PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for Phase-I study of Pembrolizumab in combination with bacillus Calmette-Guerin for patients with high-risk non-muscle invasive bladder cancer
AUTHORS	Jamil, Marcus; Deebajah, Mustafa; Sood, Akshay; Robinson, Kathy; Rao, Krishna; Sana, Sherjeel; Alanee, Shaheen

VERSION 1 - REVIEW

REVIEWER	Parminder Singh Mayo CLinic
REVIEW RETURNED	09-Feb-2019

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.

REVIEWER	Shomik Sengupta Professor of surgery EHCS Monash University Box Hill Victoria 3128 AUSTRALIA
REVIEW RETURNED	15-Feb-2019

GENERAL COMMENTS	This is a protocol description of a Phase I study of MK-3475 (Pembroluzimab) combined with Bacillus Calmette-Guerin (BCG) for BCG-refractory non-muscle invasive bladder cancer (NMIBC). Some issues need addressing before it would be suitable for publication: 1. Pembroluzimab is now well established in clinical practice, and I think it would be worth using the drug name throughout the protocol. 2. The references on clinical use of Pembrolizimab provided in the background section are old (2012-4) and some even in the form of conference abstracts – there are a lot more up to date studies, including the use in metastatic bladder cancer that would be of greater relevance. 3. There is a similar trial utilising intravesical Pembroluzimab along with BCG (NCT02808143 – details at: https://clinicaltrials.gov/ct2/show/NCT02808143)which should be referenced and discussed.

	4. Trial schema as outlined in Figure 1 is a bit confusing – it might be better to start from the point of diagnosis of recurrence after 2 induction courses or induction plus maintenance BCG. 5. The text in the methods section does not explicitly make clear that the Pembroluzimab is delivered intra-venously – the reader has to refer to Figure 4 to ascertain that. 6. I feel figure 3a & 3b would be better reformatted as tables? 7. The endpoints of the trial need to be defined and described more clearly: a. As a phase I study, presumable safety & dose-tolerability are key endpoints. Although the manuscript includes efficacy measured as a complete response (CR) rate as a secondary objective, with 15 patients planned, I am not sure this will be a reliable estimate. b. It is not clear what rate/level of AEs will rule out the safety of the study treatment c. In describing the methodology for dose escalation, it looks like there is a typo – should “If two out of three or two out of six subjects develops toxicity…”

REVIEWER	dr. KEM van Kessel Erasmus Medical Center, Rotterdam, The Netherlands
REVIEW RETURNED	10-Mar-2019

GENERAL COMMENTS	The authors describe a study protocol to analyze the safety and efficacy of combined MK-3475 and intravesical BCG therapy for BCG-unresponsive high risk non-muscle invasive bladder cancer. The research objective is very relevant and clearly portrait. Several minor comments: - What are the reasons patients are not - In the statistics section the sample size is discussed. Even though the desired effect size is mentioned, a reader also needs the desired level of confidence to be able to re-calculate the given sample size. - In the statistics section of the protocol a reference to "Kahn et al (2012)" is made. This reference is not depicted in the reference section. What article do you refer to? - In figure 3a a typo should be corrected. Line "3. (T1, T1)", should be "(Ta, T1). - Section 5.5.2. The methods of contraception read as if they only apply to female subjects. Male subjects should use condoms in heterosexual activity as well? - How will you handle / deal with potential BCG shortage / non-availability of BCG?

VERSION 1 – AUTHOR RESPONSE

Reviewer #2:

Shomik Sengupta

Dear Dr. Sengupta,

Thank you for the excellent feedback and suggestions. We have conducted a literature review of the studies you have mentioned and hope that our rationale suffices. Many of your recommendations will be implemented into this study and future studies.

1. Pembroluzimab is now well established in clinical practice, and I think it would be worth using the drug name throughout the protocol.

- We are in agreement with your recommendation and have now replaced MK-3475 with Pembrolizumab throughout the manuscript.

2. The references on clinical use of Pembrolizimab provided in the background section are old (2012-4) and some even in the form of conference abstracts – there are a lot more up to date studies, including the use in metastatic bladder cancer that would be of greater relevance.

- Thank you for this suggestion. You are correct, many of the references used in the submitted manuscript are from 2012-2014, which reflects the time frame in which the original study protocol was formed and hence retrieved from. Due to the presence of many newer studies demonstrating efficacy in agents such as Pembrolizumab, we have added several new references and discussed these papers in the discussion section of the paper.

3. There is a similar trial utilising intravesical Pembroluzimab along with BCG (NCT02808143 – details at: https://urldefense.proofpoint.com/v2/url?u=https-3A__clinicaltrials.gov_ct2_show_NCT02808143-29which&d=DwIFaQ&c=aLnS6P8Ng0zSNhCF04OWImQ_He2L69sNWG3PbxeyieE&r=BQGtlrl2IMAQIGM8SNv-jA&m=LIF6Q1qHAWY-KMFYTEAumaDg5gEw-tMpzXWE8j0OUYc&s=eQ2b9nPd386fK0IHPXXbebJ6i9G5HdO4wjVl85lSaaY&e= should be referenced and discussed.

- Thank you for this interesting reference. There are many similarities between our investigation and the investigation being carried out by Dr. Meeks at Northwestern. One notable difference is the route of administration of Pembrolizumab. Our route of administration being intravenous vs. intravesical in the study being carried out by Dr. Meeks. However, despite these differences, we are in agreement this study should be referenced in our manuscript. This has been added to the discussion portion of our manuscript. It is the belief of the investigating team, especially in the early investigations of such agents, that it is pivotal that multiple institutions preform studies with subtle differences in order to determine the most optimal dose, schedule and route of administration of these newer agents.

