combination therapy compared to monotherapies. When starting ICI in a patient with IBD, it is recommended to assess disease activity and pursue ongoing maintenance therapy. In case of relapse or immune-related diarrhoea or colitis upon ICI treatment, treatment depends on grading of diarrhoea or colitis and may include corticosteroid therapy, infliximab and/or vedolizumab.

Conclusions: In the present publication, we provided recommendations, which may assist gastroenterologists, haematologists, and oncologists for a better management of patients with pre-existing IBD before and during cancer treatment with ICI.

1. Introduction

Immune checkpoint inhibitors (ICIs) including anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and programmed cell death protein 1 (PD-1), or its ligand (PD-L1) have revolutionized treatment and prognosis of several advanced cancer [1]. ICIs act by inhibiting the suppressive T-cell co-stimulatory signals, resulting in a sustained hyperactivation of the immune system and the promotion of antitumour immunity [2]. However, activating the immune system with ICIs may lead to off-target immune-related adverse events including ICI-mediated diarrhoea and colitis (IMDC) [3,4]. Incidence of all grade diarrhoea has been estimated in 11–17% with anti-PD-1, 35–40% with anti-CTLA-4 and 32% with combination therapy of the latter ICI classes [5–8]. Concerning colitis, incidence has been estimated in 0.3–3.4% with anti-PD1, 8.4–11.3% with anti-CTLA-4, and 14% with combination [6,8–10]. The role of gut microbiota have been demonstrated to predict both IMDC as well as ICI antitumor efficacy [11–14].

Inflammatory bowel diseases (IBD) including ulcerative colitis (UC) and Crohn's disease (CD) are inflammatory progressive disease targeting the gastrointestinal tract [15,16]. Although still not fully resolved, the pathogenesis of IBD relies on an inadequate crosstalk between immune system and gut microbiota in predisposed patients [17]. Trials studying ICI have excluded patients

☆ The data underlying this article will be shared on reasonable request to the corresponding author.

* Corresponding author at: Hôpitaux Universitaires de Bicêtre – Universite Paris Saclay, 78, Avenue du Général Leclerc Le Kremlin Bicetre F-94278, France.
E-mail address: aurelien.amiot@aphp.fr (A. Amiot).

[1] All the members of the office and the educational and scientific committees of the GETAID are listed in the appendix.

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with pre-existing inflammatory disease such as IBD fearing to exacerbate disease activity [18]. Several observational studies have nonetheless reported favourable outcome with ICI in patients with pre-existing IBD [19].

However, there is currently no consensus on the optimal management of ICI in patients with pre-existing IBD. On behalf of the educational committee of the Groupe d'Étude Thérapeutique des Affections Inflammatoires du tube Digestif (GETAID), a panel of gastroenterologists has been created to build recommendations through a consensus process to be used by gastroenterologists, haematologists and oncologists when treating patients with pre-existing IBD with ICI.

2. Design and methods

In February 2021, the educational committee of the GETAID has been contacted regarding management of patients with cancer and pre-existing IBD after initiating ICI therapy. Subsequently, statements were drafted on different situations:

- What is the risk of IBD flare in patients with cancer and pre-existing IBD after initiating ICI therapy?
- What is the optimal work-up before initiating ICI therapy in patients with pre-existing IBD?
- What is the optimal management in patients with pre-existing IBD with incidental digestive symptoms on ICI therapy?

A panel of five gastroenterologists, active members of the educative or scientific committees of the GETAID, have been first assigned to perform an expert-based review of the literature through a comprehensive search of Pubmed and Cochrane database of systematic review, until March 2022, on safety of ICI in patients with pre-existing IBD and more specifically on the risk of relapse of IBD upon ICI and associated factors. Three meetings were set up to analyse and cote evidence and generate clinical key questions on this topic through a 2-round Delphi consensus process. The maximum number of statements was not pre-specified.

Statements were then submitted to all members of the office and educational and scientific committees of the GETAID for approval. All the members of the office and the educational and scientific committees of the GETAID are listed in the appendix. During the consensus meeting, participants were first asked to comment the statements and then to vote. Agreement was achieved if at least 75% of participants strongly agree with each consensus statements (>7 on a 0 to 10 agreement scale). The level of evidence was classified in four grades: high (A), moderate (B), low (C) or very low quality (D), based on the strict assessment of the quality of the evidence. Common Terminology Criteria for Adverse Events (CTCAE) grading for colitis or diarrhoea was used with severe disease defined as grade 3 to 4 diarrhoea or grade 3 to 4 colitis (Table 1) [20,21].

