

Gastrointestinal Adverse Events Associated with Immune Checkpoint Inhibitor Therapy

Lamia Aalaoui^{1*}, Mohamed Reda Khmamouche¹, Mohamed Anouar Mokhlis¹, RachidTanz¹, Hassan Errihani², Mohamed Ichou¹

¹Medical Oncology Department, Military Hospital Mohammed V, Rabat, Morocco

²Medical Oncology Department, National Institute of Oncology Sidi Mohamed Ben Abdellah, Rabat, Morocco

DOI: [10.36347/sasjm.2022.v08i02.005](https://doi.org/10.36347/sasjm.2022.v08i02.005)

| Received: 02.01.2022 | Accepted: 09.02.2022 | Published: 13.02.2022

*Corresponding author: Dr. Aalaoui Lamia

Medical Oncology Department, Military Hospital Mohammed V, Rabat, Morocco

Abstract

Review Article

The introduction of immune checkpoint inhibitors (ICIs) has significantly improved cancer management and survival outcomes. One third of patients exposed to ICI will develop gastrointestinal adverse events (GIAEs). Knowledge of these toxicities, along with effective management algorithms, is essential to enable early diagnosis and treatment, decreasing morbidity and mortality.

Keywords: Immunotherapy, gastrointestinal, toxicity.

Copyright © 2022 The Author(s): This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY-NC 4.0) which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited.

INTRODUCTION

Immunotherapy with monoclonal antibodies targeting cytotoxic T lymphocyte-Associated Antigen 4 (CTLA-4), the Programmed Death-1 receptor (PD-1) and its Ligand (PDL-1) are currently the fourth pillar of cancer treatment. They can be administered alone or combination with another immune checkpoint inhibitors (ICI), chemotherapy, or local treatment by radiotherapy or surgery. Their mechanism is to boost the ability of the immune system to detect and destroy cancer cells, which can lead to immune-mediated adverse reactions. Immune system-related adverse events (iraes) are well described in the literature and can affect any organ system [1]. The skin and the digestive tract are the most frequently affected organs. Gastrointestinal aes can involve the colon, small intestine, liver, and pancreas. The first symptoms of these reactions are not specific such as nausea, vomiting, and abdominal pain. These toxicities are often mild and require only careful monitoring. Interruption of cancer therapy is not necessary, in the otherwise, the morbidity becomes significant requiring hospitalization and sometimes the intervention of a gastroenterologist [2].

Immune checkpoint inhibitors

In recent years, immunotherapy has emerged as an effective strategy for the treatment of many malignancies. The anti-CTLA-4 blocking antibody ipilimumab was the first immune checkpoint inhibitor

wish was approved for the treatment of unresectable metastatic melanoma. Has since also demonstrated efficacy for renal cell carcinoma and microsatellite instability-high cancers [3, 4].

CTLA-4 functions as a negative regulator of T-cell activity ; is expressed on the surface of CD4 and CD8 positive T-cells and on subsets of B-cells and thymocytes [5].

The Food and Drug Administration (FDA) approved pembrolizumab and nivolumab in 2014. They blocked the interaction between the immune checkpoint PD-1 (expressed by T-cells) and its ligands PD-L1 and PD-L2 (expressed by tumor and myeloid cells).

PD-1 inhibitors are less frequently associated with high-grade toxicities than CTLA-4 inhibitors. These drugs were also approved in other cancer types (table 1).

Grading of immune-related gastrointestinal toxicities

The severity of immune-related toxicities is most often graded using the criteria of the NCI Common Terminology for Adverse Events Common Terminology for Adverse Events (CTCAE), version 5.0 (Table 2).

Knowledge of the grading of toxicity is essential because it allows to guide the treatment of immunotoxicity. Different studies have shown that PD-1 inhibitors are less frequently associated with high-grade toxicities than CTLA-4 inhibitors [6].

In metastatic melanoma, Nivolumab (PD-1 inhibitor) induced 82.1% digestive toxicity of which 16.3% was grades 3-4, whereas with ipilimumab (CTLA-4) there was 86.2% gastrointestinal adverse events and 27.3% was grade 3-4. More discontinuation of treatment with ipilimumab had (14.8%) versus 7.7% with nivolumab [7, 8].

However, the development of diarrhea and/or colitis while using a checkpoint inhibitor does not necessarily prohibit use of another [8].

