Clinical Trial Details (PDF Generation Date :- Tue, 27 Jul 2021 07:29:02 GMT)

CTRI Number	CTRI/2019/06/019634 [Registered on: 12/06/2019] - **Trial Registered Prospectively**
Last Modified On	19/04/2021
Post Graduate Thesis	No
Type of Trial	Interventional
Type of Study	Biological
Study Design	Randomized, Parallel Group, Placebo Controlled Trial
Public Title of Study	Study in Patients with surgically removable Non-Small Cell Lung Cancer (NSCLC) with Durvalumab plus Chemotherapy before and after surgical removal of tumour versus surgical removal of tumour alone with chemotherapy
Scientific Title of Study	A Phase III, Double-blind, Placebo-controlled, Multi-center International Study of Neoadjuvant/Adjuvant Durvalumab for the Treatment of Patients with Resectable Stages II and III Non-small Cell Lung Cancer (AEGEAN)

Secondary IDs if Any

Secondary ID	Identifier
D9106C00001 Version 3.0, dated 26 Nov 2019	Protocol Number

Details of Principal Investigator or overall Trial Coordinator (multi-center study)

Details of Principal Investigator	
Name	
Designation	
Affiliation	
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Details Contact Person (Scientific Query)

Details Contact Person (Scientific Query)	
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Source of Monetary or Material Support

Source of Monetary or Material Support
> AstraZeneca AB, 151 85 Sodertalje Sweden

Primary Sponsor

Primary Sponsor Details	
Name	AstraZeneca AB
Address	151 85 Sodertalje Sweden
Type of Sponsor	Pharmaceutical industry-Global

Details of Secondary Sponsor

Name	Address
AstraZeneca Pharma India Ltd	Block N1, 12th Floor, Manyata Embassy Business Park, Rachenahalli, Outer Ring Road, Bangalore – 560045, India

Countries of Recruitment

List of Countries
Argentina
Austria
Chile
Hungary
India
Japan
Mexico
Republic of Korea
Russian Federation
Taiwan
Thailand
Ukraine
United States of America
Viet Nam

Sites of Study

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Details of Ethics Committee

Name of Committee	Approval Status	Date of Approval	Is Independent Ethics Committee?
Action Cancer Hospital Ethics Committee	Approved	26/06/2019	No
Artemis Health Sciences Institutional Ethics Committee	Approved	25/07/2019	No
Bhaktivedanta Hospital Ethics Committee	Approved	13/04/2020	No
HCG Multi Specialty Ethics Committee, Ahmedabad	Approved	06/09/2019	No
Institutional Ethics Committee HCG - Bharath Hospital and Institute of Oncology	Approved	06/11/2020	No
Institutional Ethics Committee TATA Memorial Hospital, Mumbai	Approved	08/01/2021	No
Institutional Ethics Committee, PGIMER	Approved	13/08/2020	No
Institutional Ethics Committee- Clinical Studies, Apollo, Sarita Vihar, Delhi	Approved	01/10/2020	No
Institutional Ethics Committee- Clinical Studies, MAX, Patparganj	Approved	07/10/2020	No
Institutional Review Board Rajiv Gandhi Cancer Institute and Research Centre	Approved	16/01/2020	No
Institutional Review Board Tata Medical Center, Kolkata	Approved	29/03/2019	No
Kokilaben Dhirubhai	Approved	30/09/2019	No

Ambani Hospital and Medical Research Institutional Ethics Committee			
Mahatma Gandhi Cancer Hospital and Research Institute Institutional Review Board, Vishakhapatnam	Approved	30/04/2019	No
MAHE Ethics Committee- Clinical Studies	Approved	10/10/2020	No
Manavata Clinical Research Institute Ethics Committee	Approved	23/05/2019	No
Meditrina Institute Ethics Committee	Approved	23/05/2019	No
Meenakshi Mission Hospital and Research Centre (MMHRC) INSTITUTIONAL ETHICS COMMITTEE	Approved	18/02/2020	No
Noble Hospital Pvt. Ltd Institutional Ethics Committee	Approved	06/05/2019	No
Paras Hospital Ethics Committee	Approved	31/07/2020	No
Thangam Hospital - INSTITUTIONAL ETHICS COMMITTEE	Approved	29/02/2020	No

