Official Title: A Randomized, Phase 3, Double-Blind Study of Chemoradiotherapy With or Without Pembrolizumab for the Treatment of High-risk, Locally Advanced Cervical Cancer (KEYNOTE-A18/ENGOT-cx11/GOG-3047)

NCT Number: NCT04221945

Document Date: A18-04 / ENGOT-CX11 / GOG-3047 08 November 2022

Title Page

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Protocol Title: A Randomized, Phase 3, Double-Blind Study of Chemoradiotherapy With or Without Pembrolizumab for the Treatment of High-risk, Locally Advanced Cervical Cancer (KEYNOTE-A18/ENGOT-cx11/GOG-3047)

Protocol Number: A18-04 / ENGOT-cx11 / GOG-3047

Compound Number: MK-3475

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter called the Sponsor or MSD)

Legal Registered Address:

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Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	126191
EudraCT	2019-003152-37
EU CT	2022-501972-25-00

Approval Date: 08 November 2022

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 04	08-NOV-2022	To amend the SAP to take into account emerging external data in LACC from the CALLA study. In addition, changes were made throughout to align with the EU CTR.
Amendment 03	18-MAR-2022	To incorporate PET scans into RECIST 1.1 evaluations to evaluate the burden of disease more accurately, and to add flexibility for the timing of efficacy analyses.
Amendment 02	04-JUN-2021	To update the dose modification and toxicity management guidelines for irAEs, and country-specific treatment administration details were provided for Japan.
Amendment 01	06-JAN-2021	Changes were made to the objectives/endpoints and statistical analysis plan that include changing the PFS by BICR to PFS by investigator and adding PFS by BICR as a secondary endpoint. Numerous administrative changes were also made.
Original Protocol	14-NOV-2019	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendments:

To amend the SAP to take into account emerging external data in LACC from the CALLA study. In addition, changes were made throughout to align with the EU CTR.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.2 Schema, Figure 1 4.2.1.1 Efficacy Endpoints	Used term 'primary endpoints' instead of 'dual-primary endpoints' for PFS and OS	Change of multiplicity strategy in the SAP.
2.2.3 Ongoing Clinical Studies	Added emerging data from the CALLA study.	These emerging data for durvalumab + CCRT versus placebo + CRT in women with high-risk LACC are pertinent to KEYNOTE-A18, and are the basis for the SAP changes in this amendment.
4.1 Overall Design 9.1 Statistical Analysis Plan Summary	Updated the approximate number of OS events at FA from 322 to 240 based on new assumptions.	OS assumptions revised based on these emerging external data.

Section # and Name	Description of Change	Brief Rationale
9.1 Statistical Analysis Plan Summary	Changed the multiplicity, OS assumptions, and statistical power and properties with a new design outlined below: • Updated alpha passing strategy, focusing initial alpha allocation on the PFS endpoint and testing OS in a conditional step-down manner. • Updated the OS rate in the control group after incorporating the emerging external data. • Updated the OS efficacy boundaries, powers, and expected number of events at IAs and FA accordingly.	The emerging external data from the CALLA study (see Section 2.2.3) suggested a longer OS in the control arm compared with the KEYNOTE-A18 study's original assumption (see Section 9.9). The targeted number of OS events (based on original assumptions) cannot be achieved within a reasonable timeframe and the OS endpoint would likely be underpowered based on the original multiplicity strategy (ie, with initial alpha=0.0125). Focusing initial alpha allocation on the PFS endpoint and testing OS in a conditional step-down manner would give a higher POS on PFS and transfer to a higher POS on OS.
9.4.1 Primary	Removed the statement regarding claiming study success based on either PFS or OS.	Change of multiplicity strategy.
9.7.2 Efficacy Interim Analyses	Stated that subsequent analysis may be triggered by OS events, if the PFS hypothesis is rejected in an earlier IA. Updated the expected number of OS events at IAs and FA in Table 11. Added a footnote in Table 11 stating that IA2 and FA may be kept at least 8 months apart as planned.	To focus on the more relevant endpoint when another endpoint has achieved success in an earlier analysis. Due to new OS assumptions based on emerging external data. Clarification regarding timing of analyses.

Section # and Name	Description of Change	Brief Rationale
9.8 Multiplicity 9.8.1.1 Progression-free Survival 9.8.1.2 Overall Survival	Updated alpha passing strategy, focusing initial alpha allocation on the PFS endpoint and testing OS in a conditional step-down manner. Updated corresponding Figure 2 and statistical properties in Table 12 and Table 13.	The new multiplicity strategy gives a higher POS on PFS and transfer to a higher POS on OS.
9.8.1.1 Progression-free Survival	Removed note after Table 12.	Note is no longer applicable due to change in multiplicity.
9.9 Sample Size and Power Calculations	Updated the OS assumptions and OS designed power.	To take the emerging external data into account.
Title Page	Added EU CT number.	Alignment with the EU CTR.
4.4 Beginning and End of Study Definition	Added that for purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last; and if the study includes countries in the EEA, the local start of the study in the EEA is defined as FSR in any Member State.	Alignment with the EU CTR.
5 Study Population	Added a new paragraph stating that the collection and use of demographic data are to follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.	To clarify the collection, use, and confidentiality of demographic data provided by the participants as required by the EU CTR.

Section # and Name	Description of Change	Brief Rationale
6.1 Study Intervention(s) Administered	Added footnote to Table 3 stating that placebo for pembrolizumab is diluent alone (normal saline and/or dextrose); diluent is used for blinding purposes and does not contain active ingredients.	Alignment with the EU CTR.
8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events	Added that investigators need to document if an SAE was associated with a medication error, misuse, or abuse.	Alignment with the EU CTR.
10.3.1 Definitions of Medication Error, Misuse, and Abuse	Added a new section with definitions of medication error, misuse, and abuse.	To provide definitions of medication error, misuse, and abuse in alignment with the EU CTR.
Title Page 10.1.1 Code of Conduct for Clinical Trials Throughout	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
1.1 Synopsis: Intervention Groups and Duration	In the intervention groups table: • Updated 'Use' for pembrolizumab from 'Exp' (ie, Experimental) to 'Test Product' • Updated 'Use' for placebo from 'Exp' (ie, Experimental) to 'Placebo'	For consistency with Section 6.1, Table 3.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	In the 'Notes' column for the row labeled, 'CT – chest, MRI – abdomen & pelvis', clarified that the EOT scan must be performed within ±4 weeks of treatment discontinuation.	For clarity and alignment with Section 8.2.1.4.
	In the 'Notes' column for the row labeled, 'EORTC QLQ-C30, EORTC QLQ-CX24, PGI-S, PGI-C*, EQ-5D-5L', clarified that only 1 collection is required for each scheduled evaluation time point.	Clarification to ensure that sites only collect PROs once per imaging evaluation time point.
	In the 'Notes' column for the row labeled, 'Newly Obtained Tissue Collection', clarified that the sample at time of disease progression may be collected during any cycle.	To ensure that it is clear that the sample at disease progression may be collected at any cycle, including before Cycle 5.
4.4.1 Clinical Criteria for Early Study Termination	Removed list of reasons that recruitment at a particular study site(s) may be stopped and added a cross-reference to the information in Appendix 10.1.10.	To correct grammar and ensure clarity and intent of the section.
5.1 Inclusion Criteria	In Table 2, removed mention of creatinine levels from the 'Laboratory Value' column in the row for creatinine clearance and GFR and from footnote 'b'.	Due to request from multiple Health Authorities to use CrCl or GFR, regardless of creatinine levels, as the renal inclusion criterion.

Section # and Name	Description of Change	Brief Rationale
6.5 Concomitant Therapy	Clarified that the listed prohibited concomitant medications are prohibited during the treatment period. In the sentence regarding COVID-19 vaccines, added 'replication-incompetent' before 'adenoviral vaccines'. Revised the statement regarding permitted use of systemic glucocorticoids: 'To treat *asthma or* COPD exacerbations (only short-term oral or IV use in doses >10 mg/day prednisone equivalent)'.	Clarification of the time frame during which the listed concomitant medications are prohibited. Clarification regarding permitted COVID-19 vaccines. Participants may receive short-term steroids for asthma exacerbations.
8.4.7 Events of Clinical Interest	Revised list item #2 to introduce the acronym 'DILI'.	To define what a potential DILI is and to align with this acronym being used in Table 6.
5.1 Inclusion Criteria 8.1.1 Informed Consent 8.1.1.1 General Informed Consent 8.8.1 Planned Genetic Analysis Sample Collection 8.10.1 Screening 10.1.8 Data Quality Assurance	Updated informed consent language to refer to documented informed consent instead of written or signed informed consent, and other minor editorial changes to consent language.	Alignment of informed consent language across the protocol and with program standards.

Section # and Name	Description of Change	Brief Rationale
8.8.1 Planned Genetic Analysis Sample Collection	Added that the planned genetic analysis sample should be obtained predose on Day 1, but may be collected at the next scheduled blood draw, if needed.	Clarification of biomarker sample collection.
8.10.4.2 Efficacy Follow-up Visits	Added that Efficacy Follow-up visits should align with the posttreatment imaging visit schedule.	To facilitate scheduling of Efficacy Follow-up visits and to allow imaging and PROs to be performed at the same visit.
10.1.4.2 Scientific Advisory Committee	Added additional details about the role of the SAC.	Clarification of the role of the SAC.
10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Changed 'Sponsor's product' to 'study intervention' throughout section.	To be consistent with other protocol sections (eg, Study Intervention Table).
10.7.2.3 Japan	Added that cisplatin used in this study is categorized as 'test product(s)' in Japan.	Since cisplatin is not approved for the study population in Japan at the dosage and administration specified in the protocol, cisplatin is categorized as 'test product(s)' in Japan, per Japan Protocol Clarification Letter, 04-MAY-2022.
10.7.2.4 Czech Republic	Added that live vaccines must not be administered for 90 days after the last dose of study intervention in Czech Republic.	To align with Health Authority standard requirements.

Section # and Name	Description of Change	Brief Rationale
10.7.2.7 China	Added that the dose formulation for cisplatin may be powder for infusion or injection solution in China.	The dose formulation in China may not be as stated in Section 6.1, Table 3.
Throughout Document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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LIST OF FIGURES

[redacted]

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Randomized, Phase 3, Double-Blind Study of Chemoradiotherapy With or Without Pembrolizumab for the Treatment of High-risk, Locally Advanced Cervical Cancer (KEYNOTE-A18/ENGOT-cx11/GOG-3047)

Short Title: Chemoradiotherapy With or Without Pembrolizumab for the Treatment of High-risk, Locally Advanced Cervical Cancer

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

Throughout this protocol, the term Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 refers to the modification of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Refer to Section 4.2.1.1 for additional details. When tumor growth is suspected on imaging or by physical examination, an optional biopsy for confirmation of suspected disease progression is allowed at investigator discretion. Throughout the protocol, the term "histopathologic confirmation" is used when referencing a biopsy that confirms suspected disease progression either from a new lesion or a pre-existing lesion showing growth.

This study will enroll female participants, at least 18 years of age, with high-risk locally advanced cervical cancer and will include the following objectives and endpoints:

Primary Objectives	Primary Endpoints
- To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to progression-free survival per RECIST 1.1 as assessed by investigator or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1) as assessed by investigator - Hypothesis (H1): concurrent chemoradiotherapy plus pembrolizumab is superior to concurrent chemoradiotherapy plus placebo with respect to progression-free survival per RECIST 1.1 by investigator or by histopathologic confirmation as indicated	- Progression-free survival: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first

- To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to overall survival - Hypothesis (H2): concurrent chemoradiotherapy plus pembrolizumab is superior to concurrent chemoradiotherapy plus placebo with respect to overall survival	- Overall survival: The time from randomization to death due to any cause
Secondary Objectives	Secondary Endpoints
- To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to progression-free survival per RECIST 1.1 as assessed by blinded independent central review (BICR)	- Progression-free survival: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
- To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to progression-free survival at 2 years per RECIST 1.1 as assessed by investigator or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1)	- Progression-free survival at 2 years: The proportion of participants that are progression-free survival event-free at 2 years
- To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to progression-free survival at 2 years per RECIST 1.1 as assessed by blinded independent central review	- Progression-free survival at 2 years: The proportion of participants that are progression-free survival event-free at 2 years
- To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to overall survival at 3 years	- Overall survival at 3 years: The proportion of participants that are overall survival event-free at 3 years

- To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to complete response rate at 12 weeks after completion of concurrent chemoradiotherapy per RECIST 1.1 as assessed by investigator in all randomly assigned participants with measurable disease at study entry	- Complete response rate at 12 weeks after completion of concurrent chemoradiotherapy
- To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to objective response rate per RECIST 1.1 as assessed by investigator in all randomly assigned participants with measurable disease at study entry	- Objective response: complete response or partial response
- To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to complete response rate at 12 weeks after completion of concurrent chemoradiotherapy per RECIST 1.1 as assessed by blinded independent central review in all randomly assigned participants with measurable disease at study entry	- Complete response rate at 12 weeks after completion of concurrent chemoradiotherapy
- To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to objective response rate per RECIST 1.1 as assessed by blinded independent central review in all randomly assigned participants with measurable disease at study entry	- Objective response: complete response or partial response

- To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to overall survival and progression-free survival per RECIST 1.1 as assessed by investigator or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1), by PD-L1 status (by combined positivity score)	- Overall survival - Progression-free survival
- To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to overall survival and progression-free survival per RECIST 1.1 as assessed by blinded independent central review, by PD-L1 status (by combined positivity score)	- Overall survival - Progression-free survival
- To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to progression-free survival after next-line treatment (progression-free survival 2) following discontinuation of study treatment administration as determined by the investigator according to the local standard of clinical practice	- Progression-free survival 2: The time from the date of randomization until disease progression on next-line treatment or death due to any cause, whichever occurs first
- To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to change from baseline score in global quality of life and physical function using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) global health status/Quality of Life scale and Physical Function subscale	- European Organization for Research and Treatment of Cancer Quality of Life Questionnaire EORTC QLQ-C30 Global Score and Physical Function subscale

- To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to change from baseline score in symptom experience using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Symptom Score for Cervical Cancer) the EORTC CX24 symptom specific scale (11 items)	- The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Symptom Score for Cervical Cancer) EORTC QLQ-CX24 symptom specific scale
- To evaluate the safety and tolerability of pembrolizumab in combination with concurrent chemoradiotherapy	- Adverse events - Study treatment discontinuation due to adverse events

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	High-risk locally advanced cervical cancer
Population	Women with International Federation of Gynecology and Obstetrics 2014 Stage IB2-IIB (with node-positive disease) and Stage III-IVA (either node-positive or node-negative disease) cervical cancer
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Placebo
Study Blinding	Double-blind with in-house blinding
Blinding Roles	Participants or Subjects Investigator Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 63 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact. **Extension Portion of the Study in China:** The study may remain open longer than 63 months to complete an extension portion of the study in China.

Number of Participants:

Approximately 980 participants will be randomized as described in Section 9.9.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Arm 1	Pembrolizumab	200 mg	Q3W	IV	5 infusions	Test Product
		400 mg	Q6W	IV	15 infusions	Test Product
Arm 2	Placebo	0 mg	Q3W	IV	5 infusions	Placebo
		0 mg	Q6W	IV	15 infusions	Placebo
For both Arm 1 and Arm 2	Cisplatin	40 mg/m^2	Once weekly	IV	5 infusions (An optional, sixth infusion may be administered according to local practice)	Background Treatment
For both Arm 1 and Arm 2	Radiation (EBRT)	Refer to Radiation Manual	Refer to Radiation Manual	External radiotherapy (IMRT or VMAT /non-IMRT and non-VMAT) to primary tumor and nodal volumes	Within 40 days	Background Treatment
	Radiation (Brachytherapy)	Refer to Radiation Manual	Refer to Radiation Manual	High, low or pulse dose rates can be used	Brachy-therapy should be started immediately after completion of EBRT sessions. Total radiation treatment (EBRT and brachy-therapy) should not exceed 50 days (with extension to a maximum of 56 days for unforeseen delays).	Background Treatment

Abbreviations: EBRT=external beam radiotherapy; Exp=experimental; IMRT=intensity modulated radiotherapy; IV=intravenous; Q3W=dosing every 3 weeks; Q6W=dosing every 6 weeks; VMAT=volumetric modulated arc therapy
Geographic variance in total radiation dose administered, number of fractions and methodology of application may be permitted after consultation with the Sponsor.
Participants must receive 5 infusions of pembrolizumab or placebo at Q3W before moving to Q6W dosing.
Chemoradiotherapy and brachytherapy are administered during the Q3W dosing regimen. Interruptions of cisplatin, EBRT, brachytherapy, pembrolizumab or placebo are allowed according to Section 6.4.
Administration of EBRT must be completed within 40 days from start to finish. The minimum acceptable radiation dosing is 80 Gy for volume-directed and 75 Gy for point-directed. Total radiation treatment (EBRT and brachytherapy) should not exceed 50 days (with extension to a maximum of 56 days for unforeseen delays).
The maximum dosage for radiation depends on the methodology used. Please refer to the Radiation Manual for additional details such as nodal boost dosing requirements.

Total Number of Intervention Groups/ Arms	2 intervention groups
Duration of Participation	Each participant will participate in the study from the time the participant provides documented informed consent through the final protocol-specified contact. After a screening phase of up to 42 days, each participant will be assigned to receive study intervention until one of the conditions for discontinuation of study intervention is met. After the end of treatment, each participant will be followed for the occurrence of adverse events and spontaneously reported pregnancy as described under Section 8.4. Participants who discontinue for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1, withdrawal of consent, pregnancy, death, or loss to follow-up. All participants will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study. Once the study objectives have been met or the study has ended, participants will be discontinued from this study and will be enrolled in an extension study to continue protocol-defined assessments and treatment. Further details of reasons for discontinuation of study intervention during the study are provided in Section 7.1.

Study Governance Committees:

Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Scientific Advisory Committee	Yes
Study governance considerations are outlined in Appendix 1.	

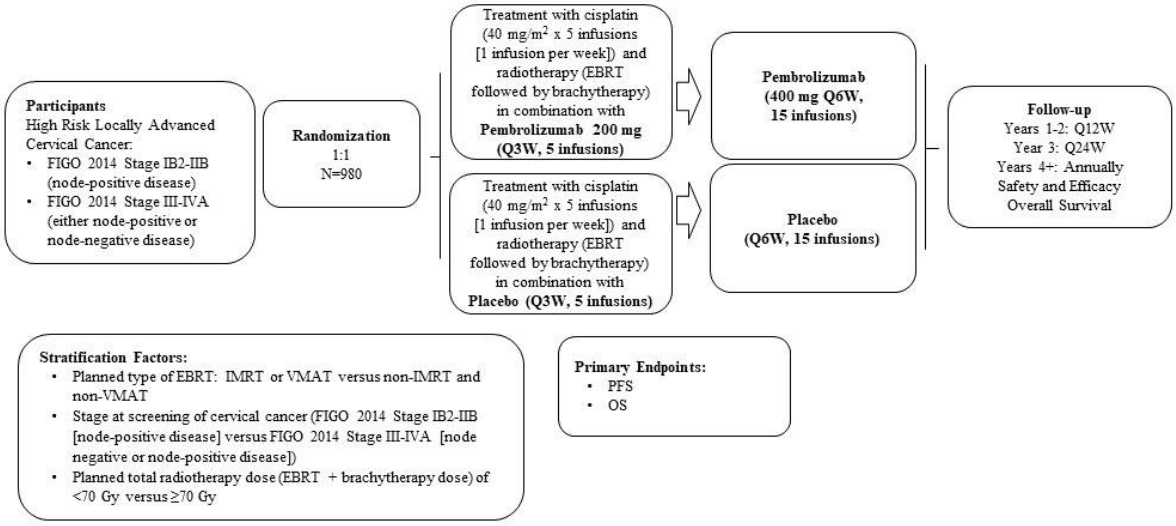
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 10.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema



Abbreviations: EBRT=external beam radiotherapy; FIGO=International Federation of Gynecologists and Obstetricians; IMRT=intensity modulated radiotherapy; OS=overall survival; PFS = progression-free survival; QW3=dosing every 3 weeks; QW6=dosing every 6 weeks; Q12W=every 12 weeks; Q24W=every 24 weeks; VMAT=volumetric modulated arc therapy

Note: For cisplatin, an optional, sixth infusion may be administered according to local practice.

Participants must receive 5 infusions of pembrolizumab 200 mg or placebo at Q3W before proceeding to pembrolizumab 400 mg or placebo Q6W dosing.

1.3 Schedule of Activities

Table 1 Study Schedule of Activities

Period	Screen-ing	Treatment		EOT	Post treatment					Notes
		Cycles 1-5	Cycles 6-20			Posttreatment Follow-up[b]				
Cycle	Screen-ing	Cisplatin (QW) plus EBRT followed by BT plus pembrolizumab or placebo (Q3W)	Pembrolizumab or placebo (Q6W)	Discon-tinuation	Safety Follow-up[a]	Years 1-2 Q12W	Year 3 Q24W	Years 4 + Annually	Survival Follow-up Q12W	Participant must receive 5 infusions (ie, Cycles) of pembrolizumab or placebo Q3W before moving to Q6W dosing. The interval between Cycle 5 and Cycle 6 is 3 weeks ±3 days. Q6W dosing starts from Cycle 6 onwards. CCRT are administered during the Q3W dosing regimen. Interruptions of cisplatin, EBRT, BT, pembrolizumab or placebo are allowed according to Section 6.4.
Scheduling	–42 days to –1 day	±1 day (cisplatin) ±3 days (pembrolizumab or placebo)	±3 days		30 days after last dose (+7 days)	±14 days	±14 days	±14 days	±14 days	
Administrative Procedures										
Informed Consent	X									Consent form may be obtained any time prior to any protocol-specific screening procedures being performed. If the investigator plans to treat beyond the initial radiographic disease progression, per RECIST 1.1, additional documented consent is required at initial site-assessed radiographic disease progression.
Informed Consent for Future Biomedical Research (optional)	X									Participant may participate in main study without documented Future Biomedical Research consent.

