Title Page

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Protocol Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Pembrolizumab (MK-3475) as Monotherapy in the Adjuvant Treatment of Renal Cell Carcinoma Post Nephrectomy (KEYNOTE-564)

Protocol Number: 564-04

Compound Number: MK-3475

Sponsor Name and Legal Registered Address:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or Merck)

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Approval Date: 13 October 2020

Sponsor Signatory

Typed Name: Date
Title:

Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
3475-564-04	13-OCT-2020	To update the censoring rules and remove the PK/ADA sample collection.
3475-564-03	11-MAY-2020	Changed the trigger for IA1 timing and total number of targeted events for final analysis of DFS by investigator review (IA2) and added secondary endpoint to compare event-free survival (EFS) as assessed by the blinded independent radiology review for participants treated with pembrolizumab versus those receiving placebo.
3475-564-02	04-SEP-2019	Because of the extension of study enrollment from 18 months to 25 months, there is not sufficient minimum follow-up time if IA1 is triggered based on the originally desired number of DFS events projected at 3 months after last participant randomized. Thus, IA2 has been retooled as IA1 where the trigger is 80% DFS events accrued. This will represent roughly a minimum follow-up of 12 months after enrollment is finished.

Document	Date of Issue	Overall Rationale
3475-564-01	02-NOV-2017	In the global implementation of protocol approved 24-FEB-2017 deficiencies were noted. The initial intent was to include metachronous and synchronous M1 NED postoperative nephrectomy ≤1 year. Since study inception, the inclusion of metachronous and synchronous M1 NED patients was intended; however, during protocol finalization metachronous was inadvertently removed. Additionally, minor adjustments are incorporated to enhance the clarity of the protocol intent, reflect real-time feedback from investigators, and address language inconsistencies
3475-564-00	24-FEB-2017	Original

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 04

Overall Rationale for the Amendment:

To update the censoring rules and to remove the sample collection for PK and ADA.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
2 Schedule of Activities (SoA)	Updated column headers for Posttreatment Visits.	Template update to provide clarity, minimize errors, and promote consistency.
2 Schedule of Activities (SoA)	Removed PK/ADA sample collection.	Correction; the collection of samples for PK/ADA was stopped under Amendment 02 of this protocol.
9.6 Pharmacokinetics 9.6.1.1 Blood Collection for PK 9.6.1.2 Blood Collection for Anti-Pembrolizumab Antibodies	Removed sections on PK and ADA sample collection and analysis.	Correction; the collection of samples for PK/ADA was stopped under Amendment 02 of this protocol.
8.1 Discontinuation of Study Treatment	Updated template language to include that a participant may withdraw from the study after discontinuation.	Clarification that continued follow-up after discontinuation is not required if a participant chooses to withdraw from the study.
9.1.8 Treatment Administration	Updated “administered” to “monitored.”	Clarification. The amended language more closely matches actual practice at sites and will reduce deviations.

Section # and Name	Description of Change	Brief Rationale
9.10.3.3 Follow-up Visits	Added updated template text to include participants who complete all cycles of treatment with those who should be followed up for efficacy.	To provide clarity, minimize errors, and promote consistency.
10.2 Responsibility for Analyses/In-house Blinding	Removed "from a subset" from the description of BICR review of imaging scans.	All images will be reviewed by BICR, not a subset.
10.6.1.1 Disease-Free Survival 10.6.1.5 Summary of Analysis Strategy	Updated censoring rules for the primary analysis and the sensitivity analysis. The new primary analysis is the old sensitivity analysis 1 and new sensitivity analysis is the old primary analysis. The old sensitivity analysis 2 is removed. Updated Tables 10 and 11.	Updated the censoring rules per the most recent oncology standard for an adjuvant study to follow ITT rule.
10.6.2 Statistical Methods for Safety Analyses	Changed "Dose Modification due to AE" to "Dose Interruption due to AE" in Table 12.	Correction: No dose modification was permitted; only interruption or discontinuation.
Overall	Minor edits to style and formatting to align with current Merck style.	To make the document amenable to structured content management.

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1. Synopsis

Protocol Title:

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Pembrolizumab (MK-3475) as Monotherapy in the Adjuvant Treatment of Renal Cell Carcinoma Post Nephrectomy (KEYNOTE-564)

Short Title:

Phase 3 Placebo-Controlled Trial of Adjuvant MK-3475 in RCC Post Nephrectomy

Objectives/Hypothesis and Endpoints:

The following objectives will be evaluated in the adjuvant treatment of participants who have undergone nephrectomy and have intermediate-high risk, high risk, or M1 NED renal cell carcinoma RCC with clear cell component.

Objective/Hypothesis	Endpoint(s)
Primary	
● Objective: To compare DFS as assessed by the investigator for participants treated with pembrolizumab versus those receiving placebo ● Hypothesis: Pembrolizumab is superior to placebo with respect to DFS	● DFS as assessed by the investigator: time from randomization to the first documented local recurrence, or occurrence of distant kidney cancer metastasis(es), or death due to any cause, whichever occurs first.
Key Secondary	
● Objective: To compare OS for participants treated with pembrolizumab versus those receiving placebo Hypothesis: Pembrolizumab is superior to placebo with respect to OS	● OS: time from randomization to death due to any cause

Other Secondary	
• To compare the safety and tolerability profiles for participants treated with pembrolizumab versus those receiving placebo	• AEs, SAEs, AEs leading to discontinuation, deaths, laboratory values, and vital signs
• To compare measures of DRSS, as assessed by the investigator, for participants treated with pembrolizumab versus those receiving placebo	• DRSS1 as assessed by the investigator: time from randomization to the first documented local recurrence of RCC • DRSS2 as assessed by the investigator: time from randomization to the first documented local recurrence with visceral lesion or occurrence of distant kidney cancer metastasis(es) with visceral lesion, whichever occurs first.
• To compare EFS as assessed by the blinded independent radiology review for participants treated with pembrolizumab versus those receiving placebo	• EFS is to be assessed by BICR. EFS is defined as time from randomization to the first documented local recurrence or occurrence of distant kidney cancer metastasis(es) among participants, which by BICR were considered M0/M1 NED; or disease progression among participants, which by BICR were considered to have M1, or death due to any cause, whichever occurs first. See Section 9.2.1 for the definition of disease progression.
• To compare DFS and OS according to participants' PD-L1 expression status (Positive, Negative) for participants treated with pembrolizumab versus those receiving placebo	• DFS as assessed by the investigator: time from randomization to the first documented local recurrence, or occurrence of distant kidney cancer metastasis(es), or death due to any cause, whichever occurs first. • OS: time from randomization to death due to any cause.
• To evaluate PROs with the EORTC-QLQ-C30 and the FKSI-DRS	• EORTC-QLQ-C30 • FKSI-DRS

Overall Design:

Trial Phase	III
Clinical Indication	Treatment of participants with RCC in the adjuvant setting
Population	Post nephrectomy; intermediate-high risk, high risk, and M1 NED RCC
Trial Type	Interventional
Type of design	Randomized
Type of control	Placebo
Trial Blinding	Double-blind
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 50 months to achieve the primary objective and 72 months to achieve the key secondary objective from the time the first participant signs the informed consent until the last participant's last study-related phone call or visit.

Number of Participants:

Approximately 950 participants will be enrolled.

Treatment Groups and Duration:

Treatment Groups	Placebo or pembrolizumab 200 mg, administered by intravenous infusion every 3 weeks. Treatment will be up to (approximately) 1 year.
Duration of Participation	Each participant will participate in the trial from the time the participant signs the informed consent form through the final protocol-specified contact. After a screening phase of up to 42 days, each participant will be assigned to receive trial treatment until disease recurrence, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, noncompliance with trial treatment or procedural requirements, administrative reasons requiring cessation of treatment, or until the participant has received 17 cycles of study treatment (approximately 1 year). After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 9.3. Participants who discontinue for reasons other than disease recurrence will have posttreatment imaging follow-up for disease status until confirmation of disease recurrence, initiating a new anticancer treatment, withdrawing consent, or becoming lost to follow-up. All participants will be followed by telephone for OS until death, withdrawal of consent, or the end of the study.

Abbreviations are not spelled out at first use. A list of abbreviations used in this document can be found in Appendix 1. Study Governance Considerations are outlined in Appendix 3.

2. Schedule of Activities (SoA)

Trial Period:	**Screening**	**Treatment**									**End of Treatment**	**Posttreatment Period**			**Notes**
Treatment Cycle/Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8[a]**	**9[a]**	**Discon**	**Safety**	**Efficacy Follow-up**	**Survival Follow-up[b]**	
Scheduling Window (Days)	**-42 to -1[c]**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**Repeat ±3**	**Repeat ±3**	**At time of discon**	**30 days post last dose (+7 days)**	**Every 12, 16, or 24 weeks (±7 days)**	**Every 12 weeks (±7 days)**	**Cycles 8 and 9 will be repeated up to 4 times, for a total of 17 doses of study treatment.**
Administrative Procedures															
Informed Consent	X														Consent must be obtained prior to performing any protocol-specified procedures. Informed consent may be collected outside of the 42-day Screening window (prior to randomization).
Informed Consent for Future Biomedical Research (optional)	X														.
Participant Identification Card	X	X													Dispense at Screening. Add randomization number at Cycle 1.
Inclusion/Exclusion Criteria	X														
Demographics and Medical History	X														Record RCC history separately.
Prior Medication Review	X														Record all medications taken within 30 days prior to first dose.

Trial Period:	**Screening**	**Treatment**									**End of Treatment**	**Posttreatment Period**			**Notes**
Treatment Cycle/Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8[a]**	**9[a]**	**Discon**	**Safety**	**Efficacy Follow-up**	**Survival Follow-up[b]**	
Scheduling Window (Days)	**-42 to -1[c]**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**Repeat ±3**	**Repeat ±3**	**At time of discon**	**30 days post last dose (+7 days)**	**Every 12, 16, or 24 weeks (±7 days)**	**Every 12 weeks (±7 days)**	**Cycles 8 and 9 will be repeated up to 4 times, for a total of 17 doses of study treatment.**
Treatment Randomization		X													Randomization should occur ≤3 days prior to treatment, but may occur the day of Cycle 1 treatment.
MK-3475 or Placebo Administration		X	X	X	X	X	X	X	X	X					Cycle 1 treatment should occur within 3 days after randomization. Treatment should begin after all predose trial procedures and assessments have been completed.
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X			Record new medications started during the trial and up to 30 days after last dose. Record all medications related to reportable SAEs and ECIs.
Poststudy Anticancer Therapy Status												X	X	X	
Survival Status		<----------												X	Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.

Trial Period:	**Screening**	**Treatment**									**End of Treatment**	**Posttreatment Period**			**Notes**
Treatment Cycle/Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8[a]**	**9[a]**	**Discon**	**Safety**	**Efficacy Follow-up**	**Survival Follow-up[b]**	
Scheduling Window (Days)	**-42 to -1[c]**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**Repeat ±3**	**Repeat ±3**	**At time of discon**	**30 days post last dose (+7 days)**	**Every 12, 16, or 24 weeks (±7 days)**	**Every 12 weeks (±7 days)**	**Cycles 8 and 9 will be repeated up to 4 times, for a total of 17 doses of study treatment.**
Efficacy Procedures															
Tumor Imaging – chest, abdomen, pelvis (CAP)	X	X									X[d]		X		Perform at Screening (within 28 days prior to randomization); during treatment (Q12W from randomization) and during Follow-up (Q12W in year 1, Q16W in years 2 to 4, Q24W in years 5 and beyond). Follow-up imaging should follow calendar days from the date of randomization.
Tumor Imaging – bone scan	X														Perform at Screening (within 28 days prior to randomization); as clinically indicated thereafter.
Tumor Imaging – brain scan	X														Perform at Screening (within 28 days prior to randomization); as clinically indicated thereafter.

Trial Period:	**Screening**	**Treatment**									**End of Treatment**	**Posttreatment Period**			**Notes**
Treatment Cycle/Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8[a]**	**9[a]**	**Discon**	**Safety**	**Efficacy Follow-up**	**Survival Follow-up[b]**	
Scheduling Window (Days)	**-42 to -1[c]**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**Repeat ±3**	**Repeat ±3**	**At time of discon**	**30 days post last dose (+7 days)**	**Every 12, 16, or 24 weeks (±7 days)**	**Every 12 weeks (±7 days)**	**Cycles 8 and 9 will be repeated up to 4 times, for a total of 17 doses of study treatment.**
EQ-5D-5L, EORTC-QLQ-C30, FKSI-DRS		X				X				X	X	X	X[e]		Administering PROs prior to study treatment administration, AE evaluation, and disease status notification is strongly recommended. PROs should be administered at Cycles 1, 5, 9, 13, and 17, treatment discontinuation, 30 day Follow-up, and annually during posttreatment Follow-up until disease recurrence or initiating a new anticancer treatment.
Safety Procedures															
Full Physical Examination	X										X				
Directed Physical Examination		X	X	X	X	X	X	X	X	X					Perform predose.
Vital Signs	X	X	X	X	X	X	X	X	X	X	X				Height at Visit 1 only.
12-lead ECG (locally performed)	X														Perform at Screening and as clinically indicated thereafter.

Trial Period:	**Screening**	**Treatment**									**End of Treatment**	**Posttreatment Period**			**Notes**
Treatment Cycle/Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8[a]**	**9[a]**	**Discon**	**Safety**	**Efficacy Follow-up**	**Survival Follow-up[b]**	
Scheduling Window (Days)	**-42 to -1[c]**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**Repeat ±3**	**Repeat ±3**	**At time of discon**	**30 days post last dose (+7 days)**	**Every 12, 16, or 24 weeks (±7 days)**	**Every 12 weeks (±7 days)**	**Cycles 8 and 9 will be repeated up to 4 times, for a total of 17 doses of study treatment.**
Pregnancy Test – Urine or Serum hCG; WOCBP only)	X														Perform a urine test within 72 hours prior to randomization; if positive or not confirmed as negative, perform a serum pregnancy test. Monthly pregnancy testing should be conducted per local regulations where applicable.
PT/INR and aPTT	X														Screening assessment should be done within 10 days prior to randomization. If abnormal at Screening, then perform at each visit or as clinically indicated thereafter.

Trial Period:	**Screening**	**Treatment**									**End of Treatment**	**Posttreatment Period**			**Notes**
Treatment Cycle/Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8[a]**	**9[a]**	**Discon**	**Safety**	**Efficacy Follow-up**	**Survival Follow-up[b]**	
Scheduling Window (Days)	**-42 to -1[c]**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**Repeat ±3**	**Repeat ±3**	**At time of discon**	**30 days post last dose (+7 days)**	**Every 12, 16, or 24 weeks (±7 days)**	**Every 12 weeks (±7 days)**	**Cycles 8 and 9 will be repeated up to 4 times, for a total of 17 doses of study treatment.**
Chemistry	X		X	X	X	X	X	X	X	X	X	X			Screening assessment should be done within 10 days prior to randomization. After Cycle 1, predose laboratory safety tests can be conducted up to 72 hours prior to dosing.
Hematology	X		X	X	X	X	X	X	X	X	X	X			Screening assessment should be done within 10 days prior to randomization. After Cycle 1, predose laboratory safety tests can be conducted up to 72 hours prior to dosing.
Urinalysis	X		X		X		X		X		X	X			Screening assessment should be done within 10 days prior to randomization. After Cycle 1, predose laboratory safety tests can be conducted up to 72 hours prior to dosing.

Trial Period:	**Screening**	**Treatment**									**End of Treatment**	**Posttreatment Period**			**Notes**
Treatment Cycle/Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8[a]**	**9[a]**	**Discon**	**Safety**	**Efficacy Follow-up**	**Survival Follow-up[b]**	
Scheduling Window (Days)	**-42 to -1[c]**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**Repeat ±3**	**Repeat ±3**	**At time of discon**	**30 days post last dose (+7 days)**	**Every 12, 16, or 24 weeks (±7 days)**	**Every 12 weeks (±7 days)**	**Cycles 8 and 9 will be repeated up to 4 times, for a total of 17 doses of study treatment.**
T3, FT4, and TSH	X		X		X		X		X		X	X			Screening assessment should be done within 10 days prior to randomization. After Cycle 1, predose laboratory safety tests can be conducted up to 72 hours prior to dosing.

Trial Period:	**Screening**	**Treatment**									**End of Treatment**	**Posttreatment Period**			**Notes**
Treatment Cycle/Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8[a]**	**9[a]**	**Discon**	**Safety**	**Efficacy Follow-up**	**Survival Follow-up[b]**	
Scheduling Window (Days)	**-42 to -1[c]**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**Repeat ±3**	**Repeat ±3**	**At time of discon**	**30 days post last dose (+7 days)**	**Every 12, 16, or 24 weeks (±7 days)**	**Every 12 weeks (±7 days)**	**Cycles 8 and 9 will be repeated up to 4 times, for a total of 17 doses of study treatment.**
AE Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X		Record all AEs and ECIs occurring within 30 days after the last dose of study treatment and SAEs for 90 days after the end of treatment or 30 days after end of treatment if the participant initiates new anticancer treatment (whichever is earlier). Participants with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anticancer treatment, whichever occurs first. Report treatment-related SAEs regardless of when they occur.
ECOG PS	X	X	X	X	X	X	X	X	X	X	X	X	X[f]		

Trial Period:	**Screening**	**Treatment**									**End of Treatment**	**Posttreatment Period**			**Notes**
Treatment Cycle/Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8[a]**	**9[a]**	**Discon**	**Safety**	**Efficacy Follow-up**	**Survival Follow-up[b]**	
Scheduling Window (Days)	**-42 to -1[c]**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**Repeat ±3**	**Repeat ±3**	**At time of discon**	**30 days post last dose (+7 days)**	**Every 12, 16, or 24 weeks (±7 days)**	**Every 12 weeks (±7 days)**	**Cycles 8 and 9 will be repeated up to 4 times, for a total of 17 doses of study treatment.**
Future Biomedical Research/Biomarkers															
Tissue Collection for Biomarker Studies	X[g]														Submit tumor tissue from nephrectomy and/or for M1 NED participants, tumor tissue from resected metastatic lesion(s), as indicated in Section 9.7.1. Adequacy of the sample for biomarker analysis will be evaluated by a central laboratory.
Blood for Genetic Analysis[h]		X													Collect predose.
Blood for RNA Analyses		X	X			X					X		X		Collect predose at Cycles 1, 2, and 5, at treatment discontinuation (due to any reason), and during Follow-up at disease recurrence.
Blood for TCR		X	X			X					X		X		Collect predose at Cycles 1, 2, and 5, at treatment discontinuation (due to any reason), and during Follow-up at disease recurrence.

Trial Period:	**Screening**	**Treatment**									**End of Treatment**	**Posttreatment Period**			**Notes**
Treatment Cycle/Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8[a]**	**9[a]**	**Discon**	**Safety**	**Efficacy Follow-up**	**Survival Follow-up[b]**	
Scheduling Window (Days)	**-42 to -1[c]**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**Repeat ±3**	**Repeat ±3**	**At time of discon**	**30 days post last dose (+7 days)**	**Every 12, 16, or 24 weeks (±7 days)**	**Every 12 weeks (±7 days)**	**Cycles 8 and 9 will be repeated up to 4 times, for a total of 17 doses of study treatment.**
Blood for Plasma Biomarker Analyses		X	X			X					X		X		Collect predose at Cycles 1, 2, and 5, at treatment discontinuation (due to any reason), and during Follow-up at disease recurrence.
Blood for Serum Biomarker Analyses		X	X			X					X		X		Collect predose at Cycles 1, 2, and 5, at treatment discontinuation (due to any reason), and during Follow-up at disease recurrence.

a. The schedule for Cycle 8 will be repeated for Cycles 10, 12, 14, and 16; the schedule for Cycle 9 will be repeated for Cycles 11, 13, 15, and 17, unless otherwise noted.
b. Participant Survival Follow-up status will be assessed approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first. For participants who discontinue treatment intervention and who will not enter the Efficacy Follow-up phase, the first Survival Follow-up contact will be scheduled 12 weeks after the discontinuation visit and/or Safety Follow-up Visit (whichever is last). For participants who completed assessments in the Efficacy Follow-up phase, the first Survival Follow-up contact will be scheduled 12 weeks after the last Efficacy Follow-up Visit has been performed.
c. Refer to Section 9.10 for Screening procedures with a window that differs from the 42-day Screening window.
d. Participants who discontinue from study treatment without documented disease recurrence should have imaging performed at the time of discontinuation if the last assessment was more than 28 days prior AND should continue with posttreatment Follow-up procedures until disease recurrence, pregnancy, the start of new anticancer treatment, death, withdrawal of consent, or study conclusion (whichever occurs first).
e. Follow-up PROs will be measured from end of treatment date, have a +14 day window, and will be administered at Week 52 , Week 104, Week 156, Week 208, Week 260, Week 312, Week 364, Week 416, Week 468, and Week 520 or until disease recurrence or start of a new anticancer treatment.
f. ECOG PS to be collected only if participants come in for a clinic visit during Follow-up.
g. Tumor archival tissue may be submitted outside the 42-day screening window (prior to randomization), as long as informed consent was signed prior to submission.
h. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. Sample will not be collected at sites where prohibited by local law, local regulation, or IRB/IEC. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the participant signs the future biomedical research consent. If the planned genetic analysis is not approved, but future biomedical research is approved and consent is given, this sample will be collected for the purpose of future biomedical research.

3. Introduction

3.1 Study Rationale

This is a clinical trial designed to evaluate the efficacy and safety of pembrolizumab in the adjuvant setting for participants with RCC with clear cell component that has an intermediate-high risk or high risk of disease recurrence or M1 no evidence of disease (M1 NED).

RCC is the seventh most common cancer in men and the ninth most common cancer in women. Worldwide, there are an estimated 209,000 newly diagnosed cases of RCC and an estimated 102,000 deaths per year [Escudier, B., et al 2014]. In the United States, the expected number of new cases and deaths from kidney and renal pelvis cancer in 2016 is 62,700 and 14,240, respectively [Siegel, R. L., et al 2016]. Approximately 90% of renal tumors are RCC and approximately 80% of these are of clear cell histology. Other less common cell types include papillary, chromophobe, translocation, and collecting duct tumors [National Comprehensive Cancer Network 2015]. Smoking and obesity are established risk factors for RCC. Several hereditary conditions, such as von Hippel-Lindau disease, predispose patients to having an increased risk of developing RCC.

The incidence of RCC is increasing continually in recent decades, and approximately two-thirds of the cases are diagnosed without evidence of metastatic disease [Siegel, R. L., et al 2016].

These patients are usually managed with a radical surgical approach, but a percentage of these patients will have recurrence and eventually die because of the disease. The estimated 5-year survival of patients with localized RCC patients is approximately 90%, decreasing to 65% in locally advanced RCC, and only 12% in metastatic RCC [National Cancer Institute 2016]. Therefore, novel agents with durable clinical benefit and a potential curative effect are still needed.

