Inclusion Criteria

1. Has gastroesophageal adenocarcinoma that is not HER-2/neu positive. Note: Participants with gastroesophageal adenocarcinoma that is known to be HER-2/neu positive are not eligible. If HER-2/neu status is unknown, site should follow local standards if HER-2/neu testing is required as SOC.
2. Has measurable disease as defined by RECIST 1.1 by scan with IV contrast as determined by the local site investigator. Lesions situated in a previously irradiated area are considered measurable if progression has been showed in such lesions since the completion of radiation (by scans with contrast).
Demographics
3. Is male or female at least 18 years of age inclusive at the time of signing the informed consent.
Male Participants
4. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 7 days after last dose of lenvatinib or 90 days after last dose of chemotherapy except oxaliplatin or 6 months after last dose of oxaliplatin, whichever comes last: ☐ Refrain from donating sperm PLUS either: ☐ Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent OR ☐ Must agree to use contraception as detailed below unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]): Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.
Female Participants
5. 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 through 120 days after last dose of pembrolizumab, 30 days after last dose of lenvatinib, or 180 days after last dose of chemotherapy, whichever occurs last, or 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. A WOCBP must have a negative highly sensitive pregnancy test ([urine or serum] as required by local regulations) within 24 hours for urine or 72 hours for serum before the first dose of study intervention.
Informed Consent
6. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study
Additional Categories
7. Has a performance status of 0 or 1 on the ECOG Performance Scale within 3 days prior to the first dose of study treatment.

8. Has provided a tumor tissue sample for PD-L1 and MSI biomarker analysis. If the initial tissue is inadequate for the analysis, an additional specimen will need to be provided.

9. Has adequately controlled BP with or without antihypertensive medications, defined as BP ≤150/90 mm Hg and no change in antihypertensive medications within 1 week prior to randomization.

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

System	Laboratory Value
Hematological[a]	
Absolute neutrophil count (ANC)	≥1500 /mcL
Platelets	≥100,000 /mcL
Hemoglobin	≥9 g/dL
Renal	
Calculated[b] creatinine clearance	≥50 mL/min
Hepatic	
Total bilirubin	≤1.5 X ULN OR Direct bilirubin ≤ ULN for participants with total bilirubin levels >1.5 ULN
AST (SGOT) and ALT (SGPT)	≤2.5 X ULN OR ≤5 X ULN for participants with liver metastases
Albumin[c]	≥3.0 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X 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 and without packed red blood cell (pRBC) transfusion within last 2 weeks and G-SCF and thrombopoietin within last 3 weeks.

[b] Estimated creatinine clearance using Cockcroft-Gault:

$$\frac{(140 - \text{age[years]} \times \text{weight[kg]})}{\text{Serum creatinine (mg/dL)} \times 72} \quad (XF)^*$$

*where F = 0.85 for females and F = 1 for males

[c] Criteria must be met without albumin supplementation within the last 72 hours.

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.