Period	Screen-ing	Treatment		EOT	Post treatment					Notes
		Cycles 1-5	Cycles 6-20			Posttreatment Follow-up[b]				
Cycle	Screen-ing	Cisplatin (QW) plus EBRT followed by BT plus pembrolizumab or placebo (Q3W)	Pembrolizumab or placebo (Q6W)	Discon-tinuation	Safety Follow-up[a]	Years 1-2 Q12W	Year 3 Q24W	Years 4 + Annually	Survival Follow-up Q12W	Participant must receive 5 infusions (ie, Cycles) of pembrolizumab or placebo Q3W before moving to Q6W dosing. The interval between Cycle 5 and Cycle 6 is 3 weeks ±3 days. Q6W dosing starts from Cycle 6 onwards. CCRT are administered during the Q3W dosing regimen. Interruptions of cisplatin, EBRT, BT, pembrolizumab or placebo are allowed according to Section 6.4.
Scheduling	–42 days to –1 day	±1 day (cisplatin) ±3 days (pembrolizumab or placebo)	±3 days		30 days after last dose (+7 days)	±14 days	±14 days	±14 days	±14 days	
Consent for Optional Tissue Collection		←	———	———	———	———	———	———	→	Optional consent.
Participant ID Card	X	X								Distribute ID card at screening and add randomization number at C1D1.
Eligibility Assessment (Inclusion / Exclusion)	X									
Demographics	X									
Medical History	X									
Cervical Cancer History	X									
Prior / Concomitant Medication Review	X	X	X	X	X	X	X			Record medications taken within 42 days prior to the start of study intervention. Concomitant medications will be recorded for 30 days after last dose (or for up to 90 days after last dose for SAEs).
Radiotherapy Planning Assessment	X	X								Approval of radiotherapy plan is required prior to randomization. Refer to the Radiation Manual and the Radiation Therapy Quality Assurance Manual for details.

Period	Screen-ing	Treatment		EOT	Post treatment					Notes
		Cycles 1-5	Cycles 6-20			Posttreatment Follow-up[b]				
Cycle	Screen-ing	Cisplatin (QW) plus EBRT followed by BT plus pembrolizumab or placebo (Q3W)	Pembrolizumab or placebo (Q6W)	Discon-tinuation	Safety Follow-up[a]	Years 1-2 Q12W	Year 3 Q24W	Years 4 + Annually	Survival Follow-up Q12W	Participant must receive 5 infusions (ie, Cycles) of pembrolizumab or placebo Q3W before moving to Q6W dosing. The interval between Cycle 5 and Cycle 6 is 3 weeks ±3 days. Q6W dosing starts from Cycle 6 onwards. CCRT are administered during the Q3W dosing regimen. Interruptions of cisplatin, EBRT, BT, pembrolizumab or placebo are allowed according to Section 6.4.
Scheduling	–42 days to –1 day	±1 day (cisplatin) ±3 days (pembrolizumab or placebo)	±3 days		30 days after last dose (+7 days)	±14 days	±14 days	±14 days	±14 days	
Randomization (via IRT)		X								First dose of CCRT and pembrolizumab or placebo may begin up to 3 days after randomization.
Subsequent Anticancer Treatment				X	X	X	X	X	X	Participants should be contacted by telephone to monitor new anticancer treatment if there is no corresponding clinic visit.
Survival Status		◄———	———	———	———	———	———	———►	X	On Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Safety Procedures (during treatment visits safety assessments and procedures should be performed prior to treatment administration)										
Adverse Event Monitoring	X	X	X	X	X	X	X	X		Report all AEs through 30 days following the last dose of study intervention. Report SAEs through 90 days following the last dose of study intervention (or 30 days following the last dose if participant initiates a new anticancer treatment).

Period	Screen-ing	Treatment		EOT	Post treatment					Notes
		Cycles 1-5	Cycles 6-20			Posttreatment Follow-up[b]				
Cycle	Screen-ing	Cisplatin (QW) plus EBRT followed by BT plus pembrolizumab or placebo (Q3W)	Pembrolizumab or placebo (Q6W)	Discon-tinuation	Safety Follow-up[a]	Years 1-2 Q12W	Year 3 Q24W	Years 4 + Annually	Survival Follow-up Q12W	Participant must receive 5 infusions (ie, Cycles) of pembrolizumab or placebo Q3W before moving to Q6W dosing. The interval between Cycle 5 and Cycle 6 is 3 weeks ±3 days. Q6W dosing starts from Cycle 6 onwards. CCRT are administered during the Q3W dosing regimen. Interruptions of cisplatin, EBRT, BT, pembrolizumab or placebo are allowed according to Section 6.4.
Scheduling	–42 days to –1 day	±1 day (cisplatin) ±3 days (pembrolizumab or placebo)	±3 days		30 days after last dose (+7 days)	±14 days	±14 days	±14 days	±14 days	
ECOG Performance Status	X	X	X	X						Perform within 7 days prior to C1D1 of study intervention. During Cycles 1-5, assess ECOG at visits when pembrolizumab / placebo is being administered.
Complete Physical Examination	X			X						
Symptom-directed Physical Examination		X	X		X					
Gynecological Examination	X			X						
Vital Signs (temperature, blood pressure, respiratory rate, heart rate, weight, height [height - screening only])	X	X	X	X	X					Assess vital signs within 72 hours prior to cisplatin and pembrolizumab/placebo administration.
Audiometry	X*			X*						*May be performed at screening and during the study per local practice as clinically indicated. This is not a required procedure.

Period	Screen-ing	Treatment		EOT	Post treatment					Notes
		Cycles 1-5	Cycles 6-20			Posttreatment Follow-up[b]				
Cycle	Screen-ing	Cisplatin (QW) plus EBRT followed by BT plus pembrolizumab or placebo (Q3W)	Pembrolizumab or placebo (Q6W)	Discon-tinuation	Safety Follow-up[a]	Years 1-2 Q12W	Year 3 Q24W	Years 4 + Annually	Survival Follow-up Q12W	Participant must receive 5 infusions (ie, Cycles) of pembrolizumab or placebo Q3W before moving to Q6W dosing. The interval between Cycle 5 and Cycle 6 is 3 weeks ±3 days. Q6W dosing starts from Cycle 6 onwards. CCRT are administered during the Q3W dosing regimen. Interruptions of cisplatin, EBRT, BT, pembrolizumab or placebo are allowed according to Section 6.4.
Scheduling	–42 days to –1 day	±1 day (cisplatin) ±3 days (pembrolizumab or placebo)	±3 days		30 days after last dose (+7 days)	±14 days	±14 days	±14 days	±14 days	
12-lead ECG	X									Additional ECGs may be performed as clinically indicated.
HIV / HBV / HCV Testing	X									Required for eligibility if mandated by local health authority. Refer to Appendix 7 for country-specific requirements.

Period	Screen-ing	Treatment		EOT	Post treatment				Notes
		Cycles 1-5	Cycles 6-20			Posttreatment Follow-up[b]			
Cycle	Screen-ing	Cisplatin (QW) plus EBRT followed by BT plus pembrolizumab or placebo (Q3W)	Pembrolizumab or placebo (Q6W)	Discon-tinuation	Safety Follow-up[a]	Years 1-2 Q12W	Year 3 Q24W	Years 4 + Annually	Survival Follow-up Q12W	Participant must receive 5 infusions (ie, Cycles) of pembrolizumab or placebo Q3W before moving to Q6W dosing. The interval between Cycle 5 and Cycle 6 is 3 weeks ±3 days. Q6W dosing starts from Cycle 6 onwards. CCRT are administered during the Q3W dosing regimen. Interruptions of cisplatin, EBRT, BT, pembrolizumab or placebo are allowed according to Section 6.4.
Scheduling	–42 days to –1 day	±1 day (cisplatin) ±3 days (pembrolizumab or placebo)	±3 days		30 days after last dose (+7 days)	±14 days	±14 days	±14 days	±14 days	
Urine or Serum Pregnancy Test (WOCBP only)	X	←	———	→						Required within 72 hours (serum) or 24 hours (urine) of C1D1 of study intervention, monthly while receiving study intervention, and up to 120 days after the last administration of pembrolizumab/placebo and up to 180 days after the last administration of chemoradiotherapy. Home pregnancy tests are acceptable when a scheduled visit does not occur within the month (per local regulation), but the site must make monthly telephone contact with the participant to determine the results of the pregnancy test. See Section 8.3.5.1 for details.

Period	Screen-ing	Treatment		EOT	Post treatment					Notes
		Cycles 1-5	Cycles 6-20			Posttreatment Follow-up[b]				
Cycle	Screen-ing	Cisplatin (QW) plus EBRT followed by BT plus pembrolizumab or placebo (Q3W)	Pembrolizumab or placebo (Q6W)	Discon-tinuation	Safety Follow-up[a]	Years 1-2 Q12W	Year 3 Q24W	Years 4 + Annually	Survival Follow-up Q12W	Participant must receive 5 infusions (ie, Cycles) of pembrolizumab or placebo Q3W before moving to Q6W dosing. The interval between Cycle 5 and Cycle 6 is 3 weeks ±3 days. Q6W dosing starts from Cycle 6 onwards. CCRT are administered during the Q3W dosing regimen. Interruptions of cisplatin, EBRT, BT, pembrolizumab or placebo are allowed according to Section 6.4.
Scheduling	–42 days to –1 day	±1 day (cisplatin) ±3 days (pembrolizumab or placebo)	±3 days		30 days after last dose (+7 days)	±14 days	±14 days	±14 days	±14 days	
PT or INR and aPTT / PTT	X									Perform within 7 days prior to C1D1 of study intervention. Additional assessments may be performed as clinically indicated.
Chemistry	X	X	X	X	X					Perform within 7 days prior to C1D1 of study intervention. While on CCRT perform within 72 hours prior to each cisplatin administration. Perform within 72 hours prior to each pembrolizumab or placebo administration. Perform more frequently as clinically indicated. Note: does not need to be performed prior to cisplatin and pembrolizumab/placebo administration at C1D1.

Period	Screen-ing	Treatment		EOT	Post treatment					Notes
		Cycles 1-5	Cycles 6-20			Posttreatment Follow-up[b]				
Cycle	Screen-ing	Cisplatin (QW) plus EBRT followed by BT plus pembrolizumab or placebo (Q3W)	Pembrolizumab or placebo (Q6W)	Discon-tinuation	Safety Follow-up[a]	Years 1-2 Q12W	Year 3 Q24W	Years 4 + Annually	Survival Follow-up Q12W	Participant must receive 5 infusions (ie, Cycles) of pembrolizumab or placebo Q3W before moving to Q6W dosing. The interval between Cycle 5 and Cycle 6 is 3 weeks ±3 days. Q6W dosing starts from Cycle 6 onwards. CCRT are administered during the Q3W dosing regimen. Interruptions of cisplatin, EBRT, BT, pembrolizumab or placebo are allowed according to Section 6.4.
Scheduling	–42 days to –1 day	±1 day (cisplatin) ±3 days (pembrolizumab or placebo)	±3 days		30 days after last dose (+7 days)	±14 days	±14 days	±14 days	±14 days	
Hematology	X	X	X	X	X					Perform within 7 days prior to C1D1 of study intervention. While on CCRT perform within 72 hours prior to each cisplatin administration. Perform within 72 hours prior to each pembrolizumab or placebo administration. Perform more frequently as clinically indicated. Note: does not need to be performed prior to cisplatin and pembrolizumab/placebo administration at C1D1.
Urinalysis	X	X	X	X	X					Perform within 7 days prior to C1D1 of study intervention. Perform within 72 hours prior to pembrolizumab or placebo administration at C2, C4, and every cycle from C6 onwards.

Period	Screen-ing	Treatment		EOT	Post treatment					Notes
		Cycles 1-5	Cycles 6-20			Posttreatment Follow-up[b]				
Cycle	Screen-ing	Cisplatin (QW) plus EBRT followed by BT plus pembrolizumab or placebo (Q3W)	Pembrolizumab or placebo (Q6W)	Discon-tinuation	Safety Follow-up[a]	Years 1-2 Q12W	Year 3 Q24W	Years 4 + Annually	Survival Follow-up Q12W	Participant must receive 5 infusions (ie, Cycles) of pembrolizumab or placebo Q3W before moving to Q6W dosing. The interval between Cycle 5 and Cycle 6 is 3 weeks ±3 days. Q6W dosing starts from Cycle 6 onwards. CCRT are administered during the Q3W dosing regimen. Interruptions of cisplatin, EBRT, BT, pembrolizumab or placebo are allowed according to Section 6.4.
Scheduling	–42 days to –1 day	±1 day (cisplatin) ±3 days (pembrolizumab or placebo)	±3 days		30 days after last dose (+7 days)	±14 days	±14 days	±14 days	±14 days	
T3 or FT3 / FT4 / TSH	X	X	X	X	X					Perform during screening, and within 72 hours prior to pembrolizumab or placebo administration at C2, C4, and every cycle from C6 onwards.
Study Treatment Administration										
Pembrolizumab (MK-3475) or placebo		X	X							For pembrolizumab: 200 mg by IV Cycles 1-5 followed by 400 mg by IV Cycles 6-20. For placebo: normal saline or dextrose Cycles 1-20. Note: Pembrolizumab/placebo should be administered prior to cisplatin when possible.
Cisplatin		X								40 mg/m^2 by IV weekly. Cisplatin must be given on a day that EBRT is scheduled and prior to that radiation treatment. An optional sixth infusion of cisplatin may be administered according to local practice. Refer to Section 6.1 for treatment requirements.

Period	Screen-ing	Treatment		EOT	Post treatment					Notes
		Cycles 1-5	Cycles 6-20			Posttreatment Follow-up[b]				Participant must receive 5 infusions (ie, Cycles) of pembrolizumab or placebo Q3W before moving to Q6W dosing. The interval between Cycle 5 and Cycle 6 is 3 weeks ±3 days. Q6W dosing starts from Cycle 6 onwards. CCRT are administered during the Q3W dosing regimen. Interruptions of cisplatin, EBRT, BT, pembrolizumab or placebo are allowed according to Section 6.4.
Cycle	Screen-ing	Cisplatin (QW) plus EBRT followed by BT plus pembrolizumab or placebo (Q3W)	Pembrolizumab or placebo (Q6W)	Discon-tinuation	Safety Follow-up[a]	Years 1-2 Q12W	Year 3 Q24W	Years 4 + Annually	Survival Follow-up Q12W	
Scheduling	–42 days to –1 day	±1 day (cisplatin) ±3 days (pembrolizumab or placebo)	±3 days		30 days after last dose (+7 days)	±14 days	±14 days	±14 days	±14 days	
External Beam Radiotherapy		X								Refer to Section 6.1 for treatment requirements.
Brachytherapy		X								Refer to Section 6.1 for treatment requirements.
Efficacy Assessments										
PET / CT Scan	X		X							Baseline PET/ CT scan to be performed within 28 days prior to randomization. A PET/CT scan will be performed 12 weeks (±14 days) after completing CCRT. For participants who are lymph node positive at baseline by PET only, a PET scan (with CT component only as necessary for attenuation correction and anatomic location) to confirm disappearance of the FDG uptake in the node(s) is required to determine that a complete response has occurred. If the nodal activity has not resolved, another PET scan should be performed at later time points, if the MRI and/or CT scan still shows complete response.

Period	Screen-ing	Treatment		EOT	Post treatment					Notes
		Cycles 1-5	Cycles 6-20			Posttreatment Follow-up[b]				
Cycle	Screen-ing	Cisplatin (QW) plus EBRT followed by BT plus pembrolizumab or placebo (Q3W)	Pembrolizumab or placebo (Q6W)	Discon-tinuation	Safety Follow-up[a]	Years 1-2 Q12W	Year 3 Q24W	Years 4 + Annually	Survival Follow-up Q12W	Participant must receive 5 infusions (ie, Cycles) of pembrolizumab or placebo Q3W before moving to Q6W dosing. The interval between Cycle 5 and Cycle 6 is 3 weeks ±3 days. Q6W dosing starts from Cycle 6 onwards. CCRT are administered during the Q3W dosing regimen. Interruptions of cisplatin, EBRT, BT, pembrolizumab or placebo are allowed according to Section 6.4.
Scheduling	–42 days to –1 day	±1 day (cisplatin) ±3 days (pembrolizumab or placebo)	±3 days		30 days after last dose (+7 days)	±14 days	±14 days	±14 days	±14 days	
CT – chest MRI – abdomen & pelvis	X	Imaging during treatment is performed according to the schedule in the 'Notes' column		X		X	X	X		Baseline CT/MRI to be performed within 28 days prior to randomization. The first postrandomization imaging will be performed 12 weeks (±14 days) after completing CCRT and Q12W (±14 days) from that point forward in years 1-2, Q24W (±14 days) in year 3, annually (±14 days) in year 4 onwards. Perform again within ±4 weeks of treatment discontinuation unless most recent scan was already performed within 4 weeks prior to discontinuation.

Period	Screen-ing	Treatment		EOT	Post treatment					Notes
		Cycles 1-5	Cycles 6-20			Posttreatment Follow-up[b]				
Cycle	Screen-ing	Cisplatin (QW) plus EBRT followed by BT plus pembrolizumab or placebo (Q3W)	Pembrolizumab or placebo (Q6W)	Discon-tinuation	Safety Follow-up[a]	Years 1-2 Q12W	Year 3 Q24W	Years 4 + Annually	Survival Follow-up Q12W	Participant must receive 5 infusions (ie, Cycles) of pembrolizumab or placebo Q3W before moving to Q6W dosing. The interval between Cycle 5 and Cycle 6 is 3 weeks ±3 days. Q6W dosing starts from Cycle 6 onwards. CCRT are administered during the Q3W dosing regimen. Interruptions of cisplatin, EBRT, BT, pembrolizumab or placebo are allowed according to Section 6.4.
Scheduling	–42 days to –1 day	±1 day (cisplatin) ±3 days (pembrolizumab or placebo)	±3 days		30 days after last dose (+7 days)	±14 days	±14 days	±14 days	±14 days	
Patient-reported Outcomes (perform in the order shown below and prior to performing any study procedures)										
EORTC QLQ-C30 EORTC QLQ-CX24 PGI-S PGI-C* EQ-5D-5L		X	X	X		X	X	X		Administer PROs prior to performing any procedures, assessments, and treatment. Collect at every cycle that pembrolizumab / placebo is administered, until treatment completion or discontinuation. Continue to collect in posttreatment follow-up until disease progression; only 1 collection is required for each scheduled evaluation time point. If pembrolizumab/ placebo is discontinued prior to the completion, continue to administer PROs every 3 weeks until discontinuation and then administer according to the schedule of activities. * PGI-C is only administered at Cycles 4, 7, 8, 10, 11, and 12.

Period	Screen-ing	Treatment		EOT	Post treatment					Notes
		Cycles 1-5	Cycles 6-20			Posttreatment Follow-up[b]				
Cycle	Screen-ing	Cisplatin (QW) plus EBRT followed by BT plus pembrolizumab or placebo (Q3W)	Pembrolizumab or placebo (Q6W)	Discon-tinuation	Safety Follow-up[a]	Years 1-2 Q12W	Year 3 Q24W	Years 4 + Annually	Survival Follow-up Q12W	Participant must receive 5 infusions (ie, Cycles) of pembrolizumab or placebo Q3W before moving to Q6W dosing. The interval between Cycle 5 and Cycle 6 is 3 weeks ±3 days. Q6W dosing starts from Cycle 6 onwards. CCRT are administered during the Q3W dosing regimen. Interruptions of cisplatin, EBRT, BT, pembrolizumab or placebo are allowed according to Section 6.4.
Scheduling	–42 days to –1 day	±1 day (cisplatin) ±3 days (pembrolizumab or placebo)	±3 days		30 days after last dose (+7 days)	±14 days	±14 days	±14 days	±14 days	
Blood and Tissue Sample Collection for Biomarker Analyses										
Archival or Newly Obtained Tissue Collection (Required)	X									Tissue is required at screening for all participants.
Newly Obtained Tissue Collection (Optional)		◄———	———	———	———	———	———	———►		During C5 and prior to C6D1 and at disease progression (any cycle) collect additional tissue for participants who are able to undergo a biopsy and provide optional tissue collection consent.
Blood for Genetic Analyses		X								Collect prior to administration of study treatment at C1D1. Refer to Section 8.8 for additional collection information.
Blood for RNA Analyses		X	X	X						Collect prior to administration of study treatment at C1D1, C6D1 and EOT.
Blood for ctDNA Analyses		X	X	X						Collect prior administration of study treatment at C1D1, C2D1, C6D1, C7D1, C8D1, and at EOT

Abbreviations: AE=adverse event; aPTT / PTT=activated partial thromboplastin time / partial thromboplastin time; BT=brachytherapy; C=Cycle; CCRT=concurrent chemoradiotherapy; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; D=day; EBRT=external beam radiotherapy; ECG=electrocardiograph, ECOG=Eastern Cooperative Oncology Group; EQ-5D-5L=EuroQoL 5 Dimension Questionnaire; EORTC QLQ-C30=European Organization for Research & Treatment of Cancer Quality of Life Questionnaire global health status; EORTC QLQ-CX24=European Organization for Research & Treatment of Cancer Quality of Life Questionnaire (Symptom Score for Cervical Cancer); EOT=end of treatment; FDG=fluorodeoxyglucose; FT3=free T3 thyroid hormone; FT4=free thyroxine; HBV= hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ID=identity; INR=international normalized ratio; IRT=interactive response technology; IV=intravenous; MRI=magnetic resonance imaging; PET=positron emission tomography; PGI-C=Patient Global Impression of Change; PGI-S=Patient Global Impression of Severity; PRO=patient-reported outcomes; PT=prothrombin time; QW=dosing every week; QW3=dosing every 3 weeks; QW6=dosing every 6 weeks; Q12W=every 12 weeks; Q24W=every 24 weeks; RECIST=Response Evaluation in Solid Tumor; RNA=ribonucleic acid; SAE=serious adverse event; T3=T3 thyroid hormone; TSH=thyroid-stimulating hormone; WOCBP=woman of childbearing potential.

a. If the Discontinuation Visit occurs ≥30 days from last dose of study treatment, a separate Safety Follow-up Visit is not required.
b. Participants who discontinue study intervention for reasons other than RECIST 1.1 radiographic disease progression (including those with histopathologic confirmation of suspected disease progression) will have posttreatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1 by the investigator, withdrawal of consent, pregnancy, death, or loss to follow-up, whichever comes first.