The recently approved immune checkpoint inhibitor nivolumab has demonstrated an overall survival (OS) benefit (compared with the standard of care, everolimus), as well as a manageable safety profile, in the treatment of patients with advanced RCC whose disease has progressed following anti-angiogenic therapy [U.S. Prescribing Information 2016]. Multiple studies are currently ongoing or planned to evaluate immune checkpoint inhibitors as monotherapy or in combination with selective vascular endothelial growth factor receptor tyrosine kinase inhibitors or other anti-angiogenic agents (eg, bevacizumab, ipilimumab) in the first-line treatment of advanced or metastatic RCC. Preliminary data from Phase 1b, 2, and 3 studies (nivolumab/ipilimumab [Checkmate-016 Phase 2; Checkmate-214 Phase 3]; bevacizumab/atezolizumab [NCT02420821 Phase 3]; pembrolizumab/axitinib [KN035 Phase 1b/2]) suggest a promising response pattern, with higher overall response rate and progression-free survival rates and tolerable toxicity, as compared with the current standard of care, sunitinib or pazopanib.

The safety and antitumor activity of checkpoint inhibitors are also being evaluated in the (neo)adjuvant setting for RCC in Phase 1/2 exploratory trials [Pinto, A. 2014], and

preliminary data suggest a possible benefit of treatment on both disease-free survival (DFS) and OS, with good tolerability in participants who have no current disease burden following surgery, but a high risk of recurrence [Ravaud, A., et al 2016].

3.2 Background

Pembrolizumab is a potent humanized immunoglobulin (Ig) G4 monoclonal antibody with high specificity of binding to the programmed cell death protein 1 (PD-1) receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. KEYTRUDA® (pembrolizumab) is indicated for the treatment across a number of cancer indications.

Refer to the Investigator's Brochure/approved labeling for detailed background information, including specific indications, for pembrolizumab (MK-3475).

3.2.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ T-regs correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and RCC. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to CD28 and CTLA-4 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig variable-type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta, protein kinase C-theta, and zeta-chain-associated protein kinase, which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et

al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 downmodulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010]. As a consequence, the PD-1/ PD-L1 pathway is an attractive target for therapeutic intervention in participants who have undergone nephrectomy and have intermediate-high risk, high risk, or M1 NED RCC with clear cell component.

3.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical trials will directly benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Pembrolizumab has been administered to a large number of cancer patients, with a well-characterized safety profile, and has received regulatory approval in the US and several other countries for advanced melanoma, NSCLC, and head and neck squamous cell carcinoma. Overall, pembrolizumab is well tolerated and has demonstrated preliminary evidence of anticancer activity in multiple tumor types.

At present, there are no curative systemic treatments for about 35% of primary treated patients with intermediate-high risk, high risk, and M1 NED RCC.

Additional details regarding specific benefits and risks for participants participating in this clinical trial may be found in the accompanying Investigator's Brochure and Informed Consent documents.

4. Objectives/Hypotheses and Endpoints

The following objectives will be evaluated in the adjuvant treatment of participants who have undergone nephrectomy and have intermediate-high risk, high risk, or M1 NED RCC with clear cell component.

Objective/Hypothesis	Endpoint(s)
Primary	
● Objective: To compare DFS as assessed by the investigator for participants treated with pembrolizumab versus those receiving placebo Hypothesis: Pembrolizumab is superior to placebo with respect to DFS	● DFS as assessed by the investigator: time from randomization to the first documented local recurrence, or occurrence of distant kidney cancer metastasis(es), or death due to any cause, whichever occurs first.

Objective/Hypothesis	Endpoint(s)
Secondary	
Key Secondary	
● Objective: To compare OS for participants treated with pembrolizumab versus those receiving placebo Hypothesis: Pembrolizumab is superior to placebo with respect to OS	● OS: time from randomization to death due to any cause.
Other Secondary	
● To compare the safety and tolerability profiles for participants treated with pembrolizumab versus those receiving placebo	● AEs, SAEs, AEs leading to discontinuation, deaths, laboratory values, and vital signs
● To compare measures of DRSS) as assessed by the investigator, in participants treated with pembrolizumab versus those receiving placebo	● DRSS1 as assessed by the investigator: time from randomization to the first documented local recurrence of RCC. ● DRSS2 as assessed by the investigator: time from randomization to the first documented local recurrence with visceral lesion or occurrence of distant kidney cancer metastasis(es) with visceral lesion, whichever occurs first.
● To compare EFS as assessed by the blinded independent radiology review for participants treated with pembrolizumab versus those receiving placebo	● EFS is to be assessed by BICR. EFS is defined as time from randomization to the first documented local recurrence or occurrence of distant kidney cancer metastasis(es) among participants, which by BICR were considered M0/M1 NED; or disease progression among participants, which by BICR were considered to have M1, or death due to any cause, whichever occurs first. See Section 9.2.1 for the definition of disease progression.

Objective/Hypothesis	Endpoint(s)
• To compare DFS and OS according to participants' PD-L1 expression status (Positive, Negative) for participants treated with pembrolizumab versus those receiving placebo	• DFS as assessed by the investigator: time from randomization to the first documented local recurrence, or occurrence of distant kidney cancer metastasis(es), or death due to any cause, whichever occurs first. • OS: time from randomization to death due to any cause.
• To evaluate PROs with the EORTC-QLQ-C30 and the FKSI-DRS	• EORTC-QLQ-C30 • FKSI-DRS
Tertiary/Exploratory	
• To evaluate PK parameters and the presence of ADA	• PK parameters (clearance and volume of distribution) • ADA to pembrolizumab
• To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab	• Biomarker analyses may include germline genetic variation, genetic (DNA) mutations from tumor, tumor and blood RNA variation, proteomics and IHC, and other blood-derived biomarkers
• To evaluate PROs with the EORTC-QLQ-C30 and FKSI-DRS and to characterize utilities with the EQ-5D-5L	• All scales, subscales, and single item measures for the EORTC-QLQ-C30, FKSI-DRS, and EQ-5D-5L

5. Study Design

5.1 Overall Design

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter, global trial to evaluate the efficacy and safety of pembrolizumab in the adjuvant treatment of RCC post nephrectomy. This trial will enroll participants with RCC with clear cell component that is intermediate-high risk, high risk, or M1 NED (M1 NED refers to participants who present not only with the primary kidney tumor, but also solid, isolated, soft tissue metastases that can be completely resected ≤1 year from the time of nephrectomy). See Section 6.1 for a definition of the risk categories.

The trial will be conducted in conformance with Good Clinical Practice.

The primary objective of the study is to evaluate the efficacy (DFS, as assessed by the investigator) of pembrolizumab compared with that of placebo in participants with RCC.

Screening Period

Individual screening procedures must be performed within the time frames reported in the schedule of activities (SoA - Section 2) and procedural details in Section 9. Participants must have undergone a nephrectomy and/or metastasectomy ≥28 days prior to signing informed consent and ≤12 weeks from randomization. Participants must be tumor-free as assessed by the investigator via CT or MRI of the CAP, bone scan, and brain scan. Tumor tissue from the participants' nephrectomy (and metastasectomy for M1 NED) must be submitted to a central laboratory for biomarker analysis.

Treatment Period and End of Treatment

Approximately 950 eligible participants will be randomized 1:1 to receive either placebo or pembrolizumab 200 mg, administered by IV infusion Q3W.

During the treatment period, participants will have routine clinical visits for administration of study treatment and monitoring of safety, wellbeing, and changes in disease status. Scheduled on-treatment imaging assessments will be performed Q12W from randomization and should not be adjusted for delays in treatment or cycle starts. Participants will also complete QoL questionnaires to assess the impact of treatment on HRQoL.

Key safety assessments include the monitoring of AEs and ECI, physical examinations, vital signs, ECGs, as clinically indicated, hematology and chemistry laboratories (including thyroid function test), and urinalysis.

Participants may receive study treatment for up to 17 cycles (approximately 1 year) or until confirmation of disease recurrence or meeting the criteria for discontinuation of study treatment as outlined in Section 8.

Participants who discontinue from treatment without documented disease recurrence should have imaging performed at the time of discontinuation if the last assessment was more than 28 days prior AND should continue with posttreatment Follow-up procedures until disease recurrence, pregnancy, the start of new anticancer treatment, death, withdrawal of consent, or study conclusion (whichever occurs first).

The End of Treatment Visit should occur at the time study treatment is discontinued for any reason (see Section 9.10.4.).

Posttreatment Follow-up Period

After the end of treatment, each participant will undergo a Safety Follow-up Visit at least 30 days (+ 7 days) after the last dose of study treatment or before the initiation of a new anticancer treatment, whichever comes first. Participants will be followed for 30 days after the last dose of study treatment for AE/ECI monitoring (SAEs will be collected up to 90 days

after the last dose of study treatment or for 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever comes first).

All participants who complete 17 cycles or discontinue from treatment for a reason other than disease recurrence will undergo radiographic imaging follow-up (Q12W during year 1, Q16W during years 2 to 4, then Q24W in years 5 and beyond) for assessment of DFS. Imaging during follow-up should continue to be scheduled from the date of randomization. QoL questionnaires will continue to be collected once per year during the follow-up period. Survival Follow-up for survival status and the initiation of subsequent anticancer treatment will be assessed Q12W.

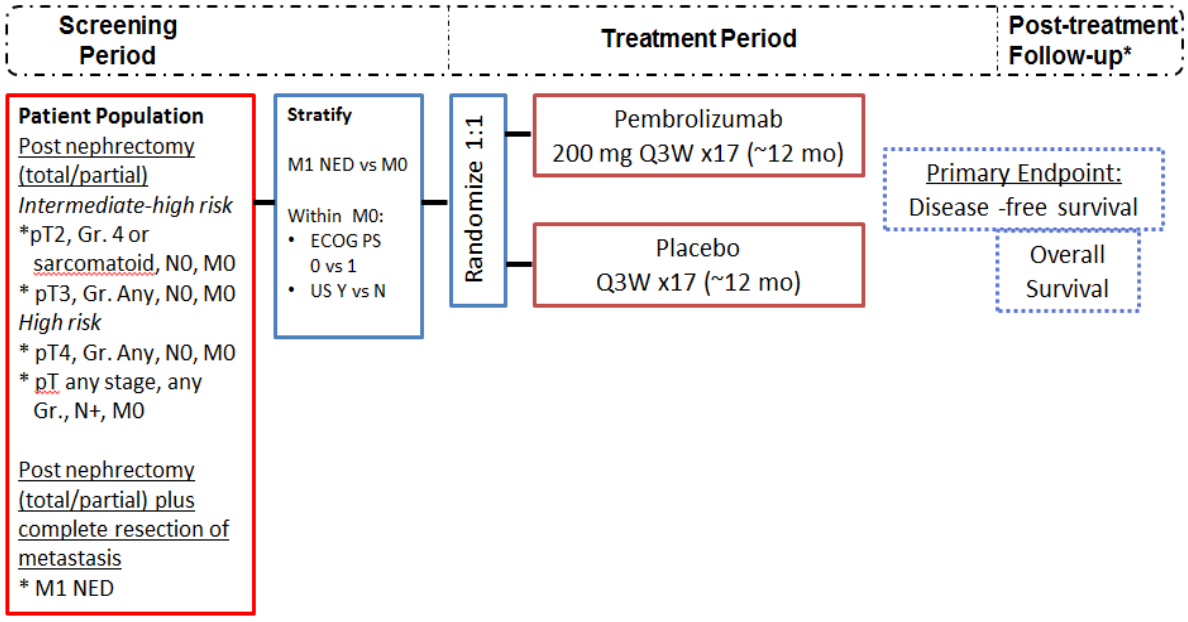
Three efficacy interim analyses may be conducted; see Section 10.7 for details.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial SoA - Section 2. Details of each procedure are provided in Section 9 – Study Assessments and Procedures.

5.1.1 Trial Diagram

The trial design is depicted in Figure 1.

Figure 1 Trial Diagram



Abbreviations: ECOG PS=Eastern Cooperative Oncology Group Performance Score; mo=month; M1 NED=M1 no evidence of disease; N=no; Q3W=every 3 weeks; US=United States; Y=yes.

* Safety Follow-up: After the last dose of study treatment or before the initiation of a new anticancer treatment.
Follow-up: Participants who discontinue trial treatment for a reason other than disease recurrence.
Survival Follow-up: Participants who experience disease recurrence or start a new anticancer therapy.

5.2 Number of Participants

Approximately 950 participants will be randomized 1:1 to pembrolizumab or placebo such that approximately 332 DFS events can be observed at the time of the final analysis of the study as described in Section 10.9.

5.3 Beginning and End of Study Definition

The overall trial begins when the first participant signs the informed consent form (ICF). The overall trial ends when the last participant completes the last study-related phone-call or visit, withdraws from the trial or is lost to follow-up (i.e. the participant is unable to be contacted by the investigator).

5.3.1 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. The trial may be stopped early for safety by the Sponsor
2. Quality or quantity of data recording is inaccurate or incomplete
3. Poor adherence to protocol and regulatory requirements
4. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to participants
5. Plans to modify or discontinue the development of the study treatment

In the event of Sponsor decision to no longer supply study treatment, ample notification will be provided so that appropriate adjustments to participant treatment can be made.

5.4 Scientific Rationale for Study Design

Selection of Patient Population

RCC has long been considered an immune-reactive malignancy based on anecdotal reports of spontaneous remissions in advanced RCC patients with evidence of antigen-specific lymphocyte infiltration of tumor tissues [Wierecky, J., et al 2006] and the fact that high-dose interleukin-2 (IL-2) could produce durable long-term response in a small subset of advanced RCC patients. In RCC, upregulation of the PD-1 receptor on tumor-infiltrating lymphocytes and its ligand PD-L1 on tumors is associated with more aggressive disease and poor prognosis [Pedoeem, A., et al 2014] [Ahmadzadeh, M., et al 2009]. The rate of PD-L1 expression in RCC has been reported to be between 10% and 30%, and PD-L2 expression has been reported as approximately 50% [Abbas, M., et al 2016] [Shin, S. J., et al 2016] [Iacovelli, R., et al 2016]. The evidence above supports targeting RCC with an immunotherapeutic approach. Single-agent antitumor activity has been demonstrated by another anti-PD-1 antibody, nivolumab, in advanced RCC [Motzer, R. J., et al 2015].

Even though vascular endothelial growth factor receptor-targeting antiangiogenic agents, such as sunitinib, pazopanib, axitinib, and bevacizumab plus IFNα, have collectively improved the outcome of advanced RCC, most patients with intermediate-high risk and high risk and most M1 NED patients will progress within 2 to 3 years following nephrectomy and/or resection of accessible metastatic lesions for M1 NED patients [Kavolius, J. P., et al 1998]. Therefore, novel treatments, including in the adjuvant setting, are needed to prevent disease recurrence in patients with higher risk RCC.

Watchful waiting or participation in an experimental clinical trial evaluating adjuvant treatment are the only options for patients with high risk of recurrence based on the National Comprehensive Cancer Network guidelines and current literature.

Other than patients with nodal involvement, the patients with the highest risk of RCC recurrence are those that present with not only the primary kidney tumor, but also solid, isolated, soft tissue metastases that can be completely resected at the time of nephrectomy, known as M1 NED. Resection of metastatic disease (metastasectomy) is performed in several situations:

- Patients with Stage IV disease at presentation, where it is performed with nephrectomy
- Patients who develop metastatic disease following nephrectomy
- Patients who have persistent disease despite systemic therapy

In selected patients with metastatic RCC, surgical resection of metastatic foci is a treatment option that can yield long-term DFS. The potential role of surgery is illustrated by the results from a series of 278 patients with recurrent RCC, in which 51% of patients underwent removal of all of their metastatic disease with curative intent, 25% underwent partial resection of their metastatic disease, and 24% were treated without surgery [Kavolius, J. P., et al 1998]. Metastases were most frequently resected from the lung, brain, bone, and soft tissue. The following findings were noted on multivariate analysis:

- The 5-year OS rate was highest in patients treated with metastasectomy with curative intent (44% versus 14% for noncurative surgery and 11% for nonsurgical intervention). Survival rates after complete resection of a second and third metastasis were not different from those after initial metastasectomy.
- The strongest predictors of prolonged survival were a disease-free interval from nephrectomy to detection of metastases of greater than 1 year (55% 5-year OS versus 9% 5-year OS for patients with a disease-free interval of a year or less); a single site of metastasis (54% 5-year OS for a single site versus 29% 5-year OS for multiple sites), especially if the site was the lung; and age younger than 60 years (49% 5-year OS versus 35% 5-year OS for age 60 years or older).

While patients after nephrectomy with a lower risk evaluation may be well served with no initiation of Follow-up treatment, in accordance with international guidelines such as those of the European Association of Urology, patients with intermediate-high risk and high risk of

recurrence within 6 to 36 months after primary treatment represent a population with a significant unmet medical need. Almost all patients with recurrence after primary nephrectomy and M1 NED patients after primary resection develop distant metastasis and require first-line metastatic treatment; a summary of Phase 3 studies of first-line treatments for RCC and their associated survival rates is shown in Table 1.

Therefore, reduction in the risk for recurrence through appropriate adjuvant treatment could be valuable in patients at a higher risk of recurrence, but to date no agent has proven to be useful in this setting. Immune therapies, hormonal therapies, and finally targeted therapy, effective in the advanced setting, have been tested for this indication, without success for this unmet medical need [Pinto, A. 2014].

Table 1 Summary of Clinical Efficacy From Randomized Phase 3 Studies in First-Line Advanced RCC

Study (N)	Median PFS (months)	Median OS (months)	ORR (%)	Reference
Sunitinib vs. IFNα (N=750)	11.0 vs. 5[a]	26.4 vs. 21.8	31 vs. 6[a]	[Motzer, R. J., et al 2007] [Motzer, R. J., et al 2009]
Pazopanib vs. placebo (N=233)	11.1 vs. 2.8[a]	22.9 vs. 20.5	30 vs. 3[a]	[Sternberg, C. N., et al 2010] [Sternberg, C. N., et al 2013]
Bevacizumab + IFNα vs. IFNα (N=649)	10.2 vs. 5.4[a]	23.3 vs. 21.3	31 vs. 13[a]	[Escudier, B., et al 2007] [Escudier, B., et al 2010]
Sunitinib vs. pazopanib (N=1110)[b]	9.5 vs. 8.4	29.3 vs. 28.4	25 vs. 31	[Motzer, R. J., et al 2013]
Axitinib vs. sorafenib (N=288; 2:1 randomization)	10.1 vs. 6.5	Not reported	32 vs. 15[a]	[Hutson, T. E., et al 2013]
Temsirolimus vs. IFNα (N=416)[c]	5.5 vs. 3.1[a]	10.9 vs. 7.3[a]	8.6 vs. 4.8	[Hudes, G., et al 2007]

EJC = European Journal of Cancer; IFNα = interferon-alpha; JCO = Journal of Clinical Oncology; NEJM = New England Journal of Medicine; ORR = overall response rate; PFS = progression-free survival.

a. Results demonstrated statistically significant improvement of the testing arm versus the control arm.
b. The sunitinib versus pazopanib study used a noninferiority design, which demonstrated that pazopanib was noninferior to sunitinib with the primary endpoint PFS meeting the predefined noninferiority margin.
c. OS was the primary endpoint for this study while other trials used PFS as the primary endpoint. This study enrolled a high-risk population while other trials enrolled a majority of participants with good or intermediate risks.

Rationale for Adjuvant Setting

When considering adjuvant therapy, it is very important to select patients who are at a higher risk of recurrence, as these patients will be the ones more likely to have any benefit from treatment. As stated previously, patients with no evidence of metastatic disease at diagnosis

might have a risk of recurrence up to 35% or 40% after surgery [Haas, N. B., et al 2016] [National Cancer Institute 2016] [Pinto, A. 2014].

For patients with a partial or radical nephrectomy, the risk of recurrence largely depends on tumor size, grade, stage, histology, performance status, and completeness of resection [Eggener, S. E., et al 2006] [Stephenson, A. J., et al 2004] [Leibovich, B. C., et al 2003]. Currently, pathologic tumor stage is the single most important prognostic factor in resected RCC, but does not fully explain disparities in survival among stages [Frank, I., et al 2005]. Some other histologic features, such as histologic subtype, and presence of necrosis or sarcomatoid component have been linked with a poorer prognosis [Kunkle, D. A., et al 2007]. Regarding histologic subtypes, chromophobe and papillary type I seem to have a more indolent clinical course, and papillary type II and clear cell RCC show a more aggressive behavior [Leibovich, B. C., et al 2003]. The most common form of RCC is clear cell disease, so named because the high lipid content in the cytoplasm is dissolved during histological preparation methods leaving a clear cytoplasm. A 4-tiered grading (Fuhrman) system based on nuclear morphology is also an important prognostic factor in clear cell RCC [Kunkle, D. A., et al 2007] [Rini, B. I., et al 2009] [Fuhrman, S. A., et al 1982].

A systematic review with meta-analysis of adjuvant therapies for locally advanced RCC was published in 2011 [Scherr, A. J., et al 2011]; it concluded that there was no support for using systemic therapy in the adjuvant setting, as there was no evidence of any benefit and there was evidence of substantial toxicity. The therapeutic modalities included in this study were mainly chemotherapy, immune therapies, and hormonal treatments, since no trial with targeted therapies had been completed at that time.

Immunotherapy was one of the standard options for metastatic RCC before the advent of targeted therapies. IL-2 and IFN were commonly used in that setting, but with poor results, achieving a response rate of 6% to 10% and some durable responses, and a median OS of 12 to 15 months [Gleave, M. E., et al 1998]. Nevertheless, none of the adjuvant trials with immune therapies has been successful. Two trials compared IFN with placebo in T3 to T4 and/or node-positive participants, without improvements in DFS or OS [Pizzocaro, G., et al 2001] [Messing, E. M., et al 2003]. Two other small trials that explored the role of IL-2, whether in monotherapy as a single-dose treatment [Clark, J. I., et al 2003] or combined with IFN [Passalacqua, R., et al 2014], also had negative results. A triple combination of IL-2, IFN, and 5-fluorouracil also failed to show an improvement in DFS compared with placebo and was associated with significant toxicity [Aitchison, M., et al 2014]. This same schedule was tested in a different trial, showing no differences in DFS, but a worse OS for the treatment arm [Atzpodien, J., et al 2005]. Some other trials have explored the potential role in the adjuvant setting of therapeutic vaccines [Patel, D. N., et al 2016].