Immune Checkpoint Inhibitor–Induced diarrhea or colitis

The most frequently recorded gastrointestinal complications secondary to ICI treatment are diarrhea with higher incidence treatment with CTLA-4 (40%) than PD-1 inhibitors (30%) [6]. It is the descending colon that is mainly affected in cases of colitis [9].

Diagnosis

Immune-related diarrhea is usually a consequence of underlying colonic inflammation. She must be mentioned in any patient on immunotherapy presenting diarrhea. The history and physical examination are the basis of diagnosis. The median onset of diarrhea is approximately 6–8 weeks after initiating treatment by ICIs [10].

The therapeutic course of action depend on the severity of the symptoms (table 2), and it is important to eliminate an infectious cause in the first time. The differential diagnosis is made by nucleic acid amplification tests and stool culture looking for clostridium and a diagnosis of giardia and cryptosporidium [11]. Tests for viruses with intestinal tropism may also be considered [11]. Abdominal imaging may be helpful if severe symptoms or abdominal pain. Scanner are not specific for checkpoint inhibitor colitis but can oriented the diagnosis and can eliminated complications, including bowel perforation, abscess, and toxic megacolon [12].

Endoscopic evaluation should be scheduled for persistent no bloody diarrhea or more than grade 2. She can also establish the diagnosis of checkpoint inhibitor colitis and guide therapy.

Sigmoidoscopy with left colon biopsy is able to make diagnosis in 95% of cases of Ipilimumab-induced colitis cases. The results can not be confirmed with the use of PD-1/ PD-L1 inhibitors [11].

The endoscopic appearance is no specific with mucosal edema, erythema, and shallow ulcers [13]. Histology reveals active colitis with neutrophilic infiltrates, increased numbers of intraepithelial lymphocytes and apoptotic crypt epithelial cells [13].

Management

There are no prospective clinical trials to guide ICI treatment. Recently, American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), established the guidelines for the management of iraes [8, 14, 15].

Patients with mild diarrhea/colitis can be managed ambulatory with oral hydration, without need interruption of their treatments. An antidiarrheal can be prescribed once infectious etiology is eliminated. Dietary modifications (bland and low fiber diet) are also beneficial.

Patients with mild symptoms (grade 1 of diarrhea/colitis) that persist for more than 2 weeks or diarrhea/colitis grade 2 or worse should be treated with glucocorticoid.

Budesonide is prescribed as first-line treatment at a dose of 9 mg/day for at least 4 weeks. The degradation is done in steps of 3 mg for a total of 4 to 6 weeks of therapy.

Prednisone is given as second line (1 mg/kg per day) for persistent grade 1 diarrhea that does not respond to budesonide and for persistent grade 2 diarrhea more than 3 days on first-line treatment. Decreasing the dose in 5 to 10 mg steps each week and stopping it over 4 to 6 weeks.

Grades 3 and 4 diarrhea are considered severe and require prompt hospitalization; in order to hydrate the patient and ensure intravenous repletion of electrolytes and intravenous steroids (1 to 2 mg/kg per day of methylprednisolone). If there is a response, methylprednisolone is converted to oral prednisone after 3 to 5 days of improvement then decrease gradually over 6 to 8 weeks, decreasing the dose in 5 mg steps each week.

For patient's refractory to steroids who do not respond to intravenous corticosteroid treatment for three days, the tumor necrosis factor alpha inhibitor infliximab (5–10 mg/kg) can be offered. Failing this, mycophenolate mofetil can be used if infliximab is unavailable [16].

Immune Checkpoint Inhibitor–Induced: Pancreatitis

Pancreatic toxicity associated with ICI therapy is uncommon, occurring in <2% of patients. In a retrospective study of 119 melanoma patients treated with nivolumab and ipilimumab, 8% had grade 3 or

worse amylase elevation, 27% had grade 3 or worse lipase elevation, and 8% patients had grade 3 elevations or worse of both enzymes [17]. Acute pancreatitis was recorded only in two cases. Moreover, pancreatic inflammation may be mediated by T lymphocytes from other organs or be the consequence of a obstruction of the pancreatic duct on metastases [18]. It can appear early especially in patients receiving anti-CTLA-4 therapy [19].

