Peer Review File

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Reviewer Comments

In this case report the authors describe a case of a 68-year-old male with NSCLC stable on nivolumab with partial response for 2 years who developed meningoencephalitis after two doses of extended-interval higher flat-dosing nivolumab. This is an interesting and important case report for practicing oncologists and neurologists and highlights the importance of being vigilant of immune-related adverse events when modifying dosing schedules of ICIs, even after years of stability on the same ICI. To this reviewers knowledge this is the first case report of a neurologic irAEs related to a ICI extended-interval dosing schedule change, though at least one non-neurologic irAE in a similar context has been reported. Comments and suggestions are listed below.

Comment 1: **********
Reply 1: **********
Changes in the text: **********

Comments:

Comment 1. The abstract should end with a conclusion sentence referring to how alternate immune checkpoint inhibitor regimens may have unique immune-related adverse event profiles. If fewer words are needed the introductory text could be shortened and the description of the case could be shortened in the abstract. For example, "We report a case of meningoencephalitis in a patient with non-small cell lung cancer that developed after two doses of extended interval flat dose nivolumab despite two years of clinical stability on prior nivolumab regimen" or something similar.

Reply 1: We have modified the abstract as advised by adding both a conclusion sentence and including a short sentence about the concept of extended interval flat dosing that will be also clarified below following suggestions on comment 2.

Changes in the text have been made in page 3, lines 57-74 and the abstract now reads as follows:

Alternative dosage regimens for some anticancer therapies have been proposed in the midst of the SARS-COV-2 pandemic in order to protect the patients from attending to health care facilities. Flat-dosing of several immune-checkpoint inhibitors, including nivolumab, have been established. Although generally well tolerated with no new safety signals, new dosages can associate novel individual toxicities. As the use of immune-checkpoint inhibitors is increasing in cancer patients, the present case report is a reminder for clinicians of potential novel toxicities, as well as the need for an interdisciplinary approach for their recognition and treatment.
We report the occurrence of a severe neurologic toxicity in a patient with non-small cell lung cancer who developed after two doses of extended higher interval flat dose nivolumab despite two years of clinical stability on prior nivolumab regimen. Patient developed fever, language impairment and altered mental status. The work-up tests excluded other potential causes and the most likely diagnosis was meningoencephalitis.
Fortunately, with medical treatment, which consisted of high dose steroids, the patient recovered to his baseline situation and symptoms did not recurred, even though nivolumab was

resumed. Alternate immune checkpoint inhibitor regimens may have unique immune-related adverse event profiles.

Comment 2. Referring to nivolumab scheduling of 480mg q4w as the "flat dose" regimen is slightly confusing as nivolumab 1mg/kg/q2w (typically in combination with ipilimumab), 3mg/q2w, 240mg flat-dose q2w, and 480 mg flat-dose q3w are all approved for various cancers in various countries. This reviewer recommends referring to the 480mg q4w nivolumab schedule as the "extended-interval higher flat dose" regimen. The authors could subsequently refer to this regimen as the "higher flat dose" regimen for simplicity. But it is important to describe clearly for the reader that this new regimen both increased the dose and extended the interval between doses for this patient, both of which could be related to a change in immune-related adverse event profiles.

Reply 2: We have modified this section according to this suggestion.

Changes in the text have been made in page 4, lines 91-96 and this part now reads as follows:

Patients were rescheduled to receive an extended-interval higher flat dose. This strategy consists of both increase the dose and extend the interval between doses for the patients, from once every two weeks (Q2W) to every four weeks (Q4W) [5].This approach has been considered safe and efficacious [6], although higher flat-dose might associate a change in immune-related adverse events (irAE) profile

In addition, we have modified flat dose to higher flat dose along the text in

Page (P) 1, line (L) 3; P2, L41; P2, L43; P3, L 66; P4, L92; P4, L95; P4,L99; P5, L126; P5, L130; P5, L 133; P9, L261; P9, L263; P10, L 280; P10, L 286; P12, L 326; P12, L330; P12 L336.