The use of radiotherapy in an adjuvant setting has not been established as a standard for this indication. In a trial published in 1987, a total of 72 participants with Stage II to III kidney cancer were randomized to adjuvant radiation therapy (50 Gy in the tumor bed and both ipsilateral and contralateral nodes) or no further treatment. This trial was closed early because of unacceptable toxicity, and no differences in recurrence rate or survival were seen between the arms [Kjaer, M., et al]. A similar trial performed even earlier, in the 1970s, also did not find a benefit from postoperative radiation therapy [Finney, R. 1973].

Some other studies explored the role of hormone therapies, with disappointing results. One prospective multicenter study compared medroxyprogesterone acetate treatment for 1 year versus no treatment after radical nephrectomy and failed to demonstrate any benefit in survival [Scherr, A. J., et al 2011]. Another trial testing chemotherapy with adjuvant tegafur and uracil was also unsuccessful [Naito, S., et al 1997].

Until recently, a number of Phase 2/3 clinical studies failed to demonstrate substantial and consistent benefit in the adjuvant setting for RCC, whether using immunotherapy, radiotherapy, hormonal therapy, or chemotherapy. Trials testing targeted therapies such as sunitinib, sorafenib, pazopanib, and axitinib have either failed (eg, ASSURE – ECOG2805) or are ongoing, dealing with significant toxicities in participants with no existing disease burden during treatment (Table 2; [Haas, N. B., et al 2016] [Pinto, A. 2014]).

Table 2 Completed and Ongoing Targeted Adjuvant Therapies

Trial (Sponsor)	Random-ization	Treatment Details	N	Status	Inclusion Criteria (Stage/Grade)	Inclusion Criteria (Histology)	Results
ASSURE (ECOG)[51]	Sorafenib	400 mg BID × 54 Wk Amendment: starting dose reduced to 400 mg daily with dose escalation	1943	Completed	pT1b N0 M0 (Grade 3-4), pT2-pT4 N0 M0, pT(any) N1 M0	Any histology[a]	**DFS**: 97.5%; HR, 0.97 (CI, 0.80-1.17) vs placebo
	Sunitinib	50 mg daily (4 wk on/2 wk off) Amendment: starting dose reduced to 37.5 mg daily with dose escalation					**DFS:** 97.5%; HR, 1.02 (CI, 0.85-1.23) vs placebo
S-TRAC (Pfizer)[2]	Sunitinib	50 mg daily (4 wk on/2 wk off), 9 cycles	615	Completed	pT3 N0 M0 (Grades 2-4), pT4 N0 M0, pT(any) N1 M0	ccRCC only	**DFS:** 6.8 y vs 5.6 y for placebo; HR, 0.76 (CI, 0.59-0.98; *P*=.03)
ATLAS (Pfizer)	Axitinib	5 mg BID × 3 y	592	Enrolling	pT2-4 N0 M0, pT(any) N1 M0	ccRCC only	
PROTECT (GlaxoSmith-Kline)	Pazopanib	800 mg daily × 1 y Amendment: starting dose reduction to 600 mg daily with dose escalation	1500	In follow-up	pT2 N0 M0 (Grades 3-4), pT3-4 N0 M0, pT(any) N1 M0	ccRCC only	
SORCE (Medical Research Council)	Sorafenib	400 mg BID × 1 y or 400 mg BID × 3 y Amendment: starting dose reduction to 400 mg daily in both arms with dose escalation	1420	In follow-up	pT1a N0 M0 (Grade 4), pT1b N0 M0 (Grades 3-4), pT2-4 N0 M0, pT1b-4 N1 M0	Any histology	
EVEREST (SWOG)	Everolimus	10 mg daily	1218	Enrolling	pT1b N0 M0 (Grades 3-4), pT2-4 N0 M0 pT(any) N1 M0	Any histology[a]	

ASSURE, Sunitinib Malate or Sorafenib Tosylate in Treating Patients With Kidney Cancer That Was Removed by Surgery; ATLAS, Adjuvant Axitinib Therapy of Renal Cell Cancer in High Risk Patients; BID, twice a day; ccRCC, clear cell renal cell carcinoma; DFS, disease-free survival; EVEREST, Everolimus in Treating Patients With Kidney Cancer Who Have Undergone Surgery; HR, hazard ratio; PROTECT, A Study to Evaluate Pazopanib as an Adjuvant Treatment for Localized Renal Cell Carcinoma; SORCE, Sorafenib in Treating Patients at Risk of Relapse After Undergoing Surgery to Remove Kidney Cancer; S-TRAC, A Clinical Trial Comparing Efficacy and Safety of Sunitinib Versus Placebo for the Treatment of Patients at High Risk of Recurrent Renal Cell Cancer; TNM, tumor, node, metastasis; wk, week/weeks; y, year/years.

[a] duct-Bellini RCC excluded

Source: [Patel, D. N., et al 2016]

In October 2016, results from a Phase 3 randomized, placebo-controlled study of sunitinib (S-TRAC) showed a median duration of DFS that was significantly longer in the sunitinib group (6.8 years; 95% CI: 5.8) to not reached compared with the placebo group (5.6 years; 95% CI: 3.8 to 6.6), with a HR of 0.76 for independent radiologic review, at the cost of a higher rate of toxic events. There were no statistically significant differences in OS data at the reported data cutoff. Dose reductions due to AEs were more frequent in the sunitinib group than in the placebo group (34.3% vs. 2%), as were dose interruptions (46.4% vs. 13.2%) and discontinuations (28.1% vs. 5.6%). Grade 3 and 4 AEs were more frequent in the

sunitinib group (48.4% and 12.1%, respectively) than in the placebo group (15.8% and 3.6%, respectively). The incidence of SAEs in the groups was similar (21.9% for sunitinib vs. 17.1% for placebo); no deaths were attributed to toxic effects related to study treatment [Ravaud, A., et al 2016].

These recent data are encouraging, as this is the first study to show a positive DFS in this patient population; however, the treatment discontinuation rate was high and the AEs created a meaningful burden for participants. Additionally, the study did not include those at the highest risk of recurrence, M1 NED, in the investigated patient population. Globally, there is no current treatment standard in the adjuvant setting for RCC after nephrectomy.

Rationale for Stratification

In previous studies [Haas, N. B., et al 2016] [Ravaud, A., et al 2016] and ongoing adjuvant RCC trials, stratification for ECOG 0 versus 1+ is considered an important strategy to equally distribute participants. Participants with an initial diagnosis of RCC and an ECOG status greater than 0 typically have underlying comorbidities and are clinically considered to have a worse long-term outcome when compared to participants with an initial diagnosis of RCC and an ECOG status of 0.

The stratification of US over rest of world addresses the potential significant treatment paradigm shift in first and second-line metastatic RCC due to early adoption of new treatment regimens and broader availability of treatments in the US over other regions of the world. This stratification factor does not impact the primary endpoint of DFS. Instead it addresses equal distribution of participants having differential access to new treatment regimens during OS Follow-up.

5.4.1 Rationale for Endpoints

5.4.1.1 Efficacy Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint, DFS as assessed by the investigator, is considered an appropriate clinical endpoint for an adjuvant trial that will evaluate the study treatment's impact on disease recurrence and has been explored in a number of ongoing pivotal Phase 3 studies serving as a surrogate for OS assessment [Ravaud, A., et al 2016] [Haas, N. B., et al 2016]. DFS has been accepted as a surrogate endpoint to support drug approval for adjuvant settings in which participants are expected to experience cancer symptoms upon recurrence (eg, adjuvant breast cancer hormonal therapy, adjuvant colon cancer, and adjuvant cytotoxic breast cancer therapy). In the proposed patient population, participants are entering the trial tumor free. In the adjuvant setting, an investigator determines the absolute recurrence of disease. This assessment is equally appropriate to an independent reviewer determination since it does not involve tumor burden level grading expected with existing advanced metastatic disease.

While OS has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies, in some oncology indications such as RCC, survival may be prolonged. In such instances where a survival endpoint would be difficult to achieve, DFS may represent a measure of clinical benefit, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile.

5.4.1.2 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs; and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCA), Version 4.0.

5.4.1.3 Pharmacokinetic Endpoints

THIS BLOOD WORK WILL NO LONGER BE COLLECTED WITH THE IMPLEMENTATION OF AMENDMENT 2.

Blood samples will be obtained to measure the PK of pembrolizumab.

PK parameters (clearance, volume of distribution) will be characterized and the effect of extrinsic and intrinsic factors will be evaluated to support the proposed dosing regimen. PK data will also be used to explore the exposure-response relationships for pembrolizumab antitumor activity/efficacy, as well as safety in the proposed patient population, if feasible.

5.4.1.4 Patient-Reported Outcomes

Symptomatic improvement is considered a clinical benefit. As part of the analyses for this trial, participants will provide information regarding their HRQoL via EORTC-QLQ-C30 and EQ-5D-5L. These PROs are not pure efficacy or safety endpoints because they are affected by both disease recurrence and treatment tolerability. Clinical experts have indicated that the FKSI-DRS instrument primarily captures disease-related, as opposed to treatment-related, changes in HRQoL.

Rationale for the EORTC-QLQ-C30

The EORTC-QLQ-C30 is the most widely used cancer-specific HRQoL instrument, which contains 30 items and measures 5 functional dimensions (physical, role, emotional, cognitive, and social), 3 symptom items (fatigue, nausea/vomiting, and pain), 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health and QoL scale. Thus, secondary objectives are to assess mean changes from baseline in the global health status/QoL scale from the EORTC-QLQ-C30.

Rationale for the FKSI-DRS

The FKSI-DRS is a patient-reported instrument that measures whether the participant has experienced any of the following 9 kidney cancer-related symptoms: lack of energy, fatigue, weight loss, pain, bone pain, shortness of breath, cough, fever, or blood in the urine. Responses to all FKSI-DRS items are summed to generate a summary symptom score

ranging from 0 to 36, with higher scores indicating improved (more favorable) symptom status. The FKSI-DRS is a reliable, valid, and responsive brief index of the most important symptoms associated with advanced kidney cancer.

Rationale for the EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcomes and will provide data for use in economic models and analyses including developing health utilities or quality-adjusted life-years. The 5 health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5-point scale from 1 (no problem) to 5 (extreme problem). The EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the participant rates his or her general state of health at the time of the assessment. This instrument has been used extensively in cancer studies, and published results from these studies support its validity and reliability.

5.4.1.5 Planned Exploratory Biomarker Research

5.4.1.6 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to the study treatment(s), the disease under study and related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases and study drug(s). Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate).

DNA samples will be analyzed for variation across the entire genome. Analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

5.4.1.7 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens consented for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of Future Biomedical Research are presented in Appendix 6 – Collection and Management of Specimens for Future Biomedical Research.

5.4.2 Rationale for the Use of Comparator/Placebo

The use of a placebo control for this trial is considered appropriate in this patient population because such a patient would have no disease burden following nephrectomy; these participants would then be followed without further treatment until disease recurrence, as no other regimens are yet approved for RCC in the adjuvant setting.

5.5 Justification for Dose

The planned dose of pembrolizumab for this trial is 200 mg Q3W. The initial dose approved by the United States Food and Drug Administration (FDA) for treatment of melanoma patients was 2 mg/kg Q3W. Currently, clinical trials evaluating pembrolizumab are using a fixed dose of 200 mg Q3W. The use of a fixed dose is based on PK findings summarized below.

The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. A population PK model, which characterized the influence of body weight and other participant covariates on exposure using available data from 1139 participants (from Keynote 001 and Keynote 002), has been performed. The majority of these participants (1077; 94.6%) had advanced melanoma. The distribution of exposures from the 200 mg fixed dose were predicted to considerably overlap those obtained with the 2 mg/kg dose and importantly maintained individual participant exposures within the exposure range established in

melanoma as associated with maximal clinical response. This comparison also demonstrated that the 200 mg Q3W regimen provided no substantive differences in PK variability (range of the distribution of individual exposures) as seen with weight-based dosing.

In translating to other solid tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in participants with melanoma can be expected, as the antitumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in participants with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at tested doses among tumor types.

A fixed-dose regimen is expected to simplify the dosing regimen (potentially reducing dosing errors), as well as be more convenient for physicians. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities, as well as reducing waste.

6. Study Population

Male and female participants with intermediate-high risk, high risk and M1 NED RCC of at least 18 years of age will be enrolled in this trial.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Type of Participant and Disease Characteristics

1. Must have histologically confirmed diagnosis of RCC with clear cell component with or without sarcomatoid features. Diagnosis of RCC with clear cell component is to be made by the investigator and does not require central histology review.

Demographics

2. Be ≥18 years of age on day of signing informed consent.

Female Participants:

3. Female participants of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to randomization. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
4. Female participants of childbearing potential must be willing to use an adequate method of contraception as outlined in Appendix 5, for the course of the trial through 120 days after the last dose of trial drug.

   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the participant.

Male Participants:

5. Male participants of childbearing potential must agree to use an adequate method of contraception as outlined in Appendix 5, starting with the first dose of trial therapy through 120 days after the last dose of trial therapy.

   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the participant.

Informed Consent

6. The participant provides written informed consent/assent for the trial. The participant may also provide consent/assent for Future Biomedical Research; however, the participant may participate in the main trial without participating in Future Biomedical Research.

Other Inclusion Criteria

7. Have intermediate-high risk, high risk, or M1 NED RCC as defined by the following pathological tumor-node-metastasis and Fuhrman grading status [Leibovich, B. C., et al 2003] [Rini, B. I., et al 2009] [Fuhrman, S. A., et al 1982]:
   a) Intermediate-high risk RCC
      - pT2, Gr. 4 or sarcomatoid, N0, M0
      - pT3, Any Gr., N0, M0
   b) High risk RCC
      - pT4, Any Gr. N0, M0
      - pT Any stage, Any Gr., N+, M0
   c) M1 NED RCC -participants who present not only with the primary kidney tumor, but also solid, isolated, soft tissue metastases that can be completely resected at one of the following:
      - the time of nephrectomy (synchronous) or,
      - ≤1 year from nephrectomy (metachronous)
8. Have received no prior systemic therapy for advanced RCC.
9. Have undergone a partial nephroprotective or radical complete nephrectomy (and complete resection of solid, isolated, soft tissue metastatic lesion(s) in M1 NED participants) with negative surgical margins.
10. Must have undergone a nephrectomy and/or metastasectomy ≥28 days prior to signing informed consent and ≤12 weeks prior to randomization.
11. Must be tumor free as assessed by the investigator and validated by either CT or MRI scan of the brain and CAP and a bone scan ≤28 days from randomization. All baseline scans must be sent to the central imaging vendor and receipt must be confirmed prior to randomization.

12. Must have provided adequate tissue per the following:

    - Nephrectomy only: tissue from nephrectomy (required).
    - Synchronous M1 NED: tissue from nephrectomy (required) AND, metastasectomy tissue (if available).
    - Metachronous M1 NED: tissue from metastasectomy (required) AND, nephrectomy tissue (if available).

    Adequacy of the samples for biomarker analysis will be evaluated by a central laboratory.

    Note: If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 14 days from the date the slides are cut (details pertaining to tumor tissue submission and guidelines for tissue adequacy can be found in the Procedure Manual).

13. Have an ECOG PS of 0 or 1.

14. Specimens must be collected within 10 days prior to randomization. Have adequate organ function as defined in the following table:

Table 3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine **OR** Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN **OR** ≥30 mL/min for participants with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN
Coagulation	
International normalized ratio (INR) **OR** prothrombin time (PT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as INR or PT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a]. Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] Creatinine clearance (CrCl) should be calculated per institutional standard.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for treatments.

6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Has had major surgery, other than nephrectomy and/or resection of preexisting metastases for M1 NED participants, within 12 weeks prior to randomization.

Note: If participants received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.

2. Has received prior radiotherapy for RCC.
3. Has preexisting brain or bone metastatic lesions.
4. Has residual thrombus post nephrectomy in the vena renalis or vena cava.
5. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study treatment.
6. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
7. Has a known additional malignancy that is progressing or required active treatment ≤3 years ago. Exceptions include early stage cancers (carcinoma in situ or Stage 1) treated with curative intent, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ cervical cancer, in situ prostate cancer, or in situ breast cancer that has undergone potentially curative therapy.
8. Has a history of (noninfectious) pneumonitis that required steroids or has current pneumonitis.
9. Has an active infection requiring systemic therapy.
10. Has a history of, or is currently on, dialysis.
11. Has a known history of human immunodeficiency virus infection. No human immunodeficiency virus testing is required unless mandated by local health authority.
12. Has a known active hepatitis B (hepatitis B surface antigen reactive) or HCV (eg, HCV RNA [qualitative] is detected).

    Note: HCV RNA testing is not required in those countries where local standard of care uses only hepatitis C antibody testing as evidence of status of hepatitis C.
13. Has a known history of active tuberculosis (*Bacillus tuberculosis*).
14. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the participant's participation for the full duration of the trial, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
15. Has a known psychiatric or substance abuse disorder that would interfere with the cooperation with the requirements of the trial in the opinion of the investigator.
16. Has had a prior solid organ transplant.
17. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients (refer to Investigator's Brochure for further details on excipients).

18. A WOCBP who has a positive urine pregnancy test within 72 hours before randomization. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Participants must be excluded/discontinued from the trial in the event of a positive or borderline positive test result.
19. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the Screening visit through 120 days after the last dose of study treatment.

Prior/Concomitant Therapy

20. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another coinhibitory T-cell receptor (ie, CTLA-4, OX-40, CD137) or has previously participated in a Merck pembrolizumab (MK-3475) clinical trial.
21. Has received prior anticancer therapy, monoclonal antibody, chemotherapy, or an investigational agent or device within 4 weeks or 5 half-lives (whichever is longer) before first dose of study treatment or not recovered (ie, must be ≤Grade 1 or at baseline) from AEs due to previously administered agents.

    Note: Upon consultation with the Sponsor, denosumab may be allowed for bone protective purposes if dosing has been stable for ≥2 weeks before screening.

    Note: Participants with ≤Grade 2 neuropathy are an exception and may qualify for the trial.
22. Has received a live vaccine within 30 days prior to the first dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

Prior/Concurrent Clinical Study Experience

23. Is currently participating in or has participated in a trial of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.

    Note: Participants who have entered the Follow-up phase of an investigational trial may participate as long as it has been 4 weeks or 5 half-lives after the last dose of the previous investigational agent.

6.3 Lifestyle Restrictions

No lifestyle restrictions are required, apart from those mentioned in the inclusion and exclusion criteria.

6.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

6.3.2 Caffeine, Alcohol, and Tobacco

There are no restrictions on caffeine, alcohol, or tobacco intake while a participant is enrolled in this trial.

6.3.3 Activity

There are no restrictions on the participant's level of activity while they are enrolled in this trial.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any adverse events or SAE meeting reporting requirements as outlined in the entry guidelines.

6.5 Participant Replacement Strategy

A participant who discontinues from study treatment or withdraws from the trial will not be replaced.

7. Treatments

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies [study treatment(s) provided by the Sponsor] will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

7.1 Treatments Administered

The study treatments to be used in this trial are outlined below in Table 4.

Table 4 Study Treatments

Study Treatment Name:	Pembrolizumab (MK-3475)	Placebo
Dosage Formulation:	Solution for infusion	Saline solution for infusion
Unit Dose Strength(s):	25 mg/mL (100 mg/4 mL)	0 mg
Dosage Level(s):	200 mg Q3W	0 mg Q3W
Route of Administration:	IV infusion	IV infusion
Sourcing:	Provided centrally by the Sponsor	Provided locally by the trial site

All trial treatments will be administered on an outpatient basis.

All supplies indicated in Table 4 will be provided per the 'Sourcing' row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to section 9.1.8 for details regarding administration of the study treatment.

7.2 Dose Modification (Escalation/Titration/Other)

7.2.1 Dose Modification and Toxicity Management Guidelines for Pembrolizumab

Dose Modification and Toxicity Management for Immune-related Adverse Events Associated With Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 5.

Table 5 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated With Pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroids should be initiated first, followed by oral steroids. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥Grade 2 diarrhea suspecting colitis should consider gastrointestinal consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
AST / ALT elevation or increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
T1DM or hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[a]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or Permanently discontinue[a]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; irAE=immune-related adverse event; IV=intravenous; T1DM= Type 1 diabetes mellitus.

a. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE: For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reaction are provided in Table 6.

Table 6 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption, but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	**Stop Infusion.** Additional appropriate medical therapy may include, but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment**	Participant may be premedicated 1.5 h (±30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include, but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study treatment.**	No subsequent dosing

IV=intravenous; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID=nonsteroidal anti-inflammatory drug; po=*per os* (orally).
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.
For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov

Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study treatment. Participants should be placed back on study treatment within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the participant's study record.

7.3 Method of Treatment Assignment

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

Treatment allocation/randomization will occur centrally using the IVRS/IWRS. There are 2 study treatment arms. Participants will be assigned randomly in a 1:1 ratio to either:

- Pembrolizumab monotherapy
- Placebo (carrier solution only)

7.3.1 Stratification

Treatment allocation/randomization will be stratified according to the following factors:

Metastasis status (M0 versus M1 NED)

Within M0 group, there will be 2 stratification factors:

a. ECOG PS (0 versus 1)

b. US participant (YES versus NO)

7.4 Blinding

A double-blinding technique will be used. MK-3475 and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified trial site personnel. The participant and the investigator who is involved in the study treatment administration or clinical evaluation of the participants are unaware of the group assignments.

See Section 9.1.10 for a description of the method of unblinding a participant during the trial, should such action be warranted.

7.5 Preparation/Handling/Storage/Accountability

7.5.1 Dose Preparation

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

The rationale for selection of doses to be used in this trial is provided in Section 5.5. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant.

7.5.2 Handling, Storage and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of study treatments in accordance with the protocol and any applicable laws and regulations.

7.6 Treatment Compliance

Study intervention will be administered by the investigator and/or study staff according to the specifications within the Pharmacy Manual.

Interruptions from the protocol specified treatment plan for greater than 3 weeks between study treatments for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study treatment require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

7.7 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

Listed below are specific restrictions for concomitant therapy during the course of the trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab

- Radiation therapy
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

  Note: Use of prophylactic corticosteroids to avoid allergic reactions (eg, IV contrast dye or transfusions) is permitted.

  Note: The use of intermittent inhaled steroids or intranasal or local injection of corticosteroids is permitted.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments (excluding the exceptions noted above) for clinical management should be removed from the trial. Participants may receive other medications that the investigator deems to be medically necessary.

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter products, herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 30 days prior to the first dose of study treatment and up to 30 days after the last dose of study treatment should be recorded. Concomitant medications administered 30 days after the last dose of study treatment should be recorded for SAEs and ECIs as defined in Section 9.3.