Presentation

Patients are usually asymptomatic with incidental findings elevated transaminases. Acute pancreatitis remains rare [19, 20], Sometimes associated with nausea, fatigue, epigastric pain [18]. Immune-mediated pancreatitis is subacute showing only pancreatic edema on CT scan [21].

Sometimes we can have a picture of chronic or exocrine pancreatitis or even a pancreatic endocrine insufficiency [22,23].

We find in the literature an incidence of 1% of onset of diabetes and accidental ketoacidosis in patients under ICI treatment [22, 24]. The Management Immunosuppression with corticosteroids should be reserved exclusively for patients with pancreas due to checkpoint inhibitors.

In the absence of symptoms, corticosteroids are not indicated, according to expert opinion [19]. In symptomatic patients or in cases with severe elevation of pancreatic enzymes, the decision to start steroids and stop immunotherapy remains controversial and related to the clinic and degree of amylase and lipase elevation [19].

In the case series by Abu-Sbeih *et al.* ,steroids and intravenous injections the use of fluids in ICPI did not impact short-term patient outcomes in terms of normalization of pancreatic enzymes, clinical improvement or duration of hospitalization[19].

Immune Checkpoint Inhibitor–Induced: hepatitis

In monotherapy the incidence of hepatitis is 10% of cases (including 1 to 2% grade 3); it can reach 30% of cases (including 15% grade 3) in combined ICI

patients [25]. ICI-induced hepatitis manifests 8 to 12 weeks after the start of treatment.

Patients with liver or gastrointestinal cancers are more exposed to hepatitis under treatment with worse prognosis [25].

Presentation

Patients are usually asymptomatic with incidental findings of elevated transaminases; sometimes it can manifest as fatigue, fever or jaundice. In rare cases, fulminant hepatitis has been reported [26].

À liver test must always be requested during follow-ups, a toxic or viral origin must always be ruled out before retaining the diagnosis.

Management

Hepatitis are very sensitive to corticosteroids even if the resolution time is 8 weeks, however, relapses remain frequent when decreasing doses of corticosteroids.

Infliximab does not have a role in the treatment of checkpoint inhibitor hepatitis because of the risk of hepatotoxicity associated with tumor necrosis factor-alpha inhibitors. If corticoreistance treatment with mycophenolate mofetil and tacrolimus can be used [8].

CONCLUSION

Immune checkpoint inhibitors are an important part of the therapeutic arsenal for many advanced cancers. Gastrointestinal toxicities are among the leading causes of immune system-related adverse effects of checkpoint blockade. Proper management of these toxicities requires in-depth knowledge and precise clinical assessment of the classification by a multidisciplinary team involving oncologist, gastroenterologist and hepatologist. Treatment of severe ICPI-related colitis and hepatitis should include discontinuation of immunotherapy and initiation of high-dose corticosteroids.

Conflicts of interest

The authors declare that there is no conflict of interests in this study.

Table-1: Food and Drug Administration-approved immune checkpoint inhibitors

Drug	Trade name	Target	Indications
Ipilimumab	Yervoy (2011)	Cytotoxic T-lymphocyte antigen 4	<ul style="list-style-type: none"> • Melanoma • Urothelial carcinoma • Non-small-cell lung
Nivolumab	Opdivo (2014)	Programmed cell death-1	<ul style="list-style-type: none"> • Melanoma • Non-small-cell lung carcinoma • Renal cell carcinoma • Hepatocellular carcinoma • Classic Hodgkin’s lymphoma • Squamous cell carcinoma of head and neck

