Submission Reference No.(For Office Use) NTEC-2020-0319

Hospital Authority

Clinical Research Ethics Review Application Form

Applying Cluster: NTEC

IRB/ REC Reference No. (For Office Use):

Instructions to applicant

1. Cluster Research Ethics Committee/Institutional Review Board (“REC/IRB”) is dedicated to oversee clinical studies conducted by Hospital Authority ("HA")/University personnel in the Cluster with the aim of protecting the rights, safety and well-being of the human subjects recruited for the studies. The Applicant / Principal Investigator must be designated to take the final responsibility for protecting the rights, safety and well-being of subjects recruited from the Cluster.
2. Please submit the application via online system, enter all information required and upload relevant application dossier files to the required fields.
3. This form is only fully functional with Microsoft Silverlight. This form can only support retrieval of the following attachments - [1] Common Image files, [2] HTML and XML files, [3] Media files, [4] Microsoft Office files (except *.mdb files), [5] PDF files, [6] Text files.
4. This Form does not support certain symbol and text format adjustment. For example, enter text “beta” instead of symbol “β” or copy and paste “β” from another source, and use symbol ^ to indicate “power”, e.g. 4x10^3 instead of 4x10³.
5. Research protocol, investigator brochures, consent forms, and written materials to subjects must be uniquely identified,for example, by Application Reference Number, document numbers, version numbers and dates.
6. For information on research ethics and methodology, please visit HA Research Ethics Intranet Website (http://cetm.home/ces/re/Home.aspx)
7. The handling and storage for data containing personal identity must comply with HA Clinical Data Policy Manual and other prevailing HA policies and if applicable university policies.
8. Selected information will be passed to the HA's and University's Central Register of Clinical Research for the purpose of central record and risk management.
9. Submit 1 hard copy of printed Application Form with original signatures and Application Dossier to the Joint CUHK-NTEC CREC office at 8/F, Lui Che Woo Clinical Sciences Building, Prince of Wales Hospital, Shatin, HK. The CREC Secretary may notify the Principal Investigator if any additional copies are required.

Reminder

1. Hospital Authority as a Research Institution

The HA is a body corporate established under the Hospital Authority Ordinance (Chapter 113 of the laws of Hong Kong). In addition to the primary responsibilities of establishing, managing, controlling and developing the public hospital system in Hong Kong and advising the Hong Kong government on healthcare policies and strategies, the HA also has the responsibility to promote, assist and take part in research relating to hospital services (Chapter 113, Section 4(f) (ii) of the laws of Hong Kong).

2. Local Regulation on Clinical Studies of Pharmaceutical Products

Clinical studies of pharmaceutical products are regulated in Hong Kong under the Pharmacy and Poisons Regulations (Chapter 138A Regulation 36B of the laws of Hong Kong). For the purpose of regulatory compliance, a Certificate for Clinical Trial ("CTC") shall be obtained before initiation of clinical study of pharmaceutical product.

☑ Acknowledge of the instruction

Clinical Research Ethics Review Application Form

Fields mark with asterisk (*) are mandatory fields

IRB/ REC Reference No. (For Office Use)

PART I: OUTLINE OF APPLICATION

1. Name of Study

1.1 Scientific Title (<500 characters)*

Local Experience with Adverse Effects of PD-1/PD-L1 Inhibitors in Cancer Patients

1.1.1 Research protocol number

1.2 Short Title (for lay public / easy quote)*

Local Experience with Adverse Effects of PD-1/PD-L1 Inhibitors in Cancer Patients

1.3 Key Words (for searching purpose, e.g. disease name, drug name, etc.)*

Adverse Effects, PD-1/PD-L1 Inhibitors, Cancer Patients

2. Applicant (Principal Investigator)

2.1 Title * (e.g. Mr, Mrs,Ms, Miss, Dr) Dr Surname * Zhou First name * Keary

Name in Chinese

2.2 Position of the Principal Investigator (PI)

2.2.1 ☑ HA staff

Position: Honorary Pharmacist

Department/Unit: Pharmacy

Hospital (1): PWH

Hospital (2):

☐ Site Coordinator (If the PI is not situated in the applying HA site, it is recommended to assign a qualified HA staff for site coordination.)

2.2.2 ☑ University staff

Position: Lecturer

Department/School/ Faculty: School of Pharmacy, Faculty of Medicine

University: CUHK

2.2.3 ☐ HA Employee ☑ University Employee

2.2.4 ☐ Full-time student ☐ Part-time student

☐ Undergraduate student ☐ Post-graduate student

Name of Program

Department/School /Faculty

Institute

2.2.4.1 Name of academic supervisor

Department/School/Faculty | Institute

Supporting document from academica

2.2.4.2 Name of site supervisor

Department/Unit

Hospital

2.3 PI's primary affiliated hospital/institution *

HA	University	Others, specify
	CUHK	

2.4 Qualifications and relevant experience (<1,000 characters or attach document)*

Dr. Keary Zhou received her Doctor of Pharmacy degree from the University of Southern California (USC) in 2007, and completed a pharmacy practice residency at the University of California San Diego (UCSD) in 2008. Prior to joining CUHK in 2009, she worked as a clinical pharmacist at the UCSD Thornton Hospital. Currently, Dr. Zhou coordinates the oncology clinical clerkship track and practice-based projects, oversees clerkship exchange programs, and participates in teaching of a variety of therapeutic topics at the School of Pharmacy. Dr. Zhou also serves as a member for the Joint CUHK-NTEC Clinical Research Ethics Committee (CREC) for the Hong Kong Hospital Authority. She has been a Board Certified Oncology Pharmacist by the US Board of Pharmaceutical Specialties since 2011 (recertified in 2019).

2.5 Phone number: 3943 6823

2.6 Fax number:

2.7 E-mail address* (<500 characters):

PI: krzhou@cuhk.edu.hk
Delegates: loksumyang@cuhk.edu.hk
Delegates: yinting.cheung@cuhk.edu.hk
FollowUpUsers: loksumyang@cuhk.edu.hk
FollowUpUsers: yinting.cheung@cuhk.edu.hk

(Please fill in all relevant email addresses of the PI, site-coordinators and other relevant members that are responsible to the communication related to the clinical research and ethics application.)

