ImmunoScience Academy

Partnering for Education & Optimizing Treatment in ImmunoScience

SUMMARY

ImmunoScience Academy Summer Edition

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Immuno-oncology and irAEs in Digestive Organs and Liver: Progress and challenges

Dr. Paul Lacante, Medical Director of Bristol Myers Squibb, welcomed the audience to this Summer Edition of the ImmunoScience Academy. He reminded the audience that this day marked the 10th anniversary of the first EMA registration approval of an immuno-oncology drug, namely ipilimumab for metastatic melanoma, changing the outcome for those patients fundamentally. Immunotherapy has since that day made enormous strides. First of all, the expansion to other tumour types has given new hope for patients with cancer. But also new challenges did arise, such as the management of a different adverse event profile. Therefore, this ISA's summer edition was devoted to gastrointestinal (GI) adverse events of immunotherapy and recent developments in the treatment of gastrointestinal tumours with this novel approach.

Lies Martens, the moderator of the evening, introduced first the scientific moderator for the evening, Dr. Jean-Luc Canon, medical oncologist and head of the department of oncology and haematology at the Grand Hôpital de Charleroi.

Dr. Canon started by defining the objectives of the meeting:

- To understand at a cellular level the principles of immunotherapy on the immune system and the mechanisms underlying immune-related adverse events (irAEs) & GI irAEs
- To discuss the available data on immunotherapy in GI tumours
- To review the importance of biomarkers in guiding the management of GI tumours
- To discuss the diagnosis and management of GI irAEs

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Mechanisms of immunotherapy and immune-related adverse events

Professor Dr. Coulie (De Duve Institute, Brussels) explained that we mainly talk about T-lymphocytes when we speak about immunotherapy in oncology. They are the main anti-tumour effector cells within the immunotherapy we know today. With T-cell development in the thymus, an enormous diversity of antigen receptors is generated, thanks to the recombination of different segments of genes. After selection on HLA interaction and filtering out the autoreactive cells, we end up with about 400 billion CD4 or CD8 positive T-cells in the periphery.
From this "naïve" repertoire, throughout life, clonal amplification occurs to build an immune repertoire – this is the so-called adaptive immunity. *(Xing Y., Hogquist KA., Cold Spring Harb Perspect Biol, 2012)*

So what are the physiological roles of the CTLA-4 and PD-1 receptors, the proteins targeted with cancer immunotherapy? They both act as inhibitors of the immune reaction: CTLA-4 dampens the immune response after the initial priming of T-cells by antigen-presenting cells (APCs) when it binds to the B7 protein on APCs, and PD-1 does the same for antigen-experienced T-cells when it binds to its ligand PD-L1, which can be present on many cell types in the body, including tumour cells.
The locations where these two receptors are active are also distinct: CTLA-4 is more important in lymphoid tissue during T-cell priming, whereas PD-1 can act anywhere in the body (including in tumours). *(Wei S. et al., Cancer Discovery 2018; 8:1069–86; Chen D. & Mellman I., Immunity 2013; 39:1–10; Pardoll DM., Nat Rev Cancer 2012; 12:252-264; Sharma P. et al., Science 2015; 348:56-61)*

Hence, the initial rationale behind blocking the CTLA-4 and PD-1 inhibitory pathways is to strengthen and prolong the immune response, including the antitumor immune response, and it does. Without going into the detailed results of all the different trials, we can see that combined immunotherapy in first-line metastatic melanoma patients gives an averaged 3-year overall survival (OS) result of 58,4% (Fig 1 - *Ugurel S, et al. Eur J Cancer 2020;130:126–130*)

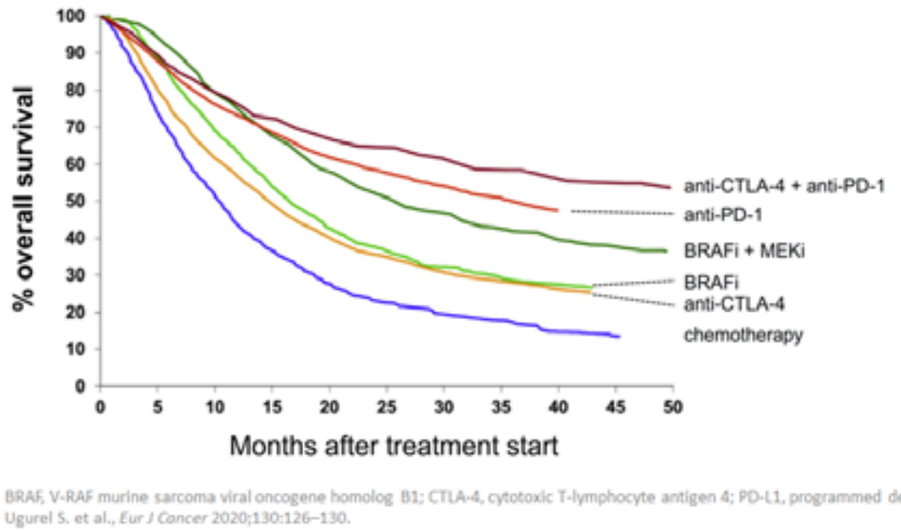


FIGURE 1 *Therapeutic progresses for patients with advanced metastatic melanoma*
No adequate well-controlled head-to-head clinical trials are available

Professor Coulie explained that blocking CTLA-4 and PD-(L)1 was expected to produce autoimmune side effects. In fact, in mice without CTLA-4 enormous, almost always fatal auto-immunity is seen. Of course, this makes sense as the inhibition occurs on all activated T-cells, including the anti-tumour T-cells and the T-cells we have against all possible antigens such as microbial antigens and, to a lesser extent, autoantigens.

During treatment with immunotherapy, more T-cells are being primed, and even some that would never have been activated under normal conditions end up in the circulation. Naturally, this also results in more immunoglobulins being produced and circulating, which in some cases can be autoantibodies.