Regulatory Clearance Status from DCGI

Status	Date
Approved/Obtained	01/05/2019

Health Condition / Problems Studied

Health Type	Condition
Patients	Malignant neoplasm of unspecifiedpart of bronchus or lung

Intervention / Comparator Agent

Type	Name	Details
Intervention	Durvalumab	Durvalumab plus Comparator Agent Placebo plus Chemotherapy
Comparator Agent	Placebo plus Chemotherapy	Durvalumab plus Comparator Agent Placebo plus Chemotherapy

Inclusion Criteria

Inclusion Criteria	
Age From	18.00 Year(s)
Age To	99.00 Year(s)
Gender	Both
Details	Informed consent 1.Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. 2. Provision of signed and dated written ICF prior to any mandatory study specific procedures, sampling, and analyses. 3. Provision of signed and dated written ICF prior to collection of sample for genetic analysis. Age 4. Age ?18 years at the time of screening. For patients aged <20 years and

enrolled in Japan, a written informed consent should be obtained from the patient and his or her legally acceptable representative.
 Type of patient and disease characteristics

 5. Histologically or cytologically documented NSCLC with resectable (Stage IIA to select [ie, N2] Stage IIIB) disease (according to Version 8 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology).

 i).At screening, complete surgical resection of the primary NSCLC must be deemed achievable, as assessed by a multidisciplinary evaluation, which must include a thoracic surgeon who performs lung cancer surgery as a prominent part of his/her practice.
 ii).Nodal status should be investigated with whole body 18F-fluoro-deoxyglucose positron emission tomography (FDG-PET), plus contrast-enhanced computed tomography (CT) in addition to or in combination with PET before surgery. If PET/CT scan is positive in the mediastinum, or if scan is negative but there is T>3 cm, central tumor, or clinical N1 (cN1), then nodal status should be proven by biopsy via endobronchial ultrasound, mediastinoscopy, or thoracoscopy. (preoperative mediastinal lymph node staging).
 iii).Mandatory brain magnetic resonance imaging (MRI; preferred) with IV contrast or brain CT with IV contrast at the time of staging.

 6. World Health Organization (WHO)/ECOG PS of 0 or 1 at enrolment.

 7. At least 1 lesion, not previously irradiated, that qualifies as a RECIST 1.1 target lesion (TL) at baseline. Tumor assessment by CT or MRI scan must be performed within 28 days prior to randomization.

 8. No prior exposure to immune-mediated therapy including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-PD-L2 antibodies, excluding therapeutic anticancer vaccines.

 9. Adequate organ and marrow function as defined below:

 i).Hemoglobin ?9.0 g/dL
 ii).Absolute neutrophil count ?1.5 × 109/L
 iii).Platelet count ?100 × 109/L
 iv).Serum bilirubin ?1.5 × the upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert’s syndrome, who will be allowed in consultation with their physician.
 v).ALT and AST ?2.5 × ULN
 vi).Measured creatinine clearance (CL) >40 mL/min or Calculated creatinine CL >40 mL/min as determined by Cockcroft-Gault (using actual body WT)
 Males:
 Creatinine CL is equal to WT (kg) × (140-Age) (mL/min) 72 × serum creatinine (mg/dL)
 Females:
 Creatinine CL is equal to WT (kg) × (140-Age) × 0.85(mL/min) 72 × serum creatinine (mg/dL)

 10. Must have a life expectancy of at least 12 weeks.

 11. Body WT >30 kg.

 Sex

 12. Male and/or female.

 Tumor sample requirements:

 13. Confirmation of a patient’s tumor PD-L1 status must occur prior to randomization using Ventana PD-L1 (SP263) immunohistochemistry (IHC) assay applied to formalin fixed paraffin embedded tissue sample with testing completed by the central laboratory.