Comment 2 a. For example, the conclusion sentence "ICI flat-dose may increase the risk of severe IR-AE. However, resume ICI at previous dose with immunosuppressors could be a safety option in some patients" is confusing in isolation. This regimen did not cause new complications because it was a flat-dose (he was on the same "flat" dose for the past two years prior, just a lower dose more frequently). Consider changing conclusion sentence to "Altering ICI schedules including to an extended-interval higher flat-dose regimen may alter the risk of severe irAEs. One the irAE is treated, resumption of the ICI at previously well-tolerated dose initially with corticosteroid taper could be an efficacious and safe option in some patients"

Reply 2a: We have changed Conclusion sentence following reviewer suggestion

Changes in the text: this part now reads as follow (page 12, lines 336-339):

Altering ICI schedules including to an extended-interval higher flat-dose regimen may alter the risk of severe irAEs. Once the irAE is treated, resumption of the ICI at previously well-tolerated dose initially with low doses of corticosteroids could be an efficacious and safe option in selected patients.

Comment 2 b. Would consider changing the title to something along the lines of "A case report of severe meningoencephalitis after switching to an extended-interval flat dose nivolumab regimen." This is more descriptive and will help readers looking for relevant information find your article.

Reply 2b We have modified the title as advised.

Changes have been made in page 1, lines 1-3 and the Title now reads:

IMMUNE-CHECKPOINT INHIBITORS FOR LUNG CANCER PATIENTS AMID THE COVID19 PANDEMIC: A CASE REPORT OF SEVERE MENINGOENCEPHALITIS AFTER SWITCHING TO AN EXTENDED-INTERVAL HIGHER FLAT-DOSE NIVOLUMAB REGIMEN.

Comment 2bi. Along these lines I would remove SARs-COV2 and Case Report from key words and include "immune-related adverse events", "flat dose", and "extended interval" to your keywords to better link this case report to the relevant field.

Reply 2b Following the reviewer advise and in order to adhere to the CARE checklist standards as well as to the TLCR editorial rules we have modified Keywords by including changes in this section.

Changes: keywords section reads now as follows (page 2, lines 44-44)

KEYWORDS: *extended-interval higher flat dose; nivolumab; meningoencephalitis; Non-small cell lung cancer (NSCLC); case report.*

Consequently, and according to the prior comments and responses, running title (page 2, lines 41) have been also initially modified as follows:

RUNNING TITLE: *Nivolumab extended-interval higher flat-dose induced-meningoencephalitis.*

However, to adhere to the Submission checklist (<60 character), our final decision for the Running Title is as follows:

RUNNING TITLE: *Nivolumab higher flat-dose induced-meningoencephalitis*

Comment 3. Palla et al. reported in 2019 a case of bullous spemphigoid associated with extended-interval flat 480mg nivolumab dose regimen in a patient who had previously tolerated 240mg biweekly for 2 years. This case supports the authors conclusion that higher flat extended-interval dosing of nivolumab may have unique risks for immune-related adverse events from traditional dosing. This report should be cited.

Reply 3: Palla et al report has been included in the discussion section.

Changes in the text have been made in the discussion section (page 10 , lines 283-290) by adding the following part:

However, another group have reported a case of bullous pemphigoid associated with extended-interval flat 480 mg nivolumab dose regimen in a patient with a metastatic renal carcinoma who had been previously treated with 240 mg Q2W for 2 years without safety concerns [16]*. While our case report and others suggest these extended-interval higher flat-dose regimens may increase or alter the propensity for ICI irAEs, clinical trial data does suggest these regimens have similar efficacy and safety profiles and are reasonable options for patients. However, when switching between ICI dosing regimens providers*

and patients need to have increased vigilance for unique irAE risks when compared to traditional dosing.

Comment 4. The phrase 'immune-related adverse events' or irAEs should be used when discussing these immune checkpoint inhibitor complications (instead of adverse events or AE) as this is the standard language used in the literature to refer to these complications and will help clinicians find this paper.

Reply 4: IR-AE and AE has been modified by irAE along the text.

Changes in the text: tracked changes show the following changes:

-irAE instead of IR-AE and AE in Page (P) 4 line (L) 96; P7, L 187; P 8, L 205; P8 L208; P 8, L 213; P10, L 271, P10, L 275; P10, L278; Pº0, L279; P10, L287, P10, L290; P11, L 308; P11, L 317; P12, L 326; P12, L 330; P12, L337.

-ir-specific event or toxicity in Page (P) 7, Line 169; P 9, L241; P9, L252; P 9, L 256; P11, L 307; P11, L 315.

Comment 5. Regarding this patient's work-up and evaluation

Reply 5: No answer is needed
Changes in the text: No changes are needed

Comment 5 a. Did he have a urine drug screen? This should be stated in the text.