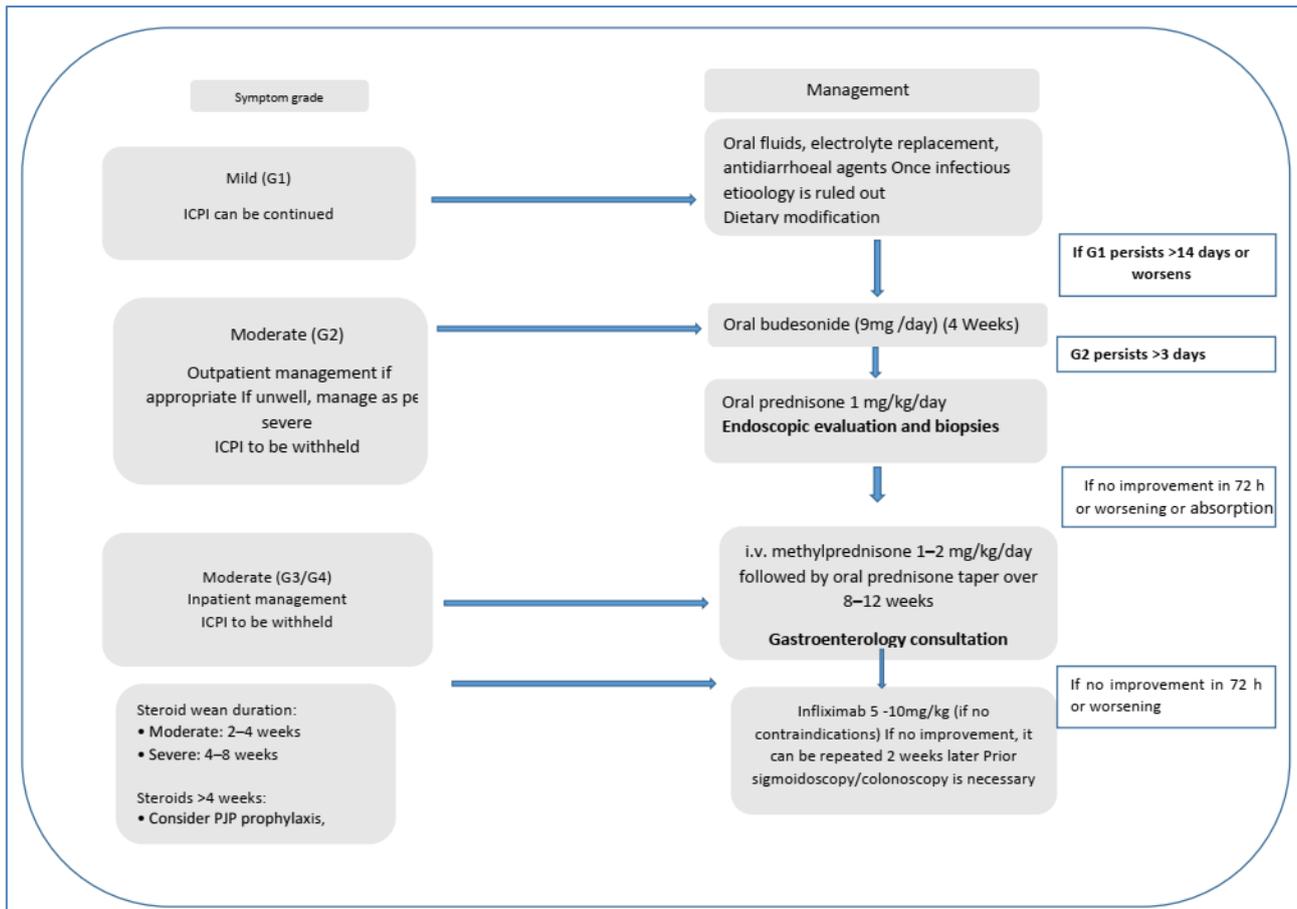
Drug	Trade name	Target	Indications
			<ul style="list-style-type: none"> • Urothelial carcinoma • MSI-H/dMMR colorectal cancer • <i>Epidermoid Esophageal Carcinoma</i> • Adenocarcinoma of the esophagogastric junction • Gastric cancer
Pembrolizumab Keytruda (2014)	Programmed cell death-1		<ul style="list-style-type: none"> • Melanoma Non-small-cell lung Squamous cell carcinoma of head and neck Carcinoma Classic Hodgkin’s lymphoma • Primary mediastinal large B-cell lymphoma Urothelial carcinoma • Non-muscle Bladder cancer • Advancer MSI-H/dMMR cancer • Advanced MSI-H/dMMR colorectal cancer Gastric or esophagogastric junction cancer • Esophageal or Esophagogastric junction cancer Cervical cancer Hepatocellular carcinoma • Merkel cell carcinoma • Renal cell carcinoma Tumor mutational burden-high cancer Cutaneous squamous cell carcinoma
Atezolizumab	Tecentriq (2016)	Programmed cell death ligand-1	<ul style="list-style-type: none"> • Non-small-cell lung carcinoma • Urothelial carcinoma • Triple negative Breast cancer
Avelumab	Bavencio (2017)	Programmed cell death ligand-1	<ul style="list-style-type: none"> • Merkel cell carcinoma • Urothelial carcinoma
Durvalumab	Imfinzi (2017)	Programmed cell death ligand-1	<ul style="list-style-type: none"> • Urothelial carcinoma • Non-small-cell lung
Cemiplimab	libtayo (2021)	Programmed cell death-1	<ul style="list-style-type: none"> • Cutaneous squamous cell carcinoma • Basal cell carcinoma • Non-small-cell lung carcinoma