3. Results

3.1. Risk of relapse

A recent meta-analysis has been recently published reporting safety and tolerability outcomes of 12 studies including 193 patients with IBD treated with ICI for cancer [19]. The primary outcome was the cumulative proportion of patients with either IBD relapse or IMDC since it was difficult to distinguish those two entities. In most patients, IBD was inactive at time of initiation of ICI. In the latter meta-analysis, eight studies ($n = 172$ patients) reporting IBD disease activity, only 18% had active disease. Of five studies ($n = 151$ patients) reporting IBD therapy, 41% were not on any IBD therapy and 34% were treated with amino-salicylates. In a median time of follow-up of 15 months, the pooled rates of relapse (of any CTCAE grade) and relapse leading to ICI discontinuation were 39.8% [26.1%–54.5%] and 35.4% [16.8%–56.7%], respectively. There was insufficient data to assess any difference between Crohn's disease and ulcerative colitis. IBD relapse was treated with steroids in 76.1% [65.4%–85.4%] and required a biological agent in 36.6% [29.9%–52.7%] (mainly infliximab and less frequently vedolizumab). Three additional studies have been published thereafter with similar findings [18,22,23]. No risk factor was identified with a trend for anti-CTLA-4 therapy, combination therapy with anti-CTLA-4 and anti-PD-1/PD-L1 and IBD involving the colon [24].

What is the risk of IBD flare in patients with cancer and pre-existing IBD after initiating ICI therapy?

3.1.1. Statement 1 [Grade B – 87.5%]

Majority of patients with IBD in clinical remission can be treated with ICI after cancer diagnosis. IBD relapse or immune-related diarrhoea or colitis may occur upon ICI treatment in up to 39.8% of patients.

3.1.2. Statement 2 [Grade C – 87.5%]

The risk of IMDC is maximal with anti-CTLA-4 and anti-CTLA-4 plus anti-PD-1 or PD-L1 combination therapy. Combination therapy of ICI should be avoided in patients with pre-existing IBD except for those with potential life-threatening complication. In patients with pre-existing IBD, monotherapy with anti-PD-1 or anti-PD-L1 may be preferred to anti-CTLA-4.

3.2. Pretherapeutic work-up

According to the meta-analysis previously cited, active IBD at time of ICI initiation was not associated with higher risk of relapse [19]. Nonetheless, a very limited number of patients in the latter meta-analysis had active disease. This is why, in the state of knowledge, that we recommend to avoid ICI in patients with active IBD and to assess systematically disease activity using clinical score, biomarkers, endoscopic and/or cross-sectional imaging according to European Crohn's and Colitis Organization (ECCO) guidelines [25,26].

What is the optimal work-up before initiating ICI therapy in patients with pre-existing IBD?

3.2.1. Statement 3 [Grade D – 75.0%]

When starting ICI in a patient with IBD, it is recommended to assess disease activity with biomarkers (CRP and faecal calprotectin levels) and endoscopic and/or cross-sectional imaging assessment if possible.

Is it possible to initiate ICI therapy in patients with active IBD?

3.2.2. Statement 4 [Grade C – 50.0%]

In patients with inactive IBD, immunosuppressive maintenance therapy of IBD can be pursued or adapted during ICI therapy according to the oncological risk.

In patients with active IBD, we proposed that ICI are temporarily contra-indicated until clinical remission could be achieved expect for those with potential life-threatening complication. After voting session, no recommendation can be made on this contra-indication, optimal delay to ICI initiation after reaching clinical remission and potential use of anti-TNF or vedolizumab in combination with ICI. The decision should be made in multidisciplinary meeting, considering life-threatening risk related to either IMDC or cancer progression. We recommend to induce clinical remission as soon as possible not to delay ICI initiation

Table 1
National Cancer Institute Common Terminology Criteria for Adverse Events of diarrhoea (A) and colitis (B)[20].

A.

Adverse event of diarrhoea*	Clinical characteristics
Grade 1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared with baseline
Grade 2	Increase of four to six stools per day over baseline; moderate increase in ostomy output compared with baseline; limiting instrumental activities of daily living
Grade 3	Increase of seven or more stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared with baseline; limiting self-care activities of daily living
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

B.

Adverse event of colitis	Clinical characteristics
Grade 1	Asymptomatic; clinical or diagnostic investigations only; intervention not indicated
Grade 2	Abdominal pain; mucus or blood in stool
Grade 3	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

* Diarrhoea is characterized by an increase in frequency and/or loose or watery bowel movements.