 Samples for PD-L1 testing may include the following:
 i).Newly acquired tumor tissue (preferred) or archival tissue (<3 months old).
 ii).If the patient’s PD-L1 status has already been assessed using the analytically validated Ventana assay as a part of the screening process for another AstraZeneca/MedImmune study, this test result can be used for the determination of eligibility.

 14. Documented EGFR and ALK status (local testing is preferred; if not feasible, central testing will be performed). If the local laboratory will perform the test, a well-validated, local regulatory-approved kit must be used. EGFR/ALK status should be available prior to randomization. If the number of patients with EGFR or ALK mutations (ie, the total number of patients summed across both types of mutations) reaches approximately 20% of the total

		randomization target patient number, the incoming patients with EGFR/ALK mutations will not be randomized. Surgery eligibility (these criteria must be assessed within 30 days prior to surgery, following neoadjuvant treatment) 15. Surgery to be performed will be lobectomy, sleeve resection, bilobectomy, or pneumonectomy, as determined by the attending surgeon based on the intraoperative findings. 16. Received 4 cycles of platinum-based chemotherapy concurrent with durvalumab or placebo i).Receipt of 3 cycles of platinum-based chemotherapy concurrent with durvalumab or placebo will be permitted only if the patient experienced chemotherapy related toxicities and Investigators judge additional safety issue will be expected with additional cycles of chemotherapy. 17. Surgery should happen within 40 days from the last IP administration. 18. Patients must have recovered from all acute, reversible toxic effects from chemotherapy (excluding alopecia) and durvalumab or placebo that could potentially adversely impact the surgical procedure or outcome according to the Investigator's judgement. 19. A contrast enhanced CT/MRI scan of chest and abdomen (including the entire liver and both adrenals) are required for RECIST 1.1 assessment and for surgical planning prior to surgery. A supplemental (whole body) FDG-PET scan may also be acquired prior to surgery in order to help identify mediastinal lymph node involvement, according to investigators judgement. 20. If preoperative CT and/or PET are suspicious for mediastinal nodal involvement, or should those be negative for mediastinal lymph node but there is T>3 cm, cN1, or central tumor, then it is recommended that invasive mediastinal staging with thoracoscopy or mediastinoscopy or endobronchial ultrasound-guided transbronchial needle aspiration be performed if those were not performed at screening and/or according to the multidisciplinary evaluation and Investigator's judgment. 21. Complete surgical resection of the primary NSCLC must be deemed achievable, as assessed by a multidisciplinary evaluation, which must include a thoracic surgeon who perform lung cancer surgery as a prominent part of his/her practice. 22. Deemed adequate cardiac and lung function, according to the multidisciplinary assessment. A pre- or post-bronchodilator forced expiratory volume in 1 second (FEV1) of 1.0 L or >40% postoperative predicted value and diffusing capacity of the lungs for carbon monoxide (DLCO) >40% predicted value is recommended. Post-surgery durvalumab or placebo administration eligibility (these criteria must be assessed within 10 weeks from surgery, prior to starting adjuvant treatment) 23. Patients must have recovered from all acute, reversible toxic effects from previous treatments that could potentially adversely impact further administration of durvalumab or placebo according to the Investigator's judgement. 24. Patients should be able to start durvalumab or placebo administration as soon as clinically feasible and within 10 weeks from surgery. A minimum of 3 weeks is recommended between NSCLC surgery and durvalumab/placebo treatment start (first post-surgical scan must be performed prior to starting adjuvant treatment). Complete post-operative wound healing must have occurred following any surgery. 25. Patients with N2 disease or patients with R1/2 post-surgical findings can receive adjuvant post-operative radiation therapy (within 8 weeks after surgery) and are eligible to receive post-surgery durvalumab/placebo (within 3 weeks from end of post-operative radiation therapy). The post-operative radiation therapy must be completed prior to durvalumab/placebo administration.
Exclusion Criteria	**Exclusion Criteria**	