2 INTRODUCTION

Cervical cancer is one of the most frequently diagnosed malignancies and causes of cancer related death among women [Bray, F., et al 2018]. Worldwide, there are an estimated 569,847 newly diagnosed cases of cervical cancer and an estimated 311,365 deaths per year [Bray, F., et al 2018]. The extent of disease at the time of diagnosis is a significant prognostic factor presenting patients with more advanced disease especially in developing countries [Pisani, P., et al 1999]. Women with LACC (Stage IB2 to IVA) have higher disease recurrence rates than those with earlier stages of disease.

According to FIGO 2014 staging, Stage IB2 is confined to the cervix with a clinically visible mass >4 cm, Stage II invades beyond uterus but not to pelvic wall or to the lower third of the vagina, Stage III extends to the pelvic sidewall and/or involves the lower third of the vagina, and/or causes hydronephrosis, or a nonfunctioning kidney, while Stage IVA invades the mucosa of the bladder or rectum, and extends beyond the true pelvis [Belhadj, H., et al 2014].

Rate of recurrence worsen by stage, and benefits of SOC treatment are greater with earlier versus more advanced stages of disease. The 5-year OS rates for Stage III to IVA versus Stage IB2 to IIB were reported as 60% versus 86%, respectively, demonstrating the impact of staging on prognosis [Cetina, L., et al 2006]. A meta-analysis from 18 randomized studies also provides clear evidence of a larger unmet medical need for patients with Stage III-IVA despite standard of care treatment [Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboratio 2008]. Most recently, patients with OS and pelvic control rates at 3 and 5 years were reported in a large, multicentral study clearly demonstrating worse control rates and survival for Stage III and IVA patients [Sturdza, A., et al 2016].

Nodal involvement has also been an established prognostic factor as shown in several studies with the help of MRI or PET [Kim, Y. S., et al 2008]. In a recent study, half of the patients developed recurrent disease with PET positive nodes. Similarly, 5 year overall survival rates were 48% versus 70%, respectively, showing worse outcomes for patients with nodal involvement [Narayan, K., et al 2009]. The 3-year survival rate of negative PALN patients was higher than that of positive PALN patients in a recently reported study (89.5±1.5% versus 67.0 ± 6.0%, $p<0.001$). The corresponding positive PALN rates were 8.4%, 11.1%, 17.2%, and 21.7% for Stage IB1, IB2, IIA1, and IIA2 disease, respectively, which suggested that patients with more advanced FIGO stage were more likely to have PALN metastasis. Pelvic LN involvement rates also increased from 30.9% at the IB1 stage to 59.4% at the IIA2 stage [Han, X., et al 2017]. Similarly, patients with positive pelvic LNM have a higher recurrence rate and poor survival outcomes compared with pelvic LNM negative ones. Patients with more than 2 pelvic nodes have even poorer outcomes than the those who have 2 or less [Liu, Y., et al 2015].

Standard of care treatment is concurrent chemoradiation followed by brachytherapy [Sturdza, A., et al 2016]. Chemoradiation was shown to be superior versus RT alone in a meta-analysis from randomized controlled studies in terms of overall survival, event-free survival and pelvic control [Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboratio 2008]

[Green, J. A., et al 2005] [Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboratio 2010]. Chemoradiation showed a reduction in risk of death which translated in to a 10% absolute improvement in survival. The survival benefit, however, significantly decreased with increasing stage. For Stage IB to IIA, IIB and III to IVA, the 5-year survival benefit was 10%, 7%, and 3%, respectively (p=0.017). An absolute improvement in PFS was higher than the absolute improvement in OS, at 13% and there was no association between staging and disease-free interval. Particularly in studies with platinum-based regimens, there was a reduction of risk in local recurrence and some trends seen toward a reduction in distant metastasis as well [Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboratio 2008].

Chemotherapy regimen is single agent cisplatin given weekly (40 mg/m2) along with RT for 5 weeks. Single agent cisplatin administered with RT was shown to have a better tolerability with similar efficacy versus cisplatin and fluorouracil given with RT with higher rate of completion of chemoradiation, less Grade 3-4 hematologic toxicities and same ORR. The OS rate reported at 4 years were also similar in this study [Kim, Y. S., et al 2008]. The number of cycles received during treatment seems important for systemic control in high-risk patients [Schmid, M. P., et al 2014], even if retrospective data analysis from Gynecologic Oncology Group 120 and Gynecologic Oncology Group 165 found no difference in efficacy for patients treated with 5 cycles versus 6 cycles of weekly cisplatin [Monk, B. J., et al 2007]. Of the note, only 50% to 70% of patients were able to complete 6 cycles of cisplatin without dose decreases or delays, mainly due to hematologic toxicities [Monk, B. J., et al 2007] [Nugent, E. K., et al 2010] [Keys, H. M., et al 1999] [Lanciano, R., et al 2005]. Another study reported inferior survival if less than 5 cycles were administered [Nugent, E. K., et al 2010].

Radiotherapy is delivered to the pelvis using external beam RT concurrently with cisplatin administration.

Brachytherapy is an absolute requisite component for the curative management of locally advanced cervical cancer and cannot be defined “optional” as referred by a recent editorial from Tanderup et al [Tanderup, K., et al 2013]. Brachytherapy is mainly administered in an effort to maximize the local control, can be intracavitary, using applicators inserted into the uterus or vagina, or interstitial, in which needles/catheters are inserted directly into the tumor. Brachytherapy should follow EBRT and concomitant chemotherapy to obtain maximal tumor regression. It can be delivered with either a low dose rate, pulse dose rate or high dose rate. Data highlighting the importance of brachytherapy derived from more than 7000 locally advanced cervical cancer patients is available in the SEER database [Han, K., et al 2013].

Overall, the concurrent use of image guided brachytherapy improves pelvic control by approximately 10% compared with conventional 2D BT with no evident impact of the use of concomitant chemotherapy. The effect was larger in advanced stages. Image guided BT combined with chemoradiotherapy led to excellent local control and pelvic control rates with limited morbidity in a study called RetroEMBRACE. A total of 731 patients from 12 centers who were treated with CCRT followed by image guided brachytherapy were analyzed [Sturdza, A., et al 2016].

Despite these improvements, approximately half of the women with high-risk cervical cancer experience a recurrence of their cervical cancer within 2 years. Thus, new treatment modalities and paradigms are needed to significantly improve the prognosis for women diagnosed with high-risk LACC.

2.1 Study Rationale

Immunotherapy is emerging as a potential strategy to enhance traditional cervical cancer treatments. It is considered that pembrolizumab and CCRT will be more beneficial to the patient via enhancing immunostimulatory activity of pembrolizumab as a single agent use.

Cervical cancer is overwhelmingly an HPV-driven cancer, with HPV DNA detected in 90% of tumors. Human papillomavirus infection, particularly types 16 and 18, are significantly associated with subsequent development of cervical cancer. Recent research on the biology of HPV-related cancers supports the strategy of targeting PD-L1 with pembrolizumab demonstrating durable responses in such tumors. The expression of high levels of PD-L1 was reported in cervical cancer, thus restoring host antitumor immunity might provide a new therapeutic strategy.

Pembrolizumab monotherapy demonstrated durable antitumor activity and manageable safety in patients with advanced cervical cancer. At ASCO in 2016, the preliminary results of KEYNOTE-028 study on cervical cancer patients were presented: 17% objective response and OS of 9 months were reported with pembrolizumab single agent in a population of 24 advanced/recurrent cervical cancer patients pretreated with platinum-based chemotherapy (96%), radiotherapy (92%) and bevacizumab (42%), in which 38% of patients received pembrolizumab at least as fourth line of chemotherapy [Frenel, J. S., et al 2017]. A subsequent Phase 2 study, KEYNOTE-158, enrolled 98 patients with pretreated advanced cervical cancer to receive single agent pembrolizumab. The ORR was 13.3%, with 3 patients with CR and 10 patients with PR [Chung, H. C., et al 2018]. On the basis of these results with pembrolizumab, the US Food and Drug Administration granted accelerated approval of pembrolizumab for patients with advanced PD-L1–positive cervical cancer who experienced progression during or after chemotherapy [Chung, H. C., et al 2019]. Recently, Hollebecque et al presented at ASCO 2017 the results of a Phase 1/2 study evaluating nivolumab 240 mg every 2 weeks in vulvar, vaginal and cervical tumors. Cervical cancer patients experienced promising clinical activity with good toxicity profile (ORR 26.3%; PFS 5.5 months) [Hollebecque, A., et al 2017].

Currently, there are limited data on the use anti-PD-1 or anti-PD-L1 in the LACC setting in combination with chemoradiotherapy. However, preclinical and preliminary clinical observations provide a strong rationale for testing RT and cisplatin as potentiators of immune checkpoint inhibitors. Radiotherapy used at therapeutic doses, as well as some cytotoxic agents induce immunogenic cell death and the release of tumor antigens that can effectively prime antigen presenting cells [Formenti, S. C. 2009] [Reits, E. A., et al 2006]. Radiotherapy and chemotherapy act on the microenvironment to decrease its immunosuppressive properties by inducing the release of cytokines and chemokines that have the ability to attract T-cells [Golden, E. B. 2015]. Radiotherapy has both systemic and local effects on the immune system which in combination with immunotherapy may lead to maximizing

antitumor responses [Grassberger, C., et al 2019]. In addition, RT may augment the TILs numbers and broaden their T-cell receptor repertoire of cytotoxic effectors cells [Derer, A., et al 2015] [Esposito, A., et al 2015]. Radiotherapy also increases the expression of PD-L1 on tumor cells, which can also explain part of the synergism [Deng, L., et al 2014]. Radiation therapy in combination with immunotherapy is being evaluated as an attractive option across gynecologic cancers [Lee, L. 2019]. In addition to immunomodulation, the abscopal effects in gynecologic and other cancers are also suggested to contribute to efficacy of the combination treatment.

Preclinical models have demonstrated synergy between RT and PD-1 blockade treatments [Zeng, J., et al 2013] and several clinical studies combining RT with immunotherapy are underway in multiple tumor types [Daly, M. E., et al 2015]. Mayedev et al reported at ASCO 2017 the safety, tolerability, and efficacy of a Gynecologic Oncology Group Phase 1 study evaluating sequential ipilimumab in combination with definitive CCRT in node-positive cervical cancer [Mayadev, J., et al 2017]. The data suggest that immunotherapy has potential activity (secondary endpoint 1-year disease-free survival was 74%) and a good toxicity profile: most common adverse events were Grade 1-2 diarrhea, rash and endocrinopathies. Incidence of Grade 3 toxicity was 16%, all of which resolved. With a median follow-up of 12 months, there were no major late toxicities reported, and a 1-year disease-free survival of 74%.

Antonia SJ et al recently reported the results of a Phase 3 study on durvalumab after CCRT in locally advanced lung cancer (PACIFIC study): 713 patients with Stage III lung cancer at completion of CCRT were randomly assigned to receive durvalumab (at a dose of 10 mg per kilogram of body weight intravenously) or placebo every 2 weeks for up to 12 months [Antonia, S. J., et al 2017]. The median PFS was 16.8 months with durvalumab versus 5.6 months with placebo (stratified HR 0.52; $p<0.001$); the response rate was higher with durvalumab than with placebo (28.4% versus 16.0%; $p<0.001$), and the median duration of response was longer (72.8% versus 46.8% of the patients had an ongoing response at 18 months); the median time to death or distant metastasis was longer with durvalumab than with placebo (23.2 months versus 14.6 months; $p<0.001$). Of note, safety was similar between the groups.

Chemoradiotherapy appears to modulate tumor microenvironment favorably for immuno-oncology as shown in the PACIFIC study. Progression-free survival was significantly longer with durvalumab than with placebo. The secondary endpoints also favored durvalumab, and safety was similar between the groups [Antonia, S. J., et al 2017].

The addition of pembrolizumab (Keytruda®) to a CCRT regimen yielded CR rates of 85% in patients with HPV-positive advanced squamous cell carcinoma of the head and neck. These findings from a Phase 1b study were presented at the 2018 Society for Immunotherapy of Cancer Annual Meeting. The study enrolled patients with HPV-positive and HPV-negative tumors, with 34 and 23 patients, respectively, evaluable for the interim analysis. All patients were eligible for definitive CCRT and were not surgical candidates. The HPV-positive cohort had at least 70% of cells staining positive for P16. The regimen's backbone was cisplatin at 40 mg/m^2 given weekly for 6 planned doses, radiation therapy at 2 Gy once daily for a total of 70 Gy, plus pembrolizumab at 200 mg every Q3W for 8 planned doses. Patients first

received pembrolizumab 1 week before chemoradiation, and this treatment was followed by 2 doses during chemoradiation and 5 doses afterward. Weekly cisplatin was chosen because it is potentially less myelosuppressive than some other regimens and avoids the need for dexamethasone, which may dampen the immune response. The primary endpoint was overall CR at Day 150. Two patients discontinued treatment due to immune-related adverse events, both of which resolved. Most adverse events were in line with previous experience with this regimen. The chemotherapy and RT regimens were able to be administered as planned, with no major delays in treatment. The addition of pembrolizumab did not impact the safety of standard chemoradiotherapy. Full radiation dose was achieved for the vast majority of patients with the intended chemotherapy dose [Frontline Medical Communications Inc. 2018].

2.2 Background

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the 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 of patients across a number of indications. For more details on specific indications refer to the IB.

2.2.1 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+ regulatory T-cells (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 renal cell carcinoma. 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 on 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 IgV–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 CD3ζ, PKCθ, and ZAP70, 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 down-modulates 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 high-risk LACC.

2.2.2 Preclinical and Clinical Studies

Accumulating evidence shows a correlation between TILs in cancer tissue and favorable prognosis in various malignancies [Lavoue, V., et al 2013]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The ligands PD-L1 and PD-L2 are commonly up-regulated in many different human tumors with PD-L1 being the predominant PD-1 ligand on solid tumors. High expression levels of PD-L1 have been shown in cervical cancer and PD-1/PD-L1 inhibitors might be a novel choice to improve the clinical outcomes of these patients [Liu, Y., et al 2019]. Importantly, many studies have described the correlation of PD-L1 with invasiveness, metastasis, and poor prognosis. When PD-1 receptor binds with its ligand (PD-L1/B7-H1), T-cell inhibition and down regulation of T-cell responses occur. This allows tumors to directly halt antitumor T-cell activity, also known as adaptive resistance. Blocking PD-1 or PD-L1 via a mAb empowers the T-cell response. To date, different mAbs against PD-1 and PD-L1 have been evaluated showing effectiveness and low toxicities in different cancer types, including melanoma, nonsmall-cell lung cancer, renal-cell carcinoma, bladder cancer, and Hodgkin's lymphoma.

Preclinical evidence seems to suggest that immunotherapy may have a potential therapeutic impact in cervical cancer and represent a promising therapeutic tool for the future [Menderes, G., et al 2016].

Preclinical models have demonstrated synergy between RT and PD-1 blockade treatments [Zeng, J., et al 2013]. Radiation therapy is thought to have immunostimulatory effects by enhancing cancer antigen presentation. Because both modalities work through immune-mediated mechanisms, combination therapy has the potential to augment immune activation by PD-1 checkpoint inhibitors [Formenti, S. C. 2009].

2.2.3 Ongoing Clinical Studies

There is an ongoing randomized Phase 2 study of chemoradiation and pembrolizumab in 88 participants with LACC to compare concurrent versus sequential use of pembrolizumab in combination with CCRT. The primary objective of the study is to assess the safety and immune response to pembrolizumab given either sequentially or with CCRT. The study

design also focuses on the effect of treatment on immune response pathways and specific immune markers (ClinicalTrials.gov Identifier: NCT02635360).

As of AUG 2019, 60 patients (of a planned total of 88) had started treatment; 52 had completed treatment. Overall, there were 22 Grade 3 and 11 Grade 4 treatment-related adverse events, the most common of which was lymphopenia (Arm 1: n=8; Arm 2: n=12). Two patients experienced the adverse event of special interest of diarrhea. Most patients completed 6 cisplatin treatments (100% in Arm 1; 82% in Arm 2). 83% of patients completed 3 infusions of pembrolizumab. All but 2 patients completed radiation (2 patients in Arm 2 withdrew from the study). As of AUG 2019, the safety and feasibility of the combination of pembrolizumab and pelvic CRT has been demonstrated and no major differences in safety were evident by arm. The safety stopping bounds were not crossed and the study is continuing with accrual [Duska, L. R., et al 2020].

Most recently a randomized, Phase 3, global, multicenter, double-blind, placebo-controlled study was initiated to compare the efficacy and safety of durvalumab + CCRT versus CRT alone as treatment for women with high-risk LACC (CALLA; ClinicalTrials.gov Identifier: NCT03830866). Results based on 770 randomized patients (N=385 per arm) with median follow-up of ~18.5 months (data cut-off 20-JAN-2022) did not show a statistically significant improvement in PFS for durvalumab + CCRT versus placebo + CRT (HR: 0.84; 95% CI: 0.65, 1.08; *p*=0.174), with 2-year PFS rates of 65.9% and 62.1%, respectively. There was no detriment to OS (HR: 0.78; 95% CI: 0.55, 1.10; nominal *p*=0.156), although data were immature (17% maturity) and not formally tested. OS rates were not reported. Grade 3/4 AEs occurred in 51.7% and 51.0% of patients in the durvalumab + CCRT and placebo + CRT arms, respectively; 12.5% and 9.6% of patients discontinued treatment due to AEs possibly related to study drug [Monk, B. J. 2022].

There are also other ongoing Phase 1/2 studies with atezolizumab, dostarlimab (TSR-042) and nivolumab in combination with CCRT mainly focusing on high-risk LACC patients.

2.3 Benefit/Risk Assessment

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

Given the high rate of relapse following chemoradiation, new treatment modalities and paradigms are needed to significantly improve the prognosis of women diagnosed with high-risk LACC. Immunotherapy is emerging as a potential strategy to enhance traditional cervical cancer treatments. Pembrolizumab and CCRT may be more beneficial to the patient via enhancing immunostimulatory activity of pembrolizumab as a single agent use. The current data discussed above suggests that the chemotherapy and radiotherapy regimens may be administered as planned, with no major delays in treatment when given in combination with pembrolizumab. Full radiation dose is expected to be achieved for the vast majority of patients with the intended chemotherapy dose providing an acceptable safety profile.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Throughout this protocol, the term RECIST 1.1 refers to the modification of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Refer to Section 4.2.1.1 for additional details. When tumor growth is suspected on imaging or by physical examination, an optional biopsy for confirmation of suspected disease progression is allowed at investigator discretion. Throughout the protocol, the term "histopathologic confirmation" is used when referencing a biopsy that confirms suspected disease progression either from a new lesion or a pre-existing lesion showing growth.

This study will enroll female participants, at least 18 years of age, with high-risk locally advanced cervical cancer and will include the following objectives and endpoints:

Objectives	Endpoints
Primary	
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to progression-free survival per RECIST 1.1 as assessed by investigator or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1) as assessed by investigator Hypothesis (H1): concurrent chemoradiotherapy plus pembrolizumab is superior to concurrent chemoradiotherapy plus placebo with respect to progression-free survival per RECIST 1.1 by investigator or by histopathologic confirmation as indicated	Progression-free survival: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to overall survival Hypothesis (H2): concurrent chemoradiotherapy plus pembrolizumab is superior to concurrent chemoradiotherapy plus placebo with respect to overall survival	Overall survival: The time from randomization to death due to any cause

Objectives	Endpoints
Secondary	
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to progression-free survival per RECIST 1.1 as assessed by blinded independent central review (BICR)	Progression-free survival: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to progression-free survival at 2 years per RECIST 1.1 as assessed by investigator or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1)	Progression-free survival at 2 years: The proportion of participants that are progression-free survival event-free at 2 years
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to progression-free survival at 2 years per RECIST 1.1 as assessed by blinded independent central review	Progression-free survival at 2 years: The proportion of participants that are progression-free survival event-free at 2 years
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to overall survival at 3 years	Overall survival at 3 years: The proportion of participants that are overall survival event-free at 3 years
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to complete response rate at 12 weeks after completion of concurrent chemoradiotherapy per RECIST 1.1 as assessed by investigator in all randomly assigned participants with measurable disease at study entry	Complete response rate at 12 weeks after completion of concurrent chemoradiotherapy

Objectives	Endpoints
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to objective response rate per RECIST 1.1 as assessed by investigator in all randomly assigned participants with measurable disease at study entry	Objective response: complete response or partial response
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to complete response rate at 12 weeks after completion of concurrent chemoradiotherapy per RECIST 1.1 as assessed by blinded independent central review in all randomly assigned participants with measurable disease at study entry	Complete response rate at 12 weeks after completion of concurrent chemoradiotherapy
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to objective response rate per RECIST 1.1 as assessed by blinded independent central review in all randomly assigned participants with measurable disease at study entry	Objective response: complete response or partial response
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to overall survival and progression-free survival per RECIST 1.1 as assessed by investigator or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1), by PD-L1 status (by combined positivity score)	Overall survival Progression-free survival
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to overall survival and progression-free survival per RECIST 1.1 as assessed by blinded independent central review, by PD-L1 status (by combined positivity score)	Overall survival Progression-free survival

Objectives	Endpoints
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to progression-free survival after next-line treatment (progression-free survival 2) following discontinuation of study treatment administration as determined by the investigator according to the local standard of clinical practice	Progression-free survival 2: The time from the date of randomization until disease progression on next-line treatment or death due to any cause, whichever occurs first
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to change from baseline score in global quality of life and physical function using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) global health status/Quality of Life scale and Physical Function subscale	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire EORTC QLQ-C30 Global Score and Physical Function subscale
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to change from baseline score in symptom experience using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Symptom Score for Cervical Cancer) the EORTC QLQ-CX24 symptom specific scale (11 items)	The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Symptom Score for Cervical Cancer) EORTC QLQ-CX24 symptom specific scale
To evaluate the safety and tolerability of pembrolizumab in combination with concurrent chemoradiotherapy	Adverse events Study treatment discontinuation due to adverse events

Objectives	Endpoints
Tertiary/Exploratory	
[redacted]	

Objectives	Endpoints
[redacted]	

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, Phase 3, placebo-controlled, multisite, double-blind study of chemoradiotherapy with or without pembrolizumab in participants with high-risk LACC.

Approximately 980 participants will be enrolled in the global portion of the study. After enrollment of the global portion of the study is complete, the study may remain open to enrollment in China alone until the target number of participants in China has been enrolled to meet local regulatory requirements. An extension portion of the study will be identical to the global study, (eg, inclusion and exclusion criteria, study endpoints, primary and secondary objectives, study procedures, and statistical analyses).