3.3. Management in case of incidental digestive symptoms (Fig. 1)

Common Terminology Criteria for Adverse Events (CTCAE) grading for colitis or diarrhoea is commonly used for IMDC (Table 1) [21]. However, there are currently no validated clinical, endoscopic, or histologic outcomes to assess disease activity in IMDC. Waiting for development and validation of reliable and dedicated outcome measures for IMDC, current IBD outcome measures may be also used to assess IMDC severity [21]. In patients with pre-existing IBD treated with ICI having digestive symptoms, similar management as for IBD relapse including stool cultures and *Clostridioides difficile* toxin testing as well as blood tests including cytomegalovirus PCR, may be useful [25,26]. In the latter meta-analysis of Meserve et al., 76.1% of patients experiencing relapse after initiating ICI required corticosteroids and 36.6% of patients required biological [19]. Of 8 studies reporting discontinuation of ICI in patients with pre-existing IBD (n = 173 patients), 82 discontinued ICI.

What are the investigations to be carried out in patients with pre-existing IBD with incidental digestive symptoms on ICI therapy?

3.3.1. Statement 5 [Grade B – 93.8%]

In patients with pre-existing IBD treated with ICI having digestive symptoms, initial investigations should include stool cultures and *Clostridioides difficile* toxin testing and blood tests (full blood count, renal function and electrolytes, C-reactive protein, liver profile, albumin, and thyroid function).

3.3.2. Statement 6 [Grade B – 87.5%]

In patients with pre-existing IBD treated with ICI having diarrhoea, endoscopic examination with at least flexible sigmoidoscopy and systematic biopsies is mandatory for CTCAE grade 3 to 4 diarrhoea or colitis (and for persistent CTCAE grade 1 to 2 diarrhoea or colitis after 3 days despite well-conducted symptomatic treatment). The optimal endoscopic examination should be discussed case by case according to prior IBD location to distinguish IBD relapse from IMDC. Additional endoscopic assessment should be considered in patients failing to respond to steroids or second-line therapy.

What treatment initiate in patients with pre-existing IBD with incidental digestive symptoms on ICI therapy?

3.3.3. Statement 7 [Grade C – 87.5%]

Treatment depends on grading of diarrhoea or colitis, type of IBD and ongoing treatment of IBD (Fig. 1). ICI should be discontinued in patients with grade 3–4 diarrhoea or postponed until resolution for those with grade 2 symptoms. We recommend that adults with sign of severity according to IBD scoring tools or CTCAE grade 3 to 4 IMDC should be admitted to hospital for assessment and intensive management [27].

In patients with pre-existing IBD treated with ICI, presenting with persistent CTCAE grade 1 to 2 IMDC despite well-conducted symptomatic treatment for at least 3 days, oral corticosteroid therapy at a dose of 0.5–1 mg/kg per day should be considered. Proximal involvement of the small intestine and microscopic colitis may be treated with conventional budesonide 9 mg per day.

In patients with CTCAE grade 3 to 4 IMDC (and in those with CTCAE grade 1 to 2 IMDC for whom oral corticosteroid therapy has failed after 3 days of treatment), intravenous methylprednisolone at a dose of 0.8 to 1 mg/kg should be considered.

3.3.4. Statement 8 [Grade C – 93.8%]

In patients with pre-existing IBD treated with ICI, infliximab (at a dose of 5 mg/kg) as well as vedolizumab should be considered in case of intravenous corticosteroids failure, and in the absence of contraindications (as perforation or uncontrolled sepsis).

3.3.5. Statement 9 [Grade D – 75.0%]

In patients with pre-existing IBD treated with ICI requiring a one to three infusions of infliximab or vedolizumab (at weeks 0, 2 and 6) for an IMDC, maintenance treatment have to be discussed on a case-by-case basis. Assessment of endoscopic and/or histological healing after induction of remission may be useful to decide whether those treatments should be pursued or discontinued.

4. Discussion

ICI therapy in patients with pre-existing IBD is a hard dilemma. On the one hand, patients may benefit of the lifesaving or life-prolonging effect of ICI. On the other hand, IBD may relapse and/or IMDC may be life-threatening and lead to ICI discontinuation.