2.8 Mailing address*: Room 801K, Lo Kwee-Seong IBSB, Area 39, CUHK, Shatin

3. Other investigators

(If the PI is not situated in the applying HA site, it is recommended to assign a qualified HA staff for site coordination.Please also specify if there is a Lead PI in addition to the PI.)

No.	Title	Surname	First name	Email	Relevant Qualifications	Department	Responsibility	HA Site	Institution	Others, Specify
1	Prof	Cheung	Yin Ting	yinting.cheung@cuhk.edu.hk	B.Sc. (Pharm.) (Hons.), Ph.D.	School of Pharmacy	Administration,Expertise Advice		CUHK	
2	Prof	Loong	Herbert	h_loong@clo.cuhk.edu.hk	MBBS, PDipMDPath, MRCP, FHKCP, FHKAM	Department of Clinical Oncology	Expertise Advice,Site Coordinator	PWH	CUHK	
3	Prof	Lau	Yat Ming	ym_lau@clo.cuhk.edu.hk	MBBS, MRCP, FHKCP, FHKAM	Department of Clinical Oncology	Expertise Advice	PWH		
4	Ms	Yang	Lok Sum	loksumyang@cuhk.edu.hk	MPharm	School of Pharmacy	Administration,Data/Sample Security,Documentation		CUHK	

4. Study Site(s)

4.1 Is this a local or international trial? * Local

4.2 Will the study be conducted in HA hospitals/institutions?* ☑ Yes ☐ No

4.2.1 Is there a plan to involve more than one HA site? ☐ Yes ☑ No ☐ Unknown

4.3 Study sites

4.3.1 Applying sites in HA

Cluster	Hospital	Department	Other sites, specify
NTEC	PWH	Pharmacy	

4.3.2 Collaborating site(s) in HA

Cluster	Hospital	Department	Other sites, specify
NTEC	PWH	Clinical Oncology	

4.3.3 Study at sites out-of-HA

Country/City	Hospital	Department	Other sites, specify
Hong Kong		School of Pharmacy	CUHK

5. Parallel Ethics Review for Cross-cluster Study

5.1 Has the protocol been reviewed by another Cluster REC/IRB? ☑ Yes ☐ No/Unknown

5.1.1 What is REC/IRB decision? Approved

(Please attach the supporting document in Part VI, e.g. approval letter)

6. Timetable

6.1 Proposed study start date 10/08/2020

6.2 Proposed study end date or date of last follow-up of all recruited subjects, whichever is later 01/08/2021

6.3 Tentative final report date to Cluster REC 01/11/2021

7. Brief Summary of Study*

(< 6,000 characters, use language that can be understood by laypersons. Technical terms are not recommended and no referral to protocols/other documents is allowed)

Treatment with immune checkpoint inhibitors is well tolerated in general. However, they can cause immune-related adverse events (irAEs) by unbalancing the immune system.2 Majority of grade 3/4 irAEs can be managed with oral or intravenous steroids but some can be serious and fatal. Even though any organ systems can be affected, irAEs most commonly involve the gastrointestinal tract, endocrine glands, skin, and liver. Less often, the central nervous system, cardiovascular, pulmonary, musculoskeletal, and hematologic systems are involved.3

According to the data presented in 2018 Palliative and Supportive Care in Oncology Symposium in San Diego, immunotherapy side effects may be more prevalent in real world than that reported in clinical trials (Checkmate series for nivolumab and Keynote series for pembrolizumab). The retrospective study included about 2,800 patients with NSCLC who took nivolumab (71.4%), pembrolizumab (25%) and atezolizumab (3.6%) between 2015 and 2017. At 60 days, pneumonitis was found in 10.9% of patients versus 3% in CheckMate-057, 5.8% in Keynote-024 and 8.3% in Keynote-042 trials. Nephritis occurred in 4% of patients, versus 0.6% in Keynote-024 and 0.5% in Keynote-042 trials.

Objectives
The study aims to characterize the safety profile of the three checkpoint inhibitors (PD-1 inhibitors nivolumab and pembrolizumab, and

PD-L1 inhibitor atezolizumab). By analyzing the incidence and management of the associated irAEs, we aim to refine provider and patient expectations for the adverse effects. It may also help with the development of monitoring guidelines if appropriate. Besides, clinical risk factors for the development of irAEs will be evaluated.

(2) Methodology

Study Design
Data of all patients who received pembrolizumab, nivolumab and atezolizumab under the care of Department of Oncology at the Prince of Wales Hospital)PWH) between June 2016 and March 2020 will be retrospectively analyzed. The timeline is set to include all the patients using the immune checkpoint inhibitors as they are first introduced in 2016 in PWH. CDARS will be used to identify the patients. Inclusion criteria includes (1) Asian patients aged 18 or above; (2) who had received treatment in PWH under oncology department; (3) who had received any of the three checkpoint inhibitors (pembrolizumab, nivolumab and atezolizumab); and (4) who had adequate documentation of the treatment course in the patient profile. Patients treated with anti-PD-1/PD-L1 agents combined with other treatments simultaneously will be excluded.

The primary outcome is the incidence of irAEs. The percentage of patients who developed irAEs will be evaluated according to types and grading. Time to onset of irAEs will be recorded and presented graphically. The secondary outcomes are management of irAEs and the risk factors for the development of irAEs.

Patient-specific information will be collected using electronic databases (EPR).
The major information evaluated includes,
(a) irAEs (including the type, grading and onset time)
(b) Management of irAEs (including cumulative steroid dose used) and
(c) Risk factors for the development of irAEs
Other data collected includes patient demographics, tumor characteristics (type, staging, metastasis), previous systemic therapies, date of first immunotherapy dose, date of death (or the last follow-up), performance status (PS), number of treatment doses and deferrals.