Hence, there are three main mechanisms by which irAEs can be explained: an exaggerated antimicrobial reaction, an increase in cytokine and chemokine production (with the associated effects thereof), and a breach of self-tolerance, leading to autoimmune reactions. See figure 2. *(Esfahani K. et al., Nat Rev Clin Oncol 2020; 17:504–15)*

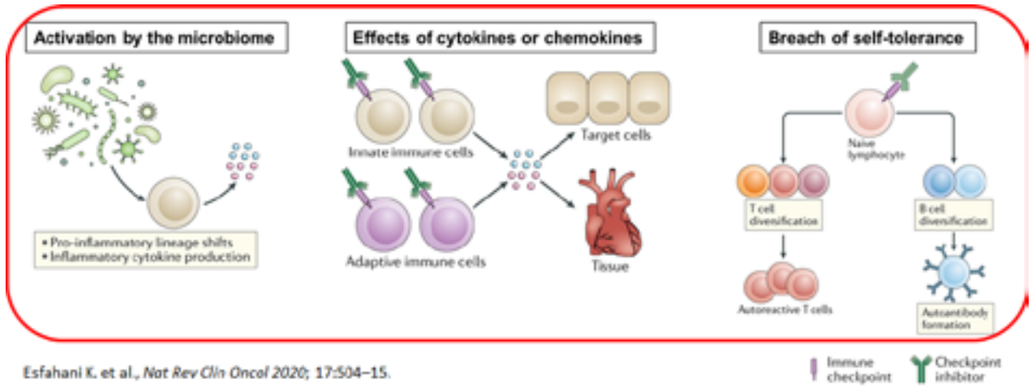


FIGURE 2 *Main immunopathogenic mechanisms proposed for irAE*

Obviously, through these mechanisms, many, if not all, organ systems can be affected, and the gastrointestinal tract is one of them. GI irAEs are more seen after CTLA-4 blockade (30%) than after PD-1 blockade (15%). *(Samaan MA. et al., Nat Rev Gastroenterol Hepatol 2018; 15:222–34)*
Prof. Coulie concluded his presentation by showing the putative mechanism by which colitis can occur when using immunotherapy. In normal circumstances, the content of the gastrointestinal tract, such as food particles and the gut microbiota, is captured by dendritic cells, which present these substances to intestinal T-cells. This process is usually very strictly regulated but can be hampered by CTLA-4 or PD-1 blockade, resulting in exaggerated cytokine production at this level, causing colitis.

In the Q&A session that followed this presentation, a question was raised if any specific characteristics influence the occurrence of gastrointestinal side effects since we all have different microbiota?

Prof. Coulie replied that there are many different ways bacteria can influence immune cells, such as through the production of immunostimulatory or inhibitory compounds and also through metabolic effects. It is a field in which a lot of fascinating research is ongoing and still to come, and a lot remains to be elucidated.

Prof. Pauwels wanted to know if there could be an impact of the use of antibiotics, as these are known to impact the gut flora. Prof. Coulie answered there is some preliminary research on this, but it is early to speculate.

Dr. Canon then asked why CTLA-4 inhibition seems more toxic than PD-(L)1 inhibition. Professor Coulie explained that because CTLA-4 has such an important role in regulating priming T-cells, its inhibition results in T-cells being stimulated and multiplying that normally wouldn't. Now, these memory T-cells can multiply very quickly, and they remain present indefinitely, hence the more significant and later impact on adverse effects.

A journey through immunotherapy in digestive oncology

Professor Dr. Eric Van Cutsem (UZ Leuven) provided an overview of the developments in immunotherapy for gastrointestinal tumours.

He explained that in recent years, a lot of progress had been made in our understanding of the various subtypes of, for instance, colorectal cancer, as well as the immune microenvironment of these cancers. We're also starting to think about ways we could transform so-called "cold" tumours into "hot" (or immunogenic) ones. *(Dienstmann R. et al., Nat Rev Cancer 2017; 17(2):79-92. - Becht et al., Advances Immunol 2016; 130:95-190)* Research by a group from Korea in collaboration with Leuven (prof. Tejpar) is contributing to this consensus on molecular subtypes through transcriptome analysis on single cancer cells. *(Lee HO et al., Nat Genet 2020; 52(6):594-603)*

We now know that there are two different important pathways: the chromosomal instability (CIN+) and the genetic or microsatellite instability (MSI-high). In colon cancer, about 15% have an MSI-high tumour. In metastatic disease, the number of patients with an MSI-high tumour is lower and estimated at around 5%. *(Andre T et al., Oral presentation at ASCO 2020. Abstract LBA4)* Similar efforts to characterise tumours more in detail are ongoing for other GI malignancies as well.

Professor Van Cutsem then discussed the results of the Keynote-177 trial, which evaluated pembrolizumab versus standard chemotherapy in MSI-H first-line metastatic colorectal cancer (CRC). The study demonstrated a statistically significant advantage in progression-free survival (PFS), with a hazard ratio (HR) of 0.60 and resulted in the first EMA approval of a checkpoint inhibitor for colorectal cancer (Figure 3) *(Andre T, Van Cutsem E et al. N Engl J Med 2020;383(23):2207-2218)*. The study also demonstrated higher response rates with pembrolizumab.