Details	Medical conditions 1. History of allogeneic organ transplantation. 2. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [eg, granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, or uveitis]). The following are exceptions to this criterion: i).Patients with vitiligo or alopecia. ii).Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on iii).hormone replacement. iv).Any chronic skin condition that does not require systemic therapy. v).Patients without active disease in the last 5 years may be included but only after consultation with the Study Physician vi).Patients with celiac disease controlled by diet alone. 3. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, active ILD, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs, or compromise the ability of the patient to give written informed consent. 4. History of another primary malignancy, except for the following: i).Malignancy treated with curative intent and with no known active disease ?5 years before the first dose of IP and of low potential risk for recurrence ii).Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease iii).Adequately treated carcinoma in situ without evidence of disease 5. History of active primary immunodeficiency 6. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), hepatitis B (known positive hepatitis B virus surface antigen [HBsAg] result), hepatitis C virus (HCV), or human immunodeficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved hepatitis B virus (HBV) infection (defined as the presence of hepatitis B core antibody and absence of HBsAg) are eligible. Patients positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV ribonucleic acid (RNA). 7. Deemed unresectable NSCLC by multidisciplinary evaluation that must include a thoracic surgeon who perform lung cancer surgery as a significant part of their practice 8. Patients who have pre operative radiotherapy treatment as part of their care plan 9 Patients who have brain metastases or spinal cord compression. All patients will have an MRI (preferred) or high quality CT with IV contrast of the brain, prior to study entry.

10. Stage IIIB N3 and Stages IIIC, IVA, and IVB NSCLC

11. Mean QT interval corrected for heart rate using Fridericias formula (QTcF) ?470 ms calculated from 3 ECGs (within 15 minutes at 5 minutes apart).

12. Mixed small cell and NSCLC histology.

13. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.

14. Any medical contraindication to treatment with platinum-based doublet chemotherapy as listed in the local labelling

15. Patients who are candidates to undergo only segmentectomies or wedge resections.

Prior/concomitant therapy

16. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment.
Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable.

17. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug.

18. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine while receiving IP and up to 30 days after the last dose of IP.

19. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP

20. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:
i) Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra articular injection)
ii) Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
iii) Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)

Prior/concurrent clinical study experience
21. Participation in another clinical study with an IP administered in the last 4 weeks.

22. Previous IP assignment in the present study.

23. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study

24. Prior randomization or treatment in a previous durvalumab clinical study regardless of treatment arm assignment.

Diagnostic assessments
Other exclusions

	25. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of IP. 26. Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements. 27. Exclusion criteria for participation in the optional (DNA) genetics research component of the study include the following: i). Previous allogeneic bone marrow transplant ii). Non-leukocyte-depleted whole blood transfusion in 120 days of genetic sample collection post-menopausal. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply: iii). Women 1 year ago, or had chemotherapy-induced menopause with last menses >1 year ago. v). Women who are surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) are eligible.

Method of Generating Random Sequence	Stratified block randomization
Method of Concealment	Centralized
Blinding/Masking	Participant and Investigator Blinded

Primary Outcome

Outcome	Timepoints
To compare the efficacy of durvalumab +chemotherapy administered prior to surgery followed by durvalumab post-surgery compared with placebo+ chemotherapy administered prior to surgery followed by placebo post-surgery in terms of EFS To assess the activity of durvalumab + chemotherapy administered prior to surgery compared with placebo+ chemotherapy administered prior to surgery in terms of mPR	EFS mPR (10% or less residual viable tumor tissue in lung primary tumor after neoadjuvant treatment at the time of resection)