Eligible participants with high-risk LACC FIGO 2014 Stage IB2-IIB (with node-positive disease) or Stage III-IVA (either node-positive or node-negative disease) will be randomly assigned in a 1:1 ratio to one of the following treatment arms:

1) Concurrent chemoradiotherapy in combination with pembrolizumab (200 mg Q3W for 5 infusions) followed by pembrolizumab alone (400 mg Q6W for 15 infusions) or

2) Concurrent chemoradiotherapy in combination with placebo (Q3W for 5 infusions) followed by placebo alone (Q6W for 15 infusions).

Standard of care CCRT is given during the Q3W dosing period of pembrolizumab (Arm 1) or placebo (Arm 2) and includes the following:

1) Cisplatin, 5 infusions given IV QW at 40 mg/m^2 (an optional, sixth infusion of cisplatin may be administered according to local practice) plus

2) EBRT over 40 days, followed by

3) Brachytherapy

Note: brachytherapy should follow the completion of EBRT, and the overall treatment time of EBRT and brachytherapy together should not exceed 50 days (with an extension to a maximum of 56 days for unforeseen delays). The minimum acceptable radiation is 80 Gy for volume-directed and 75 Gy for point-directed. Please refer to the Radiation Manual for further guidance.

Geographic variance in total radiation dose administered, number of fractions and methodology of application may be permitted after consultation with the Sponsor.

The SOC will be at least 3D conformal planning.

To limit overall treatment time, efficient organization of the whole multimodal treatment is required. This includes use of SIB in participants with lymph node involvement, minimizing treatment interruptions as much as possible and by planning the timing of brachytherapy carefully.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3 (Table 1). Details of each procedure are provided in Section 8.

There will be 2 formal interim analyses. The first interim analysis will be conducted when approximately 237 PFS events are observed. The second interim analysis will be conducted when approximately 304 PFS events are observed. A final analysis will be conducted when approximately 240 OS events are observed.

Results of the interim and final analyses will be reviewed by the external DMC, who will make recommendations to the Sponsor to continue, modify, or end the study according to the plan described in Section 9.

4.2 Scientific Rationale for Study Design

MK-3475 A18/ENGOT-CX11/GOG3047 is a randomized, Phase 3, double-blind study of chemoradiotherapy with or without pembrolizumab for the treatment of high-risk, locally advanced cervical cancer.

The purpose of this study is to evaluate the efficacy and safety of pembrolizumab plus concurrent chemoradiotherapy compared with placebo plus concurrent chemoradiotherapy in participants with locally advanced cervical cancer.

The primary hypotheses are that pembrolizumab plus concurrent chemoradiotherapy is superior to placebo plus concurrent chemoradiotherapy with respect to progression-free survival and overall survival.

High-risk LACC is a population with larger unmet medical need. Approximately half of the women treated with SOC chemoradiotherapy experience a recurrence of their cervical cancer within 2 years. Thus, new treatment modalities and paradigms are needed to significantly improve the prognosis for women diagnosed with high-risk LACC. It is considered that pembrolizumab and CCRT will be more beneficial to the patient via enhancing immunostimulatory activity of pembrolizumab. Pembrolizumab monotherapy demonstrated durable antitumor activity and manageable safety in patients with advanced cervical cancer and received accelerated approval in patients with advanced PD-L1–positive cervical cancer who experienced progression during or after chemotherapy. Preclinical and preliminary clinical observations from other tumor types provide a strong rationale for testing RT and cisplatin as potentiators of immune checkpoint inhibitors.

Study and scientific rationale are further described in Section 2.1.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

Progression-free survival and OS are primary endpoints.

This study will use PFS based on RECIST 1.1 criteria as assessed by investigator and histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1) as the primary endpoint. Locally advanced cervical cancer is a setting where disease progression is highly informed by clinical judgment, including histopathologic confirmation of disease progression with biopsy. PFS by BICR may introduce bias because of informative censoring, which results from having to censor unconfirmed investigator determined progressions. If BICR cannot confirm the locally determined progression, then these cases would be censored at the time of local progression for the BICR analysis of PFS. PFS by investigator is anticipated to result in fewer events censored from PFS analysis compared with BICR and, therefore, to preserve available power for PFS analysis. Investigator is therefore considered a more appropriate primary endpoint in this disease setting. For these reasons, the primary endpoint is PFS by investigator and PFS by BICR is now a secondary endpoint. Progression-free survival is an acceptable measure of clinical benefit for a late stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The use of PFS per RECIST 1.1 is typically considered acceptable by regulatory authorities in a double-blinded randomized controlled study.

Overall survival has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies.

Secondary efficacy endpoints include PFS based on RECIST 1.1 criteria CR at 12 weeks and ORR as assessed by investigator and BICR.

Complete response at 12 weeks and ORR, as assessed by both investigator and BICR per RECIST 1.1 criteria, are commonly accepted endpoints by both regulatory authorities and the

oncology community to assess response and the durability of these responses to oncology treatments.

RECIST 1.1

RECIST 1.1 will be used by the investigator and BICR when assessing images for efficacy measures and by the local site when determining eligibility (Section 8.2.1.5) [NA 2008]. Although traditional RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented a modification to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ.

Analyses by PD-L1 Status:

As a secondary endpoint, OS and PFS by PD-L1 status (by CPS) will be compared. Progression-free survival assessment by the investigator will include RECIST 1.1 or histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1). Cervical cancer is overwhelmingly an HPV-driven cancer, resulting in high levels of PD-L1 expression [Liu, Y., et al 2019]. The baseline PD-L1 scores may increase significantly due to radiotherapy and chemotherapy, since it has been demonstrated that both regimens may increase immunogenicity significantly. Although the CPS score in untreated cases is unknown, we may expect high prevalence given that this is an HPV-driven cancer [Liu, Y., et al 2019]. In addition, PD-L1 status at baseline (all participants), after CRT and at progression (for participants with available biopsies) will be evaluated. The PD-L1 status will be tested in “real-time” and will provide CPS information early in study. This may help deconvolute between different CPS scores and aid in potentially deciding which cutoff may be used for further analyses. Statistical analysis will be performed to assess the efficacy by PD-L1 status.

4.2.1.2 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 CTCAE, Version 5.0.

4.2.1.3 Patient-reported Outcomes

As part of the analyses for this study, participants will provide information regarding their HRQoL via the following assessment tools: European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, EORTC QLQ-C24X, PGI-S, PGI-C and EQ-5D-5L questionnaires. Patient-reported outcomes (PROs) are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.1.3.1 EORTC QLQ-C30

EORTC QLQ-C30 is the most widely used cancer-specific, health-related, QoL 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 [Aaronson, N. K., et al 1993]. The EORTC QLQ-C30 is a psychometrically and clinically validated instrument appropriate for assessing QoL in oncology studies [Aaronson, N. K., et al 1993].

4.2.1.3.2 EORTC QLQ-CX24

The EORTC QLQ-CX24 is a disease-specific questionnaire developed and validated to address measurements specific to cervical cancer. It is one of multiple disease-specific modules developed by the EORTC QLG (Quality of Life Group) designed for use in clinical studies, to be administered in addition to the EORTC QLQ-C30 to assess disease-specific treatment measurements. The 24-items are classified into 3 multi-item scales, 11 items with symptom experience domain, 3 items with body image domain, and 4 items with sexual/ vaginal functioning domain. The other domains of the questionnaire are single item scales, including lymphedema, peripheral neuropathy, menopausal symptom, sexual worry, sexual activity, and sexual enjoyment.

4.2.1.3.3 Patient Global Impression of Severity and Patient Global Impression of Change

Considering minimally important difference thresholds indicating clinically significant changes or differences for the EORTC QLQ-C30 global health status/QoL scale, EORTC QLQ-C30 Physical Function subscale and EORTC QLQ-CX24 symptom specific scale in women with LACC have not yet been established, the PGI-S and the PGI-C questionnaires will be used to validate clinically meaningful thresholds for severity and change of global health status, physical function and cervical cancer symptoms, and sexual domains from the EORTC QLQ-C30 and EORTC QLQ-CX24 questionnaires in the study population.

The PGI-S is a standard single item questionnaire for assessing the severity of disease-related symptoms. The response options of the PGI-S are as follows: none, mild, moderate and severe.

The PGI-C is a single item questionnaire for assessing the change in disease-related symptoms compared with the start of treatment. The response options of the PGI-C are as follows: much better, a little better, no change, a little worse and much worse.

4.2.1.3.4 EQ-5D-5L

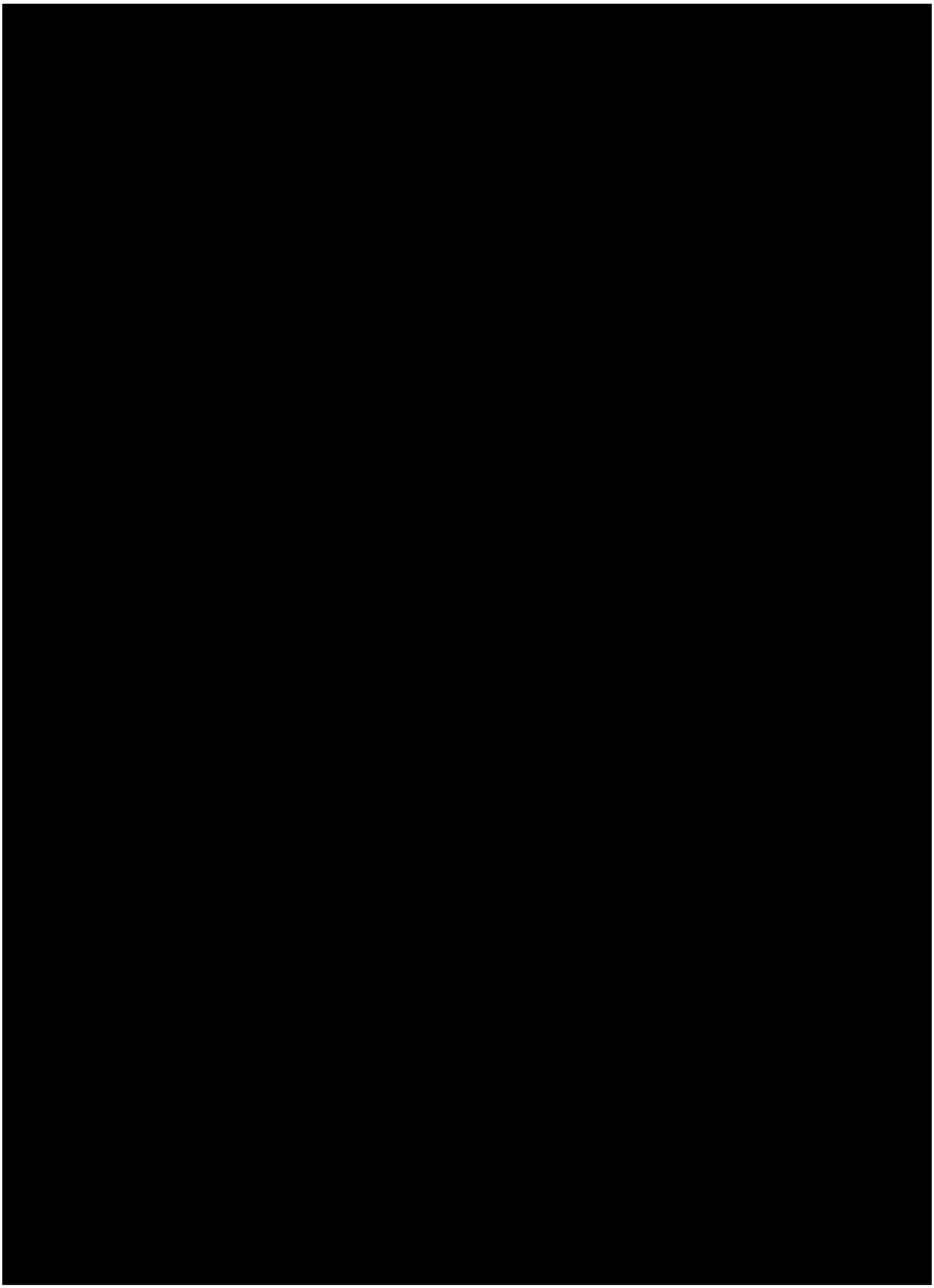
The EQ-5D-5L is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses [Rabin, R. and de Charro, F. 2001]. The 5 health state dimensions in the EQ-5D-5L include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5-point scale from 1 (no problem) to 5 (unable to/extreme problems). 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 [Pickard, A. S., et al 2007].

4.2.1.4 Pharmacodynamic Endpoints

No pharmacodynamic endpoints are planned for this study.

[redacted]



[redacted]

4.2.2 Rationale for the Use of Comparator/Placebo

The current SOC in this patient population is chemoradiotherapy followed by regular imaging surveillance for progression/recurrence of disease. In this study, SOC chemoradiotherapy will be administered with pembrolizumab (200 mg Q3W for 5 infusions followed by 400 mg Q6W for 15 infusions) or placebo. A placebo control is necessary to minimize confounding factors, such as the more frequent office visits and physical exams required for administration of pembrolizumab, as well as control for knowledge of treatment effects on participant reported outcome data.

4.3 Justification of Dose

The planned dose of pembrolizumab for this study is 200 mg Q3W for 5 infusions followed by 400 mg Q6W for a maximum of 15 infusions. The first Q6W infusion (Cycle 6) will be administered 3 weeks from the last 3QW infusion (Cycle 5). The current approved dosing regimens of pembrolizumab for IV administration are 200 mg Q3W and 400 mg Q6W for adults.

The Q3W dosing will be administered to align with the CCRT regimen. Participants will switch to a Q6W regimen once CCRT is completed. The Q6W regimen is expected to increase the compliance in a participant population that would not otherwise be receiving SOC after completion of CCRT.

200 mg Q3W

Based on the totality of data generated in the Keytruda® development program, 200 mg Q3W is an appropriate dose of pembrolizumab for adults across all indications.

400 mg Q6W

A 400 mg Q6W dosing regimen of pembrolizumab is expected to have a similar benefit-risk profile as 200 mg Q3W, in all treatment settings in which 200 mg Q3W pembrolizumab is currently approved [Lala, M., et al 2018]. Specifically, the dosing regimen of 400 mg Q6W for pembrolizumab is considered adequate based on modeling and simulation analyses, given the following rationale:

- Pharmacokinetic (PK) simulations demonstrating that in terms of pembrolizumab exposures:
    - Average concentration over the dosing interval (C_{avg}) (or AUC) at 400 mg Q6W is similar to that at the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.
    - Trough concentrations (C_{min}) at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W in the majority (>99%) of patients.
    - Peak concentrations (C_{max}) at 400 mg Q6W are well below the C_{max} for the highest clinically tested dose of 10 mg/kg Q2W, supporting that the safety profile for 400 mg Q6W should be comparable to the established safety profile of pembrolizumab.
- Exposure-response for pembrolizumab has been demonstrated to be flat across indications, and OS predictions in melanoma and NSCLC demonstrate that efficacy at 400 mg Q6W is expected to be similar to that at 200 mg or 2 mg/kg Q3W, given the similar exposures; thus, 400 mg Q6W is expected to be efficacious across indications.

4.3.1 Maximum Dose/Exposure for This Study

The maximum dose/exposure of pembrolizumab allowed in this study is 200 mg Q3W for 5 infusions followed by 400 mg Q6W for 15 infusions.

The maximum dose of CCRT is cisplatin, 5 infusions given IV QW at 40 mg/m^2 (an optional, sixth infusion of cisplatin may be administered according to local practice), plus EBRT over 40 days, followed by brachytherapy. The minimum acceptable radiation dosing for this protocol is 80 Gy for volume-directed and 75 Gy for point-directed. Refer to the Radiation Manual for further guidance.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent.

The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3).

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped as described in Appendix 10.1.10.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 10.1.1), this study includes participants of varying age, race, ethnicity, and sex. The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

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

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

1. Has high-risk LACC (a or b below):

    a. FIGO 2014 Stage IB2-IIB (with node-positive disease) – must meet criteria below for positive pelvic lymph node OR para-aortic lymph node involvement up to the L1 cephalad body level.

        - Pelvic lymph node involvement as assessed by one of the following criteria:

            - Histopathologic, biopsy-proven pelvic node involvement (high-risk LACC patient with locally evaluable disease is eligible if removal of positive lymph node[s] is documented), or

            - 2 or more positive pelvic nodes by MRI or CT (≥1.5 cm shortest dimension), or

            - 2 or more positive pelvic nodes by PET / CT with SUV (max) ≥2.5

- Para-aortic lymph node involvement as assessed by one of the following criteria:
    - Histopathologic, biopsy-proven para-aortic node involvement (high-risk LACC patient with locally evaluable disease is eligible if removal of positive lymph node[s] is documented), or
    - 1 or more positive para-aortic nodes by MRI or CT (≥1.5 cm shortest dimension), or
    - 1 or more positive para-aortic nodes by PET / CT with SUV (max) ≥2.5

b. FIGO 2014 Stages III-IVA (either node-positive or node-negative disease)

Refer to Appendix 9 for further details of FIGO 2014 staging for cervical cancer.

2. Has histologically-confirmed squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix.

3. Has not previously received any definitive surgical, radiation, or systemic therapy for cervical cancer, including investigational agents, and is immunotherapy-naïve. Note: Previous surgical procedure for localized cervical tumor is allowed.

4. Has an ECOG performance status of 0 or 1 within 7 days prior to the first dose of study intervention.

Demographics

5. Is female, at least 18 years of age at the time of documented informed consent.

Female Participants

6. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

    - Is not a WOCBP

      OR

    - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 5 during the intervention period and for at least 120 days after the last dose of pembrolizumab or placebo and 180 days following the end of chemoradiotherapy and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The investigator should evaluate the potential for contraceptive method failure

(ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 72 hours (serum) or 24 hours (urine) before the first dose of study intervention.

- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.5.1. Refer to Appendix 7 for country-specific requirements.

- Abstains from breastfeeding during the study intervention period and for at least 120 days after the last dose of pembrolizumab or placebo and 180 days following the end of chemoradiotherapy.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

7. The participant (or legally acceptable representative if applicable) has provided documented informed consent for the study. The participant may also provide consent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research. Refer to Appendix 7 for country-specific requirements.

Additional Categories

8. Has radiographically evaluable disease, either measurable or nonmeasurable per RECIST 1.1, as assessed by the local site investigator/radiology.

    - As per inclusion criterion #1, for Stage IB2-IIB (FIGO 2014) disease, if nodal involvement is assessed by CT or MRI, the participant must have measurable disease (≥1.5 cm in shortest dimension) per RECIST 1.1.

    - High-risk LACC patient with radiographically locally evaluable disease is eligible if removal of positive lymph node(s) is documented.

9. Has provided a tissue sample from a core, incisional, or excisional biopsy of a tumor to the central vendor prior to randomization. Formalin-fixed, paraffin-embedded tissue blocks are preferred to slides (details pertaining to tumor tissue submission can be found in the Laboratory Manual).

10. Has adequate organ function as defined in the following table (Table 2). Specimens must be collected within 7 days prior to the start of study intervention.

Table 2 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	
Measured or calculated[b] creatinine clearance OR GFR	≥50 mL/min OR GFR ≥50 mL/min/1.73m^2
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) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT 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 within last 2 weeks; administration of packed RBCs is allowed prior to randomization.

[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 the administration of specific chemotherapies.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. Has histological subtypes other than those allowed per inclusion criterion 2 (eg, sarcoma, small cell carcinoma with neuroendocrine differentiation, nonepithelial cancer).

2. Has FIGO 2014 Stage IVB disease. Evidence of metastatic disease per RECIST 1.1 including lymph nodes above the L1 cephalad body or in the inguinal region. Participants with inguinal lymph node involvement should be discussed with Sponsor and may potentially be eligible after confirmation of the Sponsor with participant's disease details.

3. Has undergone a previous hysterectomy defined as removal of the entire uterus or will have a hysterectomy as part of their initial cervical cancer therapy. NOTE: Women who have had a partial/subtotal hysterectomy for reasons other than cervical cancer are eligible to participate in the study. Note: Radiologically-evaluable local disease such as cervix tumor will meet the eligibility criteria for assessable disease in the absence of measurable/evaluable metastatic disease.

4. Has bilateral hydronephrosis, unless at least one side has been stented or resolved by positioning of nephrostomy or considered mild and not clinically significant in the opinion of the investigator.

5. Has anatomy or tumor geometry or any other reason or contraindication that cannot be treated with intracavitary brachytherapy or a combination of intracavitary and interstitial brachytherapy.

Prior/Concomitant Therapy

6. Has received a live vaccine within 30 days prior to the first dose of study intervention. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, BCG, 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. Refer to Appendix 7 for country-specific requirements.

   Refer to Section 6.5 for information on COVID-19 vaccines.

7. Has received treatment with systemic immunostimulatory agents, colony stimulating factors, interferons, interleukins and vaccine combinations within 6 weeks or 5 half-lives of the drug, whichever is shorter, prior to Cycle 1, Day 1.

Prior/Concurrent Clinical Study Experience

8. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).

9. Has received prior systemic anticancer therapy including investigational agents within 4 weeks prior to randomization.

10. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to randomization.

    Note: Participants who have entered the Follow-up Phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

Diagnostic Assessments

11. Has any contraindication to the use of cisplatin.

12. 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 medication.

13. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.

    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ, excluding carcinoma in situ of the bladder, that have undergone potentially curative therapy are not excluded.

14. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

15. 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.

16. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.

17. Has an active infection requiring systemic therapy.

18. Has a known history of HIV infection.

    Note: No testing for HIV is required unless mandated by local health authority. Refer to Appendix 7 for country-specific requirements.

19. Has a known history of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

    Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority. Refer to Appendix 7 for country-specific requirements.

20. Has a history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that may increase the risk associated with study participation or study

intervention administration or may interfere with the interpretation of study results, and in the judgment of the investigator or Sponsor, would make the participant inappropriate for entry into this study.

21. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

Other Exclusions

22. Has had an allogenic tissue/solid organ transplant.

23. Evidence of metastatic disease per RECIST 1.1 including lymph nodes above the L1 cephalad body, in the inguinal region. Participants with inguinal lymph node involvement should be discussed with Sponsor and may potentially be eligible after confirmation of the Sponsor with participant's disease details.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws from the study will not be replaced.

6 STUDY INTERVENTION

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

Clinical supplies will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 3.

Country-specific differences are noted in Appendix 7.