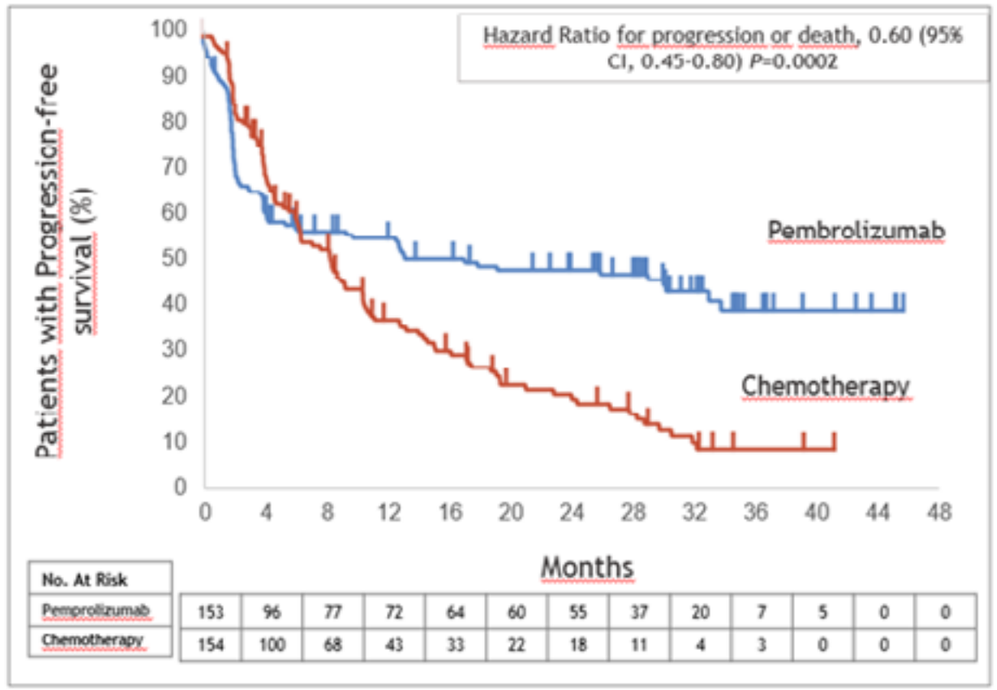


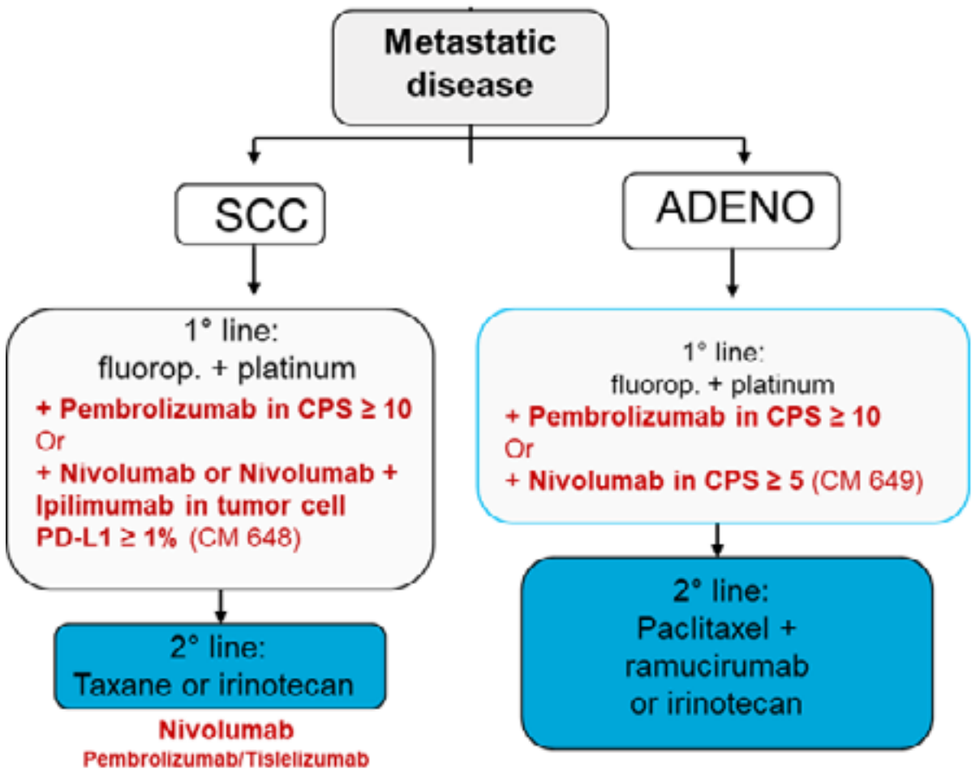
FIGURE 3 *Progression-free Survival in Patients with MSI-H Metastatic Colorectal Cancer in KEYNOTE 177*

In addition, the phase 2 CheckMate-142 trial combining nivolumab and ipilimumab in a similar population showed good responses, at 24 months, a PFS of 74% and an OS of 79%.
Moving on to oesophagal cancer, prof. Van Cutsem first mentioned the current guidelines for metastatic disease. Both in adenocarcinoma as in squamous cell carcinoma, first and second-line treatment consisted of chemotherapy with rather disappointing results. *(Muro K, Van Cutsem E et al., Ann Oncol 2019; 30:19–33)*

But recently, the results of the ATTRACTION-3 phase 3 study comparing nivolumab with standard of care chemotherapy in patients with pretreated metastatic oesophagal squamous cell cancer were published. The data of this study showed an improvement of OS from 8.4 to 10.9 months leading to an EMA approval for nivolumab (NIVO) in second-line treatment, regardless of PD-(L)1 status. *(Kato K et al., Lancet Oncol 2019; 20(11):1506-1517)*

Importantly, in the last six months, several pivotal trials assessing immunotherapy-based regimens came out with positive results in first-line treatment of metastatic oesophagal cancer and gastric cancer. Prof. Van Cutsem mentioned the KEYNOTE 590 study in first-line oesophagal cancer, showing that frontline pembrolizumab (PEMBRO) plus chemotherapy significantly improved OS, PFS, and objective response rates (ORR) compared with chemotherapy alone in patients with locally advanced unresectable or metastatic oesophagal cancer. *(Kato K et al., Oral presentation at ESMO 2020. Abstract LBA8)* CHECKMATE 649, a study in 1st line gastric cancer, gastroesophageal junction cancer, and oesophagal adenocarcinoma, randomised patients to a chemo-doublet or chemo + NIVO or NIVO + ipilimumab (IPI). The results of this third arm are yet not available, but the comparison of chemo + NIVO showed a clear benefit over chemo alone in patients with a PD-L CPS-score > 5. *(Moehler M et al., Oral presentation at ASCO 2021. Abstract 4002)*.
Finally prof. Van Cutsem mentioned the results of CHECKMATE 648 that were presented during this year's ASCO. This large study in metastatic squamous cell cancer of the oesophagus also randomised patients between chemo or chemo + NIVO or double-checkpoint inhibition with NIVO + IPI. The study was positive for comparison chemo + NIVO compared to chemo as for the comparison double-checkpoint inhibition with NIVO + IPI versus chemo. *(Chau I et al., Oral presentation at ASCO 2021. Abstract LBA4001)*

All these data will be practice-changing, and guidelines will be updated accordingly. Prof. Van Cutsem gave his own opinion how guidelines for metastatic oesophagal cancer could look like. (see fig 4)



MODIFIED by Eric Van Cutsem from Muro K, Van Cutsem E et al. *Ann Oncol 2019*; 30:19–33.

