Innovation Observatory

NHS National Institute for Health Research

EVIDENCE BRIEFING
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Durvalumab in combination with Tremelimumab for recurrent or metastatic squamous cell carcinoma of the head and neck – first line

NIHRIO ID	12826	**NICE ID**	8753
Developer/Company	AstraZeneca UK Ltd	**UKPS ID**	Not available

Licensing and market availability plans	Durvalumab in combination with Tremelimumab is currently in phase III trials.

SUMMARY

Durvalumab in combination with tremelimumab is in clinical development for the first line treatment of people with recurrent or metastatic squamous cell cancer of the head and neck. Cancers that are known collectively as head and neck cancers usually begin in the squamous cells that line the moist, mucosal surfaces inside the head and neck (for example, inside the mouth, the nose, and the throat). These squamous cell cancers are often referred to as squamous cell carcinomas of the head and neck.

Cancerous cells produce proteins to stop the body's natural immune response to recognise and respond to the disease. Durvalumab and tremelimumab are drugs that act in different unique ways to stimulate the body's natural defences that fight the cancer cells. The combined effect of the two products may produce a stronger and more targeted immune response against the cancer cells when compared to current treatments.

PROPOSED INDICATION

Squamous cell carcinoma of the head and neck (recurrent or metastatic) – first line[1]

TECHNOLOGY

DESCRIPTION

Durvalumab (Imfinzi, MEDI4736) in combination with tremelimumab (CP-675206) is in clinical development for patients with recurrent or metastatic squamous cell carcinoma of the head and neck.[1] Durvalumab is a fully human IgG monoclonal antibody that blocks programmed cell death-1 ligand (PD-L1), a protein expressed on the normally expressed on antigen-presenting cells (APC).[2] PD-L1 can bind to its receptors PD-1 and expressedon activated T cells CD80 receptor expressed on activated T cells and on APC. This can result in the inactivation of tumour-specific T cells. Anti- PDL1 is designed to inhibit the interactions of PD-L1 with PD-1 and CD80. This activity would relieve the inhibition on T-cell activity, allowing T cells to kill tumour cells. T cell activation has been shown to be a key component of a successful anti-tumour response.[2,3]

Tremelimumab is a human IgG2 monoclonal antibody that binds to and inhibits the activity of the T-cell receptor protein - cytotoxic T-lymphocyte-associated protein 4 (CTLA4).[4] Tremelimumab binds to CTLA4 and blocks the binding of the antigen-presenting cell ligands B7-1 and B7-2 to CTLA4, resulting in inhibition of B7-CTLA4-mediated down regulation of T-cell activation. This increases proliferation of T cells and prolongs their activation, thus enhancing the anti-tumour response.[4,5]

In the phase III study of durvalumab with or without tremelimumab versus standard of care chemotherapy (KESTREL; NCT02551159), subjects in the combination therapy experimental arm receive durvalumab (1500 mg) and tremelimumab (75 mg) intravenously for every 4 weeks of maximum 4 doses. Patients in all arms will continue therapy until progression.[1,6-8]

INNOVATION AND/OR ADVANTAGES

The combination of durvalumab and tremelimumab, through its mechanism of action (simultaneous inhibition of two independent pathways that acts to suppress T cell responses to tumours), provides the potential for increased effectiveness when compared with current therapies for recurrent/metastatic squamous cell carcinoma of the head and neck.