In a recent meta-analysis, Meserve *et al.* demonstrated that patients with pre-existing IBD and ICI therapy relapsed in less than 40% [19]. In case of relapse, steroids were required in approximately two thirds of patients whereas biologics were required in one third. Similarly to non-IBD patients, anti-CTLA-4 therapy were more prone to induce IBD relapse or IMDC whereas it did not reached statistical significancy.

The present expert panel opinions have provided guidance on the management of ICI therapy in patients with pre-existing IBD to help gastroenterologists, haematologists, and oncologists to deal

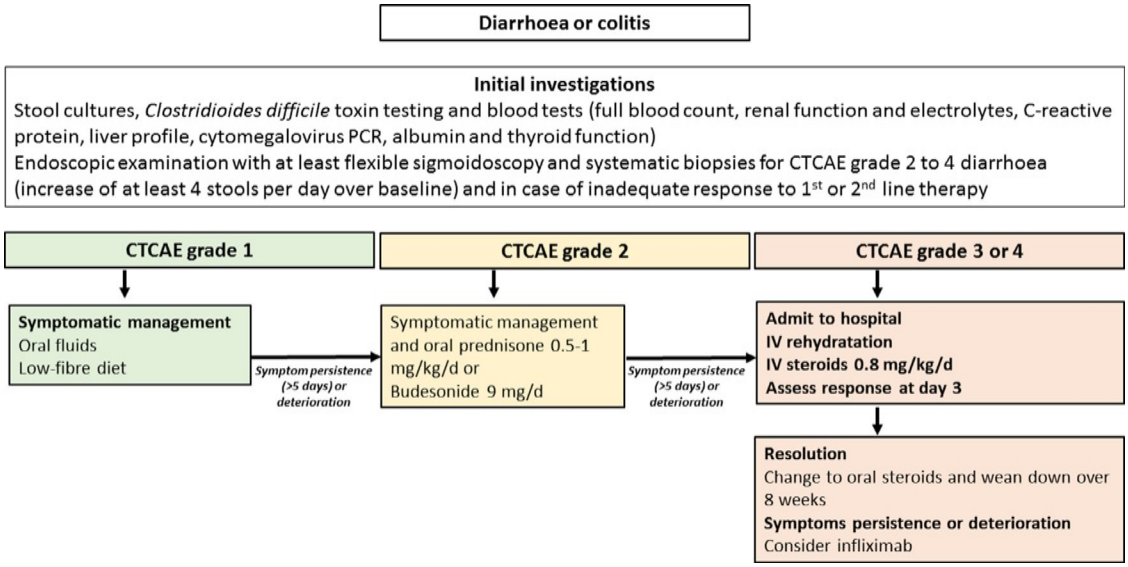

Fig. 1. Treatment algorithm for management of diarrhoea or colitis in patients with with cancer and pre-existing inflammatory bowel disease, treated with immune checkpoint inhibitor.

with that difficult situation. We thought that patients with IBD may have positive benefit-risk ratio with ICI therapy but we recommend systematic pretherapeutic work-up to assess disease activity as well as prospective digestive monitoring of ICI therapy. Of note, in a recent population-based study in the Netherlands, patients with autoimmune inflammatory diseases were as often treated with ICI for melanoma compared to those without [18]. Nonetheless, in the meta-analysis of Meserve, the rate of IBD relapse is high as well as the rate of ICI discontinuation compared to those reported in clinical trials of ICI with other pre-existing autoimmune or inflammatory diseases and in the general population [3,18,28]. This is probably linked to cumulative report of IBD relapse and/or IMDC; but more reassuring data exist, as in the Dutch population-based cohort, where incidence of immune-related adverse events of grade ≥3 did not differ between patients with and those without autoimmune and inflammatory diseases [18].

Recently, the use of ustekinumab and JAK inhibitors have been reported for treating IMDC [29,30]. Those findings suggest potential benefits of many anti-inflammatory drugs commonly used in immune-mediated inflammatory disease to treat IMDC [31]. However, such treatments can add additional toxicities and may altered ICI efficacy. In this setting, steroids whith 4–8 weeks taper schedule may be preferable on the short-term to avoid any delay in the management of IMDC while vedolizumab and anti-TNF may be preferable for treating IMDC while preserving anti-tumour immunity beyond steroids induction therapy [32]. Recently the American Gastroenterological Association recommended a daily dose of 0.5 to 2 mg/kg/day of prednisone equivalent with a taper of 4–6 weeks [33]. To our knowledge, there is insufficient evidence to support higher dose and shorter taper schedule in this setting although the shortest time to remission might be beneficial.