FIGURE 4 *Proposed guideline for metastatic oesophagal cancer*

Prof Van Cutsem also provided an updated algorithm for gastric cancer, again his own opinion, based on current evidence from recent study results. (see fig 5)

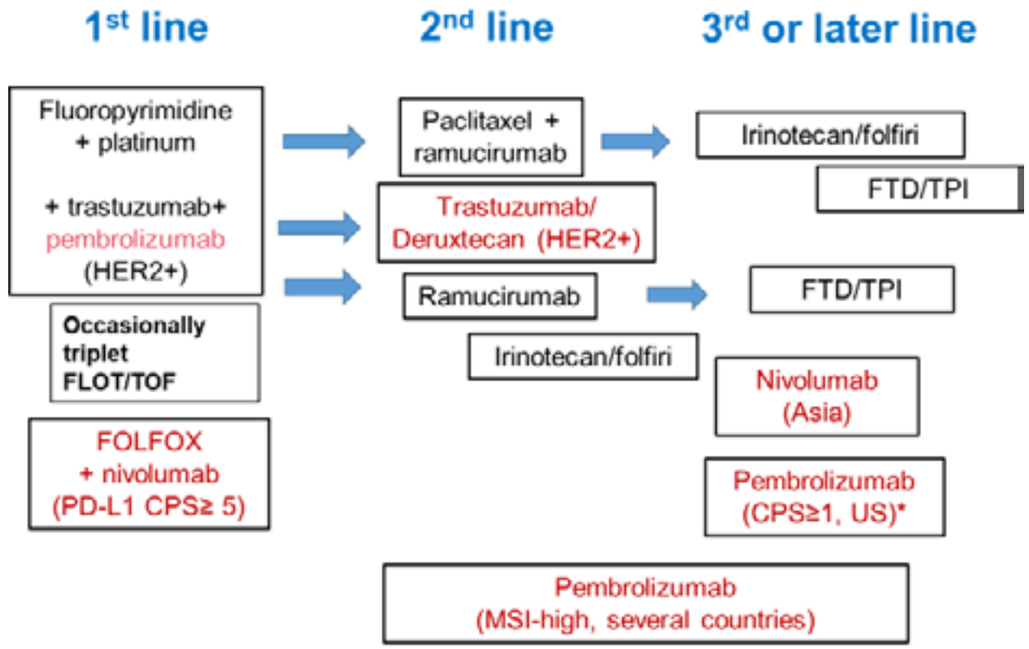


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FIGURE 5 *Proposed guideline for metastatic gastric cancer*

Finally, Prof. Van Cutsem discussed recent data in hepatocellular carcinoma. The IMbrave 150 trial showed superior results for atezolizumab + bevacizumab versus sorafenib in first-line treatment, leading to a change in guidelines here as well. *(Finn RS et al. N Engl J Med 2020; 382:1894-1905)*

Importance of biomarkers in GI tumours

Professor Dr. Pauwels, pathologist at the University Hospital Antwerp, started his presentation by saying that after listening to the previous speaker, he now realised that his job has become even more complicated, seen the various immunotherapies using different cut-offs for different biomarkers.

He explained that the **tumour proportion score**, or TPS, is the “easiest” score, as it reflects the percentage of tumour cells that shows PD-L1 staining. The **combined positive score** (CPS) takes into account not only the number of positive tumor cells but also the number of positive intratumoral immune cells. The TPS is a percentage; CPS is a number.
Professor Pauwels emphasised that it is very important when requesting a PDL1 testing to inform the pathologist about the type of test you need and the immunotherapy that will be used. Not only are the cut-off levels different, but the immunohistochemistry (IHC) staining is also specific to each drug. We should also be aware that the clinical utility of PD-L1 has been evaluated in several GI clinical trials but that the PD-L1 scoring method varies between the clinical trials of different immunotherapies. *(Moehler M et al., Oral presentation at ESMO 2020 Abstract 3047; Lei M et al., Oral presentation at ASCO 2019, Abstract 2673; Kelly RJ et al., Oral presentation at ESMO 2020. Abstract 2968; Boku N et al., Oral presentation ESMO 2020, Abstract LBA7.)*

Now, what about **MSI and mismatch repair (MMR) testing**? MMR system is a DNA repair pathway that identifies and corrects DNA mismatches. Deficient MMR (dMMR) results from the loss of expression of one or more of the proteins involved in the MMR process. dMMR can cause MSI. *(Cortes-Ciriano I et al., Nat Commun 2017; 8:15180 ; Buecher B et al., Dig Liver Dis 2013; 45:441–449)*

MSI-H/dMMR tumours are highly immunogenic, which may make these tumours susceptible to immune checkpoint inhibitors. *(Llosa NJ et al., Cancer Discov 2015; 5:43–51)* dMMR is reported to be present in 10% of CRC, while MSI-H prevalence is reported to be 13%. *(Amonkar M et al., J Clin Oncol 2019; 37(suppl 15):e15074)* Pathologic staging is a crucial determinant of CRC prognosis and treatment. However, stage-independent outcome variability in patients with CRC supports the implementation of robust prognostic and predictive markers, such as MSI-H and dMMR. *(Sargent DJ et al., J Clin Oncol 2010; 28:3219–3226)* dMMR/MSI can be assessed by IHC, polymerase chain reaction (PCR) and next-generation sequencing (NGS).

Professor Pauwels stressed that the gold standard remains to do IHC to assess presence of the major DNA damage repair proteins, as those are the “workers” (as opposed to the DNA that is just “there”). If IHC is inconclusive (as is the case in about 10%), one should consider performing an MSI PCR or other techniques. When looking at MSI, there has to be a consensus on which microsatellites to evaluate in which tumour type, as there are many different ones. For the moment, this is also the difficulty with using NGS to determine MSI, and more work is needed to validate NGS for daily practice.