Data Analysis
Descriptive statistics provide an overview of the characteristics of the study population.
(a) irAEs
irAEs are defined as all adverse events reported after treatment with immune checkpoint inhibitors, which are not present prior to the initiation of treatment. It is assumed that before attributing the cause of AEs to immune checkpoint inhibitors, the diagnosis has been accompanied by an extensive work-up to rule out the more common cause of various diseases.
irAEs will be graded using the Common Terminology Criteria for Adverse Events v4.0. They will be grouped into grades 1/2 and 3/4 as there are inherent difficulties in retrospective grading from some clinical notes. AEs of interest will be categorized into organ-specific groups for analysis. ‘General’ irAEs includes nonspecific symptoms including fatigue/lethargy, asthenia, pyrexia, and decreased appetite.
Specific clinical/ laboratory findings will also be documented, i.e.
- Endocrine system (Cortisol, ACTH, Free T4, TSH, Antibodies, HbA1c, Calcium, PTH)
- Cardiovascular system (Cardiac enzyme elevation, EF reduction)
- Hepatic system (AST/ALT/bilirubin)
- Renal system (Urine study, e.g presence of blood, acetone, glucose, protein, nitrite/ biopsy/ SCr)

Time to first grade 3/4 irAE is defined as time from first treatment dose to time of first reported irAE. Patients who did not experience grade 3/4 irAEs will be censored at time of last follow-up.
Descriptive statistics will be used to report the incidence of the irAEs.
IBM SPSS Statistics will be used to obtain Kaplan–Meier curves to describe the time to onset of irAEs.

(b) Management of irAEs
All steroids prescribed, except those for hormone-replacement therapy in adrenal insufficiency and for non-irAEs, such as brain metastasis and radiation-induced pneumonitis, will be analyzed. They will be converted to the equivalent prednisolone dose for ease of comparison. Other management may include levothyroxine, calcium supplement and insulin. Treatment outcome will also be documented.

(c) Risk factors for the development of irAEs
Multivariable log-binomial models (generalized linear models with Poisson error and log link function) will be performed to evaluate the relationship between potential predictors and irAEs incidence rates, adjusting for potential confounders (eg. cancer diagnosis, age, and sex). Relative Risk (RR) estimates and 95% confidence intervals (CI) will be reported.

8. Major Ethical Issues*

(< 6,000 characters, use language that can be understood by laypersons. Technical terms are not recommended and no referral to protocols/other documents is allowed)

No clinical intervention will be performed to the subjects in this study. Patient specific information will be collected through EPR. The major ethical issue is patients' privacy. Information recorded will not identify the subject. Individually identifiable data elements will not be recorded. All the patient data will be protected and only accessible by the PI during the study.

PART II: STUDY DETAILS (No referral to protocols/other documents is allowed)

9. Scientific basis

IRB/ REC Reference No.
(For Office Use)

9.1 Background, current evidence and key references* (< 30,000 characters)

The use of immunotherapy has been increasing in treating various cancer types, as they are promising treatment option with favorable toxicity profiles. Immunotherapy enhances a patient's immune system to fight diseases. Among different immunotherapeutic strategies, immune checkpoint blockade has shown remarkable benefit.1 Programmed cell death protein 1 (PD-1) and its ligand PD-L1 are immune checkpoints that physiologically limit autoimmunity during inflammatory responses. By blocking these checkpoints, intrinsic immunity will not be downregulated and thus increasing antitumor immunity. Monoclonal antibodies against PD-1 or PD-L1, such as nivolumab, pembrolizumab and atezolizumab have been produced to achieve stable regression of malignancy.2 They have shown efficacy in prolonging overall survival in cancer patients and have received FDA approval for clinical use.2

Treatment with immune checkpoint inhibitors is well tolerated in general. However, they can cause immune-related adverse events (irAEs) by unbalancing the immune system.2 Majority of grade 3/4 irAEs can be managed with oral or intravenous steroids but some can be serious and fatal. Even though any organ systems can be affected, irAEs most commonly involve the gastrointestinal tract, endocrine glands, skin, and liver. Less often, the central nervous system, cardiovascular, pulmonary, musculoskeletal, and hematologic systems are involved.3

According to the data presented in 2018 Palliative and Supportive Care in Oncology Symposium in San Diego, immunotherapy side effects may be more prevalent in real world than that reported in clinical trials (Checkmate series for nivolumab and Keynote series for pembrolizumab). The retrospective study included about 2,800 patients with NSCLC who took nivolumab (71.4%), pembrolizumab (25%) and atezolizumab (3.6%) between 2015 and 2017. At 60 days, pneumonitis was found in 10.9% of patients versus 3% in CheckMate-057, 5.8% in Keynote-024 and 8.3% in Keynote-042 trials. Nephritis occurred in 4% of patients, versus 0.6% in Keynote-024 and 0.5% in Keynote-042 trials.

Besides, several small retrospective studies have also highlighted the increased incidence of irAEs in clinical practice in comparison to clinical trials.4 Thus, it is thought that incidence of irAEs in clinical trials may not necessarily reflect 'real-world' experiences due to underrepresentation of the patient population. In addition, there are reports of delayed occurrence of irAEs.2 Moreover, published real-life data on irAEs with these checkpoint inhibitors are limited, especially in Asian population.

Early recognition of irAEs is key to management and can potentially reverse them, thus avoiding long-term complications.4 Therefore, there is a need to understand the characteristics of irAEs associated with anti PD-1/PD-L1 treatments to help us manage them appropriately. Guidelines on the management of irAEs have been developed by different oncology organizations, including ESMO, ASCO and NCCN. By examining the local experience with the use of these agents, hopefully we can incorporate the recommendations into local practice.