Medications intended solely for supportive care (ie, antiemetics, analgesics, megestrol acetate for anorexia) are allowed. The exclusion criteria describe other medications that are prohibited in this trial. There are no prohibited therapies during the posttreatment Follow-up phase.

7.7.1 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 7.2, Table 5 and Table 6. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is

decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 5 and Table 6 in Section 7.2 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

7.8 Treatment After the End of the Study

There is no study-specified treatment following the end of the study.

7.9 Clinical Supplies Disclosure

This trial is blinded but supplies are provided open label; therefore, an unblinded pharmacist or qualified trial site personnel will be used to blind supplies. Study treatment identity (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

The emergency unblinding call center will use the treatment/randomization schedule for the trial to unblind participants and to unmask study treatment identity. In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic treatment allocation/randomization system (IVRS/IWRS) should be used in order to unblind participants and to unmask study treatment identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 9.1.10, Participant Blinding/Unblinding, for a description of the method of unblinding a participant during the trial, should such action be warranted.

8. Discontinuation/Withdrawal Criteria

8.1 Discontinuation of Study Treatment

Discontinuation of study treatment does not represent withdrawal from the study.

As certain data on clinical events beyond study treatment discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study treatment. Therefore, all participants who discontinue study treatment prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 2 - SoA and Section 9.10.4 – Discontinued Participants Continuing to be Monitored in the Study, unless the participant withdraws from the study.

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 9.1.9 – Withdrawal/Discontinuation.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment.
- Participants with AEs meeting discontinuation criteria as described in Section 9.
- The participant has a medical condition or personal circumstance or is noncompliant to study treatments or procedures, which, in the opinion of the investigator and/or Sponsor, place the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test.
- The participant has received 17 cycles of study treatment.
- Any progression or recurrence of the malignancy under study.

  NOTE: All scans for the participant must be submitted to the central imaging vendor according to the Procedures Manual. Clinically stable participants that are first identified with disease recurrence may remain on study treatment while waiting for confirmation of recurrence by the investigator (Section 9.2.1).
- A new malignancy requiring active treatment.
  NOTE: In the event that a new malignancy is diagnosed and requires active treatment, the Sponsor should be consulted as to whether the participant should be discontinued from study treatment.
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment.
- Recurrent Grade 2 pneumonitis.
- Investigator's decision to discontinue participant.

For information about the End of Treatment Visit and Safety Follow-up Visit, please refer to Section 9.10.3.

For participants who are discontinued from study treatment but continue to be monitored in the trial, all visits and procedures, as outlined in the SoA, should be completed.

Discontinuation from study treatment is "permanent." Once a participant is discontinued, he/she shall not be allowed to restart study treatment.

8.2 Withdrawal from the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study including the procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant, as well as specific details regarding withdrawal from Future Biomedical Research are outlined in Section 9.1.9 – Withdrawal/Discontinuation.

8.3 Lost to Follow Up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (e.g. phone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow up until the last scheduled visit for the individual participant. The amount of missing data for the participant will be managed via the pre-specified data handling and analysis guidelines.

9. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Repeat or unscheduled samples and images may be taken for safety reasons or for technical issues with the samples.

9.1 Administrative and General Procedures

9.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the participant's status during the trial (eg, health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

9.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the trial.

The initial ICF, any subsequent revised written ICF and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements.

<u>Consent and Collection of Specimens for Future Biomedical Research</u>

The investigator or qualified designee will explain the Future Biomedical Research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to Future Biomedical Research. A copy of the informed consent will be given to the participant.

9.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the trial.

9.1.3 Participant Identification Card

All participants will be given a Participant Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the participant with a Participant Identification Card immediately after the participant provides written informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Participant Identification Card.

The participant identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study treatment in emergency situations where the investigator is not available.

9.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically significant. Details regarding the disease for which the participant has enrolled in this trial will be recorded separately and not listed as medical history.

9.1.4.1 History of Renal Cell Carcinoma

The investigator or qualified designee will obtain information regarding the participants' RCC. This information will include, but is not limited to, the presentation and stage at initial diagnosis, date of initial diagnosis, date of nephrectomy (and metastasectomy for M1 NED), surgical outcome and location of metastases (if applicable).

9.1.5 Prior and Concomitant Medications Review

9.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 30 days before the first dose of study treatment. Treatment for the disease for which the participant has enrolled in this trial will be recorded separately and not listed as a prior medication.

9.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial through the Safety Follow-up Visit.

All medications related to reportable SAEs and ECI should be recorded as defined in Section 9.3.

9.1.5.2.1 Poststudy Anticancer Therapy

If a participant initiates a new anticancer therapy while receiving study treatment, study treatment must be discontinued and the participant will move into the Survival Follow-up phase. If a participant initiates a new anticancer therapy within 30 days after the last dose of study treatment, the End of Treatment Visit and the 30-day Safety Follow-up Visit must occur before the first dose of the new therapy. All new anticancer therapy initiated after the study start must be recorded in the poststudy anticancer therapy eCRF.

9.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization. Each participant will be assigned only one screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the Screening Visit requirements (screening/rescreening) are provided in Section 9.10.1.

9.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

9.1.8 Treatment Administration

Study intervention will be monitored by the investigator and/or study staff according to the specifications within the Pharmacy Manual.

Study Treatment should begin within 3 days of randomization.

9.1.8.1 Timing of Dose Administration

Cycle 1 Day 1 denotes the first dose of study treatment administered. Subsequent doses of study treatment will be administered on Day 1 of each 21-day cycle (±3 days). Treatment should begin after all predose study procedures and assessments have been completed as specified in the SoA (Section 2).

Study treatment will be administered as a 30-minute IV infusion Q3W. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given

the variability of infusion pumps from site to site, a window of - 5 minutes and + 10 minutes is permitted (ie, infusion time is 25 to 40 minutes).

The Pharmacy Manual contains specific instructions for the preparation and administration of the study treatment infusion solution.

9.1.9 Withdrawal/Discontinuation

Participants who discontinue study treatment prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits.

When a participant discontinues/withdraws from participation in the trial, all applicable activities scheduled for the End of Treatment Visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 9.3 - Adverse Events, Serious Adverse Events, and Other Reportable Safety Events. Participants who complete 17 cycles of study treatment (approximately 1 year) must discontinue treatment. After discontinuing treatment period, all participants should return to the site for the End of Treatment Visit and Safety Follow-up visit and then proceed to Efficacy Follow-up (described in Section 9.10.3).

9.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for Future Biomedical Research. Participants may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's consent for Future Biomedical Research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the participant’s personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

9.1.10 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the

dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the toxicity grade of the AEs observed, the relation to study intervention, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

For studies that require nonemergency unblinding as part of the study design (eg, disease progression) to support treatment decisions, instructions in the IVRS/IWRS Unblinded Site User Manual should be followed.

Once an emergency unblinding or a nonemergency unblinding that is part of the study design has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

9.1.11 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

- Laboratory equipment – as required for inclusion laboratory results and trial assessments
- Imaging equipment – as required for trial objectives
- Infusion equipment – as required for administering drug product.

9.2 Efficacy Assessments

9.2.1 Tumor Imaging and Assessment of Disease Recurrence

The process for image collection and transmission to the central imaging vendor can be found in the Site Imaging Manual. All baseline, on-treatment, and follow-up scans must be sent to the central imaging vendor. Acceptable modalities for each anatomic region are as follows:

- For imaging of the CAP, CT is the strongly preferred modality and should be acquired with IV and oral contrast. An MRI with IV contrast should only be used when CT is contraindicated.
- For brain imaging MRI is preferred; however, CT imaging will be acceptable, if an MRI is medically contraindicated.
- For imaging of bone, bone scintillation or the local standard of care modality should be used. X-rays may also be taken for symptomatic sites even if a bone scan is negative.

The same imaging technique regarding modality and contrast should be used in a participant throughout the trial to optimize the visualization of existing and new tumor burden.

The investigator will verify that each participant is tumor free at baseline and will make the determination that a participant has met the criteria for recurrence of RCC.

To assess the adequacy of DFS as assessed by the investigator, a blinded audit for a subset of participants will be conducted as outlined in the supplemental Statistical Analysis Plan (sSAP).

Criteria for Determination of Disease Recurrence

Disease recurrence is defined as local recurrence of RCC, or occurrence of distant kidney cancer metastasis(es) and is to be determined according to the clinical, pathologic, and radiographic criteria in Table 7. Radiographic evidence for disease recurrence is required, while confirmation of recurrence by biopsy or cytology is strongly encouraged, when safely feasible. The date of disease recurrence (eg, RCC) should be the date the first radiographic image with evidence of disease recurrence was obtained even if additional confirmatory procedures (eg, repeat imaging, biopsy, and/or cytology) are performed later.

Table 7 Criteria for Determining Recurrence of Disease

Anatomic Location	**Acceptable Recurrence Criteria** (Must meet radiographic evidence of disease recurrence. Confirmation of recurrence by biopsy or cytology strongly encouraged when safely feasible.)
Lung	• Positive cytology or biopsy in the presence of a solitary lesion • Radiologic evidence of lesion(s) determined to be consistent with metastases • Neoplastic pleural effusion should be established by cytology or pleural biopsy
Liver	• Positive cytology or biopsy • Multiple new focal defects on MRI, CT, or ultrasound that are enlarging in size as documented by repeat scans • Proof of neoplastic abdominal ascites should be established by cytology or pleural biopsy
Central Nervous System	• Positive brain CT or MRI scan or cerebral spinal fluid cytology
Subcutaneous and Lymph Node Recurrence	• Positive biopsy • Progressively enlarging solid mass or node(s) as evidenced by repeat CT or MRI • Ureteral obstruction in the presence of a mass as documented on CT or MRI
Other Organs	• Positive radiographic study • Positive biopsy/aspiration cytology • Progressively enlarging solid mass or node(s) as evidenced by repeat CT or MRI
Renal Bed	• Positive radiographic study • Positive biopsy/aspiration cytology • Progressively enlarging solid mass or node(s) as evidenced by 2 CT or MRI scans separated by at least a 4-week interval
Skeletal	• Positive radiographic study such as bone scan • For a solitary lesion, unequivocal finding on scan or biopsy is required to demonstrate recurrence • MRI or CT of solitary or equivocal lesion seen on bone scan that confirms metastasis is also acceptable
CT = computed tomography; MRI = magnetic resonance imaging.	

Criteria for Determination of Disease Progression

Participants, which by BICR were considered to have baseline disease (M1 by BICR), disease progression is defined as either unequivocal progression of baseline disease or appearance of new lesions as assessed by BICR.

9.2.1.1 Initial Tumor Imaging at Screening

Initial tumor imaging during Screening (baseline) must be performed for all participants as follows:

- CT (or MRI) of CAP (within 28 days prior to date of randomization)
- A brain scan (within 28 days prior to date of randomization)
- A bone scan (within 28 days prior to date of randomization)

Scans performed as part of routine clinical management are acceptable for use as screening tumor imaging if they are of diagnostic quality, performed within timeframe specified above and are able to be assessed by the central imaging vendor.

All screening images must be submitted to the central imaging vendor prior to randomization. The central imaging vendor will verify that all scans are received and of diagnostic quality prior to randomization. Tumor-free status at baseline will be confirmed by the investigator for enrollment.

9.2.1.2 Tumor Imaging During Treatment

The timing of on-treatment imaging assessments should follow calendar days from the date of randomization and should not be adjusted for dose delays or cycle starts.

Postrandomization, on-treatment imaging assessments of CAP should be performed at the following time points:

Week 12 (± 7 days)
Week 24 (± 7 days)
Week 36 (± 7 days)
Week 48 (± 7 days)

On-treatment bone scans will be performed as clinically indicated. A bone scan may be obtained if there are new symptoms of bone pain in participants with negative bone scans at Screening. X-ray evaluation may be obtained for symptomatic sites in participants with negative bone scan evaluations.

On-treatment brain scans will be performed at Screening and as clinically indicated thereafter.

9.2.1.3 End of Treatment and Follow-up Tumor Imaging

Participants who complete all 17 cycles of study treatment or discontinue study treatment due to a reason other than disease recurrence should continue to be monitored for disease status per the follow-up imaging schedule. Imaging should continue until disease recurrence, pregnancy, the start of a new anticancer treatment, withdrawal of consent, death, or the end of the trial, whichever occurs first. Follow-up imaging should follow calendar days from the date of randomization.

For participants who discontinue study treatment for reasons other than disease recurrence, tumor imaging should be performed at the time of treatment discontinuation. If a previous scan was obtained within 28 days prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. These participants should continue to be monitored for disease status per the follow-up imaging schedule. Imaging should continue until disease recurrence, pregnancy, the start of a new anticancer treatment, withdrawal of consent, death, or the end of the trial, whichever occurs first. If a discontinuation scan is performed and the next scheduled time point is fewer than 28 days later, this scheduled time point may be skipped. In this case, the imaging should resume with the subsequent scheduled time point.

For participants who discontinue study treatment due to disease recurrence, the initial imaging demonstrating recurrence is the final required imaging, unless recurrence is confirmed with a repeat scan. In this case, the confirmatory scan is the final required imaging.

The timing of follow-up imaging assessments should follow calendar days from the date of randomization. Imaging should be performed according to the following schedule (all timepoints are from the date of randomization):

Follow-up Year 1 (Q12W)

Week 60 (± 7 days)

Week 72 (± 7 days)

Week 84 (± 7 days)

Week 96 (± 7 days)

Follow-up Years 2 to 4 (Q16W)

Week 112 (± 7 days)	Week 192 (± 7 days)
Week 128 (± 7 days)	Week 208 (± 7 days)
Week 144 (± 7 days)	Week 224 (± 7 days)
Week 160 (± 7 days)	Week 240 (± 7 days)
Week 176 (± 7 days)	Week 256 (± 7 days)

Follow-up Years 5 and Beyond (Q24W)

Week 280 (± 7 days)

Week 304 (± 7 days)

Week 328 (± 7 days)

(continue at Q24W ± 7 days)

9.2.2 Quality of Life Assessments

The EORTC-QLQ-C30, FKSI-DRS, and EQ-5D-5L PROs are to be completed electronically by study participants at various time points as specified in the SoA (Section 2), beginning

with the baseline assessment and continuing until disease recurrence or start of a new anticancer treatment.

The PROs will be administered in the following order: (1) EQ-5D-5L, (2) EORTC-QLQ-C30, and (3) FKSI-DRS. It is strongly recommended that PROs be administered prior to AE evaluation, disease notification status, and study treatment administration.

9.2.2.1 EuroQoL 5 Dimensions 5 Levels

The EQ-5D-5L is a standardized instrument for use as a measure of health outcomes. The EQ-5D-5L will provide data for use in economic models and analyses including developing health utilities or quality-adjusted life-years. The 5 health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [Rabin, R. 2001] [Pickard, A. S., et al 2007]. Each dimension is rated on a 5-point scale from 1 (no problem) to 5 (extreme problem). The EQ-5D-5L also assesses the general state of health using a visual analog scale (0 to 100). The EQ-5D-5L will always be completed by participants first, prior to completing any other PRO.

9.2.2.2 European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30

The EORTC-QLQ-C30 was developed to assess the QoL of patients with cancer. It has been translated and validated into 81 languages and used in more than 3,000 studies worldwide. It consists of 5 functioning scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, nausea/vomiting, pain), and additional single-symptom items. It is scored on a 4-point scale (1 = not at all, 2 = a little, 3 = quite a bit, 4 = very much). The EORTC-QLQ-C30 instrument also contains 2 global scales that use a 7-point scale scoring with anchors (the scores range from 1 = very poor to 7 = excellent) [Aaronson, N. K., et al 1993].

9.2.2.3 Functional Assessment of Cancer Therapy Kidney Symptom Index – Disease-Related Symptoms

The FKSI-DRS is a patient-reported instrument that measures whether the participant has experienced any of the following 9 kidney cancer-related symptoms: lack of energy, fatigue, weight loss, pain, bone pain, shortness of breath, cough, fever, or blood in the urine [Cella, D., et al 2007]. Each item is scored by using the following 5 response categories: 0, not at all; 1, a little bit; 2, somewhat; 3, quite a bit; and 4, very much. Responses to all FKSI-DRS items are summed to generate a summary symptom score ranging from 0 to 36, with higher scores indicating improved (more favorable) symptom status. The FKSI-DRS is a reliable, valid, and responsive brief index of the most important symptoms associated with advanced kidney cancer [Cella, D., et al 2007].

If, at the time of first dose of study treatment, the translated version of the FKSI-DRS – one of the PRO measures – is not available for that language/country, and it cannot be completed by the participant at Cycle 1, Day 1, then the FKSI-DRS will not be required for this participant at any point of the study. The other study PRO measures must be completed as scheduled.

Note: For some sites, the translated FKSI-DRS might become available after study startup and should be administered to participants at their time of first dose of study treatment; for some sites, the FKSI-DRS translation might not be available for the entire duration of the study. Missing FKSI-DRS for such a reason will not be considered a protocol deviation.

9.3 Adverse Events, Serious Adverse Events and Other Reportable Safety Events

The definitions of an adverse event (AE) or serious adverse event (SAE), as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE and other reportable safety event reports can be found in Appendix 4.

Progression of the cancer under study is not considered an adverse event as described in Section 9.3.5 – Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs, and Appendix 4.

AE, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs and other reportable safety events for outcome according to Section 9.3.3.

9.3.1 Time Period and Frequency for Collecting AE, SAE and Other Reportable Safety Event Information

All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

All initial and follow-up AEs, SAEs and other reportable safety events will be recorded and reported to the sponsor or designee within the timeframes as indicated in Table 8.

Table 8 Reporting Time Periods and Timeframes for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-Specified Follow-up Period	Reporting Time Period: After the Protocol Specified Follow-up Period	Timeframe to Report Event and Follow-up Information to SPONSOR:
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Non-Serious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential DILI - Require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (Do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 days of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event

9.3.2 Method of Detecting AE and SAE

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.3.3 Follow-up of AE, SAE and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE and other reportable safety events including pregnancy and exposure during breastfeeding, ECI, Cancer and Overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). In addition, the investigator will make every attempt to follow all non-serious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 4.

9.3.4 Regulatory Reporting Requirements for SAE

- Prompt notification (within 24 hours) by the investigator to the sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAE) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.3.5 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Progression/recurrence of the cancer under study is not considered a reportable event.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the participants in the trial. Any suspected endpoint which upon review is not progression/recurrence of the cancer under study will be forwarded to Global Safety as an SAE within 24 hours of determination that the event is not progression/recurrence of the cancer under study.

9.3.6 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered adverse events, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee), including the pregnancy of a male participant's female partner, that occurs during the trial are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

9.3.7 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 9.4 – Treatment of Overdose, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director; however, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this trial.

9.4 Treatment of Overdose

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab (200 mg) by 5 times (ie, any dose higher than 1000 mg) in a 3-week time period. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and the

participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

9.5 Safety

Details regarding specific safety procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pretrial to posttrial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Procedure Manual.

Planned time points for all safety assessments are provided in the SoA.

9.5.1 Physical Examinations

9.5.1.1 Full Physical Examination

The investigator or qualified designee will perform a full physical examination during the Screening period and at the End of Treatment Visit. Clinically significant abnormal findings at Screening should be recorded as medical history. The time points for full physical examinations are described in Section 2. After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs.

9.5.1.2 Directed Physical Examination

For cycles that do not require a full physical examination as defined in Section 2, the investigator or qualified designee will perform a directed physical examination as clinically indicated prior to the administration of the study treatment. New clinically significant abnormal findings should be recorded as AEs.

9.5.2 Vital Signs

Vital signs include temperature, pulse, respiratory rate, weight, and blood pressure. The investigator or qualified designee will take vital signs at Screening, prior to the administration of each dose of trial treatment, and during the End of Treatment Visit as specified in the SoA (Section 2). Height will be measured at Visit 1 only. Vital signs are to be taken before blood collection for laboratory tests and measured once the participant has been in a seated position for 5 minutes. Due to site logistics, blood draw prior to vital signs may be approved after consultation with the Sponsor

9.5.3 Electrocardiograms

A standard 12-lead ECG will be performed using local standard procedures once at Screening and as clinically indicated thereafter. Clinically significant abnormal findings at Screening should be recorded in the medical history.

9.5.4 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days (or until the initiation of a new anticancer treatment, whichever occurs first) after the last dose of study treatment, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

There may be instances when sites are unable to obtain the thyroid function testing results prior to scheduled dosing. Review of thyroid function tests (FT3, FT4 and TSH) results after dosing is acceptable.

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn over the course of the trial (from pretrial to posttrial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Procedure Manual. Refer to the SoA (Section 2) for the timing of laboratory assessments.

9.5.4.1 Laboratory Safety Evaluations (Hematology, Chemistry, and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2. All safety laboratory tests must be performed by a central laboratory. After Cycle 1, predose safety laboratory tests may be collected up to 72 hours prior to study treatment administration. If central laboratory results are not expected prior to study treatment administration the investigator may also perform laboratory tests locally. Note: local laboratory may not be used in lieu of central laboratory.

9.5.4.2 Pregnancy Test

All women who are being considered for participation in the trial, and who are not surgically sterilized or postmenopausal (refer to Appendix 5 for definitions), must be tested for pregnancy within 72 hours of randomization. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the trial in the event of a positive or borderline-positive test result.

Monthly pregnancy testing should be conducted per local regulations where applicable.

9.5.5 Performance Assessments

9.5.5.1 Eastern Cooperative Oncology Group Performance Status (ECOG PS)

The investigator or qualified designee will assess ECOG PS (see Table 9) at Screening, prior to dosing on Day 1 of each treatment cycle through Cycle 17, at treatment discontinuation, at the Safety Follow-up Visit as specified in the SoA (Section 2). During the Follow-up period, ECOG PS is to be collected only if participants come in for a clinic visit (ie, during Follow-up).

Table 9 Eastern Cooperative Oncology Group Performance Status

GRADE	Eastern Cooperative Oncology Group Performance Status
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all self-care, but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.
5	Dead.

Oken M, Creech R, Tomey et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.[Oken, M. M., et al 1982]
http://www.ecog-acrin.org/resources/ecog-performance-status

9.6 Pharmacokinetics

Blood samples for PK and ADA analysis are no longer being collected under this protocol.

9.6.1 Blood Collection for RNA Analysis and Plasma and Serum Biomarker Analysis

Blood should be collected predose for Cycles 1, 2, and 5, at the time of discontinuation, and if the participant has disease recurrence during the Follow-up period. Leftover RNA, plasma, and serum will be stored at the end of the trial for Future Biomedical Research if the participant has consented (see Section 9.8).

Further details are provided in the Procedure Manual.