Diagnosis and management of gastrointestinal immune-related adverse events. (GI irAEs)

Professor Van Cutsem announced that in this presentation, he would review the mechanisms, the clinical data and the treatment of toxicities seen when immunotherapy is given. Although these toxicities can occur in different organs, the topic of this presentation is GI toxicity, more precisely (entero)colitis and gastritis. It is clear that some of these side effects, although not extremely frequent, especially with PD-L1 antibody alone, may be severe and need a good reaction and knowledge by the clinician. The signs and symptoms of immune-related adverse reactions (IMARs) of colitis or enteritis are diarrhoea, possibly associated with blood or mucus, abdominal cramping with pain, nausea, anorexia, weight loss and fever. *(Naidoo J et al. Ann Oncol 2015; 26:2375–2391; Villadolid J et al., Transl Lung Cancer Res 2015; 4:560–575; Weber JS et al., Oncologist 2016; 21:1230–1240; Cheung VTF, Brain O. Best Gastroenterol. 2020 Oct-Dec; 48-49:101703)* It is essential to understand these IMARs' kinetics and have an idea of the time of onset. For colitis, this will usually be after several weeks of treatment, and it can even occur much later. The frequency of colitis in dual immunotherapy with IPI/NIVO lies around 26%, and between 1-12% for the PD-(L)1 inhibitors in monotherapy. (figure 6)

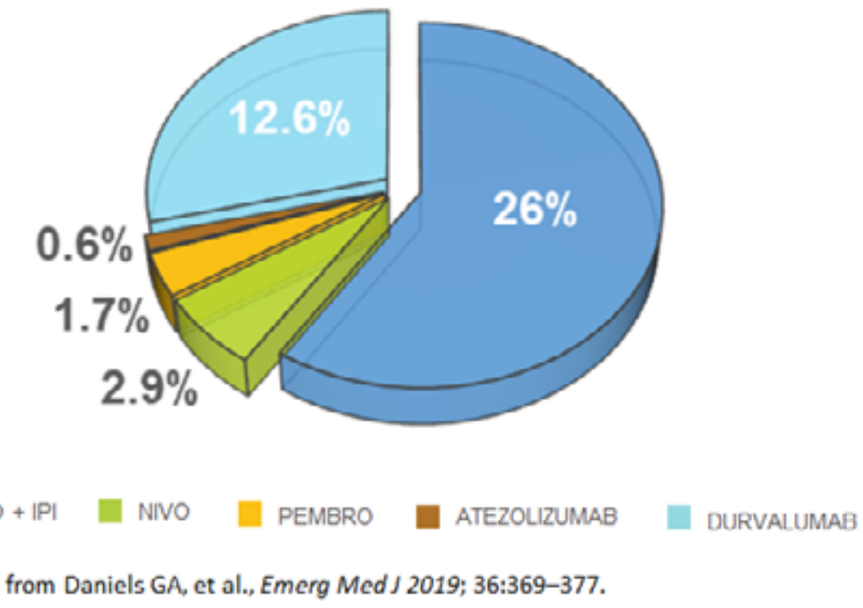


FIGURE 6 *Frequency of any-grade colitis following ICI treatment*

Prof Van Cutsem stated that clinicians should be familiar with the common terminology criteria for adverse events (CTCAE), as this is the basis for clinical management. (figure 7)

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea • A disorder characterized by an increase in the frequency and/or looseness of watery bowel movement	• Increase of < 4 stools per day over baseline • Mild increase in ostomy output compared with baseline	• Increase of 4–6 stools per day over baseline • Moderate increase in ostomy output compared with baseline • Limiting instrumental ADL	• Increase of ≥ 7 stools per day over baseline • Incontinence • Hospitalization indicated • Severe increase in ostomy output compared with baseline • Limited self-care ADL	• Life-threatening consequences • Urgent intervention indicated	Death
Colitis • A disorder characterized by an inflammation of the colon	• Asymptomatic • Clinical or diagnostic observations only • Intervention not indicated	• Abdominal pain • Mucus or blood in stool	• Severe abdominal pain • Peritoneal signs	• Life-threatening consequences • Urgent intervention indicated	Death

ADL, activities of daily living

Cheung VTF, Brain O. *Best Pract Res Clin Gastroenterol.* 2020 Oct-Dec; 48-49:101703.

FIGURE 7 *Common Terminology Criteria for adverse events (CTCAE): grading of diarrhea and colitis*

According to Professor Van Cutsem, there are various potential mechanisms underlying irAEs, as also discussed previously by professor Coulie, and colitis is mainly cytokine-mediated. Under healthy conditions, the intestinal mucosa has been described to be in a state of equilibrium involving "physiological inflammation". *(Samaan MA et al., Nat Rev Gastroenterol Hepatol 2018; 15:222–234.)*

It appears that the loss of tolerance plays an important role in checkpoint-inhibitor associated immune enterocolitis, both through hyperactivation of T-effector cells targeting luminal antigens (microbiota and dietary products), and through the loss of functional T-regulator cells, nicely depicted in figure 8.

