Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial

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Summary

Background Patients with recurrent or metastatic squamous cell carcinoma of the head and neck have few treatment options. We aimed to assess the safety, tolerability, and antitumour activity of pembrolizumab, a humanised anti-programmed death receptor 1 (PD-1) antibody, in patients with PD-L1-positive recurrent or metastatic squamous cell carcinoma of the head and neck.

Methods This study was an open-label, multicentre, phase 1b trial of patients with recurrent or metastatic squamous cell carcinoma of the head and neck. Patients were eligible for enrolment if they were aged 18 years or older, had a confirmed diagnosis of recurrent or metastatic squamous cell carcinoma of the head and neck, and had any level of PD-L1 expression (ie, at least 1% of tumour cells or stroma that were PD-L1-positive by immunohistochemistry). Patients received pembrolizumab 10 mg/kg intravenously every 2 weeks. Primary outcomes were safety in the per-protocol population and the proportion of patients with centrally reviewed overall response per Response Evaluation Criteria In Solid Tumors (RECIST, version 1.1). Overall response was analysed in the full analysis set, which was defined as all patients who had received at least one dose of pembrolizumab, had measurable disease at baseline, and one post-baseline scan or patients without a post-baseline scan who discontinued therapy because of disease progression or a drug-related adverse event. The study is registered with ClinicalTrials.gov, number NCT01848834 and is ongoing, but no longer enrolling patients.

Findings Of the 104 patients screened between June 7, 2013, and Oct 3, 2013, 81 (78%) were PD-L1-positive. Of these, 60 patients with PD-L1-positive squamous cell carcinoma of the head and neck were enrolled and treated: 23 (38%) were HPV-positive and 37 (62%) were HPV-negative. Pembrolizumab was well tolerated, with 10 (17%) of 60 patients having grade 3–4 drug-related adverse events, the most common of which were increases in alanine aminotransferase and in aspartate aminotransferase, and hyponatraemia, each occurring in two of 60 patients; one patient developed a grade 3 drug-related rash. 27 (45%) of 60 patients experienced a serious adverse event. There were no drug-related deaths. The proportion of patients with an overall response by central imaging review was 18% (eight of 45 patients; 95% CI 8–32) in all patients and was 25% (four of 16 patients; 7–52) in HPV-positive patients and 14% (four of 29 patients; 4–32) in HPV-negative patients.

Interpretation Pembrolizumab was well tolerated and demonstrated clinically meaningful antitumour activity in recurrent or metastatic squamous cell carcinoma of the head and neck, supporting further study of pembrolizumab as anticancer therapy for advanced head and neck cancers.

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Introduction

Squamous cell carcinoma of the head and neck is the seventh most common cancer worldwide.[1] Patients with recurrent or metastatic disease have a poor prognosis and few treatment options.[2,3] The combination of cetuximab, platinum, and fluorouracil is commonly used as first-line treatment for recurrent or metastatic head and neck squamous cell carcinoma,[3] although taxanes and methotrexate are used in later lines of treatment. However, a more effective and less toxic treatment is needed in this palliative setting.

Human papillomavirus (HPV)-negative squamous cell carcinoma tumours of the head and neck carry a high mutational burden that is probably linked to tobacco use, whereas HPV-positive cancers might also have mutations attributed to expression of APOBEC cytidine deaminases.[4–6] Genes involved in immunity and inflammation, such as HLA A or B and nuclear factor-κB pathway genes, are frequently mutated in patients with squamous cell carcinoma of the head and neck.[4,5] The misregulation of these particular genes might explain the frequent observation of an inflamed phenotype in squamous cell carcinoma of the head and neck with the presence of tumour-infiltrating lymphocytes in roughly 40% of tumours, and provide a rationale for the potential efficacy of immunomodulatory drugs.[6] In the healthy immune system,

Research in context

Evidence before this study

To identify other published studies of the programmed death 1 (PD-1) receptor or PD-L1 inhibitors in squamous cell carcinoma of the head and neck, we searched the PubMed database using the following search terms, not limited by date or language restrictions: "PD-1 OR PD-L1 OR MK-3475 OR lambrolizumab OR nivolumab OR BMS-936558 OR MPDL3280A OR BMS-936559 AND HNSCC." Although preclinical evidence strongly supports the use of PD-1 blockade to enhance antitumour activity in squamous cell carcinoma of the head and neck (eg, Malm and colleagues, 2015), this search did not identify any other clinical studies assessing PD-1 or PD-L1 inhibitors in patients with squamous cell carcinoma of the head and neck.