Table 3 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Form-ulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1	Experimental	Pembrolizumab (MK-3475)	Drug	Solution for Infusion	25 mg/mL	200 mg for 5 infusions followed by 400 mg for 15 infusions	IV Infusion	Q3W (200 mg) for 5 infusions followed by Q6W (400 mg) for 15 infusions	Test Product	IMP	Central
Arm 1	Experimental	Cisplatin	Drug	Solution for Infusion	Variable	40 mg/m^2	IV Infusion	Weekly for 5 infusions (an optional, sixth infusion may be administered according to local practice)	Background Treatment	NIMP/ AxMP	Local or central
Arm 1	Experimental	Radiation (EBRT)	Radiation	N/A	Refer to Radiation Manual for further guidance	Refer to Radiation Manual for further guidance	External	40 days	Background Treatment	NIMP/ AxMP	Local

Arm Name	Arm Type	Intervention Name	Type	Dose Form-ulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1	Experimental	Radiation (Brachytherapy)	Radiation	N/A	Refer to Radiation Manual for further guidance	Refer to Radiation Manual for further guidance	Internal	Total treatment duration should not exceed 50 days (with an extension to a maximum of 56 days for unforeseen delays) with radiotherapy including brachytherapy. Brachytherapy sessions should be performed immediately after EBRT sessions	Background Treatment	NIMP/ AxMP	Local
Arm 2	Placebo Comparator	Placebo	Drug	Solution for Infusion	Normal Saline or dextrose	0 mg	IV Infusion	Q3W for 5 infusions, followed by Q6W for 15 infusions	Placebo	IMP	Local
Arm 2	Placebo Comparator	Cisplatin	Drug	Solution for Infusion	Variable	40 mg/m^2	IV Infusion	Weekly for 5 infusions (an optional, sixth infusion may be administered according to local practice)	Background Treatment	NIMP/ AxMP	Local or central
Arm 2	Placebo Comparator	Radiation (EBRT)	Radiation	N/A	Refer to Radiation Manual for further guidance	Refer to Radiation Manual for further guidance	External	40 days	Background Treatment	NIMP/ AxMP	Local

Arm Name	Arm Type	Intervention Name	Type	Dose Form-ulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Arm 2	Placebo Comparator	Radiation (Brachytherapy)	Radiation	N/A	Refer to Radiation Manual for further guidance	Refer to Radiation Manual for further guidance	Internal	Total treatment duration should not exceed 50 days (with an extension to a maximum of 56 days for unforeseen delays) with radiotherapy including brachytherapy. Brachytherapy sessions should be performed immediately after EBRT	Background Treatment	NIMP/ AxMP	Local

AxMP=Auxiliary Medicinal Product; EBRT=external beam radiotherapy; IMP=investigational medicinal product; IV=intravenous; N/A=not applicable; NIMP=Non-Investigational Medicinal Product; Q3W=dosing every 3 weeks; Q6W=dosing every 6 weeks

Geographic variance in total radiation dose administered, number of fractions and methodology of application may be permitted after consultation with the Sponsor.

Participants must receive 5 infusions of pembrolizumab 200 mg or placebo at Q3W before moving to pembrolizumab 400 mg or placebo Q6W dosing. Chemoradiotherapy and brachytherapy are administered during the Q3W dosing regimen. Interruptions of cisplatin, EBRT, brachytherapy, pembrolizumab or placebo are allowed according to Section 6.4.

Administration of EBRT must be completed within 40 days from start to finish. Total radiation treatment (EBRT and brachytherapy) should not exceed 50 days (with an extension to a maximum of 56 days for unforeseen delays).

See Appendix 7 for country-specific requirements for concurrent chemoradiotherapy.

Definition Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product/Auxiliary Medicinal Product (NIMP/AxMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed. Refer to Appendix 7 for country-specific requirements.

In this protocol, placebo for pembrolizumab is diluent alone (normal saline and/or dextrose); diluent is used for blinding purposes and does not contain active ingredients.

The unit dose strength for cisplatin may vary depending on market availability.

The maximum dosage for radiation depends on the methodology used. The minimum acceptable radiation dosing for this protocol is 80 Gy for volume-directed and 75 Gy for point-directed. Please refer to the Radiation Manual for additional details such as nodal boost dosing requirements.

All study interventions will be administered on an outpatient basis. Refer to Appendix 7 for country-specific requirements.

All products indicated in Table 3 will be provided centrally by the Sponsor or locally by the study site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the study site, subsidiary, or designee, every attempt will be made to source these supplies from a single lot/batch number. The study 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 8.1.8 for details regarding administration of the study intervention. Refer to Appendix 7 for country-specific requirements for concurrent chemoradiotherapy.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual. Cisplatin will be prepared and administered as per the approved product label(s).

6.2.2 Handling, Storage, and Accountability

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

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions 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 intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study 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 study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) 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 interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to CCRT + pembrolizumab or CCRT + placebo, respectively.

6.3.2 Stratification

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

1. Planned type of EBRT: IMRT or VMAT versus non-IMRT and non-VMAT
2. Stage at screening of cervical cancer: FIGO 2014 Stage IB2-IIB (node-positive disease) versus FIGO 2014 Stage III-IVA (node-negative or node-positive disease)
3. Planned total radiotherapy dose (EBRT + brachytherapy dose) of <70 Gy (EQ2D) versus ≥70 Gy (EQ2D)

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

6.4 Study Intervention Compliance

If there are interruptions in the study intervention schedule or infusion/injection was stopped, the details of and reason for any interruption or infusion/injection cessation of study intervention will be documented in the participant's medical record.

6.4.1 Pembrolizumab or Placebo

The first infusion of pembrolizumab or placebo combined with chemoradiotherapy may begin up to 3 days after randomization.

The standard dosing window for pembrolizumab or placebo is 21 days (± 3 days) during Q3W dosing and 42 days (± 3 days) during Q6W dosing.

Interruptions from the protocol-specified treatment plan for more than 3 weeks between pembrolizumab doses for nondrug-related or administrative reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

Participants must receive 5 infusions of pembrolizumab or placebo Q3W before moving to Q6W dosing. The interval between Cycle 5 and Cycle 6 is 3 weeks ±3 days. Q6W dosing starts from Cycle 6 onwards. Chemoradiotherapy and brachytherapy are administered during the Q3W dosing regimen. Pembrolizumab or placebo infusions should be continued during cisplatin or radiotherapy delay. Note: On treatment days where both pembrolizumab/placebo and cisplatin are administered, it is preferable for pembrolizumab/placebo to be administered prior to cisplatin. However, cisplatin may be administered prior to pembrolizumab/placebo per local standard practice.

6.4.2 Chemoradiotherapy

The standard treatment includes cisplatin, EBRT, and brachytherapy. The overall chemoradiotherapy treatment (including both EBRT and brachytherapy) should be administered within 50 days (with an extension to a maximum of 56 days for unforeseen delays). Summation of EBRT and brachytherapy doses will be performed by calculation of a biologically equieffective dose in 2 Gy per fraction using the linear-quadratic model with a/b= 10 Gy for tumor effects and a/b= 3 Gy for late normal tissue damage. The repair half time is assumed to be 1.5 h. The D90 for the high-risk CTV should be higher than 85 Gy. An extension due to toxicity-related interruptions may be permitted with Sponsor consultation. Further monitoring/assessments should be performed in accordance with the local label and/or local practice for cisplatin and radiotherapy.

6.4.2.1 Concurrent Chemotherapy

Cisplatin should only be given weekly (± 1-day window) on a day that EBRT is scheduled and must be given prior to radiation treatment on that day. If due to interruptions and dosing delays cisplatin administration continues beyond EBRT, cisplatin should not be administered on a day when brachytherapy is also administered. All participants should receive 5 infusions of cisplatin regardless of the radiation fractionation schedule planned. Refer to Appendix 7 for country-specific requirements.

Note: an optional, sixth infusion of cisplatin may be administered according to local practice.

Cisplatin should not be administered during an EBRT therapy delay.

For weekly cisplatin dosing, interruptions of more than 3 days between infusions, for non-drug-related or administrative reasons, require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

Cisplatin dose interruption due to treatment-related toxicity are allowed as per local standard. Dose reductions are also allowed as follows: the cisplatin standard dose of 40 mg/m^2 may be

reduced to 30 mg/m^2. If the participant cannot tolerate 30 mg/m^2, no further dose reductions are allowed. A 70-mg dose cap of cisplatin may be applied in accordance with local practice. Refer to Section 6.6 (Dose Modification) and Section 6.6.3 (Cisplatin Dose Modifications) for additional information on dose modifications due to toxicity.

When applicable, participants should receive premedication and supportive care measures to prevent hypersensitivity reactions and minimize toxicity, according to the local label and/or per local practice. Sites should follow local standard of care for hydration prior to cisplatin administration.

6.4.2.2 External Beam Radiotherapy

Pelvic EBRT is an integral part of the overall treatment strategy with the primary aim of obtaining regional and nodal control.

It is currently delivered with different techniques: 3D conformal EBRT, IMRT, or VMAT over 40 days. Daily image guidance is mandatory with couch correction according to bony structures if IMRT or VMAT is used. The definition of primary tumor targets is CT- and MRI-based. An individualized ITV-T is recommended based on participant anatomy and target motion. Nodal target (CTV-E) is defined according to risk of nodal spread and involved nodes or parametria are boosted, when possible, using SIB to reach a minimum radiation dosing of 80 Gy for volume-directed and 75 Gy for point-directed [Landberg, T., et al 1993] [Landberg, T., et al 1999]. Refer to the Radiation Manual for further guidance.

The main advantage of IMRT is the ability to deliver a high dose of radiation to tumor tissue while restricting dose exposure of adjacent noncancerous tissues. The overall volume irradiated to 43 Gy during EBRT is known to be associated with acute and late morbidity [Stanic, S. 2013] [Sondergaard, J., et al 2014] [Letschert, J. G. J., et al 1994]. By reducing the volume of normal tissues irradiated, IMRT reduces the risk of acute [Naik, A., et al 2016] [Gandhi, A. K., et al 2013] and late [Mundt, A. J., et al 2002] [Chopra, S., et al 2015] morbidity [Kloop, A. H., et al 2016], including urinary and bowel morbidity. Furthermore, image guided radiotherapy allows tight treatment margins to be applied which has significant potential to reduce the overall volume irradiated with EBRT.

VMAT is a complex IMRT technique. In the process of irradiation, it can adjust the beam intensity from different beam directions by way of altering the dose rate and gantry rotation speed. VMAT allows to reduce treatment time, thus improving performance. It integrates the advantages of speed and dose distribution of rotational therapy and dynamic IMRT [Holt, A., et al 2011]. According to a recently reported study, VMAT plans showed superior dose coverage of the PTV, better protection of the rectum and bladder in dosimetry, and significantly reduced monitor units and treatment time compared with f-IMRT. Clinical results were similar for both plans[Guo, M., et al 2018].

In the EMBRACE I study, the utilization of IMRT and 3D CCRT was 27% and 73%, respectively. Therefore, stratification according to IMRT or VMAT versus non-IMRT and non-VMAT are considered since it is important to account for potential differences in safety and efficacy outcomes depending on EBRT technique [Potter, R., et al 2018].

Radiotherapy will not be omitted or delayed for cisplatin-related toxicities unless the investigator considers the participant too ill to be treated. Participants who fail to recover from toxicities within 21 days will not receive further protocol-directed therapy without Sponsor consultation.

Midline block (central shielding) maybe applied if required per local practice.

Geographic variance in total radiation dose administered, number of fractions and methodology of application may be permitted after consultation with the Sponsor.

6.4.2.3 Brachytherapy

Brachytherapy should follow EBRT and concomitant chemotherapy to obtain maximal tumor regression.

Intercalation of brachytherapy and EBRT is not allowed.

Please refer to the Radiation Manual for further guidance on dosing.

To achieve adequate target coverage and to reduce the dose to the organs at risk, brachytherapy could be only intracavitary or a combination of intracavitary and interstitial. Recommendations for target and organ-at-risk contouring are outlined in the ICRU/GEC ESTRO report 89 [SAGE Publications 2016].

Geographic variance in total radiation dose administered, number of fractions and methodology of application may be permitted after consultation with the Sponsor.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor's 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 intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Participants are prohibited from receiving the following concomitant therapy or vaccination during the treatment period:

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Radiosensitizers other than protocol-specified cisplatin

- Investigational agents other than pembrolizumab
- Radiation therapy not specified in this protocol

  Note: Palliative radiation to symptomatic lesions may be allowed following Sponsor consultation after assessment of disease progression has been determined.
- Use of nephrotoxic or ototoxic medications concurrently with cisplatin administration.
- Live vaccines within 30 days prior to the first dose of study intervention and up to 30 days following the last dose of study intervention. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, 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. Refer to Appendix 7 for country-specific requirements.

  Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

  Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.
- Systemic glucocorticoids except when used for the following purposes:
  - To modulate symptoms of an AE that is suspected to be related to study intervention
  - For the prevention of emesis
  - To premedicate for IV contrast allergies
  - To treat asthma or COPD exacerbations (only short-term oral or IV use in doses >10 mg/day prednisone equivalent)
  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent
- Other glucocorticoid use except when used for the following purposes:
  - For topical use or ocular use
  - Intraarticular joint use
  - For inhalation in the management of asthma or COPD

Note: The use of systemic steroids to treat AEs related to study interventions (including pembrolizumab/placebo, cisplatin, and RT), as well as prophylaxis/premedication, and use of

physiologic doses to treat AEs not related to study intervention is allowed without Sponsor consultation. However, if systemic steroids are needed at a higher dose than physiologic dose to treat any other AE not related to any of the study interventions, Sponsor consultation is required.

Participants who, in the assessment of the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from study intervention.

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, OTC products, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 42 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. Concomitant medications administered 30 days after the last dose of study intervention should be recorded for SAEs and ECIs as defined in Section 8.4, as well as recorded regardless of whether associated with an SAE or ECI.

Cytokines (eg, G-CSF, GM-CSF, or recombinant erythropoietin) should not be administered within 4 weeks before randomization, but may be administered during the treatment period per local practice.

6.5.1 Rescue Medications and 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 6.6.1, Table 4. 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 or placebo, the investigator does not need to follow the treatment guidance. Refer to Table 4 in Section 6.6.1 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.

6.6 Dose Modification (Escalation/Titration/Other)

Dose modifications in response to treatment-related adverse events are permitted to keep the participant on study medication, when appropriate. Details on the modifications for each study intervention are provided in the sections below. In general:

- Whenever treatment is withheld, toxicity should resolve to Grade 0 or 1 or to baseline (if condition was present at baseline) and

- Study drugs, cisplatin and radiation may be held together or separately at the investigator's discretion to determine which drug is the source for a given toxicity and to interrupt pembrolizumab/placebo or adjust the dosage of cisplatin / radiation therapies accordingly. If study drugs are withheld for hematological toxicity, radiation therapy may be continued at the investigator's discretion to minimize treatment delays.

Refer to Appendix 7 for country-specific requirements.

6.6.1 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)

Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immune-related response. 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 study 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, skin biopsy may be included as part of the evaluation.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 4.

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:
1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab monotherapy, coformulations or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 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 GI 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
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 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 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• 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 [d]		
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 [d]		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 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		
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (which was previously myocarditis Grade 1 using CTCAE v4.0).	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	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 event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy, coformulations or IO combinations may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab/Placebo

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/placebo associated infusion reaction are provided in Table 5.

Table 5 Pembrolizumab/Placebo 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 hrs	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/hr to 50 mL/hr). 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 drug treatment	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of study intervention 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 drug treatment.	No subsequent dosing
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 v5.0 (CTCAE) at http://ctep.cancer.gov		

Other Allowed Dose Interruption for Pembrolizumab/Placebo

Pembrolizumab/placebo may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy 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.

6.6.2 Radiation Dose Modifications

Radiation treatment may be delayed up to 21 days due to toxicity. A delay of longer than 21 days will require consultation with the Sponsor, to determine if the participant will continue study intervention and/or study. Additionally, the start of brachytherapy can be delayed up to 14 days from completion of EBRT, if needed. All radiation treatments must be delivered within a total of 50 days (with an extension to a maximum of 56 days for unforeseen delays); therefore, treatment breaks should be kept to a minimum. The reason for interruptions in radiation therapy must be recorded in the eCRF.

If EBRT treatment is delayed, then cisplatin dose should be delayed until EBRT treatment is resumed.

6.6.3 Cisplatin Dose Modifications

Toxicity due to cisplatin administration may be managed by symptomatic treatment, dose interruptions and adjustment of cisplatin dose. Recommended dose reductions are provided below. The cisplatin dose should only be reduced once to 30 mg/m^2, and future dosing should continue at the reduced dose. If the reduced dose is not tolerated, the participant may continue in the study without cisplatin (may continue to receive pembrolizumab or placebo and RT). Interruptions in cisplatin for longer than one week due to toxicity requires consultation with the Sponsor for appropriate management of the patient.

External radiation should continue while cisplatin is withheld, unless the investigator considers the patient too ill to be treated.

Gastrointestinal Adverse Effects

a. For nausea and vomiting, anti-emetics should be used prophylactically.

b. For Grade 4 nausea and vomiting, reduce cisplatin to 30 mg/m^2.

Renal/Genitourinary Adverse Effects

a. If GFR <50 mL/min [Gault, M. H., et al 1992], hold cisplatin therapy. If creatinine does not recover after a one-week delay, discontinue cisplatin for remainder of regimen.

b. Selective renal tubular defects are sometimes observed:

   i. Hypocalcemia with hypomagnesemia and hypokalemia are common and potentially severe.

   ii. Replacement of magnesium, calcium and potassium are usually effective.

   iii. Severe tubular effects, although rare, may require chronic replacement therapy.

   iv. Diagnostic tests for alternative mechanisms of hypocalcemia (eg, GI or metabolic) should be considered.

Neurologic Adverse Effects

a. Grade 1 - no change

b. Grade 2 - reduce cisplatin to 30 mg/m^2

c. Grade 3 to 4 - hold cisplatin and reduce cisplatin to 30 mg/m^2 after recovery to ≤Grade 2

Hematologic Adverse Effects

a. Cisplatin should be withheld from participants with an ANC less than 1,000 or platelet count less than 50,000. Therapy should be delayed week-by-week until these levels are exceeded. Any interruption in cisplatin for longer than one week due to toxicity requires a dose reduction of one level.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity for the duration of the study. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic intervention randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

6.9 Standard Policies

At the close of the study after unblinding, a letter is to be sent by the investigator to those participants who received placebo in the image of the Sponsor's product to provide the following advice:

"You have participated in a study conducted by the Sponsor. This letter is to advise you that you were among those who received a look-alike product. You did not receive the active drug as manufactured by MSD."

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention 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 intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.10.3.

Participants may discontinue study intervention at any time for any reason or be dropped from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the

investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9.

A participant must be discontinued from study intervention 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 intervention
- The participant interrupts study intervention administration with pembrolizumab/placebo for more than 12 consecutive weeks due to AE(s). Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.6.1 require Sponsor consultation before restarting treatment
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention
- The participant has a confirmed positive serum pregnancy test
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6
- Radiographic disease progression outlined in Section 8.2.1 (after obtaining informed consent addendum and Sponsor communication, the investigator may elect to continue treatment beyond radiographic disease progression).
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment

  Note: If only local treatment is performed for an occurrence of another malignancy, the participant may continue on study treatment upon Sponsor consultation and approval
- Completion of 20 infusions of pembrolizumab or placebo (5 infusions Q3W [concurrent with chemoradiotherapy] and another 15 infusions Q6W)

7.2 Participant 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 intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.9. 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 are outlined in Section 7.3.

7.3 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 (eg, telephone 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 missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 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.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician.

- 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 procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

- Information regarding the amount of blood collected from each participant over the duration of the study can be found in the Laboratory Manual.

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised 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 study. 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 or the participant's legally acceptable representative's dated signature.

If the investigator recommends continuation of study intervention beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent.

Specifics about the study and the study population are to be included in the study informed consent form.

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

8.1.1.3 Consent for Optional Collection of Tumor Samples

An optional tissue sample may be collected and submitted to a central laboratory for study investigational purposes for participants who are able to undergo a biopsy and provide optional tissue collection consent. The investigator or medically qualified designee will explain this optional part of the study that includes collecting fresh tumor biopsy samples during Cycle 5 and before Cycle 6, Day 1 and at disease progression and submitting the tissue sample for analysis. Study consent is not required when a tissue sample is performed for histopathologic confirmation if the tissue sample is not submitted to the central laboratory for study-specific investigational purposes.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used 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 documented informed consent. At the time of intervention 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 healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 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 important. The investigator will enter any prior cancer other than high-risk LACC as a medical history condition.

Details regarding the diagnosis of high-risk LACC will be recorded separately and not listed as medical history.

If a medical condition is diagnosed at the time of screening due to the physical examination, laboratory tests, radiologic assessment, other assessment, and/or a combination of these evaluations, the medical condition is to be recorded as a baseline condition along with the participant's other medical history unless due to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in).

8.1.4.1 Cervical Cancer History

The investigator or qualified designee will obtain prior and current details regarding the participant's cervical cancer history. This history may include but is not limited to FIGO stage, location of tumor burden at baseline, histology, and potential prior treatment for early stage disease that may have been treated prior to diagnosis with high-risk LACC.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 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 42 days before starting study intervention.

Enter all treatments for a prior cancer other than high-risk LACC even if taken more than 42 days prior to start of study medication.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant within 42 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention.

Concomitant medications administered 30 days after the last dose of study intervention should be recorded for SAEs and ECIs as defined in Section 8.4.

8.1.5.3 Subsequent Anticancer Therapy

Details of subsequent therapies for cancer (including surgical procedure and radiation) after discontinuation of study intervention will be collected. These details include but are not limited to treatment start and stop dates, reason for treatment, response to treatment, dates of

progression after the completion of subsequent treatment, and reason for discontinuation from treatment. Reasons for starting subsequent anticancer therapies including access to other PD-1/PD-L1 inhibitors or investigational drugs will be collected.

8.1.6 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 1 screening number. Screening numbers must not be re-used for different participants.

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

8.1.7 Assignment of Randomization Number

All eligible participants will be randomly allocated and will receive a randomization number. The randomization number identifies the participant for all procedures occurring after treatment randomization. Once a 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 randomization number.

8.1.8 Study Intervention Administration

Administration of study intervention will be monitored by the investigator and/or study staff.