9.7 Pharmacodynamics

9.7.1 Tumor Tissue Collection

Tissue should be obtained from participants per the following parameters:

- Nephrectomy only: tissue from nephrectomy required for predominant analysis.
- Synchronous M1 NED: tissue from nephrectomy required for predominant analysis AND, when available, metastasectomy tissue for secondary analysis.
- Metachronous M1 NED: tissue from metastasectomy required for predominant analysis AND, when available, nephrectomy tissue for secondary analysis.

At disease recurrence, if a new core or excisional biopsy of a tumor is obtained as part of standard practice, information from the pathology report should be entered into the eCRF. If the participant signs the Future Biomedical Research consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for Future Biomedical Research. Details regarding time points for collection of tumor tissue are outlined in the SoA – Section 2. Include a copy of the local pathology report with the tissue for biomarker analysis.

Detailed instructions for tissue collection, processing, and shipment are provided in the Procedure Manual.

9.8 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of Future Biomedical Research:

- DNA for future research
- Leftover plasma and serum from biomarker analysis
- Leftover RNA
- Leftover main trial tumor tissue

9.9 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA (Section 2):

- Blood for genetic analysis
- Blood for RNA analysis
- Blood for TCR
- Plasma for biomarker analysis
- Blood for serum biomarker analysis

9.9.1 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the Procedure Manual.

Samples should be collected for planned analysis of associations between genetic variants in germline/tumor DNA and drug response. If a documented law or regulation prohibits (or local IRB/Independent Ethics Committee [IEC] does not approve) sample collection for these purposes, then such samples should not be collected at the corresponding sites.

Leftover DNA extracted from planned genetic analysis samples will be stored for future biomedical research only if participant signs the Future Biomedical Research consent.

9.10 Visit Requirements

Visit requirements are outlined in Section 2 – Schedule of Activities (SoA). Specific procedure-related details are provided above in Section 9 – Study Assessments and Procedures.

9.10.1 Screening

Within 42 days prior to treatment randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 6.1 and Section 6.2. Visit requirements are outlined in the SoA (Section 2). Screening procedures may be repeated after consultation with the Sponsor.

Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a Screening test if performed within the specified time frame. Screening procedures are to be completed within 42 days prior to randomization, except for the following:

- Laboratory tests are to be performed within 10 days prior to randomization.
- For WOCBP, a urine pregnancy test will be performed within 72 hours prior to randomization. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).
- CAP, bone, and brain imaging will be performed 28 days before randomization.

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments during the initial Screening period are acceptable in lieu of a repeat Screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. Participants who are rescreened will retain their original screening number.

9.10.2 Treatment Period Visits

Visit requirements are outlined in the SoA (Section 2). Specific procedure-related details are provided in Section 9.1.

Participants who discontinue study treatment for a reason other than disease recurrence will be considered as on study and should continue with regularly scheduled assessments, (also refer to Section 9.10.3), including collecting participant information on the start of new anticancer therapy, disease recurrence, and death.

9.10.3 End of Treatment Visit

The End of Treatment Visit should occur at the time study treatment is discontinued for any reason. If the End of Treatment Visit occurs at the same time as the mandatory Safety Follow-up Visit, the End of Treatment Visit procedures and any additional Safety Follow-up procedures should be performed. Visit requirements are outlined in the SoA (Section 2).

9.10.4 Posttreatment Period

Participants who complete study treatment, and participants who discontinue for a reason other than disease recurrence, will move to Follow-up phase.

All participants who complete study treatment and who discontinue for any reason will complete an End of Treatment Visit and a Safety Follow-up Visit. The End of Treatment Visit and Safety Follow-up Visit may occur simultaneously to accommodate the participant.

9.10.4.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted at least 30 days (+7 days) after the last dose of study treatment or before the initiation of a new anticancer treatment, whichever comes first.

9.10.4.2 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or who discontinue study treatment for a reason other than disease recurrence will continue to receive scans according to Section 9.2.1.3. At Week 60, participants will move into the Efficacy Follow-up period and should be assessed Q12W in year 1, Q16W in years 2, 3, and 4, and Q24W in year 5 and beyond to monitor disease status as outlined in the SoA (Section 2) and annually to collect quality of life data. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease recurrence, death, or end of trial. Information regarding posttrial anticancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter the Survival Follow-up Phase.

9.10.4.3 Survival Follow-up Contacts

Participant Survival Follow-up status will be assessed approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

The first Survival Follow-up contact should be scheduled as described below:

- For participants who discontinue treatment intervention and who will not enter the Efficacy Follow-up phase, the first Survival Follow-up contact will be scheduled 12 weeks after the discontinuation visit and/or Safety Follow-up Visit (whichever is last).

- For participants who completed assessments in the Efficacy Follow-up phase, the first Survival Follow-up contact will be scheduled 12 weeks after the last Efficacy Follow-up visit has been performed.

9.10.5 Discontinued Participants Continuing to be Monitored in the Study

Participants who discontinue study treatment for a reason other than disease recurrence will be considered as on study and should continue with regularly scheduled assessments (also refer to Section 9.10.3), including collecting participant information on the start of new anticancer treatment, disease recurrence, and death.

9.10.6 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to, but not limited to an external

Data Monitoring Committee (eDMC) review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a previously recorded death event in the collection tool).

9.11 Medical Resource Utilization and Health Economics

All-cause hospitalizations and emergency department visits must be reported in the eCRF, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment, if the participant initiates new anticancer therapy, whichever is earlier.

10. Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analysis, will be documented in a sSAP and referenced in the Clinical Study Report for the study. Separate analysis plans may be developed for PK/modeling analysis, biomarker analysis, and genetic data analysis. Post hoc exploratory analyses will be clearly identified in the Clinical Study Report. The PRO analysis plan will be included in the sSAP.

10.1 Statistical Analysis Plan Summary

Key elements of the Statistical Analysis Plan are summarized below; the comprehensive plan is provided in Section 10.2 through Section 10.12.

Study Design Overview	This is a randomized, double-blind, multicenter Phase 3 trial to evaluate the efficacy and safety of pembrolizumab versus placebo as an adjuvant treatment for RCC post nephrectomy.
Treatment Assignment	Approximately 950 participants will be randomized 1:1 into the following 2 treatment arms: pembrolizumab 200 mg or matching placebo (saline 200 mg infusion) administered IV Q3W. Stratification factors are provided in Section 7.3.1.
Analysis Populations	Efficacy: Intention-to-Treat Safety: All Participants as Treated
Primary Endpoints	DFS as assessed by the investigator
Key Secondary Endpoints	OS
Statistical Methods for Key Efficacy Analyses	The primary and secondary hypotheses addressing DFS and OS will be evaluated by comparing pembrolizumab to placebo using a stratified log-rank test. Estimation of the hazard ratio will be done using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.

Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. There are no Tier 1 events in this trial. Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The 95% CI for the between-treatment differences in percentages will be provided using the Miettinen and Nurminen method.
Interim and Final Analyses	Three interim analyses are planned for the study (one interim analysis for DFS and 3 interim analyses for OS). Results will be reviewed by an external data monitoring committee. Details are provided in Section 10.7. • IA1 o Purpose: Interim analysis for DFS and OS. o Timing: When at least 265 disease recurrence events by investigator assessment have accrued and a minimum follow-up (time from last participant randomized to IA1) of 12 months is achieved. Approximately 94 OS events are expected at this time. • IA2 o Purpose: Final analysis for DFS and interim analysis for OS o Timing: Final analysis of DFS when approximately 332 DFS events by investigator assessment have accrued if DFS is not rejected at IA1, Approximately 132 OS events are expected at this time. • IA3 o Purpose: Interim analysis for OS o Timing: When approximately 172 OS events have accrued, • Final analysis (FA) o Purpose: Final analysis for OS o Timing: When approximately 200 OS events have accrued,
Multiplicity	The overall Type I error rate is strongly controlled at 2.5% (1-sided) with a fixed sequence testing procedure to test DFS at alpha level of 2.5% (1-sided) first and pass the alpha to OS if the hypothesis test of DFS is declared successful. A group sequential approach will be used to allocate alpha between the interim and final analyses. The study will be considered a success if DFS is demonstrated to be statistically significant under multiplicity control. Note that if the statistical criterion for success for DFS is met at an IA, a regulatory application may be submitted based on DFS for a full approval consideration and the study could still continue for OS.
Sample Size and Power	The sample size was planned for 950, but the following power calculations are based on 990, which is a number more in line with the actual final number of randomized subjects. DFS is the primary endpoint for this study. The expected median DFS time in the control group is 45 months; based on 332 events and a Poisson mixture cure rate model with assumed cure rate of 0.3, the study has 95% power to detect a hazard ratio of 0.67 (pembrolizumab versus placebo) at alpha = 2.5% (1-sided).

10.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

The Sponsor will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented in IVRS/IWRS.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete. In addition, blinded independent central imaging review will be performed on imaging scans without knowledge of the treatment group assignments of participants.

Planned interim analyses are described in Section 10.7. Blinding to treatment assignment will be maintained at all investigational sites. The results of interim analyses will not be shared with the investigators prior to the completion of the study. Participant-level unblinding will be restricted to an external unblinded statistician and external unblinded scientific programmer performing the interim analysis, who will have no other responsibilities associated with the study.

Treatment-level results of the interim analysis will be provided by the unblinded statistician to the external data monitoring committee (eDMC). Limited additional Sponsor personnel may be unblinded to the treatment-level results of the interim analysis (analyses), if required, in order to act on the recommendations of the eDMC. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the unblinded statistician.

The eDMC will serve as the primary reviewer of the unblinded results of the DFS and OS at interim analyses and will make recommendations for discontinuation of the study or modification to an EOC of the Sponsor. Depending on the recommendations of the eDMC, the Sponsor may prepare a regulatory submission. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, the EOC may be unblinded to results at the treatment level in order to evaluate and direct the Sponsor protocol team as to the appropriate actions to be taken on these recommendations. Additional logistical details, revisions to the above plan, and data monitoring guidance will be provided in the DMC Charter.

Prior to final study unblinding, the unblinded statistician and unblinded scientific programmer will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

10.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 4.

10.4 Analysis Endpoints

10.4.1 Efficacy Endpoints

10.4.1.1 Primary

Disease-Free Survival

DFS, as assessed by the investigator, is defined as the time from randomization to the first documented local recurrence, or occurrence of distant kidney cancer metastasis(es), or death due to any cause, whichever occurs first. See Section 10.6.1 for the censoring rules.

10.4.1.2 Secondary

Overall Survival

OS is defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis will be censored at the date of the last follow-up.

Disease Recurrence-Specific Survival

- DRSS1 is defined as the time from randomization to the first documented local recurrence of RCC as assessed by the investigator.
- DRSS2 is defined as the time from randomization to the first documented local recurrence with visceral lesion or occurrence of distant kidney cancer metastasis(es) with visceral lesion, whichever occurs first, as assessed by the investigator.

Event-Free Survival

EFS is to be assessed by BICR. EFS is defined as time from randomization to the first documented local recurrence or occurrence of distant kidney cancer metastasis(es) among participants, which by BICR were considered disease-free at baseline (M0/M1 NED); or disease progression among participants, which by BICR were considered to have baseline disease (M1), or death due to any cause, whichever occurs first. See Section 9.2.1 for the definition of disease progression.

10.4.2 Safety Endpoints

Safety endpoints are described in Section 5.4.1.2.

10.5 Analysis Population

10.5.1 Efficacy Analysis Population

The Intention-to-Treat population will serve as the population for the primary and key secondary efficacy analyses. All randomized participants will be included in this population. Participants will be analyzed in the treatment group to which they are randomized.

10.5.2 Safety Analysis Population

The All Participants as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who received at least 1 dose of study treatment. Participants will be analyzed in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. For most participants this will be the treatment group to which they are randomized. Participants who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received. Any participant who receives the incorrect study treatment for one cycle, but receives the correct treatment for all other cycles will be analyzed according to the correct treatment group and a narrative will be provided for any events that occur during the cycle for which the participant is incorrectly dosed.

At least 1 laboratory measurement obtained subsequent to at least 1 dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

10.6 Statistical Methods

10.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives on OS and disease recurrence-specific survival. Methods related to the secondary objective, PROs, as well as exploratory objectives will be described in the sSAP.

Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 10.8 – Multiplicity. Nominal p values may be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity.

10.6.1.1 Disease-Free Survival

The nonparametric Kaplan-Meier method will be used to estimate the DFS curve in each treatment group. The hypotheses addressing a treatment difference in DFS will be tested by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to estimate the magnitude of the treatment difference (ie, hazard ratio [HR]) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 7.3.1) will be applied to both the stratified log-rank test and the stratified Cox model.

Since participants enrolled with baseline disease by BICR could have a different time to event distribution compared to participants who were disease-free at baseline by BICR, a sensitivity analysis will be performed using the stratified Cox model and stratified log-rank test with stratification factors used for randomization with baseline disease status by BICR as an additional stratum.

Since disease recurrence is assessed periodically, disease recurrence can occur any time in the time interval between the last assessment when disease recurrence was not documented and the assessment when disease recurrence is documented. For the primary analysis, for the participants who have disease recurrence (local recurrence or occurrence of distant kidney cancer metastasis(es)) as assessed by the investigator's review, the true date of disease recurrence will be approximated by the date of the first assessment at which disease recurrence is objectively documented, regardless of discontinuation of study treatment. Death is always considered as a confirmed disease recurrence event.

In order to evaluate the robustness of the DFS endpoint, a sensitivity analysis with a different set of censoring rules may be performed. The sensitivity analysis is the same as the primary analysis except that events after 2 consecutive missed disease assessments or after new anticancer therapy, if any, should be censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessments and new anticancer therapy.

The censoring rules for primary and sensitivity analysis are summarized in Table 10.

Table 10 Censoring Rules for Primary and Sensitivity Analysis of Disease-Free Survival

Situation	Primary Analysis	Sensitivity Analysis
No recurrence and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment
No recurrence and no death; new anticancer treatment is initiated	Censored at last disease assessment	Censored at last disease assessment before new anticancer treatment
Recurrence or death documented after ≤1 missed disease assessment and before new anticancer treatment, if any	Event at date of documented recurrence or death	Event at date of documented recurrence or death
Recurrence or death documented immediately after ≥2 consecutive missed disease assessments, or after new anticancer treatment, if any	Event at date of documented recurrence or death	Censored at the last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessments and new anticancer treatment, if any

The proportional hazards assumption on DFS will be examined using both graphical and analytical methods if warranted. The log [-log] of the survival function versus time for DFS will be plotted for the comparison between pembrolizumab and the placebo arm. If the curves are not parallel, indicating that hazards are not proportional, supportive analyses may be conducted to account for the possible nonproportional hazards effect associated with immunotherapies: for example, using the Restricted Mean Survival Time method [Uno, H., et al 2014] and parametric method [Odell, P. M., et al 1994]. Further details of sensitivity analyses will be described in the sSAP.

10.6.1.2 Overall Survival

The nonparametric Kaplan-Meier method will be used to estimate the survival curves. The hypotheses of treatment difference in survival will be tested by the stratified log -rank test.

A stratified Cox proportional hazard model with Efron's method of tie handling will be used to estimate the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization will be applied to both the stratified log-rank test and the stratified Cox model.

The OS analysis will be conducted according to the hypothesis testing plan as described in Section 10.7 and Section 10.8.

10.6.1.3 Disease Recurrence-Specific Survival

The nonparametric cumulative incidence estimator will be used to estimate the DRSS1 and DRSS2 curves in each treatment group. For DRSS1, only local recurrence is counted as an event. Death, or occurrence of distant kidney cancer metastasis(es) will be censored at documented date of disease metastasis or death, whichever occurs first. For DRSS2, only disease recurrence with visceral lesion is counted as an event. Death, local recurrence without visceral lesion, distant metastasis without visceral lesion will be censored at documented date of disease recurrence or death, whichever occurs first.

10.6.1.4 Event-Free Survival

The nonparametric Kaplan-Meier method will be used to estimate the EFS curve in each treatment group. Although no formal hypothesis will be performed for testing the treatment difference in EFS, nominal p-value from stratified log-rank test will be provided to serve as a sensitivity analysis for the primary endpoint of DFS by investigator. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to estimate the magnitude of the treatment difference (ie, hazard ratio [HR]) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 7.3.1) with baseline disease status by BICR as an additional stratum will be applied to both the stratified log-rank test and the stratified Cox model.

10.6.1.5 Summary of Analysis Strategy

Table 11 summarizes the primary analysis approach for primary and key secondary efficacy endpoints. Sensitivity analysis methods are described above for DFS.

The strategy to address multiplicity issues with regard to multiple efficacy endpoints, multiple populations, and interim analyses is described in Section 10.7 - Interim Analyses and in Section 10.8 - Multiplicity.

Table 11 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method[a]	Analysis Population	Missing Data Approach
Primary Hypothesis			
DFS as assessed by the investigator	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	• Primary censoring rule • Sensitivity analysis
Key Secondary Hypothesis			
OS	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at the last date the participant was known to be alive

ITT = Intention-to-Treat; OS = overall survival; DFS = disease-free survival

[a]Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization (see Section 7.3.1) will be applied to the analysis model.

10.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and laboratory tests.

Tiered Approach

The analysis of safety results will follow a tiered approach (Table 12). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p values and 95% CI provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. There is no expectation of enhanced safety signal in this adjuvant study other than safety signals of which we are already aware from past studies. Participants do not have tumor burden and their existing safety profile might be less intensive. Hence, we do not expect any new safety signals. Therefore there are no events of interest that will be analyzed as Tier 1 safety endpoints in this study.

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

AEs (specific terms as well as system organ class terms) will be classified as belonging to "Tier 2" or "Tier 3," based on the number of events observed. Membership in Tier 2 requires that at least 10% of the subjects in any treatment group exhibit the event; all other AEs and predefined limits of change will belong to Tier 3.

The threshold of at least 10% of subjects with events was chosen because the incidence rate would allow meaningful statistical assessments; events reported in less frequent than 10% of subjects would obscure the assessment of overall safety profile and add little to the meaningful interpretation. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AEs and predefined limits of change.

Continuous measures such as changes from baseline in laboratory values that are not prespecified as Tier 1 safety parameters will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

In addition, the broad clinical and laboratory AE categories consisting of the percentage of participants with Grade 3-5 AE (incidence ≥5% of subjects in one of the treatment groups) and SAE (incidence ≥5% of subjects in one of the treatment groups) will be considered Tier 2 endpoints.

The threshold of at least 5% of subjects with events was chosen for Tier 2 Grade 3-5 AEs and SAEs because the incidence rate would allow meaningful statistical assessments; those AEs are expected to happen less frequent than specific AEs/SOCs, but important for overall safety profile assessment.

The broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, any Grade 3-5 AE, any SAE, any drug-related AE, any AE that is both drug-related and Grade 3-5, any AE that is both serious and drug-related, dose modification due to AE, discontinuation due to an AE, death, and specific AEs or SOCs with incidence <10% of subjects in all of the treatment groups will be considered Tier 3 endpoints.

Note that 95% CIs will be provided for between-treatment differences in the percentage of participants with Tier 2 events; these analyses will be performed using the Miettinen and Nurminen method, an unconditional, asymptotic method.

Table 12 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	**Specific Serious AE (incidence ≥5% of subjects in one of the treatment groups)**	**X**	**X**
	Specific Grade 3-5 AE (incidence ≥5% of subjects in one of the treatment groups)	**X**	**X**
	Specific AEs or SOCs (incidence ≥10% of subjects in one of the treatment groups)	**X**	**X**
Tier 3	**Any AE**		**X**
	Any Serious AE		**X**
	Any Grade 3-5 AE		**X**
	Any drug-related AE **Any Serious and Drug-related AE**		**X** **X**
	Any Grade 3-5 and Drug-related AE		**X**
	Dose Interruption due to AE **Discontinuation due to AE** **Death**		**X** **X** **X**
	Specific AEs or SOCs (incidence <10% of subjects in all of the treatment groups)		**X**
	Change from Baseline Results (Labs, ECGs, Vital Signs)		**X**

Abbreviations: AE = adverse event; CI = confidence interval; ECG = electrocardiogram; PDLC = predefined limit of change; SOC = system organ class.

10.6.3 Summaries of Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized, and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (eg, age), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

10.7 Interim Analyses

10.7.1 Safety Interim Analyses

The eDMC has responsibility for assessment of overall risk:benefit. The eDMC will review safety periodically with reviews about every 6 months in the first year and every 12 months thereafter. When prompted by safety concerns, the eDMC can request corresponding efficacy data. eDMC review of efficacy data to assess the overall risk:benefit to trial participants will

not require multiplicity assessment typically associated with a planned efficacy interim analysis. Any eDMC recommendation will be communicated to the Sponsor as agreed to in the eDMC charter.

10.7.2 Efficacy Interim Analyses

Three interim analyses are planned in addition to the final analysis for this trial. Results of the interim analyses (IA) will be reviewed by an eDMC. If both DFS and OS null hypotheses are rejected prior to the final analysis, the eDMC may recommend stopping the trial early for efficacy. At each IA, the eDMC may also recommend stopping the trial early for futility. Details on how the above planned analyses are incorporated into establishing statistical significance and the boundaries with regard to efficacy and futility are discussed further in Section 10.8, Multiplicity.

The analyses planned, endpoints evaluated and drivers of the timing are summarized in Table 13.

Table 13 Analyses Planned, Endpoints Evaluated, and Drivers of Timing

Analysis	Endpoint(s)	Timing
IA1	DFS, OS	Enrollment complete and at least 265 DFS events by investigator assessment have occurred and a minimum follow-up (time from last participant randomized to IA1) of 12 months is achieved.
IA2	DFS, OS	332 DFS events; if DFS rejected before IA2, timing driven by 132 OS events
IA3	OS	172 OS events
FA	OS	200 OS events

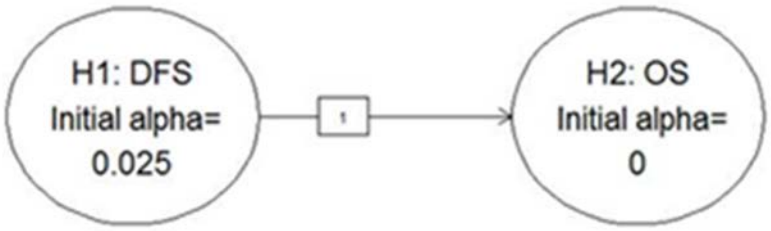
Abbreviations: DFS = disease-free survival; FA = Final analysis; IA1 – first interim analysis; IA2 = second interim analysis; IA3 = third interim analysis; OS = overall survival

10.8 Multiplicity

10.8.1 Multiplicity Control for Efficacy Analyses

The trial uses the method of Maurer and Bretz (2013)[Maurer, W. 2013] to provide strong multiplicity control for multiple hypotheses as well as interim analyses. Figure 2 shows the initial one-sided α-allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses. This is further explained below.