(10) References

(1) Longo DL, Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med 2018;378(2):158-168.
(2) Wang P, Chen Y, Song S, Wang T, Ji W, Li S, et al. Immune-Related Adverse Events Associated with Anti-PD-1/PD-L1 Treatment for Malignancies: A Meta-Analysis. Frontiers in Pharmacology 2017;8.
(3) Soldatos TG, Dimitrakopoulou-Strauss A, Larribere L, Hassel JC, Sachpekidis C. Retrospective Side Effect Profiling of the Metastatic Melanoma Combination Therapy Ipilimumab-Nivolumab Using Adverse Event Data. Diagnostics (Basel, Switzerland) 2018;8(4).
(4) So ACP, Board RE. Real-world experience with pembrolizumab toxicities in advanced melanoma patients: a single-center experience in the UK. Melanoma Management 2018;5(1).
(5) Iyer PC, Cabanillas ME, Waguespack SG, Hu MI, Thosani S, Lavis VR, et al. Immune-Related Thyroiditis with Immune Checkpoint Inhibitors. Thyroid 2018;28(10):1243-1251.
(6) Kartolo A, Sattar J, Sahai V, Baetz T, Lakoff JM. Predictors of immunotherapy-induced immune-related adverse events. Current oncology (Toronto, Ont.) 2018;25(5):e403.
(7) Sanlorenzo M, Vujic I, Daud A, Algazi A, Gubens M, Luna SA, et al. Pembrolizumab cutaneous adverse events and their association with disease progression.(Report). 2015;151(11):1206.
(8) Baxi S, Yang A, Gennarelli RL, Khan N, Wang Z, Boyce L, et al. Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis. BMJ 2018;360.
(9) Bajwa R, Cheema A, Khan T, Amirpour A, Paul A, Chaughtai S, et al. Adverse Effects of Immune Checkpoint Inhibitors (Programmed Death-1 Inhibitors and Cytotoxic T-Lymphocyte-Associated Protein-4 Inhibitors): Results of a

Retrospective Study. Journal of clinical medicine research 2019;11(4):225

9.2 Aim of study* (< 30,000 characters)

The study aims to characterize the safety profile of the three checkpoint inhibitors (PD-1 inhibitors nivolumab and pembrolizumab, and PD-L1 inhibitor atezolizumab). By analyzing the incidence and management of the associated irAEs, we aim to refine provider and patient expectations for the adverse effects. It may also help with the development of monitoring guidelines if appropriate. Besides, clinical risk factors for the development of irAEs will be evaluated.

9.3 Hypothesis (e.g. Compared to x control, y intervention leads to a greater rate of z outcome)* (< 30,000 characters)

Programmed cell death protein 1 (PD-1) and its ligand PD-L1 are immune checkpoints that physiologically limit autoimmunity during inflammatory responses. By blocking these checkpoints, intrinsic immunity will not be downregulated and thus increasing antitumor immunity. Monoclonal antibodies against PD-1 or PD-L1, such as nivolumab, pembrolizumab and atezolizumab have been produced to achieve stable regression of malignancy.2 They have shown efficacy in prolonging overall survival in cancer patients and have received FDA approval for clinical use.2

Treatment with immune checkpoint inhibitors is well tolerated in general. However, they can cause immune-related adverse events (irAEs) by unbalancing the immune system

9.4 Outcome measure(s)

9.4.1 Primary outcome(s)* (< 30,000 characters)

The primary outcome is the incidence of irAEs. The percentage of patients who developed irAEs will be evaluated according to types and grading. Time to onset of irAEs will be recorded and presented graphically.

9.4.2 Secondary outcome(s) (< 30,000 characters)

The secondary outcomes are management of irAEs and the risk factors for the development of irAEs.

9.5 In what way will the research contribute to knowledge or healthcare development?* (< 30,000 characters)

Early recognition of irAEs is key to management and can potentially reverse them, thus avoiding long-term complications.4 Therefore, there is a need to understand the characteristics of irAEs associated with anti PD-1/PD-L1 treatments to help us manage them appropriately. Guidelines on the management of irAEs have been developed by different oncology organizations, including ESMO, ASCO and NCCN. By examining the local experience with the use of these agents, hopefully we can incorporate the recommendations into local practice.

10. Study subjects

10.1 Inclusion criteria* (< 30,000 characters)

Data of all patients who received pembrolizumab, nivolumab and atezolizumab under the care of Department of Oncology at the Prince of Wales Hospital)PWH) between June 2016 and March 2020 will be retrospectively analyzed. The timeline is set to include all the patients using the immune checkpoint inhibitors as they are first introduced in 2016 in PWH. CDARS will be used to identify the patients. Inclusion criteria includes (1) Asian patients aged 18 or above; (2) who had received treatment in PWH under oncology department; (3) who had received any of the three checkpoint inhibitors (pembrolizumab, nivolumab and atezolizumab); and (4) who had adequate documentation of the treatment course in the patient profile.

10.2 Exclusion criteria* (< 30,000 characters)

-Patients below 18 years of age
-Patients treated with anti-PD-1/PD-L1 agents combined with other treatments simultaneously

10.3 Sample-size and rationale for calculation*

Sample size*(< 600 characters)

200.

based on the following rationale*(< 30,000 characters)

Sample size is based on the number of patients treated with the 3 checkpoint inhibitors of interest. The identified sample for the same study conducted at Princess Margaret Hospital is 100 patients.
Based on clinical experience and preliminary drug usage data at PWH, we estimate the

sample size to be 100 as well.

10.4 Number of subjects to be recruited locally in applying site* 100

10.5 How will subject be identified and recruited* (< 30,000 characters)

Data of all patients who received pembrolizumab, nivolumab and atezolizumab under the care of Department of Oncology at the Prince of Wales Hospital (PWH) between June 2016 and March 2020 will be retrospectively analyzed. The timeline is set to include all the patients using the immune checkpoint inhibitors as they are first introduced in 2016 in PWH. CDARS will be used to identify the patients.

Patient-specific information will be collected using electronic databases (EPR).
The major information evaluated includes,
(a) irAEs (including the type, grading and onset time)
(b) Management of irAEs (including cumulative steroid dose used) and
(c) Risk factors for the development of irAEs
Other data collected includes patient demographics, tumor characteristics (type, staging, metastasis), previous systemic therapies, date of first immunotherapy dose, date of death (or the last follow-up), performance status (PS), number of treatment doses and deferrals.

11. Ethical Review for Study

11.1 Applicant's Preference ☐ Full Review ☑ Expedited Review

11.2 Justification (< 1,000 characters)

This is a retrospective study. No interventions will be performed.

