Exclusion Criteria

Medical Conditions
1. Has had previous therapy for locally advanced unresectable or metastatic gastric/GEJ/esophageal adenocarcinoma. Note: Participants may have received prior neoadjuvant or adjuvant therapy as long as it was completed at least 6 months prior to randomization and progression occurred at least 6 months after completion of therapy.
2. Has had major surgery within 28 days prior to first dose of study interventions. Note: Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study intervention.
3. Has had radiotherapy within 14 days of randomization. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.
4. Has a known additional malignancy that is progressing or has required active treatment within the past 5 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
5. Has known CNS metastases and/or carcinomatous meningitis.
6. Has severe hypersensitivity (≥Grade 3) to treatment with an mAb or known sensitivity or intolerance to any component of lenvatinib, pembrolizumab, study chemotherapy agents and/or to any excipients, murine proteins, or platinum containing products.
7. Has had an allogeneic tissue/solid organ transplant.
8. Has perforation risks or significant GI bleeding, such as: - Has had a serious nonhealing wound, peptic ulcer, or bone fracture within 28 days prior to randomization - Has preexisting ≥Grade 3 GI or non-GI fistula - Has significant bleeding disorders, vasculitis, or has had a significant bleeding episode from the GI tract within 12 weeks prior to randomization
9. Has GI obstruction, poor oral intake (CAPOX participants), or difficulty in taking oral medication (CAPOX participants). G-tubes, J-tubes and nasogastric tubes will not be permitted for treatment administration of capecitabine. Participants with existing esophageal stent are not eligible. Also, participants with known gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that may affect the absorption of lenvatinib.
Prior/Concomitant Therapy
10. 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 coinhibitory TCR (eg, CTLA-4, OX40, CD137).
11. Has received prior therapy with anti-VEGF TKI or anti-VEGF mAb.
12. Has received a live or live-attenuated vaccine within 30 days before the first dose of study drug. Note: Killed vaccines are allowed. Note: See Section 6.5 for information on COVID-19 vaccines.
Prior/Concurrent Clinical Study Experience
13. 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 the first dose of study intervention.

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
14. 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 is not considered a form of systemic treatment and is allowed.
15. Has radiographic evidence of encasement or invasion of a major blood vessel, or of intratumoral cavitation. Note: The degree of proximity to major blood vessels should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis after lenvatinib therapy
16. Has inadequate cardiac function assessed as: – LVEF below the institutional normal range as determined by a MUGA or ECHO. – QTcF value >470 msec for males and >480 msec for females (mean of 3 measurements corrected for heart rate using Fridericia's formula). Note: If the QTcF is prolonged to >470 msec for males and >480 msec for females in the presence of a pacemaker, contact the Sponsor to determine eligibility. Cardiac function will be assessed using 12-lead ECG scan and ECHO performed by the investigator or other qualified person prior to enrollment in the study
17. Has urine protein ≥1 g/24 hours. Note: Participants with proteinuria ≥2+ (≥100 mg/dL) on urine dipstick testing (urinalysis) will undergo 24-hour urine collection for quantitative assessment of proteinuria. Participants may be eligible if 24-hour urine protein ≤1 g.
18. 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 to the first dose of study intervention.
19. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
20. Has a known history of active TB (*Mycobacterium tuberculosis*). No testing for TB is required unless mandated by local health authority.
21. Has an active infection requiring systemic therapy.
22. Has poorly controlled diarrhea (eg, watery stool, uncontrollable bowel movement with supportive medication, Grade ≥2 and number of defecations, ≥5/day).
23. Has accumulation of pleural, ascitic, or pericardial fluid requiring drainage or diuretic drugs within 2 weeks prior to enrollment. If the participant is receiving diuretic drugs for other reasons, it is acceptable. Consult with the Sponsor if the participant has more than trivial/trace fluid accumulation.
24. Has a history or current evidence of any condition (eg, but not limited to, known deficiency of the enzyme DPD, etc.), therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the investigator. Participants with a contraindication to SOC therapy should be excluded based on the following: – Has a history of a GI condition or procedure that in the opinion of the investigator may affect oral study drug absorption. – Has a history of a severe and unexpected reaction to a fluoropyrimidine-containing treatment.

– Has severe dyspnea at rest related to advanced disease stage or oxygen-dependent complications. – Has hypokalemia, hypomagnesemia, or hypocalcemia. – Participant had active hemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks or tumor bleeding within 2 weeks prior to the first dose of study intervention.
Diagnostic Assessments (continued)
25. Has peripheral neuropathy ≥Grade 2.
26. Has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the study.
27. Has clinically significant cardiovascular disease within 12 months from first dose of study intervention, including New York Heart Association Class III or IV congestive heart failure, unstable angina, myocardial infarction, cerebral vascular accident, or cardiac arrhythmia associated with hemodynamic instability. Note: Medically controlled arrhythmia would be permitted.
28. Has a known history of HIV (HIV antibodies). No testing for HIV is required unless mandated by local health authority.
29. 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. No testing for hepatitis B/C is required unless mandated by local health authority.
Other Exclusions
30. Has weight loss of >20% within the last 3 months.