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Durvalumab in combination with tremelimumab does not currently have Marketing Authorisation in the EU/UK for any indication.[9]

Durvalumab in combination with tremelimumab is currently in phase III clinical trials for:[10]

- Squamous cell carcinoma of the head and neck – second line
- Hepatocellular carcinoma
- Advanced solid malignancies
- Non-small cell lung cancer
- Urothelial cancer

Durvalumab in combination with tremelimumab is currently in phase II clinical trials for:[10]

- Malignant pleural mesothelioma
- Muscle-invasive bladder cancer
- Metastatic HER2 negative breast cancer
- Recurrent malignant glioma
- Hepatocellular carcinoma
- Germ cell tumour
- Recurrent/metastatic squamous cell carcinoma of head and neck
- Prostate cancer

PATIENT GROUP

DISEASE BACKGROUND

Head and neck squamous cell carcinoma (HNSCC) is a cancer that arises from particular cells called squamous cells. Squamous cells are found in the outer layer of skin and in the mucous membranes, which are the moist tissues that line body cavities such as the airways and intestines. HNSCC develops in the mucous membranes of the mouth, nose and throat.[11]

Head and neck cancer refers to a group of biologically diverse cancers that start in the upper aerodigestive tract (UAT), including:

- Oral Cancer (mouth, lip and oral cavity)
- Cancer of the larynx (voice box)
- Cancer of the pharynx (throat)
- Thyroid cancer (please see below)
- Other head & neck cancers

The majority of non-thyroid head and neck cancers are squamous cell carcinomas. Head and neck cancers often spread to the lymph nodes of the neck, and this is often the first sign of the disease at the time of diagnosis.[12]

HNSCC is caused by a variety of factors that can alter the DNA in cells. The strongest risk factors for developing this form of cancer are tobacco use (including smoking or using chewing tobacco) and heavy alcohol consumption. In addition, studies have shown that infection with certain strains of human papillomavirus (HPV) is linked to the development of HNSCC. HPV infection accounts for the increasing incidence of HNSCC in younger people.[11] However, in developed countries, more than half of new HNSCC cases are diagnosed in people aged 65 years or older.[13] Researchers have identified mutations in many genes in people with HNSCC, however, it is not yet clear what role most of these mutations play in the development or progression of cancer. The proteins produced from several of the genes associated with HNSCC, including TP53, NOTCH1, and CDKN2A, function as tumour suppressors, which means they normally keep cells from growing and dividing too rapidly or in an uncontrolled way. When tumour suppressors are impaired, cells can grow and divide without control, leading to tumour formation. It is likely that a series of changes in multiple genes are involved in the development and progression of HNSCC.[11]

The symptoms of head and neck cancers may include a lump or a sore that does not heal, a sore throat that does not go away, difficulty or pain in swallowing and a change or hoarseness in the voice. Other symptoms that may affect specific areas of the head and neck include bleeding of the mouth, swelling of the jaw, ear pain, headaches, paralysis of the muscles in the face, etc.[14]

In addition to the life threatening nature of HNSCC, quality of life may also be affected as the head and the neck are anatomical sites of basic functions, including speech, swallowing, hearing and breathing, which are necessary for social interaction.[15]

CLINICAL NEED AND BURDEN OF DISEASE

The age-standardised incidence rate of HNSCC in England was 19.2 per 100,000 population 2015, accounting for 3% of total cancer cases during the same year.[16] In 2016-17, there were 452 hospital admissions, and 914 finished consultant episode bed days due to malignant neoplasm of other and ill-defined sites: head, face and neck (C76.0) in England.[17] The age-standardised five-year survival rates for head and neck cancers in adults aged 15-90 years in England (2009 – 2013) were as follows: 27.8% for hypopharyngeal cancer, 65.4% (men only) for laryngeal cancer, 56.1% for oral cavity cancer, 65.6% for oropharyngeal cancer, 67% for salivary glands cancer, 51.4% for sinus cancer and 60.3% for tongue cancer.[18] Head and neck cancer is the 16th most common cause of cancer death in the UK, accounting for 2% of all cancer deaths (2016). There are around 3,900 head and neck cancer deaths in the UK every year (2014-16).[19]

The incidence and mortality rates for recurrent or metastatic HNSCC could not be estimated from available data sources.

