

Supplementary Materials

1. Study protocol

Study population:

recurrent or metastatic head and neck squamous cell carcinoma

Inclusion criteria:

1. Histologically proven head and neck squamous cell carcinoma (HNSCC)
2. Inoperable or metastatic disease
3. Age ≥ 18 years
4. More than one previous chemotherapy including at least one platinum-based regimen
5. ECOG performance status of 0 to 1
6. At least two measurable lesions
7. Adequate organ function as evidenced by the following;
 - A. Haemoglobin ≥ 9.0 g/dL
 - B. Absolute neutrophil count (ANC) $> 1.0 \times 10^9/L$
 - C. platelets $> 100 \times 10^9/L$
 - D. serum bilirubin ≤ 1.5 institutional upper limit of normal (ULN); aspartate aminotransferase (AST) (SGOT) and/or alanine transaminase (ALT) (SGPT) $\leq 2.5 \times$ ULN unless liver metastases are present, in which case it must be $\leq 5 \times$ ULN
 - E. creatinine clearance ≥ 40 mL/min by Cockcroft-Gault formula or by 24-hour urine collection for determination of creatinine clearance
8. Body weight > 30 kg
9. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
 - A. Women < 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy). Women ≥ 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause
10. Written informed consent form

11. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow-up.

Exclusion criteria:

1. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study
2. Receipt of the last dose of anticancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies) ≤ 30 days prior to the first dose of study drug. If sufficient wash-out time has not occurred due to the schedule or PK properties of an agent, a longer wash-out period will be required, as agreed by AstraZeneca and the investigator
3. Any unresolved toxicity National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade ≥ 2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria

Patients with grade ≥ 2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.

Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be included only after consultation with the Study Physician.
4. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.
5. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug
6. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.
7. History of allogenic organ transplantation.
8. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:

Patients with vitiligo or alopecia

Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone
9. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions

associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.

10. History of another primary malignancy except for
 - Malignancy treated with curative intent and with no known active disease ≥ 5 years before the first dose of IP and of low potential risk for recurrence.
 - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
 - Adequately treated carcinoma in situ without evidence of disease.
11. History of leptomeningeal carcinomatosis.
12. Brain metastases or spinal cord compression unless the patient is stable (asymptomatic; no evidence of new or emerging brain metastases; and stable and off steroids for at least 28 days prior to start of study treatment). Following radiotherapy and/or surgery of the brain metastases patients must wait 4 weeks following the intervention and before randomisation with imaging to confirm stability.
13. History of active primary immunodeficiency.
14. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥ 470 ms calculated from 3 ECGs (within 15 minutes at 5 minutes apart).
15. Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), **hepatitis B** (known positive HBV surface antigen [HBsAg] result), **hepatitis C**, or **human immunodeficiency virus** (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
16. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. The following are exceptions to this criterion
 - Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection).
 - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent.
 - Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).
17. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.

18. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
19. Prior randomisation or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment.
20. Past medical history of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease.
21. Judgment by the investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions and requirements.
22. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period.