Facing to IBD relapse, most of the patients discontinued ICI therapy irrespective of the severity of the relapse. In the present recommendations, we suggest ICI discontinuation in patients with IBD relapse and/or IMDC of grade ≥3. Although rechallenge of ICI after IBD relapse and/or IMDC may be not recommended, it may be discussed for a life-prolonging purpose. In a recent meta-analysis including 789 ICI rechallenge cases from 18 cohort studies, the pooled incidence of immune-related adverse event was 34.2% and 11.7% for severe immune-related adverse event. IMDC and shorter time interval between immune-related adverse event and ICI rechallenge were associated with higher recurrence of severe immune-related adverse event recurrence. In this setting, rechallenge ICI in patients with IBD is not recommended. It was also impossible to recommend an optimal delay between ICI initiation and previous IBD relapse.

The present recommendations were developed with IBD specialists without any expert oncologist or haematologist. We considered that patients facing relapse or IMDC will be mostly managed by their IBD specialist. However, we agree that case-by-case discussion with oncologist should - of course - be encouraged in this setting in order to make the best therapeutic decision.

In conclusion, we provided recommendations on the use of ICI therapy in patients with pre-existing IBD. Further studies are needed to understand the exact risk of IBD relapse and incidental IMDC. Rechallenge with ICI needs also to be studied in patients with lifesaving or life-prolonging purpose.

Conflict of interest

Aurelien Amiot has received consulting fees from Abbvie, Hospira, Takeda, Gilead and Biocodex as well as lecture fees and travel accommodations from Abbvie, Janssen, Biocodex, Hospira, Ferring, Takeda and MSD. This author has also received advisory board fees from Gilead, Takeda and Abbvie.

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Author contributions

Conception and design of the study: AAm, DL, GM, MS, FP.

Generation, Collection, Assembly, Analysis and/or Interpretation of data: AAm, DL, GM, MS, FP.

Drafting or revision of the manuscript: AAm, DL, GM, MS, FP.

Approval of the final version of the manuscript: AAm, DL, GM, MS, FP.

Appendix 1. GETAID organization (https://www.getaid.org/presentation.html)