Reply 5a : It was not performed

Changes in the text: This piece of information has been included in the text as follows (page 6; line 150-151):

No specific biochemistry or urine screen panel to detect alcohol or other drugs was performed.

Additionally, page 6 lines 142-143 has been corrected and now reads:

No alcohol or other substances use was reported.

Comment 5 b. What was the differential of his cells on his CSF analysis? Were they lymphocytes? This should be stated in the text.

Reply 5b: CFS analysis revealed 7 cells/mm3 (all of them were lymphocytes)

Changes in the text: This data has been included in page 6 , line 152.

CFS analysis revealed 7 cells/mm3 (all of them lymphocytes)

Comment 5 c. Did he only have VZV PCR testing? VZV PCR is notoriously poor sensitivity for VZV and CSF IgG and IgM should typically be checked.

Reply 5c: CSF IgG and IgM for VZV were not performed. It is well-known that VZV PCR does not present a good sensitivity, however the fact that the patient also presented a normal brain MRI makes unlikely the diagnosis of VZV infection.

Changes in the text: This piece of information has been included in page 6 , lines 156-157 as follows:

CSF IgG and IgM for VZV were not tested.

Comment 5 d. The serum and CSF microbiology and onconeuronal/anti-neural antibody testing in the legend of Figure 1 needs to be more clearly referred to in the text. As a reader I was wondering about several of these studies until I got the his legend at the very end.

Reply 5d: This part was included in the Figure 1, however in the corrected version we have included it in the text.

Changes in the text: Text has been modified as follows (page 6, line 154 to page 7, line 167):

A comprehensive microbiological screening, which included bacterial cultures, and Herpes Simplex virus, Herpes-6 virus, Varicella Zoster virus and Epstein Barr virus PCR was negative. VZV CFS IgG and IgM were not tested. Malignant cells screening in the CSF was negative.

Neither oligoclonal bands, nor onconeuronal or surface antibodies (Abs) were detected in the CSF or in serum. The immunologic panel in CSF and serum included the following: Oligoclonal bands, onconeural Ab (anti-Tr (DNER), anti-GAD65, anti-Zic4, anti-titin, anti-SOX1, anti-Recoverin, anti-Hu, anti-Yo, anti-Ri, anti-PNMA2, anti-CV2, anti-Amphiphysin) and surface Ab (anti-NDMA-R, anti-AMPAR1/2, anti-DPPX receptor, anti-GABA(b)R, anti-LGI1 receptor, anti-CASPR2 receptor).

Comment 5 e. The text states a brain MRI did not show enhancement. Was his brain MRI otherwise normal? Did he have an T2 signal abnormalities. This should be stated in the text.

Reply 5 e: The brain MRI was read as normal. T2 and FLAIR signal revealed slight periventricular changes attributable to the involution age-related process.

Changes in the text: For the sake of clarification, this information has been included in page 7, lines 172-174 and now reads as follows:

A brain MRI did not show enhancements suggesting brain metastases or leptomeningeal involvement. T2 and FLAIR signal revealed slight periventricular changes attributable to the involution age-related process.

Comment 5 f. Lines 153-157 that describe the onconeuronal/anti-neural antibodies tested should be included in the case description with the other results and does not need to be separately in the discussion. This description could be truncated or even just referred to Figure 1 where the testing is more clearly outlined.

Reply 5 f: We have included this information in the case report section.

Changes in the text have been included in page 6, line 159 to page 7, line 167, as follows,

Neither oligoclonal bands, nor onconeuronal or surface antibodies (Abs) were detected in the CSF or in serum. The immunologic panel in CSF and serum included the following: Oligoclonal bands, onconeural Ab (anti-Tr (DNER), anti-GAD65, anti-Zic4, anti-titin, anti-SOX1, anti-Recoverin, anti-Hu, anti-Yo, anti-Ri, anti-PNMA2, anti-CV2, anti-Amphiphysin) and surface Ab (anti-NDMA-R, anti-AMPAR1/2, anti-DPPX receptor, anti-GABA(b)R, anti-LGI1 receptor, anti-CASPR2 receptor).

Comment 5 i. Please include the manufacturer of the test used for the onconeuronal and anti-neural surface antibodies in Figure 1 legend.

