Reviewer #1:
Scientific Quality: Grade B (Very good)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: Immunotherapy becames a popular treatment against a wide variety of maligancies. The encouraging effectivity has been repeatedly repotrted from teams over the world. However, the negative sides have been largely ignored. The review article gave an extensive introduction about the immune related adverse effects (irAEs) to various organs/systems caused by immunotherapies. The article is helpful for clinicians and patients to better understand immunotherapies from both the positive and negative sides. the title "Discussion" after the section of Introduction is quite confused. The content is still the essential part of Introduction. The title is not necessary.

Response: Thank you for your suggestions and for taking the time to review our manuscript. We have removed the title discussion as recommended.

Reviewer #2:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors: This review summarizes the status quo on the adverse effects of the immunotherapeutic agents currently employed in cancer therapy. The topic covers an array of the affected systems (cardiovascular, dermatologic, endocrine, gastrointestinal, neurologic and pulmonary systems) and describes the known adverse effects caused by use of the specific agents. The reviewer finds this paper intriguing in that it is written for those who work in the clinic. It may help physicians to treat cancer patients properly with the immunotherapeutic agents and when they encounter the problems pertinent to the agents, they could find out the remedy. However, the reviewer has several concerns as follows:

Major concerns; 1. Some basic insights into the mode of adverse effects are not properly explained. ex. 1. Some investigators have hypothesized that this overexpression may lead to excess monocytic activation, which infiltrate the thyroid gland, recognize self-antigens and induce subsequent cytotoxic damage to the normal cells[23]. It is not clear whether monocytic activation per se leads to cytotoxic damage to the normal cells or the damage is mediated by the self-antigen specific CD8 T cells which were activated by the monocytic cells.

Response: Thank you for this observation. We have corrected the line to state "However, it is not entirely clear whether the monocytes are directly responsible for the cytotoxic damage, or whether the damage is mediated by monocyte-activated autoreactive CD8+ T-cells"

ex.2. but it is postulated that it may be due to autoreactive CD8+ t cell activation against pancreatic beta cells, which are now unable to bind to T cells and promote self-tolerance[27]. Readers cannot understand what the above sentence means.

Response: We have improved the wording of the sentence to state "The pathophysiology of the development of diabetes in these patients is not well understood, but it is postulated that it may

be due to autoreactive CD8+ t cell activation against pancreatic beta cells as a consequence of the blockade of inhibitory pathways, such as the PD-1/PD-L1 pathway"

ex.3. Bronchoalveolar lavage may help immunosuppressed patients or in patients difficult to establish; however, a negative BAL does not exclude infection[52]. Readers cannot understand what the above sentence means.

Response: We have improved the wording to state "Bronchoalveolar lavage (BAL) may be helpful in patients with cellular interstitial pneumonitis in that the fluid may show lymphocytosis, however there have been relatively few reports describing this finding and further research is needed[53]."

2. It is highly desirable to use unified format to designate the therapeutic agents such as monoclonal antibody and antibody. A good example is "Ipilimumab, a CTLA-4 inhibitor". It is not reader friendly to use only "Ipilimumab" as readers expect to have a brief description of the products to further their knowledge.

Response: We have made addition of designations to the agents when they are referred to in the text, as suggested

3. Related to 2, prepare a table summarizing the name of each therapeutic agent and brief description as above (ex. both Pembrolizum and Nivolumab are the humanized monoclonal antibody against PD1).

Response: We have added table 2, which summarizes the name of each agent and a brief description as suggested.

4. It is not acceptable that the authors did not discuss about CD19-expressing CAR-T cell therapy against B cell lymphoma and immune-related adverse events (irAEs). This is indispensable for the review.

Response: An entire section has been added to the review discussing CAR T Cell therapy and it unique irAEs.

Minor concerns; 1. In A "which are normally utilized by healthy cells to promote self-tolerance and inhibit T-cell destruction{8}." It is not clear from this sentence whether T cells are destructed or destruction of tumor cells are inhibited.

Response: We have corrected the sentence to read "*Immune checkpoint inhibitors (ICIs)* work through therapeutic targeting of the checkpoint molecules CTLA-4, PD-1, and PD-L1, which are normally utilized by healthy cells to promote self-tolerance and inhibit destruction by autoreactive T-cells[8]."