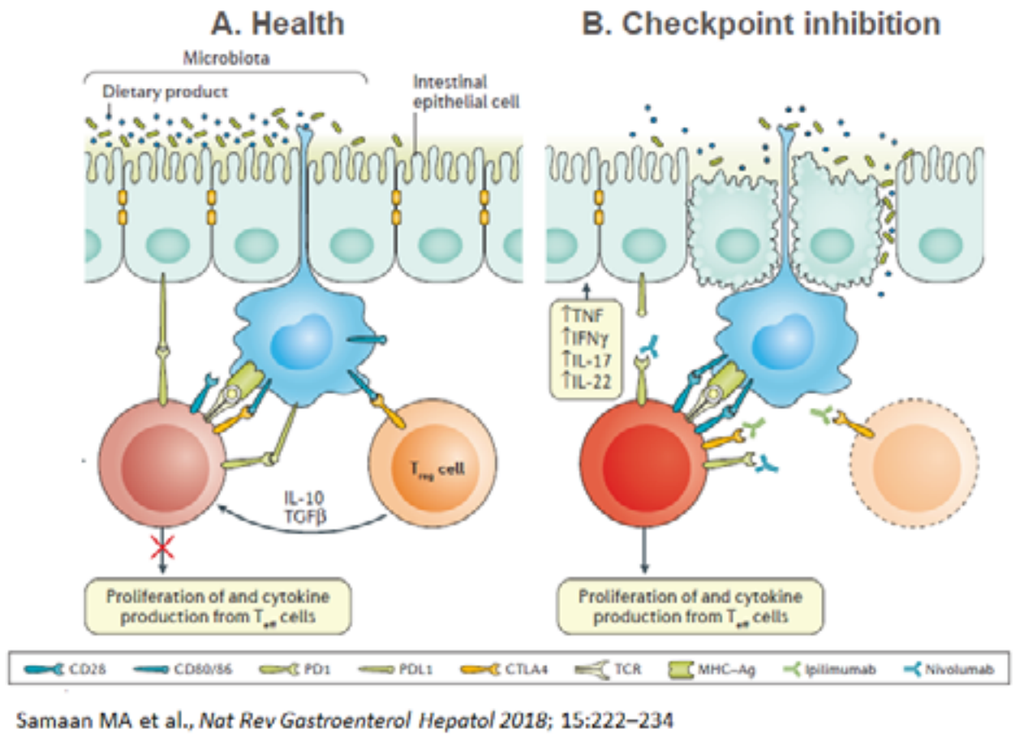


FIGURE 8 *Potential mechanisms of GI IMARs*

It's good to know that immunotherapy can also cause microscopic colitis, which by definition means there are no or very few abnormalities visible on endoscopy. These patients tend to have chronic, sometimes severe, watery, non-bloody diarrhoea. The diagnosis depends on characteristic histological findings. The use of certain drugs such as nonsteroidal anti-inflammatory agents (NSAIDs), proton-pump inhibitors, and selective serotonin reuptake inhibitors are linked to an increased risk to develop such a microscopic colitis. *(Townsend T et al., Frontline Gastroenterol 2019; 10:388–393)* ICI-related microscopic colitis has been found to require more aggressive treatment. It results in increased morbidity and mortality compared to non-ICI-related microscopic colitis, highlighting the importance of this diagnosis. In patients with these types of complaints, biopsies should be taken even if there are no endoscopic findings. *(Choi K et al., Inflamm Bowel Dis 2019; 25:385–393)*

Prof. Van Cutsem mentioned that he is often asked whether there is any way to predict who is at risk for developing colitis. Unfortunately, to date, there are no specific biomarkers. However, it is recommended that patients with an elevated faecal calprotectin level (>250µg/g) should promptly be referred for a gastroenterology consultation and endoscopic evaluation. *(Samaan MA et al., Nat Rev Gastroenterol Hepatol 2018; 15:222–234)*
Gastritis is, following Prof. Van Cutsem, less common as an irAE, but it can occur, and findings on endoscopy may include erythema, friability, hemorrhage, erosions, ulcerations and white exudates. *(Cheung VTF, Brain O., Best Pract Res Clin Gastroenterol. 2020 Oct-Dec; 48-49:101703.)*

Prof. Van Cutsem concluded this presentation by giving an overview of the treatment recommendations for immune-related colitis and diarrhoea. He explained that various professional societies, such as ESMO, ASCO, NCCN etc., have formulated their own recommendations. For that reason, Prof. Van Cutsem summarised the previous guidelines. Clinicians should be aware that using ICI agents can increase the risk of developing colitis and diarrhoea. It's also important to exclude Clostridium difficile because that may mimic the clinical picture. In patients with a grade 2 diarrhoea and colitis, the treatment with the CPI is usually stopped, and symptomatic management is given. Sometimes low-dose prednisolone or oral budesonide is given when the diarrhoea persists for more than three days. In patients with grade 3 and 4 diarrhoea, Prof. Van Cutsem proposes to hospitalise the patient and isolate him until the infection is excluded. Of course, the treatment with the CPI is stopped; higher doses of prednisolone are given, and a sigmoidoscopy or colonoscopy is done to see the severity.

Infliximab, a TNF-alfa inhibitor, should be given if no improvement is seen after three days. *(Haanen JBAG et al., Ann Oncol. 2017; 28(suppl_4):iv119–iv142.)*

Clinicians should be aware that using immunosuppressive agents to treat inflammation can increase the risk of other GI pathologies, such as small intestinal bacterial overgrowth or infective diarrhoea. Grading is essential, repeated Prof. Van Cutsem. In his opinion, the CTCAE v4 grading can even underestimate the severity of symptoms and associated burdens for patients. In addition to the number of stools, clinicians should inquire about the frequency of bowel movements, whether there are nocturnal bowel movements, whether there is urgency, and the impact on the patient's quality of life and his daily activities.

Corticosteroid-refractory patients are defined as those who do not improve with three days of IV corticosteroids. Corticosteroids appear to effective for only 60-70% of patients who have enterocolitis as an IMAR, meaning that about a third of patients may require additional biologic agents such as infliximab or vedolizumab. *(Favara DM et al. ESMO Open 2020; 5:e000585; Dougan M. Curr Gastroenterol Rep 2020; 22:15)* Retrospective studies seem to suggest that patients with severe inflammation and ulceration are more likely to be steroid-refractory. *(Geukes Foppen MH et al. ESMO Open 2018; 3:e000278; Wang Y et al., Inflamm Bowel Dis 2018; 24:1695-1705)*. Another issue to be aware of is that patients with steroid-refractory immune-mediated colitis are at risk of developing cytomegalovirus infection or reactivation. *(Postow M.)*

KEY TAKEAWAYS

Prof. Van Cutsem ended his presentation by giving some key takeaways :

- Diarrhoea and colitis may result from hyper-activated effector T-cells. Immune enterocolitis due to checkpoint inhibition is secondary to hyper-activated effector T-cells targeting luminal antigens and loss of functional regulatory T-cells.
- Consult a gastroenterologist who has experience in treating irAEs
- Biopsies are necessary for the diagnosis of GI irAEs when patients present with macroscopically normal bowels but may have microscopic colitis
- Around a third of patients with GI irAEs are corticosteroid-refractory and require immunosuppressive biologic agents, such as infliximab or vedolizumab
- Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory, immune-mediated colitis

Liver enzyme elevations and hepatotoxicity in patients treated with checkpoint inhibitor immunotherapy

Professor Dr. Christophe Van Steenkiste, gastroenterologist at the Maria Middelares Ziekenhuis Ghent and the University Hospital Antwerp joined by prof. Pauwels had the last presentation of this ISA's Summer Edition on hepatic irAEs.