Added value of this study

To our knowledge, this is the first report of the efficacy and safety of a PD-1 or PD-L1 inhibitor in patients with PD-L1-positive recurrent or metastatic squamous cell carcinoma of the head and neck. Pembrolizumab was well tolerated and showed clinically significant antitumour activity in this heavily pretreated population. Results of this study also show that pembrolizumab efficacy was associated with PD-L1 and interferon-γ-related gene expression, supporting further assessment of predictive biomarkers for pembrolizumab in future studies.

Implications of all the available evidence

The high proportions of patients achieving an overall response to PD-1 blockade and durability of responses and stable disease observed with pembrolizumab support the importance of the PD-1 pathway in squamous cell carcinoma of the head and neck, and warrants further study of pembrolizumab as an anticancer treatment for advanced head and neck cancers.

the programmed death 1 (PD-1) receptor is expressed on activated T cells and interacts with its ligands, PD-L1 and PD-L2, to protect healthy cells from excessive inflammatory or autoimmune responses.[7–10] Tumour-associated regulation of the PD-1 pathway might lead to escape from immune surveillance. Tumour cells expressing PD-L1 can reduce T-cell effector activity and terminate immune responses.[11,12] Host tumour-infiltrating T lymphocytes[6,13,14] mediate PD-L1 expression via interferon-γ secretion.[11]

Pembrolizumab is a high-affinity, humanised, IgG4-κ monoclonal PD-1 antibody. In clinical studies, pembrolizumab has shown efficacy in patients with various advanced solid tumours and is approved for the treatment of melanoma.[15–17] Additionally, PD-L1 expression has been correlated with a higher treatment response to anti-PD-1 antibodies in many cancer types.[17,18] However, patients with negative PD-L1 staining also benefit from treatment with PD-1 inhibitors, albeit at a lower frequency than those patients with PD-L1 expression.[17,18] In this study we aim to provide, to the best of our knowledge, the first safety and efficacy report for pembrolizumab in patients with recurrent or metastatic PD-L1-positive squamous cell carcinoma of the head and neck. Additionally, we also assessed RNA expression of six interferon-γ-regulated genes using a formalin-fixed paraffin-embedded (FFPE) tissue-compatible analysis method. A six-gene signature (consisting of *CXCL9, CXCL10, IDO1, IFNG, HLA-DRA,* and *STAT1*) was identified in a melanoma cohort in the KEYNOTE-001 study[19] of pembrolizumab, used in a predefined analysis in this cohort, and might serve as a predictive biomarker in the form of a composite score.

Methods

Study design and participants

This was an open-label, multi-cohort, multicentre, phase 1b trial assessing the safety and antitumour activity of pembrolizumab in patients with advanced solid tumours; here we report on the squamous cell head and neck cohort. Centres enrolling patients in this cohort were located throughout the USA and one was located in Israel (appendix p 5). Patients were eligible for enrolment if they were aged 18 years or older and had a confirmed diagnosis of recurrent (not amenable to locally curative options) or metastatic squamous cell carcinoma of the head and neck with at least 1% PD-L1 expression as determined by immunohistochemistry. Additional inclusion criteria were measurable disease based on Response Evaluation Criteria In Solid Tumors (RECIST, version 1.1), Eastern Cooperative Oncology Group performance status of 0 to 1,[20] adequate organ function determined by tests done within 10 days of treatment initiation, and provision of tumour tissue for PD-L1 expression analyses, HPV status, and biomarker assessment. The number of previous treatments the patients had received was not limited for inclusion, and treatment-naive patients were also allowed. Patients who received previous treatments specifically targeting T-cell co-stimulation or checkpoint pathways were excluded. Previous systemic immunosuppressive treatment had to be concluded within 7 days, chemotherapy within 2 weeks, and anticancer monoclonal antibody treatment within 4 weeks from the start of study treatment. Patients with additional progressing malignancies, CNS metastases, autoimmune diseases, interstitial lung disease, infections requiring systemic therapy, HIV, or hepatitis B or C were excluded.

See Online for appendix

Patients were allocated to HPV-negative and HPV-positive subgroups based on investigator HPV determination. HPV status was assessed at the local institution using p16 immunohistochemistry (where at least 70% of cells staining positive for p16 were counted as p16 positive) as a surrogate marker; this analysis was not reviewed centrally.