PROTOCOL

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4.1 PATIENTS

Approximately 800 patients with unresectable Stage III NSCLC who have previously received two cycles of platinum-based chemotherapy concurrently with CRT without disease progression will be enrolled at approximately 150 sites globally.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, including willingness to remain in the post-treatment period
- ECOG Performance Status of 0 or 1 (see Appendix 3)
- Histologically or cytologically documented NSCLC with unresectable Stage III NSCLC of either squamous or non-squamous histology

Staging should be based on the 8th revised edition of the AJCC (Amin et al. 2017)/UICC NSCLC staging system.

  - Patients with tumors of mixed NSCLC histology must be classified as being non-squamous or squamous on the basis of the major histologic component.
  - Patients with T4 primary NSCLC with a separate nodule in a different ipsilateral lobe are not eligible.
  - Patients with tumors of mixed histology containing both NSCLC and small-cell lung cancer are not eligible for the study.
- Whole-body positron emission tomography (PET)-CT scan (from the base of skull to mid-thighs) for the purposes of staging, performed prior and within 42 days of the first dose of concurrent CRT
- At least two prior cycles of platinum-based chemotherapy concurrent with RT (CRT), which must be completed within 1 to 42 days prior to randomization in the study

To ensure the best patient outcomes, sites are strongly encouraged to complete screening procedures within the first 14 days after the final dose of CRT (see Section 4.5.1).

The platinum-based chemotherapy regimen must contain one of the following agents: etoposide, a taxane (paclitaxel), pemetrexed, or vinorelbine.

Concurrent chemotherapy must be given per the NCCN® (2019) and/or the European Society of Medical Oncology guidelines (Postmus et al. 2017).

The final cycle of chemotherapy must end prior to or concurrently with the final dose of RT.

Consolidation chemotherapy is not permitted, but administration of chemotherapy prior to concurrent CRT is acceptable (but not to exceed more than one cycle).

- The RT component in the CRT must have been at a total dose of radiation of 60 (± 10) Gy (54–66 Gy) administered by IMRT (preferred) or 3D-conforming technique

Sites are encouraged to adhere to mean organ radiation dosing as follows:

  - The mean dose of radiation in the lung must be <20 Gy and/or V20 must be $<35\%$.
  - The mean dose of radiation in the esophagus must be <34 Gy.
  - The mean dose of radiation in the heart must be V45 $<35\%$ or V3 $<30\%$.

- No progression during or following concurrent platinum-based CRT
- Tumor PD-L1 expression, as determined by SP263 IHC assay and documented by means of central testing of a representative tumor tissue, in either a previously obtained archival tumor tissue or fresh tissue obtained from a biopsy prior to the first dose of CRT
- Confirmed availability of representative tumor specimens in formalin-fixed, paraffin-embedded (FFPE) blocks (preferred) or at least 15–20 unstained serial slides, along with an associated pathology report

If central testing for *EGFR* mutations and/or *ALK* translocations are required, an additional 5 unstained slides must be provided.

Tumor tissue should be of good quality based on total and viable tumor content. Acceptable samples include core-needle biopsies for deep tumor tissue (with a minimum of three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

Fine-needle aspirations, brushings, cell pellets from pleural effusions, and lavage samples are not acceptable.

Tumor tissue from bone metastases is not evaluable for tumor PD-L1 expression by IHC and is therefore not acceptable.

- Life expectancy ≥ 12 weeks
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment (Day 1 of Cycle 1):
  - ANC $\geq 1.5 \times 10^9$/L ($\geq 1500/\mu$L) without granulocyte colony-stimulating factor support
  - Lymphocyte count $\geq 0.5 \times 10^9$/L ($\geq 500/\mu$L)
  - Platelet count $\geq 100 \times 10^9$/L ($\geq 100{,}000/\mu$L) without transfusion
  - Hemoglobin ≥ 90 g/L (≥ 9 g/dL)

Patients may be transfused or receive erythropoietic treatment as per local standard of

care to meet this criterion.

- AST, ALT, and ALP $\leq 2.5 \times$ upper limit of normal (ULN), with the following exceptions:

Patients with documented liver metastases: AST and ALT $\leq 5 \times$ ULN Patients with documented liver or bone metastases: ALP $\leq 5 \times$ ULN

- Bilirubin $\leq 1.5 \times$ ULN with the following exception:

Patients with known Gilbert disease: bilirubin level $\leq 3 \times$ ULN

- Creatinine $\leq 1.5 \times$ ULN
- Creatinine clearance (CrCl) ≥ 50 mL/min, calculated using the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of CrCl:

For males:

$$\text{CrCl (mL/min)} = \frac{\text{Weight (kg) x (140 – Age)}}{72 \times \text{serum creatinine (mg/dL)}}$$