Secondary Outcome

Outcome	Timepoints
1.To compare the efficacy of durvalumab PLUS chemotherapy administered prior to surgery followed by durvalumab post-surgery compared with placebo PLUS chemotherapy administered Prior to surgery followed by placebo post-surgery in Terms of DFS	DFS
2. To compare the activity of durvalumab PLUS chemotherapy administered prior to surgery compared with placebo PLUS Chemotherapy administered prior to surgery in terms of pCR	pCR (absence of any residual viable tumor in the primary lung lesion and lymph nodes at the time of surgical resection)
3.To compare the efficacy of durvalumab PLUS chemotherapy administered prior to surgery followed by durvalumab post-surgery compared with placebo PLUS chemotherapy administered prior to surgery followed by placebo post-surgery	OS

in terms of OS	
4.To compare the efficacy of durvalumab PLUS chemotherapy administered prior to surgery followed by durvalumab post-surgery compared with placebo PLUS chemotherapy administered prior to surgery followed by placebo post-surgery in patients with PD-L1-TC?1% in terms of EFS, mPR, DFS, and pCR	EFS mPR DFS pCR
5.To compare disease-related symptoms and HRQoL in patients treated with durvalumab PLUS chemotherapy administered prior to surgery followed by durvalumab post-surgery compared with placebo PLUS chemotherapy administered prior to surgery followed by placebo post-surgery	Change from baseline and time to deterioration in EORTC QLQ-C30 and EORTC QLQ-LC13
6.To assess the PK of durvalumab ? Concentration of durvalumab	Concentration of durvalumab
7.To investigate the immunogenicity of durvalumab	Presence of ADAs for durvalumab
Safety objective: 1.To assess the safety and tolerability profile of durvalumab PLUS chemotherapy administered prior to surgery followed by durvalumab post-surgery compared with placebo PLUS chemotherapy administered prior to surgery followed by placebo post-surgery ? AEs, physical examinations, vital signs (including BP, pulse, and ECGs), and laboratory findings (including clinical chemistry, hematology, and urinalysis)	AEs, physical examinations, vital signs (including BP, pulse, and ECGs), and laboratory findings (including clinical chemistry, hematology, and urinalysis)
Exploratory objectives: 1.To investigate the effect on ctDNA, tumor protein, and/or blood RNA-based biomarkers in patients treated with durvalumab PLUS chemotherapy administered prior to surgery followed by durvalumab post-surgery compared with placebo PLUS chemotherapy administered prior to surgery followed by placebo post-surgery, and associations with clinical endpoints	ctDNA: Evaluations including, but not limited to, baseline mutations, changes in levels on-treatment prior to and following surgery, and blood TMB at baseline IHC: Including, but not limited to, PD-L1 and/or CD8 protein expression at baseline and following surgery Blood mRNA expression: Including, but not limited to, immune-relevant gene signatures at baseline
To compare the activity of durvalumab PLUS chemotherapy administered prior to surgery compared with placebo PLUS chemotherapy administered prior to surgery in terms of mPR assessed according to the immune related pathologic response criteria (Cottrell et al 2018)	mPR (10% or less residual viable tumor tissue in lung primary tumor after neoadjuvant treatment at the time of resection) in FAS
To explore the impact of treatment and disease on health state utility To explore the impact of treatment and disease on health care resource use	EQ-5D-5L, descriptor, and VAS Health care resource use will be captured, including inpatient admissions, ICU admissions, and length of stay in the hospital. Study-mandated visits are excluded from this assessment.
To investigate the effect of baseline colonic microbiome on response to treatment and the	Microbiome culture, analysis, and metabolome analysis of stool sample