MSI-H : microsatellite instability, dMMR: mismatch-repair deficiency TNBC : Triple negative Breast cancer

Table-2: Common Terminology Criteria for Adverse Events (CTCAE), Version 5

Adverse effect	Grade 1	Grade 2	Grade3	Grade 4	Grade 5
Diarrhea / Colitis	Increase of < 4 stools per day over baseline ; mild increas in ostomy output Compared to baseline without colitis symptoms	Increase of 4–6 stools per day over baseline ; moderate increase in ostomy output Compared to baseline or / and colitis symptoms Limiting instrumental ADLs	Increase of > = 7 stools per day over baseline ; (or severe increase in ostomy output compared to baseline),colitis symptoms interfering with ADLs;incontinence, hospitalization indicated Limiting self-care ADL	Life-threatening consequences : (perforation, hemodynamic instability) urgence intervention indicated	Death
Hepatitis	ASAT or ALAT< 3 X ULN and /or total Bilirubine <1,5 X ULN	ASAT or ALAT «3-5 X ULN and /or total bilirubine ≤ 3 X ULN	ASAT or ALAT > 5-20 X ULN and /or total bilirubine 3-10 X ULN	ASAT or ALAT > 20 X ULN and /or total bilirubine> 10 X ULN	Death

AST Aspartate Transaminase, ALT Alanine Transaminase, ULN upper limit of normal ,ADL Activities of daily living



REFERENCE

- Brahmer, J. R., Lacchetti, C., Schneider, B. J., Atkins, M. B., Brassil, K. J., Caterino, J. M., ... & Thompson, J. A. (2018). Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*, 36(17), 1714.
- Postow, M., & Wolchok, J. (2016). Toxicities associated with checkpoint inhibitor immunotherapy. *UpToDate*, Waltham, MA (Accessed on December 15, 2015).
- Hodi, F. S., Mihm, M. C., Soiffer, R. J., Haluska, F. G., Butler, M., Seiden, M. V., ... & Dranoff, G. (2003). Biologic activity of cytotoxic T lymphocyte-associated antigen 4 antibody blockade in previously vaccinated metastatic melanoma and ovarian carcinoma patients. *Proceedings of the National Academy of Sciences*, 100(8), 4712-4717.
- Phan, G. Q., Yang, J. C., Sherry, R. M., Hwu, P., Topalian, S. L., Schwartzentruber, D. J., ... & Rosenberg, S. A. (2003). Cancer regression and autoimmunity induced by cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma. *Proceedings of the National Academy of Sciences*, 100(14), 8372-8377.
- US Department of Health and Human Services. National Cancer Institute. Common terminology criteria for adverse events v5.0 (CTCAE). 2017.
- Lomax, A. J., & McNeil, C. (2017). Acute management of autoimmune toxicity in cancer patients on immunotherapy: common toxicities and the approach for the emergency physician. *Emergency Medicine Australasia*, 29(2), 245-251.
- Larkin, J., Chiarion-Sileni, V., Gonzalez, R., Grob, J. J., Cowey, C. L., Lao, C. D., ... & Wolchok, J. D. (2015). Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *New England journal of medicine*, 373(1), 23-34.
- Haanen, J. B. A. G., Carbonnel, F., Robert, C., Kerr, K. M., Peters, S., Larkin, J., & Jordan, K. (2017). Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, 28, iv119-iv142.
- Kumar, V., Chaudhary, N., Garg, M., Floudas, C. S., Soni, P., & Chandra, A. B. (2017). Current diagnosis and management of immune related adverse events (irAEs) induced by immune checkpoint inhibitor therapy. *Frontiers in pharmacology*, 8, 49.
- Grover, S., Rahma, O. E., Hashemi, N., & Lim, R. M. (2018). Gastrointestinal and hepatic toxicities of checkpoint inhibitors: algorithms for