Study intervention should be administered after all assessments have been completed. Study intervention should be administered in this order: pembrolizumab/placebo first, followed by cisplatin and then radiotherapy. Variation to the order of administration for pembrolizumab/placebo and cisplatin is permitted according to local practice—however cisplatin must be administered prior to radiotherapy (refer to Appendix 7 for country-specific requirements). Study intervention should begin within 3 days of and as close as possible to the date on which the participant is randomized.

8.1.8.1 Timing of Dose Administration

Pembrolizumab or Placebo

Pembrolizumab will be administered as a dose of 200 mg Q3W (Cycles 1-5) and 400 mg Q6W (Cycles 6-20) using a 30-minute IV infusion. 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 pembrolizumab/placebo reconstitution, preparation of the infusion fluid, and administration of infusion solution.

Cisplatin

Cisplatin should be administered weekly (± 1 day) on a day that EBRT is scheduled and prior to radiation treatment on that day. Cisplatin will be prepared and administered according to local practices.

Radiotherapy

External Beam Radiotherapy

Pelvic EBRT is an integral part of the overall treatment strategy with the primary aim of obtaining regional and nodal control.

It is currently delivered with different techniques: 3D conformal EBRT, IMRT, or VMAT, over 40 days. Daily image guidance is mandatory with couch correction according to bony structures if IMRT or VMAT is used. The definition of primary tumor targets is CT and MRI-based. An individualized ITV-T is recommended based on participant anatomy and target motion. Nodal Target (CTV-E) is defined according to risk of nodal spread and involved nodes or parametria are boosted, even possible, using SIB to reach the minimum acceptable radiation of 80 Gy for volume-directed and 75 Gy for point-directed. Refer to the Radiation Manual for further guidance.

Radiotherapy will not be omitted or delayed for cisplatin-related toxicities unless the investigator considers the participant too ill to be treated. Participants who fail to recover from toxicities within 21 days will not receive further protocol-directed therapy without Sponsor consultation. Refer to Radiation Manual for further guidance.

Geographic variance in total radiation dose administered, number of fractions and methodology of application may be permitted after consultation with the Sponsor.

Details of the required equipment and treatment planning for radiotherapy can be found in the Radiation Manual. The radiotherapy plan must be submitted to QARC during screening. Approval of plan will be provided following QARC receipt of all required data for the rapid review. Approval of plan is required prior to randomization. The maximum dosage for radiation depends on the methodology used. The minimum acceptable radiation dosing for this protocol is 80 Gy for volume-directed and 75 Gy for point-directed. Additional detail on radiation requirements can be found in the Radiation Manual and Radiation Therapy Quality Assurance Manual (eg, radiotherapy plan submission requirements, nodal boost dosing requirements, etc.).

Brachytherapy

Brachytherapy should follow EBRT and concomitant chemotherapy to obtain maximal tumor regression. Intercalation of brachytherapy and EBRT is not allowed.

Refer to the Radiation Manual for further guidance.

To achieve adequate target coverage and to reduce the dose to the organs at risk, brachytherapy should be intracavitary or a combination of intracavitary and interstitial. Recommendations for target and organ-at-risk contouring are outlined in the ICRU/GEC ESTRO report 89.

Geographic variance in total radiation dose administered, number of fractions and methodology of application may be permitted after consultation with the Sponsor.

Details of the required equipment and treatment planning for radiotherapy can be found in the Radiation Manual. Digital treatment plans for brachytherapy administration for each participant must be submitted to QARC within 2 weeks, or sooner if requested by the Sponsor, of brachytherapy completion. Additional detail on the radiotherapy plan submission requirements can be found in the Radiation Therapy Quality Assurance Manual.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.10.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the End of Treatment / Discontinuation Visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.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 study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study 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.

8.1.10 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.

Once an emergency unblinding has taken place, the investigator, and site personnel, may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician should continue to be monitored in the study.

Additionally, the investigator or medically qualified designee must go into the IRT system and perform the unblind in the IRT system to update drug disposition. If the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding if this is required for participant safety.

At the end of the study, random code/disclosure envelopes or lists and unblinding logs are to be returned to the Sponsor or designee.

8.1.10.1 Nonemergency Unblinding

Nonemergency unblinding to study intervention (pembrolizumab / placebo) administration may occur on an individual participant basis and only after consultation with the Sponsor under the following circumstances:

- Disease progression or recurrence with discontinuation of study intervention and the participant is being considered for alternate treatment that necessitates knowledge of prior treatment on the study.

- Adverse event necessitates discontinuation from treatment and unblinding is required for appropriate clinical management of complications.

Note: in some instances, unblinding to study treatment may be needed for appropriate clinical management of the complications but may not necessitate discontinuation of study treatment. The Sponsor's Clinical Director must be consulted to review individual requests for unblinding using the Sponsor Consultation Form with reasons to unblind and decision to remain on study treatment clearly documented.

8.1.11 Calibration of Equipment

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

8.1.12 Tumor Tissue for Biomarker Analyses

Participation in this study will be dependent on participants supplying tumor tissue prior to randomization to the central vendor. Submission of either formalin-fixed paraffin-embedded tumor blocks or unstained slides is acceptable; however, formalin-fixed paraffin-embedded tumor block is preferable. Details about collection and submission of tumor tissue samples are contained in the Laboratory Manual.

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

Efficacy will be assessed based on imaging evaluation of changes in tumor burden over time. The process for image collection and transmission to the iCRO can be found in the SIM.

For the abdomen and pelvis, tumor imaging is strongly preferred to be acquired by contrast-enhanced MRI. Imaging of the chest should be performed by contrast-enhanced CT. If the preferred imaging modality cannot be performed, please refer to the SIM for alternate options.

An MRI is the strongly preferred modality for imaging the brain when clinically indicated to rule out brain metastases at baseline or as clinically indicated during the study.

Bone scans are required for participants with new bone pain, to rule out bone metastases at baseline or as clinically indicated during the study. Any supplemental imaging performed to support a positive or negative bone scan, such as plain X-rays that may be acquired for correlation, should be submitted to the iCRO.

The same imaging technique should be used in each participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and to

improve the accuracy of the response assessment based on imaging. Note: for the purposes of assessing tumor imaging, the term "investigator" refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but which demonstrate radiologic progression, should also be submitted to the central imaging vendor.

8.2.1.1 Initial Tumor Imaging

The screening images must be submitted to the iCRO for retrospective review.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if it is of diagnostic quality and performed within 28 days prior to the date of randomization and can be assessed by the iCRO.

A contrast-enhanced PET/CT scan and baseline chest CT and MRI of the abdomen/pelvis are to be performed within 28 days prior to randomization. If the participant has had both a PET/CT scan (with the CT component of diagnostic quality) and an MRI of the pelvis and abdomen, then a separate CT of the chest is not required.

Participant eligibility will be determined using local assessment (investigator assessment).

8.2.1.2 Tumor Imaging During the Study

The first scheduled postrandomization imaging assessment required are a contrast-enhanced PET/CT scan as well as a chest CT and MRI of abdomen/pelvis that should be performed at 12 weeks (± 14 days) after the completion of CCRT.

Subsequent tumor imaging should be performed every 12 weeks (Q12W ± 14 days) thereafter from the completion of CCRT during Years 1 and 2, every 24 weeks (Q24W ± 14 days) in Year 3, and once per year (± 14 days) in Year 4 onwards. Years are calculated from the date of randomization. Unscheduled imaging due to new clinical symptoms can occur at any time, including prior to the post-CCRT Week 12 assessment, to identify either new metastatic/regional disease or recurrence of locally treated disease. Timing of tumor imaging should follow calendar days and should not be adjusted for delays in cycle starts. (Note: the date imaging is performed is the date of assessment, not the date the images are reviewed.) For participants who are lymph node positive at baseline by PET only, a PET scan (with CT scan only as necessary for attenuation correction and anatomic localization) to confirm disappearance of the FDG uptake in the node(s) is required to determine that a complete response has occurred. If the nodal activity has not resolved, another PET scan should be performed at selected later time points (with the interval to be based on the investigator's clinical judgment), until the nodal uptake is seen to have resolved, if the MRI and/or CT scan still shows complete response. Imaging should continue to be performed until radiographic disease progression is documented per RECIST 1.1 by the investigator, withdrawal of consent, pregnancy, loss to follow-up, or death, whichever occurs first.

Treatment beyond documented disease progression may be permitted at the discretion of the investigator after consultation with the Sponsor and receiving appropriate documented informed consent. Sponsor consultation should be sought after each subsequent imaging evaluations and where the investigator may continue treatment. Participants who continue treatment beyond disease progression must continue tumor assessments as described in the SoA (Section 1.3). Investigator assessments are to be documented on the eCRF, and all scans are to be submitted to the iCRO. Further progression and discontinuation of study intervention are to be determined by the investigator.

Supplemental imaging must be submitted to the central imaging vendor if it shows evidence of disease progression or recurrence.

8.2.1.3 Optional Biopsy for Confirmation of Disease Progression

When tumor growth is suspected on imaging or by physical examination, an optional biopsy for confirmation of suspected disease progression is allowed at investigator discretion. Throughout the protocol, the term “histopathologic confirmation” is used when referencing a biopsy that confirms suspected disease progression either from a new lesion or a pre-existing lesion showing growth. A redacted copy of the local pathology assessment may be requested by the Sponsor, if acceptable per local regulations.

8.2.1.4 End-of-Treatment and Follow-up Tumor Imaging

For participants who discontinue study intervention, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study intervention due to documented radiographic disease progression, this is the final required tumor imaging.

For participants who discontinue study intervention without documented radiographic disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment calculated from the date of CCRT (see Section 8.2.1.2) until radiographic disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.2.1.5 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used by the investigator as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study intervention). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

8.2.2 Patient-reported Outcomes

The questionnaires will be administered by trained site personnel and completed electronically by participants in the following order:

1) EORTC QLQ-C30
2) EORTC QLQ-CX24
3) PGI-S
4) PGI-C
5) EQ-5D-5L

The questionnaires should be administered according to the schedule in the SoA.

It is best practice and strongly recommended that ePROs are administered to randomized participants prior to drug administration, AE evaluation, and disease status notification. If the participant does not complete the ePROs at a scheduled time point, the MISS_MODE form must be completed to capture the reason the assessment was not performed.

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination during the screening period (consistent with local requirements) as per institutional standard. Height and weight will also be measured and recorded. Clinically significant abnormal findings should be recorded as medical history. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs. The time points for full physical examinations are described in the SoA (Section 1.3).

8.3.1.2 Directed Physical Examination

For cycles that do not require a full physical examination, the investigator or qualified designee will perform a symptom-directed physical examination (consistent with local requirements) per institutional standard as clinically indicated prior to study intervention

administration. New clinically significant abnormal findings should be recorded as AEs. The time points for directed physical examinations are described in the SoA (Section 1.3).

8.3.1.3 Gynecological Examination

The investigator or qualified designee will perform a gynecological examination during the screening period (consistent with local requirements) as per institutional standard. Clinically significant abnormal findings should be recorded as medical history. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs. The time points for gynecological exams are described in the SoA (Section 1.3).

8.3.2 Vital Signs

The investigator or qualified designee will measure vital signs at the time points specified in the SoA (Section 1.3) and will include temperature, systolic and diastolic blood pressure, heart rate, and respiratory rate.

8.3.3 Audiometry

Consistent with local requirements, an audiometry test may be performed and reviewed by an investigator or medically qualified designee, as outlined in the SoA (Section 1.3).

8.3.4 Electrocardiograms

A 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA (Section 1.3). Additional ECGs may be performed during the study as clinically indicated.

8.3.5 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 or medically qualified designee (consistent with local requirements) 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 nonprotocol-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 7 days after the last dose of study intervention, 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.

The specific laboratory procedures/assessments to be performed in this study are provided below. The amount of blood to be drawn/collected over the course of the study can be found in the Laboratory Manual. Refer to the SoA (Section 1.3) for the timing of laboratory assessments.

8.3.5.1 Pregnancy Testing

- Pregnancy testing requirements for study inclusion are described in Section 5.1
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention
- Pregnancy testing (urine or serum as required by local regulations) should be conducted up to 120 days after the last dose of pembrolizumab or placebo and up to 180 days after the last dose of Chemoradiotherapy
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the patient's participation in the study
- Home pregnancy tests are acceptable when a scheduled visit does not occur within the month (per local regulation), but the site must make monthly telephone contact with the participant to determine the results of the pregnancy test. The results of the test must be recorded in the participant's eCRF.

8.3.6 Performance Assessments

8.3.6.1 Eastern Cooperative Oncology Group Performance Scale

The investigator or qualified designee will assess ECOG status at screening to determine eligibility and at subsequent time points as specified in the SoA (Section 1.3).

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

The definitions of an AE or 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 3.

Progression of the cancer under study is not considered an AE as described in Section 8.4.6 and Appendix 3.

Adverse events, 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 and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 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 participant provides documented informed consent, but before intervention 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 study, 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 intervention randomization through 30 days after cessation of study intervention must be reported by the investigator.

- All AEs meeting serious criteria, from the time of intervention randomization through 90 days after cessation of study intervention or 30 days after cessation of study intervention 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 intervention randomization through 120 days after the last dose of pembrolizumab or placebo and 180 days following the end of chemotherapy, or 30 days after cessation of study intervention 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 the time specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events 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 the investigator considers the event to be reasonably related to the study intervention 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 time frames as indicated in Table 6.

Table 6 Reporting Time Periods and Time Frames 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	Time Frame to Report Event and Follow-up Information to Sponsor:
Nonserious 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
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
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
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (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 calendar days of learning of event

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 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 AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, 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 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 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 intervention 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 intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study 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.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 8.4.1.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

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

8.4.7 Events of Clinical Interest

Selected nonserious and SAEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5.

2. Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin laboratory value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase laboratory 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 study site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

8.5 Treatment of Overdose

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater (≥5 times and ≥2.5 times the indicated doses [200 mg and 400 mg, respectively]).

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for FBR. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

The planned genetic analysis sample should be obtained pre-dose on Day 1 but may be collected at the next scheduled blood draw, if needed. Sample collection, storage, and shipment instruction for planned genetic analysis samples will be provided in the operations/laboratory manual.

8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for future biomedical research, the following specimens will be obtained as part of future biomedical research:

- Leftover samples listed in Section 8.8

8.10 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.10.1 Screening

Documented informed consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant providing 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 the first dose of study intervention except for the following:

- Laboratory tests are to be performed within 7 days prior to the first dose of study intervention. An exception is hepatitis or HIV testing which may be performed up to 28 days prior to the first dose of study intervention.

- Evaluation of ECOG is to be performed within 7 days prior to the first dose of study intervention.

- For WOCBP, a urine or serum pregnancy test will be performed within 72 hours (serum) or 24 hours (urine) prior to the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

- Newly obtained tumor tissue from a core, incisional, or excisional biopsy performed prior to screening can be used.

- Approval of radiotherapy plan is required prior to 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.

8.10.2 Treatment Period

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 6.4 and Section 8.

8.10.3 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

When a participant discontinues study intervention during the treatment period, procedures for discontinuation will be performed.

The Discontinuation Visit should occur at the time study intervention is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, the Discontinuation Visit procedures and any additional safety follow-up procedures should be performed. Visit requirements are

outlined in Section 1.3. Additional details regarding participant withdrawal and discontinuation are presented in Section 7.

8.10.4 Posttreatment Visits

8.10.4.1 Safety Follow-up Visit

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

8.10.4.2 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention will begin the Efficacy Follow-up Phase and should be assessed every 12 weeks for the first 2 years, every 24 weeks during the third year, and annually thereafter to monitor disease status. Efficacy Follow-up visits should align with the posttreatment imaging visit schedule (see Section 8.2.1.2). For participants who discontinue study intervention for reasons other than radiographic disease progression (including those with histopathologic confirmation of suspected disease progression) will have posttreatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1 by the investigator, or until withdrawal of consent, pregnancy, death, or loss to follow-up, whichever comes first. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments due to documented disease progression per RECIST 1.1 must enter the Survival Follow-up Phase.

8.10.4.3 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 study, whichever occurs first.

The first survival follow-up assessment 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 assessment follow-up visit has been performed.

8.10.5 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 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 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding/final database lock, 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 E-9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to the unblinding/final database lock, will be documented in a sSAP and referenced in the CSR for the study. A separate biomarker analysis plan will be provided. Posthoc exploratory analyses will be clearly identified in the CSR. The PRO analysis plan will also be included in the sSAP.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below. The comprehensive plan is provided in Sections 9.2 through 9.12.

Study Design Overview	A Randomized Phase 3, Double-Blind Study of Chemoradiotherapy With or Without Pembrolizumab for the Treatment of High-risk, Locally Advanced Cervical Cancer
Treatment Assignment	Approximately 980 participants will be randomized in a 1:1 ratio between 2 treatment arms: Arm 1: CCRT + pembrolizumab Arm 2: CCRT + placebo Stratification factors are as follows: 1. Planned type of EBRT: IMRT or VMAT versus non-IMRT and non-VMAT 2. Stage at screening of cervical cancer FIGO 2014 Stage IB2-IIB (node-positive disease) versus FIGO 2014 Stage III-IVA (node-negative or node-positive disease) 3. Planned total radiotherapy dose (EBRT + brachytherapy dose) of <70 Gy versus ≥70 Gy (EQ2D)

Analysis Populations	Efficacy: ITT The analysis population for ORR consists of all randomly assigned participants with measurable disease. Safety: APaT
Primary Endpoints	• PFS as assessed by investigator or by histopathologic confirmation of suspected disease progression as assessed by investigator • OS
Secondary Endpoints	• PFS assessed by BICR • PFS at 2 years per RECIST 1.1 as assessed by Investigator or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1) • PFS at 2 years per RECIST 1.1 as assessed by BICR • OS at 3 years • CR rate at 12 weeks after CCRT per RECIST 1.1 as assessed by Investigator and BICR, respectively, in all randomly assigned participants with measurable disease • ORR per RECIST 1.1 as assessed by Investigator and BICR, respectively, in all randomly assigned participants with measurable disease • PFS per RECIST 1.1 as assessed by Investigator or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1) by PD-L1 status (by CPS) • PFS per RECIST 1.1 as assessed by BICR by PD-L1 status (by CPS) • OS by PD-L1 status (by CPS) • PFS2: The time from randomization to subsequent disease progression after initiation of new anticancer therapy, or death from any cause, whichever occurs first • Patient-reported quality of life by EORTC QLQ-C30 global score and physical function subscale, and EORTC QLQ-CX24 symptom specific subscale • Safety and tolerability of the 2 treatment arms
Statistical Methods for Key Efficacy Analyses	The primary hypotheses will be evaluated by comparing the treatment groups with respect to PFS and OS using a stratified log-rank test. The hazard ratio will be estimated using a stratified Cox regression model. Progression-free survival at 2 years and OS at 3 years will be estimated 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 events of interest that warrant elevation to Tier 1 events 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. The 95% CIs for the between-treatment differences in percentages will be provided using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].
Interim Analyses	Two IAs and 1 final analysis are planned in this study. Comparisons between 2 treatment arms will be conducted at the IAs and final analysis. Results of the IAs will be reviewed by an external data monitoring committee. [redacted]
Multiplicity	The overall Type I error rate over the multiple endpoints will be strongly controlled at 2.5% (1-sided) with initially 2.5% allocated to test PFS superiority. No initial alpha is allocated to the OS hypothesis. The graphical approach of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] will be applied to reallocate alpha among the hypotheses of PFS and OS. In particular, OS can be tested hierarchically following the successful outcome of PFS. Lan-DeMets O'Brien-Fleming group sequential methods will be used to allocate alpha among the interim and final analyses for the PFS and OS endpoints.

Sample Size and Power	The planned sample size is approximately 980 participants with 490 participants in each arm. [redacted] The PFS hypothesis testing is designed for one-sided $\alpha = 0.025$ and power of 95% to detect an HR of 0.660 [redacted] 304 events between the 2 arms at the [redacted] final analyses. The OS hypothesis testing is designed for one-sided $\alpha = 0.025$ and power of 86% to detect an HR of 0.671 with [redacted] 240 events between the 2 arms at the [redacted] final analyses.

9.2 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.

This study will be conducted as a double-blind study with 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 has been declared final and complete.

The Sponsor will generate the randomized allocation schedule for study treatment assignment for this protocol and the randomization will be implemented in IRT.

Blinding issues related to the planned interim analyses are described in Section 9.7.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.4 Analysis Endpoints

Efficacy, safety and PRO endpoints that will be evaluated for within- and/or between-treatment differences are listed below. Other endpoints will be described in the sSAP.

9.4.1 Primary

PFS INV: The time from randomization to the first documented disease progression per RECIST 1.1 as assessed by investigator or per histopathologic confirmation of disease progression (in the absence of radiographic disease progression per RECIST 1.1), or death due to any cause, whichever occurs first.

OS: The time from randomization to death due to any cause.

9.4.2 Secondary

PFS BICR: The time from randomization to the first documented disease progression per RECIST 1.1 as assessed by BICR, or death due to any cause, whichever occurs first.

PFS INV at 2 years: The proportion of participants that are PFS event-free at 2 years per RECIST 1.1 as assessed by investigator or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1).

PFS BICR at 2 years: The proportion of participants that are PFS event-free at 2 years per RECIST 1.1 as assessed by BICR.

OS at 3 years: The proportion of participants that are OS event-free at 3 years.

CR rate at 12 weeks after completion of concurrent chemoradiotherapy: The proportion of participants that achieve CR at 12 weeks after CCRT per RECIST 1.1 as assessed by investigator and BICR, respectively.

ORR: The proportion of participants in the analysis population who have an OR, defined as a complete response (CR) or a partial response (PR) per RECIST 1.1 as assessed by investigator and BICR, respectively.

PFS INV by PD-L1: The time from randomization to the first documented disease progression per RECIST 1.1 as assessed by investigator or by histopathologic confirmation of suspected disease progression, by PD-L1 status (by combined positivity score).

PFS BICR by PD-L1: The progression-free survival per RECIST 1.1 as assessed by BICR, or death due to any cause, whichever occurs first, by PD-L1 status (by combined positivity score).

OS by PD-L1: The time from randomization to death due to any cause, by PD-L1 status (by combined positivity score).