Figure 2 Multiplicity Graph for Type I Error Control of Study Hypotheses



Abbreviations: DFS = disease-free survival; OS = overall survival

If the DFS null hypothesis is rejected at the 2.5% level, then the OS null hypothesis may be formally evaluated for statistical significance at the 2.5% level. For each endpoint, group sequential methods will be used to adjust for the interim and final analyses planned. If the DFS null hypothesis is rejected at an interim or final analysis, each OS interim and final analysis test may be compared to its rejection boundary for formal testing. For instance, the OS hypothesis will not be formally evaluated for statistical significance until the DFS null hypothesis is rejected.

For DFS, the information fraction at each analysis will be based on the final planned number of 332 events. A Lan-DeMets O'Brien-Fleming spending approximation α-spending function is used to set efficacy bounds. Nonbinding futility spending is done by controlling the probability of crossing the futility bound under the null hypothesis (total of $1-\alpha=97.5\%$); a HSD spending function with $\gamma= -6$ is used to set testing boundaries at each analysis.

For OS, the information fraction at each analysis will be based on the final planned number of 200 deaths. A Lan-DeMets O'Brien-Fleming spending approximation α-spending function is used to set efficacy bounds. As with DFS, nonbinding futility spending is done by controlling the probability of crossing the futility bound under the null hypothesis (total of $1-\alpha=97.5\%$); an HSD spending function with $\gamma= -6$ is used to set testing boundaries at each analysis.

Bounds at the expected number of events for each hypothesis at each analysis of DFS and OS are shown in Table 14 and Table 15, respectively. Bounds will be adjusted according to the actual number of events at each analysis.

Table 14 Boundary Properties for Planned Interim and Final Analyses for DFS

Analysis	Value	Efficacy	Futility[a]
IA1: 80% (First Interim for DFS)	Z	2.2504	-0.5476
N: 990	p (1-sided)	0.0122	0.7080
Events: 265	HR at bound	0.7584	1.0696
Month: 39	P(Cross) if HR=1	0.0122	0.2920
	P(Cross) if HR=0.67	0.8402	0.0001
IA2: (Final Analysis for DFS)	Z	2.0249	2.0249
N: 990	p (1-sided)	0.0214	0.0214
Events: 332	HR at bound	0.8005	0.8005
Month: 50	P(Cross) if HR=1	0.0250	0.9750
	P(Cross) if HR=0.67	0.9490	0.0510

Abbreviations: DFS = disease-free survival; FA = Final analysis; HR = hazard ratio; IA1 – first interim analysis; IA2 = second interim analysis; OS = overall survival
[a] Futility boundary is nonbinding.

Table 15 Boundary Properties for Planned Interim and Final Analyses for OS

Analysis	Value	Efficacy	Futility[a]
IA1: 47% (First Interim for OS)	Z	3.0679	-1.7717
N: 990	p (1-sided)	0.0011	0.9618
Events: 94	HR at bound	0.5305	1.4421
Month: 39	P(Cross) if HR=1	0.0011	0.0382
	P(Cross) if HR=0.67	0.1280	0.0001
IA2: 66% (Second Interim for OS)	Z	2.5455	-1.1786
N: 990	p (1-sided)	0.0055	0.8807
Events: 132	HR at bound	0.6416	1.2281
Month: 50	P(Cross) if HR=1	0.0058	0.1247
	P(Cross) if HR=0.67	0.4033	0.0003
IA3: 86% (Third Interim for OS)	Z	2.2023	-0.2090
N: 990	p (1-sided)	0.0138	0.5828
Events: 172	HR at bound	0.7143	1.0324
Month: 63	P(Cross) if HR=1	0.0157	0.4195
	P(Cross) if HR=0.67	0.6688	0.0025
Final	Z	2.0534	2.0534
N: 990	p (1-sided)	0.0200	0.0200
Events: 200	HR at bound	0.7476	0.7476
Month: 72	P(Cross) if HR=1	0.0250	0.9750
	P(Cross) if HR=0.67	0.7930	0.2070

Abbreviations: DFS = disease-free survival; FA = Final analysis; HR = hazard ratio; IA1 – first interim analysis; IA2 = second interim analysis; IA3 = third interim analysis; OS = overall survival
[a] Futility boundary is nonbinding.

10.8.2 Multiplicity Control for Safety Analyses

To account for any multiplicity concerns raised by the DMC review of unplanned efficacy data when prompted by safety concerns, a sensitivity analysis for DFS and OS will be pre-specified in the sSAP. This analysis will be performed if requested by the eDMC. However, eDMC review of DFS and OS data beyond the planned efficacy analysis to assess the overall risk:benefit to trial participants will not require multiplicity assessment typically associated with a planned efficacy IA because these analyses are not to declare a positive efficacy finding.

10.9 Sample Size and Power Calculations

The study will randomize participants in a 1:1 ratio into the pembrolizumab and placebo arms. DFS and OS are the primary endpoint and key secondary endpoint, respectively. The sample size was planned for 950, but the following power calculations are based on 990, which is a number more in line with the actual final number of randomized participants.

For the DFS endpoint, based on a target number of 332 events and one IA at approximately 80% of the target number of events, the study has approximately 95% power to detect a HR of 0.67 at an overall alpha level of 2.5% (1-sided).

For the OS endpoint, the power is conditional on the null hypothesis of DFS being rejected, based on a target number of 200 events and 3 interim analyses at approximately 47%, 66%, and 86% of the target number of events, the study has approximately 79% power to detect a HR of 0.67 or approximately 88% power to detect a HR of 0.635 at an overall alpha level of 2.5% (1-sided).

The above sample size and power calculations for DFS and OS assume the following:

- DFS follow a Poisson mixture cure rate model [de Castro, M., et al 2010] with assumed cure rate of 0.3. The cure rate of 0.3 is estimated based on historical data [Leibovich, B. C., et al 2003].
- The median DFS is assumed to be 45 months for those not cured in the control group.
- OS follows an exponential distribution with a median of 145 months for the control group.
- Enrollment period of 27 months with monthly accrual of 20 participants during the first 5 months and monthly accrual of 30 participants from month 6 to month 21, and monthly accrual of 1 participant for the last month.
- A yearly drop-out rate of 2% for DFS and 1% for OS.

Technical details on the Poisson mixture cure rate model are in Appendix 7. The sample size and power calculation were performed using R (package “gsDesign”).

10.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint will be estimated and plotted within each category of the following classification variables:

- ECOG PS (0, 1)
- Metastasis status (M0, M1 NED)
- Type of nephrectomy (Radical, Partial)
- Geographic region (US, Non-US)
- PD-L1 status (Positive, Negative)
- Age (<65, ≥65 years)
- Sex (Female, Male)
- Race (white, non-white)
- Baseline disease status by BICR (M0/M1 NED, M1)

Country-specific populations may also be analyzed per local regulatory requirements.

10.11 Compliance (Medication Adherence)

Drug accountability data for study treatment will be collected during the study. Any deviation from protocol-directed administration will be reported.

10.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in cycles. Summary statistics will be provided on extent of exposure for the APaT population.

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12. Appendices

12.1 Appendix 1: Abbreviations and Trademarks

Abbreviation	Definition
ADA	antidrug antibodies
AE	adverse event
APaT	All Participants as Treated
aPTT	activated partial thrombin time
β-hCG	β-human chorionic gonadotropin
BICR	blinded independent central review
CAP	chest, abdomen, and pelvis
CD28	cluster of differentiation 28
CI	confidence interval
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte protein 4
DFS	disease-free survival
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DRSS	disease recurrence-specific survival
ECG	electrocardiogram
ECI	events of clinical interest
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EDC	electronic data collection
eDMC	external data monitoring committee
EFS	event-free survival
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC-QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30
EQ-5D-5L	EuroQoL 5 Dimensions 5 Levels
FDA	United States Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FKSI-DRS	Functional Assessment of Cancer Therapy Kidney Symptom Index - Disease-Related Symptoms
FSH	follicle-stimulating hormone
FT4	free thyroxine
GEP	gene expression profiling
HCV	hepatitis C virus
HR	hazard ratio
HRQoL	health-related quality of life
HSD	Hwang-Shih-DeCani

Abbreviation	Definition
IA1	first interim analysis
IA2	second interim analysis
ICF	informed consent form
IEC	Independent Ethics Committee
IFN	interferon
IFNα	interferon-alpha
IFNγ	interferon-gamma
Ig	immunoglobulin
IHC	immunohistochemistry
IL-2	interleukin-2
INR	international normalized ratio
irAE	immune-related AE
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
IVRS	interactive voice response system
IWRS	integrated web response system
M	distant metastasis
M1 NED	M1 no evidence of disease
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
OS	overall survival
PD-1	programmed cell death protein 1
PD-L1/PD-L2	programmed cell death ligand 1/2
PK	pharmacokinetic
PRO	patient-reported outcome
PT	prothrombin time
Q3W	every 3 weeks
Q12W	every 3 months
Q16W	every 4 months
Q24W	every 6 months
QoL	quality of life
RCC	renal cell carcinoma
RNA	ribonucleic acid
SAC	Scientific Advisory Committee
SAE	serious adverse event
SoA	schedule of activities
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reactions
T1DM	Type 1 diabetes mellitus
T3	triiodothyronine
TCR	T cell repertoire

Abbreviation	Definition
TSH	thyroid-stimulating hormone
US	United States
WOCBP	woman of childbearing potential

12.2 Appendix 2: Clinical Laboratory Tests

Table 16 will be performed by the central laboratory.

- Use of central laboratory is required.
- Clinical laboratory tests may be performed by a local laboratory if the investigator deems it necessary, or if the central laboratory results are not expected in time to make a study treatment decision (eg, central laboratory specimen was drawn predose on Day 1 of infusion).
- If a significant difference (e.g. one lab results report normal labs and the other lab results report an AE for the same timepoint) is noted between local and central labs the discordant lab result(s) must be entered into the eCRF.
- If local laboratory specimens are drawn for scheduled timepoints, duplicate specimens MUST also be submitted to central laboratory.
- If the local laboratory results are used for a response evaluation, adverse event assessment, or other reason as directed by Sponsor (eg. Central lab was unable to perform a test, but the local lab has results for the same timepoint) the results must be entered into the eCRF.

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 16 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes		WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate[a]	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • Glucose, protein, blood, by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Serum or urine β human chorionic gonadotropin (β-hCG) pregnancy test (as needed for WOCBP)[b] • Serology (human immunodeficiency virus antibody)[d] • PT/INR • aPTT • Total T3 or free T3, FT4, and TSH[c] • All study-required laboratory assessments will be performed by a central laboratory, with the exception of: pregnancy testing			

aPTT=activated partial thrombin time; FT4=free thyroxine; INR=international normalized ratio; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PT=prothrombin time; RBC=red blood cells; T3=triiodothyronine; TSH=thyroid-stimulating hormone (thyrotropin); WBC=white blood cells

NOTES:

[a] If this test is not done as part of local standard of care, this test does not need to be performed.

[b] Perform on women of childbearing potential within 72 hours prior to randomization. Pregnancy tests must be repeated prior to every cycle or monthly, as required or as specified per local regulatory guidance.

[c] T3 is preferred; if not available free T3 may be tested.

[d] Only if mandated by local health authority. If the local laboratory is unable to perform these tests, the site should submit the sample to the central laboratory for testing. Details are provided in the Procedure Manual.

NOTE: Report % or absolute results per standard of practice. Report the results in the same manner throughout the trial.

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Laboratory tests for Screening should be performed within 10 days prior to randomization. After Cycle 1, predose laboratory safety tests can be conducted up to 72 hours prior to dosing unless otherwise noted on the flow charts.

Laboratory test results must be reviewed by the investigator or qualified designee and found to be acceptable prior to administration of each dose of study treatment. Unresolved abnormal laboratory values that are drug-related AEs should be followed until resolution. Laboratory tests do not need to be repeated after the end of treatment if laboratory results are within the normal range.

Investigators must document their review of each laboratory safety report.

12.3 Appendix 3: Study Governance Considerations

Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participant safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine participant preferences, etc.

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Participant Protection

A. IRB/IEC review

All clinical trials will be reviewed and approved by an independent IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/IEC prior to implementation, except that changes required urgently to protect participant safety and well-being may be enacted in anticipation of IRB/IEC approval. For each site, the IRB/IEC and Merck will approve the participant informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Participants are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Participants are enrolled only after providing informed consent for participation. Participants may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research participant by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for participant referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/IEC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (eg, to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/IEC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the participant agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

Committees Structure

Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

Executive Oversight Committee

The Executive Oversight Committee (EOC) comprises members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the eDMC regarding the trial.

Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (DMC) will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the trial in any other way (eg, they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 10.7 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

Publication Policy

The results of this study may be published or presented at scientific meetings. The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the sponsor, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are participant to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in this appendix under the Merck Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

The Investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection, and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or regulatory authority as a result of an audit or inspection to cure deficiencies in the trial documentation and worksheets/case report forms.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the

study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Site Closure

The sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

12.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment. • NOTE: for purposes of AE definition, study treatment (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the sponsor for human use.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. • For all reports of overdose (whether accidental or intentional) with an associated adverse event, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect." ● Any new cancer (that is not a condition of the study). Note: Progression of the cancer under study is not a reportable event. Refer to Section 9.3.5 for additional details.

Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened. • Refer to section 9.3.5 for protocol specific exceptions

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening ● The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization ● Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.
d. Results in persistent or significant disability/incapacity ● The term disability means a substantial disruption of a person's ability to conduct normal life functions. ● This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- in offspring of participant taking the product regardless of time to diagnosis

f. Other important medical events:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Additional Events reported as SAE

Additional Events which require reporting in the same manner as SAE

- In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.
  - Is a new cancer (that is not a condition of the study);
  - Is associated with an overdose.

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the Adverse Event case report forms/worksheets at each examination.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.
  - Grade 1: Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

Assessment of Causality

- Did the Sponsor's product cause the adverse event?
  - The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the adverse event based upon the available information
  - **The following components are to be used to assess the relationship between the Sponsor's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:

- **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
  - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
  - If no, this is a negative dechallenge.

  (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this trial?
  - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
  - If no, this is a negative rechallenge.

  (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.

- **Consistency with Study treatment Profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship: There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
  - No, there is not a reasonable possibility of Sponsor's product relationship: Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)
  - For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
  - The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
  - The causality assessment is one of the criteria used when determining regulatory reporting requirements

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of AE, SAE, and Other Reportable Safety Events to the Sponsor

AE, SAE, and Other Reportable Safety Event Reporting to Sponsor via Electronic Data Collection Tool

● The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
  ● Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  ● If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  ● Reference section 9.3.1 – Time Period and Frequency for Collecting AE and SAE and Other Reportable Safety Event Information for reporting time requirements
● The site will enter the SAE data into the electronic system as soon as it becomes available.
● After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
● If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
● Contacts for SAE reporting can be found in the Investigator Trial File Binder (or equivalent).

SAE Reporting to the Sponsor via Paper CRF
● If the electronic data collection tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor. ● In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. ● Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. ● Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

12.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

Contraception Requirements

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

For this trial, male participants will be considered to be of nonreproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female participants will be considered of nonreproductive potential if they meet 1 of the following criteria:

- She is postmenopausal, defined as at least 12 months with no menses without an alternative medical cause. In women <45 years of age who are not using hormonal contraception or hormonal replacement therapy, a high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- She had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to Screening.
- She has a congenital or an acquired condition that prevents childbearing.

Female and male participants of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving trial drug and for 120 days after the last dose of trial drug by complying with 1 of the following:

- Practice abstinence from heterosexual activity.

Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the participant's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and IRBs/IECs. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

- Use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are[a]:

- Single method (1 of the following is acceptable):
    - Intrauterine device (IUD)
    - Vasectomy of a female participant's male partner
    - Contraceptive rod implanted into the skin
- Combination method (requires use of 2 of the following):
    - Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
    - Cervical cap with spermicide (nulliparous women only)

- Contraceptive sponge (nulliparous women only)
- Male condom or female condom (cannot be used together)
- Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

[a]If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for participants participating at sites in this country/region.

Participants should be informed that taking the trial medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the trial. In order to participate in the trial, participants of childbearing potential must adhere to the contraception requirement (described above) from the day of trial medication initiation (or 14 days prior to the initiation of trial medication for oral contraception) throughout the trial period up to 120 days after the last dose of trial medication. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the trial.

Pregnancy

If a female participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from trial treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The trial investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male participant impregnates his female partner, the trial personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 9.3.1 (Table 8).

Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breastfeeding are not eligible for enrollment.

12.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this trial as outlined in Section 9.8 – Future Biomedical Research Sample Collection will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Participants for Enrollment

All participants enrolled in the clinical trial will be considered for enrollment in Future Biomedical Research.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future

Biomedical Research should be presented to the participants on the visit designated in the trial flow chart. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the participant is having blood drawn for other trial purposes.

4. Confidential Participant Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link participant' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in the future biomedical research protocol and consent. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for Future Biomedical Research and ask that their biospecimens not be used for Future Biomedical Research. Participants may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for Future Biomedical Research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the participant’s personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the

participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized. No additional risks to the participant have been identified as no additional specimens are being collected for Future Biomedical Research (ie, only leftover samples are being retained).

The Sponsor has developed strict security, policies and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf
3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

12.7 Appendix 7: Poisson Mixture Model

The Poisson mixture model is applied to account for the failure rates decreasing over time in a trial in which the patient population is a mixture of participants who are susceptible to disease recurrence and participants who would not have a disease recurrence event after long-term follow-up. The latter participants are called long-term survivors. The Poisson mixture model assumes a survival function [de Castro, M., et al 2010] for a control group (c) as a function of time (t), as follows:

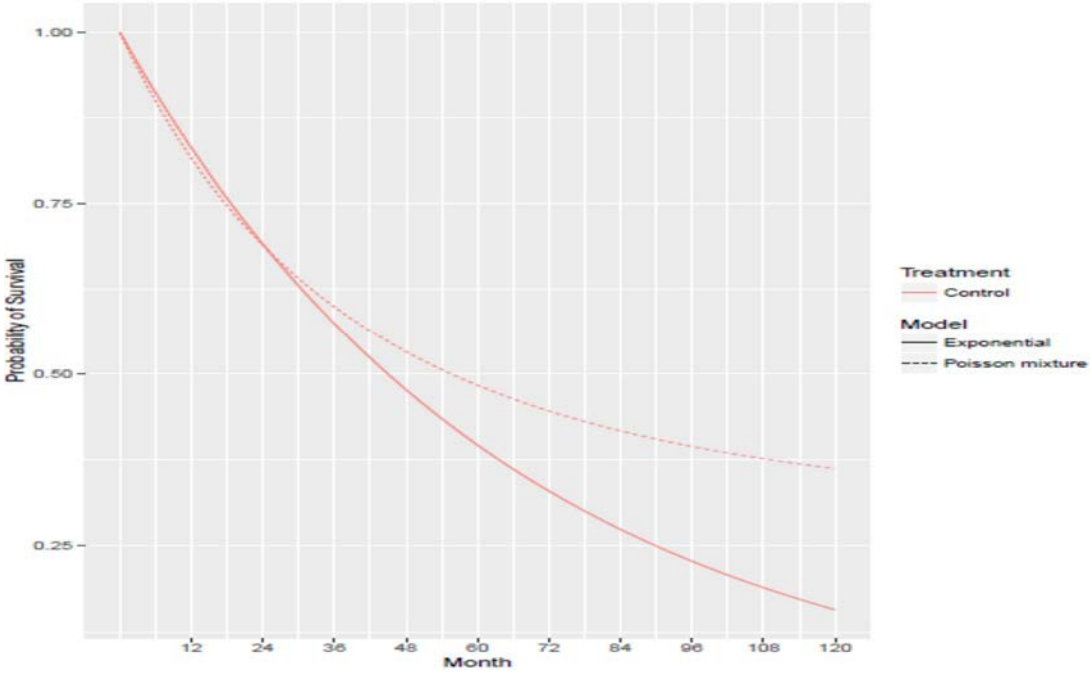
$$S(t) = \exp(-\theta(1-\exp(-\lambda t))$$

where $\theta = -\log(Cure\_Rate)$, λ is a constant hazard rate, and $t \geq 0$.

In the adjuvant setting, according to the published literature [Leibovich, B. C., et al 2003] and study assumptions, ~30% participants will be long-term survivors or will be cured in the long-term (ie, Cure_Rate=0.3), and it is more likely that after approximately 5 to 6 years after study initiation there will be minimal accumulation of DFS events.

According to the published literature [Leibovich, B. C., et al 2003], it is assumed that DFS follows a Poisson mixture model distribution with median DFS of 45 months in the placebo group. Figure 3 below shows the DFS curves using the Poisson mixture model and exponential model. Compared to the curve from the exponential model, the curve from the Poisson mixture model looks more similar to the curve in the published literature.

Figure 3 Disease-Free Survival Curves Using the Poisson Mixture Model and Exponential Model



Supplemental Statistical Analysis Plan (sSAP)

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1. INTRODUCTION

This supplemental SAP (sSAP) is a companion document to the protocol. In addition to the information presented in the protocol SAP which provides the principal features of confirmatory analyses for this trial, this supplemental SAP provides additional statistical analysis details/data derivations and documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

2. SUMMARY OF CHANGES

Section # and Name	Description of Change	Brief Rationale
3.1 Statistical Analysis Plan Summary 3.7.2 Efficacy Interim Analyses 3.8.1 Multiplicity Control for Efficacy Analyses	Per protocol amendment 3 and 4 (1) Changed the timing of interim analyses and final analysis. (2) Changed α-spending function for primary DFS from Hwang-Shih-DeCani (HSD) spending function with γ= -15 to Lan-DeMets O'Brien-Fleming spending approximation α-spending function.	(1) IA1 will be triggered by achieving approximately 265 DFS events by investigator and 12 months minimum follow up to ensure data maturity for the first IA; The trigger for IA2 is updated based on an increased total number of 332 DFS events by investigator to allow more mature DFS data and increased probability of success at the final analysis of DFS to align with the extended enrollment period and the actual number of randomized subjects. Replaced the wording of 'at least 265 DFS events' by 'approximately 265 DFS events' to allow some flexibility in the IA1 timing for this event-driven study. (2) To apply a more commonly used alpha spending function that is relative but not too conservative to ensure adequate power for the primary endpoint at IA1.
3.4.1.2 Secondary	Per protocol amendment 3, Defined event-free survival.	To define an endpoint that better represents the events to be expected in the RCC adjuvant setting for patients with or without baseline disease by BICR.