He started his presentation by saying that elevation of liver enzymes is a common occurrence in patients being treated with PD-(L)1 inhibitors, but only a minority are irAE related to the treatment. A study by Cunningham et al. reviewed patients treated with CPI in the period 2010-2018. 20% of patients had an elevation of liver enzymes. The majority of these elevations were caused by disease progression. Another part, 8%, was related to another toxin like chemo, painkillers, … 16% were related to real liver immuno toxicity. Interestingly, around 16% of cases were unrelated to either the cancer or the treatment. This could be fatty liver, sepsis, or even a reactivation of hepatitis E. (fig 9)

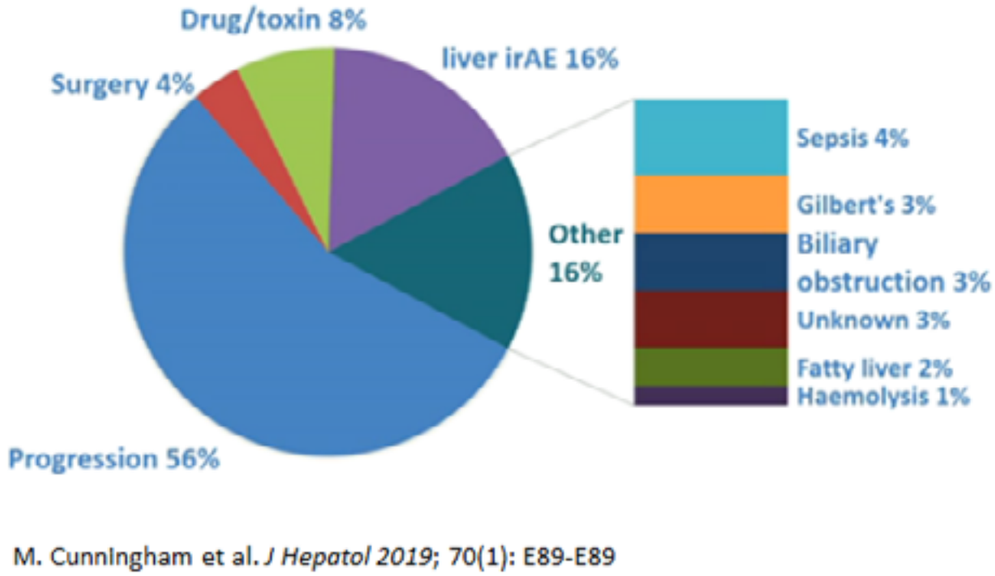


FIGURE 9 *Causes of liver enzyme elevation in patients treated with CPI*

For that reason, Prof. Van Steenkiste believes that a proper assessment is needed in patients treated with these compounds. In the same study, the authors assessed what happened when such a problem is encountered. Most of these patients received imaging to check if there was progression of the cancer, but only a minority had viral or autoimmune serologies checked, and only four patients (less than 1%) were referred to a hepatologist. *(M. Cunningham et al. J Hepatol 2019; 70(1): E89-E89)* Prof. Vansteenkiste made a plea for specialists to have a lower threshold to consult with one another, especially in these complex cases where a **multidisciplinary approach** is undoubtedly beneficial.

Professor Van Steenkiste mentioned that in preparing this particular presentation, he realised that almost all of the clinical guidelines are based on the trial protocols of the registration studies. There are no studies specific to this topic that would allow for a more evidence-based approach.
When looking at the prevalence of hepatic adverse events with immunotherapy, it is not the most frequent type of irAE, but nonetheless, these patients can be very challenging. Hepatic immuno-toxicity falls in hepatology in the so-called DILI category, which stands for drug-induced liver injury. DILI is a diagnosis of exclusion, meaning there is no one test or evaluation one can do to prove causality, and the approach is first to exclude other possible causes, schematically depicted in figure 10.

Adapted from Navarro et al. *NEJM* 2006;354:731-9

FIGURE 10 *Diagnostic approach in case of liver enzyme elevation in patients treated with CPI*

The various pathophysiologic mechanisms of injury were already discussed by professor Coulie, but Prof. Van Steenkiste wanted to highlight some recent data about liver injury specifically. A study by Pfister et al. revealed data showing that the presence of non-alcoholic steatohepatitis (NASH) can influence the response to immunotherapy and even increasing the liver damage. Data suggest that NASH aetiology limits response to immunotherapy. The authors also hypothesised that patients with metabolic syndrome and concomitant cancer at other organ sites might be at risk for liver damage in response to immunotherapy, which warrants further study. *(Pfister et al., Nature 2021; 592(7854)450-456)*

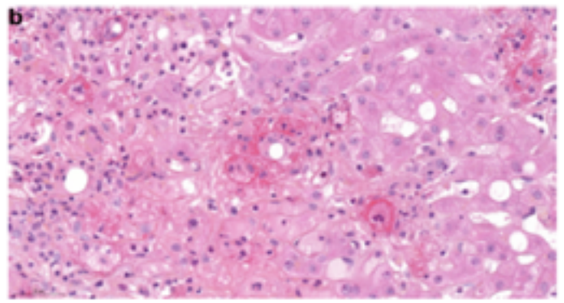
CASE HISTORY

Prof. Van Steenkiste went on to present the story of an actual patient to illustrate some of the diagnostic and management dilemmas in these cases. It concerned a 65-year-old man who was referred for grade IV hepatitis. He was treated with IPI + NIVO for metastatic melanoma spread to the lung and liver four years after initial treatment.
After only one week on combination immunotherapy, he developed jaundice, with severe transaminitis (AST and ALT >> 1,000), as well as an obstructive picture with an elevated bilirubin. So clearly, from an oncology perspective, this was a grade 4 transaminitis.

From the literature, we know that the median interval between starting immune therapy and the onset of hepatitis is around five weeks. But only after one infusion it is possible that an advanced hepatitis is seen, but also after stopping the treatment, hepatic toxicity can be observed.

The patient was evaluated, and some potentially hepatotoxic drugs, aside from the IPI and NIVO, were discontinued, namely atorvastatin and acetaminophen (paracetamol). An extensive diagnostic work-up, including hepatitis serology, markers for autoimmune disease, was done with no significant findings. The next thing to consider then is whether or not to perform a biopsy. Biopsy, of course, will not only lead the clinician to a proper diagnosis, but it will also be a great help in guiding management.