PFS2: The time from randomization to subsequent disease progression after initiation of new anticancer therapy, or death from any cause, whichever occurs first. If progression after next-line therapy cannot be measured, a PFS2 event is defined as end or discontinuation of next-line treatment or death from any cause, whichever occurs first.

PROs: Endpoints will be assessed by EORTC QLQ-C30 global score and physical function subscale, and EORTC QLQ-CX24 symptoms specific scale. Details will be provided in the sSAP.

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events, laboratory values and vital signs.

[redacted]

9.5 Analysis Populations

[redacted]

9.5.1 Efficacy Analysis Population

The ITT population will serve as the population for the primary efficacy analyses. All randomized participants will be included in this population. Participants will be analyzed in the treatment group to which they are randomized.

The analysis population for ORR consists of all randomly assigned participants with measurable disease.

9.5.2 Safety Analysis Population

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all randomized/allocated participants who received at least 1 dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who take incorrect study treatment for the entire treatment period; such

participants will be included in the treatment group corresponding to the study treatment actually received.

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

Details on the approach to handling safety analyses are provided in Section 9.6.2.

9.5.3 Patient-reported Outcome Analysis Population

The PRO analyses are based on the PRO full analysis set population, defined as participants who have at least 1 PRO assessment available and have received at least 1 dose of study medication.

9.6 Statistical Methods

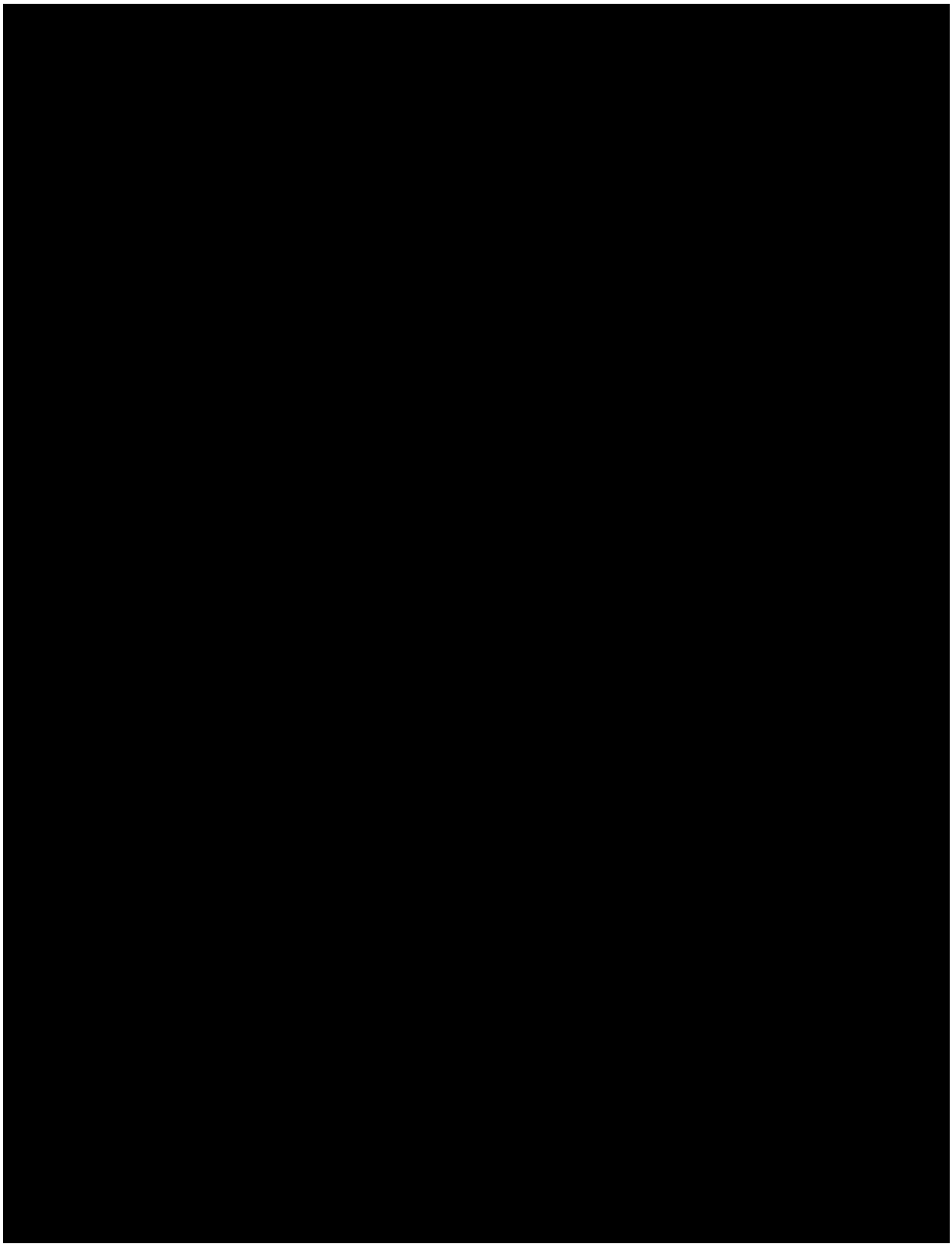
9.6.1 Statistical Methods for Efficacy Analyses

Statistical testing and inference for safety analyses are described in Section 9.6.2. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 9.8. Nominal p-values will be computed for other efficacy analyses but should be interpreted with caution due to potential issues of multiplicity.

[redacted]

9.6.1.1 Progression-free Survival

The nonparametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the 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. [redacted]



[redacted]

9.6.1.2 Overall Survival

The nonparametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test (based on the stratification factors defined in Section 6.3.2). A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess 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. [redacted]

9.6.1.3 Progression-free Survival at 2 Years

Progression-free survival at 2 years and 95% CI will be estimated using Kaplan-Meier method. The approach for testing on difference in outcome at a fixed point in time will be used for comparison of the PFS rate at 2 years between 2 treatment groups [Klein, J. P. 2003]. The difference in PFS rate at 2 years, its 95% confidence interval and nominal p-value will be reported.

9.6.1.4 Overall Survival at 3 Years

Overall survival at 3 years and 95% CI will be estimated using Kaplan-Meier method. The approach for testing on difference in outcome at a fixed point in time will be used for comparison of the OS rate at 3 years between 2 treatment groups [Klein, J. P. 2003]. The difference in OS rate at 3 years, its 95% confidence interval and nominal p-value will be reported.

9.6.1.5 Objective Response Rate

Stratified Miettinen and Nurminen's method will be used for comparison of the objective response rate (ORR) between 2 treatment groups [Miettinen, O. and Nurminen, M. 1985].

The difference in ORR and its 95% confidence interval from the stratified Miettinen and Nurminen's method with strata weighting by sample size will be reported. The stratification factors used for randomization (See Section 6.3.2) will be applied to the analysis.

9.6.1.6 Duration of Response

For participants with measurable at baseline who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. Censoring rules for DOR are summarized in Table 8. DOR will be assessed using RECIST 1.1 by investigator and BICR, respectively. For each DOR analysis, a corresponding summary of the censoring reasons for responding participant will also be provided. [redacted]

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 9.

Table 9 Efficacy Analysis Methods for Key Efficacy Endpoints

Endpoint/ Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses:			
PFS per RECIST 1.1 by investigator or by histopathologic confirmation	Testing: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 7
OS	Testing: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date
Secondary Analyses:			
PFS per RECIST 1.1 by BICR	Testing: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 7
Abbreviations: BICR=blinded independent central review; ITT=intention-to-treat; OS=overall survival; PFS=progression-free survival; RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1.			

9.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 10). The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as system organ class terms) and events that meet predefined limits of change in laboratory values, vital signs, and ECG parameters are either prespecified as "Tier 1" endpoints or will be classified as belonging to "Tier 2" or "Tier 3" based on the observed proportions of participants with an event.

Tier 1 Events

Safety parameters that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance. Adverse events of special interest that are immune-mediated or potentially immune-mediated are well documented and will be evaluated separately; however, these events have been characterized consistently throughout the pembrolizumab clinical development program and determination of statistical significance is not expected to add value to the safety evaluation. Additionally, there are no known AEs associated with participants with treatment for which determination of a p-value is expected to impact the safety assessment. Therefore, there are no Tier 1 events in this study.

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 (via the Miettinen and Nurminen method) [Miettinen, O. and Nurminen, M. 1985].

Membership in Tier 2 requires that at least 5% 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 5% 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 5% 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% participants in 1 of the treatment groups) and SAEs (≥2% 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 Safety Measures

For continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Table 10 Analysis Strategy for Safety Parameters

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

9.6.3 Statistical Methods for PRO Analyses

To evaluate the treatment effect on the HRQoL outcomes at prespecified time points, a constrained longitudinal data analysis model will be applied, with the PRO score as the response variable, and the treatment by time interaction and stratification factors as covariates. Least square mean (LSmean) change from baseline will be summarized. Group-wise comparisons will be performed and the model-based LSmean score will be provided by treatment group and study visit.

Details of other PRO analyses will be described in the sSAP.

9.6.4 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 randomized, and the primary reason for discontinuation will be displayed. Demographic variables (such as age) and baseline characteristics will be summarized by treatment either by descriptive statistics or

categorical tables. The reasons for exclusion from the ITT population (if any) will be summarized.

9.7 Interim Analyses

An eDMC will serve as the primary reviewer of the results of the interim analyses of the study and will make recommendations for discontinuation of the study or protocol modifications to an Executive Oversight Committee of the Sponsor. [redacted]

Treatment-level results from the interim analysis will be provided to the eDMC by the external unblinded statistician. Prior to final study unblinding, the external unblinded statistician 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.

9.7.1 Safety Interim Analyses

The eDMC will conduct regular safety monitoring. The timing of the safety monitoring will be specified in the eDMC charter.

9.7.2 Efficacy Interim Analyses

Two interim analyses are planned in addition to the final analysis for this study. [redacted]

[redacted]

[redacted]

9.8 Multiplicity

The study uses the graphical method of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] to control multiplicity for multiple hypotheses, as well as interim analyses. [redacted]

[redacted]

9.8.1 Efficacy Analyses

9.8.1.1 Progression-free Survival

The study initially allocates one-sided $\alpha = 0.025$ to test PFS between 2 treatment arms. [redacted]

[redacted]

9.8.1.2 Overall Survival

The OS hypothesis will be tested at $\alpha = 0.025$ (only if the null hypotheses for PFS is rejected).

[redacted]

9.8.2 Safety Analyses

The eDMC has responsibility for assessment of overall risk:benefit. When prompted by safety concerns, the eDMC can request corresponding efficacy data. External DMC review of efficacy data to assess the overall risk:benefit to study participants will not require a multiplicity adjustment typically associated with a planned efficacy interim analysis. However, to account for any multiplicity concerns raised by the eDMC review of unplanned efficacy data when prompted by safety concerns, a sensitivity analysis for OS adopting a conservative multiplicity adjustment will be prespecified in the sSAP.

9.9 Sample Size and Power Calculations

This study is well powered for both primary endpoints. Approximately 980 participants will be randomized in a 1:1 ratio between 2 treatment arms.

[redacted]

The PFS hypothesis testing is designed for one-sided α = 0.025 and power of 95% to detect an HR of 0.660 with [redacted] 304 events between the 2 arms at the [redacted] final analyses.

The OS hypothesis testing is designed for one-sided α = 0.025 (only if the null hypothesis for PFS is rejected) and power of 86% to detect an HR of 0.671 with [redacted] 240 events between the 2 arms at the [redacted] and final analyses.

[redacted]

9.10 Subgroup Analyses

[redacted]

9.11 Compliance (Medication Adherence)

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

9.12 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.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, 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 participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

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 MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud,

scientific/research misconduct or serious GCP-non-compliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. 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 such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). 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. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

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.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD 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

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD 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.

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

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

10.1.2 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.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

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 that 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.

10.1.3.1 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 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 study 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.

10.1.3.2 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 study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF 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 study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. 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.

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the DMC regarding the study.

10.1.4.2 Scientific Advisory Committee

This study was developed in collaboration with a SAC. The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide scientific and strategic guidance on various aspects of the clinical trial and/or development, which may include study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

10.1.4.3 External Data Monitoring Committee

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

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7) and recommend to the EOC whether the study 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 study 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.

10.1.5 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.

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the 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 study reimbursed to the investigator by the Sponsor.

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

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

10.1.8 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.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study 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 any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

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 participants' documented informed consent, 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.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be

traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). 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/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 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 study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 14 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2 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. Refer to Appendix 7 for country-specific requirements.

Table 14 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH		WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Chemistry	BUN or urea[a]	Potassium	AST/ SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above ULN)
	Albumin	Carbon dioxide (CO_2 or bicarbonate)[b]	Chloride	Phosphorous
	Creatinine or creatinine clearance[c]	Sodium	ALT/ SGPT	Total Protein
	Glucose (fasting or nonfasting) Thyroid-stimulating hormone (TSH)[d]	Calcium Triiodothyronine (T3)[d]	Alkaline phosphatase Free thyroxine (FT4)[d]	Lactate dehydrogenase Magnesium
Coagulation (to establish eligibility)	PT/INR aPTT/PTT			
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase[e] by dipstick or laboratory analysis Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	Follicle-stimulating hormone (as needed in women of nonchildbearing potential only) Serum or urine pregnancy test or hCG (qualitative or quantitative) (WOCBP only – as per Schedule of Activities) Serology (HIV antibody, HBV, and HCV) per local requirements T3 or FT3, FT4, and TSH			

NOTES:
Abbreviations: ALT=alanine aminotransferase; aPTT/PTT=activated partial thromboplastin time / partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; FT3=free thyroid hormone; FT4=free thyroxine; HBV=hepatitis B virus; hCG=human chorionic gonadotropin; HCV=hepatitis C virus, HIV=human immunodeficiency virus; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PT/INR=prothrombin time / international normalized ratio; RBC=red blood cell; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; T3=thyroid hormone or FT3; TSH=thyroid-stimulating hormone; ULN=upper limit of normal; WBC=white blood cell; WOCBP=women of childbearing potential.

a. Blood urea nitrogen is preferred; if not available, urea may be tested.
b. Performed only if considered local standard of care.
c. GFR (measured or calculated) or creatinine clearance can be used in place of creatinine.
d. Free T3 is acceptable where T3 cannot be determined. There may be instances when sites are unable to obtain the thyroid function testing results prior to scheduled dosing. Review of thyroid function test results after dosing is acceptable.
e. Leukocyte testing can be performed when leukocyte esterase is not possible.

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product for a perceived psychological or physiological reward or desired non-therapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- 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 intervention.

- NOTE: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting 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, 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 intervention 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 intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, 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). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 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 8.4.6 for protocol-specific exceptions.

10.3.3 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.

An 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 an SAE.) A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant'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) that 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 1 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.

10.3.4 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same time frame 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

10.3.5 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 AE CRFs/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/toxicity

- 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 CTCAE, version 5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

  - Grade 1: Mild; asymptomatic or mild 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 of 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 study intervention cause the AE?

- The determination of the likelihood that the study intervention caused the AE 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 AE based upon the available information.

- **The following components are to be used to assess the relationship between the study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**

  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention 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 study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies 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 study intervention 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 study intervention; (3) the study is a single-dose drug study; or (4) study intervention(s) is/are only used 1 time.)

  - **Rechallenge:** Was the participant re-exposed to the study intervention in this study?

    - 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 study is a single-dose drug study; or (3) study intervention(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE STUDY INTERVENTION, OR IF RE-EXPOSURE TO THE STUDY INTERVENTION 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 INIRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention 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 their 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 study intervention relationship).

  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)

- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

- 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 their 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 1 of the criteria used when determining regulatory reporting requirements.

- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

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.

10.3.6 Reporting of AEs, SAEs, 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 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 8.4.1 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 EDC 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 EDC 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 Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC 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 Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug-device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[b,c] • IUS[c,d] • Nonhormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [c] Male condoms must be used in addition to the hormonal contraception. [d] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

10.6 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[3, 4]

The specimens consented and/or collected in this study as outlined in Section 8.8 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 with which drugs/vaccines may interact
- 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[3, 4]

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in future biomedical research

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study 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 SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study 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 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 SoA. 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 study purposes.

4. Confidential Participant Information for Future Biomedical Research[3, 4]

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 study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and intervention 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 study 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 study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3, 4]

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 (eg, 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 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[3, 4]

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 investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.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 study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study 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[3, 4]

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 study 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 study, the study 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[3, 4]

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study 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[3, 4]

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[3, 4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

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 emailed directly to clinical.specimen.management@MSD.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group [Internet]: 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 [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

10.7.1 Laboratory Testing

Pregnancy Testing

While the protocol allows for more frequent pregnancy testing per the discretion of the investigator, sites should also check with their local health authority to inquire if country-specific guidance regarding the frequency of pregnancy testing is required.

HIV Status

While the protocol does not require specific testing for HIV at screening, it does require testing if required by the local health authority. Sites should check with their local health authority to inquire if country-specific guidance regarding mandatory HIV testing at screening is required. This can also be performed per the discretion of the investigator, if desired.

Hepatitis B/C Status

While the protocol does not require specific testing for hepatitis B/C at screening, it does require testing if required by the local health authority. Sites should check with their local health authority to inquire if country-specific guidance regarding mandatory hepatitis B/C testing at screening is required. This can also be performed per the discretion of the investigator, if desired.

10.7.2 Country-specific Requirements

10.7.2.1 Germany

Laboratory Testing

HIV testing and hepatitis B/C screening are required evaluations for study entry and need to be performed to evaluate eligibility. This testing can be performed at any time during the screening period.

Radiotherapy

The IMRT/VMAT radiation techniques are to be the radiation technique of choice.

Legally Acceptable Representative

In order for a participant to be eligible to participate in Germany, they must be capable of providing documented informed consent; therefore, all references to a participant's "legally acceptable representative" in the protocol are not applicable for participants in Germany.

10.7.2.2 France

Pembrolizumab Dose Modification Guidelines

Pembrolizumab or placebo should be permanently discontinued in participants with a diagnosis of Stevens-Johnson Syndrome and toxic epidermal necrolysis.

Laboratory Testing

Hepatitis B/C screening are required evaluations for study entry and need to be performed to evaluate eligibility. This testing can be performed at any time during the screening period.

10.7.2.3 Japan

Sites in Japan may follow local guidelines as specified in the Japan Radiation Manual.

Concurrent Radiotherapy

It is permissible in Japan to administer cisplatin after EBRT if part of standard of care procedures.

Study Intervention(s) Administered

The classification of IMP and NIMP in Section 6.1 is based upon guidance issued by the European Commission and applies to countries in the EEA. Diluent placebo (normal saline and/or dextrose) for this study is not considered as IMP in Japan. Cisplatin used in this study is categorized as “test product(s)” in Japan.

10.7.2.4 Czech Republic

Laboratory Testing

HIV testing, and hepatitis B/C screening are required evaluations for study entry and need to be performed to evaluate eligibility. This testing can be performed at any time during the screening period.

Section 6.5 Concomitant Therapy

In addition to all restrictions or concomitant medications listed in Section 6.5, specific concomitant therapies or vaccinations noted below are prohibited during the study:

- Live vaccines must not be administered within 30 days prior to the first dose of study intervention, while participating in the study, and for 90 days after the last dose of study intervention.

10.7.2.5 Norway

Laboratory Testing

Home pregnancy tests are acceptable, but the site must contact the participant through telephone monthly to determine the results of the pregnancy test. The results of the test must be recorded in the participant's eCRF.

10.7.2.6 United Kingdom

Concomitant Therapy

Listed below are specific concomitant therapies or vaccinations that are prohibited during the study (exceptions noted):

- Live vaccines must not be administered for 90 days after the last dose of study intervention. Refer to Section 6.5 for information on COVID-19 vaccines.

10.7.2.7 China

Section 8.8 Biomarkers

Biomarker sample collection for participants enrolled in China will be dependent on approval by the Human Genetic Resources Administration of China (HGRAC). FBR will not be conducted in China.

Section 6.1 Study Intervention(s) Administered

The dose formulation for cisplatin used in this study may be powder for infusion or injection solution in China.

10.8 Appendix 8: Description of the iRECIST Process for Assessment of Disease Progression

Not applicable.

10.9 Appendix 9: Federation of Gynecology and Obstetrics Staging for Cancer of the Cervix Uteri

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded).
IA	Invasive cancer identified only microscopically. (All gross lesions even with superficial invasion are Stage IB cancers.) Invasion is limited to measured stromal invasion with a maximum depth of 5 mm[a] and no wider than 7 mm.
IA1	Measured invasion of stroma ≤3 mm in depth and ≤7 mm width.
IA2	Measured invasion of stroma >3 mm and <5 mm in depth and ≤7 mm width.
IB	Clinical lesions confined to the cervix, or preclinical lesions greater than Stage IA.
IB1	Clinical lesions no greater than 4 cm in size.
IB2	Clinical lesions >4 cm in size.
II	The carcinoma extends beyond the uterus but has not extended onto the pelvic wall or to the lower third of vagina.
IIA	Involvement of up to the upper 2/3 of the vagina. No obvious parametrial involvement.
IIA1	Clinically visible lesion ≤4 cm.
IIA2	Clinically visible lesion >4 cm.
IIB	Obvious parametrial involvement but not onto the pelvic sidewall.
III	The carcinoma has extended onto the pelvic sidewall. On rectal examination, there is no cancer free space between the tumor and pelvic sidewall. The tumor involves the lower third of the vagina. All cases of hydronephrosis or nonfunctioning kidney should be included unless they are known to be due to other causes.
IIIA	Involvement of the lower vagina but no extension onto pelvic sidewall.
IIIB	Extension onto the pelvic sidewall, or hydronephrosis/nonfunctioning kidney.
IV	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum.
IVA	Spread to adjacent pelvic organs.
IVB	Spread to distant organs.

a The depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface of glandular, from which it originates. Vascular space invasion should not alter the staging.

Adapted from the Federation of Gynecology and Obstetrics Guidelines 2014 [Belhadj, H., et al 2014].

