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 exam, 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 signs the informed consent until the last participant's last study-related telephone call or visit. **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 Admin-istration	Regimen/ Treatment Period	Use
Arm 1	Pembro-lizumab	200 mg	Q3W	IV	5 infusions	Exp
		400 mg	Q6W	IV	15 infusions	Exp
Arm 2	Placebo	0 mg	Q3W	IV	5 infusions	Exp
		0 mg	Q6W	IV	15 infusions	Exp
For both Arm 1 and Arm 2	Cisplatin	40 mg/m^2	Once weekly	IV	5 infusions (An optional, 6th infusion may be administered according to local practice)	Back-ground 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	Back-ground Treatment
	Radiation (Brachy-therapy)	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).	Back-ground 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	2 intervention groups
Duration of Participation	Each participant will participate in the study from the time the participant signs the Informed Consent Form through the final protocol-specified contact. After a screening phase of up to 42 days, each participant will be assigned to receive 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, the start of a new anti-cancer treatment, 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:

Steering Committee	No
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.