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

Patients with recurrent cancer of the head and neck should be assessed systematically by a team experienced in the range of management options available for recurrence including surgical salvage, chemotherapy, re-irradiation and palliative care. The approach to management depends on patient factors, characteristics and site of the tumour and on the patient's treatment history. UK recommendations are available to guide the management process for recurrent or metastatic head and neck cancers.[20,21]

CURRENT TREATMENT OPTIONS

From the data available, surgery appears to be the modality that is likely to result in the best chance of cure, especially if there is the possibility of receiving adjuvant treatment post-operatively, or if the patient has HPV-positive disease. The aim of surgical treatment is to remove the whole tumour with wide clear margins, leaving no gross residual tumour behind. However, this will usually result in large defects requiring reconstruction. The resulting large functional deficits have to be balanced against the benefit of longer survival and/or or improved palliation.[20]

Patients receiving only palliative care have an average overall survival of four months after diagnosis. Outcomes from studies of palliative chemotherapy generally show longer survival rates, depending

on the regimen.[20] Cetuximab in combination with platinum-based chemotherapy is recommended as an option for treating recurrent or metastatic squamous cell cancer of the head and neck in adults if the cancer started in the oral cavity.[22]

Most patients with recurrent head and neck cancer will have had previous radical radiotherapy, which would have reached the maximal acceptable tolerance dose for critical organs such as spinal cords and/or brainstem. Therefore, re-irradiation of these patients carries significant potential risks and complications.[20]

Palliative and best supportive care should be offered routinely as part of the management package of all recurrence patients, even in the case of those who are being treated curatively. The early involvement of the palliative care physician can help control symptoms in the lead up to curative or palliative treatment. Furthermore, it provides a more seamless transition into palliative care if required. Involvement of a palliative care physician gives the patients confidence that their symptoms will be managed regardless of the outcomes of the treatment, and also can speed up the provision of support for patient and family at home.[20]

PLACE OF TECHNOLOGY

If licensed, durvalumab in combination with tremelimumab could provide a new first line treatment for recurrent or metastatic squamous cell carcinoma of the head and neck. The combined effect of the two products may produce a stronger and more targeted immune response against the cancer cells when compared to current treatments.

CLINICAL TRIAL INFORMATION

Trial	KESTREL trial, NCT02551159; durvalumab versus durvalumab with tremelimumab versus standard of care; phase III
Sponsor	AstraZeneca
Status	Ongoing
Source of Information	Trial registry[1]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, active-controlled
Participants	n=823; age ≥18 years at the time of screening; documented evidence of recurrent or metastatic squamous cell carcinoma of the head or neck (oral cavity, oropharynx, hypopharynx, or larynx); no prior systemic chemotherapy for recurrent or metastatic disease; no prior exposure to immune-mediated therapy
Schedule	Randomised in a 2:1:1 ratio to durvalumab (1500 mg) intravenously for every 4 weeks for a maximum of 4 doses, durvalumab (1500 mg) and tremelimumab (75 mg) intravenously for every 4 weeks of maximum 4 doses as combination therapy; or cetuximab (400 mg/m^2 on cycle 1 day 1 and 250 mg/m^2 weekly), 5-fluorouracil (1000 mg/m^2/day on day 1-4) (5FU), cisplatin and carboplatin (AUC of 5 mg/mL/min) for every three weeks
Follow-up	Active treatment until progression or toxicity, follow-up every 3 months for survival after progression is confirmed
Primary Outcomes	Overall survival
Secondary Outcomes	• Objective response rate

	• Progression free survival • Second progression • Duration of response • Best objective response • Time to first subsequent therapy • Time to second subsequent therapy • Pharmacokinetic profile and immunogenicity • Patient-reported outcomes (EORTC QLQ-C30 and EORTC QLQ-H&N35)
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as Dec 2018

ESTIMATED COST

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Head and neck cancer – contusugene ladenovec (ID76). Expected date of issue to be confirmed.
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NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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OTHER GUIDANCE

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