(The Cluster REC/IRB has full authority to decide the type of ethical review to be conducted)

12. Risk Assessment whether Expedited Review is suitable

		Yes	No
12.1	Will study incur extra clinical intervention(s) to subjects?*	☐	☑
12.2	Will study impose additional risk to subjects?*	☐	☑
12.3	Will study raise sensitive / important privacy concerns?*	☐	☑
12.4	Will the study involve the following vulnerable subjects?		
12.4.1	Children or adolescent (of less than 18-year-old)*	☐	☑
12.4.2	Illiterates*	☐	☑
12.4.3	Mentally incapacitated persons*	☐	☑
12.4.4	Impoverished persons*	☐	☑
12.4.5	Ethnic minority groups*	☐	☑
12.4.6	Patients in emergency conditions*	☐	☑
12.4.7	Prisoners*	☐	☑
12.4.8	Subordinates or students of investigators*	☐	☑
12.4.9	Others*	☐	☑

Specify

12.5 Are there any special precautions to protect the interest of vulnerable subjects? (<1,000 characters)

12.6 Will study impose potential hazard to clinical staff?* ☐ Yes ☑ No

12.6.1 Control measures to protect the clinical staff (<1,000 characters)

13. Study Design and Methodology

13.1 Study design* Retrospective and Cross-sectional study

If others, specify

13.1.1 Control* No control

13.1.2 Group assignment* N/A

13.2 Disease group (choose the most appropriate one)* Immune system

13.2.1 Key conditions under study (e.g. Asthma; DM; etc.)

Cancer, checkpoint inhibitors, immunotherapy

14. Methods of Data Analysis* (<30,000 characters)

Descriptive statistics provide an overview of the characteristics of the study population.
(a) irAEs
irAEs are defined as all adverse events reported after treatment with immune checkpoint inhibitors, which are not present prior to the initiation of treatment. It is assumed that before attributing the cause of AEs to immune checkpoint inhibitors, the diagnosis has been accompanied by an extensive work-up to rule out the more common cause of various diseases.
irAEs will be graded using the Common Terminology Criteria for Adverse Events v4.0. They will be grouped into grades 1/2 and 3/4 as there are inherent difficulties in retrospective grading from some clinical notes. AEs of interest will be categorized into organ-specific groups for analysis. 'General' irAEs includes nonspecific symptoms including fatigue/lethargy, asthenia, pyrexia, and decreased appetite.
Specific clinical/ laboratory findings will also be documented, i.e.
- Endocrine system (Cortisol, ACTH, Free T4, TSH, Antibodies, HbA1c, Calcium, PTH)
- Cardiovascular system (Cardiac enzyme elevation, EF reduction)
- Hepatic system (AST/ALT/bilirubin)
- Renal system (Urine study, e.g presence of blood, acetone, glucose, protein, nitrite/ biopsy/ SCr)

Time to first grade 3/4 irAE is defined as time from first treatment dose to time of first reported irAE. Patients who did not experience grade 3/4 irAEs will be censored at time of last follow-up.
Descriptive statistics will be used to report the incidence of the irAEs.
IBM SPSS Statistics will be used to obtain Kaplan–Meier curves to describe the time to onset of irAEs.

(b) Management of irAEs

All steroids prescribed, except those for hormone-replacement therapy in adrenal insufficiency and for non-irAEs, such as brain metastasis and radiation-induced pneumonitis, will be analyzed. They will be converted to the equivalent prednisolone dose for ease of comparison. Other management may include levothyroxine, calcium supplement and insulin. Treatment outcome will also be documented.

(c) Risk factors for the development of irAEs

Exacerbating factors are defined as contributors that may lead to immune dysfunction and a potentially increased risk of irAEs. These factors include a history of autoimmune disease, history of chronic infection (HIV, hepatitis or shingles), documented allergies (medication or environmental), previous irAEs, high body mass index, impaired kidney function, or specific medications such as antiarrhythmics, antihypertensives, antipsychotics, anticonvulsants, and statins.6 Furthermore, other comorbidities will be recorded and the Charlson Comorbidity Index (CCI) computed for association analysis.

Multivariable log-binomial models (generalized linear models with Poisson error and log link function) will be performed to evaluate the relationship between potential predictors and irAEs incidence rates, adjusting for potential confounders (eg. cancer diagnosis, age, and sex). Relative Risk (RR) estimates and 95% confidence intervals (CI) will be reported.

15. Handling and Storage of Personal Data

15.1 How will the personal data be handled and stored during and after the study?* (<2,000 characters)

All electronic copies of personal data will be encrypted and stored in the office computer at the study premises and only accessible by the investigator. Hard copies will be stored at a locked cabinet and the keys will be kept by the PI. The PI will be responsible for safekeeping of personal data during and after the study. The personal data will be kept for 3 years after the completion of study. All electronic copies of personal data will be deleted permanently. Hard copies will be disposed as confidential waste according to the hospital guidelines after completion of the aforesaid storage period. All the personal data will not be recovered by all means.

The investigator will permit research-related monitoring, audits, reviews, inspections and direct access to source data and documents by the NTEC-CUHK CREC and regulatory bodies.

15.2 Who will be responsible for safekeeping of the personal data during and after the study?* (<2,000 characters)

The PI will be responsible for safekeeping of personal data during and after the study.

15.3 Who will have access to the personal data during and after the study?* (<2,000 characters)

The PI will be responsible for safekeeping of personal data during and after the study. The personal data will be kept for 3 years after the completion of study.

The investigator will permit research-related monitoring, audits, reviews, inspections and direct access to source data and documents by the NTEC-CUHK CREC and regulatory bodies.

15.4 How long will the personal data be kept after the study?* (<2,000 characters)

The personal data will be kept for 3 years after the completion of study.

15.5 Plan arrangement for the personal data after completion of the aforesaid storage period?* (<2,000 characters)

All electronic copies of personal data will be deleted permanently. Hard copies will be disposed as confidential waste according to the hospital guidelines after completion of the aforesaid storage period. All the personal data will not be recovered by all means.