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APaT	All-Participants-as-Treated
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the curve
BCG	*Bacillus* Calmette–Guérin
BICR	Blinded independent central review
BT	Brachytherapy
C	Cycle
C_{avg}	Average concentration over the dosing interval
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CCRT	Concurrent chemoradiotherapy
CD28	Cluster of differentiation 28
CD3ζ	Cluster of differentiation 3 zeta
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CPS	Combined positive score
CR	Complete response
CrCl	Creatinine clearance
CRF	Case Report Form
CRT	Chemoradiotherapy
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CTV	Clinical target volume
D	Day
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DOR	Duration of response
EBRT	External beam radiotherapy
ECG	Electrocardiogram
ECI	Event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data collection
EEA	European Economic Area
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee

Abbreviation	Expanded Term
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire global health status
EORTC QLQ-CX24	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Symptom Score for Cervical Cancer)
ePROs	Electronic patient-reported outcomes
EQ-2D	Total equieffective dose
EQ-5D-5L	EuroQoL 5 Dimension Questionnaire
ESD	Early stage development
EU CTR	European Union Clinical Trials Regulation
FA	Final analysis
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDG	fluorodeoxyglucose
FIGO	International Federation of Gynecologists and Obstetricians
FSH	Follicle-stimulating hormone
FSR	First site ready
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
Gy	Gray
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
IA	Interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCRO	Imaging Contract Research Organization
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IgG4	Immunoglobulin G4
IgV	Immunoglobulin-variable
IHC	Immunohistochemistry
IMP	investigational medicinal product
IMRT	Intensity modulated radiotherapy
IND	Investigational New Drug
INR	International normalized ratio
INV	investigator
irAE	Immune-related AE
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRT	Interactive response technology
ITT	Intent-to-treat
IV	Intravenous
IVD	In vitro diagnostic
LACC	Locally advanced cervical cancer

Abbreviation	Expanded Term
LAM	Lactational amenorrhea method
LN	Lymph node
LNM	Lymph node metastasis
LSD	Late stage development
mAb	Monoclonal antibody
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MSI	Microsatellite instability
NCI	National Cancer Institute
NSAE	Nonserious adverse events
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Nonsmall-cell lung cancer
ORR	Objective response rate
OS	Overall survival
OTC	Over-the-counter
PALN	Para-aortic lymph nodes
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death 1 ligand 1
PD-L2	Programmed cell death 1 ligand 2
PET	Positron emission tomography
PFS	Progression-free survival
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PIN	Personal identification number
PK	Pharmacokinetic
PKCθ	Protein kinase C-theta
po	Orally
POS	Probability of success
PR	Partial response
PRO	Patient-reported outcome
PT	Prothrombin time
PTT	Partial thromboplastin time
QW	Once per week
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q12W	Every 12 weeks
Q24W	Every 24 weeks
QARC	Quality Assurance Review Center
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RT	Radiotherapy
SAC	Scientific Advisory Committee
SAE	Serious adverse event
SEER	Surveillance, Epidemiology, and End Results
SIB	Simultaneous integrated boosts
SIM	Site imaging manual
SoA	Schedule of activities
SOC	Standard of care
sSAP	Supplemental Statistical Analysis Plan
SUSAR	Suspected unexpected serious adverse reaction

Abbreviation	Expanded Term
SUV	Standard uptake value
T1DM	Type 1 diabetes mellitus
TEA	Treatment eligibility assessment
TILs	Tumor-infiltrating lymphocytes
US	United States
VAS	Visual Analog Scale
VMAT	Volumetric arc techniques
WOCBP	Woman/women of childbearing potential
ZAP70	Zeta-chain-associated protein kinase

11 REFERENCES

[Aaronson, N. K., et al 1993]	Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-76.	[03Q3QL]
[Antonia, S. J., et al 2017]	Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med. 2017 Nov 16;377(20):1919-29.	[04V3ZY]
[Belhadj, H., et al 2014]	Belhadj H, Berek J, Bermudez A, Bhatla N, Cain J, Denny L, et al. FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. Int J Gynaecol Obstet. 2014;125:97-8.	[058PYH]
[Bray, F., et al 2018]	Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. In press 2018.	[050XQN]
[Cetina, L., et al 2006]	Cetina L, Rivera L, Hinojosa J, Poitevin A, Uribe J, Lopez-Graniel C, et al. Routine management of locally advanced cervical cancer with concurrent radiation and cisplatin. Five-year results. BMC Womens Health. 2006 Feb 7;6:3.	[058KBM]
[Chemnitz, J. M., et al 2004]	Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.	[00VMPN]

[Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboratio 2008]	Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol. 2008 Dec 10;26(35):5802-12.	[058KCH]
[Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboratio 2010]	Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC). Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. Cochrane Database Syst Rev. 2010;(1):CD008285.	[058N3P]
[Chopra, S., et al 2015]	Chopra S, Agarwal A, Engineer R, Dora T, Thomas B, Sonawone S, et al. Intensity modulated radiation therapy (IMRT) is not superior to three-dimensional conformal radiation (3DCRT) for adjuvant gastric radiation: a matched pair analysis. J Cancer Res Ther. 2015 Jul-Sep;11(3):623-9.	[0590BS]
[Chung, H. C., et al 2018]	Chung HC, Schellens JHM, Delord JP, Perets R, Italiano A, Shapira- Frommer R, et al. Pembrolizumab treatment of advanced cervical cancer: updated results from the phase 2 KEYNOTE-158 study [abstract]. Presented at: 2018 American Society of Clinical Oncology (ASCO) Annual Meeting; 2018 Jun 1-5; Chicago, IL. J Clin Oncol. 2018;36(15 suppl). Abstract no. 5522.	[05725X]
[Chung, H. C., et al 2019]	Chung HC, Ros W, Delord JP, Perets R, Italiano A, Shapira-Frommer R, et al. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: results from the phase II KEYNOTE-158 study. J Clin Oncol. 2019;37(17):1470-8.	[058KBS]

[Daly, M. E., et al 2015]	Daly ME, Monjazeb AM, Kelly K. Clinical trials integrating immunotherapy and radiation for non-small-cell lung cancer. J Thorac Oncol. 2015 Dec;10(12):1685-93.	[058LQ9]
[Deng, L., et al 2014]	Deng L, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum RR, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. J Clin Invest. 2014 Feb;124(2):687-95.	[04G598]
[Derer, A., et al 2015]	Derer A, Deloch L, Rubner Y, Fietkau R, Frey B, Gaipl US. Radio-immunotherapy-induced immunogenic cancer cells as basis for induction of systemic anti-tumor immune responses - pre-clinical evidence and ongoing clinical applications. Front Immunol. 2015 Oct 8;6:505.	[058KBN]
[Disis, M. L. 2010]	Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28(29):4531-8.	[058SQL]
[Dudley, M. E., et al 2005]	Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.	[00VMPR]
[Duska, L. R., et al 2020]	Duska LR, Scalici JM, Petroni GR, Showalter TN. A randomized phase II study of chemoradiation and pembrolizumab for locally advanced cervical cancer: presentation of safety data [abstract]. Presented at: Society of Gynecologic Oncologists (SGO) 2020 Annual Meeting on Women's Cancer Webinar Series; 2020 Apr 28-May 31; [online meeting].	[05K6HW]

[Esposito, A., et al 2015]	Esposito A, Criscitiello C, Curigliano G. Immune checkpoint inhibitors with radiotherapy and locoregional treatment: synergism and potential clinical implications. Curr Opin Oncol. 2015 Nov;27(6):445-51.	[04G4JC]
[Formenti, S. C. 2009]	Formenti SC, Demaria S. Systemic effects of local radiotherapy. Lancet Oncol. 2009 Jul;10:718-26.	[058N3J]
[Francisco, L. M., et al 2010]	Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.	[058SQP]
[Frenel, J. S., et al 2017]	Frenel JS, Le Tourneau C, O'Neil B, Ott PA, Piha-Paul SA, Gomez-Roca C, et al. Safety and efficacy of pembrolizumab in advanced, programmed death ligand 1-positive cervical cancer: results from the phase Ib KEYNOTE-028 trial. J Clin Oncol. 2017 Dec 20;35(36):4035-41.	[058KBP]
[Frontline Medical Communications Inc. 2018]	MDedge Hematology and Oncology [Internet]. Parsippany (NJ): Frontline Medical Communications Inc.; 2019. Adding pembrolizumab to cisplatin-based CRT shows promise in HPV+ head and neck cancers [press release]. 2018 Nov 12 [cited 2019 Jun 27]; [about 7 screens]. Available from: https://www.mdedge.com/hematology-oncology/article/184301/head-neck-cancers/adding-pembrolizumab-cisplatin-based-crt-shows.	[058LMJ]
[Gandhi, A. K., et al 2013]	Gandhi AK, Sharma DN, Rath GK, Julka PK, Subramani V, Sharma S, et al. Early clinical outcomes and toxicity of intensity modulated versus conventional pelvic radiation therapy for locally advanced cervix carcinoma: a prospective randomized study. Int J Radiat Oncol Biol Phys. 2013;87(3):542-8.	[0590BT]

[Gault, M. H., et al 1992]	Gault MH, Longerich LL, Harnett JD, Wesolowski C. Predicting glomerular function from adjusted serum creatinine. Nephron 1992;62:249-56.	[03NTXQ]
[Golden, E. B. 2015]	Golden EB, Apetoh L. Radiotherapy and immunogenic cell death. Semin Radiat Oncol. 2015 Jan;25(1):11-7.	[04G54G]
[Grassberger, C., et al 2019]	Grassberger C, Ellsworth SG, Wilks MQ, Keane FK, Loeffler JS. Assessing the interactions between radiotherapy and antitumour immunity. Nat Rev Clin Oncol. In press 2019.	[058NZ8]
[Green, J. A., et al 2005]	Green JA, Kirwan JJ, Tierney J, Vale CL, Symonds PR, Fresco LL, et al. Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix [abstract]. Cochrane Database Syst Rev. 2005;(3):CD002225.	[058LMF]
[Greenwald, R. J., et al 2005]	Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515-48.	[00VMQL]
[Guo, M., et al 2018]	Guo M, Huang E, Liu X, Tang Y. Volumetric modulated arc therapy versus fixed-field intensity-modulated radiotherapy in radical irradiation for cervical cancer without lymphadenectasis: dosimetric and clinical results. Oncol Res Treat. 2018;41:105-9.	[05BPMB]
[Han, K., et al 2013]	Han K, Milosevic M, Fyles A, Pintilie M, Viswanathan AN. Trends in the utilization of brachytherapy in cervical cancer in the United States. Int J Radiat Oncol Biol Phys. 2013;87(1):111-9.	[058KBQ]
[Han, X., et al 2017]	Han X, Wen H, Ju X, Chen X, Ke G, Zhou Y, et al. Predictive factors of para-aortic lymph nodes metastasis in cervical cancer patients: a retrospective analysis based on 723 para-aortic lymphadenectomy cases. Oncotarget. 2017 Mar 8;8(31):51840-7.	[058KBR]

[Hollebecque, A., et al 2017]	Hollebecque A, Meyer T, Moore KN, Machiels JPH, De Greve J, Lopez-Picazo JM, et al. An open-label, multicohort, phase I/II study of nivolumab in patients with virus-associated tumors (CheckMate 358): efficacy and safety in recurrent or metastatic (R/M) cervical, vaginal, and vulvar cancers [abstract]. Presented at: 2017 American Society of Clinical Oncology (ASCO) Annual Meeting; 2017 Jun 2-6; Chicago, IL. J Clin Oncol. 2017;35(15 suppl). Abstract no. 5504.	[058LMG]
[Holt, A., et al 2011]	Holt A, van Vliet-Vroegindeweij C, Mans A, Belderbos JS, Damen EMF. Volumetric-modulated arc therapy for stereotactic body radiotherapy of lung tumors: a comparison with intensity-modulated radiotherapy techniques. Int J Radiat Oncol Biol Phys. 2011;81(5):1560-7.	[05BPMC]
[Hunder, N. N., et al 2008]	Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.	[00VMPX]
[Keys, H. M., et al 1999]	Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, Suggs CL 3rd, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med. 1999 Apr 15;340(15):1154-61. Erratum in: N Engl J Med 1999 Aug 26;341(9):708.	[05CFJV]
[Kim, Y. S., et al 2008]	Kim YS, Shin SS, Nam JH, Kim YT, Kim YM, Kim JH, et al. Prospective randomized comparison of monthly fluorouracil and cisplatin versus weekly cisplatin concurrent with pelvic radiotherapy and high-dose rate brachytherapy for locally advanced cervical cancer. Gynecol Oncol. 2008;108:195-200.	[058KBT]

[Klein, J. P. 2003]	Klein JP, Moeschberger ML. Survival analysis: techniques for censored and truncated data. 2nd ed. New York (NY): Springer-Verlag; c2003. Chapter 7, Hypothesis testing; p. 201-42.	[05BQ2R]
[Kloop, A. H., et al 2016]	Klopp AH, Yeung AR, Deshmukh S, Gil KM, Wenzel L, Westin SN, et al. A phase III randomized trial comparing patient-reported toxicity and quality of life (QOL) during pelvic intensity modulated radiation therapy as compared to conventional radiation therapy [abstract]. Presented at: American Society for Therapeutic Radiology and Oncology (ASTRO) 58th Annual Meeting; 2016 Sep 25-28; Boston, MA. Int J Radiat Oncol Biol Phys. 2016;96(2 suppl):S3. Abstract no. 5.	[059294]
[Lala, M., et al 2018]	Lala M, Li M, Sinha V, de Alwis D, Chartash E, Jain L. A six-weekly (Q6W) dosing schedule for pembrolizumab based on an exposure-response (E-R) evaluation using modeling and simulation [abstract]. Presented at: 2018 American Society of Clinical Oncology (ASCO) Annual Meeting; 2018 Jun 1-5; Chicago, IL. J Clin Oncol. 2018;36(15 suppl). Abstract no. 3062.	[052PYW]
[Lanciano, R., et al 2005]	Lanciano R, Calkins A, Bundy BN, Parham G, Lucci JA 3rd, Moore DH, et al. Randomized comparison of weekly cisplatin or protracted venous infusion of fluorouracil in combination with pelvic radiation in advanced cervix cancer: a gynecologic oncology group study. J Clin Oncol. 2005 Nov 20;23(33):8289-95.	[058KL3]
[Landberg, T., et al 1993]	Landberg T, Chavaudra J, Dobbs J, Hanks G, Johansson KA, Moller T, et al. ICRU Report 50: prescribing, recording and reporting photon beam therapy. J ICRU. 1993 Sep 1;[81 p.].	[05BPFS]

[Landberg, T., et al 1999]	Landberg T, Chavaudra J, Dobbs J, Gerard JP, Hanks G, Horiot JC, et al. ICRU Report 62: prescribing, recording and reporting photon beam therapy (supplement to ICRU report 50). J ICRU. 1999 Nov 1;[55 p.].	[05BPH6]
[Lavoue, V., et al 2013]	Lavoue V, Thedrez A, Leveque J, Foucher F, Henno S, Jauffret V, et al. Immunity of human epithelial ovarian carcinoma: the paradigm of immune suppression in cancer. J Transl Med. 2013 Jun 13;11:147.	[058M46]
[Lee, L. 2019]	Lee L, Matulonis U. Immunotherapy and radiation combinatorial trials in gynecologic cancer: a potential synergy? Gynecol Oncol. 2019;154:236-45.	[058P0Y]
[Letschert, J. G. J., et al 1994]	Letschert JGJ, Lebesque JV, Aleman BMP, Bosset JF, Horiot JC, Bartelink H, et al. The volume effect in radiation-related late small bowel complications: results of a clinical study of the EORTC Radiotherapy Cooperative Group in patients treated for rectal carcinoma. Radiother Oncol. 1994;32:116-23.	[0590BV]
[Liu, Y., et al 2015]	Liu Y, Zhao LJ, Li MZ, Li MX, Wang JL, Wei LH. The number of positive pelvic lymph nodes and multiple groups of pelvic lymph node metastasis influence prognosis in stage IA-IIB cervical squamous cell carcinoma. Chin Med J (Engl). 2015 Aug 5;128(15):2084-9.	[058KL4]
[Liu, Y., et al 2019]	Liu Y, Wu L, Tong R, Yang F, Yin L, Li M, et al. PD-1/PD-L1 inhibitors in cervical cancer. Front Pharmacol. 2019 Feb 1;10:65.	[058KCJ]
[Maurer, W. and Bretz, F. 2013]	Maurer W and Bretz F. Multiple testing in group sequential trials using graphical approaches. Stat Biopharm Res 2013;5(4):311-20.	[03XQVB]

[Mayadev, J., et al 2017]	Mayadev J, Brady WE, Lin YG, Da Silva DM, Lankes HA, Fracasso PM, et al. A phase I study of sequential ipilimumab in the definitive treatment of node positive cervical cancer: GOG 9929 [abstract]. Presented at: 2017 American Society of Clinical Oncology (ASCO) Annual Meeting; 2017 Jun 2-6; Chicago, IL. J Clin Oncol. 2017;35(15 suppl). Abstract no. 5526.	[058LMH]
[Menderes, G., et al 2016]	Menderes G, Black J, Schwab CL, Santin AD. Immunotherapy and targeted therapy for cervical cancer: an update. Expert Rev Anticancer Ther. 2016;16(1):83-98.	[058KL5]
[Miettinen, O. and Nurminen, M. 1985]	Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4:213-26.	[03R2SH]
[Monk, B. J. 2022]	Monk BJ. Durvalumab, in combination with and following chemoradiotherapy, in locally advanced cervical cancer: results from the phase 3 international, randomized, double-blind, placebo-controlled CALLA trial. Slides presented at: 2022 International Gynecologic Cancer Society (IGCS) Annual Globe Meeting; 2022 Sep 29-Oct 1; [online meeting].	[085D7S]
[Monk, B. J., et al 2007]	Monk BJ, Tian C, Rose PG, Lanciano R. Which clinical/pathologic factors matter in the era of chemoradiation as treatment for locally advanced cervical carcinoma? Analysis of two Gynecologic Oncology Group (GOG) trials. Gynecol Oncol. 2007;105:427-33.	[058KL2]
[Mundt, A. J., et al 2002]	Mundt AJ, Lujan AE, Rotmensch J, Waggoner SE, Yamada SD, Fleming G, et al. Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. Int J Radiat Oncol Biol Phys. 2002;52(5):1330-7.	[0590BW]

[NA 2008]	RECIST 1.1 Guidelines.	[03R684]
[Naik, A., et al 2016]	Naik A, Gurjar OP, Gupta KL, Singh K, Nag P, Bhandari V. Comparison of dosimetric parameters and acute toxicity of intensity-modulated and three-dimensional radiotherapy in patients with cervix carcinoma: a randomized prospective study. Cancer Radiother. 2016;20:370-6.	[0590CZ]
[Narayan, K., et al 2009]	Narayan K, Fisher RJ, Bernshaw D, Shakher R, Hicks RJ. Patterns of failure and prognostic factor analyses in locally advanced cervical cancer patients staged by positron emission tomography and treated with curative intent. Int J Gynecol Cancer. 2009 Jul;19(5):912-8.	[058N3T]
[Nugent, E. K., et al 2010]	Nugent EK, Case AS, Hoff JT, Zighelboim I, DeWitt LL, Trinkhaus K, et al. Chemoradiation in locally advanced cervical carcinoma: an analysis of cisplatin dosing and other clinical prognostic factors. Gynecol Oncol. 2010;116:438-41.	[058KCD]
[Okazaki, T., et al 2001]	Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71.	[00VMQ6]
[Parry, R. V., et al 2005]	Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 2005;25(21):9543-53.	[00VMQ7]
[Pickard, A. S., et al 2007]	Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 2007;5:1-8.	[00W0FM]

[Pisani, P., et al 1999]	Pisani P, Parkin DM, Bray F, Ferlay J. Estimates of the worldwide mortality from 25 cancers in 1990. Int J Cancer 1999;83:18-29.	[03QBGY]
[Potter, R., et al 2018]	Potter R, Tanderup K, Kirisits C, de Leeuw A, Kirchheiner K, Nout R, et al. The EMBRACE II study: the outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. Clin Transl Radiat Oncol. 2018;9:48-60.	[058QRC]
[Rabin, R. and de Charro, F. 2001]	Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol group. Ann Med 2001;33:337-43.	[03QM46]
[Reits, E. A., et al 2006]	Reits EA, Hodge JW, Herberts CA, Groothuis TA, Chakraborty M, Wansley EK, et al. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. J Exp Med. 2006 May 15;203(5):1259-71.	[04KLMV]
[Riley, J. L. 2009]	Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.	[00VMQ9]
[SAGE Publications 2016]	ICRU report 89, prescribing, recording, and reporting brachytherapy for cancer of the cervix [abstract]. J ICRU. 2016;13(1-2).	[058LMD]
[Schmid, M. P., et al 2014]	Schmid MP, Franckena M, Kirchheiner K, Sturdza A, Georg P, Dorr W, et al. Distant metastasis in patients with cervical cancer after primary radiotherapy with or without chemotherapy and image guided adaptive brachytherapy. Gynecol Oncol. 2014;133:256-62.	[058LZP]
[Sheppard, K-A, et al 2004]	Sheppard K-A, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574:37-41.	[00VMQC]

[Sondergaard, J., et al 2014]	Sondergaard J, Holmberg M, Jakobsen AR, Agerbaek M, Muren LP, Hoyer M. A comparison of morbidity following conformal versus intensity-modulated radiotherapy for urinary bladder cancer. Acta Oncol. 2014;53:1321-8.	[0590D0]
[Stanic, S. 2013]	Stanic S, Mayadev JS. Tolerance of the small bowel to therapeutic irradiation: a focus on late toxicity in patients receiving para-aortic nodal irradiation for gynecologic malignancies. Int J Gynecol Cancer. 2013 May;23(4):592-7.	[0590D7]
[Sturdza, A., et al 2016]	Sturdza A, Potter R, Fokdal LU, Haie-Meder C, Tan LT, Mazeron R, et al. Image guided brachytherapy in locally advanced cervical cancer: improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study. Radiother Oncol. 2016;120:428-33.	[058KCG]
[Tanderup, K., et al 2013]	Tanderup K, Beddar S, Andersen CE, Kertzscher G, Cygler JE. In vivo dosimetry in brachytherapy. Med Phys. 2013 Jul;40(7):070902.	[058N3W]
[Zeng, J., et al 2013]	Zeng J, See AP, Phallen J, Jackson CM, Belcaid Z, Ruzevick J, et al. Anti-PD-1 blockade and stereotactic radiation produce long-term survival in mice with intracranial gliomas. Int J Radiat Oncol Biol Phys. 2013 Jun 1;86(2):343-9.	[04G6TW]
[Zhang, X., et al 2004]	Zhang X, Schwartz J-CD, Guo X, Bhatia S, Cao E, Chen L, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47.	[00VMQJ]