4. Trial schema as outlined in Figure 1 is a bit confusing – it might be better to start from the point of diagnosis of recurrence after 2 induction courses or induction plus maintenance BCG.

- Following review of figure 1, we are in agreement. The recommended changes have been applied with the addition of a footnote to clarify the preceding requirements for recurrence.

5. The text in the methods section does not explicitly make clear that the Pembroluzimab is delivered intra-venously – the reader has to refer to Figure 4 to ascertain that.

- In the section of the manuscript which details the treatment dosage, formulation, preparation and frequency of pembrolizumab, the addition of “intravenous administration” has been added. Thank you for this recommendation.

6. I feel figure 3a & 3b would be better reformatted as tables?

- Thank you for this recommendation. Due to formatting issues we feel that it may be best to keep these as figures over tables. However, to ensure that these figures convey the information as clearly as possible, we have edited the figures further to enhance quality and legibility.

7. The endpoints of the trial need to be defined and described more clearly:

a. As a phase I study, presumable safety & dose-tolerability are key endpoints. Although the manuscript includes efficacy measured as a complete response (CR) rate as a secondary objective, with 15 patients planned, I am not sure this will be a reliable estimate.

- Thank you for the comment. You are correct, the primary objective of this phase-I trial is to assess the safety of the studied drug. We also agree that an n of 15 will not provide definitive evidence that the studied drug provides benefit in complete response rates, however, as the secondary objective of the study, it will provide valuable information for future studies when assessing complete response in the given study population.

b. It is not clear what rate/level of AEs will rule out the safety of the study treatment.

Parameters for determination of patient safety and for trial suspension and discontinuation are noted within the original study protocol. As per the original study protocol, Section 5.2.3.3 Table 3, all grade 4 toxicities result in permeant discontinuation from the study. Further details and exceptions are noted within the original study protocol. As noted in Section 5.8 of the original study protocol, if there are any fatal treatment toxicities or if 1 or more of the 15 subjects treated experience a grade 4 toxicity, subject accrual will be suspended and all data pertaining to the events will be reviewed by the Study Investigators and Data Safety Review Team to determine if there is the need for any corrective actions. Following review and appropriate action by the investigating team, subject accrual may recommence. If there is a second fatal treatment/morbidity event related to the study treatment or procedures, the study will be terminated. If 4 of 15 subjects experience grade 4 toxicities, the accrual will be suspended and reviewed for added appropriate measures. If 5 subjects experience grade 4 toxicity, the study will be terminated.

c. In describing the methodology for dose escalation, it looks like there is a typo – should “If two out of three or two out of six subjects develops toxicity…”

- Thank you for identifying this error, we will make the appropriate changes to the manuscript submission and protocol. As it pertains to the study, the original 3 patients were able to proceed throughout the study without any limiting toxicities.

Review #3

Reviewer Name: Kim van Kessel

Dear Dr. Kim van Kessel,

Thank you for the wonderful feedback. Below we have included our rationale behind our decisions. You have posed many excellent questions and hope that our answers suffice.

- What are the reasons patients are not selected based on their PD1 expression status?

The study was planned before selection of patients based on PD-L1 expression status was common practice. Current debate is currently had determining the benefit of pembrolizumab at various expressions of PD-L1. It is presumed that even patients with low PD-L1 expression would benefit from these medications. Also, given the patient population we have selected, there is no clear treatment alternative, therefore PD-L1 expression may be off little application. Even more so, mutational burden has now shown to be more predictive of response to PD-L1 medications compared to PD-L1 expression .

- In the statistics section the sample size is discussed. Even though the desired effect size is mentioned, a reader also needs the desired level of confidence to be able to re-calculate the given sample size.

Thank you for identifying this error, a confidence interval of 95% will be used and has been added to the manuscript.

- In the statistics section of the protocol a reference to "Kahn et al (2012)" is made. This reference is not depicted in the reference section. What article do you refer to?

Thank you for identifying this error. We have added the appropriate citation. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3504941/

- In figure 3a a typo should be corrected. Line "3. (T1, T1)", should be "(Ta, T1).

Thank you for identifying this error, the appropriate correction has been made.

- Section 5.5.2. The methods of contraception read as if they only apply to female subjects. Male subjects should use condoms in heterosexual activity as well?

This is correct. This is noted on page 15, in section 5.1.2, as is stated within the original study protocol: Male subjects of child bearing potential must agree to use an adequate method of contraception as outlined in Section 5.5.2- Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy. The acceptable forms of contraception, for both males and females, are noted on page 31 of the original study protocol, section 5.5.2, which would include condoms.

- How will you handle / deal with potential BCG shortage / non-availability of BCG?

Merck intends to supply BCG TICE to all patients enrolled within a clinical trial.

VERSION 2 – REVIEW

REVIEWER	Shomik Sengupta Professor of SurgeryEHCS, Monash University Australia
REVIEW RETURNED	19-Apr-2019

GENERAL COMMENTS	Revisions have addressed most of the queries. Remaining issues: 1. Still seems odd to have the study justified on the basis of older reports on the use of Pembro in various cancers, including Melanoma. Why not quote the studies (detailed in the discussion section) of Pembrolizimab in metastatic bladder cancer? 2. The sentence: “If two out of three or two out of six subjects develops toxicity…” in the dose-escalation section of the methods remains unchanged - is this correct?

VERSION 2 – AUTHOR RESPONSE

Dr. Sengupta,

Thank you for taking the time to review our manuscript. Below are our responses:

1. Following a review of that particular section. We are in agreement with your recommendation and therefore deleted that particular section.

2. This section as been corrected. It now reads: "three out of six"