Office	President : Pr. Laurent Peyrin-Biroulet, Gastroenterology Department, Nancy University Hospital, Université de Lorraine, Rue du Morvan, F-54511 Vandoeuvres-les-Nancy, France Vice-President : Pr David Laharie, CHU de Bordeaux, Hôpital Haut-Lévêque, Service d'Hépato-gastroentérologie et oncologie digestive – Université de Bordeaux. Avenue du Haut Leveque, F-33600 Bordeaux, France Treasurer : Pr. Arnaud Bourreille, Hepato-gastroenterology Departement, CHU Hôtel-Dieu, 1 place Alexis Ricordeau, F-44000, Nantes, France General Secretary : Pr Lucine Vuitton, Department of Gastroenterology, CHRU de Besançon, Jean Minjoz Hospital, 3 Boulevard Alexandre Fleming, F-25000, Besançon, France
Educational committee	Head: Pr Guillaume Bouguen, Hepato-gastroenterology Departement, CHU Pontchaillou 2, Rennes University, 2 Rue Henri le Guilloux, F-35000, Rennes, France Members: Pr Vered Abitbol, Department of Gastroenterology, AP-HP-Centre, Université de Paris, Hôpital Cochin, 27 Rue du Faubourg Saint-Jacques, F-75014, Paris, France Pr Aurelien Amiot, Universite Paris Est Creteil, Department of Gastroenterology, Hopitaux Universitaires Bicêtre, AP-HP, 78 rue du General Leclerc, F-94270, Le Kremlin Bicêtre, France. Dr Amelie Biron, CHU Reims. Hôpital Robert Debré. Service Hépato-gastroentérologie et cancérologie digestive, Rue du Général Koenig, F-51100, Reims, France Dr Anne Bourrier, AP-HP, Hôpital Saint-Antoine, Department of Gastroenterology, 184 rue du faubourg Saint Antoine, F-75012, Paris, France Dr Ludovic Caillo, Department of Hepatology and Gastroenterology, University Hospital of Nimes, 4 Rue du Professeur Robert Debré, F-30900, Nimes, France Pr Mathurin Fumery, Department of Gastroenterology, Amiens University hospital, and PeriTox, Université de Amiens-Picardie, 1 Rond-Point du Professeur Christian Cabrol, F-80054 Amiens cedex 1 Dr Cyrielle Gilletta, Hepato-gastroenterology Departement, Rangueil Hospital, 1 avenue du Professeur Jean Poulhès, F-31059, Toulouse Cedex 9, France Dr Laurianne Plastaras, Department of Hepato-Gastroenterology, Colmar Hospital, 39 avenue de la liberte, F68000, Colmar, France Dr Melanie Serrero, Department of Gastroenterology, University Hospital of Marseille Nord, Aix-Marseille University, APHM, Chemin Des Bourrely, F-13015, Marseille, France Dr Marion Simon, Hepato-gastroenterology Departement, Insititut Mutualiste Montsouris, 42 Boulevard Jourdan, F-75014, Paris, France Dr Stephanie Viennot, Hepato-gastroenterology Department, CHU Caen, Avenue de la cote de Nacre, F14000, Caen, France
Scientific committee	Head: Pr Philippe Seksik, Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-HP, Hôpital Saint-Antoine, Department of Gastroenterology, 184 rue du faubourg Saint Antoine, F-75012, Paris, France Members: Dr Alain Attar, Hépato-Gastro-Entérologie MICI Assistance Nutritive, Hôpital Beaujon, 100 boulevard du General Leclerc, F-92110, Clichy-La-Garenne, France Pr. Anthony Buisson, Department of Hepato-Gastroenterology, University Hospital Estaing of Clermont-Ferrand, Université d'Auvergne, 58 rue Montalembert, F-63000, Clermont-Ferrand, France Dr Benedicte Caron, Gastroenterology Department, Nancy University Hospital, Université de Lorraine, Rue du Morvan, F-54511 Vandoeuvres-les-Nancy, France Dr Maeva Charkaoui, Gastroenterology Department, Dijon Bourgogne University Hospital, Le Bocage Hospital, 1 Boulevard Jeanne D'Arc, F-21079 Dijon, France. Pr Jean-Marc Gornet (Paris), Department of Hepatology and Gastroenterology, Saint-Louis University Hospital, 1 rue Claude Vellefaux, F-75010, Paris, France Dr Lucas Guillo, Department of Gastroenterology, University Hospital of Marseille Nord, Aix-Marseille University, APHM, Chemin Des Bourrely, F-13015, Marseille, France Dr Catherine Le Berre (Nantes), Hepato-gastroenterology Departement, CHU Hôtel-Dieu, 1 place Alexis Ricordeau, F-44000, Nantes, France Pr Edouard Louis (Liège), Hepato-gastroenterology Department, CHU Sart Tilman, Liège University, Domaine Universitaire, 4000, Liège, Belgium Pr Georgia Malamut, Department of Gastroenterology, AP-HP-Centre, Université de Paris, Hôpital Cochin, 27 Rue du Faubourg Saint-Jacques, F-75014, Paris, France Pr Nicolas Mathieu (Grenoble), Department of Hepato-Gastroenterology and Digestive Oncology, Grenoble Alpes University Hospital, Av. des Maquis du Grésivaudan, F-38700, La Tronche, France Dr Maria Nachury (Lille), Department of Gastroenterology, CHU Lille, Service des Maladies de l'appareil digestif, rue Michel Polonowski, F-5900, Lille, France Pr Stephane Nancey, Department of Gastroenterology, Hospices civils de Lyon, Lyon Sud Hospital, 165 chemin du Grand Revoyet, F-69495, Pierre Benite, France Pr Stephane Paul (Saint-Etienne), INSERM, U1111, CNRS, UMR 530, Immunology and Immunomonitoring Laboratory, iBiothera, CIRI-GIMAP, UCBL 1, UJM, CIC 1408, Avenue Albert Raimond, F-42270, Saint-Priest-en-Jarez, France Pr Catherine Reenaers, Hepato-gastroenterology Department, CHU Sart Tilman, Liège University, Domaine Universitaire, 4000, Liège, Belgium Pr Xavier Treton, Gastroenterology and Nutrition Support Department, Department of Gastroenterology, Paris Sorbonne University, Beaujon Hospital, 100 boulevard du General Leclerc, F-92110, Clichy-La-Garenne, France Dr Mathieu Uzzan, Département of Gastroentérology, Hôpitaux Universitaires Henri Mondor, AP-HP, Université Paris Est Creteil, 1 rue Gustave Eiffel, F-94000 Creteil, France Dr Pauline Wils, Department of Gastroenterology, CHU Lille, Service des Maladies de l'appareil digestif, rue Michel Polonowski, F-5900, Lille, France

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