Reply 5i: Onconeural antibodies were analyzed by immunoblot using EUROLINE Paraneoplastic Neurologic Syndromes 12 Ag (IgG), Euroimmun®. Anti-neural surface antibodies were analyzed by immunofluorescence by Autoimmune Encephalitis Mosaic 6, Euroimmun®

Changes in the text: This information has been included in the Figure 1 legend (page 18 , lines 474 and 480)

c.- Immunologic study in CSF and blood included the following: *Oligoclonal bands, onconeural antibodies (Ab) by Paraneoplastic Neurologic Syndromes 12 Ag (IgG) immunoblot, Euroimmun® (anti-Tr (DNER), anti-GAD65, anti-Zic4, anti-titin, anti-SOX1, anti-Recoverin, anti-Hu, anti-Yo, anti-Ri, anti-PNMA2, anti-CV2, anti-Amphiphysin) and surface antibodies by Encephalitis Mosaic 6 immunofluorescence, Euroimmun® (anti-NDMA-R, anti-AMPAR1/2, anti-DPPX receptor, anti-GABA(b)R, anti-LGI1 receptor, anti-CASPR2 receptor)*

Comment 6. Regarding his treatment

Reply 1: No needed
Changes in the text: no needed

Comment 6 a. More details regarding his steroid treatment is needed. Which corticosteroid, IV or oral, and for many days did he get 1mg/kg corticosteroids? What dose and regimen of steroid was he discharged on and how was his steroids tapered over the next 6-months? This information will be helpful for clinicians who have patients that develop complications on this extended-interval flat dose regimen.

Reply 6a:

Patient was started on iv metilprednisolone (1 mg/Kg dose with a total dose of 80 mg/day). when he was admitted in the hospital on May 16th to May 21st, prior discharge. He was discharged on May, 22t^{h} 2020 with oral metilprednisolone (70 mg/day). After 1 week, on May 29th, dose was tapered to 60 mg/day; after 1 week dose was reduced to 50 mg/day starting on June 5th to June 12th, then to 40 mg/day from June 13th to June 19th, then to 30 mg/day from June 20th to July 3rd (this interval was longer to wait until the neurologist consultation). On July 4th metilprednisolone was tapered to 20 mg/day until July 10th, then to 15 mg/day until July 17th. A longer tapering interval was then recommended and, for prescription reasons metilprednisolone was changed to equivalent doses of prednisone (10 mg/day from July 18th to August 19th, then 5 mg/day form August 20th to September 16th, 2.5 mg from September 17th to October 21st. Essentially, patient was under corticosteroids therapy during 5 months since symptoms started; the last 3 months he had already resumed nivolumab.

Changes in the text have been included from page 7, line 182 to page 8, line 199.

Patient received 1mg/kg iv metilprednisolone (total dose 80 mg/day) while admitted in the hospital. At discharge, tapering of 10 mg/week was recommended under close surveillance. In July 2020, once the patient was on 20 mg/day of metilprednisolone with no symptoms recurrence, nivolumab 3mg/Kg/Q2 was resumed, since patient was willing to continue therapy which provided an adequate tumor control and despite the irAE occurrence; and the steroids were tapered to 15 mg/day for a week and then to 10 mg/day, at this point with prednisone to ease the tapering. From then on, in mid-July, steroids were tapered for longer intervals (to 10 mg/day a month) and then halved to 5 mg/day and 2.5 mg/day a month, respectively. Without concerning symptoms recurrence, steroids were complete in October 2020. He received 7 cycles of nivolumab while tapering the steroids (from July to October 2020) and 6 cycles off steroids (from November 2020 to January 2021). Nivolumab has been continued without new neurological toxicity and a sustained PR.

Comment 6 b. The timeline of his steroids, nivolumab restart, and how long he has remained stable on nivolumab without steroids is unclear. The authors mention 6-months after his immune-related meningoencephalitis and (~2-3-months after restarting nivolumab?) corticosteroids were stopped. Based on Figure 1, it seems he has been on nivolumab and off steroids for only 1-2 months (or 2-4 doses of nivolumab). Is that correct?