2. In B "T-Cell transfer therapy creates tumor specific T-Cells that promote immune mediated destruction of cancers." This sentence is difficult to understand for readers outside the field. Rewrite so that a wide range of readers can understand.

A. Response: This sentence has been rewritten as "*T-Cell transfer therapy* is a treatment method in which a patient's T cells are collected and modified in a laboratory setting in order to improve their ability to bind and kill cancer cells. By collecting

activated T-cells from cancer tissue, or genetically engineering T-cells, transfer therapy allows for passive immunization against cancers[9].

3. In C "Monoclonal antibodies are engineered to be antigen specific, often tumor-specific, and mediate the destruction of tumor cells via direct tumor cell killing," The above sentence is quite confusing in that it can be interpreted that monoclonal antibodies per se kill tumor cells. Tumor cell killing is not direct and is rather caused by Antigen-dependent cellular cytotoxicity (ADCC).

Response: We have corrected this sentence to include that the tumor cell killing is caused be ADCC.

4. There are some typographic errors and an error in abbreviation in the pulmonary system for "immune-related adverse events".

Response: The manuscript has been reviewed for any typographic errors thoroughly, and these have been corrected. Thank you very much for your great suggestions. They have greatly improved the quality of our manuscript.

1 Scientific quality: The manuscript describes a review of the systemic adverse effects and toxicities associated with immunotherapy. The topic is within the scope of the WJCO. (1) Classification: Grade B and Grade C; (2) Summary of the Peer-Review Report: This review summarizes the status quo on the adverse effects of the immunotherapeutic agents currently employed in cancer therapy. The topic covers an array of the affected systems (cardiovascular, dermatologic, endocrine, gastrointestinal, neurologic and pulmonary systems) and describes the known adverse effects caused by use of the specific agents. The reviewer finds this paper intriguing in that it is written for those who work in the clinic. It may help physicians to treat cancer patients properly with the immunotherapeutic agents and when they encounter the problems pertinent to the agents, they could find out the remedy. The questions raised by the reviewers should be answered; and (3) Format: There is 1 table. A total of 53 references are cited, including 27 references published in the last 3 years. There is 1 self-citation. 2 Language evaluation: Classification: Grade A and Grade B. The authors are native English speakers. 3 Academic norms and rules: No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an unsolicited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJCO. 5 Issues raised: No additional comments. 6 Recommendation: Conditional acceptance.

Response: Thank you for reviewing our manuscript. We have made the corrections as suggested by the peer reviewers.

Answering reviewers of re-review:

The authors have revised the article according to the reviewer's recommendation. The quality of the article has improved and the problems pertinent to CAR-T cell therapy have been discussed. However, the reviewer still finds minor errors in the CART section.

1. Chimeric antigen receptor (CAR) T-cell therapy is a type of T-cell transfer therapy currently approved for the treatment several hematologic malignancies, including acute lymphoblastic leukemia and diffuse large B-cell lymphoma[53]. should be Chimeric antigen receptor (CAR) T-cell therapy is a type of T-cell transfer therapy currently approved for the treatment of several hematologic malignancies, including acute lymphoblastic leukemia and diffuse large B-cell lymphoma[53].

Response: Thank you for your continued suggestions that have helped to improve our manuscript. The following changes have been made as suggested. Thank you.

2. Tocilizumab is not IL-6 inhibitor, it is an inhibitor of IL-6 receptor.

Response: Thank you for your continued suggestions that have helped to improve our manuscript. The following changes have been made as suggested. Thank you.

3. "They also recommend repeating the dose if there are not signs of clinical improvement over 24 to 48 h[56]." Should be "They also recommend repeating the dose if there are no signs of clinical improvement over 24 to 48 h[56]."

Response: Thank you for your continued suggestions that have helped to improve our manuscript. The following changes have been made as suggested. Thank you.

4. Symptoms normally being within the first 7 days following CAR T-cell infusion[59]. There is no verb.

Response: Thank you for your continued suggestions that have helped to improve our manuscript. The following changes have been made as suggested. Thank you.