Exclusion:

Patients who meet any of the following criteria will be excluded from study entry:

• NSCLC known to have a mutation in the EGFR gene or an ALK fusion oncogene are excluded from the study.

• Patients with non-squamous NSCLC who have an unknown EGFR or ALK status will be required to be tested at pre-screening or screening.

EGFR and/or ALK status may be assessed locally or at a central laboratory.

– EGFR status assessed locally must be performed on tissue or cytology using a validated health authority-approved test that detects mutations in exons 18-21.

– If samples are submitted for central EGFR and/or ALK testing, additional slides must be provided.

• Pulmonary lymphoepithelioma-like carcinoma subtype of NSCLC

• Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases

Asymptomatic patients with treated CNS lesions are eligible, provided that all of the following criteria are met:

– Measurable disease, per RECIST v1.1, must be present outside the CNS.

– The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.

– The patient has not undergone stereotactic radiotherapy within 7 days prior to randomization, whole-brain radiotherapy within 14 days prior to randomization, or neurosurgical resection within 28 days prior to randomization.

– The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anticonvulsant therapy at a stable dose is permitted.

– Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).

– There is no evidence of interim progression between completion of CNS-directed therapy and randomization.

Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan.

• Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥ 2 weeks prior to randomization.

• History of leptomeningeal disease

• Uncontrolled tumor-related pain

Patients requiring pain medication must have adequate pain control.

Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to randomization. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy, if appropriate, prior to randomization.

• Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

Patients with indwelling catheters (e.g., PleurX®) are allowed regardless of drainage frequency.

• Uncontrolled or symptomatic hypercalcemia (ionized calcium >1.5 mmol/L, calcium >12 mg/dL, or corrected calcium greater than ULN)

• Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis with the following exceptions:

Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.

Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

– Rash must cover <10% of body surface area.

– Disease is well controlled at baseline and requires only low-potency topical corticosteroids (equivalent of 10 mg/day prednisone orally).

– No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.

• History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on the screening chest computed tomography scan

History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

• Known active tuberculosis

• Current treatment with anti-viral therapy for HBV or HCV

• Positive EBV viral capsid antigen IgM test during screening

An EBV polymerase chain reaction (PCR) test should be performed as clinically indicated to screen for acute infection or suspected chronic active infection. Patients with a positive EBV PCR test are excluded.

• Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, and inherited liver disease, or current alcohol abuse

• Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina

Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction <50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.

• Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study

• History of malignancy other than NSCLC within 5 years prior to randomization, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate >90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal breast carcinoma in situ, or Stage I uterine cancer

• Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia

• Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.

• Prior allogeneic stem cell or solid organ transplantation

• Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications

• Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during study treatment or within 5 months after the final dose of study treatment

• Treatment with investigational therapy within 28 days prior to initiation of study treatment

• Any anti-cancer therapy, including hormonal therapy, within 21 days prior to initiation of study treatment

• Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-cytotoxic T lymphocyte-associated protein 4, anti-TIGIT, anti-PD-1, and anti-PD-L1 therapeutic antibodies

• Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment

• Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:

– Patients who receive acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Medical Monitor confirmation.

– Patients who receive mineralocorticoids (e.g., fludrocortisone), inhaled or low-dose corticosteroids for chronic obstructive pulmonary disease or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.

• History of severe allergic anaphylactic reactions to chimeric or humanized antibodies, fusion proteins, or platinum-containing compounds

• Known hypersensitivity to Chinese hamster ovary cell products or to any component of the tiragolumab or atezolizumab or pembrolizumab formulation

• Hearing impairment (cisplatin only)

• Grade ≥ 2 peripheral neuropathy as defined by NCI CTCAE v5.0 (cisplatin only)

• Pregnant or breastfeeding, or intending to become pregnant during the study, for 90 days after the final dose of tiragolumab or placebo, 5 months after the final dose of atezolizumab or pembrolizumab, or 6 months after the final dose of pemetrexed, carboplatin or cisplatin.

Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.