Exclusion Criteria

Subjects who meet any of the following criteria will be disqualified from entering the study:

1. Use of anticancer therapy after trastuzumab-containing treatment.
2. Medical history of myocardial infarction (MI) within 6 months before randomization/enrollment, symptomatic congestive heart failure (New York Heart Association [NYHA] Class II to IV). Subjects with troponin levels above ULN at screening (as defined by the manufacturer), and without any MI related symptoms should have a cardiologic consultation before enrollment to rule out MI.
3. Has a QT interval corrected by Fridericia's formula (QTcF) prolongation to >470 msec (female subjects) or >450 msec (male subjects) based on average of the Screening triplicate12-lead electrocardiogram (ECG).
4. Has a pleural effusion, ascites, or pericardial effusion that requires drainage, peritoneal shunt, or cell-free and concentrated ascites reinfusion therapy (CART). Drainage and CART must be at least 2 weeks prior to Screening.
5. Has a history of (non-infectious) ILD/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at Screening.
6. Lung-specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disease (eg, pulmonary emboli within 3 months of the study randomization, severe asthma, severe COPD, restrictive lung disease, pleural effusion, etc.).
7. Any autoimmune, connective tissue or inflammatory disorders (eg, rheumatoid arthritis,
Sjögren syndrome, sarcoidosis, etc.) where there is documented (or a suspicion of) pulmonary involvement at the time of Screening. Full details of the disorder should be recorded in the electronic case report form (eCRF) for patients who are included in the study.
8. Prior pneumonectomy.
9. Spinal cord compression or clinically active CNS metastases, defined as untreated and symptomatic or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms.

a. Subjects with clinically inactive brain metastases may be included in the study.

b. Subjects with brain metastases who were treated and are no longer symptomatic, and
subjects who require no treatment with corticosteroids or anticonvulsants may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole

brain radiotherapy (WBRT) and randomization/study enrollment.

10. Has multiple primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, other solid tumors curatively treated.

11. History of severe hypersensitivity reactions to either the T-DXd or inactive ingredients in T-DXd.

12. History of severe hypersensitivity reactions to other monoclonal antibodies or any components used in the ramucirumab drug product preparation.

13. Known allergy or hypersensitivity to PTX or any components used in the PTX preparation or other contraindication for taxane therapy such as peripheral neuropathy, Grade 2.

14. Current uncontrolled infection requiring antibiotics, antivirals, or antifungals or an unexplained fever >38.0°C during Screening visits or on the first scheduled day of dosing (at the discretion of the Investigator, subjects with tumor fever may be enrolled), which in the Investigator's opinion might compromise the subject's participation in the study or affect the study outcome.

15. Substance abuse or any other medical conditions such as clinically significant cardiac or pulmonary diseases or psychological conditions, that may, in the opinion of the Investigator, interfere with the subject's participation in the clinical study or evaluation of the clinical study results.

16. Social, familial, or geographical factors that would interfere with study participation or follow-up.

17. Known human immunodeficiency virus (HIV) infection, or active hepatitis B or C infection.

Subjects positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA. Subjects should be tested for HIV prior to randomization/enrollment if required by local regulations or institutional review board (IRB)/independent ethics committee (IEC).

18. Unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade ≤1 or baseline. Subjects with chronic Grade 2 toxicities may be eligible per the discretion of the Investigator after consultation with the Sponsor Medical Monitor or designee (eg, Grade 2 chemotherapy-induced neuropathy).

19. Prior treatment with an ADC consisting of an exatecan derivative that is a topoisomerase I inhibitor.

20. Pregnant, breastfeeding, or planning to become pregnant.

21. Subjects who, in the opinion of the Investigator, have symptoms or signs suggestive of clinically unacceptable deterioration of the primary disease at the time

of Screening or otherwise considered inappropriate for the study by the Investigator.
22. Clinically significant gastrointestinal disorder (eg, including hepatic disorders, bleeding, inflammation, occlusion, ileus, diarrhea Grade >1, jaundice, intestinal paralysis, malabsorption syndrome, ulcerative colitis, inflammatory bowel disease, or partial bowel obstruction) in the opinion of Investigator.