- management. *American Society of Clinical Oncology Educational Book*, 38, 13-19.
11. Immunotherapy. (2021). Accessed: October 26, 2021: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.
 12. Nishino, M., Ramaiya, N. H., Hatabu, H., & Hodi, F. S. (2017). Monitoring immune-checkpoint blockade: response evaluation and biomarker development. *Nature reviews Clinical oncology*, 14(11), 655-668.
 13. Marthey, L., Mateus, C., Mussini, C. (2016). Cancer immunotherapy with an Θ -CTLA-4 monoclonal an Θ bodies induces an infl ammatory bowel disease. *J Crohn's Colitis*, 10 ; 395-401
 14. Puzanov, I., Diab, A., Abdallah, K., Bingham, C. 3., Brogdon, C., Dadu, R., ... & Ernstoff, M. S. (2017). Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *Journal for immunotherapy of cancer*, 5(1), 1-28.
 15. Brahmer, J. R., Lacchetti, C., Schneider, B. J., Atkins, M. B., Brassil, K. J., Caterino, J. M., ... & Thompson, J. A. (2018). Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*, 36(17), 1714.
 16. Bergqvist, V., Hertervig, E., Gedeon, P., Kopljar, M., Griph, H., Kinhult, S., ... & Marsal, J. (2017). Vedolizumab treatment for immune checkpoint inhibitor-induced enterocolitis. *Cancer Immunology, Immunotherapy*, 66(5), 581-592.
 17. Friedman, C.F., Clark, V., Raikhel, A.V. (2016). Thinking cri Θ cally about classifying adverse events: incidence of pancrea Θ Θ s in pa Θ ents treated with nivolumab + ipilimumab. *J Natl Cancer Inst*, 109: djw260.
 18. Di Giacomo, A. M., Danielli, R., Guidoboni, M., Calabrò, L., Carlucci, D., Miracco, C., ... & Maio, M. (2009). Therapeutic efficacy of ipilimumab, an anti-CTLA-4 monoclonal antibody, in patients with metastatic melanoma unresponsive to prior systemic treatments: clinical and immunological evidence from three patient cases. *Cancer immunology, immunotherapy*, 58(8), 1297-1306.
 19. Abu-Sbeih, H., Tang, T., Lu, Y., Thirumurthi, S., Altan, M., Jazaeri, A. A., ... & Wang, Y. (2019). Clinical characteristics and outcomes of immune checkpoint inhibitor-induced pancreatic injury. *Journal for immunotherapy of cancer*, 7(1), 1-12.
 20. Ikeuchi, K., Okuma, Y., & Tabata, T. (2016). Immune-related pancreatitis secondary to nivolumab in a patient with recurrent lung adenocarcinoma: a case report. *Lung Cancer*, 99, 148-150.
 21. Grover, S., Rahma, O. E., Hashemi, N., & Lim, R. M. (2018). Gastrointestinal and hepatic toxicities of checkpoint inhibitors: algorithms for management. *American Society of Clinical Oncology Educational Book*, 38, 13-19.
 22. Prasanna, T., McNeil, C. M., Nielsen, T., & Parkin, D. (2018). Isolated immune-related pancreatic exocrine insufficiency associated with pembrolizumab therapy. *Immunotherapy*, 10(3), 171-175.
 23. Hofmann, L., Forschner, A., Loquai, C., Goldinger, S. M., Zimmer, L., Ugurel, S., ... & Heinzerling, L. M. (2016). Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. *European journal of cancer*, 60, 190-209.
 24. Maamari, J., Yeung, S. C. J., & Chaftari, P. S. (2019). Diabetic ketoacidosis induced by a single dose of pembrolizumab. *The American journal of emergency medicine*, 37(2), 376-e1.
 25. Chan, S. L., Yip, T. C. F., Wong, V. W. S., Tse, Y. K., Yuen, B. W. Y., Luk, H. W. S., ... & Wong, G. L. H. (2020). Pattern and impact of hepatic adverse events encountered during immune checkpoint inhibitors—A territory-wide cohort study. *Cancer Medicine*, 9(19), 7052-7061.
 26. Kim, K.W., Ramaiya, N.H., Krajewski, K.M. (2013). Ipilimumab associated hepa Θ Θ s: imaging and clinicopathologic fi ndings. *Invest New Drugs*, 31; 1071-1077.