PART III: STUDY DETAILS (Sections 16 to 19 are applicable for Prospective Study only)

16. Study Article and Arrangements

IRB/ REC Reference No.
(For Office Use)

16.1 Study design

16.1.1 How does the procedure/treatment differ from current treatment practice?*

if others, specify

16.1.2 Methods of assignment*

16.1.3 Degree of masking*

16.1.4 Phase of study*

16.2 Study article

16.2.1 Is there any study article?* ☐Yes ☐No

16.2.2 Study article details

Article	Type	Name	Duration of exposure	Dosage	Route of administration	Was it produced under GMP?	Others, specify

Control

No.	Type	Name	Duration of exposure	Dosage	Route of administration	Was it produced under GMP?	Others, specify

16.2.3 Study article licence registration

			Same indication registration			Other indication registration		
Article	Type	Name	HongKong	In Oversea	Overseas Country	Hong Kong	In Oversea	Overseas Country

** Overseas Country should be blank when the answer of In Oversea is "No"*

Control

			Same indication registration			Other indication registration		
No.	Type	Name	Hong Kong	In Oversea	Overseas Country	Hong Kong	In Oversea	Overseas Country

** Overseas Country should be blank when the answer of In Oversea is "No"*

16.2.4 Will a Certificate for Clinical Trial ("CTC") be obtained for the Study? ☐Yes ☐No

If no, justification (<500 characters)

16.3 Will the study register in public domain trial registry, e.g. ClinicalTrials.gov?

☐ Yes ☐ No/Not Applicable ☐ Unknown

If yes, Responsible party/parties for registration, e.g. sponsor, PI

If no, justification (<500 characters)

16.4 Is there a plan to apply for a clinical trial approval from China Food Drug Administration (CFDA) in the People's Republic of China?* ☐ Yes ☐ No ☐ N/A

16.5 Has a Phase I study been done?* ☐ Yes ☐ No

16.6 Number of extra visits / admission on top of usual care*

16.7 Will any of the study interventions / procedures be performed by persons other than the investigators?* ☐ Yes ☐ No

If yes, by whom

If yes, where

16.8 Will biological samples be stored for future use?* ☐ Yes ☐ No

16.8.1 What is the purpose to store the sample? (<1,000 characters)

16.8.2 State the nature of the sample (<500 characters)

16.8.3 Anticipate duration of storage

16.8.4 Will the samples be sent / stored outside Hong Kong? ☐ Yes ☐ No

16.8.5 Will consent[1] for future specified usage of the biological samples be obtained from the subjects? ☐ Yes ☐ No

16.8.5.1 When will the consent be obtained?

Justification for consent to be obtained prior to the specific future usage of the sample (<500 characters)

16.8.5.2 Where will the consent be stated?

16.8.5.3 Justification for no consent to be obtained (<1,000 characters)

17. Potential Risk Arising from Study

17.1	Induce discomfort or distress*	☐ Yes	☐ No
17.2	More invasive than the usual management *	☐ Yes	☐ No
17.3	Increase physical or psychological risk*	☐ Yes	☐ No
17.4	Involve a potential toxin, mutagen or teratogen*	☐ Yes	☐ No
17.5	Involve radiation or radioactive substance*	☐ Yes	☐ No
17.6	Incur other hazards*	☐ Yes	☐ No

17.7 If yes to any of the above, provide details (<1,000 characters)

17.8 Significant difference(s) from usual management* (<1,000 characters)

18. Anticipate Benefits to Study Subjects* (<1,000 characters)

19. Research Subject Protection

19.1	Will the subjects be provided with a card indicating their participation in study and means of urgent contact?*	☐ Yes	☐ No

If no, state how the research subjects can be identified in case of emergency (<1,000 characters)

19.2	Does the protocol state compliance with the ICH-GCP?*	☐ Yes	☐ No

If no, justification (<1,000 characters)

20. Information and Consent

(The informed consent should state Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee as one of the authorized parties to access the subjects' records related to the study for ethics review purpose.)

20.1 Methodology of obtaining consent* No (subject to wavier by REC)

20.1.1 State reasons if not use written consent (<1,000 characters)

20.1.2 Justification for applying to waive the consent requirement (<1,000 characters)

This is a retrospective study. No patient will be recruited. Data collected restrospective from CMS and CDARS will all be de identified.

20.2 Who will carry out the informed consent process with the subject? (can select more than one option)

☐ Principal investigators ☐ Other investigators

☐ Research assistant ☐ Others, specify:

20.3 Will an interpreter be available when required? ☐ Yes ☐ No

If no, justification

20.4 In obtaining informed consent from subjects, what is the minimal time given to a subject to consider after explanation has been given?

20.5 If subjects are incompetent in giving consent, what would be the arrangement? (<500 characters)

21. Data and Safety Monitoring

21.1 Will an independent committee review data and safety of study?* ☐ Yes ☑ No

If no, justification (<500 characters)

This is a retrspective study.

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[1]Obtaining consent from subjects for future use of the biological samples is compulsory.

PART IV: BUDGET AND USE OF RESOURCES

IRB/ REC Reference No. (For Office Use)

22. Source of Funding

22.1 Commercial* ☐ Yes ☑ No

22.1.1 Sponsored trial ☐ Yes ☑ No

Specify the source of funding:

No.	Name of Sponsor / donating body

22.2 Non-commercial* ☐ Yes ☑ No

22.2.1 Sponsored trial ☐ Yes ☑ No

Specify the source of funding:

No.	Type of funding	Name of Sponsor / donating body

22.3 Other funding sources (e.g. personal funded study), provide name(s) and background information (<1,000 characters or attach document)

Funding for manpower (research staff) will be from university staff.

23. Resources Implication and Conflict of interest

23.1 Will this study consume HA resources?* ☐ Yes ☑ No

23.1.1 If yes, provide details (<1,000 characters)

23.2 Will the study involve HA patients?* ☐ Yes ☑ No

If yes, estimate the number of patients planned to involved in the study? patients

If no, specify the role of HA in the study (<500 characters)

This is a retrospective study. No active patient recruitment will be conducted.

23.3 If HA resources is required, how will this affect the HA services of other patients with competing needs? (<500 characters)

23.4 Will the study site (hospital) receive reimbursement for the study? ☐ Yes ☑ No

If yes, state the format of reimbursement (<1,000 characters)

If no, state the reason(s) (<1,000 characters)

This is a non-funded study. We do not anticipate major resources reqired from HA.