For females:

$$\text{CrCl (mL/min)} = \frac{\text{Weight (kg) x (140 – Age)}}{72 \times \text{serum creatinine (mg/dL)}} \times 85$$

- Albumin ≥ 25 g/L (≥ 2.5 g/dL)
- For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 1.5 \times$ ULN
- For patients receiving therapeutic anticoagulant regimen

- Negative HIV test at screening
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Positive hepatitis B surface antibody (HBsAb) test at screening, or negative HBsAb at screening accompanied by either of the following:
  - Negative hepatitis B core antibody (HBcAb)
  - Positive HBcAb test followed by a negative (per local laboratory definition) hepatitis B virus (HBV) DNA test

The HBV DNA test will be performed only for patients who have a negative HBsAg test, a negative HBsAb test, and a positive HBcAb test.

- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

The HCV RNA test will be performed only for patients who have a positive HCV antibody test.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined below:

Women must remain abstinent or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 5 months after the final dose of study drugs. Women must refrain from donating eggs during this same period.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator
(e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

Hormonal contraceptive methods must be supplemented by a barrier method.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for
90 days after the final dose of study drugs to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.2 Exclusion Criteria

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

- Any history of prior NSCLC

- 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.
  - Patients with squamous NSCLC who have an unknown *EGFR* or *ALK* status are eligible and will not 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 (see Section 4.5.7 for details).

- If a pleural effusion is present, the following criteria must be met to exclude malignant involvement (incurable T4 disease):
  - When pleural fluid is visible on both the computed tomography (CT) scan and chest X-ray, a pleuracentesis is required to confirm that the pleural fluid is cytologically negative.
  - Patients with exudative pleural effusions are excluded regardless of cytology.
  - Patients with effusions that are minimal (i.e., not visible on chest X-ray) that are too small to safely tap are eligible.
- Any evidence of Stage IV disease, including, but not limited to, the following:
  - Pleural effusion
  - Pericardial effusion
  - Brain metastases
  - No history of intracranial hemorrhage or spinal cord hemorrhage
  - Bone metastases
  - Distal metastases
- Pulmonary lymphoepithelioma-like carcinoma subtype of NSCLC
- History of leptomeningeal disease
- Concurrent enrollment in another clinical study, unless it is an observational (non- interventional) clinical study or the follow-up period of an interventional study
- Treatment with sequential CRT for locally advanced NSCLC
- Patients with locally advanced NSCLC who have progressed during or after the definite concurrent CRT prior to randomization
- Any Grade >2 unresolved toxicity from previous CRT

Patients with an irreversible toxicity that is managed and is not expected to be exacerbated by study drug treatment may be included (e.g., hearing loss) after consultation with the Medical Monitor.

- Grade ≥ 2 pneumonitis from prior CRT
- Any concurrent chemotherapy, immunotherapy, biologic, or hormonal therapy for cancer

Note: Local treatment of isolated lesions, excluding target lesions, with palliative intent is acceptable (e.g., by local surgery or RT).

- 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 (see Appendix 10 for a more comprehensive list of autoimmune diseases and immune deficiencies), 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
  - Requirement for corticosterioids administration to > 10 mg/day oral prednisone or equivalent
- 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 CT scan
- Active tuberculosis

- 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 screening, 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
- Current treatment with anti-viral therapy for HBV or HCV
- Active EBV infection or known or suspected chronic active EBV infection at screening

Patients with a positive EBV viral capsid antigen (VCA) IgM test at screening are excluded. An EBV polymerase chain reaction (PCR) test should be performed as

clinically indicated to screen for active infection or
suspected chronic active infection. Patients with a positive EBV PCR test are excluded.

- Treatment with investigational therapy within 28 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
- Any prior Grade ≥ 3 immune-mediated adverse event or any unresolved Grade > 1 immune-mediated adverse event while receiving any previous immunotherapy agent other than immune checkpoint blockade agents
- Treatment with systemic immunostimulatory agents (including, but not limited to, IFN and interleukin-2 [IL-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–tumor necrosis factor–α [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), 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 or fusion proteins
- Known hypersensitivity to CHO cell products or to any component of the tiragolumab or atezolizumab or durvalumab formulation
- Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 5 months after the final dose of study treatment

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

- Any condition that, in the opinion of the investigator, would interfere with the evaluation of the study drug or interpretation of patient

safety or study results

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a Phase I/III, randomized, double-blind, placebo-controlled study. After written informed consent has been obtained and eligibility has been established (including determination of tumor PD-L1 status by central testing), the study site will obtain the patient's identification number and blinded treatment assignment from the interactive voice or web-based response system (IxRS).

5. ASSESSMENT OF SAFETY

5.1 SAFTEY PLAN

5.2