Section # and Name	Description of Change	Brief Rationale
3.6.1.4 Event-Free Survival	Per protocol amendment 3, provided the analysis method for evaluating event-free survival.	To provide an appropriate statistical method for the analysis of EFS.
3.9 Sample Size and Power Calculations	Per protocol amendment 3 and 4, power statement is updated for DFS and OS endpoints.	To update the power statement due to the following changes: (1) Increased total number of DFS events at IA2 due to the increased actual number of randomized subjects during an extended accrual period and correspondent to an increased targeted power (2) Updated alpha spending function for DFS that is more commonly used (3) Updated enrollment rates that are more in line with the actual enrollment rates (4) Updated the yearly drop-out rate for DFS that is more in line with the actual drop-out rate
3.6.1.1 Disease-Free Survival	Per protocol amendment 3 and 4, added two sensitivity analyses: (1) One for primary DFS by investigator assessment with participants with baseline disease by BICR as an additional stratum. (2) One for DFS by BICR with participants with baseline disease by BICR censored at baseline	To evaluate the robustness of the results from the primary analysis method after adjusting the potential confounding effect of baseline disease status

Section # and Name	Description of Change	Brief Rationale
3.6.1.1 Disease-Free Survival	Added one potential sensitivity analysis considering COVID-19 impact	To evaluate the impact of COVID-19 on primary DFS analysis if there are more than 5% of randomized participants censored due to COVID-19
3.6.1.1 Disease-Free Survival 3.6.1.2 Overall Survival (OS)	Added one potential sensitivity analysis for MaxCombo test	To account for the potential loss of power with logrank test when the proportional hazard assumption is violated
3.10 Subgroup Analyses	Per protocol amendment 3 and 4, added following subgroup analyses: Baseline disease status by BICR (NED, Non-NED) Added a requirement for subgroup analysis that number of participants in subgroup must greater than or equal to 5% of the ITT population.	To study whether the treatment effect is consistent across subgroups defined by baseline disease status by BICR. To predefine the threshold for number of participants to perform subgroup analysis to allow more meaningful estimate within subgroup and avoid potential model convergence issue due to small sample size in the subgroup.
3.6.1 Statistical Methods for Efficacy Analyses	Per protocol amendment 4, updated censoring rules for the primary analysis and the sensitivity analysis. The new primary analysis is the old sensitivity analysis 1 and new sensitivity analysis is the old primary analysis. The old sensitivity analysis 2 is removed.	Updated the censoring rules per the most recent oncology standard for an adjuvant study to follow ITT rule to produce more unbiased estimate.

Section # and Name	Description of Change	Brief Rationale
3.4.3 PRO Endpoints 3.5.3 PRO Analysis Population 3.6.4 PRO Analysis	Added PRO analysis endpoints, analysis population and statistical methods.	To provide details on endpoint definition, analysis population and analysis method for PRO endpoints.

3. ANALYTICAL AND METHODOLOGICAL DETAILS

3.1 STATISTICAL ANALYSIS PLAN SUMMARY

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Section 3.2 through Section 3.12.

Study Design Overview	This is a randomized, double-blind, multicenter Phase III trial to evaluate the efficacy and safety of pembrolizumab versus placebo as an adjuvant treatment for renal cell carcinoma (RCC) post nephrectomy.
Treatment Assignment	Approximately 950 participants will be randomized 1:1 into the following two treatment arms: pembrolizumab 200 mg or matching placebo (saline 200 mg infusion) administered intravenously (IV) every 3 weeks (Q3W). Stratification factors are provided in protocol Section 7.3.1.
Analysis Populations	Efficacy: Intention-to-Treat Safety: All Participants as Treated
Primary Endpoints	Disease-free survival (DFS) as assessed by the investigator
Key Secondary Endpoints	Overall survival (OS)
Statistical Methods for Key Efficacy Analyses	The primary and secondary hypotheses addressing DFS and OS will be evaluated by comparing pembrolizumab to placebo using a stratified log-rank test. Estimation of the hazard ratio will be done using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. There are no Tier 1 events in this trial. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals (CI) provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The 95% CI for the between-treatment differences in percentages will be provided using the Miettinen and Nurminen method.

Interim and Final Analyses	Three interim analyses are planned for the study (one interim analysis for DFS and three interim analyses for OS). Results will be reviewed by an external data monitoring committee. Details are provided in Section 10.7. • First Interim Analysis (IA1) o Purpose: Interim analysis for DFS and OS. o Timing: When approximately 265 disease recurrence events by investigator assessment have accrued and a minimum follow-up (time from last participant randomized to IA1) of 12 months is achieved. Approximately 94 OS events are expected at this time. • Second Interim Analysis (IA2) o Purpose: Final analysis for DFS and interim analysis for OS o Timing: Final analysis of DFS when approximately 332 DFS events by investigator assessment have accrued if DFS is not rejected at IA1, Approximately 132 OS events are expected at this time. • Third Interim Analysis (IA3) o Purpose: Interim analysis for OS o Timing: When approximately 172 OS events have accrued, • Final analysis (FA) o Purpose: Final analysis for OS o Timing: When approximately 200 OS events have accrued,
Multiplicity	The overall Type I error rate is strongly controlled at 2.5% (1-sided) with a fixed sequence testing procedure to test DFS at alpha level of 2.5% (1-sided) first and pass the alpha to OS if the hypothesis test of DFS is declared successful. A group sequential approach will be used to allocate alpha between the interim and final analyses. The study will be considered a success if DFS is demonstrated to be statistically significant under multiplicity control. Note that if the statistical criterion for success for DFS is met at an IA, a regulatory application may be submitted based on DFS for a full approval consideration and the study could still continue for OS.
Sample Size and Power	The sample size was planned for 950 but the following power calculations are based on 990 which is a number more in line with the actual final number of randomized subjects. DFS is the primary endpoint for this study. The expected median DFS time for those not cured in the control group is 45 months; based on 332 events and a Poisson mixture cure rate model with assumed cure rate of 0.3, the study has 95% power to detect a hazard ratio of 0.67 (pembrolizumab versus placebo) at alpha = 2.5% (1-sided).

3.2 RESPONSIBILITY FOR ANALYSES/IN-HOUSE BLINDING

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

The Sponsor will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented in IVRS/IWRS.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and

complete. In addition, blinded independent central imaging review will be performed on imaging scans without knowledge of the treatment group assignments of participants.

Planned interim analyses are described in Section 3.7. Blinding to treatment assignment will be maintained at all investigational sites. The results of interim analyses will not be shared with the investigators prior to the completion of the study. Participant-level unblinding will be restricted to an external unblinded statistician and external unblinded scientific programmer performing the interim analysis, who will have no other responsibilities associated with the study.

Blinding issues related to the planned interim analyses are described in Section 3.7.

3.3 HYPOTHESES/ESTIMATION

Objective/Hypothesis	Endpoint(s)
Primary	
• Objective: To compare DFS as assessed by the investigator for participants treated with pembrolizumab versus those receiving placebo Hypothesis: Pembrolizumab is superior to placebo with respect to DFS	• DFS as assessed by the investigator: time from randomization to the first documented local recurrence, or occurrence of distant kidney cancer metastasis(es), or death due to any cause, whichever occurs first.
Secondary	
Key Secondary	
• Objective: To compare OS for participants treated with pembrolizumab versus those receiving placebo Hypothesis: Pembrolizumab is superior to placebo with respect to OS	• OS: time from randomization to death due to any cause.
Other Secondary	
• To compare the safety and tolerability profiles for participants treated with pembrolizumab versus those receiving placebo	• Adverse events (AEs), serious AEs (SAEs), AEs leading to discontinuation, deaths, laboratory values, and vital signs
• To compare measures of disease recurrence-specific survival (DRSS), as assessed by the investigator, in participants treated with pembrolizumab versus those receiving placebo	• DRSS1 as assessed by the investigator: time from randomization to the first documented local recurrence of RCC. • DRSS2 as assessed by the investigator: time from randomization to the first documented local recurrence with visceral lesion or occurrence of distant

Objective/Hypothesis	Endpoint(s)
	kidney cancer metastasis(es) with visceral lesion, whichever occurs first.
• To compare event-free survival (EFS) as assessed by the blinded independent radiology review for participants treated with pembrolizumab versus those receiving placebo	• EFS as assessed by the blinded independent radiology review (BICR): time from randomization to the first documented local recurrence or occurrence of distant kidney cancer metastasis(es) among participants disease free at baseline (M0/M1-NED) by BICR; or disease progression among participants with baseline disease (M1) by BICR, or death due to any cause, whichever occurs first.
• To compare DFS and OS according to participants' PD-L1 expression status (Positive, Negative) for participants treated with pembrolizumab versus those receiving placebo	• DFS as assessed by the investigator: time from randomization to the first documented local recurrence, or occurrence of distant kidney cancer metastasis(es), or death due to any cause, whichever occurs first. • OS: time from randomization to death due to any cause.
• To evaluate patient-reported outcomes (PROs) with the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-QLQ-C30) and the Functional Assessment of Cancer Therapy Kidney Symptom Index – Disease Related Symptoms (FKSI-DRS)	• EORTC-QLQ-C30 • FKSI-DRS
Tertiary/Exploratory	
• To evaluate pharmacokinetic (PK) parameters and the presence of antidrug antibodies (ADA)	• PK parameters (clearance and volume of distribution) • ADA to pembrolizumab
• To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety,	• Biomarker analyses may include germline genetic variation, genetic (DNA) mutations from tumor, tumor and blood RNA variation, proteomics

Objective/Hypothesis	Endpoint(s)
pharmacodynamic activity, and/or the mechanism of action of pembrolizumab	and IHC, and other blood-derived biomarkers
• To evaluate PROs with the EORTC-QLQ-C30 and FKSI-DRS and to characterize utilities with the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L)	• All scales, sub-scales, and single item measures for the EORTC-QLQ-C30, FKSI-DRS, and EQ-5D-5L

3.4 ANALYSIS ENDPOINTS

3.4.1 Efficacy Endpoints

3.4.1.1 Primary

Disease-Free Survival

DFS, as assessed by the investigator, is defined as the time from randomization to the first documented local recurrence, or occurrence of distant kidney cancer metastasis(es), or death due to any cause, whichever occurs first. See Section 3.6.1 for the censoring rules.

3.4.1.2 Secondary

Overall Survival

OS is defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis will be censored at the date of the last follow-up.

Disease Recurrence Specific Survival

- DRSS1 is defined as the time from randomization to the first documented local recurrence of RCC as assessed by the investigator.
- DRSS2 is defined as the time from randomization to the first documented local recurrence with visceral lesion or occurrence of distant kidney cancer metastasis(es) with visceral lesion, whichever occurs first, as assessed by the investigator.

Event-Free Survival

- EFS is to be assessed by BICR. EFS is defined as time from randomization to the first documented local recurrence or occurrence of distant kidney cancer metastasis(es) among participants which by BICR were considered disease free at baseline (M0/M1 NED); or disease progression among participants which by BICR were considered to have baseline

disease (M1), or death due to any cause, whichever occurs first. See protocol Section 9.2.1 for the definition of disease progression.

3.4.2 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs; and changes in laboratory values. AEs will be assessed as defined by Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

3.4.3 Patient Reported Outcome (PRO) Endpoints

3.4.3.1 Secondary

- Mean change from baseline in EORTC QLQ-C30 global health status/quality of life scores.
- Mean change from baseline in EORTC QLQ-C30 functional subscales: physical functioning.
- Mean change from baseline in FKSI-DRS score.

3.4.3.2 Exploratory

Following are the PRO endpoints which are going to be used for exploratory analyses:

- Mean change from baseline in EORTC QLQ-C30 symptom subscales: nausea and vomiting symptom, diarrhea symptom.
- Mean change from baseline in EQ-5D-5L Health State Score using visual analogue scale (VAS).
- Proportions of deterioration / stability / improvement / stability + improvement in EORTC QLQ-C30 global health status / QoL, its functional (physical functioning) where
    - Improvement is defined as a 10 points or more increase in score (in the positive direction) from baseline at any time during the study and confirmed by a 10 points or more improvement at the next consecutive visit.
    - Stability is defined as, when the criteria for improvement are not met, a less than 10 points worsening in score from baseline at any time during the study and confirmed by a less than 10 points worsening at the next consecutive visit.
    - Stability + improvement is defined as an improvement or less than 10 points worsening in score from baseline at any time during the trial and confirmed by an improvement or less than 10 points worsening in score at the next consecutive visit.
    - Deterioration is defined as, when the criteria for improvement or stability are not met, a 10 points or greater worsening from baseline at any time during the study.

- Proportions of deterioration / stability / improvement / stability + improvement in FKSI-DRS score where

    - Improvement is defined as a 3-points or more increase in score (in the positive direction) from baseline at any time during the study and confirmed by a 3-points or more improvement at the next consecutive visit.

    - Stability is defined as, when the criteria for improvement are not met, a less than 3 points worsening in score from baseline at any time during the study and confirmed by a less than 3 points worsening at the next consecutive visit.

    - Stability + improvement is defined as an improvement or less than 3 points worsening in score from baseline at any time during the trial and confirmed by an improvement or less than 3 points worsening in score at the next consecutive visit.

    - Deterioration is defined as, when the criteria for improvement or stability are not met, a 3 points or greater worsening from baseline at any time during the study.

3.5 ANALYSIS POPULATIONS

3.5.1 Efficacy Analysis Populations

The Intention-to-Treat population will serve as the population for the primary and key secondary efficacy analyses. All randomized participants will be included in this population. Participants will be analyzed in the treatment group to which they are randomized. Details on the approach to handling missing data are provided in Section 3.6.1 – Statistical Methods for Efficacy Analyses.

3.5.2 Safety Analysis Populations

The All Participants as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who received at least 1 dose of study treatment. Participants will be analyzed in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. For most participants this will be the treatment group to which they are randomized. Participants who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received. Any participant who receives the incorrect study treatment for one cycle but receives the correct treatment for all other cycles will be analyzed according to the correct treatment group and a narrative will be provided for any events that occur during the cycle for which the participant is incorrectly dosed.

At least 1 laboratory measurement obtained subsequent to at least 1 dose of study treatment is required for inclusion in the analysis of specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety analyses are provided in Section 3.6.2–Statistical Methods for Safety Analysis.

3.5.3 PRO Analysis Population

The PRO analyses are based on the PRO full analysis set (FAS) population, defined as subjects who have at least one PRO assessment available and have received at least one dose of the study medication. Participants will be analyzed in the treatment group to which they are randomized.

3.6 STATISTICAL METHODS

3.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives on OS and disease recurrence specific survival. Separate analysis plans may be developed for PK/ADA modeling analysis, biomarker analysis, and genetic data analysis.

Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 3.8 – Multiplicity. Nominal p values may be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity.

3.6.1.1 Disease-Free Survival (DFS)

The non-parametric Kaplan-Meier method will be used to estimate the DFS curve in each treatment group. The hypotheses addressing a treatment difference in DFS will be tested by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to estimate the magnitude of the treatment difference (ie, hazard ratio [HR]) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors including Metastasis status (M0 versus M1 NED), ECOG PS (0 versus 1) and US participant (YES versus NO) will be applied to both the stratified log-rank test and the stratified Cox model.

Since participants enrolled with baseline disease by BICR could have a different time to event distribution compared to participants who were disease free at baseline by BICR, a sensitivity analysis will be performed using the stratified Cox model and stratified log-rank test with stratification factors used for randomization with baseline disease status by BICR as an additional stratum. Specifically, a total of six strata will be used: M0 + ECOG PS 0 + US participant vs. M0 + ECOG PS 0 + Non-US participant vs. M0 + ECOG PS 1 + US participant vs. M0 + ECOG PS 1 + Non-US participant vs. M1 NED vs. M1 by BICR. In addition, DFS by BICR will be analyzed as a sensitivity analysis in which participants enrolled with baseline disease by BICR will be censored at randomization date.

Since the trial was ongoing during the outbreak of COVID-19, sensitivity analyses are planned to evaluate the impact of COVID-19 on primary DFS analysis if there are more than 5% of randomized participants who were censored at last disease assessment due to COVID-19 resulted missing imaging scans. In order to stress-test the assumption of censored at random with an assumption that favors the placebo group over the experimental treatment group, we will assume COVID-19 related censoring in the experimental treatment group is informative of impending DFS event, while the censoring in the placebo group is non-informative.

Specifically, we will randomly select a certain percentage (δ) of COVID-19 related censoring and count them as events at the censoring time in the experimental group, while keep all COVID-19 related censoring as censored in placebo group. A series of sensitivity analyses could be performed with increasing values of δ to assess whether the primary DFS analysis results are robust to the deviations from censored at random assumption for the COVID-19 related censoring.

Since disease recurrence is assessed periodically, disease recurrence can occur any time in the time interval between the last assessment when disease recurrence was not documented and the assessment when disease recurrence is documented. For the primary analysis, for the participants who have disease recurrence (local recurrence or occurrence of distant kidney cancer metastasis(es)) as assessed by the investigator's review, the true date of disease recurrence will be approximated by the date of the first assessment at which disease recurrence is objectively documented, regardless of discontinuation of study treatment. Death is always considered as a confirmed disease recurrence event. In order to evaluate the robustness of the DFS endpoint, a sensitivity analysis with a different set of censoring rules may be performed. The sensitivity analysis is the same as the primary analysis except that events after 2 consecutive missed disease assessments or after new anti-cancer therapy, if any, should be censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessments and new anti-cancer therapy.

The censoring rules for primary and sensitivity analysis are summarized in Table 1.

Table 1 Censoring Rules for Primary and Sensitivity Analysis of Disease-Free Survival

Situation	Primary Analysis	Sensitivity Analysis
No recurrence and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment
No recurrence and no death; new anticancer treatment is initiated	Censored at last disease assessment	Censored at last disease assessment before new anti-cancer treatment
Recurrence or death documented after ≤1 missed disease assessment and before new anti-cancer treatment, if any	Event at date of documented recurrence or death	Event at date of documented recurrence or death
Recurrence or death documented immediately after ≥2 consecutive missed disease assessments, or after new anti-cancer treatment, if any	Event at date of documented recurrence or death	Censored at the last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessments and new anti-cancer treatment, if any

The proportional hazards assumption on DFS will be examined using both graphical and analytical methods if warranted. The log [-log] of the survival function versus time for DFS will be plotted for the comparison between pembrolizumab and the placebo arm. If the curves are not parallel, indicating that hazards are not proportional, supportive analyses may be conducted to account for the possible non-proportional hazards effect associated with immunotherapies: for example, using the Restricted Mean Survival Time method [1] and

parametric method [2]. The RMST is simply the population average of the amount of event-free survival time experienced during a fixed study follow-up time. This quantity can be estimated by the area under the Kaplan-Meier curve up to the follow-up time. The clinical relevance and feasibility should be taken into account in the choice of follow-up time to define RMST (e.g., near the last observed event time assuming that the period of clinical interest in the survival experience is the whole observed follow-up time for the trial, but avoiding the very end of the tail where variability may be high); a description of the RMST as a function of the cutoff time may be of interest. The difference between two RMSTs for the two treatment groups will be estimated and 95% CI will be provided.

A sensitivity analysis may be performed based on the MaxCombo test with logrank FH (0, 1), FH (1, 1) at the final analysis of DFS to account for the potential loss of power with logrank test when the proportional hazard assumption is violated.

3.6.1.2 Overall Survival (OS)

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The hypotheses of treatment difference in survival will be tested by the stratified log -rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to estimate the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization will be applied to both the stratified log-rank test and the stratified Cox model.

The proportional hazards assumption on OS may be examined using both graphical and analytical methods if warranted. The log [-log] of the survival function vs. time for OS will be plotted for the comparison between pembrolizumab and the placebo arm. If the curves are not parallel, indicating that hazards are not proportional, supportive analyses may be conducted to account for the possible non-proportional hazards effect associated with immunotherapies: for example, using the Restricted Mean Survival Time method [1], parametric method [2], etc.

The RMST is simply the population average of the amount of event-free survival time experienced during a fixed study follow-up time. This quantity can be estimated by the area under the Kaplan-Meier curve up to the follow-up time. The clinical relevance and feasibility should be taken into account in the choice of follow-up time to define RMST (e.g., near the last observed event time assuming that the period of clinical interest in the survival experience is the whole observed follow-up time for the study, but avoiding the very end of the tail where variability may be high); a description of the RMST as a function of the cutoff time may be of interest. The difference between two RMSTs for the two treatment groups will be estimated and 95% CI will be provided.

A sensitivity analysis may be performed based on the MaxCombo test with logrank FH (0, 1), FH (1, 1) at the final analysis of OS to account for the potential loss of power with logrank test when the proportional hazard assumption is violated.

The OS analysis will be conducted according to the hypothesis testing plan as described in Section 3.7 and Section 3.8.

3.6.1.3 Disease Recurrence Specific Survival

The non-parametric cumulative incidence estimator will be used to estimate the DRSS1 and DRSS2 curves in each treatment group. For DRSS1, only local recurrence is counted as an event. Death, or occurrence of distant kidney cancer metastasis(es) will be censored at documented date of disease metastasis or death, whichever occurs first. For DRSS2, only disease recurrence with visceral lesion is counted as an event. Death, local recurrence without visceral lesion, distant metastasis without visceral lesion will be censored at documented date of disease recurrence or death, whichever occurs first.

3.6.1.4 Event-Free Survival

The non-parametric Kaplan-Meier method will be used to estimate the EFS curve in each treatment group. The hypotheses addressing a treatment difference in EFS will be tested by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to estimate the magnitude of the treatment difference (ie, hazard ratio [HR]) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 7.3.1 in protocol) with baseline disease status by BICR as an additional stratum will be applied to both the stratified log-rank test and the stratified Cox model.

3.6.1.5 Analysis Strategy for Key Efficacy Variables

Table 2 summarizes the primary analysis approach for primary and key secondary efficacy endpoints. Sensitivity analysis methods are described above for DFS.

The strategy to address multiplicity issues with regard to multiple efficacy endpoints, multiple populations, and interim analyses is described in Section 3.7 - Interim Analyses and in Section 3.8 - Multiplicity.

Table 2 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical† Method	Analysis Population	Missing Data Approach
Primary Hypothesis #1			
DFS as assessed by the investigator	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	• Primary censoring rule • Sensitivity analysis
Key Secondary Hypothesis			
OS	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at the last date the participant was known to be alive

†Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization will be applied to the analysis model.

ITT = intention-to-treat; OS = overall survival; DFS = disease-free survival.

3.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests.

Tiered Approach

The analysis of safety results will follow a tiered approach (Table 3). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p values and 95% CI provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. There is no expectation of enhanced safety signal in this adjuvant study other than safety signals of which we are already aware from past studies. Participants do not have tumor burden and their existing safety profile might be less intensive. Hence, we do not expect any new safety signals. Therefore there are no events of interest that will be analyzed as Tier 1 safety endpoints in this study.