23.5 Is there a non-monetary sponsorship?* ☐ Yes ☑ No

23.5.1 Type of sponsorship

☐ Drug ☐ Consumable ☐ Equipment ☐ Research assistant

☐ Others, specify

24. Financial Costs and Payment to Subjects

24.1 Will the subjects be charged for the study article/service?* ☐ Yes ☑ No ☐ N/A

If yes, state the financial arrangement (<500 characters)

24.2 Will the study article continue to be available to subjects after the study (if subjects benefited from it) until it is commercially available? ☐ Yes ☑ No

If yes, state the planned financial arrangement (<500 characters)

If no, will there be any impact on disease management of the study subject? ☐ Yes ☑ No

Provide arrangement (<500 characters)

24.3 Does the consent form explain the above arrangement? ☐ Yes ☑ No

24.4 Will subjects receive any material rewards (including payments)?* ☐ Yes ☑ No

24.4.1 Reward nature* ☐ Cash ☐ Others (<200 characters)

24.4.2 Amount of payment (in HK$)

24.4.3 Mode of payment ☐ One-off

☐ By schedule (<500 characters)

25. Research Organization and Indemnity

25.1 The organization / individual responsible for the study* (<500 characters)

The principal investagator is responsible for this study.

25.2 Collaborating parties that jointly take on the responsibilities for the study

Collaborating Party	Name of organization / individual

25.3 Indemnity

25.3.1 For industry sponsored trial, will the sponsor indemnify study related claims? ☐ Yes ☐ No

If no, specify the reason and who will be responsible for the indemnity (<500 characters)

Is the indemnity agreement based on the HA approved form? ☐ Yes ☐ No

25.4 Will an insurance policy be arranged for the study?* ☐ Yes ☑ No

25.4.1 Will the policy be reviewed by HA Legal Service Department? ☐ Yes ☐ No

25.5 Will a Clinical Trial Agreement or other legal agreement/contract(s) be signed with the sponsor/supporting party?*

☐ Yes, with HA ☐ Yes, with University ☑ No

PART V: DECLARATION BY INVESTIGATOR(S)

IRB/ REC Reference No.
(For Office Use)

Note: Certain trial information will be passed to a Central Database for risk management purpose and to assist HA's finance controller in sourcing insurance coverage for clinical trial activities

26.1:Scientific Title of Study

Local Experience with Adverse Effects of PD-1/PD-L1 Inhibitors in Cancer Patients

1. I / We declare that the information supplied is to the best of our knowledge and accurate.
2. I / We declare that the protocol comply with Declaration of Helsinki.
3. I / We agree to uphold the protection of research subjects' right and safety through adherence to local laws, Declaration of Helsinki, institutional policies[2] and whenever applicable, the ICH-GCP.
4. I / We understand that approval by the Cluster REC is subject to regular renewal according to local policy.
5. I / We agree to report to the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee
   - any planned change(s) to the study, and further agree not to implement any change(s) without receiving prior approval, except to eliminate immediate hazard to research subjects or when the change(s) involve only logistical or administrative issues.
   - any fatal events in applying site within the specific time according to the Standard Operating Procedures of the Cluster REC while pending investigation, and any serious adverse events in applying site (with an extended report) preferably within seven days but not later than 15 days (from the day it was made known to me / us).
   - any new information on the project that adversely influences the risk/benefit ratio.
   - progress report(s) (as requested by the Cluster REC) and a final report (after completion of study).
6. I / We agree to keep all study documents for a period of at least three years after study closure.
7. I / We agree to maintain adequate records and to make them available for audit / inspection.
8. I / We agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

26.2:Signed by Principal Investigator and Other Investigators

Role	Title	First Name	Surname	Position	Responsibility for clinical oversight	Signature	Date (DD/MM/YYYY)
Principal investigator	Dr	Keary	Zhou	Honorary Pharmacist	Y		
Other investigators	Prof	Yin Ting	Cheung	Assistant Professor	N		
Other investigators	Prof	Herbert	Loong	Assistant Professor	Y		
Other investigators	Prof	Yat Ming	Lau	Associate Consultant	Y		
Other investigators	Ms	Lok Sum	Yang	Research Assistant	N		

26.3:For Student Project

Role	Name	Position	Responsibility For clinical oversight	Signature	Date (DD/MM/YYYY)

[2]HA Guide on Research Ethics (for Study Site & Research Ethics Committee) and Investigator's Code of Practice; HA Clinical Data Policy Manual; and other prevailing HA policies.

26.4:Endorsement by COS or Authorised Representative[3] for

Scientific Title of Study

Local Experience with Adverse Effects of PD-1/PD-L1 Inhibitors in Cancer Patients

1. I endorse the application and authorise the captioned study to be undertaken in my department upon approval by the Cluster REC/IRB.

2. I am of the opinion that the investigator(s) within my department/unit are appropriately qualified within the disease / therapeutic area involved, and are capable of undertaking this study in terms of their workload and time available, and that the study site(s) under my supervision have access to adequate facilities and support for the research to be conducted in a safe manner.

Signature	Name	Email	Post	Department	Hospital	Date
	Dr. Benjamin Lee	leesc@ha.org.hk	Phamacy Manager	Pharmacy	PWH	

[3]Should be signed by another suitable senior staff (e.g. HCE or his/her designate) if the COS is the Applicant for the study

26.5:Endorsement by Head of Department[4] Contributing to the Research

Scientific Title of Study

Local Experience with Adverse Effects of PD-1/PD-L1 Inhibitors in Cancer Patients

1. I endorse the application and authorise the captioned study to be undertaken in my department upon approval by the Cluster REC/IRB.
2. I am of the opinion that the investigator(s) within my department/unit are appropriately qualified within the disease / therapeutic area involved, and are capable of undertaking this study in terms of their workload and time available, and that the study site(s) under my supervision have access to adequate facilities and support for the research to be conducted in a safe manner.