Reply 6b: Once the patient was on oral metilprednisolone 20 mg/day he was restarted on nivolumab Q2W. He received 7 cycles of nivolumab while tapering the steroids (from July 17th to October 21st) and 6 cycles off steroids (from November 4th to January 13th 2021)

Changes in the text: This piece of information has been included in the text as follows (page 7, line 184 to page 8 line, line 199):

In July 2020, once the patient was on 20 mg/day of metilprednisolone with no symptoms recurrence, nivolumab 3mg/Kg/Q2 was resumed, since patient was willing to continue therapy which provided an adequate tumor control and despite the irAE occurrence; and the steroids were tapered to 15 mg/day for a week and then to 10 mg/day, at this point with prednisone to ease the tapering. From then on, in mid-July, steroids were tapered for longer intervals (to 10 mg/day a month) and then halved to 5 mg/day and 2.5 mg/day a month, respectively. Without concerning symptoms recurrence, steroids were complete in October 2020. He received 7 cycles of nivolumab while tapering the steroids (from July to October 2020) and 6 cycles off steroids (from November 2020 to January 2021). Nivolumab has been continued without new neurological toxicity and a sustained PR.

Figure 1 has been also clarified in this regard.

Comment 6b i. In the timeline in Figure 1 include the timing of the corticosteroid taper

Reply 6b i: Timing of the corticosteroids taper has been included in Figure 1

Changes in the text: Figure 1 has been updated with this information.

Comment 6b ii. Please update how long on nivolumab monotherapy (how many months/nivolumab cycles) he has remained without irAEs.

Reply 6bii: We understand the reviewer is referring to cycles after the irAE occurrence. As detailed in Comment and reply 6b, Once the patient was on oral metilprednisolone 20 mg/day

he was restarted on nivolumab Q2W. He received 7 cycles of nivolumab while tapering the steroids (from July 17th to October 21st) and 6 cycles off steroids (from November 4th to January 13th 2021)

Changes in the text: Changes have been included by answering Comment 6a in page 7, line 184 to page 8 line, line 199)

Comment 7. The authors nicely discuss several studies that would suggest that extended-interval flat dosing of nivolumab is safe and efficacious in patients. However, their case report providers possible evidence against this point suggesting their may be some increased, or at least different, risk profiles based on the treatment regimen. Synthesizing this dichotomy a little more in the discussion will be important for readers. Currently the case report and its conclusion and the conclusion of these studies suggesting similar rates of irAEs and similar safety are discussed in separate paragraphs without commenting on the synthesis. Something like "While our case report and others suggest these extended-interval flat dose regimens may increase or alter the propensity for ICI irAEs, clinical trial data does suggest these regimens have similar efficacy and safety profiles and are reasonable options for patients. However, when switching between ICI dosing regimens providers and patients need to have increased vigilance for possible irAEs."

Reply 7: This information has been included in the discussion section.

Changes in the text: This information reads as follow (page 10, line 285 to page 11, line 290):

While our case report and others suggest these extended-interval higher flat-dose regimens may increase or alter the propensity for ICI irAEs, clinical trial data does suggest these regimens have similar efficacy and safety profiles and are reasonable options for patients. However, when switching between ICI dosing regimens providers and patients need to have increased vigilance for unique irAE risks when compared to traditional dosing.

Comment 8. The info in Table 1 is limited/sparse and Table 1 not necessary in the context of this case report. Other case series and reviews have expansive summaries of neurologic irAEs of the CNS (and PNS). Recommend removing table 1.

Reply 8: Some irAE can be difficult to identify and treat, since their incidence is low and the differential diagnosis challenging. We believe that ,for medical oncologist using ICI and facing such type of AE, having in hand this piece of information could be helpful. For educational porpoises, we would like to consider keeping table 1

Changes in the text: not done, at this time

Comment 9. It is unclear what bradipsiquia means. This may represent an untranslated word for confusion.

Reply 9: Bradypsychia in a medical term used to defined slowness of mental reactions. This term is included in medical dictionaries, and defined slowness of mental reactions, slowed mental response, or slow mentation. However, bradypsychia has been changed to slowed mental response which is more commonly used in literature.

Changes in the text: Bradypsychia has been changed to *slowed mental response* in page 5, line 131 and page 7, line 176.

Comment 10. Make sure abbreviations are written out the first time they are used.

Reply 10: We have detected the following findings in this regard and corrected as follows:

Non-small cell lung cancer (NSCLC) page 4 line, 88.
Immune-related Adverse events (irAE) page 4, line 96.
Immune-related (ir)-meningoencephalitis page 7, line 169

Comment 11. References Palla AR, Smith E, Doll D. Bullous pemphigoid associated with the 480-mg nivolumab dose in a patient with metastatic renal cell carcinoma. Immunotherapy. 2019 Oct;11(14):1187-1192

Reply 11: We have included Palla et al in the discussion (refer to comment 3) and the reference has been also included.

Changes in the text: Palla et al is now included as part of the References (reference 16)