At this point in his presentation, professor Van Steenkiste handed over to professor Pauwels, who started by saying that there is a difference between the different immunotherapy agents and the damage to the liver. In patients on a CTLA-4 inhibitor, there is usually more necrosis, and a typical finding is the appearance of fibrin ring granulomas. (Fig 11) This is a fat vacuole surrounded by fibrin, and there around lymphocytes, epithelioid cells and even giant cells can be observed. (fig 11)



Papouin et al. *Ann Pathol 2018*; 38(6):338-351

FIGURE 11 *Histology: anti-CTLA4: fibrin ring granuloma*

With PD-(L)1 inhibitors, it's more common to see periportal inflammation and centrilobular necrosis. Occasionally cholangitis can occur as well. It was thought that hepatitis after immunotherapy would give the same image as autoimmune hepatitis. This is not the case. In immunotherapy, less plasmacytosis is observed, and in drug-induced liver injury, there is a higher presence of eosinophils
Coming back to the patient, the histology showed that there was an acute active hepatitis going on, with, among others, centrilobular inflammation and some necrosis. *(Papouin et al. Ann Pathol 2018; 38(6):338-351)*

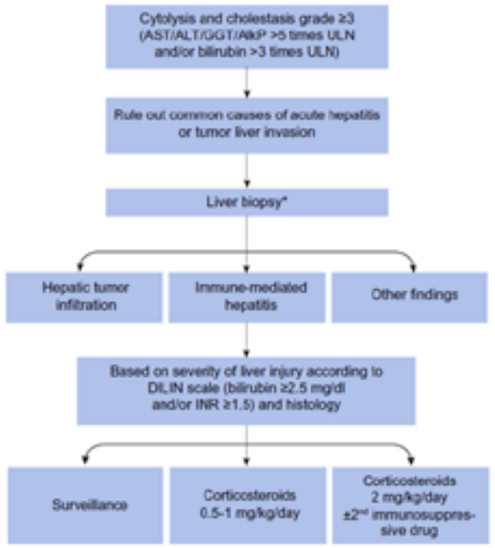


FIGURE 12 *Alternative treatment algorithm for hepatic irAEs*

Prof. Van Steenkiste continued the story, explaining that they observed the patient for some time, but the liver enzymes did not come down after 7-10 days, although fortunately, no coagulopathy occurred. It was decided to start the patient on corticosteroids.
The ESMO guidelines on the management of hepatitis in patients on immunotherapy recommend prednisolone 1mg/kg/day for grade 2 and 3, and even 2mg/kg/day for grade 4. The question may be raised if we are not overtreating these patients? *(Haanen et al., Ann of Oncology 2017; 28(4):i119-i142)*
In a recent small case series, around 40% of patients did not receive steroids or remained on low dose steroids that they were already on for other reasons and recovered spontaneously. The authors suggested an alternate algorithm, taking into account not only enzyme levels but also INR, bilirubin and histology, to decide on the use of steroids. (fig 12)This approach needs to be validated in other studies. *(De Martin et al. J Hepatol. 2018;68:1181-1190).*

Coming back to the patient: after the start of steroids, the liver enzymes and bilirubin decreased, and he recovered from his hepatitis. However, as is often the case in oncology, the tumour progressed, and the question arose whether to reintroduce immunotherapy.

A review of the literature gave some tips and tricks to be used. First of all, there is the use of budesonide prophylaxis that has proven to make the reintroduction of immunotherapy possible. *(Ziemer et al., 2017 J Hepatol 66: 657-665)*. Some authors described the successful use of plasma exchange in the case of a fulminant hepatitis when reintroducing immunotherapy. *(Riveiro-Barcela, J Hepatol 2019; 70:548-577*) A 2018 study looked at 80 patients, of whom 29 had hepatitis who restarted a PD-1 inhibitor after incurring toxicity on CTLA-4 and PD-1 inhibitor combination therapy. Half of them re-developed toxicity, sometimes in other organs. This means that clinicians can take a certain risk and balance the risks versus the benefits. Unfortunately, there were no predictive biomarkers identified. *(Pollack et al., Ann Oncol 2018; 29:250-255)*

The patient in question was started on PD-1 inhibitor monotherapy and did well, with no further hepatitis. He did develop a bout of colitis that resolved with steroid treatment.

There are cases in the literature describing patients that are refractory to corticoids. In fact, no definite recommendation for second-line treatment is available, although some data exist on the use of MMF and anti-thymocyte globulin.

To finish his presentation, Prof. Van Steenkiste touched upon what to do with patients who are found to have hepatitis B surface antigen upon screening prior to the start of immunotherapy. We used to check viral load and not treat these patients if it was negative, but it has now been shown that reactivation can occur even then, and so for patients who are HbsAg+, pre-emptive treatment of hepatitis B should be started.

KEY TAKEAWAYS

Prof. Van Steenkiste ended his presentation by giving some key takeaways:

- Hepatic irAEs are characterised by variability (clinical, biological and histological).
- Liver biopsy helps to confirm the diagnosis and evaluates the severity of liver injury.
- Corticosteroid therapy should be critically evaluated, even for grade 3-4 toxicity, according to the biological and histological severity of hepatitis.
- Reintroduction is possible with risk since predictive factors for hepatitis recurrence or other irAEs are lacking.
- The rate of irAEs seems low in patients with pre-existing cirrhosis. However, the use of CPI in NASH induced liver cirrhosis warrants further evaluation

Take-home messages

Dr. Canon then went on to summarise the take-home messages:

- CTLA-4 and PD-1 blockades act on tumor-specific but also on non-tumour-specific T cells
- irAEs are caused mostly by non-tumour-specific T cells; GI toxicity is likely caused by those recognising gut microbiota
- In 2020–2021 we witnessed important practice-changing data for immune checkpoint inhibitors, specifically in oesophagal, gastric & hepatocellular cancers, leading to new treatment algorithms
- Across multiple tumour types, response to immunotherapy is seen in patients with high expression of PD-L1, especially when PD-L1 is expressed in the immune cells
- MSI-H/dMMR tumours are highly immunogenic, which may make these tumours highly susceptible to immune checkpoint inhibitors
- Diarrhea and colitis may result from hyper-activated effector T cells
- Biopsies are necessary for the diagnosis of GI irAEs when patients present with macroscopically normal bowels but may have microscopic colitis
- Around a third of patients with GI irAEs are corticosteroid-refractory and require immunosuppressive biologic agents, such as infliximab or vedolizumab
- Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory, immune-mediated colitis
- Liver biopsy helps to confirm the diagnosis of hepatic irAEs and evaluate the severity of liver injury
  - Corticosteroid therapy should be critically assessed according to the biological and histological severity of hepatitis irAEs
  - It is of value to consult a gastroenterologist who has experience in treating irAEs

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