Signature	Name	Email	Post	Dept/School/Faculty	Institution	Date
	Prof. Anthony Chan	anthonytcchan@cuhk.edu.hk	Li Shu Fan Medical Foundation Professor of Clinical Oncology, Chief of Service	Department of Clinical Oncology	PWH and CUHK	

[4]Should be signed by another suitable senior staff (e.g. Acting Head / Senior Member in the Department) if the Head of Department is the Applicant for the study

26.6:Endorsement by COS(s) or Head(s) of Other Department(s)[5] Contributing to the Research

Scientific Title of Study

Local Experience with Adverse Effects of PD-1/PD-L1 Inhibitors in Cancer Patients

I support the captioned study and verify that the workload to be incurred will not interfere with the department's service priority.

Signature	Name	Email	Position	Department	Hospital	Date
	Prof. Joan Zuo	joanzuo@cuhk.edu.hk	Professor and Director	School of Pharmacy, CUHK		

[5]If the study involved other departments, it is the Applicant's obligation to inform and obtain agreement with the COS(s) or Head(s) of the Department(s).

IRB/REC Name

Clinical Study Categorization Form

IRB/ REC Reference No.
(For Office Use)

Note to Investigator

Please complete the following Clinical Study Categorization Form and submit the Form together with each application for research ethics review. Upon receipt of an application, the Secretariat will verify the information on the form and arrange for appropriate initial review through Full Review, Expedited Review or Full Review by Phase 1 Panel.

Risk Group	No.	Risk Factors	Yes	No
Human Subjects	1	Recruitment of human subjects	N	Y
	13	----------END----------		

Application Log

Note to Investigator

This Application Log shows all the updated information, which are extracted from your Research Ethics Review Application Form and your subsequent submissions for REC/IRB's review and approval.

General Information

Work Order Number:	WON-20200428-15141
Submission Reference Number:	NTEC-2020-0319
IRB/ REC Reference Number:	
Initial Application Submission Date :	27/05/2020
Initial Application Review Type :	
Initial Application Approval Date :	
Approval Expiry Date:	
Proposed Study Start Date:	10/08/2020
Proposed Study End Date:	01/08/2021
Actual Study Start Date:	
Actual Study End Date:	
Initial Study Subject Recruitment Date:	
CTC Expiry Date:	
CTI Expiry Date:	
Latest Progress Report Submission Date:	
Final Report Submission Date:	
Terminatation Date:	
Termination Reason:	

Status History

Date	Task	User	From	To	Open Form
28/04/2020	Initial Application Approval	Keary R. ZHOU	New	Draft	Click Here
27/05/2020	Initial Application Approval	Yin Ting Cheung	Draft	Submitted	Click Here
17/07/2020	Initial Application Approval	Jenny NG	Submitted	Returned	Click Here

Approval History

Date	Task	Application Status	Review Due Date	Review Type	Decision	Decision Date	Decision Reason
17/07/2020	Initial Application Approval	Returned					

Document Log

General Information

Work Order Number: WON-20200428-15141

Submission Reference Number: NTEC-2020-0319

IRB/ REC Reference Number:

Uploaded Documents

Date	User	Document Type	Document Name	Suggested Print Name	Upload Times
26/05/2020	Yin Ting Cheung	Research Protocol	Research Protocol_14May_v4_kz.docx		1
12/05/2020	Lok Sum Yang	Conflict of Interest Declaration by all Investigators	Signed conflict of interest form by YLT and KZ.pdf		1
14/05/2020	Lok Sum Yang	Conflict of Interest Declaration by all Investigators	2020_0513_093408-0001.pdf	Signed COI form by YLS	1
26/05/2020	Yin Ting Cheung	Conflict of Interest Declaration by all Investigators	COIs.pdf		1
14/05/2020	Keary R. ZHOU	Curriculum Vitae (CV) from Principal Investigator	CV_K Zhou CUHK_short_2019.pdf		1
16/05/2020	Yin Ting Cheung	Curriculum Vitae (CV) from other investigates	CV_YTC_15Mar18.pdf		1
16/05/2020	Yin Ting Cheung	Curriculum Vitae (CV) from other investigates	CV_YMLau_Brief_May2020.pdf		1
26/05/2020	Yin Ting Cheung	Curriculum Vitae (CV) from other investigates	Lok Sum Yang RA CV.docx		1
26/05/2020	Yin Ting Cheung	Curriculum Vitae (CV) from other investigates	Herbert Loong CV.pdf		1
27/05/2020	Yin Ting Cheung	REC/IRB decision document	KWC REC Research Ethics Review Approval KWEX-20-022(144-10).pdf		1

Application Management Team Member Form

Note to Investigator

Please complete the following Application Management Team Member Form before opening a new Application Form. Upon submission of the Form, each of the team members (PI, Delegates, Application Follow-up Users) will receive a notifying email to start contribute to this Application.

Principal Investigator :

Email	Name	Existing Account	Please sign up
krzhou@cuhk.edu.hk	Keary R. ZHOU	Y	

Assign Principal Investigator who will be responsible for the Application.

Delegates :

Email	Name	Existing Account	Please sign up
loksumyang@cuhk.edu.hk	Lok Sum Yang	Y	
yinting.cheung@cuhk.edu.hk	Yin Ting Cheung	Y	

Please assign Delegates who will help manage and edit the application forms before research ethics approval.

Application Follow Up Users :

Email	Name	Existing Account	Please sign up
loksumyang@cuhk.edu.hk	Lok Sum Yang	Y	
yinting.cheung@cuhk.edu.hk	Yin Ting Cheung	Y	

Please assign Follow-up Users who will help manage and follow up the post-approval activities.

Application Review Arrangement

Submission Ref. No. :

IRB/REC Ref. No. :

Type of Review :

Review Due Date :

Review Meeting Date :

Review Panel :

Panel Member :

Name	Gender	Institution	Department	Post	Chairman	Role	Independent

Member Review Progress :

Name	Status	Last Update	Send to Reviewer

Meeting Attendance :

Name	Decision	Attend the meeting?	Conflict of Interest?	Relationship

Decision :

Decision Date :

Approval Expiry Date :

Viewed by Applicant

Comment History :

Date	Name	Comment	To
17/07/2020	Jenny NG	Please refer to email dated 17/07/20	Applicant

Please provide your comment if needed