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events using the Miettinen and Nurminen method, an unconditional, asymptotic method [3].

Membership in Tier 2 requires that at least 10% of participants in any treatment group exhibit the event; all other AEs and predefined limits of change will belong to Tier 3. The threshold of at least 10% of participants was chosen for Tier 2 events because the population enrolled in this study is in critical condition and usually experiences various AEs of similar types regardless of treatment; events reported less frequently than 10% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, Grade 3 to 5 AEs (≥5% of participants in 1 of the treatment groups) and SAEs (≥5% of participants in 1 of the treatment groups) will be considered Tier 2 endpoints. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not as a formal method for assessing the statistical significance of the between-group differences.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. The broad AE categories consisting of the proportion of participants with any AE, a drug related AE, a serious AE, an AE which is both drug-related and serious, a Grade 3-5 AE, a drug-related Grade 3-5 AE, and discontinuation due to an AE will be considered Tier 3 endpoints. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Continuous measures such as changes from baseline in laboratory that are not pre-specified as Tier-1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Table 3 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Grade 3-5 AE (incidence ≥5% of participants in one of the treatment groups)	X	X
	Serious AE (incidence ≥5% of participants in one of the treatment groups)	X	X
	AEs (incidence ≥10% of participants in one of the treatment groups)	X	X
Tier 3	Any AE		X
	Any Grade 3-5 AE		X
	Any Serious AE		X
	Any Drug-Related AE		X
	Any Serious and Drug-Related AE		X
	Any Grade 3-5 and Drug-Related AE		X
	Discontinuation due to AE		X
	Dose Interruption due to AE		X
	Death		X
	Specific AEs, SOCs (incidence <10% of participants in all of the treatment groups)		X
	Change from Baseline Results (lab toxicity shift)		X
Abbreviations: AE = adverse event; CI = confidence interval; SOC = system organ class.			

Frequency of AE by time period from first dose (e.g., 0-3, 3-6, 6-9, 9-12 and beyond 12 months) may also be provided. In each time interval, the denominator is the number of participants at risk for the event during the particular time period, defined as participants who are event-free up until the start of the interval.

To properly account for the potential difference in follow-up time between the study arms, which is expected to be longer in the pembrolizumab arm, AE incidence adjusted for treatment exposure analyses may be performed as appropriate.

Time to Grade 3-5 AE

In addition to the tiered approach, exploratory analysis may be performed on the time to the first Grade 3-5 AE. The time to the first Grade 3-5 AE is defined as the time from the first day of study drug to the first event of a Grade 3-5 AE. Summary statistics will be provided.

3.6.3 Summaries of Baseline Characteristics and Demographics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized, and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (eg, age), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

3.6.4 Patient Reported Outcomes (PRO) Analysis

This section describes the planned analyses for the key PRO endpoints. As there is no formal hypothesis testing for PRO endpoints, nominal p-values will be provided for treatment comparisons of pembrolizumab vs. placebo. No multiplicity adjustment will be performed.

3.6.4.1 PRO compliance summary

Completion and compliance of EORTC QLQ-C30, FKSI-DRS and EQ-5D by visit and by treatment will be described. Numbers and percentages of complete and missing data at each visit will be summarized. An instrument is considered complete if at least one valid score is available according to the missing item rules outlined in the scoring manual for the instrument.

Completion rate of treated participants (CR-T) at a specific time point is defined as the number of treated participants who complete at least one item over the number of treated participants in the PRO analysis population.

$$\text{CR-T} = \frac{Number\ of\ treated\ participants\ who\ complete\ at\ least\ one\ item}{Number\ of\ treated\ participants\ in\ the\ PRO\ analysis\ population}$$

The completion rate is expected to shrink in the later visit during study period due to the participants who discontinued early. Therefore, another measurement, compliance rate of eligible participants (CR-E) will also be employed as the support for completion rate. CR-E is defined as the number of treated participants who complete at least one item over number of eligible participants who are expected to complete the PRO assessment, not including the participants missing by design such as death, discontinuation, translation not available.

$$\text{CR-E} = \frac{Number\ of\ treated\ participants\ who\ complete\ at\ least\ one\ item}{Number\ of\ eligible\ participants\ who\ are\ expected\ to\ complete}$$

The reasons of non-completion and non-compliance will be provided in supplementary table:

- Completed as scheduled
- Not completed as scheduled
- Off-study: not scheduled to be completed.

In addition, reasons for non-completion as scheduled of these measures will be collected using "miss_mode" forms filled by site personnel and will be summarized in table format. The

schedule (study visits and estimated study times) and mapping of study visit to analysis visit for PRO data collection is provided in Table 4.

Table 4 PRO Data Collection Schedule and Mapping of Study visit to Analysis Visit

Study Week	Week 0 (Baseline)	Week 12	Week 24 to Week 36 (Every 12 weeks)	Week 48	Week 52	Week 104 to Week 520 (Every 52 weeks)
Study Day	1	85	Week number *7+1	337	365	Week number *7+1
Day Range	<=1	[2, 126]	[Week number*7-41, week number*7+42]	[295, 351]	[352, 546]	[Week number*7-181, week number*7+182]

3.6.4.2 Mean change from baseline

The time point for the mean change from baseline is defined as the latest time point at which CR-T ≥ 60% and CR-E ≥ 80% and week 52 was selected based on blinded data review prior to the database lock for any PRO analysis.

To assess the treatment effects on the PRO score change from baseline in the global health status/QoL and its physical functioning, nausea and vomiting symptom, diarrhea symptom, FKSI-DRS, EQ-5D-5L VAS outcome a constrained longitudinal data analysis (cLDA) model proposed by Liang and Zeger [4] will be applied, with the PRO score as the response variable, and treatment by time interaction and stratification factors used for randomization (See Section 7.3.1) as covariates. The treatment difference in terms of least square (LS) mean change from baseline will be estimated from this model together with 95% CI. Model-based LS mean with 95% CI will be provided by treatment group for PRO scores at baseline and post-baseline time point.

The cLDA model assumes a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. In this model, the response vector consists of baseline and the values observed at each post-baseline time point. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The cLDA model is specified as follows:

$$E(Y_{ijt}) = \gamma_0 + \gamma_{jt} I(t > 0) + \beta X_i, j = 1,2;\ t = 0,1,2,3,..k$$

where Y_{ijt} is the PRO score for participant i, with treatment assignment j at visit t; γ_0 is the baseline mean for all treatment groups, γ_{jt} is the mean change from baseline for treatment group j at time t; X_i is the stratification factor (binary) vector for this participant, and β is the coefficient vector for stratification factors. An unstructured covariance matrix will be used to model the correlation among repeated measurements. If the unstructured covariance model fails to converge with the default algorithm, then Fisher scoring algorithm or other appropriate methods can be used to provide initial values of the covariance parameters. In the rare event that none of the above methods yield convergence, a structured covariance such as Toeplitz

can be used to model the correlation among repeated measurements. In this case, the asymptotically unbiased sandwich variance estimator will be used. The cLDA model implicitly treats missing data as missing at random (MAR).

Line plots for the empirical mean change from baseline in EORTC QLQ-C30 global health status/QoL, its physical functioning and FKSI-DRS will be provided across time points till Week 52 as a supportive analysis.

In addition, the model-based LS mean change from baseline to the specified post-baseline time point together with 95% CI will be plotted in bar charts for EORTC QLQ-C30 global health status/QoL and its each functioning scale, symptom scale and FKSI-DRS score.

3.6.4.3 Overall Improvement and Overall Improvement/Stability

Overall improvement rate will be analyzed, which is defined as the proportion of participants who have achieved an improvement as defined in Section 3.4.3 PRO Endpoints. Stratified Miettinen and Nurminen's method will be used for comparison of the overall improvement rate between the treatment groups. The difference in overall improvement rate and its 95% CI from the stratified Miettinen and Nurminen's method with strata weighting by sample size will be provided. The stratification factors used for randomization (See Section 7.3.1 in protocol) will be applied to the analysis.

The point estimate of overall improvement rate will be provided by treatment group, together with 95% CI using exact binomial method by Clopper and Pearson [5]. The same method will be used to analyze overall improvement/stability rate, which is defined as the proportion of participants who have achieved improvement/stability as defined in Section 3.4.3 PRO Endpoints.

3.6.4.4 Analysis Strategy for Key PRO Endpoints

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Mean change from baseline in – EORTC QLQ-C30 • Global health status/QoL • Functioning scale • Symptom scale – FKSI-DRS – EQ-5D VAS	cLDA model	FAS	Model-based.
Overall improvement and overall improvement/stability in – EORTC QLQ-C30 • Global health status/QoL • Physical functioning – FKSI-DRS	Stratified Miettinen and Nurminen method	FAS	Participants with missing data are considered not achieving improvement/stability.
Abbreviations: cLDA = constrained longitudinal data analysis, FAS = full analysis set, QoL = quality of life.			

3.7 INTERIM ANALYSES

Treatment-level results of the interim analysis will be provided by the unblinded statistician to the external data monitoring committee (eDMC). Limited additional Sponsor personnel may be unblinded to the treatment level results of the interim analysis (analyses), if required, in order to act on the recommendations of the eDMC. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the unblinded statistician.

The eDMC will serve as the primary reviewer of the unblinded results of the DFS and OS at interim analyses and will make recommendations for discontinuation of the study or modification to an Executive Oversight Committee (EOC) of the Sponsor. Depending on the recommendations of the eDMC, the Sponsor may prepare a regulatory submission. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, the EOC may be unblinded to results at the treatment level in order to evaluate and direct the Sponsor protocol team as to the appropriate actions to be taken on these recommendations. Additional logistical details, revisions to the above plan, and data monitoring guidance will be provided in the DMC Charter.

Prior to final study unblinding, the unblinded statistician and unblinded scientific programmer will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

If the trial is positive at an interim analysis for primary endpoint DFS, additional analyses, including but not limited to the protocol-specified final analysis, may be carried out for exploratory purpose or upon regulatory request.

3.7.1 Safety Interim Analyses

The eDMC has responsibility for assessment of overall risk:benefit. Periodic safety monitoring will be specified in the eDMC charter with input from the eDMC members. When prompted by safety concerns, the eDMC can request efficacy data to assess the overall risk: benefit to study participants. Any eDMC recommendation will be communicated to the Executive Oversight Committee (EOC) as agreed to in the eDMC charter.

3.7.2 Efficacy Interim Analyses

Three interim analyses are planned in addition to the final analysis for this trial. In this study, the futility bounds are non-binding. Results of the interim analyses (IA) will be reviewed by an eDMC. If both DFS and OS null hypotheses are rejected prior to the final analysis, the eDMC may recommend stopping the trial early for efficacy. At each IA, the eDMC may also recommend stopping the trial early for futility. Details on how the above planned analyses are incorporated into establishing statistical significance and the boundaries with regard to efficacy and futility are discussed further in Section 3.8, Multiplicity.

The analyses planned, endpoints evaluated and drivers of the timing are summarized in Table 5.

Table 5 Analyses Planned, Endpoints Evaluated and Drivers of Timing

Analysis	Endpoint(s)	Timing
IA1	DFS, OS	Enrollment complete and approximately 265 DFS events by investigator assessment have occurred and a minimum follow-up (time from last participant randomized to IA1) of 12 months is achieved.
IA2	DFS, OS	332 DFS events by investigator assessment; if DFS rejected before IA2, timing driven by 132 OS events
IA3	OS	172 OS events
FA	OS	200 OS events

3.8 MULTIPLICITY

3.8.1 Multiplicity Control for Efficacy Analyses

The trial uses the method of Maurer and Bretz [6] to provide strong multiplicity control for multiple hypotheses as well as interim analyses. Figure 1 shows the initial one-sided α-allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses. This is further explained below.

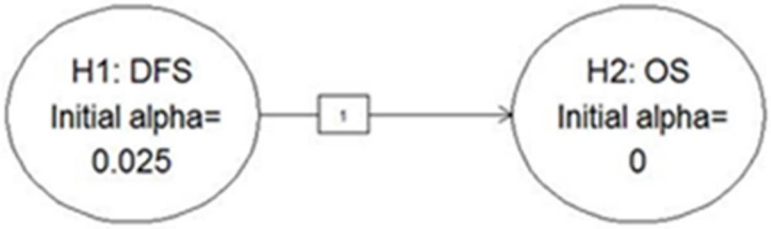

Figure 1 Multiplicity Graph for Type I Error Control of Study Hypotheses

If the DFS null hypothesis is rejected at the 2.5% level, then the OS null hypothesis may be formally evaluated for statistical significance at the 2.5% level. For each endpoint, group sequential methods will be used to adjust for the interim and final analyses planned. If the DFS null hypothesis is rejected at an interim or final analysis, each OS interim and final analysis test may be compared to its rejection boundary for formal testing. For instance, the OS hypothesis will not be formally evaluated for statistical significance until the DFS null hypothesis is rejected.

For DFS, the information fraction at each analysis will be based on the final planned number of 332 events. A Lan-DeMets O'Brien-Fleming spending approximation α-spending function is used to set efficacy bounds. Non-binding futility spending is done by controlling the

probability of crossing the futility bound under the null hypothesis (total of 1-α=97.5%); a Hwang-Shih-DeCani (HSD) spending function with γ= -6 is used to set testing boundaries at each analysis.

For OS, the information fraction at each analysis will be based on the final planned number of 200 deaths. A Lan-DeMets O'Brien-Fleming spending approximation α-spending function is used to set efficacy bounds. As with DFS, non-binding futility spending is done by controlling the probability of crossing the futility bound under the null hypothesis (total of 1-α=97.5%); an HSD spending function with γ= -6 is used to set testing boundaries at each analysis.

Bounds at the expected number of events for each hypothesis at each analysis of DFS and OS are shown in Table 6 and Table 7, respectively. If the actual number of DFS or OS events at the interim and final analyses differs from those specified in the table, the bounds will be updated using this spending function evaluated at the observed information fraction (fraction of observed over expected final events) at each analysis.

Table 6 Boundary Properties for Planned Interim and Final Analyses for DFS

Analysis	**Value**	**Efficacy**	**Futility†**
IA1: 80% (First Interim for DFS) N: 990 Events: 265 Month: 39	Z p (1-sided) HR at bound P(Cross) if HR=1 P(Cross) if HR=0.67	2.2504 0.0122 0.7584 0.0122 0.8402	-0.5476 0.7080 1.0696 0.2920 0.0001
IA2: (Final Analysis for DFS) N: 990 Events: 332 Month: 50	Z p (1-sided) HR at bound P(Cross) if HR=1 P(Cross) if HR=0.67	2.0249 0.0214 0.8005 0.0250 0.9490	2.0249 0.0214 0.8005 0.9750 0.0510

IA = Interim Analysis.
†: Futility boundary is non-binding.

Table 7 Boundary Properties for Planned Interim and Final Analyses for OS

Analysis	Value	Efficacy	Futility†
IA1: 47% (First Interim for OS) N: 990 Events: 94 Month: 39	Z p (1-sided) HR at bound P(Cross) if HR=1 P(Cross) if HR=0.67	3.0679 0.0011 0.5305 0.0011 0.1280	-1.7717 0.9618 1.4421 0.0382 0.0001
IA2: 66% (Second Interim for OS) N: 990 Events: 132 Month: 50	Z p (1-sided) HR at bound P(Cross) if HR=1 P(Cross) if HR=0.67	2.5455 0.0055 0.6416 0.0058 0.4033	-1.1786 0.8807 1.2281 0.1247 0.0003
IA3: 86% (Third Interim for OS) N: 990 Events: 172 Month: 63	Z p (1-sided) HR at bound P(Cross) if HR=1 P(Cross) if HR=0.67	2.2023 0.0138 0.7143 0.0157 0.6688	-0.2090 0.5828 1.0324 0.4195 0.0025
Final N: 990 Events: 200 Month: 72	Z p (1-sided) HR at bound P(Cross) if HR=1 P(Cross) if HR=0.67	2.0534 0.0200 0.7476 0.0250 0.7930	2.0534 0.0200 0.7476 0.9750 0.2070

IA = Interim Analysis.
†: Futility boundary is non-binding.

3.8.2 Multiplicity Control for Safety Analyses

To account for any multiplicity concerns raised by the DMC review of unplanned efficacy data when prompted by safety concerns, a sensitivity analysis for DFS and OS may be considered. This analysis will be performed if requested by the eDMC. However, eDMC review of DFS and OS data beyond the planned efficacy analysis to assess the overall risk:benefit to trial participants will not require multiplicity assessment typically associated with a planned efficacy IA because these analyses are not to declare a positive efficacy finding.

3.9 SAMPLE SIZE AND POWER CALCULATIONS

The study will randomize participants in a 1:1 ratio into the pembrolizumab and placebo arms. DFS and OS are the primary endpoint and key secondary endpoint, respectively. The sample size was planned for 950 but the following power calculations are based on 990 which is a number more in line with the actual final number of randomized participants.

For the DFS endpoint, based on a target number of 332 events and one IA at approximately 80% of the target number of events, the study has approximately 95% power to detect a HR of 0.67 at an overall alpha level of 2.5% (1-sided).

For the OS endpoint, the power is conditional on the null hypothesis of DFS being rejected, based on a target number of 200 events and three interim analyses at approximately 47%, 66%, and 86% of the target number of events, the study has approximately 79% power to detect a HR of 0.67 or approximately 88% power to detect a HR of 0.635 at an overall alpha level of 2.5% (1-sided).

The above sample size and power calculations for DFS and OS assume the following:

- DFS follow a Poisson mixture cure rate model [7] with assumed cure rate of 0.3. The cure rate of 0.3 is estimated based on historical data [8].
- The median DFS is assumed to be 45 months for those not cured in the control group.
- OS follows an exponential distribution with a median of 145 months for the control group.
- Enrollment period of 27 months with monthly accrual of 20 participants during the first 5 months and monthly accrual of 30 participants from month 6 to month 21, and monthly accrual of 1 patient for the last month.
- A yearly drop-out rate of 2% for DFS and 1% for OS.

The Poisson mixture model is applied to account for the failure rates decreasing over time in a trial in which the patient population is a mixture of patients who are susceptible to disease recurrence and patients who would not have a disease recurrence event after long-term follow-up. The latter patients are called long-term survivors. The Poisson mixture model assumes a survival function [5] for a control group (c) as a function of time t, as follows:

$$S(t) = \exp\left(-\theta(1-\exp(-\lambda t))\right),$$

where $\theta = -\log(Cure\_Rate)$, λ is a constant hazard rate, and $t \geq 0$.

In the adjuvant setting, according to the published literature [8] and study assumptions, ~30% participants will be long-term survivors or will be cured in the long-term (ie, Cure_Rate=0.3), and it is more likely that after approximately 5 to 6 years after study initiation there will be minimal accumulation of DFS events.

According to the published literature [8], it is assumed that DFS follows a Poisson mixture model distribution with median DFS of 45 months for those not cured in the placebo group. Figure 2 below shows the DFS curves using the Poisson mixture model and exponential model. Compared to the curve from the exponential model, the curve from the Poisson mixture model looks more similar to the curve in the published literature.

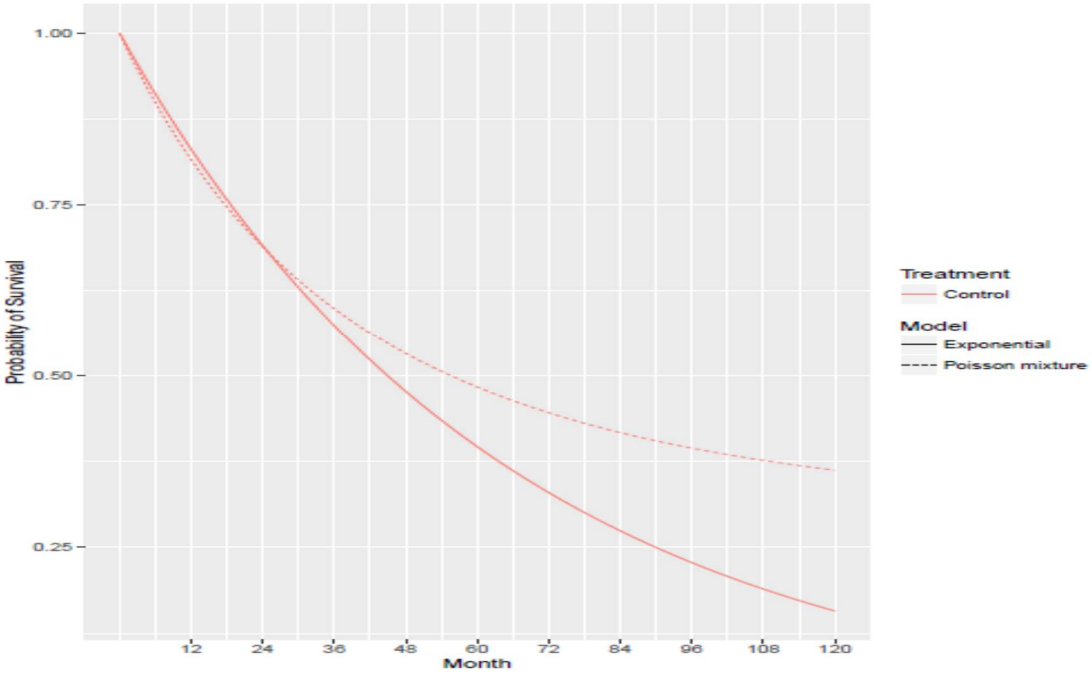

Figure 2 Disease-Free Survival Curves Using the Poisson Mixture Model and Exponential Model

The sample size and power calculation were performed using R (package "gsDesign").

3.10 SUBGROUP ANALYSES AND EFFECT OF BASELINE FACTORS

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint will be estimated and plotted within each category of the following classification variables:

- ECOG PS (0, 1)
- Metastasis status (M0, M1 NED)
- Type of nephrectomy (Radical, Partial)
- Geographic region (US, Non-US)
- PD-L1 status (Positive, Negative)
- Age (<65, ≥65 years)
- Sex (Female, Male)
- Race (White, non-White)
- Baseline disease status by BICR (NED, Non-NED)

Country-specific populations may also be analyzed per local regulatory requirements. The consistency of the treatment effect will be assessed using descriptive statistics for each category of the subgroup variables listed above. If the number of participants in a category of a subgroup variable is less than 5% of the ITT population, the subgroup analysis will not be performed for this category of the subgroup variable. The subgroup analyses will be conducted using an unstratified Cox model.

3.11 COMPLIANCE (MEDICATION ADHERENCE)

Drug accountability data for study treatment will be collected during the study. Any deviation from protocol-directed administration will be reported.

3.12 EXTENT OF EXPOSURE

The extent of exposure will be summarized as duration of treatment in cycles. Summary statistics will be provided on extent of exposure for the APaT population.

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