	effect of treatment on the microbiome over time
	To assess treatment-related symptoms using PRO CTCAE To assess the patient's overall impression of the severity of their cancer symptoms using PGIS
	Change in specific treatment-related symptoms Proportion of patients assessing current symptom severity
Target Sample Size	**Total Sample Size=**300 **Sample Size from India=**40 **Final Enrollment numbers achieved (Total)=**Applicable only for Completed/Terminated trials **Final Enrollment numbers achieved (India)=**Applicable only for Completed/Terminated trials
Phase of Trial	Phase 3
Date of First Enrollment (India)	17/06/2019
Date of First Enrollment (Global)	06/12/2018
Estimated Duration of Trial	**Years=**5 **Months=**0 **Days=**0
Recruitment Status of Trial (Global)	Open to Recruitment
Recruitment Status of Trial (India)	Open to Recruitment
Publication Details	Not yet
Brief Summary	This is a Phase III, double-blind, placebo-controlled, multi-center international study of neoadjuvant/adjuvant durvalumab for the treatment of patients with resectable Stages II and III NSCLC. Approximately 800 patients with resectable NSCLC (Stage IIA to select Stage IIIB; either squamous or non-squamous) will be randomized in a 1:1 ratio to receive either durvalumab plus platinum-based chemotherapy before surgery followed by durvalumab post-surgery or placebo plus platinum-based chemotherapy before surgery followed by placebo post-surgery. Patients will be stratified by disease stage (Stage II versus Stage III) and by PD-L1 expression status (<1% versus ?1%). The percentage of patients with *EGFR*/*ALK* mutations will be capped at approximately 20% of the patients randomized. Once the cap is reached, *EGFR*/*ALK* mutated patients will no longer be allowed to enter the study. Patients will receive 4 cycles of durvalumab or placebo plus platinum-based chemotherapy (q3w) followed by surgery. Surgery may consist of lobectomy, sleeve resection, bilobectomy, or pneumonectomy

as determined by the attending surgeon based on the intraoperative findings. Patients who are candidates to undergo only segmentectomies or wedge resections at eligibility assessment are not eligible for this study.

All patients must be staged and managed according to the National Comprehensive Cancer Network 2018 Guidelines (version 4).

An early safety evaluation by an IDMC will review the data from the first 40 patients across both treatment arms who have undergone surgery and had 21 days of follow-up, in order to assess perioperative mortality and surgery delays. Surgery is expected within 40 days from the last IP dose. The IDMC will then meet regularly at 6-month intervals to review the safety and tolerability of durvalumab plus chemotherapy as neoadjuvant regimen and of durvalumab post-surgery, until all patients across both treatment arms have undergone surgery and have had at least 6 months of follow-up. Safety reviews will be carried out by the IDMC in an unblinded manner. The IDMC will report back to the Sponsor with any recommendations regarding modifications to the study.

Patients should be able to start durvalumab or placebo administration following surgery as soon as clinically feasible and within 10 weeks from surgery (except for patients receiving post-operative radiation therapy, which must be started within 8 weeks after surgery; durvalumab/placebo must be given within 3 weeks from the end of post-operative radiation therapy). Patients randomized to receive durvalumab plus platinum-based chemotherapy prior to surgery will receive an additional 12 cycles of durvalumab 1500 mg q4w, while patients randomized to receive placebo plus platinum-based chemotherapy prior to surgery will receive an additional 12 cycles of placebo q4w.

Tumor evaluation using RECIST 1.1 will be conducted at screening (within 28 days prior to randomization); after the completion of neoadjuvant chemotherapy prior to surgery; every 12 weeks (q12w)±1 week (relative to the date of surgery) for the first year; every 24 weeks (q24w)±1 week (relative to the date of surgery) for years 2, 3, and 4; and then yearly (relative to the date of surgery) thereafter, until RECIST 1.1-defined radiological PD, consent withdrawal, or death. For patients who do not have surgery and therefore will not have a first post-surgical scan or adjuvant treatment, scans will be conducted q12w±1 week (relative to the date of the planned pre-surgery scan) for the first year; q24w±1 week (relative to the date of the pre-planned surgery) for years 2, 3, and 4; and then yearly (relative to the date of the pre-planned surgery) thereafter, until RECIST 1.1-defined radiological PD, consent withdrawal, or death.